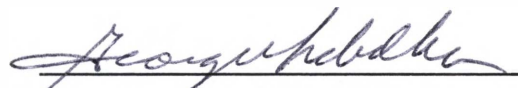
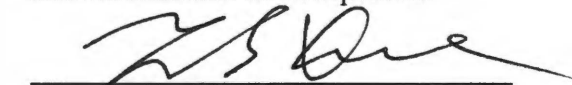
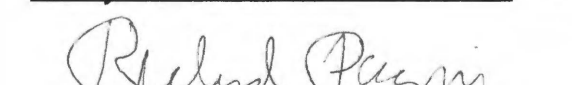
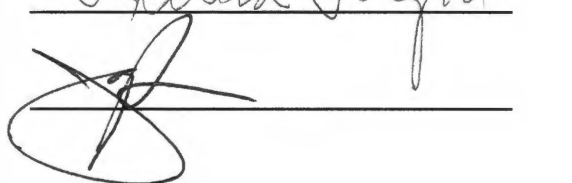


To the Graduate Council:

I am submitting herewith a dissertation written by Nisha R. Natarajan entitled "Synthesis of Boronated Analogues of Tumor Specific Agents." I have examined the final paper 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:

Accepted for the Council


Vice Provost and Dean of Graduate
Studies

**SYNTHESIS OF BORONATED ANALOGUES OF
TUMOR SPECIFIC AGENTS**

A Dissertation
Presented for the
Doctor of Philosophy
Degree

The University of Tennessee, Knoxville

Nisha R. Natarajan

August 2003

Thesis
2003b
.N36

DEDICATION

This dissertation is dedicated to
my grandmother Sulochana Pansare,
my parents Shaila and Ramaswamy Natarajan,
my sister Akhila, and
my husband Parag
who have loved and inspired me at all time in my life.
Without them, I simply could not have made it till here.

प्रिय आजी, आई, बाबा, अखू, आणि पराग यांना सप्रेम अर्पण.

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ABSTRACT

Boron neutron capture therapy (BNCT) is a binary form of cancer treatment wherein ^{10}B nuclei, when irradiated with thermal neutrons, produce high linear energy transfer particles. These particles, because of their size and energy, are confined to a radius of approximately 9-10 μm , which is comparable to the dimensions of a single cell. The success of BNCT depends upon the development of non-toxic compounds that have the ability to accumulate in tumor cells selectively in the presence of normal cells and are able to achieve concentration levels in the range of 20-35 μg of ^{10}B per gram of tumor. Potential BNCT agents reported in literature include boron-containing amino acids, carbohydrates, nucleic acids, nucleosides, antibodies, and other biomolecules.

This dissertation describes the strategies and methods employed in the synthesis of boronated analogues of a cyclooxygenase-2 (COX-2) enzyme inhibitor, celecoxib, and boronated unnatural cyclic amino acids as potential BNCT agents.

Monosubstituted boron-containing analogues of celecoxib were synthesized. Significant progress was made towards the synthesis of the disubstituted analogues. A radiolabeled analogue of celecoxib for potential use as a Single photon emission computed tomography (SPECT) agent for imaging tumors was also achieved.

The syntheses of five-membered and seven-membered boronated unnatural cyclic amino acids were accomplished. A synthetic strategy was proposed for a water soluble, carborane-containing cascade polyol derivative of the five-membered amino

acid. The progress made towards the synthesis of this water-soluble derivative is also described.

Previous studies reported in literature concerning COX-2 inhibitors and cyclic amino acids provide a good basis for their choice as potential BNCT agents. It is believed that the boronated analogues of celecoxib, and the cyclic amino acids, offer good promise for potential use in cancer treatment. A study of the biodistribution and evaluation of some of these compounds is currently underway.

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LIST OF SYMBOLS AND ABBREVIATIONS

Symbol	Description
°C	Degree Celsius
γ	Weak gamma radiation

Abbreviation	Description
ACBC	1-Aminocyclobutanecarboxylic acid
ACHC	1-Aminocycloheptanecarboxylic acid
ACPC	1-Aminocyclopentanecarboxylic acid
AOM	Azoxymethane
APC	Adenomatous polyposis coli
BNC	Boron neutron capture
BNCT	Boron neutron capture therapy
BPA	4-Dihydroxyborylphenylalanine
CCE	Calcium capacitative entry
cm	Centimeters
COX	Cyclooxygenase
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
DBDU	5-(Dihydroxyboryl)-2'-deoxyuridine
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide

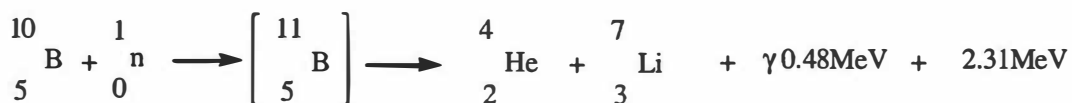
DNA	Deoxyribonucleic acid
DPPF	1,1'-bis(diphenylphosphino)ferrocene
ECT	Emission computed tomography
FAP	Familial adenomatous polyposis
FBP	Filtered back projection
g	Grams
GC	Gas chromatography
h	Hours
HRMS	High resolution mass spectrometry
Hz	Hertz
LET	Linear energy transfer
MeV	Mega electron volt
MHz	Megahertz
min	Minutes
Min	Multiple intestinal neoplasia
mL	Milliliters
mmol	Millimoles
mol	Moles
Ms	Mesyl (methanesulfonyl)
MTBE	Methyl <i>tert</i> -butyl ether
N	Normality
NCT	Neutron capture therapy

Ni-TCP	Nickel tetracarboranylphenylporphyrin
NMR	Nuclear magnetic resonance
NSAID	Nonsteroidal anti-inflammatory drug
PDT	Photodynamic therapy
PET	Positron emission tomography
PGH ₂	Prostaglandin H ₂
PGHS	Prostaglandin H Synthase
RNA	Ribonucleic acid
SPECT	Single photon emission computed tomography
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Tosyl (<i>p</i> -toluenesulfonyl)

Chapter 1 Introduction

§ 1.1 BORON NEUTRON CAPTURE THERAPY

Boron neutron capture therapy (BNCT) is a binary form of cancer treatment whereby ^{10}B nuclei, when irradiated with thermal neutrons, generate high linear energy transfer (LET) particles. These particles, because of their size and energy, are restricted to a radius of approximately 9-10 μm , comparable to the dimensions of a single cell. The lethal radiant energy of these particles thus does not affect adjacent normal cells.^{1,2} The boron neutron capture reaction obtained with thermal neutrons is shown below.



Many different classes of boron compounds have been synthesized as potential BNCT agents. These include boron-containing amino acids,³⁻⁵ hydantoins,^{6,7} carbohydrates,^{8,9} porphyrins,¹⁰⁻¹² nucleosides,^{13,14} nucleotides,^{13,14} nucleic acids,^{13,14} liposomes,¹⁵⁻¹⁷ lipoproteins,¹⁸ antibodies,^{19,20} immunoconjugates,^{19,20} and other biomolecules.

This dissertation deals with the synthesis of boron-containing analogues of the specific cyclooxygenase-2 (COX-2) enzyme inhibitor, celecoxib (commonly known as celebrex), and the synthesis of boron-containing unnatural cyclic amino acids as potential BNCT agents for cancer treatment. The former set of compounds

has also been used in this research as precursors in the synthesis of radiolabeled tumor imaging agents using Single photon emission computed tomography (SPECT). This technique will be introduced in Section 1.2.

§ 1.1.1 Celecoxib and Colon Cancer

Colon cancer is one of the leading causes of cancer deaths in western countries, including the United States.²¹ High levels of prostaglandins have been demonstrated in various cancers including colon cancer.^{22,23} Several epidemiological investigations point towards an inverse relationship between the intake of nonsteroidal anti-inflammatory drugs (NSAIDs) and colorectal cancer risk.²⁴⁻³⁴ The mechanism by which NSAIDs inhibit colon carcinogenesis is not clearly understood but could possibly involve inhibition of prostaglandin production by blockage of the cyclooxygenase (COX-1 and COX-2) enzymes.³⁵ It has been suggested that multiple mechanisms may be involved in the action of NSAIDs, many of which may be prostaglandin independent.³⁴ These mechanisms are outlined in Section 2.2.7.

Typical NSAIDs inhibit both COX-1 and COX-2 in a non-selective manner. Overexpression of the COX-2 enzyme has been observed in colon carcinomas; therefore, specific inhibitors of COX-2 activity could potentially serve as chemopreventive agents against colon carcinogenesis.^{35,36} Non-selective inhibitors of COX-1 and COX-2 have been shown to effectively inhibit tumorigenesis by 70-98% and eliminate established tumors by 75-98%.³⁴ Sulindac, a non-selective NSAID, has been shown to reduce tumor number by as much as 99% in *Apc*^{Min/+} mice.³⁷ It is not

clear if selective COX-2 inhibitors have additional chemopreventive advantages as compared to the non-selective inhibitors although serious problems of gastrointestinal ulceration can result from chronic non-selective NSAID use.

Celecoxib, a potent and specific COX-2 inhibitor, was found to inhibit the occurrence and multiplicity of colon tumors by 93 to 97% and curb the overall tumor burden by more than 87%.³⁸ Celecoxib also demonstrated potent antitumor activity *in vivo*,³⁹ signifying a novel application and potential use of this anti-inflammatory drug in the treatment of human cancer. For this reason, we have focused our efforts on analogues of celecoxib as boron carriers.

§ 1.1.2 Unnatural Cyclic Amino Acids

It is believed that amino acids are preferentially taken up by growing tumor cells. It is for this reason that boron-containing amino acid derivatives have been studied as potential BNCT agents. The only drug currently used in BNCT clinical trials in the United States is a boronated phenylalanine (BPA).⁴⁰ Positron emission tomography (PET) investigations carried out at the University of Tennessee on BNCT patients using both fluorine-18 labeled BPA and carbon-11 labeled 1-aminocyclobutanecarboxylic acid (ACBC) revealed that cyclic amino acids localize in glioblastoma multiforme (malignant brain tumor) more avidly than BPA.⁴¹ For this reason, we have focused our efforts on cyclic amino acids as boron carriers.

§ 1.2 SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)

SPECT involves the detection of gamma rays emitted singly from radionuclides and the determination of relative or absolute regional concentrations of these radionuclides as a function of time within small regions of the body.⁴² Some of the radionuclides that emit gamma rays include technetium-99m, thallium 201, iodine-123, indium-111, and gallium-67. SPECT data involve the accumulation of projection data consisting of a number of line integrals measured from different views around the patient. These data are then reconstructed using mathematical equations. In principle, a chemically stable radiolabeled compound could be used for tumor imaging via SPECT and thus provide valuable information about a particular disease.

A number of radiopharmaceuticals have been synthesized as potential SPECT agents and used as diagnostic tools in a variety of diseases such as in malignant brain tumors,⁴³ in Alzheimer's disease,⁴⁴ in non-small cell lung cancer,⁴⁵ in schizophrenic patients,⁴⁶ and in the study of anti-depressant effects in major depression.⁴⁷ To explore the possibility of SPECT as a diagnostic tool in colon cancer, we have focused our efforts on the synthesis of an iodine-123 labeled analogue of potent cyclooxygenase-2 (COX-2) enzyme inhibitor, celecoxib. High levels of the COX-2 enzyme have been found in colon tumors, hence a selective COX-2 inhibitor like celecoxib could serve as an ideal imaging agent for colon tumors.

Chapter 2 Literature Review

§ 2.1 BORON NEUTRON CAPTURE THERAPY

This section describes the origin, background, and current status of developments in boron neutron capture therapy (BNCT). BNCT was introduced as a new technique to overcome some of the limitations of the current therapies of cancer, as is described in the sections to follow.

§ 2.1.1 Contemporary Therapies of Cancer

The incentive for developing new methods for treatment of cancer has arisen from the drawbacks of existing therapies.² In the case of most cancers involving solid tumors, surgical removal of the malignant tumor is the preferred method of treatment. However, there is always doubt as to whether all the malignant cells have been removed. Residual malignant cells could become the foci for tumor recurrences either at the original site of the tumor or at other locations. The challenge in the development of new cancer therapies lies in the need to destroy malignant cells without the concomitant destruction of nearby normal cells.

In the case of radiotherapy, the dose required to destroy cancer cells is so enormous that neighboring normal cells are severely affected.⁴⁸ The key limitation in the use of radiation is normal tissue tolerance. Similarly, in the case of

chemotherapy, adjacent normal cells are compromised during treatment of malignant cells.⁴⁹

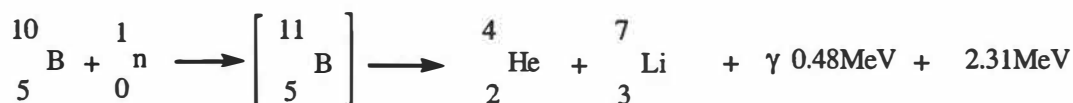
§ 2.1.2 Basis for the Development of Binary Systems for Cancer Treatment

Binary systems have originated from the need for selective and specific destruction of tumor cells.^{1,2} They involve the use of two components for the treatment of cancer. Each component is relatively harmless to mammalian cells, but their combination generates a highly lethal effect. A binary system is valuable because it allows each component to be manipulated independently. For this approach to succeed, it is vital that at least one of the components be limited specifically to the tumor cells while the second component may be exposed to all cells in a particular area. Thus, knowledge of the precise location of tumor cells in order to achieve their destruction is not necessary. Several binary systems now in various stages of development include photon activation therapy,⁵⁰ photodynamic therapy,⁵¹⁻⁵³ use of radiation sensitizers,^{54,55} gene therapy,^{56,57} and neutron capture therapy (NCT).^{1,2,13,58-61}

§ 2.1.3 Principle of Neutron Capture Therapy

Neutron capture therapy (NCT) is based upon the observation that there are certain nuclides, both radioactive and nonradioactive, whose nuclei possess a capacity for absorbing thermal or slow neutrons.⁶² NCT has largely revolved around the use of nonradioactive nuclides.² When boron-10 is the nonradioactive nuclide used, the technique is referred to as Boron neutron capture therapy (BNCT).

BNCT requires the site-specific delivery of large quantities of boron-10 to the tumor ($>15 \mu\text{g boron/g tumor}$).⁶³ After deposition of the boron-10, the area is irradiated with thermal neutrons. These neutrons have energy of approximately 0.025 eV, which is below the level of energy required to ionize tissue components. However, the interaction of the thermal neutrons with the boron-10 nuclei results in the formation of two highly energetic species, a lithium ion and an alpha particle.



The linear energy transfer (LET) of these particles dissipates within 9-10 μm in tissue, the approximate diameter of a single cell. Therefore, irradiation of sufficient quantities of boron-10 in the tumor cells should result in the destruction of tumor cells while normal neighboring cells remain essentially unaffected.

§ 2.1.4 Rationale for the Choice of Boron as a Nuclide in Neutron Capture

Therapy

Boron-10 has a high capture cross section of 3838 barns ($1 \text{ barn} = 10^{-24} \text{ cm}^2$) for thermal neutrons.⁶⁴ This value is large by nuclear standards and exceeds the value for tissue elements like carbon, hydrogen, oxygen, and other normal tissue components by at least two orders of magnitude.⁶⁴

An additional advantage of boron-10 is that many different boron compounds having hydrolytically stable linkages between boron and other elements such as carbon and nitrogen can be synthesized. In addition to covalent bonds with various

elements, there are boron clusters like polyhedral borane anions and carboranes, which possess significant hydrolytic and metabolic stability. Boron, by virtue of its small atomic size, can replace carbon in many organic structures, generating compounds that offer potential for simulating biologically those original compounds from which they are derived. Much of the activity in the area of compound development for NCT has focused upon the use of boron-10.² The term Boron neutron capture therapy (BNCT) is thus widely seen as being synonymous with Neutron capture therapy (NCT).

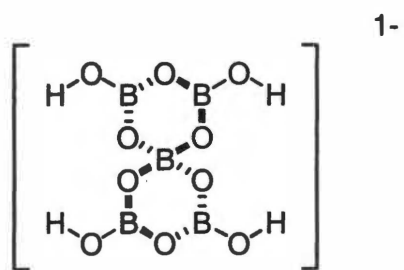
§ 2.1.5 History and Development of the Concept of BNCT

Fermi observed the capture of slow (or thermal) neutrons by certain nuclei.⁶⁵ The disintegration of these nuclei by interaction with the thermal neutrons was observed by Fermi and others, as well.⁶⁶ By 1935, a good amount of experimental information collected showed that the ability of an atomic nucleus to capture a neutron was related not to the mass of the target nucleus, but to the actual structure of the nucleus. The concept of a characteristic effective cross-sectional area of the nucleus, expressed as units of 10^{-24} cm^2 (known as barn units), was introduced. The effective nuclear cross-section of boron for neutron capture was known to be remarkably large. In 1935, Taylor described the capture of thermal neutrons by boron-10 nuclei followed by production of a lithium ion and an alpha particle.⁶⁷ The translational range of the product ions was 1.1 cm in air with 2 MeV of kinetic energy distributed between them.

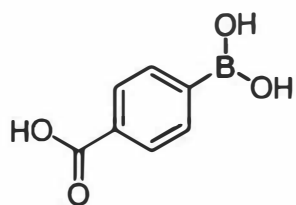
In 1936, Gordon L. Locher of the Bartol Research Foundation of the Franklin Institute in Philadelphia, Pennsylvania, first pointed out the potential medical applications of neutrons and Boron neutron capture (BNC).⁶² His concept invoked the simple neutron capture reaction by boron for a binary therapeutic method wherein a boron-10 nucleus contained in a compound that specifically localizes in the tumor, and the thermal neutron, would be the two components of the binary system and the alpha particle and lithium ion would be the cytotoxic energetic reaction products. Locher's concept of BNC was not realized for a long time due to unavailability of boron compounds for concentration in tumors and the absence of sources of low energy thermal neutrons.

The first experiment took place in 1954 when William H. Sweet, a neurosurgeon at Massachusetts General Hospital (MGH) in Boston, and L.E. Farr, of the Brookhaven National Laboratory (BNL) Medical Department, attacked malignant human brain tumors using ¹⁰B-enriched sodium borate as the target species in terminal patients.^{68,69} Five patients received a single radiation dose, and five received multiple fractionated doses. In 1959, the then new Brookhaven Medical Research Reactor was employed to treat sixteen more patients with ¹⁰B-enriched borates as the target species.^{70,71} These trials were not particularly successful because the available boron compounds failed to localize selectively in the tumor cells.

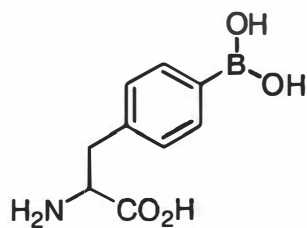
During the 1950s and early 1960s, numerous boron compounds were synthesized and evaluated for BNCT.⁷² The structures of some of these compounds are shown in Figure 2.1. These included boric acid along with its derivatives and



Boric acid
[B(OH)₃]



PCPB
p-Carboxyphenyl
boronic acid



BPA
p-Boronophenyl
alanine

Figure 2.1 Compounds used in the initial clinical studies for BNCT

substituted phenylboronic acids including 4-dihydroxyborylphenylalanine (BPA). During this time, polyhedral borane anions $B_{10}H_{10}^{2-}$ and $B_{12}H_{12}^{2-}$ were discovered and their chemistry was studied in great detail.^{73,74} Also, the icosahedral carboranes, *closo*-1,2- and *closo*-1,7- $C_2B_{10}H_{12}$, were synthesized and derivatives prepared.⁷⁵ The remarkable kinetic stability of these polyhedral ions and carboranes made them attractive candidates for BNCT.

Of the compounds evaluated by Soloway for selective tumor accumulation, the sodium salts of $B_{12}H_{11}SH^{2-}$ (BSH) and $1,10-B_{10}Cl_8(SH)_2^{2-}$ stood out with the former being sufficiently non-toxic to merit further study. Japanese neurosurgeon, Hiroshi Hatanaka, initiated a clinical trial with Japanese brain cancer patients using ^{10}B -enriched sodium mercaptoundecahydrododecaborate ($Na_2^{10}B_{12}H_{11}SH$, BSH) and thermal neutron beams of low intensity.⁷⁶ Out of the thirty eight patients treated, the reported mean survival was forty four months, significantly longer than the twelve month survival rate attainable using chemotherapy and radiation therapy. Among the long term survivors were a 70-year old woman, a 65-year old man, and a 13-year girl, who were unaffected twenty years later and appeared to be completely cured.

Hatanaka's results were good and kindled an interest in BNCT around the world. The European Collaboration was formed and began treating patients in the late 1980s.⁷⁷ Clinical trials are now continuing in Japan, are underway in the United States, and a new trial has begun in Europe.⁷⁸⁻⁸⁰ Centers in Sweden and Finland are now accepting patients. NCT centers and neutron sources are currently being

constructed in Hungary, Czech Republic, China, Taiwan, Thailand, Slovenia, and South America.⁸¹

§ 2.1.6 Potential BNCT Agents

The success of BNCT depends on the development of compounds that possess the following attributes: (1) an ability to target tumor cells selectively in the presence of normal cells; (2) sufficient concentration levels in the range of 20-35 μg ^{10}B per gram of tumor; (3) demonstrate tumor to normal tissue ratios greater than 1 and preferably 3-5; (4) show tumor to blood ratios of greater than 1 and preferably higher; and (5) are non-toxic so that the dose administered is well tolerated in patients.

In the early years of BNCT (1940-1961), only those compounds were considered that were either readily available commercially or easily synthesized. These compounds were evaluated exclusively for the treatment of brain tumors. Since then, other tumors have been considered. Although BSH and BPA are the only compounds currently being used in clinical trials, many groups have been diligently working on the design and synthesis of new tumor-targeting boron entities. Some of the classes of compounds being explored are presented below.

§ 2.1.6.1 *Amino acids*

The interest in the development of boron-containing amino acids arises from 4-dihydroxyborylphenylalanine (BPA), one of the two clinically used BNCT agents. In addition to the *para*-isomer of BPA,^{61,82} the *ortho*- and *meta*- isomers have been

synthesized and evaluated.^{83,84} Figure 2.2 contains the dihydroxyboryl analogues of phenylalanine.

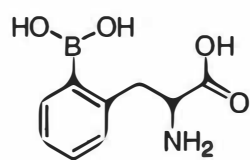
In order to increase the water solubility of BPA, many hydrophilic groups have been incorporated into its structure as shown in Figure 2.3.^{3,85,86} An interesting modification of BPA has been the addition of a carborane cage to the molecule. These polyhedral compounds permit higher percentages of boron in the molecule. Many different carborane-containing amino acids have been synthesized and evaluated.⁸⁷⁻⁹⁰ Some of these are shown in Figure 2.4. Our research group has explored non-naturally occurring cyclic amino acids.^{91,92}

§ 2.1.6.2 *Peptides*

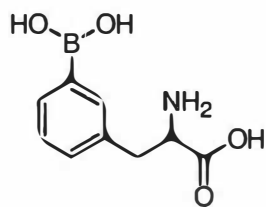
The principle for the synthesis of boron-containing peptides was based on the possibility that small peptides might cross cellular membranes and be utilized by tumor cells. Boron-containing di- and tripeptides derived from zwitterionic borane-containing amino acid analogues are shown in Figure 2.5.⁹³ There has been an emphasis on developing peptides containing polyhedral borane anions.

§ 2.1.6.3 *Nucleosides, Nucleotides, and Nucleic Acids*

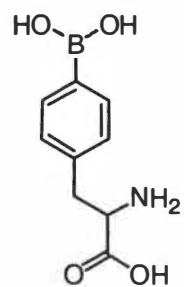
Nucleosides and nucleotides are building blocks for nucleic acids and are involved in many biological pathways.⁹⁴ Compounds in this class are made up of a sugar, an azo base, and a phosphoric acid. Nucleosides do not have the phosphorus component. The most well known nucleic acid is deoxyribonucleic acid or DNA. This class of compounds is being studied as potential BNCT agents due to its



ortho-BPA



meta-BPA



para-BPA

Figure 2.2 Analogues of BPA

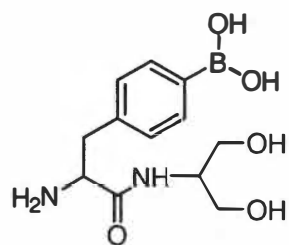
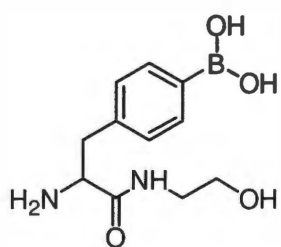


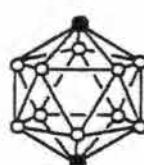
Figure 2.3 Hydrophilic derivatives of BPA



ortho-Carborane



meta-Carborane



para-Carborane

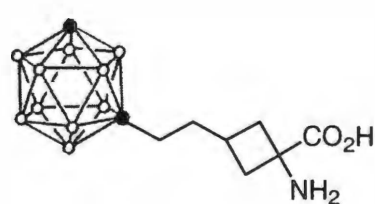
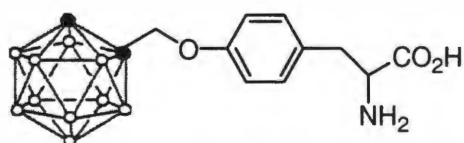


Figure 2.4 Carborane-containing amino acids

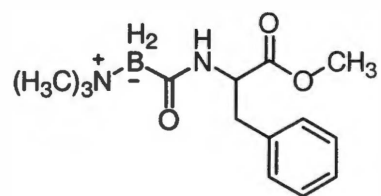
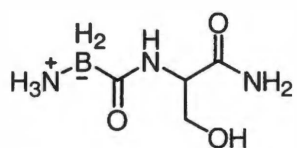


Figure 2.5 Boron-containing peptides

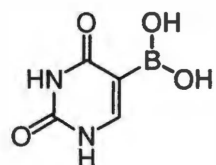
importance in the building of cells. It has been estimated that, by introducing boron into the cell nucleus via DNA, the effectiveness of BNCT would double.⁹⁵ One approach in this direction was to attach the boron moiety directly on a pyrimidine nucleus. This work led to the synthesis of 5-(dihydroxyboryl)uracil, carborane-containing pyrimidines, and subsequently led to the first boron-containing nucleoside, 5-(dihydroxyboryl)-2'-deoxyuridine (DBDU).⁹⁶⁻⁹⁸ The structures of these compounds are shown in Figure 2.6. A number of boron and carborane-containing nucleoside derivatives were also synthesized.^{99,100} Representative compounds are shown in Figure 2.6. In addition to nucleosides, nucleotides have also been prepared and biologically evaluated.^{101,102}

§ 2.1.6.4 Porphyrins

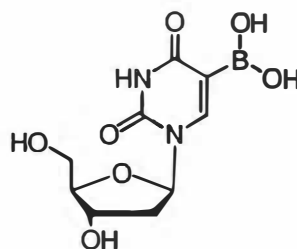
Porphyrins are extremely important compounds in biological systems. Hemoglobin and all varieties of chlorophyll contain some type of porphyrin. Porphyrins are currently used in a binary cancer treatment known as Photodynamic therapy (PDT).^{51,52} PDT studies have shown that porphyrins tend to localize in tumor cells and remain there indefinitely. A porphyrin of significant interest to scientists for BNCT is shown in Figure 2.7.^{103,104}

§ 2.1.6.5 Liposomes

Liposomes are spherical lipid bilayers that form in aqueous media. The membrane bilayer is shown in Figure 2.8. Liposomes have a large affinity for cancerous tissue and are often used to deliver highly polar medications.¹⁰⁵ Small



5-(dihydroxyboryl)uracil



5-(dihydroxyboryl)-2'-deoxyuridine
DBDU

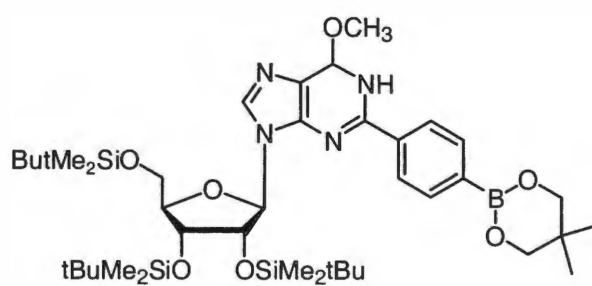
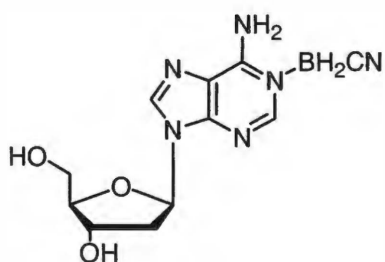
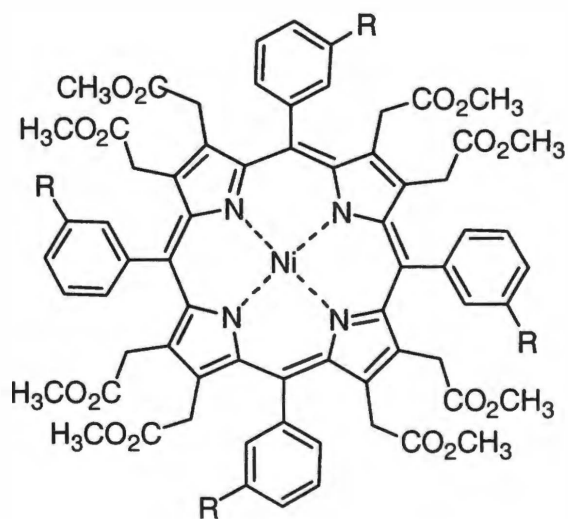


Figure 2.6 Boron-containing nucleic acid bases and nucleosides



Nickel tetracarboranylphenylporphyrin (Ni-TCP)

Figure 2.7 Carborane-containing porphyrin

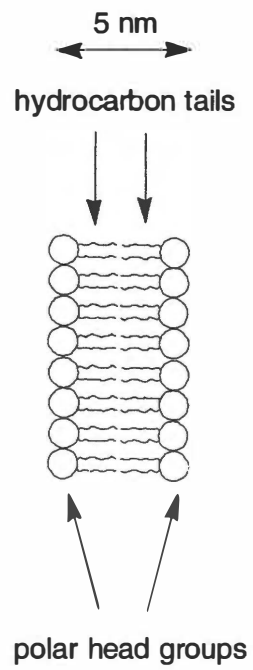


Figure 2.8 Lipid membrane bilayer of a liposome

unilamellar liposomes have been shown to penetrate the tumor cell membrane and localize intracellularly. Incorporating boron compounds within them would provide a basis for achieving selectivity between tumor and normal cells.¹⁶ The compound is incorporated either into the aqueous core of the liposome or into the membrane bilayer. BSH, various polyhedral boron compounds, and highly polar amines have been encapsulated in liposomes and appear to have significant potential as BNCT agents.¹⁵ Boronated derivatives of naturally occurring steroids like cholesterol have also been encapsulated.¹⁰⁶

§ 2.1.6.6 Carbohydrates

Compared to normal cells, the carbohydrate composition of the cell membrane surface of malignant cells differs greatly.¹⁰⁷ Incorporation of the carbohydrate moiety increases a compound's aqueous solubility. Boron and carborane-containing analogues of glucose, mannose, ribose and gulose have been prepared as shown in Figure 2.9.^{14,99} It is hoped that such structures may achieve elevated concentrations in tumors through the action of glucose transport system.¹⁰⁸

§ 2.2 CYCLOOXYGENASE-2 (COX-2) ENZYME INHIBITORS AND THEIR ROLE IN HUMAN COLORECTAL CANCER

This section describes the history and background of the cyclooxygenase-2 enzyme inhibitors and our rationale for their choice as potential BNCT agents.

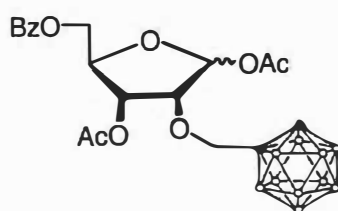


Figure 2.9 Carborane-containing analogue of carbohydrates

§ 2.2.1 Colorectal (colon) Cancer

Colorectal cancer is the third most common cancer in the world and is second only to lung cancer as the cause of cancer deaths in the United States.¹⁰⁹ This high rate of mortality calls for effective means of combating the disease. Over the past two decades, a large amount of research work has been initiated in this field including studies on the molecular genetics of colon cancer.¹¹⁰ Significant attention has been given to the development of chemopreventive agents.^{24,25,111-113}

§ 2.2.2 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Inflammation is the reaction of living tissues to injury. It involves a complex series of enzyme activation, mediator release, discharge of fluid, cell migration, tissue breakdown, and repair.¹¹⁴ Anti-inflammatory agents date back to ancient times when a variety of plant extracts containing salicylates were used for the treatment of inflammation, fever, and pain.¹¹⁵ Aspirin, the acetylated derivative of salicylic acid, was introduced in 1899.¹¹⁶ Aspirin is derived from salicin, a naturally occurring compound found in white willow tree bark and other plants. Use of salicin as a pain reliever goes back to the 5th century B.C. when its use was described by Hippocrates. However, it was noted that aspirin had risks when taken over a long period of time. Long-term aspirin use led to the development of ulcers, serious gastrointestinal bleeding (GI), and damage to the kidney. Closely related NSAIDs like ibuprofen and naproxen were subject to the same GI and renal effects.¹¹⁷ For many years, research was conducted to comprehend how aspirin and other NSAIDs work. In 1971, John

R. Vane, a British pharmacologist, proposed that the mechanism of aspirin-like drugs was through inhibition of prostaglandin synthesis from arachidonic acid via blockage of the cyclooxygenase (COX) enzyme. This pathway is shown in Figure 2.10.¹¹⁸ His group also demonstrated that aspirin interferes with the formation of blood clots by inhibiting aggregation of platelets. It was this observation that subsequently stimulated research into aspirin's potential for preventing heart attacks and recurrent small strokes. For this work, John Vane received a share of the 1982 Nobel prize in medicine.

The studies conducted by Vane generated great interest in the interaction between NSAIDs and the enzyme known to pharmacologists as cyclooxygenase (COX).

§ 2.2.3 Cyclooxygenase (COX) Enzyme

COX, also known as Prostaglandin H Synthase (PGHS), is the enzyme which catalyzes the first committed step of prostaglandin production - the conversion of arachidonic acid into Prostaglandin H₂ (PGH₂).¹¹⁹ Prostaglandins are potent mediators of important physiological processes in the body. In the early 1990s, two isoforms of the COX-enzyme were identified, COX-1 and COX-2.^{120,121} COX-1 is constitutively expressed in most tissues and synthesizes prostaglandins for normal physiological functions like renal blood flow regulation, maintenance of microvascular integrity in the gastrointestinal tract, regulation of cell division, and the production of mucus. On the other hand, COX-2 is swiftly and radically induced

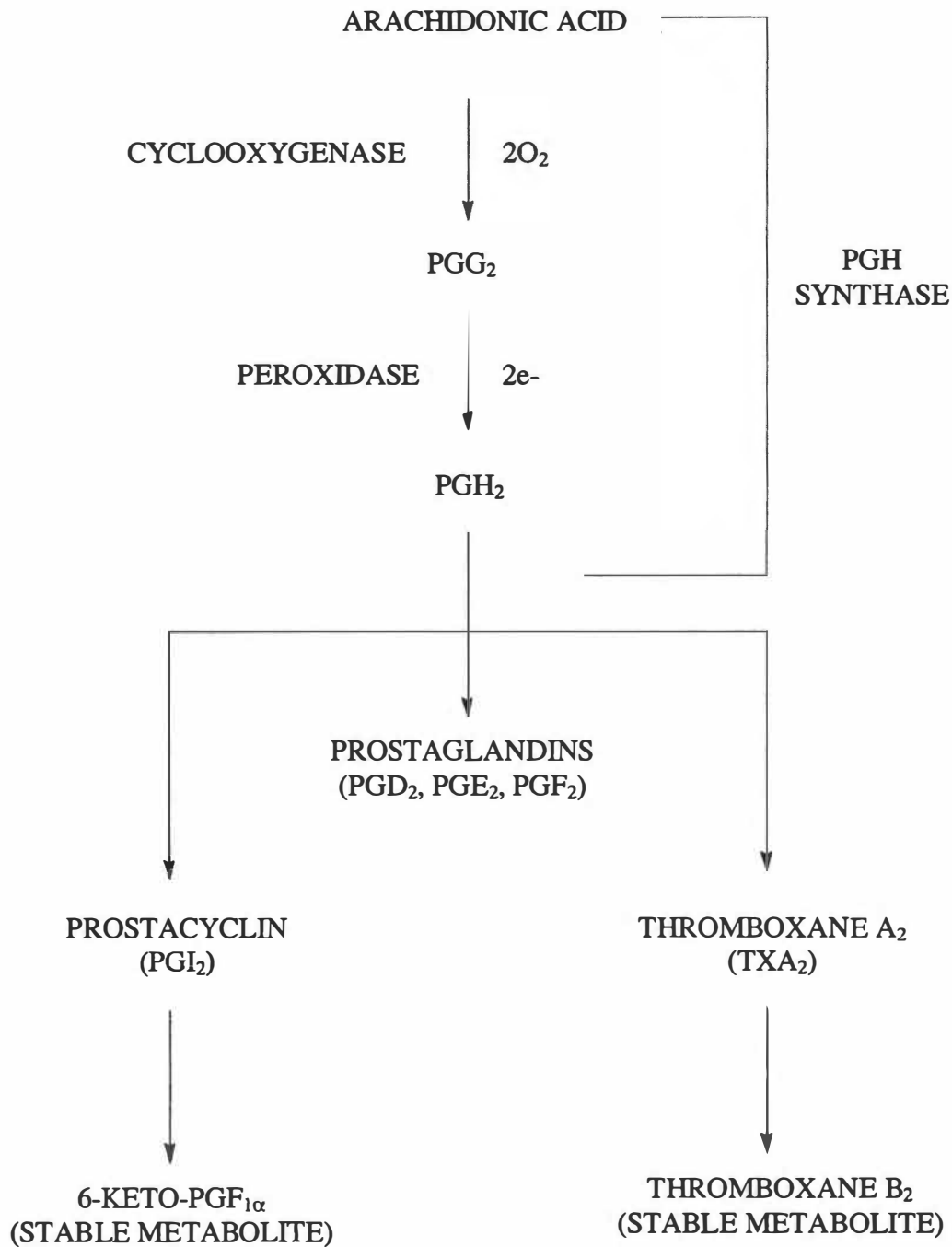


Figure 2.10 Conversion of arachidonic acid to prostaglandins, prostacyclins and thromboxanes

in response to cytokines, tumor promoters, and growth factors; all of which are thought to play a critical role in the initiation and maintenance of cancer cell survival and growth.¹²²⁻¹²⁴

Long-term use of NSAIDs has been associated with side effects like renal toxicity, gastrointestinal ulceration, and increased bleeding.¹²⁵ Current NSAIDs such as aspirin, sulindac, and indomethacin have little selectivity for inhibition of either COX-1 and COX-2.¹²⁶ In fact, it was suggested that the anti-inflammatory action of NSAIDs may be due to the inhibition of COX-2, whereas the toxic effects on the stomach and kidney were due to the inhibition of the constitutive enzyme, COX-1.¹²⁷

The above observation led to the possibility that selective inhibitors of COX-2 would have the usual beneficial effects of NSAIDs without the toxic side effects associated with the latter. The pharmaceutical industry invested immense resources in an effort to develop, test, and market a selective COX-2 inhibitor. Monsanto/Searle introduced celecoxib (celebrex) in 1999 for rheumatoid arthritis and osteoarthritis, Merck followed with rofecoxib (vioxx) and it is now believed that GlaxoSmithKline, Johnson and Johnson, Novartis, Parke Davis, Roche, Boeringer-Ingelheim, Abbott Laboratories, Procter and Gamble, Dupont, American Home Products, Japan Tobacco, and Fujisawa all have active development programs.^{117,128} The major classes of COX-2 inhibitors will be discussed briefly in Section 2.2.4.

X-ray crystallography of the 3-D structure of COX-1 and COX-2 has provided the basis for logical drug development for selective COX-2 inhibition.¹²⁹ X-ray studies have shown that COX-1 and COX-2 are similar enzymes consisting of

a long narrow hydrophobic channel. NSAIDs block COX-1 about midway down the channel and this blocking occurs by hydrogen bonding to the polar arginine at position 120.¹²⁸ Arginine 120 is also present in COX-2. A single amino acid difference is critical for selectivity of many drugs: at position 523 is an isoleucine molecule in COX-1 and a valine molecule (smaller by a single methyl group) in COX-2. This smaller molecule in COX-2 leaves a gap in the wall of the channel, creating a side pocket, which is thought to be the site of binding of many selective drugs. The bulky isoleucine at 523 in COX-1 is large enough to block access to the side pocket. It has been shown that targeted single amino acid substitution of valine for isoleucine is sufficient to turn COX-1 into an enzyme that can be inhibited by a COX-2 selective agent.¹³⁰

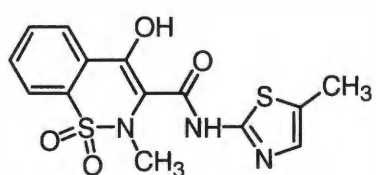
§ 2.2.4 Major Classes of COX-2 Inhibitors

§ 2.2.4.1 *Thiazoles*

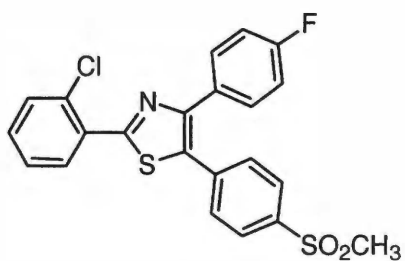
Boehringer-Ingelheim's meloxicam is the most well known member of this group of compounds.¹³¹ Searle has developed compound 1 which has shown potent activity against COX-2 and is in the process of being studied further.¹³² Both these compounds are shown in Figure 2.11.

§ 2.2.4.2 *Oxazoles*

Oxazoles are related to thiazoles in that the sulfur in the five-membered ring is replaced with an oxygen atom. Compound JTE-522 shown in Figure 2.12 is a

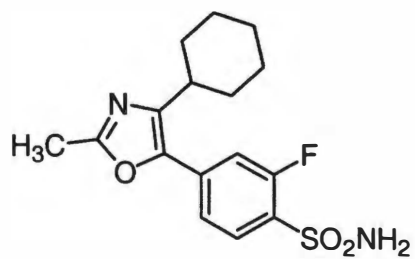


Meloxicam

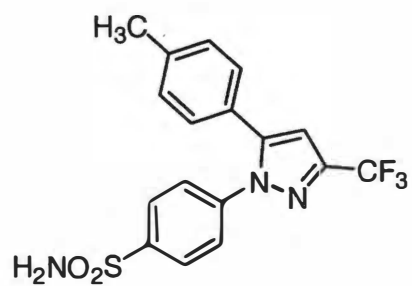


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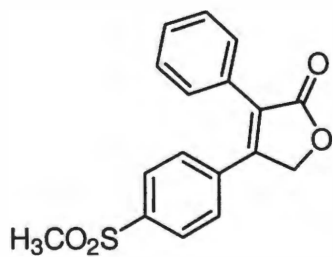
Figure 2.11 Thiazole class of COX-2 inhibitors



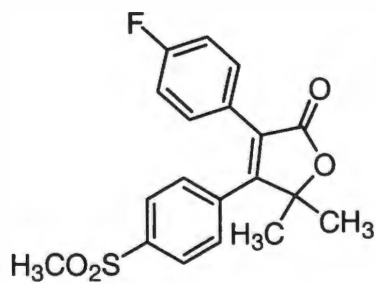
JTE-522



SC-58635
Celebrex



MK-0966
Vioxx



DFU

Figure 2.12 COX-2 inhibitors: JTE-522, SC-58635, MK-0966, DFU

potent, orally active, and highly selective COX-2 inhibitor, and is in clinical trials.¹³³

A series of oxazole-based inhibitors based on JTE-522 have been designed and investigated.

§ 2.2.4.3 1,5-Diarylpyrazoles

Celebrex (SC-58635) shown in Figure 2.12 belongs to this class of compounds.¹³⁴ It is a highly selective COX-2 inhibitor and is currently in use for the treatment of rheumatoid arthritis and osteoarthritis. It requires the presence of either a sulfonamide or a methylsulfonyl moiety for COX-2 potency. This class of compounds will be discussed in greater detail in Chapter 4.

§ 2.2.4.4 3,4-Diarylfuranones

Vioxx (MK-0966) is a member of this class of compounds and a very potent COX-2 inhibitor.¹³⁵ Merck has recently modified this furanone ring system by introduction of a hydroxyl group in the 5-position of the diarylfuranone ring system providing water-soluble, highly selective COX-2 inhibitors which facilitate intravenous formulations.¹³⁶ Merck has also developed another compound named DFU, which shows promise as a COX-2 inhibitor.¹³⁷ These compounds are shown in Figure 2.12.

§ 2.2.4.5 Ethers and Thioethers

Nimesulide¹³⁸ and NS-398¹³⁹ are well known members of this group of compounds. They have been introduced as pain relievers. Flosulide¹⁴⁰ and L-

745,337¹⁴¹ are also well established anti-inflammatory agents belonging to this group with the latter exhibiting a better pharmaceutical profile than the former in *in vivo* studies. These compounds are shown in Figure 2.13.

§ 2.2.4.6 *Fused Heterocycles*

The COX-2 inhibitors in this class include analogues of imidazothiazole,¹⁴² thiazolotriazoles,¹⁴³ thiazolofuranones,¹⁴⁴ and imidazopyridines¹⁴⁵. Examples of these compounds are shown in Figure 2.14. Of these, the thiazolotriazole, with its lactone ring, has the ability to function as a pro-drug in which the ring can be opened to the active hydroxycarboxylate.

§ 2.2.4.7 *Cyclopentenones*

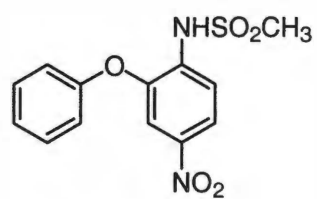
1,2-Diarylcyclopentene methyl sulfones belong to this class of compounds. They are reported to be orally active, highly potent COX-2 inhibitors.¹⁴⁶ An example of this family, compound **2**, is shown in Figure 2.15.

§ 2.2.4.8 *Cyclobutenones*

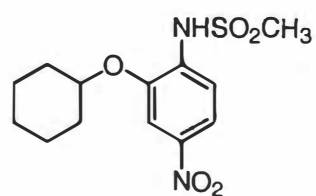
2,3-Diarylcyclobutenones is a member of this class of COX-2 inhibitors.¹⁴⁷ Compound **3**, shown in Figure 2.15, is an example of this family.

§ 2.2.4.9 *Cyclopentenones*

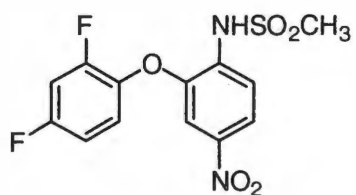
Merck is exploring 2,3-Diarylcyclopentenones as orally active, highly selective COX-2 inhibitors. 3,5-Difluorophenyl derivative (L-776,967) and 3-Pyridyl



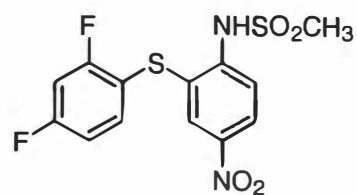
Nimesulide



NS-398

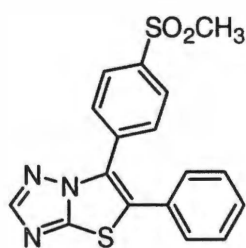


Flosulide

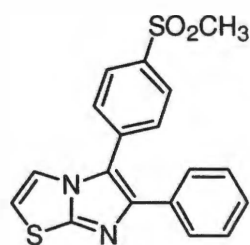


L-745,337

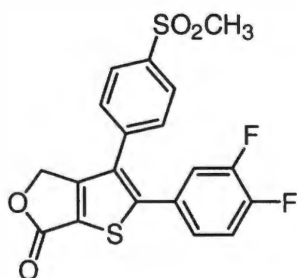
Figure 2.13 Ethers and thioethers as COX-2 inhibitors



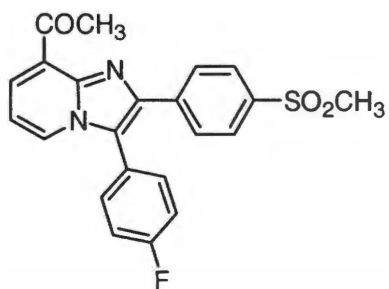
Thiazolofuranone



Imidazopyridine

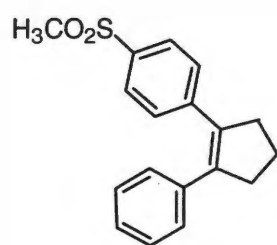


Imidazothiazole

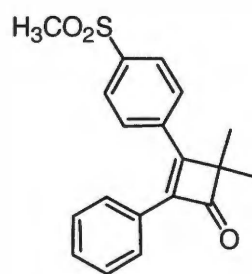


Thiazolotriazole

Figure 2.14 Fused heterocycles as COX-2 inhibitors



2



3

Figure 2.15 Cyclobutenes and cyclopentenones as COX-2 inhibitors

derivative (L-784,506), shown in Figure 2.16, belong to this class of compounds.¹⁴⁸

Both these compounds exhibit good oral bioavailability and could be potential anti-inflammatory agents.

§ 2.2.4.10 *Pyrimidin-2-amines*

The Glaxo group recently reported Pyrimidin-2-amines as selective inhibitors of COX-2.¹⁴⁹ An example of this class, compound **4**, is shown below in Figure 2.17.

§ 2.2.4.11 *Pyridazinones*

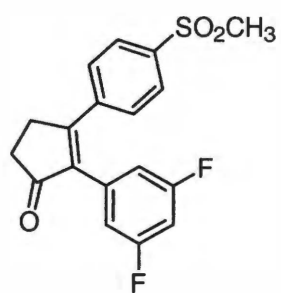
Two highly selective and orally active COX-2 inhibitors belonging to this class of compounds have been identified by the Merck group.¹⁵⁰ The structures of these two compounds, **5** and **6**, are shown in Figure 2.17.

§ 2.2.4.12 *2,3- Diarylbenzopyrans*

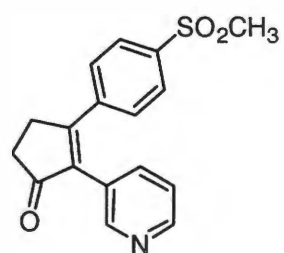
AmorePacific Corporation in South Korea has synthesized 2,3-Diarylbenzopyran as a new class of COX-2 inhibitors with naturally occurring flavone as the main skeleton.¹⁵¹ Compound **7** shown in Figure 2.18 has been identified as a potent, orally active COX-2 inhibitor.

§ 2.2.4.13 *1,1-Dihalo-2,3-Diphenylcyclopropanes*

(*Z*)- and (*E*)-1,1-dihalo-2-(4-substituted-phenyl)-3-phenylcyclopropanes have been synthesized and evaluated for potential COX-2 inhibitory activity.¹⁵² An

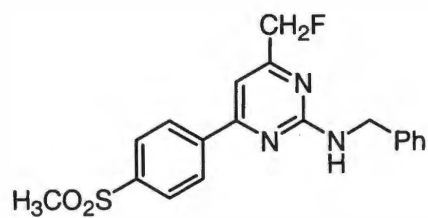


L-776,967

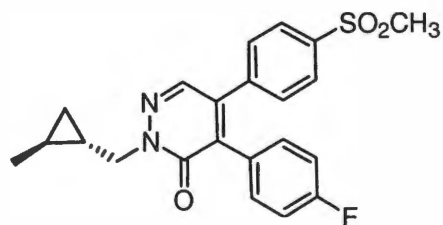


L-784,506

Figure 2.16 2,3-Diarylcyclopentenones as COX-2 inhibitors



4

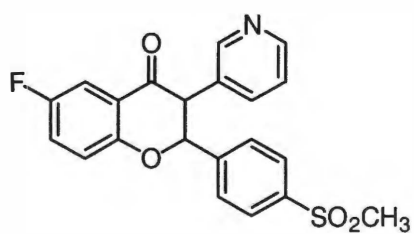


5

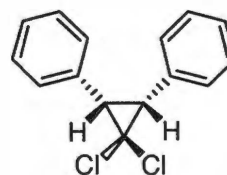


6

Figure 2.17 Pyrimidin-2-amines and pyridazinones as COX-2 inhibitors



7



8

Figure 2.18 Diarylbenzopyrans and diphenylcyclopropanes as COX-2 inhibitors

example of this class, compound 8, is shown in Figure 2.18. This group of compounds exhibited significant analgesic activity.

§ 2.2.4.14 COX-2 Inhibitors from Natural Products

Studies are in progress to find COX-2 inhibitors from natural products. COX-2 inhibitory activity has been observed in withanolide glycosides isolated from *Withania somnifera* leaves,¹⁵³ in prenylated flavanoids isolated from the leaves of *Macaranga conifera*,¹⁵⁴ and in prenylated chalcone derived from *Humulus lupulus* L.¹⁵⁵ The methanol extracts of some natural products derived from *Belamcandae rhizoma* and *Gleniae radix* have shown over 85% inhibition of COX-2 activity.¹⁵⁶

§ 2.2.5 NSAIDs and Colorectal Carcinogenesis

In 1988, Kune *et al.* documented that regular users of aspirin, a NSAID, had a 40% lower risk of the incidence of colon cancer compared to those who used no aspirin.¹⁵⁷ In 1994, Eberhart *et al.* first recorded the increased expression of the COX-2 enzyme in 85% human colorectal carcinomas (malignant growth arising in the lining of the colon).¹²³ This finding was later confirmed by other researchers.^{127,158} In 1995, Kargman *et al.* examined the expression of human COX-1 and COX-2 protein in 25 matched normal colon tissues and 25 colon cancer tissues. Their studies revealed that the COX-1 protein was present in all normal and tumor tissue whereas the COX-2 protein was not present in 23 of the 25 normal colon tissues but was present in 19 of the 25 colon tumors.

An early clue that NSAIDs might be beneficial in the treatment of colon cancer came from a case study in which the NSAID sulindac caused elimination of rectal polyps (mass of tissue protruding outward from a normal surface) in a patient with Gardner's syndrome (a condition wherein several polyps present within a person are predisposed to form cancerous tissue in the colon).¹⁵⁹ Many laboratory animal model studies have indicated that NSAIDs such as sulindac, indomethacin, piroxicam, ketoprofen, and ibuprofen inhibit chemically induced colon cancer by suppressing the incidence and multiplicity of colon tumors.^{35,112,113,159,160} One of the most compelling pieces of evidence that NSAIDs can inhibit colorectal cancer cell growth came from a randomized, double-blind, placebo controlled clinical trial in patients with the hereditary colon cancer syndrome, familial adenomatous polyposis (FAP). FAP is a genetic disease with numerous precancerous polyps in the colon and rectum. Patients with FAP possess a germline mutation in one of the alleles of the tumor suppressor gene, adenomatous polyposis coli (APC). This causes them to develop polyps throughout their gastrointestinal tract very early in life. Unless the colon is removed surgically, one or more of these polyps develop into malignant tumors.¹⁶¹ It is noteworthy that sulindac significantly reduced the number and size of colon polyps in FAP patients who are genetically predisposed towards colon cancer.¹⁶²⁻¹⁶⁴ This trend was reversed when therapy was terminated.

§ 2.2.6 Specific COX-2 Inhibitors and Colorectal Carcinogenesis

All the studies described in Section 2.2.5 were conducted with NSAIDs that inhibit both COX-1 and COX-2. COX-2 was implicated in colorectal tumorigenesis when Oshima *et al.* treated *Apc*^{Δ716} mice, a model of human FAP, with a novel COX-2 inhibitor.¹⁶⁵ Their results showed that the COX-2 inhibitor reduced polyp number more significantly than sulindac, which inhibits both COX-1 and COX-2. Oshima *et al.* also evaluated the chemopreventive activity of rofecoxib, a specific COX-2 inhibitor, in *Apc*^{Δ716} mice model and found dose-dependent inhibition in the number and size of intestinal colonic polyps.¹⁶⁶

Studies conducted with celecoxib, a specific COX-2 inhibitor, on azoxymethane (AOM) induced colon carcinogenesis in rats indicated that continuous administration of 1500 ppm of Celecoxib in diet suppressed the incidence and multiplicity of AOM-induced malignant tumors by 93 and 97% respectively.^{35,38} This degree of inhibition by celecoxib was far greater than that reported with other NSAIDs like aspirin (40%), ibuprofen (45%), sulindac (50%), and piroxicam (70%). Prolonged administration of celecoxib did not induce any toxic side effects, such as gastrointestinal ulceration, bleeding, and weight loss, commonly associated with other non-specific NSAIDs that do not selectively target COX-2. Celecoxib has also been shown to decrease polyp size in mice.¹⁶⁷ Celecoxib has been demonstrated to be effective in inhibiting the incidence and multiplicity of polyps even at lower dose levels of 500 ppm (500 µg/g of diet) and is an effective inhibitor of colon

carcinogenesis even when administered at the progression stage of cancer at dose levels of 1500 ppm.¹⁶⁸

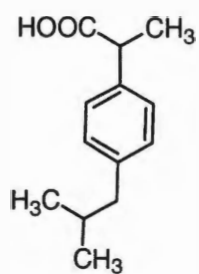
These observations raised the possibility that selective inhibitors of COX-2 could be a novel class of therapeutic agents for colon cancer and potentially serve as chemopreventive agents in colorectal carcinogenesis. Novel approaches for colon cancer prevention by COX-2 enzyme inhibitors are being studied.¹⁶⁹⁻¹⁷¹ Research is also in progress on the development of colon-targeted delivery systems for celecoxib for the prevention of colon cancer.¹⁷² For these reasons, we have focused our efforts on synthesis of boronated analogues of celecoxib as potential boron neutron capture therapy agents.

Structures of some NSAIDs and specific COX-2 inhibitors are shown in Figure 2.19.

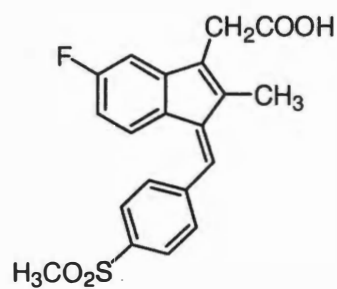
§ 2.2.7 Possible Mechanisms of Chemopreventive Effect of NSAIDs

Several mechanisms have been put forth in literature to explain the anti-tumorigenic effects of NSAIDs.^{34,173-177}

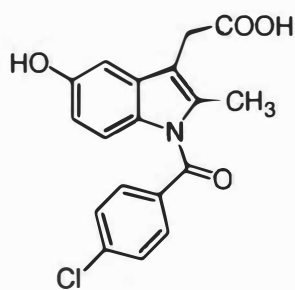
There is definite evidence for the role of COX-2 in tumorigenesis. Inhibition of the cyclooxygenase enzyme and consequent reduction in prostaglandin levels is considered to be one of the main causes for the therapeutic effects of NSAIDs. Elevated levels of prostaglandins have been found in naturally occurring and experimentally induced cancers.²² Many reports in the literature have demonstrated that COX-2 mRNA was elevated both in human and experimental animal colorectal



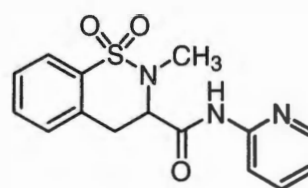
Ibuprofen



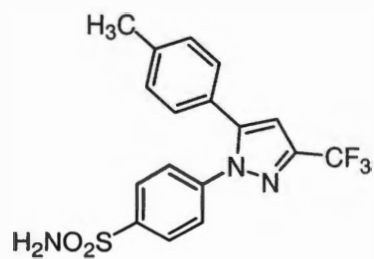
Sulindac



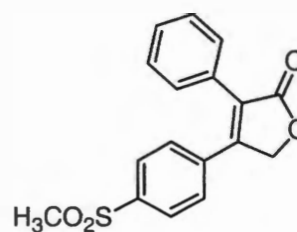
Indomethacin



Piroxicam



Celecoxib



Rofecoxib

Figure 2.19 NSAIDs and COX-2 inhibitors

tumors.^{48,123,127} These observations, about the high levels of prostaglandins and COX-2 enzyme in tumor tissue, coupled with the chemopreventive effects of NSAIDs and specific COX-2 inhibitors, outlined in Section 2.2.5 and 2.2.6, strongly suggest that the anti-tumor effects of NSAIDs in colon cancer may be mediated by the inhibition of the COX-2 enzyme.

It has also been suggested that NSAIDs may be acting in a prostaglandin (PG) independent manner. Sulindac was shown to cause regression of preexisting tumors in *Min/+* mice independent of PG synthesis.³⁷ Cell culture experiments showed that NSAIDs are able to induce apoptosis (process by which damaged or mutated cells in the colon are removed) in cells lacking the COX expression.¹⁷⁴

High doses of aspirin were shown to inhibit and destroy the pro-inflammatory factor, NF- κ B, by an apparent PG-independent mechanism.¹⁷⁸ There is also evidence in the literature demonstrating that NSAIDs attenuate proliferation of colon carcinoma cells by inhibiting calcium capacitative entry (CCE) and altering intracellular calcium levels.^{179,180} CCE is an influx of extracellular calcium to replenish intracellular calcium that is mobilized by cells.³⁴ Elevated intracellular calcium levels in tumors in *Apc^{Min/+}* mice are normalized by piroxicam.¹⁸¹ NSAIDs are also reported to attenuate cell proliferation induced by epidermal growth factors (proteins which regulate cell growth in colon cancer cells when awry) independent of prostaglandin synthesis.¹⁸²

The precise mechanism underlying the chemopreventive effects of NSAIDs is still not clear. Prostaglandins are actively involved in cell growth and cellular

transformations. Excess prostaglandins can facilitate tumor cell growth. Reports in literature support the fact that COX-2 plays a wide role in colorectal carcinogenesis. There is compelling evidence in literature supporting the principle that NSAIDs act via inhibition of prostaglandins and the COX enzyme. At the same time, there are conflicting reports. Thus, NSAIDs might be exerting their therapeutic effects via a number of mechanisms including inhibition of the COX-2 enzyme.

§ 2.3 UNNATURAL CYCLIC AMINO ACIDS

This section deals with non-naturally occurring cyclic amino acids and our rationale for their choice as potential BNCT agents. A brief overview of the history and development of boronated amino acids as potential BNCT agents is also presented.

§ 2.3.1 4-Dihydroxyborylphenylalanine (BPA)

BPA, shown in Figure 2.20, is one of two amino acid BNCT agents and is the only drug currently used in BNCT trials in the United States. BPA was first reported in 1958.¹⁸³ Interest in BPA was generated when studies using neutron irradiation experiments found BPA to be potent against B-16 melanoma (malignant tumors arising from the skin) *in vitro* and against Green's melanoma in hamsters.¹⁸⁴ Further work with melanoma in pigs and humans also demonstrated the efficacy of BPA as a BNCT agent.¹⁸⁵ Studies conducted in mice showed that ¹⁰B-enriched BPA achieved tumor concentrations of boron as high as 30 µg ¹⁰B/g tumor.¹⁸⁶

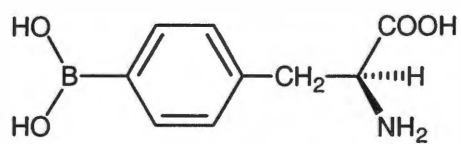


Figure 2.20 4-Dihydroxyborylphenylalanine (BPA)

Clinical trials with BPA for BNCT of human malignant melanoma have been undertaken in Japan.¹⁸⁷ The use of BPA against melanoma is based on the fact that the melanin pigment is synthesized *in vivo* from natural aromatic amino acids, phenylalanine and tyrosine. Due to this, melanoma cells incorporate both phenylalanine and tyrosine from extracellular fluid.¹⁸⁸ In order to understand the pharmacokinetics of ¹⁰B-BPA in melanoma, studies were conducted using ¹⁸F labeled BPA, which was synthesized as a positron emitting tracer, and the concentration of this compound was assessed non-invasively *in vivo* by positron emission tomography (PET).¹⁸⁹ The selectivity of ¹⁸F labeled BPA for melanoma tumors was up to 8 times higher than normal tissue.

The low aqueous solubility of BPA at physiological pH has been a constant impediment to its use. This problem has been overcome by converting BPA to water soluble boronate esters with carbohydrates, diethanolamine, and cyclodextrin derivatives. Selective tumor uptake of the BPA-fructose complex and a good tumor to blood boron concentration ratio has been observed in a recent clinical trial with melanoma patients.¹⁹⁰

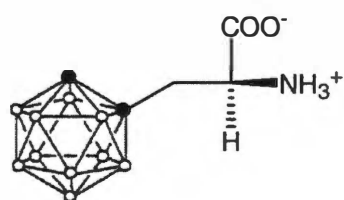
BPA has also been shown to accumulate in mammary and brain tumors and has hence been proposed for the treatment of brain cancer.¹⁸⁸ Its potential in this regard has been attributed to its ability to cross the blood brain barrier. Studies conducted on a mouse brain model with the fructose complex of BPA showed that neutron capture therapy with BPA was a safe procedure for brain cancer.¹⁹¹ BPA was proven effective in BNCT of intracerebral tumors in rats and mice.^{192,193} In a

comparative study of BNCT and X-ray radiation for treatment of rat brain tumors, it was seen that the brains and blood vessels of the rats subjected to BNCT were normal and intact without any harm to surrounding tissue in contrast to the brains of X-ray radiation survivors who showed loss of neurons, leakage of the blood-brain barrier, deterioration of brain growth, and serious intellectual deficiencies. The therapeutic use of BNCT for brain cancer was thus established.

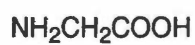
Both 2- and 3- dihydroxyborylphenylalanine have been synthesized and are undergoing evaluation.⁸²

§ 2.3.2 Amino Acids other than BPA

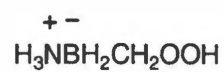
L-Carboranylalanine, shown in Figure 2.21, an analogue of L-phenylalanine, is currently undergoing *in vitro* and *in vivo* studies for efficacy in BNCT.¹⁹⁴ The ammonium carboxyborane analogue of glycine, shown in Figure 2.21, wherein a neutral carbon atom is substituted by an anionic boron atom, has also been synthesized.¹⁹⁵ The blood-brain barrier is more permeable to this ammonium carboxyborane analogue than it is to glycine. A number of such analogues are being developed and evaluated for BNCT.¹⁹⁵ A different carborane-containing amino acid has been reported in which the amino and the carboxyl functions are positioned on separate carbon atoms of the carborane nucleus.¹⁹⁶ Another class includes unnatural cyclic amino acids which will be discussed in greater detail in the next section.⁹²



L-Carboranylalanine



Glycine



Ammonium carboxyborane
analogue of glycine

Figure 2.21 Amino acids other than BPA

§ 2.3.3 1-Aminocyclobutanecarboxylic acid (ACBC) and its derivatives

It is believed that amino acids are preferentially taken up by growing tumor cells. ACBC has been known to be preferentially retained in intracerebral tumors.^{41,197} In addition, ACBC has been found to be non-toxic. It is known that 1-aminocycloalkancarboxylic acids cross the blood brain barrier.¹⁹⁸ Positron emission tomography (PET) studies carried out on BNCT patients at the University of Tennessee using fluorine-18 labeled BPA and carbon-11 labeled ACBC showed that cyclic amino acids localized in glioblastoma multiforme (malignant brain tumors) to a greater extent than BPA.⁴¹ These properties paved the way for boronated ACBC analogues as potential BNCT agents in the treatment of brain tumors.

Our research group has explored boronated, non-naturally occurring cyclic amino acids modeled after ACBC. We reported the synthesis of a series of 4-Dihydroxyborylphenyl derivatives of ACBC.¹⁹⁹ Varying numbers of methylene units were introduced between the dihydroxyborylphenyl and the ACBC moiety with the aim of making the molecule more lipophilic. Synthesis of *m*-carborane-containing ACBC derivative and a less lipophilic *nido* analogue were also accomplished.^{91,92} Incorporation of carboranes was thought to be advantageous due to their chemical stability and high boron content. However, the hydrophobic nature of the *m*-carboranyl derivative limited its *in vivo* use. The *nido* derivative provided good water solubility but the ionic character of the cage proved to be problematic in *in vivo* studies because it led to non-specific protein binding. To overcome this problem, a

water-soluble, polyol containing *m*-carboranyl-ACBC was synthesized by our group.²⁰⁰ Carbohydrates like galactose have also been incorporated into the carborane ring to increase water solubility.²⁰¹ The structures of some of the above compounds are shown in Figure 2.22.

For all the reasons aforementioned, we have focused our attention on the development of non-naturally occurring amino acids. All the compounds synthesized to date have been derivatives of ACBC. In our quest for unnatural cyclic amino acids as potential BNCT agents, we have accomplished the synthesis of 1-amino-3-boronocyclopentanecarboxylic acid (ACPC) and 1-amino-3-boronocycloheptanecarboxylic acid (ACHC). The synthesis of these molecules will be discussed in detail in Chapter 4.

§ 2.4 SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)

This section deals with a brief overview of the SPECT technique and our rationale for radioiodination of an analogue of specific COX-2 inhibitor celecoxib as a potential SPECT agent for imaging tumors.

§ 2.4.1 Development of SPECT

Emission computed tomography (ECT) provides three dimensional distributions of radiotracers *in vivo*. These data are acquired from a series of two dimensional images taken from different views surrounding the patient.⁴² Early tomographic systems consisted of four thallium-activated sodium iodide crystal detectors surrounding the patient's head. There was a rotating chair to hold the

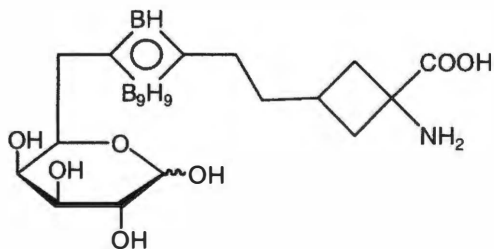
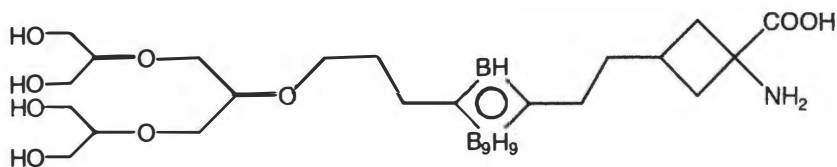
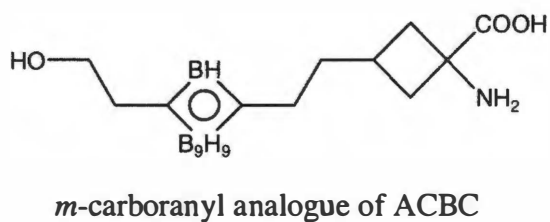
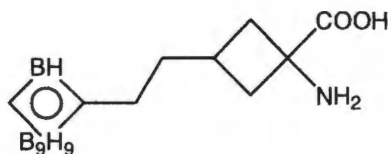
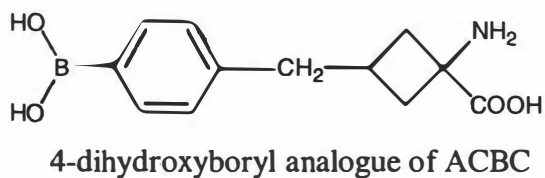
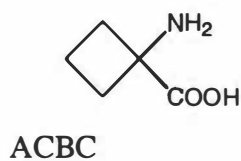


Figure 2.22 ACBC and its derivatives

patient. The first emission tomographic system was developed in 1963.²⁰² With the introduction of X-ray computed tomography and modifications in data interpretation, which accounted for such factors as scatter radiation, accurate ECT images of high quality were obtained.²⁰³

§ 2.4.2 Basic Principle of SPECT

SPECT involves the detection of gamma rays emitted singly from radionuclides and the determination of the relative or absolute regional concentrations of these radionuclides as a function of time within small regions of the body. Some of the radionuclides that emit gamma rays include technetium-99m, thallium 201, iodine-123, indium-111, and gallium-67. Iodine-123 is available widely in pure form without ¹²⁴I contamination.

§ 2.4.3 Factors Affecting SPECT

A number of factors affect SPECT, which in turn affect the exact determination of the radionuclide concentrations. Some of these factors are radionuclide decay, biokinetics of radiopharmaceuticals, patient/organ motion and location, imaging systems, and reconstruction methods for the data.⁴²

§ 2.4.4 Instrumentation

The instrumentation for SPECT consists of assemblies of thallium-activated sodium iodide detectors, which surround the patient. Lateral and rotational movement of the detector assembly permits different images of the patient.

Scintillation camera-based systems, wherein the patient is rotated in front of a stationary scintillation apparatus, are also used.²⁰⁴

§ 2.4.5 Reconstruction of SPECT Images

Along with technical factors like adequate analog to digital converters and spatial positioning of the assembly system with the patient, a variety of physical and mathematical factors need to be controlled for quality SPECT images.²⁰⁵ SPECT data involve the accumulation of projection data consisting of a number of line integrals measured from different views around the patient. These data are reconstructed using algorithms.²⁰⁶ The algorithm type most commonly in use involves mathematical equations that relate the projection and the source distribution. This method is referred to as *filtered back-projection* (FBP).²⁰⁷

§ 2.4.6 Future Development

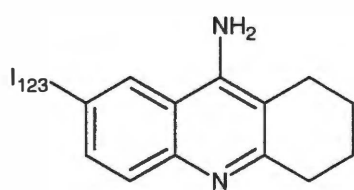
In addition to the development of new radiopharmaceuticals, better detectors that encompass a patient's full body, new detector materials, powerful computers that make SPECT systems automated and easier to use, improved algorithms for reconstruction of images, and techniques to compensate for the scatter and other disturbances should make SPECT a very effective diagnostic tool for the detection of disease.

§ 2.4.7 Medical Applications of SPECT

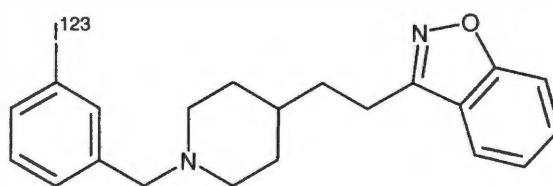
In principle, a chemically stable radiolabeled compound can be used for tumor imaging via SPECT and thus provide valuable information about a particular disease. SPECT has been used for quantitative estimation of malignant brain tumors.⁴³ *In vivo* quantification of amyloid deposits in Alzheimer's disease using iodine-123 and iodine-125 labeled hydroxybenzothiazoles has been made possible via SPECT.²⁰⁸ A technetium-99m SPECT agent has been used in predicting multi-drug resistance gene expression levels in non-small cell lung cancer.⁴⁵ SPECT has also yielded vital information about cognition in schizophrenic patients, and antidepressant treatment effects in major depression.^{46,47}

Our research group has been involved in the synthesis of potential SPECT agents for diagnostic applications in a variety of diseases. We have accomplished the synthesis of radiolabeled 9-amino-1,2,3,4-tetrahydroacridine (tacrine), shown in Figure 2.23, as a SPECT agent for Alzheimer's disease, to map the receptor sites of the enzyme acetylcholinesterase. Tacrine is a very potent and selective inhibitor of the acetylcholinesterase enzyme. It is known to be a cognitive enhancer in patients with Alzheimer's disease and has been approved for patient use.²⁰⁹ The synthesis of 3-[2-(1-3-¹²³I-iodobenzyl)-4-piperidinyl]ethyl]-1,2-benzisoxazole, shown in Figure 2.23, was also accomplished for mapping the acetylcholinesterase enzyme.²¹⁰

For diagnostic use in lung cancer, we synthesized benzylidene derivatives of anabaseine, an active and non-toxic binding ligand for α_7 -nAChR. The latter is



Tacrine



Benzisoxazole derivative

Figure 2.23 Radiolabeled tacrine and benzisoxazole as potential SPECT agents for Alzheimer's disease

known to be expressed in cell lines derived from small lung carcinoma. 3-(2,4-Dimethoxy-5-[¹²³I]iodo)benzylidene)anabaseine was synthesized via a tin precursor as a potential SPECT agent.²¹¹ An iodine-123 labeled analogue of COX-2 inhibitor celecoxib was accomplished, for diagnostic use in colon cancer, via radioiododestannylation of the tin precursor using peracetic acid.²¹²

§ 2.4.8 Synthesis of Radioiodinated Aryl Iodides via Boronate Precursors

The synthesis of radiopharmaceuticals requires suitable precursors. A variety of organometallic reagents like tin, silicon, lead, etc. have been used in this regard.²¹³ Our research group has explored the possibility of organoboranes as precursors to radiopharmaceuticals for over two decades.^{44,214} Initially, boronic acids were used as precursors but the highly basic conditions associated with their synthesis precluded their use in the creation of radiopharmaceutical precursors containing reactive substituents like esters and ketones.⁴⁴ Organotin reagents, which have been versatile precursors for a variety of radiopharmaceuticals, proved to be toxic; which created an impediment in their use in radiopharmaceutical production.²¹⁵ Thus, in pursuit of halodeboronation as a feasible approach to radiopharmaceuticals, we reported the synthesis of arylboronate esters and their direct radioiodination to generate iodine-123 labeled products.²¹⁶

A facile and direct synthesis of an iodine-123 labeled analogue of celecoxib using the above organoboronate ester technology for radioiodination was

accomplished, thereby avoiding the use of toxic tin precursors in nuclear medicine.

The synthesis will be discussed in greater detail in Chapter 4.

Chapter 3 Research Objectives

§ 3.1 SYNTHESIS OF BORONATED ANALOGUES OF COX-2 INHIBITORS AS POTENTIAL BNCT AGENTS AND PRECURSORS TO TUMOR IMAGING SPECT AGENTS

The clinical success of BNCT depends on effective delivery of a sufficient quantity of boron to the targeted tumor site. Although BNCT has potential as a cancer treatment, results to date in the United States have been moderate at best. This has been due to the lack of a suitable boron carrier, which can selectively deliver high concentrations of boron to the tumor. From Chapter 2, Section 2.2, it is seen that elevated levels of the COX-2 enzyme have been found in colon tumor tissue and not in normal colon tissue. It can therefore be concluded that highly specific COX-2 inhibitors like celecoxib could be used to deliver boron to the tumors.

This dissertation deals with the strategies and synthesis of boronated analogues of celecoxib, and also demonstrates the use of these boronated compounds as precursors in the synthesis of radiolabeled analogues as potential tumor imaging agents via SPECT. Representative examples of the analogues are shown in Figure 3.1. Synthesis of boronated monosubstituted analogues and progress towards the synthesis of disubstituted analogues is discussed in Chapter 4. The synthesis of the radiolabeled analogue is outlined in Chapter 6.

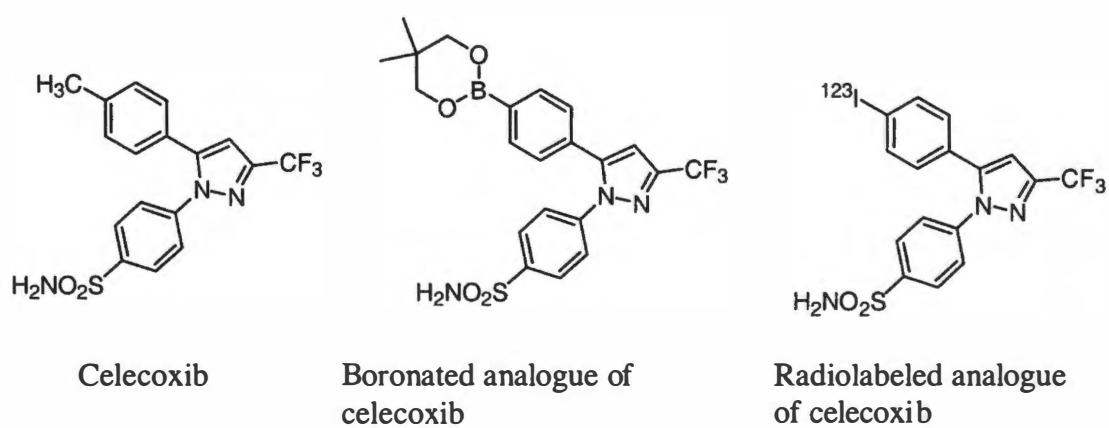
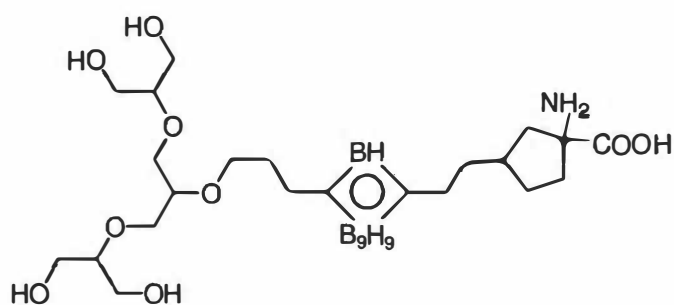
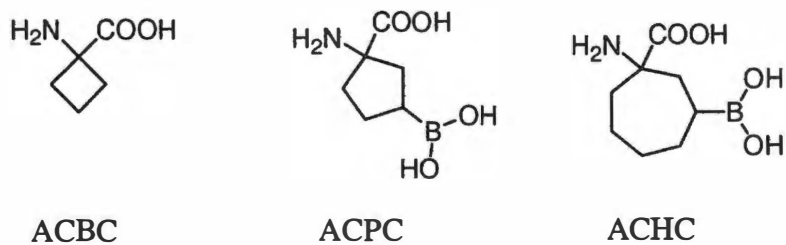


Figure 3.1 Boronated and radiolabeled analogue of celecoxib

§ 3.2 SYNTHESIS OF UNNATURAL CYCLIC AMINO ACIDS AS POTENTIAL BNCT AGENTS

4-Dihydroxyborylphenylalanine, an amino acid, is one of the two clinically used BNCT agents. Also, as mentioned in Section 2.3, 1-aminocyclobutanecarboxylic acid is preferentially retained in intracerebral tumors. Thus, amino acids serve as attractive targets for delivery of boron to the tumor site.

This dissertation deals with the synthesis and preliminary evaluation of boronated 1-aminocyclopentanecarboxylic acid (ACPC), and 1-aminocycloheptanecarboxylic acid (ACHC), as potential BNCT agents. Progress towards the synthesis of a cascade polyol derivative of carborane-containing analogue of ACPC is also discussed. The synthetic strategy for these analogues is outlined in Chapter 5. Structures of ACPC and ACHC are shown in Figure 3.2.



Polyol derivative of *meta*-carboranyl analogue of ACPC

Figure 3.2 Boronated unnatural cyclic amino acids

Chapter 4 Synthesis of Boronated Analogues of a COX-2 Enzyme Inhibitor

This chapter seeks to explain the basis for the choice of target compounds for this dissertation from a structural perspective. It also describes the synthesis of the monosubstituted boronated analogues of celecoxib and explains the strategy and progress made in the synthesis of the disubstituted analogues.

§ 4.1 SYNTHESIS OF 1,5-DIARYLPYRAZOLES

Celecoxib belongs to the 1,5-diarylpirazole class of COX-2 inhibitors. It contains a tricyclic ring system with a central pyrazole ring. This section outlines the general methods for synthesis of a pyrazole ring and the different routes used in literature for the synthesis of the 1,5-diarylpirazole ring system.

§ 4.1.1 General Methods for Synthesis of Pyrazoles

The synthesis of pyrazoles from 1,3-dicarbonyl compounds and hydrazine (or its derivatives) is the most widely used and general method for pyrazole synthesis. Acetylenic carbonyl compounds also react with hydrazine to form pyrazole ring systems. Aliphatic diazo compounds react with both acetylenic derivatives and malonic derivatives to form pyrazoles. A detailed account of the isomerism, general reactions, and syntheses of the pyrazole ring can be found in literature.²¹⁷

§ 4.1.2 Existing Synthetic Routes for the Construction of the 1,5-Diarylpyrazole Ring System

Literature examples for the synthesis of the 1,5-diarylpyrazole ring system are outlined below.

§ 4.1.2.1 *Synthesis via Epoxy Ketones*

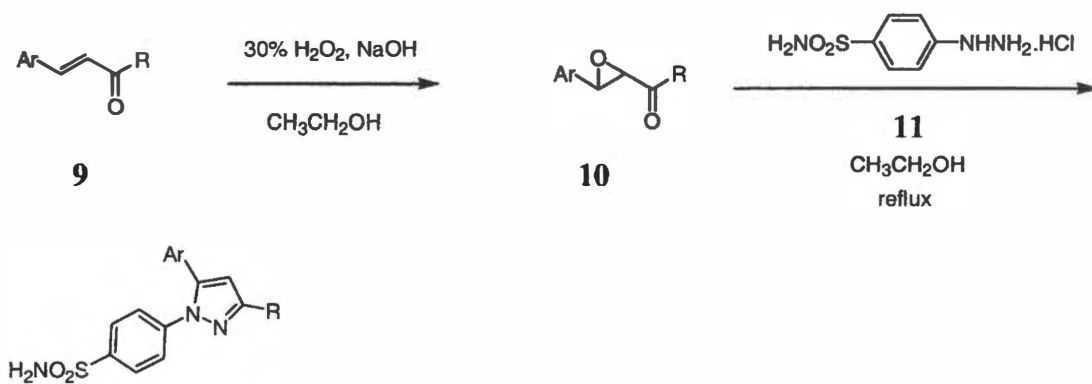
This approach has been employed by Searle Pharmaceuticals, the makers of Celecoxib, for the synthesis of 1,5-diarylpyrazoles.¹³⁴ In this method, an α,β -unsaturated ketone **9** is oxidized to an epoxyketone **10**, which is then condensed with the hydrochloride salt of (4-sulfamoylphenyl)hydrazine, **11**, to form the 1,5-diarylpyrazole ring system as shown in Scheme 4.1 This method works well for compounds which have an alkyl or an aryl group on the central pyrazole ring.

§ 4.1.2.2 *Synthesis via 1,3-diketones*

Another method, also employed by Searle Pharmaceuticals, utilizes the Claisen condensation of an acetophenone derivative **12** with ethyl trifluoroacetate to generate the 1,3-diketone **13** which is then condensed with **11** to form the 1,5-diarylpyrazole ring system as shown in Scheme 4.2. This method is more suitable when a $-\text{CF}_3$ or a $-\text{CHF}_2$ group is on the pyrazole ring.

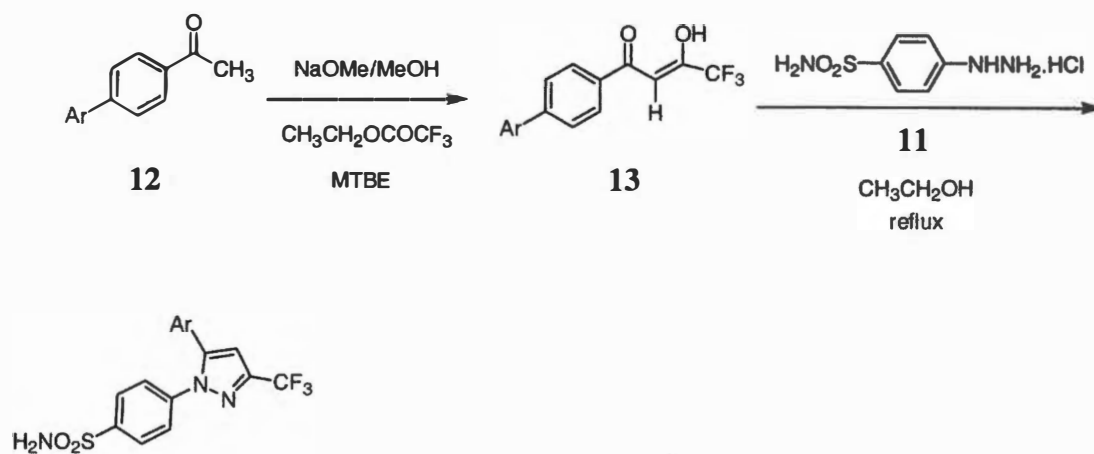
§ 4.1.2.3 *Synthesis via Arylalkynones*

The alkenylation of an aromatic compound such as **14** with 4-ethoxy-1,1,1-trifluorobut-3-ene-2-one and ZnCl_2 , followed by bromination with bromine in



R = alkyl or aryl group

Scheme 4.1 Synthesis of 1,5-diarylpyrazoles via epoxy ketones



Scheme 4.2 Synthesis of 1,5-diarylpyrazoles via 1,3-diketones

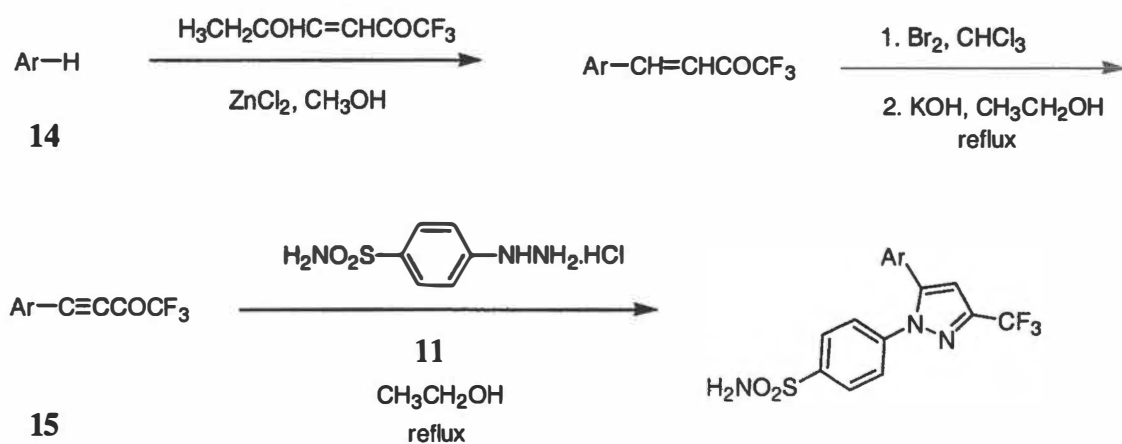
chloroform, and dehydrobromination with potassium hydroxide in ethanol can be used to form the arylalkynone **15**.^{218,219} **15** then undergoes cyclocondensation with **11** to form the 1,5-diarylpyrazole ring as shown in Scheme 4.3.

Of the three synthetic routes outlined above, the second pathway utilizing 1,3-diketones was chosen as the basic route for the synthesis of boronated COX-2 inhibitors. Modifications in the synthetic route pertaining to reagent choice, reaction times, and purification methods were employed during the course of the synthesis as required.

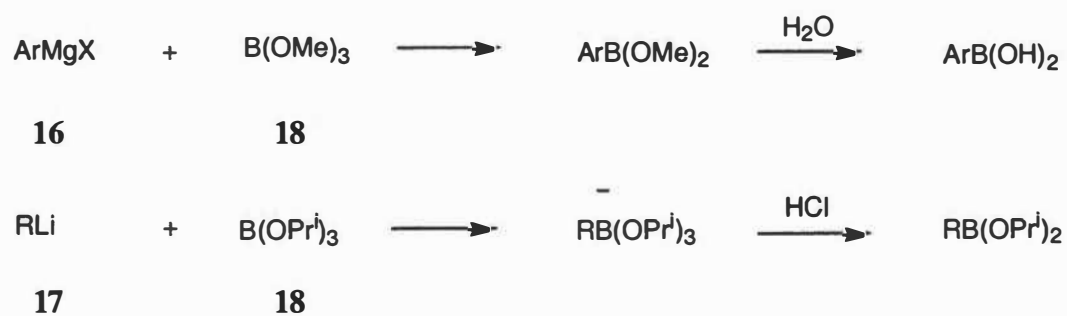
§ 4.2 STRATEGY FOR INCORPORATION OF THE BORON MOIETY INTO THE 1,5-DIARYLPYRAZOLE RING SYSTEM

It was decided to incorporate the boron moiety into the ring in the form of a boronic ester. Organoboronic esters are generally thermally stable and can be isolated by distillation.²²⁰ Pinacol diboron esters have also been isolated by flash chromatography on silica gel.^{221,222}

Arylboronic esters and acids have classically been synthesized from Grignard reagents such as **16** (or lithium reagents such as **17**) and trialkylborates **18**, as shown in Scheme 4.4.²²³ These reactions can involve bis-alkylation leading to borinic acid derivatives and the formation of trialkylboranes. In 1995, Ishiyama *et al.* reported the first one-step procedure for preparing aryl boronic esters, **21**, from aryl halides, **19**, outlined in Scheme 4.5.²²⁴ Their method utilized palladium(0)-catalyzed cross coupling of thermally stable bis(pinacolato)diboron esters, **20**, with aryl halides to

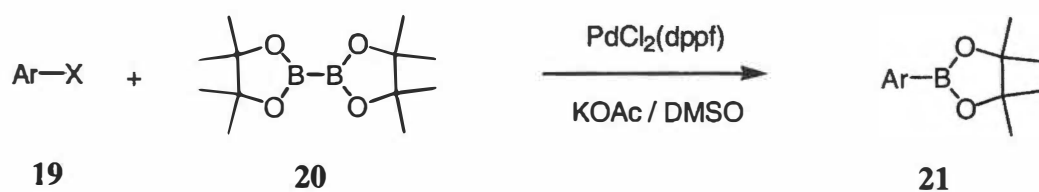


Scheme 4.3 Synthesis of 1,5-diarylpyrazoles via arylalkynones



R = aryl, alkyl, 1-alkenyl, and 1-alkynyl

Scheme 4.4 Synthesis of organoboron esters via Grignard and lithium reagents



X = iodide, bromide

Scheme 4.5 Synthesis of arylboronates via bis(pinacolato)diboron

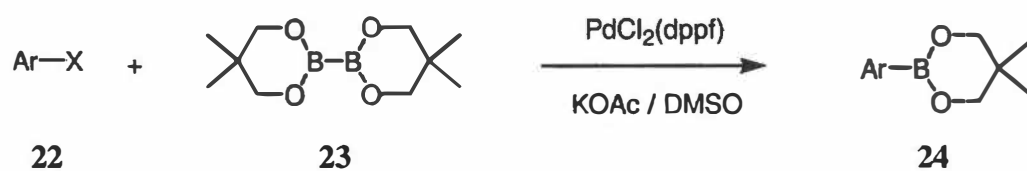
yield the arylboronate species. The advantage of this method is that various functional groups such as ester, acyl, nitrile, and nitro moieties which need to be protected while using Grignard and lithium reagents, are easily tolerated and do not need to be protected. The aryl halides employed in the coupling reaction were either iodides or bromides.

Later, Marcuccio *et al.* reported the synthesis of arylboronates, **24**, using palladium(0)-catalyzed cross coupling of thermally stable, less sterically hindered bis(neopentylglycolato)diboron ester, **23**, with aryl halides **22** under mild conditions, shown in Scheme 4.6.²²⁵⁻²²⁷ The aryl halide used is an iodide or a bromide. The reaction tolerates a variety of functional groups including acyl, ester, nitrile, nitro, amide, carboxylic acid, sulfonic acid, and trifluoromethyl groups. Fluorides and chlorides were not effective in the coupling process.

Due to the mild reaction conditions and the ability of the process to tolerate a variety of functional groups, it offered the best possibility for introduction of the boron moiety into the 1,5-diarylpyrazole ring system, and was, therefore, the method of choice.

§ 4.3 RATIONALE FOR THE CHOICE OF THE STRUCTURES OF TARGET COMPOUNDS

The reasoning behind the structures of the target molecules chosen for this dissertation work is outlined.



X = iodide, bromide

Scheme 4.6 Synthesis of arylboronates via bis(neopentylglycolato)diboron

§ 4.3.1 Structure-Activity Relationship Data

Our rationale is based largely on the structure activity relationship (SAR) data generated by Searle Pharmaceuticals, makers of celecoxib. They synthesized a number of 1,5-diarylpirazoles and evaluated them for COX-2 efficacy.¹³⁴ Several sites of modification around the pyrazole ring system were explored. They observed that the sulfonamide group on the phenyl ring at the 1-position on the central pyrazole ring was very important for COX-2 inhibition as it showed superior *in vitro* and *in vivo* efficacy. The 3-position on the pyrazole ring system, shown in Figure 4.1, was fixed to be either -CF₃ or -CHF₂, as both these showed the same *in vitro* potency and selectivity, but greater than any other groups at the same position.

The Searle group also made numerous modifications on the aryl substituent at the 5-position of the pyrazole ring. Their results revealed that this position offered the most flexibility with regards to maintaining COX-2 inhibitory activity. A number of monosubstituted and disubstituted 5-aryl derivatives were synthesized and evaluated. Introduction of substituents in the 2- and 4-positions of the 5-aryl ring (depicted as 2' and 4' in Figure 4.1) resulted in more potent COX-2 inhibition than substituents in 3-position. Substituents with halogen, alkoxy, and alkyl in the 4'-position of the 5-aryl ring seemed to show some COX-1 activity, which was modulated, with little effect on COX-2 potency, by introduction of a substituent α to the *para*-electron donating group.

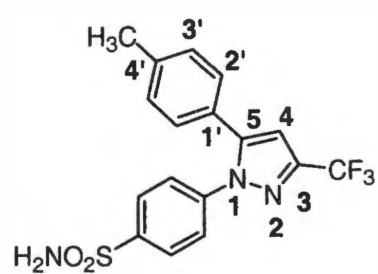


Figure 4.1 Structure of celecoxib

§ 4.3.2 Structures of Target Compounds

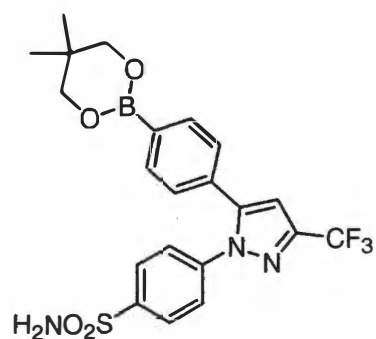
Based on the structure activity data outlined in Section 4.3.1, the target compounds chosen were **A**, **B**, **C**, and **D** modeled after COX-2 selective 1,5-diarylpirazole analogues synthesized by the Searle group.

Derivatives **A** and **B** could be visualized as analogues of **A'** and **B'**, respectively. These structures are shown in Figure 4.2. **A'** and **B'** exhibited COX-2 potency and selectivity very similar to celecoxib. **A'** exhibited IC_{50} (μM) values of 17.8 for COX-1 and 0.01 for COX-2, while **B'** exhibited IC_{50} (μM) values of 31.3 for COX-1 and 0.056 for COX-2. These values compare favorably with corresponding IC_{50} (μM) values for celecoxib of 15.0 for COX-1 and 0.04 for COX-2.

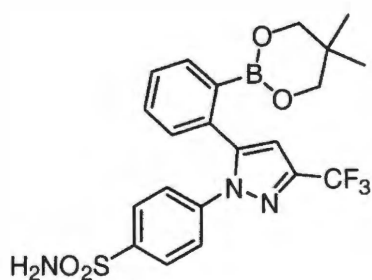
Disubstituted derivatives **C** and **D** were chosen based on SAR studies wherein groups like methyl and methoxy in the 4'-position of the 5-aryl ring, with either halogens, methyl or methoxy α to them, exhibited COX-2 potency and selectivity. Derivatives **C** and **D** could be visualized as analogues of **C'** and **D'** respectively. **C'** demonstrates IC_{50} (μM) values of 27.6 for COX-1 and 0.027 for COX-2 whereas **D'** exhibits corresponding IC_{50} (μM) values of 17.4 and 0.015. The structures of these compounds are shown in Figure 4.3.

§ 4.4 SYNTHESIS OF COMPOUND A

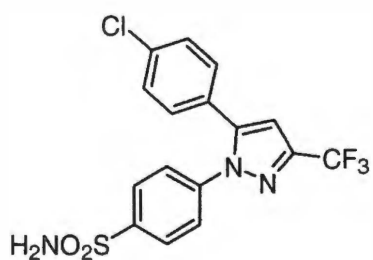
This section describes the synthesis of 4-[5-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-phenyl]-3-trifluoromethyl-pyrazol-1-yl]-



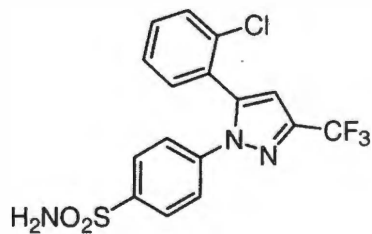
A



B



A'



B'

Figure 4.2 Monosubstituted boron-containing target compounds A and B

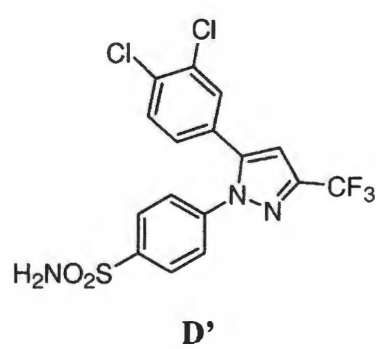
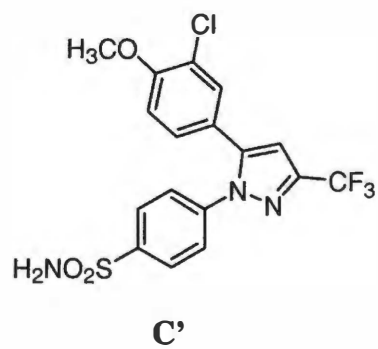
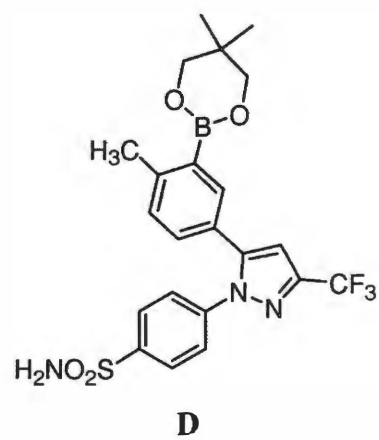
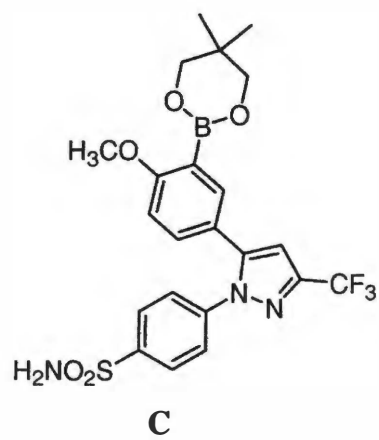


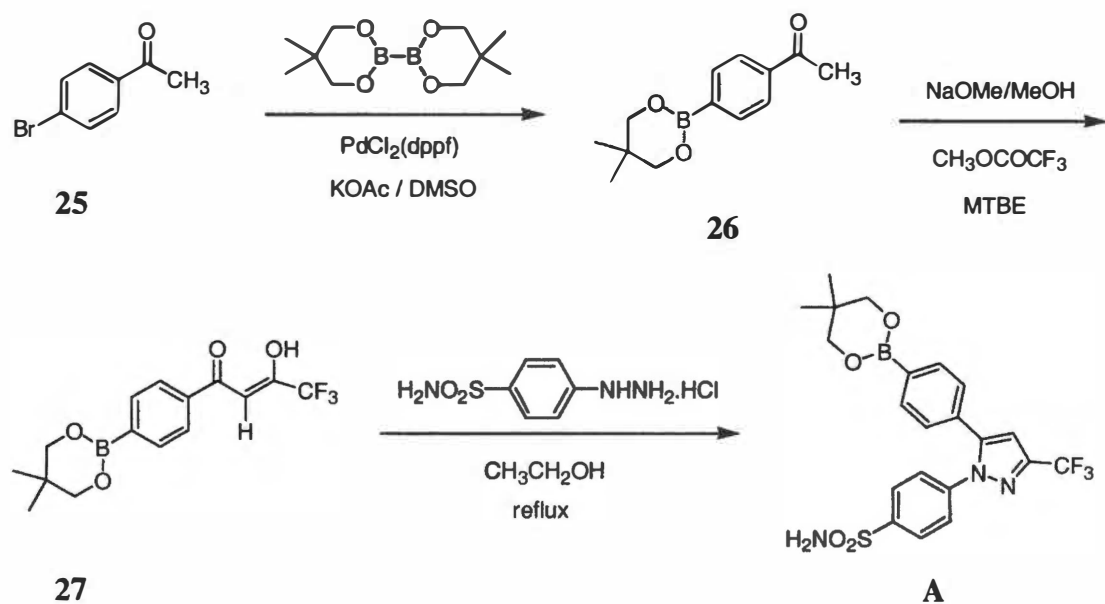
Figure 4.3 Disubstituted boron-containing target compounds C and D

benzenesulfonamide, **A**. The synthesis method for 1,5-diarylpyrazoles via 1,3-diketones, outlined in Section 4.1.2.2, was the basic route followed for the preparation of the target compound.¹³⁴ Discussions of the diverse methods attempted such as the use of different reagents and reaction conditions for 1,3-diketones, modifications to the boron moiety, and various methods for the synthesis of halogenated starting materials for disubstituted analogues are presented in the following sections. The most feasible method was then chosen and employed for the synthesis of **A**, **B**, **C**, and **D**. Experimental details are provided in the Experimental Section.

§ 4.4.1 Synthesis via a Boronated 1,3-Diketone

In this method, the boron moiety was introduced in the initial stages of the synthesis to form a boronated diketone, 1-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-phenyl]-4,4,4-trifluoro-butane-1,3-dione, **27**, which was condensed with the hydrazine hydrochloride **11** to yield **A**. Since it was decided to incorporate the boron moiety into the ring via the procedure of Ishiyama *et al.*²²⁴ and Marcuccio *et al.*²²⁵⁻²²⁷ outlined in Section 4.2, the presence of halogenated precursors in the synthetic route became necessary.

Synthesis of compound **A** was attempted via boronated diketone **27** as outlined in Scheme 4.7. Commercially available 4-bromoacetophenone, **25**, was treated with bis(neopentylglycolato)diboron, **23**, to yield 1-[4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-phenyl]-ethanone, **26**. But efforts to generate **27** via

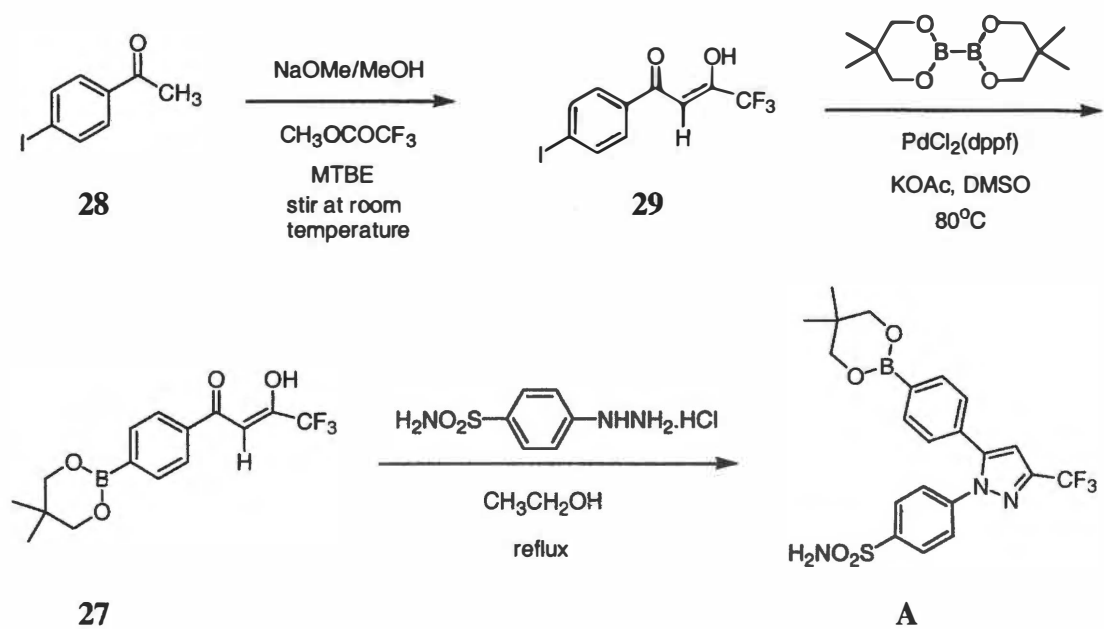


Scheme 4.7 Attempted synthesis of compound A via boronated diketone 27

Claisen condensation of **26** with sodium methoxide (NaOMe) in methanol (MeOH) failed. Changing reaction conditions by using excess base and longer reaction times failed to produce the diketone. The reaction mixture, monitored using thin layer chromatography (TLC) and gas chromatography, showed only starting material. This scheme was aborted and not investigated further.

Alternatively, it was decided to synthesize **27** by first making the halogenated 1,3-diketone and then introducing boron onto it as depicted in Scheme 4.8. **28** was allowed to react with ethyl trifluoroacetate in refluxing methanol for 24 hours, which was the method used by the Searle group for synthesis of celecoxib. This approach failed to yield the diketone. The acylation was then attempted by refluxing **28** with sodium amide (NaNH₂) in tetrahydrofuran (THF) as solvent, but the yields were low.²²⁸⁻²³⁰ Even excess sodium amide and ester did not improve yields. Finally, the acylation was attempted using methyl trifluoroacetate and sodium methoxide in methyl *tert*-butyl ether (MTBE) as solvent, with constant stirring at room temperature. The reaction was allowed to stir continuously at room temperature and monitored with TLC and GC. After stirring for about 48 hours, disappearance of the starting material was observed. The reaction was worked up and the presence of product 4,4,4-trifluoro-1-(4-iodo-phenyl)-butane-1,3-dione, **29**, was confirmed.^{134,231} Other methods for synthesis of 1,3-diketones are reported in literature.^{232,233}

Compound **29** was purified by recrystallization and subsequently allowed to react with **23** in the presence of palladium catalyst, 1,1'-



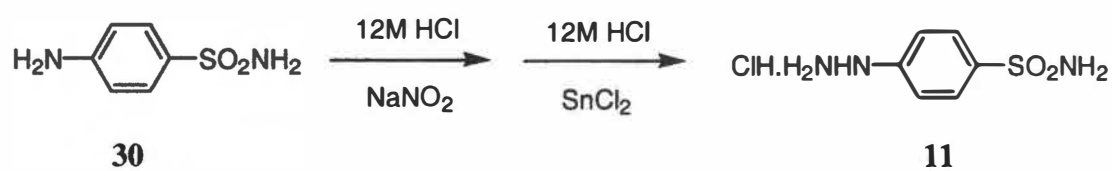
Scheme 4.8 Synthesis of compound A via boronated diketone 27

bis(diphenylphosphinoferrocene)dichloropalladium, $\text{PdCl}_2(\text{dppf})$, and potassium acetate (KOAc) in dimethyl sulfoxide (DMSO) to yield **27**.²²⁴ Product **27** was used without further purification and condensed with 4-(sulfamoylphenyl)hydrazine hydrochloride ($\text{SO}_2\text{NH}_2\text{C}_6\text{H}_4\text{NHNH}_2\cdot\text{HCl}$), **11**, to yield compound **A**, which was purified by column chromatography over silica gel using ethyl acetate and hexane as eluent.

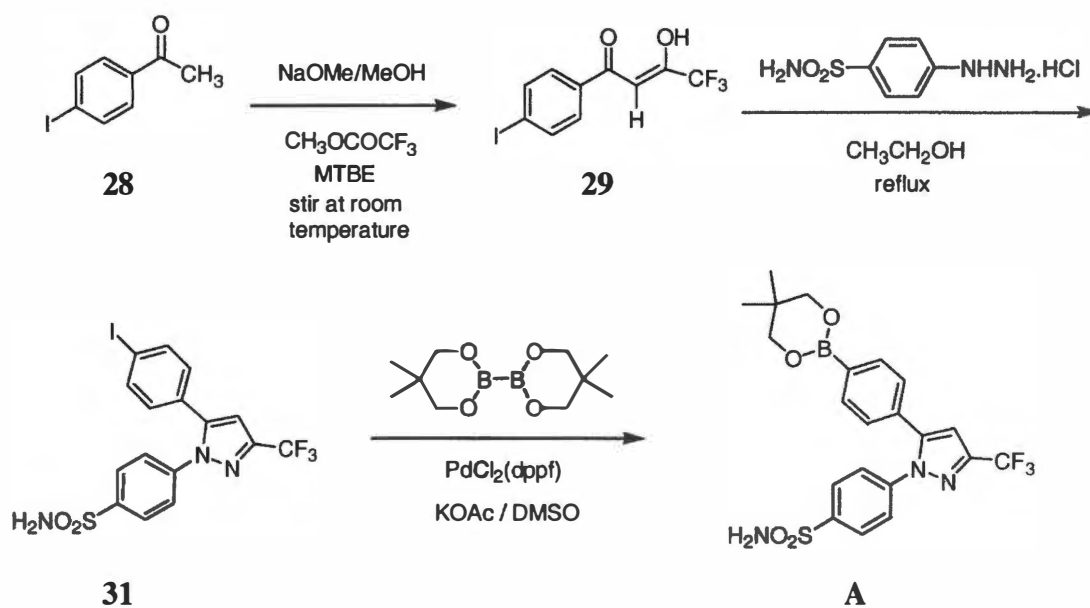
4-(Sulfamoylphenyl)hydrazine hydrochloride was synthesized by diazotization of sulfanilamide, **30**, with sodium nitrite (NaNO_2) followed by reduction with tin(II) chloride and purified by recrystallization, depicted in Scheme 4.9.²³⁴ Towards the end of this dissertation study, commercially available 4-(sulfamoylphenyl)hydrazine hydrochloride was used. The procedure outlined in Scheme 4.8 also worked well starting from 4'-bromoacetophenone.

§ 4.4.2 Synthesis via Halogenated 1,3-Diketone

In this procedure, the boron moiety was introduced in the last step of the synthesis in contrast to the earlier method. The approach is outlined in Scheme 4.10. Compound **28** was acylated using methyl trifluoroacetate and sodium methoxide, as described earlier in Section 4.4.1, to form **29**. After purification, **29** was condensed with **11** to form 4-[5-(4-iodo-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, **31**, along with the 1,3-diarylpyrazole isomer. Compound **31** was purified by flash column chromatography over silica gel. It was then treated



Scheme 4.9 Synthesis of 4-(sulfamoylphenyl)hydrazine hydrochloride



Scheme 4.10 Synthesis of compound A via iodinated diketone 29

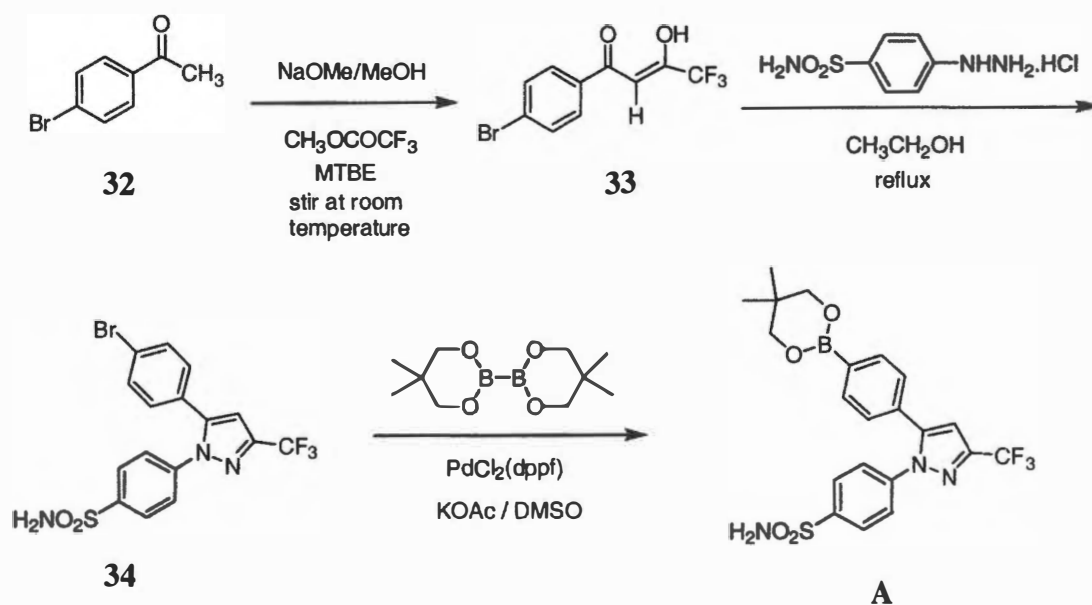
with diboron ester **23**, KOAc, and PdCl₂(dppf) to form compound **A**, which was purified by column chromatography. This procedure was also attempted using brominated starting material **32**, as depicted in Scheme 4.11. All compounds in Schemes 4.10 and 4.11 were characterized by elemental analysis and nuclear magnetic resonance (NMR) spectra.

§ 4.4.3 Synthesis Overview

Ishiyama *et al.*,²²⁴ and Marcuccio *et al.*²²⁵ had previously observed that aryl iodides were generally more effective than bromides in coupling with diboron esters. The same observation was made during this study where the aryl iodides, 1,3-diketone **29** and the benzenesulfonamide **31**, coupled more effectively with the diboron ester than their bromine counterparts. Also, it was observed that introduction of boron moiety into the ring in the last step, outlined in Section 4.4.2, proved to be more effective than introducing it at the 1,3-diketone step, in terms of obtaining a purer product and producing better yields. Thus, from preliminary studies, it was concluded that the synthesis pattern outlined in Scheme 4.10 was the most viable and was the general synthetic scheme employed for Compounds **B**, **C**, and **D**.

§ 4.5 SYNTHESIS OF COMPOUND B

The synthesis of 4-[5-[2-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-phenyl]-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, **B**, was accomplished from



Scheme 4.11 Synthesis of compound A via brominated diketone 33

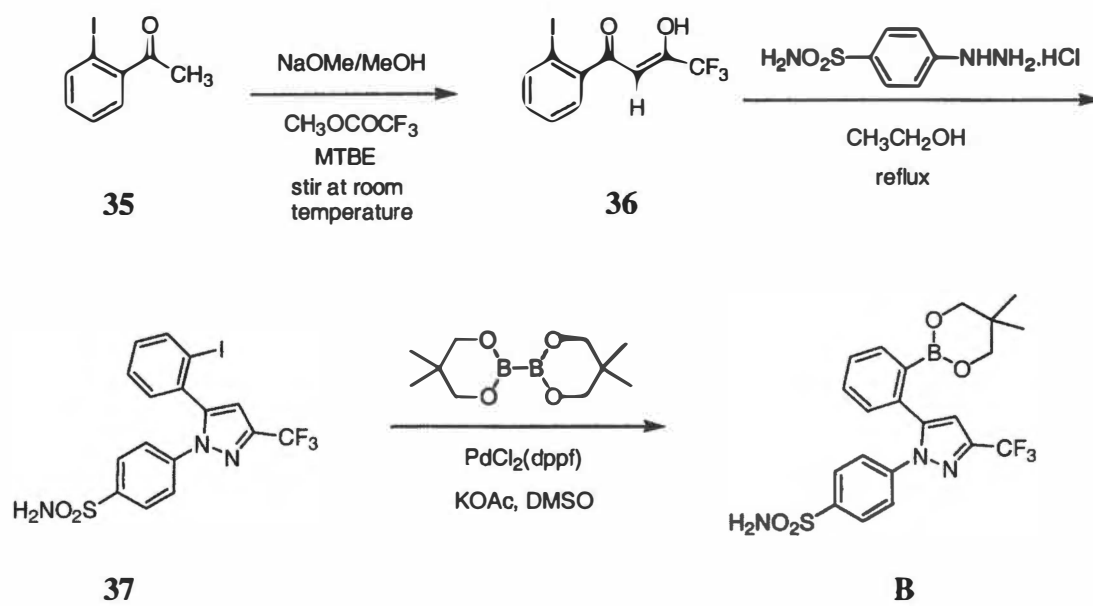
commercially available 2-iodoacetophenone as outlined in Scheme 4.12.

The same procedure used for the acylation of 4-iodoacetophenone was employed for 2-iodoacetophenone, **35**, and worked well. Compound **35** was acylated with methyl trifluoroacetate and sodium methoxide in methanol at room temperature to form 4,4,4-trifluoro-1-(2-iodo-phenyl)-butane-1,3-dione, **36**, in almost quantitative yield. Compound **36** was used in the next step without purification and condensed with **11** to form the 4-[5-(2-iodo-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, **37**. Compound **37** was treated with a mixture of diboron ester **23**, KOAc, and PdCl₂(dppf) to yield compound **B**. Both **37** and **B** were purified by column chromatography. All of the intermediates were characterized by elemental analysis and NMR spectra.

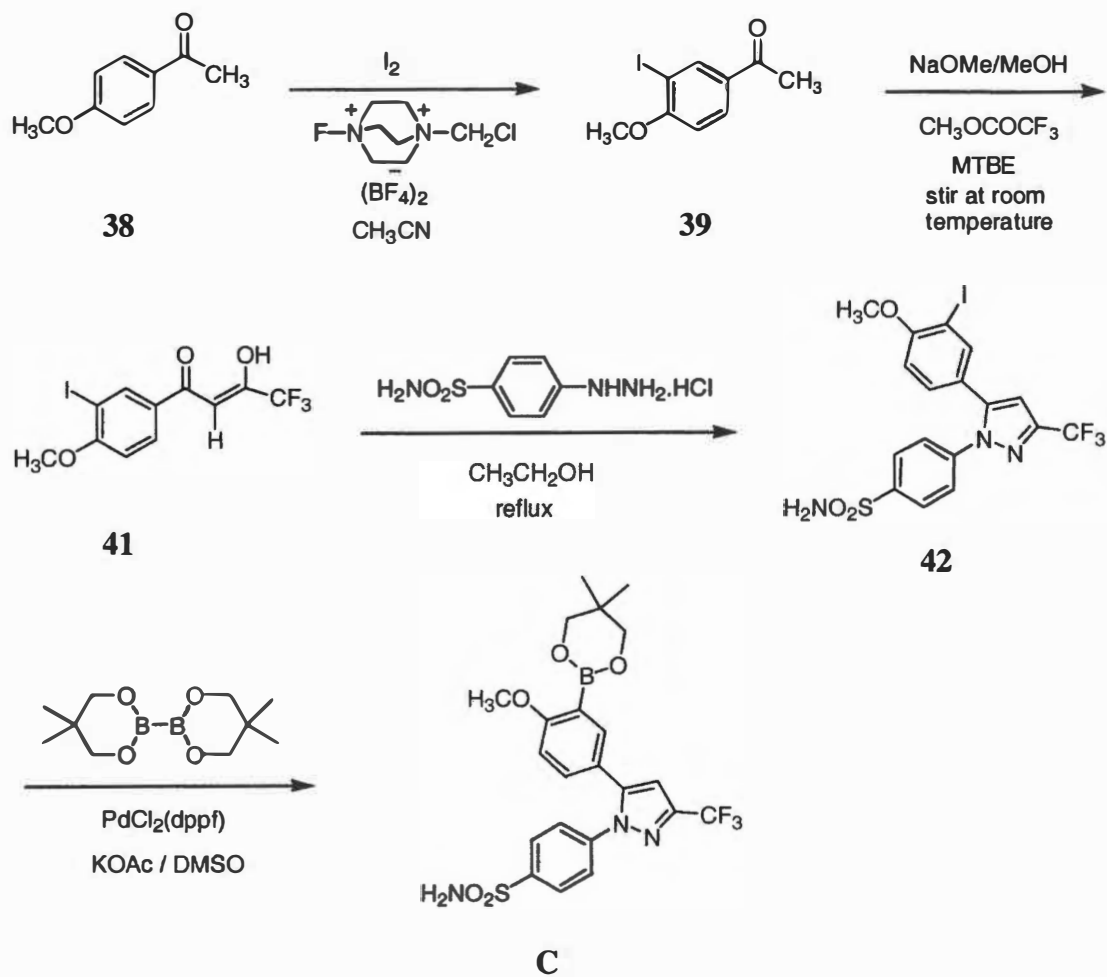
§ 4.6 PROGRESS TOWARDS SYNTHESIS OF COMPOUND C

A discussion of the synthetic strategy for 4-[5-[3-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-4-methoxy-phenyl]-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, **C**, is presented in this section. Boronated disubstituted analogue **C** was synthesized and its structure confirmed by high resolution mass spectrometry (HRMS) and NMR. However it was not isolated in pure form. The synthesis is outlined in Scheme 4.13.

To accomplish the synthesis of **C**, it was necessary to synthesize 3-iodo-4-methoxyacetophenone, **39**, with the correct regiochemistry for iodine, thus



Scheme 4.12 Synthesis of compound **B** via iodinated diketone **36**

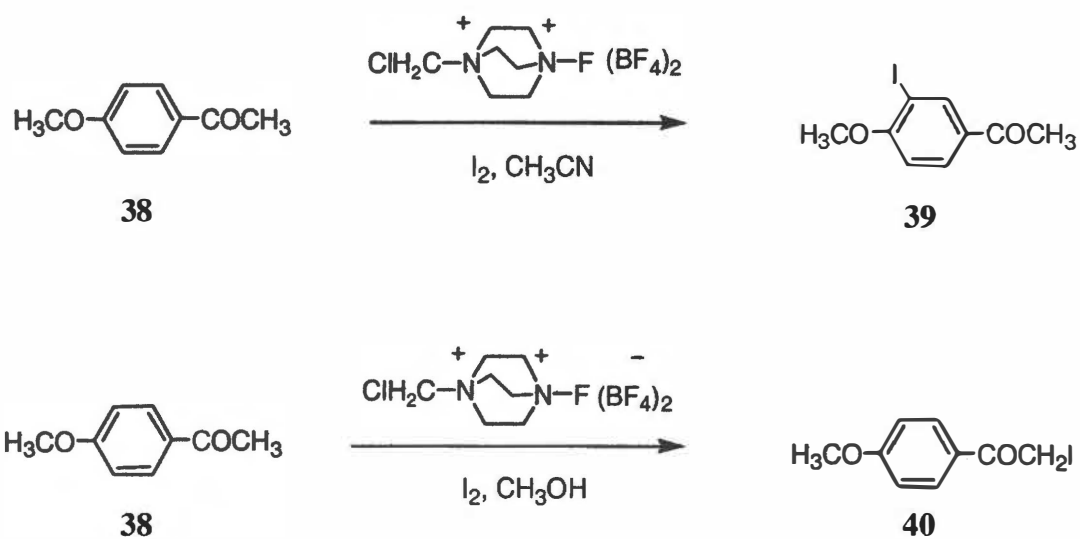


Scheme 4.13 Synthetic strategy for compound **C**

facilitating introduction of boron moiety into the ring. The Friedel-Crafts reaction^{235,236} is normally the method of choice for acylation of aromatic compounds, but it was not thought to be a viable option here due to formation of side products, as both the methoxy and the iodo group are *ortho*- and *para*-directors. Deiodination has also been observed in Friedel-Crafts reactions.^{237,238} In 1997, Zupan *et al.* reported the room temperature regioselective iodination of aromatic ethers mediated by 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF₄) commonly called SelectfluorTM. Their studies showed that the regiochemistry of iodination could be regulated by the solvent used, as shown in Scheme 4.14. Thus, this procedure afforded an excellent method for selective iodination of an activated aromatic ring either at the α -iodocarbonyl or the iodoaryl position.^{239,240}

Employing the above method, 4-methoxyacetophenone, **38**, was iodinated using elemental iodine and F-TEDA-BF₄ in acetonitrile to give **39** in good yield. Alternatively, the synthesis of **39** has also been reported by reaction of **38** with Iodine(III) tris(trifluoroacetate)²⁴¹ and from corresponding aryl bromides by reaction with nickel bromide and zinc catalyst (NiBr₂-Zn).²⁴²

Compound **39** was purified by chromatography and subjected to Claisen condensation to give 4,4,4-trifluoro-1-(3-iodo-4-methoxy-phenyl)-butane-1,3-dione, **41**, which was then condensed with **11** to give 4-[5-(3-iodo-4-methoxy-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, **42**. Product **42** was purified



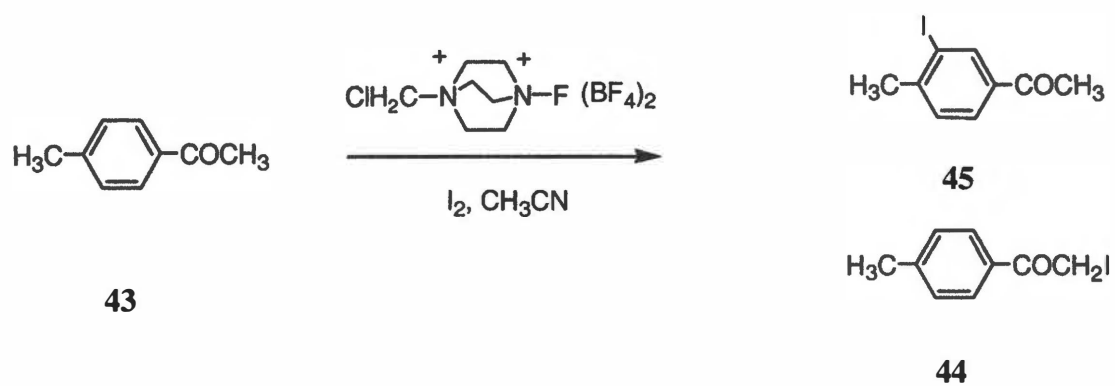
Scheme 4.14 Regioselective iodination of aromatic ethers using F-TEDA- BF_4

by column chromatography and coupled with **23** to give compound **C**. The yield of **C** was only 41%, possibly due to the steric effects of the *ortho*-methoxy and diboron ester group. NMR analysis revealed the presence of minor amounts of boronic acid.

§ 4.7 PROGRESS TOWARDS THE SYNTHESIS OF COMPOUND **D**

Progress towards the synthesis of 4-[5-[3-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-4-methyl-phenyl]-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, **D**, is outlined in this section. A pure sample of the iodinated benzenesulfonamide precursor was obtained. The synthetic strategy is outlined in Scheme 4.15.

The first step in the synthesis of **D** involved preparation of 3-iodo-4-methylacetophenone, **45**. A detailed study of Friedel-Crafts acylation of *ortho*-, *meta*-, and *para*-iodotoluene has been reported in literature.²⁴³ This study showed that acylation of *ortho*-iodotoluene afforded by-products like di- and tri-iodotoluenes and 4-iodo-3-methylacetophenone in major amounts along with the desired product **45**, hence this method was not thought feasible. The procedure of Zupan *et al.*, utilizing F-TEDA-BF₄ and elemental iodine, used in Scheme 4.14, was applied to 3-iodo-4-methylacetophenone.²⁴⁴ In contrast to the results obtained with the methoxy analogue, iodination with *ortho*-iodotoluene did not proceed regioselectively. This may be due to the fact that the aromatic ring was not as activated here as it was with the methoxy group. Both, α -iodocarbonyl derivative **44** and the iodoaryl derivative **45** were formed, shown in Scheme 4.16. Presence of starting material **43** was also detected. These were found difficult to separate. Changing reaction times and using



Scheme 4.16 Iodination of 4-methylacetophenone using F-TEDA-BF₄

excess iodinating agent and F-TEDA-BF₄ produced similar results.

Regioselectivity in iodination could not be achieved using the iodination procedures described above. Alternative procedures, using *ortho*-iodotoluene with functional groups in the *para*-position that could be transformed into the acetyl group via simple functional group manipulations, were desired. Fortunately, 3-iodo-4-methylbenzoic acid, **46**, was commercially available and was converted into the desired product, **45**, via acid chloride **47**, as depicted in Scheme 4.15. Thionyl chloride (SOCl₂) was used to convert the acid to the acid chloride **47**.²⁴⁵ Compound **47** was then treated with lithium dimethylcuprate (I), formed *in situ* from methyllithium and cuprous iodide, in diethyl ether at -78 °C to give the desired compound **45**.^{246,247} which was purified by column chromatography. Organocopper reagents are advantageous in that they are not known to add across carbon-heteroatom multiple bonds, unlike organolithium reagents, and are also not known to form diketones and keto esters from acid chlorides, unlike organocadmium and organozinc reagents.^{248,249}

Compound **45** was subjected to acylation with NaOMe and methyl trifluoroacetate to form the desired diketone, 4,4,4-trifluoro-1-(3-iodo-4-methyl-phenyl)-butane-1,3-dione, **48**, which was allowed to react with **11** to form 4-[5-(3-iodo-4-methyl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, **49**. Product **49** was purified by column chromatography and characterized by elemental analysis and NMR spectra.

The conversion of **49** to compound **D** has not yet been attempted.

§ 4.8 SUMMARY

The research objectives of synthesizing compounds **A** and **B** were realized. The analogue **C** was synthesized, as confirmed by HRMS, but showed the presence of side product, probably the boronic acid. However, pure iodinated precursors, **42** and **49**, required for the synthesis of compounds **C** and **D** respectively, were synthesized and characterized by elemental analysis and NMR spectra.

A potential diagnostic tumor-imaging agent for SPECT was synthesized from compound **A**. The synthesis of the radiolabeled analogue is discussed in Chapter 6.

Chapter 5 Synthesis of Boronated Unnatural Cyclic Amino Acids

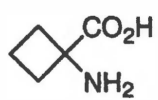
A description of the synthesis of five- and seven-membered boronated unnatural cyclic amino acids is described in this chapter. Details of the progress made towards the synthesis of a cascade polyol carborane-containing analogue of the five-membered amino acid are also presented.

§ 5.1 RATIONALE FOR THE CHOICE OF THE STRUCTURES OF TARGET COMPOUNDS

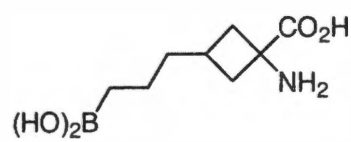
The structures of the target compounds were chosen based on 1-aminocyclobutanecarboxylic acid (ACBC), a boronic acid shown in Figure 5.1. A *meta*-carborane containing derivative of ACBC has also been reported.^{91,92} It was decided to attempt to introduce the boron moiety directly on the five-membered ring instead of on the side chain as shown in Figure 5.2. This chapter contains a summary of the synthesis of 1-amino-3-boronocyclopentanecarboxylic acid, **E**, and 1-amino-3-boronocycloheptanecarboxylic acid, **F**, shown in Figure 5.2.²⁵⁰

§ 5.2 SYNTHETIC STRATEGY

It was decided to introduce the boronic acid moiety via a diboron reagent such as bis(pinacolato)diboron, **50**. Diboron reagents are useful for the borylation of

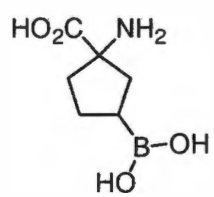


ACBC

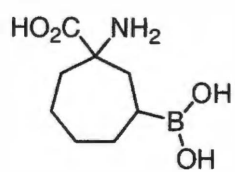


Boronic acid derivative of ACBC

Figure 5.1 Boronic acid derivative of ACBC



E



F

Figure 5.2 Target compounds E and F

unsaturated organic compounds and organic halides.^{251,252} Palladium and platinum complexes are efficient catalysts for diboration of alkenes,²⁵³ alkynes,²⁵⁴ enones,²⁵⁵ and conjugated dienes²⁵⁶ with diboron esters. 1,4-Addition of diboron reagents to α,β -unsaturated carbonyl compounds, though not extensively studied in literature, has been reported with platinum²⁵⁵ and copper²⁵⁷ catalyst.

It was decided to utilize hydantoins for the introduction of the α -amino acid moiety.^{258,259} The synthesis of hydantoins would be attempted by the Bucherer-Bergs method of hydantoin synthesis starting from carbonyl compounds. This is one of the most extensively used methods for hydantoin synthesis and is effective for many types of carbonyl compounds. It involves use of ammonium carbonate $(\text{NH}_4)_2\text{CO}_3$ and potassium cyanide (KCN) in aqueous ethyl alcohol. The carbonyl group of the starting enone could be used effectively for introducing the amino group, hence the Bucherer-Bergs method was the method of choice. A comprehensive review of the methods of synthesis of hydantoins can be found in literature.²⁵⁸

When hydantoins are hydrolyzed for relatively long periods of time, they form α -amino acids. Hydantoins are valuable in the synthesis of a variety of α -amino acids that are otherwise difficult to obtain. In fact, hydantoin synthesis of α -amino acids was first suggested as a general method by Wheeler and Hoffman and later used by them in the syntheses of tyrosine and phenylalanine.²⁶⁰ The first report of the preparation of an α -amino acid from a hydantoin was by Urech in 1872.²⁶¹

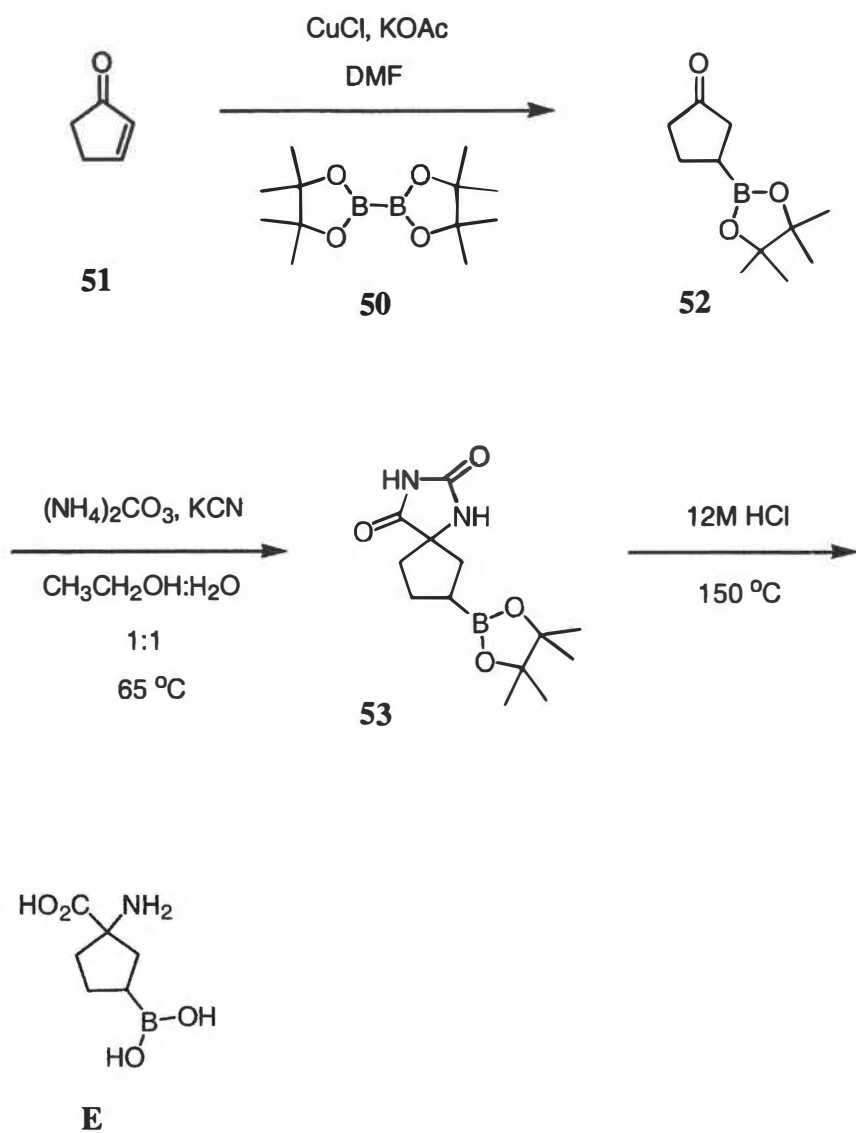
Hydantoins can be hydrolyzed to form α -amino acids with a variety of reagents including concentrated acids, barium hydroxide, and ammonium sulfide.

The synthetic strategy involved reaction of 2-cyclopentene-1-one or 2-cycloheptene-1-one with diboron reagent **50**, introduction of the boron moiety, synthesis of the hydantoin, and then hydrolysis of the boron ester to the boronic acid and the hydantoin to the amino acid.

§ 5.3 SYNTHESIS OF COMPOUND E

1-Amino-3-boronocyclopentanecarboxylic acid, **E**, was synthesized starting from 2-cyclopenten-1-one, **51**, as outlined in Scheme 5.1. It should be noted that, though 1,4-addition of diboron reagents to cyclic enones have been reported, there has been no report of such an addition with 2-cyclopenten-1-one. Nevertheless, the methodology that had been applied to six- and seven-membered cyclic enones was applied to cyclopentenone.

The first catalyst system used for 1,4-diboration with **51** was a combination of copper(I) chloride (CuCl) and tributylphosphine.²⁵⁷ This reaction did not work well with **51**. Even after running the reaction for long periods of time, little product was observed. Changing the reagent quantities did not help. TLC and GC analysis revealed presence of starting material in each case. A rhodium based catalyst, chlorotris(triphenylphosphine)rhodium(I), was then examined.²⁶² The yields with this system were also poor. GC analysis revealed formation of a number of side products. This method was abandoned.



Scheme 5.1 Synthesis of five-membered boronated amino acid **E**

Takahashi *et al.* reported the room temperature borylation of enones using copper(I) chloride and potassium acetate (KOAc) in dimethyl formamide (DMF).^{263,264} This method was applied to cyclopentenone **51** which did react to give **52**. Though the yields from this process were modest, they were better than those obtained from the rhodium and copper-phosphine catalyst.

Product **52** was column purified and treated with $(\text{NH}_4)_2\text{CO}_3$ and KCN to form the hydantoin **53**, which, on purification, was subjected to hydrolysis with concentrated hydrochloric acid (HCl) at high temperature to yield the target amino acid **E**.

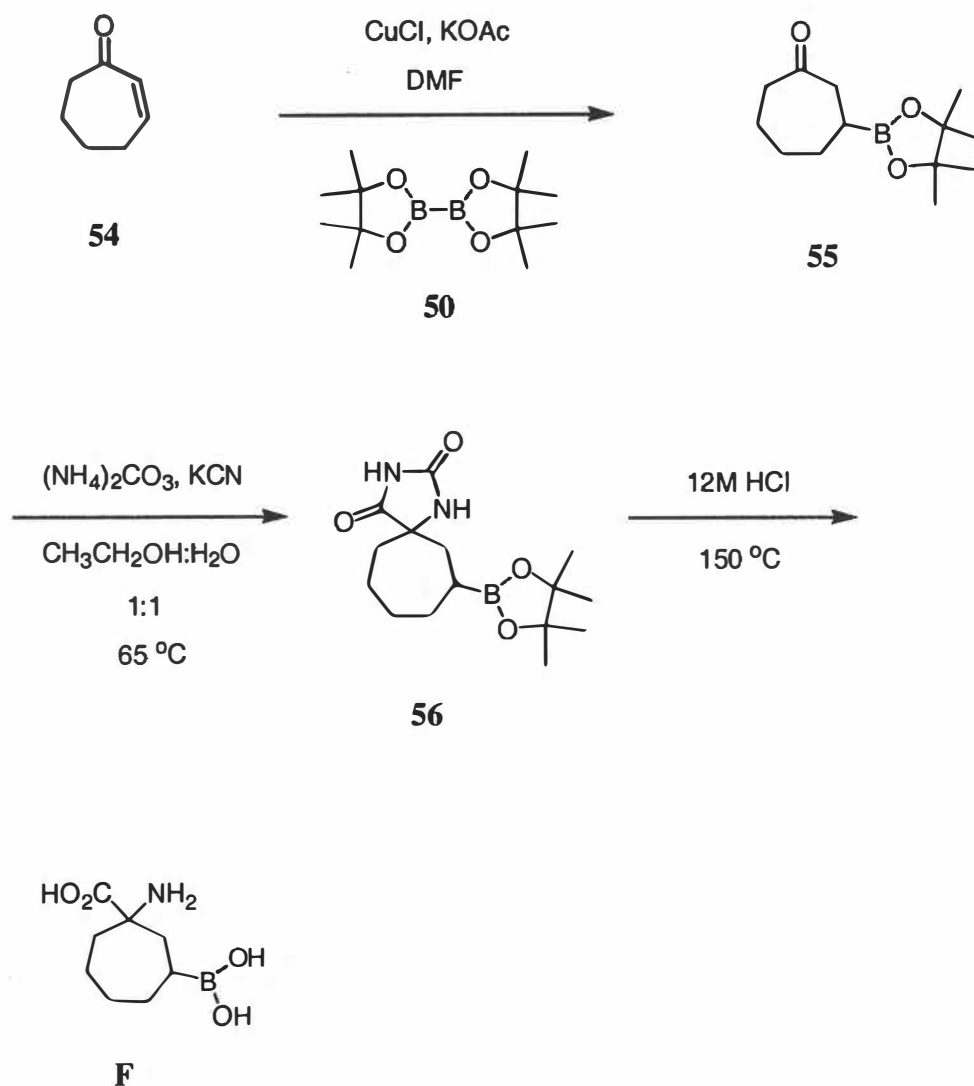
§ 5.4 SYNTHESIS OF COMPOUND F

1-Amino-3-boronocycloheptanecarboxylic acid, **F**, was synthesized using a similar synthetic strategy, outlined in Scheme 5.2.

2-cyclohepten-1-one, **54**, was treated with **50** to form boronated cycloheptanone **55**. This reaction produced better yields than the five-membered analogue. Compound **55** was purified and subjected to Bucherer-Bergs conditions for synthesis of the hydantoin **56**. Compound **56**, after column purification, was subjected to hydrolysis with concentrated HCl at 160 °C to form target amino acid **F**.

§ 5.5 RATIONALE FOR THE CHOICE OF A CARBORANYL CASCADE POLYOL DERIVATIVE OF COMPOUND E

As described in Section 2.3, carborane-containing amino acid derivatives have been synthesized in order to increase the boron content of the amino acids.⁹²



Scheme 5.2 Synthesis of seven-membered boronated amino acid F

But carboranes are lipophilic in nature. In order to solve the water solubility problem, cascade polyol derivatives of carboranes have been synthesized.^{3,86}

The cascade polyol is a good water-solubilizing agent. It has no asymmetric centers, so no diastereomers are formed when it is bonded to the carborane cage which can bear chiral or racemic biologically active molecules.²⁶⁵ This offers a distinct advantage over other solubilizing agents like chiral sugars.

Thus, it was decided to synthesize a *meta*-carboranyl analogue of 1-amino-3-boronocyclopentanecarboxylic acid using a cascade polyol as part of the molecule. This target compound **G** is shown in Figure 5.3.

§ 5.6 PROGRESS IN THE SYNTHESIS OF COMPOUND **G**

The synthetic strategy for the compound is outlined in Schemes 5.3, 5.4, and 5.5. It should be noted that the synthesis of this molecule has not been completed, but good progress has been made in that direction.

Schemes 5.3 and 5.4 outline the synthesis of intermediates **64** and **70**, which can then be coupled to form the target compound **G**. The final coupling sequence is outlined in Scheme 5.5. The synthesis of polyol tosylate intermediate **64** and of compound **69**, required for coupling with *meta*-carborane, has been accomplished, and will be described in this dissertation work.

The reaction scheme in Figure 5.5 for the coupling of the two intermediates has not yet been attempted.

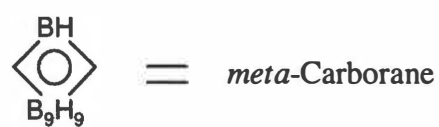
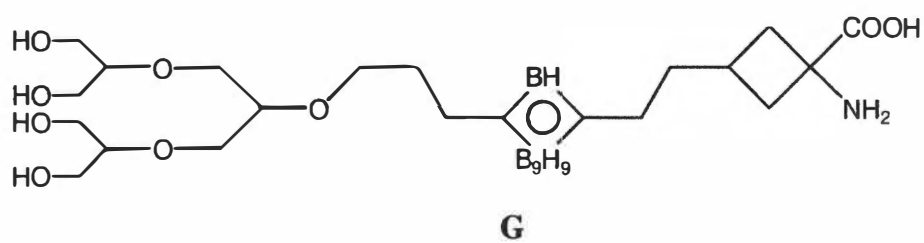
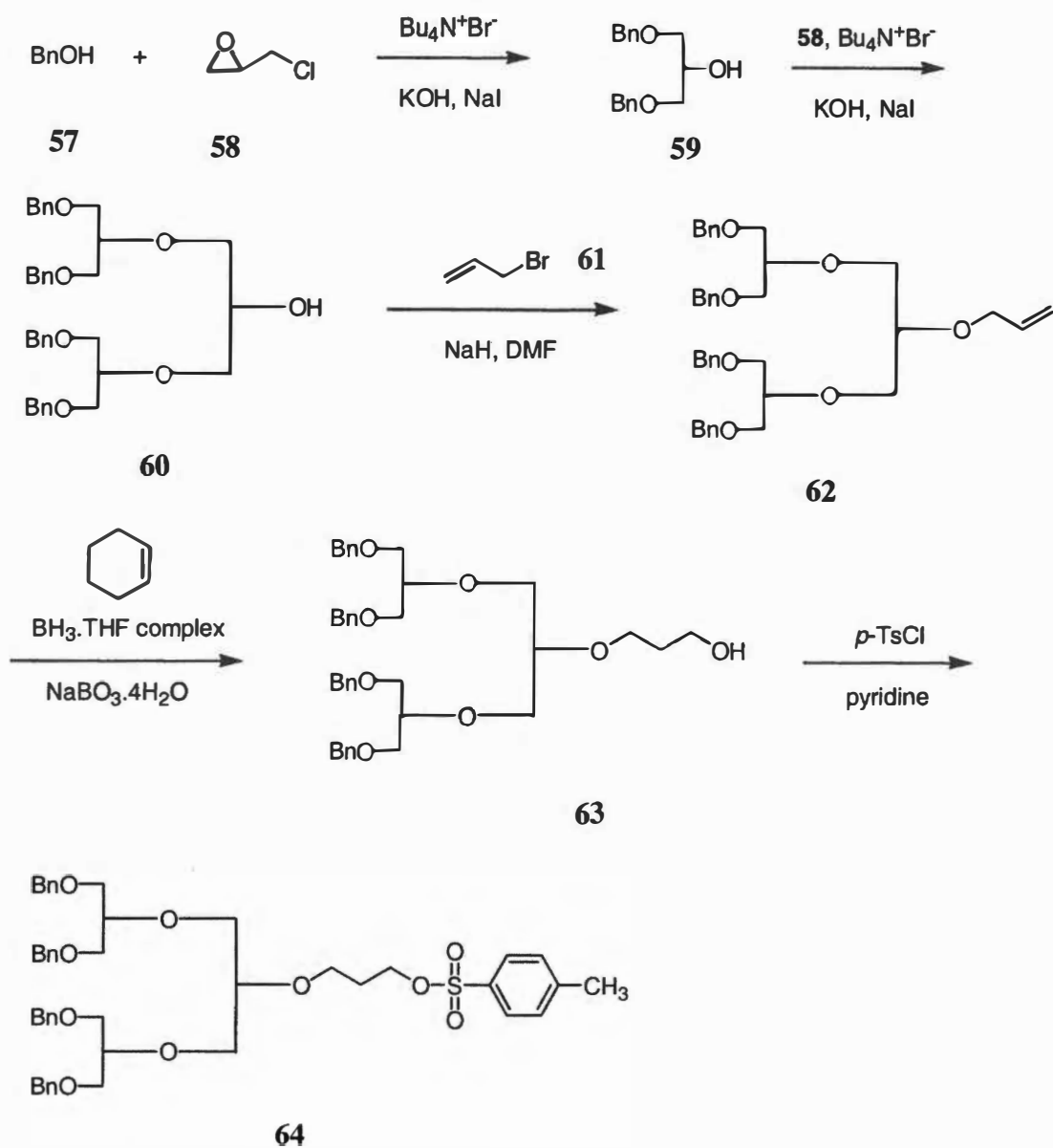
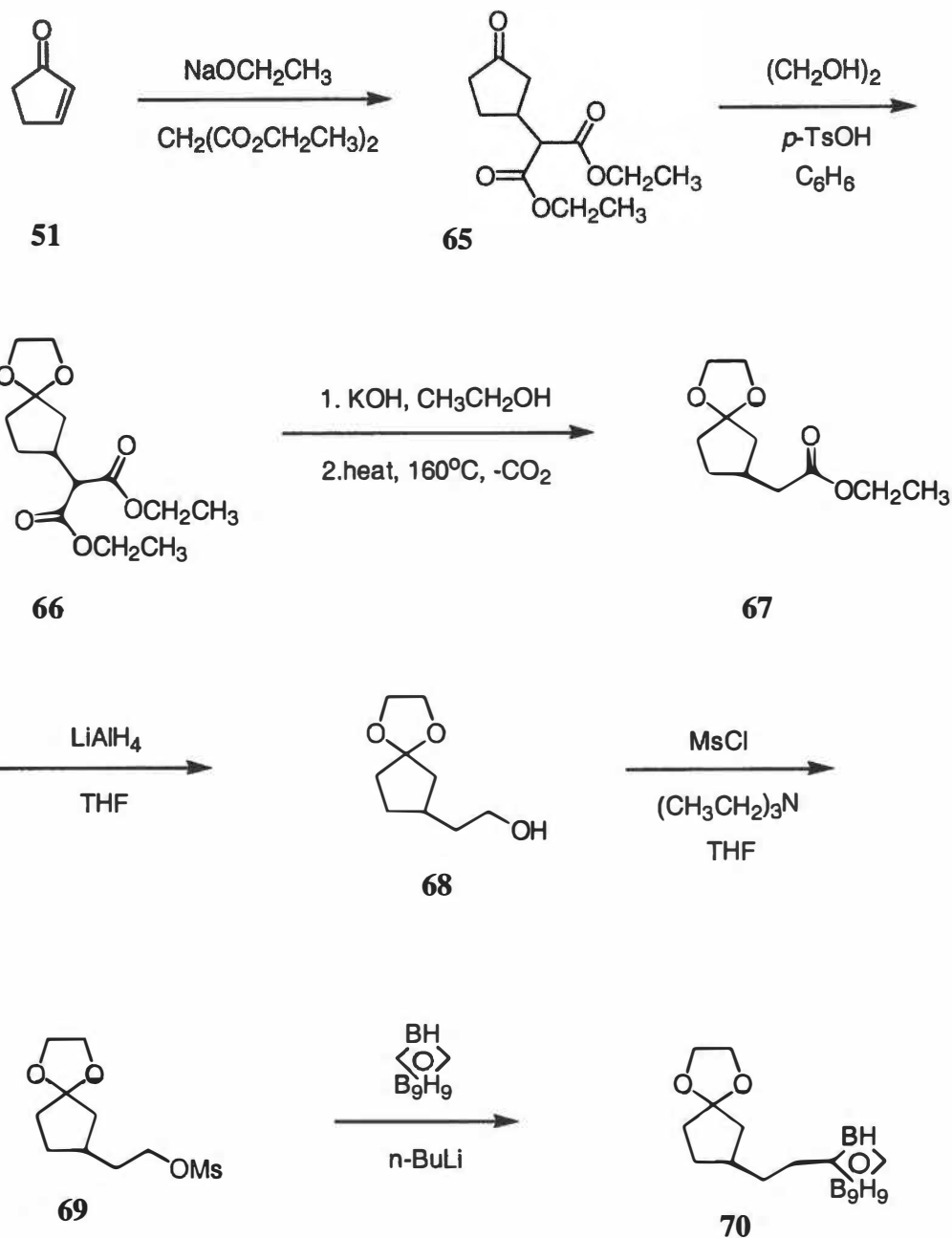


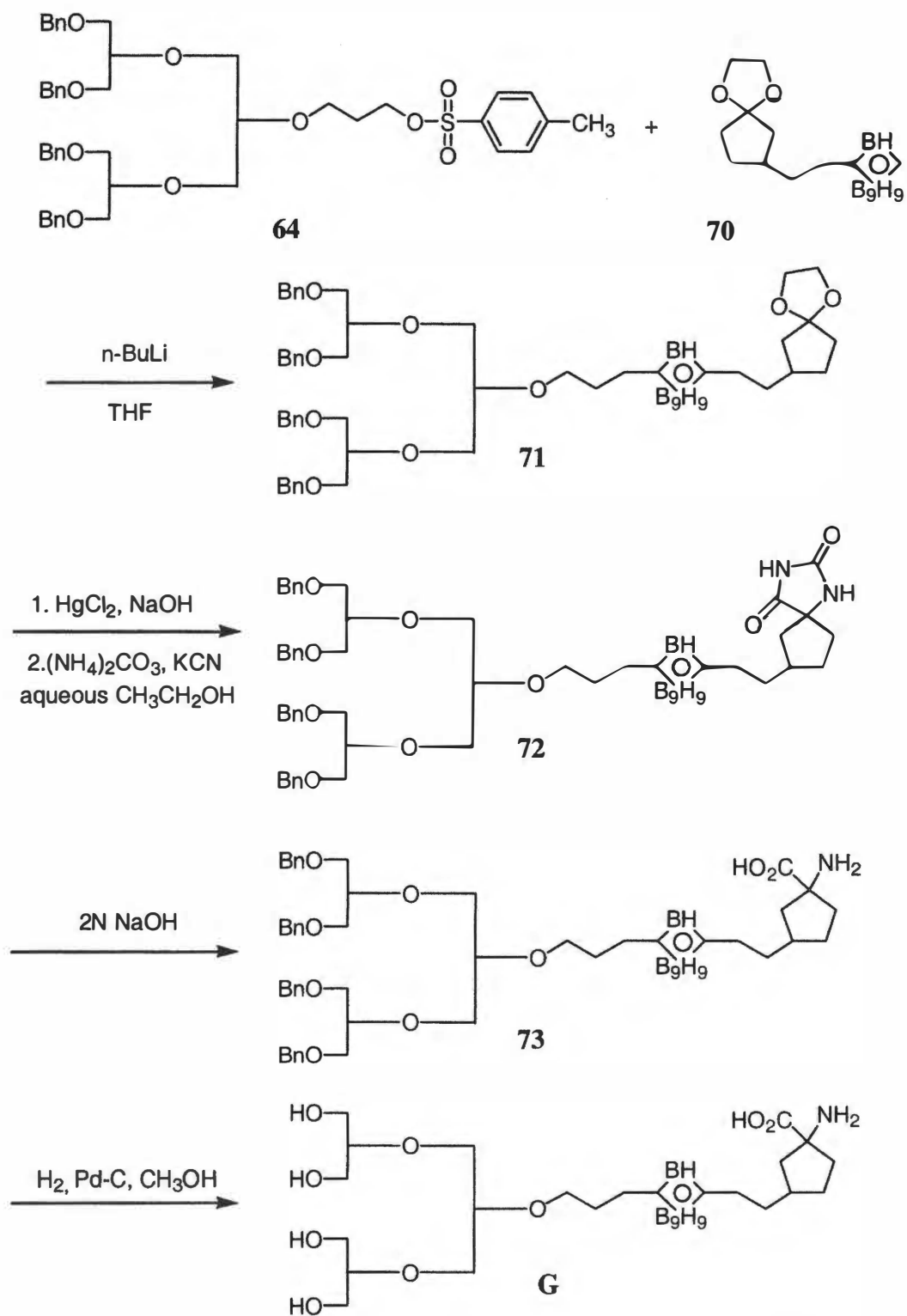
Figure 5.3 Target compound G



Scheme 5.3 Synthesis of polyol tosylate 64



Scheme 5.4 Synthesis of intermediate 69



Scheme 5.5 Proposed synthesis of compound G from compounds 64 and 70

Polyol tosylate **64** was synthesized first. Benzyl alcohol (BnOH), **57**, was treated with epichlorohydrin **58**, tetrabutylammonium bromide ($\text{Bu}_4\text{N}^+\text{Br}^-$), and sodium iodide (NaI) to form **59**.²⁶⁵ Intermediate **59** was then subjected to the same sequence to form the higher homologue **60**. Compound **60** was allylated with allyl bromide, **61**, and sodium hydride (NaH) in DMF as a solvent to form alkene **62**, which on hydroboration followed by oxidation, yielded the cascade polyol **63**.²⁰⁰ Polyol **63** was converted to the desired tosylate **64** by the action of *para*-toluenesulfonic acid (*p*-TsOH) in pyridine ($\text{C}_6\text{H}_5\text{N}$).²⁶⁶

The synthesis of intermediate **70** was initiated from 2-cyclopentene-1-one. Michael addition of **51** with sodium ethoxide ($\text{NaOCH}_2\text{CH}_3$) and diethyl malonate furnished **65**.²⁶⁷ The carbonyl group of **65** was protected as a ketal by treatment with ethylene glycol to give **66**.²⁶⁸ Intermediate **66** was converted to the monoester **67** by basic hydrolysis of the diester moiety with potassium hydroxide (KOH) followed by thermal decarboxylation.²⁶⁹ Compound **67** was subjected to lithium aluminum hydride (LiAlH_4) reduction of the ester group to yield alcohol **68**.^{270,271} Mesylation of **68** yielded **69**.²⁵⁹

§ 5.7 SUMMARY

The synthesis of five- and seven-membered amino acids has been accomplished. The biodistribution of these compounds is currently being evaluated in mice. For compound **G**, key cascade polyol intermediate **64** has been synthesized and pure mesylate compound **69** has been prepared for coupling with *meta*-

carborane in order to generate the intermediate **70**. The chemistry outlined in Scheme 5.5 has been proposed for the coupling procedure and should provide a feasible route for the synthesis of the target molecule.

Chapter 6 Synthesis of an Iodine-123 Labeled Analogue of a COX-2 Enzyme Inhibitor

Radiolabeled compounds are important in diagnostic medical imaging as they permit noninvasive, *in vivo*, three-dimensional imaging of internal organs. The motivation for preparing a radiolabeled analogue of celecoxib as a potential SPECT agent for colon tumor imaging has been put forth in Sections 2.2 and 2.4. This chapter outlines the synthesis of radiolabeled analogue, compound **H**, shown in Figure 6.1, via an arylboronate precursor, **A**.

§ 6.1 SYNTHETIC APPROACH

§ 6.1.1 Iodine-123 Isotope

Radiohalogens have been widely used in nuclear medicine. A number of radioiodination techniques have been developed due to the availability of a variety of useful iodine isotopes.²¹³ Iodine-123 is a single photon-emitting isotope of iodine with a half-life of 13.2 hours. It is being widely used in medicine due to its decay characteristics and commercial availability. A number of ¹²³I-labeled agents, shown in Figure 6.2, have been effective in clinical investigations.^{272,273}

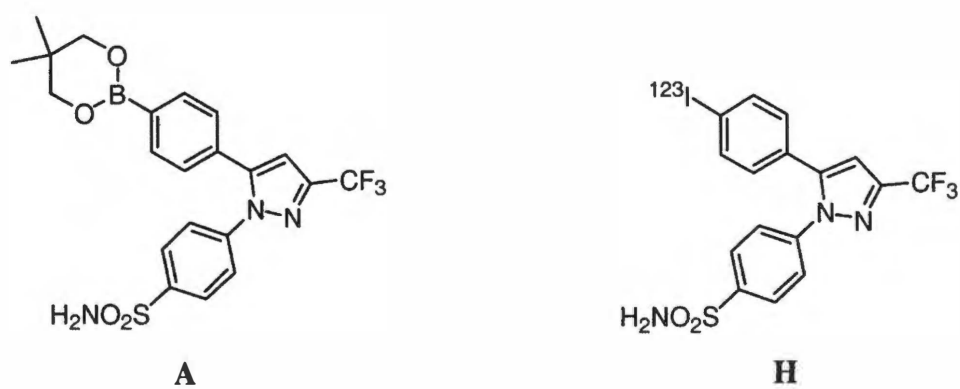


Figure 6.1 Target molecule H and boronate precursor A

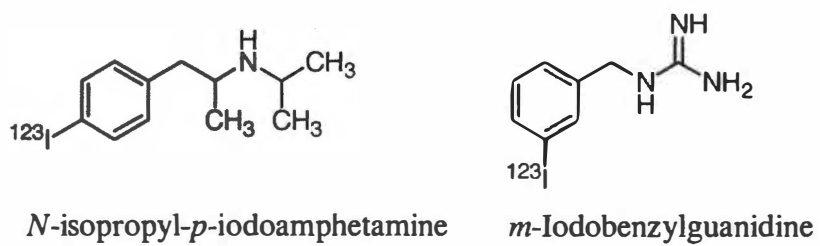


Figure 6.2 Clinically effective iodine-123 labeled agents

§ 6.1.2 Rationale for Use of Radiolabeled Sodium Iodide in Radioiodination

The reaction of organoboranes with molecular iodine was developed by Brown *et al.*²⁷⁴ This method involves use of sodium methoxide as a base and molecular iodine. It is not considered to be an effective radioiodination technique as the sodium methoxide can affect other functional groups in the molecule. Also, it involves the use of molecular iodine, which is dangerous (due to its volatility) and an expensive chemical form for iodine radioisotopes.²¹³

Investigations into the mechanism of the reaction have shown that it proceeds via the electrophilic attack of iodine on an electron-rich organoborane complex. This meant that any electrophilic form of iodine could be utilized.²⁷⁵ A new iodine methodology using *in situ* oxidation of radiolabeled sodium iodide using mild oxidants such as chloramine-T was developed.²⁷⁶ This methodology has been used in this dissertation work for the synthesis of the electrophilic species required for radioiodination. An important feature of this methodology is that it permits radioiodinations to be carried out on a 'no-carrier-added' basis which is important as it ensures that the quantity of labeled agent is kept below the pharmacological dosages during nuclear medicine procedures.²⁷⁷

§ 6.1.3 Rationale for Choice of Arylboronate Esters as Precursors for

Radioiodinations

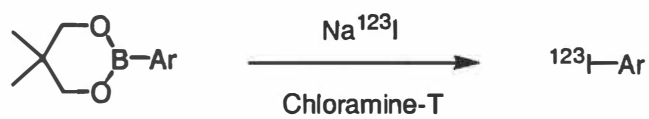
Over the years, many organometallic reagents have been used as precursors for a variety of pharmaceuticals. Reagents based on tin, mercury, thallium, silicon,

germanium, and lead have been used.²¹³ Organotin reagents have been widely used but the toxicity of tin compounds, the rather harsh stannylation procedures, and the strength of the carbon-tin bond have been serious drawbacks in this process.²¹⁵ Our research group has focused on the use of organoboranes as precursors to radiohalogenated pharmaceuticals. Initial studies included the use of boronic acids and trialkylboranes as precursors.²¹⁴ The prerequisite arylboronic acids were prepared under highly basic conditions using aryllithium and arylmagnesium halides. These highly reactive reagents are not suitable for preparing pharmaceutical precursors containing reactive substituents like esters, and ketones.

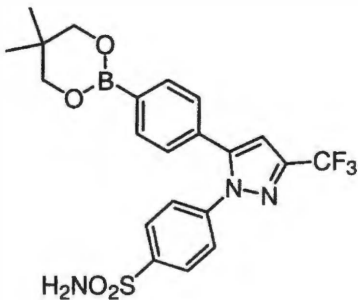
Attention was then focused on arylboronate esters as possible precursors for radioiodinated compounds. Our group reported the direct radioiodination of arylboronate esters using radiolabeled sodium iodide, shown in Scheme 6.1.²¹⁶ The arylboronate esters were prepared under mild conditions using the procedure developed in our labs.^{278,279}

§ 6.2 SYNTHESIS OF COMPOUND H

The synthesis of compound **H** was accomplished starting from compound **A** using the boronate ester as precursor, as outlined in Scheme 6.1. Arylboronate, **A**, was synthesized as outlined in Chapter 4, Scheme 4.10. No-carrier-added sodium iodide was allowed to react with chloramine-T in the presence of boronated compound **A** in THF to yield compound **H**, as shown in Scheme 6.2. The total



Scheme 6.1 Radioiodination via arylboronate esters

**B**

synthesis time was 3 hours. A detailed procedure is presented in the Experimental Section.

§ 6.3 SUMMARY

The synthesis of a radiolabeled analogue of a COX-2 inhibitor was accomplished in good yield, and with a high purity of 99.5% from an arylboronate prepared under mild conditions. Given the possible relationship of the COX-2 enzyme and colon cancer, outlined in detail in Section 2.2, this agent and other such analogues could be used as potential SPECT agents for colon tumor imaging, physiological mapping, and studying *in vivo* pharmacokinetics, which could provide valuable information about the disease.

Chapter 7 Conclusions and Future Work

§ 7.1 CONCLUSIONS

The syntheses of monosubstituted boronated analogues of celecoxib, **A** and **B**, were achieved. The synthesis of key iodinated benzenesulfonamide derivatives **42** and **49**, required for the preparation of the disubstituted boronated analogues of celecoxib, was also accomplished. A potential SPECT agent **E** was made from compound **A**.

Unnatural cyclic amino acids, **E** and **F**, which mimic the tumor specific ACBC, were synthesized.

§ 7.2 FUTURE WORK

Future work should focus on the evaluation of **A**, **B**, and radiolabeled analogue **E** *in vitro* and *in vivo*. Results from these studies can be correlated with their structures and provide clues in designing other target molecules. Incorporation of the carborane moiety into the COX-2 inhibitor structures should also be investigated. Efforts should be made for the isolation of pure compound **C**. The synthesis and isolation of **D** via boronated precursor **49** should be attempted.

Results from the biodistribution study of **E** and **F** should be utilized for the design of other target boronated amino acids. The synthesis of carboranyl cascade

polyol **G** should be pursued. The synthesis route for this compound, outlined in Scheme 5.5, should provide a feasible method for its preparation.

Chapter 8 Experimental Section

§ 8.1 GENERAL METHODS

Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance spectra were acquired either on a Bruker WP250 at 250.13 and 62.89 MHz, or on a Varian Mercury 300 at 300.09 and 75.46 MHz, or on a Bruker Avance 400 spectrometer at 400.04 and 100.59 MHz respectively. Chemical shifts are reported in parts per million (ppm) using residual protons in deuterated solvents and are referenced to tetramethylsilane. The splitting patterns are abbreviated as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, and m = multiplet. Boron (^{11}B) NMR spectra (^1H -decoupled) were obtained on a Bruker Avance 400 at 128.38 MHz. In the case of ^{11}B spectra, chemical shifts were measured with reference to an external $\text{BF}_3\cdot\text{etherate}$ sample and resonances observed upfield of the reference were assigned negative chemical shift values. The mass spectral analyses were obtained on a VG Quattro II electrospray mass spectrometer. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA and are within $\pm 0.4\%$ of the theoretical values. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

All commercial reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used as received without further purification unless otherwise noted. All solvents were reagent grade and were distilled from appropriate drying

agents under nitrogen atmosphere prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Benzene was distilled from calcium hydride and stored under nitrogen.

Column chromatography was performed using silica gel (60 Å, 32-63 mesh) obtained from Bodman Chemical, Aston, PA. Analytical thin layer chromatography (TLC) was performed using 250 µm silica gel plates obtained from Analtech, Newark, DE, which were visualized with ultraviolet illumination at 254 nm and phosphomolybdic acid or development in an iodine chamber. The pH of a solution was determined using Whatman pH Indicator Paper.

All glassware, syringes, and needles were dried in an oven and cooled under nitrogen prior to use.

§ 8.2 EXPERIMENTAL PROCEDURES FOR BORONATED ANALOGUES OF CELECOXIB (A, B, C, AND D)

§ 8.2.1 Synthesis of 4-(Sulfamoyl)phenylhydrazine hydrochloride, 11.²³⁴

A suspension of sulfanilamide (1.72 g, 10.0 mmol) in 20 mL of concentrated HCl was cooled to -5 °C and diazotized with 0.69 g (10.0 mmol) of NaNO₂. After stirring for 30 min at -5 °C, the reaction mixture was added slowly to a cold solution of SnCl₂ (5.69 g, 30.0 mmol) in 10 mL of concentrated HCl. The mixture was stirred for 45 min at 0 °C (ice bath) and the precipitate formed was filtered off. The crude product was recrystallized from a methanol/ether solution, and dried to give 1.46 g (65.4%) of **11** as a white solid: ¹H NMR (250 MHz, DMSO-*d*₆) δ 7.01 (d, *J* = 8.8 Hz,

2H), 7.18 (s, 2H), 7.70 (d, $J = 8.7$ Hz, 2H), 8.81 (br s, 1H), 10.33 (br s, 2H); ^{13}C NMR (63 MHz, DMSO- d_6) δ 113.2, 127.0, 136.1, 148.4.

§ 8.2.2 Synthesis of 3-iodo-4-methoxyacetophenone, **39**.^{240,280,281}

To a solution of 4-methoxyacetophenone (4.55 g, 30.0 mmol) in 300 mL of CH_3CN was added elemental iodine (3.89 g, 15.3 mmol) and 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate (F-TEDA- BF_4) (10.63 g, 30.0 mmol). After stirring for 16 h at room temperature, the solvent was removed *in vacuo*, the residue was dissolved in 750 mL of CH_2Cl_2 , and the insoluble material filtered off. The solution was washed sequentially with 300 mL of 5% aqueous sodium thiosulfate pentahydrate and water. The organic layer was dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (20% ethyl acetate in hexane) to yield 6.33 g (76.4%) of **39**; ^1H NMR (250 MHz, CDCl_3) δ 2.54 (s, 3H), 3.94 (s, 3H), 6.40 (d, $J = 8.6$ Hz, 1H), 7.94 (s, $J = 8.6$ Hz, 1H), 8.37 (s, 1H); ^{13}C NMR (63 MHz, CDCl_3) δ 26.2, 58.5, 85.8, 109.9, 130.4, 131.7, 140.0, 161.6, 195.3.

§ 8.2.3 Synthesis of 3-iodo-4-methylbenzoyl chloride, **47**.²⁴⁵

To 3-iodo-4-methylbenzoic acid (10.81 g, 40.0 mmol) **46** contained in a 100-mL round-bottomed flask fitted with an inverted drying tube packed with moistened glass wool was added SOCl_2 (33.0 mL, 452.4 mmol). The reaction mixture was refluxed for 5 h and then cooled to room temperature. Excess SOCl_2 was distilled out and the mixture was left to dry on a vacuum pump to yield 10.18 g (90.7%) of

product **47**: ^1H NMR (250 MHz, CDCl_3) δ 2.50 (s, 3H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.97 (s, $J = 8.0$ Hz, 1H), 8.48 (s, 1H); ^{13}C NMR (63 MHz, CDCl_3) δ 28.5, 100.8, 129.8, 130.9, 132.0, 141.3, 149.9, 166.4.

§ 8.2.4 Synthesis of 3-iodo-4-methylacetophenone, **45**.^{247,282}

Into a dry three-necked, 100-mL round-bottomed flask equipped with a rubber septum and a magnetic stir bar was added of CuI (2.86 g, 15.0 mmol). The flask was evacuated and filled with nitrogen. This purging procedure was repeated two more times. Freshly distilled anhydrous ether (50 mL) was added to the flask and the system cooled to -5°C . Methyllithium (18.8 mL, 30.0 mmol) was added and, after about 10 min, the temperature was lowered to -78°C . A precooled ethereal solution of **47** (1.40 g, 5.0 mmol) was injected into the yellowish reaction mixture. After 40 min at -78°C , anhydrous methanol (2.22 mL, 55.0 mmol) was added and the reaction allowed to reach room temperature. The mixture was poured, with stirring, into saturated aqueous ammonium chloride (NH_4Cl), the organic layer extracted with ether, washed with brine, dried over MgSO_4 , and the solvent removed on a rotary evaporator to give a reddish brown liquid. The crude product was purified by column chromatography (10% ethyl acetate in hexane) to give 0.98 g (75.4%) of **45**: ^1H NMR (250 MHz, CDCl_3) δ 2.46 (s, 3H), 2.55 (d, 3H), 7.29 (d, $J = 7.9$ Hz, 1H), 7.81 (d, $J = 7.9$ Hz, 1H), 8.35 (s, 1H); ^{13}C NMR (63 MHz, CDCl_3) δ 26.9, 28.2, 101.0, 127.9, 129.6, 136.2, 138.8, 146.9, 196.2.

§ 8.2.5 Preparation of 1,3-diketones 29, 33, 36, 41, and 48 via Claisen

Condensation of Acetophenone Derivatives with Methyl

Trifluoroacetate.¹³⁴

§ 8.2.5.1 Synthesis of 4,4,4-trifluoro-1-(4-iodo-phenyl)-butane-1,3-dione, 29.

To a solution of methyl trifluoroacetate (4.23 g, 33.0 mmol) in 60 mL of methyl *tert*-butyl ether (MTBE) was added 25% NaOMe in MeOH (8.82 mL, 39.0 mmol). A solution of 4-iodoacetophenone (7.382 g, 30.0 mmol) in 115 mL of MTBE was added to the mixture dropwise via an addition funnel. After stirring for 48 h at room temperature, aqueous 3 N HCl (14.0 mL) was added. The organic layer was extracted with ether, washed with water and then brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo* to give a brownish solid which was recrystallized from isooctane to give 8.11 g (78.9%) of product **29**: mp 37 °C; ¹H NMR (250 MHz, CDCl₃) δ 6.53 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (63 MHz, CDCl₃) δ 92.2, 102.2, 117.0 (q, *J* = 283.4 Hz), 128.8, 132.3, 138.4, 177.5 (q, *J* = 36.2 Hz), 185.1. Anal. Calcd for C₁₀H₆F₃IO₂: C, 35.11; H, 1.77; I, 37.10. Found: C, 35.19; H, 1.74; I, 36.90.

§ 8.2.5.2 Synthesis of 4,4,4-trifluoro-1-(4-bromo-phenyl)-butane-1,3-dione, 33.

To a solution of methyl trifluoroacetate (4.23 g, 33.0 mmol) in 50 mL of MTBE was added 25% NaOMe in MeOH (8.82 mL, 39.0 mmol). A solution of 4-bromoacetophenone (5.97 g, 30.0 mmol) in 40 mL of MTBE was added to the mixture dropwise. After stirring for 48 h at room temperature, aqueous 3 N HCl

(14.0 mL) was added. The organic layer was extracted with ether, washed with water and then brine, dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo* to yield the crude product which was recrystallized from isooctane to afford 6.17 g (70.0%) of product **33**: mp 40 °C; ^1H NMR (250 MHz, CDCl_3) δ 6.53 (s, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 8.6 Hz, 2H); ^{13}C NMR (63 MHz, CDCl_3) δ 92.3, 121.6 (q, J = 283.4 Hz), 129.0, 129.3, 131.8, 132.4, 177.4 (q, J = 36.3 Hz), 185.1. Anal. Calcd for $\text{C}_{10}\text{H}_6\text{BrF}_3\text{O}_2$: C, 40.71; H, 2.05; Br, 27.08. Found: C, 40.78; H, 1.98; Br, 27.09.

§ 8.2.5.3 Synthesis of 4,4,4-trifluoro-1-(2-iodo-phenyl)-butane-1,3-dione, **36**.

To a solution of methyl trifluoroacetate (1.20 g, 8.9 mmol) in 20 mL of MTBE was added 25% NaOMe in MeOH (2.40 mL, 10.6 mmol). A solution of 2-iodoacetophenone (2.0 g, 8.1 mmol) in 40 mL of MTBE was added to the reaction mixture dropwise. After stirring for 48 h at room temperature, aqueous 3 N HCl (6 mL) of was added. The organic layer was extracted with ether, washed with water and then brine, dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo* to give 2.05 g (73.6%) of product **36**: ^1H NMR (250 MHz, CDCl_3) δ 6.39 (s, 1H), 7.17 (m, 1H), 7.45 (m, 2H), 7.97 (d, J = 7.8 Hz, 1H); ^{13}C NMR (63 MHz, CDCl_3) δ 92.8, 97.5, 117.1 (q, J = 282.7 Hz), 127.9, 128.3, 129.6, 132.8, 139.3, 141.1, 174.6 (q, J = 36.7 Hz), 190.53. Anal. Calcd for $\text{C}_{10}\text{H}_6\text{F}_3\text{IO}_2$: C, 35.11; H, 1.77; I, 37.10. Found: C, 35.48; H, 1.77; I, 36.70.

§ 8.2.5.4 Synthesis of 4,4,4-trifluoro-1-(3-iodo-4-methoxy-phenyl)-butane-1,3-dione, 41.

To a solution of methyl trifluoroacetate (1.55 g, 11.9 mmol) in 30 mL of MTBE was added 25% NaOMe in MeOH (3.23 mL, 14.1 mmol). A solution of **39** (3.00 g, 10.9 mmol) in 90 mL of MTBE was added to the mixture dropwise via an addition funnel. After stirring for 72 h at room temperature, aqueous 3 N HCl (6 mL) was added. The organic layer was extracted with ether, washed with water and then brine, dried over anhydrous MgSO₄, filtered, and concentrated using a rotary evaporator to give 3.52 g (86.9%) of **41** as a pale brown solid: ¹H NMR (250 MHz, CDCl₃) δ 3.97 (s, 3H), 6.47 (s, 1H), 6.88 (d, *J* = 8.7 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 8.35 (s, 1H); ¹³C NMR (63 MHz, CDCl₃) δ 56.7, 86.4, 91.8, 110.4, 117.2 (q, *J* = 282.9 Hz), 127.1, 129.9, 139.2, 162.7, 174.7 (q, *J* = 36.3 Hz), 184.7. Exact mass calcd for C₁₁H₈F₃IO₃ *m/z* 371.9470; found *m/z* 371.9467.

§ 8.2.5.5 Synthesis of 4,4,4-trifluoro-1-(3-iodo-4-methyl-phenyl)-butane-1,3-dione, 48.

To a solution of methyl trifluoroacetate (0.415 g, 3.2 mmol) in MTBE (5 mL) was added 25% NaOMe in MeOH (0.87 mL, 3.8 mmol). A solution of **45** (0.765 g, 2.9 mmol) in 10 mL of MTBE was added to the mixture dropwise. After stirring for 39 h at room temperature, aqueous 3 N HCl (1.5 mL) was added. The organic layer was extracted with ether, washed with water and then brine, dried over anhydrous MgSO₄, filtered, and concentrated using a rotary evaporator to give 0.862 g (82.3%)

of **48** as a reddish brown liquid: ^1H NMR (250 MHz, CDCl_3) δ 2.49 (s, 3H), 6.49 (s, 1H), 7.33 (d, $J = 7.4$ Hz, 1H), 7.77 (d, $J = 7.9$ Hz, 1H), 8.33 (s, 1H); ^{13}C NMR (63 MHz, CDCl_3) δ 28.5, 92.2, 101.3, 117.1 (q, $J = 283.1$ Hz), 127.2, 130.0, 132.0, 137.9, 148.3, 176.9 (q, $J = 36.8$ Hz), 184.5. Exact mass calcd for $\text{C}_{11}\text{H}_8\text{F}_3\text{IO}_2$ m/z 355.9521; found m/z 355.9528.

§ 8.2.6 Synthesis of Halogenated Benzenesulfonamides **31**, **34**, **37**, **42**, and **49** via

Condensation of 1,3-diketones with **11**.¹³⁴

§ 8.2.6.1 Synthesis of 4-[5-(4-iodo-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, **31**.

To a stirred solution of diketone **29** (4.10 g, 12.0 mmol) in 120 mL of ethanol was added 4-(sulfamoylphenyl)hydrazine hydrochloride (2.95 g, 13.2 mmol). The mixture was refluxed for 24 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and then brine, dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo* to give a pale brown solid. The crude product was purified by column chromatography (30% ethyl acetate in hexane) to give 5.39 g (91.1%) of **31** as a white solid. mp 180 °C: ^1H NMR (250 MHz, CDCl_3) δ 5.04 (s, 2H), 6.78 (s, 1H), 6.97 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.7$ Hz, 2H), 7.73 (d, $J = 8.4$ Hz, 2H), 7.93 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (63 MHz, CDCl_3) δ 95.9, 106.7, 116.6 (q, $J = 270.3$ Hz), 125.6, 127.6, 128.0, 130.3, 138.3, 141.8, 142.1, 144.0, 144.9 (q, $J = 38.4$ Hz).

Anal. Calcd for $C_{16}H_{11}F_3IN_3O_2S$: C, 38.96; H, 2.25; N, 8.52; I, 25.73. Found: C, 38.98; H, 2.26; N, 8.42; I, 25.49.

§ 8.2.6.2 Synthesis of 4-[5-(4-bromo-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, 34.

To a stirred solution of diketone **33** (5.29 g, 18.0 mmol) in 180 mL of ethanol was added 4-(sulfamoylphenyl)hydrazine hydrochloride (4.43 g, 19.8 mmol). The mixture was refluxed for 24 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and then brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give solid. The crude product was purified by column chromatography (30% ethyl acetate in hexane) to give 5.24 g (65.2%) of **31** as a white solid. ^1H NMR (250 MHz, $CDCl_3$) δ 5.03 (s, 2H), 6.78 (s, 1H), 7.12 (d, $J = 8.3$ Hz, 2H), 7.46 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 8.3$ Hz, 2H), 7.93 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 106.7, 120.8 (q, $J = 269.6$ Hz), 124.1, 125.5, 127.4, 127.6, 130.3, 132.3, 141.8, 142.0, 144.1 (q, $J = 38.7$ Hz), 144.0. Anal. Calcd for $C_{16}H_{11}BrF_3N_3O_2S$: C, 43.06; H, 2.48; N, 9.42; Br, 17.91. Found: C, 42.97; H, 2.56; N, 9.15; Br, 17.71.

§ 8.2.6.3 Synthesis of 4-[5-(2-iodo-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, 37.

To a stirred solution of diketone **36** (0.598 g, 1.8 mmol) in 30 mL of ethanol was added 4-(sulfamoylphenyl)hydrazine hydrochloride (0.430 g, 1.9 mmol). The

mixture was refluxed for 26 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and then brine, dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (35% ethyl acetate in hexane) to give 0.535 g (62%) of **37**: mp 117 °C; ^1H NMR (250 MHz, CDCl_3) δ 5.25 (s, 2H), 6.75 (s, 1H), 7.15 (m, $J = 7.4$ Hz, 1H), 7.30 (m, 1H), 7.40 (d, $J = 8.2$ Hz, 2H), 7.42 (s, 1H), 7.81 (d, $J = 8.5$ Hz, 2H), 7.89 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (63 MHz, CDCl_3) δ 99.4, 107.9, 116.6 (q, $J = 269.6$ Hz), 123.0, 124.5, 127.3, 128.6, 131.5, 134.4, 139.9, 141.2, 142.2, 143.7 (q, $J = 38.4$ Hz), 146.1. Anal. Calcd for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{IN}_3\text{O}_2\text{S}$: C, 38.96; H, 2.25; N, 8.52; I, 25.73. Found: C, 39.04; H, 2.33; N, 8.37; I, 25.49.

§ 8.2.6.4 Synthesis of 4-[5-(3-iodo-4-methoxy-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, **42.**

To a stirred solution of diketone **41** (0.744 g, 2.0 mmol) in 35 mL of ethanol was added 4-(sulfamoylphenyl)hydrazine hydrochloride (0.507 g, 2.2 mmol). The mixture was refluxed for 24 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and then brine, dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (40% ethyl acetate in hexane) to give 0.605 g (57.8%) of **42** as a white solid: mp 186 °C; ^1H NMR (250 MHz, $\text{DMSO}-d_6$) δ 3.82 (s, 3H), 6.99 (d, $J = 8.6$ Hz, 1H), 7.19

(m, 2H), 7.54 (s, 2H), 7.58 (d, $J = 8.7$ Hz, 2H), 7.83 (d, $J = 2.0$ Hz, 1H), 7.91 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (63 MHz, DMSO- d_6) δ 56.6, 86.5, 106.3, 111.3, 121.3 (q, $J = 269.2$ Hz), 122.3, 126.0, 126.8, 130.4, 139.2, 141.0, 142.7 (q, $J = 37.6$ Hz), 143.5, 144.1, 158.5. Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{IN}_3\text{O}_3\text{S}$: C, 39.02; H, 2.50; N, 8.03; I, 24.25. Found: C, 39.34; H, 2.57; N, 7.94; I, 23.90.

§ 8.2.6.5 Synthesis of 4-[5-(3-iodo-4-methyl-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, 49.

To a stirred solution of diketone **48** (0.70 g, 1.9 mmol) in 30 mL of ethanol was added 4-(sulfamoylphenyl)hydrazine hydrochloride (0.50 g, 2.2 mmol). The mixture was refluxed for 24 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and then brine, dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo* to yield a yellow solid. The crude product was purified by column chromatography (30% ethyl acetate in hexane) to give 0.509 g (51.0%) of **49** as a white solid: mp 177 °C; ^1H NMR (250 MHz, DMSO- d_6) δ 2.35 (s, 3H), 7.11 (d, $J = 7.4$ Hz, 1H), 7.28 (m, 2H), 7.56 (m, 4H), 7.90 (m, $J = 7.6$ Hz, 3H); ^{13}C NMR (63 MHz, DMSO- d_6) δ 27.3, 101.5, 106.6, 121.2 (q, $J = 269.5$ Hz), 126.1, 126.6, 127.5, 128.7, 129.8, 138.5, 140.9, 142.2 (q, $J = 38.1$ Hz), 142.3, 143.3, 144.2. Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{IN}_3\text{O}_2\text{S}$: C, 40.25; H, 2.58; N, 8.28; I, 25.02. Found: C, 40.55; H, 2.73; N, 8.07; I, 24.76.

§ 8.2.7 Synthesis of Target Compounds A and B via Coupling of 31 and 37 with
Diboron Ester 23.²²⁴⁻²²⁷

§ 8.2.7.1 Synthesis of 4-[5-(4-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, A.

Into a dried, three-necked round-bottomed flask was added PdCl₂(dppf) (0.115 g, 0.16 mmol), KOAc (1.54 g, 15.7 mmol), and bis(neopentylglycolato)diboron 23 (1.30 g, 5.7 mmol) in a glove bag. The flask was flushed with nitrogen and then charged with 20 mL of DMSO. After stirring for 15 min, aryl iodide 31 (2.58 g, 5.2 mmol) dissolved in 16 mL of DMSO was added to the reaction mixture. The flask was fitted with a reflux condenser and heated at 80 °C for 20 h. The reaction mixture was then cooled to room temperature, extracted with ethyl acetate, washed with water, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo* to give a copper colored solid. The product was purified by column chromatography over silica gel (45% ethyl acetate in hexane) to give 1.61 g (64.1%) of the target compound A as a crystalline white solid: ¹H NMR (400 MHz, CDCl₃) δ 1.01 (s, 6H), 3.75 (s, 4H), 5.46 (s, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 8.5 Hz 2H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (63 MHz, CDCl₃) δ 21.8, 31.9, 72.4, 106.6, 121.0 (q, *J* = 269.6 Hz), 125.5, 127.5, 127.9, 130.4, 134.4, 141.5, 142.4, 144.1 (q, *J* = 38.6 Hz), 145.3; ¹¹B NMR (128 MHz, CDCl₃) δ 27.7. Anal. Calcd for C₂₁H₂₁BF₃N₃O₄S: C, 52.63; H, 4.42; N, 8.77. Found: C, 52.91;

H, 4.62; N, 8.53; Exact mass calcd for $C_{21}H_{21}BF_3N_3O_4S$ m/z 479.130; found m/z 479.131.

§ 8.2.7.2 Synthesis of 4-[5-(2-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-phenyl)-3-trifluoromethyl-pyrazol-1-yl]-benzenesulfonamide, B.

Into a dried, three-necked round-bottomed flask was added $PdCl_2(dppf)$ (0.098 g, 0.13 mmol), KOAc (1.31 g, 13.5 mmol), and bis(neopentylglycolato)diboron **23** (1.11 g, 4.9 mmol) in a glove bag. The flask was flushed with nitrogen and then charged with 20 mL of DMSO. After stirring for 15 min, aryl iodide **37** (2.20 g, 4.5 mmol) dissolved in 10 mL DMSO was added to the reaction mixture. The flask was fitted with a reflux condenser and heated at 80 °C for 24 h. The reaction mixture was then cooled to room temperature, product extracted with ethyl acetate, washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to yield a solid. The crude product was purified via column chromatography (40% ethyl acetate in hexane) to give 1.10g (51.6%) of the product: ^1H NMR (250 MHz, acetone- d_6) δ 0.83 (s, 6H), 3.51 (s, 4H), 6.67 (s, 2H), 6.79 (s, 1H), 7.47 (m, 5H), 7.85 (m, 3H); ^{13}C NMR (63 MHz, acetone- d_6) δ 21.9, 32.1, 72.7, 107.4, 120.6 (q, $J = 289.6$ Hz), 125.4, 127.6, 129.6, 131.3, 131.3, 135.1, 135.7, 143.0, 143.4, (q, $J = 36.6$ Hz), 144.1, 147.7; ^{11}B NMR (128 MHz, acetone- d_6) δ 26.7. Exact mass calcd for $C_{21}H_{21}BF_3N_3O_4S$ m/z 479.1302; found m/z 479.1313.

§ 8.3 EXPERIMENTAL PROCEDURES FOR UNNATURAL CYCLIC AMINO ACIDS E AND F.

§ 8.3.1 Synthesis of 1,4-diboration Products **52** and **54**

§ 8.3.1.1 *Synthesis of 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)- cyclopentanone, **52**.*²⁶⁴

A dry three-necked round-bottomed flask flushed with nitrogen was charged with CuCl (0.980 g, 9.9 mmol) in a glove bag. DMF (54 mL) was added to the flask and the mixture stirred for 1 h. KOAc (0.972 g, 9.9 mmol) was then added followed by bis(pinacolato)diboron, **50** (2.51 g, 9.9 mmol). After stirring for 20 min, cyclopentenone **51** (0.77 mL, 9.0 mmol) was added to the reaction mixture dropwise. The resulting solution was stirred at room temperature for 24 h, and then quenched with 20 mL of water. The mixture was extracted with benzene, the combined organic layers were washed with water, dried over anhydrous MgSO₄, and solvent removed under reduced pressure on a rotary evaporator to yield a pale yellow liquid. The crude product was purified by column chromatography (30% ethyl acetate in hexane) to give 1.52 g (24.1%) of the product **52** as a colorless liquid: ¹H NMR (250 MHz, CDCl₃) δ 1.25 (s, 12H), 1.67 (m, 1H), 1.85 (m, 1H), 2.02-2.35 (m, 7H); ¹³C NMR (63 MHz, CDCl₃) δ 24.6, 25.1, 38.7, 40.0, 83.3, 220.7; ¹¹B NMR (128 MHz, CDCl₃) δ 34.7. Exact mass calcd for C₁₁H₁₉BO₃ *m/z* 210.1429; found *m/z* 210.1434.

§ 8.3.1.2 *Synthesis of 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-cycloheptanone, 55.*²⁶⁴

A dry three-necked round-bottomed flask flushed with nitrogen was charged with CuCl (2.47 g, 25.0 mmol) in a glove bag. DMF (180 mL) was added to the flask and the mixture stirred for 1 h. KOAc (2.45 g, 25.0 mmol) was then added followed by bis(pinacolato)diboron, **50** (6.34 g, 25.0 mmol). After stirring for 20 min, cycloheptenone **54** (2.50 g, 22.7 mmol) was added to the reaction dropwise. The reaction mixture was stirred at room temperature for 24 h, and then quenched with water. The mixture was extracted with benzene, the combined organic layers were washed with water, dried over anhydrous MgSO₄, and solvent removed under reduced pressure on a rotary evaporator to yield a white solid. The crude product was purified by column chromatography (10% ethyl acetate in hexane) to give 2.02 g (37.4%) of the product **55** as a white crystalline solid. ¹H NMR (250 MHz, CDCl₃) δ 1.23 (s, 12H), 1.49 (m, 2H), 1.55-1.63 (m, 1H), 1.78-1.96 (m, 4H), 2.51 (m, 4H); ¹³C NMR (63 MHz, CDCl₃) δ 24.2, 24.6, 30.9, 31.9, 43.6, 44.7, 83.2, 215.1; ¹¹B NMR (128 MHz, CDCl₃) δ 34.7. Exact mass calcd for C₁₃H₂₃BO₃ *m/z* 238.1743; found *m/z* 238.1739.

§ 8.3.2 Synthesis of Boronated Hydantoins 53 and 56

§ 8.3.2.1 *Synthesis of 7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-diazaspiro[4.4]nonane-2,4-dione, 53.*²⁵⁹

An Ace pressure tube was charged with a mixture of **52** (0.420 g, 2 mmol), $(\text{NH}_4)_2\text{CO}_3$ (0.961 g, 10.0 mmol), and KCN (0.470 g, 7.0 mmol) in 10 mL of ethanol and 10 mL of water. The reaction vessel was sealed and heated to 65 °C in an oil bath for 18 h. The reaction was then cooled to room temperature and opened carefully in a hood. The solvent was removed under reduced pressure using a rotary evaporator. The resultant white solid was taken up into ethyl acetate and washed with water and then brine. The organic layer was dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure to yield a white solid. The crude product was purified by column chromatography over silica gel using ethyl acetate as eluent to yield 0.318 g (56.7%) of **53**: ^1H NMR (250 MHz, $\text{DMSO}-d_6$) major diastereomer δ 1.16 (s, 12H), 1.40-2.10 (m, 7H), 8.16 (br s, 1H), 10.50 (br s, 1H); ^{13}C NMR (63 MHz, DMSO) δ 24.5, 27.0, 37.8, 40.0, 69.3, 82.9, 156.3, 178.8; ^{11}B NMR (128 MHz, $\text{DMSO}-d_6$) δ 35.7. Exact mass calcd for $\text{C}_{13}\text{H}_{21}\text{BN}_2\text{O}_4$ m/z 280.1597; found m/z 280.1599.

§ 8.3.2.2 *Synthesis of 7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3-diazaspiro[4.6]undecane-2,4-dione, 56*

An Ace pressure tube was charged with a mixture of **54** (0.714 g, 3 mmol), of $(\text{NH}_4)_2\text{CO}_3$ (1.44 g, 15.0 mmol), and KCN (0.705 g, 10.5 mmol) in 10 mL of ethanol

and 10 mL of water. The reaction vessel was sealed and heated to 65 °C in an oil bath for 18 h. The reaction was then cooled to room temperature and opened carefully in a hood. The solvent was removed under reduced pressure using a rotary evaporator. The resultant white solid was taken up into ethyl acetate and washed with water and then brine. The organic layer was dried over anhydrous MgSO_4 and concentrated under reduced pressure to yield a white solid. The crude product was purified by column chromatography (80% ethyl acetate in hexane) to yield 0.46 g (50%) of **56**: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) major diastereomer δ 1.06 (s, 1H), 1.16 (s, 12H), 1.56-1.90 (m, 10H), 8.24 (br s, 1H), 10.47 (br s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 21.8, 24.8, 28.6, 29.3, 36.4, 38.4, 65.4, 82.9, 156.3, 179.4; Exact mass calcd for $\text{C}_{15}\text{H}_{25}\text{BN}_2\text{O}_4$ m/z 308.190; found m/z 308.1915.

§ 8.3.3 Synthesis of Boronated Amino Acids E and F

§ 8.3.3.1 *Synthesis of 1-amino-3-boronocyclopentanecarboxylic acid, E*

An Ace pressure tube was charged with hydantoin **53** (0.140 g, 0.5 mmol) and concentrated HCl (5 mL). The tube was sealed and heated to 150 °C in an oil bath for 24 h. The resulting mixture was cooled to room temperature and opened carefully in a hood. TLC indicated disappearance of starting material. The reaction mixture was treated with charcoal and filtered through Celite. The Celite pad was washed repeatedly with water. The filtrate, and the washes were combined and the water removed to yield a diastereomeric mixture of **E** as the solid hydrochloride. The solid turns brown at 256 °C without melting. R_f = 0.71 (isopropanol:water:acetic

acid, 1.0:1.0:0.5): ^1H NMR (250 MHz, D_2O) major diastereomer δ 1.50-2.50 (m); ^{13}C NMR (63 MHz, D_2O) δ 28.0, 37.2, 38.8, 65.7, 175.2; ^{11}B NMR (128 MHz, D_2O) δ 28.8. Exact mass calcd for $\text{C}_9\text{H}_{18}\text{BNO}_5$ ($\text{M}+\text{H}-\text{Cl}+\text{gly}-2\text{H}_2\text{O}$, obtained in a glycerol matrix) m/z 230.120; found m/z 230.137.

§ 8.3.3.2 *Synthesis of 1-amino-3-boronocycloheptanecarboxylic acid, F*

An Ace pressure tube was charged with hydantoin **56** (0.154 g, 0.5 mmol) and concentrated HCl (5 mL). The tube was sealed and heated to 150 °C in an oil bath for 24 h. The resulting mixture was cooled to room temperature and opened carefully in a hood. TLC indicated disappearance of starting material. The reaction mixture was treated with charcoal and filtered through Celite. The Celite pad was washed repeatedly with water. The filtrate, and the washes were combined and the water removed under reduced pressure to yield a diastereomeric mixture of **F** as the solid hydrochloride. The solid turns brown at 248 °C without melting. R_f = 0.65 (isopropanol:water:acetic acid, 1.0:1.0:0.5): ^1H NMR (400 MHz, D_2O) major diastereomer δ 1.16-1.20 (m), 1.30-1.50 (m), 1.70-1.90 (m), 2.07-2.31 (m); ^{13}C NMR (100 MHz, D_2O) δ 24.7, 32.9, 33.6, 38.1, 38.5, 66.2, 177.5; ^{11}B NMR (128 MHz, D_2O) δ 31.7. Exact mass calcd for $\text{C}_{11}\text{H}_{22}\text{BNO}_5$ ($\text{M}+\text{H}-\text{Cl}+\text{gly}-2\text{H}_2\text{O}$, obtained in a glycerol matrix) m/z 258.151; found m/z 258.150.

§ 8.4 SYNTHESIS OF INTERMEDIATES 64 AND 69 FOR PREPARATION OF COMPOUND G

§ 8.4.1 Synthesis of Polyol Tosylate, 64.²⁰⁰

§ 8.4.1.1 *Synthesis of 1,3-bis-benzyloxy-propan-2-ol, 59.*

A three-necked 500-mL round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and an addition funnel was charged with KOH (84.0 g, 1.5 mol) and 10 mL of water. After stirring for 20 min, benzyl alcohol (208 mL, 2 mol) was added to the mixture. After stirring for 10 min, tetra-*n*-butylammonium bromide (32.2 g, 0.10 mol) and sodium iodide (15.0 g, 0.10 mol) was added. The reaction mixture turned yellow. After stirring for 40 min, epichlorohydrin (39.2 mL, 0.5 mol) was added dropwise to the reaction mixture with vigorous stirring. The resulting solution was heated to 70 °C for 72 h. After cooling to room temperature, the reaction mixture was diluted with aqueous 3 N HCl (100mL), extracted with ether, washed with water and then brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure on a rotary evaporator. The residue was purified by Kugelrohr distillation: first fraction (60 °C-120 °C) excess benzyl alcohol; second fraction (160 °C-210 °C) product: to yield 148.92 g (54.8%) of **59** as a pale yellow oil. ¹H NMR (250 MHz, CDCl₃) δ 2.90 (br s, 1H), 3.50 (m, 4H), 3.98 (m, 1H), 4.49 (s, 4H), 7.29 (s, 10H); ¹³C NMR (63 MHz, CDCl₃) δ 69.3, 70.0, 73.2, 127.5, 128.05, 128.2, 137.8.

§ 8.4.1.2 Synthesis of 1,3-bis-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-propan-2-ol, 60.

A three-necked 500-mL round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and an addition funnel was charged with KOH (14.3 g, 0.26 mol) in 7 mL of water. After stirring for 20 min, **59** (91.8 g, 0.34 mol) was added to the mixture. After stirring for 10 min, tetra-*n*-butylammonium bromide (5.48 g, 0.02 mol) and sodium iodide (2.55 g, 0.02 mol) were added. The reaction mixture turned yellow. After stirring for 40 min, epichlorohydrin (6.66 mL, 0.09 mol) was added dropwise to the reaction mixture with vigorous stirring. The resulting solution was heated to 70 °C for 72 h. After cooling to room temperature, the reaction mixture was diluted with aqueous 3 N HCl (40 mL), extracted with ether, washed with water and then brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure on a rotary evaporator. The residue was purified by Kugelrohr distillation to yield 66.2 g (64.5%) of **60** as a pale yellow oil. ¹H NMR (250 MHz, CDCl₃) δ 2.89 (s, 1H), 3.48 (m, 9H), 3.62 (m, 5H), 3.90 (m, 5H), 4.47 (s, 8H), 7.23 (s, 20H); ¹³C NMR (63 MHz, CDCl₃) δ 69.2, 69.9, 71.1, 71.6, 73.1, 78.5, 127.4, 128.1, 137.8.

§ 8.4.1.3 Synthesis of 3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxy-methyl)ethoxy]]propene, 62.

Sodium hydride (10.3 g, 430.7 mmol) was added to a solution of alcohol **60** (64.6 g, 107.7 mmol) in 265 mL of DMF added at 0 °C. After stirring for 30 min,

ally bromide (46.6 mL, 538.4 mmol) was added to the reaction mixture dropwise. After completion of addition, the reaction mixture was stirred in an ice-bath for 60 min and then stirred at room temperature for 18 h. The reaction mixture was then carefully treated with water (40 mL) to remove unreacted sodium hydride, diluted with ether, washed successively with water and brine, dried over anhydrous MgSO_4 , and filtered. The solvent was removed under reduced pressure to give a yellow oil which was purified by column chromatography over silica gel (20% ethyl acetate in hexane) to yield 52.8 g (76.5%) of product **62**: ^1H NMR (250 MHz, CDCl_3) δ 1.22 (t, $J = 7.0$ Hz, 2H), 2.00 (s, 2H), 3.50-3.80 (m, 15H), 4.10 (m, 3H), 4.49 (s, 8H), 5.09 (dd, $J = 10.5, 1.7$ Hz, 1H), 5.22 (dd, $J = 17.2, 1.5$ Hz, 1H), 5.90 (m, 1H), 7.28 (s, 20H); ^{13}C NMR (63 MHz, CDCl_3) δ 69.9, 70.2, 71.0, 73.1, 77.5, 78.5, 116.3, 127.4, 128.1, 135.2, 138.2.

§ 8.4.1.4 Synthesis of 3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxy-methyl)ethoxy]]propan-1-ol, **63.**

A three-necked round-bottomed flask was charged with $\text{BH}_3 \cdot \text{THF}$ (30.1 mL, 30.1 mmol) under nitrogen atmosphere. The solution was cooled to 0 °C in an ice-bath and cyclohexene (6.10 mL, 60.1 mmol) was added via a syringe. After stirring for 2 h, alkene **62** (9.64 g, 15.0 mmol) THF (15 mL) was added to the flask and the resulting mixture was stirred under nitrogen atmosphere for 15h at room temperature. The reaction mixture was then cooled to 0 °C in an ice-bath and the organoborane was oxidized using a mixture of sodium perborate tetrahydrate (13.9 g,

90.2 mmol) and water (10 mL). The reaction mixture was allowed to come to room temperature and concentrated *in vacuo*. The residue was extracted with ether, washed with water and then brine, dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to obtain a pale yellow oil. The product was purified by column chromatography over silica gel (50% ethyl acetate in hexane) to obtain 7.34 g (75%) of **63** as a colorless liquid: ¹H NMR (250 MHz, CDCl₃) δ 1.78 (m, 2H), 3.30 (br s, 1H), 3.54 (m, 9H), 3.75 (m, 10H), 4.51 (s, 8H), 7.30 (s, 20H); ¹³C NMR (63 MHz, CDCl₃) δ 32.0, 61.2, 69.2, 69.9, 73.3, 78.1, 127.5, 128.2, 137.9.

§ 8.4.1.5 Synthesis of toluene-4-sulfonic acid-3-[2-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-1-(2-benzyloxy-1-benzyloxymethyl-ethoxymethyl)ethoxy)]propyl ester, **64.**

A dry, three-necked round-bottomed flask was charged with polyol **63** (0.855 g, 1.30 mmol) and pyridine (2.85 mL, 35.1 mmol). The solution was cooled to -5 °C in an ice-bath. *p*-toluenesulfonyl chloride (0.372 g, 1.9 mmol) was added to the reaction mixture and the solution was stirred for 6 h while maintaining the bath temperature at -5 °C. The reaction mixture was then poured into a mixture of ether (80 mL), ice (10 g), and concentrated HCl (3 mL). The ether layer was separated, washed with cold water, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo* to yield 0.898 g (84.9%) of tosylate **64**. ¹H NMR (250 MHz, CDCl₃) δ 1.89 (m, 2H), 2.38 (s, 3H), 3.48-3.80 (m, 17H), 4.13 (m, 4H), 4.50 (s, 8H), 7.28 (s, 22H),

7.75 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (63 MHz, CDCl_3) δ 21.5, 29.5, 65.6, 67.7, 69.7, 70.0, 73.2, 78.5, 127.5, 127.7, 128.2, 129.7, 133.0, 138.1, 144.5.

§ 8.4.2 Synthesis of Mesylate 69.²⁵⁹

§ 8.4.2.1 Synthesis of 2-(3-oxo-cyclopentyl)-malonic acid diethyl ester, 65.²⁸³

A dry three-necked round-bottomed flask was charged with diethyl malonate (4.55 mL, 30 mmol) in anhydrous ethanol (21 mL) under nitrogen atmosphere. The solution was cooled to $-5\text{ }^{\circ}\text{C}$ and sodium ethoxide in ethanol (0.1 mL, 0.28 mmol) was added to it. After stirring the reaction mixture for 30 min, 2-cyclopentene-1-one (2.57 mL, 30 mmol) in 20 mL of ethanol was added dropwise at $-5\text{ }^{\circ}\text{C}$. After the addition was complete, the solution was allowed to warm to room temperature and stirred for 15 h. The reaction mixture was then treated with acetic acid (2 mL), concentrated *in vacuo*, extracted into ether, washed with water and then brine, dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo* to give a pale yellow liquid. The product was purified by column chromatography over silica gel (20% ethyl acetate in hexane) to yield 6.19 g (85.2%) of **65** as a colorless liquid: ^1H NMR (250 MHz, CDCl_3) δ 1.27 (t, $J = 7.1$ Hz, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.67 (m, 1H), 2.03 (dd, $J = 18.4, 11.0$ Hz, 1H), 2.51 (dd, $J = 18.3, 7.2$ Hz, 1H), 2.20-2.36 (m, 3H), 2.84 (m, 1H), 3.35 (d, $J = 9.4$ Hz, 1H), 4.22 (m, 4H); ^{13}C NMR (63 MHz, CDCl_3) δ 13.9, 27.3, 36.1, 38.0, 42.7, 56.3, 61.4, 167.9, 168.0, 216.9.

§ 8.4.2.2 Synthesis of 2-(1,4-dioxo-spiro[4.4]non-7-yl)-malonic acid diethyl ester, **66.²⁸³**

To a solution of **65** (2.33 g, 9.6 mmol) in 150 mL of benzene contained in a round-bottomed flask was added ethylene glycol (1.07 mL, 19.2 mmol), and *p*-toluenesulfonic acid (0.037 g, 0.19 mmol). The flask was fitted with a Dean Stark apparatus and a reflux condenser. After being refluxed at 110 °C for 27 h, the mixture was cooled to room temperature and treated with aqueous 3 N NaOH. The organic benzene layer was washed with water and then brine, dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to give a yellow liquid which was purified by column chromatography over silica gel (15% ethyl acetate in hexane) to yield 2.26 g (82.2%) of **66** as a colorless liquid: ¹H NMR (250 MHz, CDCl₃) δ 1.26 (t, *J* = 7.3 Hz, 6H), 1.44 (m, 1H), 1.59 (dd, *J* = 13.5, 9.6 Hz, 1H), 1.75-2.00 (m, 3H), 2.09 (dd, *J* = 13.6, 7.9 Hz, 1H), 2.67 (m, 1H), 3.27 (d, *J* = 10.12 Hz, 1H), 3.85-3.92 (m, 4H), 4.18 (q, *J* = 7.0 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H); ¹³C NMR (63 MHz, CDCl₃) δ 14.0, 28.1, 35.4, 36.6, 40.5, 57.0, 61.1, 64.1, 116.9, 168.4, 168.5.

§ 8.4.2.3 Synthesis of (1,4-dioxo-spiro[4.4]non-7-yl)-acetic acid ethyl ester, **67.²⁸³**

To a solution of KOH (1.80 g, 27.9 mmol) in 45 mL of anhydrous ethanol was added diester **66** (7.99 g, 27.9 mmol) in 5 mL of anhydrous ethanol under a nitrogen atmosphere. After stirring for 6 h at room temperature, the reaction mixture was quenched by addition of dilute HCl (1.5 mL, 3:1, HCl:H₂O). Ethanol was removed under reduced pressure, and the residue added to a mixture of 8 g of ice and

2 mL of concentrated HCl. The product was extracted immediately into CH₂Cl₂, washed with brine, dried over anhydrous MgSO₄ and concentrated *in vacuo* to yield a dark yellow liquid. This residue was heated at 160 °C for 6 h under reduced pressure to afford a reddish brown liquid which was which was purified by column chromatography over silica gel (10% ethyl acetate in hexane) to yield 4.0 g (66.9 %) of monoester **67**: ¹H NMR (250 MHz, CDCl₃) δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.34 (m, 1H), 1.50 (dd, *J* = 13.4, 8.4 Hz, 1H), 1.79-1.96 (m, 3H), 2.09 (dd, *J* = 13.4, 7.2 Hz, 1H), 2.33-2.36 (m, 3H), 3.86-3.92 (m, 4H), 4.10 (q, *J* = 7.1 Hz, 2H); ¹³C NMR (63 MHz, CDCl₃) δ 14.1, 30.0, 33.9, 35.8, 40.2, 42.3, 60.1, 64.1, 64.1, 117.5, 172.6.

§ 8.4.2.4 Synthesis of 2-(1,4-dioxa-spiro[4.4]non-7-yl)-ethanol, **68**.

To a suspension of LiAlH₄ (0.320 g, 7.9 mmol) in THF (20 mL) at -5 °C was added ester **67** (1.14 g, 5.3 mmol) via syringe dropwise under nitrogen. The mixture was stirred for 40 min at -5 °C and then heated to reflux for 4 h. The reaction mixture was then cooled to -5 °C and hydrolyzed with water. The mixture was stirred for an additional 30 min at room temperature. The resulting white solid was filtered and the filtrate poured into a mixture of ether and water. The organic layer was dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to give a pale yellow liquid which was chromatographed over silica gel (50% ethyl acetate in hexane) to yield 0.329 g (35.9%) of a **68** as a colorless liquid: ¹H NMR (250 MHz, CDCl₃) δ 1.44 (m, 2H), 1.66 (m, 2H), 1.86 (m, 3H), 2.04 (m, 2H), 2.26 (br s, 1H),

3.62 (t, J = 6.8 Hz, 2H), 3.89 (m, 4H); ^{13}C NMR (63 MHz, CDCl_3) δ 30.3, 34.3, 35.8, 38.6, 42.6, 61.4, 63.9, 64.1, 117.7.

§ 8.4.2.5 Synthesis of 2-(1,4-dioxa-spiro[4.4]non-7-yl)methanesulfonic acid ethyl ester, 69.

To a solution of alcohol **68** (0.270 g, 1.6 mmol) in dry THF (4 mL) was added triethylamine (0.440 mL, 3.14 mmol) and a solution of methanesulfonyl chloride (0.18 mL, 2.4 mmol) in THF (1 mL) at $-5\text{ }^\circ\text{C}$ under nitrogen. The yellow reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was yellow in color. After stirring for 4 h, the mixture was treated with aqueous saturated solution of sodium bicarbonate (5 mL). The resulting solution was extracted into ether, washed with water and brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure to afford product which was chromatographed over silica gel (40% ethyl acetate in hexane) to yield 0.250 g (63.6%) of **69**: ^1H NMR (250 MHz, CDCl_3) δ 1.32-1.42 (m, 4H), 1.77-1.88 (m, 4H), 2.00-2.02 (m, 1H), 3.00 (s, 3H), 3.89 (m, 4H), 4.22 (t, J = 6.5 Hz, 2H), 3.89 (m, 4H); ^{13}C NMR (63 MHz, CDCl_3) δ 29.9, 33.8, 34.8, 35.7, 37.2, 42.3, 64.0, 64.1, 68.7, 117.3.

§ 8.5 EXPERIMENTAL PROCEDURE FOR SYNTHESIS OF RADIOLABELED ANALOGUE OF CELECOXIB, H, VIA BORONATE ESTER, A.

§ 8.5.1 Synthesis of Boronate Ester, A.

The synthesis of boronated precursor, A, was accomplished using the procedure outlined in Section 8.2.7.1.

§ 8.5.2 Radiolabeling Procedure

No-carrier-added Na¹²³I (74 MBq in 0.1% aqueous NaOH) was placed into a 2 mL Wheaton vial containing boronate ester A (100 µL of 2.08 x 10⁻² M solution in 50% aqueous THF). To this was added chloramine-T (100 µL of 5.01 x 10⁻² M solution in 50% aqueous THF). The reaction vial was sealed and covered with aluminum foil. After stirring for 3 h at room temperature, a drop of sodium thiosulfate pentahydrate was added to decompose the excess iodine and the radiochemical product was isolated by passing it through a silica gel Sep-pak cartridge (eluted with petroleum ether-ethyl acetate, 2:1). The radiochemical yield was determined by radio-TLC (aluminum backed silica gel plate; petroleum ether-ethyl acetate, 2:1), $R_f = 0.44$. The radiochemical yield was determined to be 56% and the decay corrected radiochemical purity was 99.55%.

LIST OF REFERENCES

- (1) Hawthorne, F.M. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 950-984.
- (2) Soloway, A.H.; Tjarks, W.; Barnum, B.A.; Rong, F.-G.; Barth, R.F.; Codogni, I.M.; Wilson, J.G. *Chem. Rev.* **1998**, *98*, 1515-1562.
- (3) Takagaki, M.; Ono, K.; Oda, Y.; Kikuchi, H.; Nemoto, H.; Iwamoto, S.; Cai, J.; Yamamoto, Y. *Cancer Res.* **1996**, *56*, 2017.
- (4) Yong, J.-H.; Barth, R.; Wyzlic, I.M.; Soloway, A.H.; Rotaru, J.H. *Anticancer Res.* **1995**, *15*, 2033-2038.
- (5) Kirihaata, M.; Morimoto, T.; Ichimoto, I.; Kobayashi, M.; Kitaoka, Y. *Biosci. Biotech. Biochem.* **1996**, *60*, 157-158.
- (6) Kazantsev, A.V.; Kazantsev, Y.A. *Izv. Akad. Nauk, Resp.Kaz., Ser. Khim.* **1992**, *2*, 66-70.
- (7) Brattsev, V.A.; Al'perovich, N.E.; Stanko, V.I. *Zh.Obshch.Khim* **1970**, *40*, 1328.
- (8) Dahlhoff, W.V.; Bruckmann, J.; Angermund, K.; Kruger, C. *Liebigs Ann. Chem.* **1993**, *8*, 831-835.
- (9) Tjarks, W.; Anisuzzaman, A.K.M.; Soloway, A.; Liu, L.; Barth, R.F. *Advances in Neutron Capture Therapy* New York, **1993**, 289-292.
- (10) Haushalter, R.C.; Butler, W.M.; Rudolph, R.W. *J. Am. Chem. Soc.* **1981**, *103*, 2620-2627.
- (11) Murikami, H.; Nagasaki, T.; Hamachi, I.; Shinkai, S. *Tetrahedron Lett.* **1993**, *34*, 6273.
- (12) Dougherty, T.J. *Photochem. Photobiol.* **1983**, *38*, 377-379.
- (13) Goudgaon, N.M.; Fulcrand El-Kattan, G.; Schinazi, R.F. *Nucleosides Nucleotides* **1994**, *13*, 849-880.
- (14) Tjarks, W.; Anisuzzaman, A.K.M.; Soloway, A.H. *Nucleosides Nucleotides* **1992**, *11*, 1765-1779.
- (15) Johnsonn, M.; Bergstrand, N.; Edwards, K. *J. Liposome Res.* **1999**, *9*, 53.
- (16) Feakes, D.A.; Shelly, K.; Hawthorne, F.M. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 1367-1370.

- (17) Feakes, D.A.; Shelley, K.; Hawthorne, M.F.; Schimdt, P.G.; Krisch, T.A.; Bauer, W.F. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9039-9043.
- (18) Leppala, J.; Kallio, M.; Nikula, T.; Nikkinen, P.; Liewendahl, K.; Jaaskelainen, J.; Savolainen, S.; Gylling, H.; Hiltunen, J.; Callaway, J.E.A. *Br. J. Cancer* **1995**, *71*, 383-387.
- (19) Guan, L.; Wims, L.; Kane, R.R.; Smuckler, M.B.; Morrison, S.L.; Hawthorne, M.F. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 13206-13210.
- (20) Ferro, V.A.; Morris, J.H.; Stimson, W.H. *Drug Des. Dis.* **1995**, *13*, 13-25.
- (21) Landis, S.H.; Murray, T.; Bolden, S.; Wingo, P.A. *CA Cancer J. Clin.* **1999**, *49*, 8-31.
- (22) Rigas, B.; Goldman, I.S.; Levine, L. *J. Lab. Clin. Med.* **1993**, *122*, 518-523.
- (23) Mclemore, T.L.; Hubbard, W.C.; Litterst, C.L.; Liu, M.C.; Miller, S.; McMahon, M.A.; Eggleston, J.C.; Boyd, M.R. *Cancer Res.* **1988**, *48*, 3140-3147.
- (24) Thun, M.J.; Namboodiri, M.M.; Heath, C.W.J. *N. Engl. J. Med.* **1991**, *325*, 1593-1596.
- (25) Thun, M.J.; Namboodiri, M.M.; Calle, E.E.; Flanders, W.D.; Heath, C.W.J. *Cancer Res.* **1993**, *53*, 1322-1327.
- (26) Suh, O.; Mettlin, C.; Petrelli, N.J. *Cancer* **1993**, *72*, 1171-1177.
- (27) Peleg, I.I.; Maibach, H.T.; Brown, S.H.; Wilcox, C.M. *Arch. Intern. Med.* **1994**, *154*, 394-399.
- (28) Muscat, J.E.; Stellmann, S.D.; Wynder, E.L. *Cancer* **1994**, *74*, 1847-1854.
- (29) La Vecchia, C.; Negri, E.; Franceschi, S.; Conti, E.; Montella, M.; Giacosa, A. *Br. J. Cancer* **1997**, *76*, 675-677.
- (30) Rosenberg, L.; Palmer, J.R.; Zauber, A.G.; Warshauer, M.E.; Stolley, P.D.; Shapiro, S. *J. Natl. Cancer. Inst.* **1991**, *83*, 355-358.
- (31) Sandler, R.S.; Galanko, J.C.; Murray, S.C.; Helm, J.F.; Woosley, J.T. *Gastroenterology* **1998**, *114*, 441-447.
- (32) Giovannucci, E.; Rimm, E.B.; Stampfer, M.J.; Colditz, G.A.; Ascherio, A.; Willett, W.C. *Ann. Intern. Med.* **1994**, *121*, 241-246.

- (33) Giovannucci, E.; Egan, K.M.; Hunter, D.J.; Stampfer, M.J.; Colditz, G.A.; Willett, W.C. *N. Engl. J. Med.* **1995**, *333*, 609-614.
- (34) Whelan, J.; McEntee, M.F. *COX-2 Blockade in Cancer Prevention and Therapy*; Harris, R. E., Ed.; Humana Press Inc., **2003**, 117-145.
- (35) Reddy, B.S.; Rao, C.V.; Seibert, K. *Cancer Res.* **1996**, *56*, 4566-4569.
- (36) Chulada, P.C.; Thompson, M.B.; Mahler, J.F.; Doyle, C.M.; Gaul, B.W.; Lee, C.; Al, E. *Cancer Res.* **2000**, *60*, 4705-4708.
- (37) Chiu, C.-H.; McEntee, M.F.; Whelan, J. *Cancer Res.* **1997**, *57*, 4267-4273.
- (38) Kawamori, T.; Rao, C., V.; Seibert, K.; Reddy, B.S. *Cancer Res.* **1998**, *58*, 409-412.
- (39) Masferrer, J.L.; Leahy, K.M.; Koki, A.T.; Zweifel, B.S.; Settle, S.L.; Woerner, B.M.; Edwards, D.A.; Flickinger, A.G.; Moore, R.J.; Seibert, K. *Cancer Res.* **2000**, *60*, 1306-1311.
- (40) Coderre, J.; Rubin, P.; Freedman, A.; Hansen, J.; Wooding, T.S.; Joel, D.; Gash, D. *Int. J. Rad. Oncol. Biol. Phys.* **1994**, *28*, 1067-1077.
- (41) Hubner, K.F.; Thie, J.A.; Smith, G.T.; Kabalka, G.W.; Keller, I.B.; Kliefoth, A.B.; Campbell, S.K.; Buonocore, E. *Clin. Positron Imaging* **1998**, *1*, 165-173.
- (42) Jaszczak, R.J.; Tsui, B.M.W. *Principles of Nuclear Medicine*; Second ed.; Wagner, Szabo, Buchanan, Eds., **1995**, 317-341.
- (43) Carvalho, P.A.; Schwartz, R.B.; Alexander, E.R.; Loeffler, J.S.; Zimmerman, R.E.; Nagel, J.S.; Holman, B.L. *J. Nucl. Med.* **1991**, *32*, 322-324.
- (44) Kabalka, G.W.; Sastry, K.A.R.; Pagni, R.G. *J. Radioanal. Chem.* **1982**, *74*, 315-319.
- (45) Aratani, T.; Narabayashi, I.; Komori, T.; Utsonomiya, K.; Sueyoshi, K.; Tachibana, S.; Sasaki, S. *Ann. Nucl. Med.* **2001**, *15*, 313-319.
- (46) Vaiva, G.; Thomas, P.; Llorca, P.M.; Dupont, S.; Cottencin, O.; Devos, P.; Mazas, O.; Rascle, C.; Steinling, M.; Goudemand, M. *Psychiatry Res.* **2002**, *115*, 37-48.
- (47) Smith, G.S.; Robeson, K.; Sublette, M.E.; Pollock, B.G. *Med. Psychiatry* **2003**, *19*, 283-319.

- (48) Sano, K. *Neurosurg. Rev.* **1986**, *9*, 13-22.
- (49) Kornblith, P.L.; Walker, M.J. *J. Neurosurg.* **1988**, *68*, 1-17.
- (50) Laster, B.H.; Thomlinson, W.C.; Fairchild, R.G. *Radiat. Res.* **1993**, *133*, 219.
- (51) Diamond, I.; Granelli, S.; Mcdonagh, A.F.; Nielson, S.; Wilson, C.B.; Jainicke, R. *Lancet* **1972**, *2*, 1175-1177.
- (52) Bonnett, R. *Chem. Soc. Rev.* **1995**, *24*, 19-33.
- (53) Wainwright, M. *Chem. Soc. Rev.* **1996**, *25*, 351-360.
- (54) Kennedy, K.A. *Anti-Cancer Drug Des.* **1987**, *2*, 181-194.
- (55) Kennedy, K.A.; Teicher, B.A.; Rockwell, S.; Sartorelli, A.C. *Biochem. Pharmacol.* **1990**, *29*, 1.
- (56) Culver, K.W. *CNS Drugs* **1996**, *6*, 1-11.
- (57) Caruso, M. *Mol. Med. Today* **1996**, *2*, 212-217.
- (58) Barth, R.F.; Soloway, A.H.; Brugger, R.M. *Cancer Invest.* **1996**, *14*, 534-550.
- (59) Larrison, B.; Crawford, J.; Weinrich, R. *Advances in Neutron Capture Therapy*; Elsevier: Amsterdam, Netherlands, **1997**, Vol. 1, Medicine and Physics.
- (60) Larrison, B.; Crawford, J.; Weinrich, R. *Advances in Neutron Capture Tehrapy*; Elsevier: Amsterdam, Netherlands, **1997**, Vol. 2, Chemistry and Biology.
- (61) Morin, C. *Tetrahedron* **1994**, *50*, 12521-12569.
- (62) Locher, G.L. *Am. J. Roentgenol.* **1936**, *36*, 1-13.
- (63) Fairchild, R.G.; Bond, V.P. *J. Radiat. Oncol. Biol. Phys.* **1985**, *11*, 831-840.
- (64) Friedlander, G.; Kennedy, J.W.; Macias, E.S.; Miller, J.M. *Nuclear and Radiochemistry*; 3rd ed.; John Wiley and Sons: New York, **1981**, 684.
- (65) Fermi, E.; Amaldi, O.; Agostino, F.D.; Rasetti, F.; Segre, E. *Proc. R. Soc. London A* **1934**, *146*, 483-500.

- (66) Dunning, J.R.; Pegram, J.B.; Fink, G.A.; Mirchell, D.P. *Phys. Rev.* **1935**, *48*, 265-280.
- (67) Taylor, H.J. *Proc. R. Soc. London A* **1935**, *47*, 873-876.
- (68) Slatkin, D.A. *Brain* **1991**, *114*, 1609.
- (69) Farr, L.E.; Sweet, W.H.; Robertson, J.S.; Foster, C.G.; Locksley, H.B.; Sutherland, D.L.; Mendelsohn, M.L.; Stickley, E.F. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **1954**, *71*, 279-293.
- (70) Archambeau, J.D. *Radiology* **1970**, *94*, 179.
- (71) Farr, L.E.; Haymaker, W.; Konikowski, T.; Lippincott, S.W. *Int. J. Neurol.* **1962**, *3*, 564.
- (72) Soloway, A.H.; Wright, R.L.; Messer, J.R. *J. Pharm. Exp. Ther.* **1961**, *134*, 117-122.
- (73) Pitochelli, A.R.; Hawthorne, F.M. *J. Am. Chem. Soc.* **1960**, *82*, 3228-3230.
- (74) Hawthorne, F.M.; Pitochelli, A.R. *J. Am. Chem. Soc.* **1959**, *81*, 5519.
- (75) Heying, T.L.; Ager, J.W.; Clark, S.L.; Mangold, D.J.; Goldstein, H.L.; Hillman, M.; Polak, R.J.; Szymanski, J.W. *Inorg. Chem.* **1963**, *2*, 1089-1092.
- (76) Hatanaka, H. *J. Neurol.* **1975**, *209*, 81-94.
- (77) Haritz, D.; Gabel, D.; Huiskamp, R. *Int. J. Radiation Oncology Biol. Phys.* **1994**, *28*, 1175-1181.
- (78) Madoc-Jones, H.; Zamenhof, R.G.; Solares, G.; Harling, O.; Yam, C.-S.; Riley, K.; Kiger, S.I.; Wazer, D.; Rogers, G.; Atkins, M., Eds. *Cancer Neutron Capture Therapy*; Plenum Press: New York, **1996**, 707-716.
- (79) Mishima, Y., Ed. *Cancer Neutron Capture Therapy*; Plenum Press: New York, **1996**, 1.
- (80) Sauerwein, W.; Hideghety, K.; Gabel, D.; Moss, R.L. *Nucl. News* **1998**, *2*, 54.
- (81) Frankhauser, H.; *Advances in Neutron Capture Therapy*; Elsevier: Amsterdam, Netherlands, **1997**, Vol. 1, 26.

- (82) Kirihata, M.; Morimoto, T.; Ichimoto, I. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 55-57.
- (83) Kuszewski, J.R.; Lennarz, W.J.; Snyder, H.R. *J. Org. Chem.* **1968**, *33*, 4479-4483.
- (84) Yoshino, K.; Watanabe, N.; Takahashi, H.; Watanabe, S.; Mori, Y.; Ishihashi, M.; Kakihana, H.; Mishima, Y. *Cancer Neutron Capture Therapy*; Plenum: New York, **1996**, 91-97.
- (85) Nemoto, H.; Iwamoto, S.; Nakamura, H.; Yamamoto, Y. *Chem. Lett.* **1993**, 465-468.
- (86) Nemoto, H.; Cai, J.; Asao, N. *J. Med. Chem.* **1995**, *38*, 1673-1678.
- (87) Prashar, J.K.; Lama, D.; Moore, D.E. *Tetrahedron Lett.* **1993**, *34*, 6779-6800.
- (88) Wyzlic, I.M.; Tjarks, W.; Soloway, A.H.; Perkins, D.J.; Burgos, M.; O'reilly, K.P. *Inorg. Chem.* **1996**, *35*, 4541-4547.
- (89) Malmquist, J.; Sjoberg, S. *Tetrahedron* **1996**, *52*, 9207-9218.
- (90) Jacobs, P.M.; Sneath, R.L.J.; Soloway, A.H.; Dey, A.S. *J. Pharm. Sci* **1976**, *65*, 604-606.
- (91) Srivastava, R.R.; Kabalka, G.W. *J. Org. Chem.* **1997**, *62*, 8730-8734.
- (92) Srivastava, R.R.; Singhaus, R.R.; Kabalka, G.W. *J. Org. Chem.* **1997**, *62*, 4476-4478.
- (93) Sood, A.; Sood, C.K.; Spielvogel, B.F.; Hall, I.H. *Eur. J. Med. Chem.* **1990**, *25*, 301-308.
- (94) Zubay, G. *Biochemistry*; Macmillen: New York, **1988**.
- (95) Wyzlic, I.M.; Tjarks, W.; Soloway, A.H.; Anisuzzaman, A.K.M.; Rong, F.-G.; Soloway, A.H.; Barth, R.F. *Int. J. Radiation Oncology Biol. Phys.* **1994**, *28*, 1203-1213.
- (96) Schinazi, R.F.; Prusoff, W.H. *J. Org. Chem.* **1985**, *50*, 841-847.
- (97) Schinazi, R.F.; Prusoff, W.H. *Tetrahedron Lett.* **1978**, *50*, 4981-4984.
- (98) Liao, T.K.; Pondrebarac, E.G.; Cheng, C.C. *J. Am. Chem. Soc.* **1964**, *86*, 1869-1870.

- (99) Tjarks, W.; Anisuzzaman, A.K.M.; Liu, L.; Soloway, A.H.; Barth, R.F.; Perkins, D.J.; Adams, D.M. *J. Med. Chem.* **1992**, *35*, 1628-1633.
- (100) Yamamoto, Y.; Seko, T.; Nemoto, H. *J. Org. Chem.* **1989**, *54*, 4734-4736.
- (101) Thomasz, J.; Shaw, B.R.; Porter, K.; Spielvogel, B.F.; Sood, A. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1373-1375.
- (102) Soloway, A.H.; Anisuzzaman, A.K.M.; Alam, F.; Liu, L.; Barth, R.F. *Pure Appl. Chem.* **1991**, *63*, 411-413.
- (103) Miura, M.; Micca, P.L.; Fisher, C.D.; Heinrichs, J.C.; Donaldson, J.A.; Finkel, G.C.; Slatkin, D.A. *Int. J. Cancer* **1996**, *68*, 114-119.
- (104) Kahl, S.B.; Koo, M.-S. *J. Chem. Soc., Chem. Commun.* **1990**, *24*, 1769-1771.
- (105) Moraes, A.M.; Santana, H.A.; Carbonell, R.G. *J. Microencapsulation* **1999**, *16*, 647-664.
- (106) Feakes, D.A.; Spinler, J.K.; Harris, F.R. *Tetrahedron* **1999**, *55*, 11177-11186.
- (107) Magiardi, J.R. *Brain tumors. An Encyclopedic Approach*; Churchill Livingstone: Edinburgh, **1995**.
- (108) Gabel, D.; Harfst, S.; Moller, D.; Ketz, H.; Peymann, T.; Rosler, J. *Current Topics in the Chemistry of Boron*; The Royal Society of Chemistry: Cambridge, **1994**, 161-164.
- (109) Wingo, P.A.; Tong, T.; Bolden, S. *CA Cancer J. Clin.* **1995**, *45*, 8-30.
- (110) Hamilton, S.R. *Gastroenterology* **1993**, *105*, 3-7.
- (111) Suh, O.; Mettlin, C.; Petrilli, N.J. *Cancer* **1993**, *72*, 1171-1177.
- (112) Reddy, B.S.; Maruyama, H.; Kelloff, G. *Cancer Res.* **1987**, *47*, 5340-5346.
- (113) Reddy, B.S.; Nayini, J.; Tokumo, K.; Riggoty, J.; Zang, E.; K Elloff *Cancer Res.* **1990**, *50*, 2562-2568.
- (114) Vane, J.R.; Botting, R. *Improved Non-Steroid Anti-Inflammatory Drugs: COX-2 Enzyme Inhibitors* London, **1995**.
- (115) Vane, J.R.; Flower, R.J.; Botting, R.M. *Stroke* **1990**, *21*, 12-23.
- (116) Dreser, H. *Pfluegers Arch.* **1899**, *76*, 306.

- (117) Hart, C. *Modern Drug Discovery* **1999**, 5/6, 55-59.
- (118) Vane, J.R. *Nature* **1971**, 231, 232-235.
- (119) Smith, W.L.; Marnett, J.L. *Biochim. Biophys. Acta* **1991**, 1083, 1-17.
- (120) Loll, P.J.; Garavito, R.M. *Expert Opin. Invest. Drugs* **1994**, 3, 1171-1180.
- (121) Fu, J.-Y.; Masferrer, J.L.; Karen, S.; Raz, A.; Needleman, P. *J. Biol. Chem.* **1990**, 265, 16737-16740.
- (122) Seibert, K.; Zhang, Y.; Leahy, K.M.; Hauser, S.D.; Masferrer, J.; Perkins, D.J.; Lee, L.; Isakson, P. *Proc. Natl. Acad. Sci.* **1994**, 91, 12013-12017.
- (123) Eberhart, C.E.; Coffey, R.J.; Radhika, A.; Giardiello, F.M.; Ferrenbach, S.; Dubois, R.N. *Gastroenterology* **1994**, 107, 1183-1188.
- (124) Seed, M.P. *Expert Opin. Invest. Drugs* **1996**, 5, 1617-1637.
- (125) Henry, D.; Lim, L.L.; Garcia Rodriguez, L.A.; Perez, G.S.; Carson, J.L.; Griffin, M. *BMJ* **1996**, 312, 1563-1566.
- (126) Battistini, B.; Botting, R.; Bakhle, Y.S. *Drug News Perspect.* **1994**, 7, 501-512.
- (127) Kargman, S.L.; O'Neill, G.P.; Vickers, P.J.; Evans, J.F.; Mancini, J.A.; Serge, J. *Cancer Res.* **1995**, 55, 2556-2559.
- (128) Hawkey, C.J. *Lancet* **1999**, 353, 307-314.
- (129) Picot, D.; Loll, P.J.; Michael, G. *Nature* **1994**, 367, 243-249.
- (130) Gierse, J.K.; McDonald, J.J.; Hauser, S.D.; Rangwala, S.H.; Koboldt, C.M.; Seibert, K. *J. Biol. Chem.* **1996**, 271, 15810-15814.
- (131) Lazer, E.S.; Miao, C.K.; Cywin, C.L.; Sorcek, R.; Wong, H.-C.; Meng, Z.; Potaki, I.; Hoermann, M.; Snow, R.J.; Tschantz, M.A.; Kelly, T.A.; Mcneil, D.W.; Coutts, S.J.; Churchill, L.; Graham, A.J.; David, E.; Grob, P.M.; Emgel, W.; Meier, H.; Trumlitz, G. *J. Med. Chem.* **1997**, 40, 980-989.
- (132) Carter, J.S.; Rogier, D.J.; Graneto, M.J.; Seibert, K.; Kobolt, C.M.; Zhang, Y.; Talley, J.J. *Bioorg. Med. Chem. Lett.* **1999**, 9, 1167-1170.
- (133) Davis, N.M.; Skjodt, N.M. *Clin. Pharmacokinet.* **1999**, 36, 115-126.

- (134) Penning, T.D.; Talley, J.J.; Bertenshaw, S.R.; Carter, J.S.; Collins, P.W.; Docter, S.; Graneto, M.J.; Lee, L.F.; Malecha, J.W.; Miyashiro, J.M.; Rogers, R.S.; Rogier, D.J.; Yu, S.S.; Anderson, G.D.; Burton, E.J.; Cogburn, N.J.; Gregory, S.A.; Koboldt, C.M.; Perkins, W.E.; Seibert, K.; Veenhuizen, A.W.; Zhang, Y.Y.; Isakson, P. *J. Med. Chem.* **1997**, *40*, 1347-1365.
- (135) Chan, C.-C.; Boyce, S.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J.F.; Ford -Hutchinson, A.W.; Forrest, M.J.; Gauthier, J.Y.; Gordon, R.; Gresser, M.; Guay, K.; Kargmann, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, J.; O'Neill, G.P.; Ouellet, M.; Patrick, D.; Percival, M.D.; Perrier, H.; Prasit, P.; Rodgers, I.; Tagari, P.; Therien, M.; Vickers, P.; Visco, D.; Wang, Z.; Wong, E.; Xu, L.-J.; Young, R.N.; Zamboni, R.; Riendeau, D. *J. Pharmacol. Exp. Ther.* **1999**, *290*, 551-560.
- (136) Black, C.W.; Brideau, C.; Chan, C.-C.; Charleson, S.; Cromlish, W.; Gordon, R.; Grimm, E.L.; Hughes, G.H.; Leger, S.; Li, C.-S.; Riendeau, D.; Therien, M.; Wang, Z.; Xu, L.-J.; Prasit, P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1195-1198.
- (137) Riendeau, D.; Percival, M.D.; Boyce, S.; Brideau, C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J.F.; Falgoutyret, J.-P.; Ford -Hutchinson, A.W.; Gordon, R.; Greig, G.; Guay, J.; Kargman, S.; Leger, S.; Mancini, J.; O'Neill, G.P.; Ouellet, M.; Rodger, I.W.; Therien, M.; Wang, Z.; Webb, J.K.; Wong, E.; Xu, L.-J.; Young, R.N.; Zamboni, R.; Prasit, P.; Chan, C.-C. *British J. Pharmacol.* **1997**, *121*, 105-117.
- (138) Davis, R.; Brogden, R.N. *Drugs* **1994**, *48*, 431-454.
- (139) Masferrer, J.; Zweifel, B.S.; Manning, P.T.; Hauser, S.D.; Leahy, K.M.; Smith, W.G.; Isakson, P.C.; Seibert, K. *Proc. Natl. Acad. Sci.* **1994**, *91*, 3228.
- (140) Klein, T.; Nurisng, R.M.; Pheilschifter, J.; Ullrich, V. *Biochem. Pharmacol.* **1994**, *48*, 1605-1610.
- (141) Li, C.-S.; C.W., B.; Chan, C.-C.; Ford -Hutchinson, A.W.; Gauthier, J.Y.; Gordon, R.; Daniel, G.; Kargman, S.; Lau, C.K.; Mancini, J.; Quimet, N.; Roy, P.; Vickers, P.; Wong, E.; Young, R.N.; Zambooni, R.; Prasit, P. *J. Med. Chem.* **1995**, *38*, 4897-4905.
- (142) Therien, M.; Brideau, C.; Chan, C.-C.; Cromlish, W.A.; Gauthier, J.Y.; Gordon, R.; Greig, G.; Kargman, S.; Lau, C.K.; Leblanc, Y.; Li, C.; O'Neill, G.P.; Reindeau, D.; Roy, P.; Wang, Z.; Xu, L.-J.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 47-52.

- (143) Roy, P.; Leblanc, Y.; Ball, R.G.; Brideau, C.; Chan, C.C.; Chauret, N.; Cromlish, W.; Ethier, D.; Gauthier, J.Y.; Gordon, R.; Greig, G.; Kargman, S.; Lau, C.K.; O'Neill, G.P.; Silva, J.M.; Therien, M.; Von Staden, C.; Xu, L.-J.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 57-62.
- (144) Prasit, P.; Guay, J.; Wang, Z.; Leger, S.; Therien, M. *PCT Int. Appl.*, **1996**, WO 9606840.
- (145) Beswick, P.J.; Campbell, I.B.; Naylor, A. *PCT Int. Appl.*, **1996**, WO 9631509.
- (146) Reitz, D.B.; Li, J.J.; Norton, M.B.; Reinhard, E.J.; Collins, J.T.; Anderson, G.D.; Gregory, S.A.; Koboldt, C.M.; Perkins, W.E.; Seibert, K.; Isakson, P. *J. Med. Chem.* **1994**, *37*, 3878-3881.
- (147) Friesen, R.W.; Dube, D.; Fortin, R.; Frenette, R.; Prescott, S.; Cromlish, W.A.; Greig, G.M.; Kartman, S.; Wong, E.; Chan, -C.C.; Gordon, R.; Xu, L.-J.; Riendeau, R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2677-2682.
- (148) Black, C.W.; Brideau, C.; Chan, C.-C.; Charleson, S.; Chauret, N.; Claveau, D.; Ethier, D.; Gordon, R.; Grieg, G.; Guay, J.; Hughes, G.; Jolicoeur, P.; Leblanc, Y.; Nathalie, N.-G.; Ouimet, N.; Riendeau, D.; Visco, D.; Wang, Z.; Xu, L.; Prasit, P. *J. Med. Chem.* **1999**, *42*, 1274-1281.
- (149) Carter, M.C.; Naylor, A.; Payne, J.J.; Pegg, N.A. *PCT Int. Appl.*, **2003**, WO 0314091.
- (150) Li, C.S.; Brideau, C.; Chan, -C.C.; Savoie, C.; Claveau, D.; Charleson, S.; Gordon, R.; Greig, G.; Gauthier, J.Y.; Lau, C.K.; Riendeau, D.; Therien, M.; Wong, E.; Prasit, P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 597-600.
- (151) Joo, Y.H.; Kim, J.K.; Kang, S.-H.; Noh, M.-S.; Ha, J.-Y.; Choi, J.K.; Lim, K.M.; Lee, C.H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 413-417.
- (152) Rao, P.N.; Habeeb, A.J.; Knaus, E.E. *Drug Dev. Res.* **2002**, *55*, 79-90.
- (153) Jayaprakasam, B.; Nair, M.G. *Tetrahedron* **2003**, *59*, 841-849.
- (154) Jang, S.D.; Cuendet, M.; Hawthorne, M.E.; Kardono, L.B.S.; Kawanisih, K.; Fong, H.H.S.; Mehta, R.G.; Pezutto, J.M.; Kinghorn, A.D. *Phytochemistry* **2002**, *61*, 867-872.

- (155) Gerhauser, C.; Alt, A.; Heiss, E.; Gamal-Eldeen, A.; Klimo, K.; Knauf, J.; Neumann, I.; Scherf, H.-R.; Frank, N.; Bartsch, H.; Becker, H. *Mol. Cancer Therapeutics* **2002**, *1*, 959-969.
- (156) Min, K.R.; Kim, Y.; Kang, S.-H.; Mar, W.; Lee, K.S.; Ro, J.S.; Lee, S.H.; Kim, Y.S. *Nat. Product Sci.* **1996**, *2*, 82.
- (157) Kune, G.A.; Kune, S.; Watson, L.F. *Cancer Res.* **1988**, *48*, 4399-4404.
- (158) Sano, H.; Kawahito, Y.; Wilder, R.L.; Hashiramoto, A.; Mukai, S.; Asai, K.; Kimura, S.; Kato, H.; Kondo, M.; Hla, T. *Cancer Res.* **1995**, *55*, 3785-3789.
- (159) Waddell, W.R.; Ganser, G.F.; Cerise, E.J.; Loughry, R.W. *Am. J. Surg.* **1989**, *157*, 175-179.
- (160) Reddy, B.S.; Tokumo, K.; Kulkarni, N.; Aligia, C.; Kelloff, G. *Carcinogenesis* **1992**, *13*, 1019-1023.
- (161) Kinzler, K.W.; Nilbert, M.C.; Vogelstein, B.; Bryan, T.M.; Levy, D.B.; Smith, K.J.; Al, E. *Science* **1991**, *251*, 1366-1370.
- (162) Giardiello, F.M.; Hamilton, S.R.; Krush, A.J.; Piantadosi, S.; Hyland, L.M.; Celano, P.; Al, E. *N. Engl. J. Med.* **1993**, *328*, 1313-1316.
- (163) Labayle, D.; Fischer, D.; Vielh, P.; Drouhin, F.; Pariente, A.; Bories, C. *Gastroenterology* **1991**, *101*, 635-639.
- (164) Nugent, K.P.; Farmer, K.C.; Spiegelman, A.D.; Williams, C.B.; Phillips, R.K. *Br. J. Surg.* **1993**, *80*, 1618-1619.
- (165) Oshima, M.; Dinchuk, J.E.; Kargman, S.L.; Oshima, H.; Hancock, B.; Kwong, E.; Trzaskos, J.M.; Evans, J.F.; Taketo, M.M. *Cell* **1996**, *87*, 803-809.
- (166) Oshima, M.; Murai, N.; Kargman, S.; Arguello, M.; Luk, P.; Kwong, E.; Al, E. *Cancer Res.* **2001**, *61*, 1733-1740.
- (167) Jacoby, R.F.; Cole, C.E.; Siebert, K.; Kelloff, G.; Lubert, R.A. *Gastroenterology* **1999**, *116*, A428.
- (168) Reddy, B.S.; Hirose, Y.; Lubet, R.; Steele, V.; Kelloff, G.; Paulson, S.; Al, E. *Cancer Res.* **2000**, *60*, 293-297.
- (169) Messersmith, W.; Laheru, D.; Hidalgo, M. *Expert Opin. Invest. Drugs* **2003**, *12*, 423-434.

- (170) Markowitz, S.D.; Dawson, D.M.; Willis, J.; Willson, J. *Cancer Cell* **2002**, *1*, 233-236.
- (171) Reddy, B.S.; Rao, C.V. *J. Environ. Pathol. Toxicol. Oncol.* **2002**, *21*, 155-164.
- (172) Krishnaiah, Y.S.R.; Satyanarayana, V.; Kumar, B.D.; Karthikeyan, R.S. *J. Drug Targeting* **2002**, *10*, 247-254.
- (173) Smalley, W.E.; Dubois, R.N. *Adv. Pharmacol.* **1997**, *39*, 1-20.
- (174) Schiff, S.J.; Rigas, B. *Gastroenterology* **1998**, *113*, 1992-1998.
- (175) Ricchi, P.; Zarrilli, R.; Di Palma, A.; Acquaviva, A.M. *Br. J. Cancer* **2003**, *88*, 803-807.
- (176) Gupta, R.A.; Dubois, R.N. *Gastroenterology* **1998**, *114*, 1095-1100.
- (177) Elder, D.J.E.; Paraskeva, C. *Gastroenterology* **1997**, *113*, 1999-2008.
- (178) Kipp, E.; Ghosh, S. *Science* **1994**, *265*, 956-959.
- (179) Weiss, H.; Amberger, A.; Widschwentner, M.; Margreiter, R.; Ofner, D.; Dietl, P. *Int. J. Cancer* **2001**, *92*, 877-892.
- (180) Kokoska, E.R.; Wolff, A.B.; Smith, G.S.; Miller, T.A. *J. Surg. Res.* **2000**, *88*, 97-103.
- (181) Hansen-Petrik, M.B.; McEntee, M.F.; Jull, B.; Shi, H.; Zhemel, M.B.; Whelan, J. *Cancer Res.* **2001**, *62*, 403-408.
- (182) Kokoska, E.R.; Smith, G.S.; Wolff, A.B.; Deshpande, Y.; Miller, T.A. *J. Surg. Res.* **1999**, *84*, 186-192.
- (183) Snyder, H.R.; Reedy, A.J.; Lennarz, W.J. *J. Am. Chem. Soc.* **1958**, *80*, 835-838.
- (184) Mishima, Y.; Ichihashi, M.; Nakanishi, T.; Tsuji, M.; Ueda, M.; Nakagawa, T. *Proc. First Int. Symp. Neutron Capture Ther. (Brookhaven Nat. Lab.)*, **1983**, 355-364.
- (185) Mishima, Y.; Honda, C.; Ichihashi, M.; Obara, H.; Hiratsuka, J.; Fukuda, H.; Karashima, H.; Kobayashi, T.; Kanda, K.; Yoshino, K. *Lancet* **1989**, *2*, 388-389.

- (186) Coderre, J.; Glass, J.D.; Fairchild, R.G.; Roy, U.; Cohen, S.; Fand, I. *Cancer Res.* **1987**, *47*, 6377-6383.
- (187) Mishima, Y.; Ichihashi, M.; Hatta, S.; Honda, C.; Sasase, A.; Yamamura, K.; Kanda, K.; Kobayashi, T.; Fukuda, H. *Clinical Aspects of Neutron Capture Therapy*; Fairchild, R. G., Bond, V. P., Woodhead, A. D., Eds.; Plenum Publishing Corporation: New York, **1989**, 251-260.
- (188) Coderre, J.A.; Glass, J.D.; Fairchild, R.G.; Micca, P.L.; Fand, I.; Joel, D.D. *Cancer Res.* **1990**, *50*, 138-141.
- (189) Kubota, R.; Yamada, S.; Ishiwata, K.; Tada, M.; Ido, T.; Kubota, K. *Br. J. Cancer* **1993**, *67*, 701-705.
- (190) Mallesch, J.L.; Moore, D.E.; Allen, B.J.; McCarthy, W.H.; Jones, R.; Stening, W.A. *Int. J. Rad. Oncol. Biol. Phys.* **1994**, *28*, 1183-1188.
- (191) Setiawan, Y.; Halliday, G.M.; Harding, A.J.; Moore, D.E.; Allen, B.J. *Cancer Res.* **1995**, *55*, 874-877.
- (192) Saris, S.C.; Solaris, G.R.; Wazer, D.E.; Cano, G.; Kerley, S.E.; Joyce, M.A.; Adelman, L.S.; Harling, O.K.; Madoc-Jones, H.; Zamenhof, R.G. *Cancer Res.* **1992**, *52*, 4672-4677.
- (193) Coderre, J.A.; Joel, D.D.; Micca, P.L.; Nawrocky, M.M.; Slatkin, D.N. *Radiat. Res.* **1992**, *129*, 290-296.
- (194) Radel, P.A.; Kahl, S.B. *Advances in Neutron Capture Therapy*, **1993**; Vol. 5th, 277-280.
- (195) Spielvogel, B.F. *Mol. Struct. Energ.* **1988**, *5*, 329-342.
- (196) Kahl, S.B.; Kasar, R.A. *J. Am. Chem. Soc.* **1996**, *118*, 1223-1224.
- (197) Washburn, L.C.; Sun, T.T.; Byrd, B.L.; Hayes, R.L.; Butler, T.A. *J. Nucl. Med.* **1980**, *20*.
- (198) Aoyagi, M.; Agranoff, G.W.; Washburn, L.C.; Smith, O.R. *J. Neurochem.* **1988**, *50*, 1220-1226.
- (199) Srivastava, R.R.; Singhaus, R.R.; Kabalka, G.W. *J. Org. Chem.* **1999**, *64*, 8495-8500.
- (200) Das, B.C.; Kabalka, G.W.; Srivastava, R.R.; Bao, W.; Das, S.; Li, G. *J. Organomet. Chem.* **2000**, *614-615*, 255-261.

- (201) Kabalka, G.W.; Das, B.C.; Das, S.; Li, G.; Srivastava, R.R.; Natarajan, N.; Khan, M.K. *Collect. Czech. Chem. Commun.* **2002**, *67*, 836-842.
- (202) Kuhl, D.E.; Edwards, R.Q. *Radiology* **1963**, *80*, 653-662.
- (203) Cormack, R.M. *Phys. Med. Biol.*, **1973**, *18*, 195-207.
- (204) Muehllehner, G.; Wetzel, R.A. *J. Nucl. Med.* **1968**, *9*, 337.
- (205) Jaszczak, R.J.; Coleman, R.E. *Single-photon Emission Computed Tomography*; J.A., S., Ed.; Society of Nuclear Medicine: New York, **1980**, 45-59.
- (206) Brooks, R.A.; Di Chiro, G. *Radiology* **1975**, *117*, 561-572.
- (207) Ramachandran, G.N.; Lakshminarayanan, A.V. *Proc. Natl. Acad. Sci.* **1971**, *68*, 2236-2240.
- (208) Wang, Y.; Klunck, W.E.; Huang, G.-F.; Debnath, M.L.; Holt, D.P.; Mathis, C.A. *J. Mol. Neurosci.* **2002**, *19*, 11-16.
- (209) Akula, M.R.; Kabalka, G.W. *J. Labelled Compd. Radiopharm.* **1999**, *42*, 959-964.
- (210) Akula, M.R.; Singhaus, R.R.; Zhang, R.R.; Kabalka, G.W.; Ulrich, P., Voges, R., Eds.; John Wiley and Sons Ltd.: Dresden, **2000**, 388-391.
- (211) Kabalka, G.W.; Akula, M.R.; Zhang, J. In *Abstracts of Papers, 222nd ACS National Meeting*; American Chemical Society: Chicago, IL, **2001**.
- (212) Kabalka, G.W.; Akula, M.R.; Zhang, J. In *Abstracts of Papers, 224th ACS National Meeting*; American Chemical Society: Boston, MA, **2002**.
- (213) Kabalka, G.W.; Varma, R.S. *Tetrahedron* **1989**, *45*, 6601-6621.
- (214) Kabalka, G.W.; Sastry, K.A.R.; Muralidhar, K. *J. Labelled Compd. Radiopharm.* **1982**, 795-799.
- (215) Hasrat, A.; Lier, V. *Synthesis* **1996**, 423-445.
- (216) Kabalka, G.W.; Akula, M.R.; Zhang, J. *Nucl. Med. Biol.* **2002**, *29*, 841-843.
- (217) Behr, L.C.; Fusco, R.; Jarboe, C.H. *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings*; Wiley, R. H., Eds., **1967**.

- (218) Reddy, M.V.R.; Bell, S.C. *PCT Int. Appl.*, **2003**, WO 032440.
- (219) Reddy, M.V.R.; Bell, S.C. *PCT Int. Appl.*, **2003**, WO 0324958.
- (220) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.
- (221) Wass, J.R.; Sidduri, A.R.; Knochel, P. *Tetrahedron Lett.* **1992**, *33*, 3717-1720.
- (222) Hoffmann, R.W.; Dresely, S. *Synthesis* **1988**, *2*, 103-106.
- (223) Matteson, D.S.; Liedtke, J.D. *J. Am. Chem. Soc.* **1965**, *87*, 1526-1531.
- (224) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508-7510.
- (225) Marcuccio, S.M.; Rodopoulos, M.; Weigold, H. *PCT Int. Appl.*, **1998**, WO 9845265.
- (226) Marcuccio, S.M.; Rodopoulos, M.; Weigold, H.; Osvath, P. *PCT Int. Appl.*, **2000**, WO 0021966.
- (227) Marcuccio, S.M.; Weigold, H. *PCT Int. Appl.*, **2001**, WO 0129051.
- (228) Muir, W.M.; Ritchie, P.D.; Lyman, D.J. *J. Org. Chem.* **1966**, *31*, 3790-3793.
- (229) Adams, J.T.; Hauser, C.R. *J. Am. Chem. Soc.* **1944**, *66*, 1220-1222.
- (230) Levine, R.; Conroy, J.A.; Adams, J.T.; Hauser, C.R. *J. Am. Chem. Soc.* **1945**, *67*, 1510-1512.
- (231) Black, H.T. *Org. Prep. Proc. Int.* **1989**, *21*, 179.
- (232) Katritzky, A.R.; Alfredo, A. *J. Org. Chem.* **2000**, *65*, 3672-3682.
- (233) Baker, R.B.J.; Garth, P.R.; Otterbacher, E.W.; Gall, J.A. *US Patent*, **1990**, US 4922026.
- (234) Wrzeciono, U.; Krzysztefik, B.; Danieleu, E. *Acta Pol. Pharm.* **1975**, *32*, 149-158.
- (235) Peto, A.G. *Freidel-Crafts and Related Reactions*, **1964**; Vol. 2, 653, 700, 726.
- (236) Gore, P.H. *Freidel-Crafts and Related Reactions*, **1964**; Vol. 2, 163.

- (237) Strain, W.E.; Plati, J.T.; Warre, S.L. *J. Am. Chem. Soc.* **1942**, *64*, 1436-1440.
- (238) Hoffmann, E. *Annalen* **1891**, *264*, 160.
- (239) Stavber, S.; Jereb, M.; Zupan, M. *Chem. Commun.* **2002**, 488-489.
- (240) Zupan, M.; Iskra, J.; Stavber, S. *Tetrahedron Lett.* **1997**, *38*, 6305-6306.
- (241) Norihiro, F.; Nishino, H.; Kurusawa, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4363-4368.
- (242) Takagi, K.; Hayama, N.; Okamoto, T. *Chem. Lett.* **1978**, *2*, 191-192.
- (243) Gore, P.H.; Thorburn, S.; Weyell, D.J. *J. Chem. Soc. Perkins Trans. 1* **1973**, *23*, 2940-2948.
- (244) Stavber, S.; Kralj, P.; Zupan, M. *Synlett* **2002**, *4*, 598-600.
- (245) Hwang, Y.C.; Fowler, F.W. *J. Org. Chem.* **1985**, *50*, 2719-2726.
- (246) Posner, G.H.; Whitten, C.E. *Tetrahedron Lett.* **1970**, *53*, 4647-4650.
- (247) Posner, G.H.; Whitten, C.E.; Mcfarland, P.E. *J. Am. Chem. Soc.* **1972**, *94*, 5106-5108.
- (248) Bartlett, P.D.; Lefferts, E.B. *J. Am. Chem. Soc.* **1955**, *77*, 2804-2805.
- (249) Shirley, D.A. *Organic Reactions*, **1958**, Vol. 8, 28.
- (250) Kabalka, G.W.; Das, B.C.; Das, S. *Tetrahedron Lett.* **2001**, *42*, 7145-7146.
- (251) Beleskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957.
- (252) Irvine, G.J.; Gerald, M.J.; Marder, T.B.; Norman, N.C.; Rice, C.R.; Robins, E.G.; Roper, W.R.; Whittell, G.R.; Wright, L.J. *Chem. Rev.* **1998**, *28*, 2685-2722.
- (253) Ishiyama, T.; Miyaura, N. *J. Synthetic Org. Chem Japan* **1999**, *57*, 503-511.
- (254) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018-11019.
- (255) Lawson, Y.J.; Lesley, M.J.G.; Marder, T.B.; Norman, N.C.; Rice, C.R. *Chem. Commun.* **1997**, *21*, 2051-2052.

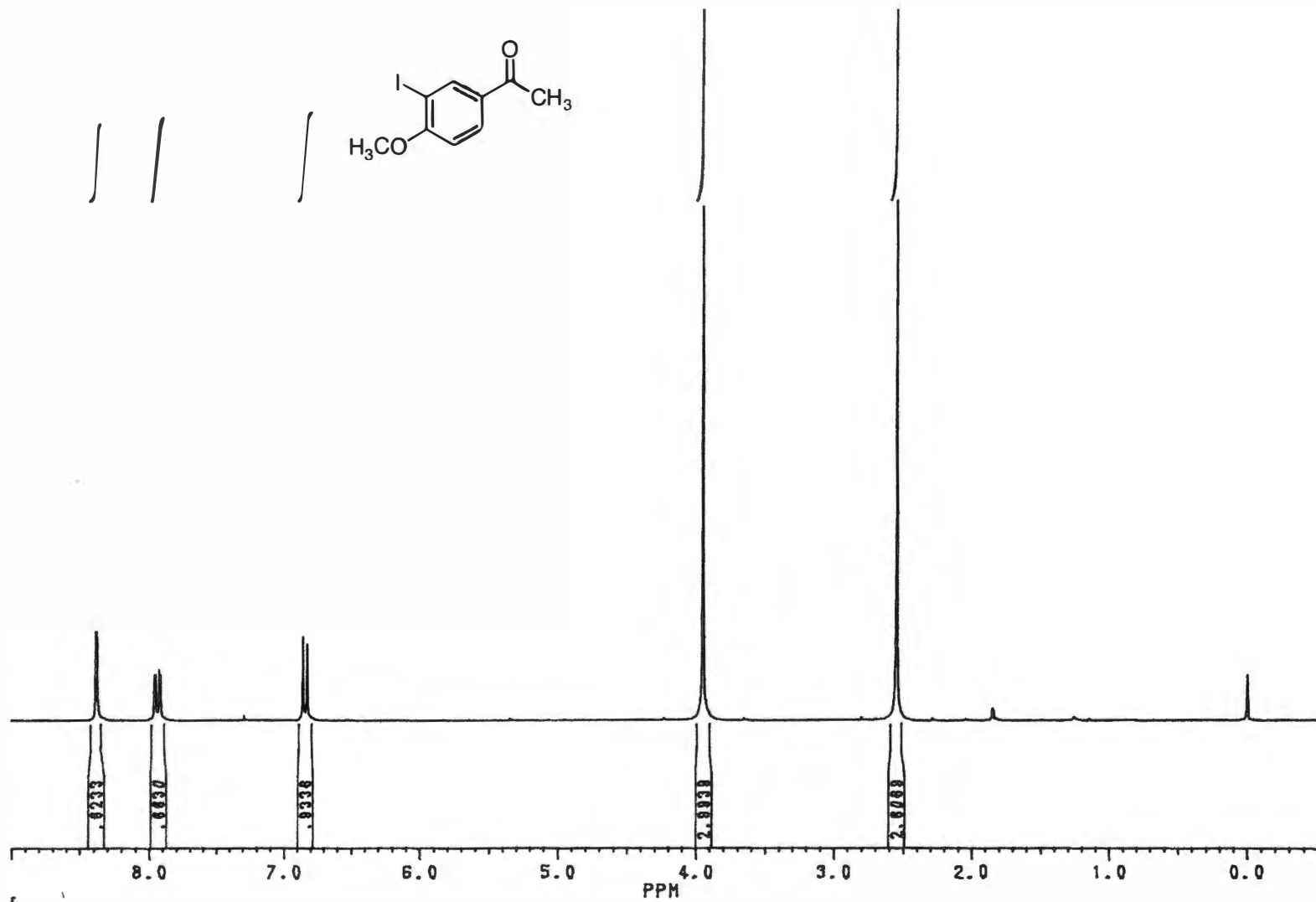
- (256) Ishiyama, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* **1996**, 17, 2073-2074.
- (257) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, 41, 6821-6825.
- (258) Ware, E. *Chem. Rev.* **1950**, 46, 403-470.
- (259) Alonso, F.; Mico, I.; Najera, C.; Sansano, J.; Yus, M. *Tetrahedron* **1995**, 51, 10259-10280.
- (260) Wheeler, H.L.; Hoffman, C. *Am. Chem. J.* **1911**, 45, 368-383.
- (261) Urech, F. *Ann.* **1872**, 164, 255-279.
- (262) Kabalka, G.W.; Das, B.C.; Das, S. *Tetrahedron Lett.* **2002**, 43, 2323-2325.
- (263) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 9, 982-983.
- (264) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, 625, 47-53.
- (265) Nemoto, H.; Wilson, G.J.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1992**, 57, 435-435.
- (266) Marvel, C.S.; Sekera, V.C. *Org. Syn. Coll., Vol.*, **1955**; Vol. 3, 366.
- (267) Fraueglass, E.; Meinwald, J. *J. Am. Chem. Soc.* **1960**, 82, 5235-5239.
- (268) Burckhalter, J.H.; Brown, B.A. *J. Org. Chem.* **1965**, 30, 1291-1292.
- (269) Etheredge, S.H. *J. Org. Chem.* **1966**, 31, 1990-1994.
- (270) Middlesworth, V. *J. Org. Chem.* **1986**, 51, 5019-5021.
- (271) Brown, W.G. *Org. Rxns.*, **1951**; Vol. VI, 469-510.
- (272) Geatti, O.G.; Shapiro, S.; Sisson, J.C.; Hutchinson, R.J.; Mallette, S.; Eyre, P.; Beierwaltes J. *Nucl. Med.* **1985**, 26, 736-742.
- (273) Von Schultess, G.K.; Ketz, E.; Schubiger, P.A.; Bekier, A. *Journal of Nuclear Medicine* **1985**, 26, 9.
- (274) Brown, H.C.; Rathke, M.W.; Rogic, M.M. *J. Am. Chem. Soc.* **1968**, 90, 5038-5040.

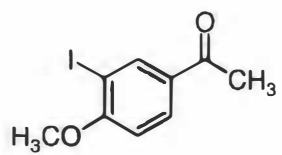
- (275) Kabalka, G.W.; Gooch, E.E. *J. Org. Chem.* **1980**, *45*, 3578-3580.
- (276) Kabalka, G.W.; Gooch, E.E.; Otto, C.A. *J. Radioanal. Chem.* **1981**, *65*, 115-121.
- (277) Kabalka, G.W. *DOE Symposium Series*, **1985**; Vol. 56, 377-383.
- (278) Kabalka, G.W.; Gooch, E.E.; Smith, T.L.; Sells, M.A. *Int. J. Appl. Rad. Isot.* **1982**, *33*, 223-224.
- (279) Kabalka, G.W.; Gooch, E.E.; Sastry, K.A.R. *J. Nucl. Med.* **1981**, *22*, 908-912.
- (280) Pillay, M.K.; Palanivelu, S. *J. Indian. Chem. Soc.* **1987**, *64*, 257-258.
- (281) Pillay, M.K.; Mubarak, S. *J. Indian. Chem. Soc.* **1992**, *69*, 392-393.
- (282) Jost, R.; Rimmelin, P.; Sommer, J.M. *Tetrahedron Lett.* **1971**, *32*, 3005-3007.
- (283) Nara, S.; Toshima, H.; Ichihara, A. *Tetrahedron* **1997**, *53*, 9509-9524.

APPENDIX

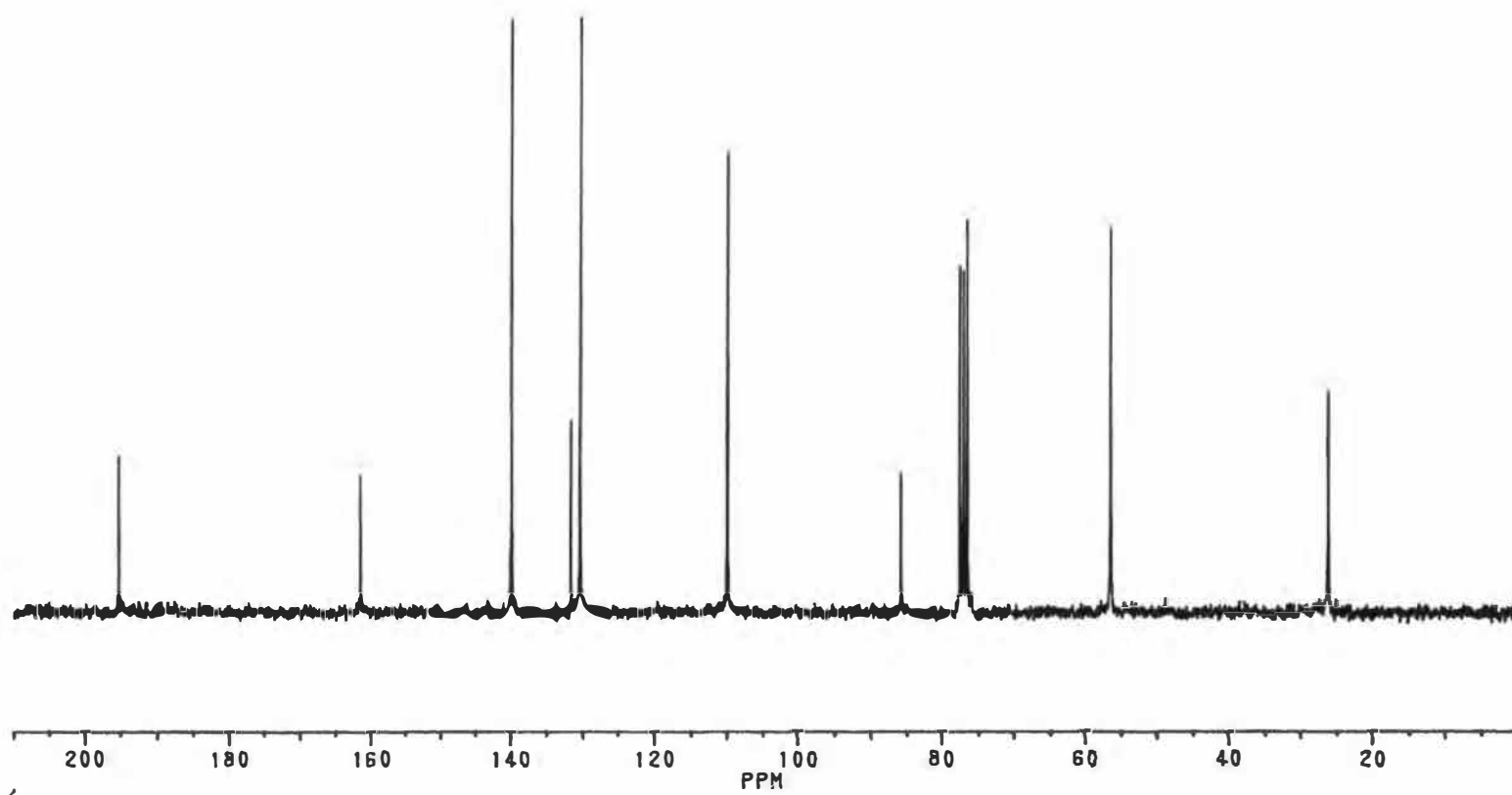
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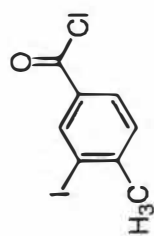
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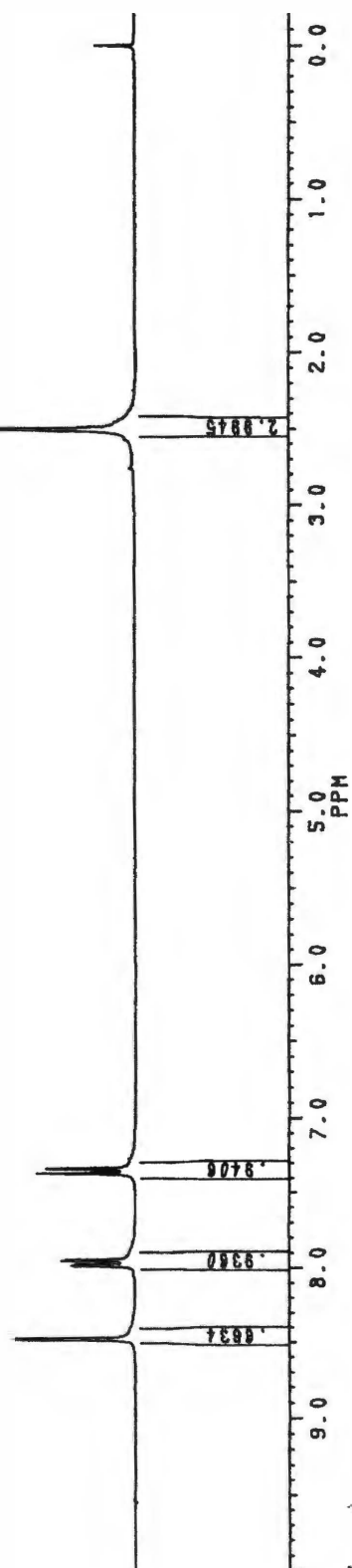


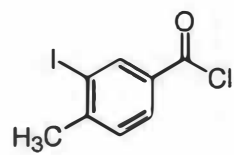
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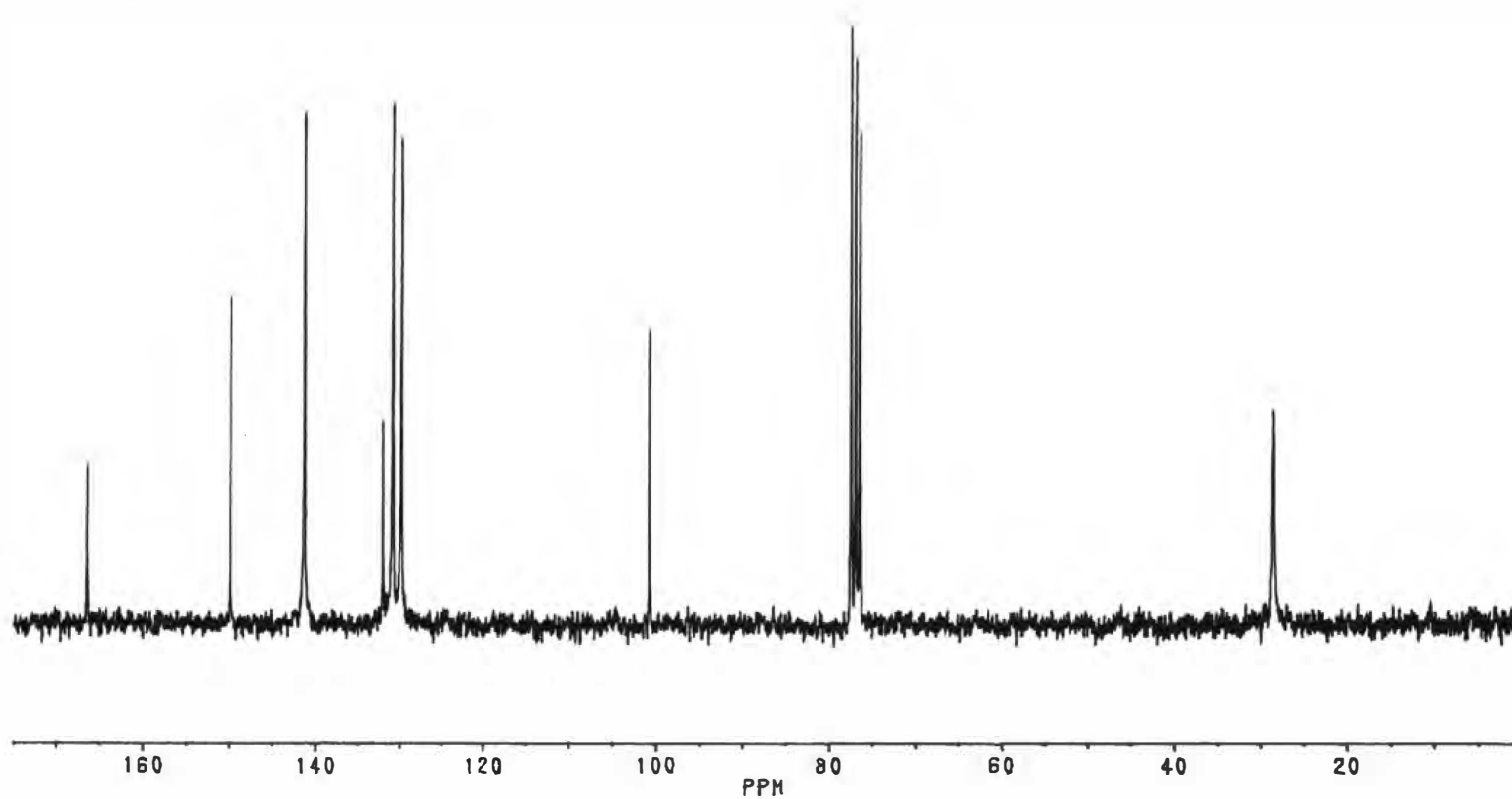


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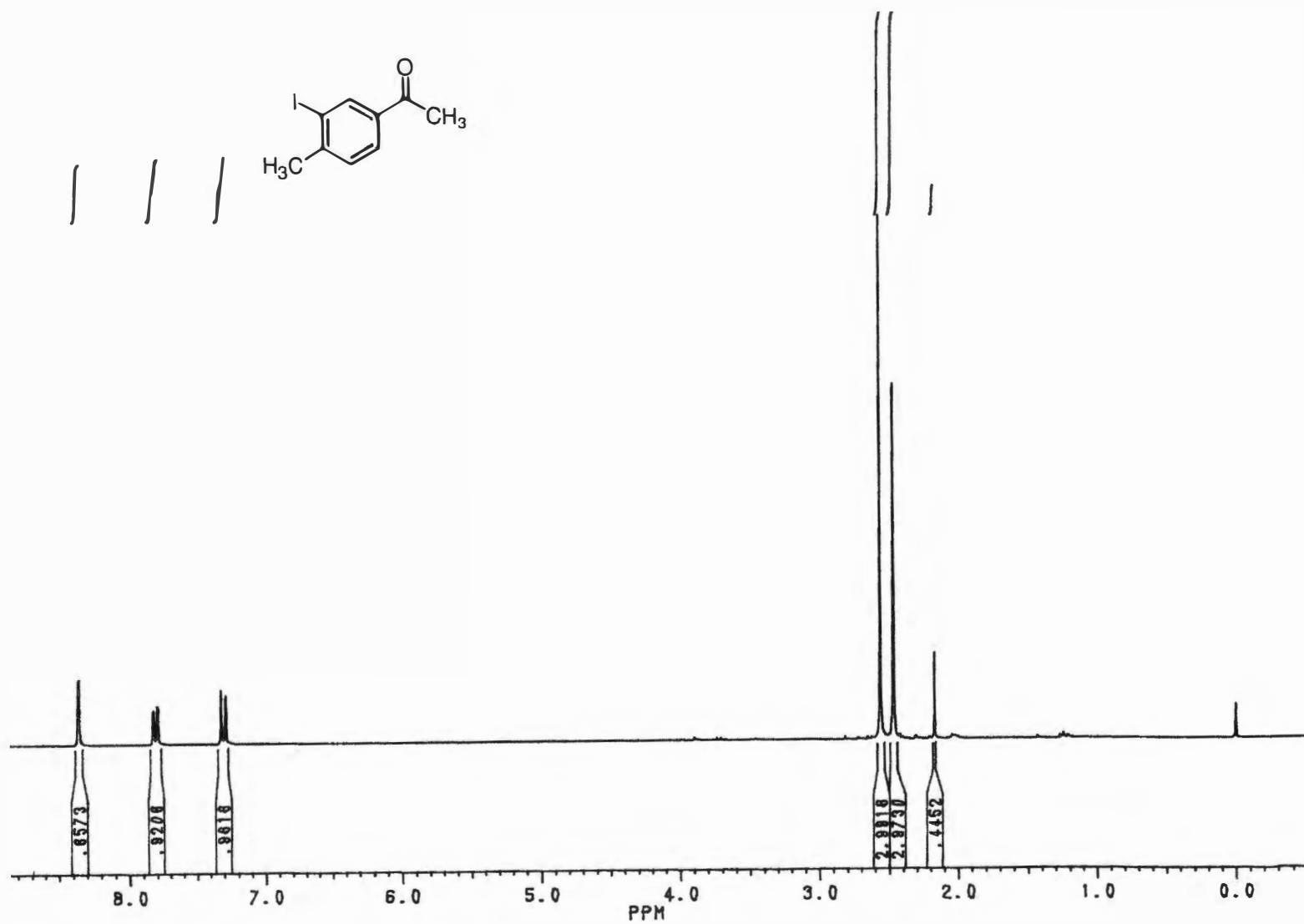


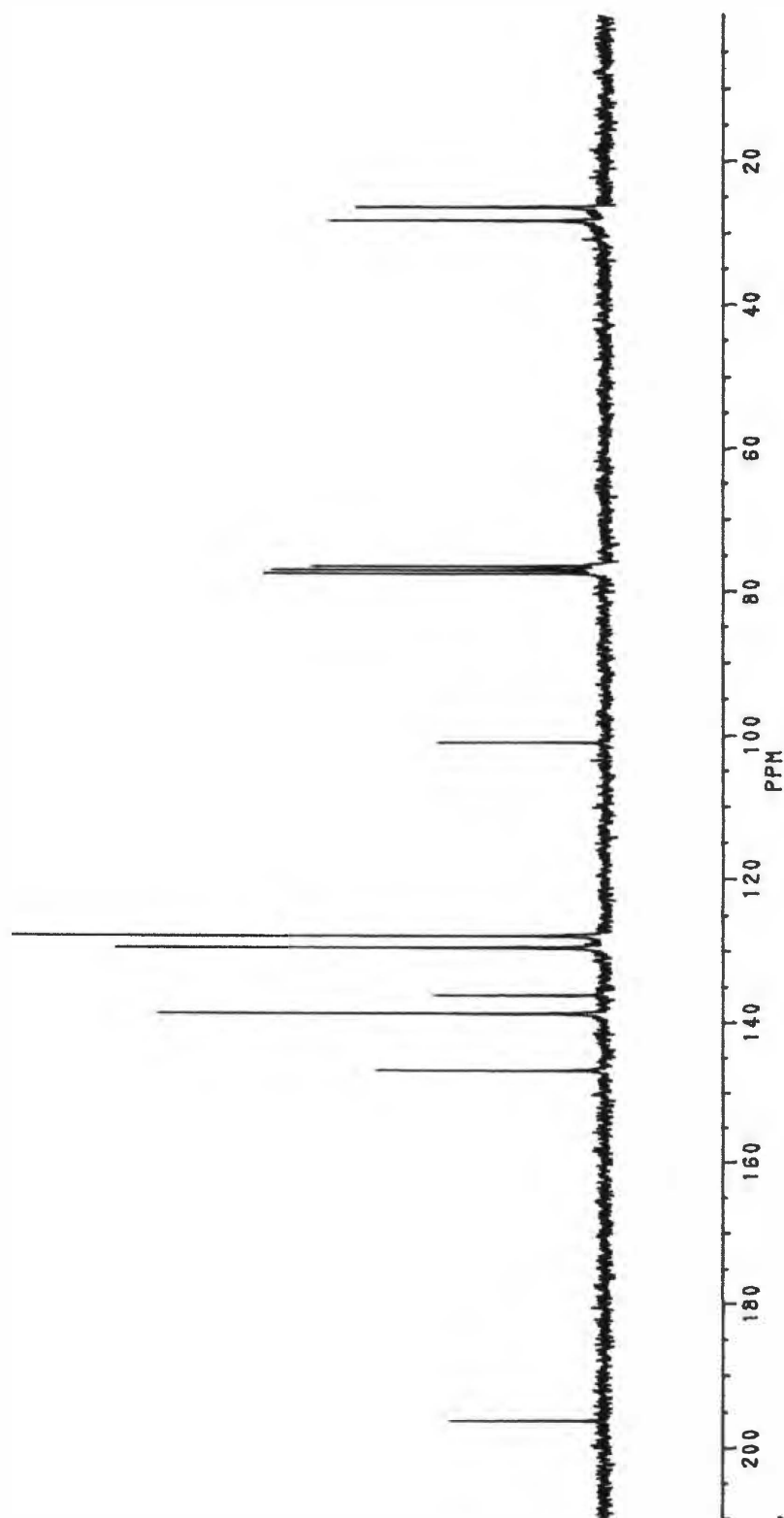
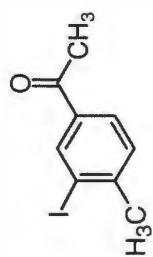


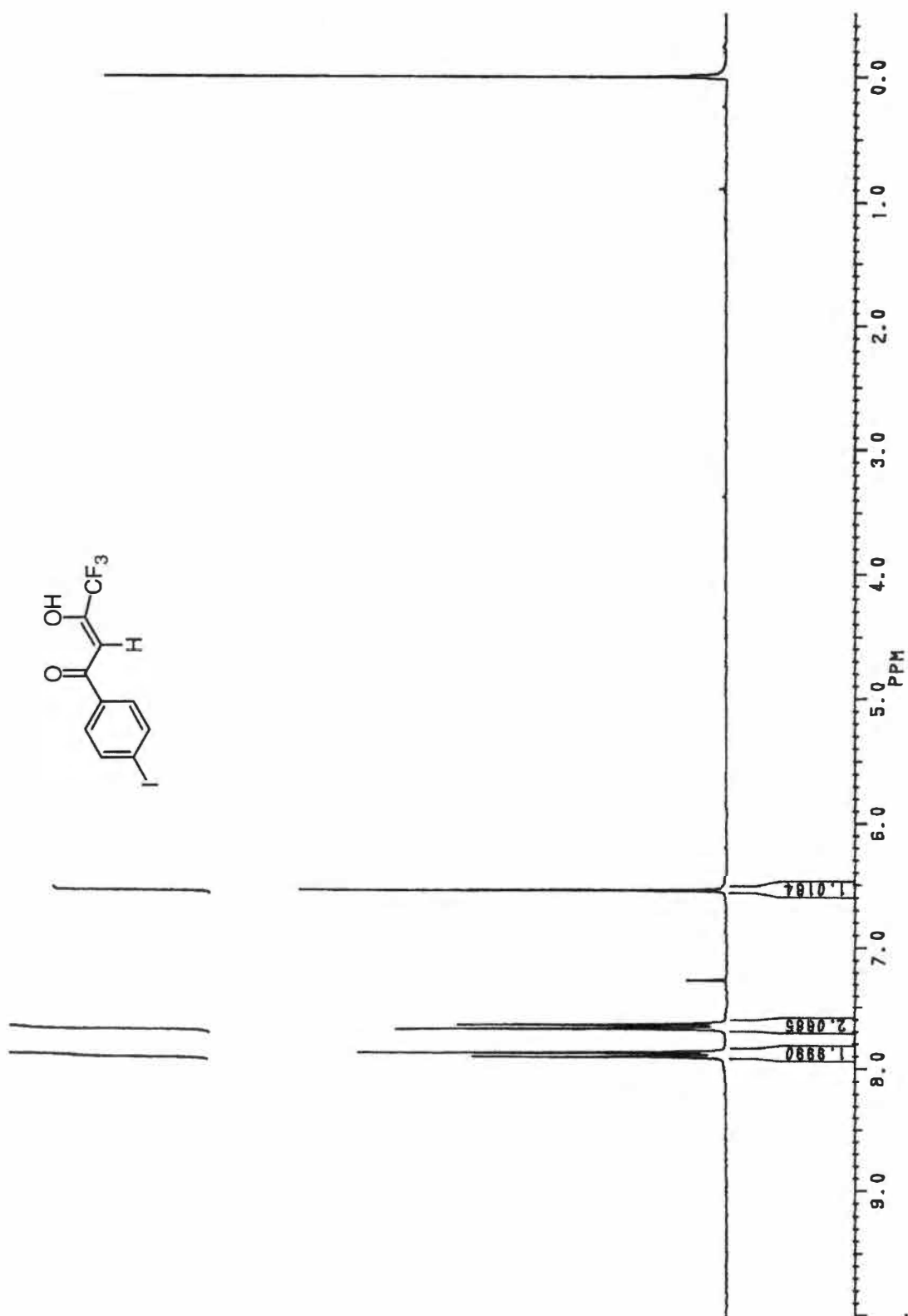
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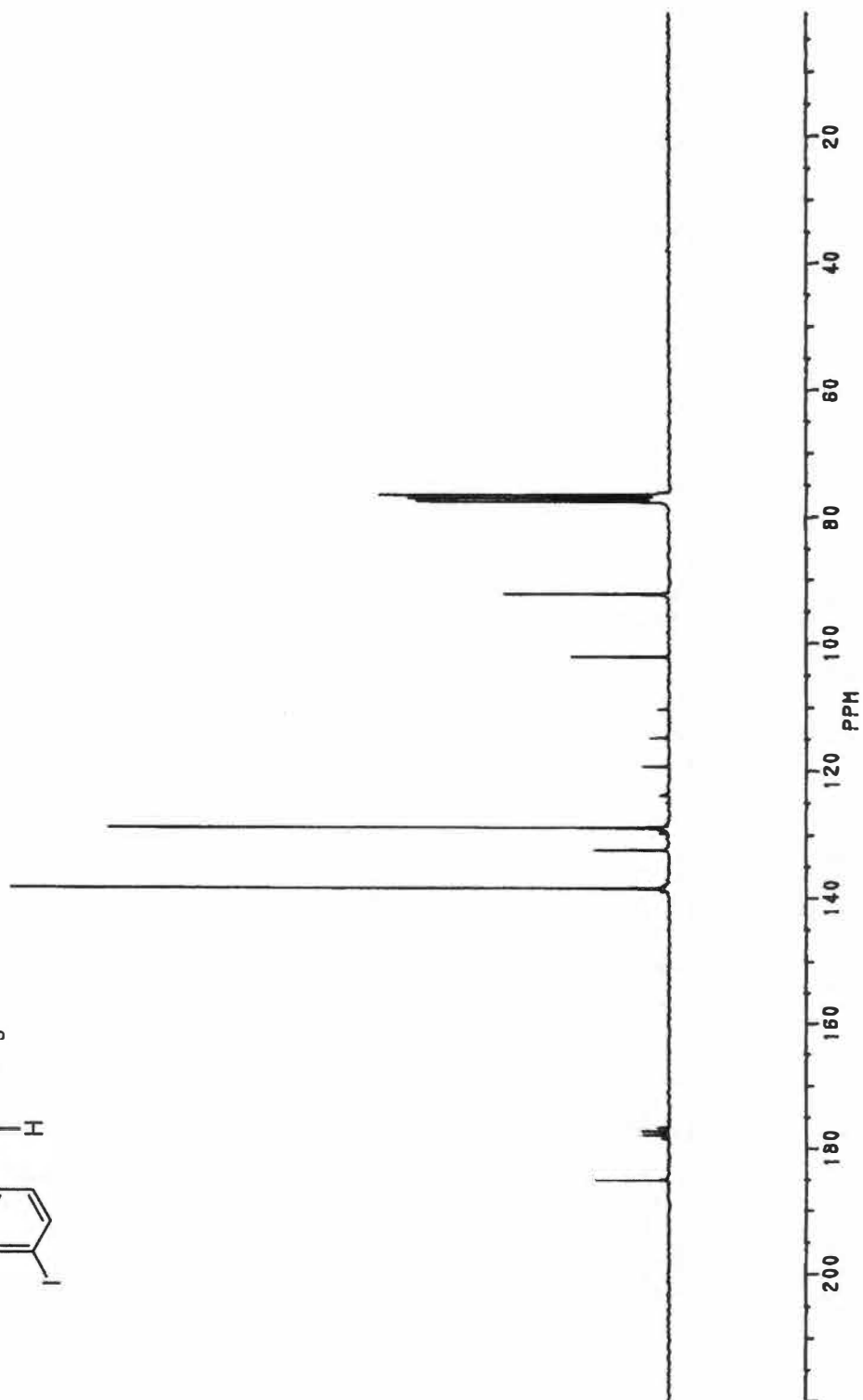
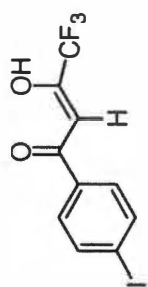


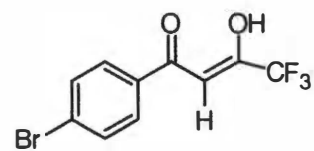
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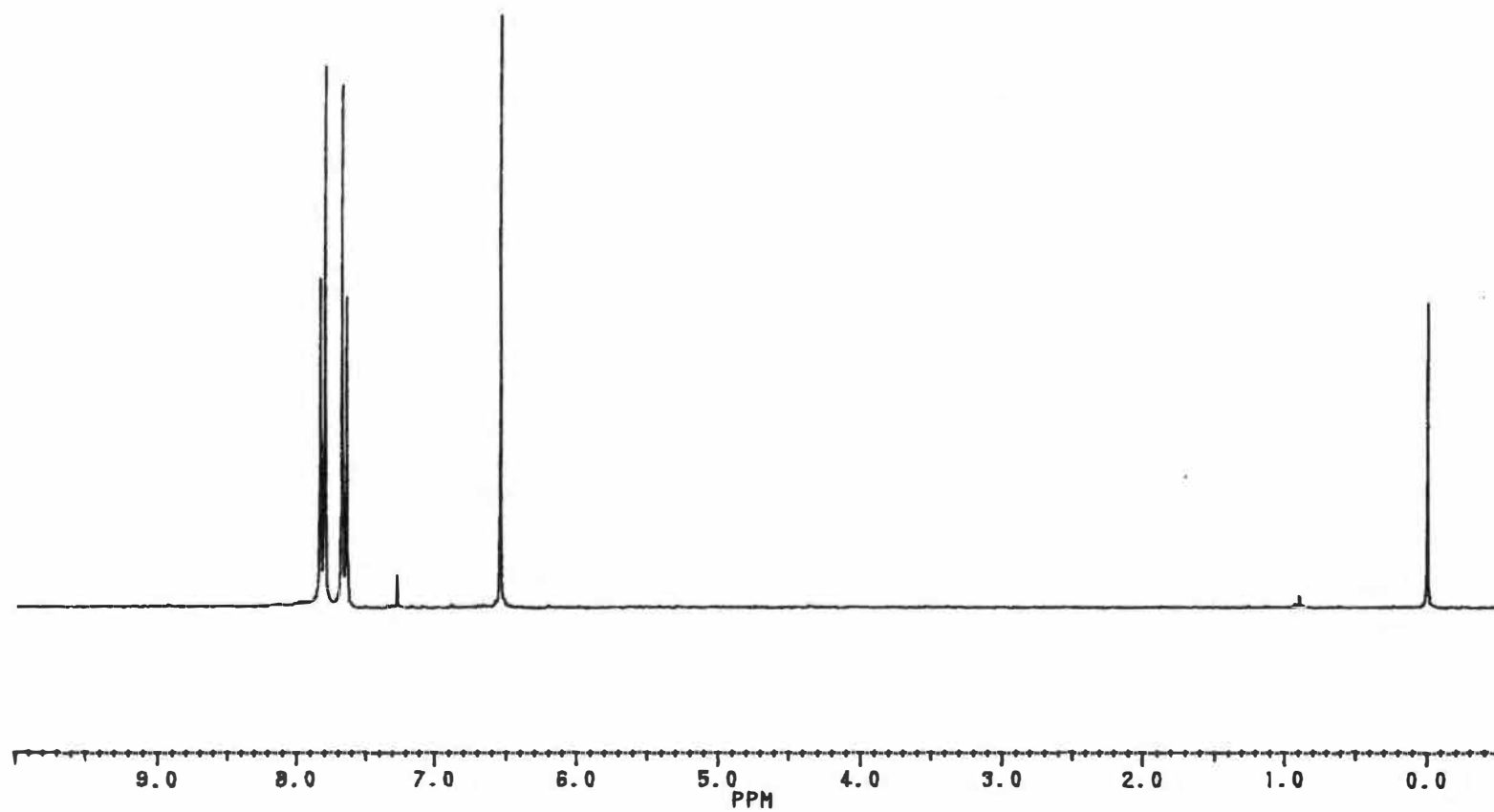


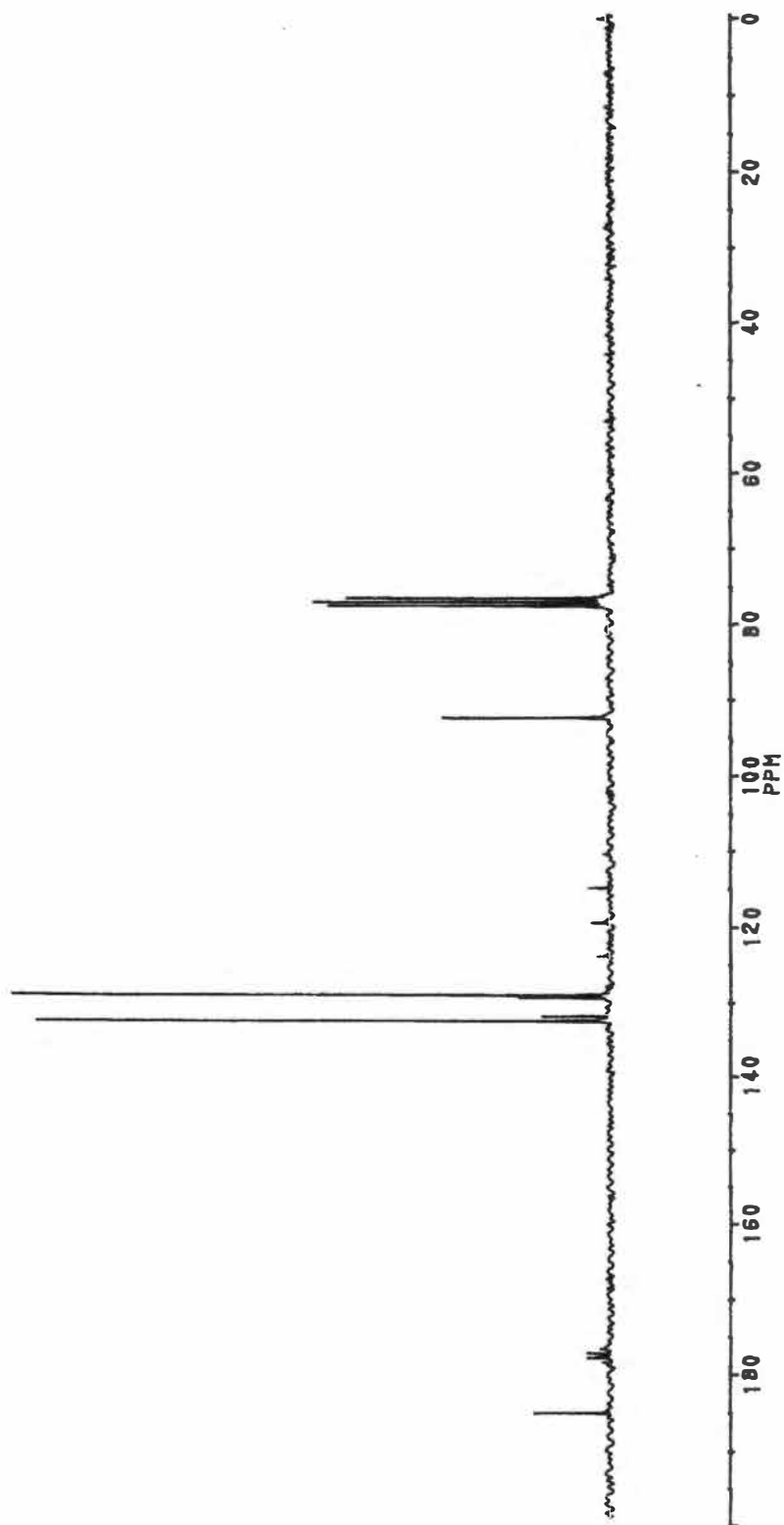
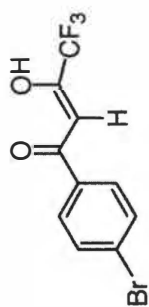




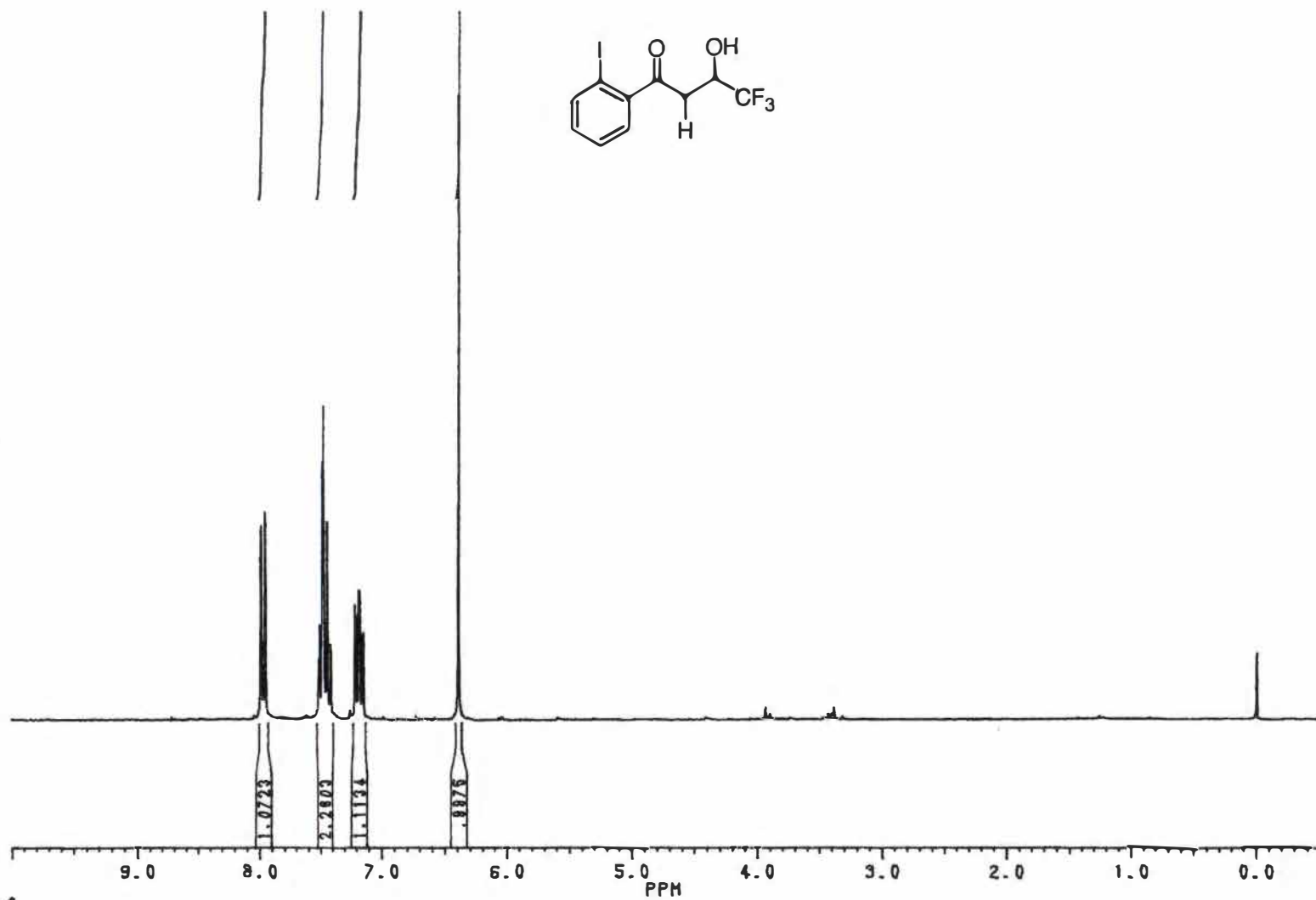


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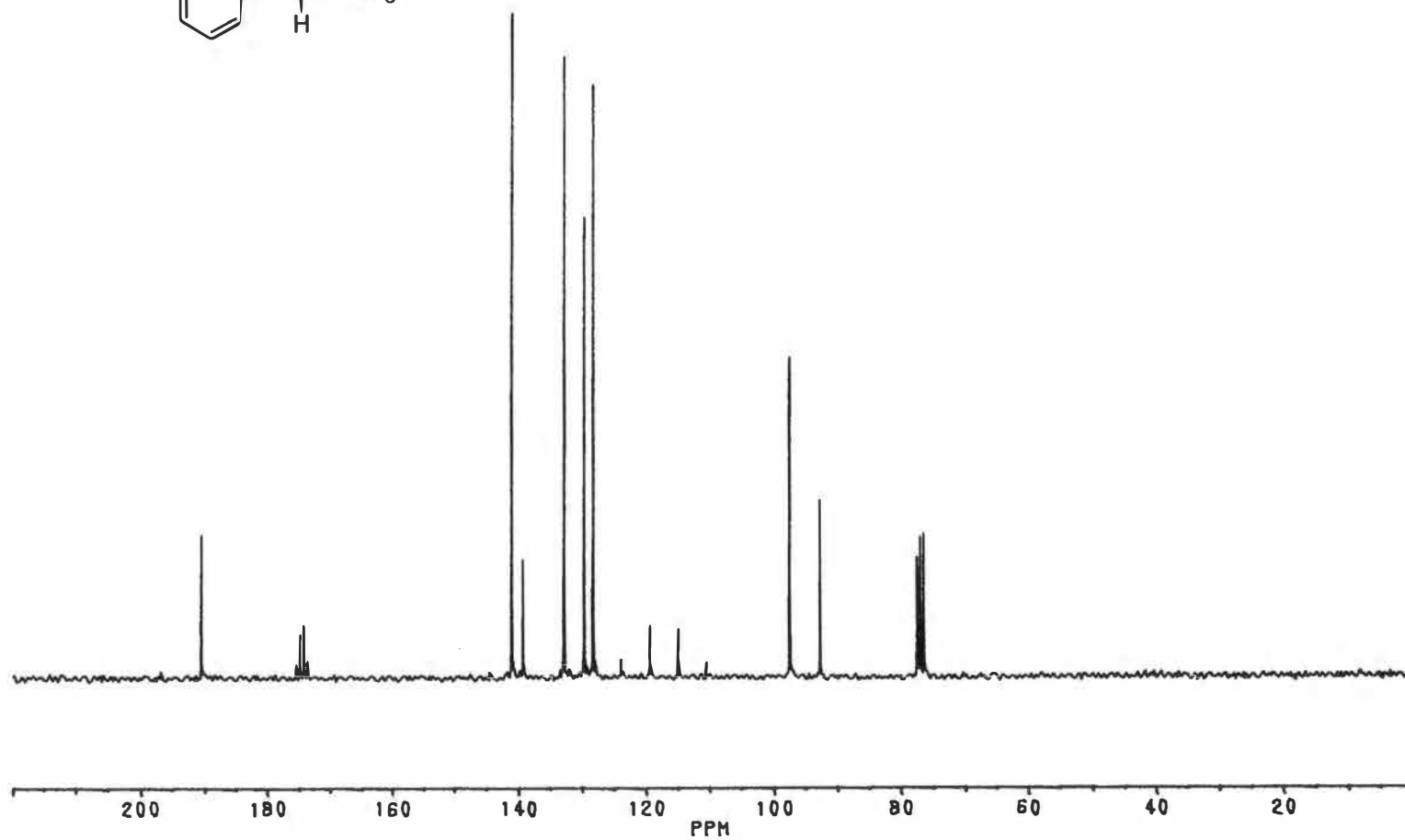
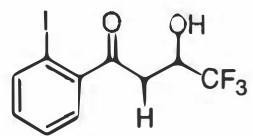




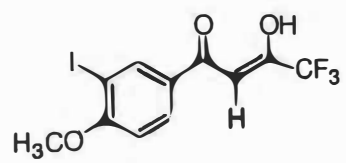
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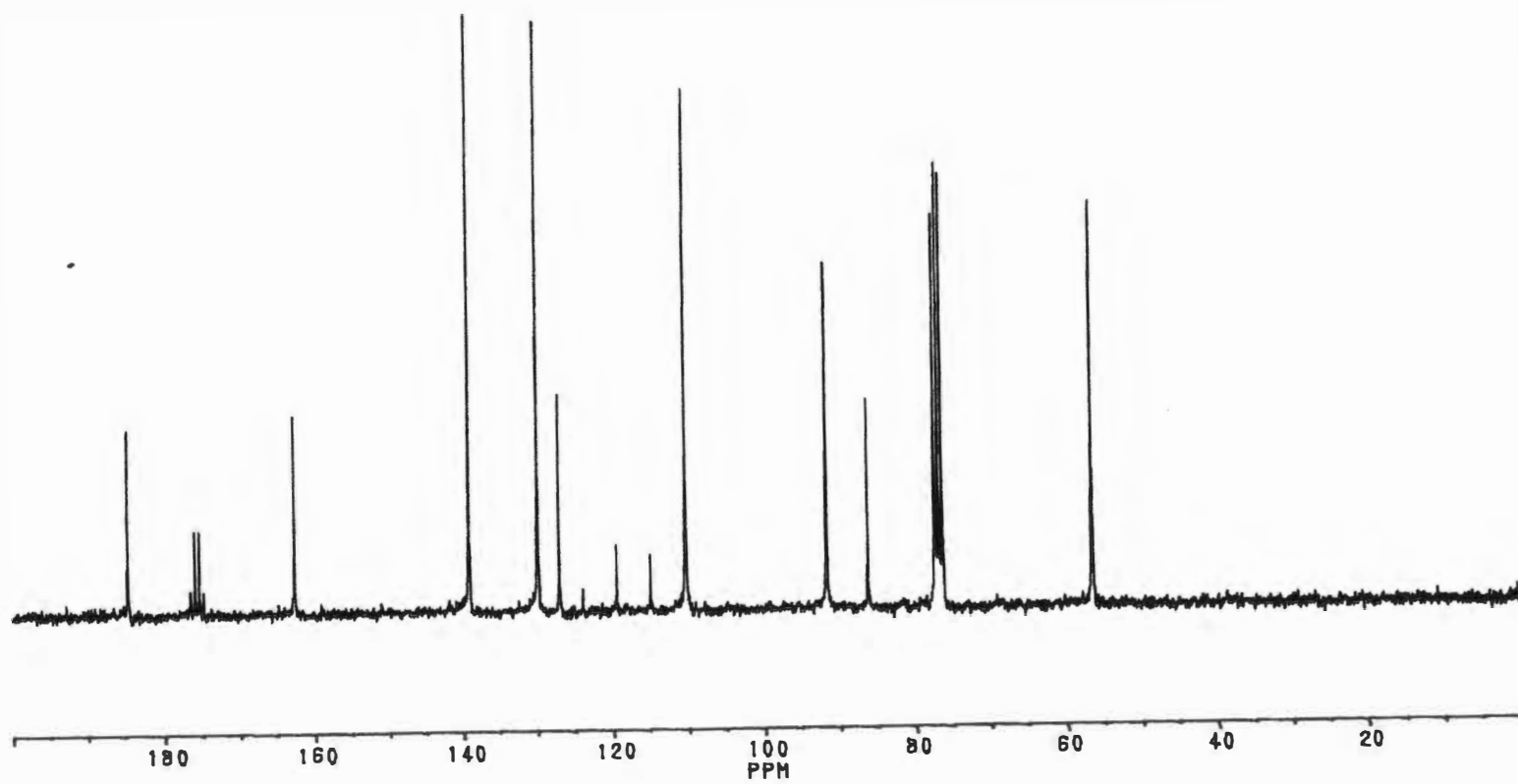
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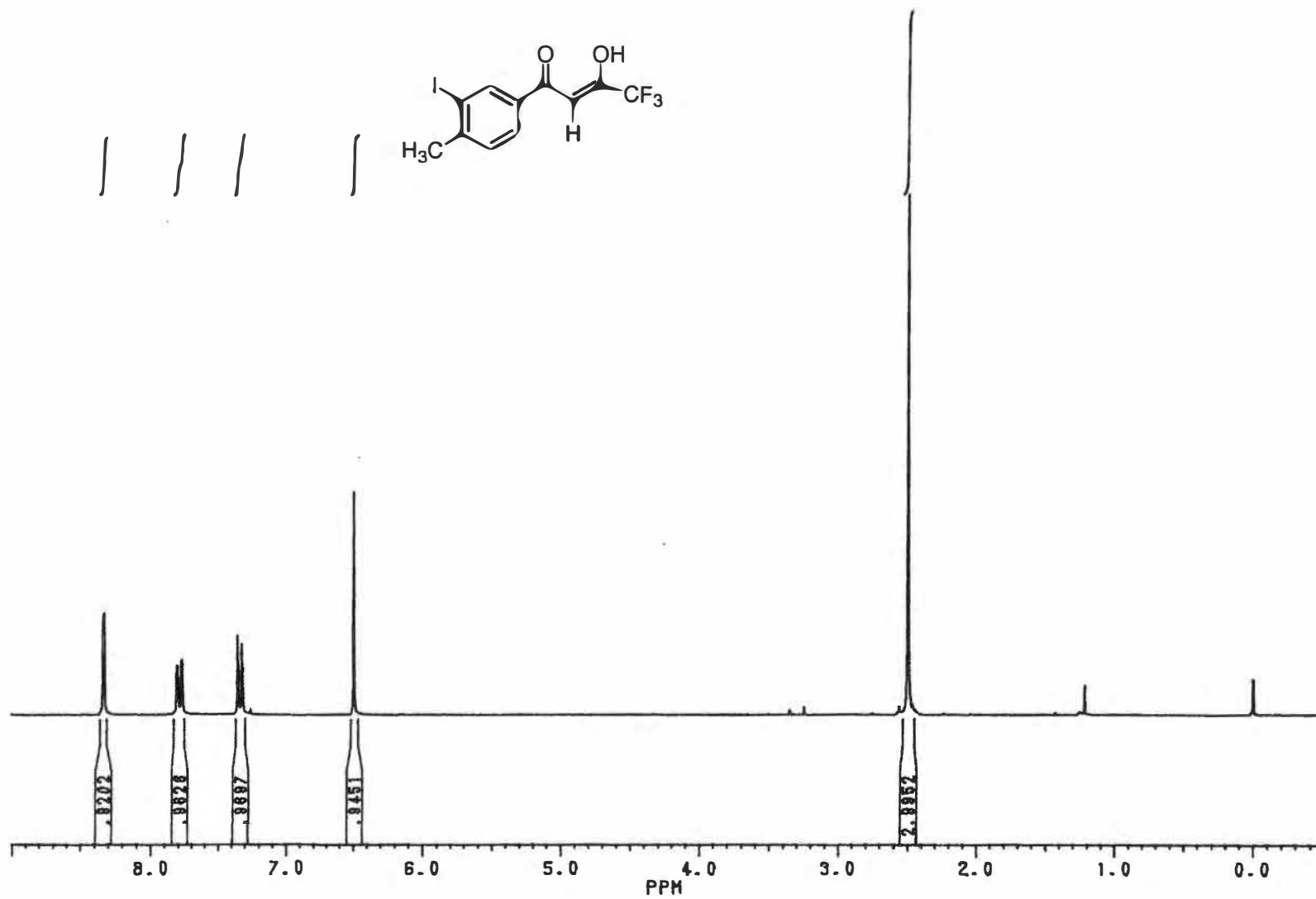


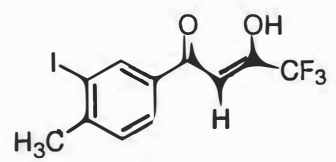


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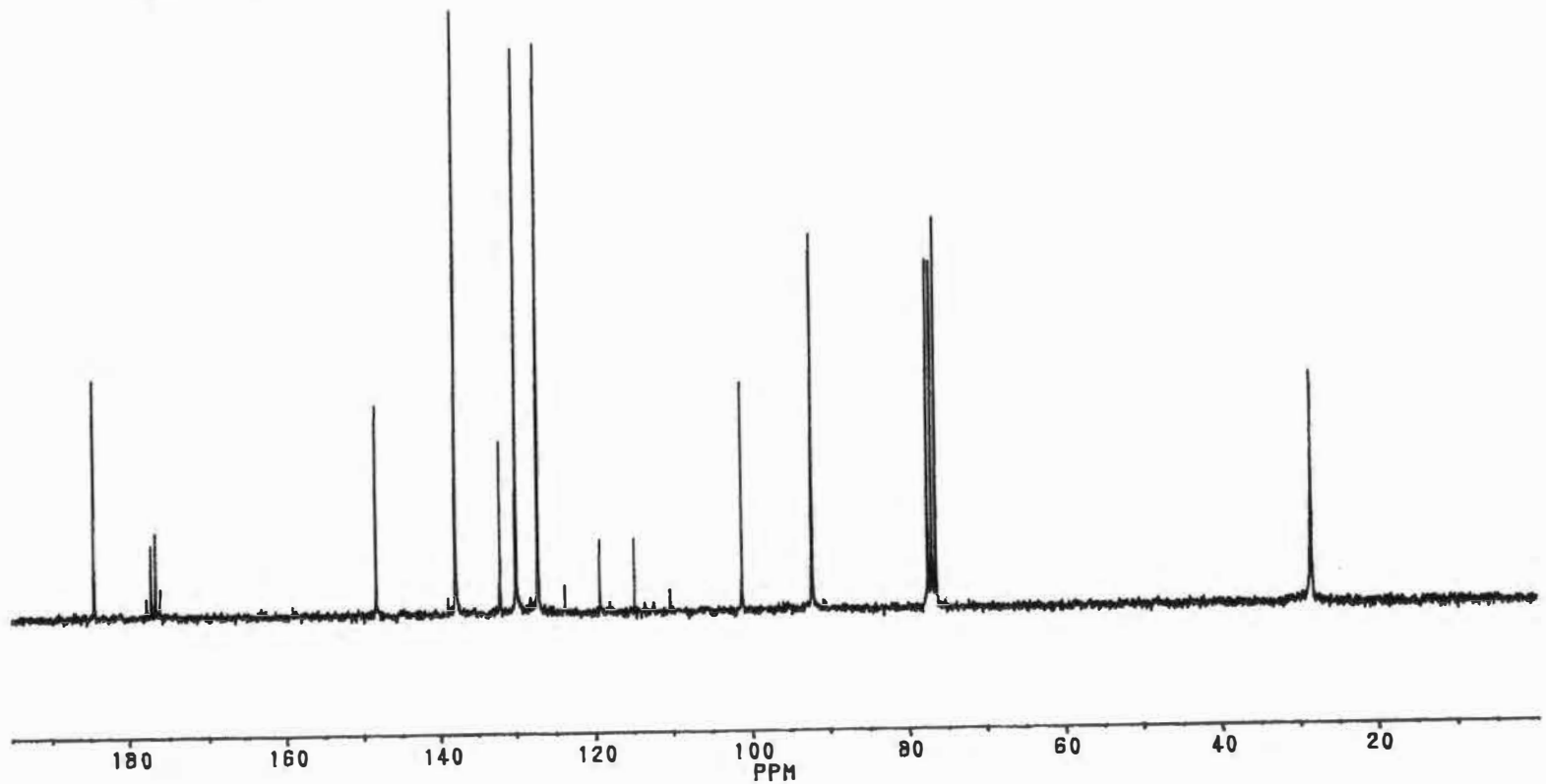


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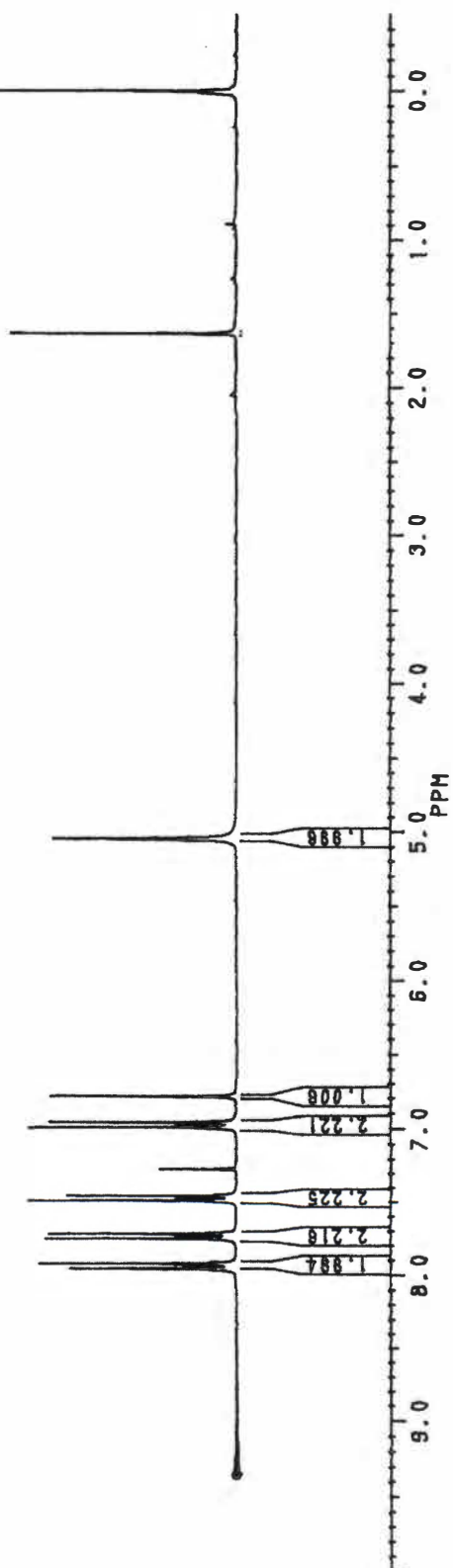
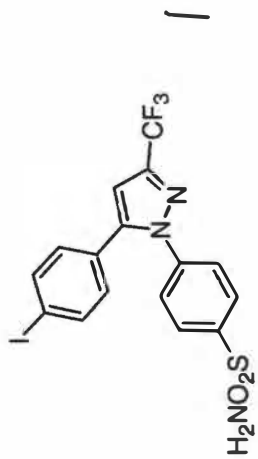


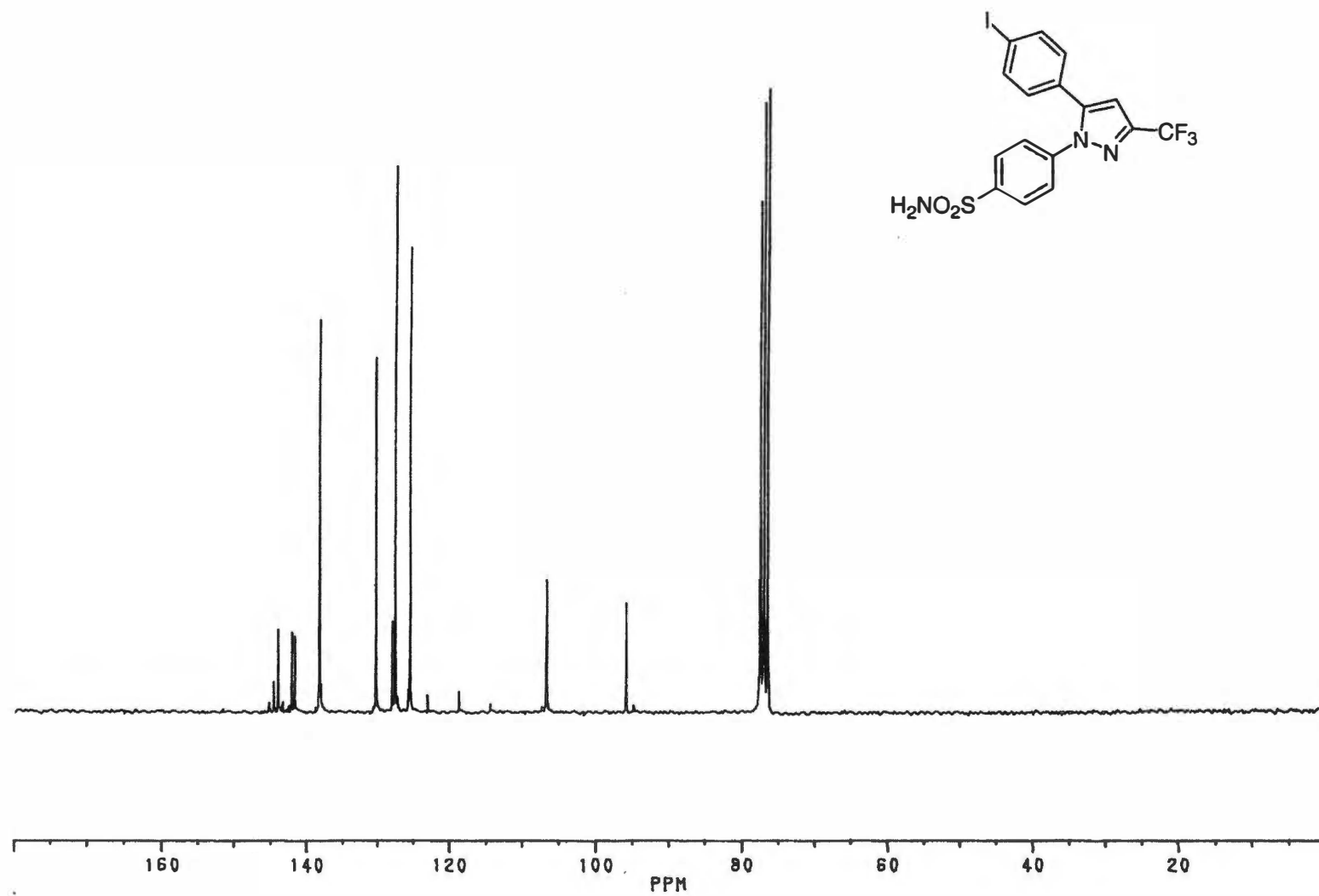


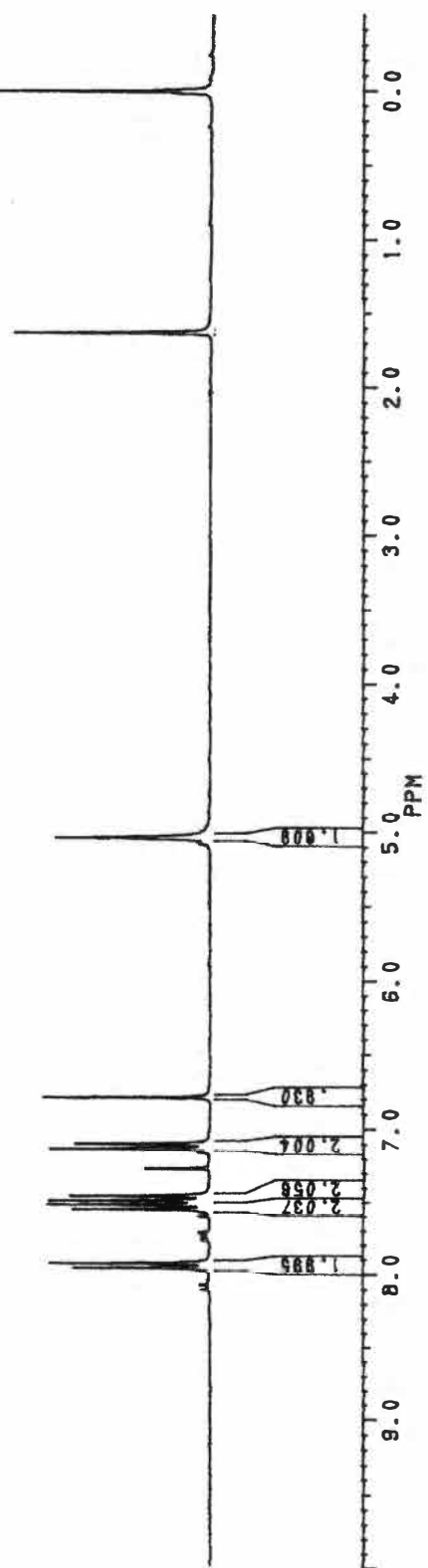
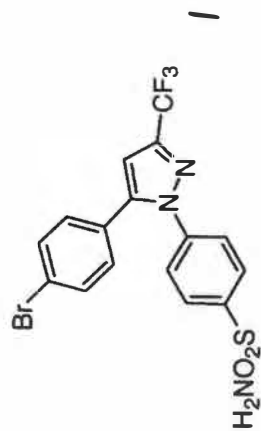
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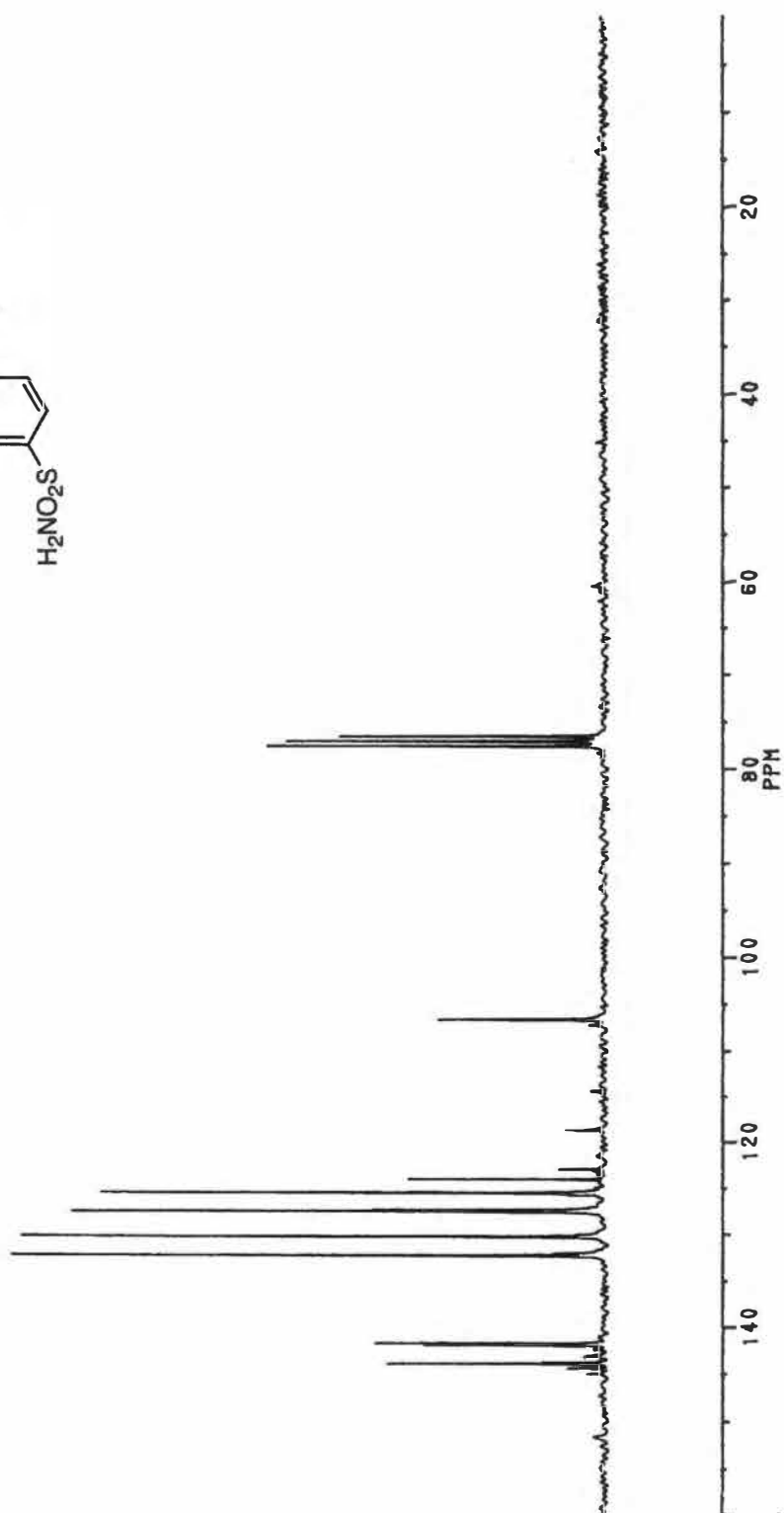
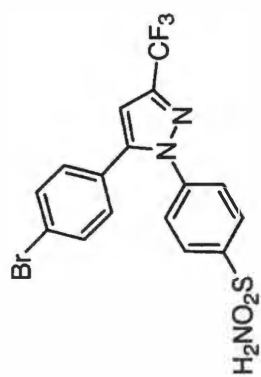


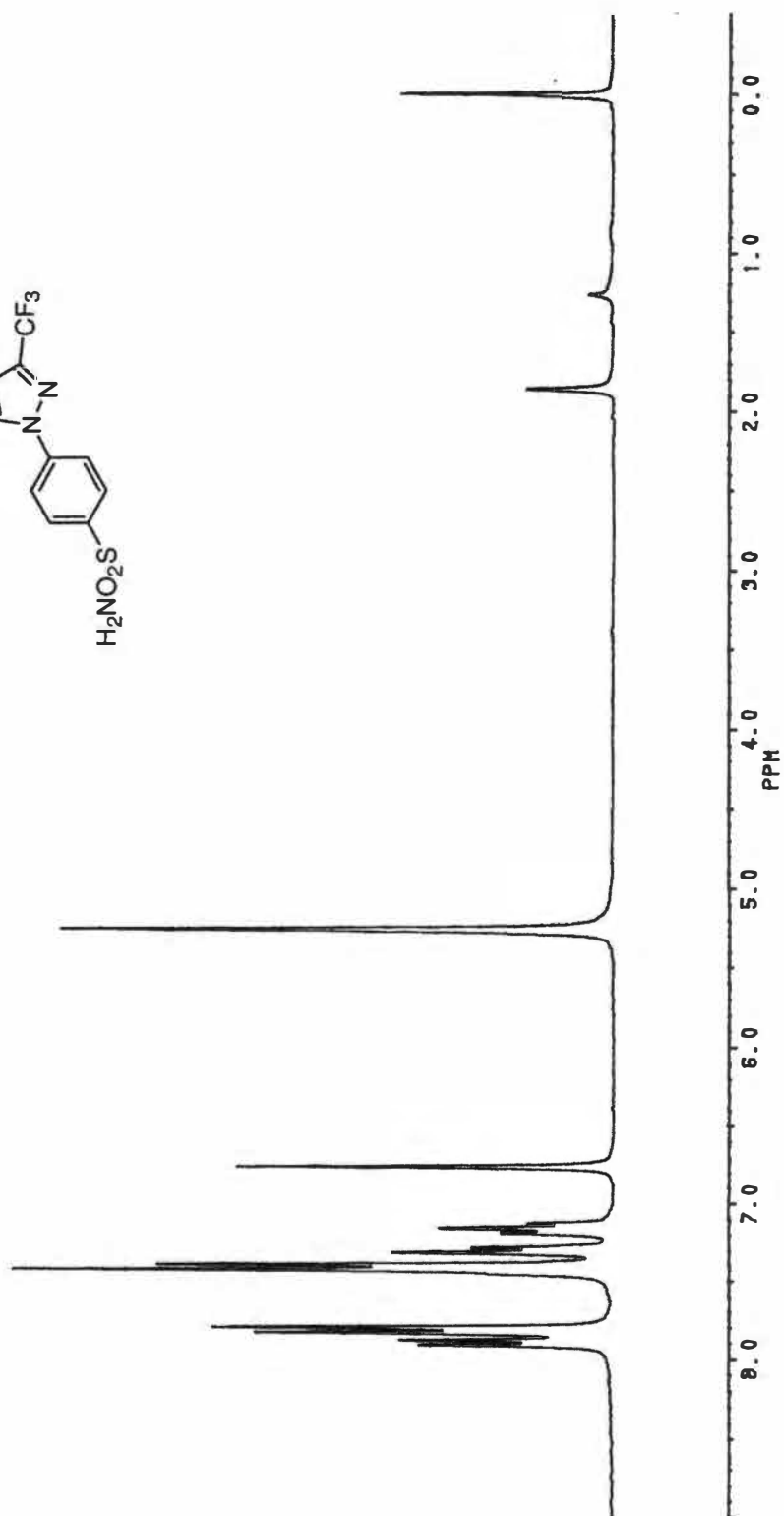
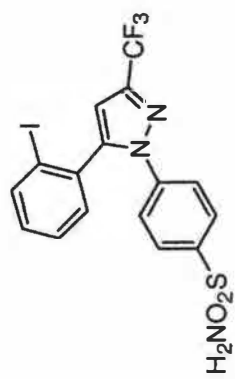
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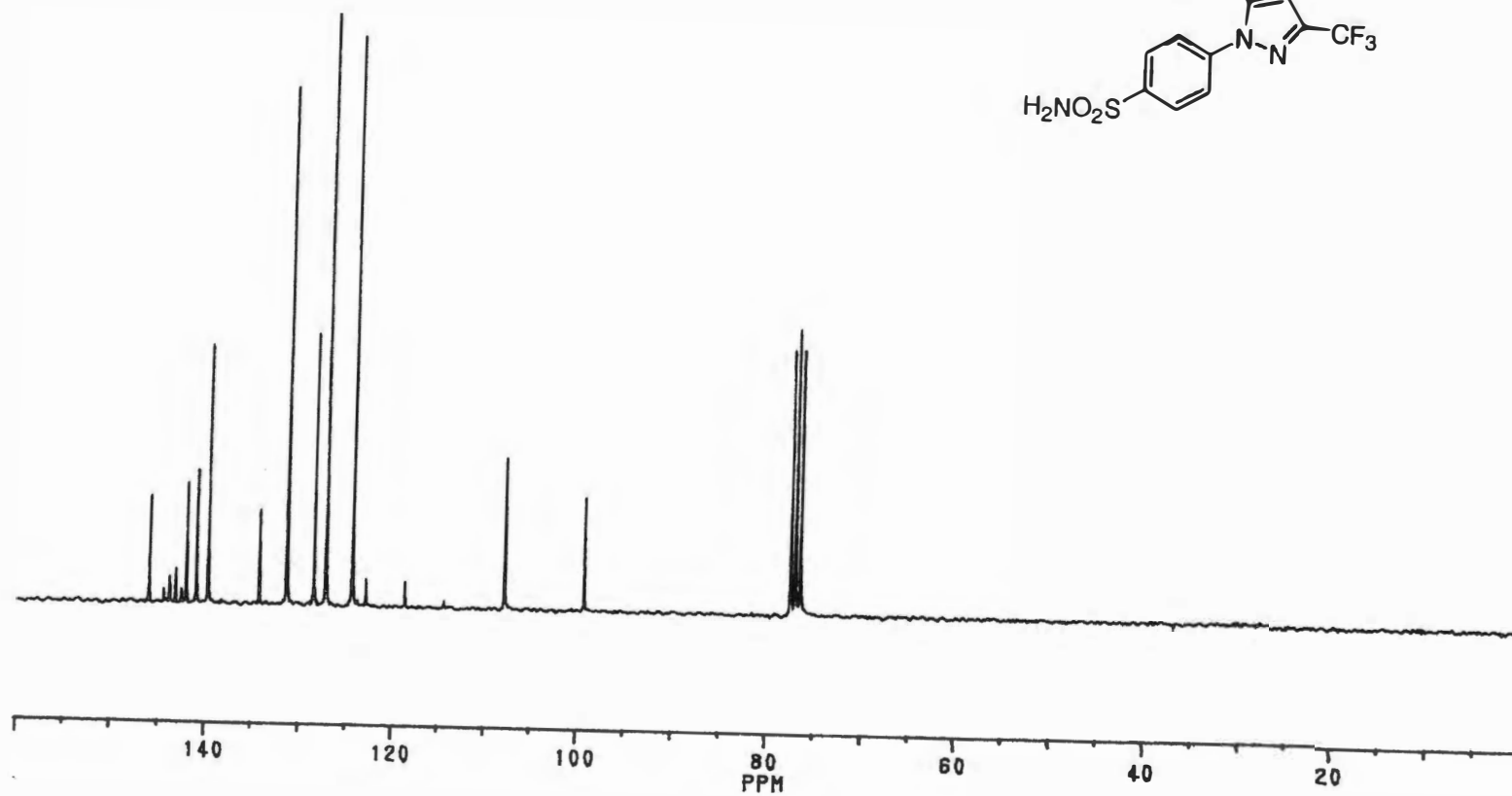


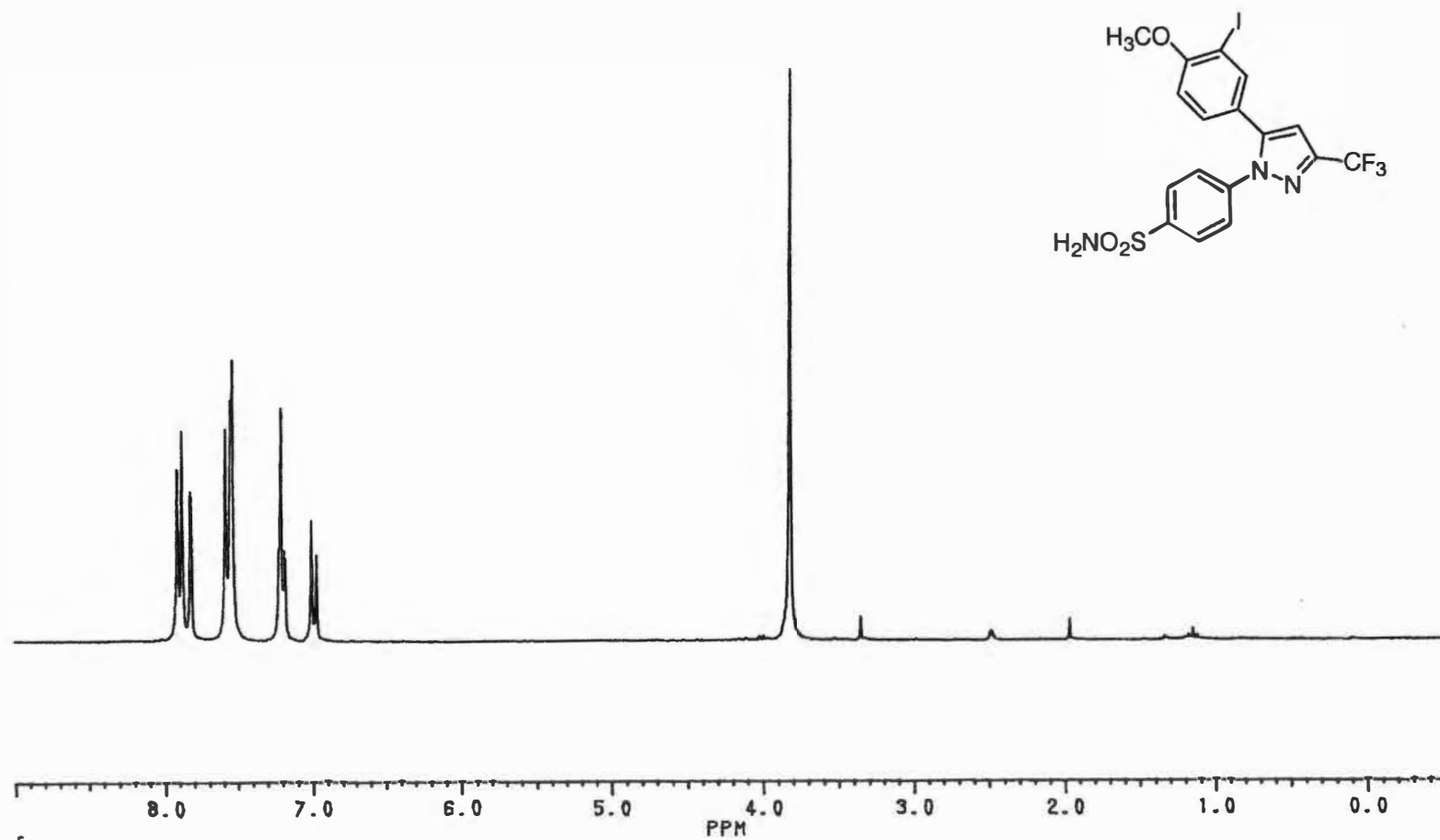


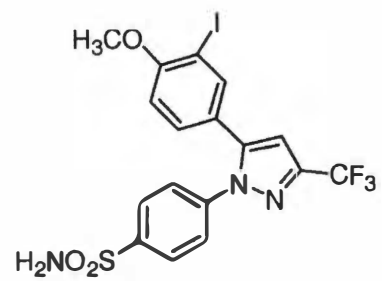




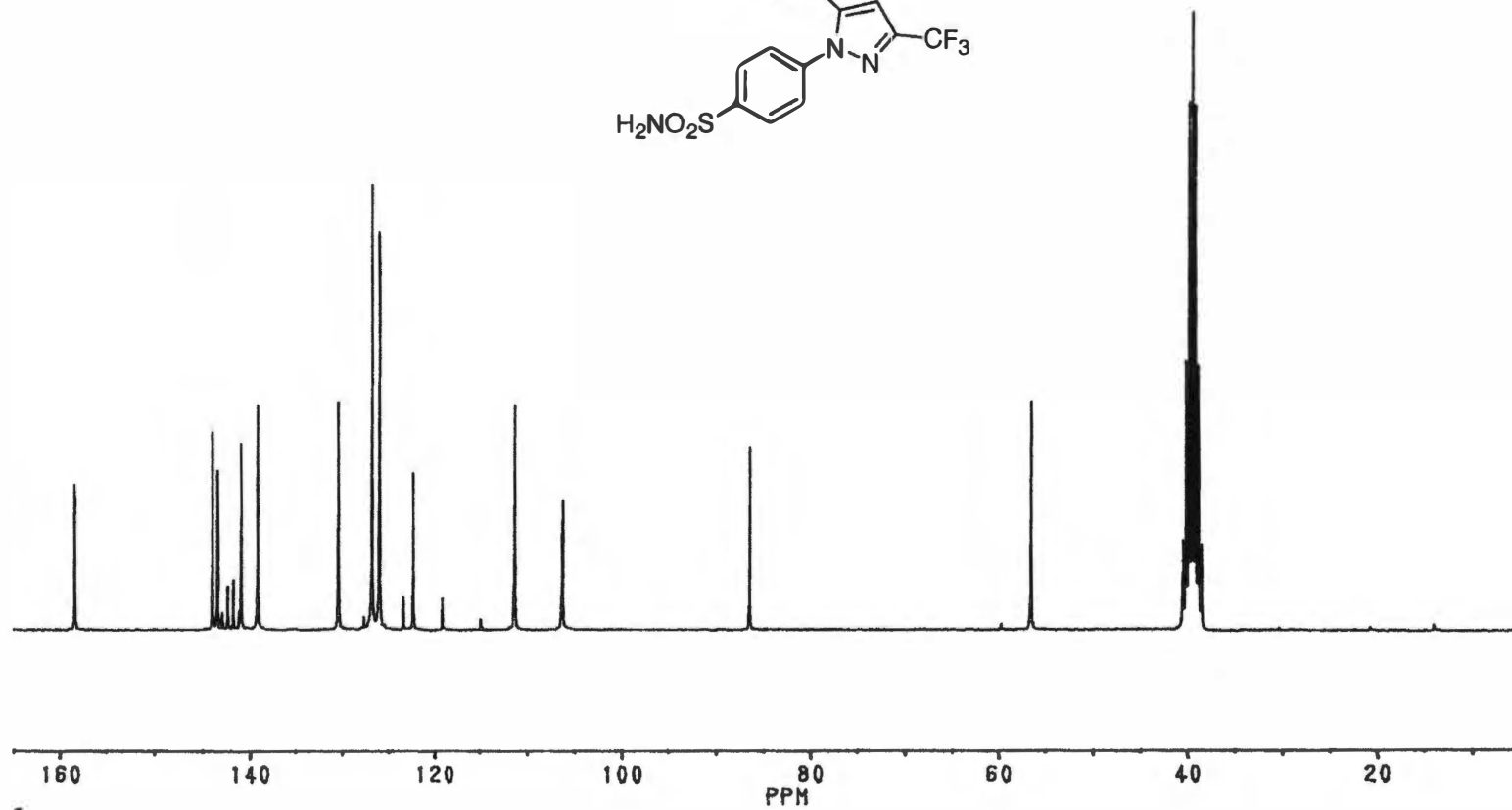
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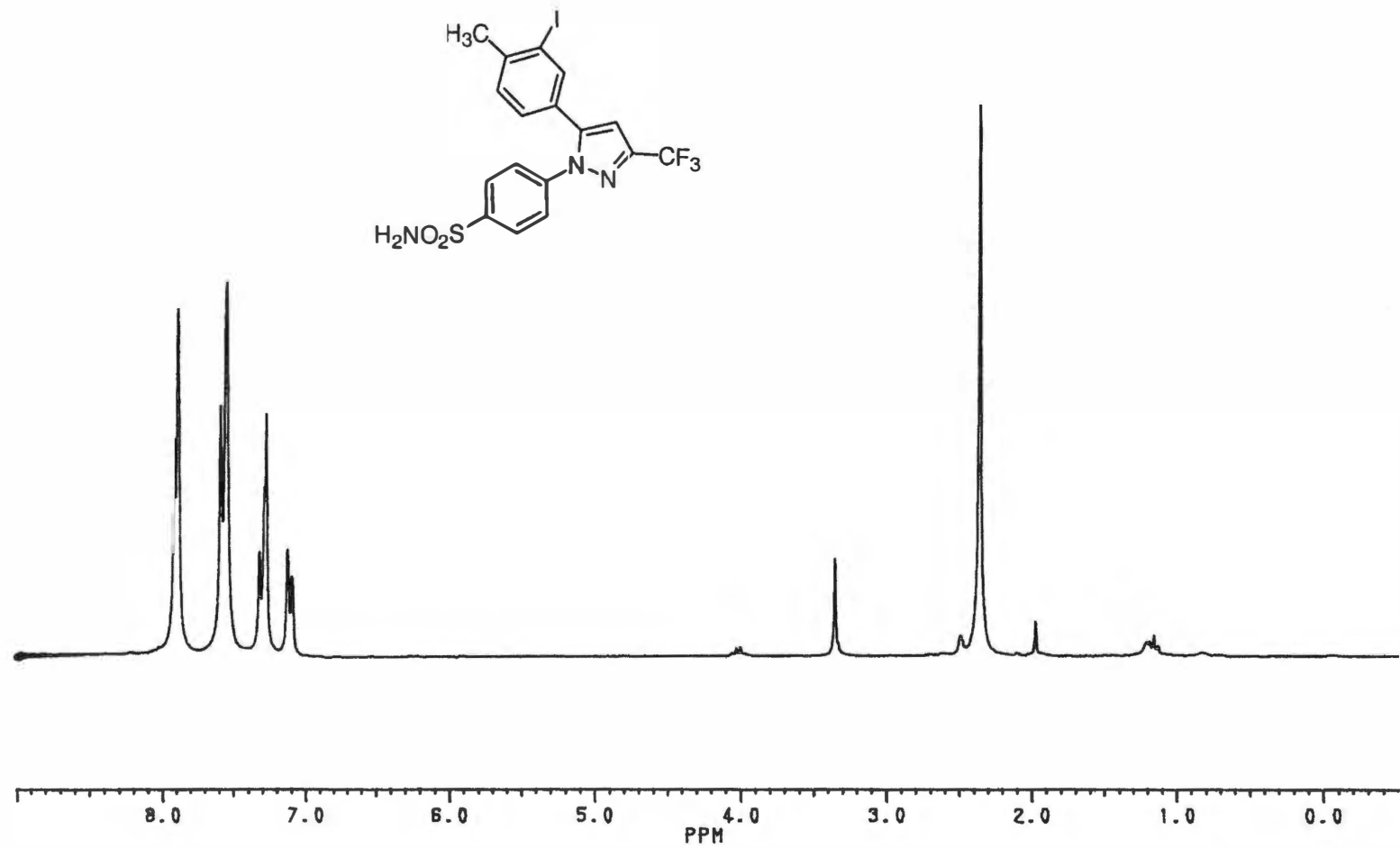


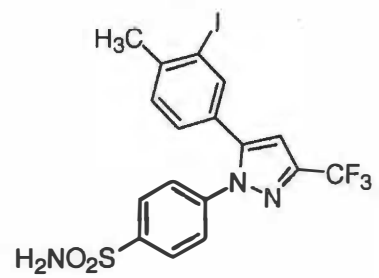




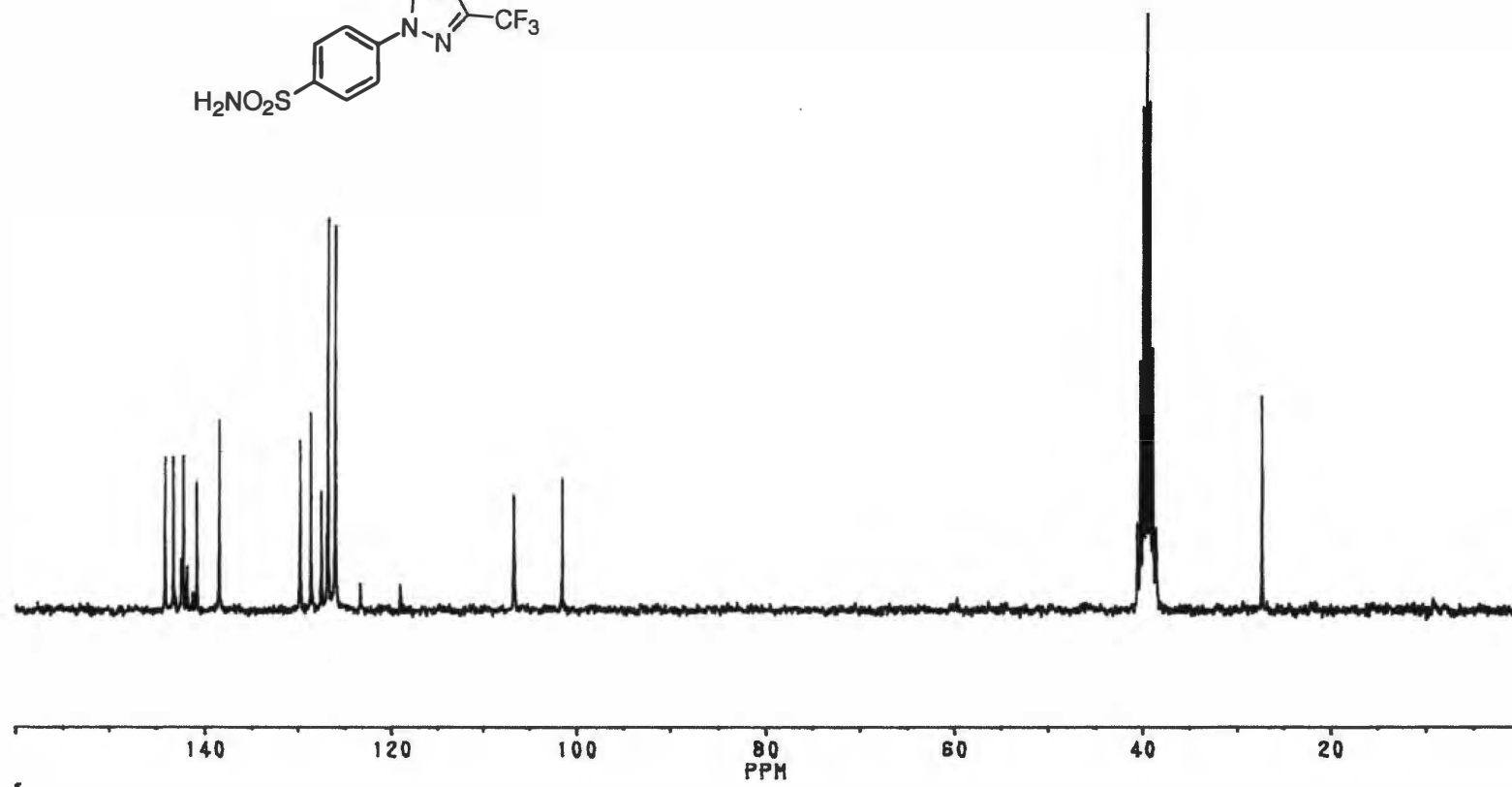
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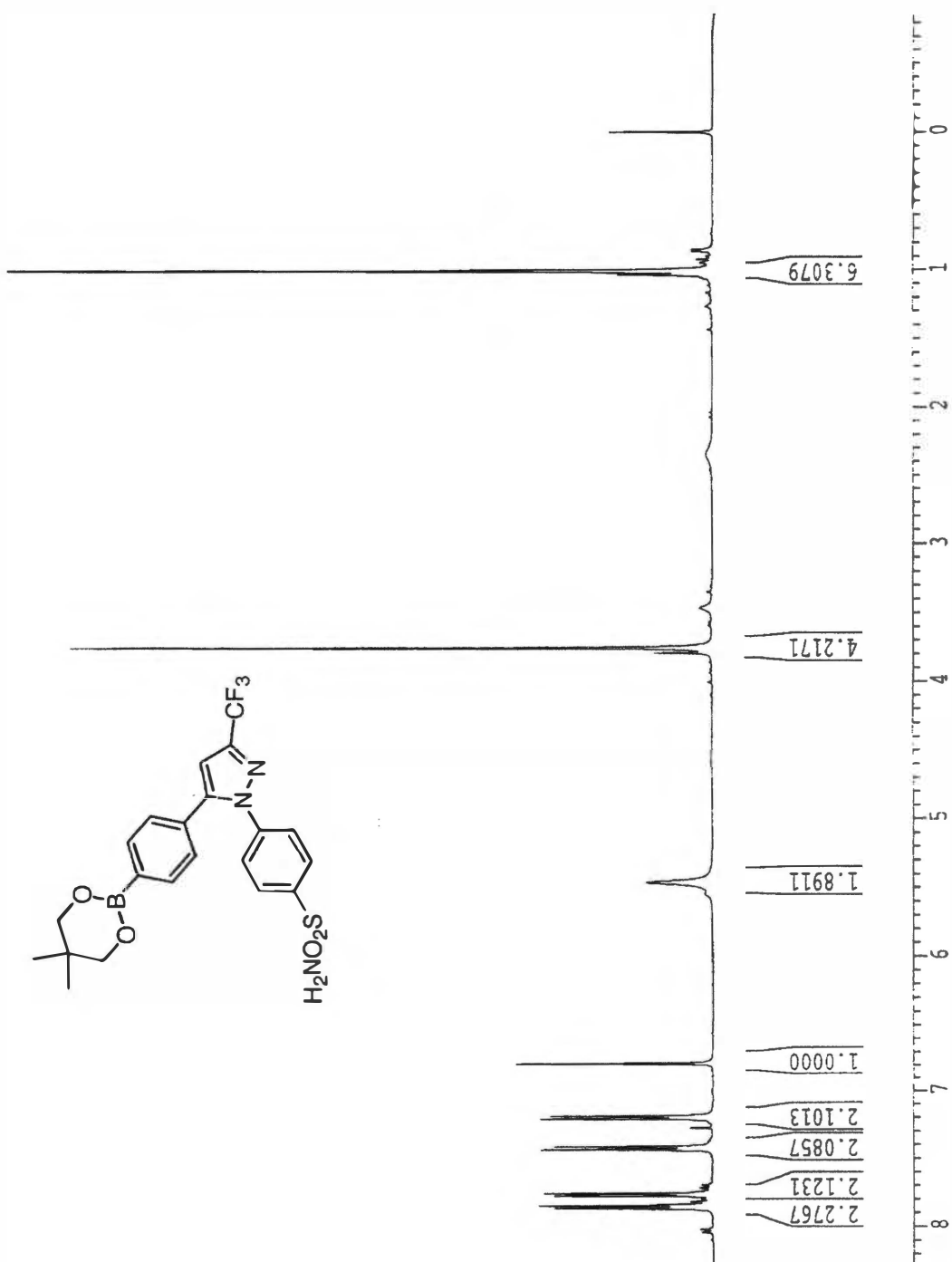


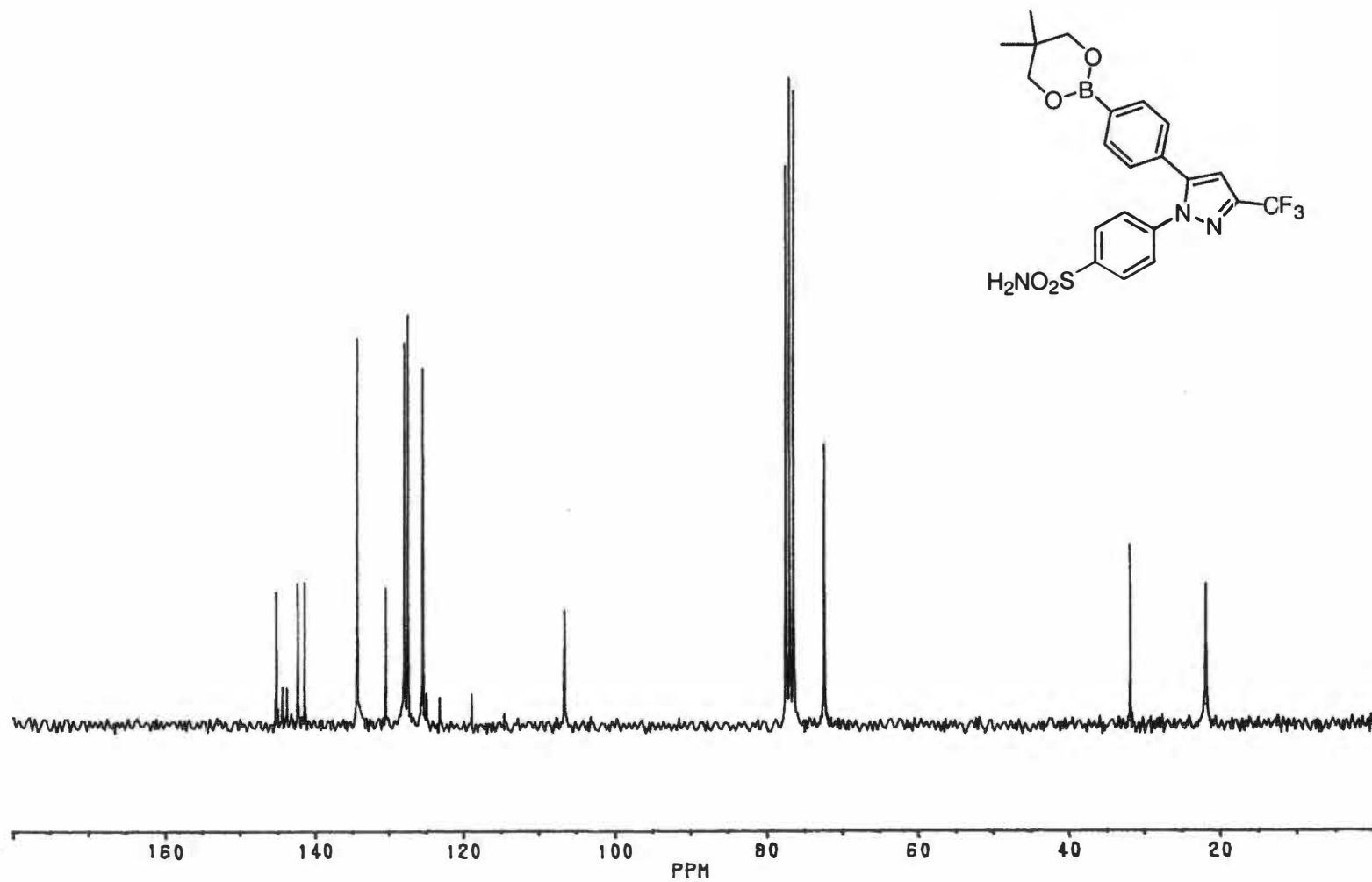


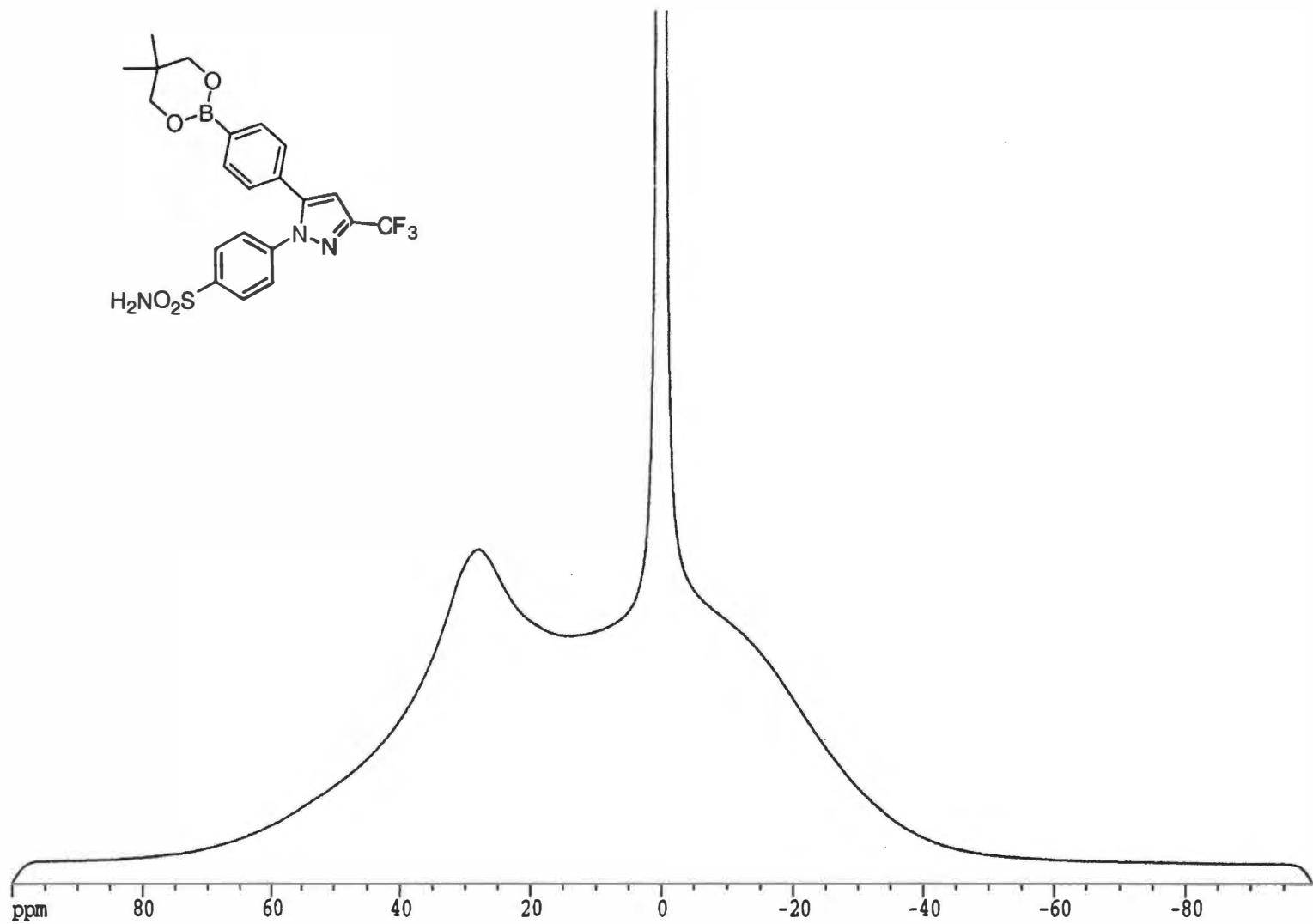
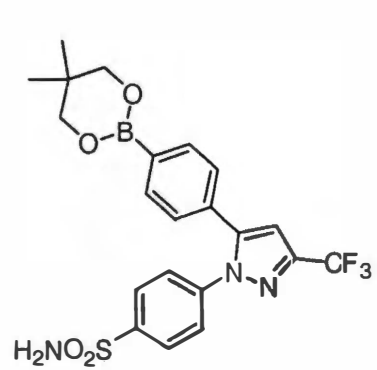


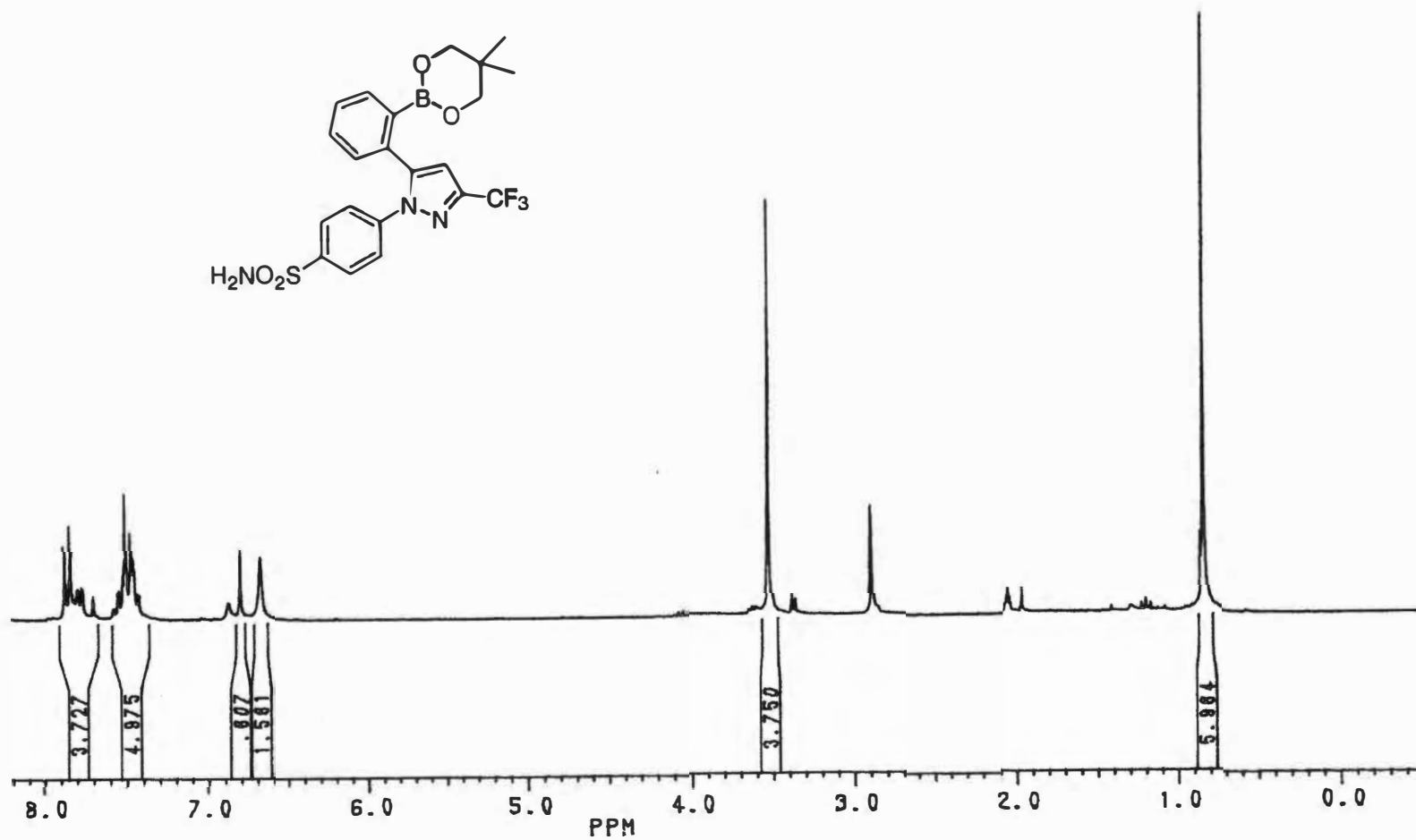
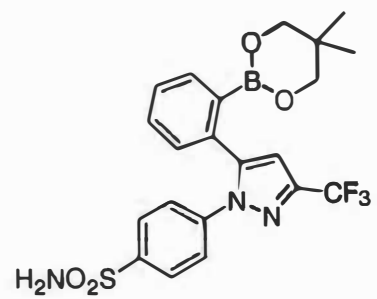
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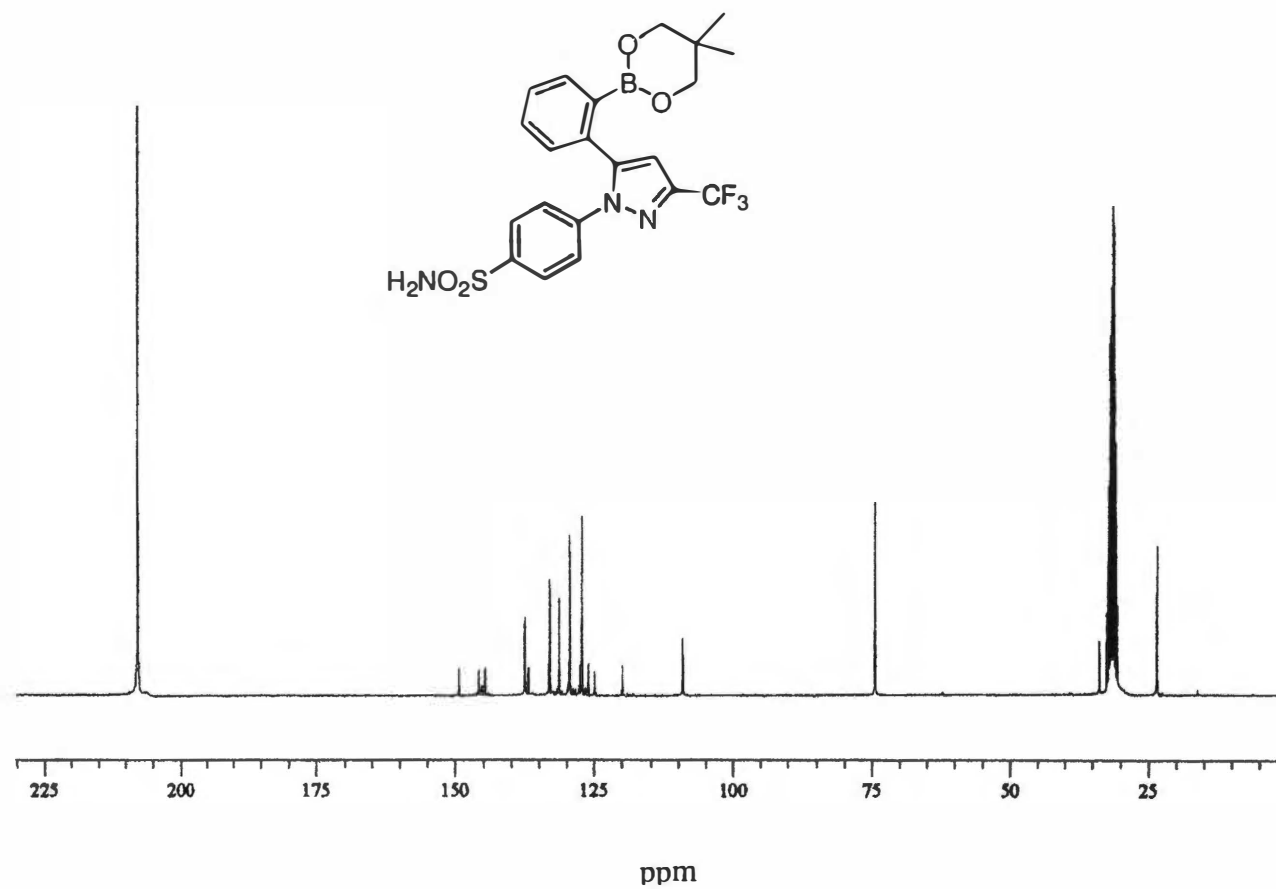




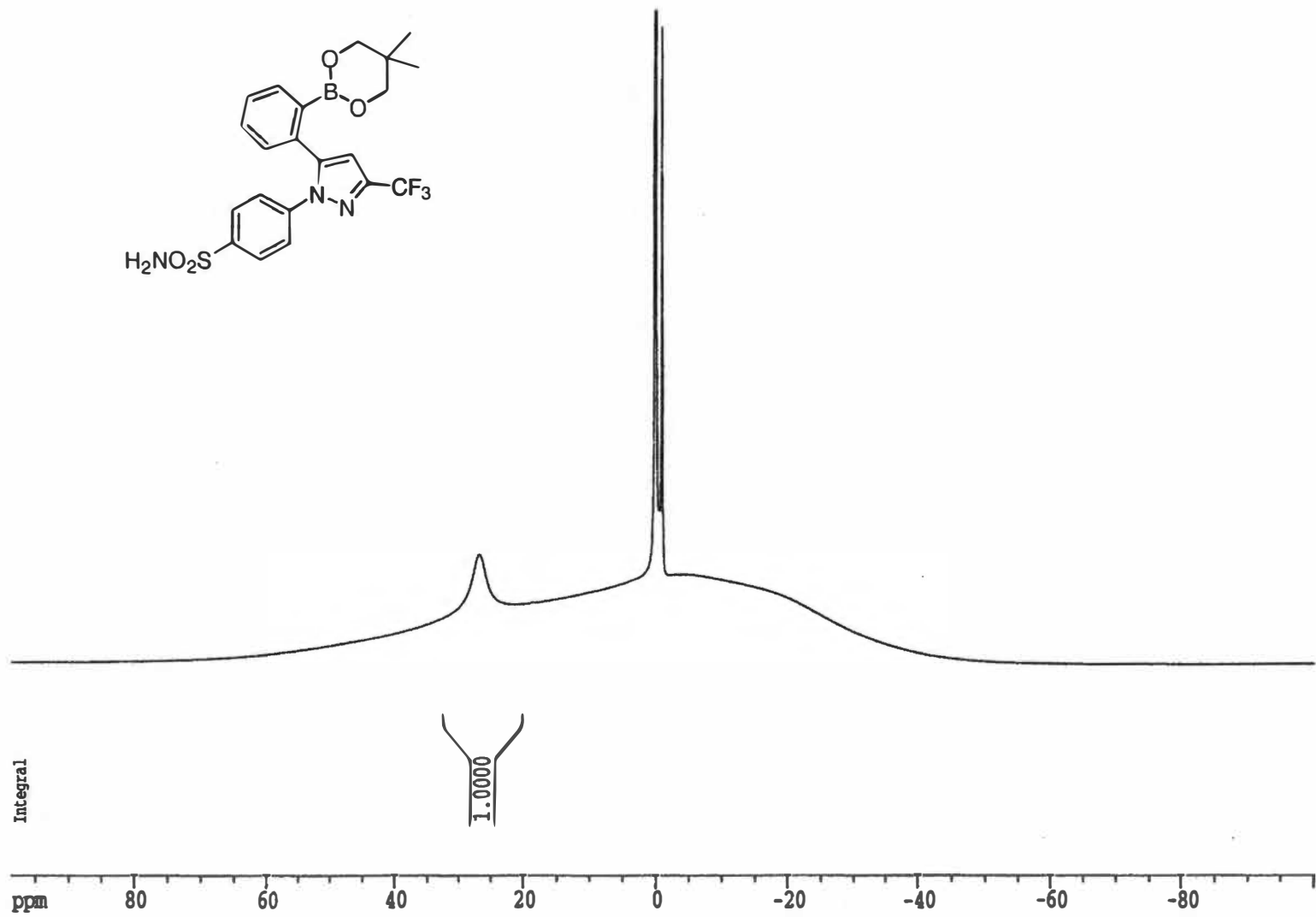


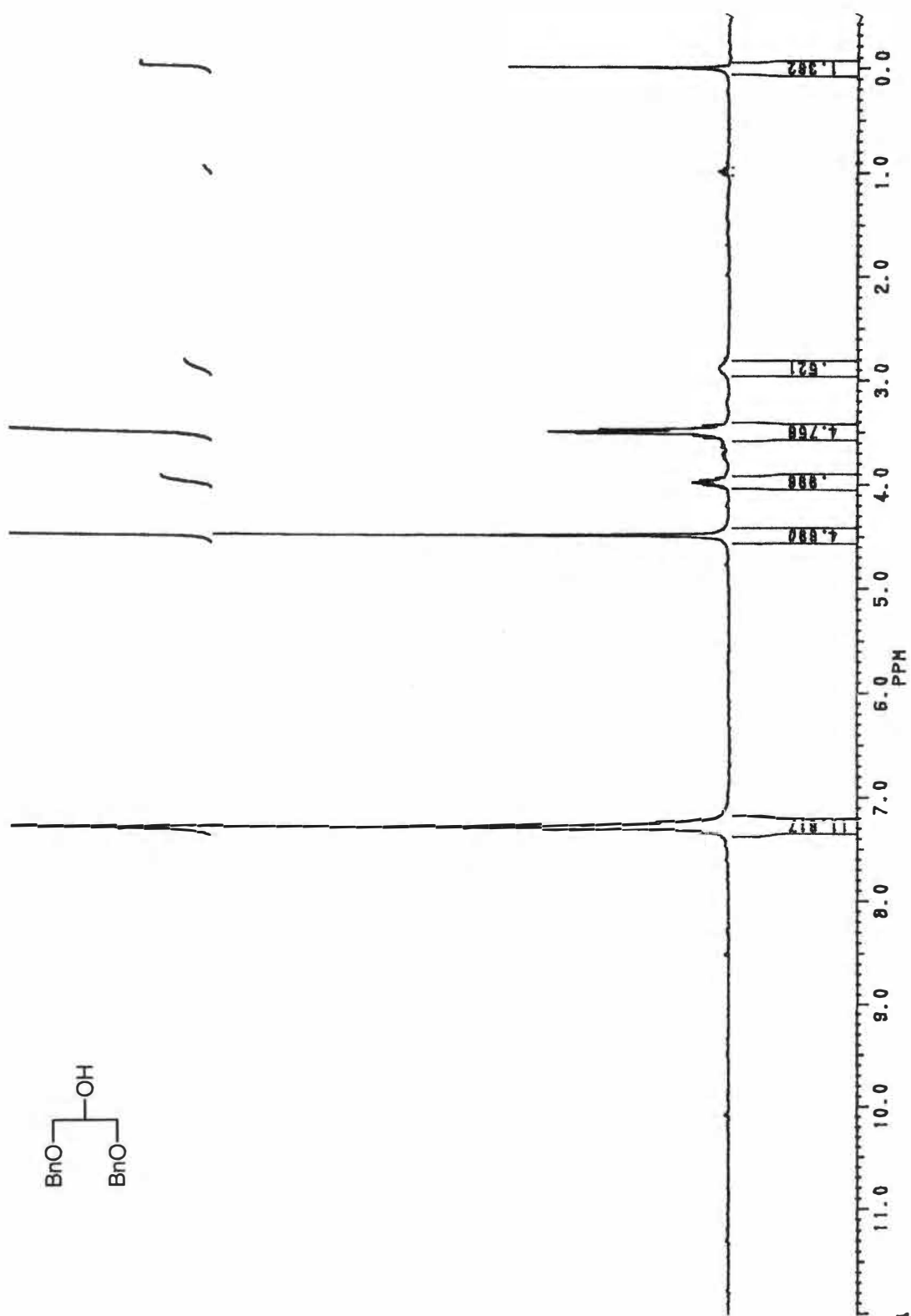


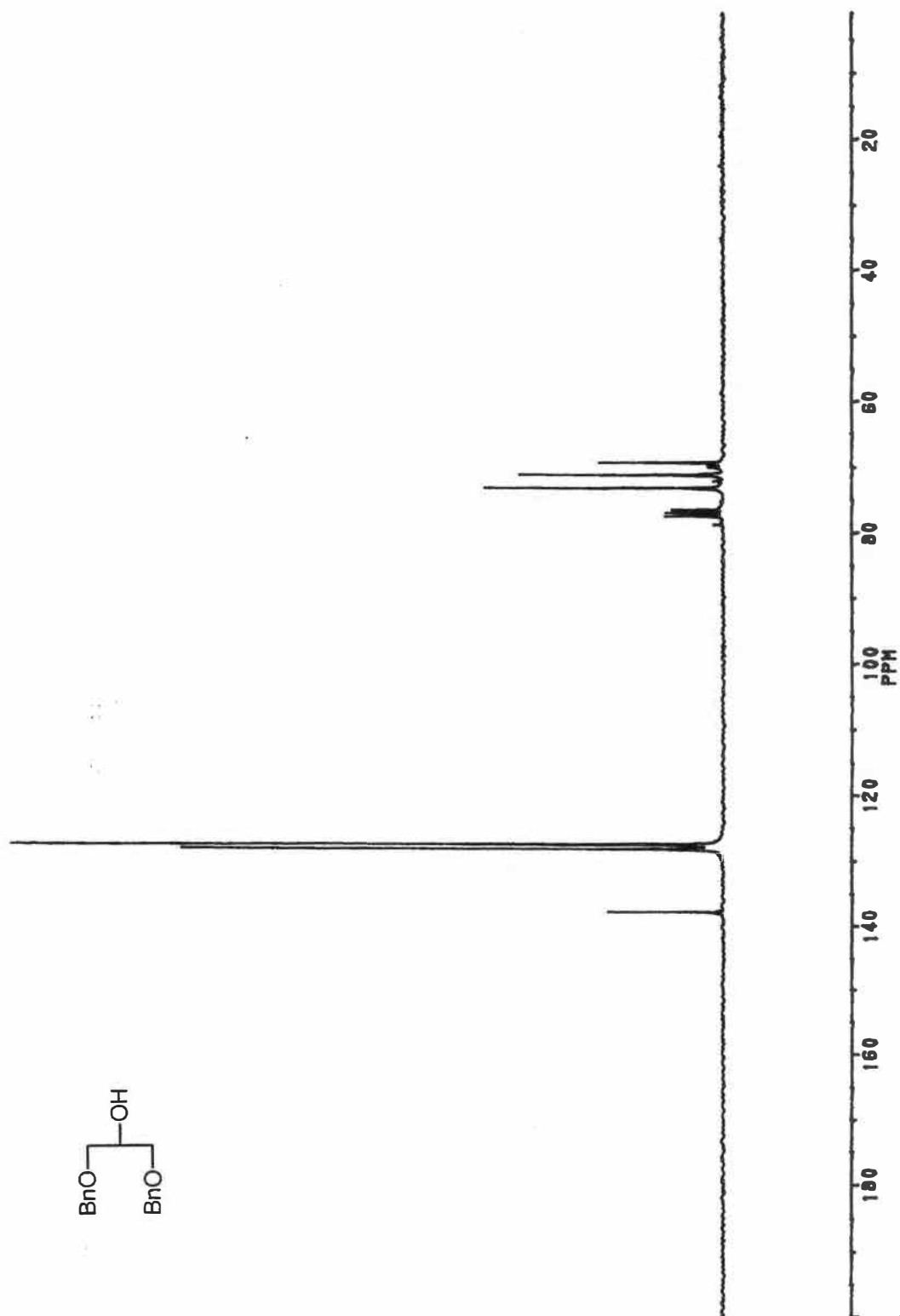


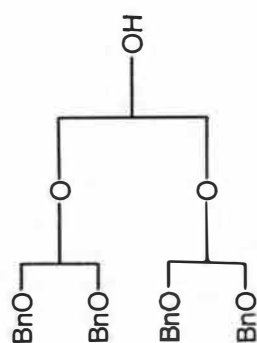


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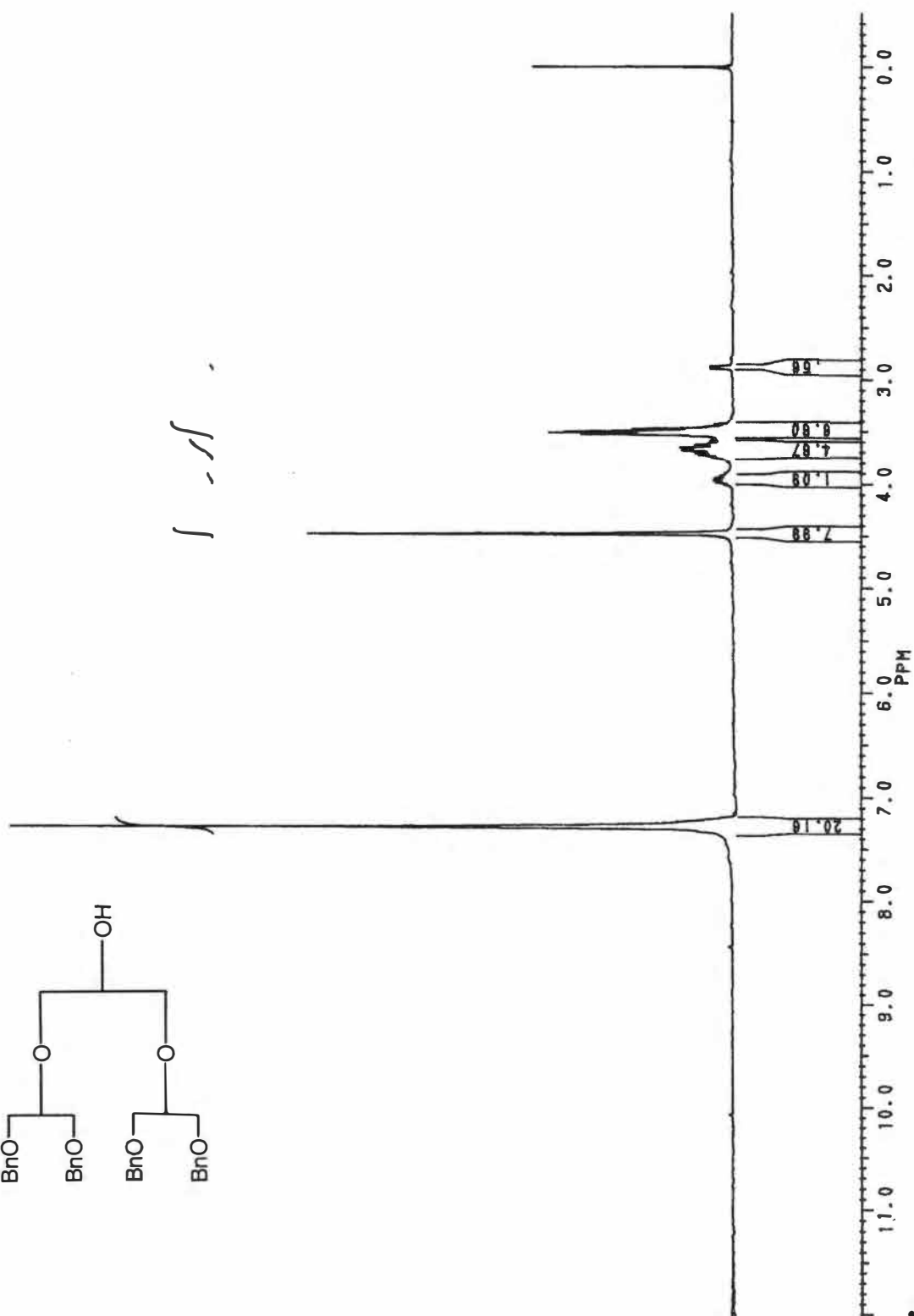


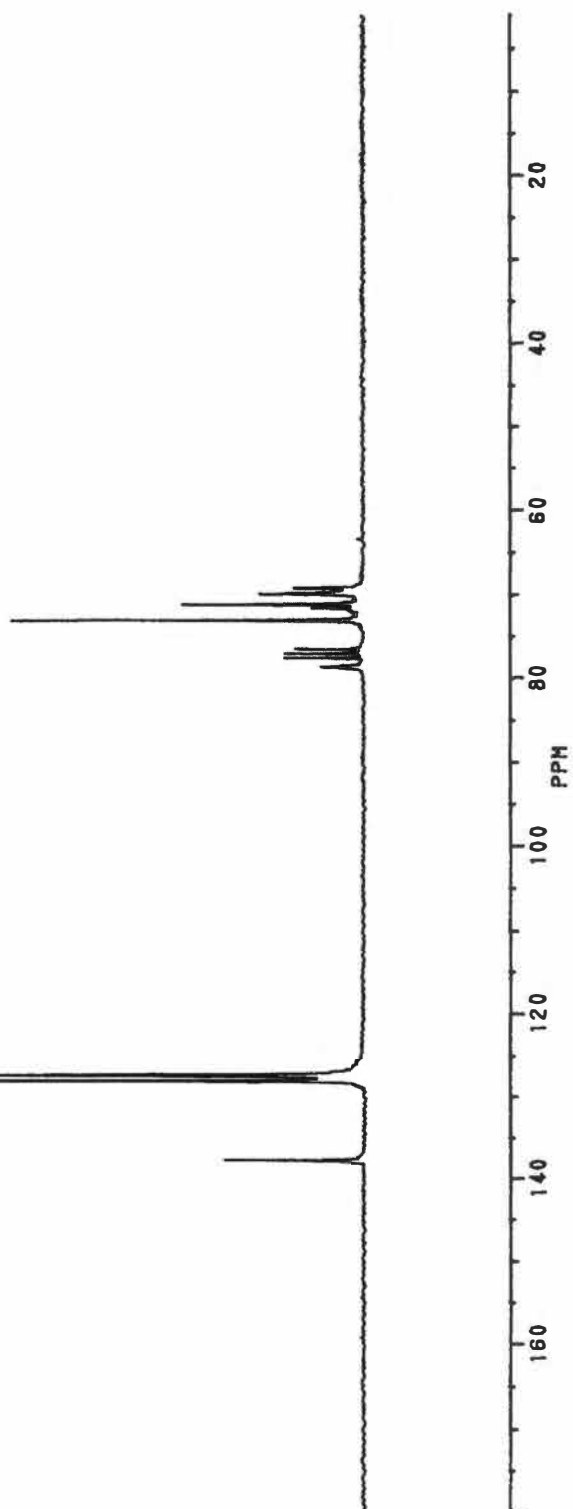
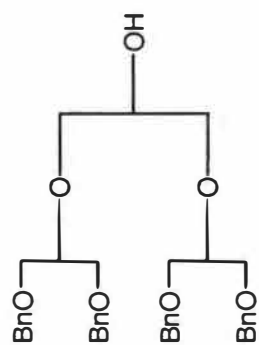


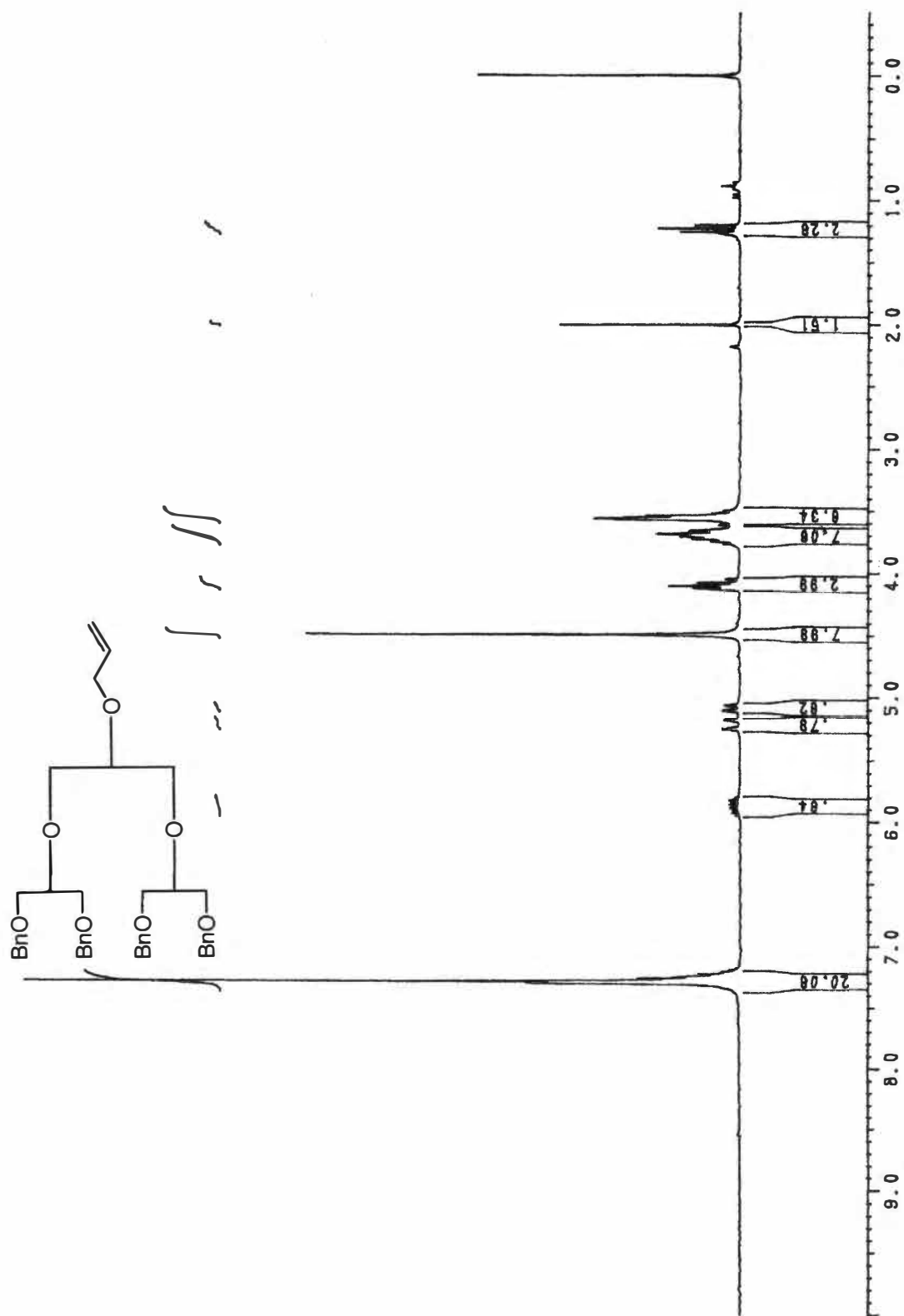


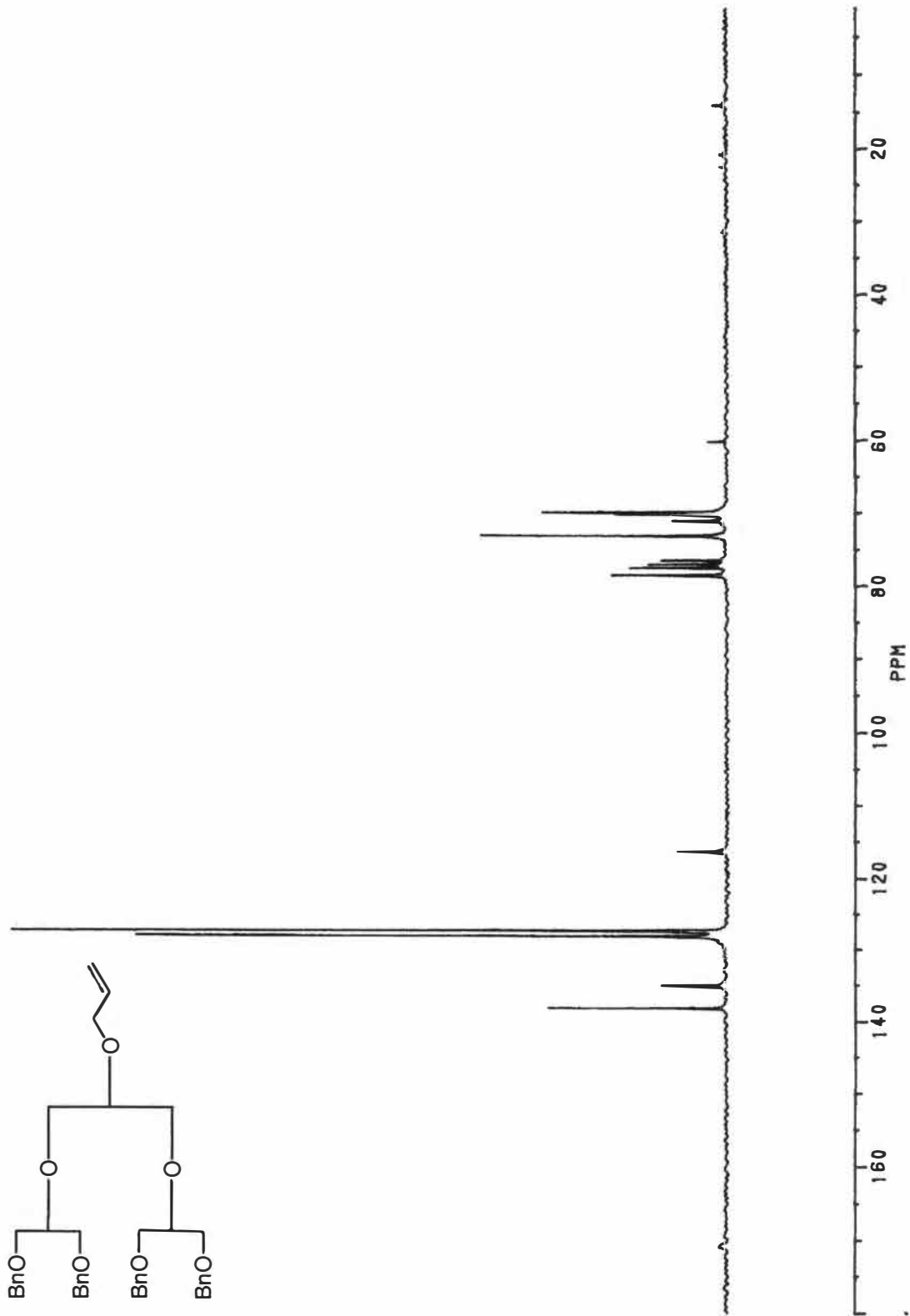


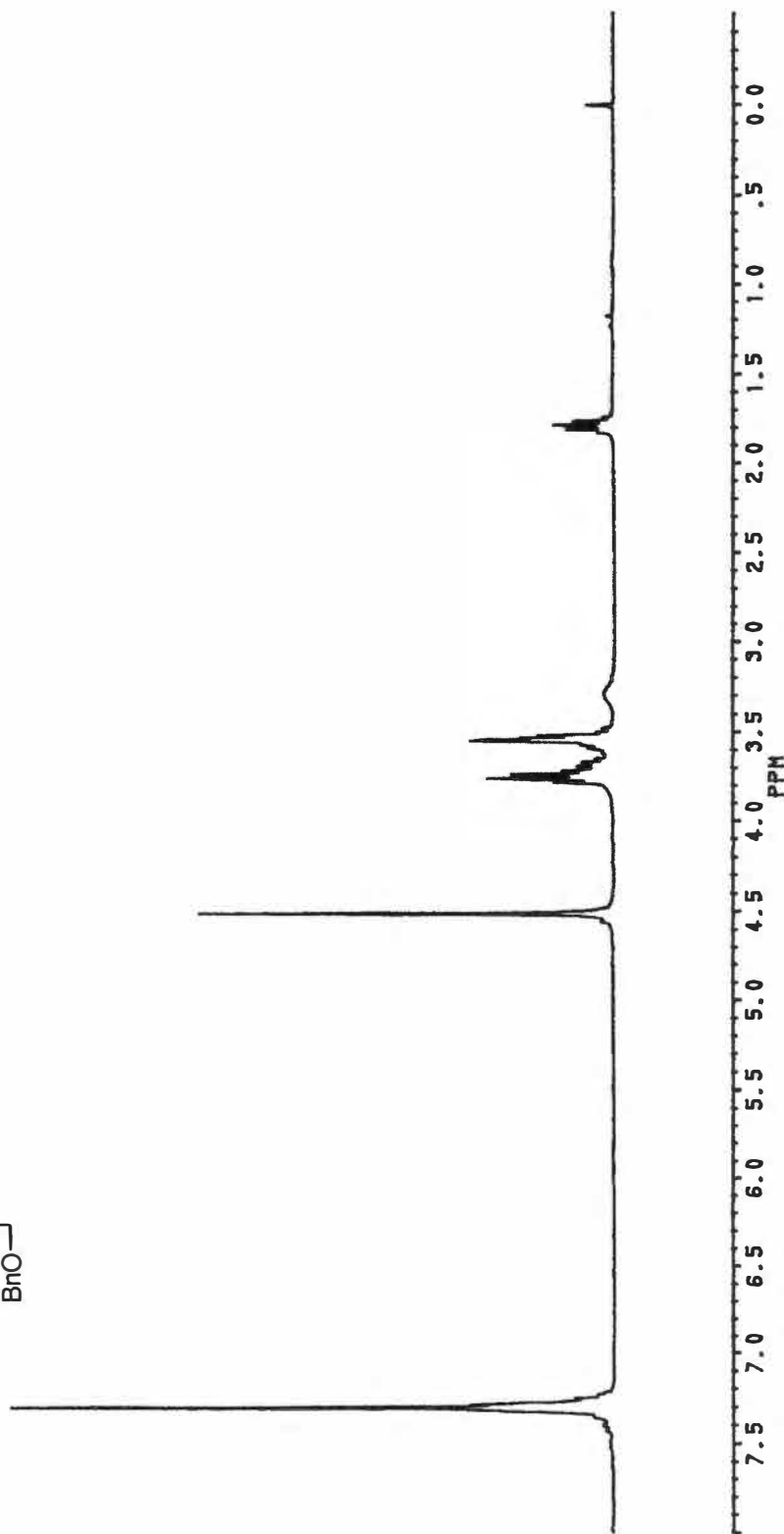
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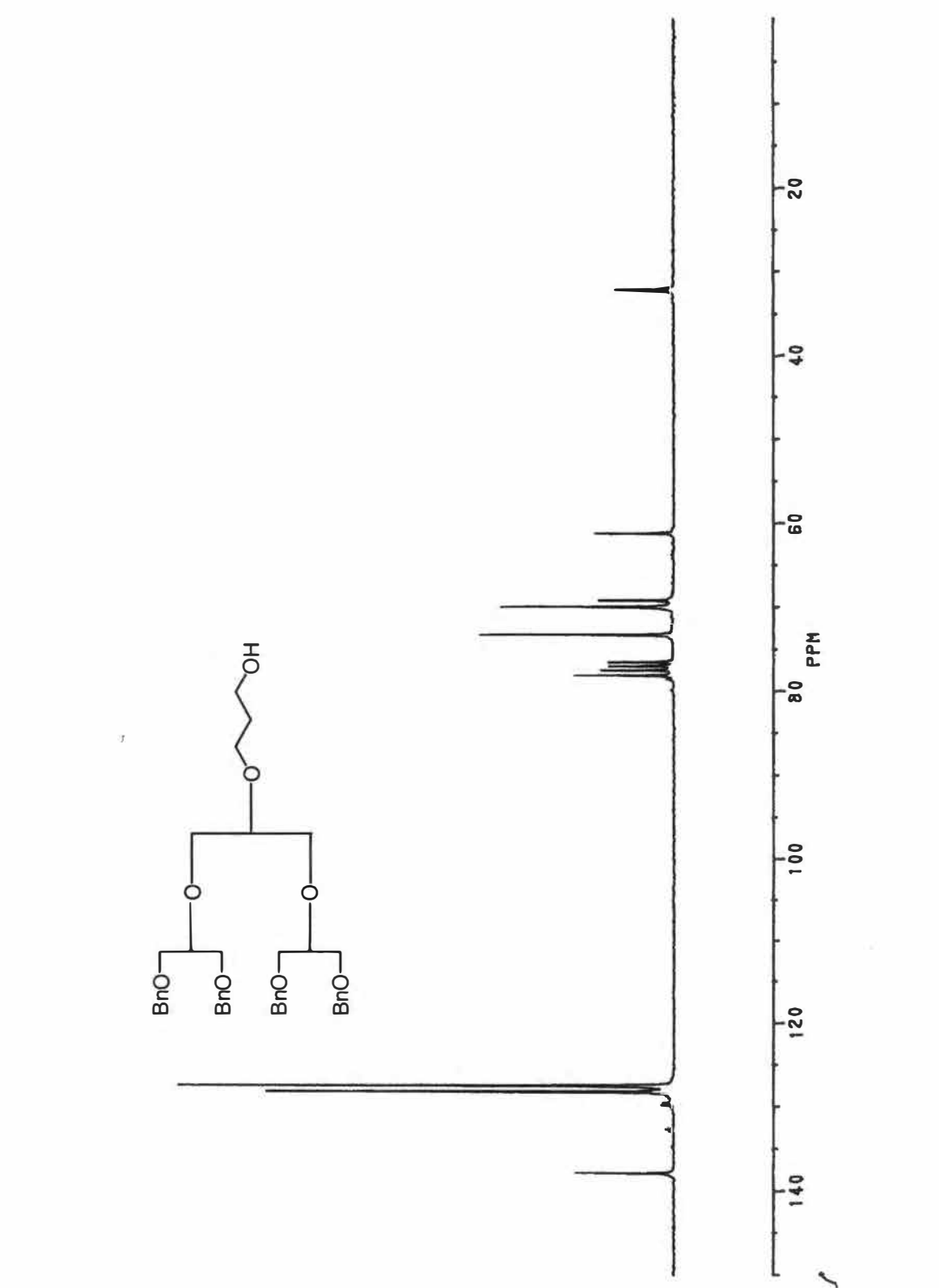
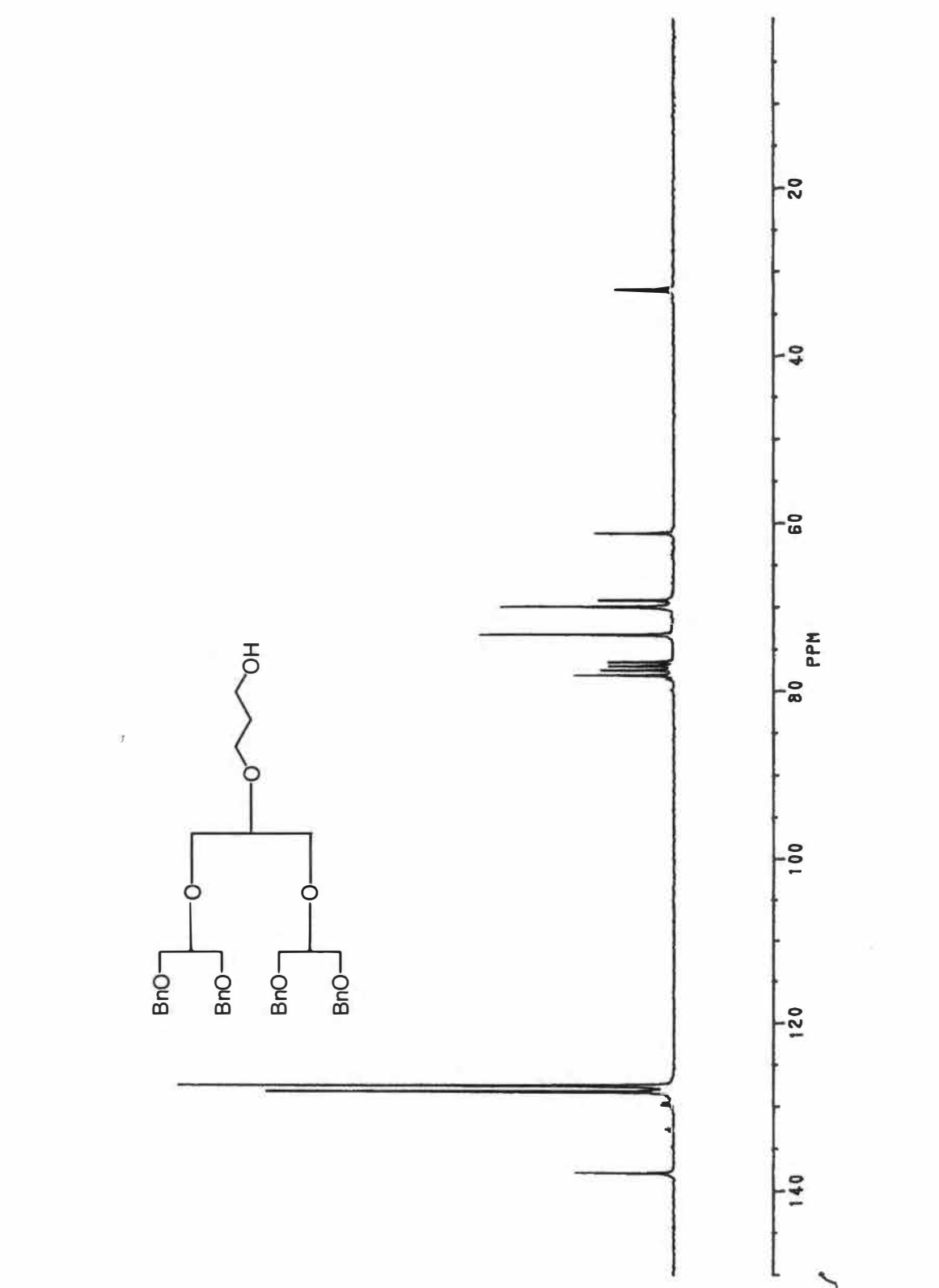


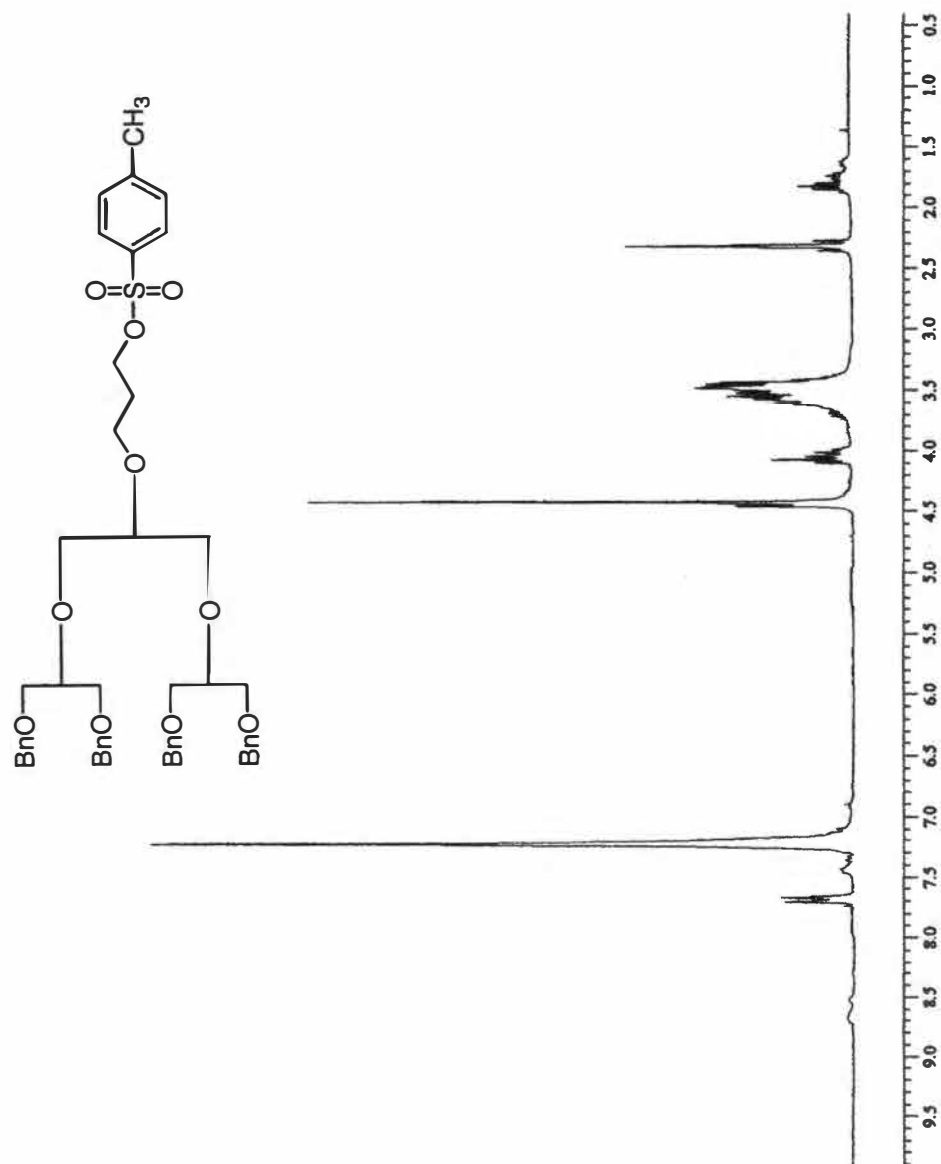


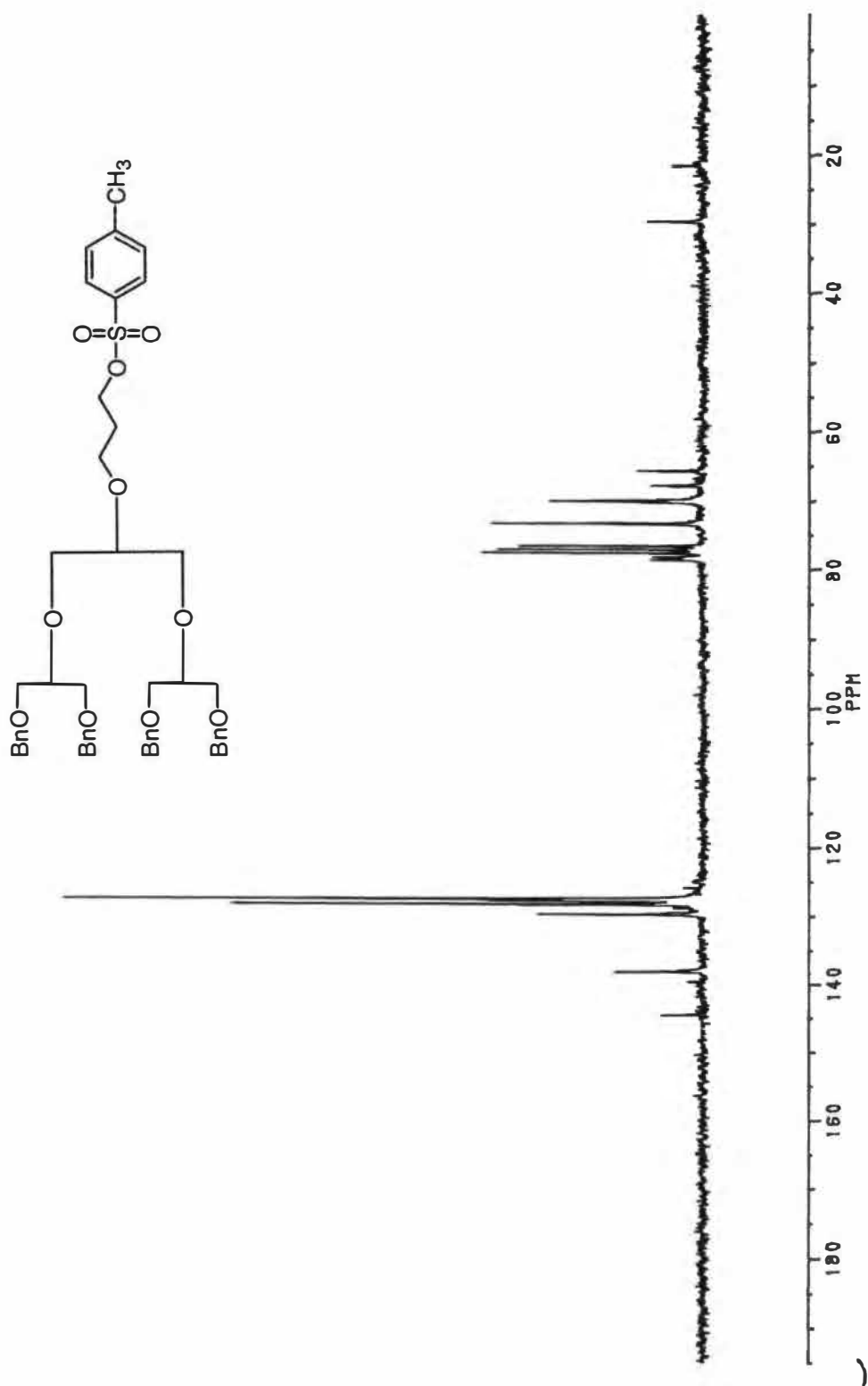


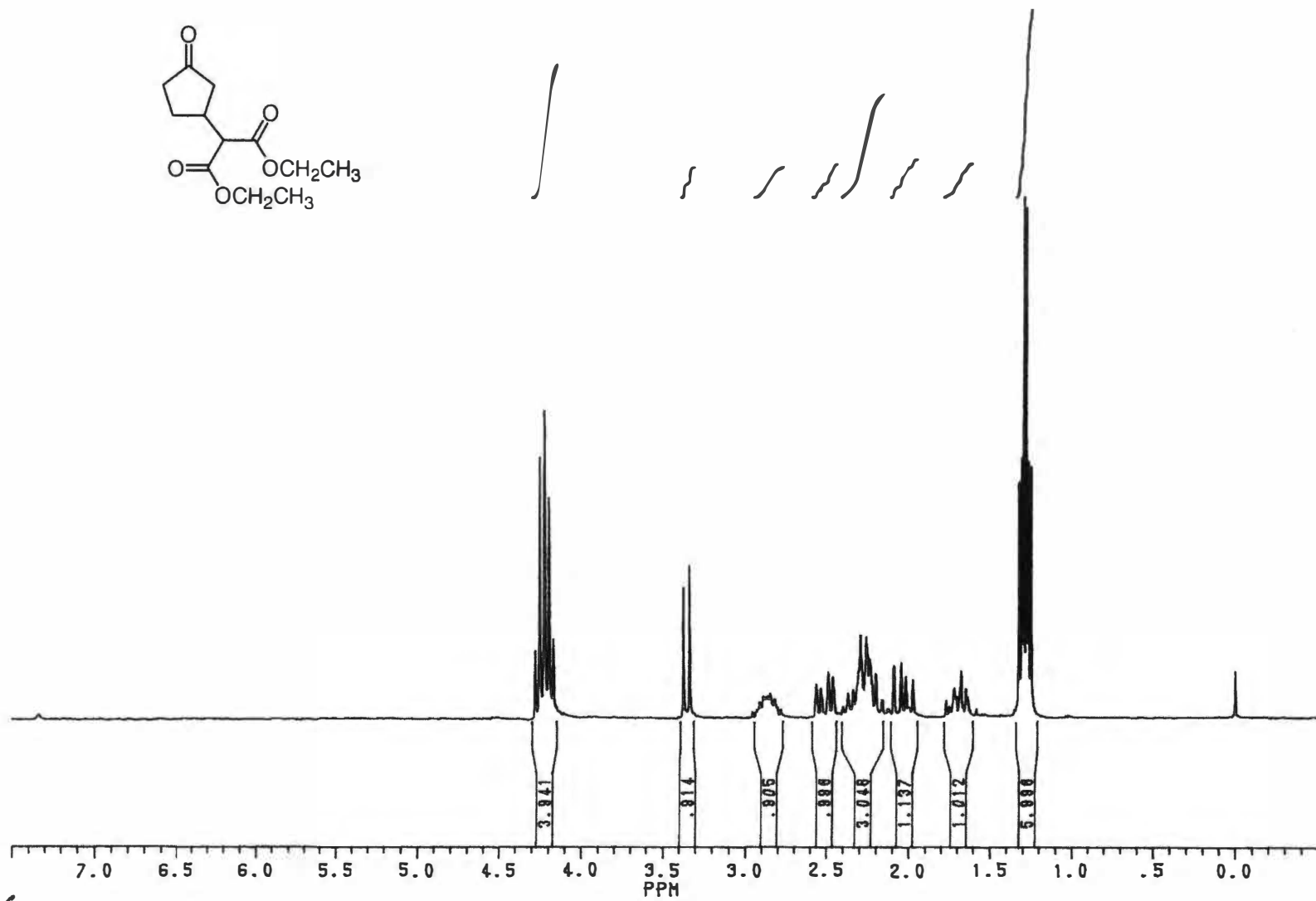
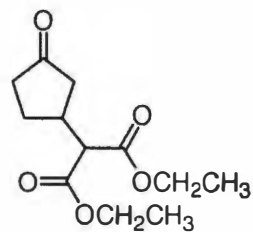


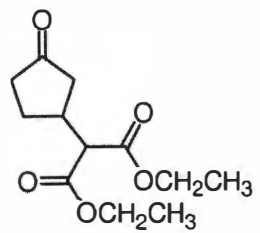




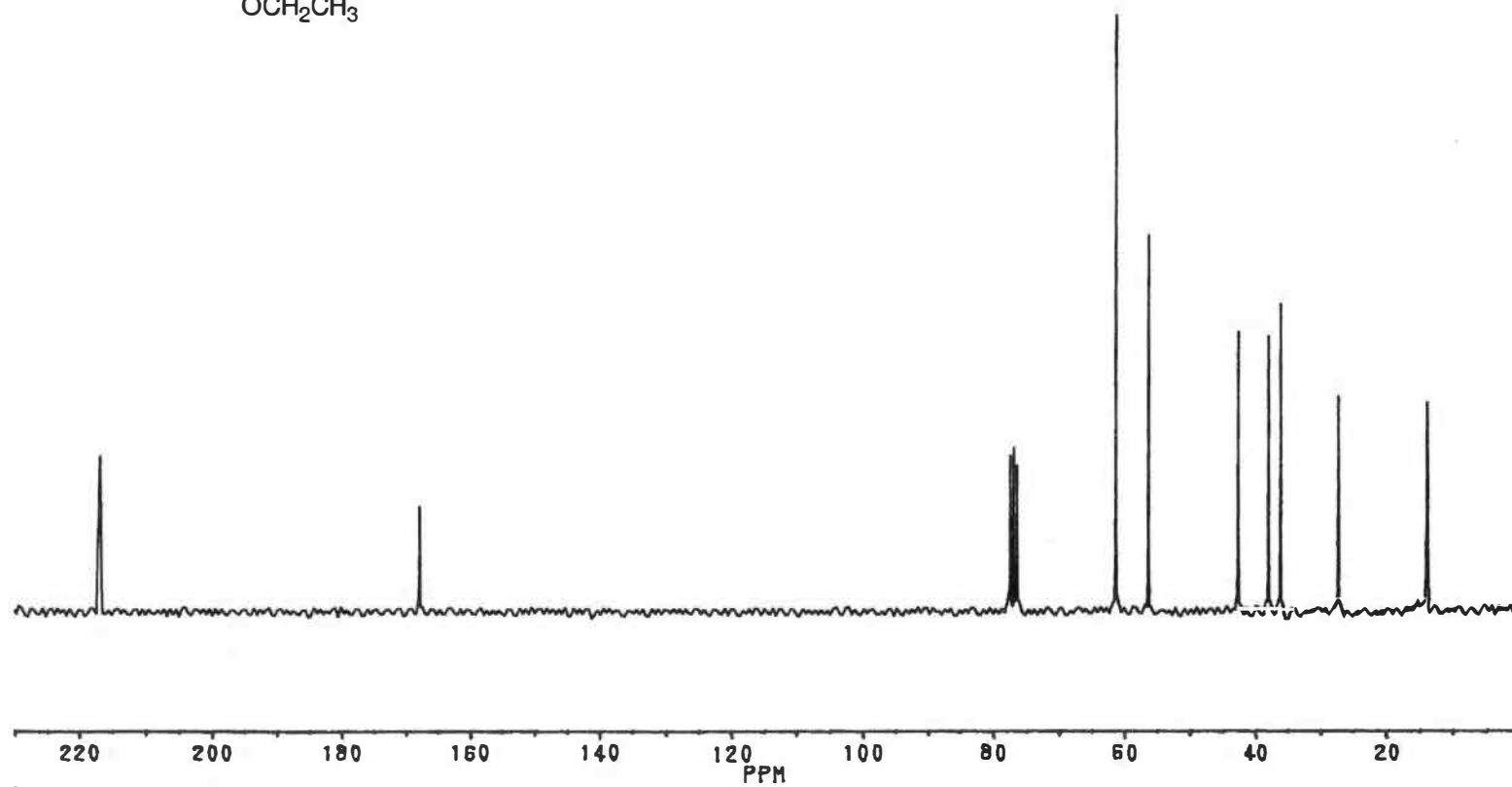


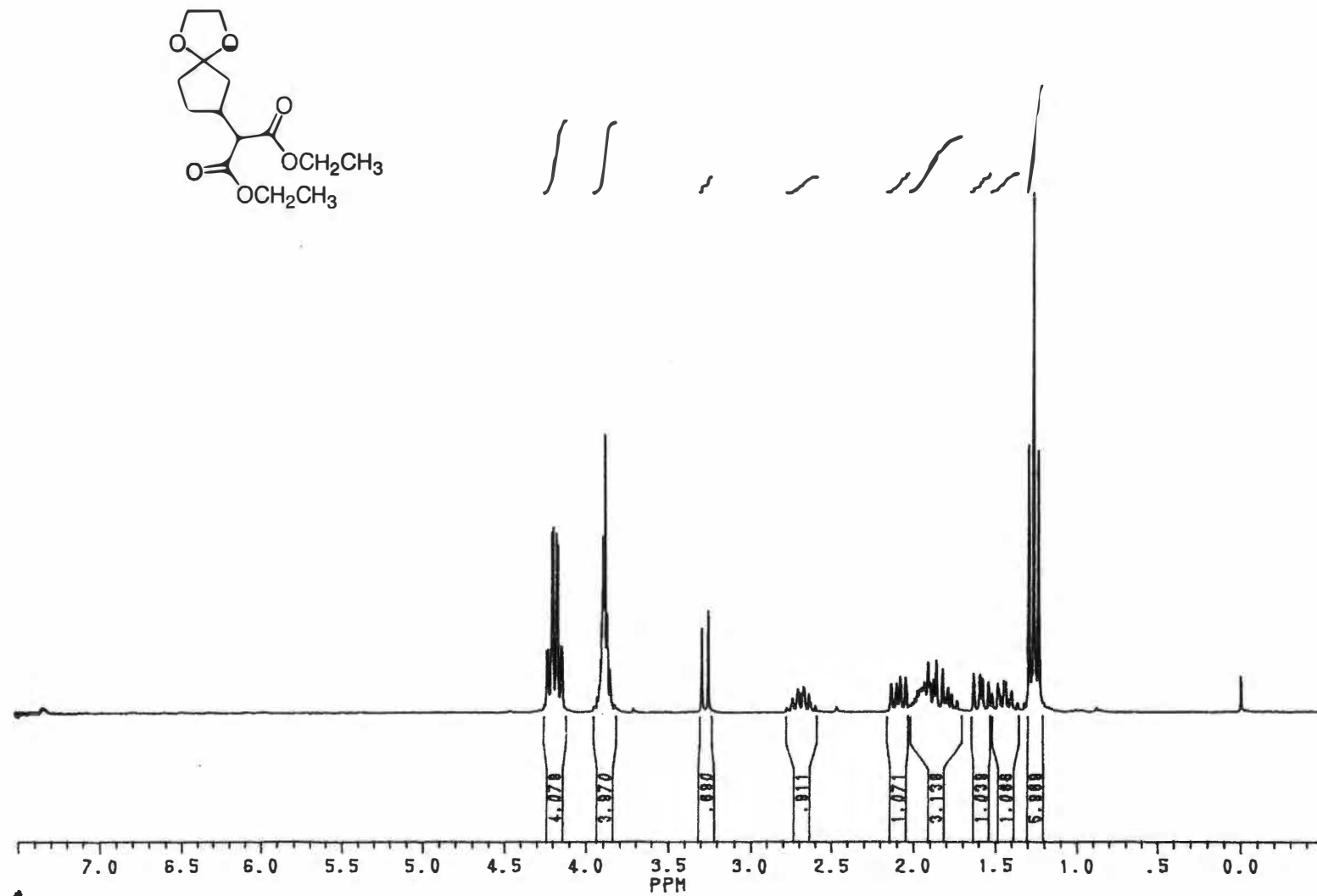


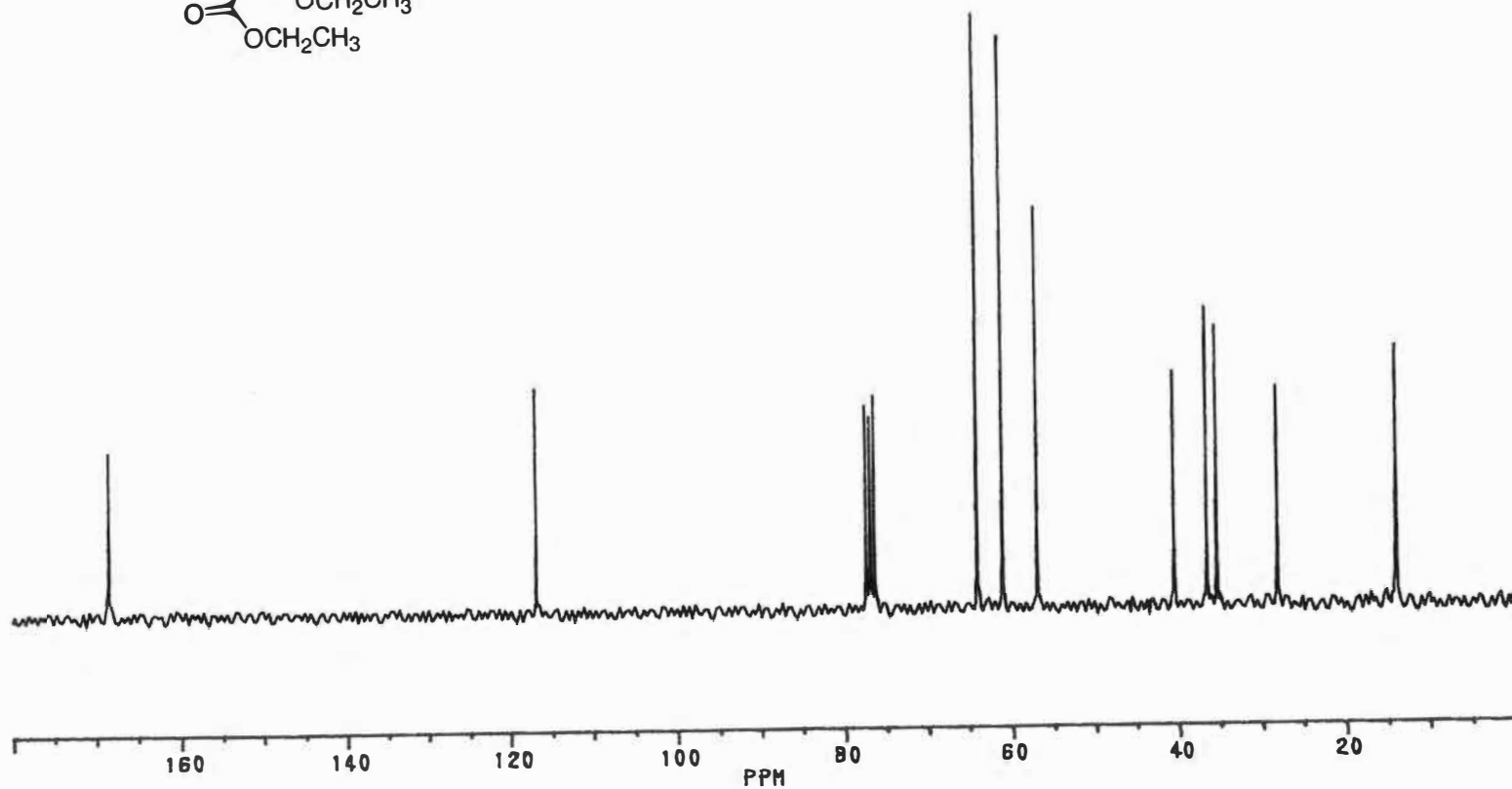
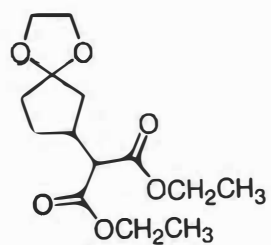


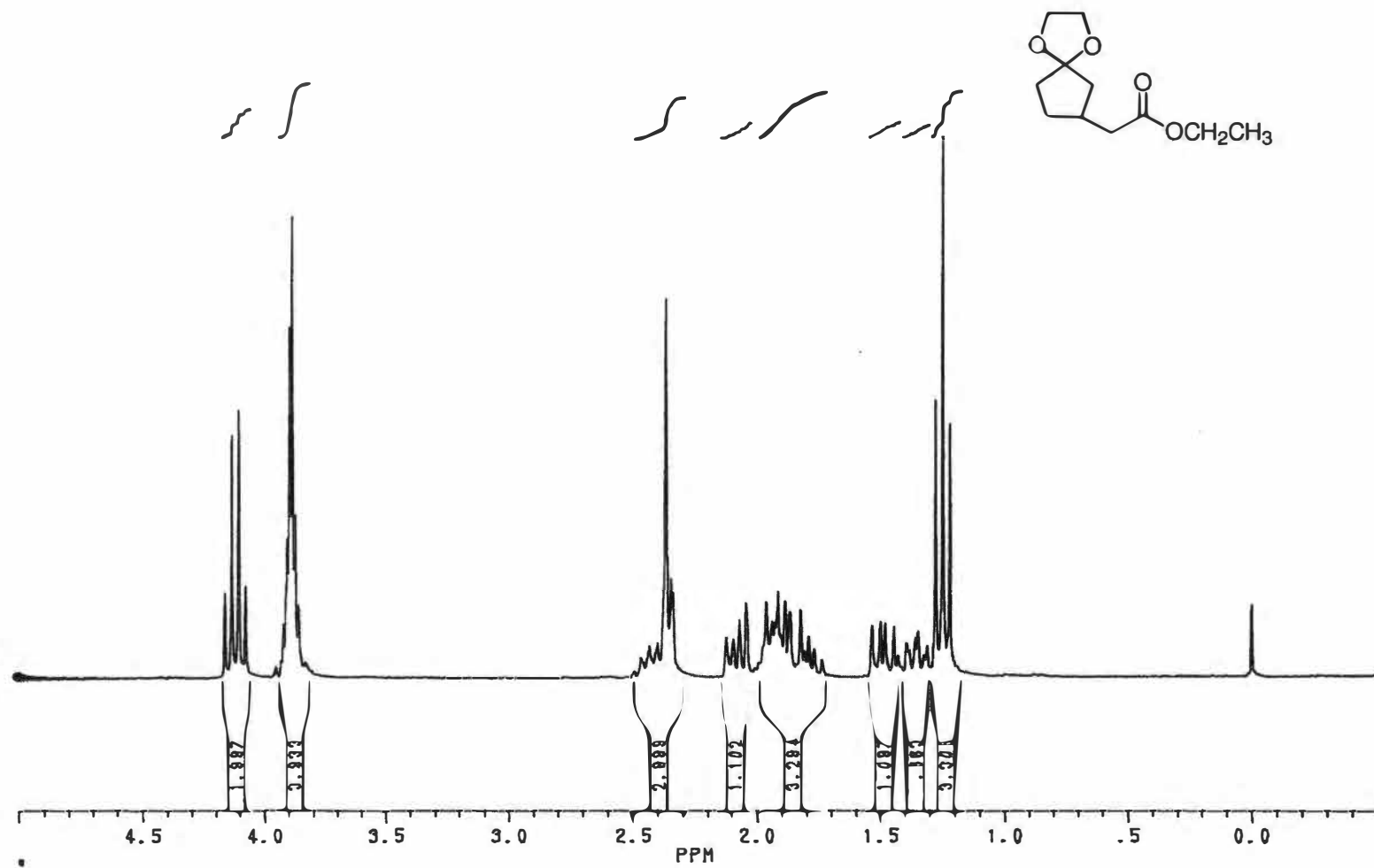


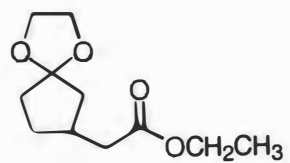
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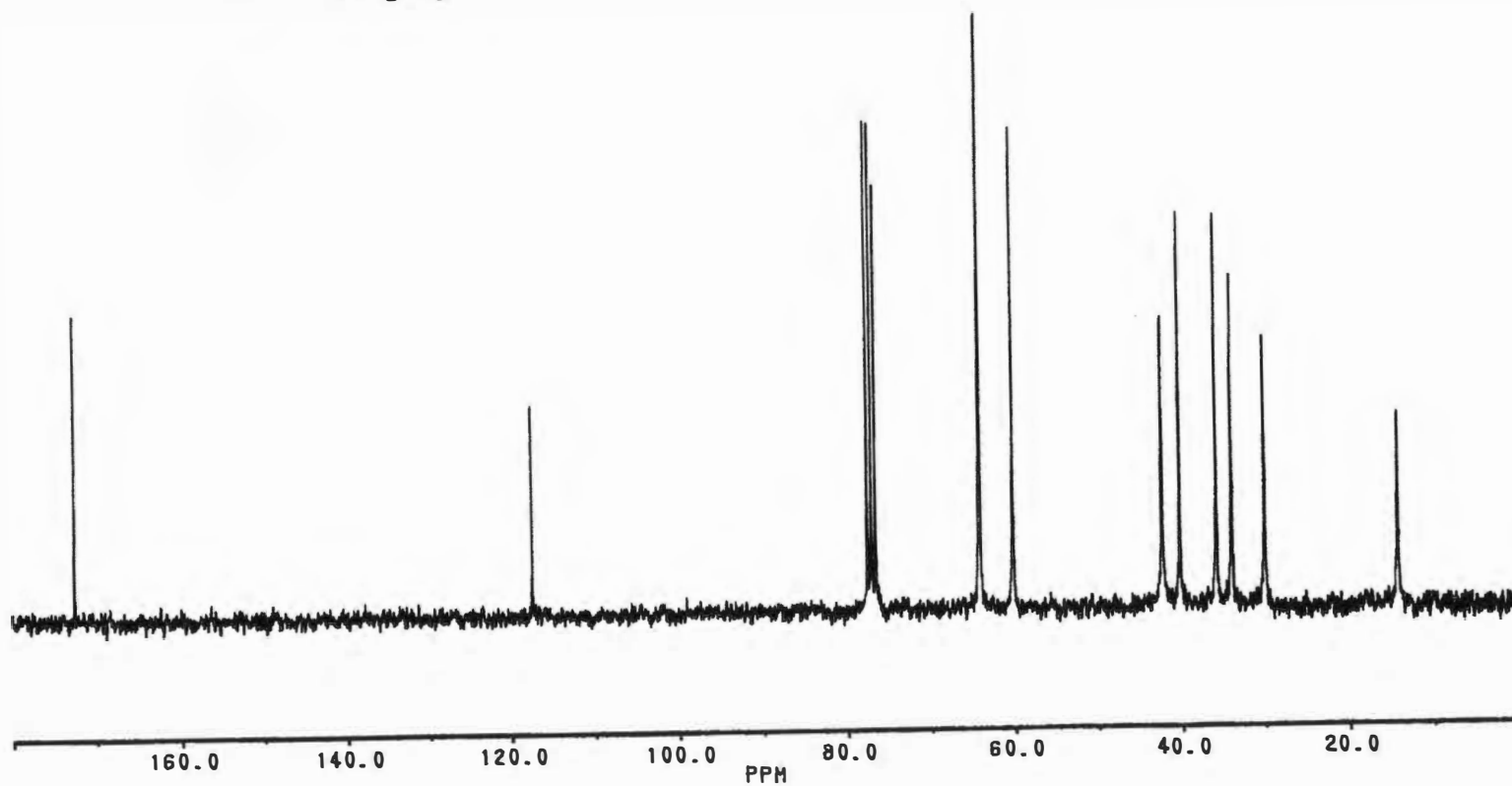


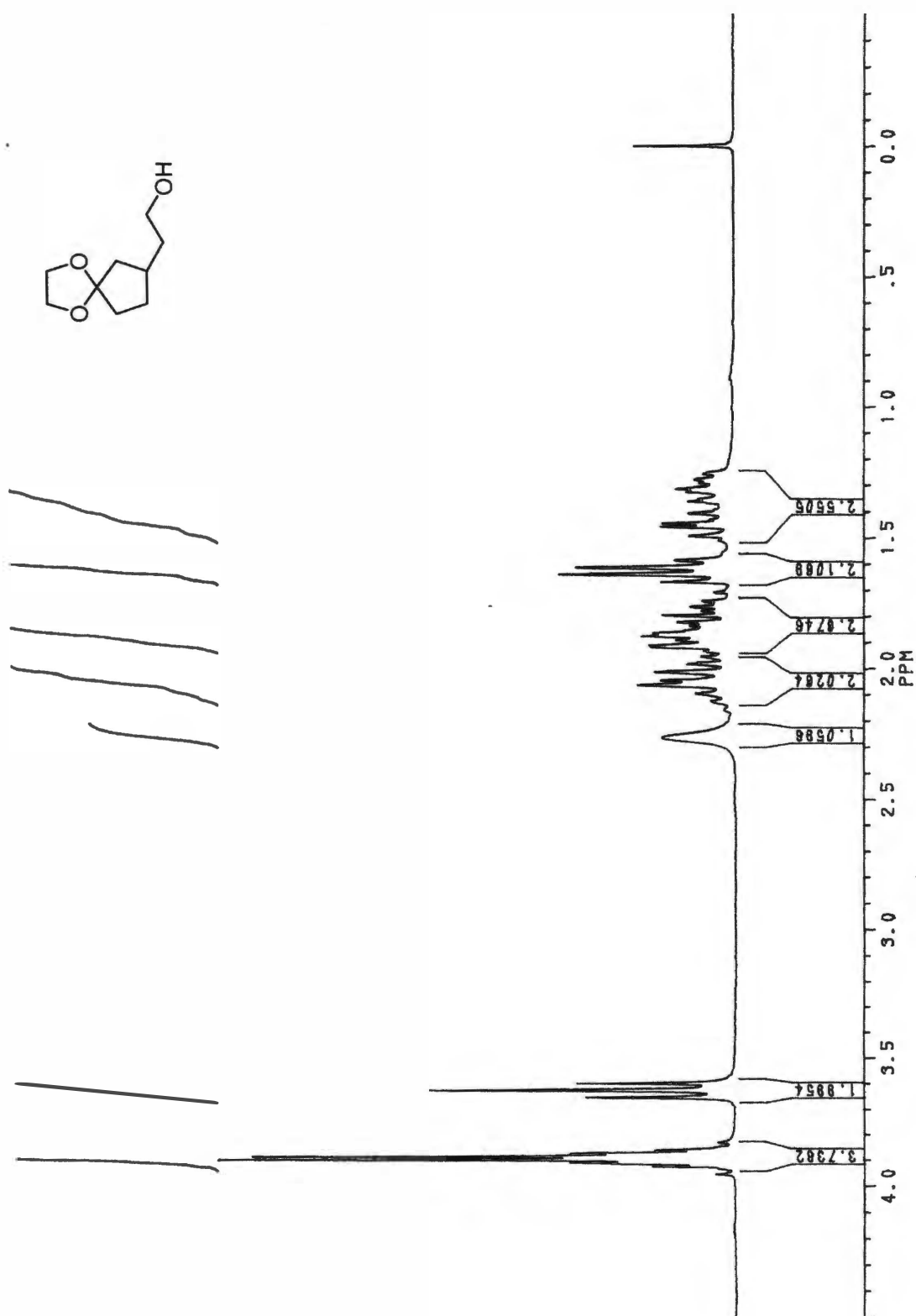


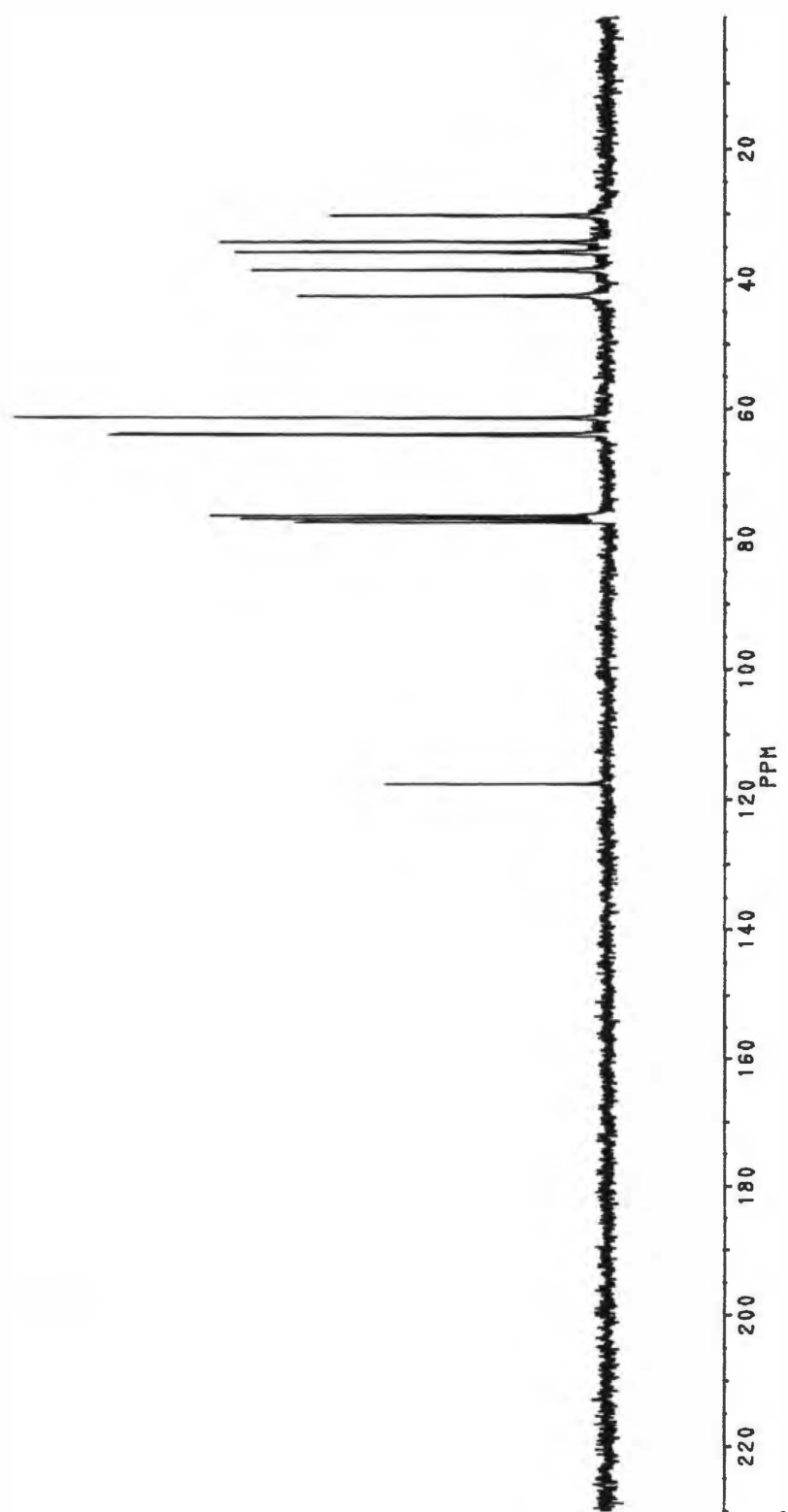
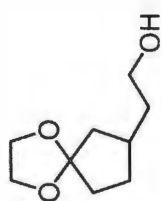


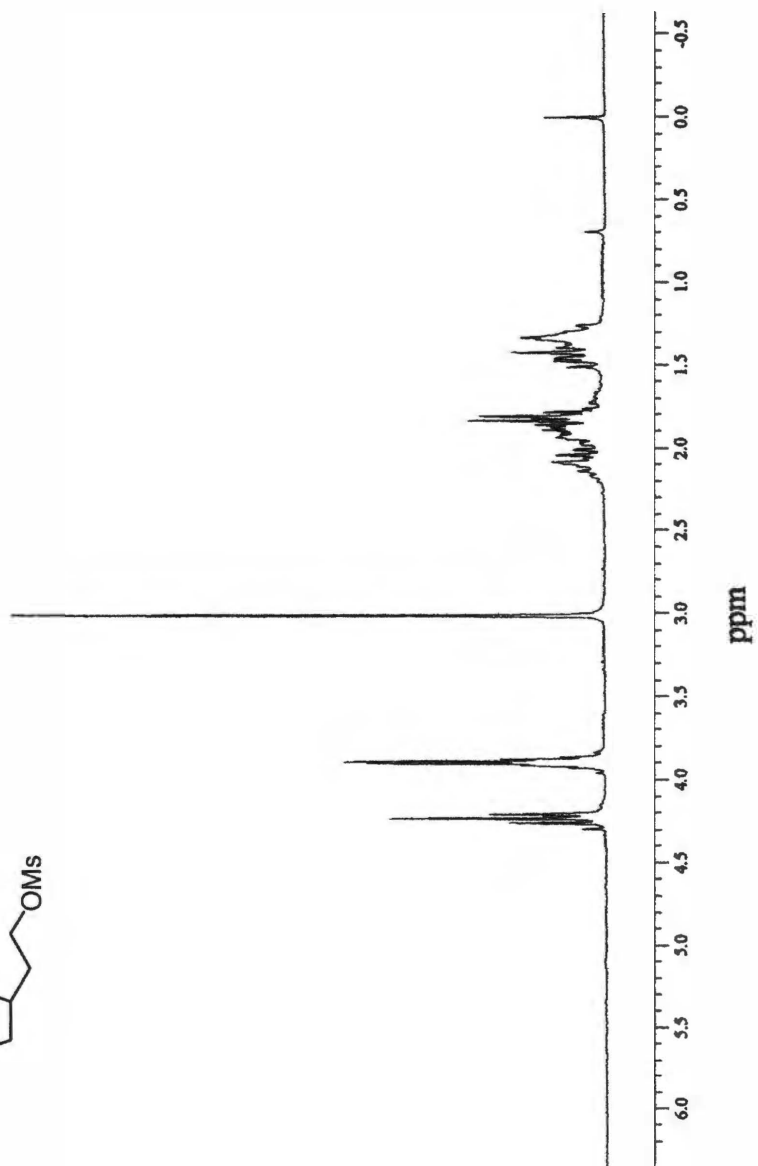
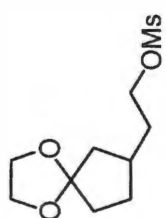


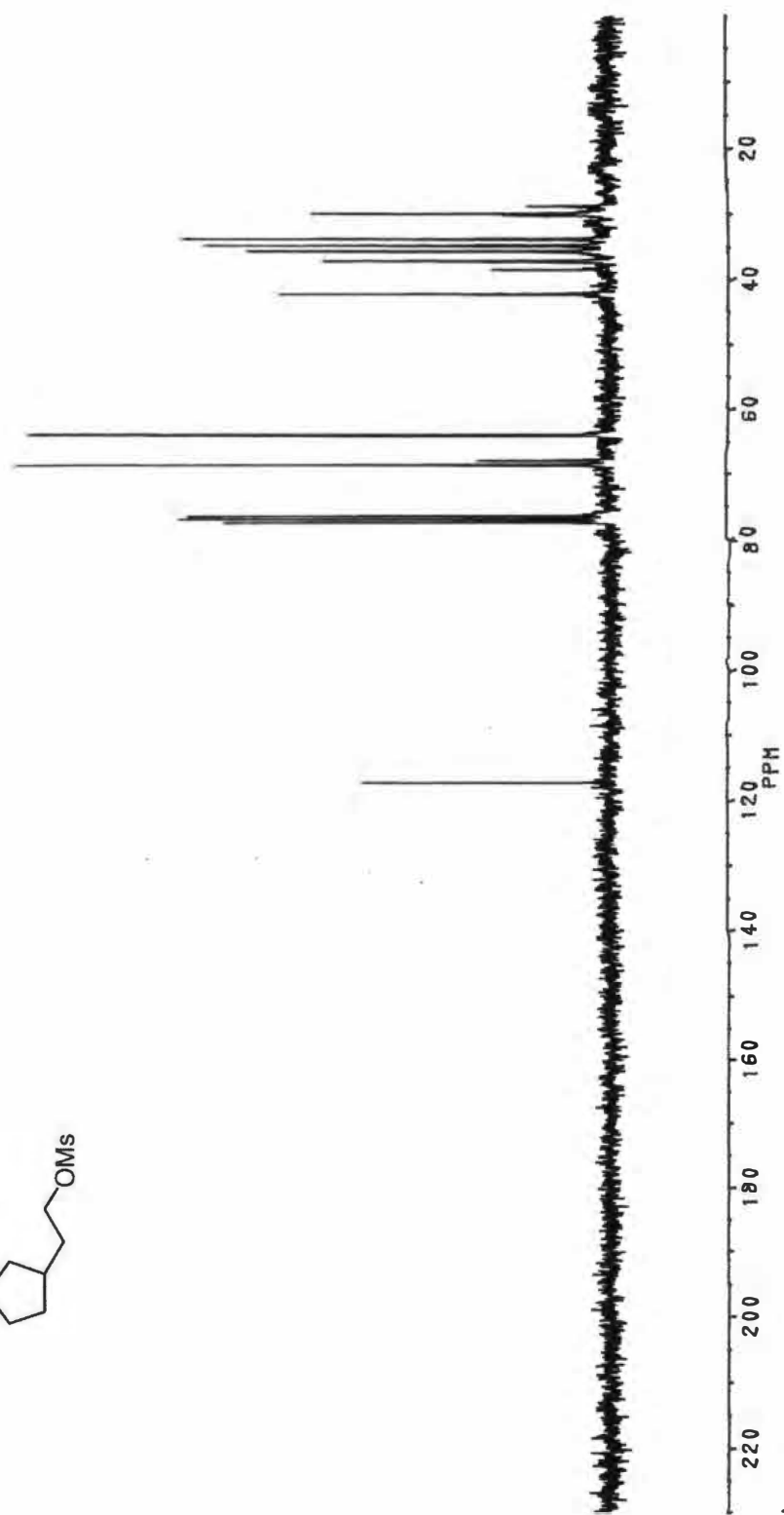
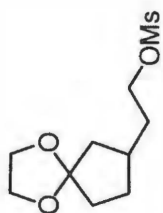
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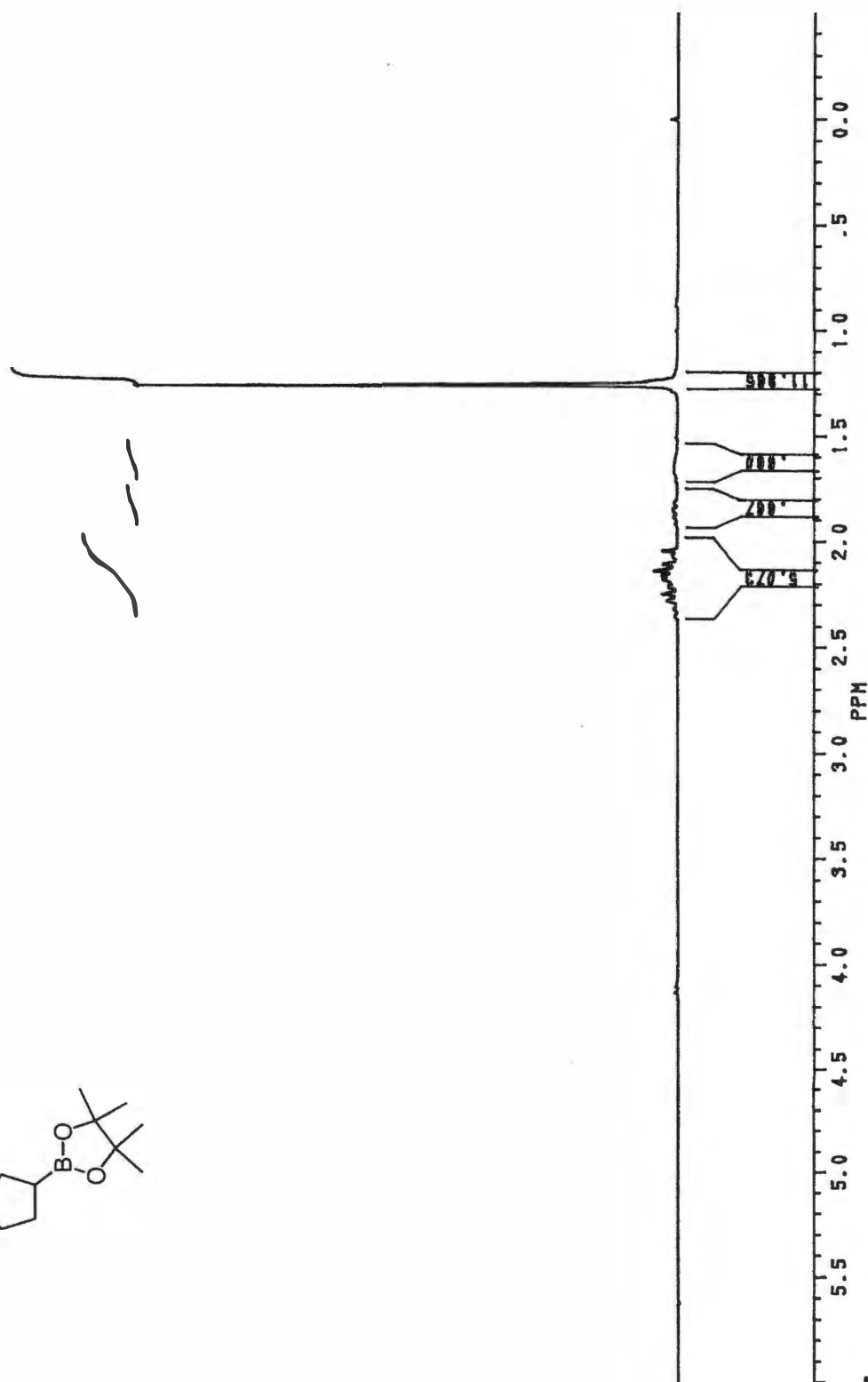
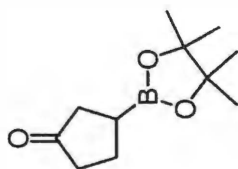


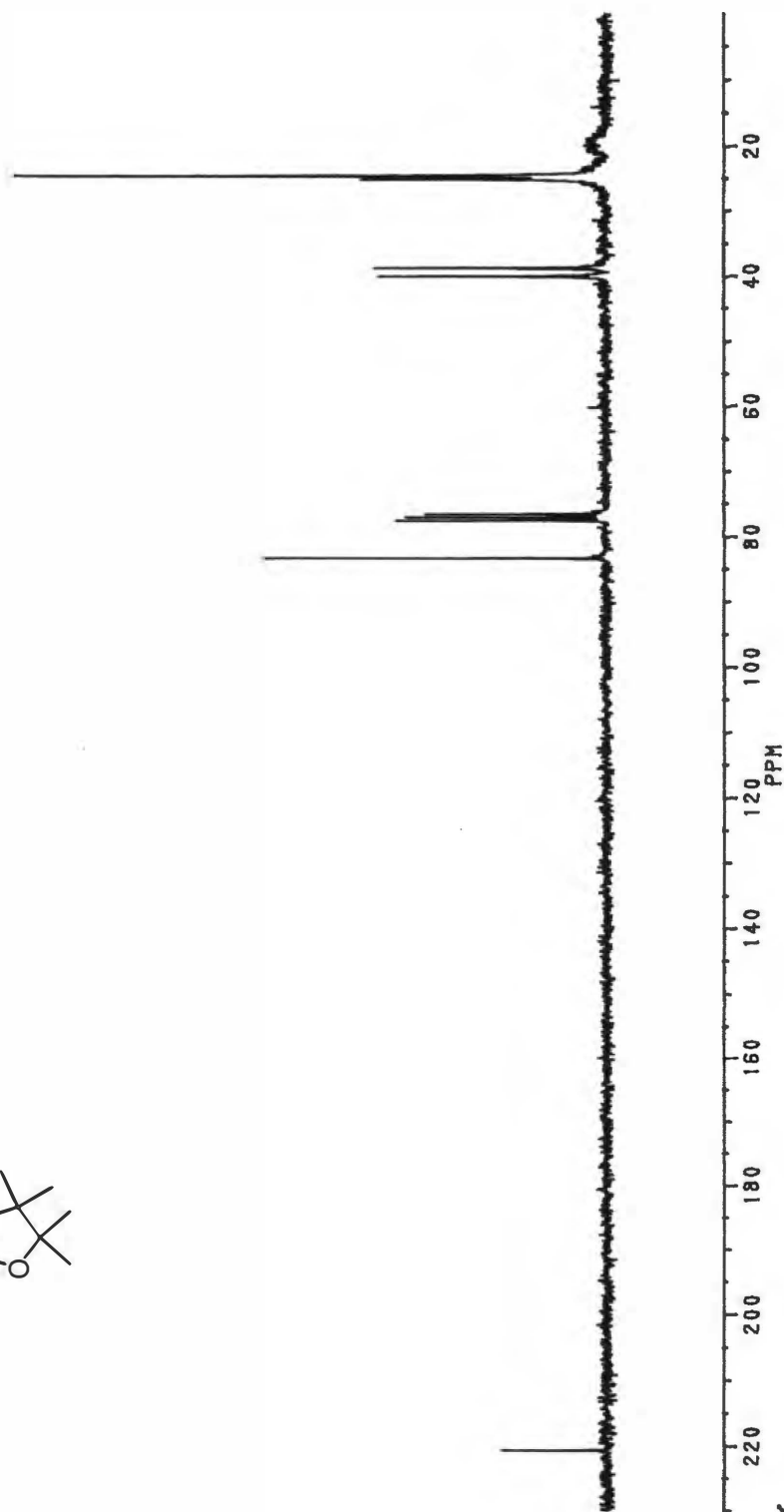
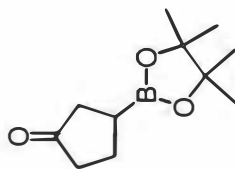


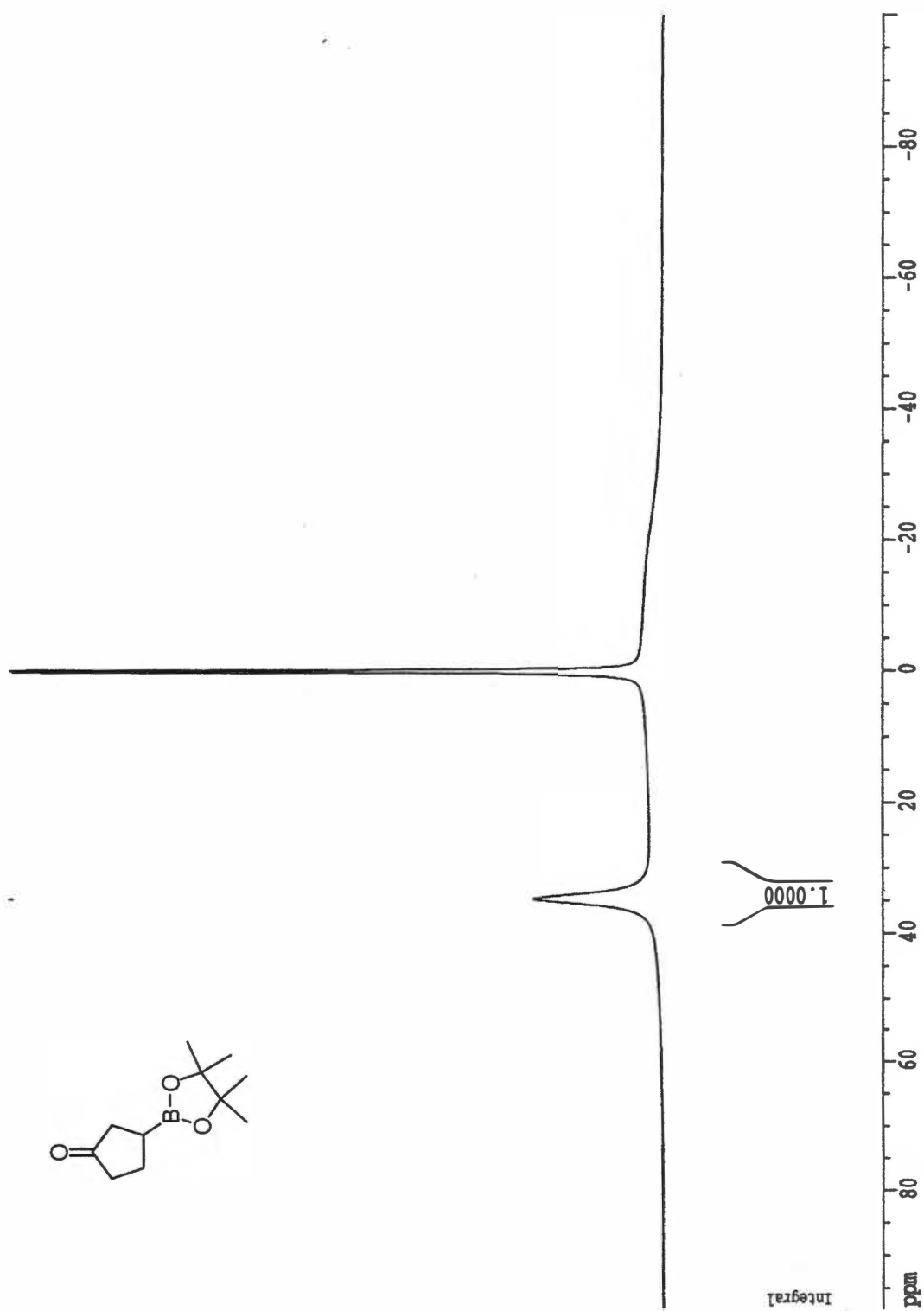


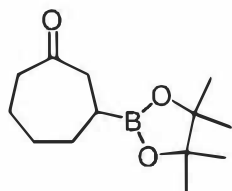




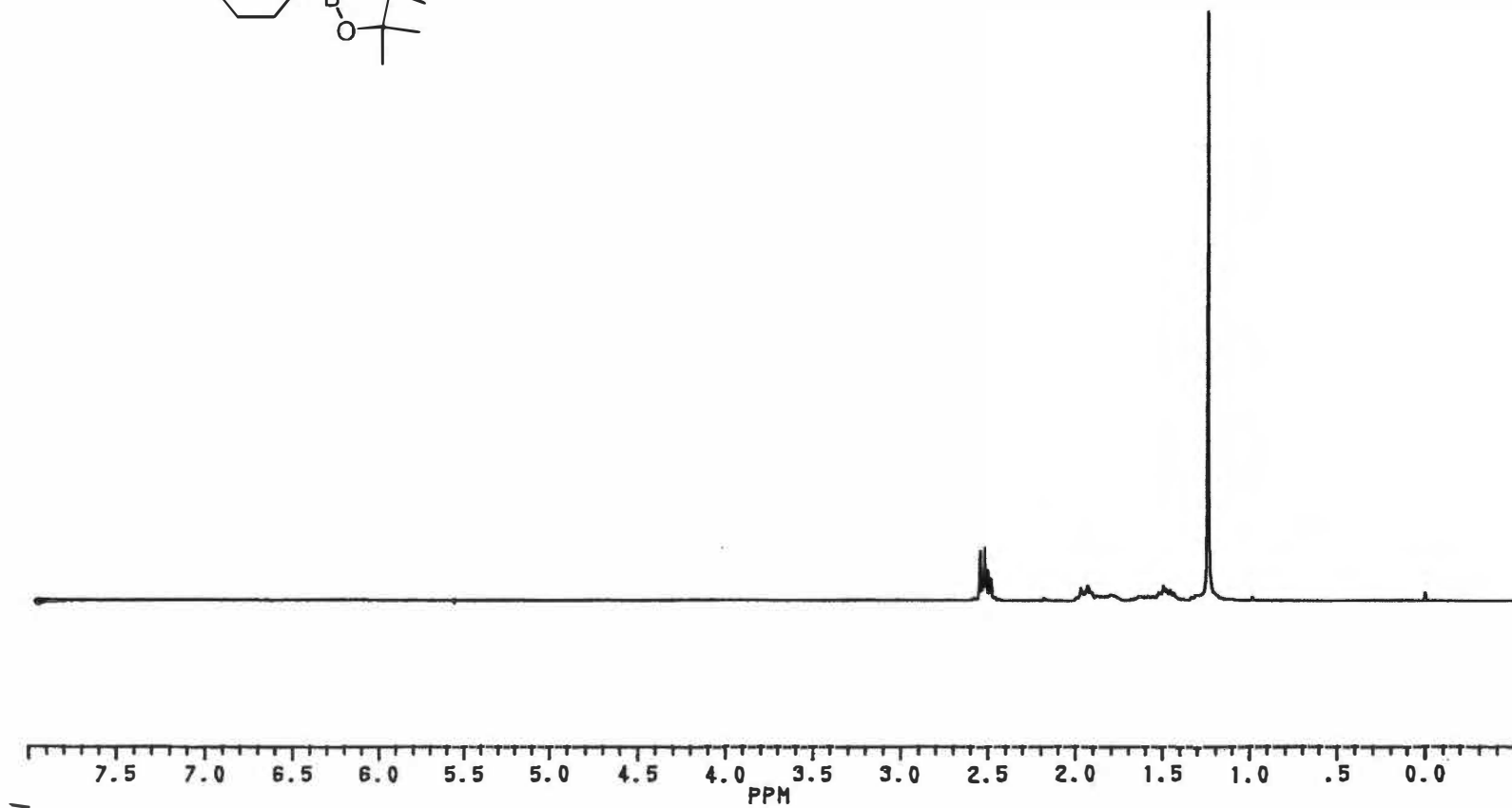


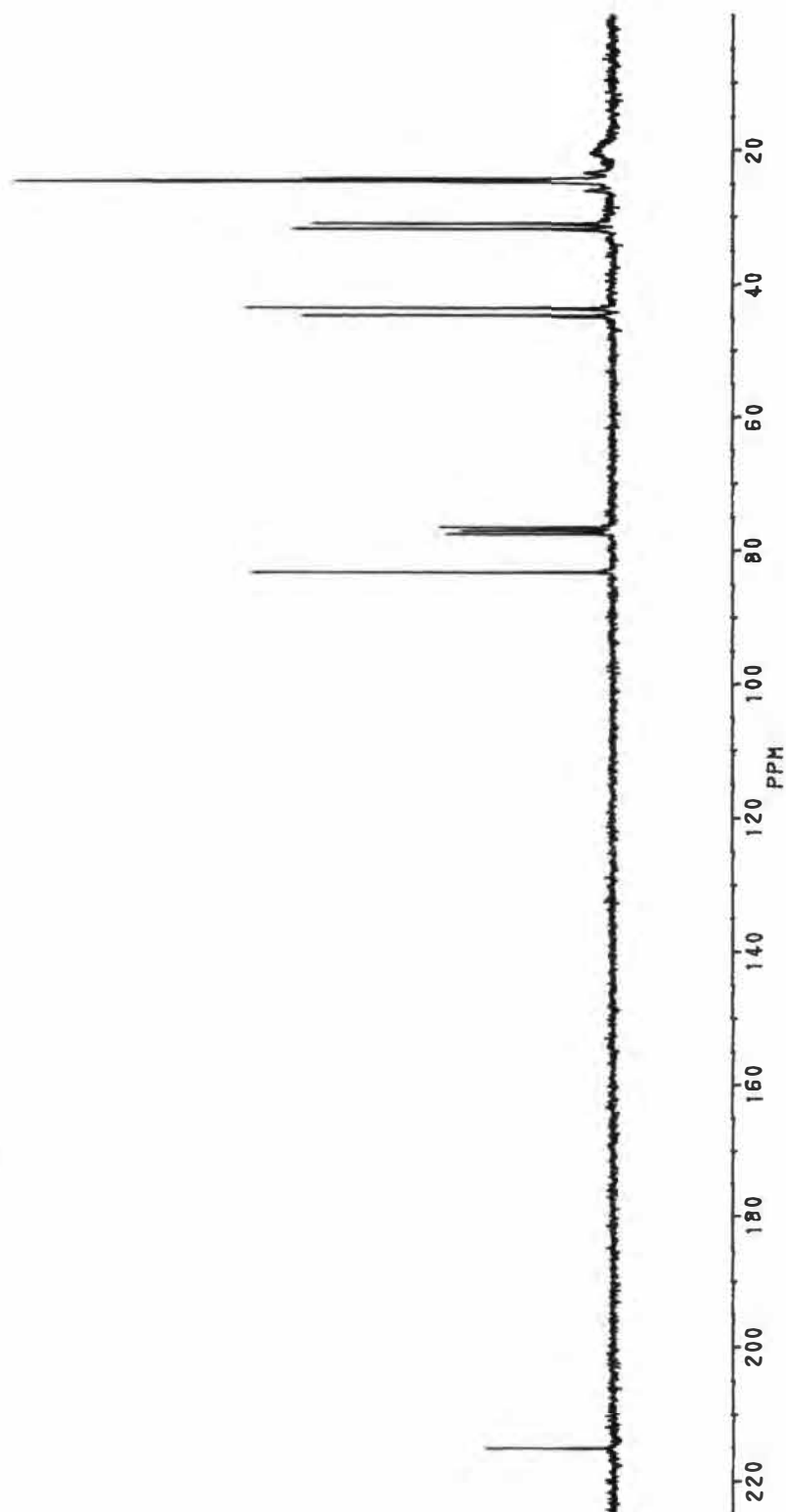
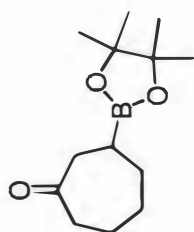


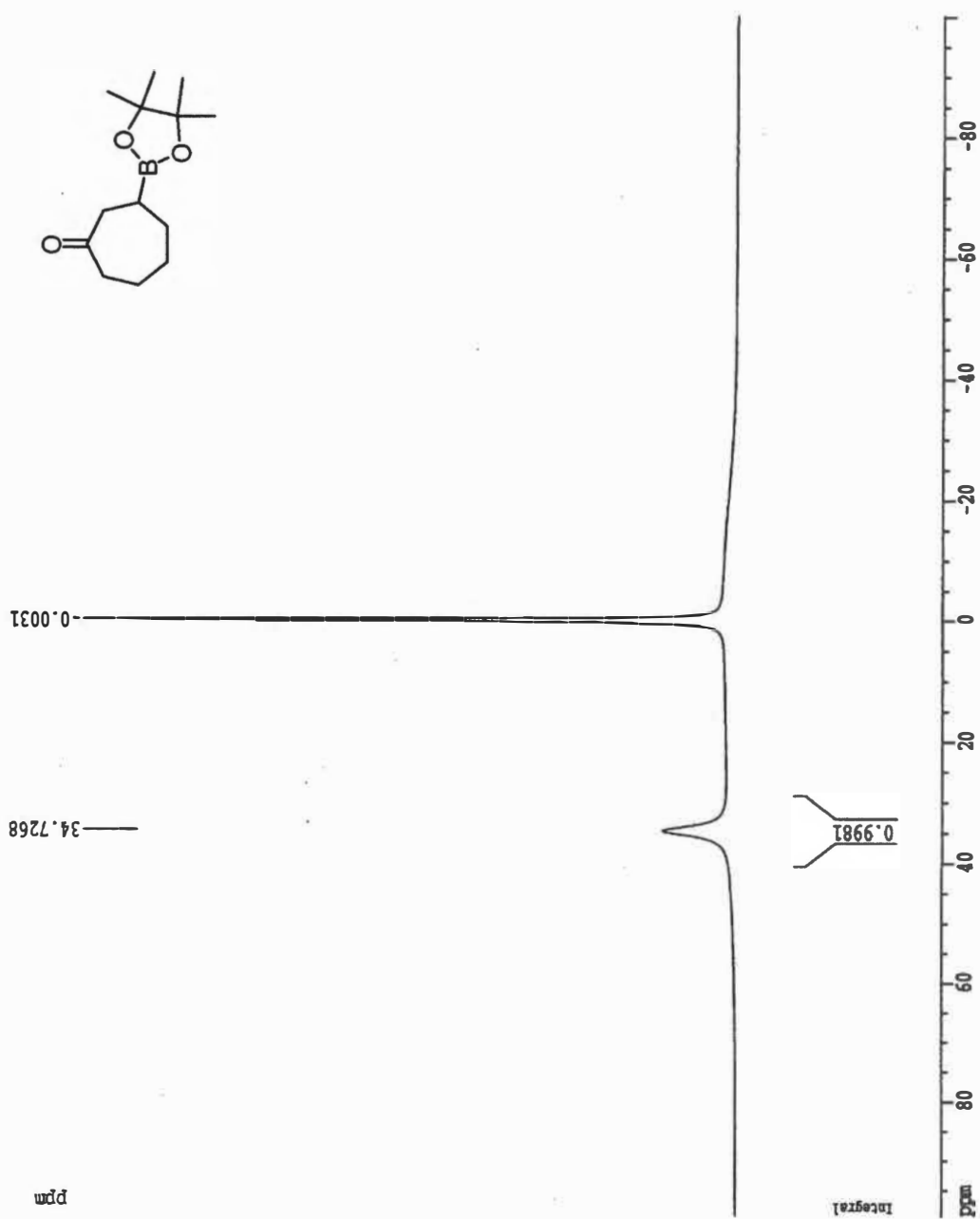


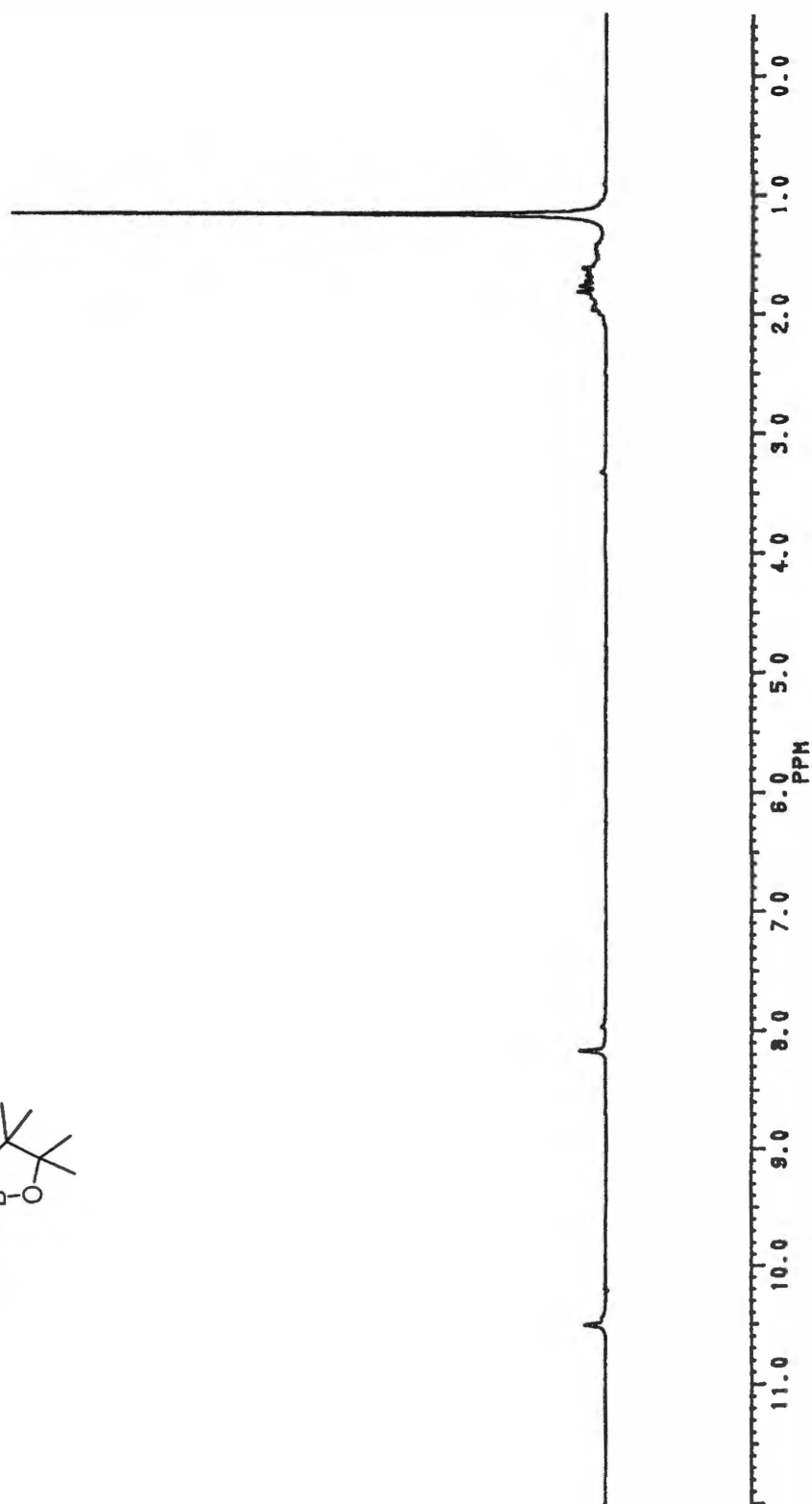
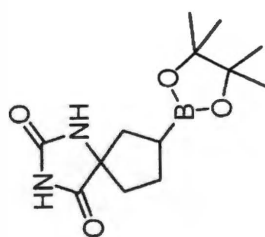


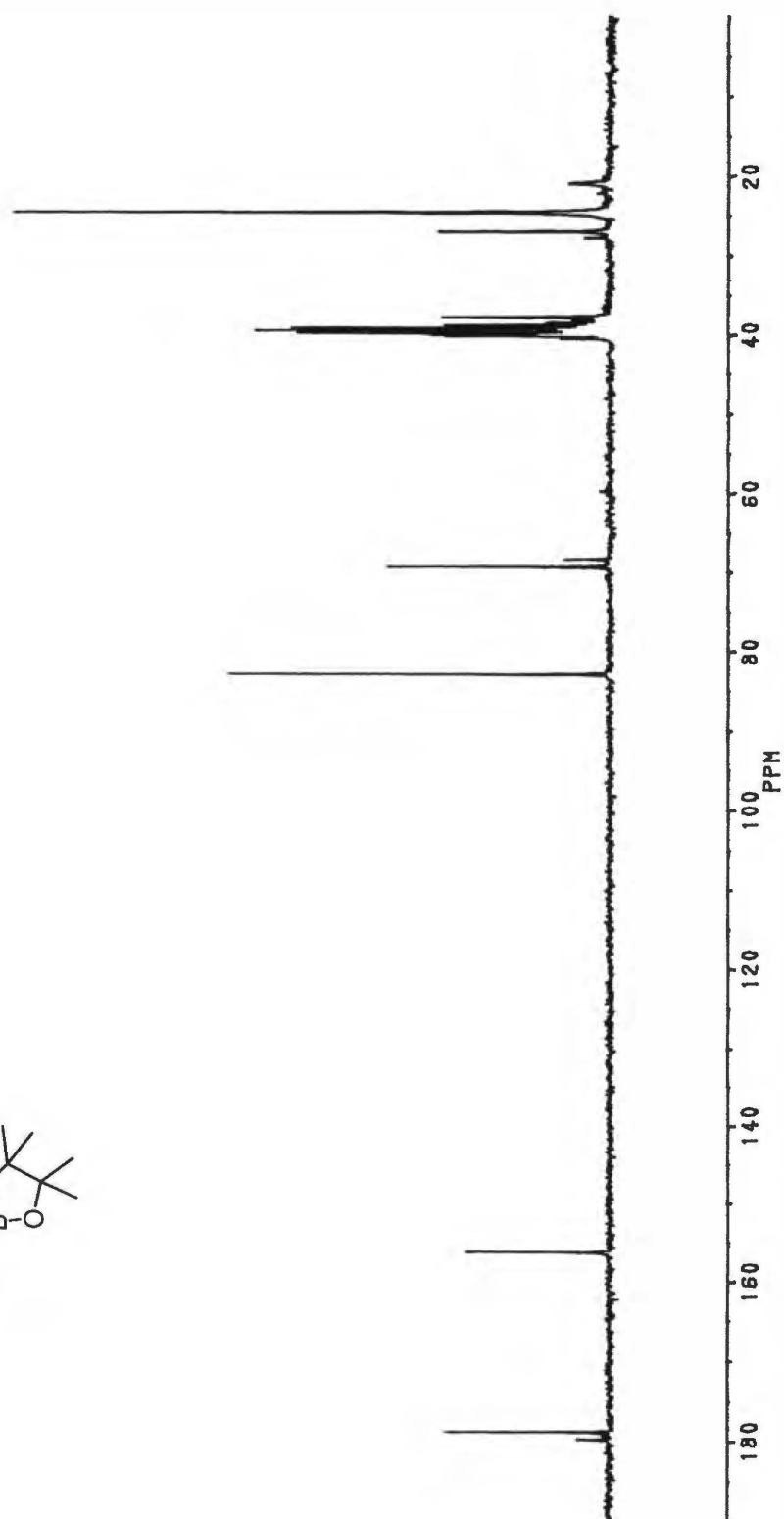
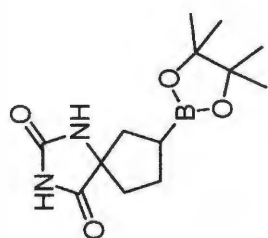
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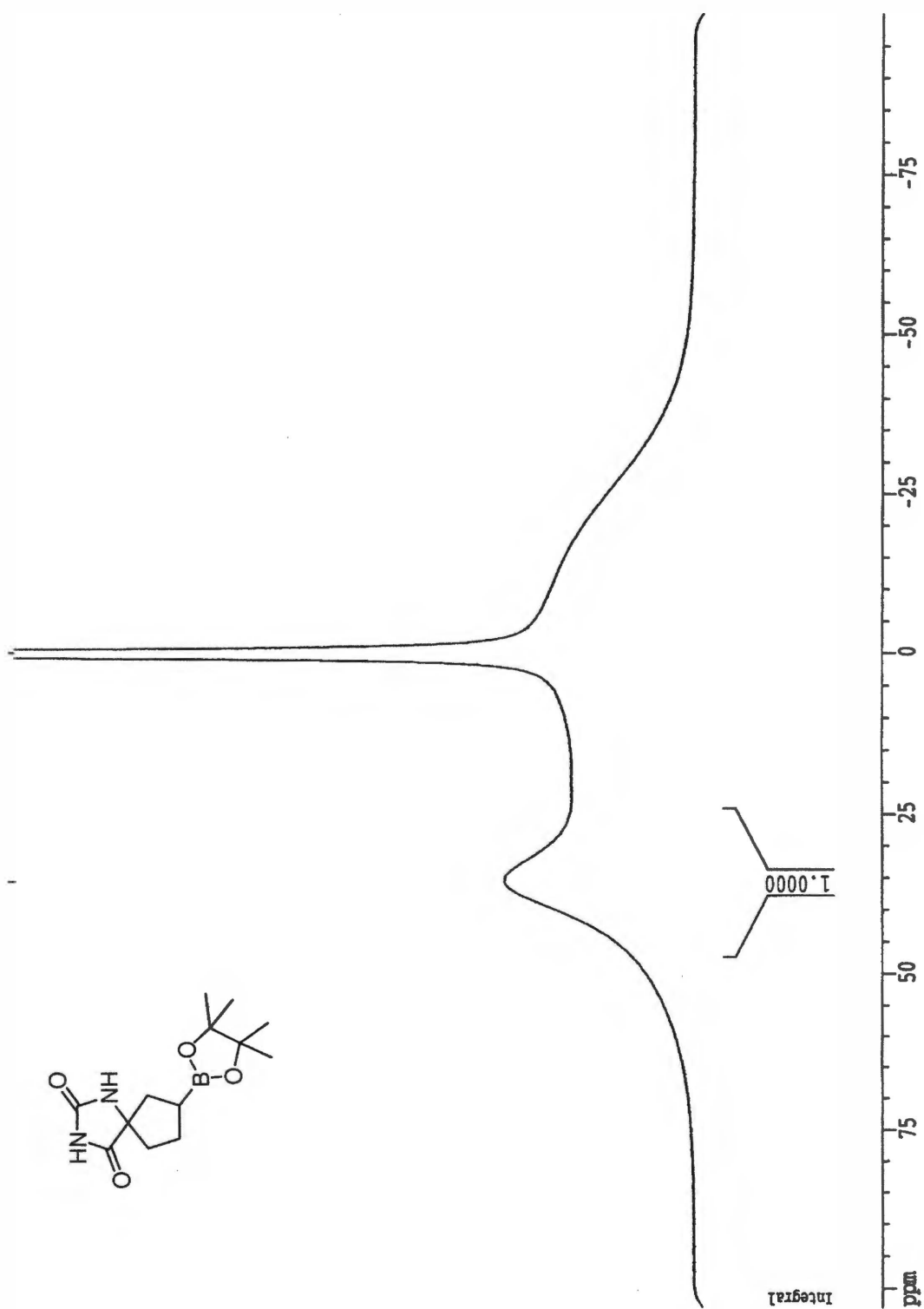


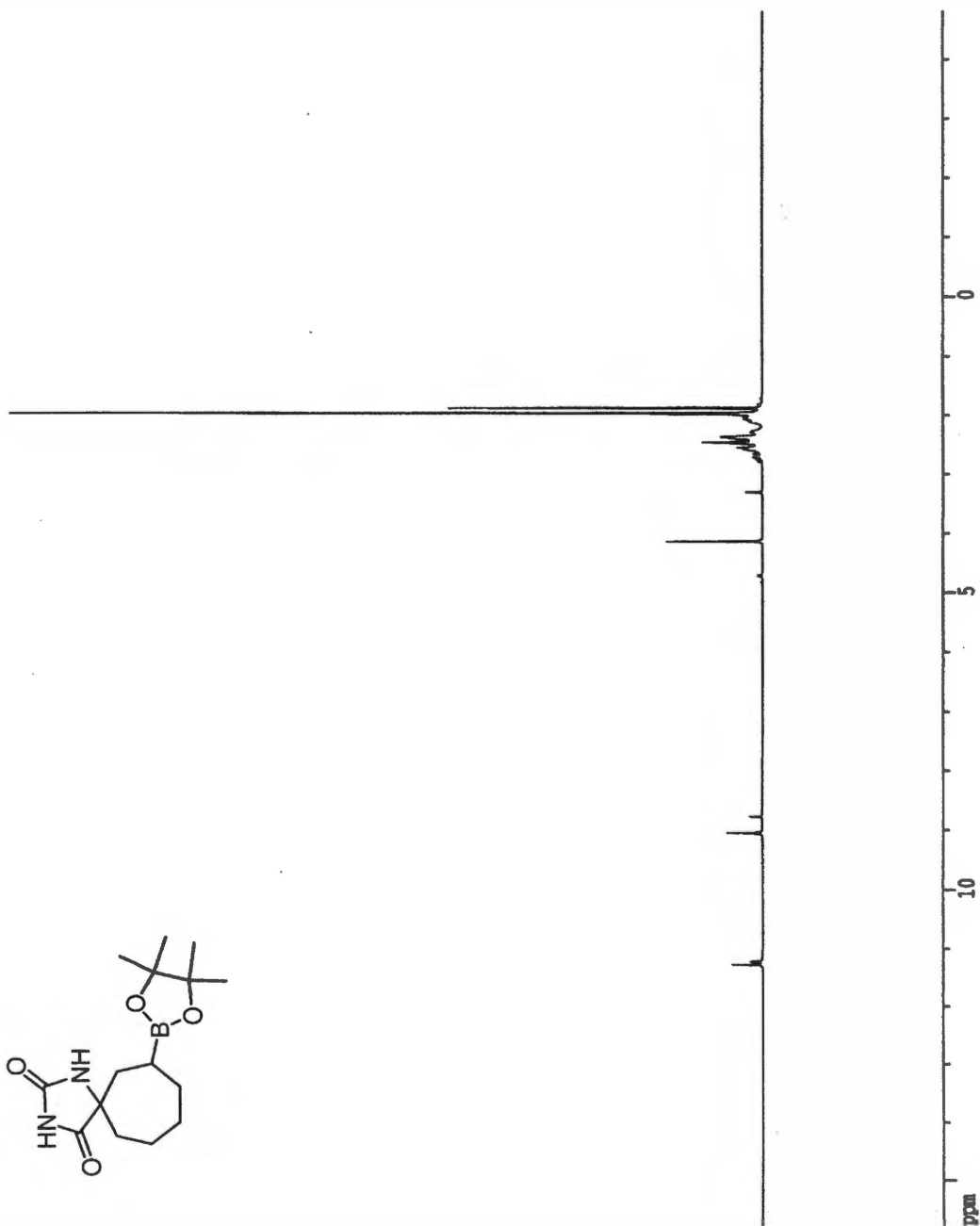


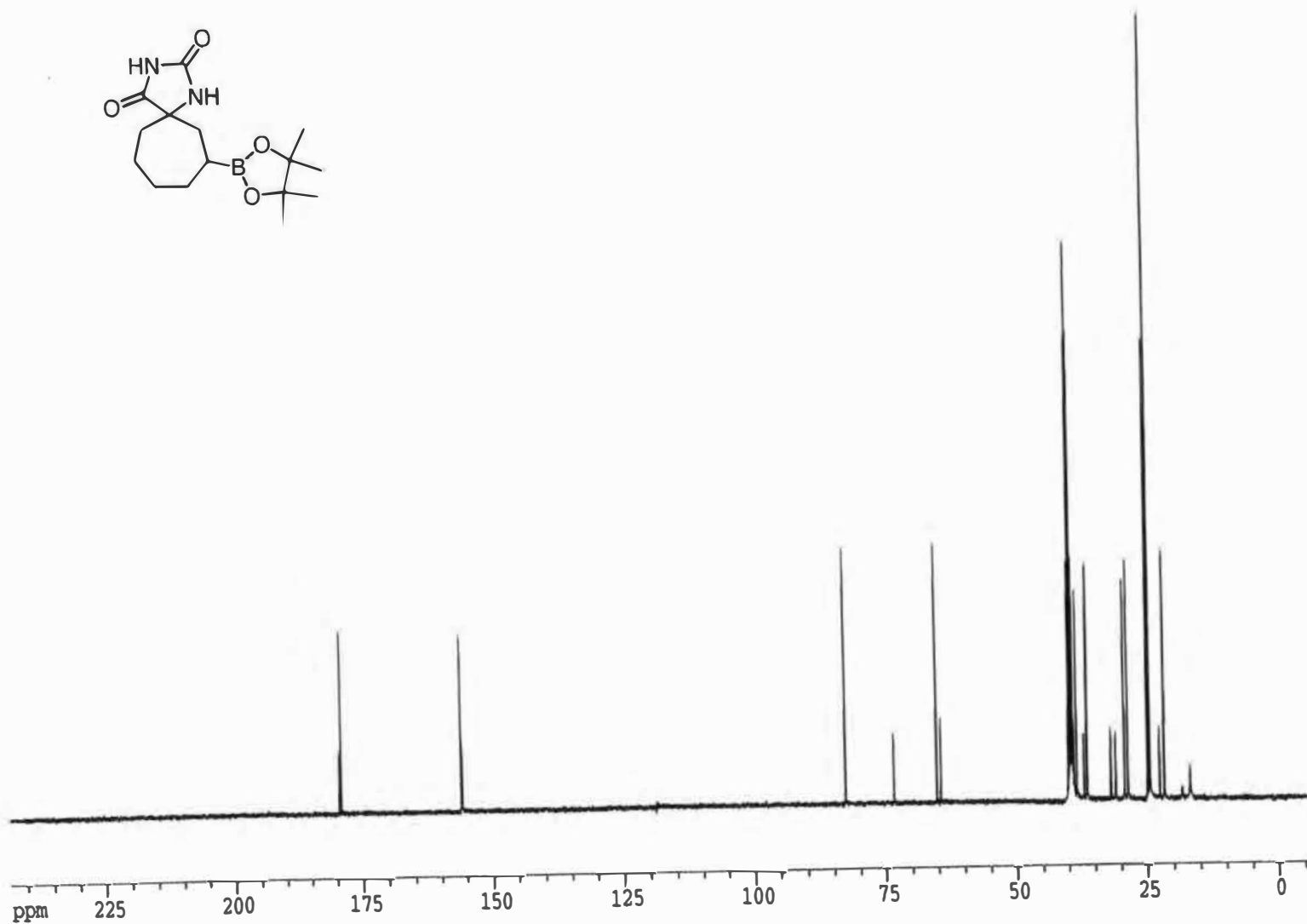
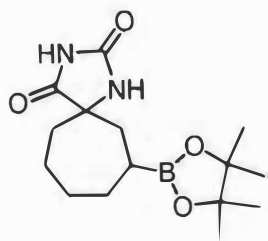




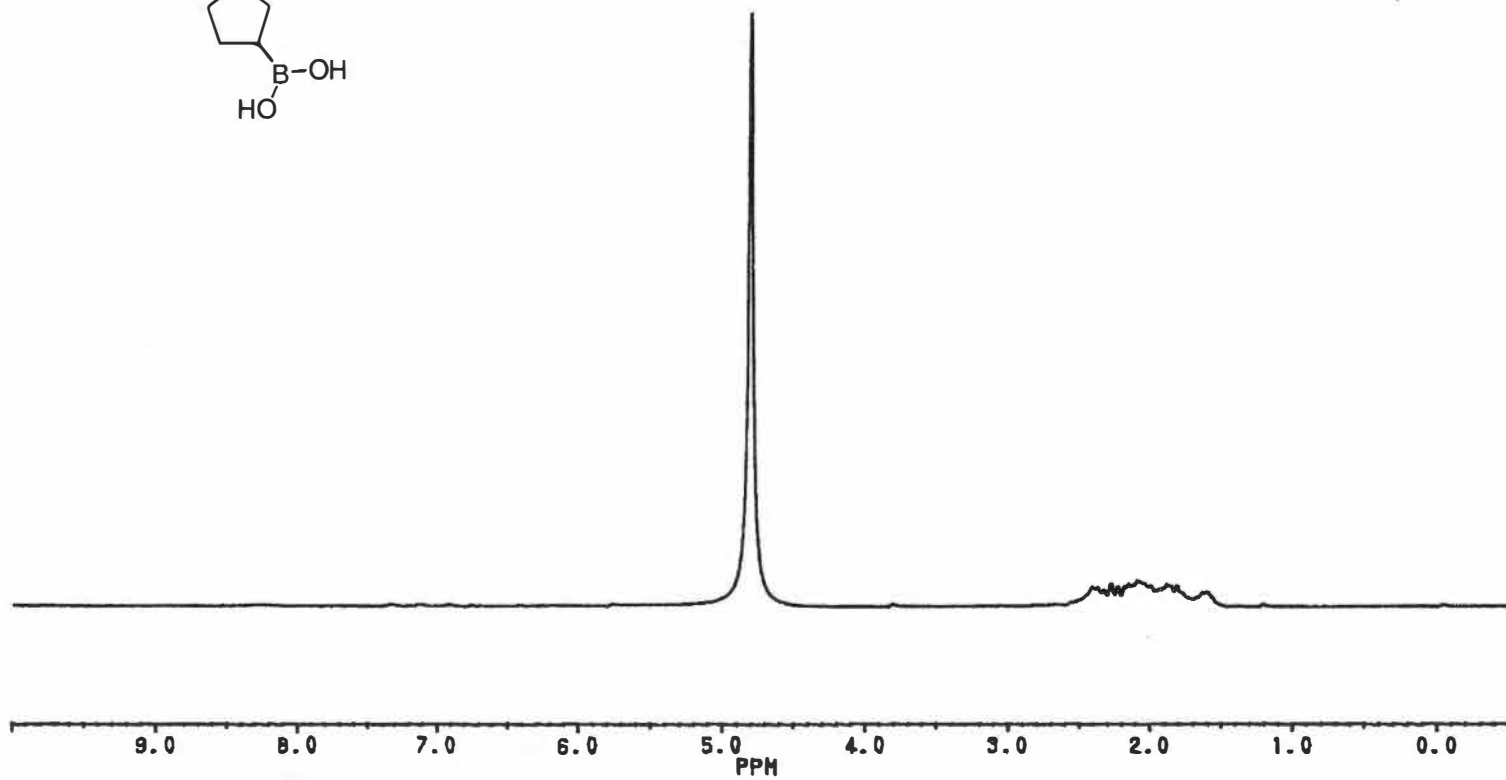
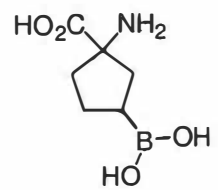


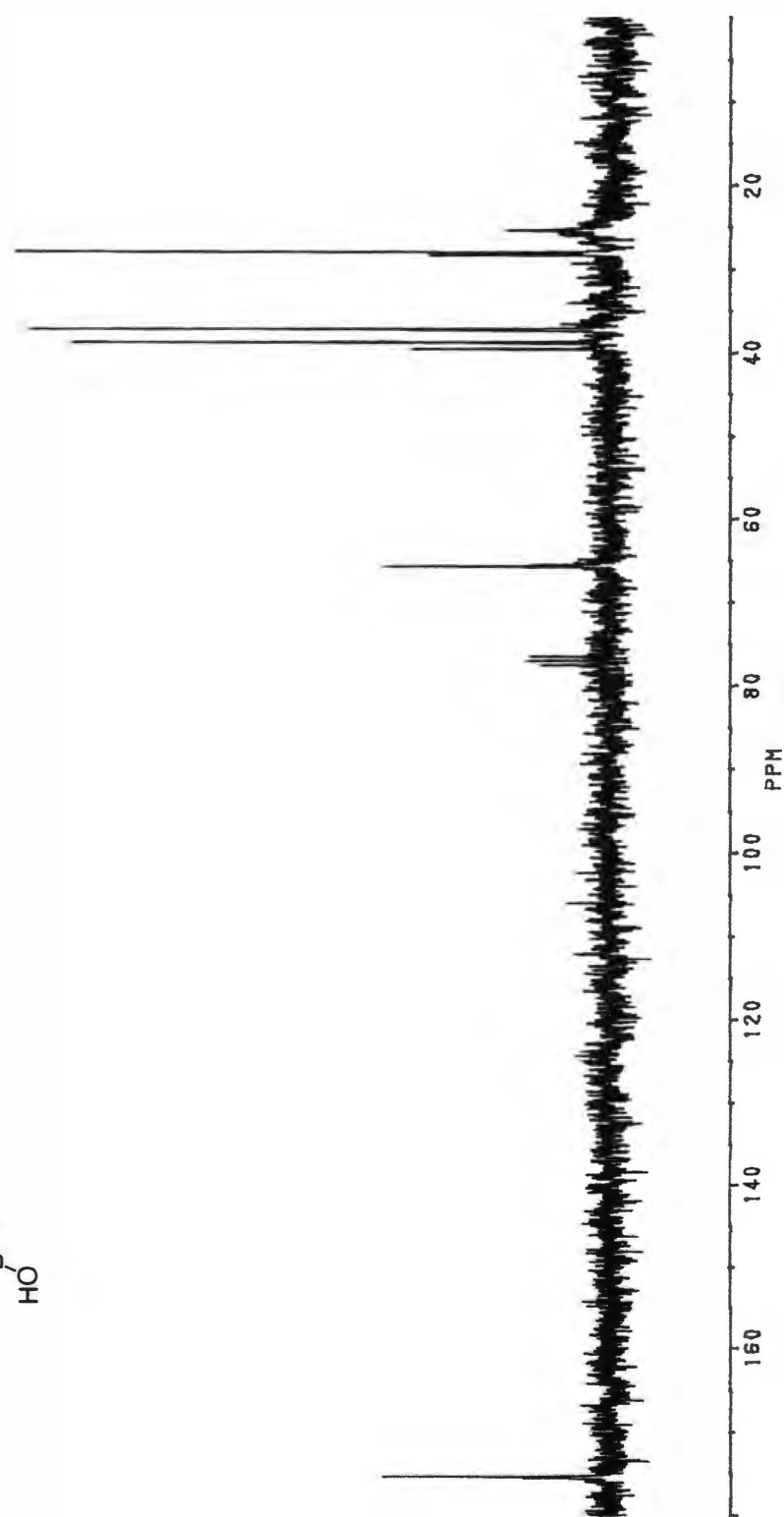
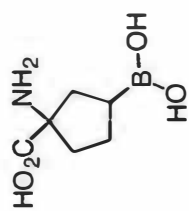


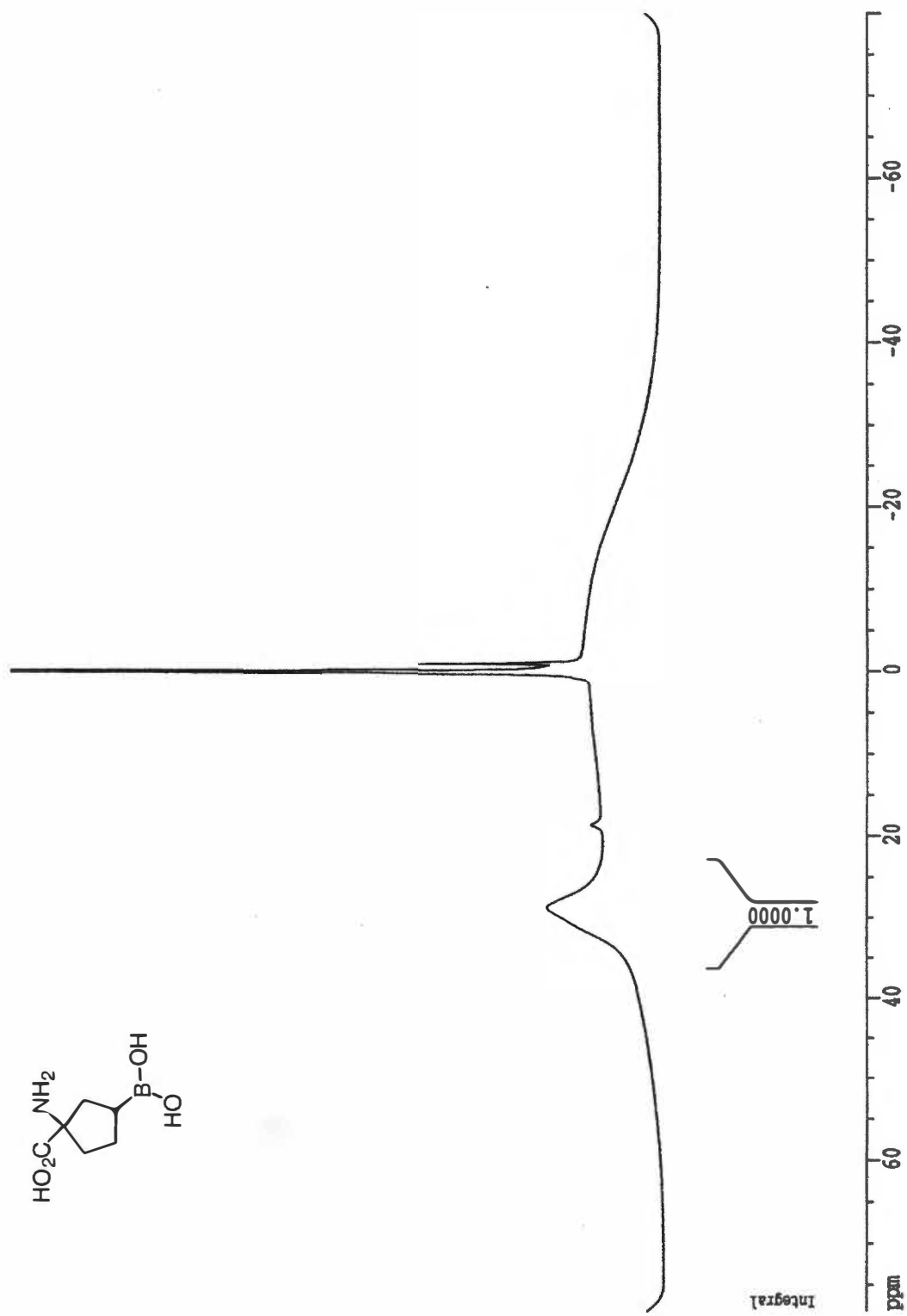


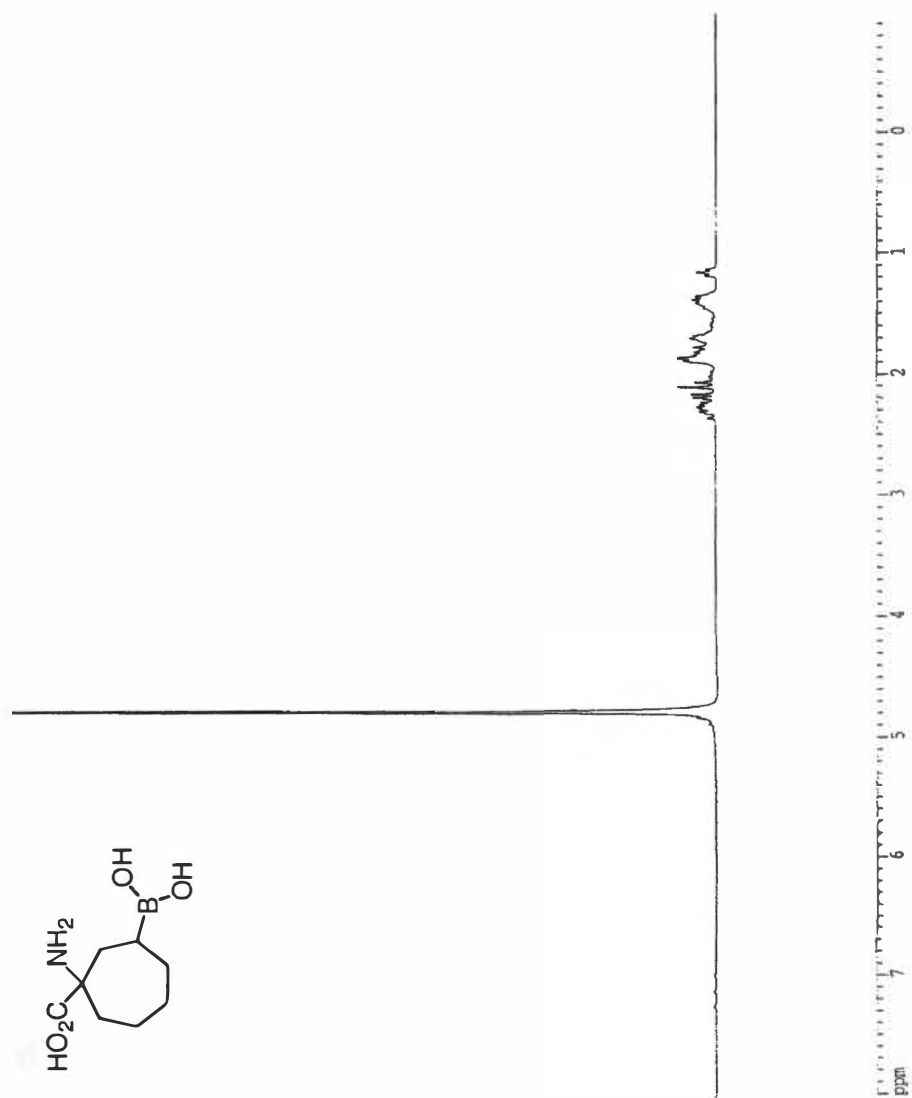


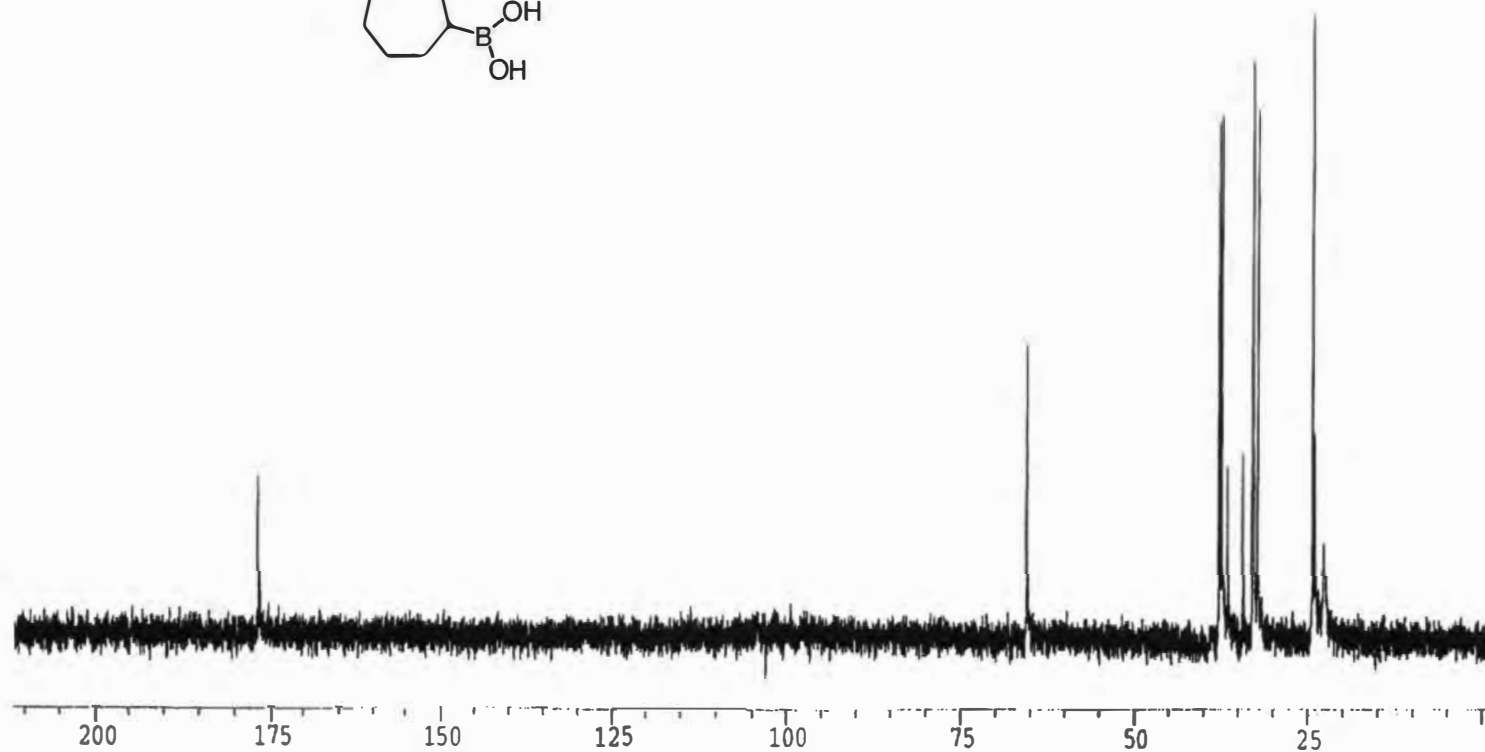
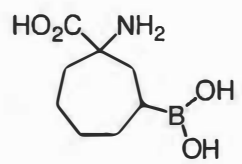
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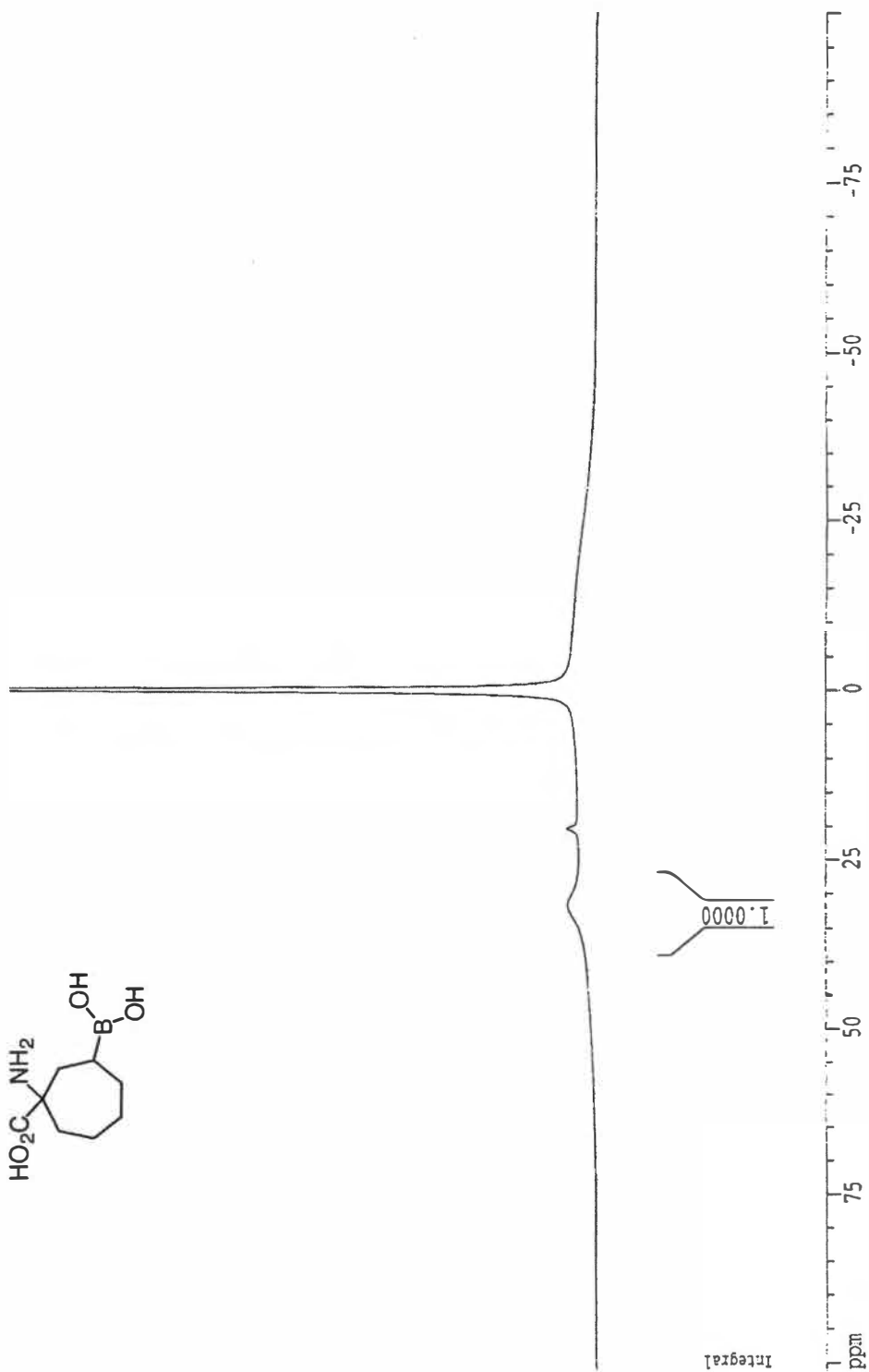
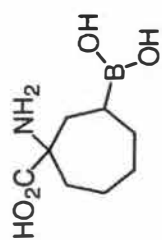




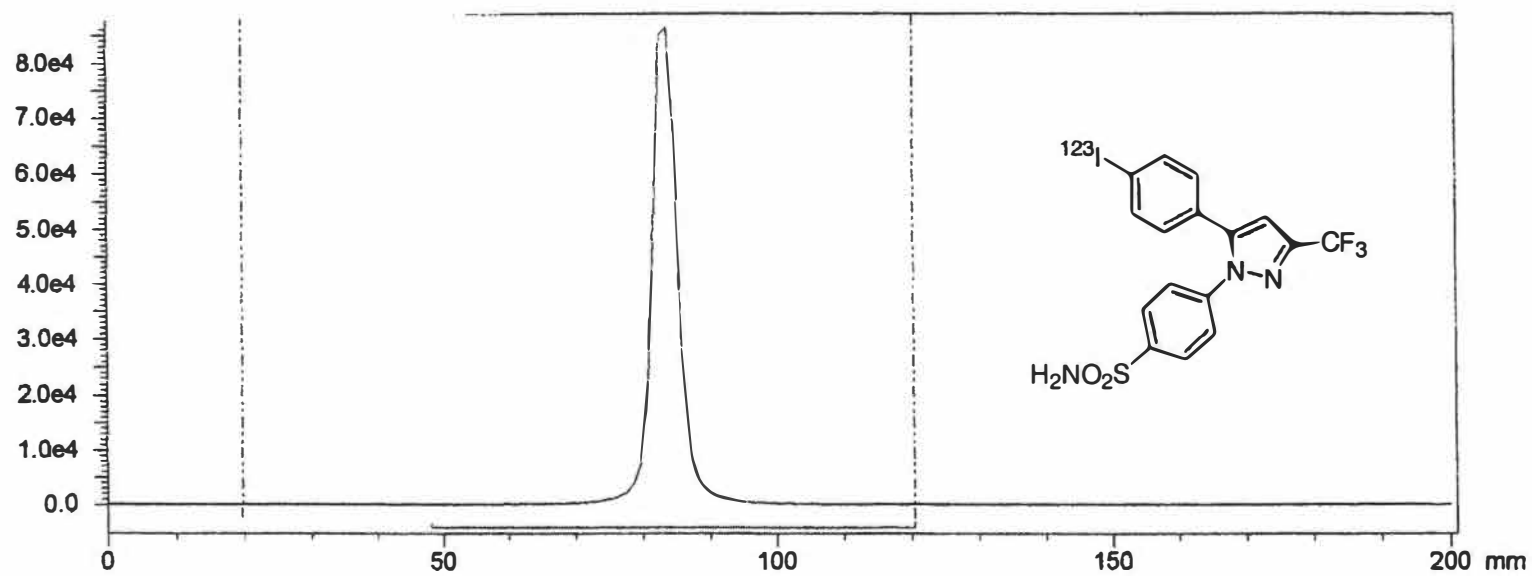








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VITA

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