To the Graduate Council:

I am submitting herewith a dissertation written by Anand Mayasundari entitled "Synthetic and Structural Studies on Anti-HIV Agents." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

David C. Baker

David C. Baker, Major Professor

We have read this dissertation
and recommend its acceptance:

Accepted for the Council:

Associate Vice Chancellor and
Dean of The Graduate School

SYNTHETIC AND STRUCTURAL STUDIES ON ANTI-HIV AGENTS

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Anand Mayasundari
August 1998

DEDICATION

This dissertation is dedicated to my grandmother,

Mrs. Sarada Ramakrishnan,

my mother, Prof. R. Maya Sundari,

my sister, Mrs. Radha Shekhar,

and my wife, Chitra.

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ABSTRACT

Work described in this dissertation focuses on synthesis and biological evaluation of anti-HIV agents. The leads for the three projects discussed were obtained from the National Cancer Institute's developmental therapeutics program.

Recently, there has been a lot of interest in compounds that target the highly conserved retroviral zinc fingers of the nucleocapsid p7 (NCp7) protein as inhibitors of HIV-1. Described here is the synthesis and anti-HIV-1 evaluation of analogs of the lead compounds, *cis*- and *trans*-4,5-dihydroxy-1,2-dithiane 1,1-dioxides. Also, described here is the resolution of the most active compound, (±)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide, into its enantiomers using an optically active ancillary group and evaluation of their anti-HIV-1 activity. Finally, the absolute configuration of these enantiomers was established by obtaining a single-crystal X-ray structure of the bis-'Mosher' ester of the (−)-enantiomer.

Calanolide A is a potent non-nucleoside reverse transcriptase inhibitor of HIV-1. Analogs of this natural product were synthesized in racemic form in our laboratory and evaluated for anti-HIV-1 activity. The 5-isoproxy analog was found to be the most active compound in this series.

The last project discussed here also deals with non-nucleoside reverse transcriptase inhibitors of HIV-1. Analogs of the lead compound, (±)-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide, were synthesized and evaluated for anti-HIV-1 activity. The lead compound was resolved into its enantiomers using chiral HPLC

and the (+)-enantiomer was found to be the active component. Also, described here is the work done towards determining the absolute configuration of the enantiomers of (±)-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide.

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LIST OF ABBREVIATIONS

Ac	Acetyl
AIDS	Acquired Immune deficiency syndrome
Bz	Benzoyl
DEAD	Diethyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EC_{50}	50% Effective concentration
HIV	Human immunodeficiency virus
HPLC	High pressure liquid chromatography
IC_{50}	50% Inhibitory concentration
LTR	Long terminal repeats
NCI	National Cancer Institute
Nef	Negative factor
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
ORF	Open reading frame
Rev	Regulator of Env
RNA	Ribonucleic acid
RT	Reverse transcriptase

SAR	Structure–activity relationship
Tat	Transactivator of transcription
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TI_{50}	50% Therapeutic index
TLC	Thin layer chromatography

PART ONE

HUMAN IMMUNODEFICIENCY VIRUS

AND ITS INHIBITORS

I. INTRODUCTION

In 1982 physicians first became aware of a new sexually transmitted disease that was associated with an unusual form of cancer (Kaposi's sarcoma) and a variety of unusual infections.[1] The disease was named *acquired immune deficiency syndrome* (AIDS), since both these problems reflected a severe deficiency in the helper T cells of the immune system. A retrovirus, called *human immunodeficiency virus* (HIV), was found to be the causative agent of AIDS.

A. Human Immunodeficiency Virus (HIV) and its Structure

HIV is a member of a family of viruses called lentiviruses that are part of a large group of viruses known as the Retroviridae.[2] Some of the other members of the group are the closely related simian, feline and bovine immunodeficiency viruses. This group of viruses display a variety of common features:

- A genome made up of ribonucleic acid (RNA).
- A viral structure which contains three polyprotein genes—group-specific antigen (*gag*), polymerase (*pol*) and envelope (*env*).
- A life cycle which involves insertion of the viral genome into the host genome.
- An ability to modify their genomes by mutation.

Two genetically different yet related species of the human immunodeficiency virus called HIV-1 and HIV-2 are known. HIV-1 is the prototype and is the cause of the AIDS throughout Africa, Europe, Asia and USA, whereas, HIV-2 is confined to certain

parts of West Africa and appears to be less pathogenic than HIV-1.[2] The structure of the HIV-1 genome is depicted in Figure 1. The location of the known genes and the function of the protein products are shown. The HIV-2 genome contains the *vpx* gene instead of the *vpr* gene present in HIV-1 in a similar location. The HIV genome carries open reading frames (ORFs) for many regulatory proteins in addition to *gag, pol,* and *env* polyprotein genes that are common to all retroviruses.

Human immunodeficiency virus is roughly spherical in shape with a diameter of 110 nm. The virus contains a cone-shaped core which measures 100 nm in length and 50 nm tapering to 40 nm in width. All the genetic and biochemical information required for replication of HIV is present in the core. This includes the HIV RNA genome, a cellular transfer RNA (tRNA) and three enzymes called reverse transcriptase (RT), integrase (IN) and protease (PR). Two identical strands of RNA are present in every HIV particle, and each of these strands contains the entire genetic code for the structure and life cycle of the virus. The HIV genome contains only 9800 nucleotides and is about 100 000 times smaller than the genome of humans.[2]

B. The Replication Cycle of HIV

The life cycle of HIV involves the following stages:

1. Attachment of the viral particle to the host cell
2. Fusion and entry into the host cell
3. Reverse transcription
4. Integration

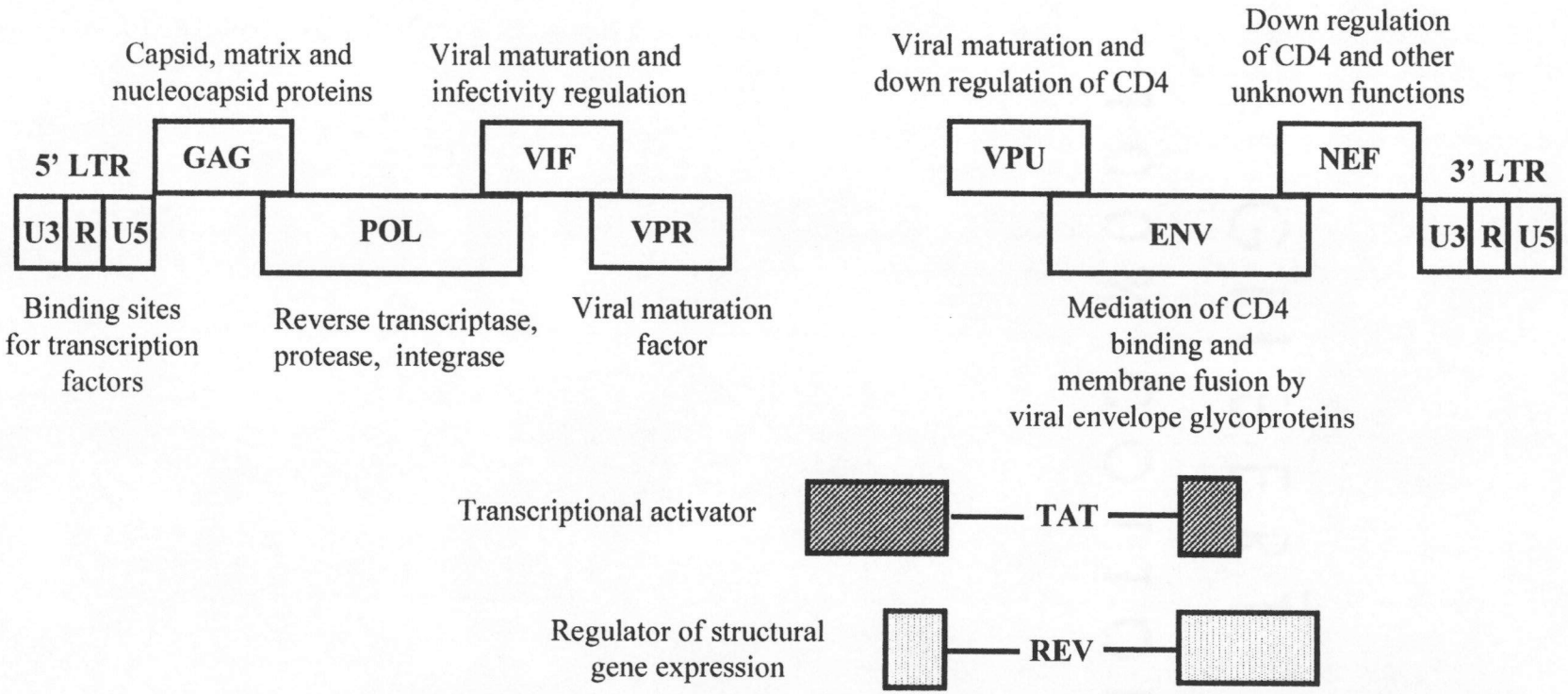


Figure 1. Structure of the HIV-1 genome.

5. Synthesis of HIV RNA
6. Expression of HIV RNAs
7. Assembly and budding of the immature virion
8. Release and maturation of the HIV particle catalyzed by the protease enzyme

The replication cycle of HIV is shown schematically in Figure 2.

C. Molecular Targets for Anti-HIV Chemotherapy

Several factors that make HIV a very deadly virus are the following:

- Unlike many other retroviruses it kills rather than live in symbiosis with the helper T cells, which are vital in defending us against infection.
- The provirus tends to persist in a latent form in the chromosomes of an infected cell until it is activated by an unknown rare event.
- Its extreme tendency to mutate to forms that are resistant to existing antiviral therapies.

The fact that it has a extreme tendency to mutate to forms that are resistant to existing antiviral therapies[3] greatly complicates attempts to treat the infection with antiviral drugs. Most of the current research in AIDS is aimed at understanding the life cycle of HIV. AIDS research has been targeted towards inhibition of the virus at different stages of the its life cycle.

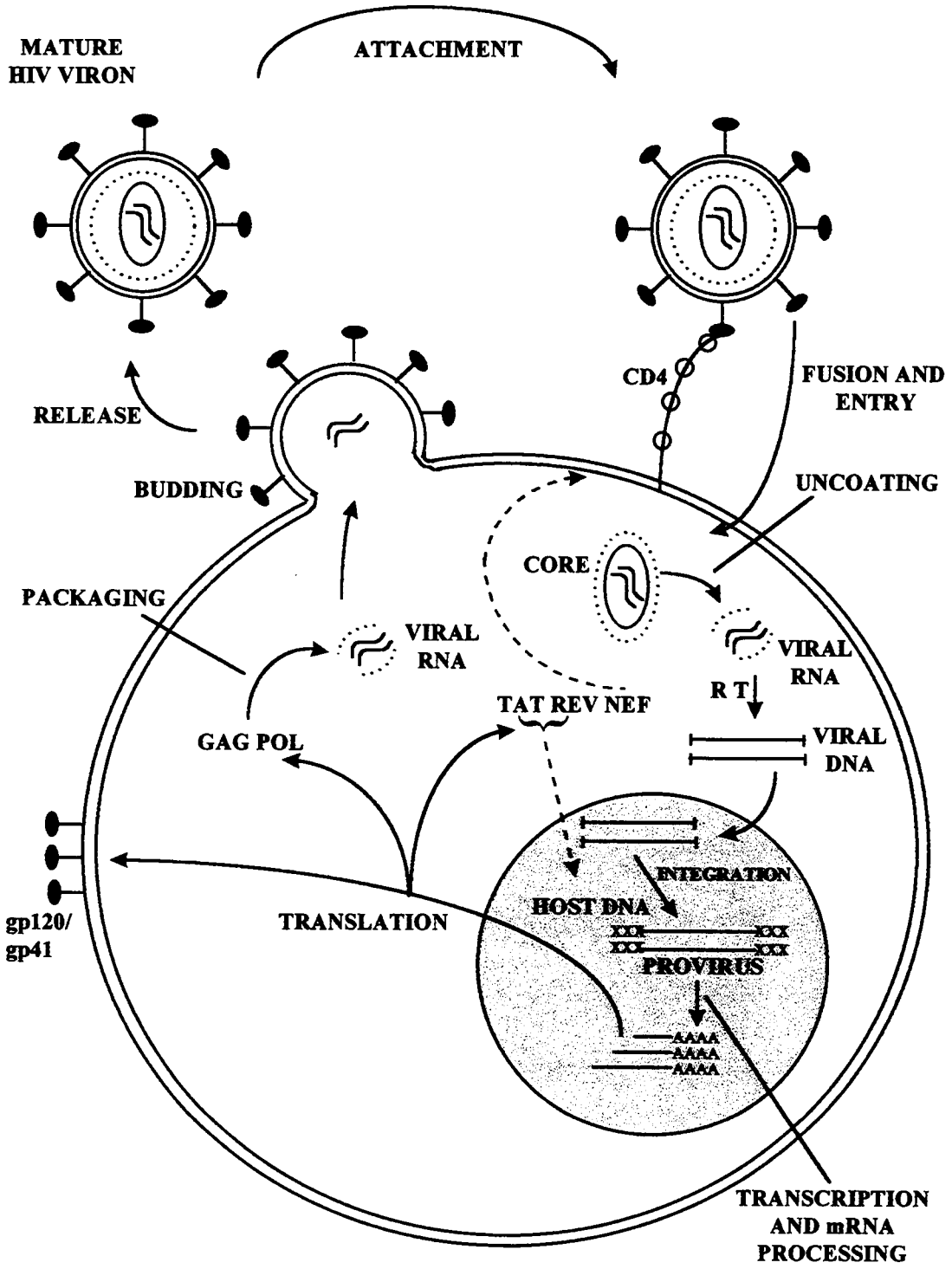


Figure 2. Life cycle of HIV.

The molecular target for HIV inhibitors can be broadly classified into the following classes:

1. Reverse transcriptase (RT) enzyme
2. Protease enzyme
3. Integrase enzyme
4. Regulatory proteins
5. Zinc finger domains in the nucleocapsid p7 protein

A brief overview of these molecular targets and the anti-HIV agents that act on them is presented in the sections below.

1. HIV Reverse Transcriptase (RT)

The normal flow of genetic information is from DNA to RNA to protein, and hence HIV, which is a retrovirus, must first convert its genomic RNA into a double-stranded DNA in order to start its replication cycle in the host-cell. This conversion takes place in the host cell cytoplasm with the help of a viral enzyme called reverse transcriptase (RT) that catalyzes a series of biochemical reactions involved in this process. This makes reverse transcriptase (RT) enzyme an attractive target for HIV inhibitors.[4–11] HIV RT inhibitors can be broadly classified into nucleoside and non-nucleoside RT inhibitors. The mode of action of these two class of compounds are different in nature.

The nucleoside HIV RT inhibitors are competitive inhibitors that to bind to the catalytic site of the enzyme and their mode of action appears to be through their

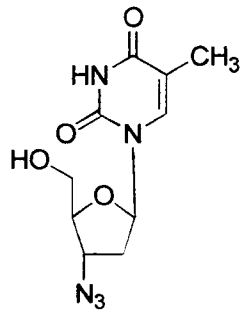
triphosphates (produced in the cytoplasm of the host cell) that act as RT enzyme inhibitors through incorporation and termination of the growing viral DNA chain.[12–18] Some of the nucleoside RT inhibitors are shown in Figure 3.

However, all non-nucleoside reverse transcriptase inhibitors (NNRTIs) are non-competitive inhibitors of the RT enzyme, and they bind to an 'allosteric' site with influence on the catalytic site.[19–24] Hence, they are also referred to as 'second-site' RT inhibitors. In general, at nanomolar concentrations NNRTIs inhibit HIV-1 *in vitro* with minimum or no cytotoxicity but do not inhibit HIV-2 or other retroviruses.[19,20,25–28] Some non-nucleoside RT inhibitors are shown in Figure 4.

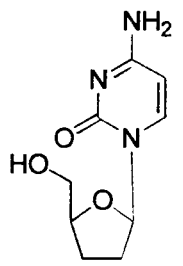
2. HIV Protease

The HIV protease enzyme is virally encoded and is essential for the reproduction of the virus.[29] It is a homodimer in which each subunit contains the full-length protease gene product, a protein of 99 amino acids. The mature homodimer is an aspartyl protease that is characterized by C_2 symmetry, and so rotation by 180° around this axis leads to exactly the same orientation present before it was rotated.[30] This characteristic has been exploited by some drug discovery programs in their discovery of chemical leads with activity against this enzyme.

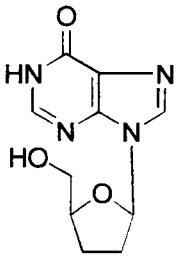
The components of the p55 Gag and p160 Gag-Pol polyproteins have to be separated in order to form a mature infectious HIV particle. The protease (PR) domain of the Gag-Pol precursor catalyzes this highly specific process. Protease activity is regulated in that it functions only when the two PR domains combine. The active dimeric



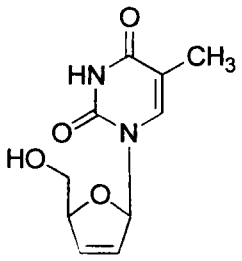
AZT



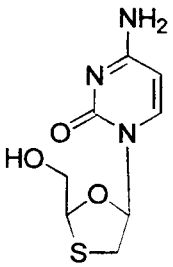
ddC



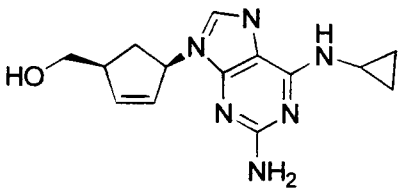
ddI



d4T

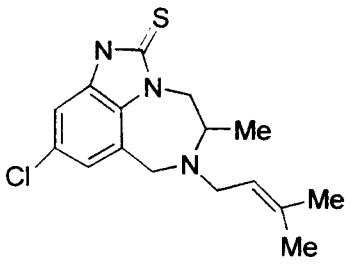


3TC

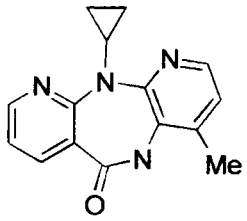


Abacavir

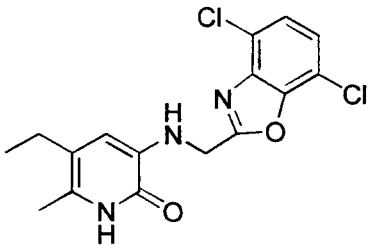
Figure 3. Nucleoside HIV reverse transcriptase inhibitors.



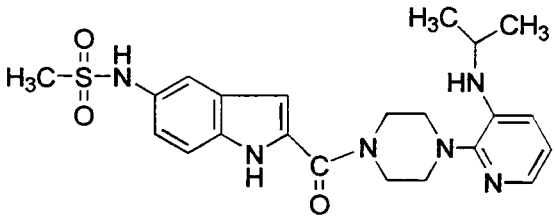
Chloro-TIBO



Nevirapine



L-697, 661



Delavirdine

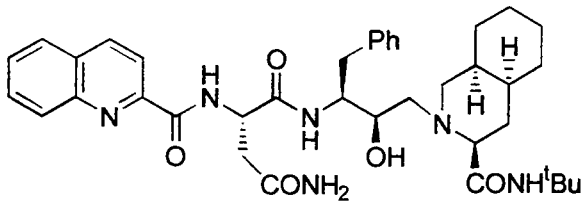
Figure 4. Non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs).

protease cleaves itself first from the p160 Gag-Pol precursor, and then cleaves the p55 and p160 precursors at seven other sites.

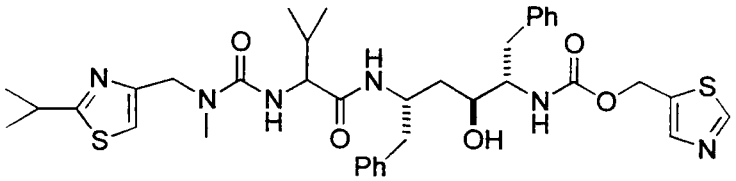
It has been demonstrated that interruption of the protease open reading frame leads to the production of non-infectious particles.[29] Morphology which is typical for immature virions prior to release from the cell are displayed by these non-infectious virus particles. Moreover, the activity of the individual proteins contained within the Gag-Pol precursor are reduced or eliminated in the absence of protease activity, and hence, they become effectively nonfunctional.[31,32] Thus, it can been seen that anti-retroviral agents that bind strongly to the protease enzyme could prevent its activity and thereby interfere with viral reproduction.[33–40] The leading HIV-1 protease inhibitors are shown in Figure 5.

3. HIV Integrase

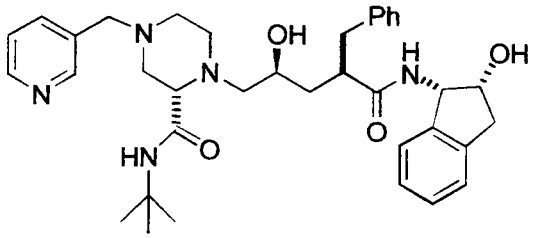
Double-stranded HIV DNA is transported into the host cell nucleus in the form of a protein–nucleic acid complex. In the nucleus, HIV DNA is integrated into the host cell DNA, and this three-step process is catalyzed by the viral integrase protein.[41–43] Two bases are first removed from the 3′-ends of the two DNA strands to form reactive hydroxy groups. A staggered cut is then made in the host DNA, and this leaves five bases overhanging on either side of the duplex. This cleavage takes place in a concerted reaction in which phosphate bonds are formed with the hydroxy groups flanking the 3′-ends of the HIV DNA . Finally, the nicks are repaired to form a fully integrated HIV



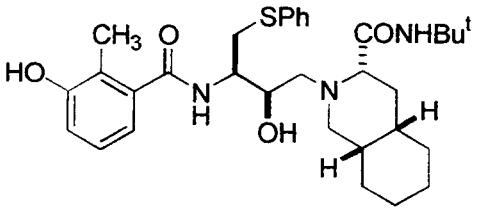
Saquinavir



Ritonavir



Indinavir



Nelfinavir

Figure 5. HIV protease inhibitors.

DNA genome and this is called the HIV provirus. Some inhibitors[44] that target the integration process are shown in Figure 6.

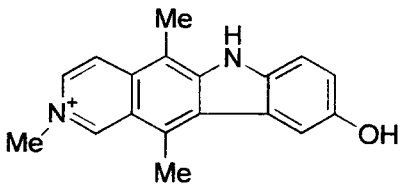
4. Regulatory Proteins

The regulatory proteins Tat, Rev and Nef can serve as molecular targets for anti-retroviral chemotherapy. These are relatively new targets in comparison to well known targets like reverse transcriptase, protease, and integrase, and are briefly outlined in the sections below:

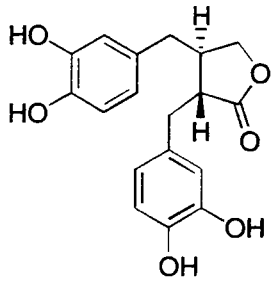
i. Tat

The provirus is flanked by long terminal repeats (LTR), which are derived during reverse transcription from the 5′- and 3′-ends of the viral RNA. The 5′- and 3′-LTR's serve different functions in the regulation of viral expression. The 5′-LTR binds transcription factors that regulate initiation of mRNA synthesis, whereas the 3′-LTR is responsible for the termination of mRNA synthesis.[45,46] HIV-1 and HIV-2 encode additional transcription factors that enhance mRNA synthesis from the 5′-LTR.[47]

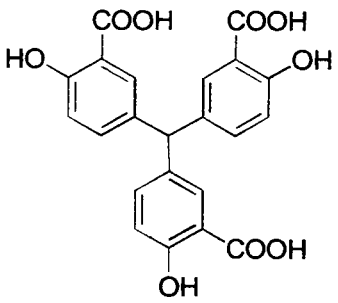
The first HIV-1 encoded transcription factor identified is called Tat (TransActivator of Transcription) and the target sequence is called TAR (TransActivation Response element). It was seen that infectivity of proviral clones were reduced to undetectable levels when the *tat* gene was deleted from these clones.[48] This indicates that Tat is essential for the growth and transmission of the virus, and so the interaction between Tat and TAR can serve as a target for anti-retroviral drugs. Some inhibitors of Tat function are shown in Figure 7.



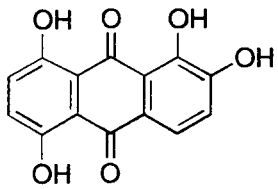
NMHE



(2*R*,3*R*)-2,3-Bis(3,4-dihydroxybenzyl)-butyrolactone

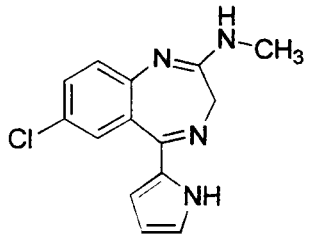


Aurintricarboxylic acid

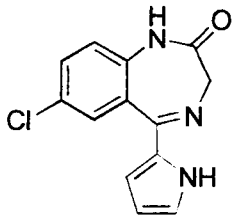


Quinalizarin

Figure 6. HIV integrase inhibitors.

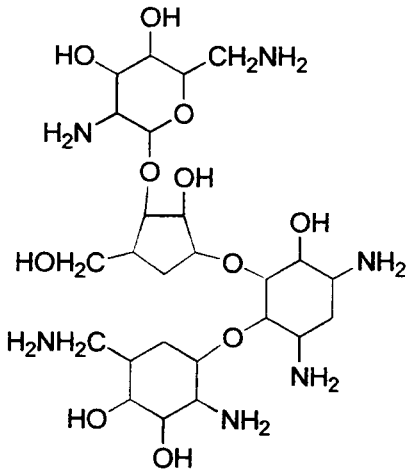


Ro24-7429

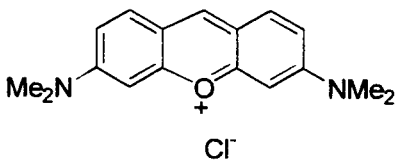


Ro5-3335

HIV Tat inhititors



Neomycin B



Pyronin Y

HIV Rev inhititors

Figure 7. HIV Tat and Rev inhibitors.

ii. Rev

HIV expresses three classes of mRNA that are approximately 2 kb, 4 kb and 9 kb in size. The regulatory protein Rev (Regulator of Env) balances the expression of long unspliced or partially spliced messages (9 and 4 kb) and the short multiple-spliced messages (2 kb).[45,46] In the absence of Rev, HIV is not able to express normal levels of the Gag and Env proteins, due to the absence of 4 kb and 9 kb classes of mRNA in the cytoplasm of infected cells. Since viruses that are not able to express active Rev protein are non-infectious, Rev appears to be a good target for anti-retroviral drugs. Two Rev inhibitors are shown in Figure 7. Two Rev-specific processes which are good molecular targets for intervention are the initial binding of Rev to RRE (Rev Response Element) which is located in the Env coding region of HIV mRNA and multimerization of Rev. Using mutant Rev proteins like M10 that have a '*trans*dominant phenotype' the multimerization step can be inhibited.[49] Gene therapy has been tried where retroviruses have been used to introduce M10 protein into cells, and this approach differs from the traditional approach of using small-molecule inhibitors.[50]

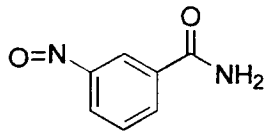
iii. Nef

Nef (Negative factor) is the third regulatory protein that can serve as a molecular target for anti-retroviral chemotherapy. Antiviral agents that can target the HIV Nef protein are in the initial stages of development.

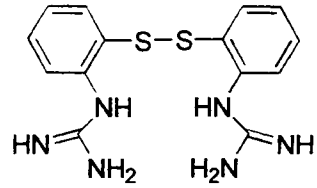
5. Zinc Finger Domains in the Nucleocapsid p7 Protein

Attempts have been made to slow down the onset of AIDS using HIV-1 reverse transcriptase (RT) and protease inhibitors, but it has been seen that many of the anti-HIV drugs are not effective against the mutant forms of the virus.[51] Strategies that target the highly conserved and mutationally intolerant retroviral features need to be developed to combat AIDS. In all lenti- and oncoretroviruses, the nucleocapsid (NC) proteins contain one or two highly conserved Cys-Xaa_2-Cys-Xaa_4-His-Xaa_4-Cys (CCHC) peptide segments (where Xaa is any amino acid) that are coordinated to zinc, and hence, are known as the retroviral zinc fingers.[52–57] The spacing and the zinc-chelating residues (three Cys and one His) of the zinc finger motif are absolutely conserved, and mutations in the metal-chelating residues lead to a noninfectious virus.[58] The zinc finger domains within the Pr55 Gag and Pr160 Gag-Pol precursor polyproteins are required for packaging of viral genomic RNA.[59–65] The mature NCp7 protein results from the processing of these precursor polyproteins,[66] and the zinc fingers of this protein are needed to initiate further infection.[67–71] Hence, compounds that attack the retroviral zinc finger may function as inhibitors in more than one step of the HIV-1 replication cycle.

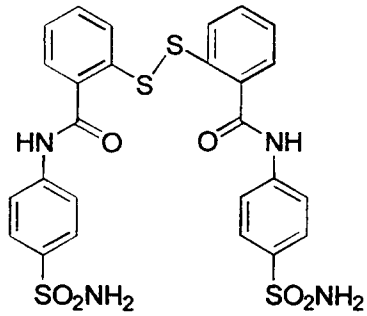
It has been recently shown that in HIV-1 nucleocapsid p7 protein, the sulfur atoms of the Cys residues that are coordinated to zinc are covalently modified by electrophilic attack on them by functional groups like aromatic C-nitroso compounds, maleimides, and disulfides, resulting in ejection of zinc from the zinc finger.[72–77] Some zinc finger inhibitors are shown in Figure 8.



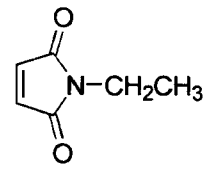
NOBA



NSC 20625



DIBA-1



N-Ethylmaleimide

Figure 8. Inhibitors of HIV nucleocapsid protein zinc fingers.

D. Combination Therapy

Antiviral therapy with zidovudine (AZT) has prolonged the life of patients with AIDS and delayed the onset of AIDS in people with HIV infection.[78–82] However, monotherapy with AZT or other drugs has its limitations as the AIDS virus mutates to phenotypes that are resistant to the drug.[80,81,83] Moreover, with prolonged monotherapy patients continue to have progression of HIV disease and also develop associated complications.[80,81,83] There are quite a few drugs in the market today to fight this disease, and at present doctors and researchers think that the best approach to counter AIDS is to use more than one drug. A sequential use of different antivirals was first recommended.[84] However, despite sequential treatment with nucleoside antiretroviral agents, HIV disease continued to progress, and there was a lack of sustained improvement in immunological measures.[85,86] These limitations suggested that other strategies, like a combination of agents, be considered to combat AIDS. Combination therapy involves the use of a concoction of two or more drugs that act at the same or different stages of the viral life cycle.[87–94]

The most important goals of combination therapy are:

- To maximize the suppression of HIV
- To prevent the conversion of the virus to more virulent phenotypes
- To delay the development of resistance to anti-HIV agents
- To increase efficacy in different cell types or cell states
- To decrease toxicity

One issue that needs to be considered in combination therapy is whether to use agents that target the same step of the viral replication cycle (convergent therapy) or to use a combination of agents, each acting at different steps of the life cycle (divergent therapy).[95] Combinations of two or three nucleoside RT inhibitors or combinations of nucleoside and non-nucleoside RT inhibitors or combinations of one or two nucleoside RT inhibitors with a protease inhibitor have been used in AIDS therapy. Combination therapy appears to be more effective compared to zidovudine (AZT) monotherapy.[96–99] Thus, combination therapy seems more likely than monotherapy to succeed in the fight against HIV and AIDS.

PART TWO

SYNTHESIS AND ANTI-HIV-1 EVALUATION OF COMPOUNDS CONTAINING –S–S– AND –S–SO_2– LINKAGES

I. STATEMENT OF THE PROBLEM

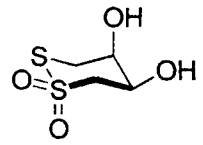
A. Objectives

The objectives in this project are as follows:

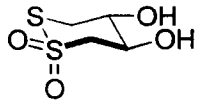
- To synthesize analogs of the lead compounds in racemic form.
- To evaluate these analogs for biological activity against HIV-1 and develop structure–activity relationships.
- To obtain the enantiomers of the most active compound in order to determine the activity of the individual enantiomers against HIV-1.
- To determine the absolute configration of the enantiomers of the most active compound.

B. Research Plan

The National Cancer Institute's drug screening program had identified *cis*- and *trans*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide as inhibitors of HIV-1 replication in their XTT assay. The structures of these lead compounds are shown in Figure 9. In an effort to probe structure–activity relationships, analogs of these two lead compounds had to be synthesized and tested for anti-HIV activity. As the lead compounds had two stereogenic centers, it was possible to synthesize two series of compounds, namely the *cis*-series and the *trans*-series, depending on the precursor chosen. We decided to make analogs in each series as well as vary the size of the ring in order to ascertain structure–activity relationships.



(±)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (**NSC 624151**)



(±)-*trans*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (**NSC 624152**)

Figure 9. Structures of the lead compounds **NSC 624151** and **NSC 624152**

McCormick and McElhinney have synthesized *cis*- and *trans*-4,5-dihydroxy-1,2-dithianes from *meso*- and (±)-1,4-dichloro-2,3-butane-diols, respectively,[100] which in turn were made from *trans*-1,4-dichloro-2-butene.[101] Cleland has made these dithianes by ferricyanide oxidation of dithioerythritol and dithiothretiol, respectively.[102] We decided to use the first route as it was more economical. Field and co-workers have oxidized the 3,4-dihydroxy-1,2-dithianes directly to the corresponding sulfoxides[103] and sulfones[104] using hydrogen peroxide and tungstic acid, while other workers before them had difficulties oxidizing the dihydroxy compounds using other oxidants, even though oxidation of the 3,4-diacetoxy-1,2-dithianes to the diacetate monoxides and diacetate 1,1-dioxides have been reported previously.[100] We decided to do these oxidation using the method of Field and co-workers.[103,104]

We envisioned that the dialkoxy and the diacyloxy analogs of the lead compounds could be made in order to explore their anti-HIV activity. We hoped that these analogs would give us a decent idea of the structure–activity profile and guide us in our quest for more potent anti-HIV drugs.

William G. Rice and co-workers at the National Cancer Institute were also interested in these compounds as candidates that could interact with the highly conserved zinc finger motif of the HIV-1 p7 nucleocapsid (NCp7) proteins. They have looked at a number of disulfide compounds and found some of them to be inhibitors of HIV-1.[72–77]

Analogs that were synthesized were submitted to the NCI for biological screening against HIV-1 using the XTT and NCp7 zinc finger assays. The most active compound was identified from these assays.

The anti-HIV activity results obtained from the NCI indicated that all the analogs submitted from Prof. Baker's laboratory were less active than the lead compounds. It was also seen that the *cis*-4,5-dihydroxy-1,2-dithaine 1,1-dioxide was more potent than *trans*-isomer in the XTT assay and equally active in the zinc finger assay. So, we formulated the next stage of this project as described in the sections that follow.

Nature produces compounds in optically pure form and the biological activity of a natural product usually resides in one of its enantiomers. Even if both the enantiomers of a natural product are active, it is seen that one is invariably more active than the other. Keeping this in mind, the second stage of this project would be obtain the two enantiomers of *cis*-4,5-dihydroxy-1,2-dithaine in optically pure form. One could either resort to asymmetric synthesis to obtain the individual enantiomers, or the racemic compound could be resolved. Given the fact that this compound has an $-S-SO_2-$ linkage that is not very stable to many reaction conditions, we figured that asymmetric synthesis would not be a easy task and hence, decided to first attempt to resolve the most active compound into its enantiomers.

We planned to do enzymatic resolution or use chiral HPLC to resolve *cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide into its enantiomers. Alternatively, we would use a chiral entity like (*R*)- or (*S*)-Mosher acid chloride to convert the racemic compound into a pair of diester diastereomers which should be separable. Hydrolysis of the ester functionality would yield the pure enantiomers.

The absolute configuration of *cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide was not known. There were NMR techniques available in the literature that could possibly help us determine the absolute stereochemistry.[105–108] Alternatively, we figured that we would use X-ray crystallographic techniques to solve the absolute structure.

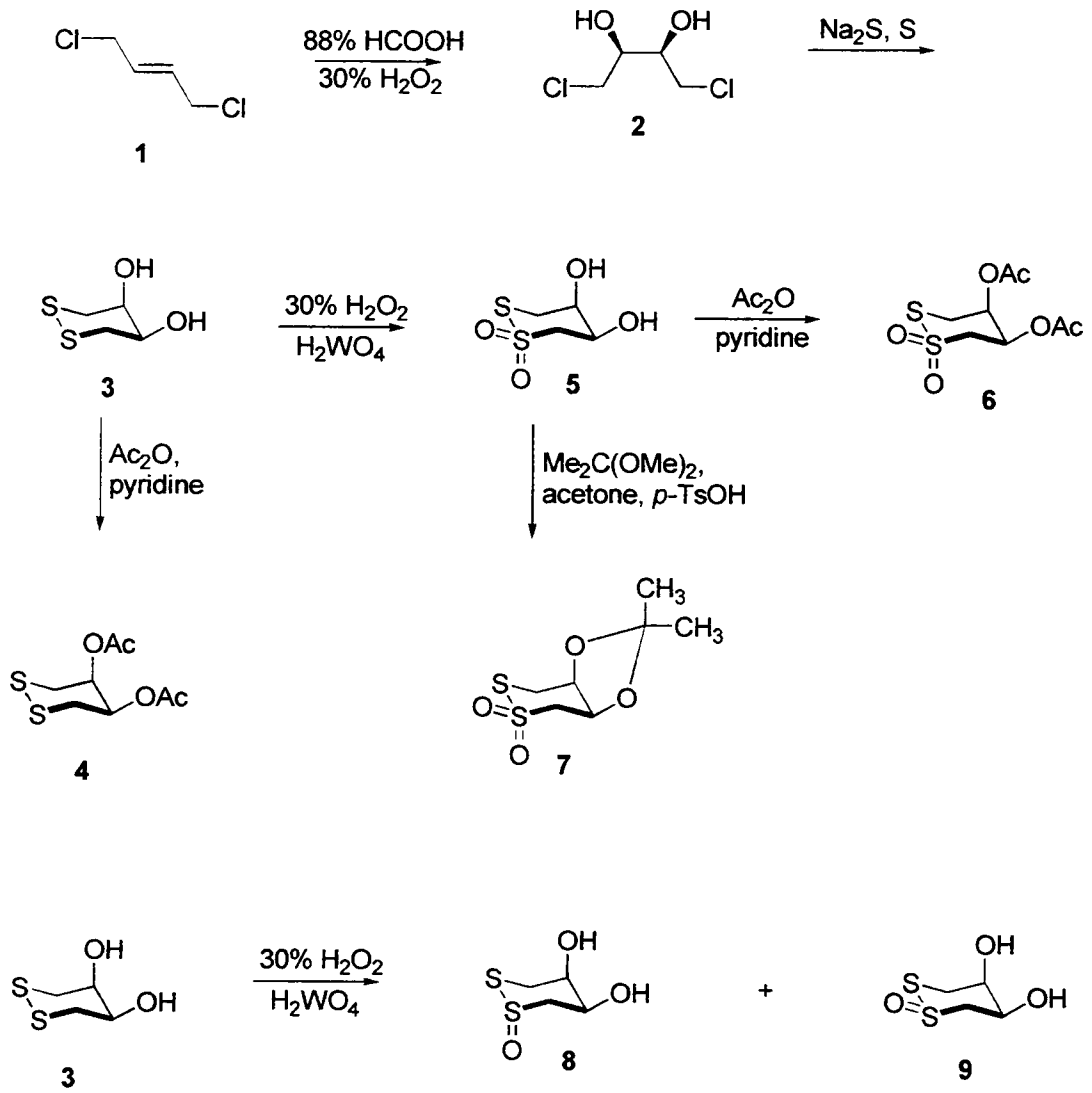
C. Significance

These 1,2-dithiane compounds have aroused considerable interest to us and co-workers at the NCI as potential inhibitors of HIV-1. If completed, this project would identify potent inhibitors of HIV-1 replication that target the highly conserved zinc finger motif of the HIV-1 p7 nucleocapsid (NCp7) proteins. It would determine the more active enantiomer of *cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide and also establish its the absolute stereochemistry.

II. RESULTS AND DISCUSSION

A. *cis*-Series

trans-1,4-Dichloro-2-butene (**1**) was hydroxylated using the literature procedure[101] with performic acid generated *in situ* from 88% formic acid and 30% hydrogen peroxide to give the *meso*-1,4-dichlorobutane-2,3-diol (**2**) in 50% yield (Scheme 1). Compound **2** was treated with sodium sulfide and sulfur[100] to give the *cis*-4,5-dihydroxy-1,2-dithiane (**3**) in 55% yield. When the ^{1}H NMR spectrum of this compound was recorded at room temperature on a 250-MHz instrument, only broad peaks were obtained, whereas, at −40 °C on a 400-MHz instrument nice sharp peaks were obtained. This could be attributed to the rapid flipping of the six-membered ring between its two chair conformations. Therefore, the ^{1}H and ^{13}C NMR of **3** were recorded in CD_3OD at 400 MHz and 100 MHz, respectively. Compound **3** was acetylated with Ac_2O and pyridine to give **4** in 95% yield.[100] NMR spectra of compound **4** were also recorded at −40 °C, as peaks were broad at room temperature. Dithiane **3** was oxidized in 24 h to the dioxide **5** in 35% yield using 30% H_2O_2 and H_2WO_4 as the catalyst.[104] In an effort to make analogs of the dioxide **5**, it was converted to the diacetate **6** in 91% yield using Ac_2O and pyridine. This compound had been made before by oxidizing *cis*-4,5-diacetoxy-1,2-dithiane with H_2O_2 and acetic acid.[100] The *O*-isopropylidene derivative **7** was prepared in 51% yield from **5** by reacting it with 2,2-dimethoxypropane in acetone in the presence of *p*-tolunesulfonic acid. Oxidation of dithiane **3** with 30% H_2O_2 using H_2WO_4 as the catalyst gave in 5 h the sulfoxides **8** and **9**

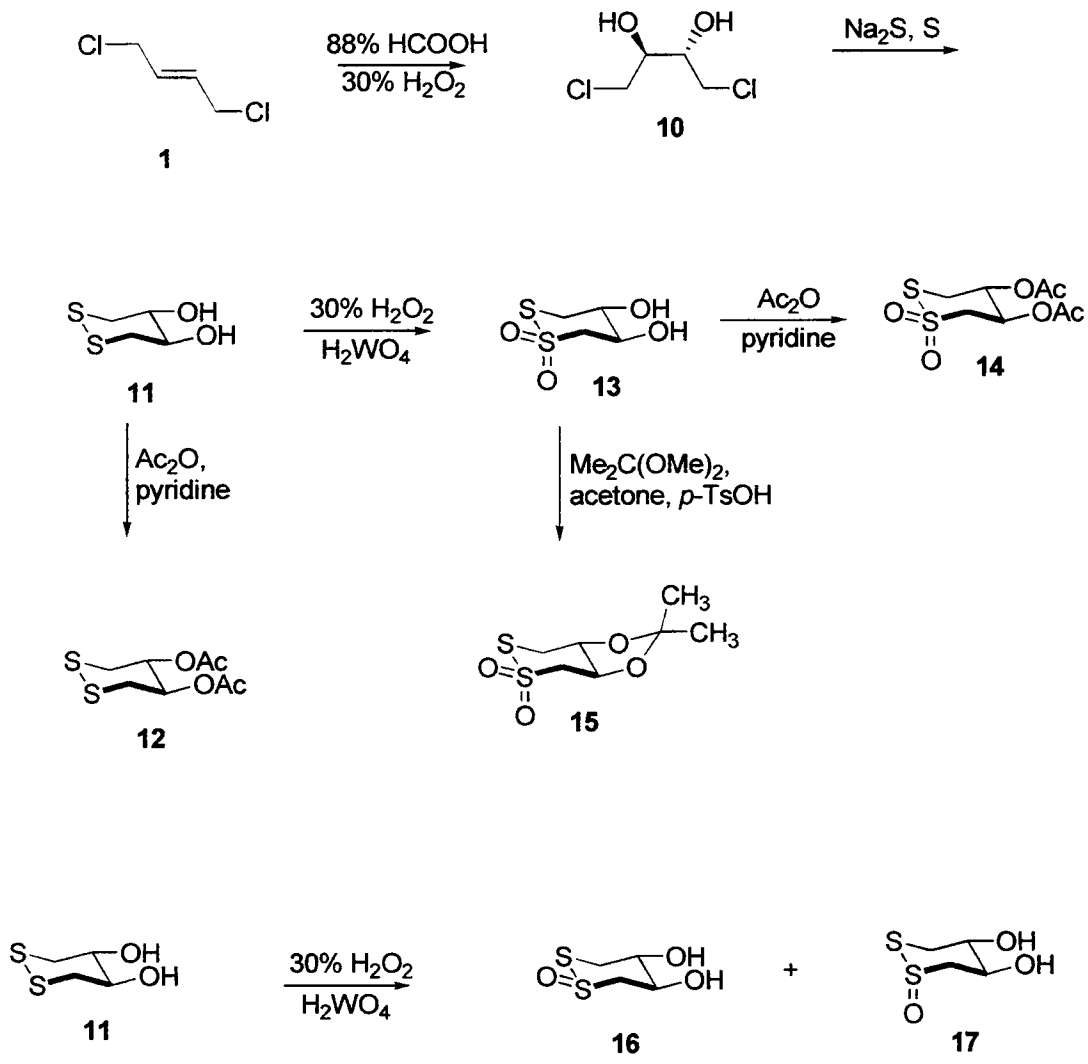


Scheme 1. Synthesis of *cis*-dithiane analogs.

in 27% and 45% yields, respectively.[103] Although, Field and co-workers reported an approximately 1:1 isomeric ratio for compounds **8** and **9**, it was observed that **9** was obtained as the major isomer.

B. *trans*-Series

Compounds in the *trans*-series were prepared (Scheme 2) in a manner similar to the *cis*-series, starting from *trans*-1,4-dichloro-2-butene (**1**). The (±)-diol **10** was obtained in 50% yield by hydroxylation of **1** with $KMnO_4$.[101] The diol **10** on reaction with Na_2S and sulfur[100] gave the *trans*-dithiane **11 in** 59% yield, which was converted to the diacetate **12** (91%) by reaction with Ac_2O and pyridine.[100] In the case of the compounds **11** and **12,** accepable NMR spectra were obtained at room temperature. Compound **11** was converted to the dioxide **13** using H_2WO_4 and 30% H_2O_2 as the oxidant in 34% yield.[104] The diacetate **14** was made from the dioxide **13** in 92% yield by treating it with Ac_2O and pyridine. As in the case of the *cis*-isomer, this compound had been made before by oxidizing *trans*-4,5-diacetoxy-1,2-dithiane with H_2O_2 and acetic acid.[100] The *O*-isopropylidine derivative **15** was made from compound **13** in 53% yield by reacting it with 2,2-dimethoxypropane in acetone in the presence of *p*-toluenesulfonic acid. Oxidation of dithiane **11** with 30% H_2O_2 and H_2WO_4 gave in 7 h the sulfoxides **16** and **17** in 13% and 71% yields respectively.[103] Again, it was seen that compound **17** was obtained as the major product, although, Field and co-workers had reported an approximately 1:1 isomeric ratio for compounds **16** and **17**. Attempts to make a dimethoxy analog of compound **13** using CH_3I and Ag_2O or CH_3I and NaH were not



Scheme 2. Synthesis of *trans*-dithiane analogs.

successful. The presence of an –S–S– linkage in these compounds renders them unstable to many reaction conditions.

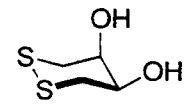
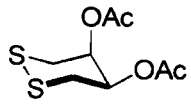
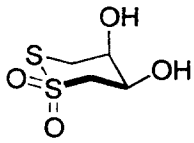
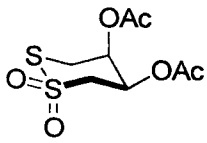
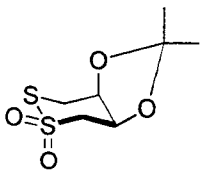
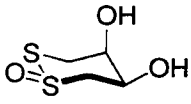
C. Anti-HIV-1 Evaluation Data

Most of the above analogs were submitted to the NCI for evaluation of their activity against HIV-1 in NCI's primary screen using the XTT cytoprotection assay.[109] In the *cis*-series only the lead compound (*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide) was active. A similar pattern was observed in the *trans*-series in NCI's primary screen. On repeating the XTT assay on some of the analogs, the NCI found that compound **17** showed moderate activity. These results are summarized in Table 1 (*cis*-series) and Table 2 (*trans*-series).

Dr. Kuai-lin Sun, a co-worker in our laboratory synthesized some five-membered ring analogs and an acyclic analog (**NSC 665550**). The lead compound (**NSC 72270**) in the five-membered ring series showed moderate anti-HIV activity. The sulfone analogs, **NSC 661126** and **NSC 661127**, showed moderate anti-HIV activity. The sulfoxide analog, **NSC 661754**, was initially found to be inactive, but showed moderate activity when the assay was repeated at a later date. The acyclic analog (**NSC 665550**) also showed moderate anti-HIV activity. These results are summarized in Table 3.

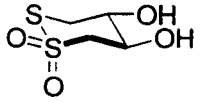
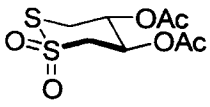
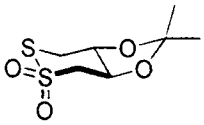
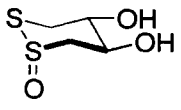
In general, the sulfone (1,1-dioxide) analogs were active or moderately active,

Table 1. Anti-HIV-1 evaluation data for compounds in the *cis*-series

Compound	EC_{50} (M)	IC_{50} (M)	TI_{50} = IC_{50}/EC_{50}	Zn finger Trp37 assay[a]	Activity
 **3 (NSC 667089)**	–	1.34×10^{-5} to 3.88×10^{-5}	–	4	Inactive
 **4 (NSC 667093)**	–	$> 2.00 \times 10^{-4}$	–	0	Inactive
 **5 (NSC 624151)**	1.50×10^{-6} to 3.66×10^{-5}	4.56×10^{-5} to $> 2.00 \times 10^{-4}$	2.93×10^{0} to $2.81 \times 10^{+1}$	78	Active
 **6 (NSC 667091)**	–	8.05×10^{-6} to 9.52×10^{-6}	–	71	Inactive
 **7 (NSC 684420)**	–	1.09×10^{-5} to 1.12×10^{-5}	–	NA[b]	Inactive
 **9 (NSC 667090)**	–	5.04×10^{-5} to 1.47×10^{-4}	–	0	Inactive

a. Trp37 assay was used to measure the % decrease in relative fluorescence units (RFU).
b. NA: Data not available.

Table 2. Anti-HIV-1 evaluation data for compounds in the *trans*-series.

Compound	EC_{50} (M)	IC_{50} (M)	TI_{50} = IC_{50}/EC_{50}	Zn finger Trp37 assay[a]	Activity
 **11 (NSC 663605)**	4.33×10^{-5}	$> 2.00 \times 10^{-4}$	$> 4.62 \times 10^{0}$	4	Inactive
 **12 (NSC 667092)**	–	$> 2.00 \times 10^{-4}$	–	0	Inactive
 **13 (NSC 624152)**	9.81×10^{-6} to 1.63×10^{-5}	1.03×10^{-4} to 1.66×10^{-4}	$1.02 \times 10^{+1}$ to $1.05 \times 10^{+1}$	78	Active
 **14 (NSC 663604)**	1.59×10^{-6} to 3.94×10^{-6}	9.70×10^{-6} to 3.40×10^{-5}	3.21×10^{0} to 8.25×10^{0}	78	Inactive
 **15 (NSC 684421)**	–	1.04×10^{-5} to $> 2.00 \times 10^{-5}$	–	NA[b]	Inactive
 **17 (NSC 663603)**	9.58×10^{-8} to 4.96×10^{-5}	3.80×10^{-5} to 1.33×10^{-4}	2.04×10^{0} to $1.37 \times 10^{+3}$	6	Moderate

a. Trp37 assay eas used to measure % decrease in relative fluorescence units (RFU).
b. NA: Data not available.

Table 3. Anti-HIV-1 evaluation data of five-membered ring and acyclic compounds.

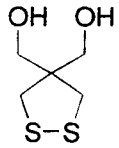
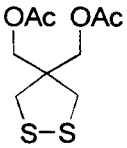
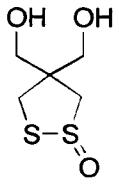
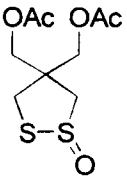
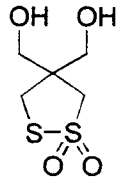
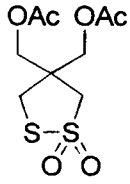
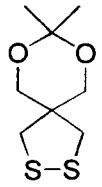
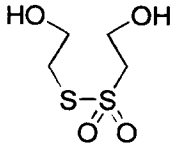
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Zn finger Trp37 assay[a]	Activity
 **(NSC 72270)**	9.39×10^{-4} to 1.01×10^{-3}	$> 1.50 \times 10^{-3}$	$> 1.48 \times 10^{0}$ to $> 1.60 \times 10^{0}$	5	Moderate
 **(NSC 660167)**	–	$> 2.00 \times 10^{-4}$	–	0	Inactive
 **(NSC 661753)**	–	$> 2.00 \times 10^{-4}$	–	0	Inactive
 **(NSC 661754)**	4.24×10^{-5} to 6.71×10^{-5}	1.70×10^{-4} to $> 2.00 \times 10^{-4}$	2.98×10^{0} to 4.72×10^{0}	12, 17	Moderate

Table 3, continued.

Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Zn finger Trp37 assay[a]	Activity
 **(NSC 661127)**	8.50×10^{-6} to 7.20×10^{-5}	3.30×10^{-4} to 4.20×10^{-4}	8.90×10^{0} to $5.00 \times 10^{+1}$	NA[b]	Moderate
 **(NSC 661126)**	8.60×10^{-6} to 1.20×10^{-5}	2.10×10^{-5} to 3.40×10^{-5}	2.40×10^{0} to 2.80×10^{0}	82	Moderate
 **(NSC 661752)**	–	1.70×10^{-4} to $> 2.00 \times 10^{-4}$	–	NA[b]	Inactive
 **(NSC 665550)**	3.00×10^{-5} to 1.70×10^{-4}	$> 2.00 \times 10^{-4}$	1.20×10^{0} to 6.70×10^{0}	NA[b]	Moderate

a. Trp37 assay was used to measure the % decrease in relative fluorescence units (RFU).
b. NA: Data not available.

while the disulfide and sulfoxide (monoxide) compounds were inactive or of diminished activity. Moreover, it was seen that conversion of OH to OR groups led to diminished activity or loss of activity and the acyclic example was also of diminished activity. Cyclic sulfone analogs that had free OH groups were found to be the most active compounds.

These compounds were found to target the highly conserved retroviral zinc fingers of HIV-1 p7 nucleocapsid protein. Molecular target-based assay of these compounds on the zinc finger of the HIV-1 nucleocapsid p7 (NCp7) protein were carried out in Dr. William Rice's laboratory at the NCI. These results, which were obtained using the NCp7 Trp37 assay,[110] are summarized in Table 1 (*cis*-series), Table 2 (*trans*-series) and Table 3 (five-membered ring and acyclic compounds). The percent decrease in relative fluorescence units (RFU) was calculated based on measurement of fluorescence of the NCp7 protein in a Shimadzu RF5000 spectrofluorimeter with λ_{Ex} = 280 nm and λ_{Em} = 351 nm before, and after 10 minutes of treatment with 25 μM of each compound at room temperature. Following loss of zinc from the C-terminal zinc finger, the Trp37 residue folds away from the aqueous environment and experiences a loss of fluorescence. The greater the percent decrease, the better was the ability of the compound to eject zinc from the zinc finger. It can be seen from Table 3 that the five-membered ring compound, **NSC 661126**, was most effective in ejection of zinc from the zinc finger. Among the six-membered ring compounds, the leads, **5** and **13**, the *trans*-diacetate **14** were equally effective in ejection of zinc. The *cis*-diacetate **6** was slightly inferior in its ability to eject zinc. The other analogs listed in Tables 1, 2, and 3 were inferior in their ability to eject zinc from the C-terminal zinc finger.

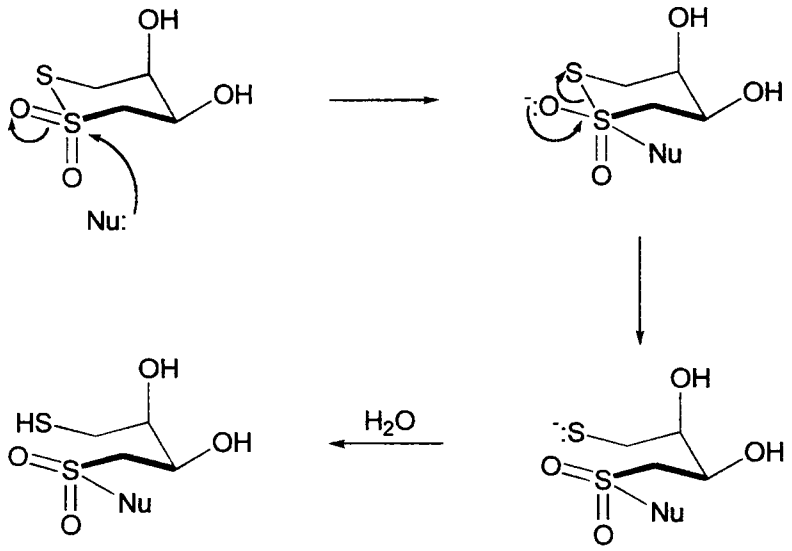
The mode of action of these compounds on the zinc fingers is not well understood. Two alternate mechanisms by which these compounds could be interacting with the cystine residues of the zinc fingers have been proposed in Scheme 3. We think that the sulfur atom in the cystine residues act as nucleophiles and interact with these compounds, which results in disruption of the zinc finger. Since, these CCHC zinc fingers are required for the selection and packaging of viral genomic RNA, as well as in a number of other events required for infection, these compounds can be effective anti-HIV-1 agents.

D. Resolution of (±)-*cis*-4,5-Dihydroxy-1,2-dithiane 1,1-dioxide (5)

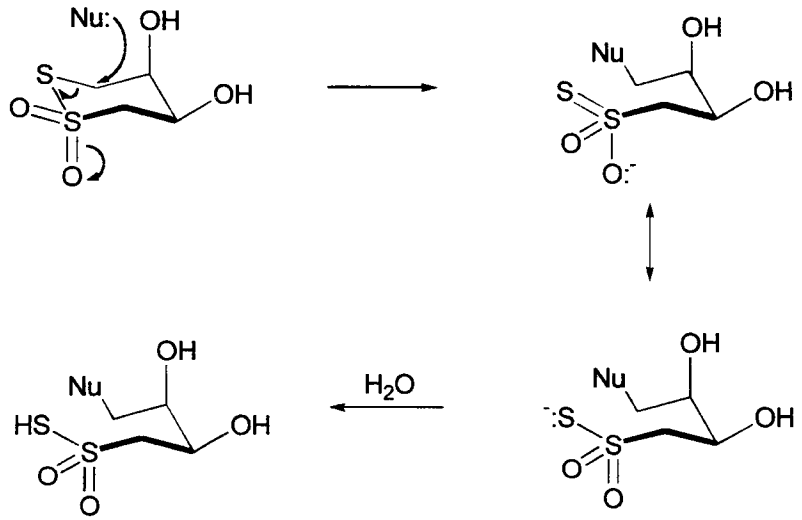
(±)-*cis*-4,5-Dihydroxy-1,2-dithiane 1,1-dioxide **(5)** was found to be the most active compound among the analogs tested. It was necessary to resolve racemic **5** in order to determine which of its enantiomers might be the more active compenent,

In an attempt to resolve **(±)-5** using enzymes, a trans-esterification screening kit called ChiroScreen-TE containing 31 enzymes in separate vials was obtained from Altus Biologics, Inc. To each vial was added compound **5** and vinyl acetate in toluene as the solvent (Scheme 4). The trans-esterification reactions were monitored by TLC for 24 h. Three enzymes that gave the best results were selected, and the above reaction was carried out a 100-mg scale. The three enzymes used were *Candida rugosa* lipase, ChiroCLEC^{TM}-CR Dry and ChiroCLEC^{TM}-PC Dry (Penicillin acylase). Among the three enzymes, ChiroCLEC^{TM}-PC Dry gave the best results. Further investigations were carried out using this enzyme. A ^{1}H NMR spectrum of the reaction product indicated

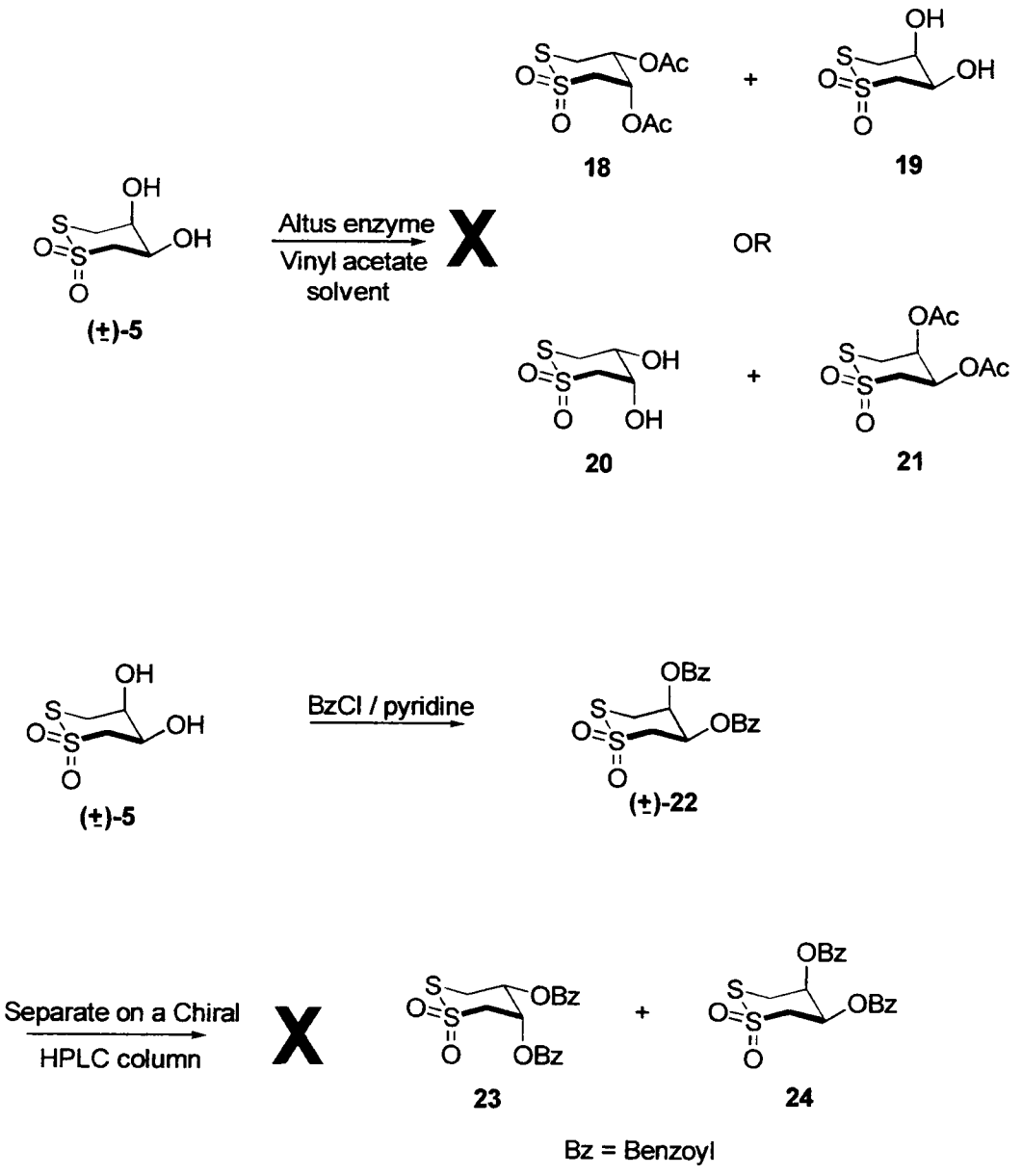
Mechanism 1



Mechanism 2



Scheme 3. Proposed mechanism for nucleophilic attack on dithiane 1,1-dioxides.



Scheme 4. Attempted resolution of (+/-)-5 into its enantiomers.

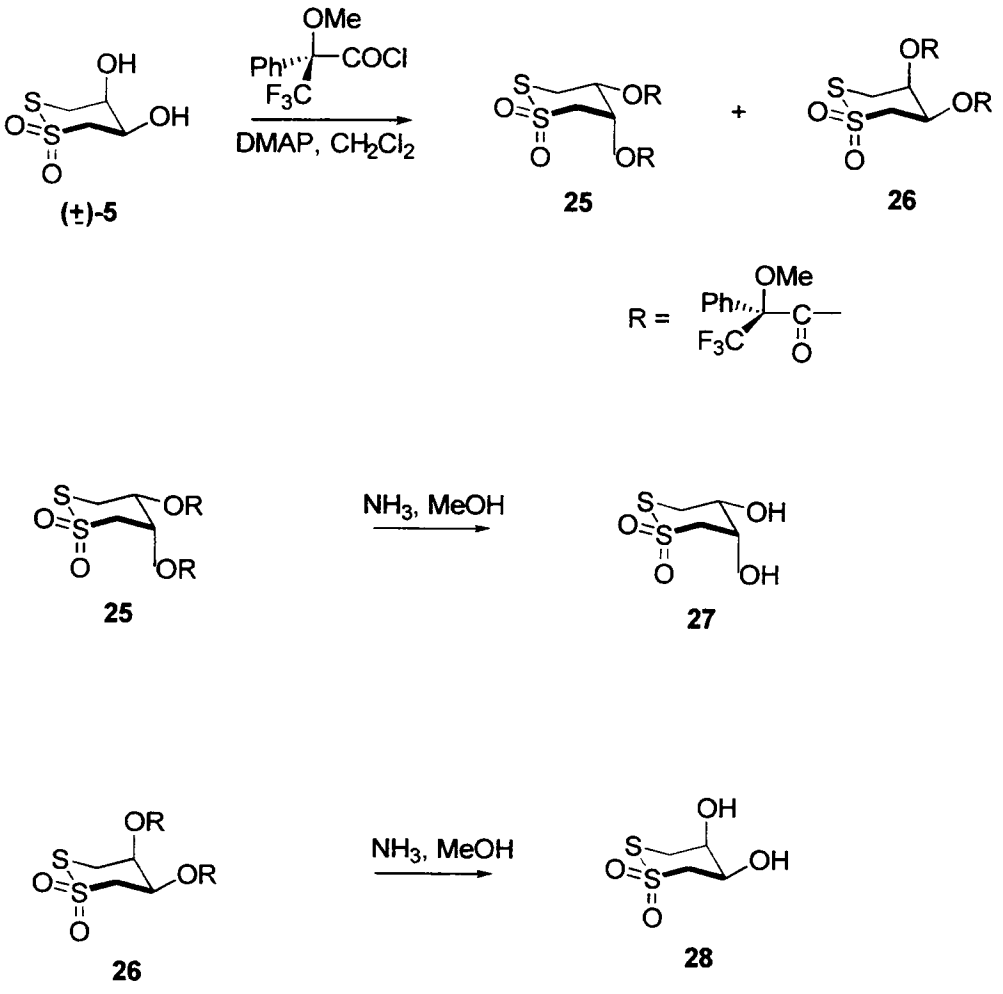
that the monoacetylated compound was the major product. This product was benzoylated using benzoyl chloride and pyridine and analyzed using a Regis Pirkle D-phenylglycine chiral HPLC column. Two peaks were seen, even though TLC showed only one spot, indicating that the enzyme was not specific in its action. As separation of products was not an easy task, this approach was abandoned.

The second approach in an attempt to resolve compound **5** into its enantiomers was using chiral HPLC (Scheme 4). Since compound **5** did not have any chromophores that were strongly UV active, it was first converted into its dibenzoyl derivative **22**. Attempts to separate the di-*O*-benzoyl derivative **22** into its enantiomes **23** and **24** on a Regis Pirkle D-phenylglycine HPLC column also proved futile. Even on an analytical scale, barely any separation was observed.

Finally, the Mosher ester methodology was used to resolve compound **5** into its enantiomers (Scheme 5). Racemic **5** was converted into a pair of diastereomeric Mosher esters **25** and **26** using (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride and DMAP.[111] The diastereomers **25** and **26** were then separated on a silica gel column and then hydrolyzed with 40% NH_3 in MeOH to the respective diols **27** and **28**.[136]

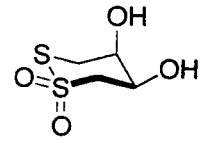
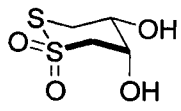
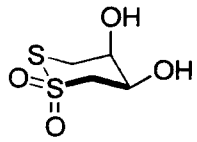
Antiviral evaluations of diols **27** and **28** was done at the NCI using the XTT cytoprotection assay.[109] These results are summarized in Table 4. It can be seen from Table 4 that the (−)-enantiomer **28** is about twice as active as its (+)-counterpart **27** in the XTT assay.

Molecular target based assay was carried out on the zinc finger of the HIV-1



Scheme 5. Resolution of (+/-)-5 into its enantiomers **27** and **28.**

Table 4. Anti-HIV-1 evaluation data of (±)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide and its enantiomers

Compound	EC_{50} (M)	IC_{50} (M)	TI_{50} = IC_{50}/EC_{50}	Zn finger Trp37 assay[a] 0	3	10	30 min
 **(±)-5 (NSC 624151)**	1.22×10^{-5}	1.22×10^{-4}	$1.00 \times 10^{+1}$	295	136	75	42
 **(+)-27 (NSC 693194)**	1.62×10^{-5}	1.34×10^{-4}	8.27×10^{0}	280	146	75	41
 **(−)-28 (NSC 693195)**	8.8×10^{-6}	1.32×10^{-4}	$1.50 \times 10^{+1}$	279	117	69	45

a. Trp37 assay was used to measure the relative fluorescence units (RFU) at indicated times.

nucleocapsid p7 (NCp7) protein by Dr. William G. Rice at the NCI. The (−)-enantiomer was slightly more effective than the (+)-enantiomer in ejection of zinc from the C-terminal zinc finger of the HIV-1 nucleocapsid p7 (NCp7) protein in the Zn finger Trp37 assay.[110] The decrease in fluorescence of the NCp7 protein was measured at indicated times in a Shimadzu RF5000 spectrofluorimeter with λ_{Ex} = 280 nm and λ_{Em} = 351 nm. The NCp7 protein was treated with 25 μM of each compound at room temperature. Following loss of zinc from the C-terminal zinc finger, the Trp37 residue folds away from the aqueous environment and experiences a loss of fluorescence. These results are summarized in Table 4.

E. Determination of the Absolute Configuration of the Enantiomers of the Lead Compound NSC 624151

Initially, we hoped that we could use NMR spectroscopy to determine the absolute configuration of the enantiomers of (±)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide.[105–108] This involved making both Mosher esters of an enantiomer using the (*R*)- and (*S*)-Mosher acid chlorides. Differences in ^{1}H NMR chemical shifts between the two Mosher esters of that enantiomer is used in assigning its absolute configuration. We found that the absolute configuration of all the compounds that had been assigned by this method had only one OH group present in the molecule.[105–108] In our case, there were two adjacent OH groups present in the molecule, which would lead to lot of overlapping proton signals and make the picture very complicated. Hence, we abandoned this approach after some initial investigation.

We had already made Mosher esters of compound **5** using (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. Compound **26** was found to crystallize from hexanes–ethyl acetate. Therefore, a single-crystal X-ray structure of compound **26** was obtained in order to determine the absolute stereochemistry at the C-4 and C-5 carbons. Extrapolating this data we concluded that the (−)-enantiomer **28** was the (4*S*, 5*R*)-compound. The ORTEP view of compound **26** as 50% thermal ellipsoids is shown in Figure 10 and its crystal structure data is given in Table 5. The crystal coordinates of compound **26** were imported into the molecular modeling program SYBYL, and the Crysin command was used to generate the absolute structure of compound **26** and verify its absolute configuration. The structure generated using the Crysin command in SYBYL is shown in Figure 11.

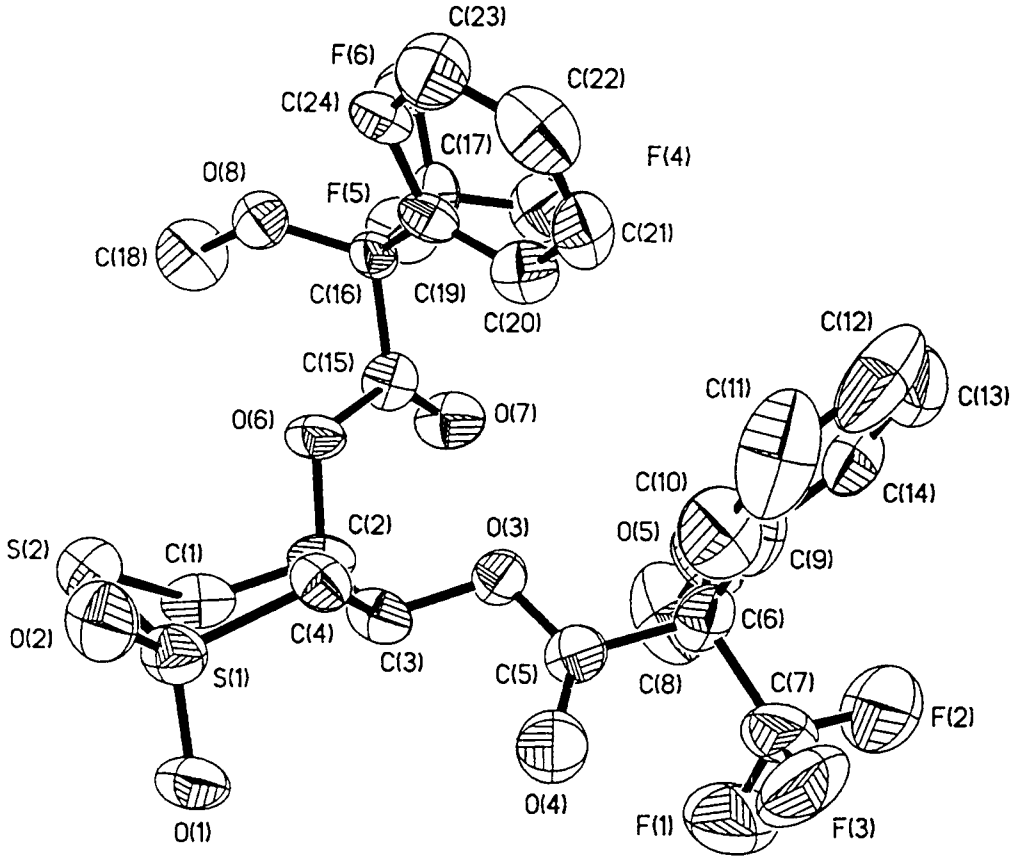
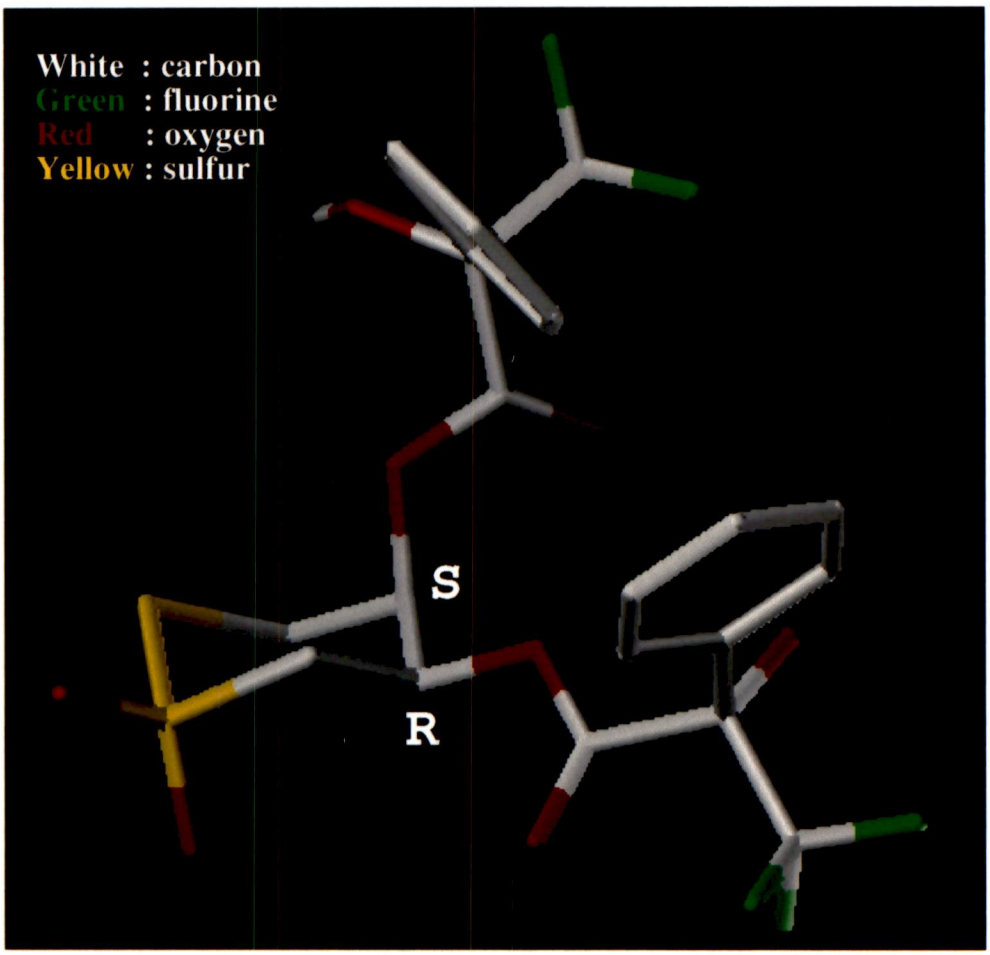


Figure 10. ORTEP view of compound **26** shown as 50% thermal ellipsoids.

Table 5. Crystal structure data for compound **26**.

Empirical formula	$C_{24}H_{22}F_6O_8S_2$	
Formula weight	616.54	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$ (no. 19)	
Unit cell dimensions	a = 7.536(3) Å	alpha = 90°
	b = 12.886(5) Å	beta = 90°
	c = 27.470(11) Å	gamma = 90°
Volume, Z	2668(2) Å^3, 4	
Density (calculated)	1.535 mg/m^3	
Absorption coefficient	0.288 mm^{-1}	
F(000)	1264	
Crystal size	0.30 × 0.22 × 0.20 mm	
θ range for data collection	2.17 to 22.58°	
Limiting indices	$0 \le h \le 8$, $0 \le k \le 13$, $-29 \le l \le 29$	
Reflections collected	4158	
Independent reflections	3443 (R_{int} = 0.1354)	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3440 / 0 / 361	
Goodness-of-fit on F^2	1.108	
Final R indices [I>2σ(I)]	$R1$ = 0.0857, $wR2$ = 0.1324	
R indices (all data)	$R1$ = 0.2059, $wR2$ = 0.1865	
Absolute structure parameter	0.0(3)	
Largest diff. peak and hole	0.308 and −0.289 eÅ^{-3}	

Figure 11. The absolute structure of compound **26** generated using the SYBYL molecular modeling program.


White : carbon
Green : fluorine
Red : oxygen
Yellow : sulfur
S
R

III. CONCLUSIONS

Analogs of the lead compounds were synthesized and evaluated for anti-HIV-1 activity. They were generally found to be inferior to the lead compounds in anti-HIV-1 activity. In addition to being active in NCI's primary screen, compounds containing an $-SO_2-$ group targeted the zinc finger of the HIV-1 nucleocapsid p7 protein. In general, it can be seen from these results that an $-SO_2-$ group is essential for these compounds to show anti-HIV-1 activity. Thus, it is possible that these compounds act as non-nucleoside RT inhibitors as well as zinc finger inhibitors of HIV-1.

(±)-*cis*-4,5-Dihydroxy-1,2-dithiane 1,1-dioxide was found to be the most active compound. It was resolved into its enantiomers, and the enantiomers were evaluated for anti-HIV-1. The (−)-enantiomer was about twice as active as its (+)-counterpart in the XTT assay. It was also slightly more effective in ejection of zinc from the C-terminal zinc finger of the HIV-1 nucleocapsid p7 (NCp7) protein.

The absolute configuration of the enantiomers of (±)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide was determined by obtaining a single-crystal X-ray structure of the di-Mosher ester of the (−)-enantiomer. From the X-ray crystal structure analysis, the (−)-enantiomer was found to the (4*S*, 5*R*)-compound.

IV. EXPERIMENTAL SECTION

A. General Methods

Melting points were determined by the capillary method and are uncorrected. Analytical TLC was performed on aluminum-backed plates coated with E. Merck Silica Gel-60 F-254. The developed plates were air dried and visualized by irradiation with UV light and/or by dipping in 10 wt-% phosphomolybdic acid solution in ethanol and heated at 120–140 °C. Flash column chromatography was performed on Silica Gel-60 (230–400 mesh). All HPLC analysis were carried out on a Beckman System Gold instrument using a Regis no. 731221 Pirkle D-phenylglycine (25 cm × 1 cm i.d.) column. Optical rotations were measured with a Perkin-Elmer Model 243 automatic polarimeter for solutions in a 1-dm cell at the indicated temperature. ^{1}H and ^{13}C NMR spectra were recorded at 250 MHz and 62.9 MHz, respectively, on a Bruker AC 250 instrument or at 400 MHz and 100.6 MHz, respectively, on a Bruker AMX 400 instrument using the indicated solvent. ^{1}H NMR shifts are reported as δ (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard; multiplicities are first-order values in Hz: s, singlet; bs, broad singlet; d, doublet; t, triplet; dd, double of doublets; db, broad doublet; q, quartet; m, multiplet. ^{13}C NMR chemical shifts are reported as δ (ppm) relative to the chemical shift of the solvent used ($CDCl_3$: 77.0 ppm; DMSO-d_6: 39.5 ppm; CD_3OD: 49.0 ppm). Elemental analyses were performed by Atlantic Microlabs, Inc. of Atlanta, GA. Chemicals were of reagent grade and were used directly. Solvents were distilled and dried by

literature procedures before use. All evaporations were carried out with a rotary evaporator under vacuum and below 40 °C.

B. Preparation of Compounds 2–28

***meso*-1,4-Dichlorobutane-2,3-diol (2).** To a stirred solution of formic acid (88%, 75 mL) and H_2O_2 (30%, 22.5 mL, d 1.110) was added *trans*-1,4-dichloro-2-butene (**1**, 18.0 g, 144 mmol) at room temperature. The reaction mixture was gradually raised to 45 °C and stirred at that temperature for 22 h. The reaction mixture was diluted with water (75 mL), and the oil bath temperature was raised to 120 °C. The reaction mixture was stirred at that temperature for 15 min, then evaporated to dryness under reduced pressure. The solid residue was recrystallized from ethyl acetate-benzene to give **2** (10.2 g, 45%) as white crystals. Another 1.26 g of product was obtained from the mother liquor . (Total yield 50%): mp 126–128 °C (lit.[1] 127 °C); ^{1}H NMR (DMSO-d_6) δ 5.36 (m, 2H), 3.79 (m, 2H), 3.64 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 70.97, 48.36. Anal. Calcd for $C_4H_8Cl_2O_2$: C 30.21, H 5.07, Cl 44.59. Found: C 30.31, H 5.03, Cl 44.52.

(±)-*cis*-4,5-Dihydroxy-1,2-dithiane (3). A stirred mixture of sodium sulfide nonahydrate (15.4 g, 64.1 mmol) and sulfur (2.05 g, 63.9 mmol) in ethanol (180 mL, 95%) were refluxed for 15 min under N_2. The greenish-yellow colored solution was treated dropwise with a solution of **2** (6.79 g, 42.7 mmol) in ethanol (105 mL, 95%) over a period of 8 h, stirring and heating throughout. The reaction mixture was refluxed for an additional 10 h, then the solvent was evaporated, and the residue was extracted with boiling chloroform (3 × 35 mL). The dark tar left behind was treated with methanol (50

mL) and filtered. The filtrate and chloroform extract were combined and concentrated *in vacuo*. Chromatography on silica gel using CH_2Cl_2–MeOH (98:2) as the eluent afforded **3** (3.60 g, 55%) as a white solid: mp 130–131 °C (lit.[2] 129–131 °C); ^{1}H NMR (CD_3OD, 400.13 MHz at −40 °C) δ 4.07 (m, 1H), 3.63 (m, 1H), 3.30 (dd, 1H, J = 14.0 Hz, J = 1.3 Hz), 3.16 (dd, 1H, J = 12.8 Hz, J = 11.4), 2.98 (dd, 1H, J = 14.0 Hz, J = 4.8 Hz), 2.48 (dd, 1H, J = 12.9 Hz, J = 3.7 Hz); ^{13}C NMR (CD_3OD, 100.61 MHz at −40 °C) δ 71.64, 68.10, 43.24, 33.29. Anal. Calcd for $C_4H_8O_2S_2$: C 31.56, H 5.30, S 42.12. Found: C 31.64, H 5.26, S 41.99.

(±)-*cis*-4,5-Diacetoxy-1,2-dithiane (4). To a solution of **3** (0.100 g, 0.657 mmol) in pyridine (1.0 mL) was added Ac_2O (1.0 mL) at room temperature under nitrogen, and the reaction mixture was stirred for 17 h, concentrated *in vacuo* and chromatographed on a silica gel column using CH_2Cl_2 as the eluent to provide **4** (0.148 g, 95%) as a glassy solid: mp 76 °C (lit.[2] 75–76.5 °C); ^{1}H NMR ($CDCl_3$, 400.13 MHz at −40 °C) δ 5.33 (m, 1H), 5.05 (m, 1H), 3.41 (dd, 1H, J = 14.6 Hz, 1.3 Hz), 3.35 (dd, 1H, J = 12.9 Hz, 11.5 Hz), 3.17 (dd, 1H, J = 14.6 Hz, J = 4.8 Hz), 2.68 (dd, 1H, J = 13.0 Hz, 3.7 Hz), 2.24 (s, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.61 MHz at −40 °C) δ 170.42, 169.91, 70.91, 66.35, 39.09, 30.61, 21.27, 21.10 . Anal. Calcd for $C_8H_{12}O_4S_2$: C 40.66, H 5.12, S 27.14. Found: C 40.75, H 5.14, S 27.07.

(±)-*cis*-4,5-Dihydroxy-1,2-dithiane 1,1-dioxide (5). To a stirred solution of **3** (3.50 g, 23.0 mmol) and H_2WO_4 (0.490 g, 1.96 mmol) in MeOH (210 mL) was added H_2O_2 (30%, 9.71 mL, d 1.110) in H_2O (70 mL) at room temperature over a period of 15

min. The reaction mixture was stirred at room temperature for 24 h, then a pinch of MnO_2 was added, and stirring was continued for another 15 h. The mixture was filtered and the solvent was removed under reduced pressure to give a syrup. Chromatography on silica gel with 3–5% MeOH in CH_2Cl_2 afforded **5** (1.47 g, 35%) as a white solid: mp 133–134 °C (lit.[3] 134–135 °C); ^{1}H NMR (CD_3OD) δ 4.20 (m, 1H), 4.13 (m, 1H), 3.66 (dd, 1H, J = 12.7 Hz, 10.9 Hz), 3.47 (dd, 1H, J = 14.7 Hz, J = 1.4 Hz), 3.38 (m, 2H) ; ^{13}C NMR (CD_3OD) δ 71.47, 65.95, 61.65, 38.66. Anal. Calcd for $C_4H_8O_4S_2$: C 26.08, H 4.38, S 34.81. Found: C 26.33, H 4.33, S 34.56.

(±)-*cis*-4,5-Diacetoxy-1,2-dithiane 1,1-dioxide (6). The procedure used to make compound **4** was repeated using **5** (0.075 g, 0.41 mmol) to obtain **6** (0.099 g, 91%) as white crystals: mp 144–145 °C (lit.[2] 148–150 °C); ^{1}H NMR ($CDCl_3$) δ 5.47 (m, 2H), 3.82 (dd, 1H, J = 12.9 Hz, J = 10.8 Hz), 3.55 (m, 3H), 2.18 (s, 3H), 2.09 (s, 3H); ^{13}C ($CDCl_3$) δ 169.71, 169.07, 69.29, 64.15, 58.81, 34.57, 20.72, 20.57. Anal. Calcd for $C_8H_{12}O_6S_2$: C 35.81, H 4.51, S 23.90. Found: C 35.84, H 4.52, S 23.84.

(±)-*cis*-4,5-*O*-Isopropylidene-1,2-dithiane 1,1-dioxide (7). To *cis*-dithiane dioxide (**5**, 0.097 g, 0.53 mmol) in acetone (5.0 mL) was added *p*-toluenesulfonic acid (0.020 g, 0.10 mmol) and $Me_2C(OMe)_2$ (0.42 g, 4.1 mmol) at room temperature under N_2. The reaction mixture was stirred at this temperature for 2 h, quenched with water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, concentrated, and the residue was purified on a silica gel column using hexanes–ethyl acetate (75:25) to give **7** (0.060 g, 51%) as a white solid: mp 103–104 °C; ^{1}H NMR ($CDCl_3$) δ 4.66 (m, 1H), 4.40 (m, 1H), 3.75 (dd, 1H, J = 15.3 Hz, J =

3.1 Hz), 3.65 (m, 2H), 3.51 (dd, 1H, J = 13.6 Hz, J = 8.7 Hz), 1.55 (s, 3H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 110.02, 74.39, 68.11, 59.39, 33.97, 28.13, 26.18. Anal. Calcd for $C_7H_{12}S_2O_4$: C 37.48, H 5.39, S 28.59. Found: C 37.38, H 5.44, S 28.62.

(±)-1,2-Dithiane-t-4,t-5-diol r-1-Oxide (8) and (±)-1,2-dithiane-c-4,c-5-diol r-1-Oxide (9). To a stirred solution of **3** (0.600 g, 3.94 mmol) and H_2WO_4 (0.084 g, 0.34 mmol) in MeOH (36 mL) was added H_2O_2 (30%, 1.3 mL, d 1.110) in H_2O (12 mL) at 0 °C over a period of 15 min. The reaction mixture was raised to room temperature and stirred at that temperature for 5 h, and then, when no more starting material was present, the reaction mixture was filtered through Celite, a pinch of MnO_2 was added to the filtrate, and stirring was continued for another 15 h. The mixture was filtered and the solvent was removed under reduced pressure to give a syrup. Chromatography on silica gel using 3–5% MeOH in CH_2Cl_2 afforded the t-4, t-5 oxide **8** (0.177 g, 27%) as the 1st fraction: mp 156–158 °C (lit.[4] 156–158 °C); ^{1}H NMR (CD_3OD) δ 4.32 (m, 1H), 3.94 (m, 2H), 3.78 (dd, 1H, J = 13.4 Hz, J = 11.1 Hz), 3.29 (dd, 1H, J = 14.1 Hz, J = 2.4 Hz), 2.83 (dd, 1H, J = 13.4 Hz, J = 3.2 Hz); ^{13}C NMR (CD_3OD) δ 70.86, 69.78, 58.59, 24.50. The c-4,c-5 oxide **9** (0.296 g, 45%) was obtained as the 2nd fraction: mp 169–171 °C (lit.[4] 168–169 °C); ^{1}H NMR (CD_3OD) δ 4.29 (m, 1H), 4.20 (m, 1H), 3.85 (dd, 1H, J = 14.6 Hz, J = 1.2 Hz), 3.26 (m, 3H); ^{13}C NMR (CD_3OD) δ 66.99, 62.47, 52.50, 33.91. Anal. Calcd for $C_4H_8O_3S_2$: C 28.56, H 4.79, S 38.12. Found: C 28.66, H 4.72, S 38.05.

(±)-1,4-Dichlorobutane-2,3-diol (10). To *trans*-1,4-dichloro-2-butene (**1**, 15.0 g, 120 mmol) in ethanol (95%, 225 mL) was added dropwise $KMnO_4$ (15.0 g) and $MgSO_4$ (11.3 g) in water (300 mL) at −15 °C over a period of 2 h. The reaction mixture, which

turned into a thick brown slurry, was gradually raised to room temperature and stirred at that temperature for 3 h. Then, $NaHSO_3$ (22.5 g) dissolved in water (100 mL) was added, stirred for a few minutes, and 4 N H_2SO_4 (50 mL) was added to give a clear solution that turned Congo Red paper blue. The reaction mixture was concentrated to about 100 mL under reduced pressure, extracted with diethyl ether (4 × 50 mL), and the ether layer was dried over anhydrous $MgSO_4$ and concentrated to give an oil that solidified on addition of a little petroleum ether. The crude solid was recrystallized from benzene–petroleum ether to give **10** (9.50 g, 50%) as white crystals: mp 75 °C (lit.[101] 62 °C, lit.[112] 75 °C); ^{1}H NMR δ 4.89 (bs, 2H), 3.69 (m, 4H), 3.51 (m, 2H) ; ^{13}C NMR (DMSO-d_6) δ 70.89, 45.73. Anal. Calcd for $C_4H_8Cl_2O_2$: C 30.21, H 5.07, Cl 44.59. Found: C 30.05, H 5.01, Cl 44.42.

(±)-*trans*-4,5-Dihydroxy-1,2-dithiane (11). The procedure used to make compound **3** was repeated using sodium sulfide nonahydrate (16.0 g, 66.6 mmol), sulfur (2.14 g, 66.7 mmol) and **10** (7.07 g, 44.5 mol) to afford **11** (4.00 g, 59%) as a white solid: mp 130–132 °C (lit.[2] 130–132 °C); ^{1}H NMR (DMSO-d_6) δ 5.21 (d, 2H, J = 4.0 Hz), 3.35 (m, 2H), 3.04 (dd, 2H, J = 13.3 Hz, J = 2.6 Hz), 2.74 (m, 2H); ^{13}C NMR (CD_3OD) δ 75.34, 41.67. Anal. Calcd for $C_4H_8O_2S_2$: C 31.56, H 5.30, S 42.12. Found: C 31.64, H 5.31, S 42.04.

(±)-*trans*-4,5-Diacetoxy-1,2-dithiane (12). By the same procedure used to synthesize compound **4**, **12** (0.141 g, 91 %) was obtained from **11** (0.100 g, 0.657 mmol) as a white solid: mp 54–55 °C (lit.[2] 54–55.5 °C); ^{1}H NMR ($CDCl_3$) δ 5.02 (m, 2H), 3.10

(m, 4H), 2.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 169.71, 72.01, 38.24, 20.81. Anal. Calcd for $C_8H_{12}O_4S_2$: C 40.66, H 5.12, S 27.14. Found: C 40.72, H 5.09, S 27.07.

(±)-*trans*-4,5-Dihydroxy-1,2-dithiane 1,1-dioxide (13). The procedure used for compound **5** was repeated using **11** (2.70 g, 17.7 mmol), H_2WO_4 (0.380 g, 1.52 mmol), and H_2O_2 (30%, 7.4 mL, d 1.110) to afford **13** (1.12 g, 34%) as a white solid: mp 125–126 °C (lit.[3] 125–126.5 °C); ^{1}H NMR (CD_3OD) δ 3.97 (m, 1H), 3.74 (m, 2H), 3.52 (dd, 1H, J = 13.3 Hz, J = 10.2 Hz), 3.34 (dd, 1H, J = 14.2 Hz, J = 3.8 Hz), 3.21 (dd, 1H, J = 14.2 Hz, J = 9.9 Hz); ^{13}C NMR (CD_3OD) δ 72.77, 72.35, 65.41. 36.21. Anal. Calcd for $C_4H_8O_4S_2$: C 26.08, H 4,38, S 34.81. Found: C 26.18, H 4.37, S 34.73.

(±)-*trans*-4,5-Diacetoxy-1,2-dithiane 1,1-dioxide (14). By the same procedure used to make compound **4**, **13** (0.090 g, 0.49 mmol) yielded compound **14** (0.12 g, 92%) as white crystals: mp 145–146 °C (lit.[2] 144–145 °C); ^{1}H NMR ($CDCl_3$) δ 5.44 (m, 1H), 5.14 (m, 1H), 3.83 (dd, 1H, J = 13.5 Hz, J = 4.0 Hz), 3.62 (m, 2H), 3.45 (dd, 1H, J = 14.6 Hz, J = 8.5 Hz), 2.13 (s, 3H), 2.11 (s, 3H); ^{13}C ($CDCl_3$) δ 169.51, 168.99, 69.23, 67.93, 60.59, 32.86, 20.69, 20.59. Anal. Calcd for $C_8H_{12}O_6S_2$: C 35.81, H 4.51, S 23.90. Found: C 35.75, H 4.47, S 23.81.

(±)-*trans*-4,5-*O*-Isopropylidene-1,2-dithiane-1,1-dioxide (15). The procedure used for compound **7** was repeated using *trans*-dithiane dioxide (**13**, 0.096 g, 0.52 mmol), acetone (5.0 mL) *p*-toluenesulfonic acid (0.020 g, 0.10 mmol) and $Me_2C(OMe)_2$ (0.42 g, 4.1 mmol) to yield **15** (0.062 g, 53%) as a white solid: mp 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 4.13 (m, 1H), 3.96 (m, 2H), 3.65 (m, 1H), 3.47 (dd, 1H, J = 13.1 Hz, J = 10.9 Hz), 3.25 (dd, 1H, J = 13.1 Hz, J = 3.5 Hz), 1.48 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 110.95,

76.27, 75.28, 64.80, 32.55, 26.46, 26.30. Anal. Calcd for $C_7H_{12}O_4S_2$: C 37.48, H 5.39, S 28.59. Found: C 37.35, H 5.48, S 28.62.

(±)-1,2-Dithiane-t-4,c-5-diol r-1-Oxide (16) and (±)-1,2-dithiane-c-4,t-5-diol r-1-Oxide (17). The procedure used to make compounds **8** and **9** was repeated using **11** (0.800 g, 5.26 mmol), H_2WO_4 (0.112 g, 0.448 mmol), and H_2O_2 (30%, 2.2 mL, d 1.110), but running the reaction for 7 h instead of 5 h, to yield the t-4, c-5 oxide **16** (0.113 g, 13%) as the 1st fraction: mp 146–148 °C (lit.[4] 135–137.5 °C); ^{1}H NMR (CD_3OD) δ 4.05 (m, 3H), 3.39 (d, 2H, J = 3.0 Hz), 2.87 (m, 1H); ^{13}C NMR (CD_3OD) δ 69.26, 65.78, 50.95, 26.35. The c-4, t-5 oxide **17** (0.625 g, 71%) was obtained as the 2nd fraction: mp 130–131 °C (lit.[4] 147–149 °C); ^{1}H NMR (CD_3OD) δ 4.19 (m, 1H), 3.79 (m, 1H), 3.68 (dd, 1H, J = 13.3 Hz, J = 3.6 Hz), 3.50 (dd, 1H, J = 13.8 Hz, J = 11.0 Hz), 3.09 (m, 2H); ^{13}C NMR (CD_3OD) δ 74.21, 66.98, 60.89, 30.91. Anal. Calcd for $C_4H_8O_3S_2$: C 28.56, H 4.79, S 38.12. Found: C 28.74, H 4.85, S 37.95.

(±)-*cis*-4,5-Dibenzoyloxy-1,2-dithiane 1,1-dioxide (22). To **5** (0.100 g, 0.543 mmol) in pryidine (1 mL) was added benzoyl chloride (1 mL) at room temperature under nitrogen, and the reaction mixture was stirred for 12 h, concentrated *in vacuo* and chromatographed on a silica gel column using CH_2Cl_2 as the eluent to yield **22** (0.190 g, 89%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 8.07 (m, 2H), 7.94 (m, 2H), 7.68–7.37 (m, 6H), 5.90–5.84 (m, 2H), 4.04 (dd, 1H, J = 12.8, 10.6 Hz), 3.8–3.74 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 165.12, 164.64, 133.92, 133.80, 129.84, 128.89, 128.74, 128.56, 70.03, 64.99, 59.46, 34.91.

(2*S*,4*R*,5*S*)-(+) -3,3,3-Trifluoro -2-methoxy-2-phenylpropionic acid 1,1-dioxo-4-[(2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyloxy][1,2]dithiane-5-yl ester (25) and (2*S*,4*S*,5*R*)-(−)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid 1,1-dioxo-4-[(2*S*)-2-methoxy-2-phenyl-3,3,3-trifluoropropionyloxy][1,2]dithiane-5-yl ester (26). To **5** (0.225 g, 1.22 mmol) and *N*, *N*-dimethylaminopyridine (0.597 g, 4.89 mmol) in dry CH_2Cl_2 (5 mL) was added (R)-(−)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride (0.750 g, 2.97 mmol) over 30 min at 0 °C under N_2. The reaction mixture was allowed to gradually rise to room temperature with stirring at that temperature for 20 h. Then, the reaction mixture was cooled in an ice bath, washed with 1N HCl, followed by satd $NaHCO_3$ and finally with dist H_2O. The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4, concentrated, and the residue was purified on a silica gel column with hexanes–ethyl acetate (85:15) to obtain **25** 0.252 g, 34%) as the 1st fraction; mp: 162–163 °C; $[\alpha]^{21}_D$ + 81° (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 10H), 5.79 (m, 1H), 5.59 (m, 1H), 3.67 (m, 3H), 3.49 (s, 3H), 3.40 (dd, 1H, *J* = 15.5 Hz, *J* = 5.1 Hz), 3.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.35, 165.19, 131.29, 131.14, 130.10, 129.95, 128.77, 128.61, 126.91, 125.16, 120.59, 116.02, 85.40, 84.94, 84.44, 84.01, 70.78, 65.73, 58.47, 55.52, 55.38, 34.15. Anal. Calcd for $C_{24}H_{22}F_6O_8S_2$: C 46.75, H 3.60, S 10.40. Found: C 46.79, H 3.58, S 10.29. The 2nd fraction yielded the other diastereomer, **26** (0.250 g, 33%) as white crystals: mp: 184–185 °C; $[\alpha]^{21}_D$ –120° (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 10H), 5.76 (m, 2H), 3.73 (d, 1H, *J* = 15.4 Hz), 3.54 (m, 3H), 3.45 (s, 3H), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.41, 165.31, 131.17, 131.07, 130.07,130.01, 128.73, 128.65, 127.31, 126.96, 125.27, 125.18, 120.67, 120.58, 116.09, 115.97, 85.38,

84.93, 84.48, 84.03, 70.84, 66.28, 58.36, 55.58, 55.32, 34.47. Anal. Calcd for $C_{24}H_{22}F_6O_8S_2$: C 46.75, H 3.60, S 10.40. Found: C 46.68, H 3.66, S 10.32.

(+)-*cis*-4,5-Dihydroxy-1,2-dithiane 1,1-dioxide (27). To **25** (0.167 g, 0.271 mmol) was added 40% NH_3 in MeOH (4 mL) over 5 min under N_2 at room temperature. The solid went into solution as 40% NH_3 in MeOH was added, and the reaction mixture turned pale yellow in color. After the reaction mixture was stirred for 1.5 h, TLC showed complete disappearance of the diester. The reaction mixture was then concentrated under vacuum, and the crude oil was purified on a silica gel column using CH_2Cl_2–MeOH (95:5) as the eluent to obtain **27** (0.0212 g, 43%) as a white solid: mp 133–134 °C; $[\alpha]^{21}_D$ +151° (*c* 0.5, CH_3OH); ^1H NMR (CD_3OD) δ 4.20 (m, 1H), 4.13 (m, 1H), 3.66 (dd, 1H, J = 12.6 Hz, J = 11.0 Hz), 3.47 (dd, 1H, J = 14.7 Hz, J = 1.4 Hz), 3.37 (m, 2H); ^{13}C NMR (CD_3OD) δ 71.44, 65.92, 61.62, 38.63. Anal. Calcd for $C_4H_8O_4S_2 \cdot 0.13C_4H_8O_2$: C 27.74, H 4.66, S 32.77. Found: C 27.75, H 4.58, S 32.57.

(−)-*cis*-4,5-Dihydroxy-1,2-dithiane 1,1-dioxide (28). To **26** (0.159 g, 0.258 mmol) was added 40% NH_3 in MeOH (4 mL) over 5 min under N_2 at room temperature. The solid went into solution as 40% NH_3 in MeOH was added, and the reaction mixture turned pale yellow in color. After the reaction mixture was stirred for 1.5 h, TLC showed complete disappearance of the diester. The reaction mixture was then concentrated under vacuum, and the crude oil was purified on a silica gel column using CH_2Cl_2–MeOH (95:5) as the eluent to obtain **28** (0.019 g, 40%) as a white solid: mp 131–132 °C; $[\alpha]^{21}_D$ −146° (*c* 0.5, CH_3OH); ^1H NMR (CD_3OD) δ 4.19 (m, 1H), 4.13 (m, 1H), 3.66 (dd, 1H, J = 12.8 Hz, J = 10.9 Hz), 3.47 (dd, 1H, J = 14.7 Hz, J = 1.5 Hz),

3.37 (m, 2H); ^{13}C NMR (CD_3OD) δ 71.42, 65.91, 61.62, 38.63. Anal. Calcd for $C_4H_8O_4S_2 \cdot 0.14C_4H_8O_2$: C 27.86, H 4.68, S 32.62. Found: C 27.85, H 4.59, S 32.44.

C. X-ray Crystal Structure of Compound 26

The X-ray crystal structure of **26** was determined at 20 °C on a Siemens R3m/V diffractometer. A suitable crystal was mounted using epoxy on a glass fiber. Unit cell dimensions were calculated from the angular setting of 35 well-centered reflections having 2θ values between 15 and 25°. Compound **26** was found to crystallize in the orthorhombic system. Axial dimensions were confirmed by use of axial photographs. Two unique octants of data were collected for a total of 4158 (3443 unique) reflections. Corrections for Lorentz and polarization effects were applied during data reduction; absorption effects were ignored ($m = 0.288$ mm^{-1}). The |E*E–1| statistics, as well observed systematic absences, were uniquely consistent with the space group $P2_12_12_1$. The structure was solved by direct methods using the Siemens SHELXTL-93 (Version 5.0) proprietary software package, and refined by Full-Matrix Least Squares on F^2 until the structure converged to R (R_wF^2) = 8.57% (13.24%). All non-hydrogen atoms were anisotropically refined. Hydrogen atoms were placed at calculated positions and introduced into the refinement as fixed contributors with an isotropic U value of 0.08 Å^2. The ORTEP view of bis-Mosher ester **26,** as 50% thermal ellipsoids, is shown in Figure 10.

PART THREE

SYNTHESIS AND ANTI-HIV-1 EVALUATION OF (±)-CALANOLIDE A ANALOGS

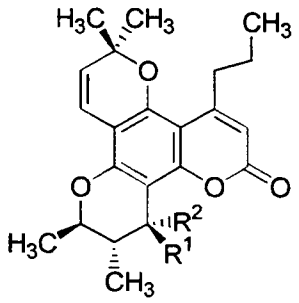
I. STATEMENT OF THE PROBLEM

A. Objective

The goal of this project was to synthesize analogs of calanolide A in racemic form and evaluate them as inhibitors of HIV-1 replication.

B. Research Plan

Boyd and co-workers at the NCI had isolated calanolide A, calanolide B and six other callophyllum coumarin compounds from the tropical rainforest tree, *Calophyllum lanigerum*, and found them to be non-nucleoside RT inhibitors of HIV-1.[113] Calanolide A was the most potent HIV-1 inhibitor of them all. Calanolide A has a chromene, a coumarin and a chromanol ring built around a phloroglucinol core. The structure of calanolide A and calanolide B are shown in Figure 12.



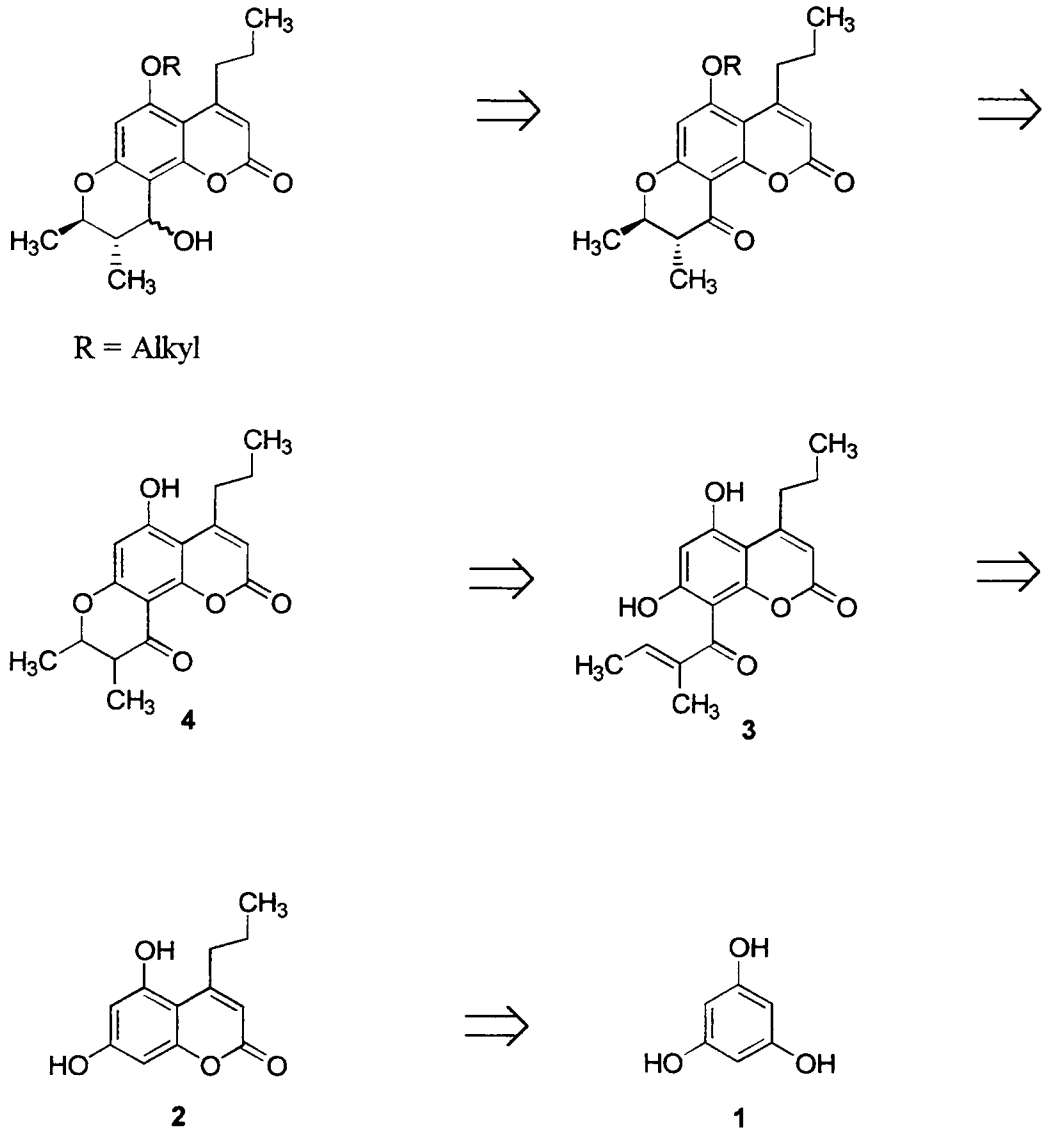
calanolide A: R^1 = OH; R^2 = H
calanolide B: R^1 = H; R^2 = OH

Figure 12. Structure of calanolide A and calanolide B.

Calanolide A is quite a complex molecule with three stereogenic centers. There is scope for a lot of structural modifications in this molecule. We envisioned that the chromanol ring which contains all the three stereogenic centers must be essential for its activity. This left us with the coumarin and chromene rings as targets for structural modification. We decided to replace the chromene ring with 5-alkoxy groups as this would enable us to study the effect of these structural changes on activity and at the same time make the synthesis a lot easier. Dreyer and co-workers at SmithKline Beecham Pharamceuticals had reported the total synthesis of (±)-calanolide A at the time we were beginning this project.[114] We decided to base our synthesis along the lines of their synthetic pathway. Accordingly, the general retrosynthetic pathway for (±)-calanolide A analogs is outlined in Scheme 6.

C. Significance

This project should identify analogs of calanolide A that could be equipotent or more potent inhibitors of HIV-1 replication than the parent compound itself. The biological data obtained from anti-HIV evaluation of these analogs should help us in determining structure–activity relationships and in designing possibly more potent anti-HIV drugs.



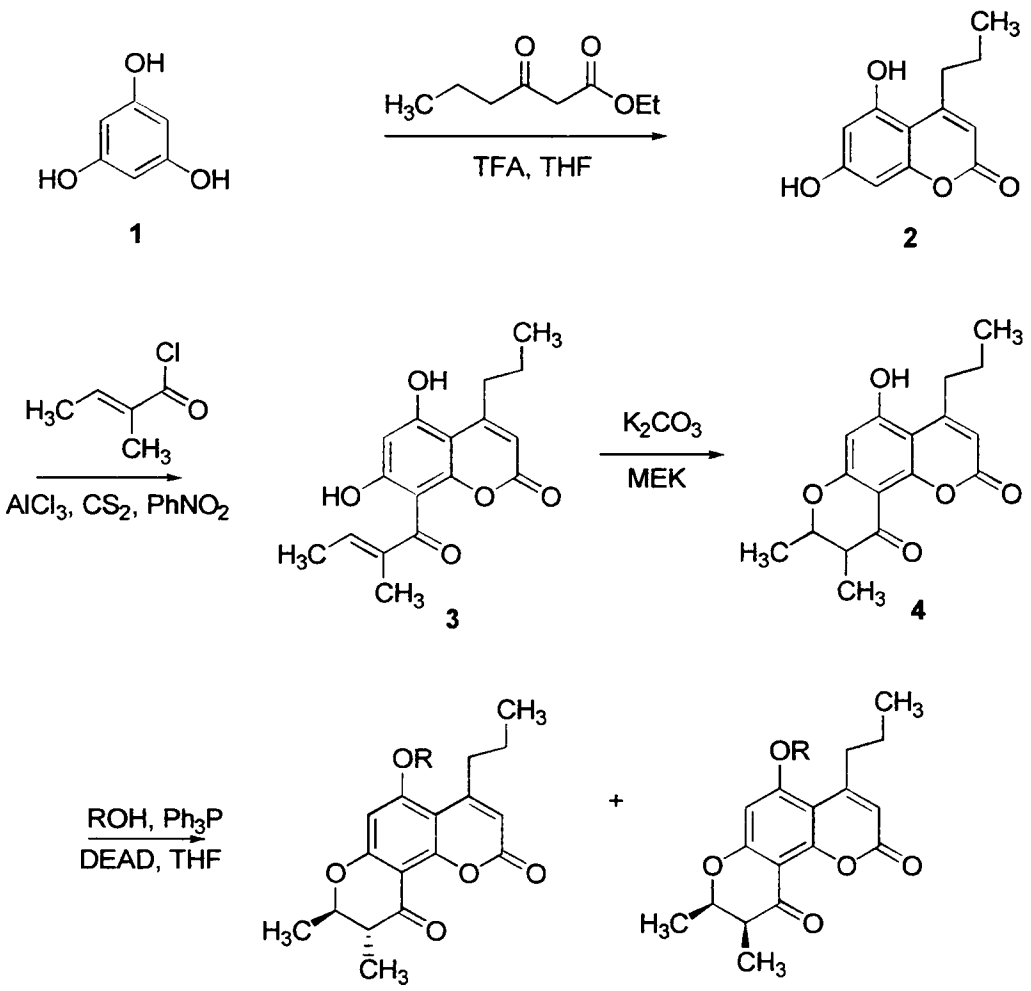
Scheme 6. General retrosynthetic analysis of calanolide analogs.

II. RESULTS AND DISCUSSION

A. Synthesis of (±)-Calanolide A Analogs

As stated before, the goal of this project was to replace the chromene ring of (±)-calanolide A with alkyl groups in order to probe their effect on anti-HIV-1 activity. The first task was to build the coumarin ring compound **2**, which was accomplished in 74% yield by reacting anhydrous phlorogucinol with ethyl butyrylacetate in THF/TFA (Scheme 7).[114] Friedel–Crafts acylation[115] of coumarin **2** with tigloyl chloride[116] and $AlCl_3$ at 75 °C in CS_2 and nitrobenzene gave compound **3** in 72% yield.[114]

Intramolecular Michael addition[114,117,118] of **3** in methyl ethyl ketone induced by K_2CO_3 resulted in a 1.3:1 *cis*:*trans* epimeric mixture of 2,3-dimethyl benzopyranones **4**.[114] In the literature procedure, they reported that they obtained a 1:1 epimeric mixture. It is felt that the epimeric ratio is dependent on reaction time. Longer reaction times result in more of the thermodynamically stable *trans* product being formed. But this is just an observation based on ratios obtained in different batches of this reaction and has not been systematically studied. There was a paper published by other workers after this work was completed on how this epimeric ratio varies with reaction conditions.[119] In this paper K_2CO_3 and THF was used as one of the reaction conditions and by carrying out the reaction for 1 day at 60 °C, they obtained a 3:7 *cis*:*trans* epimeric ratio. Even in our own laboratory a co-worker, Dr. Mikhail Goncharenko, obtained a 1:3 *cis*:*trans* epimeric mixture of **4** by heating compound 3 in silicon oil at 200 °C for 10 min. The epimers could not be separated and were used as a mixture for the next step.



R = propargyl	**5t**	**5c**
R = propyl	**6t**	**6c**
R = ethyl	**7t**	**7c**
R = sec-butyl	**8t**	**8c**

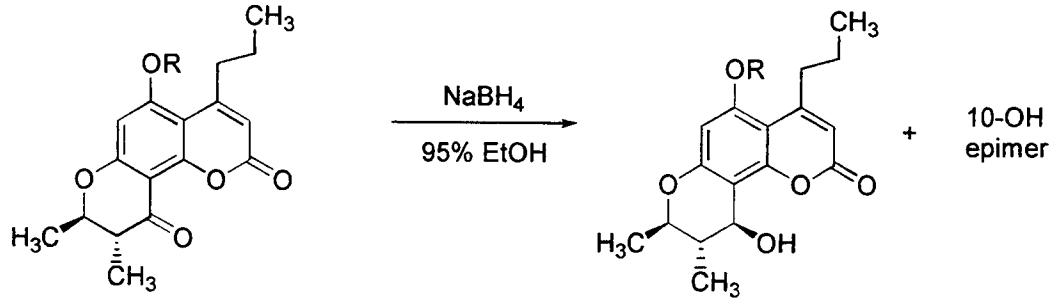
Note. Alkylation of **4** to give **5t + 5c** was done using propargyl bromide, K_2CO_3, acetone at 40 °C

Scheme 7. Synthesis of keto compounds **5t-8t** and **5c-8c**.

This common intermediate **4** was used to make analogs of Calanolide A (Scheme 7). When **4** was treated with alkyl halide and K_2CO_3 and refluxed in acetone, a ring opened compound (**12** when R = ethyl) rather than the desired alkylation products was obtained (Scheme 9). The stereochemistry of the double bond formed on ring opening was determined by doing a NOE difference experiment. It was found that the two methyl groups on the double bond were *cis* to one another. The NOE difference spectrum of compound **12** is shown in Appendix B. The proposed mechanism for the formation of this unexpected alkylation product is shown in Scheme 10.

The *trans*-propargyl ketone **5t** and its *cis*-**5c** were made by treatment of **4** with propargyl bromide and K_2CO_3 in acetone. The desired products were obtained by carefully controlling the reaction temperature at 40 °C. These diastereomers were separated on a silica gel column. It was observed that if the reaction mixture was refluxed strongly, the undesired alkylation product shown in Scheme 9 was obtained. Hence, we decided to use the Mitsunobu reaction[120] to make the other 5-alkyloxy analogs of calanolide A. The *trans*-propyl ketone **6t** and its *cis*-isomer **6c** were made by treatment of **4** in dry THF with *n*-propyl alcohol at room temperature in the presence of Ph_3P and diethyl azodicarboxylate. Similarly, the ethyl ketones (**7t** and **7c**) and the *sec*-butyl ketones (**8t** and **8c**) were synthesized using the corresponding alcohols.

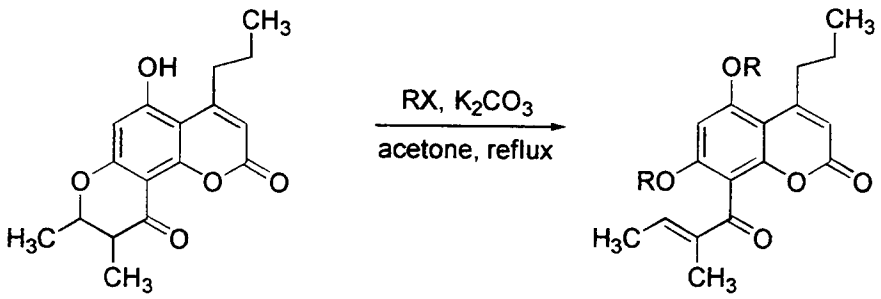
As we were interested in (±)-calanolide A analogs, our next task was to reduce the trans-ketones to the corresponding alcohols (Scheme 8). Reduction of the *trans*-ketones **5t** with $NaBH_4$ in ethanol afforded a 2:1 mixture (by ^1H NMR) of alcohol **9** and its 10-hydroxy epimer.[114] Separation of these epimers on a silica gel column was a very



R = propargyl	**5t**	**9**
R = propyl	**6t**	**10**
R = *sec*-butyl	**8t**	**11**

Note. Reduction of **6t** to **10** was done using $NaBH_4$, $CeCl_3$, 95% EtOH.

Scheme 8. Synthesis of calanolide A analogs **9**, **10**, and **11**.

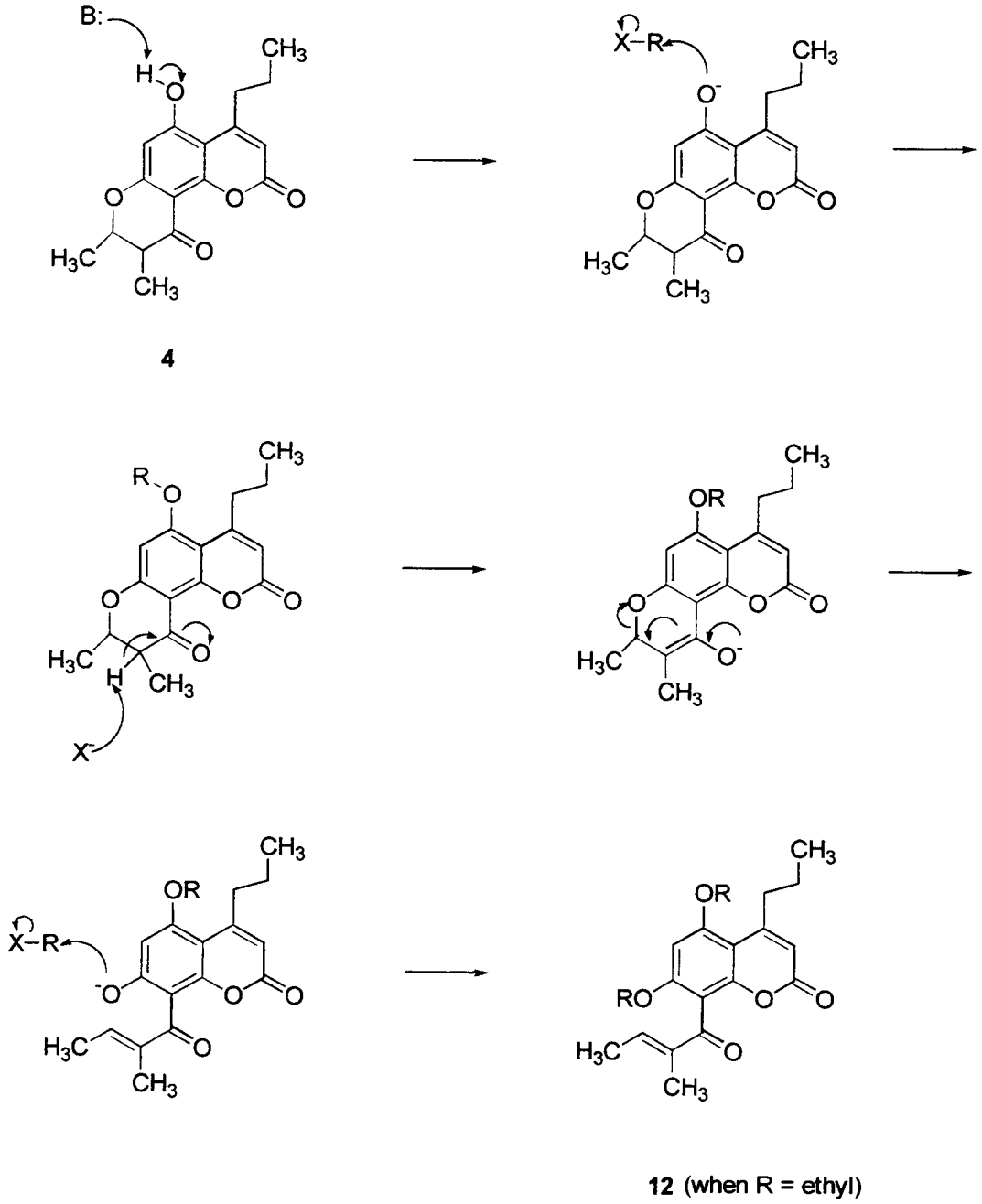


4

R = alkyl

12 (when R = ethyl)

Scheme 9. Unexpected alkylation reaction product.



Scheme 10. Proposed mechanism for formation of the unexpected alkylation product shown in Scheme 9.

tedious job. Only a sufficient amount of **9** required for biological evaluation was separated on a silica gel column using gradient elution. Similarly, the trans-ketone **8t** afforded a 2:1 mixture (by ^{1}H NMR) of alcohol **11** and its 10-hydroxy epimer on $NaBH_4$ reduction. In this case also, a only sufficient amount of compound required for biological evaluation was separated on a silica gel column using gradient elution. Luche reduction[114,121] of the trans-ketone **6t** was more stereoselective, providing a 4:1 mixture (by ^{1}H NMR) of alcohol **10** and its 10-hydroxy epimer. Even though the diastereoselectivity was better in this case, separation of the diastereomers was not an easy task, and only partial separation was possible.

B. Anti-HIV-1 Evaluation Data

The biological evaluation data of some 5-alkyloxy calanolide analogs made in our laboratory is summarized in Table 6. These compounds were evaluated for activity against HIV-1 in NCI's primary screen using the XTT assay.[109] The isopropyl analog of (±)-calanolide A (NSC 666371) was the most active compound. Its activity was comparable to that of natural calanolide A. The allyl (**NSC 669042**), *sec*-butyl (**NSC 681718**), methoxyisopropyl (**NSC 687950**) analogs of (±)-calanolide A and the isoproyl analog of (±)-calanolide B (**NSC 666372**) showed moderate activity. All other analogs listed in Table 6 were inactive.

It was seen that the 10-keto analog of (±)-calanolide A (**NSC 670365**) was active against HIV-1. So, a number of (±)-5-alkoxy-10-keto-calanolide analogs made in our

Table 6. Anti HIV-1 evaluation data for (±)-calanolide A analogs.

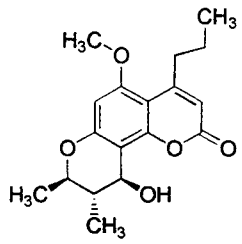
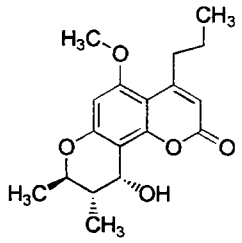
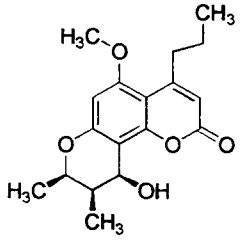
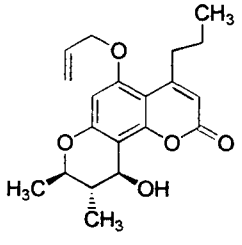
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **(NSC 664398)**	–	$> 2.00 \times 10^{-4}$	–	Inactive
 **(NSC 664399)**	–	4.40×10^{-5} to 5.60×10^{-5}	–	Inactive
 **(NSC 664397)**	–	3.60×10^{-5} to 3.90×10^{-5}	–	Inactive
 **(NSC 669042)**	4.26×10^{-6} to 1.42×10^{-5}	9.66×10^{-6} to 2.36×10^{-5}	1.67×10^{0} to 2.58×10^{0}	Moderate

Table 6, continued.

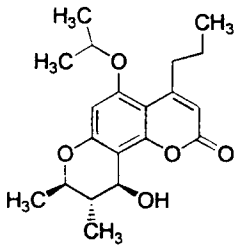
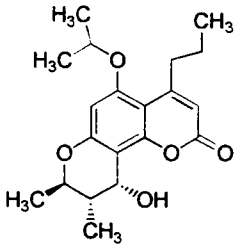
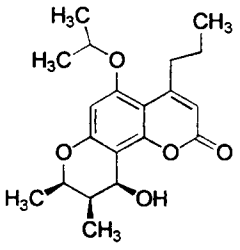
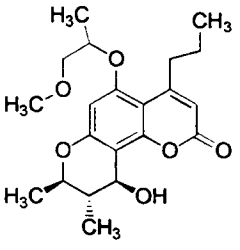
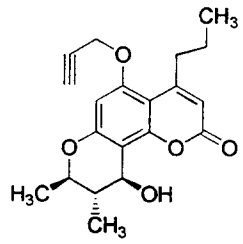
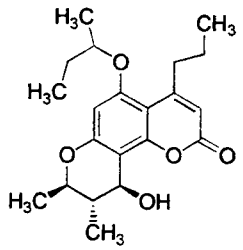
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **(NSC 666371)**	2.61×10^{-7} to 7.65×10^{-6}	3.15×10^{-5} to 5.35×10^{-5}	4.46×10^{0} to $1.90 \times 10^{+2}$	Active
 **(NSC 666372)**	2.95×10^{-7} to 1.58×10^{-6}	1.43×10^{-6} to 1.29×10^{-5}	2.73×10^{0} to $4.37 \times 10^{+1}$	Moderate
 **(NSC 666373)**	–	3.52×10^{-5} to 7.00×10^{-5}	–	Inactive
 **(NSC 687950)**	3.86×10^{-6} to 5.20×10^{-6}	2.84×10^{-5} to 3.15×10^{-5}	5.45×10^{0} to 7.95×10^{0}	Moderate

Table 6, continued.

Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **(NSC 670467)**	–	$> 2.00 \times 10^{-4}$	–	Inactive
 **(NSC 681718)**	1.44×10^{-6} to 3.66×10^{-6}	2.39×10^{-5} to 3.74×10^{-5}	$1.02 \times 10^{+1}$ to $1.66 \times 10^{+1}$	Moderate

NSC 666371, NSC 666372, NSC 666373, NSC 664398, NSC 664399, NSC 664397 were made by Dr, Kuai-lin Sun.
NSC 687950 was made by Dr. Mikhail Goncharenko.
NSC 669042 was made by Dr. Frank Tagliaferri.

laboratory were evaluated for anti-HIV activity at the NCI using their XTT assay.[109] These results are summarized in Table 7. The isopropyl (**NSC 666028**) and the methoxy isopropyl (**NSC 684416**) analogs showed moderate anti-HIV-1 activity. All the other analogs listed in Table 7 were inactive. The ring-opened compound **12** (**NSC 679901**) was also found to be inactive in the XTT assay.

Table 7. Anti HIV-1 evaluation data of (±)-10-keto-calanolide A analogs.

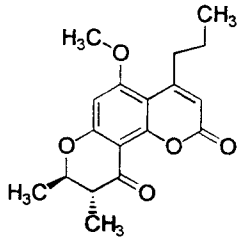
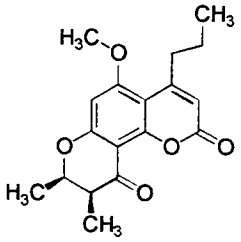
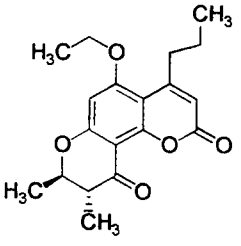
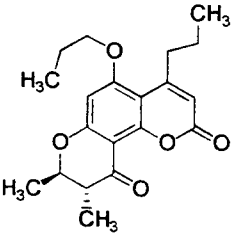
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **(NSC 663601)**	–	3.70×10^{-5} to 9.30×10^{-5}	–	Inactive
 **(NSC 663602)**	–	3.90×10^{-5} to 9.40×10^{-5}	–	Inactive
 **(NSC 683579)**	–	4.41×10^{-6} to 1.07×10^{-5}	–	Inactive
 **(NSC 683578)**	–	4.20×10^{-6} to 1.30×10^{-5}	–	Inactive

Table 7, continued.

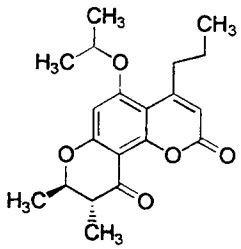
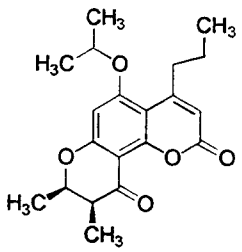
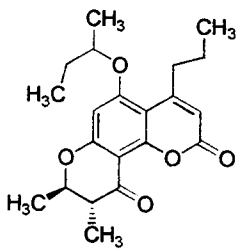
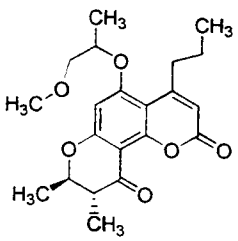
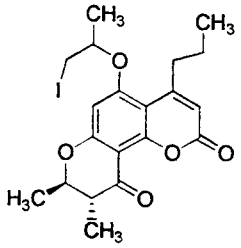
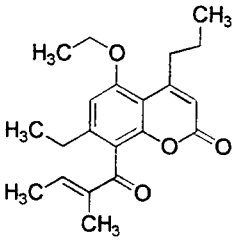
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **(NSC 666028)**	5.17×10^{-6} to 4.40×10^{-5}	$> 2.00 \times 10^{-4}$	$> 4.54 \times 10^{0}$ to $> 3.87 \times 10^{+1}$	Moderate
 **(NSC 666029)**	–	2.83×10^{-5} to 3.20×10^{-5}	–	Inactive
 **(NSC 679902)**	–	1.05×10^{-5} to 1.30×10^{-5}	–	Inactive
 **(NSC 684416)**	4.46×10^{-6}	1.00×10^{-5} to 1.74×10^{-5}	3.30×10^{0}	Moderate

Table 7, continued.

Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **(NSC 692004)**	–	4.75×10^{-6} to $> 2.00 \times 10^{-4}$	–	Inactive
 **(NSC 679901)**	–	8.31×10^{-7} to 1.59×10^{-6}	–	Inactive

NSC 663601, NSC 663602, NSC 666028, NSC 666029 were made by Dr. Kuai-lin Sun.
NSC 684416 was made by Dr. Mikhail Goncharenko.
NSC 692004 was made by Dr. Steve Adah.

III. CONCLUSIONS

Analogs of (±)-calanolide A, in which the chromene was replaced by 5-alkoxy groups were synthesized in racemic form and evaluated for anti-HIV-1 activity. The isopropyl analog (**NSC 666371**) was the most active compound. The allyl (**NSC 669042**), *sec*-butyl (**NSC 681718**), and methoxyisopropyl (**NSC 687950**) analogs of (±)-calanolide A, and the isoproyl analog of (±)-calanolide B (**NSC 666372**) showed moderate activity. Among the 10-keto compounds, the isopropyl (**NSC 666028**) and the methoxyisopropyl (**NSC 684416**) analogs showed moderate anti-HIV-1 activity.

An unexpected ring opening reaction was observed when compound **4** was refluxed in acetone with an alkyl halide and K_2CO_3. To circumvent this problem, we generally used the Mitsunobu reaction to alkylate the hydroxy group in compound **4**.

IV. EXPERIMENTAL SECTION

A. General Methods

Melting points were determined by the capillary method and are uncorrected. Analytical TLC was performed on aluminum-backed plates coated with E. Merck Silica Gel-60 F-254. The developed plates were air dried and visualized by irradiation with UV light and/or by spray–heat development using a *p*-anisaldehyde–sulfuric acid reagent. Flash column chromatography was performed on Silica Gel-60 (230–400 mesh). Optical rotations were measured with a Perkin-Elmer Model 243 automatic polarimeter for solutions in a 1-dm cell at the indicated temperature. ^{1}H and ^{13}C NMR were recorded at 250.13 MHz and 62.89 MHz, respectively, on a Bruker AC 250 instrument or at 400.13 MHz and 100.61 MHz, respectively, on a Bruker AMX 400 instrument using the indicated solvent. ^{1}H NMR shifts are reported as δ (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard; multiplicities are first-order values in Hz: s, singlet; bs, broad singlet; d, doublet; t, triplet; dd, double of doublets; db, broad doublet; q, quartet; m, multiplet. ^{13}C NMR chemical shifts are reported as δ (ppm) relative to the chemical shift of the solvent used ($CDCl_3$: 77.0 ppm; DMSO-d_6: 39.5 ppm; CD_3OD: 49.0 ppm). Elemental analyses were performed by Atlantic Microlabs, Inc. of Atlanta, GA. Chemicals were of reagent grade and were used directly. Solvents were distilled and dried by literature procedures before use. All evaporations were carried out with a rotary evaporator under vacuum and below 40 °C.

B. Preparation of Compounds 2–12

(±)-5,7-Dihydroxy-4-propylchromen-2-one (2). To phloroglucinol (**1**, 25.0 g, 0.198 mol) in dry THF (100 mL) was added ethyl butyryl acetate (34.5 g, 0.218 mol) and trifluoroacetic acid (37.5 mL) at room temperature under N_2. The reaction mixture was refluxed for 24 h, then cooled to room temperature and poured into ice (150 g) and water (500 mL) with stirring. A pale yellow-colored solid that separated was filtered off and the mother liquor was concentrated to yield more product. The combined crude product was recrystallized from ethanol (95%) to yield **2** (32.3 g, 74%): mp 236–237 °C (lit.[114] 236–238 °C) : ^{1}H NMR (DMSO-d_6) δ 10.61 (s, 1H), 10.33 (s, 1H), 6.30 (d, 1H, J = 2.2 Hz), 6.22 (d, 1H, J = 2.1 Hz), 5.84 (s, 1H), 2.87 (t, 2H, J = 7.5 Hz), 1.61 (m, 2H), 0.96 (t, 3H, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 160.95, 160.25, 158.56, 157.47, 156.89, 108.29, 101.43, 99.32, 94.79, 37.29, 22.56, 13.83.

(±)-5,7-Dihydroxy-8-(2-methylbut-2-enoyl)-4-propylchromen-2-one (3). To **2** (5.00 g, 22.7 mmol) and $AlCl_3$ (12.9 g, 95.5 mmol) in CS_2 (50 mL) was added tigloyl chloride (3.00 g, 25.3 mmol) in CS_2 (2 mL), and the resulting mixture was stirred at room temperature for 30 min. Nitrobenzene (20 mL) was then added, and the mixture was heated at 75 °C for 18 h. The reaction mixture was then cooled to room temperature and poured into ice (50 g) and HCl (1 M, 200 mL). Solid product that separates was filtered and washed with hexanes. The mother liquor was extracted with 95:5 $CHCl_3$–CH_3OH (3 × 100 mL), the organic layer was washed with saturated NaCl, dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to yield more product. The combined crude product was chromatographed on silica gel using CH_2Cl_2–CH_3OH (95:5) as the

eluent to yield **3** (4.94 g, 72%) as a white solid: mp 207–210 °C (lit.[114] 266–268 °C); ^{1}H NMR (DMSO-d_6) δ 10.84 (s, 1H), 10.51 (s, 1H), 6.47 (q, 1H, J = 6.9 Hz), 6.42 (s, 1H), 5.86 (s, 1H), 2.88 (t, 2H, J = 7.3 Hz), 1.82 (m, 6H), 1.61 (m, 2H), 0.96 (t, 3H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 194.26, 159.55, 158.56, 157.73, 157.27, 153.32, 142.36, 138.60, 108.46, 108.02, 101.07, 98.86, 37.38, 22.57, 14.76, 13.83, 10.48.

(±)-5-Hydroxy-8,9-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (4). To **3** (2.00 g, 6.62 mmol) in methyl ethyl ketone (30 mL) was added K_2CO_3 (2.75 g, 19.9 mmol), and the reaction mixture was refluxed for 2 h. The mixture was then cooled to room temperature, acidified with HCl (1 N, 75 mL), and extracted with ethyl acetate (3 × 75 mL). The organic layer was washed with saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated to remove the solvent. The crude product was chromatographed on a silica gel column using CH_2Cl_2–CH_3OH (97:3) as the eluent to yield a mixture of two diastereomers **4** (1.68 g, 84%) as a white solid: mp 269 °C; ^{1}H NMR ($CDCl_3$) δ 6.33 (d, 1H, J = 3.4 Hz), 6.00 (s, 1H), 4.62 (m, 0.56H), 4.22 (m, 0.43H), 2.93 (t, 2H, 7.5 Hz), 2.61 (m, 0.56H), 2.48 (m, 0.43H), 1.65 (m, 2H), 1.48 (d, 1.3H, J = 6.3 Hz), 1.37 (d, 1.7H , J = 6.6 Hz), 1.18 (d, 1.3H, J = 6.9 Hz), 1.13 (d, 1.7H , J = 7.2 Hz), 0.99 (t, 3H, 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 190.70, 189.21, 163.81, 163.59, 161.73, 161.63, 159.18, 157.86, 156.19, 155.92, 110.22, 103.42, 102.24, 101.70, 98.92, 78.50, 76.30, 46.47, 45.14, 37.46, 22.49, 19.27, 15.51, 13.72, 10.22, 9.05. The ^{1}H and ^{13}C NMR spectra were found to be in agreement with the spectral data given in ref. 114.

(±)-8,9-*trans*-Dimethyl-5-propargyloxy-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (5t) and (±)-8,9-*cis*-dimethyl-5-propargyloxy-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (5c). To **4** (0.428 g, 1.42 mmol) and K_2CO_3 (1.28 g, 9.26 mmol) in acetone (40 mL) was added propargyl bromide (0.252 g, 2.12 mmol), and the reaction mixture was stirred at 40 °C for 8 h. It was then cooled to room temperature and filtered, and the filtrate was concentrated to obtain an oil, which was chromatographed on a silica gel column using hexanes–ethyl acetate (4:1) to obtain the *trans*-isomer **5t** (0.222 g, 46%): mp 141–142 °C; ^{1}H NMR ($CDCl_3$) δ 6.37 (s, 1H), 6.06 (s, 1H), 4.80 (d, 2H, J = 2.4 Hz), 4.31 (m, 1H), 2.86 (t, 2H, J = 7.6 Hz), 2.65 (t, 1H, J = 2.4 Hz), 2.56 (m, 1H), 1.61 (m, 2H), 1.53 (d, 3H, J = 6.3 Hz), 1.21 (d, 3H, J = 6.9 Hz), 1.01 (t, 3H, J = 7.3 Hz) and the *cis*-isomer **5c** (0.140 g, 29%); ^{1}H NMR ($CDCl_3$) δ 6.40 (s, 1H), 6.06 (s, 1H), 4.82 (d, 2H, J = 2.3 Hz), 4.71 (m, 1H), 2.86 (t, 2H, J = 7.6 Hz), 2.68 (m, 2H), 1.62 (m, 2H), 1.41 (d, 3H, J = 6.6 Hz), 1.15 (d, 3H, J = 7.2 Hz), 1.01 (t, 3H, J = 7.3 Hz).

(±)-8,9-*trans*-Dimethyl-5-propoxy-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (6t) and (±)-8,9-*cis*-dimethyl-5-propoxy-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (6c). To a stirred mixture of **4** (0.680 g, 2.25 mmol) and Ph_3P (0.649 g, 2.474 mmol) in THF (20 mL) was added 1-propanol (0.149 g, 2.474 mmol) under N_2 at room temperature. Diethyl azodicarboxylate (0.431 g, 2.474 mmol) was then gradually added, and the reaction mixture was stirred at room temperature for 15 h. The reaction was then quenched by adding water (75 mL), and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layer was

washed with saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated to obtain an oil. The crude product was chromatographed on a silica gel column using hexanes–ethyl acetate (4:1) as the eluent to yield the *trans*-isomer **6t** (0.302 g, 39%): mp 118–120 °C; ^{1}H NMR ($CDCl_3$) δ 6.29 (s, 1H), 6.05 (s, 1H), 4.29 (m, 1H), 4.03 (t, 2H, J = 6.6 Hz), 2.89 (t, 2H, J = 7.6 Hz), 2.53 (m, 1H), 1.89 (m, 2H), 1.63 (m, 2H), 1.51 (d, 3H, J = 6.3 Hz), 1.21 (d, 3H, J = 6.9 Hz), 1.10 (t, 3H, J = 7.4 Hz), 0.99 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 189.63, 164.61, 161.62, 159.73, 157.27, 156.12, 111.52,104.89, 103.57, 95.95, 79.49, 71.30, 47.22, 38.74, 22.71, 22. 11, 19. 54, 13.71, 10.64, 10.46. Anal. Calcd for $C_{20}H_{24}O_5 \cdot 0.18\ H_2O$: C 69.10, H 7.06. Found: C 69.11, H 7.06 and the *cis*-isomer **6c** (0. 233 g, 30%); ^{1}H NMR ($CDCl_3$) δ 6.30 (s, 1H), 6.06 (s, 1H), 4.69 (m, 1H), 4.04 (t, 2H, J = 6.6 Hz), 2.90 (t, 2H, J = 7.6 Hz), 2.67 (m, 1H), 1.91 (m, 2H), 1.60 (m, 2H), 1.40 (d, 3H, J = 6.6 Hz), 1.12 (m, 6H), 1.00 (t, 3H, J = 7.3 Hz).

(±)-5-Ethoxy-8,9-*trans*-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (7t) and (±)-5-ethoxy-8,9-*cis*-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (7c). The procedure used to synthesize **6t** and **6c** was repeated using **4** (0.400 g, 1.32 mmol) and ethanol (100%, 0.067 g, 1.46 mmol) to yield the *trans*-isomer **7t** (0.188 g, 43%): mp 131–132 °C; ^{1}H NMR ($CDCl_3$) δ 6.26 (s, 1H), 6.03 (s, 1H), 4.29 (m, 1H), 4.15 (q, 2H, J = 7.0 Hz), 2.87 (t, 2H, J = 7.6 Hz), 2.54 (m, 1H), 1.59 (m, 8H), 1.21 (d, 3H, J = 6.9 Hz), 0.99 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 189.66, 164.65, 161.64, 159.76, 157.29, 156.15, 111.55, 104.91, 103.60, 95.97, 79.52, 65.21, 47.25, 38.76, 23.05, 19. 57, 14.30, 13.73, 10.49. Anal. Calcd for $C_{19}H_{22}O_5$: C 69.08, H 6.71. Found: C 68.92, H 6.73 and the *cis*-isomer **7c**

(0.175 g, 40%); ^{1}H NMR ($CDCl_3$) δ 6.28 (s, 1H), 6.05 (s, 1H), 4.68 (m, 1H), 4.15 (q, 2H, J = 7.0 Hz), 2.88 (t, 2H, J = 7.6 Hz), 2.66 (m, 1H), 1.58 (m, 5H), 1.40 (d, 3H, J = 6.6 Hz), 1.15 (d, 3H, J = 7.2 Hz), 1.00 (t, 3H, J = 7.3 Hz).

(±)-5-*sec*-Butoxy-8,9-*trans*-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (8t) and (±)-5-*sec*-butoxy-8,9-*cis*-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (8c). The procedure used to synthesize **6t** and **6c** was repeated using **4** (0.400 g, 1.32 mmol) and *sec*-butanol (0.162 g, 2.19 mmol) to yield the *trans*-isomer **8t** (0.320 g, 45%): mp 114–116 °C; ^{1}H NMR ($CDCl_3$) δ 6.26 (s, 1H), 6.03 (s, 1H), 4.50 (m, 1H), 4.29 (m, 1H), 2.87 (m, 2H), 2.54 (m, 1H), 1.82 (m, 2H), 1.62 (m, 2H), 1.52 (d, 3H, J = 6.3 Hz), 1.41 (dd, 3H, J = 6.1, 2.8 Hz), 1.21 (d, 3H, J = 6.9 Hz), 1.02 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 189.64, 164.63, 161.62, 159.74, 157.27, 156.13, 111.54, 104.90, 103.58, 95.95, 79.51, 76.95, 47.24, 38.74, 28.92, 23.04, 19. 55, 18.96, 14.29, 10.63, 10.04. Anal. Calcd for $C_{21}H_{26}O_5$: C 70.37, H 7.31. Found: C 70.45, H 7.32 and the *cis*-isomer **8c** (0. .292 g, 41%); ^{1}H NMR ($CDCl_3$) δ 6.26 (s, 1H), 6.04 (s, 1H), 4.68 (m, 1H), 4.49 (m, 1H), 2.89 (m, 2H), 2.65 (m, 1H), 1.83 (m, 2H), 1.63 (m, 2H), 1.41 (d, 6H, J = 6.6 Hz), 1.15 (d, 3H, J = 7.2 Hz), 1.02 (m, 6H).

(±)-10-Hydroxy-8,9-*trans*-dimethyl-5-propargyloxy-4-propyl-9,10-*trans*-dihydro[8*H*]pyrano[2,3-*f*]chromen-2-one (9). To **5t** (0.200 g, 0.588 mmol) in ethanol (95%, 15 mL) was added $NaBH_4$ (0.111 g, 2.94 mmol). The reaction mixture was stirred for 45 min at room temperature, then it was quenched with H_2O (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated to remove the solvent. The crude product was

chromatographed on a silica gel column using hexanes–ethyl acetate (1:1) to yield a 2:1 mixture (by ^{1}H NMR) of **9** and its hydroxy epimer (0.200 g, 100% total yield). Compound **9** (0.034 g) was obtained from this mixture by running a gradient silica gel column using 5–20% ethyl acetate in hexanes: mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 6.32 (s, 1H), 5.99 (s, 1H), 4.72 (s, 3H), 3.95 (m, 1H), 3.56 (s, 1H), 2.90 (m, 2H), 2.58 (s, 1H), 1.94 (m, 1H), 1.63 (m, 2H), 1.45 (d, 3H, J = 6.3 Hz), 1.15 (d, 3H, J = 6.8 Hz), 1.02 (t, 3H, J = 7.2 Hz). Anal. Calcd for $C_{20}H_{22}O_5 \cdot 0.88H_2O$: C 67.06, H 6.68. Found: C 67.06, H 6.69.

(±)-10-Hydroxy-8,9-*trans*-dimethyl-5-propoxy-4-propyl-9,10-*trans*-dihydro[8*H*]pyrano[2,3-*f*]chromen-2-one (10). To **6t** (0.154 g, 0.447 mmol) and $CeCl_3$ (0.121 g, 0.492 mmol) in ethanol (95%, 10 mL) was added $NaBH_4$ (0.845 g, 2.24 mmol). The reaction mixture was stirred for 45 min at room temperature, then quenched with H_2O (15 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with saturated NaCl, dried over anhydrous $MgSO_4$ and concentrated to remove the solvent. The crude product was chromatographed on a silica gel column using hexanes–ethyl acetate (1:1) to yield a 4:1 mixture (by ^{1}H NMR) of **10** and its hydroxy epimer (0.145 g, 94% total yield). Compound **10** (0.046 g) was obtained from this mixture by running a gradient silica gel column using 5–20% ethyl acetate in hexanes: mp 85–87 °C; ^{1}H NMR ($CDCl_3$) δ 6.24 (s, 1H), 5.96 (s, 1H), 4.72 (d, 1H, J = 7.6 Hz), 3.94 (m, 3H), 3.56 (bs, 1H), 2.90 (m, 2H), 1.89 (m, 3H), 1.63 (m, 2H), 1.45 (d, 3H, J = 6.5 Hz), 1.14 (d, 3H, J = 6.8 Hz), 1.07 (t, 3H, J = 7.4 Hz), 1.00 (t, 3H, J = 7.3 Hz); ^{13}C

NMR ($CDCl_3$) δ 160.52, 159.11, 157.88, 157.54, 155.57, 109.84, 106.35, 104.35, 96.35,76.49, 70.72, 66.93, 40.40, 38.79, 22.90, 22.29, 18.93, 15.14, 13.83, 10.71.

(±)-5-*sec*-Butoxy-10-hydroxy-8,9-*trans*-dimethyl-4-propyl-9,10-*trans*-dihydro[8*H*]pyrano[2,3-*f*]chromen-2-one (11). By the same procedure used for making compound **9**, **11** and its hydroxy epimer (0.301 g, 100% total yield) were obtained as a 2:1 mixture (by ^{1}H NMR) from **8t** (0.300 g, 0.837 mmol). Compound **11** (0.055 g) was obtained as an oil from this mixture by running a gradient silica gel column using 5–20% ethyl acetate in hexanes: ^{1}H NMR ($CDCl_3$) δ 6.22 (s, 1H), 5.95 (s, 1H), 4.72 (dd, 1H, J = 7.6, 2.8 Hz), 4.41 (m, 1H), 3.93 (m, 1H), 3.57 (d, 1H, J = 2.9 Hz), 2.87 (m, 2H), 1.99–1.52 (m, 5H), 1.45 (d, 3H, J = 6.4 Hz), 1.35 (t, 3H, J = 6.4 Hz), 1.15 (d, 3H, J = 6.8 Hz), 1.00 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 160.49, 159.21, 157.85, 156.36, 155.76, 109.67, 106.11, 104.87, 104.81, 96.92, 96.83, 75.88, 66.99, 66.93, 40. 47, 38.91, 28.90, 28.72, 23.05, 18.93, 18.84, 18.75, 15.11, 13.83, 9.95, 9.83. Anal. Calcd for $C_{21}H_{28}O_5 \cdot 0.35\ H_2O$: C 68.77, H 7.89. Found: C 68.75, H 7.90.

5,7-Diethoxy-8-(2-methylbut-2-enoyl)-4-propylchromen-2-one (12). To **4** (1.00 g, 3.31 mmol) and K_2CO_3 (1.37 g, 9.92 mmol) in acetone (50 mL) was added ethyl iodide (0.774 g, 4.96 mmol), and the reaction mixture was refluxed for 12 h. The mixture was then cooled to room temperature and filtered, and the filtrate concentrated to obtain a pale yellow-colored solid, that was chromatographed on a silica gel column using hexanes–ethyl acetate (1:1) to obtain **12** (0.635 g, 54%) as a white solid: mp 165–167 °C; ^{1}H NMR ($CDCl_3$) δ 6.42 (dq, 1H, J = 7.0, 1.1 Hz), 6.31 (s, 1H), 5.93 (s, 1H), 4.10 (m, 4H), 2.87 (t, 2H, J = 7.6 Hz), 1.94 (s, 3H), 1.83 (d, 3H, J = 7.1 Hz), 1.64 (m,

2H), 1.52 (t, 3H, J = 7.0 Hz), 1.32 (t, 3H, J = 7.0 Hz), 1.01 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 194.27, 194.01, 160.19, 158.59, 158.21, 157.61, 153.22, 142.24, 139.59, 111.23, 103.61, 92.46, 64.71, 64.57, 38.67, 22.92, 14.93, 14.44, 13.81, 10.55. Anal. Calcd for $C_{21}H_{26}O_5$: C 70.37, H 7.31. Found: C 70.40, H 7.32.

PART FOUR

SYNTHESIS AND ANTI-HIV-1 EVALUATION OF SULTAM ANALOGS

I. STATEMENT OF THE PROBLEM

A. Objectives

The objectives is this project are as follows:

- To synthesize analogs of the lead compound (**NSC 108406**) in racemic form.
- To evaluate these analogs for biological activity against HIV-1 and develop a structure–activity relationship profile.
- To resolve the lead compound into its enantiomers in order to determine the activity of the individual enantiomers against HIV-1.
- To determine the absolute configuration of the enantiomers of the lead compound.

B. Research Plan

The lead in this project again was provided by the National Cancer Institute. They had found that (±)-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**NSC 108406**) was a potent non-nucleoside HIV-1 RT inhibitor. Our first task was to synthesize analogs of this compound in racemic form and have them evaluated for anti-HIV activity at the NCI. This would help us develop a structure–activity relationship profile, based on which more potent inhibitors could be synthesized. This molecule has three rings; two of which are phenyl rings (rings A and C) and the third is a heterocyclic five-membered ring (ring B) known as a sultam (a cyclic sulfonamide). We could make

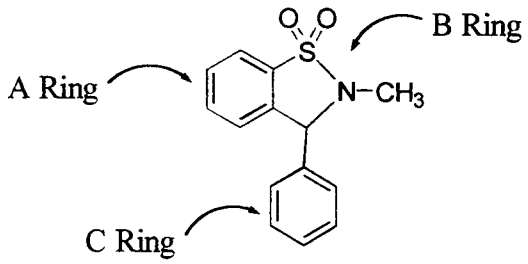


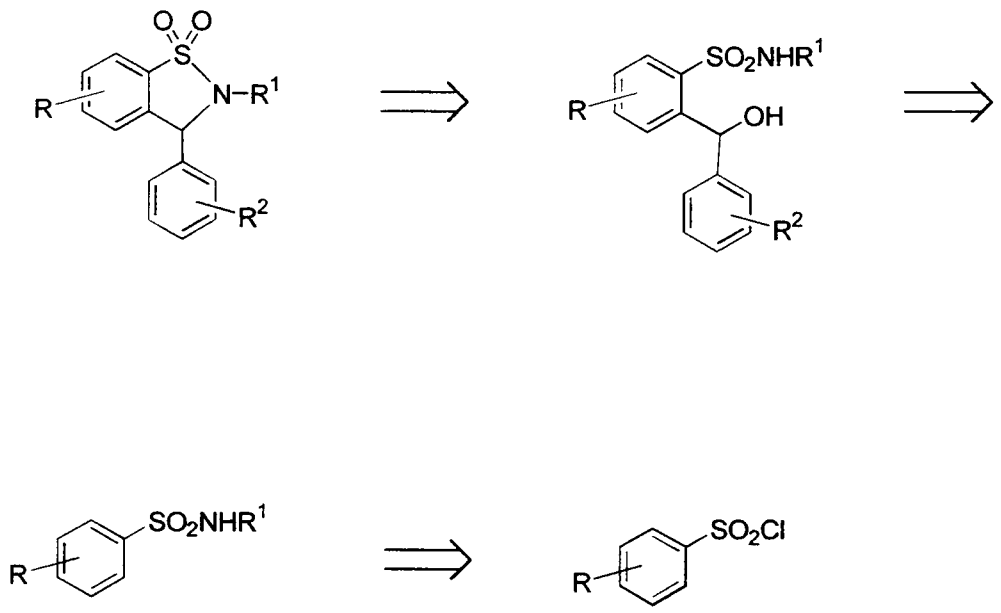
Figure 13. Structure of lead compound **NSC 108406**.

structural modifications in any of the three rings, in order to study the effect of different substituents on the anti-HIV-1 activity of these compounds. The structure of the lead compound **NSC 108406** is shown in Figure 13.

The molecular modeling staff at the NCI had docked this molecule in the HIV reverse transcriptase enzyme, based on which they provided some suggestions for structural modification. They felt that the A-ring modifications would result in better binding of the molecule to the RT enzyme and hence result in enhanced anti-HIV activity.

There were a few methods available in the literature to make these compounds in racemic form. We decided to use the method of Watanabe and co-workers as our main synthetic route to these analogs.[122] The general retrosynthetic analysis for these sultam analogs is shown in Scheme 11. Initially, we planned to make analogs with substituents in the A-ring. Then, we proposed to look at C-ring and B-ring modifications.

Our next goal was to obtain the indivudal enantiomers of the lead compound. This molecule has one stereogenic center which is a benzylic carbon, and hence asymmetric synthesis was not easy task. Therefore, we decided that we would try to resolve the racemic compound into its enantiomers on a chiral HPLC column.



Scheme 11. General retrosynthetic analysis of sultam analogs.

Our final goal for this project was to establish the absolute configuration of the lead compound. We planned to use X-ray crystallographic techniques to determine the absolute configuration of the lead compound.

C. Significance

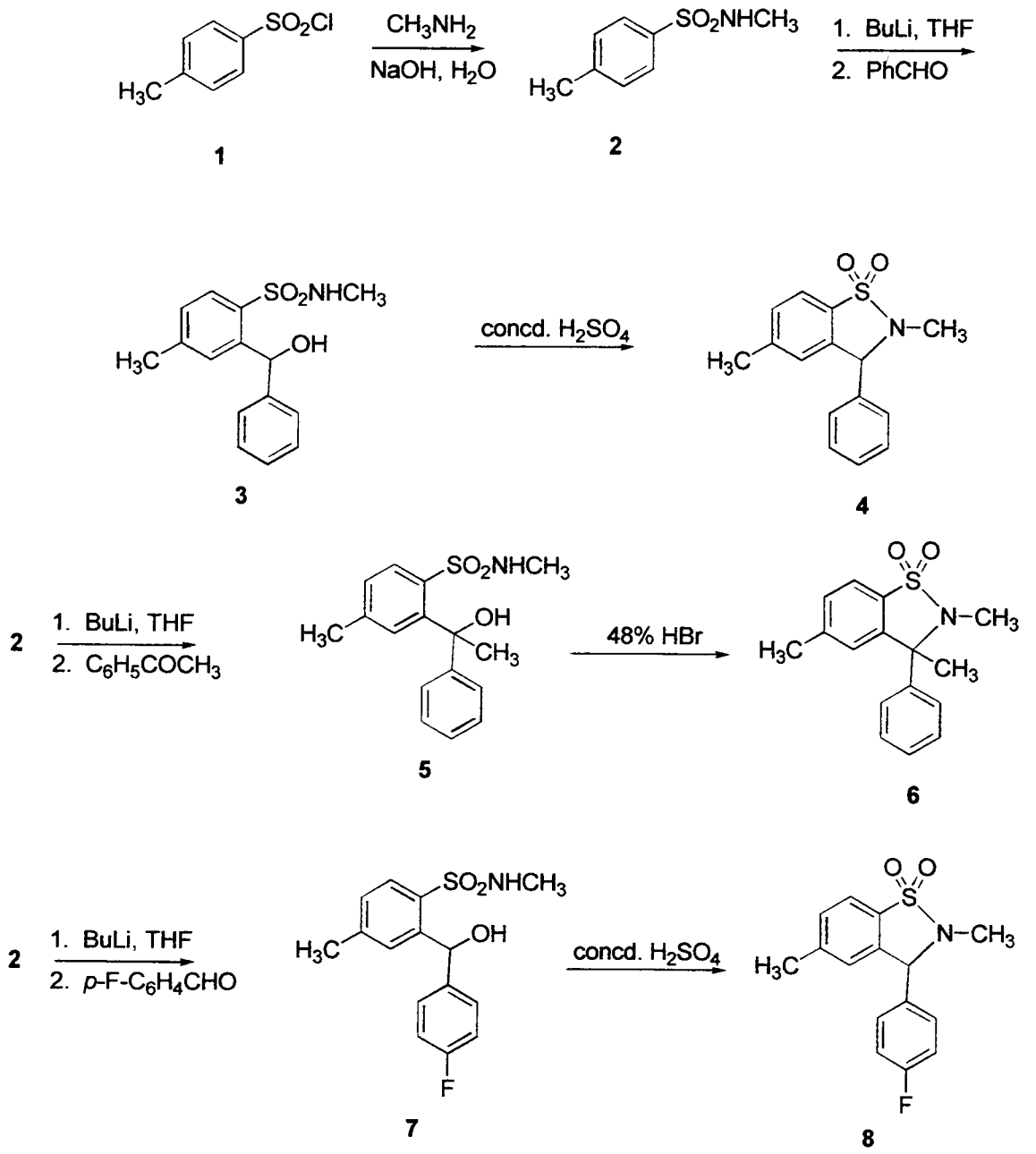
This project should map out a structure–activity relationship profile and help identify potent anti-HIV agents. Our goal was to identify the active enantiomer of the lead compound and determine its absolute configuration, which should give us insights on how these compounds bind to the RT enzyme. Such knowledge is essential to enable us design more potent anti-HIV inhibitors.

II. RESULTS AND DISCUSSION

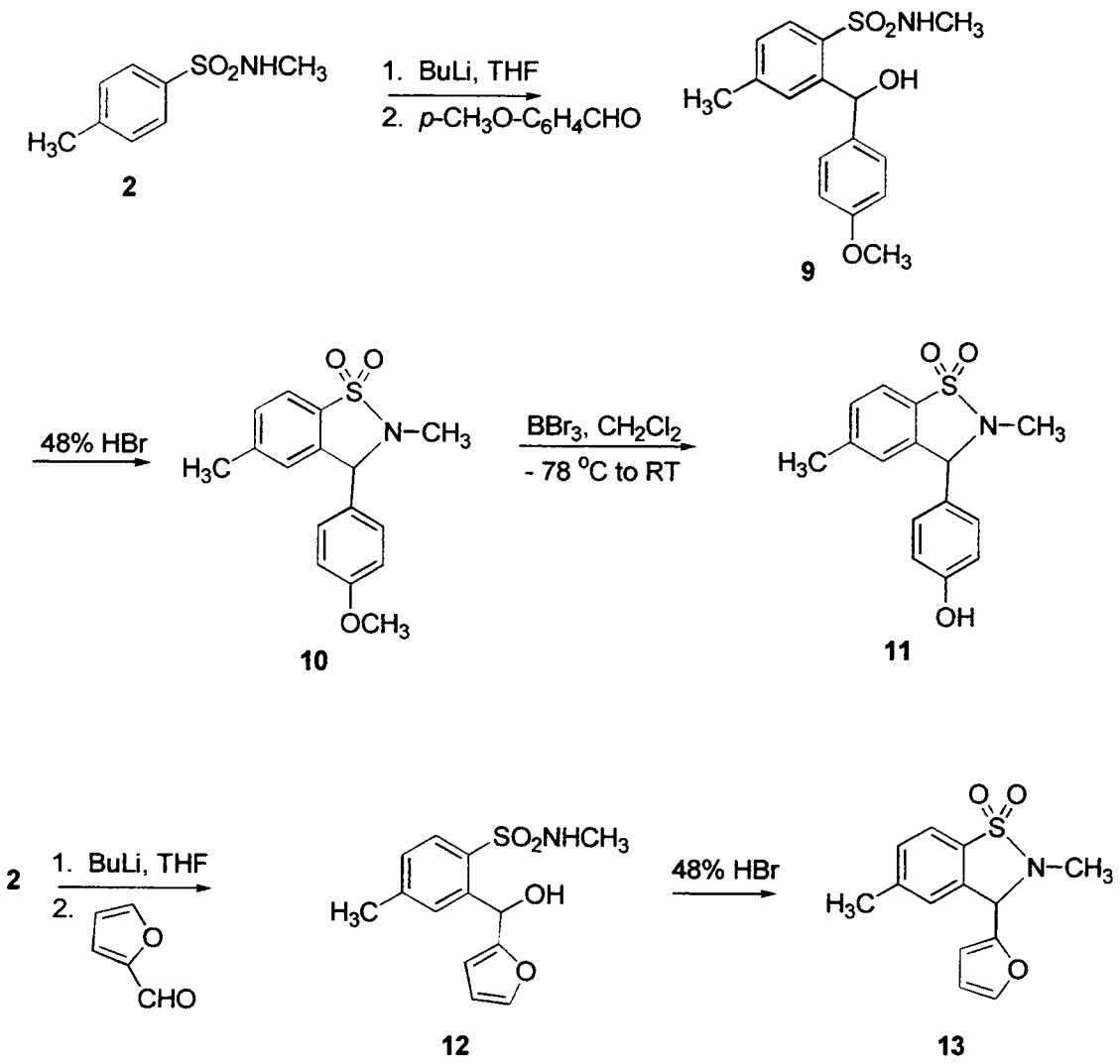
A. Synthesis and Anti-HIV-1 Evaluation of Sultam Analogs

The molecular modeling staff at the NCI had suggested that the A-ring of the lead compound be modified in order to enhance its anti-HIV-1 activity. We decided to make some 5-methyl analogs of the lead compound. The obvious starting material was *N*-methyl *p*-toluenesulfonamide (**2**), which was made from *p*-toluenesulfonyl chloride by reaction with methyl amine (see Scheme 12). Compound **2** was lithiated with 2.5 M *n*-BuLi in hexanes to generate a dilithiated intermediate *in situ*, which on treatment with benzaldehyde afforded in 86% yield the hydroxy sulfonamide **3**.[122] Dehydration of **3** with concd H_2SO_4 yielded the desired product **4** in 83% yield.[122] Similarly, by using acetophenone and condensing it with the dilithiated intermediate generated *in situ* from **2**, compound **5** was obtained in 64% yield. Cyclization of **5** was done at reflux in 48% HBr to afford compound **6** in 83% yield.[122] The 4-fluoro analog **8** was obtained in a similar manner as compound **3** using 4-fluorobenzaldehyde.

Treatment of the dilithiated intermediate generated from **2** with 4-methoxybenzaldehyde, yielded the hydroxy sulfonamide **9** (see Scheme 13). But attempts to cyclize **9** with concd H_2SO_4 did not yield the desired product **10**. The H_2SO_4 method failed, possibly due to the sulfonation of the aromatic ring containing the methoxy group. Cyclization of **9** was performed at room temperature using 48% HBr. Demethylation of compound **10** was done using BBr_3 to afford the phenol **11** in 90% yield.[123,124] In order to make the five-membered ring analog with a heteroatom in the ring, 2-furaldehyde was



Scheme 12. Synthesis of sultam analogs **4**, **6**, and **8**.



Scheme 13. Synthesis of sultam analogs **10**, **11**, and **13**.

condensed with the dilithiated intermediate generated from **2** to afford compound **12** in 86% yield. Cyclization using concd H_2SO_4 failed in this case too, but compound **13** was obtained in 84% yield using 48% HBr.

Dr. Shijia Yan, in our laboratory had made some 5-chloro analogs of the lead compound using a different synthetic route.[125] The 5-methyl and 5-chloro analogs were evaluated at the NCI for anti-HIV-1 activity using the XTT assay.[109] These were found to be inferior to the lead compound in their anti-HIV-1 activity. These results are summarized in Table 8.

We therefore turned our attention to the C-ring substituted analogs of the lead compound. We also wanted to look at the effect on anti-HIV activity of replacing the *N*-methyl group by other alkyl groups. This had been done in the 5-chloro series, were the *N*-methyl group had been replaced by *N*-ethyl and *N*-propyl groups, but because of the presence of a chloro substituent in the A-ring, it was not possible to draw firm conclusions from the test data.

The C-ring substituted compounds were made using *N*-methyl benzenesulfonamide **(15)** as the common starting material, which was prepared by treatment of benzenesulfonyl chloride with methylamine. In a manner similar to compound **2, 15** was lithiated using 2.5 M *n*-BuLi in hexanes to produce a dilithiated intermediate *in situ,* which on treatment with 2-chlorobenzaldehyde afforded the hydroxysulfonamide **16** in 81% yield. Compound **16** was easily cyclized to **17** in 92%

Table 8. Anti HIV-1 evaluation data for (±)-sultam analogs.

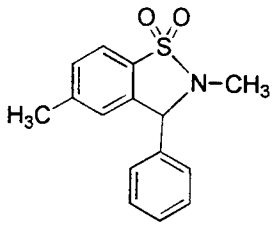
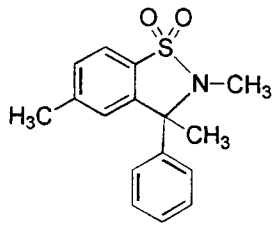
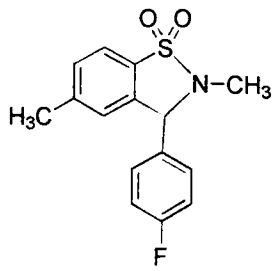
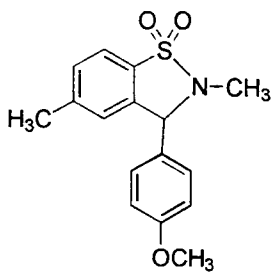
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **4 (NSC 696208)**	2.69×10^{-5} to 3.50×10^{-5}	1.56×10^{-4} to $> 2.00 \times 10^{-4}$	$> 5.72 \times 10^{0}$ to 5.79×10^{0}	Moderate
 **6 (NSC 696207)**	–	8.04×10^{-5} to 1.34×10^{-4}	–	Inactive
 **8 (NSC 698620)**	–	2.42×10^{-5} to 1.35×10^{-4}	–	Inactive
 **10 (NSC 696995)**	–	$> 2.00 \times 10^{-4}$	–	Inactive

Table 8, continued.

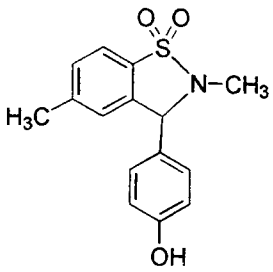
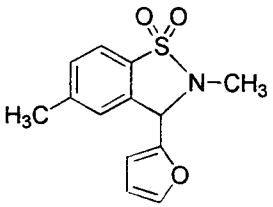
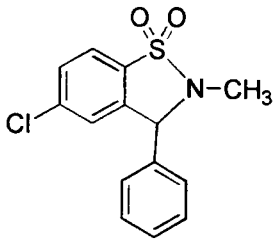
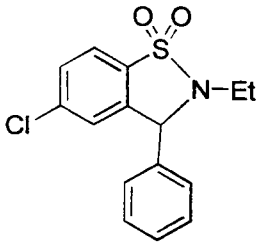
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **11 (NSC 696994)**	–	1.40×10^{-4} to 1.41×10^{-4}	–	Inactive
 **13 (NSC 698224)**	–	$> 2.00 \times 10^{-4}$	–	Inactive
 **(NSC 696209)**	1.42×10^{-5} to 3.85×10^{-5}	7.95×10^{-5} to $> 2.00 \times 10^{-4}$	2.92×10^{0} to $> 1.34 \times 10^{+1}$	Moderate
 **(NSC 696210)**	1.26×10^{-5} to 3.04×10^{-5}	4.38×10^{-5} to 7.38×10^{-5}	2.11×10^{0} to 4.96×10^{0}	Moderate

Table 8, continued.

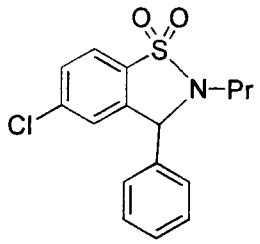
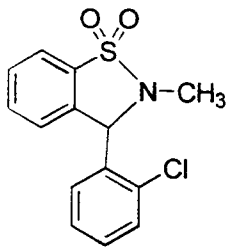
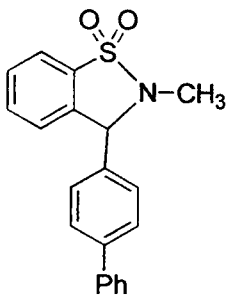
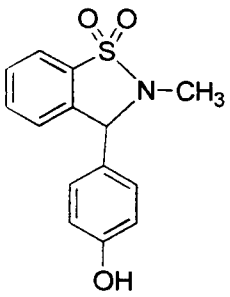
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **(NSC 696211)**	–	3.00×10^{-5} to 4.54×10^{-5}	–	Inactive
 **17 (NSC 700888)**	4.60×10^{-8} to 1.40×10^{-6}	$> 2.00 \times 10^{-6}$ to 3.98×10^{-5}	$> 1.43 \times 10^{+1}$ to $> 4.35 \times 10^{+2}$	Active
 **(NSC 699061)**	–	$> 2.00 \times 10^{-4}$	–	Inactive
 **38 (NSC 698622)**	–	$> 2.00 \times 10^{-4}$	–	Inactive

Table 8, continued.

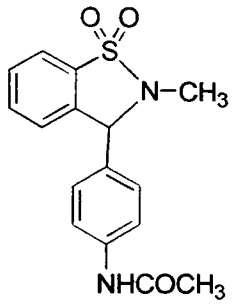
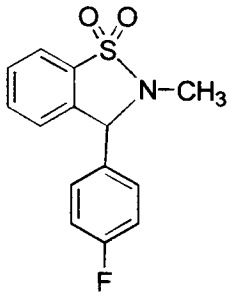
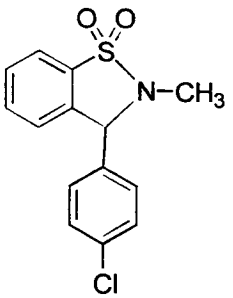
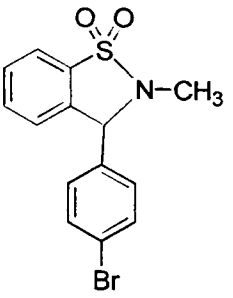
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **22 (NSC 700387)**	–	$> 2.00 \times 10^{-4}$	–	Inactive
 **(NSC 698223)**	2.19×10^{-5} to 5.36×10^{-5}	1.11×10^{-4} to $> 2.00 \times 10^{-4}$	2.08×10^{0} to $> 7.64 \times 10^{0}$	Moderate
 **(NSC 701268)**	1.96×10^{-5}	1.77×10^{-5} to 2.90×10^{-5}	1.48×10^{0}	Inactive
 **(NSC 699065)**	9.79×10^{-6} to 1.22×10^{-5}	3.34×10^{-5} to 4.28×10^{-5}	2.77×10^{0} to 4.38×10^{0}	Moderate

Table 8, continued.

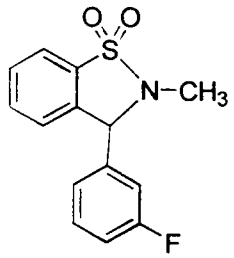
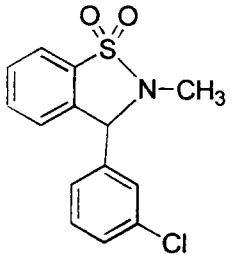
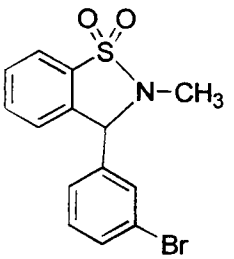
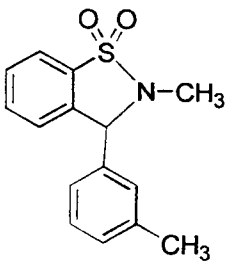
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **(NSC 700889)**	9.95×10^{-8} to 3.05×10^{-7}	4.88×10^{-5} to 7.44×10^{-5}	$2.44 \times 10^{+2}$ to $5.11 \times 10^{+2}$	Active
 **(NSC 698619)**	1.19×10^{-7} to 9.15×10^{-7}	4.58×10^{-5} to $> 2.00 \times 10^{-4}$	$5.01 \times 10^{+1}$ to $> 1.68 \times 10^{+3}$	Active
 **(NSC 700388)**	1.28×10^{-7} to 2.35×10^{-6}	2.50×10^{-5} to 9.19×10^{-5}	$1.23 \times 10^{+1}$ to $2.76 \times 10^{+2}$	Active
 **(NSC 701294)**	3.40×10^{-8} to 3.82×10^{-8}	$> 2.00 \times 10^{-5}$	$> 5.23 \times 10^{+2}$ to $> 5.87 \times 10^{+2}$	Active

Table 8, continued.

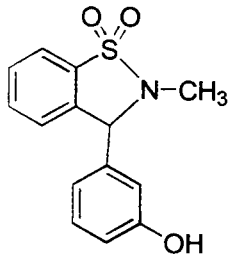
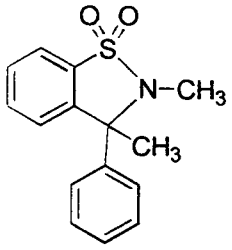
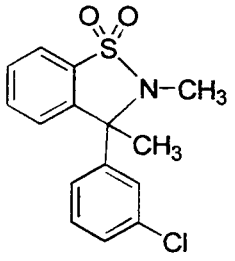
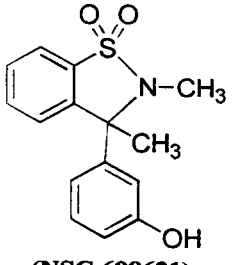
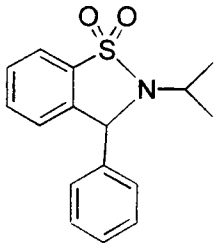
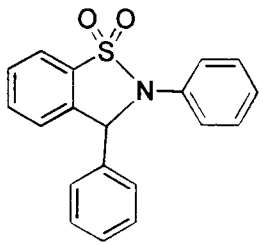
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **(NSC 698222)**	6.08×10^{-6} to 2.79×10^{-5}	$> 2.00 \times 10^{-4}$	$> 7.17 \times 10^{0}$ to $3.29 \times 10^{+1}$	Moderate
 **(NSC 108408)**	2.61×10^{-6} to 6.44×10^{-6}	1.12×10^{-4} to 1.25×10^{-4}	$1.74 \times 10^{+1}$ to $4.40 \times 10^{+1}$	Active
 **(NSC 701753)**	1.24×10^{-7} to 2.47×10^{-7}	2.43×10^{-5} to 4.08×10^{-5}	$9.84 \times 10^{+1}$ to $2.02 \times 10^{+2}$	Active
 **(NSC 698621)**	8.90×10^{-6} to 6.71×10^{-5}	$> 2.00 \times 10^{-4}$	$> 2.98 \times 10^{0}$ to $> 2.25 \times 10^{+1}$	Moderate

Table 8, continued.

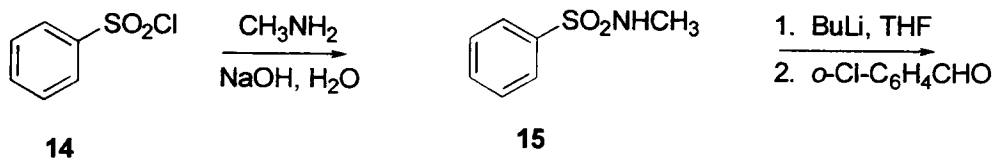
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **20 (NSC 700386)**	2.13×10^{-6} to 4.07×10^{-6}	3.12×10^{-5} to 9.69×10^{-5}	$1.16 \times 10^{+1}$ to $2.68 \times 10^{+1}$	Active
 **(NSC 699063)**	–	$> 2.00 \times 10^{-4}$	–	Inactive

NSC 696209, NSC 696210 and NSC 696211 were made by Dr. Shijia Yan.
NSC 698223, NSC 699061, NSC 698619, NSC 700388 and NSC 699063 were made by Mr. James Miller.
NSC 699065, NSC 700889, NSC 701294, NSC 108408 and NSC 701753 were made by Ms. Sarah Sanzenbacher.

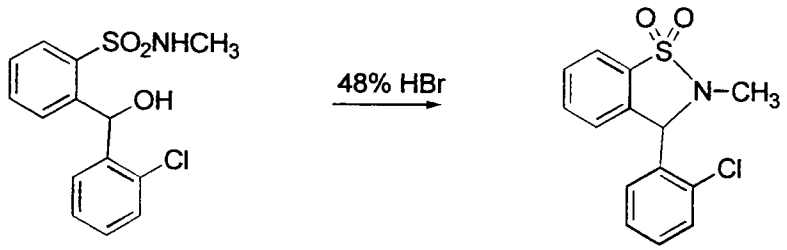
yield using H_2SO_4 (Scheme 14). Most of the other C-ring substituted analogs were made by James Miller and Sarah Sanzenbacher, two summer students who worked with me on this project.

An *N*-isopropyl analog **20** was made in a similar manner from *N*-isopropyl benzenesulfonamide **18** and benzaldehyde (Scheme14). A *N*-phenyl analog was made by James Miller. A few analogs, like compound **6**, that had methyl group at the stereogenic center were also synthesized using the appropriate ketones. These compounds were evaluated for anti-HIV-1 activity at the National Cancer Institute using the XTT assay.[109] The results are summarized in Table 8.

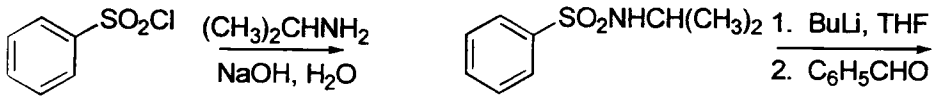
Some very interesting anti-HIV-1 results were obtained for these sultam analogs summarized in Table 8. As stated before substitution in the 5-position of the A-ring led to diminished anti-HIV-1 activity. Substitution in the C-ring yielded mixed results. Substitution at the meta position of the C-ring with a halogen or a methyl led to enhanced activity. The presence of a polar hydroxy group at the meta position resulted in moderate activity. Analogs with nonpolar substituents, like a halogen atom, at the para position showed moderate activity. Surprisingly, the *p*-choro analog was inactive. Presence of polar substituents, such as a hydroxy or an acetamido group or a bulky substituent, like a phenyl group at the para-position, resulted in loss of activity. An *o*-chloro analog, which was the only ortho-substituted analog tested, was found to be very active. The presence of an nonpolar methyl group at the stereogenic carbon had a favorable effect on activity. In addition to the stereogenic methyl group, a nonpolar chloro group at the meta-position led to enhanced activity. But, if the non-polar chloro group at the meta-position was



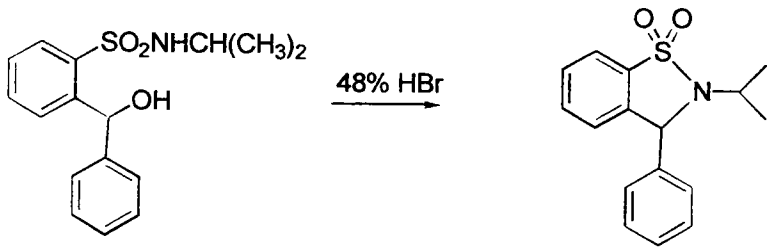
14 **15**



16 **17**



14 **18**



19 **20**

Scheme 14. Synthesis of sultam analogs **17** and **20.**

replaced by a polar hydroxy group, it led to diminished activity. The *N*-isopropyl analog of the lead compound was found to be active, whereas, the *N*-phenyl analog was inactive. From these anti-HIV data a structure–activity relationship profile can be mapped out. It can be easily seen that both steric and electronic factors play a important role in determining the anti-HIV activity of these compounds. Steric factors play a major role, while electronic factors are the minor contributors. The active site in these compounds is the region between the nitrogen atom on the B-ring and the meta-position of the C-ring. Presence of small, nonpolar group in this region leads to enhanced anti-HIV-1 activity.

B. Resolution of the Lead Compound NSC 108406 and Other Analogs into their Enantiomers on a Chiralcel OD HPLC Column

The lead compound, (±)-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide, was resolved into its (+)-enantiomers (**NSC 694444**, t_R = 19.1 min) and (−)-enantiomer (**NSC 694445**, t_R = 28.4 min) on a Chiralcel OD HPLC column using hexanes–2-propanol (9:1) as the eluent and a flow rate of 3 mL/min.. The *p*-methyl (C-ring substituents) analogs was resolved into its (+)-enantiomers (**NSC 700384**, t_R = 14.1 min) and (−)-enantiomer (**NSC 700385**, t_R= 20.1 min) on this column using the same conditions. In a similar manner, the *m*-chloro (C-ring substituent) analog was resolved into its (+)-enantiomers (**NSC 701751**, t_R = 18.7 min) and (−)-enantiomer (**NSC 701752**, t_R= 26.0 min) on this column. The anti-HIV-1 evaluation data of these compounds are summarized in Table 9. The *p*-methoxy (C-ring substituent) analog **35**

Table 9. Anti HIV-1 evaluation data for (+)- and (−)-sultam analogs.

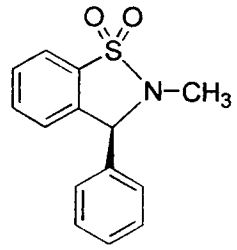
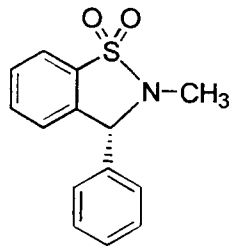
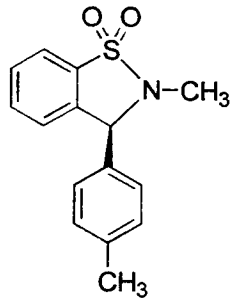
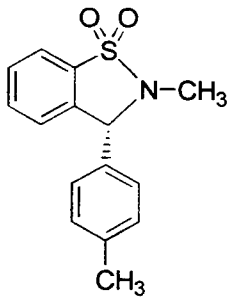
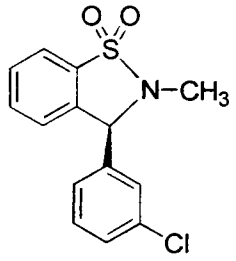
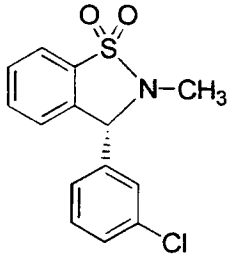
Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **30 (NSC 694444)**	4.58×10^{-7} to 4.83×10^{-7}	$> 3.16 \times 10^{-4}$	$> 6.54 \times 10^{+2}$ to $> 6.90 \times 10^{+2}$	Active
 **31 (NSC 694445)**	–	$> 3.16 \times 10^{-4}$	–	Inactive
 **(NSC 700384)**	6.82×10^{-7} to 2.65×10^{-6}	2.97×10^{-5} to $> 2.00 \times 10^{-4}$	$4.36 \times 10^{+1}$ to $> 2.03 \times 10^{+2}$	Active
 **(NSC 700385)**	–	3.22×10^{-5} to 7.60×10^{-5}	–	Inactive

Table 9, continued.

Compound	EC_{50} (M)	IC_{50} (M)	$TI_{50} = IC_{50}/EC_{50}$	Activity
 **(NSC 701751)**	4.07×10^{-8} to 1.38×10^{-7}	$> 2.00 \times 10^{-6}$	$> 1.45 \times 10^{+1}$ to $> 4.92 \times 10^{+1}$	Active
 **(NSC 701752)**	4.89×10^{-6} to 9.43×10^{-6}	3.66×10^{-5} to 3.71×10^{-5}	3.94×10^{0} to 7.48×10^{0}	Moderate

NSC 701751 and NSC 701752 were made by Mr. James Miller.

was also resolved into its enantiomers on this column. The enantiomers of **35** have been submitted to the NCI for anti-HIV-1 evaluation and the results are not available at this time. An interesting feature about these separations is that in every case the (+)-enantiomer eluted from the column before the (−)-enantiomer. The interaction between the enantiomers and the column's stationary phase can be compared to that of an enzyme and a substrate.

It can be seen form the data in Table 9 that only the (+)-enantiomer (**NSC 694444**) of the lead compound was active. The same was true in the case of *p*-methyl analog. In the case of the *m*-chloro analog the (+)-enantiomer (**NSC 701751**) was active, whereas, the (−)-enantiomer (**NSC 701752**) showed only moderate activity.

C. Determination of the Absolute Configuration of the Enantiomers of the Lead Compound NSC 108406

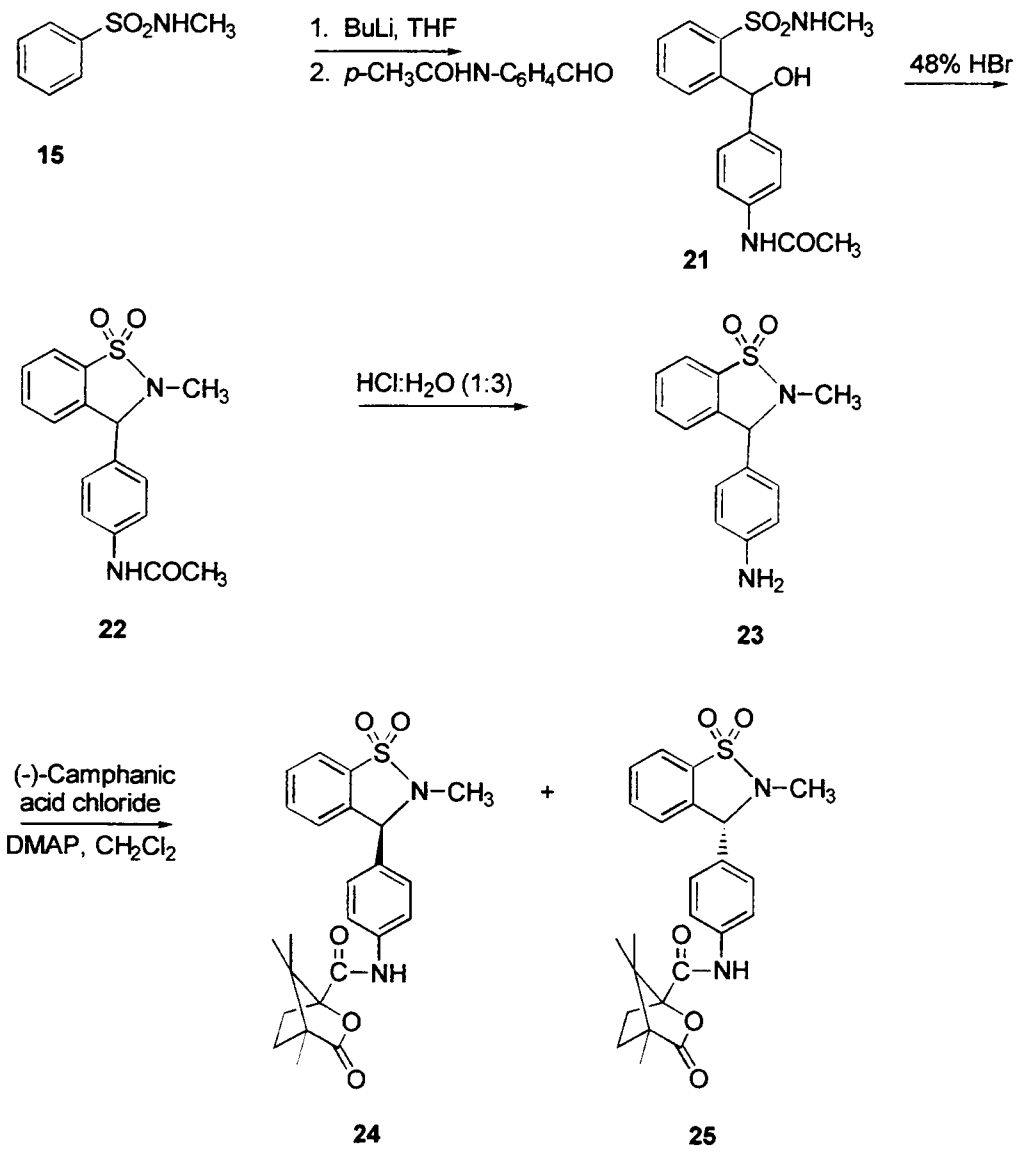
A key aspect that needed to be addressed was the absolute configuration of the enantiomers of the lead compound (**NSC 108406**). This information would be valuable in understanding how the molecule fits into the reverse transcriptase enzyme and thus help in designing more potent inhibitors. The molecular modeling staff at the NCI had assigned the (+)-enantiomer to have a 'R' absolute configuration based on molecular modeling that seemed to best relate areas of hydrophobic binding to the complementary binding domains within the active site on HIV reverse transcriptase. The lead compound, did not have a OH or NH_2 group which could be used to convert a racemic compound

into pair of diastereomeric esters or amides by reaction with either enantiomer of a chiral acid chloride, like camphanic acid chloride.

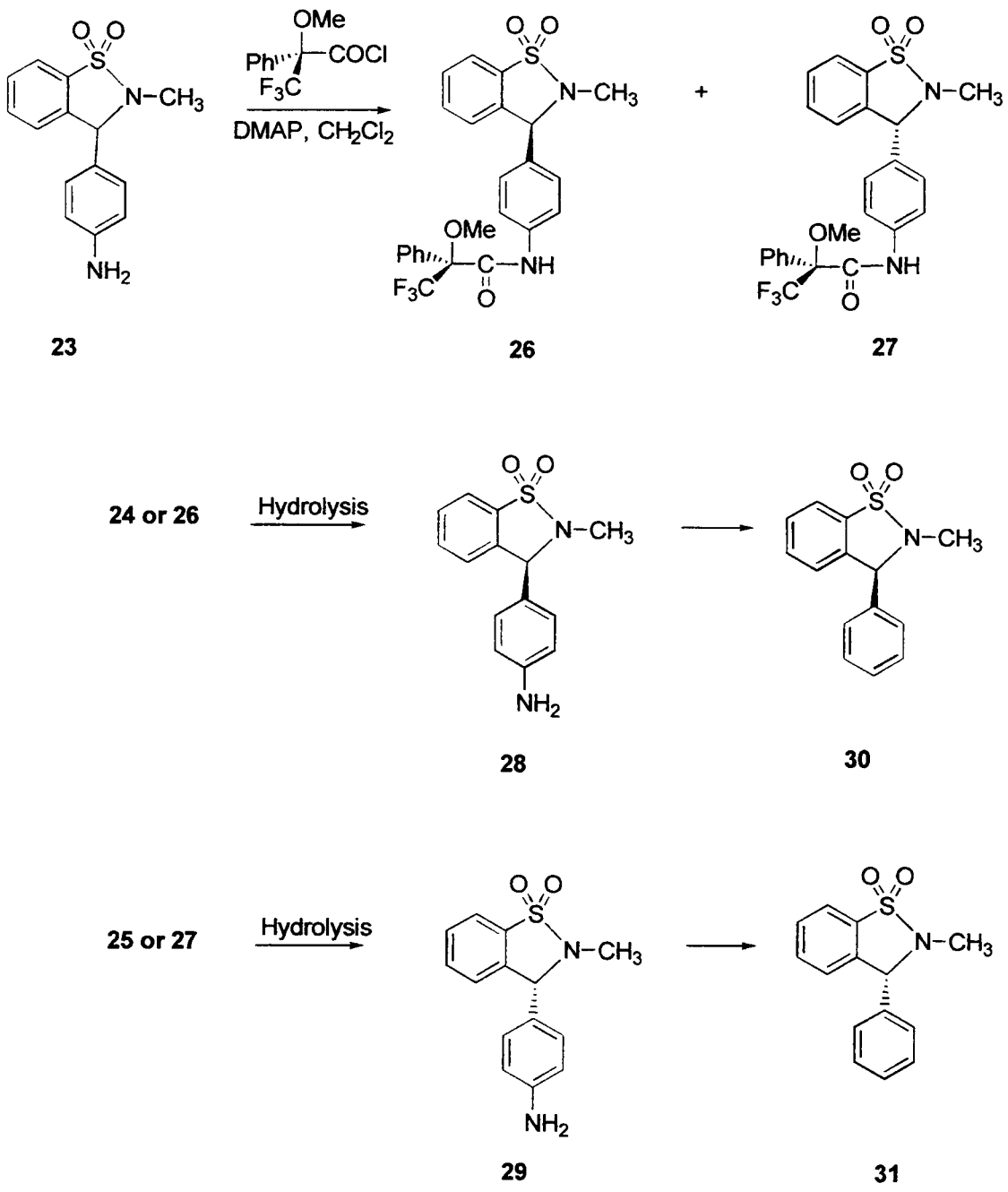
So, our first strategy was to start with an analog that had an amino group in the molecule, convert it to a pair of diastereomeric amides by reaction with either enantiomer of the Mosher acid chloride or camphanic acid chloride, separate the diastereomers, hydrolyze the amides to generate the individual enantiomers of the amino analog, and finally, remove the amino group to obtain the enantiomers of the lead compound. We hoped that by determining the single-crystal X-ray structure of one of the diastereomeric amides, we would be able to determine the absolute configuration for the enantiomers of the lead compound. The sequence of $-NH(C=O)R \rightarrow -NH_2 \rightarrow H$ would serve to relate the amide directly to the parent (unsubstituted) compound by the sequence of (a) amide hydrolysis, followed by (b) deamination.

Our first task was to make the *p*-amino derivative **23** of the lead compound (Scheme 15). *N*-methyl benzenesulfonamide (**15**) was lithiated using 2.5 M *n*-BuLi in hexanes to generate the dilithiated intermediate *in situ*, which was condensed with commercially available *p*-acetamidobenzaldehyde to yield compound **21**.[122] Cyclization of **21** to the *p*-acetamido derivative **22** was effected using 48% HBr.[122] The *p*-acetamido group was hydrolyzed at reflux using a 1:3 mixture of $HCl–H_2O$ to yield the *p*-amino derivative **23**.[126]

The *p*-amino derivative **23** was converted into a pair of distereomeric amides **24** and **25** by treatment with (−)-camphanic acid chloride and DMAP in CH_2Cl_2.[127–131] The diastereomers could not be separated on a regular silica gel column as only one spot was



Scheme 15. Initial strategies to resolve the lead compound into its enantiomers **30** and **31**.



Scheme 15, continued.

seen on TLC for the two compounds. Attempts to separate the diastereomers **24** and **25** on Diacel's Chiralcel OD HPLC column were not successful either, even though two peaks were seen. The presence of the amide function results in a lot of tailing and hence peaks overlapped when separation was attempted on a preparative scale (100-μL injection). We wanted to see if the amides **24** and **25** could be hydrolyzed before we proceeded any further with their separation, as there was no point separating them if they could not be hydrolyzed to the amine. So, we set about attempting to hydrolyze the diastereomeric amides **24** and **25** as a mixture. This amide mixture could not be hydrolyzed with a 1:3 mixture of HCl–H_2O at reflux. Refluxing in concd HCl, 5% NaOH or treatment with TMSI at room temperature, however, did not yield the desired amino compound.

We then made the Mosher amides **26** and **27** from the amine **23** by treatment with (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and DMAP in CH_2Cl_2 (Scheme 15).[111] Attempts to hydrolyze the diastereomeric amides **26** and **27** as a mixture with HCl–H_2O (1:3) at reflux, concd HCl at reflux, and 40% NH_3 in MeOH at room temperature only resulted in recovery of the starting material. Separation of **26** an **27** on a silica gel column was not possible as only one spot was seen on TLC. The problem encountered with the camphanyl amides **24** and **25,** was observed when we attempted to separate **26** and **27** on Diacel's Chiralcel OD HPLC column.

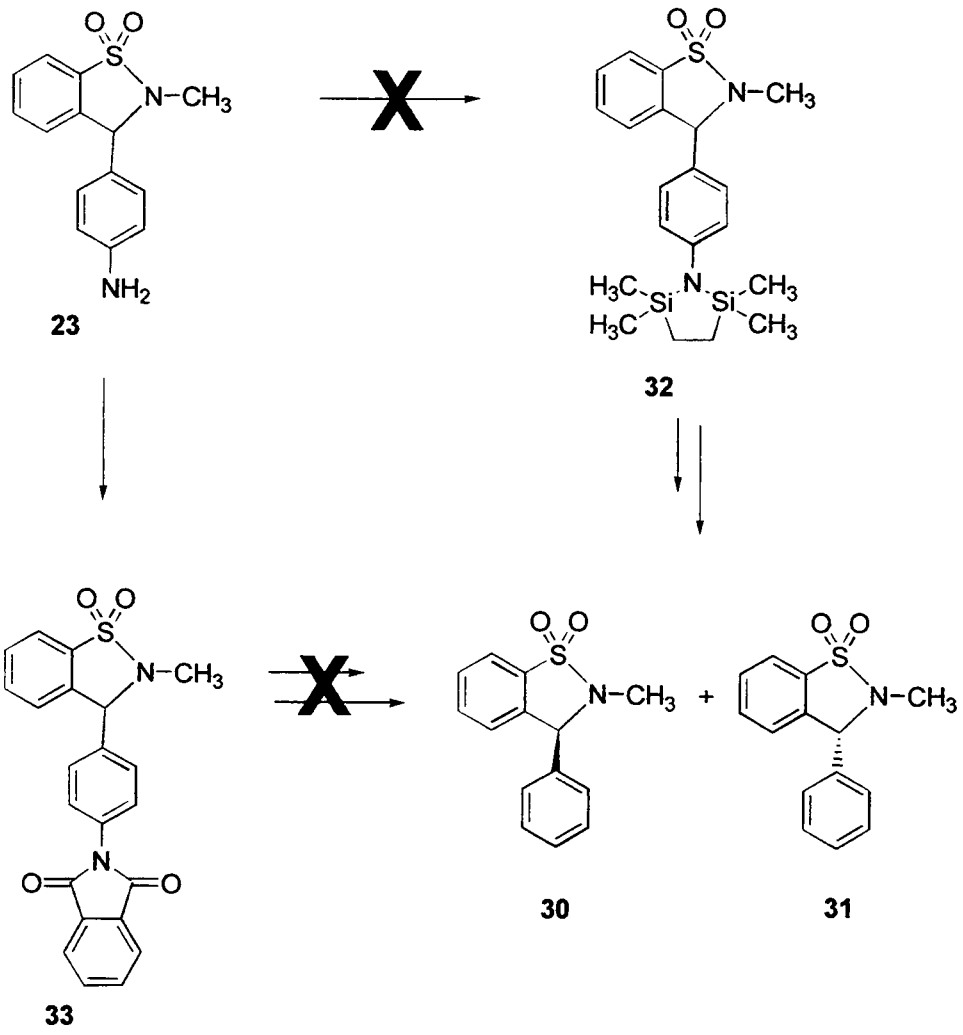
We then attempted to separate the *p*-amino compound **23** into its enantiomers on the Chiralcel OD HPLC column. But, more tailing and overlapping of peaks was observed as the amine **23** is more basic then the above amides. An additional problem

was the poor solubility of amine **23** in solvents that could be used in Chiralcel OD column, and hence, the amount of compound that could be loaded per each injection was rather small.

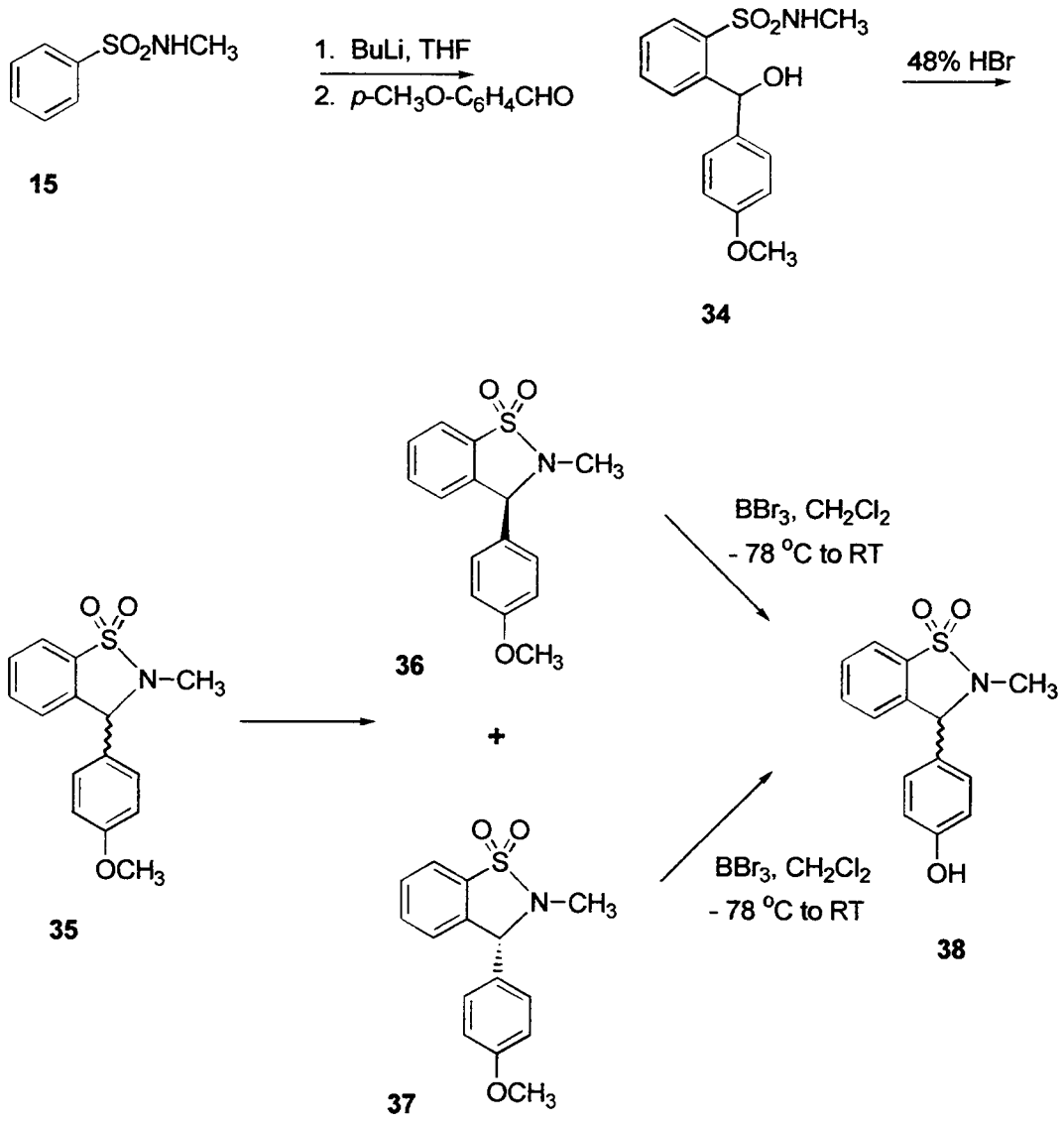
We decided to convert **23** into a silyl derivative **32** in order to reduce tailing of the peaks, which could result in better separation on the Chiralcel OD HPLC column. But, unfortunately, compound **32** could not be made by reacting amine **23** with 1,2-bis(chlorodimethylsilyl)ethane and *n*-BuLi or NaH (Scheme 16).[132,133] Attempts to make compound **32** from **23** using 1,1′-ethylenebis(*N*,*N*,1,1-tetramethylsilanamine) and ZnI_2 was not successful either (Scheme 16).[134]

The amine **23** was refluxed with phthalic anhydride in $CHCl_3$ to yield the pthalimido derivative **33** in 68% yield (Scheme 16).[135] We hoped we could separate this compound into its enantiomers on the Chiralcel OD HPLC column, as tailing should reduce for a less basic diamide with no hydrogens on the nitrogen atom. Then, the phthalimido function of each enantiomer could be hydrolyzed to obtain the free amines. Unfortunately, compound **33** tended to stick to the Chiralcel OD HPLC column and had to be flushed out of the column using 1:1 hexanes–2-propanol as the eluent. As things did not work the way we anticipated, we decided to abandon the approach of using the *p*-amino analog **23** to determine the absolute configuration of the enantiomers of the lead compound, **NSC 108406**.

Our next approach was to make the *p*-methoxy analog **35** (Scheme 17), separate the enantiomers on the Chiralcel OD HPLC column, and then demethylate each enantiomer to obtain the enantiomers (**41** and **42**) of the *p*-hydroxy compound **38**. We



Scheme 16. Unsuccessful attempts to synthesize compounds **30** and **31** from **23**.



Note. Separated **35** into its enantiomers **36** and **37** on a Chiralcel OD HPLC column

Scheme 17. Attempted synthesis of the enantiomers of compound **38**.

then hoped to take either **41** or **42** and convert it to a camphanyl ester **39** or **40** using (−)-camphanic acid chloride and DMAP in CH_2Cl_2.[127–131] We should then be able to crystallize the camphanyl ester and obtain a single-crystal X-ray structure. This would give us the absolute configuration of the enantiomers (**41** and **42**) of the *p*-hydroxy analog **38**, which could safely be extended to the lead compound.

We needed to make the *p*-methoxy analog **35** for two reasons: the first reason was that the OH group had to be protected before it was condensed with the dilithiated intermediate generated *in situ* by the reaction of **15** with *n*-BuLi. Secondly, we felt that it would be easier to separate the *p*-methoxy rather than the *p*-hydroxy compound on the Chiralcel OD HPLC column, as the *p*-methoxy analog was less polar.

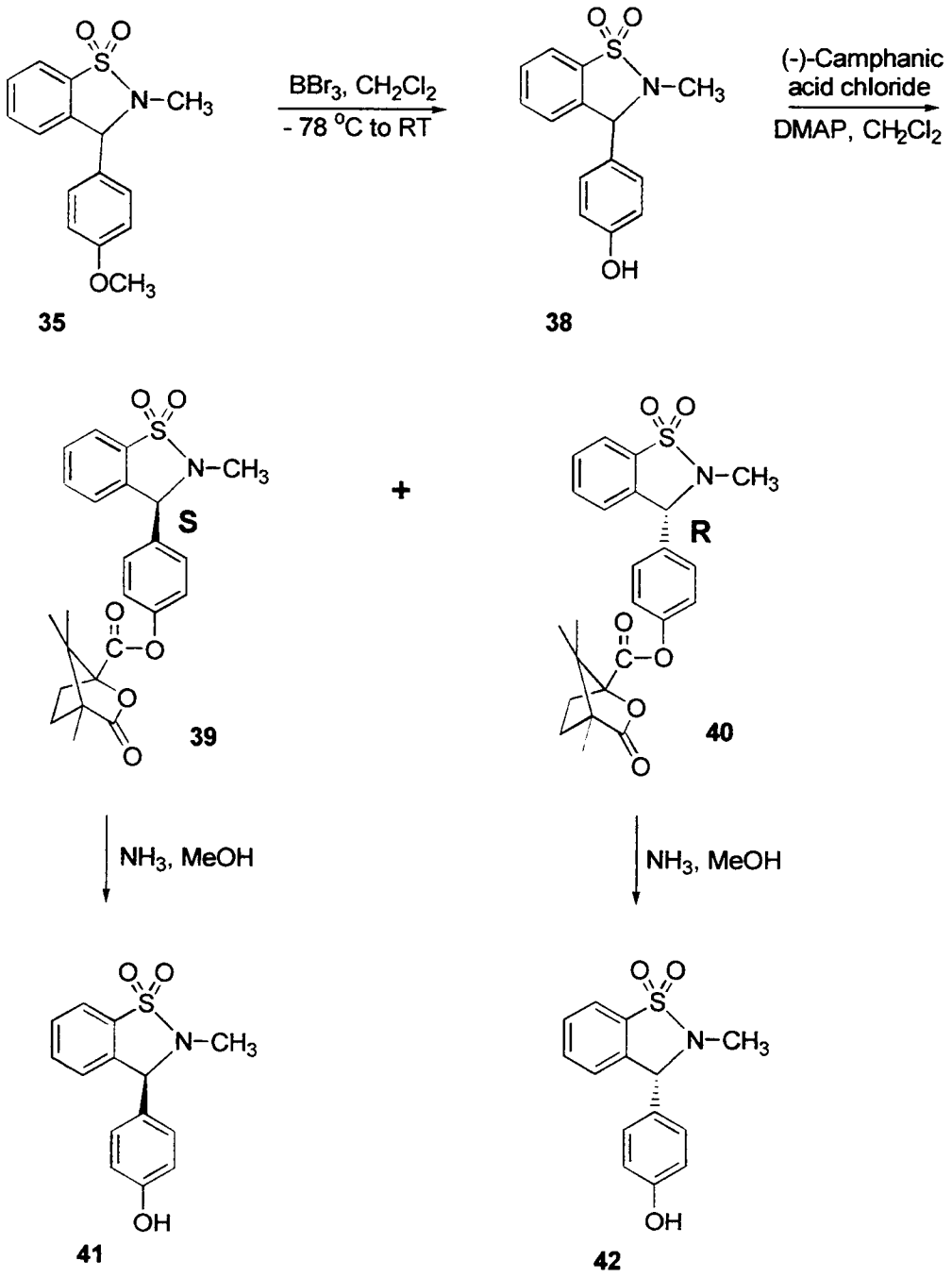
N-methyl benzenesulfonamide (**15**) on treatment with 2.5 M *n*-BuLi in hexanes yielded the dilithiated intermediate *in situ*, which was condensed with *p*-anisaldehyde to yield compound **34** in 95% yield. Compound **34** was cyclized to the *p*-methoxy analog **35** in 84% yield using 48% HBr. Compound **35** was separated into its enantiomers **36** and **37** on the Chiralcel OD HPLC column (Scheme 17). When **36** was demethylated using boron tribromide[123,124] and the product was analyzed on the Chiralcel OD HPLC column, we found two peaks to our surprise. The same result was obtained with **37**. To our dismay, we found that the optical rotation's of the demethylated products were also zero. Racimization had taken place during demethylation of **36** an **37**, and so the same product **38** was obtained in either case.

As a last resort, we took compound **35** and demethylated it to **38** using BBr_3 in CH_2Cl_2.[123,124] The phenol **38** was converted into a pair of diastereomeric esters **39** and **40**

using (−)-camphanic acid chloride and DMAP in CH_2Cl_2.[127–131] Compounds **39** and **40** were not separable on a regular silica gel column. They were separated on the Chiralcel OD HPLC column using hexanes–2-propanol (85:15) as the eluent and a flow rate of 3 mL/min. Even in this case there was some overlap of the two peaks when separation was done on a preparative scale (100 μL injection). The (+)-camphanyl ester **39** was hydrolyzed with 40% NH_3 in MeOH to yield the (+)-phenol **41** in 95% yield.[136] In a similar manner, the (−)-camphanyl ester **40** gave the (−)-phenol **42** (Scheme 18).

Compound **39** was crystallized from hexanes–ethyl acetate, and its single-crystal X-ray structure was obtained. The absolute configuration of the stereogenic center (C-3 carbon of the sultam ring) was assigned as 'S', relative to the known '1*S*' configuration of the (−)-camphanic acid chloride moiety. Therefore, the (+)-phenol **41** also has the 'S' absolute configuration. The ORTEP view of compound **39** as 50% thermal ellipsoid is shown in Figure 14 and the crystal structure data is given in Table 10. The crystallographic coordinates of this molecule were read into the molecular modeling program SYBYL as protein database (pdb) format file, and the absolute configuration of the stereogenic centers in compound **39** was confirmed. The absolute structure of compound **39** generated using SYBYL is shown in Figure 15.

As the lead compound and the *p*-hydroxy analog **38** have the same carbon skeleton, and since a remote OH group should not reverse the sign of optical rotation, we safely concluded that the stereogenic center of the (+)-enantiomer of the lead compound (**NSC 694444**) also had a 'S' configuration. This was contrary to predications of the molecular modeling personnel at the NCI. Further proof for this assignment came in the



Scheme 18. Resolution of compound **38** into its enantiomers **41** and **42**.

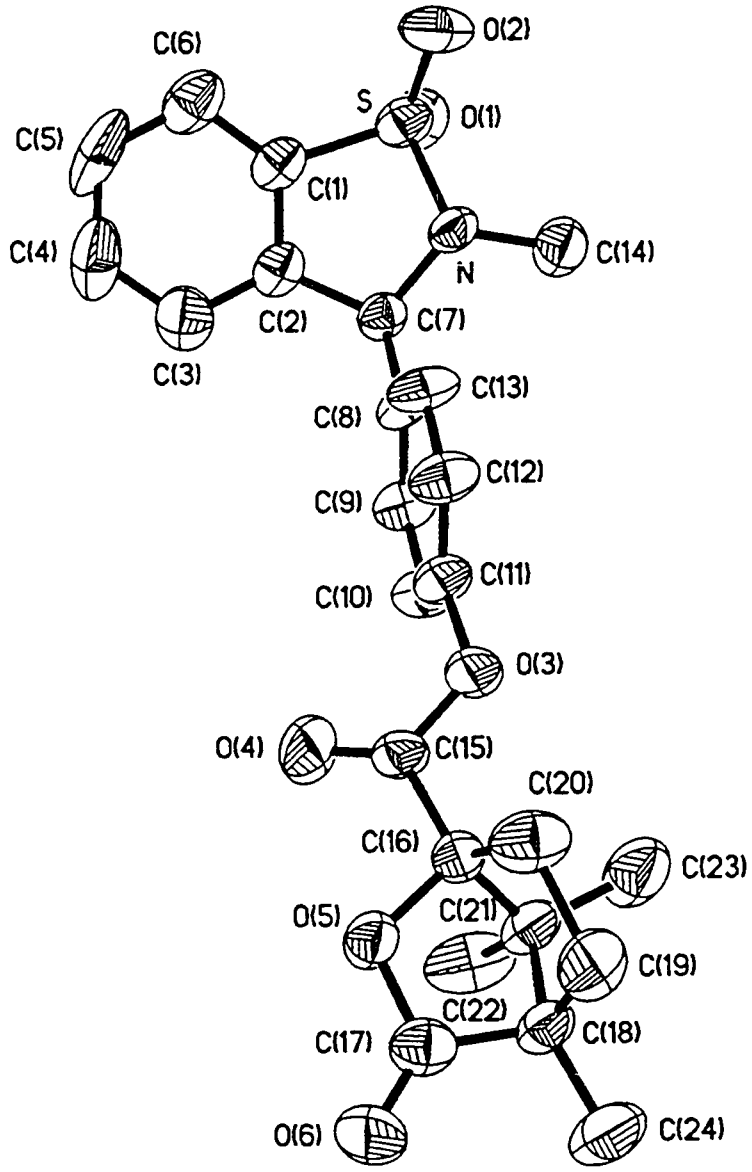
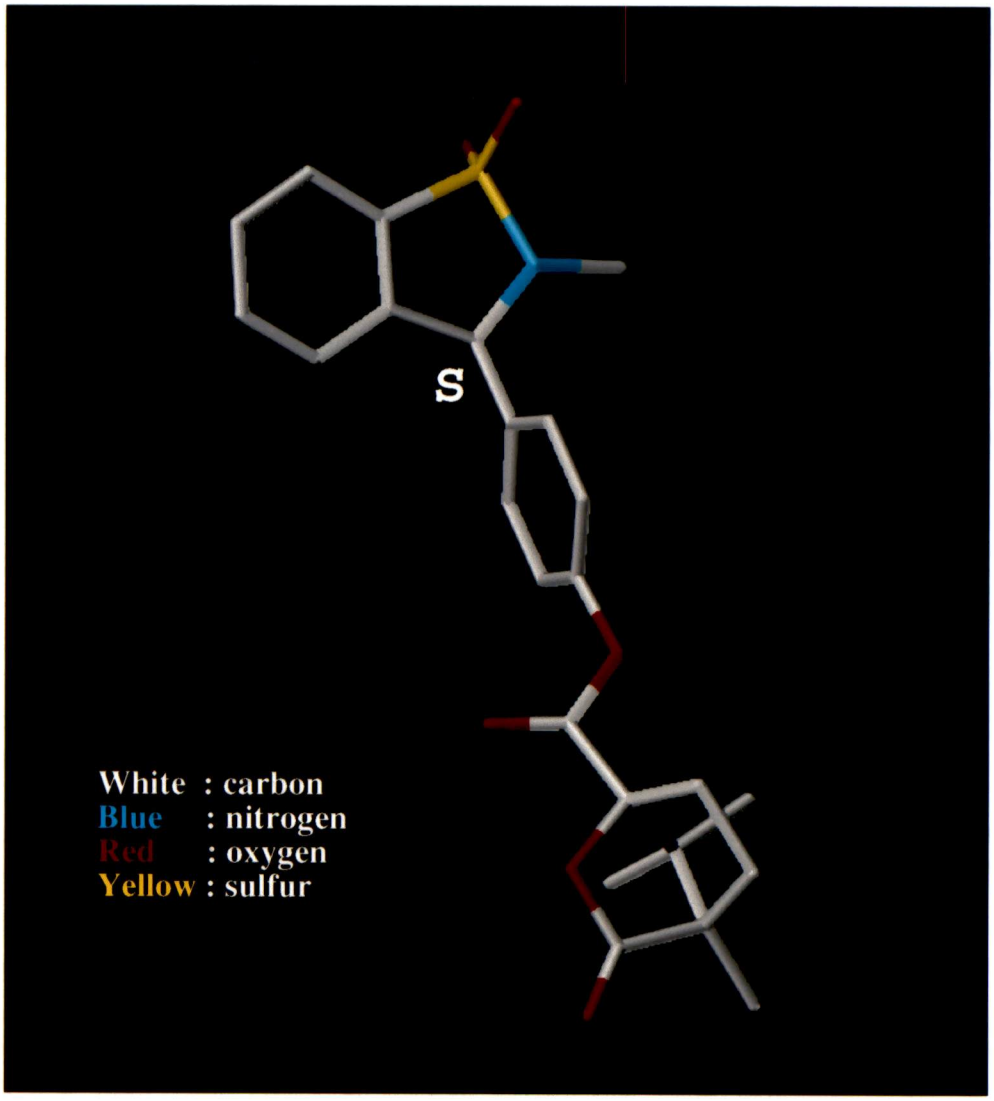


Figure 14. ORTEP view of compound **39** shown as 50% thermal ellipsoid.

Table 10. Crystal structure data for compound **39**.

Empirical formula	$C_{24}H_{25}NO_6S$	
Formula weight	455.51	
Temperature	292(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$ (no. 19)	
Unit cell dimensions	a = 6.667(3) Å	alpha = 90°
	b = 11.334(5) Å	beta = 90°
	c = 29.643(13) Å	gamma = 90°
Volume, Z	2240(2) Å^3, 4	
Density (calculated)	1.351 mg/m^3	
Absorption coefficient	0.185 mm^{-1}	
F(000)	960	
Crystal size	0.70 × 0.30 × 0.06 mm	
θ range for data collection	1.92 to 25.05°	
Limiting indices	$0 \le h \le 7$, $0 \le k \le 13$, $-31 \le l \le 35$	
Reflections collected	4150	
Independent reflections	3509 (R_{int} = 0.0484)	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3505 / 0 / 289	
Goodness-of-fit on F^2	1.156	
Final R indices [I>2σ(I)]	$R1$ = 0.0727, $wR2$ = 0.1217	
R indices (all data)	$R1$ = 0.1480, $wR2$ = 0.1570	
Absolute structure parameter	0.0(2)	
Largest diff. peak and hole	0.222 and −0.260 eÅ^{-3}	

Figure 15. The absolute structure of compound **39** generated using the SYBYL molecular modeling program.


S
White : carbon
Blue : nitrogen
Red : oxygen
Yellow : sulfur

form of single-crystal X-ray structures obtained in our laboratory by Dr. Jianmin Mao on the (+)-enantiomers of the *m*-chloro and *m*-bromo (C-ring substituents) analogs of the lead compound. The (+)-enantiomers of both these compounds were also found to have the 'S' configuration.

III. CONCLUSIONS

These compounds were shown to be extremely potent non-nucleoside HIV-1 reverse transcriptase inhibitors. Many analogs of the lead compound showed enhanced anti-HIV-1 activity over that of the lead itself. Meta, and ortho substitution on the C-ring of the lead compound by relatively nonpolar groups produced analogs that were extremely active. The lead compound was resolved into its enantiomers on Diacel's Chiralcel OD HPLC column. The (+)-enantiomer was highly active against HIV-1, while the (−)-enantiomer was inactive.

Attempts to determine the absolute configuration of the enantiomers of the lead compound was unsuccessful. Hence, a single-crystal X-ray structure of the camphanic ester of the (+)-enantiomer of the *p*-hydroxy (C-ring substitution) analog was obtained. The above ester was hydrolyzed to the *p*-hydroxy compound, which was found to be the (+)-enantiomer. The absolute configuration of the stereogenic center in (+)-enantiomer of the *p*-hydroxy analog was determined to be 'S'. As the lead compound and the *p*-hydroxy analog have the same carbon skeleton, and since a remote OH group should not reverse the sign of optical rotation, we safely concluded that the stereogenic center of the (+)-enantiomer of the lead compound (**NSC 694444**) also had the 'S' configuration.

IV. EXPERIMENTAL SECTION

A. General Methods

Melting points were determined by capillary method and are uncorrected. Analytical TLC was performed on aluminum-backed plates coated with E. Merck Silica Gel-60 F-254. The developed plates were air dried and irradiated with UV light and/or by spray–heat development using a *p*-anisaldehyde–sulfuric acid reagent. Flash column chromatography was performed on Silica Gel-60 (230–400 mesh). All HPLC separations were carried out on a Beckman System Gold instrument using Diacel's Chiralcel OD HPLC (25 cm × 1cm i.d.) column . The retention times reported are for analytical scale (20 μL) injections. Optical rotations were measured with Perkin-Elmer Model 243 automatic polarimeter for solutions in a 1-dm cell at the indicated temperature. ^{1}H and ^{13}C NMR spectra were recorded at 250.13 MHz and 62.89 MHz, respectively, on a Bruker AC 250 instrument or at 400.13 MHz and 100.61 MHz, respectively, on a Bruker AMX 400 instrument using the indicated solvent. ^{1}H NMR shifts are reported as δ (ppm) downfield from tetramethylsilane (TMS), which was used as a internal standard; multiplicities are first-order values in Hz: s, singlet; bs, broad singlet; d, doublet; t, triplet; dd, double of doublets; db, broad doublet; q, quartet; m, multiplet. ^{13}C NMR chemical shifts are reported as δ (ppm) relative to the chemical shift of the solvent used ($CDCl_3$: 77.0 ppm; DMSO-d_6: 39.5 ppm; CD_3OD: 49.0 ppm). Elemental analyses were performed by Atlantic Microlabs, Inc. of Atlanta, GA. Chemicals were of reagent grade and were used directly. Solvents were distilled and dried by literature procedures before

use. All evaporations were carried out with a rotary evaporator under vacuum and below 40 °C.

B. Preparation of Compounds 2–42

(±)-*N*-Methyl-*p*-toluenesulfonamide (2). To methylamine (40%, 4.48 mL) in water (45 mL) containing NaOH pellets (2.10 g, 52.5 mmol) was added at 0 °C *p*-toluenesulfonyl chloride (**1**, 10.0 g, 52.5 mmol) over 5 min. The reaction mixture was stirred for 3 h at 0 °C, then diluted with water and extracted with ethyl acetate (3 × 30 mL). The ethyl acetate layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to obtain a white-colored solid. The crude product was chromatographed on a silica gel column using hexanes–ethyl acetate (3:1) as the eluent to afford **2** (8.75 g, 90%): mp 75–77 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (d, 2H, J = 8.3 Hz), 7.32 (d, 2H, J = 8.2 Hz), 4.73 (bs, 1H), 2.63 (d, 3H, J = 3.9 Hz), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.44, 135.71, 129.67, 127.22, 29.23, 21.46.

(±)-2-(Hydroxyphenylmethyl)-4,*N*-dimethylbenzenesulfonamide (3). To **2** (1.0 g, 5.4 mmol) in dry THF (22 mL) was added BuLi in Hexanes (2.5 M, 5.4 mL, 13.5 mmol) at 0 °C under N_2 over 5 min. Initially, the reaction mixture turned yellow and then to a dirty green suspension after the addition was complete. The reaction mixture was stirred at 0 °C for 30 min., at which the lithation was assumed to be complete. To the suspension was added benzaldehyde (0.92 g, 8.6 mmol) in dry THF (9 mL) at 0 °C over 2–3 min. The reaction mixture first turned brown, then purple, green and finally, into a pale yellow solution when addition was complete. After stirring the reaction mixture for

45 min. at 0 °C, HCl (5%, 15 mL) was added, and the reaction mixture was allowed to warm up to room temperature. The THF layer was separated from the aqueous layer, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layer was washed with brine, dried with anhydrous $MgSO_4$, and concentrated to obtain a pale yellowish-white solid. The crude product was chromatographed on silica gel using hexanes–ethyl acetate (1:1) to yield **3** (1.4 g, 86%) as a white solid: mp 178–179 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1H, J = 7.9 Hz), 7.36 (m, 5H), 7.25 (m, 2H), 6.57 (d, 1H, J = 4.7 Hz), 3.94 (q, 1H, J = 5.2 Hz), 3.48 (d, 1H, J = 5.8 Hz), 2.38 (s, 3H), 2.34 (d, 3H, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 143.89, 141.95, 141.61, 132.94, 131.22, 130.89, 128.56, 128.37, 127.91, 126.94, 72.30, 29.27, 21.46.

(±)-2,5-Dimethyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (4). To **3** (0.500 g, 1.72 mmol) was added concd H_2SO_4 (5.0 mL) at room temperature, and the reaction mixture was stirred at that temperature for 1.5 h. The mixture was then dumped into ice and extracted with CH_2Cl_2 (3 × 15 mL), washed with saturated NaCl, and dried with anhydrous $MgSO_4$, and concentrated to remove the solvent. The crude product was chromatographed on silica gel using hexanes–ethyl acetate (3:1) to obtain compound **4** (0.39 g, 83%) as a white solid: mp 165–167 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 1H, J = 8.0 Hz), 7.35 (m, 6H), 6.82 (s, 1H), 5.15 (s, 1H), 2.74 (s, 3H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.81, 138.44, 136.65, 131.18, 130.10, 128.95, 128.90, 127.97, 120.61, 66.69, 27.22, 21.51. Anal. Calcd for $C_{15}H_{15}NO_2S{\cdot}0.15H_2O$: C 65.26, H 5.59, 5.07, S 11.62. Found: C 65.13, H 5.56, N 5.02, S 11.65.

(±)-2-(1-Hydroxyphenylethyl)-4,*N*-dimethylbenzenesulfonamide (5). The procedure used for making **3** was repeated using **2** (0.50 g, 2.7 mmol) and acetophenone (0.52 g, 4.3 mmol) to yield **5** (0.53 g, 64%) as a white solid: mp 153–155 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 1H, J = 8.2 Hz), 7.59 (s, 1H), 7.30 (m, 6H), 5.89 (s, 1H), 2.68 (q, 1H, J = 5.3 Hz), 2.47 (s, 3H), 2.11 (d, 3H, J = 5.4 Hz), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.11, 145.45, 143.48, 133.26, 132.80, 130.13, 128.22, 128.10, 127.25, 125.50, 76.29, 32.78, 29.30, 21.48.

(±)-2,3,5-Trimethyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (6). To **5** (0.24 g, 0.79 mmol) was added HBr (48%, 8.0 mL) at room temperature, and the reaction mixture was gently refluxed for 6 h. The mixture was then diluted with H_2O and extracted with CH_2Cl_2 (3 × 10 mL), washed with saturated NaCl and dried with anhydrous $MgSO_4$ and concentrated to remove the solvent. The crude product was chromatographed on silica gel using hexanes–ethyl acetate (3:1) to obtain compound **6** (0.19 g, 83%) as a white solid: mp 148–149 °C; ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 1H, J = 8.0 Hz), 7.34 (m, 6H), 6.85 (s, 1H), 2.64 (s, 3H), 2.33 (s, 1H), 1.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 144.36, 143.97, 140.32, 130.26, 129.92, 128.74, 128.16, 126.82, 124.25, 120.76, 67.18, 23.12, 21.67. Anal. Calcd for $C_{16}H_{17}NO_2S$: C 66.87, H 5.96, 4.87, S 11.16. Found: C 66.81, H 5.91, N 4.83, S 11.20.

(±)-2-[4-Fluorophenyl)hydroxymethyl]-4,*N*-dimethyl-benzenesulfonamide (7). By the same procedure used for making compound **3**, **7** was obtained from **2** (0.50 g, 2.7 mmol) and 4-fluorobenzaldehyde (0.48 g, 4.3 mmol) as a white solid (0.69 g, 83%): mp 161–162 °C ; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1H, J = 8.0 Hz), 7.35 (m, 2H),

7.23 (d, 1H, J = 8.0 Hz), 7.07 (m, 3H), 6.63 (d, 1H, J = 4.9 Hz), 4.41 (bq, 1H, J = 4.9 Hz), 3.40 (d, 1H, J = 5.0 Hz), 2.47 (d, 3H, J = 5.4 Hz), 2.35 (s, 3H); ^{13}C NMR (CD_3OD) δ 165.27, 161.39, 144.86, 144.58, 141.02, 135.18, 131.64, 130.33, 129.81, 129.67, 129.24, 115.87, 115.53, 70.37, 29.05, 21.40.

(±)-3-(4-Fluorophenyl)-2,5-dimethyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (8). The same procedure used for making compound **4** was repeated using **7** (0.20 g, 0.65 mmol) to give compound **8** (0.15 g, 80%) as a white solid: mp 94–95 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 1H, J = 8.0 Hz), 7.31 (m, 3H), 7.10 (t, 2H, J = 8.5 Hz), 6.79 (s, 1H), 5.13 (s, 1H), 2.74 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.86, 160.91, 143.96, 138.27, 132.58, 131.19, 130.25, 129.89, 129.76, 125.01, 120.66, 116.15, 115.81, 65.97, 27.23, 21.51. Anal. Calcd for $C_{15}H_{14}FNO_2S$: C 61.84, H 4.84, 4.81, S 11.01. Found: C 61.94, H 4.92, N 4.77, S 11.09.

(±)-2-[Hydroxy-(4-methoxyphenyl)methyl]-4,*N*-dimethylbenzenesulfonamide (9). By the same procedure used to synthesize compound **3**, **9** (1.3 g, 75%) was obtained from compound **2** (1.0 g, 5.4 mmol) and *p*-anisaldehyde (1.2 g, 8.6 mmol) as a white solid: mp 103–104 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1H, J = 8.0 Hz), 7.24 (m, 4H), 6.88 (d, 2H, J = 8.7 Hz), 6.56 (s, 1H), 4.22 (q, 1H, J = 5.1 Hz), 3.81 (s, 3H), 3.46 (s, 1H), 2.35 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 159.24, 143.78, 141.78, 133.95, 132.74, 130.83, 130.77, 128.32, 128.22, 113.94, 71.75, 55.28, 29.31, 21.48.

(±)-3-(4-Methoxyphenyl)-2,5-dimethyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (10). To **9** (0.140 g, 0.436 mmol) was added HBr (48%, 5.0 mL) at room temperature, and the reaction mixture was stirred for 2 h. The mixture was then diluted

with H_2O and extracted with CH_2Cl_2 (3 × 10 mL), washed with saturated NaCl, and dried with anhydrous $MgSO_4$,and concentrated to remove the solvent. The crude product was chromatographed on silica gel using hexanes–ethyl acetate (3:1) to obtain compound **10** (0.126 g, 95%) as a white solid: mp 165–166 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 1H, J = 8.0 Hz), 7.31 (d, 1H, J = 7.9 Hz), 7.24 (d, 2H, J = 8.7 Hz), 6.92 (d, 2H, J = 8.7 Hz), 6.80 (s, 1H), 5.09 (s, 1H), 3.83 (s, 3H), 2.74 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.13, 143.87, 139.01, 131.43, 130.15, 129.47, 128.59, 125.17, 120.75, 114.42, 66.40, 55.28, 27.21, 21.67. Anal. Calcd for $C_{16}H_{17}NO_3S{\cdot}0.20H_2O$: C 62.60, H 5.71, N 4.56, S 10.44. Found: C 62.56, H 5.64, N 4.49, S 10.40.

(±)-4-(2,5-Dimethyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenol (11). To **10** (0.126 g, 0.415 mmol) in dry CH_2Cl_2 (15 mL) was added BBr_3 (99+ %, 0.156 g, 0.623 mmol) at –78 °C under N_2, and the reaction mixture was allowed to gradually warm to room temperature. The reaction was complete in 3 h and was then dumped into ice and extracted with CH_2Cl_2 (3 × 10 mL), washed with saturated NaCl, and dried with anhydrous $MgSO_4$, and concentrated to remove the solvent. The crude product was chromatographed on silica gel using hexanes–ethyl acetate (1:1) to obtain compound **11** (0.108 g, 90%) as a white solid: mp 210–211 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 1H, J = 8.0 Hz), 7.32 (d, 1H, J = 8.0 Hz), 7.19 (d, 2H, J = 8.4 Hz), 6.86 (d, 2H, J = 8.6 Hz), 6.81 (s, 1H), 5.08 (s, 1H), 5.02 (s, 1H), 2.73 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (CD_3OD) δ 159.54, 145.88, 141.09, 132.73, 131.54, 130.84, 128.99, 126.73, 121.59, 116.96, 67.76, 27.44, 21.78. Anal. Calcd for $C_{15}H_{15}NO_3S$: C 62.27, H 5.22, N 4.84, S 11.08. Found: C 62.17, H 5.28, N 4.80, S 10.98.

(±)-2-(Furan-2-yl-hydroxymethyl)-4,*N*-dimethylbenzenesulfonamide (12). The procedure used for compound **3** was repeated using **2** (0.50 g, 2.7 mmol) and 2-furaldehyde (0.42 g, 4.3 mmol) to yield **12** (0.65 g, 86%) as a white solid: mp 172–174 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 1H, J = 8.0 Hz), 7.40 (m, 2H), 7.28 (d, 1H, J = 7.4 Hz), 6.63 (d, 1H, J = 4.8 Hz), 6.40 (m, 2H), 4.25 (bq, 1H, J = 5.2 Hz), 3.26 (d, 1H, J = 5.6 Hz), 2.44 (m, 6H); ^{13}C NMR (CD_3OD) δ 157.16, 144.83, 143.54, 142.07, 134.73, 131.24, 130.64, 129.51, 111.20, 108.68, 65.86, 28.90, 21.48.

(±)-3-Furan-2-yl-2,5-dimethyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (13). By the same procedure as for compound **10**, **13** was obtained from **12** (0.100 g, 0.355 mmol) as a white solid (0.079 g, 84%): mp 151–152 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 1H, J = 8.0 Hz), 7.45 (d, 1H, J = 0.8 Hz), 7.36 (d, 1H, J = 7.9 Hz), 7.04 (s, 1H), 6.43 (m, 2H), 5.33 (s, 1H), 2.83 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.05, 143.99, 143.82, 135.60, 131.65, 130.59, 124.90, 120.92, 110.51, 110.38, 59.97, 27.68, 21.64. Anal. Calcd for $C_{13}H_{13}NO_3S$: C 59.30, H 4.98, N 5.32, S 12.18. Found: C 59.29, H 5.05, N 5.21, S 12.04.

(±)-*N*-Methylbenzenesulfonamide (15). The procedure used for making compound **2** was repeaed using benzenesulfonyl chloride (**14**, 14.3 g, 81.0 mmol) and methylamine (40%, 6.9 mL, 89.1 mmol) to afford **15** as a syrup (12.6 g, 91%): ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 2H), 7.54 (m, 3H), 5.25 (bs, 1H), 2.61 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.41, 132.52, 128.94, 126.95, 29.03.

(±)-2-[(2-Chlorophenyl)hydroxymethyl]-*N*-methylbenzenesulfonamide (16). By the same procedure used for making compound **3**, **16** (0.74 g, 81%) was obtained

from **15** (0.50 g, 2.9 mmol) and 2-chlorobenzaldehyde (0.66 g, 4.7 mmol) as a white solid: mp 93–94 °C; ^{1}H NMR ($CDCl_3$) δ 7.98 (m, 1H), 7.74 (d, 1H, J = 7.5 Hz), 7.32 (m, 5H), 6.88 (m, 2H), 5.50 (bq, 1H, J = 5.0 Hz), 4.20 (bs, 1H), 2.57 (d, 3H, J = 4.7 Hz); ^{13}C NMR ($CDCl_3$) δ 140.47, 138.63, 136.46, 133.07, 132.13, 130.25, 129.40, 129.14, 128.92, 128.25, 128.01, 126.85, 68.63, 29.15.

(±)-3-(2-Chlorophenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (17). The same procedure used for compound **4** was repeated using **16** (0.25 g, 0.80 mmol) to obtain compound **17** (0.22 g, 92%) as a white solid: mp 156 °C; ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 1H), 7.52 (m, 3H), 7.31 (m, 3H), 7.21 (m, 1H), 5.94 (s, 1H), 2.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.44, 134.54, 133.96, 133.10, 130.07, 129.93, 129.42, 129.05, 127.98, 124.79, 121.22, 62.72, 27.62. Anal. Calcd for $C_{14}H_{12}ClNO_2S$·0.065 CH_2Cl_2: C 56.44, H 4.08, Cl 13.39, N 4.68, S 10.71. Found: C 56.33, H 4.18, Cl 13.40, N 4.66, S 10.80.

(±)-*N*-Isopropylbenzenesulfonamide (18). The procedure for compound **2** was repeated using isopropylamine (3.71 mL, 43.6 mmol) and benzenesulfonyl chloride (**14**, 7.00 g, 39.6 mmol) to afford **18** as a syrup (6.71 g, 85%): ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.53 (m, 3H), 4.73 (bd, 1H, J = 6.7 Hz), 3.48 (m, 1H, J = 6.7 Hz), 1.08 (d, 6H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 140.95, 132.20, 128.82, 126.71, 45.86, 23.28.

(±)-2-(Hydroxyphenylmethyl)-*N*-isopropylbenzenesulfonamide (19). The procedure used to synthesize compound **3** was repeated using **18** (0.66 g, 3.3 mmol) and benzaldehyde (0.56 g, 5.3 mmol) to yield **19** (0.79 g, 79%) as a white solid: mp 114–116

°C; ^{1}H NMR ($CDCl_3$) δ 7.99 (m, 1H), 7.39 (m, 8H), 6.69 (s, 1H), 4.63 (bd, 1H, J = 6.2 Hz), 3.71 (bs, 1H), 3.35 (m, 1H, J = 6.3 Hz), 0.93 (d, 3H, J = 6.5 Hz), 0.87 (d, 3H, 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 141.81, 141.61, 138.65, 132.80, 130.29, 129.62, 128.64, 127.92, 127.22, 71.92, 46.24, 23.48.

(±)-2-Isopropyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (20). By using the procedure for compound **4**, **20** (0.27 g, 97%) was obtained from **19** (0.30 g, 0.98 mmol) as a white solid: mp 141 °C; ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 1H), 7.41 (m, 7H), 7.02 (m, 1H), 5.55 (s, 1H), 3.94 (m, 1H, J = 6.8 Hz), 1.47 (d, 3H, J = 6.8 Hz), 1.13 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 139.58, 138.31, 134.23, 132.70, 129.10, 129.01, 128.70, 127.62, 124.94, 120.73, 62.32, 46.60, 21.81, 20.27. Anal. Calcd for $C_{16}H_{17}NO_2S$: C 66.87, H 5.96, N 4.87, S 11.16. Found: C 66.94, H 6.00, N 4.83, S 11.23.

(±)-*N*[4-[Hydroxy(2-methylsulfamoylphenyl)methyl]phenyl]acetamide (21). The procedure used to synthesize compound **3** was repeated using **15** (2.00 g, 11.7 mmol) and 4-acetamidobenzaldehyde (2.10 g, 12.9 mmol), which was added as a solid to obtain a yellow-colored product. The crude product was chromatographed on silica gel using ethyl acetate as the eluent to yield **21** (1.3 g, 33%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 9.85 (s, 1H), 7.77 (d, 1H, J = 7.8 Hz), 7.58 (d, 2H, J = 3.3 Hz), 7.46 (m, 4H), 7.26 (d, 2H, J = 8.5 Hz), 6.57 (d, 1H, J = 4.6 Hz), 5.86 (d, 1H, J = 4.6 Hz), 2.46 (d, 3H, J = 4.8 Hz), 1.99 (s, 3H); ^{13}C NMR (CD_3OD) δ 171.67, 144.81, 140.63, 138.98, 138.10, 133.88, 131.31, 130.18, 128.67, 128.48, 120.10, 70.84, 29.17, 23.81.

(±)-*N*-[4-(2-Methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenyl]-acetamide (22). The procedure used for making compound **10** was repeated using **21** (0.80 g, 0.24 mmol) to yield an orangish yellow product. The crude product was chromatographed on silica gel using hexanes–ethyl acetate (2:1) as the eluent to obtain compound **22** (0.65 g, 86%) as a white solid: mp 221 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (s,1H), 7.82 (m, 1H), 7.53 (m, 4H), 7.22 (d, 2H, J = 8.4 Hz), 7.02 (m, 1H), 5.15 (s, 1H), 2.73 (s, 3H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.83, 139.05, 138.33, 133.86, 133.07, 131.80, 129.37, 128.73, 125.07, 120.91, 120.31, 66.51, 27.26, 24.40. Anal. Calcd for $C_{16}H_{16}N_2O_3S$: C 60.74, H 5.10, N 8.85, S 10.13. Found: C 60.71, H 5.10, N 8.82, S 10.24.

(±)-4-(2-Methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenylamine (23). The acetamido compound **22** (0.100 g, 0.316 mmol) was taken in concd HCl (1 mL) and stirred at room temperature for 2 min. After all the solid had dissolved, H_2O (3 mL) was added, and the reaction mixture was refluxed for 1 h and then allowed to cool to room temperature. It was diluted with H_2O and then neutralized with solid $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), washed with saturated NaCl, dried with anhydrous $MgSO_4$,and concentrated to obtain a yellow-colored solid. The crude product was chromatographed with hexanes–ethyl acetate (1:1) to yield **23** (0.079 g, 91%): mp 219–220 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (m, 1H), 7.63 (m, 2H), 7.12 (d, 1H, J = 7.0 Hz), 6.94 (d, 2H, J = 8.4 Hz), 6.56 (d, 2H, J = 8.4 Hz), 5.28 (s, 1H), 5.26 (s, 2H), 2.59 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.17, 139.12, 134.16, 132.83, 129.46,

129.10, 125.90, 125.07, 120.93, 115.33, 66.69, 27.07. Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C 61.29, H 5.14, N 10.21, S 11.69. Found: C 61.10, H 5.13, N 10.14, S 11.63.

(1*S*,4*R*)-4,7,7-Trimethyl-2-oxa-3-oxobicyclo[2.2.1]heptane-1-carboxylic acid [4-[(3*RS*)-2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenyl]amides (24 and 25). To **23** (0.010 g, 0.037 mmol) and DMAP (0.018 g, 0.146 mmol) in dry CH_2Cl_2 (2mL) was added (−)-camphanic acid chloride (0.012 g, 0.055 mmol) under N_2 at 0 °C. The reaction mixture was allowed to warm to room temperature and stir at that temperature for 1 h. The reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was washed with saturated NaCl, dried with anhydrous $MgSO_4$,and concentrated to obtain a yellow oil. The crude product was chromatographed on a silica gel column using hexanes–ethyl acetate (1:1) as the eluent to obtain a mixture of two diastereomers (**24** + **25**, 0.013 g, 78%): ^{1}H NMR ($CDCl_3$) δ 8.21 (s, 1H), 7.86 (m, 1H), 7.65 (d, 2H, J = 8.5 Hz), 7.53 (m, 2H), 7.33 (d, 2H, J = 8.5 Hz), 7.03 (m, 1H), 5.17 (s, 1H), 2.77 (s, 3H), 2.61 (m, 1H), 2.01 (m, 2H), 1.75 (m, 1H), 1.17 (d, 6H, J = 4.8 Hz), 0.99 (s, 3H).

(2*R*)-3,3,3-Trifluoro-2-methoxy-*N*-[4-[(3*RS*)-2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*] isothiazol-3-yl]phenyl]- 2-phenylpropionamides (26 and 27). To **23** (0.049 g, 0.178 mmol) and DMAP (0.087 g, 0.713 mmol) in dry CH_2Cl_2 (5mL) was added (R)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.050 g, 0.198 mmol) under N_2 at 0 °C. The reaction mixture was allowed to warm to room temperature and stir at that temperature for 1 h. The reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with

saturated NaCl, dried with anhydrous $MgSO_4$, and concentrated to obtain a yellow oil. The crude product was chromatographed on a silica gel column using hexanes–ethyl acetate (1:1) as the eluent to obtain a mixture of two diastereomers (**26** + **27**, 0.066 g, 76%): ^{1}H NMR ($CDCl_3$) δ 8.73 (s, 1H), 7.80 (m, 1H), 7.66 (d, 2H, J = 8.4 Hz), 7.54 (m, 4H), 7.43 (m, 3H), 7.30 (d, 2H, J = 8.5 Hz), 7.02 (m, 1H), 5.16 (s, 1H), 3.50 (s, 3H), 2.75 (s, 3H).

(±)-2-[4-(2-Methyl-1,1-dioxo-2,3-dihydro[*d*]isothiazol-3-yl)phenyl]isoindole-1,3-dione (33). To **23** (0.10 g, 0.037 mmol) in $CHCl_3$ (2 mL) was added phthalic anhydride (0.007 g, 0.044 mmol) at room temperature. The reaction mixture was refluxed for 12 h and concentrated to obtain an oil, which was columned on a silica gel column using hexanes–ethyl acetate (1:1) as the eluent to yield **33** (0.10 g, 68%): ^{1}H NMR ($CDCl_3$) δ 7.98 (m, 2H), 7.84 (m, 3H), 7.52 (m, 6H), 7.12 (m, 1H), 5.26 (s, 1H), 2.83 (s, 3H).

(±)-2-[(4-Methoxyphenyl)hydroxymethyl]-*N*-methylbenzenesulfonamide (34). To **15** (1.00 g, 5.84 mmol) in dry THF (44 mL) was added BuLi in hexanes (2.5 M, 5.84 mL, 14.6 mmol) at 0 °C under N_2 over 5 min. Initially, the reaction mixture turned yellow and then to an orange suspension after addition was complete. The reaction mixture was stirred at 0 °C for 30 min., at which time lithation was assumed to be complete. To the above suspension was added 4-methoxybenzaldehyde (1.27 g, 9.34 mmol) at 0 °C in dry THF (9 mL) at 0 °C over 2–3 min. The reaction mixture turned reddish brown, then dirty green, and finally into a-pale yellow solution when addition was complete. After stirring for 60 min. at 0 °C, HCl (5%, 15 mL) was added, and the

reaction mixture was allowed to warm up to room temperature. The THF layer was separated from the aqueous layer, and then the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layer was washed with brine, dried with anhydrous $MgSO_4$,and concentrated to obtain a yellow-colored oil. The crude product was chromatographed on silica gel using ethyl acetate as the eluent to yield **34** (1.7 g, 95%) as a white solid: mp 86–88 °C; ^{1}H NMR (DMSO-d_6) δ 7.78 (d, 1H, J = 8.0 Hz), 7.56 (m, 3H), 7.42 (m, 1H), 7.29 (d, 2H, J = 8.6 Hz), 6.85 (d, 2H, J = 8.7 Hz), 6.59 (d, 1H, J = 4.6 Hz), 5.87 (d, 1H, J = 4.7 Hz), 3.70 (s, 3H), 2.47 (d, 3H, J = 4.9 Hz); ^{13}C NMR (DMSO-d_6) δ 157.97, 144.64, 136.85, 136.57, 132.38, 130.08, 127.75, 127.56, 127.17, 113.25, 67.91, 54.97, 28.58.

(±)-3-(4-Methoxyphenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (35). To **34** (0.88 g, 2.85 mmol) was added HBr (48%, 28 mL) at room temperature, and the reaction mixture was stirred at that temperature for 2 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 × 20 mL), washed with saturated NaCl, dried with anhydrous $MgSO_4$, and concentrated to yield a pale-yellow solid. The crude product was chromatographed on silica gel using hexanes–ethyl acetate (3:1) to obtain compound **35** (0.69 g, 84%) as a white solid: mp 135 °C; ^{1}H NMR ($CDCl_3$) δ 7.82 (m, 1H), 7.50 (m, 2H), 7.23 (d, 2H, J = 8.6 Hz), 7.04 (m, 1H), 6.91 (d, 2H, J = 8.7 Hz), 5.14 (s, 1H), 3.81 (s, 3H), 2.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.09, 138.66, 133.98, 132.83, 129.37, 129.13, 128.31, 124.95, 120.82, 114.38, 66.33, 55.20, 27.07. Anal. Calcd for $C_{15}H_{15}NO_3S$: C 62.27, H 5.22, N 4.84, S 11.08. Found: C 62.20, H 5.24, N 4.81, S 11.09.

(*S*)-(+)-3-(4-Methoxyphenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (36) and (*R*)-(−)-3-(4-methoxyphenyl)-2-methyl-2,3-dihydro-benzo[*d*]isothiazole 1,1-dioxide (37). Compound **35** (0.300 g) was separated into its enantiomers on a Chiralcel OD HPLC column (25 cm × 1 cm i.d.) using hexanes–2-propanol (9:1) as the eluent to yield the (+)-enantiomer **36** (0.103 g) as the 1st fraction: t_R = 19.3 min; mp 166–167 °C ; $[\alpha]^{20}_D$ +119° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 1H), 7.50 (m, 2H), 7.24 (d, 2H, *J* = 8.6 Hz), 7.03 (m, 1H), 6.92 (d, 2H, *J* = 8.6 Hz), 5.14 (s, 1H), 3.81 (s, 3H), 2.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.113, 138.69, 134.04, 132.83, 129.40, 129.13, 128.34, 124.95, 120.87, 114.41, 66.39, 55.23, 27.11. Anal. Calcd for $C_{15}H_{15}NO_3S$: C 62.27, H 5.22, N 4.84, S 11.08. Found: C 62.33, H 5.25 N 4.78, S 11.15. The (−)-enantiomer **37** (0.096 g) was obtained as the 2nd fraction: t_R = 27.6 min; mp 166 °C; $[\alpha]^{20}_D$ −120° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 1H), 7.51 (m, 2H), 7.24 (d, 2H, *J* = 8.6 Hz), 7.03 (m, 1H), 6.92 (d, 2H, *J* = 8.5 Hz), 5.14 (s, 1H), 3.82 (s, 3H), 2.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.16, 138.72, 134.07, 132.85, 129.43, 129.16, 128.37, 124.98, 120.91, 114.44, 66.42, 55.26, 27.14. Anal. Calcd for $C_{15}H_{15}NO_3S$: C 62.27, H 5.22, N 4.84, S 11.08. Found: C 62.32, H 5.28, N 4.78, S 11.00. Compound **35** (0.092 g) was obtained as a mixed fraction due to partial overlap of the two enantiomers.

(±)-4-(2-Methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenol (38). To **35** (0.230 g, 0.795 mmol) in dry CH_2Cl_2 (15 mL) was added BBr_3 (99+ %, 0.298 g, 1.19 mmol) at −78 °C under N_2,and the reaction mixture was allowed to gradually warm to room temperature. The reaction was complete in 2.5 h, and the mixture was then

dumped into ice and extracted with CH_2Cl_2 (3 × 20 mL), washed with saturated NaCl, and dried with anhydrous $MgSO_4$, and concentrated to remove the solvent. The crude product was chromatographed on silica gel using hexanes–ethyl acetate (1:1) to obtain compound **38** (0.206 g, 94%) as a white solid: mp 183 °C; ^{1}H NMR (CD_3OD) δ 7.79 (m, 1H), 7.54 (m, 2H), 7.09 (m, 3H), 6.80 (d, 2H, J = 8.6 Hz), 5.21 (s, 1H), 2.66 (s, 3H); ^{13}C NMR (CD_3OD) δ 159.35, 140.55, 135.18, 134.33, 130.67, 130.48, 128.66, 126.45, 121.60, 116.83, 67.60, 27.25. Anal. Calcd for $C_{14}H_{13}NO_3S$: C 61.07, H 4.76, N 5.09, S 11.65. Found: C 60.92, H 4.82, N 5.01, S 11.64.

Demethylation of **36** {$[\alpha]^{20}_D$+119° (*c* 1.0, $CHCl_3$)} and **37** {$[\alpha]^{20}_D$ −120° (*c* 1.0, $CHCl_3$)} under the above conditions yielded **38** {$[\alpha]^{20}_D$ 0° (*c* 1.0, CH_3OH)}. Two peaks were seen for the demethylation product from **36** (t_R = 21. 9 min and 26.5 min) on the Chiralcel OD HPLC column using hexanes–2-propanol (85:15) as the eluent and a flow rate of 3 mL/min. Similarily, the demethylation product from **37** gave two peaks (t_R = 21.5 min and 25.7 min). The ^{1}H and ^{13}C NMR's were identical to those obtained on demethylation of compound **35**.

(1*S*,4*R*)-(+)-4,7,7-Trimethyl-2-oxa-3-oxobicyclo[2.2.1]heptane-1-carboxylic acid 4-[(3*S*)-2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenyl ester (39) and (1*S*,4*R*,)-(–)-4,7,7-trimethyl-2-oxa-3-oxobicyclo[2.2.1]heptane-1-carboxylic acid 4-[(3*R*)-1,1-dioxo-2-methyl-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenyl ester (40). To **38** (0.197 g, 0.715 mmol) and DMAP (0.350 g, 2.86 mmol) in dry CH_2Cl_2 (15 mL) was added (−)-camphanic acid chloride (0.233 g, 1.07 mmol) under N_2 at 0 °C. The reaction mixture was allowed to warm to room temperature and stir at that temperature

for 1 h. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer washed with saturated NaCl, dried with anhydrous $MgSO_4$,and concentrated to remove the solvent. The crude product was chromatographed on a silica gel column using hexanes–ethyl acetate (1:1) as the eluent to obtain a mixture of two diastereomers (**39** + **40**, 0.277 g, 85%). The two diastereomers (**39** + **40**, 150 g) were separated on a chiralcel OD HPLC column (25 cm × 1 cm i.d.) using hexanes–2-propanol (8:2) as the eluent and a flow rate of 3 mL/min to yield **39** (0.054 g) as the 1st fraction: t_R = 32.3 min; mp 251 °C; $[\alpha]^{20}_D$ +84° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 1H), 7.54 (m, 2H), 7.40 (d, 2H, *J* = 8.4 Hz), 7.20 (d, 2H, *J* = 8.4 Hz), 7.05 (m, 1H), 5.22 (s,1H), 2.79 (s, 3H), 2.57 (m, 1H), 2.20 (m, 1H), 2.01 (m, 1H), 1.77 (m, 1H), 1.16 (d, 6H, *J* = 4.5 Hz), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 177.65, 165.92, 150.47, 137.85, 134.91, 133.98, 133.05, 129.49, 129.37, 124.95, 122.12, 121.15, 90.67, 66.26, 54.84, 54.68, 30.74, 28.88, 27.46, 16.83, 9.63. Anal. Calcd for $C_{24}H_{25}NO_6S$: C 63.28, H 5.53, N 3.07, S 7.04. Found: C 63.22, H 5.54, N 3.06, S 6.96. Compound **40** (0.051g) was obtained as the 2nd fraction: t_R = 43.5 min; mp 239–240 °C; $[\alpha]^{20}_D$ -100° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 1H), 7.54 (m, 2H), 7.40 (d, 2H, *J* = 8.4 Hz), 7.20 (d, 2H, *J* = 8.3 Hz), 7.05 (m, 1H), 5.22 (s,1H), 2.78 (s, 3H), 2.57 (m, 1H), 2.20 (m, 1H), 2.01 (m, 1H), 1.77 (m, 1H), 1.17 (d, 6H, *J* = 3.3 Hz), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 177.62, 165.88, 150.43, 137.83, 134.89, 133.94, 133.04, 129.46, 129.35, 124.94, 122.08, 121.10, 90.65, 66.23, 54.81, 54.65, 30.71, 28.86, 27.43, 16.82, 9.68. Anal. Calcd for $C_{24}H_{25}NO_6S$: C 63.28, H 5.53, N 3.07, S 7.04. Found: C

63.24, H 5.53, N 2.97, S 6.99. A mixed fraction (0.040 g) of the two distereomers (**39** + **40**) was obtained due to partial overlap of the two.

(+)-4-[(3*S*)-2-Methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenol (41). To **39** (0.033 g, 0.071 mmol) was added 40% NH_3 in MeOH (1 mL) at room temperature. The reaction mixture was stirred at this temperature for 1.5 h and then concentrated to remove excess of NH_3 and solvent. The crude product was chromatographed on a silica gel column using hexanes–ethyl acetate (2:1) as the eluent to yield **41** (0.019 g, 95%) as a white solid: t_R = 21.5 min on a Chiralcel OD HPLC column using hexanes–2-propanol (85:15) as the eluent, flow rate = 3 mL/min; mp 178–180 °C; $[\alpha]^{20}_D$ +102° (*c* 0.8, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.81 (m, 1H), 7.58 (m, 2H), 7.11 (m, 3H), 6.80 (d, 2H, *J* = 8.6 Hz), 5.24 (s, 1H), 2.68 (s, 3H); ^{13}C NMR (CD_3OD) δ 159.44, 140.65, 135.30, 134.34, 130.69, 130.51, 128.72, 126.48, 121.64, 116.84, 67.68, 27.24. Anal. Calcd for $C_{14}H_{13}NO_3S$: C 61.07, H 4.76, N 5.09, S 11.65. Found: C 60.97, H 4.77, N 5.01, S 11.59.

(−)-4-[(3*R*)-2-Methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenol (42). In a similar manner compound **40** (0.036 g, 0.078 mmol) yielded the other enantiomer **42** (0.020 g, 91%) as a white solid: t_R = 25.8 min on a Chiralcel OD HPLC column using hexanes–2-propanol (85:15) as the eluent, flow rate = 3 mL/min; mp 178–179 °C; $[\alpha]^{20}_D$ −105° (*c* 0.85, CH_3OH); ^{1}H NMR (CD_3OD) δ 7.81 (m, 1H), 7.57 (m, 2H), 7.11 (m, 3H), 6.81 (d, 2H, *J* = 8.6 Hz), 5.23 (s, 1H), 2.68 (s, 3H); ^{13}C NMR (CD_3OD) δ 159.42, 140.64, 135.28, 134.36, 130.69, 130.51, 128.72, 126.48, 121.64, 116.84, 67.68,

27.25. Anal. Calcd for $C_{14}H_{13}NO_3S$: C 61.07, H 4.76, N 5.09, S 11.65. Found: C 60.97, H 4.71, N 5.05, S 11.56.

C. X-ray Crystal Structure of Compound 39

The X-ray crystal structure of **39** was determined at 292(2) K on a Siemens R3m/V diffractometer. A suitable specimen of dimensions 0.70 × 0.30 × 0.06 mm was cut from a larger crystal and glued to the end of a glass fiber. Unit cell dimensions were calculated from the angular setting of 46 carefully centered reflections in reciprocal space, and confirmed by the use of axial photographs. Compound **39** was found to crystallize in the orthorhombic system. A total of 4150 (3509 unique) reflections between $3.5 < 2\theta < 50°$ were collected by ω scans using Mo Kα radiation. The data were corrected for Lorentz and polarization effects during data reduction. Absorption effects were ignored ($\mu = 1.9$ cm^{-1}). The mean |E*E-1| statistics, calculated *Z*, and observed systematic absences were uniquely consistent with the space group $P2_12_12_1$ (no.19). The sulfur atom was located by Patterson map, and the structure was completed by successive Fourier syntheses. Full-Matrix Least Squares refinements on F^2 converged the structure to $R(R_wF^2) = 7.27$ (15.40)%. Hydrogen atoms were placed at calculated positions and introduced into the refinement as fixed contributors with isotropic U values of 0.08 Å^2. All calculations were performed using the Siemens SHELXTL-93 (Version 5.0) proprietary software package. The ORTEP view of compound **39**, as 50% thermal ellipsoids, is shown in Figure 14.

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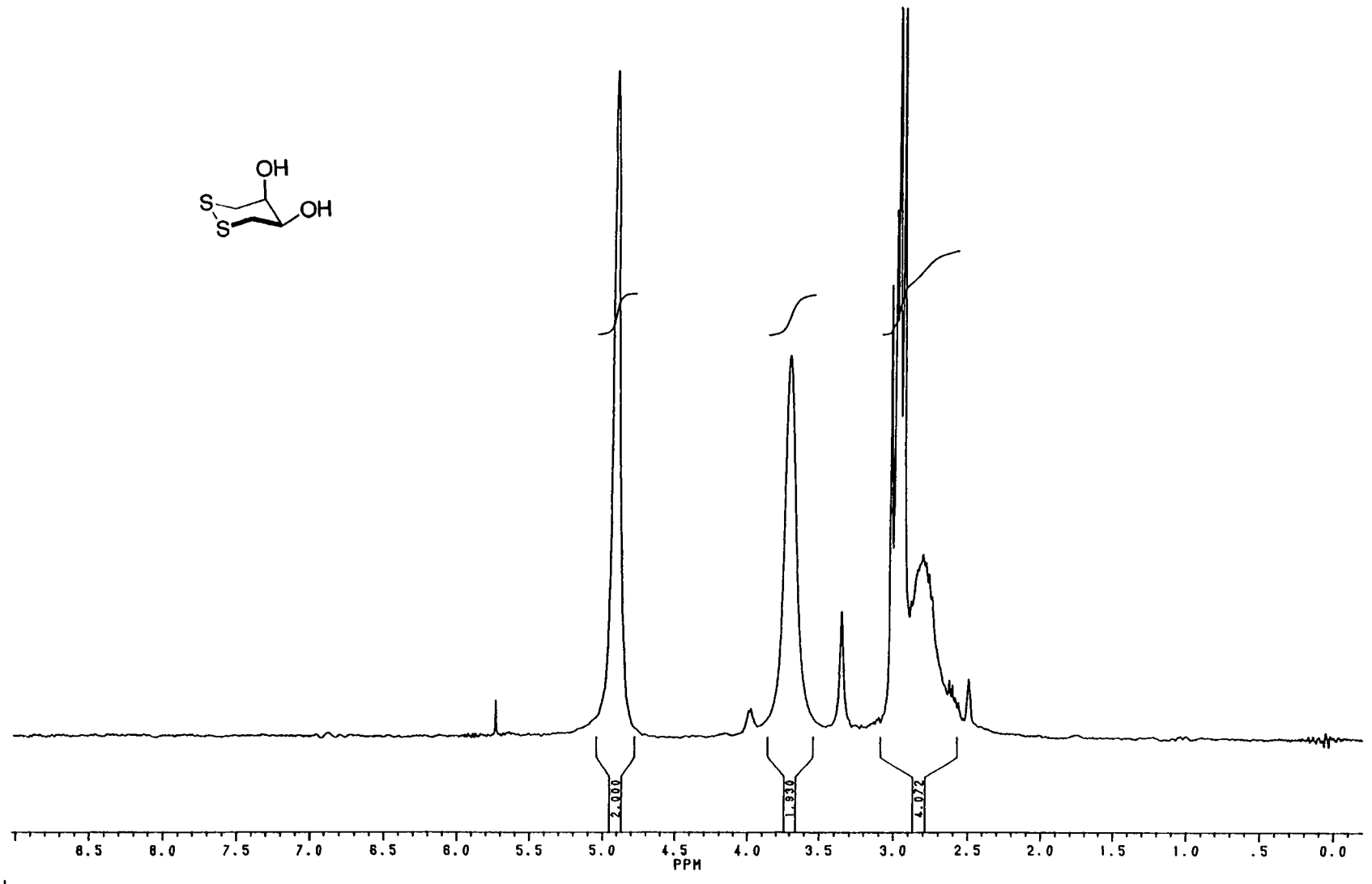
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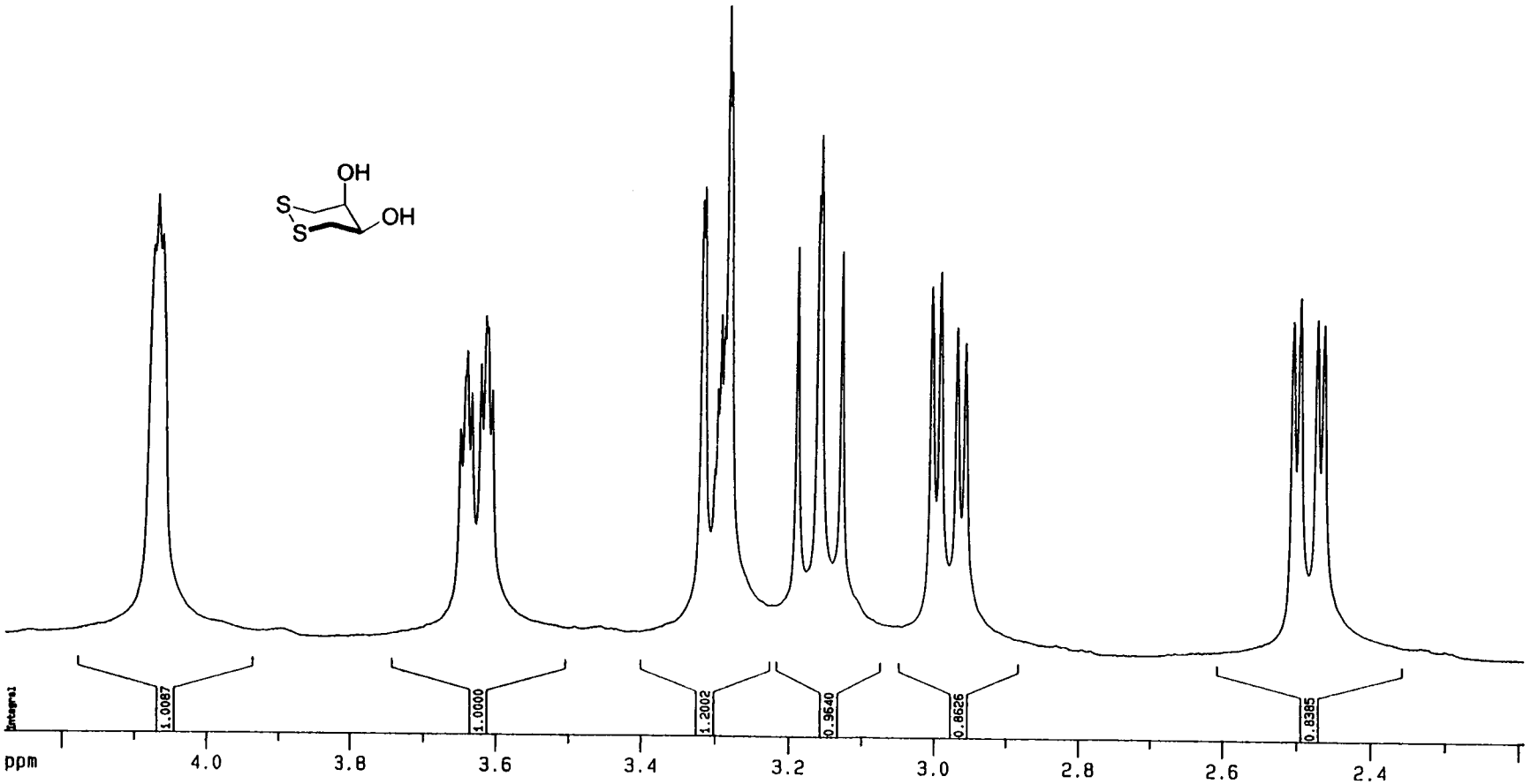
APPENDICES

APPENDIX A. ^{1}H and ^{13}C NMR Spectra for Compounds

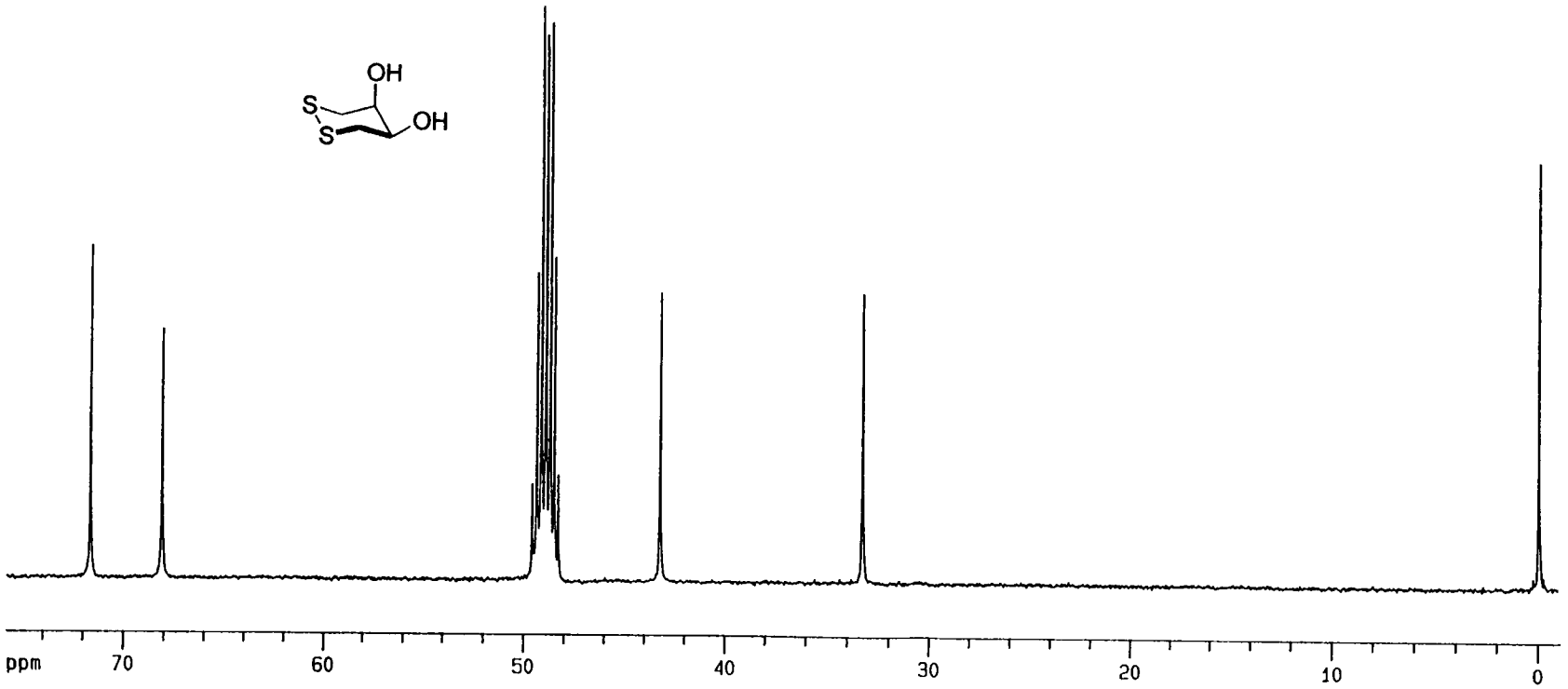
Containing –S–S– and –S–SO_2– Linkages



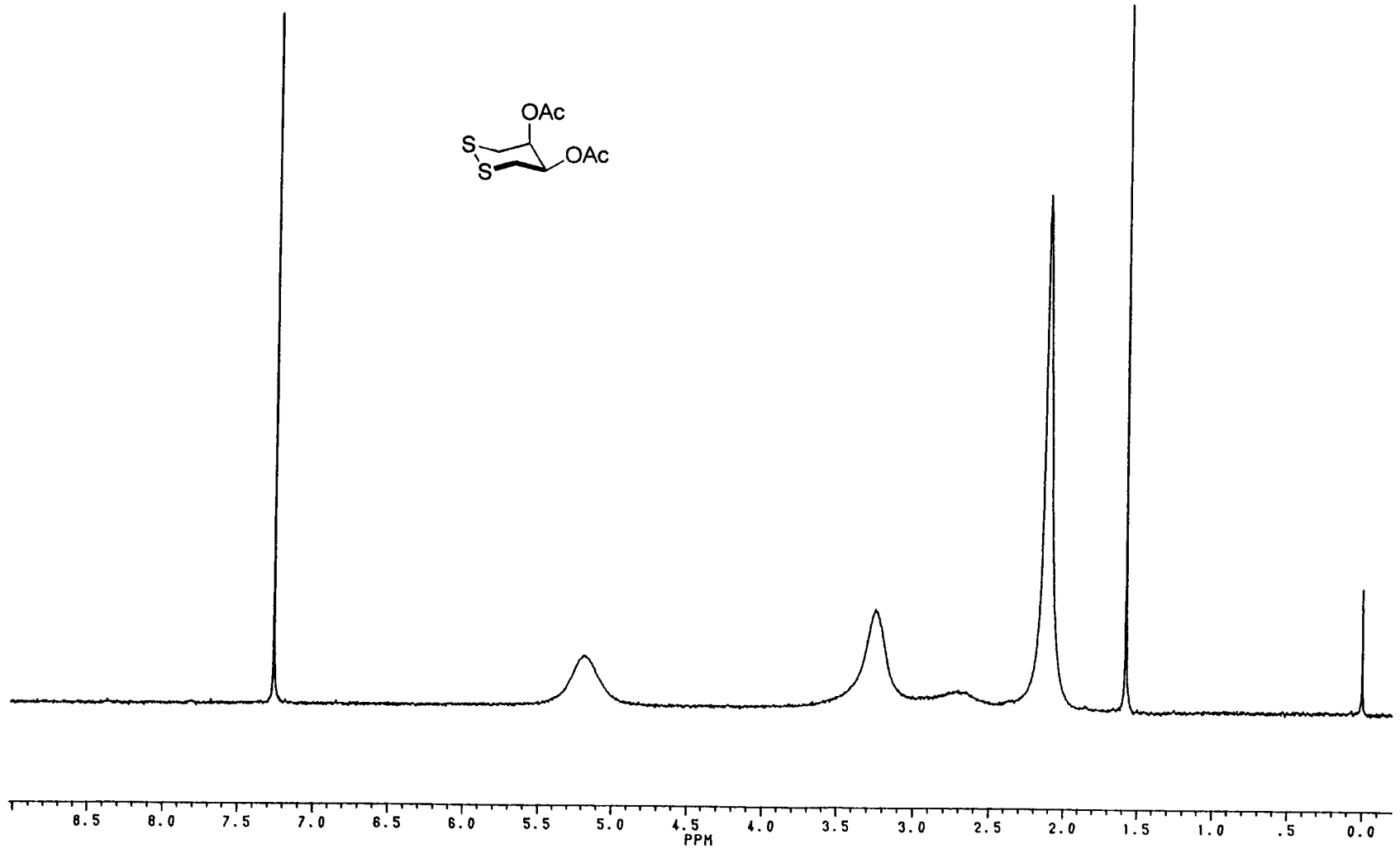
^{1}H NMR spectrum (250 MHz, DMSO-d_6) of (±)-*cis*-4,5-dihydroxy-1,2-dithiane (**3**).



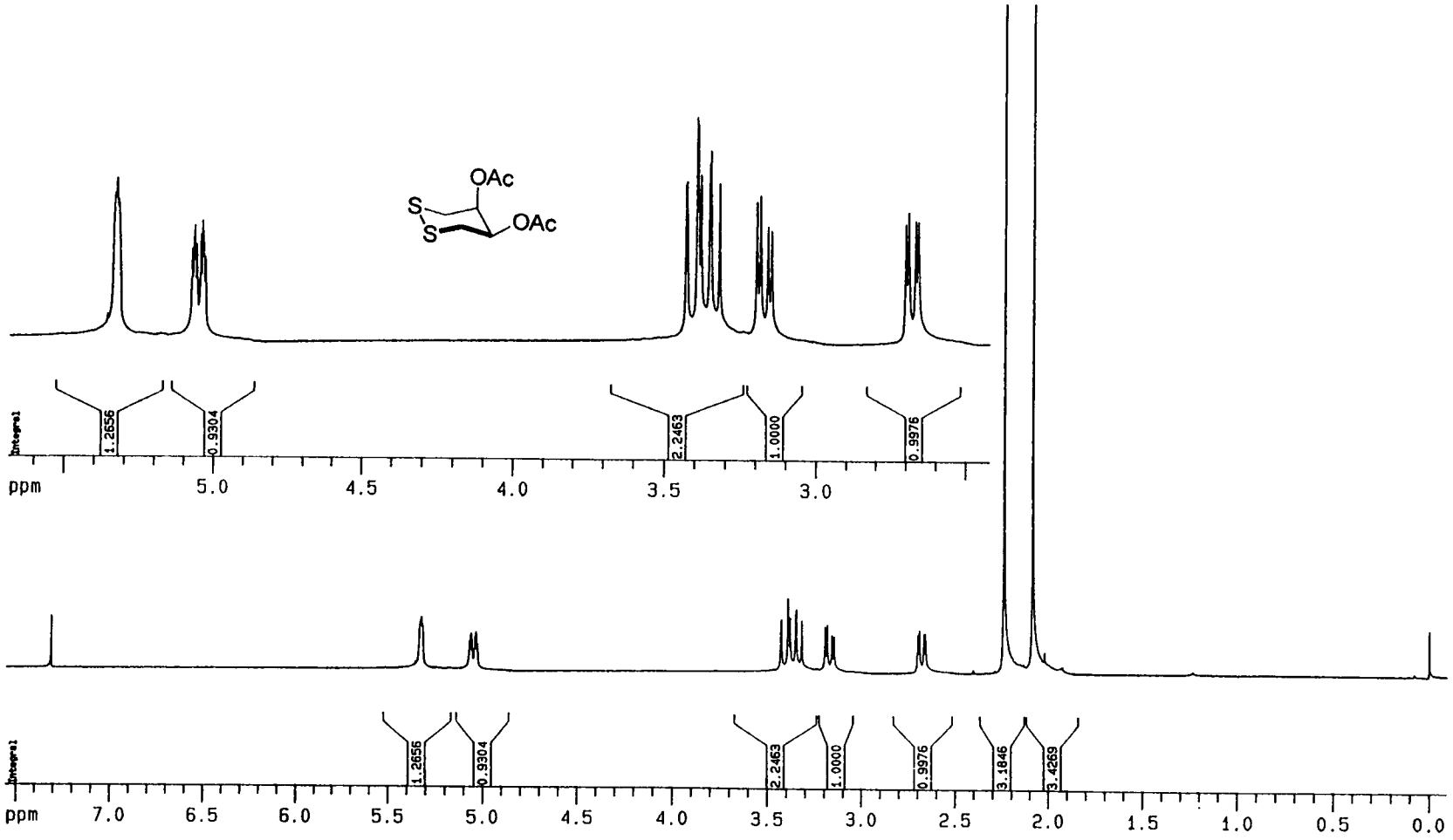
^{1}H NMR spectrum (400 MHz, CD_3OD, −40 °C) of (±)-*cis*-4,5-dihydroxy-1,2-dithiane (**3**).



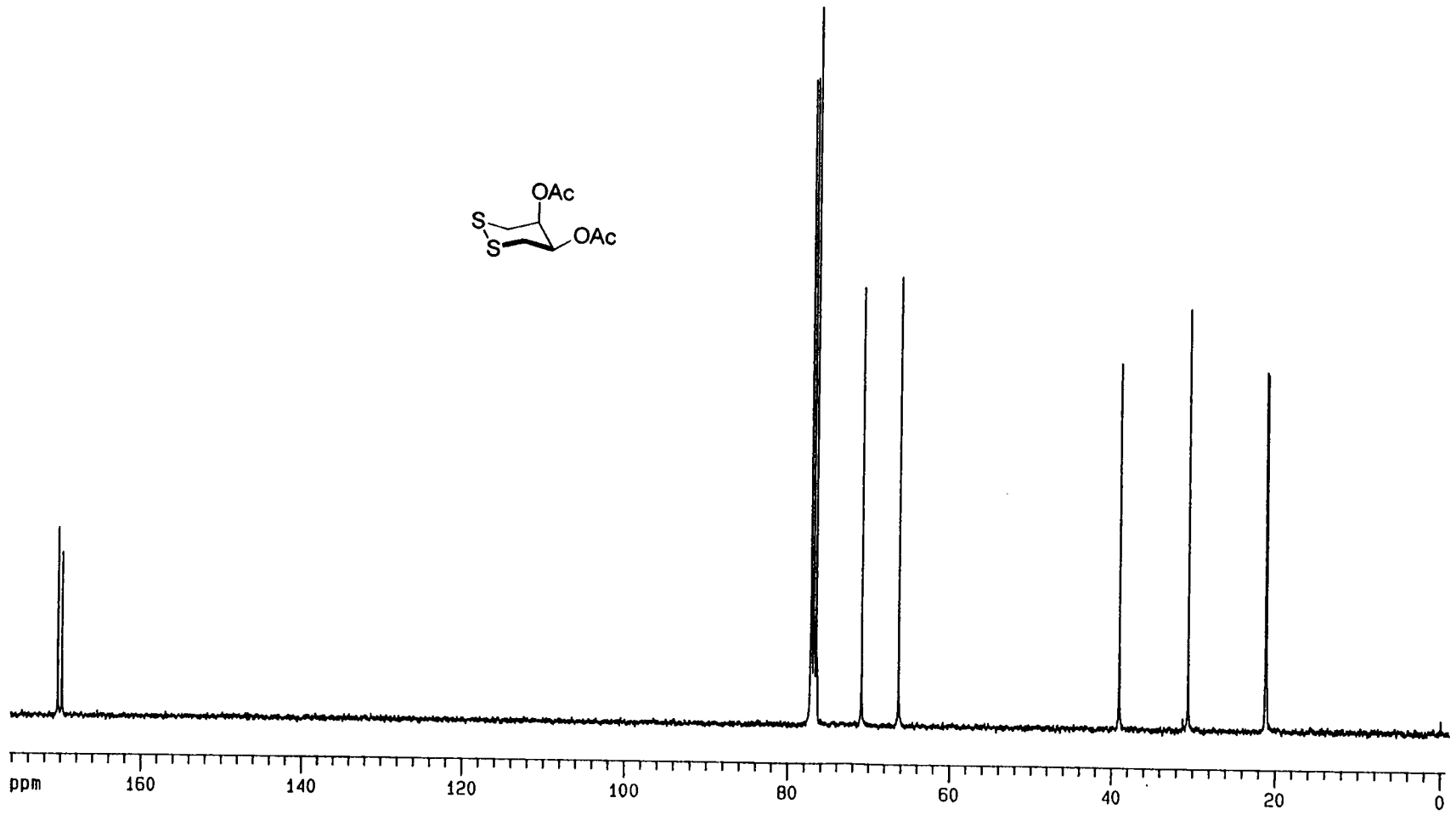
^{13}C NMR spectrum (100.6 MHz, CD_3OD, −40 °C) of (±)-*cis*-4,5-dihydroxy-1,2-dithiane (**3**).



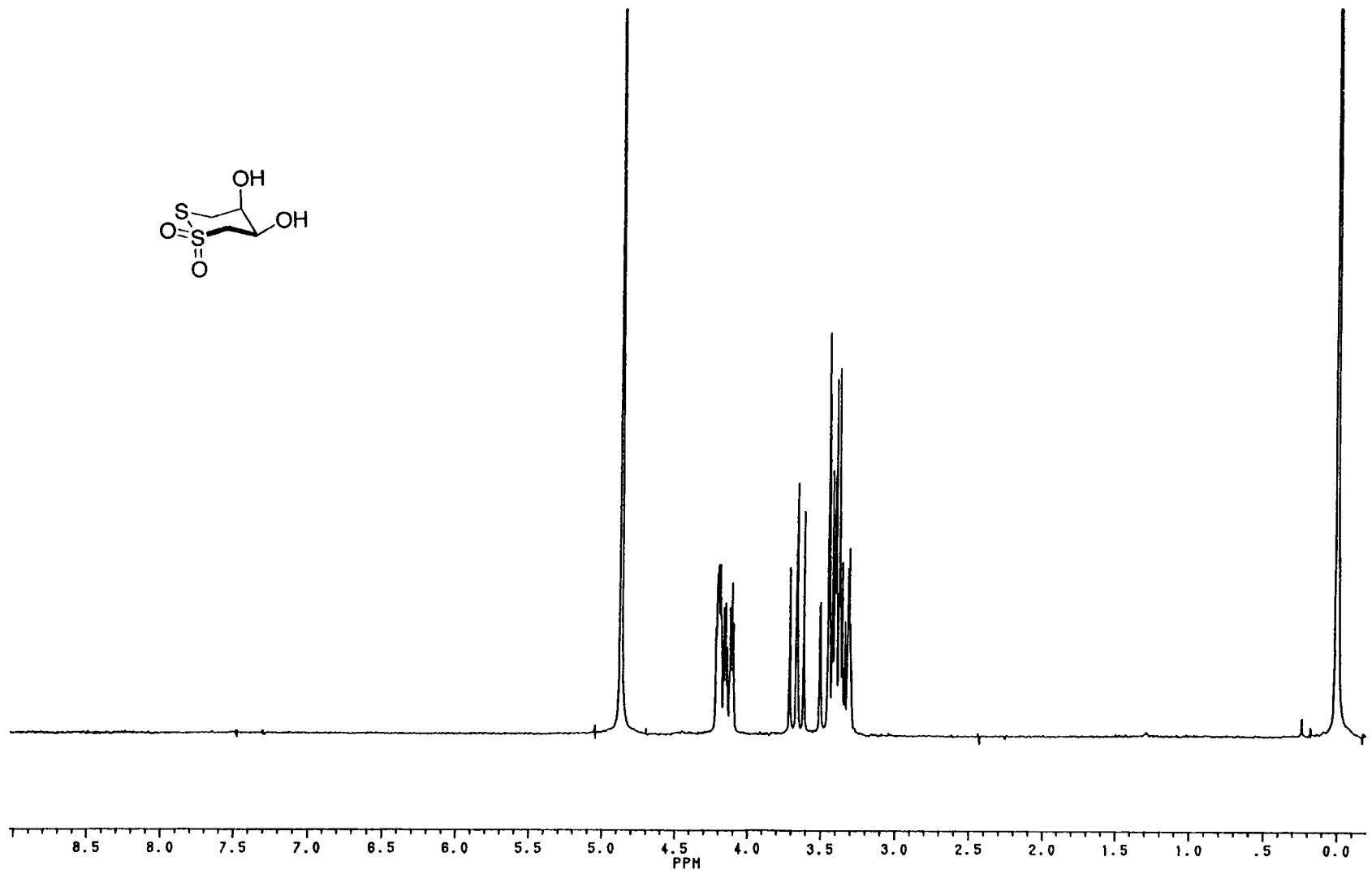
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-*cis*-4,5-diacetoxy-1,2-dithiane (**4**).



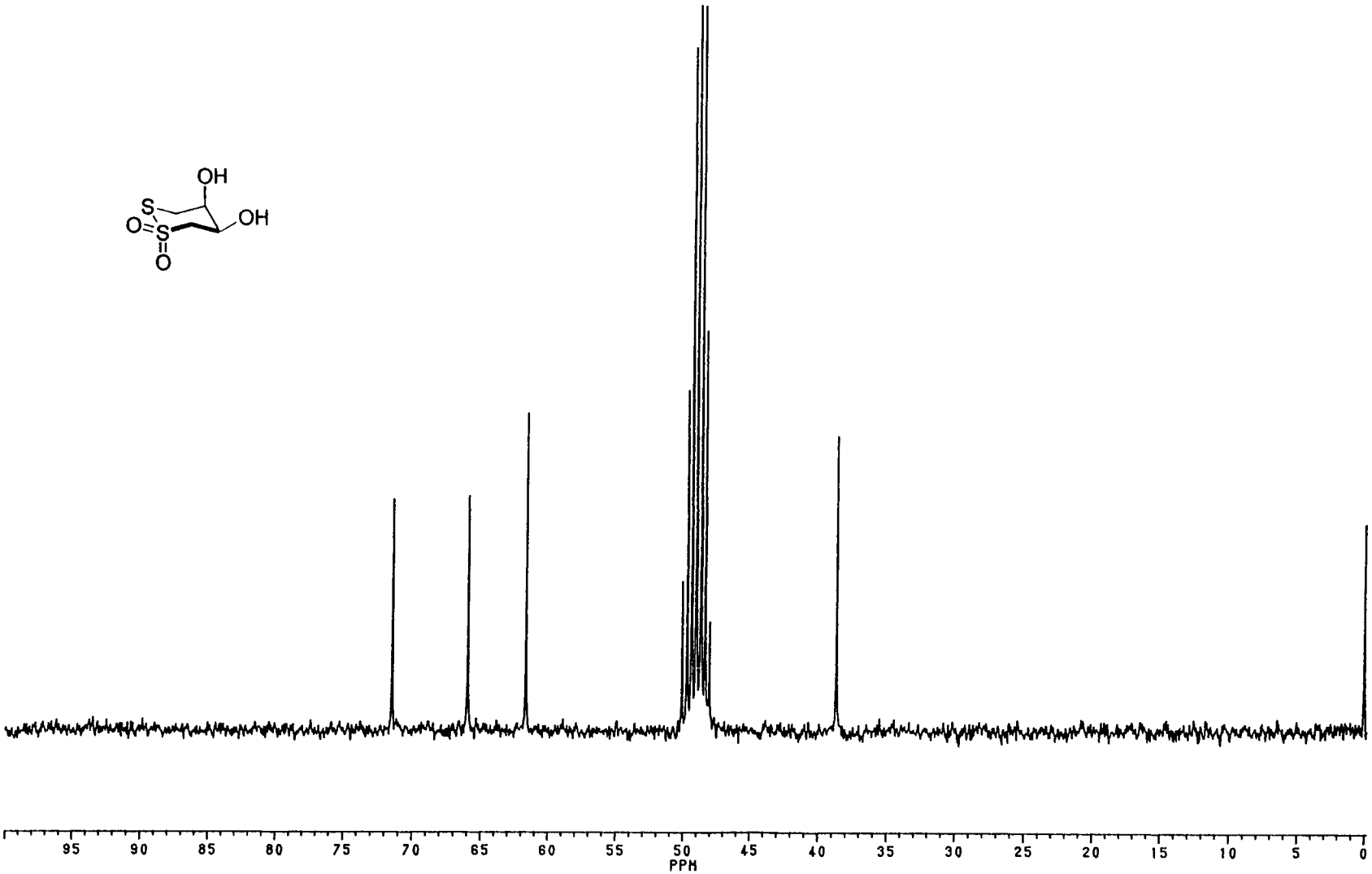
^{1}H NMR spectrum (400 MHz, $CDCl_3$, −40 °C) of (±)-*cis*-4,5-diacetoxy-1,2-dithiane (**4**).



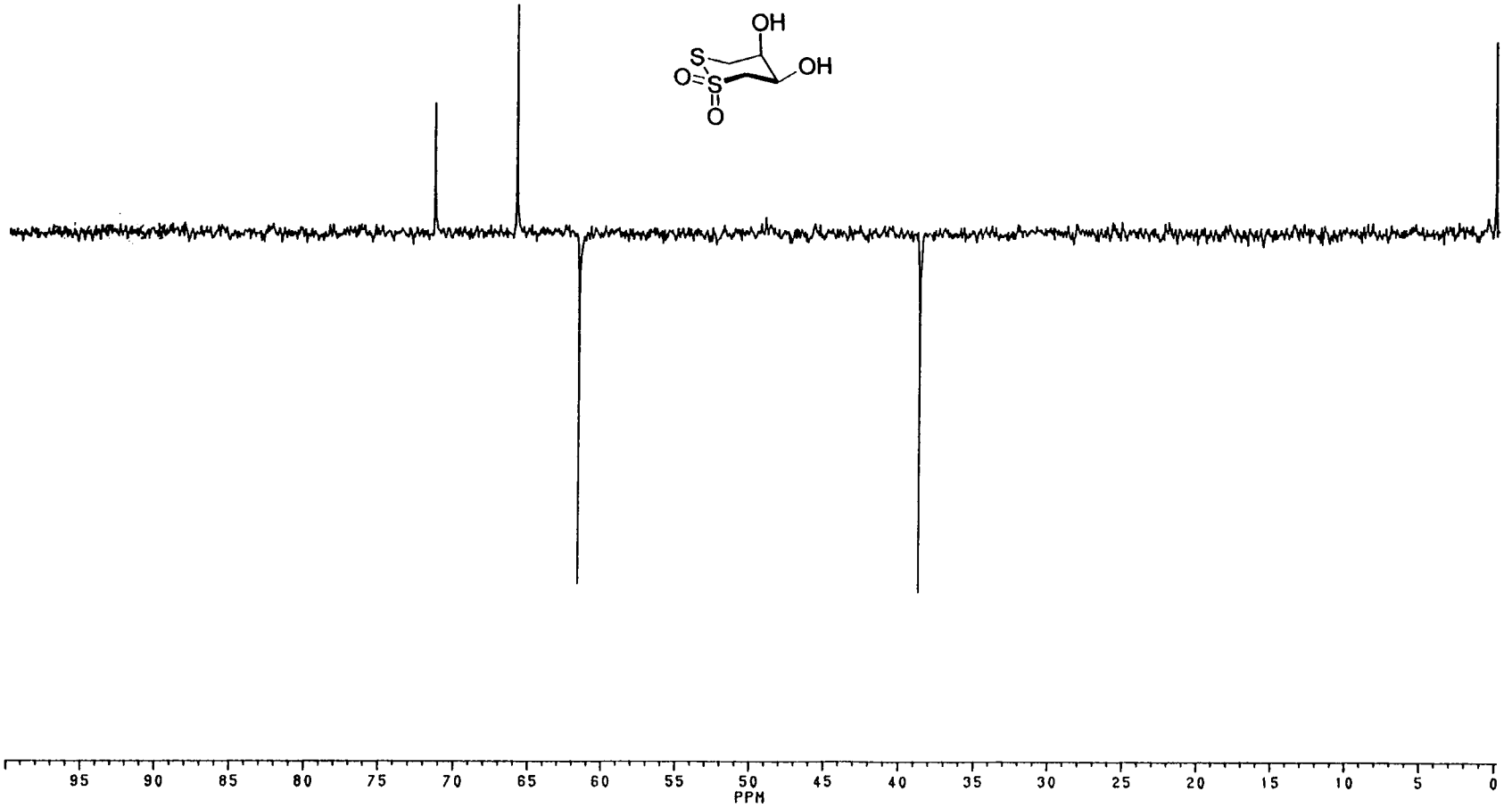
^{13}C NMR spectrum (100.6 MHz, $CDCl_3$, −40 °C) of (±)-*cis*-4,5-diacetoxy-1,2-dithiane (**4**).



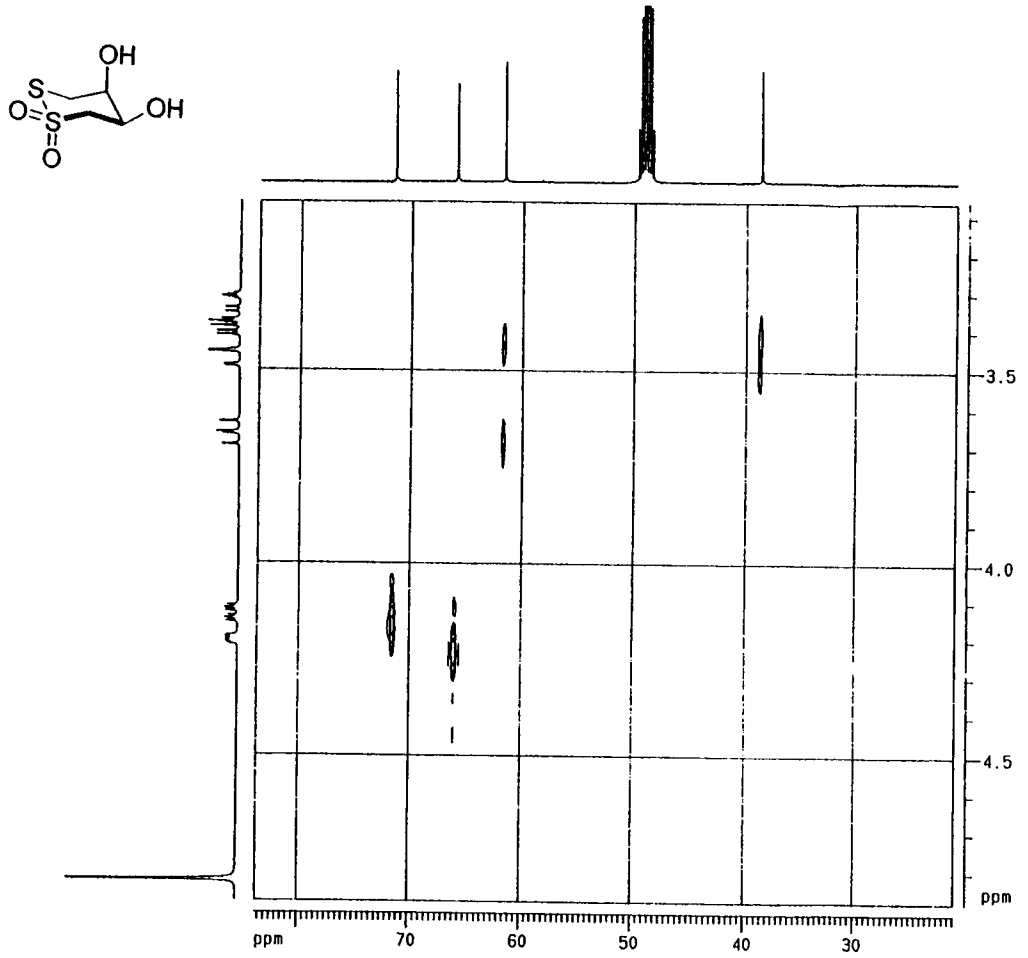
^{1}H NMR spectrum (250 MHz, CD_3OD) of (±)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (**5**).



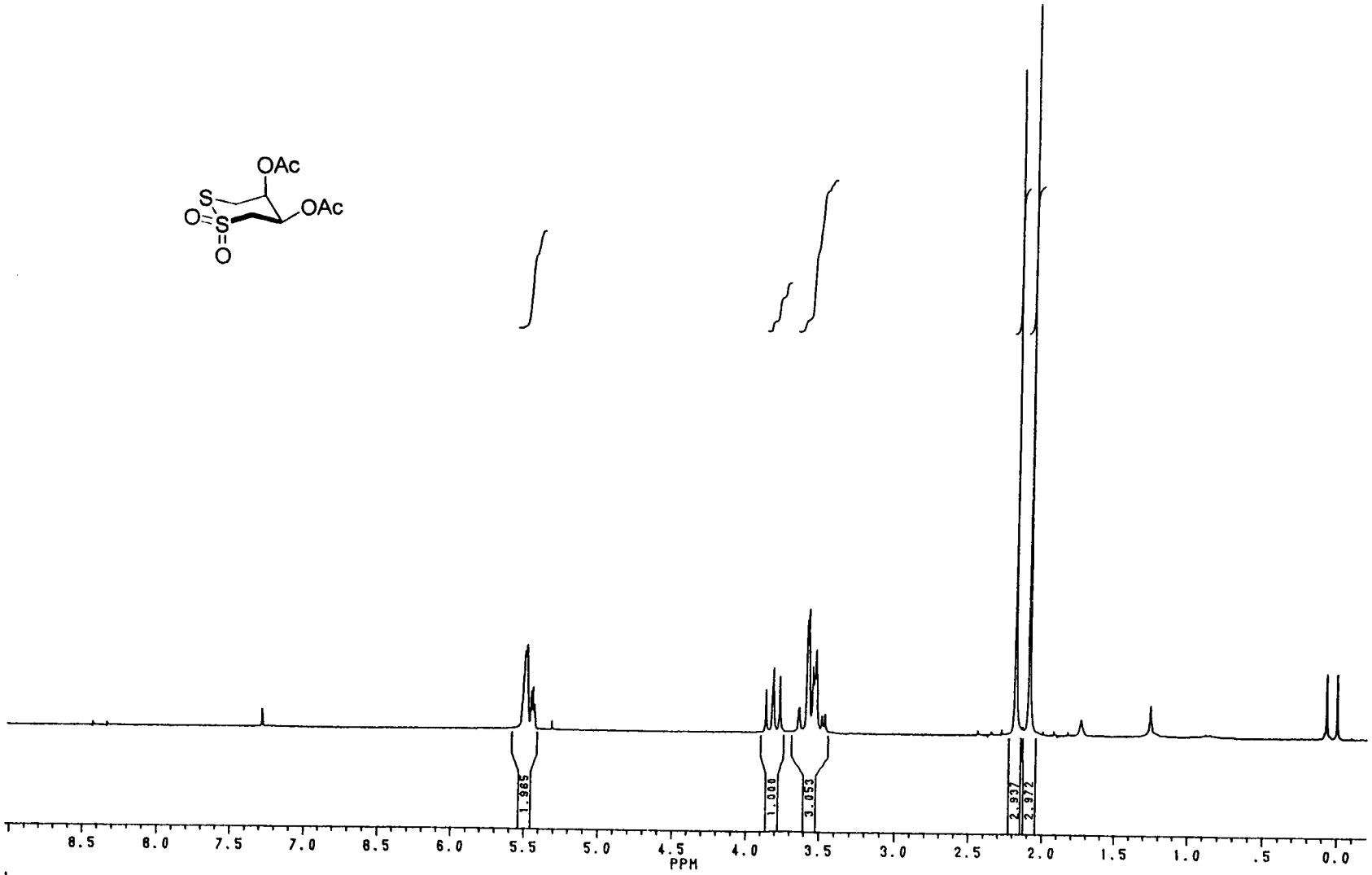
^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (±)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (**5**).



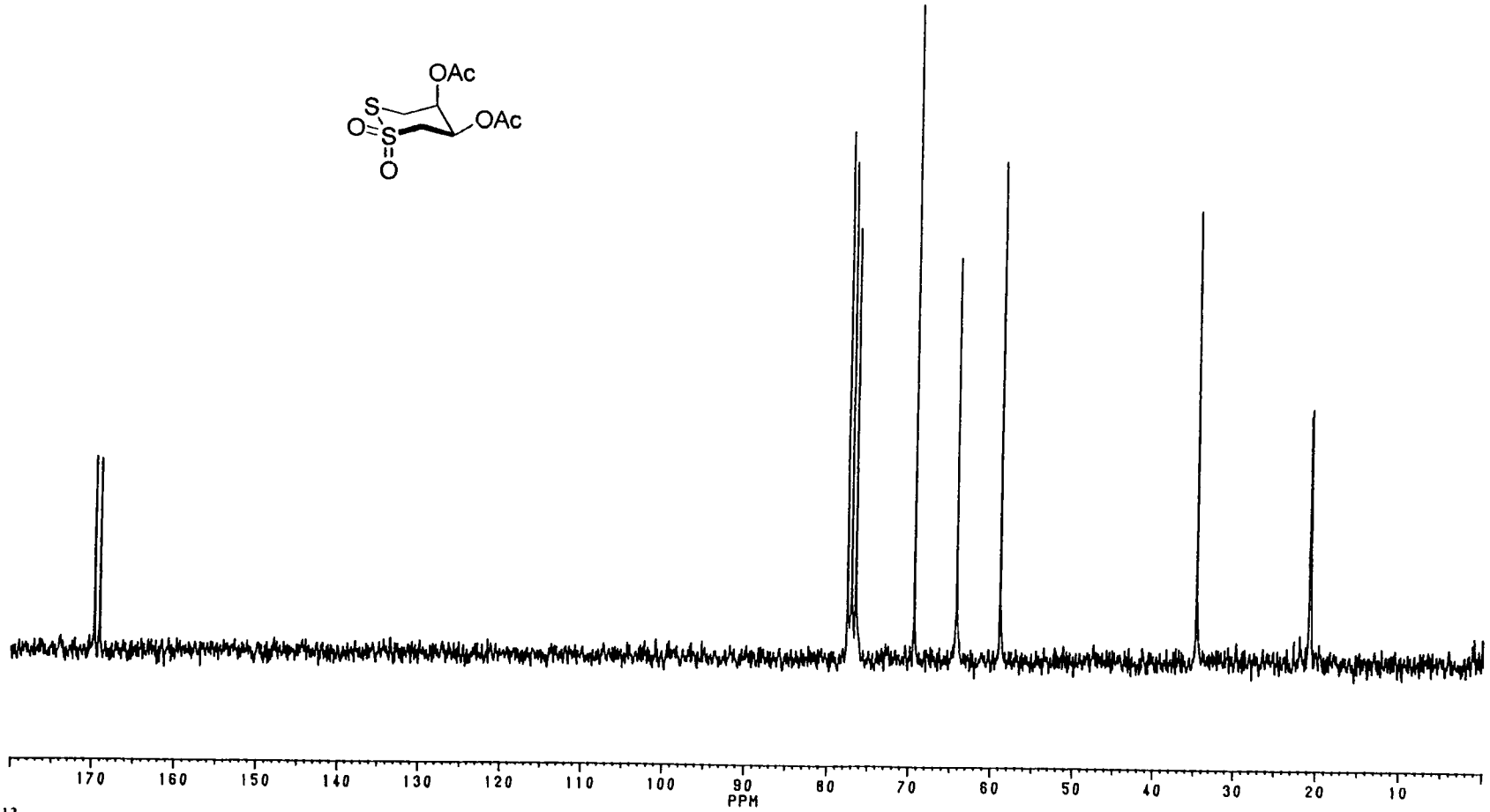
DEPT-135 spectrum (62.9 MHz, CD_3OD) of (±)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (**5**).



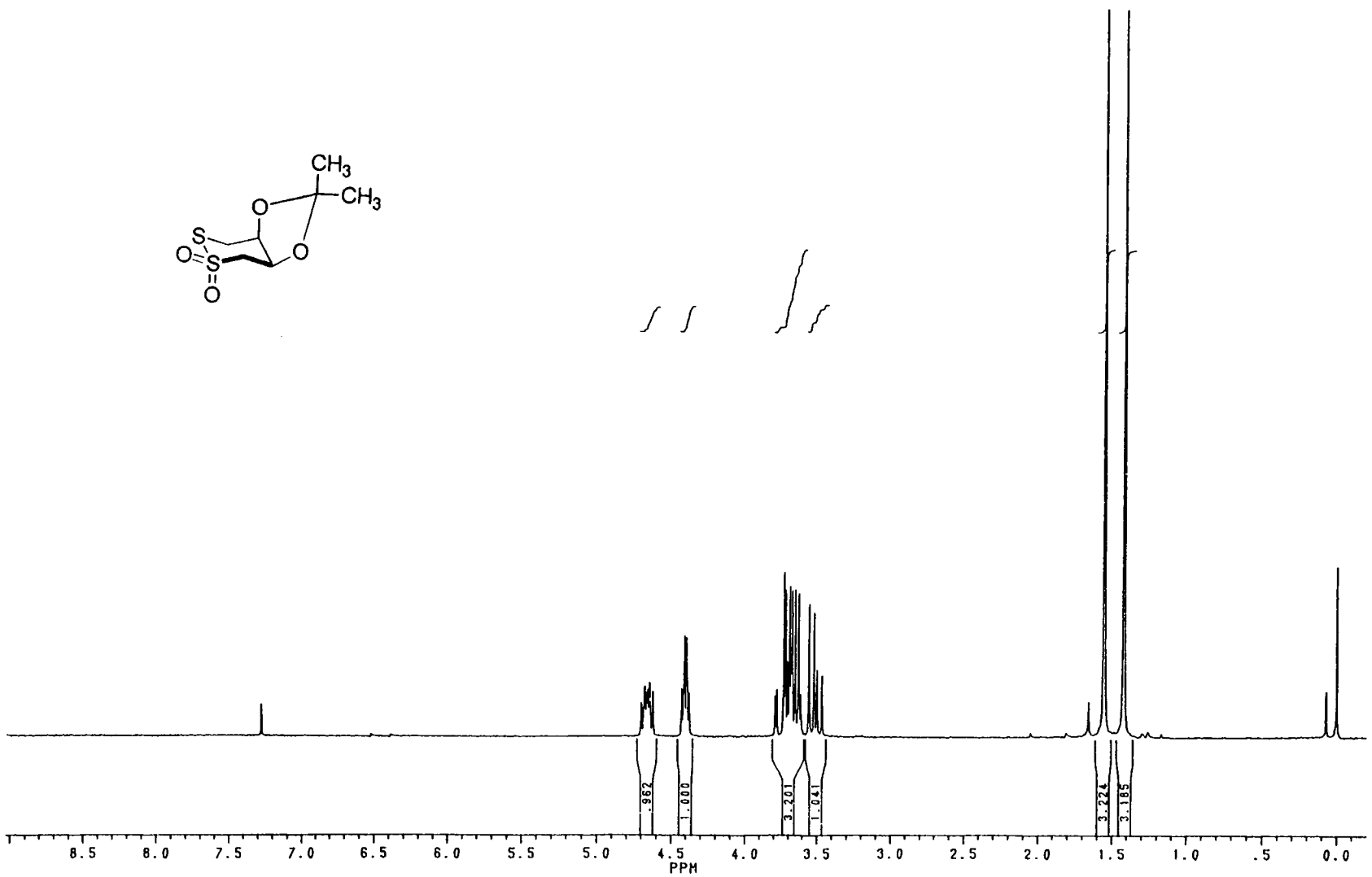
HETCOR spectrum (400 MHz–100.6 MHz, CD_3OD) of (±)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (**5**).



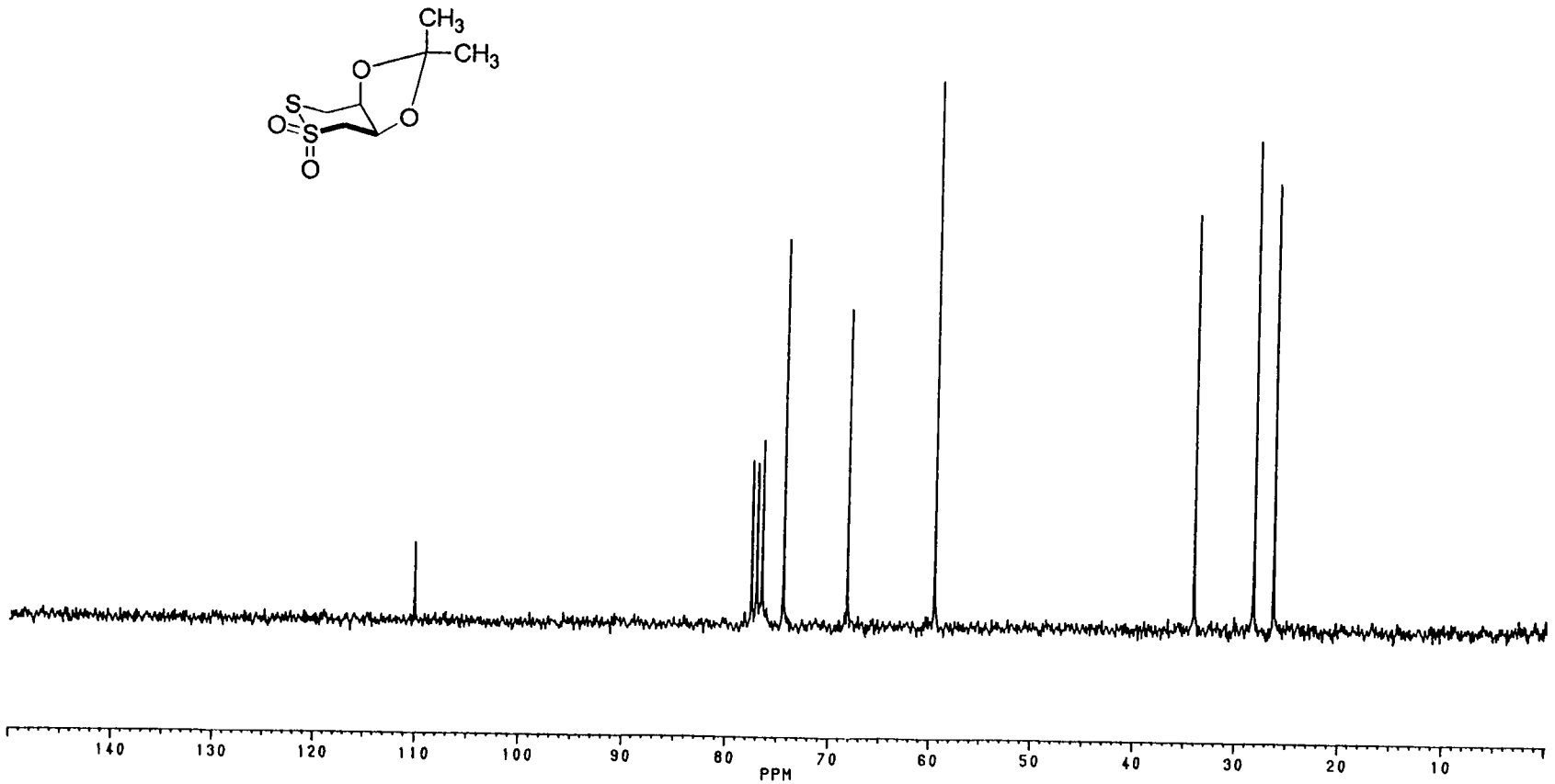
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-*cis*-4,5-diacetoxy-1,2-dithiane 1,1-dioxide (**6**).



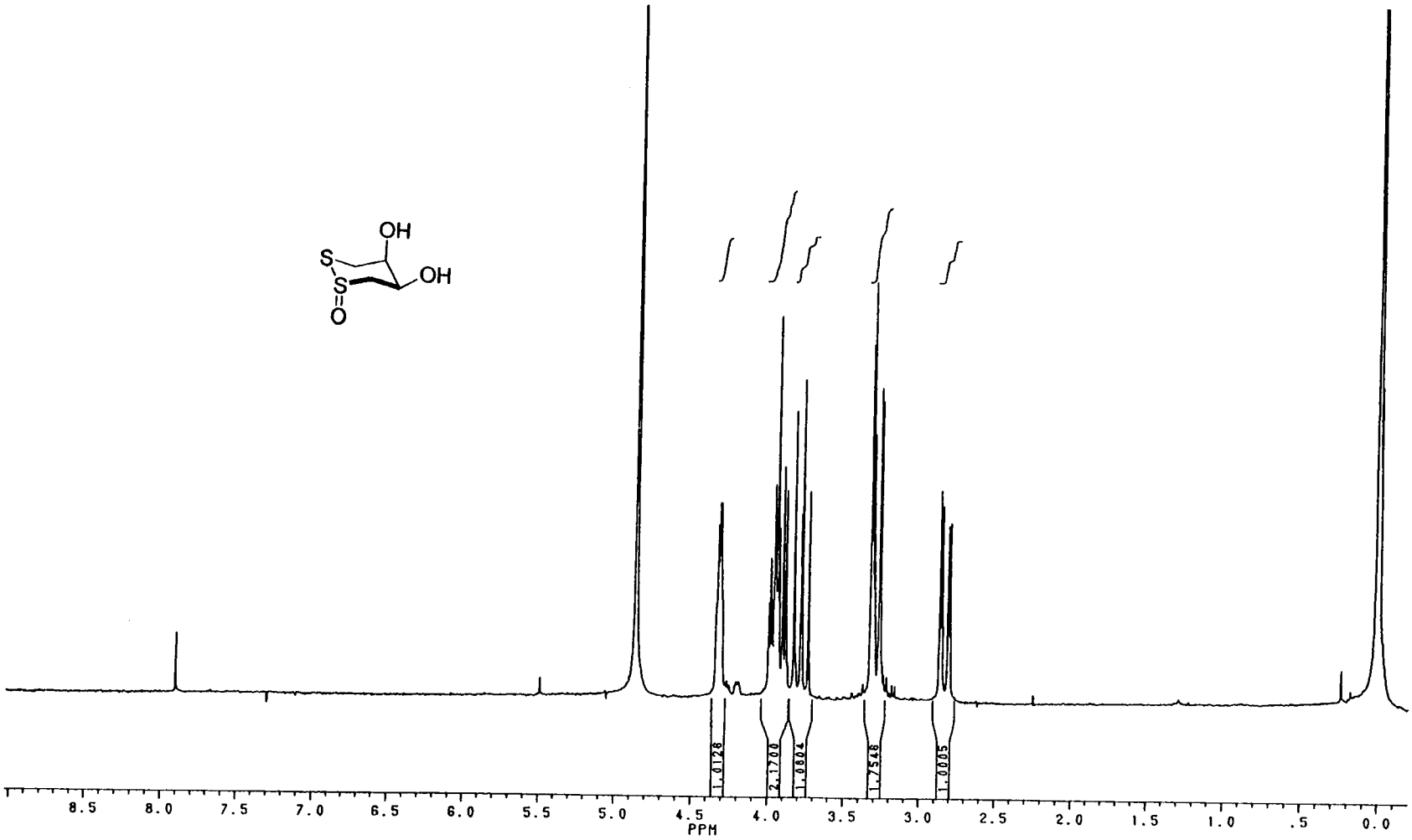
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-*cis*-4,5-diacetoxy-1,2-dithiane 1,1-dioxide (**6**).



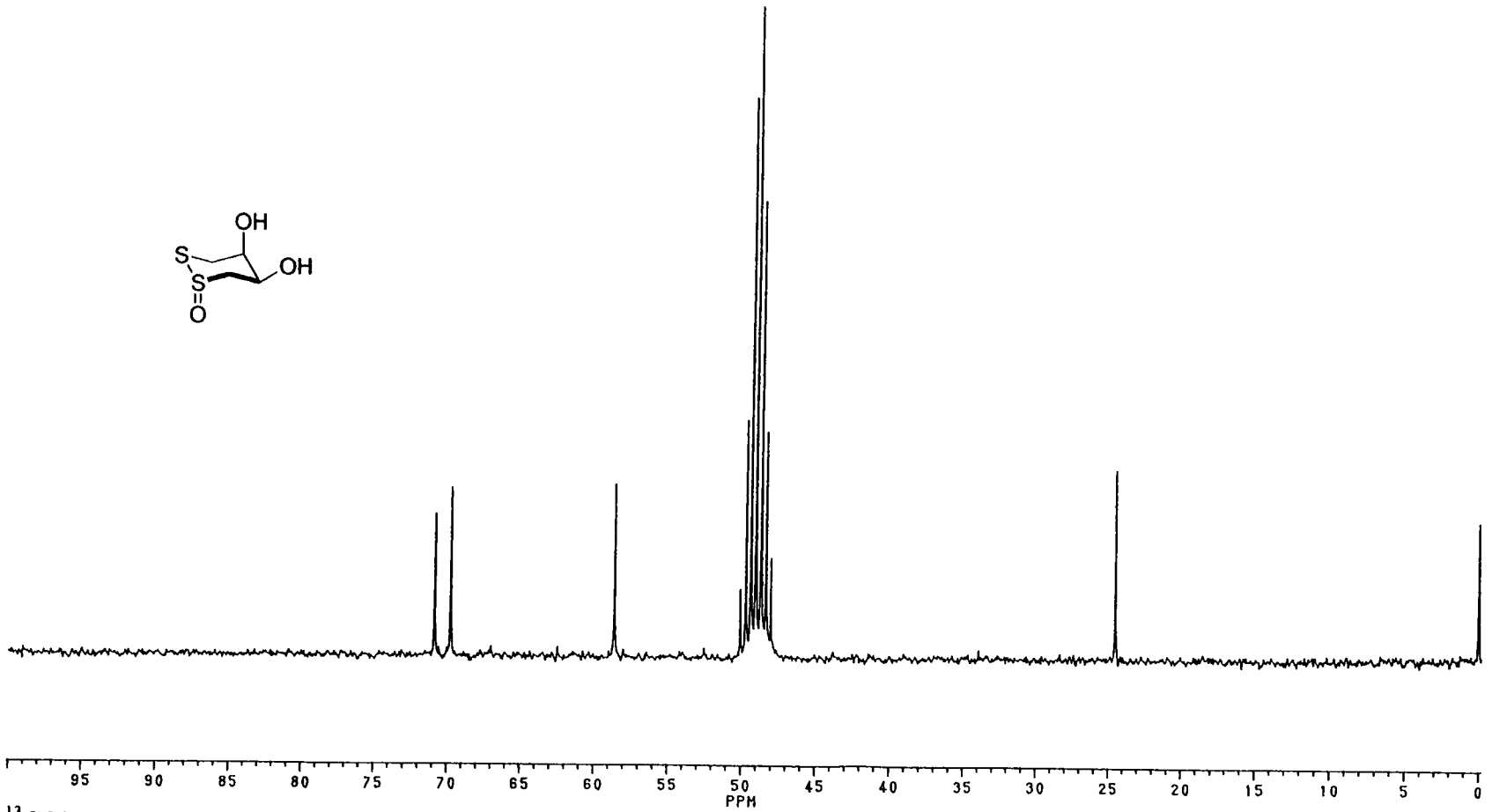
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-*cis*-4,5-*O*-isopropylidene-1,2-dithiane 1,1-dioxide (7).



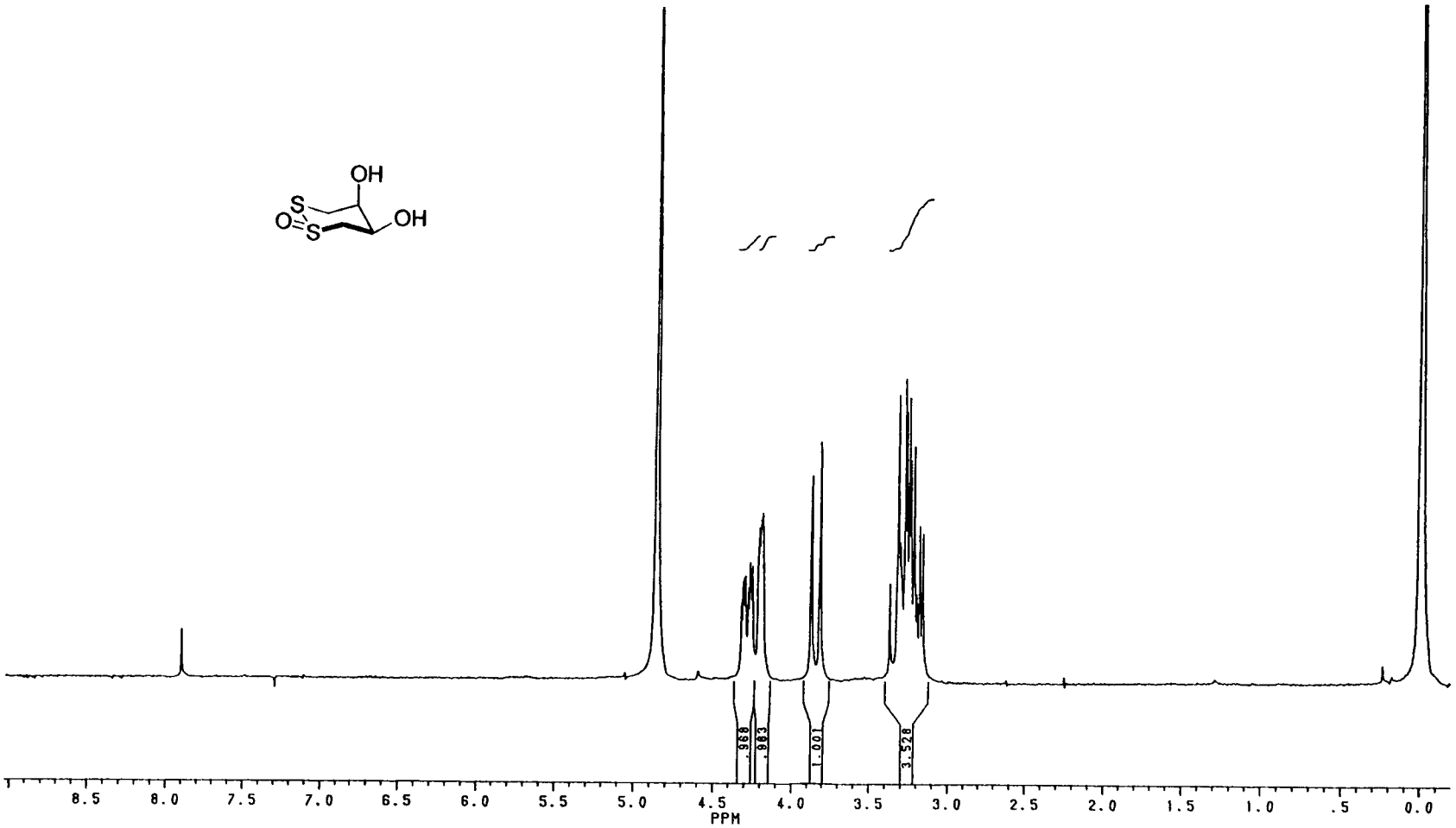
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-*cis*-4,5-*O*-isopropylidene-1,2-dithiane 1,1-dioxide (**7**).



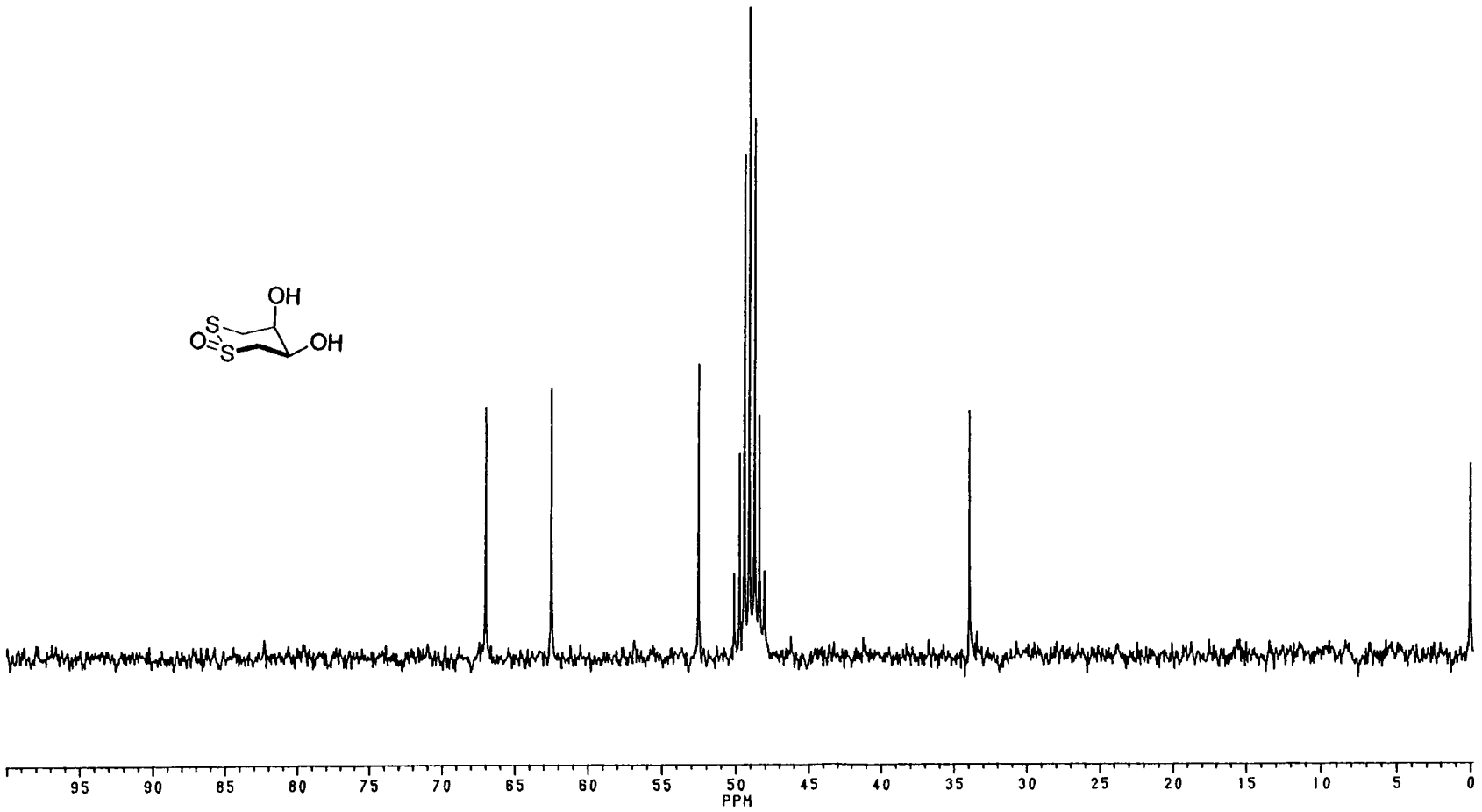
^{1}H NMR spectrum (250 MHz, CD_3OD) of (±)-1,2-dithiane-t-4,t-5-diol r-1-Oxide (**8**).



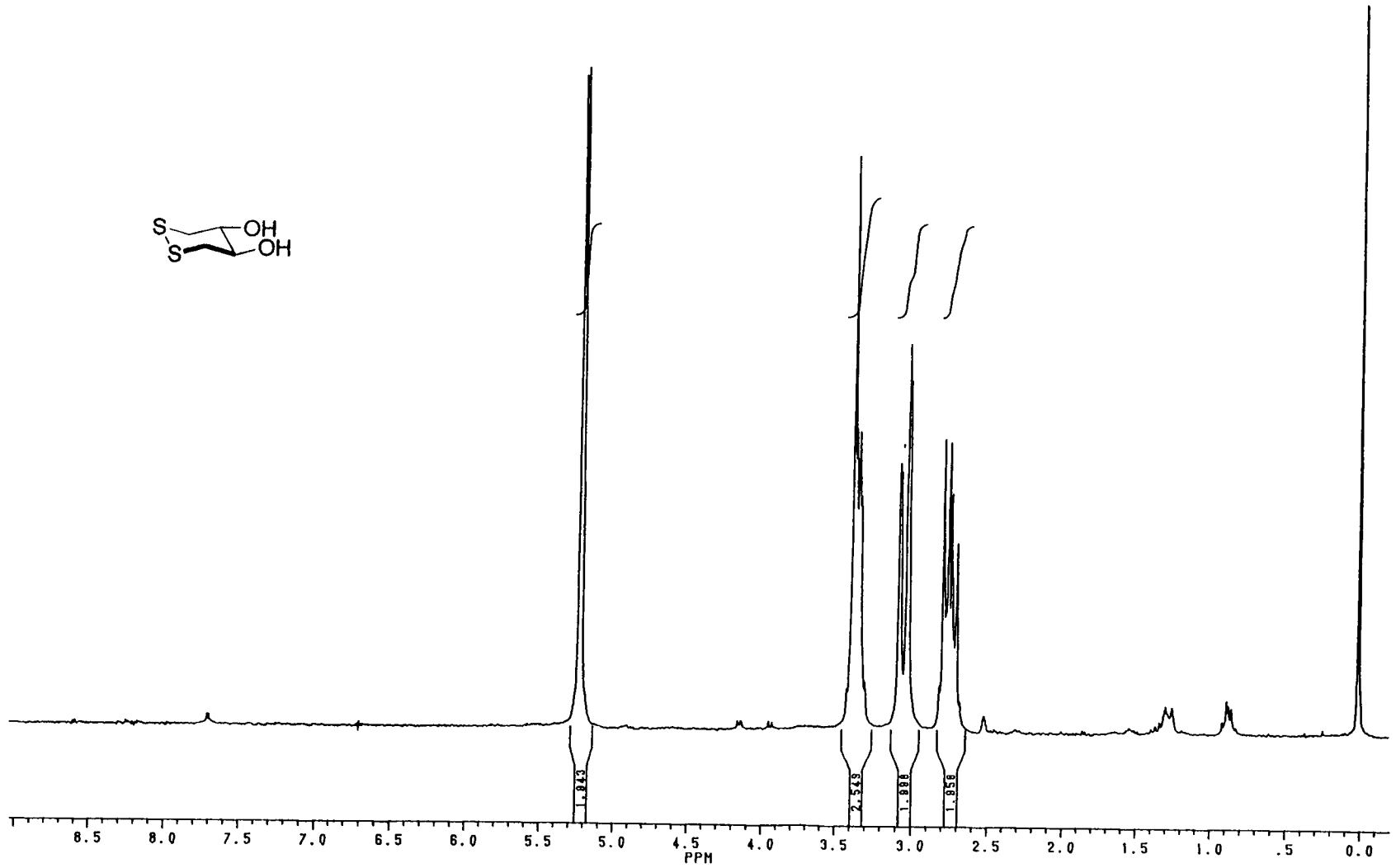
^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (±)-1,2-dithiane-t-4,t-5-diol r-1-Oxide (**8**).



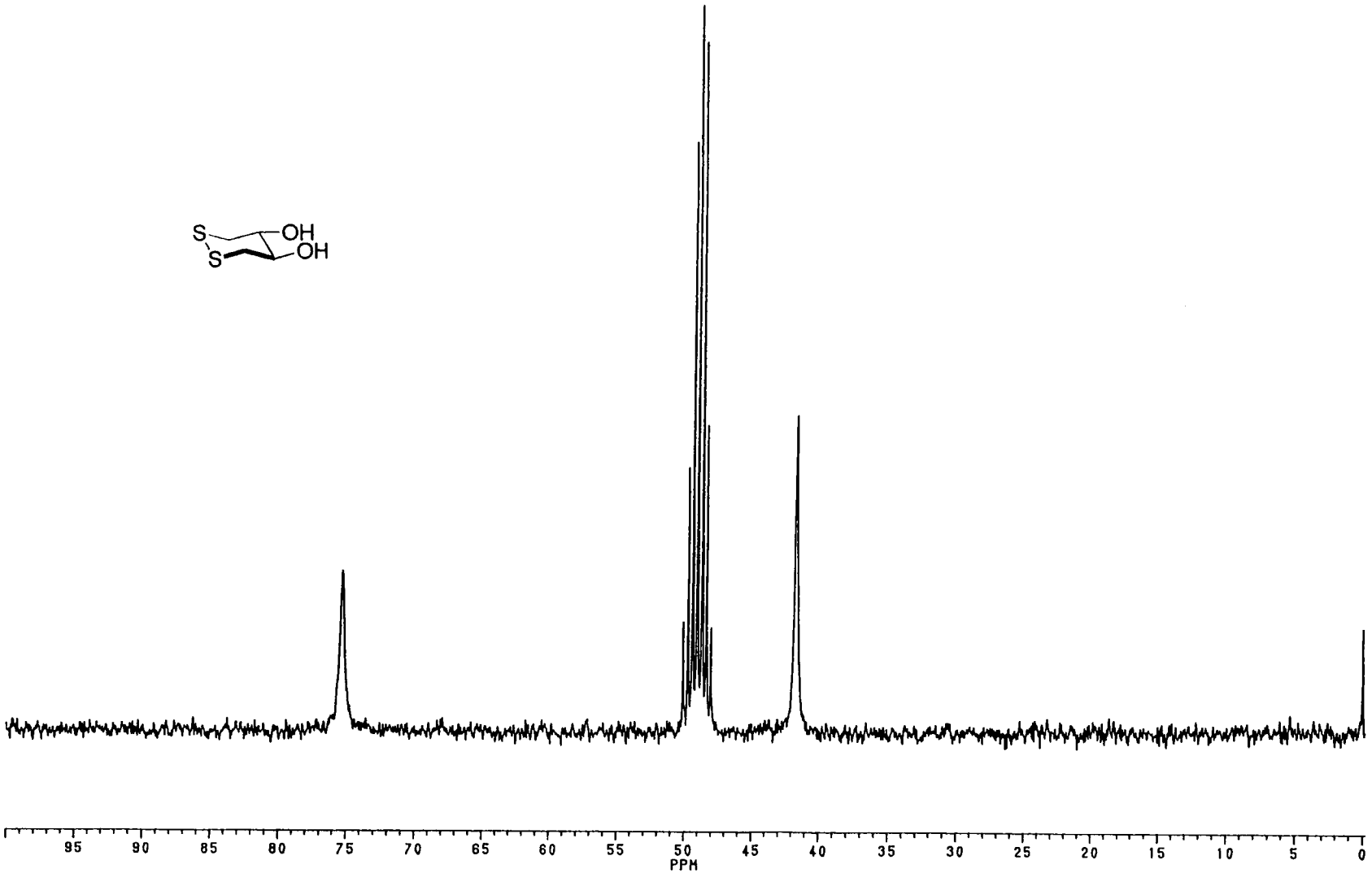
^{1}H NMR spectrum (250 MHz, CD_3OD) of (±)-1,2-dithiane-c-4,c-5-diol r-1-Oxide (**9**).



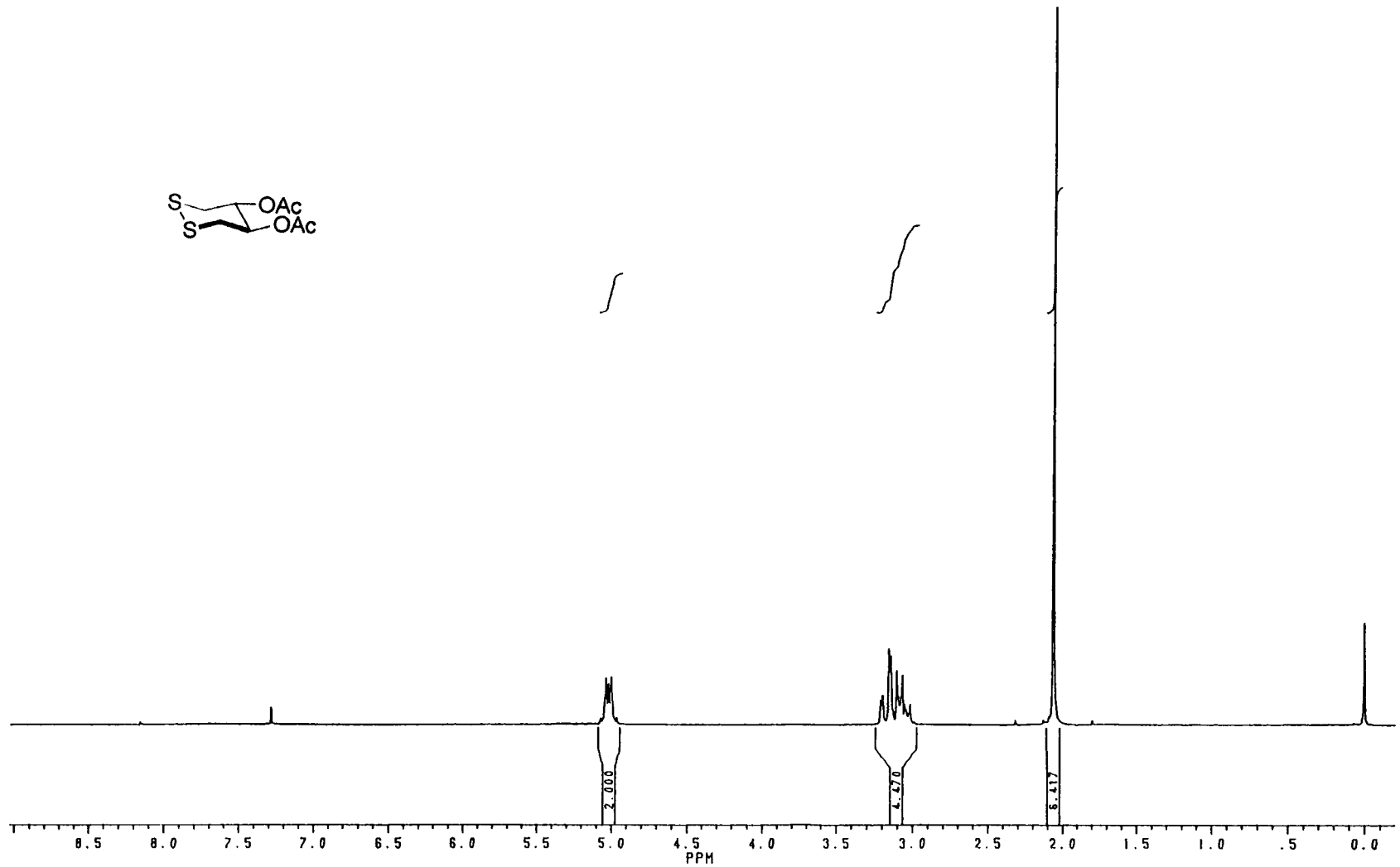
^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (±)-1,2-dithiane-c-4,c-5-diol r-1-Oxide (**9**).



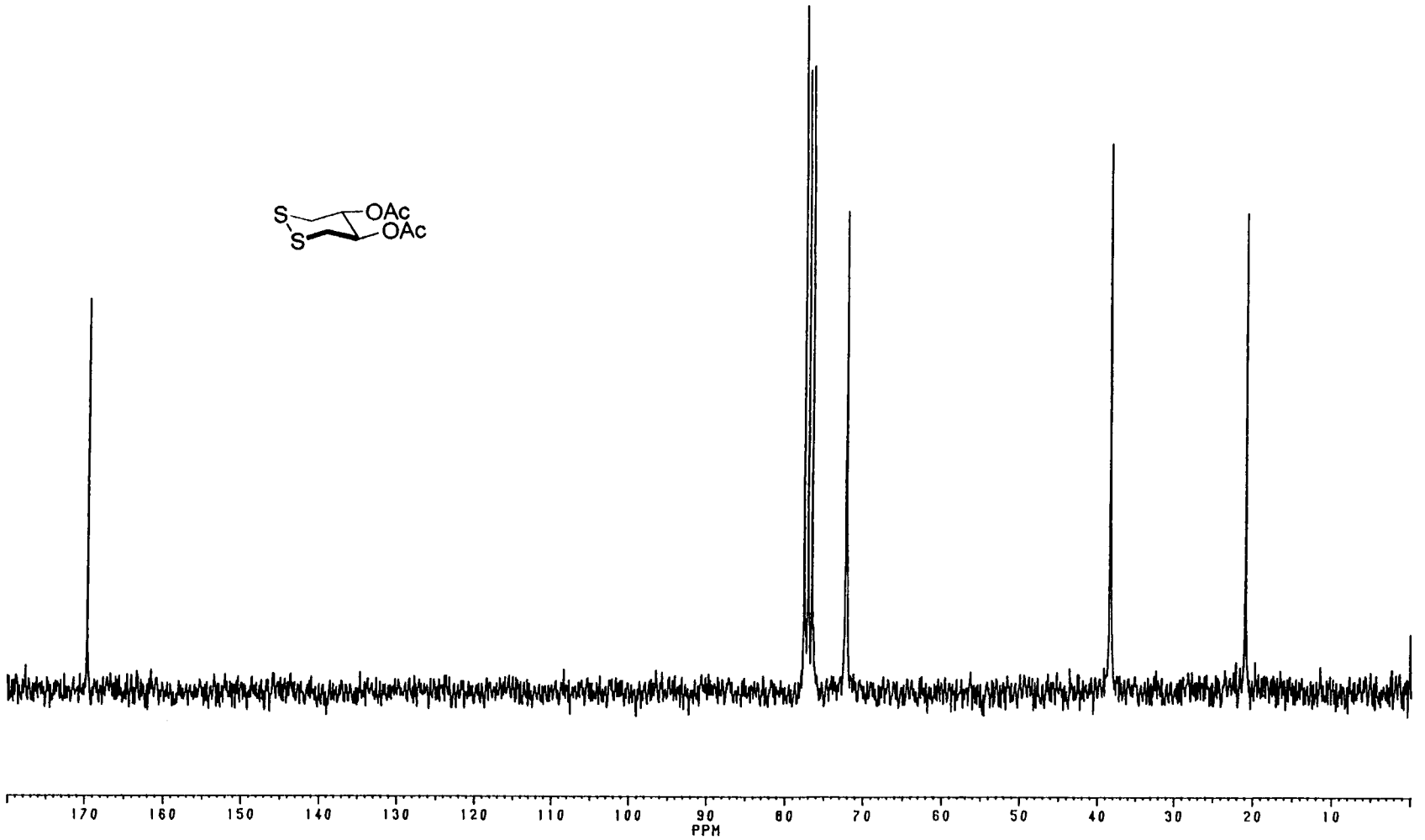
^{1}H NMR spectrum (250 MHz, DMSO-d_6) of (±)-*trans*-4,5dihydroxy-1,2-dithiane (**11**).



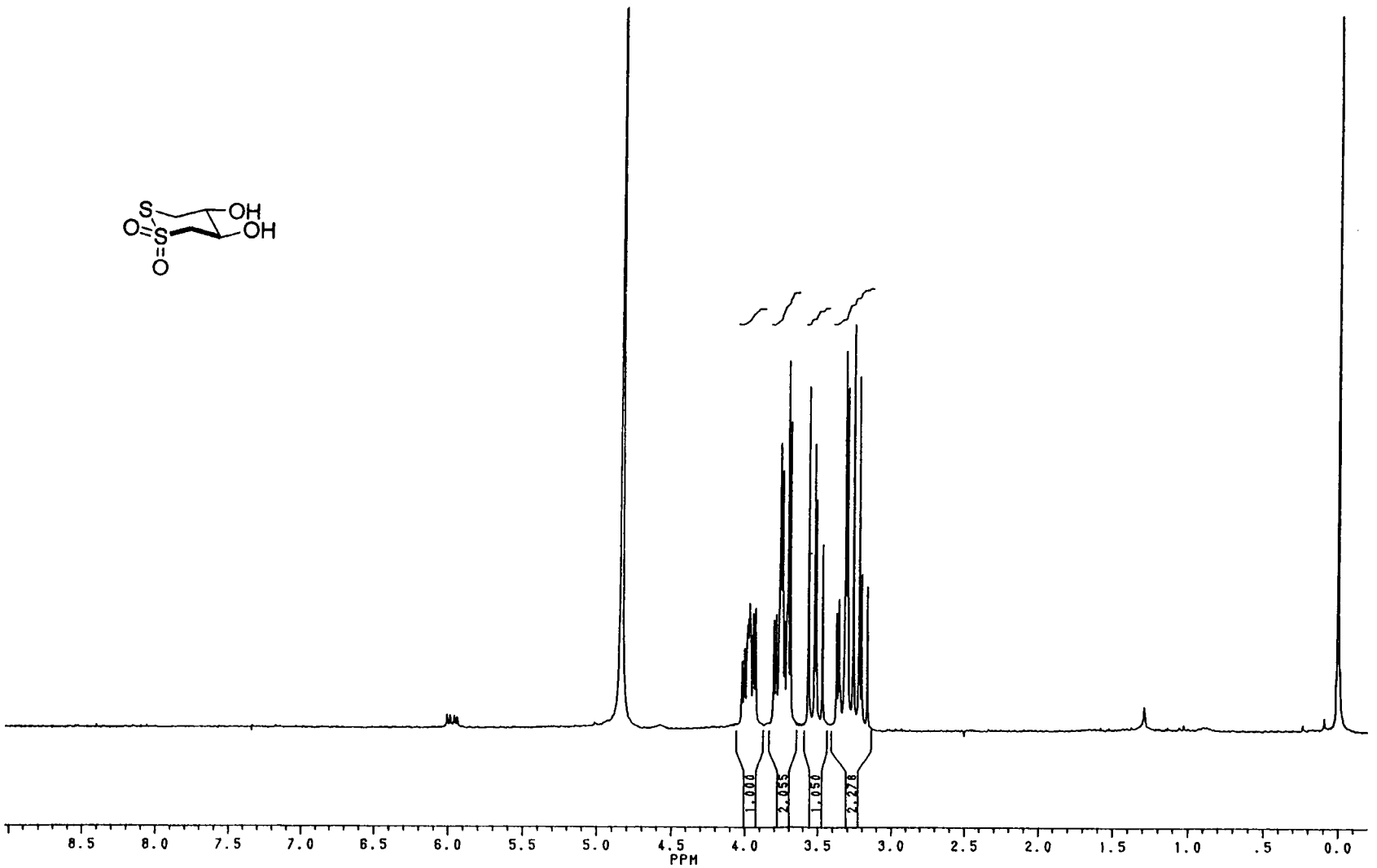
^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (±)-*trans*-4,5-dihydroxy-1,2-dithiane (**11**).



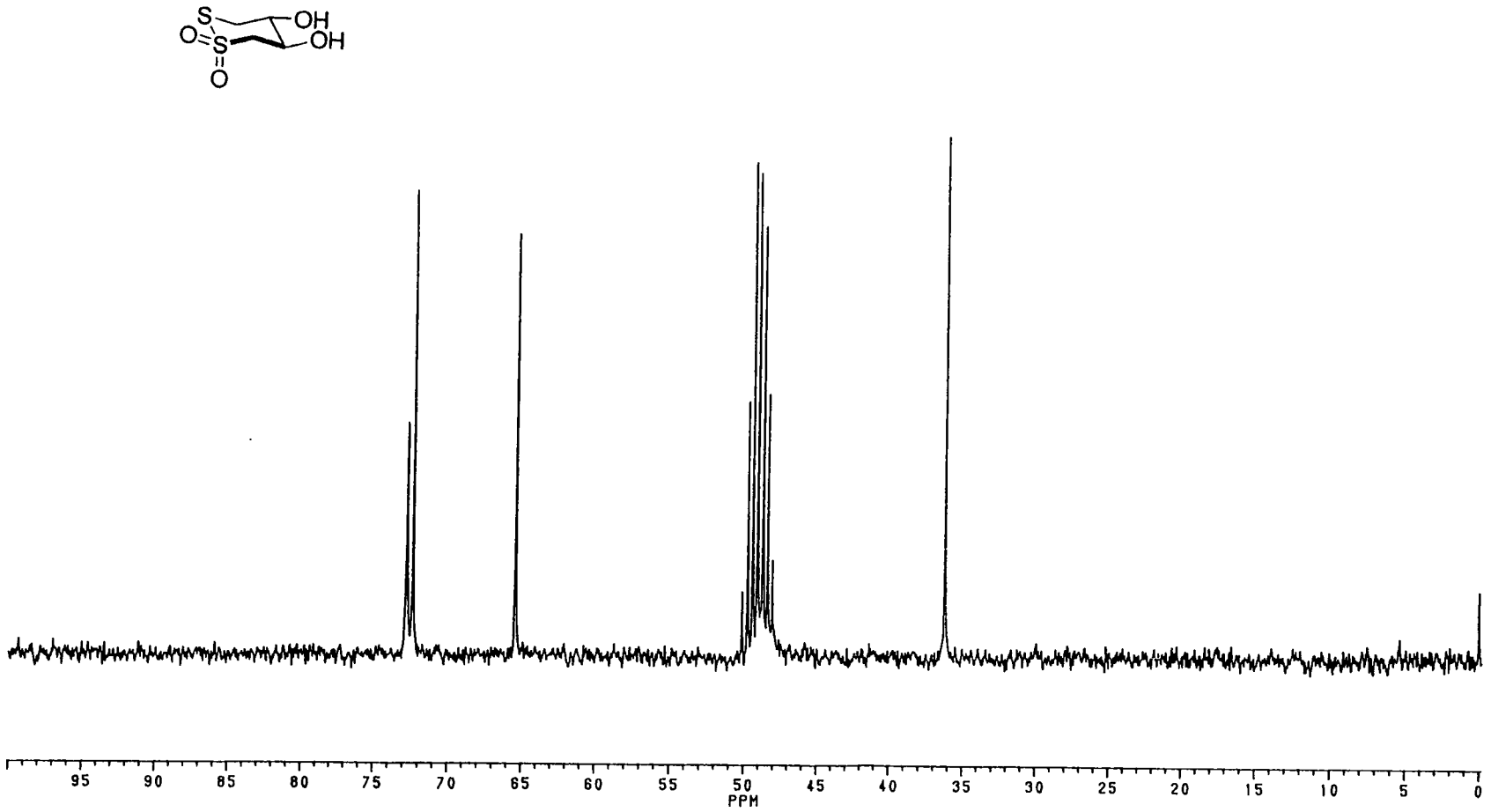
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-*trans*-4,5-diacetoxy-1,2-dithiane (**12**).



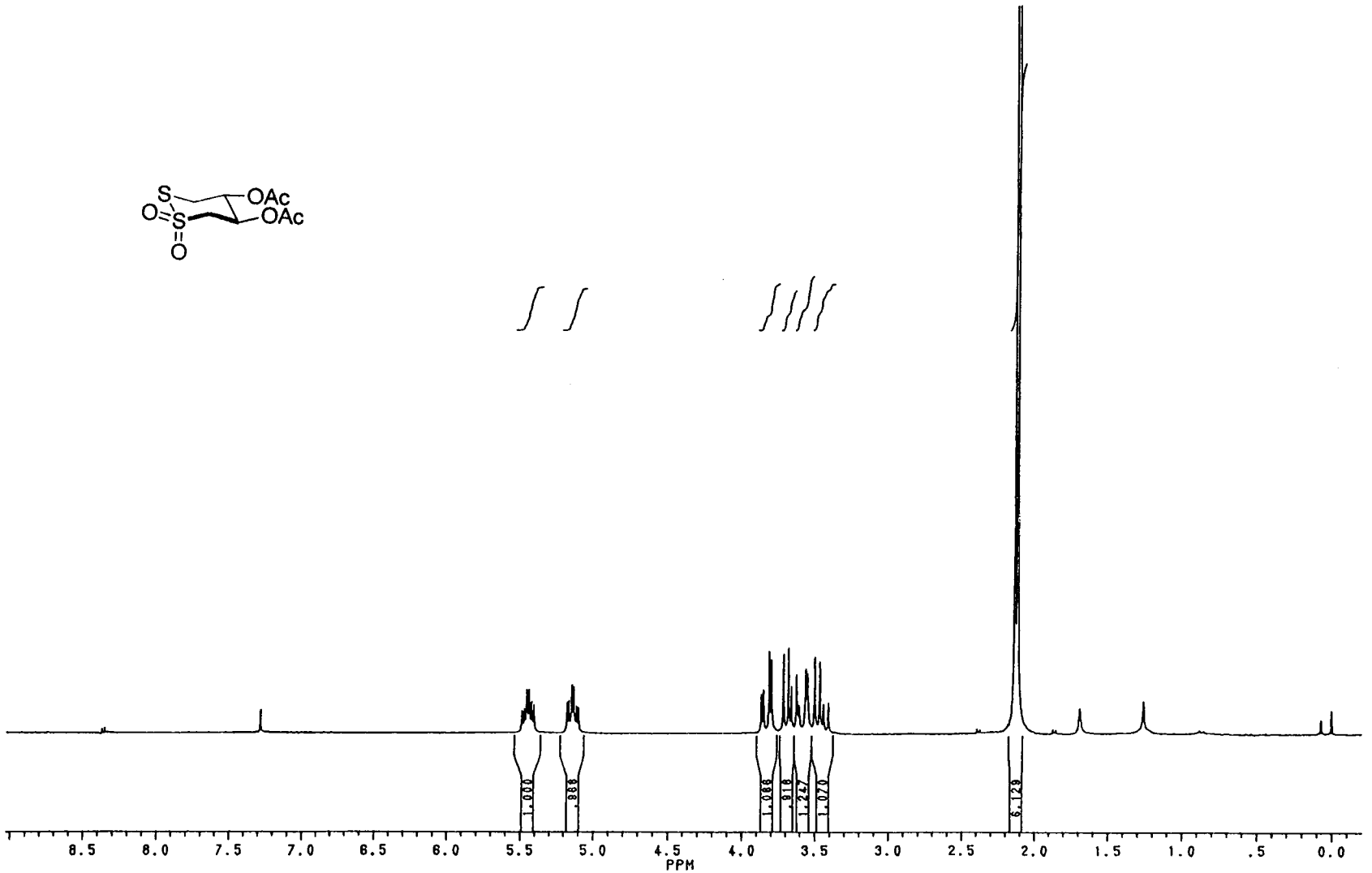
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-*trans*-4,5-diacetoxy-1,2-dithiane (**12**).



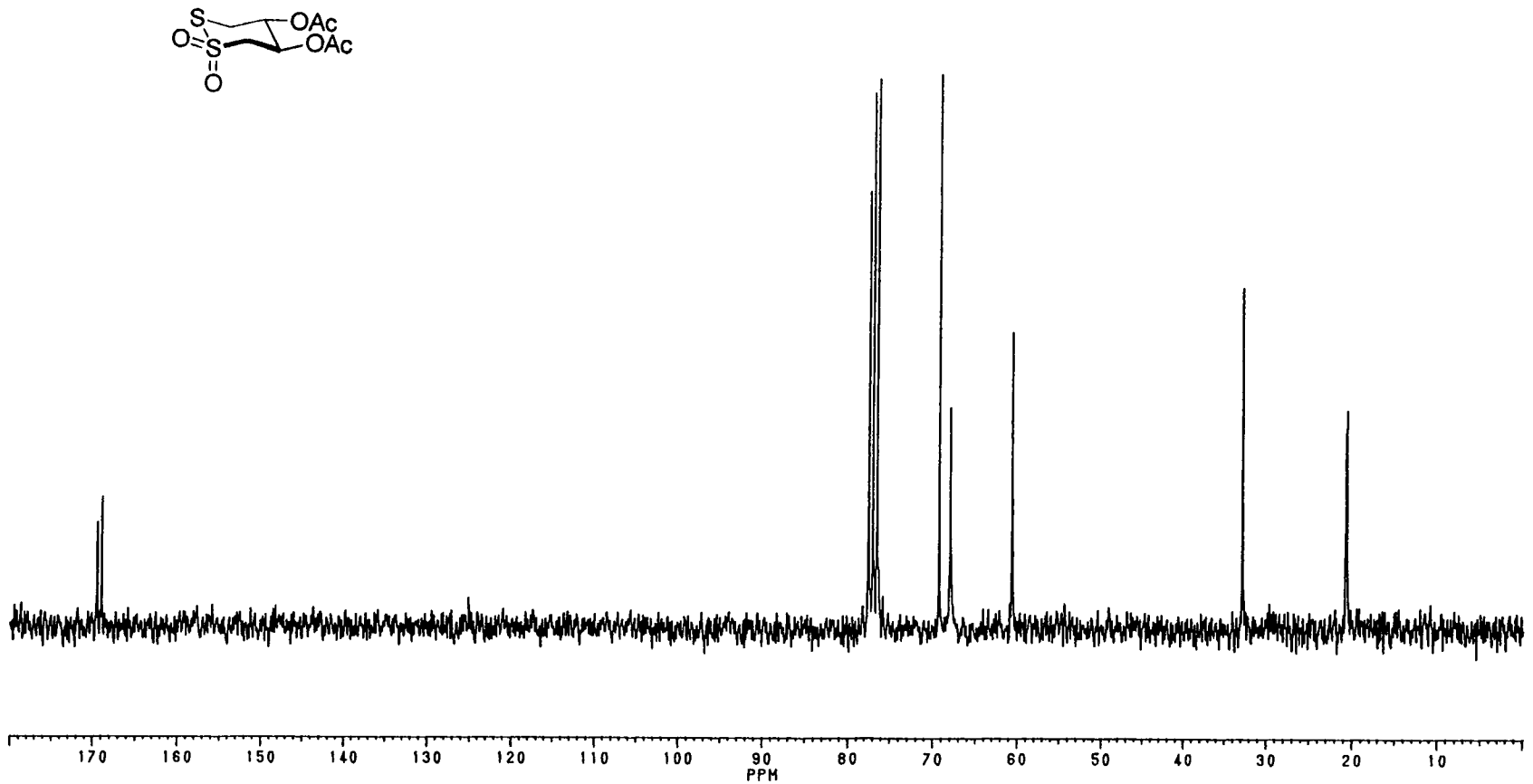
^{1}H NMR spectrum (250 MHz, CD_3OD) of (±)-*trans*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (**13**).



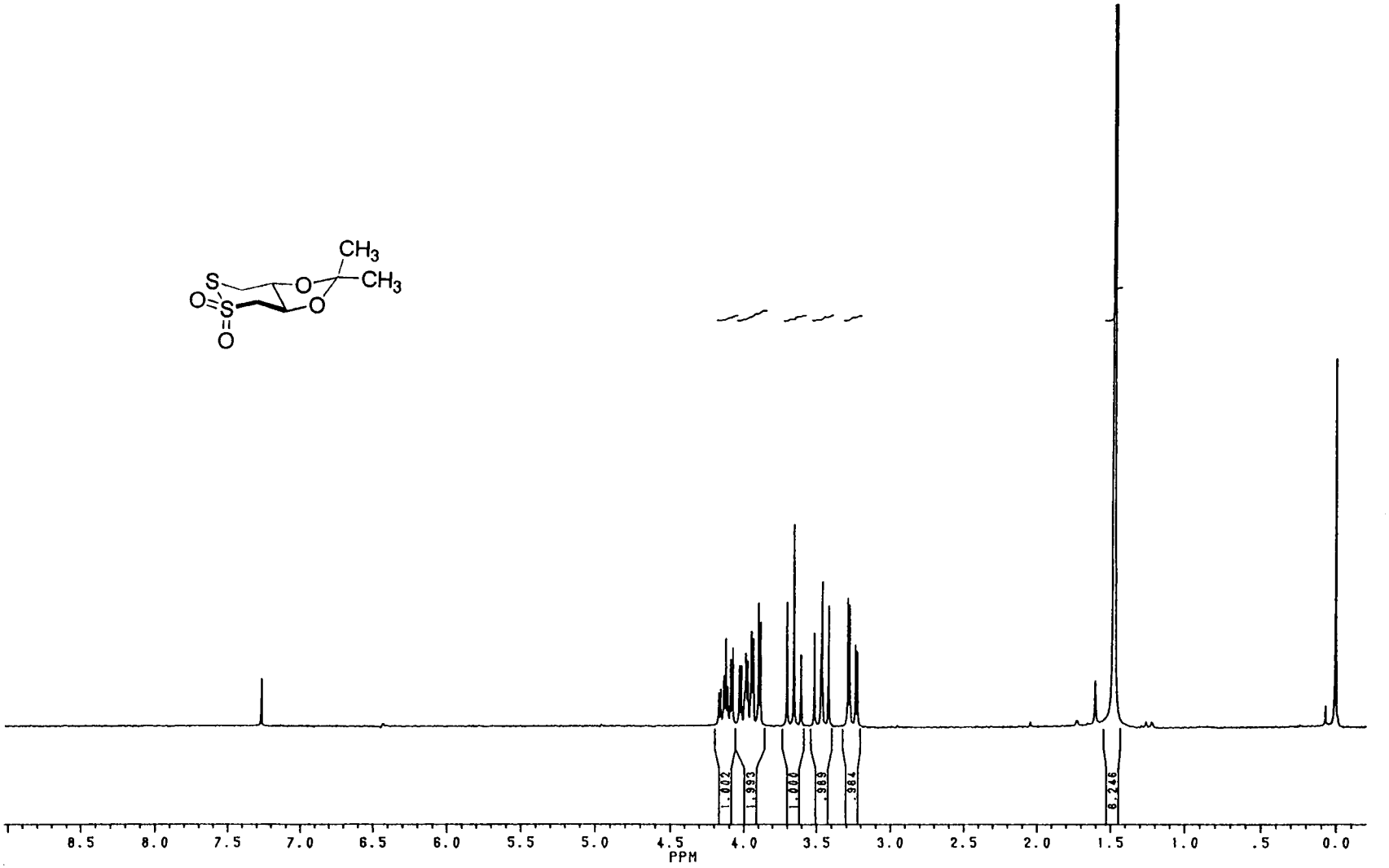
^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (±)-*trans*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (**13**).



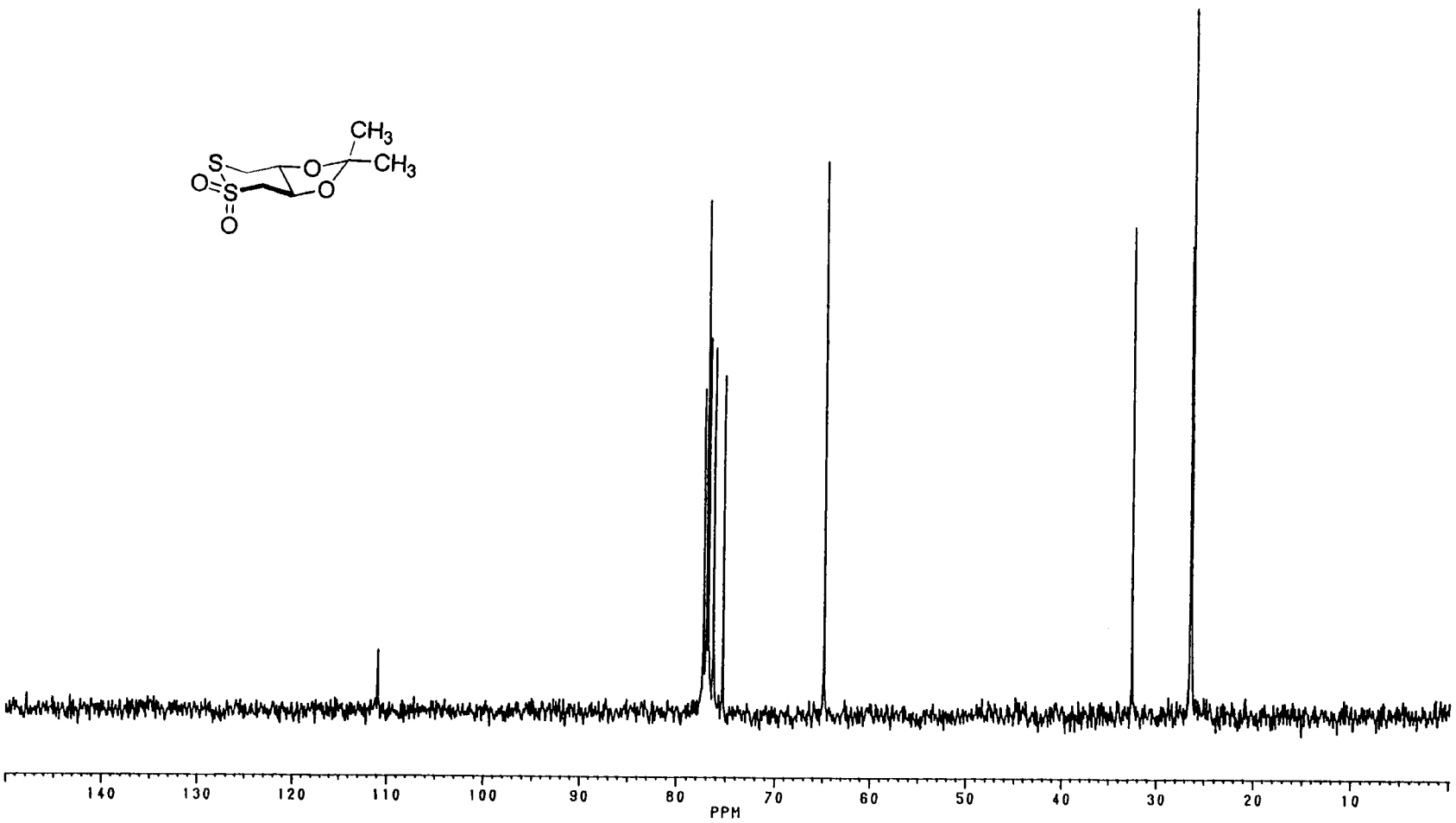
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-*trans*-4,5-diacetoxy-1,2-dithiane 1,1-dioxide (**14**).



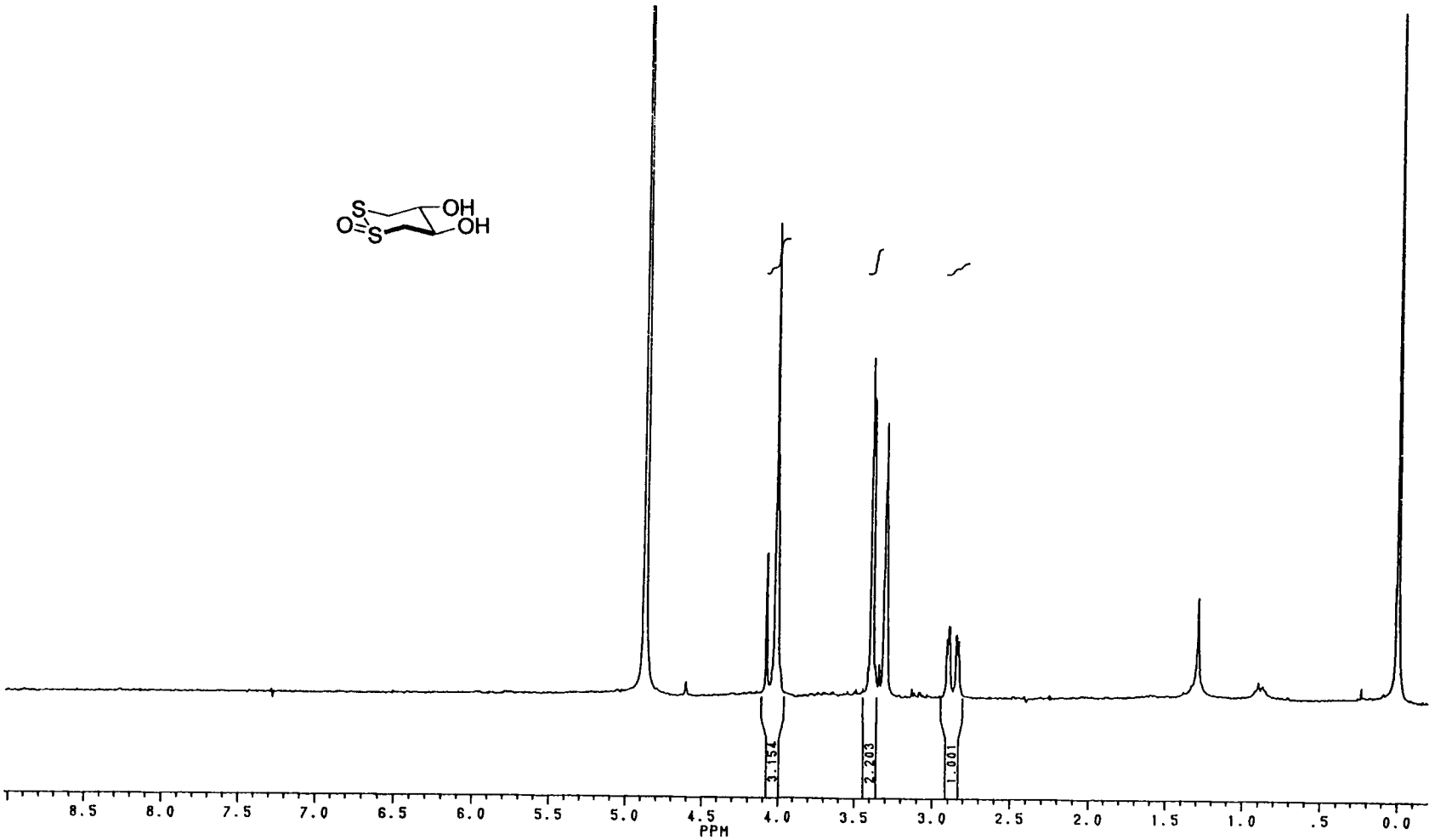
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-*trans*-4,5-diacetoxy-1,2-dithiane 1,1-dioxide (**14**).



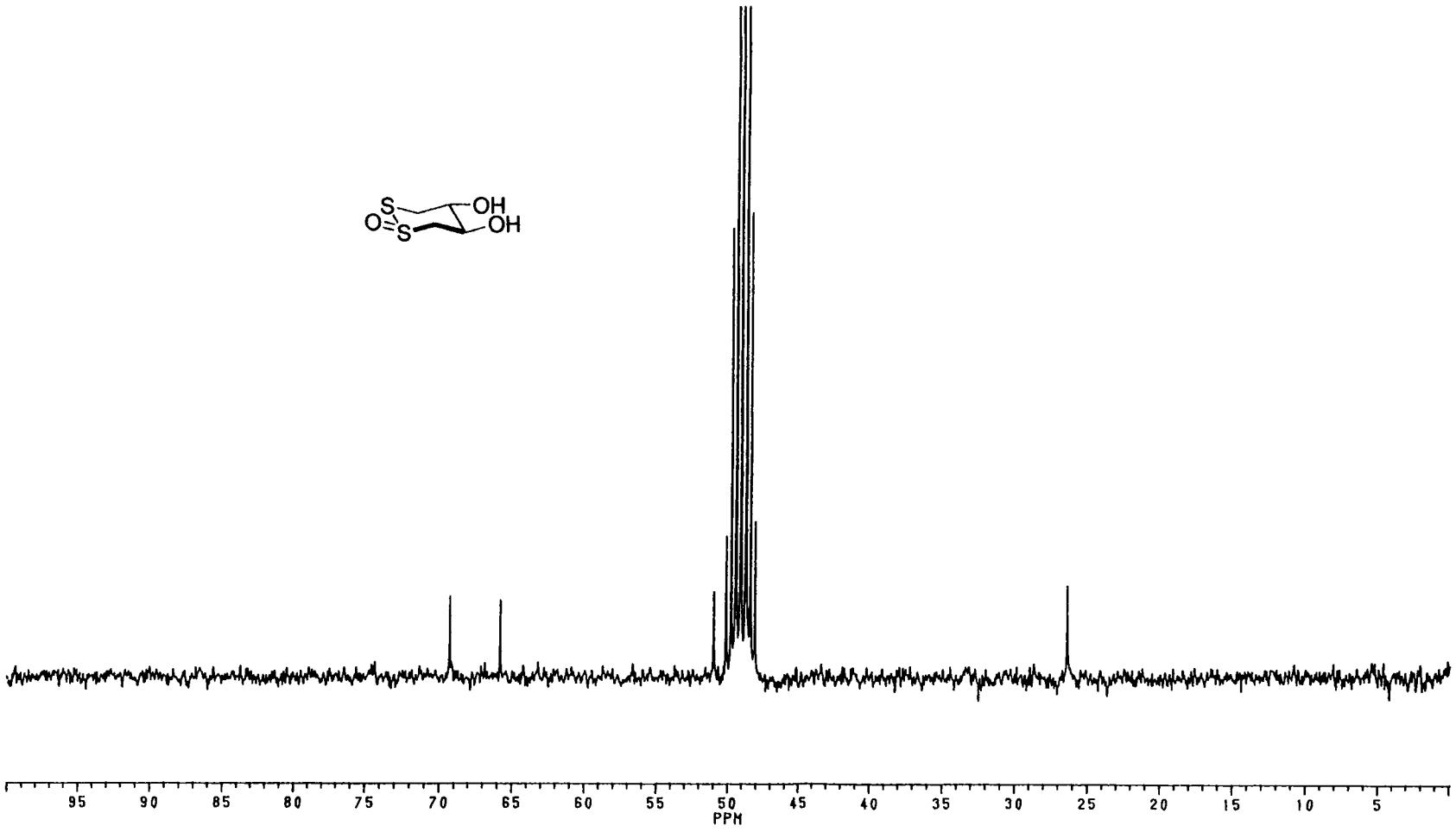
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-*trans*-4,5-*O*-isopropylidene-1,2-dithiane 1,1-dioxide (**15**).



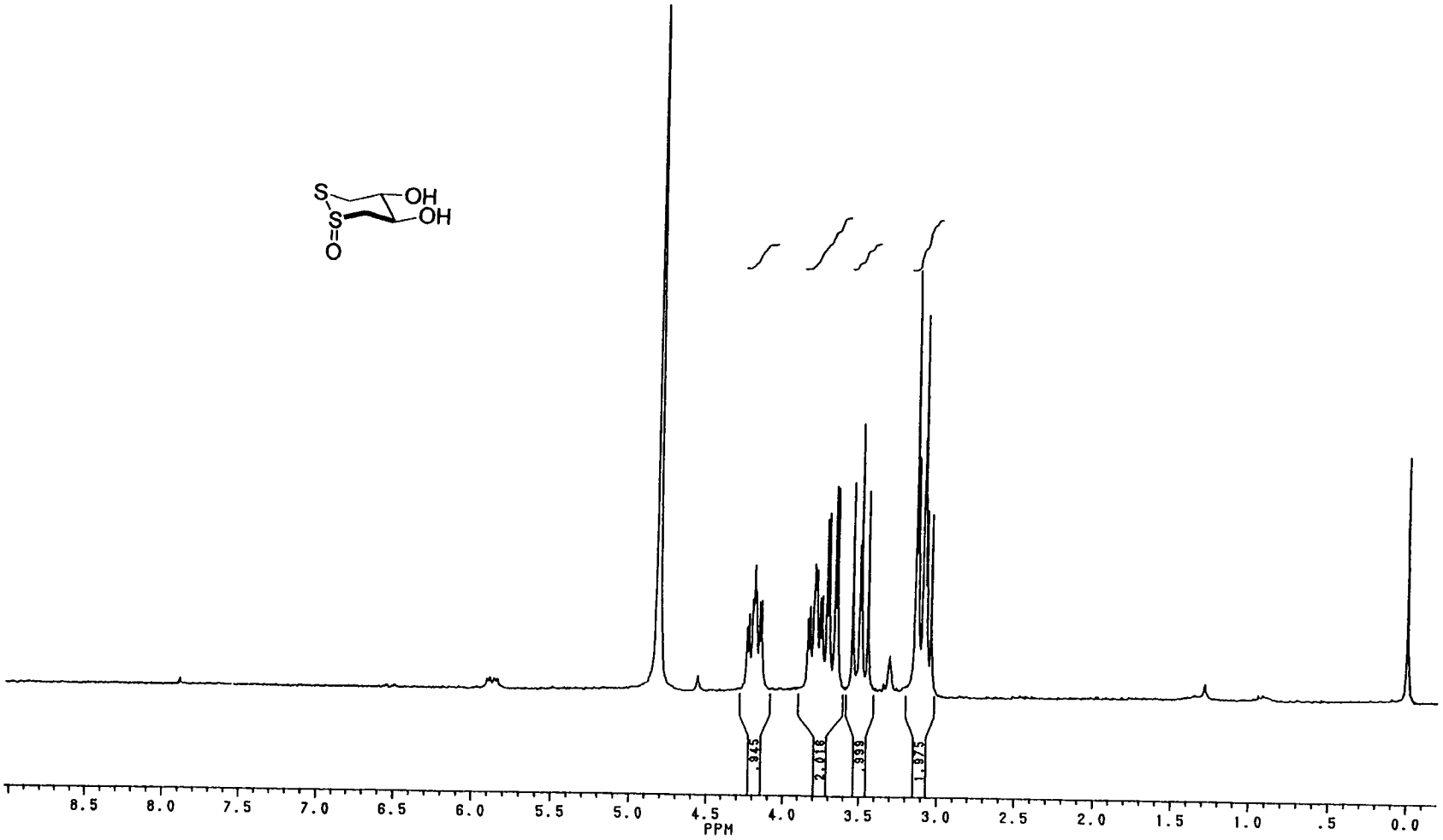
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-*trans*-4,5-*O*-isopropylidene-1,2-dithiane 1,1-dioxide (**15**).



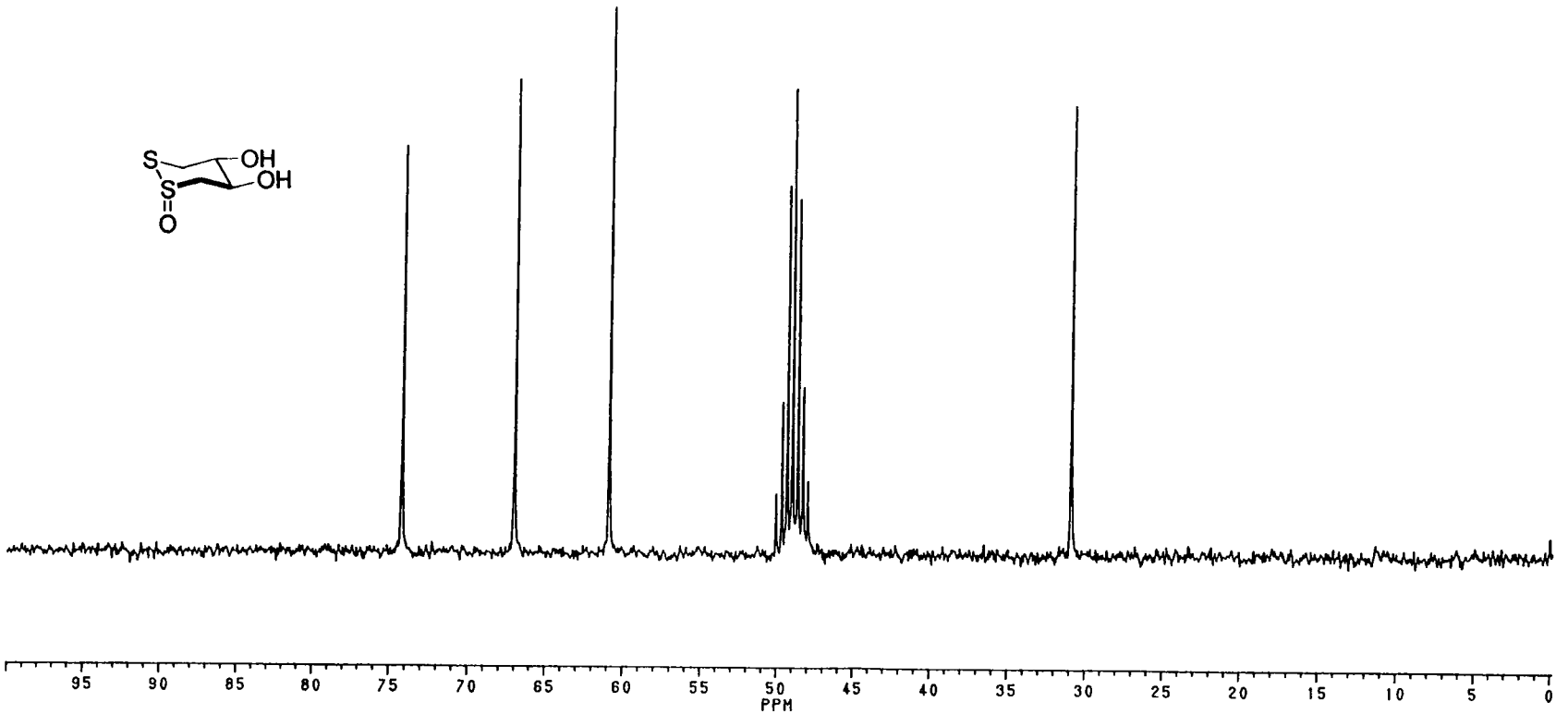
^{1}H NMR spectrum (250 MHz, CD_3OD) of (±)-1,2-dithiane-t-4,c-5-diol r-1-Oxide (**16**).



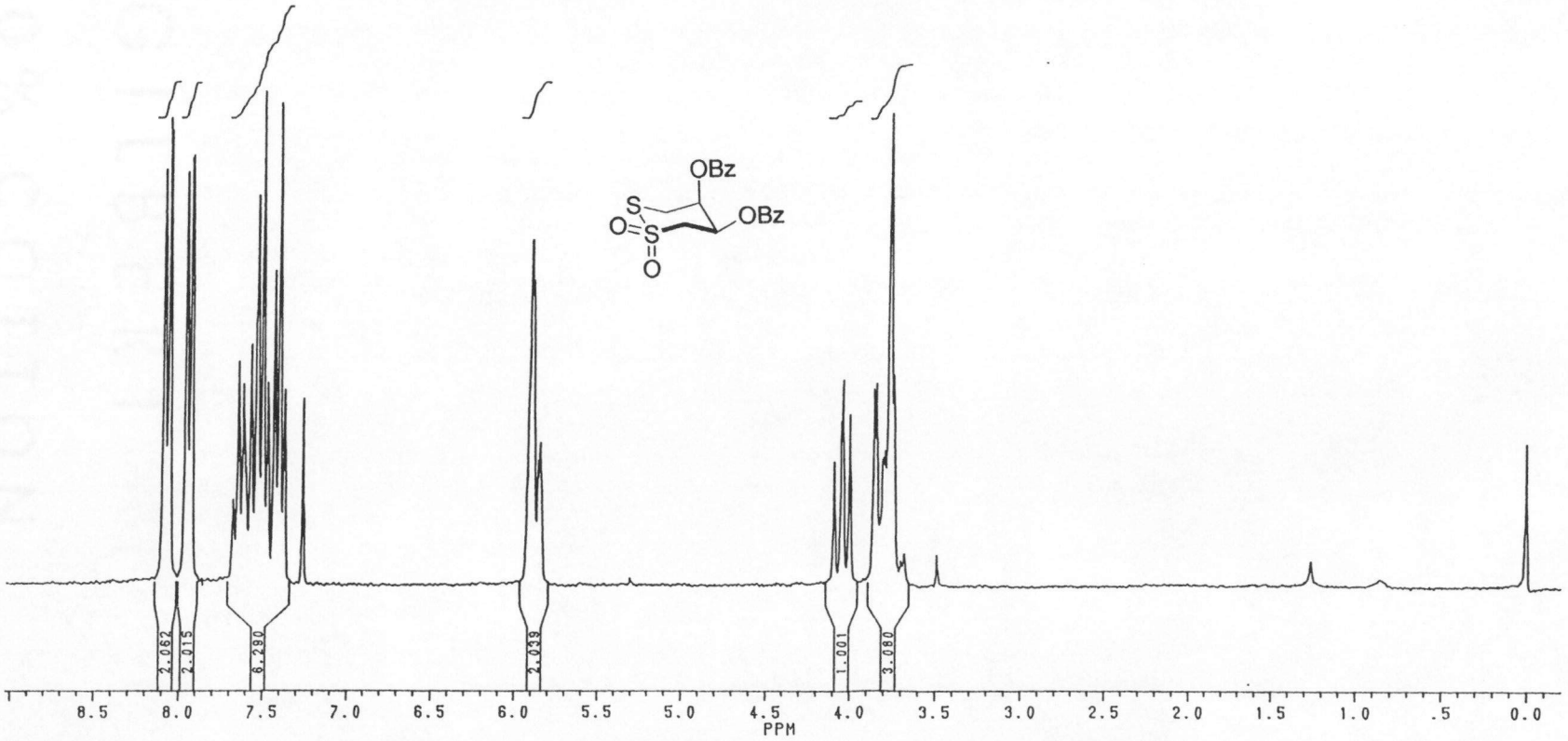
^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (±)-1,2-dithiane-t-4,c-5-diol r-1-Oxide (**16**).



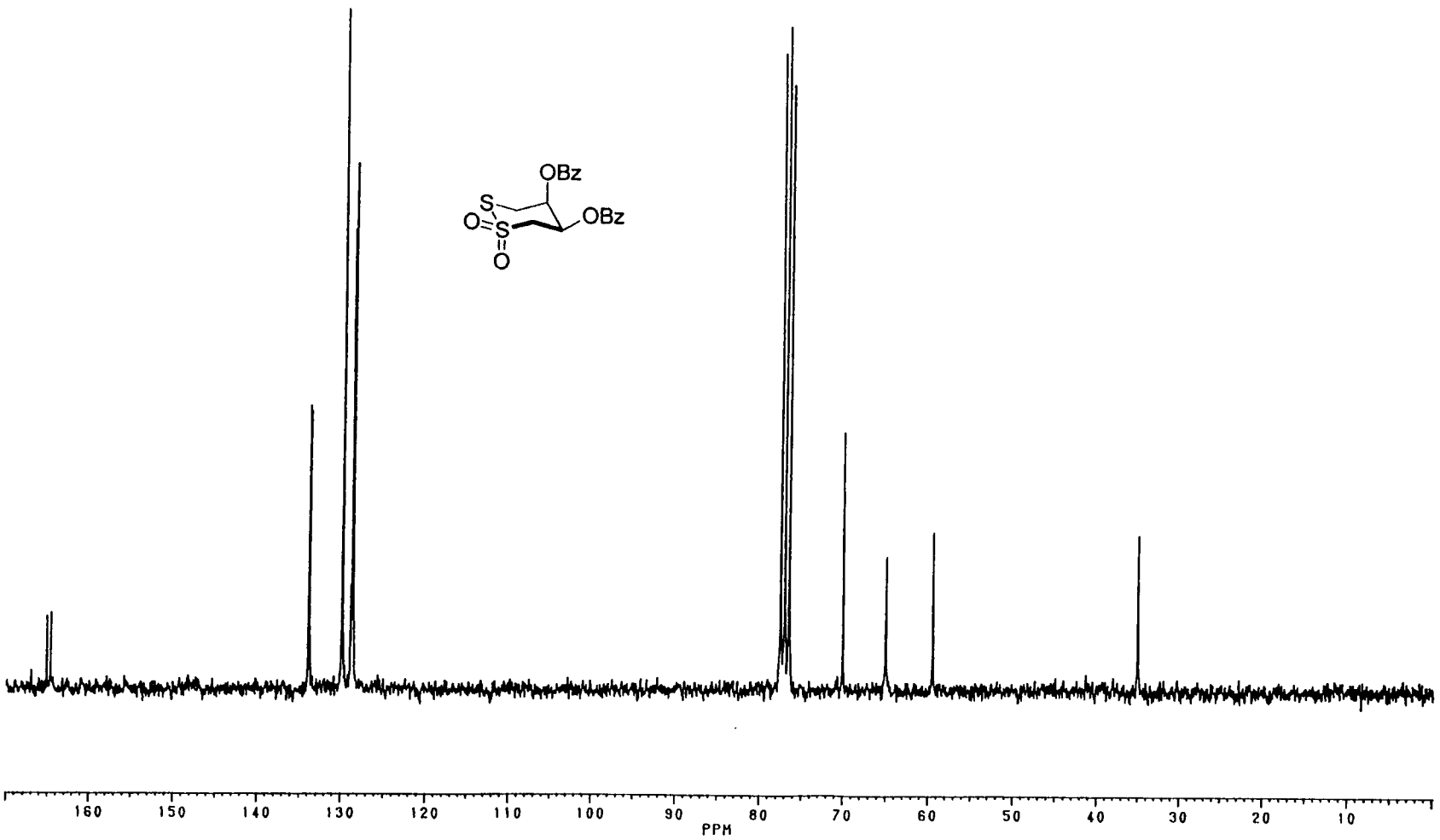
^{1}H NMR spectrum (250 MHz, CD_3OD) of (±)-1,2-dithiane-c-4,t-5-diol r-1-Oxide (**17**).



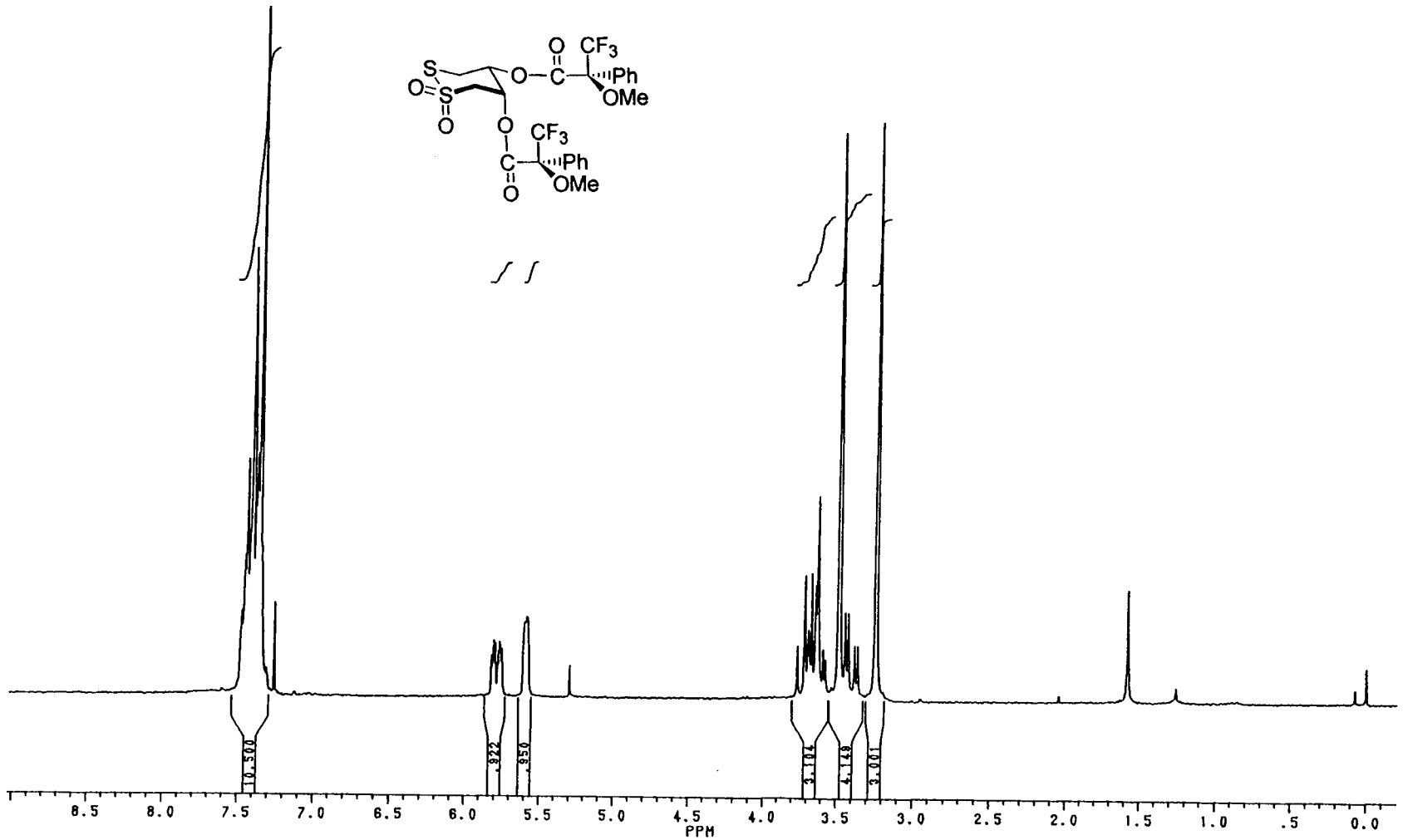
^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (±)-1,2-dithiane-c-4,t-5-diol r-1-Oxide (**17**).



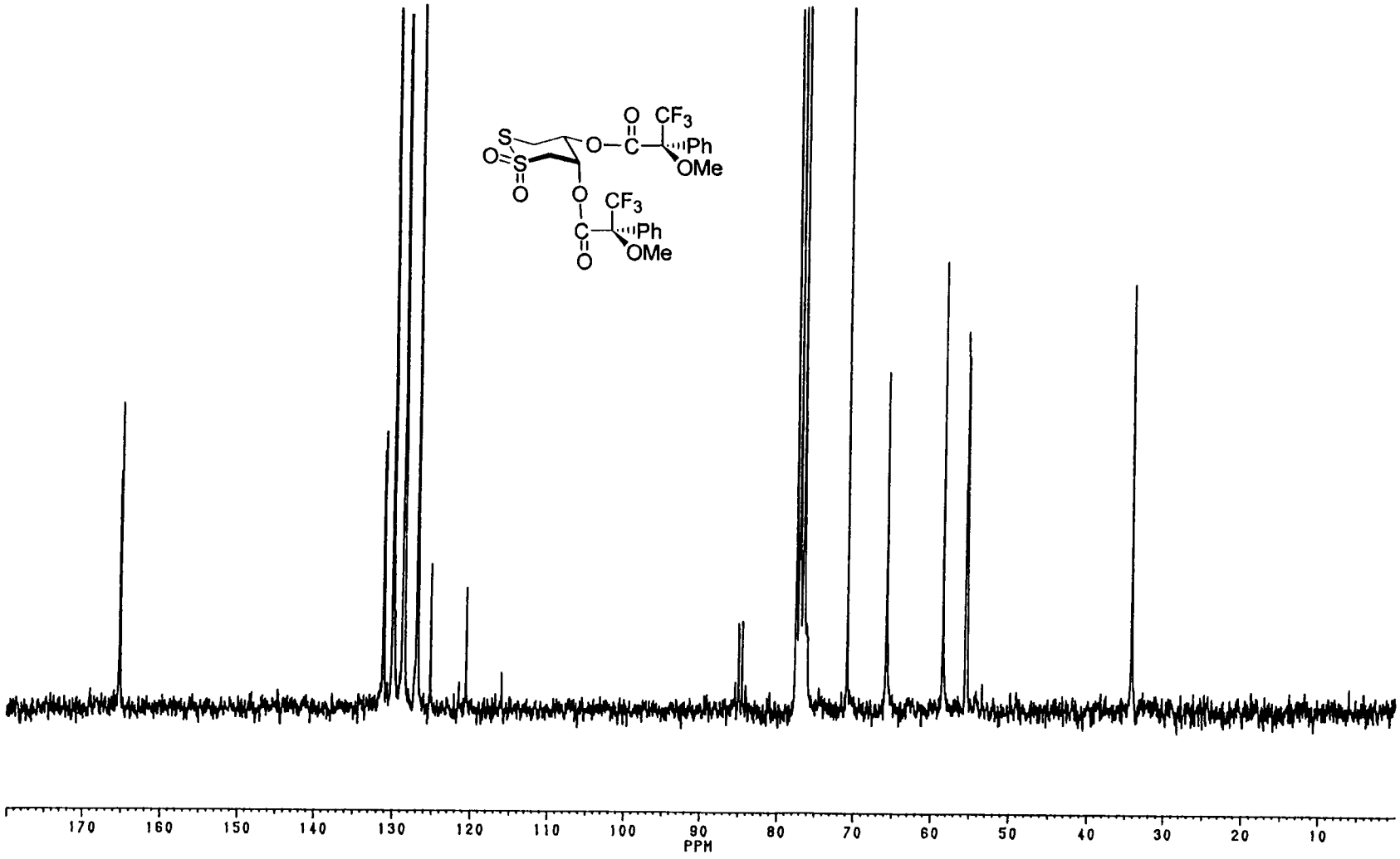
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-*cis*-4,5-dibenzoyloxy-1,2-dithiane 1,1-dioxide (**22**).



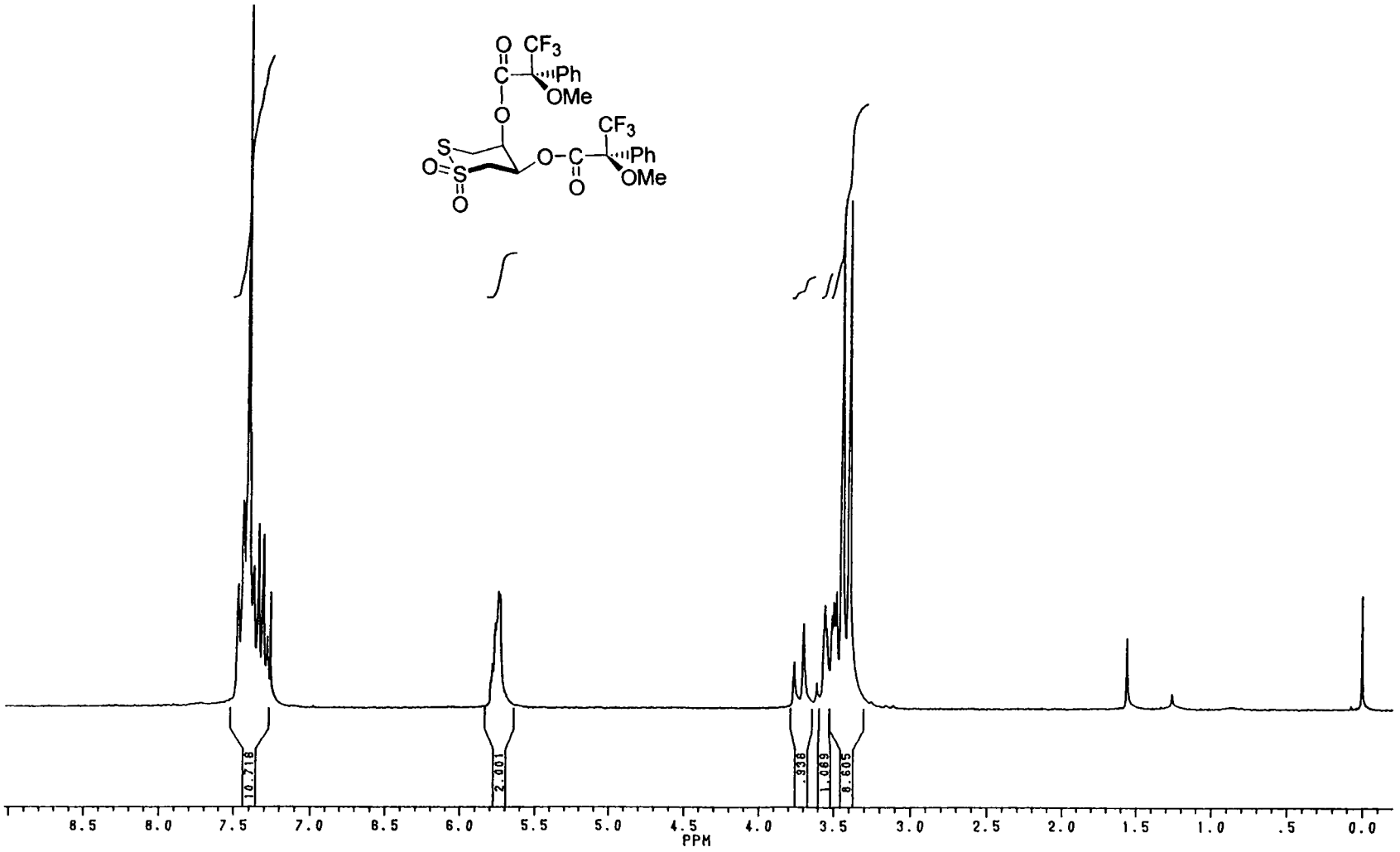
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-*cis*-4,5-dibenzoyloxy-1,2-dithiane 1,1-dioxide (**22**).



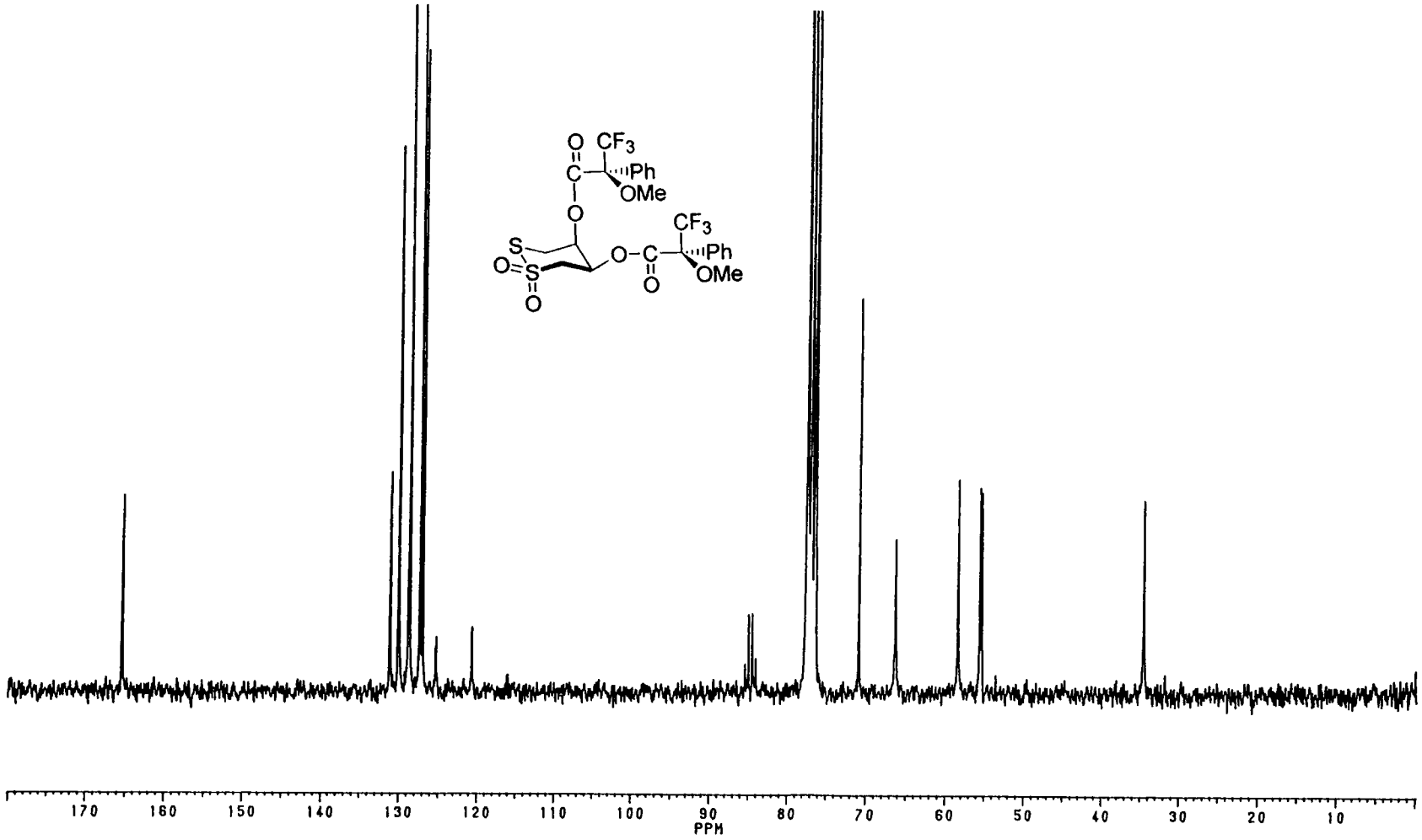
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (2*S*,4*R*,5*S*)-(+)-3,3,3-trifluoro -2-methoxy-2-phenylpropionic acid 1,1-dioxo-4-[(2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyloxy][1,2]dithiane-5-yl ester (**25**).



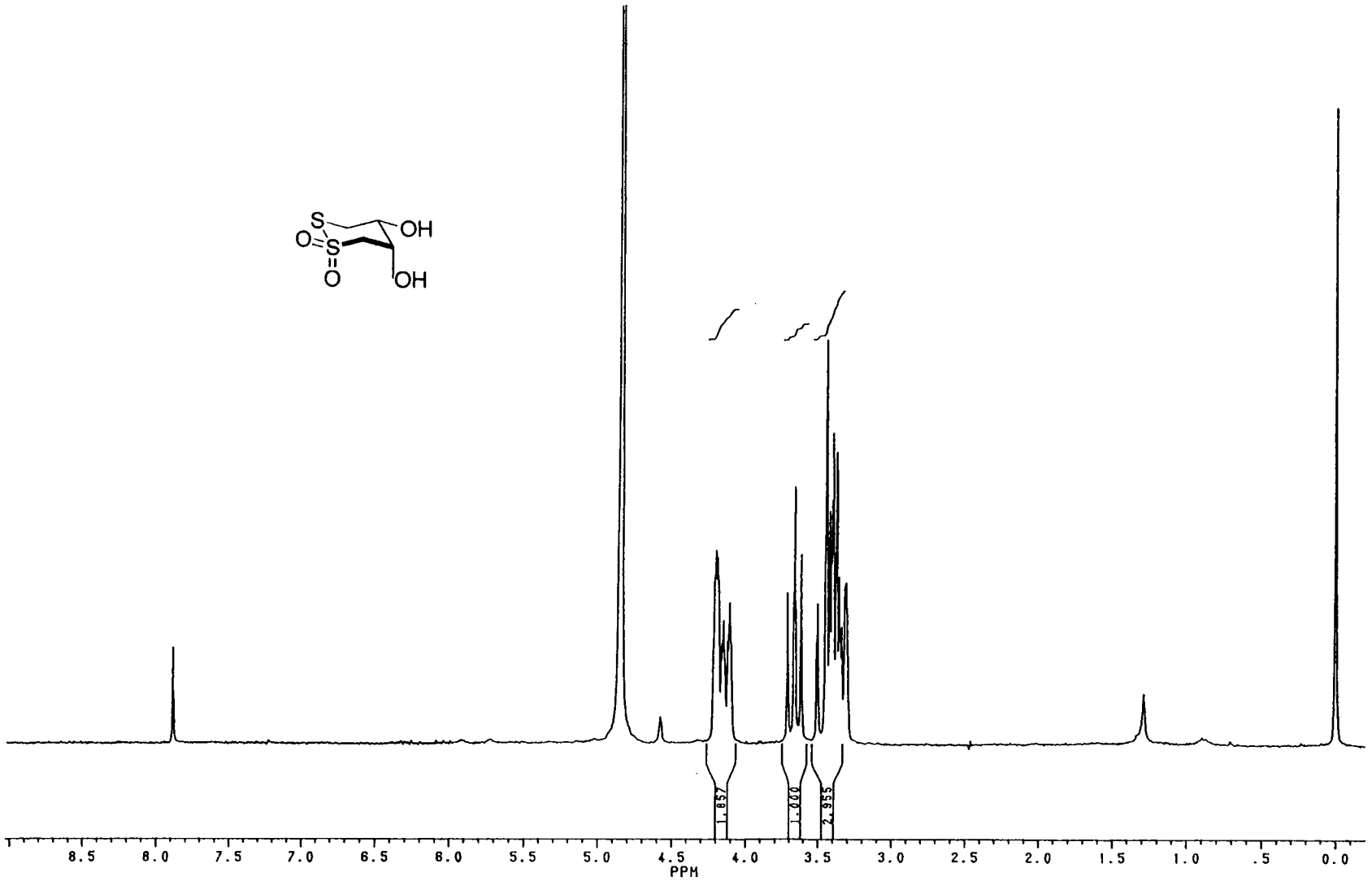
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (2*S*,4*R*,5*S*)-(+)-3,3,3-trifluoro -2-methoxy-2-phenylpropionic acid 1,1-dioxo-4-[(2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyloxy][1,2]dithiane-5-yl ester (**25**)



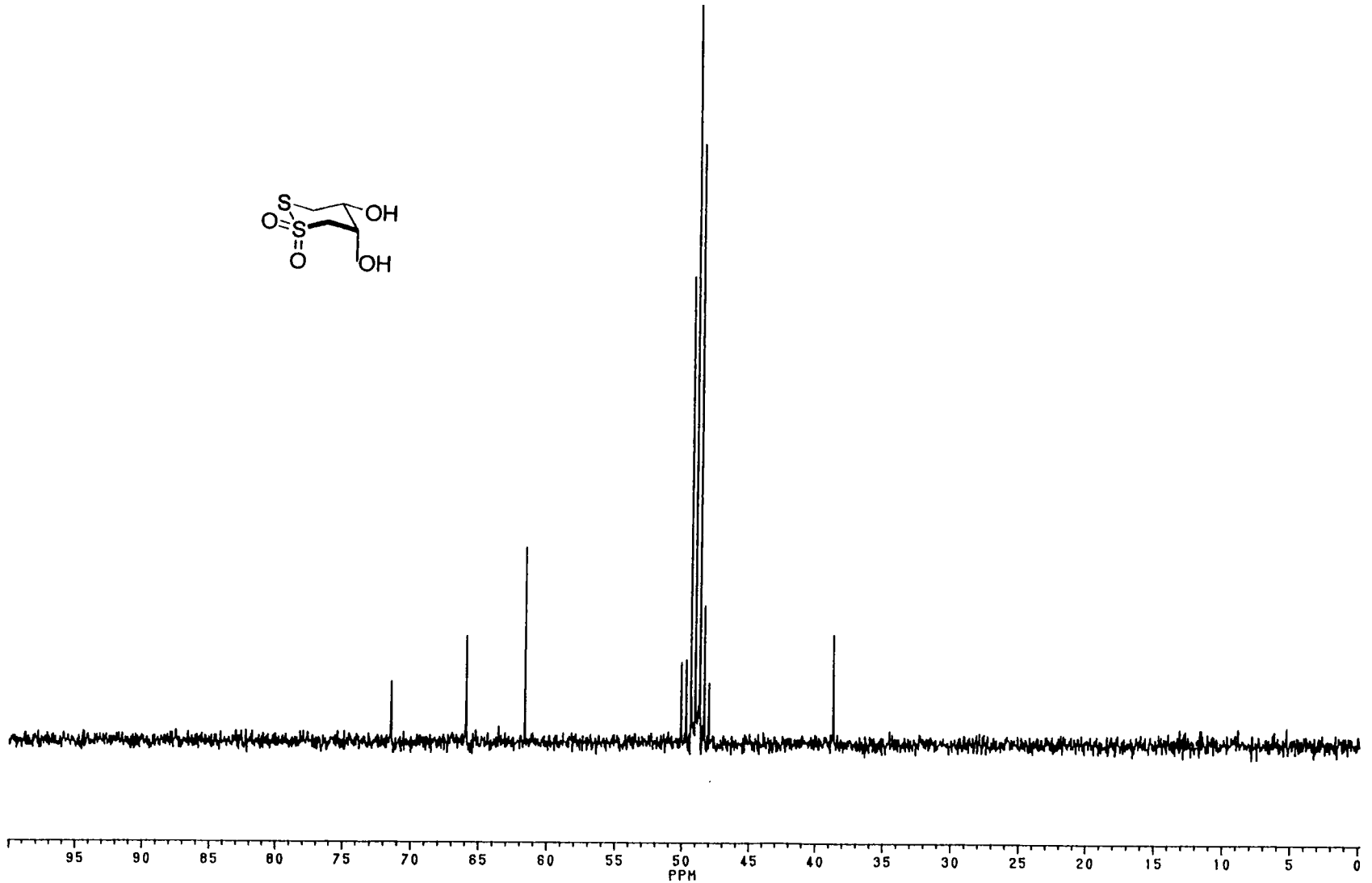
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (2*S*,4*S*,5*R*)-(−)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid 1,1-dioxo-4-[(2*S*)-2-methoxy-2-phenyl-3,3,3-trifluoropropionyloxy][1,2]dithiane-5-yl ester (**26**).



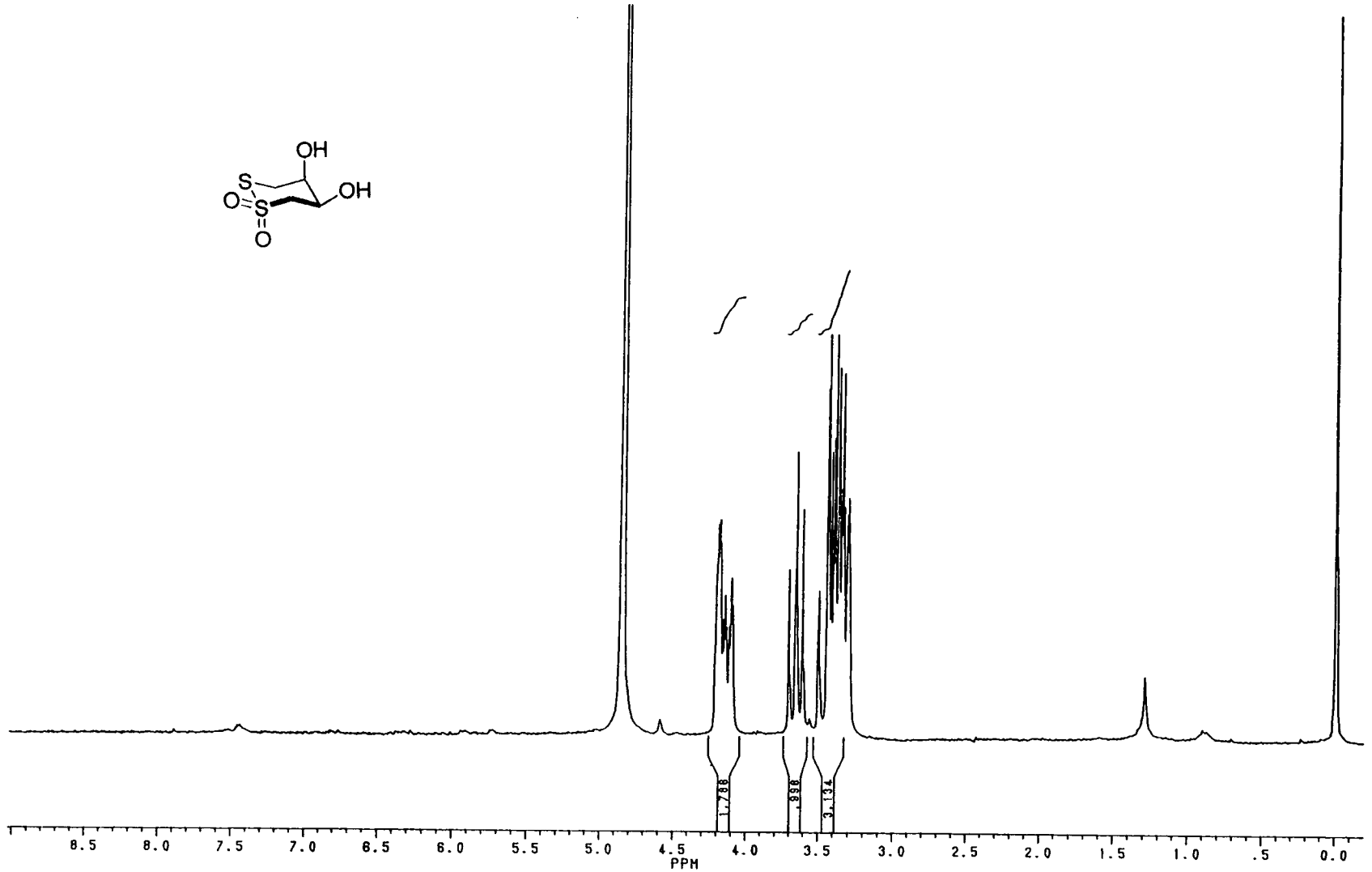
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (2*S*,4*S*,5*R*)-(−)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid 1,1-dioxo-4-[(2*S*)-2-methoxy-2-phenyl-3,3,3-trifluoropropionyloxy][1,2]dithiane-5-yl ester (**26**).



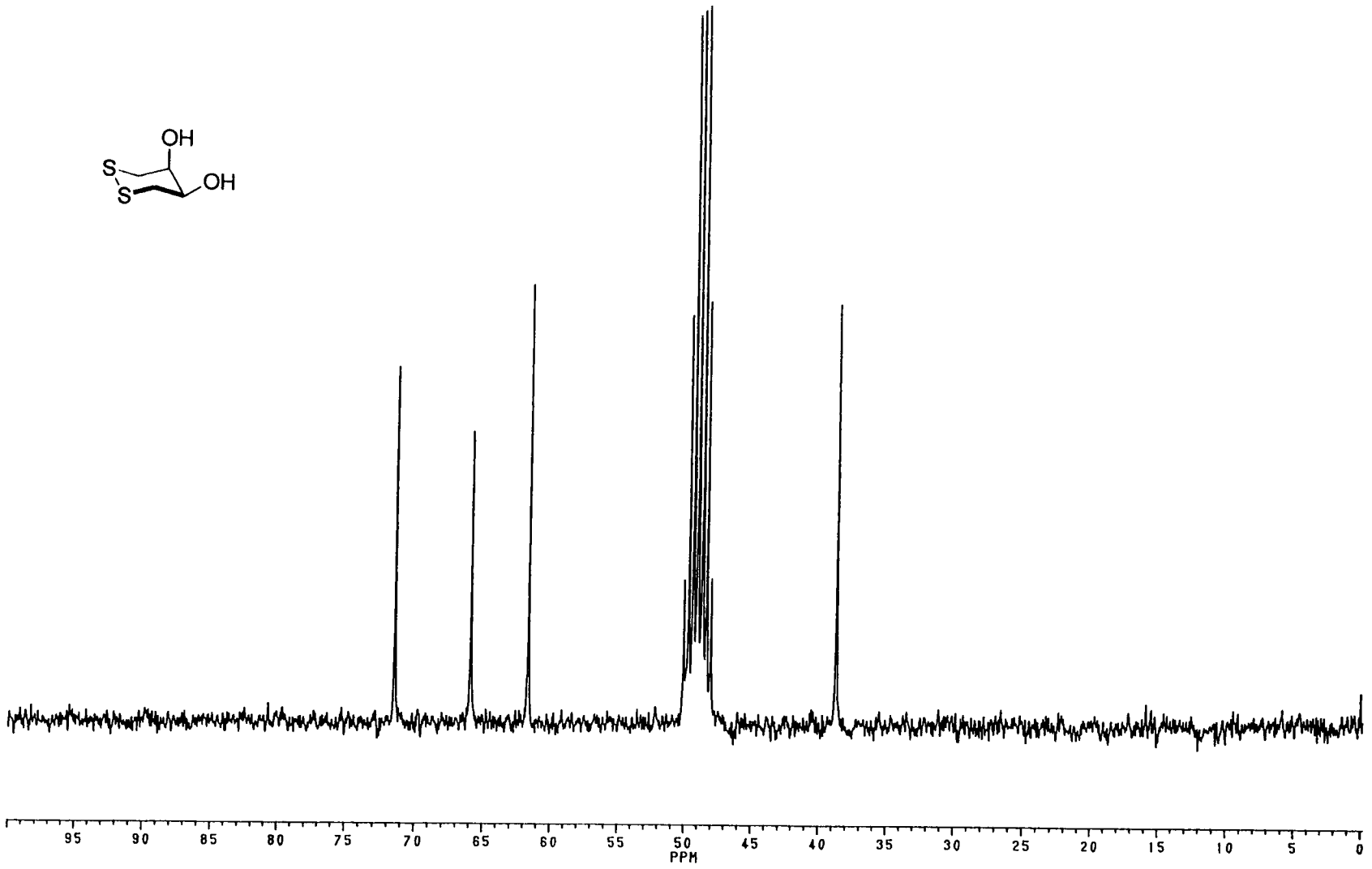
^{1}H NMR spectrum (250 MHz, CD_3OD) of (+)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (27).



^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (+)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (**27**).

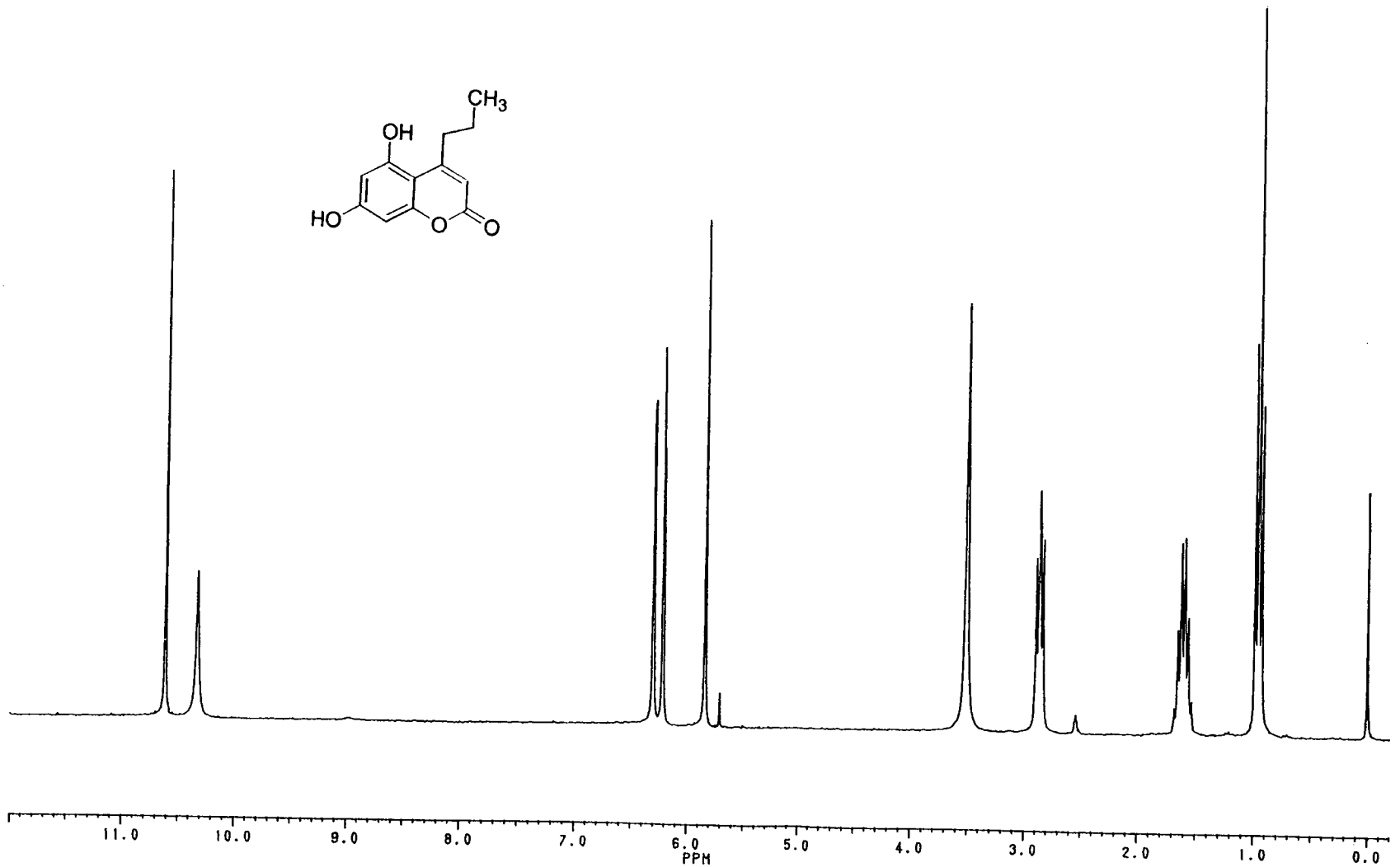


^{1}H NMR spectrum (250 MHz, CD_3OD) of (–)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (**28**).

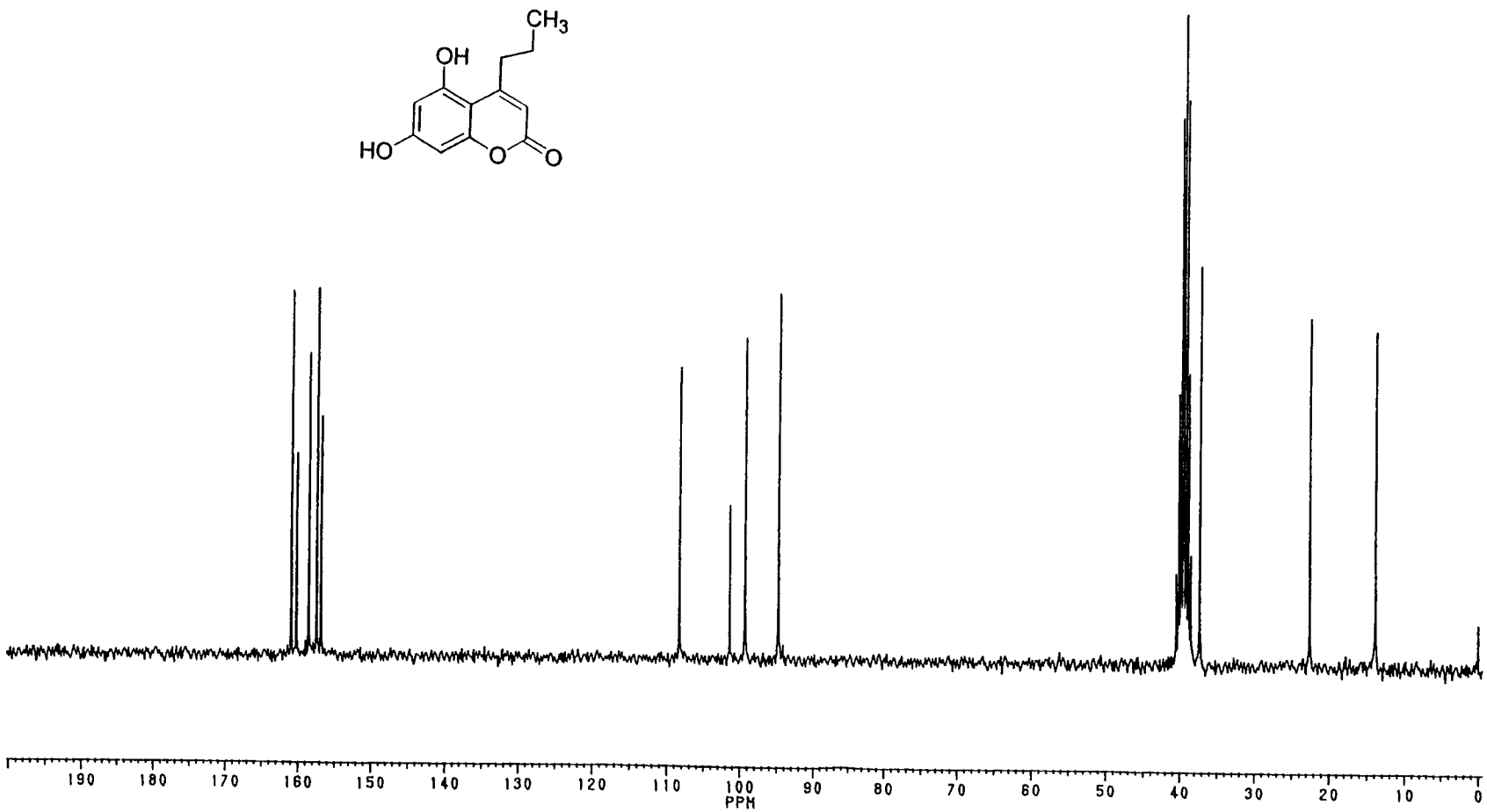


^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (–)-*cis*-4,5-dihydroxy-1,2-dithiane 1,1-dioxide (**28**).

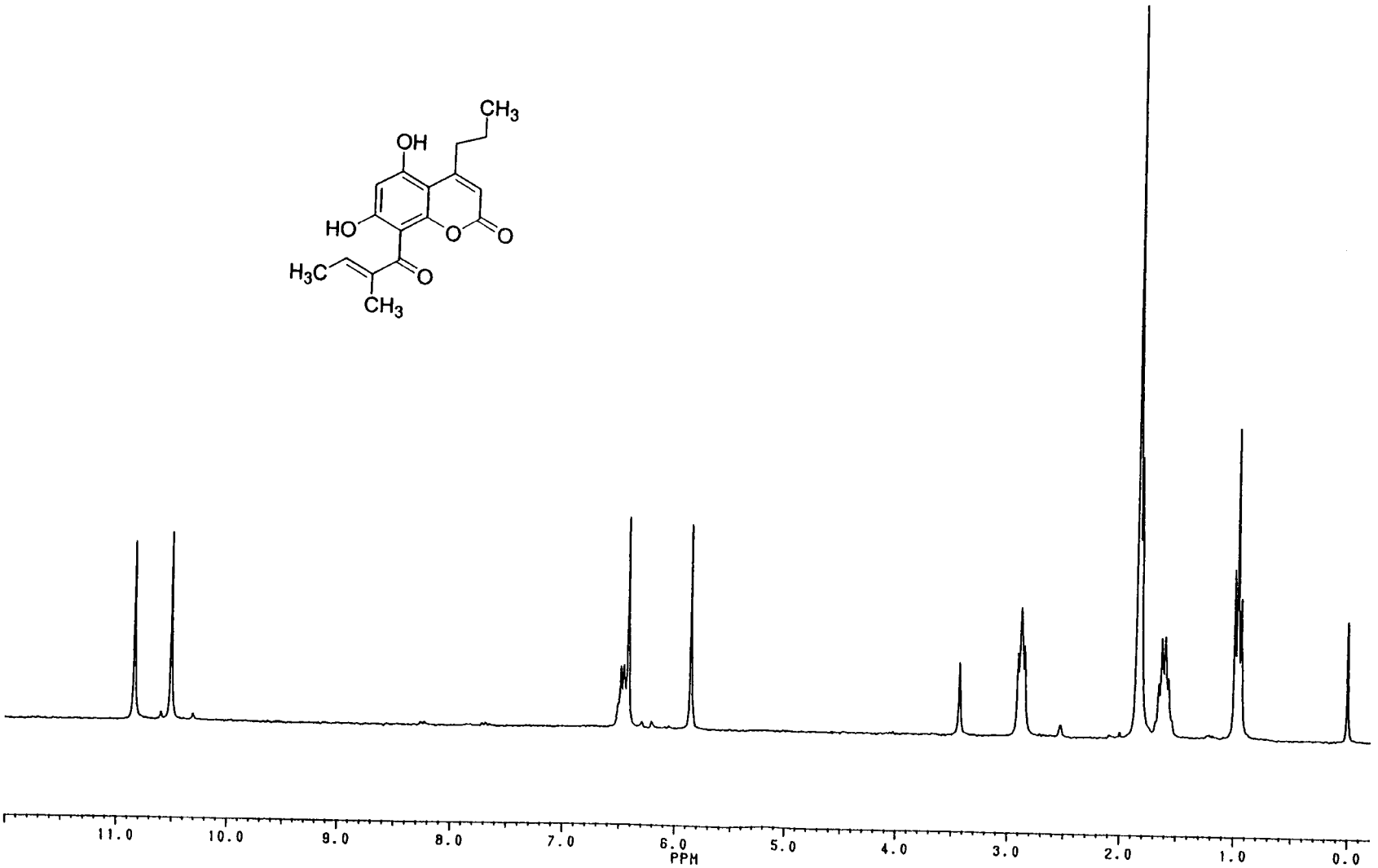
APPENDIX B. ^{1}H and ^{13}C NMR Spectra of (±)-Calanolide A Analogs



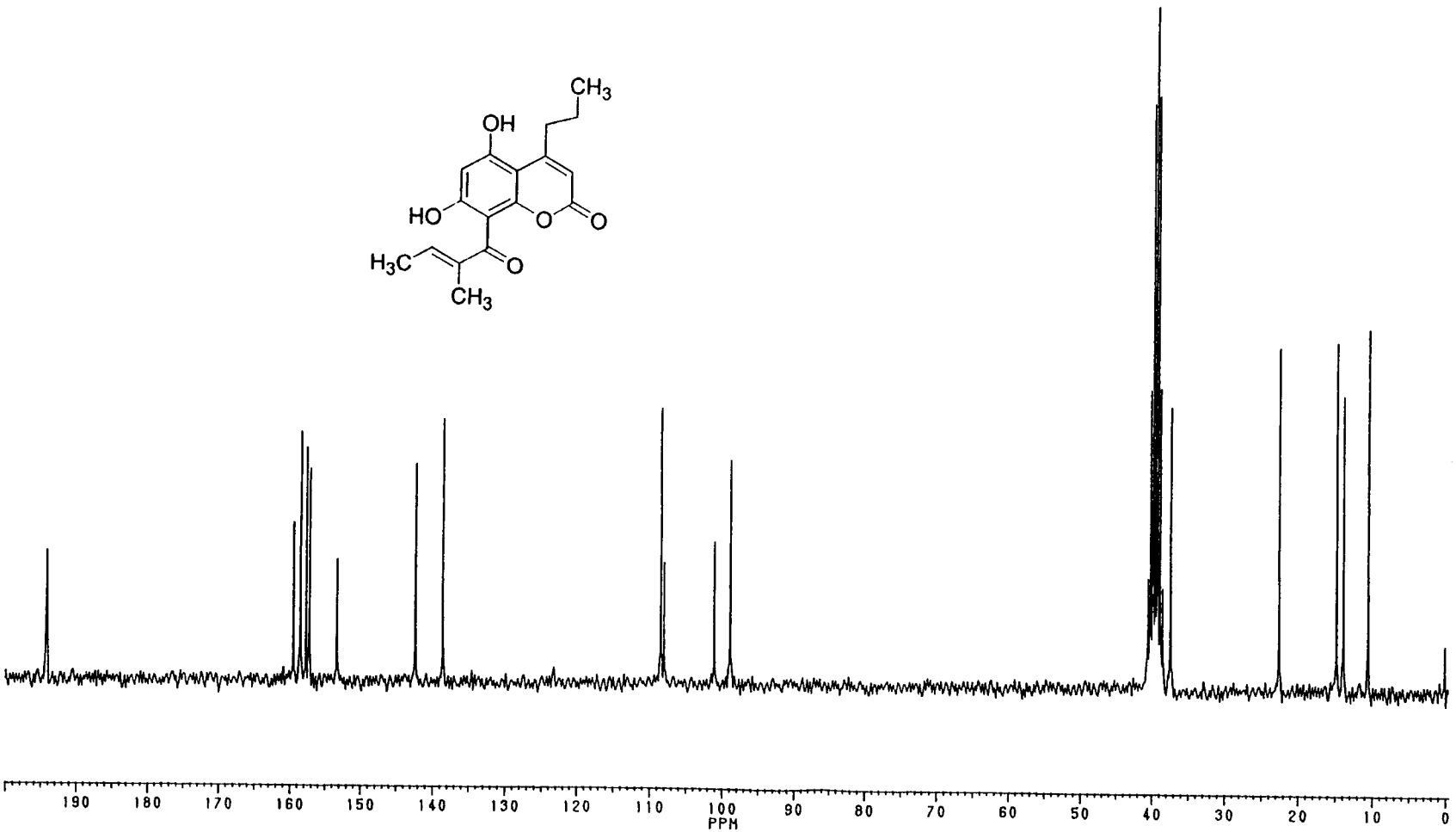
^{1}H NMR spectrum (250 MHz, DMSO-d_6) of (±)-5,7-dihydroxy-4-propylchromen-2-one (**2**).



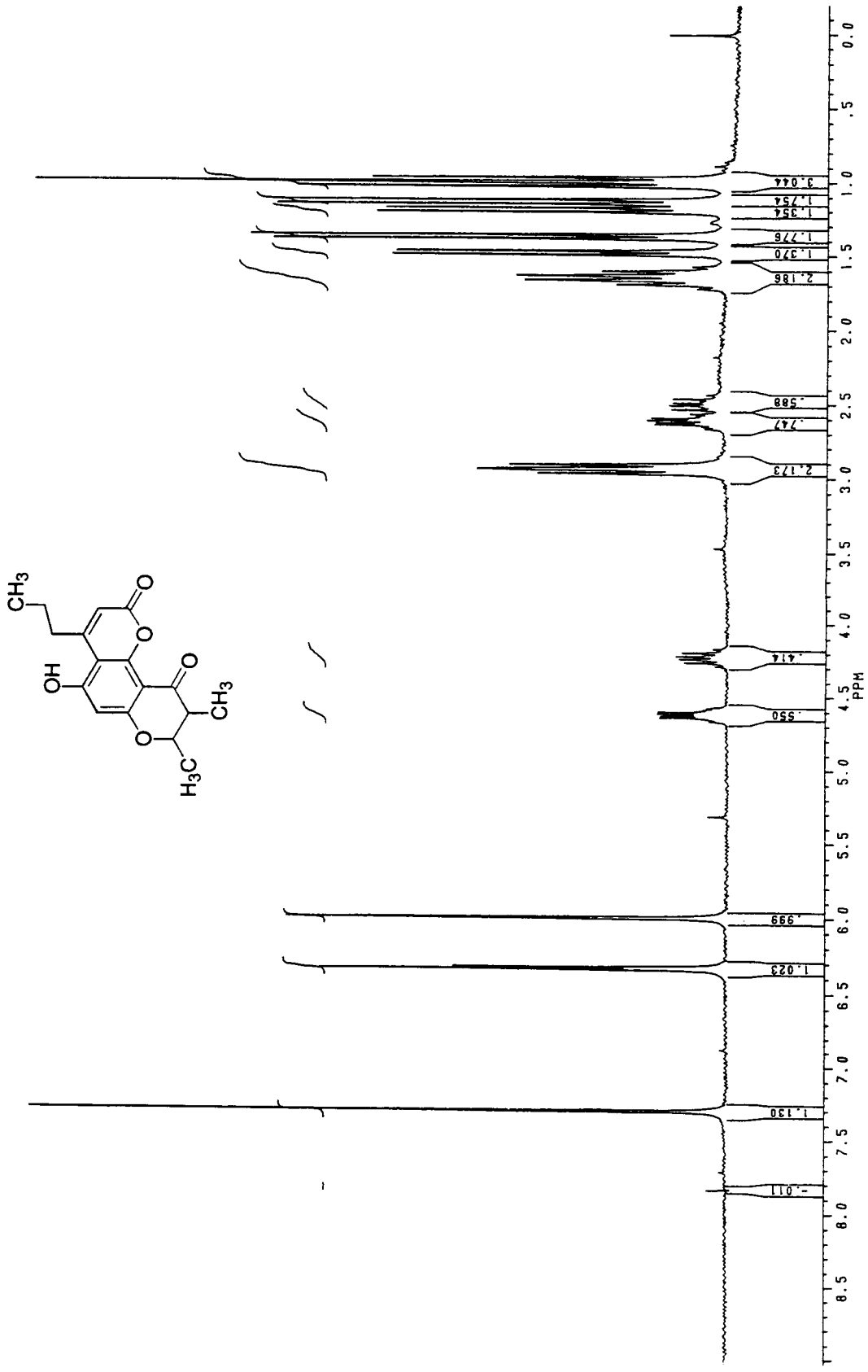
^{13}C NMR spectrum (62.9 MHz, DMSO-d_6) of (±)-5,7-dihydroxy-4-propylchromen-2-one (**2**).



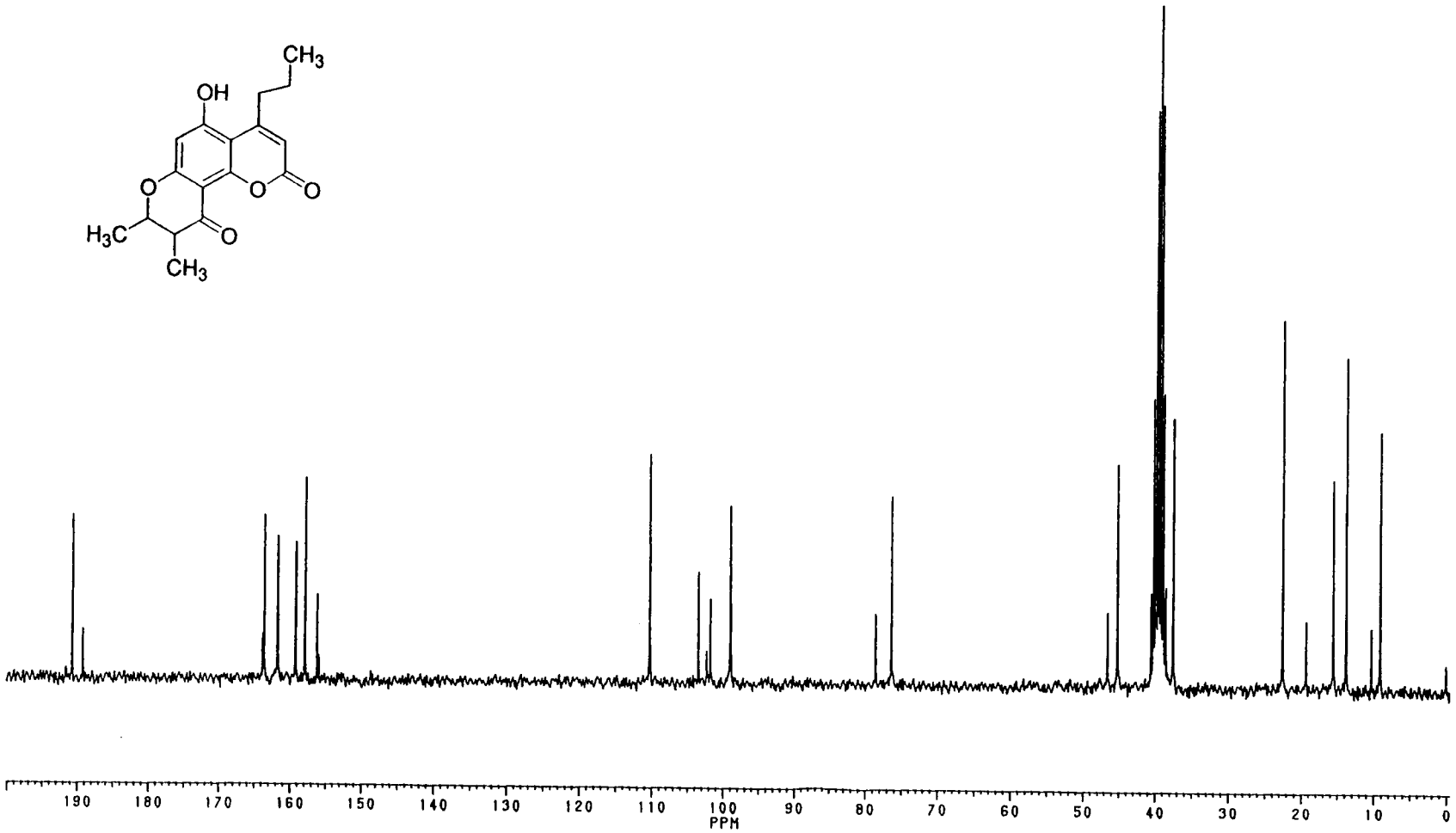
^{1}H NMR spectrum (250 MHz, DMSO-d_6) of (±)-5,7-dihydroxy-8-(2-methylbut-2-enoyl)-4-propylchromen-2-one (**3**).



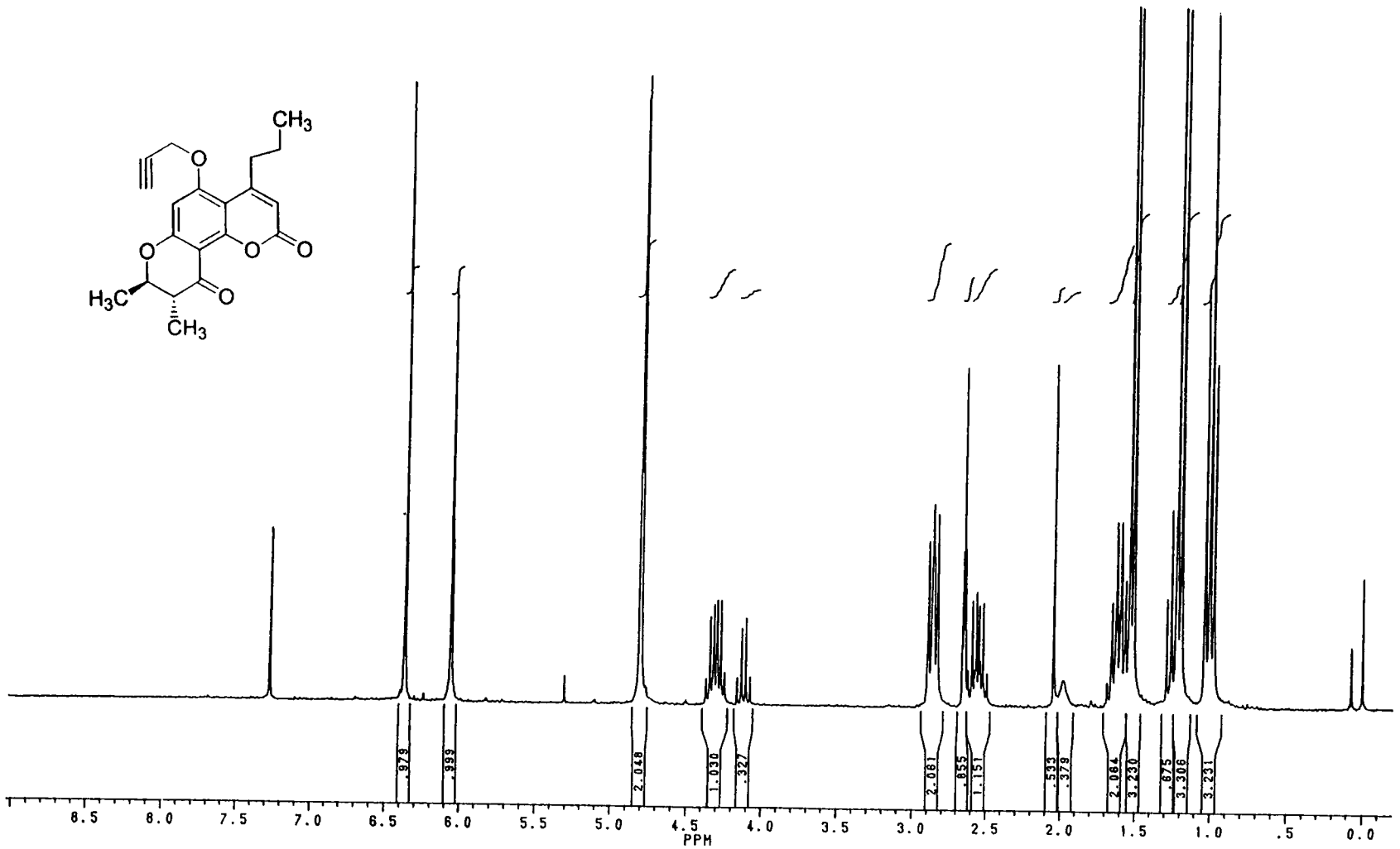
^{13}C NMR spectrum (62.9 MHz, DMSO-d_6) of (±)-5,7-dihydroxy-8-(2-methylbut-2-enoyl)-4-propylchromen-2-one (**3**).



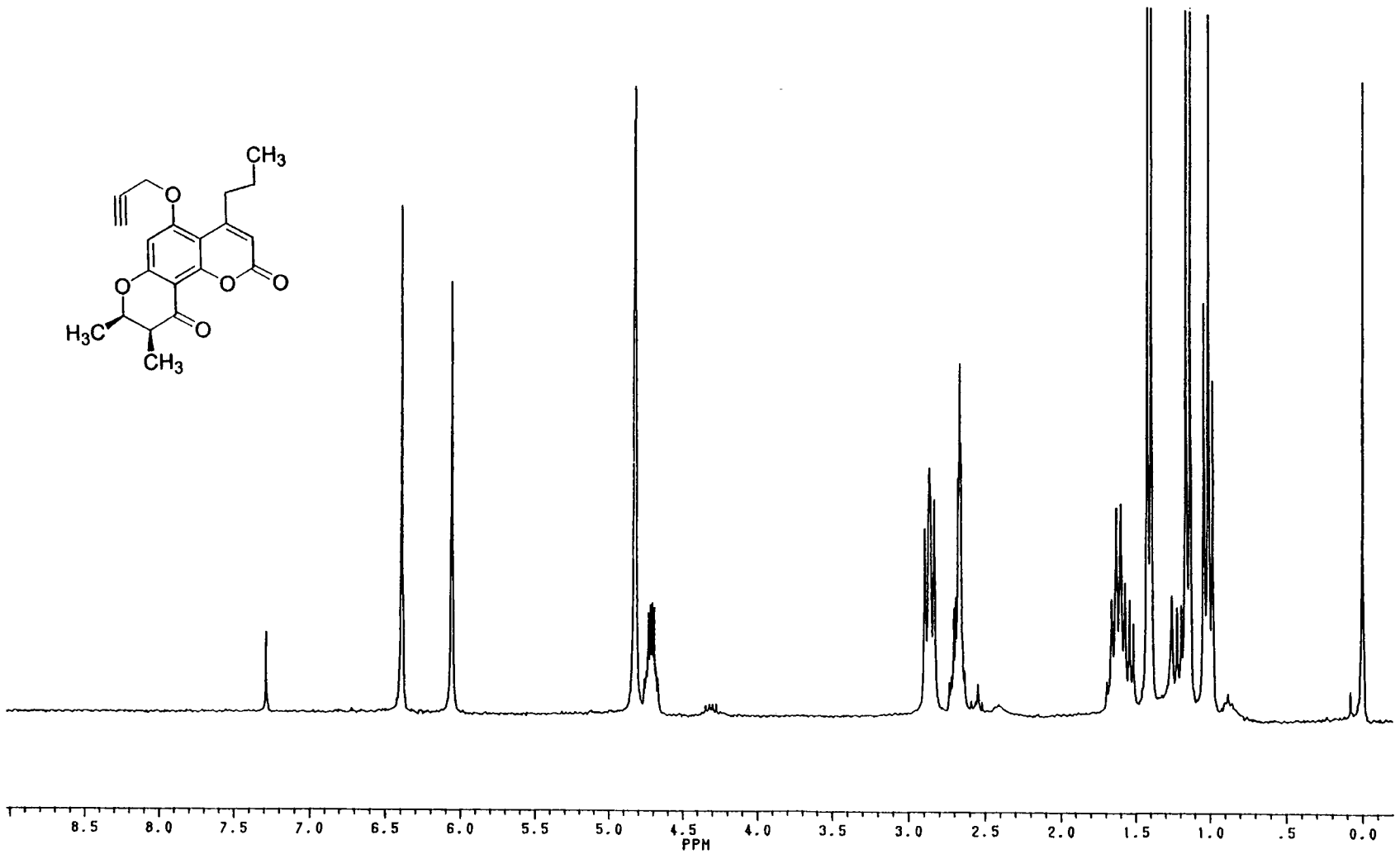
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-5-hydroxy-8,9-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**4**).



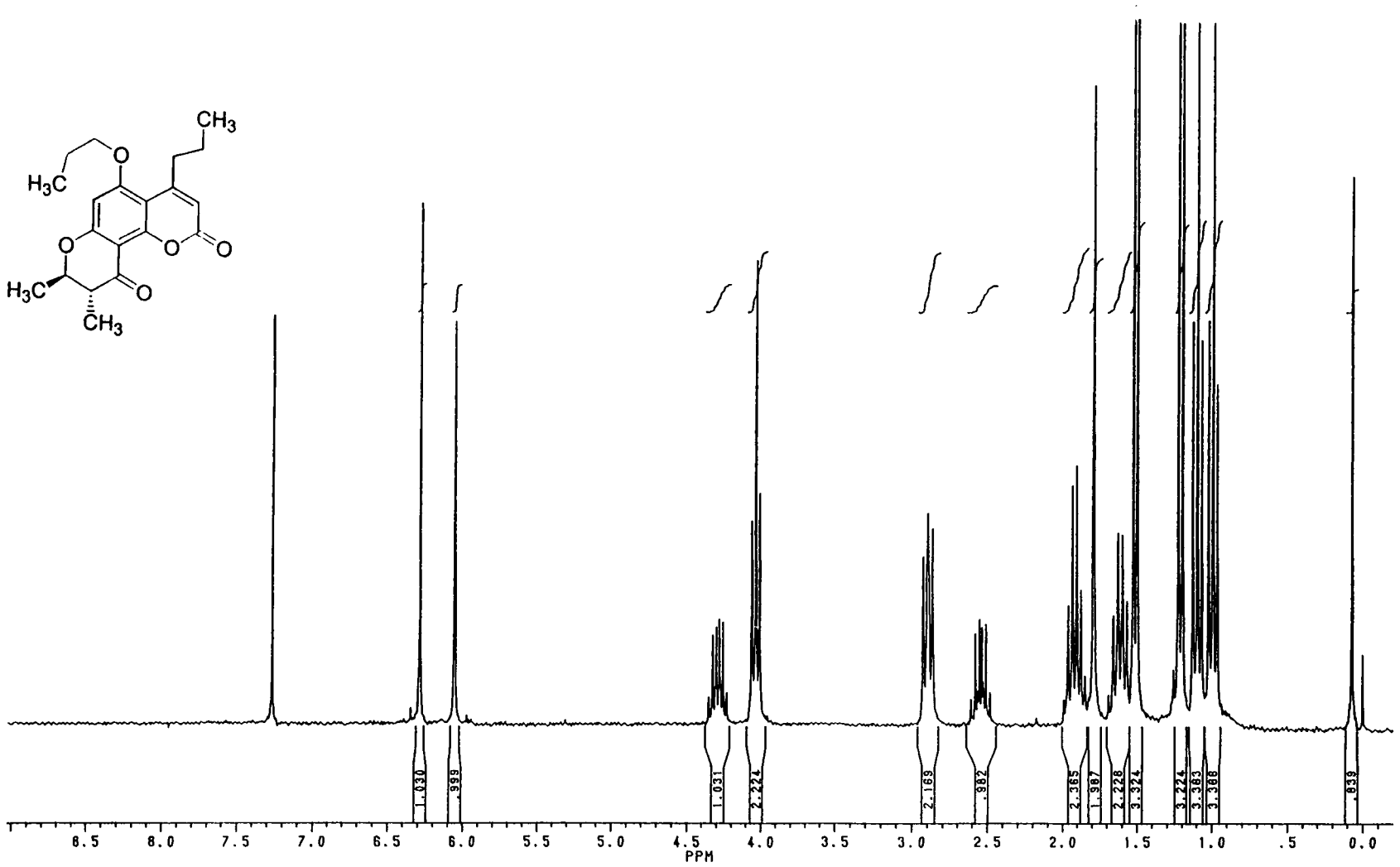
^{13}C NMR spectrum (62.9 MHz, DMSO-d_6) of (±)-5-hydroxy-8,9-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**4**).



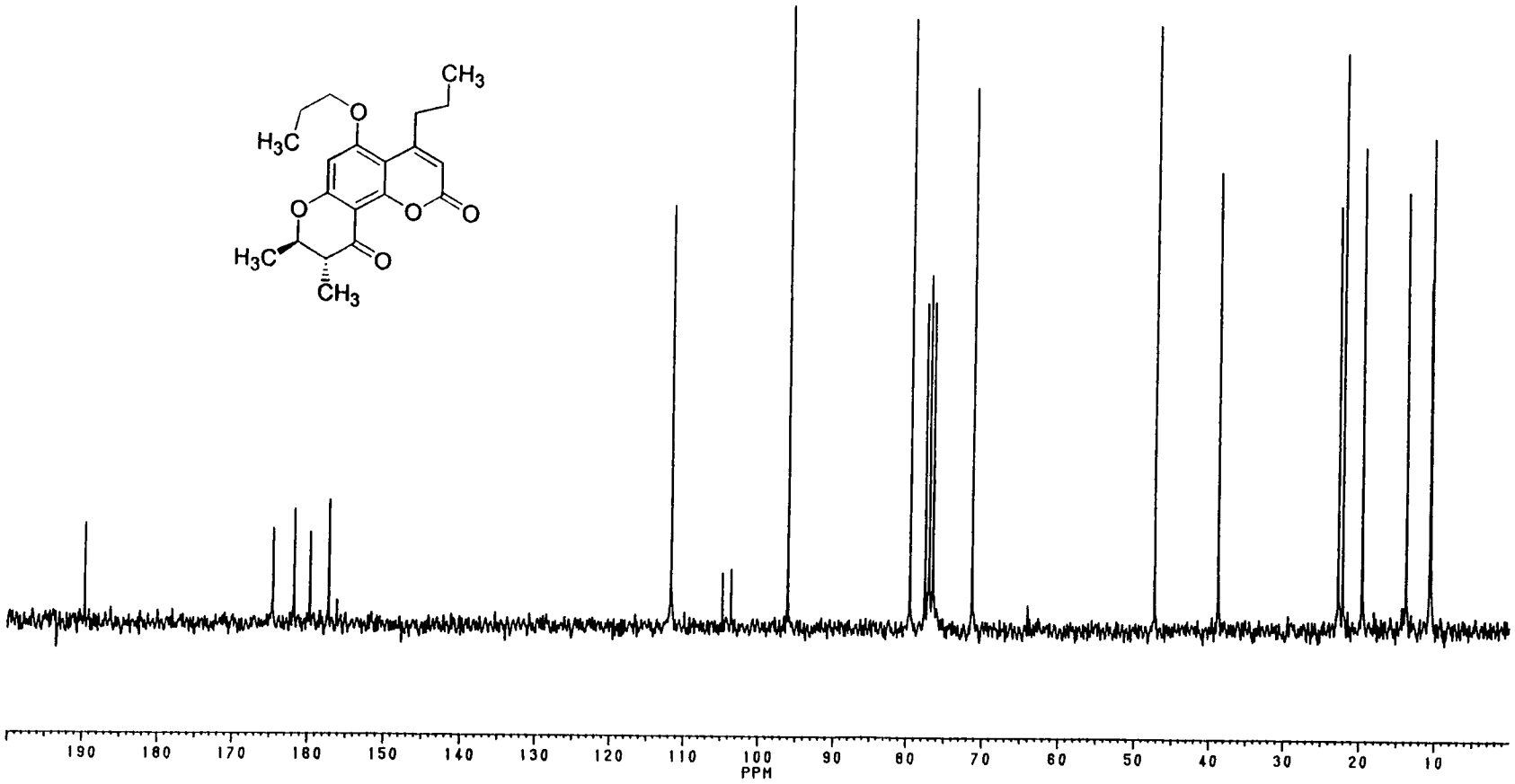
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-8,9-*trans*-dimethyl-5-propargyloxy-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**5t**).



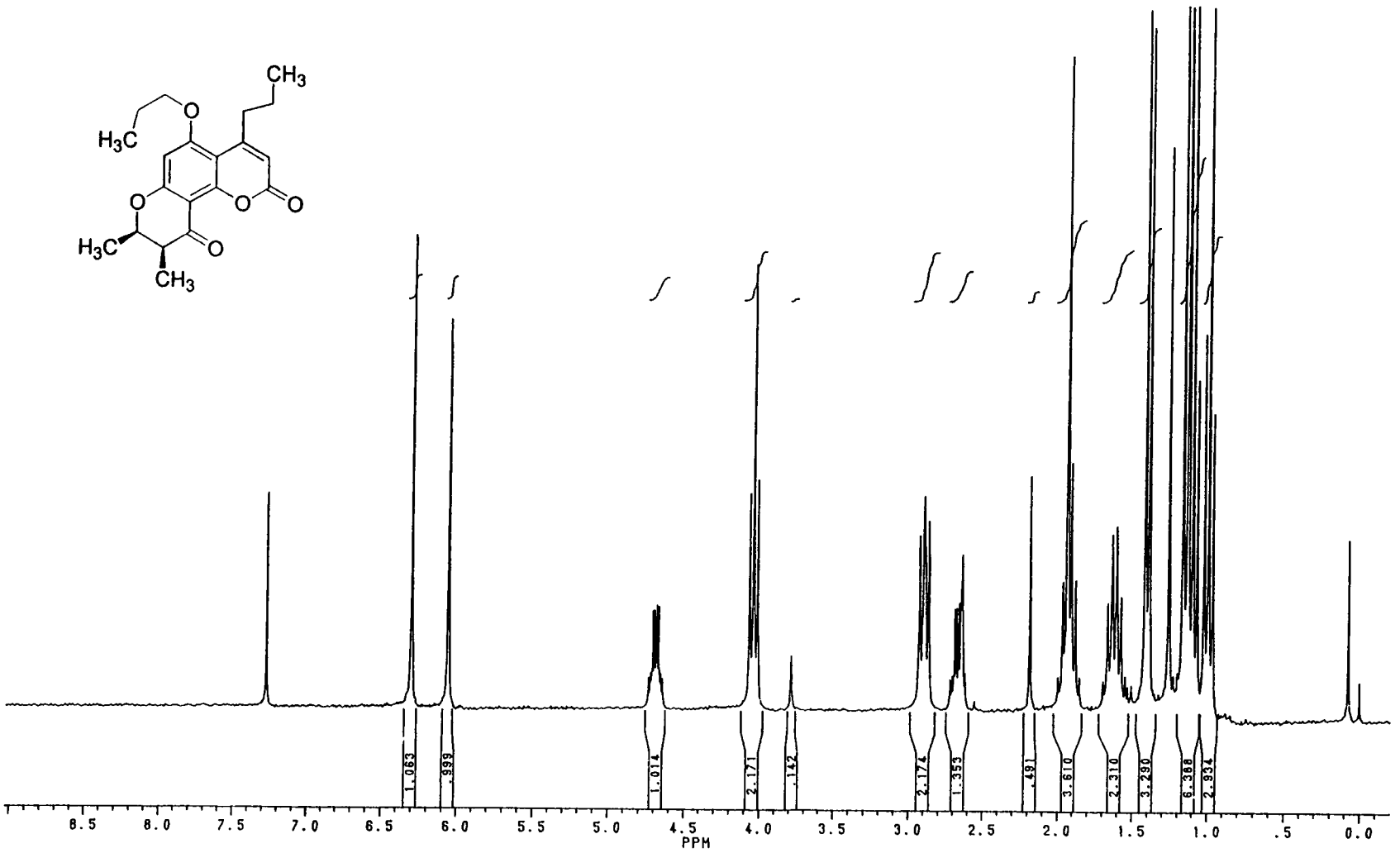
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-8,9-*cis*-dimethyl-5-propargyloxy-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**5c**).



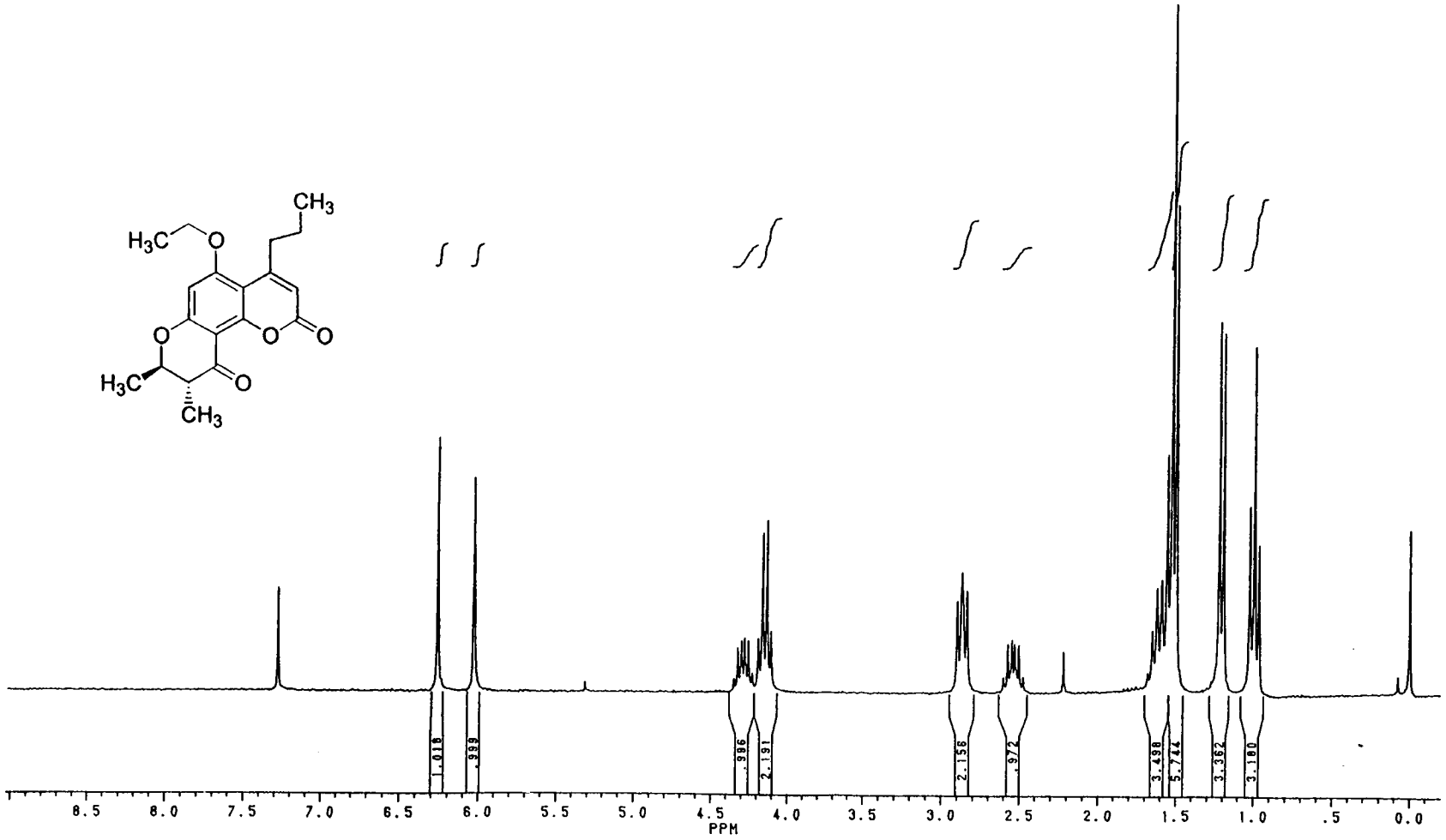
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-8,9-*trans*-dimethyl-5-propoxy-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**6t**).



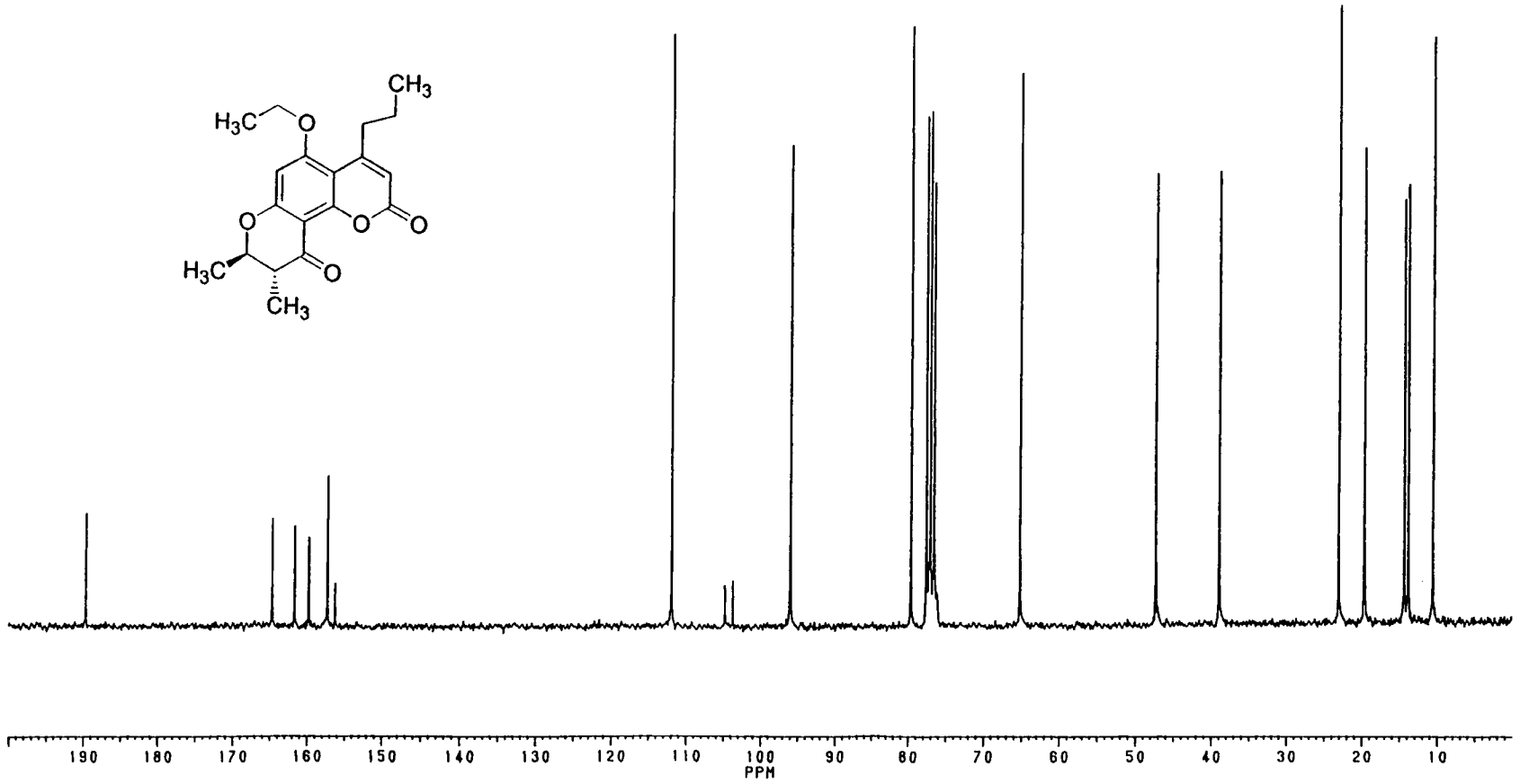
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-8,9-*trans*-dimethyl-5-propoxy-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**6t**).



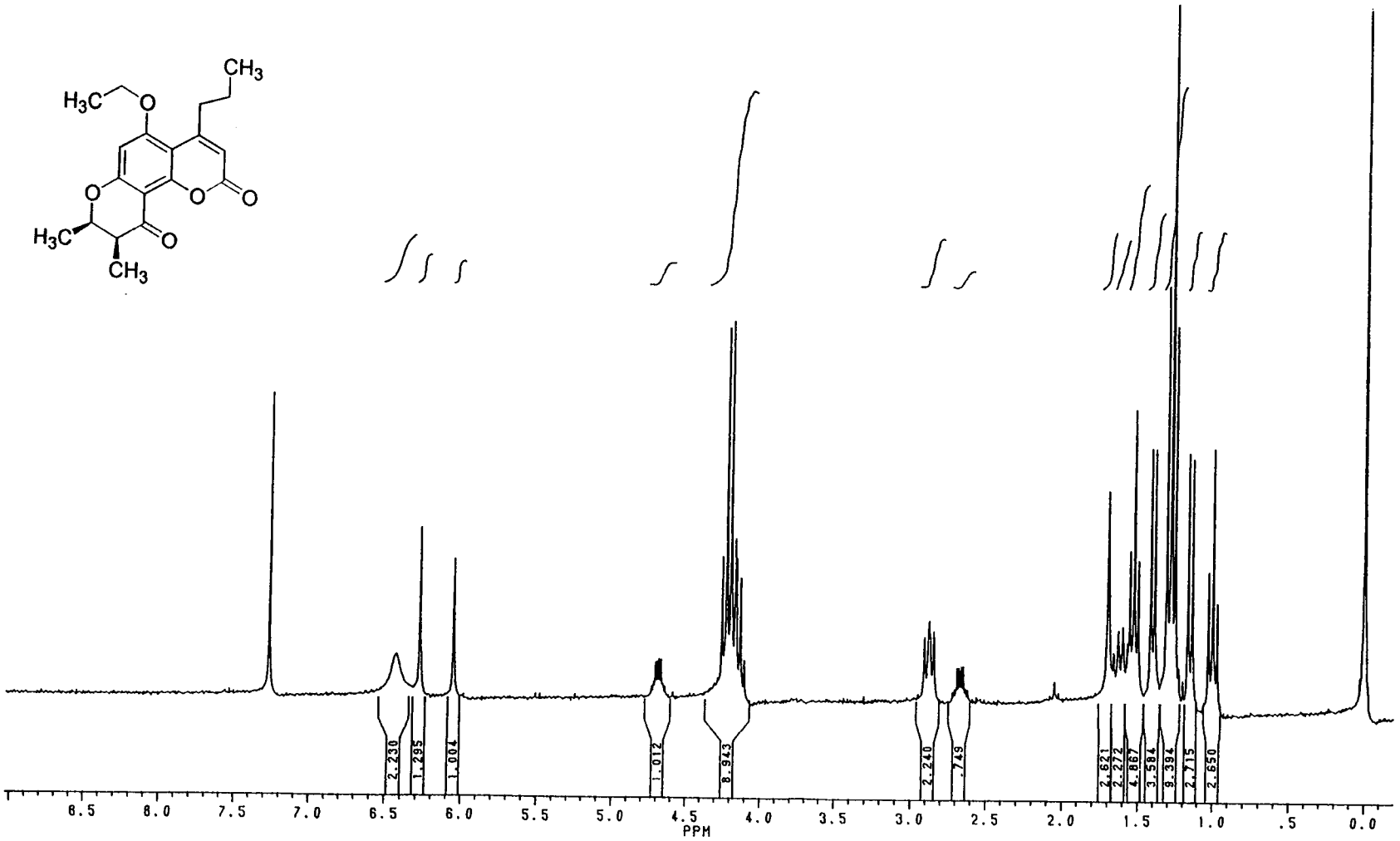
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-8,9-*cis*-dimethyl-5-propoxy-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**6c**).



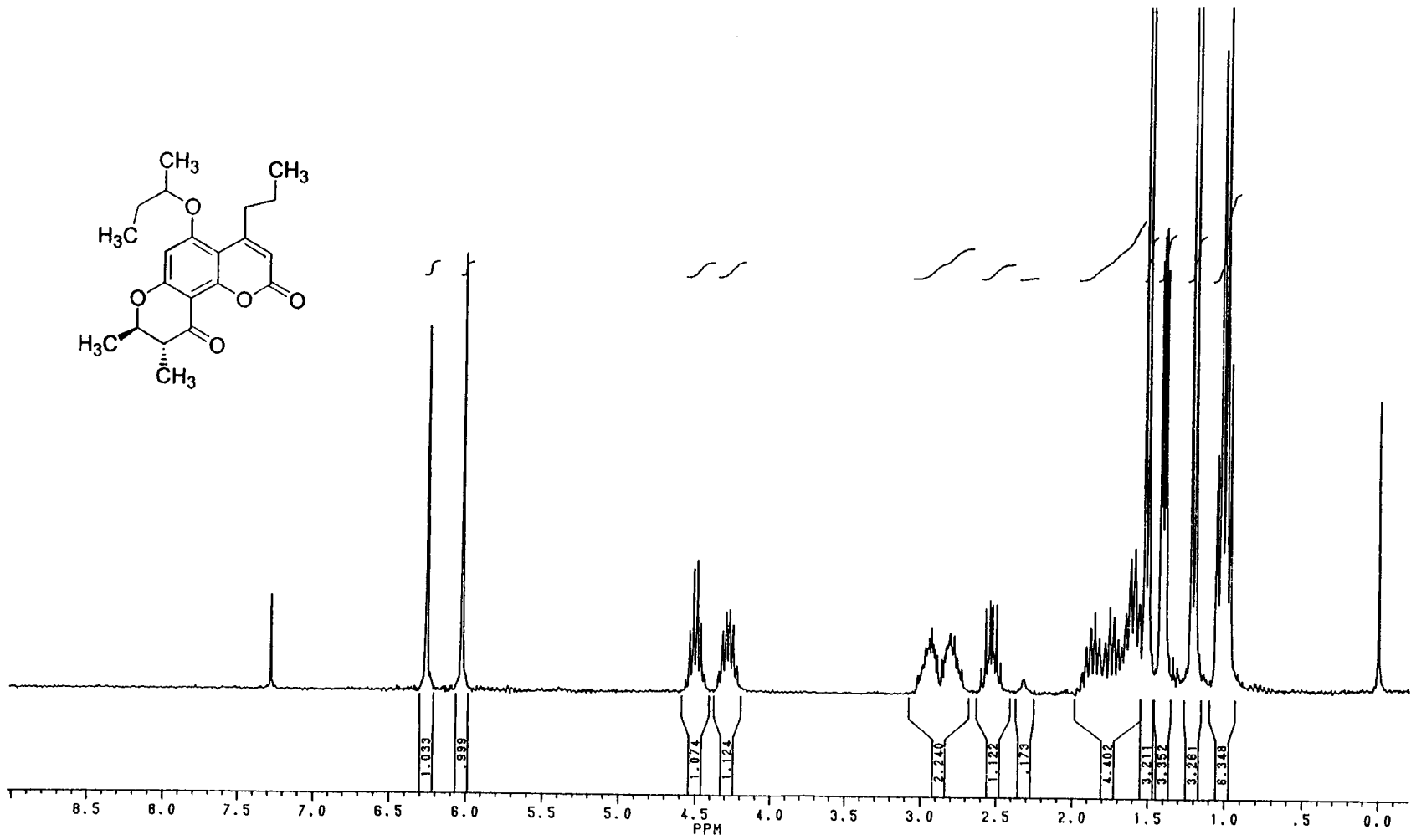
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-5-ethoxy-8,9-*trans*-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**7t**).



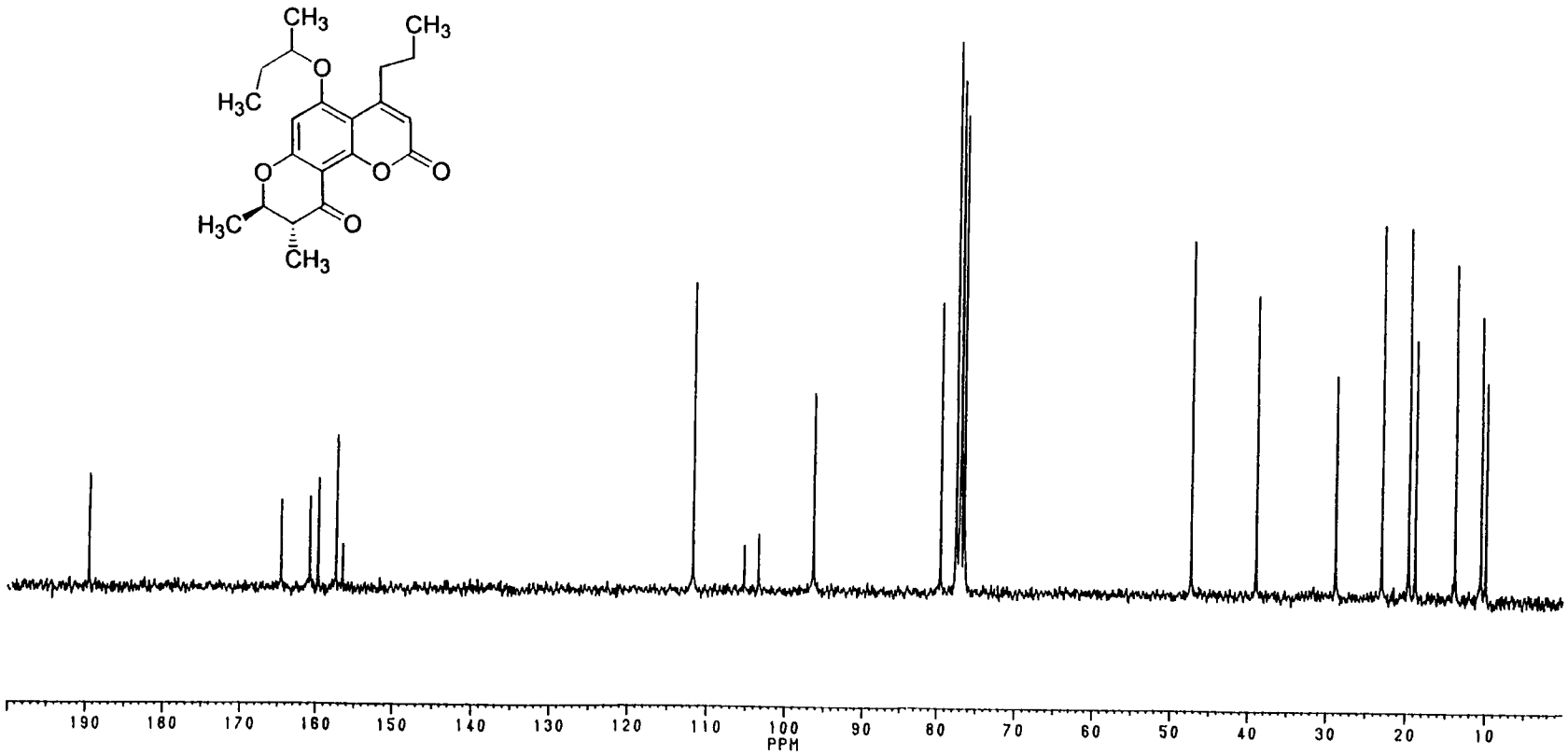
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-5-ethoxy-8,9-*trans*-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**7t**).



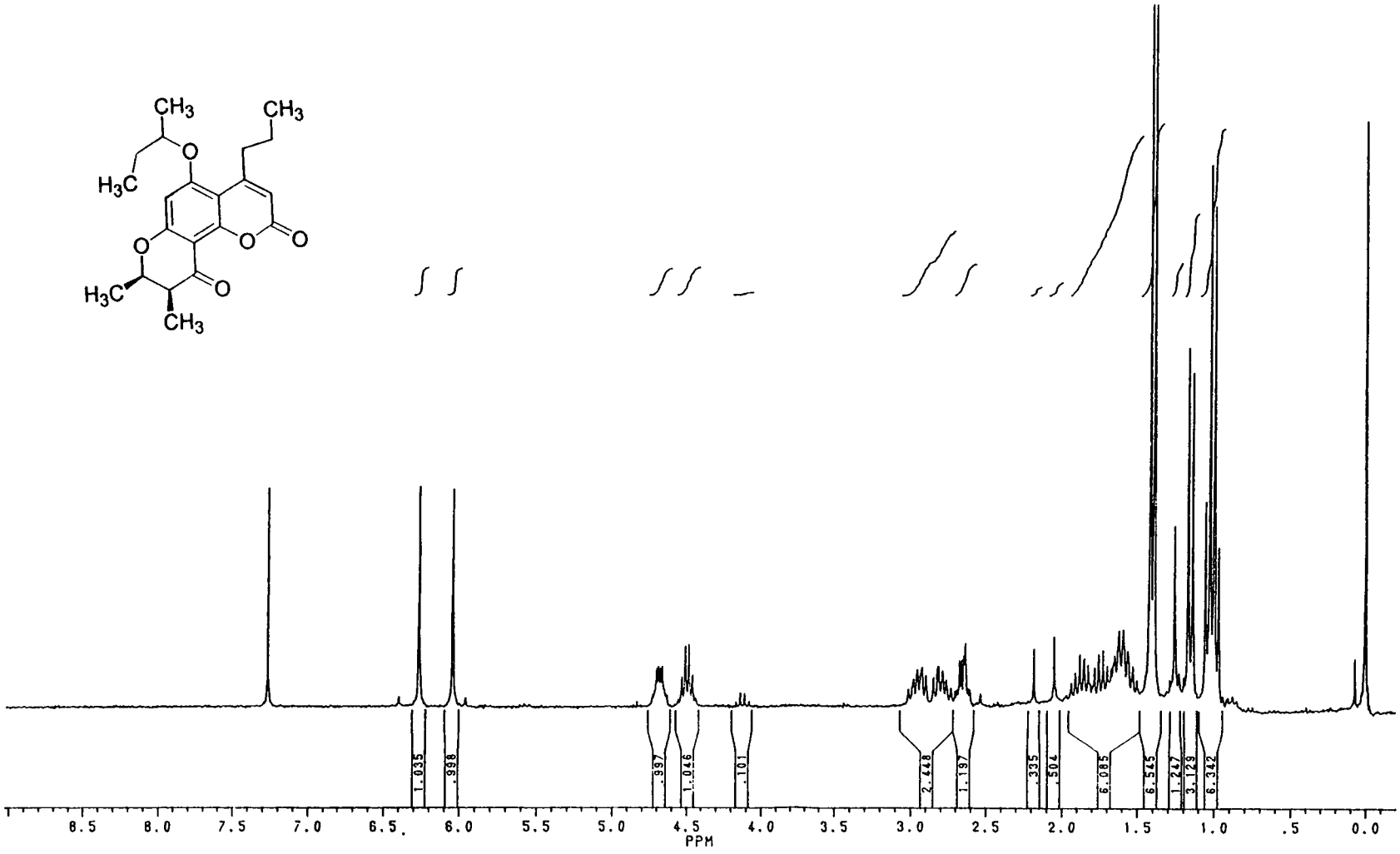
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-5-ethoxy-8,9-*cis*-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**7c**).



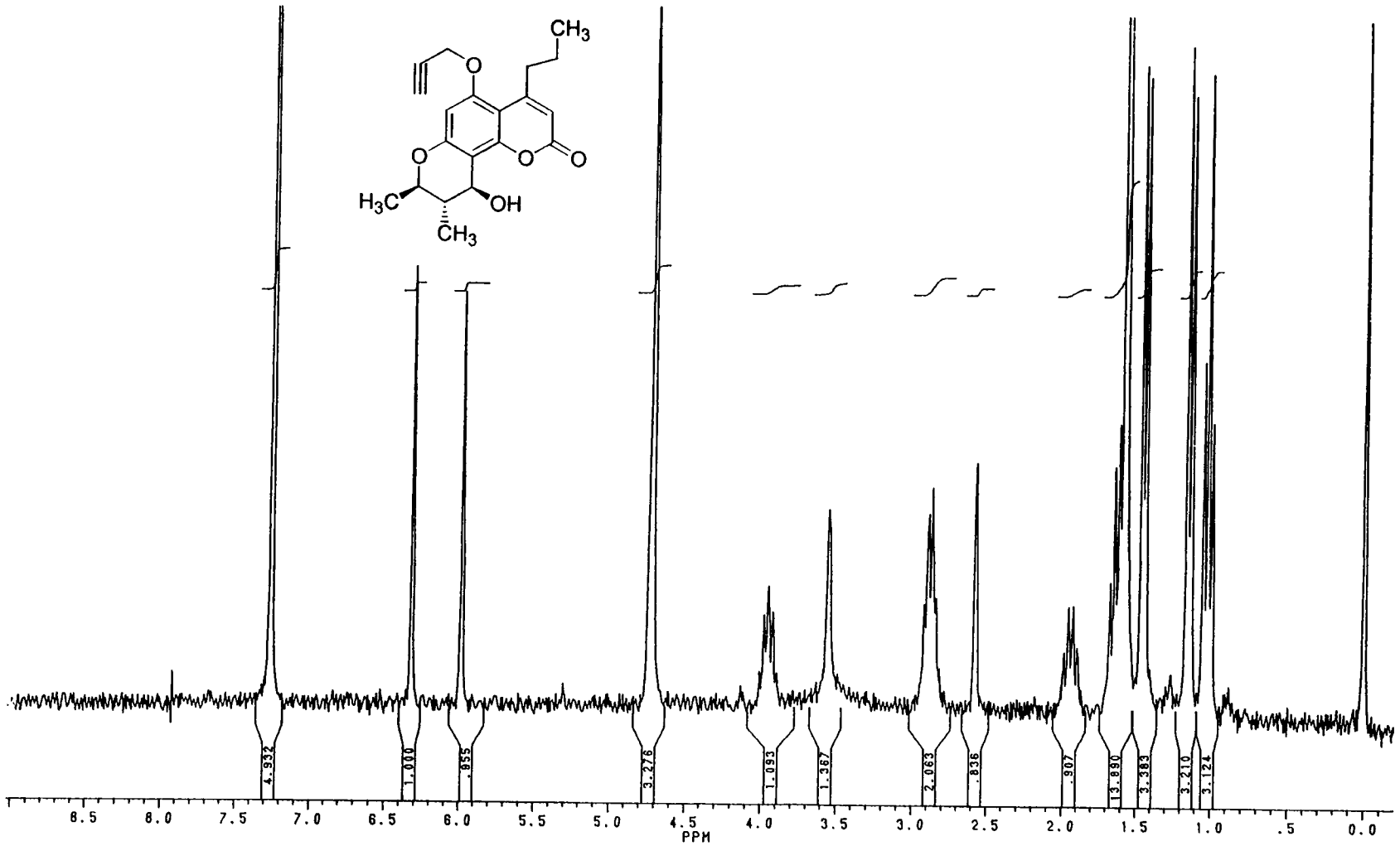
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-5-*sec*-butoxy-8,9-*trans*-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**8t**).



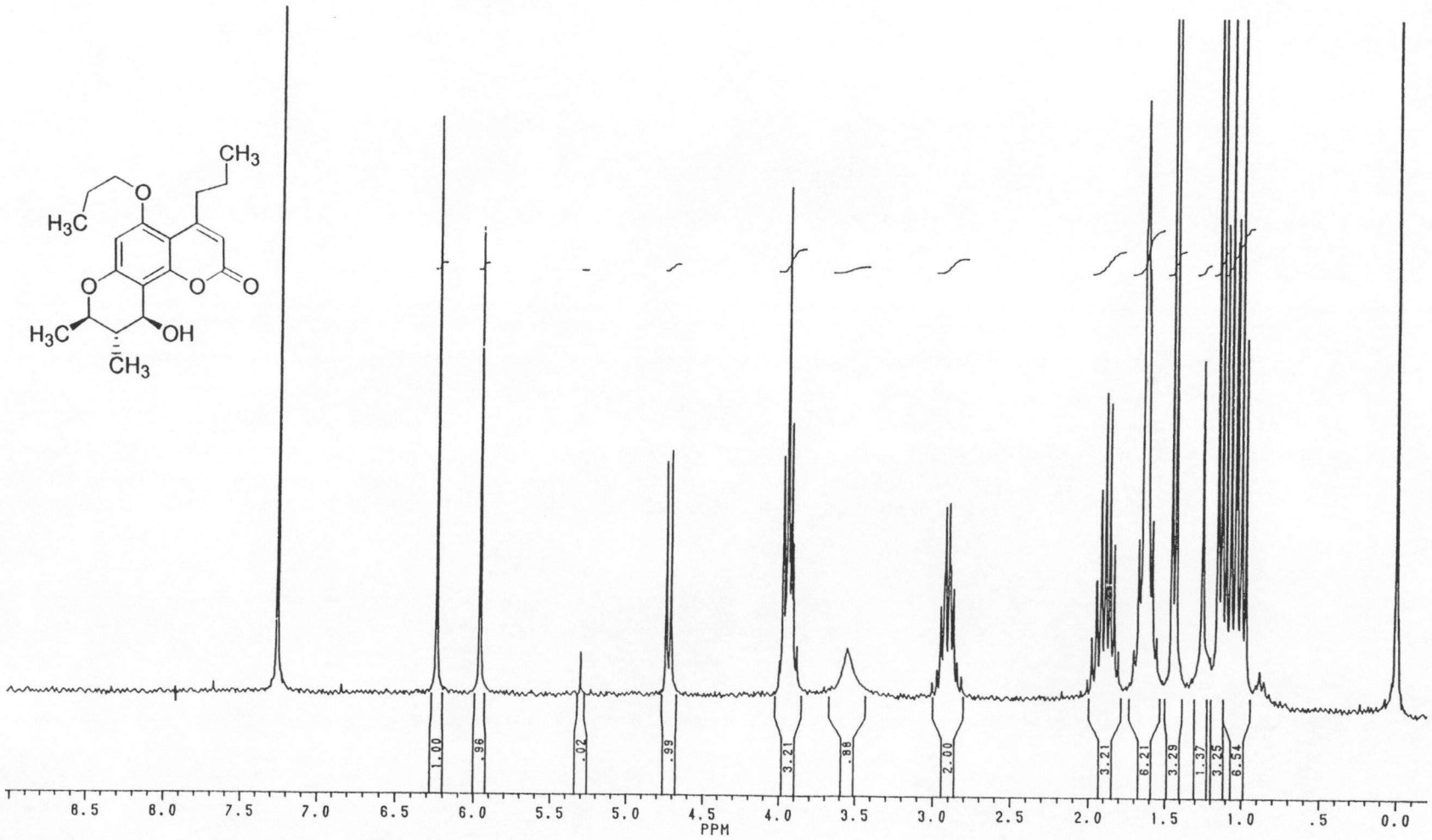
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-5-*sec*-butoxy-8,9-*trans*-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**8t**).



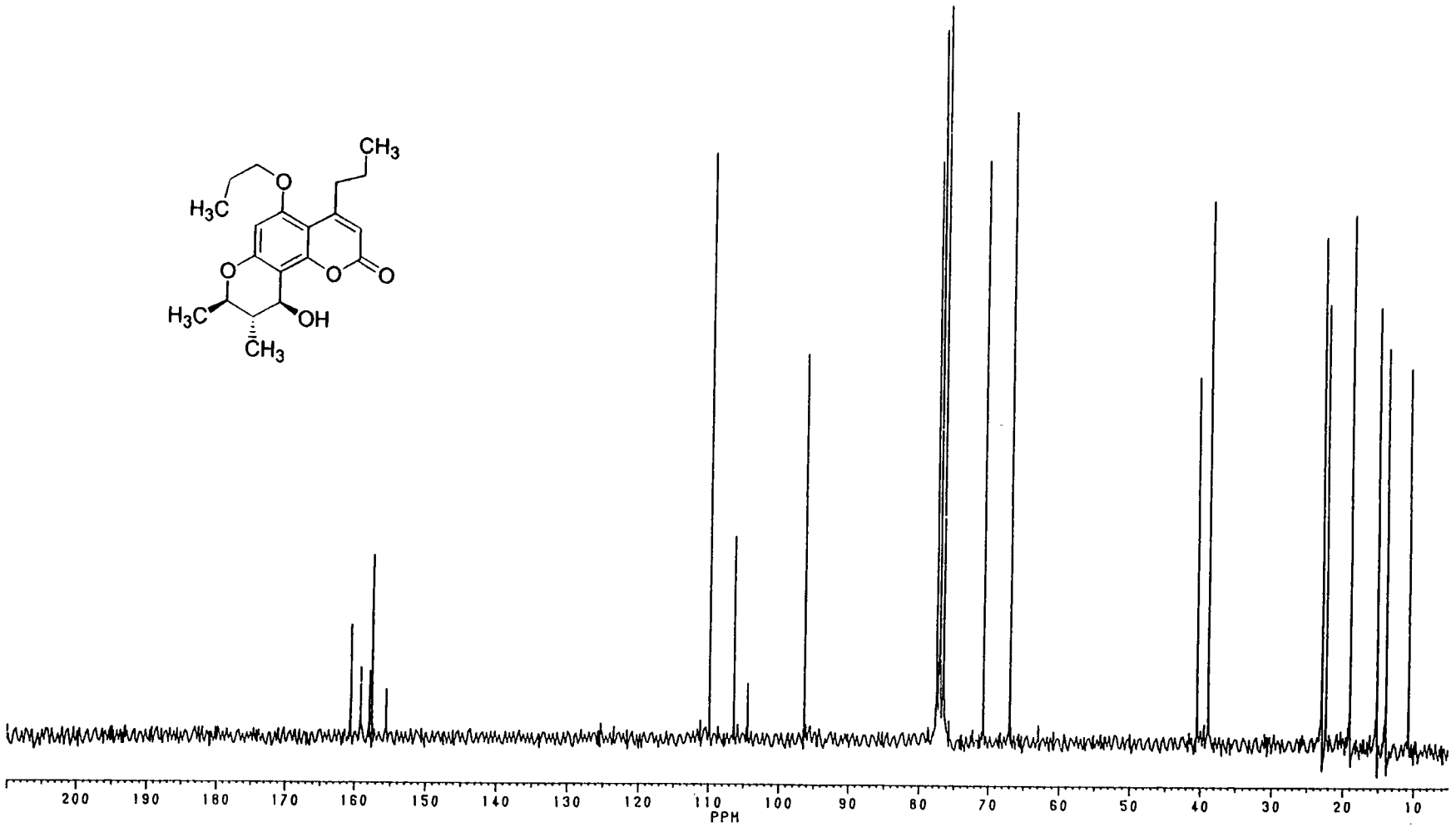
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-5-*sec*-butoxy-8,9-*cis*-dimethyl-4-propyl-8,9-dihydropyrano[2,3-*f*]chromene-2,10-dione (**8c**).



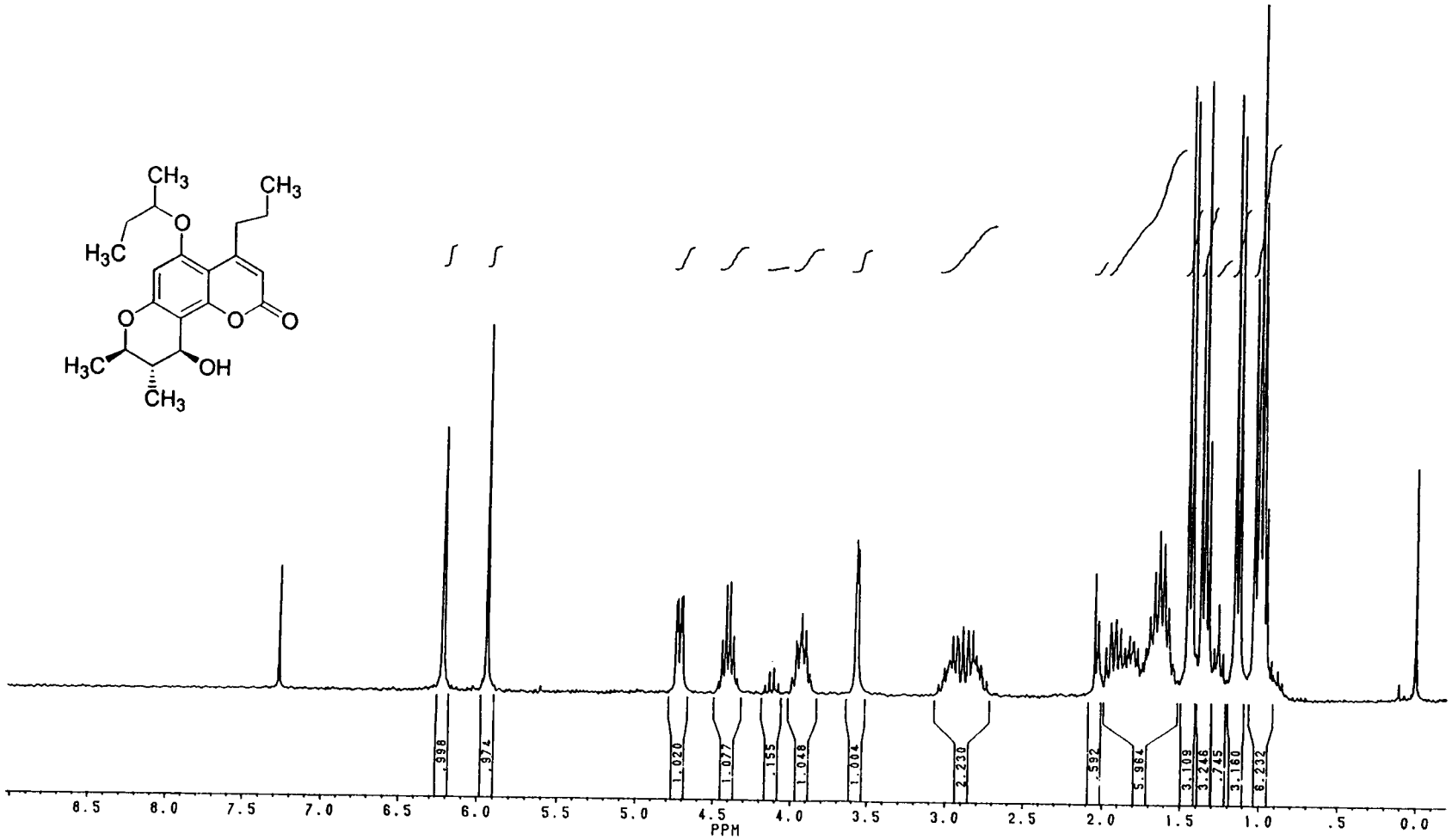
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-10-hydroxy-8,9-*trans*-dimethyl-5-propargyloxy-4-propyl-9,10-*trans*-dihydro[8*H*]pyrano[2,3-*f*]chromen-2-one (**9**).



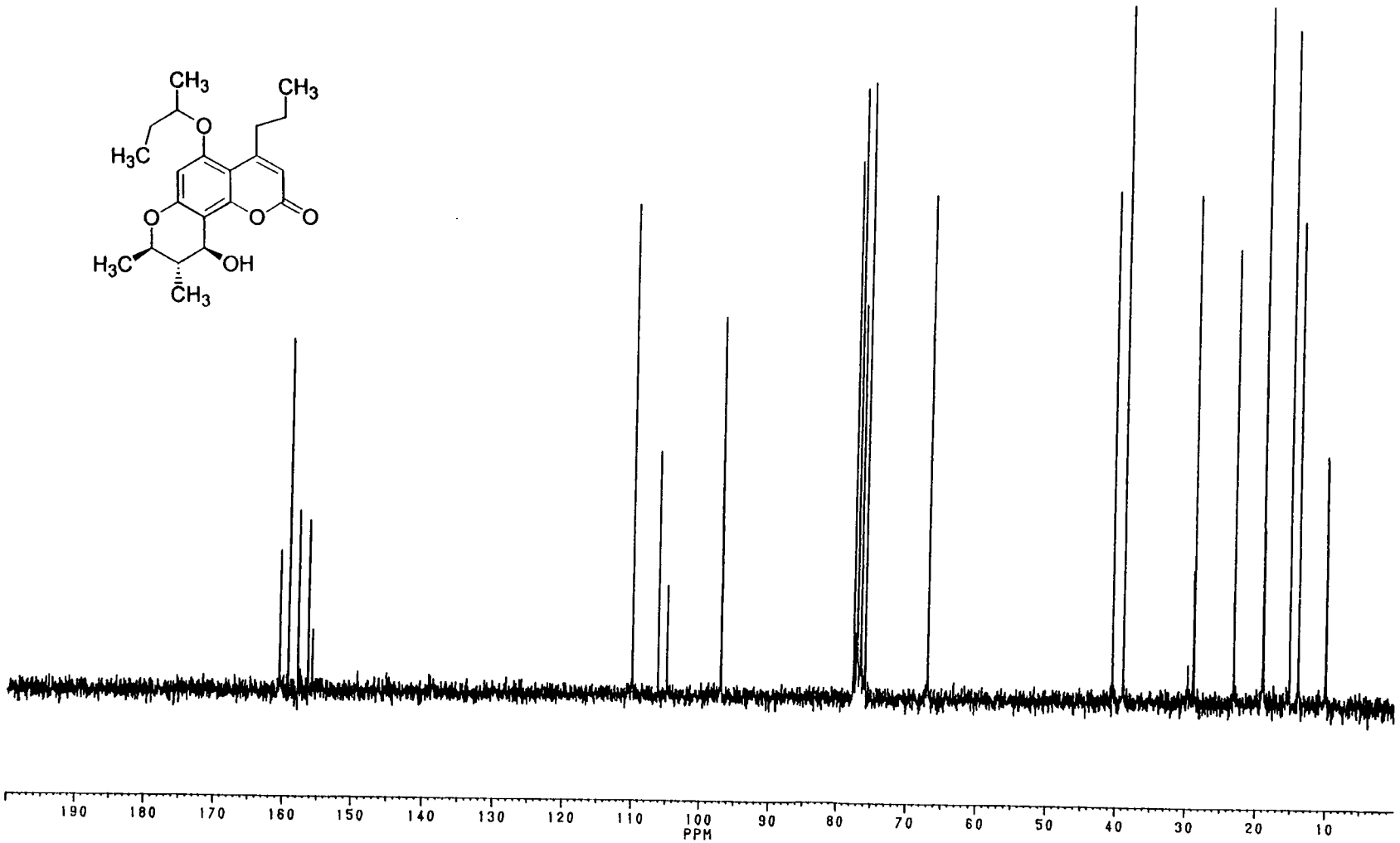
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-10-hydroxy-8,9-*trans*-dimethyl-5-propoxy-4-propyl-9,10-*trans*-dihydro[8*H*]pyrano[2,3-*f*]chromen-2-one (**10**).



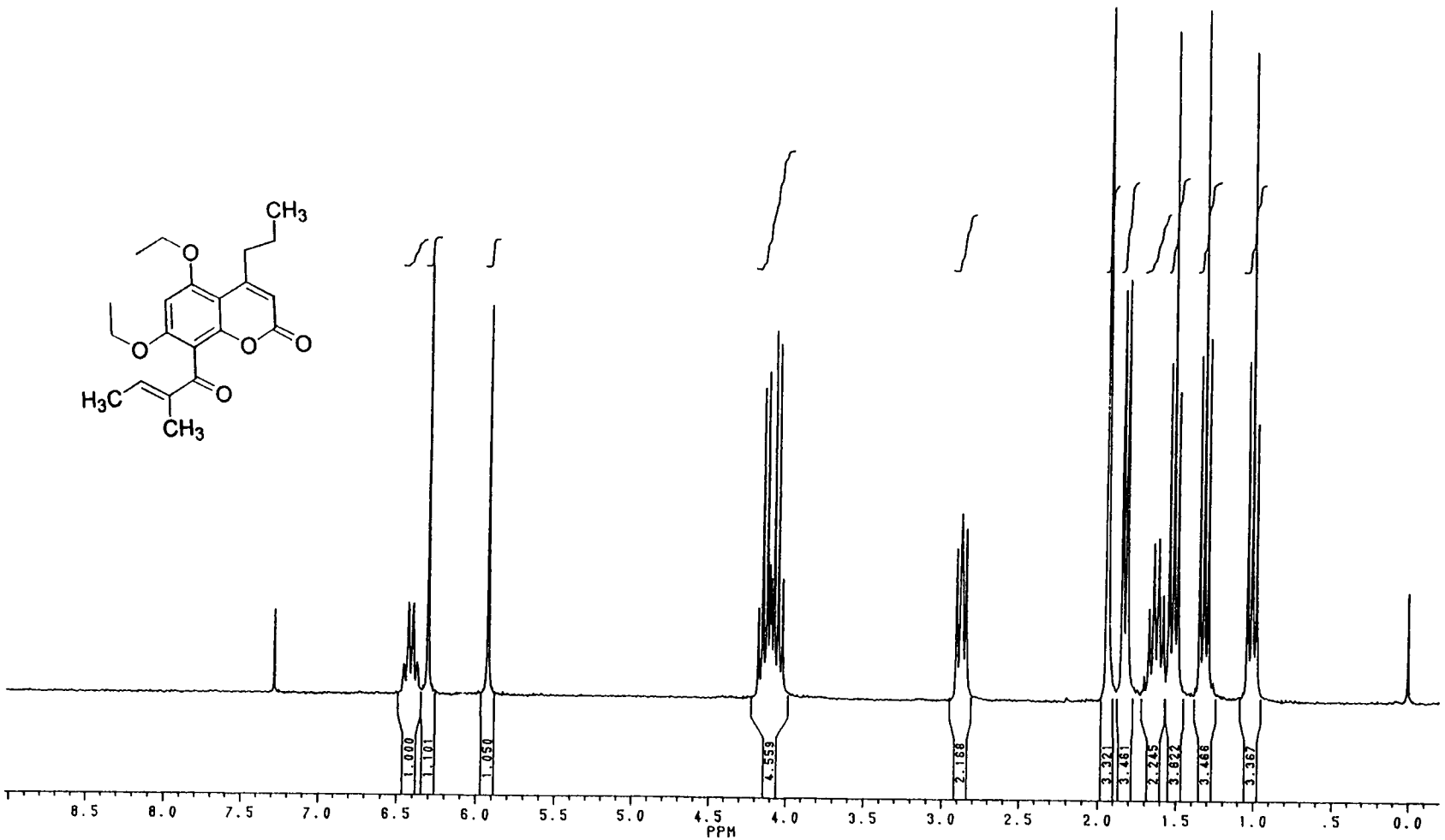
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-10-hydroxy-8,9-*trans*-dimethyl-5-propoxy-4-propyl-9,10-*trans*-dihydro[8*H*]pyrano[2,3-*f*]chromen-2-one (**10**).



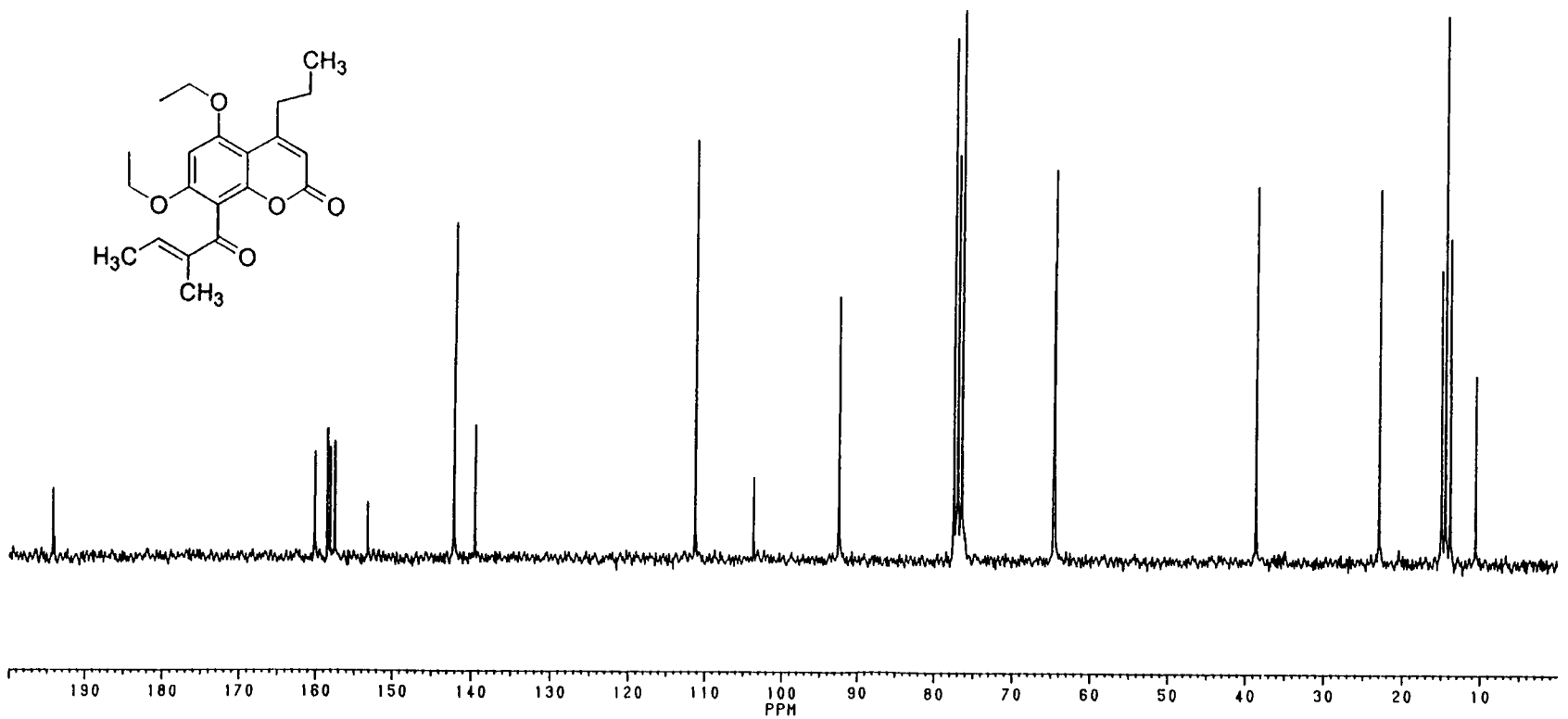
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-5-*sec*-butoxy-10-hydroxy-8,9-*trans*-dimethyl-4-propyl-9,10-*trans*-dihydro[8*H*]pyrano[2,3-*f*]chromen-2-one (**11**).



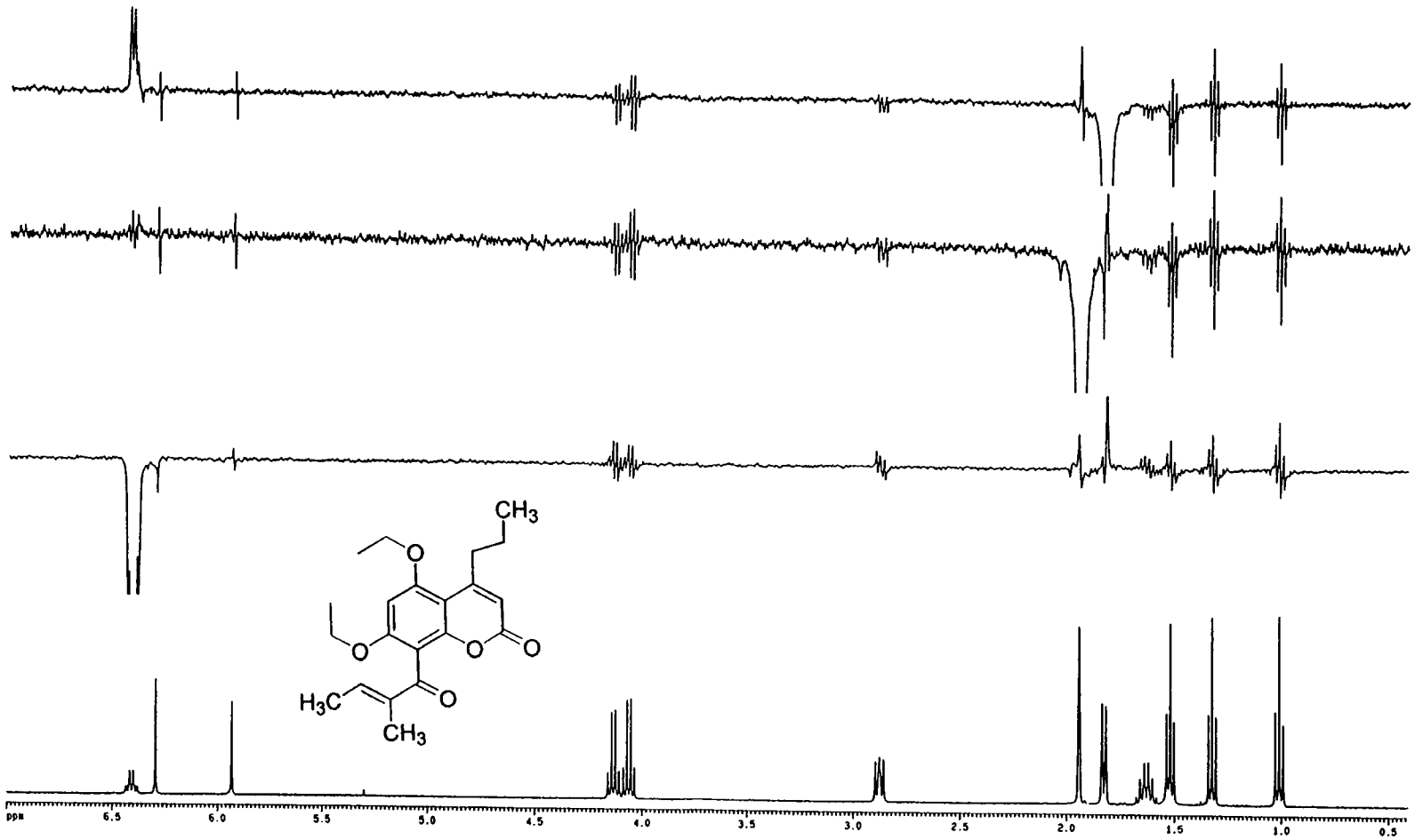
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-5-*sec*-butoxy-10-hydroxy-8,9-*trans*-dimethyl-4-propyl-9,10-*trans*-dihydro[8*H*]pyrano[2,3-*f*]chromen-2-one (**11**).



^{1}H NMR spectrum (250 MHz, $CDCl_3$) of 5,7-diethoxy-8-(2-methylbut-2-enoyl)-4-propylchromen-2-one (**12**).

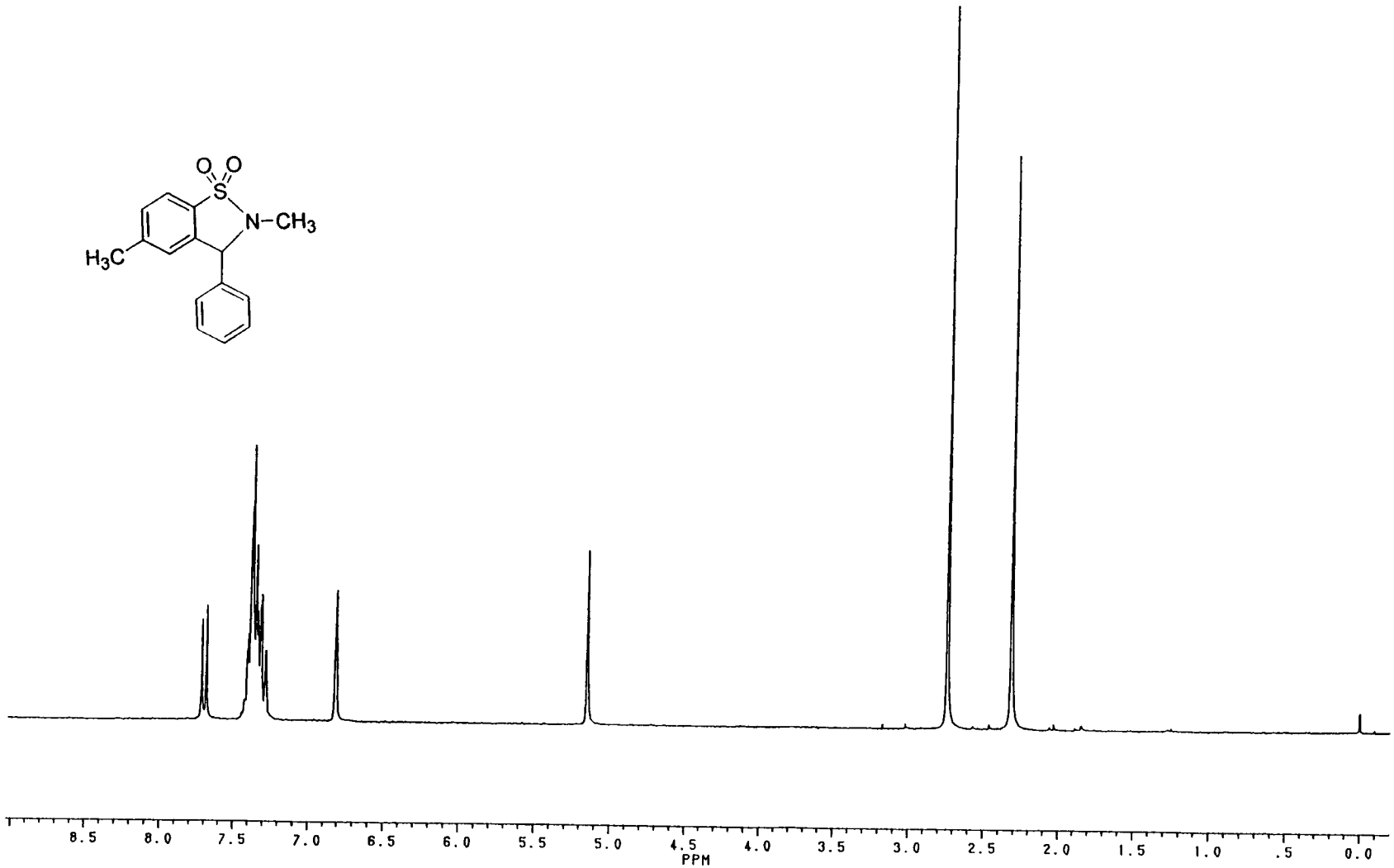


^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of 5,7-diethoxy-8-(2-methylbut-2-enoyl)-4-propylchromen-2-one (**12**).

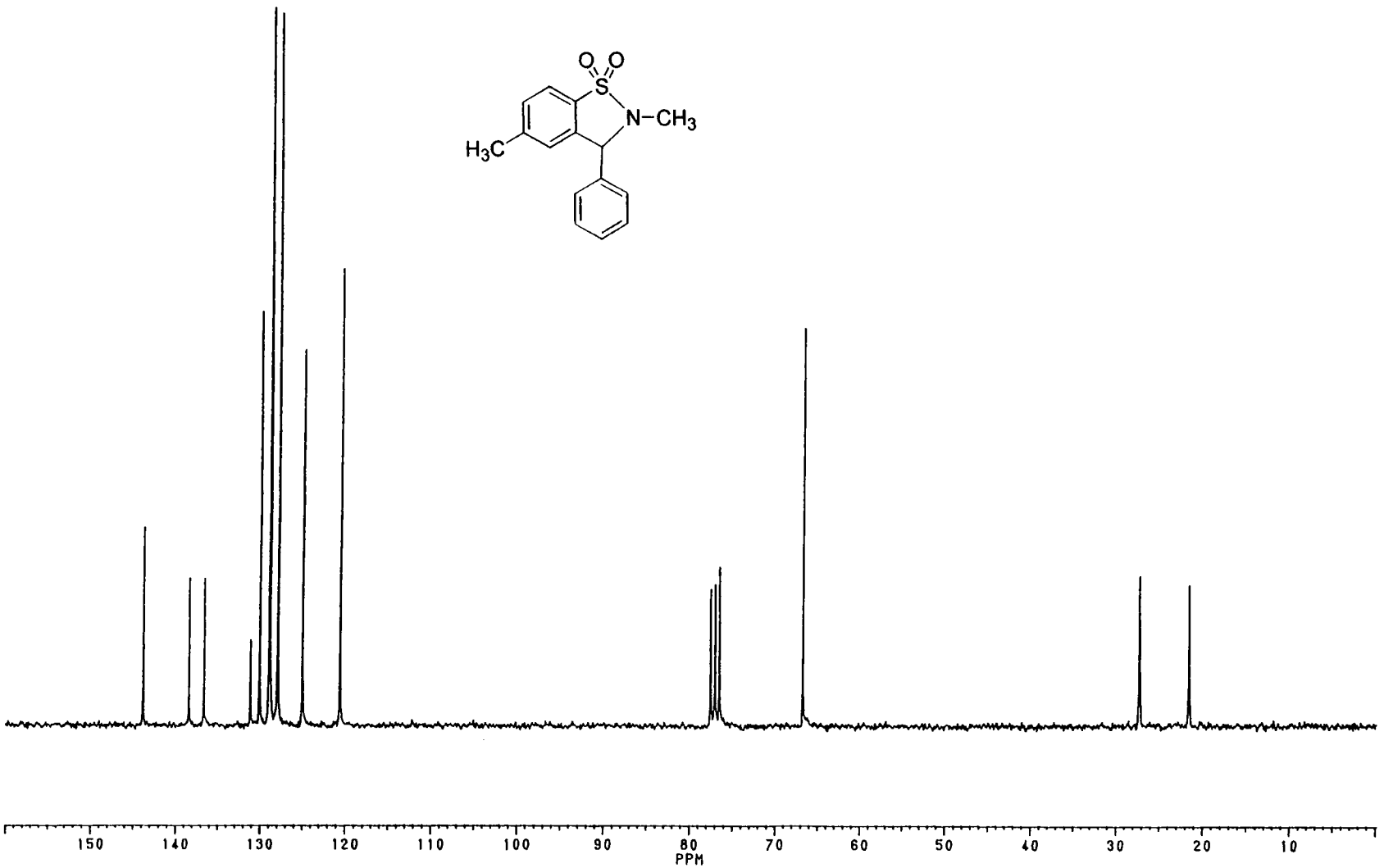


NOE difference spectrum (400 MHz, $CDCl_3$) of 5,7-diethoxy-8-(2-methylbut-2-enoyl)-4-propylchromen-2-one (**12**).

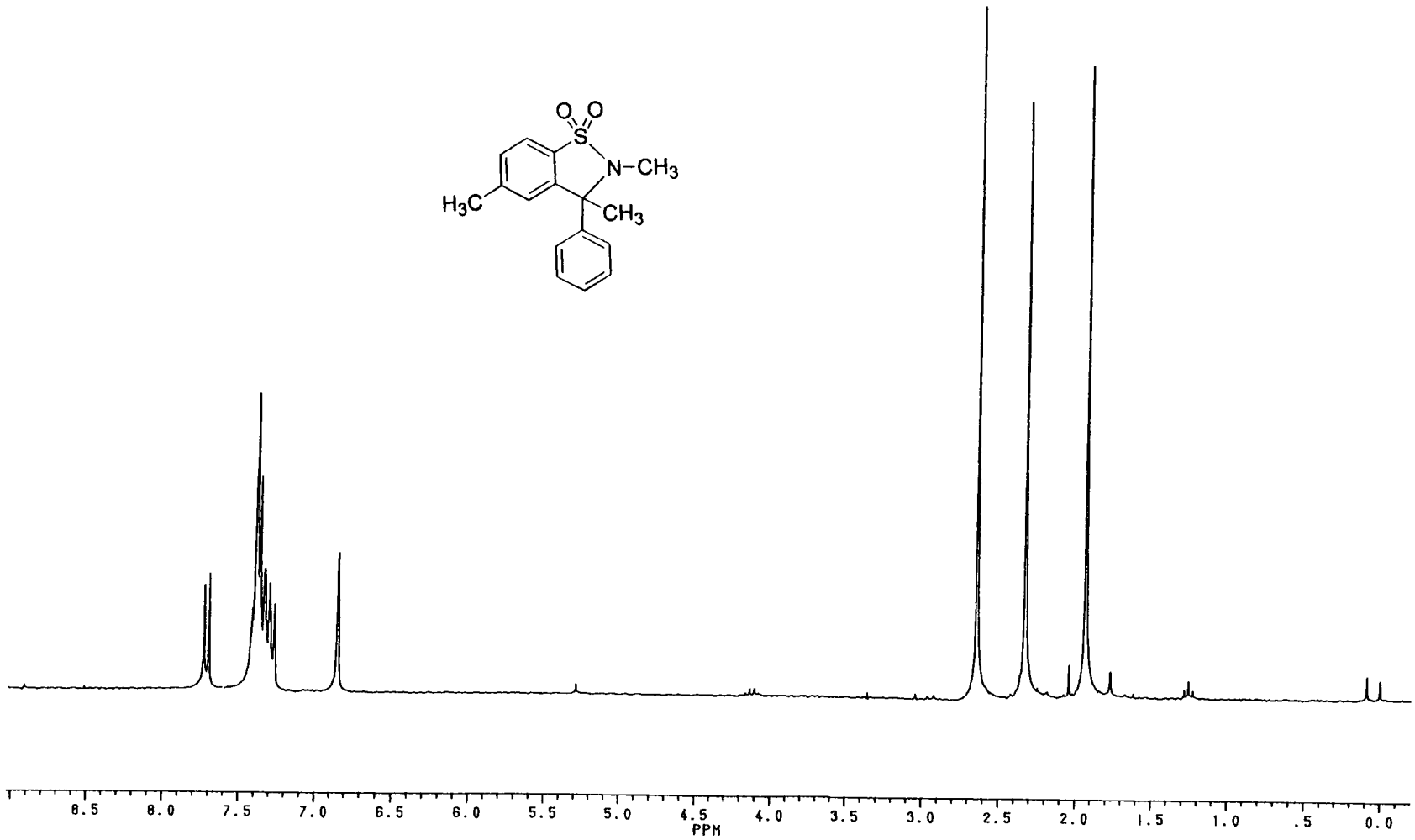
APPENDIX C. ^{1}H and ^{13}C NMR Spectra of Sultam Analogs



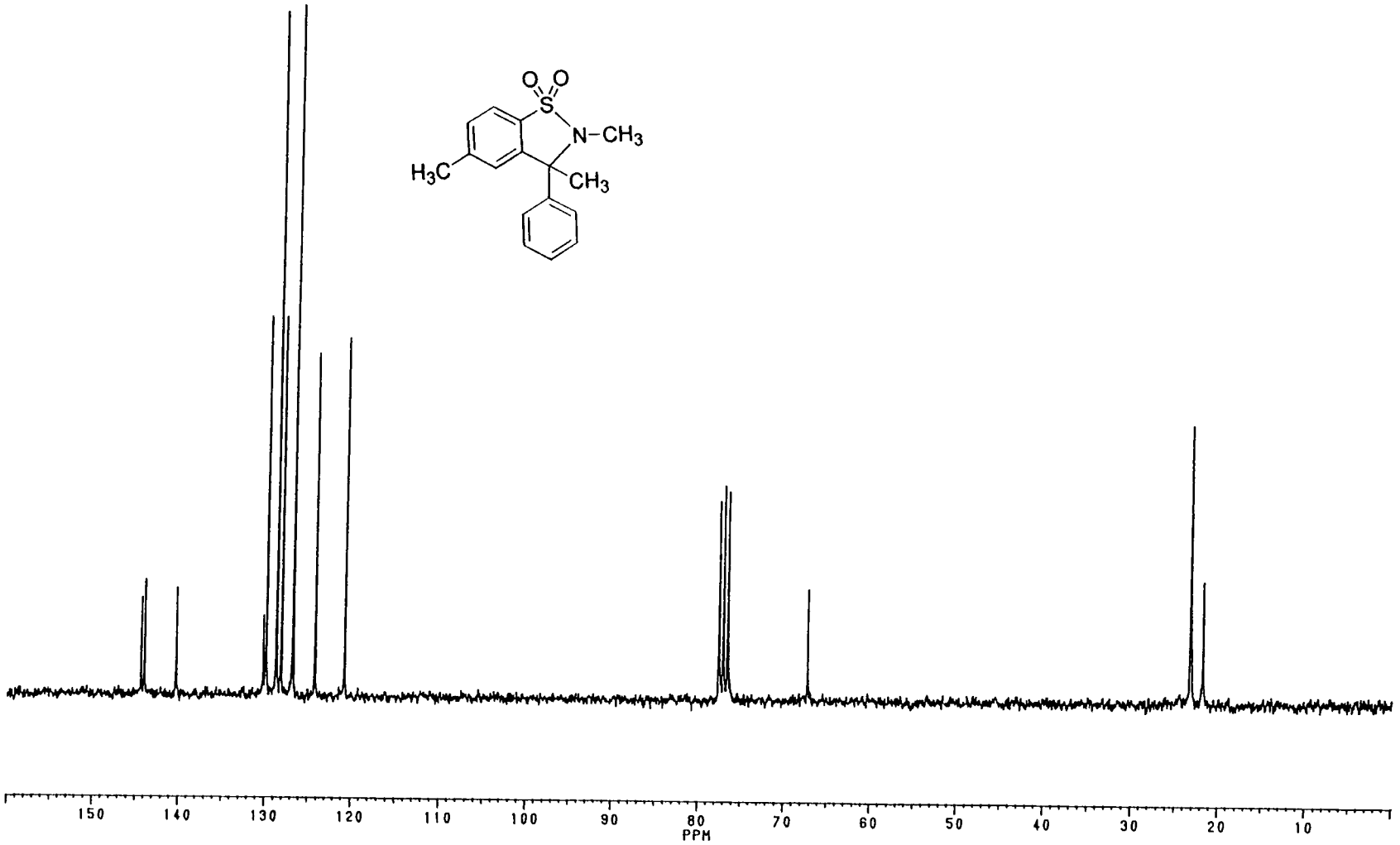
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-2,5-dimethyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**4**).



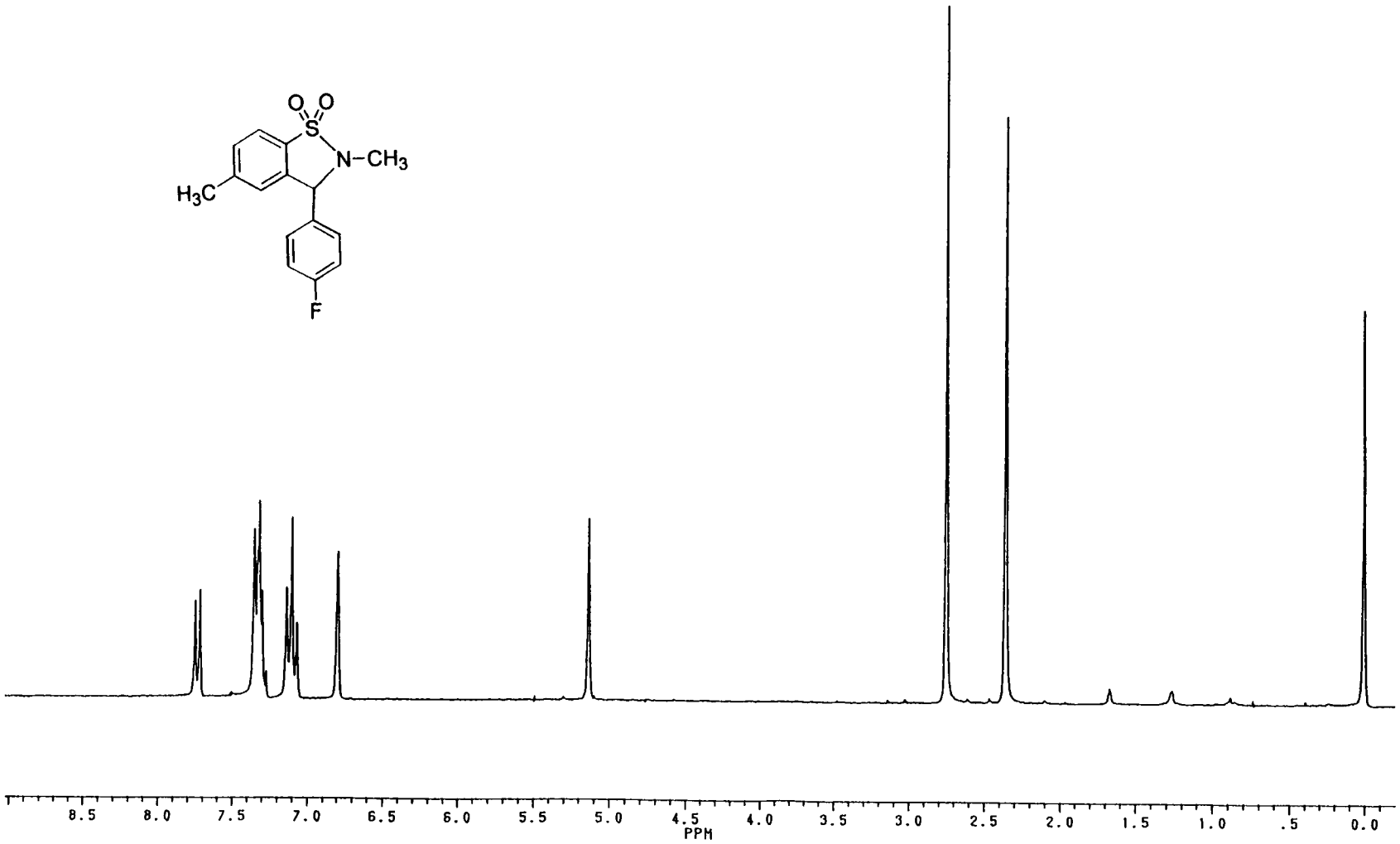
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-2,5-dimethyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**4**).



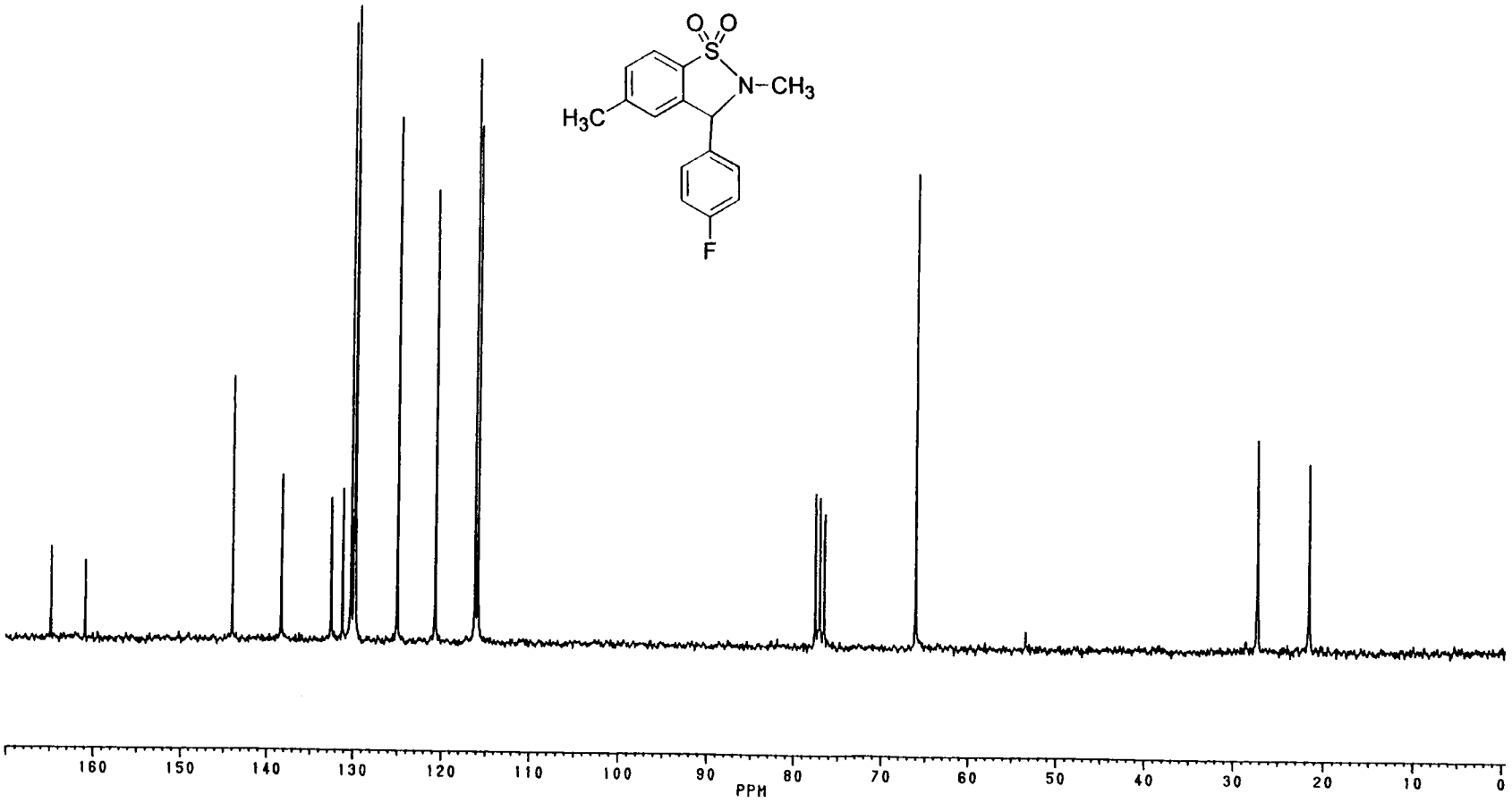
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-2,3,5-trimethyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**6**).



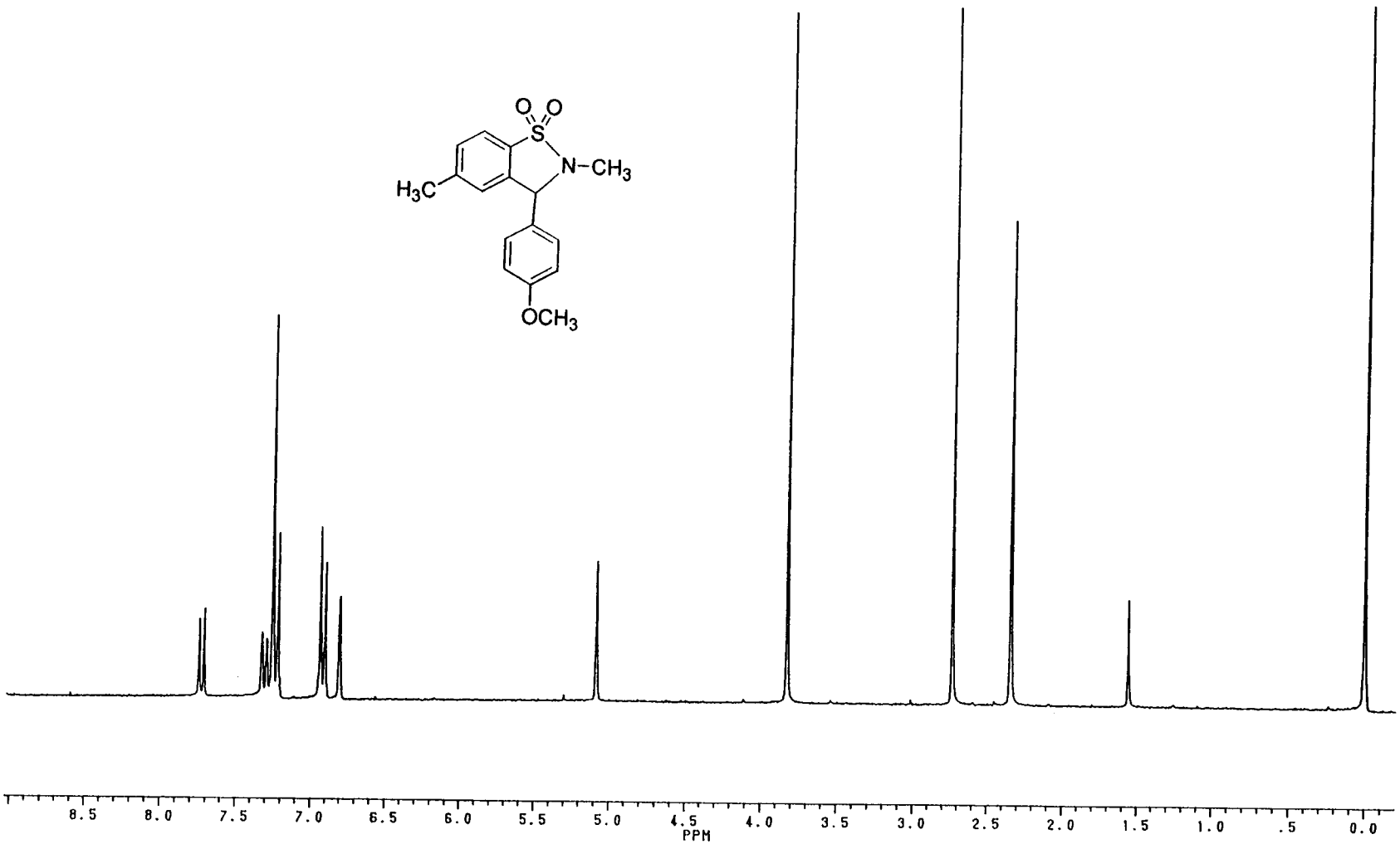
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-2,3,5-trimethyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**6**).



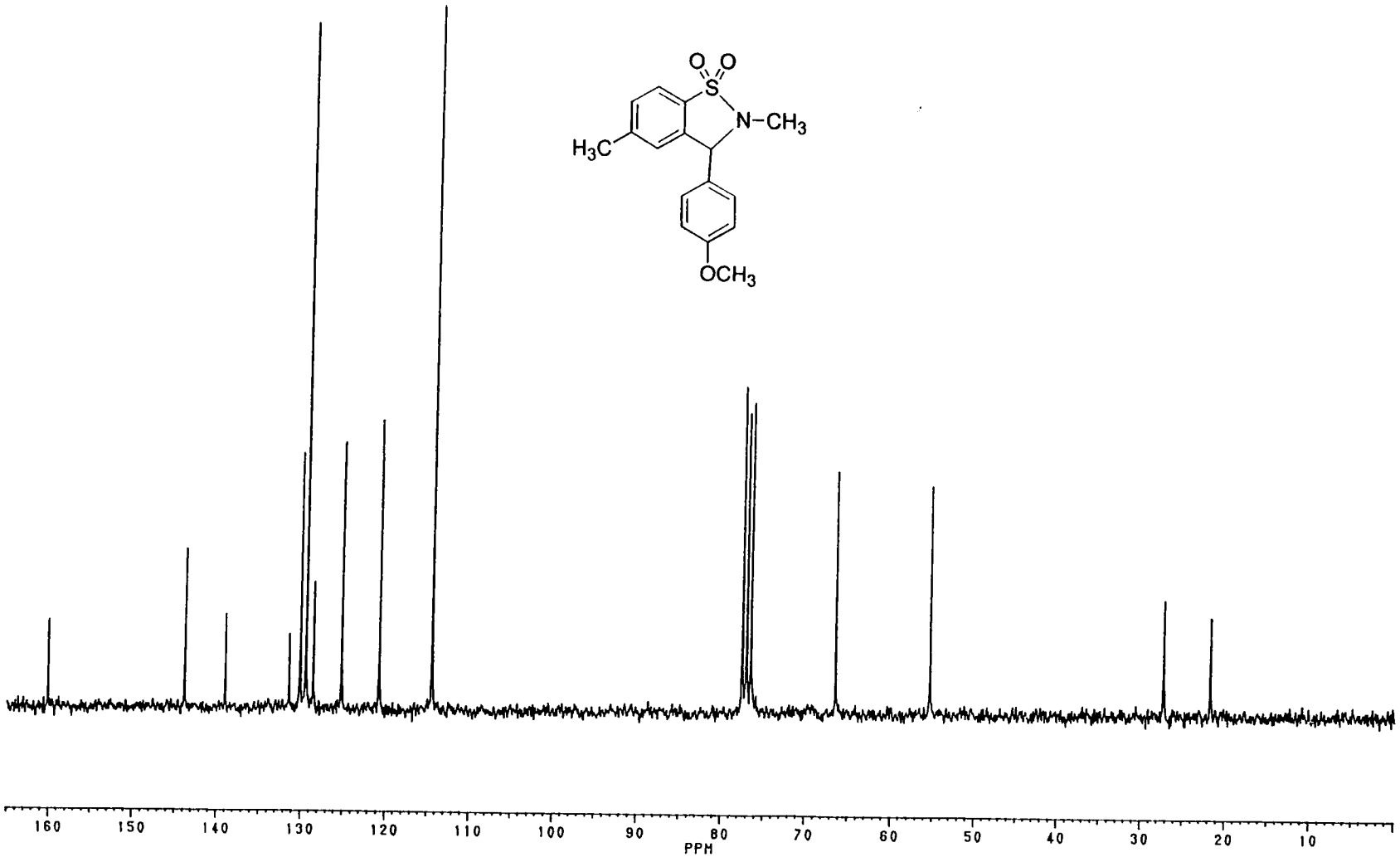
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-3-(4-fluorophenyl)-2,5-dimethyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**8**).



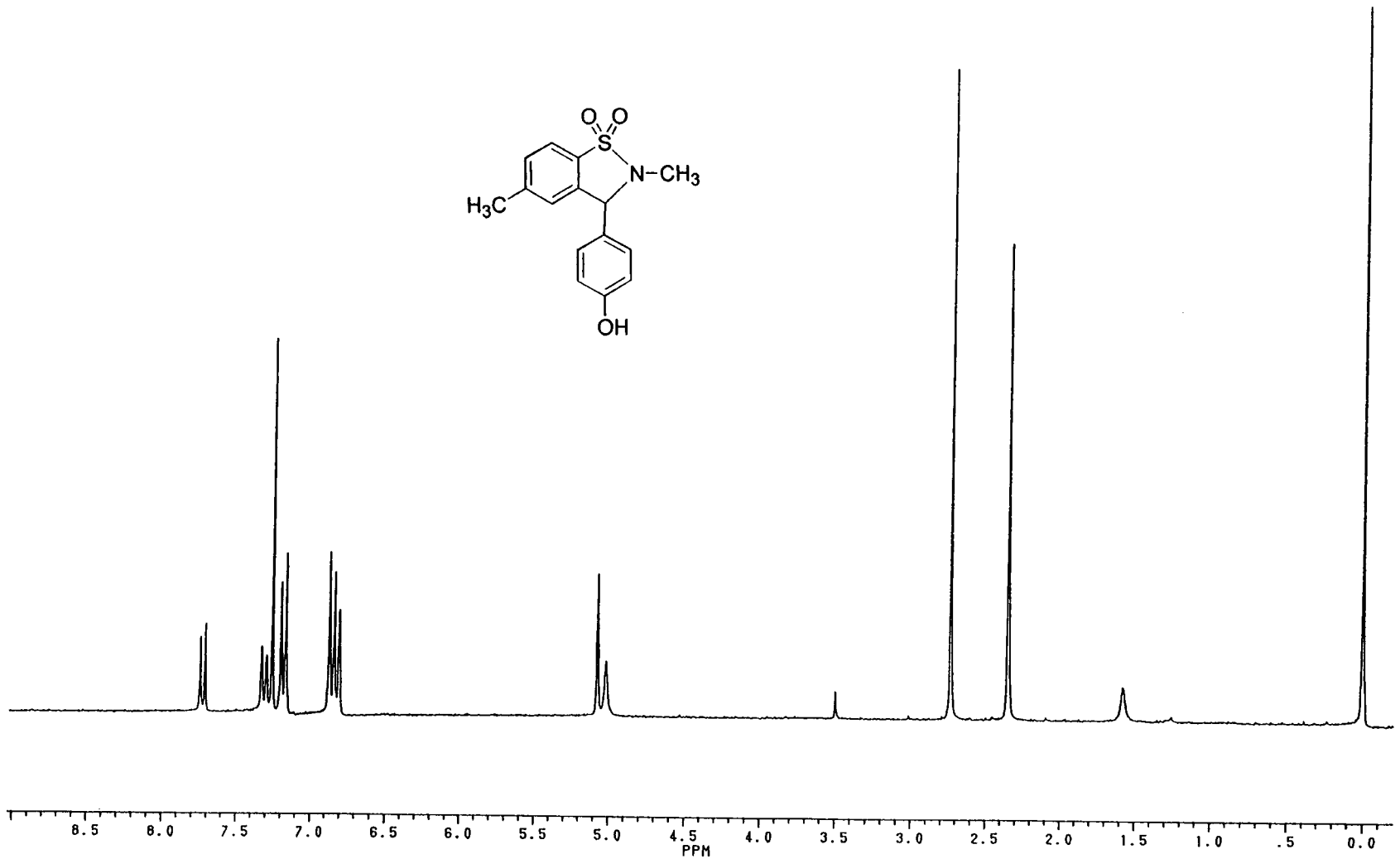
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-3-(4-fluorophenyl)-2,5-dimethyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**8**).



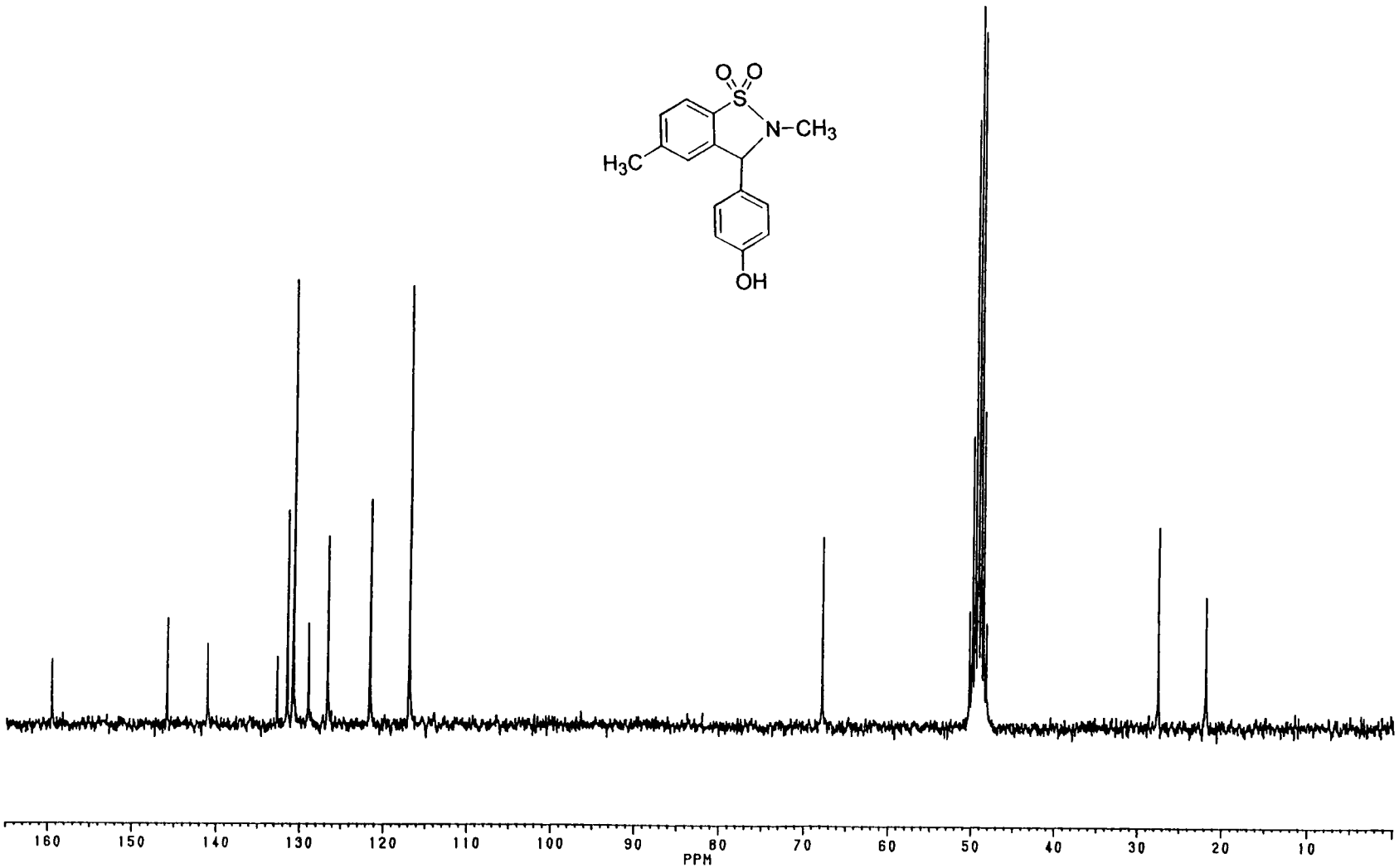
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-3-(4-methoxyphenyl)-2,5-dimethyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**10**).



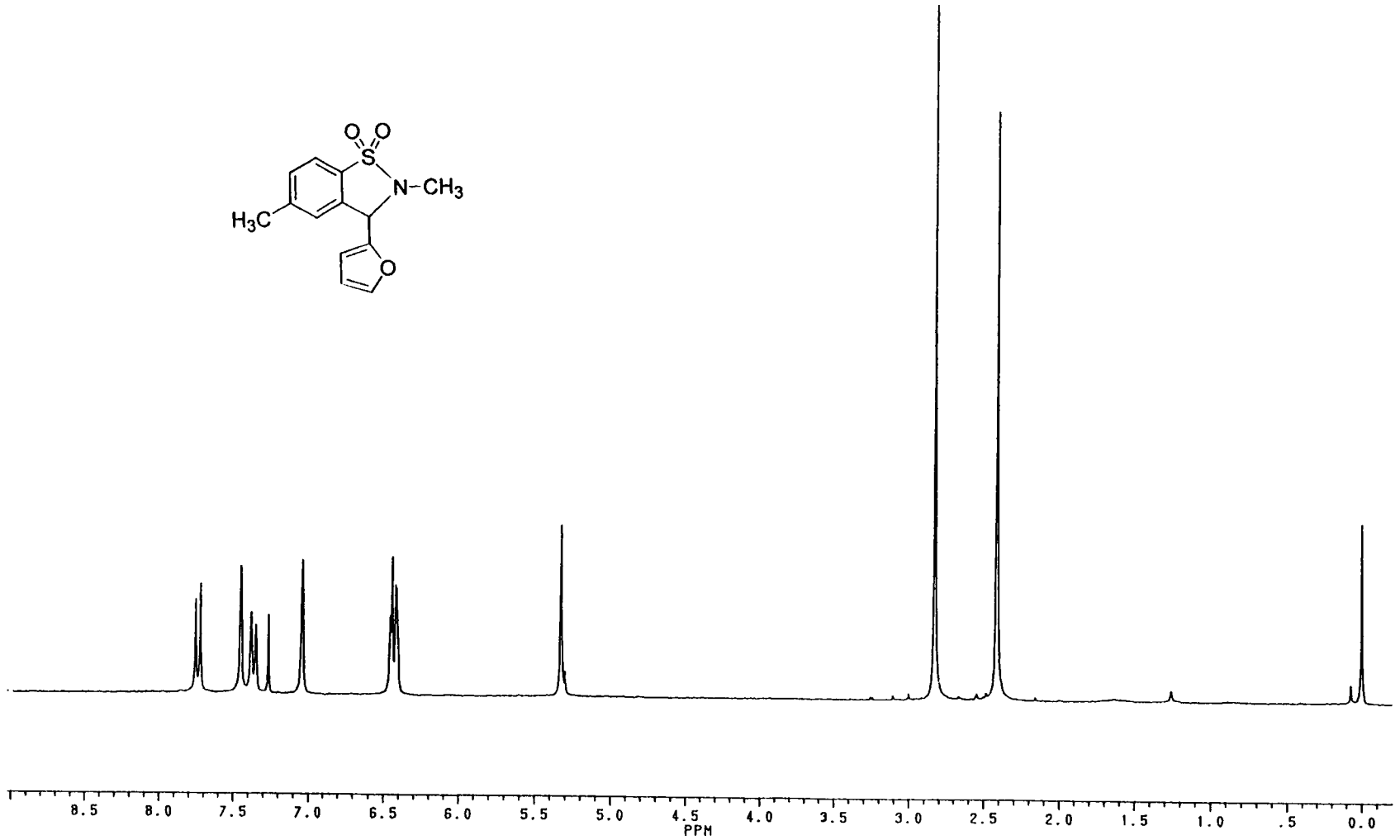
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-3-(4-methoxyphenyl)-2,5-dimethyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**10**).



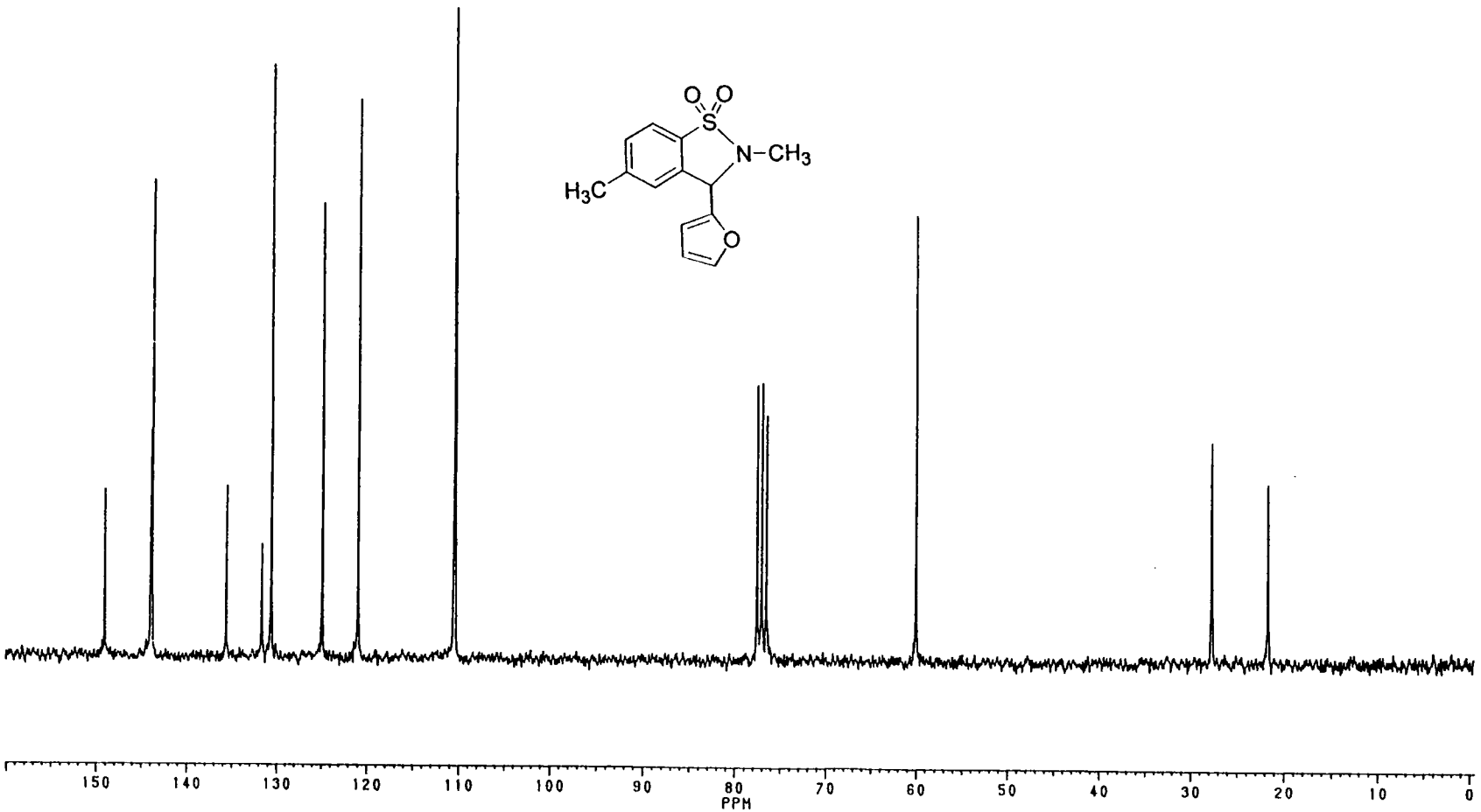
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-4-(2,5-dimethyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenol (**11**).



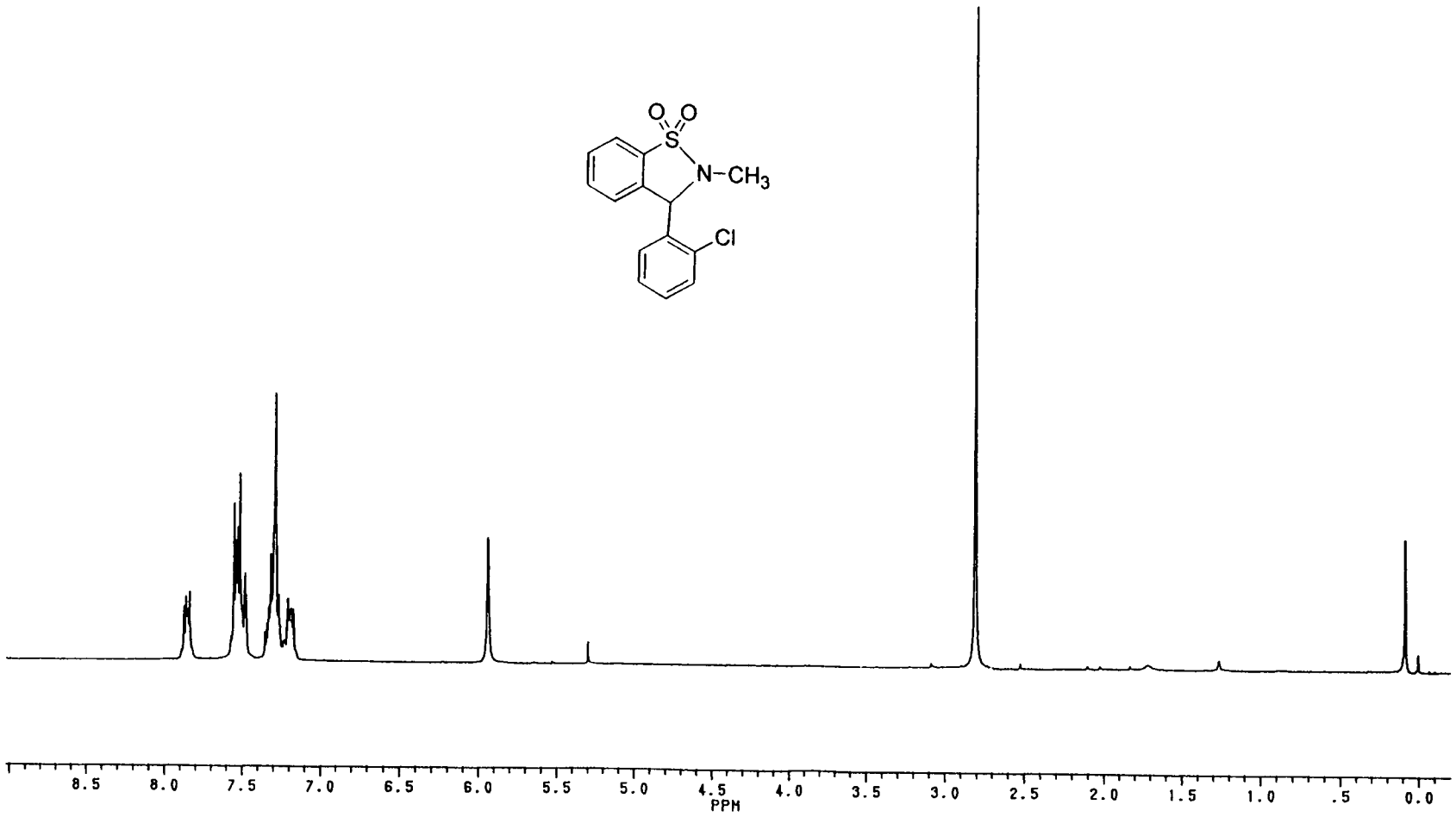
^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (±)-4-(2,5-dimethyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenol (**11**).



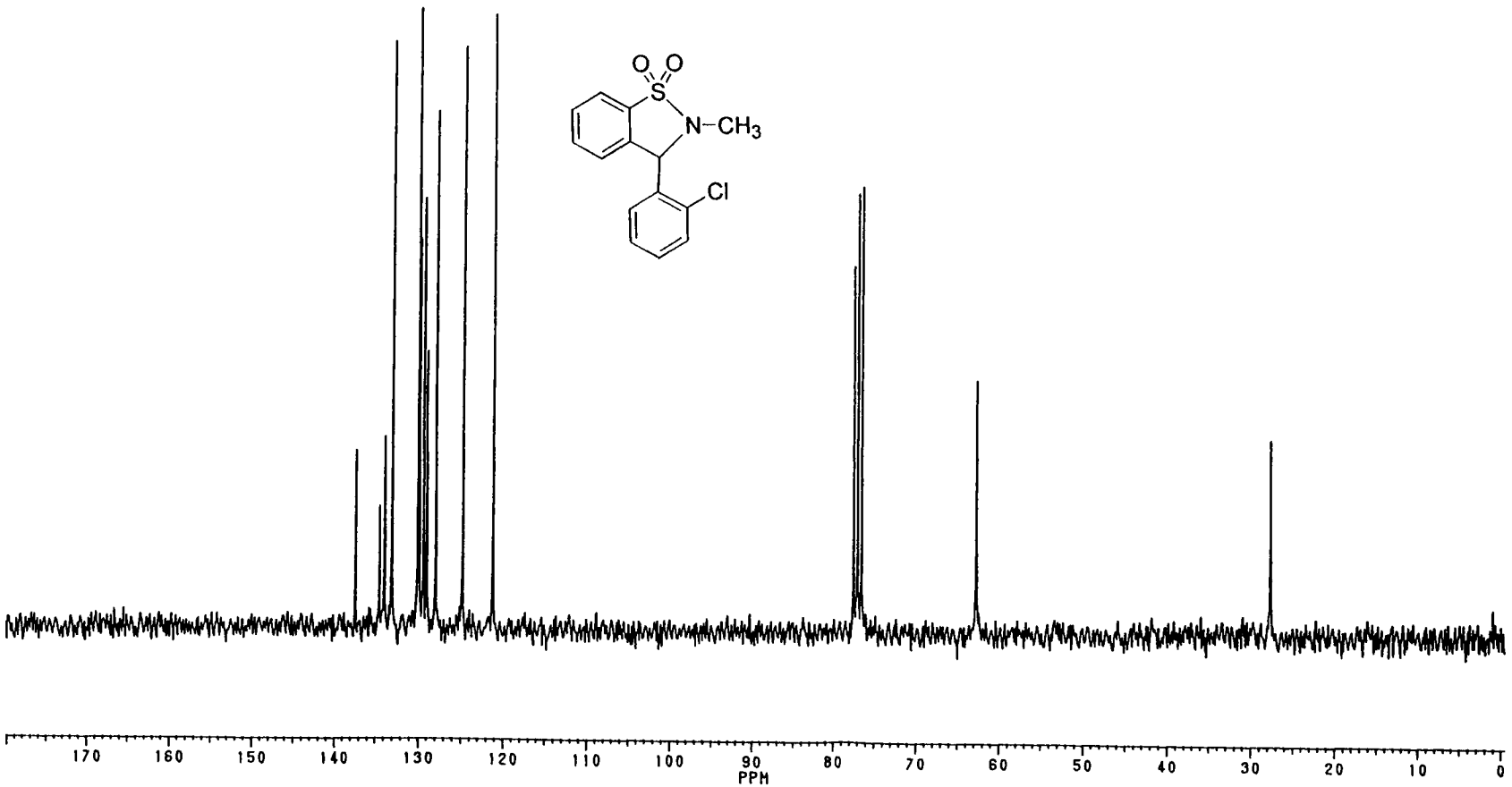
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-3-furan-2-yl-2,5-dimethyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**13**).



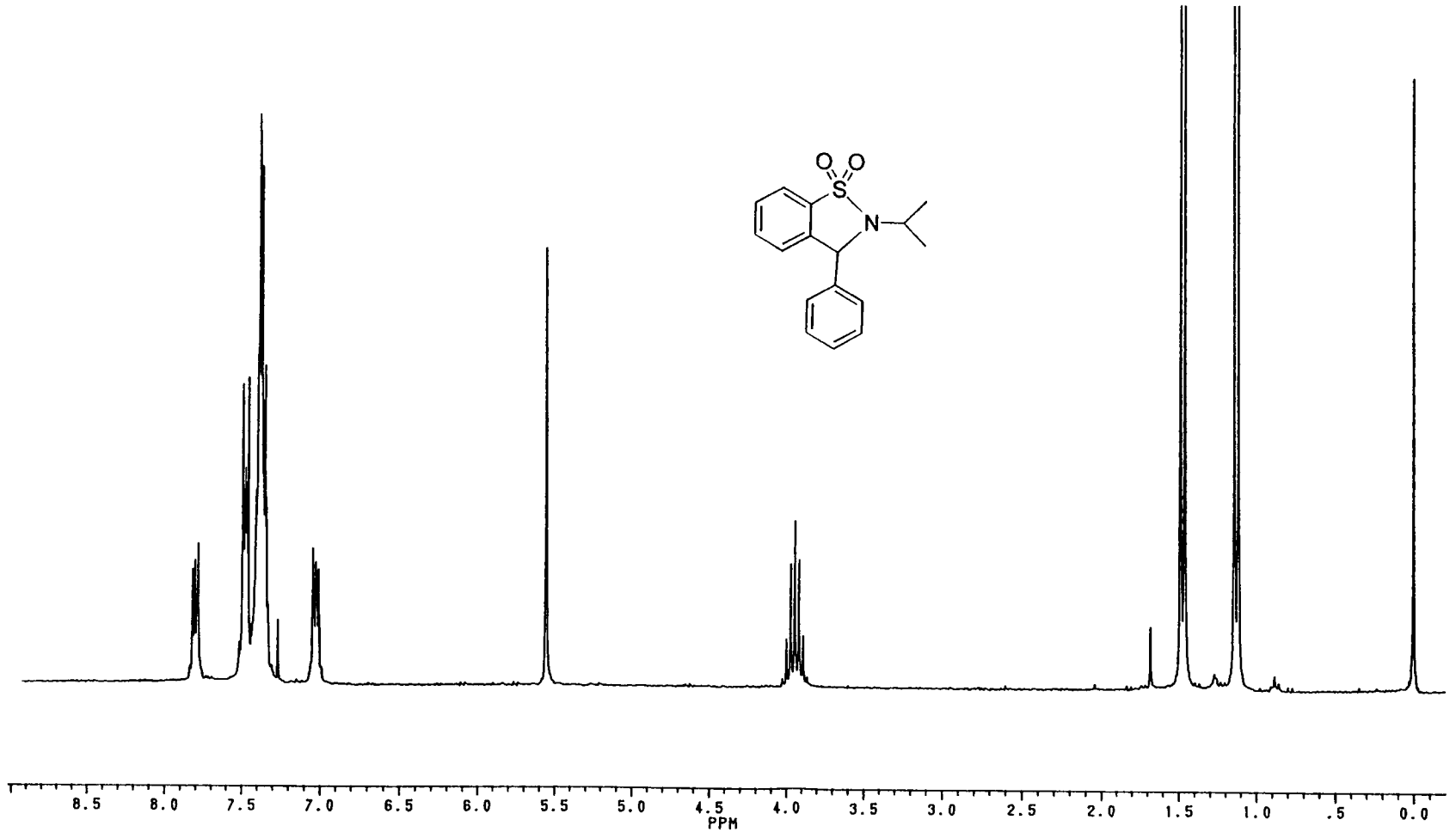
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-3-furan-2-yl-2,5-dimethyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**13**).



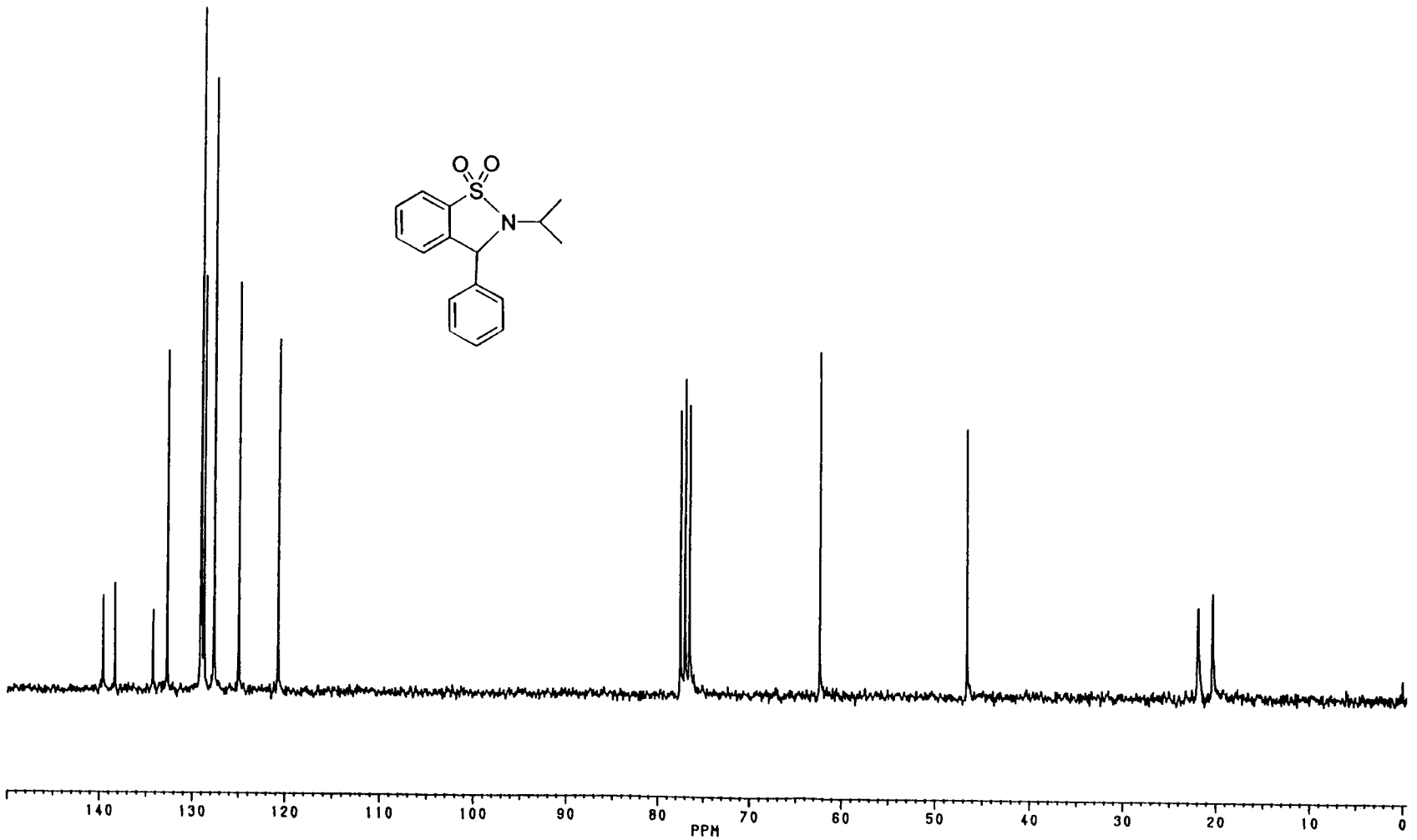
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-3-(2-chlorophenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**17**).



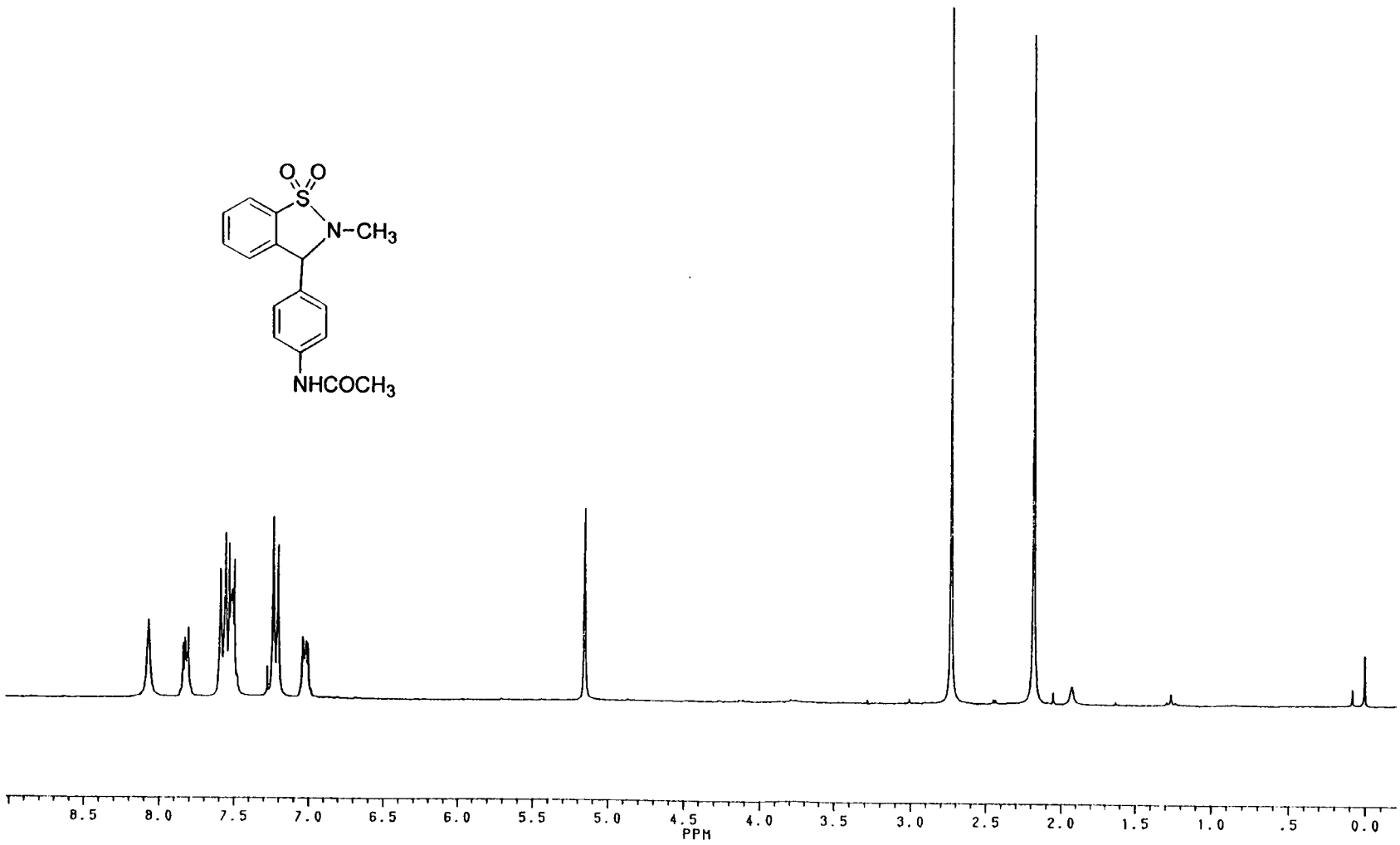
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-3-(2-chlorophenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**17**).



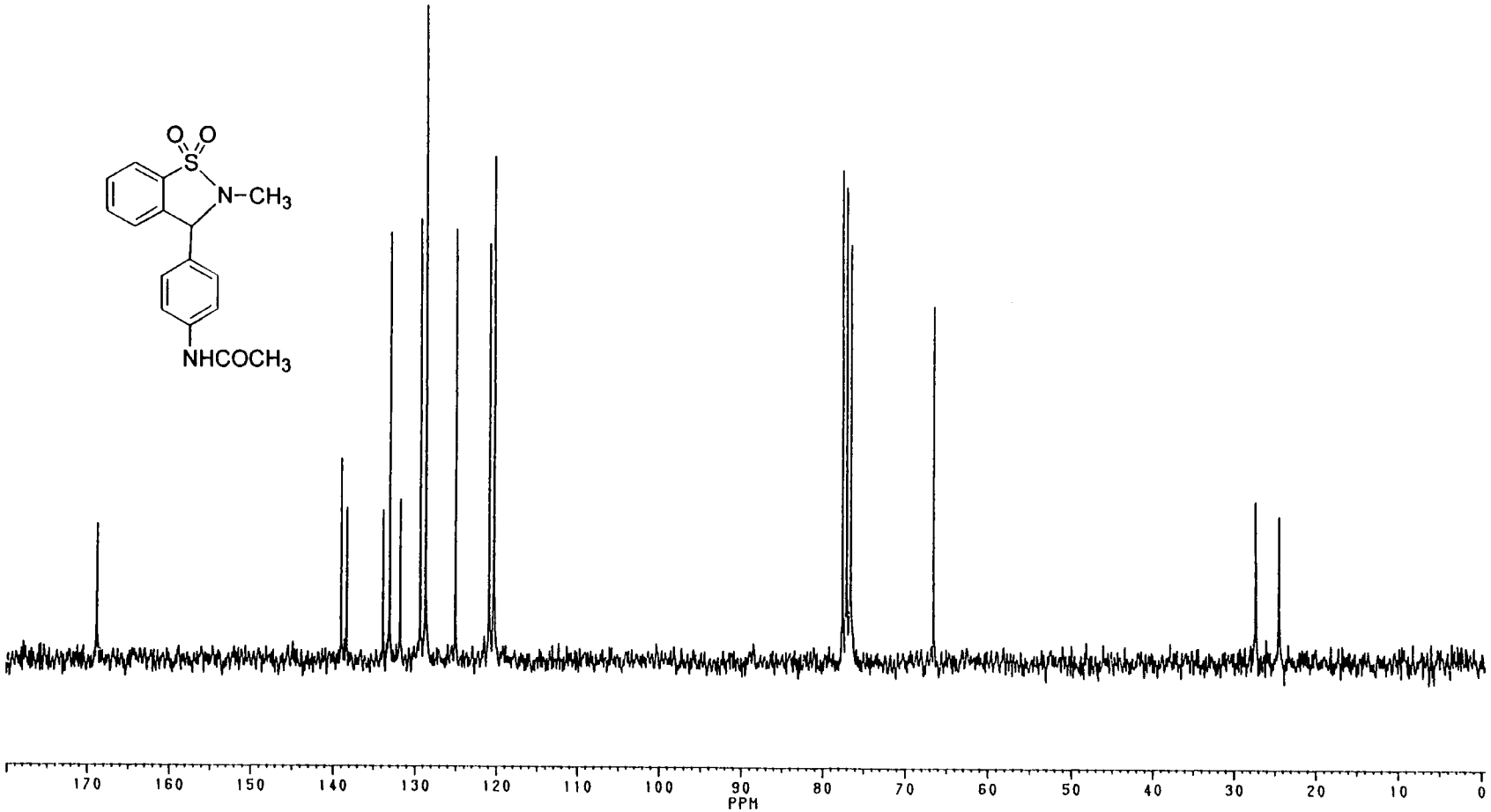
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-2-isopropyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**20**).



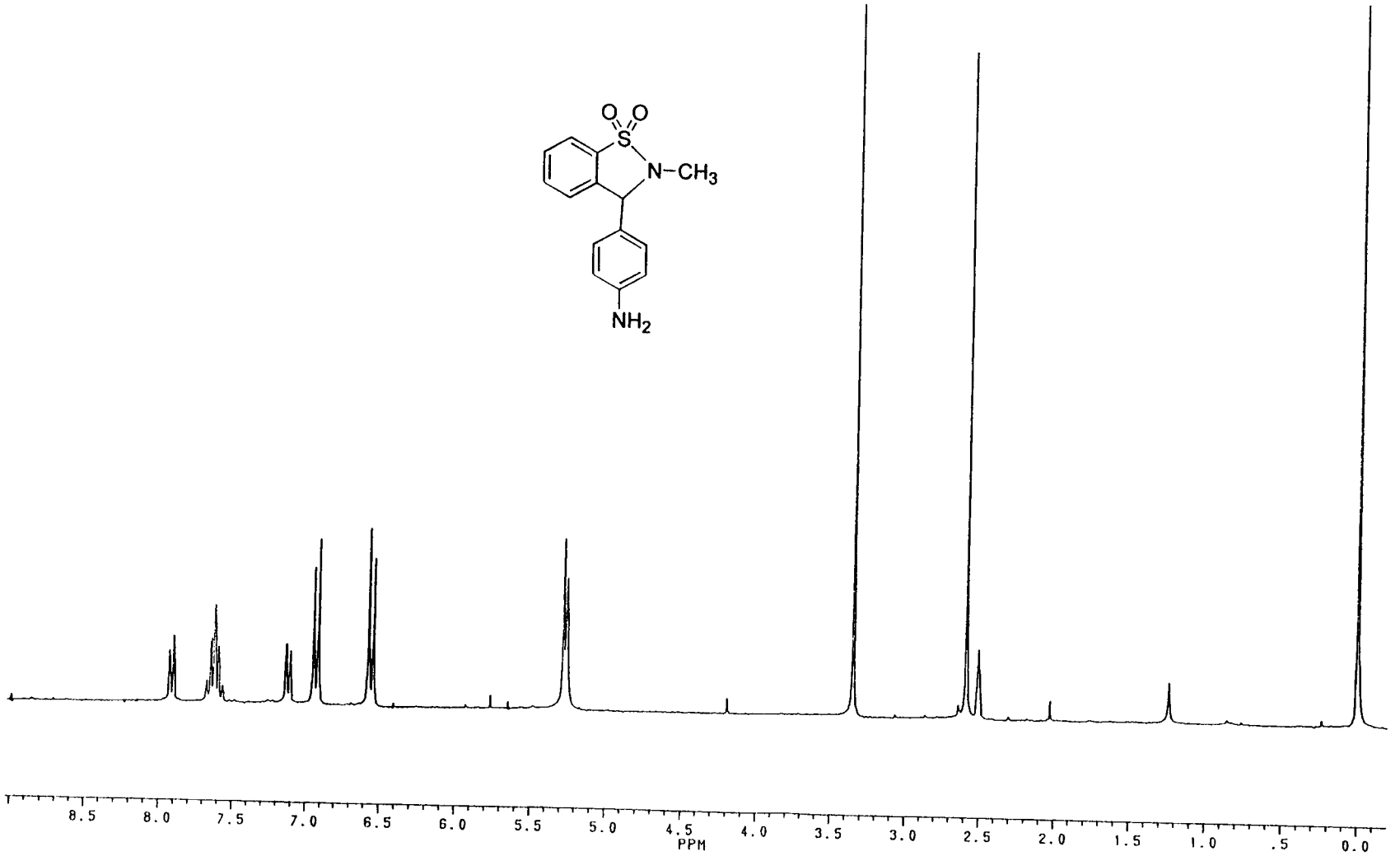
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-2-isopropyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**20**).



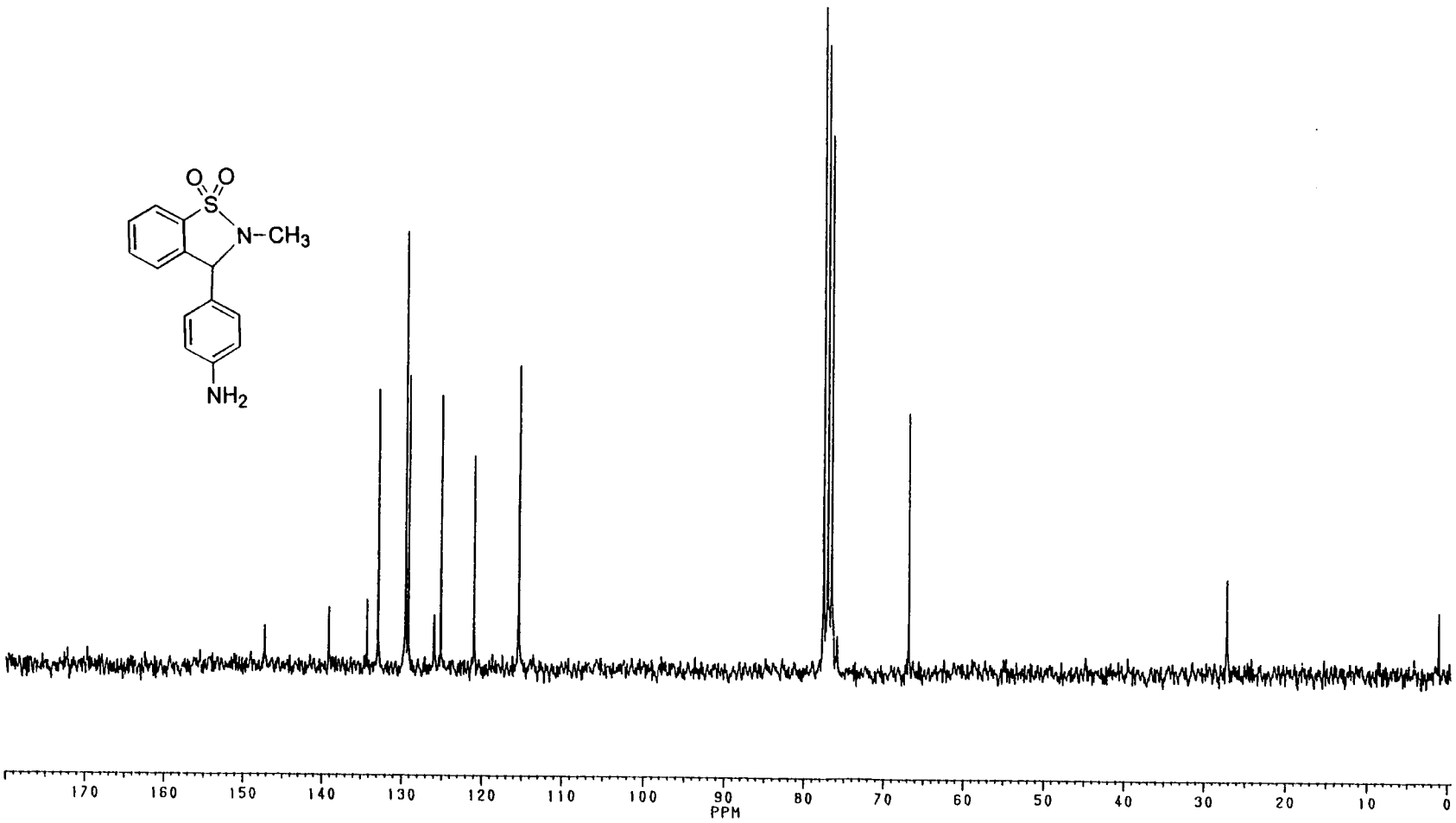
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-*N*-[4-(2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenyl]-acetamide (**22**).



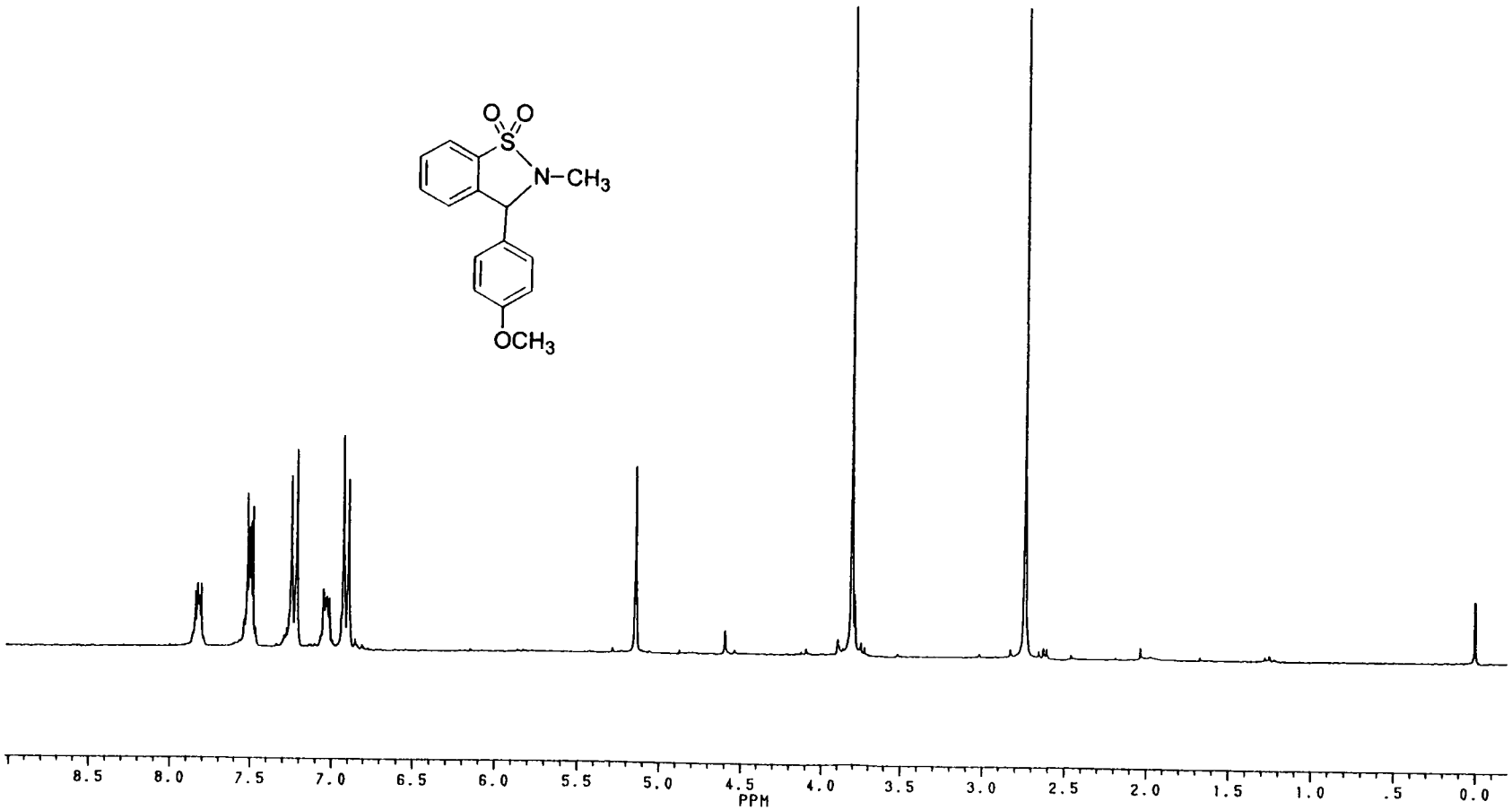
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-*N*-[4-(2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenyl]-acetamide (**22**).



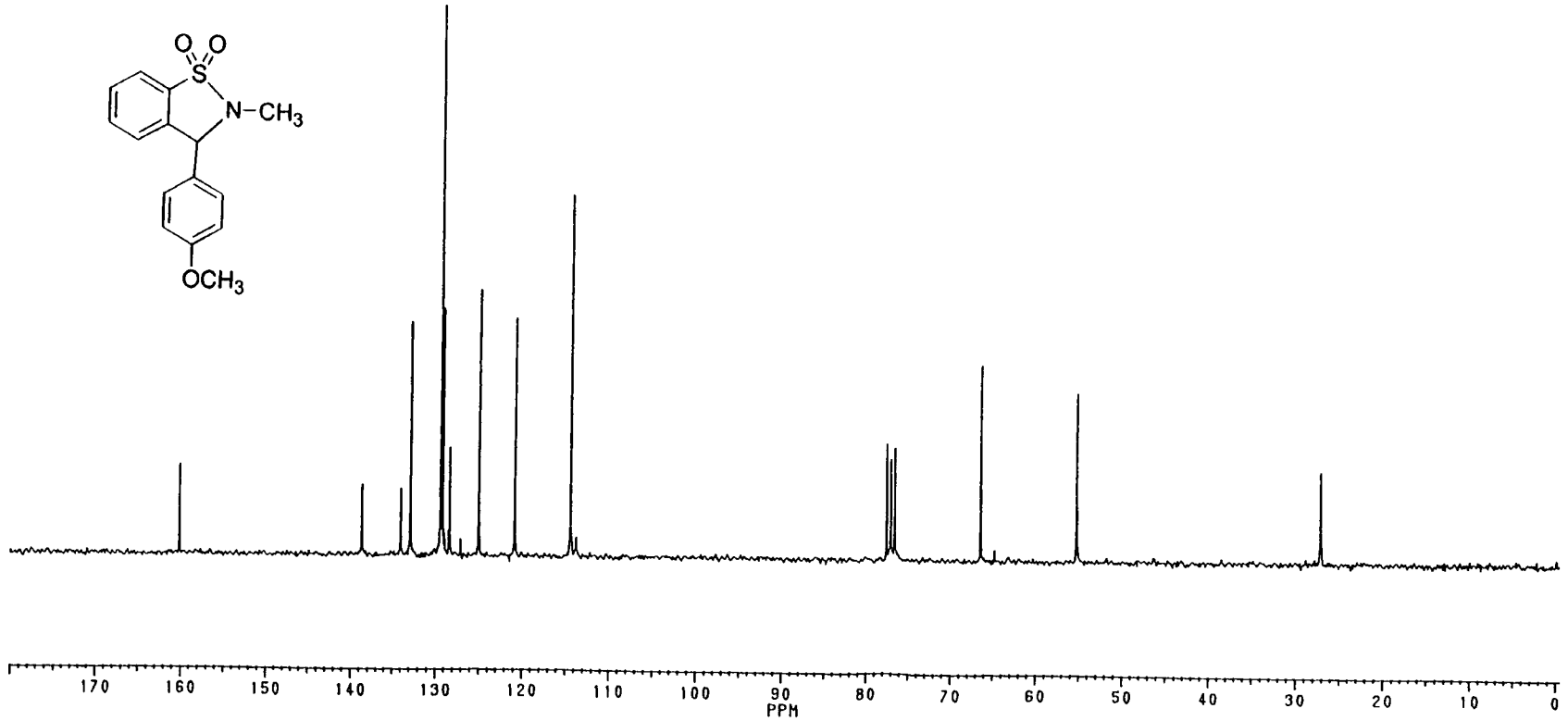
^{1}H NMR spectrum (250 MHz, DMSO-d_6) of (±)-4-(2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenylamine (**23**).



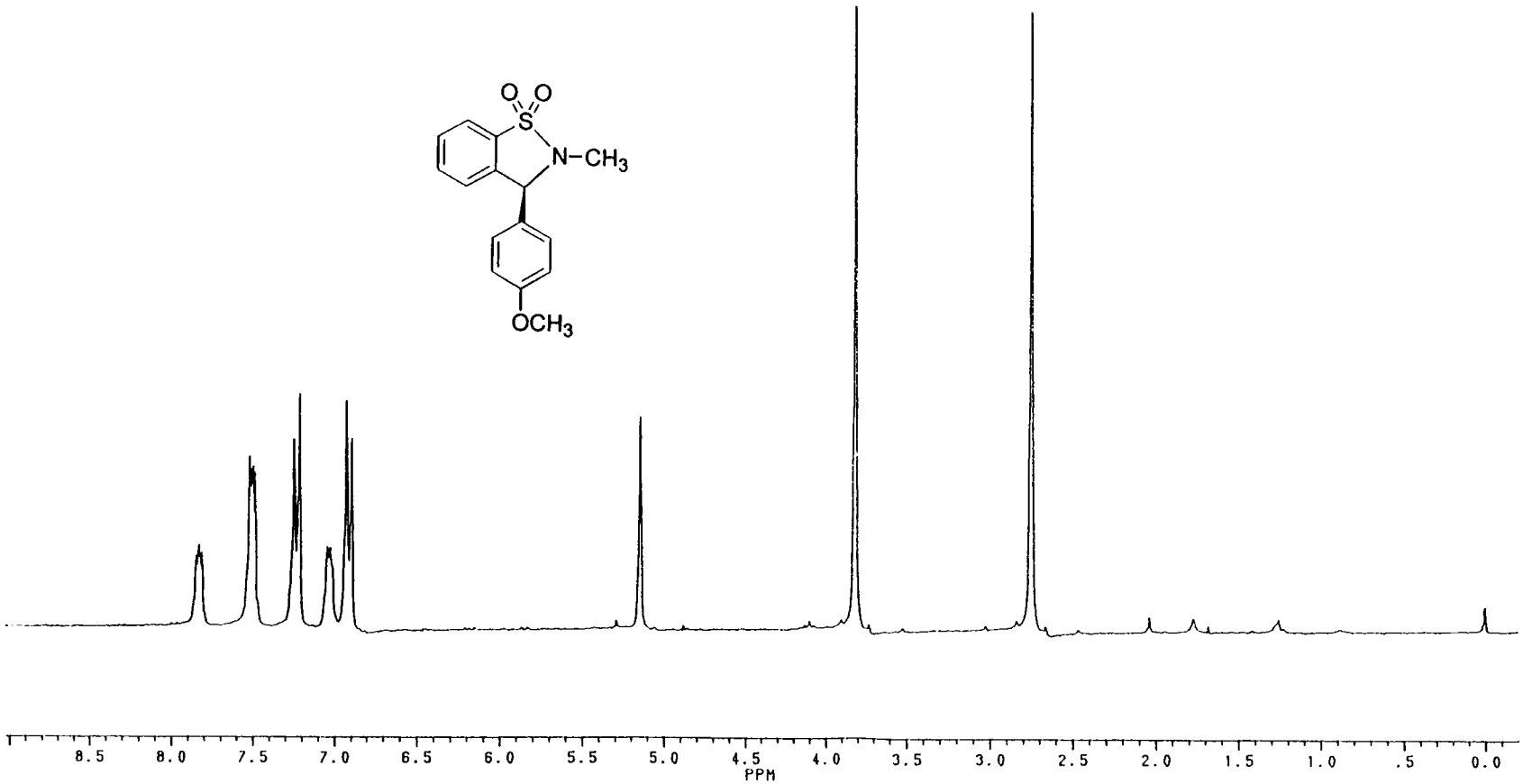
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-4-(2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenylamine (**23**).



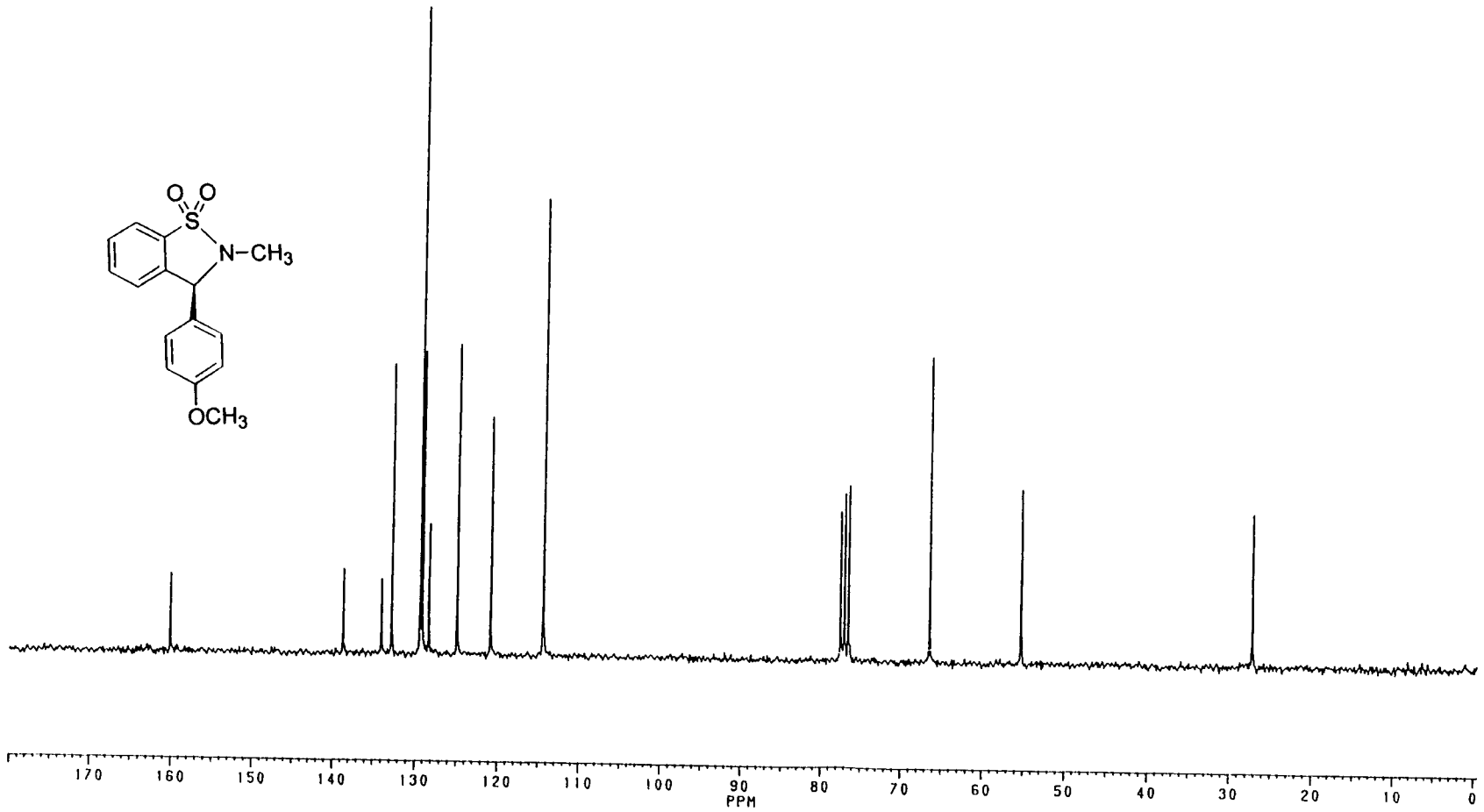
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-3-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**35**).



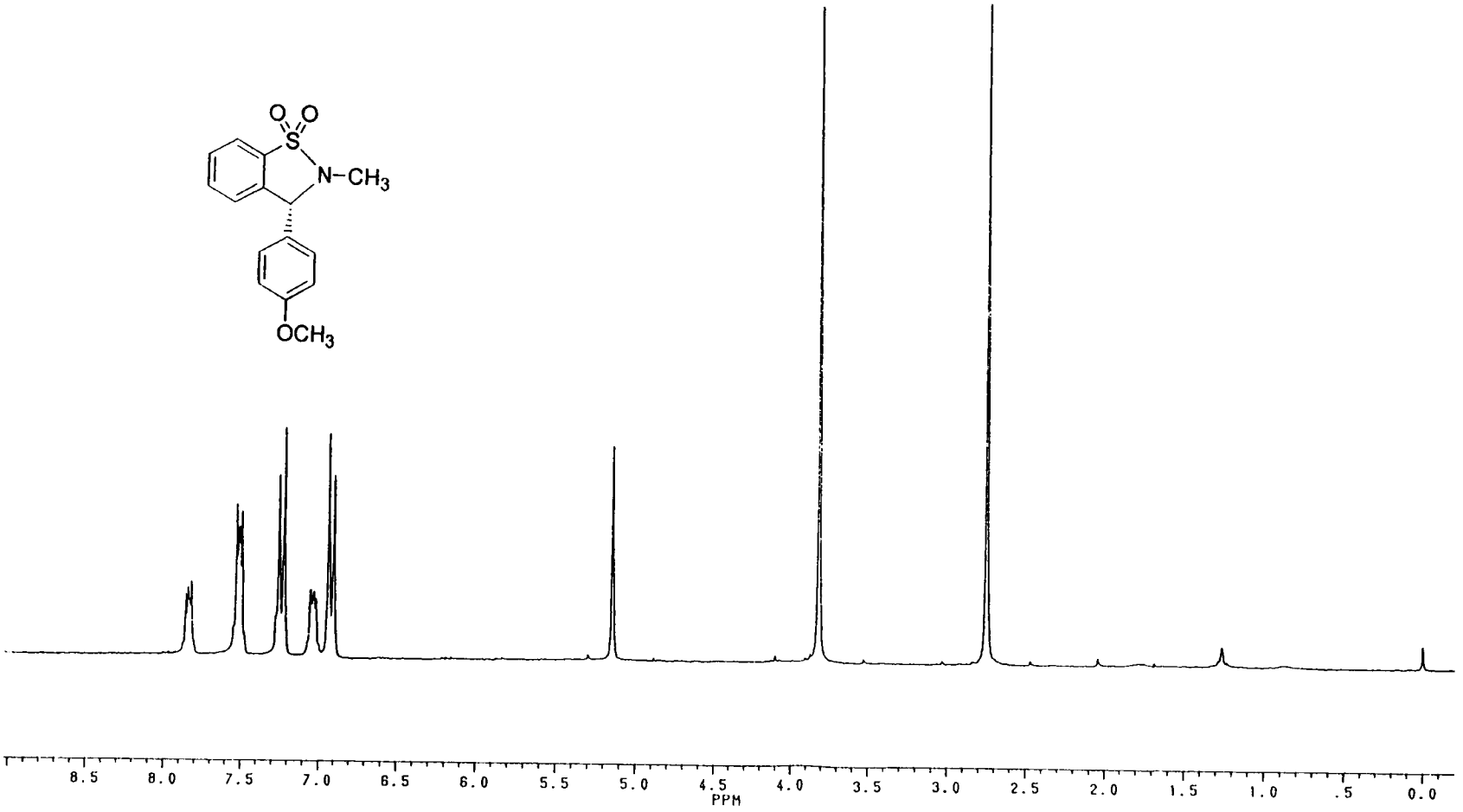
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (±)-3-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**35**).



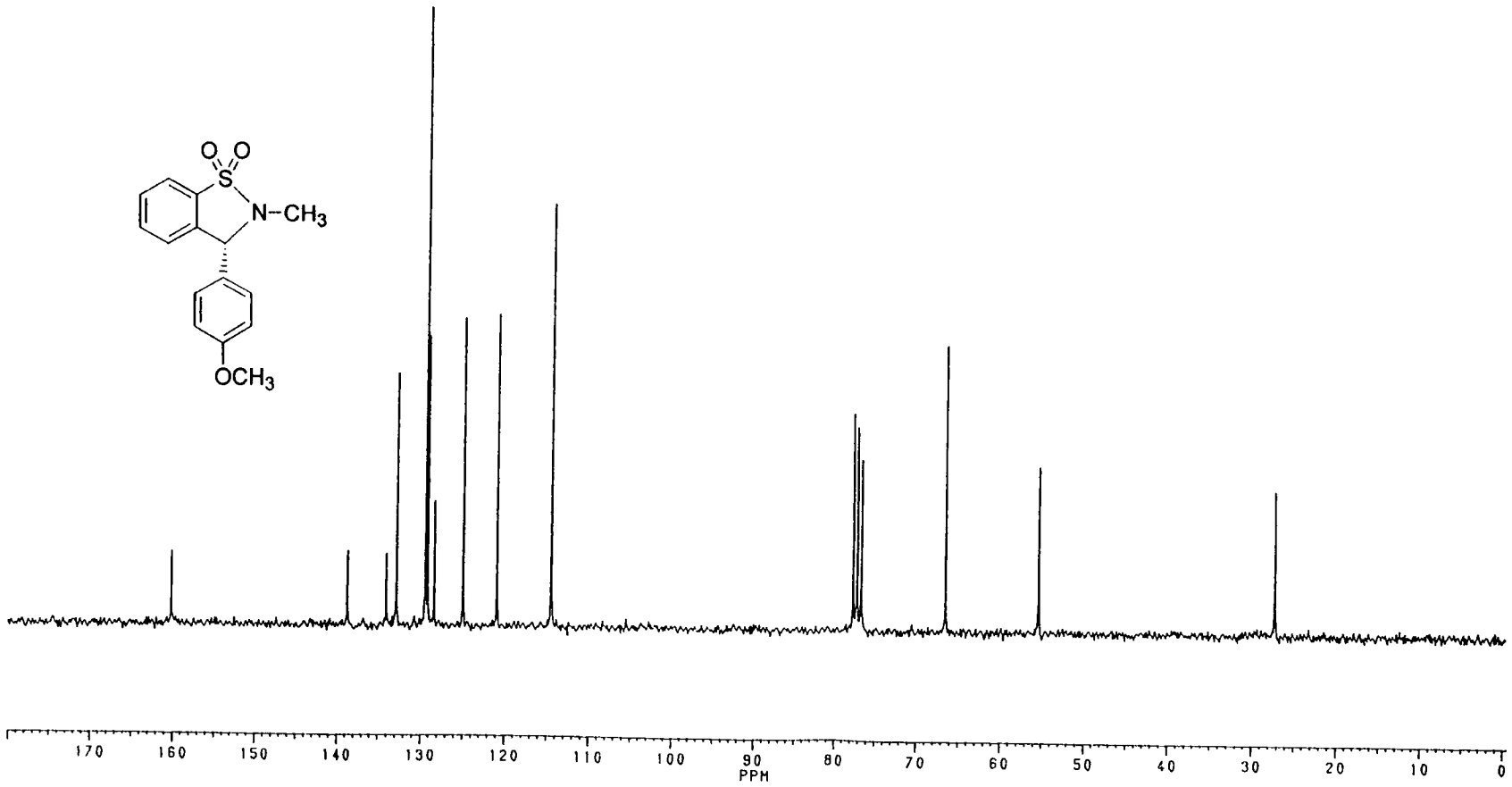
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (3*S*)-(+)-3-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**36**)



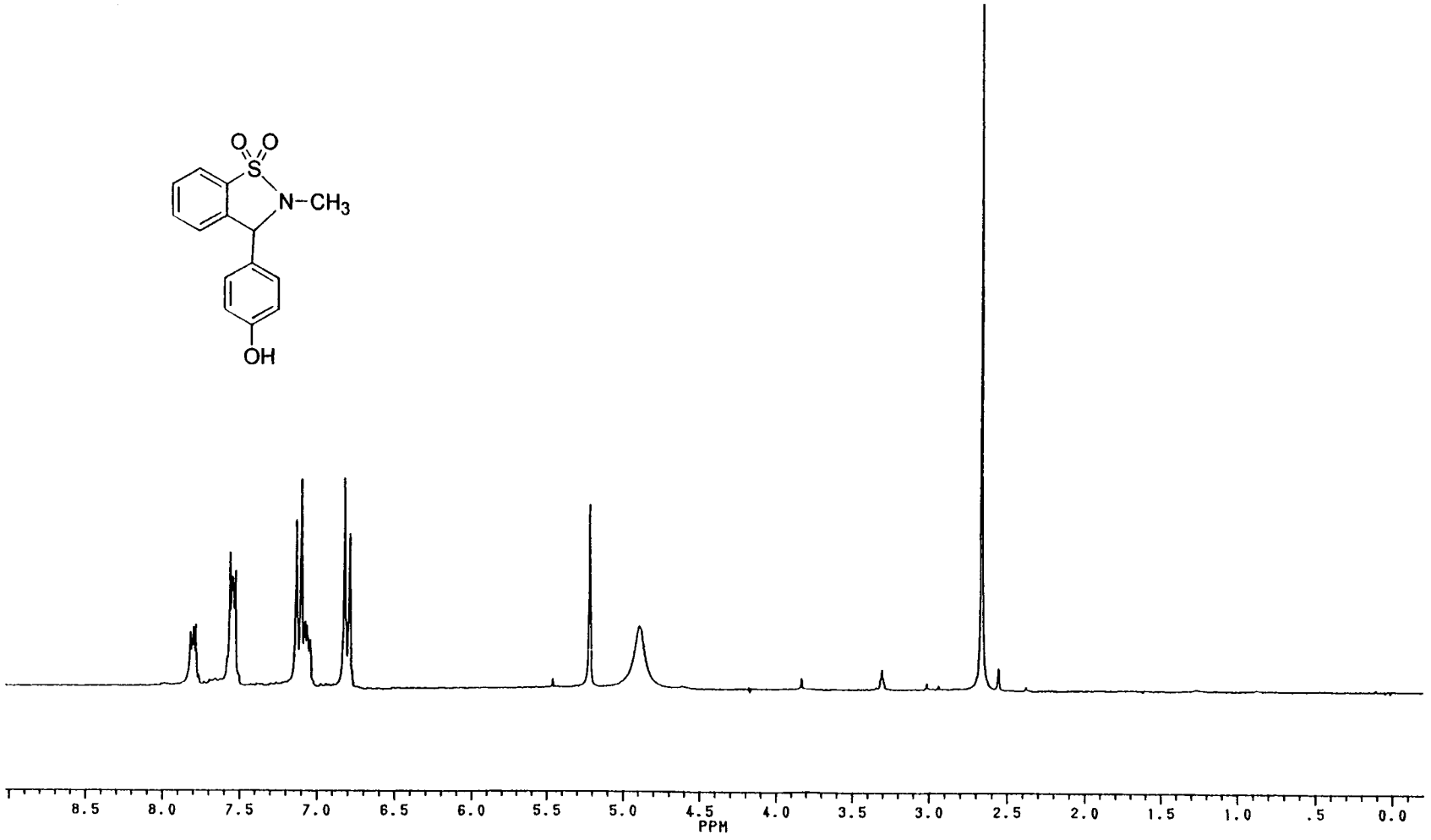
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (3*S*)-(+)-3-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**36**)



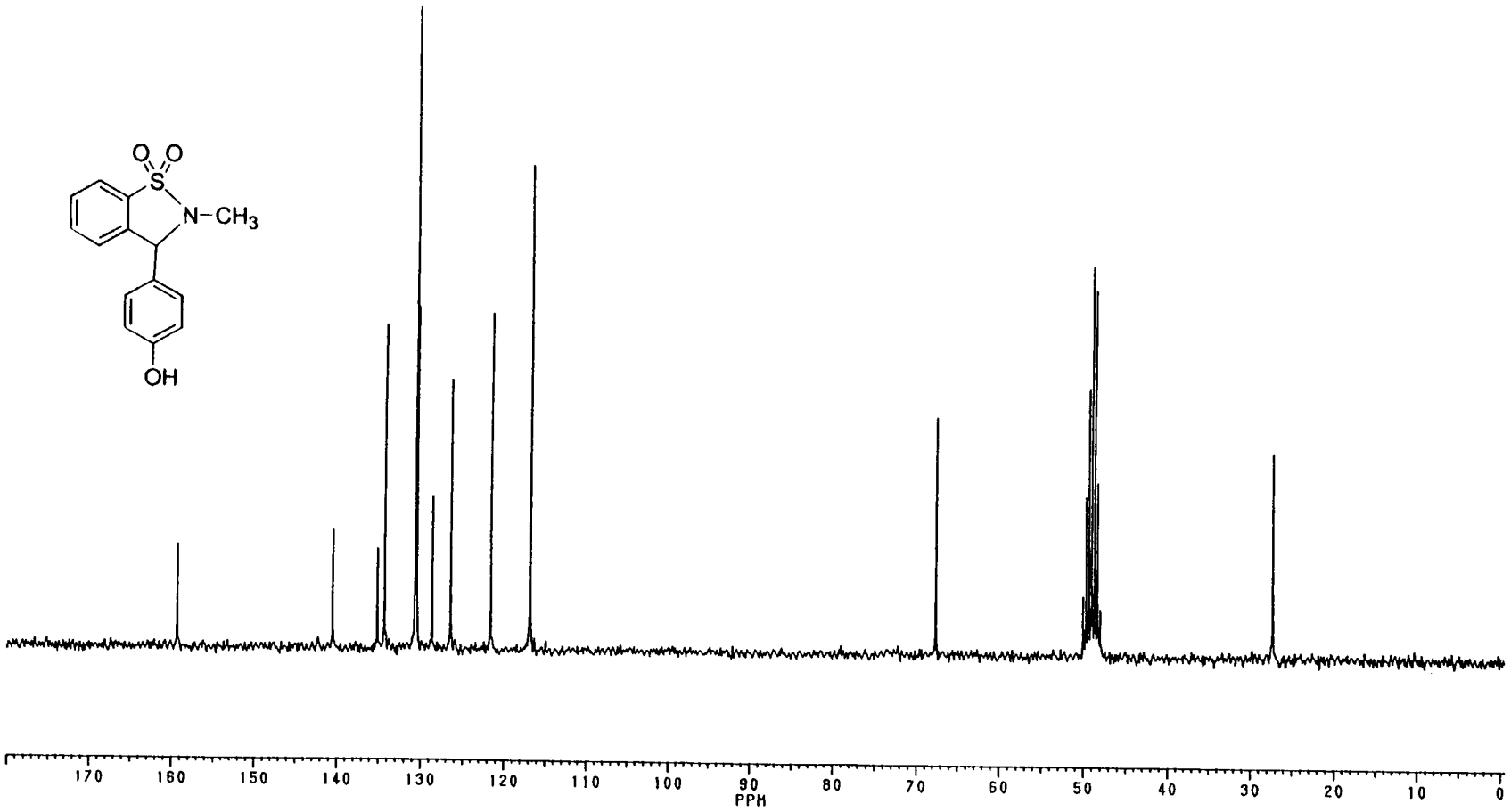
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (3*R*)-(−)-3-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**37**).



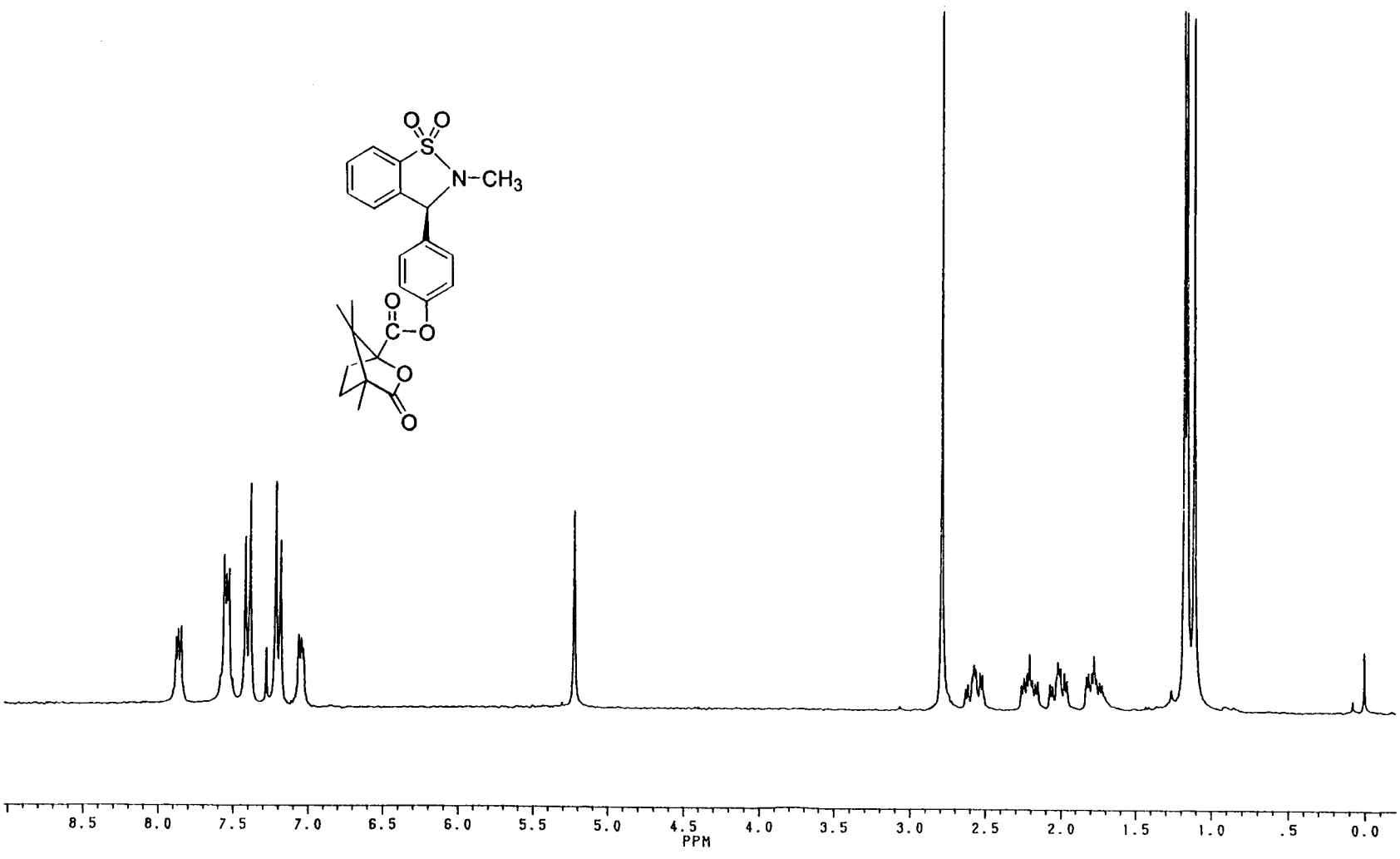
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (3*R*)-(−)-3-(4-methoxyphenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**37**).



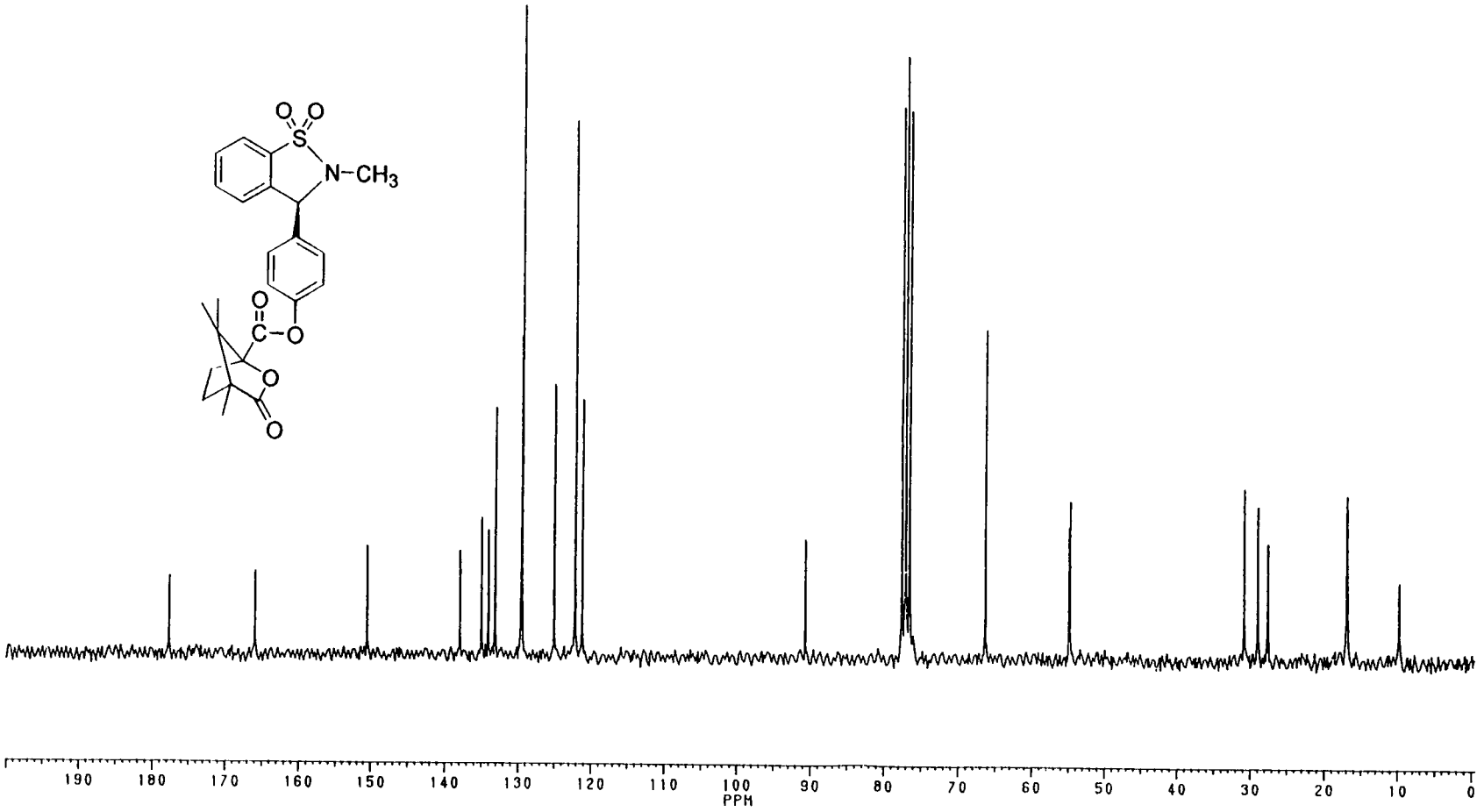
^{1}H NMR spectrum (250 MHz, CD_3OD) of (±)-4-(2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenol (**38**).



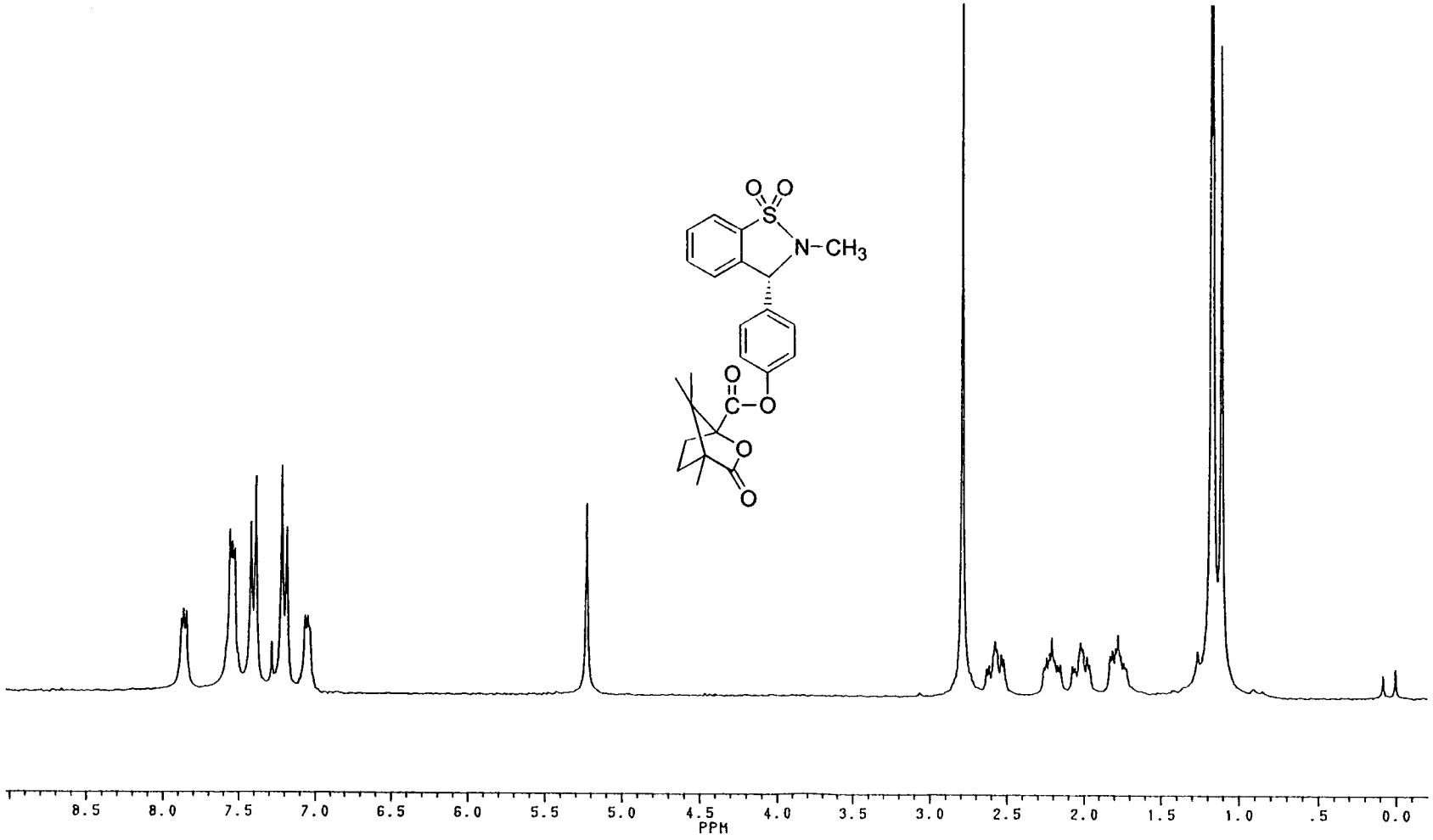
^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (±)-4-(2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl)phenol (**38**).



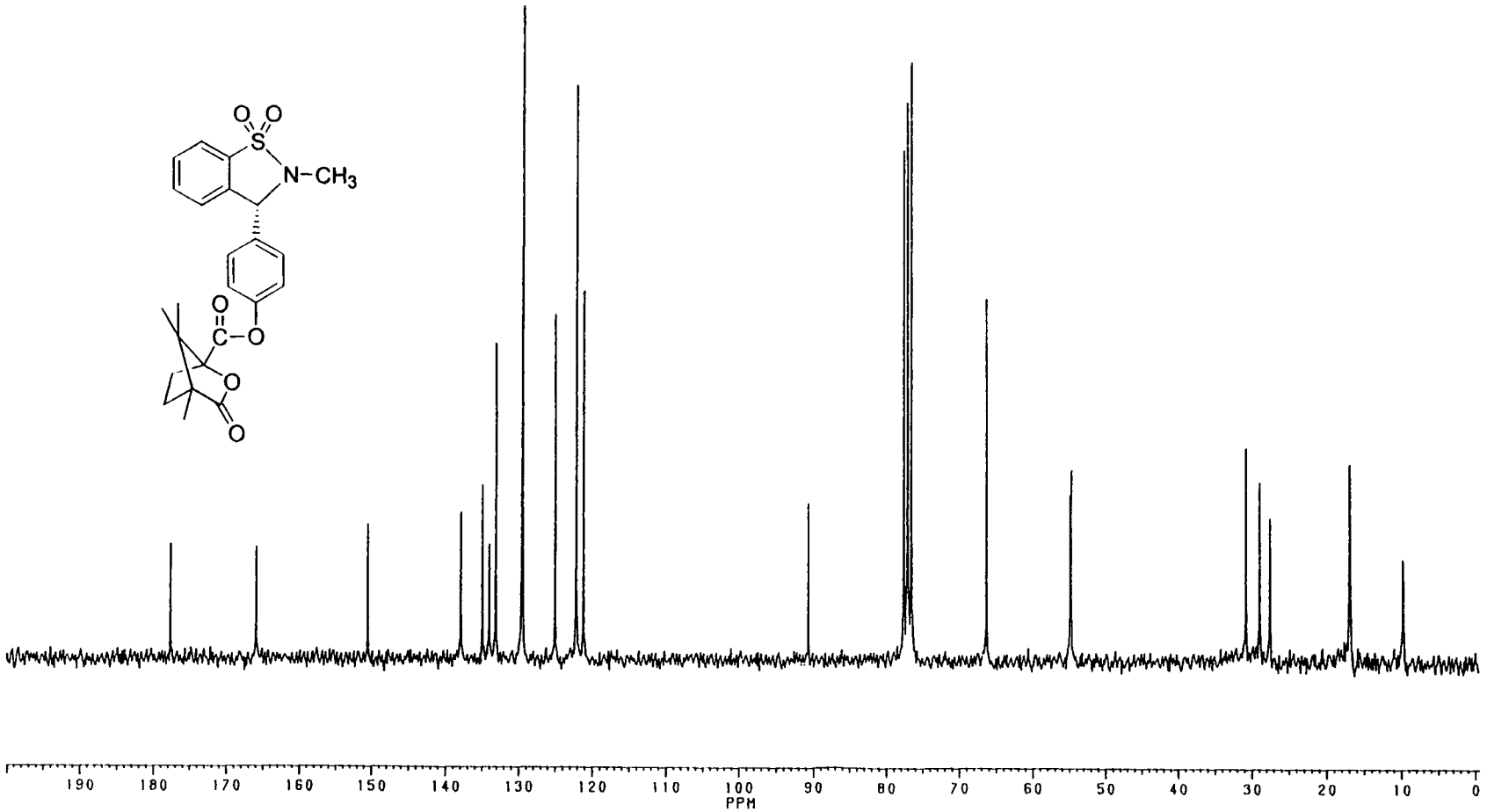
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (1*S*,4*R*)-(+)-4,7,7-trimethyl-2-oxa-3-oxobicyclo[2.2.1]heptane-1-carboxylic acid 4-[(3*S*)-2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenyl ester (**39**).



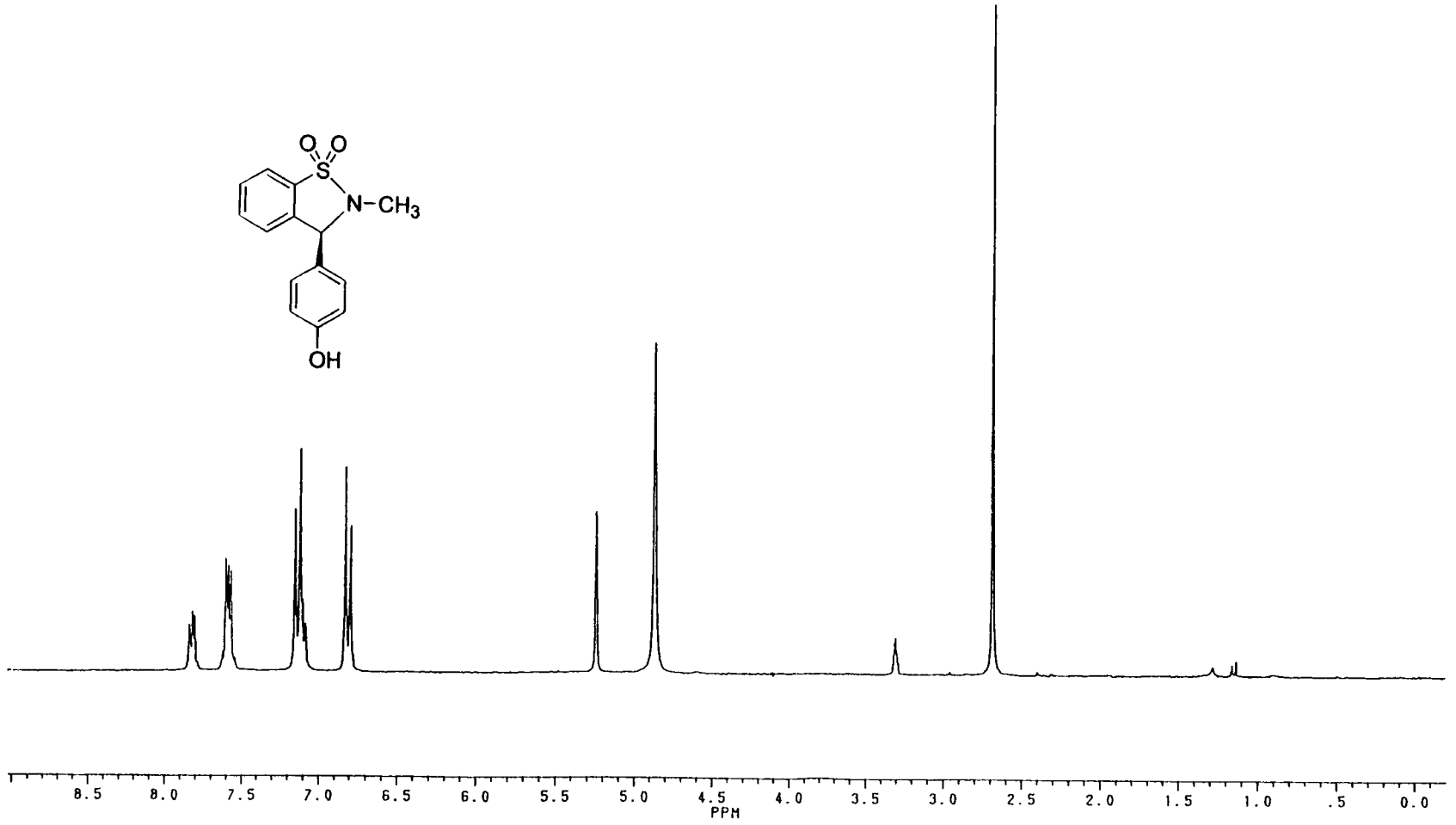
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (1*S*,4*R*)-(+)-4,7,7-trimethyl-2-oxa-3-oxobicyclo[2.2.1]heptane-1-carboxylic acid 4-[(3*S*)-2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenyl ester (**39**).



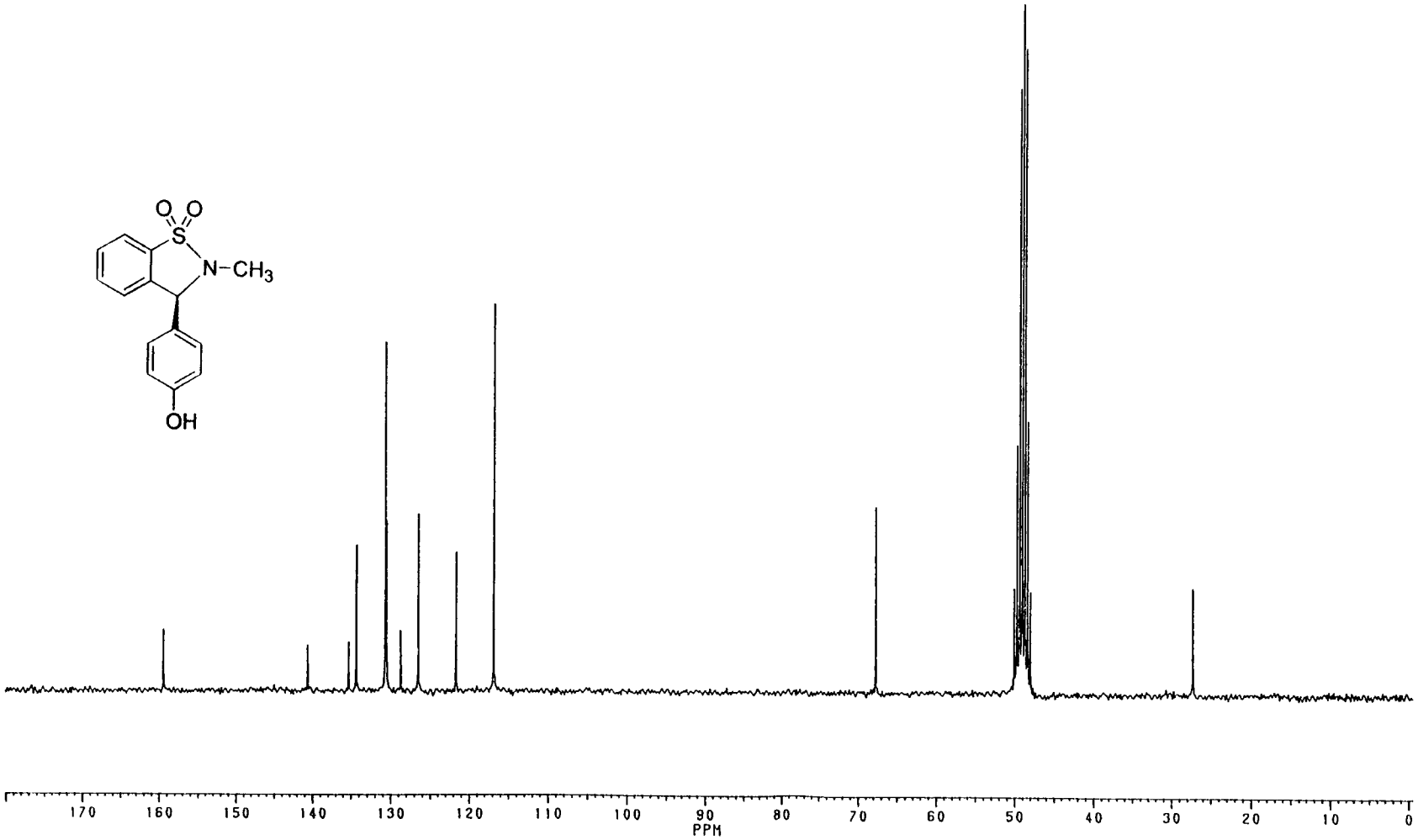
^{1}H NMR spectrum (250 MHz, $CDCl_3$) of (±)-(1*S*,4*R*)-(–)-4,7,7-trimethyl-2-oxa-3-oxobicyclo[2.2.1]heptane-1-carboxylic acid 4-[(3*R*)-1,1-dioxo-2-methyl-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenyl ester (**40**).



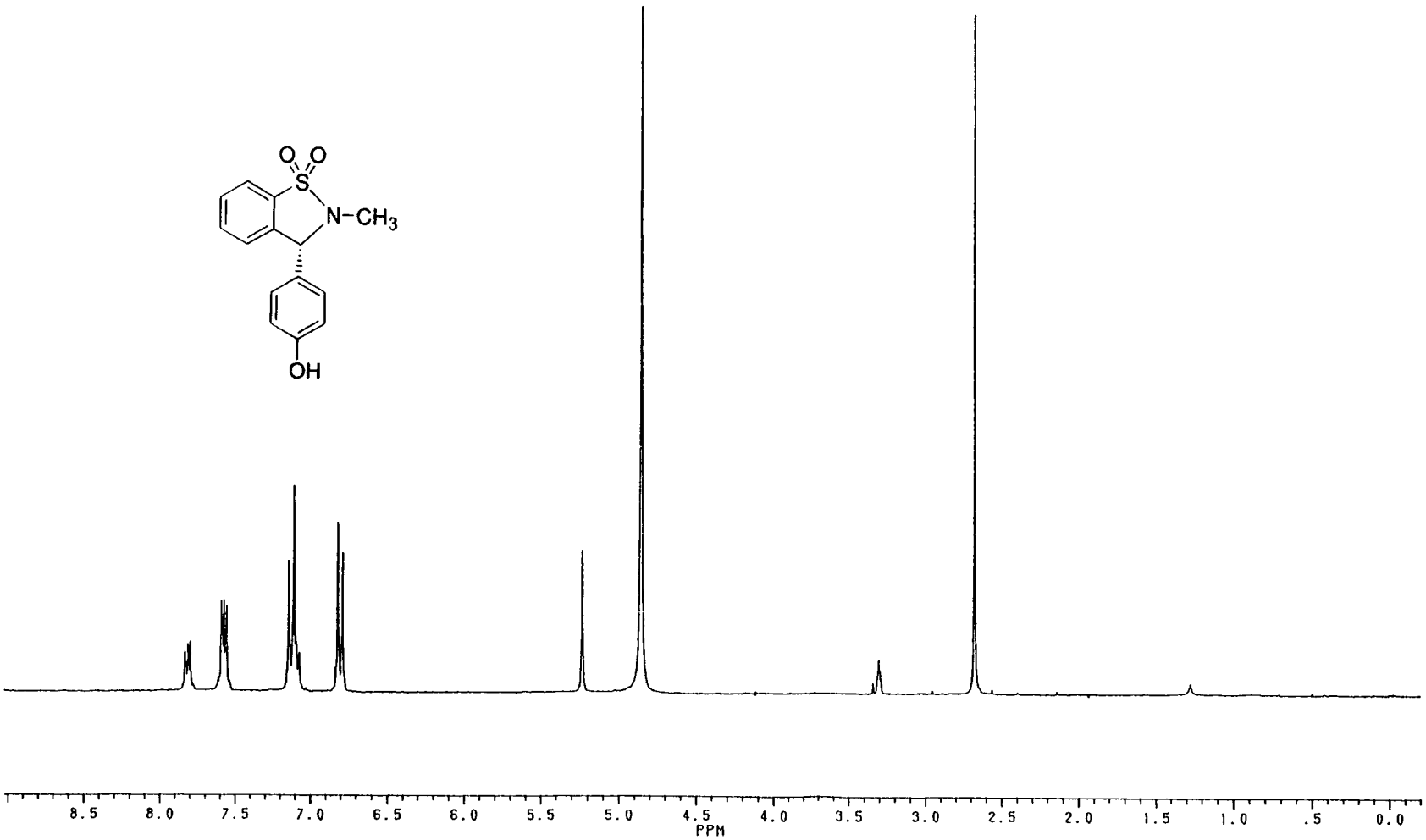
^{13}C NMR spectrum (62.9 MHz, $CDCl_3$) of (1*S*,4*R*)-(–)-4,7,7-trimethyl-2-oxa-3-oxobicyclo[2.2.1]heptane-1-carboxylic acid 4-[(3*R*)-1,1-dioxo-2-methyl-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenyl ester (**40**).



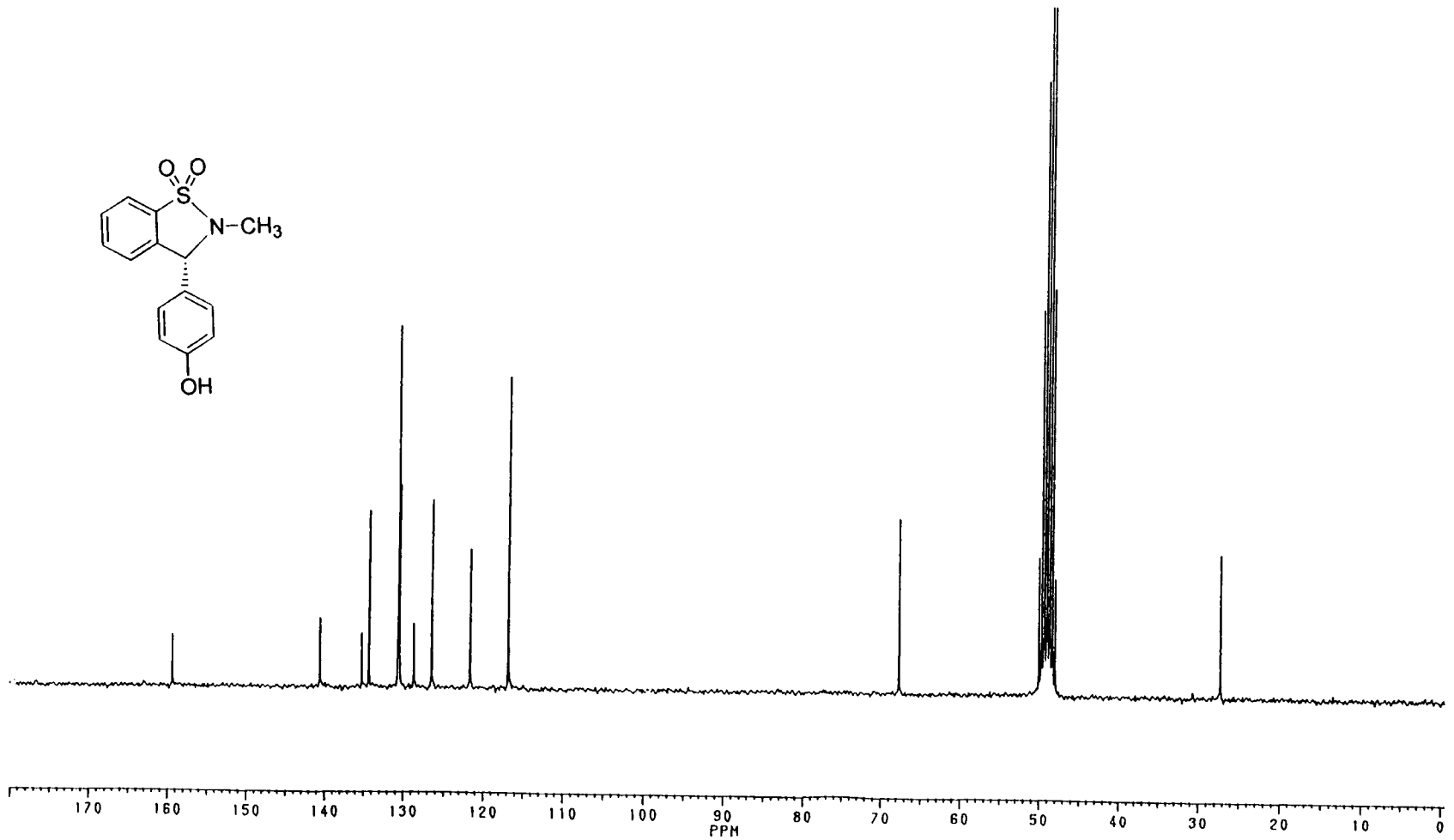
^{1}H NMR spectrum (250 MHz, CD_3OD) of (+)-4-[(3*S*)-2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenol (**41**).



^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (+)-4-[(3*S*)-2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenol (**41**).



^{1}H NMR spectrum (250 MHz, CD_3OD) of (−)-4-[(3*R*)-2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenol (**42**).



^{13}C NMR spectrum (62.9 MHz, CD_3OD) of (−)-4-[(3*R*)-2-methyl-1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazol-3-yl]phenol (**42**).

VITA

Anand Mayasundari was born in Madras, India on October 3, 1964. He had his primary school education at St. Michael's Academy, Madras and graduated from New Science College, Hyderabad in 1982. He entered Vivekananda College, Madras and obtained his Bachelor's Degree in Chemistry from the University of Madras, India in 1985. From 1985 to 1988 he studied at the University Department of Chemical Technology (U.D.C.T.), University of Bombay, India and obtained his second Bachelor's Degree, majoring in Technology of Intermediates and Dyes. After working for a short time as a technical sales officer, he returned to the University of Bombay and obtained his Master's Degree in the same area under the guidance of Prof. S. Seshadri. In August of 1992, he came to the United States for graduate study in Chemistry at the University of Tennessee, Knoxville, where he joined Prof. David C. Baker's laboratory and conducted research in synthetic and structural aspects of some anti-HIV agents. After completing his Ph.D. in 1998, he accepted a position as Post-Doctoral Research Associate with Dr. David G. Young at the University of Tennessee, Knoxville.