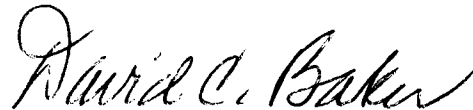


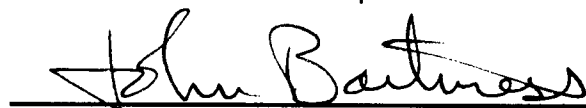
To the Graduate Council:

I am submitting herewith a thesis written by Farhad Azizbigloo entitled "Synthesis of Sterically Hindered 5'-Esters of 6-Chloro-9-(2,3-dideoxy- β -D-glycero-pentofuranosyl)purine." I have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.

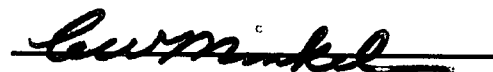


David C. Baker, Major Professor

We have read this thesis
and recommend its acceptance:



Accepted for the Council:



Associate Vice Chancellor and
Dean of The Graduate School

Synthesis of Sterically Hindered 5'-Esters of 6-Chloro-9-(2,3-dideoxy- β -D-*glycero*-pentofuranosyl)purine as Anti-HIV Agents

A Thesis

Presented for the

Master of Science

Degree

The University of Tennessee, Knoxville

Farhad Azizbigloo

December 1997

DEDICATION

I would like to dedicate this thesis to

To my mother, Mehrangiz.

ACKNOWLEDGMENT

I would like to thank professor David Baker for helping, guiding, and financially supporting me in achieving this degree. I would also like to thank my committee, Professor David Baker, Professor John Bartmess, and Professor Frederick Grimm, for their devotion and outstanding commitment to chemistry in both teaching and research.

ABSTRACT

The purpose of this research was to synthesize sterically hindered 5'-esters of 6-chloro-9-(2,3-dideoxy- β -D-*glycero*-pentofuranosyl)purine as a prodrug of the anti-HIV drug ddl, expecting to show resistance to intestinal ADA and intestinal esterase enzymes and consequently higher oral bioavailability.

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I. INTRODUCTION

A. A Background of AIDS Virus.

Acquired immune deficiency syndrome (AIDS) or human immunodeficiency virus (HIV) that was identified in 1983 is "a deadly scrap of genetic code", as described by G. Cowley,¹ the virus particle essentially is made up of a 9.7 kilobase genome-size RNA² with a protein coating. There are two main reasons that make it difficult to deal with this virus. First, it is able to penetrate into the helper T cells (lymphocytes), and by killing them it sets in motion a cascade of events that ultimately leads to the destruction of the human immune system. Second, the viral RNA reverse transcriptase makes many mistakes during transcription that result in each offspring being genetically different from the other,² making it very difficult to formulate a vaccine effective on the virus. The more the population of these mutated HIV viruses increases, the more the T cells, which are responsible for killing the antibodies by a cell-to-cell contact mechanism, are destroyed. Their population will drop to a point that any foreign invader, say a protozoan, e.g.,

Pneumocystis carinii, can cross the weakened human immune system, infect the patient and cause the patient to die from pneumonia.

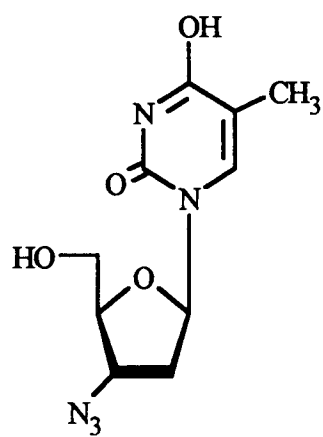
There is a glycoprotein on the surface of the T cells called CD₄ that is used as a receptor for complex communications to start or terminate the immune response among the cells. The AIDS virus unfortunately can bind to this receptor and enter the cell through a receptor-mediated endocytosis mechanism.² Once the virus gets into the cell, the deadly replication steps start. A viral RNA-directed DNA polymerase called reverse transcriptase (RT) that is contained within the viral particles begins catalyzing the synthesis of viral DNA, a DNA strand complimentary to viral RNA. In the next step, the synthesized viral DNA is joined to the chromosome of the host cell by an enzyme called integrase (I), forming viral genes which upon activation can transcribe and produce new viral RNA strands. These new viral RNA strands are now capable of producing protein and other essential components of the virus. The produced inactive polyprotein is divided into smaller activated units by a cellular protease (P) and these activated units now can associate together as new HIV capsules. The reproduction cycle repeats and continues as the newborn AIDS viruses get out of the infected cell and start infecting new cells.

B. Anti-HIV Drugs

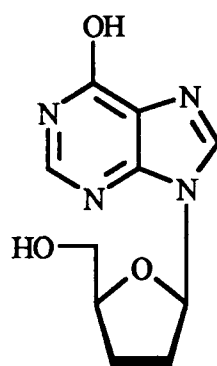
If the virus reproduction cycle is stopped at any stage of development, there is hope that a human life can be saved. There are three steps in the reproduction cycle which are catalyzed by three distinct enzymes mentioned above: (1) reverse transcriptase, (2) integrase, and (3) protease. If a drug can totally inhibit any of these enzymes, the procedure catalysed by that enzyme will stop, and the therapeutic goal is reached.

AIDS treatment began in 1986 when the family of nucleoside drugs known as RT-inhibitors came on to the market. The first of this family was 3'-azido-2',3'-dideoxythymidine (AZT), which had been previously synthesized by J. P. Horwitz in 1964 for the purpose of serving as an anticancer agent. The drug failed the original purpose at that time, but later in 1985 it turned out to be an effective anti-AIDS drug.² This observation led to the development of other anti-HIV drugs such as 2',3'-dideoxyinosine (ddI), 2',3'-dideoxycytidine (ddC), 3'-deoxy-2',3'-didehydrothymidine (d₄T), and 3'-thio-2',3'-dideoxycytidine (3-TC) (Figure 1). All five of these drugs are now used in clinical practice.

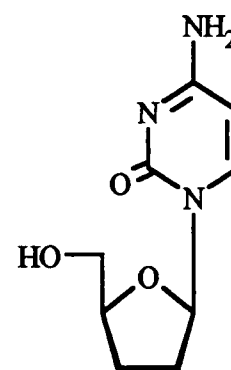
The mechanism of inhibition of reverse transcriptase by the nucleoside drugs involves in the conversion of these drugs to their respective nucleoside 5'-triphosphates through a series of enzymatic reactions after being taken up by T lymphocytes. Considering the fact that binding of these nucleoside 5'-triphosphates to the RT enzyme is favored compared to the binding of the naturally occurring



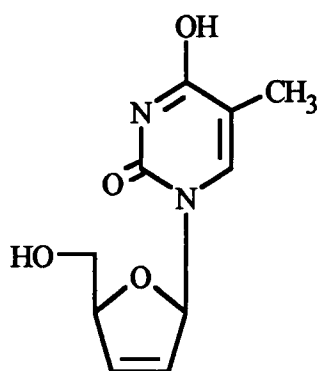
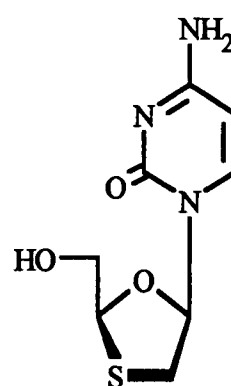
AZT



ddI



ddC

d₄T

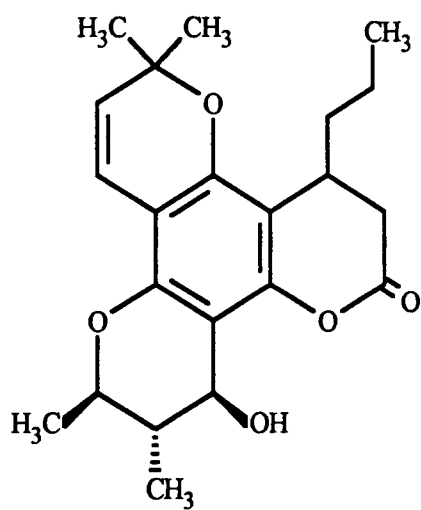
3-TC

Figure 1. Nucleoside RT-Inhibitor Drugs.

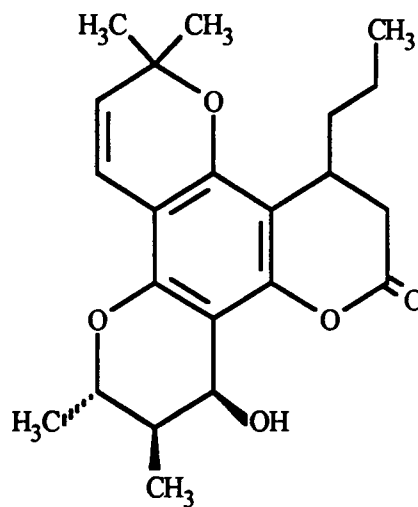
deoxythymidine 5'-triphosphate (dTTP) due to the higher affinity that the enzyme show for them, the dTTP binding to the enzyme will be competitively inhibited . Such competitive inhibition indicates that the drug binds at the nucleoside binding site, and consequently an RNA chain starts growing with the 2',3'-dideoxynucleoside 5'-triphosphate added to its 3'-end. Due to the lack of 3'-hydroxyl group on the 2',3'-dideoxynucleoside, the RNA chain prematurely stops, and viral RNA synthesis is thus terminated. Since the cellular polymerase on the other hand favors binding to dTTP rather than these nucleoside triphosphates, these drugs are relatively nontoxic to normal lymphocytes. As an example, AZT can affect HIV-RT at a low concentration of 1–5 μM , which is well below the toxicity level for normal DNA polymerases.²

There is also a family of nonnucleoside RT-inhibitors that we can mention: (1) calanolides A and B, (2) nevirapine, and (3) delavirdine (Figure 2). These drugs each have a different mechanism of interaction with RT-enzyme. The mechanism involves the binding of the drug to the enzyme at a site remote from the nucleoside-binding site, thus altering the shape of the catalytic active site of the enzyme via classical noncompetitive inhibition.

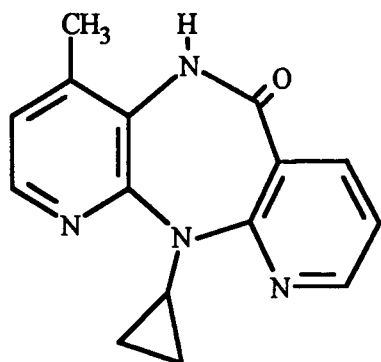
More recently new drugs called protease inhibitors have arrived on the market as nelfinavir (ABT-378), saquinavir, zidovudine, and didanosine (Figure 3) among which ABT-378 is the first that HIV-infected children can take as well.¹ These drugs inhibit the viral protease that is responsible for the splicing activation procedure in which the gag-pol polyprotein, which itself is inactive, gets cut into gag and pol



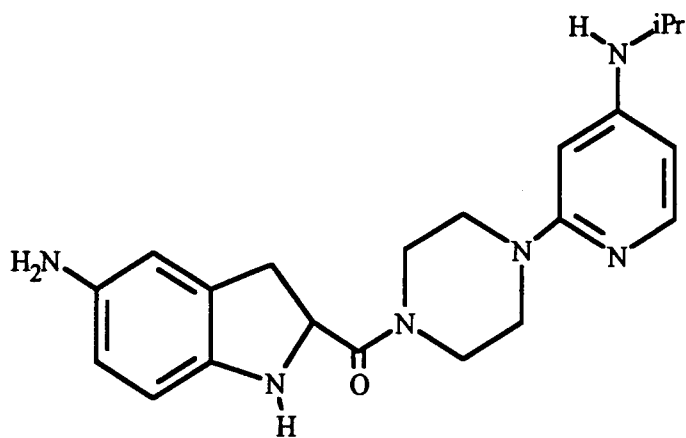
(+)-calanolide A



(-)-calanolide B

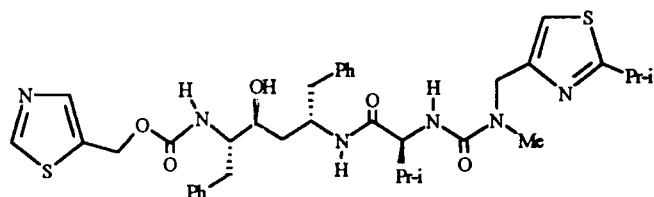


nevirapine

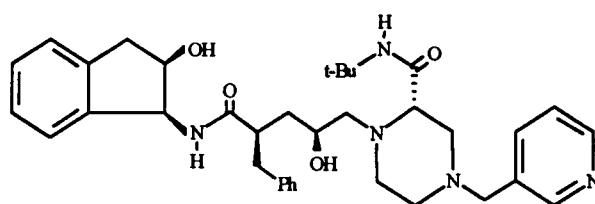


delavirdin

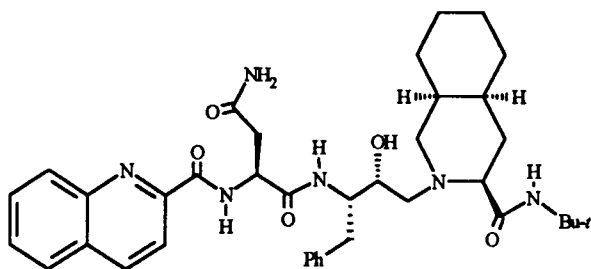
Figure 2. Nonnucleoside RT-Inhibitor Drugs.



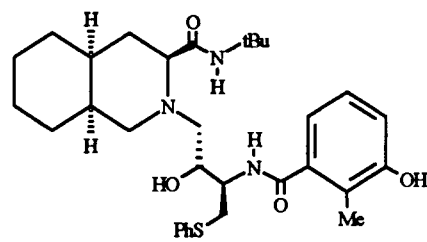
ritonavir



indinavir



saquinavir



nelfinavir

Figure 3. Protease Inhibitor Drugs.

proteins, both of which are active in cell-wall forming processes. It is hoped that the combination of RT-inhibitor and P-inhibitor drugs will work better than either drug above administered alone, serving to at least in part circumvent the problems associated with the viral mutations.

It is important to keep in mind that due to the high rate of mutation and reproduction of genetically varied offspring, any of these drugs can fail in blocking the HIV reproduction cycle for a long period of time, because the drug will invariably miss a few of the mutations and the survivors will regenerate unimpeded at a high rate and start reinfected the cells with a new viral strain that is resistant to the original drug.

C. The Prodrug Approach.

A major concentration of HIV virus has been shown to be located in the brain and spinal cord due to the ability of the virus to pass through the blood-brain barrier (BBB) and penetrate the central nervous system (CNS).³ Considering this fact an effective drug that would eradicate HIV in the CNS should have considerable (1) oral bioavailability, (2) intestinal absorption, and (3) membrane permeability that would enable it to maintain a favorable brain:plasma concentration.⁴

Among the nucleoside RT-inhibitors, only AZT and d₄T have been reported to show penetration into the CNS system at a moderate rate and have been determined to have a cerebrospinal fluid (CSF):plasma concentration ratio about 0.2–0.3 for human and rats.^{3,5-7} For ddI, ddC, and 3-TC this ratio has been found out to have an unacceptably poor value of 0.05^{3, 8-10} and this fact has been explained to be due to low lipophilicity and the possibility of the glycosidic C–N bond undergoing hydrolysis under acidic conditions (in ddI) of the stomach.¹¹ AZT, despite its moderate oral bioavailability, has been reported to be toxic to bone marrow cells, exposing the patient to development of anemia, and this has been concluded as a barrier to its use.^{2,3,12,13} In the family of the nonnucleoside RT-inhibitors, nevirapine has been reported to have a CSF:plasma value of 0.45 in humans.^{3,5, 14-16} This shows a high oral CNS bioavailability; however, it has been reported that using this drug in the long term ends up with production of resistant

strains of HIV in both the systemic circulation and in the CNS.^{3,14,17} It has been concluded from this observation, together with the consideration of the synergistic effects that nonnucleoside RT-inhibitors show with majority of nucleoside RT-inhibitors,^{3,5,15} that the alternative of a combination therapy with nevirapine and an RT-nucleoside inhibitor with improved bioavailability and CNS penetration might show good results.^{3,18} Protease inhibitors have been reported to show a very poor CNS penetration, among which saquinavir is an example with its CFS:plasma ratio reported to be negligible.^{3,5,14-16}

These observations and facts lead to the necessity of design of a prodrug which is an improved altered form of the original drug, being inactive but meeting the desired conditions, and capable of being converted back to its original active form by enzyme catalyzed or any other reaction.¹⁹ The first condition that in this situation the prodrug should meet has been mentioned as an optimum lipophilicity, high enough to have noticeable intestinal absorption and membrane permeability and, consequently, CNS penetration, but not too high to avoid passive diffusion back across the BBB.^{3,20-22} To achieve this goal, two class of prodrugs of ddl were tried namely 6-halo-2',3'-dideoxypurine (6-halo-ddP), which are adenosine deaminase-activated prodrugs of ddl, and 5'-ester prodrugs. The 5'-ester prodrugs have been reported to be good substrates for nonspecific esterase enzymes and to be cleaved back to ddl (Figure 4) in the intestinal absorption transport process and systemic circulation before reaching CNS. This fact has been mentioned as a reason for the failure of these prodrugs in showing any noticeable improvement

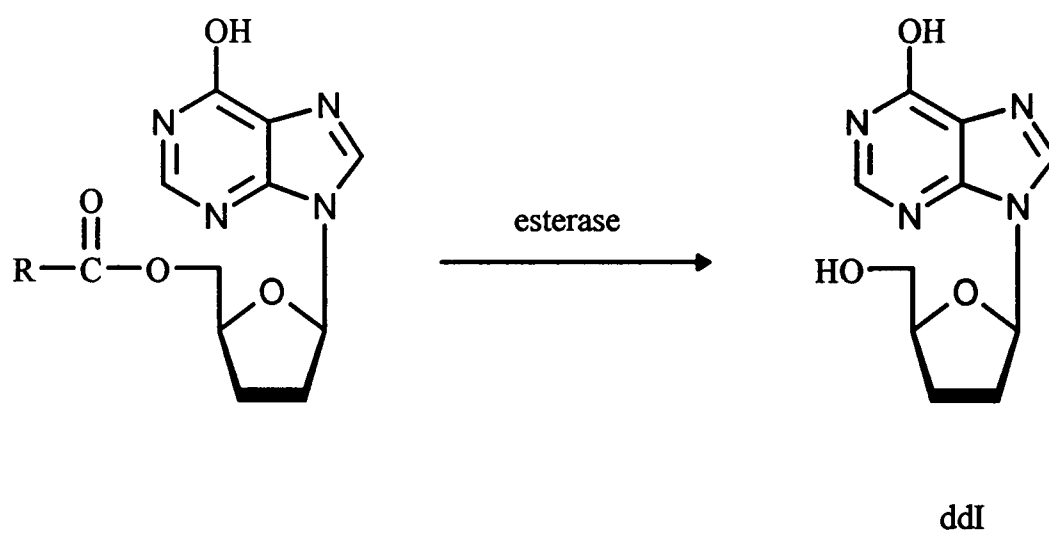


Figure 4. Bio-conversion of 5'-Esters of ddI to ddI Catalyzed by Esterase

in the oral bioavailability of the parent drug in CNS penetration.^{3,23,24} 6-Halo-ddP prodrugs, which are biochemically converted back to the parent ddl drug through the action of an enzyme called adenosine deaminase (Figure 5), have been reported to show higher oral bioavailability of 4 to 10 times more CNS penetration than the parent ddl for 6-Cl-ddP and 6-Br-ddP, and lower bioavailability than ddl for 6-I-ddP.^{3,23,24} The enzyme ADA is present in the CNS and intestinal membrane, but its highest activity has been found to be in the BBB. This is a desired condition in that the prodrug can be eventually converted back to parent ddl in the CNS; however, as observed in the study on rats, the intestinal ADA, even not being at its high activity, has been reported to be still able to convert more than half of the absorbed 6-Cl-ddP back to ddl in the period of its transport leading to only 7% net oral bioavailability.^{3,11}

If we focus on the binding energy of the enzyme ADA to its nucleoside substrate, since Wolfenden et al. showed that 4 kcal of the total binding energy between ADA and its substrate belongs to the 5'-hydroxyl functional group,^{3,26,27} it was concluded that esterification of this group can drop this binding affinity.³ The 5'-ester prodrugs of 6-Cl-ddP, named as double prodrugs of ddl by D. Singal,³ was expected to show more resistance to intestinal ADA, as was observed for vidarabine-5'-esters.^{3,28} However, early cleavage of these esters by nonspecific esterase enzymes in the intestinal transport system before reaching the systemic circulation has been cited as a barricade to the overall bioavailability of these prodrugs.^{3,29,30}

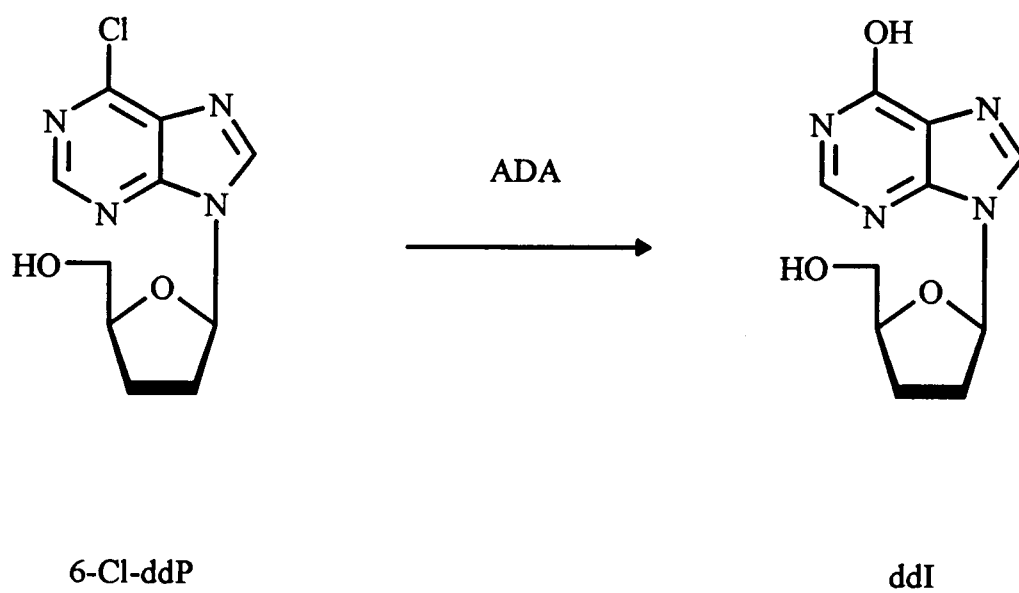


Figure 5. Bioconversion of 6-Cl-ddP to ddI by ADA.

II. STATEMENT OF THE PROBLEM

A. Sterically Hindered 5'-Esters of 6-Cl-ddP.

Studies on the nucleoside RT-inhibitor drugs have indicated that an effective prodrug of 6-Cl-ddP should meet the following conditions and properties: (1) high intestinal absorption, membrane permeability, and, consequently, CNS penetration; (2) resistance to intestinal ADA and limited conversion back to ddi by this enzyme; (3) resistance to cleavage by intestinal nonspecific esterase enzymes in the transport process (intestinal absorption); (4) and, especially, ready bioconversion back to 6-Cl-ddP in the systemic circulation at high rates of at least 0.5 min^{-1} or more.³

Since the 6-Cl-ddP prodrug has been reported to show the best results so far in delivery of ddi to the CNS,³ the goal of this project is to synthesize modified sterically hindered 5'-esters of 6-Cl-ddP, including a charged one, that will be resistant to cleavage by the esterases in the intestinal wall due to steric hindrance on the acyl moiety. The target ester prodrugs should meet the three above

mentioned important properties of having high intestinal absorption and membrane permeability, being resistant to intestinal ADA, and particularly convertible back to 6-Cl-ddP in the systemic circulation at a considerable rate before reaching the CNS. Such would lead to a desired high oral bioavailability and, ultimately, CNS penetration. The hindered 5'-esters of ddP to be synthesized in this project are 2,2-dimethylsuccinoyl, 3,3-dimethylsuccinoyl (the charged ones), 2-ethylbutyryl, 2,2-diphenylpropionyl, and 2,2-diethylbutyryl esters which the latter two have steric parameter, v , of the acyl moiety of greater than 2^{3,31,32} (Figure 6).

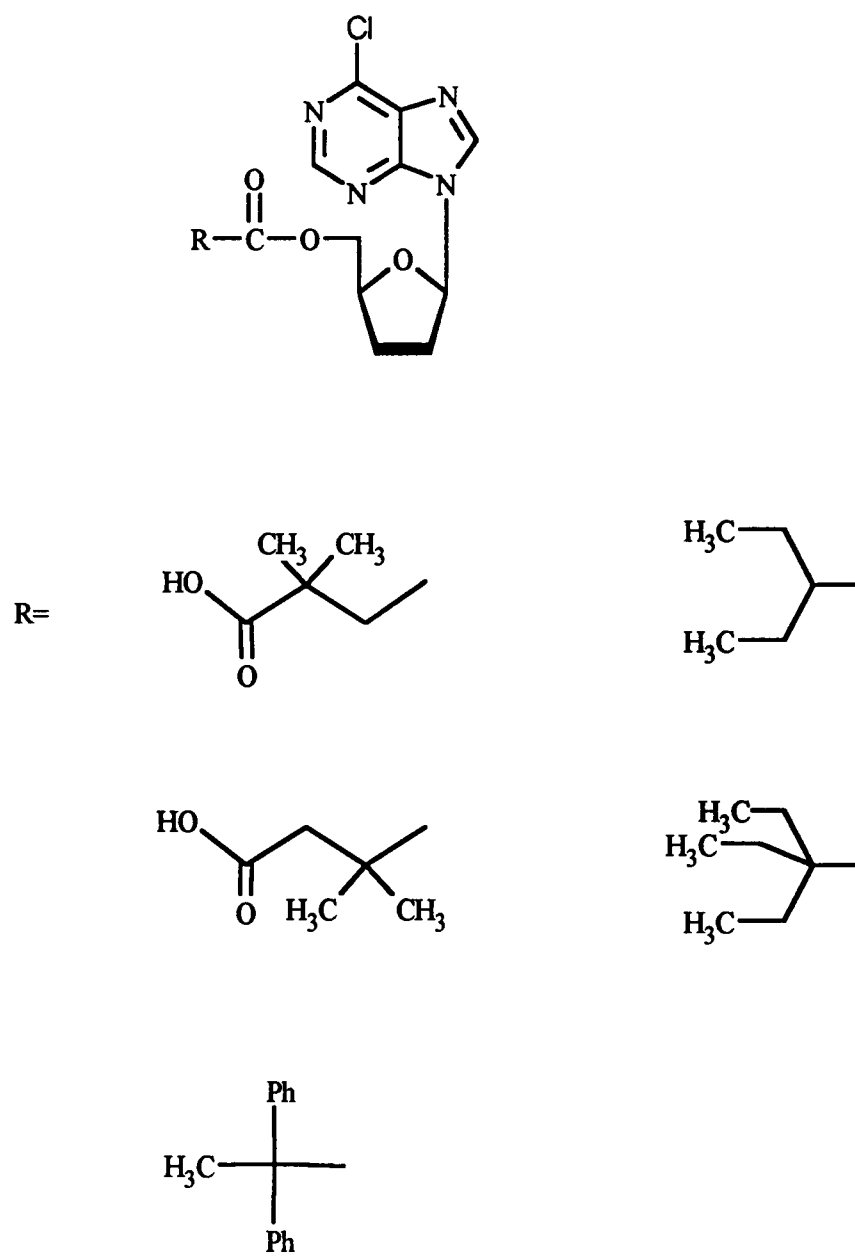


Figure 6. Sterically Hindered Esters of 6-Cl-ddP.

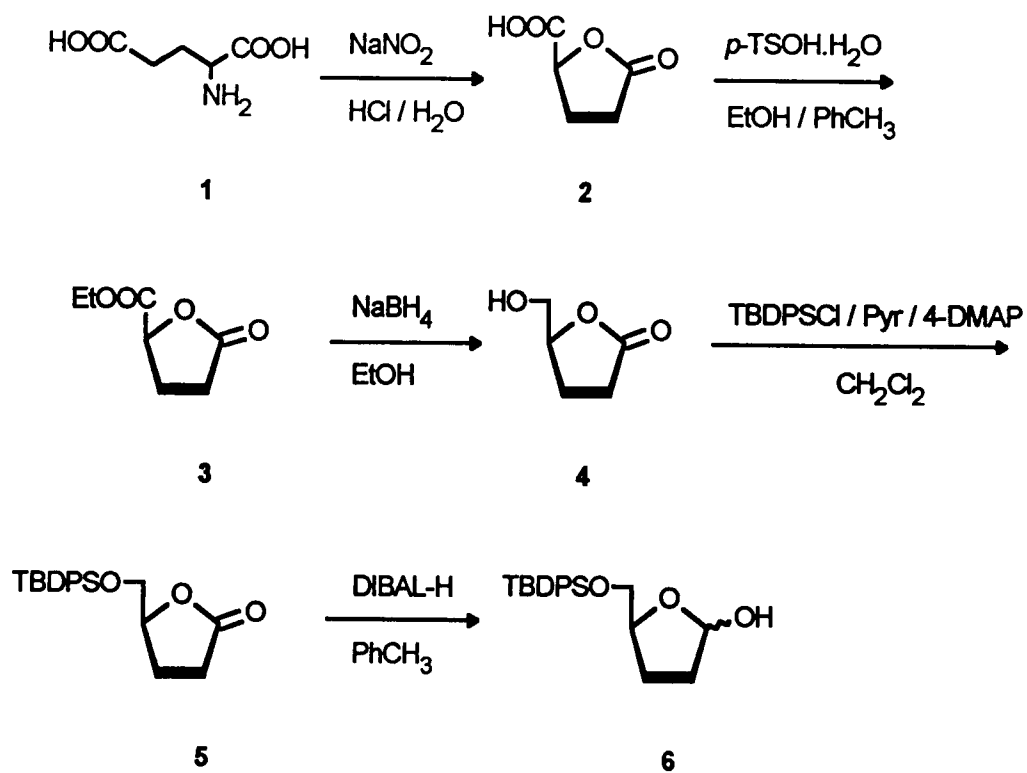
III. RESULTS AND DISCUSSION

A. Synthesis of

5-*O*-*tert*-Butyldiphenylsilyl-2,3-dideoxy-D-glycero-pentofuranose (6)

The strategy for the synthesis of the required D-glycero-pentofuranose ring system (Scheme 1) is based on the well known formation of a γ -carboxy- γ -butyrolactone ring through a deamination reaction carried out on L-glutamic acid (**1**), a cheap starting material, followed by reduction of the γ -carboxyl group to a hydroxyl group, protection of the γ -hydroxyl group, and reduction of the carbonyl group on the lactone ring.³³⁻³⁹

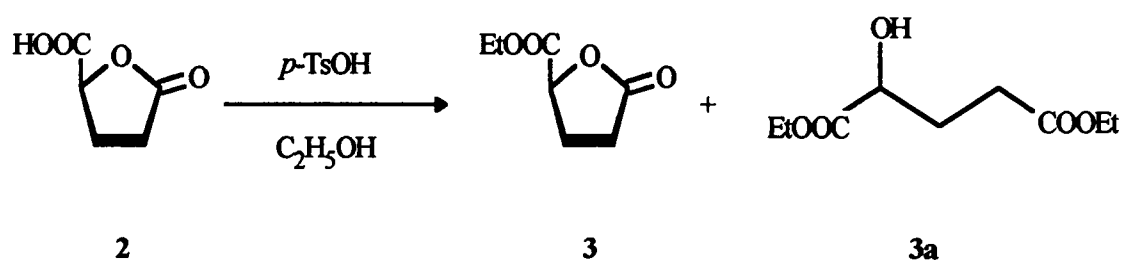
Because of the neighboring group participation effect of the adjacent α -carboxyl group in L-glutamic acid (**1**), the deamination–ring closure is reported to result in a unique substitution product that retains its configuration, yielding only (S)- γ -carboxyl- γ -butyrolactone (**2**).³⁵⁻³⁹ *p*-Toluenesulfonic acid (*p*-TsOH) catalyzed esterification of the carboxyl group of **2** can lead to (S)- γ -ethoxycarbonyl- γ -butyrolactone (**3**); however, according to Uzi Ravid et al.,³⁴ due to the possible



SCHEME 1. Synthesis of 5-*O*-*tert*-Butyldiphenylsilyl-2,3-dideoxy-*D*-glycero-pentofuranose.

acid-catalyzed opening of the lactone ring, side product **3a**, (*R*)-diethyl α -hydroxyglutarate, is also expected (Scheme 1a). Selective reduction of ester group in **3** leading to (*S*)- γ -hydroxymethyl- γ -butyrolactone (**4**), is expected, since the previous observations have shown the α -hydroxy esters to be more reactive towards sodium borohydride reduction compared to the respective α -unsubstituted ones. *tert*-Butyldiphenylsilyl (TBDPS) protection of 5-hydroxyl group, followed by DIBAL-H reduction of the lactone carbonyl group, easily yields 5-*O-tert*-butyldiphenylsilyl-2,3-dideoxy-D-*glycero*-pentofuranose (**6**).³⁹

Compound **4** was prepared in three steps starting with L-glutamic acid according to the procedures by M. Taniguchi et al. and Uzi Ravid et al..³⁴ Nitrous acid deamination of **1** upon reaction with 1.5 equivs of sodium nitrite (NaNO_2) in aqueous acidic (HCl) solution gave carboxylic acid **2** in 64% yield, which was separated from the aqueous medium and isolated by extraction with ethyl acetate. The reaction conditions were improved compared to literature by keeping the reaction mixture at $-5\text{ }^\circ\text{C}$ during the whole period of addition of the NaNO_2 aqueous solution using an ice–acetone–liquid nitrogen bath and letting its temperature increase very gradually to r.t. by keeping the reaction flask in the bath during the overnight stirring. This is very important due to the instability of the diazonium salt intermediate, and by maintaining these conditions the blue color due to the formation of the diazonium intermediate was observed during the whole period of the reaction. The carboxylic acid product **2** was crystallized upon evaporation of solvent, and its structure was confirmed by proton nuclear magnetic resonance



SCHEME 1a. Ring Opening of (S)- γ -Carboxyl- γ -butyrolactone (**2**) Upon Esterification.

spectroscopy (^1H NMR) and carbon-13 nuclear magnetic resonance spectroscopy (^{13}C NMR), the data from which were consistent with those reported in the literature (See Appendix, pp 68 and 69). *p*-TsOH-catalyzed esterification of carboxylic acid **2** upon refluxing with 0.5 equiv of ethanol in toluene as cosolvent gave a mixture of esters **3** and **3a** with a total yield of 77% (based on ethanol), isolated by vacuum distillation. The identity of a mixture of two components, consistent with the observation of Uzi Ravid et al.,³⁴ was confirmed by ^1H NMR spectroscopy (See Appendix, p 70). The ^1H NMR spectrum of the mixture product matched with the individual ^1H NMR data of compounds **3** and **3a** from the literature insofar as chemical shift and relative ratio of protons, especially the CH_3 and CH_2 protons of the ethyl ester groups, are concerned. Attempts to improve the conditions in order to prevent the opening of the lactone ring by lowering the reflux temperature by using benzene as the cosolvent were not successful. The desired product **3** was not separated from the product mixture since it was easier to do so after the next reduction step. Selective NaBH_4 reduction of the mixed products **3** and **3a** by reacting them with 0.65 equiv of NaBH_4 at r.t. in absolute ethanol as solvent yielded the γ -hydroxy lactone **4**, which was separated from the reaction mixture after workup by vacuum distillation. The reaction had a low yield of 34% due to the presence of the undesired linear byproduct **3a** from the previous step, due to the ring opening. The structure of the lactone product **4** was confirmed by ^1H NMR spectroscopy, being consistent with the data reported in the literature (See Appendix, p 71). TBDPS protection of the γ -hydroxy group of alcohol **4** was

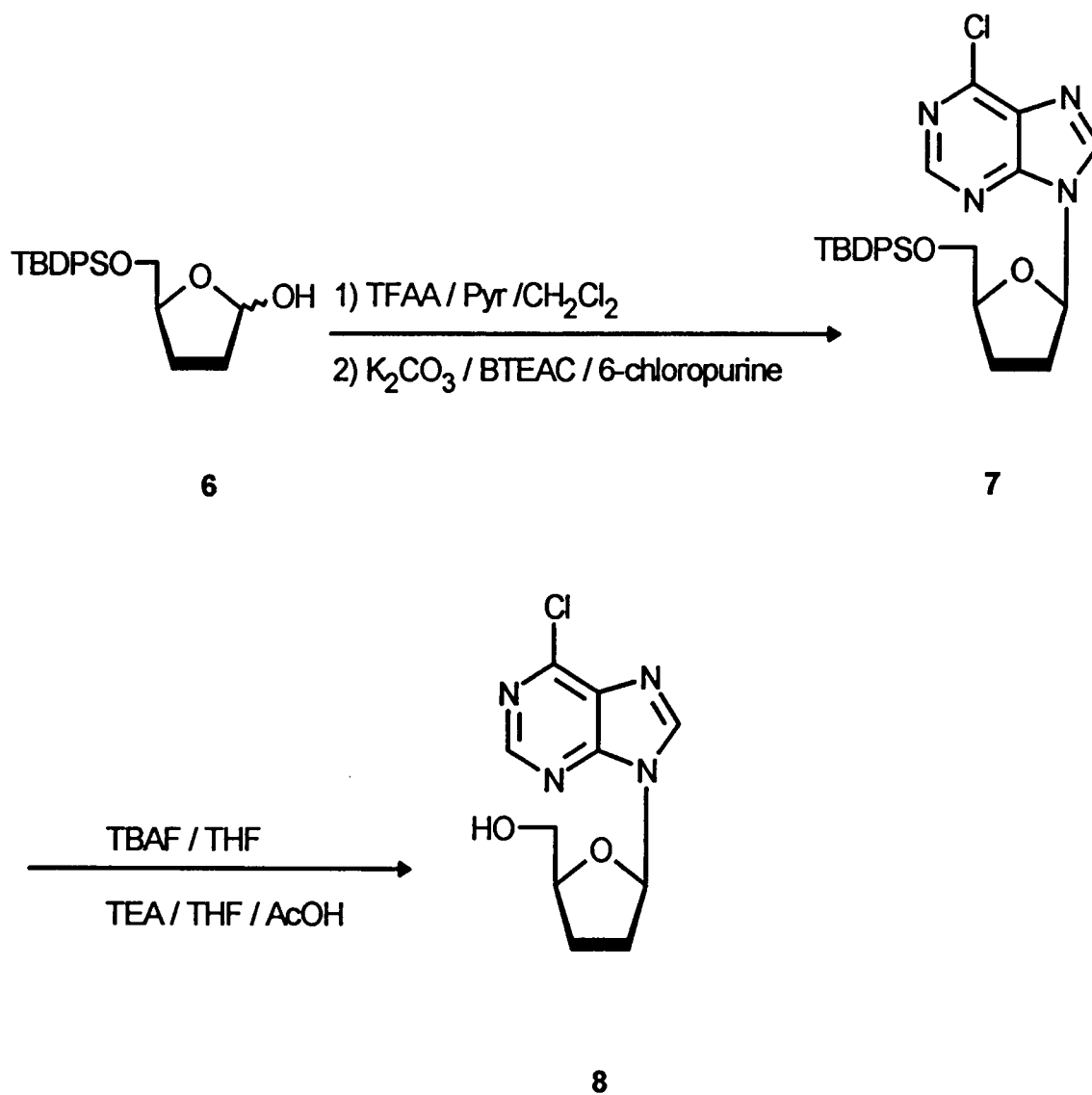
achieved by refluxing a basic solution of **4** in pyridine/ CH_2Cl_2 with 1.2 equiv of *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) in presence of 4-dimethylaminopyridine (4-DMAP) as catalyst, giving product **5** in 63% yield, isolated and purified through silica gel column chromatography and by recrystallization from hexane. Structural elucidation of compound **5** was accomplished through ^1H NMR spectroscopy as follows: (See Appendix, p 72) (1) The *tert*-butyl group is seen as a singlet at δ 1.0–1.1. (2) The hydrogens on the two phenyl rings resonate at δ 7.3–7.8 as a multiplet, typical for aromatic protons. (3) The lactone ring's H-2 and H-3 lie at δ 2.1–2.8 as a multiplet, being pulled downfield by the carbonyl group and split by each other. H-4 can be designated at δ 4.5–4.7 as a complex multiplet, being shifted downfield due to C-4 that is bonded directly to and pulled by an oxygen atom and split by H-3, H-3', and H-5. The two magnetically different H-5 hydrogens being split by H-4 and each other, show two doublet of doublets at δ 3.0–3.9 (AB of an ABX system). DIBAL-H reduction of the lactone carbonyl in compound **5** was performed according to a procedure by Okabe, M. and the co-workers³⁹ with some changes in the conditions. Their procedure was involved in the reduction of the corresponding *tert*-butyldimethylsilyl-protected lactone. DIBAL-H (1.3 equivs compared to 1.1 equivs, in literature) was reacted with lactone **5** in toluene as the solvent at low temperature ($-78\text{ }^\circ\text{C}$) using extremely anhydrous conditions. DIBAL-H (as a solution in toluene) was added to the solution of compound **5** in toluene over a period of 5 min, whereas in the literature³⁹ the addition period was 45 min. The reaction mixture was stirred for 45 min (5 min, in the literature) and was

quenched with a mixed solution of EtOAc/AcOH/H₂O (in the literature, MeOH was used). The product was extracted into CH₂Cl₂, stirring for 15 min in the presence of MgSO₄(anhydrous) (in the literature, it was extracted into EtOAc, stirring for 2 h in the presence of saturated NaHCO₃ and overnight after addition of Na₂SO₄). Since the DIBAL-H reagent can attack the carbonyl from either face of the lactone ring, product **6** was isolated as a mixture of α and β anomers in 99% yield upon silica gel column chromatography purification and recrystallization of the product from hexane. The structure of **6** was proved by ¹H NMR spectroscopy (See Appendix, p 73), which for most resonances showed two sets of peaks due to the α,β -mixture of products. The H-1 and OH group created after reduction of the carbonyl group are seen at δ 5.4–5.6 as a multiplet and at δ 2.0–2.5 as two singlets (α and β anomers), respectively. H-1 is shifted downfield as C-1 is subjected to the electron-withdrawal effects of the two directly bonded oxygen atoms. H-1 undergoes spin-spin splitting by H-2 and H-2' on the sugar ring. The two methyl groups of the TBDPS group are found at δ 1.1–1.5 as two singlets. Protons H-2, H-3, H-4, and H-5 are shifted slightly upfield compared with the starting protected lactone **5** due to anisotropic effect of the lactone carbonyl group. H-4 protons are observed at δ 3.3–3.9 as two sets of doublets of doublets, one set being shifted more upfield. With this protection strategy, we have the anomeric hydroxyl group on C-1 ready for coupling while the γ -hydroxyl group on C-5 is protected.³⁹

B. Preparation of

6-Chloro-9-(2,3-dideoxy- β -D-*glycero*-pentofuranosyl)purine (8)

Coupling the sugar ring, a protected D-*glycero*-pentofuranose, to the nucleic acid base, 6-chloropurine, at the anomeric carbon (C-1') to build the nucleoside skeleton is performed by converting the anomeric hydroxyl group to a good leaving group and reacting the compound with the nucleic acid base, which acts as a nucleophile, in an S_N2 substitution-type reaction. Chang K. Chu and co-workers⁴⁰ have reported a strategy of conversion the anomeric hydroxyl group of the sugar to an acetate group, followed by reaction with trimethylsilylated 6-chloropurine in presence of trimethylsilyl triflate in 1,2- dichloroethane. In this project the anomeric hydroxyl group was converted to a trifluoroacetyl group, which is a better leaving group, through reaction with 1.3 equivs of trifluoroacetic anhydride (TFAA) in pyridine/ CH_2Cl_2 (Scheme 2) and was coupled to 0.7 equiv of 6-chloropurine in acetonitrile (CH_3CN) in presence of potassium carbonate (K_2CO_3) and benzyltriethylammonium chloride (BTEAC). Since the trifluoroacetyl group is very reactive, the reaction was conducted at $-40\text{ }^\circ\text{C}$ and under extremely anhydrous conditions. Pyridine, catalyzing the reaction through nucleophilic catalysis, also maintains a basic medium which is safe for the trifluoroacetyl ester (after formation) and purine 6-chloro group, which are very sensitive to acidic hydrolysis. The nucleophile, 6-chloropurine is added right after the first step (conversion of



SCHEME 2. Synthesis of 6-Chloro-9-(2,3-dideoxy- β -D-glycero-pentofuranosyl)purine.

anomeric hydroxyl group to trifluoroacetoxy) as a suspension in a polar solvent, acetonitrile, with increased polarity and ionic character due to the presence of K_2CO_3 and BTEAC, a good set of conditions for an S_N2 process. Following the above-mentioned conditions resulted in 6-chloro-9-[5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-D-*glycero*-pentofuranosyl]purine, as a mixture of α and β anomers after purification of the reaction mixture by silica gel column chromatography. The β anomer, the desired compound **7**, which is crystalline, was separated from the α anomer, which is a syrup and has a higher R_f value in a hexane–ethyl acetate solvent system (faster moving spot). By applying preparative HPLC using a hexane–ethyl acetate solvent system, an improved faster open-column technique, different from that in the literature (in the literature silica gel open column chromatography has been used), followed by recrystallization in hexane, to give nucleoside **7** in 28.6% yield (based on 6-chloropurine). Its structure was confirmed by ^1H NMR spectroscopy, which was consistent with that reported in the literature (See Appendix, p 74).

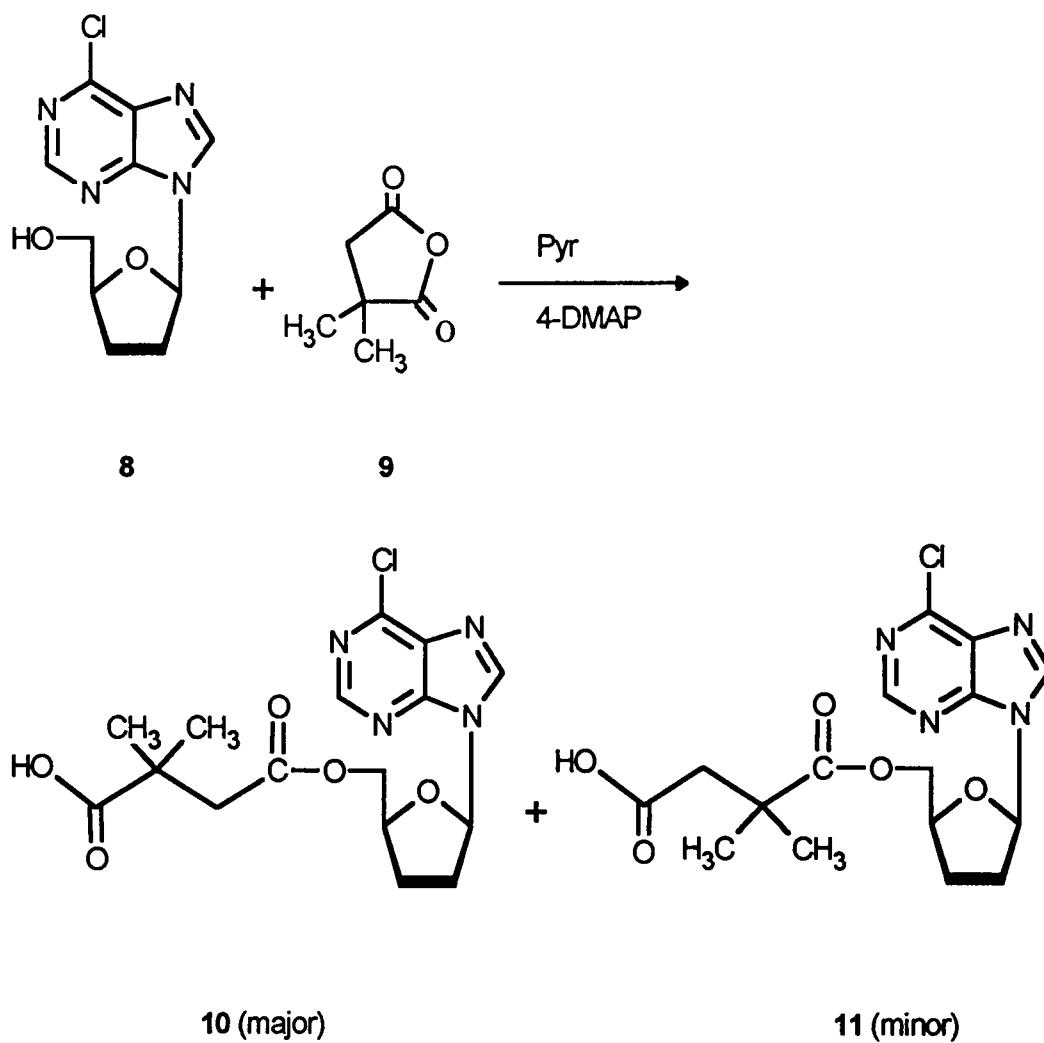
Deprotection of the silyl protecting groups was accomplished upon treatment with tetrabutylammonium fluoride (TBFA) in THF. Reaction of the silyl-protected nucleoside **7** with 2.0 equivs of TBAF in THF, a buffer system of Et_3N /THF/AcOH to protect the 6-chloro group on the purine ring from possible hydrolysis, at r.t. afforded 6-chloro-9-(2,3-dideoxy- β -D-*glycero*-pentofuranosyl)purine (6-Cl-ddP, **8**), in 83% yield after purification by silica gel column chromatography. The purity of product **8** was confirmed by HPLC, showing a single peak, and the structural

elucidation was accomplished through ^1H NMR and ^{13}C NMR spectroscopy (See Appendix, pp 75 and 76), and ultraviolet spectrophotometry (UV). Both the ^1H NMR and UV data of **8** are consistent with those reported in the literature.⁴⁰ ^{13}C NMR shows the four sugar ring carbons and C-5' at δ 86.92, 32.98, 25.05, 63.39, and 82.34; accordingly, carbons 1', 4', and 5' are shifted downfield due to the electron-withdrawing effect of the adjacent oxygen atoms, and the five purine ring carbons at δ 132.25, 144.50, 150.59, 151.00, and 151.51, are far downfield compared to the sugar ring carbons due to sp^2 hybridization. Thus all carbons appear at the expected chemical shifts.

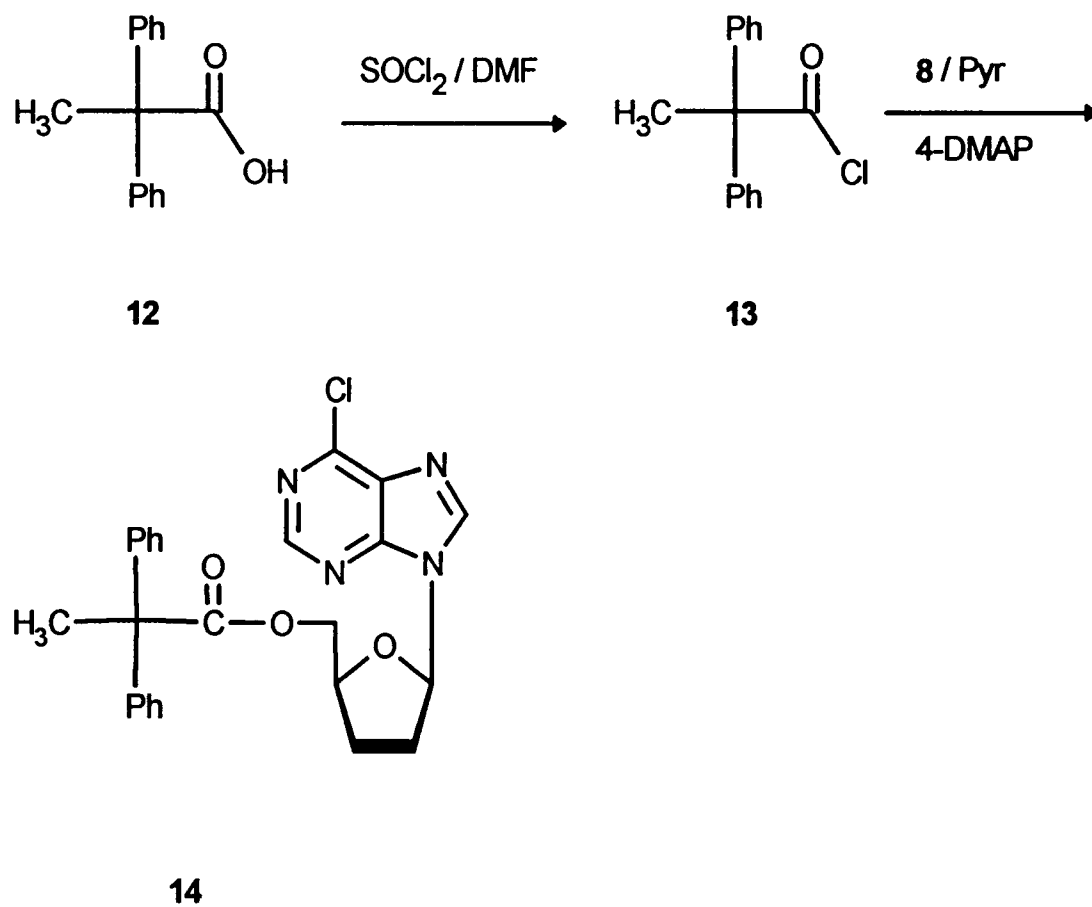
C. Design And Synthesis of The Sterically Hindered 5'-Esters of 6-Cl-ddP

The 5'-esters of 6-Cl-ddP were designed, each having a highly hindered acyl moiety that was selected based on the published steric parameter, v , of the respective acyl group defined by Charton⁴¹ as the difference between van der Waals radius of X and H atom in the esterification reaction for a generic carboxylic acid, XCOOH . Apparently v is zero for X group being an H atom and proportionally increases as the X group becomes bulkier. Four 5'-esters, (see Table 1), 2-ethylbutyryl (**17**) with a v value of 1.51; 2,2-diethylbutyryl (**22**), and 2,2-diphenylpropionyl (**14**), with v values of 2.38 and 2.34, respectively, greater than 2, and one bearing a free carboxyl group (a negative charge at physiological pH), 2,2-dimethylsuccinoyl (**10**), were designed to be synthesized.

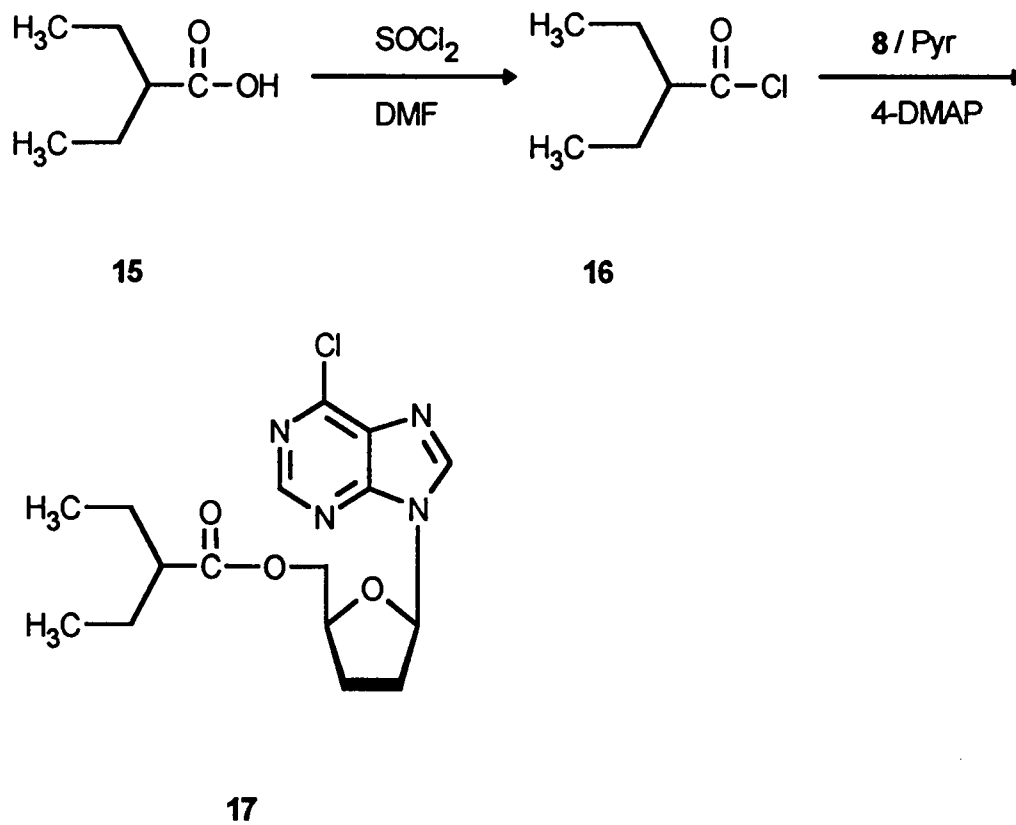
To synthesize the 5'-esters (Schemes 3 to 6) according to the procedure by T. Kawaguchi and co-workers,⁴ the appropriate acid chloride or acid anhydride was reacted with the stirred nucleoside alcohol, 6-Cl-ddP, in pyridine in presence of 4-DMAP as catalyst. Due to the reactivity and sensitivity of the acid chloride and acid anhydrides to moisture undergoing hydrolysis, the reactions were performed under anhydrous conditions. Pyridine used as the solvent, and 4-DMAP both catalyzes the reaction by attacking the acyl carbonyl site, replacing the chloro group, and forming an acyl-pyridinium and acyl-4-dimethylaminopyridinium salt intermediate (nucleophilic catalysis). 4-DMAP, being a better nucleophile, is the more efficient catalyst. The acyl chlorides were synthesized from the appropriate carboxylic acids, refluxing with thionyl chloride in presence of DMF as catalyst, which reacts with thionyl chloride and forms the a Vilsmeier complex intermediate. In case of the 5'-O-2,2-diethylbutyryl ester, since the corresponding 2,2-diethylbutyric acid (**20**) was not available, it was synthesized from the available 2-ethylbutyric acid (**15**), which, in order to protect the carboxyl group, was converted to the ethyl ester **18** by refluxing with EtOH in the presence of sulfuric acid. An ethyl group was introduced at C-2 of the ester **18** by making the enolate ion using a kinetic base, lithium diisopropylamide (LDA), followed by involving the enolate ion in an S_N2 reaction with ethyl iodide.⁴²⁻⁴⁵ Cleaving the resulting ethyl 2,2-diethylbutyrate (**19**) to produce 2,2-diethylbutyric acid (**20**), due to the high degree of steric hindrance of the bulky triethyl substituted-acyl moiety was not possible with the ordinary sodium hydroxide base-catalyzed hydrolysis. The cleavage was accomplished by



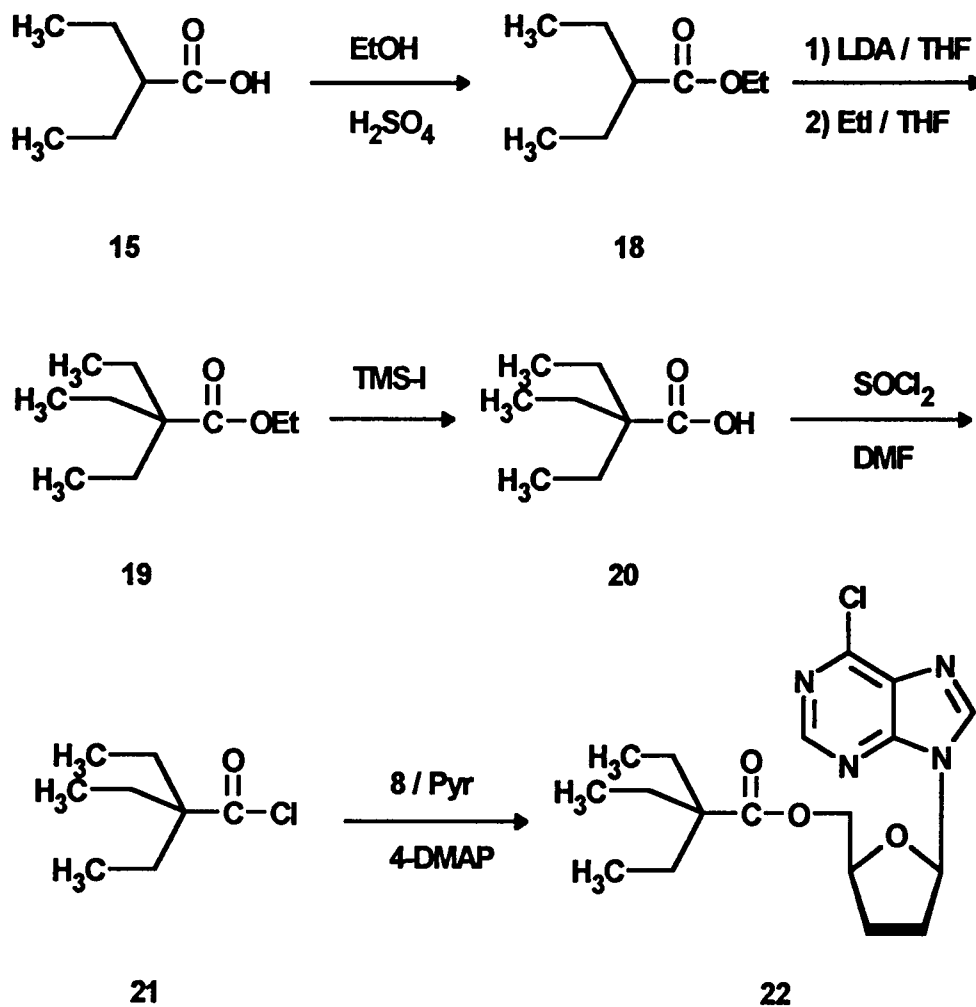
SCHEME 3. Synthesis of 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-dimethylsuccinoyl)-β-D-*glycero*-pentofuranosyl]purine (major product) and 6-Chloro-9-[2,3-dideoxy-5-O-(3,3-dimethylsuccinoyl)-β-D-*glycero*-pentofuranosyl]purine (minor product).



SCHEME 4. Synthesis of 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-diphenylpropionyl)- β -D-glycero-pentofuranosyl]purine.



SCHEME 5. Synthesis of 6-Chloro-9-[2,3-dideoxy-5-O-(2-ethylbutyryl)-β-D-glycero-pentofuranosyl]purine.



SCHEME 6. Synthesis of 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-diethylbutyryl)- β -D-glycero-pentofuranosyl]purine

reacting the ester **19** with trimethylsilyl iodide (TMS-I) at elevated temperature. As suggested by G. A. Olah et al.,⁴⁶ the first step involves reaction of the ester with TMS-I in a fast equilibrium process, leading to a silylated ester iodide intermediate, which in a slow irreversible second step through an S_N2 mechanism continues to the trimethylsilylated product. The trimethylsilyl ester, which is much more unstable and sensitive to hydrolysis, cleaves upon acidic workup to the desired carboxylic acid **20**.

C-1. Synthesis of

6-Chloro-9-[2,3-dideoxy-5-O-(2,2-dimethylsuccinoyl)-β-D-glycero-pentofuranosyl]purine (10, Major Product) and
6-Chloro-9-[2,3-dideoxy-5-O-(3,3-dimethylsuccinoyl)-β-D-glycero-pentofuranosyl]purine (11, Minor Product)

According to procedure followed by T. Kawaguchi and coworkers,²⁰ nucleoside alcohol **8** was reacted with 2 equivs of the available 2,2-dimethylsuccinic anhydride (Scheme 3) in pyridine in the presence of 1 equiv of 4-DMAP catalyst at r.t.. Unfortunately, since there are two carbonyl positions at C-1 and C-4 available for the attack of the hydroxyl nucleophile, the one at C-1 being more hindered due to the presence of the dimethyl groups, the reaction yielded in a mixture of two isomers as monitored by TLC as a slow-moving double zone compared to the starting nucleoside **8** in CH₂Cl₂-MeOH solvent system. As

confirmed by HPLC, after purification of the product by silica gel column chromatography, the 5'-O-(2,2 dimethylsuccinoyl) product **10**, resulting from the nucleophilic attack of the 6-Cl-ddP hydroxyl group to the less hindered carbonyl C-4, was produced as the major product in a ratio of 3:1 to the minor 5'-O-(3,3-dimethylsuccinoyl) product **11**. The yield of both isomers was 50%, and structural elucidation was achieved using ^1H NMR spectroscopy (See Appendix, p 77). The dimethyl groups are seen at δ 1.25–1.30 as a singlet, while the $\text{CH}_2\text{--CO}$ protons appear at δ 2.7 as a singlet overlapped with H-2' hydrogens of the sugar ring. The H-5' lies at δ 4.35 as a multiplet formed by collapse of the two doublet of doublets due to the stereo-magnetic effect of the succinoyl acyl group, causing the two H-5' hydrogens to become nearly magnetically equivalent. The other protons of the sugar and the purine ring show the same pattern as the starting compound, ddP, with H-1' located at δ 6.34–6.35 as a multiplet, and H-8 and H-2 designated at δ 8.46 and 8.74, respectively, as singlets. The Cl-35 and Cl-37 [M^+] isotopic peaks with the respective molecular weights of 381.1 and 383.1 shown in the electrospray-ionization mass spectrum (ESIMS) of the product correspond with the calculated molecular weights of 381.1 and 383.1 for the respective isotopes of the product within 0.0 mass units.

**C-2. Synthesis of 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-diphenylpropionyl)-
 β -D-glycero-pentofuranosyl]purine (14)**

The available 2,2-diphenylpropionic acid (**12**) was converted to its acid chloride according to the procedure by S. Takeuchi et al.⁴⁸ by stirring and refluxing with 6.4 equivs of thionyl chloride in presence of catalytic amount of DMF (the latter was not used in literature) (Scheme 4) to give 2,2-diphenylpropionyl chloride (**13**) in 74% yield after isolation by vacuum distillation. The structure of acyl chloride **13** was confirmed through ¹H NMR spectroscopy (See Appendix, p 78). The methyl group appears at δ 2.08 as a singlet, and the two phenyl groups are seen at δ 7.10–7.40 as a multiplet, all being slightly shifted downfield compared to the starting carboxylic acid due to the increased electronegativity of the acyl chloro group. No acidic proton is seen far downfield.

To prepare the nucleoside 5'-ester from the acyl chloride **13**, 1.6 equivs of **13** was reacted with the nucleoside 6-Cl-ddP in pyridine and in the presence of 1 equiv of the catalyst, 4-DMAP, at r.t. (Scheme 4). The progress of the reaction was easily monitored by TLC using EtOAc as the developing solvent. As the slow-moving zone, the starting material, 6-Cl-ddP, disappeared, and the fast-moving spot, the 5'-ester product, appeared. The reaction afforded the 5'-ester nucleoside **14** in 59% yield after purification by silica gel column chromatography, and its structure was elucidated in the light of ¹H NMR and ¹³C NMR spectroscopy (See Appendix, pp 79 and 80). The methyl protons are seen at δ 1.93 as a singlet,

slightly shifted upfield compared to the starting acyl chloride due to the smaller electron-withdrawing effect of the ester functional group. The H-4' and H-5' hydrogens are overlapped, appearing at δ 4.30–4.47 as a multiplet. The two phenyl groups are seen at δ 7.10–7.30, and almost the same pattern as in 6-Cl-ddP is seen for the reminder of the sugar and purine ring protons. The ^{13}C NMR is consistent with the combination of 6-Cl-ddP and diphenylpropionyl ester parts, the methyl appearing at δ 27.10, and the two phenyl groups as five peaks at δ 126.85–128.09. The quaternary central carbon bonded to diphenyl, methyl, and the carbonyl groups lies at δ 56.61 as a small peak, shifted downfield by the combined electron-withdrawing effect of the carbonyl and two phenyl groups. The carbonyl group is seen far downfield at δ 174.86. The sugar and purine ring carbons follow almost the same pattern as in 6-Cl-ddP, with a slight upfield and downfield shift of some carbons. The Cl-35 and Cl-37 isotopic $[\text{M}^+ + \text{Na}]$ peaks with the respective molecular weights of 485.0 and 487.0 are observed in the electrospray-ionization mass spectrum (ESIMS) of the product and correspond with the calculated molecular weights of 485.1 and 487.1 for the respective isotopes of the product within 0.1 mass units.

C-3. Synthesis of 6-Chloro-9-[2,3-dideoxy-5-O-(2-ethylbutyryl)-***β*-D-glycero-pentofuranosyl]purine (17)**

2-Ethylbutyryl chloride (16) was prepared by reacting 2-ethylbutyric acid (15) with 6.6 equivs of thionyl chloride in presence of a catalytic amount of DMF (Scheme 5), following essentially the same procedure as in part C-2. The yield after isolation of the product by simple distillation was 72%, and its structure was confirmed by ^1H NMR spectroscopy (See Appendix, pp 81 and 82). The two methyl protons appear at δ 0.97 as a triplet being split by adjacent CH_3 and CH protons. The CH_2 protons are in turn split by the CH_3 and CH protons and are seen as a multiplet at δ 1.60–1.80, while the CH protons appear at δ 2.70 as a multiplet as being split by the two CH_2 protons. All the hydrogens, compared to those of the starting carboxylic acid 15, are shifted downfield, being affected by the more electron-withdrawing acyl chloride functional group.

The acyl chloride 16 was reacted with 6-Cl-ddP in a 2:1 molar ratio in pyridine and in the presence of 4-DMAP catalyst, following essentially the same procedure as in part C-2 (Scheme 5). The coupling reaction, due to less steric hindrance of the diethyl-substituted acyl moiety compared to the other esters, proceeded rather quickly, and the TLC-monitored reaction mixture showed complete conversion of the slow-moving spot, 6-Cl-ddP, to the fast moving spot, the 5'-ester 17, in about 5 min (eluting solvent was EtOAc). The 5'-ester 17, which was purified by silica gel column chromatography, had a yield of 67%. Its purity was

confirmed through HPLC, and its structural elucidation was accomplished by ^1H NMR and ^{13}C NMR spectroscopy (See Appendix, pp 83 and 84). The two methyl protons appear at δ 0.83–0.91 slightly shifted upfield compared to the corresponding signal in the starting acyl chloride **16** as two triplets very close to each other, showing that they are now in two magnetically different environments due to the stereomagnetic effect of the coupled nucleoside. The two CH_2 hydrogens of the acyl group show up at δ 1.48–1.61 as a multiplet, also being slightly shifted upfield. The CH of the acyl group is overlapped with H-2' and H-3' of the sugar ring designated at δ 2.10–2.71 as a multiplet. The H-4' and H-5' protons are overlapped in contrast to the corresponding protons in 6-Cl-ddP, being seen at δ 4.36–4.49 as a multiplet. The rest of the sugar and purine ring protons follow almost the same pattern as 6-chloro-ddP. The acyl CH_3 , CH_2 , CH, and carbonyl group carbons appear at δ 11.6, 24.6, 48.6, and 175.8, respectively, shifted downfield in the order of distance from the electron-withdrawing oxygen atoms of the ester group. The rest of the carbons on the sugar and purine ring show almost the same pattern, C-5' and C-4' being slightly shifted upfield and downfield, accordingly, compared to those of the parent nucleoside. The Cl-35 and Cl-37 isotopic $[\text{M}^+ + \text{Na}]$ peaks with the respective molecular weights of 374.9 and 376.9 are observed in the electrospray-ionization mass spectrum (ESIMS) of the product correspond with the calculated molecular weights of 375.1 and 376.9 for the respective isotopes of the product within 0.2 mass units.

**C-4. Synthesis of 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-diethylbutyryl)-
 β -D-glycero-pentofuranosyl]purine (22)**

2-Ethylbutyric acid (**15**) was refluxed with 0.5 equiv of ethanol in the presence of sulfuric acid as catalyst, resulting in ethyl 2-ethylbutyrate (**18**) in 64% yield after isolation by simple distillation. The structure of product **18** was confirmed by ^1H NMR and ^{13}C NMR spectroscopy (See Appendix, pp 85 and 86). The CH_3 , CH_2 , and CH group hydrogens of the acyl part resonate at δ 0.89, 1.55, and 2.18 as a triplet, multiplet, and multiplet, respectively, being slightly shifted upfield compared with the corresponding resonances of the starting carboxylic acid **15**. The CH_3 and CH_2 hydrogens of the ethyl ester group are seen at δ 1.23 and 4.16 as a triplet and a quartet accordingly. The ^{13}C NMR spectrum shows six magnetically different carbons, $\text{C}=\text{O}$ and acyl CH_3 , CH_2 , and CH and ethyl ester CH_3 and CH_2 , observed at δ 175.54, 11.34, 24.78, 48.59, 13.95, and 59.41, respectively.

The ester **18** was reacted with 1.3 equivs of LDA in THF at -78°C , and then the resulting enolate ion was treated with 1.5 equivs of ethyl iodide in THF under the same conditions. Due to the steric problems involved in a bulky molecule, LDA, approaching the sterically hindered enolic proton, H-2, of the ester, the improved conditions (different from those in the literature)⁴⁹ using an excess of 1.3 equivs of LDA (compared to 1.0 equiv in literature) and stirring the reaction mixture for 3 h after addition of LDA (only 40 min in literature), resulted in the completion of the reaction. No ethyl 2-ethylbutyrate, the starting compound, was left, which would be

very difficult to separate from the desired product, ethyl 2,2-diethylbutyrate (**19**) due to their similar boiling points. The structure of the triethyl-substituted product **19**, which was obtained in a yield of 53% after isolation by simple distillation, was proved by ^1H NMR spectroscopy (See Appendix, p 87). The nine hydrogens belonging to the three methyl groups of the acyl moiety are seen at δ 0.76 as a triplet, while the three acyl CH_2 protons are located at δ 1.53–1.62 as a quartet, and the ethyl ester CH_2 and CH_3 hydrogens are designated at δ 4.09–4.1 and 1.25 as a quartet and a triplet, respectively.

The ester product **19** was cleaved reacting with 2.0 equivs of iodotrimethylsilane at 100 °C for 24 h, a longer time than used by Tse-Lok Ho et al.⁴⁷ because of the very high steric hindrance of ester **19**, affording 2,2-diethylbutyric acid (**20**) in 63% yield after recrystallization from chloroform. The structure of carboxylic acid product **20** was confirmed through ^1H NMR spectroscopy (See Appendix, p 88). The three acyl CH_3 and CH_2 group hydrogens are seen at δ .81 and 1.60 as a triplet and a quartet, respectively, slightly shifted downfield compared to those of the starting ester **19**. The acidic proton appears at δ 11.7 as a small, broad peak due to its low proton ratio.

Carboxylic acid **20** was converted to its acid chloride by reacting with 6.3 equivs of thionyl chloride in presence of a catalytic amount of DMF, stirring and refluxing for a longer time of 2 h and 3 h accordingly than reported in literature,⁴⁸ due to the sterically hindered carboxyl group. The acyl chloride, 2,2-diethylbutyryl chloride **21**, was obtained in a yield of 67% after being purified by simple distillation.

Its structure was confirmed by ^1H NMR spectroscopy (See Appendix, p 89). The three acyl CH_3 and CH_2 groups are observed at δ 0.85 and 1.66–1.75 as a triplet and a quartet, accordingly, slightly shifted downfield compared to those in the starting carboxylic acid **20**, due to the increased electron-withdrawing effect of the acyl chloride functional group.

The 2,2-diethylbutyryl 5'-ester of 6-Cl-ddP **22**, was synthesized by coupling 6.0 equivs of the acyl chloride **21** with 6-Cl-ddP **8**, in pyridine in the presence of 2.3 equivs of the catalyst 4-DMAP at r.t. Due to the high sterically hindered nature of the triethyl ester moiety, higher equiv ratios of the acyl chloride and 4-DMAP were used. The reagents were added in four portions during the lengthy period of time of the reaction (41 h) required to reach completion, as monitored by TLC. Product **22** was obtained in 67% yield after purification by silica gel column chromatography. Its purity was confirmed as a single peak by HPLC, and its structure was elucidated by ^1H NMR and ^{13}C NMR spectroscopy (See Appendix, pp 90 and 91). The three acyl CH_3 and CH_2 group protons are seen at δ 0.56–0.68 and 1.37–1.46 as a triplet and a quartet, respectively, shifted slightly upfield compared to those of the starting acyl chloride **21**, a result that is expected because of the more electron-withdrawing property of acyl chloride compared to ester functional group. Other protons belonging to the sugar and purine rings, being slightly shifted upfield, follow almost the same pattern as those observed in the starting nucleoside 6-Cl-ddP, except for H-5' which is observed as a triplet instead of doublet of doublets. CH_3 and CH_2 carbons of the acyl group appear at δ 7.98 and 25.78, the central quaternary

carbon of the acyl group is seen at δ 49.82 as a weak peak that is typical for a quaternary carbon. The carbonyl carbon resonance shows up at δ 176.61. The other carbons belonging to sugar and purine rings follow almost the same pattern as the starting 6-Cl-ddP, C-3' and C-5' being slightly shifted down and upfield, respectively. The high resolution electron fast atom bombardment mass spectrum (HRFABMS) of product **22** showed a $[M^+ + H]$ peak with the molecular mass of 381.172, which corresponds to the calculated molecular mass of 381.169 within 0.003 mass units.

D. The Observed Effect of the Sterically Hindered 5'-Ester Double Prodrugs of ddl on the Bioavailability of ddl

A total of five hindered 5'-esters of 6-Cl-ddP were made available for studies on bioavailability and conversion to ddl for enhanced CNS delivery: (1) the 5'-O-pivaloyl-, (2) the 5'-O-(2-methylbenzoyl)-, both of which were previously prepared by Dr. Shijia Yan in this laboratory,⁵⁰ and (3) the 5'-O-(2-ethylbutyryl)- (**17**), (4) the 5'-O-(2,2-diphenylpropionyl)- (**14**), and (5) the 5'-O-(2,2-diethylbutyryl)-6-Cl-ddP (**22**), all from the this thesis work. Bioconversion studies were conducted by Mr. Dhamendra Singal in the laboratory of Prof. Bradley D. Anderson of the College of Pharmacy, The University of Utah. Details of these studies are available in D. Singal's Ph.D. Dissertation.³ Due to problems encountered with its toxicity toward rats used in the studies, the 5'-O-(2,2-dimethylsuccinoyl)-6-Cl-ddP (**10**) and its

isomer **11** were not evaluated.

As a measure of general systemic susceptibility of the compounds to esterases, all were evaluated in rat-liver homogenates, and the rates of ester hydrolysis were determined. Details are provided in Table 1. In general, steric bulk was found effective in decreasing the rates of hydrolysis toward the liver esterases; however, a linear relationship with steric bulk, e.g., comparison with the Verloop et al. steric factors,^{31,32} was not observed. Esterase activity is complex and is dependent upon perhaps a number of factors, including aqueous solubility, lipophilicity, steric bulk, and charge densities, to name a few parameters.

In a complex system developed to measure intestinal perfusion of prodrugs in a rat,³ attempts were made to determine if these sterically hindered, double-prodrugs would be effective in providing systemic pools of prodrugs that might enhance delivery to the CNS. The results, unfortunately, were complicated by a number of factors, the major one being water solubility that varied considerably over the range of prodrugs evaluated, necessitating the use of polyethyleneglycol to enhance solubility, which resulted in altered lipase (esterase) activity in the intestinal wall. Nonetheless, the experiments did demonstrate that the two most sterically bulky prodrugs, the 5'-O-(2,2-diphenylpropionyl)- (**14**) and the 5'-O-(2,2-diethylbutyryl)-6-Cl-ddP (**22**) were able to cross the intestinal wall and provide significant levels of the double-prodrugs in the blood. Thus presystemic bioconversion of these prodrugs was blocked. It remains for further studies to establish the efficacy (or lack thereof) of such compounds, particularly in

Table 1. Rate constants of hydrolytic degradation, k , and steric parameters, v , of 6-Cl-ddP-5'-esters in the liver homogenate.^a

Ester	v	k (min ⁻¹)
6-Cl-ddP		
5'-O-pivaloyl-6-Cl-ddP (100 % aqueous)	1.24	11.7 ± 1.1
5'-O-pivaloyl-6-Cl-ddP (50% PEG-400)	1.24	11.7 ± 1.1
5'-O-(2-methylbenzoyl)-6-Cl-ddP	0.9	21.8 ± 1.5
5'-O-(2-ethylbutyryl)-6-Cl-ddP	1.51	50.6 ± 6.6
5'-O-(2,2-diphenylpropionyl)-6-Cl-ddP	2.34	2.9 ± 0.5
5'-O-(2,2-diethylbutyryl)- 6-Cl-ddP	2.38	4.4 ± 0.5

^aData taken from the Ph.D. dissertation of Dr. D. Singal (University of Utah), ref. 3.

demonstrating that they are effective in delivering adequate levels of ddl to the CNS.

Further refinements in ester structure may be needed to find a suitable balance among presystemic bioconversion in the intestinal wall, systemic hydrolysis of the prodrugs, as well as final bioconversion to ddl at or near the CNS. Also, the problem of acute toxicities observed with **10** and **11** remain unexplained.

IV. EXPERIMENTAL

A. General Methods. All solvents and reagents were reagent grade and were used directly unless noted otherwise. Ethyl iodide (EtI) was predried over anhydrous calcium sulfate (CaSO_4) for 24 h. Anhydrous solvents were prepared as follows: dichloromethane (CH_2Cl_2), pyridine, and acetonitrile (CH_3CN) were distilled from calcium hydride; toluene (PhCH_3) was distilled from calcium hydride and sodium metal; *N,N*-dimethylformamide (DMF) was distilled from calcium hydride at 20 torr; tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl. Solvents were evaporated with a Büchi rotary evaporator at 30–40 °C/30 torr. Rotary evaporations carried out at pressures less than 5 torr have been noted as “under high vacuum”. All reactions and column separations were monitored by TLC on 0.2-mm aluminum-backed plates (E. Merck Silica Gel 60), and open-column column chromatography was carried out using coarse (63–200 μm) or fine (230–400 μm) bulk silica gel accordingly. Visualization of the TLC plates was carried out by 254-nm UV light and by spray–heat development using a *p*-anisaldehyde–sulfuric acid, or a 3% phosphomolybdic acid dip whereby the

compound showed up as a dark gray spot with light gray background or a dark green spot with light green background accordingly. All the melting points were determined using a Thomas–Hoover capillary melting point apparatus coupled with a Cole–Parmer 8520-50 Digi-Sence digital thermocouple. Ultraviolet spectra were measured for solutions in absolute ethanol (EtOH) in 1-cm cells on a Shimadzu model UV-2101 PC UV-vis scanning spectrophotometer. Routine ^1H and ^{13}C NMR spectra were measured at 250 MHz and 62.5 MHz, respectively, as 1–2% (w/v) solutions in chloroform-*d* (CDCl_3) dimethyl sulfoxide-*d*₆ ($\text{DMSO-}d_6$) using a Bruker AM 250 instrument. Chemical shifts are reported as δ (ppm) downfield from an internal standard of tetramethylsilane (TMS). Multiplicities are first-order values in Hz and are recorded as: s, singlet; t, triplet; d, doublet; dd, doublet of doublets; s, singlet; q, quartet; m, multiplet. ^{13}C NMR chemical shifts are reported as δ (ppm) relative to CDCl_3 (77.00 ppm) as a standard. HPLC was carried out using Beckman 100A instrument with a C_{18} reversed-phase column and UV 254-nm detection. Preparative HPLC was performed on a Waters 500A/prep system. High-resolution mass spectroscopy was done on a ZAB-EQ mass spectrometer (VG-Analytical, Manchester, England). Electrospray-ionization mass spectrometry was performed on a Micromass Quattro II Instrument.

B. Preparation of (S)- γ -Carboxy- γ -butyrolactone (2). To a $-5\text{ }^\circ\text{C}$ cooled (ice–acetone–liquid nitrogen bath) stirred suspension of L-glutamic acid (1, 180 g, 1.20 mol) in concentrated HCl (252 mL) and H_2O (480 mL) was added dropwise over a period of 4 h a solution of sodium nitrite (NaNO_2 , 126 g, 1.80 mol) in H_2O

(270 mL). In the whole period of addition, the temperature was kept at $-5\text{ }^{\circ}\text{C}$, and a blue color due to the formation of the diazonium salt was observed. The reaction mixture was stirred overnight from $-5\text{ }^{\circ}\text{C}$ to r.t.. High-vacuum rotary evaporation of water at $50\text{ }^{\circ}\text{C}$, followed by freeze drying, gave a white solid that was extracted with ethyl acetate (EtOAc, 600 mL). The mixture was suction filtered, and the organic filtrate was dried over anhydrous magnesium sulfate (MgSO_4), filtered, rotary-vacuum and high-vacuum evaporated, and dried in a pistol (CH_2Cl_2 reflux) for 72 h to give the product **2** (102.1 g, 785 mmol, 63.8%) as a pale-yellow solid.

Physicochemical data: ^1H NMR (CDCl_3 , 250 MHz): δ 2.40–2.70 (m, 4H, H-2 and H-3) 5.00 (m, 1H, H-4), 10.00 (bs, 1H, H-5), [Lit.³⁴ (CD_3OD , 100 MHz): 1.8–2.3 (m, 4H, H-2 and H-3), 4.2 (m, 1H, H-4)]; ^{13}C NMR ($\text{DMSO}-d_6$, 62.5 MHz) 26.00 (C-3), 27.00 (C-2), 76.00 (C-4), 172.00 (C-1), 177.00 (C-5), [Lit.³⁴ (60.0 MHz): 26.00 (C-3), 27.1 (C-2), 76.0 (C-4), 172.5 (C-1), 177.5 (C-5)].

C. Preparation of (S)- γ -Ethoxycarbonyl- γ -butyrolactone (3). To a solution of (S)- γ -carboxy- γ -butyrolactone (**2**, 50.0 g, 384 mmol) in absolute EtOH (150 mL) and dry PhCH_3 (320 mL) was added *p*-toluenesulfonic acid monohydrate (*p*-TsOH $\cdot$ H $_2$ O, 2 g, 11 mmol), and the mixture was refluxed using a Dean–Stark apparatus and a CaSO_4 drying tube for 5 h. After rotary vacuum evaporation of solvent, PhCH_3 (200 mL) and EtOAc (200 mL) were added, and the mixture was washed with 10% Na_2CO_3 (3 $\times$ 400 mL, pH 7) and dried over anhydrous MgSO_4 . High-vacuum rotary evaporation of solvent, followed by vacuum distillation, gave the product **3** (46.5 g, 294 mmol, 76.6%) as a clear, colorless oil.

Physicochemical data: bp 96–106 °C/0.005 mm, (Lit.^{33,34} bp 135–140 °C/10 mm); ¹H NMR (CDCl₃, 250 MHz): δ 1.23–1.34 (2t, 3H, H-7), 1.91–2.70 (m, 4H, H-2 and H-3), 4.10–4.30 (2q, 2H, H-6), 4.40–4.95 (m, 1H, H-4), [Lit. (CCl₄, 100 MHz) 1.32 (t, 3H, H-7), 2.1–2.9 (m, 4-H, H-2 and H-3), 4.23, q, 2H, H-6), 4.85 (m, 1H, H-4)].

D. Preparation of S-(+)-Hydroxy-γ-butyrolactone (4). To a stirred suspension of sodium borohydride (NaBH₄, 7.2 g, 19 mmol) in absolute EtOH (175 mL) at r.t. was added dropwise a solution of (S)-γ-ethoxycarbonyl-γ-butyrolactone (**3**, 46.5 g, 294 mmol) in absolute EtOH (250 mL), and the temperature was maintained at 20–25 °C by use of an ice-bath. The reaction mixture was stirred at r.t. for 1 h, and then 10% HCl was added until pH = 3. Rotary vacuum evaporation of solvent, followed by coevaporation with methanol (CH₃OH, 4 × 400 mL), resulted in formation of a precipitate that was gravity filtered. The filtrate after evaporation of solvent, followed by vacuum distillation, gave product **4** (11.6 g, 100 mmol, 34.0%) as a clear, colorless oil.

Physicochemical data: bp 120–140 °C/0.005 mm, (Lit.^{33,34} 131–147 °C/7 mm); ¹H NMR data (CDCl₃, 250 MHz): δ 2.0–2.8 (m, 4H, H-2 and H-3), 3.6–4.0 (m, 3H, H-5 and H-6), 4.6–4.7 (m, 1H, H-4), [Lit.^{33,34} (100 MHz) 2.0–2.8 (m, 4-H, H-2 and H-3) 3.6–4.0 (m, 3H, H-5 and H-6), 4.65 (m, 1H, H-4)].

E. *S*-(+)-*tert*-Butyldiphenylsilyloxymethyl- γ -butyrolactone (5). To a stirred solution of *S*-(+)- γ -hydroxymethyl- γ -butyrolactone (**4**, 11.6 g, 100 mmol), 4-dimethylaminopyridine (4-DMAP, 3.7 g, 30 mmol), and pyridine (13.0 mL, 160 mmol) in dry CH_2Cl_2 (100 mL) under anhydrous conditions, with a nitrogen atmosphere, and at r.t., was added *tert*-butyldiphenylsilyl chloride (TBDPS-Cl, 31.2 mL, 120 mmol), and the reaction mixture was stirred at r.t. for 13 h and refluxed (dry conditions using a CaSO_4 drying tube) for 5 h (completion of the reaction was monitored by TLC). The reaction mixture was cooled to r.t., washed with water (2 $\times$ 250 mL), and dried over anhydrous MgSO_4 , giving a pale yellow-brown syrup. The syrup was purified by column chromatography, eluting with a solvent system of hexane– CH_2Cl_2 with an increasing ratio of CH_2Cl_2 (5:1 to 5:3). Upon evaporation of the desired fractions, the compound was collected, which after recrystallization from hexane, gave product **5** (22.2 g, 63.0 mmol, 63%) as white crystals.

Physicochemical data: mp 76–77 °C; R_f 0.34 (4:1 CH_2Cl_2 –hexane); ^1H NMR (CDCl_3 , 250 MHz): δ 1.0–1.1 (s, 9H, *tert*-butyl), 2.1–2.8 (m, 4H, H-2 and H-3), 3.6–3.9 (2dd, 2H, H-5), 4.5–4.7 (m, 1H, H-4), 7.3–7.8 (m, 10H, phenyl).

F. 5-*O*-*tert*-Butyldiphenylsilyl-2,3-dideoxy-D-glycero-pentofuranose (6).

To a stirred solution of *S*-(+)-*tert*-butyldiphenylsilyloxymethyl- γ -butyrolactone (**5**, 14.7 g, 41.5 mmol) in dry PhCH_3 (200 mL) cooled to –78 °C (acetone–dry-ice bath) under anhydrous conditions and a nitrogen atmosphere was added diisobutylaluminum hydride (DIBAL-H, 36.0 mL, 1.5 M PhCH_3 , 54.0 mmol) slowly over a period of 5 min. The reaction mixture was stirred at –78 °C for 45 min, and

then EtOAc (2.5 mL), AcOH (2.0 mL), and H₂O (2.5 mL) were added. The cold bath was removed, CH₂Cl₂ (50 mL) was added, followed by anhydrous MgSO₄ (12 g) while stirring, and the mixture was stirred for 15 min and vacuum filtered. The precipitate was washed with 1:1 CHCl₃–EtOAc until the filtrate was not UV active on TLC. Rotary vacuum evaporation of solvent, followed by purification on a column of silica gel, eluting with hexane, 3:1 hexane–CH₂Cl₂, and 2:1:1 hexane–CH₂Cl₂–EtOAc, collection/evaporation of desired fractions, and recrystallization from hexane gave product **6** (14.6 g, 41.0 mmol, 98.8%) as a white solid.

Physicochemical data: *R*_f 0.59 (2:1:1 hexane–CH₂Cl₂–EtOAc); ¹H NMR(CDCl₃, 250 MHz): δ 1.0 and 1.5 (s, 9H, *tert*-butyl), 1.7–2.2 (m, 4H, H-2 and H-3), 2.0 and 2.4–2.5 (s, 1H, -OH), 3.3–3.9 (2dd, 2H, H-5), 4.1–4.4 (m, 1H, H-4) 5.4–5.6, (m, 1H, H-1), 7.3–7.8 (m, 10H, phenyl).

G. 6-Chloro-9-[5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-β-D-glycero-pentofuranosyl]purine (7). To a stirred solution of 5-O-*tert*-butyldiphenylsilyl-2,3-dideoxy-D-glycero-pentofuranose (**6**, 14.6 g, 41.0 mmol) in dry CH₂Cl₂ (75 mL) cooled to –78 °C (acetone–dry ice bath) under anhydrous conditions and a nitrogen atmosphere was added a solution of trifluoroacetic anhydride (TFAA, 6.6 mL, 53.0 mmol) and pyridine (3.8 mL, 47 mmol), and the mixture was stirred at –40 °C to –20 °C for 40 min. The cold bath was removed, and the reaction mixture was added to a stirred and cooled (ice bath, 0 °C) suspension of potassium carbonate (K₂CO₃, 17.3 g, 125 mmol), benzyltriethylammonium chloride (BTEAC, 7.3 g, 32

mmol), and 6-chloropurine (4.3 g, 28 mmol) in dry CH_3CN (350 mL). The resulting yellow mixture was stirred at r.t. for 3.3 h. Rotary vacuum evaporation of solvent at r.t. resulted in an orange-brown syrup to which CH_2Cl_2 (400 ml) was added, and the mixture was stirred at r.t. for 15 min. Vacuum filtration, followed by high-vacuum rotary evaporation at 45–50 °C gave a brownish residue. Purification of the residue by silica gel column chromatography, eluting with hexane and 4:1 hexane–EtOAc, followed by preparative HPLC separation, eluting with 65:35 hexane–EtOAc and recrystallization from hexane, yielded the desired product **7**, the β -anomer (4.0 g, 8 mmol, 19.5%) as white crystals.

Physicochemical data: R_f 0.53 (1:1 hexane–EtOAc); ^1H NMR (CDCl_3 , 250 MHz): δ 1.00–1.10 (s, 9H, *tert*-butyl), 2.05–2.25 (m, 2H, H-3'), 2.50–2.65 (m, 2H, H-2'), 3.70–4.00 (2dd, 2H, H-5'), 4.25–4.40 (m, 1H, H-4'), 6.35–6.42 (t, 1H, H-1'), 7.30–7.70 (m, 10H, phenyl), 8.45 (s, 1H, H-8), 8.70 (s, 1H, H-2), [Lit.⁴⁰ 1.06 (s, 9H), 2.09 (m, 2H), 2.52 (m, 2H), 3.71 and 3.93 (2dd, 2H), 6.36 (t, 1H), 7.25–7.70 (m, 10H), 8.44 (s, 1H), 8.69 (s, 1H)].

H. Preparation of 6-Chloro-9-(2,3-dideoxy- β -D-glycero-pentofuranosyl)purine (8). To a stirred solution of 6-Chloro-9-[5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy- β -D-glycero-pentofuranosyl]purine (**7**, 5.0 g, 10 mmol) in THF (50 mL) at r.t. was added tetrabutylammonium fluoride (TBFA, 22 mL, 1 M THF, 22 mmol), followed by a buffer of triethylamine (TEA, 1.3 g, 13 mmol), AcOH (780 mg, 13 mmol), and THF (10 mL). The resulting mixture was stirred at r.t. for 35 min (TLC monitored). Vacuum rotary evaporation of the solvent at 30 °C

gave a syrup that was purified on a column of silica gel, eluting with 85:15 hexane–EtOAc, 2:1 hexane–EtOAc, EtOAc, and then 9:1 CHCl₃–MeOH. Collection and evaporation of the desired fractions, followed by recrystallization in hexane, afforded the product **8** (2.1 g, 8.3 mmol, 83%) as white crystals.

Physicochemical data: mp 100–103 °C; *R_f* 0.62 (9:1 CH₂Cl₂–MeOH); UV (EtOH): λ_{max} 265 nm, [Lit. (MeOH) 265 nm]; HPLC (3:2 MeOH–H₂O, 1 mL/min): *t_R* 5.5 min; ¹H NMR (CDCl₃, 250 MHz): δ 2.05–2.75 (m, 4H, H-2' and H-3'), 3.65–4.15 (2dd, 2H, H-5'), 4.20–4.45 (m, 1H, H-4'), 6.31 (t, 1H, H-1'), 8.55 (s, 1H, H-8), 8.75 (s, 1H, H-2), [Lit.⁴⁰ 1.95–2.80 (m, 4H), 3.88(m, 2H), 4.38(m, 1H), 6.31(t, 1H), 8.50(s, 1H), 8.74(s, 1H)]; ¹³C NMR (CDCl₃, 62.5 MHz): δ 25.05 (C-3'), 32.98 (C-2'), 63.39 (C-4'), 82.34 (C-5'), 132.25 (C-5), 144.50 (C-1'), 150.59 (C-4), 151.00 (C-6), 151.51 (C-2).

I. 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-dimethylsuccinoyl)-β-D-glycero-pentofuranosyl]purine (10, Major Product) and 6-Chloro-9-[2,3-dideoxy-5-O-(3,3-dimethylsuccinoyl)-β-D-glycero-pentofuranocyl]purine (11, Minor Product). To a stirred solution of 6-chloro-9-(2,3-dideoxy-β-D-glycero-pentofuranosyl)purine (**8**, 100 mg, 0.400 mmol) and 4-DMAP (50 mg, 0.4 mmol) in dry pyridine (4 mL) at r.t. and under anhydrous conditions with a nitrogen atmosphere was added dropwise a solution of 2,2-dimethylsuccinic anhydride (**9**, 100 mg, 0.800 mmol) in dry pyridine (3 mL). The resulting yellowish mixture was stirred at r.t. overnight. After completion of the reaction (monitored by TLC), the brownish reaction mixture was high-vacuum rotary evaporated at 40–45 °C to give

a dark-brown syrup that was purified by column chromatography over silica gel, eluting with CH_2Cl_2 with an increasing percentage of MeOH (0.0 to 7.5%). Collection and evaporation of the desired fractions gave esters **10** and **11** (75 mg, 0.20 mmol, 50%) as a yellow foam.

Physicochemical data: UV (EtOH): λ_{max} 264.5 nm; HPLC (80:20 H_2O –MeOH, 1.5 mL/min): t_{R} 19.5 (major), 21.5 (minor); ^1H NMR (CDCl_3 , 250 MHz): δ 1.25–1.30 (s, 6H, methyl), 2.12–2.67 (m, 6H, CH_2 , H-2', and H-3'), 4.35–4.44 (m, 3H, H-4' and H-5'), 6.34–6.35 (m, 1H, H-1'), 8.46 (s, 1H, H-8), 8.74 (s, 1H, H-2); ESIMS data: Calcd for $\text{C}_{16}\text{H}_{18}\text{ClN}_4\text{O}_5$: 381.1 (Cl-35 isotope) and 383.1 (Cl-37 isotope). Found: 381.1 (Cl-35 isotope) and 383.1 (Cl-37 isotope).

J. Preparation of 2,2-Diphenylpropionyl Chloride (13). Thionyl chloride (SOCl_2 , 20.0 mL, 284 mmol) was added to 2,2-diphenylpropionic acid (**12**, 10.0 g, 44.2 mmol) at r.t., followed by DMF (2–3 drops). The resulting yellowish solution was stirred at r.t. for 1 h and then refluxed for 2 h (CaSO_4 drying tube). Rotary-vacuum evaporation of the excess reagents at 45 °C resulted in a brown oil that was vacuum distilled to give product **13** (8.0 g, 32.6 mmol, 74%) as a clear, colorless oil.

Physicochemical data: bp 160–165 °C/22 mm; ^1H NMR (CDCl_3 , 250 MHz) δ : 2.08 (s, 3H, CH_3), 7.10–7.40 (m, 10H, phenyl).

K. 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-diphenylpropionyl)- β -D-glycero-pentofuranosyl]purine (14). To a stirred solution of 6-chloro-9-(2,3-dideoxy- β -D-glycero-pentofuranosyl)purine (**8**, 100 mg, 0.400 mmol) and 4-DMAP (50 mg, 0.4 mmol) in dry pyridine (3 mL) at r.t. and under anhydrous conditions with a nitrogen

atmosphere was added dropwise a solution of 2,2-diphenylpropionyl chloride (**13**, 150 mg, 0.610 mmol) in dry pyridine (3 mL). The resulting yellowish solution was stirred at r.t. overnight. After completion of the reaction (monitored by TLC), the brownish reaction mixture was high- vacuum rotary evaporated at 40–45 °C to give a dark-brown syrup that was purified by column chromatography over silica gel, eluting with hexane with an increasing ratio of EtOAc (10:1 to 5:1). Collection and evaporation of the desired fractions resulted in the isolation of product **14** (107 mg, 0.23 mmol, 59%) as a white foam.

Physicochemical data: R_f 0.45 (EtOAc); UV (EtOH): $\lambda_{\max}$ 265 nm; HPLC (50:50 MeOH–H₂O, 2 mL / min): t_R 10.80 min; ¹H NMR (CDCl₃, 250 MHz): δ 1.93 (s, 3H, CH₃), 1.75–2.50 (m, 4H, H-2' and H-3'), 4.30–4.47 (m, 2H, H-4'), 6.25 (m, 1H, H-1'), 7.10–7.30 (m, 10H, phenyl), 8.10 (s, 1H, H-8), 8.72 (s, 1H, H-2); ¹³C NMR (CDCl₃, 62.5 MHz): δ 26.08 (C-3'), 27.10 (CH₃), 32.00 (C-2'), 56.61 (C-CH₃), 65.77 (C-4'), 78.82 (C-5'), 85.88 (C-1'), 126.85, 126.97, 127.86, 128.04, and 128.09 (phenyl), 143.35 (C-5), 143.50 (C-8), 144.17 (C-4), 150.98 (C-6), 151.74 (C-2), 174.86 (C=O); ESIMS data: Calcd for C₂₅H₂₃ClN₄O₃Na: 485.1 (Cl-35 isotope) and 487.1 (Cl-37 isotope). Found: 485.0 (Cl-35 isotope) and 487.0 (Cl-37 isotope).

L. Preparation of 2-Ethylbutyryl Chloride (16). Thionyl chloride (40 mL, 569.0 mmol) was added to 2-ethylbutyric acid (**15**, 10.8 g, 86.1 mmol) dropwise while stirring under dry conditions (CaSO₄ drying tube) at r.t., followed by DMF (2–3 drops). The resulting yellowish solution was stirred at r.t. for 1 h and refluxed for 2 h (CaSO₄ drying tube). Rotary vacuum evaporation of the excess reagents at 45

°C resulted in a brown oil that was distilled under atmospheric pressure to give product **16** (8.3 g, 62 mmol, 72%) as a clear colorless oil.

Physicochemical data: bp 130–132 °C/1 atm; ^1H NMR (CDCl_3 , 250 MHz): δ 0.97 (t, 6H, CH_3), 1.60–1.80 (m, 4H, CH_2), 2.70 (m, 1H, CH).

M. 6-Chloro-9-[2,3-dideoxy-5-O-(2-ethylbutyryl)- β -D-glycero-pentofuranosyl]purine (17**).** To a stirred solution of 6-chloro-9-(2,3-dideoxy- β -D-glycero-pentofuranosyl)purine (**8**, 200 mg, 0.800 mmol) and 4-DMAP (100 mg, 0.800 mmol) in dry pyridine (5 mL) at r.t. and under anhydrous conditions with a nitrogen atmosphere was added dropwise a solution of 2-ethylbutyryl chloride (**16**, 216 mg, 1.60 mmol) in dry pyridine (3 mL). The resulting yellowish solution was stirred at r.t. for 5 min, at which time the reaction was completed (TLC monitoring). High-vacuum rotary evaporation of the solvent gave an orange syrup that purified by column chromatography over silica gel, eluting with hexane with an increasing portion of EtOAc (4:1 to 1:1). Collection of the appropriate fractions, followed by evaporation of the solvent, gave product **17** (188 mg, 0.53 mmol, 67%) as a pale-yellow syrup.

Physicochemical data: R_f 0.59 (EtOAc); UV (EtOH): λ_{max} 264.4 nm; HPLC (9:1 H_2O –MeOH, 2 mL/min): t_R 11 min; ^1H NMR (CDCl_3 , 250 MHz): δ 0.83–0.91 (t, 6H, CH_3), 1.48–1.61 (m, 4H, CH_2), 2.10–2.27 and 2.64–2.71 (m, 5H, CH, H-2', and H-3'), 4.36–4.49 (m, 3H, H-4' and H-5'), 6.40 (q, 1H, H-1'), 8.48 (s, 1H, H-8), 8.75 (s, 1H, H-2); ^{13}C NMR (CDCl_3 , 62.5 MHz) δ : 11.6 (CH_3), 24.9 (CH_2), 25.7 (C-3'), 32.6 (C-2'), 48.6 (CH), 64.3 (C-4'), 79.6 (C-5'), 86.2 (C-1'), 132.2 (C-5), 143.5

(C-8), 150.7 (C-4), 150.8 (C-6), 151.7 (C-2), 175.8 ($\underline{\text{C}}=\text{O}$); ESIMS data: Calc for $\text{C}_{16}\text{H}_{21}\text{ClN}_4\text{O}_3\text{Na}$: 375.1 (Cl-35 isotope) and 377.1 (Cl-37 isotope). Found: 374.9 (Cl-35 isotope) and 376.9 (Cl-37 isotope).

N. Preparation of Ethyl 2-Ethylbutyrate (18). To stirred solution of 2-ethylbutyric acid (**15**, 100 mg, 0.860 mol) in absolute EtOH (25 mL, 0.43 mol) at r.t. and under dry conditions (CaSO_4 drying tube) was added concentrated H_2SO_4 (5 mL), and the resulting solution was refluxed for 14 h. The reaction mixture was then cooled down to r.t. and was poured into H_2O (800 mL) while stirring. The organic layer was separated, washed with H_2O (5 $\times$ 400 mL) and saturated sodium bicarbonate (NaHCO_3 , 3 $\times$ 400 mL), dried over anhydrous MgSO_4 , and distilled under atmospheric pressure to afford product **18** (45.7 g, 0.3 mol, 75%) as a clear, colorless oil.

Physicochemical data: bp 140–145 $^\circ\text{C}/1$ atm; ^1H NMR (CDCl_3 , 250 MHz): δ 0.89 (t, 6H, CH_3), 1.23 (t, 3H, CH_3), 1.55 (m, 4H, CH_2), 2.18 (m, 1H, CH), 4.16 (q, 2H, $\text{CH}_2\text{-O}$); ^{13}C NMR (CDCl_3 , 62.5 MHz): δ 11.34 ($\underline{\text{C}}\text{H}_3$), 13.95 ($\underline{\text{C}}\text{H}_3$), 24.78 ($\underline{\text{C}}\text{H}_2$), 48.59 ($\underline{\text{C}}\text{H}$), 59.41 ($\underline{\text{C}}\text{H}_2\text{-O}$), 175.54 ($\underline{\text{C}}=\text{O}$).

O. Preparation of Ethyl 2,2-Diethylbutyrate (19). To a stirred solution of ethyl 2-ethylbutyrate (**18**, 36.6 g, 254 mmol) in dry THF (500 mL) at -78 $^\circ\text{C}$ (dry ice–acetone bath), under anhydrous conditions, with a nitrogen atmosphere, was added dropwise lithium diisopropylamide (LDA, 165 mL of a 2M solution in heptane–THF–ethylbenzene, 330 mmol) during 30 min. The resulting red-brownish reaction mixture was stirred for 3 h at -78 $^\circ\text{C}$, then a solution of EtI (58.5 g, 375

mmol) in dry THF (70 mL) was added dropwise during 30 min, and stirring was continued at $-78\text{ }^{\circ}\text{C}$ for 3h. The reaction mixture that had turned yellow was slowly warmed up to r.t. and was poured into a stirred saturated brine solution (500 mL) and was extracted with ether ($2 \times 300\text{ mL}$). The ether layer was then dried over anhydrous MgSO_4 . Rotary vacuum evaporation of solvent, followed by simple distillation, yielded product **19** (23.3 g, 135 mmol, 53%) as a clear, colorless oil.

Physicochemical data: bp $165\text{ }^{\circ}\text{C}/1\text{ atm}$, [Lit.⁴² $177\text{--}184\text{ }^{\circ}\text{C}$]; R_f 0.5 (3:2 hexane- CH_2Cl_2); $^1\text{H NMR}$ (CDCl_3 , 250 MHz): δ 0.76 (t, 9H, CH_3), 1.25 (t, 3H, CH_3), 1.53–1.62 (q, 1H, CH_2), 4.09–4.18 (q, 2H, $\text{CH}_2\text{-O}$), [Lit.⁴² 0.78 (t, 9H), 1.24 (t, 3H), 1.58 (q, 6H), 4.12 (q, 2H)].

P. Preparation of 2,2-Diethylbutyric Acid (20). Trimethylsilyl iodide (TMS-I, 66.0 g, 47.0 mL, 330 mmol) was added to ethyl 2,2-diethylbutyrate (**19**, 28.4 g, 165 mmol) at r.t., while stirring under anhydrous conditions with a nitrogen atmosphere. The resulting brown solution was stirred at $100\text{ }^{\circ}\text{C}$ (oil bath) for 24 h, then was cooled to room temperature. Ether (250 mL) was added, and the resulting solution was washed with 0.5 N NaOH ($3 \times 300\text{ mL}$). The combined alkaline solution was acidified with concentrated HCl and was extracted with CHCl_3 ($3 \times 300\text{ mL}$) until no product was observed in the CHCl_3 layer (by TLC monitoring). The combined CHCl_3 extract was dried over anhydrous MgSO_4 . Vacuum rotary evaporation, followed by high-vacuum evaporation of the solvent, gave the desired product **20** (15.0 g, 104 mmol, 63%) as pale-yellow crystals.

Physicochemical data: mp $36\text{--}38\text{ }^{\circ}\text{C}$ [Lt.⁴² $31\text{--}34\text{ }^{\circ}\text{C}$]; R_f 0.36 (2:3

hexane-CH₂Cl₂); ¹H NMR (CDCl₃, 250 MHz): δ 0.81 (t, 9H, CH₃), 1.60 (q, 6H, CH₂), 11.7 (bs, 1H, CO₂H) [Lit.⁴² 0.73 (t, 9H), 1.57 (q, 6H), 10.0 (s, 1H)].

Q. Preparation of 2,2-Diethylbutyryl Chloride (21). Thionyl chloride (25.0 mL, 350 mmol) was added to 2,2-diethylbutyric acid (**20**, 8.0 g, 56 mmol) dropwise while stirring under dry conditions (CaSO₄ drying tube) at r.t., followed by the addition of DMF (2–3 drops). The resulting yellowish solution was stirred at r.t. for 2 h and then refluxed for 3 h (CaSO₄ drying tube). Rotary vacuum evaporation of excess reagents at 45 °C resulted in a brown oil that was distilled under atmospheric pressure to give product **21** (6.2 g, 38 mmol, 67%) as a clear, colorless oil.

Physicochemical data: bp 170 °C/1 atm; ¹H NMR (CDCl₃, 250 MHz): δ 0.85 (t, 9H, CH₃), 1.66–1.75 (q, 6H, CH₂).

R. 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-diethylbutyryl)-β-D-glycero-pentofuranosyl]purine (22). To a stirred solution of 6-chloro-9-(2,3-dideoxy-β-D-glycero-pentofuranosyl)purine (**8**, 250 mg, 0.982 mmol) and 4-DMAP (100 mg, 0.80 mmol) in dry pyridine (10 mL) at r.t. and under anhydrous conditions with a nitrogen atmosphere was added dropwise a solution of 2,2-diethylbutyryl chloride (**21**, 960 mg, 5.88 mmol) in dry pyridine (10 mL) in four portions during 41 h. The reaction was shown to be complete at the end of this time (TLC monitoring). High-vacuum rotary evaporation of the greenish reaction mixture gave a dark green residue, which was purified by column chromatography on silica gel eluting with hexane with an increasing portion of EtOAc (4:1 to 3:2). Collection of the appropriate fractions,

followed by evaporation of solvent, gave product **22** (252 mg, 0.662 mmol, 67%) as a pale-yellow solid.

Physicochemical data: R_f .59 (EtOAc); UV (EtOH): $\lambda_{\max}$ 264.4 nm; HPLC (3:7 H₂O–MeOH, 2 mL/min): t_R 6 min; ¹H NMR (CDCl₃, 250 MHz): δ .57–.68 (t, 9H, CH₃), 1.37–1.46 (q, 6H, CH₂), 1.90–2.11 (m, 4H, H-2' and H-3'), 4.19 (t, 2H, H-5'), 4.35 (m, 1H, H-4'), 6.22–6.26 (q, 1H, H-1'), 8.30 (s, 1H, H-8), 8.60 (s, 1H, H-2); ¹³C NMR (CDCl₃, 62.5 MHz): δ 7.98 (CH₃), 25.78 (CH₂), 26.04 (C-3'), 32.10 (C-2'), 49.82 (C), 64.59 (C-4'), 79.33 (C-5'), 86.14 (C-1'), 132.07 (C-5), 143.45 (C-8), 150.60 (C-6), 151.49 (C-2), 176.61 (C=O); HRFABMS data: Calcd for C₁₈H₂₆ClN₄O₃: 381.169. Found: 381.172.

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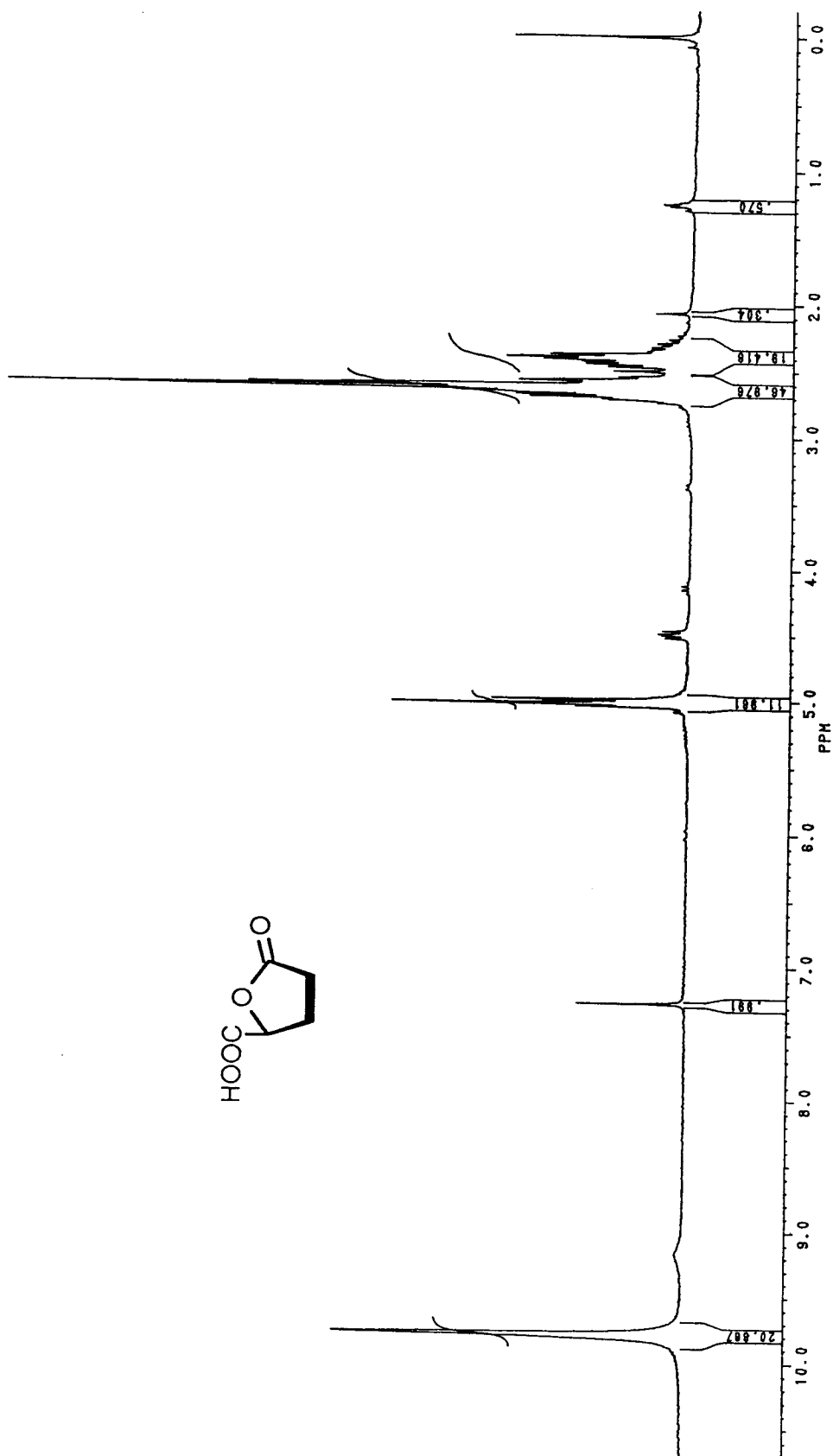
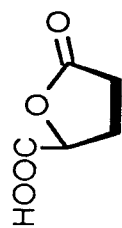
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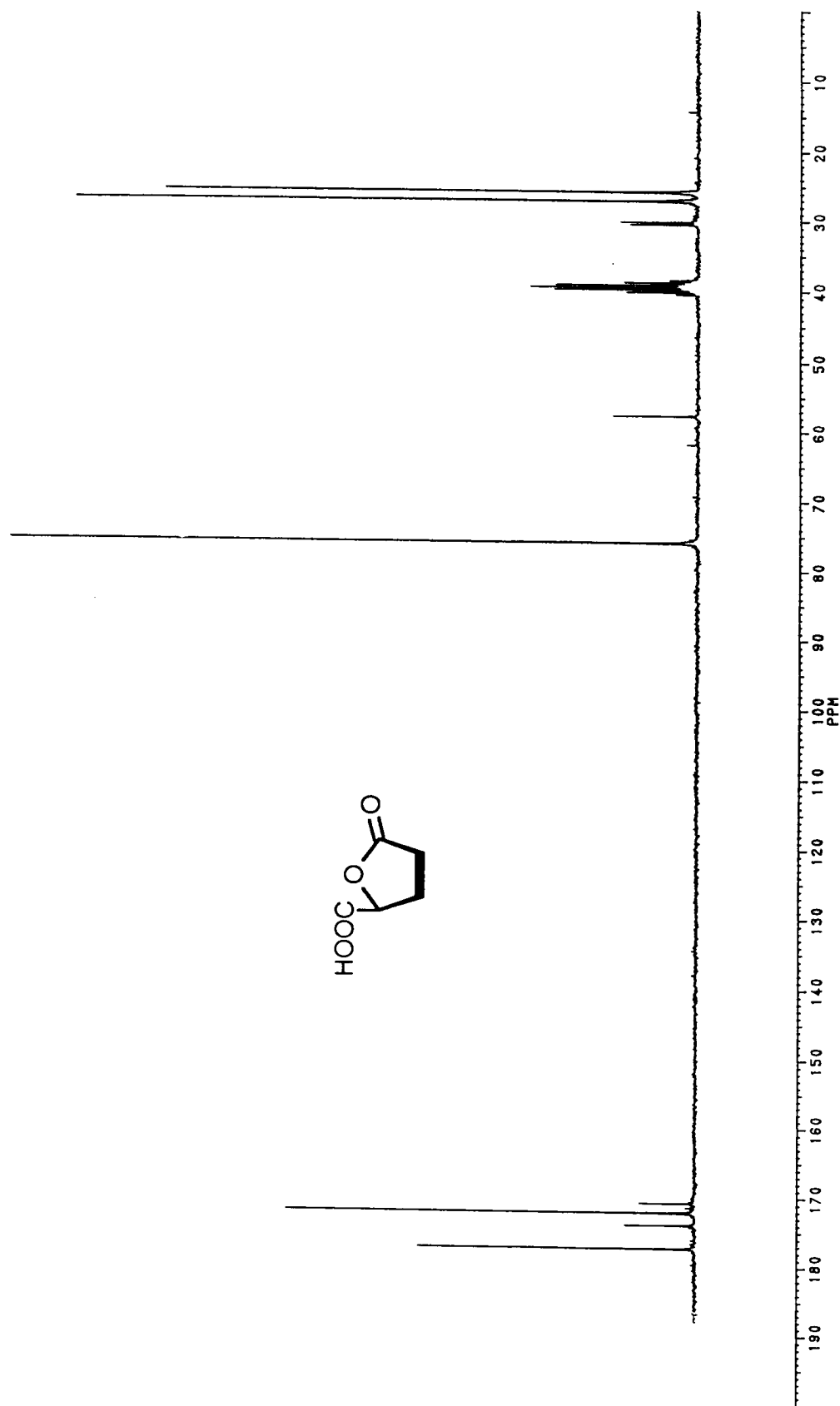
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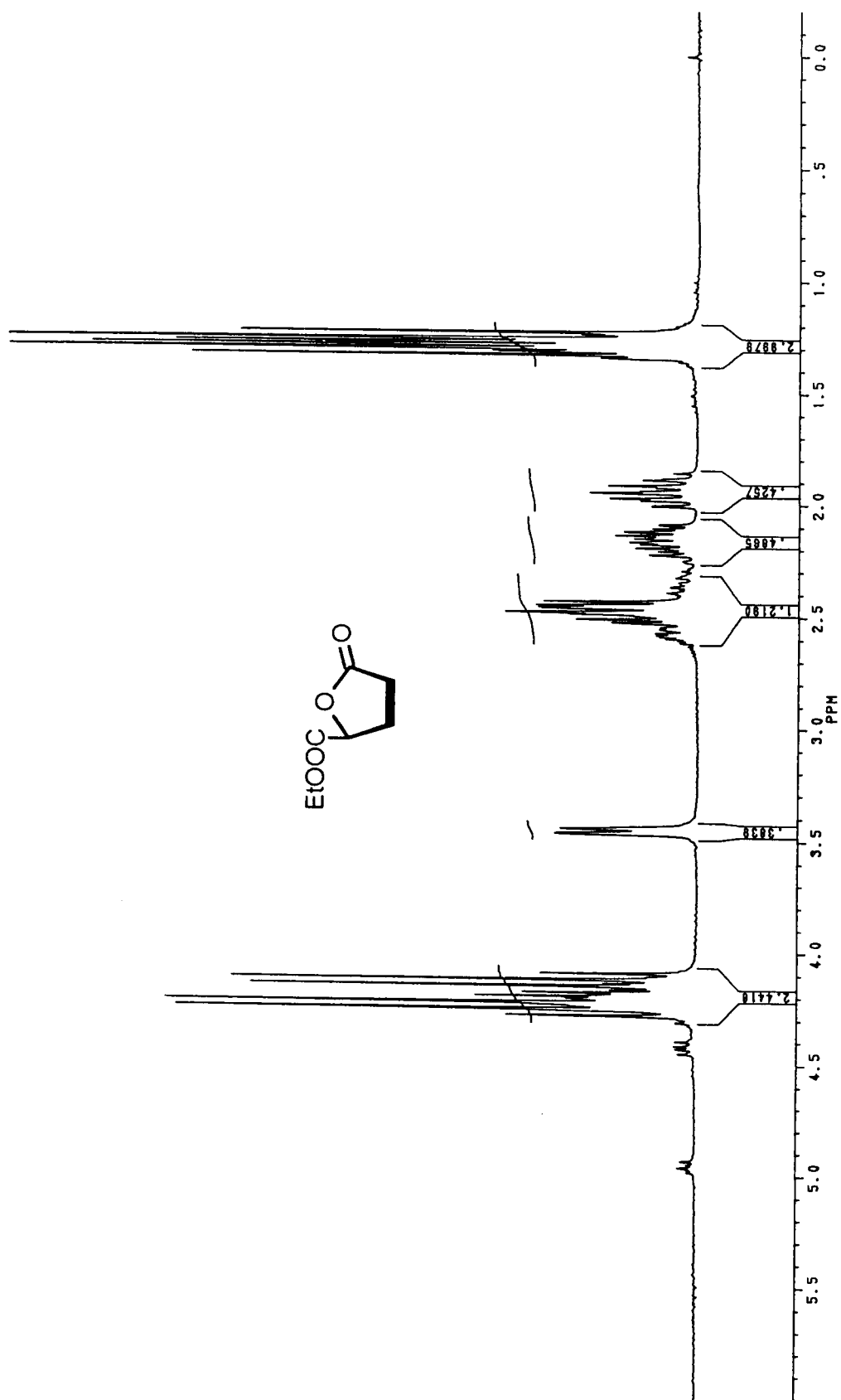
APPENDIX

^1H AND ^{13}C NMR SPECTRA FOR INTERMEDIATE AND TARGET COMPOUNDS

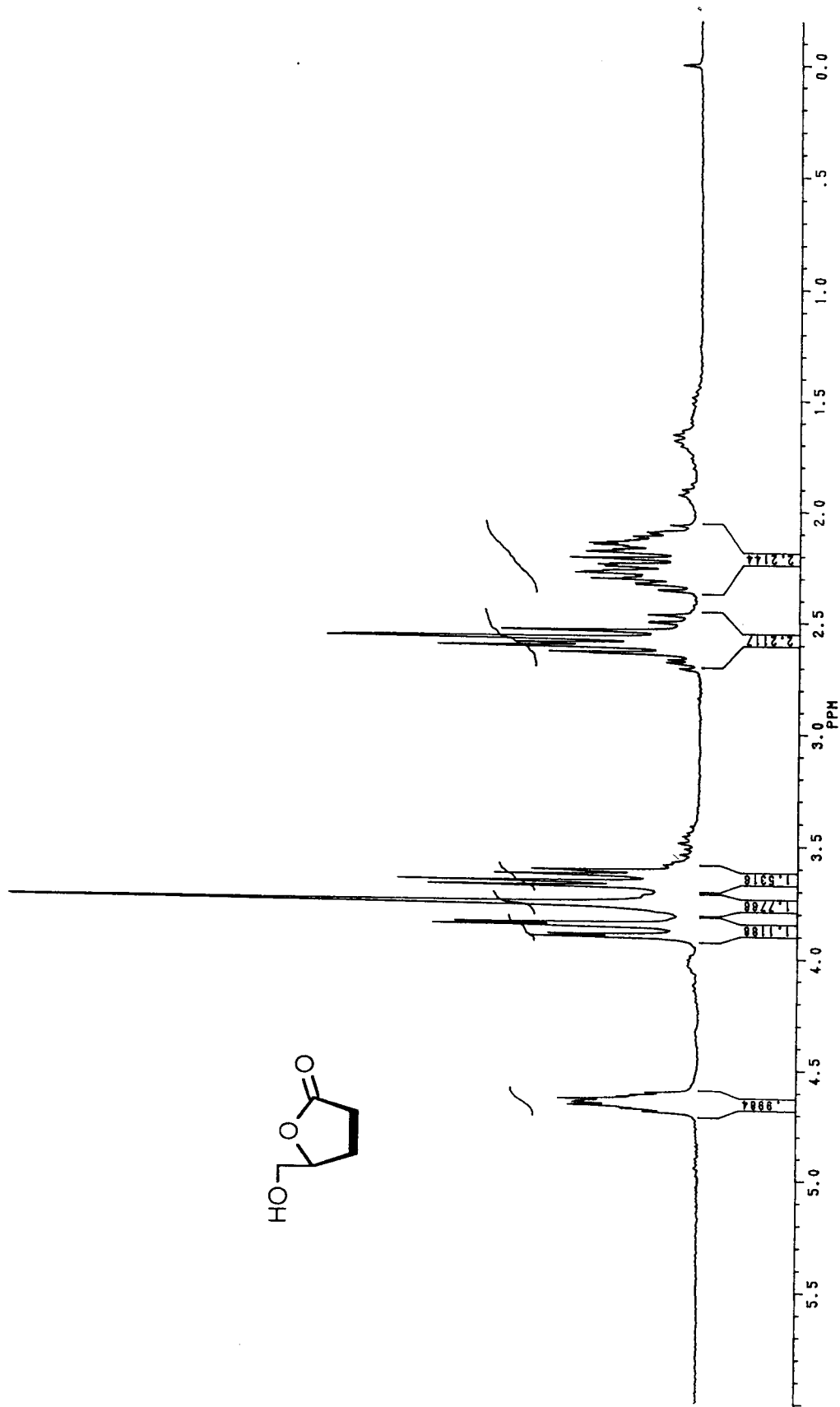


¹H NMR (CDCl₃, 250 MHz) Spectrum of (S)-γ-Carboxy-γ-butyrolactone (2).

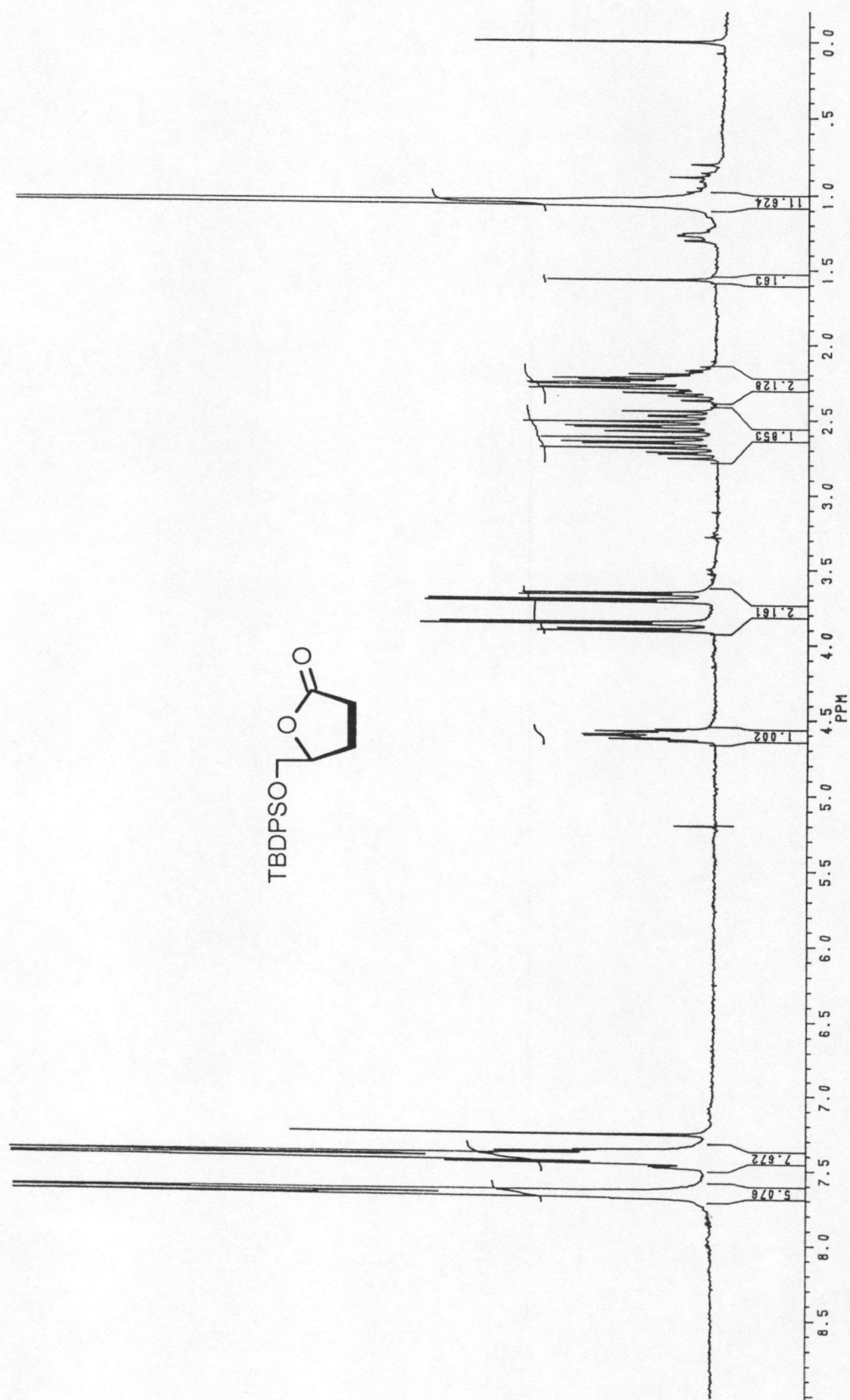




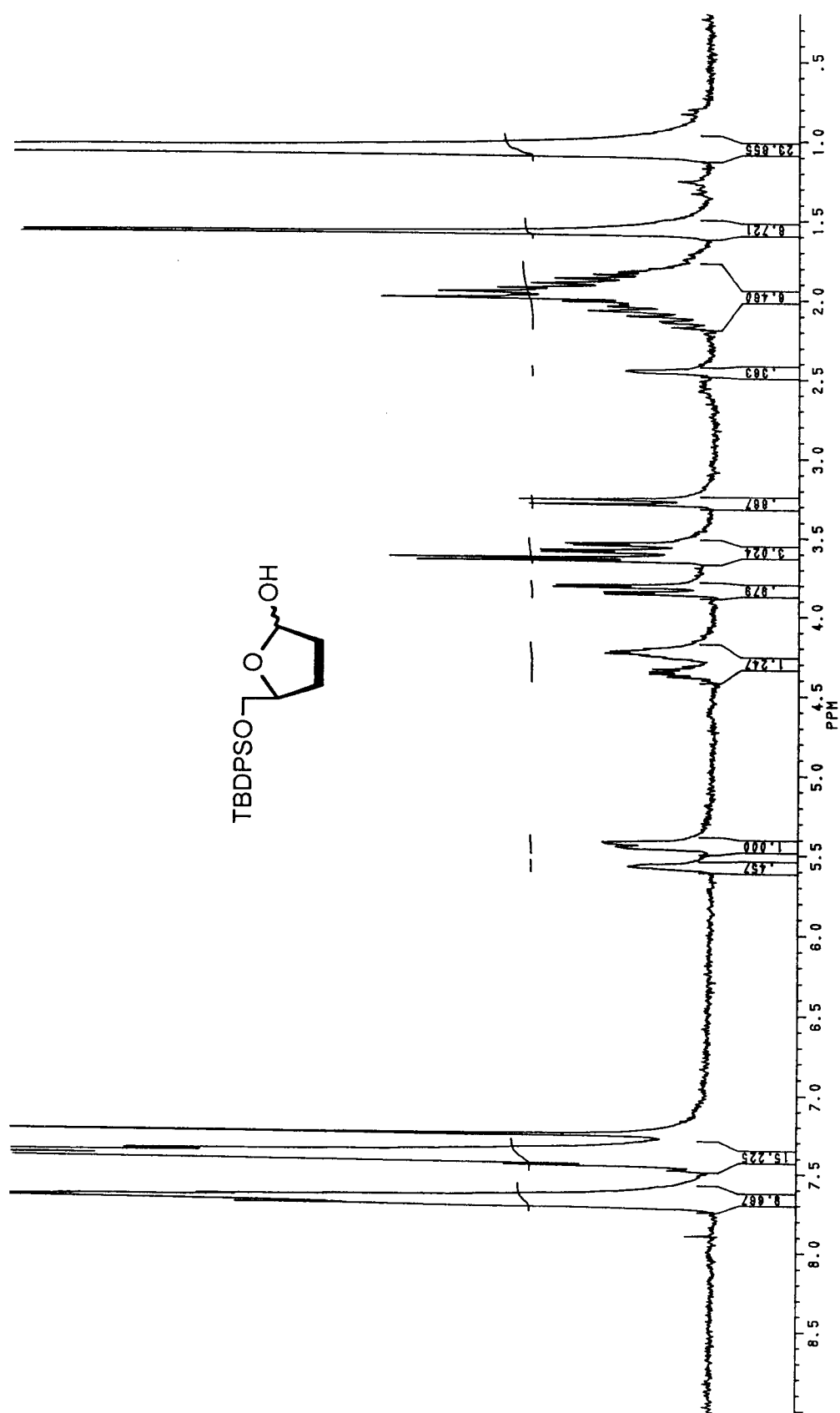
^1H NMR (CDCl_3 , 250 MHz) Spectrum of (S)- γ -Ethoxycarbonyl- γ -butyrolactone (**3**).



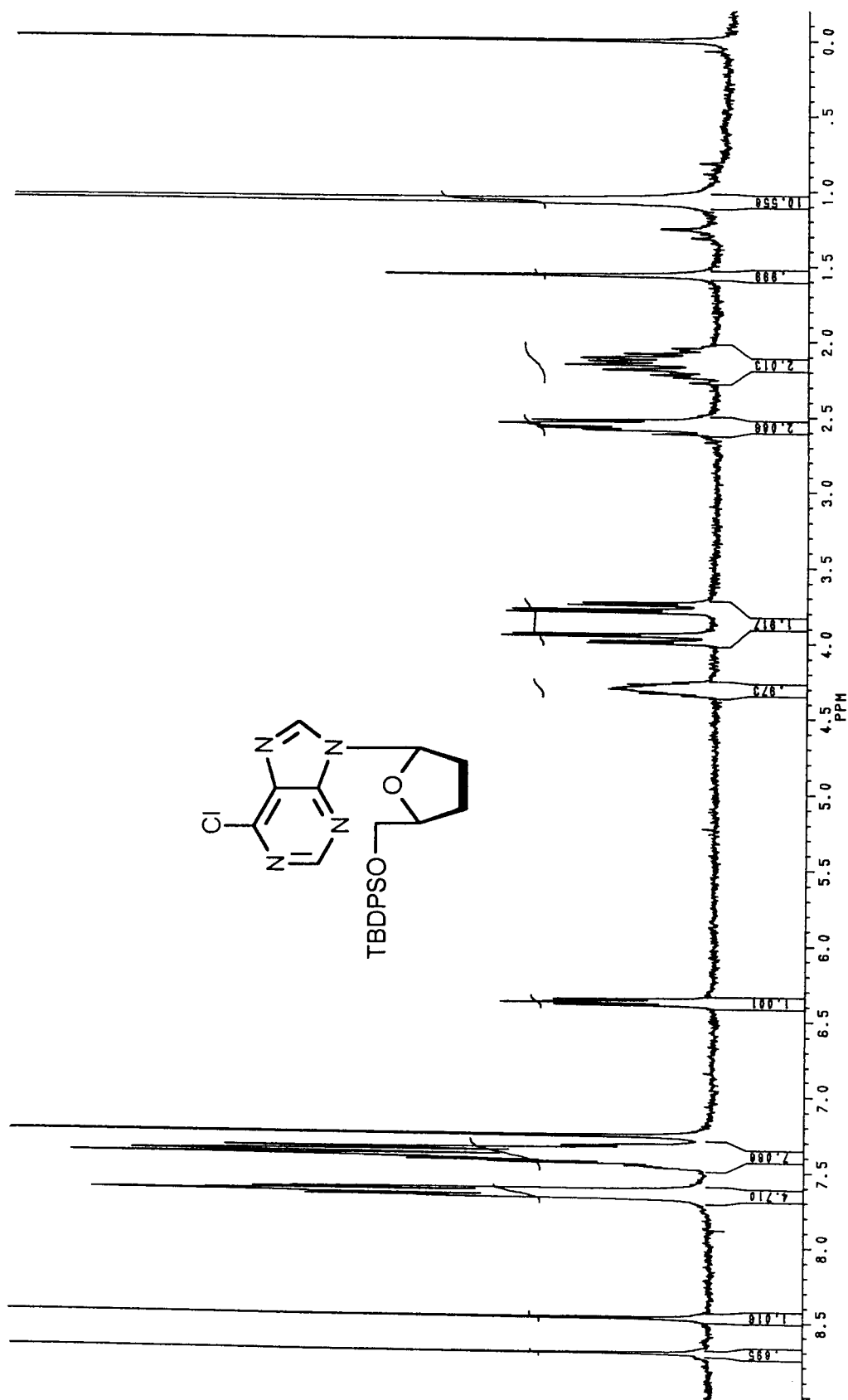
^1H NMR (CDCl_3 , 250 MHz) Spectrum of S-(+)-Hydroxy- γ -butyrolactone (4).



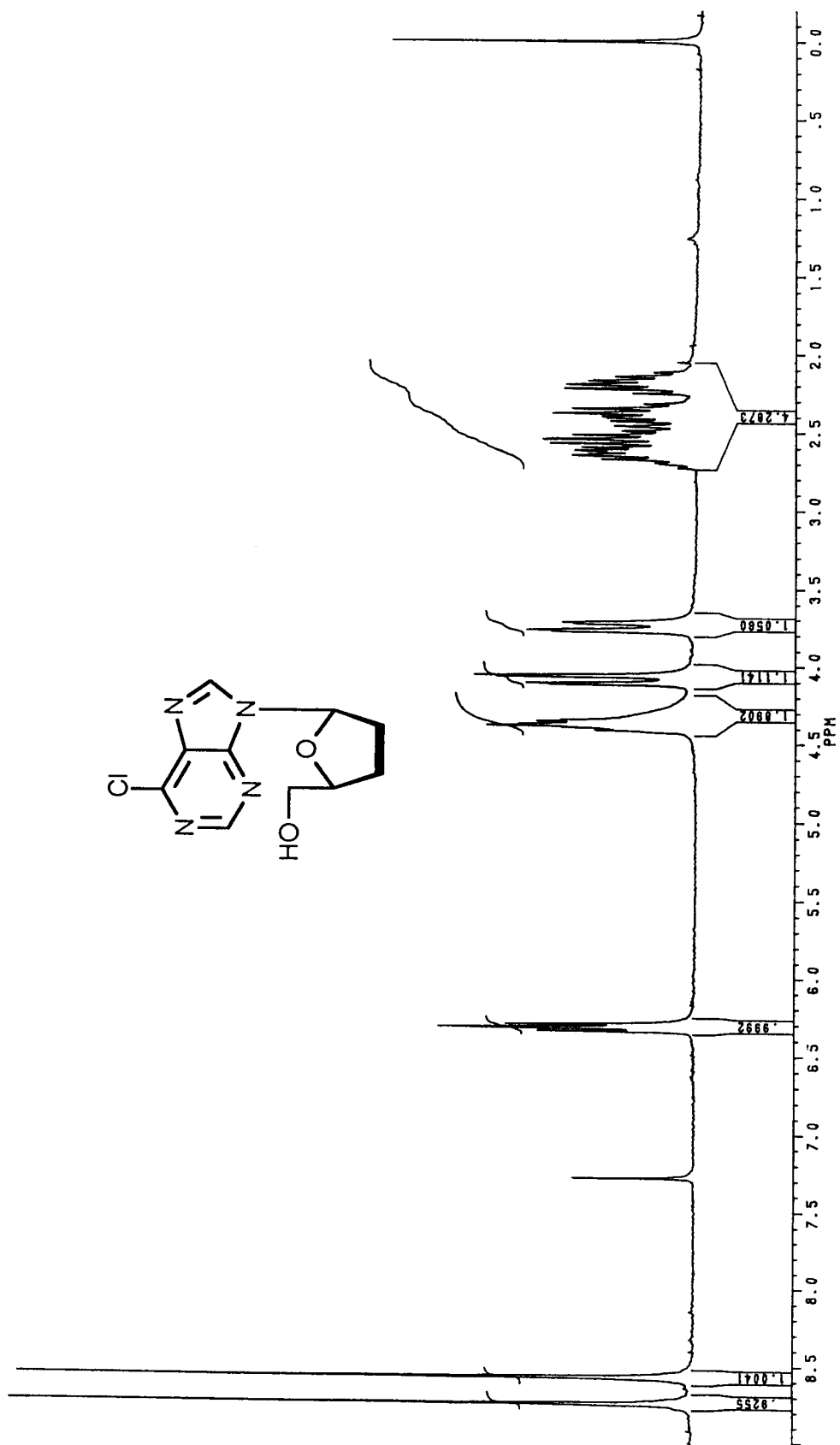
^1H NMR (CDCl_3 , 250 MHz) Spectrum of S-(+)-*tert*-Butyldiphenylsilyloxymethyl- γ -butyrolactone (**5**).



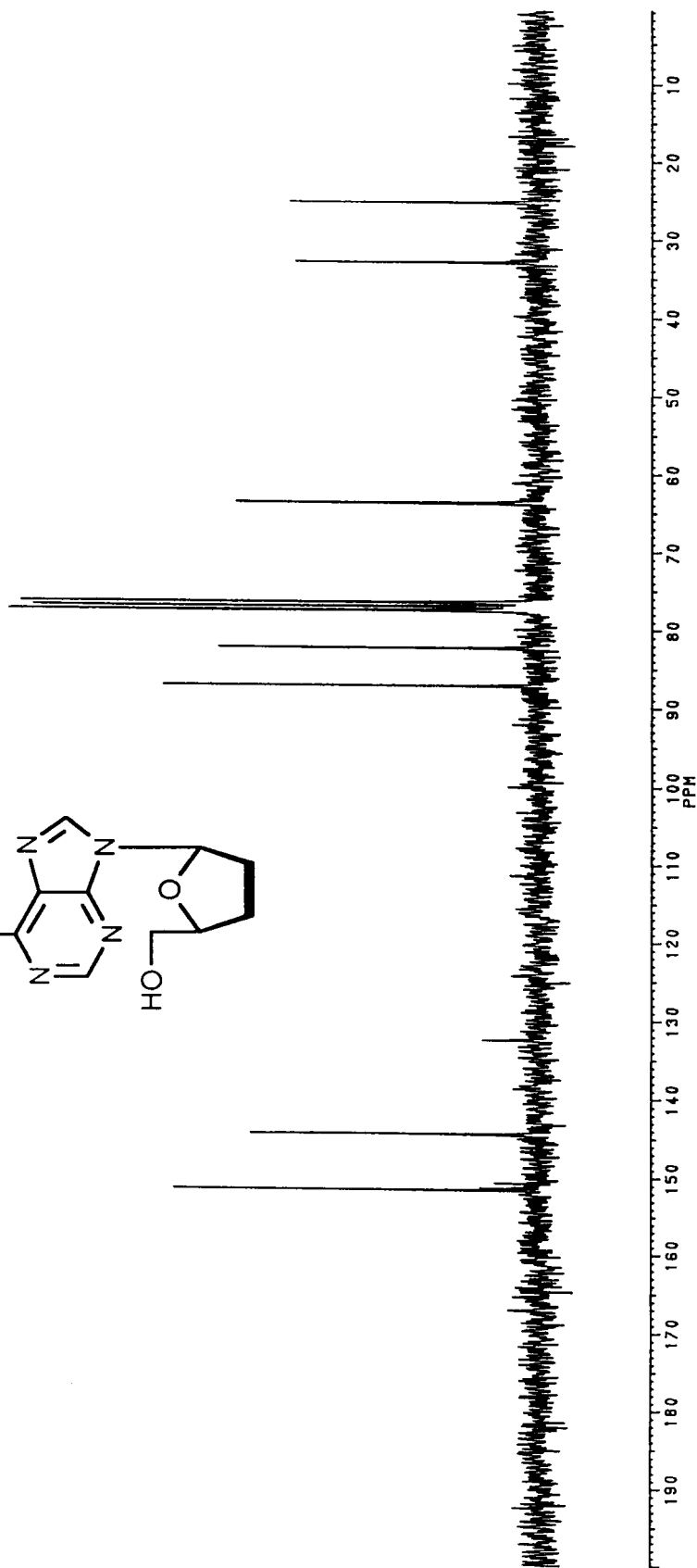
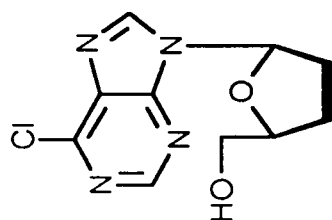
¹H NMR (CDCl₃, 250 MHz) Spectrum of 5-O-*tert*-Butyldiphenylsilyl-2,3-dideoxy-D-glycero-pentofuranose (6).



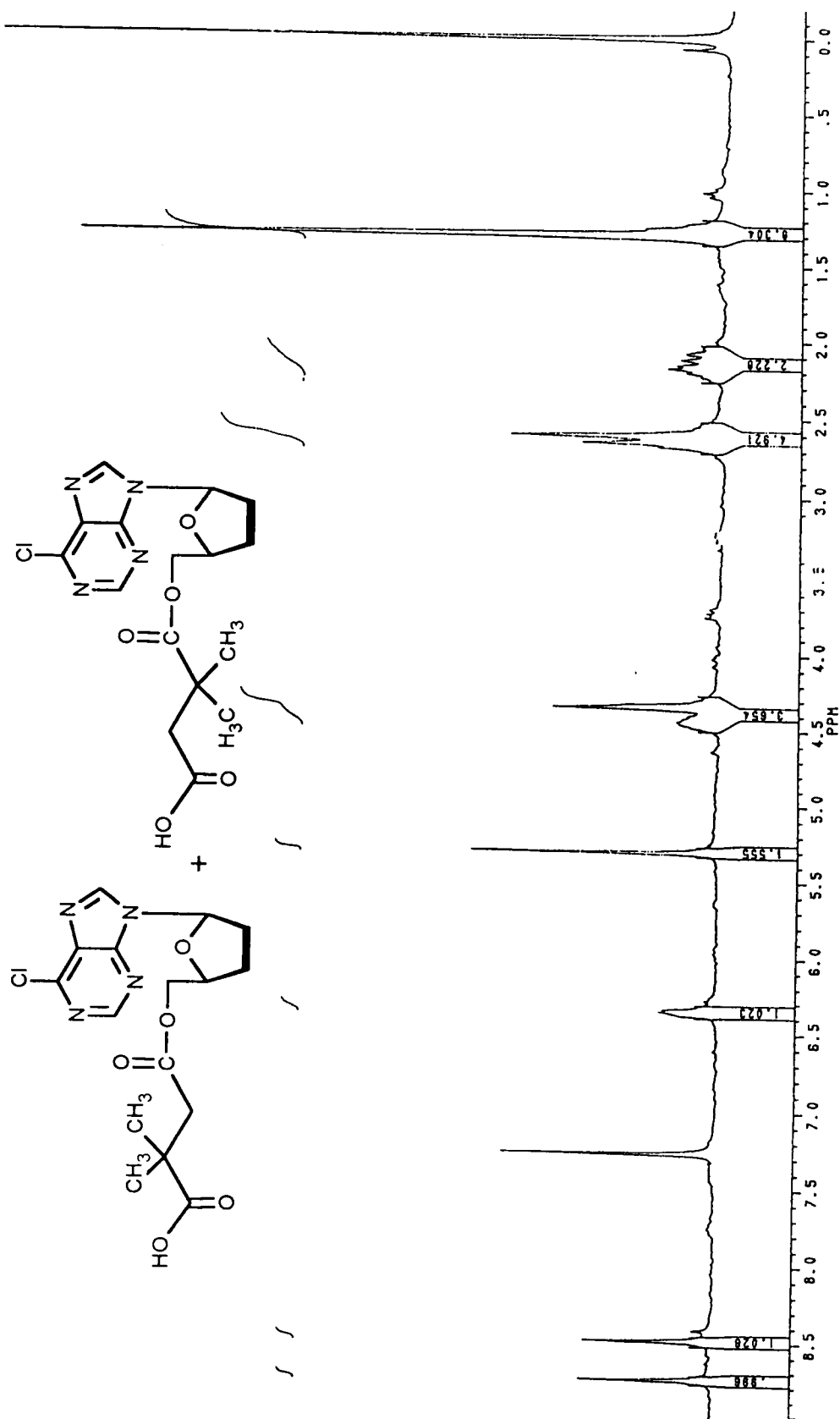
¹H NMR (CDCl₃, 250 MHz) Spectrum of 6-Chloro-9-[5-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-β-D-glycero-pentofuranosyl]purine (7).



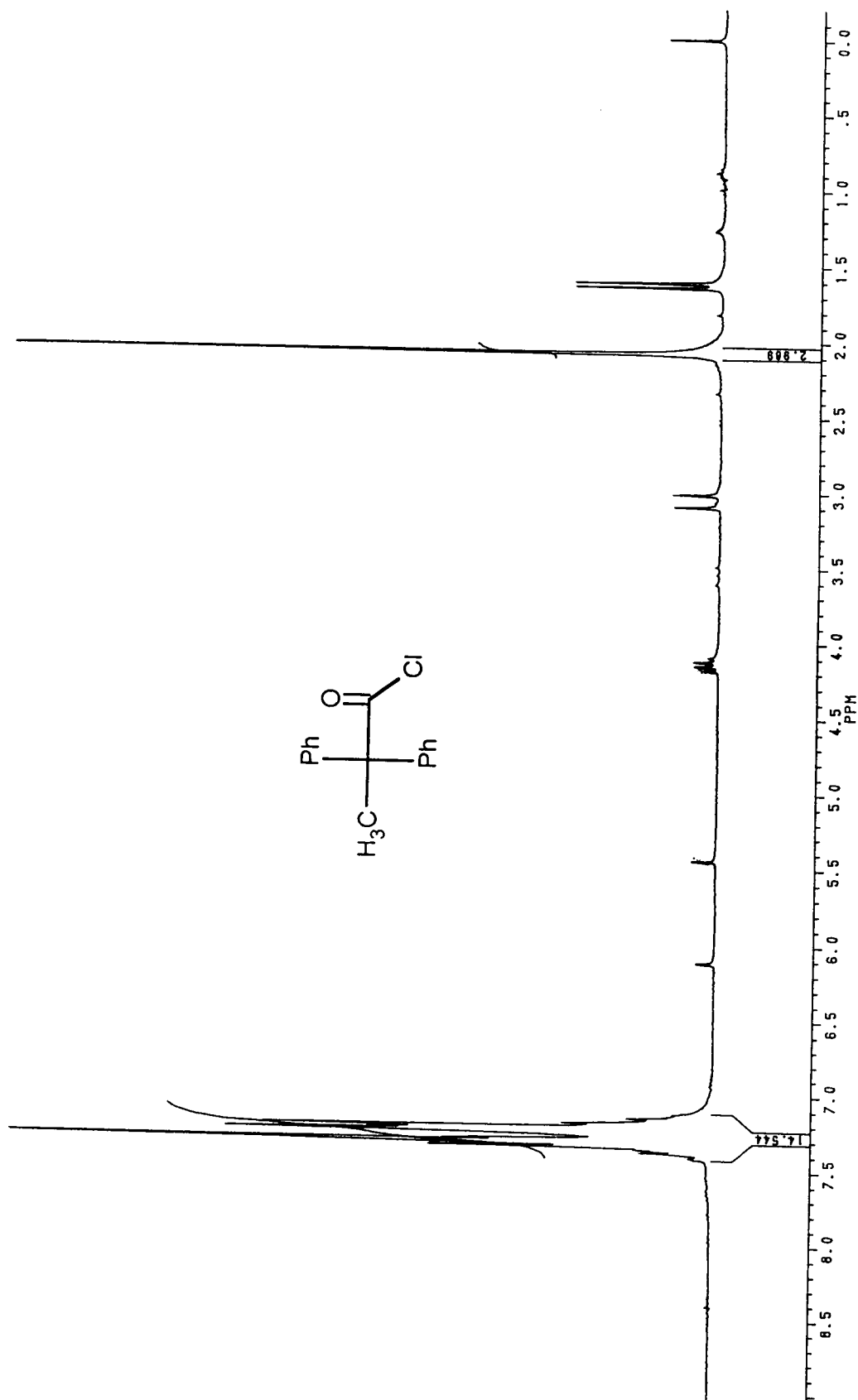
¹H NMR (CDCl₃, 250 MHz) Spectrum of 6-Chloro-9-(2,3-dideoxy-β-D-glycero-pentofuranosyl)purine (8).



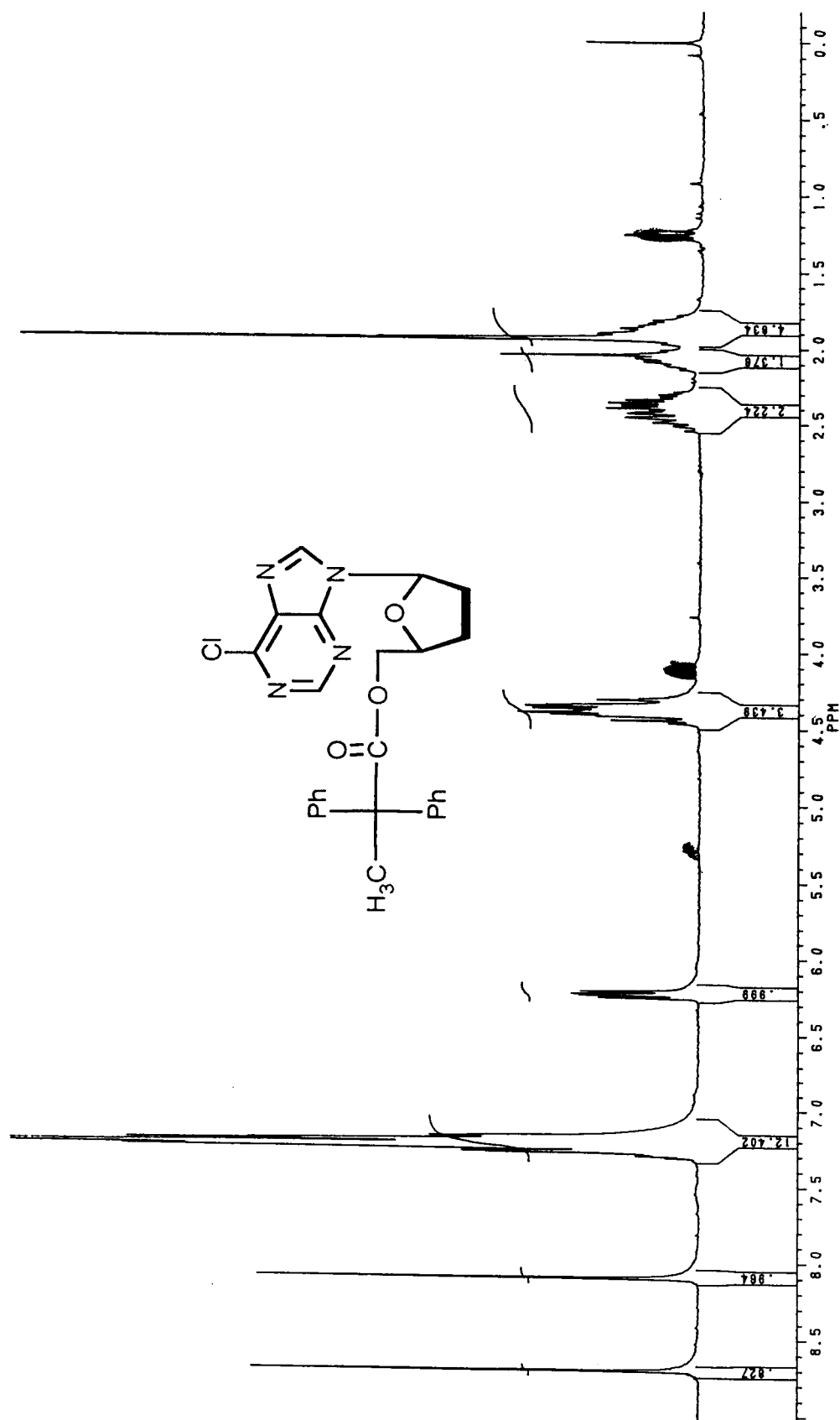
^{13}C NMR (CDCl_3 , 62.5 MHz) Spectrum of 6-Chloro-9-(2,3-dideoxy- β -D-glycero-pentofuranosyl)purine (**8**).



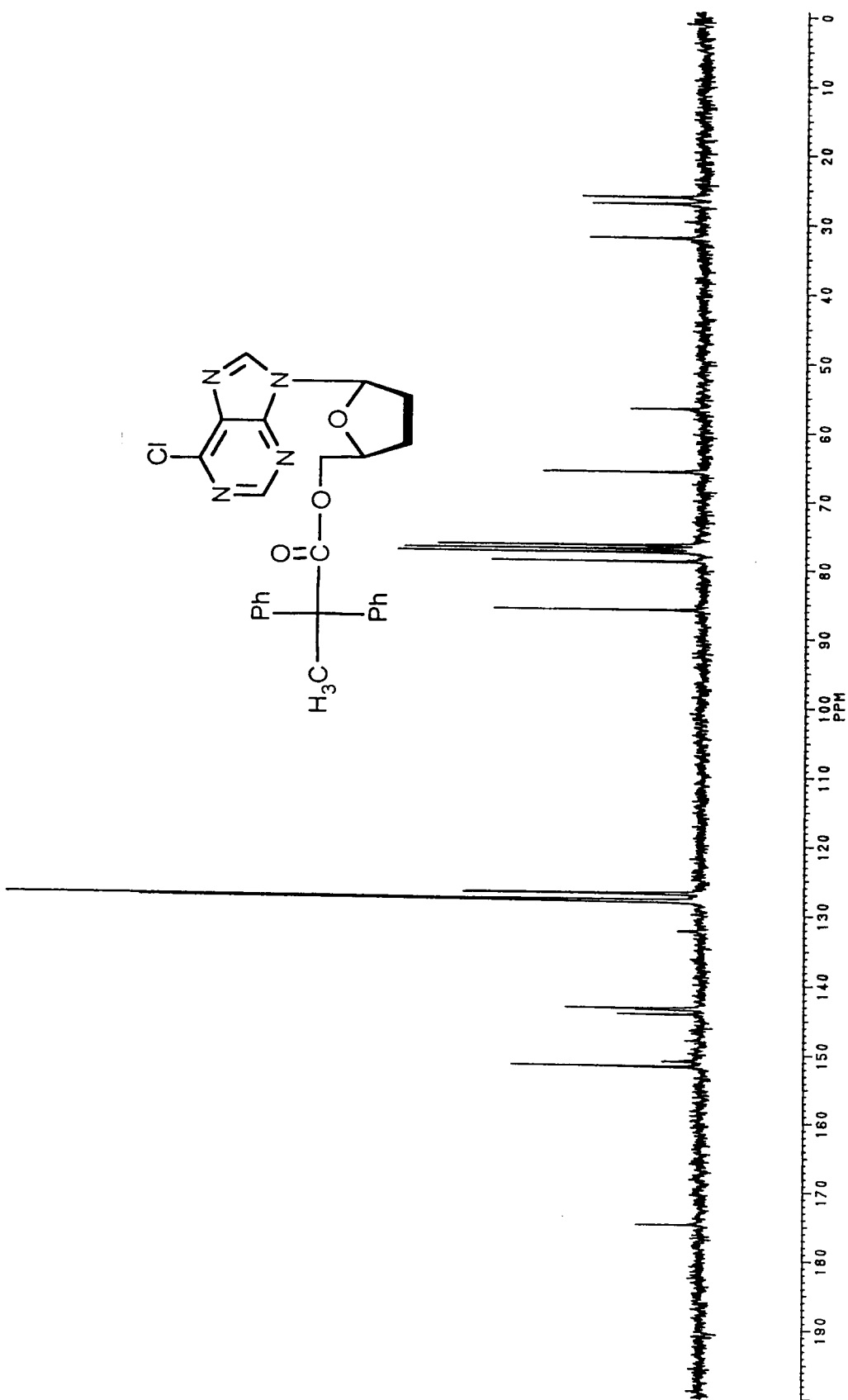
^1H NMR (CDCl_3 , 250 MHz) Spectrum of 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-dimethylsuccinoyl)]- β -D-glycero-pentofuranosyl]purine (**10**, major) and 6-Chloro-9-[2,3-dideoxy-5-O-(3,3-dimethylsuccinoyl)]- β -D-glycero-pentofuranosyl]purine (**11**, minor).



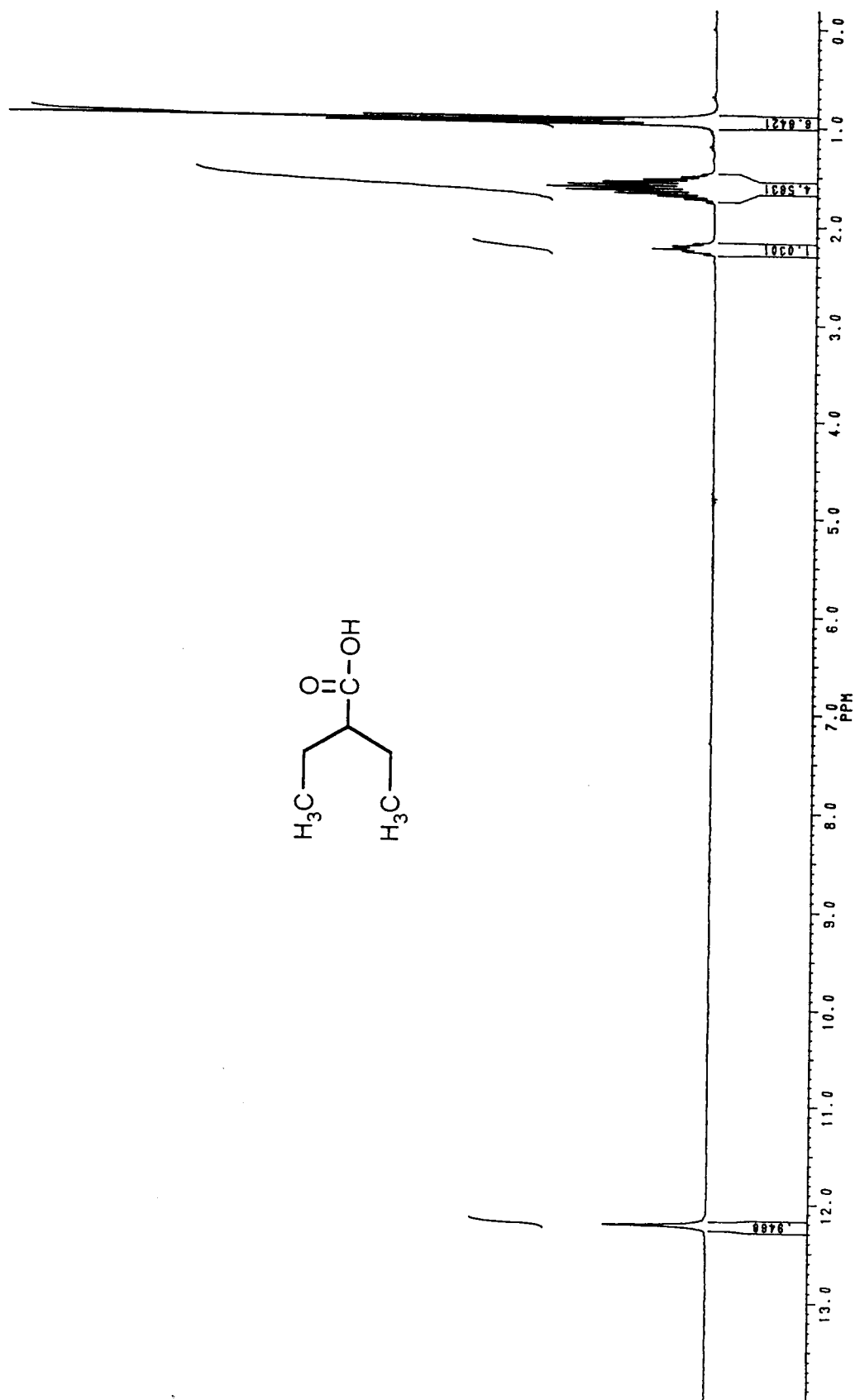
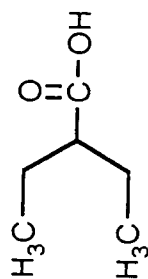
^1H NMR (CDCl_3 , 250 MHz) Spectrum of 2,2-Diphenylpropionyl chloride (**13**).



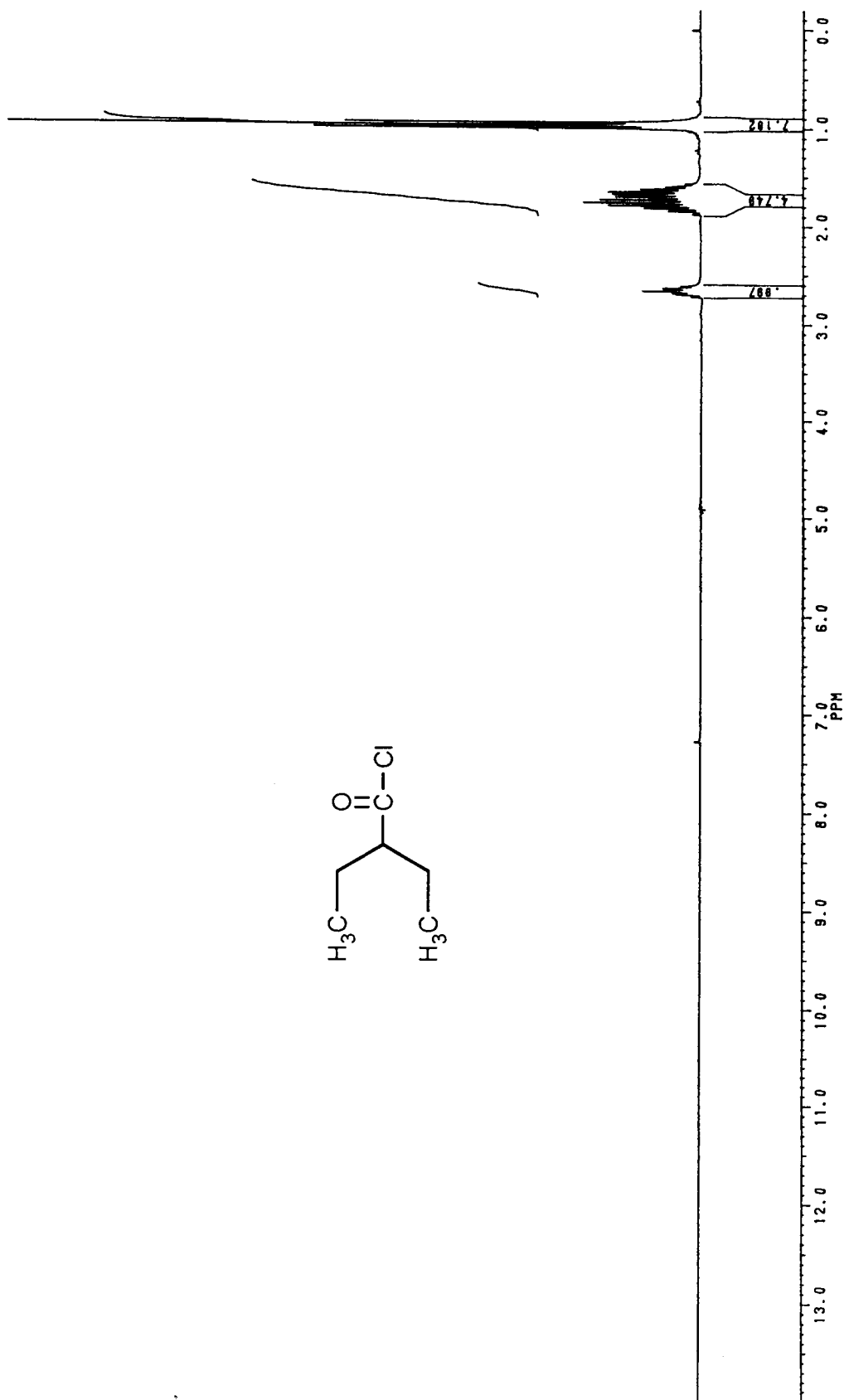
¹H NMR (CDCl₃, 250 MHz) Spectrum of 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-diphenylpropionyloxy)-β-D-glycero-pentofuranosyl]purine (**14**).

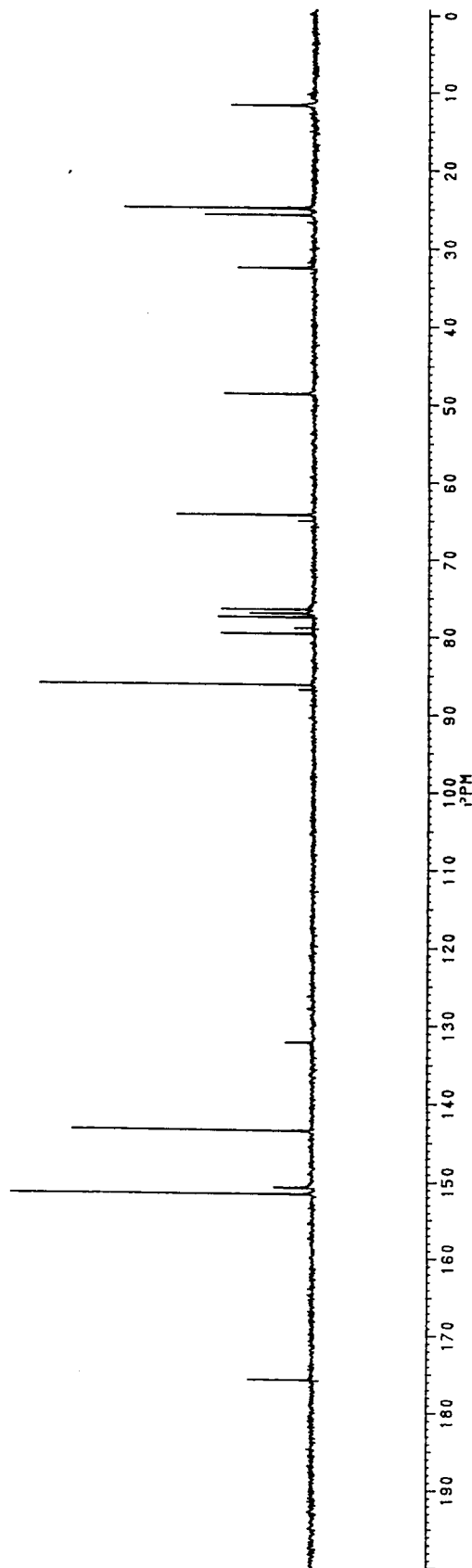
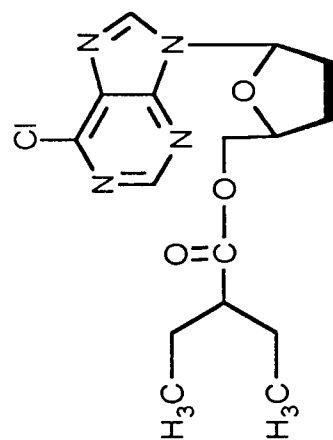


¹³C NMR (CDCl₃, 62.5 MHz) Spectrum of 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-diphenylpropiony)-β-D-glycero-pentofuranosyl]purine (**14**).

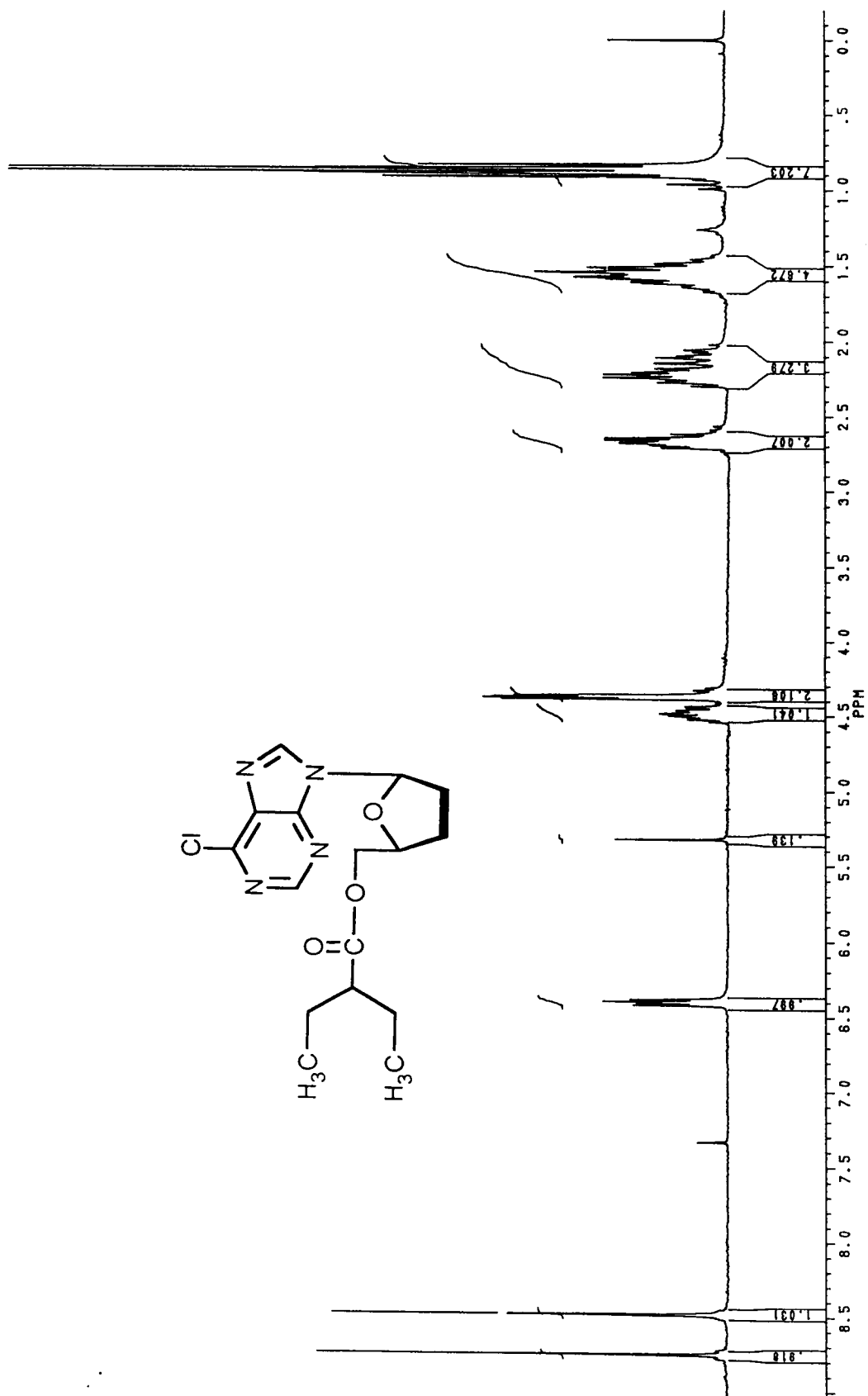
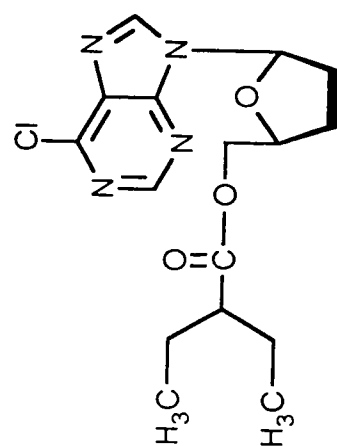


¹H NMR (CDCl₃, 250 MHz) Spectrum of 2-Ethylbutyric acid (15).

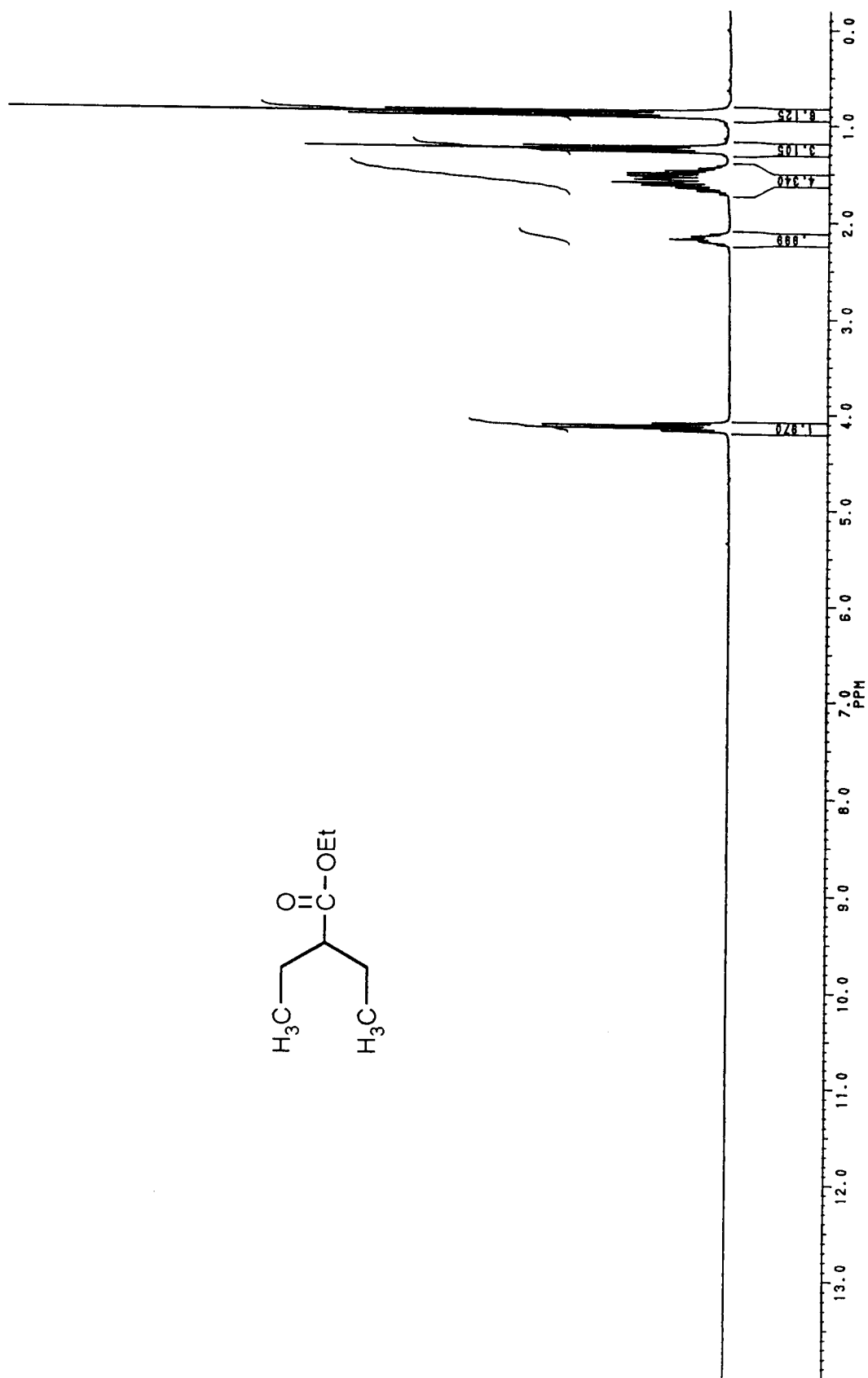




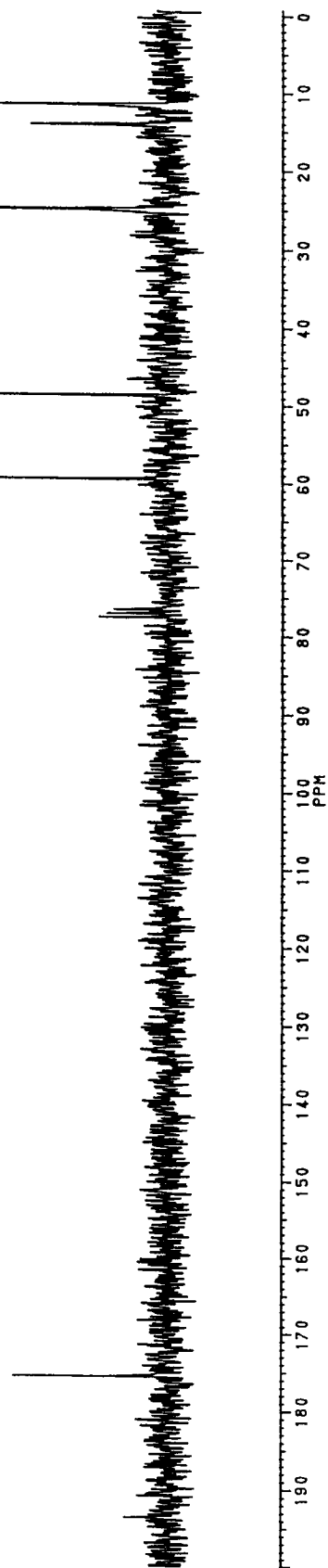
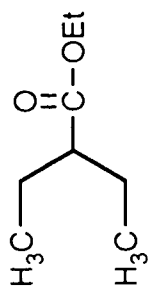
^{13}C NMR (CDCl_3 , 62.5 MHz) Spectrum of 6-Chloro-9-[2,3-dideoxy-5-O-(2-ethylbutyryl)- β -D-glycero-pentofuranosyl]purine (**17**).



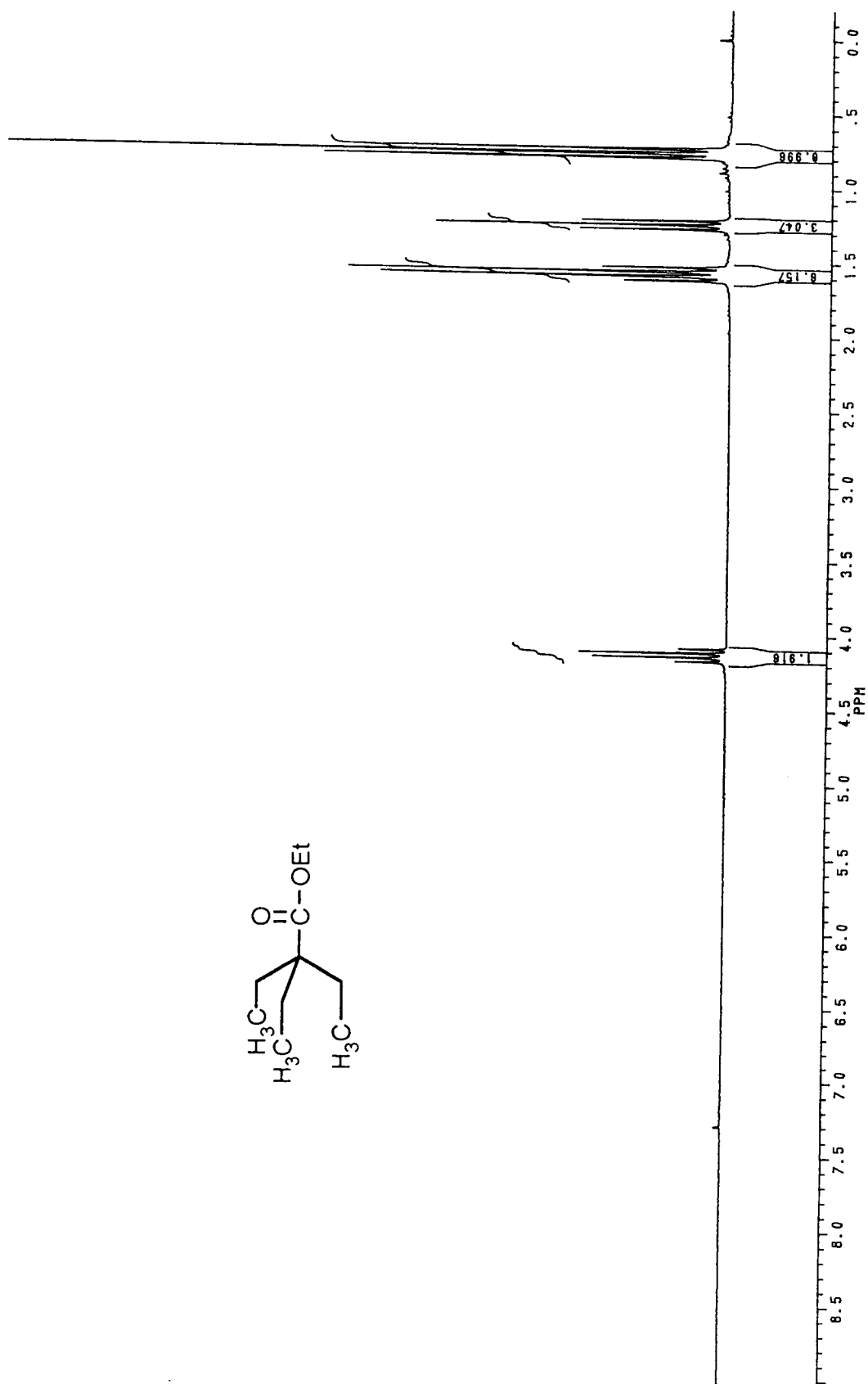
¹H NMR (CDCl₃, 250 MHz) Spectrum of 6-Chloro-9-[2,3-dideoxy-5-O-(2-ethylbutyryl)-β-D-glycero-pentofuranosyl]purine (17).



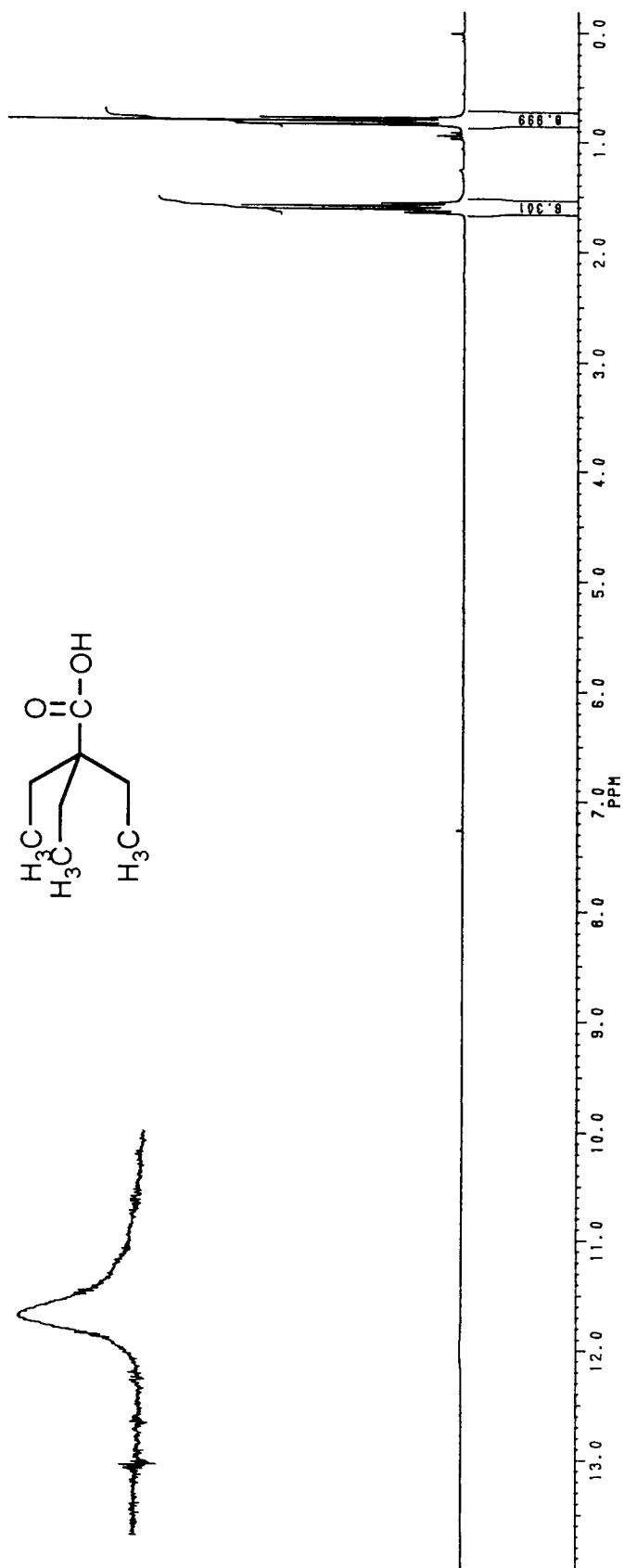
¹H NMR (CDCl₃, 250 MHz) Spectrum of Ethyl 2-ethylbutyrate (18).



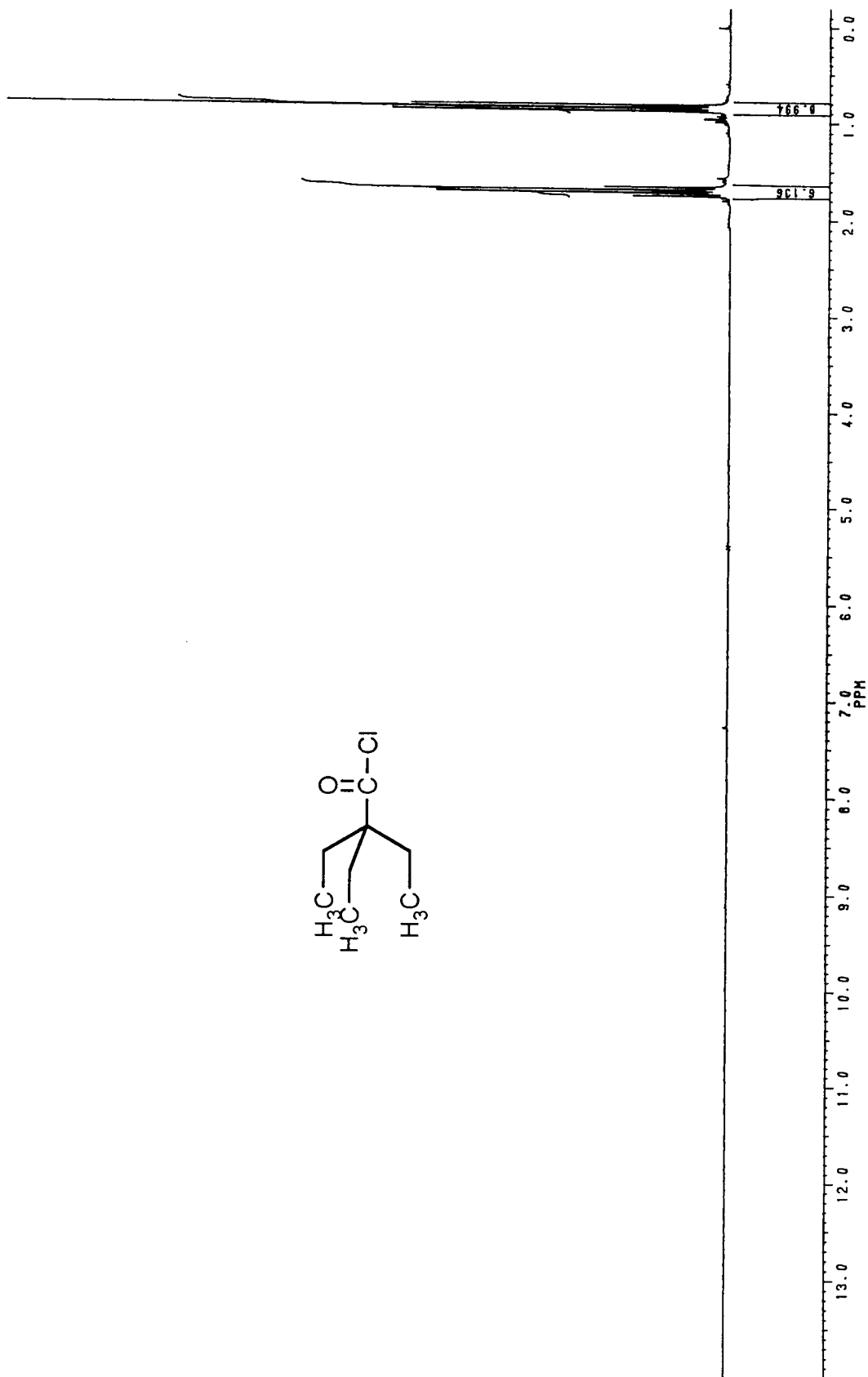
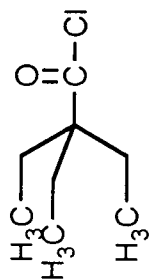
¹³C NMR (CDCl₃, 62.5 MHz) Spectrum of Ethyl 2-ethylbutyrate (18).



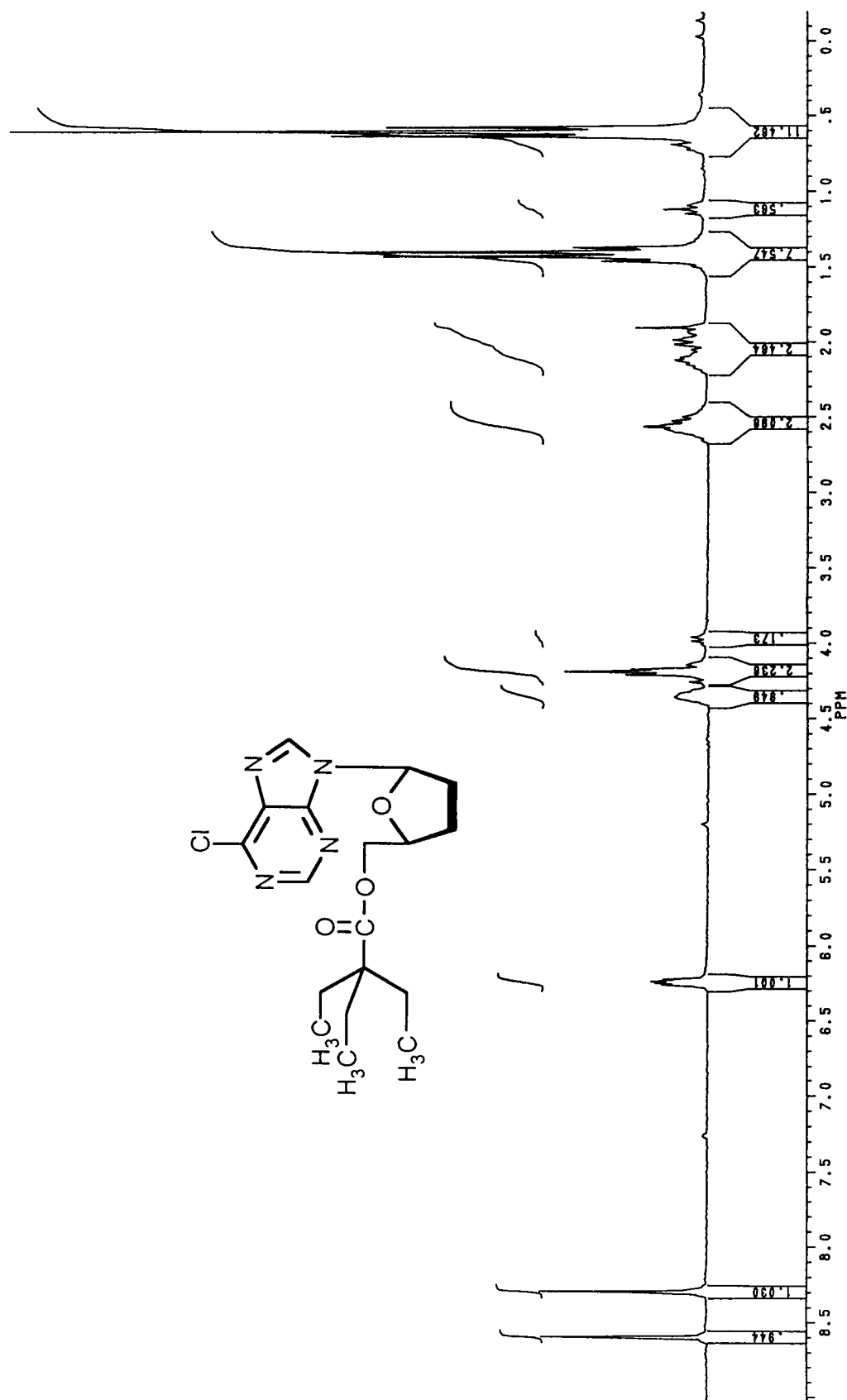
^1H NMR (CDCl_3 , 250 MHz) Spectrum of Ethyl 2,2-diethylbutyrate (19).



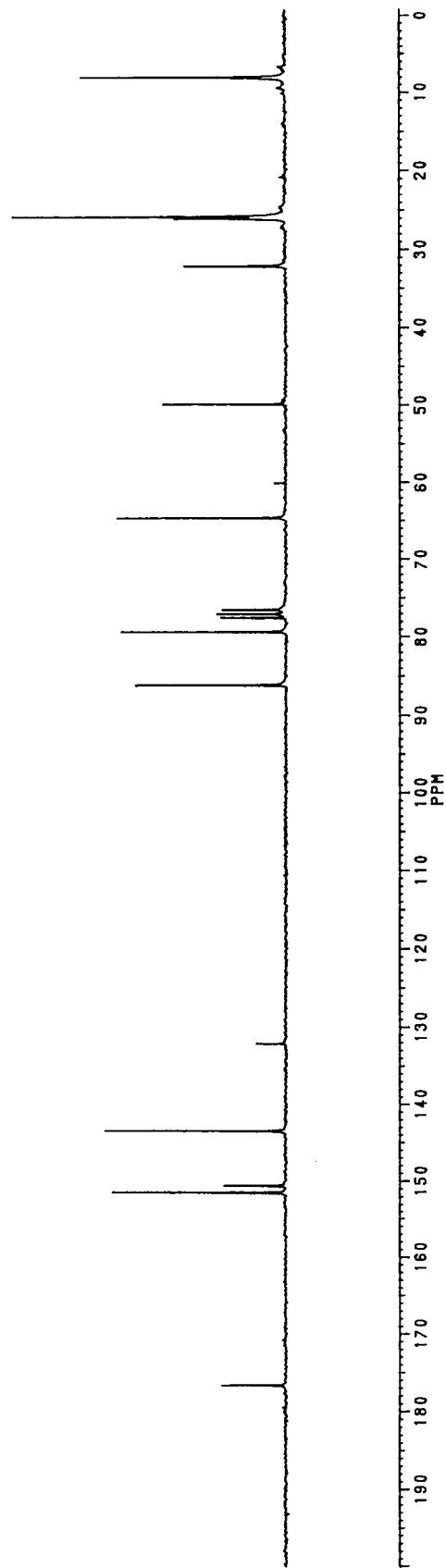
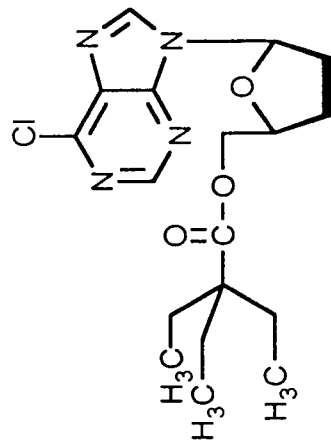
^1H NMR (CDCl_3 , 250 MHz) Spectrum of 2,2-Diethylbutyric acid (20).



¹H NMR (CDCl₃, 250 MHz) Spectrum of 2,2-Diethylbutyryl chloride (21).



¹H NMR (CDCl₃, 250 MHz) Spectrum of 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-diethylbutyryl)-β-D-glycero-pentofuranosyl]purine (22).



^{13}C NMR (CDCl_3 , 62.5 MHz) Spectrum of 6-Chloro-9-[2,3-dideoxy-5-O-(2,2-diethylbutyryl)- β -D-glycero-pentofuranosyl]purine (**22**).

VITA

Farhad Azizbigloo graduated from Sharif (Aryamehr) University of Technology (Tehran, Iran) with a master's degree in chemistry in 1977. Before pursuing his second master's degree at The University of Tennessee, Knoxville, he worked for The Ministry of Energy (Isotope Division) in Tehran, Iran, as a laboratory expert.