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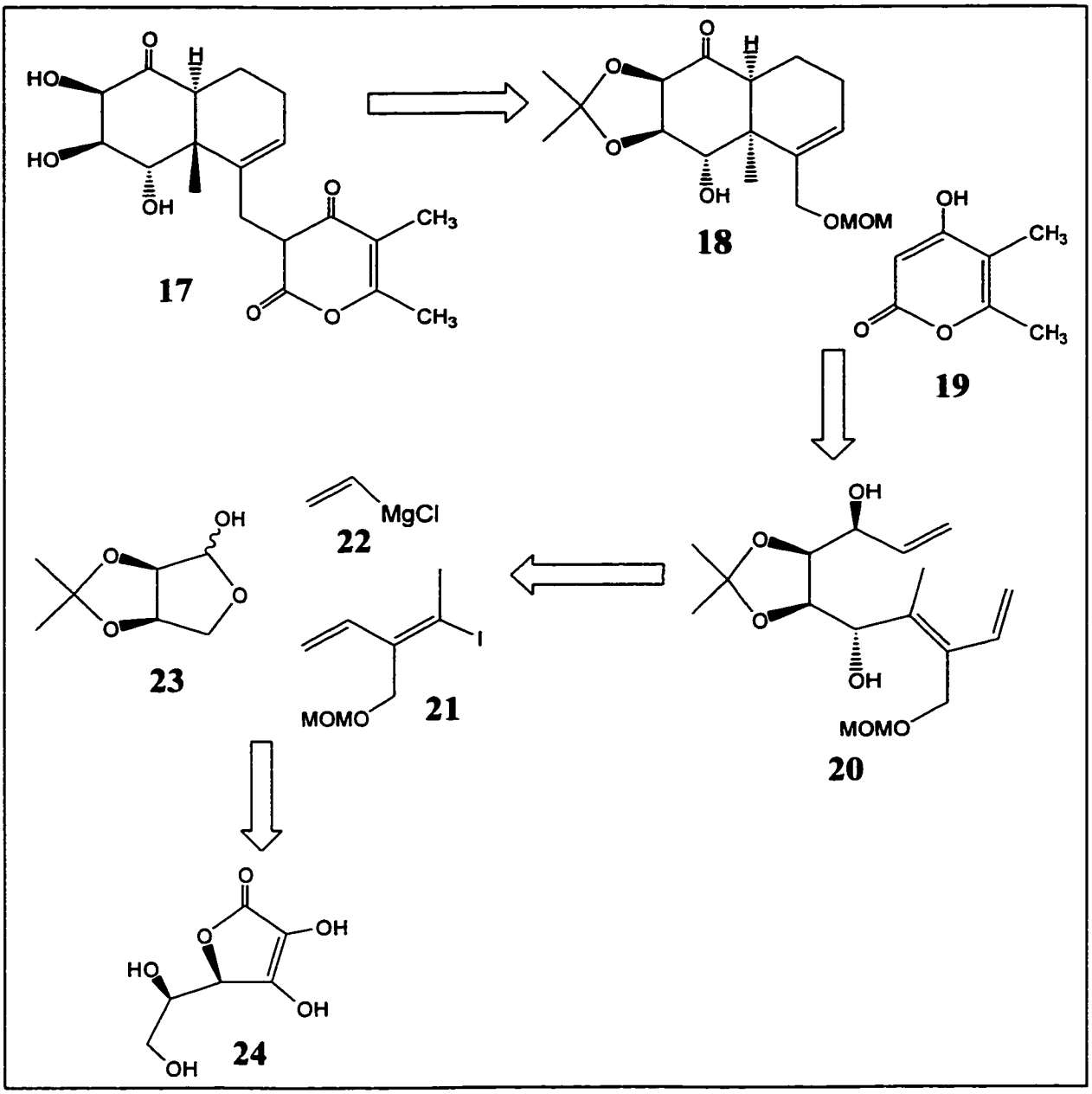
Abstract

A novel synthetic strategy for the potential analogue **17** of the immunosuppressive agents subglutinols A (**3**) and B (**4**) was investigated. Neither of these molecules, nor any analogues, have been synthesized previously. The route selected employed a *cis*-isopropylidene control group in the tether to facilitate the key synthetic step, an intramolecular Diels-Alder reaction. This approach afforded the tricyclic core of **18** in an efficient and direct manner. The Diels-Alder precursor **20** was constructed from D-isoascorbic acid (**24**), vinylmagnesium chloride (**22**), and 4-iodo-3-methoxymethoxymethyl-penta-1,3-diene (**21**). The synthesis of the lactone **19** and the attempts to remove the MOM group from **18** were also investigated. Unfortunately, however, the final target analogue **17** was not realized due to unsuccessful attempts at removing the MOM group from **18**. Thus, an efficient route to the decalin core was established, though the coupling of the lactone **19** awaits further study.


HO
HO
OH
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H
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CH3
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O
CH3
17
18
OMOM
OH
19
OH
CH3
O
O
CH3
MgCl
22
OH
23
I
MOMO
21
OH
OH
MOMO
20
O
OH
HO
OH
OH
24

Dedication

I dedicate this work to my loving husband, Hisham, my wonderful parents, Hosni and Fereal, and my lovely sisters, Gehan, Hadeel, Reema and Leena.

Acknowledgements

I sincerely thank Dr. Alex G. Fallis for his support and guidance in the last two years. It has been a wonderful experience being part of his group.

Special thanks go to Dr. Alex Melekhov and Dr. Pat Forgione for their technical assistance and advise. A special thank you must also be said to Arvin Moser for his time and helpful comments in proofreading this thesis on a short notice. I would also like to thank Raj Capoor for all his help and NMR samples he ran for me on a last minute notice.

To Paulina (Nidia), I specially thank you for being such a dear friend, I will always remember our good times and laughs in the lab. To Beth, Nadia, and Ditte, thank you for being such great friends. Overall, I thank all of my colleagues in the Fallis lab for all their help and support.

To Hisham, I would never have gotten this far without you, I owe you my success. To my parents and sisters, thank you for everything, you guys are wonderful.

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List of Abbreviations

Ac	acetyl
br	broad
^{i}Bu	isobutyl
n-BuLi	*n*-butyllithium
sec-BuLi	*sec*-butyllithium
tert-BuLi	*tert*-butyllithium
calc'd	calculated
d	doublet
DIBAL-H	diisobutylaluminum hydride
equiv.	equivalents
Et	ethyl
Ether	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
Et_3Si	triethyl silyl
h	hour
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
Hz	hertz
IMDA	intramolecular Diels-Alder
IR	infrared spectroscopy
J	coupling constant
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	moles per litre
Me	methyl
MHz	megahertz
min	minute
mmol	millimole
MOM	methoxymethyl
mp	melting point
NMR	nuclear magnetic resonance
[O]	oxidation
Ph	phenyl
Piv	pivaloyl

PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
^{i}Pr	isopropyl
$^{i}Pr_2EtN$	N,N-diisopropylethylamine
PTSA	*p*-toluenesulfonic acid
R	alkyl
R_f	retention factor
s	singlet
SM	starting material
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBSCl	*t*-butyldimethylsilyl chloride
TFB	trifluoroboron etherate
TFS	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSI	trimethylsilyl iodide
Ts	tosyl

1 Introduction

Mother nature has been the focus of extensive research for a long period of time. The early discoveries of naturally-occurring drugs have set a worldwide search for biologically active agents for all types of human diseases, particularly immuno-related diseases and dysfunctions. The vertebrate human immune system normally rejects non-self components such as parasites, bacteria, viruses and their possible toxic products. In addition, it participates in the elimination of tumorigenic cells that are continuously being produced. A consequence of the immune system's ability to recognize and reject non-self is the rejection of grafted tissues, a phenomenon that does not normally occur in nature. As soon as it was clear that allograft rejection was mediated by an immune reaction against foreign non-self transplantation antigens, it was proposed that suppression of the host's immune response would permit acceptance of the allograft, with its functional integrity preserved. Hence, an extensive international search for immunosuppressive agents was launched which resulted in the discovery of many potentially active immunosuppressive drugs.[1,2,3,4]

1.1 Natural Products with Immunosuppressive Activity

The first naturally occurring drug discovered and applied in the prevention of graft rejection in transplant patients was cyclosporin A (CsA) **1** (Figure 1). CsA was first isolated in 1970 and was described as an antifungal metabolite of the fungi *Cylindrocarpon lucidum* Booth and *Tolypocladium inflatum* Gams. The immunosuppressive properties of CsA were first

discovered by Borel and co-workers in 1972.[5] Clinical practice has shown this drug to be exceptionally effective in the treatment of graft rejection. The introduction of CsA in immunosuppressive therapy has markedly improved survival in liver and heart transplant recipients. However, side effects to the administration of this drug are many, including nephrotoxicity, neurotoxicity and diabetogenicity.[1,2,3,4]

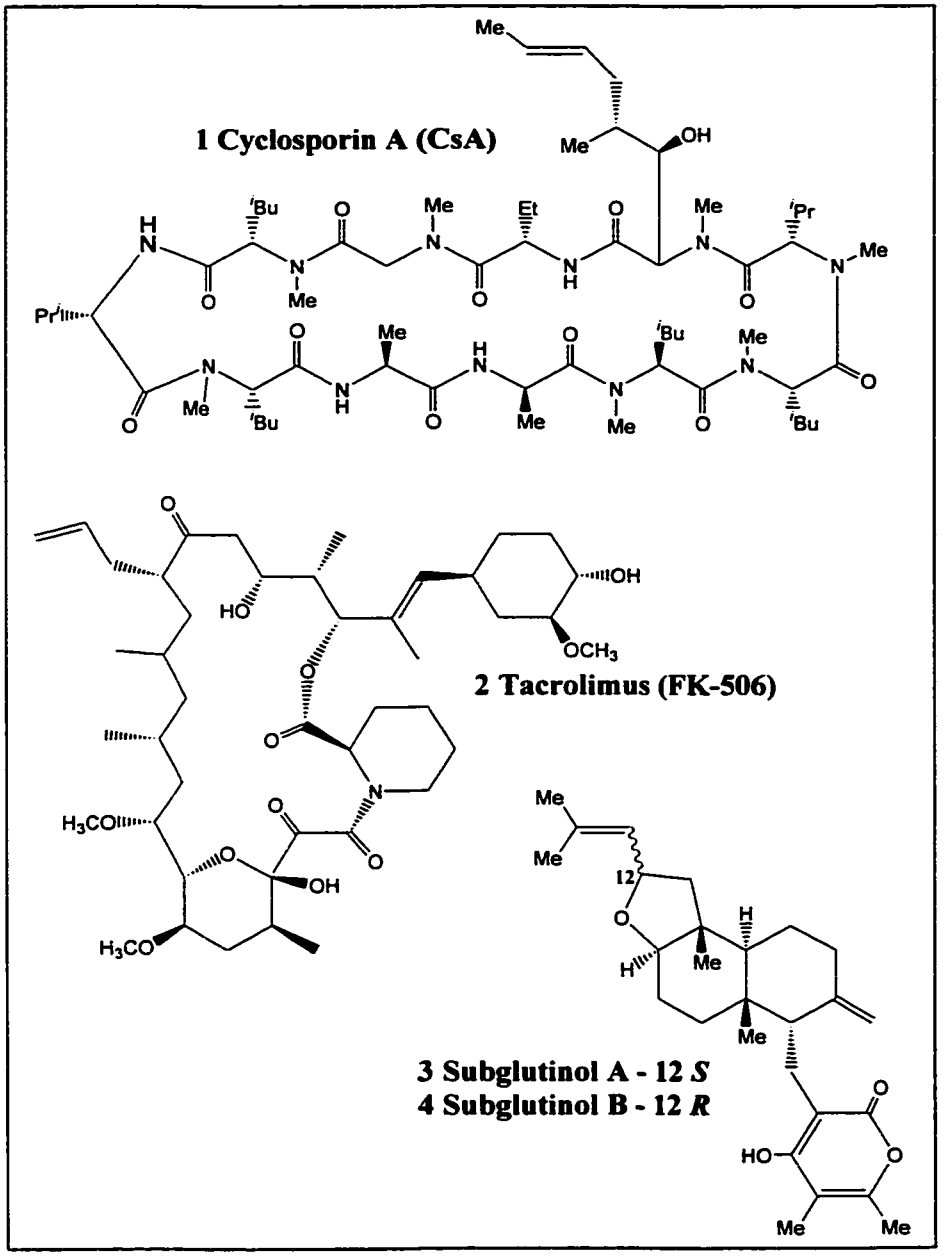


Figure 1: Examples of natural immunosuppressant drugs

Tacrolimus (**2**, formerly known as FK-506, Figure 1) is an immunosuppressive agent whose development has progressed rapidly since its discovery in 1984. It was first isolated from the fungus *Streptomyces tsukubaensis*, and was discovered to have immunosuppressive properties in 1987.[6] The first clinical use of tacrolimus was to rescue patients with failing liver allografts. The success with rescue therapy for liver transplants led to the first trials of tacrolimus as the primary immunosuppressive agent after liver transplantation. In all clinical studies, tacrolimus was found to be a powerful immunosuppressive agent, with at least 100-fold greater potency than CsA. The principal side effects of this drug are similar to those seen with CsA.[1,2,3,4]

The resulting undesirable side effects of CsA, tacrolimus and other existing drugs in the market had researchers continually searching for better immunosuppressive agents. Two recently discovered agents are the subglutinols A (**3**) and B (**4**) (Figure 1). They were discovered by Clardy and co-workers as part of a screening project of the endophytic fungi of the perennial twining vine *Tripterygium wilfordii*. These diterpene pyrones were found to have immunosuppressive activity with no cytotoxic effects. Clardy *et al* illustrated that both subglutinols A and B have similar activity in the mixed lymphocyte reaction (MLR) assay and thymocyte proliferation (TP) assay. These findings suggest that the side chain at C12 (Figure 1) plays no role in biological activity. They also found that CsA has similar activity to **3** and **4** in the MLR assay but was 10^4 more active in the TP assay. However, **3** and **4** show no cytotoxic effects promoting additional studies towards their detailed biological activity.[7]

The current study investigates a novel first synthetic attempt for the synthesis of an analogue of **3** and **4**. The key step in this planned synthesis is an intramolecular tether-controlled Diels-Alder reaction (IMDA). The role of the

tether is to hold both the diene and dienophile parts together in close proximity. The advantages of IMDA are many. One is the formation of the two-ring system in a single step. Also, IMDA reactions have shown to enhance regio- and stereoselectivity.[8] The vital step in attaining the target analogue is the Diels-Alder cycloaddition reaction.

1.2 Diels-Alder Chemistry

1.2.1 General Introduction

The Diels-Alder cycloaddition reaction is one of the most powerful tools in modern synthetic chemistry. It was first discovered by Diels and Alder in 1928. It is a thermally allowed [4+2] cycloaddition allowing the construction of highly stereospecific six-membered rings.[9] Therefore, two new σ bonds and a π bond are formed resulting in the formation of up to four new asymmetric centres. Typically, good yields, mild reaction conditions, high regio- and stereoselectivity are observed. This makes the Diels-Alder reaction one of the most widely used methods for ring construction.[8e,10]

The Diels-Alder reaction requires the diene and the dienophile to approach each other in parallel planes so that the terminal carbons of each component are directly above each other. This concerted reaction requires that the diene adopt the cisoid conformation. As a result, the orbital lobes of the two components (being of the same symmetry) interact more efficiently for the formation of the new σ bonds (Figure 2).[10,11,12]

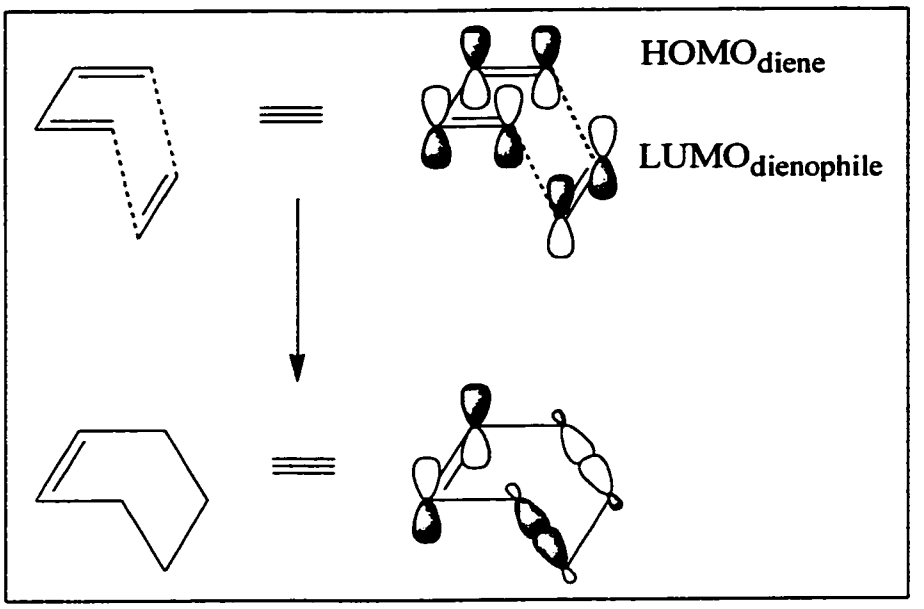


Figure 2: Diels-Alder reaction transition state

1.2.2 Electronic Requirements

The interactions in the Diels-Alder reaction are between the highest occupied molecular orbital (HOMO) of one component (usually the diene), and the lowest unoccupied molecular orbital (LUMO) of the second component (usually the dienophile), as shown in Figure 3. Electron-withdrawing groups lower the energy of the HOMO and the LUMO while electron-donating substituents increase their energies. Therefore, with complementary electronic substituents on the diene and the dienophile, the efficiency of the Diels-Alder reaction is maximized.[12]

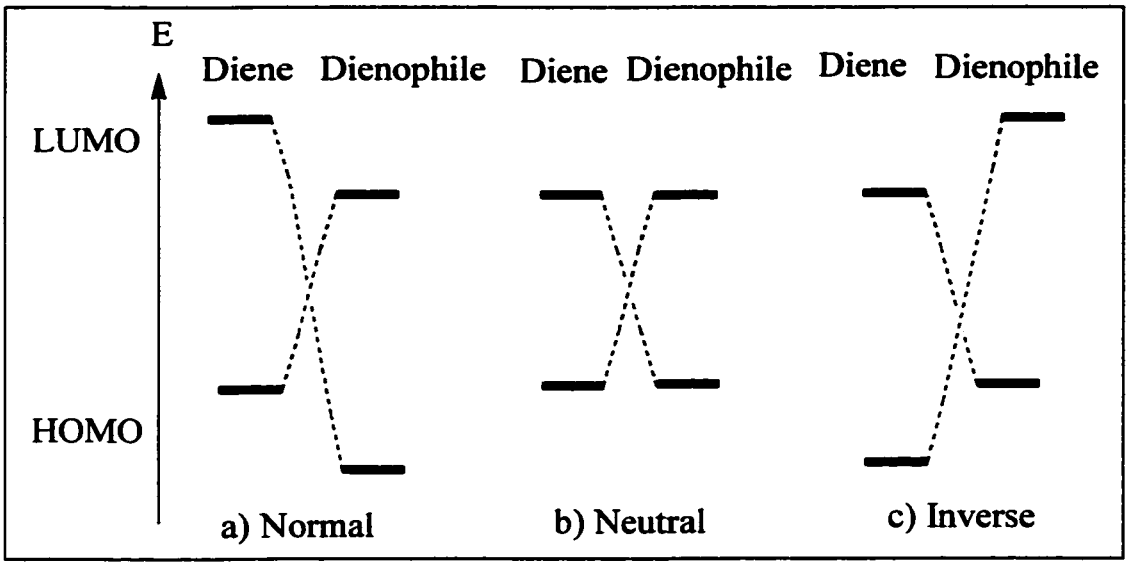
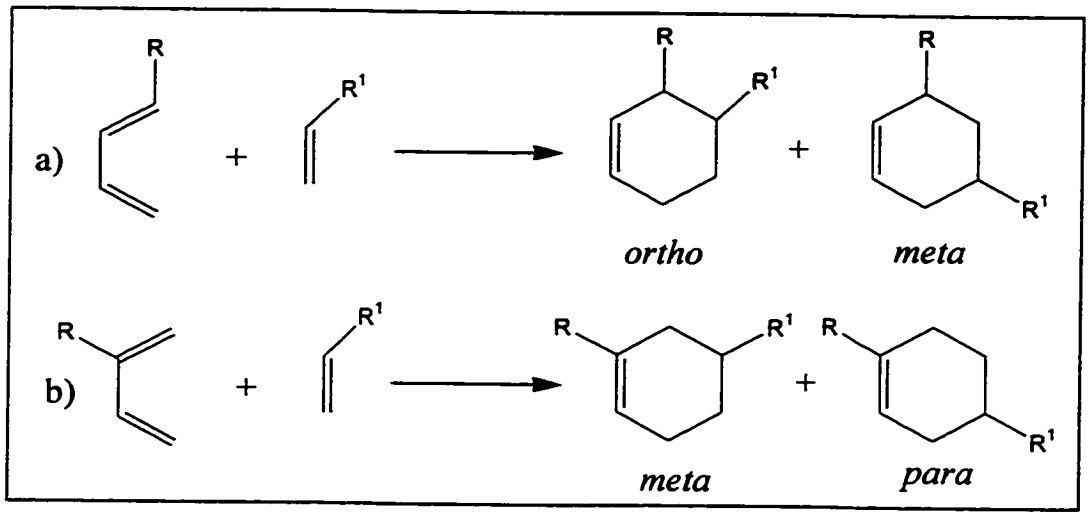


Figure 3: HOMO-LUMO orbital arrangements for the Diels-Alder reaction[12]

The 'neutral electron demand' reaction occurs when both the HOMO and the LUMO orbitals are of equal energy levels. However, in the 'normal electron demand' reaction, the electron-donating substituents on the diene raise its HOMO energy, while electron-withdrawing substituents on the dienophile lower its LUMO energy. The reverse case constitutes the 'inverse electron demand' reaction, as illustrated in Figure 3c. The net result is an increase in reactivity between the diene and the dienophile due to the decrease in the energy gap between the HOMO and the LUMO partners.[12]

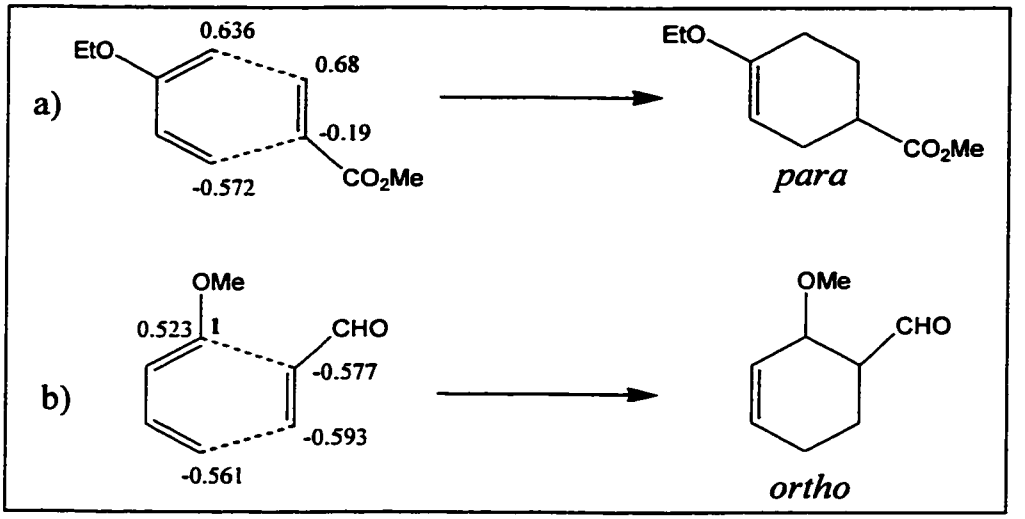
1.2.3 Regioselectivity of the Diels-Alder reaction

In the Diels-Alder reaction, the cycloaddition results in two regioisomeric adducts arising from two different orientations of the reactants when both the diene and the dienophile are unsymmetrical (Scheme 1).



Scheme 1: Possible regioisomers from a Diels-Alder reaction involving unsymmetrical reactants.

The regioselectivity depends on the electronic effects of the substituents (being electron-donating or electron-withdrawing) on both the diene and the dienophile. Examination of the orbital coefficients of the HOMO and the LUMO, the *ortho*, *meta* or *para* nature of the cycloadducts may be predicted. The higher terminal coefficients of each component will preferentially bond in the transition state (Scheme 2).[10,12] A review of the calculation of molecular orbital coefficients has been reported.[13]

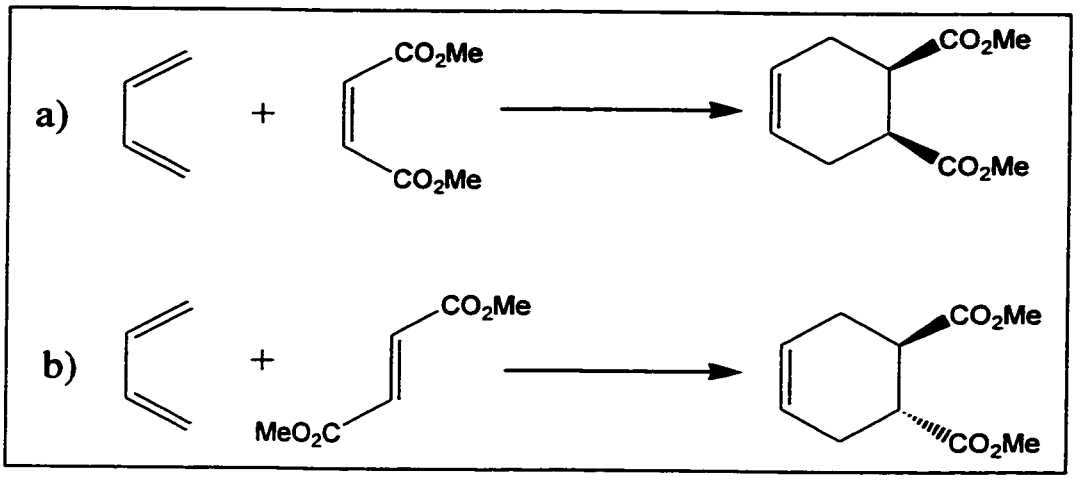


Scheme 2: Molecular orbital coefficients and regioselectivity in the Diels-Alder reaction[10,12]

A general rule regarding regioselectivity in the Diels-Alder reaction is the *ortho* effect or *ortho* rule.[10] Thus, when a dienophile containing a heteroatom reacts with a diene substituted at the C1 position, as depicted in Scheme 2b, the *ortho* product is usually preferred and is independent of the nature of the substituents on the diene.

1.2.4 Stereoselectivity in the Diels-Alder reaction

In the Diels-Alder reaction, the diene and the dienophile relative configurations are retained in the adduct, known as the *cis*-principle.[10,12] For example, the *cis* and *trans* relationship between the alkene substituents in Scheme 3a and 3b, respectively, are retained in their corresponding cycloadducts.



Scheme 3: Retention of dienophile stereochemistry in the Diels-Alder reaction[12]

For the stereochemistry of the diene to be maintained in the cycloadduct, the relative motions of the substituents during the ring formation must be disrotatory. An example is depicted in Figure 4.

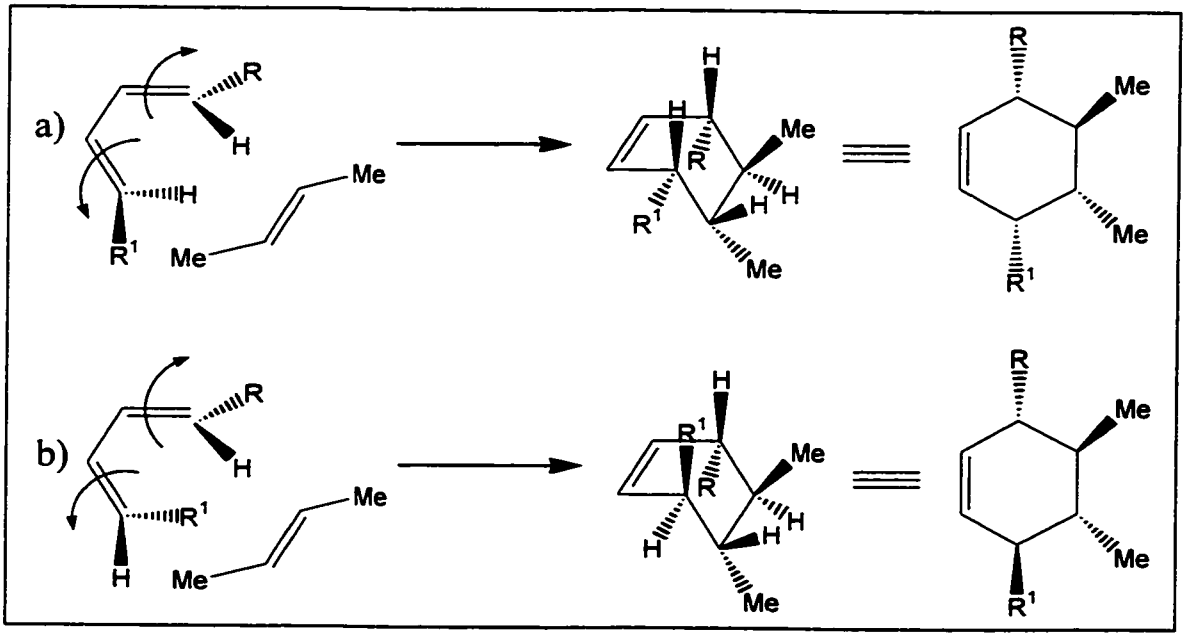


Figure 4: Retention of diene configuration in the Diels-Alder reaction[10]

One must also consider the cases where the dienophile is unsymmetrical when discussing the stereo- and regiochemistry of the Diels-Alder reaction. In this case, two different orientations are possible when the diene and the dienophile align themselves in parallel planes. These two approaches are called *endo* and *exo*. The *exo* approach is when the dienophile substituent is pointing away from the diene. On the contrary, the *endo* approach is when the substituent of the dienophile is pointing towards, and is under, the π orbitals of the diene (Figure 5). In the case where a π bond bearing substituent is on the dienophile, i.e. a carbonyl group, the endo approach is favourable due to the increased stabilization of the transition state resulting from secondary orbital overlap (Figure 5). Therefore, the *endo* product is favoured, and this is termed the *endo* rule.[10,11,12]

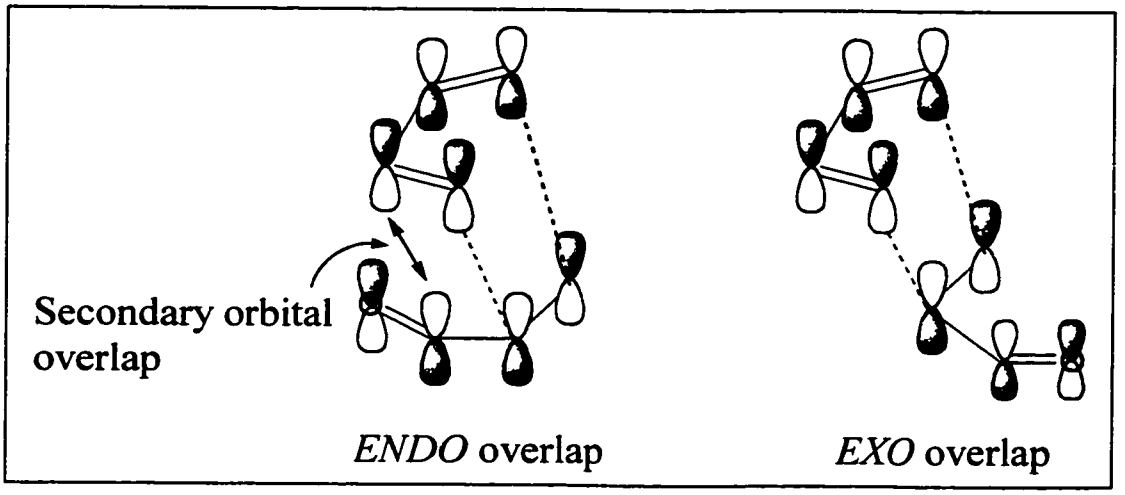


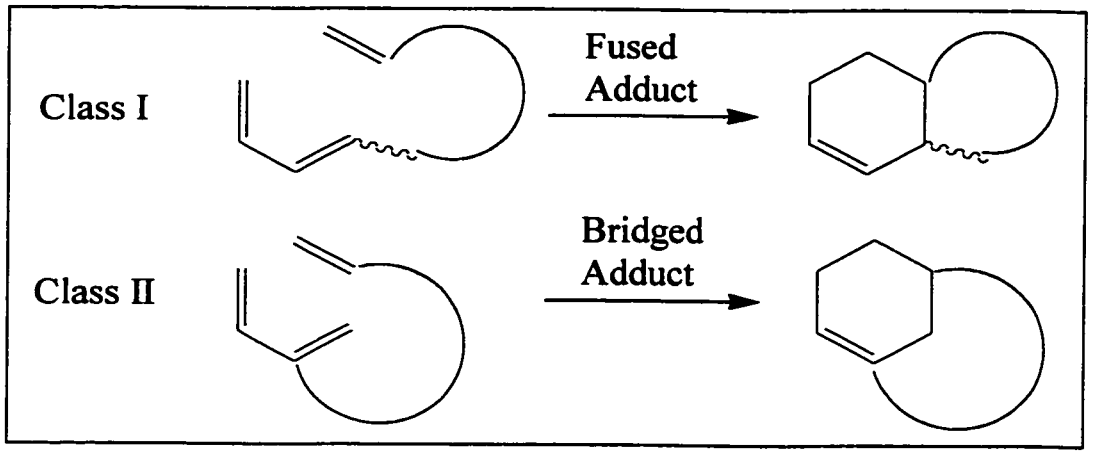
Figure 5: Endo and exo transition states in a Diels-Alder reaction[14]

1.2.5 Intramolecular Diels-Alder Reactions

An intramolecular Diels-Alder reaction (IMDA) occurs when the diene and the dienophile are joined by a connecting chain. This results in the formation of two rings in a single step. There are many advantages to the

IMDA reaction including increased reactivity, regio-, stereo-, and diastereoselectivity, which make it a versatile tool in the synthesis of natural products.[8e] Taking advantage of the improved regio- and stereoselectivity, IMDA reactions have been employed in the synthesis of monocyclic products utilizing removable tethers.[15]

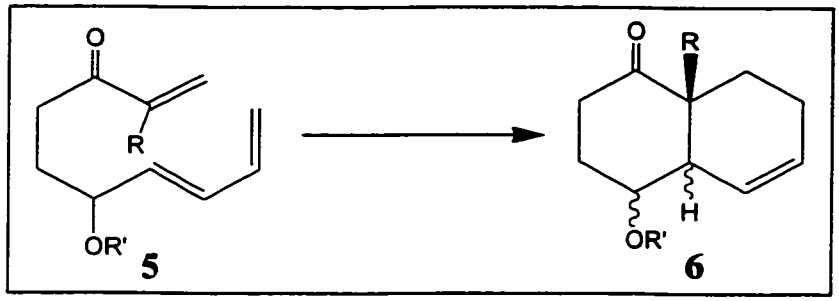
IMDA reactions may be divided into two major classes based on the point of connection between the diene and the dienophile. The first class of reactions consists of substrates where the dienophile is tethered to the diene terminus, giving rise to fused adducts. The second class involves substrates with the dienophile tethered to one of the internal diene positions, resulting in bridged adducts. Scheme 4 shows an example of each class of reactions.[16]



Scheme 4: Types of intramolecular Diels-Alder reaction[16]

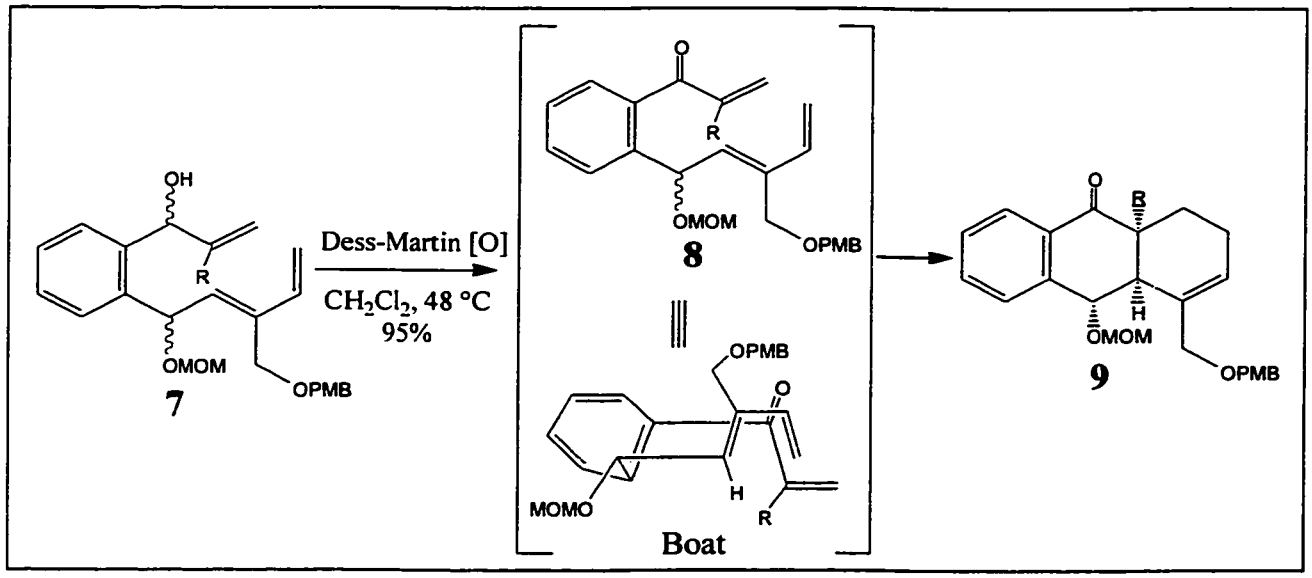
In the current study, a key step in the planned synthesis utilizes an IMDA reaction. However, IMDA reactions don't always provide the best levels of reactivity and stereoselectivity. As shown in Scheme 5, trienes, such as **5**, usually require high reaction temperatures, long reaction times, and yield complex mixtures of cycloadducts, such as **6**.[8e,17] Imposing a conformational constraint on the molecule by incorporating a planar moiety, such as an

aromatic ring[18], or isopropylidene acetals[19] should enhance the cyclization of substituted trienes in IMDA reactions. This limited flexibility of the tether would hold both the diene and the dienophile closer and enhance the interactions in the transition state. These interactions would facilitate the IMDA reaction based on entropic grounds.



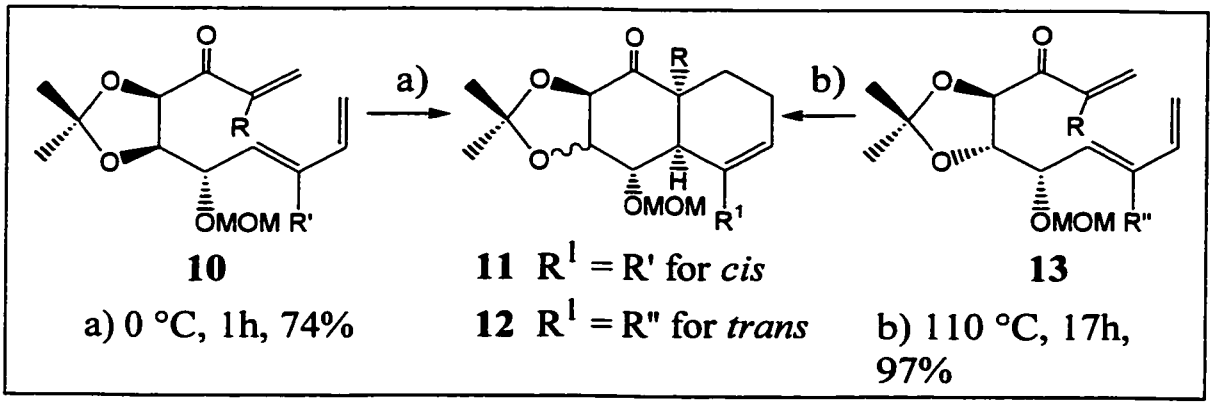
Scheme 5: IMDA reaction with no tether-control group

Fallis and co-workers have implemented the aromatic ring moiety in the efforts to synthesize Taxol® analogues (Scheme 6).[18] The reaction occurs spontaneously upon gentle heating during an oxidation reaction.



Scheme 6: IMDA with planar aromatic tether-control group

In addition, they have also demonstrated that tartrate and carbohydrate derived *trans*-isopropylidene acetals have significantly improved reaction rates and outputs.[20] Later studies have reported *cis*-isopropylidene acetals to be even better in facilitating the overlap required for cyclizations.[21,22] To demonstrate the difference in reactivity between the *cis* and the *trans* isomers, an example of closely related systems is shown in Scheme 7. Here, the *cis* isomer **10** gave the desired product with very mild reaction conditions while the *trans* isomer **13** required harsher conditions.



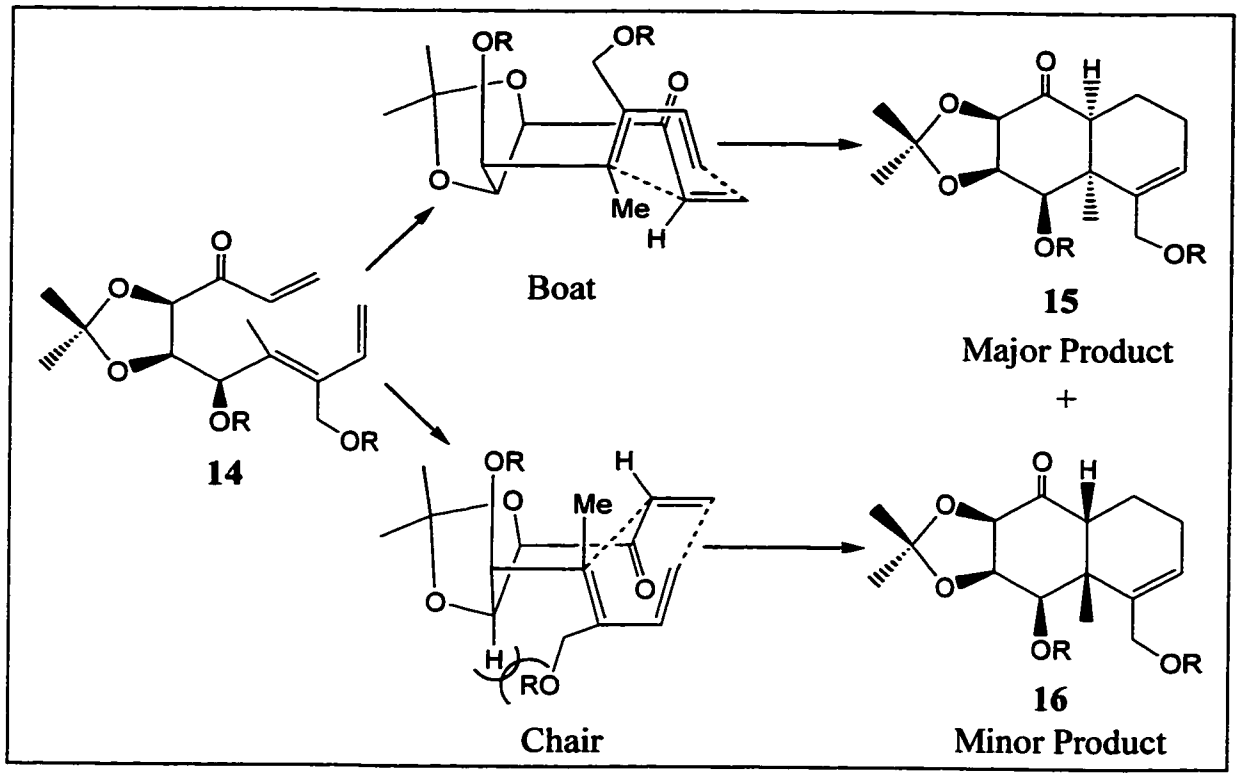
10 **11** R^1 = R' for *cis* **13**

12 R^1 = R" for *trans*

a) 0 °C, 1h, 74% b) 110 °C, 17h, 97%

Scheme 7: comparison between *cis*- and *trans*-acetals in IMDA reactions[21,22]

The presence of an "inside" substituent on the diene poses some difficulty on cycloaddition reactions, which inhibits the formation of the desired s-*cis*-diene conformer.[23] However, the use of a control group (*cis*-isopropylidene in this case) enhances the stereochemical control in the transition state. Illustrated in Scheme 8, the boat-like conformation is clearly preferred due to the minimal occurrence of non-bonded interactions, thus giving rise to the desired isomer as the major adduct.[21]



Scheme 8: Endo transition states of *cis*-acetals in IMDA reactions[21]

1.3 Research Objectives

1.3.1 Retrosynthetic Plan

The planned synthesis of the tricyclic nucleus of the decalin system **18** (Figure 6) has been proposed and utilized in our laboratory for the synthesis of many natural product analogues (see section *1.3.2* below).[21,22] This route is also used in the current study in an effort to construct the model molecule **17** of the immunosupressant, naturally occurring subglutinols A (**3**) and B (**4**). The synthesis involved an intramolecular Diels-Alder reaction in which a cyclic *cis*-isopropylidene control group would be utilized within the tether. The retrosynthetic plan is shown in Figure 6, where a detachment of the side chain in **17** would afford the IMDA cyclized system **18** and the lactone system **19**. A

double disconnection between C1-C2 and C3-C4 in **18** would provide the tether controlled IMDA precursor **20**. Further disconnections between C5-C6 and C7-C8 show that the IMDA precursor could in turn be constructed from commercially available D-isoascorbic acid **24**, vinylmagnesium chloride **22**, and the diene **21** which is readily prepared in our laboratory from 2-butyn-1-ol.[24]

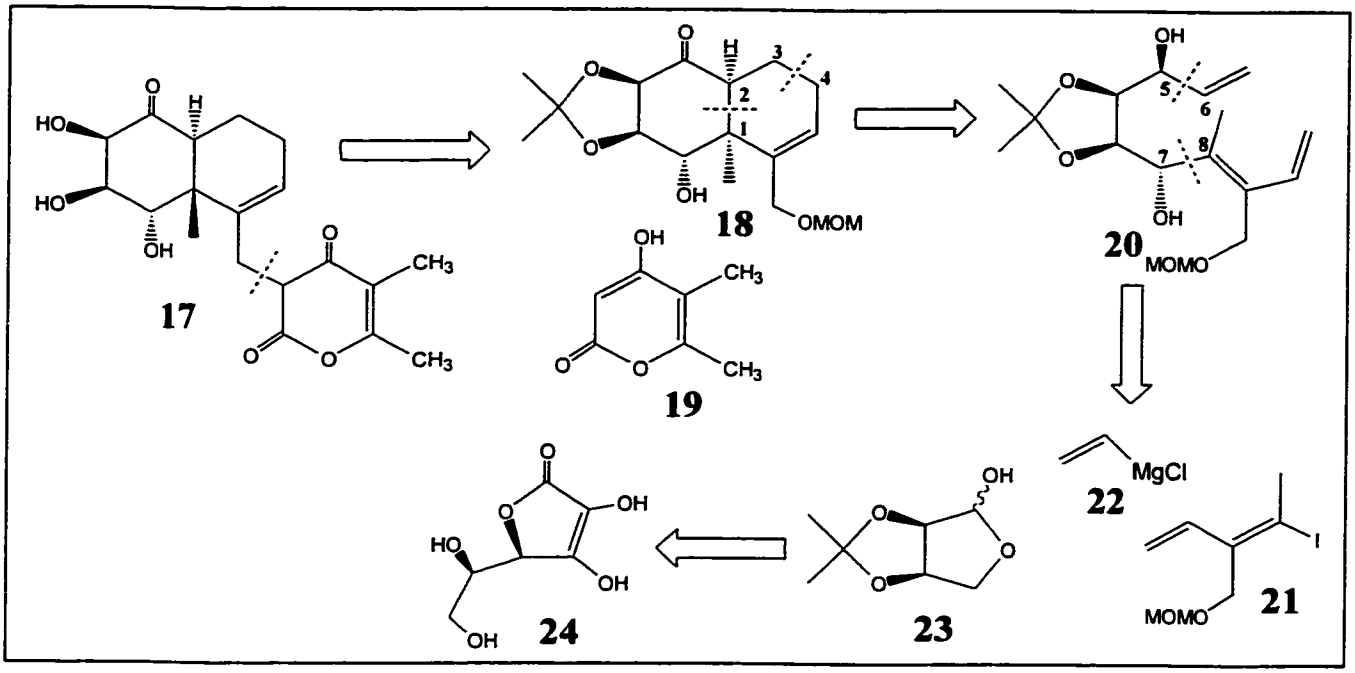


Figure 6: Retrosynthetic plan for the synthesis of analogue **17**

1.3.2 Preliminary Work

Many synthetic routes have been planned and attempted in our laboratory for the synthesis of the naturally occurring K-76 molecule[22,25] (**25**, Figure 7). The principle plan was the synthesis of a *cis*-decalin core as a single enantiomer, then its isomerization to the *trans* geometry found in **25**. Comparison between the structures of **25** and **3** (and **4**) suggested that a closely related route could be employed for the core structure in the synthesis of subglutinol analogue **17**. The synthetic route to the decalin system **18** employed in the current study (Figure 8) was developed in our laboratory by A.

Melekhov and P. Forgione.[21,22] Further developments to the procedural details were introduced in the scope of this study where distinctive and encouraging results were obtained. These modifications and findings are discussed in more detail in the relevant chapters of this thesis.

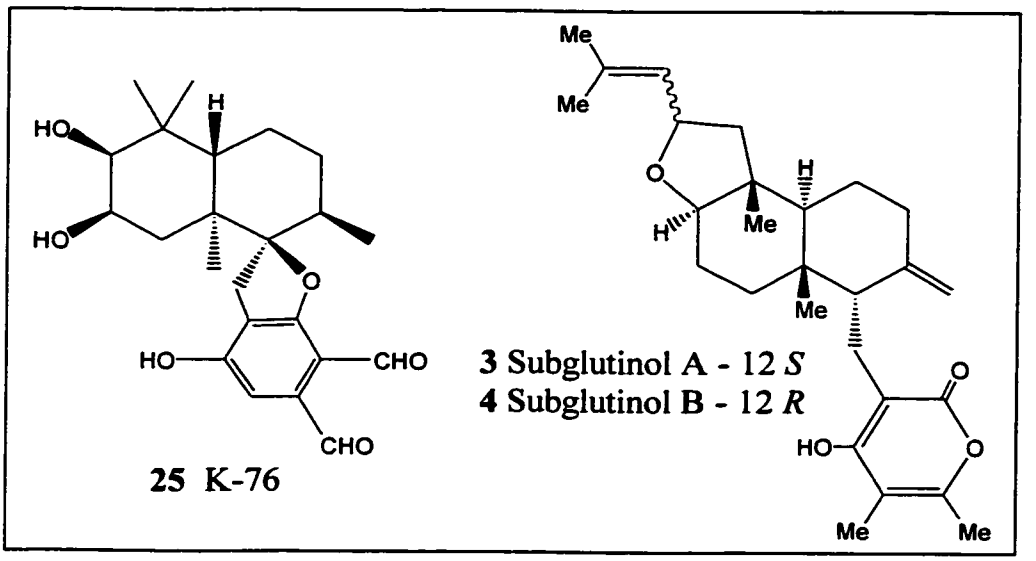


Figure 7: Comparison of the core structure between **25** and **3**(and **4**)

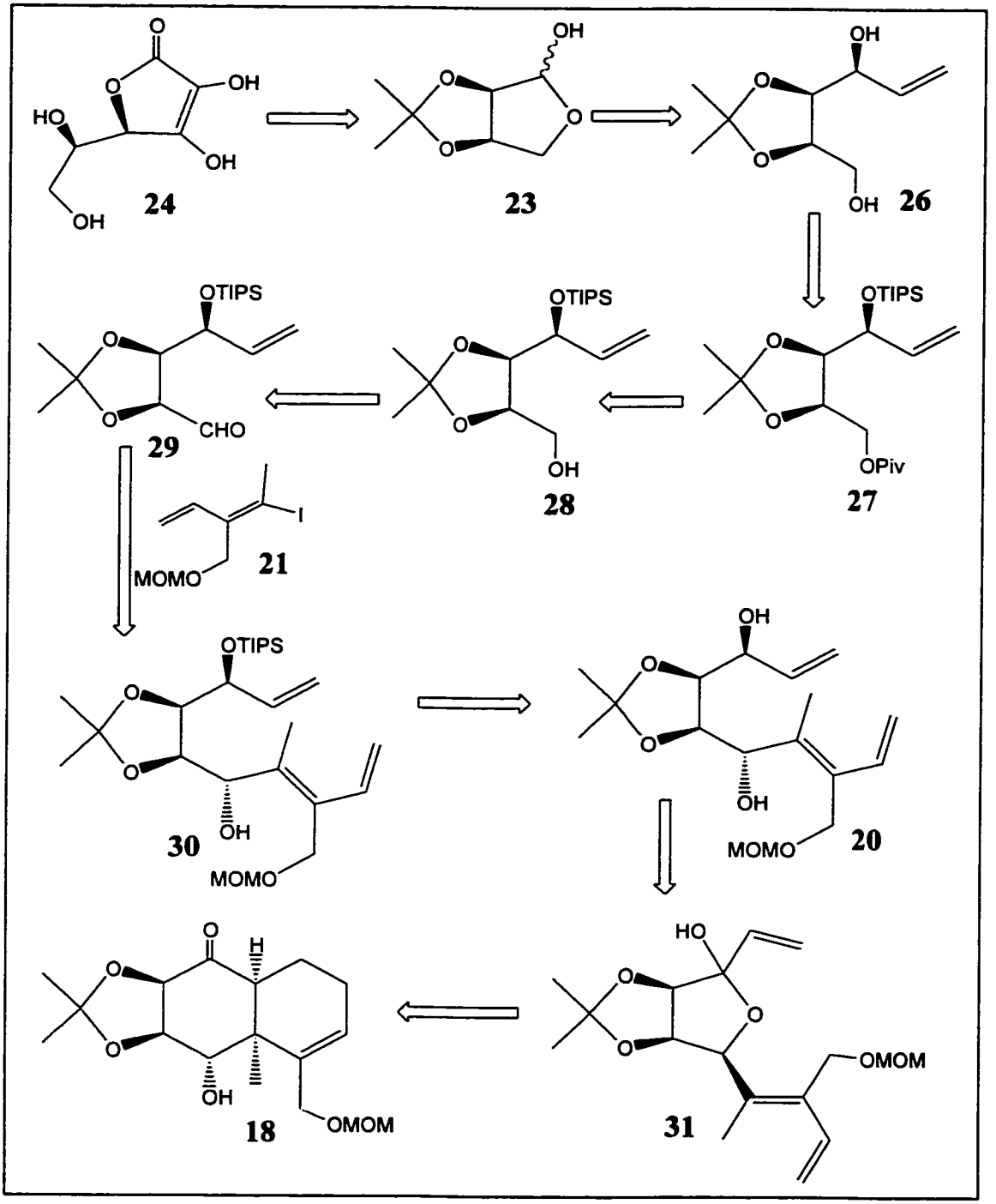


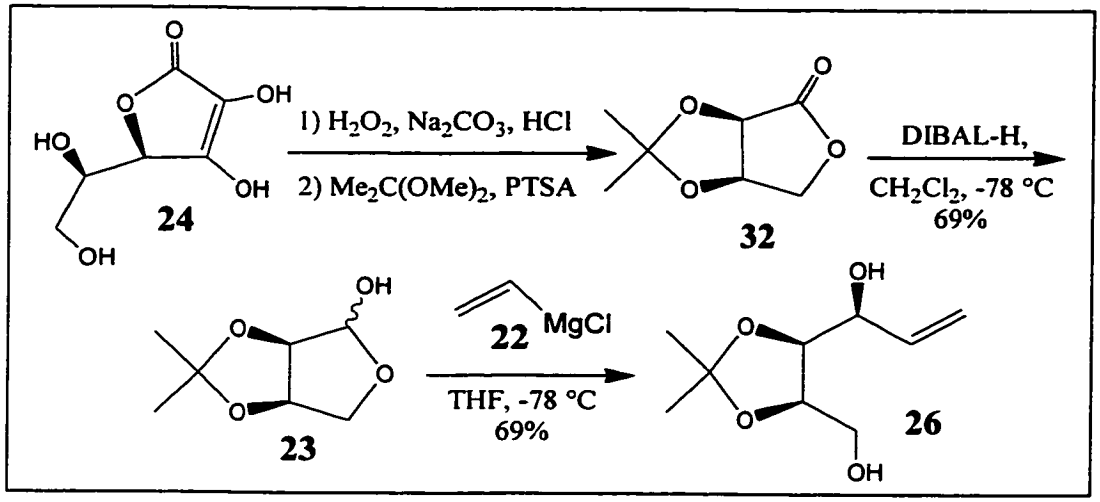
Figure 8: Full synthetic scheme to the decalin **18**

2 Results and Discussion

2.1 *Synthesis of the cis-Decalin Skeleton 18*

2.1.1 Preparation of the Dienophile Moiety

The starting material used for the synthesis of the dienophile was the inexpensive D-isoascorbic acid (**24**) ($48/500 g, Aldrich). It was converted into the diol **26** by following the reported oxidation-acetal formation literature procedures[26,27] with one modification.



Scheme 9

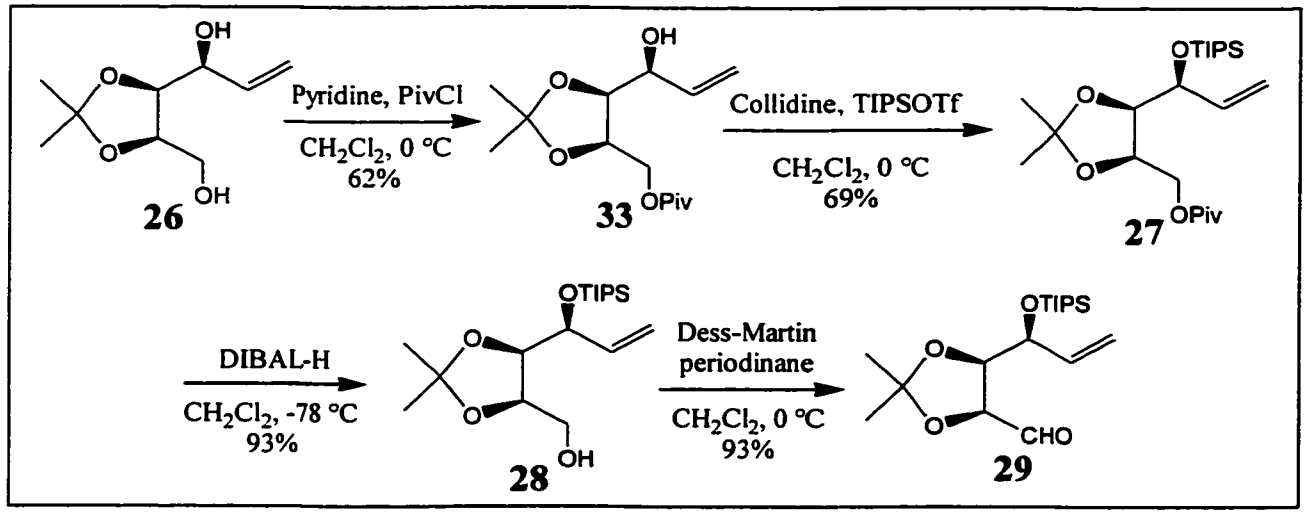
The initial experiment involved the treatment of D-isoascorbic acid with hydrogen peroxide and sodium carbonate. However, a problem was encountered when the recovered white-crystalline diol was treated with $Me_2C(OMe)_2$ and PTSA to install the *cis*-isopropylidene group. Only black tar was obtained after the reaction work-up and concentration. The ^{13}C NMR of the diol crystals showed a distinct peak of a carboxylic acid carbon at δ 180 ppm, which obviously didn't belong to the targeted diol. Examining the by-

products of the reaction, it was concluded that the ^{13}C NMR signal belonged to the oxalic acid crystallizing with the diol causing its decomposition in the second step. Therefore, the required crystals were obtained by carrying out the recrystallization slowly at room temperature overnight, as opposed to 5 °C for a few hours reported by Cohen and co-workers.[26]

Lactol **23** was obtained after treatment of lactone **32** with DIBAL-H. The ^1H NMR spectrum of the crude product clearly indicated the presence of a pure sample with no further purification required. It showed an alcohol signal as a doublet at δ 3.41 ppm, and a new doublet for the geminal hydrogen at δ 5.37 ppm. Treatment of lactol **23** with **22** at -78 °C afforded the desired diol **26**. The vinylic hydrogens appeared on the crude ^1H NMR spectrum at δ 5.27 (doublet), 5.38 (doublet), and 6.00 ppm (doublet of doublet of doublets).

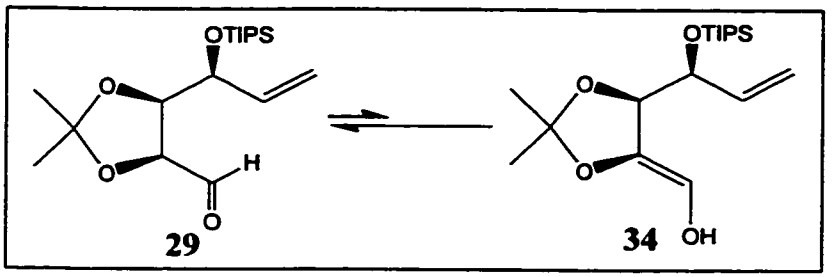
2.1.2 Preparation of Aldehyde 29

The desired aldehyde **29** for the addition of the diene was acquired through a series of protection and deprotection steps performed in the order illustrated in Scheme 10.



Scheme 10

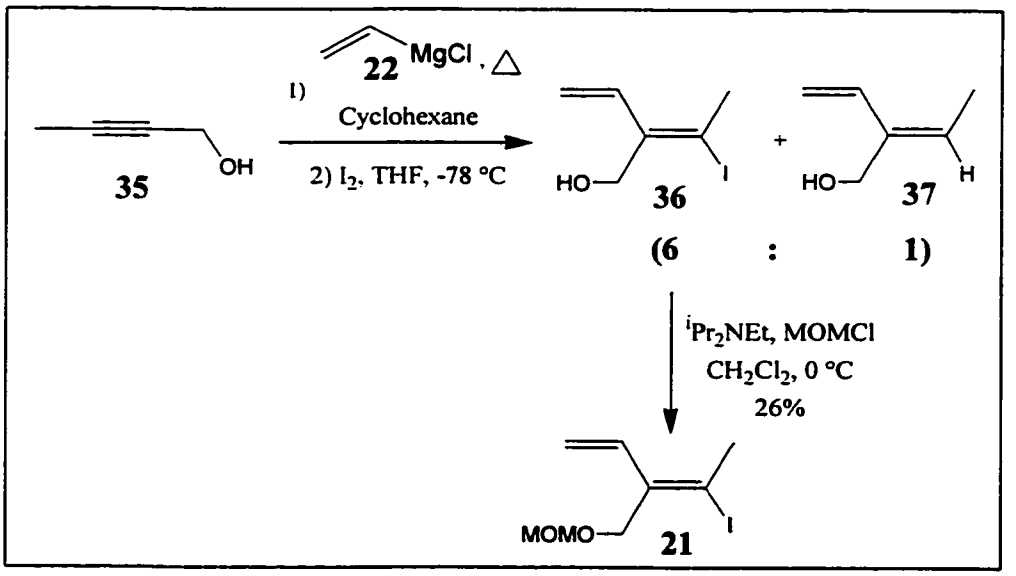
First, the reactive primary alcohol in **26** was protected as a pivaloyl ether to yield alcohol **33**. Full spectroscopic data of the alcohol **33** in terms of NMR, IR, and HRMS was obtained in this study, as it was not, to our knowledge, previously reported in the literature. The ^{1}H NMR showed a new signal at δ 1.19 ppm accounting for 9 hydrogens, thus, confirming the successful monoprotection of the primary alcohol. The IR confirmed the compound contained a carbonyl group (1719 cm^{-1}) and an alcohol (3466 cm^{-1}). The secondary alcohol in **33** was converted into its corresponding triisopropylsilyl ether **27**. The ^{1}H NMR clearly indicated the presence of the silyl group at δ 1.02-1.08 ppm integrating for 21 hydrogens. The primary alcohol **28** was reconstructed by removal of the pivaloyl group using DIBAL-H. The ^{1}H NMR showed the compound had lost the signal at δ 1.20 ppm, and the IR showed the presence of an alcohol group (3482 cm^{-1}). Upon oxidation of the alcohol **28** with Dess-Martin periodinane, the required aldehyde **29** was obtained. The ^{1}H NMR spectrum showed a signal at δ 9.63 ppm, which was characteristic of an aldehyde. The IR also indicated that the compound contained a carbonyl group (1733 cm^{-1}). This sequence of protection and deprotection steps has proven to be very effective in improving the yields obtained. Yields as high as 93% were attained in the present study for compounds **28** and **29**, as compared to previously reported yields of 73% and 81%, respectively.[21] All spectroscopic data obtained for compounds **27**, **28** and **29** were in agreement with previously reported values.[21,25] It is very important to note that the aldehyde **29** is very sensitive to enolization (Scheme 11). Therefore, complete removal of any trace solvent was essential. Storage of the aldehyde in frozen dry benzene avoided this complication and allowed for longer storage periods.



Scheme 11

2.1.3 Synthesis of Diene 21

The preparation of the diene **21** utilized a magnesium mediated carbometallation sequence developed in our laboratory,[24] as depicted in Scheme 12. 2-Butyn-1-ol (**35**) in cyclohexane was reacted with vinylmagnesium chloride in THF (3.1 equiv.) at 0 °C. The reaction was heated to reflux overnight. Iodine (3.0 equiv.), dissolved in THF, was added dropwise with vigorous stirring to the cold (-78 °C) reaction mixture. This method of adding iodine as a THF solution to the reaction was an important improvement, as opposed to adding it as a dry solid. A better yield of the desired alcohol **36** was obtained due to the ease of stirring of the viscous mixture, which was present.

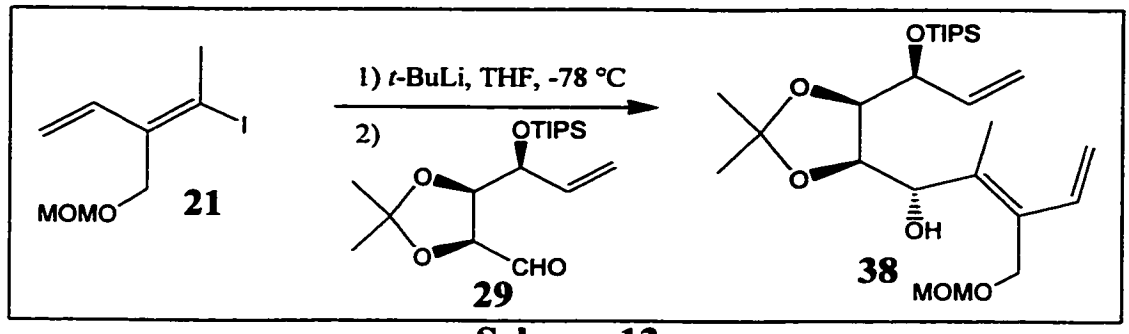


Scheme 12

The reaction was quenched and analyzed immediately by ^{1}H NMR which confirmed the major product was the desired Z-iodo diene **36**, with a small amount of the corresponding protonated diene **37** (**36/37** 6:1, Scheme 12). Without further purification, the protection of the unstable iodo-alcohol was achieved by converting it into the corresponding methoxymethyl ether to yield the desired diene **21**. The ^{1}H NMR spectrum indicated the presence of the MOM group with signals at δ 3.41 ppm and δ 4.45 ppm accounting for 3 and 2 hydrogens, respectively. Exposure of the iodo diene to light and heat should be avoided, and it must be wrapped in aluminum foil and kept in the freezer while not in use in order to minimize decomposition. The low yield obtained (26%) is mainly due to the fact that, during purification with conventional column chromatography, only fractions containing the pure iodo diene were collected and combined. The fractions containing impurities with the desired diene (as revealed by TLC) were discarded, since further purification attempts would result in further decomposition of the product.

2.1.4 Coupling of the Diene 21 with the Aldehyde 29

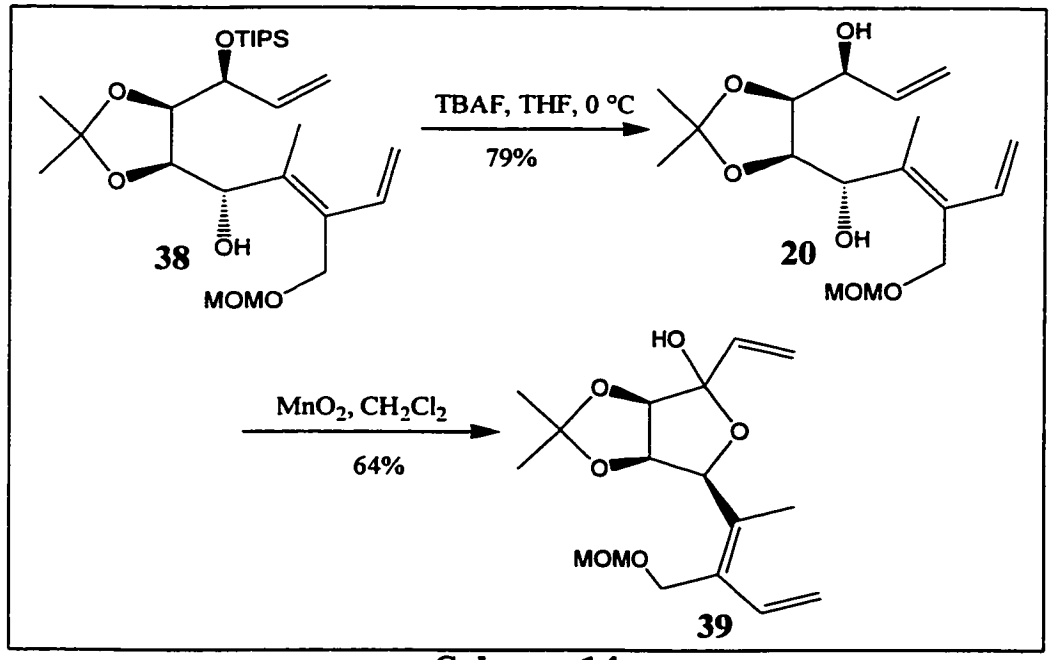
Freshly prepared iodo diene **21** (2.3 equiv.) was converted into the corresponding dienyllithium by adding it to a cold (-78 °C) solution of *tert*-butyllithium (4.1 equiv.) in THF. The mixture was stirred for 15 minutes, and aldehyde **29** was added to afford the desired adduct **38** as concluded from the ^{1}H NMR of the crude reaction mixture. The reaction time of 15 minutes was critical as longer periods resulted in considerable decomposition of the desired product as determined by TLC.



Scheme 13

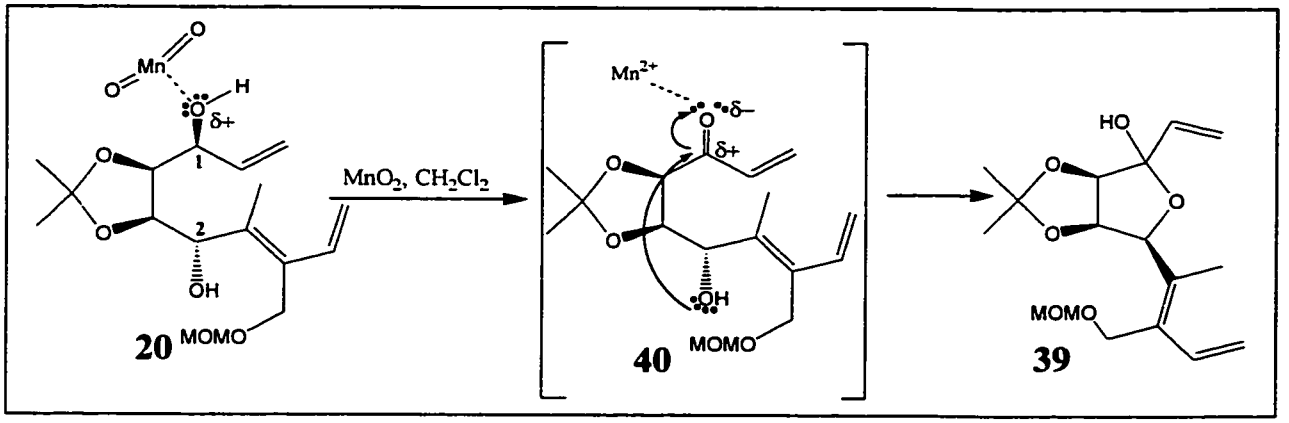
2.1.5 The Intramolecular Diels-Alder Reaction of Lactol 39

Diels-Alder reactions are highly efficient when an electron rich diene and an electron poor dienophile are present. To generate the dienophilic component, **38** was manipulated as shown in Scheme 14. The triisopropylsilyl ether was removed by treatment with tetra-*n*-butylammonium fluoride (1.6 equiv.). A. Melekhov has previously obtained NMR and HRMS data of compound **20**.[25] Verification of such data was carried out in the present study in addition to further characterization by IR spectroscopy. The IR spectrum confirmed that the compound contained an alcohol group (3421 cm^{-1}).



Scheme 14

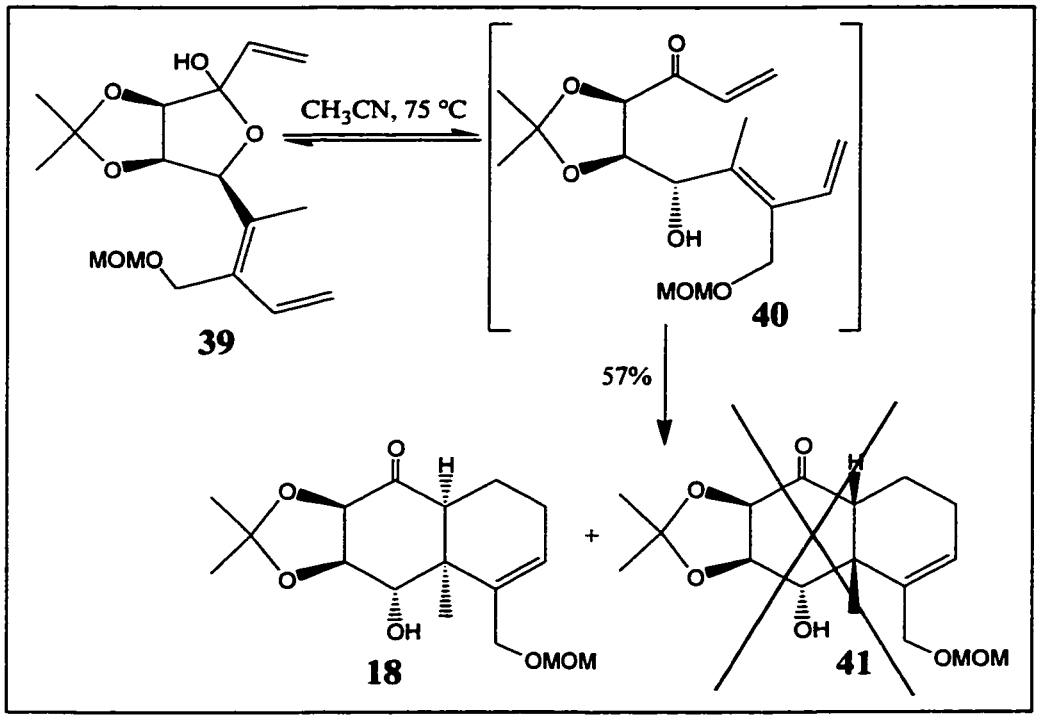
The resulting diol **20** was oxidized using manganese dioxide to afford the lactol **39**. This generated the required electron poor dienophile. It is important to note that the oxidation step was performed to selectively oxidize the vinylic alcohol at C-1 (Scheme 15) to afford **40**. This selective oxidation is the result of the increased hindrance of the vinylic alcohol group at C-2, making its oxidation to the ketone significantly slower. The manganese ions may complex to the ketone group in **40** producing an electrophilic carbon, which was susceptible to attack by the alcohol group at C-2 to afford the lactol **39**. NMR data of **39** was previously obtained in our laboratory by A. Melekhov.[25] Further characterization of this compound by IR spectroscopy and HRMS was performed in the current study. The IR spectrum clearly indicated the absence of a carbonyl group and the presence of an alcohol functionality (3403 cm^{-1}).



Scheme 15

Lactol **39** was heated in acetonitrile to 75-78 °C for 71 hours. The desired decalin **18** was obtained as a single diastereomer (Scheme 16), as opposed to a mixture of diastereomers in a ratio of 11:1 (**18** : **41**) previously reported.[22] The ^1H NMR spectrum indicated the presence of a vinylic hydrogen at δ 5.85 ppm, and the methyl of the MOM group at δ 3.37 ppm. Full NMR analysis of **18** was previously reported by A. Melekhov.[22] Further analysis of

compound **18** by IR spectroscopy and HRMS was carried out in the present study. The IR showed that the compound contained a carbonyl group (1725 cm^{-1}) and an alcohol (3448 cm^{-1}).



Scheme 16

2.1.6 Characterization of the Diels-Alder Product 18

The proposed transition states for the Diels-Alder reaction are illustrated in Figure 9a. As described earlier, when the dienophile contains a substituent bearing a π bond such as a carbonyl group, the endo product is usually preferred as a result of favourable secondary orbital overlap (endo rule).[10,11,12] Therefore, only the four possible transition state geometries with an endo conformation are shown in Figure 9a. These endo transition states would thus lead to the formation of the *cis*-fused ring system found in **18** and **41**.

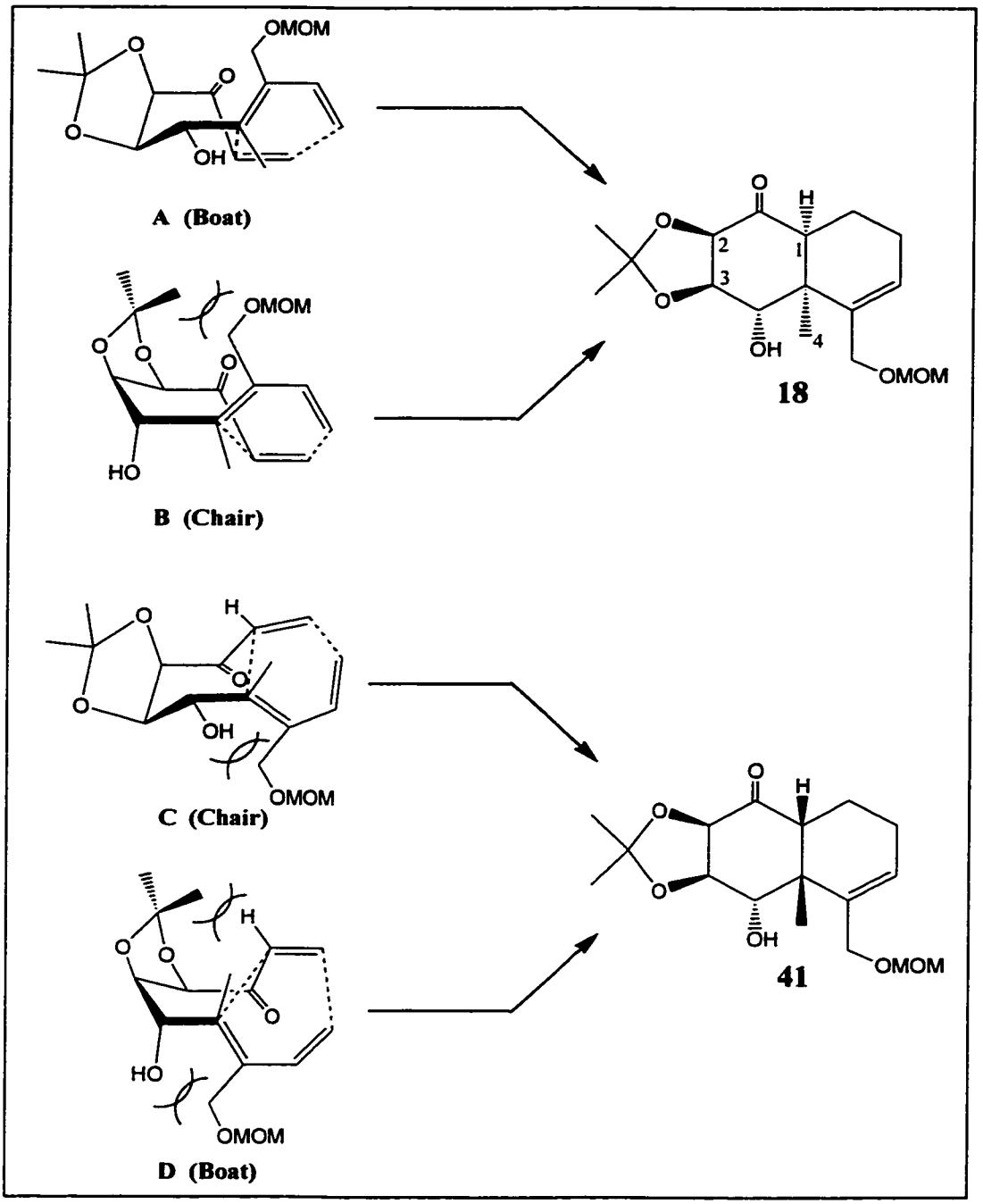


Figure 9a: Proposed Diels-Alder transition states of **18** and **41**

Examining the transition states in Figure 9a, the boat-like orientation (A) is clearly preferred in the formation of **18** compared to the competing chair-like conformation (B), due to the minimization of non-bonded interactions in the boat-like arrangement. The same argument applies for the formation of **41**, where the chair-like transition state (C) is more favourable than the boat-like conformation (D). The two favoured transition states leading to the formation of **18** and **41** (A and C, respectively) clearly explain, in terms of non-bonded interactions, the formation of **18** as a single diastereomer.

NOESY experiments were also performed in the current study on the cyclized product **18** to confirm the stereochemistry at C1 and C4 (Figure 9b). The resulting spectrum clearly indicated the couplings between the proton signals of C1 (δ 2.45 ppm), C2 (δ 4.65 ppm), and C3 (δ 4.61 ppm) and the proton signal of C4 (δ 1.22 ppm) (Figure 9). Couplings between the protons of C2 (δ 4.65 ppm) and C3 (δ 4.61ppm), and between these two and the proton of C1 (δ 2.45 ppm) were evident. As a result, the relative stereochemistry of C4 and the hydrogens at C1, C2, and C3 was determined with confidence to be the one found in the decalin **18**.

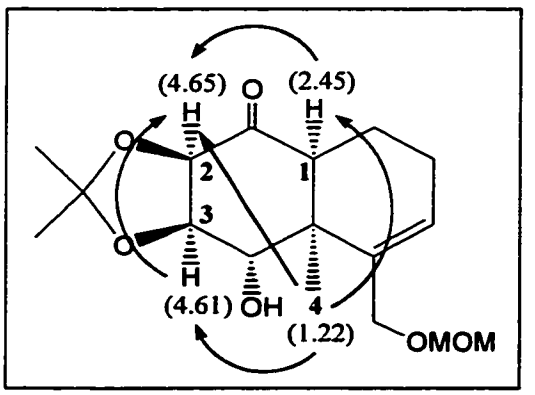
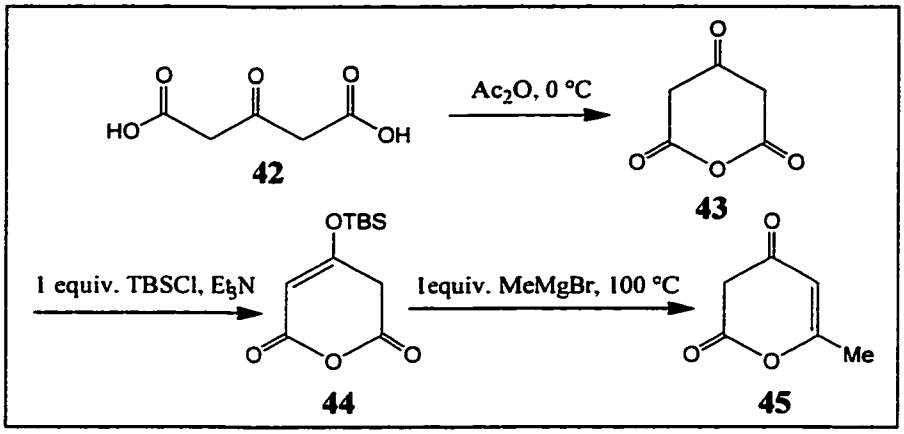


Figure 9b: NOESY correlations of the decalin **18**

2.2 Preparation of the Lactone System 19

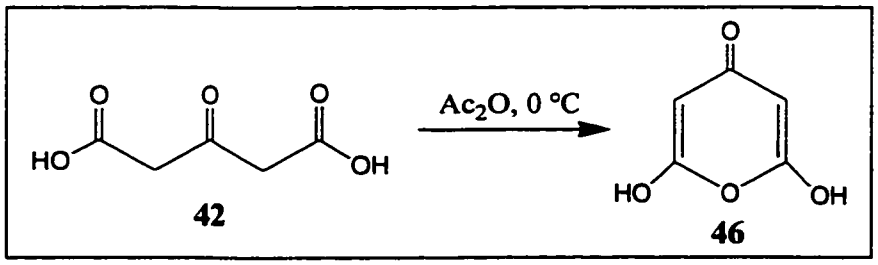
2.2.1 Preliminary Synthetic Route

The preliminary route investigated toward the synthesis of the lactone system **19** is illustrated in Scheme 17. Initially, a model system was selected to investigate the chemistry required.



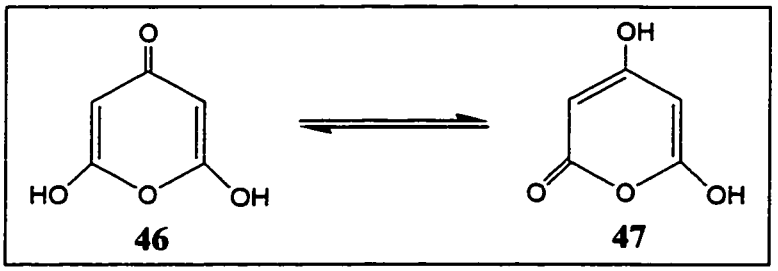
Scheme 17

The conversion of 1,3-acetonedicarboxylic acid (**42**) to the corresponding anhydride **43** was investigated. However, the resulting anhydride exclusively existed in the enol form **46** (Scheme 18). The crude ^{1}H NMR spectrum showed a singlet at δ 5.35 ppm and a broad singlet at δ 3.00ppm, each signal integrating for 2 equivalent hydrogens (compared to peaks of starting material remaining).



Scheme 18

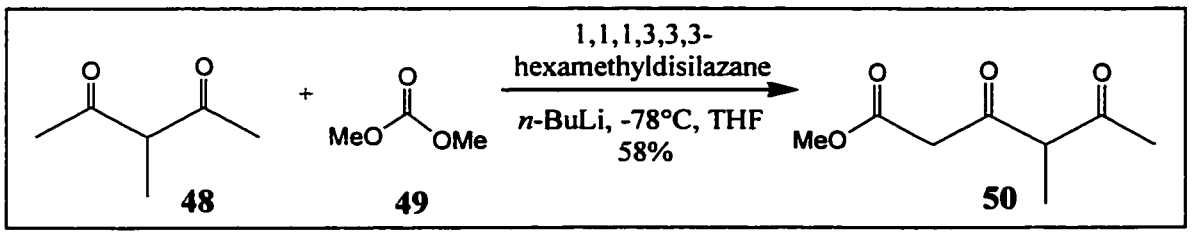
This was not a desired structure since it will not lead to the target intermediate **44** for the addition of methylmagnesium bromide. Manipulation of reaction conditions would be necessary to set-up the equilibrium between the enol forms **46** and **47** shown in Scheme 19. However, both isomers would undergo protection with TBSCl and addition of the methyl group, introducing further complications during product separation. Therefore, this route was abandoned with no further investigations and an existing route in literature was adopted.



Scheme 19

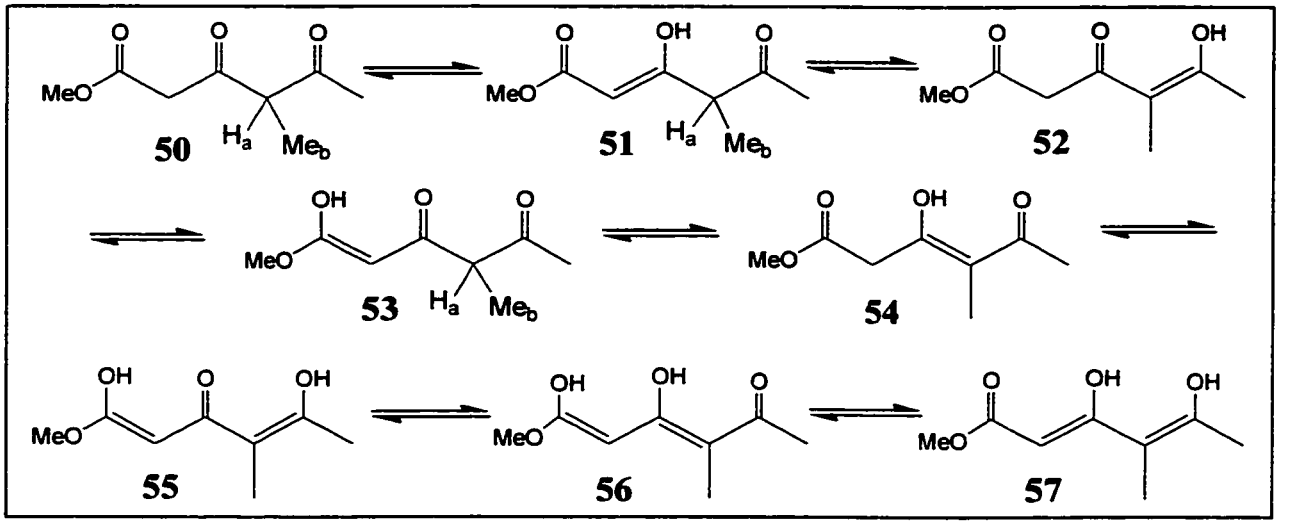
2.2.2 Synthesis of the Lactone 19

The synthesis of the desired lactone **19** was carried out as reported in literature.[28] 3-Methyl-2,4-pentanedione (**48**) was converted into 4-methyl-3,5-dioxo-hexanoic acid methyl ester (**50**) using dimethyl carbonate (**49**) in THF (Scheme 20). After stirring for 18 hours, a bright yellow solid was observed in the reaction flask, which upon acidification, redissolved resulting in a uniform clear yellow solution.



Scheme 20

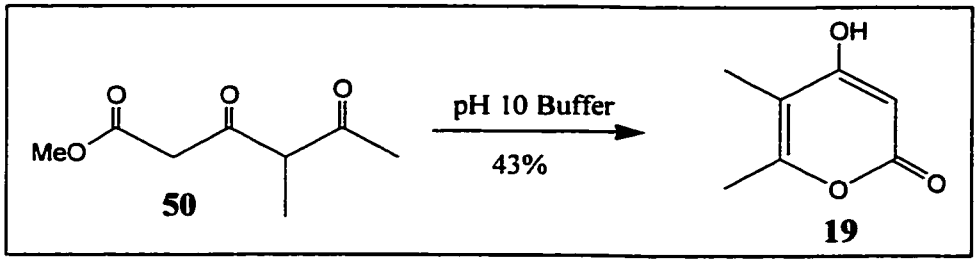
Analysis of the ^{1}H NMR spectrum of the purified compound was quite challenging due to the presence of many keto-enol tautomers, as illustrated in Scheme 21. The ^{1}H COSY spectrum showed a hydrogen at δ 3.82 ppm (quartet) that was coupled to three hydrogens at δ 1.32 ppm (doublet). The spectrum also indicated the presence of another hydrogen at δ 3.23 ppm (quartet) that was coupled to three hydrogens at δ 1.26 ppm (doublet). These signals were characteristic of H_a and Me_b that were found in the keto form **50** and both enol forms **51** and **53** (Scheme 21). This compound had a bright yellow colour despite purification by conventional column chromatography supporting the presence of keto-enol tautomers.



Scheme 21

The newly synthesized compound was stirred in a basic buffer solution at pH 10 for 20 hours, affording the desired pyrone system **19** as a white solid. Analysis of the ^{1}H NMR of this compound showed a broad but distinct peak around δ 10-11 ppm, which was not reported by Barrett and co-workers.[28] The fact that a peak appeared this far downfield for this compound was confusing at

first, but it was later assigned to the hydrogen of the alcohol group. This signal assignment correlated with the high acidity of this hydrogen due to the pseudo-aromatic ring system found in pyrone **19**.



Scheme 22

2.3 Attempts to Remove the MOM Group in Decalin 18

2.3.1 Removing the MOM Group Using Trifluoromethane-sulfonic Acid

The first trial to remove the MOM group was carried out using 10% (v/v) trifluoromethanesulfonic acid (TFS). Decalin **18** (32 mg) was dissolved in THF and cooled to 0 °C. TFS was added dropwise to the reaction mixture while monitoring the reaction by TLC (4:1, ethyl acetate/hexane). TLC analysis revealed that only two spots were observed for the reaction mixture over a course of five minutes. One spot was more polar than the starting material (SM) spot, and the second one was less polar than the SM spot (Figure 10). This was evidence that no more SM was left. Surprisingly, for the co-spot on the TLC (where the SM and the reaction were spotted together), only the two spots of the reaction mixture were observed, with no trace of SM.

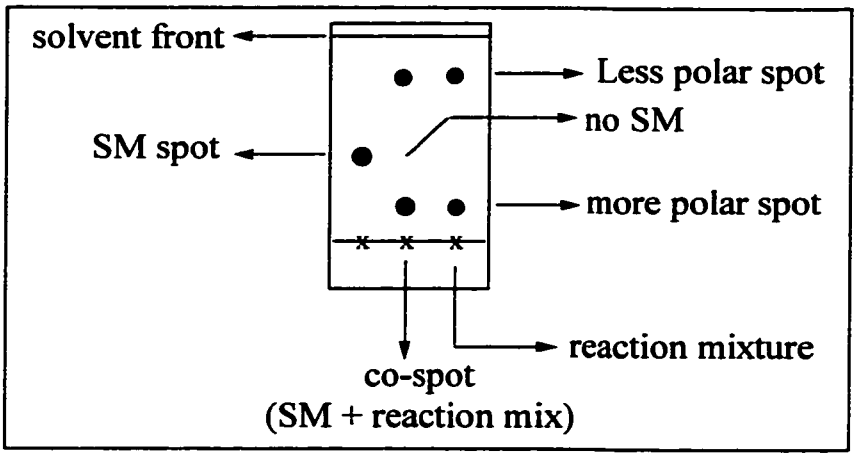
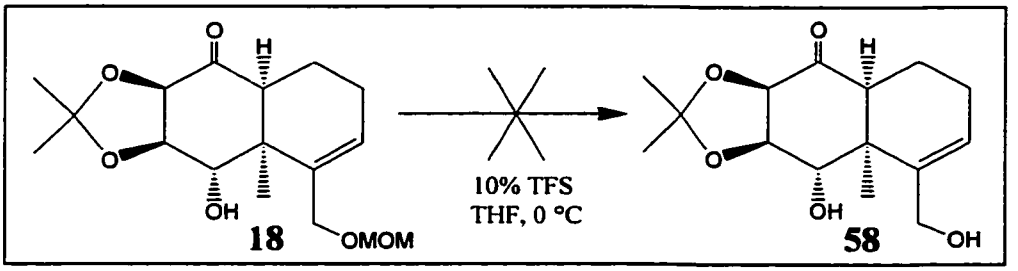


Figure 10: TLC sketch

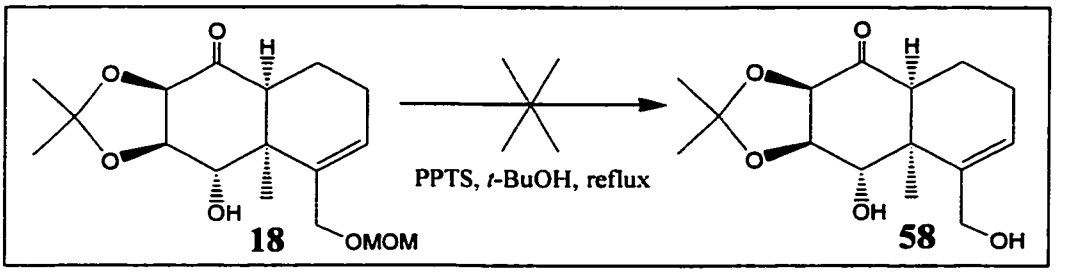
Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed the presence of a peak at δ 3.35 ppm, which is characteristic of the methyl of the MOM group. Separation of the two spots by preparative TLC and subsequent analysis using ^{1}H NMR of the two fractions separately showed that the less polar spot on the TLC was made up of decomposed material, while the more polar spot contained the distinct peak of the methoxy group at δ 3.35 ppm. With no further analysis, it was concluded that the attempt to remove the MOM group using TFS was unsuccessful.



Scheme 23

2.3.2 Removing the MOM Group Using Pyridinium *p*-Toluenesulfonate

A second attempt to remove the MOM group was examined with pyridinium *p*-toluenesulfonate (PPTS), which was reported to remove allylic MOM groups.[29] Decalin **18** (50 mg) and PPTS were dissolved in *tert*-butanol and heated to reflux for five hours. The reaction was monitored by TLC (4:1, ethyl acetate/hexane). The TLC plates showed five spots, one of which belonged to some remaining starting material (SM). The major two spots were less polar compared to the SM spot, while the other two minor spots were more polar. Separation of the spots by preparative TLC and analysis by ^{1}H NMR revealed that the two less polar spots were decomposed products, while the two more polar ones contained extremely small amounts of material. Unfortunately, this precluded unambiguous analysis and structural assignment, which diverted our attention to other procedures described below.

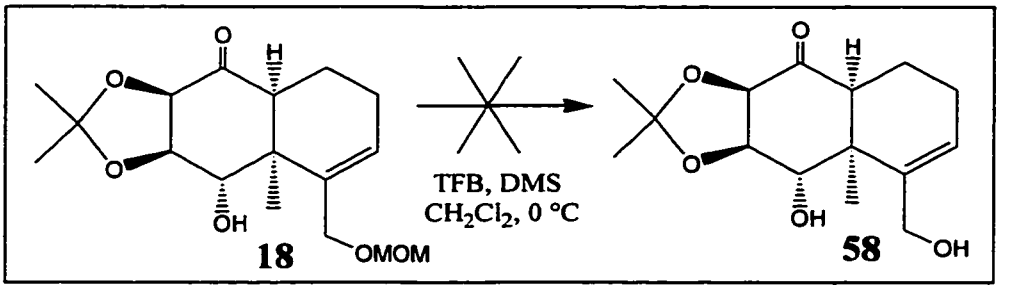


Scheme 24

2.3.3 Removing the MOM Group Using Trifluoroboron Etherate

A further attempt at hydrolysis of the MOM group employed trifluoroboron etherate (TFB).[30] Decalin **18** (50 mg) and dimethyl sulfide were

dissolved in dichloromethane and cooled to 0 °C. TFB was added dropwise and the reaction stirred for an additional 40 minutes. Monitoring by TLC (4:1, ethyl acetate/hexane) revealed that the starting material (SM) was consumed at this point. However, the major spot was located at a higher R_f value than the SM, and four minor spots were located at smaller R_f values. Using preparative TLC, it was possible to separate the major spot from the other minor ones. Analysis of the ^1H NMR spectra showed that the major spot was decomposed material, while no conclusions were possible from the minor spots' NMR spectra. Thus, this procedure was concluded to be unsuccessful in removing the MOM group.

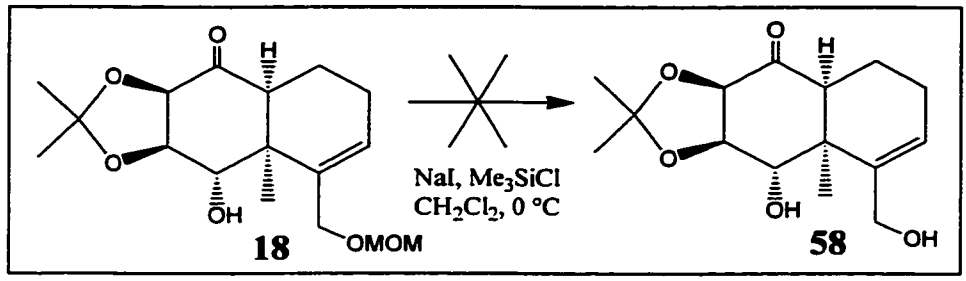


Scheme 25

2.3.4 Removing the MOM Group Using Trimethylsilyl Iodide

The last attempt at removing the MOM group was using trimethylsilyl iodide (TMSI) prepared *in situ*.[31] Decalin **18** (45 mg) was dissolved in dichloromethane, and sodium iodide was added at room temperature (21-22 °C). Trimethylsilyl chloride was added dropwise to the yellow cold (0 °C) solution. Monitoring the reaction by TLC (4:1, ethyl acetate/hexane) indicated no trace of the starting material (SM) after stirring for 3 hours. However, many overlapping spots (total of approximately 8) were observed at lower R_f value than the SM. No further separations or analyses were done on the crude

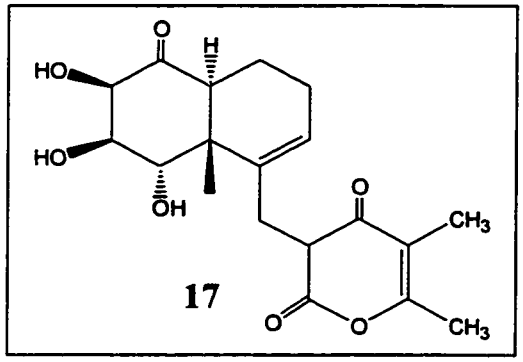
sample, concluding that this is not the best procedure to remove the MOM group from the decalin system **18**.



Scheme 26

3 Conclusions

The main objective of this research project was to synthesize the immunosupresant analogue **17** based on the targets **3** and **4**. Unfortunately, the synthesis of the final target was not realized. However, improvements in the synthesis of decalin **18** gave an intramolecular Diels-Alder cycloaddition adduct as a consequence of employing a *cis*-isopropylidene tether control group. This facilitated the cycloaddition reaction and improved the stereoselectivity. The lactone **19** was successfully synthesized following the same approach reported in literature.[28]



17

Figure 11: Target analogue

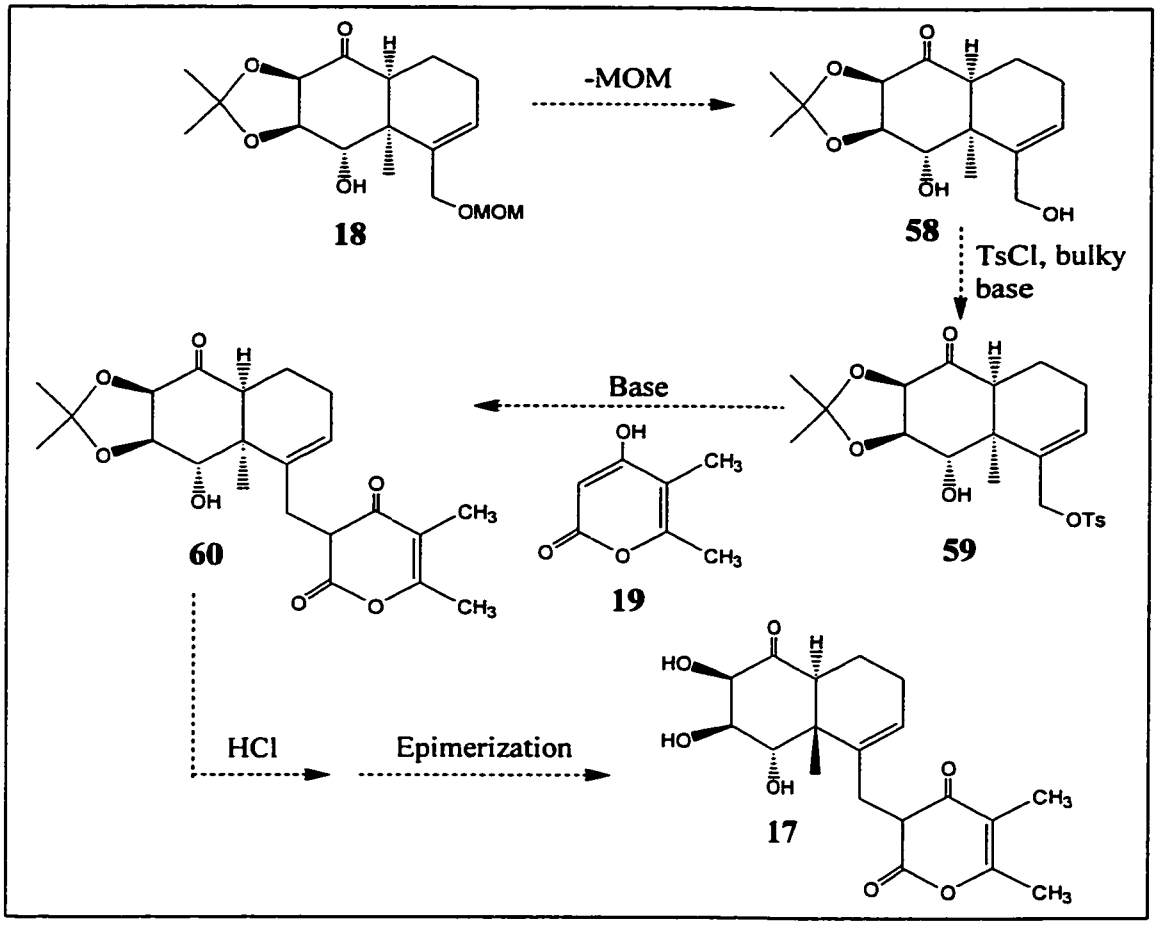
The tricyclic system **18** was prepared following a path developed in our laboratory utilizing an IMDA reaction. The required precursor **20** was readily synthesized from D-isoascorbic acid (**24**), vinylmagnesium chloride (**22**), and the diene **21**. Attachment of the diene **21** onto the aldehyde **29** was achieved via a Grignard-type addition reaction. The Diels-Alder precursor **20** readily underwent cyclization at 75-78 °C in 71 hours to afford the *cis*-fused ring system **18**. The placement of an acetonide control group in the tether helped

ease the cyclization where it held the diene and the dienophile in the geometric arrangement required for the transition state.

The ring system **17** was not fully constructed due to unsuccessful attempts in removing the methoxymethyl (MOM) protecting group in the IMDA product **18**. All efforts for its removal resulted in decomposition of the starting material. The task of removing the MOM group has proven to be very challenging in our laboratory.[32]

3.1 Future Studies

Additional work is required to complete the synthesis of the target analogue **17** (Scheme 27). Further research must be done to successfully remove the MOM group in the IMDA product **18** in quantitative yields. Another possibility for an improvement would be the replacement of the MOM group with a different protecting group such as PMB, which is removed by oxidation. The resulting primary alcohol would then be selectively converted into a good leaving group (i.e. tosylate group), without affecting the secondary alcohol present, by using a bulky base to perform the deprotonation. The lactone **19**, transformed to the enolate form in a basic medium, would then be installed via an S_N2 reaction. Removal of the *cis*-isopropylidene protecting group using concentrated HCl and *cis-trans* epimerization of the decalin core would yield the desired target analogue **17**. The epimerization step proved to be troublesome when examined in our laboratory,[25] where the equilibrium favoured the *cis* (undesired) isomer. A proposed retrosynthetic plan for the full synthesis of **3** and **4** is shown in Figure 12 as a guideline for future synthetic investigations.



Scheme 27

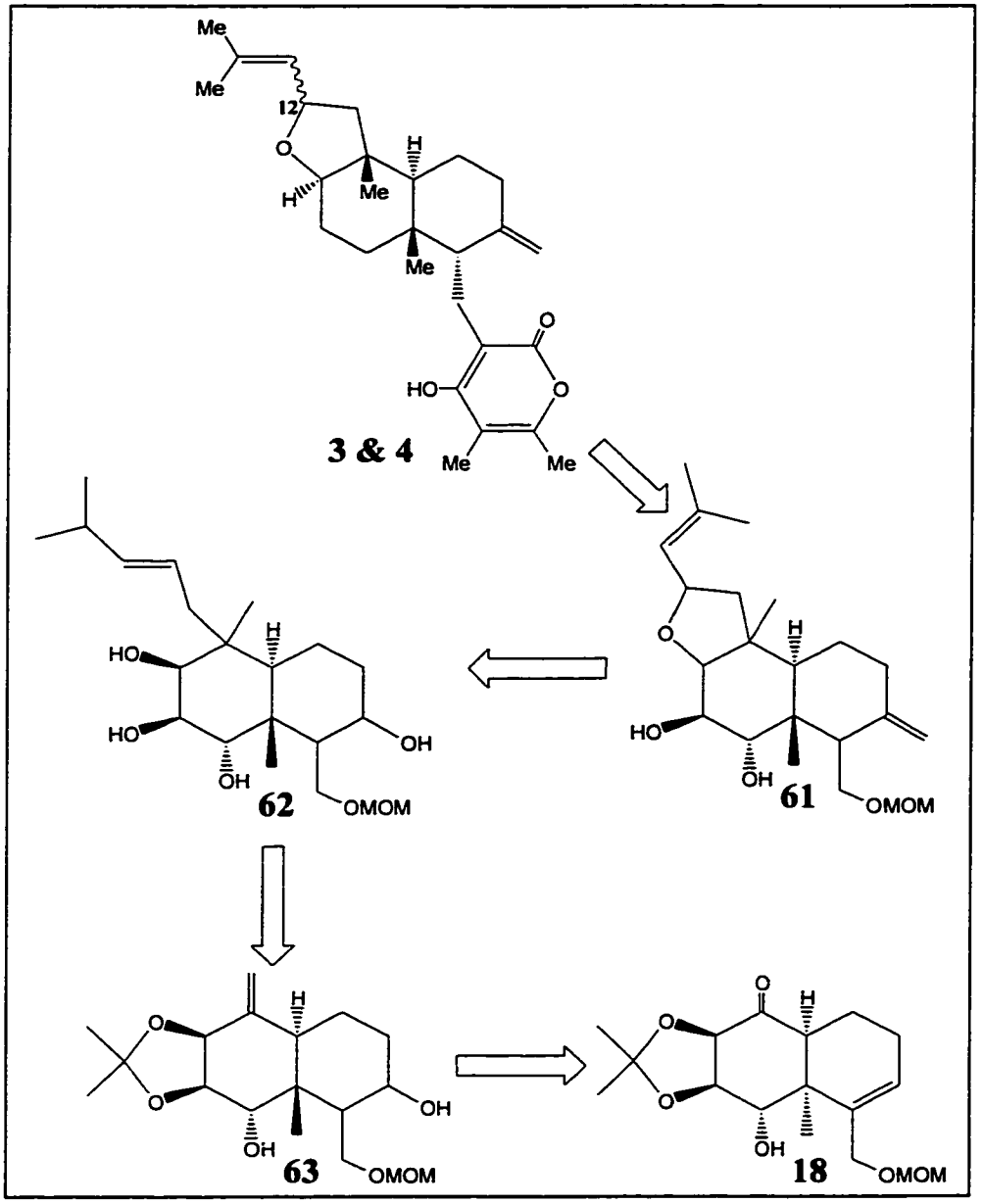


Figure 12: Retrosynthetic plan of **3** and **4**

4 Experimental Section

General Procedures:

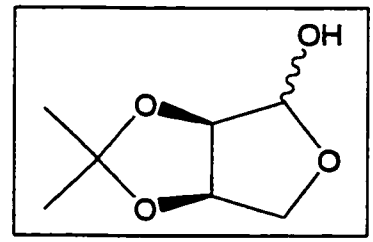
All Proton magnetic resonance spectra (^{1}H NMR, 500 MHz) and Carbon magnetic resonance spectra (^{13}C NMR, 125 MHz) were run on a Bruker AMX500. All NMR spectra were measured in deuterochloroform solutions unless otherwise stated. All NMR data are reported in parts per million (ppm) downfield from tetramethylsilane on the δ-scale. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad), coupling constants (Hz), and number of protons. All melting points were measured in capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were acquired either as neat films, or as a thin film of a dichloromethane solution of the compound on sodium chloride discs. All IR spectra were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FT-IR) and the data are reported in reciprocal centimetres (cm^{-1}). High-resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-IIA mass spectrometer at 70 eV ionizing energy. EI (electron ionization) conditions were employed, unless otherwise stated. The purity of each reported compound was judged to be >95% as concluded by the combined analyses of ^{1}H NMR, ^{13}C NMR and HRMS.

All non-aqueous reactions were performed under a dry nitrogen atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum. Standard inert atmosphere techniques were employed in handling all air and moisture sensitive reagents. Reactions were monitored by

thin-layer chromatography (TLC) using commercial aluminum-backed silica gel plates (E. Merck). The TLC spots were viewed under ultraviolet light and developed by heating the plate after its treatment with a permanganate stain (4.5 g $KMnO_4$, 30 g K_2CO_3, 7.5 mL of 5% aqueous NaOH, 450 mL water). Product purification by column chromatography was carried out using E. Merck Silica Gel (70-230 or 230-400 mesh). Reaction mixtures after work-up were dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator connected to an air or water aspirator. Trace solvents were removed on a vacuum pump. All purified compounds were stored at -15 °C in vials after being flushed with nitrogen. Vinylmagnesium chloride was obtained from Fluka Chemika-BioChemika and titrated before usage against diphenyl ditelluride.

Tetrahydrofuran was freshly distilled from benzophenone/sodium. Dry dichloromethane, diisopropylethylamine, benzene and toluene were freshly distilled from calcium or sodium hydride. Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30-60 °C. Ether refers to diethyl ether. All commercial starting materials were purchased from the Aldrich Chemical Company.

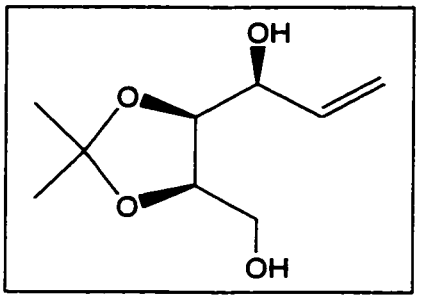
2,2-Dimethyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-ol (23)



Lactone **32** (11.39 g, 72.1 mmol), synthesized as described by Cohen *et al*[26], was dissolved in dichloromethane (205 mL) and cooled to -78 °C.

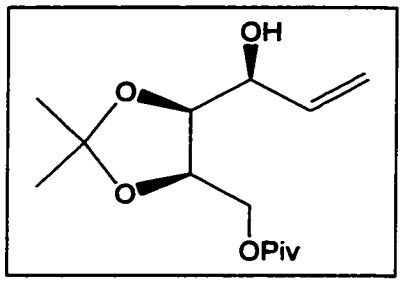
Diisobutylaluminum hydride (1.5 M toluene solution, 57.5 mL, 86.3 mmol) was added dropwise via an addition funnel to the cold reaction mixture and the resulting solution was allowed to stir for an additional 2 h. The reaction was quenched by the addition of methanol (11 mL) followed by brine (5 mL). The reaction was allowed to warm to room temperature (21-22 °C), at which ether (300 mL) and $MgSO_4$ (83 g) were added and the reaction was vigorously stirred for 4 h. The mixture was filtrated through a sintered glass funnel, washed with ether (500 mL), and concentrated to yield the crude lactol (7.90 g, 69%) as a clear colorless oil, which was used for the next step without further purification.

1-(5-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-propenol (26)



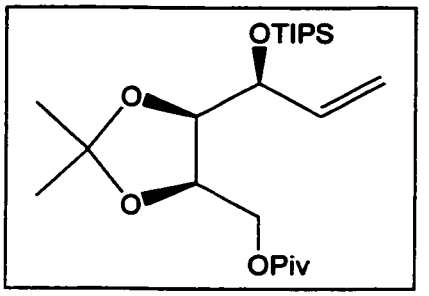
Vinylmagnesium chloride (80 mL, 120.0 mmol) was added dropwise via an addition funnel to a stirred solution of lactol **23** (4.60 g, 28.6 mmol) in THF (103 mL) at -78 °C. The dark brown solution was stirred at -78 °C for an additional 5 min, then warmed to room temperature and stirred for 5.5 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (40 mL). The resulting mixture was then diluted with water (40 mL), extracted with EtOAc (3x40 mL), washed with brine and dried. Concentration and purification by column chromatography (2:1 to 1:1, hexane/ethyl acetate) afforded the desired diol (3.73 g, 69%) as a clear oil, which was used in the next step without further analysis.

2,2-Dimethyl-propionic acid 5-(1-hydroxy-allyl)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester (33)



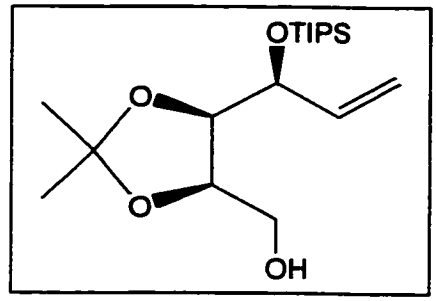
Pyridine (5.0 mL, 61.9 mmol) was added to a solution of the diol **26** (3.71 g, 19.7 mmol) in dichloromethane (100 mL) stirred at 0 °C. Pivaloyl chloride (2.7 mL, 21.9 mmol) was added to the stirring solution. The reaction mixture was allowed to warm to room temperature and stirring was continued for 10 h. The reaction was diluted with ether (250 mL), washed with water (60 mL), 2 M HCl (2x30 mL), $NaHCO_3$ (25 mL), brine and dried. Concentration and purification by column chromatography (2:1, petroleum ether/ether) afforded the desired alcohol (3.34 g, 62%) as a clear oil. ^{1}H NMR: δ 1.19 (s, 9H), 1.32 (s, 3H), 1.43 (s, 3H), 2.09 (d, J = 4.0 Hz, 1H), 4.01 (dd, J = 7.8, 5.9 Hz, 1H), 4.23 (ddd, J = 11.2, 6.4, 4.0 Hz, 2H), 4.34-4.41 (m, overlapping signals, 2H), 5.25 (d, J = 10.6 Hz, 1H), 5.35 (d, J = 17.3 Hz, 1H), 5.99 (ddd, J = 17.3, 10.8, 5.9 Hz, 1H); ^{13}C NMR: δ 25.3, 27.1, 27.6, 38.7, 63.1, 70.8, 75.5, 79.2, 108.8, 116.7, 137.5, 178.3; IR (neat) 3466, 2983, 2934, 2909, 2878, 1719, 1287, 993; HRMS (M^+-CH_3) calc'd 257.1389, found 257.1416.

2,2-Dimethyl-propionic acid 2,2-dimethyl-5-(1-triisopropylsilanyloxy-allyl)-[1,3]dioxolan-4-ylmethyl ester (27)



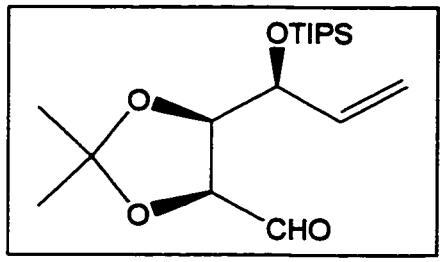
Collidine (7.5 mL, 56.7 mmol) was added to a stirred solution of the alcohol **33** (3.29 g, 12.1 mmol) in dry dichloromethane (75 mL) at 0 °C. TIPSOTf (4.5 mL, 56.7 mmol) was added dropwise via a syringe, and the mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with ether (400 mL), washed with water (100 mL), 2.0 M HCl (20 mL), brine and dried. Concentration followed by column chromatography (20:1, hexane/ethyl acetate) afforded the desired compound (3.55 g, 69%) as a clear oil. ^{1}H NMR: δ 1.02-1.08 (m, 21H), 1.20 (s, 9H), 1.32 (s, 3H), 1.43 (s, 3H), 4.05 (dd, J = 6.2, 6.2 Hz, 1H), 4.22 (dd, J = 11.5, 8.2 Hz, 1H), 4.29-4.32 (m, 1H), 4.38 (dd, J = 11.5, 2.5 Hz, 1H), 4.45-4.48 (m, 1H), 5.24 (d, J = 10.3 Hz, 1H), 5.29 (d, J = 17.2 Hz, 1H), 5.85 (ddd, J = 17.2, 10.3, 7.6 Hz, 1H); ^{13}C NMR: δ 12.7, 18.1, 18.1, 25.5, 27.2, 27.7, 38.7, 64.3, 73.5, 75.8, 79.6, 108.6, 118.0, 138.1, 178.3; IR (neat) 2942, 2868, 1732, 1480, 1381, 1283, 1160, 990, 926; HRMS (M^{+}-CH_3) calc'd 413.2723, found 413.2750. All spectroscopic data are in agreement with those previously reported.[25]

[2,2-Dimethyl-5-(1-triisopropylsilanyloxy-allyl)-[1,3]dioxolan-4-yl]-methanol (28)



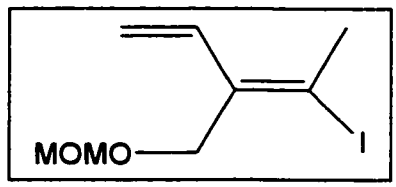
Diisobutylaluminum hydride (1.5 M in toluene, 3.3 mL, 5.0 mmol) was added dropwise at -78 °C to a stirred solution of **27** (1.00 g, 2.3 mmol) in dichloromethane (17 mL). The reaction mixture was allowed to stir for 1 h at -78 °C. The reaction was quenched by the addition of methanol (1 mL) then ether (30 mL) and allowed to warm to room temperature. The resulting solution was washed with 2.0 M HCl (20 mL), water, $NaHCO_3$, brine and dried. After concentration and column chromatography (2:1, petroleum ether/ether), the desired alcohol (0.90 g, 93%) was obtained as a clear, colorless oil. ^1H NMR: δ 1.06 (s, br, 21H), 1.33 (s, 3H), 1.44 (s, 3H), 2.77 (s, br, 1H), 3.68-3.78 (m, 2H), 4.04 (dd, J = 5.8, 5.8 Hz, 1H), 4.19 (dd, J = 11.5, 5.8 Hz, 1H), 4.57 (dd, J = 7.2, 5.8 Hz, 1H), 5.24 (d, J = 10.4 Hz, 1H), 5.29 (d, J = 17.3, 1H), 5.86 (ddd, J = 17.3, 10.4, 7.4 Hz, 1H); ^{13}C NMR: δ 12.6, 18.0, 25.6, 27.8, 61.8, 73.5, 77.7, 79.7, 108.2, 118.0, 137.7; IR (neat) 3482, 2942, 2867, 1464, 1421, 1307, 1246, 923, 882; HRMS (M^+-CH_3) calc'd 329.2149, found 329.2133. All spectroscopic data obtained support previously reported values.[21]

2,2-Dimethyl-5-(1-triisopropylsilanyloxy-allyl)-[1,3]dioxolane-4-carbaldehyde (29)



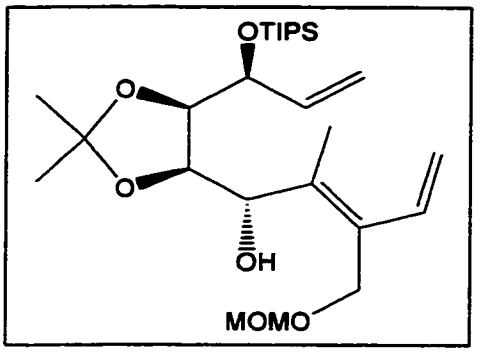
Alcohol **28** (0.77 g, 2.2 mmol) was dissolved in dichloromethane (16.6 mL) and cooled to 0 °C. Dess-Martin periodinane (1.48 g, 3.5 mmol) was added to the reaction mixture followed by $NaHCO_3$ (1.34 g). The resulting suspension was allowed to stir for 3 h after warming up to room temperature. The reaction was quenched by addition of ether (30 mL), washed with a mixture of 2.0 M $Na_2S_2O_3$ (20 mL) and saturated $NaHCO_3$ (20 mL), water, brine and dried. Concentration followed by column chromatography (2:1, petroleum ether/ether) yielded the desired aldehyde (0.71 g, 93%). ^{1}H NMR: δ 1.00-1.06 (s, br, 21H), 1.36 (s, 3H), 1.57 (s, 3H), 4.32-4.33 (m, 1H), 4.64-4.66 (m, 1H), 5.21 (d, J = 10.4 Hz, 1H), 5.25 (d, J = 17.3 Hz, 1H), 5.85 (ddd, J = 17.3, 10.4, 7.3 Hz, 1H), 9.63 (d, J = 2.8 Hz, 1H); ^{13}C NMR: δ 12.4, 17.9, 25.0, 27.0, 73.4, 80.6, 83.9, 110.4, 117.8, 137.5, 199.1; IR (neat) 2922, 2865, 1733, 1464, 1382, 1249, 1217, 1068, 997, 935, 934, 883; HRMS (M^+-CH_3) calc'd 327.1993, found 327.1986. All spectroscopic data are in agreement with those previously reported.[21]

4-Iodo-3-methoxymethoxymethyl-penta-1,3-diene (21)



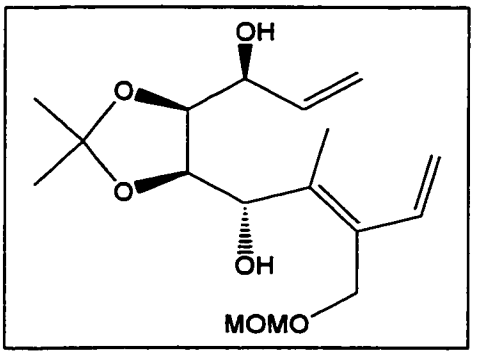
Vinylmagnesium chloride (86.0 mL, 129.0 mmol) was added to a stirred solution of 2-butyn-1-ol (3.0 g, 42.0 mmol) in cyclohexane (86 mL) at 0 °C, and the mixture was allowed to reflux overnight. I_2 (32.7 g, 128.0 mmol) in THF (40 mL) was added dropwise via an addition funnel to the resulting brown mixture at -78 °C with vigorous stirring. The reaction mixture was then slowly warmed up to room temperature and stirred for an additional 1 h. The reaction was quenched at 0 °C by the addition of saturated solution of NH_4Cl (50 mL) and 2.0 M solution of $Na_2S_2O_3$, extracted with ether (3x70 mL), washed with $Na_2S_2O_3$, brine, and dried. Concentration followed by analysis of ^1H NMR of crude alcohol shows the presence of the desired diene **36** properly quenched by I_2 and a small amount of the protonated diene **37** in a 6:1 ratio, respectively. The crude alcohol was re-dissolved in CH_2Cl_2 (160 mL) and cooled to 0 °C. Freshly distilled $^iPr_2EtN$ (20.0 mL, 115.0 mmol) was added to the reaction mixture, followed by the addition of MOMCl (10.0 mL, 131.7 mmol), and the reaction stirred at room temperature over night. The reaction was quenched at 0 °C with saturated solution of $NaHCO_3$ (60 mL), and stirred for an additional 0.5 h. The resulting mixture was extracted with CH_2Cl_2 (3x50 mL), dried then concentrated. Purification by column chromatography (95:5, petroleum ether/ether) afforded the desired protected alcohol along with the corresponding protonated diene (3.0 g in total yield, 26%) as a yellow oil. ^1H NMR: δ 2.71 (s, 3H), 3.41 (s, 3H), 4.45 (s, 2H), 4.66 (s, 2H), 5.23 (d, J = 11.2 Hz, 1H), 5.46 (d, J = 17.3 Hz, 1H), 6.66 (dd, J = 11.2, 17.3 Hz, 1H); ^{13}C NMR: δ 31.0, 55.6, 73.2, 96.2, 106.9, 116.1, 129.7, 138.5; IR (neat) 2936, 2878, 2813, 1150, 1102, 915; HRMS unstable.

1-[2,2-Dimethyl-5-(1-triisopropylsilanyloxy-allyl)-[1,3]dioxolan-4-yl]-3-methoxymethoxymethyl-2-methyl-penta-2,4-dien-1-ol (30)



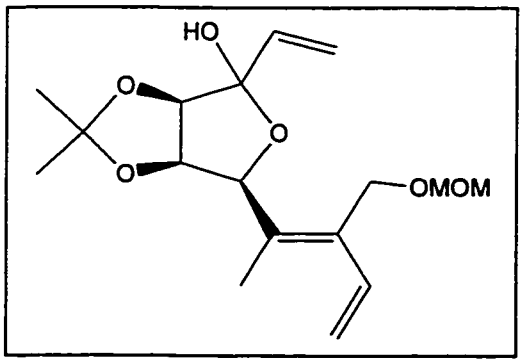
Tert-butyllithium (9.5 mL, 14.3 mmol) was added to THF (90 mL) at -78 °C, followed by dropwise addition of a solution of the iododiene **21** (2.14 g, 8.0 mmol) in THF (8 mL). The resulting mixture was stirred for an additional 15 min. A solution of the aldehyde **29** (1.20 g, 3.5 mmol) in THF (10 mL) was slowly added to the organolithium mixture. After 10 min, the reaction was quenched with a saturated solution of $NaHCO_3$ (15 mL), diluted with ether (100 mL), washed with water (20 mL), NH_4Cl (25 mL), brine and dried. Concentration followed by flash column chromatography afforded the desired product which was used without further purification.

1-[5-(1-Hydroxy-allyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-3-methoxymethoxymethyl-2-methyl-penta-2,4-dien-1-ol (20)



Tetra-*n*-butylammonium fluoride (1.0 M, 2.8 mL, 2.8 mmol) was added to a solution of the alcohol **30** (0.88 g, 1.8 mmol) in THF (18 mL) at 0 °C. The reaction mixture was allowed to stir for 45 min. The reaction was quenched with NH_4Cl (10 mL), extracted with ether (100 mL), washed with water (30 mL), brine, dried and concentrated. Purification by column chromatography (1:1, petroleum ether/ether) afforded the desired product (0.72 g, 79%) as a clear oil. ^1H NMR: δ 1.33 (s, 3H), 1.53 (s, 3H), 1.91 (s, 3H), 3.11 (s, br, 1H), 3.37 (s, 3H), 4.02 (dd, J = 7.6, 6.5 Hz, 1H), 4.19 (dd, J = 6.4, 2.2 Hz, 1H), 4.27 (d, J = 11.4 Hz, 1H), 4.31 (d, J = 11.4 Hz, 1H), 4.50-4.55 (m, 1H), 4.61 (s, 2H), 5.12 (s, br, 1H), 5.18 (d, J = 11.2 Hz, 1H), 5.25 (d, J = 10.6 Hz, 1H), 5.40 (d, J = 17.6 Hz, 1H), 5.44 (d, J = 17.2 Hz, 1H), 6.02 (ddd, J = 17.3, 10.6, 5.1 Hz, 1H), 6.70 (dd, J = 17.4, 11.2 Hz, 1H); IR (neat) 3421, 2985, 2934, 1458, 1381, 1216, 1148, 1029, 918, 875. All spectroscopic data are identical to those previously reported.[25]

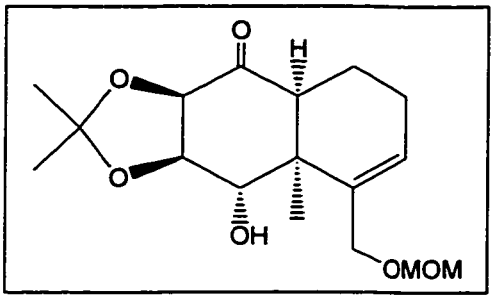
6-(2-Methoxymethoxymethyl-1-methyl-buta-1,3-dienyl)-2,2-dimethyl-4-vinyl-tetrahydro-furo[3,4-*d*][1,3]dioxol-4-ol (31)



Diol **20** (0.72 g, 2.2 mmol), dissolved in dry dichloromethane (30 mL), was treated with activated manganese dioxide (0.91 g, 10.5 mmol) at room temperature. The reaction mixture was allowed to stir overnight. Filtration followed by concentration and column chromatography (1:1, petroleum

ether/ether) afforded the desired lactol (0.459 g, 64%) as a colorless oil. ^{1}H NMR: δ 1.24 (s, 3H), 1.44 (s, 3H), 1.94 (s, 3H), 2.36 (s, 1H), 3.37 (s, 3H), 4.25 (d, J = 11.5 Hz, 1H), 4.33 (d, J = 11.5 Hz, 1H), 4.50 (d, J = 5.8 Hz, 1H), 4.61 (d, J = 1.7 Hz, 2H), 4.86 (dd, J = 5.8, 4.1 Hz, 1H), 5.16-5.19 (m, 2H), 5.36 (dd, J = 10.7, 1.3 Hz, 1H), 5.41 (d, J = 17.4 Hz, 1H), 5.59 (dd, J = 17.4, 1.3 Hz, 1H), 6.11 (dd, J = 17.4, 10.7 Hz, 1H), 6.75 (dd, J = 17.4, 11.2 Hz, 1H); ^{13}C NMR: δ 15.1, 24.0, 25.6, 55.5, 61.9, 78.4, 83.4, 86.2, 95.4, 103.8, 112.5, 114.5, 117.3, 130.2, 134.1, 136.5, 136.7; IR (neat) 3403, 2991, 2938, 2888, 1381, 1271, 1210, 1095, 989, 885; HRMS (M^+-CH_3) calc'd 311.1495, found 311.1518. All spectroscopic data are in agreement with those previously reported.[25]

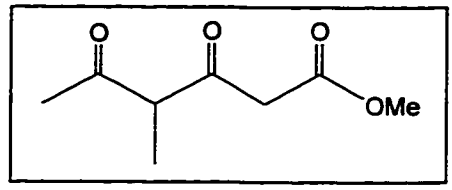
9-Hydroxy-8-methoxymethoxymethyl-2,2,8a-trimethyl-4a,5,6,8a,9,9a-hexahydro-3a*H*-naphtho[2,3-*d*][1,3]dioxol-4-one (18)



Lactol **31** (0.46 g, 1.4 mmol) was dissolved in acetonitrile (5.8 mL) and heated to 75-78 °C for 71 h. After concentration and column chromatography (2:1, hexane/ethyl acetate), the desired decalin (0.26 g, 57%) was obtained as a clear oil, along with recovered starting material (0.15 g, 33%). ^{1}H NMR: δ 1.22 (s, 3H), 1.35 (s, 3H), 1.45 (s, 3H), 1.71-1.78 (m, 1H), 2.03-2.14 (m, 2H), 2.31-2.38 (m, 1H), 2.45 (dd, J = 8.4, 3.9 Hz, 1H), 3.37 (s, 3H), 3.93 (d, J = 6.4 Hz, 1H), 3.99 (d, J = 11.4 Hz, 1H), 4.08 (s, br, 1H), 4.15 (d, J = 11.4 Hz, 1H), 4.39-4.44 (m, 2H), 4.61 (d, J = 6.5 Hz, 1H), 4.65 (d, J = 6.5 Hz, 1H), 5.85 (t, J = 3.7 Hz,

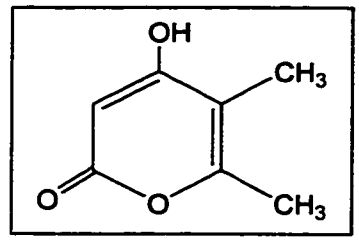
1H); ^{13}C NMR: δ 20.8, 21.7, 24.0, 25.4, 27.3, 42.2, 53.0, 55.8, 69.4, 74.5, 77.3, 79.3, 95.3, 110.7, 131.9, 137.4, 207.8; IR (neat) 3448, 2931, 1725, 1463, 1375, 1240, 924; HRMS (M^+) calc'd 326.1729, found 326.1706. All spectroscopic data obtained support previously reported values.[25]

4-Methyl-3,5-dioxo-hexanoic acid methyl ester (50)



A solution of lithium 1,1,1,3,3,3-hexamethyldisilazide was prepared as follows: 1,1,1,3,3,3-hexamethyldisilazane (17 mL, 80.5 mmol) was added to *n*-butyllithium (2.3 M hexane solution, 35 mL, 84.0 mmol) in THF (60 mL) at -78 °C. 3-Methylpentane-2,4-dione (**48**) (3.0 g, 26 mmol) was added to the cold solution and the mixture was allowed to warm to room temperature and stir for 4 h. The reaction mixture was re-cooled to -78 °C at which dimethyl carbonate (**49**) (2.3 mL, 27.3 mmol) was added. The mixture was then warmed to room temperature and allowed to stir overnight. A yellow precipitate was observed in the reaction flask, which, upon quenching the reaction with HCl (3 mL), disappeared. The reaction was then diluted with EtOAc, dried and concentrated. Purification by column chromatography (4:1 to 1:1, petroleum ether/ether) afforded the desired product (2.6 g, 58%) as a yellow oil with spectroscopic properties identical to those reported.[28]

4-Hydroxy-5,6-dimethyl-pyran-2-one (19)



The keto-ester **50** (1.0 g, 5.8 mmol) was added to a pH 10 buffer (Aldrich, 100 mL) and stirred at room temperature overnight. Drops of 10% HCl solution were added to the reaction until it was acidic by litmus paper. The resulting solution was extracted with EtOAc, concentrated, and recrystallized from chloroform to afford the desired pyrone (0.35 g, 43%) as a white solid. ^{1}H NMR (acetone-d_6/$CDCl_3$): δ 1.86 (s, 3H), 2.16 (s, 3H), 5.39 (s, 1H), 10.41 (s, br, 1H); ^{13}C NMR: δ 9.9, 17.8, 90.2, 159.5, 165.4, 171.1, 206.9; m.p. 200-201 °C (lit.[28] 204-206°C); HRMS (M^+) calc'd 140.0473, found 140.0471. All spectroscopic data obtained support previously reported values.[28]

Attempts to Remove the MOM Group in Decalin 18:

A. Using Trifluoromethanesulfonic Acid

Decalin **18** (32 mg, 0.098 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. Trifluoromehtanesulfonic acid (10% v/v, 3 mL) was added dropwise to the cold solution and stirred for 5 min while monitored by TLC (4:1 ethyl acetate/hexane). Two new spots were observed and no trace of starting material remained. The reaction mixture was extracted with ether (2x5 mL), washed with $NaHCO_3$ (5 mL), H_2O (5mL), brine and dried. The solution was concentrated and the products were separated by preparative TLC (4:1 ethyl

acetate/hexane). Analysis of the ^{1}H NMR of each spot revealed that the MOM group was not successfully removed from decalin **18**.

B. Using Pyridinium *p*-Toluenesulfonate

Pyridinium *p*-toluenesulfonate (0.01 g, 0.04 mmol) was added to a solution of the decalin **18** (50 mg, 0.15 mmol) in *t*-butanol (5 mL). The reaction mixture was then heated to reflux for 5 h. The reaction was allowed to cool to room temperature, washed with $NaHCO_3$ (2x5 mL), H_2O (7 mL), and dried. Four new spots were visible on the TLC plate beside the starting material spot. Separation of the products by preparative TLC (4:1 ethyl acetate/hexane) and subsequent analysis of the ^{1}H NMR spectra indicated that the new spots seen on the TLC plate were either decomposed material (major spots), or contained minute amount of material insufficient for any proper structural assignments.

C. Using Trifluoroboron Etherate

Dimethyl sulfide (1.0 mL, 13.6 mmol) was added to a stirred solution of the decalin **18** (50 mg, 0.15 mmol) in dichloromethane (2.0 mL) stirred at 0 °C. Trifluoroboron etherate (0.07 mL, 0.55 mmol) was then added dropwise to the cold solution. After stirring for 40 min, there was no trace of the starting material on the TLC plate. The reaction was then warmed to room temperature, washed with solid $NaHCO_3$, H_2O (1 mL), and dried. A total of 5 new spots were observed on the TLC plate. After separation by preparative TLC (4:1 ethyl acetate/hexane), the ^{1}H NMR spectra indicated that the major spot (has higher R_f value than SM) was decomposed material, while no conclusions were possible for the minor spots (have smaller R_f values than SM).

D. Using Trimethylsilyl Iodide

Sodium iodide (96.6 mg, 0.64 mmol) was added to a stirred solution of the decalin **18** (45 mg, 0.13 mmol) in dichloromethane (3.0 mL) at room temperature. The solution turned yellow. The reaction mixture was cooled to 0 °C and trimethylsilyl chloride (0.09 mL, 0.71 mmol) was added dropwise. The reaction was allowed to stir for an additional 3 h while monitoring by TLC (4:1 ethyl acetate/hexane). Many overlapping spots were observed on the TLC plate (total of approximately 8 spots). The reaction was quenched by the slow addition of H_2O (10 mL), extracted with ethyl acetate (2x5 mL), washed with H_2O (5 mL), $Na_2S_2O_3$ (5 mL), dried and concentrated. A dark brown solid was left in the flask. The crude mixture was checked again on a TLC plate revealing too many minor spots. No further separations were performed.

Claims to Original Research

1. A novel first attempt to synthesize a subglutinol analogue by constructing the decalin system **18** was investigated.
2. The general utility of the magnesium mediated carbometallation of propargyl alcohols has been established and its application to construct the IMDA precursor **20** has been demonstrated.
3. The highly substituted decalin system **18** was prepared *via* an IMDA reaction with high stereoselectivity and provided additional evidence of the versatility of this strategy.
4. A noteworthy feature is the role of the *cis*-isopropylidene tether control group, which allowed the incorporation of an "inside" vinyl methyl group in the IMDA reaction. This chemistry is impossible on open chain systems, which rotate freely.

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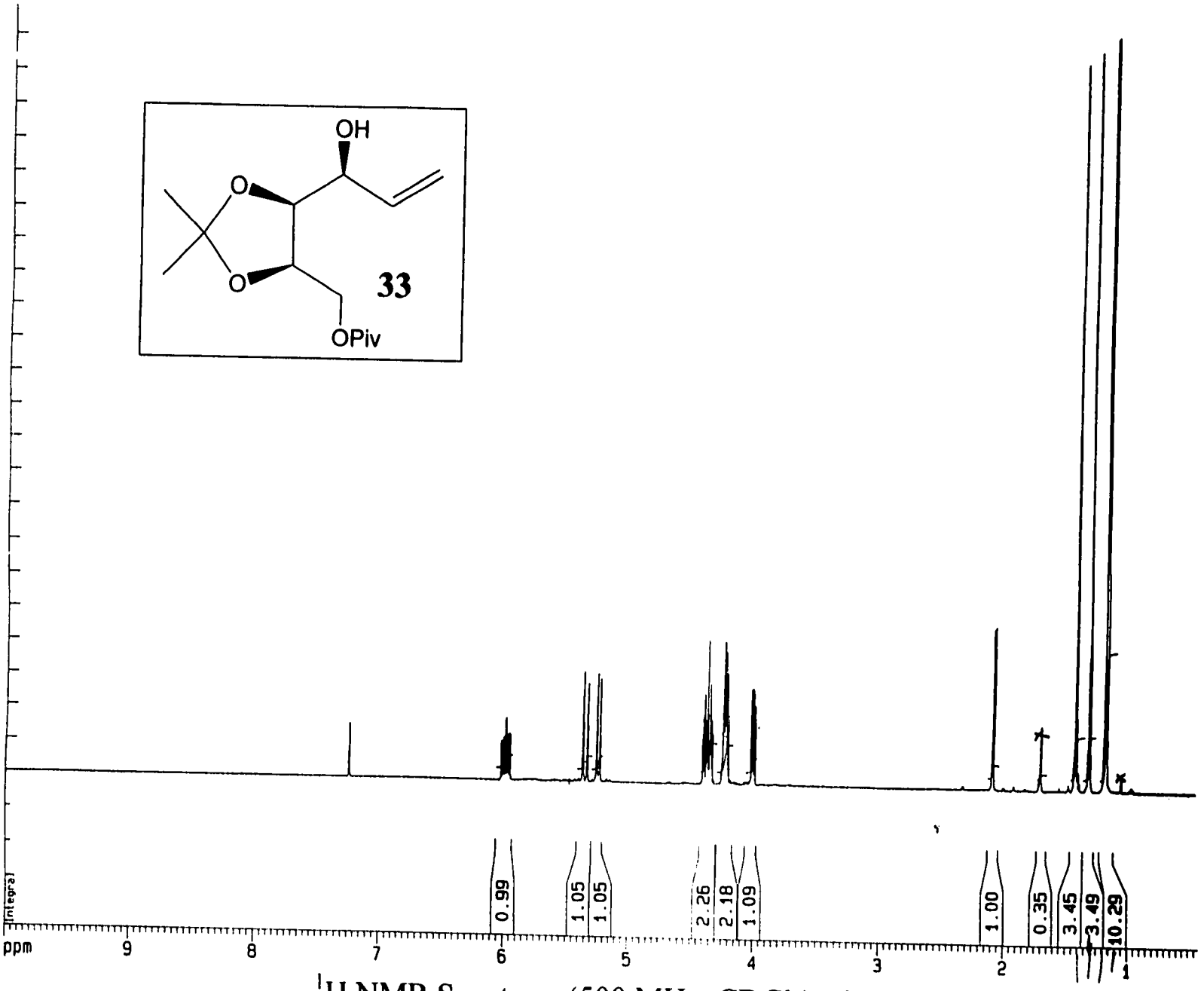
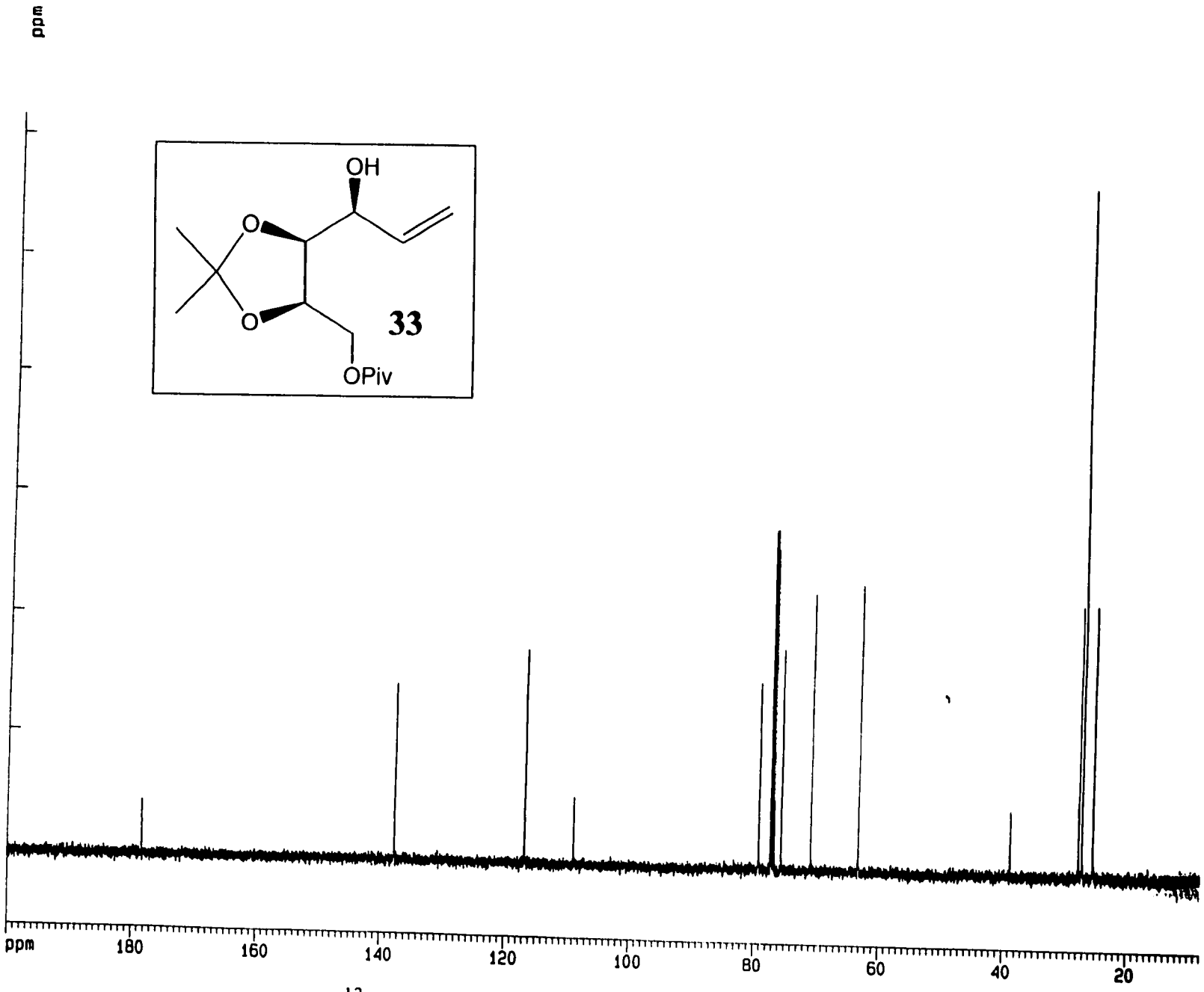
Appendix I

Selected Spectra



^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of **33**



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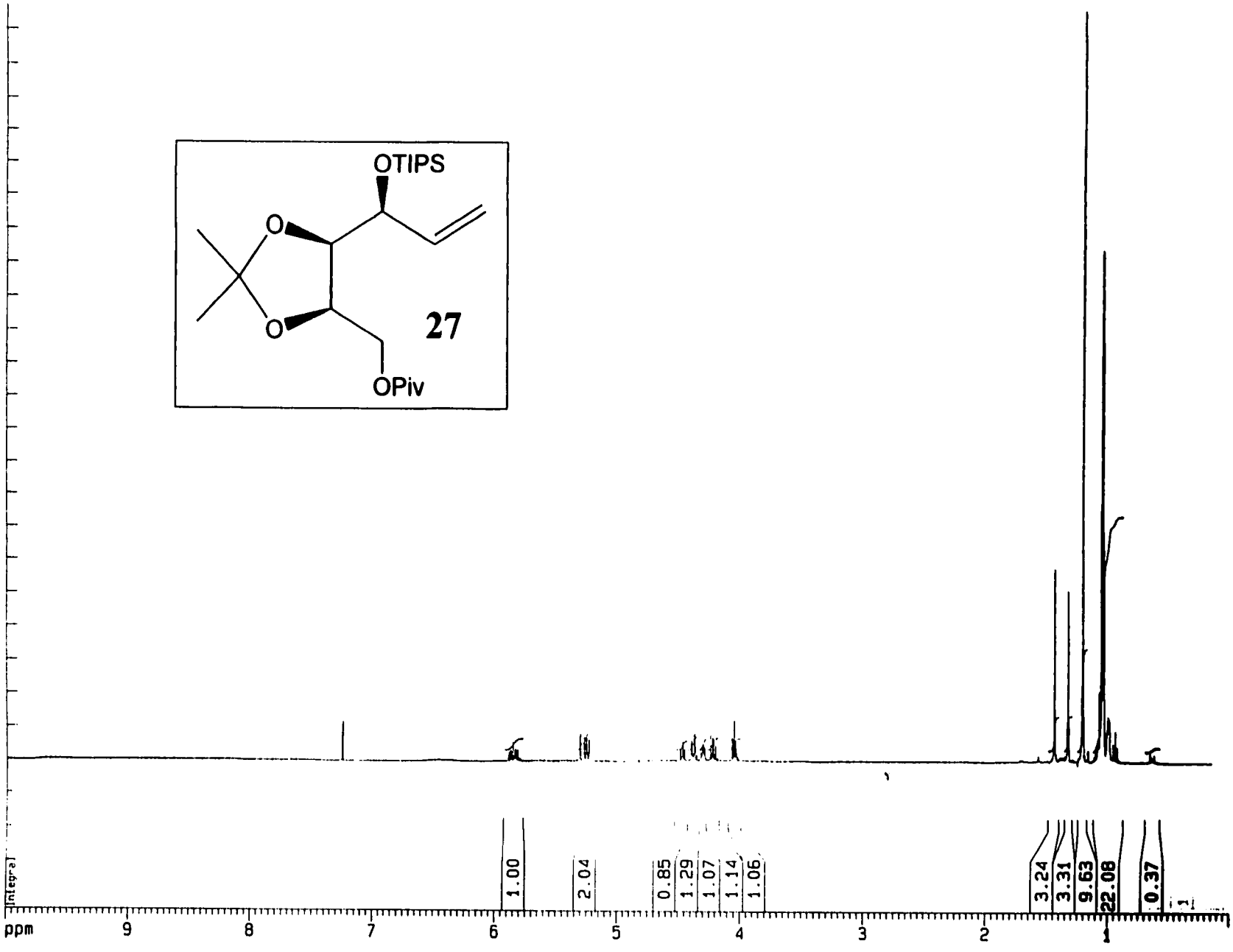

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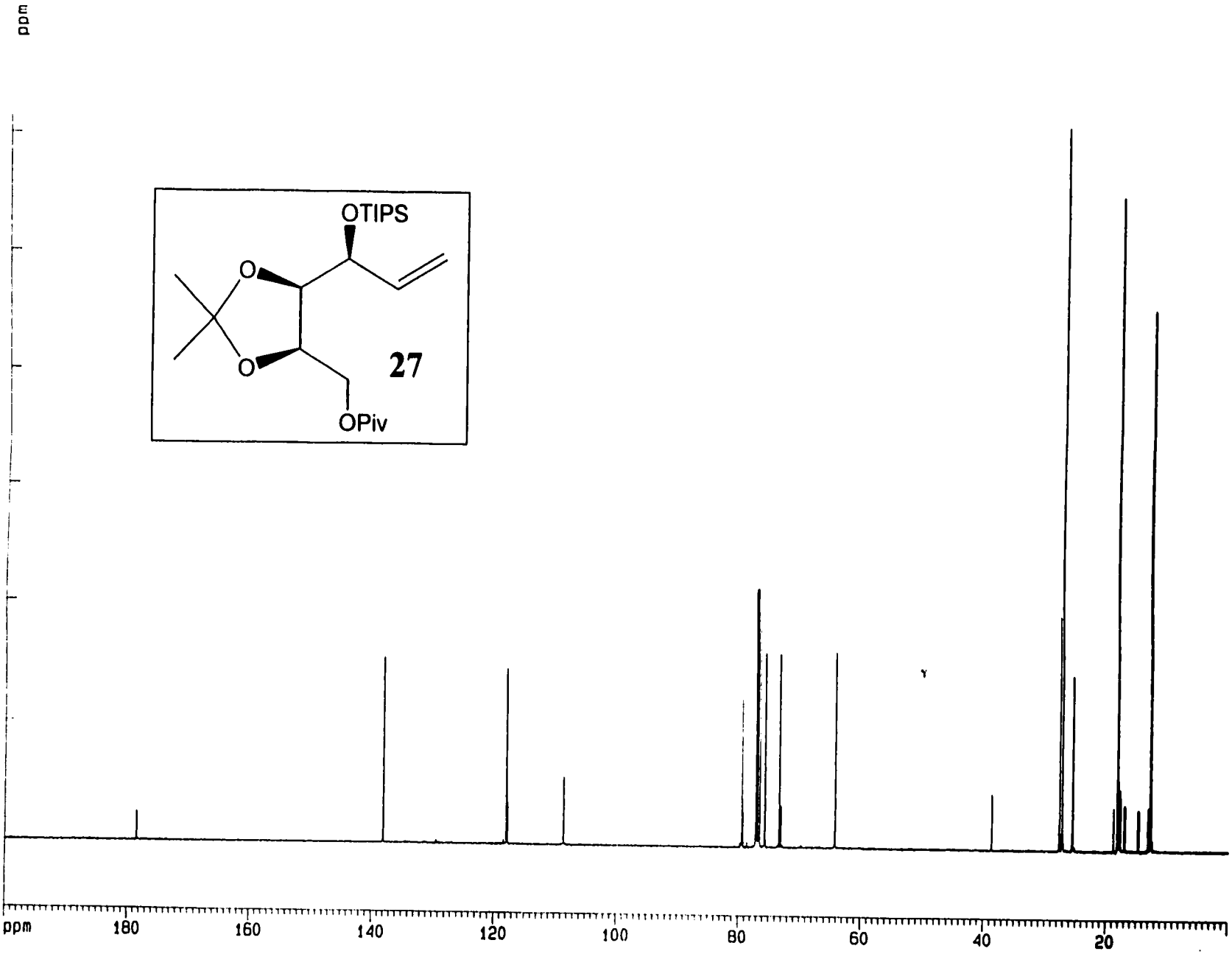

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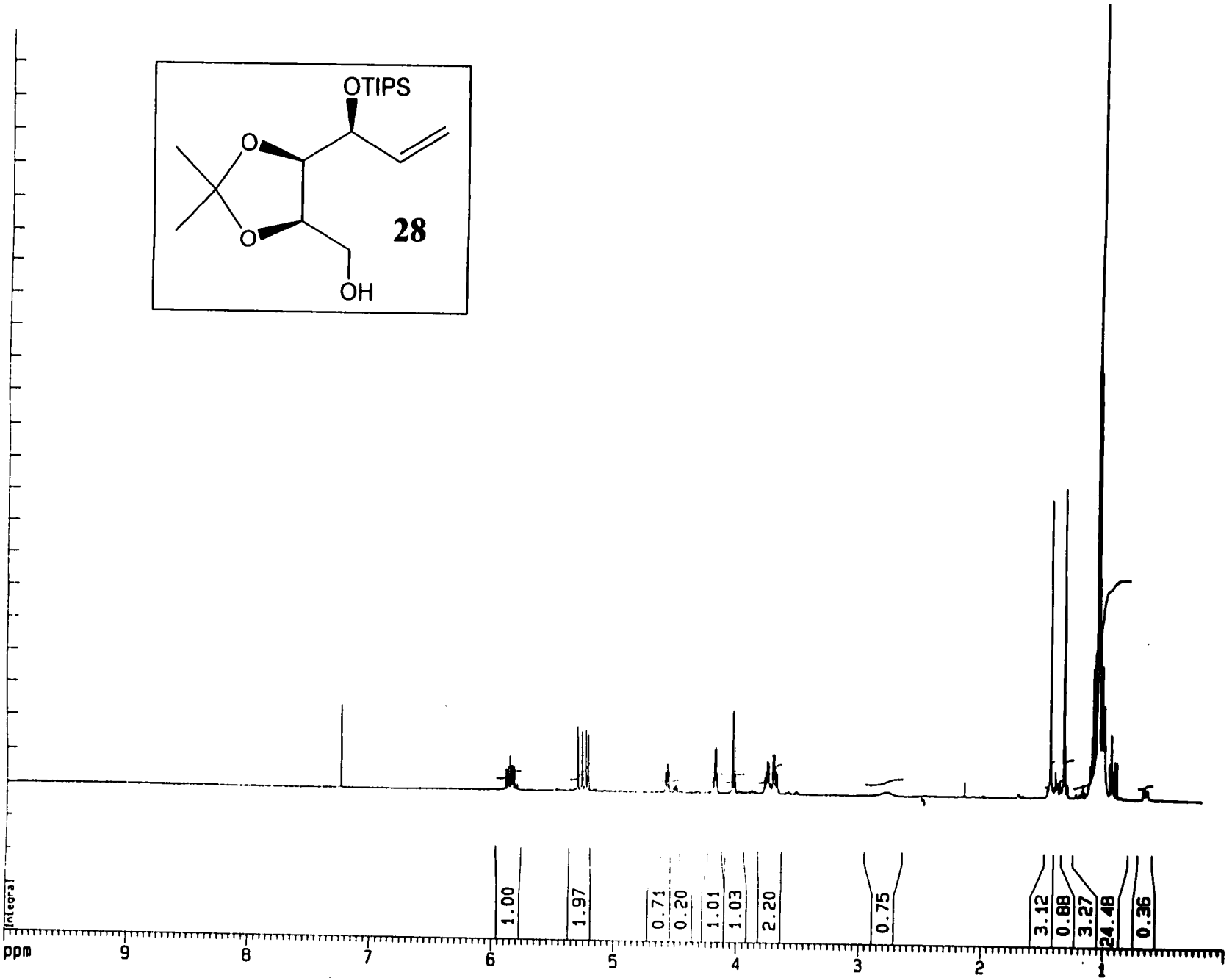

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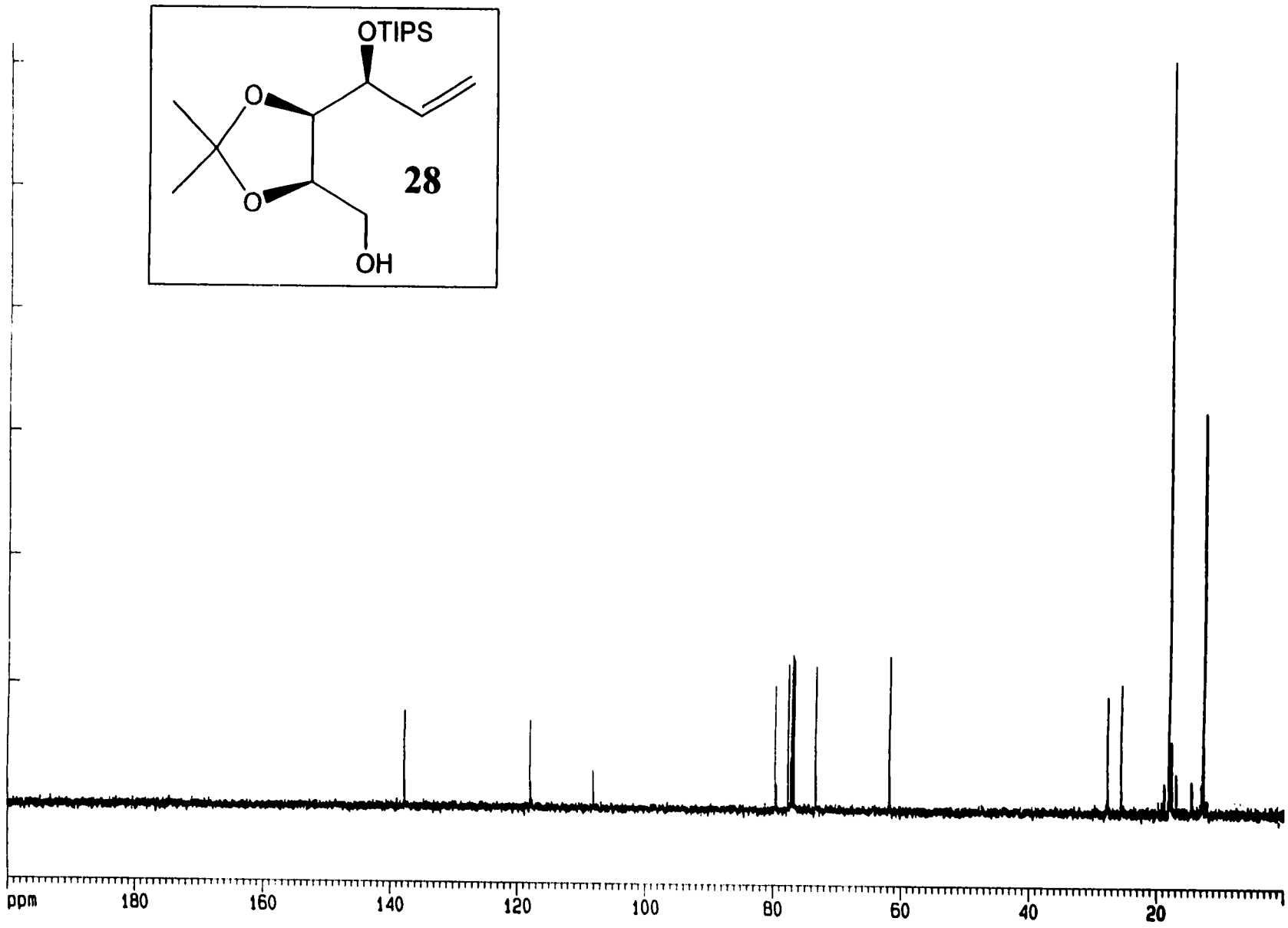

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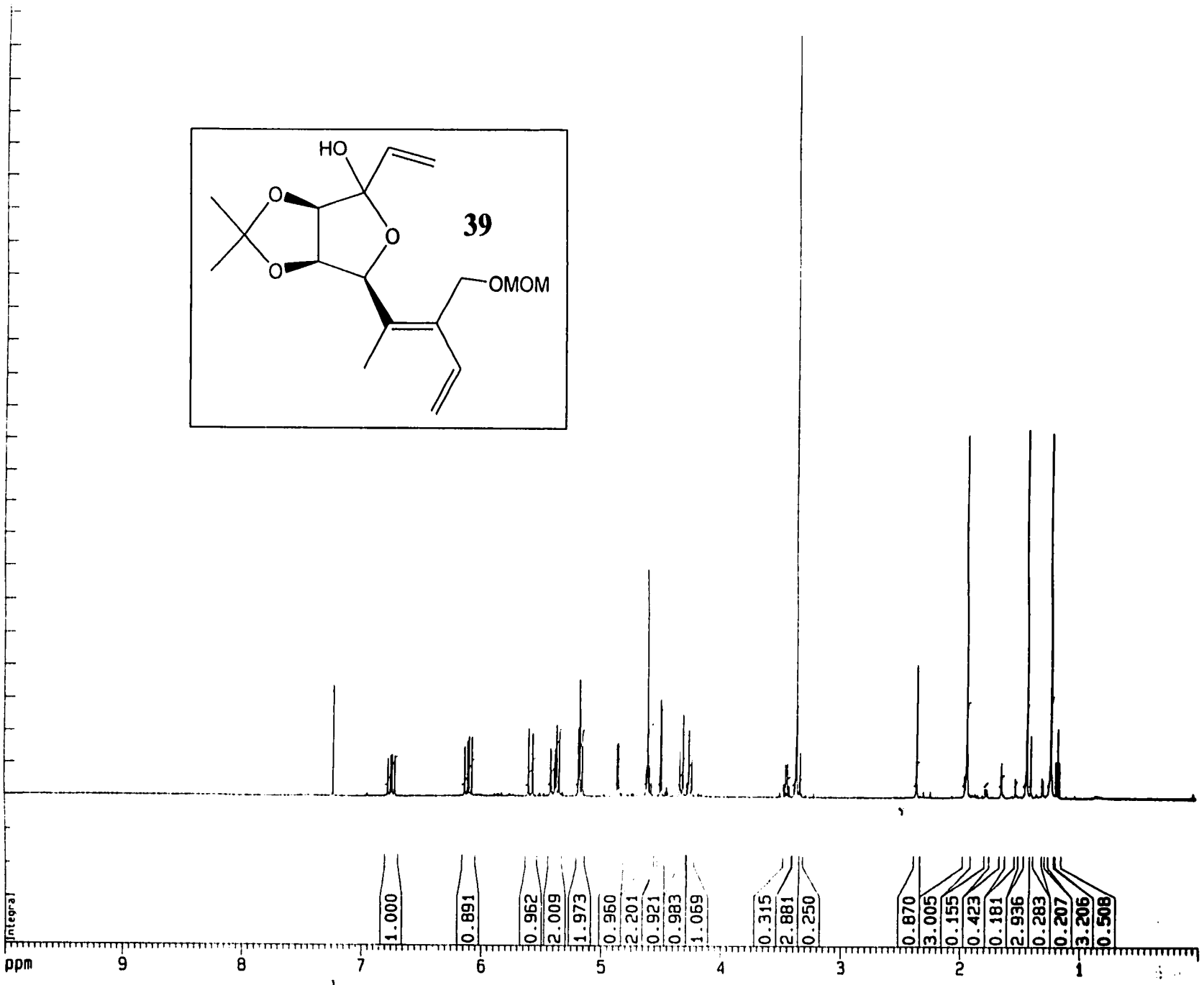

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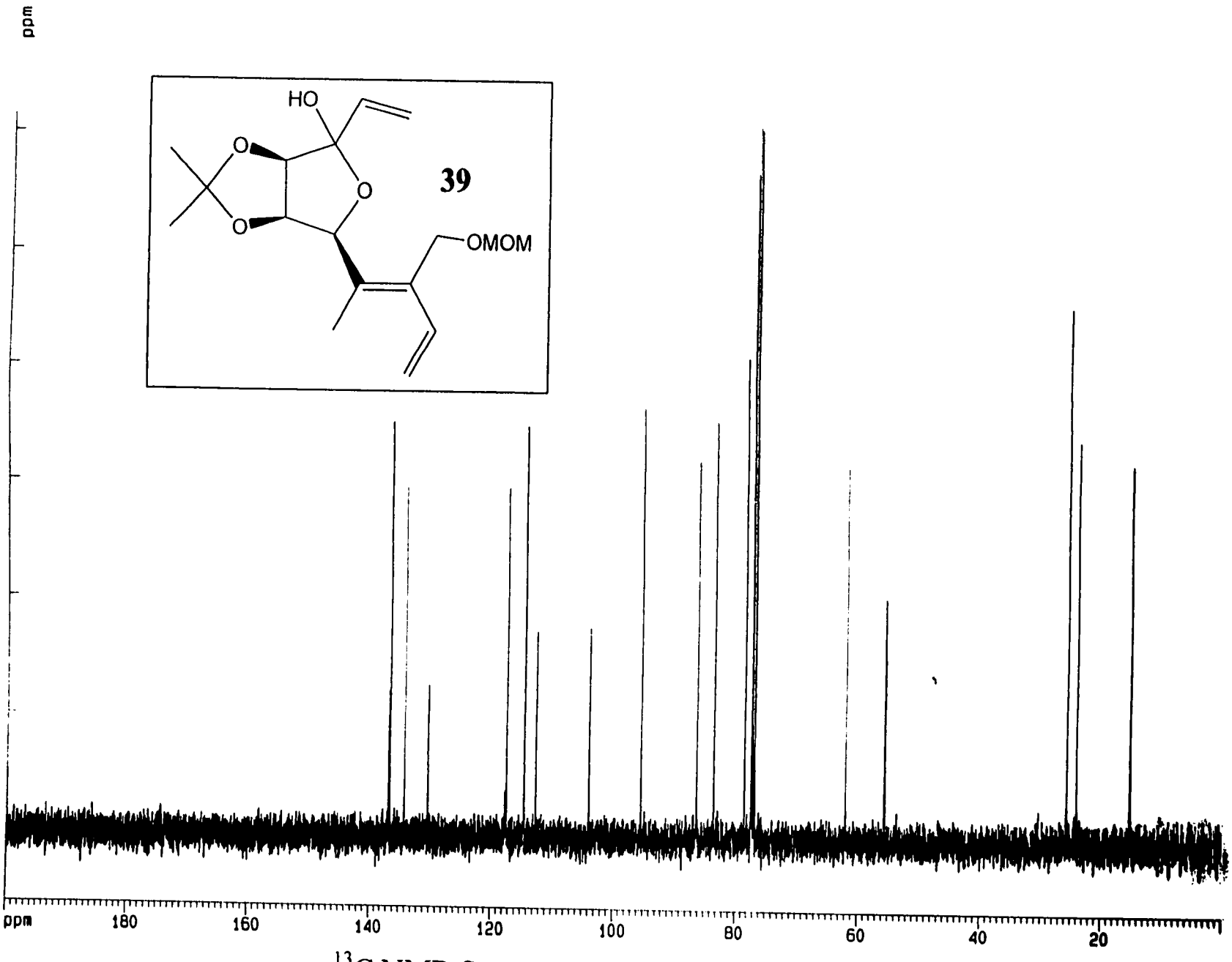

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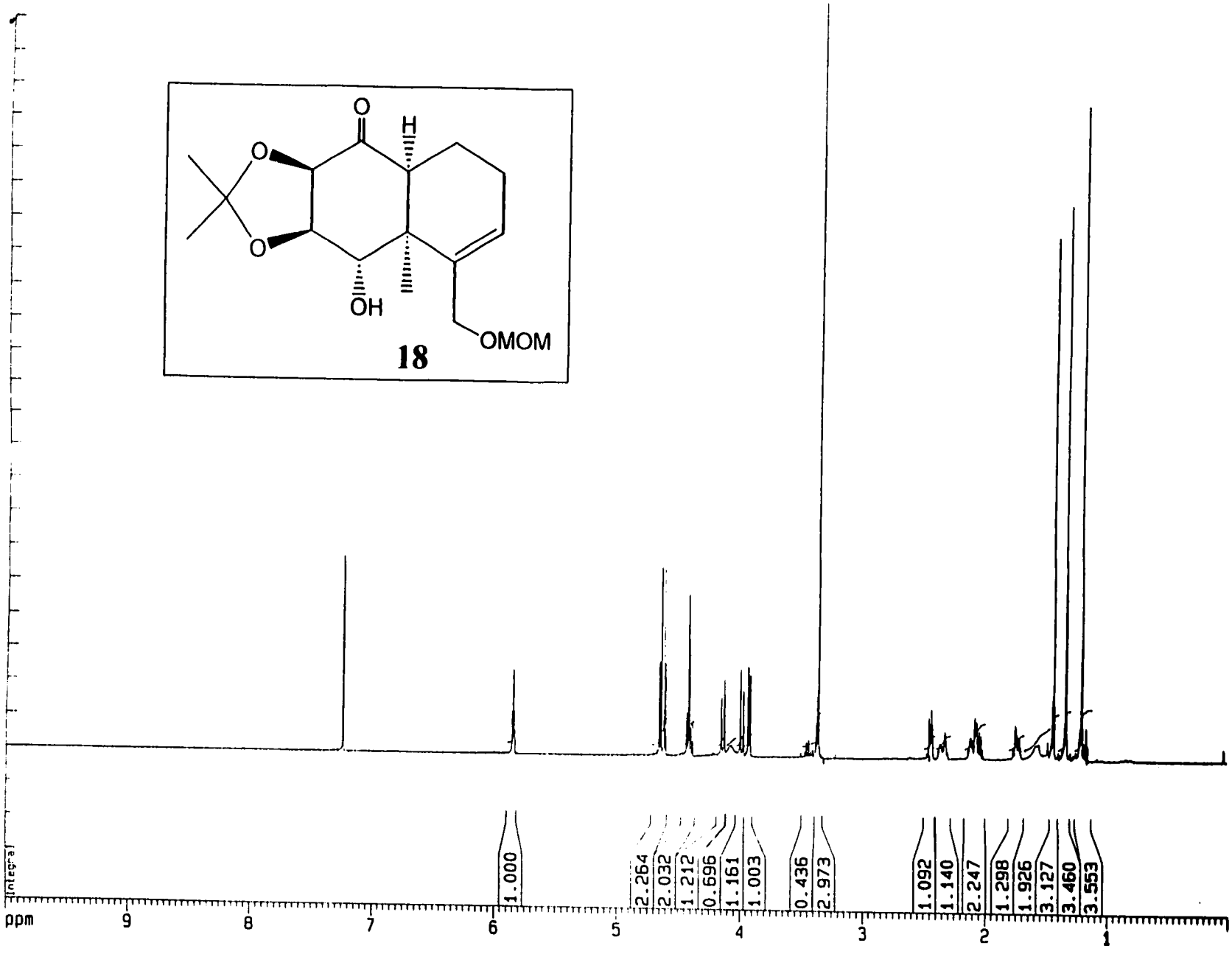
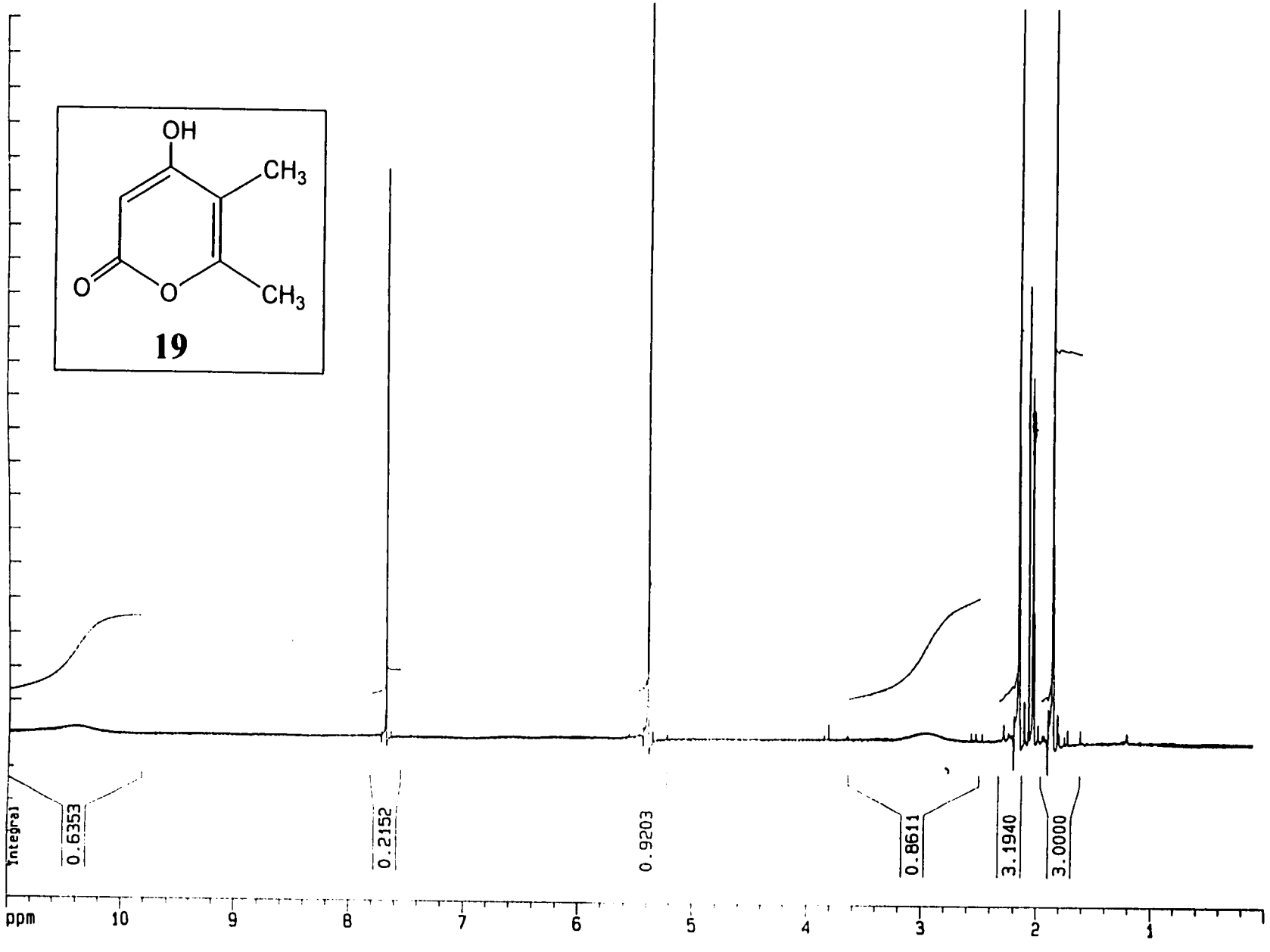


^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of **18**

^{13}C NMR Spectrum (125 MHz, $CDCl_3$) of **18**



^{1}H NMR Spectrum (500 MHz, acetone-d_6/$CDCl_3$) of **19**