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Attempted Enantioselective Total Synthesis of Podophyllotoxin

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Abstract

An enantioselective approach via an intramolecular Diels-Alder reaction to the total synthesis of podophyllotoxin, an antimitotic lignan, is described. The two requisite synthons, an *o*-quinodimethane precursor, and a chiral tether/dienophile derived from tartrate, were efficiently synthesized, but all attempts at effecting the convergent etherification step failed, likely due to a lack of nucleophilicity of the tartrate-derived primary alcohol. Very reproducible synthetic sequences were developed for the synthesis of a number of different chiral potential tether/dienophile molecules based on tartrate, but connection of these molecules to the diene precursor was never successful.

Also described is some investigative work into the synthesis and use in synthesis of diaryl phosphonates as (*Z*)-selective Horner-Wadsworth-Emmons olefination reagents. An efficient synthesis of alkyl diphenyl phosphites and the success of subsequent Arbuzov reactions of these phosphites with halides has led to the synthesis of a number of new olefination reagents, for which evaluation of the (*Z*)-selectivity is ongoing.

Contents

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Abbreviations

DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
THF	tetrahydrofuran
*n*BuLi	*n*-butyllithium
LDA	lithium diisopropyl amide
LHMDS	lithium hexamethyldisilazide
TMS	trimethylsilyl
TBS	*t*-butyldimethylsilyl
TBAF	tetrabutylammonium fluoride
CSA	camphorsulfonic acid
p-TsOH	*p*-toluenesulfonic acid monohydrate
p-TsCl	*p*-toluenesulfonyl chloride
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
TPAP	tetrapropylammonium perruthenate
NMO	*N*-methyl-morpholine-*N*-oxide
TEMPO	2,2,6,6-tetramethyl piperidinyl-*N*-oxide
DCC	dicyclohexylcarbodiimide
DMAP	*N,N*-dimethylaminopyridine
DEAD	diethylazodicarboxylate
DPPA	diphenyl phosphoryl azide
HWE	Horner-Wadsworth-Emmons
AD-mix	Asymmetric Dihydroxylation mixture
Me	methyl
Et	ethyl
Ph	phenyl

EWG	electron withdrawing group
NMR	nuclear magnetic resonance
IR	infrared
EI-MS	mass spectrum - electron ionization
TLC	thin layer chromatography

Part 1

Introduction

Chapter 1

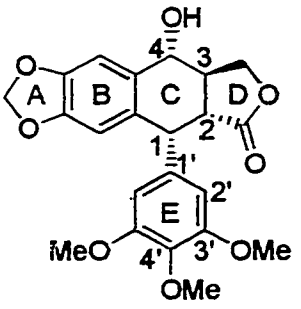
A Brief History of Podophyllotoxin, its Origin, Chemistry, and Biological Activity

1.1 Early Uses, Isolation, and Determination of Structure

The May Apple, or American mandrake, known as *Podophyllum peltatum*, has long been known for its medicinal properties. North American Indians knew its extracts to have anthelmintic and cathartic uses, as well as activity as a poison. North American colonists used the podophyllin extracted from the roots of the May Apple as an emetic, and as a result it was included in the US Pharmacopoeia from 1820 to 1942[1]. It was then removed due to its severe toxicity. At about the same time, podophyllin in oil was discovered to be an effective treatment for venereal warts, and shortly afterward, in 1946, the biological activity of podophyllin was found to be due to an antimitotic mode of action[1].

In 1835, the resin from the roots of the May Apple was found to have a high concentration of the biologically active component. The compound, of still unknown structure, was isolated and named podophyllotoxin in 1880[1]. The better part of a century later, in 1956, the structure and absolute configuration of podophyllotoxin were proposed

by Hartwell and Schrecker[2]. Finally, in 1973, the X-ray structure of 2'-bromopodophyllotoxin was solved[3] and confirmed that Hartwell's assignment of absolute stereochemistry as [1R, 2R, 3R, 4R] to the tetracyclic compound was in fact correct, and thus podophyllotoxin is properly depicted as **1**.



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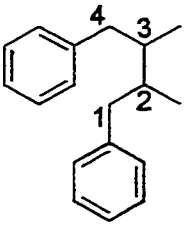


2

In the late 1960s, glycosides of podophyllotoxin were used in cancer chemotherapy, resulting in a renewed interest in this and other related lignans and their derivatives. Lignans are a class of natural products that contain a 2,3-dibenzyl butane moiety as exemplified by **2**. The carbon skeleton of podophyllotoxin is entirely composed of this structural unit, as can be seen by comparing structures **1** and **2**. Many lignans have biological activity, and with the advent of these anti-cancer podophyllotoxin derivatives, there arose a significant interest in devising methods of synthesis of these potentially medicinally useful compounds, and analogs thereof.

Key structural features of the podophyllotoxin molecule include the four contiguous stereocenters around the tetrahydronaphthalene ring, and the *trans*-fused 5-membered

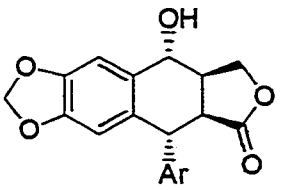
lactone which accounts for two of these stereocenters. The pendant C1 trimethoxyaryl ring E, which is *cis* relative to the lactone carboxylate, is forced to lie nearly perpendicular to the plane of the other rings, as it adopts a pseudoaxial position. Lastly, the C4 benzylic hydroxyl group accounts for the fourth chiral center.

1.2 Chemistry of Podophyllotoxin and its Isomers

Podophyllotoxin's *trans*-fused CD ring junction, which results in a considerable amount of strain on the ring system, as well as the axial position of the E aryl ring, impart on the molecule a propensity to isomerize at C2 via its ester enolate. In fact, treatment of the natural product with weak base such as sodium acetate in ethanol[4] delivers the isomeric picropodophyllotoxin, with its more stable *cis*-fused lactone, in nearly quantitative yield. This has naturally been a significant challenge to overcome in synthetic attempts at podophyllotoxin, as any base-mediated steps after installation of the stereocenters will likely isomerize C2 to the undesired picro configuration.

Several other isomers of podophyllotoxin are known, but, with the exception of epipodophyllotoxin, they generally show little, if any, biological activity. While picropodophyllotoxin (**3**) is epimeric at C2, epipodophyllotoxin (**4**) is epimeric at C4, epiisopodophyllotoxin (**5**) is epimeric at both C1 and C4, and neopodophyllotoxin (**6**) has the correct configuration at all centers, but has an isomeric lactone involving the benzylic oxygen. All of these isomers have been converted into the biologically active

podophyllotoxin, so any total synthesis of these isomers does constitute a formal total synthesis of the medicinally useful lignan[5].



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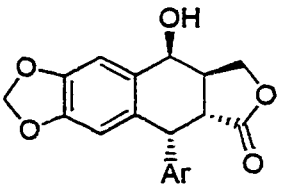

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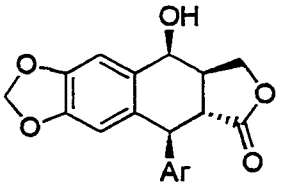

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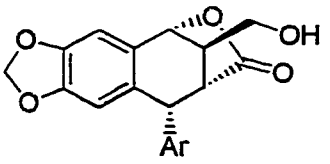


6

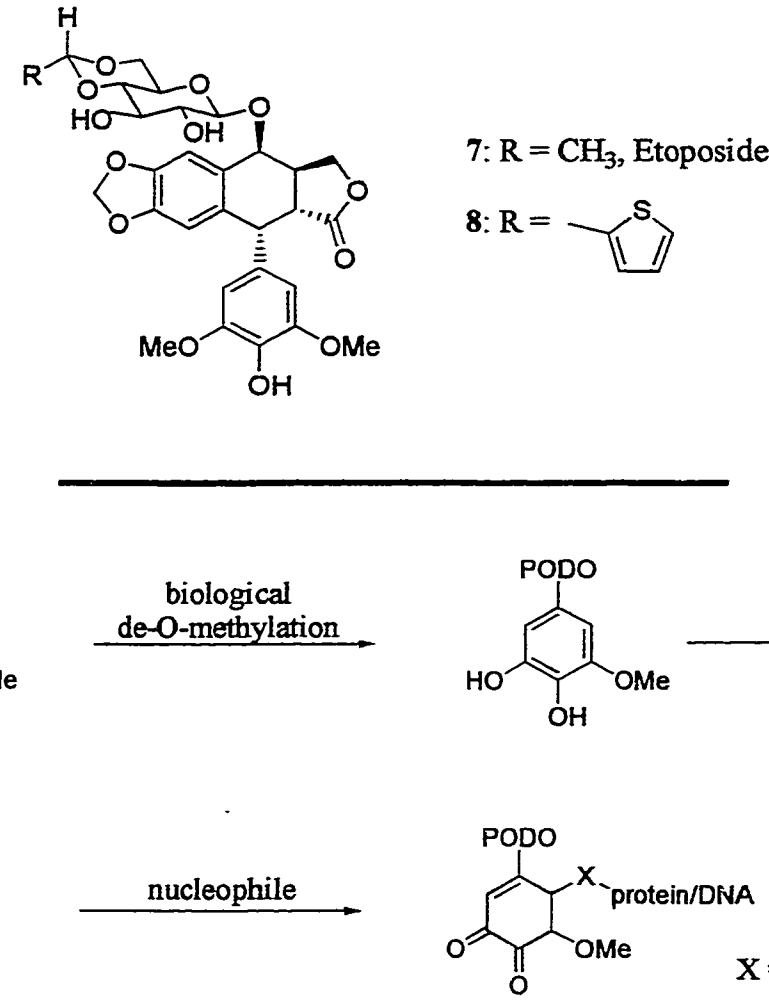
Ar = 3,4,5-trimethoxyphenyl here and in all schemes and figures in this thesis, unless otherwise noted.

1.3 Biological Activity of Podophyllotoxin and its Derivatives

Podophyllum, the crude extract of *P. peltatum*, has been used as a cathartic[6], but in resin form, called podophyllin, is too concentrated and therefore too caustic to be used internally. It has veterinary use as a topical caustic agent for warts[6]. Podophyllotoxin itself has been used as a topical antiviral[6], especially in the treatment of genital warts. Otherwise, its cytotoxicity has not often been taken advantage of clinically since its

therapeutic index is very low, that is its overall toxicity is much too high relative to its potential antitumour effects that could be derived from its cytotoxicity. This is a problem with most cancer chemotherapeutic agent candidates. This cytotoxicity is derived from its antimitotic activity, which is in turn is due to the lignan's tubulin binding properties. In binding to tubulin, and also depolymerizing microtubules, the lignan prevents mitotic cell division, and is therefore especially toxic to fast growing tissues such as tumours and warts. Podophyllotoxin is therefore known as a spindle poison and has a similar mode of action to colchicine, vinblastine and vincristine. Analogs and derivatives were and still are being synthesized in order to try to maximize the therapeutic index, that is to minimize the toxic side effects while retaining the cytotoxicity. Two useful derivatives of podophyllotoxin have resulted and have been used clinically. These are Etoposide (**7**) and Teniposide (**8**), two O-glycoside derivatives of the C4 epimer of the natural product, which are also C4' demethylated[7]. These are licensed to Sandoz (Basel, Switzerland), and Etoposide is one of the most effective agents against small cell lung cancer, however it generally only gives under a year of remission, without any long term cure.

Etoposide and podophyllotoxin are known to exhibit their cytotoxic activities via different modes of action, as determined by biochemical studies[8]. Etoposide does not bind tubulin and does not act as an antimitotic as its aglycone is known to do. While the actual biochemical mode of action of podophyllotoxin is still unknown, a mechanism of action has been proposed for Etoposide[9]. It has been proposed that Etoposide is O-demethylated at the C3' methoxy group, which enables facile oxidation of the catechol ring to the ortho-quinone (Scheme 1.1). This functionality could then act as an excellent Michael acceptor



Scheme 1.1

for biochemical nucleophiles such as proteinaceous thiols or amines, or nucleophilic moieties of DNA, forming covalent links between the drug and the protein or DNA. This would likely inactivate the protein, or, in the case of DNA, interfere with the replication of the genetic material.

More recently, it has been suggested that Etoposide is actually a DNA topoisomerase II poison. Thus, upon entry into the cell, and then into the nucleus, the drug binds to DNA topoisomerase II, the enzyme responsible for unwinding and rewinding the DNA double

helix during transcription. There results a drug-DNA-enzyme complex that has been termed a "cleavable complex," since the breaking of one the DNA strands follows. This mechanism of action is similar in nature to that of the anthracycline, ellipticine, aminoacridine, and anthracenedione anticancer agents[10]. Still, in this proposed mode of activity, the lignan derivative must be 4' de-O-methylated, and is again de-O-methylated at the adjacent 3' position in the cell. Regardless of its actual biochemical mode of action, it is very likely that the glycoside is required as a means of entry into the tumour cells via cell surface recognition markers, which generally have high affinities for certain sugars.

The cytotoxicity of podophyllotoxin is still driving a considerable amount of research into analog production and testing, and several promising lead compounds are currently being tested. These efforts are equally distributed between exploiting the lignan's antimitotic and DNA topoisomerase inhibitory properties. As examples, recent reports of aza-podophyllotoxin analogs that still show considerable tubulin binding and thus antimitotic activity have shown promise due to reduced toxicity and yet improved cytoxicity relative to the natural lignan. These analogs involve the replacement of both C2 and C4 of the natural product skeleton with nitrogen[11]. As well, analogs of Etoposide (topoisomerase inhibitors), have recently been developed that are more potent, more bioavailable and metabolically stable, more water soluble and thus easier to administer, and even better for accumulation within tumour cells than the original Etoposide[12].

It is therefore apparent that despite its extremely lengthy history as a pharmacological agent, podophyllotoxin and analogs still show great promise in the realm of drug therapy,

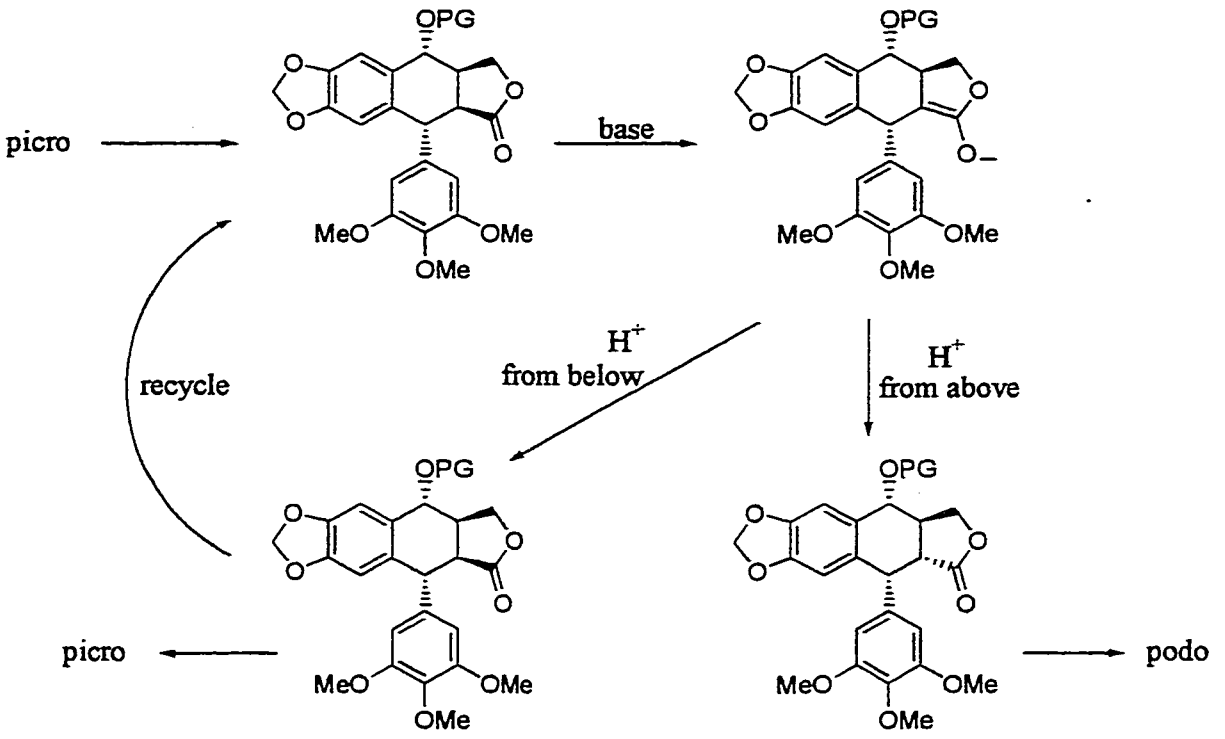
especially for the treatment of cancer. Therefore, it is still of great interest to discover more efficient, more stereoselective, and perhaps more modular asymmetric syntheses of the natural lignan.

Chapter 2

Representative Total Syntheses of Podophyllotoxin

2.2 Early Syntheses Involving Picropodophyllotoxin as Intermediate

In 1966, the first report of a podophyllotoxin total synthesis was reported by Gensler[13], and this paper was concerned only with the final step in the synthesis, the epimerization of C3 of the more stable picropodophyllotoxin to the less thermodynamically stable desired natural product. This constituted the completion of the total synthesis, since picropodophyllotoxin had been synthesized years earlier[14]. This epimerization, which has since been used as the final step in several other groups' synthetic efforts[15], involves the kinetic reprotonation of the ester enolate of the lactone (Scheme 2.1). Unfortunately, this conversion, regardless of variations of bases, solvents, hydroxyl protecting groups, or proton sources, has never led to more than about 45% isolation of podophyllotoxin, with recovery of mostly the starting undesired isomer. This isomer can of course be recycled, but this is a tedious process. Since these early synthetic endeavours towards podophyllotoxin, several groups have reported the successful installation of the four contiguous stereocenters without the need for the Gensler epimerization. Most of these syntheses have produced racemic material; in the late 1980s the first route towards optically active lignan was reported, but it did terminate with an epimerization step. Only

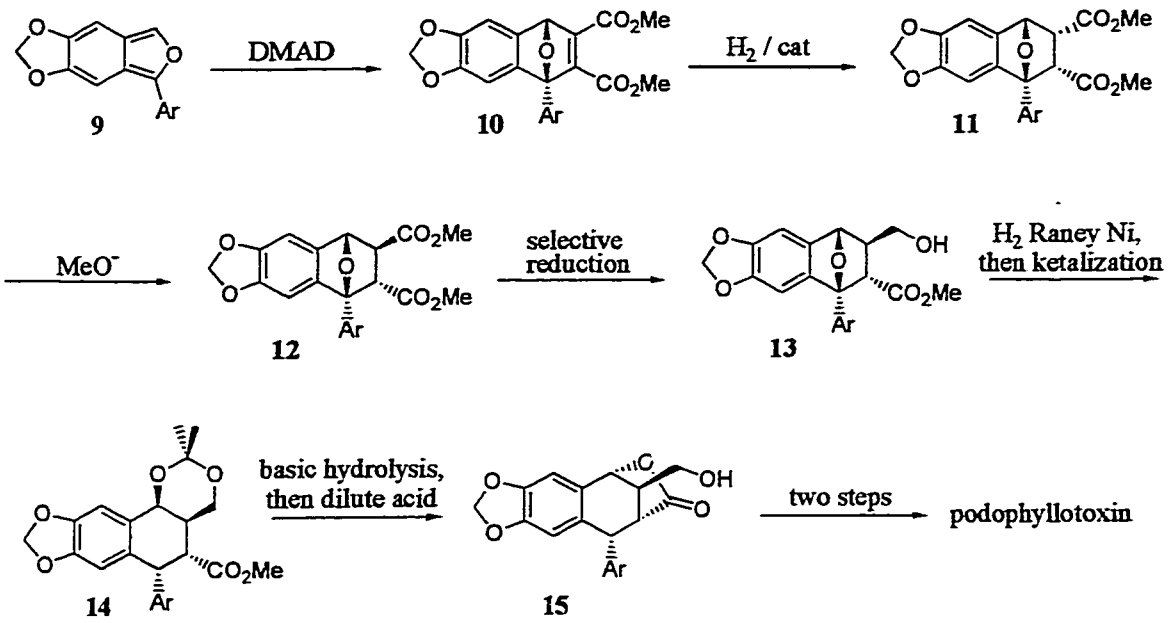


Scheme 2.1

the 1990s has seen enantioenriched podophyllotoxin produced by total synthesis not involving isomerizations. Some of these varied approaches will be outlined in the following sections.

2.2 **Racemic Synthesis by Rodrigo**

In 1981, Rodrigo and Rajapaksa reported the first successful construction of podophyllotoxin without recourse to epimerization reactions[16] (Scheme 2.2). The key step in this scheme was the Diels-Alder reaction of isobenzofuran **9** with dimethyl-acetylenedicarboxylate, yielding the complete carbon skeleton (**10**) of the desired lignan.



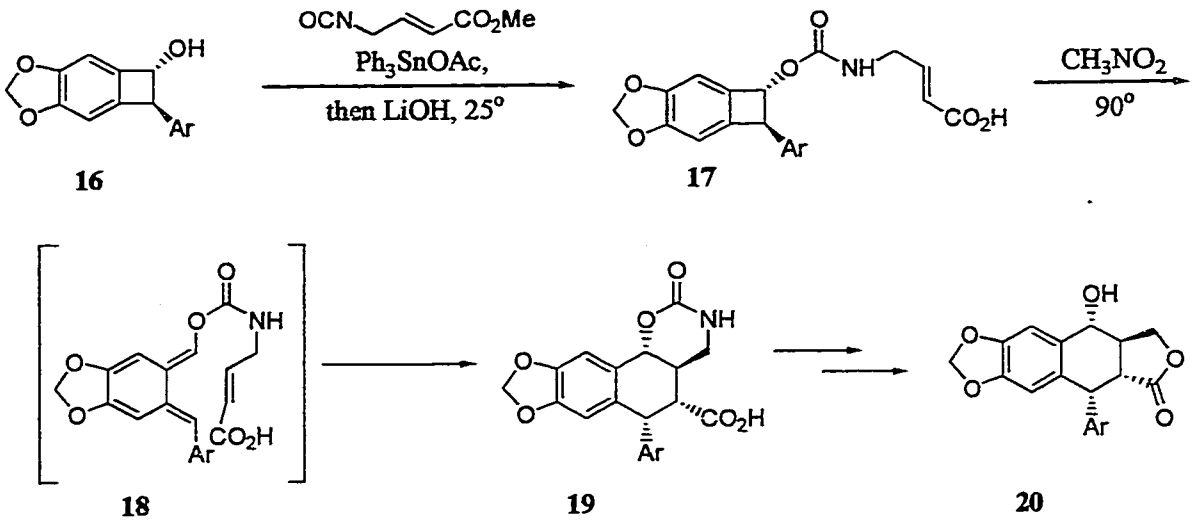
Scheme 2.2

From there, gentle and stereospecific catalytic hydrogenation of the double bond without cleaving the doubly benzylic ether afforded **11**, which was isomerized under basic conditions to yield the thermodynamically more stable *trans* diester **12**. At this point, the correct relative stereochemistry has been established at C1, C2, and C3. Selective reduction of the less hindered methyl ester, followed by Raney nickel hydrogenolysis of the doubly benzylic ether bond delivered the corresponding diol, which was readily ketalized to afford **14**. The ketalization resulted in the formation of a *cis*-decalin like structure, forcing the C2 ester into the equatorial conformation, and thus the tendency for epimerization at this position was alleviated, such that basic ester hydrolysis could be effected without compromise of this stereocenter. Acidic acetonide hydrolysis with concomitant lactonization finally afforded neopodophyllotoxin **15** in very good overall yield, and thus the formal total synthesis of podophyllotoxin was complete. This

elaboration of the antineoplastic lignan exemplifies the use of conformational analysis to predict stereochemical reactivity, and as such is an ingenious route to the desired product.

2.3 **Racemic Synthesis by Durst**

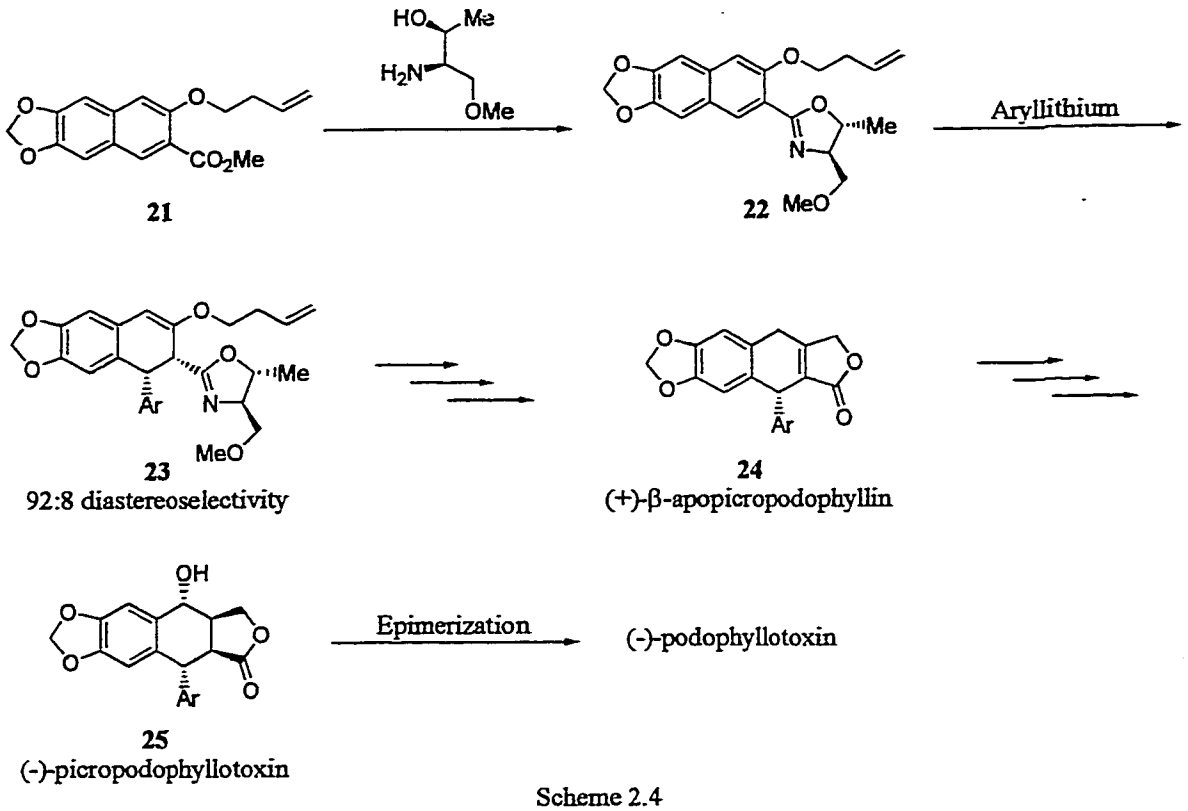
An intramolecular Diels-Alder approach to podophyllotoxin was reported by this laboratory in 1988[17]. This highly stereoselective approach (Scheme 2.3) involved an *o*-quinodimethane generated from the appropriately substituted *trans*-benzocyclobutene **16**. Lewis acid assisted attachment of the crotonyl isocyanate to the *trans*-2-arylbenzocyclobutenol followed by ester hydrolysis afforded carbamate **17**, which upon thermolysis yielded the transient *E,E* *o*-quinodimethane **18** by conrotatory cyclobutene ring opening. The subsequent intramolecular Diels-Alder reaction proceeded predominantly in the endo fashion, with the formation of **19** as the major cycloadduct. Urethane hydrolysis followed by diazotization of the the amino group led to the lactonized final product, racemic synthetic podophyllotoxin. The use of the intramolecular cycloaddition reaction in this synthesis resulted in complete regiocontrol, therefore eliminating the need for most of the functional group manipulation that was required in the Rodrigo and other syntheses. This key reaction also resulted in the formation of all four stereocenters in one step and as such has proven to be a very efficient method for the construction of this lignan.



Scheme 2.3

2.4 Meyers' Enantioselective Synthesis

In the same year as the Durst and Macdonald synthesis appeared, Andrews, Teague and Meyers reported the first total synthesis of optically enriched podophyllotoxin[18]. This strategy involved the diastereoselective addition of the C1 aryl ring as an aryl anion to a chiral naphthalene-bearing oxazoline (Scheme 2.4). Functionalized naphthalene **21** was the starting point for the introduction of the chiral Meyers' oxazoline, which was derived from *l*-threonine. This produced, after protecting group manipulation, the chiral electrophile **22**, ready for attack of trimethoxyaryllithium from the less hindered back face. This proceeded with quite good diastereoselectivity, yielding a ratio of 92:8 in favor of the desired stereochemistry at the newly created doubly benzylic center. Removal of the oxazoline and the silyl groups, followed by a lactonization step with double bond



Scheme 2.4

migration afforded (+)-β-apopicropodophyllotoxin **24**. This is a known degradation product of podophyllotoxin, and it was converted via a few more steps into an enantioenriched version of an intermediate used by Kende[15a] in his racemic synthesis. Thus the penultimate product was, unfortunately, (-)-picropodophyllotoxin. Once again, a variation of Gensler epimerization was used to yield optically active (-)-podophyllotoxin in about 93% ee.

2.5 Recent Syntheses

Since the Rodrigo and Durst syntheses demonstrated that podophyllotoxin could be produced stereoselectively and without recourse to the picro to podophyllotoxin epimerization sequence, and since Meyers' first enantioselective synthesis, many more reports of more efficient and more ingenious strategies for the construction of this lignan have surfaced. Many of these have been covered in a relatively recent review by Ward[19], but even more recent examples include another *o*-quinodimethane route[20], a chemoenzymatic strategy towards enantiopure lignan[21], and several variations of carbanionic approaches (via a tandem conjugate addition route) to build up the podophyllotoxin skeleton[22].

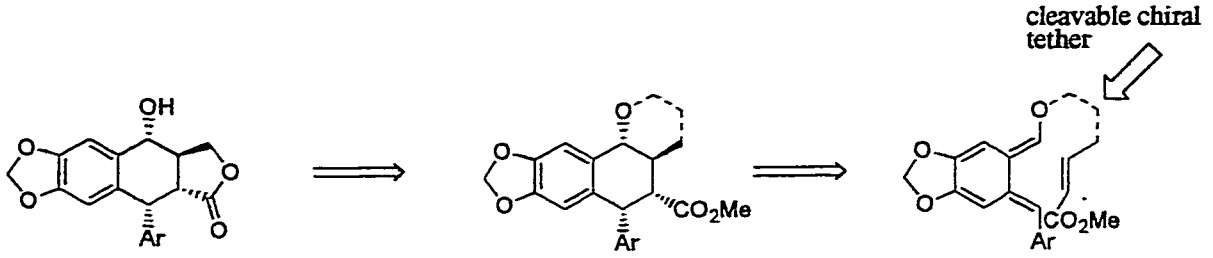
Chapter 3

An Enantioselective Approach to (-)-Podophyllotoxin Based on an Intramolecular Diels-Alder Reaction

3.1 Background

Upon inspection of the previous synthetic strategies towards podophyllotoxin, it becomes readily apparent that the most powerful method for rapid introduction of all four contiguous stereocenters into the target molecule is the intramolecular Diels-Alder reaction[17]. The Durst racemic synthesis was efficient, convergent, allowed for analog preparation, and set up the correct relative stereochemistry at all centers in one cycloaddition step. It is for these reasons that an enantioselective route analogous to this strategy was sought.

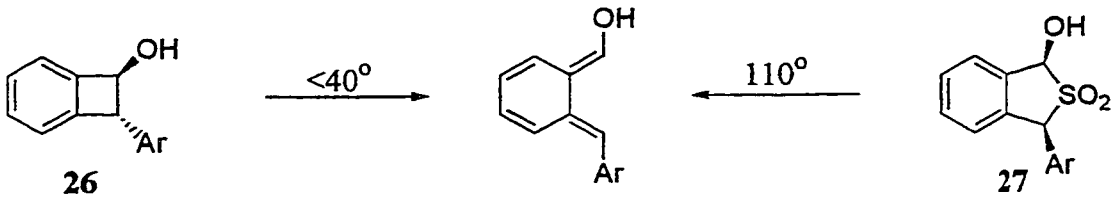
Appropriate diene and dienophile precursors were thus required, as well as a source of chirality that would be built into the tether. An appropriate *o*-quinodimethane should serve as diene in the same way as the previous synthesis. An inexpensive source of chirality was required as tether as well as face selective directing group, and it was of utmost importance that this tether be cleavable after the cycloaddition step, yielding a reasonable lactone oxygen precursor (Scheme 3.1).



Scheme 3.1

3.2 Retrosynthetic Considerations

Several choices of *o*-quinodimethane precursors were available, and in fact this laboratory was well experienced in the use of several of them. Given that we required attachment of a tether to the "enol" oxygen of the *o*-quinodimethane, photoenolization of *o*-benzyl benzaldehydes was not an option, however two different synthetic equivalents to the photoenol products were at our disposal. These were the *trans*-aryl benzocylobutenols **26**, and the *cis*-hydroxy-aryl dihydrobenzo[*c*]thiophene dioxides **27** (which shall henceforth be named hydroxy-sulfones). Thermolysis of either of these compounds leads to the requisite (*E,E*) *o*-quinodimethane dienes (Scheme 3.2).

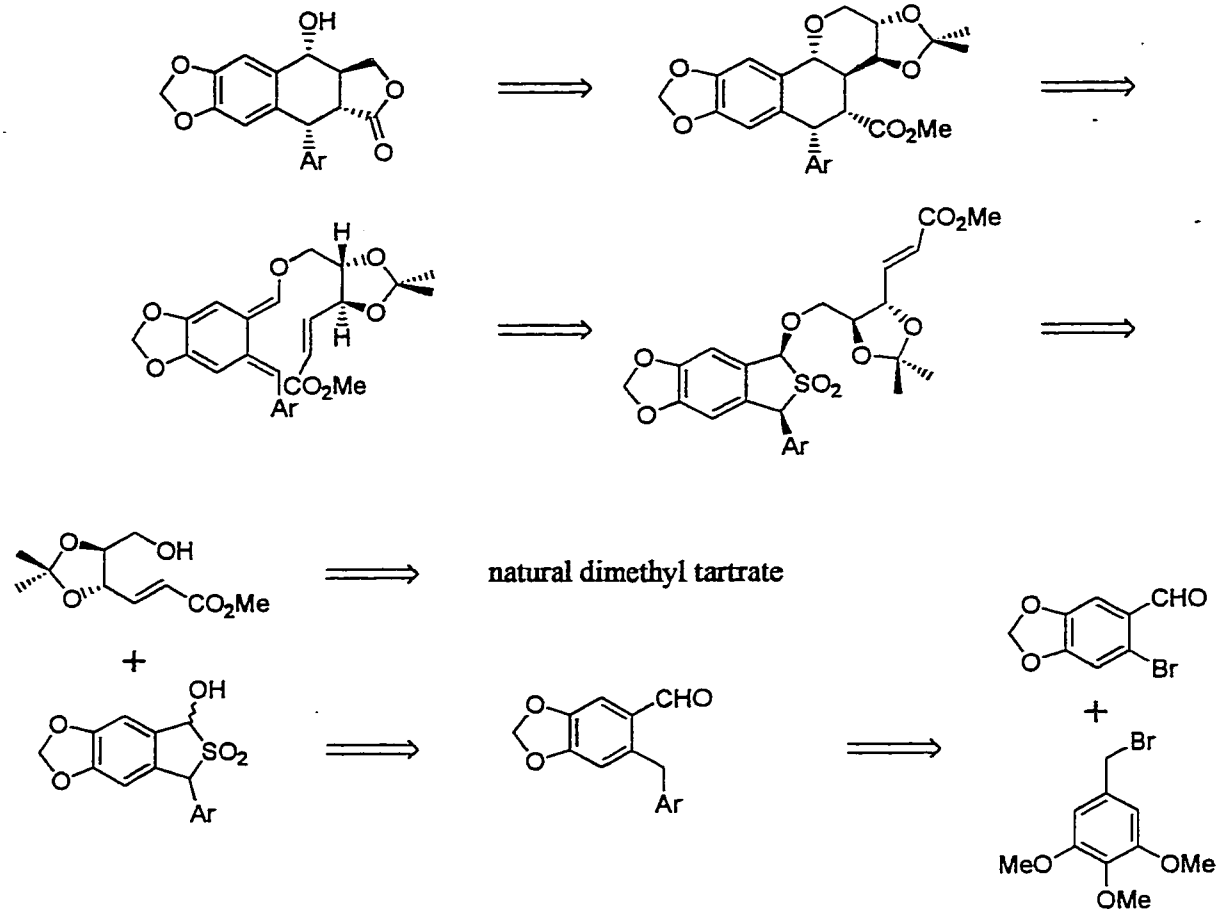


26 **27**

Scheme 3.2

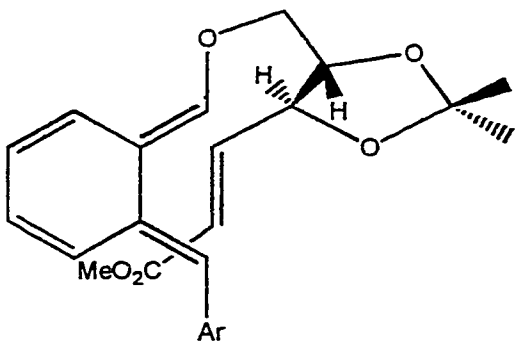
Given the extreme lability of the *trans*-aryl benzocyclobutenols, such that they readily isomerize to the corresponding benzaldehydes at just above room temperature and decompose swiftly in non-neutral conditions[23], the obvious choice was to use derivatives of the hydroxy-sulfone. Durst and Charlton have shown that these *o*-quinodimethane precursors are readily available in good yields by trapping the photoenol of the corresponding benzaldehyde with sulfur dioxide[24]. These hydroxy-sulfones are generally isolated after a basic workup as a mixture of the *cis* and *trans* diastereomers, however upon exchange of the hydroxyl group with an alkyl alcohol under acidic conditions, the resulting ether is isolated in good yield as only the *cis* diastereomer[25]. Since cheletropic extrusion of sulfur dioxide occurs in a disrotatory fashion (suprafacial elimination), the *cis* diastereomer should lead exclusively to the formation of the (*E,E*) *o*-quinodimethane. Therefore, attachment of the dienophile through the chiral tether as an ether to the diene precursor should set up perfectly for thermolysis and subsequent asymmetric intramolecular Diels-Alder reaction.

Significant work in the field of asymmetric intramolecular Diels-Alder reactions incorporating chiral tether groups has been done at this institution. Fallis has shown that chiral isopropylidene acetals derived from tartrate or carbohydrates serve as powerful directing groups in [4+2] cycloadditions[26]. A protected version of the requisite chiral alcohol incorporating the acetal and the α,β-unsaturated ester dienophile had been prepared previously and was well described in the literature[27]. Therefore, the retrosynthetic analysis seen in Scheme 3.3 materialized as a very logical approach to optically active podophyllotoxin.

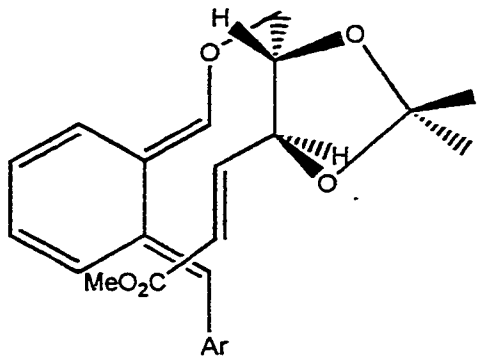


Scheme 3.3

The highly oxygenated *o*-benzyl benzaldehyde had been previously synthesized in the Durst laboratory[28] from bromopiperonal and trimethoxybenzyl bromide. Trapping of the photoenol of closely related systems with sulfur dioxide had been carried out successfully. Essentially, the two major synthons were quite readily accessible. The convergent step of forming the ether from the tartrate-derived alcohol followed by thermolysis to induce



Dienophile approaching from below:
sterically more demanding transition state



Dienophile approaching from above:
sterically accessible transition state

Figure 3.1

cycloaddition were the procedures remaining to complete the carbon skeleton of the natural product. At this point, introduction of the four contiguous stereocenters, presumably with effective chirality transfer from the chiral tether, would be complete. The facial selectivity should hopefully derive from the sterically crowded and thus disfavored transition state arising from dienophile approach from below (Figure 3.1). Simple molecular models suggest that dienophile approach from above would result in a sterically very accessible transition state. Naturally, dipolar interactions could either help or hinder the facial selectivity derived from the steric interactions, and only experimental results can ascertain whether the diastereoselectivity of the cycloaddition will be satisfactory. Thus, if the predictions are correct, the carbon skeleton of podophyllotoxin with all stereocenters in place would be readily attainable. Several steps of functional group manipulation should lead to enantioenriched (-)-podophyllotoxin.

3.3 Precedent for the Viability of the Synthesis

Very reasonable precedents had been set for the majority of the steps of the proposed synthesis. The two major synthons were essentially known compounds, the use of tartrate-derived tether control groups was well documented, and the racemic synthesis of the target in this laboratory established the viability of the *o*-quinodimethane intramolecular cycloaddition reaction to set up the desired relative stereochemistry. Model studies on the convergent step were performed on the simpler hydroxy-sulfone derived from *o*-benzyl benzaldehyde. These results will be discussed in the Results and Discussion section.

Part 2

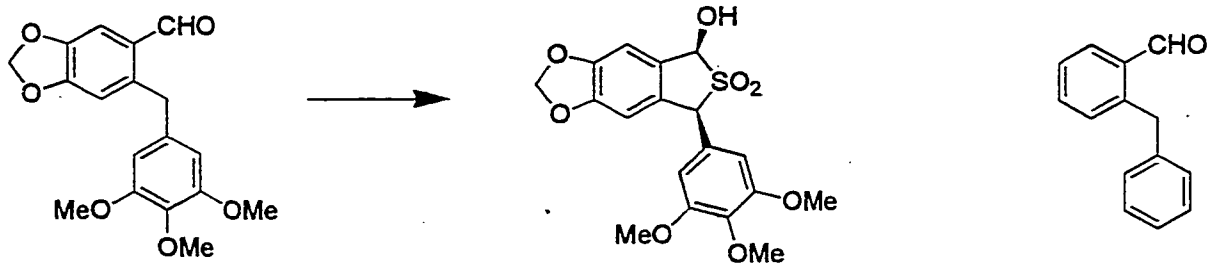
Results and Discussion

Chapter 4

Attempts to Prepare *o*-Quinodimethane Precursor Model Systems

4.1 The Model *o*-Quinodimethane Precursor

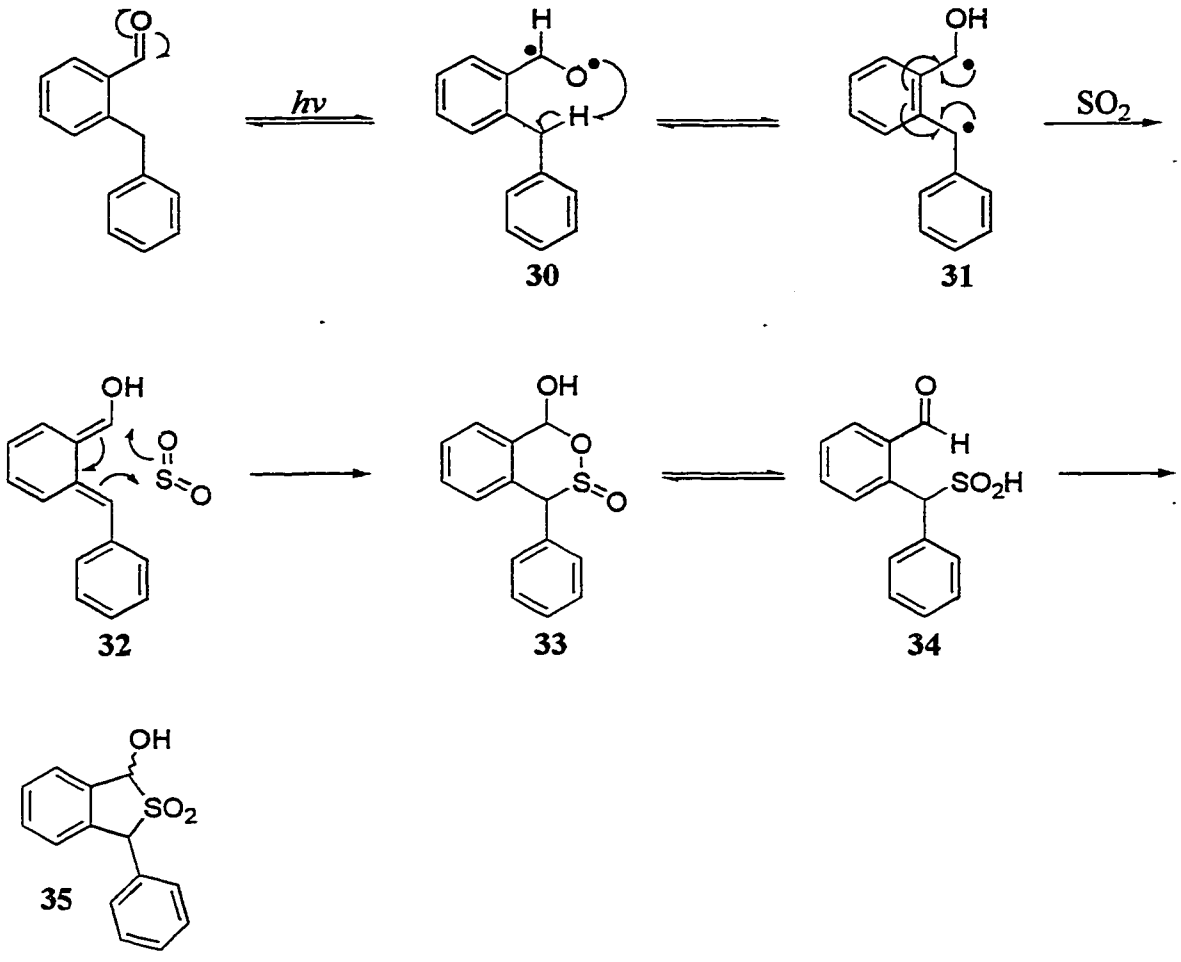
Rather than prepare in quantity the more complex diarylmethane **28** as a hydroxy-sulfone and thus *o*-quinodimethane precursor, it was reasoned that the unoxygenated **29** would be more suitable to studying the convergent etherification step and subsequent Diels-Alder



28 **29**

reaction. Thus the known **29** was prepared by lithium aluminum hydride reduction of commercial *o*-benzyl benzoic acid followed by reoxidation to the benzaldehyde by a two-phase Jones oxidation[25]. Photolysis of this product in benzene containing 10% sulfur dioxide using a Hanovia 450 watt medium pressure mercury lamp generated the

photoenol, which was efficiently trapped by the excess sulfur dioxide to yield the hydroxy-sulfone model **35**. This reaction proceeds as in Scheme 4.1 via benzylic hydrogen abstraction by the benzaldehyde ketyl (**30**) oxygen yielding a 1,4 diradical **31** which is equivalent to the *o*-quinodimethane **32**. This photoenol intermediate can then be trapped by [4+2] cycloaddition reaction with sulfur dioxide yielding the sultine **33** which isomerizes via the ring-opened aldehyde-sulfinic acid **34** to the more stable cyclic sulfone **35**. The hydroxy-sulfone product was isolated by base extraction of a methylene chloride solution of the crude reaction residue. This extraction removes essentially pure **35** in the

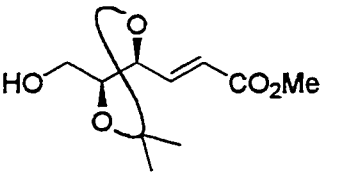


Scheme 4.1

form of the water soluble salt of the sulfinic acid **34**, and upon reacidification, the desired product is recovered in 60 to 65% yield on scales of up to 40 mmol (eight grams of aldehyde) as per the literature procedure[25]. The resulting white foam was a 1:1 mixture of the *cis* and *trans* diastereomers. It was stable indefinitely if stored under nitrogen in the freezer; at warmer temperatures reversion to starting materials was observed.

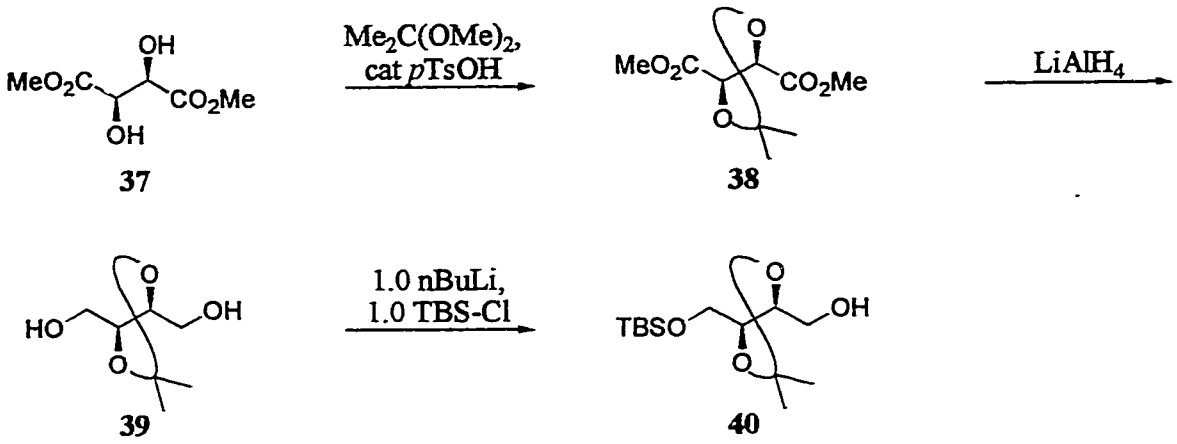
4.2 The Chiral Tether and Dienophile

The requisite chiral tether and dienophile were to be derived from natural tartrate, specifically the inexpensive dimethyl-*L*-tartrate. The original target synthon was to be α,β-unsaturated ester **36**[27].



36

The protection of dimethyl-*L*-tartrate **37** as its acetonide under standard conditions followed by purification by distillation afforded **38** in nearly quantitative yield. The protected diester was then fully reduced to the diol **39** using excess lithium aluminum hydride in diethyl ether, which after flash chromatography, was obtained in 85% yield. Alternatively, the diol could be isolated in as much as 80% yield for the two steps without

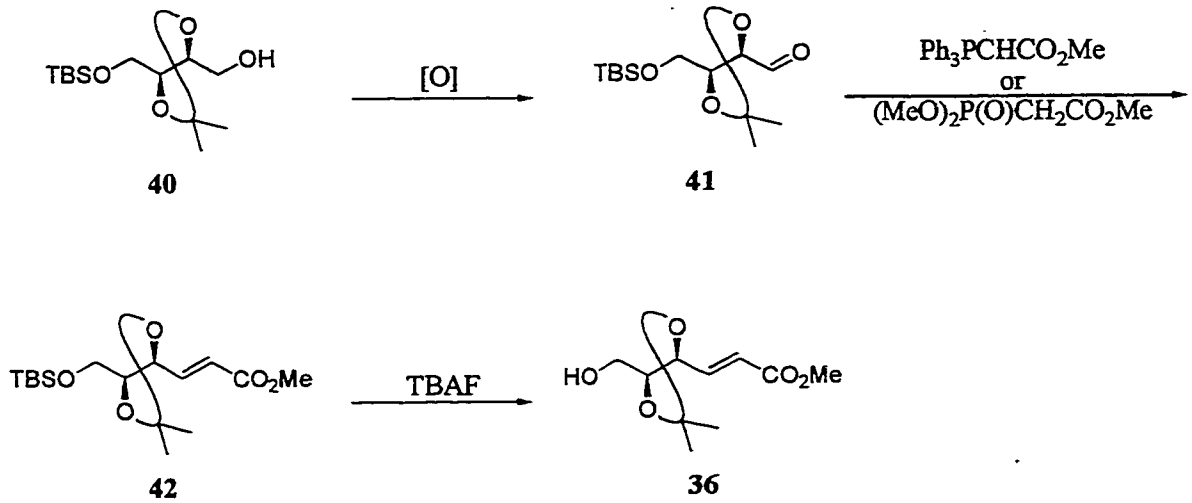


Scheme 4.2

distillation of **38**, but overall this was not as reproducible. Monoprotection of the diol with the *tert*-butyldimethylsilyl group was effected as per the literature conditions[27], with one equivalent of sodium hydride in THF, followed by treatment with *tert*-butyldimethylsilyl chloride. This reaction's success is dependent on the insolubility of the mono alkoxide of **39**, which prevents deprotonation of the second hydroxyl group. Unfortunately, this protocol was found to be highly irreproducible, often yielding a nearly statistical mixture of unprotected, monoprotected, and diprotected products. A report by Marshall[29] that the similar di-*O*-benzyl threitol (**39** with benzyl protecting groups instead of the acetonide) was monosilylated using one equivalent of nBuLi as base prompted the examination of these conditions on our threitol. Indeed, the reaction did proceed with much more success. The mono lithium alkoxide was visibly insoluble in THF at 0°, forming a milky white suspension. Simple aqueous workup after addition of the silyl electrophile yielded nearly quantitatively the monoprotected threitol **40**, which as a crude reaction product was clean by thin layer chromatography, and showed only a trace of diprotected product by ^{1}H NMR. Oddly, if the crude product was purified by flash

chromatography, the pure material was obtained in consistently only about 80% yield. For scaleup purposes, however, the crude product was clean enough for subsequent oxidation.

This oxidation of the monosilylated tartrate derivative (Scheme 4.3) proved to be quite problematic, even upon adoption of the reported procedures. Some literature procedures for the tartrate-derived primary alcohol to aldehyde conversion include Swern[27]and Dess-Martin[29] oxidations. These conditions were initially attempted with little success, as were PCC, PDC, catalytic TEMPO/bleach, and catalytic TPAP/NMO. In all cases except for the TPAP conditions, starting material was completely consumed as indicated by TLC and ^{1}H NMR of the crude reaction mixtures. Generally, the TLC analysis indicated clean conversion to a single product with a slightly higher Rf than the starting alcohol. It was seen as an elongated streak, as many aldehydes are upon TLC analysis, due to reversible hydration-dehydration on the silica surface. However, the NMR spectra all showed only minor amounts of aldehyde by integration of the narrowly spaced doublet at 9.75 ppm



Scheme 4.3

with respect to the acetonide and TBS peaks. In addition, the aliphatic areas of the spectra were completely indecipherable. Attempts to isolate the minor aldehyde component by rapid flash chromatography[27b] resulted in unreliable yields of between 10 and 45%, very disappointing given the high literature yields[27, 29]. Distillation of the crude product sometimes resulted in higher yields of aldehyde, therefore it was postulated that perhaps this compound is extremely prone to hydration due to the β ether oxygen serving as an excellent hydrogen bond acceptor (Figure 4.1). The hydration of aldehydes is usually found to be important in the cases of "small" aldehydes, as in formaldehyde and acetaldehyde, as well in aldehydes bearing electronegative groups such as trichloroacetaldehyde. It seems likely that the proposed hydrogen bonding could also contribute to hydration of this particular aldehyde. This would result in the loss of most of the aldehyde ^{1}H NMR signal, along with a significant increase in complexity of the rest of the spectrum, especially if the hydration-dehydration equilibrium is fast relative to the spectrometer time scale. Additionally, the *gem*-diol carbon also becomes a pseudo-chiral center and could lead to the formation of two diastereomeric hydrogen bonded products,

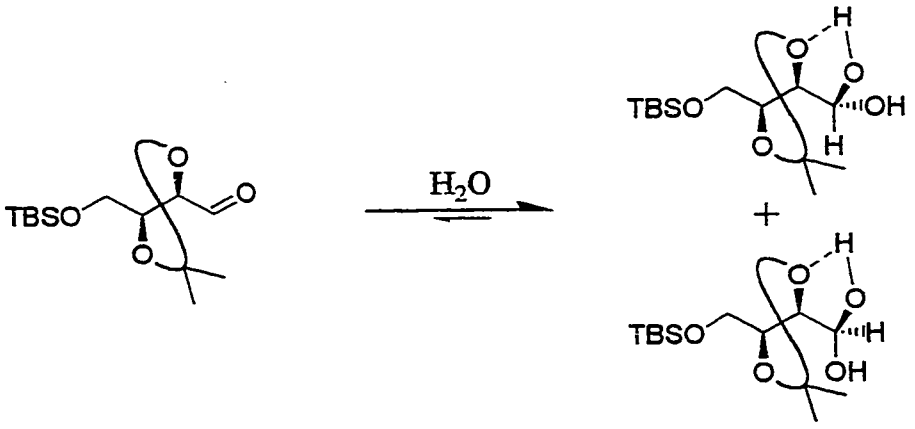


Figure 4.1

thus potentially complicating the spectrum further. This hydrated structure is consistent with the spectral observations, and it is also corroborated by the fact that the yields were slightly better upon distillation, since distillation is known to effect dehydration of *gem*-diols[30]. Attempts to keep reaction conditions neutral or slightly basic to try to suppress the hydration, such as the incorporation of buffered Dess-Martin and TEMPO oxidation conditions along with mildly basic workups also failed. It was eventually found that slow distillation of the crude product from the Dess-Martin or especially the Swern reaction conditions using a Kugelrohr apparatus effected clean dehydration and yielded the product in up to 92% yield on up to 50 mmol scales. It is interesting that none of the previous reports[27] of this and related compounds[29] mention any problem with hydration whatsoever.

The introduction of the α,β-unsaturated ester via standard Wittig chemistry was attempted next. It was found that heating a toluene solution of the freshly distilled aldehyde with 1.5 equivalents of methyl (triphenylphosphoranylidene)acetate to 50° for two hours effected clean conversion to two much less polar products by TLC. ^{1}H NMR of the crude mixture confirmed complete reaction of the starting material, as well as formation of a 4.5:1 mixture of α,β-unsaturated esters with the desired *E* isomer predominating. The ratio was determined by examination of the olefin proton resonances (*E* isomer: 6.94 ppm, doublet of doublets, 15Hz, 5.5Hz and 6.11ppm, doublet of doublets, 15Hz, 1.5Hz / *Z* isomer: 6.17 ppm, doublet of doublets, 11Hz, 8Hz and 5.90 ppm, doublet of doublets, 11Hz, 1Hz). Interestingly, the selectivity for the *E* isomer was considerably better than in the literature procedure[27b], which afforded a 68:32 ratio of *E*:*Z* isomers using dichloromethane

as solvent and the corresponding ethyl ester ylide. These isomers were barely separable by silica gel chromatography, and even when isolated as a mixture, the combined yield was only 63%, despite the clean transformation observed by NMR. It is possible that some of the product remained in the insoluble plug of triphenylphosphine oxide that precipitated at the top of the chromatography column, thereby decreasing the yield. Both the problems involving low yield and double bond geometry selectivity were solved upon adoption of the Horner-Wadsworth-Emmons olefination procedure. Thus, when one equivalent of trimethyl phosphonoacetate was added to a suspension of dry sodium hydride at 0°, followed by addition of the freshly distilled aldehyde, the resultant *trans* unsaturated ester was obtained in nearly pure form after aqueous workup. The undesired *Z* isomer was barely perceptible (less than two percent) by ^{1}H NMR. After purification by flash chromatography, the pure product **42** was obtained as a viscous, clear colorless oil in 91% yield. Finally, deprotection of the silyl protecting group was effected under standard conditions to yield the desired chiral tether / dienophile **36** in 92% yield.

Although these products, with the exception of **36**, are known in the literature, this scheme of six reactions is now, in our hands, much more reproducible than the literature methods were found to be. In fact, the valuable chiral synthon **36** can be reliably produced in multi-gram quantities in 50% overall yield from dimethyl-*L*-tartrate. All products in Schemes 4.2 and 4.3 exhibit spectral characteristics virtually identical to those reported in the literature[27]. The final product **36** was identified by its similarities by ^{1}H NMR to silyl ether **42** with the lack of resonances corresponding to the TBS group, and the appearance of a hydroxyl peak. ^{13}C NMR spectral characteristics were also in good accord with the

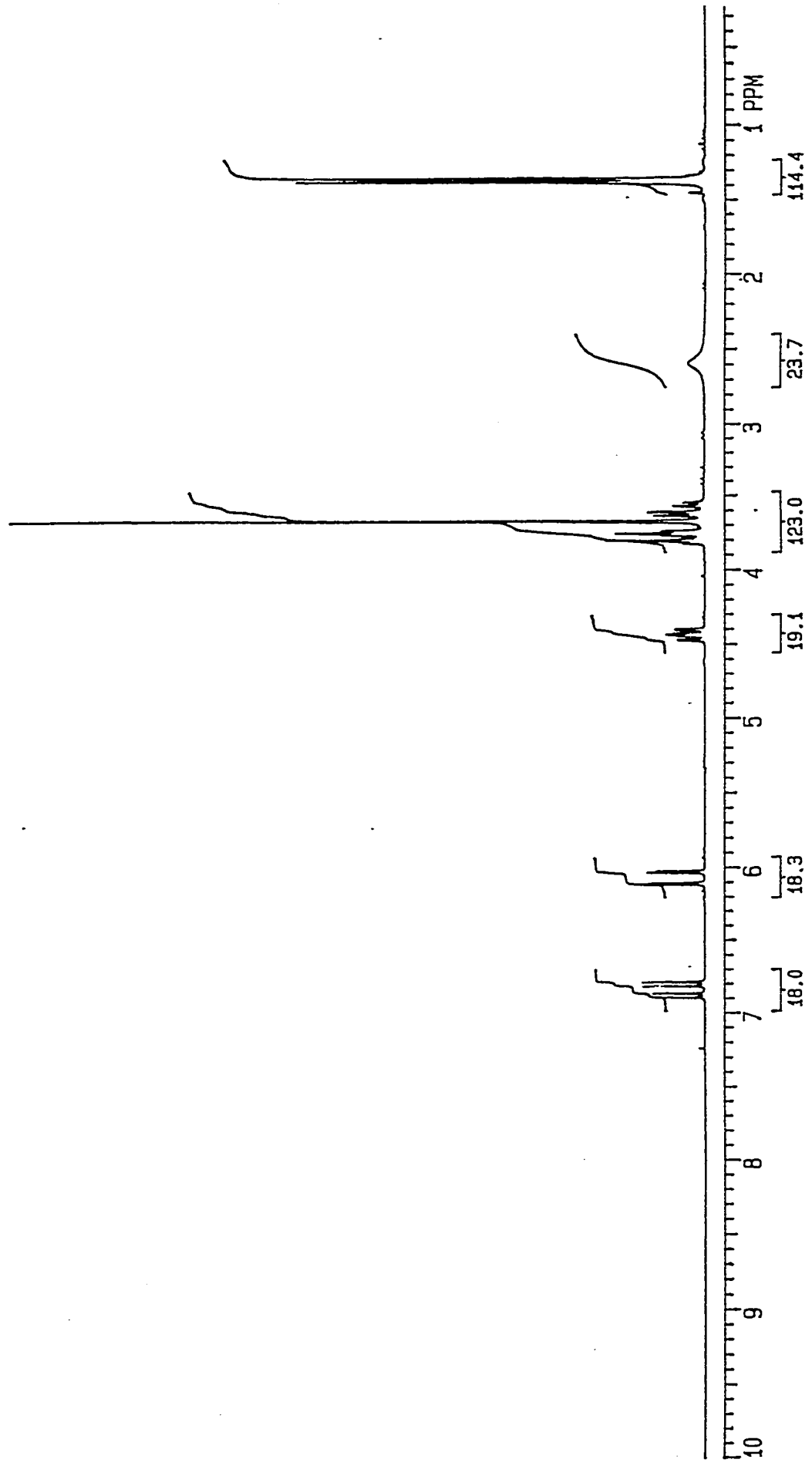
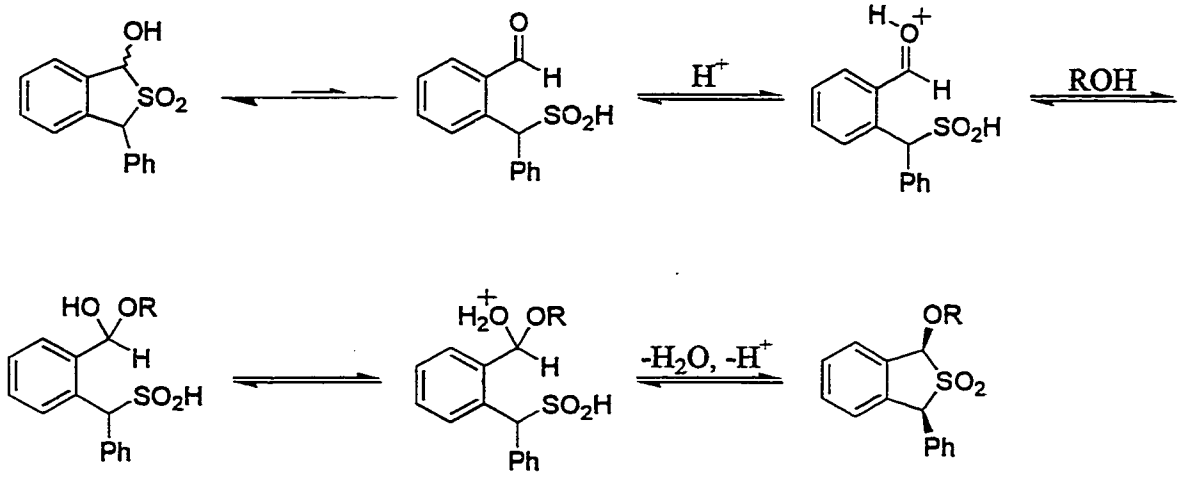


Figure 4.2: 200 MHz ^{1}H NMR Spectrum of Alcohol **36**.

desired structure. Hydroxyl absorption at 3423 cm^{-1} and conjugated ester absorptions at 1722 and 1664 cm^{-1} helped to confirm the structure along with HRMS data for the peak at m/e of 201 corresponding to the M-CH_3 (98.6% of base) peak. The 2,2-dimethyl-1,3-dioxolane structural motif that corresponds to the acetonide of a *vic*-diol is known to lose a methyl group from the quaternary carbon under mass spectral conditions.

4.3 Attempts to Connect Potential Diene and Dienophile

At this point, the stage was set for the convergent step, the connection of hydroxy-sulfone **35** to the chiral dienophile **36** via an ether linkage. It was hoped that the acid-catalyzed reaction of the chiral alcohol with the model hydroxy-sulfone would proceed as uneventfully as the many similar examples of this kind of etherification that had been

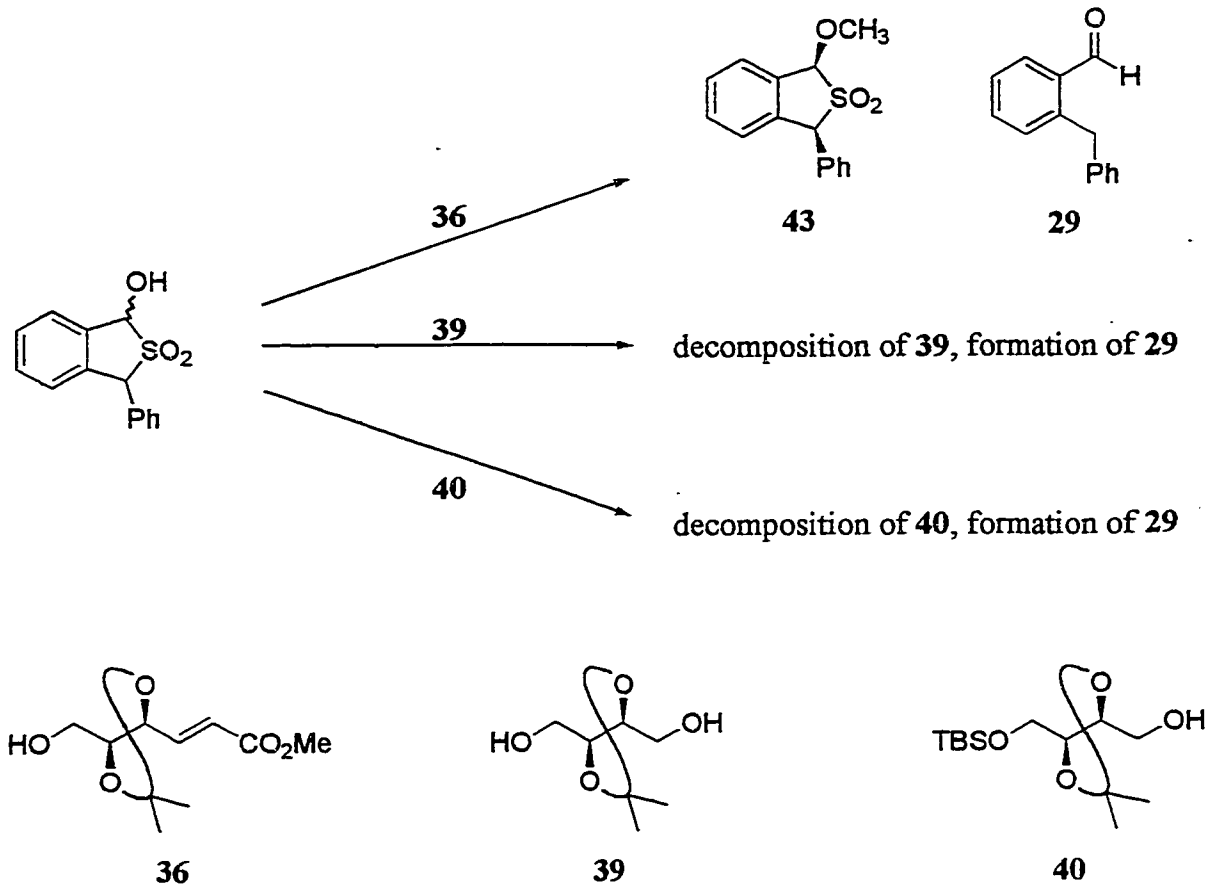


Scheme 4.4

reported by Charlton[31]. The mechanism for this ether-forming reaction likely involves the reversible ring opening of the five-membered sulfone ring to the aldehyde-sulfinic acid, which are proposed to be in an equilibrium analogous to the lactol–hydroxyaldehyde equilibrium of sugars (Scheme 4.4). Protonation of the aldehyde oxygen by the acid catalyst then allows for hemiacetal formation after nucleophilic attack by the alcohol. Further protonation of the hemiacetal can lead to ring closure with expulsion of either neutral alcohol or water, but in the conditions of excess alcohol or removal of water, the ether becomes the major product of this series of equilibrium steps. It has also been documented that the more stable *cis* geometry about the sulfone ring is the only observed product[25].

The literature procedure for this type of condensation, in which the hydroxy-sulfone, alcohol, and *p*-toluenesulfonic acid catalyst were dissolved in dichloromethane and heated to reflux, was attempted with **35** and the tartrate-derived alcohol **36**, with added molecular sieves. Very little reaction occurred after continued exposure to these conditions for twenty hours with the exception of slight degradation of the hydroxy-sulfone to the aldehyde and some other minor decomposition products. Attempts to effect this convergent step with a Lewis acid instead of a protic one did not lead to any improvement. After five hours with one equivalent of boron trifluoride etherate in refluxing dichloromethane, a new product became perceptible by TLC. After forty-eight hours, the majority of the tartrate-derived alcohol was consumed, so the reaction was stopped and the new product was isolated. It was identified as the known methyl ether **43** (Scheme 4.5) of the hydroxysulfone by comparison of its ^{1}H NMR spectral

characteristics[25]. Apparently, given enough time under these conditions, slow acidic hydrolysis of the methyl ester occurs allowing for formation of this undesired product. Again, small amounts of aldehyde were detected by proton NMR. Thus there was a concern of the acid stability of the alcohol **36**, certainly in terms of the methyl ester functionality, and potentially the acetonide as well. Also, there was a potential problem with reversion of the hydroxy-sulfone to its aldehyde precursor, which implied that higher temperatures would likely not be beneficial.



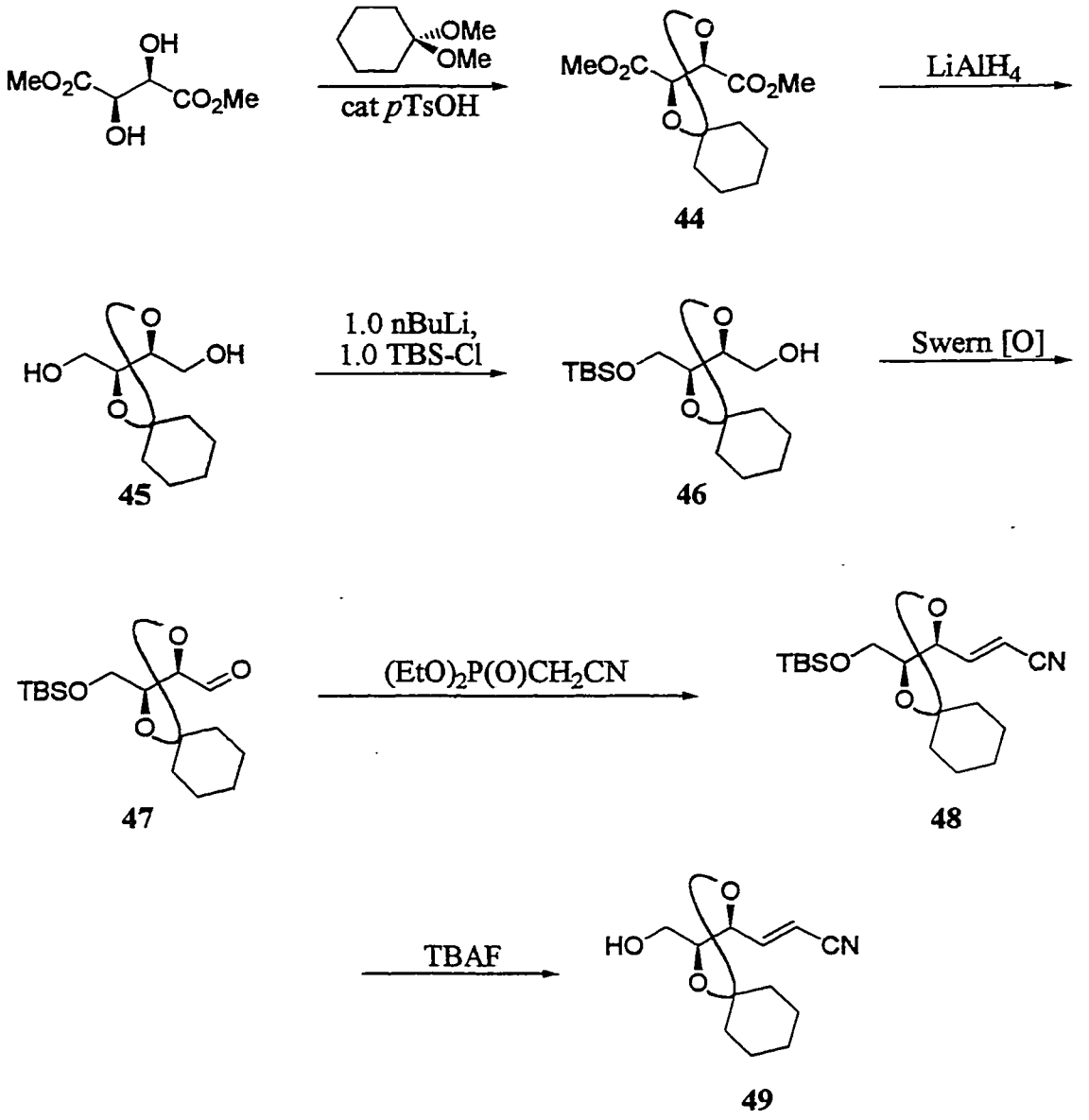
Scheme 4.5

A combination of reasons could account for the failure of the coupling reaction. For example, the tartrate-derived alcohol, despite being primary and relatively unhindered, may not be a particularly nucleophilic compound due to the inductively electron withdrawing effect of the protected diol moiety. Alternatively, the hydroxyl group could be involved in reasonably strong intramolecular hydrogen bonding with the β ether oxygen, in much the same fashion as the hydrated aldehyde (Figure 4.1) was proposed to be stabilized. This could result in the hydroxyl group being held in a more sterically encumbered environment than expected for a primary alcohol. Also, the five basic sites in the chiral alcohol could compete with the aldehyde carbonyl for the acid catalyst thereby greatly diminishing the rate of protonation and subsequent hemiacetal and ether formation relative to those observed with simple alkanols (approximately five hours for primary and secondary alcohols without heteroatom substituents[25]).

In order to learn more about this system, attempts to attach two of our intermediates from the dienophile synthesis to the hydroxysulfone were carried out (Scheme 4.5). Reaction of symmetrical diol **39** under both protic and Lewis acid conditions resulted in very sluggish reaction of any kind, with eventual formation of the aldehyde **29** from the hydroxysulfone, and deterioration of the diol (likely degradation of the isopropylidene protecting group). Similar results were obtained in the reaction of the monosilylated tartrate derivative **40**, except that decomposition of the chiral alcohol was more rapid, presumably due to the acid lability of the TBS group.

4.4 A More Acid Stable Chiral Dienophile

In order to decipher the source of the etherification reaction problem, and hopefully to rectify it, more acid stable tartrate derivatives were synthesized. The idealized synthon



Scheme 4.6

had the methyl ester replaced with a nitrile, and a more stable cyclohexylidene acetal substituted for the potentially labile isopropylidene acetal. Unfortunately, the electronegative effect of the protected diol could not be avoided. The synthesis of this molecule **49** was attacked in an identical manner to that for the previous dienophile (Scheme 4.5). Attempts to form the cyclohexylidene acetal from excess cyclohexanone and dimethyl-*L*-tartrate under standard acidic conditions using a soxhlet extractor to remove water were not terribly successful. Less than 50% yield of the desired product was obtained after distillation. Attempts with trimethyl orthoformate additive (in order to remove water and to form the more reactive cyclohexanone dimethyl acetal *in situ*) were met with similar results. Finally, it was found in the literature[32] that cyclohexylidene acetals of 1,2 diols can often only be reliably synthesized from cyclohexanone dialkyl acetals, and these reagents themselves are not trivial to make. It seems that the use of excess molecular sieves to drive the reaction to completion actually diminishes the rate of reaction due to the removal of the acid catalyst from solution by the molecular sieves. In order to acquire a significant amount of product, excess *p*-toluenesulfonic acid needed to be added in several portions. Thus the dimethyl acetal reagent was made according to the literature procedure, and upon reaction with dimethyl-*L*-tartrate with catalytic *p*-toluenesulfonic acid in chloroform using a soxhlet extractor filled with activated molecular sieves, the desired ketal **44** was isolated by Kugelrohr distillation in 98% yield. Lithium aluminum hydride reduction to diol **45** proceeded uneventfully in 90% yield after chromatography affording a white semisolid (melting point just above room temperature) which crystallized on storage at 4°C. The ^{1}H and ^{13}C NMR data were consistent with the

symmetry of the diol, and solution IR verified hydroxyl group presence with a broad absorption band centered at 3460 cm^{-1} as well as a sharp band at 3598 cm^{-1} corresponding to non-hydrogen bonded O-H stretching. Monosilylation of the diol under identical conditions as for the acetonide derivative yielded the desymmetrized product **46** in 85% unoptimized yield. Some disilylated product was observed, likely due to the increased solubility of this monoalkoxide in THF relative to the alkoxide of **38**. The ^{1}H and ^{13}C NMR spectra for the product clearly indicated the lack of symmetry. All six protons α to oxygen atoms overlapped in the 200 MHz proton spectrum forming a large multiplet between 3.6 and 4.0 ppm. The presence of only one silyl protecting group was established by the integration of the *tert*-butyl group relative to the cyclohexylidene resonances, as well as by the observation of a hydroxyl resonance. The hydroxyl group was also clearly observed in the IR spectrum at 3438 cm^{-1}. Swern oxidation of the alcohol afforded the aldehyde **47** in 88% yield as a semisolid after slow Kugelrohr distillation (boiling point 130°C at .05mm Hg). This aldehyde, while still prone to hydration, was more stable than its acetonide equivalent, as it could be stored indefinitely under an inert atmosphere in the freezer without decomposition. Horner-Wadsworth-Emmons reaction of the aldehyde with the reagent prepared from bromoacetonitrile and triethyl phosphite using nBuLi as base yielded the α,β unsaturated nitrile in a disappointing 70% yield as a 2:1 ratio of *E*:*Z* isomers. Adoption of the procedure of Roush[33] in which a tertiary amine base is used in the presence of lithium chloride with acetonitrile as solvent showed a dramatic improvement. The optimized conditions, using freshly distilled acetonitrile and freshly distilled DBU as base, furnished the desired nitrile **48** in 85% yield in a 6:1 ratio in favor of the *trans* geometry. The two isomers were separable by careful column

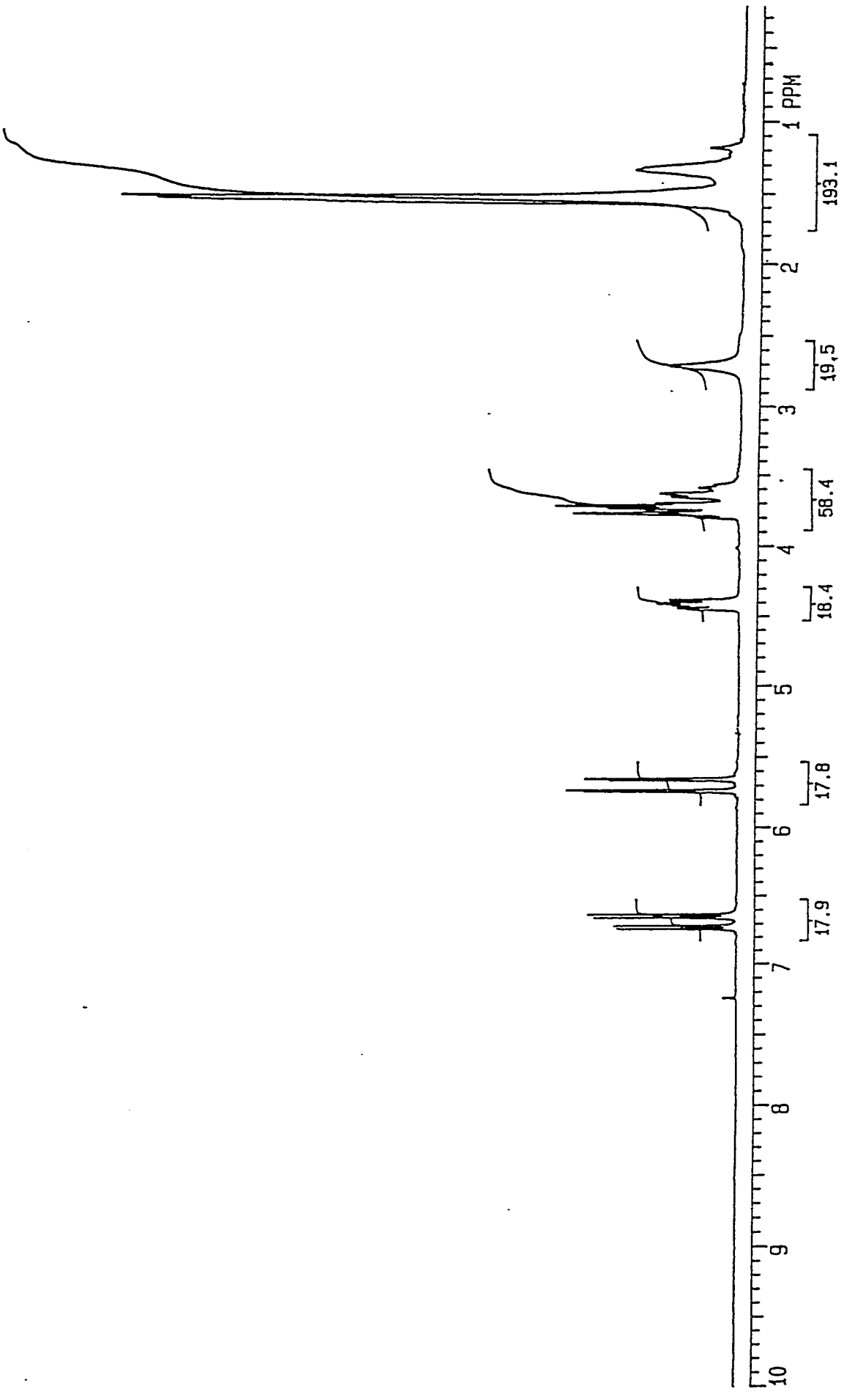


Figure 4.3; 200 MHz ^{1}H NMR Spectrum of Alcohol **49**.

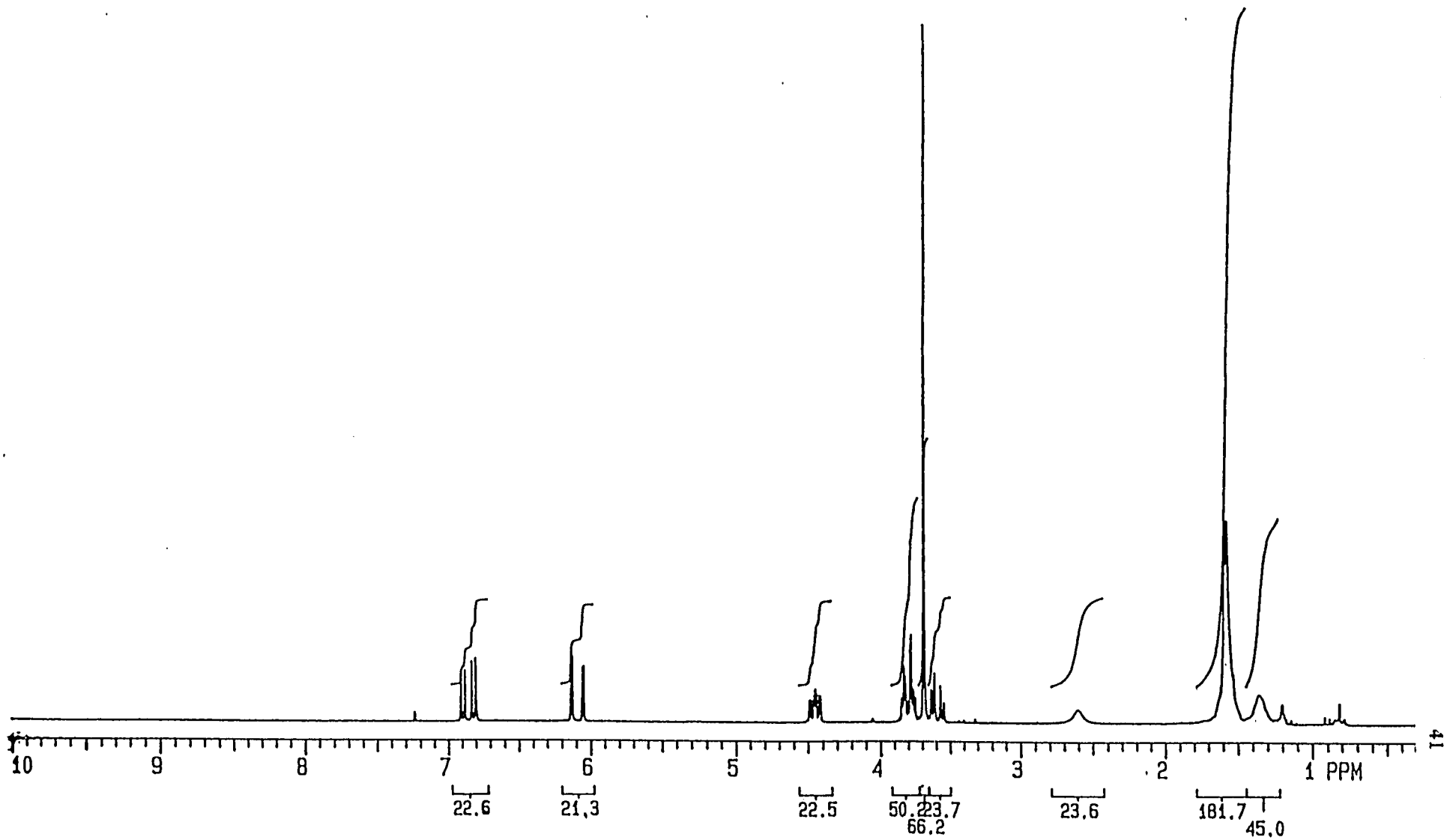
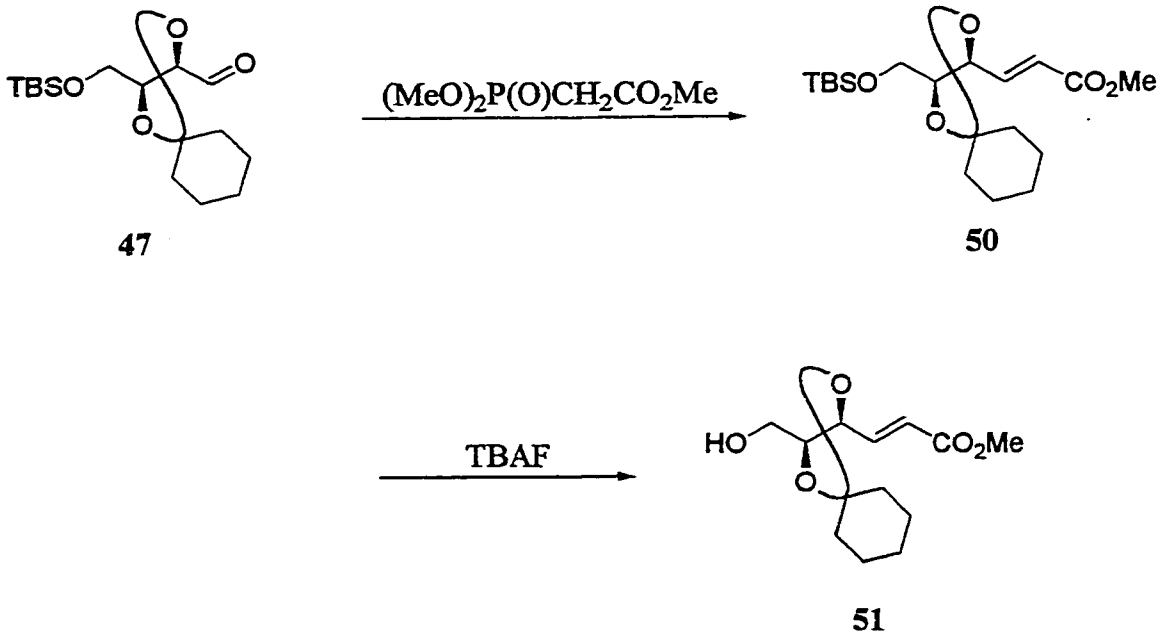


Figure 4.4: 200 MHz ^{1}H NMR Spectrum of Alcohol **51**.

chromatography, and **48** exhibited expected spectral characteristics, with the IR spectrum particularly indicative of the unsaturated nitrile as absorption bands were seen at 2228 and 1640cm^{-1}. Finally, TBAF deprotection afforded the chiral alcohol **49** in 95% yield, for which spectral data were in accordance with the structure.

The cyclohexylidene analog of ester **42** was also synthesized in two steps from the aldehyde (Scheme 4.7). Horner-Wadsworth-Emmons reaction of **47** under identical conditions as used in the preparation of **42** afforded ester **50** in 94% yield, for which spectral data were virtually identical to those of **42**, with the obvious exception of the cyclohexylidene group. Fluoride-mediated silyl group removal furnished hydroxy ester **51**, another possible chiral dienophile, although it was anticipated that methyl ester hydrolysis would still occur under the acidic etherification conditions. This compound was made also in the hopes of using it as a dienophile in a slightly different approach to podophyllotoxin that will be discussed in a following chapter.

At this point, attempts to attach the more acid stable dienophile to the model hydroxy-sulfone were undertaken. The earlier conditions employing catalytic *p*-toluenesulfonic acid as well as boron trifluoride etherate led to absolutely no product formation, even after forty-eight hours in dichloromethane at reflux. No decomposition of **49** took place under these conditions, but as expected, some aldehyde formation from the hydroxy-sulfone did take place. Attempts involving ten-fold excesses of either reagent were no more fruitful. Changing solvents to the higher boiling 1,2 dichloroethane, or to the more polar THF or



Scheme 4.7

even nitromethane did not lead to any desired product formation. Similar results were observed for cyclohexylidene methyl ester **51**, along with the observation of the anticipated methylated hydroxy-sulfone **43**.

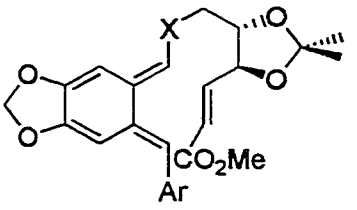
At this point, it appeared that the lack of success in the convergent step was likely due to the lack of nucleophilicity of tartrate-derived primary alcohols. This was made most clear by the fact that the very stable **49** did not decompose at all, and still did not react even with increased temperature and prolonged reaction times. It was thus decided to embark upon an alternate route towards the asymmetric intramolecular *o*-quinodimethane Diels-Alder reaction, in the hopes of finding a successful route to enantio-enriched (-)-podophyllotoxin.

Chapter 5

The Use of Imines in an *o*-Quinodimethane Strategy Towards Podophyllotoxin

5.1 Previous Examples of *o*-Quinodimethane Generation from Ammonium and Iminium Salts

Due to the problems associated with attaching our dienophile via the ether linkage, we sought other methods of arriving at our goal, which are adequately depicted in general structure **52**. All attempts at reaching the structure in which X is an oxygen atom had



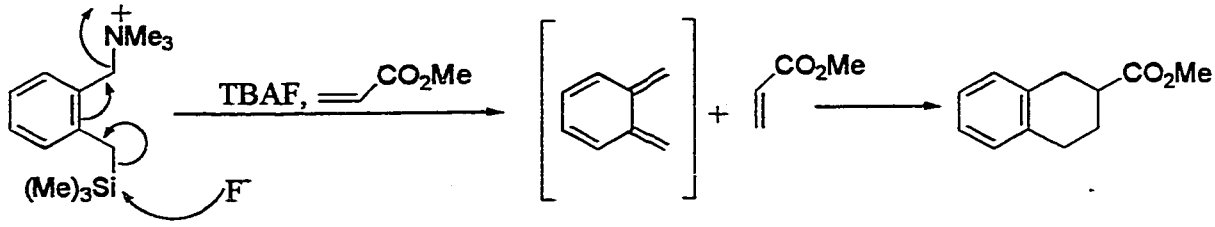
52: X = heteroatom, preferably O, NR, or S.

failed. It was reasoned, therefore, that the replacement of oxygen by another heteroatom, most likely nitrogen due to its trivalency, may result in success. Although thiols have been reacted with hydroxysulfones to form the corresponding *cis* sulfides[33], it was thought that there may result a significant challenge in the replacement of the sulfide with a hydroxyl

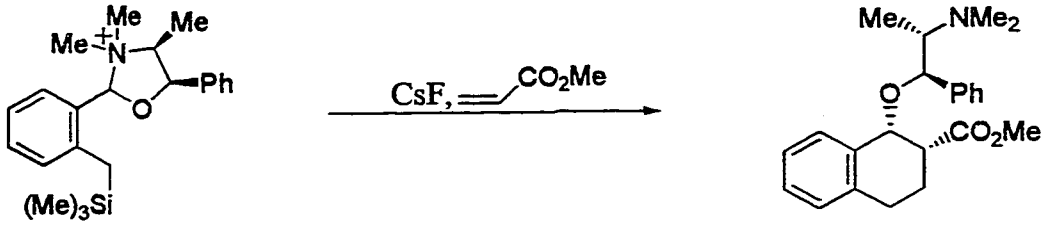
group in the later stages of the synthesis. Also, a thiol derived dienophile synthon may not be stable due to potential oxidation to the disulfide upon storage, as well as possible intramolecular Michael reaction of the thiol to the unsaturated ester. In addition to these potential problems, the relative ease of sulfide oxidation to sulfoxides and sulfones could prove to be very problematic, especially given the required periodate oxidation of the *vic*-diol moiety later in the synthesis. Nonetheless, given sulfur's greater nucleophilicity and lesser propensity towards hydrogen bonding, a tartrate-derived thiol may have served to be quite effective in at least the convergent step.

After some deliberation, and some research into nitrogen substituted *o*-quinodimethanes, it was decided to embark upon this path. In so doing, we also chose to leave behind the sulfur dioxide cheletropic extrusion methodology for generating the *o*-quinodimethane, and to focus on ionic mechanisms for formation of the reactive intermediate. Important precedents for this strategy have been published by the group of Saegusa and Ito, and Magnus' group.

Saegusa and Ito used benzylic ammonium salts as electron sinks to form *o*-quinodimethanes by generating anions at the *ortho* tolyl site. They used the trimethylsilyl group as a masked carbanion, synthesized the ammonium salt at the *ortho* position and initiated with fluoride ion a 1,4 elimination reaction to form the reactive diene, which was then trapped intermolecularly (Scheme 5.1)[34]. They have also managed to adapt this transformation to create optically active products (Scheme 5.2)[35]. The use of an optically active oxazolidine derived from ephedrine, which was then methylated to form the



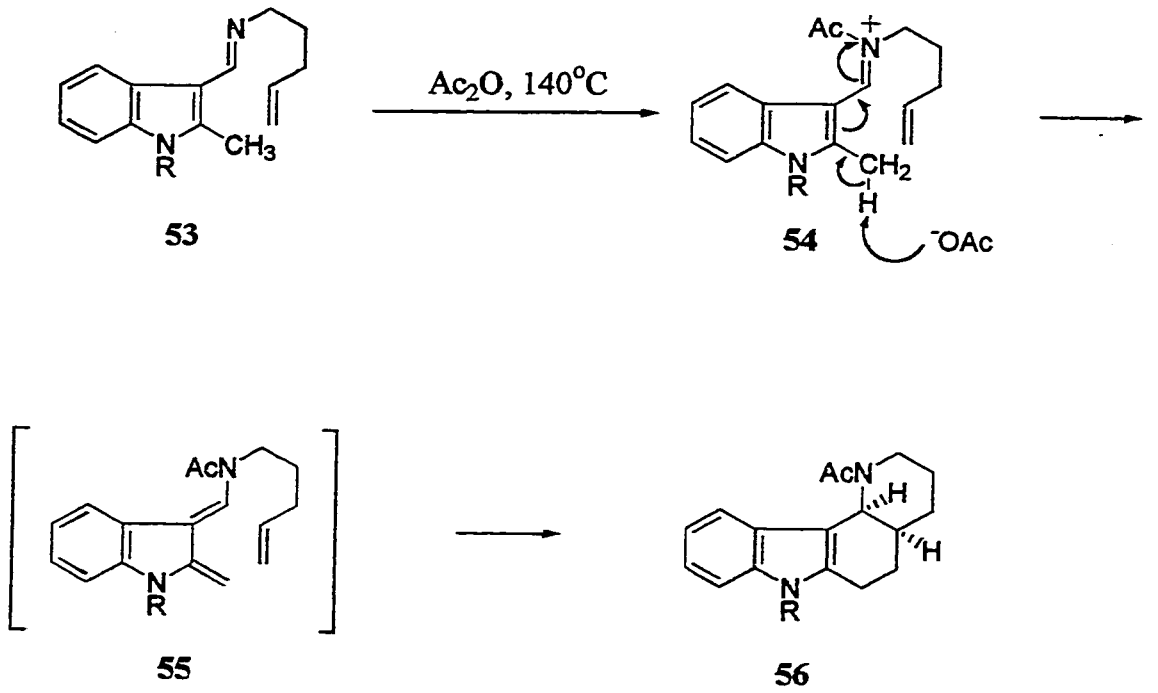
Scheme 5.1



Scheme 5.2

ammonium salt, led upon treatment with fluoride to an *o*-quinodimethane with a decided facial bias for dienophile approach. As a result, a 2:1 diastereomeric mixture was produced, with the depicted isomer predominating. Thus *o*-quinodimethane cycloadditions are amenable to asymmetric induction. This work also demonstrates the feasibility of using ammonium salts as electron sinks for *o*-quinodimethane generation.

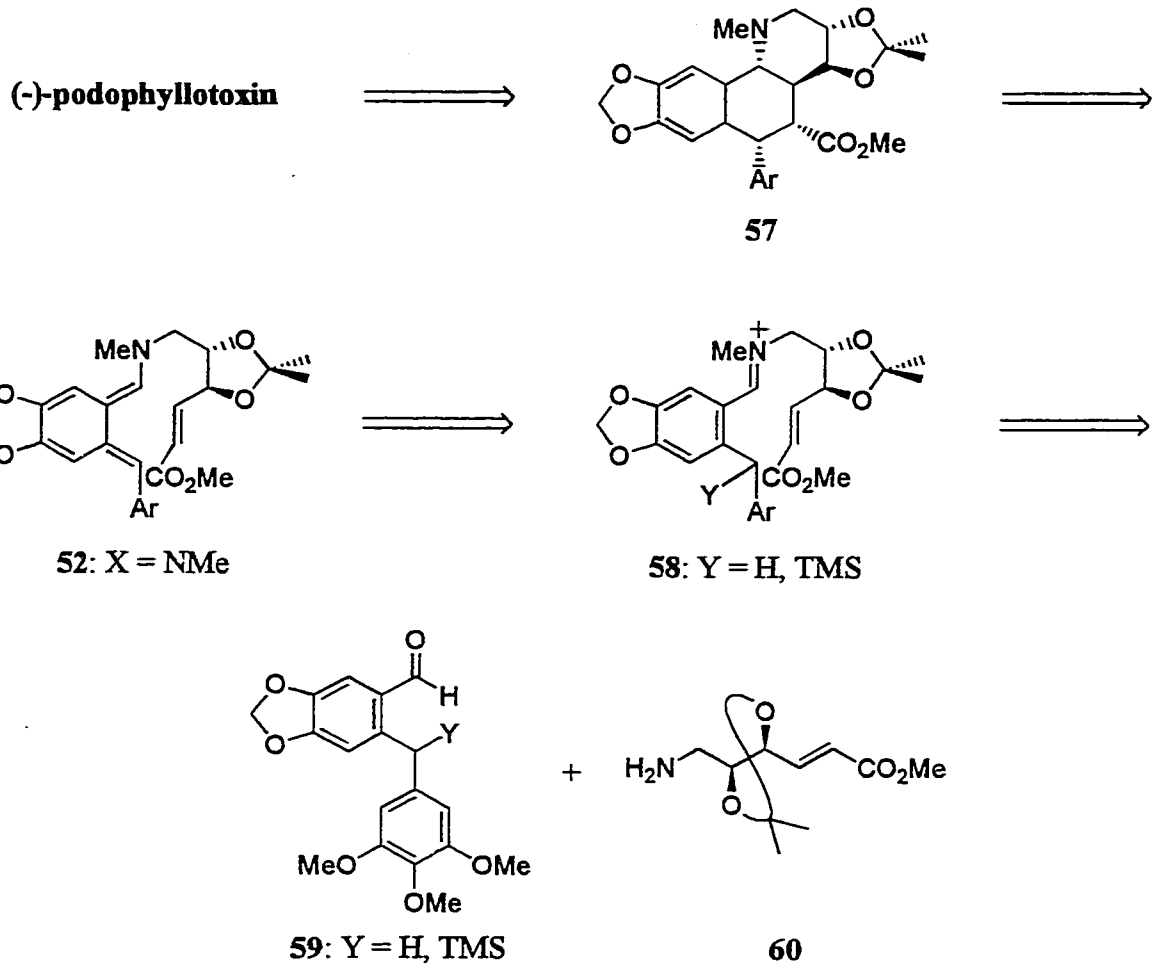
The prospect of using iminium salts rather than ammonium salts as powerful electron withdrawing groups had extensive precedence in the literature, predominantly through the work of Magnus. For the most part, the work done by this group focused on the generation of the related indole-2,3-quinodimethane from N-acyl iminium salts and the intramolecular trapping of this intermediate with dienophiles[36]. In these systems, the use of silicon as a masked carbanion was viable, however not necessary since the lesser



Scheme 5.3

amount of resonance energy present in the indole five-membered ring enables the quinodimethanes to be generated by deprotonation at the 2-methyl group with non-destructive bases. For example, 2-methyl-3-iminoindole **53**, when heated in acetic anhydride as solvent, formed iminium salt **54**, in which the protons of the "benzylic" methyl group were significantly activated towards removal by base. At the elevated temperature of the reaction, the acetate counterion was strong enough a base to deprotonate at this position and thus through a 1,4 elimination type pathway the indole-2,3-quinodimethane **55** was generated. Intramolecular trapping with even such an unactivated dienophile delivered the tetracycle **56** in 64% yield.

This work, coupled with the results of Saegusa and Ito, led us to attempt to make our *o*-quinodimethane **52** (X = NMe) via a hybrid of these two methodologies (Scheme 5.4). The new retrosynthetic analysis thus requires *o*-quinodimethane precursor **58**, an iminium salt derived from the methylation of the imine product of the condensation of two key fragments **59** and **60**. The diaryl methane **59** (Y = H) has been synthesized before[28], and tartrate-derived amine **60** should be readily available from the chiral dienophiles that we already had in hand. It was decided to synthesize the fully oxygenated diarylmethane in

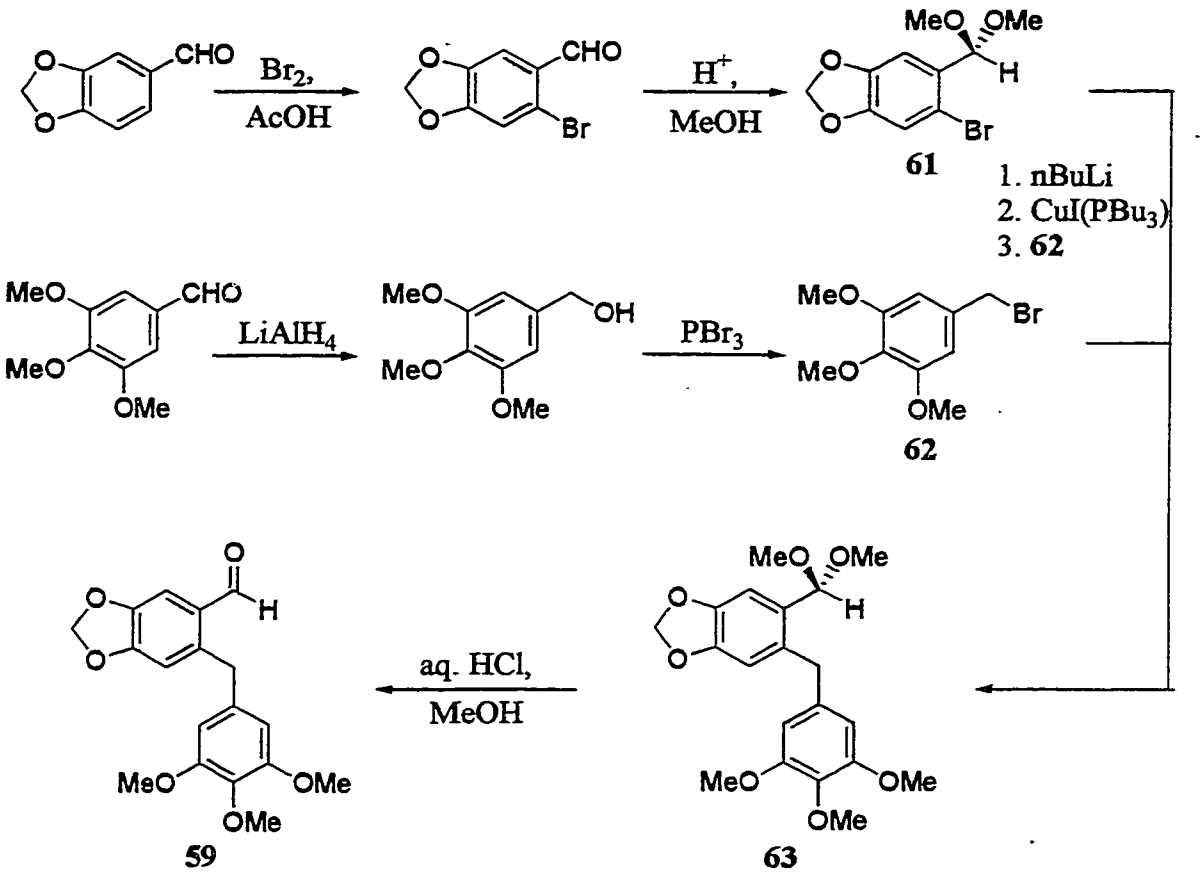


Scheme 5.4

this instance, since it seemed unlikely that the model system would act as a reasonable model, due to significant differences in imine stabilities and pKa's of relevant protons.

5.2 Synthesis of the Fully Functionalized Diarylmethane

Following the procedure of Glinski and Durst[28], **59** was synthesized in large quantities. Bromination of piperonal with bromine in acetic acid afforded 2-bromopiperonal in 67% yield after recrystallization from ethanol. Acetalization of the aldehyde proceeded



Scheme 5.5

smoothly using catalytic Dowex 50W200 acidic resin and trimethyl orthoformate in methanol at reflux. Pure **61** was obtained in 97% yield after passing the crude product through a plug of silica gel. Next, reduction of trimethoxybenzaldehyde with sodium borohydride in *iso*-propanol yielded the benzyl alcohol in pure enough form for use in the next step. Thus, treatment of the alcohol with two equivalents of freshly distilled phosphorus tribromide in dichloromethane for twenty-four hours, followed by evaporation

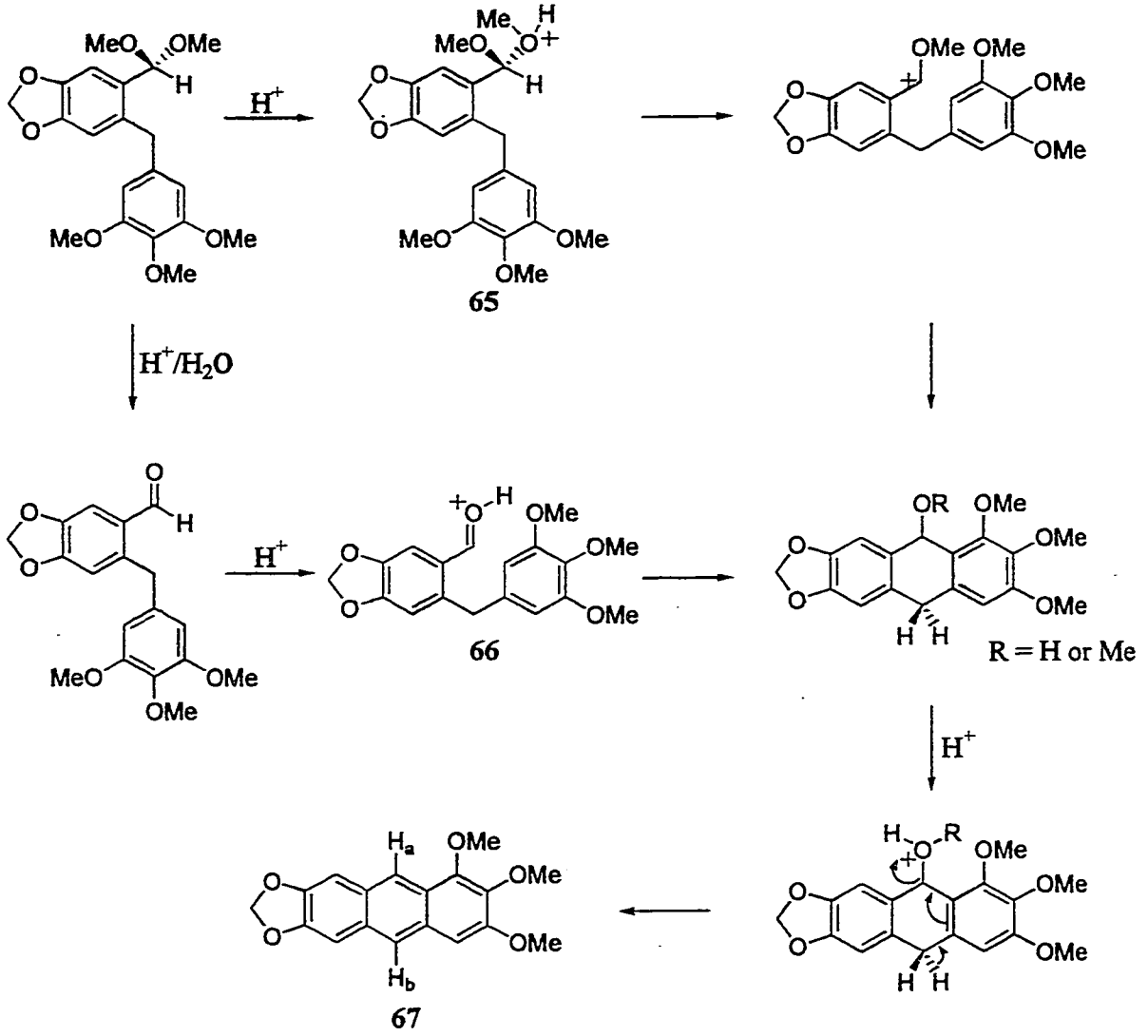
62 **64**

of solvent and excess reagent, and a bicarbonate workup delivered the bromide **62**. The product was homogeneous by ^{1}H and ^{13}C NMR, showed very minor byproducts by TLC, but was coloured an intense burgundy red. Mass spectral data confirmed the incorporation of the bromine atom. Previous reports of syntheses of this compound[28] never mentioned any abnormal coloration, and it was assumed that this was simply due to a highly coloured trace impurity, likely of structure **64**. Since spectral data implied that the product was quite pure, no attempts were made to further purify the relatively unstable benzyl bromide, and it was used as is in the subsequent coupling step. The reported coupling protocol, which involved forming the arylcuprate reagent derived from **61** by halogen-metal exchange followed by transmetalation with soluble copper iodide and subsequent reaction with electrophile **62**, had been known to be somewhat irreproducible[37]. The 84% yield previously reported[28] was, in our hands, never attainable,

however when the copper iodide-tributylphosphine catalyst was freshly prepared[38], the yield of the coupling was consistently about 65%, even on scales of up to 35 mmoles. The copper reagent can be stored at -30° C for up to one year in the dark and under an inert atmosphere. After a few hours at room temperature or in light the very faint green solid begins to convert into a deep green sludge.

The final step to deliver the desired aldehyde **59** was expected to be a very simple acid catalyzed hydrolysis of the acetal **58**. Interestingly, subjection of the acetal to catalytic aqueous HCl in methanol for several hours resulted in the precipitation of light pink needles from the reaction mixture. It was assumed that this was the desired product, but filtration and inspection of this product by ^{1}H and ^{13}C NMR revealed that the starting acetal had been cleanly converted into a crystalline product that did not bear an aldehyde. The first hint as to the structure of this compound came from TLC analysis, which showed a very non-polar, highly fluorescent compound. This, coupled with mass spectral results showing a base peak at M-H_2O relative to the desired aldehyde led us to look for dehydration products that could account for fluorescence. The lack of significant fragmentation in the EI-MS implied a very stable product. ^{1}H NMR showed resonances at 8.36 ppm and 7.98 ppm, with no sign of any aldehyde resonance. The lack of aldehyde functionality was also observed in the ^{13}C NMR and IR spectra. It was therefore proposed that an intramolecular Friedel-Crafts reaction of the trimethoxyaryl group onto either the protonated acetal **65** or the protonated aldehyde **66** had occurred, followed by a dehydration to yield the ultimate product, anthracene **67** (Scheme 5.6). It is likely that the resonances in the ^{1}H NMR spectrum at 8.36 and 7.98 ppm belong to H_a and H_b

respectively; this is in the usual range for the protons on the middle ring of anthracenes. The formation of this product and its mechanism agree with Charlton's report of anthracene formation during attempts to trap the photoenols of very electron rich *o*-benzyl benzaldehydes with sulfur dioxide[37b]. In his case, the intramolecular cyclization/ dehydration sequence of the aldehyde was catalyzed by trace amounts of sulfurous acid in



Scheme 5.6

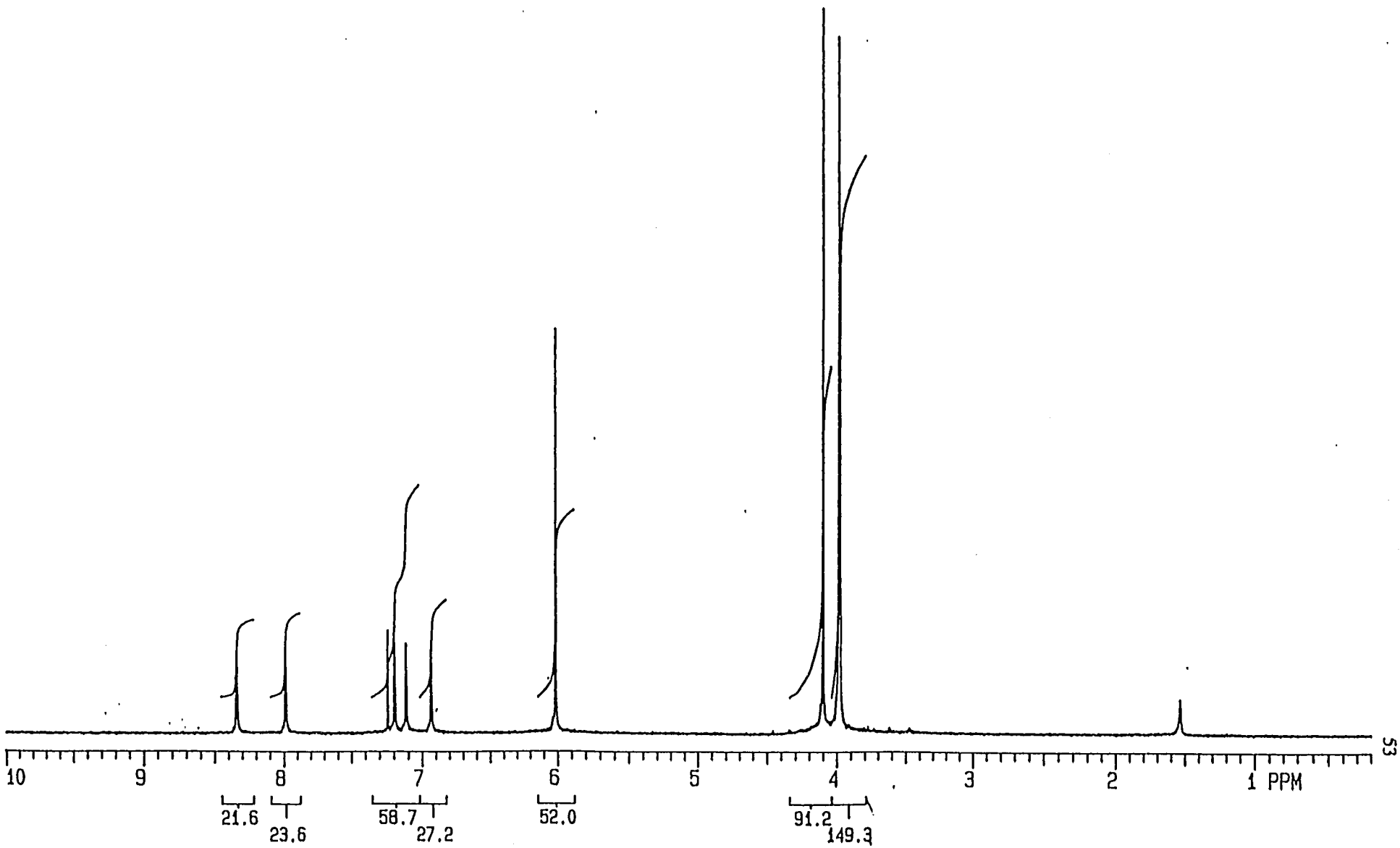
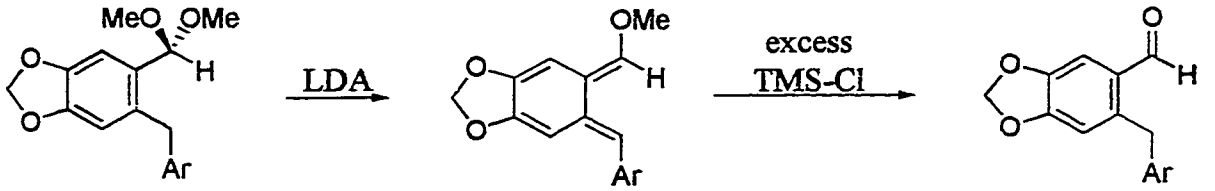


Figure 5.1; 200 MHz ^{1}H NMR Spectrum of Anthracene **67**.

the reaction medium. For the purposes of acquiring the desired aldehyde **59**, it sufficed to react the acetal with aqueous 10% HCl / methanol 10:1 for fifteen minutes, at which point some of the desired product began to precipitate out of solution. Neutralization of the mixture with solid sodium bicarbonate followed by an extractive workup afforded pure aldehyde in quantitative yield.

Attempts to introduce the silyl group as the masked benzylic carbanion were next initiated. The acetal **63** was seen as the most likely candidate to undergo benzylic silylation, since there was no obvious electrophile to complicate the deprotonation at the doubly benzylic position by strong organolithium bases. Thus treatment of **63** with one equivalent of *n*-butyllithium in THF at -78° C followed by quenching with excess trimethylsilyl chloride led to a clear solution in which consumption of most of the starting acetal and formation of a more polar compound was visualized by TLC. ^{1}H NMR showed significant quantities of the aldehyde **59** and a minor amount of anthracene, with no remaining acetal. Attempts to effect this silylation reaction using LDA as base resulted in quantitative conversion to the aldehyde, which was pure by TLC and NMR analysis after aqueous workup. A probable explanation for this clean and unexpected deprotection of the aldehyde stems from Rickborn's observations that 1,4 elimination of methanol from *o*-tolualdehyde dimethyl acetal leads efficiently to the methoxy substituted *o*-quinodimethane, which can then be trapped by suitable dienophiles (Scheme 5.7)[39]. If we assume that the doubly benzylic proton is being removed, causing a 1,4 elimination of methanol in this case also, then we would obtain, at least transiently, the *o*-quinodimethane that is also essentially an

Scheme 5.7



Scheme 5.8

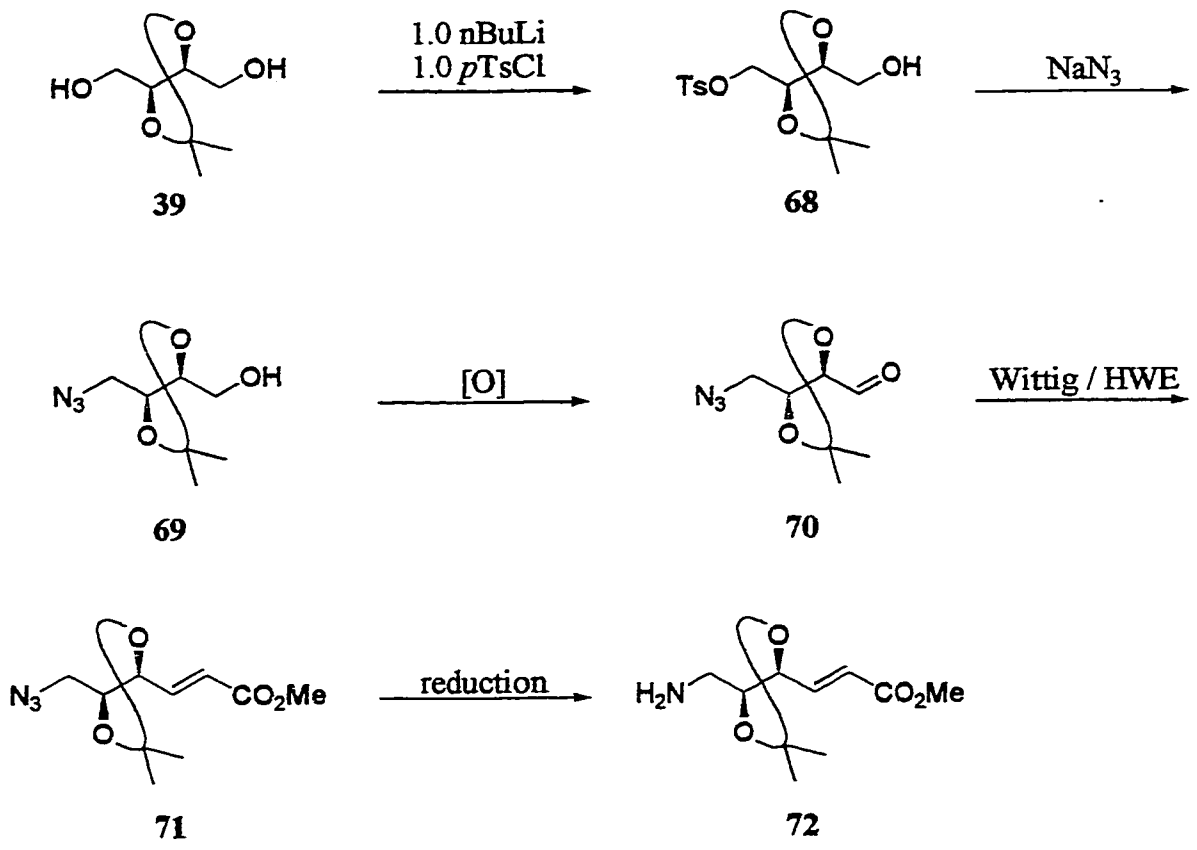
unstable methyl enol ether. The excess TMS-Cl present could then promote hydrolysis of this ether to form either the conjugated enol which would tautomerize rapidly back to the aldehyde, or the silyl enol ether that would be hydrolyzed upon aqueous workup or on contact with silica gel. Assuming that this was a correct analysis, it was an encouraging result, since it implies that deprotonation at the doubly benzylic position proceeds efficiently with organolithium bases, thus the synthetic plan calling for 1,4 elimination in a more activated system may have a reasonable chance of success.

Although it appeared unlikely that the silyl group was necessary for the generation of the *o*-quinodimethane via this ionic mechanism, two more attempts at its introduction were nonetheless undertaken. It was thought that perhaps the aldehyde itself may be a reasonable candidate, since deprotonation was likely to be favoured by the *ortho* electron withdrawing group, and it was known that non-nucleophilic strong bases such as LDA

were likely to be strong enough for the deprotonation. Therefore, in two separate events, **59** was treated with LDA and LHMDS in the presence of excess TMS-Cl. The only product discernible by TLC and ^{1}H NMR of the crude reaction mixtures was anthracene **67**. Otherwise, mostly aldehyde remained. This result implied that TMS-Cl was a sufficiently strong Lewis acid to catalyze the intramolecular Friedel-Crafts and subsequent dehydration reactions leading to the unwanted anthracene. As a test of this hypothesis, the aldehyde was stirred in THF at room temperature in the presence of five equivalents of the Lewis acid, and complete conversion to anthracene was observed by TLC and ^{1}H NMR within thirty minutes. Furthermore, it was found that treatment of the aldehyde with LHMDS followed by a quench with D_2O led to complete recovery of starting material with absolutely no deuterium incorporation seen by NMR. These are strange results, given that deprotonation of the dimethyl acetal does seem to occur. Since it was hoped that *o*-quinodimethane generation from the iminium salt should be a more efficient process, no further study of the silylation was undertaken, and effort was concentrated on attempts to manufacture the chiral amine as tether / dienophile.

5.3 Attempted Synthesis of the Tartrate-Derived Amine Dienophile

Given that a reliable method for the production of large quantities of tartrate-derived alcohols **36**, **49**, and **51** was available, it was anticipated that the corresponding amines



Scheme 5.9

would be easily accessible. Originally, it was thought that the most efficient manner to synthesize the desired amine would involve monotosylation of the symmetrical tartrate-derived diol **39**, followed by displacement with azide (Scheme 5.9). Oxidation of the remaining hydroxyl group to the aldehyde **70** and subsequent Wittig or Horner-Wadsworth-Emmons olefination should yield the azide **71**, requiring only selective reduction to afford the amine **72**.

In practice, the monotosylation reaction worked nearly as efficiently as the monosilylation of **39** using the same conditions for generation of the lithium monoalkoxide followed by addition of *p*-toluenesulfonyl chloride. This yielded the tosylate in 95% yield, which was

not particularly stable, so it was immediately reacted with excess sodium azide in DMF for five hours at 80° C to yield the monoazide **69** in 85% yield. This product demonstrated the expected hydroxyl and azide absorption bands in the IR spectrum at 3419 and 2127 cm^{-1} respectively. Unfortunately, the oxidation of this tartrate-derived primary alcohol was no simpler a task than it had been for the other similar compounds with which we had already dealt. Attempted oxidations using Swern conditions, Dess-Martin reagent, and TEMPO/NaOCl all afforded very messy crude products, likely the hydrated aldehyde once again. In this particular case, distillation was not a reasonable option due to the presence of the azide functionality. Another problem arose in these reactions, the mass balance was always very low after aqueous workup. This could likely be attributed to the water solubility of the hydrate, or perhaps the volatility of the product, although this is somewhat less likely. We nonetheless attempted to olefinate the hydrate under conditions of excess Wittig reagent and managed to isolate the desired unsaturated ester **71** and the corresponding *Z* isomer in a 55:45 ratio in a combined yield of only 45%. These were easily separable by flash chromatography and showed ^1H NMR characteristics that were very similar to the related alcohol **36**, with an upfield shift of the protons α to the azide; these proton resonances were seen as two doublets of doublets at 3.25 and 3.58 ppm for the desired *E* isomer. Alternatively, to try to maximize the *E*:*Z* ratio, a Horner-Emmons-Wadsworth reaction using the Roush conditions was attempted on the crude Swern product. The fact that this reaction is supposedly very sensitive to water did not seem to interfere in this case, as we simply used 2.5 equivalents of all reagents in order to remove the water of hydration and regenerate the aldehyde *in situ*. The only isolable product was the desired *E* isomer but the overall yield in this case was on the order of 25%, due mostly

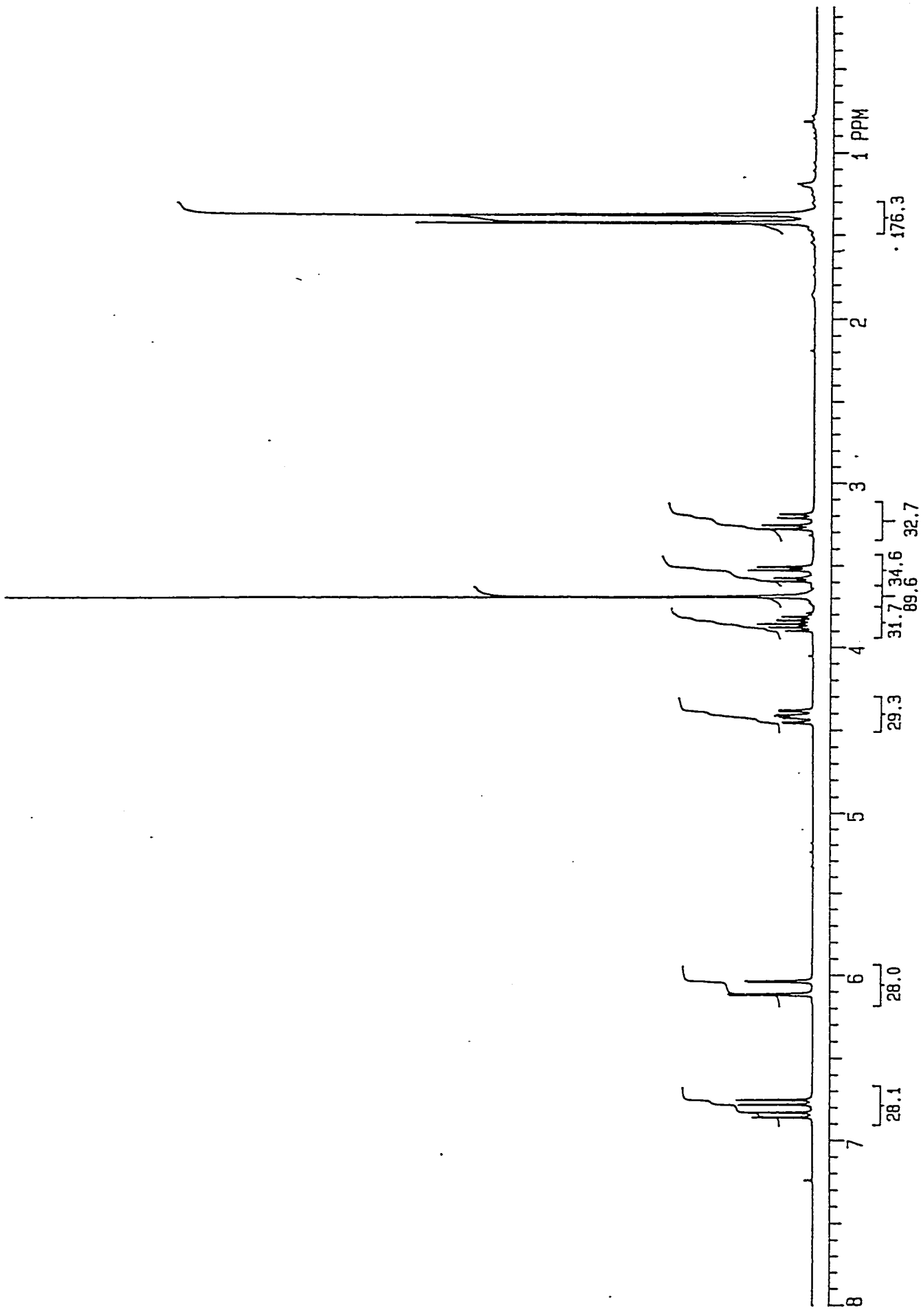


Figure 5.2: 200 MHz ^{1}H NMR Spectrum of Azide (*E*)-71.

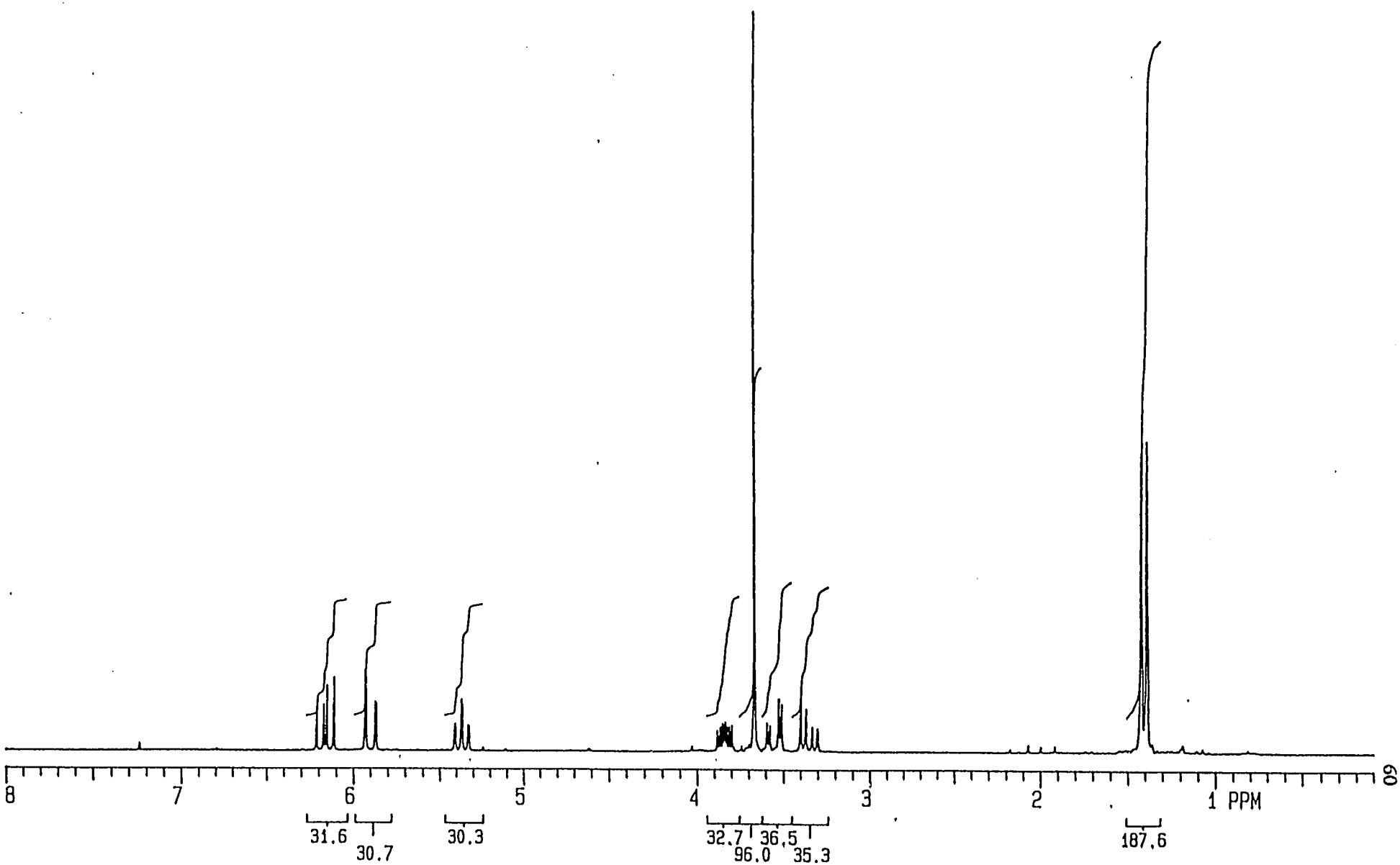
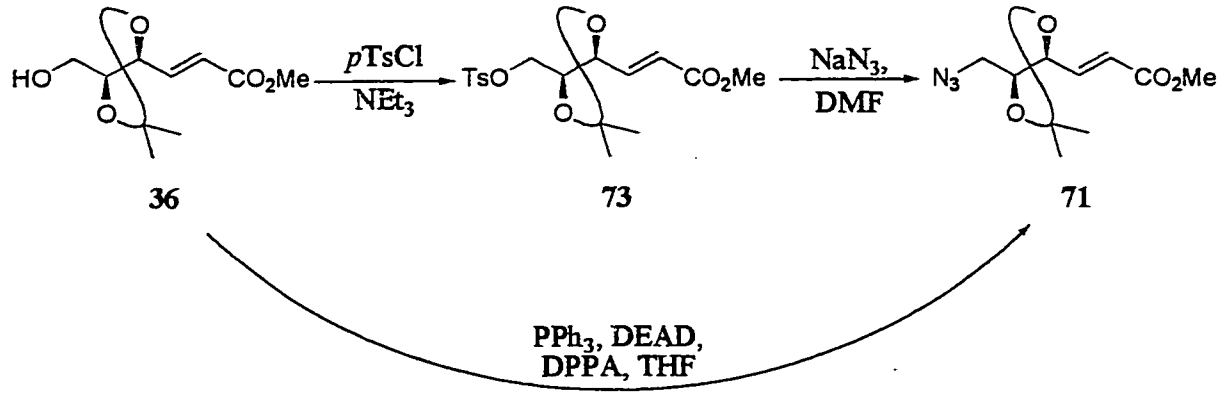


Figure 5.3: 200 MHz ^{1}H NMR Spectrum of Azide (*Z*)-**71**.

to losses in the Swern workup. A slightly modified strategy involving oxidation and subsequent olefination of the monotosylate **68** failed to result in any improvement, due likely to the instability of the tosylate to distillation temperatures. At this point, since we required significant quantities of the azide, and multi-gram quantities of the alcohol **36** were then in hand, we decided to convert this compound into **71** (Scheme 5.10). Tosylation of the hydroxyl group proceeded uneventfully to yield **73** in quantitative yield. Treatment of the tosylate with sodium azide required temperatures of at least 75° C in DMF for reasonable reaction rates, and under these conditions some byproducts were observed. The azide was isolated in up to 58% yield, and several other products were detected in the ^{1}H NMR of the crude reaction mixture; the major one appeared to be derived from the conjugate addition of azide to the unsaturated ester, as no double bond proton resonances were seen. As expected, the desired product showed identical spectral characteristics to the one produced from the route depicted in Scheme 5.9. In order to try to maximize the yield of azide **71**, a Mitsunobu azidation reaction with diphenyl-



Scheme 5.10

phosphoryl azide (DPPA)[40] was attempted. In this reaction, DPPA plays the role of the acidic component in the Mitsunobu process, replacing the less convenient hydrogen azide gas, while diethyiazodicarboxylate (DEAD) and triphenylphosphine serve as usual to activate the hydroxyl group towards nucleophilic attack. This reaction proceeds very smoothly with the use of two equivalents of all three reagents, and complete conversion is effected in about three hours at room temperature in THF. Unfortunately, the excess DPPA has an Rf nearly identical to the desired product in every solvent combination attempted. The best possible separation was accomplished using toluene as eluant and then the product was isolated in about 90% yield, but with about 10 mol % of DPPA contaminant (close to 80% yield of the azide). Attempts to use one equivalent of DPPA, or to replace it with other azide sources such as $TMSN_3$ resulted in simpler separations, but less efficient reactions.

Thus three different, somewhat reliable routes to **71** had been worked out, and given that the azide was not particularly stable (significant decomposition overnight at room temperature, about 10% decomposition overnight in the freezer), reduction to the amine and convergent formation of the imine were investigated.

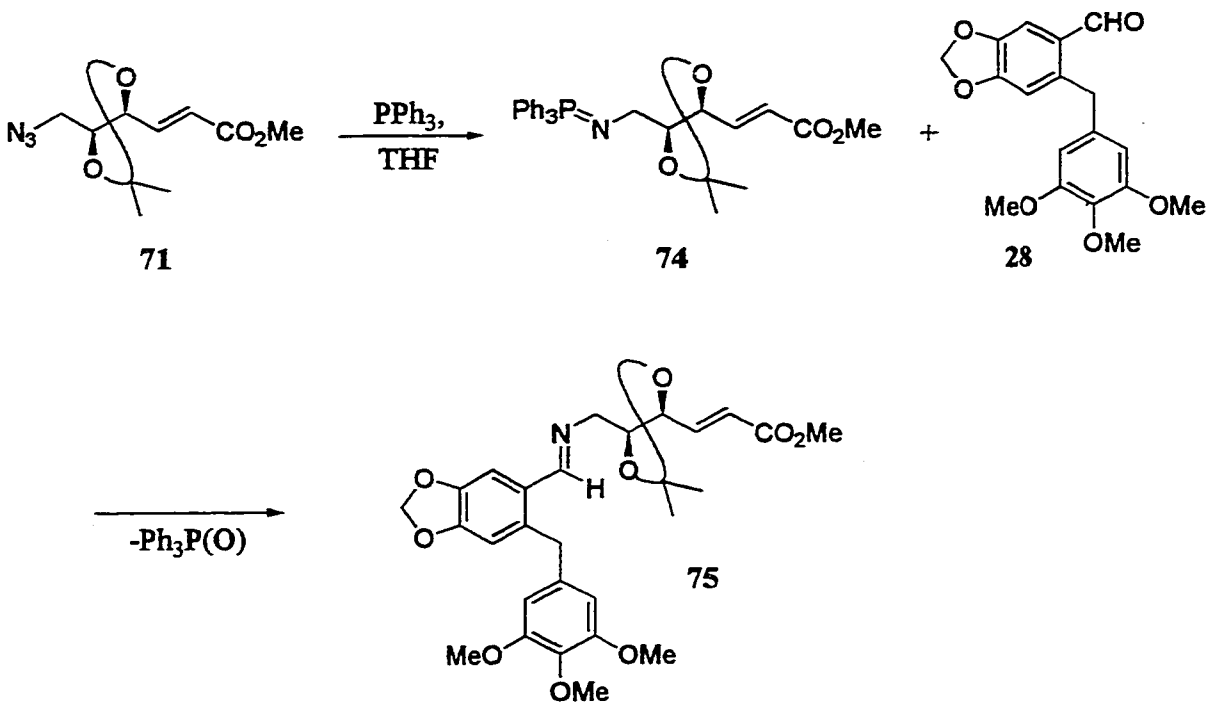
Selective reduction of the azide to the amine without disruption of double bond functionality has wide precedence. Some of the known procedures include the Staudinger reaction using triphenylphosphine followed by aqueous workup[41], reduction with hydrogen and Lindlar's catalyst[42], and the use of dibutyltin dihydride[43], stannous

chloride[44], or dithiols[45] as reducing agents. Subjection of the azide **71** to Staudinger reaction conditions did not result in any isolated product whatsoever, which is a curious result since the use of the intermediate iminophosphorane in an aza-Wittig reaction with our substituted benzaldehyde did in fact work reasonably well (discussed in Section 5.4). Reduction with hydrogen and Lindlar's catalyst seemed to proceed very cleanly by TLC, and this did result in the isolation of relatively clean amine **72** as a clear colorless oil on a 135 mg scale. The crude yield was nearly quantitative. The ^{1}H NMR clearly demonstrated an upfield shift in the resonances due to the protons adjacent to nitrogen; the two doublets of doublets were seen at 2.98 and 2.82 ppm for the amine. The double bond of the unsaturated ester was completely unaffected. The product was stored frozen in benzene overnight, but had decomposed significantly nonetheless. Attempts to purify the amine by careful chromatography resulted in the isolation of only 25mg of reasonably clean product, a mere 20% yield. This result was only reproduced with any success one more time; in other cases significant double bond reduction was effected, or nearly complete decomposition occurred. The use of dibutyltin dihydride, which was made from the lithium aluminum hydride reduction of dibutyltin dichloride[46], did not yield substantially better results. The crude product, which amounted to only about 60% recovery, consisted mostly of **72**, but any attempts to purify the compound, either by chromatography or by isolation as the hydrochloride or tosylate salts did not improve the purity and resulted in dramatic losses in yield. The reason for the instability of this product as compared to the corresponding alcohol **36** is not evident. It is conceivable that the amine, a better nucleophile than the hydroxyl group, may attack the α,β unsaturated ester intramolecularly at a reasonable rate, forming a highly substituted pyrrolidine

product. This hypothetical product, however, has not been purified or characterized, but a product without double bond resonances has been seen in the proton spectra in all three of the different reaction mixtures and in the decomposing product. No further work on the preparation of the amine was undertaken, since it seemed likely that the reduction itself was not a difficult process, but the instability of the resultant product precluded the isolation of quantities of reasonably pure **72**. The *in situ* generation of the amine equivalent, an iminophosphorane, and its reaction with the aldehyde **28** was the next avenue that was investigated.

5.4 Attempted Formation of the Imine *o*-Quinodimethane Precursor

It was hoped that the convergent step involving imine formation would fare better than the attempted formation of the ether of the hydroxy-sulfone in Chapter 4. The most reasonable approach given the instability of amine **72** involved an aza-Wittig reaction between azide **71** and aldehyde **28** (Scheme 5.11). In the aza-Wittig reaction, triphenylphosphine (or other phosphines or phosphites) attacks the azide, releasing nitrogen gas and forming an iminophosphorane intermediate **74**, which is essentially a phosphorus-nitrogen ylide. This nucleophilic ylide then attacks the aldehyde in much the same way as a regular Wittig reagent does, forming an intermediate betaine which collapses to yield the imine **75** and triphenylphosphine oxide. This reaction was attempted several times with the freshly purified azide, one equivalent of triphenylphosphine, and one equivalent of aldehyde in THF at reflux. Within two hours, the reactions were essentially



Scheme 5.11

complete, and the resulting ^{1}H NMR spectra generally indicated a level of purity that correlated well with the purity of the starting azide. The characteristic imine proton resonance was observed at 8.49 ppm, and disappearance of the azide was noted by the slight shift in all resonances attributed to the tartrate derived synthon, with substantial downfield shift of the protons adjacent to the nitrogen from 3.25 and 3.58 ppm for the azide to a multiplet around 3.7 to 3.8 ppm in the imine. The imine product was hydrolytically very unstable. Decomposition was rapid on silica, even if washed with an ether solution of triethylamine followed by thorough drying at 130° C for 24 hours. Attempts to remove the triphenylphosphine oxide byproduct by filtering through a short column of dried basic alumina even resulted in substantial decomposition to the aldehyde and amine (which decomposed further). Treatment of the crude imine with excess methyl

iodide in ether did result in the precipitation of an off-white solid, but upon filtration under a stream of nitrogen, the solid rapidly decomposed to a brown gum, which was identified as a mixture predominantly of aldehyde and some of the expected *N*-methyl secondary amine along with other contaminants. Naturally, it was to be expected that if the imine was rapidly and easily hydrolyzed, the iminium salt should be even more prone to such decomposition. Since it seemed that removal of the triphenylphosphine oxide was not going to be trivial, the only options left were to attempt to isolate pure amine **72** again and attempt to condense it directly with either the aldehyde **28** or its dimethyl acetal **63**. Generation of the *o*-quinodimethane and subsequent cycloaddition would then be attempted on the crude imine, with purification only afterwards. Unfortunately, reasonably pure amine **72** was only ever isolated in reasonable quantity once, and thus reaction of the acetal **63** with the somewhat pure amine was carried out on only a 0.5 mmol scale, with catalytic *p*-toluenesulfonic acid and activated molecular sieves in benzene at reflux. ^{1}H NMR did reveal near completion of the reaction and an adequately pure product, with a trace of anthracene (**67**) formation. After neutralization and evaporation of the solvent, the product was carefully divided in two; methylation with excess methyl iodide followed by treatment with LDA to try to induce *o*-quinodimethane generation was carried out on one half, and the other portion was subjected to treatment with boiling acetic anhydride (Magnus' conditions). No clean products that spectroscopically resembled the desired cycloadducts were isolable from either reaction mixture.

A final approach to the amino-*o*-quinodimethane was made by alteration of the sequence in which the iminium salt was made. Instead of attempting to form the unstable imine **74**

and then alkylating the imine nitrogen, it was considered that perhaps more success would arise from the formation of a stable imine, followed by alkylation of the nitrogen with a tartrate-derived electrophile (Scheme 5.12). Given that imines with electron-rich aryl substituents are known to be more stable than alkyl-substituted imines, acetal **63** was condensed with one equivalent of *p*-anisidine using camphorsulfonic acid as catalyst in benzene with activated molecular sieves to drive the equilibrium towards products. Following addition of solid potassium carbonate to neutralize the acid and subsequent filtration and removal of solvent, a beige solid was isolated in quantitative yield that was identified as the spectroscopically pure imine **76**. The imine proton was visible in the ^{1}H NMR spectrum at 8.63 ppm, and the imine C=N stretch was strongly visible at 1601cm^{-1} in the infrared spectrum. The tartrate-derived electrophile needed to be synthesized next. Given that there was a substantial supply of cyclohexylidene protected compound **51**, it was chosen as a logical substrate for sulfonation to deliver the requisite electrophile. Thus, exposure of alcohol **51** to excess *p*-toluenesulfonyl chloride and triethylamine in dichloromethane afforded the desired tosylate **77** in 76% isolated yield. The addition of imine **76** to one equivalent of electrophile **77** and stirring at room temperature in dichloromethane for twenty-four hours did not result in any reaction whatsoever when monitored by TLC. Although it was expected that the iminium salt product would be labile under TLC conditions, it was anticipated that this method of analysis would still be useful in visualizing the disappearance of starting materials, and the appearance of the iminium salt's hydrolysis products, the secondary amine **78** and aldehyde **59**, should also be detectable. Therefore the reaction mixture was heated to reflux for another twenty-

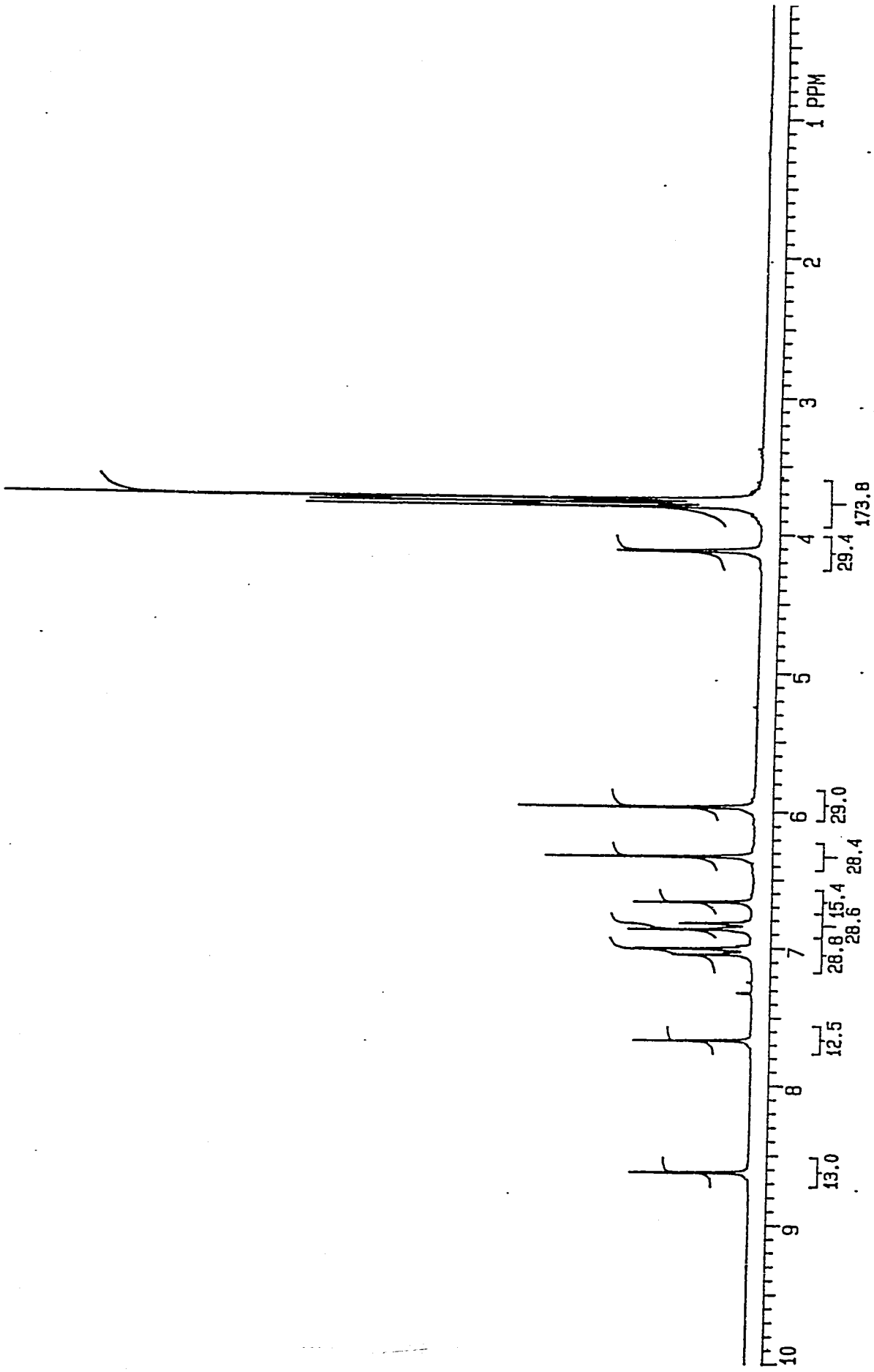


Figure 5.4: 200 MHz ^{1}H NMR Spectrum of Imine **76**.

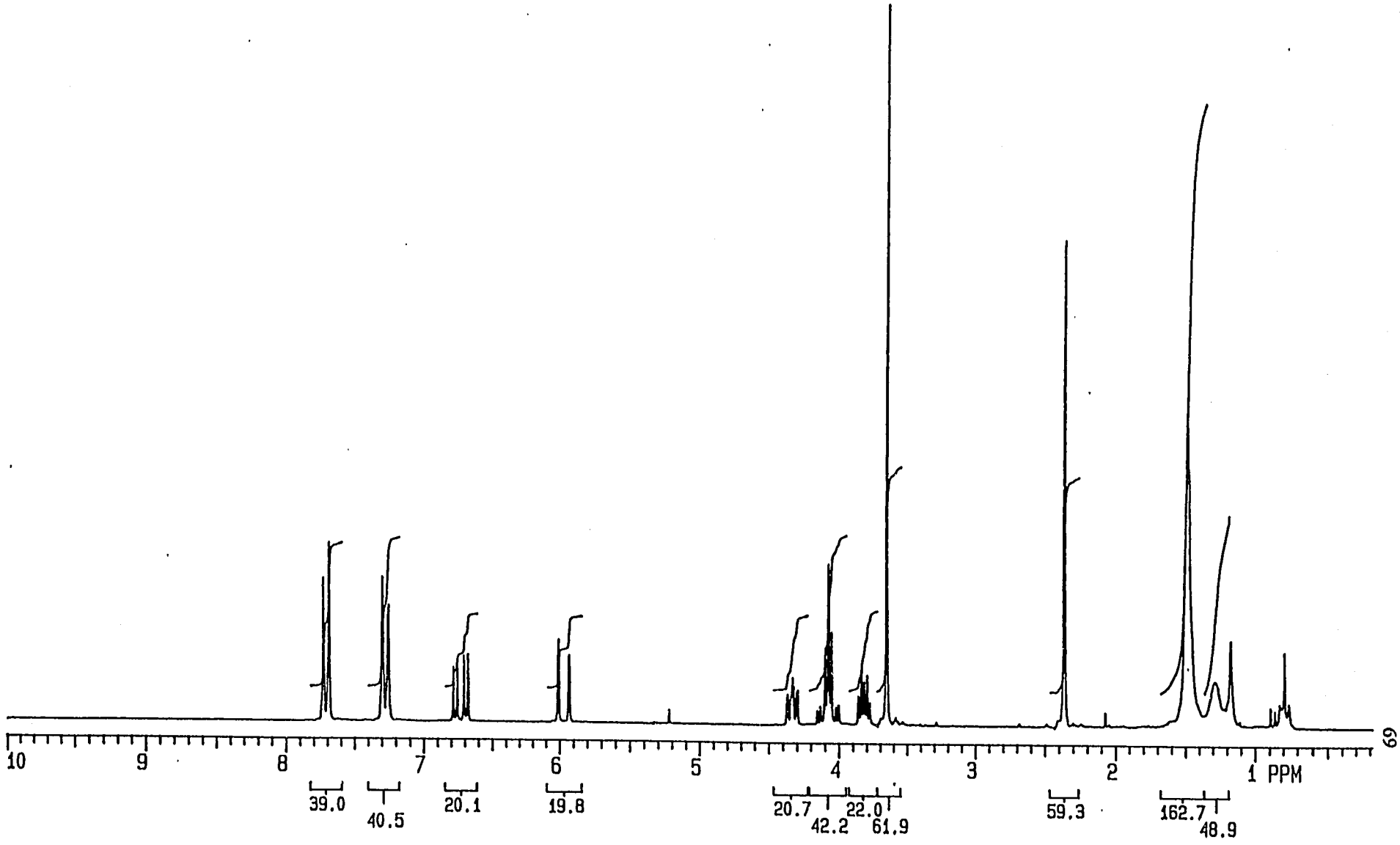
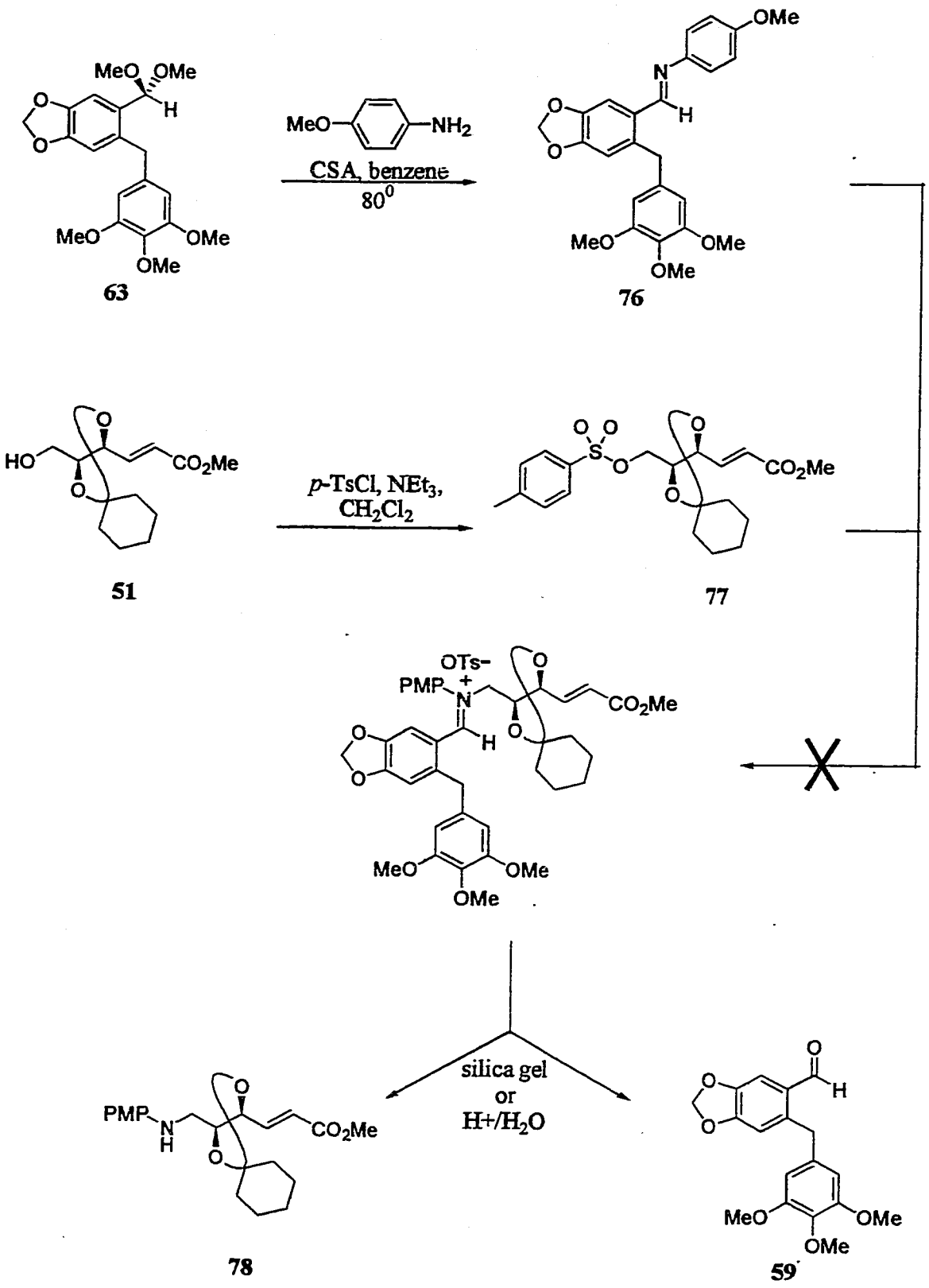


Figure 5.5: 200 MHz ^{1}H NMR Spectrum of Tosylate 77.


MeO
OMe
H
MeO
NH2
CSA, benzene
80°
OMe
N
H
MeO
OMe
OMe
63
76
HO
CO2Me
p-TsCl, NEt3,
CH2Cl2
51
77
OTs-
PMP
N
H
CO2Me
silica gel
or
H+/H2O
PMP
N
H
CO2Me
78
59

Scheme 5.12

four hours, and still no progress had occured by TLC or ^{1}H NMR. To ascertain whether or not this system would react at all, the solvent was replaced with toluene, and this was heated to reflux with no effect. Finally 10 mol % tetrabutylammonium iodide was added to see if iodide may be a better and less encumbering leaving group, but again starting materials were recovered in good yield, with only a trace of anthracene **67** visible by TLC and ^{1}H NMR.

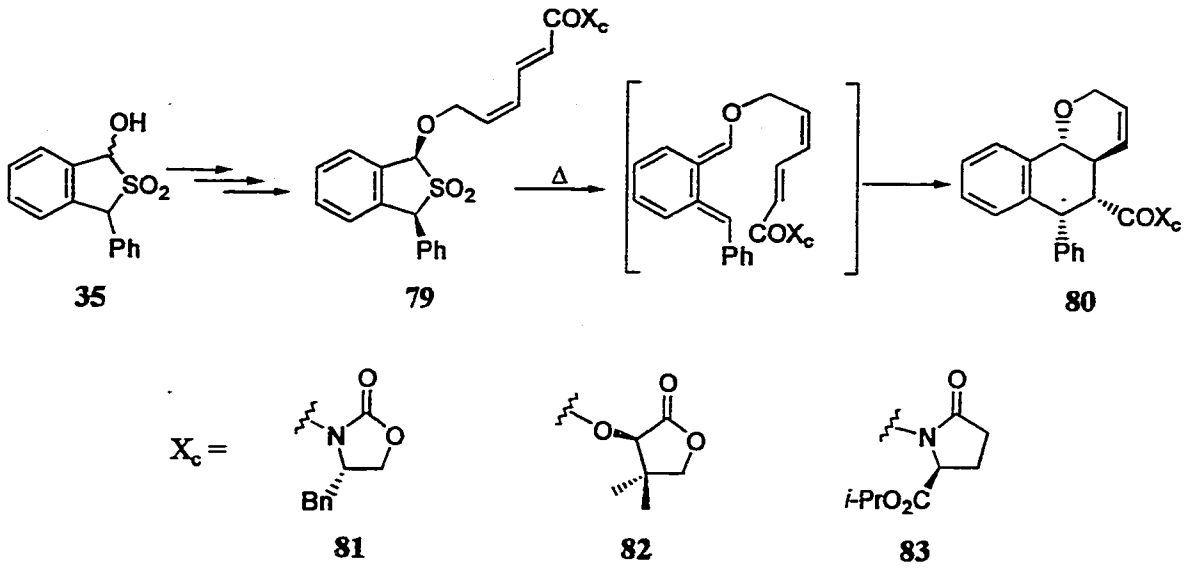
At his point, due to the instability and difficulty in purification of the azide, the amine, the imine and the iminium salt, and the complete lack of reactivity of the imine nitrogen as a nucleophile, the nitrogen based *o*-quinodimethane route towards podophyllotoxin was abandoned.

Chapter 6

Miscellaneous Synthetic Approaches and Related Methodology

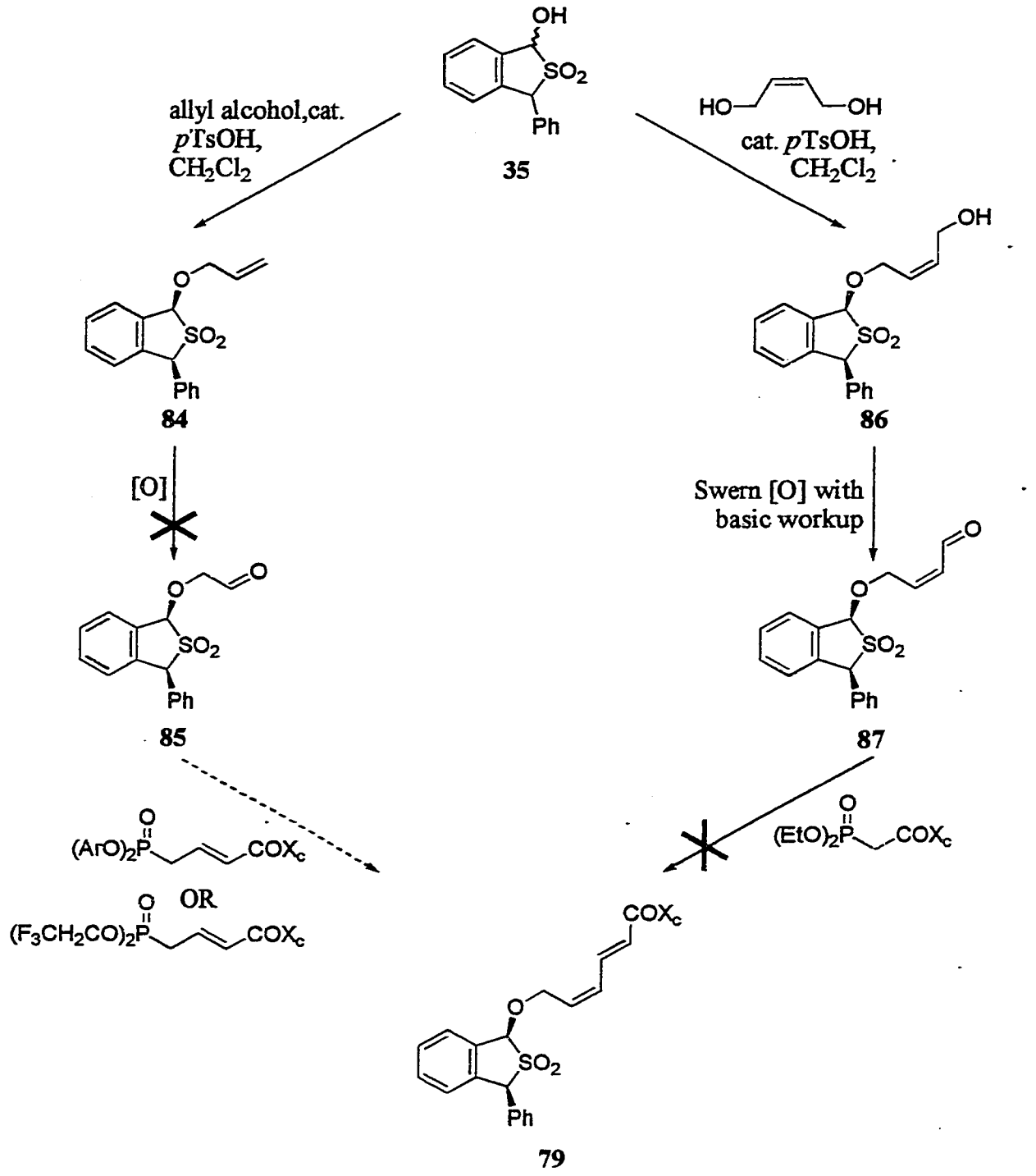
6.1 Attempts to Build a New Chiral Dienophile onto the Hydroxysulfone

Since all convergent attempts at setting up the intramolecular Diels-Alder reaction had failed, a less convergent approach was briefly examined in the hopes of validating the concept behind the synthetic approach. A general approach was adopted with general structure **79** as a goal (Scheme 6.1). Chiral induction was to be derived from an auxiliary at the terminal end of the unsaturated ester dienophile. In this approach, the more easily available hydroxy-sulfone derived from *o*-benzyl benzaldehyde was again used as a model compound. It was hoped that significant diastereofacial bias would be imparted on the *o*-quinodimethane intermediate due to the presence of these chiral moieties, resulting in a diastereomerically enriched aryl-tetralin system **80**. The simplest chiral auxiliaries available for use in this proposed system were the Evans' oxazolidinones, (*R*)-pantolactone, and esters of pyroglutamic acid, as shown in the partial structures **81**, **82**, and **83** respectively. Since all attempts at connecting complex and electron deficient alcohols to the hydroxy-sulfone had failed, the chiral dienophile was, in this case, going to be constructed from a simpler ether of the hydroxy-sulfone.



Scheme 6.1

It was well established that simple alkanols react easily with the parent hydroxy-sulfone, forming the corresponding alkyl ethers in good yield with a *cis* geometry about the five-membered sulfone ring. Two obvious approaches materialized, one beginning with the allyl ether **84** of the hydroxy-sulfone, and the second beginning with the ether **86** derived from *cis*-2-butene-1,4-diol (Scheme 6.2). It was hoped that the allyl ether could be oxidatively cleaved to the β-alkoxy aldehyde **85**, which could in turn be olefinated with a (*Z*)-selective unsaturated Horner-Wadsworth-Emmons reagent derived from one of the chiral auxiliaries to form the desired **79**. The second, and likely more realistic approach, involved oxidation of the allylic alcohol **86** to a *cis*-α-β-unsaturated aldehyde **87**, which could then undergo a normal (*E*)-selective olefination with a reagent incorporating one of the chiral auxiliaries.



Scheme 6.2

First of all, the allyl ether was synthesized uneventfully in an unoptimized yield of 70% by heating the hydroxy-sulfone in a dichloromethane solution of allyl alcohol with catalytic

acid. The ^{1}H NMR spectrum clearly demonstrated the formation of only one diastereomer, assumed to be the *cis* isomer by analogy to all of the simple alkyl ethers made by Charlton and Durst[25] via this procedure. The spectrum displayed the expected allyl ether pattern (internal alkene proton at 6.00 ppm, dddd; terminal alkene protons at 5.44 and 5.36 ppm) as well as the two benzylic proton resonances as clean singlets at 5.59 and 5.34 ppm. The AB pattern corresponding to the diastereotopic methylene protons was also clearly visible at 4.66 and 4.43 ppm. One attempt to perform the oxidative cleavage of the double bond with catalytic osmium tetroxide, *N*-methyl-morpholine-*N*-oxide and sodium periodate did not furnish any aldehyde products detectable by ^{1}H NMR of the complex mixture. Ozonolysis of this compound was not attempted, although this may have led to better results in the production of β-alkoxy aldehyde **85**. Due in part to this negative result, as well as the likelihood of difficulty in the subsequent olefination procedure (including the synthesis of the (*Z*)-selective reagents), focus was placed upon the second route described in Scheme 6.2.

Reaction of the hydroxy-sulfone with a slight excess of *cis*-2-butene-1,4-diol under identical conditions used for the formation of the allyl ether furnished the new alcohol **86** in 60% yield as a single diastereomer. The absence of the *trans* isomer was demonstrated by both the ^{1}H and ^{13}C NMR spectra. Oxidation of this compound to this *cis* α,β-unsaturated aldehyde did not prove trivial however. Standard Swern oxidation conditions yielded two isomeric aldehydes in nearly quantitative combined yield. The major product, which accounted for approximately 80% of the mixture, was assigned the *trans* configuration about the double bond by analysis of the chemical shifts and coupling

constants of the alkenyl proton resonances. It seemed very likely that rapid isomerization to the thermodynamically more stable isomer was occurring during the ammonium chloride workup. Similar problems had been encountered in the oxidation of related *cis* allylic alcohols in the Fallis group[47], and the rapid isomerization had been circumvented by the use of the Dess-Martin periodinane[48] buffered with bicarbonate. Attempts using these conditions furnished a 1:1 mixture of the geometric isomers. Upon addition of 1M aqueous acetic acid to a dichloromethane solution of the crude mixture, rapid isomerization to the *trans* isomer occurred, resulting in a final ratio of approximately 95:5. Thus the supposition that it was an acid catalyzed isomerization was supported, and attempts to find neutral or slightly basic oxidation conditions were undertaken. Activated manganese dioxide in chloroform yielded predominantly the undesired isomer, as did catalytic tetrapropyl ammonium perruthenate[49] with *N*-methyl-morpholine-*N*-oxide. The best results were finally obtained using Swern conditions with freshly distilled reagents followed by a bicarbonate workup, which resulted in the isolation of a 9:1 ratio of *cis*:*trans* isomers in quantitative crude yield. Naturally the desired isomer was not stable to silica gel chromatography, but fortunately the crude mixture was pure enough for subsequent olefination attempts.

At this point, Wittig or Horner-Wadsworth-Emmons reagents derived from chiral auxiliaries were required (Scheme 6.3). From related projects in this laboratory, there were significant quantities of *iso*-propyl glutamate[50] **88** and iodoacetylated (*R*)-pantolactone[51] **91**. The glutamate ester was bromoacetylated in 59% yield using the non-nucleophilic base lithium hexamethyldisilazide, yielding **89**. This compound was then

subjected to the standard Arbuzov reaction conditions: it was added to one equivalent of triethyl phosphite and heated at 125°. The resulting Horner-Wadsworth-Emmons (HWE) reagent **90** was quite pure by ^{1}H and ^{13}C NMR. Attempts to synthesize the Wittig reagent from **89** and triphenylphosphine resulted in complete destruction of the starting material in the base mediated ylide formation step.

Iodoacetate **91** was subjected to identical Arbuzov conditions and the resulting HWE reagent **92** was isolated in quite pure form. The bromoacetate **93** of Evans' oxazolidinone was made according to literature conditions[52], and was used to synthesize HWE reagent **94**. These three new olefination reagents **90**, **92**, and **94** were characterized by ^{1}H NMR, and coupling to phosphorus was observed for the methylene protons adjacent to phosphorus ($^{2}J_{P\text{-}H}$ = 22.2 Hz for **90** is representative). For the compound derived from pyroglutamate, the ^{13}C NMR spectrum also demonstrated the expected carbon-phosphorus coupling ($^{1}J_{P\text{-}C}$ = 132.4 Hz). Again, attempts to synthesize the stabilized ylides of both **91** and **93** were undertaken, with complete destruction of the starting material in the case of the pantolactone derivative; however the Wittig reagent of the Evans' auxiliary **95** was isolated in good yield.

All olefination trials with *cis* unsaturated aldehyde **87** unfortunately failed, with either of the new HWE reagents or the ylide **95**. A complete survey of all possible conditions was not performed, in the case of the phosphonate reactions, deprotonation with sodium hydride or lithium hexamethyldisilazide in THF at 0° followed by addition of the aldehyde was adopted as a standard set of conditions; for the attempted Wittig reaction the

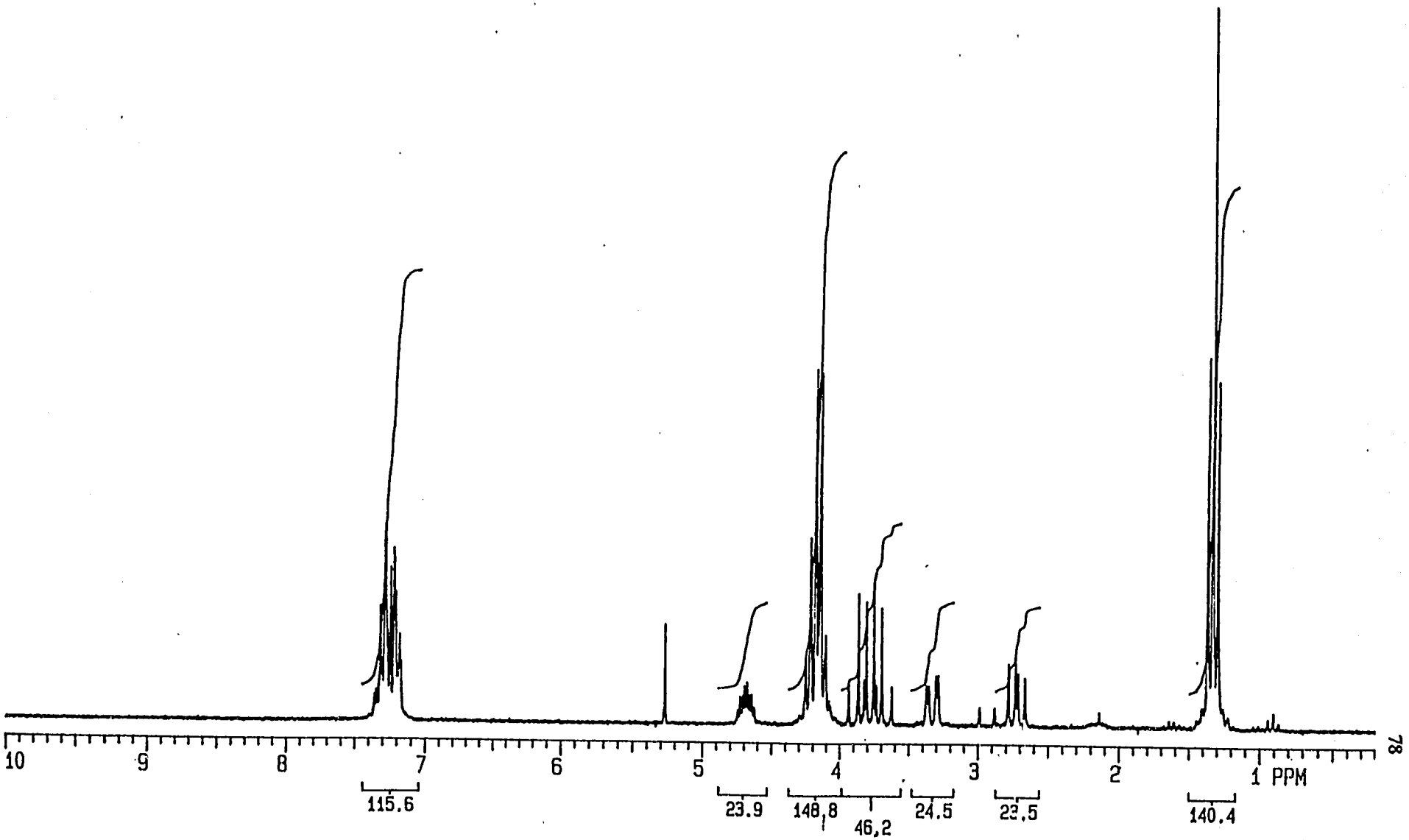
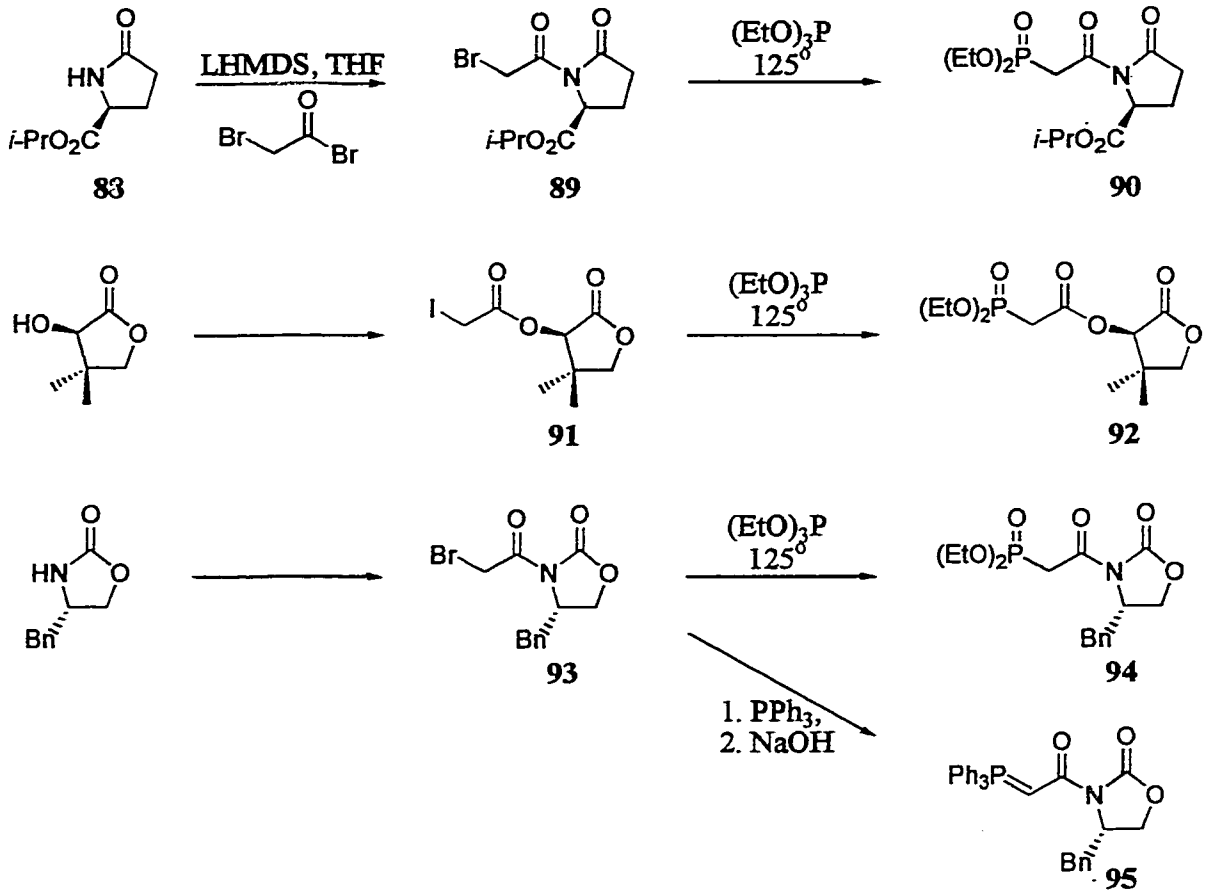


Figure 6.1: 200 MHz ^{1}H NMR Spectrum of Chiral HWE Reagent **94** (Crude).



83 89 90

91 92

93 94 95

Scheme 6.3

olefination reagent was added in slight excess to the aldehyde in either toluene or THF. In all cases, consumption of the starting aldehyde was rapid, but ^{1}H NMR spectra of the crude reaction mixtures never suggested the presence of any new olefin resonances. The HWE reagents were always still discernible in the reaction mixtures. At this juncture, this line of attack was deserted, due in most part to the lack of success in the olefination procedures, but also since the likelihood of achieving substantial asymmetric induction in the cycloaddition step was slight. In the cases where the Evans' auxiliary or pantolactone are used in intramolecular Diels-Alder reactions, useful levels of diastereomeric excess are

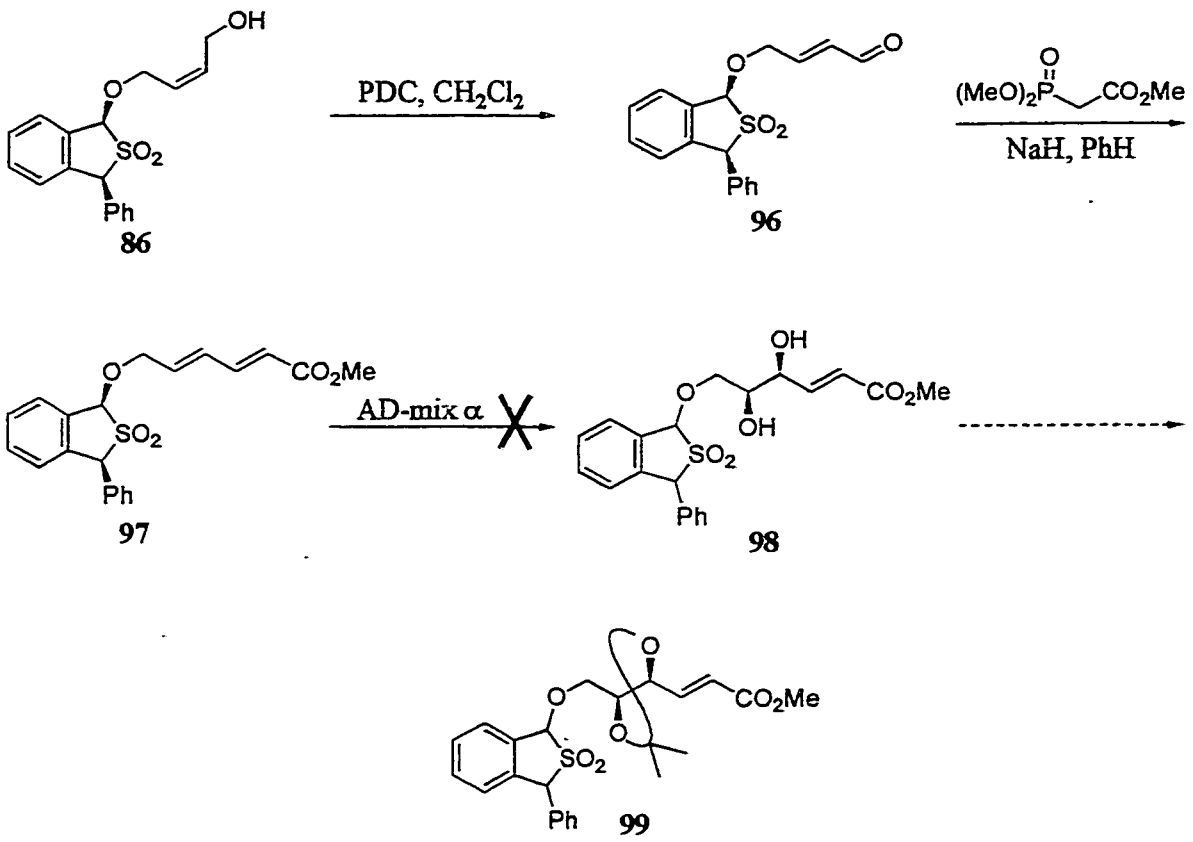
only arrived at when Lewis acids are used to increase the reaction rate such that the temperatures can be significantly decreased, and to form chelates which hold the dienophiles in the best conformation for asymmetric induction[53]. At the temperatures required for sulfur dioxide extrusion, Lewis acids would likely not be able to maintain the ordered, chelated dienophile conformation, and it is unlikely that any cycloaddition product derived from the simple thermal Diels-Alder process would be diastereomerically enriched to any great extent.

6.2 Attempted Validation of the Originally Proposed Asymmetric Diels-Alder Reaction: Building in the Tartrate Tether/Dienophile

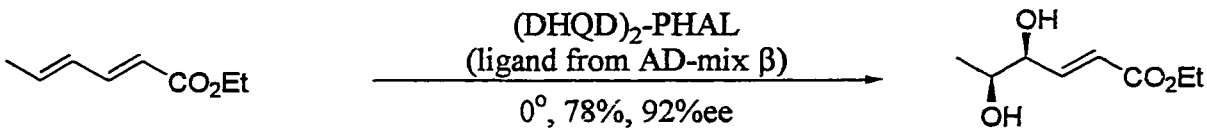
Although the original proposal for convergent attachment of the chiral dienophile to the hydroxy-sulfone had failed, there remained some interest in discovering whether or not the key step - the asymmetric cycloaddition step - would occur with reasonable facial selectivity. Since some experience had been gathered in the elaboration of butenediol ethers of the hydroxy-sulfone and in the preparation and utilization of Horner-Wadsworth-Emmons reagents, it was contemplated that the tartrate-derived dienophile might be enantioselectively built onto the hydroxy-sulfone (Scheme 6.4). This concept appeared even more appealing upon the perusal of some results from the Sharpless laboratory in which regioselective asymmetric dihydroxylation reactions of conjugated polyenes had been studied[54]. Since the *trans* unsaturated aldehyde **96** was readily available from Swern oxidation of allylic alcohol **86** followed by acid catalyzed isomerization, only a simple

HWE reaction needed to be performed on this aldehyde to deliver dienoic ester **97**. With the regioselective asymmetric dihydroxylation of ethyl sorbate (Scheme 6.5) as a reasonable precedent, it was hoped that with the use of AD-mix α, regioselective and enantioselective dihydroxylation of **97** would occur to afford diol **98**. Protection of the diol as its acetonide would deliver the *o*-quinodimethane precursor **99** that had been long sought after.

Instead of utilizing Swern conditions followed by an isomerization step, the use of a mildly acidic oxidation reagent was chosen in order to effect the isomerization *in situ*. Reaction of the allylic alcohol **86** with a slight excess of pyridinium dichromate in dichloromethane afforded the desired *trans* unsaturated aldehyde in an unoptimized yield of 45% after flash chromatography. As previously, the geometry about the double bond was confirmed by examination of the ^{1}H NMR chemical shifts and coupling constants of the alkenyl protons (6.77ppm, J=15.9Hz, J=4.1Hz; 6.32ppm, J=15.9Hz, J=7.8Hz, J=1Hz). The infrared spectrum clearly revealed the presence of an aldehyde with absorptions at 2836 and 2735cm^{-1} as well as the unsaturated carbonyl stretch at 1694cm^{-1}. Olefination of this compound with trimethyl phosphonoacetate in benzene using sodium hydride as base afforded 85% of the desired (*E*,*E*) dienoic ester **97** after separation from the (*E*,*Z*) isomer (10%) by flash chromatography. The ^{1}H NMR spectrum demonstrated four distinct alkenyl proton resonances at 7.11, 6.45, 6.19 and 5.91ppm. The infrared data were again particularly diagnostic, as two clearly separate conjugated C=C stretches were visible at 1651 and 1620cm^{-1}, while the conjugated ester carbonyl absorption was strong and sharp at 1716cm^{-1}.



Scheme 6.4



Scheme 6.5

The key step in this sequence, the regioselective asymmetric dihydroxylation of the dienoic ester, was expected to be somewhat sluggish given the electron withdrawing ester group at one end and the inductively electron withdrawing ether group at the other end. The assumption was made that the ligands developed for the asymmetric dihydroxylation would be effective enough to override any induction from the distal stereocenter on the

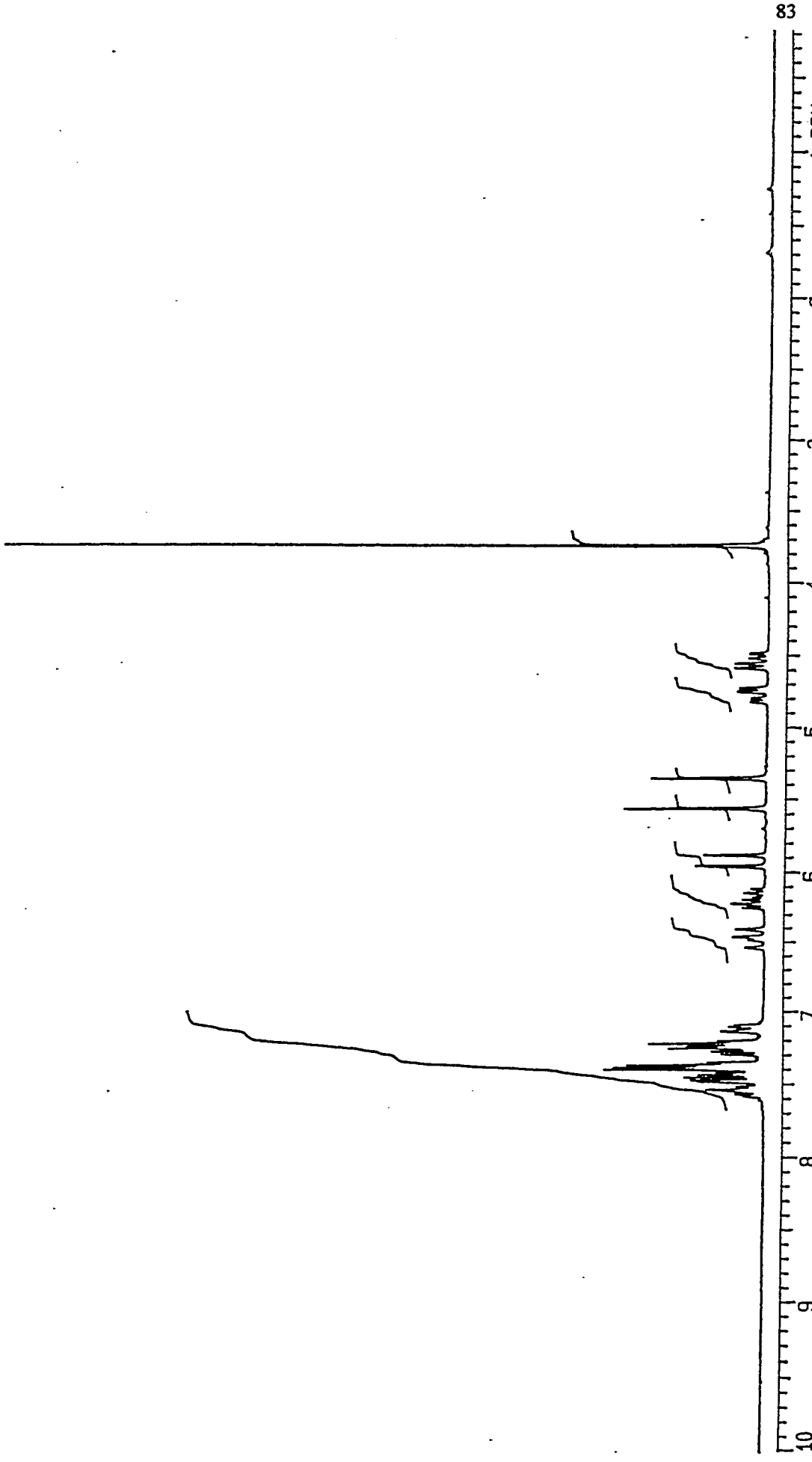


Figure 6.2: 200 MHz ^{1}H NMR Spectrum of Dienoic Ester **97**.

sulfone ring. The regioselectivity of this reaction is in theory governed mostly by electronics and secondarily by sterics. Given that the steric environments of both alkenes are quite similar, it was hoped that, as in the case of ethyl sorbate, dihydroxylation would occur preferentially at the more electron-rich double bond. In addition to simple electronics, Sharpless has also proposed a "disruption of conjugation" effect that results in the preferential reaction of the double bond removed from the ester, so as to minimize disturbance of the conjugated series of pi bonds; this also seems favorable for the case of dienoic ester **97.** However, unlike ethyl sorbate, **97** also had the competing effect of the benzylic ether adjacent the desired reaction site. Dissolution of the substrate in *t*-butanol-water mixture at 0° followed by addition of excess AD-mix α and one equivalent of methanesulfonamide did not result in any reaction progress after 6 hours. The mixture was allowed to stir at room temperature for 24 hours, still with no success. Sodium sulfite workup afforded essentially pure starting material as identified by TLC and ^{1}H NMR. This was a somewhat unexpected result given that ethyl sorbate reacted quite efficiently at 0° in five hours under otherwise identical conditions. Since no other options for effecting this reaction were readily apparent (attempts to react **97** with stoichiometric osmium tetroxide should result in a slower reaction due to the lack of ligand acceleration effects), this avenue of approach was left aside. Perhaps, in hindsight, it would have been well advised to verify the potency of the AD-mix reagent, given that it was several years old, or to have run the reaction with AD-mix as well as added osmium tetroxide, but these options were not considered at the time.

6.3 One Final Attempt to Utilize the Tartrate-Derived Dienophile

Since endeavours to connect the tartrate-derived dienophile to the hydroxy-sulfone under acid-catalyzed alkoxy exchange conditions did not prove fruitful, an alternate tethering strategy was considered. Oxidation of the primary alcohol of the dienophile to the carboxylic acid, followed by conversion to the acid chloride should yield an electrophile that could be attacked by the hydroxy group of the hydroxy-sulfone (Scheme 6.6). Other esterification conditions may also prove useful, such as DCC/DMAP coupling conditions. Naturally, a mixture of *cis* and *trans* diastereomeric hydroxy-sulfones would lead to the same mixture of diastereomers in the products, and since the *o*-quinodimethane precursor was not only diastereomerically heterogeneous but also racemic, the final product should result in the formation of four diastereomeric sets of enantiomers. However, it is possible to obtain the *cis* hydroxy-sulfone as a diastereomerically pure compound if it is isolated from the SO_2 trapping experiment by crystallization instead of by basic workup[55]. Therefore, if the initial coupling experiments appeared to be at all successful, access to the required *cis* diastereomer was available.

Oxidation of alcohol **51** to the carboxylic acid **100** was cleanly effected with excess pyridinium dichromate in DMF[56] in 56% unoptimized yield after basic workup. ^{1}H and ^{13}C NMR both confirmed the presence of the carboxylic acid moiety, as did the infrared spectrum which showed the characteristically broad O-H stretching from about 3400 to 2500 cm^{-1}. Attempted coupling of the acid to the hydroxy-sulfone with a slight excess of

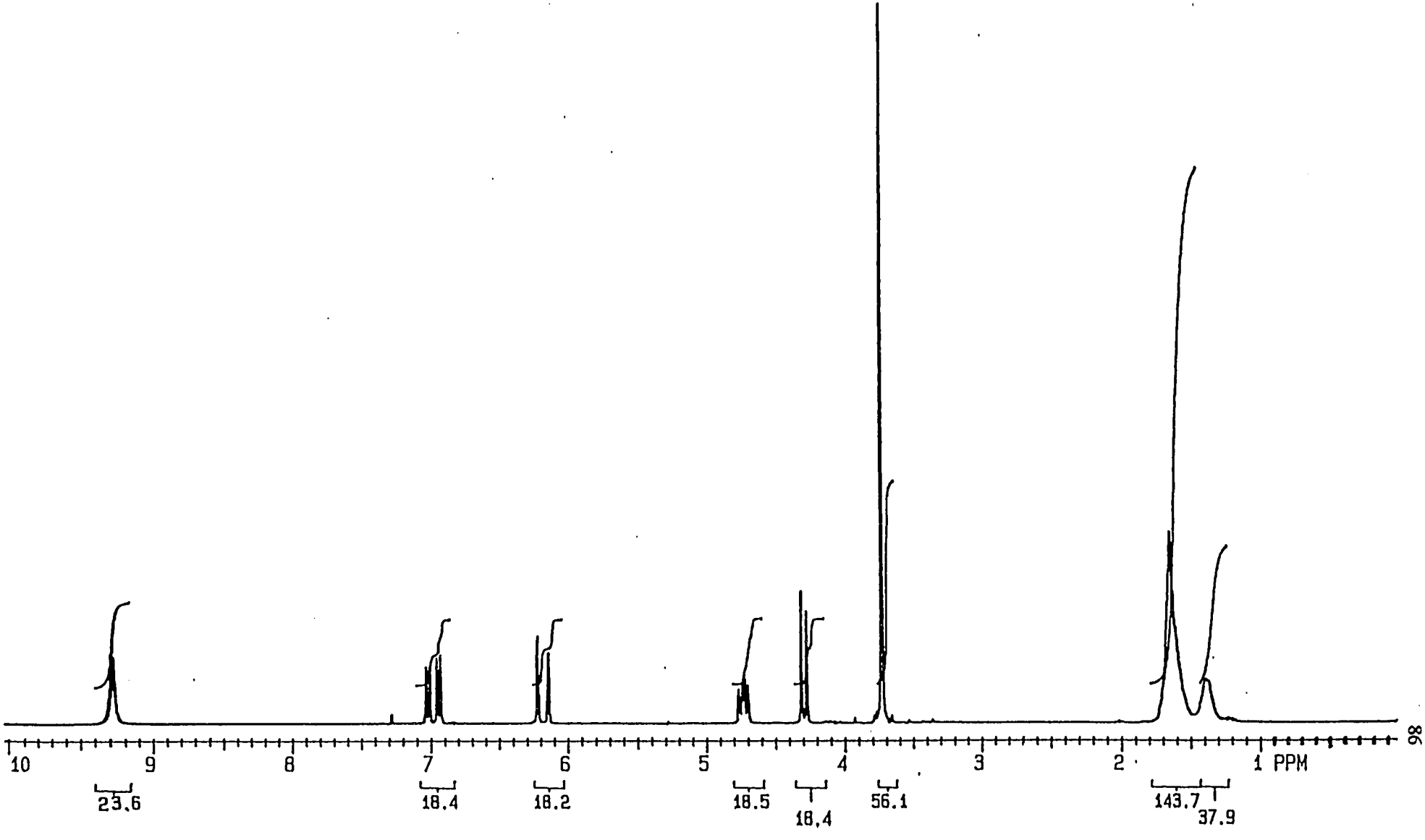
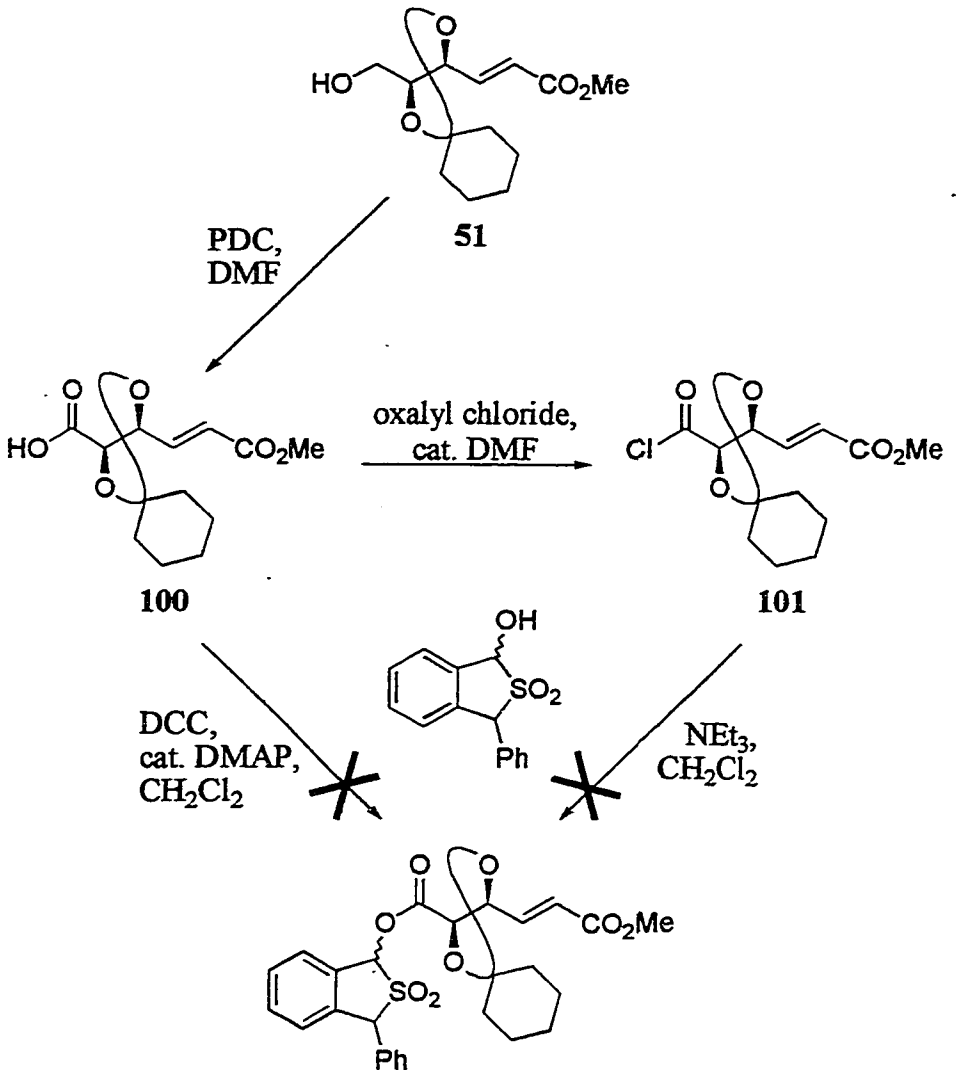


Figure 6.3: 200 MHz ^{1}H NMR Spectrum of Carboxylic Acid **100**.



Scheme 6.6

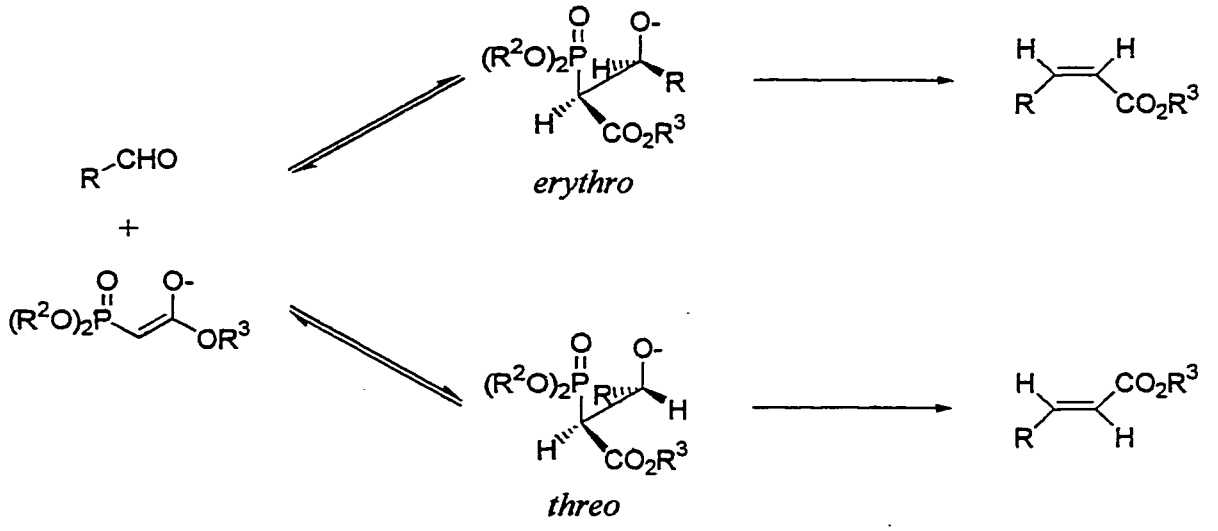
DCC and catalytic DMAP in dichloromethane did not result in any coupled product; the only isolated products were the aldehyde corresponding to loss of SO_2 from the hydroxy-sulfone, and two different but unidentified derivatives of the acid and DCC. The acid chloride **101** was synthesized using oxalyl chloride and catalytic DMF in dichloromethane, and it was isolated by removal of the volatiles under high vacuum. The presence of the acid chloride functionality was verified by IR, which clearly showed a lack of carboxylic

acid O-H stretch as well as a new characteristic absorption due to the acid chloride carbonyl stretching at 1815 cm^{-1}. The crude product was then redissolved in dichloromethane, and triethylamine and a solution of the hydroxy-sulfone were added. After stirring for two hours at room temperature, TLC indicated the formation of at least a dozen new products, and upon inspection of the ^1H NMR of the crude, no resonances that appeared to be related to the desired products were seen. As a test reaction, the hydroxy-sulfone was treated with propionyl chloride under identical conditions, and the two major products appeared to be the diastereomeric esters by analysis of the ^1H NMR spectrum. Unfortunately, yet another convergent step that seemed to have merit in theory, failed in practice. One potential problem that would have required addressing, had the union of the two synthons been met with success, was that the preferred ester conformation may not have even allowed approach of the dienophile to the *o*-quinodimethane upon thermolysis. At this point, no further attempts at the total synthesis project were undertaken.

6.4 New (*Z*)-Selective Horner-Wadsworth-Emmons Reagents

As a result of some of the investigations described in Section 6.1, the prospect of synthesizing rather complex (*Z*)-selective olefination reagents came to bear. The two best and most reliable type of reagents currently known are the bis(trifluoroethyl) phosphonates of Still[57] and Ando's recently described diaryl phosphonates[58]. The selectivity of the HWE reagents is determined by a combination of the stereoselectivity in

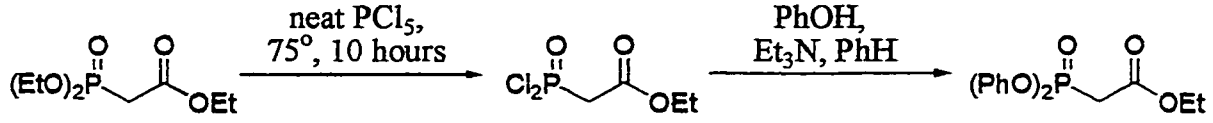
the initial carbon-carbon bond formation step as well as the reversibility of this initial step back to starting materials (Scheme 6.7). As such, the outcome of the reaction in terms of selectivity is the result of both kinetic and thermodynamic control[59]. "Regular" alkyl phosphonate HWE reagents have a noted tendency to deliver (*E*) olefins selectively. With the advent of Still's electrophilic bis(trifluoroethyl) phosphonates, it became clear that more electrophilic phosphonates led to a bias towards the generation of (*Z*) olefins. The (*Z*) selectivity is attributed in this case to an increase in the rate of elimination of the originally formed adduct relative to the rate of equilibration of the intermediate adducts. The elimination rate is increased due to the greater electrophilicity of the phosphonate group. The kinetically preferred adduct is the *erythro* diastereomeric β-hydroxy phosphonate that upon elimination leads to the *cis* or (*Z*) olefin. Thus any electrophilic phosphonate should lead to the increased formation of (*Z*) olefins. This was Ando's reasoning during the development of the highly selective diaryl phosphonates[58]. One way



Scheme 6.7

to rationalize the results is to examine the electron-withdrawing capabilities of the groups on phosphorus: pK_a for PhOH = 10.0, for CF_3CH_2OH = 12.4, for EtOH = 16. Thus, the phosphonate group of Still's reagents are significantly more electrophilic than the regular HWE reagents, and Ando's are still more electrophilic.

The diaryl phosphonate reagents are highly selective, affording nearly quantitative yields of unsaturated esters with at least 90% (*Z*) selectivity, regardless of aldehyde structure. The usefulness of Ando's reagents in synthesis will no doubt be tremendous if a simple way to manufacture diarylphosphonates of diverse structure is developed; Still's variant of the HWE reaction has already found widespread use[59]. At this time, the only reported synthesis of these diaryl compounds for use as olefination reagents is by Ando, and it involves a harsh two-step conversion of dialkylphosphonates into the desired compounds (Scheme 6.8). Conversion of the starting material to the dichloride was effected by heating to 75° in neat phosphorus pentachloride followed by distillation. The final product was then delivered in 60% yield after treatment with phenoxide and column chromatography. Several problems are immediately discernible in this synthesis, most notably the need for the dialkyl phosphonate starting material. The use of this new type of HWE reagent in complex synthesis should not have to be limited to those derived from

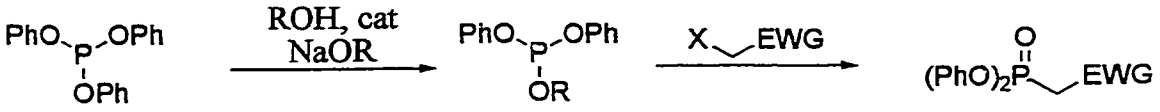


Scheme 6.8

simple, commercially available dialkyl phosphonates that are acid stable enough to withstand heating in neat PCl_5. In order to be able to provide access to some of these more complex and sensitive compounds, a simple Arbuzov synthesis should prove mild and efficient enough. Thus a simple synthesis of an alkyl diphenyl phosphite was sought. Two literature references were uncovered, one in which ethyl diphenyl phosphite is made by treatment of diphenyl chlorophosphite with ethoxide[60], and the other involving the exchange of a phenoxy group with an alkoxy group by heating triphenylphosphite in the presence of catalytic alkoxide and one equivalent of alkanol[61] (as in Scheme 6.9). Since diphenyl chlorophosphite itself is not even commercially available, and given the ready availability and inexpense of triphenyl phosphite, the latter method was chosen. Thus an equimolar mixture of triphenyl phosphite and anhydrous methanol with catalytic sodium methoxide was heated to 110° for four hours. ^1H NMR of the crude mixture revealed two major sets of methyl peaks (split by phosphorus), one likely corresponding to the desired product, and the other one perhaps belonging to the phenyl dimethyl phosphite byproduct. It was anticipated that the desired product would be easily separable from the other product and from the phenol generated in the reaction by distillation under reduced pressure. This was in fact the case, and methyl diphenyl phosphite was isolated at a boiling point of 130 to 140° at 50mTorr, in approximately 50% yield (80 grams isolated, starting with 200 grams of triphenyl phosphite). It was apparent at this point that there should be no difficulty in keeping a reasonable supply of this reagent on hand. NMR spectral data, including ^{31}P, infrared and mass spectral data all confirmed that the desired product had been isolated. A substantial amount of ethyl diphenyl phosphite was also made by the same procedure in an unknown but lesser yield.

In both references describing the synthesis of this type of phosphite, there were also descriptions of its use in Arbuzov reactions with alkyl bromides. One described ethyl diphenyl phosphite's reaction with a protected form of 6-bromo-6-deoxy-glucopyranose to form the 6-deoxy-6-(diphenyl phosphonate) derivative[60]. Also, 2-bromoacetophenone was cited to react with propyl diphenyl phosphite to yield the corresponding β-keto phosphonate reagent in 79% yield[61]. Thus it seemed probable that many of these Ando-type HWE reagents could be synthesized with ease via the Arbuzov reactions of methyl or ethyl diphenyl phosphite.

A survey of the efficiency of these Arbuzov reactions was conducted next. Since it is well known that HWE reagents bearing anion-stabilizing groups adjacent to phosphorus are the most useful, the only Arbuzov reactions studied in this initial work involved halides that would result in this type of product (α-halo esters, ketones, nitriles, etc. were used, as in Scheme 6.9). The results, some of which involved ethyl diphenyl phosphite, and others making use of methyl diphenyl phosphite, are summarized in Table 6.1. The first part of the Table summarizes the conditions used and yields obtained in the reaction of a stoichiometric amount of ethyl diphenyl phosphite with halides. These reactions were all



R = Me, Et; X = halide; EWG = C(O)R, CO_2R, CN, $CH{=}CHCO_2R$

Scheme 6.9

Table 6.1: Synthesis of Various Ando-Type Olefination Reagents

R	EWG	Phosphite:Halide	Conditions	Yield (%)
Et	CN	1:1	150°, 16h	78
Et	C(O)Ph	1:1	150°, 16h	74
Et	$C(O)CMe_3$	1:1	150°, 16h	82
Et	$CH{=}CHCO_2Me$	1:1	150°, 16h	65
Me	$C(O)CMe_3$	2:1	125°, 16h	88
Me	$CH{=}CHCO_2Me$	2:1	125°, 16h	87
Me	CO_2Me	2:1	125°, 16h	91

performed at the rather elevated temperature of 150°, but the yields are all quite reasonable. Having synthesized a large quantity of the methyl diphenyl phosphite, several reactions were run with this reagent, all with a two-fold excess of the phosphite in order to hopefully maximize the yields of the resulting product. These reactions were all complete after heating at 125° overnight, and the yields were all very good. It seems that the reaction of the methyl diphenyl phosphite with halides is significantly faster, and as such requires lower temperatures than does the ethyl derivaitve. A test reaction was run in which both alkyl phosphites were heated in the presence of methyl bromoacetate as a limiting reagent. Nearly all of the methyl diphenyl phosphite was consumed while the

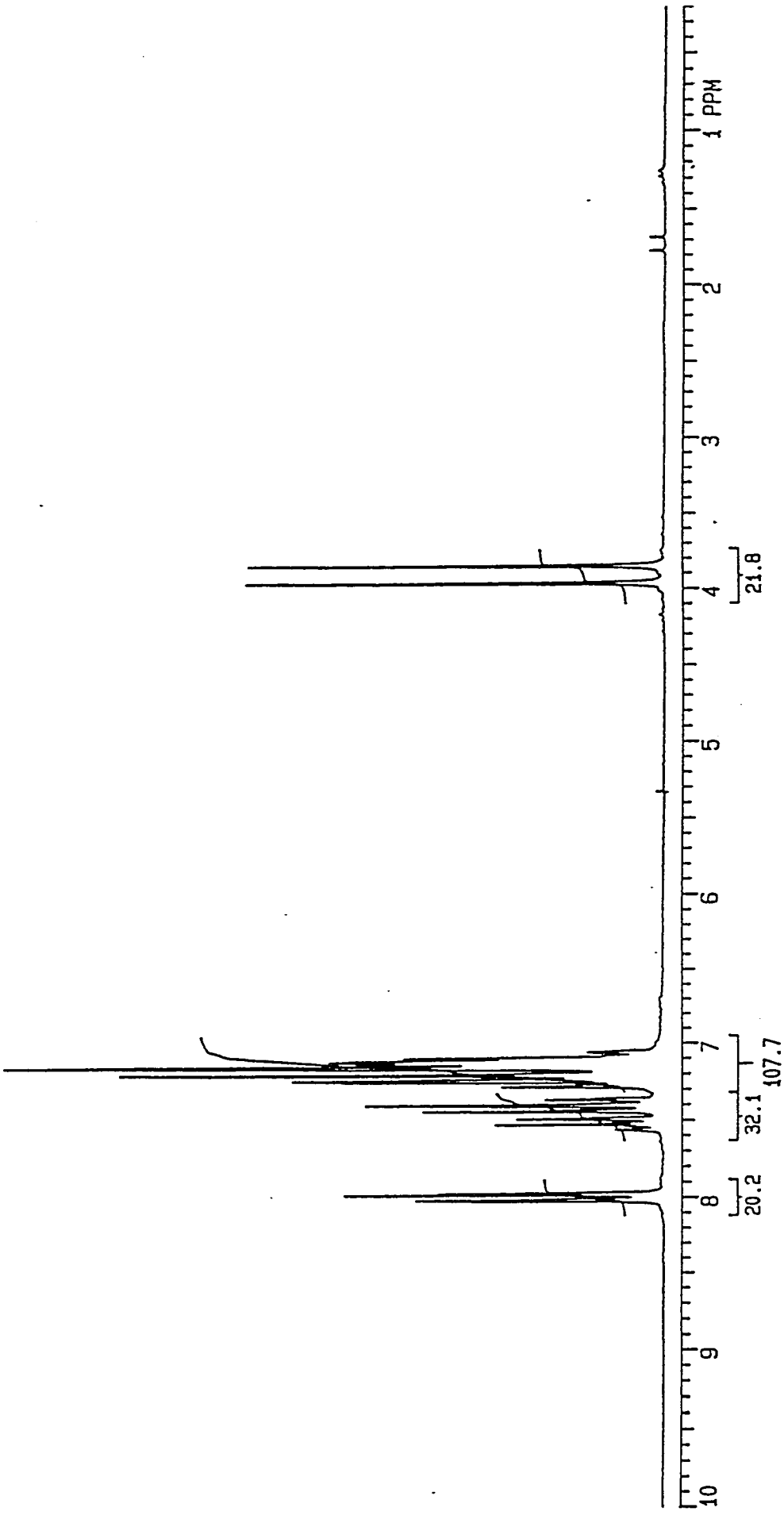


Figure 6.4: 200 MHz ^{1}H NMR Spectrum of Phosphonate Derived from Acetophenone.

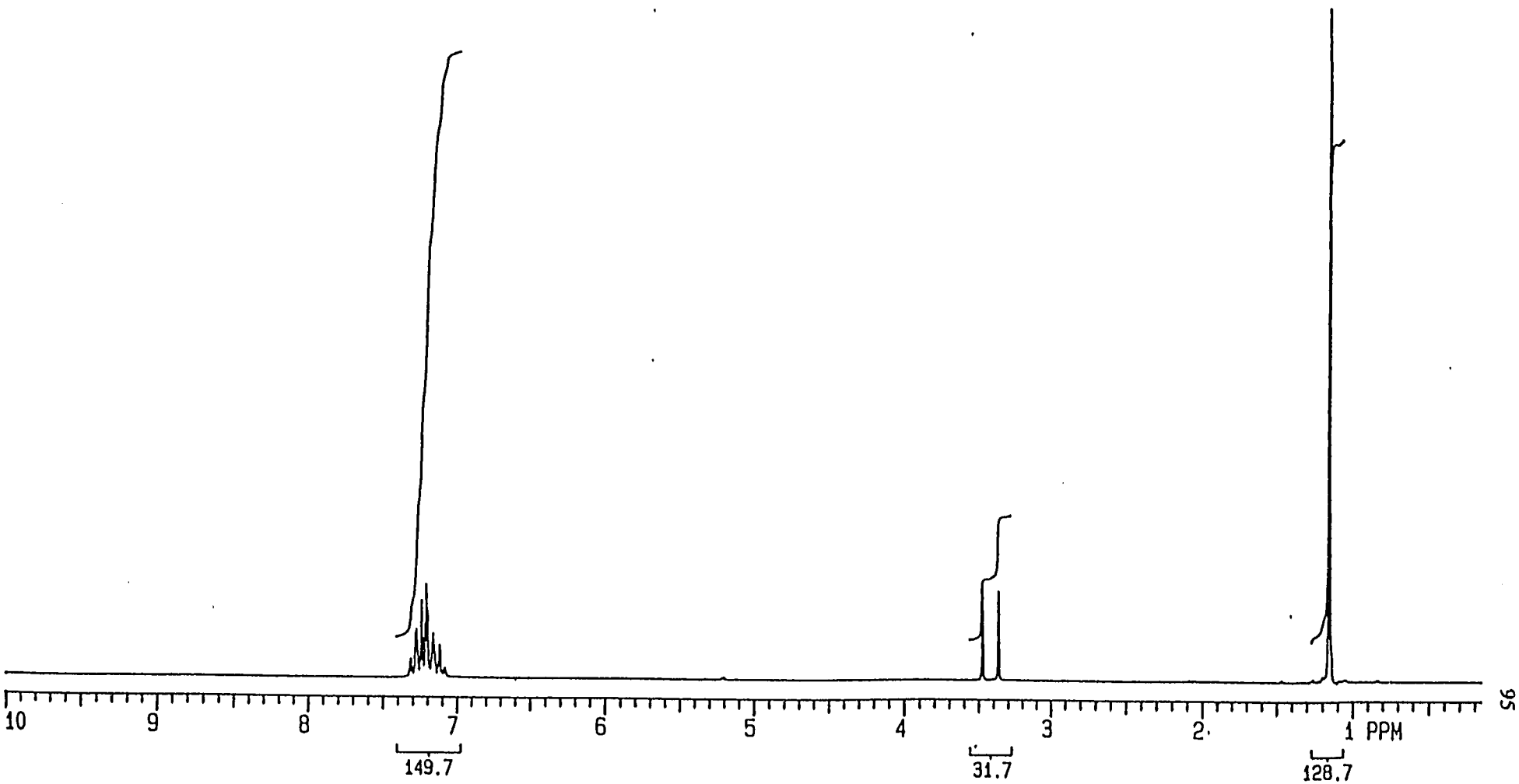
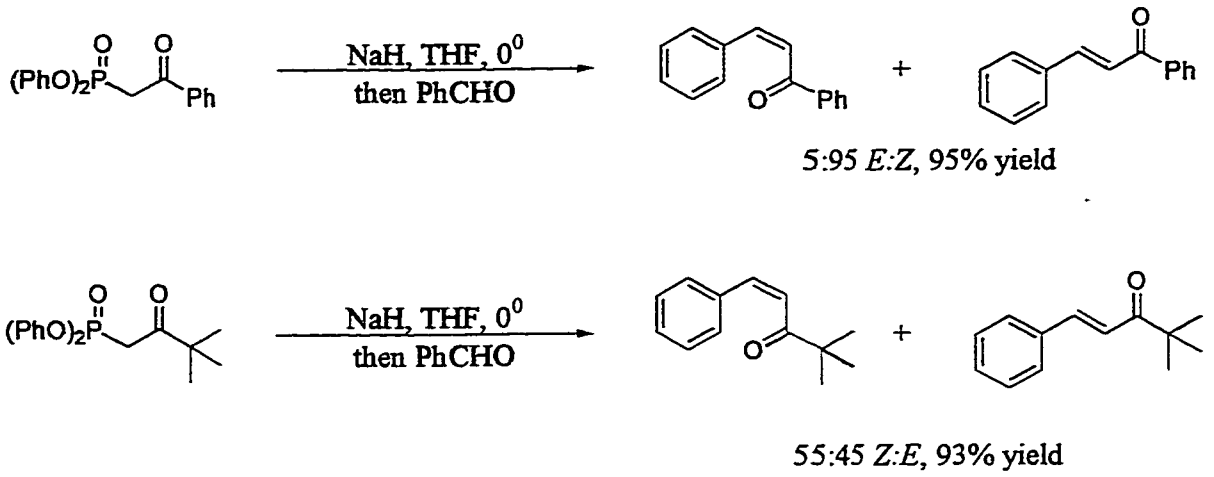


Figure 6.5: 200 MHz ^{1}H NMR Spectrum of Phosphonate Derived from Pinacolone.

majority of the ethyl derivative remained unreacted. This is likely just a steric effect involving crowding about the central phosphorus atom. Any further endeavours in the synthesis of these HWE reagents should thus concentrate on the use of methyl diphenyl phosphite as a milder Arbuzov substrate. Another interesting aspect of these reactions is that, when using an excess of the phosphite to try to maximize phosphonate yields, which does in fact seem to work, the formation of one major byproduct was always observed in the ^{1}H NMR spectra. This product showed a wide doublet centered at 1.75 ppm, while the desired products all showed wide doublets (due to coupling to phosphorus) in the 3 to 4 ppm range due to the adjacent electron withdrawing groups. After a quick analysis of the mechanism of the Arbuzov reaction, it was noted that methyl bromide is formed as a byproduct, which, having a boiling point of only 4°, was expected to evaporate off rapidly at the 125° reaction temperature. Apparently, methyl bromide is quite soluble in the phosphite reaction mixtures, and remains in solution to undergo its own Arbuzov reaction, forming the methyl phosphonate, the isomer of the starting material, in very good yields. It is interesting to note, however, that when only one equivalent of phosphite is used in these reactions, this byproduct is only formed to a very minor extent (<5% in most cases). This result requires that the halides with adjacent electron withdrawing groups added as starting materials react significantly faster than the methyl bromide (as expected), and yet the volatile halide does remain in the medium long enough to react with all of the excess phosphite, as no starting phosphite is ever detected. While at first thought this does not appear to be detrimental to the results of the Arbuzov reactions, it does result in considerable difficulty in the purification of the desired phosphonates, since both products are often of nearly identical Rf and thus only very careful flash chromatography will

deliver pure material. For the larger and higher boiling Arbuzov products, this impurity can be distilled off under reduced pressure (boiling point of the methyl phosphonate 140 to 145° at 50 mTorr.) leaving the desired phosphonates behind in pure enough form to be used in HWE reactions. After all of these details had been worked out, the five different phosphonate products shown in Table 6.1 have been synthesized, purified, and fully characterized. Unfortunately, the Arbuzov synthesis of phosphonates derived from α-substituted halides such as methyl 2-bromopropionate does not occur readily, and better conditions to drive these reactions to completion will need to be worked out. As well, the synthesis of more complex phosphonates will need to be examined, as this is the purpose for which the methodology is being designed. As a final interesting point, α-bromo ketones are historically not known to undergo Arbuzov reactions with much success[62], in fact other syntheses of these compounds have been worked out involving, among others, alkyl cuprate addition to 2-phosphonoacetyl chlorides. As demonstrated by the results involving both bromopinacolone and bromoacetophenone, this does not seem to be the case with this particular type of alkyl diphenyl phosphite.

Only two attempts have been made thus far to probe the selectivity of these new olefination reagents (Scheme 6.10). The treatment of both HWE reagents derived from bromopinacolone and bromoacetophenone with sodium hydride in THF at 0° followed by addition of benzaldehyde led to very good yields of the resulting unsaturated ketones, but with less than monumental selectivity. In fact, in the case of the phosphonate derived from acetophenone, the desired (*Z*) isomer was barely perceptible by ^{1}H NMR. This was not at



Scheme 6.10

all expected, and perhaps some isomerization occurred upon ammonium chloride workup; this will be examined in greater detail. In the case of the *t*-butyl ketone phosphonate reagent, there was some selectivity for the desired *cis* unsaturated ketone, which accounted for 55% of the olefin formed (combined yield 93%, unoptimized). These isomers were not readily separable, and to date have only been analyzed by ^{1}H NMR of the mixture. Further experimentation is currently underway with emphasis on the optimization of conditions to maximize the selectivity of these new reagents, as well as the synthesis of new, more complex selective HWE reagents.

Part 3

Summary

In Chapter 1, the medicinal properties and uses of podophyllotoxin were described, and the continued synthetic interest in this and related lignans due to their potential for cancer chemotherapy was also elaborated. Accounts of several representative syntheses of this natural product were given in Chapter 2; these were either racemic syntheses, or schemes that terminated in a low-yielding epimerization step to convert the more stable picropodophyllotoxin into the desired lignan. With these precedents, the plan for an enantioselective total synthesis of podophyllotoxin involving the simultaneous establishment of all four contiguous stereocenters via an asymmetric intramolecular Diels-Alder reaction was detailed in Chapter 3. This cycloaddition reaction was to involve an *o*-quinodimethane as diene, and the dienophile was to be tethered to the diene via a chiral tartrate-derived isopropylidene acetal.

The efficient synthesis of several tartrate-derived tether / dienophiles of different levels of acid stability were detailed in Chapter 4; these compounds were all primary alcohols, as they were to be attached to a hydroxy-sulfone *o*-quinodimethane precursor via an ether bridge. The oxygen linkage was to be made under acidic conditions in which the hydroxyl group of the hydroxy-sulfone was exchanged for the primary alcohol, but in all cases, even involving acid stable tether / dienophiles, no coupled product was ever isolated.

Chapter 5 described a change of approach, in which the tethering atom was changed from oxygen to nitrogen, and the *o*-quinodimethane generation strategy was going to involve ionic species instead of thermolytic sulfur dioxide extrusion. Thus tartrate-derived primary amines were synthesized for the purposes of forming substituted benzaldimines as

o-quinodimethane precursors, but the coupled products were hydrolytically too unstable for isolation or purification.

Finally, two attempts at constructing the chiral dienophiles from simple ethers of the hydroxy-sulfone were undertaken with no success, however it was discovered that these alkoxy-sulfones are quite robust to varied synthetic manipulations. As a result of one of these attempts to build in a chiral tether / dienophile, interest was developed in (*Z*) selective Horner-Wadsworth-Emmons reagents. A new synthesis of potentially selective olefination reagents was developed involving a simple Arbuzov reaction of halides with alkyl diphenyl phosphites, and the resulting diaryl phosphonates have begun to be evaluated for olefination efficiency and selectivity.

Part 4

Experimental

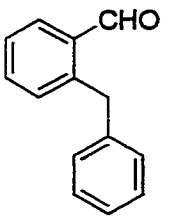
General

Tetrahydrofuran and benzene were distilled over sodium-benzophenone ketyl immediately prior to use. Dichloromethane was distilled over calcium hydride immediately prior to use. DMF, DMSO and actonitrile were distilled over activated molecular sieves and stored under nitrogen over molecular sieves. All other solvents were distilled or were of reagent grade quality. Unless stated otherwise, all non-aqueous reactions were performed under an atmosphere of dry nitrogen.

Flash chromatography refers to silica gel column chromatography using 230-400 mesh silica under nitrogen pressure using the specified eluant mixture. Thin layer chromatography (TLC) was performed on Merck 60F 254 precoated silica gel plates.

Infrared spectra were obtained as thin films using a Bomem FT-IR model MB-100 using sodium chloride plates unless specified otherwise. Mass spectra were recorded on KRATOS Concept IH or Concept IIH mass spectrometers. Peak intensities are given as percentage of the base peak intensity. Unless otherwise indicated, all NMR spectra were recorded in chloroform-*d*, using a Varian Gemini-200 spectrometer, operating at 200 MHz for proton and 50 MHz for carbon spectra, or a Varian XL-300 spectrometer, operating at 300 MHz for proton and 50 MHz for carbon spectra. The coupling patterns are described as (s) singlet, (d) doublet, (t) triplet, (q) quartet, (dd) doublet of doublets), (dt) doublet of triplets (etc.), (br) broadened, or (m) multiplet.

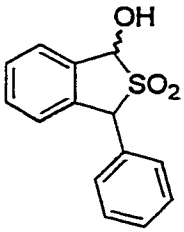
For Chapter 4



29

To a stirred suspension of 3.6 grams (94 mmoles) of lithium aluminum hydride in 200 ml diethyl ether at 0° was added slowly over 15 minutes via a dropping funnel a solution of 10.0 grams (47 mmoles) of *o*-benzyl benzoic acid. Once the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for 2 hours. The mixture was cooled back to 0° and quenched by the dropwise sequential addition of 3.6 ml of water, 3.6 ml of 15% sodium hydroxide, and 10.8 ml of water. The resultant mixture was then dried with excess magnesium sulfate, filtered and concentrated *in vacuo* to afford 9.8 grams of crude *o*-benzyl benzyl alcohol as a clear, colourless viscous oil. The crude product was then redissolved in 100 ml of diethyl ether and cooled to 0°. 100 ml (50 mmoles) of Jones' reagent (5 grams of chromium trioxide dissolved in 100 ml of 10% sulfuric acid) was added slowly to the vigorously stirred ether solution. After 30 minutes of stirring at 0°, the two-phase mixture was separated, and the organic layer was washed (5x50 ml) with saturated sodium bicarbonate solution until the extracts were clear. The ether solution was then dried over magnesium sulfate and concentrated *in vacuo* to afford 8.5 grams (92%) of *o*-benzyl benzaldehyde as a pale yellow, clear viscous oil.

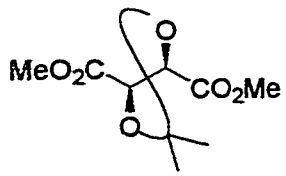
^{1}H NMR: δ(ppm) 4.45 (s, 2H), 7.11-7.56 (m, 8H), 7.87 (dd, J=7.0Hz, J=1.5Hz, 1H), 10.24 (s, 1H).



35

7.7 grams (39.3 mmoles) of *o*-benzyl benzaldehyde **29** were dissolved in 200 ml of a 10% solution of sulfur dioxide in dry benzene. This solution was transferred to a 200 ml capacity quartz photochemical reactor, in which it was degassed with nitrogen for five minutes. The solution was then irradiated for 20 hours with a Hanovia 450W medium pressure mercury lamp while being water cooled. The benzene was evaporated and the residue was redissolved in 150 ml of dichloromethane. The organic solution was then extracted (3x75 ml) with saturated sodium bicarbonate solution, the combined aqueous extracts were carefully reacidified with concentrated hydrochloric acid, and the resultant aqueous suspension was extracted with dichloromethane (3x100 ml). The organic extracts were dried over magnesium sulfate, and the solvent was evaporated *in vacuo* to afford 6.4 grams of hydroxy-sulfone **35** as a white foam.

^{1}H NMR: δ(ppm) 4.10 (br, 1H), 5.39 (s, 0.5H), 5.58 (s, 0.5H), 5.70 (s, 0.5H), 5.79 (s, 0.5H), 7.01-7.63 (m, 9H).

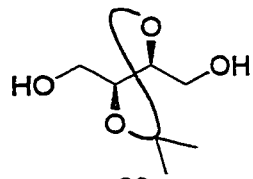


38

To a solution of 12.0 grams (67.4 mmoles) of dimethyl-(*L*)-tartrate in 150 ml chloroform were added 16.6 ml (14.0 grams, 134.8 mmoles) of dimethoxypropane, followed by a catalytic amount of *p*-toluenesulfonic acid monohydrate. The reaction flask was fitted with a soxhlet extractor containing activated 4A molecular sieves and a reflux condenser. The mixture was then heated to reflux for 4 hours, after which approximately one gram of solid anhydrous potassium carbonate was added to neutralize the acid. Filtration and concentration of the resulting solution afforded crude **38**, which was purified by bulb-to-bulb distillation (boiling point 90 to 95° at 50 mTorr.) to yield 14.5 grams (99%) of the desired product as a clear colourless oil.

^{1}H NMR: δ(ppm) 1.25 (s, 6H), 3.60 (s, 6H), 4.57 (s, 2H).

^{13}C NMR: δ(ppm) 25.79 (2C), 52.17 (2C), 76.51 (2C), 113.24, 169.57 (2C).



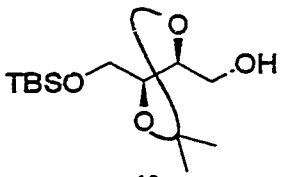
39

General Procedure for Ester Reduction: To a stirred suspension of 4.87 grams (128.3 mmoles) of lithium aluminum hydride in 200 ml of anhydrous diethyl ether cooled to 0° was added a 50 ml ether solution of 14.0 grams (64.2 mmoles) of diester **38** dropwise via a dropping funnel. After the addition was complete, the mixture was allowed to warm to

room temperature and was stirred for 5 hours. After cooling back to 0°, the excess hydride was quenched by the sequential and dropwise addition of 4.9 ml of water, 4.9 ml of 15% sodium hydroxide solution, and 14.7 ml of water. The resulting slurry was dried with magnesium sulfate and filtered. The filter cake was rinsed through extensively with ethyl acetate, and the solution was concentrated to afford the crude diol as a viscous yellow oil in approximately 95% yield. Flash chromatography (3:1 diethyl ether:hexanes) of the crude product yielded 8.77 grams (85%) of **39** as a clear, colourless and viscous oil.

^{1}H NMR: δ(ppm) 3.94 (m, 2H), 3.70 (m, 4H), 2.90 (br, 2H), 1.37 (s, 6H).

^{13}C NMR: δ(ppm) 26.57 (2C), 61.94 (2C), 78.22 (2C), 108.86.



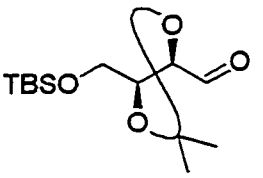
40

General Procedure for Diol Monosilylation: To a solution of 1.20 grams (7.40 mmoles) of diol **39** in 25 ml dry THF at 0° was added *n*BuLi (2.45M in hexanes, 3.0 ml, 7.4 mmoles) dropwise. The milky-white suspension was stirred at 0° for 30 minutes and then a THF solution of 1.21 grams (7.78 mmoles) of *tert*-butyldimethylsilyl chloride was added dropwise via cannula. After one hour at room temperature, the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride. Diethyl ether was added, and the two phases were separated. The aqueous phase was extracted with ether (2x25 ml), the organic extracts were combined, washed with brine, dried over magnesium sulfate, and concentrated to afford the crude monoprotected diol. Crude **40**

was isolated in 98% yield (2.0 grams) as a clear, pale yellow, viscous oil that was quite pure by TLC and NMR analysis. Flash chromatography (2:1 hexanes:diethyl ether) afforded 1.64 grams of pure product as a colourless oil.

^{1}H NMR: δ(ppm) 0.01 (s, 6H), 0.83 (s, 9H), 1.32 (s, 3H), 1.34 (s, 3H), 2.71 (br, 1H), 3.54-3.69 (m, 3H), 3.76 (m, 1H), 3.82 (m, 1H), 3.91 (m, 1H).

^{13}C NMR: δ(ppm) -5.41 (2C), 18.18, 25.74 (3C), 26.79, 26.92, 62.59, 63.53, 77.88, 79.94, 108.97.



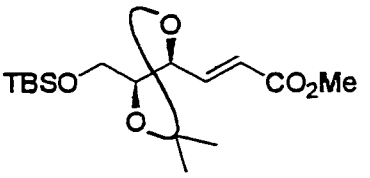
41

General Procedure for Swern Oxidation: To a solution of 5.3 ml (7.74 grams, 61.0 mmoles) of oxalyl chloride in 100 ml of dry dichloromethane at -78° was added dropwise via cannula a solution of 8.7 ml (9.53 grams, 122.0 mmoles) of distilled DMSO in 50 ml of dichloromethane. After stirring for 15 minutes, a solution of 13.5 grams (48.8 mmoles) of alcohol **40** in 75 ml of dichloromethane was added slowly via cannula to the mixture, which was maintained at -78°. After the addition was complete, the mixture was stirred for 30 minutes before 33 ml (244 mmoles) of triethylamine were slowly added. The cold bath was removed and the reaction was allowed to warm to room temperature, at which point the mixture was diluted with diethyl ether and 150 ml of saturated aqueous sodium bicarbonate solution was added. The phases were separated and the aqueous phase was

extracted with ethyl acetate (3x50 ml). The combined organics were then dried over magnesium sulfate and the solvent was evaporated. Slow Kugelrohr distillation (boiling point 90 to 95° at 50 mTorr.) afforded the desired aldehyde as a clear, pale yellow oil in 92% yield (12.35 grams).

^{1}H NMR: δ(ppm) 0.05 (s, 6H), 0.87 (s, 9H), 1.39 (s, 3H), 1.45 (s, 3H), 3.78 (d, J=4.3Hz, 2H), 4.11 (m, 1H), 4.31 (dd, J=7.2, J=1.6Hz, 1H), 9.75 (d, J=1.6Hz, 1H).

^{13}C NMR: δ(ppm) -5.48, -5.39, 18.10, 25.81 (3C), 26.27, 26.78, 26.94, 62.86, 77.53, 81.95, 111.43, 200.81.



42

General Procedure for Horner-Wadsworth-Emmons Olefination: To a suspension of 1.12 grams (44.4 mmoles) of sodium hydride (dry, 95%) in 150 ml dry benzene at 0° was added a solution of 7.19 ml (8.09 grams, 44.4 mmoles) trimethyl phosphonoacetate in 30 ml of benzene, and stirring was continued for one hour at 0°. 12.2 grams (44.4 mmoles) of aldehyde **41** were dissolved in 50 ml of benzene and added dropwise via cannula to the mixture at 0°. After one hour of stirring at this temperature, the heterogeneous mixture was poured into 500 ml of cold water, the phases were separated, and the aqueous phase was extracted further with benzene (2x150 ml). The combined organics were dried over magnesium sulfate and the solvent was evaporated leaving the crude product as a pale

yellow viscous oil, which was quite pure by TLC and NMR analysis, showing only a trace of the (*Z*) isomer. Flash chromatography (7:1 hexanes:diethyl ether) afforded 13.4 grams (91%) of pure **42**, a clear colourless oil.

^{1}H NMR: δ(ppm) 0.04 (s, 6H), 0.87 (s, 9H), 1.39 (s, 3H), 1.40 (s, 3H), 3.71 (s, 3H), 3.70-3.81 (m, 3H), 4.49 (m, 1H), 6.10 (dd, J=15.7, J=1.6Hz, 1H), 6.93 (dd, J=15.7, J=5.1Hz).

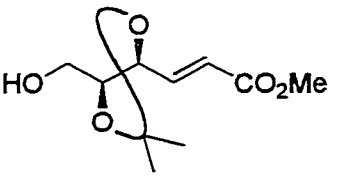
^{13}C NMR: δ(ppm) -5.37, -5.30, 18.33, 25.90 (3C), 26.85, 27.00, 51.69, 62.82, 77.85, 80.93, 110.02, 121.50, 145.20, 166.63.

IR: ν(cm^{-1}) 1729, 1664.

EI-MS: *m/e*(%) 315 [M-CH_3] (17.1), 215 (100), 185 (30.2).

HRMS: calcd for $C_{15}H_{27}O_5Si$ 315.16281, found 315.16529.

$[\alpha]^{20}_D$: -12.2° (c=2.3, MeOH).



36

General Procedure for Silyl Protecting Group Removal: To a solution of 2.85 grams (8.62 mmoles) of ester **42** in 50 ml of THF at 0° was added 10.3 ml of a 1.0M solution of tetrabutylammonium fluoride (10.3 mmoles) in THF. After stirring for 45 minutes at 0°, the solution was diluted with ether, washed with brine, dried over magnesium sulfate and

concentrated *in vacuo*. After flash chromatography (1:1 hexanes:diethyl ether), the alcohol **36** was isolated in pure form as a clear, colourless oil in 92% yield (1.69 grams).

^{1}H NMR: δ(ppm) 1.36 (s, 3H), 1.38 (s, 3H), 2.60 (br, 1H), 3.59 (m, 1H), 3.68 (s, 3H), 3.78 (m, 2H), 4.44 (m, 1H), 6.07 (dd, J=15.6, J=1.1Hz, 1H), 6.84 (dd, J=15.6, J=5.6Hz, 1H).

^{13}C NMR: δ(ppm) 26.58, 26.78, 51.65, 60.72, 76.02, 80.71, 109.97, 122.10, 144.20, 166.33.

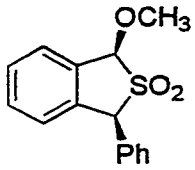
IR: ν(cm^{-1}) 3422, 1722, 1664.

EI-MS: *m/e*(%) 201 [M-CH_3] (98.6), 185 (24.0), 127 (54.1), 98 (100).

HRMS: calcd for $C_9H_{13}O_5$ 201.07629, found 201.07516.

$[\alpha]^{20}_D$: -14.4 (c=3.1, $CHCl_3$).

Attempted Coupling of 35 and 36, and Accidental Formation of 43.

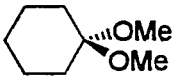


43

160 mg (0.61 mmoles) of hydroxy-sulfone **35** and 133 mg (0.61 mmoles) of alcohol **36** were dissolved in 5 ml of dry dichloromethane. 88 ul (0.67 mmoles) of boron trifluoride etherate was added dropwise, and the mixture was heated to reflux. After five hours, the solution was cooled to room temperature, diluted with diethyl ether, washed with dilute sodium bicarbonate solution, dried over magnesium sulfate, and concentrated *in vacuo*.

Flash chromatography (4:1 hexanes:diethyl ether) resulted in the isolation of 45 mg (25%) of methylated hydroxy-sulfone **43** as only the *cis* diastereomer.

^{1}H NMR: δ(ppm) 3.88 (s, 3H), 5.33 (s, 1H), 5.42 (s, 1H), 7.05-7.58 (m, 9H).

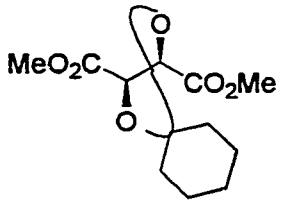


Cyclohexanone Dimethyl Acetal

In 500 ml of dry hexanes were dissolved 50 ml (47.4 grams, 480 mmoles) of cyclohexanone and 80 ml (1.92 moles) of dry methanol. The solution was cooled to 0° and 18.3 grams (20 mole %, 96 mmoles) of *p*-toluenesulfonic acid monohydrate were added and the mixture was stirred at 0° for 15 minutes. 55 grams of activated 3Å molecular sieves were added and the mixture was stirred for 15 minutes more. Another addition of 18.3 grams of *p*-toluenesulfonic acid monohydrate was made and after 15 minutes more stirring, the mixture was filtered to remove the molecular sieves and the excess acid. The reaction was complete when analyzed by ^{1}H NMR. The solvent was evaporated and reasonably pure cyclohexanone dimethyl acetal was obtained after distillation under reduced pressure (boiling point 57-60° at 15 Torr.). 45 grams (64%) of the desired product was obtained as a clear, colourless oil.

^{1}H NMR: δ(ppm) 1.20-1.40 (m, 6H), 1.41-1.52 (m, 4H), 2.98-3.03 (m, 6H).

^{13}C NMR: δ(ppm) 22.45, 25.54, 32.49, 47.02, 99.80.



44

To a solution of 20.0 grams (112.4 mmoles) of dimethyl-(*L*)-tartrate in 300 ml chloroform were added 32.0 grams (225 mmoles) of cyclohexanone dimethyl acetal, followed by 4.0 grams of *p*-toluenesulfonic acid monohydrate. The reaction flask was fitted with a soxhlet extractor containing activated 4A molecular sieves and a reflux condenser. The mixture was then heated to reflux for 90 minutes, after which the mixture was cooled, diluted with dichloromethane, washed with saturated sodium bicarbonate solution followed by water, dried over magnesium sulfate and then concentrated *in vacuo*. Crude **44** was purified by bulb-to-bulb distillation (boiling point 115 to 120° at 50 mTorr.) to yield 28.3 grams (98%) of the desired product as a clear colourless oil.

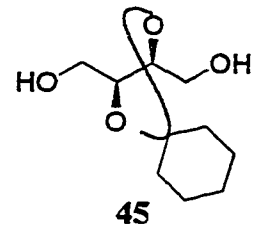
^{1}H NMR: δ(ppm) 1.15-1.28 (m, 2H), 1.35-1.53 (m, 8H), 3.61 (s, 6H), 4.61 (s, 2H).

^{13}C NMR: δ(ppm) 23.27 (2C), 24.39, 35.33 (2C), 52.20 (2C), 76.29 (2C), 114.09, 169.87 (2C).

IR: ν(cm^{-1}) 1753.

EI-MS: *m/e*(%) 258 (14.7), 229 (19.6), 215 (100).

HRMS: calcd for $C_{12}H_{18}O_6$ 215.11034, found 215.11315.



45

Using the **General Procedure for Ester Reduction** from above, 28.0 grams (108.4 mmoles) of diester **44** were reduced to the diol, affording 19.7 grams (90%) of **45** after flash chromatography (9:1 hexanes:diethyl ether) as a white semi-solid, which completely crystallized upon storage at 4°.

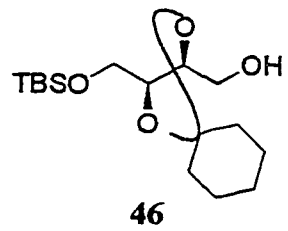
^{1}H NMR: δ(ppm) 1.28-1.40 (m, 2H), 1.45-1.62 (m, 8H), 3.11 (br, 2H), 3.68 (s, 4H), 3.90 (m, 2H).

^{13}C NMR: δ(ppm) 23.71 (2C), 24.92, 36.45 (2C), 62.24 (2C), 77.89 (2C), 109.76.

IR (CH_2Cl_2 solution): ν(cm^{-1}) 3598, 3460.

EI-MS: *m/e*(%) 202 (32.5), 173 (37.7), 159 (96.4).

HRMS: calcd for $C_{10}H_{18}O_4$ 202.12054, found 202.11760.



46

Following the **General Procedure for Diol Monosilylation** above, 1.20 grams of diol **45** were protected as its mono-*tert*-butyldimethylsilyl ether. The clear, colourless, viscous oil was obtained in 85% yield (1.60 grams) after purification by flash chromatography (3:1 hexanes:diethyl ether).

^{1}H NMR: δ(ppm) 0.04 (s, 6H), 0.85 (s, 9H), 1.29-1.39 (m, 2H), 1.51-1.61 (m, 8H), 2.54 (br, 1H), 3.45-3.98 (m, 6H).

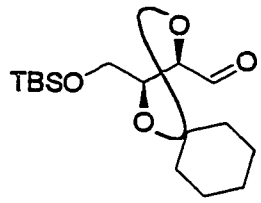
^{13}C NMR: δ(ppm) -5.38 (2C), 18.15, 23.72, 23.81, 25.02, 25.78 (3C), 36.40, 36.53, 62.82, 63.85, 77.64, 79.69, 109.78.

IR: ν(cm^{-1}) 3438, 1101.

EI-MS: *m/e*(%) 316 (17.9), 273 (49.3), 259 (23.1).

HRMS: calcd for $C_{16}H_{32}O_4Si$ 316.20706, found 316.20628.

$[\alpha]^{20}_D$: +7.26° (c=5.4, $CHCl_3$).

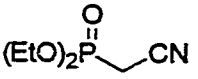


47

According to the **General Procedure for a Swern Oxidation** above, 31.3 grams (98.9 mmoles) of alcohol **46** were oxidized to the aldehyde, affording 27.4 grams (88%) of a pale yellow semi-solid after bulb-to-bulb distillation (boiling point 130-135° at 50 mTorr:). Aldehyde **47** crystallized completely upon storage at 4°.

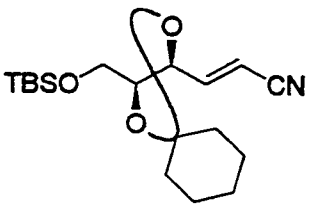
^{1}H NMR: δ(ppm) 0.02 (s, 6H), 0.83 (s, 9H), 1.30-1.42 (m, 2H), 1.50-1.66 (m, 8H), 3.73 (d, J=4.5Hz, 1H), 4.06 (m, 1H), 4.25 (dd, J=7.0, J=1.7Hz, 1H).

^{13}C NMR: δ(ppm) -5.52, -5.44, 18.20, 23.63, 23.74, 24.89, 25.74 (3C), 35.71, 36.34, 62.98, 77.08, 81.61, 111.97, 200.96.



5.0 grams of bromoacetonitrile (41.7 mmoles) and 7.6 grams (45.9 mmoles) of triethyl phosphite were stirred together at 125° for 2 hours. The mixture was allowed to cool to room temperature, and then excess triethyl phosphite was removed under high vacuum at 60° for 10 hours. The resulting pale yellow oil was isolated in quantitative yield (7.6 grams) and was spectroscopically homogeneous.

^{1}H NMR: δ(ppm) 1.24 (dt, J=7.1, J=0.6Hz, 6H), 2.80 (d, J=21.0Hz, 2H), 4.13 (m, 4H).



48

To a stirred supension of 360 mg (8.40 mmoles) of anhydrous lithium chloride in 50 ml of freshly distilled acetonitrile was added via cannula 1.49 grams (8.40 mmoles) of the phosphonate derived from bromoacetonitrile in 10 ml of acetonitrile. 1.05 ml (7.00 mmoles) of freshly distilled DBU were added, and after 10 minutes of stirring at room temperature, 2.20 grams (7.00 mmoles) of aldehyde **47** in 20 ml of acetonitrile were added via cannula. The reaction was complete after stirring for one hour at room temperature, and was quenched by the addition of saturated ammonium chloride solution. The resulting mixture was extracted with dichloromethane (3x50 ml) and the combined organics were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The crude

product was filtered through a pad of silica (elution with diethyl ether) to afford the pure products as a 6:1 mixture of (*E*):(*Z*) isomers in 85% combined yield (2.00grams). The two isomers could be separated by careful column chromatography (95:5 hexanes:diethyl ether).

^{1}H NMR: δ(ppm) 0.00 (s, 6H), 0.83 (s, 9H), 1.26-1.37 (m, 2H), 1.47-1.57 (m, 8H), 3.58-3.83 (m, 3H), 4.38 (m, 1H), 5.67 (dd, J=16.2, J=1.9Hz, 1H), 6.68 (dd, J=16.2, J=4.2Hz, 1H).

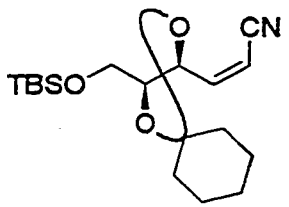
^{13}C NMR: δ(ppm) -5.67 (2C), 18.01, 23.54 (2C), 24.76, 25.60 (3C), 35.88, 36.24, 62.96, 77.72, 79.71, 99.56, 110.63, 116.71, 151.51.

IR: ν(cm^{-1}) 2228, 1640.

EI-MS: *m/e*(%) 337 (4.9), 294 (24.1), 243 (13.7), 222 (19.6), 182 (83.9), 152 (100).

HRMS: calcd for $C_{18}H_{31}O_3NSi$ 316.20743, found 337.20871

$[\alpha]^{20}_D$: -0.72° (c=3.5, $CHCl_3$).



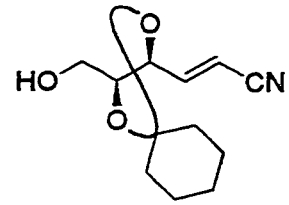
^{1}H NMR: δ(ppm) 0.03 (s, 6H), 0.84 (s, 9H), 1.28-1.39 (m, 2H), 1.51-1.64 (m, 8H), 3.70-3.83 (m, 3H), 4.71 (ddd, J=10.8, J=5.4, J=0.9Hz, 1H), 5.43 (dd, J=8.2, J=0.9Hz, 1H), 6.39 (dd, J=10.8, J=8.2Hz, 1H).

^{13}C NMR: δ(ppm) -5.63, -5.57, 18.14, 23.66 (2C), 24.86, 25.70 (3C), 36.24 (2C), 62.65, 76.42, 80.40, 101.67, 111.21, 114.83, 150.48.

IR: $\nu(cm^{-1})$ 2224, 1631.

EI-MS: *m/e*(%) 337 (5.3), 294 (23.2), 280 (45.8), 222 (28.4), 182 (68.8), 152 (100).

HRMS: calcd for $C_{18}H_{31}O_3NSi$ 316.20743, found 337.20905.



49

Following the **General Procedure for Silyl Protecting Group Removal** above, 1.52 grams (4.50 mmoles) of unsaturated nitrile **48** were deprotected affording 0.96 grams (95%) of alcohol **49** as a clear, colourless, viscous oil after flash chromatography (1:1 hexanes:diethyl ether).

^{1}H NMR: δ(ppm) 1.27-1.40 (m, 2H), 1.43-1.62 (m, 8H), 2.71 (br, 1H), 3.55-3.82 (m, 3H), 4.42 (m, 1H), 5.70 (dd, J=16.2, J=1.7Hz, 1H), 6.69 (dd, J=16.2, J=4.5Hz, 1H).

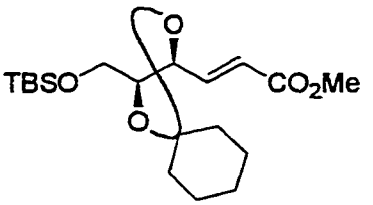
^{13}C NMR: δ(ppm) 23.46, 23.54, 24.67, 35.84, 36.19, 60.84, 76.04, 79.83, 100.23, 110.85, 116.67, 151.13.

IR: $\nu(cm^{-1})$ 3439, 2229,1640.

EI-MS: *m/e*(%) 223(12.8), 194 (12.8), 180(76.5).

HRMS: calcd for $C_{12}H_{17}O_3N$ 223.12091, found 223.12127.

$[\alpha]^{20}_D$: -1.38° (c=2.1, $CHCl_3$).



50

According to the **General Procedure for Horner-Wadsworth-Emmons Olefination** above, 27.4 grams (87.12 mmoles) of aldehyde **47** was homologated to unsaturated ester **50** in 94% yield (30.4 grams) as a clear, colourless, viscous oil after flash chromatography (9:1 hexanes:diethyl ether).

^{1}H NMR: δ(ppm) 0.03 (s, 6H), 0.85 (s, 9H), 1.32-1.41 (m, 2H), 1.45-1.64 (m, 8H), 3.70 (s, 3H), 3.66-3.80 (m, 3H), 4.47 (m, 1H), 6.09 (dd, J=15.7, J=1.5Hz, 1H), 6.69 (dd, J=15.7, J=5.0Hz, 1H).

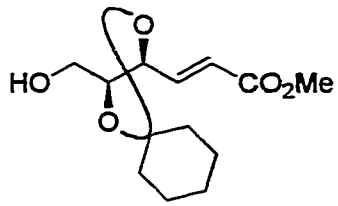
^{13}C NMR: δ(ppm) -5.50, -5.45, 18.20, 23.76 (2C), 25.02, 25.76 (3C), 36.22, 36.44, 51.56, 62.85, 77.40, 80.28, 110.45, 121.13, 145.50, 166.52.

IR: ν(cm^{-1}) 1730, 1663.

EI-MS: *m/e*(%) 370 (10.0), 327 (24.6), 255 (10.6), 215 (100).

HRMS: calcd for $C_{19}H_{34}O_5Si$ 370.21762, found 370.21981.

$[\alpha]^{20}_D$: -3.29° (c=1.7, $CHCl_3$).



51

Following the **General Procedure for Silyl Protecting Group Removal** above, 30 grams (81.0 mmoles) of unsaturated ester **50** were deprotected affording 15.6 grams (75%) of alcohol **51** as a clear, colourless, viscous oil after flash chromatography (2:1 hexanes:diethyl ether).

^{1}H NMR: δ(ppm) 1.30-1.46 (m, 2H), 1.49-1.67 (m, 8H), 2.62 (br, 1H), 3.60 (dd, J=13.0, J=4.6Hz, 1H), 3.71 (s, 3H), 3.77-3.89 (m, 2H), 4.48 (ddd, J=6.5, J=5.6, J=1.5Hz, 1H), 6.11 (dd, J=15.6, J=1.5Hz, 1H), 6.80 (dd, J=15.6, J=5.6Hz, 1H).

^{13}C NMR: δ(ppm) 23.60, 23.73, 24.88, 36.15, 36.37, 51.66, 60.77, 75.65, 80.26, 110.63, 122.03, 144.57, 166.37.

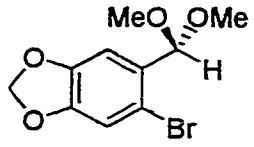
IR: ν(cm^{-1}) 3437, 1720,1662.

EI-MS: *m/e*(%) 256(23.3), 226 (15.4), 213 (100).

HRMS: calcd for $C_{13}H_{20}O_5$ 256.13110, found 256.12871.

$[\alpha]^{20}_D$: -14.3° (c=4.75, $CHCl_3$).

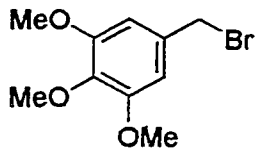
For Chapter 5



61

To a solution of 20.8 grams (90.8 mmoles) of 2-bromopiperonal in 300 ml of dry methanol were added 11.0 ml (99.9 mmoles) of trimethyl orthoformate and a catalytic amount (approx. 1 gram) of Dowex 50W200 acidic resin. The resulting mixture was heated to reflux for 20 hours. It was then allowed to cool to room temperature, filtered to remove the resin, and the solvent was evaporated. The residue was then filtered through a plug of silica using dichloromethane as eluant to afford, after removal of solvent, 23.7 grams (95%) of acetal **61** as a clear, colourless oil.

^{1}H NMR: δ(ppm) 3.34 (s, 6H), 5.43 (s, 1H), 5.94 (s, 2H), 6.96 (s, 1H), 7.06 (s, 1H).



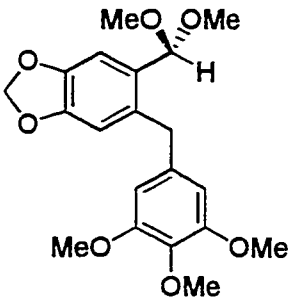
62

To a solution of 12.0 grams (60.5 mmoles) of 3,4,5-trimethoxybenzyl alcohol in 150 ml of dry dichloromethane were added slowly 11.5 ml (121 mmoles) of freshly distilled phosphorus tribromide. The resulting solution was stirred at room temperature for 20 hours, after which the solvent and excess phosphorus tribromide were removed under high vacuum. The residue was redissolved in dichloromethane and was added slowly to a moist paste of sodium bicarbonate. The two phase mixture was stirred until gas evolution

had stopped, then excess magnesium sulfate was added and after filtration and concentration *in vacuo*, 13.8 grams (87%) of a deep red solid were recovered. Based upon spectral analysis, this rather unstable solid was sufficiently pure for use in subsequent reactions.

^{1}H NMR: δ(ppm) 3.81 (s, 3H), 3.84 (s, 6H), 4.43 (s, 2H), 6.59 (s, 2H).

EI-MS: *m/e*(%) 262 (7.3), 260 (7.3), 181 (100).



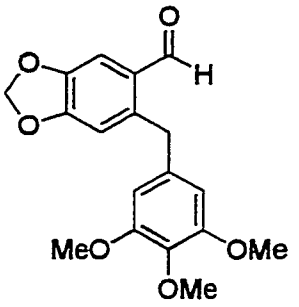
63

19.5 grams (70.9 mmoles) of aryl bromide **61** were dissolved in 100 ml of dry THF and cooled to -78°. 28.9 ml of *n*BuLi (2.45M in hexanes, 70.9 mmoles) were added dropwise followed five minutes later by 13.9 grams (35.5 mmoles) of copper iodide-tributyl phosphine complex in 40 ml of THF via cannula. Stirring at -78° was continued for five minutes to ensure complete generation of the aryl cuprate reagent, after which 9.25 grams (35.5 mmoles) of benzyl bromide **62** in 40 ml of THF were added via cannula. The resulting solution was stirred for one hour at this temperature, before slowly warming to room temperature. The reaction was quenched with saturated ammonium chloride solution, then diluted with ether, and the phases were separated. The aqueous phase was extracted with ether (3x75 ml) and the combined organics were dried over magnesium

sulfate. After evaporation of the solvent, the crude product was purified by flash chromatography (2:1 hexanes:diethyl ether) to afford 8.5 grams (64%) of diarylmethane **63** as a white solid.

^{1}H NMR: δ(ppm) 3.26 (s, 6H), 3.76 (s, 6H), 3.79 (s, 3H), 3.91 (s, 2H), 5.36 (s, 1H), 5.89 (s, 2H), 6.33 (s, 2H), 6.55 (s, 1H), 7.08 (s, 1H).

^{13}C NMR: δ(ppm) 37.66, 53.07 (2C), 55.91 (2C), 60.74, 100.94, 100.98, 105.67 (2C), 107.06, 110.20, 129.40, 132.47, 136.12, 136.28, 145.85, 147.45, 153.06.

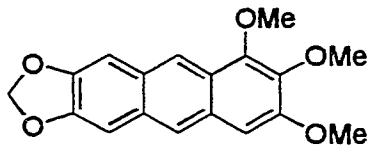


59

To a solution of 450 mg (1.20 mmoles) of acetal **63** in 20 ml of methanol were added 2 ml of 10% aqueous hydrochloric acid. The mixture was stirred at room temperature for 15 minutes, at which point a white precipitate began to accumulate. Neutralization of the mixture with solid sodium bicarbonate followed by removal of the methanol, extraction with dichloromethane (3x25ml), drying with magnesium sulfate and evaporation of the solvent afforded the desired aldehyde **59** in quantitative yield (400 mg) as a white solid.

^{1}H NMR (acetone-*d6*): δ(ppm) 3.66 (s, 3H), 3.74 (s, 6H), 4.35 (s, 2H), 6.11 (s, 2H), 6.53 (s, 2H), 6.89 (s, 1H), 7.28 (s, 1H), 10.23 (s, 1H).

^{13}C NMR: δ(ppm) 37.63, 55.99, 60.75 (2C), 101.95, 105.50 (2C), 108.84, 110.90, 128.38, 135.78, 136.43, 140.24, 146.93, 152.43, 153.27 (2C), 189.51.



67

To a solution of 500 mg (1.33 mmoles) of acetal **63** in 20 ml of methanol were added 2 ml of 10% aqueous hydrochloric acid. The mixture was stirred at room temperature for 20 hours, after which substantial white precipitate had accumulated. Filtration and rinsing with cold methanol afforded 260 mg (59%) of anthracene **67** as long pink needles.

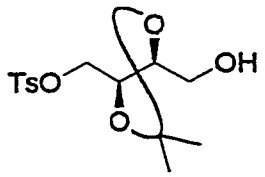
^{1}H NMR: δ(ppm) 4.00 (s, 6H), 4.11 (s, 3H), 6.02 (s, 2H), 6.93 (s, 1H), 7.12 (s, 1H), 7.20 (s, 1H), 7.98 (s, 1H), 8.36 (s, 1H).

^{13}C NMR: δ(ppm) 56.37, 61.86, 61.97, 101.26, 101.52, 102.60, 103.49, 119.49, 123.57, 128.56, 129.11, 130.16, 140.73, 147.50, 147.89, 148.40, 153.52.

IR: ν(cm^{-1}) 3011, 2833, 1103, 1037.

EI-MS: *m/e*(%) 312 (100), 297 (26.0), 282 (5.0), 269 (11.7), 254 (17.5).

HRMS: calcd for $C_{18}H_{16}O_5$ 312.09978, found 312.09773.



68

To a solution of 2.5 grams (15.6 mmoles) of diol **39** in 75 ml of dry THF cooled to 0° were added 6.5 ml of *n*BuLi (2.4M in hexanes, 15.6 mmoles) dropwise. The mixture was stirred for 45 minutes at 0°, then a solution of 3.0 grams (15.6 mmoles) of *p*-toluenesulfonyl chloride in 25 ml of THF was added dropwise via cannula. The reaction mixture was warmed to room temperature and stirred for 20 hours. The reaction was quenched and stirred with saturated sodium bicarbonate solution. Extraction with ether (3x50 ml), drying of the organics with magnesium sulfate and evaporation of solvent afforded the crude product in 97% yield (4.80 grams), which was spectroscopically pure, but which still smelled of *p*-toluenesulfonyl chloride. Rapid flash chromatography (1:1 hexanes:ethyl acetate) afforded 4.70 grams (95%) of pure **68** as a clear, colourless oil.

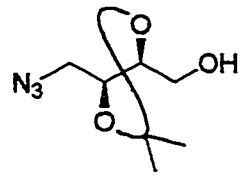
^{1}H NMR: δ(ppm) 1.22 (s, 3H), 1.27 (s, 3H), 2.33 (s, 3H), 2.76 (br, 1H), 3.51 (dd, J=11.9, J=4.5Hz, 1H), 3.65 (dd, J=11.9, J=3.8Hz, 1H), 3.85 (m, 1H), 3.91-4.13 (m, 3H), 7.25 (d, J=8.3Hz, 2H), 7.68 (d, J=8.3Hz, 2H).

^{13}C NMR: δ(ppm) 21.32, 36.40, 26.66, 61.44, 38.88, 74.51, 77.56, 109.69, 127.65 (2C), 129.67 (2C), 132.08, 144.92.

IR: ν(cm^{-1}) 3466, 1365, 1212, 1077.

EI-MS: *m/e*(%) 301 [M-CH_3] (4.1), 207 (6.9).

HRMS: calcd for $C_{13}H_{17}O_6S$ [M-CH_3] 301.07461, found 301.07524.



69

2.80 grams (8.85 mmoles) of monotosylate **68** were dissolved in 10 ml DMF. 2.88 grams (44.3 mmoles) of sodium azide were added, and the resulting mixture was heated to 85° for 20 hours. The light brown solution was cooled to room temperature, diluted with 200 ml of water, and exhaustively extracted with dichloromethane (5x75 ml). The combined organics were dried over magnesium sulfate and the solvent was evaporated to yield essentially pure monoazide contaminated only with DMF. Flash chromatography (1:1 hexanes:diethyl ether) afforded 1.40 grams (85%) of pure **69** as a clear pale yellow oil.

^{1}H NMR: δ(ppm) 1.35 (s, 3H), 1.38 (s, 3H), 2.72 (br, 1H), 3.25 (dd, J=13.2, J=4.6Hz, 1H), 3.48 (dd, J=13.2, J=3.7Hz, 1H), 3.57 (dd, J=11.9, J=4.1Hz, 1H), 3.69 (dd, J=11.9, J=3.6Hz, 1H), 3.85-4.03 (m, 2H).

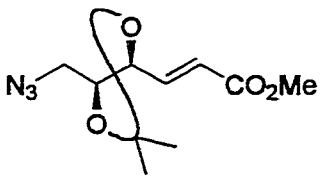
^{13}C NMR: δ(ppm) 26.63, 26.84, 51.54, 61.56, 76.03, 78.24, 109.65.

IR: ν(cm^{-1}) 3419, 2127.

EI-MS: *m/e*(%) 172 [M-CH_3] (71.8), 172 (71.8), 162 (29.8), 143 (25.1), 131 (61.5).

HRMS: calcd for $C_6H_{10}O_3N_3$ [M-CH_3] 172.07230, found 172.07068.

$[\alpha]^{20}_D$: -6.89° (c=4.25, $CHCl_3$).



71

A: According to the **General Procedure for Swern Oxidation**, 550 mg (2.94 mmoles) of azido-alcohol **69** were oxidized to the corresponding aldehyde, affording 500 mg of crude product, mostly as the hydrated form, after aqueous workup. The crude product was redissolved in 10 ml of benzene, to which was added 2.46 grams (7.35 mmoles) of methyl (triphenylphosphoranylidene) acetate. The reaction was warmed to 40° and was complete by TLC analysis after 20 minutes. The mixture was cooled to 0° and most of the triphenyl phosphine oxide and excess Wittig reagent were precipitated by addition of hexanes. After filtration and evaporation of solvent, the crude product was analyzed by ^{1}H NMR, revealing a 55:45 mixture of (*E*):(*Z*) isomers. Flash chromatography (9:1 hexanes:diethyl ether) afforded 162 mg (23% from alcohol **69**) of **71** and 155 mg (22%) of the (*Z*) isomer. Both products were isolated as clear, colourless, viscous oils. Alternatively, HWE olefination under Roush conditions (as per the synthesis of **48**) of the crude Swern product with excess phosphonate anion (2.5 equiv.) resulted in a 25% two-step yield of only the desired (*E*) isomer.

B: 1.70 grams (4.59 mmoles) of tosylate **73** (see below) were dissolved in 5 ml of DMF. 750 mg (11.48 mmoles) of sodium azide were added, and the resulting mixture was heated to 85° for one hour. The mixture was cooled to room temperature, diluted with 100 ml of water, and extracted exhaustively with ether (5x50 ml). The combined

organics were washed with brine, dried over magnesium sulfate, concentrated *in vacuo*, and purified by flash chromatography (9:1-4:1 hexanes:diethyl ether). Pure azide **71** was isolated in 58% yield (640mg) as a clear, colourless, viscous oil.

C: 200 mg (0.92 mmoles) of alcohol **36** and 610 mg (2.31 mmoles) of triphenylphosphine were dissolved in 10 ml of dry THF. 0.39 ml (2.31 mmoles) of diethyl azodicarboxylate were added dropwise, followed by a 5 ml THF solution of 655 mg (2.31 mmoles) of diphenylphosphoryl azide (via cannula). The resulting mixture was allowed to stir at room temperature for 4 hours. Evaporation of the volatiles followed by flash chromatography (9:1 hexanes:diethyl ether) afforded 200 mg of desired azide **71** that was contaminated by approximately 10% DPPA (overall yield about 80%).

^{1}H NMR: δ(ppm) 1.36 (s, 3H), 1.41 (s, 3H), 3.22 (dd, J=13.3, J=4.5Hz, 1H), 3.52 (dd, J=13.3, J=3.7Hz, 1H), 3.67 (s, 3H), 3.84 (ddd, J=8.2, J=4.5, J=3.7Hz, 1H), 4.40 (ddd, J=8.2, J=5.7, J=1.4Hz, 1H), 6.07 (dd, J=15.6, J=1.4Hz, 1H), 6.80 (dd, J=15.6, J=5.7Hz, 1H).

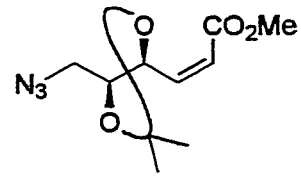
^{13}C NMR: δ(ppm) 26.61 (2C), 50.46, 51.66, 76.91, 79.21, 110.52, 122.68, 143.21, 166.02.

IR: ν(cm^{-1}) 2126, 1727, 1664.

EI-MS: *m/e*(%) 226 [M-CH_3] (100), 198 (9.9), 185 (95.4), 156 (27.6).

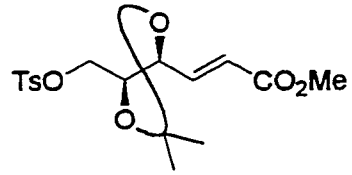
HRMS: calcd for $C_9H_{12}O_4N_3$ [M-CH_3] 226.08286, found 226.08457.

$[\alpha]^{20}_D$: -102.6° (c=3.85, $CHCl_3$).



^{1}H NMR: δ(ppm) 1.40 (s, 3H), 1.43 (s, 3H), 3.37 (dd, J=12.9, J=5.7Hz, 1H), 3.54 (dd, J=12.9, J=3.8Hz, 1H), 3.68 (s, 3H), 3.84 (ddd, J=8.4, J=5.7, J=3.8Hz, 1H), 5.47 (ddd, J=8.6, J=8.4, J=1.2Hz, 1H), 5.91 (dd, J=11.8, J=1.2Hz, 1H), 6.17 (dd, J=11.8, J=8.6Hz, 1H).

^{13}C NMR: δ(ppm) 26.80, 26.86, 51.57, 51.67, 74.01, 79.83, 110.47, 122.35, 145.96, 165.73.



73

1.50 grams (6.94 mmoles) of alcohol **36** and 4.0 grams (20.8 mmoles) of *p*-toluenesulfonyl chloride were dissolved in 50 ml of dry dichloromethane and 2.9 ml (20.8 mmoles) of triethylamine were added. The resulting mixture was stirred at room temperature for 20 hours, after which saturated sodium bicarbonate solution was added and the two-phase mixture was stirred vigorously for 30 minutes. The phases were separated and the organic phase was washed with dilute sodium bicarbonate, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (2:1 hexanes:diethyl ether) to afford 2.6 grams (quantitative yield) of tosylate **73**.

^{1}H NMR: δ(ppm) 1.29 (s, 3H), 1.30 (s, 3H), 2.37 (s, 3H), 3.66 (s, 3H), 3.82 (ddd, J=8.2, J=4.2, J=4.1Hz, 1H), 4.05 (dd, J=10.9, J=4.2Hz, 1H), 4.10 (dd, J=10.9, J=4.1Hz, 1H), 4.33 (ddd, J=7.8, J=5.7, J=1.3Hz, 1H), 5.96 (dd, J=15.6, J=1.4Hz, 1H), 6.73 (dd, J=15.6, J=5.7Hz, 1H), 7.28 (d, J=8.4 Hz, 2H), 7.71 (d, J=8.4Hz).

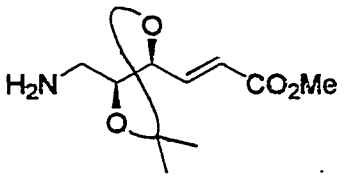
^{13}C NMR: δ(ppm) 21.52, 26.51, 26.57, 51.66, 67.46, 76.42, 77.59, 110.66, 122.89, 127.86, 129.74, 129.86, 142.90, 145.17, 165.89.

IR: ν(cm^{-1}) 1720, 1664, 1362, 1181, 1106.

EI-MS: *m/e*(%) 355 [M-CH_3] (40.7), 281 (6.9), 249 (3.3), 213 (4.9).

HRMS: calcd for $C_{16}H_{19}O_7S$ [M-CH_3] 355.08517, found 355.08572.

Attempted Reductions of Azide 71 to Amine 72:



72

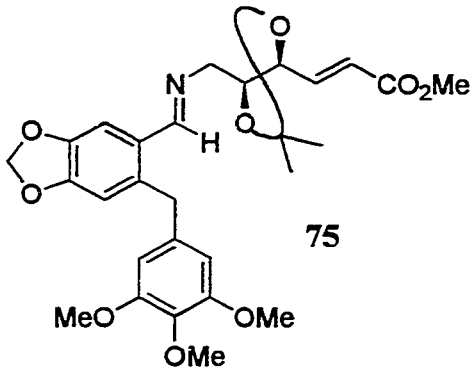
A: 135 mg (0.56 mmoles) of azide **71** were dissolved in 5 ml of dry methanol, and 40 mg of Lindlar's catalyst were added. The mixture was stirred for 3 hours under one atmosphere of hydrogen, at which point TLC analysis indicated complete reaction of starting material. The reaction mixture was filtered to remove the catalyst (rinsing with methanol) and the solvent was evaporated to afford 120 mg (quantitative crude yield) of a pale yellow, viscous, clear oil. After storage in frozen benzene overnight, TLC and ^{1}H NMR of the crude revealed that significant decomposition had occurred. Purification by

flash chromatography (95:5 dichloromethane:methanol) yielded 25 mg (19%) of reasonably pure amine **72**.

B: 180 mg (0.75 mmoles) of azide **71** were dissolved in 5 ml of dry benzene, and 925 mg (3.75 mmoles) of dibutyltin dihydride were added. The reaction mixture was stirred at room temperature for 4 hours at which point TLC analysis indicated complete reaction of the starting azide. The benzene was evaporated and the residue was redissolved in 10 ml of dichloromethane, and 10 ml of 10% hydrogen peroxide were added, and the two phase mixture was stirred vigorously for one hour. The mixture was further diluted with dichloromethane and dilute aqueous sodium carbonate, the phases were separated, and the organic phase was washed with dilute sodium carbonate once more, dried over magnesium sulfate, and concentrated *in vacuo*. The crude product (120 mg, approx. 73% crude yield) was an opaque, clear oil and analysis by ^{1}H NMR revealed that it consisted mostly of the desired amine. Immediate purification by rapid flash chromatography (92:8 dichloromethane:methanol) afforded 56 mg of a yellow oil, which was no purer than the crude product. Attempts to purify via the hydrochloride salt resulted in the isolation of only 22 mg of impure product.

^{1}H NMR (C_6D_6): δ(ppm) 0.75 (br, 2H), 1.26 (s, 3H), 1.33 (s, 3H), 2.32-2.61 (m, two unresolved dd's, 2H), 3.39 (s, 3H), 3.46 (m, 1H), 4.22 (m, 1H), 6.25 (dd, J=15.5, 1.2Hz, 1H), 7.02 (dd, J=15.5, J=5.2Hz, 1H).

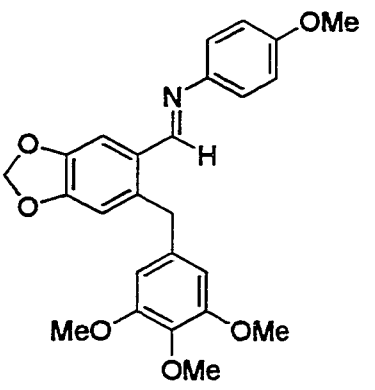
Attempted Formation of Imine 75:



75

330 mg (1.37 mmoles) of reasonably pure azide **71** and 360 mg (1.37 mmoles) of triphenylphosphine were dissolved in 5 ml of dry THF and stirred at room temperature for one hour to allow formation of the ylide (reaction progress was monitored by nitrogen gas evolution). 425 mg (1.23 mmoles) of aldehyde **28** were added and the resulting mixture was heated to reflux. After 24 hours, consumption of all of the azide was confirmed by TLC, and the solvent was evaporated. Analysis of the crude product by ^{1}H NMR revealed only three major compounds in the mixture: triphenylphosphine oxide, unreacted aldehyde, and the desired imine, for which the spectral data is given. Any attempts to purify the imine resulted in hydrolysis to the aldehyde and the amine, which decomposed further.

^{1}H NMR: δ(ppm) 1.37 (s, 3H), 1.41 (s, 3H), 3.71 (s, 3H), 3.62-3.88 (m, 2H), 3.76 (s, 6H), 3.80 (s, 3H), 4.07 (s, 2H), 4.51 (m, 2H), 5.95 (s, 2H), 6.12 (dd, 1H), 6.29 (s, 2H), 6.58 (s, 1H), 6.94 (dd, 1H), 7.31 (s, 1H), 8.49 (s, 1H).



76

500 mg (1.33 mmoles) of acetal **63** and 165 mg (1.33 mmoles) of *p*-anisidine were dissolved in 10 ml of toluene. Activated 4A molecular sieves and catalytic camphorsulfonic acid were added, and the flask was fitted with a Dean-Stark trap and a reflux condenser. The mixture was heated to reflux for 2 hours, cooled to room temperature, and solid potassium carbonate was added to neutralize the catalytic acid. Filtration of the mixture followed by solvent evaporation afforded 570 mg (99%) of spectroscopically pure imine **76** as a beige solid.

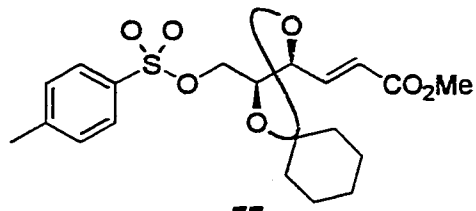
^{1}H NMR: δ(ppm) 3.74 (s, 6H), 3.76 (s, 3H), 3.79 (s, 3H), 4.12 (s, 2H), 5.96 (s, 2H), 6.32 (s, 2H), 6.66 (s, 1H), 6.84 (d, J=8.8Hz, 2H), 7.02 (d, J=8.8Hz, 2H), 7.66 (s, 1H), 8.62 (s, 1H).

^{13}C NMR: δ(ppm) 38.48, 55.30, 55.89 (2C), 60.70, 101.36, 105.35 (2C), 106.63, 110.39, 114.17 (2C), 121.94 (2C), 128.49, 136.00, 136.21, 145.18, 146.84, 149.90, 153.18 (2C), 155.69, 157.90.

IR (CH_2Cl_2 solution): ν(cm^{-1}) 1601.

EI-MS: *m/e*(%) 435 (73.6), 418 (29.8), 404 (11.4), 388 (5.5), 312 (100), 282 (63.2).

HRMS: calcd for $C_{25}H_{25}NO_6$ 435.16825, found 435.16645.



77

1.00 grams (3.90 mmoles) of alcohol **51** and 2.2 grams (11.7 mmoles) of *p*-toluenesulfonyl chloride were dissolved in 30 ml of dry dichloromethane and 1.65 ml (11.7 mmoles) of triethylamine were added. The resulting mixture was stirred at room temperature for 20 hours, after which saturated sodium bicarbonate solution was added and the two-phase mixture was stirred vigorously for 30 minutes. The phases were separated and the organic phase was washed with dilute sodium bicarbonate, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (3:1 hexanes:diethyl ether) to afford 1.22 grams (76%) of tosylate **77**.

^{1}H NMR: δ(ppm) 1.20-1.38 (m, 2H), 1.40-1.56 (m, 8H), 2.38 (s, 3H), 3.67 (s, 3H), 3.83 (ddd, J=7.9, J=4.1, J=4.1Hz, 1H), 4.07 (dd, J=10.8, J=4.1Hz, 1H), 4.09 (dd, J=10.8, J=4.1Hz, 1H), 4.34 (ddd, J=7.9, J=5.7, J=1.3Hz, 1H), 5.98 (dd, J=15.6, J=1.3Hz, 1H), 6.74 (dd, J=15.6, J=5.7Hz, 1H), 7.29 (d, J=8.3 Hz, 2H), 7.72 (d, J=8.3Hz).

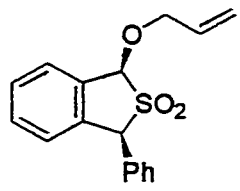
^{13}C NMR: δ(ppm) 21.41, 23.47 (2C), 24.68, 35.97 (2C), 51.52, 67.69, 76.09, 77.15, 111.21, 122.60, 127.75 (2C), 129.77 (2C), 132.30, 143.27, 145.04, 165.83.

IR: ν(cm^{-1}) 1725, 1663, 1360, 1185.

EI-MS: *m/e*(%) 410 (47.2), 381 (11.7), 367 (100).

HRMS: calcd for $C_{20}H_{26}O_7S$ 410.13998, found 410.13180.

For Chapter 6

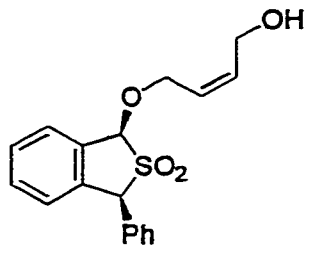


84

To a solution of 200 mg (0.77 mmoles) of hydroxy-sulfone **35** in 20 ml of dry dichloromethane were added 60 ul (0.84 mmoles) of allyl alcohol, activated 4A molecular sieves and a catalytic amount of *p*-toluenesulfonic acid monohydrate. The resulting mixture was heated to reflux for 6 hours, cooled to room temperature and filtered through a plug of silica, eluting with dichloromethane. The resulting product was isolated in 70% yield (163 mg) as a single diastereomer, and was a colourless glassy solid.

^{1}H NMR: δ(ppm) 4.43 (ddd, 1H), 4.66 (ddd, 1H), 5.34 (s, 1H), 5.36 (m, 1H), 5.44 (m, 1H), 5.59 (s, 1H), 6.00 (dddd, 1H), 7.05-7.59 (m, 9H).

^{13}C NMR: δ(ppm) 70.31, 73.03, 92.07, 119.87, 126.49, 126.64, 128.76 (2C), 129.14, 129.22, 130.48 (2C), 130.84, 131.63, 132.42, 132.79, 134.84.

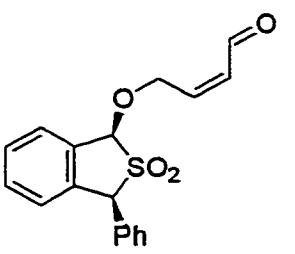


86

To a solution of 200 mg (0.77 mmoles) of hydroxy-sulfone **35** in 20 ml of dry dichloromethane were added 120 ul (1.15 mmoles) of *cis*-1,4-butenediol, activated 4A molecular sieves and a catalytic amount of *p*-toluenesulfonic acid. The resulting mixture was heated to reflux for 20 hours, cooled to room temperature, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (1:1 hexanes:ethyl acetate) to afford 150 mg (60%) of ether **86** as a clear, colourless oil.

^{1}H NMR: δ(ppm) 3.02 (br, 1H), 4.02-4.35 (m, 2H), 4.60 (d, J=6.2Hz, 2H), 5.35 (s, 1H), 5.62 (s, 1H), 5.74 (m, 1H), 5.85 (m, 1H), 6.98-7.54 (m, 9H).

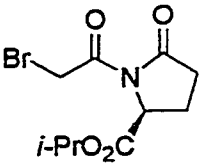
^{13}C NMR: δ(ppm) 57.84, 67.20, 69.86, 91.98, 125.11, 126.13, 126.32, 128.57 (2C), 129.01, 129.06, 130.29, 130.39 (2C), 130.93, 132.51, 134.29, 134.84.



87

According to the **General Procedure for Swern Oxidation**, 1.00 gram (3.03 mmoles) of *cis* allylic alcohol **86** was oxidized to the corresponding aldehyde. The unsaturated aldehyde was isolated as a 9:1 mixture of geometric isomers favouring the desired (*Z*) isomer in quantitative crude yield (0.99 grams) following a basic workup. The white foam was quite unstable, and needed to be used directly in subsequent manipulations.

^{1}H NMR: δ(ppm) 5.00 ppm (dd, 1H), 5.11 (dd, 1H), 5.38 (s, 1H), 5.61 (s, 1H), 6.11 (ddd, 1H), 6.72 (m, 1H), 7.08-7.60 (m, 9H), 9.95 (d, J=5.9Hz, 1H).



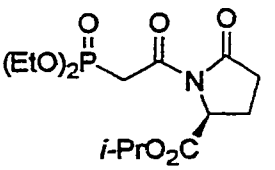
89

To a solution of 5.0 grams (29.2 mmoles) of isopropyl pyroglutamate in 100 ml of dry THF cooled to -78° were added 29.2 ml (1.0M in hexanes, 29.2 mmoles) of lithium hexamethyldisilazide. The mixture was stirred at -78° for 30 minutes, then at 0° for 30 minutes, and was cooled back down to -78°. A solution of 3.1 ml (35.0 mmoles) of bromoacetyl bromide was added by cannula to the mixture, which was then slowly allowed to warm to room temperature. The reaction was quenched with saturated

ammonium chloride solution, the volatiles were evaporated, and the remaining aqueous phase was extracted with dichloromethane (3x50 ml), the combined organics were washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography (3:2 hexanes:diethyl ether) to afford 5.00 grams (59%) of the bromide **89** as a clear, colourless oil.

^{1}H NMR: δ(ppm) 1.22 (t, J=6.3Hz, 6H), 2.06 (m, 1H), 2.33 (m, 1H), 2.62 (m, 2H), 4.44 (d, J=13.0Hz, 1H), 4.50 (d, J=13.0Hz, 1H), 4.68 (dd, J=9.3, J=2.7Hz, 1H), 5.02 (sept, J=6.3Hz, 1H).

^{13}C NMR: δ(ppm) 21.43 (2C), 21.51, 29.49, 31.29, 58.16, 69.61, 166.25, 169.77, 174.25.

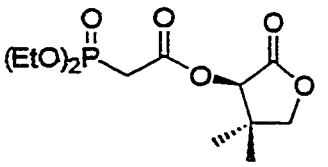


90

To 1.30 grams (4.45 mmoles) of bromoacetate **89** was added 815 mg (4.90 mmoles) of triethyl phosphite, and the resulting mixture was heated to 125° for 3 hours. The solution was cooled, and the excess triethyl phosphite was removed under high vacuum at 45° for 6 hours. The resulting clear, pale yellow oil was spectroscopically pure and was isolated in quantitative yield (1.56 grams).

^{1}H NMR: δ(ppm) 1.12-1.33 (m, 12H), 1.99 (m, 1H), 2.36 (m, 1H), 2.45-2.88 (m, 2H), 3.38 (dd, J=22.2, J=14.3Hz, 1H), 3.98-4.19 (m, 5H), 4.66 (dd, J=9.3, J=2.5Hz, 1H), 4.99 (sept, J=6.3Hz, 1H).

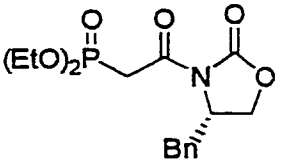
^{13}C NMR: δ(ppm) 16.15, 16.28, 20.95, 21.44, 21.53, 31.75, 34.99 (d, J=132.4Hz), 58.33, 62.40 (d, J=6.1Hz), 62.60 (d, J=6.3Hz), 69.44, 165.22, 170.09, 174.27.



92

600 mg (2.00 mmoles) of iodoacetate **91** and 370 mg (2.20 mmoles) of triethyl phosphite were heated together at 125° with stirring for 3 hours. The mixture was cooled and the excess triethyl phosphite was removed under high vacuum at 45° for 6 hours. The resulting clear, pale yellow oil was spectroscopically pure and was isolated in quantitative yield (700 mg).

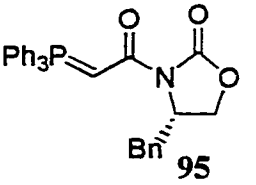
^{1}H NMR: δ(ppm) 1.12 (s, 3H), 1.21 (s, 3H), 1.32 (t, J=7.0Hz, 6H), 3.02 (dd, J=20.2, J=8.4Hz, 1H), 3.14 (dd, J=20.2, J=8.4Hz, 1H), 4.02 (s, 1H), 4.16 (m, 4H), 5.37 (s, 1H).



94

500 mg (1.68 mmoles) of bromoacetate **93** and 310 mg (1.84 mmoles) of triethyl phosphite were heated together at 125° with stirring for 3 hours. The mixture was cooled and the excess triethyl phosphite phosphite was removed under high vacuum at 45° for 6 hours. The resulting clear, pale yellow, viscous oil was spectroscopically pure and was isolated in quantitative yield (595 mg).

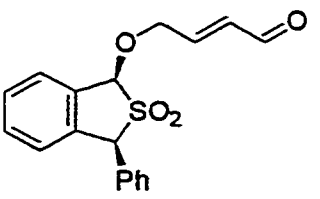
^{1}H NMR: δ(ppm) 1.34 (t, J=7.2Hz, 6H), 2.73 (dd, J=12.3, J=9.7Hz, 1H), 3.33 (dd, J=12.3, J=2.8Hz, 1H), 3.72 (dd, J=21.7, J=8.6Hz, 1H), 3.84 (dd, J=21.7, J=8.6Hz, 1H), 4.10-4.28 (m, 4H), 4.70 (m, 1H), 7.16-7.38 (m, 5H).



95

500 mg (1.68 mmoles) of bromoacetate **93** and 500 mg (1.84 mmoles) of triphenylphosphine were dissolved in 15 ml of acetonitrile. The mixture was heated to 50° and stirred for 24 hours. The mixture was cooled to room temperature, 10 ml of 2N sodium hydroxide were added and the resulting solution was stirred for 15 minutes. The mixture was then extracted with ether (3x25 ml) and the combined organics were dried over magnesium sulfate and concentrated *in vacuo*. The crude product was isolated in 90% yield (725 mg) as a pale yellow foam.

^{1}H NMR: δ(ppm) 2.81 (dd, J=12.1, J=9.8Hz, 1H), 3.27 (dd, J=12.1, J=2.8Hz, 1H), 3.95-4.20 (m, 2H), 4.69-4.80 (m ,1H), 4.75 (d, J=24.4Hz, 1H0, 7.05-7.33 (m, 5H), 7.40-7.75 (m, 15H).



96

To a solution of 660 mg (2.00 mmoles) of *cis* allylic alcohol **86** in 25 ml of dry dichloromethane were added 1.13 grams (3.00 mmoles) of pyridinium dichromate. The resulting suspension was stirred at room temperature for 20 hours. The mixture was then filtered through celite, concentrated *in vacuo*, and the residue was purified by flash chromatography (2:1 diethyl ether:hexanes). 270 mg (41%) of a clear, viscous, colourless oil was isolated as exclusively the *trans* isomer.

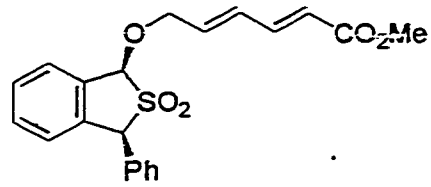
^{1}H NMR: δ(ppm) 4.64 (ddd, J=16.2, J=4.4, J=1.8Hz, 1H), 4.90 (ddd, J=16.2, J=3.8, J=1.8Hz, 1H), 5.37 (s, 1H), 5.56 (s, 1H), 6.32 (dddd, J=15.9, J=7.8, J=1.8, J=1.8Hz, 1H), 6.77 (ddd, J=15.9, J=4.4, J=3.8Hz, 1H), 7.05-7.23 (m, 3H), 7.32-7.59 (m, 6H), 9.51 (d, J=7.8Hz, 1H).

^{13}C NMR: δ(ppm) 70.01, 70.17, 92.79, 126.55, 126.69, 128.64 (2C), 129.08, 129.28, 130.18 (2C), 130.84, 131.65, 131.89, 134.81, 150.15, 192.81.

IR: ν(cm^{-1}) 2836, 2745, 1694.

EI-MS: *m/e*(%) 264 [M-SO_2] (1.4), 195 (100), 178 (32.1), 165 (45.0).

HRMS: calcd for $C_{18}H_{16}O_2$ [M-SO_2] 264.1151, found 264.1707.



97

Following the **General Procedure for Horner-Wadsworth-Emmons Olefination**, 240 mg (0.73 mmoles) of unsaturated aldehyde **96** was homologated to the (*E,E*) dienoic ester **97**. The product was isolated in 85% yield (240 mg) after flash chromatography (3:2 hexanes:diethyl ether) as a clear, colourless, viscous oil. Traces (approx. 10%) of the (*E,Z*) product were visible in the ^{1}H NMR spectrum of the crude product, but were easily removed.

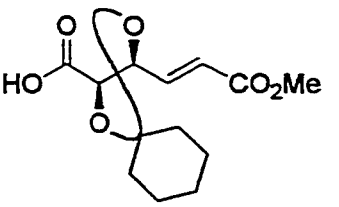
^{1}H NMR: δ(ppm) 3.73 (s, 3H), 4.54 (dd, J=14.3, J=6.3Hz, 1H), 4.72 (dd, J=14.3, J=4.4Hz, 1H), 5.34 (s, 1H), 5.55 (s, 1H), 5.91 (d, J=15.4Hz, 1H), 6.19 (ddd, J=15.9, J=6.2, J=5.6Hz, 1H), 6.45 (dd, J=15.4, J=6.2Hz, 1H), 7.11 (m, 1H), 7.17-7.29 (m, 3H), 7.33-7.60 (m, 6H).

^{13}C NMR: δ(ppm) 51.58, 70.32, 71.52, 92.45, 122.20, 126.59, 126.68, 128.77 (2C), 129.19, 129.31, 130.41 (2C), 130.73, 131.22, 131.61, 132.47, 134.86, 135.61, 143.16, 167.05.

IR: ν(cm^{-1}) 1716, 1651, 1620.

EI-MS: *m/e*(%) 320 [M-SO_2] (6.5), 195 (100), 178 (41.0), 165 (33.2).

HRMS: calcd for $C_{21}H_{20}O_3$ [M-SO_2] 320.14130, found 320.13744.



100

To a solution of 250 mg (0.98 mmoles) of alcohol **51** in 3 ml of DMF was added 1.28 grams of pyridinium dichromate (3.41 mmoles). The resulting dark brown solution was stirred at room temperature for 20 hours. The mixture was diluted with 100 ml of water, and extracted exhaustively with dichloromethane (5x25 ml). The combined organics were extracted with sodium bicarbonate solution (3x50 ml), and the aqueous extracts were combined and acidified with 10% hydrochloric acid. The new aqueous phase was reextracted with dichloromethane (3x50 ml), and the combined organics were dried over magnesium sulfate and concentrated *in vacuo*. 150 mg (56%) of a clear, colourless gum was isolated which was pure by TLC and NMR.

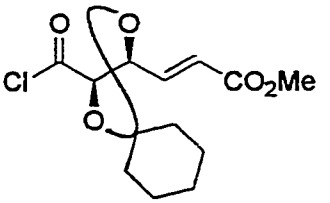
^{1}H NMR: δ(ppm) 1.31-1.48 (m, 2H), 1.50-1.73 (m, 8H), 3.69 (s, 3H), 4.25 (d, J=7.7Hz, 1H), 4.69 (ddd, J=7.7, J=5.0, J=1.5Hz, 1H), 6.14 (dd, J=15.7, J=1.5Hz, 1H), 6.94 (dd, J=15.7, J=5.0Hz, 1H), 9.24 (br, 1H).

^{13}C NMR: δ(ppm) 23.42, 23.48, 24.63, 34.99, 36.06, 51.71, 77.04, 77.67, 113.05, 122.28, 143.49, 166.40, 173.39.

IR: ν(cm^{-1}) 3400-2500, 1735, 1720, 1665.

EI-MS: *m/e*(%) 270 (9.0), 241 (9.3), 227 (40.5), 195 (4.6).

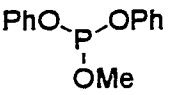
HRMS: calcd for $C_{13}H_{18}O_6$ 270.11034, found 270.11131.



101

To a solution of 150 mg (0.585 mmoles) of carboxylic acid **100** in 5 ml of dry dichloromethane at 0° were added 77 ul (0.878 mmoles) of oxalyl chloride. After the addition, the reaction was allowed to warm to room temperature, and was stirred for 6 hours (reaction progress could be monitored by observing gas evolution). The solvent and excess oxalyl chloride were evaporated under high vacuum to afford a clear yellow oil, which was used immediately in subsequent synthetic manipulations.

IR: $\nu(cm^{-1})$ 1815, 1727, 1669.



200 grams (64.5 mmoles) of triphenyl phosphite and 26 ml (64.5 mmoles) of methanol were combined, and a catalytic amount of sodium methoxide in methanol was added. The mixture was heated to 110° for 4 hours, cooled, and then the most volatile byproducts were removed by distillation under aspirator pressure (up to 130° at 200 mTorr.). Large scale bulb to bulb distillation then afforded 80 grams (50%) of methyl diphenyl phosphite as a clear, colourless oil.

^{1}H NMR (500MHz): δ(ppm) 3.84 (d, J=9.0Hz, 3H), 7.13-7.18 (m, 3H), 7.33-7.37 (m, 2H).

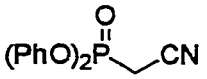
^{13}C NMR (125.77MHz): δ(ppm) 48.98 (br), 120.19 (d, J=7.7Hz, 2C), 123.77, 129.66 (2C), 152.08 (d, J=6.4Hz).

^{31}P NMR (202.46MHz): δ(ppm) 46.55 (q, J=9.0Hz).

IR: ν(cm^{-1}) 3064, 3040, 2949, 2838, 1591, 1488, 1207, 1071, 1025.

EI-MS: *m/e*(%) 248 (33.8), 217 (4.6), 155 (100).

HRMS: calcd for $C_{13}H_{13}O_3P$ 248.06020, found 248.06029.



General Procedure for Phosphonate Synthesis via Arbuzov Reaction (A): 280 ul (480 mg, 3.86 mmoles) of bromoacetonitrile were combined with 1.00 grams of ethyl diphenyl phosphite (3.86 mmoles) and the resulting mixture was heated to 150° for 16 hours with stirring. The mixture was cooled to room temperature and then purified by flash chromatography (2:1 hexanes:diethyl ether) to afford 820 mg (78%) of phosphonate reagent as a white semi-solid..

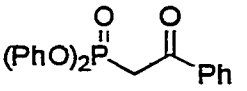
^{1}H NMR: δ(ppm) 3.17 (d, J=21.1Hz, 2H), 7.14-7.28 (m, 6H), 7.29-7.42 (m, 4H).

^{13}C NMR: δ(ppm) 16.27 (d, J=146.9Hz), 111.60, 120.34 (d, J=4.5Hz, 4C), 126.12 (2C), 130.07 (4C), 149.34 (d, J=8.5Hz, 2C).

IR: ν(cm^{-1}) 2258.

EI-MS: *m/e*(%) 273 (41.0), 248 (49.6), 192 (6.8), 170 (40.7), 155 (17.5).

HRMS: calcd for $C_{14}H_{12}NO_3P$ 273.05556, found 273.05275.



Following the **General Procedure for Phosphonate Synthesis via Arbuzov Reaction (A)**, 790 mg (3.86 mmoles) of bromoacetophenone were combined with 1.00 gram of ethyl diphenyl phosphite (3.86 mmoles) to afford 1.01 grams (74%) of phosphonate reagent as a clear, colourless, viscous oil after flash chromatography (4:3 diethyl ether:hexanes).

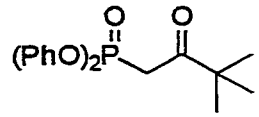
^{1}H NMR: δ(ppm) 3.93 (d, J=22.7Hz, 2H), 7.11-7.23 (m, 6H), 7.24-7.36 (m, 4H), 7.44-7.66 (m, 3H), 8.03 (m, 1H).

^{13}C NMR: δ(ppm) 37.41 (d, J=133.5Hz), 120.29 (d, J=4.5Hz, 4C), 125.16 (2C), 128.44 (2C), 128.72 (2C), 129.50 (4C), 133.64, 149.69 (d, J=8.7Hz, 2C), 190.46 (d, J=6.9Hz).

IR: ν(cm^{-1}) 1683.

FAB-MS: *m/e*(%) 353 [MH^+] (100), 352 [M^+] (3.9), 259 (24.8), 133 (27.2).

HRMS: calcd for $C_{20}H_{17}O_4P$ 352.0865, found 352.1206. calcd for $C_{20}H_{17}O_4PH^+$ 353.0943, found 353.1338.



General Procedure for Phosphonate Synthesis via Arbuzov Reaction (B): 1.90 grams (90%, tech., 10.1 mmoles) of bromopinacolone were combined with 5.00 grams of methyl diphenyl phosphite (20.2 mmoles) and the resulting mixture was heated to 125° for 16 hours with stirring. The mixture was cooled to room temperature and then purified by flash chromatography (3:1 hexanes:diethyl ether) to afford 2.95 grams (88%) of phosphonate reagent as a white solid..

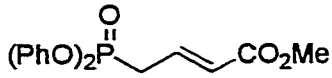
^{1}H NMR: δ(ppm) 1.18 (s, 9H), 3.43 (d, J=21.7Hz, 2H), 7.11-7.24 (m, 6H), 7.27-7.36 (m, 4H).

^{13}C NMR: δ(ppm) 25.79 (3C), 34.74 (d, J=138.7Hz), 45.27 (d, J=4.1Hz), 120.47 (d, J=4.5Hz, 4C), 125.16 (2C), 129.58 (4C), 149.89 (d, J=8.7Hz, 2C), 205.63.

IR: ν(cm^{-1}) 1710.

EI-MS: *m/e*(%) 332 (1.3), 289 (4.1), 275 (9.9), 264 (3.1), 248 (16.1).

HRMS: calcd for $C_{18}H_{21}O_4P$ 332.11783, found 332.11917.



Following the **General Procedure for Phosphonate Synthesis via Arbuzov Reaction (B)**, 2.11 grams (85%, tech., 10.1 mmoles) of methyl 4-bromocrotonate were combined with 5.00 grams of methyl diphenyl phosphite (20.2 mmoles) to afford 2.69 grams (87%)

of phosphonate reagent as a clear, colourless, viscous oil after flash chromatography (3:2 hexanes:diethyl ether).

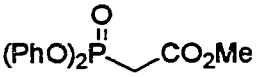
^{1}H NMR: δ(ppm) 2.99 (ddd, J=23.0, J=6.5, J=1.3Hz, 2H), 3.64 (s, 3H), 5.99 (dd, J=15.6, J=5.2Hz, 1H), 6.92 (m, 1H), 7.03-7.17 (m, 6H), 7.18-7.27 (m, 4H).

^{13}C NMR: δ(ppm) 29.94 (d, J=139.5Hz), 51.27, 120.11 (d, J=4.3Hz, 4C), 125.07 (2C), 126.66 (d, J=14.4Hz), 129.49 (4C), 135.90 (d, J=11.5Hz), 149.65 (d, J=8.8Hz, 2C), 165.30.

IR: ν(cm^{-1}) 1724, 1657.

FAB-MS: *m/e*(%) 333 [MH^+] (88.6), 332 [M^+] (4.2), 301 (100), 249 (24.4).

HRMS: calcd for $C_{17}H_{17}O_5P$ 332.0814, found 332.1163. calcd for $C_{17}H_{17}O_5PH^+$ 353.0892, found 353.1233.



Following the **General Procedure for Phosphonate Synthesis via Arbuzov Reaction (B)**, 1.58 grams (10.1 mmoles) of methyl bromoacetate were combined with 5.00 grams of methyl diphenyl phosphite (20.2 mmoles) to afford 2.81 grams (91%) of phosphonate reagent as a clear, colourless, viscous oil after flash chromatography (3:2 hexanes:diethyl ether).

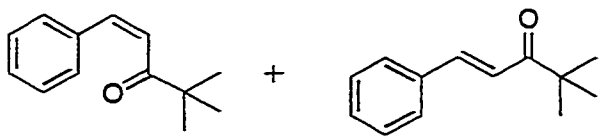
^{1}H NMR: δ(ppm) 3.62 (d, J=21.7Hz, 2H), 3.72 (s, 3H), 7.12-7.28 (m, 6H), 7.29-7.40 (m, 4H).

^{13}C NMR: δ(ppm) 33.60 (d, J=137.6Hz), 52.65, 120.43 (d, J=4.5Hz, 4C), 125.39 (2C), 129.67 (4C), 149.75 (d, J=8.6Hz, 2C), 164.99.

IR: ν(cm^{-1}) 1743.

FAB-MS: *m/e*(%) 306 (2.8), 248 (62.2), 170 (45.3), 155 (21.9).

HRMS: calcd for $C_{15}H_{15}O_5P$ 306.06575, found 306.06649.



Following the **General Procedure for Horner-Wadsworth-Emmons Olefination**, 315 mg (0.94 mmoles) of phosphonate reagent derived from bromopinacolone were used to olefinate 100 mg (0.94 mmoles) of benzaldehyde. After flash chromatography (9:1 hexanes:diethyl ether), 165 mg (93%) of the desired product were isolated as a 55:45 (*Z*:*E*) mixture of geometric isomers (the same ratio was seen in the ^{1}H NMR spectrum of the crude product).

For (*Z*) isomer: **^{1}H NMR**: δ(ppm) 1.20 (s, 9H), 6.42 (d. J=13.0Hz, 1H), 6.74 (d, J=13.0Hz, 1H), 7.25-7.38 (m, 3H), 7.49-7.56 (m, 2H).

For (*E*) isomer: **^{1}H NMR**: δ(ppm) 1.22 (s, 9H), 7.12 (d. J=15.6Hz, 1H), 7.68 (d, J=15.6Hz, 1H), 7.24-7.36 (m, 3H), 7.47 -7.55 (m, 2H).

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Claims to Original Research

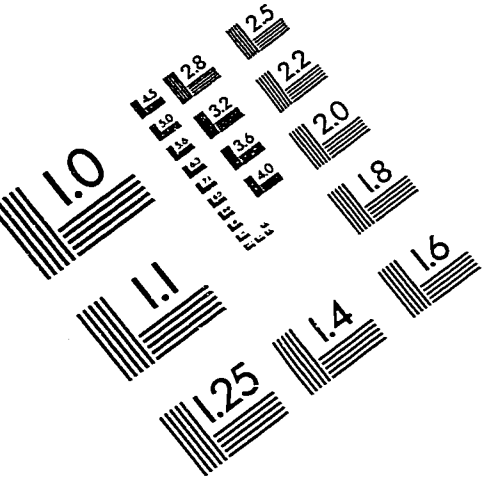
1. Efficient and reliable syntheses of chiral tartrate derivatives **36**, **49** and **51** (alcohols) and the related azide **71** have been devised. Dramatic improvements in reproducibility in the synthesis of **36** as compared to the literature methods have been realized.

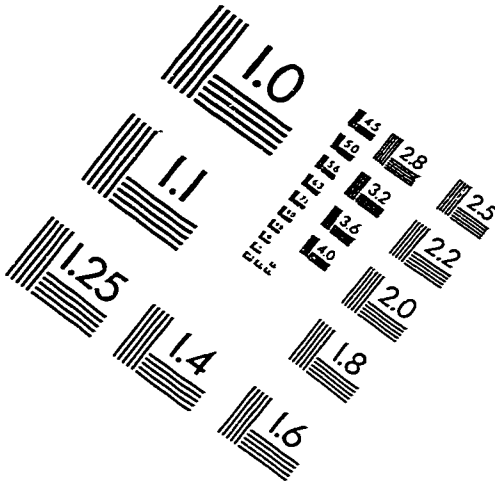
2. Imine **75** was synthesized by aza-Wittig reaction of azide **71** and aldehyde **28**. This was likely to have been an excellent *o*-quinodimethane precursor, if only conditions for purification of the imine and quaternization of the imine nitrogen could have been worked out.

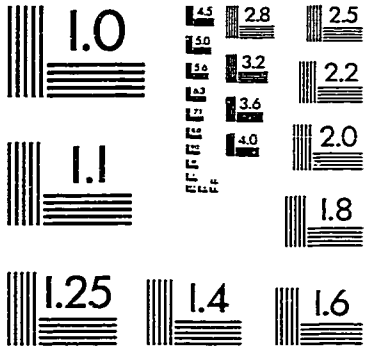
3. Horner-Wadsworth-Emmons reagents **90**, **92** and **94** derived from known chiral auxiliaries were synthesized and attempts were undertaken to olefinate the *cis*-unsaturated aldehyde **87** derived from hydroxy-sulfone **35**. These endeavours were unsuccessful, but this, coupled with work involving the attempted construction of the tartrate-derived dienophile onto the hydroxy-sulfone (synthesis of dienoic ester **97**) did prove that ethers of these *o*-quinodimethane precursors are chemically robust enough to undergo further derivatization.

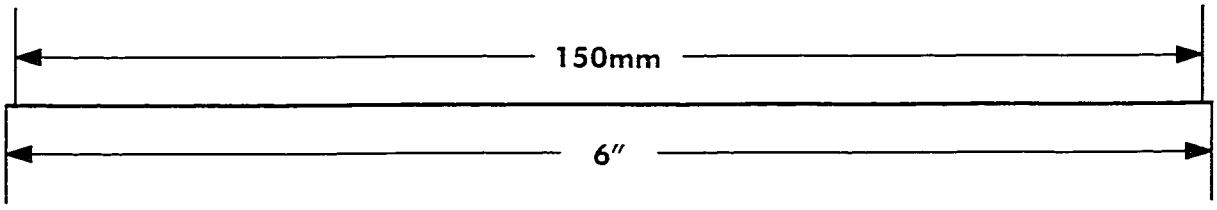
4. A practical and reliable synthesis of diaryl phosphonates as (*Z*)-selective Horner-Wadsworth-Emmons reagents was developed. Five different new reagents were synthesized and fully characterized, and preliminary examination of their stereoselectivity in reactions with benzaldehyde has been commenced.

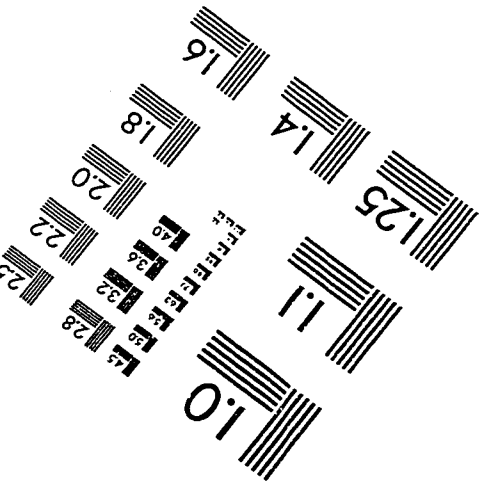
IMAGE EVALUATION
TEST TARGET (QA-3)

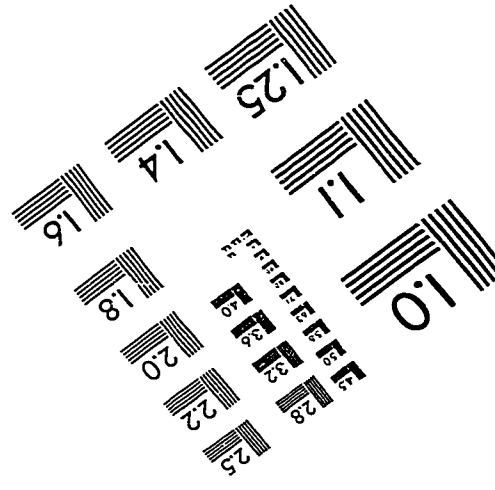












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