To the Graduate Council:

I am submitting herewith a dissertation written by Donald Elton Bierer Jr. entitled "Synthetic Approaches to Iodovinyl Amino Acids." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

George W. Kabalka, Major Professor

We have read this dissertation and recommend its acceptance:

Leaf Huang

Craig E Barnes

Richard Pagni

Accepted for the Council:

Vice Provost
and Dean of The Graduate School

SYNTHETIC APPROACHES TO IODOVINYL AMINO ACIDS

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Donald Elton Bierer Jr.

August 1988

VOLUME I

DEDICATION

The author wishes to dedicate this work to his late father, Donald Elton Bierer Sr., who passed away on 1 March 1969, and to his son, Donald Elton Bierer III. For their love, support, and understanding the author wishes to further dedicate this work to his mother, Mary Jean Hulbert, and his sister, Sue Anne North. Finally, the author wishes to extend a special dedication to his girlfriend, Elizabeth M. Zippi, without whose love, completion of this degree would not have been possible.

ACKNOWLEDGEMENTS

The author wishes to thank Professor Dr. George W. Kabalka for his advice and generous support during the course of this work. The author also wishes to express his thanks and appreciation to the Science Alliance Center of Excellence and the University of Tennessee for financial support during the course of his graduate studies, and to the faculty of the University of Tennessee Chemistry Department for the recognition received in the form of a graduate teaching assistant award, and two graduate research awards.

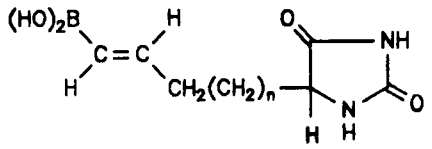
The author would like to extend his appreciation to Dr. Fred Schell for the use of his ketene generator. The author would also like to extend thanks to Dr. Kunda A. R. Sastry and to Dr. Mohammed Mohammmadi, for their advice and friendship during the formative years of his graduate studies. A warm acknowlegement is also extended to Dr. Laila Guindi for her help in teaching the author to use the WIMP molecular drawing program.

The author also wishes to thank his girlfriend, Elizabeth M. Zippi, for her assistance with the figures and illustrative art work within this dissertation, and for her friendship and encouragement.

Finally, to my ex-wife, who did everything possible to hinder completion of this degree, I offer no thanks.

ABSTRACT

A site specific radiopharmaceutical for imaging of the pancreas is currently not available. Based on previous studies involving unnatural amino acids, iodovinyl-α-methyl-α-amino acids appear to be promising candidates. A number of synthetic approaches to the iodovinyl-α-methyl-α-amino acids were investigated. One approach involved the use of an intermediate vinylboronic acid hydantoin (I). By use of this methodology, the synthesis of a model compound, 2-amino-12-iodo-11-dodecenoic acid (II) was realized.



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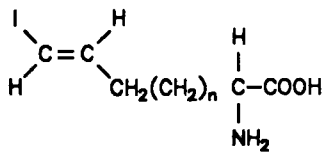


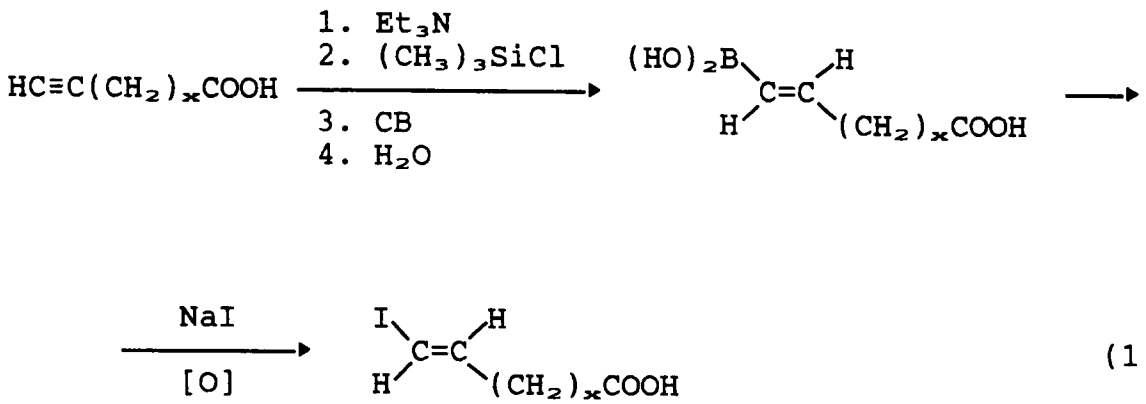
II

Detailed investigations of synthetic pathways involving protected hydantoins were carried out. New approaches to hydantoin precursors were also developed.

A direct approach involving the hydroboration of acetylenic amino acids was investigated. This approach had never been reported. Protection of the carboxylic acid functionality as the trimethylsilyl ester during the hydroboration reaction was investigated. Hydroboration of unsaturated trimethylsilyl esters was successful with all

hydroborating agents studied, including $BH_3 \cdot THF$. The intermediate organoboranes can be converted by standard organoborane transformations, including halogenation, oxidation, and protonolysis.

Isolation of the intermediate trimethylsilyl ester is often unnecessary. A convenient procedure involving the <u>in situ</u> formation of the trimethylsilyl ester followed by hydroboration was developed. This methodology offers a new route to iodovinyl fatty acids (equation 1).



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BACKGROUND

A. Introduction

The research program described in this dissertation has, as a central focus, the synthesis of physiologically active amino acids labeled with medically useful, short lived isotopes. Numerous synthetic strategies are described which incorporate synthetic methods involving organometallic reagents, amino acids, silanes, and a variety of halogenation and oxidation sequences. In this chapter, background material is presented which serves to set the foundation for subsequent chapters.

B. General Considerations

1. Historical

Organoboranes were first prepared in 1859 by Frankland [1,2,3,4]. They were prepared by transmetallation reactions involving dialkylzinc species and trialkoxyboranes. Other preparations of organoboranes involving transmetallations followed; the most important preparations involved the reaction of Grignard reagents[5] and organometallic derivatives[6,7] of lithium, mercury, aluminum, and tin with boron esters[8] (equation 1-1) or boron halides[9] (equation 1-2).

$$3PhMgBr + (MeO)_3B \longrightarrow Ph_3B + 3MgBrOMe \quad (1\text{-}1)$$

$$3Et_2Zn + 2BCl_3 \longrightarrow 2Et_3B + 3ZnCl_2 \quad (1\text{-}2)$$

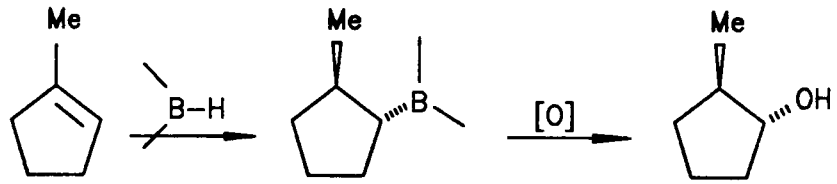
Since the synthesis of an organoborane involved the prior formation of an organometallic compound, there was little incentive to investigate the utility of organoboranes in organic synthesis. However, in 1938 Johnson and Van Campen[10,11] showed that oxidation of organoboranes by various reagents gave alcohols in good yields, and until the 1950's, this remained the only reaction of synthetic interest to organic chemists.

The discovery of the hydroboration reaction in 1956 by Nobel Laureate H. C. Brown and B. C. Subba Rao provided a new and convenient route to organoborane derivatives[12,13], and led to a wealth of new chemistry. The ease with which organoboranes can be prepared, the numerous transformations that can be accomplished via organoborane intermediates, and the tolerance of various functional groups to hydroboration conditions have made the organoboranes one of the more versatile classes of organometallic reagents available to organic chemists today.

2. The Hydroboration Reaction

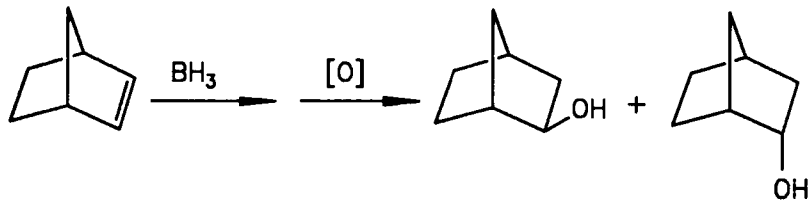
The hydroboration reaction involves the addition of a boron-hydrogen moiety across an unsaturated carbon-carbon

bond[14,15,16] (equation 1-3). The reaction occurs, predominantly, from the less hindered side of the double bond[14,16],



(1-3)

is essentially quantitative, and proceeds rapidly at room temperature and lower[14,15,16,17,18] (equation 1-4). Oxida-



99·5 0·5

(1-4)

tion of the intermediate organoborane, which involves the replacement of the boron atom by a hydroxyl group, results in an overall anti-Markownikov addition of water across the double bond[14,16].

The simplest hydroborating species, borane (BH_3), is gaseous, and exists as a dimer (B_2H_6). However diborane itself is difficult to handle, and reacts sluggishly with alkenes in the gas phase[19,20,21,22,23]. The reactivity of diborane is markedly enhanced by utilizing it in the presence of weak Lewis bases (ethers, sulfides); this effect is attributed to the symmetrical dissociation of the dimeric species into a reactive borane complex[14,15,16] (equation 1-5) which then reacts rapidly with alkenes to give alkyl

boranes[24] (equation 1-6).

$$B_2H_6 + 2XR_2 \longrightarrow 2H_3B{\cdot}XR_2 \qquad (1\text{-}5)$$

$$RCH{=}CH_2 + BH_3{\cdot}XR_2 \longrightarrow (RCH_2CH_2)_3B + XR_2 \qquad (1\text{-}6)$$

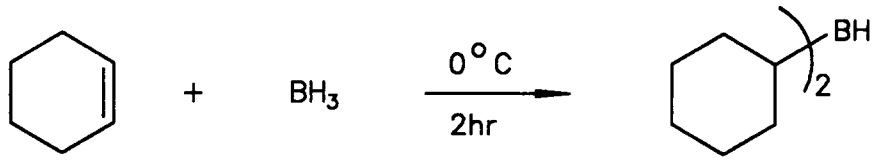
$$X = O, S; \quad R = \text{alkyl}$$

Hydroborations are conveniently carried out utilizing solutions of diborane in THF[16] or neat borane - dimethylsulfide complex[25]. These two reagents have become the most commonly employed hydroborating agents due to their commercial availability.

Borane is a trifunctional molecule and it can react with alkenes to give three types of products: mono-, di- and trialkylboranes. Most alkenes undergo hydroboration with borane to form the triorganoborane, although the reaction can be controlled to give partially alkylated derivatives[16]. The extent to which the hydroboration reaction proceeds depends mainly on the structure of the olefin, and to some extent, on the reaction conditions. In general, terminal and unhindered disubstituted internal alkenes give trialkylboranes, regardless of reaction conditions (equation 1-7). Trisubstituted olefins and some

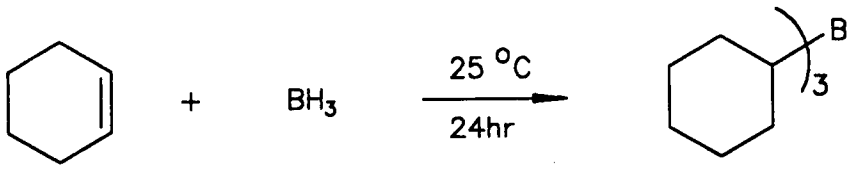
$$CH_3(CH_2)_3CH{=}CH_2 + BH_3 \longrightarrow [CH_3(CH_2)_3CH_2]_3B \qquad (1\text{-}7)$$

unhindered internal alkenes give rise to dialkylboranes (equation 1-8). Further reaction to the trialkylborane



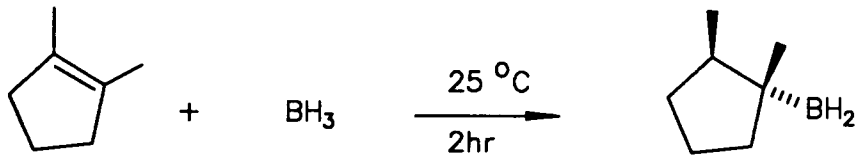
(1-8)

stage is sluggish, and can only be attained by forcing conditions (equation 1-9). Tetrasubstituted alkenes provide



(1-9)

monoalkylboranes initially (equation 1-10), with further

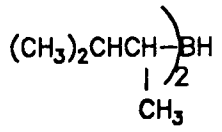


(1-10)

reaction to the subsequent dialkylboranes occurring only in concentrated solutions over long periods of time.

Many dialkyl- and monoalkylboranes can react with less hindered olefins and proceed to the subsequent stage of hydroboration via stepwise hydroboration. This capability has made many mono- and dialkylboranes effective hydroborating agents. Among the most commonly employed dialkylboranes are disiamylborane[26] (I), dicyclohexylborane[27] (II), and

9-borabicyclononane[28] (III). The use of such reagents in hydroboration provides mixed trialkylborane intermediates of



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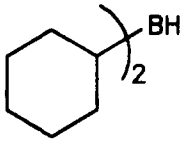

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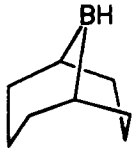
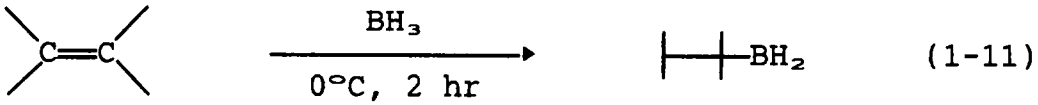


III

the type $R_2R'B$, which have proven to be useful intermediates[29].

Thexylborane, prepared by reaction of 2,3-dimethyl-2-butene with borane-THF or neat borane-dimethylsulfide[30,31] (equation 1-11) is the most commonly used monoalkylborane.

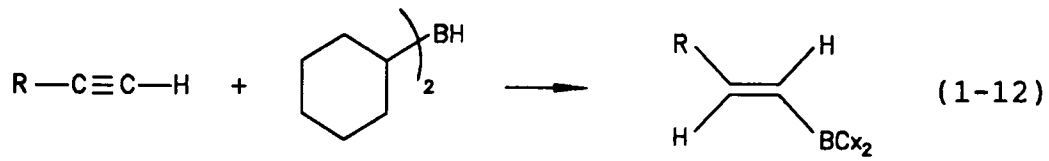


(1-11)

With the exception of monosubstituted 1-alkenes, which give dihydroboration products[32], thexylborane reacts with most alkenes to give thexylmonoalkylboranes in nearly quantitative yields[33]. The resulting mixed dialkylborane has been shown to hydroborate most olefins at -20 to -25°C to provide mixed trialkylboranes of the type $R_1R_2R_3B$, which have also been proven to be useful synthetic intermediates[34].

Hydroboration of alkynes is also a facile reaction. With borane, a theoretical amount of hydride is consumed to give dihydroboration products, predominantly gem-dibora

derivatives[35,36,37]. The reaction can be controlled to provide alkenylboranes, but this is best accomplished using borane derivatives like dicyclohexylborane or 9-BBN[16,38] (equation 1-12).



(1-12)

The hydroboration of alkenes involves the predominant placement of the boron atom on the least substituted carbon of the olefin. Reaction of simple terminal olefins (IV) with borane proceeds with placement of 94% of the boron atom at the terminal carbon, whereas disubstituted 1-alkenes (V) react such that 99% of the boron is at the terminal carbon[39]. The regiochemistry of the hydroboration can be greatly enhanced by using bulky dialkylboranes such as 9-BBN[28] or disiamylborane[40,41]. Thus hydroboration of 1-

	$Bu_nCH{=}CH_2$	
	↑	↑
BH_3	6	94
Sia_2BH	1	99
9-BBN		>99

IV

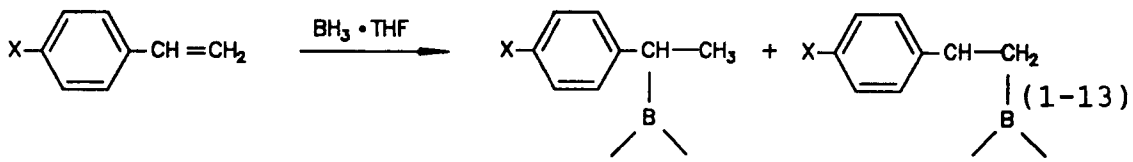
	Me	
	|	
	$EtC{=}CH_2$	
	↑	↑
	1	99
		>99
		>99

V

hexene (IV) with disiamylborane and 9-BBN results in 99% and

>99% of the boron atom being placed at the terminal carbon, increase the amount of benzylic product. Likewise, in the hydroboration of unsymmetrical internal olefins, bulky dialkylboranes offer high regioselectivity.

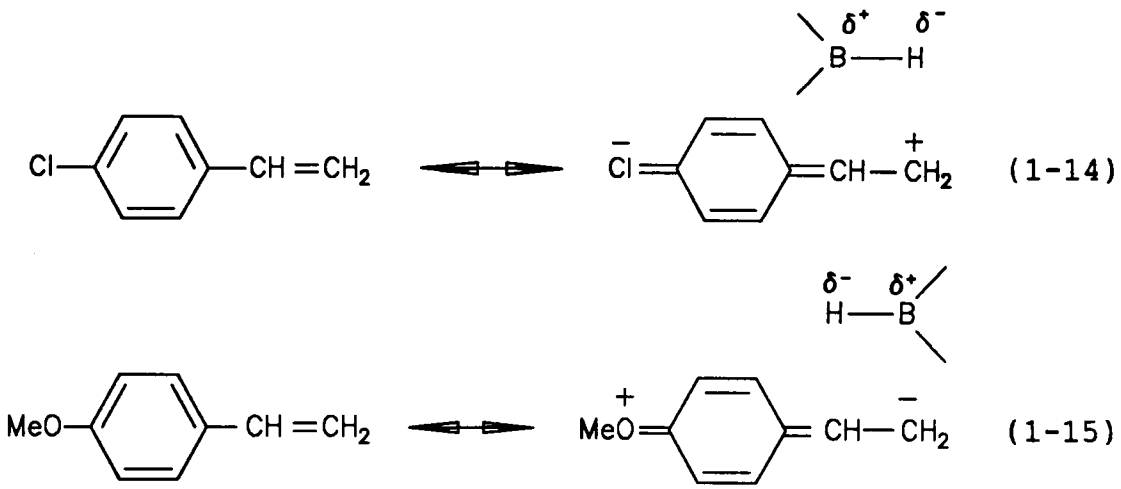
Electronic factors also play a role in determining the regiochemical outcome of the hydroboration reaction. In the hydroboration of styrene with BH_3, for example, 19% of the boron atom becomes attached to the benzylic carbon[42,43], whereas for simple terminal olefins, as was noted earlier, only 6% of the boron is attached to the internal olefinic carbon. Electron withdrawing groups on the aromatic ring increase the amount of benzylic product. In contrast, electron donating substituents, like OMe, decrease it[44] (equation 1-13). These results have been explained on the



(1-13)

	↑	↑
X = H	19	81
X = Cl	27	73
X = OMe	7	93

basis that the direction of addition in the hydroboration reaction is controlled by the hydridic character of the boron hydrogen bond, $B^{\delta+}$-$H^{\delta-}$[39] (equations 1-14, 1-15). Likewise, directive effects in the hydroboration of



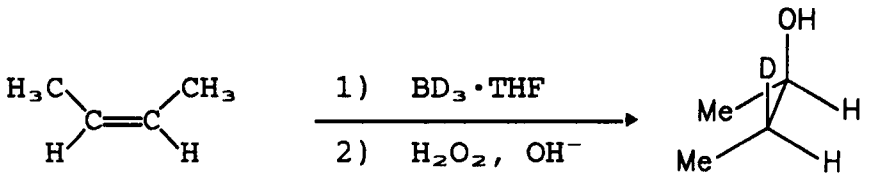
(1-14)

(1-15)

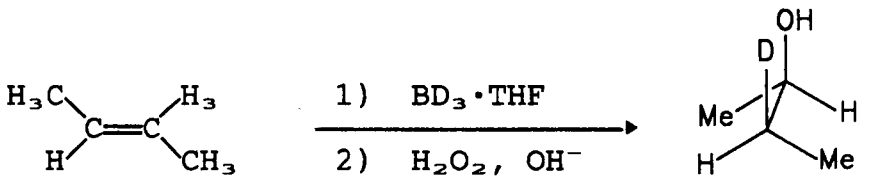
unsymmetrically substituted alkynes are controlled by steric and electronic effects, both in alkyne and in borane. Terminal alkynes are hydroborated with nearly exclusive placement of the boron at the terminal position by all borane derivatives[37,38,45,46,47,48].

The hydroboration reaction involves the <u>syn</u> addition of a boron hydrogen moiety across a double or triple bond. This conclusion was long accepted as fact based on stereochemical analyses of the products obtained in the hydroboration - oxidation and hydroboration - protonolysis sequences, assuming retention of configuration during the second step[16,41,49]. Kabalka and Bowman subjected <u>cis</u>-2-butene and <u>trans</u>-2-butene to deuterioboration - oxidation and found that <u>erythro</u>-2-butanol-3-d (equation 1-16) and <u>threo</u>-2-butanol-3-d, respectively, were the sole reaction products[50]

(equation 1-17). Thus, the products that would result for

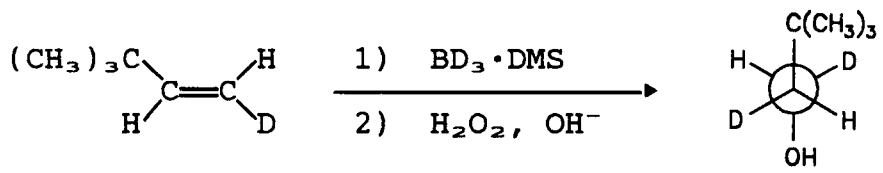


(1-16)

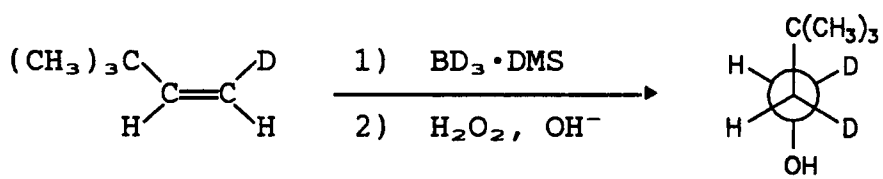


(1-17)

the expected <u>syn</u> hydration were observed. In a similar experiment involving a terminal olefin, Bergbreiter and Rainville showed that when (Z)-3,3-dimethylbutene-1-d was deuterioborated with BD_3·DMS and then oxidized with alkaline peroxide, <u>threo</u>-3,3-dimethylbutan-1-ol-1,2-d_2 was obtained as the sole product (equation 1-18). Likewise, (E)-3,3-dimethylbutene-1-d gave the corresponding <u>erythro</u> analogue stereospecifically[51] (equation 1-19). Recently, NMR studies

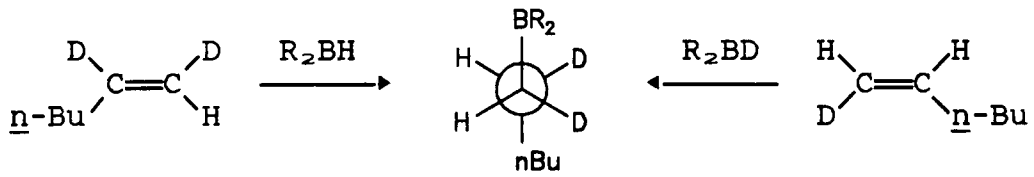


(1-18)



(1-19)

of organoboranes obtained from deuterated 1-hexene and dialkylboranes provided the first direct evidence that the hydroboration reaction proceeded in a stereospecific syn fashion[52] (equations 1-20, 1-21).



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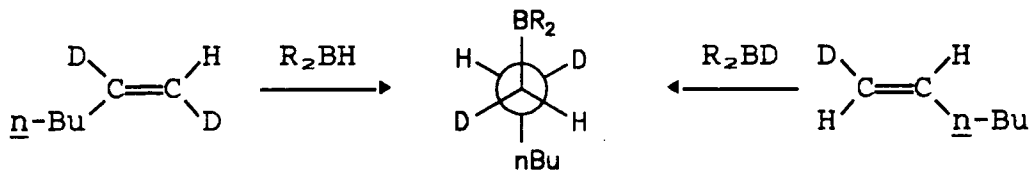
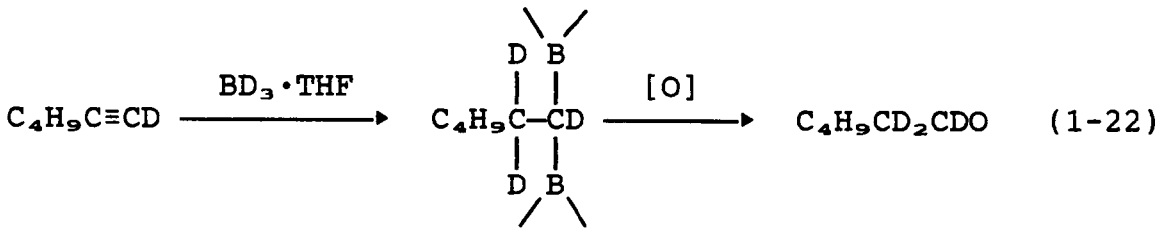


(1-21)

Deutererioboration has also been utilized to confirm the stereo- and regiochemistry of the hydroboration, and protonolysis reactions of alkynes. Zweifel and Arzoumanian, in a study designed to determine the regiochemical preference of dihydroboration of alkynes, showed that deuterioboration of 1-hexyne-1-d gave exclusively the gem-dibora derivatives[37] (equation 1-22), while use of dialkyl[38] and dialkoxyboranes for monohydroboration have provided exclusively trans alkenes or trans alkenylboronic esters[51,53,54] (equation 1-23).

The regio- and stereochemistry, stereospecific syn addition of the B-H moiety, and lack of rearrangement of



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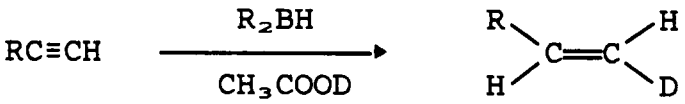
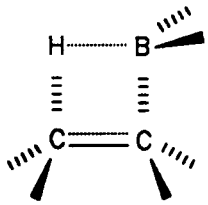


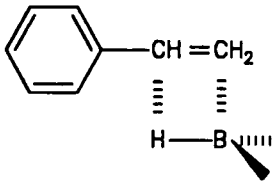
(1-23)

organoboranes was originally accounted for by Brown in terms of a concerted four center transition state, with the boron hydrogen bond being polarized[55] (VI). The steric and

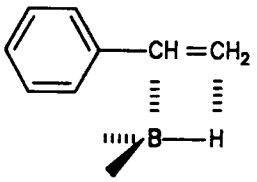


VI

electronic effects exerted by substituents are readily explained on the basis of this model. Thus one observes an increase in hydroboration at the terminal position when electron donating groups are present, because transition state VII is stabilized, whereas transition state VIII is stabilized when electron withdrawing groups are present. However, the model failed to predict the correct product in the hydroboration of cis-1-butene-1-d with (-)-diisopino-

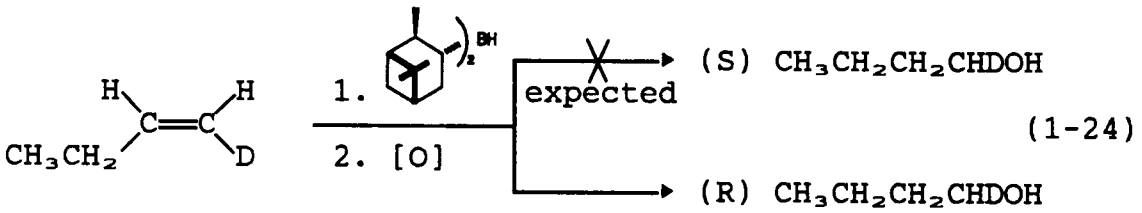


VII



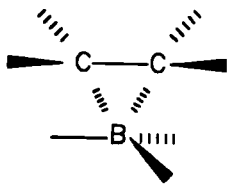
VIII

camphenylborane[56] (equation 1-24). To account for the



(1-24)

observed results, Streitweiser proposed an intermediate trigonal alkene-borane π complex (IX), and a transition



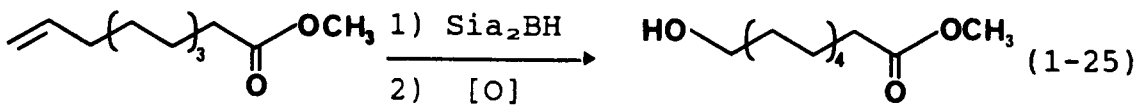
IX

state that requires only a small perturbation of the trigonal structure. The proposed transition state is the subject of much debate. Arguments against the trigonal intermediate have been presented on the basis of other stereochemical results[57], Hammett correlations[42,43,58], and the kinetic isotope effect which has been observed. Support for this intermediate has been offered on the basis of a consideration of the molecular orbitals by Jones[59], and

numerous theoretical studies which have been reported as well[60,61,62,63,64].

3. Hydroboration of Functionalized Alkenes: General

The hydroboration reaction is not limited to simple hydrocarbons, but can be carried out in the presence of a wide variety of functional groups[65]. The enhanced reactivity of carbon-carbon double and triple bonds over many other functionalities enhances the synthetic utility of the hydroboration reaction by allowing it to be carried out in the presence of functional groups which might otherwise be reduced. In addition, borane derivatives are often more selective than BH_3 and, by proper choice of hydroboration agent, one can carry out a hydroboration reaction in exceedingly complex molecules with generally only aldehydes, ketones and carboxylic acids requiring protection[66]. For example, disiamylborane[67] does not reduce esters, whereas 9-BBN does so at a moderate rate[68]. Thus by using disiamylborane, it is possible to carry out the hydroboration of methyl 10-undecenoate without competitive reduction[69] (equation 1-25).



(1-25)

Disiamylborane[67] and dicyclohexylborane[70,71] have been even reported not to reduce carboxylic acids at 0°C (equation 1-26). Selective hydroboration of enynes can be accomplished

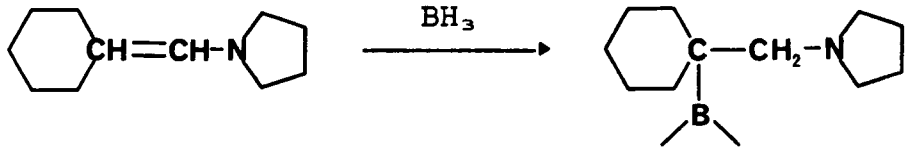
$$H_2C{=}CH(CH_2)_x\overset{O}{\overset{\|}{C}}{-}OH \xrightarrow{R_2BH} \xrightarrow{[O]} HOCH_2CH_2(CH_2)_x\overset{O}{\overset{\|}{C}}{-}OH \qquad (1\text{-}26)$$

by using 9-BBN as the hydroborating agent, a property unique to 9-BBN[72] (equation 1-27).

$$RC{\equiv}C(CH_2)_xCH{=}CH_2 \xrightarrow[2.\ [O]]{1.\ 9\text{-BBN}} RC{\equiv}C(CH_2)_xCH_2CH_2OH \qquad (1\text{-}27)$$

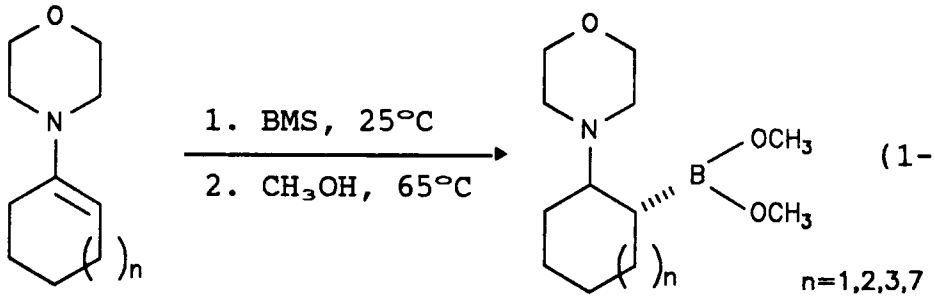
The proximity of the hetero substituent to the alkene or alkyne is very important in determining the regiochemistry of the addition of the boron-hydrogen moiety. Remote functional groups generally exert little influence on both the regio- and stereoselectivity of the addition[73,74]. However, in the case of allylic and vinylic derivatives, these directing effects can be pronounced. In general, vinyl substituents with a strong M^+ effect, like an ether[75,76] or amino[77,78,79] group, direct boron primarily, and in some cases, exclusively to the position beta to the functional group. Enamines of cyclic ketones have been shown to yield the hydroboration product with the boron

atom in the beta position[77,80,81] (equation 1-28).



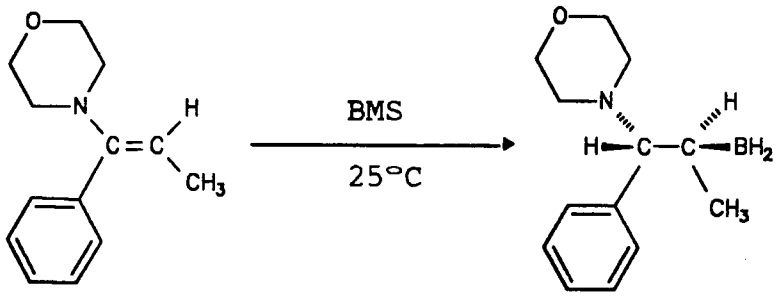
(1-28)

Recently a detailed study on the hydroboration of enamines revealed that even 7, 8, and 12-membered morpholine enamines cleanly provided exclusively ß-amino boronate esters after methanolysis of the corresponding organoborane[81] (equation 1-29). Similar results are often obtained with acyclic



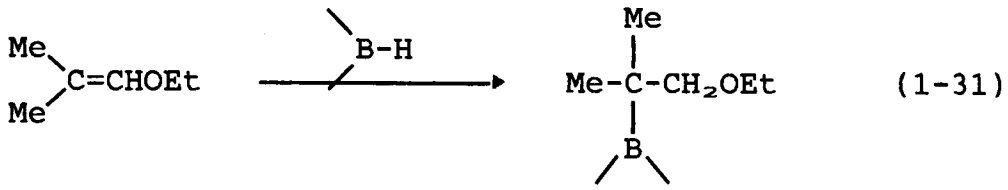
(1-29)

enamines as well[77,79]. For example, the hydroboration of the acyclic enamine (E)-1-morpholino-1-phenyl-1-propene, recently reported by Brown[81], gave the expected ß-amino monoalkyl organoborane exclusively (equation 1-30).



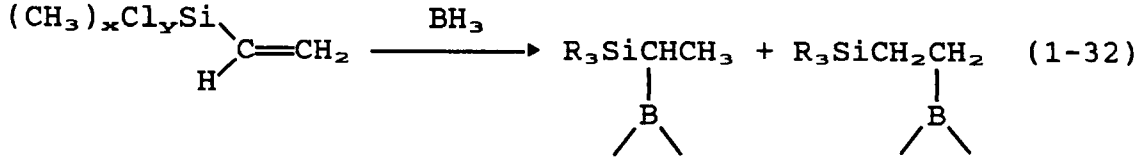
(1-30)

Like vinyl amines, a vinyl ether group exerts a powerful directive effect providing, in most cases, a complete reversal of regiochemistry from the parent alkene. The hydroboration of isobutenyl ethyl ether is a representative example[75] (equation 1-31).



(1-31)

A substituent which exerts an electron withdrawing resonance effect, like silicon, directs a larger percentage of the boron atom alpha to the substituent[82]. When halogens are present on the silicon atom, the directive effect is even more pronounced, with the predominant product being the one with the boron atom located alpha to the silyl group[83,84] (equation 1-32). Application of bulky dialkylboranes

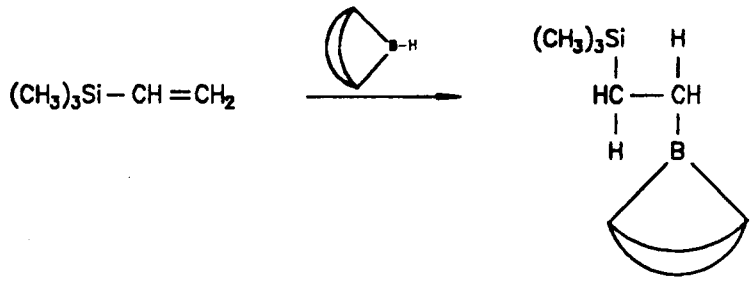


(1-32)

x = 3, y = 0	33%	67%
x = 2, y = 1	70%	30%
x = 1, y = 2	90%	10%

negates the directive effect of the silicon atom. In a recent study conducted by Brown and Soderquist, the hydroboration of trimethylvinylsilanes with 9-BBN gave regio-

specific placement of the boron atom beta to the trimethylsilyl group, while other dialkylboranes were shown to be very regioselective (95%)[85] (equation 1-33).

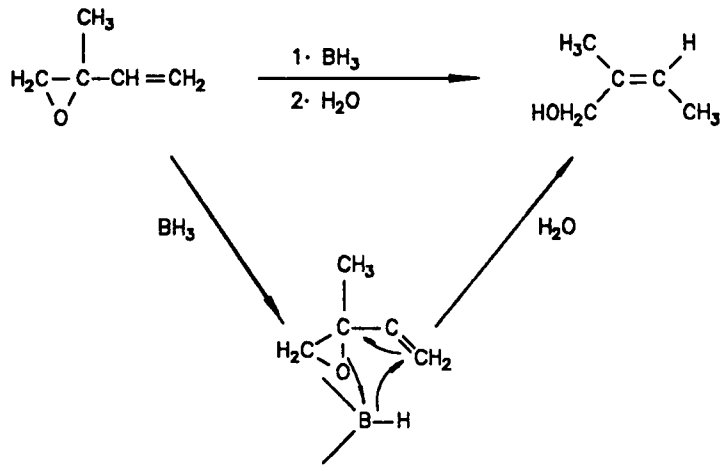


(1-33)

The hydroboration of substituted allylic compounds provide beta- and gamma-substituted organoboranes, with the relative amounts of each depending on the electronegativity of the allylic functional group. The directive effect of the allylic substituent is purely inductive, with the amount of ß-organoborane increasing with increasing electronegativity[86,87]. Brown and coworkers have carried out hydroborations of a number of allylic derivatives, including tosylates[88], chlorides[88], acetates[86], ethers[86], and thioethers[86], and the effect of decreasing electronegativity is evident. Thus allyl tosylates gave 45% of the ß-organoborane; chlorides, 40%; acetates, 35%; phenylether, 32%; alcohol, 24%; phenyl thioether, 22%; and ethyl ether, 19%[86]. Hydroboration with a sterically demanding borane reduces the amount of ß-organoborane, even in the very polar case. Thus, whereas hydroboration of allyl chloride with BH_3 gave 40% of the ß-organoborane, use of disiamylborane resulted in only 2% of the beta adduct[86].

Hydroboration of 3-butenyl-substituted derivatives exhibits directive effects analogous to those observed in the allylic system, although the inductive effect of the substituent is diminished. The amount of boron addition gamma to the functional group ranged from 18% for 4-chloro-1-butene, to 11% for 4-methoxy-1-butene, with the same electronegativity trend being observed[89]. As was the case with allylic derivatives, application of sterically demanding borane reagents negates the inductive effect of the substituent, providing a highly stereoselective route to the 4-hydroxy derivative[89].

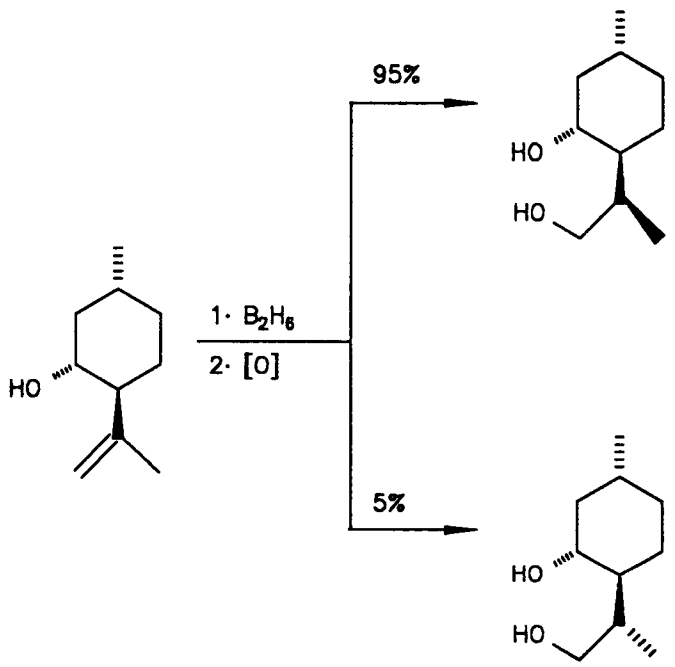
Functional groups, when properly located in a molecule, can direct the addition not only by steric and electronic effects, but also by the formation of cyclic transition states. Zaidlewicz and colleagues have investigated the hydroboration of allylic epoxides which were found to provide convenient access to stereochemically pure allylic alcohols[90,91] (equation 1-34). The reaction is believed



(1-34)

to involve a cyclic transition state, with initial coordination of the boron atom to the oxygen, followed by delivery of the hydride to the terminal double bond carbon and then isomerization.

Proximal hydroxy substituents can also direct the addition of the hydroborating agent. Ohloff and Schulte-Elte conducted a detailed investigation on the stereochemical course of the hydroboration-oxidation of diastereomeric (1R) isopulegols[92] (equation 1-35). The major

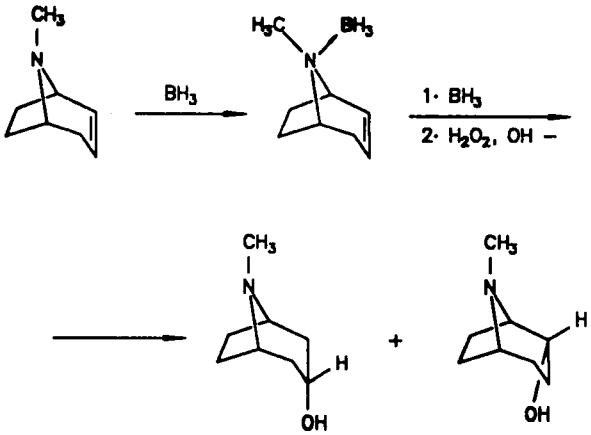


(1-35)

product resulted from the antiperiplanar trans-addition of the hydroborating agent to the isopropenyl unit of the initially formed cyclic borate. In a similar fashion an ester functionality, when properly located in a molecule, can exhibit directed hydroboration by an intramolecular

process[93].

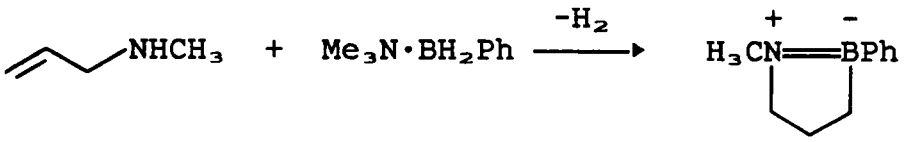
Amine groups, on the other hand, due to their ability to form strong complexes with borane can block one face of a double bond, when appropriately located in the molecule, thus directing hydroboration to the opposite face[94]. Tropidine derivatives undergo such directed hydroboration reactions, with borane addition occurring predominantly from the α face[95] (equation 1-36).



(1-36)

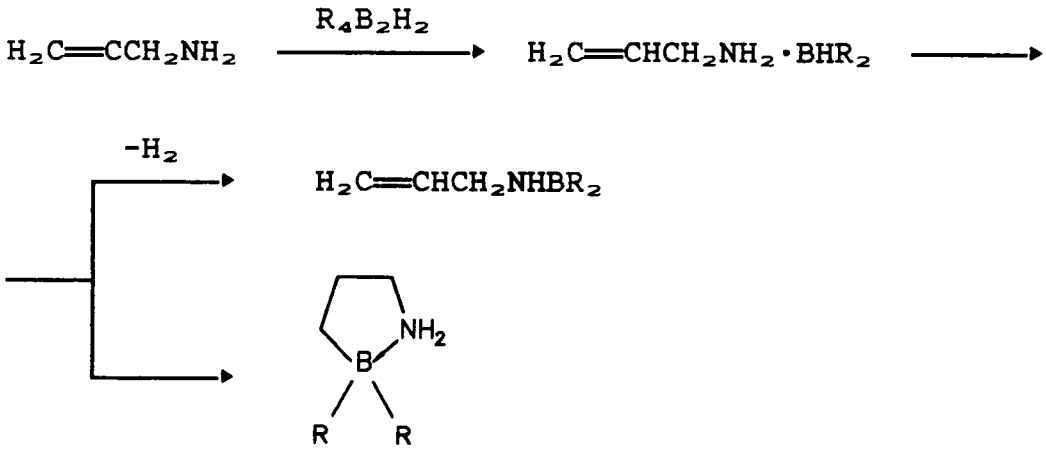
4. Hydroboration of Unsaturated Amines

The hydroboration of an unsaturated amine compound was first reported by Adams and Poholsky[96]. Upon reaction of N,N dimethylallylamine with trimethylamineborane in refluxing toluene, they obtained a cyclic amineborane in a 25% yield. In an almost simultaneous report, White reported the synthesis of a similar compound from reaction of N-methylallylamine with trimethylaminophenylborane[97] (equation 1-37). Mikhailov and coworkers also studied the reaction of allyl amine with tetraalkyldiborane and determined that the



(1-37)

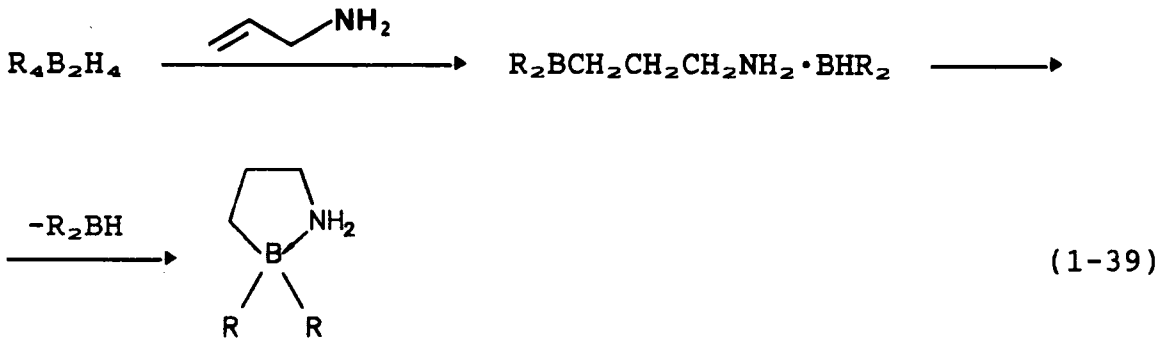
course of the reaction depended on the order of mixing of the reagents[98]. They discovered that when the tetraalkyldiborane is added to an ethereal solution of allyl amine (1:1 stoichiometry) a coordination adduct is formed initially which then is either converted to an amine borane with loss of H_2, or undergoes intra- or intermolecular hydroboration to form a cyclic monoalkylborane[99] (equation 1-38).



(1-38)

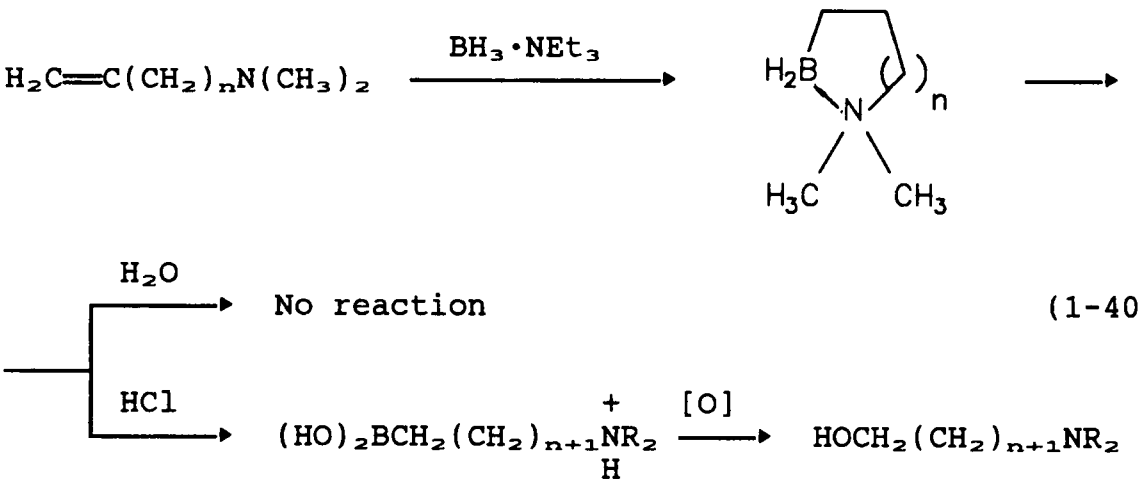
When the order of addition is reversed, a diboro adduct is formed, with concomitant loss of the coordinately bound dialkylborane to form the cyclic monoalkylborane (equation 1-39).

Unlike unsaturated hydrocarbons, hydroborations of unsaturated amines proceed only to the monoalkylborane



(1-39)

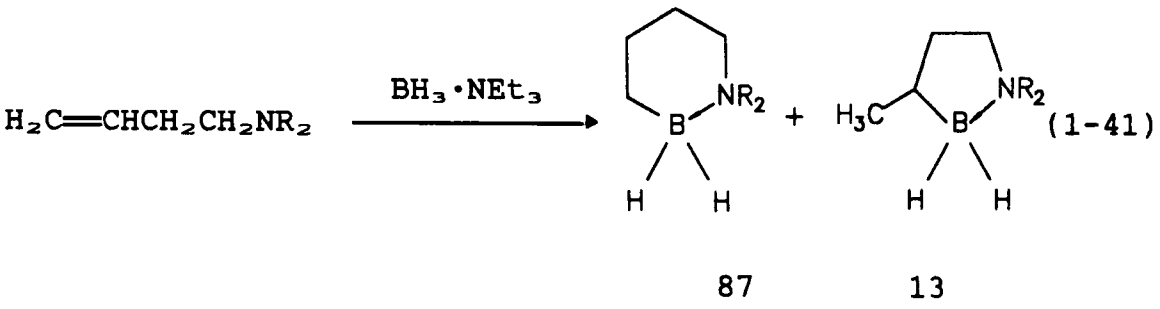
stage. The resultant cyclic monoalkylboranes are very stable. They are unreactive to water[89] and are also resistant to direct oxidation by alkaline hydrogen peroxide[100]. To obtain amino alcohols from olefinic amines, pretreatment of the intermediate organoborane with hydrochloric acid is required[100] (equation 1-40). Polívka, Ferles, and cowork-



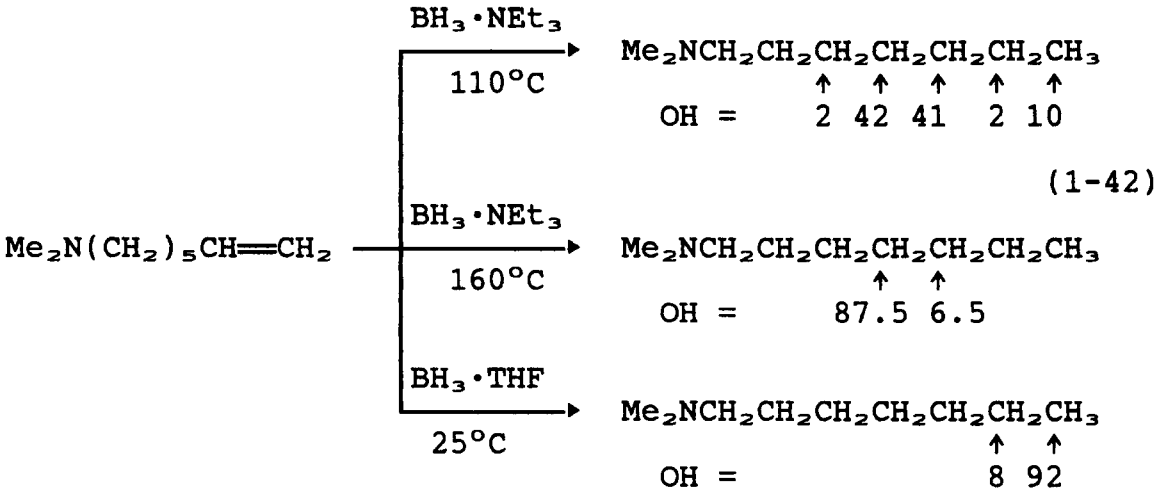
(1-40)

ers[100,101,102,103] have conducted a detailed investigation of the hydroboration of Ω-dimethylamino alkenes, and the

thermal decompositions of the Ω-dimethylaminoalkylboranes formed in the process. Hydroboration of 4-dimethylamino-1-butene with triethylamine-borane gave a mixture of the two cyclic isomers in a 87:13 ratio, while the similar C5 compound yielded a 96:4 ratio of the 7-membered and 6-membered ring analogues[102] (equation 1-41). Higher members

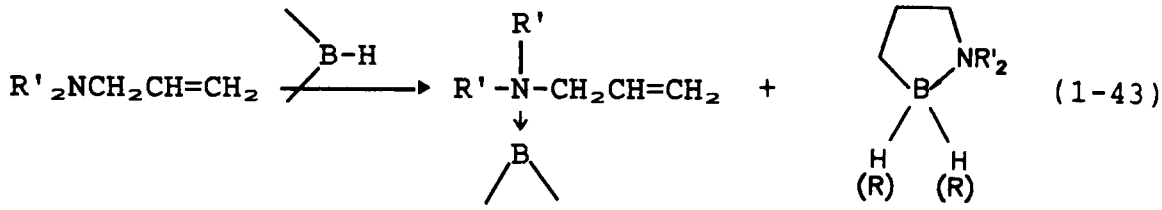


of this aminoolefinic series also produce a mixture of cyclo(N-B-Ω-dimethylamino)alkylboranes, with the product distribution being dependent on the reaction temperature. The hydroboration of 7-dimethylamino-1-heptene is representative (equation 1-42). Hydroboration with BH_3•THF at 25°C afforded the expected hydroboration products in a 92:8 ratio after oxidation, whereas hydroboration with triethylamine-borane at 110°C gave a mixture of five isomeric products[102]. At 160°C, thermal isomerization occured readily, producing an 87.5:6.5 mixture of 4-hydroxy- and 3-hydroxy-1-aminoheptane, after oxidation, indicating that the 6-membered boroheterocyclic monoalkylborane is thermodynamically the most stable product[103].



Lattes, Baboulène, Torregrosa, and Spéziale have systematically investigated the hydroboration of substituted allylic amines with various other hydroboration agents[104]. The choice of hydroborating agent was found to be a critical factor in determining the equilibrium between the linear amine borane and the cyclic amine-borane. As shown for the case of N,N-allylmethylaniline, whereas, the linear amine-borane derived from triethylamine-borane gave, upon thermolysis, a quantitative yield of the cyclic monoalkylborane, the linear amine-borane derived from catecholborane (CB), or 9-BBN gave mixtures[104] (equation 1-43).

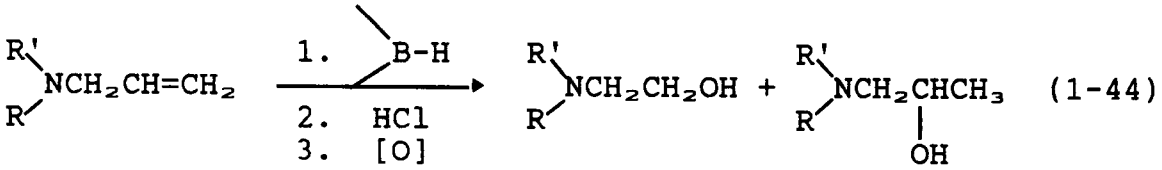
The basicity of the amine is an important factor in determining the regiochemistry of borane addition in allylic amine systems. In general, the more basic the amine, the stronger the inductive effect, and the more of the secondary



(1-43)

$Et_3N \cdot BH_3$	<1	>99
CB	40	60
9-BBN	30	70

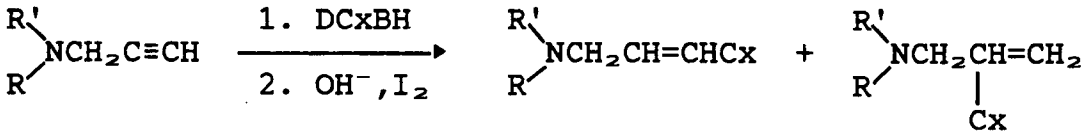
alcohol that is obtained upon oxidation of the organoborane[104] (equation 1-44).



(1-44)

$R = R' = CH_3$	100	0
$R = CH_3$, $R' = Ph$	100	0
$R = R' = -CH_2(CH_2)_2CH_2-$	90	10
$R = R' = -(CH_2)_2N(CH_3)(CH_2)_2-$	80	20

The first hydroboration of a propargylic amine was recently made by Lattes and coworkers[105]. In a study devoted to the synthesis of ethylenic amines via the route published by Zweifel[106,107], Lattes carried out the hydroboration of a series of propargylic amines with various dialkylboranes (equation 1-45). As was the case with the amines, the regiochemistry of the addition was dependent on the nature of the substituents on the nitrogen atom, with



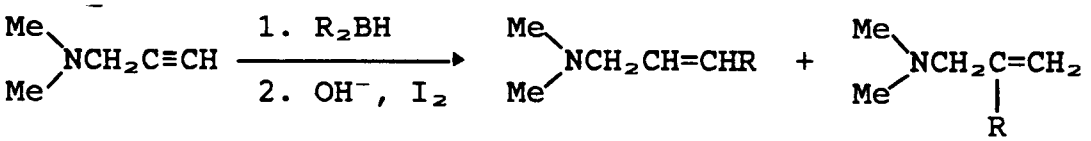
(1-45)

R = CH_3, R' = Ph	100	0
R = R' = CH_3	80	20
R = R' = $-CH_2(CH_2)_2CH_2-$	10	90

more of the internal hydroboration product being formed with increasing basicity of the amine.

Internal propargylic amines were also investigated to evaluate the effect of the steric environment on the regiochemistry of the hydroboration reaction[105]. The regiochemical outcome of N,N-dimethylamino-2-propyne was similar to that reported for the hydroboration of 2-methyl-4-pentyne[46].

The steric and electronic effects inherent in the propargylic amine system can be overcome by utilizing a sterically demanding dialkylborane. Whereas hydroboration of N,N-dimethylpropargylamine gave 80:20 ratio of terminal vs. internal hydroboration product, use of dithexylborane or diisopinylcamphenylborane afforded, exclusively, the terminal vinylorganoborane (equation 1-46).



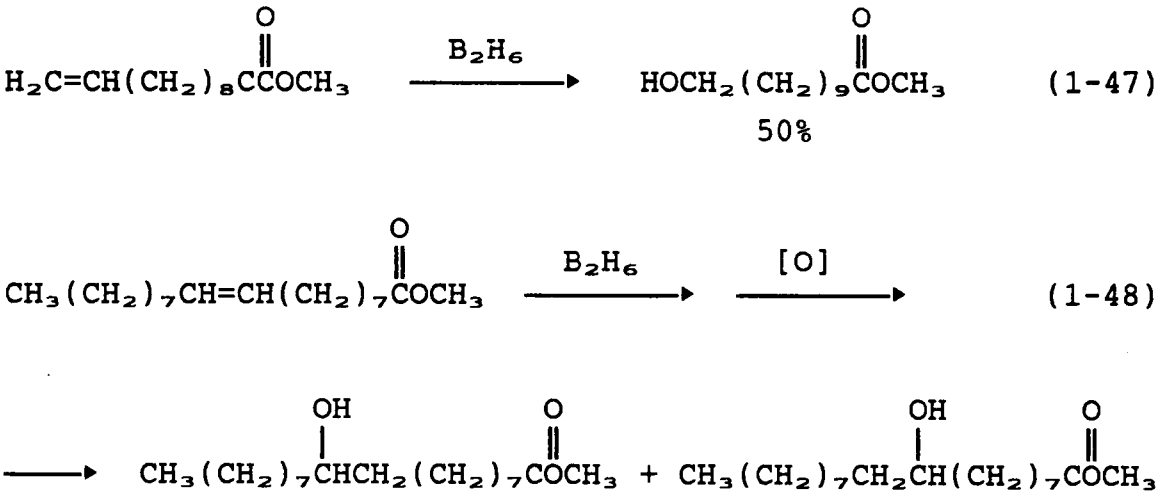
R = Cyclohexyl	80	20	(1-46)
R = Thexyl	0	100	
R = Isopinylcamphenyl	0	100	

5. Hydroboration of Unsaturated Esters

a. Competitive Hydroboration vs. Reduction

Esters are slowly reduced by diborane, requiring 12-24 hours for complete uptake of two hydrides[108]. Aromatic esters are reduced even more slowly[108]. However, since the rate of hydroboration is much faster than ester reduction, hydroborations in the presence of ester functionality is possible provided careful control of the reaction temperature is maintained[13,109,110]. For example, hydroboration-oxidation of cyclohexene in the presence of an equimolar amount of ethyl benzoate produced cyclohexanol with no reduction of the benzoate ester[109]. Competitive hydroboration in the presence of an aliphatic ester, on the other hand, gave partial reduction of the ester to butanol (16%), in addition to the desired product[69].

The first report on the hydroboration of an olefinic ester were simultaneously reported by Dulou and Crétien-Bessière[111] and by Fore and Bickford[112]. Methyl 10-undecenoate (equation 1-47) and methyl oleate (equation 1-48)



(1-47)

(1-48)

were converted to the corresponding hydroxyesters, respectively, in moderate yields. Presumably, the lower yields in the above two instances were attributed to competitive reduction of the ester functionality[113]. Brown and Keblys carried out a detailed study on the hydroboration of terminal unsaturated esters[69]. In all cases studied, when diborane was the hydroborating agent, there was a significant amount of diol formation due to competitive reduction of the ester; the amount of reduced product increased with reduced distance between the ester and olefin functionalities (equation 1-49). Alternatively, disiamylborane offers better selectivity in competitive hydroboration-reduction situations, since disiamylborane does not reduce esters[67,114]. Disiamylborane offers a highly chemoselective route to hydroxy esters[69], as shown for 4-pentenoate and 3-butenoate (equation 1-50). In addition, the use of

$$H_2C{=}CH(CH_2)_nCOC_2H_5 \xrightarrow{BH_3\cdot THF} \xrightarrow{[O]}$$

$$HOCH_2(CH_2)_{n+1}COC_2H_5 \quad (\text{includes 2-OH}) \quad + \quad HOCH_2(CH_2)_{n+1}CH_2OH \quad (\text{includes 2-OH}) \qquad (1\text{-}49)$$

n = 1	42	58
n = 2	55	45
n = 7	77	23

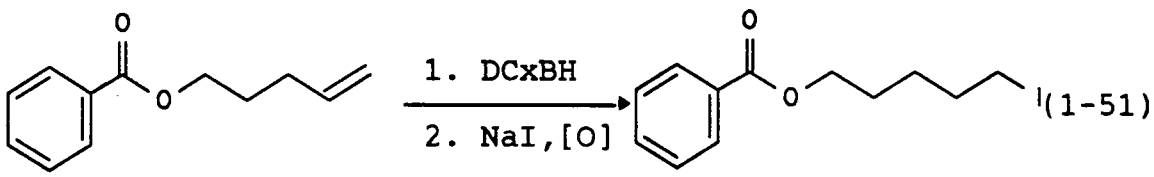
$$H_2C{=}CH(CH_2)_nCOEt \xrightarrow{Sia_2BH} \xrightarrow{[O]} \qquad (1\text{-}50)$$

$$\longrightarrow HO(CH_2)_{n+1}COEt + CH_3CH(OH)(CH_2)_nCOEt + HOCH_2(CH_2)_nCH_2OH$$

n = 1	88%	1-2%	<1%
n = 2	92%	1%	<1%

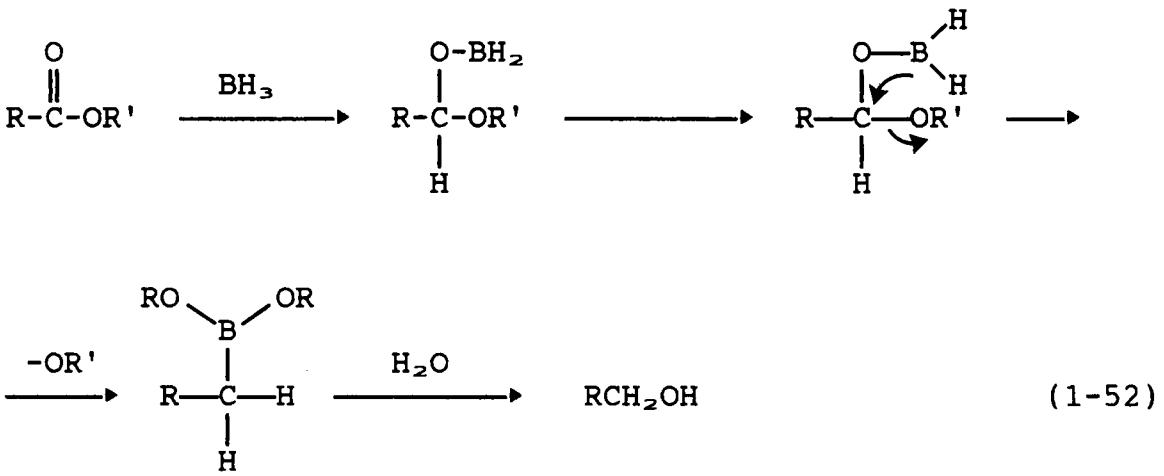
disiamylborane offers better regiochemical control as well.

Although no systematic study on the reducing properties of dicyclohexylborane has been conducted, hydroboration of unsaturated esters have been carried out with this reagent with excellent results[115,116] (equation 1-51).



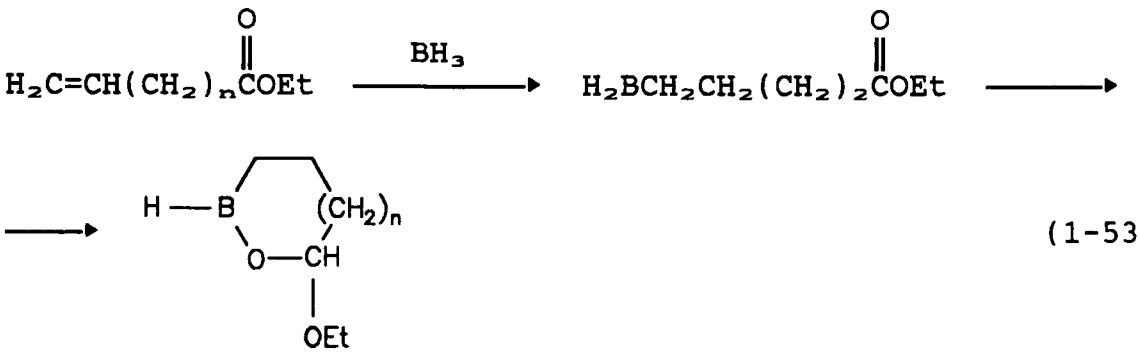
(1-51)

The reduction of esters by borane reagents has been postulated to proceed via the mechanism outlined below[109] (equation 1-52). In the case of olefinic esters, the first



(1-52)

step is the rapid addition of the borane to the olefin. Then a rapid intramolecular reaction of the borane intermediate with the ester functionality occurs, to form a cyclic intermediate. The greatly enhanced reactivity of ester groups near double bonds is accounted for by this cyclic transition state. It also explains why the amount of ester reduction decreases with increasing chain length. Since 5 and 6 membered rings are more stable thermodynamically, unsaturated esters capable of forming 5 and 6-membered rings, such as ethyl 4-butenoate should undergo reduction more readily than longer chain olefinic esters[69] (equation 1-53).



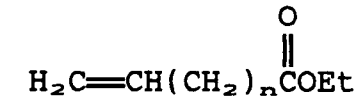
(1-53)

b. Regiochemistry

As will be seen in Chapter VI, one aspect of this dissertation involves the hydroboration of unsaturated esters, specifically, trimethylsilyl esters. Thus for a more thorough understanding of the work presented in Chapter VI, a brief discussion of the regiochemistry of the hydroboration reaction with unsaturated esters is in order.

The proximity of ester functionality to the double bond is important in determining the regiochemical outcome of the hydroboration reaction. With borane, the amount of secondary isomer that normally accompanies hydroborations of olefins (6%) increases with decreasing distance between the ester and olefinic groups (X). However, the inductive and polar effects of the carboxyl group can be overcome by application of a bulky dialkyborane such as disiamylborane (equation 1-50, p. 30).

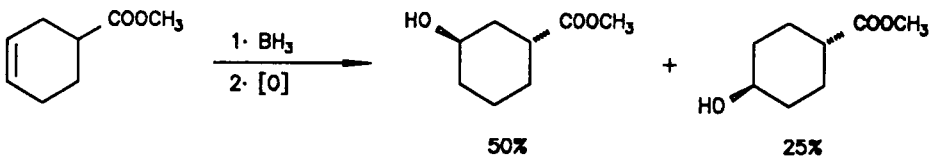
Cyclic systems have been the subject of study by a number of workers[117,118]. Avrahami and coworkers[119] investigated the regiochemistry of B-H addition in cyclohexene



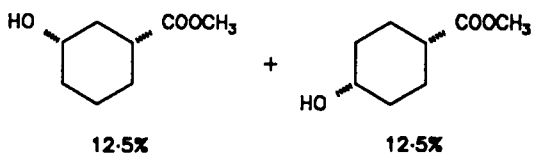
	↑	↑
n = 1	81	19
n = 2	93	17
n = 7	91	9

X

carboxylates. Methyl cyclohexene-4-carboxylate led to a mixture of difficult-to-separate isomers (4:2:1:1) with the trans-3-hydroxy ester predominating in an overall yield of 57% (no information was given as to possible reduction products), (equation 1-54). Dimethyl-cis-tetrahydro-



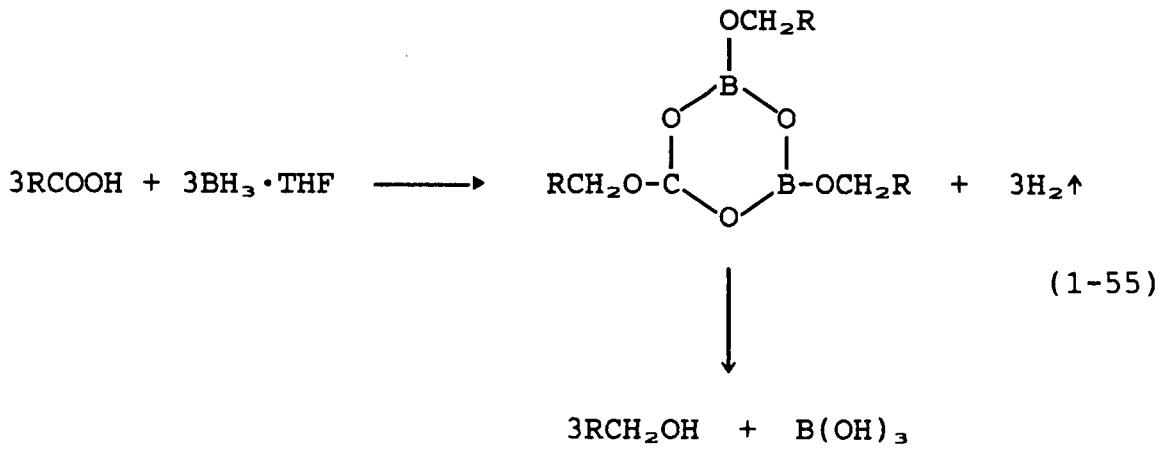
(1-54)



phthalate gave only trans-hydroxy ester in a 75% yield, while the trans-tetrahydrophthalate afforded a mixture of two isomeric hydroxy diesters. The regio- and stereochemistry of the addition was explained on the basis of inductive and polar effects of the carboxyl group directing hydroboration predominantly to the 3-position in a trans fashion.

6. Hydroboration and Reduction of Unsaturated Carboxylic Acids

Carboxylic acids are the most reactive functional group towards $BH_3 \cdot THF$, or the more reactive $NaBH_4$-BF_3 reagent, and undergo extremely fast reduction to the corresponding primary alcohols in a quantitative fashion[108] (equation 1-55).



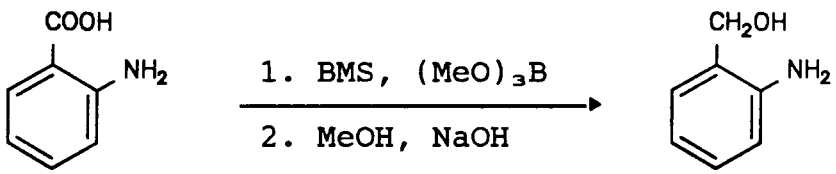
(1-55)

Brown and Korytnyk measured the relative rates of reduction, by diborane, for a number of representative classes of organic compounds. On the basis of competitive experiments, they determined that the rate of reduction decreases in the order: carboxylic acids ≥ olefins > ketones > nitriles > epoxides > esters > acid chlorides[109]. Among carboxylic acid derivatives, the ordering is : COOH > $CONR_2$ > CONHR > $CONH_2$ > COOR > ROCONHR[120,121,122,123]. Nitro groups[108], alkyl and aryl halides[124], sulfides and disulfides[108] are all inert towards diborane.

Another borane source, borane - dimethylsulfide(BMS) reduces carboxylic acids at room temperature[125,126] (equation 1-56). Aromatic acids are reduced more slowly than

$$Br(CH_2)_{10}COOH \xrightarrow[2.\ MeOH]{1.\ BMS} Br(CH_2)_{10}CH_2OH \qquad (1\text{-}56)$$

their aliphatic counterparts, which offers the possibility of selective reduction of an aliphatic acid in the presence of an aromatic acid under proper reaction conditions[127]. However, reduction of aromatic acids occurs much more rapidly in the presence of trimethylborate[127] (equation 1-57).

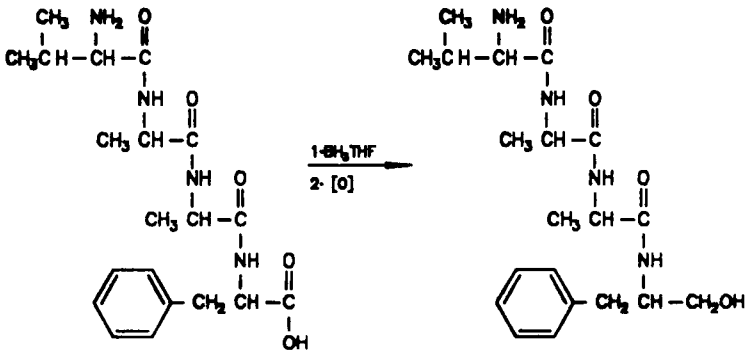


(1-57)

The use of borane reagents provides a convenient method for selectively reducing the carboxylic acid group in the presence of other potentially reactive functional group[124]. Reductions of carboxylic acids have been successful in the presence of nitro[123], amino[128], ketones[129], esters[130], nitriles[131], amides[132], lactones[133], and carbamates[134].

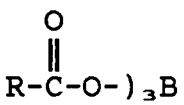
The mildness and selectivity of reductions with borane

reagents has found application in biological systems. For example, specific reduction of the C-terminal carboxyl group is possible in model peptides and proteins without competing reduction of the amide linkage[135,136] (equation 1-58).



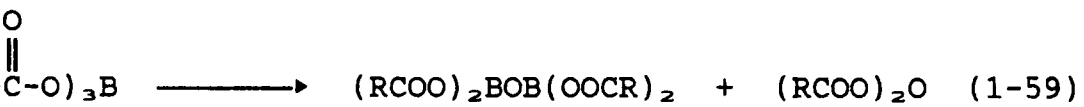
(1-58)

The mechanism of the reduction of carboxylic acids is extremely complex. The reduction was originally thought to occur through a triacyloxyborane (XI) intermediate[113,123].



XI

Pelter and coworkers later reported that triacyloxyboranes can undergo rapid dismutation to the anhydride and oxybis-(diacyloxyborane), and that this may be the actual species being reduced[137] (equation 1-59). More recently, Brown and

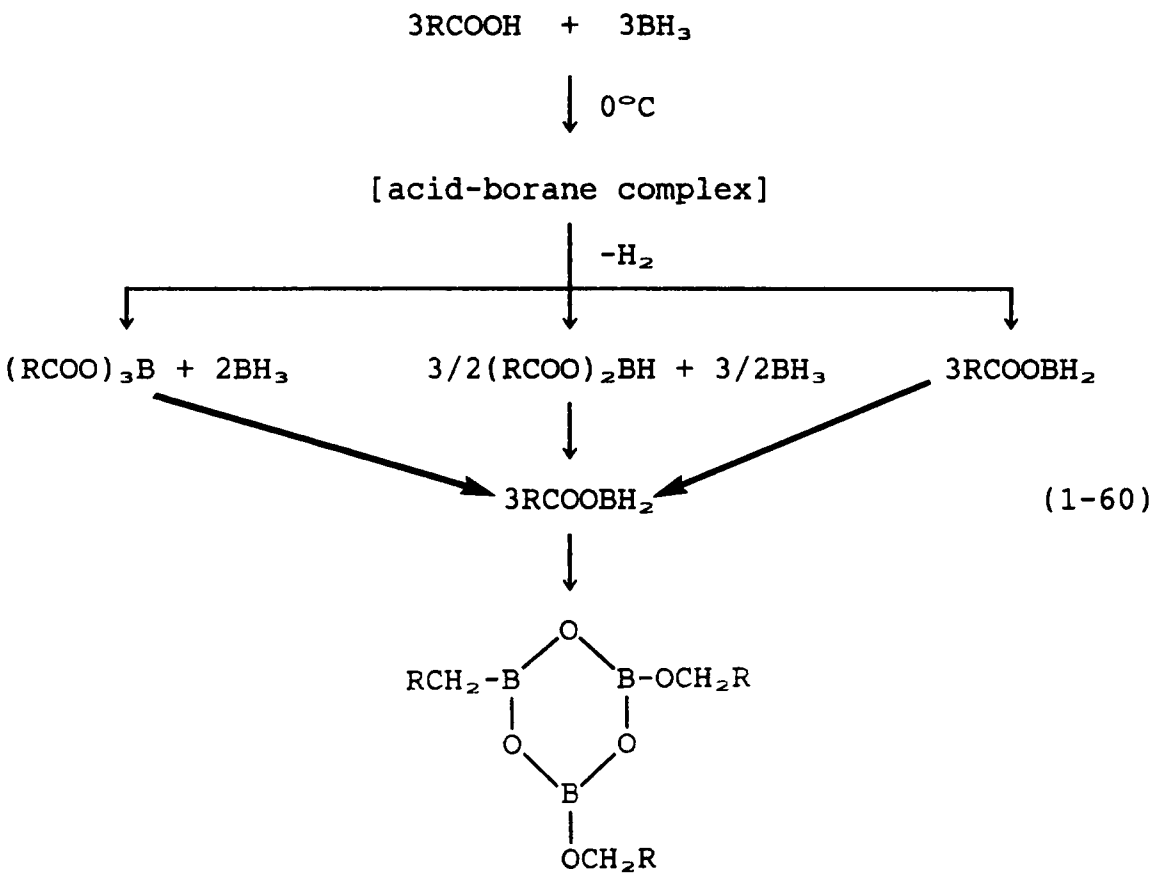


(1-59)

Stocky conducted a detailed mechanistic investigation on the reduction of carboxylic acids by BH_3·THF and BMS. Although

they agreed with Pelter's observation that the triacyloxyborane can undergo rapid dismutation, they disputed the contention that the anhydride, or the oxybis(diacyloxyborane), was the species undergoing reduction[138]. However, Brown's original contention that the triacyloxyborane was the species being reduced was also proven incorrect. A study involving the rate of hydrogen evolution from various carboxylic acid substrates revealed a dependence of acid strength on the rate of hydrogen evolution; the stronger the carboxylic acid, the slower the evolution of hydrogen. Brown concluded that a simple protonation of the boron was not involved. Instead, coordination of the borane with the carboxylic acid was a necessary condition for reaction: the stronger the acid, the weaker the coordination, and the slower the evolution of hydrogen[138]. Based on their study of a series of mono-, di- and triacyloxyboranes, the reduction of carboxylic acids was proposed to proceed through an initial acid-borane complex, which upon evolution of hydrogen, results in either mono-, di-, or triacyloxyboranes. Regardless of which one forms first, Brown proposed that the actual reduction step occurs through a common intermediate, the monoacyloxyborane, which is formed by exchange with free BH_3 in solution[138] (equation 1-60).

Carboxylate salts have been the subject of relatively few studies. Although their reduction was first reported to



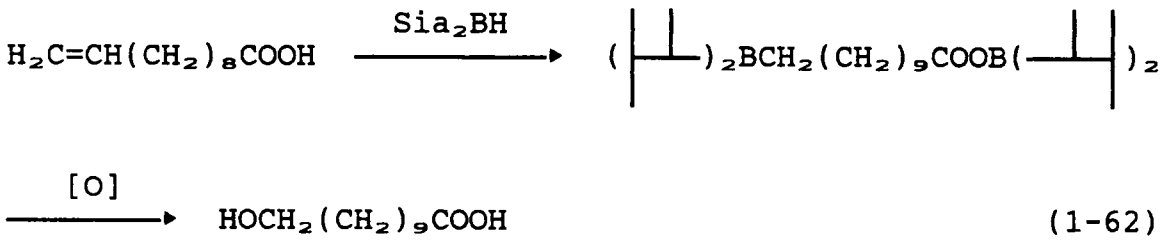
(1-60)

be rather sluggish[113]. A recent reinvestigation revealed that rapid reduction occurs with two molar equivalents of $BH_3 \cdot THF$, presumably via an acyloxyborane intermediate[139] (equation 1-61). Similarly, catecholborane reduces acid

$$RCOONa \xrightarrow{BH_3} RCOOBH_3^-Na^+ \longrightarrow RCOOBH_2 \longrightarrow \xrightarrow{fast} RCH_2OB \xrightarrow{H_2O} RCH_2OH \qquad (1\text{-}61)$$

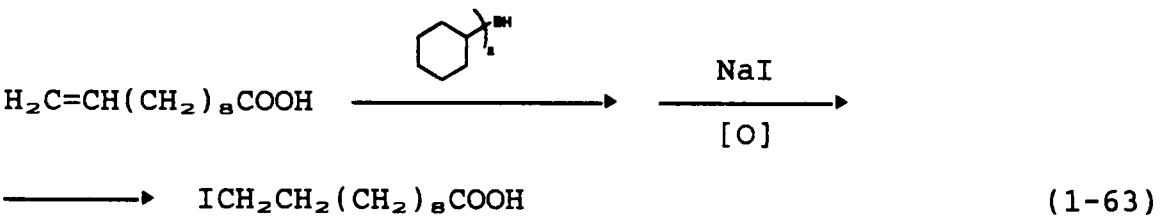
functionality when three molar equivalents are used[140].

Selective hydroboration of olefins and alkynes in the presence of carboxylic acid functionality is generally not feasible due to competing reduction. Disiamylborane is an exception, as its steric bulk prevents reduction of carboxylic acids under hydroboration conditions[67]. Thus hydroboration of unsaturated fatty acids with disiamylborane offers a convenient route to the corresponding hydroxy acids[114,67] (equation 1-62).



(1-62)

Dicyclohexylborane, with reducing properties similar to those of disiamylborane, has also been utilized to selectively hydroborate unsaturated fatty acids in transformations to the corresponding alkyl iodides[70] (1-63).



(1-63)

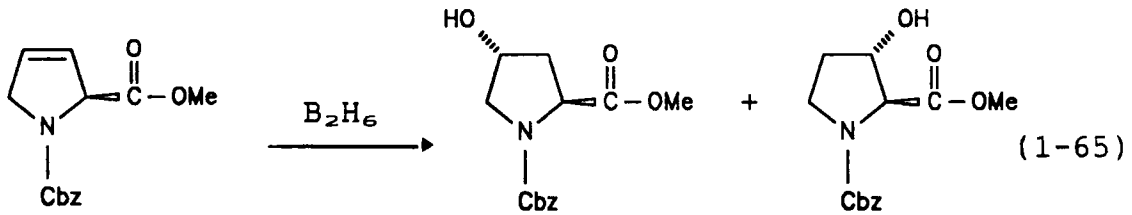
Recently, in a study focused on the reduction of trimethylsilyl esters by various hydride reagents, Larsen and coworkers reported that unsaturated carboxylic acids could be

hydroborated with $BH_3 \cdot THF$ and BMS if the corresponding trimethylsilyl ester was prepared first[141] (equation 1-64).

$$H_2C{=}CH(CH_2)_8COOTMS \xrightarrow[2.\ [O]]{1.\ BH_3 \cdot THF} HOCH_2(CH_2)_9COOH \qquad (1\text{-}64)$$

7. Hydroboration of Amino Acid Derivatives

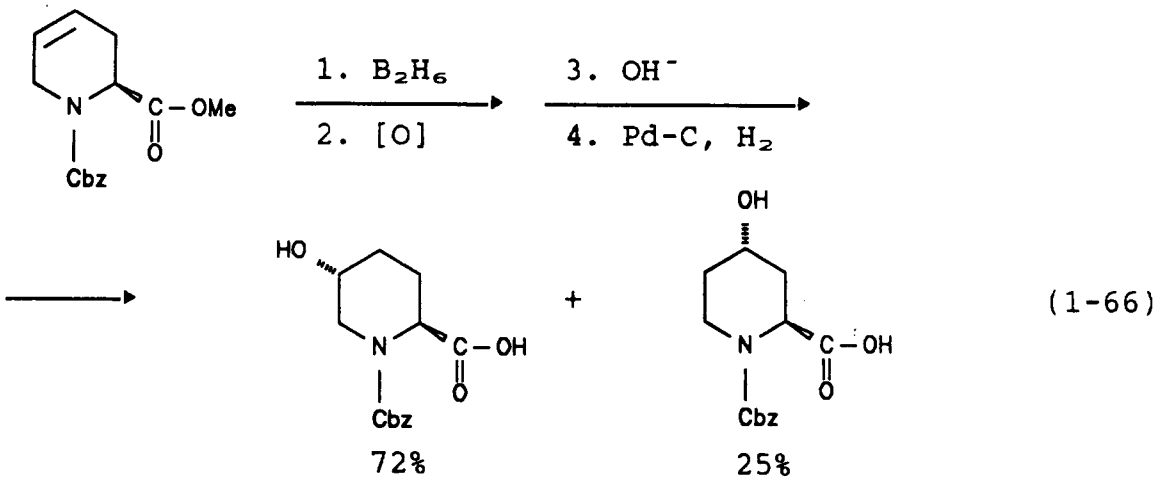
Very few examples exist in the literature on the hydroboration of amino acid derivatives (no case involving the hydroboration of an unprotected amino acid being hydroborated without reduction of acid functionality has been cited). Perhaps the earliest published example was the hydroboration of N-benzyloxycarbonyl-3,4-dehydro-DL-proline methyl ester reported by Witkop and coworkers, which proceeded in a stereospecific fashion to give predominantly trans-3-hydroxy-DL-proline after saponification and hydrogenolysis, along with a minor amount of the 4-hydroxy isomer[142] (1-65). Similarly, the hydroboration of DL



(1-65)

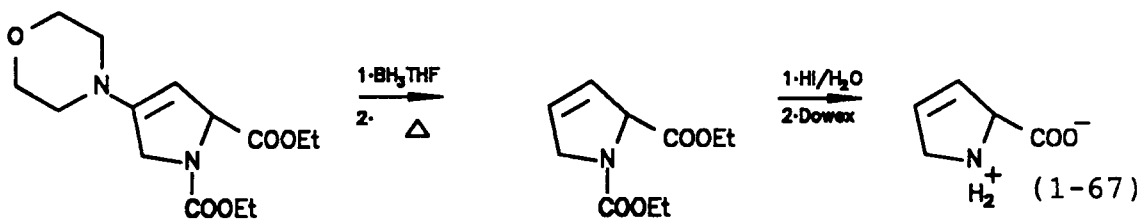
10% 68%

baikain (4,5,dehydro-DL-pipecolic acid) via its N-carbobenzyloxy methyl ester derivative led, after removal of the protecting groups, to a mixture of trans-5-hydroxy- and trans-4-hydroxy-DL-pipecolic acid in an overall yield of 27% (72:28 isomeric ratio)[143] (equation 1-66). More recent



(1-66)

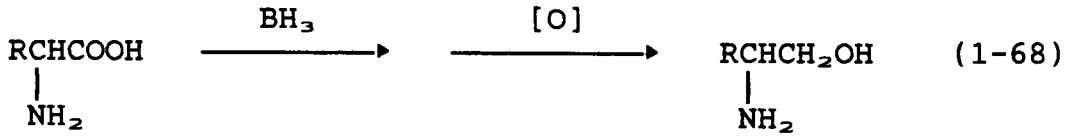
ly, dehydroproline has been obtained from 3-oxo-N-carboethoxyproline ethyl ester via hydroboration of the intermediate enamine[144] (equation 1-67). Both ester



(1-67)

and urethane functionalities were reported to be stable under the hydroboration conditions employed. Lack of protection of the carboxyl function leads to the production

of amino alcohols[145,146] (equation 1-68).

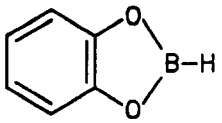


(1-68)

8. Hydroboration of Alkynes and Alkenes with Heteroboranes

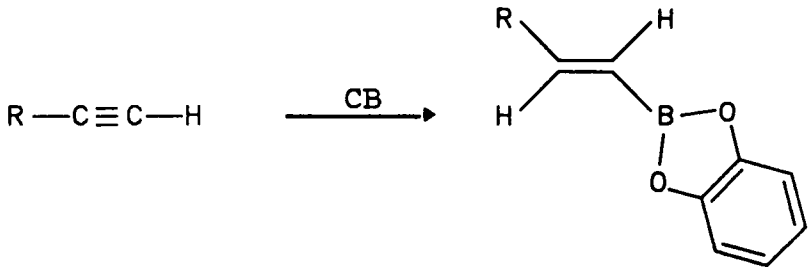
As was briefly noted earlier, hydroboration of alkynes with borane gives predominantly gem-dibora derivatives[35,36,37]. Monohydroboration products can be obtained by using borane derivatives like dicyclohexylborane or 9-BBN[147]. Alternatively, alkynes can be hydroborated with heteroboranes. Heterosubstituted boranes offer numerous possibilities and advantages over simple dialkylboranes as the reactivity of the borane is altered significantly by the presence of heteroatoms adjacent to the boron atom. A number of such borane derivatives have been studied[148,149,150,151,152,153,154,155], many of which are effective hydroborating agents[156,157,158,159].

Of importance to the work presented here is catecholborane (XII), the most studied heteroborane reagent. It is readily prepared by reaction of catechol with $BH_3 \cdot THF$[160], or BMS[30]. Alkenes and alkynes can be readily hydroborated with catecholborane. Hydroboration of alkynes with



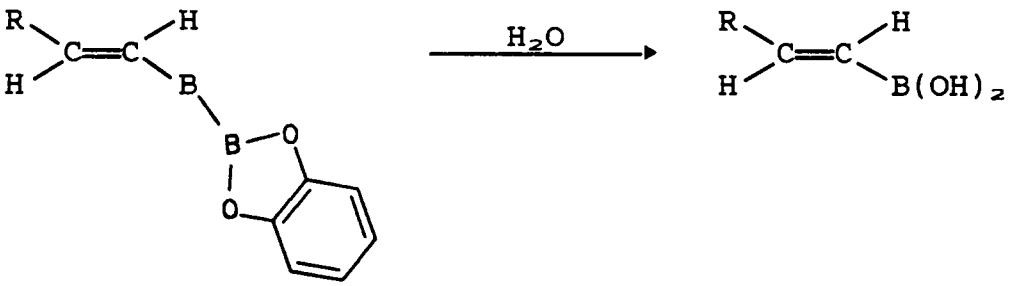
(XII)

catecholborane proceeds only to the monoadduct, producing trans-B-alkenylcatecholboranes in a stereospecific fashion[54,157] equation 1-69). The alkyl and alkenylboronic



(1-69)

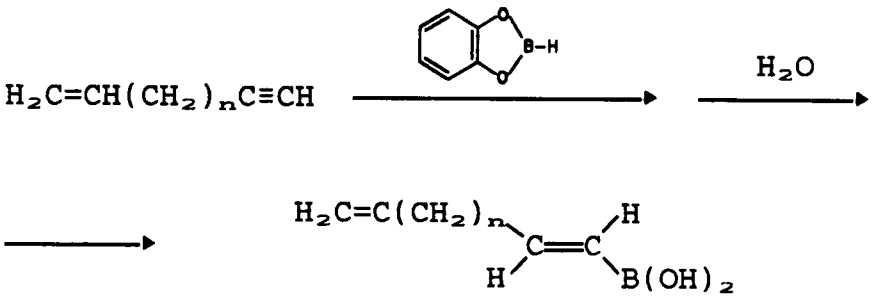
esters thus obtained have proven to be valuable synthetic intermediates in further organoborane transformations[159]. Alternatively, the B-alkyl- and B-alkenylboronic esters can be readily hydrolyzed with a large excess of water to afford B-alkyl- and trans-B-alkenyl boronic acids[157] which also have proven to be useful synthetic intermediates[159,161,162,163,164] (equation 1-70).



(1-70)

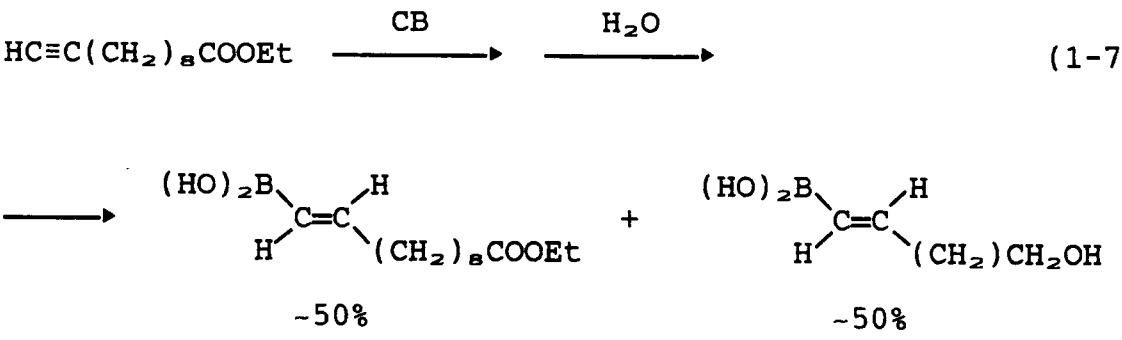
Hydroborations with catecholborane are normally carried out with the neat reagent, as the presence of solvent

reduces the rate of reaction[57]. Alkenes hydroborate cleanly at 100°C, while only 70°C is required for alkynes using neat catecholborane. This differential reactivity has permitted the selective hydroboration of alkynes in the presence of alkenes[165] (equation 1-71).



(1-71)

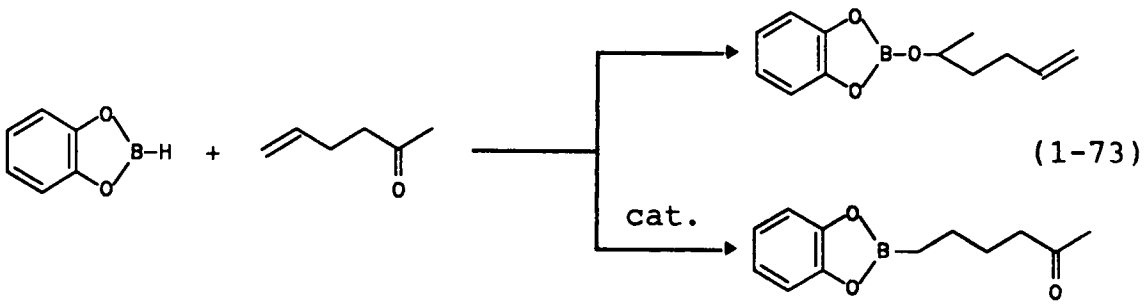
A large number of functional groups are inert to catecholborane, including alkyl and aryl halides, nitro groups, sulfones, disulfides, thiols, primary amides, ethers, sulfides, and alcohols[65]. Nitriles, acid chlorides and esters are reduced more slowly, so selective hydroboration in the presence of these functional groups should be feasible[166]. However, attempted hydroborations of methyl-10-undecynoate with catecholborane has been shown to offer little selectivity[167] (equation 1-72). The lack of selec-



(1-72)

selectivity exhibited by catecholborane in the hydroboration of alkynyl esters provides the basis for work presented in a later chapter.

Recently, rhodium complexes were reported to catalyze the hydroboration reaction with catecholborane. Whereas alkynes and alkenes require temperatures of 70°C and 100°C (2-24 hr) respectively for completion of the hydroboration reaction, use of the catalyst allows the reaction to proceed at room temperature[168]. Using this procedure, alkenes and alkynes can be hydroborated selectively in the presence of the reactive ketone group (equation 1-73).



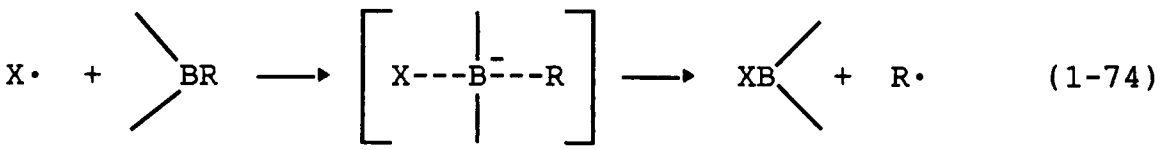
(1-73)

cat = $[ClRh\{P(C_6H_5)_3\}_3]$

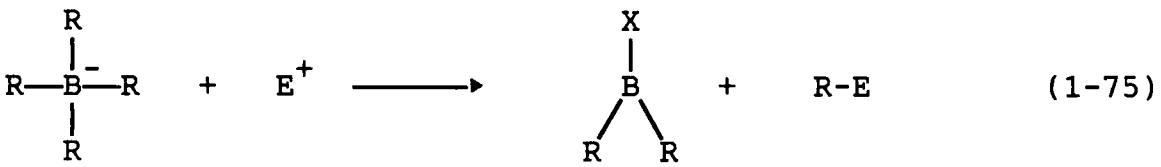
C. Organoborane Transformations

Triorganoboranes are versatile and synthetically useful intermediates. The synthetic utility of the organoboranes is due to the fact that the boron atom is readily replaced by a wide variety of nuclides[15,16,169]. The electrophilic

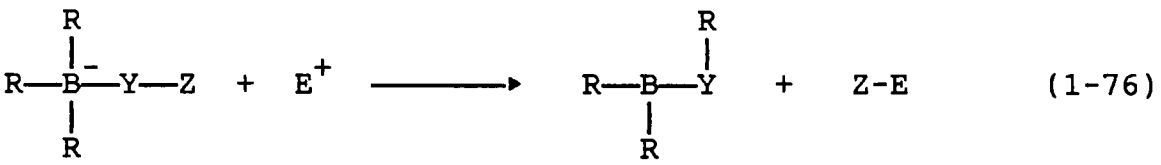
or Lewis acidic nature of organoboranes, brought about by the empty p-orbital, accounts for their observed reactivity. The mechanisms of such transfers fall into three general categories; one involves free radical intermediates (equation 1-74), a second involves an intermolecular transfer of an alkyl group to an external electrophile (equation 1-75), and a third involves a 1,2 migration of an organic group from an organoborate to an adjacent electrophilic center[170] (1-76). Depending upon reaction conditions, either one,



(1-74)



(1-75)



(1-76)

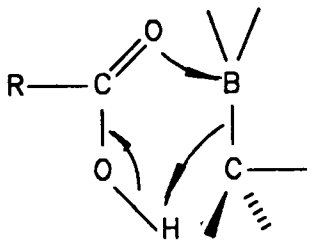
two, or three groups can transfer. Selective removal of R groups can be accomplished by use of mixed trialkylboranes, with secondary or tertiary alkyl groups being used as blocking groups.

1. Protonolysis

Triorganoboranes are remarkably resistant to hydrolysis with water or mineral acids[10,171]. However, they are readily protonylized by reaction with carboxylic acids, providing an alternative to catalytic hydrogenation (equation 1-77). Two alkyl groups are removed at room tempera-

$$R_3B + 3\ HOAc \longrightarrow 3\ RH + B(OAc)_3 \qquad (1\text{-}77)$$

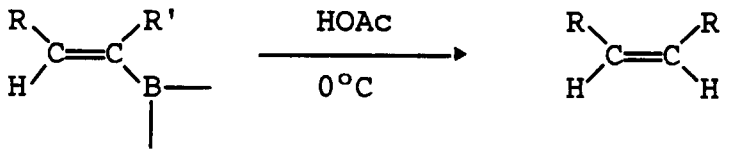
ture[172], and the third can be removed by reflux for 2-3 hours in diglyme[173,174]. Little selectivity between primary and secondary alkyl groups is observed in mixed boranes, but tertiary alkyl groups are more difficult to remove[175]. The enhanced reactivity of organoboranes toward carboxylic acids has been interpreted in terms of a concerted cyclic mechanism, and has been suggested to result from an initial coordination of the organoborane leading to a six-membered transition state[176] (XIII).



XIII

An elegant experiment conducted by Kabalka and coworkers proved earlier postulations[174,177], that the protonolysis reaction proceeds with retention of configuration of the migrating alkyl group[178].

Alkenylboranes are more readily protonolyzed by carboxylic acids than are alkylboranes, as all three groups are cleaved at 0°C[36] (equation 1-78). Protonolysis of



(1-78)

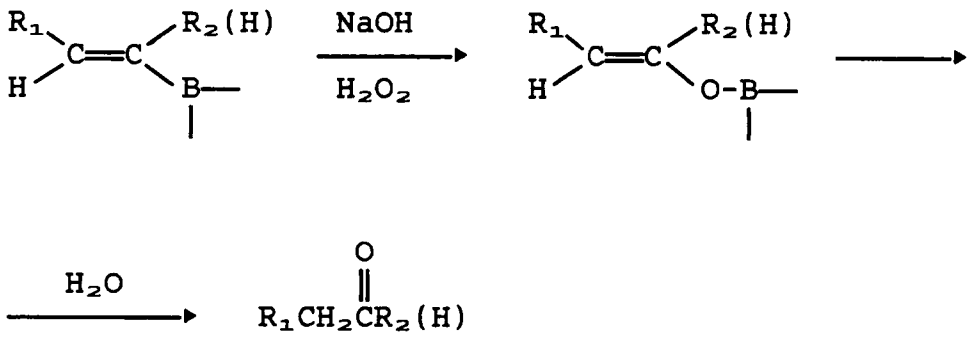
alkenylboranes proceeds with retention of configuration of the migrating alkyl group, thus providing a stereospecific method of cis hydrogenation[36,54].

2. Oxidation

The oxidation of organoboranes has been used extensively as a convenient preparation of alcohols in an anti-Markovnikov fashion[179]. A variety of reagents have been utilized to accomplish this synthetic transformation. Alkaline hydrogen peroxide oxidation, first reported by Van Campen and Johnson[11], has been the method most commonly employed (equation 1-79). The reaction proceeds with retention of configuration at the migrating carbon and affords quantitative transfer of all three alkyl groups[180].

$$R_3B + NaOH + 3\ H_2O_2 \longrightarrow 3\ ROH + NaB(OH)_4 \qquad (1\text{-}79)$$

Oxidation of vinyl organoboranes provides the corresponding aldehydes and ketones[36] (equation 1-80).



(1-80)

For functional groups which are sensitive to the basic conditions employed in the alkaline peroxide oxidation procedure, modifications of the standard procedure have been developed. The simultaneous addition of base and peroxide was found to be useful in the oxidation of vinyl organoboranes to aldehydes[181,36]. The use of milder bases, such as sodium acetate[182] and the sodium phosphate/dipotassium phosphate buffer system[183] have found successful applications.

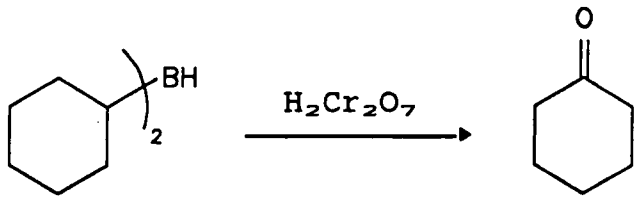
Other oxidation methods are available. Trimethylamine-N-oxide offers a mild but efficient method of oxidizing organoboranes to the corresponding alcohols[177,184] (equation 1-81). The reaction occurs with strict retention of

$$R_3B + 3\ Me_3\overset{+}{N}\text{-}\overset{-}{O} \longrightarrow B(OR)_3 \xrightarrow{H_2O} 3\ ROH \qquad (1\text{-}81)$$

configuration at the migrating carbon and allows the presence of sensitive functionality to be present. Kabalka and coworkers modified the procedure by using the commercially available triethylamine-N-oxide dihydrate, obtaining comparable results to those of the anhydrous reagent[185]. Unlike the alkaline peroxide oxidation procedure, the reaction with triethylamine-N-oxide is controllable, with tertiary alkyl undergoing migration more readily than cyclic secondary alkyl substituents > acyclic secondary > n-primary > branched primary > vinyl[186,187]. By control of the reaction temperature, one, two, or all three alkyl groups could be selectively oxidized[187] (equation 1-82).

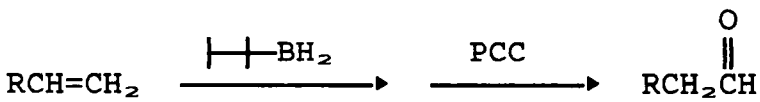
$$R_3B \xrightarrow{Et_3N^+O^-} \begin{cases} \xrightarrow{25^\circ C} \xrightarrow{H_2O} R_2BOR + ROH \\ \xrightarrow{66^\circ C} \xrightarrow{H_2O} RB(OH)_2 + 2\ ROH \\ \xrightarrow{138^\circ C} \xrightarrow{H_2O} B(OH)_3 + 3\ ROH \end{cases} \qquad (1\text{-}82)$$

Ketones can be obtained by oxidation of secondary organoboranes with chromic acid[188] (equation 1-83).



(1-83)

Moderate yields are obtained, but the tedious extraction and strongly acidic conditions has limited the applicability of this method. For example, bicyclic organoboranes have been reported to give rearranged products[188]. The less acidic chromyl trichloroacetate has been used as an alternative to chromic acid with some success[189]. More recently, pyridinium chlorochromate has been used as a mild alternative to chromic acid oxidation. Oxidation of organoboranes derived from C_6 - C_{12} cycloalkenes afforded high yields of the corresponding cyclic ketones[190]. The inherent mildness of pyridinium chlorochromate allows the synthesis of aldehydes from terminal olefins[191,192] (equation 1-84), and has been



(1-84)

shown to eliminate some of the problems associated with chromic acid oxidation of bicyclic organoboranes[193]. PCC has also found useful application in the oxidation of trialkylborates to aldehydes[194] and in a useful reduction - oxidation sequence which offers a convenient "net" reduction

of carboxylic acids to the corresponding aldehydes[195] (equation 1-85).

$$3\ RCOOH \xrightarrow{BMS} (RCH_2OBO)_3 \xrightarrow{PCC} RCHO \qquad (1\text{-}85)$$

Oxidation of organoboranes with molecular oxygen can provide a useful preparation of alcohols if the stoichiometry of the reactants are controlled[196]. The reaction of trialkylboranes at 0°C with 1.5 equivalents of oxygen affords, after aqueous alkaline treatment, quantitative yields of alcohols (equation 1-86).

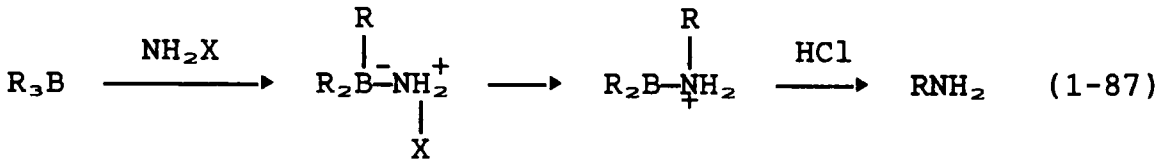
$$R_3B \xrightarrow{1.5\ O_2} R_{1.5}B(OOR)_{1.5} \xrightarrow{NaOH} (RO)_3B \xrightarrow{H_2O} 3\ ROH \qquad (1\text{-}86)$$

The reaction is radical in nature[197,198], and occurs in a non-stereospecific fashion[199].

3. Amination

The synthesis of amines via organoboranes is an important synthetic transformation. Primary amines can be obtained from trialkylboranes upon treatment with chloramine[200], or more conveniently with hydroxylamine-O-sulfonic

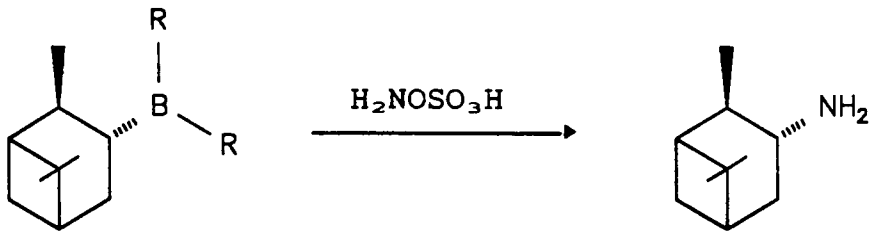
acid[201] (equation 1-87). The reaction involves strict



(1-87)

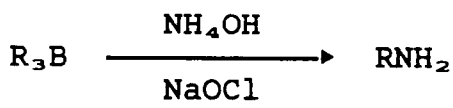
X = Cl, OSO_3H, 2,4,6-$Me_3H_2SO_2$

retention of configuration of the migrating carbon (equation 1-88). Two alkyl groups are utilized in the amination



(1-88)

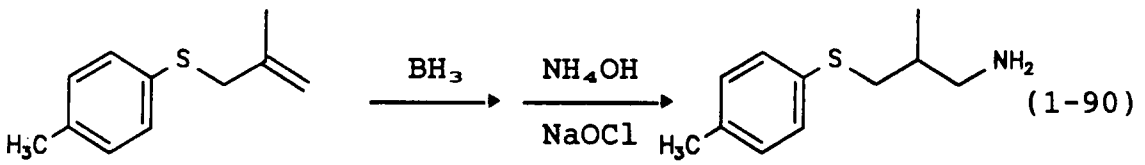
procedure. Use of O-mesitylsulfonylhydroxylamine gives comparable results, but offers the advantage of being soluble in most common organic solvents[202]. More recently, a highly convenient amination procedure[203] involving the <u>in situ</u> formation of chloramine was developed (equation 1-89).



(1-89)

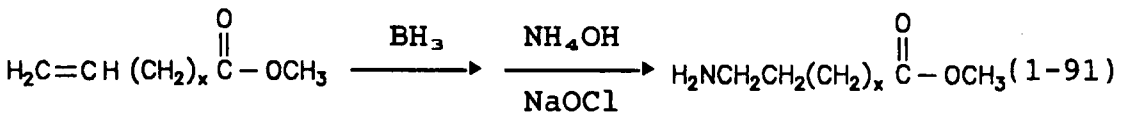
The results obtained parallel those of the earlier procedures, as only two alkyl groups migrate. However, the mild reaction conditions offered by this modified procedure

tolerates the presence of sensitive functionality. Thus, 3-(p-tolylthio)-2-methyl-1-propene (equation 1-90) and methyl-10-undecenoate (equation 1-91) can both be readily converted



(1-90)

37%



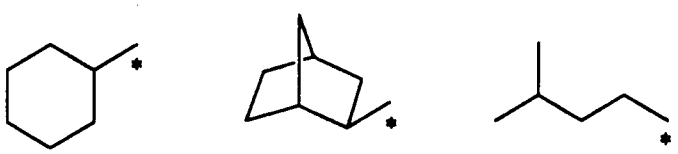
(1-91)

50%

to the corresponding amines in a one pot synthesis. The above amination procedures offers very little selectivity in the migration of alkyl groups, which can be a severe limitation of the procedure when expensive alkyl substituents are used. The use of blocking groups has not been successful in eliminating this problem[204].

The reaction of organoboranes with hydrazoic acid was recently reported by Kabalka, Henderson, and Varma as a route to primary amines[205] (equation 1-92). Because of the explosive nature of hydrazoic acid, an experimentally more convenient procedure was developed involving the in situ

$$R_3B \xrightarrow[HCl]{NaN_3} RNH_3^+Cl^- \xrightarrow{NaOH} RNH_2 \qquad (1\text{-}92)$$

R = 

preparation of hydrazoic acid. A similar reaction of organoboranes with trimethylsilylazide has recently proved to be a useful preparation of primary amines[206] (equation 1-93).

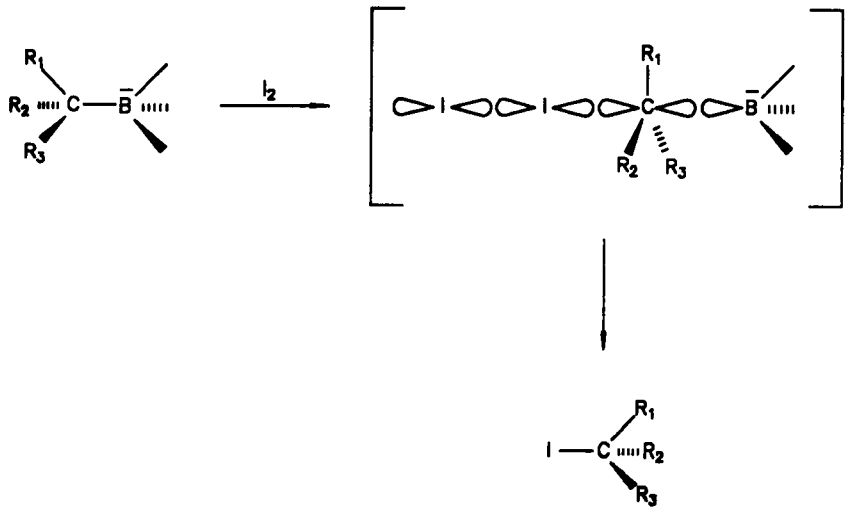
$$R_3B \xrightarrow{(CH_3)_3SiN_3} RNH_3^+Cl^- \xrightarrow{NaOH} RNH_2 \qquad (1\text{-}93)$$

4. Iodination

The incorporation of iodine in organic substrates is a synthetically useful reaction. Under neutral conditions, organoboranes react very sluggishly with molecular iodine[10]. However, when basic conditions are employed, a very rapid reaction with iodine occurs, providing alkyl iodides[207,208] (equation 1-94). In contrast to most organoborane

$$R_3B \xrightarrow[I_2]{NaOH} RI \qquad (1\text{-}94)$$

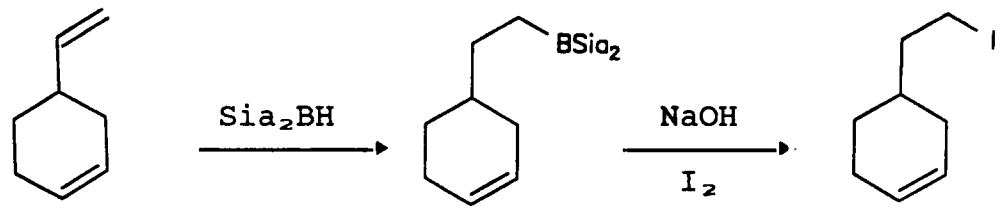
transformations, the iodination reaction proceeds with inversion of configuration at the migrating carbon; the observed inversion of configuration being consistent with an S_E2 mechanism involving attack by iodine on the back lobe of the B-C orbital at the carbon end[209] (equation 1-95). Thus,



(1-95)

hydroboration - iodination provided the first reported synthesis of endo-norbornyl iodide[210], while hydroboration of cis-2-butene with (-)-diisopinocampenylborane followed by iodination gave (R)-2-iodobutane in 84% optical activity[210]. Two of the three alkyl groups are utilized in the transformation, limiting the maximum yield to 67%. The use of disiamylborane circumvents this disadvantage, as primary alkyl groups migrate selectively over secondary groups[207]. In addition, the use of disiamylborane allows the selective iodination of a terminal olefin[207] (equation 1-96).

The use of strong base to initiate the iodination



(1-96)

reaction does create problems when sensitive functionality is present in the molecule. Additionally, in terms of radiopharmaceutical applications, the use of molecular iodine is not economically feasible, as one-half of the radionuclide is lost as iodide. To alleviate this problem, Kabalka and Gooch developed a mild alternative to Brown's iodination procedure employing sodium acetate as the initiating base, and iodine monochloride as the electrophilic iodine source[211] (equation 1-97). Two alkyl groups

$$R_3B \xrightarrow[NaOAc/MeOH]{ICl} RI \qquad (1\text{-}97)$$

are used in the transformation with organoboranes derived form terminal olefins, however, when organoboranes derived from internal olefins are subjected to the iodination procedure, only one alkyl group rapidly migrates[211]. The mild reaction conditions allows the presence of sensitive functionality and, as in the earlier iodination reaction, strict inversion of configuration of the migrating carbon is

observed[211].

A more recent modification of this reaction employs sodium iodide as the iodine source. Under mild oxidizing conditions (reaction of sodium iodide with chloramine T[212]) an electropositive iodine source is generated <u>in situ</u> (presumably iodine monochloride or a hydrated iodonium ion species) which iodinates organoborates in a manner analogous to the iodine monochloride procedure[213] (equation 1-98).

$$R_3B \xrightarrow[[O]]{NaI} RI \qquad (1\text{-}98)$$

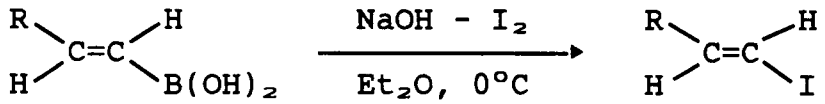
Use of dicyclohexylborane as the hydroborating agent allows efficient use of the olefinic group, and also provides a highly efficient and direct synthesis of iodo fatty acids[213] (equation 1-99).

$$H_2C{=}CH(CH_2)_{19}COOH \xrightarrow[2.\ NaI/[O]]{1.\ DCxBH} ICH_2(CH_2)_{20}COOH \qquad (1\text{-}99)$$

91%

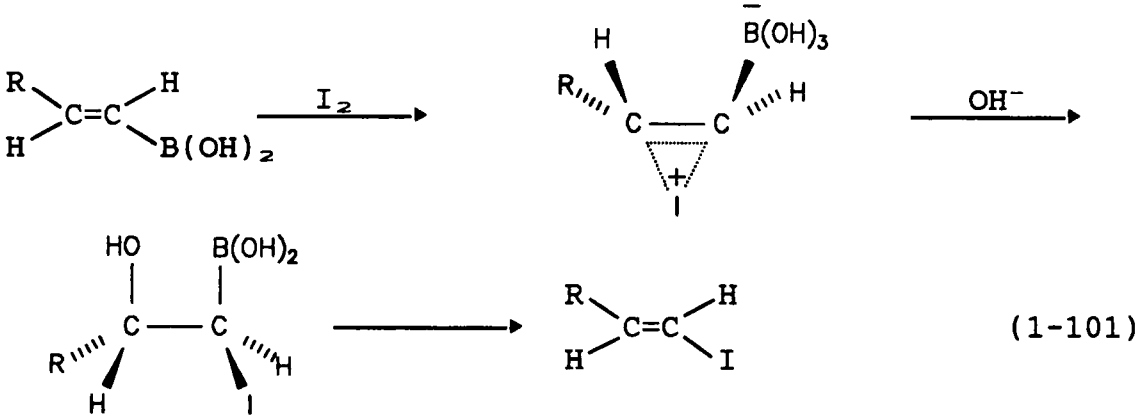
<u>Trans</u>-1-alkenylboronic acids, readily prepared via the hydroboration of 1-alkynes with catecholborane followed by hydrolysis[157], undergo a rapid reaction with iodine under the influence of sodium hydroxide at 0°C in ethereal

solvents to give quantitatively trans-1-alkenyl iodides in a stereospecific fashion[162] (equation 1-100). Alternatively,



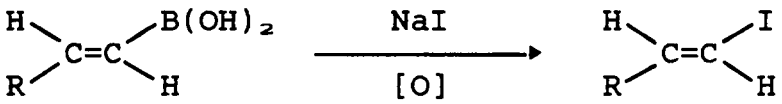
(1-100)

the intermediate vinyl boronic acid can be prepared by hydroboration with dibromoborane-dimethylsulfide, followed by hydrolysis with sodium hydroxide (two equivalents)[48]. A mechanism involving an iodonium ion intermediate, nucleophilic attack by base, followed by cis elimination of boronic acid has been proposed to explain the observed stereochemistry[162,214] (equation 1-101).



(1-101)

More recently the in situ methodology utilizing the sodium iodide-chloramine T reagent has been applied to the iodination of vinyl boronic acids[215] (equation 1-102). Near quantitative yields of exclusively trans-iodovinyl olefins are obtained, and the extremely mild reaction conditions



(1-102)

allows sensitive functionality to be present.

D. Carbon-Carbon Bond Forming Reactions

Organoboranes can also participate in carbon-carbon bond forming reactions, as numerous such transformations exist[14,15,16]. Such reactions can be divided into two broad catagories: those involving radical intermediates, and anionotropic rearrangements involving an intramolecular shift of an organyl group from boron to an electron deficient carbon atom[29]. These reactions are beyond the scope of this discussion.

E. Radiopharmaceutical Applications of Organoboranes

Isotopically labelled compounds have played an important role in medical and biomedical research since they were first proposed by Hevesey[216]. Historically, radioactive elements, such as carbon-14, were used more extensively than their stable counterparts, e.g., carbon-13, because detection methods were available for measuring small amounts of the elements quantitatively. More recently, with the advent of relatively inexpensive medical cyclotrons, a variety of medically useful radioactive isotopes have become

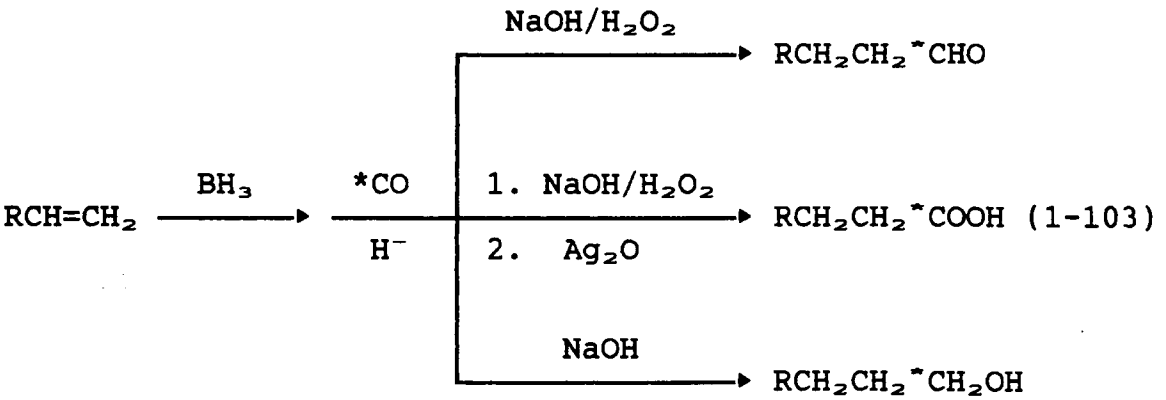
available. These cyclotrons make the production of short-lived radionuclides, such as carbon-11 and nitrogen-13 possible, which are easily detected using modern scintillation cameras (positron and single photon emission tomography)[217,218,219,220]. As a result, there has been renewed interest in the incorporation of radionuclides into organic substrates.

The synthesis of isotopically labelled organic compounds normally involve the use of small, rather stable isotopically labeled materials such as carbon dioxide, halide salts, water, or nitric oxide, because they can be readily obtained from cyclotrons in pure form[221,222]. However, the use of such simple reagents seriously limits the number of routes available to the synthetic chemist[221]. In addition, increased demands are placed on the synthetic chemist when short-lived radionuclides are used, such as carbon-11($t_{1/2}$=20 minutes), since the isotopes will decay beyond the limits of detection if the synthesis time exceeds 5 half-lives[223].

Organoboranes undergo a number of facile transformations with such simple precursors, and have proved to be extremely effective precursors for incorporating radionuclides into organic molecules[223], since their use was first proposed by Kabalka in 1978[224]. The stereospecificity associated with organoborane reactions, the high yields

generally obtained in organoborane transformations, and the fact that a wide variety of functional groups are tolerated by the hydroboration reaction and during synthetic manipulations, have made organoboranes a viable alternative to more traditional isotope incorporation methodologies[221,225,226,227]. An additional advantage not immediately obvious is that by use of organoboranes, the isotope can be incorporated in the final stages of the synthesis, a significant advantage when the isotope is either expensive, or has a short half-life; for example, the 10-minute half-life of nitrogen-13[223].

The versatile reaction that organoboranes undergo with carbon monoxide has been exploited to incorporate carbon isotopes into organic substrates. Carbon-14[228], carbon-13[229,230], and carbon-11[231,232] labelled aldehydes, alcohols, and carboxylic acids have been prepared by carbonylation of organoborane precursors (equation 1-103).

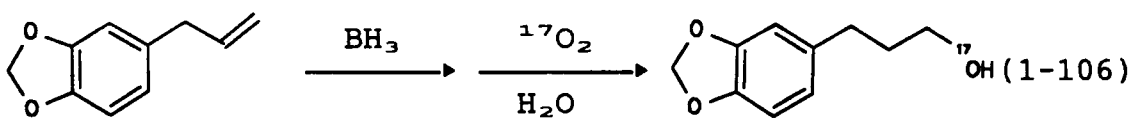


The rapid amination reaction of organoboranes involving the in situ formation of chloramine from readily available labelled ammonium chloride provides an ideal route to nitrogen labelled compounds. The sequence has been employed to prepare a variety of nitrogen-15[233] (equation 1-104) and nitrogen-13[234] (equation 1-105) labelled amines.

$$MeOC(CH_2)_8CH{=}CH_2 \xrightarrow[2.\ {}^{15}NH_4CL/\ NaOCl]{1.\ BH_3} MeOC(CH_2)_9CH_2{}^{15}NH_2 \quad (1\text{-}104)$$

$$CH_3(CH_2)_7CH{=}CH_2 \xrightarrow[2.\ {}^{13}NH_4Cl/\ NaOCl]{1.\ BH_3} CH_3(CH_2)_8CH_2{}^{13}NH_2 \quad (1\text{-}105)$$

Oxygen labelled alcohols can be prepared by utilizing the facile oxidation reaction which organoboranes undergo with molecular oxygen. A number of oxygen-17 labelled alcohols have been prepared in this manner[235] (equation 1-106). Recently, the first oxygen-15 labelled organic



(1-106)

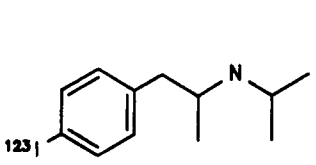
compound, oxygen-15 labelled butanol, was prepared by this

methodology[236]; providing a true test to the speed and versatility of oganoboranes as isotope incorporation precursors, as oxygen-15 has a half-life of 2.0 minutes (equation 1-107).

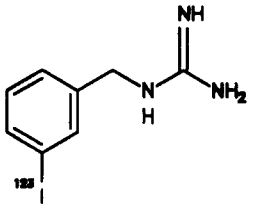
$$(CH_3CH_2CH_2CH_2)_3B \xrightarrow{^{15}O_2} CH_3CH_2CH_2CH_2OH \qquad (1\text{-}107)$$

By far, the most important radioisotopes for nuclear medicine purposes are the radiohalogens; more specifically, the iodine isotopes[237,238,239]. In fact, radioiodine was the first isotope to be routinely used in therapeutic nuclear medicine. A number of medically useful iodine isotopes are available[240]. Iodine-131 has had a long history in nuclear medicine[241]. More recently, with the advent of cyclotron production, iodine-125 and iodine-123 have gained popularity[242]. Among these, iodine-123 has proved extremely promising, as its short half-life($t_{1/2}$ = 13.3 hours) and desirable decay characteristics (single-photon-emitter, 159keV)[243], fulfills the criteria of an ideal gamma-emitting nuclide for in situ and in vivo diagnostic procedures more closely than any other isotope of iodine[223,240,244,245]. For example, the 159-keV photons are of optimum energy for tissue penetration[246], and are readily detected by single photon emission tomography. Additionally, by virtue of its availability in high-purity form and

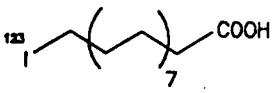
its short half-life, the iodine-123 labelled pharmaceutical can be administered in low dosages well below the pharmacological limit, and, at frequent intervals[247]. A number of iodine-123 labelled radiopharmaceuticals, such as N-isopropyl-p-iodoamphetamine[248,249] (XIV), m-iodobenzylguanidine[250,251] (XV), and 17-iodoheptadecanoic acid[252] (XVI) have proven to be quite effective in clinical studies.



XIV



XV

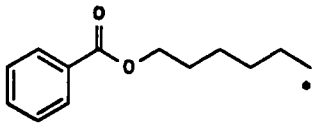


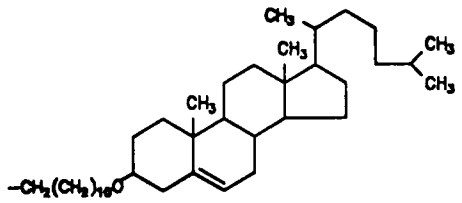
XVI

The most convenient procedure to radioiodinate organoboranes involves the in situ generation of an electrophilic iodine species in the presence of a mild oxidant, such as chloramine T[213]. This procedure employs the most inexpensive and readily available form of radioiodine, sodium iodide, provides in most instances, near quantitative yields of radioiodinated materials, and the mild reaction conditions allow the presence of a variety of functional groups, a factor of extreme importance when biological molecules are used. This methodology has proven quite effective in radioiodinating a variety of functionalized substrates, and a number of iodine-125[115,253] and iodine-

123^{254} labelled products have been prepared (equation 1-108).

$$R_3B \xrightarrow[[O]]{NaI^*} R\text{-}^*I \qquad (1\text{-}108)$$

R = $-CH_2(CH_2)_{16}COOH$ 



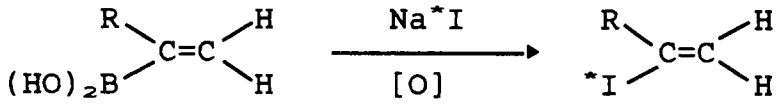
A significant aspect of the in-situ iodination methodology is that the radioiodinations can be carried out on a "no-carrier-added" basis[255]. This insures that the quantity of the labelled agent administered is kept well below pharmacological limits[223].

Unlike their radiobromine counterparts[256], however, simple alkyl iodides undergo significant in vivo deiodination, limiting their use as imaging agents in nuclear medicine[257,258]. Thus, it is necessary to stabilize the radioiodine label in order to minimize loss due to metabolic pathways. One method commonly used to stabilize radioiodine is to incorporate the label into an aromatic ring[259,260,261,262,263].

Another method more recently developed to minimize the in vivo loss of radioiodine is to stabilize it as the iodovinyl group[264,265,266]. Although it was first assumed that

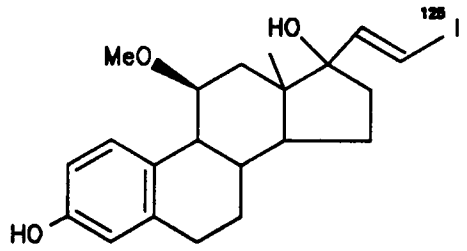
vinyl iodide moiety would be metabolically unstable, it was demonstrated on the contrary that radioiodinated iodovinyl derivatives have unusually long half-lives in vivo[223]. Thus, the preparation of radiolabeled iodovinyl compounds has received considerable interest of late.

As was discussed earlier, vinyl boranes, more specifically, vinyl boronic acids, are extremely useful precursors to vinyl iodides because of their inherent stability and ease of preparation. More importantly, they undergo an extremely facile, stereospecific reaction with electrophilic iodine species to produce near quantitative yields of the corresponding vinyl iodides[267,215] (equation 1-109). The

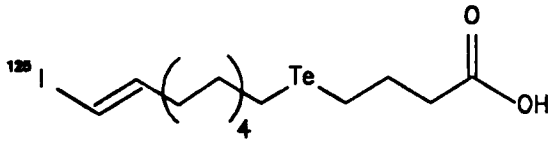


(1-109)

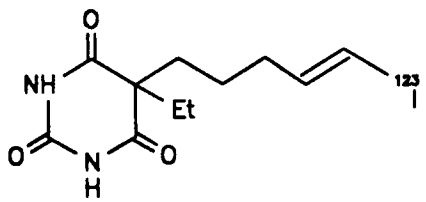
in-situ radioiodination of vinylboronic acids is the most convenient procedure, and one which has made a significant impact among the radiopharmaceutical community. This methodology has been used to incorporate radioiodine in a wide variety of functionalized substrates, such as iodovinyl steroids[266,268] (XVII), iodovinyltellurium fatty acids[269,270] (XVIII), barbiturates[271,272] (XIX), and organic cations of phosphorous, arsenic, and nitrogen[273,274] (XX). It is this reaction which plays a key role in this



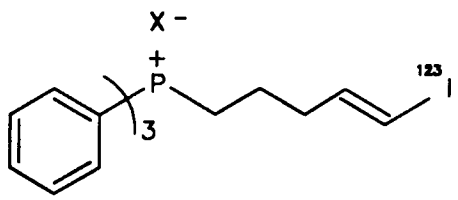
XVII



XVIII



XIX



XX

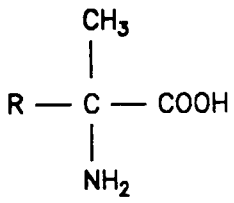
dissertation. As outlined in Chapter 2, the iodovinyl group can be used to label radiopharmaceutical analogues of amino acid and amino acid derivatives used in nuclear medicine. A background of the synthetic methodology used to obtain the desired amino acid derivatives will be discussed in the following sections.

F. Amino Acids

1. Introduction

Amino acids are important biological compounds, as well as useful synthetic precursors[275,276]. Thus, the synthesis of amino acids has long been a synthetic target of organic

chemists, and a wide range of synthetic methodologies are available[277,278,279]. Of importance to the work presented here are unnatural amino acids, specifically, α-amino acids, where the α-hydrogen has been replaced with an alkyl group (XXI). Such α-alkyl amino acids can be useful pharmaceutical agents, as the α-alkyl substituent prevents the uptake of these compounds in the normal metabolic pathways.



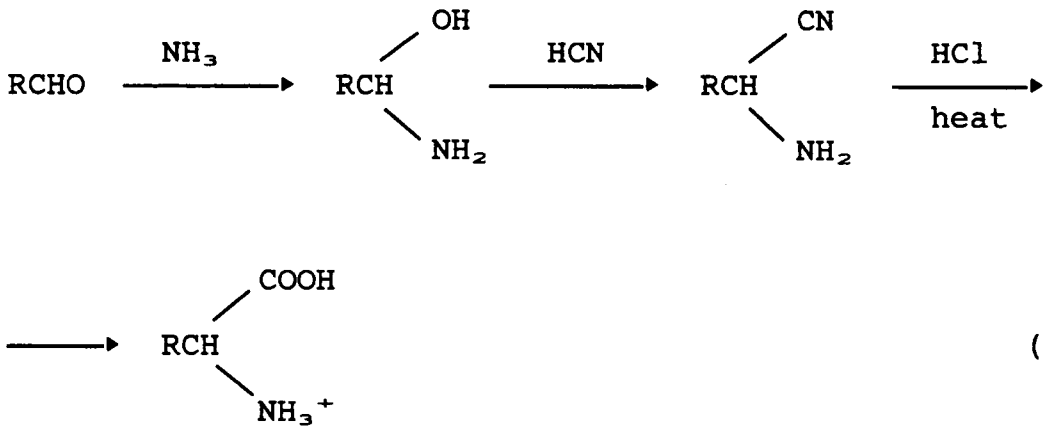
XXI

Numerous routes to α-alkyl-amino acids exist[280], but a thorough review on the many methods available is beyond the scope of this dissertation. However a background on the amino acid chemistry used in this work, as well as the more recent preparations of amino acids via organoborane technology, will be presented here.

2. Strecker Synthesis

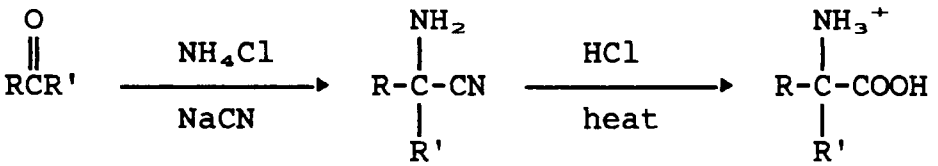
The Strecker synthesis is the oldest known route to amino acids[281]. Although first reported over 135 years ago, the utility of this route to amino acids still remains, especially in the synthesis of α-alkyl-α-amino acids and radiolabelled α-amino acids[282]. As first reported, the

reaction involves treatment of an aldehyde with ammonia and anhydrous hydrogen cyanide to give an aminocyanohydrin which is hydrolyzed to the amino acid[281] (equation 1-110).



(1-110)

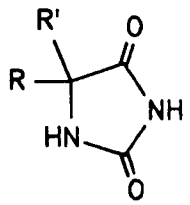
A number of modifications of the original procedure have been reported. Early modifications centered around changing the order of addition[283], use of an intermediate bisulfite addition product[284,285,286,287,288,289], or the use of ammonium and cyanide salts such as ammonium cyanide[290] or the more convenient ammonium chloride/alkali cyanide mixture[291,292,293], which is the method employed today[294] (equation 1-111).



(1-111)

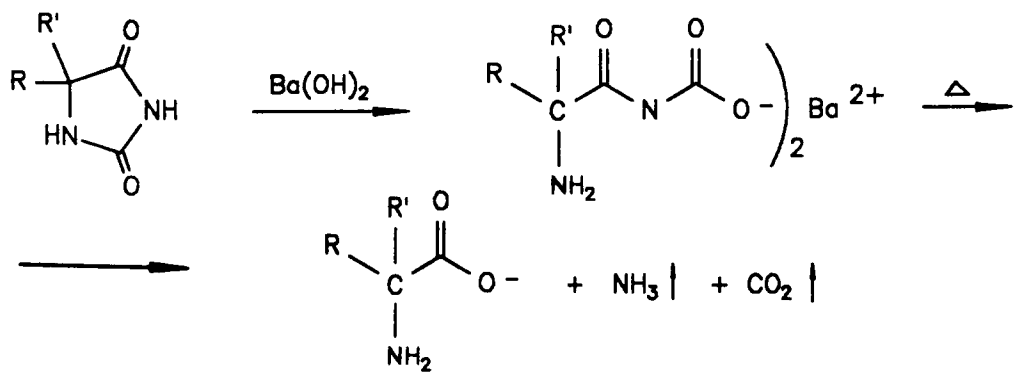
Of utmost importance to the work presented here is the Strecker modification utilizing an intermediate carbonyl

derivative commonly known as a hydantoin (XXII).



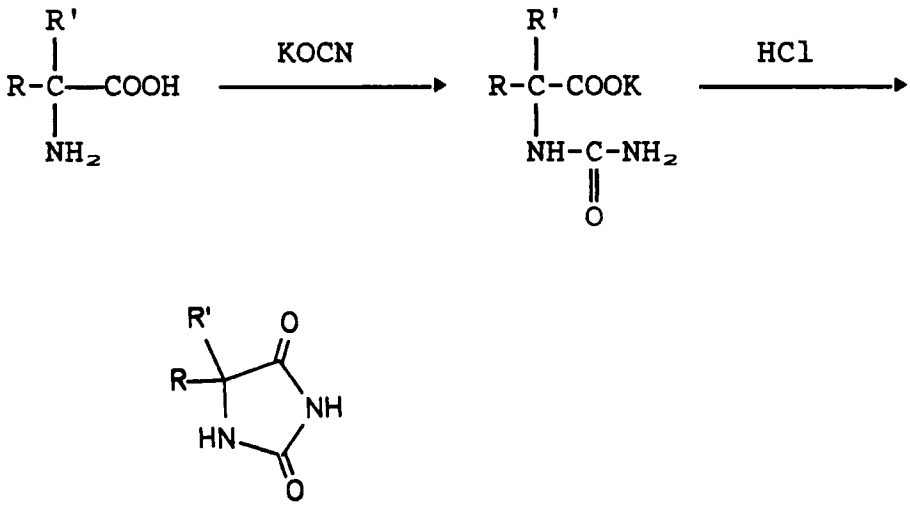
XXII

The hydantoin ring, discovered in 1861 by Baeyer[295], has led to the traditional approach to the amino acid functionality since it was first suggested by Wheeler[296] in 1911. While a number of reagents can be employed to convert the hydantoin moiety to the corresponding amino acid[229,297,298,299,300,-301,302,303,304], the one most commonly employed is barium hydroxide[297]. The hydrolysis to amino acids proceeds in a stepwise manner; under the action of refluxing aqueous barium hydroxide, hydrolysis to the salt of hydantoic acid occurs[305]. Longer reaction time, or higher temperatures gives a more profound breakdown to the corresponding amino acid[296] (equation 1-112).



(1-112)

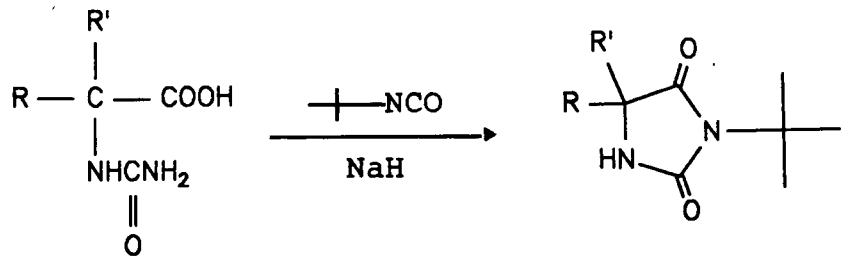
The chemistry of the hydantoin ring is well established, and a number of routes to this heterocyclic ring structure are available. They can be prepared by reaction of amino acids[306,307,308], amides[309], nitriles[300] or amino nitriles[310] with potassium cyanate. The following reaction with an amino acid is representative (equation 1-113).



(1-113)

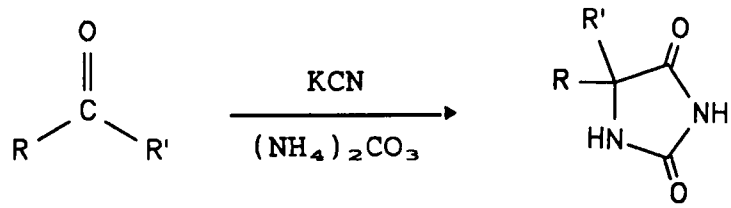
Under the basic conditions employed, the reaction leads to a salt of an α-ureido acid (hydantoic acid), which upon acidolysis provides the corresponding hydantoin. Similarly, the use of isocyanates instead of potassium cyanate provides a direct route to 3-N-substituted hydantoin derivatives[311,312]. The recent example provided by Timberlake[313] is representative (equation 1-114).

More importantly, hydantoins can also readily be prepared directly from carbonyl compounds. Although



(1-114)

originally reported by Bergs[314], and later modified by Bucherer[301,315] the conversion is most conveniently carried out by treatment of an aldehyde or ketone with potassium cyanide and ammonium carbonate in aqueous ethanol[316] (equation 1-115). The use of a methyl ketone in the above



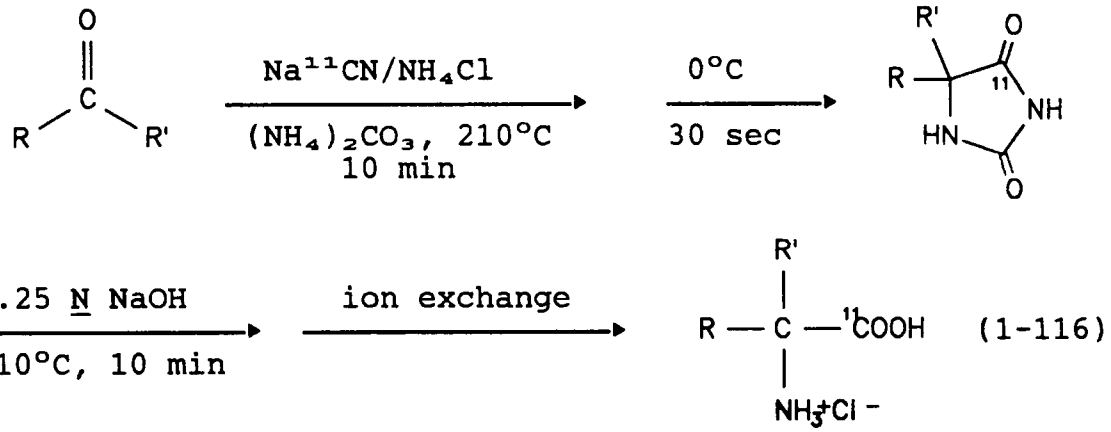
(1-115)

reaction provides unnatural α-methyl-α-amino acids. Alternatively the use of potassium cyanate instead of cyanide ion has been reported to provide high yields of hydantoin derivatives as well[317].

The conversion of carbonyl compounds to amino acids via the intermediate hydantoins, termed the Bucherer-Strecker synthesis, has been widely used, and its synthetic utility remains today. Although much more elaborate and efficient methodologies for the preparation of amino acids have been developed, it is still the most widely utilized method of

preparing α-alkyl-α-amino acids.

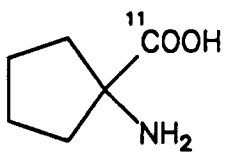
Another useful application of the Bucherer-Strecker reaction that still remains is in the area of radiopharmaceuticals; specifically, the preparation of ^{11}C-labeled amino acids. Washburn, Hayes, and other collaborators have developed a rapid, high temperature, high pressure technique for the synthesis of C-11 labelled amino acids employing a steel reaction vessel[304,318] (equation 1-116). The reaction



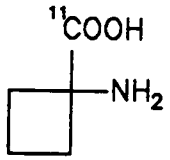
(1-116)

is carried out using excess carbonyl compound, with the limiting reagent being carbon-11 potassium cyanide. The procedure is quite rapid, with total preparation and purification time being around 40 minutes, and is applicable to the synthesis of a variety of natural and unnatural carbon-11 carboxyl labeled amino acids, including 1-aminocyclopentane carboxylic acid (XXIII), 1-aminocyclobutane carboxylic acid (XXIV), 2-amino-3-methylbutanoic acid (XXV),

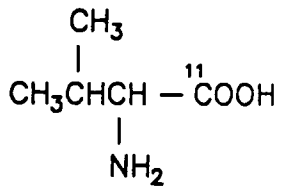
2-amino-3-methylpentanoic acid (XXVI), and 2-amino-2-methylbutanoic acid (XXVII).



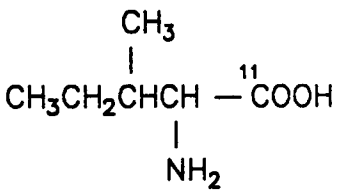
XXIII



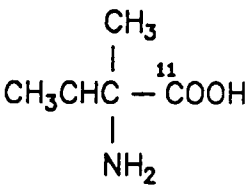
XXIV



XXV



XXVI



XXVII

3. Elaboration of the Hydantoin Ring

a. General

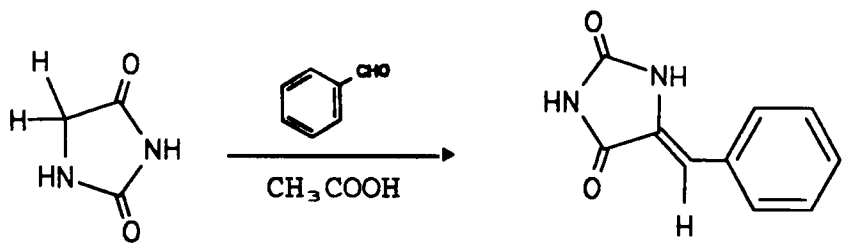
Although the hydantoin ring is a relatively stable system (a topic which will be discussed in greater detail in chapter IV), it is susceptible to further functionalization reactions[297]. For example, the active methylene site at C-5 is susceptible to aldol condensation[296] and various other alkylation reactions[319]. In addition, the nitrogen atoms are quite susceptible to alkylation, or substitution by other heteroatoms[297].

During the course of the studies presented here, such alkylation and heteroatom substitution reactions at both

C-5 and more importantly, at the hydantoin nitrogens, were encountered as troublesome side reactions. For example, the nitrogen atoms are quite reactive under the electrophilic iodination conditions employed in the vinylboronic acid iodination procedure. Protection of the hydantoin nitrogens was chosen as one possible alternative of avoiding this problem. Thus, a general overview of relevant hydantoin chemistry is presented below in order to provide a background to the discussions which follow in later chapters.

b. Alkylation of the C-5 Position

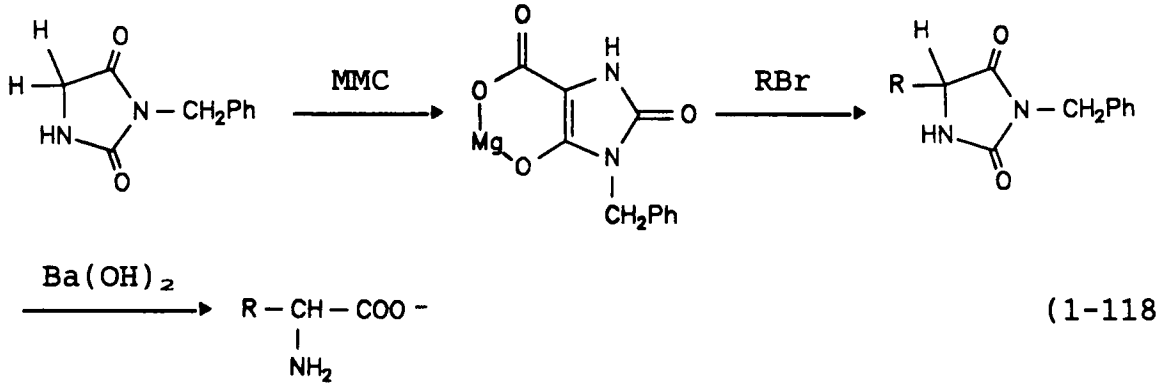
Modification of the hydantoin ring at the C-5 position is one approach used by a number of investigators as a means of preparing higher analogues of amino acids. For example, Wheeler reported very early that 5-substituted hydantoins could be prepared by condensation in an aldol-like manner with aromatic aldehydes. Tyrosine and phenylalanine were synthesized by this method[296] (equation 1-117). More



(1-117)

recently, more elaborate procedures have been developed. Finkbeiner reported that the active methylene site at C-5 was susceptible to carboxylation with methyl magnesium

carbonate, and that the resulting magnesium chelate could be alkylated with a variety of alkyl halides[320] (equation 1-118). Double alkylation of the magnesium chelate is also

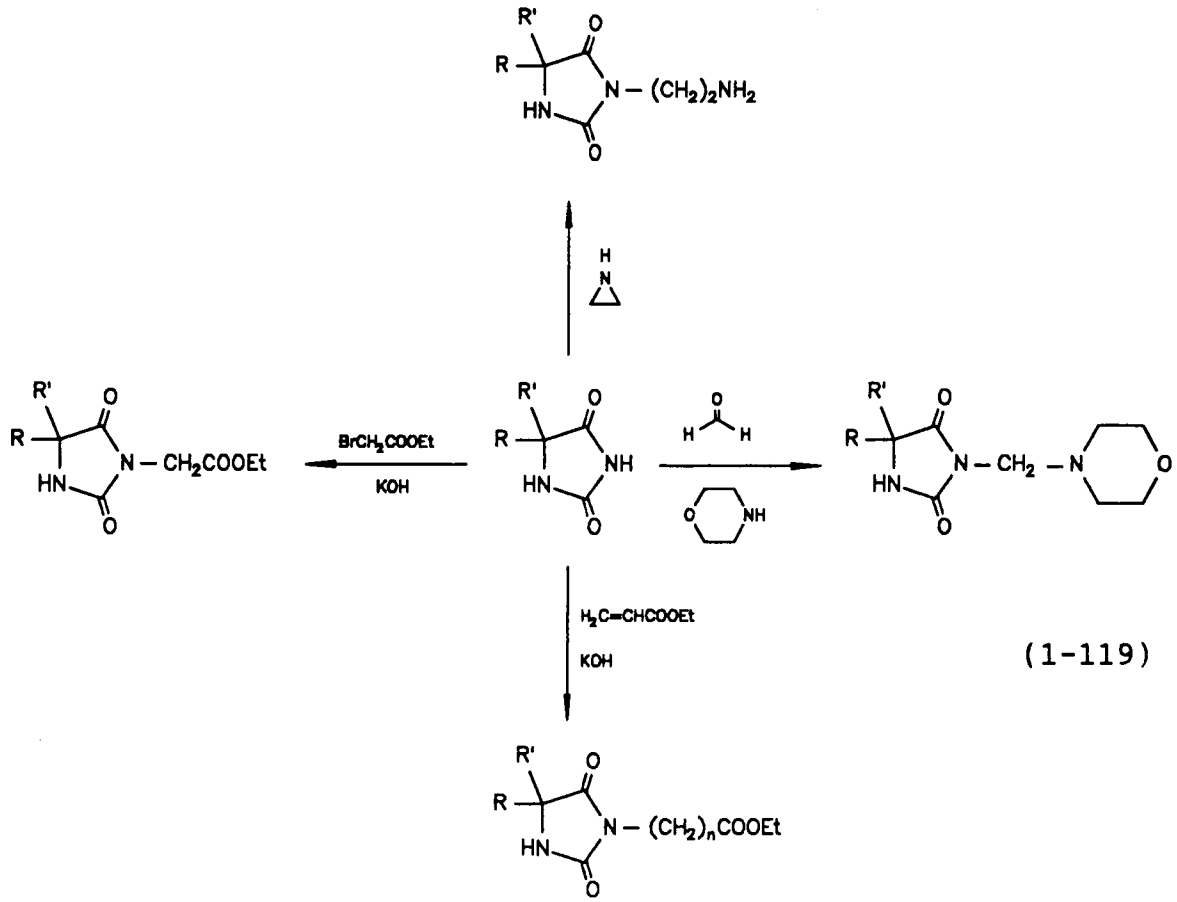


possible (equation 1-118, RX = $Br(CH_2)_4Br$), yielding proline homologues[320]. Similarly, hydantoins substituted at the C-5 position can also be prepared from the corresponding 5-alkoxy derivatives. Alkyl[321], cycloalkyl[322], and aryl[323] substituents have been introduced in this manner.

c. Nitrogen Alkylation and Heteroatom Substitution

The nitrogen atoms in the hydantoin ring are also susceptible to alkylation. Since the acidity of the imide nitrogen (pKa = 9.12)[324] is much greater than that of the amide nitrogen at N-1 (pKa ≈ 14)[325,326], selective alkylation at N-3, in general, can be achieved. For example, aminomethylation via a Mannich-type reaction[326,327], aminoethylation with ethyleneimine[328], Michael condensations[329],

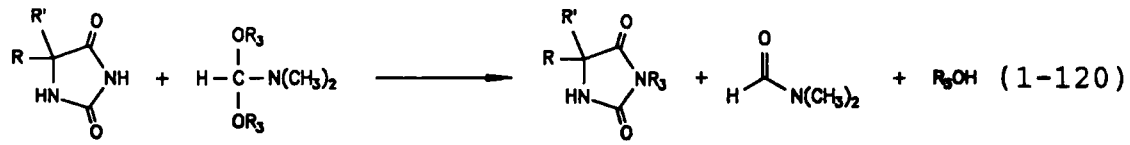
and alkylation with ethyl haloacetates[330] or propionates[329] all selectively afforded N-3 alkylated derivatives (equation 1-119).



(1-119)

Some of the above procedures are complicated by competitive N-1 alkylation, as, for example, in the amino-methylation procedure[326], where di-N-alkylated products have been obtained[331], or gave moderate yields of the monoalkylated product. In addition, the classical N-3 alkylation procedure[300] employing the sodium salt of the hydantoin with

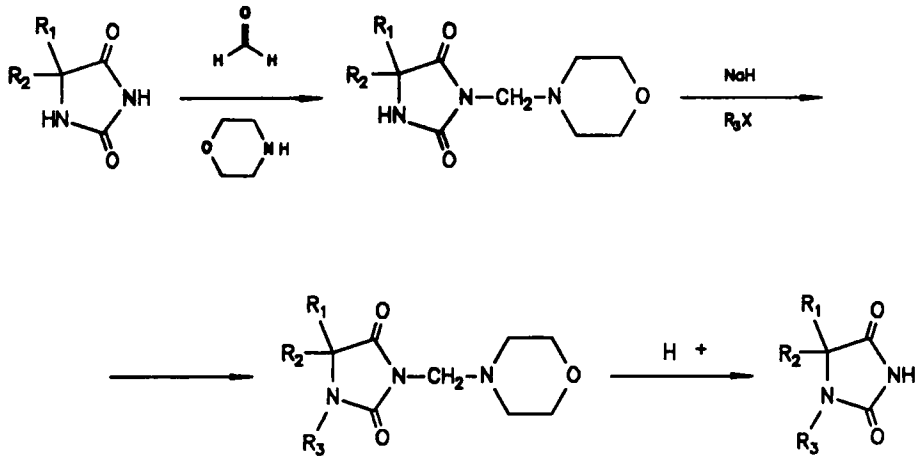
an alkyl halide or a dialkyl sulfate is not very selective, as the desired product is always contaminated with variable amounts of the di-N-alkylated derivative[332], providing yields no better than 60-70%. A more recent procedure employing an anhydrous KOH/DMSO reagent offers improved yields, but is still plagued by competitive N-1 alkylation[333]. The problem seems to finally be solved with the recent report by Poupaert and coworkers involving the use of dimethylformamide dialkyl acetates[334]. Quantitative alkylation at the N-3 position can be achieved with a stoichiometric amount of reagent (equation 1-120).



(1-120)

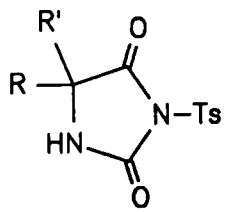
Amide nitrogen (N-1) alkylation occurs under more vigorous conditions, during which time, both nitrogens are alkylated. Selective N-1 alkylation is not possible, unless the imide nitrogen has been protected first[335]. For example, a convenient method of preparing N-1 substituted derivatives using a labile protecting group was reported by Orazi and Corral[336] (equation 1-121).

Heteroatom substitution at the nitrogen atoms of the hydantoin ring is also possible[337,338,339,340,341]. Of



(1-121)

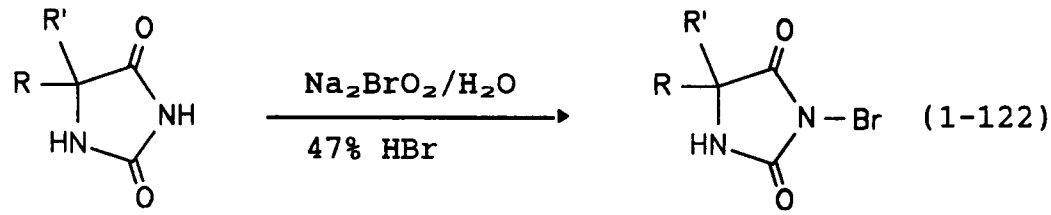
importance to the work presented in this dissertation are N-3-tosylhydantoins (XXVIII). N-3-Tosyl derivatives were



XXVIII

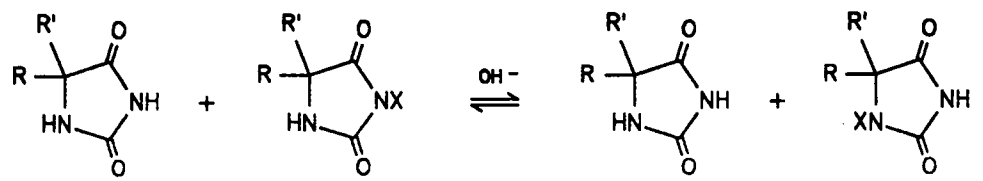
prepared by Hiroi and coworkers as a means of providing a mild hydrolytic ring cleavage to the corresponding hydantoic acids and amino acids[342]. The reaction conditions employed, however, did not permit truly selective tosylation, as moderate yields of the monotosylated derivative were obtained. A more detailed discussion on the hydrolysis of hydantoins to amino acids will be presented in a later chapter.

N-Halogenated derivatives of hydantoins are also known. The formation of such compounds has proven to be a troublesome side reaction in the work presented in later chapters. A recent preparation of 1,3-dibromohydantoin utilizes the new reagent sodium bromite (equation 1-122). Hypobromous



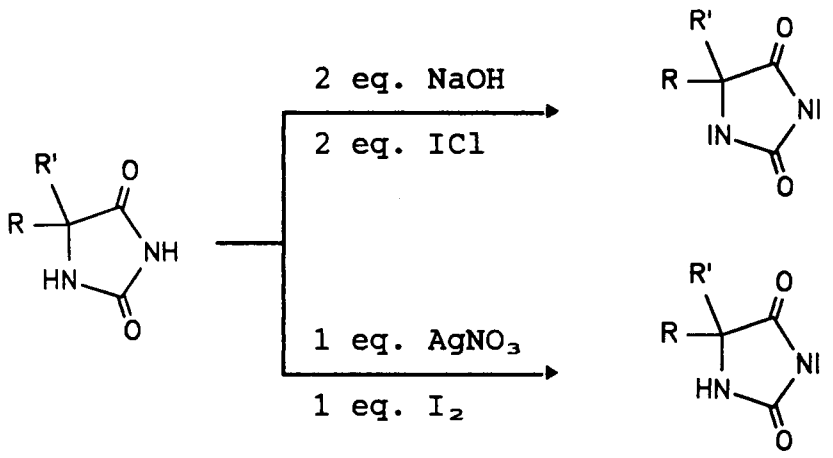
(1-122)

acid has been postulated to be the brominating species[343]. Numerous other methods of preparing dibromohydantoins have been reported[344,345,346,347,348,349]. Selective halogenation of the N-3 position can be achieved using an equivalent amount of base in aqueous media[345,350] or via the silver salt with a stoichiometric amount of halogen[351]. Selective halogenation of the N-1 position can only be accomplished by use of a protecting group at N-3[352], or by treatment with sodium hypohalites under thermodynamic conditions[349] (excess base), whereby halogen transfer from the initially formed N-3 halo derivative to the N-1 position of another hydantoin molecule readily occurs (equation 1-123).



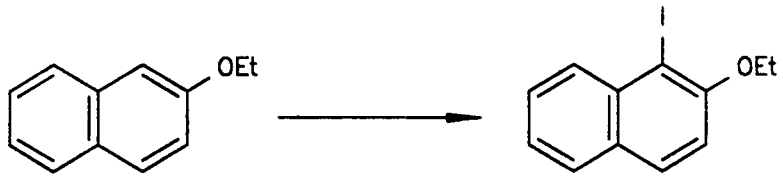
(1-123)

N-Chlorohydantoins were reported much earlier, and have been prepared in a variety of ways analogous to their N-bromo counterparts[349,353,354,355,356,357]. More recently, N-iodohydantoins have been prepared. Diiodhydantoins can be prepared by reaction of iodine monochloride in aqueous alkaline medium[358,359], while selective N-3 iodination can be accomplished by treatment of the silver salt with iodine[358,360] (equation 1-124).



1-124)

The N-iodohydantoins thus obtained have been used as an electrophilic halogen source in electrophilic aromatic substitution reactions. The following reaction to produce 1-iodo-2-ethoxynapthalene[360] is representative (equation 1-125).

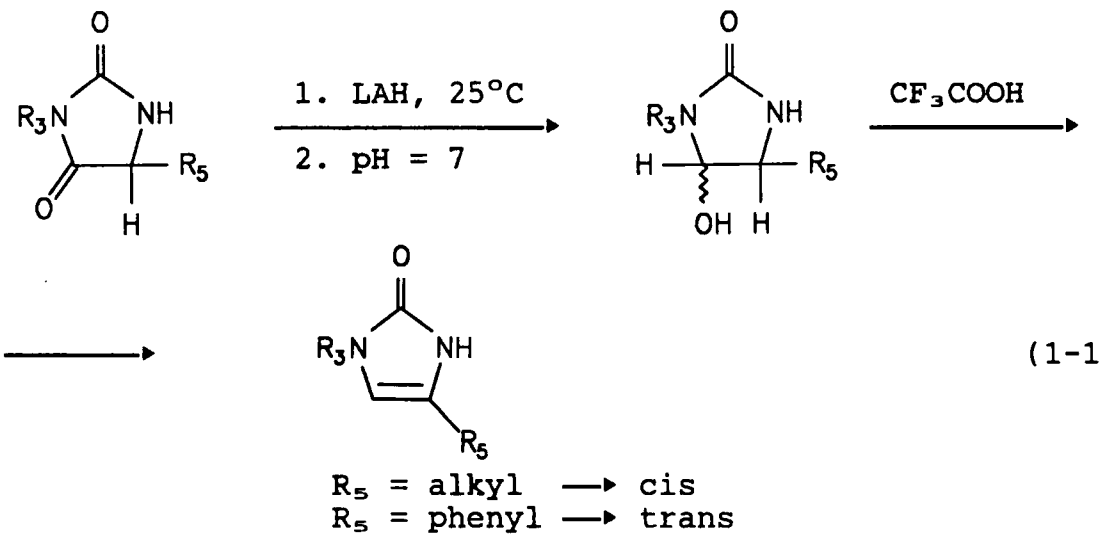


(1-125)

4. Organometallic Reactions of the Hydantoin Ring

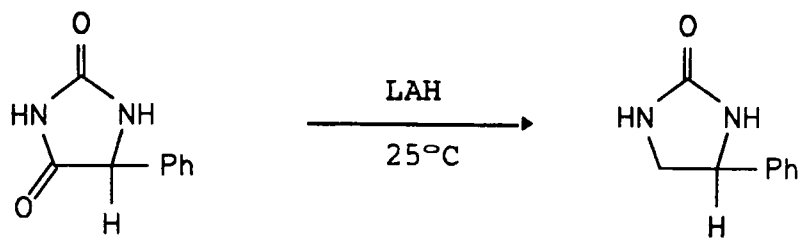
The synthetic scheme outlined in Chapter IV involves the use of catecholborane in the presence of hydantoin functionality. This is a previously unreported reaction. In fact, studies involving the use of organometallic reagents with molecules containing the hydantoin moiety are rather limited, most likely due to the fact that organometallic reagents have only been developed within the last 30 years while hydantoin chemistry has been a relatively unexplored area during this time frame. However, a brief discussion on what has been reported to date is relevant for reasons which will be delineated in a later chapter.

Very little has been reported on the reduction of the hydantoin ring, with lithium aluminum hydride (LAH) and bis(2-methoxyethoxy) aluminum hydride[361] being the only reagents studied. Selective reduction of the C-4 carbonyl occurs when hydantoins are treated with LAH at room temperature[362]. For example, reduction of 3-substituted hydantoins provides moderate yields of 4-hydroxy-2-imidazolidinones (equation 1-126). As expected[296], the 4-hydroxy adducts are stable only under neutral conditions, and undergo rapid dehydration in the presence of trifluoroacetic acid to provide the corresponding imidazolone[362,363,364] (equation 1-126). Substrates bearing an alkyl group at the N-3 position give preferential cis-4-hydroxy products.



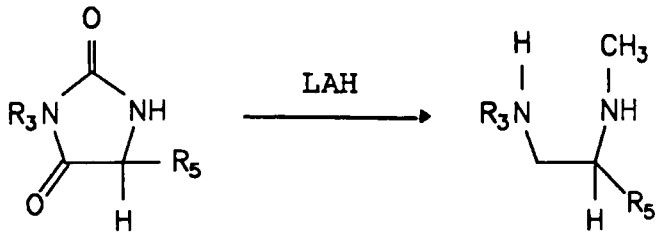
(1-126)

Conversely, when a phenyl substituent is present at N-3, the trans-4-hydroxy adduct predominates. The results were explained on the basis of steric constraints, as epimerization was ruled out[362]. The dependence of a substituent being present at N-3 on the outcome of the reduction process was observed in the reduction of 5-methyl- and 5-phenylhydantoins. In both instances, overreduction occurs readily at room temperature, to provide exclusively the corresponding 2-imidazolidinones[362,365] (equation 1-127).



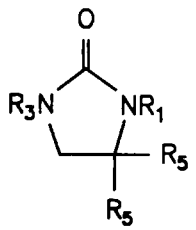
(1-127)

A more extensive reduction occurs with LAH under more vigorous conditions (reflux, THF), as ring opened N-methyl-ethylenediamines are obtained[362] (equation 1-128). Partial

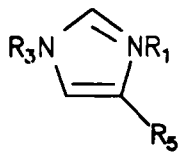


(1-128)

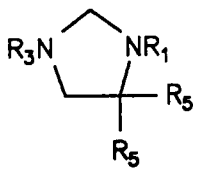
reduction to 2-imidazolinones[365] (XXIX), imidazoles[363] (XXX), and imidazidines[363] (XXXI) has also been observed under varying conditions.



XXIX



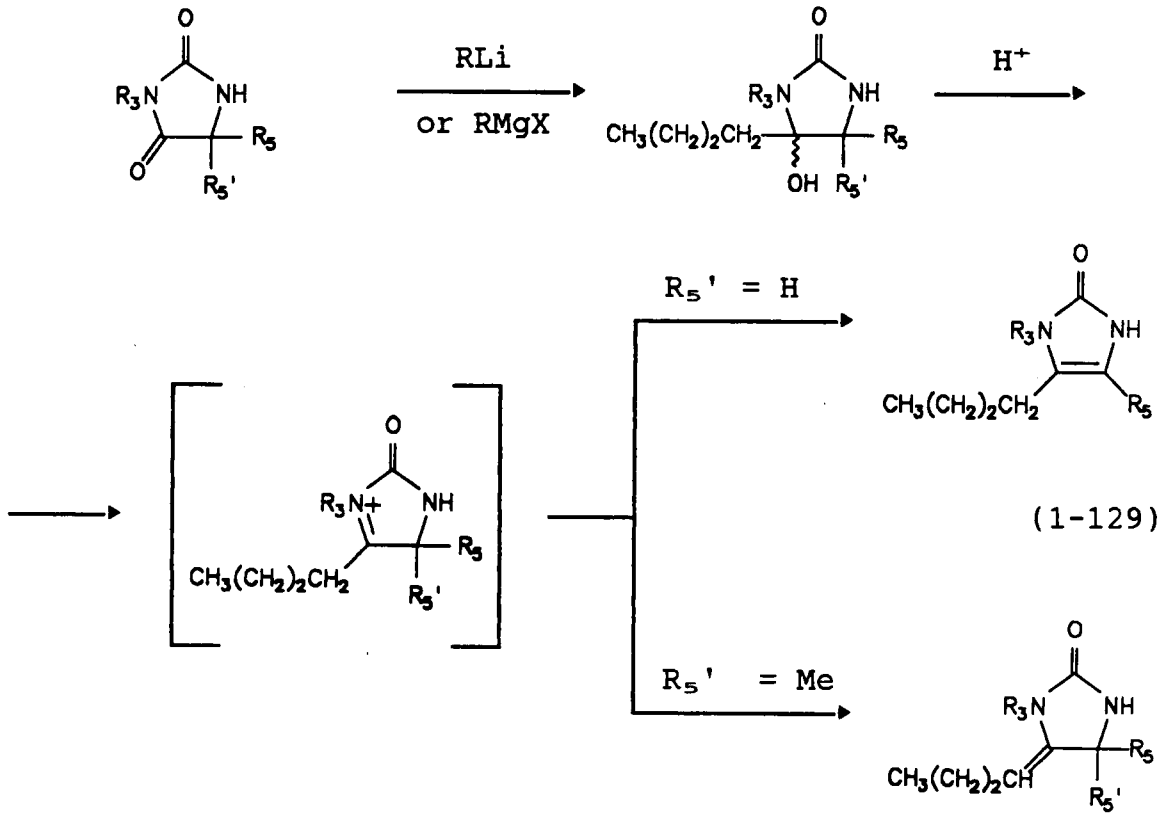
XXX



XXXI

Alkylation of the hydantoin ring have also been studied with organometallic reagents such as organolithium and Grignard reagents. 4-Hydroxy-4-substituted-imidazolidin-2-one derivatives are obtained with such reagents upon neutral workup, while in the presence of acid, a facile dehydration process via an N-carbamoyliminium ion occurs[366] (equation 1-129).

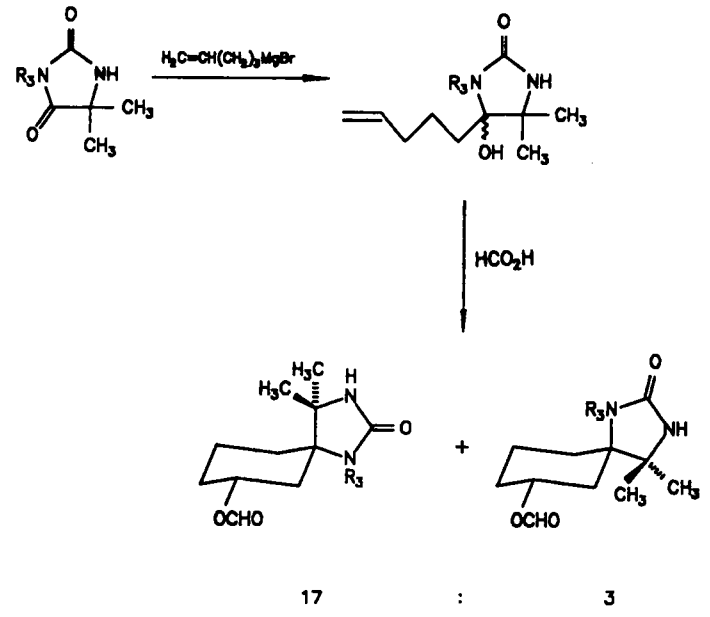
The use of carbamoyliminium ions has recently been exploited in annelation[333,367,368], ring expansion[369], and in



spirocyclization reactions[366]. For example, when 3-benzyl-4-(pent-4-enyl)-4-hydroxy-5,5-dimethylimidazolidin-2-one, prepared by Grignard alkylation of the corresponding hydantoin, is treated with formic acid, spiroimidazolidin-2-ones are obtained[366] (equation 1-130).

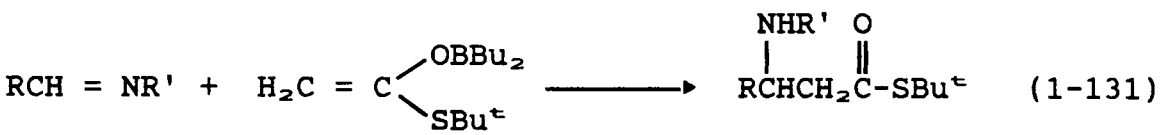
5. Synthesis of Amino Acids Via Organoborane Technology

Organoboranes are versatile intermediates for the formation of carbon-carbon bonds[16]. In recent years organoboranes have found application in the synthesis of

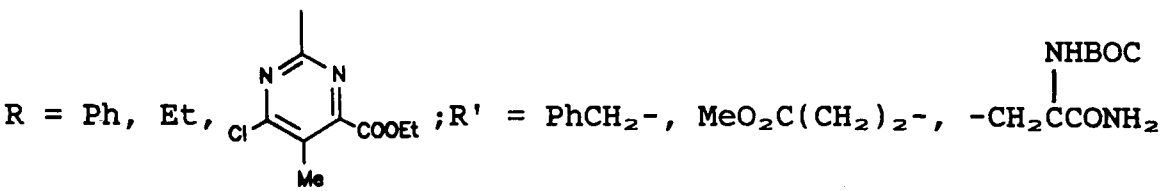


(1-130)

amino acid and amino acid derivatives. Perhaps the first report of the use of organoboranes as synthetic intermediates in the synthesis of amino acids was that of Ohno and coworkers[370]. They reported an efficient synthesis of ß-amino acid derivatives via the reaction of vinyloxyborane with Schiff bases (equation 1-131). The procedure requires

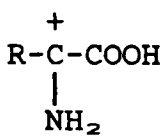


(1-131)



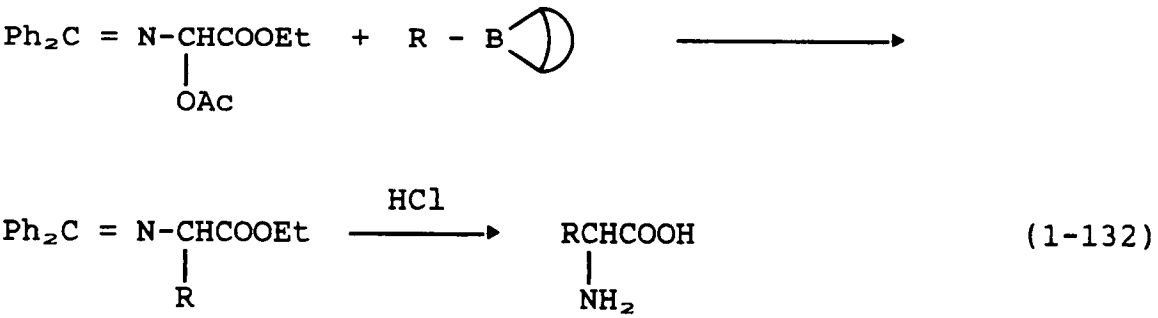
only mild conditions, is highly efficient, and is broadly applicable to the preparation of a variety of ß-amino acid derivatives.

More recently, organoborane technology has been used in the synthesis of α-amino acids. One novel approach reported by O'Donnell employs B-alkyl-9BBN derivatives with an electrophilic glycine synthon[371] (XXXII). The reaction is



XXXIII

carried out in the presence of a hindered base, which prevents nucleophilic side reactions[372,373,374,375]. Hydrolysis of the intermediate alkylated α-iminoester affords the desired α-amino acid in good yield (equation 1-132).



(1-132)

CHAPTER II

DISCUSSION OF PROBLEM

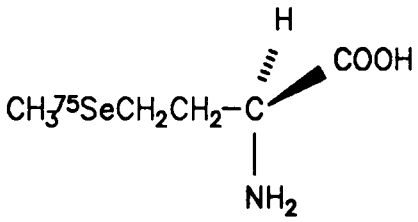
A. Discussion of Problem

The use of radiopharmaceuticals in noninvasive methods for the diagnosis of the functional state of an organ is an important modality in medicine[239,376,377,378]. Of utmost importance is the design of a radiopharmaceutical which has a specific affinity for the organ of interest. Such radiopharmaceuticals provide a means for function measurement and/or imaging of the desired organ using modern scintillation cameras. A number of such tissue specific radiopharmaceuticals that can be utilized for medical imaging purposes are available for such diverse organ sites as the brain, liver, kidney, and bone[239,379,380,381]. However the development of a site specific radiopharmaceutical for the pancreas is truly lacking[379].

Cancer of the pancreas is the fourth most frequent cause of cancer related deaths[380]. Additionally, the prognosis in cases of known pancreatic carcinoma is very unfavorable: the 5-year survival rate is less than 5%. Thus, the development of diagnostic methods for the early detection of pancreatic cancer is of great importance.

One possible design of radiopharmaceuticals for

pancreas scanning depends on the high turnover rate of amino acids within the pancreas, owing to the large requirement this organ has for exogenous amino acids[381,382,383]. Thus, the physiological role which that organ plays in synthesizing monomeric amino acids into digestive enzymes offers an attractive rational for the preparation of pancreatotrophic radiopharmaceuticals[384]. Along these lines, a number of labelled amino acids have been prepared and evaluated for pancreatic uptake in animals and man. For example, selenium-75-labeled-L-selenomethionine (XXXIII) was developed

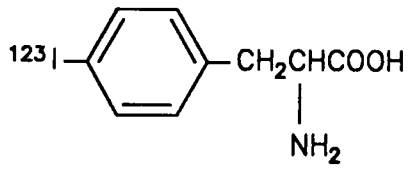


XXXIII

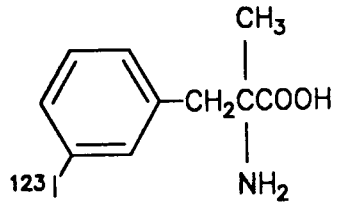
as an analogue of methionine, and is the current radiopharmaceutical used for pancreatic imaging[385]. The choice of the selenium-75 analogue of L-methionine was based on the demonstrated uptake of L-methionine[386], and on the basis that the sulfur atom could be readily replaced by the gamma-emitting selenium-75 radionuclide. However, although ^{75}Se-L-selenomethionine is readily incorporated into protein in vivo, this compound possesses a number of drawbacks, including the high radiation dose received by the patient as a result of the long physical half-life of the selenium-75

radionuclide (120 days), and the long biological half-life of the selenium-75 labeled methionine derivative[387]. Nevertheless, the radiation exposure is below the maximum allowable limit, and the drug can be administered safely. In fact, the major limitation of this agent is not the undesirable decay properties or the higher--than--desired radiation exposure to the patient, but its poor imaging characteristic. Unlike L-methionine, the selenium labelled analogue is not specific enough for the pancreas, a common phenomenon when foreign labelling of a site specific agent is attempted[388,389]. Marked uptake of this material is observed in the liver, causing interferences in the observed images, although techniques have been developed to reduce this interference[390]. In addition, tumorous pancreatic tissue appears as cold defects on the scintillation image[391], whereas the reverse situation would be desirable. Furthermore, the normal variations in shape and position of the pancreas create a high incidence of false-positive and false-negative diagnoses, making routing diagnosis difficult[392,393]. Other selenium labeled amino acids, such as ^{75}Se-selenocysteine[394], as well as the unnatural methyl and ethyl analogues[395,396,397] have been studied, but offer less selectivity and result in higher liver uptake than ^{75}Se-L-selenomethionine, and their use in nuclear medicine has since been abandoned.

Radiohalogenated amino acids represent the largest group of compounds studied as potential pancreatic imaging agents. Iodine-123 labeled 3- and 4-iodophenylalanine[398] (XXXIV), iodine-125 labeled 2-, 3-, and 4-iodophenylalanine-[399,400,401,402,403,404,405], and iodine-125-α-methyl-m-iodophenylalanine[403] (XXXV) all exhibit excellent pancreatic specificity and high pancreas--to--liver ratios (5-9:1) in rodents, but results with larger animals, such as dogs and monkeys, or man gave poor results[402,403,404,405]



XXXIV

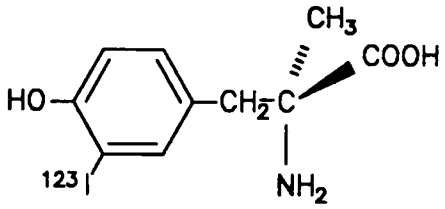


XXXV

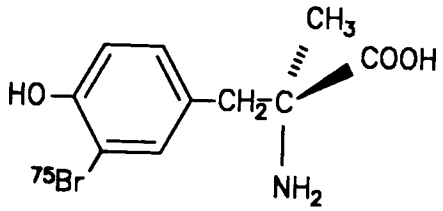
Iodine-123-5- and 6-iodotryptophan[398], as well as the iodine-125[406] and iodine-131[407] were found to be unacceptable as pancreas imaging agents due to lack of specificity. Likewise, ^{131}I-N-acetyliodotryptophan[385], ^{131}I-3-iodotyrosine[385], and ^{131}I-3,5-diiodotyrosine[408], and well as the iodine-123 derivatives[409] also show no pancreatic specificity.

Interestingly, the unnatural amino acid L-3-iodo-α-methyltyrosine (XXXVI) has a high pancreatic specificity in rodents, e.g. pancreas:liver ratios of 8.6:1 for the first hour after intravenous injection[410]. However, as was the

case with other amino acids studied, lack of specificity of the agent was observed in clinical studies[411]. The analogous bromine-75, L-3-^{75}Br-α-methyltyrosine (XXXVII), offers more promise. This agent gave higher pancreas:liver ratios than the corresponding radioiodinated derivative in laboratory studies involving rodents, and quantitative tomographic images were also obtained without interferences from the kidneys[411].



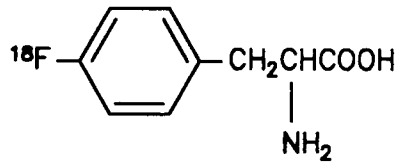
XXXVI



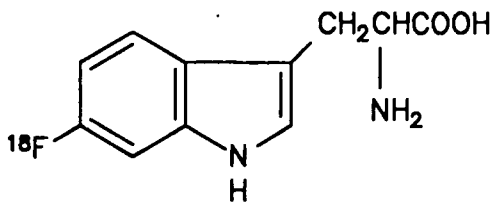
XXXVII

The possibility that fluorine-18 labeled aromatic amino acids might be useful pancreatic imaging agents has also been explored. A number of fluorine-18 labelled amino acids including ^{18}F-3-fluorotyrosine[412,381], ^{18}F-o-, m-, and p-fluorophenylalanine[413], and ^{18}F-5- and 6-fluoro-tryptophan[381,413,414] all exhibit high pancreatic uptake in rodents. However in larger animals such as dogs and rabbits, a much lower uptake was observed. Only two of these compounds, ^{18}F-p-fluorophenylalanine (XXXVIII) and ^{18}F-6-fluorotryptophan (XXXIX) were found suitable for clinical studies, and both gave undesirable results, as *in vivo* defluroination of the aromatic amino acids occurred

extensively, precluding their use as imaging agents[381].



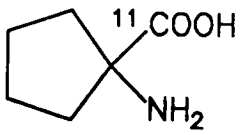
XXXVIII



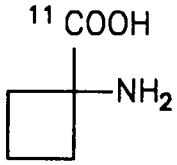
XXXIX

Unnatural, nonmetabolizable ^{11}C-labeled amino acids, exhibit a high affinity for tumorous pancreatic tissue, and have been demonstrated by Hübner and coworkers to provide a means of locating and assessing tumors in the pancreas[415,-416,417,418]. Their studies were based on earlier observations that cancer cells extract amino acids to a greater extent than do normal cells[419,420]. In addition, previous studies by Berlinquet and coworkers had shown that there was selective uptake of the unnatural amino acid 1-aminocyclopentanecarboxylic acid (ACPC), (XL), by malignant tumor tissue. The amino acids presumed antitumor action was the inhibitory effect it displayed in valine utilization by tumor cells[421,422]. More recently, the analogous aminocyclobutanecarboxylic acid (ACBC), (XLI) was shown to display an even more pronounced uptake by tumorous tissue than any other amino acid studied, including ACPC[416,423,-424]. Both agents have shown significant potential for imaging soft tissue tumors in humans[416,418]. Unfortunately, the extremely short half-life of carbon-11 limits the

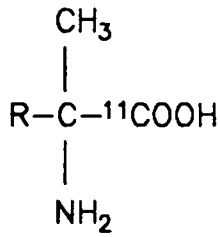
availability of this agent to those few centers equipped with a cyclotron and special tomographic units. Recently, carbon-11 labeled α-methyl-α-amino acids (XLII) have also been shown to concentrate in pancreatic tumor tissue in preference to normal tissue[425].



XL



XLI



XLII

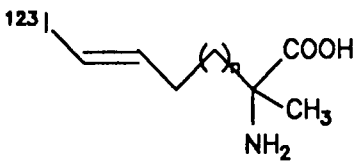
B. Statement of Problem

The development of a site specific radiolabeled amino acid for pancreas imaging was the goal of this research project. The characteristics of the ideal tumor imaging agent include the pronounced uptake and slow washout of the amino acid, coupled with convenient, commercially available, clinical detection systems. Iodine-123, with its optimum emission of 159 KeV photons and relatively short half-life (13.3 hours) would appear to be an ideal candidate for radiolabeling amino acid substrates which exhibit pancreatic specificity.

Based on earlier studies conducted by Hübner and co-workers which demonstrated the enhanced affinity of

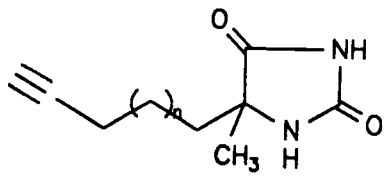
pancreatic tumors for unnatural 1-aminocyclobutanecarboxylic acid (ACBC)[415,416,417,418], ^{123}I-labeled iodovinylamino-cyclobutanecarboxylic acid derivatives (XLIII) were chosen as the target molecules. In addition, relatively, small, unnatural α-methyl-α-amino acids containing the radioiodinated iodovinyl moiety were also chosen (XLIV).

XLIII

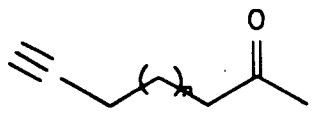


XLIV

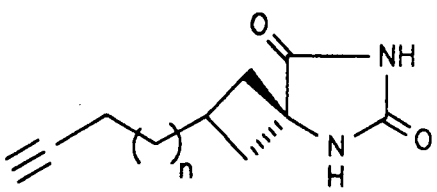
One route to the iodovinyl-α-methyl-α-amino acid system would involve preparation of the corresponding acetylenic hydantoin precursor (XLV), which could be synthesized from the appropriate alkynyl carbonyl derivative (XLVI) via the Bucherer-Strecker reaction. Likewise, the 3-(iodovinyl-alkyl-1)-1-aminocyclobutane-1-carboxylic acid system could be prepared in a similar manner (XLVII and XLVIII).



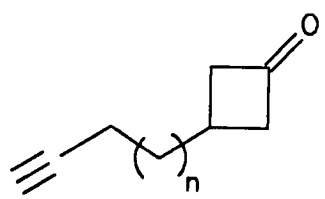
XLV



XLVI

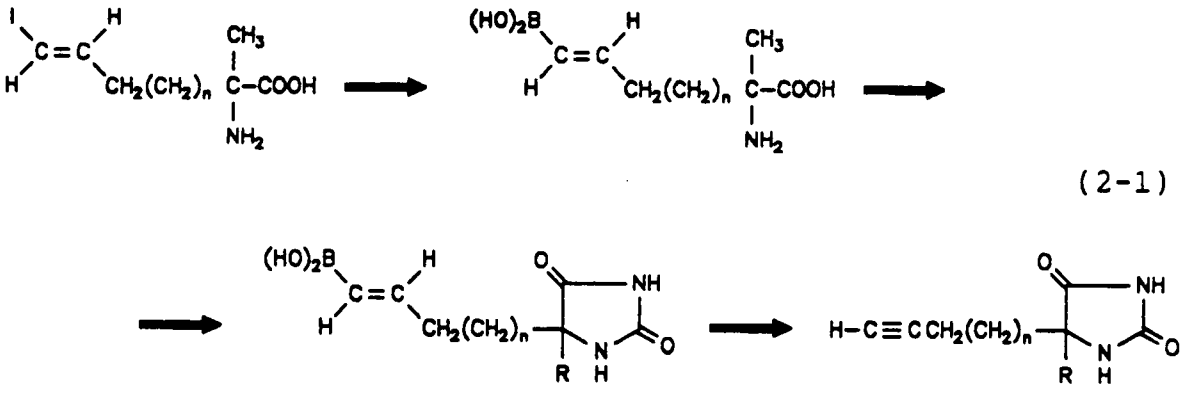


XLVII

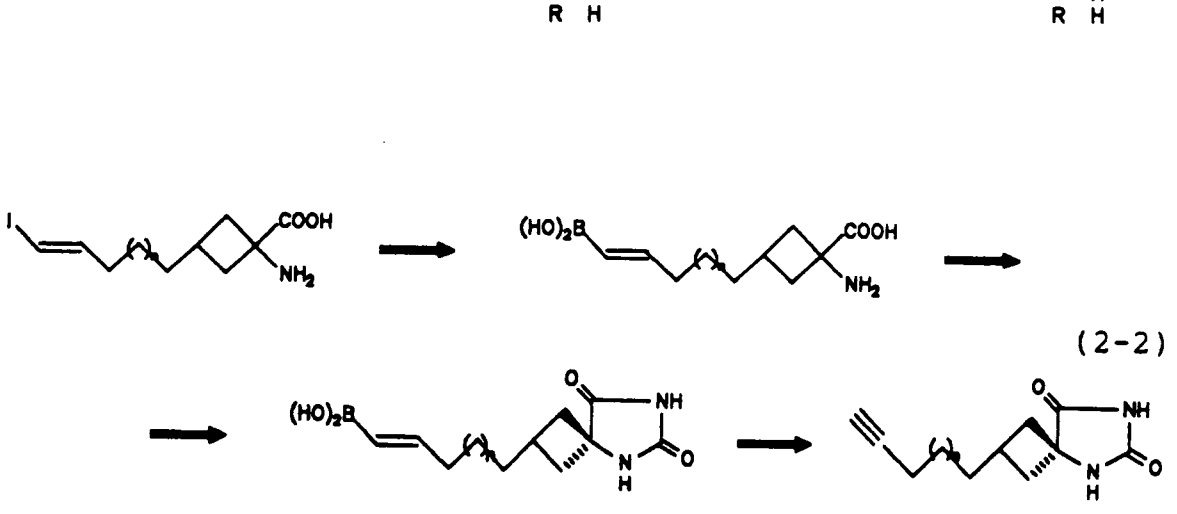


XLVIII

Hydroboration of the alkynyl moiety with catecholborane[54] followed by hydrolysis of the intermediate catechol vinylboronic ester would give the vinylboronic acid hydantoin. Cleavage of the hydantoin moiety employing standard methodology, such as aqueous barium hydroxide[426] would result in the desired vinylboronic acid amino acid which could then be iodinated under mild oxidizing conditions to afford the iodovinylamino acid (equations 2-1, 2-2).



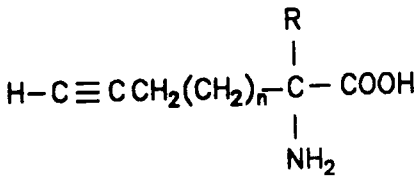
(2-1)



(2-2)

A more direct approach to iodovinyl-α-methyl-α-amino acids would involve preparation of an acetylenic amino acid

(XLIX). However, this route possessed an obvious drawback: the acid functionality would be readily reduced by catechol-

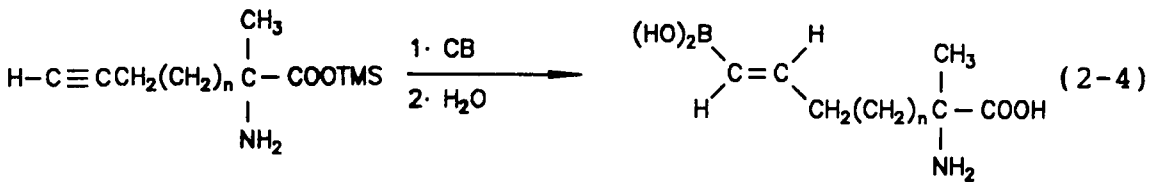


R = H, CH_3

XLIX

borane[140]. In fact, as was previously discussed in Chapter I, hydroboration of an unsaturated amino acid has never been reported, and a limited number of studies have been conducted on protected amino acid derivatives. However, with the discovery that the trimethylsilyl moiety effectively protected carboxylic acid functionality, during the hydroboration (the subject of Chapter VI), this route became a feasible alternative (equations 2-3, 2-4).

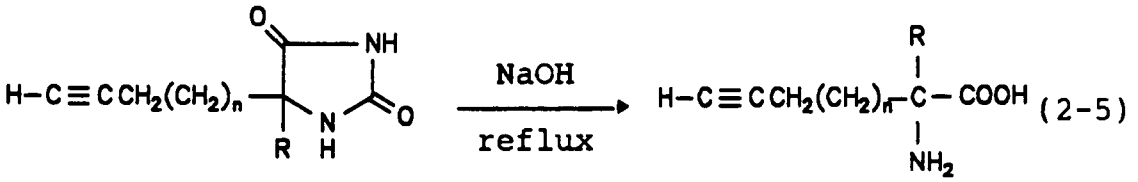
(2-3)



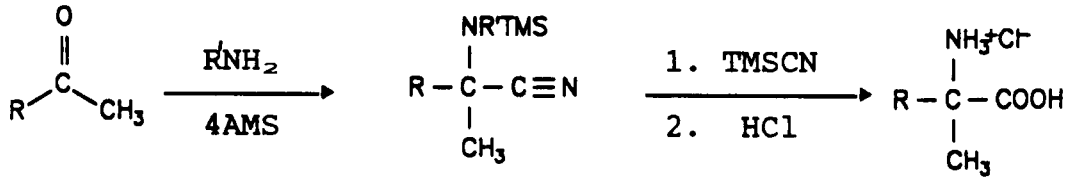
(2-4)

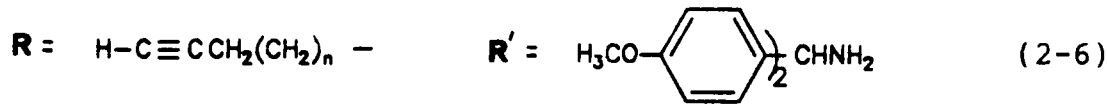
Three approaches to the alkynyl amino acid were chosen. One involved hydrolysis of an alkynyl hydantoin (equation

2-5). A second route involved a modified Strecker reaction

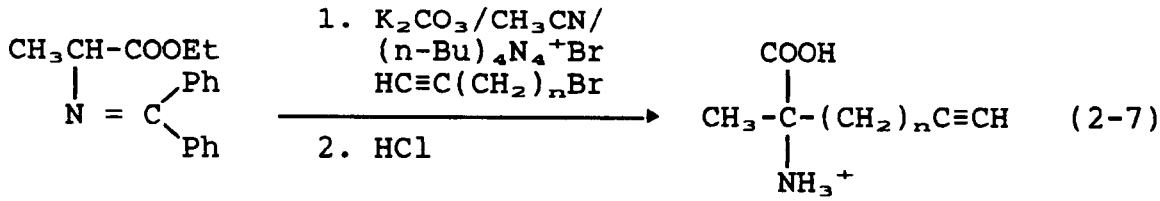


reported by Greenlee employing trimethylsilylcyanide[427] (equation 2-6). A third route which was explored involved the





alkylation of the Schiff base derivative of alanine, employing the recently published procedures by O'Donnell, Ghosez, and coworkers[428,429,430,431] (equation 2-7).



Both basic approaches toward the synthesis of an iodovinyl-α-methyl-α-amino acid were investigated. The synthesis of an iodovinyl-α-amino acid via hydroboration -

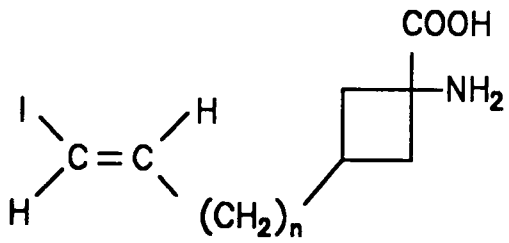
iodination of an alkynyl hydantoin is presented in Chapter V. Model studies directed toward the synthesis of a 3-(iodovinylalkyl-1-)1-aminocyclobutane-1-carboxylic acid derivative are presented in Chapter III. The three approaches described above for the synthesis of an alkynyl amino acid were investigated and are presented in Chapter VII.

CHAPTER III

PREPARATION OF 3-(1-OCTYL)CYCLOBUTEN-1-ONE: MODEL STUDIES DIRECTED AT THE TOTAL SYNTHESIS OF 3-(11-IODO-10-UNDECEN-1-YL)-1-AMINOCYCLOBUTANE-1-CARBOXYLIC ACID

A. Introduction

^{123}I-labeled iodovinylaminocyclobutanecarboxylic acid derivatives would appear to be attractive candidates for possible pancreatic imaging based on earlier studies conducted by Hübner and coworkers which demonstrated the enhanced affinity of pancreatic tumors for unnatural ^{13}C-carboxyl labeled 1-aminocyclobutanecarboxylic acid (ACBC)[415, 416, 417, 418]. The 3-substituted ACBC derivatives (where the alkyl group at position three contains the terminal iodovinyl moiety), (L), would most closely emulate the known



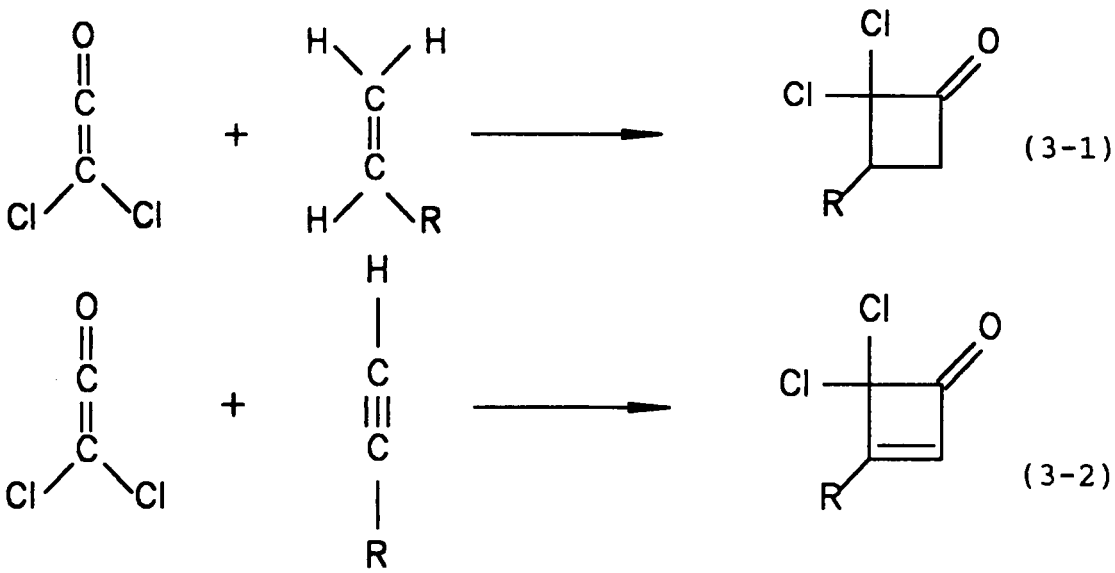
L

where n = 0 through 11

pancreatic tumor specificity exhibited by the parent compound. However, prior to radiolabelling experiments,

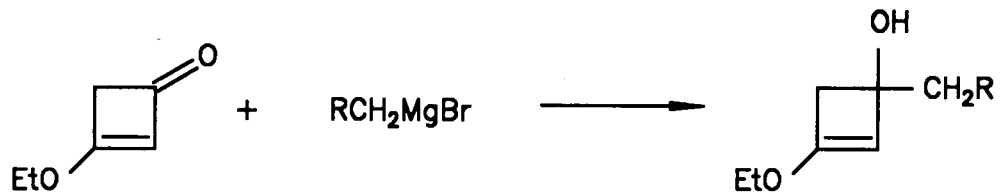
viable synthetic routes to 3-(Ω-iodovinylalk-1-yl)-1-amino-cyclobutane-1-carboxylic acid derivatives had to be developed. 3-(11-Iodo-10-undecen-1-yl)-1-aminocyclobutane-1-carboxylic acid (x = 9 in (L)) was chosen as the target molecule for initial studies on the basis of availability of appropriate starting materials. The large size of the molecule would also make the isolation of the water soluble amino acid less troublesome.

Cyclobutanones have been known for over fifty years and they have been prepared by a variety of methodologies including substitution, ring expansion, and cycloaddition reactions[432,433,434,435,436]. However, routes to 3-substituted cyclobutanones are somewhat limited. One straightforward approach to such compounds involves the facile $2_s + 2_a$ cycloaddition reaction of dichloroketene with alkenes[441,437] (equation 3-1) and alkynes[438] (equation 3-2). Removal

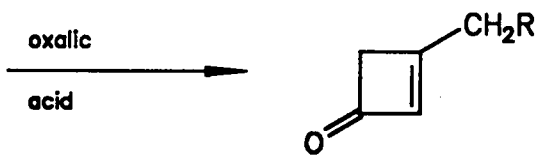


of the chlorines could then be achieved using mild reducing agents such as $CrCl_2$[438], or Zn/HOAc[439] which would not affect the alkynyl group. However, due to the limited availability of the requisite eneynes and diynes this approach was soon discarded.

A more versatile synthetic scheme for the preparation of 3-substituted cyclobutanones involves the addition of a Grignard reagent to 3-ethoxycyclobutenone[440,441], which was recently reported by Wasserman[442], Ficini[443], and Keana[444] (equation 3-3). The versatility of this scheme rests upon



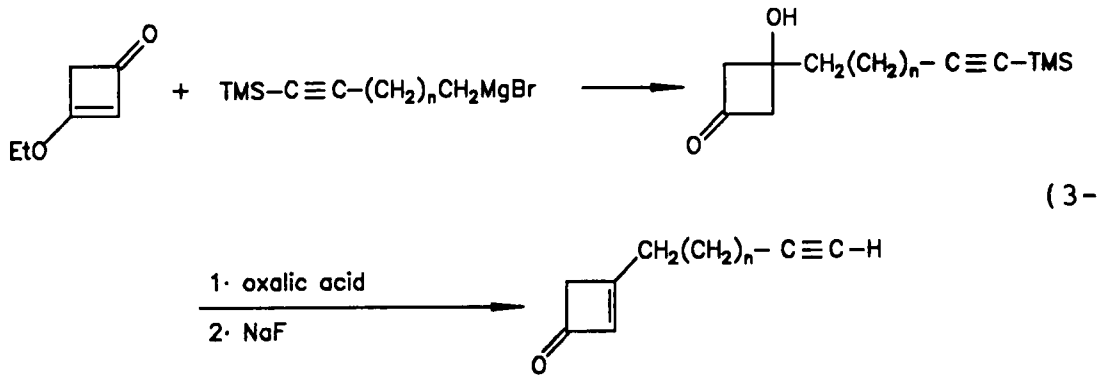
(3-3)



the availability of a wide variety of alkynyl bromides that can be readily prepared from the corresponding alkynyl alcohols by successive tosylation[445] and bromination[269] (equation 3-4). After protection of the terminal acetylene

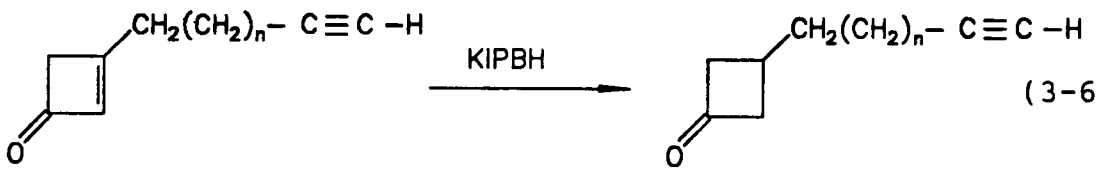
(3-4)

with the trimethylsilyl moiety[446], followed by tosylation, bromination, and conversion to the necessary Grignard reagent, alkylation should lead to the desired 3-substituted cyclobutenone following acid catalyzed dehydration[444,447,448,449] (equation 3-5). Conversion of the 3-substituted



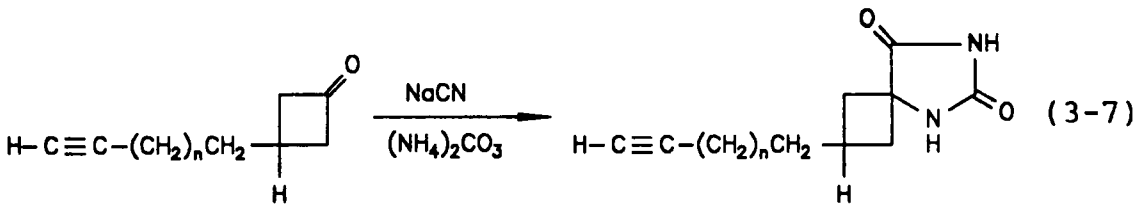
(3-5)

cyclobutenone to the desired iodovinylaminocyclobutane carboxylic acid system could be accomplished in the following manner. Reduction of the conjugated enone could be accomplished in a 1,4 manner by use of a selective reducing agent such as potassium isopropoxyborohydride (K-Selectride)[450] (equation 3-6). Application of the Bucherer-Berg



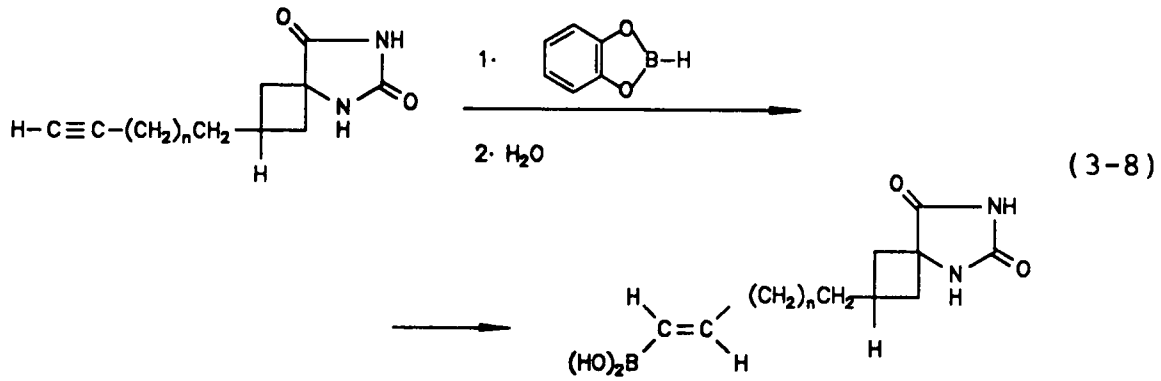
(3-6)

reaction would provide the 3-(1-alkynyl)-1-spirocyclobutylhydantoin[316] (equation 3-7). Hydroboration with catecholborane, followed by water hydrolysis, would lead to the 3-



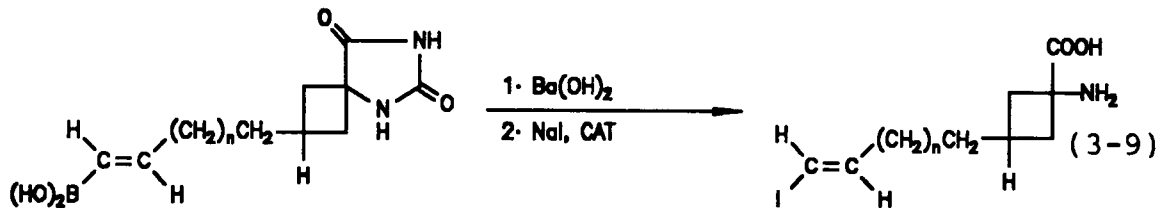
(3-7)

(vinylboronic acid)-spirocyclobutyl hydantoin (equation 3-8). Basic hydrolysis of the hydantoin moiety[426], followed



(3-8)

by electrophilic iodination, would then provide the desired 3-(iodovinylalkyl)-1-aminocyclobutane-1-carboxylic acid derivative (equation 3-9).



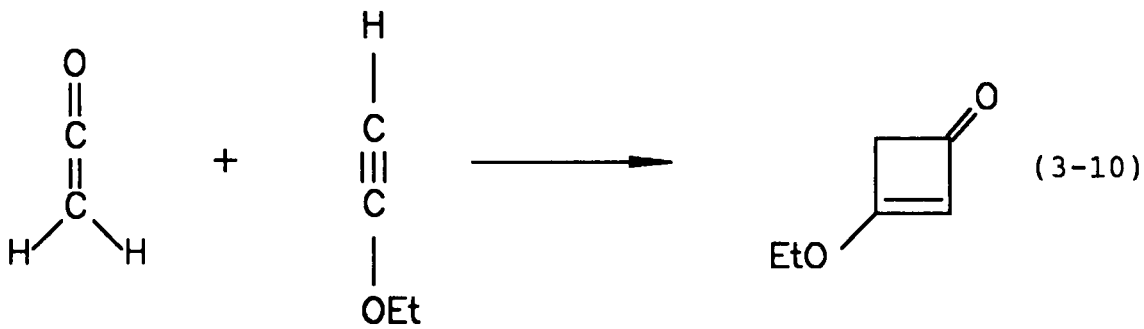
(3-9)

B. Results and Discussion

The synthesis of 3-(10-undecen-1-yl)-cyclobuten-1-one began with the preparation of the alkynyl bromide component. Protection of 10-undecyn-1-ol with the trimethylsilyl moiety according to a procedure described in the next chapter

(procedure 4.D.2.b, p. 161) gave 11-trimethylsilyl-10-undecyn-1-ol in near quantitative yield. Conversion of the alcohol functionality to the tosylate derivative proceeded without incident in a 95% yield after chromatography[269]. Treatment of the tosylate with lithium bromide in refluxing methyl ethyl ketone afforded the desired 1-bromo-11-trimethylsilyl 10-undecyne in quantitative yield[269] (equation 3-4, p. 103).

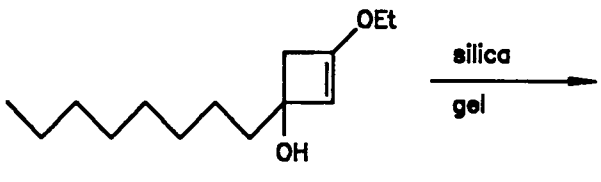
The cyclobutenone component was prepared by the $2_s + 2_a$ cycloaddition of ethoxyacetylene[451,452] with ketene using the procedure developed by Wasserman[440,442]. The ketene employed was generated by pyrolysis of acetone using a ketene generator[453,454] (equation 3-10). Thus, bubbling



(3-10)

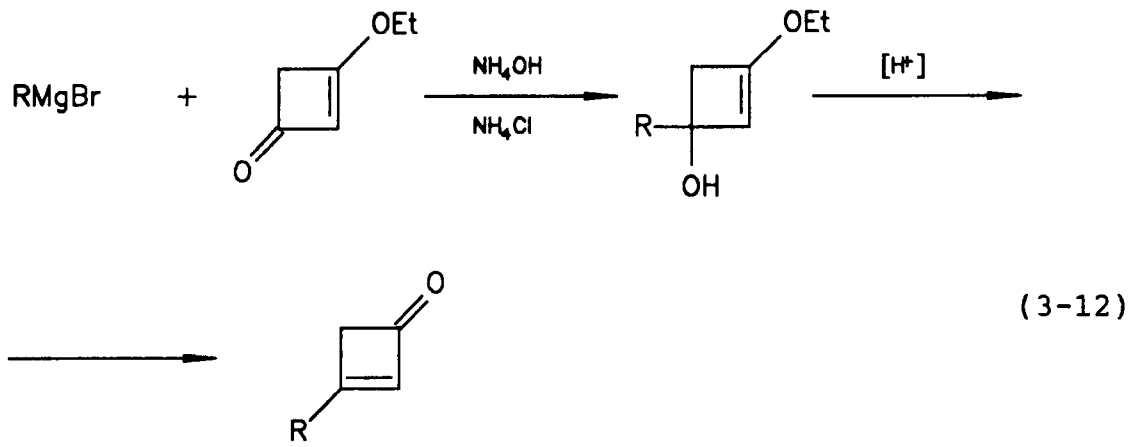
ketene through a methylene chloride solution of 3-ethoxyacetylene afforded 3-ethoxycyclobuten-1-one in a 31% isolated yield after column chromatography and recrystallization. The cyclobutenone thus obtained was very unstable, and had to either be used immediately, or stored under dry, nitrogen atmosphere at -78°C.

The coupling with the alkynyl bromide was optimized using octyl bromide. Reaction of octylmagnesium bromide with 3-ethoxycyclobuten-1-one provided a product mixture of 91%, which contained the desired 1-hydroxy-1-octyl-3-ethoxy-2-cyclobutene resulting from 1,2 carbonyl addition. Unfortunately, TLC analysis of the crude reaction mixture also revealed the presence of 6 other impurities, which were not identified. Chromatographic isolation of this compound was not possible, as this material is very unstable, and undergoes a facile dehydration on silica gel to give a product that was tentatively identified as 3-ethoxy-1-(1-octen-1-yl)-2-cyclobutene (equation 3-11). Consequently, the crude



(3-11)

product from the Grignard coupling reaction was used directly for the next step; treatment with a methanolic solution of oxalic acid afforded the desired 3-octyl-2-cyclobutenone in an overall yield of 23% (two steps) after chromatography (equation 3-12, R = octyl). Further attempts to improve the yield of this compound gave comparable results. A more convenient one pot procedure for preparation of this compound was developed, incorporating an acid hydrolysis step used by Danheiser[447] in a similar reaction.



(3-12)

Thus, treatment of a THF solution of 3-ethoxycyclobuten-1-one (4.19 mmol) with octylmagnesium bromide, followed by quenching of the reaction mixture with aqueous HCl (10%) gave 3-(1-octyl)-cyclobuten-1-one in a 25% yield after purification by column chromatography. Figures 3-1 and 3-2 show the ^{1}H- and ^{13}C-NMR spectra of this compound.

With the key coupling step optimized, the attempted preparation of 3-(11-trimethylsilyl-10-undecyn-1-yl)-cyclobuten-1-one was carried out in a similar fashion. Grignard coupling of 11-trimethylsilyl-10-undecyn-1-yl magnesium bromide with 3-ethoxycyclobutenone gave what appeared to be the intermediate cyclobutenol upon basic (NH_4OH/NH_4Cl) workup, along with a number of other side products. Evidence for the formation of the desired cyclobutenol rested on the observance of peaks at 172 ppm, 99.72 ppm, 64.37 ppm, 47.22 ppm, and 14.10 ppm in the ^{13}C-NMR spectrum which were comparable to those observed with the model compound, along with the two alkynyl carbon resonances

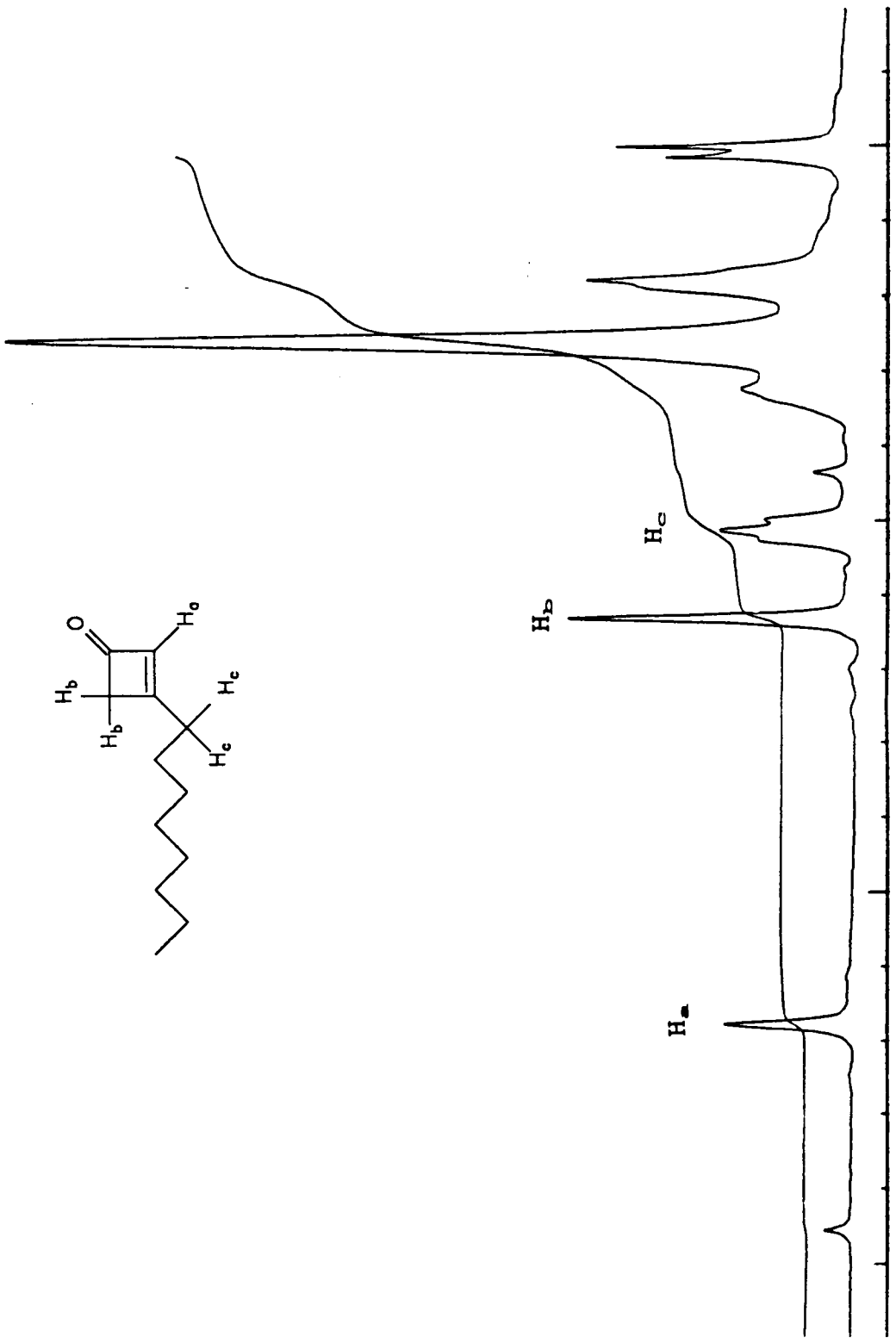


Figure 3-1. Proton NMR Spectrum of 3-(1-Octyl)-cyclobutene-1-one.

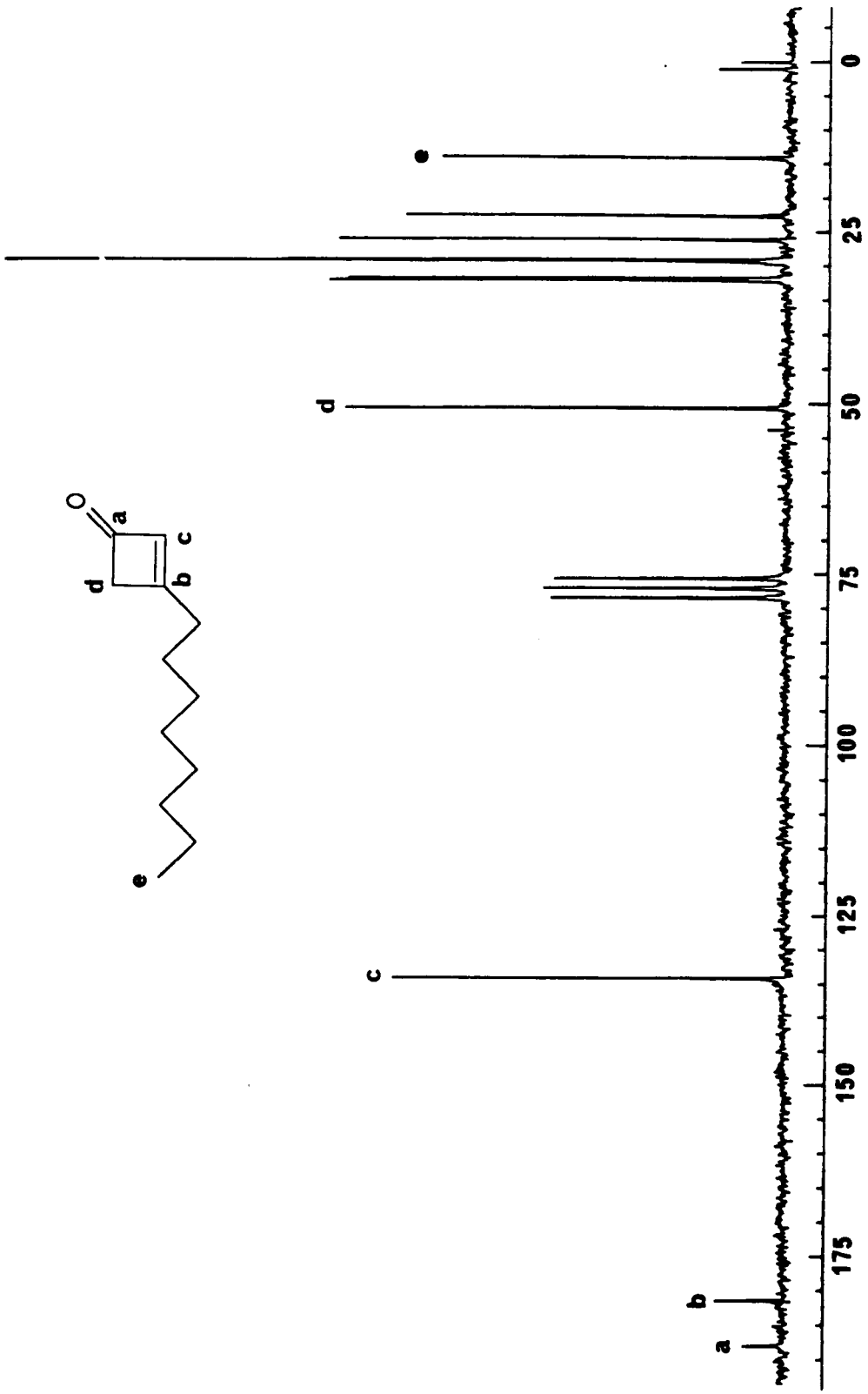


Figure 3-2. Carbon-13 NMR Spectrum of 3-(1-Octyl)-cyclobutene-1-one.

at 107.65 ppm and 84.22 ppm. Without isolation, acid catalyzed dehydration step was carried out. However, following chromatography, no identifiable product was realized (equation 3-12, p. 108, R = TMSC≡C(CH_2)-). Although yields approaching 60 - 70% involving similar compounds were reported by Ficini[443,448] further attempts provided similar results. It was later determined that the procedure used to prepare the starting protected alkynyl alcohol, e.g. the use of n-butyllithium for proton abstraction, resulted in minor amounts of a propargyl silylation, which would obviously result in contaminated products (equation 3-13). [Propargyl silylation can be eliminated

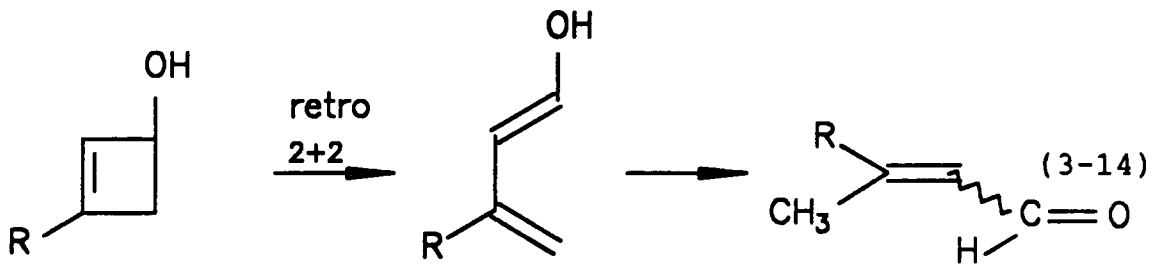
$$H-C\equiv C-CH_2(CH_2)_nCH_2OH \xrightarrow[\text{2. 2 equiv } (CH_3)_3SiCl \text{ 3. HOAc}]{\text{1. 2 equiv n-BuLi}}$$

(3-13)

$$\longrightarrow \quad (CH_3)_3Si-C\equiv C-CH_2(CH_2)_nCH_2OH \quad + \quad (CH_3)_3Si-C\equiv C-\underset{\displaystyle Si(CH_3)_3}{\underset{|}{CH}}(CH_2)_nCH_2OH$$

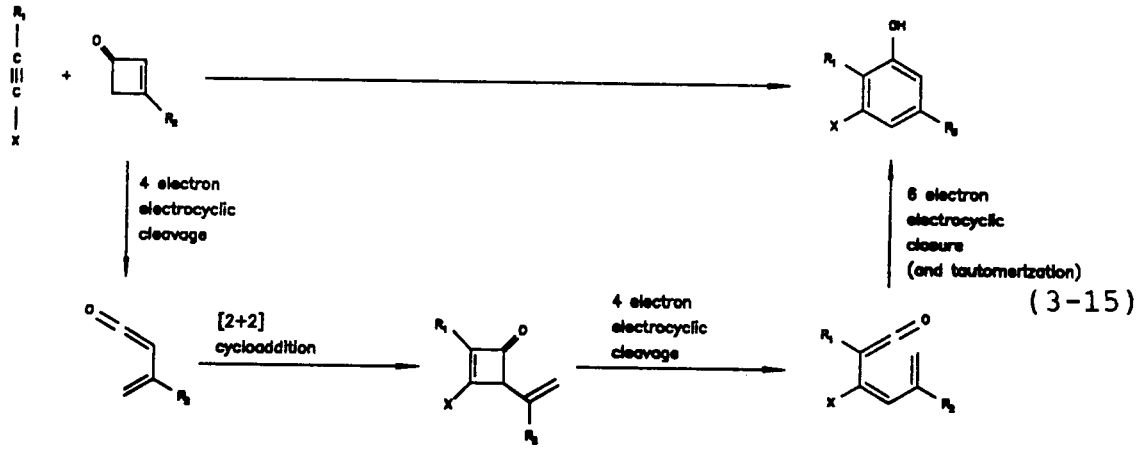
by use of ethylmagnesium bromide as the base instead of n-butyllithium (see Chapter VII, p. 483.] However, the major factor in the low isolated yields obtained for the model compound, as well as the negative result obtained in the desired alkynyl case would appear to be due to the thermal instability of the cyclobutenol and cyclobutenone products, as well as the 3-ethoxycyclobutenone. For example, retro

2 + 2 cycloadditions to give butadiene derivatives[444,455] (equation 3-14) and the formation of aromatic phenols upon



(3-14)

reaction of cyclobutenones with alkyne substrates via a cascade of pericyclic processes[456] are known to occur (equation 3-15). The presence of trace amounts of acid or



(3-15)

base can also catalyze further reactions[444,447,451,457,458,459]. In addition, polymerization of the starting 3-ethoxycyclobuten-1-one has been reported[440], and the presence of moisture can degrade the starting material to 1,3-cyclobutanedione[442], or result in the formation of ß-ethoxycrotonic acid[440]. Although efforts were not made to identify any of the side reaction products, they are offered here as a possible explanation why the observed yield was so

low. It may also be possible that the alkynyl compound may prove to be even more fragile than the octyl derivative, and therefore require more care in its preparation.

The synthesis of the iodovinyl ACBC derivative was not finished. During the course of these studies, it was determined by our collaborators at Oak Ridge that small acyclic derivatives of unnatural amino acids might prove valuable as potential imaging agents. In addition, it provided the opportunity to carry out the synthesis of a model compound so that the synthetic methodology could be optimized. Thus, the synthesis of the ACBC derivative was discontinued.

C. Conclusion

The model compound 3-(1-octyl)-cyclobuten-1-one was obtained in a 25% isolated yield. Unfortunately, the key intermediate, 3-(11-trimethylsilyl-10-undecyn-1-yl)-cyclobuten-1-one intermediate was not obtained. The prerequisite coupling reaction was attempted numerous times with no improvement of results. One disadvantage of this methodology is that elaborate synthetic procedures are required, and tedious separation methods (multiple columns) are often required. For example, pure 3-ethoxycyclobuten-2-one was obtained after two separations by column chromatography, followed by recrystallization at -50°C. In addition, the 3-ethoxycyclobuten-1-one and intermediate cyclobutene

derivatives, are quite unstable. Thus, it is conceivable that three successive synthetic transformations, e.g. Grignard coupling, dehydration, and reduction, to the cyclobutanone would have to be carried out expeditiously to achieve the desired results. Finally, in order for a reasonably efficient synthesis to be realized, a method of improving the yield of the coupling step would need to be achieved, as a number of synthetic transformations in the methodology described remain after this key step.

D. Experimental

1. General

All glassware, syringes, and syringe needles were oven-dried 24 hours prior to use. All NMR spectra were recorded on a JEOL-FX-90Q pulsed FT-NMR spectrometer in deuterio-chloroform ($CDCl_3$) or deuterioacetone ($(CD_3)_2C=O$) solutions. The ^{1}H-NMR spectra were referenced using tetramethylsilane, TMS, as an internal standard (δ = 0.0 ppm). Exchangeable protons were determined by shaking with deuterium oxide. The ^{13}C-NMR spectra were referenced to either $CDCl_3$ (δ = 77.1 ppm), acetone-d_6 (δ = 30.3 ppm), or TMS (δ = 0.0 ppm). ^{13}C-NMR Single Frequency Off Resonance Decoupled Spectra (SFORD) were obtained by setting the irradiation frequency of the decoupler upfield of the tetramethylsilane signal, and are reported in parentheses along with the ^{13}C-NMR data.

Infrared spectra were obtained on a Perkin-Elmer Model 1330 spectrometer. Melting points were recorded using a Fisher-Johns melting point apparatus and are uncorrected. Thin layer chromatographic analyses were performed on Fisherbrand silica gel GF 250 μm TLC plates using either a phosphomolybdic acid, a 2,4-dinitrophenylhydrazine solution, or UV detection as an indicator. Column chromatographic separations were accomplished using Davisil 40-200 mesh silica gel. Elemental analyses of the new cyclobutenyl ketones were not performed due to the instability of the compounds. The commercially available chemicals, their manufacturers, and the methods of purification used, when applicable, are listed in Table 3-1. 11-Trimethylsilyl-10-undecyne-1-ol was prepared according to procedure 4.D.2.b (p. 161) and is not duplicated here. All other reagents were prepared as described below.

2. 11-Trimethylsilyl-10-undecyn-1-yl Toluene Sulfonate

The procedure reported by Knapp and coworkers[269] was used here[460]. To a 250 mL round-bottomeded flask equipped with a magnetic stirring bar and addition funnel were placed p-toluenesulfonyl chloride (22.0 mmol, 4.20 g), chloroform (50 mL) and pyridine (22.0 mmol, 1.74 g, 1.78 mL). While cooling at 0°C, a solution of 11-trimethylsilyl-10-undecyn-1-ol (10 mmol, 2.40 g) in chloroform (10 mL) was added

Table 3-1: Manufacturer and Methods of Purification of Commercially Available Chemicals

Reagent	Manufacturer[a]	Method of Purification[b]
Acetone (reagent grade)	F	
Ammonium chloride	F	
Aqueous Ammonia, 28%	F	
2-Butanone	F	
1-Bromooctane	A	
Chloroform	F	
Ethyl Acetate	F	
Ethylene Dibromide	F	
Ethyl Ether	F	
Ethyl Ether, anhydrous	F	1, 2
Ethyl Ethynyl Ether	A, W	
Hexanes	F	
Hydrochloric Acid	F	
Lithium Bromide	F	
Magnesium, turnings	F, R	
Magnesium Sulfate, anhydrous	F	
Methanol	F	
Methylene Chloride, anhydrous	F	3, 4, 5
4A Molecular Sieves	F	6

Table 3-1 (continued)

Reagent	Manufacturer[a]	Method of Purification[b]
Petroleum ether	F	7
Pyridine, anhydrous	BJ, F	3, 4, 5
Silica Gel	DA	
Sodium Bicarbonate	F	
Sodium Chloride	F, DC	
Sodium Thiosulfate	F	
Tetrahydrofuran, anhydrous	F, M	8, 2

[a]Manufacturers
A = Aldrich Chemical Company
BJ = Burdick and Jackson Laboratories
DA = Davison Chemical Company
DC = Diamond Salt Company
F = Fisher Chemical Company
R = Reade Manufacturing Company
W = Wiley Organics

[b]Methods of Purification
1. Distilled from LAH under nitrogen
2. Distilled from Na/benzophenone under argon
3. Pre-dried over KOH
4. Distilled from P_2O_5 under nitrogen
5. Stored over activated 4A molecular sieves under nitrogen
6. Dried under vacuum at 100°C for 24 hours prior to use
7. Distilled
8. Pre-dried over CaH_2

dropwise, and the reaction mixture gradually allowed to warm to room temperature and stirred overnight. The reaction mixture was extracted with 10% HCl (3x50 mL), followed by successive washing with saturated sodium bicarbonate (3x50 mL) and water (1x50 mL). Filtration, followed by removal of the solvent, gave the crude tosylate as a cloudy oil, which solidified upon standing. Alternatively, removal of the solvent under reduced pressure afforded the crude tosylate (as a pyridine solution). Purification of the crude product by column chromatography (silica gel, 3% ether-petroleum ether → 10% ether-petroleum ether produced 3.40 g (86%) of 11-trimethylsilyl-10-undecyn-1-yl toluene sulfonate a pale yellow oil, which later solidified. Further purification by recrystallization from petroleum ether provided the tosylate as fine white needles, 2.44 g (62%); mp 54.5°C; ^{1}H-NMR ($CDCl_3$): δ 7.85-7.25 (m, 4H, AA'BB', aromatic H's), 4.01 (t, 2H, J=6.2 Hz, $\underline{CH_2}OTs$); 2.17 (t, 2H, J=6.4 Hz, $\underline{CH_2}C{\equiv}C$-), 1.7-1.2 (m, 14H), 0.14 ($(CH_3)_3Si$); ^{13}C-NMR ($CDCl_3$): δ 144.68 (aromatic $\underline{C}CH_3$), 133.30 (aromatic $\underline{C}$-S), 129.86 (aromatic C, ortho to CH_3), 127.94 (aromatic C, meta to CH_3), 107.74 ($(CH_3)_3Si\underline{C}{\equiv}C$), 84.31 ($(CH_3)_3SiC{\equiv}\underline{C}$), 70.73 ($\underline{CH_2}OTs$), 29.21, 28.91, 28.77, 28.64, 25.39, 21.71 ($Ph\underline{CH_3}$), 19.89, 0.26 ($(CH_3)_3Si$); IR (neat): 3012 cm^{-1} aromatic C-H), 2916 cm^{-1} (CH_3), 2845 cm^{-1} (CH_2), 2170 cm^{-1} (C≡C), 1588 cm^{-1} (aromatic C=C), 1353 cm^{-1} (OS=O), 1243 cm^{-1} (C-Si), 1210

cm^{-1}, 1184 cm^{-1}, 1170 cm^{-1}, 1092 cm^{-1} (OS=O), 840 cm^{-1}, 753 cm^{-1}.

3. 1-Bromo-11-trimethylsilyl-10-undecyne

The procedure reported by Knapp and coworkers[269] was used here. To a 250 mL round-bottomed flask were added 11-trimethylsilyl-10-undecyn-1-yl toluene sulfonate (5 mmol, 1.97 g), lithium bromide (50 mmol, 4.34 g), and 2-butanone (75 mL). The flask was equipped with a reflux condenser and the mixture refluxed for 18 hours. The solvent was removed under reduced pressure, hexanes (75 mL) and water (75 mL) added, and the resulting mixture separated. The organic layer was washed with aqueous sodium thiosulfate (1 M, 50 mL), water (50 mL) and then dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure, followed by purification by column chromatography (silica gel, petroleum ether, R_F = 0.42) afforded 1.52 g (99%) of 1-bromo-11-trimethylsilyl-10-undecyne as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 3.41 (t, 2H, J=6.8 Hz, RCH_2Br), 2.20 (t, 2H, J=6.4 Hz, $R\underline{CH_2}C{\equiv}C$), 1.9-1.7 (m, 2H), 1.7-1.2 (m, 12H), 0.14 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR ($CDCl_3$): δ 107.76 ($(CH_3)_3Si-\underline{C}{\equiv}C$), 84.36 ($(CH_3)_3SiC{\equiv}\underline{C}$), 34.03 ($RCH_2Br$), 32.92, 29.34, 29.05, 28.80, 28.67, 28.24, 19.92 ($(CH_3)_3SiC{\equiv}C\underline{CH_2}R$), 0.28 ($(CH_3)_3Si$); IR (neat): 2920 cm^{-1} (CH_3), 2845 cm^{-1} (CH_2), 2165 cm^{-1} (C≡C), 1242 cm^{-1} (C-Si), 837 cm^{-1}, 754 cm^{-1}.

4. 3-Ethoxycyclobuten-1-one

a. Ketene Generation

Ketene was prepared from the pyrolysis acetone at 700-750°C according to the procedure described by Williams and Hurd[453,454,461] using a ketene generator[462,463]. A detailed description of the apparatus (depicted in Figure 3-3) is reported elsewhere[453], and will not be repeated here. The ketene thus obtained was used immediately. Extreme caution should be exercised in the preparation of ketene (bp -41°C) as it is a poisonous gas on the same order of toxicity as phosgene[464]. Thus, all operation should be carried out in an efficient hood and the system should be checked for leaks prior to use. Prior to opening of the apparatus, the system should be flushed with nitrogen.

b. Cycloaddition of Ketene and Ethoxyacetylene

A 1000 mL round-bottomed flask fitted with a septum inlet and 10/25 female ball joint (A), ketene generator (B), spiral condenser (C), connecting tube (D), spiral condenser (E), drain stopcock (F), connecting tube (G), dry ice traps (H) and (I), glass dispersion tube (J), and 250 mL round-bottomed flask (K) fitted with a septum opening that led to a mercury bubbler, was constructed as depicted in Figure 3-3. The apparatus was flushed with nitrogen, flame dried, and allowed to cool under a stream of nitrogen. Round-

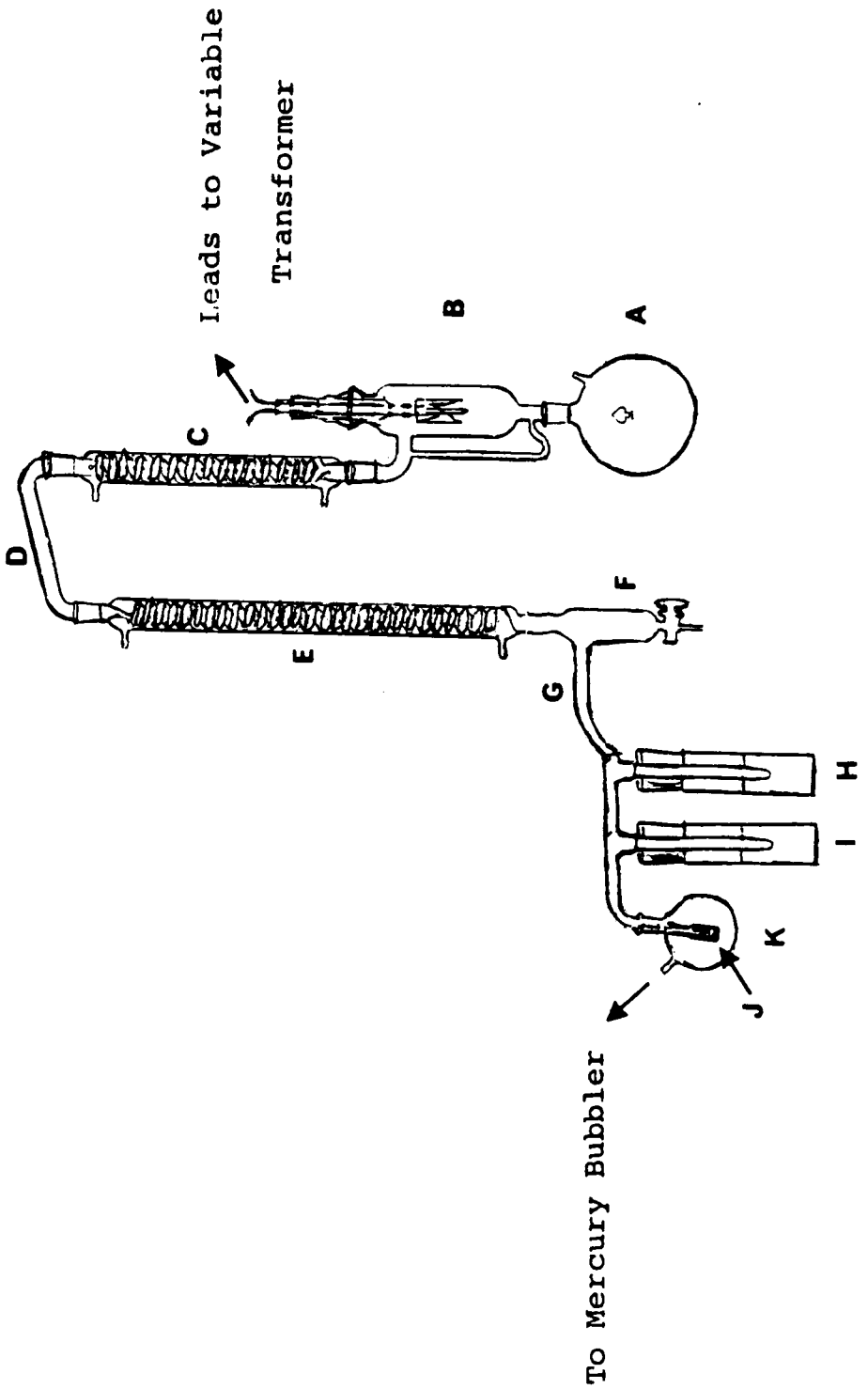


Figure 3-3. Ketene Generator.

bottomed flask (A) was momentarily removed while flushing the system with nitrogen, acetone (800 mL, reagent grade) introduced, and the apparatus reassembled. Anhydrous methylene chloride (200 mL) and a solution of ethyl ethynyl ether (72.12 mmol, 10.11 g of a 50% solution by weight in hexanes) in anhydrous methylene chloride (20 mL) were introduced to round-bottomed flask (K) by cannula. The cold finger traps (H) and (I) were cooled to -78°C, reaction flask (K) cooled to -20°C, and then the acetone in flask (A) was heated to a gentle reflux. Once a gentle reflux of acetone was achieved, current (controlled by use of a variable transformer) was passed through the Chromel filament of the ketene generator until the filament obtained a dull red glow (temperature = 700-750°C). Soon after the ketene generator was turned on, the stream of nitrogen was removed, as the ketene being generated gave a continuous stream of gas bubbles through the gas dispersion tube (J). Ketene was allowed to bubble into the methylene chloride solution of ethyl ethynyl ether at -20°C for 5 hours, during which time, the reaction mixture became very dark in color. After the ketene generator was turned off, the system was flushed with nitrogen prior to opening. Removal of the solvent under reduced pressure gave a yellow brown liquid, which showed the presence of numerous compounds upon TLC analysis. Purification by column chromatography (silica

gel) by successive elution with 10%, 20%, and then 40% ether-petroleum ether gave the desired cyclobutenone, 3.85 g (47%), as a pale yellow liquid (R_F = 0.34, 50% ether-petroleum ether), along with an unidentified minor impurity. Further purification by recrystallization from 50:50 ether-petroleum ether followed by filtration in the cold afforded pure 3-ethoxy-cyclobuten-1-one as pale yellow crystals, 2.48 g (31%), which melt at room temperature; mp 22-25°C (lit[442] 22-25°C). The pure 3-ethoxycyclobuten-1-one could be stored for a number of days without significant degradation if kept in a dry inert atmosphere (stored over activated 4A molecular sieves at -78°C; ^{1}H-NMR (acetone-d_6): δ 4.96 (s, 1H, vinyl H), 4.31 (q, 2H, J=7.0 Hz, $CH_3\underline{CH_2}O$), 3.12 (s, 2H, ring CH_2), 1.42 (t, 3H, $\underline{CH_3}CH_2O$); ^{13}C-NMR ($CDCl_3$): δ 184.18 (s, C=O), 181.22 (s, HC=$\underline{C}$OEt), 106.84 (d, H$\underline{C}$=CHOEt), 69.60 (t, O$\underline{CH_2}CH_3$), 48.28 (t, ring CH_2), 14.18 (q, CH_3); ^{13}C-NMR (acetone-d_6): δ 183.80 (C=O), 182.53 (HC=$\underline{C}$OEt), 107.90 (H$\underline{C}$=CHOEt), 70.93 (O$\underline{CH_2}CH_3$), 49.07 (ring CH_2), 14.94 (CH_3); IR (neat): 1750 cm^{-1} (C=O), 1570 cm^{-1} (C=C), 1323 cm^{-1}, 1014 cm^{-1} (C-O).

5. 3-Octylcyclobutene-1-one

a. Preparation of the Grignard Reagent

In an oven-dried 50 mL round-bottomed flask fitted with a septum inlet were placed magnesium turnings (5 mg-atom,

120 mg). The flask was equipped with a magnetic stirring bar, Claisen head adapter, addition funnel, reflux condenser, and gas outlet (mercury bubbler), flame dried, and the system purged with nitrogen. Anhydrous THF (20 mL) and ethylene dibromide (0.04 mL) were introduced to the reaction flask, followed by dropwise addition of 1-bromooctane (5.80 mmol, 1.12 g) at such a rate so as to maintain a reaction temperature around 30°C (water bath). Stirring was allowed to continue until all of the magnesium disappeared. The reagent thus prepared was used immediately for the alkylation step.

b. Grignard Alkylation of 3-Ethoxycyclobuten-1-one: 3-Ethoxy-1-(1-octyl)-2-cyclobuten-1-ol

A 50 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, addition funnel, and gas outlet (mercury bubbler), the apparatus flame dried, and purged with nitrogen. Freshly distilled, anhydrous THF (5 mL) and 3-ethoxycyclobuten-1-one (3.65 mmol, 0.41 g) were introduced, and the resulting mixture cooled to 0°C. The solution of octylmagnesium bromide (5.00 mmol) prepared above was added dropwise at 0°C over a 15 minute period, and the resulting mixture allowed gradually to warm to room temperature and stir overnight. An aqueous ammonium chloride/ammonium hydroxide solution (10 mL, 1M in both

components) was added to quench the reaction, the aqueous layer saturated with sodium chloride, and the organic layer separated. The aqueous layer was extracted three times with ether (50 mL portions), and the combined organic layers were dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent under reduced pressure, gave, 0.75 g (91%) of the crude cyclobutenol. TLC analysis of this product revealed that it was a mixture of 6 compounds, however the product was used directly for the next step as attempted purification of the produce mixture led to dehydration to a conjugated diene tentatively identified as 3-ethoxy-1,1-(1-octenyl)-2-cyclobutene, although NMR data is inconclusive.

c. Dehydration to the 3-Octylcyclobutenone

The crude 3-ethoxy-1-octyl-2-cyclobuten-1-ol was placed in a 50 mL round-bottomed flask equipped with a magnetic stirring bar and methanol (10 mL) and aqueous 2 N oxalic acid were sequentially added to the flask. The resulting mixture was stirred at room temperature for 3 hours. The methanol was evaporated under reduced pressure, aqueous saturated sodium chloride solution added (15 mL), and the residue extracted into ether (3x50 mL). The combined ether layers after drying (anhydrous $MgSO_4$) were filtered and then the solvent removed to give 0.68 g of an orange liquid. TLC

analysis of this material revealed 9 spots. Purification by column chromatography (silica gel, 5% ether-petroleum ether (500 mL), then 10% ether-petroleum ether) yielded 160 mg (23%) of 3-(1-octyl)-2-cyclobutene-1-one (R_F = 0.36, 10% ether-petroleum ether) as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 5.88 (s, 1H, vinyl H), 3.15 (s, 2H, ring CH_2), 2.56 (t, 2H, J=7.2 Hz, R$\underline{CH_2}$R'CH=CHR), 1.8-1.1 (m, 14H), 0.89 (m, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 188.08 (s, C=O), 181.44 (s, $R_2\underline{C}$=CHR), 134.17 (d, R_2C=$\underline{C}$HR), 50.74 (ring CH_2), 32.19, 31.84, 29.72, 29.32, 29.18, 26.15, 22.68, 14.13 (CH_3); ^{1}H-NMR (acetone-d_6): δ 5.90 (s, 1H, vinyl H), 3.11 (s, 2H, ring CH_2), 2.62 (t, 2H, J=6.8 Hz, R$\underline{CH_2}$R'CH=CHR), 1.8-1.1 (m, 14H), 0.88 (m, 3H, CH_3); ^{13}C-NMR (acetone-d_6): δ 187.84 (C=O), 182.72 ($R_2\underline{C}$=CHR), 134.94 (R_2C=$\underline{C}$HR), 51.62 (ring CH_2), 32.95, 32.84, 30.41, 27.24, 23.69, 14.75 (CH_3), remaining CH_2 peaks overlap with acetone-d_6 septet.

6. 3-Octylcyclobutene-1-one: One-Pot Procedure

The above procedure was modified using the acid hydrolysis step reported for a similar reaction by Danheiser[447]. A 50 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, addition funnel, and gas outlet (mercury bubbler), the apparatus flame dried, and purged with nitrogen. Freshly distilled, anhydrous THF (10 mL) and 3-ethoxycyclobuten-1-

one (4.19 mmol, 0.41 g) were introduced, and the resulting mixture cooled to 0°C. A solution of octylmagnesium bromide (5.00 mmol) prepared above was added dropwise at 0°C over a 15 minute period, and the resulting mixture allowed gradually to warm to room temperature and stir for a total of three hours. The reaction was quenched by the addition of 10% aqueous HCl (10 mL), stirred for 5 minutes, and the organic layer separated. The aqueous layer was extracted with ether (3x30 mL), and the combined ethereal layer was dried (anhydrous $MgSO_4$). Filtration, followed by evaporation of the solvent under reduced pressure, gave the crude product, 0.72 g (95%) as a orange-brown oil. TLC analysis of this product revealed that it was a mixture of 4 compounds. Purification by column chromatography (silica gel, 5% ether-petroleum ether (500 mL), then 10% ether-petroleum ether) yielded 190 mg (25%) of 3-(1-octyl)-2-cyclobutene-1-one (R_F = 0.36, 10% ether-petroleum ether) as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 5.88 (s, 1H, vinyl H), 3.15 (s, 2H, ring CH_2), 2.56 (t, 2H, J=7.2 Hz, R$\underline{CH_2}$R'CH=CHR), 1.8-1.1 (m, 14H), 0.89 (m, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 188.08 (s, C=O), 181.44 (s, $R_2\underline{C}$=CHR), 134.17 (d, R_2C=$\underline{C}$HR), 50.74 (ring CH_2), 32.19, 31.84, 29.72, 29.32, 29.18, 26.15, 22.68, 14.13 (CH_3).

7. <u>3-(11-Trimethylsilyl-10-undecyn-1-yl)2-cyclobutene-1-one</u>

To an oven-dried 250 mL round-bottomed flask fitted

with a septum inlet were placed magnesium turnings (12.2 mg-atom, 300 mg). The flask was equipped with a magnetic stirring bar, addition funnel, reflux condenser, and gas outlet (mercury bubbler), flame dried, and the system purged with nitrogen. Anhydrous THF (23 mL) and ethylene dibromide (0.10 mL) were introduced to the reaction flask, followed by dropwise addition of 1-bromo-11-trimethylsilyl-10-undecyne (11.10 mmol, 3.38 g) at such a rate so as to maintain a reaction temperature around 30°C (water bath). Stirring was allowed to continue until all of the magnesium disappeared (approx. 3 hours). The contents were cooled to 0°C and then a solution of 3-ethoxy-2-cyclobutenone (8.9 mmol, 1.00 g) in dry THF (40 mL) was introduced dropwise over a 15 minute period, and the resulting mixture was allowed to gradually warm to room temperature and stir for a total of three hours (The reaction mixture turned orange-brown in color upon addition). After cooling to 0°C, the reaction was quenched by the addition of 10% aqueous HCl (40 mL), stirred for 5 minutes, and the organic layer separated. The aqueous layer was extracted with ether (3x50 mL), and the combined ethereal layer was dried (anhydrous $MgSO_4$). Filtration, followed by evaporation of the solvent under reduced pressure gave the crude product, 2.41 g (93%) as a orange-brown oil. TLC analysis of the crude product revealed that it was a mixture of approximately 15 compounds.

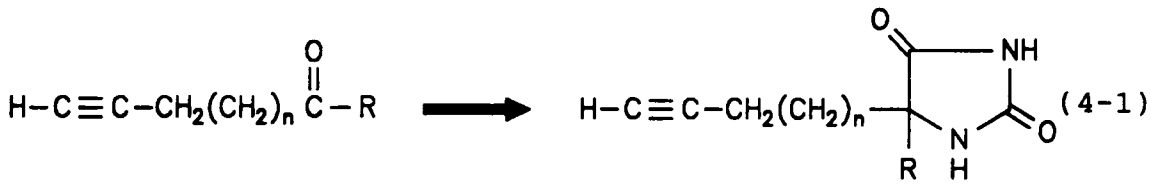
Purification by column chromatography (silica gel, 5% ether-petroleum ether (500 mL), then 10% ether-petroleum ether) yielded no identifiable product.

CHAPTER IV

PREPARATION OF Ω-ALKYNYL ALDEHYDES AND KETONES

A. Introduction

The Strecker and Bucherer-Strecker reactions provide a straightforward synthesis of amino acids from the corresponding carbonyl compound via the intermediate hydantoins. The use of ketones as the carbonyl precursor results in α-methyl-α-amino acids (or the corresponding hydantoin), while the use of aldehydes provides members of the natural α-amino acid series. As was discussed in the Chapter II, one approach to iodovinylamino acids involves an intermediate alkynyl hydantoin. Of necessity, this required the use of acetylenic ketones and aldehydes, which are not commercially available (equation 4-1).



R = H, CH_3

Two basic approaches to these valuable compounds were undertaken. One approach involved a high yield modification of the traditional mercury-catalyzed hydration of an alkyne[465] employing a Hg(II)-Nafion catalyst developed recently by Olah[466,467] (equation 4-2). The strategy was to carry

$$H-C\equiv C-R \xrightarrow[H_2O]{\text{Nafion}-Hg^{II}} CH_3\overset{O}{\overset{\|}{C}}R \qquad (4\text{-}2)$$

out the above reaction on a diyne precursor utilizing a stoichiometric amount of water such that a near statistical distribution of products would be obtained. Separation of the unwanted diketone would then provide the desired acetylenic ketone (equation 4-3). However, the published

$$H-C\equiv C-(CH_2)_n-C\equiv C-H \xrightarrow[1\ \text{equiv}\cdot H_2O]{\text{Nafion}-Hg^{II}} \qquad (4\text{-}3)$$

$$H-C\equiv C-(CH_2)_n\overset{O}{\overset{\|}{C}}CH_3 \quad + \quad H_3C\overset{O}{\overset{\|}{C}}(CH_2)_n\overset{O}{\overset{\|}{C}}CH_3$$

procedure employed a large excess of hydrating agent (water), which, for obvious reasons, would be detrimental to the desired outcome. Thus, the success of this approach rested upon the development of a modified approach using the Hg(II)/Nafion catalyst, whereby a stoichiometric amount of water could be used. Preliminary results employing this methodology on model compounds proved to be quite promising, as the large excess of water used by Olah[467] was found to be unnecessary. For example, heterogeneous Hg(II) catalyzed hydration of 1-octyne using a stoichiometric amount of water provided a 72% isolated yield (95% yield based on recovered

starting material) of 2-octanone (equation 4-4).

$$H-C\equiv C-(CH_2)_5CH_3 \xrightarrow[1\ \text{equiv}\cdot\ H_2O]{\text{Nafion-Hg}^{II}} H_3CC(=O)(CH_2)_5CH_3 \qquad (4\text{-}4)$$

Although Nafion-Hg(II) catalyzed hydration of alkyne substrates using a stoichiometric amount of water appeared to be a viable direct means of preparing acetylenic methyl ketones, the approach was soon discarded due to the limited availability of the necessary dialkyne precursors.

A more convenient approach to alkynoic carbonyl compounds involved the oxidation acetylenic primary alcohols because of the ready availability of the corresponding starting materials. Oxidation of alcohols is a well established route to carbonyl compounds, and numerous methodolologies exist[468]. Among these, oxidation with chromium (VI) reagents has traditionally been the method employed[469]. More recently, a number of chromium oxidizing agents have been reported to oxidize selectively primary alcohols to aldehydes[470,471,472,473,474,475,476,477]. These "non-aqueous" chromium (VI) reagents are more conducive to complexation of the substrate to the chromium (VI) species and therefore to mild oxidation. Four such reagents were considered for the present studies due to their reaction under mild conditions: Collins' reagent (dipyridine chromium (VI) oxide)[478,479,480], pyridinium dichromate

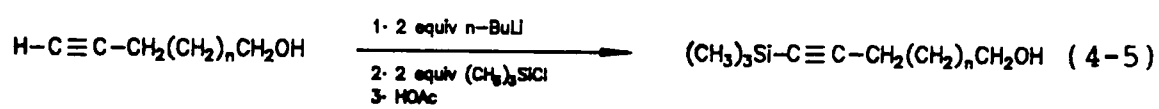
(PDC)[470,481] pyridinium chlorochromate (PCC)[471,482], and polyvinylpyridiniumdichromate (PVPDC)[475]. The most popular of these, the Collins' reagent[476], provides excellent yields of carbonyl compounds, but it presents several difficulties: the chromium trioxide-pyridine complex must be used in large molar excess (6-10 molar equivalents), which makes large scale synthesis impractical; and, the complex is unstable, hygroscopic, and its preparation involves a dangerous procedure (it can ignite spontaneously[479,483]). A more convenient reagent, pyridinium chlorochromate (PCC), efficiently oxidizes a wide range of alcohols to carbonyl compounds using only a modest excess of reagent. Unfortunately, its mild acidic character precludes its use with acid labile substrates or products[482]. Pyridinium dichromate is another effective reagent for the oxidation of alcohols to carbonyl compounds and has received considerable attention in recent years. Numerous modifications of the original procedure have been reported[484,485,486,487,488,489], and it has been reported to be an effective means of preparing α-iodoketones from olefins[490], α,ß-unsaturated-α-iodoaldehydes from the corresponding propargylic alcohols[491], and lactams and lactones from amino alcohols and diols respectively[492]. The mild characteristics of this reagent were also attractive for the oxidation of trimethylsilyl protected terminal acetylenic alcohols, which had

never been reported. Interestingly, PDC had never been used to oxidize non-conjugated alkynyl alcohols. For these reasons, pyridinium dichromate was initially chosen for the oxidation of acetylenic alcohols.

B. Results and Discussion

1. Preparation of Alkynyl Aldehydes and Ketones with Pyridinium Dichromate

A number of alkynyl primary and secondary alcohols were oxidized using PDC, and the results are presented in Table 4-1. The secondary alcohols were not commercially available, and were prepared in the following manner. Beginning with the appropriate commercially available Ω-alkynyl primary alcohol, the terminal acetylenic functionality was first protected with the trimethylsilyl moiety by a procedure reported by Brandsma[446]. Successive treatment of the alkynyl alcohol with two equivalents of n-butyllithium and two equivalents of chlorotrimethylsilane, followed by acetic acid hydrolysis gave the 1-trimethylsilylalkynyl primary alcohol (equation 4-5). Oxidation of the protected alkynyl



(4-5)

alcohol with pyridinium dichromate proceeded smoothly to the corresponding aldehyde without affecting the trimethylsilyl

Table 4-1: Oxidation of Alkynyl Alcohols with Pyridinium Dichromate

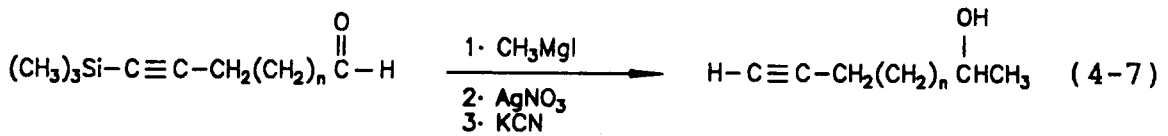
Alcohol	Ratio of Alcohol:PDC	Product	Isolated Yield
4-Pentyn-1-ol	1:2	4-Pentynal	21%
5-Hexyn-1-ol	1:1.5	5-Hexynal	52%
10-Undecyn-1-ol	1:1.5	10-Undecynal	64%
6-Trimethylsilyl-5-hexyn-1-ol	1:1.5	6-Trimethylsilyl-5-hexynal	57%
11-Trimethylsilyl-10-undecyn-1-ol	1:2	11-Trimethylsilyl-10-undecynal	63%
6-Heptyn-2-ol	1:2[a]	6-Heptyn-2-one	80%
11-Dodecyn-2-ol	1:2[a]	11-Dodecyn-2-one	81%
12-Trimethylsilyl-11-dodecyn-2-ol	1:2[a]	12-Trimethylsilyl-11-dodecyn-2-one	84%

[a]Oxidation of the secondary alcohol was performed in the presence of pyridinium trifluoroacetate (0.4 equiv.)[47o]

moiety (equation 4-6). Grignard alkylation with methylmag-

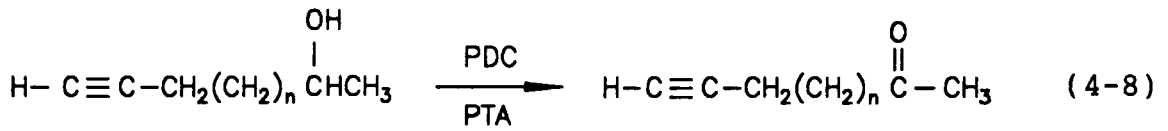
(4-6)

nesium iodide[493], followed by removal of the protecting group by successive treatment with silver nitrate and potassium cyanide[494], gave the desired alkynyl secondary alcohols (equation 4-7). Final oxidation with pyridinium



(4-7)

dichromate in the presence of a catalytic amount of pyridinium trifluoroacetate (PTA) then provided the desired acetylenic methyl ketone[470] (equation 4-8).



(4-8)

Oxidations with pyridinium dichromate were found to be most effective when freshly distilled methylene chloride and freshly ground pyridinium dichromate were used. In some instances, ester formation was observed as a complicating side reaction, possibly indicating over oxidation. This problem was generally eliminated when the reaction

temperature was carefully monitored, and freshly distilled solvent and dry reagents were used. (The oxidation is slightly exothermic, but use of a water bath allows the reaction temperature to be maintained near room temperature). For reactions involving volatile products, sealed reaction tubes were used on occasion. However, inefficient mixing of the reagents brought about by the use of the sealed tube generally did not significantly improve the yield; an increase of the ester side product was observed in some instances. One low molecular weight compound, which consistently gave low isolated yields of the oxidized product with the standard PDC procedure, was 6-trimethylsilyl-5-hexynal. A number of variations of the standard procedure were attempted on this material in an effort to improve the yield of the desired acetylenic aldehyde; these included different isolation techniques, the use of a sealed reaction tube, and the use of a modified PDC procedure employing 4Å molecular sieves and a catalytic amount of anhydrous acetic acid[488]. The results of these studies are presented in Table 4-2. From these results, it is apparent that the use of fresh reagents, followed by chromatographic workup, produces the highest yield of the desired product. As noted earlier, the use of sealed tubes did not lead to a higher yield of the aldehyde due to a side reaction involving ester formation. Likewise, although the modified

Table 4-2: Pyridinium Dichromate Oxidation of 6-Trimethylsilyl 5-Hexyn-1-ol Using Various Modified Procedures

Procedure[a]	Method of Purification[b]	Isolated Yield
A	1,3	47%
A,D	4,2	57%
A	4,2	40%
B	4,2	49%
C	4,2	30%
B	4,2,3	38%
B,D	1,3	27%
B,D,E	4,2	65%
A,D,E	4,2	77%

[a]Procedure
A = Corey procedure[470]
B = Corey procedure; sealed reaction tube; 42-48 hour reaction time
C = Czernecki procedure[489]
D = Freshly distilled anhydrous methylene chloride used
E = Freshly ground pyridinium dichromate used

[b]Method of Purification
1. Removal of solvent by fractional distillation
2. Final distillation of product
3. Column chromatography
4. Removal of solvent under reduced pressure

procedure reported by Czernecki[489] greatly enhanced the rate of reaction (the reaction was over within 15 minutes), the procedure did not lead to an increase in the amount of desired product.

2. Oxidation of Ω-Alkynyl and Trimethylsilyl Protected Alkynyl Alcohols with Various Chromium (VI) Oxidants

During the course of these studies, other chromium (VI) oxidizing agents were also investigated, including the Collins' reagent[475,478], dipyridine chromium(VI) oxide - acetic acid (CPA)[473], pyridinium chlorochromate (PCC)[482], pyridinium chlorochromate buffered with sodium acetate[471], and polyvinylpyridinium dichromate (PVPDC)[475]. A number of Ω-alkynyl and trimethylsilyl protected alkynyl primary alcohols were subjected to these oxidants, and the results are presented in Table 4-3. Results obtained using the normal PDC procedure are also included for comparison. A number of points deserve elaboration. Although hailed as an effective and cost efficient oxidant, poor results were obtained using the polymer supported reagent; unreacted starting material was the major compound recovered upon workup. As shown in Table 4-3, better yields of alkynyl aldehydes were obtained when either the Collin's reagent or PCC were employed as the oxidizing agent. Surprisingly, the trimethylsilyl moiety was stable to two of the other

Table 4-3: Oxidation of Terminal Alkynyl and Trimethylsilyl Protected Primary Alcohols with Various Chromium (VI) Reagents

Substrate	Oxidant[a]	Isolated Yield Alkynyl Aldehyde
4-Pentyn-1-ol	PDC	21%
4-Pentyn-1-ol	Collins	29%
4-Pentyn-1-ol	PCC	28%
5-Hexyn-1-ol	PDC	52%
5-Hexyn-1-ol	CPA	13%
5-Hexyn-1-ol	PCC/NaOAc	86%
10-Undecyn-1-ol	PDC	64%
10-Undecyn-1-ol	PVPDC	8%
10-Undecyn-1-ol	Collins	91%
10-Undecyn-1-ol	PCC	67%
10-Undecyn-1-ol	PCCb	81%
10-Undecyn-1-ol	PCC[b,c]	95%
6-Trimethylsilyl-5-hexyn-1-ol	PDC	47%
6-Trimethylsilyl-5-hexyn-1-ol	Collins	79%
6-Trimethylsilyl-5-hexyn-1-ol	PCC/NaOAc	99%
11-Trimethylsilyl-10-undecyn-1-ol	PDC	63%
11-Trimethylsilyl-10-undecyn-1-ol	PCC/NaOAc	93%

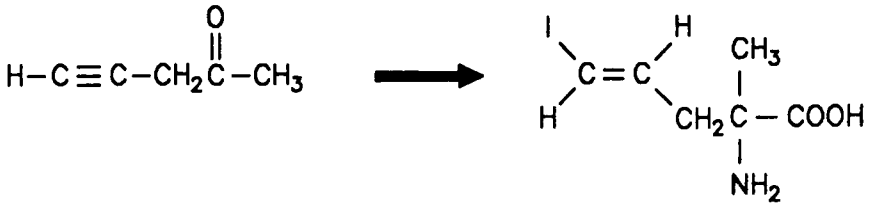
Table 4-3 (continued)

[a]Unless otherwise noted, the published procedure (referenced in text above) was used
[b]PCC was dried under vacuum 24 hours prior to use
[c]Freshly distilled, anhydrous methylene chloride was used

oxidants tested: the Collins' reagent, and to pyridinium chlorochromate as long as the reaction medium was buffered with sodium acetate. The later result was unexpected, since silicon-carbon bond cleavage has been observed in the presence of mild bases such as sodium bicarbonate[495], potassium carbonate[496,497,498], and sodium borate[499,500]. Clearly, the modified pyridinium chlorochromate procedure was the method of choice for the oxidation of trimethylsilyl protected alkynyl alcohols. No attempt was made to oxidize a trimethylsilyl alkynyl alcohol using the standard PCC procedure due to suspected protodesilyation. Finally, the use of freshly prepared reagents made a difference in observed yield in pyridinium chlorochromate oxidations as well, as shown in the two entries involving PCC oxidation of 10-undecyn-1-ol. In the latter case, use of freshly distilled anhydrous methylene chloride and anhydrous PCC (the pyridinium chlorochromate was dried under vacuum 24 hours prior to use) gave a near quantitative yield of 10-undecynal.

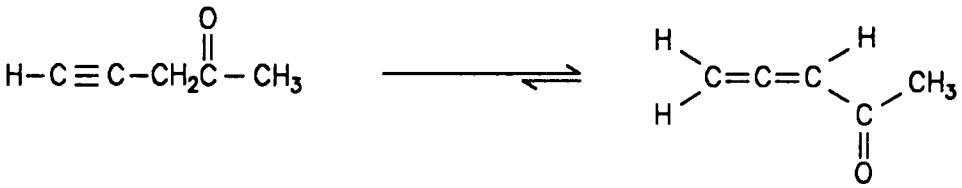
3. Attempted Isolation of 4-Pentyn-2-one

Of particular interest was 4-pentyn-2-one; conversion of this carbonyl compound to the corresponding iodovinyl amino acid would result in a pharmaceutical agent of optimum chain length for imaging studies[425] (equation 4-9). This



(4-9)

compound has eluded numerous investigators, and very few successful reports of its synthesis have been reported[501,-502]. Isomerization of the thermodynamically more stable allenic isomer occurs readily (equation 4-10).

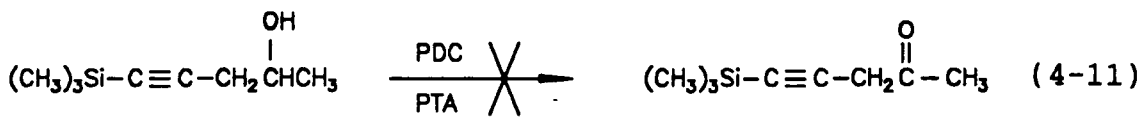


(4-10)

Although numerous attempts to isolate this compound were made, all met with failure. In almost all instances, the presence of an acetylenic ketone in the crude reaction mixture was observed on the basis of TLC and IR analysis, but pure product was never obtained. Product volatility is an obvious problem; however, steps were taken to minimize this as the source of failure. For example, in one experiment, Corey's PDC - DMF procedure[470] was used to oxidize 4-pentyn-2-ol, with the intention of distilling the product from the higher boiling dimethylformamide. Thin layer chromatography analysis of the product mixture using a 2,4-dinitrophenylhydrazine indicator[503] showed the presence of

a carbonyl compound. Room temperature vacuum distillation coupled with a double liquid nitrogen trap led to a 1% yield of the desired 4-pentyn-2-one. However, even this material was contaminated with trace amounts of DMF which, unfortunately, prohibited crystallization of the 2,4-dinitrophenylhydrazone derivative. The apparatus used in this experiment is shown in Figure 4-1.

Two attempts at increasing the molecular weight of the starting alkynyl alcohol by using a protecting group were also made. The 5-trimethylsilyl-4-pentyn-2-ol analogue was prepared by a procedure described earlier. Oxidation of this material with pyridinium dichromate in the presence of pyridinium trifluoroacetate[470] using a sealed reaction vessel, followed by careful fractional distillation, also gave no isolated product, although as usual, the presence of a carbonyl compound was indicated by TLC analysis (equation 4-11). In another experiment, the dicobalt hexacarbonyl



(4-11)

complex[504,505] of 4-pentyn-2-ol was prepared (equation 4-12). This complex was previously used as a protecting group for the alkyne functionality during the hydroboration reaction[506] (equation 4-13). However, upon oxidation of this

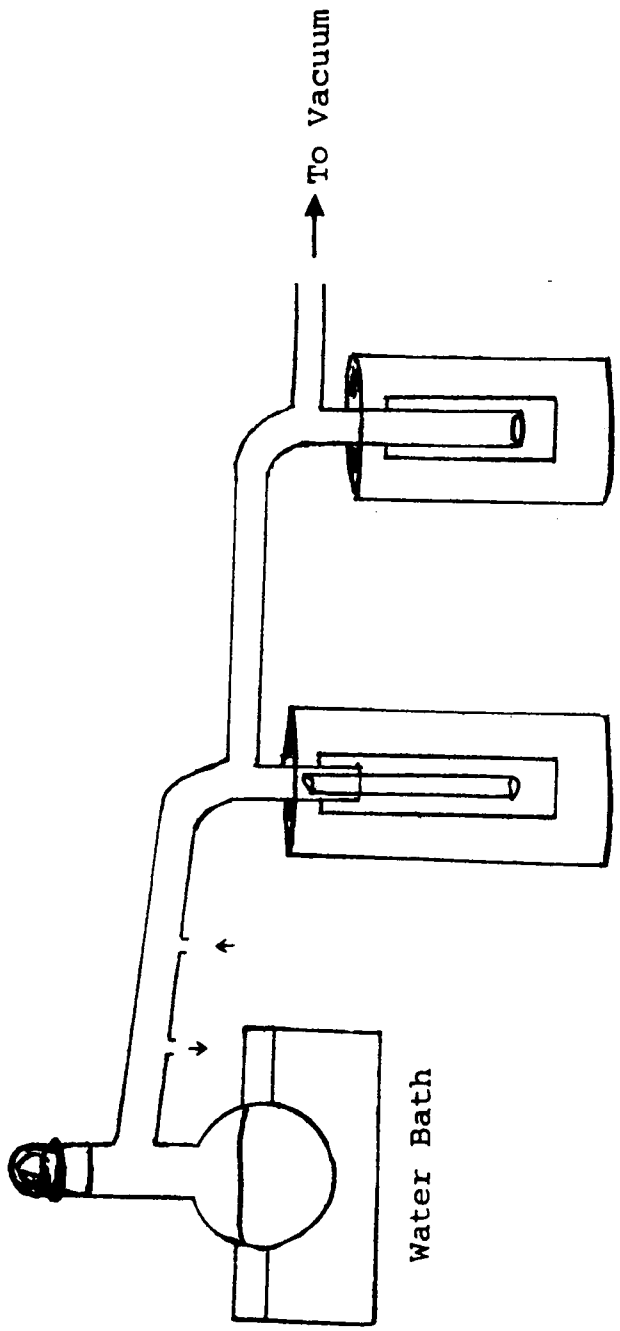
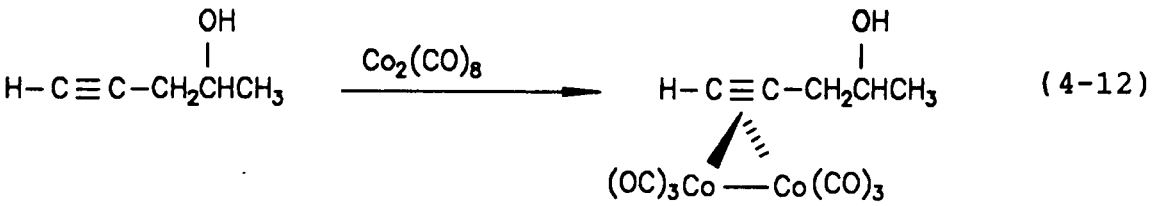
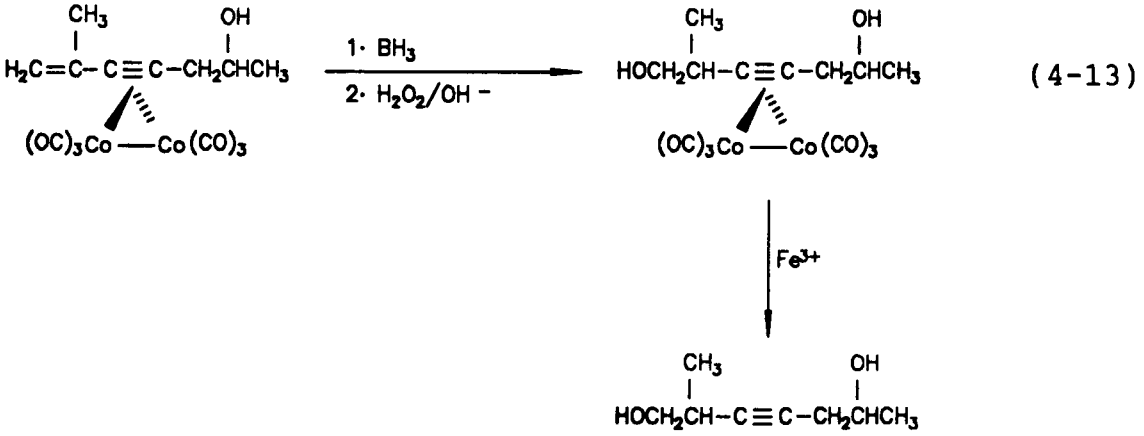


Figure 4-1. Apparatus Used for Attempted Preparation of 4-Pentyne-2-one Using PDC - DMF Procedure.

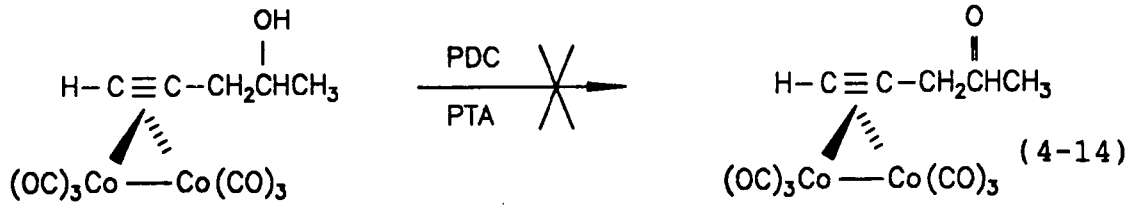


(4-12)



(4-13)

complex using the modified PDC procedure reported by Hercovici and Antonakis[484], only unreacted starting material was recovered, in a 40% yield. Neither the desired compound, nor the unprotected propargylic ketone was obtained (equation 4-14). The results of the various experiments



(4-14)

performed in an attempt to prepare 4-pentyn-2-one are shown in Table 4-4.

Table 4-4: Attempts to Prepare 4-Pentyn-2-one

Procedure[a]	Method of Isolation[b]	Isolated Yield	Result[c]
PCC	A	0%	1
PDC/PTA	A	0%,	1
PDCd	B	0%	1,2
PDC-DMF	C	--	1,3,4
PDC-DMF	D	1%	1,3,5

[a]Unless otherwise noted, the published procedure was used

[b]Methods used in attempted isolation
- A = Removal of solvent by fractional distillation
- B = Removal of solvent and distillation of product by trap-to-trap distillation under reduced pressure
- C = Fractional distillation of product from reaction mixture
- D = Distillation of product from higher boiling reaction mixture by fractional vacuum distillation employing a liquid nitrogen trap

[c]Results
1. Presence of a ketone product confirmed by TLC analysis
2. Codistillation with methylene chloride observed
3. Product identified by GC and NMR analysis
4. No yield was able to be determined due to presence of pyridine and dimethylformamide which codistilled
5. Presence of trace amounts of pyridine and dimethyl formamide in the isolated product inhibited crystalization of the 2,4-dinitrophenylhydrazine derivative

[d]Czernecki procedure[488] with sealed reaction tube used

4. Air Oxidation of Aldehydes in the Presence of Alkyne Functionality

During the course of these studies, an extremely fast air oxidation of 10-undecynal was observed. For example, if a pure sample of the prepared aldehyde was left open to the air overnight, nearly complete oxidation of this compound to the corresponding carboxylic acid was observed by the following day (equation 4-15). This turned out to be

$$H-C\equiv C-CH_2(CH_2)_7CHO \xrightarrow{air} H-C\equiv C-CH_2(CH_2)_7COOH \quad (4\text{-}15)$$

inconvenient at first, and therefore fresh batches of this material had to be prepared and used immediately in the next step of the synthesis. Although simple air oxidation of aldehydes is well known, the speed with which the oxidation of this compound proceeded was quite surprising and, for purposes of this work, unfortunate. Preliminary studies were conducted on a model compound (heptaldehyde) to investigate this facile oxidation. Oxidations of heptaldehyde in the presence of an alkyne (octyne) were investigated. A solution of heptaldehyde (5 mmol) and 1-octyne (5 mmol) was allowed to set open to the air for three days. In a parallel experiment, a trace amount of decanoic acid was added to the reaction. A control experiment using the neat heptaldehyde reagent was also included. After three days

open to the air, ^{1}H- and ^{13}C-NMR spectra were obtained on each reaction mixture. The NMR spectra of these model studies were analyzed in the following manner. The integrated peak areas of the carboxylic acid and aldehyde proton resonances provided a COOH:CHO ratio, corresponding to the amounts of each compound in the reaction mixture. Similar ratios were obtained by comparing the intensities of the carbon resonances associated with the methylene carbon adjacent (α) to the aldehyde and carboxylic acid functionality; the intensities of the carbon resonance corresponding to the methylene carbon beta to the aldehyde and carboxylic acid functionalities were also measured. For example, in the experiment involving the solution containing heptaldehyde and 1-octyne with a trace amount of added decanoic acid, the ^{13}C-NMR spectrum of the reaction mixture after three days gave plotted peak intensities of 8118 and 879 for the ^{13}C-NMR resonances corresponding to the methylene carbon adjacent to the carboxyl and aldehyde group, providing a COOH:CHO ratio of 9.24:1. The corresponding resonances associated with the methylene carbon beta to the carboxylic acid and aldehyde functionalities gave integrated peak intensities of 10474 and 1101 respectively, yielding a COOH:CHO ratio of 9.51:1. Analysis of the integrated peak area associated with the carboxylic acid and aldehyde proton resonances gave a comparable COOH:CHO ratio of 9:1.

Analysis of the spectra obtained from the other experiments was conducted in the same manner and the results are tabulated in Table 4-5. As is apparent from the data presented, although partial autoxidation of the aldehyde is observed over the three day period, the rate was enhanced in the presence of added 1-octyne. An even more pronounced rate enhancement was observed in the presence of both added 1-octyne and a trace amount of decanoic acid.

The effect of vigorous agitation was also investigated. When an equimolar mixture of heptaldehyde and 1-octyne were stirred under air for four hours, NMR analysis of the reaction mixture revealed that nearly complete oxidation to the carboxylic acid had occurred (COOH:CHO ratios of 11:1 and 13.3:1 were obtained, respectively, from the ^{1}H- and ^{13}C-NMR spectra). As a control experiment, neat heptaldehyde was stirred in an open flask for a four hour period. As was expected, simple stirring of a neat solution of heptaldehyde catalyzed the auto oxidation reaction. Ratios of 8.3:1 and 9.0:1 were obtained from the ^{1}H- and ^{13}C-NMR spectra of this reaction mixture, respectively. However, as can be seen from the NMR data presented above, it would appear the presence of 1-octyne in the reaction mixture further enhanced the rate of the autoxidation process. The results of these experiments are also included in Table 4-5.

A solution to the autoxidation problem was found from

Table 4-5: Effects of Added Alkyne and Carboxylic Acid on the Autoxidation of Heptaldehyde

Reagents[a]	Conditions[b]	COOH:CHO ratio(^{1}H)[c]	COOH:CHO ratio(^{13}C)[c] α-CH_2	β-CH_2	average
Heptaldehyde	A	0.30	0.30	0.29	0.30
Heptaldehyde + Decanoic acid	A	0.33	0.35	0.29	0.32
Heptaldehyde + 1-Octyne	A	2.19	2.35	2.56	2.45
Heptaldehyde + Decanoic acid + 1-Octyne	A	9.0	9.51	9.24	9.38
Heptaldehyde	B	8.3	8.92	9.08	9.00
Heptaldehyde + 1-Octyne	B	11	14.3	12.4	13.3
Heptaldehyde	C	0	0	0	0
Heptaldehyde + 1-Octyne	C	0	0	0	0

[a]Amounts of each reagent were as follows: heptaldehyde (5mmol), 1-octyne (5mmol), decanoic acid (1 drop).
[b]Conditions
A = Neat reagents, reaction mixture left open to the air undisturbed for three days
B = Neat reagents, reaction mixture was stirred open to air for four hours
C = Reagents were disolved in THF (5 mL) and stirred for six hours open to the air

[c]COOH:CHO ratios are normalized. For example, a value of 0.30 corresponds to a ratio of 0.30:1.

the results of two further experiments employing THF solutions. When a THF solution of heptaldehyde was stirred under air for 6 hours, no oxidation to the carboxylic acid. Likewise, when an equimolar mixture of heptaldehyde and 1-octyne in THF was stirred under air for 6 hours, no autoxidation was observed (equation 4-16). The presence of THF

$$CH_3(CH_2)_5CHO \xrightarrow[\text{air, THF}]{\text{1-octyne}} \text{No Reaction} \qquad (4\text{-}16)$$

apparently inhibits the autoxidation process. Thus, 10-undecynal could be stored by dissolving it in THF. It was later recognized that commercial THF, which was used in these experiments, contains hydroquinone as an added stablizer. It is quite probable that the hydroquinone which is present, is responsible for quenching the autoxidation process, and not the THF. No experiments employing distilled THF were conducted to ascertain this fact.

C. Conclusion

The oxidation of Ω-alkynyl alcohols with pyridinium dichromate proved to be a viable and convenient route to the corresponding alkynyl aldehydes and ketones. Excluding the C-5 ketone discussed, good yields of the desired alkynyl carbonyl compounds were obtained using the pyridinium dichromate procedure. Oxidation of such compounds had

previously gone unreported. In efforts to improve isolated yields of the acetylenic aldehydes, a number of modifications of the PDC procedure were attempted. Best results were obtained when care was taken to insure strict anhydrous conditions and when freshly ground pyridinium dichromate was employed. The previously unreported PDC oxidation of trimethylsilyl protected acetylenic alcohols also proved successful.

Isolated yields of the alkynyl aldehydes were consistently lower than those obtained when alkynyl secondary alcohols were oxidized with pyridinium dichromate. This led to the study involving the use of other chromium (VI) oxidants. Collins' oxidation invariably gave comparable or better yields of the desired acetylenic aldehydes than did the PDC procedure, however the use of this reagent for large scale synthesis proved quite dangerous and impractical (even a 50 mmol scale oxidation requires 300 mmoles of the chromium oxide - pyridine complex and 1500 mL of anhydrous methylene chloride). But for small scale synthesis (<5mmol), it is an extremely mild and efficient route to alkynyl aldehydes and ketones. A much more practical method employs pyridinium chlorochromate as the oxidizing agent. When care is taken to insure strictly anhydrous conditions, near quantitative yields of the desired acetylenic aldehyde can be obtained. For the oxidation of

trimethylsilyl protected primary alcohols, the buffered PCC procedure is without doubt the superior method, providing quantitative yields of the corresponding trimethylsilylated acetylenic aldehyde.

All attempts at isolation of the unstable 4-pentyne-2-one proved fruitless. In only one instance, when distillate was collected with a liquid nitrogen trap, was product realized, but, only in a 1% yield.

The mercury (II) catalyzed hydration of an alkyne procedure employing the Nafion-Hg catalyst proved to be a promising route to alkynyl methyl ketones. In model studies, the use of a stoichiometric amount of water as the hydrating species gave high yields of the ketone. As new methods of obtaining dialkynes are discovered, this methodology could provide a viable route to acetylenic methyl ketones.

D. Experimental

1. General

All glassware, syringes, and syringe needles were oven-dried 24 hours prior to use. All NMR spectra were recorded on a JEOL-FX-90Q pulsed FT-NMR spectrometer in deuteriochloroform, $CDCl_3$ solutions. The 1H spectra were referenced using tetramethylsilane, TMS, as an internal standard (δ = 0.0 ppm). Exchangeable protons were determined by shaking

with deuterium oxide. The ^{13}C-NMR spectra were referenced to either $CDCl_3$ (δ = 77.1 ppm), or TMS (δ = 0.0 ppm). Infrared spectra were obtained on a Perkin-Elmer Model 1330 spectrometer. Melting points were recorded using a Fisher-Johns melting point apparatus and are uncorrected. Thin layer chromatographic analyses were performed on Fisherbrand Silica Gel GF 250 μm TLC plates using either a phosphomolybdic acid or a 2,4-dinitrophenylhydrazine solution as an indicator. Column chromatographic separations were accomplished using Davisil 60-200 mesh silica gel. Gas chromatographic analyses were obtained using a Varian Model 3700 gas chromatograph employing an SE-30 column which was interfaced with a Hewlett-Packard Model 3390A integrator. Elemental analyses were performed on each of the new alkynyl ketones by Galbraith Laboratories, Knoxville, Tennessee. Elemental analyses were not generally performed on intermediate 1-trimethylsilyl-alkynyl alcohols and aldehydes since they were utilized to prepare ketones which were fully characterized. The commercially available chemicals, their manufacturers, and the methods of purification used, when applicable, are listed in Table 4-6. All other reagents were prepared as described below.

Table 4-6: Manufacturer and Methods of Purification of Commercially Available Chemicals

Reagent	Manufacturer[a]	Method of Purification[b]
Acetic Acid	F, M	
Acetic Acid, anhydrous	F	1
Acetone	F, AS	
Benzophenone	A	
Boric Acid	M	
n-Butyllithium, 1.6 M	A	
3-Butyn-1-ol	FN	
3-Butyn-2-ol	FN	
Celite	F	
Chlorotrimethylsilane	A	
Chromium Trioxide, anhydrous	F	2
Decanoic Acid	E	3
Dimethyl Formamide, anhydrous	F	4, 5, 6
2,4-Dinitrophenylhydrazine	E	
Ethanol	AS, US	
Ethyl Acetate	F, M	
Ethyl Ether	F, M	
Ethyl Ether, anhydrous	F, M	7, 8
Florisil	F	

Table 4-6 (continued)

Reagent	Manufacturer[a]	Method of Purification[b]
Heptaldehyde	E	3
5-Hexyn-1-ol	FN, W	
Hydrochloric Acid	F, M	
Iodine	F	
Magnesium, turnings	F, R	
Magnesium Sulfate, anhydrous	F, M	
Mercuric Oxide	F	
Methylene Chloride	F, AS	3
Methylene Chloride, anhydrous	F	4, 9, 6
Methyl Iodide	A	
3A Molecular Sieves	F	10
4A Molecular Sieves	F	11
Nafion	D	10
Dicobalt Octacarbonyl	AL	
1-Octyne	W	
Pentane	M	
4-Pentyn-1-ol	W	
4-Pentyn-2-ol	W	
Petroleum Ether	F, AS	3
Phosphomolybdic Acid	G	

Table 4-6 (continued)

Reagent	Manufacturer[a]	Method of Purification[b]
Polyvinylpyridinium-Dichromate	A	12
Potassium Cyanide	F	
Pyridine, anhydrous	BJ, F	4, 9, 6
Pyridinium Dichromate	A	2
Pyridinium Trifluoroacetate	A	
Silica Gel	DA	
Silver Nitrate	M	
Sodium	A	
Sodium Acetate, anhydrous	F	
Sodium Chloride	F, DC	
Sodium Thiosulfate	F	
Sulfuric Acid	F, M	
Tetrahydrofuran	F	
Tetrahydrofuran, anhydrous	F, M	13, 8
10-Undecyn-1-ol	FN, W	

[a]Manufacturers
A = Aldrich Chemical Company
AL = Alfa Chemical Company
AS = American Scientific Company
BJ = Burdick and Jackson Laboratories
D = Dupont Chemical Company
DA = Davison Chemical Company

Table 4-6 (continued)

DC = Diamond Salt Company
E = Eastman Chemical Company
F = Fisher Chemical Company
FN = Farchan Acetylenes
G = General Chemical Company
R = Reade Manufacturing Company
US = US Industrial Chemicals
W = Wiley Organics

[b]Methods of Purification

1. Distilled from triacetylborate (prepared by heating boric acid and acetic anhydride, 1:5 w/w at 60°C overnight, and then filtering and drying the crystalline product) under nitrogen
2. Dried under vacuum 24 hours prior to use
3. Distilled
4. Pre-dried over KOH
5. Distilled from anhydrous barium oxide under nitrogen
6. Stored over activated 4A molecular sieves under nitrogen
7. Distilled from LAH under nitrogen
8. Distilled from Na/benzophenone under argon
9. Distilled from P_2O_5 under nitrogen
10. Prepared as described in experimental section
11. Dried under vacuum at 100°C for 24 hours prior to use
12. Reagent was soaked in distilled water for one hour prior to use
13. Pre-dried over CaH_2

2. Protection of Terminal Alkynes

a. General Procedure

The synthesis of 6-trimethylsilyl-5-hexyn-1-ol is representative. A 250 mL round-bottomed flask equipped with a septum inlet, magnetic stirring bar, pressure equalizing funnel, and gas outlet (mercury bubbler) was assembled while hot, and then flushed with nitrogen while flame drying. The reaction flask was cooled to -78°C under a stream of nitrogen and then n-butyllithium (20 mmol, 12.9 mL of a 1.55 M solution in hexane) was transferred into the reaction flask by means of a double-ended needle. Anhydrous THF (20 mL) was added to the flask via syringe and the solution cooled to -78°C. A solution of 5-hexyn-1-ol (10 mmol, 0.98 g) in anhydrous THF (10 mL) was transferred to the addition funnel, and added dropwise to the flask while stirring at-78°C for 0.5 hours. Chlorotrimethylsilane (21 mmol, 2.66 mL) was then added dropwise, at -78°C, and the mixture stirred for 2.5 hours. During this period, the flask was allowed to warm gradually to 0°C. Acetic acid (25%, 40 mL) was then added at 0°C, and mixture stirred at room temperature for 1 hour. The organic layer was separated and the aqueous layer extracted into ether (4x50 mL). The combined etheral layer was washed with aqueous 1 N HCl (50 mL), saturated brine (50 mL) and dried over anhydrous $MgSO_4$. Filtration, followed by evaporation of the solvent,

gave a crude yellow oil. Purification by flash column chromatography (silica gel, 15% ethyl acetate-petroleum ether) afforded 1.65 g (96%) of 6-trimethylsilyl-5-hexyn-1-ol as a colorless oil, bp 219.5°C; ^{1}H-NMR ($CDCl_3$): δ 4.42 (s, 1H, OH), 3.65 (t, 2H, J=5.9 Hz, $\underline{CH_2}OH$), 2.26 (t, 2H, J=6.6 Hz, $\underline{CH_2}C{\equiv}C$), 2.75-2.5 (m, 4H, 0.14 (s, 9H, $(CH_3)_3Si$-); ^{13}C-NMR ($CDCl_3$): δ 107.16 ($(CH_3)_3Si\underline{C}{\equiv}C$), 84.71 ($(CH_3)_3Si$-$C{\equiv}\underline{C}$), 62.04 ($\underline{CH_2}OH$), 31.59, 24.88, 19.57 ($CH_2$'s), 0.12 ($(CH_3)_3Si$-); IR (neat): 3340 cm^{-1} (br, OH), 2180 cm^{-1} (C≡C).

b. 11-Trimethylsilyl-10-undecyn-1-ol

Reaction of 10-undecyn-1-ol (25 mmol, 4.21 g) with n-butyllithium (50 mmol, 32.3 mL of a 1.55 M solution) at -78° C, followed by successive treatment with chlorotrimethylsilane (52.5 mmol, 6.7 mL) and acetic acid (25%, 20 mL) gave 5.98 g (99%) of 11-trimethylsilyl-10-undecyn-1-ol as a colorless oil after purification by flash column chromatography (silica gel, 10% ethyl acetate-petroleum ether) bp 297°C, 98-108°C (0.10-0.15 Torr); ^{1}H-NMR ($CDCl_3$): δ 3.62 (t, 2H, J=6.4 Hz, $\underline{CH_2}OH$), 2.20 (t, 2H, J=6.4 Hz, $\underline{CH_2}C{\equiv}C$-), 1.81 (s, 1H, OH), 1.31 (m, 14H), 0.14 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR ($CDCl_3$): δ 107.76 ($(CH_3)_3Si\underline{C}{\equiv}C$), 84.31 ($(CH_3)_3Si$-$C{\equiv}\underline{C}$), 62.96 ($\underline{C}H_2OH$), 32.81, 29.48, 29.40, 29.05, 28.80, 28.64, 25.77, 19.87 (CH_2's), 0.21 ($(CH_3)_3Si$); IR (neat):

3340 cm^{-1} (br, OH), 2180 cm^{-1} (C≡C).

c. 5-Trimethylsilyl-4-pentyn-2-ol

Reaction of 4-pentyn-2-ol (50 mmol, 4.21 g) with n-butyllithium (100 mmol, 64.6 mL of a 1.55M solution) at -78°C, followed by successive treatment with chlorotrimethylsilane (105 mmol, 11.41 g) and acetic acid (20 mL, 25% solution gave 7.40 g (95%) of 5-trimethylsilyl-4-pentyn-2-ol after flash column chromatography (10% ethyl acetate-petroleum ether); ^{1}H-NMR ($CDCl_3$): δ 4.05 (s, 1H, OH), 3.91 (m, 1 H, RC<u>H</u>(OH)CH_3), 2.40 (d, 2H, J=7.6 Hz, HC≡C<u>C</u>H_2CH(OH)-CH_3), 1.27 (d, 3H, RCH(OH)<u>C</u>H_3), 0.16 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR ($CDCl_3$): δ 103.27 ($(CH_3)_3Si$<u>C</u>≡CR), 87.26 ($(CH_3)_3$SiC≡<u>C</u>R), 66.35 (HC≡CCH$_2$<u>C</u>H(OH)CH_3), 30.27 (CH_2), 22.09 (CH_3), 0.01 ($(CH_3)_3Si$).

3. Oxidation of Primary Alkynyl Alcohols with Pyridinium Dichromate by Standard Method[470]

a. General Procedure

The synthesis of 11-trimethylsilyl-10-undecynal is representative. To an oven-dried 250 mL round-bottomed flask fitted with a septum inlet was added freshly ground pyridinium dichromate (63.46 mmol, 23.87 g). The flask was equipped with a magnetic stirring bar, reflux condenser, and a gas outlet (mercury bubbler). The apparatus was assembled

while hot, purged with nitrogen while flame drying, and allowed to come to room temperature under a stream of nitrogen. Anhydrous methylene chloride (60 mL) was added to the flask, followed by a solution of 11-trimethylsilyl-10-undecyn-1-ol (31.73 mmol, 7.63 g) dissolved in anhydrous methylene chloride (5 mL). The mixture was stirred at room temperature for 20 hours, during which time the reaction mixture became dark and thick. The reaction mixture was diluted with ether (50 mL) and the liquid layer decanted. The tarry residue was washed repeatedly with ether (50 mL portions) until the residue became powdery. The combined etheral layers were then filtered through a short column of silica gel to remove the insoluble chromium by-products. Evaporation of the solvent, followed by purification by column chromatography (silica gel, 5% ethyl acetate-petroleum ether), gave 4.80 g (63%) of 11-trimethylsilyl-10-undecynal as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 9.76 (t, 1H, J=1.75 Hz, CHO), 2.43 (t, 2H, J=6.5 Hz, $\underline{CH_2}CHO$), 2.21 (t, 2H, J=6.4 Hz, $\underline{CH_2}C{\equiv}C$), 1.32 (m, 12H), 0.14 (s, 9H, $(CH_3)_3$-Si); ^{13}C-NMR ($CDCl_3$): δ 202.81 (CHO), 107.65 ($(CH_3)_3Si\underline{C}{\equiv}C$-R), 43.92 ($\underline{CH_2}CHO$), 29.21, 29.10, 28.86, 28.70, 28.59, 22.09, 19.84 (CH_2's), 0.23 ($(CH_3)_3Si$); IR (neat) 2932 cm^{-1} (CH_2's), 2722 cm^{-1} (CHO), 2185 cm^{-1} (C≡C, 1730 cm^{-1} (C=O), 1243 cm^{-1}, 845 cm^{-1}, 767 cm^{-1}; 2,4-dinitrophenylhydrazone derivative, mp 74.5-75.5°C. Anal. calc for $C_{20}H_{30}N_4O_4Si$:

C, 57.39; H, 7.22; N, 13.39; Si, 6.71. Found: C, 57.22; H, 7.25; N, 13.41; Si, 6.39.

b. 6-Trimethylsilyl-5-hexynal

Reaction of 6-trimethylsilyl-5-hexyn-1-ol (5.93 mmol, 1.00 g) with pyridinium dichromate (9.0 mmol, 3.39 g) in anhydrous methylene chloride (8.5 mL) gave 0.57 g (57%) of 6-trimethylsilyl-5-hexynal as a colorless oil after column chromatography (silica gel, methylene chloride); ^{1}H-NMR ($CDCl_3$): δ 9.80 (t, 1H, J=1.3 Hz, CHO), 2.59 (t, 2H, J=7.0 Hz, $\underline{CH_2}CHO$), 2.30 (t, 2H, J=6.8 Hz, $\underline{CH_2}C{\equiv}C$), 1.83 (m, 2H, CH_2), 0.14 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR ($CDCl_3$): δ 201.73 (CHO), 105.87 ($(CH_3)_3Si\underline{C}{\equiv}CR$), 85.77 ($(CH_3)_3SiC{\equiv}\underline{C}R$), 42.65 ($\underline{CH_2}CHO$), 21.00, 19.21 ($CH_2$'s), 0.07 ($(CH_3)_3Si$); IR (neat): 2920 cm^{-1} (CH_2), 2860 cm^{-1}, 2760 cm^{-1} (CHO), 2178 cm^{-1} (C≡C), 1730 cm^{-1} (C=O), 1245 cm^{-1}, 848 cm^{-1}, 768 cm^{-1}; 2,4-dinitrophenylhydrazone derivative, mp 109.5-110°C.

c. 10-Undecynal

Reaction of 10-undecyn-1-ol (50 mmol, 8.41 g) with pyridinium dichromate (75 mmol, 28.2 g) in anhydrous methylene chloride (75 mL) gave 5.32 g (64%) of 10-undecynal as a colorless oil after column chromatography (silica gel, 5% ethyl acetate-petroleum ether); ^{1}H-NMR ($CDCl_3$): δ 9.75 (t, 1H, J=1.75 Hz, CHO), 2.42 (t, 2H, J=7.2 Hz, $\underline{CH_2}CHO$), 2.16

(t, 2H, $\underline{CH_2}C{\equiv}C$), 1.97 (t, 1H, J=2.8 Hz, $\underline{H}C{\equiv}C$), 1.93 (m, 12H); ^{13}C-NMR ($CDCl_3$): δ 202.87 (CHO), 84.66 ($HC{\equiv}\underline{C}R$), 68.16 ($H\underline{C}{\equiv}CR$), 43.89 ($\underline{CH_2}CHO$), 29.21, 29.10, 28.89, 28.64, 28.42, 22.06, 18.38 (CH_2's); IR (neat): 3295 cm^{-1} (C≡CH), 2840 cm^{-1}, 2720 cm^{-1} (CHO), 2120 cm^{-1} (C≡C), 1718 cm^{-1} (C=O); 2,4-dinitrophenylhydrazone derivative, mp 85.5°C (lit[507] 86°C).

d. 5-Hexynal

Reaction of 5-hexyn-1-ol (20 mmol, 1.96 g) with pyridinium dichromate (30 mmol, 11.29 g) in anhydrous methylene chloride (30 mL) gave 1.0 g (52%) of 5-hexynal as a colorless oil after column chromatography (silica gel, 10% ethyl acetate-petroleum ether); ^{1}H-NMR ($CDCl_3$): δ 9.80 (t, 1H, J=1.3 Hz, CHO), 2.63 (t, 2H, J=7.0 Hz, $\underline{CH_2}CHO$), 2.28 (t, 2H, J=6.8 Hz, $C{\equiv}C\underline{CH_2}$), 2.0-1.7 (m, 3H, CH_2, HC≡C); ^{13}C-NMR ($CDCl_3$): δ 201.73 (C=O), 83.17 ($HC{\equiv}\underline{C}R$), 69.38 ($H\underline{C}{\equiv}CR$), 42.54 ($\underline{CH_2}CHO$), 20.84, 17.78 (CH_2's); IR (neat): 3295 cm^{-1} (H-C≡C), 2920 cm^{-1} (CH_2), 2840 cm^{-1}, 2740 cm^{-1} (CHO), 2130 cm^{-1} (C≡C), 1725 cm^{-1} (C=O), 1112 cm^{-1}, 906 cm^{-1}, 845 cm^{-1}; 2,4-dinitrophenylhydrazone derivative, mp 102.5°C (lit[133] 90-91°C. Anal. Calc. for $C_{12}H_{12}N_4O_4$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51,71; H, 4.46; N, 19.94.

e. 4-Pentynal

4-Pentyn-1-ol (297.2 mmol, 25.0 g) was treated with pyridinium dichromate (594 mmol, 223.6 g) in anhydrous methylene chloride (500 mL). After 20 hours, the mixture was diluted with ether (100 mL) and the liquid layer decanted off. The tarry residue was washed repeatedly with ether (100 mL portions) until the residue became granular. The combined ethereal fractions were filtered through a short silica gel column to yield a light brown oil. Purification by column chromatography (silica gel, methylene chloride), removal of the solvent by fractional distillation using a 40 cm packed glass bead column, and final distillation of the product (40°C, 20 Torr) gave 5.04 g (21%) of 4-pentynal as a colorless oil; ^{1}H-NMR ($CDCl_3$): 9.80 (t, 1H, J=1.8 Hz, CHO, 3.0-2.4 (m, 4H), 1.97 (t, 1H, J=2.8 Hz, HC≡C); ^{13}C-NMR ($CDCl_3$): δ 200.08 (CHO), 82.33 (HC≡<u>C</u>R), 69.25 (H<u>C</u>≡CR), 42.41 (<u>CH_2</u>CHO), 11.55 HC≡C<u>CH_2</u>); IR (neat): 3292 cm^{-1} (H-C≡C-), 2920 cm^{-1} (CH_2), 2840 cm^{-1} (CHO), 2740 cm^{-1} (CHO), 2130 cm^{-1} (C≡C), 1725 cm^{-1} (C=O); 2,4-dinitrophenylhydrazone derivative, mp 132.5-133.5°C (lit[508]130°C); R_F=0.57, 20% ethyl acetate-petroleum ether. Anal. calc. for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.84; N, 21.36. Found: C, 50.39; H, 3.88; N, 21.26. A second component, which was isolated from the distillation (bp 68°C, 0.30 Torr) was identified as (4-pentyn-1-oyl)-4-pentynoate (6.24 g, 25.6%, 51.2% based on

starting material); R_F=0.78, 20% ethyl acetate-petroleum ether; ^{1}H-NMR ($CDCl_3$): δ 4.22 (t, 2H, J=6.4 Hz, R(C=O)OR'), 2.65-2.45 (m, 4H, HC≡C$\underline{CH_2}CH_2COOR'$, $COOCH_2CH_2\underline{CH_2}C{\equiv}CH$), 2.45-2.15 (m, 2H, -$CH_2\underline{CH_2}CH_2$-), 2.1-1.7 (m, 4H, HC≡C$CH_2\underline{CH_2}COOR$, both $\underline{H}C{\equiv}CR's$); ^{13}C-NMR ($CDCl_3$): δ 171.69 (C=O), 82.92 (HC≡$\underline{C}R$), 82.41 (HC≡$\underline{C}R$), 69.08 (H$\underline{C}$≡CR's), 63.23 (RCOOC$\underline{CH_2}R'$), 33.30 (R$\underline{CH}$2COOR'), 27.50 ($CH_2\underline{CH_2}CH_2$), 14.37 (HC≡C$\underline{CH_2}R$), 14.12 (HC≡C$\underline{CH_2}R$).

4. Preparation of Secondary Alkynyl Alcohols

a. General Procedure

The synthesis of 11-dodecyn-2-ol is representative. Magnesium turnings (19.1 mmol, 0.47 g) were placed in an oven-dried, 100 mL round-bottomed flask fitted with a septum inlet. The flask was equipped with a magnetic stirring bar, Claisen head adapter, addition funnel, and dry ice condenser. The apparatus was assembled hot, flame dried, purged with nitrogen, and allowed to cool under a stream of nitrogen. An iodine crystal was added and the system flushed with nitrogen. The condenser was cooled to -78°C, and anhydrous ether (25 mL) was added and the mixture stirred at room temperature until the magnesium dissolved (≈ 30 minutes). The reaction flask was cooled to 0°C, and then a solution of 11-trimethylsilyl-10-undecynal (17.74 mmol, 4.23 g) in anhydrous ethyl ether was transferred to the

addition funnel, and added dropwise to the reaction mixture. After the addition, the mixture was stirred at 0°C for 3 hours. Water (10 mL) and conc. HCl (5 mL) were added sequentially (dropwise) to the mixture at 0°C, and the stirring continued until all of the precipitate had dissolved. The ether layer was separated, and the aqueous layer extracted with ether (3x25 mL). The combined ethereal extracts were washed sequentially with a sodium thiosulfate solution (5%, 25 mL), and water (25 mL), and then dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent gave, 4.5 g of a yellow oil. The crude alcohol was dissolved in ethanol (40 mL) and placed in a 500 mL round-bottomed flask equipped with a magnetic stirring bar and addition funnel. A 0.66 M solution of silver nitrate (47.9 mmol, 8.13 g dissolved in 72 mL of 1:3 H_2O-EtOH) was placed in the addition funnel and added dropwise at room temperature over a 15 minute period. The mixture was stirred at 50°C for 1.5 hours, during which time a black precipitate formed. Potassium cyanide (240 mmol, 15.63 g) was added dropwise as a 10 M aqueous solution at 50°C, and stirred until all the precipitate had dissolved. The reaction mixture was extracted with ether (5x100 mL) and the combined ether layers dried ($MgSO_4$). Filtration and evaporation of the solvent gave the crude alcohol. Purification by column chromatography (silica gel, 20% ethyl

acetate-petroleum ether) gave 2.95 g (91% from 11-trimethylsilyl-10-undecynal) of 11-dodecyn-2-ol as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 3.9-3.6 (m, 1H, $CH_2\underline{CH}(OH)CH_3$), 2.16 (m, 2H, $HC{\equiv}C\underline{CH_2}R$), 1.94 (t, 1H, J=2.5 Hz, $\underline{H}C{\equiv}CR$), 1.75-1.0 (m, 18H, doublet shoulder at 1.21 and 1.14, J=6.2 Hz, is RCH-(OH)$\underline{CH_3}$); ^{13}C-NMR ($CDCl_3$): δ 84.81 ($HC{\equiv}\underline{C}R$), 68.20 ($R\underline{CH}$-$(OH)CH_3$, 68.13 ($H\underline{C}{\equiv}CR$, 39.35, 29.60, 29.48, 29.06, 28.75, 28.49, 25.77, 23.48, 18.41: IR (neat): 3640-3060 cm^{-1} (b,OH), 3310 cm^{-1} (H-C≡C), 2963 cm^{-1} (CH_3), 2925 cm^{-1} (CH_2), 2860 cm^{-1} (R_3C-H), 2120 cm^{-1} (C≡C), 1345 cm^{-1}. Anal. calc. for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.27; H, 11.82.

b. <u>6-Heptyn-2-ol</u>

Reaction of methylmagnesium iodide [21.15 mmol, prepared by treatment of 21.15 mmol (0.52 g) of magnesium turnings with methyl iodide (22.15 mmol, 3.14 g) in anhydrous ether (10 mL)] with 6-trimethylsilyl-5-hexynal (20.14 mmol, 3.14 g) dissolved in anhydrous ether (10 mL) gave 3.71 g of a yellow oil. The crude alcohol was dissolved ethanol (50 mL) and treated successively with silver nitrate (54.38 mmol, 9.24 g, 0.66 <u>M</u> in 1:3 H_2O-EtOH) and with potassium cyanide (257.8 mmol, 16.79 g, 10 <u>M</u> in H_2O) at 50°C. Purification by flash column chromatography (silica gel, 10% ethyl acetate-petroleum ether) gave 1.53 g (68%

from 6-trimethylsilyl-5-hexynal) of 6-heptyn-2-ol as a colorless oil; bp 185°C (lit.[509] 75-77°C, 12 Torr); ^{1}H-NMR ($CDCl_3$): δ 4.0-3.65 (m, 1H, $RCH_2\underline{CH}(OH)CH_3$), 2.24 (m, 2H, $HC{\equiv}C\underline{CH_2}CH_2R$), 1.96 (t, 1H, J=2.6 Hz, $\underline{H}C{\equiv}CCH_2R$), 1.85 (s, 1H, OH), 1.60 (m, 4H, CH_2's), 1.24, 1.17 (d, 3H, J=6.2 Hz, CH_3); ^{13}C-NMR ($CDCl_3$): δ 84.39 ($HC{\equiv}\underline{C}R$), 68.57 ($\underline{H}C{\equiv}CR$), 67.64 ($R\underline{CH}OHCH_3$), 38.20 ($-CH_2\underline{CH_2}CH_2-$), 24.71 ($R\underline{CH_2}CH)OH)CH_3$), 23.58 ($CH_3$), 18.40 ($HC{\equiv}C\underline{CH_2}R$); IR: 3690-3020 cm^{-1} (br, OH), 3305 cm^{-1} (HC≡C), 2963 cm^{-1} (CH_3), 2925 cm^{-1} (CH_2), 2678 cm^{-1} (R_3CH), 2120 cm^{-1} (C≡C), 1253 cm^{-1}, 1133 cm^{-1}, 845 cm^{-1}.

c. 7-Trimethylsilyl-6-Heptyn-2-ol

A solution of 6-trimethylsily-5-hexynal (7.72 mmol, 1.30 g, prepared according to procedure 4.D.4.b, p. 170) dissolved in anhydrous ether (10 mL) was added dropwise at 0°C over a 15 minute period to a freshly prepared solution of methyl magnesium iodide [8.2 mmol, prepared by treatment of 8.2 mmol (0.20 g) of magnesium turnings with methyl iodide (8.6 mmol, 1.22 g) in anhydrous ether (10 mL)]. After the addition, the mixture was stirred at 0°C for 3 hours. Water (10 mL) and concentrated HCl (5 mL) were added sequentially (dropwise) to the mixture at 0°C, and the stirring continued until all of the precipitate had dissolved. The ether layer was separated, and the aqueous

layer was saturated with sodium chloride amd extracted into ether (3x50 mL). The combined ethereal extracts were washed sequentially with a sodium thiosulfate solution (5%, 25 mL), 10% sodium bicarbonate (1x50 mL)[510], and water (25 mL), and then dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent, gave 1.27 g of a yellow oil. Purification by flash column chromatography (silica gel, 10% ethyl acetate-petroleum ether) gave 0.61 g (43%) of 7-trimethylsilyl-6-heptyn-2-ol as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 4.0-3.65 (m, 1H, $RCH_2\underline{CH}(OH)CH_3$), 2.25 (m, 2H, $HC{\equiv}C\underline{CH_2}CH2R$), 1.70-1.4 (m, 5H, CH_2's, OH), 1.20 (d, 3H, J=6.2 Hz, CH_3) 0.14 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR ($CDCl_3$): δ 107.30 ($(CH_3)_3Si\underline{C}{\equiv}CR$), 84.82 ($(CH_3)_3C{\equiv}\underline{C}R$), 67.65 ($R\underline{CH}OHCH_3$), 38.39 ($-CH_2\underline{CH_2}CH_2-$), 24.93 ($R\underline{CH_2}CH)OH)CH_3$), 23.63 ($CH_3$), 19.87 ($(CH_3)_3SiC{\equiv}C\underline{CH_2}R$), 0.20 ($(CH_3)_3Si$); IR (neat): 3600-3080 cm^{-1} (br, OH), 2958 cm^{-1} (CH_3), 2925 cm^{-1} (CH_2), 2175 cm^{-1} (C≡C), 1242 cm^{-1}, 836-1, 755 cm^{-1}. Anal. calc. for $C_{10}H_{20}O$ Si: C, 65.15; H, 10.94; Si, 15.24. Found: C, 64.89; H, 10.95; Si, 14.91.

5. Oxidation of Secondary Alkynyl Alcohols with Pyridinium Dichromate.

a. General Procedure

The synthesis of 11-dodecyn-2-one is representative. Pyridinium dichromate (19.4 mmol, 7.30 g) and pyridinium

trifluoroacetate (3.89 mmol, 0.75 g) were placed into an oven dried 100 mL round-bottomed flask fitted with a septum inlet. The flask was equipped with a magnetic stirring bar, reflux condenser, and gas outlet to a mercury bubbler, assembled while hot, and allowed to cool under a stream of nitrogen. Anhydrous methylene chloride (20 mL) was introduced, followed by a solution of 11-dodecyn-2-ol (9.71 mmol, 1.77 g) in anhydrous methylene chloride (5 mL). The mixture was stirred at room temperature for 20 hours, and then diluted with ether (10 mL). The liquid portion was decanted and the residue washed with ether until it became granular. The combined ether layers were then filtered through a short column of silica gel. Evaporation of the solvent gave 2.04 g of the crude ketone. Purification by column chromatography (silica gel, 5% ethyl acetate-petroleum ether) afforded 1.42 g (81%) of 11-dodecyn-2-one as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 2.45 (t, 2H, J=6.8 Hz, $R\underline{CH_2}(C{=}O)CH_3$), 2.3-2.0 (m, 4H), 1.96 (t, 1H, J=2.6 Hz, $\underline{H}C{\equiv}CCH_2R$), 1.8-1.15 (m, 13H, CH_2's, CH_3); ^{13}C-NMR ($CDCl_3$): δ 209.10 (C=O), 84.60 ($HC{\equiv}\underline{C}R$), 68.10 ($H\underline{C}{\equiv}CR$), 43.70, 29.81, 29.24, 29.07, 28.89, 28.64, 28.42, 23.77 (CH_2's, CH_3), 18.35 ($\underline{CH_2}C{\equiv}CH$); IR (neat) 3295 cm^{-1} (H-C≡C), 2932 cm^{-1} (CH_3), 2860 cm^{-1} (CH_2), 2125 cm^{-1} (C≡C), 1715 cm^{-1} (C=O), 1362 cm^{-1}, 1170 cm^{-1}; 2,4 dinitrophenylhydrazone derivative, mp 78.5-79.5°C. Anal. calc. for $C_{18}H_{24}H_4O_4$: C, 59.99; H, 6.71; N, 15.54. Found:

C, 59.73; H, 6.62; N, 15.42.

b. 6-Heptyn-2-one

Reaction of 6-heptyn-2-ol (6.42 mmol, 0.72 g) with pyridinium dichromate (12.84 mmol, 4.83 g) and pyridinium trifluoroacetate (2.57 mmol, 0.50 g) in anhydrous methylene chloride (13 mL) gave 570 mg (80.3%) of 6-heptyn-2-one as a colorless oil after column chromatography (silica gel, methylene chloride); ^{1}H-NMR ($CDCl_3$): δ 2.60 (t, 2H, J=7.0 Hz, R$\underline{CH_2}$(C=O)CH_3), 2.4-2.1 (m, 5H, with a singlet at 2.16 (3H, CH_3)), 2.0-1.6 (m, 3H, triplet centered at 1.96, J=2.6 Hz, is $\underline{H}$C≡C); ^{13}C-NMR ($CDCl_3$): δ 200.12 (C=O), 83.57 (HC≡$\underline{C}$R), 69.05 (H$\underline{C}$≡CR), 42.02, 30.05 (CH_3), 22.25, 17.75; IR (neat): 3295 cm^{-1} (H-C≡C), 2940 cm^{-1}, 2125 cm^{-1} (C≡C), 1714 cm^{-1} (C=O), 1375 cm^{-1}, 1166 cm^{-1}; 2,4-dinitrophenylhydrazone derivative, mp 115-116°C (lit[511] 118-119°C).

c. 12-Trimethylsilyl-11-dodecyn-2-one

Reaction of 12-trimethylsilyl-11-dodecyn-2-ol (3.26 mmol, 0.83 g) with pyridinium dichromate (6.8 mmol, 2.55 g) and pyridinium trifluoroacetate (1.36 mmol, 260 mg) in anhydrous methylene chloride (6.4 mL) gave 690 mg (84%) of 12-trimethylsilyl-11-dodecyn-2-one as a colorless oil after column chromatography (silica gel, methylene chloride); ^{1}H-NMR ($CDCl_3$): δ 2.5-1.9 (m, 7H, contains triplet centered at

2.28 and a singlet at 1.99 (CH_3)), 1.7-1.0 (m, 12H), 0.03 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR ($CDCl_3$): δ 209.01 (C=O), 107.60 ($(CH_3)_3Si\underline{C}\equiv CR$), 84.20 ($(CH_3)_3SiC\equiv\underline{C}R$), 43.70, 29.78, 29.21, 29.05, 28.86, 28.64, 28.53, 23.76, 19.78, 0.15 ($(CH_3)_3Si$); IR (neat): 2920 cm^{-1}, 2855 cm^{-1}, 2371 cm^{-1} (C≡C), 1716 cm^{-1} (C=O), 1360 cm^{-1}. 1250 cm^{-1}, 1168 cm^{-1}, 840 cm^{-1}, 757 cm^{-1}, 698 cm^{-1}; 2,4-dinitrophenylhydrazone derivative, mp 30-31°C. Anal. calc. for $C_{21}H_{32}N_4O_4Si$: C, 58.31: H, 7.46; N, 12.95; Si, 6.49. Found: C, 58.35; H, 7.70; N, 13.11; Si, 4.87.

d. 4-Pentyn-2-one

To an oven dried 500 mL round-bottomed flask fitted with a septum inlet pyridinium dichromate (200 mmol, 75.24 g) and pyridinium trifluoroacetate (40 mmol, 7.72 g) were added. The flask was equipped with a magnetic stirring bar, Claisen head adapter, reflux condenser, and gas outlet (mercury bubbler), assembled while hot, flushed with nitrogen, flame dried, and allowed to cool under a stream of nitrogen. Anhydrous methylene chloride (190 mL) was added by cannula, followed by the addition of 4-pentyn-2-ol (100 mmol, 8.41 g) at room temperature (a water bath was used to maintain the reaction temperature as close to room temperature as possible, as the reaction is slightly exothermic). The contents were stirred overnight at room temperature,

during which time the mixture became very thick. The reaction mixture was diluted with ether (25 mL), stirring continued for 15 minutes, and the contents of the flask filtered through a short column of silica gel. The dark gummy residue which remained was washed with a copious amount of ether until it became granular. The filtrate was then concentrated by fractional distillation using a 40 cm packed glass bead column, and purified by column chromatography (silica gel, methylene chloride. The fractions containing the alkynyl ketone were combined, and the solvent removed by fractional distillation through a 40 cm packed glass bead column. Final distillation of the product using a 5 cm packed glass bead column gave four distillate fractions: fraction #1 (bp range, 40-47°C, 0.52 g), fraction #2 (bp range 47-52°C, 0.70 g), fraction #3 (bp range 67-120°C, 0.89 g), fraction #4 (bp range 120-122°C, 2.36 g). The first and second fractions were shown by IR, and TLC, analyses to contain the desired 4-pentyn-2-one, 1.42 g (17%), but the fraction was mainly comprised of solvent (methylene chloride) and unreacted 4-pentyn-2-ol. Thus, an accurate yield of 4-pentyn-2-one could not be obtained. IR (neat): 3290 cm^{-1} (H-C≡C), 2965cm^{-1} (CH_3), 2925 cm^{-1}, 2910 cm^{-1} (CH_2), 2120 cm^{-1} (C≡C), 1708 cm^{-1} (C=O). No 2,4 dinitrophenylhydrazone derivative could be obtained. Fraction #4 contained only unreacted

4-pentyn-2-ol (2.36 g, 28%); ^{1}H-NMR ($CDCl_3$) δ (4.2-3.8 (m, 1H, $-CH_2\underline{CH}(OH)CH_3$), 2.45-2.3 (m, 2H, CH_2), 2.07 (t, 1H, J=2.4 Hz, $\underline{H}C\equiv C$), 1.27 (d, 3H, J=6.1 Hz, CH_3); ^{13}C-NMR ($CDCl_3$) δ 80.89 ($HC\equiv\underline{C}R$), 70.79 ($R_2\underline{CH}(OH)$, 66.24 ($H\underline{C}\equiv CR$), 28.97 (CH_2), 22.27 (CH_3).

6. Oxidation of Alkynyl Alcohols with Pyridinium Dichromate by Modified Procedures

a. Sealed Tube Method

The synthesis of 6-trimethylsilyl-5-hexynal is representative. To an oven dried reaction tube equipped with a magnetic stirring bar was added freshly ground pyridinium dichromate (66.84 mmol, 25.15 g). The reaction tube was constructed of 2" O. D. thick walled glass tubing 8" long, with the top narrowing to a 10mm septum opening. The reaction tube was equipped with a piece of tygon tubing, a short section of 10mm glass tubing, and a rubber septum as depicted in Figure 4-2. The apparatus was purged with nitrogen, and freshly distilled anhydrous methylene chloride (63 mL) added by canulla transfer. The contents of the tube were cooled to -78°C, 6-trimethylsilyl-5-hexyn-1-ol (44.56 mmol, 7.59 g) added by means of a nitrogen flushed syringe, the contents further cooled to liquid nitrogen temperature, and the reaction tube sealed after closing off the tube with a pinch clamp. The contents of the tube were gradually

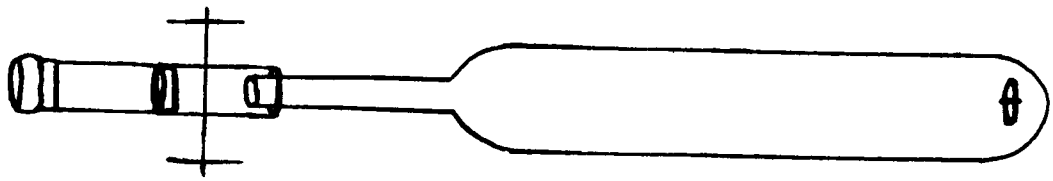


Figure 4-2. Reaction Tube Used in Pyridinium Dichromate Oxidations of Volatile Alkynyl Alcohols.

allowed to come to room temperature, and stirred for seven days. The reaction tube was cooled to liquid nitrogen temperature, the tube cut open using a glass cutter, the reaction mixture diluted with ether (25 mL), and the resulting mixture was stirred for 15 minutes. The supernatant was decanted off, and the tarry residue washed repeatedly with ether (50 mL portions) until the residue became powdery. The combined etheral layers were then filtered through a short column of silica gel to remove the insoluble chromium by-products. Evaporation of the solvent, followed by purification by column chromatography (silica gel, 5% ethyl acetate-petroleum ether, R_F=0.45) gave 4.91 g (65%) of 6-trimethylsilyl-5-hexynal as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 9.80 (t, 1H, J=1.3 Hz, CHO), 2.59 (t, 2H, J=7.0 Hz, $\underline{CH_2}CHO$), 2.30 (t, 2H, J=6.8 Hz, $\underline{CH_2}C{\equiv}C$), 1.83 (m, 2H, CH_2), 0.14 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR ($CDCl_3$): δ 201.73 (CHO), 105.87 ($(CH_3)_3Si\underline{C}{\equiv}CR$), 85.77 ($(CH_3)_3SiC{\equiv}\underline{C}R$), 42.65 ($\underline{CH_2}CHO$), 21.00, 19.21 ($CH_2$'s), 0.07 ($(CH_3)_3Si$); IR (neat): 2920 cm^{-1} (CH_2), 2860 cm^{-1}, 2760 cm^{-1} (CHO), 2178 cm^{-1} (C≡C), 1730 cm^{-1} (C=O), 1245 cm^{-1}, 848 cm^{-1}, 768 cm^{-1}; 2,4-dinitrophenylhydrazone derivative, 109.5-110°C. A second compound was isolated from the column (R_F=0.55, 5% ethyl acetate-petroleum ether), which was identified to be (6-trimethylsilyl-5-hexyn-1-oyl)-6-trimethylsilyl-5-hexynoate (13%, 26% molar yield); ^{13}C-NMR ($CDCl_3$): δ 173.29 (C=O),

106.71 ($(CH_3)_3SiC\equiv C$), 106.03 ($(CH_3(SiC\equiv C$), 85.87 ($(CH_3)_3Si-C\equiv C$), 85.69 ($(CH_3)SiC\equiv C$), 64.04 ($R(C=O)OCH_2R'$), 33.06, 27.80, 25.15, 23.82, 19.54 ($(CH_3)_3SiC\equiv CCH_2R$), 19.24 ($(CH_3)_3-SiC\equiv CCH_2R$). In a similar experiment, reaction of pyridinium dichromate (75 mmol, 28.22 g, used as received) with 6-trimethylsilyl-5-hexyn-1-ol (50 mmol, 8.51 g) in freshly distilled anhydrous methylene chloride using a sealed reaction tube (reaction time 42 hours) gave 2.25 g of 6-trimethylsilyl-5-hexynal (27%) after filtration through a short column of silica gel, removal of the solvent by fractional distillation, and final distillation of the product; bp 58°C, 40 Torr. In another experiment, the sealed tube reaction containing 6-trimethylsilyl-5-hexyn-1-ol (35.75 mmol, 6.09 g) and pyridinium dichromate (57.86 mmol, 21.77 g, used as received) in anhydrous methylene chloride (55 mL, previously distilled, stored under nitrogen) gave 2.31 g of 6-trimethylsilyl-5-hexynal (38%) as a colorless oil (reaction time 48 hours) after column chromatography (silica gel, 10% ethyl acetate-petroleum ether), removal of the solvent by fractional distillation using a 50 cm packed glass bead column, and final distillation of the product. In a final experiment, oxidation of 6-trimethylsilyl-5-hexyn-1-ol (20 mmol, 3.41 g) with pyridinium dichromate (30 mmol, 11.29 g, used as received) in anhydrous methylene chloride (28 mL, previously distilled and stored

under nitrogen atmosphere) using a sealed reaction tube (reaction time 42 hours) afforded 1.66 g (49%) of 6-trimethylsilyl-5-hexynal after column chromatography (silica gel, 10% ethyl acetate-petroleum ether).

b. Czernecki Method[488].

(1). Oxidation Procedure

To an oven dried 250 mL round-bottomed flask fitted with a septum inlet was added freshly ground pyridinium dichromate (15 mmol, 5.64 g) and dry crushed 3A molecular sieves (6.0 g, see procedure 6.b.(2) for details). NOTE: The dry crushed molecular sieves must be allowed to come to room temperature in a desiccator prior to the addition to the pyridinium dichromate; combustion of the pyridinium dichromate occurs when hot molecular sieves are added to PDC. The flask was equipped with a magnetic stirring bar, reflux condenser, and gas outlet to a mercury bubbler, and flushed with nitrogen. Anhydrous methylene chloride (50 mL) was transferred to the flask by canulla, followed by the addition of a solution of 6-trimethylsilyl-5-hexyn-1-ol in anhydrous methylene chloride (5 mL) in one portion. Immediately thereafter, anhydrous acetic acid (1 mL) was added by syringe and the mixture stirred at room temperature (water bath used to control reaction temperature). TLC analysis of the reaction mixture showed that the reaction

was complete within 45 minutes, during which time the contents became very dark and thick. Celite (5 g) was added, and the resulting mixture stirred for 20 minutes. Filtration through a sintered glass funnel, followed by washing with ether and evaporation of the solvent under reduced pressure gave a dark brown liquid. Purification by flash column chromatography (silica gel, 5% ethyl acetate-petroleum ether) afforded 0.37 g (30%) of 6-trimethylsilyl-5-hexynal as a colorless oil.

(2). Preparation of Activated, Crushed 3A Molecular Sieves

The 3A molecular sieves were activated by first drying in the oven for 24 hours at 200°C. The sieves were then crushed while hot using a mortar and pestle. The powdered sieves were then heated in a porcelain crucible for two hours, and allowed to cool under nitrogen atmosphere in a desiccator.

7. Oxidation of Alkynyl Alcohols with Dipyridine Chromium (VI) Oxide (Collins' Reagent)

a. Preparation of the Collins' Reagent

An oven dried 2000 mL three-neck round-bottomed flask was equipped with a mechanical stirrer with teflon seal adaptor, gas inlet, addition funnel, and gas outlet (mercury bubbler). The apparatus was assembled while hot, purged

with nitrogen, and then freshly distilled anhydrous pyridine (535 mL) was transferred into the flask by canulla. The reaction flask was cooled to 0°C with an ice bath. The addition funnel was temporarily removed, and anhydrous chromium trioxide (662.1 mmol, 66.20 g, previously dried under vacuum at 100°C 48 hours prior to use) was added slowly in small portions with stirring. NOTE: care must be exercised in adding anhydrous chromium trioxide to anhydrous pyridine to avoid fires[479]. During the addition the reaction turned a darker red-brown color. (The color of the reaction mixture at this point varied from a bright yellow slurry, to a brick orange slurry, and is not an indication as to the success or failure of the preparation[483]). The mixture was stirred at 10-15°C for 1.5 hours, and then filtered under nitrogen (Hood!). The solid material obtained was washed with a copious amount of anhydrous petroleum ether. Drying under vacuum 24 hours afforded 148.7 g of a dark red-brown solid (87%). (Other preparations of this material gave product color varying from yellow orange to brick orange).

b. 6-Trimethylsilyl-5-hexynal

The oxidation of 6-trimethylsilyl-5-hexyn-1-ol with the anhydrous dipyridine chromium (VI) oxide reagent is representative. To an oven dried 250 mL round-bottomed flask

fitted with a septum inlet was added anhydrous dipyridine chromium (VI) oxide (6 mmol, 7.75 g) under nitrogen atmosphere (glove bag). The flask was equipped with a magnetic stirring bar and gas outlet (mercury bubbler), flame dried, and allowed to cool under a stream of nitrogen. Anhydrous methylene chloride (155 mL) was placed into the flask by use of a canulla, followed by the addition of a solution of 6-trimethylsilyl-5-hexyn-1-ol (5.0 mmol, 0.85 g) in anhydrous methylene chloride (10 mL). The contents were stirred at room temperature, during which time the reaction mixture became very dark. TLC analysis of the reaction mixture showed that the oxidation was complete after 45 minutes. The reaction mixture was filtered using a short column of silica gel to remove the reduced chromium by-product, and the residue washed with a copious amount of petroleum ether and ether. Removal of the solvent under reduced pressure gave 0.93 g of a brown liquid. Final purification by column chromatography (silica gel, 5% ethyl acetate-petroleum ether) afforded 0.66 g (79%) of pure 6-trimethylsilyl-5-hexynal; ^{1}H-NMR ($CDCl_3$): δ 9.80 (t, 1H, J=1.3 Hz, CHO), 2.59 (t, 2H, J=7.0 Hz, $\underline{CH_2}CHO$), 2.30 (t, 2H, J=6.8 Hz, $\underline{CH_2}C{\equiv}C$), 1.83 (m, 2H, CH_2), 0.14 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR ($CDCl_3$): δ 201.73 (CHO), 105.87 ($(CH_3)_3Si\underline{C}{\equiv}CR$), 85.77 ($(CH_3)_3SiC{\equiv}\underline{C}R$), 42.65 ($\underline{CH_2}CHO$), 21.00, 19.21 ($CH_2$'s), 0.07 ($(CH_3)_3Si$); IR (neat): 2920 cm^{-1} (CH_2), 2860 cm^{-1}, 2760

cm^{-1} (CHO), 2178 cm^{-1} (C≡C), 1730 cm^{-1} (C=O), 1245 cm^{-1}, 848 cm^{-1}, 768 cm^{-1}; 2,4-dinitrophenylhydrazone derivative, 109.5-110°C.

c. 10-Undecynal

Reaction of 10-undecyn-1-ol (51 mmol, 8.58 g) with dipyridine chromium (VI) oxide (300 mmol, 77.71 g) in anhydrous methylene chloride (1500 mL) gave 7.76 g of 10-undecynal as a colorless oil after column chromatography; ^{1}H-NMR ($CDCl_3$): δ 9.75 (t, 1H, J=1.75 Hz, CHO), 2.42 (t, 2H, J=7.2 Hz, $\underline{CH_2}CHO$), 2.16 (t, 2H, $\underline{CH_2}C{\equiv}C$), 1.97 (t, 1H, J=2.8 Hz, $\underline{H}C{\equiv}C$), 1.93 (m, 12H); ^{13}C-NMR ($CDCl_3$): δ 202.87 (CHO), 84.66 (HC≡$\underline{C}$R), 68.16 (H$\underline{C}$≡CR), 43.89 ($\underline{CH_2}$CHO), 29.21, 29.10, 28.89, 28.64, 28.42, 22.06, 18.38 (CH_2's); IR (neat): 3295 cm^{-1} (C≡CH), 2840 cm^{-1}, 2720 cm^{-1} (CHO), 2120 cm^{-1} (C≡C), 1718 cm^{-1} (C=O); 2,4-dinitrophenylhydrazone derivative, mp 85.5°C (lit.[512] 86°C).

d. 4-Pentynal

Reaction of 4-pentyn-1-ol (50 mmol, 4.20 g) with anhydrous dipyridine chromium (VI) oxide (300 mmol, 77.45 g) in dry methylene chloride (1550 mL) gave a combined yield of 7.46 g of a colorless oil after filtration, removal of the solvent by fractional distillation through a 50 cm packed glass bead column, and final distillation of the product.

GC analysis of the distillate revealed that only (29%) of this material was the desired product, 4-pentynal, with the major impurities being methylene chloride, pyridine, and the ester.

8. Oxidation with Dipyridine Chromium (VI) Oxide - Acetic Acid (CPA)

a. 1.6 **M** CPA Reagent

Chromium trioxide (0.40 mol, 40.0 g) was added in small portions with stirring at 20°C to a mixture of pyridine (0.8 mol, 63.2 g) and acetic acid (150 mL). after dissolution, dilution to 250 mL afforded the 1.6 M CPA reagent.

b. 5-Hexynal

To a 100 mL round-bottomed flask equipped with a magnetic stirring bar was added 5-hexyn-1-ol (20 mmol, 1.96 g). The flask was cooled to -5°C, and the CPA reagent (60 mmol, 1.6 M) was added slowly with stirring. After one minute, the cold bath was removed, and stirring continued for an additional 10 minutes. TLC analysis of the reaction mixture showed the presence of two spots, one with R_F=0.35 (10% ether-petroleum ether) and the other at the baseline. The reaction mixture was extracted into ether (4x100 mL) and the combined ether layers were washed successively with 4 M HCl (3x100 mL), 1 M sodium bicarbonate, water (2x100 mL),

and then dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent, gave 1.57 g of a brown cloudy liquid. NMR analysis showed the crude product to be a mixture of aldehyde and carboxylic acid. Purification by column chromatography (silica gel, 10% ether-petroleum ether) afforded the pure aldehyde, 0.25 g (13%); ^{1}H-NMR ($CDCl_3$): δ 9.80 (t, 1H, J=1.3 Hz, CHO), 2.63 (t, 2H, J=7.0 Hz, $\underline{CH_2}CHO$), 2.28 (t, 2H, J=6.8 Hz, $C{\equiv}C\underline{CH_2}$), 2.0-1.7 (m, 3H, CH_2, $HC{\equiv}C$); ^{13}C-NMR ($CDCl_3$): δ 201.73 (C=O), 83.17 ($HC{\equiv}\underline{C}R$), 69.38 ($H\underline{C}{\equiv}CR$), 42.54 ($\underline{CH_2}CHO$), 20.84, 17.78 (CH_2's); IR (neat): 3295 cm^{-1} (H-C≡C), 2920 cm^{-1} (CH_2), 2840 cm^{-1}, 2740 cm^{-1} (CHO), 2130 cm^{-1} (C≡C), 1725 cm^{-1} (C=O), 1112 cm^{-1}, 906 cm^{-1}, 845 cm^{-1}.

9. Oxidation of Alkynyl Alcohols with Pyridinium Chlorochromate (PCC)

a. Preparation of Pyridinium Chlorochromate[471]

To 6 M HCl (184 mL) in a 1 L three-neck round-bottomed flask equipped with a mechanical stirrer was added chromium trioxide (1 mol, 100 g) with rapid stirring. The flask was cooled to 0°C, the flask equipped with an addition funnel, and then pyridine (1 mol, 79.1 g, 80.9 mL) was slowly added over a 10 minute period. Recooling of the mixture resulted in a yellow-orange solid, which was collected by filtration. Washing of the solid with water, followed by drying under

vacuum gave 175.3 g of PCC (81.3%).

b. 10-Undecynal. General Procedure

The oxidation of 10-undecyn-1-ol with pyridinium chlorochromate is representative. To an oven dried 500 mL round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler) was added anhydrous pyridinium chloromate (22.5 mmol, 4.85 g, dried under vacuum 24 hours immediately prior to use). Freshly distilled anhydrous methylene chloride (30 mL) was transferred to the flask by canulla, followed by the addition of a solution of 10-undecyn-1-ol (15.0 mmol, 2.52 g) dissolved in dry methylene chloride (5 mL). TLC analysis showed that the oxidation was complete within 3 hours, during which time the reaction mixture became very dark and viscous. The reaction mixture was diluted with ether (25 mL), stirred for 15 minutes, and the liquid layer decanted off. The black gummy residue which remained was washed repeatedly with ether until it became a granular solid. The combined ether layers, after concentration under reduced pressure, were filtered through a short column of silica gel. Removal of the solvent under reduced pressure gave 2.52 g (99%) of 10-undecynal as a colorless oil (one spot on TLC).

b. 4-Pentynal

Reaction of pyridinium chlorochormate (90 mmol, 19.4 g) with 4-pentyn-1-ol (60 mmol, 5.05 g) in anhydrous methylene chloride (120 mL) gave the crude aldehyde after fractional distillation (6 cm vigreaux column). Final distillation of the product gave 1.47 g (28%) of 4-pentynal as a colorless oil (93% purity by GC, with main impurity being pyridine).

10. Oxidation of Trimethylsilyl Protected Alkynyl Alcohols Using Pyridinium Chlorochromate-Sodium Acetate

a. 6-Trimethylsilyl-5-hexynal

To an oven dried 500 mL round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler) was placed pyridinium chlorochromate (7.5 mmol, 1.62 g) and anyhydrous sodium acetate (1.5 mmol, 123 mg). The apparatus was flame dried and purged with nitrogen, and anhydrous methylene chloride (15 mL) was transferred to the flask by canulla, followed by the addition of a solution of 6-trimethylsilyl-5-hexyn-1-ol (5.0 mmol, 0.85 g) dissolved in dry methylene chloride (5 mL). TLC analysis showed that the oxidation was complete within 3 hours, during which time the reaction mixture became very dark and viscous. In addition only one spot (R_F=0.50, 5% ethyl acetate-petroleum ether) was evident by TLC analysis

of the reaction mixture. The reaction mixture was diluted with ether (25 mL), stirred for 15 minutes, and the liquid layer decanted off. The black gummy residue was washed repeatedly with ether until it became powdery. The combined ether layers were reduced in volume and filtered through a short column of silica gel (5% ether-petroleum ether eluant). Evaporation of the solvent under reduced pressure afforded the pure aldehyde, 0.84 g (99%), as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 9.80 (t, 1H, J=1.3 Hz, CHO), 2.59 (t, 2H, J=7.0 Hz, $\underline{CH_2}CHO$), 2.30 (t, 2H, J=6.8 Hz, $\underline{CH_2}C{\equiv}C$), 1.83 (m, 2H, CH_2), 0.14 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR ($CDCl_3$): δ 201.73 (CHO), 105.87 ($(CH_3)_3Si\underline{C}{\equiv}CR$), 85.77 ($(CH_3)_3SiC{\equiv}\underline{C}R$), 42.65 ($\underline{CH_2}CHO$), 21.00, 19.21 ($CH_2$'s), 0.07 ($(CH_3)_3Si$); IR (neat): 2920 cm^{-1} (CH_2), 2860 cm^{-1}, 2760 cm^{-1} (CHO), 2178 cm^{-1} (C≡C), 1730 cm^{-1} (C=O), 1245 cm^{-1}, 848 cm^{-1}, 768 cm^{-1}; 2,4-dinitrophenylhydrazone derivative, 109.5-110°C.

b. <u>11-Trimethylsilyl-10-undecynal</u>

Reaction of pyridinium chlorochromate (22.27 mmol, 4.80 g) and anhydrous sodium acetate (4.46 mmol, 366 mg) with 11-trimethylsilyl-10-undecyn-1-ol (14.85 mmol, 3.57 g) in anhydrous methylene chloride (20 mL) under nitrogen atmosphere gave 3.32 g (93%) of 11-trimethylsilyl-10-undecynal as a colorless oil after filtration through a short silica gel column and removal of the solvent; ^{1}H-NMR ($CDCl_3$): δ

9.76 (t, 1H, J=1.75 Hz, CHO), 2.43 (t, 2H, J=6.5 Hz, $\underline{CH_2}CHO$), 2.21 (t, 2H, J=6.4 Hz, $\underline{CH_2}C{\equiv}C$), 1.32 (m, 12H), 0.14 (s, 9H, $(CH_3)_3Si$); ^{13}C-NMR ($CDCl_3$): δ 202.81 (CHO), 107.65 ($(CH_3)_3Si\underline{C}{\equiv}CR$), 43.92 ($\underline{CH_2}CHO$), 29.21, 29.10, 28.86, 28.70, 28.59, 22.09, 19.84 (CH_2's), 0.23 ($(CH_3)_3Si$); IR (neat) 2932 cm^{-1} (CH_2's), 2722 cm^{-1} (CHO), 2185 cm^{-1} (C≡C, 1730 cm^{-1} (C=O), 1243 cm^{-1}, 845 cm^{-1}, 767 cm^{-1}; 2,4-dinitrophenylhydrazone derivative, mp 74.5-75.5°C. Anal. calc for $C_{20}H_{30}N_4O_4Si$: C, 57.39; H, 7.22; N, 13.39; Si, 6.71. Found: C, 57.22; H, 7.25; N, 13.41; Si, 6.39.

11. Oxidation of 10-Undecyn-1-ol with Polyvinylpyridinium Dichromate (PVPDC)

To a 50 mL round-bottomed flask equipped with a magnetic stirring bar was added PVPDC (2.0 g, activated by soaking in water and filtering prior to use, dry weight), hexane (10 mL), and 10-undecyn-1-ol (5 mmol, 0.84 g). The flask was fitted with a reflux condenser and heated at 70°C for 72 hours. After the allotted reaction time, TLC analysis showed partial conversion of the aldehyde. Filtration, followed by evaporation of the solvent gave the crude aldehyde. Purification by column chromatography afforded 70 mg (8.4%) of 10-undecynal as a colorless oil.

12. Attempts at the Preparation of the 4-Pentyn-2-one System

a. Pyridinium Chlorochromate Procedure

To an oven dried 100 mL round-bottomed flask was added pyridinium chlorochromate (30 mmol, 6.47 g). The flask was equipped with a magnetic stirring bar, reflux condenser, and gas outlet, purged with nitrogen, and flame dried. Anhydrous methylene chloride (40 mL) was introduced by syringe, followed by the addition of 4-pentyn-2-ol (20 mmol, 1.68 g). The reaction mixture was stirred for two hours at room temperature, and then quenched by the addition of dry ether. The supernatant was decanted off, and the black gummy residue washed with copious amounts of ether until it became powdery. The combined organic layers were filtered through a short column of Florisil, and the solvent removed by fractional distillation (30 cm vigreaux column) to give the crude product, which showed the presence of a carbonyl compound by TLC using a 2,4-dinitrophenylhydrazine indicator. Column chromatography (silca gel, 10% ether-petroleum ether), followed by removal of the solvent by fractional distillation as before, gave 1.12 g of a light orange liquid, which by TLC showed the presence of a carbonyl compound. However, the attempt to prepare the 2,4-dinitrophenylhydrazine derivative of this material by standard methodology[503] failed. No yield of the desired

compound was obtained.

b. Modified Czernecki Procedure

To an oven dried reaction tube (described earlier) were added pyridinium dichromate (15 mmol, 5.64 g), and crushed dry 3A molecular sieves (8.0 g, anhydrous, activated according to procedure 4.D.6.b.(1)). A tube was fitted with a rubber septum, flushed with nitrogen, and anhydrous methylene chloride (50 mL) was introduced. The tube was cooled to -2°C (ice acetone bath), and then 4-pentyn-2-ol (10 mmol, 0.84 g, 0.95 mL) and anhydrous acetic acid (1 mL) were added sequentially. Following the addition, the tube was immediately cooled to liquid nitrogen temperature until solid, and the tube sealed. The reaction mixture was then allowed to warm gradually to room temperature and mechanically agitated using a Fisher brand touch mixer for 2 hours. The reaction mixture was refrozen (liquid nitrogen), the reaction tube opened on the top with a glass cutter, and celite (5 g) added to the mixture. The resulting mixture was agitated an additional 20 minutes under nitrogen, and then filtered through a short pad of celite. The black gummy residue was washed with ether until powdery (care was taken to use as little ether as possible, since solvent will have to be removed from a volatile product). The solvent was removed by room temperature vacuum distillation with the

volatile components being trapped with two traps, the first containing dry ice-acetone, the later containing liquid nitrogen. The apparatus used was depicted earlier in Figure 4-1, p. 145). When the traps became clogged, the vacuum was momentarily turned off, and the contents allowed to melt. The distillation process was continued until no more volatile components distilled off. Five fractions from the dry ice-acetone trap, and four from the liquid nitrogen trap were collected. Each was tested by TLC for the presence of a ketone product. Those fractions containing the ketone were combined. The synthesis of the 2,4-dinitrophenyl-hydrazine derivative was attempted. No such derivative resulted.

c. Pyridinium Dichromate-Dimethyl Formamide Method

To an oven dried reaction tube was added freshly crushed pyridinium dichromate (75 mmol, 28.21 g). The vessel was flushed with nitrogen, equipped with a rubber septum, and then anhydrous dimethyl formamide (60 mL) was introduced. Upon addition of the DMF, the contents were immediately frozen (liquid nitrogen) and the tube sealed. The reaction mixture was allowed to warm gradually to room temperature, and mechanically agitated using a Fisher brand touch mixer for 18 hours. The tube was refrozen, opened, and the contents poured into a round-bottomed flask. Room

temperature distillation and trapping the volatile components with a series of liquid nitrogen traps (apparatus used was shown earlier in Figure 4-1, p. 145) provided 0.43 g (1%) of a colorless liquid. TLC analysis confirmed the presence of a ketone. GC, IR, and NMR analyses provided evidence that the product possibly was 4-penty-2-one, but this could not be absolutely confirmed. Also, the product was contaminated with pyridine and dimethylformamide. Additionally, attempted formation of the 2,4-dinitrophenylhydrazone derivative of this material proved futile. ^{13}C-NMR (neat, TMS added as an internal standard): 172.95 (presumably C=O), 81.8 (H-C≡$\underline{C}$$CH_2$-), 72.05 (H-$\underline{C}$≡$CCH_2$), 66.17 ($CH_2$), 22.78 ($CH_3$); IR (neat): 3290 cm^{-1} (H-C≡C), 2965 cm^{-1} (CH_3), 2925 cm^{-1}, 2910 cm^{-1} (CH_2), 2120 cm^{-1} (C≡C), 1708 cm^{-1} (C=O).

d. Oxidation of 5-Trimethylsilyl-4-Pentyn-2-ol

The pyridinium dichromate-pyridinium trifluroacetate procedure described earlier (see 4.D.5.(a)), along with the sealed tube modification (procedure 4.D.6.(a), was used here. The attempted reaction of 5-trimethylsilyl-4-pentyn-2-ol (29.17 mmol, 4.56 g) with pyridinium dichromate (43.76 mmol, 16.46 g) and pyridinium trifluoroacetate (11.67 mmol, 2.25 g) in anhydrous methylene chloride yielded after silica gel filtration and fractional distillation of the reaction

mixture using a 50 cm packed glass bead column, no recovered product.

e. Dicobalt Hexacarbonyl Method

(1) Complex of 4-Pentyn-2-ol. Preparation

The protection of the acetylene functionality of 4-pentyn-2-ol was carried out according the procedure described by Seyferth[504,505], and Nicholas[506]. To an oven dried 500 mL round-bottomed flask fitted with a septum inlet was added dicobalt octacarbonyl (50 mmol, 17.10 g, weighed out in a glove bag under nitrogen atmosphere!) and the flask equipped with a rubber septum prior to removing from the glove bag. While flushing with nitrogen, the flask was equipped with a magnetic stirring bar, addition funnel, and gas outlet (mercury bubbler). Freshly distilled anhydrous ethyl ether (150 mL) was introduced, followed by the slow dropwise addition of a solution of 4-pentyn-2-ol (50 mmol, 4.21 g, 4.72 mL) in anhydrous ether (50 mL) (evolution of CO_2!). The reaction mixture was stirred overnight at room temperature, and then evaporated to dryness under reduced pressure. Column chromatography (silica gel, 10% ethyl acetate-petroleum ether) provided 14.99 g (81%) of the dicobalt hexacarbonyl complex of 4-pentyn-2-ol as a red brown liquid, which later solidified; TLC (10% ethyl acetate-petroleum ether) R_F=0.47; ^{13}C-NMR ($CDCl_3$): 200.10

(broad peak (202-198), $(O=\underline{C})_3Co\text{-}Co(\underline{C}=O)_3$), 92.16 (complexed $HC\equiv\underline{C}CH_2$-), 73.98 (complexed $H\underline{C}\equiv CCH_2$), 68.62 (CH), 43.76 ($CH_2$), 23.55 ($CH_3$).

b. Oxidation of the Hexacarbonyl Complex of 4-Pentyn-2-ol

The 3A molecular sieve catalyzed PDC procedure described by Herscovici[484] [procedure identical to the Czernecki modification described earlier (see procedure 4.D.6.(a)) but omits the use of anhydrous acetic acid] was used here. To an oven dried 250 round-bottomed flask fitted with a septum inlet were added pyridinium dichromate (60.8 mmol, 22.87 g, freshly crushed) and freshly prepared dry, powdered 3A molecular sieves (procedure 4.D.6.(b)). The flask was equipped with a magnetic stirring bar, dry ice cold finger condenser, gas outlet (mercury bubbler), assembled while hot, and purged with nitrogen while cooling. Anhydrous methylene chloride (60 mL) was introduced by canulla, followed by the addition of a solution of the hexacarbonyldicobalt complex of 4-pentyn-2-ol (40.53 mmol, 15.0 g) in anhydrous methylene chloride (20 mL). However upon first addition of the cobalt complex, the reaction became very vigorous! Therefore, the addition was momentarily stopped, the solution cooled to -78°C, and the addition completed. The reaction mixture was permitted to warm gradually to room temperature and stirred for 4 hours.

The crude product mixture was very thick and sludge like. Silica gel was added until the product became powdery, and the resulting solid poured onto a large silica gel column and filtered. Detailed separation was not attempted. Instead, all red colored fractions were combined and the solvent removed under reduced pressure to give 5.42 g of a red brown oil, which was identified by NMR spectroscopy to be the unreacted hexacarbonyldicobalt complex of 4-pentyn-2-ol, 5.42 g (36%). No observed oxidation took place, however, mass balance was not obtained either.

13. Mercury (II) Catalyzed Hydration of Alkynes Using Nafion-Hg (II)

a. Preparation of the Nafion-Hg (II) Reagent

(1). Conversion to Nafion-H^+

Nafion[513], a perfluorinated sulfonic acid resin, is commercially available in the sodium ion form. The Nafion used in these experiments came in plastic sheets, and thus had to be rendered into a more usable form[514]. A plastic sheet of Nafion was cut with scissors into small pieces (approx. 1x1cm), and placed into a porcelain mortar. Liquid nitrogen was poured into the crucible to freeze the polymer, and the Nafion crushed with a pestle into as fine a powder as possible. The crushed Nafion thus obtained was placed into a 250 mL round-bottomed flask, excess 50% HNO_3 added,

and the slurry stirred for 1 hour. The polymer reagent was then filtered, washed with deionized water, and dried in the oven until constant weight was obtained. The Nafion reagent, now in the H+ form, was then used to prepare Nafion-Hg (II).

(2). Conversion to Nafion-Hg (II)

In a round-bottomed flask equipped with a magnetic stirring bar were placed mercuric oxide (9.23 mmol, 2 g), deionized water (50 mL), concentrated sulfuric acid (1 mL), and Nafion-H^+ (0.5 g, dry weight), and the mixture stirred overnight at room temperature. Filtration, followed by washing of the polymeric resin with deionized water (5x20 mL) and drying to constant weight in an oven, provided the Nafion-Hg (II) reagent used for the hydration of alkyne substrates.

b. Preparation of 2-Octanone. General Procedure

To a 50 mL round-bottomed flask equipped with a magnetic stirring bar were added 1-octyne (10 mmol, 1.11 g), deionized water (10 mmol, 0.18 g), and ethanol (10 mL). Nafion-Hg (II) (500 mg, dry weight) was introduced and the resulting mixture stirred overnight (16 hours). The organic layer was separated, and the solid catalyst washed with ether (3x10 mL) by stirring each ether portion with the

catalyst for 15 minutes. The ethanolic organic layer was washed with saturated sodium chloride solution (2x20 ml) and the ethereal layer separated. The aqueous layer was extracted twice more with ether (20 mL portions), and the combined organic layer dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent under reduced pressure, gave the crude ketone. (If ethanol remains at this point, it can be removed by further distillation). Alternatively, column chromatography (silica gel, petroleum ether) gave, after removal of the solvent, 1.03 g (80.4%) of 2-octanone. The spectral characteristics of this compound matched those of known 2-octanone. ^{1}H-NMR ($CDCl_3$): δ 2.42 (t, 2H, J=7.2 Hz, $CH_3(C{=}O)\underline{CH_2}R$), 2.13 (s, 3H, $\underline{CH_3}$-$(C{=}O)CH_2R$), 1.70-1.1 (m, 10H), 0.88 (t, 3H, J=7.0 Hz, $RCH_2\underline{CH_3}$); ^{13}C-NMR ($CDCl_3$): δ 209.31 (C=O), 43.81. 31.62, 29.83, 28.85, 23.85, 22.51, 14.02.

14. Autoxidation of Heptaldehyde: Effect of Added Alkyne and Carboxylic Acids

a. Heptaldehyde: Control experiment

Heptaldehyde (5 mmol, 571 mg) was placed in a round-bottomed flask and left open to the air for three days. The product mixture was then analyzed by ^{1}H- and ^{13}C-NMR spectroscopy.

b. Heptaldehyde + Decanoic acid

Heptaldehyde (5 mmol, 571 mg) and decanoic acid (1 drop) were placed in a round-bottomed flask and left open to the air for three days. The product mixture was then analyzed by ^{1}H- and ^{13}C-NMR spectroscopy. No rate enhancement was observed.

c. Heptaldehyde + 1-Octyne

Heptaldehyde (5 mmol, 571 mg) and 1-octyne (5 mmol, 551 mg) were placed in a round-bottomed flask and left open to the air for three days. The product mixture was then analyzed by ^{1}H- and ^{13}C-NMR spectroscopy. The amount of hexanoic acid obtained increased by a factor of 8.16 (2.45/0.30, see Table 4-5, p. 151) compared to the control experiment.

d. Heptaldehyde + Decanoic Acid + 1-Octyne

Heptaldehyde (5 mmol, 571 mg), decanoic acid (1 drop) and 1-octyne (5 mmol, 551 mg) were placed in a round-bottomed flask and left open to the air for three days. The product mixture was then analyzed by ^{1}H- and ^{13}C-NMR spectroscopy. The amount of hexanoic acid obtained increased by a factor of 31.3 (9.38/0.30, see Table 4-5, p. 151) compared to the control experiment.

e. Effect of Mixing: Heptaldehyde: Control Experiment

Heptaldehyde (5 mmol, 571 mg) was placed in a round-bottomed flask and stirred in air for four hours. The product mixture was then analyzed by ^{1}H- and ^{13}C-NMR spectroscopy.

f. Effect of Mixing: Heptaldehyde + 1-Octyne

Heptaldehyde (5 mmol, 571 mg) and 1-octyne (5 mmol, 551 mg) were placed in a round-bottomed flask and stirred in air for four hours. The product mixture was then analyzed by ^{1}H- and ^{13}C-NMR spectroscopy. The amount of hexanoic acid obtained increased by a factor of 1.47 (13.3./9.00, see Table 4-5, p. 151) compared to the control experiment.

g. Solvent Effect: Heptaldehyde

Heptaldehyde (5 mmol, 571 mg) and THF (5 mL) were placed in a round-bottomed flask and stirred under air for six hours. The product mixture was then analyzed by ^{1}H- and ^{13}C-NMR spectroscopy. No oxidation to hexanoic acid was observed.

h. Solvent Effect: Heptaldehyde + 1-Octyne

Heptaldehyde (5 mmol, 571 mg), 1-octyne (5 mmol, 551 mg), and THF (5 mL) were placed in a round-bottomed flask and stirred under air for six hours. The product mixture

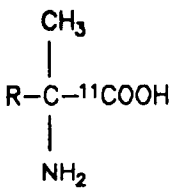
was then analyzed by ^{1}H- and ^{13}C-NMR spectroscopy. No oxidation to hexanoic acid was observed.

CHAPTER V

IODOVINYLAMINO ACIDS VIA HYDANTOIN METHODOLOGY

A. Introduction

In addition to the ^{123}I-labeled iodovinylaminocyclobutanecarboxylic acid derivatives discussed in Chapter III, ^{123}I-labeled iodovinyl-α-methyl-α-amino acid (LI) derivatives also appear to be attractive candidates for possible pancreatic imaging based on studies conducted by collaborators at Oak Ridge Associated Universities which demonstrated that ^{11}C-labelled, unnatural, nonmetabolizable amino acids exhibit a high affinity for tumorous pancreatic tissue and provide a means of locating and assessing tumors in the pancreas[415,416,417,418,419,420]. Additionally, the

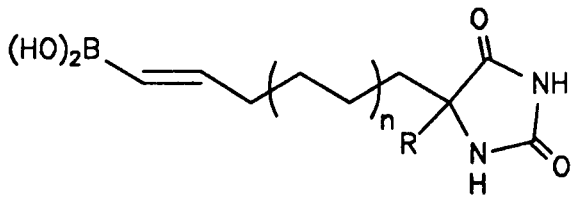


LI

aliphatic compounds could serve as model compounds for the development of a synthetic route to the more--difficult--to--attain aminocyclobutanecarboxylic acid (ACBC) derivatives. Thus, the syntheses of such acyclic iodovinyl amino acids were undertaken and are described in this chapter.

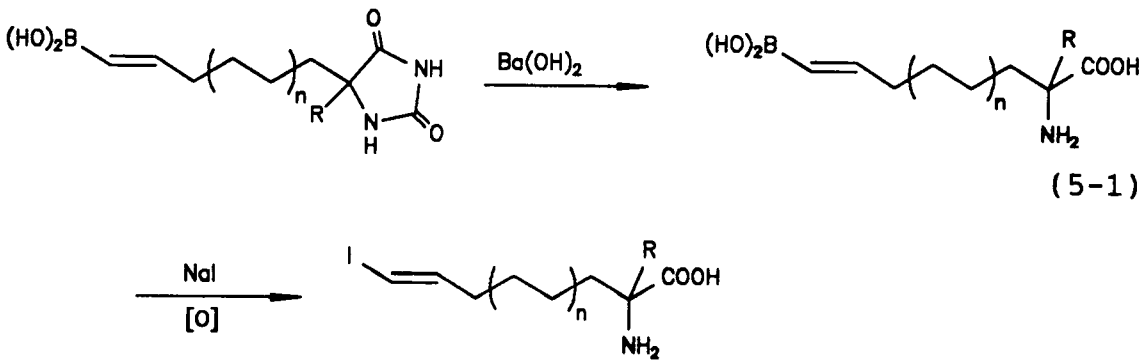
B. Route to Iodovinyl-α-Methyl- and Iodovinyl-α-Amino Acids

As was discussed in Chapter II, one route to the iodo vinyl-α-methyl and iodovinyl-α-amino acid systems involves preparation of the corresponding vinylboronic acid hydantoin precursor (LII). Cleavage of the hydantoin moiety employing



LII

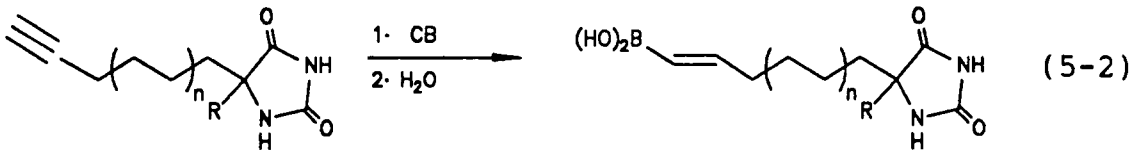
standard methodology, such as the use of aqueous barium hydroxide[426], would result in the desired vinylboronic acid amino acid[296], which could then be iodinated under mild oxidizing conditions to afford the iodovinylamino acid (equation 5-1). The 5-(Ω-boroalken-1-yl)2,4-imidazolidine-



(5-1)

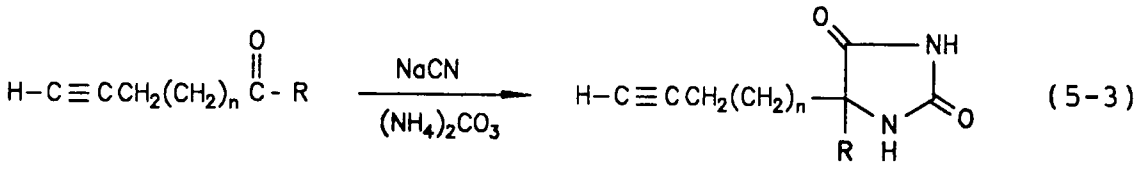
1,3-diones (LII) could be obtained from the corresponding alkynyl hydantoin by hydroboration of the alkynyl moiety with catecholborane[54]; hydrolysis of the intermediate

catechol vinylboronic ester providing the desired vinylboronic acid hydantoin (equation 5-2). The necessary



(5-2)

acetylenic hydantoin could be prepared from the corresponding ketone or aldehyde by use of the Bucherer-Bergs reaction[316] (equation 5-3). The requisite acetylenic methyl

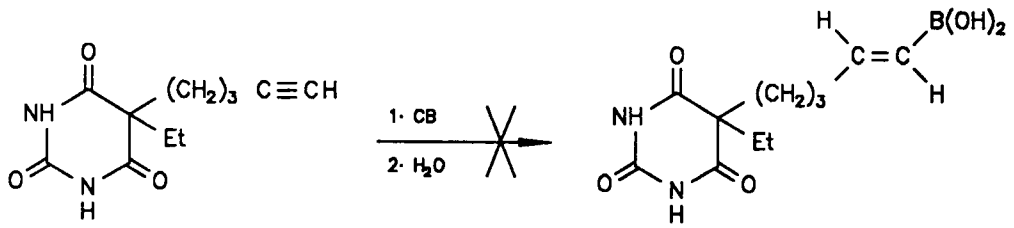


(5-3)

ketone or aldehydes were obtained in a straightforward stepwise fashion from the corresponding alkynyl primary alcohol by the methodologies discussed in the previous chapter.

A number of unanswered questions had to be addressed concerning the proposed route. The stability of the hydantoin functionality towards borane reagents was an important one. Few organometallic reactions involving the hydantoin moiety had been explored. The few reagents discussed to date reduce carbonyl functions, or lead to even more profound degradation. Although hydroboration in the presence of amides is normally successful with most borane

reagents[515], hydroboration in the presence of the hydantoin moiety had never been reported. In addition, hydroboration of a similar system with catecholborane, an alkynyl barbiturate, was reported to be unsuccessful[269] (equation 5-4).



(5-4)

Three other potential problems existed in this synthetic scheme: the iodination reaction in the presence of amino acid functionality, the oxidation reaction with pyridinium dichromate in the presence of the protected silyl alkyne, and the stability of the vinylboronic acid to the harsh conditions required to hydrolyze the hydantoin moiety. The latter of these proved to be a serious problem, and required modifying the above synthetic scheme.

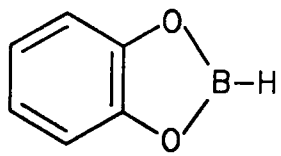
Thus, it was necessary to carry out a series of control experiments. The oxidation with pyridinium dichromate, as well as with other oxidants, in the presence of the trimethysilyl alkynyl functionality, was found to proceed without incident. This, and the oxidation of other alkynyl alcohols, was the subject of Chapter III. The hydroboration of alkynes in the presence of the hydantoin ring, as well as the iodination of a vinylboronic acid in the presence of

amino acid functionality, also proved feasible, and the results of these initial studies will be discussed below. The successful synthesis of an iodovinylamino acid via an acetylenic hydantoin precursor will also be presented.

C. Results and Discussion

1. Initial Experiments

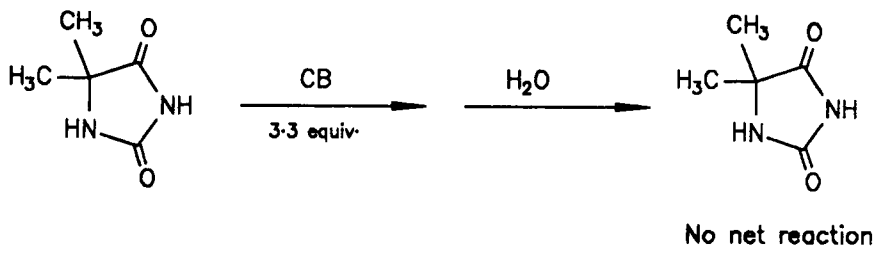
The first problem addressed was the stability of the hydantoin ring to hydroboration conditions. Based on earlier studies conducted in our laboratory[65,140], it appeared that catecholborane (LIII) would be the hydro-



LIII

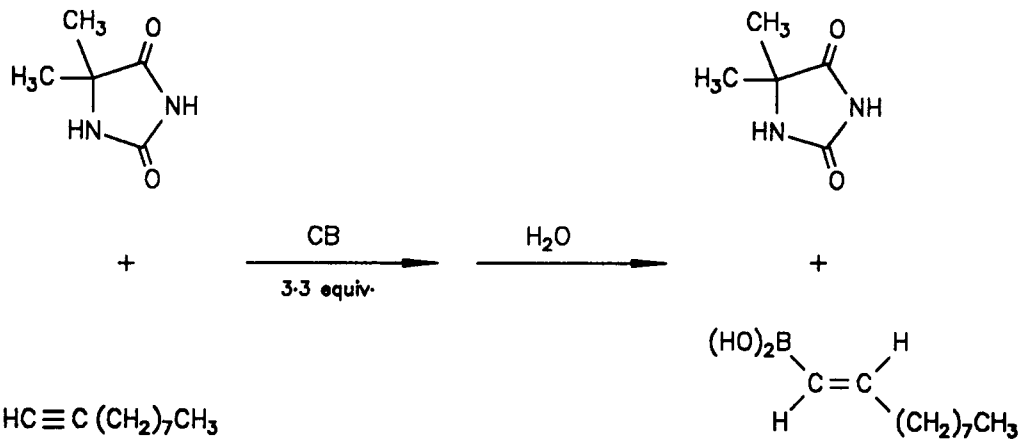
borating agent most suitable for the desired result. In order to investigate the feasability of carrying out a hydroboration reaction with catecholborane in the presence of the hydantoin functionality, a series of control experiments were carried out. The first experiment involved the hydroboration of 1-decyne with excess catecholborane (experiment A) (hydroborations with catecholborane are routinely carried out using 10 - 20 % mole excess). In a second experiment, 5,5-dimethylhydantoin was treated with a

stoichiometric amount of catecholborane (experiment B) under the same hydroboration conditions employed in experiment A. Assuming that both N-H groups would be reactive to catecholborane, a third experiment (experiment C) subjected 5,5-dimethylhydantoin to similar hydroboration conditions except that 3.3 equivalents of hydride reagent were used (equation 5-5). In a final experiment (experiment D) a mixture of



(5-5)

1-decyne and 5,5-dimethylhydantoin was subjected to the same hydroboration conditions, 3.3 equivalents catecholborane (equation 5-6). The experiments were carried out in



(5-6)

ethereal solvent (THF) under inert atmosphere at 40°C for

4 hours, and then an aliquot of the reaction mixture was removed for analysis by ^{13}C- and ^{11}B-NMR, using the chemical shift for THF (δ = 67.0) as the reference peak. In experiment A, the ^{13}C-NMR resonances at 83.3 and 68.0 ppm for the alkynyl carbons of 1-decyne disappeared over the four hour period, and a new peak appeared at 157 ppm, corresponding to the vinyl carbon beta to the boron in the catechol boronic ester product. [The vinyl carbon attached to the boron generally does not appear due to line broadening caused by the quadrapole moment of boron]. Figure 5-1 and Figure 5-2 show the spectra for the starting material, 1-decyne, and the reaction mixture for experiment A, respectively. The ^{11}B-NMR spectrum of the reaction mixture, Figure 5-3, gave two resonances at 31 and 18 ppm, corresponding to the formation of a boronic ester and that of unreacted catecholborane respectively. Overnight hydrolysis of the reaction mixture, followed by standard workup gave decenylboronic acid in a 92% yield.

In experiment B, 5,5-dimethylhydantoin was treated with one equivalent of catecholborane for four hours at 40°C. Vigorous evolution of hydrogen gas was observed upon addition of the catecholborane, followed by the formation of a milky white precipitate after the reaction had proceeded for approximately one hour. After the alloted reaction time, water was added to effect hydrolysis of the reaction

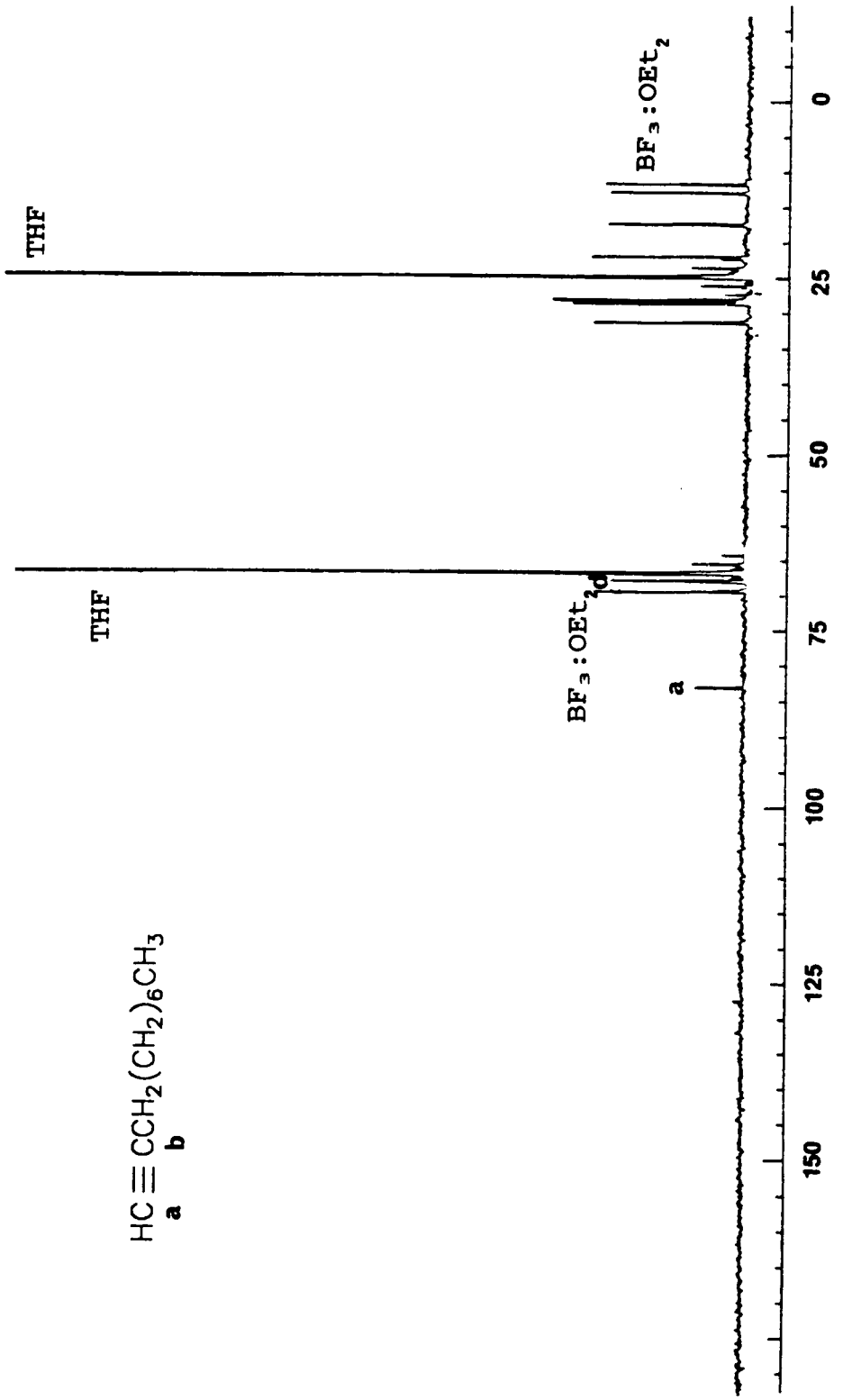


Figure 5-1. Carbon-13 NMR Spectrum of 1-Decyne in THF.

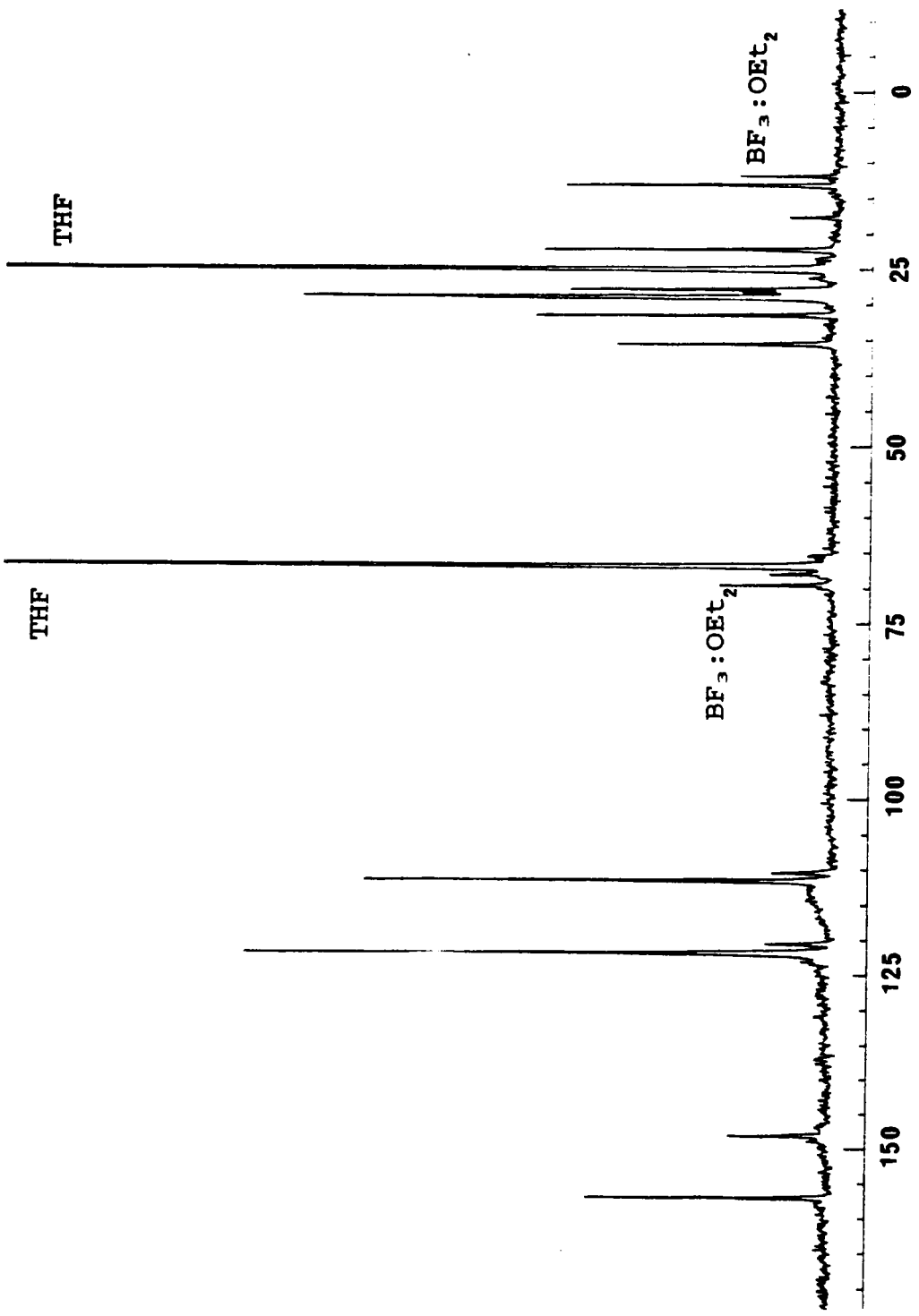


Figure 5-2. Carbon-13 NMR Spectrum of 1-Decyne and Catecholborane Reaction Mixture in THF (Experiment A).

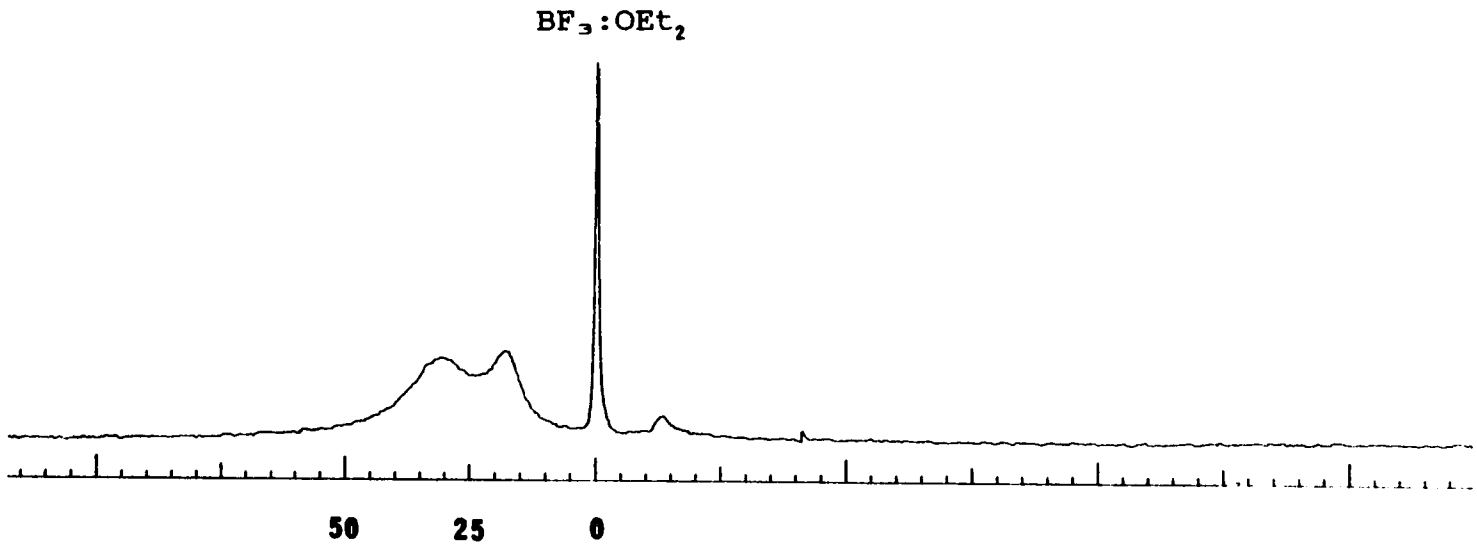


Figure 5-3. Boron-11 NMR Spectrum of 1-Decyne and Catecholborane Reaction Mixture in THF (Experiment A).

mixture, and then an aliquot removed. ^{13}C-NMR analysis of the aliquot revealed the presence of carbonyl resonances at 180 and 157 ppm, indicating that the hydantoin ring survived the reaction (Figure 5-4). The ^{13}C-NMR spectrum of 5,5-dimethylhydantoin in THF solvent is shown in Figure 5-5 for reference.

In experiment C, involving the reaction of excess catecholborane with 5,5-dimethylhydantoin, it was observed, from NMR analysis of the reaction mixture prior to hydrolysis, that the carbonyl peaks at 178 ppm remained over the four hour reaction time (although shifted slightly to 177 ppm), while a peak at 147 ppm appeared at the expense of the carbonyl resonance at 156 ppm (Figure 5-6). In addition, the quaternary carbon resonance normally at 59 ppm disappeared, with the formation of a new resonance at (presumably) 63 ppm (This portion of the ^{13}C-NMR spectrum is obscured by the strong solvent sidebands arising from the THF solvent). The ^{11}B-NMR spectrum of the reaction mixture revealed a broad peak at 19 ppm, indicating the formation of tricoordinate boron atom with three oxygens bonded to it (Figure 5-7). Interestingly, upon hydrolysis of the reaction mixture, the hydantoin ring reformed, as indicated by the presence of the carbonyl resonances at 178 ppm and 156 ppm, and the quaternary carbon peak at 59 ppm (Figure 5-8). Isolation of organic components from the reaction mixture gave a near

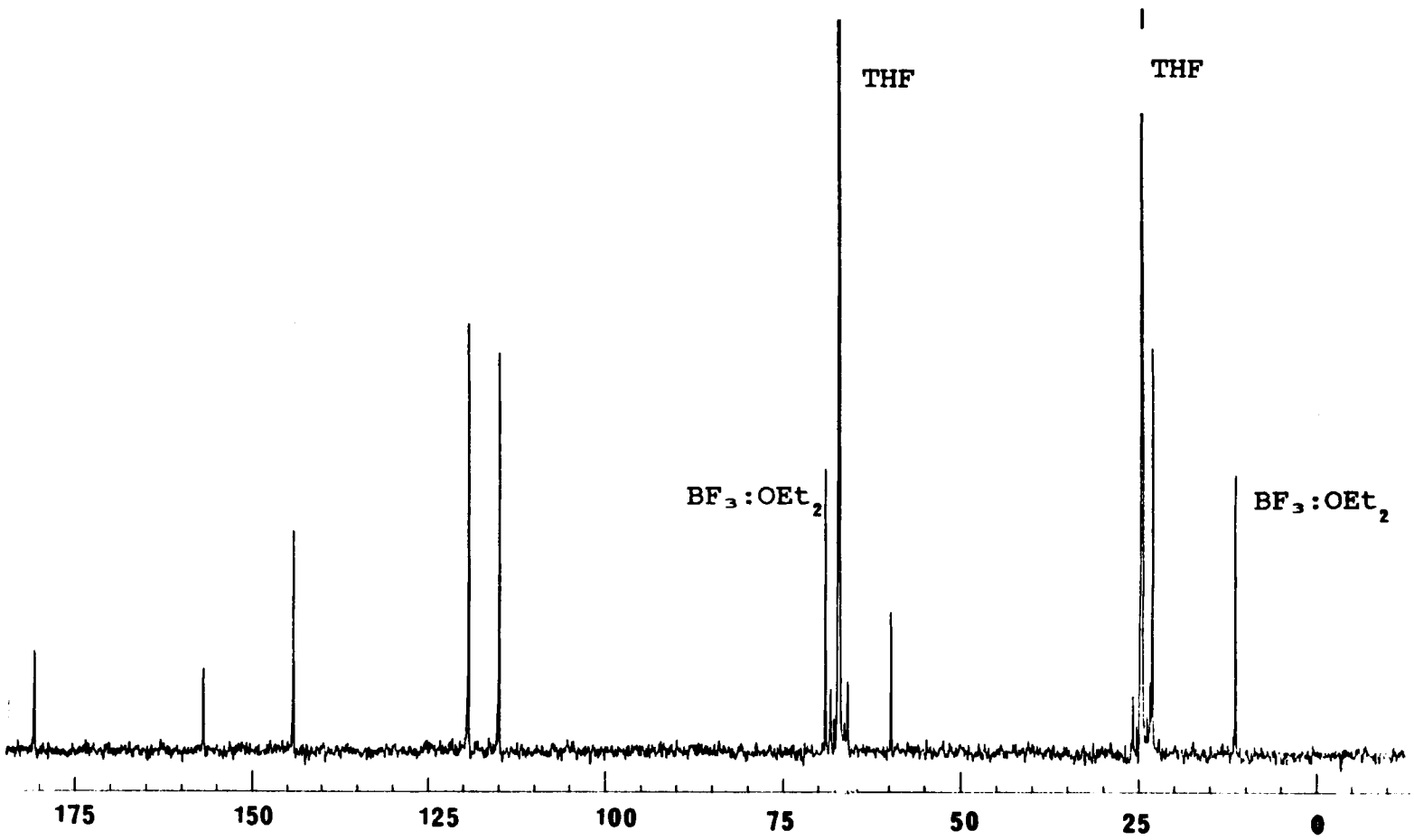


Figure 5-4. Carbon-13 NMR Spectrum of 5,5-Dimethylhydantoin and Catecholborane (1 equiv.) Reaction Mixture After Hydrolysis in Aqueous THF (Experiment B).

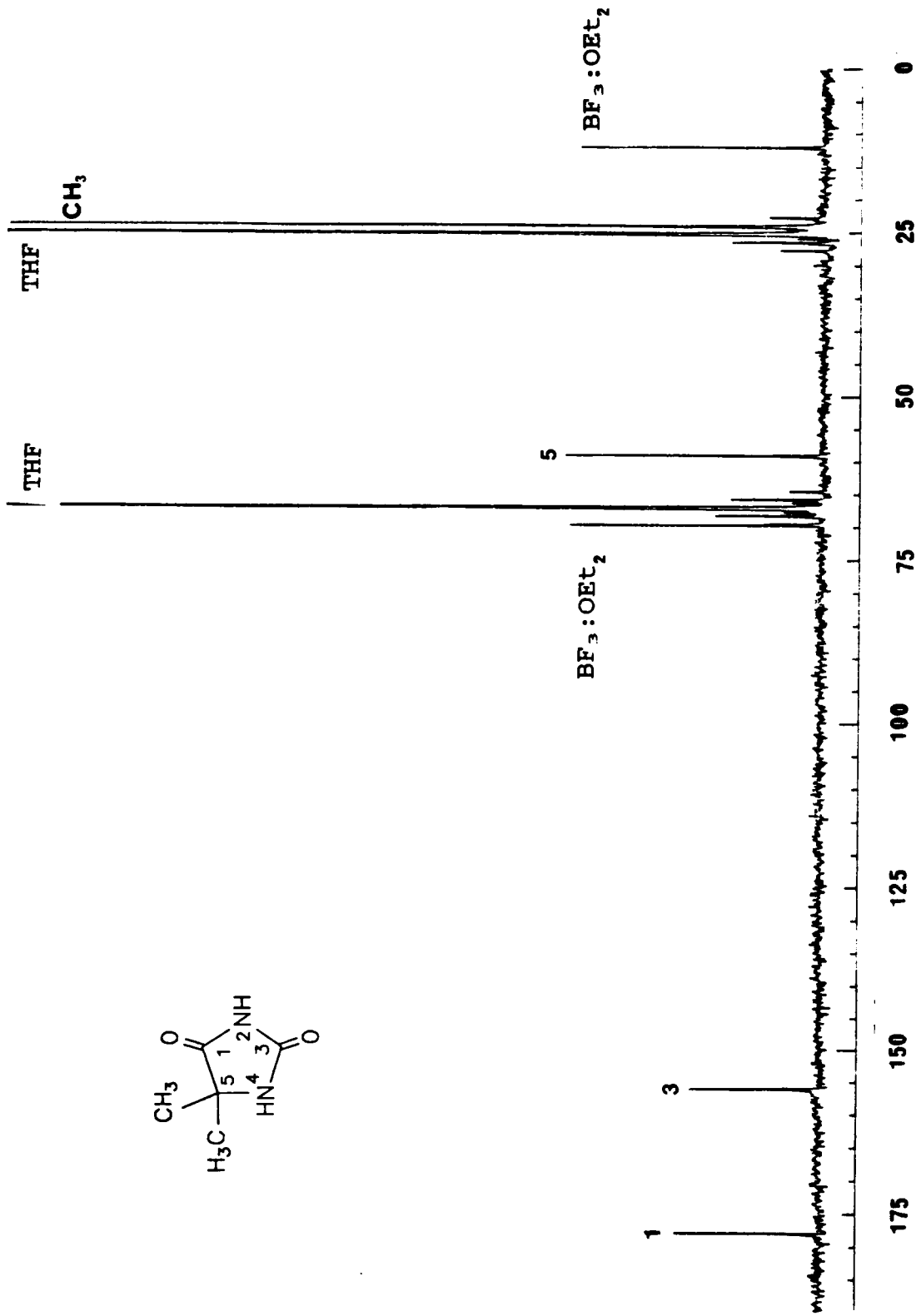


Figure 5-5. Carbon-13 NMR Spectrum of 5,5-Dimethylhydantoin in THF.

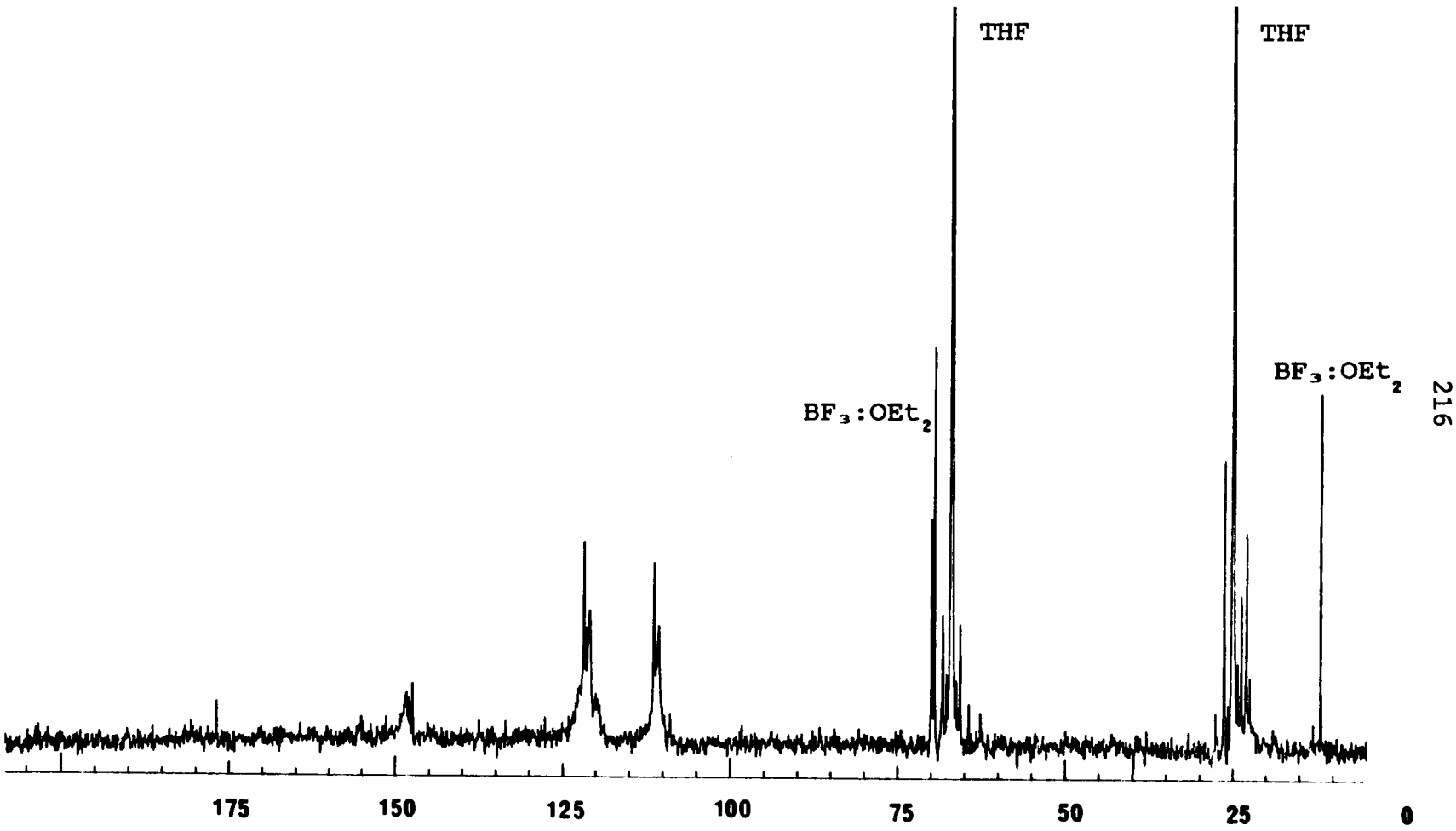


Figure 5-6. Carbon-13 NMR Spectrum of 5,5-Dimethylhydantoin and Catecholborane (excess) Reaction Mixture Prior to Hydrolysis in THF (Experiment C).

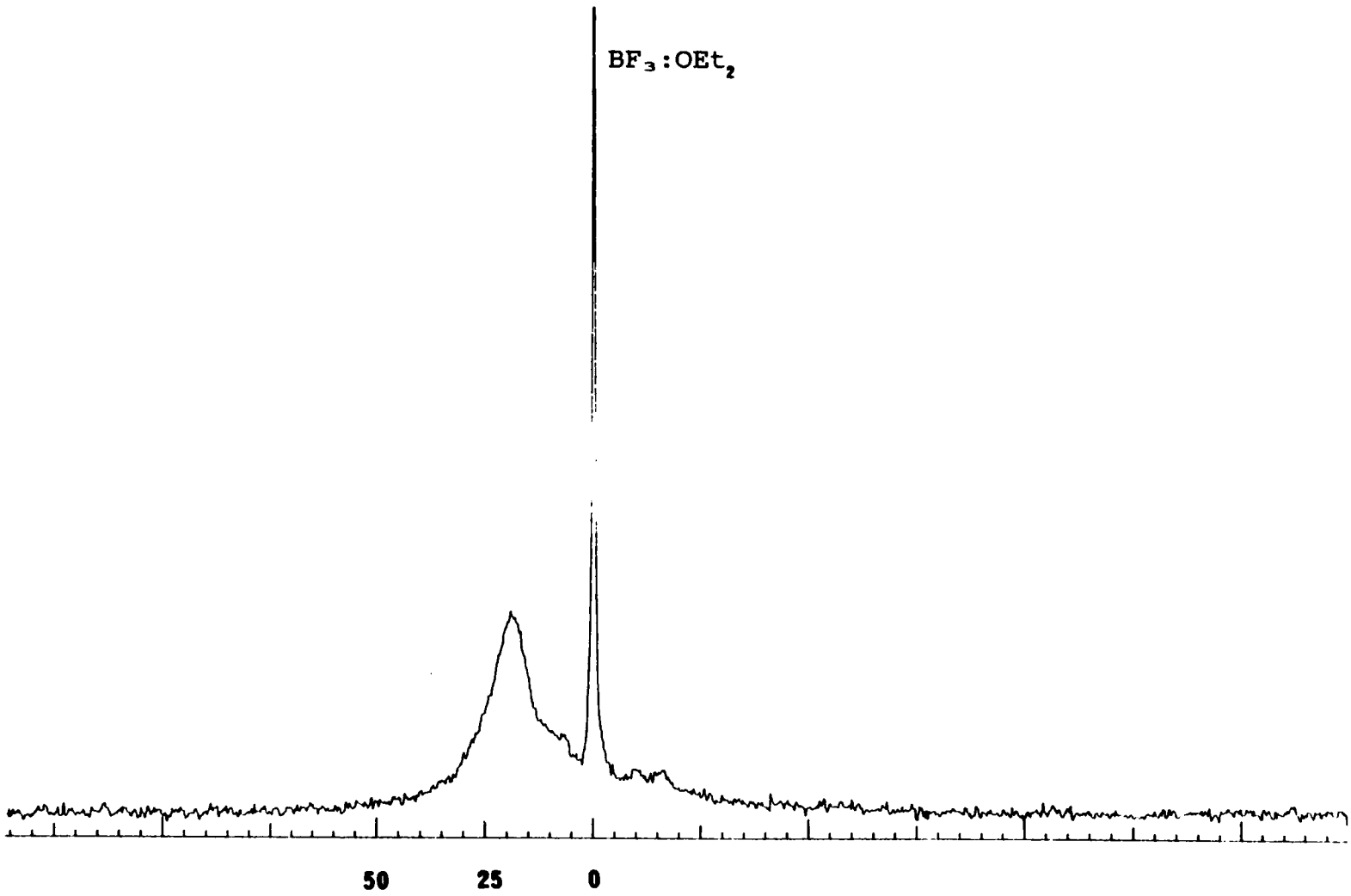


Figure 5-7. Boron-11 NMR Spectrum of 5,5-Dimethylhydantoin and Catecholborane (excess) Reaction Mixture Prior to Hydrolysis in THF (Experiment C).

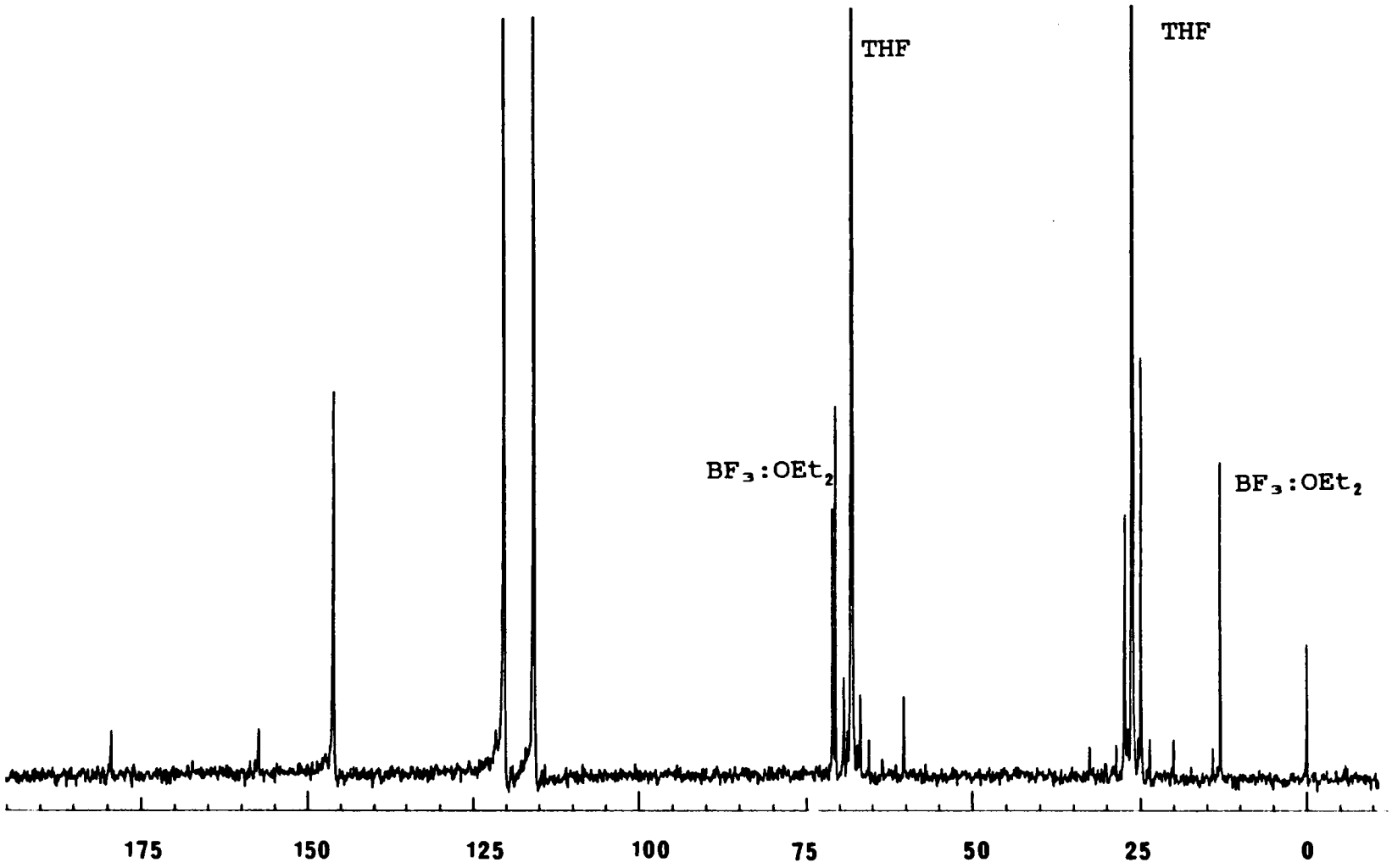
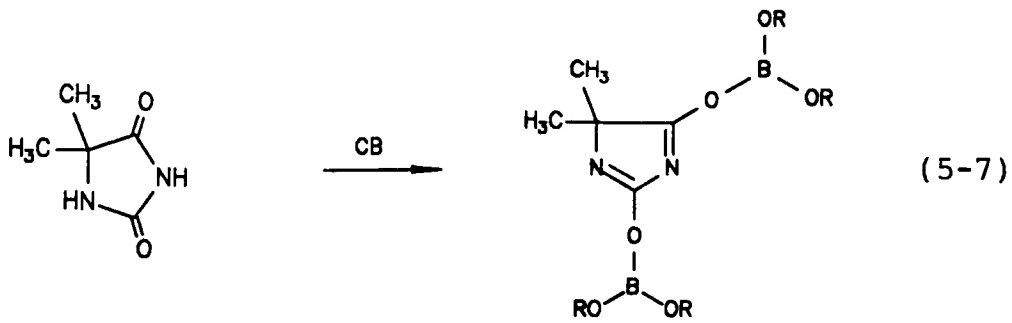


Figure 5-8. Carbon-13 NMR Spectrum of 5,5-Dimethylhydantoin and Catecholborane (excess) Reaction Mixture After Hydrolysis in Aqueous THF (Experiment C).

mass balance (98%) of a mixture of catechol and 5,5-dimethylhydantoin.

Finally, in experiment D, the alkynyl resonances at 83 ppm and 68 ppm disappeared as expected with the simultaneous appearance of the product peak at 157 ppm. Additionally, while the carbonyl resonance at 178 ppm remained, the peaks that were previously at 156 ppm and 59 ppm shifted to 147 and 63 ppm respectively, (Figure 5-9). The ^{11}B-NMR spectrum of the reaction mixture revealed a very broad peak at 20 ppm, indicating the formation of tricoordinate boron atom with three oxygens bonded to it (Figure 5-10), (equation 5-7). As expected from the results of experiment C, hydrolysis regenerated the hydantoin ring, as shown in Figure 5-11 (return of the carbonyl resonances at 178 ppm and 156 ppm and that of the quaternary carbon peak at 59 ppm). Extractive workup of the reaction mixture following hydrolysis gave 90%, 88%, and 80% yields respectively of decenylboronic acid, catechol, and recovered 5,5-dimethylhydantoin (equation 5-8).



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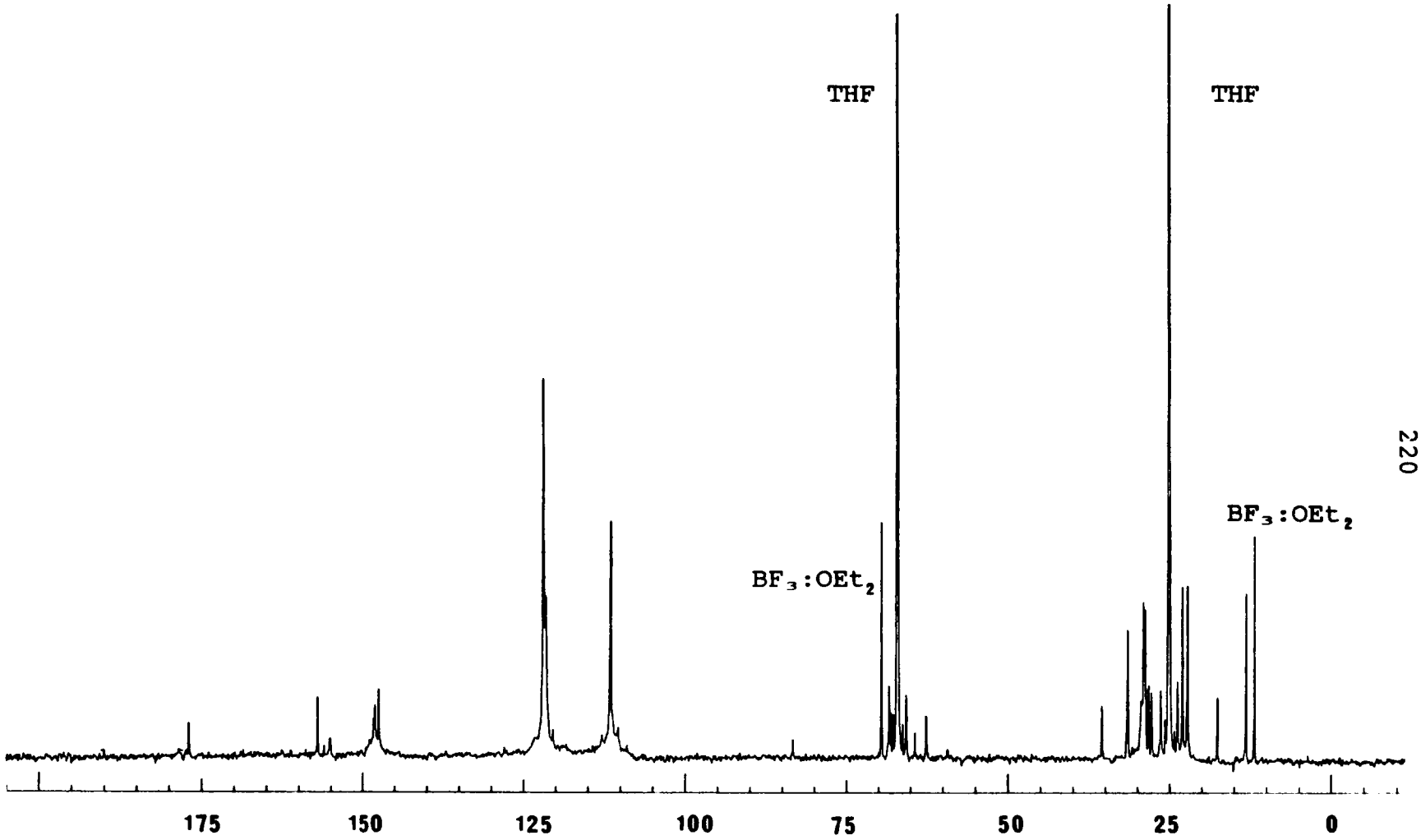


Figure 5-9. Carbon-13 NMR Spectrum of 5,5-Dimethylhydantoin, 1-Decyne, and Catecholborane (excess) Reaction Mixture Prior to Hydrolysis in THF (Experiment D).

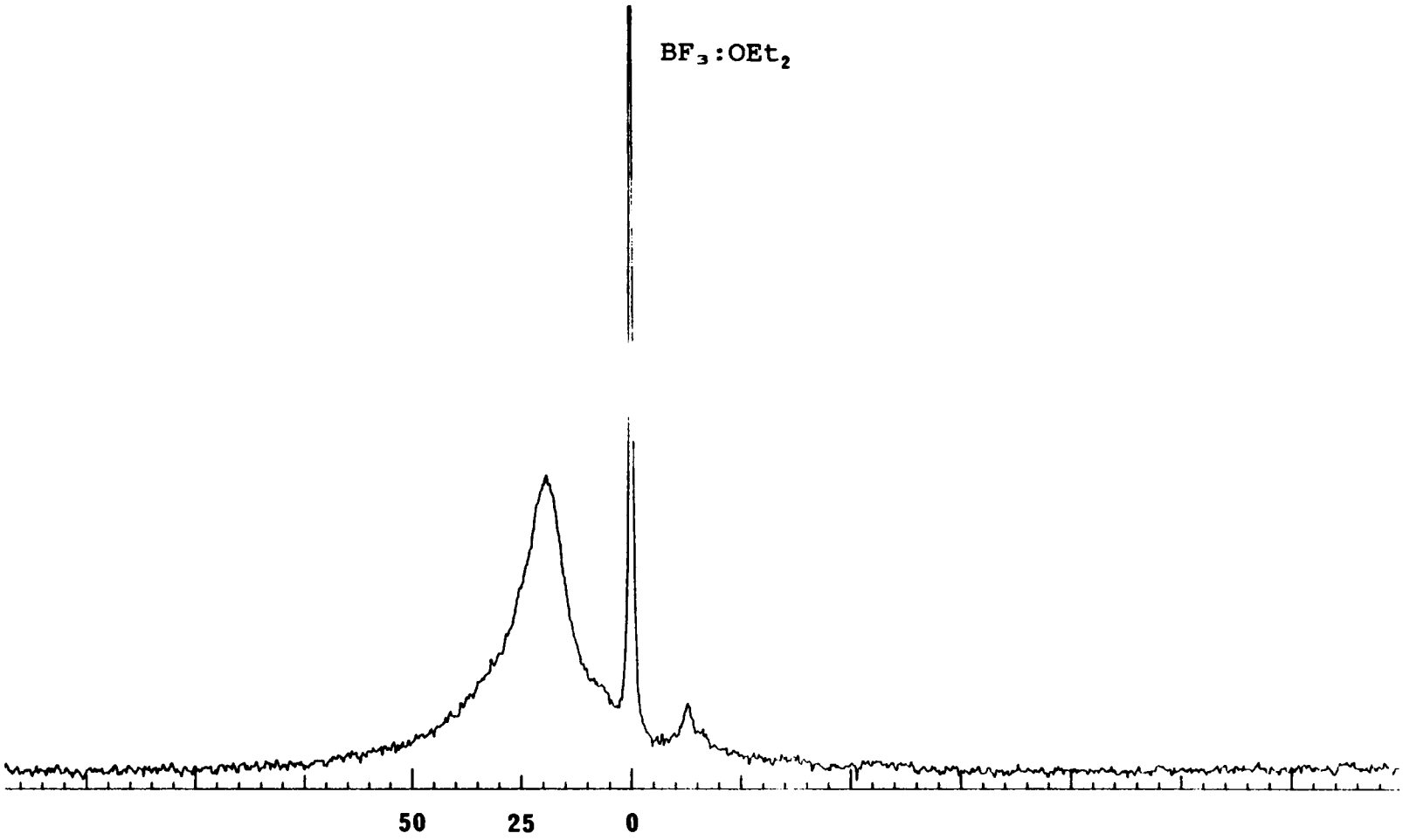


Figure 5-10. Boron-11 NMR Spectrum of 5,5-Dimethylhydantoin, 1-Decyne, and Catecholborane (excess) Reaction Mixture Prior to Hydrolysis in THF (Experiment D).

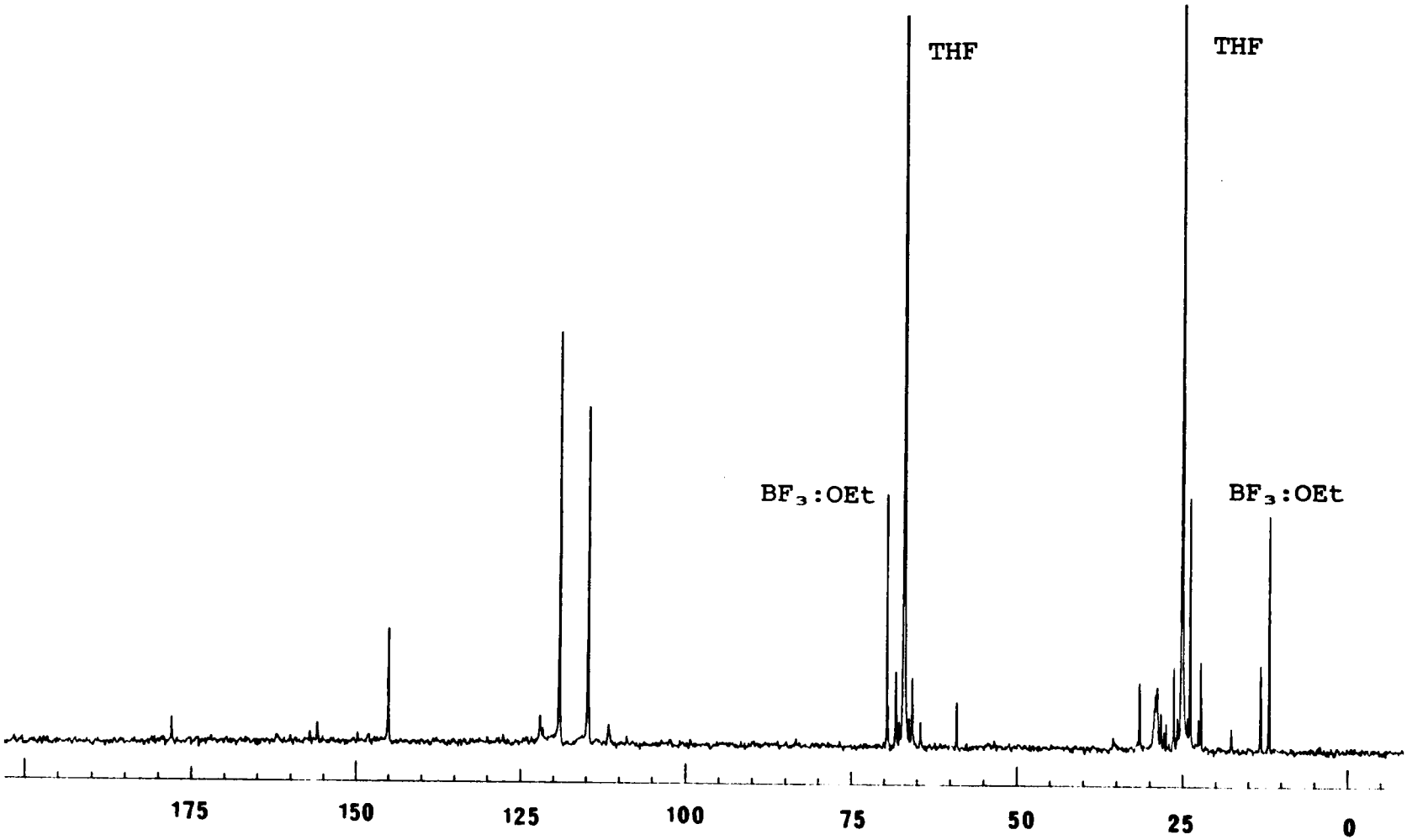
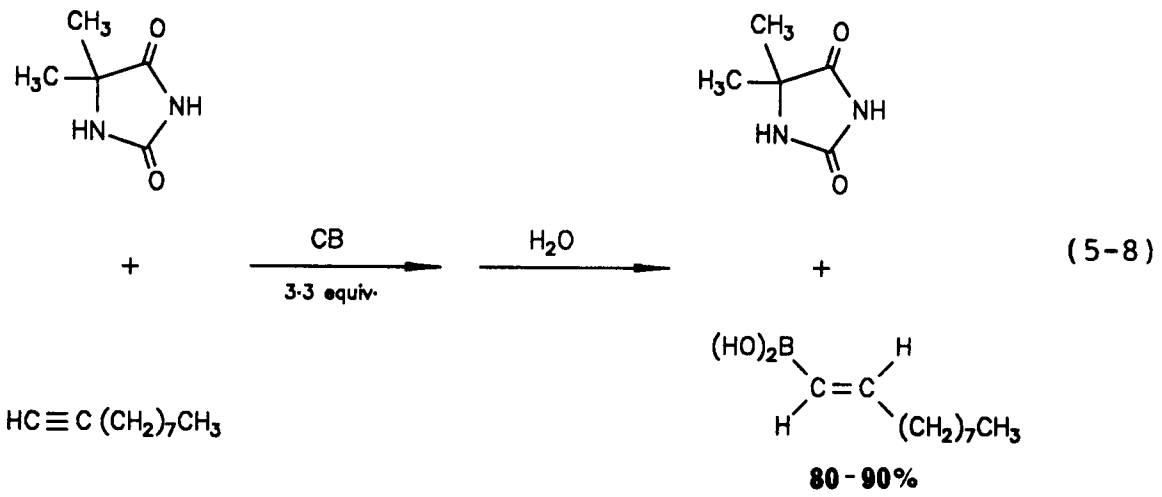
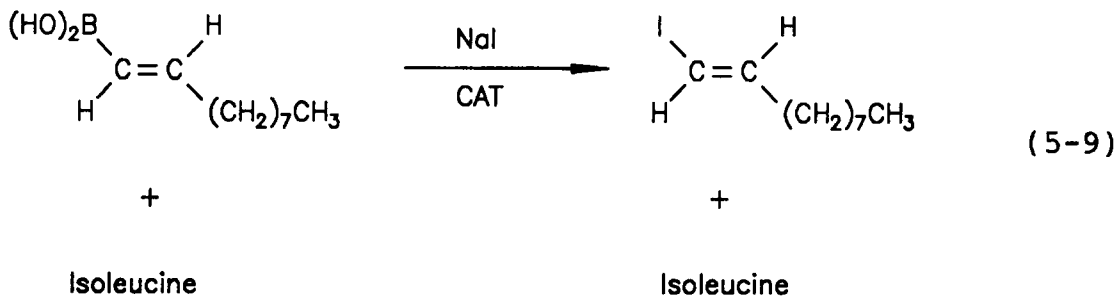


Figure 5-11. Carbon-13 NMR Spectrum of 5,5-Dimethylhydantoin, 1-Decyne, and Catechol borane (excess) Reaction Mixture After Hydrolysis in Aqueous THF (Experiment D).



(5-8)

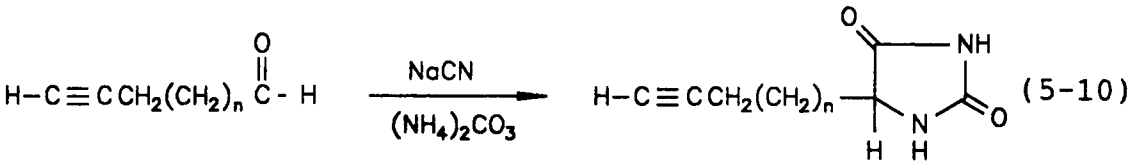
The second aspect of the proposed stategy which had to be addressed was whether or not the iodination reaction would be successful in the presence of amino acid functionality. As a test, a mixture of decenylboronic acid (2.5 mmol) and isoleucine (2.5 mmol) were subjected to the standard iodination reaction employing 1 molar equivalent of sodium iodide and two equivalents of chloramine T in aqueous THF solution. After workup and chromatography, trans-1-iodo-1-decene, 0.50 g (76%), was obtained (equation 5-9).



(5-9)

2. Preparation of Alkynyl Hydantoins

With successful results being obtained for the hydroboration and iodinations in the presence of hydantion and amino acid funtionality respectively, the synthesis of an iodovinylamino acid was initiated. Conversion of 10-undecynal to its hydantoin derivative via the Bucherer-Berg reaction led to 5-(10-undecynl-yl)-2,4-imidazolidine-1,3-dione in an 83% isolated yield (equation 5-10). A number of



(5-10)

carbonyl compounds were converted to their hydantoin derivatives, and the results are summarized in Table 5-1. ^{13}C-NMR data for the heterocyclic ring of each of these compounds are tabulated in Table 5-2. A few points deserve elaboration. In the preparation of the hydantoin derivatives of 10-undecynal and 4-pentynal, simple recrystallization generally afforded products of NMR purity. Further purification required repetitive recrystallization or chromatography, with a reduction in the yield obtained. During the course of these studies, it was observed that best results are obtained when the temperature of the reaction is strictly maintained between 55-60°C[516,517]; too high a temperature resulted in lower observed yields of the

Table 5-1: Preparation of Alkynyl and Alkyl Hydantoins

Carbonyl Compound	Isolated yield Hydantoin	Method of Purification[a]	mp, °C
10-Undecynal	83%	A	113
10-Undecynal	50%	B	116
11-Dodecyn-2-one	93%	B	79
4-Pentynal	57%	A	129
4-Phenyl-3-butyn-2-one	44%[b]	A,B	184[c]
Cyclopentanone	66%	A	204
Heptaldehyde	20%	A,B	148
2-Octanone	29%	A	108

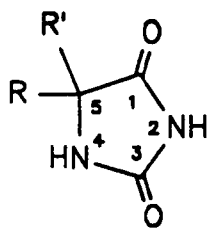
[a]Method of Purification
A = recrystallization
B = column chromatography

[b]Contains unknown impurity
[c]Sample decomposed

Table 5-2: ^{13}C-NMR Data of Hydantoin Derivatives[a]

R	R'	Solvent	C_1=O	C_3=O	C_5	R'
$HC\equiv C(CH_2)_8$-	H	$CDCl_3$	175.4	158.5	58.92	--
$HC\equiv CCH_2CH_2$-	CH_3	acetone-d_6	176.19	158.56	58.28	--
$HC\equiv C(CH_2)_8$-	CH_3	$CDCl_3$	178.10	157.58	63.83	23.82
$PhC\equiv C$-	CH_3	acetone-d_6	174.10	156.49	58.20	26.50
-$(CH_2)_4$-		DMSO-d_6	179.43	156.55	68.32	--
-$(CH_2)_4$-		CH_3OD	181.74	158.78	70.49	--
$CH_3(CH_2)_5$-	H	acetone-d_6	175.80	157.68	58.81	--
$CH_3(CH_2)_5$	CH_3	$CDCl_3$	178.41	157.98	63.93	23.71

[a]The hydantoin ring is numbered according to IUPAC nomenclature (LIV):

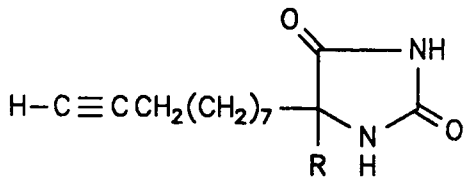


LIV

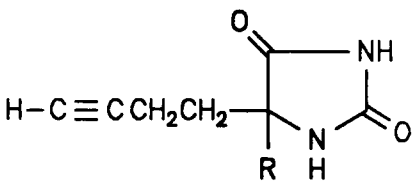
desired product and in formation of impurities.

3. Hydroboration of Alkynyl Hydantoins

Two compounds, 5-(10-undecen-1-yl)-2,4-imidazolidine-1,3-dione (LV), and 5-(4-pentyn-1-yl)-2,4-imidazolidine-,3-dione (LVI) were chosen as model compounds to assess the

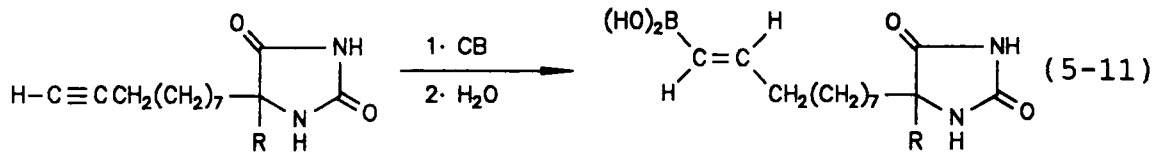


LV



LVI

the remaining synthetic steps. As anticipated, hydroboration of LV with catecholborane, followed by hydrolysis led to the corresponding vinylboronic acid hydantoin in 79% yield (equation 5-11). However, the desired vinylboronic



(5-11)

acid hydantoin was not obtained when the analogous hydroboration was attempted with LVI. Instead, it appears that reduction of the hydantoin ring occurred. Figures 5-12 and 5-13 show the ^{13}C- and proton NMR spectra of the crude product mixture which was obtained after hydrolysis. For reference, the ^{13}C-NMR spectrum of 5-(4-pentyn-1-yl-)-

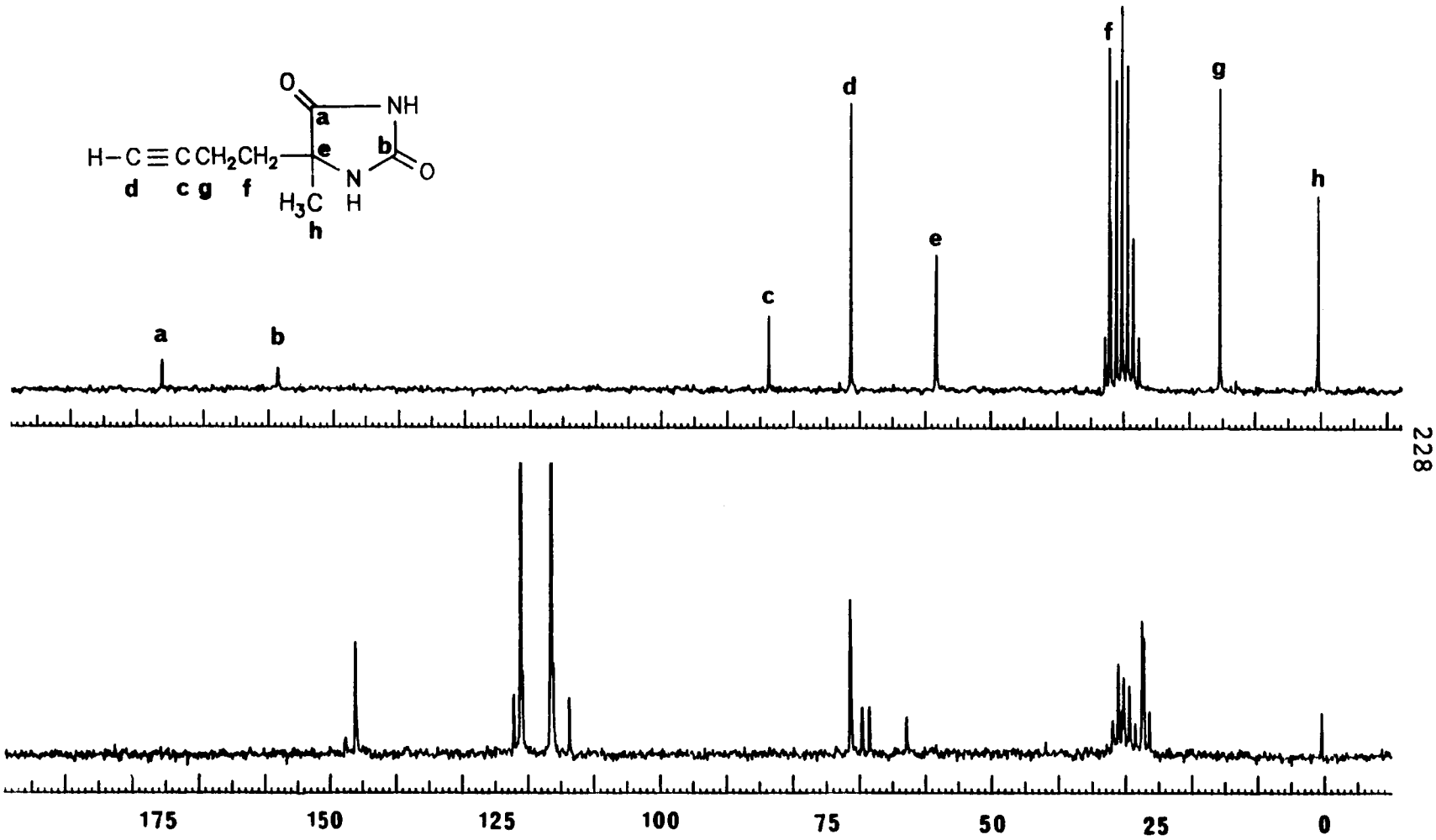


Figure 5-12. Carbon-13 NMR Spectra of 5-(4-Pentyn-1-yl)-2,4-imidazolidine-1,3-dione and Catecholborane (excess) Reaction Mixture After Hydrolysis in Acetone-d_6 and of 5-(4-Pentyn-1-yl)-2,4-imidazolidine-1,3-dione in Acetone-d_6 (above).

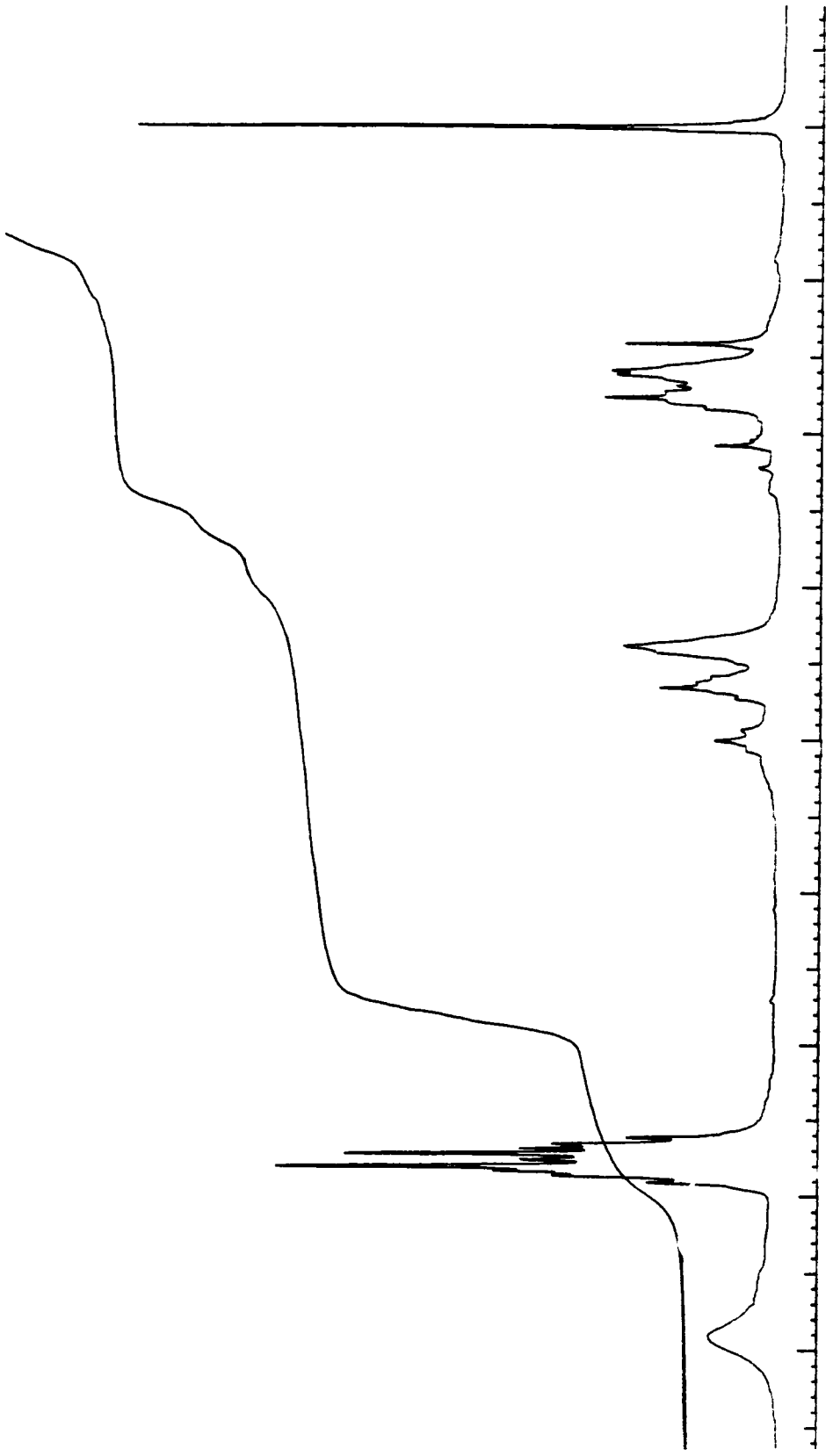
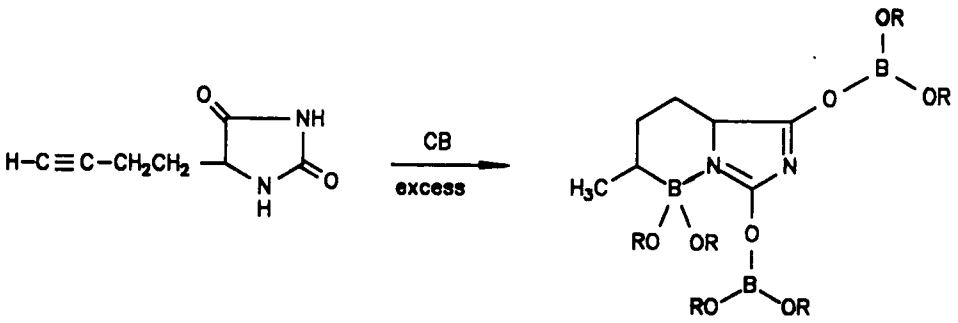


Figure 5-13. Proton NMR Spectrum of 5-(4-Pentyn-1-yl)-2,4-imidazolidine-1,3-dione and Catecholborane (excess) Reaction Mixture After Hydrolysis in Acetone-d_6.

hydantoin is also shown superimposed in Figure 5-12. It is readily apparant that the hydantoin peaks at 176, 158, and 58 ppm associated with the two carbonyls and the C_5 tertiary carbon of the hydantoin ring have disappeared. Now evident are carbon resonances in the 62 - 72 ppm range, the portion of the ^{13}C-NMR spectrum normally associated with alcohol functionality. In addition, the proton spectrum of the crude reaction mixture reveals the presence of three multiplets within the 3.2 - 4.2 ppm region in an approximate 1:1.5:2.0, possibly indicating the formation of reduced hydantoin product [one of the three multiplets undoubtedly corresponds to the C_5-H of the heterocyclic ring (originally at δ 4.2)]. Finally, the ^{11}B-NMR spectrum reveals a resonance at 17.8 ppm, indicating $B(OH)_3$ formation, not $RB(OH)_2$. Although a detailed study to determine the fate of the C_5-alkynyl hydantoin has not been carried out, it is conceivable that the close proximity of the hydantoin functionality affects the outcome of the reaction, for example, in the formation of a cyclic intermediate, a phenomenon well precedented and discussed in detail in Chapter I. In this experiment, initial loss of hydrogen was observed. Formation of a nitrogen-boron-alkyne complex could result (6-membered ring!), which, upon hydrolysis, may lead to a secondary alcohol at the original internal alkyne carbon (equation 5-12). The conditions of the above



(5-12)

reaction were the same as those used in the preparation of the hydantoin boronic acid of 5-(10-undecyn-1-yl)hydantoin, e.g., 4 equivalents of catecholborane, THF solvent, 60-70°C. [Note: although the hydroboration of 5-(10-undecyn-1yl)hydantoin was originally carried out at 45-50°C, it was later observed that the slightly higher temperature did not affect the yield.] Anticipating that the higher reaction temperature could lead to reduction of the hydantoin moiety in the C_5 alkynyl hydantoin, the reaction was repeated at 45-50°C for five hours. Unfortunately, the same results were obtained.

4. Test Experiments On the Hydrolysis of the Hydantoin Functionality in the Presence of the Vinylboronic Acid Moiety

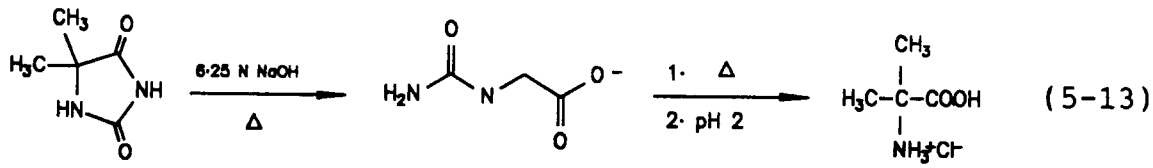
Having prepared a vinylboronic acid hydantoin, the next step of the synthesis involved the hydrolysis of the hydantoin functionality to the amino acid. However, before the hydrolysis step was attempted using this compound, one final

question needed to be addressed: specifically, the stability of the vinylboronic acid functionality to the harsh condition required to hydrolyze the hydantoin ring. Although the preparation of amino acids through hydantoins is well established, the hydantoin ring is generally resistant to cleavage by acid or base, acid hydrolysis being particularly more difficult than an alkaline one[297]. For example, in acid hydrolysis, hydantoins are typically refluxed in 6 N HCl for 96 hours at 110°C in order to obtain good yields of α-amino acids[303]. On the other hand, under alkaline conditions hydantoins are, in general, hydrolyzed to the corresponding amino acids in good yields at 110°C after 24 hours in aqueous sodium hydroxide solution[303]. Barium hydroxide is also frequently used to effect the hydrolysis; a temperature of 150-160°C for several hours being required[296,426]. Many modifications of the alkaline hydrolysis procedure have been introduced for the purpose of increasing the yield and shortening the reaction time[342,518,519,520]. One approach to the problem involves carrying out the alkaline hydrolysis at high temperatures and pressure[521,522,523]. This approach been has exploited for application toward the synthesis of ^{11}C-carboxyl labelled amino acids: hydrolysis of the hydantoin can be accomplished by reaction with 6.25 N NaOH at 210-220°C in a stainless steel bomb for 10 minutes[318].

It has been recognized that 5,5-dialkylhydantoins are much more resistant to hydrolysis than the corresponding 5-monoalkylhydantoins under the foregoing alkaline conditions[524]; the ease of hydrolysis following the general pattern: spirocyclopropylhydantoin > spirocyclobutylhydantoin > 5-methylhydantoin > 5,5-dimethylhydantoin > 5-ethyl-5-methylhydantoin > 5-methyl-5-pentylhydantoin >> 5,5-diisobutylhydantoin > 5,5-diisopropylhydantoin[524,525]. In one study[342], the hydrolysis of 5-ethyl-5-methylhydantoin required refluxing for 60 hours with 20% aqueous barium hydroxide at atmospheric pressure to effect hydantoin cleavage, while the extremely resistant 5,5-diisopropylhydantoin yielded only starting material at 180°C and 50 lbs/ins^2 pressure in an autoclave for several hours[525].

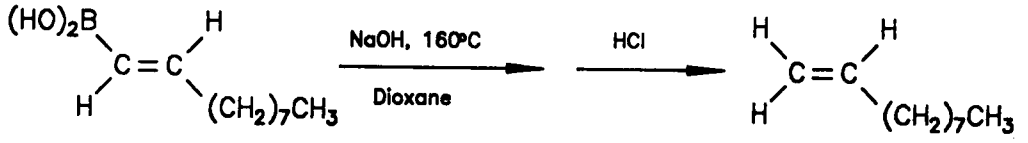
Although vinylboronic acids are generally stable to aqueous conditions, it was felt that high temperatures and long reaction times in strongly alkaline medium might be detrimental to the boronic acid functionality (base induced organoborate rearrangements are well known). In order to investigate the feasability of carrying out the hydrolysis in the presence of the vinylboronic acid functionality, a number of test experiments were conducted prior to proceeding with the synthesis of the iodovinyamino acid. Dimethylhydantoin and decenylboronic acid were chosen as model compounds for this study. When dimethylhydantoin was subjected

to basic hydrolysis with 6.25 N sodium hydroxide for 5 hours at 120°C (oil bath temperature), ^{13}C-NMR analysis (D_2O, basic, MeOH reference) of the crude reaction mixture following evaporation to dryness revealed carbon resonances at 186.83 (C=O, s), 56.17 (quaternary carbon, s) and 28.78 ppm (CH_3, q), indicating that sodium α-methyl-alaninate was the sole product. This was confirmed by comparison to standard spectra. Acidification of the reaction product (pH=2) gave the protonated α-methyl alanine [δ 175.3 (COOH), 57.84 (R_3C-NH_3^+), 24.03 (CH_3)] (equation 5-13). However, under the



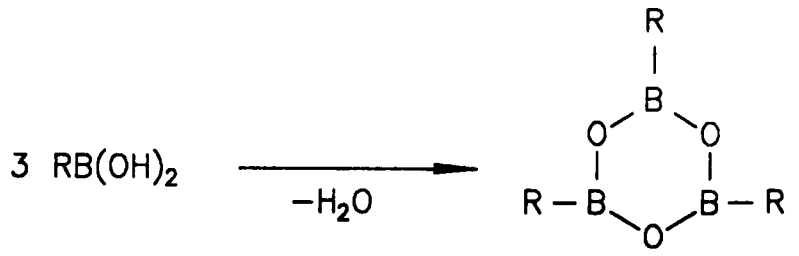
(5-13)

similar reaction conditions (dioxane was added to provide a homogeneous solution), decenylboronic acid did not appear to survive; upon heating, the reaction mixture became very dark in color. After neutralization of the reaction mixture with aqueous HCl, the ^{11}B-NMR spectrum revealed a peak at 19.6 ppm, indicating the possible presence of boric acid, whereas the starting vinylboronic acid exhibited a boron resonance at 28 ppm in aqueous medium. Presumably, the proton source is a strong enough electrophile to bring about protonation of the vinylboronic acid, with the resultant elimination of boric acid (equation 5-14).



(5-14)

In addition, it is probable that the high reaction temperature led to boroxine formation, as boronic acids are known to undergo facile dehydration[526] (equation 5-15). Thus, it



(5-15)

likely that the boroxine is actually undergoing the protonolysis reaction, rather than the boronic acid (equation 5-13). Further evidence for both of these side reactions will be discussed later in the chapter.

The failure of the vinylboronic acid functionality to survive the hydrolysis condition led to the search for an alternative hydrolysis method, preferably a room temperature hydrolysis procedure. A number of hydrolysis conditions were attempted using dimethylhydantoin as a test compound, and the results are displayed in Table 5-3. Decenylboronic acid was then subjected to some of the more promising hydrolysis conditions to determine whether or not the vinylboronic acid would survive. The results of these

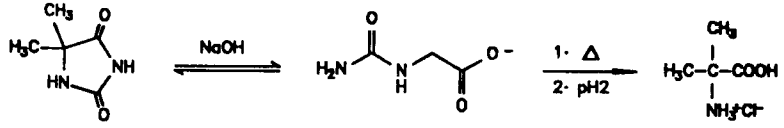
Table 5-3: The Hydrolysis of Dimethylhydantoin Under Various Conditions[a]

Hydrolysis Agent	Reaction Conditions[c]	^{13}C-NMR Relative Peak Intensity (CH_3)[b]			Product distribution[d,e]			Ref.
		I	II	III	I	II	III	
NaOH	A	--	--	8408	<5	<5	>90	318
$Ba(OH)_2$	B	3895	2305	11038	22.2	13.2	63.0	428
$NaOH/NH_4OH$	C	365	283	1660	15.8	12.3	71.9	523
$NaOH/NH_4OH$	D	--	--	5277	<5	<5	>90	523
NH_4OH/ZnO	E	5842	--	--	>90	<5	<5	527
NaOH	F	5822	1005	--	81.2	14.0	<5	--
NaOH	G	5853	3594	--	59.0	36.2	<5	--
NaOH	H	8666	3773	5788	47.5	20.7	31.7	--
$NaOH/V_2O_5$/PVP[f]	I	2844	1904	405	55.2	36.9	7.8	518[g]
H_2SO_4	J	10106	--	--	>90	<5	<5	297

[a]The hydrolysis of the hydantoin moiety (I) to the amino acid (III) is a stepwise process, involving the intermediate formation of the salt of hydantoic acid (II)[305];

Table 5-3 (continued)

longer reaction time, or higher temperatures gives a more profound breakdown to the corresponding amino acid (III)[296]. The above data is tabulated from the ^{13}C-NMR spectrum of the crude product mixture (basic!) using the plotted relative peak intensities obtained from the methyl resonances for the hydantoin (I), hydantoic acid (II), and amino acid (III) present (equation 5-16).



(5-16)

I II III

[b] ^{13}C-NMR recorded in D_2O solution (basic) and referenced to methanol (δ 49.8) or to dioxane (δ 68.0). Methyl resonances of the hydantoin (I), hydantoic acid (II), and α-methyl alanine (III) appeared at 25.10 ppm, 26.83 ppm, and 28.76 ppm respectively.

[c] Reaction conditions
A = 6.25N NaOH, 120°C, 5 hours
B = 2 equiv. $Ba(OH)_2$, 160°C, 6 hours
C = 6.25N NaOH (50:50 H_2O/Dioxane, 100°C, 6 hours
D = 6.25N NaOH (H_2O), 150°C, 8 hours
E = 9% NH_4OH, 6.5 equiv ZnO, 120°C, 6 hours
F = 2 equiv. NaOH, 50 mL H_2O, 25°C, 5 days
G = 2 equiv. NaOH, 50 mL H_2O, 25°C, 5 days, ultrasound
H = 2 equiv. NaOH, 50 mL H_2O, 140°C, 15 minutes
I = 4N NaOH (50 mL) , PVP (1g), V_2O_5 (1.5 mmol), 45°C, 72 hours, ultrasound
J = 60% H_2SO_4 (25 mL), 45°C, 16 hours, ultrasound

Table 5-3 (continued)

[d]Product ratio was determined by comparing ^{13}C-NMR relative peak intensities for the methyl resonance of the hydantoin, hydantoic acid, and methyl alanine and are reported as percentages. For example, in line 2, the 22.2% value for the hydantoin entry was calculated as follows: 3895/(3895 + 2305 + 11038) x 100 = 22.2%.

[e]The detection limit of the NMR instrument was assumed to be 5%. Thus, a value reported as >90% essentially means that neither of the other two components were detected.

[f]PVP = polyvinylpyridine

[g]Other pertinent references are: Chem. Abstr. 84, 44666k; Chem. Abstr. 83, 10844f; Chem. Abstr. 94, 46804.

experiments are shown in Table 5-4. In some cases, dual experiments were conducted (equimolar mixture of 5,5-dimethylhydantoin and decenylboronic acid were simultaneously subjected to identical hydrolysis conditions). These results are also summarized in Table 5-4. The survival or decomposition of the vinyl boronic acid moiety to the various hydantoin hydrolysis conditions was based on the observed chemical shift in the ^{11}B-NMR spectrum, and from the presence or absence and observed chemical shift of the vinylic carbon resonances in the ^{13}C-NMR spectrum of the crude reaction mixture. Since, the observed chemical shift in the ^{11}B-NMR spectrum for organoboron compounds is frequently solvent dependent, it was necessary to determine the chemical shift for decenylboronic acid in various solvent systems so as to have an accurate standard for comparison. Thus, the ^{11}B-NMR spectrum of known decenylboronic acid was recorded in the various solvent systems used in the hydrolysis experiments, and the data are tabulated in Table 5-5. Likewise, for similiar reasons, the ^{13}C-NMR data for decenylboronic acid in the various solvent systems is presented in Table 5-5 as well. It was quite surprising to find out that both vinylic carbon resonances are observed in $CDCl_3$ solutions, whereas in ethereal solvents such as THF, only the vinylic carbon beta to the boronic acid group is observed, due to boron's quadrapole

Table 5-4: Study on the Survival of Decenylboronic Acid to Various Hydantoin Hydrolysis Conditions

Hydrolysis Agent	Reaction Conditions[a]	NMR Analysis[b,c,d] Crude Product, δ ^{11}B	^{13}C	Solvent	Result
NaOH	A	29	138.47 113.41	THF	Decomposed
NaOH	B	29	150.14 138.47 113.41	THF	Decomposed
NaOH[e]	C	28[f]	150.14	THF	Stable[g]
$NaOH/NH_4OH$/ Dioxane	D	29	157.87 155.41 143.95 125.59	$CDCl_3$	Decomposed
$NaOH/NH_4OH$/ Dioxane[e]	E	19	138.45 113.42	THF	Decomposed
NH_4OH/ Dioxane	F	19	152.60	NH_4OH/ Dioxane	Stable
NH_4OH[e]	G	28[f]	149.75	THF	Stable
Na_2CO_3[e]	H	28[f]	149.75	THF	Stable
$(NH_4)_2CO_3$[e]	I	29	157.74	THF	Stable

[a]Reaction Conditions
A = 6.25 N NaOH, 160°C, 6 hours
B = 1.5 N NaOH, 120°C, 20 minutes
C = 6.25 N NaOH (100 mL), room temperature, 14 days
D = Solid NaOH (31.25 mmol, 1.25 g), concentrated NH_4OH (28%, 10 mL), dioxane (10 ml), 160°C, 3 hours
E = Solid NaOH (200 mmol, 8.0 g), concentrated NH_4OH (28%, 32 mL), dioxane (20 mL), nitrogen atmosphere, 150°C, 5 hours
F = NH_4OH (28%, 5 mL), dioxane (5 mL), 100°C, 6 hours
G = NH_4OH (28%, 100 mL), nitrogen atmosphere, room temperature, 17 days

Table 5-4 (continued)

H = Na_2CO_3 (100 mmol), water (200 mL), nitrogen atmosphere, room temperature, 17 days
I = $(NH_4)_2CO_3$ (100 mmol), water (200 mL), nitrogen atmosphere, room temperature, 17 days

[b] ^{11}B-NMR spectra were referenced to BF_3:OEt_2 (δ = 0.0)
^{13}C-NMR spectra were referenced to the NMR solvent

[c] See Table 5-5 for reference spectral data of known decenylboronic acid in various solvents

[d] ^{13}C-NMR data are reported for vinylic carbons

[e] Dual experiment involving equimolar mixture of decenylboronic acid and 5,5-dimethylhydantoin

[f] Crude product was neutralized to pH 6.5 and extracted into ether prior to NMR analysis

[g] The presence of other small vinylic carbon peaks are noted, indicating possible partial decomposition

Table 5-5: ^{11}B-NMR and ^{13}C-NMR Data of Decenylboronic Acid in Various Solvents

Solvent	^{11}B-NMR	$(HO)_2BCH=\underline{C}HR$	$(HO)_2B\underline{C}H=CHR$
THF	28	149.53	absent
$CDCl_3$	28	157.98	153.21
$CDCl_3$/THF	28	157.73	152.29[a]
Dioxane	27	152.10	144[d]
Dioxane/H_2O 50:50	21	--	--
Dioxane/NH_4OH[b] 50:50	19	151.90	absent
Dioxane/NaOH[c] 1:2	2.4	--	--

[a]small peak

[b]28% NH_4OH used

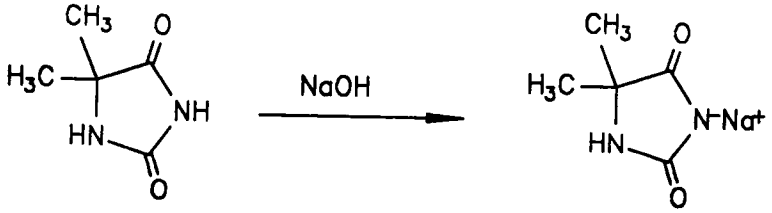
[c]1.5 N NaOH

[d]small broad hump centered at 144 ppm

moment. In order to investigate the effect of added base on decenylboronic acid in dioxane solution, a common solvent system used in the hydrolysis reactions, a sample of decenylboronic acid in dioxane was placed in a 10 mm NMR tube and its ^{11}B-NMR spectrum recorded. Upon addition of aqueous ammonium hydroxide (28%, 5 drops), a shift in the ^{11}B-NMR spectrum from 27 ppm to 21 ppm was observed, indicating the formation of a boron nitrogen complex. Further addition of aqueous NH_4OH did not change the chemical shift further. When aqueous NaOH was added to this solution, The broad peak at 21 ppm disappeared, with the concurrent formation of a sharp peak at 2.4 ppm, indicating the formation of the organoborate salt. Acidification of this mixture resulted in the observance of a broad peak at 18 ppm, presumably due to the regenerated vinylboronic acid. To confirm that the vinylboronic acid was indeed regenerated upon acidification of the organoborate complex, a sample of decenylboronic acid in dioxane was made basic with 6.25 N NaOH, and then reacidified with 1 N HCl. The product was extracted into ether, dried, and solvent removed to give a quantitative recovery of decenylboronic acid, as confirmed by a ^{11}B-NMR peak at 28 ppm (THF) and a vinylic resonance at 149 ppm (THF) in the ^{13}C-NMR spectrum. Thus, the vinyl boronic acid moiety proved to be stable to the base - acid transformation, required during the hydrolysis conditions

for the hydantoin ring. These results are also included in Table 5-5.

Equally important to the interpretation of the data, was an understanding of solvent and acid - base effects on the chemical shift of the carbonyl resonances of the hydantoin ring. Thus, the ^{13}C-NMR spectra of 5,5-dimethylhydantoin in various solvent systems were recorded, and the data are presented in Table 5-6. The large observed chemical shift changes observed for the hydantoin carbonyls should be noted. In basic solution, the C-1 carbonyl shifted from 182.8 ppm to 197.44 ppm, while the C-3 carbonyl shifted from 158.5 to 173.4 ppm (D_2O/dioxane). However, the spacing (in Hertz) between the two peaks remained unchanged. This was interpreted to indicate formation of the sodium salt of the hydantoin (equation 5-17).



(5-17)

As can be seen from the data presented, those hydrolysis conditions which effected hydrolysis of the hydantoin to the amino acid resulted in decomposition of the vinylboronic acid moiety. In contrast, hydrolysis conditions which were found to be conducive to the survival of the

Table 5-6: ^{13}C-NMR Data of 5,5-Dimethylhydantoin in Various Solvents

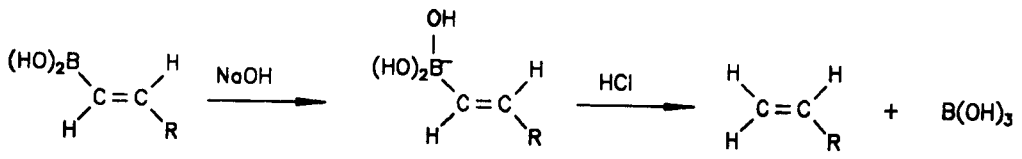
Solvent	C_1=O	C_3=O	C_5	CH_3
THF	177.98	155.98	59.01	24.96
D_2O	182.76	158.47	61.33	24.31
D_2O/NaOH	197.44	173.20	61.60	22.86

boronic acid functionality did not result in the hydrolysis of the hydantoin moiety to the amino acid. This is presented in a more concise format in Table 5-7. In the high temperature experiments involving sodium hydroxide or sodium hydroxide/ammonium hydroxide mixtures as the hydrolytic agent, a shift in the vinyl carbon resonances occurred. For example, in the experiment involving sodium hydroxide/ammonium hydroxide in dioxane, the vinyl carbon adjacent to the boronic acid group ($CDCl_3$) shifted from 153.21 to 155.21, while a shift from 157.98 to 157.87 was observed for the beta carbon, indicating boroxine formation. In addition, two other olefinic resonances were observed at 143.95 and 125.59, providing evidence that protonation of vinylboronic acid occurs. Peaks due to oxidation products were also present in the ^{13}C-NMR spectra of some hydrolysis mixtures. For example, when aqueous sodium hydroxide/ammonium hydroxide was used as the hydrolysis agent, a ketone resonance at 195.42 and an alcohol resonance at 65.53 were observed. Even the room temperature hydrolysis with sodium hydroxide (17 day period) had minor amounts of oxidized products in the reaction mixture. On the other hand, when hydrolysis was done under inert atmosphere, no oxidation products were observed. Thus, decenylboronic acid was stable to hydrolytic conditions at room temperature under inert atmosphere when either ammonium hydroxide, sodium

Table 5-7: Summary of Hydrolysis Experiments Involving 5,5-Dimethylhydantoin and Decenylboronic Acid

Hydrolysis Conditions	Amino Acid Formed from Hydantoin?	Decenylboronic Survived?
NaOH, 100 - 160$_{o}$C	Yes	No
NaOH/NH_4OH, 160°C	Yes	No
NaOH/NH_4OH, 150°C, N_2	Yes	No
$Ba(OH)_2$, 160°C	Yes	No
NaOH, 25°C, 17 days	No	No
NaOH, 25°C, 17 days, N_2	No	Yes
NH_4OH, 25°C, 17 days, N_2	No	Yes
NH_4OH, 100°C, 6 hours	No	Yes
Na_2CO_3, 25°C, 17 days, N_2	No	Yes
$(NH_4)_2CO_3$, 25°C, 17 days, N_2	No	Yes

carbonate, or ammonium carbonate were employed as the base. However, hydrolysis at high temperature under inert atmosphere still resulted in decomposition of the boronic acid. For example, alkene formation was indicated (entry 5, Table 5-4, p. 240), from the olefinic carbon resonances at 138 and 113 ppm and the missing olefinic carbon resonance at 149. Presumably, intramolecular rearrangement of the organoborate occurs with protonation of the vinyl carbon - boron bond and resultant elimination of boric acid (equation 5-18).

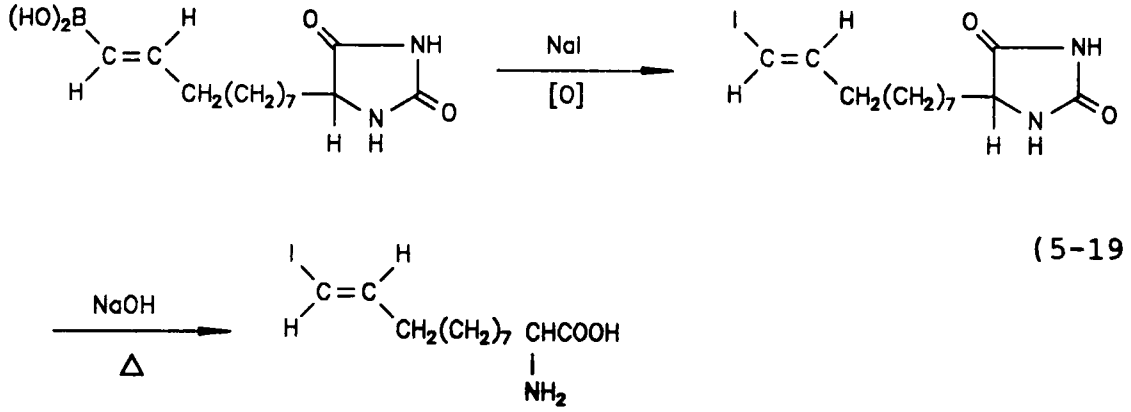


(5-18)

As is summarized in Table 5-7, all attempts at finding a set of hydrolysis conditions which would provide the amino acid in the presence of vinylboronic acid functionality met with failure. Even ultrasound agitation (Table 5-3, p. 236, entry 7), or other known catalytic hydrolysis procedures (Table 5-3, p. 236, entries 5 and 9), failed to provide the corresponding amino acid at room temperature. Presumably, the 5,5-dialkylhydantoin system is too stable to be hydrolyzed effectively at room temperature. Unfortunatly, the vinyl boronic acid is not stable to high temperature conditions.

5. Synthesis of 2-Amino-12-iodo-11-dodecenoic acid

The failure to find a suitable set of hydrolysis conditions lead to a modification of the synthetic strategy which was being used to prepare the iodovinyl amino acid. A simple modification involved reversing the last two steps of the synthetic scheme: iodination of the hydantoin-vinylboronic acid would provide the iodovinylhydantoin, which could then be hydrolyzed to the corresponding amino acid (equation 5-19).

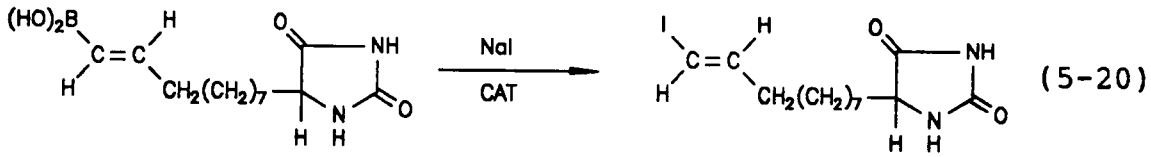


(5-19)

This approach was not considered at first because it had been presumed that the iodovinyl functionality would not be stable to the harsh conditions required to hydrolyze the hydantoin ring to the amino acid. More importantly, radiopharmaceutical considerations led us initially to reject this pathway, since in radiopharmaceutical synthesis, it is highly desirable to radiolabel the molecule in the last step of the synthesis due to nuclide half-life considerations.

Surprisingly, the iodovinyl moiety was found to be stable to the hydrolytic conditions required to bring about hydantoin hydrolysis, as treatment of 1-iododecene with 6.25 N NaOH in dioxane at 150°C for 4 hours afforded a quantitative recovery of starting material. Thus, this approach became a viable alternative.

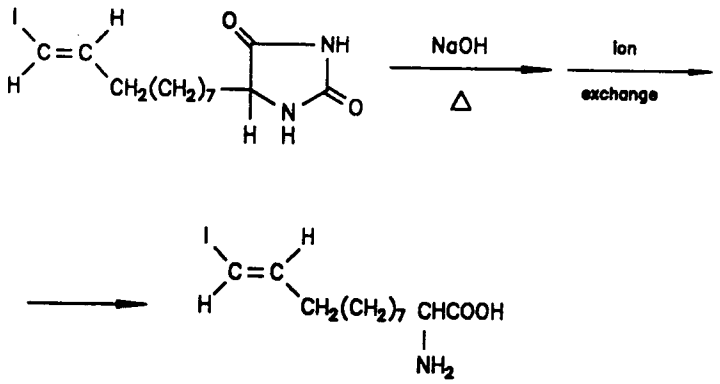
As before, 5-(10-undecenylboronic acid-1-)2,4-imidazolidine-1,3-dione was chosen as the model compound. Unfortunately, anticipated iodination of the vinylboronic acid hydantoin using the standard iodination conditions [1 equiv. NaI, 2 equiv. chloramine T, THF/H_2O (50%)] resulted in a low yield of the desired iodovinyl derivative. TLC analysis of the crude reaction mixture revealed numerous impurities (9-10 spots), which required tedious separation. After three purifications by column chromatography, a 13.7% yield (100mg) of the desired 5-(11-iodo-10-undecec-1-yl-)2,4-imidazolidine-1,3-dione was realized (equation 5-20).



(5-20)

Having obtained the desired iodovinyl hydantoin, basic hydrolysis (6.25 N NaOH, dioxane, 150°C 4 hours) gave the desired iodovinyl amino acid, following purification by ion

exchange chromatography (equation 5-21).



(5-21)

The standard sodium iodide-chloramine T procedure for preparing iodoalkenes from vinylboronic acids proved to have a troublesome aspect associated with it when applied to the preparation of the iodovinylhydantoins. The toluenesulfonamide by-product, by coincidence, had nearly same R_F as that of the product in a number of solvent systems, requiring tedious separation procedures in order to obtain pure product. For this reason, the iodine monochloride procedure developed by Kabalka and Gooch[267] was also tried. Although purification of the desired product was less troublesome using this method, the yield of the iodovinyl hydantoin did not improve. In fact, treatment of the vinylboronic acid hydantoin with a stoichiometric amount of iodine monochloride in the presence of sodium acetate gave only 8 mg (2%) of the anticipated iodovinylhydantoin.

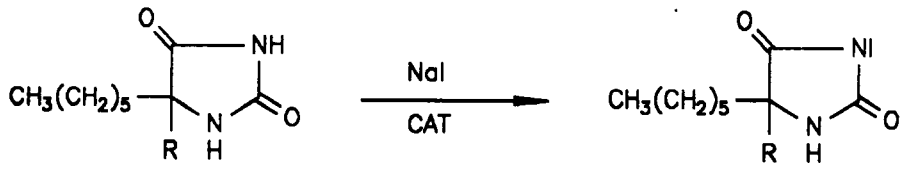
In both procedures, the reaction proceeded in a manner similar to the iodination of a simple aliphatic vinylboronic

acid. For example, upon addition of the chloramine T solution to the reaction mixture containing the boronic acid and one equivalent of sodium iodide, the reaction mixture became dark brown in color, suggesting the formation of the electrophilic "I^+" species. Within 30 seconds, the dark color disappeared. With simple boronic acids, the disappearance of the dark brown color signified the uptake of the electropositive iodine, and completion of the reaction. However, in the iodination of the hydantoinylvinylboronic acid, although the dark brown color was observed to disappear, very little of the desired iodovinyl derivative was obtained. It soon became apparent that the hydantoin functionality was consuming the electrophilic iodine.

6. Iodination in the Presence of the Hydantoin Moiety: Protection of the Hydantoin Ring

The consumption of electrophilic iodine by the hydantoin moiety was a problem that was not anticipated. Inspection of the literature revealed a series of papers published by Orazi and Corrall involving the preparation of N-halohydantoin derivatives[345,346,347,348,349,352,358,359,360], a topic which was discussed in Chapter I. In order to investigate the iodination reaction in the presence of hydantoin functionality more thoroughly, a number of model experiments were conducted. 5,5-Dimethylhydantoin was

subjected to the standard sodium iodide/chloramime T iodination procedure employing one equivalent sodium iodide and two equivalents chloramine T. Within 30 seconds of the addition of the final reagent, chloramine T, the dark brown color had disappeared, indicating the consumption of the electrophilic iodine species. TLC analysis of the crude reaction mixture revealed the absence of the starting material, and the presence of a faster moving spot, as well as a minor spot near the solvent front (40% ethyl acetate-petroleum ether). NMR analysis confirmed that selective N-3 iodination of the hydantoin ring had occurred. Further confirmation of this was provided by comparing the spectrum obtained with that of a known sample of 3-N-iodohydantoin prepared via a published procedure by Orazi[358,360]. The iodination of 5-(hexyl-1-)2,4-imidazolidine-1,3-dione proceeded in a similar manner (equation 5-22). Although



(5-22)

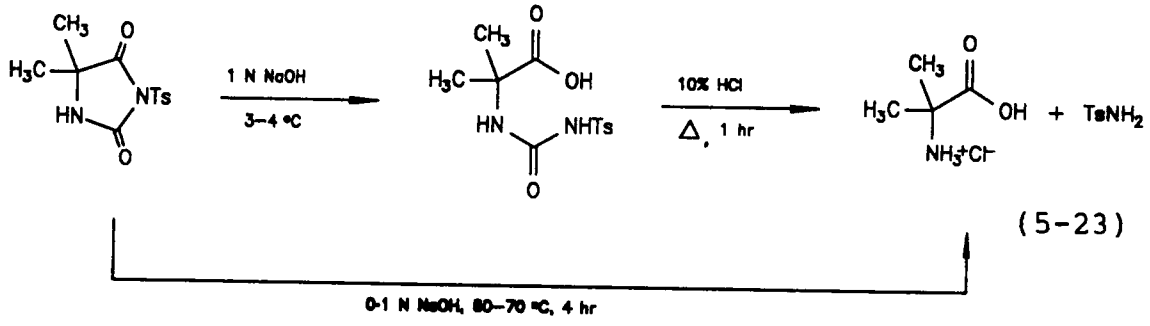
the observed iodination was an undesirable result in terms of the desired application, the procedure does offer a new alternative to the known preparation of 3-N-iodohydantoins.

Two basic approaches were undertaken to circumvent the iodination of the hydantoin nitrogens. One approach

involved carrying out the iodination reaction in aqueous, acidic medium. Such an approach was used successfully by the Kabalka group in the preparation of p-iodo-N-isopropyl amphetamine from the p-boronic acid precursor. Hexylhydantoin was chosen as the test example because it more closely approximated the C-11 model compound. When this compound was treated with one molar equivalent of sodium iodide and aqueous chloramine T in 10% HCl, and the reaction monitored by TLC, no reaction was observed. TLC analysis showed only the presence of starting material. In addition, the dark brown color never really disappeared, but changed to a brown-green color. However, the failure of this reaction probably was due to limited solubility of the hexylhydantoin in aqueous medium rather than protection of the hydantoin moiety by protonation. When the reaction was repeated using 5-(10-undecenylboronic acid-1-)hydantoin, with THF added to provide a homogeneous solution, a different course of events was observed. The dark brown color readily disappeared within 30 seconds, indicating that the electropositive iodine had been consumed. TLC analysis of this mixture, however, revealed the presence of numerous spots, similar to that observed with the standard iodination method, and ^{1}H-NMR revealed only a trace (nonintegratable) of an iodovinyl group. No attempt was made to isolate the small amount of product from the reaction mixture.

A second approach to circumventing the iodination of the nitrogen atoms of the hydantoin ring involved the use of protecting groups. Very litle information is available on the use of protecting groups with the hydantoin moiety. In fact, the results of a very thorough literature search on the hydantoin molecule were discussed in Chapter I. As was noted earlier, since the acidity of the imide nitrogen (pKa = 9.12)[528] is much greater than that of the amide nitrogen at N-1 (pKa ≈ 14)[326,529], selective substitution at the N-3 site, in principle, can be achieved. Unfortunately, with the exception of a very recent alkylation procedure reported by Poupaert[334], known methodologies of preparing substituted hydantoin derivatives have not been selective, and have been invariably plagued with competitive N-1 substitution as well[297,326,331,332,333]. Alkylation of the hydantoin ring was not considered as a viable protection means, due to the eventual difficulty of removing the protecting group. Very few reports on N-heterosubstituted hydantoins exist in the literature[335,337,338,339,340,341,342,530]. Among these, only the N-3-tosyl derivatives, prepared by Hiroi and co-workers as a means of providing a mild hydrolytic ring cleavage of the hydantoin ring to the corresponding hydantoic acids and amino acids[342], were considered to be a candidate for use as a protecting group. The advantage of using the tosylate group at the N-3 position as a protecting

group is immediately obvious. Not only would this functionality provide a means of protecting the N-3 site from iodination, its presence would permit the use of much milder hydrolytic conditions to effect the hydrolysis of the hydantoin ring as a result of the group's electron withdrawing capability. For example, whereas hydrolysis of the hydantoin to the amino acid normally requires temperatures in excess of 150°C for many hours under strongly alkaline conditions, the presence of the tosyl group has been reported to provide initial hydrolysis to the hydantoic acid stage upon treatment with 0.1 N sodium hydroxide at 3-4°C for four hours, while final cleavage to the amino acid could be accomplished by further reaction of the tosylureido acid with 10% HCl at reflux temperature for one hour (equation 5-23). Alternatively, the amino acid can be prepared directly

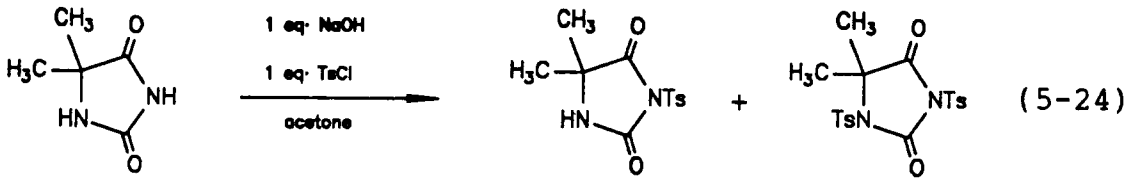


(5-23)

from the 3-N-tosylhydantoin by treatment with 0.1 N sodium hydroxide at 60-70°C for 4 hours for even the most resistant of hydantoins (equation 5-23, R = R' = iosbutyl). Finally, removal of the protecting group is automatically

accomplished during the final hydrolysis step (decarboxylation), the elimination products being toluenesulfonamide and carbon dioxide (equation 5-23).

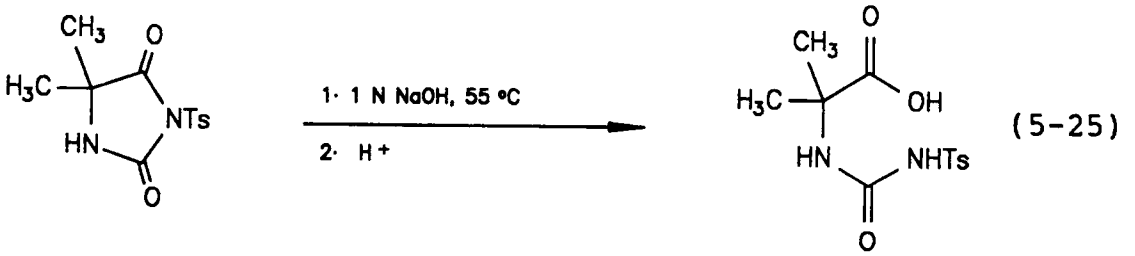
With this in mind, a number of model experiments to test the feasability of this methodology were conducted. Tosylation of 5,5-dimethylhydantoin provided a mixture of the mono (9.4%) and ditosyl adducts (24.2%) which were separated by recrystallization from different solvents (equation 5-24). As was expected the yield of the desired



(5-24)

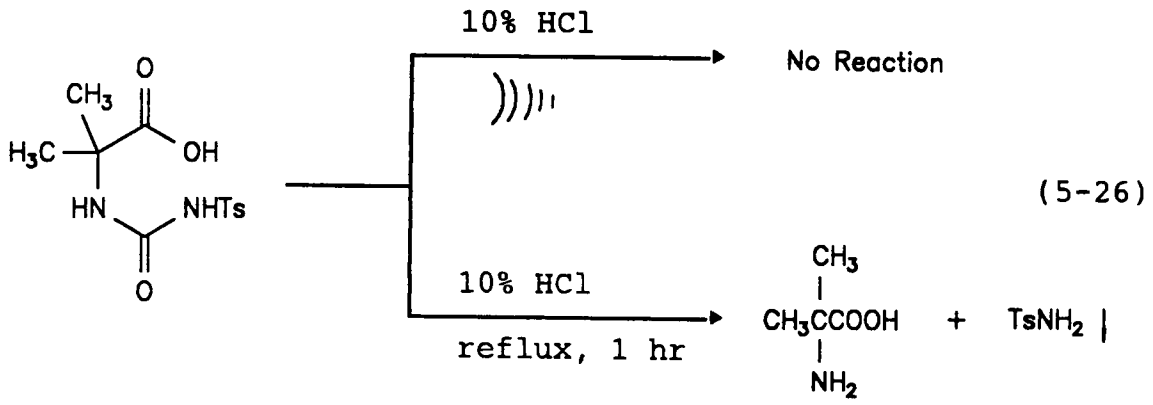
N-3 tosyl derivative was low, and the procedure was not very selective in providing the monotosyl derivative.

Using the monotosyl derivative thus prepared, treatment with 1 N sodium hydroxide at 55°C for 3.5 hours, followed by acidification of the reaction mixture upon cooling to room temperature (pH < 2) gave 2,2-dimethyl-5-tosylhydantoic acid in a 54% (literature yield = 32%) isolated yield (equation 5-25). With the preparation of this compound, an attempt



(5-25)

was made to determine how mild the reaction conditions must be in order to obtain the amino acid. Unfortunately, treatment of this compound with 10% HCl (DMSO, 2 mL, being added to dissolve the starting material) in an ultrasonic bath for 24 hours produced only unreacted starting material (equation 5-26). Use of the literature procedure[342] (10%

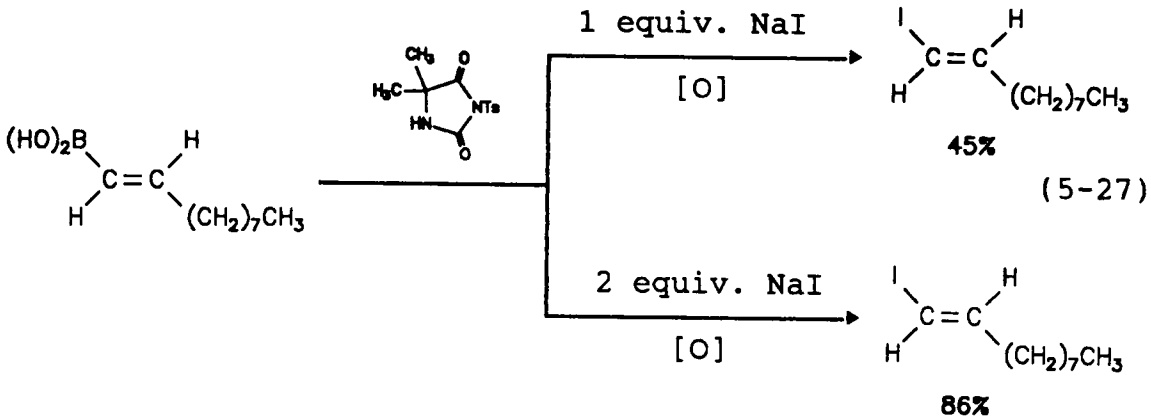


(5-26)

HCl reflux, 1 hour), however, afforded the desired 2-amino-2-methyl-propanoic acid hydrochloride in a 29% yield after recrystallization (equation 5-26).

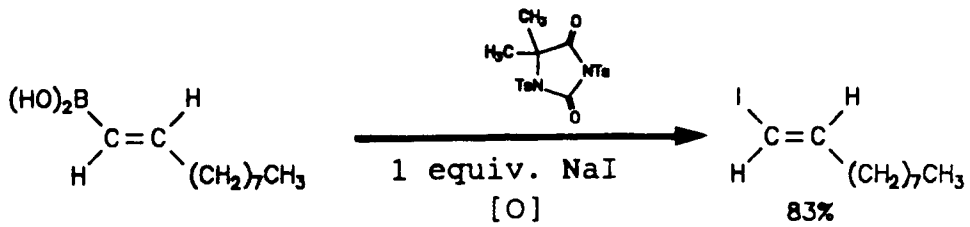
In order to investigate whether the tosyl group would protect the imide nitrogen, two test experiments were conducted. The first experiment involved treatment of an equimolar mixture of decenylboronic acid and 3-N-tosylhydantoin with one equivalent of sodium iodide under oxidizing conditions (chloramine T). As before, the dark brown color disappeared within 30 seconds, indicating completion of the reaction. After workup and purification by column

chromatography, (E)-1-iododecene was obtained in a 45% yield (equation 5-27). In the second experiment, when an equimolar mixture of decenylboronic acid and 3-N-tosylhydantoin with two equivalents of sodium iodide under oxidizing conditions (chloramine T), an 86% yield of (E)-1-iododecene was obtained (equation 5-27). In final experiment, an



(5-27)

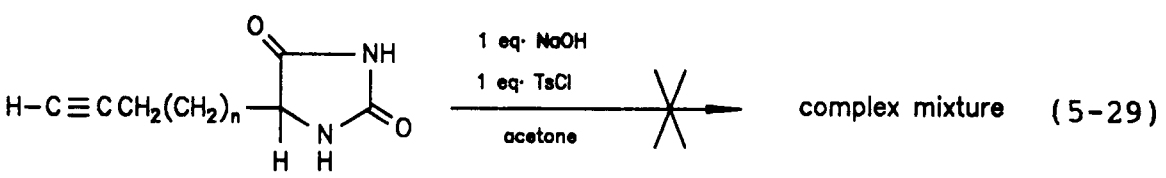
equimolar mixture of decenylboronic acid and N,N-ditosylhydantoin was treated with one equivalent of sodium iodide. In this case, an 83% yield of (E)-1-iododecene was realized (equation 5-28).



(5-28)

From these experiments, it was determined that at least three equivalents of iodide would be necessary in order to carry out a high yielding iodination reaction of a

vinylboronic acid hydantoin. Thus, an obvious solution to the iodination problem would involve the use of excess iodinating agent. Unfortunately, from a radiopharmaceutical standpoint, this is a highly undesirable solution; the cost of the radionuclide makes this a prohibitive alternative. The use of the ditosyl hydantoin derivative was not considered as a viable solution either, because ultimately, the tosyl group on the N-1 position would have to be removed. Additionally, the yield of the ditosyl compound was very low (<10%). At this point, it was decided to proceed with the use of the N-3 tosylated hydantoin on the model compound, and accept a 50% yield, using one equivalent of iodination agent, as the maximum attainable yield. Unfortunately, the tosylation of the model compound, 5-(10-undecenylboronic acid-1-)2,4-imidazolidine-1,3-dione did not proceed as planned; a complex mixture of tosylated compounds were obtained (broad humps in the aromatic region were observed in the ^{13}C-NMR spectrum of the crude reaction mixture, indicating the presence of many aromatic lines) (equation 5-29). No separation of the reaction mixture was attempted.



(5-29)

With this failure, the approach using the tosyl group for

protection of the hydantoin moiety was abandoned.

Amine functionality is commonly protected with urethane groups[531]. Among the many protecting groups available, the t-butoxycarbonyl group (BOC)[532,533] is widely used and of utmost importance, especially for its use in amino acid and peptide chemistry[534]. Although the use of the t-butoxycarbonyl group has never been reported with the hydantoin moiety, it was a logical choice for the desired application. The procedure chosen for introducing the BOC group was the one reported by Dean[535] involving the use of di-t-butyl dicarbonate. Upon treatment of 5-(10-undecyn-1-yl)-2,4-imidazolidine-1,3-dione with triethylamine (two equivalents) and di-t-butyl dicarbonate (2.2 equivalents), two products were obtained. The first product isolated by column chromatography (faster moving spot on TLC) was the di-BOC derivative, which was isolated in a 16% yield. The second product was the BOC derivative resulting from selective N-3 substitution, which was obtained in a 39% yield. Unfortunately, the protection method was not selective in introducing the BOC group to the N-3 position. This, however, was not surprising, given that most subsutitution reactions involving the nitrogen atoms of the hydantoin ring are not selective. In order to explain further results, it is necessary to show the NMR spectra obtained for these two compounds. Thus, Figures 5-14, 5-15, 5-16, and 5-17) show

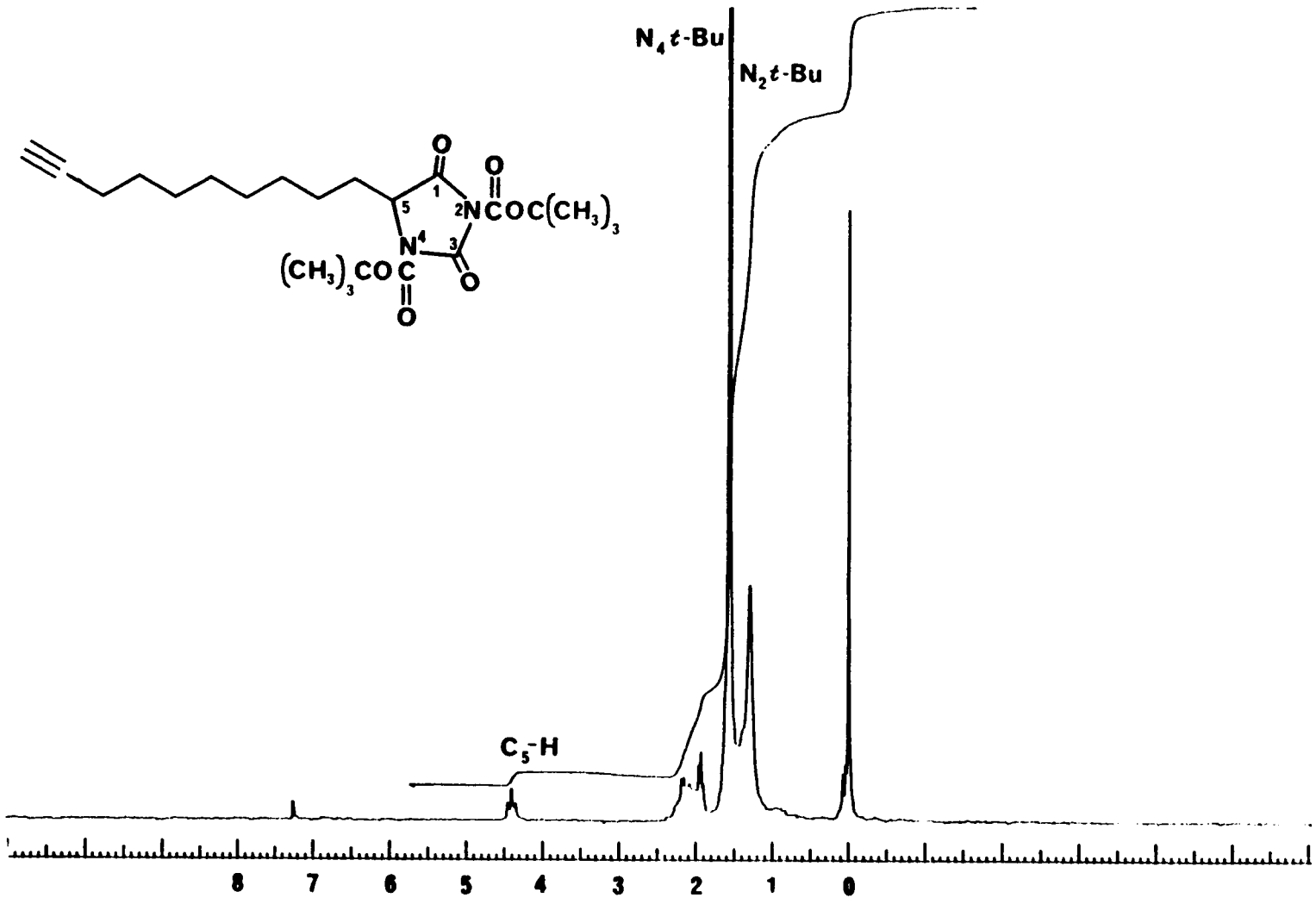


Figure 5-14. Proton NMR Spectrum of N,N-Di-t-Butoxycarbonyl-5-(10-Undecyn-1-yl)-2,4-Imidazolidine-1,3-dione.

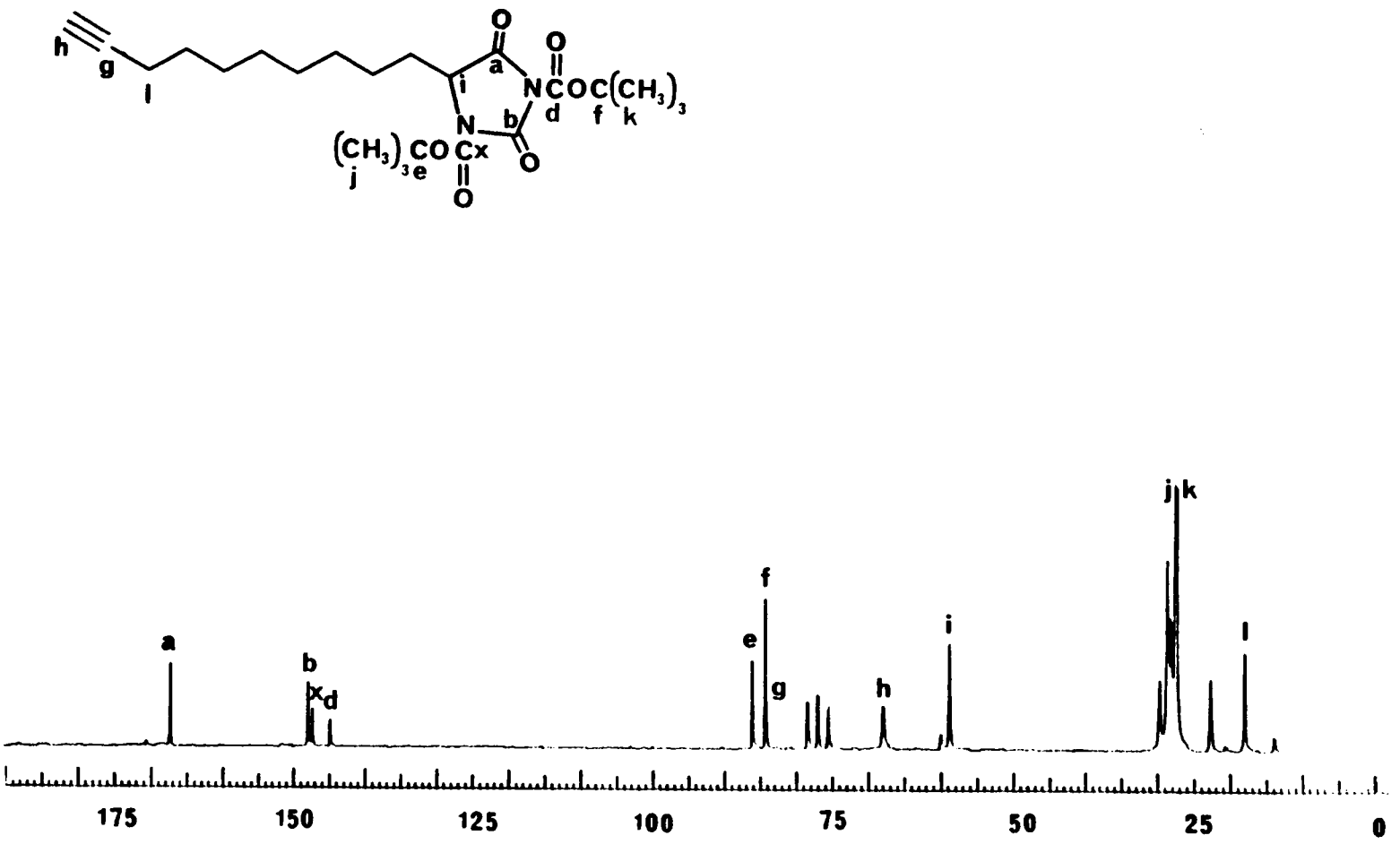


Figure 5-15. Carbon-13 NMR Spectrum of N,N-Di-t-Butoxycarbonyl-5-(10-Undecyn-1-yl)-2,4-Imidazolidine-1,3-dione.

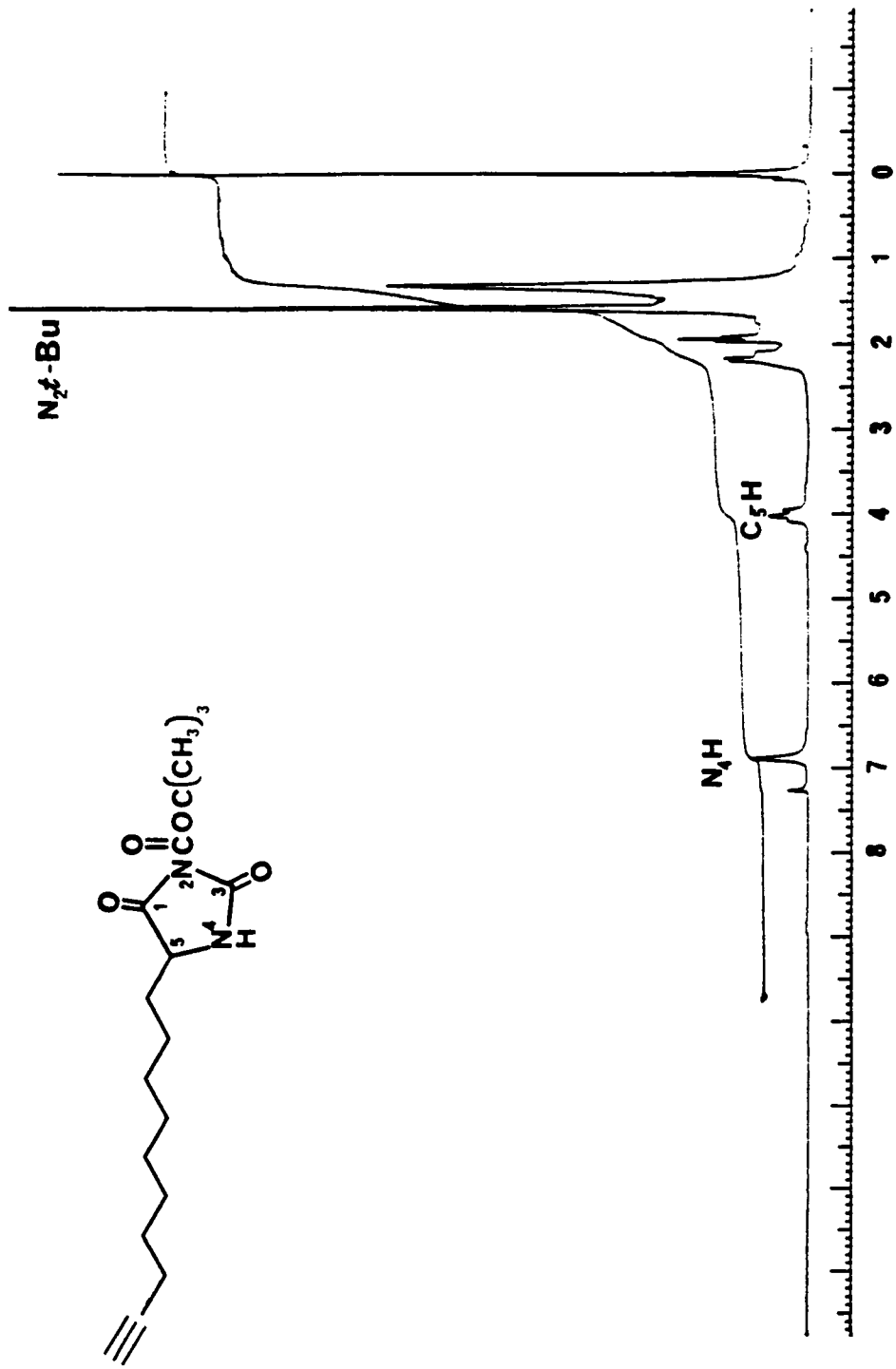


Figure 5-16. Proton NMR Spectrum of 3-N-t-Butoxycarbonyl-5-(10-Undecyn-1-yl)-2,4-Imidazolidine-1,3-dione.

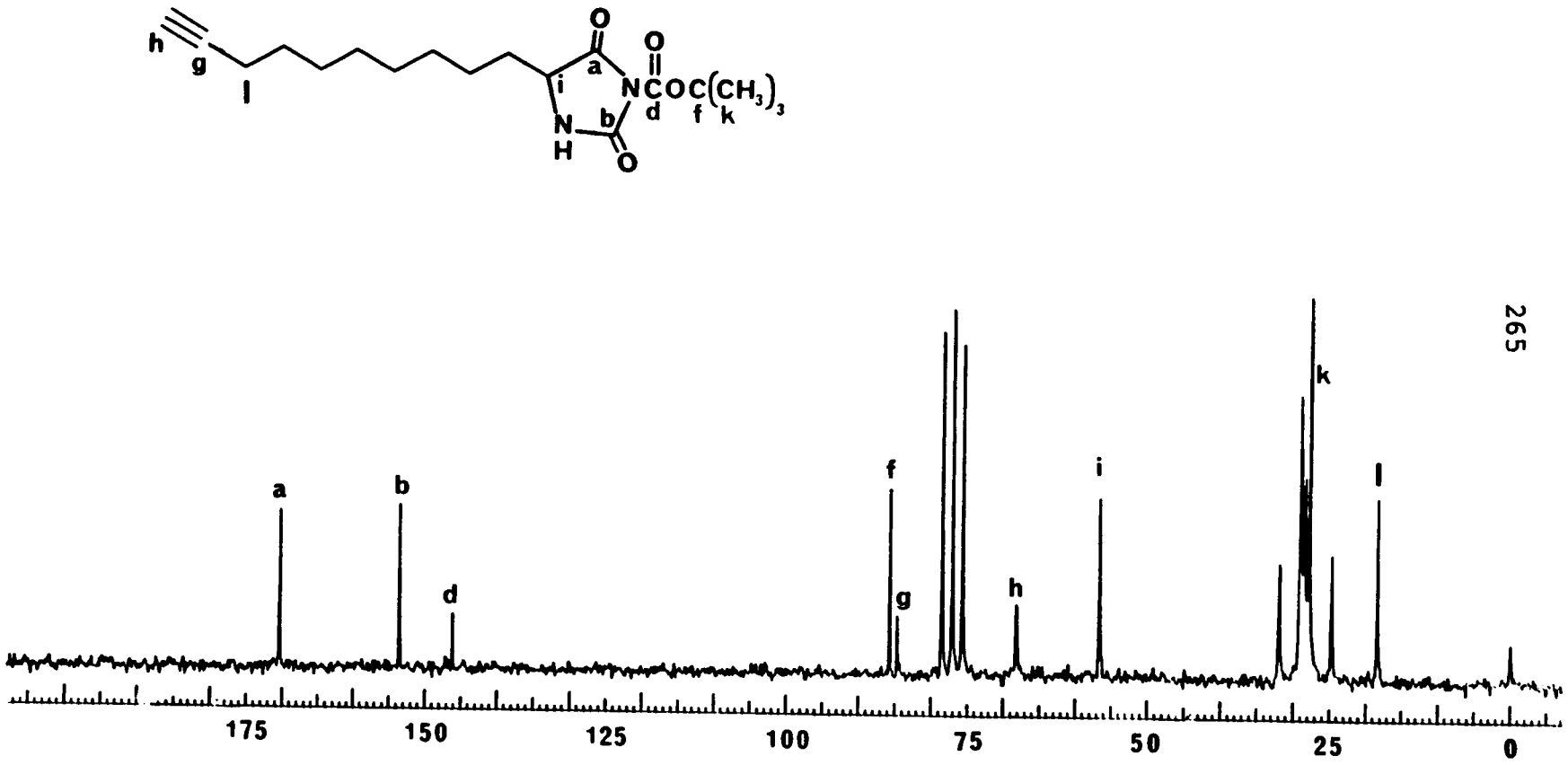


Figure 5-17. Carbon-13 NMR Spectrum of 3-N-t-Butoxycarbonyl-5-(10-Undecyn-1-yl)-2,4-Imidazolidine-1,3-dione.

the ^{1}H-NMR and ^{13}C-NMR spectra obtained for the di-BOC and N-3-BOC-hydantoin derivatives, respectively. Also, for a means of comparison, the ^{1}H- and ^{13}C-NMR spectra for the starting alkynyl hydantoin are shown in Figures 5-18 and 5-19. Some points of interest deserve elaboration. In the case of the di-BOC hydantoin, note the absence of the two N-H resonances at 9.29 and 6.76, which are observed in the starting material, and the two singlets at 1.59 ppm and 1.56 ppm corresponding to two the two t-butyl groups (18H) in the proton spectrum (Figure 5-14). The ^{13}C-NMR spectrum of this material clearly shows two urethane carbonyls at 147.47 ppm and 144.95 ppm, the two quaternary carbon resonances of the BOC groups at 86.2 ppm and 84.41 ppm, and the two t-butyl methyl lines at 28.34 and 28.18 ppm (Figure 5-15). The selective formation of the N-3 monoBOC hydantoin is clearly apparant from the proton resonances for the N_1-H and t-butyl group at 6.89 ppm and 1.58 ppm respectively (Figure 5-16), and the ^{13}C-NMR resonances for the t-butoxycarbonyl group at 146.17 (C=O), 85.74 (quaternary carbon), and 27.88 (CH_3) shown in Figure 5-17.

Since the t-butoxycarbonylation method was not selective, and since it was felt that both nitrogens required protection, the reaction was carried out using excess di-t-butyl dicarbonate (3.3 equivalents). Under such conditions, a high yield (86%) of the di-BOC adduct was obtained

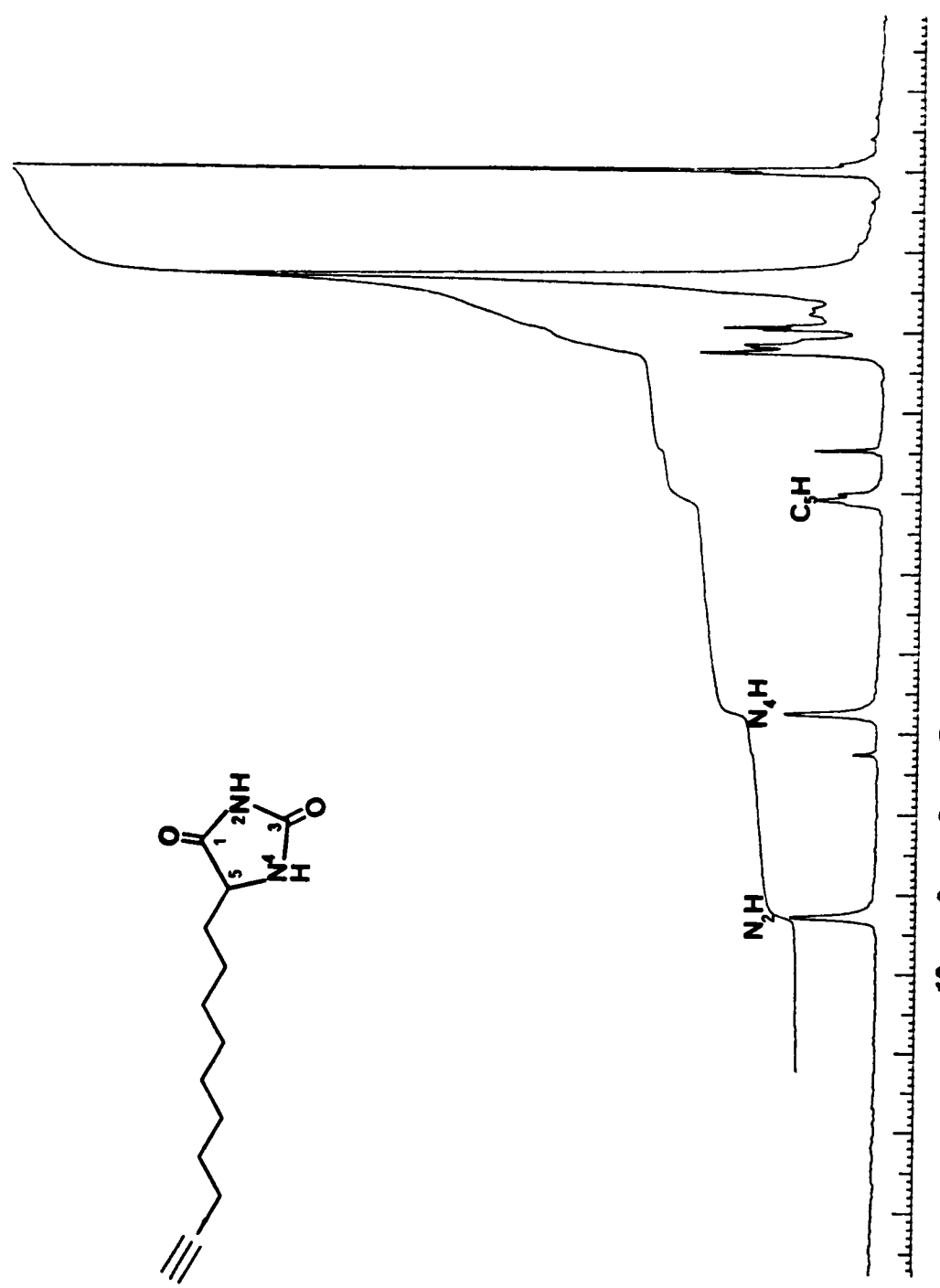


Figure 5-18. Proton NMR Spectrum of 5-(10-Undecyn-1-yl)2,4-Imidazolidine-1,3-dione.

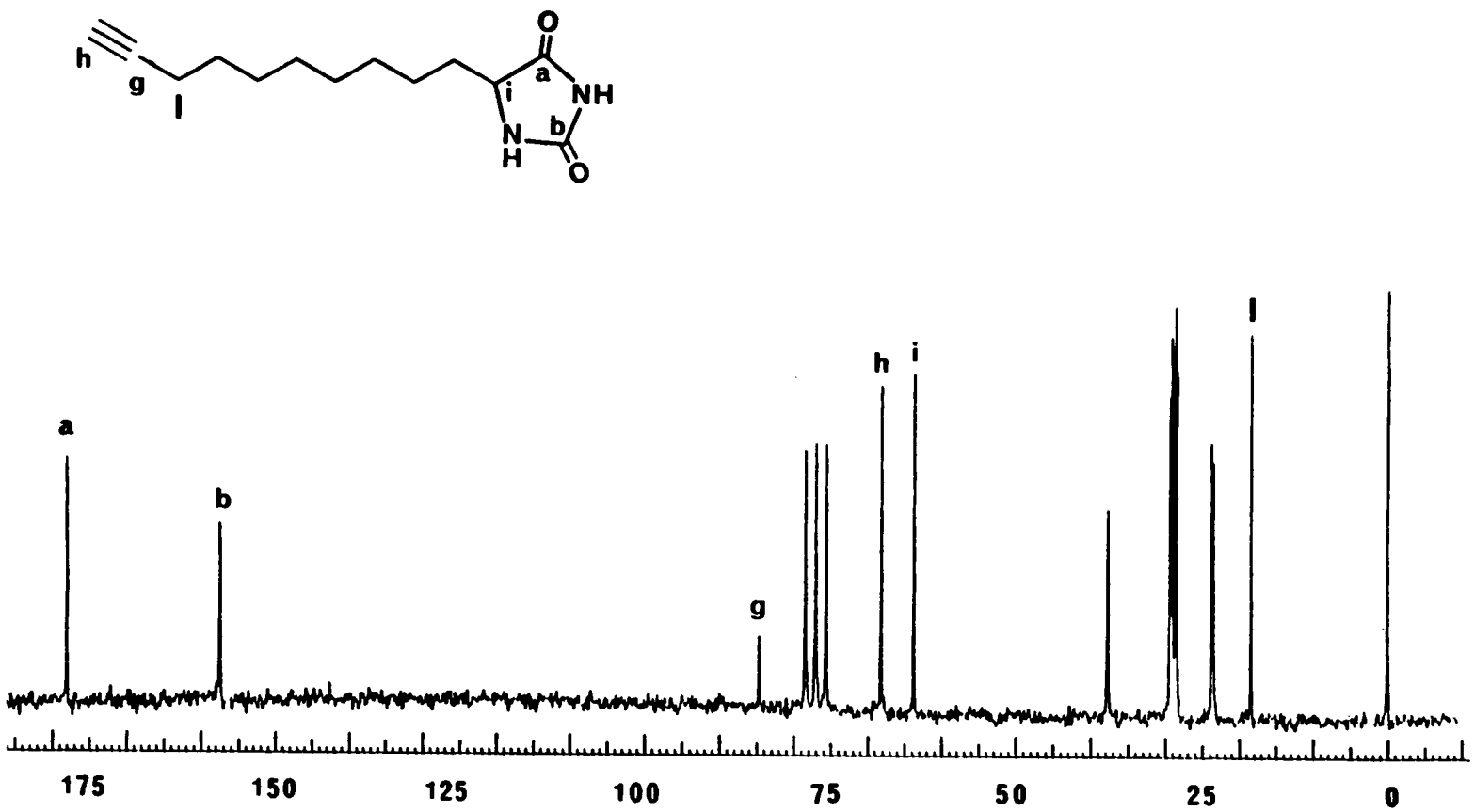
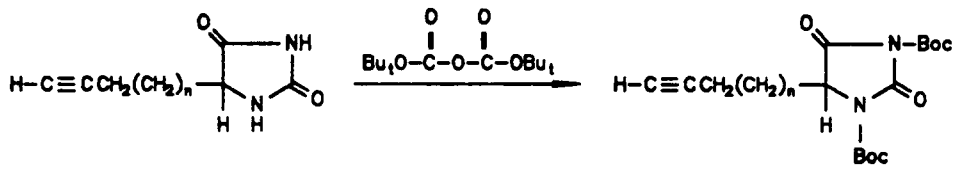


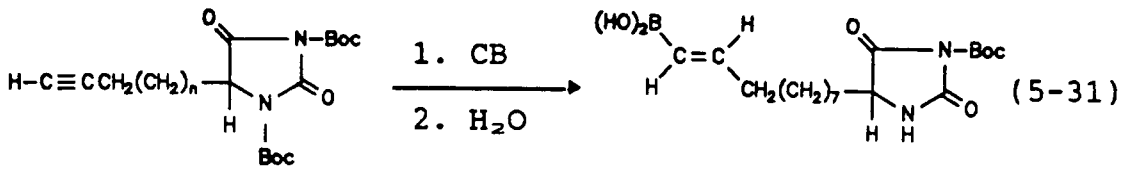
Figure 5-19. Carbon-13 NMR Spectrum of 5-(10-Undecyn-1-yl)2,4-Imidazolidine-1,3-dione in $CDCl_3$.

(equation 5-30).



(5-30)

Having the doubly protected alkynyl hydantoin in hand, the next step was to carry out the hydroboration reaction. The hydroboration of this compound was carried out using three equivalents of catecholborane. When the experiments were first carried out, it was thought that the hydroboration proceeded as anticipated, except that the t-butoxycarbonyl group at the N-1 position was selectively cleaved by the catecholborane (or hydrolysis conditions), affording a 98% yield of the crude boronic acid (equation 5-31).



(5-31)

Figures 5-20 and 5-21 shows the ^{13}C- and ^{1}H-NMR spectra of the crude boronic acid recorded in THF-d_5. Evidence for this was based on the N_1-H peak at 6.8 ppm in the proton spectrum, and the observation of only one urethane carbonyl (151.05) and only two hydantoin carbonyls (176.8 ppm and 159 ppm in the ^{13}C-NMR spectrum. In addition, the difference in chemical shift (spacing in Hertz) between the hydantoin

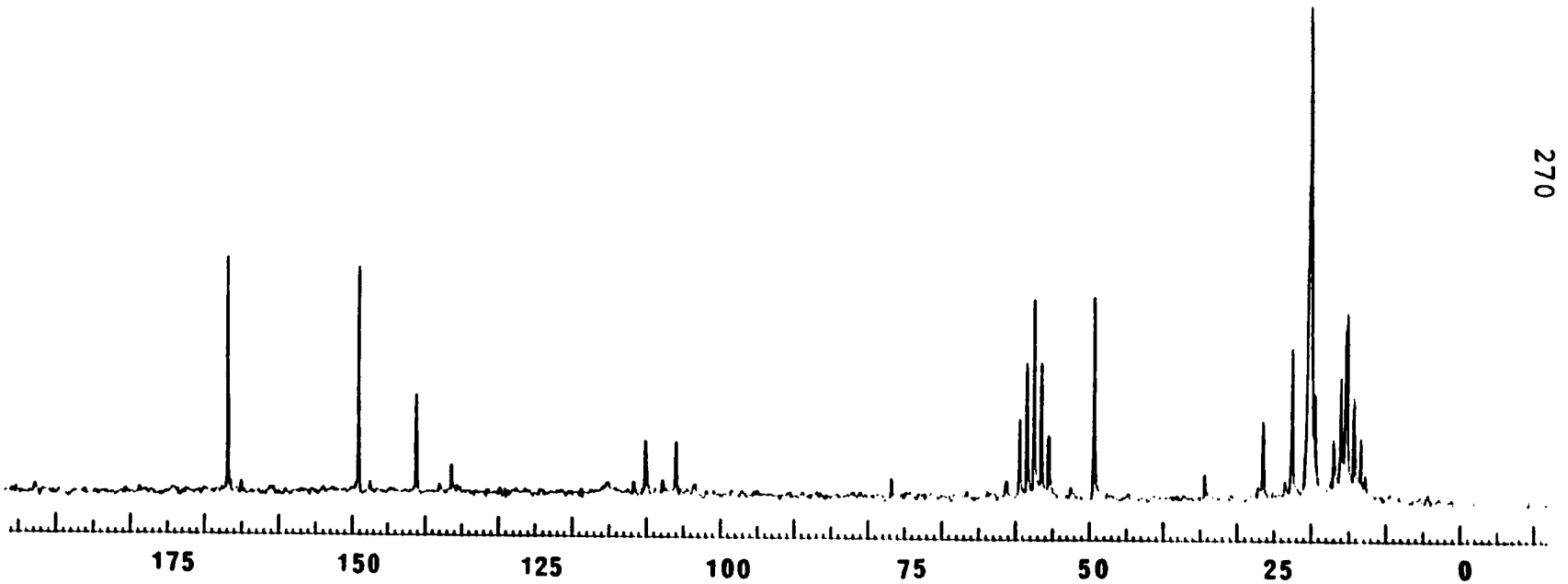


Figure 5-20. Carbon-13 NMR Spectrum of the Crude Product from the Hydroboration of N,N-Di-t-Butoxycarbonyl-5-(10-Undecyn-1-yl)-2,4-Imidazolidine-1,3-dione with Catecholborane.

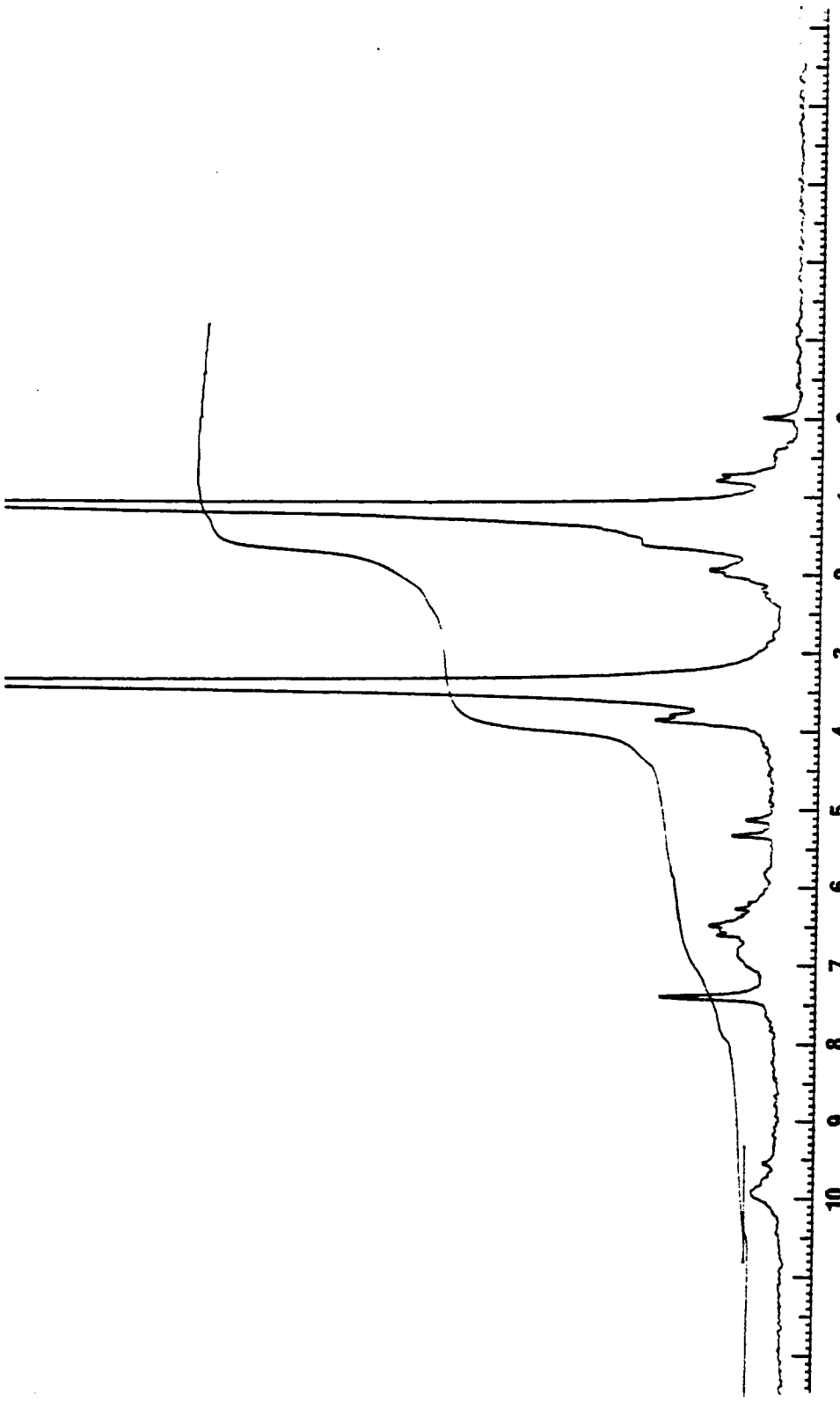
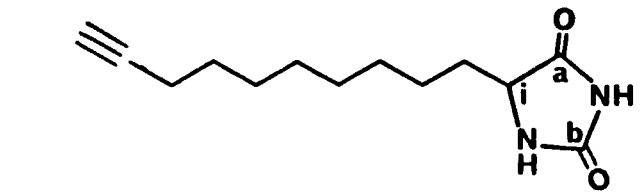


Figure 5-21. Proton NMR Spectrum of the Crude Product from the Hydroboration of N,N-Di-t-Butoxycarbonyl-5-(10-Undecyn-1-yl)-2,4-Imidazolidine-1,3-dione with Catecholborane.

carbonyl at 159.04 ppm and the peak at 151.14 was identical to that of the N-3 monoBoc alkynyl hydantoin. However, re-examination of the NMR data from this experiment reveals the the initial interpretation of the experiment may have been incorrect. Although reduction of urethane carbonyls was not expected to occur with catecholborane, this may have in fact occurred. Thus, the crude product mixture might actually be a mixture of vinylboronic acid products containing both reduced and unreduced t-butoxycarbonyl group. The following interpretation supports this notion. The ^{13}C-NMR peak at 151.04 may actually be the vinyl carbon beta to the boron. Figure 5-22 shows the ^{13}C-NMR spectrum for 5-(10-undecyn-1-yl-)hydantoin in DMSO-d_6. The spacing in Hertz between all three peaks is identical to that displayed in Figure 5-20, when the two spectra are superimposed on one another. In addition the chemical shift values of the three downfield peaks in Figure 5-20 (176.8, 159, and 151.5 ppm) for this compound are almost identical to the three downfield resonances in Figure 5-22 for the known vinylboronic acid-hydantoin. The smaller peak at 146.28 ppm would then correspond to the unreacted t-butoxycarbonyl group on the N-3 position (compare this to the corresponding resonance for the monoBoc hydantoin (Figure 5-17, p. 265) at 146.17 ppm. Additionally the small peak at 86.71 ppm would then correspond to the quaternary carbon on the unreduced BOC group



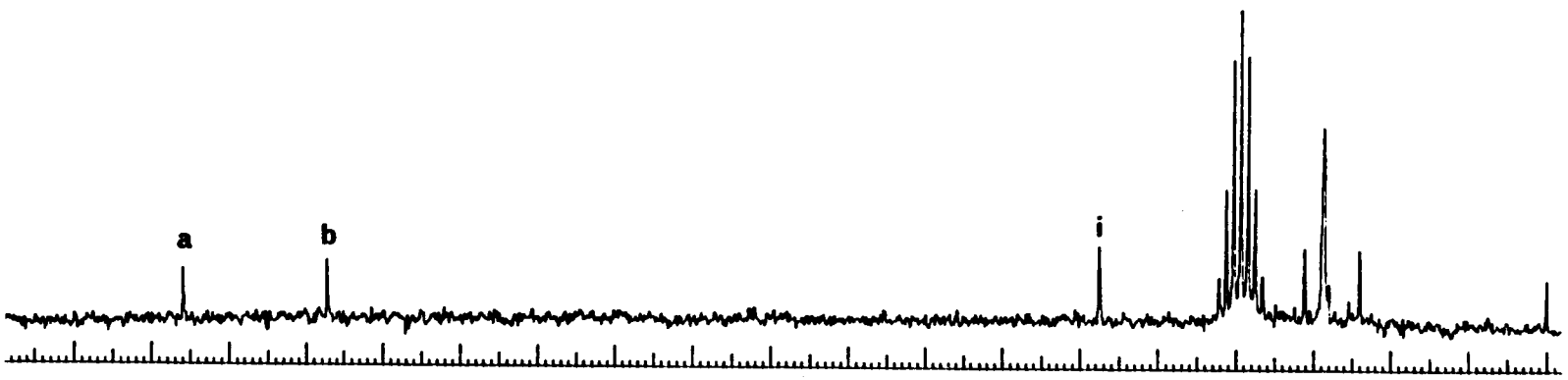
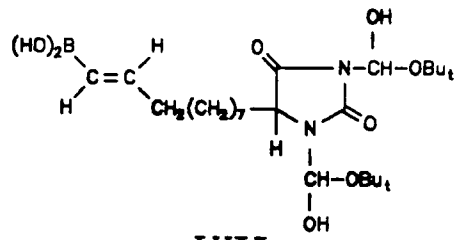


Figure 5-22. Carbon-13 NMR Spectrum of 5-(10-Undecyn-1-yl)-2,4-Imidazolidine-1,3-dione in DMSO-d_6.

at N-3 (compare this to the corresponding peak at 85.74 in Figure 5-17, p. 265). Apparently, the N-1 Boc group is more susceptible to reduction than the N-3 Boc group, based on the absence of a of a corresponding carbonyl quaternary carbon resonances for the unreduced N-1 Boc group. The two resonances at 120.05 ppm and 115.91 ppm, which were unexplainable by the earlier explanation, most likely correspond to the quaternary carbon of the reduced Boc groups. Based on the chemical shift of these two peaks, they are probably both hemiketal carbons (LVII).



LVII

As noted above, it was originally thought that the hydroboration of the di-Boc derivative had proceeded as planned. With this interpretation in mind, the loss of the BOC group at N-1 was disappointing, but was not disasterous, since it could quite readily be replaced by treatment with another equivalent of di-t-butyl dicarbonate. Before this was attempted, however, it was decided to attempt the iodination step to determine whether the BOC group would be stable to an electropositive iodide species. Unfortunately, when this vinylboronic acid was treated with one equivalent

of sodium iodide, the reaction did not proceed as planned. Instead of turning a light golden color following consumption of the electropositive iodine species, within 15 seconds of addition of the chloramine T solution, the reaction mixture became deep bluish-purple in color. Even after allowing the reaction to continue for a three hour period, no further visable change was observed. Obviously, the t-butoxycarbonyl moiety (or the reduced Boc group) was affecting the reaction in some unknown manner. The reaction was repeated using two equivalents of sodium iodide. In this case, some vinyl iodide was present in the reaction mixture, as shown in the ^{1}H-NMR spectrum, Figure 5-23, of the crude reaction mixture. The desired product, however was not isolated.

Regardless of the outcome of the hydroboration step, the subsequent iodination step was not sucessful. The requirement for excess iodine made the protection step pointless. (If excess iodine was required, then there was no reason to try to protect the hydantoin ring). With the failure of these reactions the synthesis of iodovinyl amino acids via the hydantoin methodology was discontinued. An additional reason for discontinuing this synthetic approach was the discovery of a successful hydroboration reaction of an alkyne with catechoborane in the presence of carboxylic acid by "in situ" protection of the acid functionality with

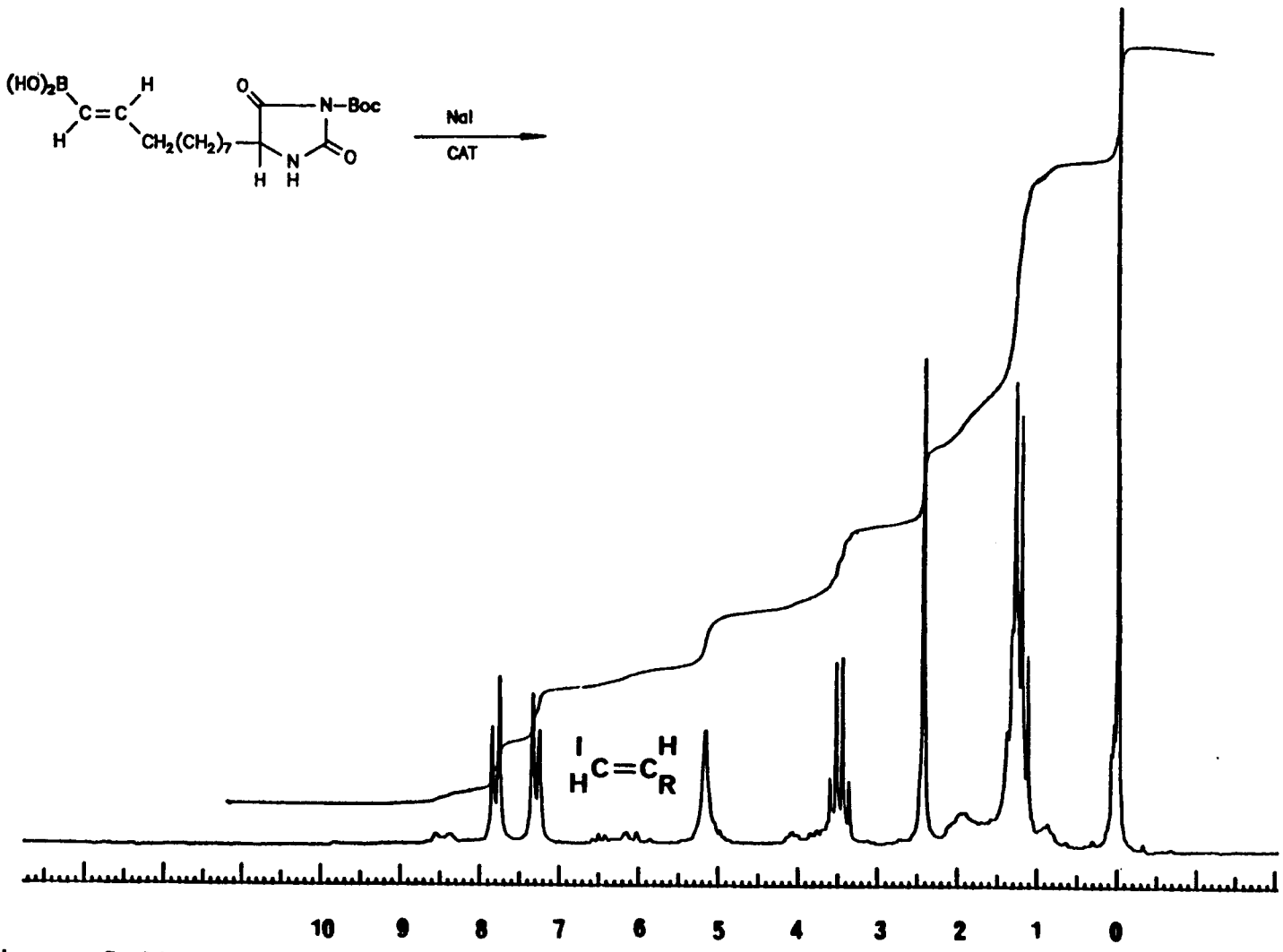
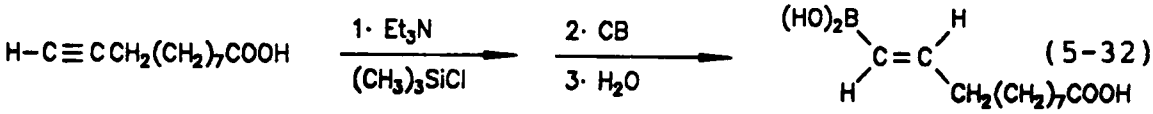


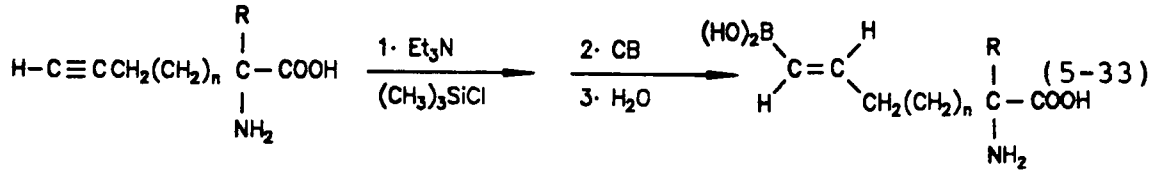
Figure 5-23. Proton NMR Spectrum of the Crude Product from the Iodination of of 3-N-Di-t-Butoxycarbonyl-5-(10-Undecenylboronic acid-1-)-2,4-Imidazolidine-1,3-dione (Crude Product) with Excess Sodium Iodide.

the trimethylsilyl moiety (equation 5-32). This made the



(5-32)

direct hydroboration of an alkynyl amino acid a promising possibility, and one which deserved further attention (equation 5-33). An extensive study on the hydroboration of



(5-33)

unsaturated trimethylsilyl esters is the subject of the next chapter.

Thus, the synthesis of iodovinylamino acids via the hydantoin methodology was discontinued. However, for completeness, an iodination of the model compound using excess sodium iodide (3 equivalents) was carried out. Reaction of 5-(10-undecenylboronic acid-1-)hydantoin with sodium iodide (three equivalents) and chloramine T (six equivalents) in aqueous THF gave the crude iodovinyl-N,N-diiodohydantoin. The ^{1}H-NMR spectrum of the crude reaction mixture is shown in Figure 5-24. The trans iodovinyl group is apparent from the multiplets between 6.5-5.7 ppm. Without isolation, the crude product was heated to 160°C for four hours with 6.25 N NaOH in aqueous dioxane.

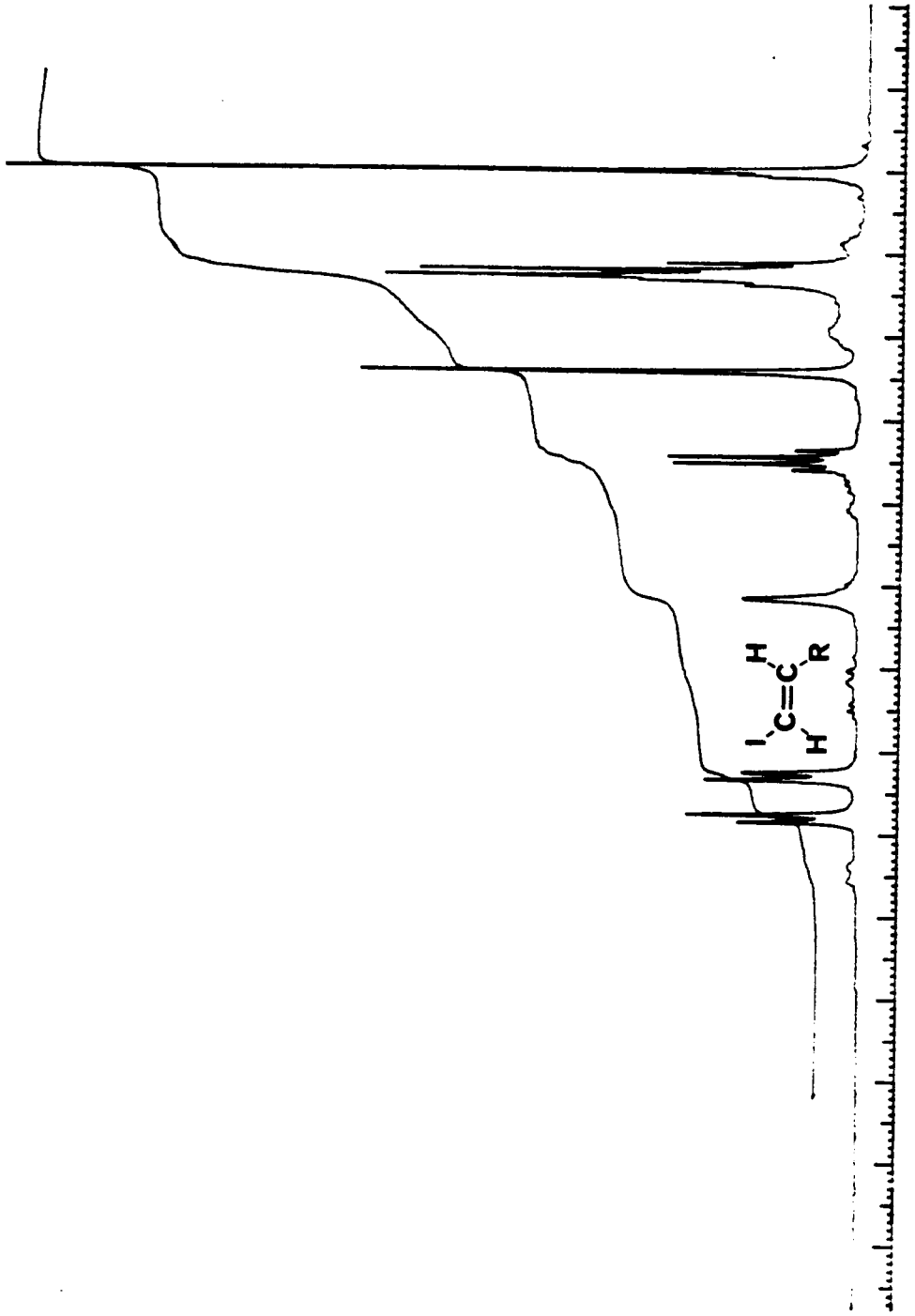


Figure 5-24. Proton NMR Spectrum of the Crude Product from the Iodination of 5-(10-Undecenylboronic acid-1-)-2,4-Imidazolidine-1,3-dione with Excess Sodium Iodide.

Unfortunately, even after acidification, a mixture of iodinated amino acid products were obtained.

D. Conclusion

The synthesis of a model iodovinyl amino acid proceeded as planned up to the step where the hydantoin ring was hydrolyzed to the amino acid. Unfortunately, the vinylboronic acid functionality proved too sensitive to survive the hydrolysis procedures. (A number of attempts at finding an alternate low temperature hydrolysis reaction of the hydantoin ring all met with failure.) Since hydrolysis of the hydantoin in the presence of the vinylboronic acid proved not to be feasable, modification of the synthetic methodology was attempted; the iodination step was carried out prior to the hydrolysis of the hydantoin ring. Iodination in the presence of the hydantoin ring proved troublesome, as amide bonds in the hydantoin ring consumed the electrophilic iodine species, requiring the use of excess sodium iodide. This, of course, was highly undesirable, since the cost of radioiodine makes the use of excess radiolabel prohibitive. Protection of the amide and imide groups of the hydantoin ring was attempted as a means of circumventing this problem. Protection as the quaternary ammonium salt, proved impractical. Two other protecting groups, the tosyl group and the t-butoxycarbonyl group

(Boc), were tried. Unfortunately, the attempted tosylation of the model compound, 5-(10-undecen-1-yl)2,4-imidazolidine-1,3-dione, met with failure, as a complex mixture of tosylated materials were obtained. Thus, the use of the tosyl group as the protecting group was discarded. The well known t-butoxycarbonyl group was then chosen. The use of this protecting group with the hydantoin ring had never been reported. t-Butoxycarbonylation of the model compound proceeded reasonably well. Hydroboration with catecholborane, unfortunately, led to probable reduction of the Boc protecting groups.

At this point, the decision was made to discontinue the synthesis via the hydantoin route. Also important to the decision to discontinue the synthesis was the discovery of the previously unknown hydroboration reaction of alkynes in the presence of carboxylic acid functionality. This new reaction deserved attention, and also opened up the opportunity of carrying out the direct hydrobortation of an alkynyl amino acid, which ultimately, could lead to an efficient synthesis of iodovinylamino acids.

E. Experimental

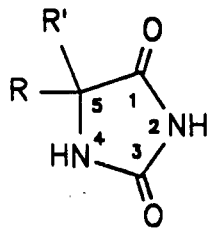
1. General

When required, glassware, syringes, and syringe needles were oven-dried 24 hours prior to use. NMR spectra were

recorded on a JEOL-FX-90Q pulsed FT-NMR spectrometer in either deuteriochloroform, $CDCl_3$, acetone-d_6, dimethylsulfoxide-d_6, methanol-d_1, methanol-d_4, tetrahydrofuran-d_5, deuterium oxide (by use of an external reference in a sealed 5 mm NMR tube or, alternatively, by employing a small amount of dioxane or methanol as an internal reference), dioxane, tetrahydrofuran, sulfuric acid, deuterium oxide/sodium hydroxide, or deuterium hydroxide/sodium hydroxide-d_1 solutions. The ^{1}H-NMR spectra were referenced using tetramethylsilane, TMS, as an internal standard (δ = 0.0 ppm). Alternatively, for those samples which were insoluble in organic solvents, an external reference containing TMS, $CDCl_3$ (δ = 7.25 ppm), acetone-d_6 (δ = 2.05 ppm), or benzene-d_6 (δ = 7.3) in a sealed 5 mm NMR or capillary tube was used. Exchangeable protons were determined by shaking with deuterium oxide. The ^{13}C-NMR spectra were referenced to either $CDCl_3$ (δ = 77.1 ppm), acetone-d_6 (δ = 30.3 ppm), dimethylsulfoxide-d_6 (δ = 39.5 ppm), methanol-d_1 (δ = 49.0 ppm) methanol-d_4 (δ = 49.0 ppm), tetrahydrofuran-d_5 (δ = 67.4), dioxane (δ = 68.0 ppm), tetrahydrofuran (δ = 67.4 ppm) solutions, or TMS (δ = 0.0 ppm). The ^{13}C Single Frequency Off Resonance Decoupled Spectra (SFORD) were obtained by setting the irradiation frequency of the decoupler off upfield of that used for tetramethylsilane, and are reported in parentheses along with the ^{13}C-NMR data.

In reporting chemical shift data for hydantoin derivatives, IUPAC numbering of the hydantoin ring (LVIII) is used throughout to avoid confusion. The ^{11}B-NMR spectra were referenced to boron trifluoride-etherate (δ = 0.0 ppm) by use of a sealed capillary external reference. Infrared spectra were obtained on a Perkin-Elmer Model 1330 spectrometer. Melting points were recorded using a Fisher-Johns melting point apparatus and are uncorrected. Thin layer chromatographic analyses were performed on Fisherbrand GF 250 μm TLC plates using either a phosphomolybdic acid or a 2,4-dinitrophenylhydrazine solution as an indicator. Column chromatographic separations were accomplished using Davisil silica gel. Ion exchange chromatography was performed on Dowex 1-X10 or Dowex 1-X8 anion exchange resin (previously converted to the hydroxide form by washing it with 1 N NaOH) and/or on Dowex 50W-X12 cation exchange resin (previously converted to the H^+ form by washing with 1 N HCl). Paper chromatographic analysis of amino acid compounds was performed on Kodak cellulose TLC sheets using a ninhydrin solution as an indicator (0.2 g ninhydrin in 50 mL H_2O). The presence of a purple spot on the paper chromatograph after drying it in an oven, or alternatively, with a hot air gun, provided evidence indicated the presence of an amino acid. pH measurements were obtained using a Fisher pH meter equipped with a glass combination pH electrode. Elemental

analyses were performed on each of the new alkynyl hydantoins by Galbraith Laboratories, Knoxville, Tennessee. The commercially available chemicals, their manufacturers, and the methods of purification used, when applicable, are listed in Table 5-8. Reagents previously listed in Table 3-1 or 4-6 are not repeated here. The alkynyl aldehydes and alkynyl ketones used were prepared by the methods outlined in Chapter IV. All other reagents were prepared as described below.



LVIII

2. Initial Experiments

a. Hydroboration of 1-Decyne with Catecholborane

To an oven-dried 100 mL round-bottomed flask fitted with a septum inlet and equipped with a magnetic stirring bar, reflux condenser, and gas outlet were added 1-decyne (10.27 mmol, 1.42 g) and anhydrous THF (20 mL). Catecholborane (11 mmol, 1.12 mL) was added dropwise by syringe and the resulting mixture was stirred for four hours at 40°C. After the allotted reaction time, a representative aliquot was transferred to oven-dried, nitrogen-flushed 10mm NMR

Table 5-8: Manufacturer and Methods of Purification of Commercially Available Chemicals

Reagent	Manufacturer[a]	Method of Purification[b]
Acetone-d_6	WG, CI, A, N, MSD	
Ammonium Carbonate	F, M	
Ammonium Chloride	F	
Aqueous Ammonia	F, M	
Barium Hydroxide Octahydrate	JT	
Boron Trifluoride Etherate	A	
Catecholborane	A	
Chloramine T Trihydrate	A	
Chloroform	F, M	
1-Decyne	A	
Deuteriochloroform	N, A	
Deuterium Oxide	N, A, CI	
5,5-Dimethylhydantoin	D	
Dimethylsulfoxide-d_6	A, CI, SI	
Dioxane	F	
Di-t-butyl Dicarbonate	A	
Dowex 1-X8	A	1
Dowex 1-X10	BR	1
Dowex 50W-X8	JT, DW	2

Table 5-8 (continued)

Reagent	Manufacturer[a]	Method of Purification[b]
Dowex 50W-X12	JT	2
Ethanol, 95%	F, AS	
Ethanol, 100%	AA	
Iodine Monochloride	A, HL	
Isoleucine	E	
Methanol	F, AS	
Methanol, anhydrous	F	3
Methanol-d_1	A	
Methanol-d_4	A	
Ninhydrin	JT	
2-Octanone	E	
4-Phenyl-3-butyn-2-one	FN	
Poly(-2-vinylpyrindine)	A	
Sodium Carbonate	F, M	
Sodium Cyanide	F, A	
Sodium Hydroxide	F, M	
Sodium Iodide	JT	
Sodium Sulfate, anhydrous	F, M	
Tetrahydrofuran-d_5	N, MSD	
Tetramethylsilane	N	

Table 5-8 (continued)

Reagent	Manufacturer[a]	Method of Purification[b]
p-Toluenesulfonyl Chloride	A, E	
Triethylamine	A	
Vanadium Pentaoxide	F	

[a]Manufacturer
- A = Aldrich Chemical Company
- AA = AAPER Alcohol and Chemical Company
- BR = Bio-Rad Laboratories
- AS = American Scientific Company
- CI = Cambridge Isotope Laboratories
- D = Dupont Chemical Company
- DW = Dow Chemical Company
- E = Eastman Chemical Company
- F = Fisher Chemical Company
- F = Farchan Acetylenes
- HL = Hartman-Leddon Company
- JT = J.T. Baker Chemical Company
- M = Malinkrodt
- MSD = MSD Isotopes
- N = Norell, Inc.
- SI = Stohler Isotope Chemicals
- W = Wiley Organics
- WG = Wilmad Glass Company

[b]Methods of Purification
1. Converted to the hydroxide form prior to use by washing a column bed of resin with 1 N NaOH
2. Converted to the hydrogen ion form prior to use by washing a column bed of resin with 1 N HCl
3. Distilled from sodium methoxide under inert atmosphere

tube equipped with a rubber septum using a cannula, and the ^{13}C-NMR and ^{11}B-NMR spectra obtained. Water (50 mL) was added and the mixture stirred overnight, during which time a solid precipitate formed. The precipitate was filtered, disolved in a minimum amount of acetone, and reprecipitated by the addition of petroleum ether to afford 1.71 g (93%) of decenylboronic acid as a white powder. The sample matched the spectral characteristics of known decenylboronic acid; ^{13}C-NMR (CH_3OD): δ = 153.98 ($(HO)_2B$- CH=CHR), 36.91, 33.00, 30.51, 30.30, 29.70, 23.69, 14.42.

b. Reaction of 5,5-Dimethylhydantoin with Catecholborane: Procedure A

To an oven-dried 100 mL round-bottomed flask fitted with a septum inlet was added 5,5-dimethylhydantoin (7.81 mmol, 1.00 g). The flask, which was fitted with a magnetic stirring bar, reflux condenser, and gas outlet, was flame dried and purged with nitrogen while allowing to cool. Anhydrous THF was added in sufficient quantity to dissolve the hydantoin (approx. 20 mL), followed by the addition of catecholborane (7.80 mmol, 0.80 mL), which was added dropwise by syringe due to the vigorous evolution of hydrogen gas. The resulting mixture was stirred for four hours at 40°C, during which time a milky white suspension formed. After the allotted reaction time, an aliquot was

transferred to oven-dried, nitrogen-flushed 10mm NMR tube equipped with a rubber septum using a cannula, and the ^{13}C- and ^{11}B-NMR spectra were obtained. Following NMR analysis, the reaction was quenched with water (20 mL) and an aliquot removed again for NMR analysis.

c. Reaction of 5,5-Dimethylhydantoin with Catecholborane: Procedure B:

To an oven-dried 100 mL round-bottomed flask fitted with a septum inlet was added 5,5-dimethylhydantoin (7.81 mmol, 1.00 g). The flask, which was fitted with a magnetic stirring bar, reflux condenser, and gas outlet, was flame dried and purged with nitrogen while cooling. Anhydrous THF was added in sufficient quantity to dissolve the hydantoin (approx. 20 mL), followed by the addition of catecholborane (23.4 mmol, 2.40 mL), which was added dropwise by syringe due to the vigorous evolution of hydrogen gas. The resulting mixture was stirred for four hours at 40°C, during which time a milky white suspension formed. After the allotted reaction time, an aliquot was transferred to an oven-dried, nitrogen-flushed 10mm NMR tube equipped with a rubber septum using a cannula, and the ^{13}C- and ^{11}B-NMR spectra were obtained. Following NMR analysis, the reaction was quenched with water (20 mL), the reaction medium saturated with sodium chloride, and the layers separated. The aqueous

layer was extracted twice more with THF and the combined THF layers were dried (anhydrous $MgSO_4$). Filtration, followed by evaporation of the solvent, led to a white crystalline solid, 3.50 g (98%), which was identified to be a mixture of 5,5-dimethylhydantoin and catechol by comparison to known samples of each; ^{13}C-NMR (THF): δ 178.33 (C_1=O), 156.25 (C_3=O), 144.90 (aromatic C-OH), 119.90 (aromatic C=C-OH), 114.70 (aromatic C=C-C-OH), 59.25 (quaternary carbon, hydantoin), 29.06 (CH_3).

d. Reaction of 5,5 Dimethylhydantoin and 1-Decyne with Catecholborane

To an oven-dried 250 mL round-bottomed flask fitted with a septum inlet was added 5,5-dimethylhydantoin (10.00 mmol, 1.28 g). The flask, which was fitted with a magnetic stirring bar, reflux condenser, and gas outlet, was flame dried and purged with nitrogen while the flask cooled. Anhydrous THF (20 mL) and 1-decyne (10 mmol, 1.38 g) were added, followed by the addition of catecholborane (33.0 mmol, 3.35 mL), which was added dropwise by syringe due to the vigorous evolution of hydrogen gas. The resulting mixture was stirred for four hours at 40°C, during which time a milky white suspension formed. After the allotted reaction time, an aliquot was transferred an oven-dried, nitrogen-flushed 10mm NMR tube equipped with a rubber septum

using a cannula, and the ^{13}C- and ^{11}B-NMR spectra were obtained. Following NMR analysis, the reaction was quenched with water (150 mL) and stirred overnight. After the supernatant liquid was decanted off, the solid boronic acid was dissolved in a minimun amount of acetone, and reprecipitated by the addition of petroleum ether to afford 1.67 g (90%) of decenylboronic acid, which was compared to a known sample. ^{13}C-NMR (THF): δ 149.45 ($(HO)_2B$-CH=CHR), 35.40, 31.65, 29.51, 29.13, 28.99, 22.33, 13.23; ^{11}B-NMR ($CDCl_3$): δ 28.11. The supernatant liquid was saturated with sodium chloride and extracted with ether (4x50 mL). The combined ether layers were dried over anhydrous magnesium sulfate. Filtration, followed by evaporation of the solvent under reduced pressure, gave 3.20 g (88%) of an off-white solid, which was identified as catechol; ^{13}C-NMR (THF): δ 145.03, (aromatic C-OH), 119.03 (aromatic C=C-OH), 114.64 (aromatic C=C-C-OH). The aqueous layer was further extracted with THF (4x50 mL), the combined THF layers were dried over anhydrous magnesium sulfate. Filtration, followed by evaporation of the solvent gave 1.02 g (80%) of recovered 5,5-dimethylhydantoin; ^{13}C-NMR (THF): δ 177.98 (C_1=O), 155.98 (C_3=O), 59.01 (quaternary carbon, C_5), 29.06 (CH_3).

e. Iodination of Decenylboronic Acid in the Presence of Added Isoleucine

In a 100 mL round-bottomed flask equipped with a magnetic stirring bar, decenylboronic acid (2.5 mmol, 460 mg), isoleucine (2.5 mmol, 330 mg), and aqueous THF (50/50, 20 mL). The flask was wrapped with aluminum foil to shield it from light, cooled to 0°C, and aqueous sodium iodide (1 M, 2.5 mmol) and chloramine T solution (50/50 THF-H_2O, 0.5 M, 5 mmol) were added. The contents were stirred for 15 minutes, then petroleum ether (25 mL) added, and the reaction mixture filtered. From the filtrate, the organic layer was removed, and the filtrate extracted with petroleum ether (3x25 mL). The combined organic layer was dried ($MgSO_4$), filtered, and the solvent removed to provide 0.50 g (76%) of (E)-1-iodo-1-decene as a colorless oil, whose spectral characteristics matched those of the known material; ^{1}H-NMR ($CDCl_3$): δ 6.75-6.3 (m, 1H, IHC=C<u>H</u>CH_2-), 5.95 (dt, 1H, J_{trans}=14.3 Hz, I<u>H</u>C=CHCH_2-), 2.25-1.85 (m, 2H, IHC=CH<u>C</u>H_2-), 1.85-1.1 (broad envelope, 12H), 0.88 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 146.82 (IHC=<u>C</u>HCH_2R), 74.31 (IH<u>C</u>=CHCH_2R), 36.12 (IHC=CH<u>C</u>H_2R), 31.92, 29.40, 29.21, 29.02, 28.45, 22.73, 14.18 (CH_3).

3. Preparation of Hydantoins

a. 5-(10-Undecyn-1-yl)2,4 imidazolidine-1,3-dione: General Procedure

The synthesis of 5-(10-undecyn-1-yl)hydantoin is representative. A 500 mL round-bottomed flask equipped with a magnetic stirring bar was charged with sodium cyanide (89.7 mmol, 4.40 g), ammonium carbonate (179.4 mmol 17.24 g, ground prior to use), aqueous ethanol (220 mL, 50%), and a solution of 10-undecynal (44.8 mmol, 7.45 g) in aqueous ethanol (10 mL, 50%), fitted with a reflux condenser, and heated to 55-60°C for 5 hours. The reaction mixture was concentrated to about one-third of its original volume and water (20 mL) added, followed by the slow addition of concentrated HCl (5 mL) [CAUTION: Use HOOD! HCN vapors are given off!]. After cooling to 0°C to allow complete crystallization, filtration and washing of the product with water afforded a light yellow waxy solid. Recrystallization from methanol - water (minimum amount of methanol used) afforded 8.83 g of 5-(10-undecyn-1-yl)2,4-imidazolidine-1,3-dione as white crystals, mp 113°C. Further purification by column chromatography (silica gel) by successive elution with 20% ethyl acetate-petroleum ether, 30% ethyl acetate-petroleum ether, 40% ethyl acetate-petroleum ether, and finally, with 60% ethyl acetate-petroleum ether afforded the analytical sample, mp 116°C; R_F = 0.58 (60% ethyl acetate-

petroleum ether); ^{1}H-NMR ($CDCl_3$): δ 9.30 (s, 1H, N_2-H), 6.86 (s, 1H, N_4-H), 4.10 (dd, 1H, $R_2C\underline{H}CHH'CH_2R$), 2.5-1.1 (broad envelope containing a multiplet at 2.19 ppm, 2H, which corresponds to $HC{\equiv}C\underline{CH_2}R$, and well defined triplet at 1.95 ppm, 1H, J=2.2 Hz, which corresponds to $\underline{H}C{\equiv}CCH_2R$);. ^{13}C-NMR ($CDCl_3$): δ 175.43 ($C_1$=O, s), 158.47 ($C_3$=O, s), 84.76 ($HC{\equiv}\underline{C}CH_2R$, s, actually a fine doublet split by long range coupling to terminal acetylenic proton), 68.27 ($H\underline{C}{\equiv}CCH_2R$, d), 58.92 (ring C-H, d), 31.62 (t), 29.15 (t), 28.97 (t), 28.67 (t), 28.45 (t), 24.88 (t), 18.40 ($HC{\equiv}C\underline{CH_2}R$, t); ^{13}C-NMR (acetone-d_6): δ 176.91 (C_1=O), 159.01 (C_3=O), 85.63 ($HC{\equiv}\underline{C}CH_2R$), 70.42 ($H\underline{C}{\equiv}CCH_2R$), 59.79 (ring C-H), 33.12, 30.54, 29.95, 25.99, 19.35 ($HC{\equiv}C\text{-}\underline{CH_2}R$), some peaks obscured by acetone-d_6 septet; ^{13}C-NMR (DMSO-d_6): δ 177.97 (C_1=O), 159.00 (C_3=O), 86.33 ($HC{\equiv}\underline{C}CH_2R$), 70.49 ($H\underline{C}{\equiv}CCH_2R$), 59.06 (ring C-H), 31.54, 29.13, 28.83, 28.64, 28.48, 24.39, 18.35 ($HC{\equiv}C\underline{CH_2}R$); IR (thin film): 3296 cm^{-1} (H-C≡C), 3460-2980 cm^{-1} (N-H), 2955 cm^{-1} (CH_3), 2923 cm^{-1} (CH_2), 2848 cm^{-1} (R_3CH) 2248 cm^{-1} (C≡C), 1765 cm^{-1} (C=O), 1690 cm^{-1} (C=O); IR ($CDCl_3$): 1712 cm^{-1} (br, shoulder at 1755 cm^{-1}, C=O). Anal. calc. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 65.92; H, 8.43; N, 11.70.

b. 5-(4-Pentyn-1-yl)2,4-imidazolidine-1,3-dione

A 250 mL round-bottomed flask equipped with a magnetic

stirring bar was charged with sodium cyanide (115.23 mmol, 5.65 g), ammonium carbonate (230.46 mmol, 22.15 g, ground prior to use), aqueous ethanol (100 mL, 50%), and a solution of 4-pentynal (57.6 mmol, 4.73 g) in aqueous ethanol (10 mL, 50%), fitted with a reflux condenser, and heated to 65-70°C for 5 hours, and stirred overnight at room temperature. The solvent was evaporated to near dryness and water (30 mL) added, followed by the slow addition of concentrated HCl (30 mL) [CAUTION: Use HOOD! HCN vapors are given off!]. This hydantoin derivative proved to be water soluble, and did not crystallize from solution even upon cooling. Therefore, the solvent was removed and the residue exhaustively extracted with methanol. The solvent was removed under reduced pressure to give 13.84 g of a yellow solid, which was a mixture of the hydantoin and inorganic salt. The residue was recrystallized from a minimal amount of water, dissolved in acetone, and dried over anhydrous magnesium sulfate. After filtration, followed by removal of the solvent, recrystallization twice from acetone-petroleum ether afforded 4.96 g (57%) of 5-(4-pentyn-1-yl)2,4-imidazolidine-1,3-dione as off-white crystals, which was pure by TLC (R_F = 0.53, 60% ethyl acetate-petroleum ether); mp 129°C; ^{13}C-NMR (acetone-d_6): 176.19 (C_1=O, s), 158.56 (C_3=O, s), 83.77 (HC≡$\underline{C}$CH_2-, s (really a fine doublet split <5Hz, which is characteristic of the internal carbon of a terminal

alkyne)), 71.39 ($H\underline{C}\equiv CCH_2$-, d), 58.28 (ring C-H, d), 32.22 $HC\equiv CCH_2\underline{C}HH'CH$-ring, dd), 15.40 ($HC\equiv C\underline{CH_2}$, t). Anal. calc. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.11; H, 5.35; N, 18.35.

c. 5-(10-Undecyn-1-yl)5-methyl-2,4-imidazolidine-1,3-dione

A 50 mL round-bottomed flask equipped with a magnetic stirring bar was charged with sodium cyanide (9.43 mmol, 360 mg), ammonium carbonate (14.9 mmol, 1.43 g, ground prior to use), aqueous ethanol (20 mL, 50%), and a solution of 11-dodecyn-2-one (3.71 mmol, 670 mg) in aqueous ethanol (5 mL, 50%), fitted with a reflux condenser, and heated to 60-65°C for 5 hours, and stirred overnight at room temperature. The solvent was evaporated to near dryness and water (30 mL) added, followed by the slow addition of conc. HCl (10 mL) [CAUTION: Use HOOD! HCN vapors are given off!]. After cooling to 0°C to allow complete crystallization, filtration and washing of the product with water afforded light yellow crystals. Purification by column chromatography (silica gel, 20% ethyl acetate-petroleum ether (500 mL), 30% ethyl acetate-petroleum ether (500 mL), and finally 40% ethyl acetate petroleum ether) gave 0.87 g (93%) of 5-(10-undecyn-1-yl)5-methyl-2,4-imidazolidine-1,3-dione as white crystals, mp 79-80°C ; R_F = 0.73 (60% ethyl acetate-petroleum ether); ^{1}H-NMR ($CDCl_3$): 9.19 (s, 1H, N_2-H), 6.65

(s, 1H, N_4-H), 2.16 (m, 2H, $HC{\equiv}CCH_2$-), 1.93 (t, 1H, J=1.7 Hz, $HC{\equiv}CCH_2$-), 1.9-1.1 (broad envolope, 17H, containing a singlet at 1.44 ppm, 3H, which corresponds to CH_3); ^{13}C-NMR ($CDCl_3$): δ 178.1 (C_1=O), 157.58 (C_3=O), 84.77 ($HC{\equiv}\underline{C}CH_2$-), 68.27 ($H\underline{C}{\equiv}CCH_2$-), 63.83 (ring C-H), 37.44 ($HC{\equiv}CCH_2\underline{C}HH'CH$-ring), 29.40, 29.24, 29.02, 28.70, 28,45, 23.82 (CH_3), 23.52, 18.43 ($HC{\equiv}C\underline{C}H_2$). Anal. calc. for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.06; H, 8.66; N, 11.29.

d. 5-(2-Phenylethynyl)5-methyl-2,4-imidazolidine-1,3-dione

A 500 mL round-bottomed flask equipped with a magnetic stirring bar was charged with sodium cyanide (40.0 mmol, 1.96 g), ammonium carbonate (80.0 mmol, 7.68 g, ground prior to use), aqueous ethanol (110 mL, 50%), and a solution of 4-phenyl-3-butyne-2-one (20.0 mmol, 2.80 g) in ethanol (5 mL), fitted with a reflux condenser, and heated to 55-60°C for 5 hours, and stirred overnight at room temperature. The reaction mixture was reduced to approximately one - fourth of its original, and water (15 mL) added, followed by the slow addition of conc. HCl (15 mL) [CAUTION: Use HOOD! HCN vapors are given off!]. This hydantoin derivative proved to be water soluble, and did not crystallize from solution even upon cooling. Therefore, the solvent was removed and the residue exhaustively extracted with acetone. The acetone

insoluble portion was filtered off (0.32 g of a cream colored solid) [Note: not desired hydantoin], and the acetone soluble fraction was evaporated to dryness (reduced pressure). TLC and ^{13}C-NMR analyses revealed the presence of a hydantoin derivative, by the carbonyl resonances at 174 ppm and 156 ppm, although the crude product possessed many impurities, which required multiple chromatography in order to obtain the pure hydantoin. The crude product was poured onto a large column of silica gel and eluted with a solvent gradient of ethyl acetate-petroleum ether. Elution with 10% ethyl acetate-petroleum ether was continued until the fractions containing a compound posessing an R_F = 0.33 (10% ethyl acetate-petroleum ether) came off the column. Then the solvent was switched to 20% (500 mL), 30% (500 ml), and finally 50% ethyl acetate-petroleum ether. The fractions containing compound with R_F = 0.5-0.6 (50% ethyl acetate-petroleum ether) were combined, the solvent removed, and further purified by column chromatography (silica gel, 50% ethyl acetate-petroleum ether). The fractions containing a compound possessing an R_F = 0.56 (50% ethyl acetate-petroleum ether) were combined, and the solvent removed to give 1.89 g of 5-(2-phenylethynyl)5-methyl-2,4-imidazolidine-1,3-dione as a red crystalline solid, mp 184°C (dec.); ^{1}H-NMR ($CDCl_3$): δ 8.80 (s, 1H, N_2-H), 7.55-7.15 m, 5H, aromatic), 6.35 (s, 1H, N_4-H), 1.81 (s, 3H, CH_3);

^{13}C-NMR (acetone-d_6): δ 174.10 (C_1=O), 156.49 (C_3=O), 132.90 (aromatic, ortho to C≡C), 130.30 (aromatic, para to C≡C), 129.84 (meta to C≡C), 123.07 (aromatic, C-C≡C), 87.23 (PhC≡C), 85.07 (PhC≡C, acetylene assignments may be reversed), 58.20 (C_5 ring), 26.50 (CH_3); IR (KBr): 3640-2900 cm^{-1}, broad region containing 3310 cm^{-1} (N-H), 3180 cm^{-1} (N-H), 3070 cm^{-1} aromatic C-H), 2710 cm^{-1}, 2222 cm^{-1} (C≡C), 1760-1680 cm^{-1} (C=O), 1483 cm^{-1} (aromatic C=C), 1438 cm^{-1} (CH_3), 1397 cm^{-1} (C-N), 1250 cm^{-1}, 1152 cm^{-1}, 1103 cm^{-1}, 1012 cm^{-1}.

e. 5,5-Cyclopentyl-2,4-imidazolidine-1,3-dione

A 500 mL three-neck round-bottomed flask equipped with a magnetic stirring bar was charged with sodium cyanide (200 mmol, 9.80 g), ammonium carbonate (400 mmol, 38.43 g, ground prior to use), and aqueous ethanol (300 mL, 50%). The flask was equipped with an addition funnel, reflux condenser, and glass stopper, and a solution of cyclopentanone (100 mmol, 8.41 g) in aqueous ethanol (50 mL) was added dropwise with stirring, and the resulting mixture heated to 65-70°C for 5 hours, [Note: during heating, the reflux condenser frequently became clogged with a solid material, which had to be removed. This was also observed with other large scale preparations of hydantoin derivatives] and then overnight at room temperature. The solvent was evaporated to about one-third of its original volume and then concentrated HCl (15

mL) added slowly [CAUTION: Use HOOD! HCN vapors are given g off!]. After cooling to 0°C to allow complete crystallization, filtration and washing of the product with water afforded off-white crystals. Recrystallization from ether afforded cyclopentylhydantoin, 10.16 g (66%) as white crystals, mp 204°C (lit[516] 204-205°C); ^{13}C-NMR (DMSO-d_6): 179.43 (C_1=O), 156.35 (C_3=O), 68.32 (C_5), 37.17 (-C_5<u>CH_2</u>-(CH_2)$_2$<u>CH_2</u>C_5-), 24.71 (-C_5CH_2<u>CH_2</u><u>CH_2</u>CH_2C_5-); ^{13}C-NMR (CH_3OD): 181.74 (C_1=O), 158.78 (C_3=O), 70.49 (C_5), 38.53 (-C_5<u>CH_2</u>-(CH_2)$_2$<u>CH_2</u>C_5-), 26.13 (-C_5CH_2<u>CH_2</u><u>CH_2</u>CH_2C_5-).

f. <u>5-(Hexyl)2,4-imidazolidine-1,3-dione</u>

A 1000 mL three-neck round-bottomed flask was charged with sodium cyanide (200 mmol, 9.80 g), ammonium carbonate (400 mmol, 38.43 g, ground prior to use), and aqueous ethanol (600 mL, 50%). The flask was equipped with an addition funnel, reflux condenser, and mechanical stirrer, and then a solution of heptaldehyde (100 mmol, 8.41 g) in aqueous ethanol (50 mL) was added dropwise with stirring, and the resulting mixture heated to 65-70°C for 5 hours [Note: during heating, the reflux condenser frequently became clogged with a solid material, which had to be removed], and then overnight at room temperature. The solvent was evaporated to about one - third of its original volume and then concentrated HCl was added slowly until the

reaction mixture was acidic (pH = 3) [CAUTION: Use HOOD! HCN vapors are given off!]. After cooling to 0°C to allow complete crystallization, filtration and washing of the product with water gave a orange solid. Recrystallization from acetone-water afforded 3.76 g (20.4%) of 5-(hexyl)-hydantoin as off-white crystals, mp 147-148°C (lit.[541] 148°C); ^{1}H-NMR (DMSO-d_6): δ 10.54 (N_2-H), 7.89 (N_4-H) 3.98 (dd, 1H, C-H, C_5 ring), 1.9-1.0 (broad envelope, 10H), 0.86 (t, 3H, CH_3); ^{13}C-NMR (acetone-d_6): 175.80 (C_1=O), 157.68 (C_3=O), 58.81 (C_5 ring), 32.35, 32.16, 29.45, 25.31, 23.01, 14.17 (CH_3).

g. 5-(Hexyl)-5-methyl-2,4-imidazolidine-1,3-dione

A 1000 mL three-neck round-bottomed flask was charged with sodium cyanide (0.50 mol, 24.50 g), ammonium carbonate (1.00 mol, 96.10 g, ground prior to use), aqueous ethanol (600 mL, 50%), and 2-octanone (0.25 mol, 32.05 g). The flask was equipped with a reflux condenser, glass stopper, and mechanical stirrer, and the resulting mixture heated to 65-70°C for 5 hours, [Note: during heating, the reflux condenser frequently became clogged with a solid material, which had to be removed) and then overnight at room temperature. The solvent was evaporated to about one - third of its original volume and then concentrated HCl was added slowly until the reaction mixture was acidic (pH = 3)

[CAUTION: Use HOOD! HCN vapors are given off!]. After cooling to 0°C to allow complete crystallization, filtration and washing of the product with water, recrystallization from acetone-water afforded 14.54 g (29.3%) of 5-(hexyl)-5-methyl hydantoin as off-white crystals, mp 109-110°C (lit[541] 107.5-108°C); ^{1}H-NMR ($CDCl_3$) δ: 9.51 (s, 1H, N_2-H), 7.01 (s, 1H, N_4-H), 1.8-1.1 (broad envelope, 13H, contains a singlet at 1.77 (C_5-$\underline{C}H_3$)), 0.86 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ: 178.41 (C_1=O), 157.98 (C_3=O), 63.83 (C_5-hydantoin), 37.72 (t), 31.54 (t), 29.10 (t), 23.71 (q, C_5-$\underline{C}H_3$), 23.43 (t), 22.55 (t), 14.04 (q, CH_3).

4. Hydroboration of Alkynyl Hydantoins

a. 5-(10-Undecenylboronic acid-1)-2,4-imidazolidine-1,3-dione

To an oven-dried 250 mL round-bottomed flask fitted with a septum inlet was added 5-(10-undecyn-1-yl)hydantoin (4.23 mmol, 1.00 g). The flask was equipped with a magnetic stirring bar, reflux condenser, and gas outlet, flame dried, and purged with nitrogen. Anhydrous THF (10 mL) was added to the flask to dissolve the hydantoin, followed by the slow addition at 25°C of catecholborane (17.78 mmol, 1.80 mL). A vigorous reaction ensued, with evolution of hydrogen. After the reaction subsided, the contents were heated to 45 °C for four hours, during which time a gelatinous product was

formed. The reaction was quenched by the addition of water (200 mL), and stirred overnight to effect the hydrolysis to the boronic acid. The crude product was filtered, redissolved in a mimimal amount of THF, and precipitated by the addition of petroleum ether to afford 0.90 g (76%) of the hydantoin boronic acid as a white powder; ^{1}H-NMR (DMSO-d_6): δ 10.56 (s, 1H, N_2-H), 7.91 (s, 1H, N_4-H), 6.7-6.2 (m, 1H, $(HO)_2HBC=C\underline{H}R$), 5.8-5.4 (m, 1H, J=17 Hz, $(HO)_2B\underline{H}C=CHR$), 3.97 (dd, 1H, C_5-H ring), 2.09 (m, 2H, $(HO)_2HBC=CH\underline{C}HH'R$), 1.9-1.0 (broad envelope, 14H); ^{13}C-NMR (DMSO-d_6): δ 176.12 (C_1=O), 157.44 (C_3=O), 149.99 ($(HO)_2BHC=\underline{C}HR$), 57.51 ($C_5$ ring), 31.18, 28.78 (br), 28.63, 28.07, 24.09; ^{11}B-NMR (THF): δ 28.0.

b. Attempt to Prepare 5-(4-Pentenylboronic acid-1-)2,4-imidazolidine-1,3-dione

To an oven-dried 250 mL round-bottomed flask fitted with a septum inlet was added 5-(4-pentyn-1-yl)hydantoin (5.00 mmol, 0.76 g). The flask, which was equipped with a magnetic stirring bar, reflux condenser, and gas outlet, was flame dried and purged with nitrogen. Anhydrous THF (10 mL) was added to the flask to dissolve the hydantoin, followed by the slow addition at 25°C of catecholborane (20.0 mmol, 2.10 mL). A vigorous reaction ensued, with evolution of hydrogen. After the reaction subsided, the contents were

heated to 50°C for four hours, during which time a gelatinous product was formed. The reaction was quenched by the addition of water (200 mL), and stirred overnight to effect the hydrolysis to the boronic acid. No precipitate formed upon hydrolysis, but a yellow oil separated from solution. To the reaction mixture was added THF (25 mL), sodium chloride (until saturated), and the organic layer separated. The aqueous layer was extracted twice more with THF (25 mL portions, and the combined THF layers were dried ($MgSO_4$). Filtration, followed by removal of the solvent, afforded a yellow oil. ^{13}C-NMR analysis of this material revealed the presence of number of peaks in the olefinic region, in addition to catechol, as well as four resonances within the alcohol region (60 - 70 ppm). However, the vinyl boronic acid resonance at 157 ppm, and the hydantoin resonances at 175, 158, and 58 ppm were absent. ^{11}B-NMR analysis of the crude product, and of the water layer after removal of the solvent showed only one broad peak at 17.2 ppm, indicating that only boric acid was present; ^{1}H-NMR (acetone-d_6): δ 7.95 (OH, 2H, catechol), 7.0-6.5 (aromatic, catechol), 4.00 (m), 3.66 (m), 3.43 (m), 2.1-1.4 (m); ^{13}C-NMR (acetone-d_6): δ 147.05, 146.83, 145.34 (catechol, C-OH), 121.45, 120.45 (catechol), 120.15, 115.73 (catechol), 112.97, 70.66, 70.50, 68.85, 67.79, 62.29, 29.05, 27.78, 26.70, 26.53, 26.43, 25.64; ^{11}B-NMR (acetone-d_6): δ 17.28.

5. Hydrolysis of 5,5-Dimethyl-2,4-imidazolidine-1,3-dione (5,5-Dimethylhydantoin): Test Experiments

a. Hydrolysis with NaOH: Procedure A

To a 100 mL round-bottomed flask were added 5,5-dimethylhydantoin (15.6 mmol, 2.0 g), sodium hydroxide, (200 mmol, 8.0 g), and water (32 mL, to make a 6.25 N NaOH solution). The flask was equipped with a magnetic stirring bar and reflux condenser, and the contents were heated to 120°C (oil bath temperature) for 5 hours. After evaporation of the reaction mixture to dryness, the basic reaction mixture was analyzed by ^{13}C-NMR spectroscopy; ^{13}C-NMR (D_2O, MeOH reference): δ 186.03 (COO^-), 55.36 (quaternary carbon), 27.98 (CH_3). The crude reaction mixture was acidified with 3 N HCl (pH 2), reduced in volume (rotary evaporator), and then acetone added until precipitation of a white solid occurred. After drying this solid (vacuum), ^{13}C-NMR analysis revealed that this precipitate was inorganic. The aqueous layer was evaporated to dryness, to give a white solid, 5.91 g (>100%), which was still contaminated with inorganic salt; ^{1}H-NMR (D_2O, TMS external reference): δ 1.69 (CH_3); ^{13}C-NMR (D_2O, dioxane reference): δ 175.88 (COOH), 58.43 (quaternary carbon), 24.64 (CH_3) 3500-2500 cm^{-1} (br, OH), 1630-1420 cm^{-1}, 1400 cm^{-1}, 1355 cm^{-1}, 1260 cm^{-1}, 1180 cm^{-1}, 890 cm^{-1}, 780 cm^{-1}.

b. Hydrolysis with NaOH: Procedure B

In a 50 mL round-bottomed flask were placed 5,5-dimethylhydantoin (4.06 mmol, 0.52 g), sodium hydroxide solution (3 N, 5 mL), and water (5 mL). The flask was equipped with a magnetic stirring bar and reflux condenser, and the contents stirred overnight at room temperature, and then heated to 100°C (oil bath temperature) for 20 minutes. The basic reaction mixture was poured onto a 3 cm x 15 cm Dowex 1-X10 anion exchange resin column which had previously been washed with 1 N NaOH to convert it to the hydroxide form. The column was washed with distilled water (150 mL) to remove the neutral and cationic impurities, and the product eluted with 1 N HCl. The progress of the column was monitored by analyzing the collected fractions by paper chromatography [paper chromatograms were developed by spraying with an aqueous ninhydrin solution (0.2 g in 50 mL H_2O). Upon drying the paper chromatograms in an oven, the presence of a purple spot indicated the presence of the amino acid. The fractions containing the acidic solution of amino acid were combined and poured onto a 3 cm x 25 cm cation exchange column of Dowex 50W-X12 that had previously been washed with water and 1 N HCl to convert it to the hydrogen ion form. The column was eluted with water (150 mL) and finally with 1 N NaOH. The fractions containing the amino acid (paper chromatography) were combined, and the pH

adjusted to a value of 6.0 (pH meter). Because very little compound precipitated near the isoelectric point, the solution was reduced in volume and the product precipitated by the addition of acetone. α-Methyl alanine was obtained as a white solid, which was also contaminated with inorganic salt; ^{1}H-NMR (D_2O, TMS external reference): δ 1.53 (CH_3); ^{13}C-NMR (D_2O, methanol reference): δ 177.72 (COO^-), 58.41 (quaternary carbon), 24.37 (CH_3).

c. Hydrolysis with NaOH: Procedure C

To a 100 mL round-bottomed flask were added 5,5-dimethylhydantoin (15.6 mmol, 2.0 g), sodium hydroxide, (31.2 mmol, 1.25 g), and water (50 mL). The flask was equipped with a magnetic stirring bar, and the contents stirred at room temperature for 5 days. After evaporation of the reaction mixture to dryness, the basic reaction mixture was analyzed by ^{13}C-NMR proton NMR, showing a mixture of hydantoic acid and unreacted hydantoin; ^{13}C-NMR (D_2O, MeOH reference): δ 197.83 (C_1=O, hydantoin), 182.97 (COO^-, hydantoic acid), 173.49 (C_3=O, hydantoin), 160.41 ($H_2N(C=O)$-NHR, hydantoic acid), 61.76 (C_5, hydantoin), 57.21 (quaternary carbon, hydantoic acid), 25.92 (CH_3, hydantoic acid), 24.19 (CH_3, hydantoin).

d. Hydrolysis with NaOH: Procedure D

In a 100 mL round-bottomed flask were placed 5,5-dimethylhydantoin (15.6 mmol, 2.0 g), sodium hydroxide, (31.2 mmol, 1.25 g), and water (50 mL). The flask was equipped with a magnetic stirring bar, and the flask placed in an ultrasonic bath and subjected to ultrasound agitation for 14 hours. After evaporation of the reaction mixture to dryness, the basic reaction mixture was analyzed by ^{13}C-NMR spectroscopy. This revealed a mixture of hydantoic acid and unreacted hydantoin; ^{13}C-NMR (D_2O, MeOH reference): δ 197.83 (C_1=O, hydantoin), 182.97 (COO^-, hydantoic acid), 173.49 (C_3=O, hydantoin), 160.41 ($H_2N(C=O)NHR$, hydantoic acid), 61.76 (C_5, hydantoin), 57.21 (quaternary carbon, hydantoic acid), 25.92 (CH_3, hydantoic acid), 24.19 (CH_3, hydantoin).

e. Hydrolysis with NaOH: Procedure E

To a 100 mL round-bottomed flask were added 5,5-dimethylhydantoin (15.6 mmol, 2.0 g), sodium hydroxide, (31.2 mmol, 1.25 g), and water (50 mL). The flask was equipped with a magnetic stirring bar and reflux condenser, and the contents heated at 140°C (oil bath temperature) for 15 minutes. After evaporation of the reaction mixture to dryness, the basic reaction mixture was analyzed by ^{13}C-NMR spectroscopy, showing a mixture of α-methyl alanine,

hydantoic acid, and unreacted hydantoin; ^{13}C-NMR (D_2O, MeOH reference): δ 197.87 (C_1=O, hydantoin), 186.06 (COO^-, amino acid), 182.97 (COO^-, hydantoic acid), 173.71 (C_3=O, hydantoin), 160.55 ($H_2N(C=O)NHR$, hydantoic acid), 61.84 (C_5, hydantoin), 57.28 (quaternary carbon, hydantoic acid), 55.39 (quaternary carbon, amino acid), 27.95 (CH_3, amino acid), 25.92 (CH_3, hydantoic acid), 24.19 (CH_3, hydantoin).

f. Hydrolysis with $NaOH/NH_4OH$

To a 100 mL round-bottomed flask were placed 5,5-dimethylhydantoin (15.6 mmol, 2.0 g) and sodium hydroxide, (200 mmol, 8.0 g). Concentrated aqueous ammonia (28%, 32 mL, to make a 6.25 N NaOH solution) was added slowly [Note: vigorous evolution of NH_3 is observed upon addition of the concentrated ammonium hydroxide], the flask equipped with a magnetic stirring bar and reflux condenser, and the contents were heated at 150°C (oil bath temperature) for 8 hours. After evaporation of the reaction mixture to dryness, the basic reaction mixture was analyzed by ^{13}C-NMR spectroscopy, showing only the presence of α-methyl alanine; ^{13}C-NMR (D_2O, MeOH reference): δ 186.06 (COO^-), 55.34 (quaternary carbon), 28.15 (CH_3). The solution containing the crude amino acid was adjusted to pH 6.5 (pH meter) with aqueous HCl (50%, 0.2 N, near equivalence point). The neutral solution was reduced in volume, heated until the solid amino

acid dissolved, and allowed to cool (0°C). The neutral amino acid was precipitated from solution by addition of acetone to the cold solution to give, after drying, α-methyl alanine, 1.3 g (81%) as a white powdery solid; ^{1}H-NMR (D_2O, TMS external reference): δ 1.51 (CH_3); ^{13}C-NMR (D_2O, dioxane reference): δ 179.48 (COOH), 59.73 (quaternary carbon), 25.12 (CH_3).

g. Hydrolysis with $NaOH/NH_4OH$/Dioxane

To a 100 mL round-bottomed flask were added 5,5-dimethylhydantoin (15.6 mmol, 2.0 g) and sodium hydroxide, (200 mmol, 8.0 g), and water (16 mL). Concentrated aqueous ammonia (28%, 16 mL, to make an overall 6.25 N NaOH solution) was added slowly [Note: vigorous evolution of NH_3 is observed upon addition of the concentrated aqueous ammonia], the flask equipped with a magnetic stirring bar and reflux condenser, and the contents were heated at 150°C (oil bath temperature) for 8 hours. After evaporation of the reaction mixture to dryness, the basic reaction mixture was analyzed by ^{1}H- and ^{13}C-NMR spectroscopy, showing the presence of α-methyl alanine along with minor amounts of the hydantoic acid and unreacted hydantoin; ^{1}H-NMR (D_2O, TMS external reference): δ 1.39 (s, CH_3, hydantoin), 1.31 (s, CH_3, hydantoic acid), 1.25 (s, CH_3, amino acid; ^{13}C-NMR (D_2O, dioxane reference): δ 187.40 (COO^-), 58.55 (quaternary

carbon, hydantoic acid), 56.62 (quaternary carbon, amino acid), 28.91 (CH_3, amino acid), 27.10 (CH_3, hydantoic acid), 25.37 (CH_3, hydantoin). The crude amino acid was dissolved in a minimal amount of water and acidified (pH 2) with aqueous HCl (50%). Evaporation to dryness in vacuo, gave α-methyl alanine as the hydrochloride salt (contaminated with inorganic salt); ^{13}C-NMR (D_2O, dioxane reference): δ 175.89 (COOH), 58.44 (quaternary carbon), 24.61 (CH_3).

h. Hydrolysis with NaOH/V_2O_5/Polyvinylpyridine (PVP)

In a 100 mL round-bottomed flask fitted with a septum inlet were placed 5,5-dimethylhydantoin (15.6 mmol, 2.0 g), sodium hydroxide, (200 mmol, 8.0 g), polyvinylpyridine (1.0 g), vanadium pentoxide (1.56 mmol, 280 mg), and water (50 mL). The flask, which was equipped with a gas outlet (mercury bubbler), was purged with nitrogen and placed in an ultrasonic bath and subjected to ultrasound agitation for 72 hours (ultrasonic bath temperature approx. 45-50°C). The reaction mixture was filtered, concentrated, and the basic reaction mixture was analyzed by ^{13}C-NMR spectroscopy. This revealed a mixture of hydantoic acid, and unreacted hydantoin; ^{13}C-NMR (D_2O, MeOH reference): δ 199.12 (C_1=O, hydantoin), 184.25 (COO^-, hydantoic acid), 174.71 (C_3=O, hydantoin), 161.77 ($H_2N(C=O)NHR$, hydantoic acid), 63.07 (C_5, hydantoin), 58.51 (quaternary carbon, hydantoic acid), 29.15

CH_3, amino acid), 27.23 (CH_3, hydantoic acid), 25.50 (CH_3, hydantoin).

i. Hydrolysis with NH_4OH/ZnO

To a 50 mL round-bottomed flask were added 5,5-dimethylhydantoin (7.8 mmol, 1.0 g), zinc oxide (6.5 mmol, 0.53 g), and aqueous ammonia (9% solution, 20 mL). The flask was equipped with a magnetic stirring bar and reflux condenser, and the contents heated at 120°C (oil bath temperature) for 6 hours. After evaporation of the reaction mixture to dryness, the basic reaction mixture was analyzed by ^{13}C-NMR spectroscopy, showing only unreacted hydantoin; ^{13}C-NMR (D_2O, MeOH reference): δ 194.44 (C_1=O), 169.72 (C_3=O), 61.65 (C_5), 24.21 (CH_3).

j. Hydrolysis with Barium Hydroxide

In a 250 mL round-bottomed flask were placed 5,5-dimethylhydantoin (15.6 mmol, 2.0 g), barium hydroxide octahydrate (32 mmol, 10.10 g), and water (65 mL). The flask was equipped with a magnetic stirring bar and reflux condenser, and the contents heated to 160°C (oil bath temperature) for 5 hours. After cooling, ammonium carbonate (32 mmol, 3.08 g was added to precipitate the excess barium ion. Filtration of the barium carbonate precipitate, followed by removal of the solvent from the filtrate

afforded the crude product, which was analyzed by ^{13}C-NMR spectroscopy; ^{13}C-NMR (D_2O/NaOD, MeOH reference): δ 184.47 (COO^-), 182.83 (COO^-), 178.19 (COO^-), 162.81, 160.27, 159.84, 61.78 (quaternary carbon), 58.18 (quaternary carbon), 57.18 (quaternary carbon), 25.63 (CH_3), 23.73 (CH_3), 23.53 (CH_3). The crude reaction mixture was acidified with 3 N HCl (pH 6.5), evaporated to dryness, and the solid residue analyzed by ^{13}C-NMR spectroscopy; ^{13}C-NMR (D_2O, MeOH reference): δ 178.08 (COOH), 58.43 (quaternary carbon, $R_3CNH_3^+$), 25.66 (CH_3, hydantoic acid), 25.71 (CH_3, amino acid) 23.52 (CH_3, hydantoin).

k. Sulfuric Acid/Room Temperature Hydrolysis

To a 50 mL round-bottomed flask were added 5,5-dimethylhydantoin (7.8 mmol, 1.0 g), and sulfuric acid (60%, 25 mL). The flask was equipped with a magnetic stirring bar, placed in an ultrasonic bath, and subjected to ultrasonic agitation for 16 hours. After evaporation of the reaction mixture to dryness, the residue was analyzed by ^{13}C-NMR spectroscopy, showing only unreacted hydantoin; ^{13}C-NMR (60% H_2SO_4, methanol reference): δ 178.08 (C_1=O), 157.06 (C_3=O), 60.93 (quaternary carbon), 20.28 (CH_3).

6. Stability of Decenylboronic Acid to Hydantoin Hydrolysis Conditions

a. Sodium Hydroxide Hydrolysis: Procedure A

To a 50 mL round-bottomed flask were added decenylboronic acid (3.9 mmol, 0.50 g), sodium hydroxide solution (6.25 N, 10 mL), and dioxane (enough to dissolve the boronic acid), the flask equipped with a magnetic stirring bar and reflux condenser, and the contents heated to 160°C for 6 hours, during which time the contents of the flask became dark in color. The reaction mixture was saturated with sodium chloride, acidified with aqueous HCl (1 N, pH 3-4) and the product extracted into ether (3x25 mL). Removal of the solvent afforded a brown oil, which was a mixture of boroxime and oxidative decomposition products; ^{13}C-NMR ($CDCl_3$): δ 195.42 (C=O), 157.87 RHC=CHB$(OR)_2$, 155.41 (RHC=CHB$(OR)_2$), 143.95, 125.59, 65.53, 35.77, 31.97, 30.40, 29.78, 29.51, 29.35, 29.02, 28.86, 28.78, 28.29, 24.12, 22.76, 14.18; ^{11}B-NMR (THF) δ 29 (br, RB$(OR)_2$).

b. Sodium Hydroxide Hydrolysis: Procedure B

In a 50 mL round-bottomed flask were placed decenylboronic acid (3.9 mmol, 0.50 g) and sodium hydroxide solution (1.5 N, 10 mL). The flask was equipped with a magnetic stirring bar and reflux condenser, and the contents heated to 120°C for 15 minutes, during which time the

contents of the flask became dark in color. Intermediate ^{11}B-NMR analysis of the reaction mixture revealed a sharp peak a 2.4 ppm, indicating formation of the organoborate. The reaction mixture was acidified with aqueous HCl (1 N, pH 3-4), saturated with sodium chloride, and the product extracted into ether (3x25 mL). Removal of the solvent afforded a brown oil, which was a mixture of mostly boroxine and small amounts of oxidative decomposition products; ^{13}C-NMR ($CDCl_3$): δ 195.42 (C=O), 157.87 RHC=CHB(OR)$_2$, 155.41 (RHC=CHB(OR)$_2$), 143.95, 125.59, 65.53, 35.77, 31.97, 30.40, 29.78, 29.51, 29.35, 29.02, 28.86, 28.78, 28.29, 24.12, 22.76, 14.18; ^{11}B-NMR (THF): δ 29 (br, RB(OR)$_2$).

c. Sodium Hydroxide/Ammonium Hydroxide Hydrolysis

To a 50 mL round-bottomed flask were added decenylboronic acid (1.36 mmol, 0.25 g), sodium hydroxide (31.25 mmol, 1.25 g), concentrated (28%) aqueous ammonia (10 mL) and dioxane (enough to dissolve the boronic acid), the flask equipped with a magnetic stirring bar and reflux condenser, and the contents heated to 160°C for 3 hours, during which time the contents of the flask became dark in color. Intermediate ^{11}B-NMR analysis of the reaction mixture revealed a sharp peak a 2.4 ppm, indicating formation of the organoborate. The reaction mixture was acidified with aqueous HCl (1 N, pH 3-4), saturated with sodium chloride, and the

product extracted into ether (3x25 mL). Removal of the solvent afforded a yellow oil, which was a mixture of boroxime, olefin, and oxidative decomposition products; ^{13}C-NMR ($CDCl_3$): δ 195.42 (C=O), 157.87 RHC=CHB$(OR)_2$, 155.41 (RHC=CHB$(OR)_2$), 143.95, 125.59, 65.53, 35.77, 31.97, 30.40, 29.78, 29.51, 29.35, 29.02, 28.86, 28.78, 28.29, 24.12, 22.76, 14.18; ^{11}B-NMR ($CDCl_3$): δ 29 (br, RB$(OR)_2$).

d. Aqueous Ammonia Hydrolysis

In a 50 mL round-bottomed flask were placed decenylboronic acid (1.36 mmol, 0.25 g), concentrated (28%) aqueous ammonia (5 mL) and dioxane (5 mL), the flask equipped with a magnetic stirring bar and reflux condenser, and the contents heated to 100°C for 6 hours. ^{11}B-NMR analysis of the reaction mixture revealed a broad peak at 20 ppm, which corresponded to unreacted decenylboronic acid; ^{11}B-NMR (NH_4OH/dioxane) δ 20 (br, RB$(OH)_2$).

7. Stability of Decenylboronic Acid to Hydantoin Hydrolysis Conditions: Dual Experiments

a. Sodium Hydroxide/Aqueous ammonia/Inert Atmosphere Hydrolysis

In a 50 mL round-bottomed flask were placed 5,5-dimethylhydantoin (7.8 mmol, 1.0 g), decenylboronic acid (3.9 mmol, 0.72 g), sodium hydroxide (200 mmol, 8.0 g),

concentrated aqueous ammonia (28%, 32 mL), and dioxane (20 mL). The flask was equipped with a magnetic stirring bar and gas outlet (mercury bubbler), and the contents heated to 150°C (oil bath temperature) for 5 hours, during which time the contents of the flask became dark in color. The reaction mixture was acidified with aqueous HCl (1 N, pH 3-4), saturated with sodium chloride, and the product extracted into ether (3x25 mL). After drying ($MgSO_4$) and filtration, removal of the solvent afforded a yellow oil, which was a mixture of an olefin (presumably decene), unreacted 5,5-dimethylhydantoin, and boric acid; ^{13}C-NMR ($CDCl_3$): δ 178.11 (C_1=O, hydantoin), 156.14 (C_3=O), 138.45 (RH<u>C</u>=CH_2), 113.43 (RHC=<u>C</u>H_2), 59.12 (C_5, hydantoin), 33.36, 31.49, 29.56, 29.15, 28.89, 28.75, 28.61, 24.85 (CH_3, hydantoin), 22.23, 13.29; ^{11}B-NMR (THF): δ 19 (br, $B(OH)_3$). The aqueous layer was reduced in volume, heated to redissolve the solid, and acetone added to precipitate a solid white material. This turned out to be inorganic salt. After repeating this process several times, the remaining solution was evaporated to dryness to give α-methyl alanine as a white crystalline solid (still contaminated with some inorganic salt, no yield calculated); ^{1}H-NMR (D_2O, TMS external reference): 1.51 (CH_3); ^{13}C-NMR (D_2O, dioxane reference): δ 175.44 (COOH), 58.51 (quaternary carbon), 24.65 (CH_3); ^{11}B-NMR (D_2O): 18 ($B(OH_3)$).

b. Room Temperature Sodium Hydroxide/Inert Atmosphere Hydrolysis

In a 250 mL round-bottomed flask fitted with a septum inlet were placed 5,5-dimethylhydantoin (7.8 mmol, 1.0 g), decenylboronic acid (3.9 mmol, 0.72 g), and sodium hydroxide solution (6.25 N, 100 mL). The flask equipped with a magnetic stirring bar and gas outlet (mercury bubbler), the apparatus purged with nitrogen, and the contents stirred at room temperature for 14 days. The reaction mixture was acidified with aqueous HCl (1 N, pH 3-4), saturated with sodium chloride, and the product extracted into ether (3x50 mL). After drying ($MgSO_4$) and filtration, removal of the solvent afforded an off-white solid, which was a mixture of unreacted 5,5-dimethylhydantoin and unreacted decenylboronic acid (the presence of other small vinylic carbon peaks are noted, indicating possible partial decomposition); ^{13}C-NMR ($CDCl_3$): δ 178.63 (C_1=O, hydantoin), 156.71 (C_3=O), 150.18 (RHC=CHB$(OH)_2$), 136.24, 124.28, 69.44, 59.47 (C_5, hydantoin), 35.15, 31.41, 29.51, 29.02, 28.81, 28.21, 23.69 (CH_3, hydantoin), 22.14, 13.20, 11.80; ^{11}B-NMR (THF): δ 28 (br, R$B(OH)_2$).

c. Room Temperature Aqueous Ammonia/Inert Atmosphere Hydrolysis

To a 250 mL round-bottomed flask fitted with a septum

inlet were added 5,5-dimethylhydantoin (7.8 mmol, 1.0 g), decenylboronic acid (3.9 mmol, 0.72 g), and aqueous ammonia solution (28%, 100 mL). The flask was equipped with a magnetic stirring bar and gas outlet (mercury bubbler), the apparatus purged with nitrogen, and the contents stirred at room temperature for 17 days. The reaction mixture was acidified with aqueous HCl (1 N, pH 3-4), saturated with sodium chloride, and the product extracted into ether (3x50 mL). After drying ($MgSO_4$) and filtration, the solvent was removed; this afforded 1.55 g of an off-white solid, which was a mixture of unreacted 5,5-dimethylhydantoin, and unreacted decenylboronic acid; ^{13}C-NMR (THF): δ 178.03 (C_1=O, hydantoin), 156.20 (C_3=O), 149.75 (RHC=CHB(OH)$_2$), 59.06 (C_5, hydantoin), 35.25, 31.59, 29.56, 29.21, 28.94, 28.45, 23.71 (CH_3, hydantoin), 22.30, 13.29 (CH_3); ^{11}B-NMR (THF): δ 28 (br, RB(OH)$_2$). The aqueous layer was reduced in volume, heated to redissolve the solid, and acetone added to precipitate a white solid material. This turned out to be inorganic salt. After repeating this process several times, the remaining solution was evaporated to dryness to give unreacted 5,5-dimethylhydantoin as a white crystalline solid (still contaminated with some inorganic salt, no yield calculated); ^{1}H-NMR (D_2O, TMS external reference): 1.38 (CH_3); ^{13}C-NMR (D_2O, $CDCl_3$ external reference): δ 182.36 (C_1=O), 157.96 (C_3=O), 60.87 (quaternary carbon), 23.79

(CH_3).

d. Room Temperature Sodium Carbonate/Inert Atmosphere Hydrolysis

In a 250 mL round-bottomed flask fitted with a septum inlet were placed 5,5-dimethylhydantoin (7.8 mmol, 1.0 g), decenylboronic acid (3.9 mmol, 0.72 g), sodium carbonate (100 mmol, 10.6 g), and water (150 mL). The flask was equipped with a magnetic stirring bar and gas outlet (mercury bubbler), the apparatus purged with nitrogen, and the contents stirred at room temperature for 17 days. The reaction mixture was acidified with aqueous HCl (1 N, pH 3-4), saturated with sodium chloride, and the product extracted into ether (3x50 mL). The solvent was dried ($MgSO_4$), filtered, and removed; this afforded 1.55 g of an off-white solid, which was a mixture of unreacted 5,5-dimethylhydantoin, and unreacted decenylboronic acid; ^{13}C-NMR (THF): δ 178.06 (C_1=O, hydantoin), 156.17 (C_3=O), 149.75 (RHC=CHB(OH)$_2$), 59.06 (C_5, hydantoin), 35.25, 31.59, 29.56, 29.21, 28.94, 28.45, 23.71 (CH_3, hydantoin), 22.30, 13.29 (CH_3); ^{11}B-NMR (THF): δ 28 (br, RB(OH)$_2$). The aqueous layer was reduced in volume, heated to redissolve the solid, and acetone added to precipitate a white solid material. This turned out to be inorganic salt. After repeating this process several times, the remaining solution

was evaporated to dryness to give unreacted 5,5-dimethylhydantoin as a white crystalline solid (still contaminated with some inorganic salt, no yield calculated); ^{1}H-NMR (D_2O, TMS external reference): 1.38 (CH_3); ^{13}C-NMR (D_2O, dioxane reference): δ 182.76 (C_1=O), 158.36 (C_3=O), 61.36 (quaternary carbon), 24.39 (CH_3).

e. Room Temperature Ammonium Carbonate/Inert Atmosphere Hydrolysis

To a 250 mL round-bottomed flask fitted with a septum inlet were added 5,5-dimethylhydantoin (7.8 mmol, 1.0 g), decenylboronic acid (3.9 mmol, 0.72 g), ammonium carbonate (100 mmol, 10.6 g), and water (150 mL). The flask was equipped with a magnetic stirring bar and gas outlet (mercury bubbler), the apparatus purged with nitrogen, and the contents stirred at room temperature for 17 days. The reaction mixture was acidified with aqueous HCl (1 N, pH 3-4), saturated with sodium chloride, and the product extracted into ether (3x50 mL). After drying ($MgSO_4$) and filtration, the solvent was removed; this afforded 0.89 g of an off-white solid, which was a mixture unreacted 5,5-dimethylhydantoin, and unreacted decenylboronic acid; ^{13}C-NMR (THF): δ 178.06 (C_1=O, hydantoin), 156.17 (C_3=O), 149.75 (RHC=CHB(OH)$_2$), 59.06 (C_5, hydantoin), 35.25, 31.59, 29.56, 29.21, 28.94, 28.45, 23.71 (CH_3, hydantoin), 22.30,

13.29 (CH_3); ^{11}B-NMR (THF): δ 29 (br, $RB(OH)_2$). The aqueous layer was reduced in volume, heated to redissolve the solid, and acetone added to precipitate a solid white material. This turned out to be inorganic salt. After repeating this process several times, the remaining solution was evaporated to dryness to give unreacted 5,5-dimethyl-hydantoin as a white crystalline solid (still contaminated with some inorganic salt, no yield calculated); ^{1}H-NMR (D_2O, TMS external reference): 1.38 (CH_3); ^{13}C-NMR (D_2O, dioxane reference): δ 182.76 (C_1=O), 158.36 (C_3=O), 61.36 (quaternary carbon), 24.39 (CH_3).

f. <u>^{11}B-NMR Study: Effect of Added Base and Acid on the ^{11}B-NMR Chemical Shift of Decenylboronic Acid</u>

A sample of decenylboronic acid (1 mmol, 184 mg) dissolved in dioxane (2.5 mL) was placed in a 10 mm NMR tube and the ^{11}B-NMR spectrum recorded. A broad resonance at 27.4 ppm was observed. Five drops of concentrated aqueous ammonia were added, and the ^{11}B-NMR spectrum recorded (20.4 ppm, br). Ten more drops of concentrated aqueous ammonia were added and the ^{11}B-NMR spectrum recorded again (20.4 ppm, br). Fifteen drops of 1 <u>N</u> NaOH were then added and the ^{11}B-NMR spectrum recorded (2.38 ppm, sharp). Finally, ten drops of concentrated HCl were added and the ^{11}B-NMR spectrum recorded (18.13 ppm). A known sample of

decenylboronic acid was dissolved in dioxane/9% NH_4OH, the ^{11}B-NMR spectrum recorded (19 ppm), and the result compared with the above experiment. Thus, it appears that decenylboronic acid is stable to the above reaction conditions, and was regenerated upon acidification.

8. Stability of 1-Iododecene to Hydantoin Hydrolysis Conditions

a. 1-Iodo-1-decene

Decenylboronic acid was prepared according to procedure 5.D.2.a described earlier. In a 100 mL round bottom flask equipped with a magnetic stirring bar were placed decenylboronic acid (10 mmol, 1.84 g) and THF/H_2O (50%, 25 mL). the flask was shielded from light with aluminum foil, and then sodium iodide (1 M, 10 mmol) and chloramine T (0.5 M in THF/H_2O, 20 mmol) were added sequentially. The contents were stirred for 1 minute, and the product extracted into petroleum ether (3x50 mL). The combined petroleum ether layers were dried ($MgSO_4$), filtered, and the solvent removed to provide 2.6 g of a yellow oil. Purification by column chromatography (silica gel, petroleum ether, R_F = 0.9 in petroleum ether) afforded 2.43 g (91%) of (E)-1-iododecene as a colorless oil; ^1H-NMR ($CDCl_3$): 6.7-6.3 (m, 1H, IHC=CHR), 6.1-58 (m, 1H, J_{trans}=14.6 Hz, IHC=CHR), 2.25-1.85 (m, 2H, IHC=CHCH_2), 1.55-1.1 (broad envelope, 12H), 0.88

(CH_3); 146.82 (IHC=CHR), 74.38 (IHC=CHR), 36.15 (IHC=CH_2-R), 31.95, 29.43, 29.31, 29.02, 28.47, 22.76 (RCH_2CH_3), 14.18 (CH_3).

b. Stability of (E)-1-Iododecene to Hydantoin Hydrolysis Conditions: Test Reaction

To a 100 mL round bottom flask were placed (E)-1-iododecene (5.37 mmol, 1.43 g), dioxane (16 mL), and sodium hydroxide solution (6.25 N, 16 mL). The flask was equipped with a magnetic stirring bar, reflux condenser, and gas outlet. The apparatus shielded from light with aluminum foil, purged with nitrogen, and the contents refluxed for 4 hours at 150°C (oil bath temperature) under nitrogen atmosphere. After cooling, the product was extracted into ether (3x50 mL) and the combined ether layers dried over anhydrous magnesium sulfate. Filtration, followed by evaporation of the solvent, gave recovered (E)-1-iododecene, 1.42 g (99%), without isomerization! ^{1}H-NMR ($CDCl_3$): 6.7-6.3 (m, 1H, IHC=CHR), 6.1-58 (m, 1H, J_{trans}=14.6 Hz, IHC=CHR), 2.25-1.85 (m, 2H, IHC=CH_2), 1.55-1.1 (broad envelope, 12H), 0.88 (CH_3); 146.82 (IHC=CHR), 74.38 (IHC=CH-R), 36.15 (IHC=CH_2R), 31.95, 29.43, 29.31, 29.02, 28.47, 22.76 (RCH_2CH_3), 14.18 (CH_3).

9. 5-(10-Undecenylboronic Acid-1-)2,4-imidazolidine-1,3-dione

a. Sodium Iodide/Chloramine T Procedure

To a 50 mL round-bottomed flask were added 5-(10-undecenylboronic acid-1-)2,4-imidazolidine-1,3-dione (2.0 mmol, 0.56 g) and THF/H_2O (15 mL, 2:1). The flask was equipped with a magnetic stirring bar and shielded from light with aluminum foil. The contents were cooled to 0°C, and then sodium iodide (2.0 mmol, 1 M in H_2O) and chloramine T (4 mmol, 0.5 M in 50% THF/H_2O) were added sequentially. After the disappearance of the dark brown color (5 minutes), the crude product was extracted into ether (3x25 mL). The combined ether layers were dried ($MgSO_4$), filtered, and the solvent removed to give a dark brown liquid. TLC analysis of the crude reaction mixture revealed the presence of ten spots. Preliminary purification of the crude material was accomplished by column chromatography (silica gel, 2% MeOH-methylene chloride). Those fractions containing spots with R_F values between 0.2-0.4 (TLC, 2% methanol-methylene chloride; R_F = 0.3-0.8, 60% ethyl acetate-petroleum ether) were combined and purified further by flash column chromatography [silica gel (40 micron), 2% methanol-methylene chloride]. This afforded 100 mg (14%) of 5-((E)-11-iodo-10-undecen-1-yl-)2,4-imidazolidine-1,3-dione as a light yellow solid; ^{1}H-NMR ($CDCl_3$): δ 8.57 (s, 1H, N_2-H), 6.7-6.25 (m,

1H, IHC=CHR), 6.23 (s, 1H, N_4-H), 6.05-5.85 (m, 1H, J_{trans}= 14.5 Hz, IHC=CHR), 4.01 (dd, 1H, RCHH'CH-ring), 2.2-1.15 (broad envelope, 16H); ^{13}C-NMR ($CDCl_3$): δ 174.91 (C_1=O), 157.66 (C_3=O), 146.74 (IHC=CHR), 74.39 (IHC=CHR), 58.90 (C_5 hydantoin), 36.04 (IHC=CHCH_2R), 31.62, 29.37, 29.21, 28.86, 28.34, 24.82, 21.57.

b. Iodine Monochloride Procedure

To a 50 mL round-bottomed flask were added 5-(10-undecenylboronic acid-1-)2,4-imidazolidine-1,3-dione (1.28 mmol, 360 mg) and THF (20 mL). The flask was equipped with a magnetic stirring bar and shielded from light with aluminum foil. The contents were cooled to -78°C, and sodium acetate (2.6 mmol, 1 M in anhydrous methanol) and iodine monochloride (2.6 mmol, 1.0 M in anhydrous methanol) were added sequentially. The reaction mixture was stirred for one hour while gradually allowing the temperature to come to 0°C, during which time the disappearance of the dark brown color was observed. The crude product was extracted into ether (3x25 mL). The combined ether layers were dried ($MgSO_4$), filtered, and then the solvent removed to give a dark brown liquid. TLC analysis of the crude reaction mixture revealed the presence of ten spots. Preliminary purification of the crude material was accomplish by column chromatography (silica gel, 5% MeOH-10% ethyl acetate-

methylene chloride). Those fractions containing the spot of R_F = 0.63 (TLC, ether) were combined and the solvent removed to afford 8 mg (2%) of 5-((E)-11-iodo-10-undecen-1-yl-)2,4-imidazolidine-1,3-dione as a light yellow solid; ^{1}H-NMR ($CDCl_3$): δ 8.57 (s, 1H, N_2-H), 6.7-6.25 (m, 1H, IHC=CHR), 6.23 (s, 1H, N_4-H), 6.05-5.85 (m, 1H, J_{trans}=14.5 Hz, IHC=CHR), 4.01 (dd, 1H, RCHH'CH ring), 2.2-1.15 (broad envelope, 16H); ^{13}C-NMR ($CDCl_3$): δ 174.91 (C_1=O), 157.66 (C_3=O), 146.74 (IHC=CHR), 74.39 (IHC=CHR). 58.90 (C_5), 36.04 (IHC=CH_2R), 31.62, 29.37, 29.21, 28.86, 28.34, 24.82, 21.57.

10. 2-Amino-12-iodo-11-dodecenoic Acid

To a 50 mL round bottom flask were added 5-(10-undecenylboronic acid-1-)2,4-imidazolidine-1,3-dione (0.19 mmol, 70 mg), solid sodium hydroxide (3.84 mmol, 150 mg), water (5 mL), and dioxane (25 mL, to dissolve the iodohydantoin). The flask, which was equipped with a magnetic stirrer, reflux condenser, and gas outlet, was purged with nitrogen, and then heated at 150°C (oil bath temperature) for four hours. The reaction mixture was evaporated to near dryness, and the highly basic mixture loaded onto a column of Dowex 1-X8 anion exchange resin (previously washed with 1 N NaOH to convert it to the hydroxide form). The column was eluted first with distilled water, and finally with 1 N HCl.

Evaporation to dryness of the fractions containing the amino acid (paper chromatography, ninhydrin detection) gave (E)-2-amino-12-iodo-11-dodecenoic acid as a light yellow solid; ^{13}C-NMR (D_2O/NaOD, dioxane reference): δ 182.90 (COO^-), 147.25 (IHC=CHR), 76.50 (IHC=CHR), 65.02 ($RHC(NH_2)COOH$), 36.95 ($IHC=CHCH_2R$), 34.46, 34.38, 34.13, 33.84, 25.52; IR (KBr): 3650-2600 cm^{-1} (br, NH_3^+), 2600-2000 (br, continuation of 3650-2600 region, overtone and combination region, overtone at 2545 cm^{-1}), 1630 cm^{-1}, 1610 cm^{-1} (COO^-), 1522 cm^{-1}, 1477 cm^{-1}, 1200-1000 (br), 935 cm^{-1} (C=C).

11. Protection of the Hydantoin Ring

a. Test Reaction: Iodination of 5-(Hexyl-1-)2,4-imidazolidine-1,3-dione

In a 50 mL round-bottomed flask equipped with a magnetic stirring bar were placed 5-hexylhydantoin (2.71 mmol, 500 mg), and 50% aqueous THF (10 mL). The flask was shielded from light, and then sodium iodide (5.4 mmol, 1 M in H_2O) and chloramine T (10.8 mmol, 0.5 M in 50% aqueous THF) were sequentially added. The dark color disappeared within 30 seconds, indicating the consumption of the electrophilic iodine. TLC analysis of the crude reaction mixture revealed the disappearance of the starting hydantoin and the presence of a faster moving spot. The reaction mixture was saturated with sodium chloride, and the aqueous

layer extracted with ether (3x25 mL). After filtration and removal of the solvent, the crude product was analyzed by NMR spectroscopy.

b. Test Reaction: Iodination of 5,5-Dimethyl-2,4-imidazolidine-1,3-dione

To a 50 mL round-bottomed flask equipped with a magnetic stirring bar were added 5,5-dimethylhydantoin (7.8 mmol, 1.0 g), and 50% aqueous THF (10 mL). The flask was shielded from light, and then sodium iodide (7.8 mmol, 1 M in H_2O) and chloramine T (15.6 mmol, 0.5 M in 50% aqueous THF) were sequentially added. The dark color disappeared within 30 seconds, indicating the consumption of the electrophilic iodine. TLC analysis of the crude reaction mixture revealed the disappearance of the starting hydantoin and the presence of a faster moving spot. The reaction mixture was saturated with sodium chloride, and the aqueous layer extracted with ether (3x25 mL). After filtration and removal of the solvent, the crude product was analyzed by NMR spectroscopy.

c. Test Reaction: Iodination of 5-(Hexyl-1-)2,4-imidazolidine-1,3-dione Using NaI/HCl Procedure

In a 50 mL round-bottomed flask equipped with a magnetic stirring bar were placed 5-hexylhydantoin (2.71

mmol, 500 mg), water (5 mL) and 10% HCl (10 mL). (The hydantoin remained as a suspension.) The flask was shielded from light, and then sodium iodide (2.7 mmol, 1 M in H_2O) and chloramine T (2.7 mmol, 0.1 M in water) were sequentially added. The reaction mixture immediately turned dark in color, but did not disappear over a four hour period. TLC analysis of the crude reaction mixture revealed only the starting hydantoin. The reaction mixture was saturated with sodium chloride and the reaction mixture extracted with THF. After drying of the combined ether layers ($MgSO_4$), filtration and removal of the solvent gave a yellow solid, which was identified as a mixture of unreacted hexylhydantoin and toluenesulfonamide.

d. Tosylation of 5,5-Dimethyl-2,4-imidazolidine-1,3-dione

To a 500 mL round-bottomed flask was added a solution of 5,5-dimethylhydantoin (78.05 mmol, 10 g) dissolved in 1 M KOH (64 mL). The flask was equipped with a magnetic stirring bar, and addition funnel, and after the contents were cooled to 0°C, a solution of tosyl chloride (78.05 mmol, 14.88 g) in acetone (45 mL) was added dropwise. The resulting mixture was stirred at 0°C for 1 hour. The ice bath was removed and the contents heated to 35°C, afterwhich 1 M KOH was added dropwise for 1 hour; the solution was then stirred for an additional 5 hours at 35°C. With the

reaction mixture at 35°C, the solid precipitate in the reaction flask was removed by filtration to give a white solid. Recrystallization of this material from chloroform-ether (minimal amount) gave 1.61 g (9.4%) of a white fluffy solid, identified as the di-tosyl derivative; mp 191°C; ^{1}H-NMR ($CDCl_3$): δ 8.1-7.2 (m, 8H, AA'BB', aromatic), 2.45 (s, 6H, CH_3-Ar), 1.72 (s, 6H, CH_3, hydantoin); ^{13}C-NMR ($CDCl_3$): δ 169.90 (C_1=O), 147.09 (aromatic, C-OTs (N_4)), 146.80 (C_3=O), 146.14 (aromatic, C-OTs (N_2)), 134.99 (aromatic, C-Me (N_4)), 134.01 (aromatic, C-Me (N_2)), 130.22 (aromatic, meta to S (N_4)), 129.87 (aromatic, meta to S (N_2)), 128.91 (aromatic, ortho to S), 128.70 (aromatic, ortho to S), 66.51 (C_5, hydantoin), 24.20 (CH_3, hydantoin), 21.84 (CH_3, tosyl), 21.76 (CH_3, tosyl). The filtrate was cooled to 0°C, upon which a second precipitate formed. Following filtration of this white solid, recrystallization from chloroform-ether (minimal amount) afforded 4.41 g (24.2%) of N-3-tosyl-5,5-dimethylhydantoin as a white fluffy solid; mp 150.5°C (lit[342] 146-147°C); ^{1}H-NMR ($CDCl_3$): 8.1-7.2 (m, 4H, AA'BB', aromatic), 7.11 (s, 1H, N-H), 2.45 (s, 3H, CH_3, tosyl), 1.41 (s, 6H, CH_3, hydantoin); ^{13}C-NMR ($CDCl_3$): δ 172.82 (C_1=O), 150.70 (C_3=O), 146.30 (aromatic, C-S), 134.79 (aromatic, C-Me), 129.94 (aromatic, meta to S), 128.24 (aromatic, ortho to S), 58.90 (C_5, hydantoin), 24.82 (CH_3, hydantoin), 21.71 (CH_3, tosyl).

e. 2,2-Dimethyl-5-Tosylhydantoic Acid

A solution of 3-N-tosyl-5,5-dimethylhydantoin (3.54 mmol, 1.00 g) dissolved in 1 N NaOH was heated at 55°C for 3.5 hours. The reaction mixture was acidified with concentrated HCl (pH = 2) and the white precipitate which formed was filtered. Recrystallization from acetone-chloroform gave 0.38 g (36%) of 2,2-dimethyl-5-tosylhydantoic acid as white crystals; mp 142°C (lit 142-142.5[342]); ^{1}H-NMR (DMSO-d_6): δ 10.4 (br, 1H, COOH), 8.0-7.2 (m, 4H, AA'BB', aromatic), 6.89 (s, 1H, N_3-H), 2.39 (s, 3H, CH_3, tosyl), 1.32 (s, 6H, CH_3); ^{13}C-NMR (DMSO) δ 175.51 (COOH, s), 150.53 (aromatic C-S, s), 143.81 (-HN(C=O)NHTs, s), 137.52 (aromatic C-Me, s), 129.61 (aromatic, meta to S, d), 129.26 (aromatic ortho to S, d), 55.48 (quaternary carbon, s), 24.87 (CH_3's, q), 21.19 (CH_3, tosyl, q).

f. α-Methyl Alanine Hydrochloride: Hydrolysis of 2,2-Dimethyl-5-Tosylhydantoic Acid

A mixture of 2,2-dimethyl-5-N-tosylhydantoic acid and 10% HCl (50 mL) was refluxed for one hour. After allowing the reaction mixture to stand overnight, the separated white precipitate was removed by filtration to give, after recrystallization from ether, 65 mg (23%) of toluenesulfonamide, which was identical to a known sample; ^{1}H-NMR ($CDCl_3$): δ 7.9-7.15 (m, 4H, AA'BB', aromatic), 5.95 (s, br,

2H, NH_2), 2.43 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 143.68 (aromatic, C-S), 139.21 (aromatic, C-Me), 129.81 (aromatic, meta to S), 126.56 (aromatic, ortho to S), 21.60 (CH_3). The filtrate was evaporated to dryness, the residue dissolved in hot ethanol, and then allowed to recrystallize after the addition of a minimal amount of ether to the hot ethanolic solution. α-Methyl alanine, 68 mg (29%) was thus obtained as a white crystalline solid; ^{1}H-NMR (D_2O, dioxane reference): δ 1.50 (CH_3); ^{13}C-NMR (D_2O, dioxane reference): δ 175.86 (COOH), 57.73 (R_3C-NH_3^+), 23.87 (CH_3).

g. Attempted Ultrasonic Hydrolysis of 2,2-Dimethyl-5-Tosylhydantoic Acid

A mixture of 2,2-dimethyl-5-N-tosylhydantoic acid and 10% HCl (50 mL) was sonicated in an ultrasonic bath for 16 hours. After evaporation of the reaction mixture to dryness, the residue was analyzed by NMR spectroscopy. The residue only contained the unreacted hydantoic acid; ^{1}H-NMR (DMSO-d_6): δ 10.4 (br, 1H, COOH), 8.0-7.2 (m, 4H, AA'BB', aromatic), 6.89 (s, 1H, N_3-H), 2.39 (s, 3H, CH_3, tosyl), 1.32 (s, 6H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 175.51 (COOH,), 150.53 (aromatic C-S), 143.81 (-HN(C=O)NHTs), 137.52 (aromatic C-Me), 129.61 (aromatic, meta to S), 129.26 (aromatic ortho to S), 55.48 (quaternary carbon), 24.87 (CH_3's), 21.19 (CH_3, tosyl).

h. Test Reaction: Iodination of Decenylboronic Acid and 5,5-Dimethyl-3-N-tosylhydantoin with Sodium Iodide (One Equivalent)

To a 100 mL round-bottomed flask were added 5,5-dimethyl-3-N-tosylhydantoin (2 mmol, 569 mg), decenylboronic acid (2 mmol, 368 mg), THF (10 mL), and water (5 mL). The flask was shielded from light, and sodium iodide (2 mmol, 1 M in H_2O) and chloramine T (4 mmol, 0.5 M in 50% aqueous THF) were sequentially added. After 15 minutes, the dark color of the reaction mixture had disappeared, indicating completion of reaction. The reaction mixture was saturated with sodium chloride, the product extracted into ether (3x25 mL), and the combined ether layers were dried ($MgSO_4$). Filtration, followed by removal of the solvent, gave the crude product as a mixture of a yellow oil and solid. Purification by column chromatography (silica gel, petroleum ether, R_F = 0.9 in petroleum ether), afforded 241 mg (45%) of (E)-1-iododecene as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 6.7-6.3 (m, 1H, IHC=C<u>H</u>R), 6.1-58 (m, 1H, J_{trans}= 14.6 Hz, I<u>H</u>C=CHR), 2.25-1.85 (m, 2H, IHC=CHC<u>H</u>$_2$), 1.55-1.1 (broad envelope, 12H), 0.88 (CH_3); 146.82 (IHC=<u>C</u>H-R), 74.38 (IH<u>C</u>=CHR), 36.15 (IHC=CH<u>C</u>H$_2$R), 31.95, 29.43, 29.31, 29.02, 28.47, 22.76 (R<u>C</u>H$_2$CH$_3$), 14.18 (CH_3).

i. Test Reaction: Iodination of Decenylboronic Acid and 5,5-Dimethyl-3-N-tosylhydantoin with Sodium Iodide (Two Equivalents

To a 100 mL round-bottomed flask were added 5,5-dimethyl-3-N-tosylhydantoin (2 mmol, 569 mg), decenylboronic acid (2 mmol, 368 mg), THF (10 mL), and water (5 mL). The flask was shielded from light, and sodium iodide (4 mmol, 1 M in H_2O) and chloramine T (8 mmol, 0.5 M in 50% aqueous THF) were sequentially added. After 15 minutes, the dark color of the reaction mixture had disappeared, indicating completion of reaction. The reaction mixture was saturated with sodium chloride and extracted with ether (3x25 mL), and the combined ether layers were dried ($MgSO_4$). Filtration, followed by removal of the solvent, gave the crude product as a mixture of a yellow oil and solid. Purification by column chromatography (silica gel, petroleum ether, R_F = 0.9 in petroleum ether), afforded 556 mg (86%) of (E)-1-iodo-decene as a colorless oil; ^{1}H-NMR ($CDCl_3$): 6.7-6.3 (m, 1H, IHC=C<u>H</u>R), 6.1-58 (m, 1H, J_{trans}= 14.6 Hz, I<u>H</u>C=CHR), 2.25-1.85 (m, 2H, IHC=CH<u>C</u>H_2), 1.55-1.1 (broad envelope, 12H), 0.88 (CH_3); 146.82 (IHC=<u>C</u>HR), 74.38 (IH<u>C</u>=CHR), 36.15 (IHC=CH<u>C</u>H_2R), 31.95, 29.43, 29.31, 29.02, 28.47, 22.76 (R<u>C</u>H_2CH_3), 14.18 (CH_3).

j. Test Reaction: Iodination of Decenylboronic Acid and 5,5-Dimethyl-1,3-N,N-ditosylhydantoin

To a 100 mL round-bottomed flask were added 5,5-dimethyl-N,N-ditosylhydantoin (1 mmol, 436 mg), decenylboronic acid (1 mmol, 184 mg), THF (12.5 mL), and water (7.5 mL). The flask was shielded from light, and sodium iodide (1 mmol, 1 M in H_2O) and chloramine T (2 mmol, 0.5 M in 50% aqueous THF) were sequentially added. After 15 minutes, the dark color of the reaction mixture had disappeared, indicating completion of reaction. The reaction mixture was saturated with sodium chloride and extracted with petroleum ether (3x25 mL), and the combined organic layers were dried ($MgSO_4$). Filtration, followed by removal of the solvent, gave the crude product as a pink oil. Purification by column chromatography (silica gel, petroleum ether, R_F = 0.9 in petroleum ether), afforded 221 mg (83%) of (E)-1-iododecene as a colorless oil.

k. Attempted Tosylation of 5-(10-Undecen-1-yl-)2,4-imdazolidine-1,3-dione

In a 500 mL round-bottomed flask was placed a solution of 5-(10-undecen-1-yl)hydantoin (16.76 mmol, 3.96 g) dissolved in acetone (30 mL). The flask, which was equipped with a magnetic stirring bar, addition funnel, was cooled to 0°C, and a solution of tosyl chloride (24.14 mmol, 4.79 g)

in acetone (30 mL) was added dropwise, afterwhich it was stirred at 0°C for 1 hour. The ice bath was removed and the contents were heated to 35°C; then, 1 M KOH was added dropwise for 1 hour. The resulting solution was stirred for an additional 16 hours at 35°C. Precipitation of the reaction product in this instance did not occur; thus, the reaction mixture was reduced in volume, saturated with sodium chloride, and the reaction mixture extracted with ethyl acetate (3x50 mL). After drying the combined organic layers ($MgSO_4$), filtration, followed by evaporation of the solvent, gave a white solid. TLC and NMR analysis of the crude product revealed the presence a complex mixture of products. Attempted purification of this mixture by column chromatography (silica gel, solvent gradient of ethyl acetate-petroleum ether mixtures (10-60%)) did not provide the desired compound.

1. t-Butoxycarbonylation of 5-(10-Undecen-1-yl)-2,4-imidazolidine-1,3-dione

To an oven-dried 100 mL round-bottomed flask fitted with a septum inlet was added 5-(10-undecen-1-yl)-2,4-imidazolidine-1,3-dione (1.00 mmol, 236 mg). The flask was fitted with a reflux condenser, magnetic stirring bar, and gas outlet (mercury bubbler). The apparatus was flushed with nitrogen, and then anhydrous methylene chloride (20 mL)

and triethylamine (2.2 mmol, 222 mg, 306 µL) were added. After stirring for ten minutes at room temperature, di-t-butyl dicarbonate (2.2 mmol, 480 mg, 520 µL) was added by syringe, and the resulting mixture heated to 50°C for 3 hours, and finally stirred for an additional 5 hours at room temperature. The reaction was quenched by the addition of water (20 mL) and 0.1 N HCl (20 mL). The contents were stirred for five minutes, saturated with sodium chloride, and the organic layer was separated. The aqueous layer was extracted with methylene chloride (3x25 mL), and the combined methylene chloride layers were washed with 1 M NH_4Cl/NH_4OH (25 mL) and then with water (25 mL), and finally dried over anhydrous sodium sulfate. Filtration, followed by removal of the solvent, gave 0.83 g of a cloudy oil. TLC analysis of the crude product revealed the presence of two products of R_F = 0.85 and R_F = 0.40 (30% ethyl acetate-petroleum ether). Purification of the crude product by column chromatography (silica gel, solvent gradient of ethyl acetate-petroleum ether mixtures (10-30%)) gave pure samples of both compounds. Fractions containing the faster moving compound were combined, and the solvent removed to give 70 mg (16%) of 2,4-diBOC-5-(10-undecen-1-yl-)2,4-imidazolidine-1,3-dione as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 4.41 (dd, 1H, J=4.8 Hz, RCHH'CH-ring), 2.4-1.85 (broad multiplet, 5H, $HC{\equiv}C\underline{CH_2}R$, RCHH'CH-ring, and contains triplet at δ 1.93 which

corresponds to HC≡CR), 1.7-1.2 (broad envelope, 30H, contains two singlets at δ 1.59 and 1.56 (t-butyl groups)); ^{13}C-NMR ($CDCl_3$): δ 167.35 (C_1=O), 148.07 (C_3=O), 147.47 ((N(C=O)Ot-Bu), (N_2)), 144.95 ((N(C=O)Ot-Bu), (N_4)), 86.20 ($C(CH_3)_3$), 84.41 ($C(CH_3)_3$), 84.28 (HC≡CR), 68.05 (HC≡CR), 58.87 (C_5, hydantoin), 29.83, 28.83, 28.61, 28.34, 28.18, 27.72 ($(CH_3)_3C$), 27.50 ($(CH_3)_3C$), 22.81, 18.10 ($HC\equiv CCH_2R$). Fractions containing the slower moving compound were combined and the solvent removed to give 130 mg of 2-N-BOC-5-(10-undecen-1-yl)-2,4-imidazolidine-1,3-dione as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 6.89 (s, 1H, N_2-H), 4.03 (dd, 1H, J=4.8 Hz, RCHH'CH-ring), 2.4-1.1 [broad envelope, 27H, containing triplet at δ 1.93 (J=2.6 Hz, HC≡CR) and a singlet at 1.58 (t-butyl group); ^{13}C-NMR ($CDCl_3$): δ 170.39 (C_1=O), 153.57 (C_3=O), 146.17 (N(C=O)Ot-Bu), 85.74 ($(CH_3)CO$), 84.68 (HC≡CR), 68.21 (HC≡CR), 56.65 (C_5, hydantoin), 31.95, 28.13, 28.97, 28.64, 28.42, 27.88, 24.71, 18.40 ($HC\equiv CCH_2R$).

m. N,N-Di-t-Butoxycarbonyl-5-(10-undecen-1-yl)-2,4-imidazolidine-1,3-dione

In an oven-dried 250 mL round-bottomed flask fitted with a septum inlet was placed 5-(10-undecen-1-yl)-2,4-imidazolidine-1,3-dione (8.29 mmol, 1.96 g). The flask, which was fitted with a reflux condenser, magnetic stirring bar, and gas outlet (mercury bubbler), was flushed with nitrogen,

and then anhydrous methylene chloride (70 mL) and triethylamine (24,9 mmol, 2.52 g, 3.47 mL) were added. After stirring for ten minutes at room temperature, di-t-butyl dicarbonate (24.9 mmol, 5.43g, 5.72 mL) was added by syringe, and the resulting mixture was heated at 50°C for 13 hours. TLC analysis of the reaction mixture prior to workup showed complete conversion of the reactant to the di-Boc hydantoin derivative (R_F=0.82, 30% ethyl acetate-petroleum ether). The reaction was quenched by addition of water (50 mL) and 0.1 N HCl (100 mL), then stirred for ten minutes. After saturation of the reaction mixture with sodium chloride the organic layer was separated. The aqueous layer was extracted with methylene chloride (3x75 mL), and the combined methylene chloride layers were washed sequentially with 1 M NH_4Cl/NH_4OH (100 mL), water (100 mL) and saturated brine (100 mL), and finally dried over anhydrous sodium sulfate. Filtration, followed by removal of the solvent, gave 6.20 g of a yellow oil. Purification of the crude product by column chromatography (silica gel, 10% ethyl acetate-petroleum ether, R_F = 0.82 in 10% ethyl acetate-petroleum ether) gave 3.13 g of N,N-di-t-butoxycarbonyl-5-(10-undecen-1-yl)-2,4-imidazolidine-1,3-dione as a colorless viscous oil; ^{1}H-NMR ($CDCl_3$): δ 4.41 (dd, 1H, J=4.8 Hz, RCHH'CH-ring), 2.4-1.85 (broad multiplet, 5H, $HC{\equiv}C\underline{CH_2}R$, RCHH'CH-ring, and contains triplet at δ 1.93 which

corresponds to HC≡CR), 1.7-1.2 (broad envelope, 30H, contains two singlets at δ 1.59 and 1.56 (t-butyl groups)); ^{13}C-NMR ($CDCl_3$): δ 167.35 (C_1=O), 148.07 (C_3=O), 147.47 ((N(C=O)Ot-Bu), (N_2)), 144.95 ((N(C=O)t-OtBu), (N_4)), 86.20 ($C(CH_3)_3$), 84.41 ($C(CH_3)_3$), 84.28 (HC≡CR), 68.05 (HC≡CR), 58.87 (C_5, hydantoin), 29.83, 28.83, 28.61, 28.34, 28.18, 27.72 (($CH_3)_3$C), 27.50 ((CH_3,3C), 22.81, 18.10 (HC≡CCH_2R).

n. Hydroboration of N,N-Di-t-butoxycarbonyl-5-(10-undecen-1-yl)-2,4-imidazolidine-1,3-dione

An oven dried 500 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, reflux condenser, and gas outlet, assembled while hot, flame dried, and flushed with nitrogen. The di-Boc hydantoin (5.11 mmol, 2.23 g) dissolved in anhydrous THF (20 mL) was transferred to the flask by use of a double-ended needle, and then catecholborane (16.10 mmol, 1.63 mL) was introduced slowly at room temperature. The contents were stirred at 65-70°C for 6 hours, during which time most of the solvent was allowed to evaporate off. A viscous oil remained at the termination of the reaction. Water (300 mL) was added, and the contents stirred overnight. The precipitated boronic acid was removed by filtration, washed successively with a copious amount of water and ether, and then dried to give 1.71 g (99%) of the boronic acid as a cream-white solid;

^{1}H-NMR (THF-d_5): δ 7.41 (s, 1H, N_4-H), 7.1-6.2 (m, 1H, $(HO)_2BHC=C\underline{H}R$), 5.4-5.1 (m, 1H, J_{trans} = 17.6 Hz), 3.88 (dd, 1H $C\underline{H}$, C_5), 1.9-1.0 (broad envelope, 26H); ^{13}C-NMR (THF-d_5): δ 176.80 (C_1=O), 159.03 (C_3=O), 151.04 ($(HO)_2BHC=\underline{C}HR$), 146.28 ($(N(\underline{C}=O)O\underline{t}Bu$, N_2), 120.05, 115.91, 59.27 (C_5, hydantoin), 36.41, 32.51, 30.15 ($\underline{C}(CH_3)_3$), 29.50, 26.96, 26.06, 25.41, 25.17, 24.27, 23.41; ^{11}B-NMR (THF-d_5): δ 22.0.

o. Attempted Iodination of N-2 BOC Protected Hydantoin

The crude BOC protected hydantoin (0.17 mmol, 56 mg) was dissolved in aqueous THF (15 mL, 2:1 THF/H_2O) and shielded from light (aluminum foil was wrapped around the flask). Sodium acetate (0.34 mmol, 27.3 mg), sodium iodide (0.17 mmol, 1.7 mL of a 0.1 M solution), and chloramine T (0.34 mmol, 0.67 mL of a 0.5 M solution in 50% aqueous THF) were sequentially added. The reaction mixture became dark in color, but with in one minute, the contents became a dark blue-purple color. Stirring the mixture for an additional three hours caused no visible change in color. The reaction mixture was saturated with sodium chloride, and the product extracted into THF (5x25mL). The combined THF layer was dried ($MgSO_4$), filtered, and the solvent removed to give a deep blue solid. Column chromatography of this crude product gave only recovered toluenesulfonamide and unidentified side products.

SYNTHETIC APPROACHES TO IODOVINYL AMINO ACIDS

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Donald Elton Bierer Jr.

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VOLUME II

CHAPTER VI

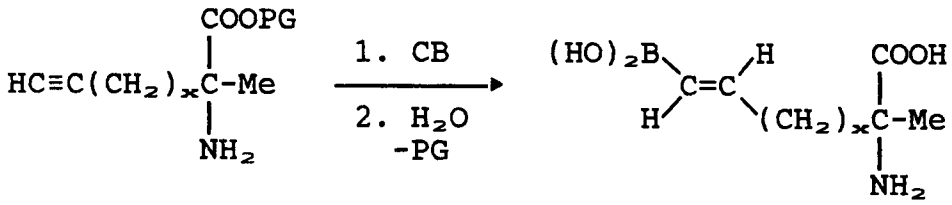
SILICON ESTERS: PROTECTION OF CARBOXYLIC ACID FUNCTIONALITY DURING HYDROBORATION

A. Introduction

A more direct approach to iodovinyl-α-methyl-α-amino acids would involve hydroboration of an acetylenic amino acid. Unfortunately, carboxylic acids are readily reduced by catecholborane[140]. In fact, the successful hydroboration of an unsaturated amino acid has never been reported, and only a few studies have been conducted on protected amino acid derivatives. However, this direct approach was reconsidered because of the limited success achieved via the hydantoin and protected hydantoin methodologies. In order for the hydroboration of an amino acid to be successful, a suitable protecting group for the carboxylic acid functionality had to be found.

The ester functionality is commonly used as a protecting group for carboxylic acids[531] and amino acids[534]. However, the use of a simple alkyl or aryl ester would result in an additional deprotection step in the synthesis. The ideal protecting group would be prepared efficiently under mild conditions, would prevent reduction of the carboxylic acid functionality during hydroboration, and

could be removed during the boronic acid water hydrolysis step (equation 6-1, PG = protecting group). The trimethyl-



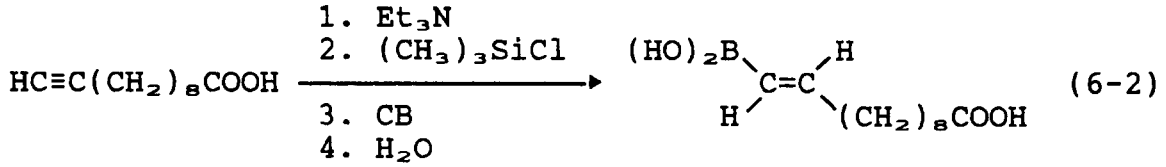
(6-1)

silyl group appeared to meet these criteria.

B. Results and Discussion

1. Initial Experiments

Since an acetylenic amino acid was not readily available, 10-undecynoic acid was chosen as a model compound. In the initial experiment, the trimethylsilyl ester was prepared *in situ* by sequential treatment with triethylamine and trimethylsilyl chloride (one equivalent each). The resulting precipitate (triethylamine hydrochloride) was filtered off under argon, and the filtrate treated with catecholborane (one equivalent) for 18 hours at 60°C. After water hydrolysis, a 39% yield of (E)-11-borono-10-undecenoic acid was realized (equation 6-2). Unreacted 10-undecynoic acid was also recovered from the reaction mixture following workup. Although the reaction was sluggish and only a modest yield of the desired vinylboronic acid was obtained, the results were promising; more important was the fact that



(6-2)

little or no reduction of the acid functionality occurred. Repeating the experiment led to no further improvement of the yield. Since hydroborations of alkyne substrates are normally carried out neat[54] with 10-20% molar excess of catecholborane, it was felt that the large volume of solvent resulting from the filtration process, and possibly the use of a stoichiometric amount of catecholborane were responsible for the sluggish reaction and moderate yield (hydroboration of alkynes in the presence of solvent normally required higher reaction temperatures for quantitative yields to be obtained[54]). The reaction was repeated at 85°C for 16 hours using 1.2 equivalents of catecholborane. Unfortunately, the use of excess catecholborane at the increased reaction temperature did not lead to an improvement in the desired result; a 39% yield of the vinylboronic acid carboxylic acid was obtained, along with a slightly lower yield of unreacted starting material (42%). The higher reaction temperature was detrimental; ^{13}C-NMR analysis of the crude product revealed a small carbon peak at 62 ppm, indicating that partial reduction of the TMS ester group. When the reaction was repeated with 2 molar

equivalents of catecholborane at 65°C for 5 hours, a 70% yield of the vinylboronic acid carboxylic acid was obtained after recrystallization. More importantly, ^{13}C-NMR analysis of the crude product indicated that no starting material remained, and that no reduction of the carboxylic acid had occurred. These results are summarized in Table 6-1.

2. Hydroboration of Unsaturated Trimethylsilyl Esters

The hydroboration of an alkynylcarboxylic acid by temporary protection of the acid functionality as a TMS ester had never been reported. It offered a convenient route to vinylboronic acid derivatives of carboxylic acids[169] (equation 6-3). A survey of the literature

(6-3)

revealed a single instance of a trimethylsilyl ester group being used under hydroboration conditions. In a study focused on the reduction of TMS esters with various hydride reagents, Larson reported that both aromatic and aliphatic trimethylsilyl esters were not reduced by BH_3·THF[141]. Thus, when an equimolar mixture of cyclohexene and trimethylsilyl octanoate were treated with excess BH_3·THF, cyclohexanol (77% yield) and octanoic acid (79% yield) were recovered after oxidation. The reaction of trimethylsilyl

Table 6-1: Hydroboration of 10-Undecynoic Acid With Catecholborane by Temporary Protection as the Trimethylsilyl Ester Under Various Conditions

Ratio alkyne:borane	Conditions	Yield Boronic Acid	Recovered Starting Alkyne
1 : 1	60°C, 18 hr	39%	51%
1 : 1.2	85°C, 16 hr	39%	42%[a]
1 : 2.2	65°C, 5 hr	70%	0%

[a]Some reduction of the acid functionality was observed

4-pentenoate was reported to proceed in a similar manner, to give 5-hydroxypentanoic acid (87%) yield after oxidation (equation 6-4). No other hydroborating agents were studied.

$$H_2C{=}CH(CH_2)_2COOTMS \xrightarrow[2.\ H_2O_2/NaOH\ \ 3.\ H_3O^+]{1.\ BH_3\cdot THF} HOCH_2(CH_2)_3COOH \qquad (6\text{-}4)$$

Thus, a more thorough study on the hydroboration of unsaturated trimethylsilyl esters was undertaken.

The trimethylsilyl esters of various olefinic and alkynyl carboxylic acids were prepared by a procedure similar to that reported by Fechtig and coworkers[536]. The typical procedure involved sequential treatment of the unsaturated acid with a stoichiometric amount of triethylamine and chlorotrimethylsilane in anhydrous THF. Filtration of the precipitate under inert atmosphere, followed by removal of the solvent, afforded, after distillation of the product, good yields of the corresponding trimethylsilyl ester (equation 6-5). The results are summarized in Table 6-2.

$$RCOOH \xrightarrow[2.\ (CH_3)_3SiCl]{1.\ Et_3N} RCOOSi(CH_3)_3 \qquad (6\text{-}5)$$

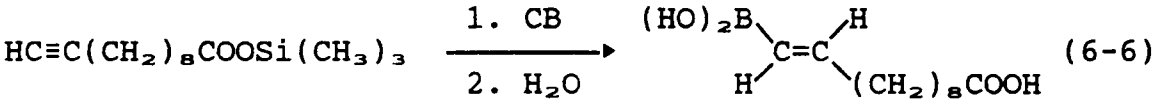
Table 6-2: Preparation of Trimethylsilyl Esters of Various Carboxylic Acids[a]

Carboxylic Acid	%Yield of Ester
10-Undecenoic Acid	89
4-Pentenoic Acid	80
Hexanoic Acid	85
Oleic Acid	84
3-Cyclohexene-1-Carboxylic Acid	73
endo-5-Norbornene-2,3-Di-carboxylic Acid	70
p-Carboxystyrene	76
10-Undecynoic Acid	82
Alanine	34[b]

[a]Stoichiometric amounts of triethylamine and chlorotrimethylsilane were used. Two equivalents of each were used for 5-norbornene-2,3-dicarboxylic acid and alanine.

[b]Yield reported is given for the bis-N,O-TMS derivative.

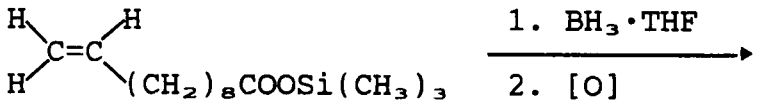
Hydroboration of the alkynyl trimethylsilyl ester with catecholborane proceeded as expected; hydrolysis of the intermediate vinyl boronic ester afforded an 87% yield of the vinylboronic acid carboxylic acid (equation 6-6).



(6-6)

However, attempted hydroboration of the olefinic counterpart, trimethylsilyl 10-undecenoate, with $BH_3 \cdot THF$ gave different results. In one experiment involving a stoichiometric amount of borane, hydroboration under normal conditions (0°C initially, with gradual increase to room temperature, 7 hours total) gave a 67% NMR yield of the expected hydroboration product, 11-hydroxyundecanoic acid, with the remainder being a mixture of unreacted olefinic acid and diol (the product from reduction of the ester functionality). In addition, a small singlet peak at 0.07 ppm in the proton NMR spectrum of the crude product was observed, corresponding to the formation of trimethylsilanol. When the reaction was repeated with excess $BH_3 \cdot THF$ (1.34 molar equivalents), under identical conditions, almost complete reduction of the ester functionality was observed. In addition, a peak at 0.07 ppm was observed in the proton NMR spectrum of the crude product, once again indicating the

formation of trimethylsilanol. Upon workup of the reaction mixture, a 95% yield of 1,11-undecandiol was obtained. Fortunately, the reduction of the ester functionality by borane can be eliminated if the reaction is carried out at below 0°C. This is best exemplified by the following experiment: trimethylsilyl 10-undecenoate was treated with a stoichiometric amount of $BH_3 \cdot THF$ at -78°C and the reaction allowed to proceed for a twelve day period at -5°C (freezer), a 63% yield of the hydroxyalkanoic acid was obtained upon workup, along with a 37% yield of unreacted undecenoic acid [excess hydride was present upon workup of the reaction] (equation 6-7). The hydroboration of trimethylsilyl



$$\longrightarrow \quad HOCH_2(CH_2)_9COOH + HOCH_2(CH_2)_9CH_2OH \qquad (6\text{-}7)$$

10-undecenoate could be forced to completion if excess borane was utilized. This offers a more convenient procedure for isolating the hydroboration product; no unreacted unsaturated acid remained in the reaction mixture to complicate separation of the desired hydroxyalkanoic acid from the competitive reduction product. However, the reaction in the presence of excess borane is very temperature and time dependent; carrying out the reaction at too high of a

temperature, or for too long a period, results in an increase of the diol side product. For example, reaction at 0 → 20°C for one hour with two molar equivalents of BH_3·THF gave a 57% isolated yield of 11-hydroxyundecanoic acid, while carrying out the reaction at 0°C resulted in a 68% yield of the desired hydroxyalkanoic acid. When the reaction was carried out with only one molar equivalent of BH_3·THF at -10°C for 30 minutes, the yield of the hydroxyalkanoic acid improved to 87%. The results of these experiments are tabulated in Tables 6-3 and 6-4.

The observed results contradict those reported by Larson. Although selective hydroboration was observed from our initial experiments, reduction did in fact occur. However, no experimental details were given in the Larson communication, and it is possible that their experiments were conducted at a temperature where reduction of the ester was sluggish. It is also possible that reduction did occur in their experiments. In their competitive experiment involving cyclohexene and trimethylsilyl octanoate, only a 79% yield of octanoic acid was recovered. No mention of the remaining mass was made.

As a result of this discrepancy, and since reaction temperature can be an important factor in hydroboration reactions, a series of experiments were conducted to investigate the reduction of trimethylsilyl esters with BH_3·THF

Table 6-3: Hydroboration of Trimethylsilyl 10-Undecenoate with Borane·THF Under Various Conditions: ^{1}H-NMR Product Ratios

Equivalents BH_3·THF	Reaction Conditions	^{1}H-NMR Integrated Peak Area[a]		
		Unreacted Olefin	Alcohol	Ester
0.34	0°C, 30 min r.t. 5 hr	7	7	14
0.34	0°C → 25°C 7 hours	1.5	11.5	9.5
0.34	0°C → 20°C 4 hours	7.8	13	18.3
0.34	0°C, 3 hours	7	8	19
0.34	-5°C, 12 days	3	8	11
1.34	0°C → 25°C 7 hours	nd[b]	18	2

[a]Terminal olefinic multiplet (δ = 5.15-4.8, 2H), alcohol triplet centered at 3.49 ppm ($C\underline{H}_2OH$), and acid triplet centered at 2.19 ppm ($C\underline{H}_2COOH$) were used for determination of product ratios

[b]nd = none detected

Table 6-4: Hydroboration of Trimethylsilyl 10-Undecenoate with Borane·THF Under Various Conditions: Isolated Yields of 11-Hydroxyundecanoic Acid

Equivalents BH_3·THF	Reaction Conditions	Isolated yield, % 11-Hydroxyundecanoic acid
1.5	0°C, 30 min 25°C, 8 hours	0
2	0°C → 20°C 1 hour	57
2	0°C, 40 min	68
1	-10°C, 30 min	87
1	-30°C, 30 min	76
1	-30°C, 2 hours	91

in greater detail, using trimethylsilyl hexanoate as a model compound (LIX).

$CH_3(CH_2)_4COOSi(CH_3)_3$

LIX

The reduction of trimethylsilyl esters with various aluminum hydride reagents has in fact been shown to be temperature dependent[141]. In initial experiments, we found that trimethylsilyl hexanoate reacted only slowly with BH_3·THF at temperatures below -30°C. As the reaction temperature increased, the rate of ester reduction also increased. For example, when trimethylsilyl hexanoate was treated with a stoichiometric amount of borane at -30°C, an 84% yield of hexanoic acid was recovered, with only 16% of the TMS ester being reduced. However, when the reaction was carried out at -20°C, the yield of recovered hexanoic acid was only 45%; 52% of the TMS ester was reduced to 1-hexanol. Increasing the amount of BH_3, or, reaction time, led to a further increase in the amount of reduction product obtained (Table 6-5).

Following the reaction by ^{11}B- and ^{29}Si-NMR gave a more thorough understanding of the effect of temperature on the reduction process. In an NMR experiment, 2 mmoles of trimethylsilyl hexanoate was treated with 2 mmoles of BH_3·THF

Table 6-5: Reduction of Trimethylsilyl Hexanoate with $BH_3 \cdot THF$

Equivalents $BH_3 \cdot THF$	Reaction Temperature (°C)	Reaction Time (minutes)	Isolated Yield %	
			Hexanoic Acid	Hexanol
1	-30	30	84	16
1	-30	60	72	24
1	-20	30	45	52
2	-20	30	34	66
1	25	30	nd[a]	96

[a]nd = none detected

at -78°C and the progress of the reaction monitored by ^{11}B-NMR spectroscopy. At -78 → 50°C, only a single sharp peak at -0.5 ppm was evident, corresponding to BH_3·THF. As the temperature was raised to -30°C, a peak at 26 ppm developed (Figure 6-1), which gradually increased in size with time (Figure 6-2). As the reaction mixture was warmed to -18°C, a second peak at 17 ppm appeared (Figure 6-3). A further increase in temperature led to the gradual disappearance of the peak at 26 ppm, while the peak at 17 ppm increased in size (Figures 6-4, 6-5). Quenching the reaction (hydrolysis), followed by workup of the reaction mixture, gave a quantitative yield of 1-hexanol. Although the products giving rise to the resonances at 17 and 26 ppm have not been identified, the boronate esters resulting from reduction of the carboxylic acid derivatives would be expected to give rise to resonances in the 10 to 30 ppm region of the ^{11}B-NMR spectra. A similar sequence of events was observed in an NMR experiment involving trimethylsilyl 10-undecenoate with excess BH_3·THF (2 equivalents), except that the peaks at 26 and 17 ppm did not develop until the temperature was raised to -20 and -10°C, respectively. Oxidation of the reaction mixture from this experiment afforded a quantitative yield of 1,11-undecandiol. In a parallel experiment utilizing equimolar quantities of trimethylsilyl 10-undecenoate and hydride, ^{11}B-NMR analysis revealed that the

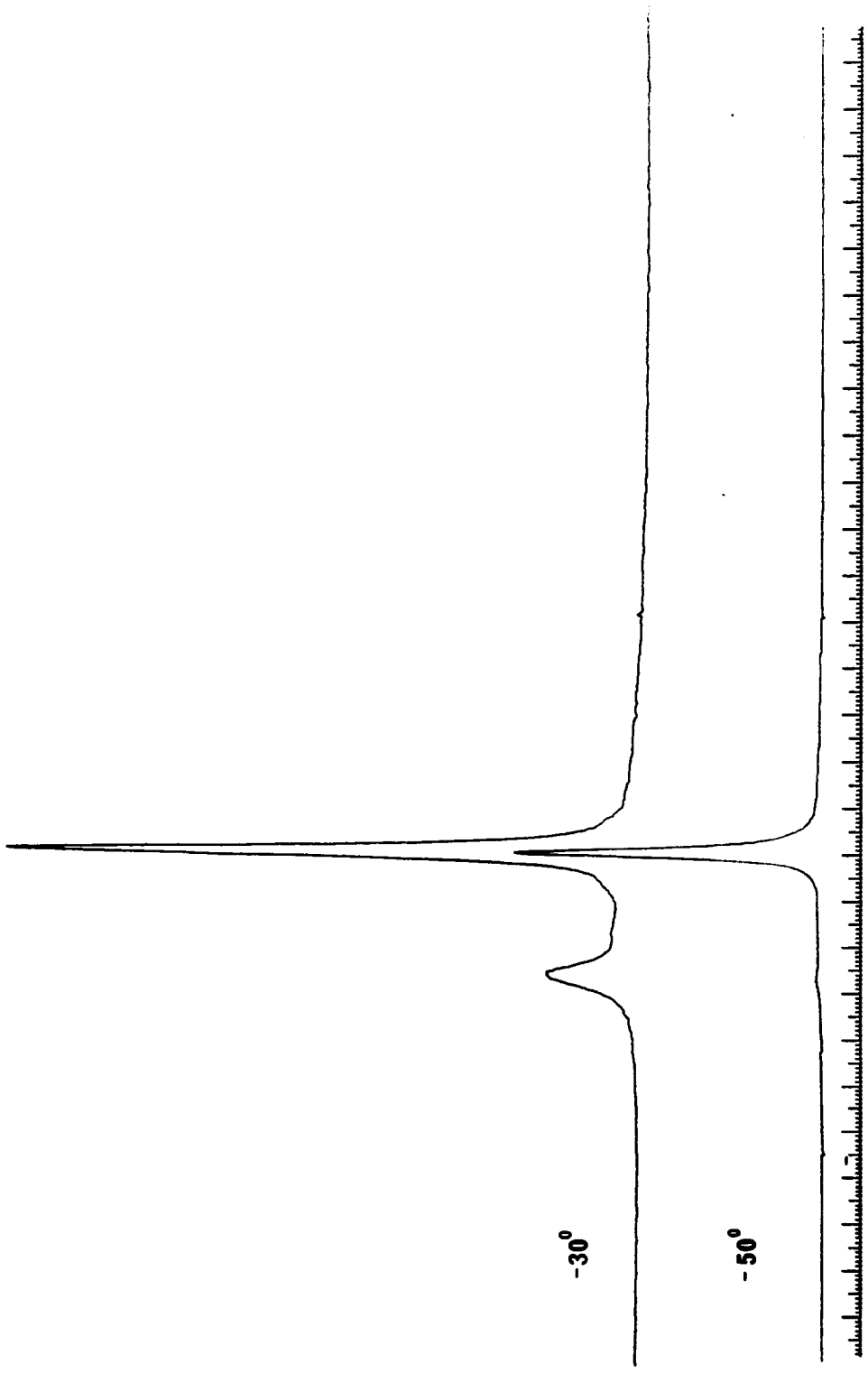


Figure 6-1. Boron-11 NMR Spectra of Trimethylsilyl Hexanoate and $BH_3 \cdot THF$ (1:1 Ratio) Reaction Mixture at -50°C and at -30°C.

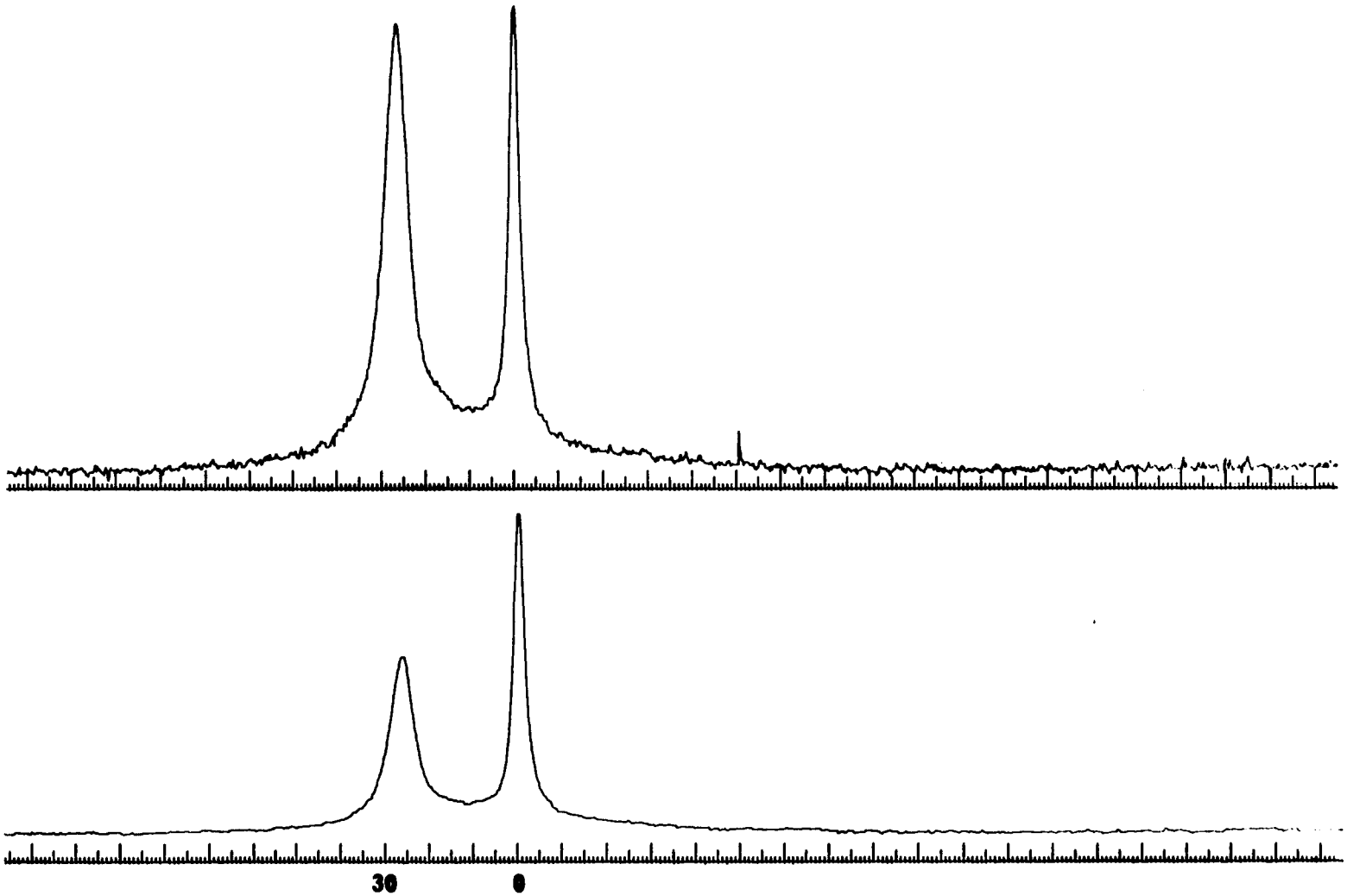


Figure 6-2. Boron-11 NMR Spectra of Trimethylsilyl Hexanoate and $BH_3 \cdot THF$ (1:1 Ratio) Reaction Mixture After 15 Minutes and after 30 Minutes at -30°C.

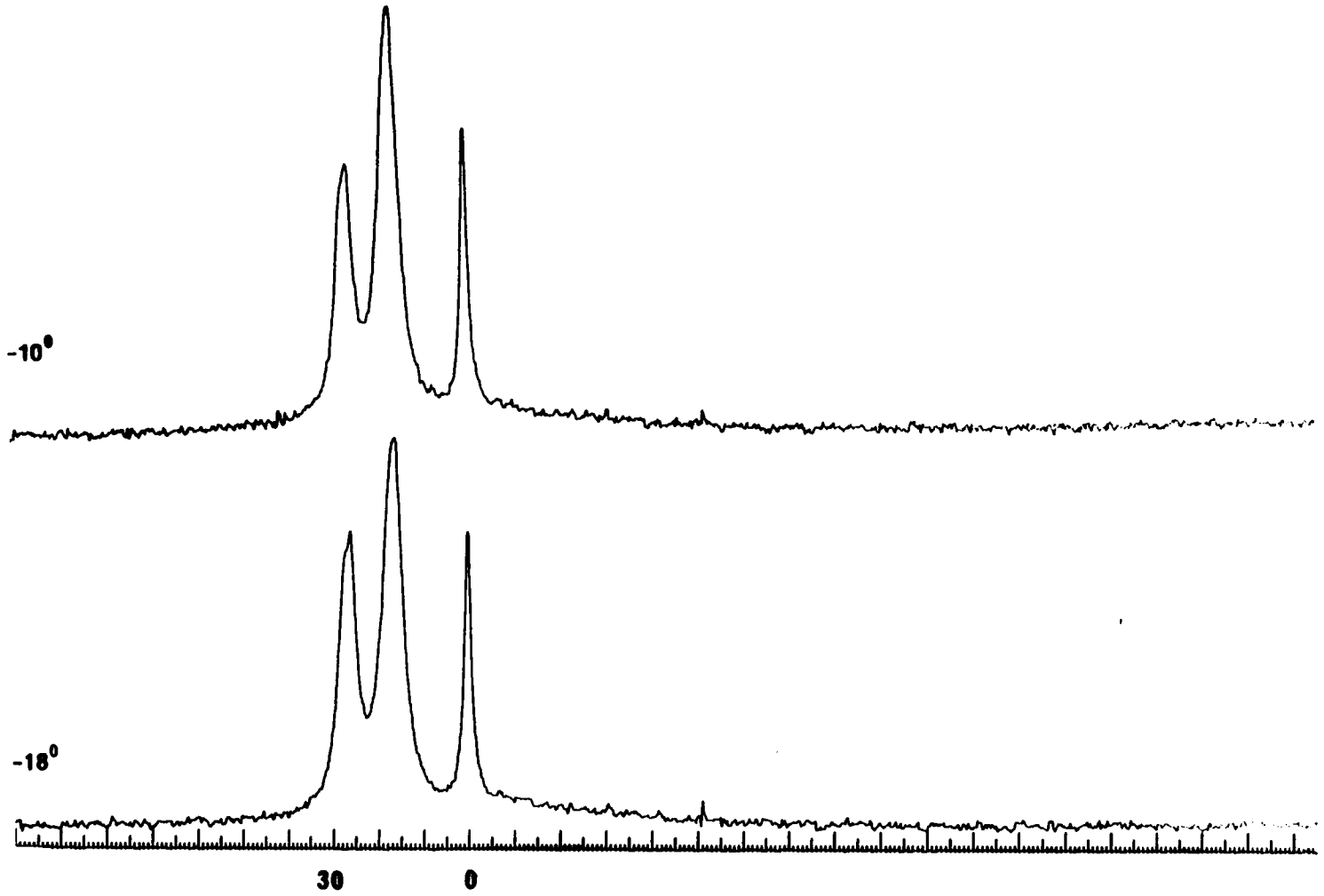


Figure 6-3. Boron-11 NMR Spectra of Trimethylsilyl Hexanoate and $BH_3 \cdot THF$ (1:1 Ratio) Reaction Mixture at -18°C and at -10°C.

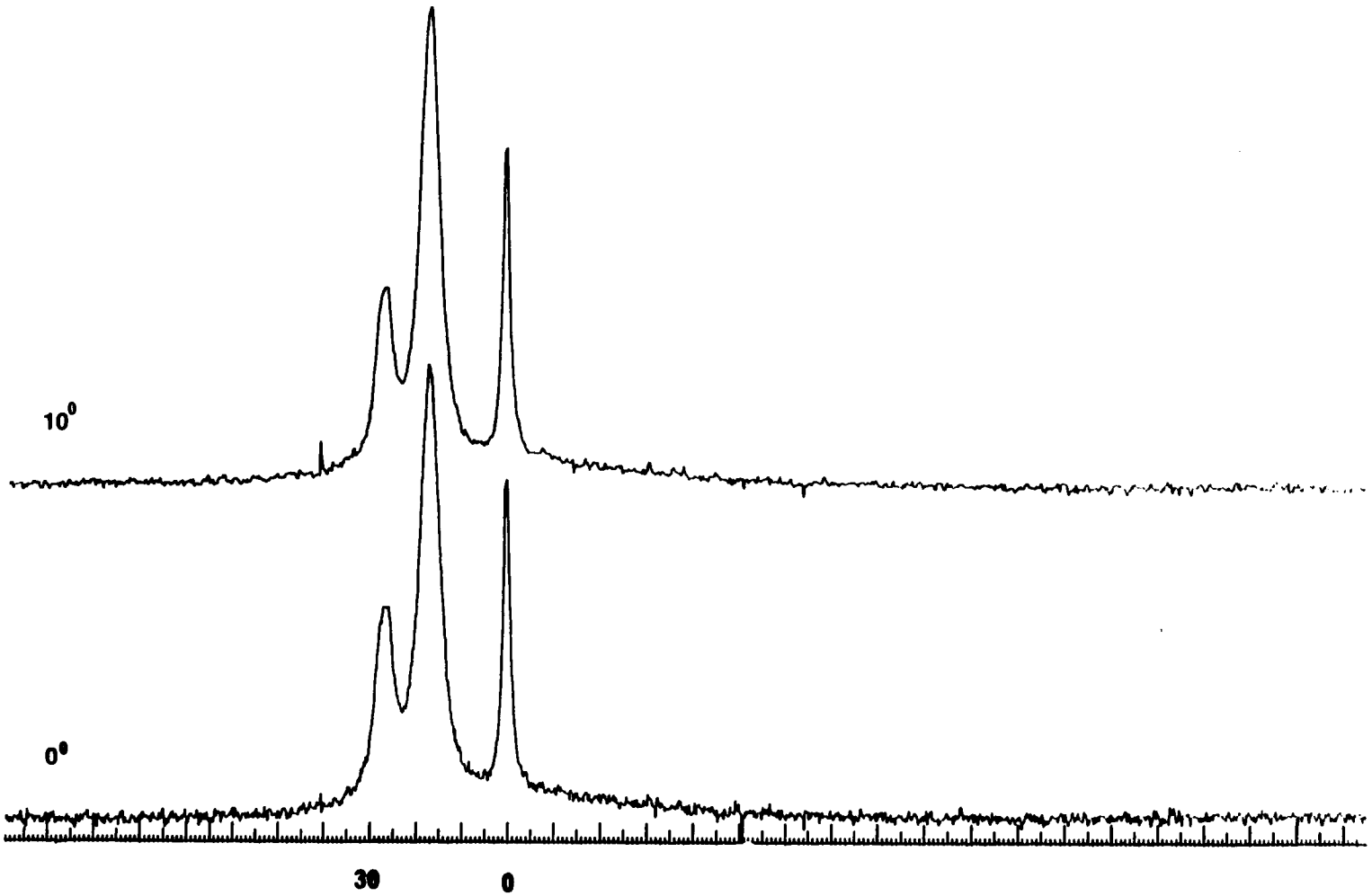


Figure 6-4. Boron-11 NMR Spectra of Trimethylsilyl Hexanoate and $BH_3 \cdot THF$ (1:1 Ratio) Reaction Mixture at 0°C and at 10°C.

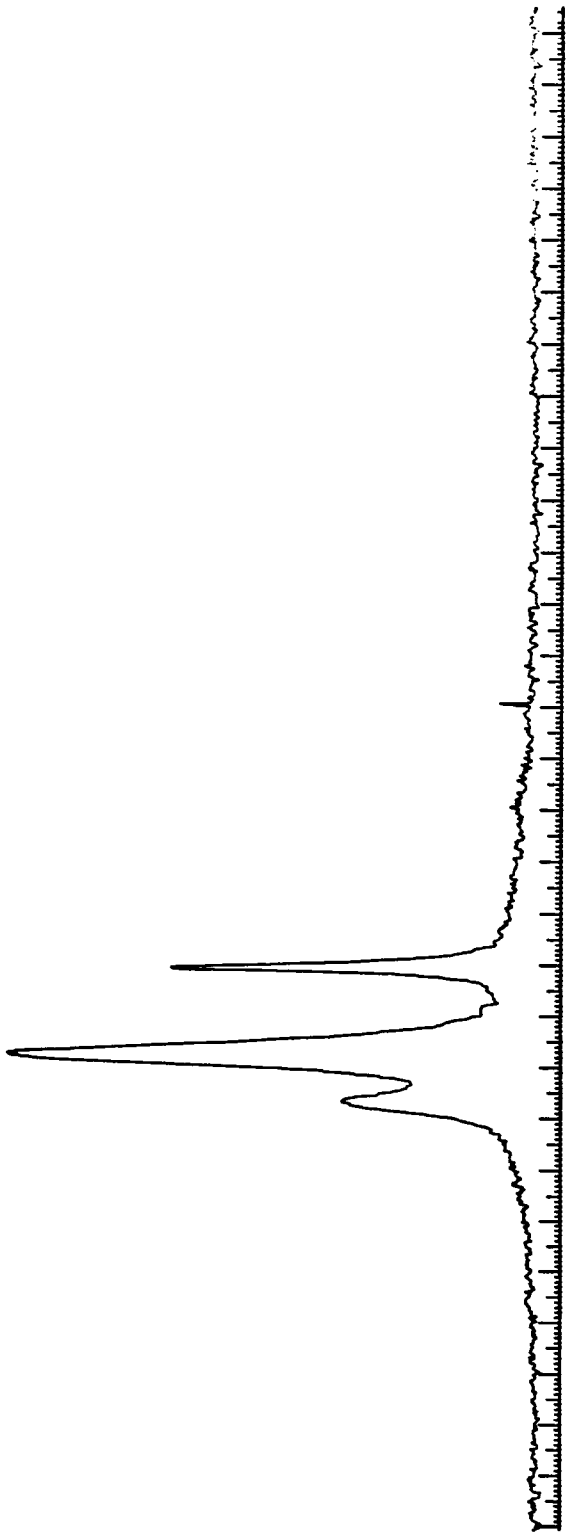
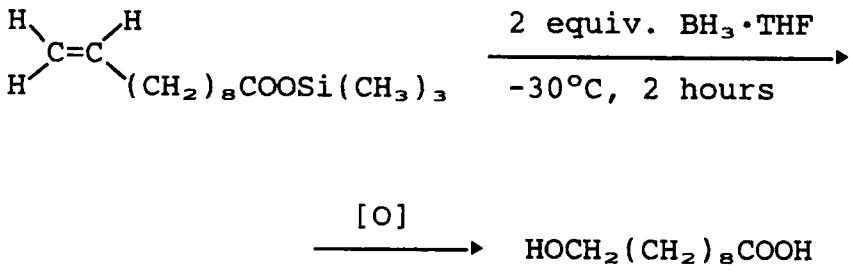


Figure 6-5. Boron-11 NMR Spectrum of Trimethylsilyl Hexanoate and $BH_3 \cdot THF$ (1:1 Ratio) Reaction Mixture at 30°C.

peak at 16 ppm began to appear only after the temperature rose above 0°C (Figures 6-6, 6-7). At 20°C, a broad peak centered at 80 ppm was observed, which became fully developed when the temperature was raised to 30°C (Figure 6-8). This peak corresponds to the formation of trialkylborane. Oxidative workup of the reaction mixture yielded 60% hydroxyalkanoic acid and 32% of a mixture of unreacted alkene and diol.

Having found the optimum temperature to carry out a hydroboration reaction of an unsaturated trimethylsilyl ester to be -30°C, hydroboration of trimethylsilyl 10-undecenoate with 2 equivalents of $BH_3 \cdot THF$ at -30°C for 2 hours afforded a 91% yield of 11-hydroxyundecanoic acid (equation 6-8).



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Interestingly, the borane - dimethylsulfide (BMS) complex appears to hydroborate unsaturated silyl esters more effectively than the THF complexes. Furthermore, control experiments revealed that no reduction of the ester group occurs as long as the reaction temperature is kept at or

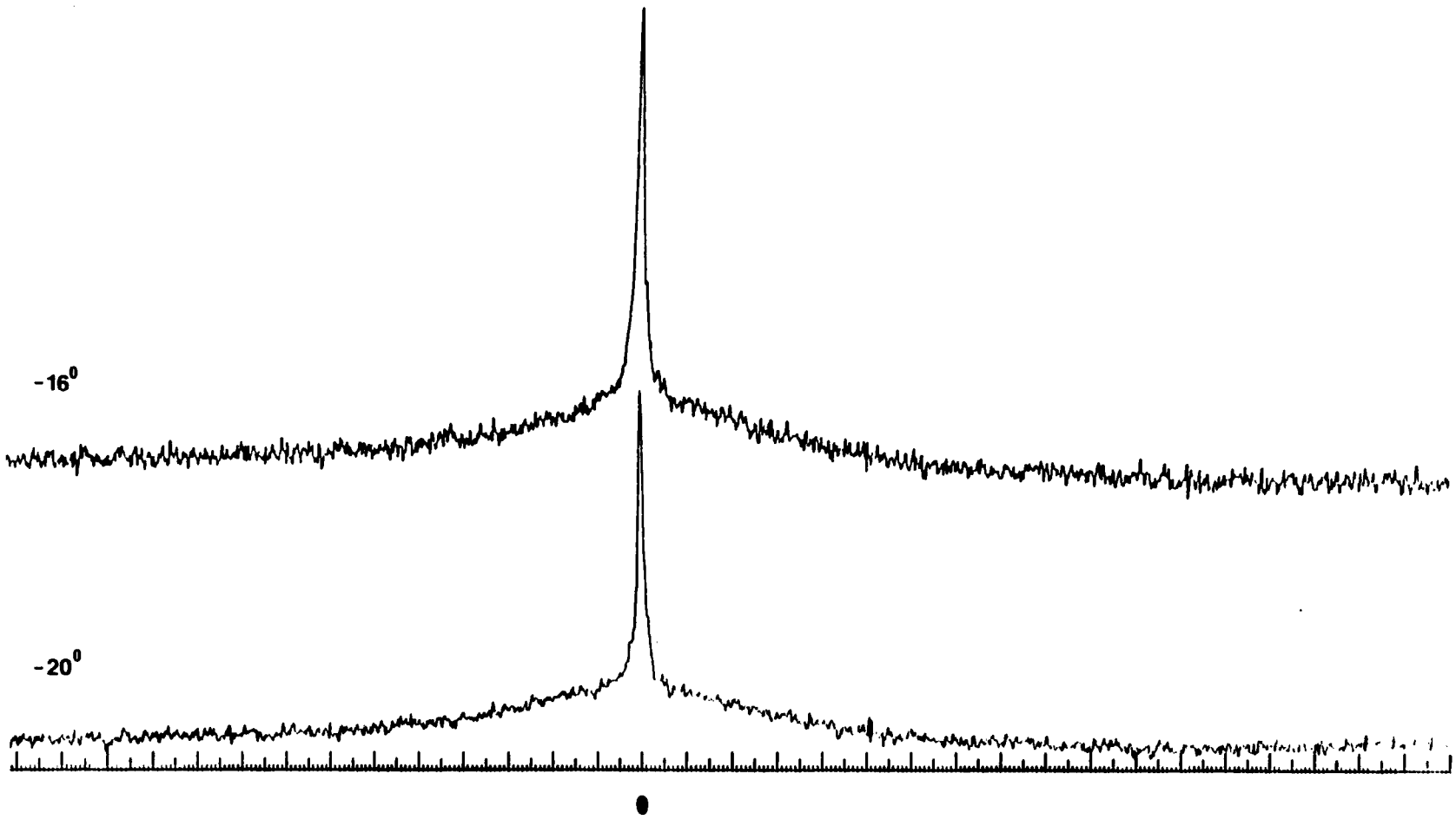


Figure 6-6. Boron-11 NMR Spectra of Trimethylsilyl 10-Undecenoate and BH_3·THF (3:1 Ratio) Reaction Mixture at -20°C, and at -16°C after four hours.

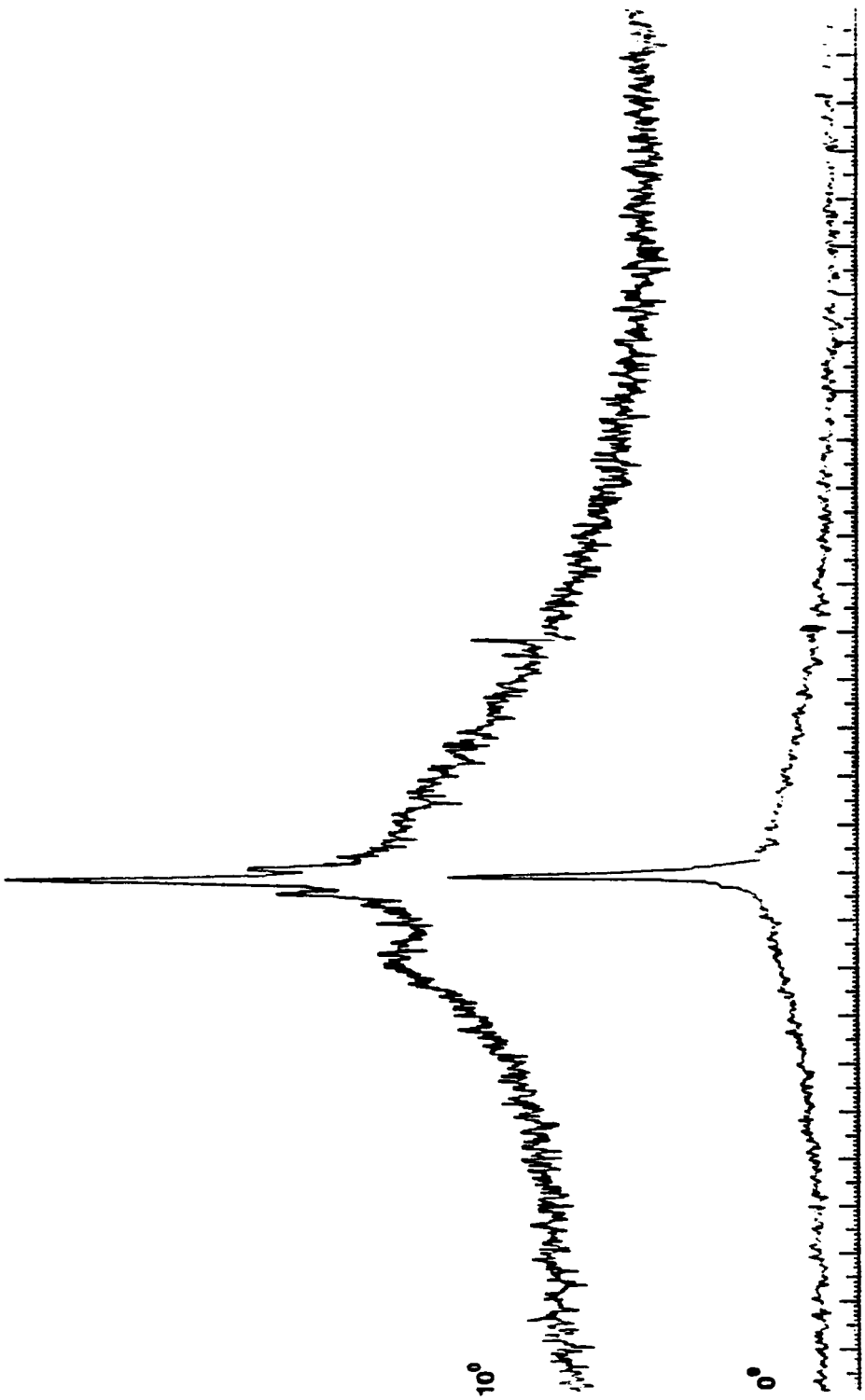


Figure 6-7. Boron-11 NMR Spectra of Trimethylsilyl 10-Undecenoate and BH_3·THF (3:1 Ratio) Reaction Mixture at 0°C after one hour, and at 10°C.

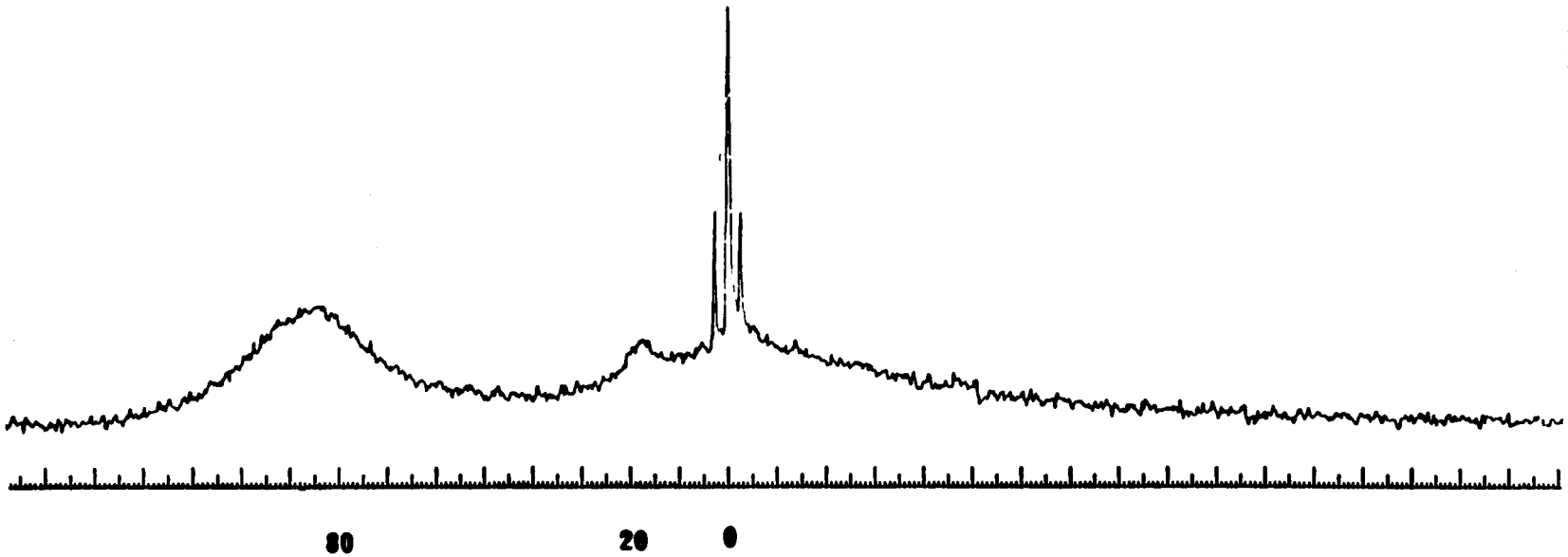


Figure 6-8. Boron-11 NMR Spectrum of Trimethylsilyl 10-Undecenoate and $BH_3 \cdot THF$ (3:1 Ratio) Reaction Mixture at 30°C.

below 0°C. For example, when 2 mmoles of trimethylsilyl hexanoate were mixed with 2 mmoles of BMS at -78°C and the reaction monitored by ^{11}B-NMR, only a sharp peak at 0.1 ppm was observed as the reaction temperature was increased to 0°C (Figure 6-9). At 10°C a small peak appeared at 48 ppm, but even when the reaction was left at 10°C for 1 hour, this peak did not increase significantly in intensity (Figure 6-9). As the temperature rose to 20°C, the peak at 48 ppm became larger and a new peak at 38.6 ppm began to appear (Figure 6-10). When the reaction was allowed to come to probe temperature (37°C), the peak at 38.6 ppm increased in size (Figure 6-10). Quenching the reaction (hydrolysis) produced a quantitative yield of 1-hexanol. Thus, the critical temperature for avoiding reduction with BH_3·THF appears to be -30°C, whereas, 0°C seems to be the crucial temperature when BMS is utilized. Like BH_3·THF, BMS reactions involving equivalent quantities of hydride and olefin proceed rather slowly at the reduced temperatures, but unlike BH_3·THF, reduction of the ester functionality does not occur under normal hydroboration conditions. For example, in one experiment involving a stoichiometric amount of BMS, a quantitative yield of a mixture 11-hydroxyundecanoic acid and unreacted 10-undecenoic acid was obtained upon acid-base workup of the reaction mixture following oxidation. No reduced product was observed.

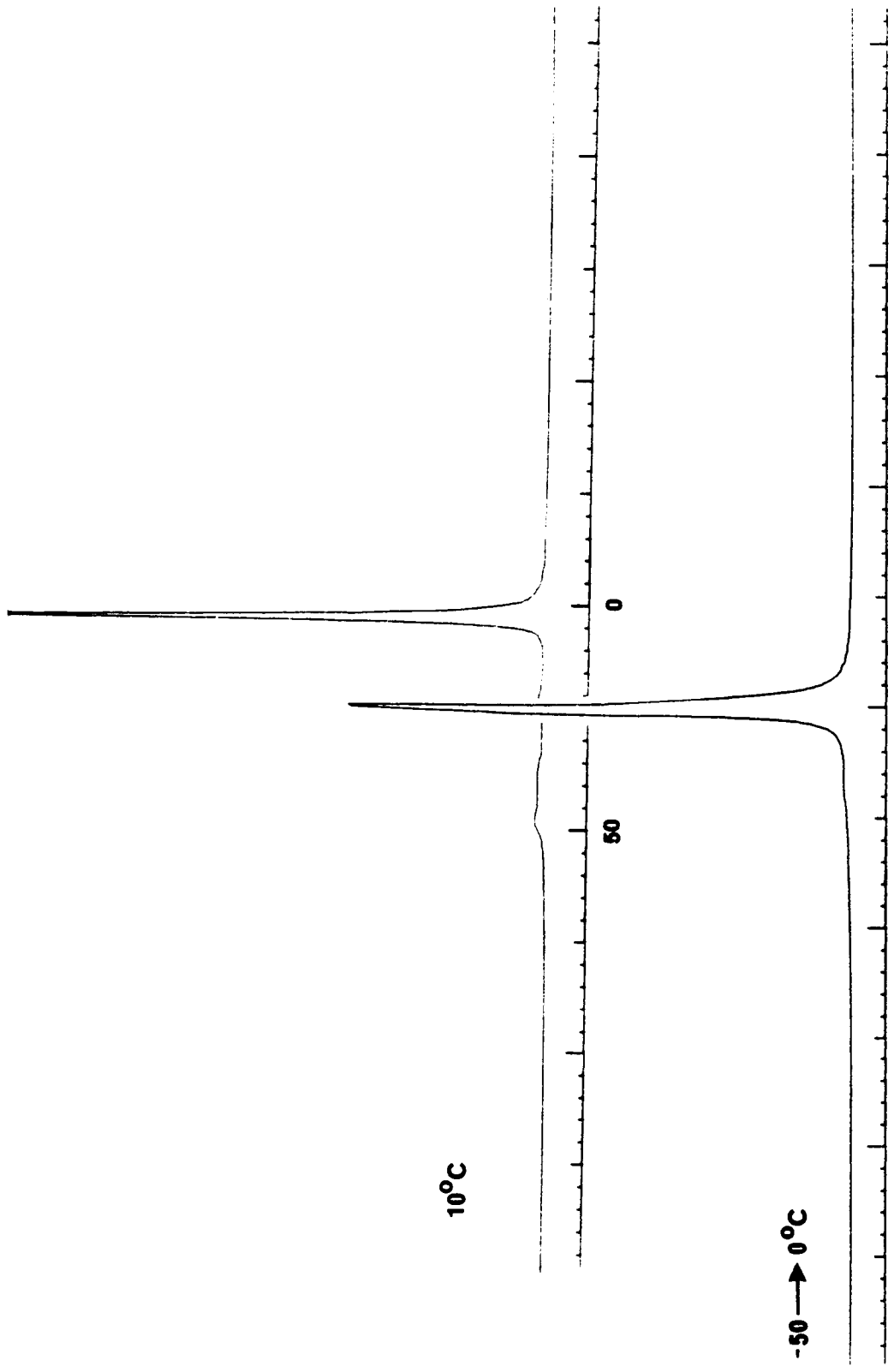


Figure 6-9. Boron-11 NMR Spectra of Trimethylsilyl Hexanoate and $BH_3 \cdot DMS$ (1:1 Ratio) Reaction Mixture at -50°C → 0°C and at 10°C.

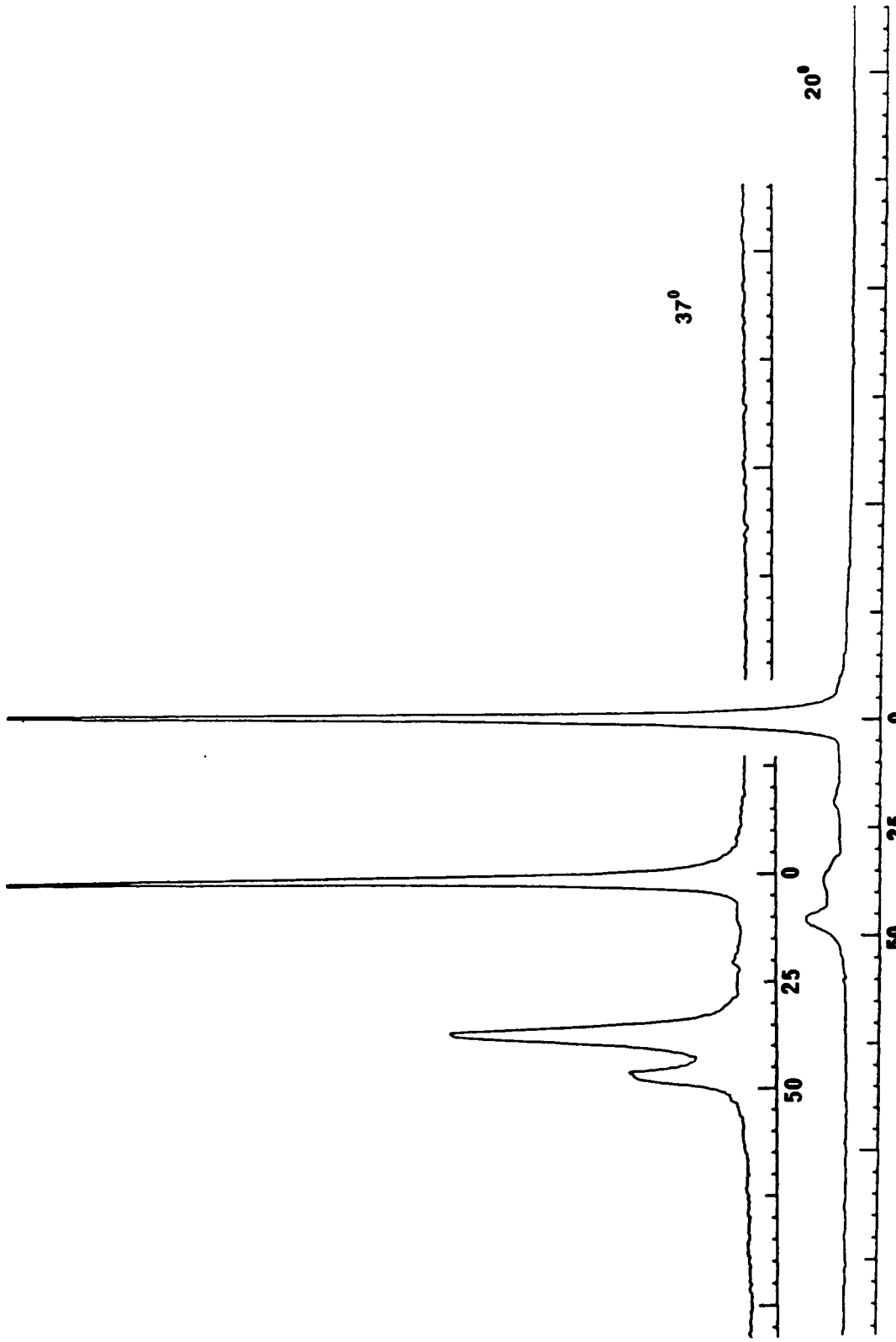
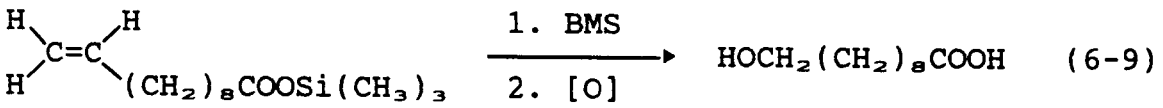


Figure 6-10. Boron-11 NMR Spectra of Trimethylsilyl Hexanoate and $BH_3 \cdot DMS$ (1:1 Ratio) Reaction Mixture at 20°C and at 37°C.

Recrystallization of the crude product afforded a 62% yield of the hydroxyalkanoic acid. Thus, whereas hydroboration of trimethylsilyl 10-undecenoic acid with a stoichiometric amount of $BH_3 \cdot THF$ under normal hydroboration conditions gave approximately 66% of the hydroboration product (hydroxyalkanoic acid), with 33% of the mass balance being a mixture of reduced product (diol) and unreacted undecenoic acid, hydroboration with BMS under similar conditions gave approximately 66% of the hydroxyalkanoic acid, and 33% of the mass balance as unreacted olefinic acid. Fortunately, unlike $BH_3 \cdot THF$, hydroborations with a stoichiometric of BMS will go to completion. Thus the reaction of 1.67 mmoles of BMS with 5 mmoles of the TMS ester of 10-undecenoic acid yielded, after 4 days at 0°C (mixing temperature -78°C), 4.9 mmoles of the expected hydroxyalkanoic acid after oxidation. The same result could be obtained in a matter of hours when excess BMS was used at -5°C (equation 6-9). The results are shown in Table 6-6.



(6-9)

The reaction of trimethylsilyl 10-undecenoate with a number of common hydroborating agents was also investigated, and the results are summarized in Table 6-7. It is readily

Table 6-6: Hydroboration of Trimethylsilyl 10-Undecenoate with BMS

Ratio Borane:Olefin	Reaction Conditions	Isolated Yield 11-Hydroxyundecanoic Acid
0.33:1	0 → 25°C 12 hours	62%[a]
0.33:1	-30 → -5°C 4 hours, then -5°C 4 days	99%
0.33:1	-30°C initial, then -5°C 4 hours, then → 25°C 18 hours	99%
1:1	-5°C 30 min	76%
2:1	-5°C 30 min	96%

[a]Remaining mass balance was recovered as unreacted 10-undecenoic acid

Table 6-7: Hydroboration of Trimethylsilyl 10-Undecenoate and Conversion to 11-Hydroxyundecanoic Acid

Reagent	Ratio Borane:alkene	Yield, %[c]
$BH_3 \cdot THF$	2:1	91[a]
$BH_3 \cdot DMS$	2:1	96[a]
Dicyclohexylborane	1:1	93[b]
Disiamylborane	1:1	96[b]
9-Borabicyclononane	1:1	95[b]
Catecholborane	1.35:1	71[d]
Thexylborane	1:1	98[b]

[a]HB reaction was carried out at -10°C (-30°C for BH_3 THF) for 1-3 hours, water was added to hydrolize any remaining hydride, and then the mixture oxidized with H_2O_2/NaOH.

[b]HB reactions were carried out at -10°C and then warmed to room temperature for 4-12 hours; the mixture was then oxidized with H_2O_2/NaOH.

[c]Isolated product

[d]Catecholborane reaction was carried out in absence of solvent at 110°C.

apparent that the trimethylsilyl moiety effectively protects the carboxylic acid functionality during hydroboration reactions.

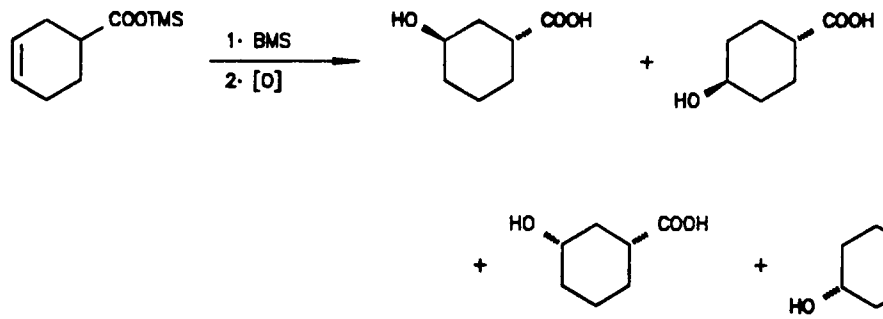
A series of olefinic trimethylsilyl esters were hydroborated with 9-BBN and with BMS, and these results are presented in Table 6-8. In the hydroboration of trimethylsilyl 3-cyclohexene-1-carboxylate with 9-BBN at 0°C, unreacted 3-cyclohexene-1-carboxylic acid was the major component recovered, presumably due to the reduced reactivity of 9-BBN at lower temperatures with internal double bonds. No reduction of the ester functionality was observed. However, when the hydroboration was carried out in refluxing THF, competitive reduction of the ester functionality was observed. Interestingly, in an effort to determine whether reduction of trimethylsilyl esters with 9-BBN at elevated temperatures was the general course of events or simply an artifact of the 3-cyclohexene-1-carboxylate system, treatment of trimethylsilyl hexanoate with 9-BBN in refluxing THF for one hour gave a near quantitative yield of unreduced hexanoic acid. Thus, it appears that the reduction observed for 9-BBN is not a general reaction, but becomes competitive with hydroboration only with hindered internal double bonds or when proximal ester functionality can affect the normal course of the hydroboration reaction[69,537]. Hydroboration with BMS was more successful, no reduction of the ester

Table 6-8: Hydroboration of Various Unsaturated Trimethylsilyl esters with 9-BBN, BMS, and DCxBH

TMS Ester	Borane	Ratio Borane : Alkene	Yield, %[a] Hydroxyacid
TMS Oleate	9-BBN	1:1	47[b]
TMS Oleate	BMS	1:1	73[b]
TMS Oleate	DCxBH	1:1	56[b]
TMS 10-Undecenoate	9-BBN	1:1	83
TMS 10-Undecenoate	BMS	1:1	76
TMS 4-Pentenoate	9-BBN	1:1	56[c]
TMS 4-Pentenoate	9-BBN	1:1	78
TMS 4-Pentenoate	BMS	0.34:1	81[d,e]
TMS 3-Cyclohexene-1-carboxylate	BMS	2:1	51[f]
TMS 3-Cyclohexene-1-carboxylate	BMS	0.5:1	57[f]
TMS 3-Cyclohexene-1-carboxylate	9-BBN	1:1	0
Bis-TMS endo-2,3-5-norbornene-di-carboxylate	9-BBN	2:1	53[f]
Bis-TMS endo-2,3-5-norbornene-di-carboxylate	BMS	0.34:1	53[d,f]

[a]Isolated yield
[b]Remaining mass balance was recovered as unreacted olefinic acid
[c]Isolated yield determined as silver salt[538,539]
[d]Reported yield also includes unreacted olefinic acid
[e]A mixture of the 4- and 5-hydroxy adducts were obtained
[f]A complex mixture of hydroxyalkanoic acids was obtained

group occurred. However, a mixture of hydroxyalkanoic acid products were obtained from the hydroboration of trimethylsilyl 3-cyclohexene-1-carboxylate with BMS (equation 6-10). Although the regiochemical outcome was not determined, these



(6-10)

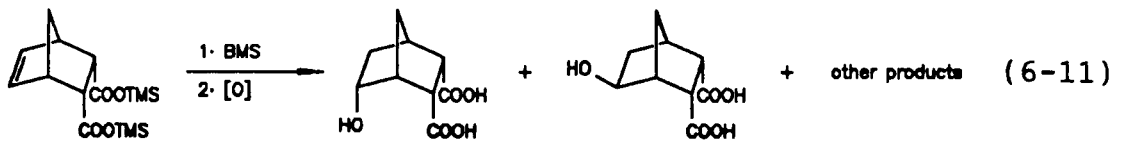
findings are in accord with results obtained by Klein and coworkers[119] who obtained a complex mixture of alcohols in the hydroboration of 3-cyclohexene-1-carboxylates with diborane (equation 1-54, p. 33).

The directive effect of the ester group is apparent in the case of trimethylsilyl 4-pentenoate. Although the regiochemical distribution of products was not determined, hydroboration with BMS gave a mixture of 4-hydroxy- and 5-hydroxypentanoic acids.

As was noted in Chapter I, the proximity of the ester functionality can play a role in competitive reduction-hydroboration. For example, hydroboration of methyl 4-pentenoate with diborane gave nearly twice as much (45%) of the reduced product as did methyl 10-undecenoate (23%) when one molar equivalent of diborane was used[69]. A similar

observation was noted in the hydroboration of trimethylsilyl 4-pentenoate. Once again, although a detailed investigation of regiochemistry was beyond the scope of this work, competitive reduction of the ester functionality did occur with BMS and, surprisingly, to a greater extent with 9-BBN. This sharply contrasts with the results obtained with trimethylsilyl 10-undecenoate, where no reduction of ester functionality was observed with both of these hydroborating agents. Fortunately, with careful control of the reaction temperature, the amount of reduced product could be kept to a minimum.

The hydroboration of bistrimethylsilyl endo-5-norbornene-2,3-dicarboxylate also produced a complex mixture of hydroxyalkanoic acids were obtained, presumably due to the effect that proximal ester functionality can have on directing the hydroboration reaction[93] (equation 6-11).



(6-11)

Finally, in an effort to show the synthetic utility of the use of the trimethylsilyl moiety as a temporary protecting group during the hydroboration reaction, a series of standard organoborane transformations were carried out;

these results are summarized in Table 6-9. Attempted amination gave undesirable results, as a mixture of products was obtained (equation 6-12). Such lack of chemoselectivity in

$$R_2B(CH_2)_xCOOTMS \xrightarrow[NaOCl]{NH_4OH} H_2N(CH_2)_xCOOH + RNH_2 \qquad (6\text{-}12)$$

the amination procedure has been previously observed in the Kabalka laboratory[540]. Attempted carbon - carbon bond formation using one of the well known anionotropic rearrangement reactions (ethyl-α-bromo acetate) also met with failure[375,541,542] (equations 6-13). Presumably, nucleo-

$$R'_2BR \xrightarrow[2.\ BrCH_2COOEt]{1.\ K^+\underline{t}\text{-}BuO^-} RCH_2COOEt \qquad (6\text{-}13)$$

$$R' = -CH_2(CH_2)_xCOOTMS$$

philic attack at the silicon atom by t-butoxide occurs, although competitive alkylation at the position alpha to the TMS ester functionality cannot be ruled out.

3. Hydroboration of Unsaturated Carboxylic Acids by Temporary Protection as the Trimethylsilyl Ester

The use of the trimethylsilyl moiety as a protecting group during hydroboration reactions provides a convenient means of carrying out the hydroboration reaction in the presence of sensitive acid functionality with virtually any

Table 6-9: Organoborane Transformations Utilizing Trimethylsilyl Esters

Substrate	Reagents	Product	% Yield[a]
TMS 10-Undecenoate	DCxBH/ NaI,CAT	11-Iodoundecanoic acid	88
TMS 10-Undecenoate	BMS/HOAc	Undecanoic acid	82
TMS 10-Undecenoate	DCxBH/ NaOH,H_2O_2	11-Hydroxyundecanoic acid	93
TMS 4-Pentenoate	DCxBH/ NaI,CAT	5-Iodopentanoic acid	76
TMS 10-Undecynoate	CB/ H_2O	10-Undecenylboronic acid	87

[a]Isolated yield

borane reagent. The high yield with which silicon ester can be obtained, and the ease of removing the protecting group adds a useful reaction to the organic chemist's repertoire. However, isolation of the intermediate silicon ester can be tedious, and is often unnecessary. A more convenient procedure involves the "in situ" protection of the carboxylic acid functionality with the TMS moiety. Thus, sequential treatment of 10-undecenoic acid with triethylamine, trimethylsilyl chloride, and filtration, followed by hydroboration with excess $BH_3 \cdot THF$ at -30°C for two hours and subsequent oxidation, afforded 11-hydroxyundecanoic acid in a 73% yield (70% after recrystallization) (equation 6-14).

$$H_2C{=}CH(CH_2)_xCOOH \xrightarrow[\substack{2.\ TMSCl \\ 3.\ R_2BH \\ 4.\ [O]}]{1.\ Et_3N} HOCH_2(CH_2)_xCH_2COOH \quad (6\text{-}13)$$

The yields obtained by this method are somewhat lower, than those obtained when the trimethylsilyl ester is actually isolated; nonetheless, good yields are still obtained. (The overall yields for this method are comparable those obtained for the two-step method.) The "in situ" methodology has been extended to other organoborane transformations, including protonolysis, and halogenation. Iodination following hydroboration with excess $BH_3 \cdot THF$ was unsuccessful, presumably due to the uptake of the electrophilic

iodine by other boronic acid compounds in solution. Fortunately, iodination was successful when dicyclohexylborane was used as the hydroborating agent. The results of the "in situ" methodology are tabulated in Table 6-10.

4. t-Butyldimethylsilyl Esters

Partial reduction of the TMS ester functionality during hydroboration with $BH_3 \cdot THF$ under normal conditions neccessitated the use of excess borane at lower temperatures in order to achieve complete hydroboration. However, the use of excess borane requires careful monitoring of the reaction temperature and reaction time, and is detrimental for successful organoborane transformations which require trialkylborane species, such as iodination, amination, and anionotropic rearrangements. As noted in Chapter I, steric constraints play an important role in the hydroboration reaction. It was anticipated that use of a more bulky silicon ester protecting group might slow down or even stop reduction of the ester with $BH_3 \cdot THF$. In order to investigate this proposal further, an NMR experiment with t-butyldimethylsilyl hexanoate was carried out similar to those described earlier (equation 6-15). At -78°C, only a

$$CH_3(CH_2)_4COOTBDMS + BH_3 \cdot THF \xrightarrow[-78 \rightarrow 37°C]{?} CH_3(CH_2)_5OH \quad (6\text{-}15)$$

Table 6-10: Hydroboration of Unsaturated Carboxylic Acids Via Temporary Protection of the Acid Functionality as the Trimethylsilyl Ester

Unsaturated Acid	Borane	Reagents	Product	Isolated Yield, %
10-Undecenoic Acid	$BH_3 \cdot THF$	H_2O_2/ NaOH	11-Hydroxyun-decanoic Acid	73
10-Undecenoic Acid	DCxBH	H_2O_2/ NaOH	11-Hydroxyun-decanoic Acid	84
10-Undecenoic Acid	9-BBN	H_2O_2/ NaOH	11-Hydroxyun-decanoic Acid	56[a]
10-Undecenoic Acid	$BH_3 \cdot THF$	HOAc	Undecanoic Acid	69
10-Undecenoic Acid	9-BBN	HOAc	Undecanoic Acid	61[a]
10-Undecenoic Acid	DCxBH	NaI CAT	11-Iodoundec-anoic Acid	79
10-Undecynoic Acid	CB	H_2O	11-Borono-10-undecenoic Acid	70
10-Undecynoic Acid	CB	HOAC	10-Undecenoic Acid	67

[a]Remaining mass was unreacted 10-undecenoic acid

sharp peak at -1.6 ppm was observed, corresponding to unreacted $BH_3 \cdot THF$. At -60°C, a small hump at 26 ppm began to appear, which did not appear to increase in size appreciably over 30 minute time period. As the temperature was gradually increased to -10°C, the peak at 26 ppm increased in intensity at the expense of the peak at -1.6 ppm. Integration at -10°C revealed the peak at 26 ppm represented 89% of the boron in the sample. After 30 minutes at -10°C, a small shoulder began to appear, which developed into a peak at 16 ppm upon warming to 0°C. Further warming above 0°C caused the peak at 17 ppm to grow at the expense of the peak at 26 ppm. Although the peak at 26 ppm never fully disappeared, it represented only 37% of the integrated peak area after 50 minutes at 37°C. Hydrolysis of the reaction mixture at this point gave a 73% yield of 1-hexanol and a 15% yield of hexanoic acid. From this experiment, it appears that the more bulky t-butyldimethylsilyl group hinders the reduction process somewhat. In the case of trimethylsilyl esters the reduction peak at 17 ppm began to appear at -20°C, whereas the peak did not begin to form until the temperature was raised to 0°C (appeared as a shoulder) with the corresponding t-butyldimethylsilyl ester, and did not fully develop into a separate peak until the temperature was further raised to 10°C.

With this promising result at hand, hydroboration of

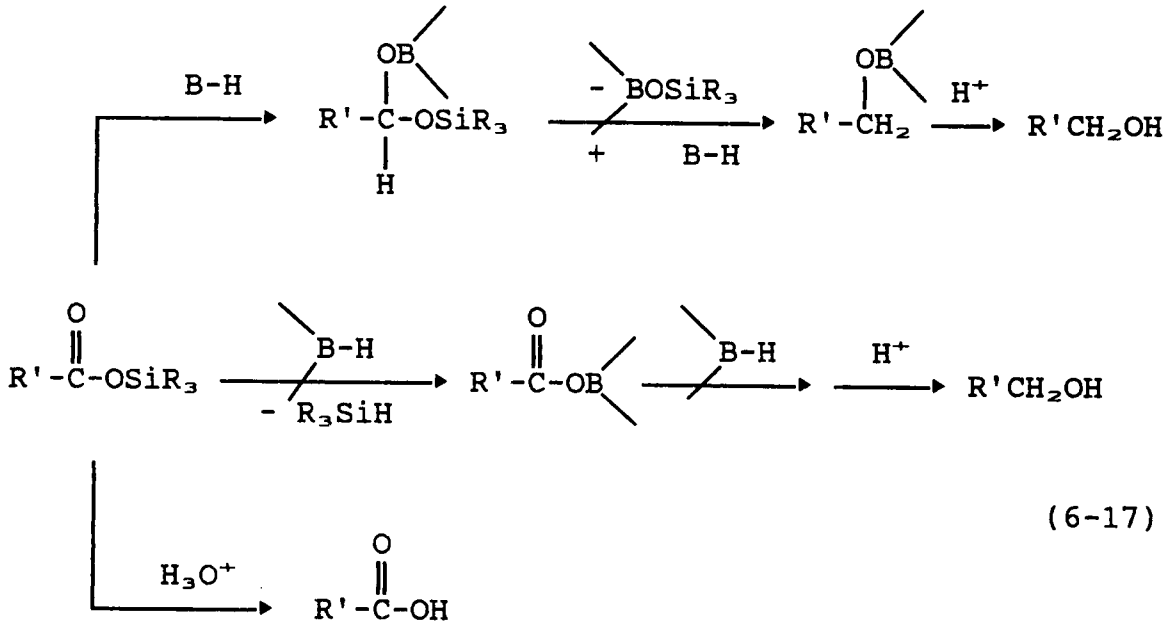
t-butyldimethylsilyl 10-undecenoate was attempted with a stoichiometric amount of $BH_3 \cdot THF$. Although complete reaction of the olefin was not realized when an equivalent amount of hydride was used, complete reaction occurred when excess hydride was utilized, even when the reaction was allowed to warm to room temperature over a 18 hour period! Upon oxidation, an 87% yield (94% crude yield) of 11-hydroxyundecanoic acid was realized after recrystallization (equation 6-16). Thus, the use of the t-butyldimethylsilyl

$$H_2C{=}CH(CH_2)_8COOSiTBDMS \xrightarrow[2.\ [O]]{1.\ BH_3 \cdot THF} HO(CH_2)_9COOH \qquad (6\text{-}16)$$

ester instead of the trimethylsilyl moiety allows near quantitative hydroboration with only a slight excess of $BH_3 \cdot THF$, and provides a much more convenient procedure for hydroborations of olefinic acids with $BH_3 \cdot THF$, as critical monitoring of the reaction temperature and reaction time is not required.

The reduction of silicon esters with borane reagents to give alcohols could arise from hydride attack of the ester carbonyl, followed by reduction of the intermediate acetal-like intermediate with an additional equivalent of hydride, with concomitant loss of a borotrialkylsiloxy species ($BOSiR_3$). Alternatively, hydride attack at the silicon atom could occur with simultaneous loss of a trialkylsilane

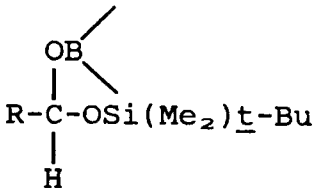
(R_3SiH) to give an acyloxyborane, which could then be reduced according to the mechanistic pathway discussed in Chapter I (equation 6-17). Hydrolysis would then provide



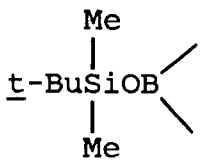
(6-17)

the corresponding alcohol, whereas hydrolysis of any unreacted trimethylsilyl ester would give the carboxylic acid back. Larson and coworkers have suggested that the reduction of trimethylsilyl esters occurs via hydride attack at the ester carbonyl, but offered no supporting evidence. Monitoring the reduction process by ^{29}Si-NMR, could be used to determine which pathway was occurring, as trimethylsilane exhibits a chemical shift of -15.5 ppm (relative to tetramethylsilane); trimethylsiloxane species give rise to silicon resonances in the 20-30 ppm range[543]. The reduction of t-butyldimethylsilyl hexanoate was carried out at

-78°C → 37°C as before and the progress of the reaction monitored by ^{29}Si-NMR. From -60°C to -20°C, only a single peak at peak at 21.97 ppm was observed, corresponding to the unreacted TBDMS ester. At -5°C, this peak split into two peaks at 21.97 and 21.81 ppm (the peak at 21.81 ppm was 2.5 times as intense as the peak at 21.97). Further warming to 5°C led to the disappearance of the peak at 21.97 ppm, and only a single resonance at 21.81 ppm. Upon further warming to 37°C, the peak at 21.81 ppm split into two peaks at 21.81 and 21.68 ppm. This experiment provides supporting evidence that the reduction of t-butyldimethylsilylhexanoate occurs by reduction of the ester carbonyl with subsequent loss of a t-butyldimethylsiloxy species. Furthermore, it appears that the peak at 21.81 ppm corresponds to the acetal-like species (LX), while the resonance at 21.68 ppm corresponds to the t-butyldimethylsiloxyborane species (LXI).



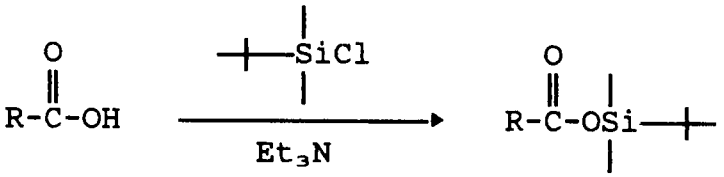
LX



LXI

The necessary t-butyldimethylsilyl esters were prepared by a procedure similar to that used to prepare the trimethylsilyl esters. Although the use of

chlorotrimethylsilane and a tertiary amine such as pyridine has been a traditional approach to TMS esters[536,544,545], use of the triethylamine - chlorosilane mixture seems to have been overlooked as a general procedure for preparing t-butyldimethylsilyl esters (equation 6-18). Thus a series of



(6-18)

t-butyldimethylsilyl esters were prepared and the results are tabulated in Table 6-11. The procedure gave good yields of silicon esters of simple aliphatic and aromatic carboxylic acids. Good yields of disilyl derivatives of amino acids were also realized, although the yield was somewhat lower than those obtained with simple carboxylic acids. Thus the procedure offers a convenient means of preparing t-butyldimethylsilyl esters of various saturated, unsaturated, and aromatic amino acids.

C. Conclusion

Trimethylsilyl esters of carboxylic acids are stable to a variety of hydroborating agents, with BH_3·THF being the only exception among the borane reagents studied. Selective hydroborations with BH_3·THF can be accomplished with excess borane by carefully monitoring the reaction temperature and

Table 6-11: Preparation of t-Butyldimethylsilyl Esters

Carboxylic acid	Yield of Ester[a], %
Hexanoic Acid	86
Decanoic Acid	85
Octadecanoic Acid	86
Pivalic Acid	76
4-Pentenoic Acid	58
10-Undecenoic Acid	82
10-Undecynoic Acid	86
Maleic Acid	64[b]
Salicyclic Acid	71[b,c]
4-Vinylbenzoic Acid	39
4-Methoxybenzoic Acid	74
Alanine	64[b,d]

[a]Isolated, unoptimized yield

[b]Two equivalents each of triethylamine and t-butyldimethylsilyl chloride were used

[c]Yield reported for the disilyl derivative

[d]Yield reported for the N,O-bis silyl derivative

reaction time. Use of one equivalent BH_3·THF at -30°C for two hours provides high yields of the desired hydroxyalkanoic acid product. Since TMS esters can be prepared relatively easily in high yields, and since deprotection of the acid occurs upon simple water hydrolysis, the trimethylsilyl moiety provides a convenient and much needed means of protecting carboxylic acid functionality during hydroboration reactions than existing methodologies. These readily available carboxylic acid derivatives can be utilized to prepare a number of mixed trialkylboranes which can then be converted to functionalized carboxylic acids via well known organoborane transformations.

The reduced reactivity of BH_3·DMS over BH_3·THF in reducing TMS esters can be accounted for in terms of a tighter coordination between the boron and sulfur atoms. This tighter coordination results in a reduction of the Lewis acidic character of the borane reagent, which in turn reduces the affinity of the borane reagent to complex to the ester carbonyl and begin the reduction process.

A more convenient procedure involves the use of the trimethylsilyl moiety as a temporary protecting group by preparing the ester "in situ". Thus hydroboration of unsaturated carboxylic acids can be carried directly without isolation of the TMS ester.

The more hindered t-butyldimethylsilyl group partially

prevents the reduction of the ester functionality, thus allowing selective hydroboration of an olefinic ester with a near stoichiometric amount of BH_3·THF, without reduction of the ester.

The results of the experiments reported in this chapter provided promise for the direct hydroboration of an alkynyl amino acid by temporarily protecting the acid functionality as a silicon ester. Since an alkynyl amino acid was not available commercially to test this proposal, the synthesis of one was undertaken. This will be the subject of the next chapter.

D. Experimental

1. General

All glassware, syringes, and syringe needles were oven-dried 24 hours prior to use. All NMR spectra were recorded on a JEOL-FX-90Q pulsed FT-NMR spectrometer in deuterio-chloroform, $CDCl_3$, acetone-d_6, dimethylsulfoxide-d_6, or deuterium oxide (by use of an external reference in a sealed 5 mm NMR tube) solutions. The ^{1}H-NMR spectra were referenced using tetramethylsilane, TMS, as an internal standard (δ = 0.0 ppm). Exchangeable protons were determined by shaking with deuterium oxide. The ^{13}C-NMR spectra were referenced to either $CDCl_3$ (δ = 77.1 ppm), acetone-d_6 (δ = 30.3 ppm), dimethylsulfoxide-d_6 (δ = 39.5 ppm), methanol-d_1

(δ = 49.0 ppm) methanol-d_4 (δ = 49.0 ppm), or TMS (δ = 0.0 ppm). ^{13}C Single Frequency Off Resonance Decoupled Spectra (SFORD) were obtained by setting the irradiation frequency of the decoupler off upfield of that used for tetramethylsilane, and are reported in parentheses along with the ^{13}C-NMR data. The ^{11}B-NMR spectra were referenced to boron trifluoride-etherate (δ = 0.0 ppm) using a sealed capillary tube external reference. The ^{31}P-NMR spectra were referenced to phosphoric acid (δ = 0.0) using a sealed capillary tube external reference. The ^{29}Si-NMR spectra were referenced to tetramethylsilane (δ = 0.0 ppm). Low temperature NMR experiments were carried out in nitrogen or argon flushed 10 mm NMR tubes with septum caps using a JEOL NMR VTS variable temperature controller equipped with a liquid nitrogen dewar attachment to the NMR probe. Infrared spectra were obtained on a Perkin-Elmer Model 1330 spectrometer. Melting points were recorded using a Fisher-Johns melting point apparatus and are uncorrected. Thin layer chromatographic analyses were performed on Fisher Silica Gel GF 250 μm TLC plates using a phosphomolybdic acid solution as an indicator, or alternatively, UV detection. Column chromatographic separations were accomplished using Davisil silica gel. Gas chromatographic analyses were obtained using a Varian Model 3700 gas chromatograph employing an SE-30 column interfaced with a Hewlett-Packard 3390A

integrator. Elemental analyses were performed on each of the new silicon ester by Galbraith Laboratories, Knoxville, Tennessee. The commercially available chemicals, their manufacturers, and the methods of purification used, when applicable, are listed in Table 6-12. Reagents previously listed in Tables 3-1, 4-6, or 5-8 are not repeated here. All other reagents used were prepared as described below.

2. Preparation of Trimethylsilyl Esters: General Procedure

a. Trimethylsilyl 10-Undecenoate

The synthesis of trimethylsilyl 10-undecenoate is representative. An oven dried 500 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, addition funnel, and gas outlet (mercury bubbler). The apparatus was flame dried, and allowed to cool under a stream of argon. In the flask by cannula was placed 10-undecenoic acid (200 mmol, 36.86 g), followed by anhydrous THF (200 mL), and triethylamine (200 mmol, 27.9 mL). The contents were cooled to 0°C, and trimethylsilyl-chloride (200 mmol, 25.4 mL) was added dropwise (exothermic!). After the addition was complete, the reaction mixture was stirred at room temperature for one hour.

A separate apparatus consisting of a 250 mL round-bottomed flask equipped with a septum inlet, magnetic stirring bar, and a sintered glass fritted funnel with

Table 6-12: Manufacturer and Methods of Purification of Commercially Available Chemicals

Reagent	Manufacturer[a]	Method of Purification[b]
Alanine	F	
Benzoyl Peroxide	F	
9-Borabicyclo[3.3.1]nonane, Dimer	A	1
9-Borabicyclo[3.3.1]nonane, 0.5 M solution in THF	A	
Borane Dimethylsulfide Complex, 10.0 M solution in Dimethylsulfide	A	
Borane Tetrahydrofuran Complex, 1.0 M solution in THF	A	
N-Bromosuccinimide	A	
t-Butyldimethylsilylchloride	A	
Carbon Tetrachloride	M	
Cyclohexene	A	2
3-Cyclohexene-1-carboxylic Acid	I	
Decanoic Acid	E	2
2,3-Dimethyl-2-butene	A	
Ethylene Glycol Dimethyl Ether	A	3
Formaldehyde, 38% aqueous solution	F	
Hexanoic Acid	E	2

Table 6-12 (continued)

Reagent	Manufacturer[a]	Method of Purification[b]
Hydrogen Peroxide, 30% aqueous solution	A	
Maleic Acid	A	4
4-Methoxybenzoic acid	A	4
2-Methyl-2-Butene	A	
endo-5-Norbornene-2,3-dicarbocylic Acid	A	
Octadecanoic Acid	D	
Oleic Acid	E	
4-Pentenoic Acid	A	
Propionic Acid	F	
Salicylic Acid	F	
Sodium Acetate	F	
Sodium Sulfate	F, M	
Sodium Thiosulfate	F	
Triethylamine	F, A	5
Trimethylacetic Acid	A	
Trimethylsilyl Chloride	A	5
Triphenylphosphine	A	
Toluic Acid	F	
10-Undecenoic Acid	A	

Table 6-12 (continued)

Reagent	Manufacturer[a]	Method of Purification[b]
10-Undecen-1-ol	A	
10-Undecynoic Acid	FN	

[a]Manufacturers
- A = Aldrich Chemical Company
- D = Dupont Chemical Company
- E = Eastman Chemical Company
- F = Fisher Scientific Company
- FN = Farchan Acetylenes
- I = ICN Biomedicals
- M = Malinkrodt

[b]Methods of Purification
1. Recrystallized from anhydrous monoglyme
2. Distilled
3. Distilled from sodium/benzophenone under argon
4. Dried under vacuum prior to use
5. Distilled from Calcium hydride under argon

a rubber septum was assembled while hot, flame dried, and flushed with argon. The reaction mixture was then filtered under argon through the filtering funnel by transferring it into the fritted funnel using a 12 ga. double-ended needle. The solvent was removed from the filtrate by slow distillation under argon to give the crude ester. Bulb-to-bulb distillation under reduced pressure yielded 45.31 g (82%) of trimethylsilyl 10-undecenoate as a pale yellow oil; bp 112°C (116 Torr) [lit[546] bp 96-100°C (2 Torr)]; ^{1}H-NMR ($CDCl_3$): δ 6.05-5.5 (m, 1H, J_{ab}=6.6Hz, $H_2C=C\underline{H}_aCH_bR$), 5.1-4.75 (m, 2H, J_{trans}= 17.1Hz, J_{cis}=9.2Hz, $\underline{H}_2C=CHCH_2R$), 2.29 (t, 2H, J=7.0 Hz, $\underline{CH}_2COOTMS$), 2.15-1.85 (m, 2H, $H_2C=CH\underline{CH}_2R$), 1.75-1.1 (broad envelope, 12H), 0.27 (s, 9H, $(\underline{CH}_3)_3Si$); ^{13}C-NMR ($CDCl_3$)δ: 174.45 ($\underline{C}OOTMS$), 139.05 ($H_2C=\underline{C}HR$), 114.16 ($H_2\underline{C}=CH-R$), 35.90, 33.98, 33.82, 29.26, 29.07, 28.91, 24.96, 24.71, -0.23 [$(CH_3)_3Si$]; ^{29}Si-NMR ($CDCL_3$): δ 22.77.

b. Trimethylsilyl 4-Pentenoate

Reaction of 4-pentenoic acid (108.1 mmol, 10.82 g) with triethylamine (108.1 mmol, 10.94 g. 15.1 mL) and chlorotrimethylsilane (108.1 mmol, 11.74 g, 13.72 mL) in anhydrous THF (100 mL) according to the general procedure gave 14.8 g (80%) of trimethylsilyl 4-pentenoate as a colorless oil after bulb-to-bulb distillation; bp 66°C (14 Torr) [lit[547] bp 70-72°C (8 Torr)]; ^{1}H-NMR ($CDCl_3$): δ 6.0-5.6 (m. 1H,

$H_2C=C\underline{H}R$), 5.1-4.9 (m, 2H, J_{trans}=17.5 Hz, J_{cis}=11 Hz, $\underline{H}_2C=CHR$), 2.5-2.1 (m, 4H, $-CH_2CH_2-$), 0.28 (s, 9H, $COOSi(C\underline{H}_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 173.56 ($\underline{C}OOSi(CH_3)_3$), 136.83 ($H_2C=\underline{C}HR$), 115.29 ($H_2\underline{C}=CHR$), 35.12 ($\underline{CH}_2COOSi(CH_3)_3$), 29.02 ($H_2C=CH\underline{CH}_2-$); ^{29}Si-NMR ($CDCl_3$): δ 23.69.

c. Trimethylsilyl Hexanoate

Reaction of hexanoic acid (195.76 mmol, 22.74 g) with triethylamine (210 mmol, 21.25 g. 29.3 mL) and chlorotrimethylsilane (210 mmol, 22.81 g, 26.65 mL) in anhydrous THF (100 mL) according to the general procedure gave 32.25 g (87%) of trimethylsilyl hexanoate as a colorless oil after bulb-to-bulb distillation; bp 44°C (0.2 Torr); ^{1}H-NMR ($CDCl_3$): δ 2.30 (t, 2H, J=7.0 Hz, $\underline{CH}_2COOSi(CH_3)_3$), 1.8-1.2 (m, 6H), 0.90 (t, 3H, J=6.1 Hz), 0.28 (s, 9H, $Si(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 174.56 ($COOSi(CH_3)_3$), 35.96 ($\underline{C}H_2COOSi(CH_3)$), 31.35, 24.74, 22.41, 13.94 (CH_3); ^{29}Si-NMR ($CDCl_3$): δ 23.50.

d. Trimethylsilyl (Z)-9-Octadecenoate

Reaction of oleic acid (100 mmol, 28.25 g) with triethylamine (105 mmol, 10.62 g. 14.6 mL) and chlorotrimethylsilane (105 mmol, 11.41 g, 13.33 mL) in anhydrous THF (100 mL) according to the general procedure gave 29.81 g (84%) of trimethylsilyl (Z)-9-octadecenoate as a colorless oil after

bulb-to-bulb distillation; bp 166°C (0.9 Torr); 5.45-5.2 (m, 2H, RHC=CHR'), 2.29 (t, 2H, $CH_2COOSi(CH_3)_3$, 2.15-1.85 (m, 4H), 1.75-1.1 (broad envelope, 22H), 0.88 (t, 3H, CH_3), 0.27 (s, 9H, $Si(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 174.56 (COOSi), 130.03 (RCH=CHR'), 129.81 (RCH=CHR'), 36.01 (RCH_2COOSi), 32.70, 32.65, 32.01, 29.67, 29.59, 29.43, 29.26, 29.16, 29.05, 25.06 (RCH_2CH_2COOSi), 22.76, 14.18 (CH_3), -0.14 ($Si(CH_3)_3$); ^{29}Si ($CDCl_3$): δ 22.77.

e. Trimethylsilyl 3-Cyclohexene-1-carboxylate

Reaction of 3-cyclohexene-1-carboxylic acid (78.31 mmol, 9.88 g) with triethylamine (78.3 mmol, 7.92 g, 10.9 mL) and chlorotrimethylsilane (78.3 mmol, 8.50 g, 9.94 mL) in anhydrous THF (100 mL) according to the general procedure gave 11.32 g (73%) of trimethylsilyl 3-cyclohexene-1-carboxylate as a colorless oil after bulb-to-bulb distillation; bp 67°C (2.1 Torr); ^{1}H-NMR ($CDCl_3$): δ 5.67 (s, 2H, RHC=CHR'), 2.7-1.6 (m, 7H), 0.28 (s, 9H, $Si(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 176.40 (COOSi), 126.64 ($RC_3H=C_4HR'$), 125.34 ($RC_3H=C_4HR'$), 40.58 ($R'C_4=C_3HCH_2CH(COOSi)R$), 27.50 RCH_2-$C_4=CH_3R'$), 25.09, 24.47, -0.23 ($Si(CH_3)_3$).

f. Trimethylsilyl 10-Undecynoate

Reaction of 10-undecynoic acid (20 mmol, 3.64 g) with triethylamine (20 mmol, 2.02 g, 2.78 mL) and

chlorotrimethylsilane (20 mmol, 2.17 g, 2.54 mL) in anhydrous THF (50 mL) according to the general procedure gave 4.14 g (82%) of trimethylsilyl 10-undecynoate as a colorless oil after bulb-to-bulb distillation (99.6% purity by GC); bp 150-155°C (0.1-0.12 Torr); ^{1}H-NMR ($CDCl_3$): δ 2.4-2.05 (m, 4H, $HC{\equiv}CC\underline{H}_2R$, $-C\underline{H}_2COOSi$), 1.92 (t, 1H, J=2.6 Hz, $\underline{H}C{\equiv}CR$, 1.7-1.2 (m, 12 H), 0.26 (s, 9H, $COOSi(C\underline{H}_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 174.42 (COOSi), 84.58 ($HC{\equiv}\underline{C}R$), 68.13 ($H\underline{C}{\equiv}CR$), 35.85 ($\underline{C}H_2CH_2$-COOSi), 29.13, 28.99, 28.91, 28.64, 28.42, 24.90 ($\underline{C}H_2CH_2$-COOSi), 18.35, ($HC{\equiv}C\underline{C}H_2R$), -0.26 ($Si(CH_3)_3$). Anal. calc. for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30; Si, 11.04. Found: C, 66.28; H, 10.49; Si, 8.80.

g. <u>(Bis)Trimethylsilyl endo-5-Norbornene-2,3-dicarboxylate</u>

Reaction of <u>endo</u>-5-norbornene-2,3-dicarboxylic acid (27.45 mmol, 5.0 g) with triethylamine (54.90 mmol, 5.56 g, 7.65 mL) and chlorotrimethylsilane (54.90 mmol, 5.96 g, 6.97 mL) in anhydrous THF (50 mL) according to the general procedure gave 6.32 g (70%) of (bis)trimethylsilyl endo-5-norbornene-2,3-dicarboxylate as a white crystalline solid upon cooling after bulb-to-bulb distillation; bp 130°C (0.1 Torr); mp 153°C (sub); ^{1}H-NMR ($CDCl_3$): δ 6.18 (m, 2H, $R\underline{H}C{=}C\underline{H}R'$), 3.25-3.0 (m, 4H endo H's, bridgehead H's), 1.4-1.2 (m, 2H, CHH'), 0.28 (s, 18H, $Si(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 172.61 (COOSi), 134.83 ($RH\underline{C}{=}\underline{C}HR$), 49.82

(bridgehead, 48.73 (bridge CH_2), 46.65 (RR'$\underline{C}$HCOOSi), -0.10 ($Si(CH_3)_3$).

h. Bis-N,O-Trimethylsilyl 2-Aminopropanoate

Reaction of alanine (100 mmol, 8.91 g) with triethylamine (200 mmol, 20.24 g, 27.9 mL) and chlorotrimethylsilane (200 mmol, 21.73 g, 25.4 mL) in anhydrous THF (100 mL) [Note: alanine did not dissolve, but remained as a suspension] according to the general procedure gave 6.32 g (70%) of bis-N,O-trimethylsilyl 2-aminopropanoate as a colorless oil after bulb-to-bulb distillation; bp 56°C (0.25 Torr); ^{1}H-NMR ($CDCl_3$): δ 3.7-3.25 (m, 1H, C-H), 1.32 (d, 2H, CH_3, overlaps with N-H, 1H), 0.27 ($(CH_3)_3Si$-N), 0.04 ($(CH_3)_3Si$-OOC); ^{13}C-NMR ($CDCl_3$): δ 177.21 (COOSi), 51.42 (C-H), 23.22 (CH_3), 0.12 ($(CH_3)_3Si$-N), -0.34 (($\underline{C}H_3)_3Si$-OOC); ^{29}Si-NMR ($CDCl_3$): δ 24.03 ($COOSi(CH_3)_3$), 3.78 ($(CH_3)_3Si$-N).

3. Preparation of t-Butyldimethylsilyl Esters

a. t-Butyldimethylsilyl 10-Undecenoate

The synthesis of $\underline{t}$-butyldimethylsilyl 10-undecenoate is representative. An oven-dried 100 mL round-bottomed flask equipped with a septum inlet, magnetic stirring bar, and gas outlet was assembled hot, and flushed with argon while flame drying. After allowing the apparatus to cool, 10-undecenoic acid (10 mmol, 2.0 mL), anhydrous THF (40 mL), and

triethylamine (10 mL), 1.4 mL) were added sequentially. A solution to t-butyldimethylsilyl chloride (10 mmol, 1.51 g) in anhydrous THF (10 mL) was transfered slowly by cannula, and the contents stirred for 30 minutes at room temperature. The triethylamine hydrochloride precipitate was then filtered off, and the solvent removed under reduced pressure to give 3.0 g of a light yellow oil. Purification by column chromatography (silica gel, methylene chloride) afforded 2.44 g (82%) of t-butyldimethylsilyl 10-undecenoate as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 6.0-5.6 (m, 1H, $H_2C=CHR$), 5.1-4.8 (m, 2H, J_{trans}=17.1 Hz, J_{cis}=10.5 Hz, $H_2C=CHR$), 2.3 (t, 2H, J=7.0 Hz, $-CH_2COOR$), 2.15-1.2 (m, 14H), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.26 (s, 6H, $Si(CH_3)_2$); ^{13}C-NMR ($CDCl_3$): δ 174.2 (COOR), 139.16 ($H_2C=CHR$), 114.18 ($H_2C=CHR$), 36.09 (CH_2COOSi), 33.84, 29.37, 29.32, 29.13, 28.96, 25.63 ($RCOOSi-(CH_3)_2C(CH_3)_3$), 25.15, 17.64 ($RCOOSi(CH_3)_2C(CH_3)_3$), -4.75 ($RCOOSi(CH_3)_2C(CH_3)_3$); ^{29}Si-NMR ($CDCl_3$): δ 24.44; IR (neat): 3090 cm^{-1} (olefinic C-H), 2965 cm^{-1}, 2930 cm^{-1}, 2863 cm^{-1} (CH_2), 1720 cm^{-1} (COOSi), 1643 cm^{-1} (C=C), 1252 cm^{-1}, 1194 cm^{-1}, 1176 cm^{-1}, 1005 cm^{-1}, 992 cm^{-1}, 910 cm^{-1}, 824 cm^{-1}, 789 cm^{-1}, 733 cm^{-1}, 677 cm^{-1}.

b. t-Butyldimethylsilyl Hexanoate

Reaction of hexanoic acid (40 mmol, 4.64 g), triethyl amine (40 mmol, 5.57 mL), and t-butyldimethylchlorosilane

(40 mmol, 6.03 g) in anhydrous THF (120 mL) according to the general procedure gave 7.95 g (86%) of a colorless oil after distillation through a vacuum jacketed column; bp 210-215°C; ^{1}H-NMR ($CDCl_3$): δ 2.30 (t, 2H, J= 7.0 Hz, -$\underline{CH_2}$COOR), 1.8-1.15 (m, 6H), 0.93 (broad singlet, 12 H, COOSi$(CH_3)_2C(\underline{CH_3})_3$, CH_3), 0.26 (s, 6H, COOSi$(\underline{CH_3})_2C(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 174.26 (COOSi), 36.04 ($\underline{C}H_2$COOSi), 31.32, 25.58 (COOSi-$(CH_3)_2C(\underline{C}H_3)_3$), 24.79, 22.38, 17.62, (COOSi$(CH_3)_2\underline{C}(CH_3)_3$), 13.91 ($CH_3$), -4.81 (COOSi$(\underline{C}H_3)_2C(CH_3)_3$); ^{29}Si-NMR ($CDCl_3$): δ 24.41; IR (neat): 2962 cm^{-1} (CH_3), 2939 cm^{-1}, 2864 cm^{-1} (CH_2), 1720 cm^{-1} (COOSi), 1250 cm^{-1}, 1176 cm^{-1}, 1097 cm^{-1}, 938 cm^{-1}, 839 cm^{-1}, 824 cm^{-1}, 787 cm^{-1}.

c. t-Butyldimethylsilyl Decanoate

Reaction of decanoic acid (10 mmol, 1.72 g), triethyl amine (10 mmol, 1.01 g, 1.39 mL), and t-butyldimethylchlorosilane (10 mmol, 1.51 g) in anhydrous THF (30 mL) according to the general procedure gave 2.43 g (85%) of a colorless oil after column chromatography (silica gel, 20% methylene chloride-petroleum ether); ^{1}H-NMR ($CDCl_3$): δ 2.30 (t, 2H, J= 7.0 Hz, -$\underline{CH_2}$COOR), 1.7-1.1 (m, 14H), 0.93 (broad singlet, 12 H, $-C(CH_3)_3$, CH_3), 0.26 (s, 6H, COOSi$(\underline{CH_3})_2C(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 174.26 (COOSi), 36.01 ($\underline{C}H_2$COOSi), 31.82, 29.45, 29.32, 29.13, 25.53 (COOSi$(CH_3)_2C(\underline{C}H_3)_3$), 25.09, 22.66, 17.56 (COOSi$(CH_3)_2\underline{C}(CH_3)_3$), 14.07 ($CH_3$), -4.86

(COOSi($\underline{C}H_3)_2C(CH_3)_3$); ^{29}Si-NMR ($CDCl_3$): δ 24.38; IR (neat): 2970 cm^{-1} (CH_3), 2943 cm^{-1}, 2873 cm^{-1} (CH_2), 1726 cm^{-1} (COOSi), 1256 cm^{-1}, 1196 cm^{-1}, 1178 cm^{-1}, 940 cm^{-1}, 843 cm^{-1}, 826 cm^{-1}, 790 cm^{-1}.

d. t-Butyldimethylsilyl Octadecanoate

Reaction of octadecanoic acid (10 mmol, 2.84 g), triethylamine (10 mmol, 1.72 g), and t-butyldimethylchlorosilane (10 mmol, 1.51 g) in anhydrous THF (30 mL) according to the general procedure gave 3.42 g (86%) of a colorless oil, after column chromatography (silica gel, 20% methylene chloride-petroleum ether), which crystallized upon standing; ^{1}H-NMR ($CDCl_3$): δ 2.30 (t, 2H, J= 7.0 Hz, -$\underline{C}H_2$COOR), 1.7-1.1 (broad envelope, 30H), 0.93 (broad singlet, 12 H,-$C(CH_3)_3$, CH_3), 0.26 (broad singlet, 6H, COOSi($C\underline{H}_3)_2C(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 174.23 (COOSi), 36.06 ($\underline{C}H_2$COOSi), 32.00, 29.72, 29.56, 29.40, 29.18, 25.58 (COOSi$(CH_3)_2C(\underline{C}H_3)_3$), 25.15, 22.73, 17.59 (COOSi$(CH_3)_2\underline{C}(CH_3)_3$), 14.12 ($CH_3$), -4.80 (COOSi($\underline{C}H_3)_2C(CH_3)_3$); ^{29}Si-NMR ($CDCl_3$): δ 24.37; IR (neat): 2956 cm^{-1} (CH_3), 2920 cm^{-1}, 2856 cm^{-1} (CH_2), 1718 cm^{-1} (COOSi), 1460 cm^{-1}, 1252 cm^{-1}, 1173 cm^{-1}, 934 cm^{-1}, 836 cm^{-1}, 821 cm^{-1}, 786 cm^{-1}.

e. t-Butyldimethylsilyl 4-Pentenoate

Reaction of 4-pentenoic acid (10 mmol, 1.00 g, 1.02

mL), triethylamine (10 mmol, 1.01 g, 1.39 mL), and t-butyldimethylchlorosilane (10 mmol, 1.51 g) in anhydrous THF (30 mL) according to the general procedure gave 1.41 g (58%) of a colorless oil after column chromatography (silica gel, 20% methylene chloride-petroleum ether); ^{1}H-NMR ($CDCl_3$): δ 6.05-5.55 (m, 1H, $H_2C=C\underline{H}R$), 5.1-4.9 (m, 2H, J_{trans}=17.1 Hz, J_{cis}=10.1 Hz, $\underline{H}_2C=CHR$), 2.39 (m, 4H, CH_2's), 0.93 (s, 9H, $COOSi(CH_3)_2C(C\underline{H}_3)_3$), 0.26 (s, 6H, $COOSi(C\underline{H}_3)_2C(CH_3)_3$; ^{13}C-NMR ($CDCl_3$): δ 173.20 ($\underline{C}OOR$), 136.72 ($H_2C=\underline{C}HR$), 115.21 ($H_2\underline{C}=CHR$), 35.14 ($-\underline{C}H_2COOSi$), 29.02, ($H_2C=CH\underline{C}H_2R$), 25.50 ($RCOOSi(CH_3)_2C(\underline{C}H_3)_3$), 17.51 ($RCOOSi(CH_3)_2\underline{C}(CH_3)_3$), -4.89 ($RCOOSi(\underline{C}H_3)_2C(CH_3)_3$); ^{29}Si-NMR ($CDCl_3$): δ 25.04; IR (neat): 3090 cm^{-1} (olefinic C-H), 2965 cm^{-1}, 2939 cm^{-1}, 2863 cm^{-1} (CH_2), 1720 cm^{-1} (COOSi), 1643 cm^{-1} (C=C), 1252 cm^{-1}, 1176 cm^{-1}, 992 cm^{-1}, 938 cm^{-1}, 839 cm^{-1}, 824 cm^{-1}, 789 cm^{-1}, 733 cm^{-1}. Anal. calc. for $C_{11}H_{22}O_2Si$: C, 61.63; H, 10.34; Si, 13.10 Found: C, 61.18; H, 10.37; Si, 12.00.

f. t-Butyldimethylsilyl 10-Undecynoate

Reaction of 10-undecynoic acid (20 mmol, 3.64 g), triethylamine (20 mmol, 2.02 g, 2.79 mL), and t-butyldimethylchlorosilane (20 mmol, 3.01 g) in anhydrous THF (60 mL) according to the general procedure gave 5.12 g (86%) of a colorless oil after column chromatography (silica gel, 20% chloroform-petroleum ether); ^{1}H-NMR ($CDCl_3$): δ 2.4-2.05 (m,

4H, $HC{\equiv}CC\underline{H}_2R$, $-CH_2COOR$), 1.92 (t, 1H, J=2.6 Hz, $\underline{H}C{\equiv}CR$, 1.7-1.2 (m, 12 H), 0.93 (s, 9H, $COOSi(CH_3)_2C(C\underline{H}_3)_3$), 0.26 (s, 6H, $COOSi(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 174.21 ($\underline{C}OOSi$), 84.57 ($HC{\equiv}\underline{C}R$), 68.13 ($H\underline{C}{\equiv}CR$), 36.01 ($-\underline{C}H_2COOSi$), 29.15, 29.05, 28.94, 28.67, 28.45, 25.58 ($RCOOSi(CH_3)_2C(\underline{C}H_3)_3$), 25.06, 18.37 ($HC{\equiv}C\underline{C}H_2R$), 17.59 ($RCOOSi(CH_3)_2\underline{C}(CH_3)_3$), -4.81 ($RCOOSi(\underline{C}H_3)_2C(CH_3)_3$); ^{29}Si-NMR ($CDCl_3$): δ 24.45; IR (neat): 3285 cm^{-1} (alkynyl C-H), 2910 cm^{-1}, 2840 cm^{-1} (aliphatic C-H), 2110 cm^{-1} (C≡C), 1725 cm^{-1} (COOSi), 1435 cm^{-1}, 1338 cm^{-1}, 1230 cm^{-1}, 1171 cm^{-1}, 1159 cm^{-1}, 990 cm^{-1}, 923 cm^{-1}, 828 cm^{-1}, 815 cm^{-1}, 800 cm^{-1}, 778 cm^{-1}. Anal. calc. for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88; Si, 9.47 Found: C, 68.94; H, 11.05; Si, 8.78.

g. t-Butyldimethylsilyl Trimethylacetate

Reaction of trimethylacetic acid (10 mmol, 1.02 g), triethylamine (10 mmol, 1.01 g, 1.40 mL), and t-butyldimethylchlorosilane (10 mmol, 1.51 g) in anhydrous THF (30 mL) according to the general procedure gave 1.63 g (76%) of a colorless oil after column chromatography (silica gel, 20% chloroform-petroleum ether); ^{1}H-NMR ($CDCl_3$): δ 1.18 (s, 9H, $C\underline{H}_3CCOOSi$), 0.95 (s, 9H, $COOSi(CH_3)_2C(C\underline{H}_3)_3$), 0.26 (s, 6H, $COOSi(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 179.11 ($\underline{C}OOSi$), 39.80 ($(CH_3)_3\underline{C}COOSi$), 25.58 ($RCOOSi(CH_3)_2C(\underline{C}H_3)_3$), 17.75 ($RCOOSi(CH_3)_2\underline{C}(CH_3)_3$), -4.91 ($RCOOSi(\underline{C}H_3)_2C(CH_3)_3$); ^{29}Si-NMR

($CDCl_3$): δ 24.59; IR (neat): 2965 cm^{-1}, 2945 cm^{-1} (aliphatic C-H), 2873 cm^{-1}, 1715 cm^{-1} (COOSi), 1396 cm^{-1} (t-butyl), 1365 cm^{-1} (t-butyl), 1292 cm^{-1}, 1252 cm^{-1}, 1165 cm^{-1}, 1029 cm^{-1}, 1004 cm^{-1}, 900 cm^{-1}. Anal. calc. for $C_{11}H_{24}O_2Si$: C, 61.05; H, 11.18; Si, 12.98 Found: C, 60.84; H, 11.05; Si, 12.28.

h. Bis(t-Butyldimethylsilyl) Maleate

Reaction of maleic acid (10 mmol, 1.16 g, dried in vacuum oven at 80°C for 48 hours prior to use), triethylamine (20 mmol, 2.02 g, 2.79 mL), and t-butyldimethylchlorosilane (20 mmol, 3.01 g) in anhydrous THF (30 mL) according to the general procedure gave 2.05 g (64%) of a colorless oil after short path distillation [Note: product desilylated on attempted purification by column chromatography]; ^{1}H-NMR ($CDCl_3$): δ 6.16 (s, 2H, olefinic C-H), 0.95 (s, 18H, $COOSi(CH_3)_2C(\underline{C}H_3)_3$), 0.26 (s, 12H, $COOSi(\underline{C}H_3)_2C(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 164.86 ($\underline{C}OOSi$), 25.58 ($RCOOSi(CH_3)_2C(\underline{C}H_3)_3$), 17.51 ($RCOOSi(CH_3)_2\underline{C}(CH_3)_3$), -5.03 ($RCOOSi(\underline{C}H_3)_2C(CH_3)_3$); ^{29}Si-NMR ($CDCl_3$): δ 27.10.

i. t-Butyldimethylsilyl 4-Methoxybenzoate

Reaction of 4-methoxybenzoic acid (10 mmol, 1.52 g), triethylamine (10 mmol, 1.01 g, 1.40 mL), and t-butyldimethylchlorosilane (10 mmol, 1.51 g) in anhydrous THF (30

mL) according to the general procedure gave 1.98 g (74%) of a light yellow oil after column chromatography (silica gel, 20% methylene chloride-petroleum ether); ^{1}H-NMR ($CDCl_3$): δ 8.10-6.75 (m, 4H, AA'BB', aromatic H), 3.81 (s, 3H, $OC\underline{H}_3$), 1.02 (s, 9H, $COOSi(CH_3)_2C(C\underline{H}_3)_3$), 0.36 (s, 6H, $COOSi(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 166.16 ($\underline{C}OOSi$), 163.29 (aromatic $\underline{C}$-OCH_3), 132.00 (aromatic carbon ortho to COOH), 123.82 (aromatic $\underline{C}$-COOH), 113.42 (aromatic carbon ortho to OCH_3), 55.19 (OCH_3), 25.58 ($RCOOSi(CH_3)_2C(\underline{C}H_3)_3$), 17.70 ($RCOOSi(CH_3)_2\underline{C}(CH_3)_3$), -4.83 ($RCOOSi(\underline{C}H_3)_2C(CH_3)_3$). Anal. calc. for $C_{14}H_{22}O_3Si$: C, 63.12; H, 8.32; Si, 10.54 Found: C, 63.25; H, 8.59; Si, 10.04.

j. 2-t-Butyldimethylsilyloxy-t-butyldimethylsilylbenzoate

Reaction of 2-hydroxybenzoic acid (5 mmol, 0.69 g), triethylamine (10 mmol, 1.01 g, 1.40 mL), and t-butyldimethylchlorosilane (10 mmol, 1.51 g) in anhydrous THF (30 ml) according to the general procedure gave 1.30 g (71%) of a light yellow oil after column chromatography (silica gel, chloroform); ^{1}H-NMR ($CDCl_3$): δ 7.9-7.7 (m, 1H, aromatic H ortho to COOSi and meta to OSi), 7.45-7.2 (m, 1H, aromatic H para to COOSi and meta to OSi), 7.05-6.75 (m, 2H, aromatic carbon meta to COOSi and para to OSi), 1.01 (s, 18H, $COOSi(CH_3)_2C(C\underline{H}_3)_3$), 0.35 (s, 6H, $COOSi(C\underline{H}_3)_2C(CH_3)_3$), 0.21 (s, 6H, $OSi(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 165.32 ($\underline{C}OOSi$),

155.93 (aromatic C-OSi), 132.90 (aromatic carbon para to COOSi), 131.62 (aromatic carbon ortho to COOSi and meta to OSi), 124.29 (aromatic C-COOSi), 121.71 (aromatic carbon meta to COOSi and para to OSi), 120.76 (aromatic carbon meta to COOSi and ortho to OSi), 25.85 (both $RCOOSi(CH_3)_2C-(\underline{C}H_3)_3$), 18.51 ($OSi(CH_3)_2\underline{C}(CH_3)_3$), 17.91 ($RCOOSi(CH_3)_2\underline{C}-(CH_3)_3$), -4.27 ($OSi(\underline{C}H_3)_2C(CH_3)_3$), -4.51 ($RCOOSi(\underline{C}H_3)_2C-(CH_3)_3$); ^{29}Si-NMR ($CDCl_3$): δ 25.17, 22.02.

k. N,O-Bis(t-butyldimethylsilyl) 2-Aminopropanoate

Reaction of alanine (20 mmol, 1.78 g), triethylamine (40 mmol, 4.08 g, 5.57 mL), and t-butyldimethylchlorosilane (40 mmol, 6.03 g) in anhydrous THF (100 mL) for 48 hours according to the general procedure gave 2.98 g (64%) of a colorless oil after distillation; ^{1}H-NMR ($CDCl_3$): δ 3.7-3.3 (m, 1H, C-H), 1.27 (d, 3H, CH_3), 0.95 (s, 9H, $COOSi-(CH_3)_2C(C\underline{H}_3)_3$), 0.87 (s, 9H, $NHSi(CH_3)_2C(C\underline{H}_3)_3$), 0.36 (s, 6H, $COOSi(C\underline{H}_3)_2C(CH_3)_3$), -0.02 (s, 6H, $NHSi(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 177.02 (COOSi), 52.12 (CH), 26.23 ($NHSi-(CH_3)_2C(\underline{C}H_3)_3$), 25.58 ($RCOOSi(CH_3)_2C(\underline{C}H_3)_3$), 23.79 ($CH_3$), 18.10, ($NHSi(CH_3)_2\underline{C}(CH_3)_3$), 17.61, ($RCOOSi(CH_3)_2\underline{C}(CH_3)_3$), -4.75, -4.89 [($RCOOSi(C\underline{H}_3)_2C(CH_3)_3$), ($NHSi(C\underline{H}_3)_2C(CH_3)_3$); ^{29}Si-NMR ($CDCl_3$): δ 25.56 (RCOOSi), 8.12 (NHSi).

l. α-Bromo-p-Toluic Acid

The procedure of Tuleen and Hess was used[548]. p-Toluic acid (200 mmol, 27.23g), N-bromosuccinimide (202 mmol, 35.95 g) benzoyl peroxide (8.3 mmol, 2.01 g) (Note: care should be taken to ensure benzoyl peroxide does not remain on the ground glass joint], and carbon tetrachloride were placed in a 1 L round bottom flask and refluxed for one hour. The reaction was complete when evolution of bromine ceased. The contents were filtered, washed with petroleum ether (3x100 mL), and the product transferred to a conical flask. Water (500 mL) was added, the mixture refluxed briefly (to dissolve any remaining succinimide), and the remaining solid material filtered while hot. This process was repeated, and the remaining solid dissolved in THF and dried ($MgSO_4$). Filtration, followed by evaporation of the solvent gave α-bromo-p-benzoic acid, 28.29 g (66%), as a white solid; ^{13}C-NMR (DMSO): δ 166.21 (COOH), 141.97 (aromatic C-COOH), 129.75 (aromatic C-CH_2Br), 128.91 (aromatic), 128.59 (aromatic), 32 43 (CH_2Br).

m. p-Carboxybenzyltriphenylphosphonium Bromide

The procedure of Tavernier and Anteunis was followed[549]. To a 1 L round bottom flask containing p-carboxybenzyl bromide (100 mmol, 21.51 g) and acetone (600 mL) was added a solution of triphenylphosphine (100 mmol, 26.23

g dissolved in 100 mL acetone. The flask was fitted with a magnetic stirring bar and reflux condenser, and the mixture refluxed for one hour. After cooling to 0°C, the precipitated salt was filtered and washed with ether (100 mL) to give, after drying, 34.07 g (71 %) of p-carboxytriphenylphosphonium bromide as a powder; ^{1}H-NMR (DMSO-d_6): δ 8.0-7.6 (m, 17 H, aromatic), 7.25-7.05 (m, 2H, aromatic), 5.5 (d, CH_2P); ^{13}C-NMR (DMSO-d_6): 166.72 (COOH), 166.67, 135.09, 134.25, 133.79, 133.30, 132.95, 131.21, 130.97, 130.64, 130.38, 129.83, 129.51, 129.40, 119.49, 115.67, 29.6 and 27.0 (CH_2P); ^{31}P-NMR (DMSO-d_6): δ 23.14.

n. 4-Vinylbenzoic Acid

The procedure described by Broos, Tavernier, and Anteunis was followed[549] To a 250 mL round-bottomed flask were added 4-carboxybenzyltriphenylphosphonium bromide (20 mmol, 9.41 g) and aqueous formaldehyde solution (37%, 80 mL). The flask was equipped with a magnetic strirring bar and addition funnel, and then an aqueous sodium hydroxide solution (6 g in 30 mL water) was added with stirring over a 15 minute period. On initial addition of the sodium hydroxide solution, the phosphonium salt dissolved, but on continued addition of base, a white precipitate formed. The contents were stirred for an additional 60 minutes and the precipitate (triphenylphosphine oxide) was filtered and

washed with water. Acidification of the filtrate (pH = 2) gave a white precipitate which was filtered. Recrystallization from H_2O-EtOH (70:30) afforded 4-vinylbenzoic acid, 2.10 g (71%) as white plates; mp 150.5-151.51°C (lit[55]°142-143°C); ^{1}H-NMR ($CDCl_3$): δ 11.70 (br, 1H, COO<u>H</u>) 8.20-7.35 (m, 4H, AA'BB', aromatic H), 7.0-6.55 (m, 1H, H_2C=C<u>H</u>Ph), 6.0-5.25 (m, 1H, J_{trans}=17.6 Hz, <u>H</u>H'C=CHPh), 6.5-6.2 (m, 1H, J_{cis}=10.1 Hz, H<u>H'</u>C=CHPh); ^{13}C-NMR ($CDCl_3$): δ 142.92 (aromatic <u>C</u>-CH=CH_2), 136.04 (Ph<u>C</u>H=CH_2), 130.65 (aromatic carbon ortho to COOH), 128.51 (aromatic <u>C</u>-COOH), 126.31 (aromatic carbon ortho to -CH=CH_2), 117.03 (PhCH=<u>C</u>H_2).

o. <u>t-Butyldimethylsilyl 4-Vinylbenzoate</u>

Reaction of 4-vinylbenzoic acid (5 mmol, 0.74 g), triethylamine (5 mmol, 0.51 g, 0.74 mL), and <u>t</u>-butyldimethylchlorosilane (5 mmol, 0.76 g) in anhydrous THF (25 mL) according to the general procedure gave 0.46 g (39%) of a colorless oil after column chromatography (silica gel, 20% methylene chloride-petroleum ether); ^{1}H-NMR ($CDCl_3$): δ 8.10-7.30 (m, 4H, AA'BB', aromatic H), 6.95-6.5 (m, 1H, H_2C=C<u>H</u>Ph), 6.0-5.25 (m, 1H, J_{trans}=17.6 Hz, <u>H</u>H'C=CHPh), 6.45-6.2 (m, 1H, J_{cis}=10.6 Hz, H<u>H'</u>C=CHPh), 1.02 (s, 9H, $COOSi(CH_3)_2C(C\underline{H}_3)_3$), 0.37 (s, 6H, $COOSi(C\underline{H}_3)_2C(CH_3)_3$); ^{13}C-NMR ($CDCl_3$): δ 166.27 (COOSi), 141.89 (aromatic <u>C</u>-CH=CH_2), 136.01 (Ph<u>C</u>H=CH_2), 130.65 (aromatic carbon ortho to COOH),

126.02 (aromatic carbon ortho to $-CH=CH_2$), 116.32 ($Ph-CH=\underline{C}H_2$), 25.63 ($RCOOSi(CH_3)_2C(\underline{C}H_3)_3$), 17.81 ($RCOOSi(CH_3)_2\underline{C}(CH_3)_3$), -4.78 ($RCOOSi(\underline{C}H_3)_2C(CH_3)_3$).

4. Hydroboration of Trimethylsilyl Esters

a. Hydroboration of Trimethylsilyl 10-Undecenoate with Excess BH_3·THF at -30°C: General Procedure

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) was added to the flask by syringe, and cooled to -30°C (bromobenzene-dry ice bath). A cooled solution (-30°C) of BH_3·THF (1 M, 5 mmol) was introduced slowly over a 10 minute period, and the reaction mixture stirred at -30°C for 2 hours. At -30°C, the reaction was quenched by adding acetone (5 mL) and then water (5 mL). Aqueous sodium hydroxide (3 M, 1.67 mL) and hydrogen peroxide (30%, 1.5 mL) were added sequentially. The contents were heated for 1 hr at 50°C, and then cooled to room temperature. The acetone was removed under reduced pressure, the pH adjusted to 10 with 1 N NaOH, and the mixture was washed with ether (3x25 mL). The aqueous layer was acidified (pH 2) with 1 N HCl, saturated with NaCl, and the product extracted into ether (3x25 mL). The combined

ethereal layers were dried (Na_2SO_4), filtered, and the solvent removed to give 0.92 g (91%) of 11-hydroxyundecanoic acid, which was determined by NMR spectroscopy to be essentially pure. Recrystallization from ether-petroleum ether afforded 0.80 g (80%) of a white powder; mp 69-70°C [lit[551] 70°C]; ^{1}H-NMR ($CDCl_3$): δ 6.55 (s, 2H, OH), 3.64 (t, 2H, J=6.6Hz, RC<u>H</u>$_2$OH), 2.33(t, 2H, J=7.0Hz, RC<u>H</u>$_2$COOH), 1.8-1.1 (m, 16H); ^{13}C-NMR ($CDCl_3$): δ 179.33 (<u>C</u>OOH), 63.01 (R<u>C</u>H$_2$OH), 34.11, 32.62, 29.51, 29.37, 29.21, 29.07, 25.74, 24.77.

b. <u>Hydroboration of Trimethylsilyl 10-Undecenoate with Excess BH_3·THF at -30°C</u>

Reaction of trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) with BH_3·THF (1 <u>M</u>, 5 mmol) at -30°C (bromobenzene-dry ice bath) according to the general procedure for 30 minutes, followed by oxidation with aqueous sodium hydroxide (3 <u>M</u>, 1.67 mL) and hydrogen peroxide (30%, 1.5 mL) for 1 hr at 50°C, gave, upon workup, 1.01 g of the crude product (approximately 20% unreacted olefinic acid by ^{1}H-NMR integration). Recrystallization from ether-petroleum ether afforded 0.80 g (80%) of 11-hydroxyundecanoic acid as a white powder; mp 69-70°C.

c. Hydroboration of Trimethylsilyl 10-Undecenoate with Excess BH_3·THF at -10°C

Reaction of trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) with BH_3·THF (1 M, 5 mmol) at -10°C (ice-acetone bath) according to the general procedure for 30 minutes, followed by oxidation with aqueous sodium hydroxide (3 M, 1.67 mL) and hydrogen peroxide (30%, 1.5 mL) for 1 hr at 50°C, gave, upon workup 0.70 g of the crude product. Recrystallization from ether-petroleum ether afforded 0.61 g (60%) of 11-hydroxyundecanoic acid as a white powder; mp 68-69°C.

d. Hydroboration of Trimethylsilyl 10-Undecenoate with Excess BH_3·THF at 0°C

Reaction of trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) with BH_3·THF (1 M, 10 mmol) at 0°C (ice bath) according to the general procedure for 40 minutes, followed by oxidation with aqueous sodium hydroxide (3 M, 3.34 mL) and hydrogen peroxide (30%, 3.0 mL) for 1 hr at 50°C, gave, upon workup, 0.69 g of the crude product. Recrystallization from ether-petroleum ether afforded 0.68 g (68%) of 11-hydroxyundecanoic acid as a white powder; mp 68-69°C.

e. Hydroboration of Trimethylsilyl 10-Undecenoate with Excess BH_3·THF at 0-20°C

Reaction of trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) with BH_3·THF (1 M, 10 mmol) at 0°C (ice bath) according to the general procedure for 60 minutes (reaction temperature 20°C at end of one hour reaction period) followed by oxidation with aqueous sodium hydroxide (3 M, 3.34 mL) and hydrogen peroxide (30%, 3.0 mL) for 1 hr at 50°C, gave, upon workup, 0.60 g of the crude product. Recrystallization from ether-petroleum ether afforded 0.58 g (57%) of 11-hydroxyundecanoic acid as a white powder; mp 67-69°C.

f. Hydroboration of Trimethylsilyl 10-Undecenoate with a Stoichiometric Amount of BH_3·THF: General Procedure

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) and anhydrous THF (20 mL) were added to the flask by syringe, and cooled to 0°C (ice salt bath). A cooled solution (0°C) of BH_3·THF (1 M, 1.67 mmol) was introduced slowly, and the contents stirred for seven hours, during which time the reaction mixture was allowed to come to room temperature. The flask was cooled to 0°C, and

aqueous sodium hydroxide (3 M, 560 µL) and hydrogen peroxide (30%, 500 µL) added sequentially; the contents were then heated for 1 hr at 50°C, and cooled to room temperature. The aqueous mixture was saturated with salt, and the THF layer was separated. The aqueous layer was extracted with THF (3x25 mL), and the combined ether layers were dried ($MgSO_4$). Filtration, followed by removal of the solvent, gave 1.11 g of the crude product, which was a mixture the desired hydroxyalkanoic acid, unreacted olefinic acid, and diol. Recrystallization from ether-petroleum ether afforded 0.60 g (59%) of a white powder; mp 64-65°C [lit[551] 70°C]; ^{1}H-NMR ($CDCl_3$): δ 6.55 (s, 2H, OH), 3.64 (t, 2H, J=6.6Hz, $RC\underline{H}_2OH$), 2.33(t, 2H, J=7.0Hz, $RC\underline{H}_2COOH$), 1.8-1.1 (m, 16H); ^{13}C-NMR ($CDCl_3$): δ 179.33 ($\underline{C}OOH$), 63.01 ($R\underline{C}H_2OH$), 34.11, 32.62, 29.51, 29.37, 29.21, 29.07, 25.74, 24.77.

g. Hydroboration of Trimethylsilyl 10-Undecenoate with a Stoichiometric Amount of BH_3·DMS: General Procedure

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) was added to the flask by syringe, and cooled to 0°C (ice salt bath). A cooled solution (0°C) of BMS (1 M, 1.67 mmol, 180 µL) was introduced slowly, and

the contents stirred for twelve hours, during which time the reaction mixture was allowed to come to room temperature. The flask was cooled to 0°C, aqueous sodium hydroxide (3 M, 560 µL) and hydrogen peroxide (30%, 500 µL) added sequentially, and the contents were heated for 1 hr at 50°C and then cooled to room temperature. The aqueous mixture was made basic (pH 10) with 1 N NaOH, and extracted with ether (3x25 mL). The combined ether layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to afford no product (No diol!). The aqueous layer was acidified with 1 N HCl to pH 2 (care must be exercised to avoid esterification of the hydroxyalkanoic acid) and the precipitated product filtered and washed with petroleum ether to give 0.76g of the crude product. Recrystallization from ether-petroleum ether afforded 0.63 g (62%) of 11-hydroxyundecanoic acid as a white powder; mp 67-68°C [lit[551] 70°C]; ^{1}H-NMR ($CDCl_3$): δ 6.55 (s, 2H, OH), 3.64 (t, 2H, J=6.6Hz, $RC\underline{H}_2OH$), 2.33 (t, 2H, J=7.0Hz, $RC\underline{H}_2COOH$), 1.8-1.1 (m, 16H); ^{13}C-NMR ($CDCl_3$): δ 179.33 ($\underline{C}OOH$), 63.01 ($R\underline{C}H_2OH$), 34.11, 32.62, 29.51, 29.37, 29.21, 29.07, 25.74, 24.77. The filtrate was saturated with salt and extracted with THF (3x25 mL), and the combined THF layers dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent, gave 0.34 g of unreacted 10-undecenoic acid; ^{1}H-NMR ($CDCl_3$): δ 10.48 (br, COOH), 6.05-5.5 (m, 1H, J_{ab}=6.6Hz,

$H_2C{=}C\underline{H}_aCH_bR$), 5.1-4.75 (m, 2H, J_{trans}= 17.1Hz, J_{cis}=9.2Hz, $\underline{H}_2C{=}CHCH_2R$), 2.29 (t, 2H, J=7.0 Hz, $C\underline{H}_2COOH$), 2.15-1.85 (m, 2H, $H_2C{=}CHC\underline{H}_2R$), 1.75-1.1 (broad envelope, 12H); ^{13}C-NMR ($CDCl_3$): δ 180.03 ($\underline{C}OOH$), 139.02 ($H_2C{=}\underline{C}HR$), 114.12 ($H_2\underline{C}{=}CH$-R), 34.08, 33.76, 33.01, 29.48, 29.24, 29.18, 29.02, 28.89, 24.65.

h. Hydroboration of Trimethylsilyl 10-Undecenoate with a Stoichiometric Amount of BH_3·DMS: -30 → -5°C

Reaction of trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) with BH_3·THF (1 M, 10 mmol) at -30°C (bromobenzene-dry ice bath) according to the general procedure for 10 minutes and then at -5°C for 4 days (freezer), followed by oxidation with aqueous sodium hydroxide (3 M, 3.34 mL) and hydrogen peroxide (30%, 3.0 mL) for 1 hr at 50°C, gave, upon workup, 0.99 g of the crude product. Recrystallization from ether-petroleum ether afforded 0.85 g (84%) of 11-hydroxyundecanoic acid as a white powder; mp 66-67°C.

i. Hydroboration of Trimethylsilyl 10-Undecenoate with a Stoichiometric Amount of BH_3·DMS: -30 → 25°C

Reaction of trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) with BH_3·THF (1 M, 10 mmol) at -30°C bromobenzene-dry ice bath) according to the general procedure for 10 minutes, at -5°C for 4 hours, and then for an additional 18

hours with gradual warming to room temperature, gave following oxidation for 1 hour at 50°C with aqueous sodium hydroxide (3 M, 3.34 mL) and hydrogen peroxide (30%, 3.0 mL) and workup, 1.01 g (99%) of the crude product. Recrystallization from ether-petroleum ether afforded 0.73 g (72%) of 11-hydroxyundecanoic acid as a white powder; mp 68-69°C.

j. Hydroboration of Trimethylsilyl 10-Undecenoate with Excess BH_3·DMS: General Procedure

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) was added to the flask by syringe, and cooled to -5°C (ice-salt bath). A cooled solution (0°C) of BH_3·THF (1 M, 5 mmol) was introduced slowly over a 10 minute period, and the reaction mixture stirred at -5°C for 0.5 hours. At -5°C, the reaction was quenched by adding acetone (5 mL) and then water (5 mL). Aqueous sodium hydroxide (3 M, 1.67 mL) and hydrogen peroxide (30%, 1.5 mL) were added sequentially, and the contents were heated for 1 hr at 50°C, and then cooled to room temperature. The acetone was removed under reduced pressure, the pH adjusted to a value of 10 with 1 N NaOH, and the mixture was washed with ether (3x25 mL). The aqueous layer (ice was added to

hinder esterification) was acidified (pH = 2) with 1 N HCl, upon which a white precipitate formed. Filtration of the precipitate, followed by washing with petroleum ether and drying, afforded 0.80 g (80%) of the crude product, which was essentially pure. Recrystallization from ether-petroleum ether afforded 0.76 g (76%) of 11-hydroxyundecanoic acid as a white powder; mp 69-70°C [lit[552] 70°C].

k. Hydroboration of Trimethylsilyl 10-Undecenoate with 9-Borabicyclononane

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl 10-undecenoate (5 mmol) was added to the flask by syringe, and cooled to -10°C (salt-ice bath). A cooled solution (0°C) of 9-BBN (5 mmol) was introduced slowly over a 10 minute period, and the reaction mixture gradually allowed to come to room temperature over a 4 hour period. The flask was cooled to 0°C, and then sodium hydroxide (3 M, 1.67 mL) and hydrogen peroxide (30%, 1.5 mL) added sequentially. The mixture was heated for 1 hr at 50°C, and then cooled to room temperature. The pH was adjusted to a value of 10 and the mixture was washed with ether (3x25 mL). The aqueous layer was acidified (pH 2) with 1 N HCl, saturated with NaCl, and the product

extracted into ether (3x25 mL). The combined ethereal layers were dried (Na_2SO_4), filtered, and the solvent removed to give 0.96 g (95%) of 11-hydroxyundecanoic acid, which was essentially pure. Recrystallization from ether-petroleum ether afforded 0.84 g (83%) of a white powder; mp 68-69°C [lit[557] 70°C]; ^{1}H-NMR ($CDCl_3$): δ 6.55 (s, 2H, OH), 3.64 (t, 2H, J=6.6Hz, $RC\underline{H}_2OH$), 2.33 (t, 2H, J=7.0Hz, $RC\underline{H}_2COOH$), 1.8-1.1 (m, 16H); ^{13}C-NMR ($CDCl_3$): δ 179.33 ($\underline{C}OOH$), 63.01 ($R\underline{C}H_2OH$), 34.11, 32.62, 29.51, 29.37, 29.21, 29.07, 25.74, 24.77.

1. Hydroboration of Trimethylsilyl 10-Undecenoate with Disiamylborane

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar, dry ice condenser, and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. 2-Methyl-2-butene (10 mmol, 2.5 M solution in anhydrous THF) and anhydrous THF (5 mL) were added to the flask, and cooled to -15°C (ice-acetone bath). BH_3·THF (5 mmol, 1 M) was added slowly, and the resulting mixture stirred for 2 hours at -15°C. Trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) was added slowly at -15°C, and the mixture gradually allowed to come to room temperature and stirred for 12 hours. After cooling to 0°C, sodium hydroxide (3 M, 1.67

mL) and hydrogen peroxide (30%, 1.5 mL) were added sequentially, and the mixture was then heated for 1 hr at 50°C. After cooling to room temperature, the pH was adjusted to a value of 10 with 1 N NaOH and extracted with ether (3x25 mL). The aqueous layer was acidified (pH = 2) with 1 N HCl, saturated with NaCl, and the product extracted into ether (3x25 mL). The combined ethereal layers were dried (Na_2SO_4), filtered, and the solvent removed to give 0.97 g (96%) of 11-hydroxyundecanoic acid. Recrystallization from ether-petroleum ether afforded 0.83 g (82%) of the hydroxyalkanoic acid as a white powder; mp 68-69°C.

m. Hydroboration of Trimethylsilyl 10-Undecenoate with Dicyclohexylborane

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar, dry ice condenser, and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Cyclohexene (10.96 mmol, 0.90 g) was introduced by syringe and the contents of the flask cooled to -10°C (ice-acetone bath). BH_3·THF (5 mmol, 1 M) was added slowly, and the resulting mixture stirred for 3 hours at 0°C (dicyclohexylborane precipitates from solution). Trimethylsilyl 10-undecenoate (5.47 mmol, 1.40 g, 1.61 mL) was slowly added, and the resulting mixture was stirred at 0°C for two hours, then

allowed gradually to come to room temperature and stirred for an additional 7 hours. The reaction mixture was cooled to 0°C, and aqueous sodium hydroxide (3 M, 1.82 mL) and hydrogen peroxide (30%, 1.64 mL) added sequentially. The reaction mixture was heated for 1 hr at 45°C, adjusted to pH = 10 with 1 N NaOH, and extracted with ether (3x25 mL). The aqueous layer was acidified (pH = 2) with 1 N HCl, saturated with NaCl, and the product extracted into ether (3x25 mL). The combined ethereal layers were dried (Na_2SO_4), filtered, and the solvent removed to give 1.02 g (93%) of 11-hydroxyundecanoic acid, which was essentially pure. Recrystallization from ether-petroleum ether afforded 0.83 g (82%) of the hydroxyalkanoic acid as a white powder; mp 68-69°C.

n. Hydroboration of Trimethylsilyl 10-Undecenoate with Thexylborane

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar, dry ice condenser, and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. BH_3·THF (5 mmol, 1 M) was introduced by syringe, the contents cooled to -15°C (ice-acetone bath), and then a solution of 2,3-dimethyl-2-butene (2.5 M, 1.0 mL) in anhydrous THF was slowly added. The reaction mixture was stirred for 2 hours, while maintaining the temperature between -15 - 0°C.

Trimethylsilyl 10-undecenoate (5.0 mmol, 1.28 g, 1.47 mL) was slowly added and stirred at 0°C for two hours, then allowed to gradually come to room temperature and stirred for an additional 12 hours. The flask was cooled to 0°C, and aqueous sodium hydroxide (3 M, 2.5 mmol) and hydrogen peroxide (30%, 7.5 mmol) added sequentially. The reaction mixture was heated to 50°C for one hour, adjusted to pH = 10 with 1 N NaOH, and extracted with ether (3x25 mL). The aqueous layer was acidified (pH 2) with 1 N HCl, saturated with NaCl, and the product extracted into ether (3x25 mL). The combined ether layers were dried (Na_2SO_4), filtered, and the solvent removed to give 1.01 g (98%) of 11-hydroxyundecanoic acid. Recrystallization from ether-petroleum ether afforded 0.84 g (83%) of the hydroxyalkanoic acid as a white powder; mp 70°C.

o. Hydroboration of Trimethylsilyl 10-Undecenoate with Catecholborane

A 250 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl 10-undecenoate (5.0 mmol, 1.28 g, 1.47 mL) was introduced by syringe, catecholborane (6.78 mmol, 0.89 g, 0.69 mL) slowly added at room temperature, and the mixture heated to 110°C

for 24 hours. The reaction mixture was cooled to 0°C, treated sequentially with aqueous sodium hydroxide (3 M, 6.78 mmol) and hydrogen peroxide (30%, 5 mmol), and then heated to 45°C for one hour. The reaction mixture was made basic (pH = 10) with 1 N NaOH, and extracted with ether (3x25 mL). The aqueous layer was separated, acidified (pH = 2) with 1 N HCl, saturated with NaCl, and the product extracted into ether (3x25 mL). The combined ether layers were washed with ice water (10x100 mL) to remove any remaining catechol. The ether layer was then dried (Na_2SO_4), filtered, and the solvent removed to give 0.72 g (71%) of 11-hydroxyundecanoic acid. Recrystallization from ether-petroleum ether afforded 0.61 g (60%) of the hydroxyalkanoic acid as a white powder; mp 70-71°C.

p. Hydroboration-Oxidation of Trimethylsilyl cis-9-Octadecenoic Acid with 9-BBN

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl oleate (4.62 mmol, 1.64g) was added to the flask by syringe, and cooled to -10°C (salt-ice bath). A cooled solution (0°C) of 9-BBN (4.62 mmol, 0.41 M) was introduced slowly over a 10 minute period, and the reaction mixture gradually allowed to come

to room temperature over a 4 hour period; the contents were then stirred for an additional 8 hours at room temperature. Intermediate ^{11}B-NMR analysis of the reaction mixture showed the presence of peaks at 89 and 58 ppm indicating the formation of trialkylborane and unreacted 9-BBN. The flask was cooled to 0°C, and then sodium hydroxide (3 M, 1.67 mL) and hydrogen peroxide (30%, 1.5 mL) were added sequentially. The mixture was heated for 1 hr at 50°C, and then cooled to room temperature. The pH was adjusted to a value of 10 and the mixture was washed with ether (3x25 mL). The combined ether layer was dried, filtered and the solvent removed to give 0.37 g (37%) of a light yellow oil, which solidified upon standing. Analysis of this by-product by NMR spectroscopy revealed that only cyclooctanediol was present. ^{13}C-NMR ($CDCl_3$): δ 71.41 (CHOH), 36.09 (α-CH_2), 20.13 (β-CH_2). The aqueous layer was acidified (pH = 2) with 1 N HCl, saturated with NaCl, and the product extracted into ether (3x25 mL). The combined ethereal layers were dried (Na_2SO_4), filtered, and the solvent removed to give 1.29 g (93%) of a mixture of the two hydroxyalkanoic acid products and unreacted oleic acid (74:26 ratio by ^{1}H-NMR), along with some of the remaining cyclooctandiol. Recrystallization from petroleum ether afforded 0.64 g (47%) of 9- and 10-hydroxyoctadecenoic acid as a white powder; ^{1}H-NMR ($CDCl_3$): δ 5.74 (s, 2H, OH), 3.59 (m, 1H, $R_2C\underline{H}OH$), 2.36 (t,

2H, J=7.0Hz, $RC\underline{H}_2COOH$), 1.8-1.1 (broad envelope, 28H) 0.88 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 179.27 ($\underline{C}OOH$), 72.19 ($R_2\underline{C}HOH$), 37.45, 36.25, 34.14, 31.97, 29.78, 29.67, 29.40, 29.21, 29.07, 25.68, 24.77, 22.74, 20.08, 14.18 (CH_3).

q. Hydroboration-Oxidation of Trimethylsilyl-cis-9-Octadecenoic Acid with Dicyclohexylborane

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Cyclohexene (10.0 mmol, 0.82 g, 1.01 mL) was introduced by syringe and the contents of the flask cooled to -10°C (ice-acetone bath). BH_3·THF (5 mmol, 1 M) was added slowly, and the resulting mixture stirred for 3 hours at 0°C (dicyclohexylborane precipitates from solution). Trimethylsilyl oleate (5.0 mmol, 1.77g), was slowly added and stirred at 0°C for two hours, then allowed to come gradually to room temperature and stirred for an additional 4 hours. The flask was cooled to 0°C, sodium hydroxide (3 M, 1.67 mL) and hydrogen peroxide (30%, 1.5 mL) were added sequentially, and the mixture was heated for 1 hr at 50°C. After cooling to room temperature, the reaction mixture was made basic (pH = 10) with 1 N NaOH and then washed with ether (3x25 mL). The combined ether layer was dried, filtered, and the solvent removed to give 1.00 g

(99%) of a light yellow oil. Analysis of this by-product by NMR spectroscopy revealed that only cyclohexanol was present. ^{13}C-NMR ($CDCl_3$): δ 69.76 (CHOH), 35.20 (α-CH_2), 25.34 (Γ-CH_2), 24.06 (ß-CH_2). The aqueous layer was acidified (pH = 2) with 1 N HCl, saturated with NaCl, and the product extracted into ether (3x25 mL). The combined ethereal layers were dried (Na_2SO_4), filtered, and the solvent removed to give 1.50 g (99%) of a mixture of the two hydroxyalkanoic acid products and unreacted oleic acid (75:25 ratio by ^{1}H-NMR). Recrystallization from petroleum ether afforded 0.84 g (56%) of 9- and 10-hydroxyoctadecenoic acid as a white powder; ^{1}H-NMR ($CDCl_3$): δ 5.74 (s, 2H, OH), 3.59 (m, 1H, $R_2C\underline{H}OH$), 2.36 (t, 2H, J=7.0Hz, $RC\underline{H}_2COOH$), 1.8-1.1 (broad envelope, 28H) 0.88 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 179.27 ($\underline{C}OOH$), 72.19 ($R_2\underline{C}HOH$), 37.45, 36.25, 34.14, 31.97, 29.78, 29.67, 29.40, 29.21, 29.07, 25.68, 24.77, 22.74, 20.08, 14.18 (CH_3).

r. Hydroboration-Oxidation of Trimethylsilyl-cis-9-Octadecenoic Acid with BMS

A 50 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl oleate (2.5 mmol, 0.89 g, 1.00 mL) was introduced by syringe and the

contents of the flask cooled to -20°C (ice-acetone bath). BH_3·DMS (2.5 mmol, 10 M, 272 µL) was added slowly, and the resulting mixture stirred for 1 hour at -20 - 0°C. At 0°C, the reaction was quenched by the slow addition of water (5 mL); sodium hydroxide (3 M, 0.83 mL) and hydrogen peroxide (30%, 0.25 mL) were added sequentially, and the resulting mixture was heated for 1 hr at 50°C. After cooling to room temperature, the reaction mixture was made basic (pH = 10) with 1 N NaOH and then washed with ether (3x25 mL). The combined ether layer was dried filtered and the solvent removed. No by-product was recovered from this layer (no diol!). The separated aqueous layer was acidified (pH = 2) with 1 N HCl, saturated with NaCl, and the product extracted into ether (3x25 mL). The combined ethereal layers were dried (Na_2SO_4), filtered, and the solvent removed to give 0.78 g (99%) of a mixture of the two hydroxyalkanoic acid products and a small amount of unreacted oleic acid (80:20 ratio by ^{1}H-NMR). Recrystallization from petroleum ether afforded 0.55 g (73%) of 9- and 10-hydroxyoctadecenoic acid as a white powder; ^{1}H-NMR ($CDCl_3$): δ 5.74 (s, 2H, OH), 3.59 (m, 1H, $R_2C\underline{H}OH$), 2.36 (t, 2H, J=7.0Hz, $RC\underline{H}_2COOH$), 1.8-1.1 (broad envelope, 28H) 0.88 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 179.27 ($\underline{C}OOH$), 72.19 ($R_2\underline{C}HOH$), 37.45, 36.25, 34.14, 31.97, 29.78, 29.67, 29.40, 29.21, 29.07, 25.68, 24.77, 22.74, 20.08, 14.18 (CH_3).

s. Hydroboration-Oxidation of Trimethylsilyl 4-Pentenoate with 9-BBN: Synthesis of Silver 5-Hydroxypentanoate

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl 4-pentenoate (4.82 mmol, 0.83 g) was added to the flask by syringe, and cooled to -20°C (ice-acetone bath). A cooled solution (0°C) of 9-BBN (9.64 mmol, 0.50 M) was introduced slowly over a 10 minute period, and the reaction mixture was stirred at 0°C for two hours, gradually allowed to come to room temperature over a 2 hour period, then stirred for an additional 8 hours at room temperature. The flask was cooled to 0°C, sodium hydroxide (3 M, 1.60 mL) and hydrogen peroxide (30%, 1.45 mL) added sequentially, and the resulting mixture was heated for 1 hr at 50°C. After cooling to room temperature, the pH was adjusted to 10 with 1 N NaOH and the mixture extracted with ether (3x25 mL). The combined ether layer was dried, filtered, and the solvent removed to give 0.20 g (19%) of a light yellow oil. Analysis of this by-product by NMR spectroscopy revealed that cyclooctanediol was present, along with a small amount of what appears to be 1,4-pentanediol resulting from reduction; ^{13}C-NMR ($CDCl_3$): [cyclooctanediol]: δ 71.41 (CHOH), 36.09 (α-CH_2), 20.13 (β-CH_2); [1,4-pentanediol]: 72.25 (CHOH), 29.72, 28.28, 25.26. The

aqueous layer was evaporated to dryness and the residue analyzed by ^{13}C-NMR spectroscopy, revealing that the sodium salt of the hydroxyalkanoic acid was present, along with cyclooctanediol; ^{13}C-NMR (D_2O, DMSO internal reference): δ 183.84 (COO^-), 62.04 (CH_2OH), 37.93, 31.91, 22.87. The solid residue was dissolved in water (50 mL) and solid $AgNO_3$ (0.94 g, 5.53 mmol) added. The greyish black precipitate which formed was filtered, washed with water, and dried (vacuum oven) to give 0.60 g (56%) of 5-hydroxypentanoic acid as its silver salt.

t. Hydroboration-Oxidation of Trimethylsilyl 4-Pentenoate with 9-BBN: Synthesis of 4-Hydroxypentanoic Acid

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl 4-pentenoate (4.82 mmol, 0.83 g) was added to the flask by syringe, which was cooled to -20°C (ice-acetone bath). A cooled solution (0°C) of 9-BBN (9.64 mmol, 0.50 M) was introduced slowly over a 10 minute period, and the reaction mixture was stirred at 0°C for two hours, gradually allowed to come to room temperature over a 2 hour period, then stirred for an additional 6 hours at room temperature. The flask was cooled to 0°C, sodium hydroxide (3 M, 1.60 mL) and hydrogen

peroxide (30%, 1.45 mL) added sequentially, and the resulting mixture was heated for 1 hr at 50°C. After cooling to room temperature, the pH was adjusted to a value of 10 with 1 N NaOH and the mixture extracted with ether (3x25 mL). The combined ether layer was dried, filtered, and the solvent removed to give 0.41 g (67%) of a light yellow oil. NMR analysis of this by-product revealed that cyclooctanediol was present, along with a small amount of diol. The aqueous layer was evaporated to dryness and the residue analyzed by ^{13}C-NMR spectroscopy, revealing that the sodium salt of the hydroxyalkanoic acid was present, along with cyclooctanediol; ^{13}C-NMR (D_2O, DMSO internal reference): δ 183.84 (COO^-), 62.04 (CH_2OH), 37.93, 31.91, 22.87. The solid residue was dissolved in water (50 mL), washed with ether (3x25 mL), acidified to pH = 3 with 1 N HCl, and the product extracted into ether. The combined ether layer was dried, filtered, and the solvent removed to give 0.41 (82%) of 4-hydroxypentanoic acid; ^{13}C-NMR ($CDCl_3$): δ 175.8 (COOH), 62.37 (CH_2OH), 34.46 ($\underline{C}H_2COOH$), 32.76 ($\underline{C}H_2CH_2OH$), 22.33 ($\underline{C}H_2CH_2COOH$).

u. Hydroboration-Oxidation of Trimethylsilyl 3-Cyclohexene-1-Carboxylate with Excess BMS

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury

bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl 3-cyclohexene-1-carboxylate (2.37 mmol, 0.47 g) was introduced by syringe and the contents of the flask cooled to -20°C (ice-acetone bath). BH_3·DMS (4.74 mmol, 10 M, 474 µL) was added slowly, and the resulting mixture stirred for 1.5 hours, while allowing the contents to gradually warm to 0°C. At 0°C, the reaction was quenched by the slow addition of water (2 mL); sodium hydroxide (3 M, 1.6 mL) and hydrogen peroxide (30%, 0.25 mL) were added sequentially, and the resulting mixture was heated for 1 hr at 50°C. After cooling to room temperature, the reaction mixture was made basic (pH = 10) with 1 N NaOH and then washed with ether (3x25 mL). The combined ether layer was dried, filtered, and the solvent evaporated in vacuo. No by-product remained from this extraction. The separated aqueous layer was evaporated to dryness and the residue analyzed by ^{13}C-NMR spectroscopy, revealing that the sodium salt of the four possible hydroxyalkanoic acids was present; ^{13}C-NMR (D_2O, benzene-d_6 external reference): δ 186.83 (COO^-), 186.61 (COO^-), 186.45 (COO^-), 71.33 (R_2CHOH), 71.18 (R_2CHOH), 68.19 (R_2CHOH), 68.19 (R_2CHOH), 47.04, 45.55, 42.08, 40.08, 39.59, 38.75, 36.74, 35.66, 34.96, 32.98, 29.97, 29.26, 28.37, 25.52, 24.47, 20.95. The solid residue was dissolved in water (40 mL) and solid $AgNO_3$ (0.35 g, 3.08 mmol) added. The greyish black precipitate

which formed was filtered, washed with water, and dried (vacuum oven) to give 0.30 g (51%) of a mixture of the hydroxyalkanoic acids as their silver salts.

v. Hydroboration-Oxidation of Trimethylsilyl 3-Cyclohexene-1-Carboxylate with a Near Stoichiometric Amount of BMS

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl 3-cyclohexene-1-carboxylate (4.74 mmol, 0.94 g) was introduced by syringe and the contents of the flask cooled to -20°C (ice-acetone bath). BH_3·DMS (2.37 mmol, 10 M, 172 µL) was added slowly, and the resulting mixture stirred for 2.5 hours, while allowing the contents to warm gradually to 0°C. At 0°C, the reaction was quenched by the slow addition of water (2 mL); sodium hydroxide (3 M, 1.6 mL) and hydrogen peroxide (30%, 0.25 mL) were added sequentially, and the resulting mixture was heated for 1 hr at 50°C. After cooling to room temperature, the reaction mixture was made basic (pH = 10) with 1 N NaOH and then washed with ether (3x25 mL). The combined ether layer was dried, filtered and the solvent evaporated under reduced pressure. No by-product remained from this extraction. The separated aqueous layer was evaporated to dryness and the residue analyzed by ^{13}C-NMR spectroscopy,

revealing that the sodium salt of the four possible the hydroxyalkanoic acids was present, along with some of the unreacted olefinic acid; ^{13}C-NMR (D_2O, CCl_4 internal reference): δ 185.70 (COO^-), 185.46 (COO^-), 185.32 (COO^-), 127.52 (olefinic), 126.68 (olefinic) 70.17 (R_2CHOH), 69.99 (R_2CHOH), 67.05 (R_2CHOH), 66.57 (R_2CHOH), 47.06, 45.96, 45.52, 44.44, 42.68, 41.03, 39.10, 38.67, 38.26, 37.86, 35.77, 34.72, 34.31, 34.01, 32.06, 31.52, 30.08, 28.89, 28.49, 28.24, 26.02, 25.86, 25.72, 24.67, 24.53, 23.47, 19.95. The solid residue was dissolved in water, which was adjusted to pH = 4 with 1 N HCl and extracted with ether. After drying the combined ether layers (Na_2SO_4), filtration, followed by removal of the solvent, gave, 0.31 g of a yellow oil, which was a mixture of unreacted olefinic acid and some of the desired hydroxyalkanoic acid products. The separated aqueous layer was saturated with sodium chloride, and extracted with THF (3x25 mL) to give after drying, filtration, and evaporation of the solvent, 0.39 g (57%) of the hydroxyalkanoic acids; ^{13}C-NMR ($CDCl_3$): δ 181.34 (COO^-), 180.97 (COO^-), 70.17 (R_2CHOH), 68.00 (R_2CHOH), 66.25 (R_2CHOH), 41.97, 37.88, 34.30, 32.57, 28.83, 26.96, 25.66, 23.63, 21.27.

w. Hydroboration-Oxidation of Bis(Trimethylsilyl) 5-Norbornene-endo-2,3-dicarboxylate

A 25 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. The flask was opened momentarily to introduce solid bis(trimethylsilyl) endo-5-norbornene-2,3-dicarboxylate (1.0 mmol, 0.32 g) and 9-BBN dimer [1.5 mmol (3.0 mmol in monomeric 9-BBN), 0.37 g], and the apparatus flushed with argon and the contents of the flask cooled to -20°C (ice-acetone bath). A cold solution (-20°C) of anhydrous THF (20 mL) was added, the contents were stirred for one hour at -20°C, and then gradually allowed to come to room temperature over a three hour period. At 0°C, the reaction was quenched by the slow addition of water (2 mL); sodium hydroxide (3 M, 1.0 mL) and hydrogen peroxide (30%, 0.70 mL) were added sequentially, and the resulting mixture was heated for 1 hr at 50°C. After cooling to room temperature, the reaction mixture was made basic (pH = 10) with 1 N NaOH and then washed with ether (3x25 mL). The combined ether layer was dried, filtered, and the solvent removed to give 0.48 g of a colorless oil, which was shown to be a mixture of 1,4-cyclooctandiol and some reduction products; ^{13}C-NMR ($CDCl_3$): δ 71.70 (endo C-OH), 71.55 (cyclooctanediol, C-OH), 70.68

(exo C-OH), 65.75 (CH_2OH), 36.22 cyclooctanediol, α-CH_2), 35.55, 32.16, 26.39, 26.13, 22.03, 20.30, 20.08 (cyclooctanediol, ß-CH_2), 15.13, 1.26 $(CH_3)_3SiOH$). The aqueous layer was acidified (pH = 3) with 1 N HCl, saturated with salt, and extracted with THF (3x20 mL). The combined THF layer was dried ($MgSO_4$), filtered, and the solvent removed to give a mixture of hydroxyalkanoic acids, 106 mg (53%), as a light yellow oil which were not separated; ^{13}C-NMR (acetone-d_6): δ 174.51 (br, COOH), 73.10 (br, endo C-OH's), 71.80 (br, exo C-OH's), 48.80, 48.50, 47.52, 46.55, 45.52, 40.78, 40.35, 37.61, 37.10, 36.72, 36.37, 35.37, 21.71 (br), 21.26.

x. Hydroboration-Oxidation of Bis(Trimethylsilyl) endo-5-Norbornene-2,3-dicarboxylate with a Stoichiometric Amount of BMS

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. The flask was opened momentarily to introduce solid bis(trimethylsilyl) endo-5-norbornene-2,3-dicarboxylate (2.0 mmol, 0.65 g) and the apparatus flushed with argon and the contents of the flask cooled to -20°C (ice-acetone bath). A cold solution (-20°C) of BMS (0.67 mmol, 10 M, 72 µL) was added, the

contents stirred for two hours at -20°C, and then gradually allowed to come to room temperature over a four hour period. The reaction mixture was cooled to 0°C, sodium hydroxide (3 M, 220 µL) and hydrogen peroxide (30%, 200 µL) sequentially added, and the resulting mixture was heated for 1 hr at 50°C. After cooling to room temperature, the reaction mixture was made basic (pH = 10) with 1 N NaOH and then washed with ether (3x25 mL). The combined ether layer was dried, filtered, and the solvent removed. No product was present in this layer. The aqueous layer was acidified (pH = 3) with 1 N HCl, saturated with sodium chloride, and extracted with ether (3x20mL). The combined ether layer was dried ($MgSO_4$), filtered, and the solvent removed to give unreacted endo-5-norbornene-2,3-dicarboxylate, 110 mg (30%), as a white solid; ^{13}C-NMR (acetone-d_6): δ 174.27 (COOH), 135.99 (olefinic C), 49.50 (bridge CH_2), 48.99, 47.64. The aqueous layer was then extracted with THF (3x25 mL), and the combined THF layer dried ($MgSO_4$), filtered, and solvent removed to give 5-hydroxynorbornyl endo-2,3-dicarboxylic acid (stereochemistry not assigned), along with some unreacted endo-5-norbornene-2,3-dicarboxylate, 280 mg (70%); ^{13}C-NMR (THF, benzene-d_6 external reference): δ 174.53 (COOH), 174.40 (COOH), 68.45 (C-OH), 48.17, 46.13, 44.60, 39.55, 37.25, 35.57.

5. Hydroboration of Trimethylsilyl Esters: Organoborane Transformations

a. Hydroboration/Iodination of Trimethylsilyl 10-Undecenoate with Dicyclohexylborane

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Cyclohexene (10 mmol, 0.82 g) was introduced by syringe and the contents of the flask cooled to -10°C (ice-acetone bath). BH_3·DMS (5 mmol, 10 M, 500 µL) was added slowly, and the resulting mixture stirred for 3 hours at 0°C (dicyclohexylborane precipitates from solution). Trimethylsilyl 10-undecenoate (5.0 mmol, 1.28 g, 1.47 mL) was slowly added and the solution stirred at 0°C for four hours, which was then allowed to come gradually to room temperature and stirred for an additional 7 hours. The reaction mixture was cooled to 0°C, and methanolic sodium acetate (1 M, 10 mmol), aqueous sodium iodide (1 M, 5 mmol), and methanolic chloramine T (0.5 M, 10 mmol) were sequentially added. The contents were stirred for one minute and quenched by addition of sodium thiosulfate (1 M, 5 mL), and 1.2 N HCl (5 mL). Water (20 mL) and petroleum ether (20 mL) were added, and the organic layer separated. The aqueous layer was extracted twice more with petroleum ether (20 mL portions), and the combined organic layer was dried ($MgSO_4$).

Filtration, followed by removal of the solvent under reduced pressure, gave the crude product as a white solid. Purification by column chromatography (silica gel, 10%, then 15% ethyl acetate-petroleum ether) afforded 11-iodoundecanoic acid, 1.38 g (88%), as a colorless oil, which solidified upon standing; mp 48-50°C [lit[71] 47-50°C]; ^{1}H-NMR ($CDCl_3$): δ 10.50 (COOH), 3.18 (t, 2H, J=7.0 Hz, CH_2I), 2.35 (t, 2H, J=6.5 Hz, $C\underline{H}_2COOH$), 2.05-1.1 (broad envelope, 16H); ^{13}C-NMR ($CDCl_3$): δ 180.30 (COOH), 34.08, 33.54, 30.48, 29.29, 29.15, 29.02, 28.48, 24.63, 7.24 (CH_2I).

b. Hydroboration/Protonolysis of Trimethylsilyl 10-Undecenoate

A 250 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) was added to the flask by syringe, and the contents were cooled to 0°C (ice salt bath). A cooled solution (0°C) of BMS (1 M, 1.67 mmol, 170 μL) was introduced slowly, and the resulting mixture was stirred for three hours, during which time the reaction mixture was allowed to warm gradually to 15°C. The flask was cooled to 0°C, anhydrous THF (10 mL) and propionic acid (10 mL) were added, and the contents refluxed at 125°C (oil

bath temperature) for four hours. The reaction mixture was extracted into ether (4x50 mL), and the combined ether layers were washed with 1.2 N HCl (50 mL) and dried over anhydrous $MgSO_4$. Filtration, followed by removal of the solvent, gave a yellow oil containing the product and propionic acid. Water (100 mL) was added, and the precipitated product was removed by filtration. The crude product was dissolved in ether, aqueous sodium hydroxide (1 M, 25 mL) was added, and the ether layer removed. The separated aqueous layer was acidified with 1.2 N HCl (pH = 3), and the product extracted into ether (3x25 mL). Filtration, followed by removal of the solvent under reduced pressure, gave 0.93 g of the crude acid. Recrystallization from methanol-water afforded, after drying under vacuum, undecanoic acid, 0.76 g (82 %), as a white solid; mp 28°C [lit[553] 28.5°C] ^{1}H-NMR ($CDCl_3$): δ 9.06 (br, 1H, COOH), 2.34 (t, 2H, J=7.0 Hz, $C\underline{H}_2COOH$), 1.8-1.1 (broad envelope, 16 H), 0.87 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 180.25 (COOH), 34.16, 31.95, 29.62, 29.51, 29.34, 29.12, 24.74, 22.73, 14.15 (CH_3).

c. Hydroboration/Iodination of Trimethylsilyl-4-Pentenoate

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to

cool under a stream of argon. Cyclohexene (4 mmol, 0.33 g) was introduced by syringe and the contents of the flask cooled to -10°C (ice-acetone bath). BH_3·THF (2 mmol, 1 M, 2 mL) was added slowly, and the resulting mixture stirred for 3 hours at 0°C (dicyclohexylborane precipitates from solution). Trimethylsilyl 4-pentenoate (2.0 mmol, 0.35 g, 0.44 mL) was slowly added to the flask and the solution stirred at 0°C for two hours, and then gradually allowed to come to room temperature. The contents were stirred for an additional 2 hours at room temperature. The reaction mixture was cooled to 0°C, shielded from light by wrapping the flask with aluminum foil, and sodium acetate (1 M in anhydrous methanol, 4 mmol) and iodine monochloride (1 M in anhydrous methanol, 2 mmol) were sequentially added. The contents were stirred for one minute and quenched by addition of sodium thiosulfate (1 M, 5 mL). The reaction mixture was adjusted to pH = 10 with 1 N NaOH, water (20 mL) and ether (20 mL) were added, the reaction mixture saturated with salt, and the organic layer separated. The aqueous layer was washed twice more with ether (20 mL portions), acidified to pH = 3 with 1 N HCl, and extracted with ether (3x25 mL). The combined organic layer was then dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent under reduced pressure, gave the crude product. Purification by column chromatography

(silica gel, solvent gradient, 10%, then 15%, then 20% ethyl acetate-petroleum ether) afforded 5-iodopentanoic acid, 0.27 g (76%), as a colorless oil, along with a minor inseparable unknown impurity; ^{1}H-NMR ($CDCl_3$): δ 6.2 (br, COOH), 3.19 (t, 2H, J=6.6 Hz, CH_2I), 2.39 (t, 2H, J=6.6 Hz, $C\underline{H}_2COOH$), 2.05-1.5 (m, 4H); ^{13}C-NMR ($CDCl_3$): δ 178.60 (COOH), 32.87 ($-\underline{C}H_2COOH$), 32.68 ($R\underline{C}H_2CH_2I$), 25.63 ($R\underline{C}H_2CH_2COOH$), 5.67 ($CH_2I$).

d. Hydroboration/Iodination of Trimethylsilyl-4-Pentenoate Using the Sodium Iodide/Chloramine T Reagent

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. Cyclohexene (4 mmol, 0.33 g) was introduced by syringe and the contents of the flask cooled to -10°C (ice-acetone bath). BH_3·THF (2 mmol, 1 M, 2 mL) was added slowly, and the resulting mixture stirred for 3 hours at 0°C (dicyclohexylborane precipitates from solution). Trimethylsilyl 4-pentenoate (2.0 mmol, 0.35 g, 0.44 mL) was slowly added, and the resulting mixture stirred at 0°C for two hours. Then the reaction mixture was gradually allowed come to room temperature and stirred for an additional 2 hours. The reaction mixture was cooled to 0°C, shielded from light by wrapping the flask with aluminum

foil, and sodium acetate (1 M in anhydrous methanol, 4 mmol), aqueous sodium iodide 1 M, 2 mmol), and methanolic chloramine T (0.5 M, 4 mmol) were sequentially added. The contents were stirred for one minute and quenched by addition of sodium thiosulfate (1 M, 5 mL). The reaction mixture was adjusted to pH = 10 with 1 N NaOH, water (20 mL) and ether (20 mL) were added, the reaction mixture saturated with sodium chloride, and the organic layer separated. The aqueous layer was extracted twice more with ether (20 mL portions), and the combined organic layer was dried ($MgSO_4$). Filtration, followed by removal of the solvent under reduced pressure, gave the crude product. Attempted purification by column chromatography proved fruitless as the product and the chloramine sulfonamide by-product eluted together. Thus, although only one spot was present on TLC analysis of the crude product mixture, no yield could be determined.

e. Hydroboration of Trimethylsilyl 10-undecynoate with Catecholborane

An oven dried 250 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar and gas outlet, flame dried, and purged with nitrogen. Trimethylsilyl 10-undecynoate (4.82 mmol, 1.23 g), was introduced to the flask, followed by the slow addition of catecholborane (4.82 mmol, 0.51 mL). The contents were

stirred at 40°C for 19 hours. Water (150 mL) was added and the mixture stirred overnight to hydrolyze the boronic ester. The aqueous layer was decanted off, the solid boronic acid dissolved in ether, washed with cold water (2x50 mL), and the product precipitated by addition of petroleum ether. The product was redissolved in ether and crystallized by the addition of petroleum ether to afford 0.96 g (87%) of 10-undecenylboronic acid as a white powder. ^{1}H-NMR (DMSO-d_6): 11.8 (br, COOH), 6.65-6.2 (m, 1H, $(HO)_2BHC=C\underline{H}R$)), 5.45-5.15 (m, 1H, J_{trans}=18.0 Hz, $(HO)_2$-$B\underline{H}C=CHR$)), 2.3-1.8 (m, 4H, $(HO)_2BHC=CHC\underline{H}_2R$), $C\underline{H}_2COOH$), 1.7-1.1 (broad envelope, 12H); ^{13}C-NMR (DMSO-d_6): δ 174.50 (COOH), 150.01 ($(HO)_2BHC=\underline{C}HR$)), 35.08, 33.70, 28.66, 28.12, 24.55; ^{13}C-NMR (acetone-d_6): δ 175.74 (COOH), 152.20 ($(HO)_2BHC=\underline{C}HR$)), 36.76, 34.79, 30.67, 30.48, 30.4, 29.86, 26.15; ^{11}B-NMR (THF): 27.3.

6. Reduction of Trimethylsilyl Esters

a. Reduction of Trimethylsilyl Hexanoate: General Procedure

A 50 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar and gas outlet, flame dried, and purged with argon. Trimethylsilyl hexanoate (5.31 mmol, 1.0 g) was placed in the flask by syringe, and cooled to -23°C (carbon tetrachloride-dry ice bath). A

cold solution of $BH_3 \cdot THF$ (9.88 mmol, 1.0 M) at -23°C was added to the cold solution of the silyl ester, and the mixture stirred at -23°C for 30 minutes. At -23°C, the reaction was quenched by the slow addition of water (5 mL), and the contents allowed to come to room temperature. The reaction mixture was made basic (pH = 10) with 1 N NaOH and extracted with ether (3x10 mL). The combined ether layer was dried over anhydrous sodium sulfate, filtered, and the solvent removed to give 0.41 g (66%) of 1-hexanol; ^{13}C-NMR ($CDCl_3$): δ 62.74 (CH_2OH), 32.68 (ß-CH_2), 31.68 (δ-CH_2), 25.44 (Γ-CH_2), 22.62 ($CH_3\underline{C}H_2R$), 13.96 (CH_3). The aqueous layer was acidified with 1 N HCl (pH = 2) and extracted with ether (3x25 mL). The combined ether layers were dried (Na_2SO_4), filtered, and solvent removed to give 0.21 g (34%) of recovered hexanoic acid; ^{13}C-NMR ($CDCl_3$): δ 179.92 (COOH), 34.14 ($\underline{C}H_2COOH$), 31.38 (ß-CH_2), 24.50 (δ-CH_2), 22.33 (Γ-CH_2), 13.80 (CH_3).

b. Reduction of Trimethylsilyl Hexanoate with $BH_3 \cdot THF$ at -30°C, 30 Minutes

Reaction of trimethylsilyl hexanoate (5.31 mmol, 1.0 g) with $BH_3 \cdot THF$ at - 30°C (bromobenzene-dry ice bath) for 30 minutes according to the general procedure gave hexanol, 0.10 g (16%), and hexanoic acid, 0.52 g, (84%) upon workup.

c. Reduction of Trimethylsilyl Hexanoate with BH_3·THF at -30°C, 60 Minutes

Reaction of trimethylsilyl hexanoate (5.31 mmol, 1.0 g) with BH_3·THF at - 30°C (bromobenzene-dry ice bath) for 60 minutes according to the general procedure gave hexanol, 0.15 g (24%), and hexanoic acid, 0.45 g, (73%) upon workup.

d. Reduction of Trimethylsilyl Hexanoate with BH_3·THF at -20°C

Reaction of trimethylsilyl hexanoate (5.31 mmol, 1.0 g) with BH_3·THF at - 30°C (bromobenzene-dry ice bath) for 30 minutes according to the general procedure gave hexanol, 0.32 g (52%), and hexanoic acid, 0.28 g, (45%) upon workup.

e. Reduction of Trimethylsilyl Hexanoate with BH_3·THF at 25°C

Reaction of trimethylsilyl hexanoate (5.31 mmol, 1.0 g) with BH_3·THF at 0°C for 30 minutes according to the general procedure gave hexanol, 0.61 g (98%). No hexanoic acid was recovered.

f. Reduction of Trimethylsilyl Hexanoate with BH_3·THF: NMR Experiment:

To an oven dried NMR tube fitted with a septum cap and

flushed with argon was added trimethylsilyl hexanoate (2.27 mmol, 430 mg, 0.50 mL) and the tube cooled to -78°C. To this was added a cold solution of BH_3·THF (2.27 mmol, 1.0 M) at -78°C, and the progress of the reaction monitored by ^{11}B-NMR spectroscopy, while varying the reaction temperature from -60 → 37°C. After completion of the reaction, the contents of the tube were poured into a round-bottomed flask, and the mixture hydrolyzed by the slow addition of water (5 mL). The reaction mixture was made basic (pH = 10) with 1 N NaOH, and the product extracted into ether (3x20 mL). After drying the combined ether layers ($MgSO_4$), filtration, followed by removal of the solvent, afforded 1-hexanol, 231 mg (99%).

g. Reduction of Trimethylsilyl Hexanoate with BH_3·DMS: NMR Experiment:

To an oven dried NMR tube fitted with a septum cap and flushed with argon was added trimethylsilyl hexanoate (3.36 mmol, 690 mg) and the tube cooled to -78°C. To this was added a cold solution of BH_3·DMS (3.36 mmol, 9.27 M) at -78°C, and the progress of the reaction monitored by ^{11}B-NMR while varying the reaction temperature from -60 → 37°C. After completion of the reaction, the contents of the tube were poured into a round-bottomed flask, and the mixture hydrolyzed by the slow addition of water (5 mL). The

reaction mixture was made basic (pH = 10) with 1 N NaOH, and the product extracted into ether (3x20 mL). After drying of the combined ether layers ($MgSO_4$), filtration, followed by removal of the solvent, afforded 1-hexanol, 350 mg (95%). The aqueous layer was acidified to pH = 2 (1 N HCl), extracted with ether (3x20 mL), and then dried over anhydrous magnesium sulfate. Filtration followed by removal of the solvent afforded 20 mg of remaining hexanoic acid (5%).

h. Reduction of Trimethylsilyl 10-Undecenoate with Excess BH_3·THF: NMR Experiment:

In an oven dried NMR tube fitted with a septum cap and flushed with argon was placed trimethylsilyl 10-undecenoate (1.5 mmol, 385 mg, 0.44 mL) and the tube cooled to -78°C. To this was added a cold solution of BH_3·THF (3.0 mmol, 1.0 M) at -78°C, and the progress of the reaction monitored by ^{11}B-NMR spectroscopy while varying the reaction temperature from -60 → 37°C.

i. Reduction of Trimethylsilyl 10-Undecenoate with a Stoichiometric Amount of BH_3·THF: NMR Experiment:

To an oven dried NMR tube fitted with a septum cap and flushed with argon was added trimethylsilyl 10-undecenoate (6.0 mmol, 1.54 g, 1.77 mL) and the tube cooled to -78°C. To this was added a cold solution of BH_3·THF (2.0 mmol, 1.0

M) at -78°C, and the progress of the reaction monitored by ^{11}B-NMR spectroscopy while varying the reaction temperature from -60 → 37°C. After completion of the reaction, the contents of the tube were cooled to 0°C, aqueous sodium hydroxide (2 mmol, 3 M) and hydrogen peroxide (30%, 6 mmol) added, and the mixture heated at 50°C for one hour. After allowing the mixture to cool to room temperature, acidification of the mixture to pH = 2 with 1 N HCl gave a white precipitate, which was filtered, washed with petroleum ether, and dried. A 41% yield (0.51 g) of 11-hydroxyundecanoic acid was realized.

j. Reduction of Trimethylsilyl 10-Undecenoate with Excess BH_3·THF

A 250 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, and gas outlet, flame dried, and purged with nitrogen. Trimethylsilyl 10-undecenoate (5 mmol, 1.28 g, 1.47 mL) and anhydrous THF (20 mL) were added, and the contents cooled to 0°C. BH_3·THF (1.34 mmol, 1 M) was added and the contents stirred at 25°C overnight. The solution was cooled to 0°C, aqueous sodium hydroxide (6.7 mmol, 2.33 mL) and aqueous hydrogen peroxide (30%, 5 mmol, 500 µL) were added sequentially, and the contents stirred at 50°C for one hour. The reaction mixture was made basic (pH = 10) with 1 N NaOH, and

extracted with ether (3x25 mL). The combined ether layers were dried, filtered, and the solvent removed to afford 0.95 g (100%) of 1,11-undecanediol as a white solid; ^{1}H-NMR ($CDCl_3$): δ 4.0-3.6 (m, 6H, $C\underline{H}_2OH$, $O\underline{H}$, exchangeable proton evident by D_2O shake), 1.9-1.1 (broad envelope, 18H); ^{13}C-NMR ($CDCl_3$): δ 62.20 (CH_2OH), 32.43 ($\underline{C}H_2OH$), 29.42, 29.29, 25.63. The product was verified by comparison with an actual sample of 1,11-undecanediol, prepared from the hydroboration of 10-undecen-1-ol.

k. Hydroboration/Oxidation of 10-Undecen-1-ol

A 250 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, and gas outlet, flame dried, and purged with nitrogen. 10-Undecen-1-ol (10 mmol, 1.70 g, 2.00 mL) was introduced to the flask and the contents cooled to 0°C. BH_3·THF (1.34 mmol, 1 M) was added and the resulting mixture stirred at 25°C overnight. The solution was cooled to 0°C, and aqueous sodium hydroxide (13.33 mmol, 4.45 mL) and aqueous hydrogen peroxide (30%, 10 mmol, 1 mL) added, and the contents stirred at 50°C for one hour. The reaction mixture was made basic (pH = 10) with 1 N NaOH, and extracted with ether (3x25 mL). The combined ether layers were dried, filtered, and the solvent removed to afford 1.87 g (99%) of 1,11-undecanediol as a white solid; ^{1}H-NMR ($CDCl_3$): δ 4.0-3.6 (m,

6H, $C\underline{H}_2OH$, $O\underline{H}$, exchangeable proton evident by D_2O shake), 1.9-1.1 (broad envelope, 18H); ^{13}C-NMR ($CDCl_3$): δ 62.20 (CH_2OH), 32.43 ($\underline{C}H_2OH$), 29.42, 29.29, 25.63.

1. Reaction of Trimethylsilyl Hexanoate with 9-BBN

A 25 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, reflux condenser, and gas outlet, flame dried, and purged with argon. Trimethylsilyl hexanoate (6.64 mmol, 1.25 g, 1.0 mL) was introduced to the flask and the contents cooled to 0°C. A solution of 9-BBN (6.64 mmol, 0.5 M in anhydrous THF) was added, and the reaction heated to 50°C for one hour. The reaction mixture was extracted with ether (3x20 mL), and the combined ether layers were dried, filtered, and the solvent removed. ^{13}C-NMR analysis of the reaction mixture revealed only the presence of unreacted hexanoic acid. No reduction to the aldehyde, or alcohol was observed.

7. Hydroboration of Unsaturated Carboxylic Acids by Temporary Protection as the Trimethylsilyl Ester

a. Hydroboration/Oxidation of 10-Undecenoic Acid with $BH_3 \cdot THF$

An oven dried 100 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler). The

apparatus flame dried and allowed to cool under a stream of argon. Placed in the flask by cannula was 10-undecenoic acid (10 mmol, 1.84 g, 2.02 mL), followed by anhydrous THF (50 mL), and triethylamine (10 mmol, 1.01 g, 1.39 mL). The contents were cooled to 0°C, and then trimethylsilyl chloride (10 mmol, 1.09 g, 1.27 mL) was added dropwise (exothermic!). After the addition was complete, the reaction mixture was stirred at room temperature for one hour.

A separate apparatus consisting of a 250 mL round-bottomed flask equipped with a septum inlet, magnetic stirring bar, and a sintered glass fritted funnel with septum was assembled while hot, flame dried, and flushed with argon. The reaction mixture was then filtered under argon through the filtering funnel by transferring it into the fritted funnel using a 12 ga. double-ended needle (Figure 6-11). After washing the precipitate ($Et_3NH^+Cl^-$) with anhydrous THF, the sintered glass funnel was removed, and replaced with a gas outlet, which was then connected to a coldfinger solvent stripper apparatus (Figure 6-12). After most of the solvent was removed under reduced pressure, the reaction mixture cooled to -30°C (bromobenzene-dry ice). A cold solution of BH_3·THF (20 mmol, 1 M) at -30°C was added, and the resulting mixture stirred at -30°C for two hours. At -30°C, the reaction was quenched by the

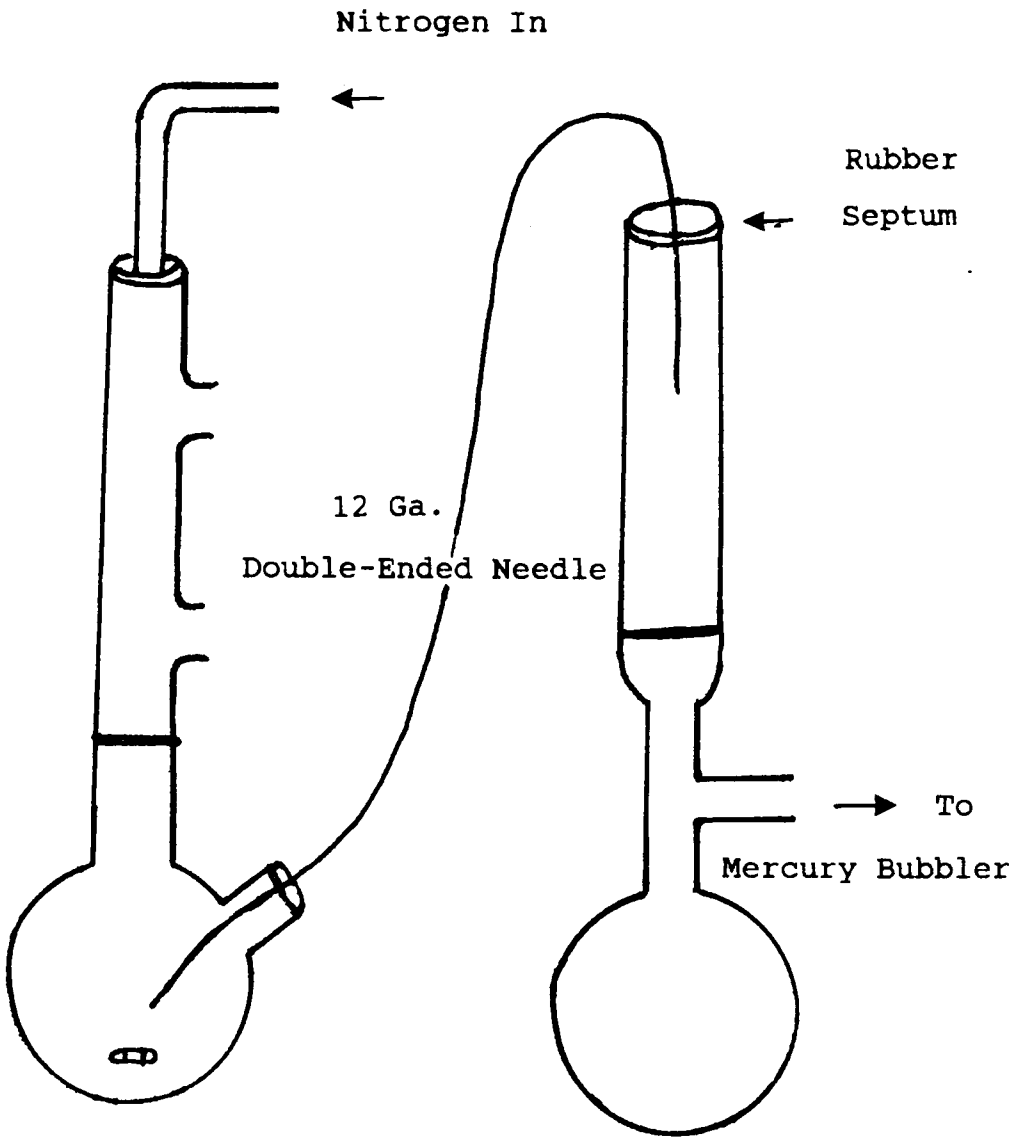


Figure 6-11. Apparatus Used For Filtration Under Inert Atmosphere.

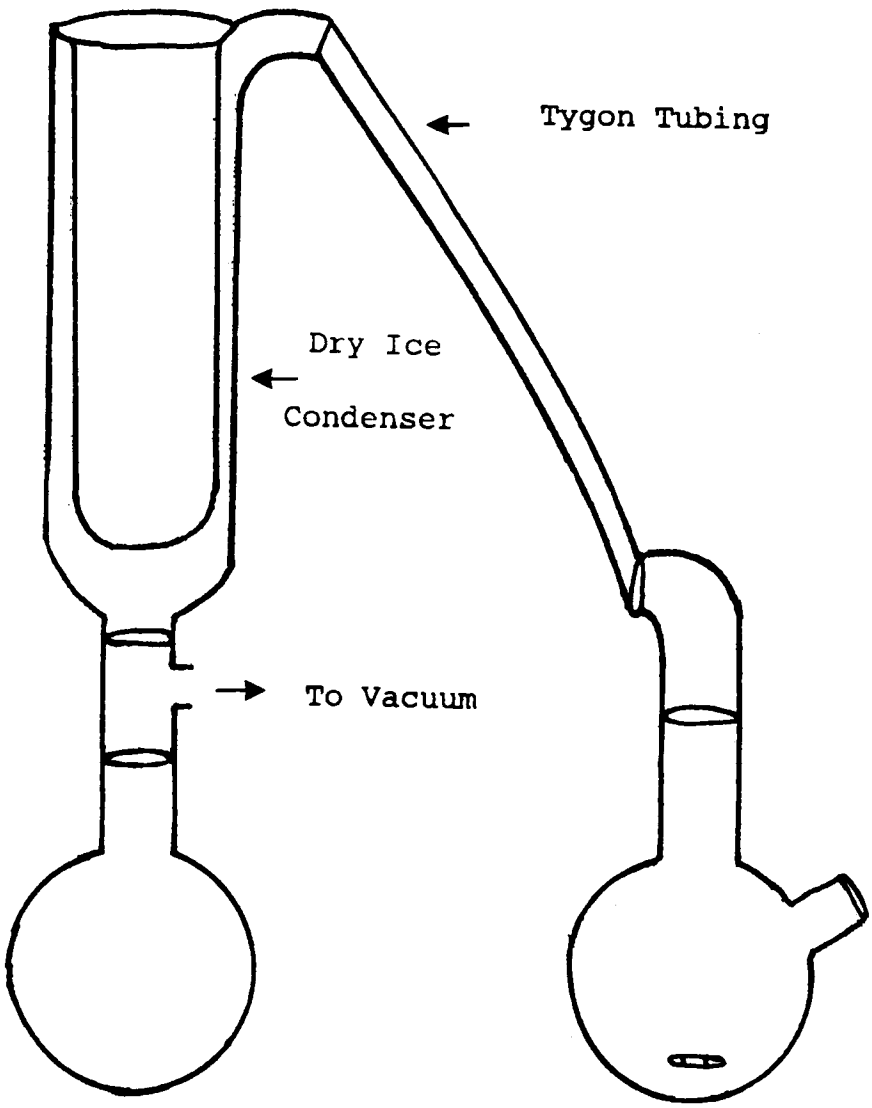


Figure 6-12. Apparatus Used For Solvent Removal Under Inert Atmosphere.

addition of water (5 mL), and the contents were allowed to warm to 0°C. Aqueous sodium hydroxide solution (3 M, 20 mmol) and hydrogen peroxide solution (30%, 20 mmol) were added sequentially, and the contents heated to 50°C for one hour. The reaction mixture was reduced in volume to remove most of the THF, adjusted to pH = 10 with 1 N NaOH, and extracted with ether (3x25 mL). The aqueous layer was then acidified (pH = 2) with 1 N HCl and the product extracted into ether (3x25 mL). The combined ether layers were dried ($MgSO_4$), filtered, and the solvent removed to give 1.48 g (73%) of 11-hydroxyundecanoic acid, which was essentially pure by NMR spectroscopy. Recrystallization from ether-petroleum ether afforded 1.32 g (70%) of white crystals; mp 69-70°C [lit[551] 70°C]; ^{1}H-NMR ($CDCl_3$): δ 6.55 (s, 2H, OH), 3.64 (t, 2H, J=6.6Hz, $RC\underline{H}_2OH$), 2.33(t, 2H, J=7.0Hz, $RC\underline{H}_2$-COOH), 1.8-1.1 (m, 16H); ^{13}C-NMR ($CDCl_3$): δ 179.33 (COOH), 63.01 ($R\underline{C}H_2OH$), 34.11, 32.62, 29.51, 29.37, 29.21, 29.07, 25.74, 24.77.

b. Hydroboration/Oxidation of 10-Undecenoic Acid with 9-BBN

An oven dried 100 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler). The apparatus flame dried and allowed to cool under a stream of

argon. Placed in the flask by cannula was 10-undecenoic acid (10 mmol, 1.84 g, 2.02 mL), followed by anhydrous THF (50 mL), and triethylamine (10 mmol, 1.01 g, 1.39 mL). The contents were cooled to 0°C, and then trimethylsilyl chloride (10 mmol, 1.09 g, 1.27 mL) was added dropwise (exothermic!). After the addition was complete, the reaction mixture was stirred at room temperature for one hour.

A separate apparatus consisting of a 250 mL round-bottomed flask equipped with a septum inlet, magnetic stirring bar, and a sintered glass fritted funnel with septum was assembled while hot, flame dried, and flushed with argon. The reaction mixture was then filtered under argon through the filtering funnel by transferring it into the fritted funnel using a 12 ga. double-ended needle. After washing the precipitate ($Et_3NH^+Cl^-$) with anhydrous THF, the sintered glass funnel was removed, and replaced with a gas outlet, which was then connected to a coldfinger solvent stripper apparatus. After most of the solvent was removed under reduced pressure, the reaction mixture cooled to 0°C. A cold solution of 9-BBN (10 mmol, 0.5 M) at 0°C was added, and the resulting mixture stirred at 0°C for two hours, and then allowed to come to room temperature, where it was stirred overnight. The reaction mixture was cooled to 0°C, and aqueous sodium hydroxide solution (3 M, 10 mmol)

and hydrogen peroxide solution (30%, 10 mmol) were added sequentially, and the contents heated to 50°C for one hour. The reaction mixture was reduced in volume to remove most of the THF, adjusted to pH = 10 with 1 N NaOH, extracted with ether (3x25 mL), and ether layers removed. The combined ether layers were dried, filtered, and the solvent removed to give 0.85 g of a yellow oil, which was shown to only contain unreacted undecenoic acid, cyclooctanediol, and trimethylsilanol. The aqueous layer was then acidified with 1 N HCl to pH = 2 and the product extracted into ether (3x25 mL). The combined ether layers were dried ($MgSO_4$), filtered, and the solvent removed to give 1.83 g (91%) of a mixture of 11-hydroxyundecanoic acid and 10-undecenoic acid. Recrystallization from ether petroleum ether afforded 1.13 g (56%) of white crystals; mp 69-70°C [lit[551] 70°C]; ^{1}H-NMR ($CDCl_3$): δ 6.55 (s, 2H, OH), 3.64 (t, 2H, J=6.6Hz, $RC\underline{H}_2OH$), 2.33(t, 2H, J=7.0Hz, $RC\underline{H}_2COOH$), 1.8-1.1 (m, 16H); ^{13}C-NMR ($CDCl_3$): δ 179.33 ($\underline{C}OOH$), 63.01 ($R\underline{C}H_2OH$), 34.11, 32.62, 29.51, 29.37, 29.21, 29.07, 25.74, 24.77.

c. Hydroboration/Oxidation of 10-Undecenoic Acid with Dicyclohexylborane

An oven dried 100 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler). The

apparatus was flame dried and allowed to cool under a stream of argon. Placed in the flask by cannula was 10-undecenoic acid (10 mmol, 1.84 g, 2.02 mL), followed by anhydrous THF (50 mL), and triethylamine (10 mmol, 1.01 g, 1.39 mL). The contents were cooled to 0°C, and then trimethylsilyl chloride (10 mmol, 1.09 g, 1.27 mL) was added dropwise (exothermic!). After the addition was complete, the reaction mixture was stirred at room temperature for one hour. A separate apparatus consisting of a 250 mL round-bottomed flask equipped with a septum inlet, magnetic stirring bar, and a sintered glass fritted funnel with septum was assembled while hot, flame dried, and flushed with argon. The reaction mixture was then filtered under argon through the filtering funnel by transferring it into the fritted funnel using a 12 ga. double-ended needle. After washing the precipitate ($Et_3NH^+Cl^-$) with anhydrous THF, the sintered glass funnel was removed, and replaced with a gas outlet, which was then connected to a coldfinger solvent stripper apparatus. Most of the solvent was removed under reduced pressure, and the reaction mixture cooled to 0°C. To a cold solution of dicyclohexylborane (10 mmol, prepared as described earlier, p. 420) at 0°C, was added slowly the crude TMS ester solution, and the resulting mixture stirred at 0°C for two hours, and then gradually allowed to come to room temperature and stirred overnight.

The reaction mixture was cooled to 0°C, and aqueous sodium hydroxide solution (3 M, 10 mmol) and hydrogen peroxide solution (30%, 10 mmol) were added sequentially; the contents were then heated to 50°C for one hour. The reaction mixture was reduced in volume to remove most of the THF, adjusted to pH = 10 with 1 N NaOH, extracted with ether (3x25 mL), and ether layers removed. The combined ether layers were dried, filtered, and the solvent removed to give 2.35 g of a yellow oil, which was shown by NMR spectroscopy to contain cyclohexanol, trimethylsilanol, and a small amount of unreacted undecenoic acid. The aqueous layer was then acidified (pH = 2) with 1 N HCl and the product extracted into ether (3x25 mL). The combined ether layers were dried ($MgSO_4$), filtered, and the solvent removed to give 1.83 g (90%) of a mixture of 11-hydroxyundecanoic acid and 10-undecenoic acid. Recrystallization from ether-petroleum ether afforded 1.70 g (84%) of 11-hydroxyundecanoic acid as white crystals; mp 69-70°C [lit[551] 70°C]; ^{1}H-NMR ($CDCl_3$): δ 6.55 (s, 2H, OH), 3.64 (t, 2H, J=6.6Hz, $RC\underline{H}_2OH$), 2.33(t, 2H, J=7.0Hz, $RC\underline{H}_2COOH$), 1.8-1.1 (m, 16H); ^{13}C-NMR ($CDCl_3$): δ 179.33 ($\underline{C}OOH$), 63.01 ($R\underline{C}H_2OH$), 34.11, 32.62, 29.51, 29.37, 29.21, 29.07, 25.74, 24.77.

d. Hydroboration/Protonolysis of 10-Undecenoic Acid with $BH_3 \cdot THF$

An oven dried 100 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler). The apparatus was flame dried and allowed to cool under a stream of argon. Placed in the flask by cannula was 10-undecenoic acid (10 mmol, 1.84 g, 2.02 mL), followed by anhydrous THF (25 mL), and triethylamine (10 mmol, 1.01 g, 1.39 mL). The contents were cooled to 0°C, and then trimethylsilyl chloride (10 mmol, 1.09 g, 1.27 mL) was added dropwise (exothermic!). After the addition was complete, the reaction mixture was stirred at room temperature for one hour. A separate apparatus consisting of a 250 mL round-bottomed flask equipped with a septum inlet, magnetic stirring bar, and a sintered glass fritted funnel with septum was assembled while hot, flame dried, and flushed with argon. The reaction mixture was then filtered under argon through the filtering funnel by transferring it into the fritted funnel using a 12 ga. double-ended needle. After washing the precipitate ($Et_3NH^+Cl^-$) with anhydrous THF, the sintered glass funnel was removed, and replaced with a gas outlet, which was then connected to a coldfinger solvent stripper apparatus. Most of the solvent was removed under reduced pressure. The reaction mixture was then

cooled to -30°C, and a cold solution of BH_3·THF (10 mmol, 1 M) added at -30°C, and the resulting mixture stirred for two hours at -30°C. The reaction was quenched at -30°C by the addition of water (5 mL) and the mixture allowed to warm to 0°C. Propionic acid (20 mL) was added, and the contents heated to 110°C for four hours. The reaction mixture was adjusted to pH = 10 with 1 N NaOH, extracted with ether (3x25 mL), and ether layers removed. The aqueous layer was then acidified (pH = 2) with 1 N HCl and the product extracted into ether (3x25 mL). The combined ether layers were dried ($MgSO_4$), filtered, and the solvent removed to give a yellow oil, which contained the product along with propionic acid. Water (50 mL) was added to precipitate the product, and the resulting solid was removed by filtration and washed with water. Recrystallization from methanol-water afforded, after drying under vacuum, undecanoic acid, 1.28 g (69%), as a white solid; mp 28°C [lit[553] 28.5°C] ^{1}H-NMR ($CDCl_3$): δ 9.06 (br, 1H, COOH), 2.34 (t, 2H, J=7.0 Hz, CH_2COOH), 1.8-1.1 (broad envelope, 16 H), 0.87 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 180.25 (COOH), 34.16, 31.95, 29.62, 29.51, 29.34, 29.12, 24.74, 22.73, 14.15 (CH_3).

e. Hydroboration/Protonolysis of 10-Undecenoic Acid with 9-BBN

An oven dried 100 mL round-bottomed flask fitted with a

septum inlet was equipped with a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler). The apparatus was flame dried and allowed to cool under a stream of argon. Placed in the flask by cannula was 10-undecenoic acid (10 mmol, 1.84 g, 2.02 mL), followed by anhydrous THF (25 mL), and triethylamine (10 mmol, 1.01 g, 1.39 mL). The contents were cooled to 0°C, and then trimethylsilyl chloride (10 mmol, 1.09 g, 1.27 mL) was added dropwise (exothermic!). After the addition was complete, the reaction mixture was stirred at room temperature for one hour. A separate apparatus consisting of a 250 mL round-bottomed flask equipped with a septum inlet, magnetic stirring bar, and a sintered glass fritted funnel with septum was assembled while hot, flame dried, and flushed with argon. The reaction mixture was then filtered under argon through the filtering funnel by transferring it into the fritted funnel using a 12 ga. double-ended needle. After washing the precipitate ($Et_3NH^+Cl^-$) with anhydrous THF, the sintered glass funnel was removed, and replaced with a gas outlet, which was then connected to a coldfinger solvent stripper apparatus. Most of the solvent was removed under reduced pressure. The reaction mixture was cooled to 0°C, and a cold solution of 9-BBN (10 mmol, 0.5 M) added at 0°C. The resulting mixture was stirred at 0°C for two hours, and then overnight while allowing the contents to

come gradually to room temperature. Propionic acid (20 mL) and glyme (25 mL) were added, and the contents heated at 150°C for two hours. The reaction mixture was adjusted to pH = 10 with 1 N NaOH, extracted with ether (3x25 mL), and ether layers removed. The aqueous layer was then acidified (pH = 2) with 1 N HCl and the product extracted into ether (3x25 mL). The combined ether layers were washed with water (3x100 mL), dried ($MgSO_4$), filtered, and the solvent removed to give 1.87 g (99%) of a white solid which was a mixture of undecanoic acid and unreacted 10-undecenoic acid. Purification by column chromatography (silica gel, 10% → 20% ethyl acetate-petroleum ether), followed by recrystallization from methanol-water afforded, after drying under vacuum, undecanoic acid, 1.14 (61%), as a white solid; mp 28°C [lit[553] 28.5°C]; ^{1}H-NMR ($CDCl_3$): δ 9.06 (br, 1H, COOH), 2.34 (t, 2H, J=7.0 Hz, $C\underline{H}_2COOH$), 1.8-1.1 (broad envelope, 16 H), 0.87 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ 180.25 (COOH), 34.16, 31.95, 29.62, 29.51, 29.34, 29.12, 24.74, 22.73, 14.15 (CH_3).

f. Hydroboration/Hydrolysis of 10-Undecynoic Acid with Catecholborane

An oven dried 100 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler). The

apparatus flame dried, and allowed to cool under a stream of argon. Placed in the flask by cannula was 10-undecynoic acid (20 mmol, 3.64 g,) followed by anhydrous THF (30 mL), and triethylamine (20 mmol, 2.02 g, 2.78 mL). The contents were cooled to 0°C, and then trimethylsilyl chloride (20 mmol, 2.17 g, 2.54 mL) was added dropwise (exothermic!). After the addition was complete, the reaction mixture was stirred at room temperature for one hour. A separate apparatus consisting of a 250 mL round-bottomed flask equipped with a septum inlet, magnetic stirring bar, and a sintered glass fritted funnel with septum was assembled while hot, flame dried, and flushed with argon. The reaction mixture was then filtered under argon through the filtering funnel by transferring it into the fritted funnel using a 12 ga. double-ended needle. After washing the precipitate (Et_3NH^+-Cl^-) with anhydrous THF, the sintered glass funnel was removed, and replaced with a gas outlet, which was then connected to a coldfinger solvent stripper apparatus. Most of the solvent was removed under reduced pressure. The reaction mixture was cooled to 0°C, catecholborane (44 mmol, 4.68 mL) introduced, and the resulting mixture heated at 65°C for five hours. Water (200 mL) was added and the mixture stirred overnight to hydrolyze the boronic ester. The water layer was decanted off, the crude boronic acid dissolved in methanol and precipitated by the addition of

water. Recrystallization from methanol-water afforded 3.03 g (70%) of 10-undecenylboronic acid as a cream-white solid; ^{1}H-NMR (DMSO-d_6): δ 11.8 (br, COOH), 6.65-6.2 (m, 1H, $(HO)_2BHC=C\underline{H}R$)), 5.45-5.15 (m, 1H, J_{trans}=18.0 Hz, $(HO)_2$-$B\underline{H}C=CHR$)), 2.3-1.8 (m, 4H, $(HO)_2BHC=CHC\underline{H}_2R$), $C\underline{H}_2COOH$), 1.7-1.1 (broad envelope, 12H); ^{13}C-NMR (DMSO-d_6): δ 174.50 (COOH), 150.01 ($(HO)_2BHC=\underline{C}HR$)), 35.08, 33.70, 28.66, 28.12, 24.55; ^{13}C-NMR (acetone-d_6): δ 175.74 (COOH), 152.20 ($(HO)_2BHC=\underline{C}HR$)), 36.76, 34.79, 30.67, 30.48, 30.4, 29.86, 26.15; ^{11}B-NMR (THF): δ 27.3.

g. Hydroboration/Protonolysis of 10-Undecynoic Acid with Catecholborane

An oven dried 100 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler). The apparatus was flame dried and allowed to cool under a stream of argon. Placed in the flask by cannula was 10-undecynoic acid (20 mmol, 3.64 g,) followed by anhydrous THF (30 mL), and triethylamine (20 mmol, 2.02 g, 2.78 mL). The contents were cooled to 0°C, and then trimethylsilyl chloride (20 mmol, 2.17 g, 2.54 mL) was added dropwise (exothermic!). After the addition was complete, the reaction mixture was stirred at room temperature for one hour. A separate apparatus consisting of a 250 mL round-bottomed flask

equipped with a septum inlet, magnetic stirring bar, and a sintered glass fritted funnel with septum was assembled while hot, flame dried, and flushed with argon. The reaction mixture was then filtered under argon through the filtering funnel by transferring it into the fritted funnel using a 12 ga. double-ended needle. After washing the precipitate ($Et_3NH^+Cl^-$) with anhydrous THF, the sintered glass funnel was removed, and replaced with a gas outlet, which was then connected to a coldfinger solvent stripper apparatus. Most of the solvent was removed under reduced pressure. The reaction mixture cooled to 0°C, and catechol-borane (44 mmol, 4.68 mL) introduced. The resulting mixture heated at 65°C for five hours. Acetic acid (20 mL) was added, and the contents heated to 40°C for two hours. The reaction mixture was adjusted to pH = 10 with 1 N NaOH, extracted with ether (3x25 mL), and ether layers removed. The aqueous layer was then acidified (pH = 2) with 1 N HCl and the product extracted into ether (3x25 mL). The combined ether layers were dried ($MgSO_4$), filtered, and the solvent removed to give a yellow oil, which contained the product along with some acetic acid. The crude product was dissolved in ether (30 mL), washed repeatedly with water (50 mL portions), and the separated ethereal layer was dried. Filtration, followed by removal of the solvent, gave the crude carboxylic acid. Purification by column

chromatography (silica gel, solvent gradient, 10% → 25 % ethyl acetate, petroleum ether afforded 10-undecenoic acid, 2.47 g (67%), as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 10.5 (br singlet, COOH), 6.10-5.55 (m, 1H, J_{ab}=6.6Hz, $H_2C=C\underline{H}_a-CH_bR$), 5.15-4.85 (m, 2H, J_{trans}= 17.1Hz, J_{cis}=9.2Hz, $\underline{H}_2C=CHCH_2R$), 2.34 (t, 2H, J=7.0 Hz, $C\underline{H}_2COOH$), 2.15-1.80 (m, 2H, $H_2C=CHC\underline{H}_2R$), 1.75-1.1 (broad envelope, 12H); ^{13}C-NMR ($CDCl_3$): δ 180.57 (COOH), 139.10 ($RH\underline{C}=CH_2$), 114.18 ($RHC=\underline{C}H_2$), 34.17, 33.82, 29.23, 29.07, 28.94, 24.67.

h. Hydroboration/Iodination of 10-Undecenoic Acid with Dicyclohexylborane

An oven dried 100 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, reflux condenser, and gas outlet (mercury bubbler). The apparatus was flame dried and allowed to cool under a stream of argon. Placed in the flask by cannula was 10-undecenoic acid (10 mmol, 1.84 g, 2.02 mL), followed by anhydrous THF (25 mL), and triethylamine (10 mmol, 1.01 g, 1.39 mL). The contents were cooled to 0°C, and then trimethylsilyl chloride (10 mmol, 1.09 g, 1.27 mL) was added dropwise (exothermic!). After the addition was complete, the reaction mixture was stirred at room temperature for one hour. A separate apparatus consisting of a 250 mL round-bottomed flask equipped with a septum inlet, magnetic

stirring bar, and a sintered glass fritted funnel with septum was assembled while hot, flame dried, and flushed with argon. The reaction mixture was then filtered under argon through the filtering funnel by transferring it into the fritted funnel using a 12 ga. double-ended needle. After washing the precipitate ($Et_3NH^+Cl^-$) with anhydrous THF, the sintered glass funnel was removed, and replaced with a gas outlet, which was then connected to a coldfinger solvent stripper apparatus. Most of the solvent was removed under reduced pressure; the reaction mixture cooled to 0°C, and added to freshly prepared dicyclohexylborane [10 mmol, prepared from cyclohexene (20 mmol, 1.64 g) and BH_3·DMS (10 mmol, 10 M) according to procedure 6.D.4.p) at -10°C. The contents were stirred at -10 - 0°C for four hours, then allowed to come gradually to room temperature and stirred for an additional 7 hours. The reaction mixture was cooled to 0°C, and methanolic sodium acetate (1 M, 20 mmol), aqueous sodium iodide (1 M, 10 mmol), and methanolic chloramine T (0.5 M, 20 mmol) were added sequentially. The contents were stirred for one minute and quenched by addition of sodium thiosulfate (1 M, 10 mL), and 1.2 N HCl (10 mL). Water (20 mL) and petroleum ether (20 mL) were added, and the organic layer separated. The aqueous layer was extracted twice more with petroleum ether (20 mL portions), and the combined organic layer was dried ($MgSO_4$).

Filtration, followed by removal of the solvent under reduced pressure, gave the crude product as a white solid. Purification by column chromatography (silica gel, 10% → 15% ethyl acetate-petroleum ether) afforded 11-iodoundecanoic acid, 2.47 g (79%), as a colorless oil, which solidified upon standing; mp 48-50°C [lit[71] 47-50°C]; ^{1}H-NMR ($CDCl_3$): δ 10.50 (COOH), 3.18 (t, 2H, J=7.0 Hz, CH_2I), 2.35 (t, 2H, J=6.5 Hz, $C\underline{H}_2COOH$), 2.05-1.1 (broad envelope, 16H); ^{13}C-NMR ($CDCl_3$): δ 180.30 (COOH), 34.08, 33.54, 30.48, 29.29, 29.15, 29.02, 28.48, 24.63, 7.24 (CH_2I).

8. Reactions Involving t-Butyldimethylsilyl Esters

a. Hydroboration/Oxidation of t-Butyldimethylsilyl 10-Undecenoate

A 100 mL round-bottomed flask fitted with a septum inlet, a magnetic stirring bar and gas outlet (mercury bubbler) was flame dried, purged with argon, and allowed to cool under a stream of argon. t-Butyldimethylsilyl-10-undecenoate (1.24 mmol, 370 mg) was added to the flask by syringe, and the flask cooled to -20°C (salt-ice-acetone bath). A cooled solution (-30°C) of BH_3·THF (1.0 M, 0.42 mmol, 413 µL) was introduced dropwise, and the reaction mixture stirred at -20°C for 2 hours, and then for an additional 16 hours while gradually allowing the reaction mixture to come to room temperature. ^{13}C-NMR analysis of

the reaction mixture showed there to be unreacted olefin left. The flask was cooled to -20°C, and additional BH_3·THF (1.0 M, 0.42 mmol, 413 µL) was added dropwise, and the contents stirred overnight. The flask was cooled to 0°C, aqueous sodium hydroxide (3 M, 0.28 mL) and hydrogen peroxide (30%, 120 µL) were added sequentially, and the contents were heated for 1 hr at 50°C, and then cooled to room temperature. The reaction mixture was saturated with sodium chloride, the pH adjusted to a value of 10 with 1 N NaOH, and the mixture was washed with ether (3x25 mL). The aqueous layer was separated, ice was added, the pH was carefully adjusted to a value of 2 with 1 N HCl, and the product extracted into ether (3x25 mL). The combined ethereal layers were dried (Na_2SO_4), filtered, and the solvent removed to give 0.37 g (94%) of 11-hydroxyundecanoic acid, which was essentially pure. Recrystallization from ether-petroleum ether afforded 0.34 g (87%) of a white powder; mp 69-70°C [lit[551] 70°C]; ^{1}H-NMR ($CDCl_3$): δ 6.55 (s, 2H, OH), 3.64 (t, 2H, J=6.6Hz, $RC\underline{H}_2OH$), 2.33(t, 2H, J=7.0Hz, $RC\underline{H}_2COOH$), 1.8-1.1 (m, 16H); ^{13}C-NMR ($CDCl_3$): δ 179.33 ($\underline{C}OOH$), 63.01 ($R\underline{C}H_2OH$), 34.11, 32.62, 29.51, 29.37, 29.21, 29.07, 25.74, 24.77.

b. Hydroboration/Hydrolysis of t-Butyldimethylsilyl 10-Undecynoate with Catecholborane

An oven dried 100 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar and gas outlet, flame dried, and purged with nitrogen. t-Butyldimethylsilyl 10-undecynoate (5.56 mmol, 1.65 g), was introduced to the flask and the contents cooled to 0°C. This was followed by the slow addition of catecholborane (4.82 mmol, 0.51 mL). The resulting mixture was stirred at 70°C for 6 hours. Water (150 mL) was added, and the mixture stirred overnight to hydrolyze the boronic ester. The aqueous layer was decanted off and the solid boronic acid was dissolved in ether which was washed with cold water (3x100 mL). The product precipitated by addition of petroleum ether. The product was redissolved in ether and crystallized by the addition of petroleum ether to afford 0.56 g (44%) of 10-undecenylboronic acid as a white powder. ^{1}H-NMR (DMSO-d_6): 11.8 (br, COOH), 6.65-6.2 (m, 1H, $(HO)_2BHC=C\underline{H}R$)), 5.45-5.15 (m, 1H, J_{trans}=18.0 Hz, $(HO)_2$-$B\underline{H}C=CHR$)), 2.3-1.8 (m, 4H, $(HO)_2BHC=CHC\underline{H}_2R$), $C\underline{H}_2COOH$), 1.7-1.1 (broad envelope, 12H); ^{13}C-NMR (DMSO-d_6): δ 174.50 (COOH), 150.01 ($(HO)_2BHC=\underline{C}HR$)), 35.08, 33.70, 28.66, 28.12, 24.55; ^{13}C-NMR (acetone-d_6): δ 175.74 (COOH), 152.20 ($(HO)_2BHC=\underline{C}HR$)), 36.76, 34.79, 30.67, 30.48, 30.4, 29.86, 26.15; ^{11}B-NMR (THF): 27.3.

c. Reduction of t-Butyldimethylsilyl Hexanoate with $BH_3 \cdot THF$: ^{11}B-NMR Experiment

In an oven dried NMR tube fitted with a septum cap, which had been flushed with argon, was placed t-butyldimethylsilyl hexanoate (2.60 mmol, 0.60 g); the tube was cooled to -78°C. To this was added a cold solution of $BH_3 \cdot THF$ (2.27 mmol, 1.0 M) at -78°C. The progress of the reaction was monitored by ^{11}B-NMR spectroscopy while varying the reaction temperature from -60 → 37°C. After completion of the reaction, the contents of the tube were poured into a round-bottomed flask, and the mixture hydrolyzed by the slow addition of water (5 mL). The reaction mixture was made basic (pH = 10) with 1 N NaOH, and the product extracted into ether (3x20 mL). After drying the combined ether layers ($MgSO_4$), filtration, followed by removal of the solvent, afforded a light yellow oil, identified to be a mixture of 1-hexanol and t-butyldimethylsiloxane; ^{13}C-NMR ($CDCl_3$): [1-hexanol]: δ 62.74 (CH_2OH), 32.70, 31.68, 25.47, 13.99, [t-butyldimethylsiloxane]: 25.66 $(CH_3)_2Si$-$C(CH_3)_3$, 18.91 $(CH_3)_2SiC(CH_3)_3$, -3.62 $((CH_3)_2SiC(CH_3)$.

d. Reduction of t-Butyldimethylsilyl Hexanoate with $BH_3 \cdot THF$: ^{29}Si-NMR Experiment

In an oven dried NMR tube fitted with a septum cap, which had been flushed with argon, was placed

t-butyldimethylsilyl hexanoate (2.60 mmol, 0.60 g); the tube was cooled to -78°C. To this was added a cold solution of BH_3·THF (2.27 mmol, 1.0 M) at -78°C, and the progress of the reaction monitored by ^{29}Si-NMR spectroscopy while varying the reaction temperature from -60 → 37°C.

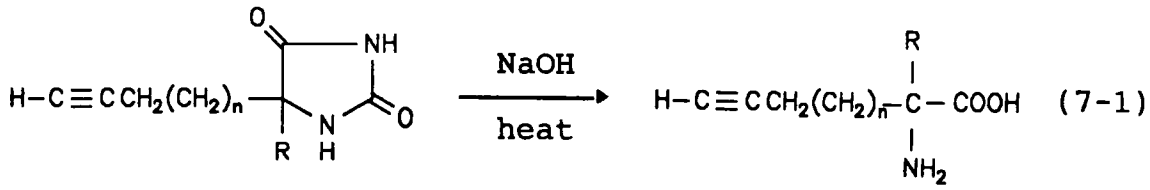
CHAPTER VII

SYNTHESIS OF AN ACETYLENIC AMINO ACID

A. Introduction

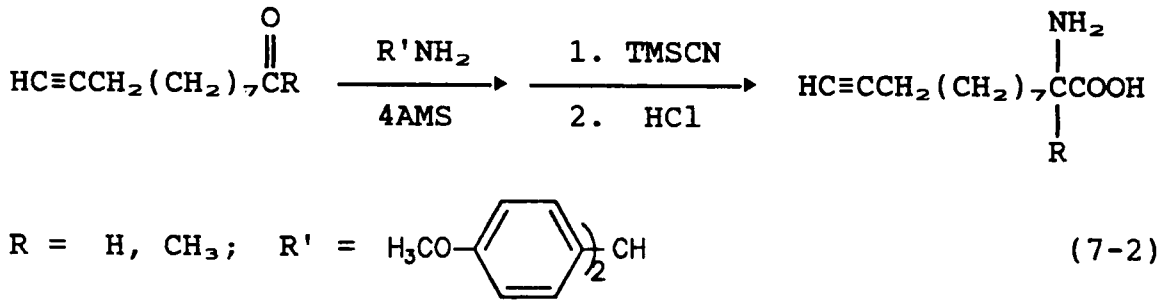
With the successful use of the trimethylsilyl moiety as a protecting group for carboxylic acid functionality during the hydroboration reaction, attention was focused on its application to an unsaturated amino acid. As noted in the previous chapter, a suitable alkynyl amino acid was not commercially available. Thus, the synthesis of one was required if the new methodology was to be tested.

Four basic approaches to the alkynyl amino acid were chosen. One approach involved basic hydrolysis of an alkynyl hydantoin (equation 7-1). Another approach to an



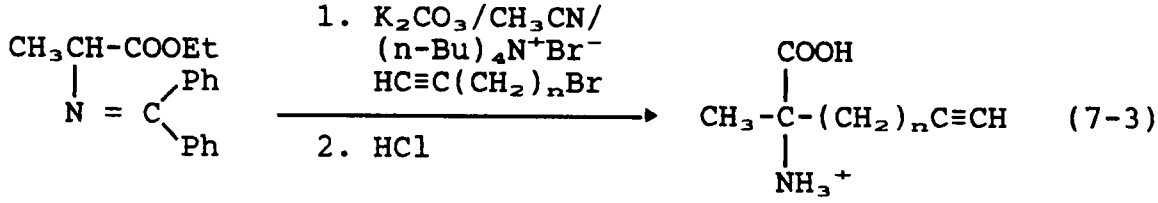
(7-1)

alkynyl amino acid involved use of the Strecker reaction. A more recent modification of the Strecker reaction reported by Greenlee[427] was also attempted (equation 7-2). A third route to an alkynyl amino acid which was explored involved the alkylation of the Schiff base derivative of alanine, employing the recently published procedures by O'Donnell,



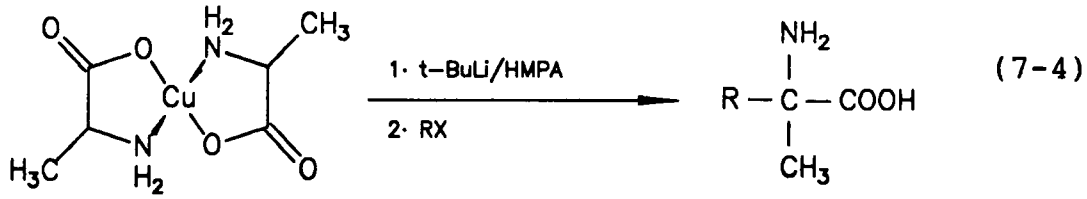
R = H, CH_3; R' = H_3CO-(C$_6$H$_4$)$_2$-CH (7-2)

Ghosez, and coworkers[428,429,430,431] (equation 7-3).



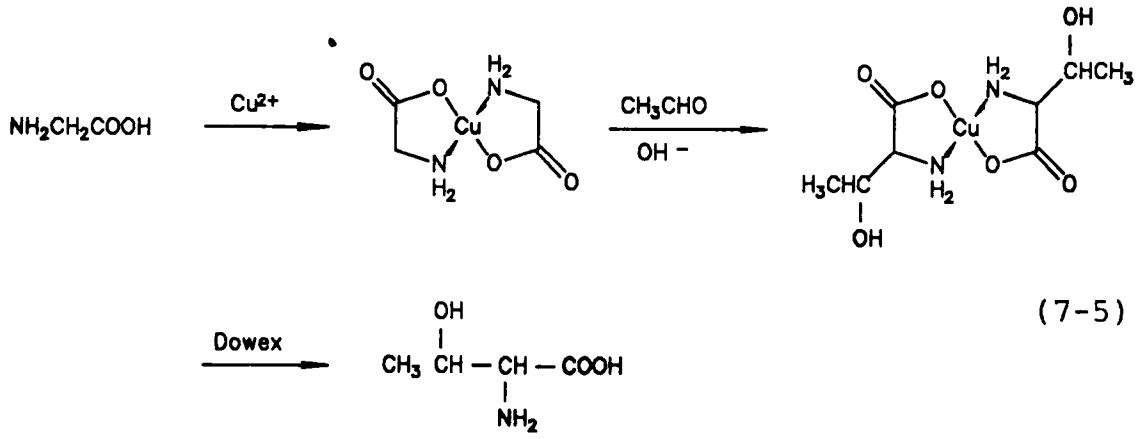
(7-3)

Alkylation of the alanine Schiff base using more standard methodology (LDA) was also attempted. A final approach which was briefly investigated involved preparation and alkylation of the copper complex of alanine[554] (equation 7-4). Although aldol condensation of amino acid copper com-



(7-4)

plexes is a well known industrial process for preparing threonine derivatives[555] (equation 7-5), it is virtually an unexplored area as a standard laboratory procedure for



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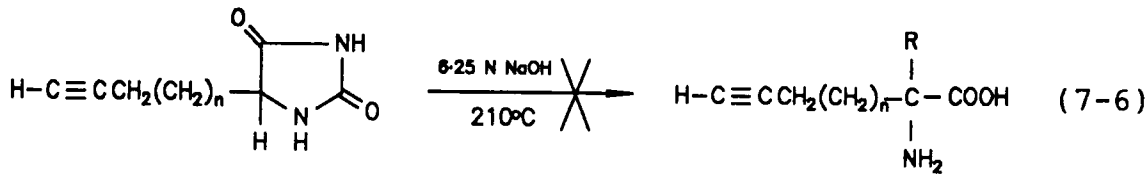
preparing alkylated amino acid derivatives.

B. Results and Discussion

The most logical approach to an alkynyl amino acid based on the work presented in this dissertation involved the hydrolysis of an alkynyl hydantoin. Attempted hydrolysis of 5-(10-undecyn-1-yl-)2,4-imidazolidine-1,3-dione using the high temperature, high pressure procedure developed by Washburn and associates[304,318] provided an amino acid, but also led to degradation of the alkyne functionality (equation 7-6). A similar result was obtained in the attempted



(7-6)

hydrolysis of 5-(4-pentyn-1-yl)2,4-imidazolidine-1,3-dione in a Parr bomb; ^{13}C-NMR analysis of the product isolated by

ion exchange chromatography revealed the presence of a carboxyl peak at 172.6 ppm, but absence of the alkyne peaks. When the hydrolysis was repeated using milder conditions (aqueous dioxane, 6 N NaOH, 160°C, four hours), incomplete hydrolysis occurred; a mixture of unreacted hydantoin and the alkynyl ureido amino acid was obtained. This was somewhat surprising, since similar conditions had been employed successfully in the hydrolysis of 5,5-dimethylhydantoin to α-methylalanine in test experiments (Chapter V). Carrying out the hydrolysis reaction for a longer period of time, unfortunately, led to results similar to those observed with the Washburn procedure; ^{13}C-NMR analysis of the reaction mixture (D_2O, NaOH) gave a carboxyl resonance at 184.6 ppm, but the alkyne resonances (85.76 and 70.54 ppm in the starting alkynylhydantoin, d_6-acetone) were absent.

A more direct approach to an alkynyl amino acid involved the use of the Strecker reaction. Treatment of 10-undecynal with potassium cyanide (1 equiv.) and ammonium chloride (3 equiv.) for 6 hours at 70°C, followed by refluxing the reaction mixture with 50% HCl for 18 hours, did not lead to the desired product (equation 7-7). ^{13}C-NMR

$$HC{\equiv}C(CH_2)_8CHO \xrightarrow[NH_4Cl]{KCN} HC{\equiv}C(CH_2)_8\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH \qquad (7\text{-}7)$$

analysis of the ethyl acetate extract of the reaction mixture after acid hydrolysis revealed the presence of two carbonyl resonances at 175 and 172 ppm, and two larger peaks in the olefinic region at 144 ($-HN(C=O)NH_2$) and 113 ($C\equiv N$) ppm; the alkynyl resonances at 85 and 70 ppm were very small in comparison to the remaining peaks in the spectrum. Evaporation of the aqueous layer and analysis of the residue by ^{13}C-NMR spectroscopy revealed a carboxyl resonance at 174 ppm; no resonances corresponding to any unsaturation were present. Thus, it would appear that the alkyne functionality is unstable to the reaction conditions employed in the Strecker reaction.

Since the alkyne functionality did not appear to survive the traditional Strecker sequence, the procedure reported by Greenlee employing trimethylsilyl cyanide appeared to be an attractive alternative. The procedure was recently used to prepare a series of ß,Γ-unsaturated amino acids from the corresponding aldehydes, including the highly desired vinylglycine, and offers improved yields over the traditional Strecker synthesis (equation 7-2, p. 474). Furthermore, the use of benzhydrylamine as the amine component further enhances the synthetic utility of this approach, as the amine functionality can be deprotected simultaneously during the acid hydrolysis step. Thus, it was anticipated that this methodolology would be well suited

for the preparation of α-methylalkynyl-α-amino acids. Initial results using this procedure were promising. Using 2-octanone as a model compound to test the feasibility of this approach (ketones had not been tested via this methodology), sequential treatment of the ketone (20 mmol) with benzylamine (20 mmol) and trimethylsilyl cyanide (22 mmol) gave the intermediate aminonitrile as expected. ^{13}C-NMR analysis of this crude intermediate showed complete conversion of the ketone to the aminonitrile based on loss of the ketone peak at 201 ppm and the presence of a peak at 122 ppm corresponding to a nitrile. Furthermore, the peak at 55.4 ppm was shown to be due to a quaternary carbon from the Single Frequency Off Resonance Decoupled spectrum of this compound. Figure 7-1 shows the ^{13}C-NMR spectrum of the intermediate aminonitrile. However, attempted hydrolysis of this compound led to reformation of the starting ketone, which was recovered in an 86% yield. In addition, following pH adjustment of the reaction mixture (pH = 10) and re-extraction with chloroform, a 94% yield of benzylamine was recovered.

As was discussed in Chapter I, the hydrolysis of amino nitriles to amino acids is an equilibrium process[297]. Conversion of an aminonitrile back to its carbonyl analogue involves loss of HCN and NH_3 (In the present case, the amine component was benzylamine.), (equation 7-8). Anticipating

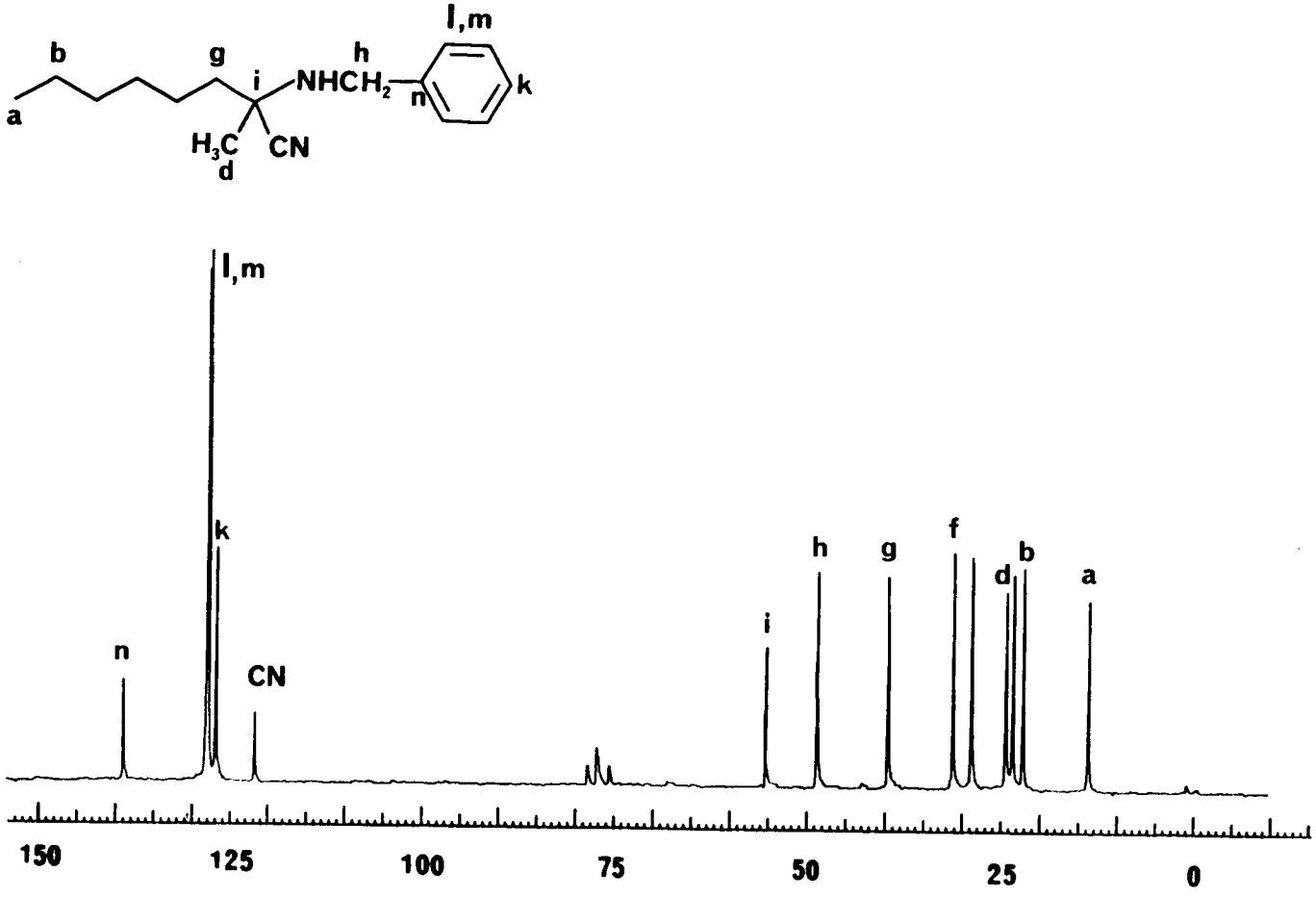
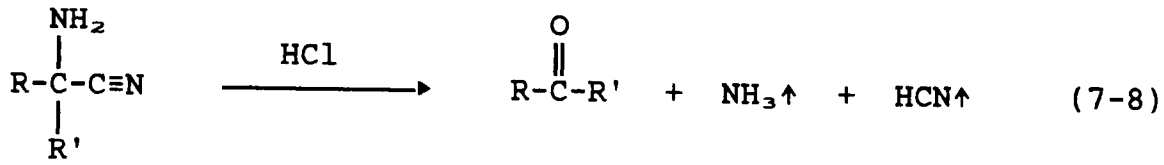


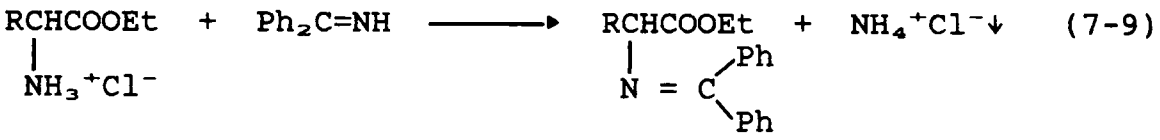
Figure 7-1. Carbon-13 NMR Spectrum of N-Benzyl-2-Amino-2-cyanooctane.



(7-8)

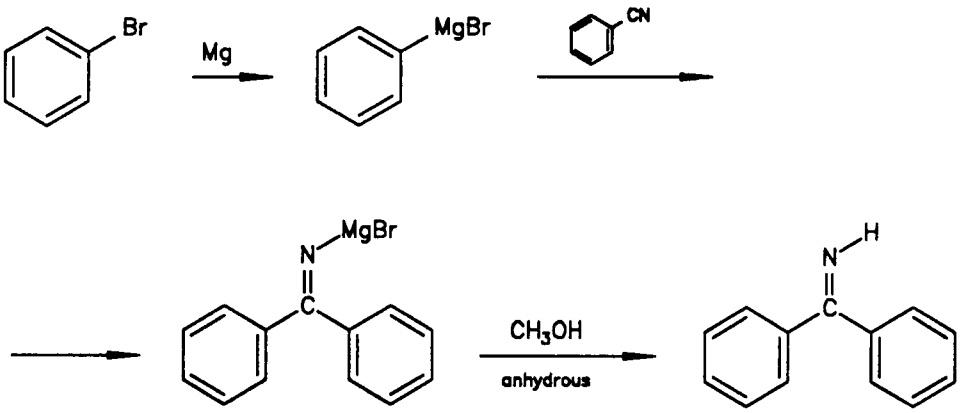
that the equilibrium process could be forced to the amino acid stage if the reaction was carried out under pressure, the reaction was modified by carrying out the hydrolysis step in a sealed reaction tube. Unfortunately, this approach also failed; a 76% yield of 2-octanone was recovered after workup. With this result, the Strecker approach to an acetylenic amino acid was discarded.

A third approach to an alkynyl amino acid involved alkylation of the Schiff base of alanine. Alkylation of the Schiff base derivatives of amino acids has been an approach to higher amino acid which has received considerable attention in recent years[280,556]. A heterogeneous phase transfer modification of this approach, recently reported by O'Donnell[428,429,430,431] (equation 7-3, p. 474), was the method chosen. The necessary benzophenone imine Schiff base derivative of alanine was prepared by condensation of diphenylketimine with alanine ethyl ester hydrochloride using the convenient procedure developed by O'Donnell and Polt[433] (equation 7-9). The required diphenylketinimine was prepared in an 82% overall yield from bromobenzene using the procedure reported by Pickard and Tolbert[557]



(7-9)

(equation 7-10). Treatment of alanine with thionyl



(7-10)

chloride in anhydrous ethanol[558,559] afforded the ethyl ester hydrochloride salt in a 91% yield (0.5 mol scale). Treatment of alanine ethyl ester hydrochloride with a stoichiometric amount of diphenylketimine in anhydrous methylene chloride gave, following distillation of the product, ethyl N-(diphenylmethylene)alaninate in a 66% yield (equation 7-9).

The requisite Ω-alkynyl bromide was prepared from the corresponding tosylate using the procedure described earlier in Chapter III. 1-Bromo-10-undecyne and 1-bromo-4-pentyne were thus obtained in a 93% and 84% yield, respectively. Prior to carrying out the coupling experiment with the

Ω-alkynyl bromide, the procedure was tested using 4-bromo-1-butene, which is commercially available. When ethyl N-(diphenylmethylene)alaninate was treated with a stoichiometric amount of 4-bromo-1-butene and powdered potassium carbonate in acetonitrile in the presence of tetra-n-butylammonium bromide according to the literature procedure, no reaction occurred; only unreacted alanine and the benzophenone Schiff base were recovered. When the reaction was repeated under anhydrous conditions (water was removed from the potassium carbonate and phase transfer agent by azeotropic distillation using a large excess of previously dried acetonitrile), only partial alkylation was observed. This was apparent from the presence of the methyl doublet in the proton NMR spectrum of the crude reaction mixture at 1.45 ppm and the presence of the C-H carbon peak at 61 ppm (doublet in SFORD) spectrum while the new quaternary carbon peak (small) appeared at 67 ppm. The literature procedure called for a reaction time of one hour, although O'Donnell reported that the progress of the reaction could be monitored by HPLC. However, only partial alkylation was observed after a seven hour reaction time in refluxing acetonitrile. When the reaction was repeated one more time for 40 hours at reflux, the same result was obtained. Since incomplete alkylation would cause further separation problems, no attempt at purification of the reaction mixture

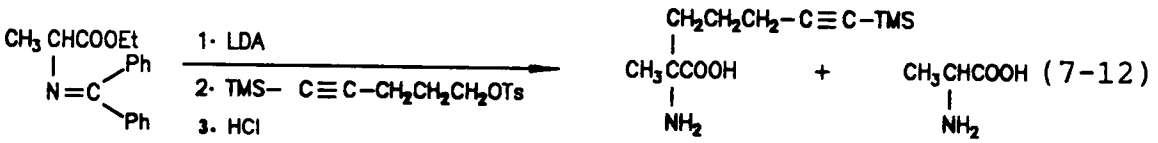
beyond extractive separation was attempted.

With the limited success of this procedure, attention was turned to a more standard alkylation method; specifically, alkylation using lithium diisopropyl amide (LDA) as the base[560,561]. This approach required protection of the alkyne functionality. Sequential treatment of 4-pentyn-1-ol with two equivalents of ethylmagnesium bromide and trimethylsilyl chloride, followed by acetic acid hydrolysis, gave the desired protected alkyne in an 88% yield following distillation (equation 7-11). It should be noted that this

$$H-C\equiv C-CH_2CH_2CH_2OH \xrightarrow[2.\ 2\ equiv\ (CH_3)_3SiCl\ \ 3.\ HOAc]{1.\ 2\ equiv\ n-BuLi} (CH_3)_3Si-C\equiv C-CH_2CH_2CH_2OH \quad (7\text{-}11)$$

procedure eliminated the competitive propargyl silylation problem which was experienced in the earlier n-butyllithium procedure (equation 3-13, p. 111). Preparation of the tosylate derivative using the procedure reported by Kabalka[562] proceeded without incident to give the desired TMS protected alkynyl tosylate in quantitative yield, thus expanding the synthetic utility of this procedure. Since it was felt that the tosylate group might be a better leaving group than the bromide, an attempt using this compound was made. Treatment of the Schiff base with an equivalent amount of LDA in THF/HMPA followed by addition of a THF solution of the alkynyl tosylate gave, unfortunately, a mixture of the

desired alkylated product, along with unreacted starting material (once again, based on the presence of the alanine doublet at 1.1 ppm in the proton NMR spectrum and the presence of the corresponding carbon peak at 61 ppm in the ^{13}C-NMR spectrum of the crude product. ^{29}Si-NMR analysis of the intermediate reaction products gave a single peak at -18.9 ppm, which corresponded to that of the starting TMS-protected alkynyl tosylate. Hydrolysis of the reaction mixture gave a mixture of the desired amino acid, along with the unreacted alanine (equation 7-12).



(7-12)

Since the tosylate group did not work well, one final experiment using, 4-bromo-1-butene as the test case was carried out. Treatment of the Schiff base derivative with an equivalent amount of LDA in THF/HMPA, followed by addition of a THF solution of 4-bromo-1-butene, gave, as with the earlier experiments, a mixture of the desired alkylated product, along with the unreacted starting material.

One final approach to the alkylated alkynyl amino acid system was briefly investigated. The copper complex of alanine was prepared by treating an aqueous solution of

alanine with an equivalent amount of sodium hydroxide, followed by the addition of copper oxide. The residual copper hydroxide was removed by bubbling H_2S gas into the basic solution. After filtration to remove the copper sulfide, precipitation of the product by the addition of acetone, and drying, a 76% yield of the copper complex was obtained. Alkylation of this compound was attempted with 4-bromo-1-butene and t-butyl lithium in anhydrous HMPA. Partial alkylation of the complex appears to have occurred based on the presence of a new peak at 57.09 ppm relative to the CH peak of alanine, which occurs at 51 ppm. The olefinic carbon peaks are also present. However, the procedure has a number of experimental difficulties which need to be addressed, before it can be considered a general route to alkylated amino acids.

C. Conclusion

The successful synthesis of an alkynyl amino acid, was never realized. Thus, hydroboration of the TMS ester of an alkynyl amino acid could not be tested. Numerous routes to the α-methyl-Ω-alkynyl-α-amino acid system were tried but failed. Hydrolysis of an alkynyl hydantoin led to concomitant degradation of the alkyne functionality, as would be expected. Attempted synthesis of an alkynyl amino acid via the Strecker reaction also led to degradation of the

alkyne group. The convenient Strecker modification employing trimethylsilyl cyanide appeared, at first, promising, as the intermediate aminonitrile formed to the exclusion of any side products. Unfortunately, upon attempted hydrolysis, the aminonitrile reverted back to the starting ketone, instead of being hydrolyzed to the amino acid. It should be noted that the Greenlee procedure was not tested previously as a method of preparing α-alkyl-α-amino acids.

Attempted preparation of the desired amino acid via alkylation of the Schiff base derivative was met with limited success; only partial alkylation was observed in all experimental procedures attempted. Even use of the tosylate, which apparently is a better leaving group than bromide, gave results analogous to those observed in the other experiments.

Finally, alkylation of the copper complex of alanine appeared to show limited success, but the experimental difficulties which remain to be worked out preclude its use at this time as a viable route to the desired alkynyl amino acids.

D. Experimental

1. General

When required, glassware, syringes, and syringe needles were oven-dried 24 hours prior to use. NMR spectra were

recorded on a JEOL-FX-90Q pulsed FT-NMR spectrometer in either deuteriochloroform, $CDCl_3$, acetone-d_6, dimethylsulfoxide-d_6, deuterium oxide (by use of an external reference in a sealed 5 mm NMR tube or, alternatively, by employing a small amount of dioxane or methanol as an internal reference), dioxane, or deuterium hydroxide/sodium hydroxide solutions. The ^{1}H-NMR spectra were referenced using tetramethylsilane, TMS, as an internal standard (δ = 0.0 ppm). Alternatively, for those samples which were insoluble in organic solvents, an external reference containing TMS or another deuterated solvent in a sealed 5 mm NMR or capillary tube were used. Exchangeable protons were determined by shaking with deuterium oxide. The ^{13}C-NMR spectra were referenced to either $CDCl_3$ (δ = 77.1 ppm), acetone-d_6 (δ = 30.3 ppm), benzene-d_6 (δ = 128.0 ppm), dioxane (δ = 68.0 ppm), or TMS (δ = 0.0 ppm). ^{13}C Single Frequency Off Resonance Decoupled Spectra (SFORD) were obtained by setting the irradiation frequency of the decoupler off upfield of the resonance for tetramethylsilane, and are reported in parentheses along with the ^{13}C-NMR data. In reporting chemical shift data for hydantoin derivatives, IUPAC numbering of the hydantoin ring (LVIII, p. 281) is used throughout to avoid confusion. The ^{29}Si-NMR spectra were referenced to tetramethylsilane (δ = 0.0 ppm). Infrared spectra were obtained on a Perkin-Elmer Model 1330

spectrometer. Melting points were recorded using a Fisher-Johns melting point apparatus and are uncorrected. Gas chromatographic analyses were obtained using a Varian Model 3700 gas chromatograph employing an SE-30 column which was interfaced with a Hewlett-Packard Model 3390A integrator. Thin layer chromatographic analyses were performed on Fisherbrand GF 250 μm TLC plates using a phosphomolybdic acid (5% w/v in ethanol) solution as an indicator. Column chromatographic separations were accomplished using Davisil silica gel. Ion exchange chromatography was performed on Dowex 1-X10 or 1-X8 anion exchange resin (previously converted to the hydroxide form by washing it with 1 N NaOH). Paper chromatographic analysis of amino acid compounds was performed on Kodak cellulose TLC sheets using a ninhydrin solution as an indicator (0.2 g ninhydrin in 50 mL H_2O). The presence of a purple spot on the paper chromatograph after drying it in an oven, or alternatively, with a hot air gun, indicated the presence of an amino acid. The commercially available chemicals, their manufacturers, and the methods of purification used, when applicable, are listed in Table 7-1. Reagents previously listed in Tables 3-1, 4-6, 5-8, or 6-12 are not repeated here. The alkynyl aldehydes used in this chapter were prepared by the PCC/Na-OAc or PDC procedures outlined in Chapter IV. The alkynyl hydantoins used in this chapter were prepared via the

Table 7-1: Manufacturer and Methods of Purification of Commercially Available Chemicals

Reagent	Manufacturer[a]	Method of Purification[b]
Acetonitrile	F	
Acetonitrile, anhydrous	F	1
Alanine	F	
Alanine, anhydrous	A	2
Alumina	F	
Benzene	F	
Benzene-d_6	N, A, W	
Benzonitrile	A	3
Benzylamine	A	3
Bromobenzene	F	3
t-Butyllithium, 1.6 M solution in Hexanes	A	
4-Bromo-1-butene	Fl	
Calcium Chloride	F	
Copper Oxide	F	
Diisopropylamine	F	1
4,4'-Dimethoxybenzophenone	A	
Ethanol, anhydrous	US	4
Hexamethylphosphoramide	A	
Hexamethylphosphoramide, anhydrous	A	1

Table 7-1 (continued)

Reagent	Manufacturer[a]	Method of Purification[b]
Hydrochloric Acid, gas	M	
Lithium Aluminum Hydride	F	
Lithium Diisopropylamide, 1.0 M solution in THF	A	
Methanol, anhydrous	AS	5
4Å Molecular Sieves	F	6
2-Octanone	E	
Potassium Carbonate	F	
Sodium Sulfide Nonahydrate	F	
Tetra-n-Butylammonium Bromide	A	
Thionylchloride	A	
Trimethylsilylcyanide	A	

[a]Manufacturers
A = Aldrich Chemical Company
AS = American Scientific Company
E = Eastman Chemical Company
F = Fisher Scientific Company
Fl = Fluka Chemical Corporation
M = Matheson
US = US Industrial Chemicals

[b]Methods of Purification
1. Distilled from Calcium hydride under argon
2. Dried by azeotropic removal of water with benzene followed by drying under vacuum prior to use
3. Distilled
4. Distilled from sodium ethoxide under argon
5. Distilled from sodium methoxide under argon
6. Dried under vacuum at 150°C prior to use

Bucherer-Bergs reaction outlined in Chapter V. All other reagents were prepared as described below.

2. Route Via Alkynyl Hydantoins

a. Attempted Hydrolysis of 5-(4-Pentyn-1-yl)2,4-Imidazolidine-1,3-dione Under Pressure

Into the stainless steel Parr bomb depicted in Figure 7-2 that was equipped with a magnetic stirring bar were placed 5-(4-pentyn-1-yl)2,4-imidazolidine-1,3-dione (2.41 mmol, 400 mg) and sodium hydroxide solution (6.25 N, 10 mL). The bomb was sealed, and the contents placed in a preheated oil bath (210°C) for 30 minutes. After cooling the contents in an ice bath, the bomb was opened, and the basic solution loaded onto a 2 cm x 30 cm column of Dowex 1X-8 (previously converted to the hydroxide form). The column was eluted with distilled water until the eluant was neutral (pH paper), and the product eluted off with 1 N HCl. The first few acidic fractions contained the amino acid (ninhydrin detection). The fractions containing the amino acid were evaporated to dryness, dissolved in D_2O, and the product analyzed by ^{13}C-NMR spectroscopy; this revealed that the alkyne functionality had decomposed; ^{13}C-NMR (D_2O, external benzene-d_6 reference): δ 172.61 (COO^-), 172.28 (COO^-), 67.70, 57.44, 37.76, 32.36, 27.04, 25.66, 24.96, 23.39, 9.9.

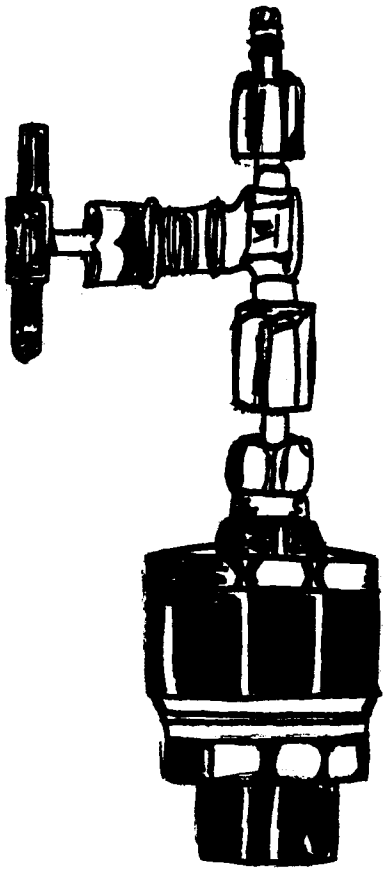


Figure 7-1. Parr Bomb Used in Attempted Hydantoin Hydrolysis

b. Attempted Hydrolysis of 5-(10-Undecyn-1-yl)2,4-Imidazolidine-1,3-dione Under Pressure

To a stainless steel bomb equipped with a magnetic stirring bar were added 5-(10-undecyn-1-yl)2,4-imidazolidine-1,3-dione (4.23 mmol, 1.0 g) and sodium hydroxide solution (6.25 N, 10 mL). The bomb was sealed, and the contents placed in a preheated oil bath (210°C) for 30 minutes. After cooling the contents in an ice bath, the bomb was opened, and the contents evaporated to dryness and analyzed by ^{13}C-NMR spectroscopy; this revealed that the alkyne group had decomposed; ^{13}C-NMR (D_2O-NaOH, dioxane internal reference): δ 185.28 (COO^-), 57.56, 55.81, 36.23, 31.86, 29.83, 29.61, 26.42, 24.61, 20.52.

c. Attempted Basic Hydrolysis of 5-(10-Undecyn-1-yl)2,4-Imidazolidine-1,3-dione

To a 100 mL round-bottomed flask were added 5-(10-undecyn-1-yl)hydantoin (4.23 mmol, 1.00 g), sodium hydroxide (84.6 mmol, 3.38 g), and water (15 ml). Dioxane (25 mL) was added to dissolve the hydantoin. The flask was equipped with a magnetic stirring bar and reflux condenser, and the contents refluxed for 4 hours (oil bath temperature 160°C). After cooling, the contents were evaporated to dryness under reduced pressure and analyzed by ^{13}C-NMR spectroscopy. This showed that incomplete hydrolysis had occurred; ^{13}C-NMR

(DMSO-d_6): δ 177.97 (C_1=O), 159.08 (C_3=O), 86.33 (HC≡<u>C</u>R), 70.48 (H<u>C</u>≡CR), 59.06 (C_5, hydantoin), 53.77, 32.29, 31.56, 31.43, 29.12, 28.83, 28.47, 25.58, 24.39, 18.32 (HC≡C<u>C</u>H_2R). The crude product was redissolved in 6.25 <u>N</u> NaOH (15 ml) and dioxane (15 mL) and the solution was heated at 160°C (oil bath temperature) for 18 hours. After cooling, the contents were evaporated to dryness, dissolved in D_2O, and analyzed by ^{13}C-NMR spectroscopy, which showed that the alkyne functionality had dissappeared; ^{13}C-NMR (D_2O-NaOH, dioxane added as an internal reference): δ 184.7 (COO^-), 56.86, 55.21, 35.62, 31.68, 30.40, 29.53, 29.24, 29.02, 25.82, 24.12, 19.92.

3. <u>Route Via Strecker Reaction</u>

To a 250 mL round-bottomed flask were added ammonium chloride (45 mmol, 2.41 g), potassium cyanide (15 mmol, 0.98 g), ethanol (30 mL), and 10-undecynal (15 mmol, 2.49 g). The flask was equipped with a magnetic stirring bar, reflux condenser, and gas outlet, and the contents were heated at 70°C for 6 hours, and then stirred overnight at room temperature. The reaction mixture was evaporated to dryness, and 50% HCl (30 mL) was added <u>slowly</u> (Caution: USE HOOD! HCN vapors are given off!). The mixture was refluxed for 18 hours, cooled, saturated with salt, and extracted with ethyl acetate (3x25 mL). The combined organic layer

was dried ($MgSO_4$), filtered, and the solvent removed to give a dark brown oil; ^{13}C-NMR (acetone-d_6): δ 206.23 (C=O), 175.46 (COO^-), 172.86 (COO^-), 143.85 (-NH(C=O)NH), 112.92 (C≡N), 84.96 (HC≡CR, very small), 70.06 (HC≡CR, very small), 44.01, 39.80, 34.61, 31.05, 30.13, 29.46, 28.05, 25.79, 24.58, 21.17, 19.00. The aqueous layer was evaporated to dryness under reduced pressure, dissolved in D_2O, and analyzed by ^{13}C-NMR spectroscopy; ^{13}C-NMR (D_2O-NaOH): δ 184.7 (COO^-), 56.86, 55.21, 35.62, 31.68, 30.40, 29.53, 29.24, 29.02, 25,82, 24.12, 19.92. The combined residue (ethyl acetate and aqueous layers) was loaded onto a 2 cm x 30 cm column of Dowex 1X-8 anion exchange resin (previously converted to the hydroxide ion form) and the column eluted with distilled water until the eluant from the column was neutral (pH paper). The product was washed off using 1 N HCl and the fractions containing an amino acid (ninhydrin detection) were combined. After evaporation to dryness, the resulting cream-colored solid was analyzed by ^{13}C-NMR spectroscopy; ^{13}C-NMR (D_2O, dioxane added as an internal reference): δ 173.61 (C=O), 54.35, 44.81, 30.97, 29.48, 29.42, 25.39, 24.67.

4. Route Via Modified Strecker Reaction

a. 4,4'-Dimethoxybenzhydrol

The procedure described by Hanson and Law[563] was used

here. An oven dried 1000 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, claisen head adapter, addition funnel, reflux condenser, and gas outlet, assembled while hot, and purged with argon. The flask was momentarily opened while flushing with argon to introduce solid lithium aluminum hydride (165.14 mmol, 6.27 g), and the apparatus closed and purged with argon. Anhydrous ether (300 mL) was added by double ended needle, and then a solution of 4,4'-dimethoxybenzophenone (82.57 mmol, 20.0 g) in anhydrous THF (200 mL) was transferred to the addition funnel by use of a canula and added dropwise. After the addition was complete, the contents were heated to reflux for 3 hours, and then stirred overnight at room temperature. The flask was cooled to 0°C and the excess LAH was destroyed by the dropwise addition of water [Note: The addition of water was continued until the dark grey slurry had turned light grey in color]. Aqueous HCl (1 N) was added until the lithium salts dissolved, the ether layer was separated, and the aqueous layer extracted with ether (2x25 mL). The combined ether layers were washed with saturated brine, and then dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent, gave a yellow oil, which solidified upon standing. Recrystallization from petroleum ether afforded 4,4'-dimethoxybenzhydrol, 16.60g (82%), as silky white needles;

mp 71°C [lit[564] 72°C]; ^{1}H-NMR ($CDCl_3$): δ 7.4-6.8 (m, 16H, AA'BB', aromatic), 5.60 (s, 1H, C<u>H</u>OH), 3.73 (s, 12H, CH_3O-), 2.88 (s, 1H, CHO<u>H</u>); ^{13}C-NMR ($CDCl_3$): δ 152.64 (MeO<u>C</u>, aromatic C), 130.38 (<u>C</u>-CHOH, aromatic carbon), 121.60 (aromatic carbon meta to MeO), 107.57 (aromatic carbon ortho to MeO), 69.02 (<u>C</u>HOH), 49.03 (O<u>C</u>H_3).

b. <u>4,4'-Dimethoxybenzhydryl chloride</u>

An oven dried three-neck 1000 mL round-bottomed flask was equipped with a rubber septum, glass stopper, and gas outlet (mercury bubbler), flame dried, and purged with argon. 4,4'-Dimethoxybenzhydrol (56.69 mmol, 13.85 g) dissolved in anhydrous ether (200 mL) was introduced into the flask by use of a double ended needle, and anhydrous HCl gas bubbled into the ethereal solution through a glass pipet fitted through the rubber septum. The HCl gas was bubbled into the solution for thirty minutes, during which time the solution turned pink. Removal of the ether under reduced pressure yielded a residue which was redissolved in ether. Drying the ethereal solution over anhydrous magnesium sulfate, and filtration yielded, after removal of the solvent <u>in vacuo</u>, 13.01 g (99%) of 4,4'-dimethoxybenzhydryl chloride as a pink solid; ^{1}H-NMR ($CDCl_3$): δ 7.4-6.8 (m, 16H, AA'BB', aromatic), 6.05 (s, 1H, C<u>H</u>Cl), 3.65 (s, 12H, CH_3O-); ^{13}C-NMR ($CDCl_3$): δ 159.06 (MeO<u>C</u>, aromatic C),

133.33 (C-CHOH, aromatic carbon), 128.78 (aromatic carbon meta to MeO), 113.59 (aromatic carbon ortho to MeO), 64.02 (CHCl), 54.89 (OCH_3).

c. 4,4'-Dimethoxybenzhydrylamine

To a 1000 mL round-bottomed flask equipped with a magnetic stirring bar, septum inlet (to mercury bubbler), dry ice condenser, and gas outlet (for introduction of ammonia gas) was assembled while hot, purged with nitrogen, and flame dried. The flask was momentarily opened while flushing with nitrogen to introduce solid 4,4'dimethoxybenzhydryl chloride (43.68 mmol, 10.08 g). Dry ice was placed in the dry ice condenser, and the flask cooled to -78°C. Ammonia gas was introduced through the gas outlet, and the addition continued until approximately 250 mL had been collected in the flask. The contents were allowed to stir at -78°C for three hours, and then the stirring continued while gradually allowing the contents to come to room temperature, during which time the liquid ammonia evaporated. The next day, the solid residue was dissolved in ether, and the solution washed with saturated brine (50 mL), and then with water (50 mL). After drying ($MgSO_4$), filtration and removal of the solvent yielded 8.64 g of the crude product as a yellow oil. Purification by column chromatography (silica gel, solvent gradient from 1% MeOH-methylene

chloride to 5% MeOH-methylene chloride) gave 5.40 g (51%) of 4,4'-dimethoxybenzhydrylamine as a light yellow oil, which solidified upon standing. An additional 1.00 g of impure amine was collected from the column. Recrystallization of this material from petroleum ether/minimal benzene at -30°C gave an additional 0.89 g of the pure amine (total yield, 6.29 g (59%); mp 58-59°C [lit.[565] 58-59°C; ^{1}H-NMR ($CDCl_3$): δ 7.4-6.8 (m, 16H, AA'BB', aromatic), 5.10 (s, 1H, C<u>H</u>NH_2), 3.76 (s, 12H, CH_3O-), 1.81 (s, 2H, NH_2); ^{13}C-NMR ($CDCl_3$): δ 158.52 (MeO<u>C</u>, aromatic C), 138.29 (<u>C</u>-$CHNH_2$ aromatic carbon), 127.91 (aromatic carbon meta to MeO), 113.86 (aromatic carbon ortho to MeO), 58.57 (<u>C</u>HNH_2), 55.32 (O<u>C</u>H_3).

d. <u>Attempted Preparation of 2-Methyl-2-Aminooctanoic Acid</u>

The procedure reported by Greenlee[427] was used. To an oven dried 100 mL round-bottomed flask fitted with a septum inlet was added activated 4Å molecular sieves (6.0 g). The flask was equipped with a rubber septum (mercury bubbler), and purged with argon. Anhydrous methylene chloride (40 mL), 2-octanone (20 mmol, 2.56 g), and benzylamine (20 mmol, 2.14 g, 2.18 mL) were sequentially added by syringe, and the contents stirred at room temperature for 3 hours. Trimethylsilyl cyanide (22 mmol, 2.18 g, 2.93 mL) was added by syringe, and the contents stirred for 72 hours. The reaction mixture was filtered, and the solvent removed to

give a cloudy yellow oil. ^{13}C-NMR analysis of the crude intermediate showed complete formation of the aminonitrile; ^{1}H-NMR ($CDCl_3$): δ 7.3-7.0 (broad singlet, 5H, aromatic), 3.72 (s, 2H, N-CH_2-Ar), 1.8-1.1 (broad envelope, 13 H), 1.0-0.7 (broad envelope, 3H, CH_2CH_3); ^{13}C-NMR ($CDCl_3$): δ 139.10 (d, NH-CH_2-C), 128.19 (d), 128.02 (d, aromatic carbons ortho and meta to CCH_2), 126.99 (d, aromatic carbon para to CCH_2), 121.93 (CN), 55.43 (s, quaternary C-CN), 48.85 (t, $NHCH_2$), 39.69 ($RCH_2C(4°)$), 31.29 ($CH_3CH_2CH_2R$), 28.91, 24.47, 23.58, 22.75 (CH_3CH_2), 13.77 (CH_3). Aqueous 6 M HCl (60 mL) was added to the crude amimonitrile and the mixture was refluxed for 7 hours. TLC analysis of the crude reaction mixture indicated the presence of a carbonyl compound (2,4-dinitrophenylhydrazine indicator). The reaction mixture was extracted with ether (3x50 mL), and the combined ether layers were dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent, gave 2.21 g (86%) of a brown oil, which was identified to be 2-octanone; ^{13}C-NMR ($CDCl_3$): 208.85 (C=O), 43.54 ($-CH_2(C=O)CH_3$), 31.43 ($CH_3CH_2CH_2$), 29.51 ($R(C=O)CH_3$), 28.67, 23.63, 22.30 (CH_3CH_2-R), 13.73 (CH_3). The aqueous layer was adjusted to ph = 10 and extracted with chloroform (3x25 mL). The combined organic layer was dried ($MgSO_4$), filtered, and the solvent removed to give 2.02 g (94%) of benzylamine; ^{1}H-NMR ($CDCl_3$): δ 7.23 (broad singlet, 5H, aromatic), 3.74 (s, 2H, CH_2),

1.88 (CH_3); ^{13}C-NMR ($CDCl_3$): δ 142.73 (C-CH_2NH_2, aromatic), 128.02, 128.61 (aromatic), 126.29 (aromatic, para to CH_2NH_2), 45.87 (CH_2).

e. Attempted Preparation of 2-Methyl-2-Aminooctanoic Acid by the Sealed Tube Hydrolysis of the Aminonitrile

The aminonitrile (20 mmol) was prepared according to the procedure described above in part 7.D.4.d. The crude aminonitrile was placed in a reaction tube similar to that depicted earlier in Figure 4-2 (p. 177). Aqueous 6 M HCl (30 mL) was added to the crude amimonitrile, the contents of the tube frozen, flushed with argon, and the tube sealed. The reaction mixture was heated at 140°C for 7 hours. The tube was cooled and opened. TLC analysis of the crude reaction mixture indicated the presence of a carbonyl compound (2,4-dinitrophenylhydrazine indicator). The reaction mixture was extracted with ether (3x50 mL), and the combined ether layers were dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent, gave 2.06 g (80%) of a brown oil, which was identified to be 2-octanone; ^{13}C-NMR ($CDCl_3$): 208.85 (C=O), 43.54 (-CH_2(C=O)-CH_3), 31.43 ($CH_3CH_2CH_2$), 29.51 (R(C=O)CH_3), 28.67, 23.63, 22.30 (CH_3-CH_2R), 13.73 (CH_3).

5. Route Via Alkylation of Ethyl (N-Diphenylmethylene) Alaninate: Phase Transfer Catalysis Method

a. 4-Pentyn-1-yl Toluenesulfonate

The procedure described by Kabalka was followed here[562]. In a 500 mL round-bottomed flask equipped with a magnetic stirring bar were placed chloroform (100 mL, filtered through a plug of alumina prior to use) and 4-pentyn-1-ol (100 mmol, 8.41 g). The solution was cooled to 0°C (ice bath) and pyridine (200 mmol, 15.82 g) was added, followed by the addition of p-toluenesulfonylchloride (150 mmol, 28.60 g) in small portions with constant stirring. After 2.5 hours at 0°C, the reaction was still not quite complete (monitored by TLC), so the contents were allowed to come to room temperature and stir for an additional 4 hours. Ether (300 mL) and water (70 mL) were added, and the aqueous layer separated and washed twice more with ether (50 mL portions). The combined organic layer (very cloudy) was washed sequentially with 2 N HCl (2x100 mL), 5% $NaHCO_3$ solution (2x100 mL), and water (100 mL) and then dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent under reduced pressure, afforded 37.10 g (>100%) of a yellow oil. Purification by column chromatography (silica gel, solvent gradient of 2.5→10% ethyl acetate-petroleum ether) gave 4-pentyn-1-yl toluene-sulfonate, 22.05 g (92.5%) as a white crystalline solid;

R_F = 0.41 [5% ethyl acetate-petroleum ether [Note: The first fraction from the column was excess tosyl chloride, R_F = 0.76 in 5% ethyl acetate-petroleum ether.]; ^{1}H-NMR ($CDCl_3$): δ 7.9-7.2 (m, 4H, AA'BB', aromatic), 4.13 (t, 2H, CH_2OTs), 2.43 (s, 3H, CH_3), 2.35-2.15 (m, 2H, $HC{\equiv}CC\underline{H}_2R$), 2.0-1.75 (m, 3H, $\underline{H}C{\equiv}CR$, $-CH_2C\underline{H}_2CH_2OTs$); ^{13}C-NMR ($CDCl_3$): δ 144.79 (aromatic carbon $\underline{C}$-S), 132.93 (aromatic carbon $\underline{C}$-CH_3), 129.81 (aromatic carbon meta to S), 127.83 (aromatic carbon ortho to S), 82.06 ($HC{\equiv}\underline{C}R$), 69.41 ($H\underline{C}{\equiv}CR$), 68.70 ($\underline{C}H_2OTs$), 27.67 ($\underline{C}H_2CH_2OTs$), 21.54 ($HC{\equiv}C\underline{C}H_2R$).

b. 1-Bromo-4-Pentyne

To a 1 L round-bottomed flask were placed 4-pentyn-1-yl toluenesulfonate (40 mmol, 9.53 g), lithium bromide (200 mmol, 17.37 g) and acetone (500 mL). The contents were refluxed over a steam bath for 24 hours. After cooling, the acetone was removed under reduced pressure, water (100 mL) and petroleum ether (100 mL) were added, and the organic layer was separated. The aqueous layer was extracted twice more with petroleum ether (50 mL portions), and the combined organic layer was dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent, afforded the crude bromide as a light yellow oil. Purification by column chromatography (silica gel, petroleum ether) yielded 1-bromo-4-pentyne, 4.93 g (84%), as a colorless oil; ^{1}H-NMR

($CDCl_3$): δ 3.53 (t, 2H, J=6.2 Hz, $C\underline{H}_2Br$), 2.50-2.35 (m, 2H, $HC{\equiv}CC\underline{H}_2R$), 2.15-1.95 (m, 3H, $\underline{H}C{\equiv}CR$, $-CH_2C\underline{H}_2CH_2Br$); ^{13}C-NMR ($CDCl_3$): δ 82.35 ($HC{\equiv}\underline{C}R$), 69.38 ($H\underline{C}{\equiv}CR$), 32.11 ($\underline{C}H_2Br$), 31.19, ($\underline{C}H_2CH_2Br$), 17.10 ($HC{\equiv}C\underline{C}H_2R$).

c. 10-Undecyn-1-yl Toluenesulfonate

To a 500 mL round-bottomed flask equipped with a magnetic stirring bar were added chloroform (150 mL, filtered through a plug of alumina prior to use) and 10-undecyn-1-ol (150.2 mmol, 25.27 g). The solution was cooled to 0°C (ice bath) and pyridine (300 mmol, 23.73 g, 24.25 mL) was added, followed by the addition of p-toluenesulfonyl chloride (225 mmol, 42.89 g) in small portions with constant stirring. After 2.5 hours at 0°C, the reaction was still not quite complete (monitored by TLC), so the contents were stirred an additional 4 hours while allowing the flask to come to room temperature. Ether (450 mL) and water (110 mL) were added, and the aqueous layer separated and washed twice more with ether (50 mL portions). The combined organic layer (very cloudy) was washed sequentially with 2 N HCl (2x100 mL), 5% $NaHCO_3$ solution (2x100 mL), and water (100 mL) and then dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent under reduced pressure, afforded 37.10 g (>100%) of a yellow oil. Purification by column chromatography (silica gel, solvent

gradient of 2.5 → 10% ethyl acetate-petroleum ether) gave 10-undecyn-1-yl toluenesulfonate, 45.58 g (94.1%) as a white crystalline solid; R_F = 0.31 [10% ether-petroleum ether [Note: The first fraction from the column was excess tosyl chloride, R_F = 0.44 in petroleum ether.]; ^{1}H-NMR ($CDCl_3$): δ 7.8-7.2 (m, 4H, AA'BB', aromatic), 4.01 (t, 2H, CH_2OTs), 2.45 (s, 3H, CH_3), 2.35-2.15 (m, 2H, $HC{\equiv}C\underline{CH_2}R$), 1.93 (m, 1H, $\underline{H}C{\equiv}CR$), 1.75-1.2 (broad envelope, 14H); ^{13}C-NMR ($CDCl_3$): δ 144.68 (aromatic carbon $\underline{C}$-S), 133.30 (aromatic carbon $\underline{C}$-CH_3), 129.84 (aromatic carbon meta to S), 127.94 (aromatic carbon ortho to S), 84.74 ($HC{\equiv}\underline{C}R$), 70.71 ($H\underline{C}{\equiv}CR$), 68.16 ($\underline{C}H_2OTs$), 29.26, 28.97, 28.86, 28.69, 28.48, 25.34, 18.43 ($HC{\equiv}C\underline{C}H_2R$).

d. 1-Bromo-10-Undecyne

In a 500 mL round-bottomed flask were placed 10-undecyn-1-yl toluenesulfonate (15 mmol, 4.84 g), lithium bromide (75 mmol, 6.51 g) and 2-butanone (200 mL). The contents were refluxed over a steam bath for 22 hours. After cooling, the 2-butanone was removed under reduced pressure, water (100 mL) and petroleum ether (100 mL) were added, and the organic layer was separated. The aqueous layer was extracted twice more with petroleum ether (50 mL portions), and the combined organic layer was dried over anhydrous magnesium sulfate. Filtration, followed by

removal of the solvent, afforded the crude bromide as a light yellow oil. Purification by column chromatography (silica gel, petroleum ether, R_F = 0.55 in petroleum ether) yielded 1-bromo-10-undecyne, 3.41 g (98%), as a colorless oil; ^{1}H-NMR ($CDCl_3$): δ 3.40 (t, 2H, J=7.0 Hz, $C\underline{H}_2Br$), 2.30-2.10 (m, 2H, $HC{\equiv}CC\underline{H}_2R$), 2.00-1.70 (m, 3H, $\underline{H}C{\equiv}CR$ (triplet centered at 1.93, J=2.6 Hz is $\underline{H}C{\equiv}CR$) $-CH_2C\underline{H}_2CH_2Br$); ^{13}C-NMR ($CDCl_3$): δ 84.68 ($HC{\equiv}\underline{C}R$), 68.13 ($H\underline{C}{\equiv}CR$), 33.95 ($\underline{C}H_2Br$), 32.86, ($\underline{C}H_2CH_2Br$), 29.32, 29.02, 28.72, 28.48, 28.18, 18.43 ($HC{\equiv}C\underline{C}H_2R$).

e. Ethyl Alaninate Hydrochloride

An oven dried 1 L three-neck round-bottomed flask was equipped with a magnetic stirring bar, glass stopper, dropping addition funnel, and a powder addition funnel. The apparatus was assembled while hot, flame dried, and purged with argon. Dry ethanol (290 mL) was introduced to the flask by use of a cannula, and the flask was cooled to -5°C. To the chilled solution was added, dropwise, thionyl chloride (500 mmol, 59.5 g, 36.5 mL). After the addition was completed, the solution was stirred at -5°C for 5 minutes, and then alanine (500 mmol, 36.47 g, previously dried by azeotropic removal of water with benzene) was added as a solid in small portions with constant stirring while maintaining the bath temperature at -5°C. The resulting

milky white suspension was stirred at -5°C for three hours, and then gradually allowed to come to room temperature and stirred overnight, during which time the solution became clear. The ethanol was removed under reduced pressure, and the resulting yellow oil dissolved in THF (100 mL), and ether (500 mL). The solvent was evaporated under reduced pressure until crystallization of the product began, and the product then permitted to crystallize. Filtration, followed by washing of the precipitate with ether, gave 76.7 g of a white solid (99%). Recrystallization from acetone-ether (minimum amount of acetone) yielded ethyl alaninate hydrochloride, 69.6 g (91%) as white crystals; ^{1}H-NMR ($CDCl_3$): δ 8.68 (s, 3H, NH_3^+, D_2O exchange), 4.5-4.05 (m, 3H, C-H, OCH_2CH_3), 1.72 (d, 3H, J=7.0 Hz, CH_3CH-), 1.29 (t, 3H, J=7.0 Hz, OCH_2CH_3); ^{13}C-NMR ($CDCl_3$): δ 169.98 (COOR), 62.26 (OCH_2CH_3), 49.23 (CH), 15.86 (CH_3CH_2), 13.85 (OCH_2CH_3); ^{1}H-NMR (D_2O, benzene-d_6 external reference): δ 5.15-4.75 (m, 3H, C-H, OCH_2CH_3), 2.27 (d, 3H, J=7.0 Hz, CH_3CH-), 1.89 (t, 3H, J=7.0 Hz, OCH_2CH_3); ^{13}C-NMR (D_2O, benzene-d_6 external reference): δ 171.80 (s, COOR), 64.57 (t, OCH_2CH_3), 49.97 (d, CH), 16.27 (q, CH_3CH_2), 14.34 (q, OCH_2CH_3).

f. Diphenylketimine

The procedure reported by Pickard and Tolbert was used[557]. To a 2 L three-neck round-bottomed flask was added

magnesium turnings (1.10 g-atom, 26.8 g). The flask, which was fitted with a magnetic stirring bar, reflux condenser, addition funnel, gas outlet (mercury bubbler), and rubber septum, was assembled while hot, flame dried, and flushed with argon. After allowing the apparatus to cool under a stream of argon, anhydrous ether (400 mL) was introduced to the flask by use of a canula. Bromobenzene (1.10 mol, 95.3 mL) was transferred to the addition funnel by double-ended needle, and 5 mL were added initially to induce the reaction. After the reaction started, the remaining bromobenzene was added dropwise such that a constant reflux was maintained. After the addition was completed, the contents were heated at reflux for 30 minutes. The reaction mixture was cooled to room temperature, and then a solution of benzonitrile (1.0 mol, 103.1 g, 102 mL) in anhydrous ether (200 mL) was added dropwise so as to maintain a constant reflux. Anhydrous methanol (250 mL) was added by "fast-drop addition" according to the above reference over a 15 minute period to hydrolyze the intermediate magnesium salt, and then the contents stirred for an additional 30 minutes. Filtration, followed by removal of the solvent under reduced pressure, gave the crude ketimine. Distillation of the crude product through a 10 cm vigreaux column gave a forerun, which was collected at 120-130°C (3 Torr). The product was collected at 130-131°C (3 Torr), [lit[557] 127-128°C (3.5

Torr)]. This material was slightly yellow in color. Final distillation through a 25 cm silver-coated vacuum jacketed glass helices column afforded 127.6 g (70%) of diphenylketimine as a colorless oil; bp 110°C (0.15 Torr); GC: 99+% pure; ^{1}H-NMR ($CDCl_3$): δ 9.71 (s, 1H, NH), 7.37 (broad s, 10H aromatic); ^{13}C-NMR ($CDCl_3$): δ 177.81 (C=N), 129.95, 128.02.

g. Ethyl N-(Diphenylmethylene)Alaninate

A 1000 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, and gas outlet, flame dried, and flushed with argon. The flask was momentarily opened while flushing with argon to introduce ethyl alaninate (100 mmol, 15.36 g). The flask was sealed, and then anhydrous methylene chloride (400 mL) added. With stirring, a solution of diphenylketimine (100 mmol, 18.12 g) was added dropwise, and the contents stirred at room temperature for 24 hours. The reaction mixture was filtered to remove the precipitated ammonium chloride, and then the methylene chloride evaporated under reduced pressure. The residue was dissolved in ether (100 mL) and water (100 mL), and the layers separated. The aqueous layer was extracted with ether (2x100 mL) and the combined ether layers were washed with water (200 mL) and dried ($MgSO_4$). Filtration, followed by removal of the solvent, gave 27.8 g of a cloudy

oil. Distillation through a 5 cm vacuum jacketed column afforded ethyl N-(diphenylmethylene)alaninate, 18.57 g (66%) as a colorless oil; bp 151°C (0.08 Torr); GC: 99% pure; ^{1}H-NMR ($CDCl_3$): δ 7.9-7.05 (m, 10H, aromatic H), 4.15 (m, 3H, C<u>H</u>, OC<u>H</u>$_2$CH$_3$), 1.42 (d, 3H, J=7.0 Hz, C<u>H</u>$_3$CH), 1.17 (t, 3H, J=7.0 Hz, OCH$_2$C<u>H</u>$_3$); ^{13}C-NMR ($CDCl_3$): δ 172.82 (s, C=O), 169.60 (s, C=N), 139.53 (s), 136.31 (s), 130.24 (d, aromatic carbon para to C=N), 128.75 (d), 128.56 (d), 127.99 (d), 127.67 (d), 60.79 (d, CH), 60.63 (t, O<u>C</u>H$_2$CH$_3$), 19.16 (<u>C</u>H$_3$CH), 14.21 (OCH$_2$<u>C</u>H$_3$).

h. <u>Attempted Alkylation of Ethyl N-(Diphenylmethylene) Alaninate with 4-Bromo-1-Butene: Literature Procedure[427]</u>

To a 100 mL round-bottomed flask were added ethyl N-(diphenylmethylene)alaninate (5 mmol, 1.40 g), finely powdered potassium carbonate (15 mmol, 2.08 g), 4-bromo-1-butene (5 mmol, 0.68 g), tetra-<u>n</u>-butylammonium bromide (0.5 mmol, 0.16 g), and acetonitrile (10 mL). The flask was equipped with a magnetic stirring bar, reflux condenser, and drying tube ($CaCl_2$). The contents were refluxed for two hours, the acetonitrile was removed under reduced pressure, and the residue dissolved in ether (25 mL). 1 <u>N</u> HCL (5 mL) was added, and the contents stirred for one hour at room temperature. The aqueous layer was separated, acidified by

the addition of concentrated HCl (5 mL), and the resulting solution was refluxed for three hours. Ether (25 mL) was added, and the aqueous layer separated. The aqueous layer was evaporated to dryness and analyzed by NMR spectroscopy, which showed only unreacted alanine and tetra-n-butylammonium bromide; ^{1}H-NMR (D_2O, no reference,) alanine $C\underline{H}_3CH$ present upfield; ^{13}C-NMR (D_2O, external TMS reference): δ 175.16 (COOH), 51.48 (CH, alanine), 18.08 (CH_3, alanine), 60.88 ($NH_3^+\underline{C}H_2$, tetra-n-butylammonium bromide), 25.91 (tetra-n-butylammonium bromide), 21.90 (tetra-n-butylammonium bromide), 15.79 (CH_3, tetra-n-butylammonium bromide).

i. Attempted Alkylation of Ethyl N-(Diphenylmethylene) Alaninate with 4-Bromo-1-Butene: Anhydrous Conditions

A 100 mL round-bottomed flask fitted with a septum inlet was equipped with a magnetic stirring bar, Dean-Stark trap, reflux condenser, and gas outlet (mercury bubbler). The flask was opened momentarily to introduce finely ground potassium carbonate (15 mmol, 2.08 g) and tetra-n-butylammonium bromide (0.5 mmol, 0.16 g). The flask was sealed and flushed with argon. Dry acetonitrile (70 mL) was added to the flask, and the mixture refluxed overnight (to dry the reagents). The next day, the collected volume in the trap was removed, the trap permitted to fill again, emptied, and

the process repeated until the solution volume was approximately 15-20 mL. The flask was cooled, and the Schiff base (5.0 mmol, 1.40 g) and 4-bromo-1-butene (5 mmol, 0.68 g) were added sequentially. The flask was momentarily opened under a stream of argon to introduce activated 4Å molecular sieves (500 mg), resealed, and the reaction mixture refluxed for seven hours (no reaction appeared to occur after one hour on the basis of TLC analysis). The reaction mixture was filtered, the acetonitrile removed under reduced pressure, and the residue dissolved in ether (25 mL) and water (25 mL). Hydrochloric acid (1 N, 5 mL) was added, and the contents stirred at room temperature for one hour. The ether layer was separated, and the aqueous layer washed with ether (1x20 mL). The combined ether layers were dried, filtered, and the solvent removed to give 1.19 g of a yellow oil, which was a mixture of benzophenone, and unreacted 4-bromo-1-butene 8.0-1.15 (aromatic) 5.9-5.5 (m, $H_2C=C\underline{H}R$), 5.2-4.95 (m, $\underline{H}_2C=CHR$), 4.22 (d), 3.6-3.3 (m), 1.55-1.1 (m), 1.0-0.8; ^{13}C-NMR (CDCl3): δ 196.26 (C=O), 137.53 (s), 132.30 (s), 129.95, 128.73, 128.18, 117.32, 68.02 (t), 65.72 (t), 38.72 (d), 30.45 (t), 28.89 (t), 23.74 (t), 22.93 (t), 15.21 (t), 13.99 (t), 10.90 (q). Concentrated HCl (5 mL) was added to the separated aqueous layer, and the resulting mixture refluxed for three hours. The reaction mixture was extracted with ether (2x25 mL) and

the combined ether dried ($MgSO_4$). Filtration, followed by removal of the solvent, gave 1.19 g of the light yellow oil, which was identified as benzophenone; ^{13}C-NMR ($CDCl_3$): δ 196.26 (C=O), 137.35, 132.18, 129.77, 128.06. The separated aqueous layer was evaporated to dryness to give 4.06 g of a cream colored solid; ^{1}H-NMR (D_2O, no reference): $C\underline{H}_3CH$ doublet of alanine present); ^{13}C-NMR (D_2O, TMS external reference): δ 174.75 (COOH), 51.39 (CH, alanine), 18.08 (CH_3, alanine), 60.71 ($NH_3^+\underline{C}H_2$, tetra-n-butylammonium bromide), 25.77 (tetra-n-butylammonium bromide), 21.74 (tetra-n-butylammonium bromide), 15.77 (CH_3, tetra-n-butylammonium bromide).

6. Route Via Alkylation of Ethyl (N-Diphenylmethylene) Alaninate: Alkylation Under Anhydrous Conditions

a. 5-Trimethylsilyl-4-pentyn-1-ol

A 1 L three-neck round-bottomed flask, which was equipped with a magnetic stirring bar, glass stopper, addition funnel, dry ice condenser, and gas outlet (mercury bubbler), was flame dried and purged with argon. The flask was opened momentarily to introduce magnesium turnings (350 mg-atom, 8.41 g), and the apparatus flame dried again. Anhydrous THF (350 mL) was transferred to the flask by use of a double-ended needle and dry ice was placed into the condenser; ethyl bromide (350 mmol, 26.12 g) was then added

dropwise at such a rate so as to maintain a constant reflux. The contents were stirred for 30 minutes. After the addition was completed, the flask was cooled to 0°C, and then a solution of 4-pentyn-1-ol (175 mmol, 14.72 g) in anhydrous THF (50 mL) was added dropwise with stirring at 0°C. The reaction mixture was stirred for an additional 3 hours at 0-15°C, the flask cooled to 0°C, and trimethylsilyl chloride (175 mmol, 44.5 mL) was added dropwise. The contents were stirred overnight, while gradually allowing the reaction mixture to come to room temperature. Aqueous acetic acid (15%, 200 mL) was added, and the resulting mixture was stirred for 30 minutes. The reaction mixture was saturated with salt, and the organic layer was separated. The aqueous layer was extracted with ether (2x75 mL), and the combined ether layers were washed with saturated brine (100 mL), 5% sodium bicarbonate solution (until basic, 100 mL portions), saturated salt solution (100 mL), and then dried ($MgSO_4$). Filtration, followed by removal of the solvent, gave 40.84 g of a yellow oil. Purification by column chromatography (silica gel, solvent gradient of 5% → 20% ethyl acetate-petroleum ether) yielded a colorless oil after removal of the solvent. Final distillation of the product yielded 24.11 g (88%) of 5-trimethylsilyl-4-pentyn-1-ol; bp 118-121°C, 38-39 Torr (a forerun was collected at 60-115°C, 40 Torr); ^{1}H-NMR ($CDCl_3$): δ 3.73 (t, 2H, J=6.2

Hz, C<u>H</u>$_2$OH), 2.52 (t, 1H, J=3.3 Hz, CH$_2$O<u>H</u>), 2.34 (t, 2H, J=6.6 Hz, TMSC≡CC<u>H</u>$_2$R), 1.95-1.6 (tt, 2H, -CH$_2$C<u>H</u>$_2$CH$_2$OH), 0.15 (s, 9H, (CH$_3$)$_3$Si); ^{13}C-NMR ($CDCl_3$): δ 106.73 (TMS<u>C</u>≡CR), 85.14 (TMSC≡<u>C</u>R), 61.55 (<u>C</u>H$_2$OH), 31.21 (CH$_2$<u>C</u>H$_2$CH$_2$OH), 16.48 (<u>C</u>H$_2$OH); ^{29}Si-NMR ($CDCl_3$): δ -19.03.

b. <u>5-Trimethylsilyl-4-pentyn-1-yl Toluenesulfonate</u>

In a 500 mL round-bottomed flask equipped with a magnetic stirring bar were placed chloroform (100 mL, filtered through a plug of alumina prior to use) and 5-trimethylsilyl 4-pentyn-1-ol (91.68 mmol, 14.33 g). The solution was cooled to 0°C (ice bath) and pyridine (183 mmol, 14.50 g) was added, followed by the addition of <u>p</u>-toluenesulfonyl chloride (137.5 mmol, 26.22 g) in small portions with constant stirring. After 2.5 hours at 0°C, the reaction was still not quite complete (monitored by TLC), so the contents were stirred overnight while allowing the flask to come to room temperature. Ether (300 mL) and water (70 mL) were added, and the aqueous layer separated and washed twice more with ether (75 mL portions). The combined organic layer (very cloudy) was washed sequentially with 2 <u>N</u> HCl (2x100 mL), 5% $NaHCO_3$ solution (2x100 mL), water (100 mL), and then dried over anhydrous magnesium sulfate. Filtration, followed by removal of the solvent under reduced pressure, afforded the crude product as a

yellow oil. Purification by column chromatography (silica gel, solvent gradient of 2.5 → 5% ethyl acetate-petroleum ether) gave 5-trimethylsilyl 4-pentyn-1-yl toluenesulfonate, 24.24g (85.2%) as a white crystalline solid; [Note: The first fraction from the column was excess tosyl chloride, R_F = 0.44 in petroleum ether.]; mp 53°C; ^{1}H-NMR ($CDCl_3$): δ 7.9-7.2 (m, 4H, AA'BB', aromatic), 4.13 (t, 2H, J-6.2 Hz, CH_2OTs), 2.43 (s, 3H, CH_3), 2.27 (t, 2H, TMSC≡CC$\underline{H}_2$R), 2.0-1.7 (tt, 2H, $CH_2C\underline{H}_2CH_2OTs$); ^{13}C-NMR ($CDCl_3$): δ 144.68 (aromatic carbon $\underline{C}$-S), 132.95 (aromatic carbon $\underline{C}$-CH_3), 129.81 (aromatic carbon meta to S), 127.75 (aromatic carbon ortho to S), 104.70 (TMS$\underline{C}$≡CR), 85.68 (TMSC≡$\underline{C}$R), 68.84 ($\underline{C}H_2$-OTs), 27.77, 21.49 (Ph-$\underline{C}H_3$), 15.97 (TMSC≡C$\underline{C}H_2$R), -0.07 ($(CH_3)Si$); ^{29}Si-NMR ($CDCl_3$): δ -18.89.

c. Attempted Alkylation of Ethyl N-(Diphenylmethylene) Alaninate with 5-Trimethylsilyl-4-pentyn-1-yl Toluenesulfonate Using Lithium Diisopropyl Amide

A 500 ml round-bottomed flask, which was fitted with a septum inlet, addition funnel and gas outlet, was flame dried, and flushed with argon. n-Butyllithium (1.6 M in hexanes, 5 mmol) was introduced to the flask, followed by the addition of anhydrous THF (50 mL) and anhydrous HMPA (20 mL). The contents were cooled to -78°C, a solution of diisopropylamine (5 mmol, 0.50 g) in anhydrous THF (10 mL)

was added dropwise, and the resulting mixture stirred at -78°C for one hour. At -78°C, a solution of ethyl N-(diphenylmethylene)alaninate (5 mmol, 1.40 g) in anhydrous THF (10 mL) was added stirred for one hour. A solution of 5-trimethylsilyl-4-pentyn-1-yl toluenesulfonate (5 mmol, 1.23 g) in anhydrous THF (10 mL) was added dropwise at -78°C, stirred for one hour, and then for an additional two hours while allowing the contents of the reaction to warm to room temperature. Water was added (100 mL), the mixture saturated with sodium chloride, and the organic layer was separated. The combined ether layers were washed with 1 N HCl (3x100 mL), dried, filtered, and the organic layer removed. The aqueous layer was adjusted to pH = 9 with aqueous sodium bicarbonate solution (saturated), and extracted with ether (3x50 mL). The combined ether layers were dried, filtered, and the solvent removed to give 2.92 g of an orange-yellow oil, which contained benzophenone, unreacted Schiff base, and some of the desired alkylated Schiff base; ^{1}H-NMR ($CDCl_3$): δ 7.8-7.1 (aromatic), 4.3-4.05 (m, C<u>H</u>, OC<u>H</u>$_2$CH$_3$, Schiff base), 2.65 (d, 2.43 s, Ar-C<u>H</u>$_3$), 2.0-1.7 (m), 1.43 (d, C<u>H</u>$_3$CH, Schiff base), 1.25 (t, OCH$_2$C<u>H</u>$_3$, Schiff base); ^{13}C-NMR ($CDCl_3$): δ 197.15 (C=O, benzophenone), 172.69 (<u>C</u>OOEt), 169.52 (C≡N), 144.05, 139.48 (<u>C</u>H=CH$_2$), 136.25, 130.19, 129.81, 129.10, 128.94, 128.70, 128.40, 128.51, 127.94, 127.83, 127.62, 104.32 (CH=<u>C</u>H$_2$),

68.84 ($\underline{C}H_2OTs$), 67.86 (quaternary carbon), 60.74 (CH, Schiff base) 60.57 (CH, Schiff base), 36.87, 36.68 (CH_2), 27.80, 25.53 (CH), 21.54, 19.10, 16.02 ($\underline{C}H_3CH$), 14.15 (CH_3), -0.40 $(CH_3)_3Si$; ^{29}Si-NMR ($CDCl_3$): δ -18.9.

d. Attempted Alkylation of Ethyl N-(Diphenylmethylene) Alaninate with 4-Bromo-1-Butene Using Lithium Diisopropyl Amide

A 500 mL round-bottomed flask fitted with a septum inlet was equipped with an addition funnel and gas outlet, flame dried, and flushed with argon. A solution of ethyl N-(diphenylmethylene)alaninate (5 mmol, 1.40 g) in anhydrous THF (10 mL) was introduced to the flask, followed by the addition of anhydrous THF (50 mL) and anhydrous HMPA (20 mL). The contents were cooled to -78°C, a solution of lithium diisopropylamide (1.0 M, 5 mL) was added dropwise, and the resulting mixture stirred at -78°C for one hour. At -78°C, 4-bromo-1-butene (5 mmol, 0.68 g, 0.51 mL) was added dropwise, stirred for one hour, and then for an additional 2 hours while allowing the contents to come gradually to room temperature. Water was added (100 mL), the mixture saturated with salt, and the organic layer was separated. The combined ether layers were washed with 1 N HCl (3x100 mL), dried, filtered, and the solvent removed to give 0.67 g of a yellow oil. The crude residue contained unreacted Schiff

base, and benzophenone; ^{1}H-NMR ($CDCl_3$): δ 7.8-7.2 (aromatic), 4.3-4.05 (m, C<u>H</u>, OC<u>H</u>$_2$CH$_3$, Schiff base), 1.41 (d, C<u>H</u>$_3$CH, Schiff base), 1.28 (t, OCH$_2$C<u>H</u>$_3$, Schiff base); ^{13}C-NMR ($CDCl_3$): δ 197.15 (C=O, benzophenone), 172.42 (<u>C</u>OOEt), 169.22 (C≡N), 139.21, 137.23, 135.96, 132.06, 129.92, 129.62, 128.40, 128.24, 127.94, 127.67, 127.31, 60.41 (CH, Schiff base) 60.30, 36.58, 36.41, 18.81 <u>C</u>H$_3$CH, Schiff base), 13.88, OCH$_2$<u>C</u>H$_3$, Schiff base). The aqueous layer was adjusted to pH = 9 with aqueous sodium bicarbonate solution (saturated), and extracted with ether (3x50 mL). The combined ether layers were dried, filtered, and the solvent removed to give 2.90 g of an orange-yellow oil, which contained benzophenone, unreacted Schiff base, and some of the desired alkylated Schiff base; ^{1}H-NMR ($CDCl_3$): δ 7.8-7.2 (aromatic), 4.3-4.05 (m, C<u>H</u>, OC<u>H</u>$_2$CH$_3$, Schiff base), 1.50-1.0 (this region is not the normal doublet-triplet pattern seen before, but contains a singlet at 1.15 ppm which disturbs the pattern; ^{13}C-NMR ($CDCl_3$): δ 197.15 (C=O, benzophenone), 172.69 (<u>C</u>OOEt), 169.52 (C≡N), 166.40, 144.05, 141.05, (<u>C</u>H=CH$_2$) 139.48, 138.56, 137.53, 137.28, 136.25, 132.25, 129.92, 128.70, 128.51, 128.40, 128.15, 127.94, 127.72, 127.59, 125.48, 114.32 (CH=<u>C</u>H$_2$), 65.89 (quaternary carbon), 60.68 (CH, Schiff base) 60.57, 60.18 (O<u>C</u>H$_2$CH$_3$, alkylated Schiff base), 42.21, 28.80 (CH$_2$), 28.42, 24.42 (CH), 19.05, 15.53 (<u>C</u>H$_3$CH), 14.10 (CH$_3$), 13.77, (CH$_2$<u>C</u>H$_3$,

Schiff base).

7. Route Via Alkylation of Alanine Copper Complex

a. Copper Complex of Alanine

Alanine (449 mmol, 40 g) was suspended in water (300 mL) and sodium hydroxide (449 mmol, 17.97 g) added. The contents of the flask were stirred until the alanine had dissolved, and then copper oxide 449 mmol, 35.7 g) was added in portions. The solution was stirred for one hour. Hydrogen sulfide gas (externally generated by the addition of 50% HCl to an aqueous solution of disodium sulfide, HOOD!) was bubbled into the solution to precipitate the excess copper hydroxide. The solution filtered through a pad of celite and the complex precipitated by the addition of acetone. Recrystallization from acetone-water gave, after drying, 40.9 g (76%) of a blue colored solid; ^{1}H-NMR (D_2O, benzene-d_6 external reference): δ 8.0-0.8 (broad noisy hump), 1.5-1.2 (m, CH), 0.14 (s, CH_3). The complex was only slightly soluble in D_2O; a ^{13}C-NMR spectrum could not be obtained.

b. Attempted Alkylation of the Alanine Copper Complex With 4-Bromo-1-Butene

The dry copper complex (5 mmol, 1.20 g, dried by azeotropic removal of water with benzene, followed by drying

under vacuum) was placed in a 100 mL round-bottomed fitted with a septum inlet. The flask was equipped with a magnetic stirring bar and gas outlet, flame dried, and flushed with argon. Dry hexamethylphosphoramide (40 mL) was introduced to the flask, the contents cooled to -10°C, and t-butyllithium added slowly. The blue solution turned green. The solution was stirred for one hour at -10°C; 4-bromo-1-butene (10 mmol, 1.36 g, 1.02 mL) was then added dropwise and the resulting mixture stirred for three hours, during which time the contents were gradually allowed to warm to room temperature. The reaction mixture was made basic (pH = 10), washed with ether (3x25 mL), and the aqueous layer reduced in volume and analyzed by ^{13}C-NMR spectroscopy; ^{13}C-NMR (D_2O, dioxane added as an internal standard): δ 172.23 (COO^-), 171.0 (COO^-), 135.09 ($\underline{C}H=CH_2$), 118.68 ($CH=\underline{C}H_2$), 65.5, 61.42, 57.09, 49.80, 43.71, 37,60 (HMPA), 31.87, 29.86, 28.70, 17.00. The basic mixture was poured onto a column of Dowex 1X-8 (previously converted to the hydroxide form), eluted with distilled water until the eluant was neutral, and then washed with 1 N HCl. The acidic fractions containing an amino acid were combined and evaporated to dryness. Only alanine was recovered from the column; ^{1}H-NMR (D_2O, external TMS reference): δ 1.45 (d, $C\underline{H}_3CH$); ^{13}C-NMR (D_2O, dioxane was added as an internal reference): δ 177.21 (COOH), 51.94 (CH), 36.01 (HMPA), 17.64 (CH_3).

CHAPTER VIII

CONCLUSIONS OF THE STUDY

The development of a site specific radiolabeled amino acid was the goal of this research project. Specifically unnatural iodovinyl-α-methyl-α-amino acids appeared to be promising candidates. The synthesis of a model amino acid, 2-amino-12-iodo-11-dodecenoic acid, was achieved in a 13.7% yield (over the final two steps).

The synthesis of the unnatural amino acids involved the use of hydantoin methodology. The planned synthesis of a model compound, 2-amino-2-methyl-12-iodo-11-dodecenoic acid, proceeded as planned up to the preparation of the vinylboronic acid precursor. The strategy developed included a totally new approach to the synthesis of acetylenic carbonyl compounds; the study was summarized in an article which appeared in Organic Preparations and Procedures International (**1988**, 20, 63). However, the vinylboronic acid functionality proved too heat sensitive to survive known hydrolysis procedures. A number of attempts at finding an alternative low temperature hydrolysis reaction of the hydantoin ring, such that the vinyl boronic acid could survive were unsuccessful. Modification of the synthetic strategy (reversing the iodination and hydantoin hydrolysis steps also proved

troublesome, as the nitrogen functionality of the hydantoin ring interfered with the iodination reaction, requiring the use of excess iodide ion (a highly undesirable solution from a radiopharmaceutical standpoint). Attempted use of protecting groups (H^+, tosyl, BOC) for the hydantoin nitrogens was also not successful.

It is possible that the route employing the tosyl protecting group was abandoned prematurely. Recent experiments have indicated that the tosylation step will occur if the C-5 position of the hydantoin ring is fully substituted. For example, 5-hexyl-5-methylhydantoin gave a 45% yield of the N-3 tosyl derivative (result similar to that reported earlier with 5,5-dimethylhydantoin). Low selectivity, however, is still a problem, as an appreciable amount of the ditosyl derivative is also formed (18%). Recall that the model compound, 5-(10-undecyn-1-yl)2,4-imidazolidine-1,3-dione), possessed a C-5 hydrogen. The failure of this compound to yield tosylated hydantoins probably was a result of a competitive reaction at the C-5 site. If a selective means of protecting the hydantoin moiety with the tosyl group can be found, then this route could provide a high yielding synthesis of iodovinyl amino acids.

Finally, the direct iodination of an unprotected alkynyl hydantoin deserves re-examination. In a recent

experiment, an equimolar mixture of 5,5-dimethylhydantoin and (E)-decenylboronic acid was subjected to electrophilic iodination using N-chlorosuccinimide (2 equiv.) as the oxidant instead of chloramine T. When only one equivalent of NaI was used in the above procedure, a 93% yield of a compound was isolated from column chromatography (TLC, one spot, R_F=solvent front, petroleum ether). NMR analysis of this material revealed that the compound isolated was actually a mixture of 3 products, most of which was the desired (E)-1-iododecene. However, two other impurities were also present, which could possibly be either the (Z)-iodo compound, or a chlorovinyl adduct, both of which have never been observed in previous iodination reactions. In a final experiment, when the reaction was repeated using an equivalent amount of sodium acetate to buffer the reaction mixture, similar results were observed.

During the course of these studies, a previously unreported hydroboration of silicon protected alkynyl carboxylic acids was discovered, which led to a detailed investigation of the hydroboration and reduction of silicon esters. The results of this study have been submitted for publication in Organometallics. A convenient procedure involving the in situ formation of the TMS ester during the hydroboration reaction was also developed. These results will soon be submitted to Synthetic Communications.

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VITA

Donald Elton Bierer Jr. was born on 4 July 1958 in Mansfield, Ohio. After a series of moves and the death of his father, he settled in Indiana, Pennsylvania in 1970, where he attended Indiana Area Junior High School and Indiana Area Senior High School. He graduated from Indiana Area Senior High School in June 1976. In September 1976, he entered the Indiana University of Pennsylvania (IUP) and graduated in December 1980 with a Bachelor of Science degree in Chemistry and Criminology. In February 1981, he accepted a position with Rola Company, a Division of International Jensen, where he was employed as an analytical chemist until September 1982. In September 1982, he entered the University of Tennessee, Knoxville, and began his graduate studies under the direction of Dr. George W. Kabalka. He has coauthored a publication which appeared in Organic Preparations and Procedures International (**1988**, 20, 63) and another which will appear in Organometallics. He has presented papers at three regional meetings and one national meeting of the American Chemical Society. He married Tamela E. Farren in September 1981 and a son, Donald E. Bierer III was born on 28 May 1984. He was divorced in March 1988. He has accepted a post-doctoral position at the University of California, Berkeley under the direction of Professor Henry Rapoport.