THE SYNTHESIS OF AN ELECTRON DEFICIENT DIENE AND PROGRESS TOWARDS THE FIRST TOTAL SYNTHESIS OF JATRORRHIZINE

ALAN SWINAMER

THE SYNTHESIS OF AN ELECTRON DEFICIENT DIENE

and

PROGRESS TOWARDS THE FIRST TOTAL SYNTHESIS OF JATRORRHIZINE

by

ALAN SWINAMER

B. Sc. (1993), Dalhousie University

Halifax, Nova Scotia, CANADA

A thesis submitted to the School of Graduate Studies

in partial fulfillment of the requirements

for the degree of Master of Science

Department of Chemistry

Memorial University of Newfoundland

St. John's, Newfoundland, Canada

DECEMBER 1997

Abstract

The methodology for the synthesis of a new electron deficient 1,3-diene **44** was developed utilizing readily available starting materials. Generation of the diene was accomplished by introducing α,β-unsaturation to an ester group *via* a sulfoxide elimination reaction. The diene itself polymerized readily, thus it was not isolated but was generated *in situ* in the presence of dienophiles with which the diene could react. The Diels-Alder properties of the diene have not as yet been studied but preliminary work on appropriate conditions for its generation was accomplished. This work suggested that the generation of the diene can be accomplished under sufficiently mild conditions that Diels-Alder reactions of the diene may occur before polymerization. Related work on similar electron deficient 1,3-dienes which are not generated *in situ* indicated that Diels-Alder reactions were occurring between these types of dienes and a variety of dienophiles, including electron rich, electron neutral and electron deficient dienes.

A new approach to the first total synthesis of the protoberberine alkaloid, jatrorrhizine **154**, was investigated using readily available starting materials. This convergent synthesis featured a Suzuki-type biaryl cross-coupling reaction between a triflate **308** and a boronic acid **342** which proceeded in good yield. The present synthesis is the first known case of the synthesis of a protoberberine alkaloid using the biaryl cross-coupling methodology. The synthesis was accomplished on a small scale only as the isoquinolinol **318** was available in limited quantities. This synthesic route can be readily applied to the synthesis of other members of the protoberberine family of alkaloids, many of which have shown potential medicinal uses.

Acknowledgments

I am deeply grateful to my supervisor, Dr. Graham Bodwell, for his enthusiastic supervision, attitude and encouragement. Generous financial support is also sincerely appreciated.

I would like to thank Dr. C. Jablonski, Ms. Nathalie Brunet, Mr. David Miller and Mr. Ed Vessey for excellent NMR services and Ms. Marion Baggs and Dr. B. Gregory for exceptional Mass Spectral Analyses. The support of the Chemistry Department and the School of Graduate Studies is also appreciated. Special thanks go to Dr. J. Burnell and Dr. P. Golding for valued discussions. Thanks to the General Office and Stores Staff for providing their respective invaluable services.

Many thanks and best wishes to my fellow graduate students for helpful discussions, both professional and social. Special recognition is extended to Heather Davis, Chris Sheppard, Steve Copp, Colin Cameron, Zulan Pi, Murray Park, Yvette Favaro, Sue Budge, Jim Farrell, Shuguang Zhu, Sheldon Crane, Ron Buckle and Lori Burry for being a happening bunch of Chem Geeks. Thanks to the undergraduate society, especially Jane, Neale, Mark, Jeff and Ian, for keeping the Horse running.

All the best to Krista Blundell, Gerry MacDonald, Don Hodder, Kathleen Murphy, Michelle Young and Lisa Gillis for helping to distract me from the lab.

My most heartfelt appreciation goes to Leigh Bishop for being there through everything. Take good care of Sam!

CALVIN ON RESEARCH...

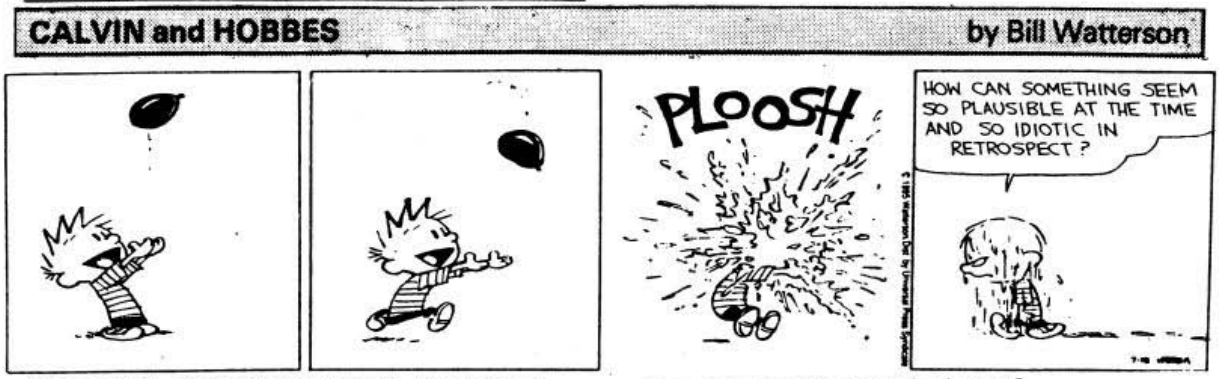


Table of Contents

List of Figures

List of Schemes

List of abbreviations

Ac	acetyl
acac	acetylacetonate
APT	attached proton test
Bn	benzyl (CH_2Ph)
t-Boc	*tert*-butoxycarbonyl
b.p.	boiling point
Bu	*n*-butyl
BuLi	*n*-butyllithium
COSY	^1H-^1H correlation spectroscopy
d	doublet
D-A	Diels-Alder
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMG	directed metalation group
DNA	deoxyribonucleic acid
DoM	directed *ortho* metalation
ee	enantiomeric excess
eq.	equivalents
ERG	electron releasing group
Et	ethyl
EtOAc	ethyl acetate

eV	electron Volt
EWG	electron withdrawing group
FMO	Frontier Molecular Orbital
HETCOR	^{13}C-^{1}H heteronuclear correlation
HOMO	highest occupied molecular orbital
h	hour
HRMS	high resolution mass spectrometry
hυ	light
Hz	Hertz
IED	inverse electron demand
IR	infrared
LDA	lithium diisopropylamide
lit.	literature
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
m	multiplet
m	meta
Me	methyl
mes	methanesulfonyl (mesyl)
MHz	Megahertz
mm	millimetres
MMTS	methyl methylthiomethylsulfoxide
m.p.	melting point
MS	mass spectrometry
m/z	mass/charge ratio

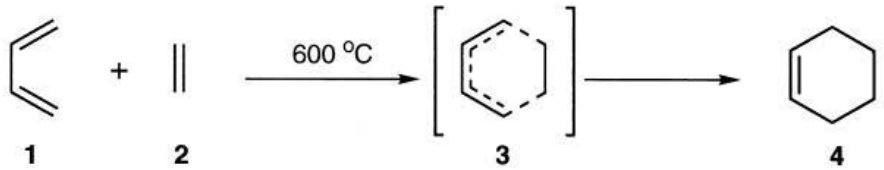
NBS	*N*-bromosuccimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
o	ortho
OTf	trifluoromethanesulfonoxy (triflate)
p	para
Ph	phenyl
PPA	polyphosphoric acid
ppm	parts per million
i-Pr	isopropyl
R	alkyl
RNA	ribonucleic acid
r.t.	room temperature
s	singlet
TBDMS	*tert*-butyldimethylsilyl
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulfonyl (tosyl)
p-TsOH	*para*-toluenesulfonic acid
UV	ultraviolet

To my parents

Chapter 1

Introduction to Diels-Alder Chemistry

The Diels-Alder reaction[1] is widely used in organic synthesis for the formation of 6-membered rings.[2] The reaction is a [$_{\pi}4_s + _{\pi}2_s$] cycloaddition which occurs between a conjugated diene **1** and another multiple bond **2**, called a dienophile, to give a cyclohexene **4** as the Diels-Alder adduct (Scheme 1.1).[3] The example shown proceeds



Scheme 1.1 Diels-Alder reaction of butadiene with ethylene[3]

only under very vigorous conditions[3b] and, as described below, functionalized dienes and dienophiles are normally used. Both the diene and the dienophile can be carbon-based to provide a carbocyclic adduct or may contain a heteroatom to provide a heterocyclic adduct. Normally, the reaction proceeds by a concerted mechanism[4] (Scheme 1.1) and the regiochemical and stereochemical outcome can often be predicted and controlled.[5] Frontier Molecular Orbital (FMO) theory has been successfully used to explain the reactivity and the selectivity of a cycloaddition between a diene-dienophile pair.[6] Another theory based on complementary reactivity surfaces of the diene and the dienophile has been put forward[7] to explain experimental results inconsistent with FMO predictions, although this theory has been disputed.[8] FMO theory continues to be the more effective and widely used method of explaining Diels-Alder reactions.

There are three types of Diels-Alder reactions (Figure 1.1)[2d] and the classifications are based on the electronic nature of the diene and dienophile and the resulting interactions of the molecular orbitals involved.[9] The three types of reaction are the normal electron demand, the inverse electron demand and the neutral electron demand

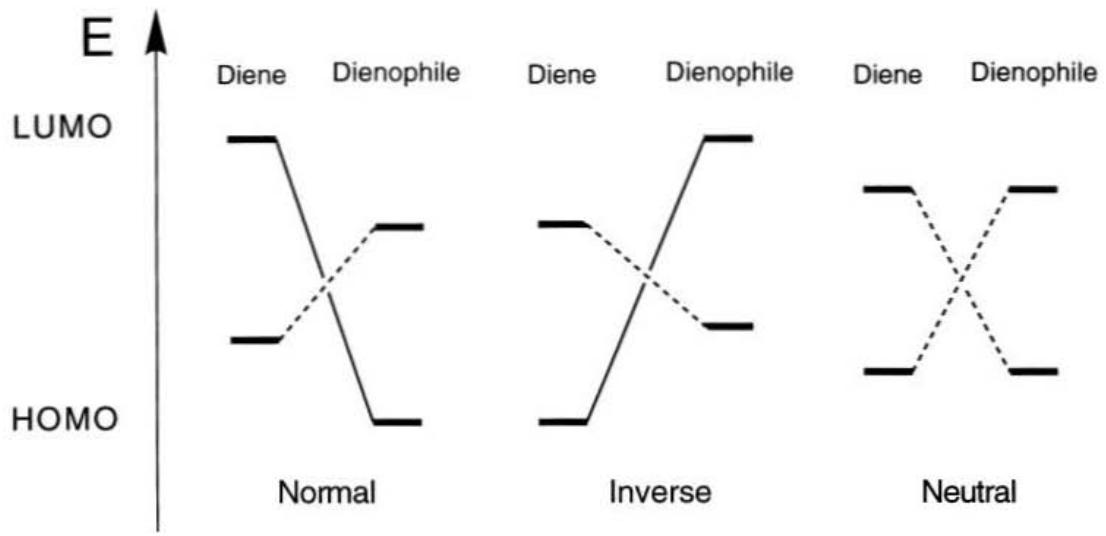


Figure 1.1 HOMO-LUMO orbital arrangements for the Diels-Alder reaction.[2d]

Diels-Alder reactions. According to FMO theory, a normal electron demand reaction occurs between the Highest Occupied Molecular Orbital (HOMO) of the diene and the Lowest Unoccupied Molecular Orbital (LUMO) of the dienophile. By contrast, the inverse electron demand reaction is the result of interaction between the diene LUMO and the dienophile HOMO. In a neutral electron demand reaction, neither interaction dominates.

The degree of reactivity between any diene-dienophile pair depends on the HOMO-LUMO energy difference. Any factor that decreases this energy difference will cause a Diels-Alder reaction proceed more rapidly. The extent of this energy difference is based largely on the type of substituent(s) present on the two reacting partners. Electron-withdrawing groups lower both the HOMO and the LUMO energy of both the diene and the dienophile while electron-donating groups raise both the HOMO and the LUMO energy (Figure 1.2).[2d]

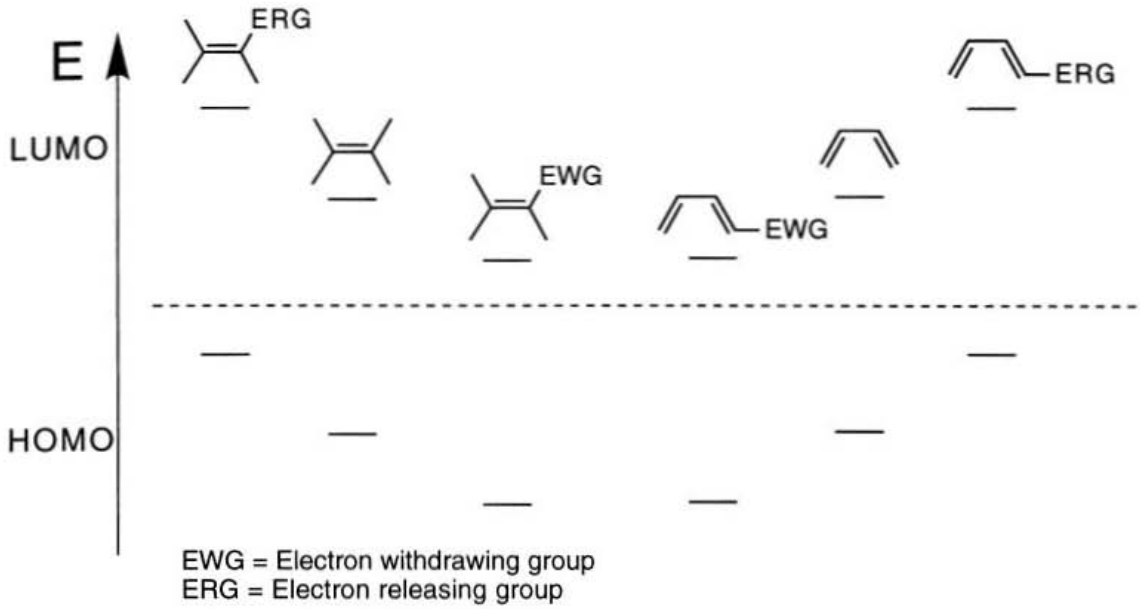
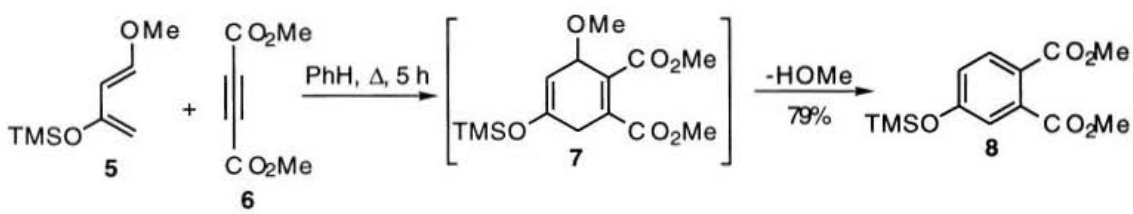


Figure 1.2 Representation of substituent effects on orbital energies.[2d]

The most common Diels-Alder reaction is the normal electron demand reaction in which an electron-rich diene reacts with an electron-deficient dienophile. In Figure 1.2, it can be seen that this involves a low energy dienophile LUMO and a high energy diene HOMO giving a small LUMO-HOMO energy difference. A typical example of a normal electron demand Diels-Alder reaction is shown in Scheme 1.1, with "Danishefsky's diene" **5**, (*E*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene),[10-13] a commonly used electron-rich diene (Scheme 1.2). Danishefsky's diene was first reported in 1974[10a] and has found



Scheme 1.2 Typical reaction of Danishefsky's diene

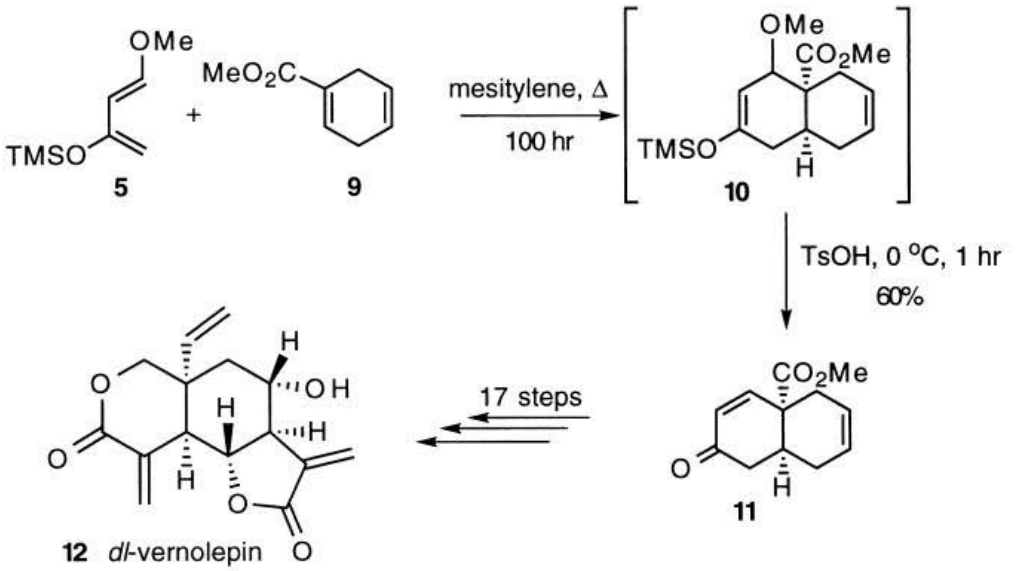
widespread utility in organic synthesis.[10] It is easily prepared in large quantities[11] and has become commercially available.[12] It exhibits good reactivity with a variety of typical electron-deficient dienophiles. The regiochemistry of the adducts is predictable and this has been well rationalized by FMO theory. The two electron donating groups in Danishefsky's diene increase the orbital coefficient at C-4 and decrease that at C-1 relative to butadiene **1** (Scheme 1.3). The molecular orbitals for a monosubstituted electron-deficient dienophile are also unequal due to the substitution. Thus, the

a. More favourable interaction b. Less favourable interaction

Scheme 1.3 Frontier orbital coefficients of Danishefsky's diene and an electron-deficient dienophile

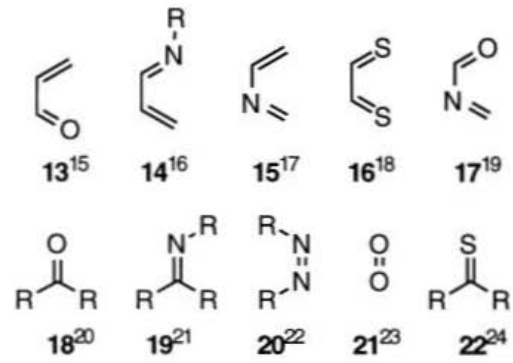
diene-dienophile pair approach each other as in Scheme 1.3.a., there would be more effective orbital overlap than if the dienophile approaches as in Scheme 1.3.b. The energetic difference between these two modes of approach results in good to complete regiochemical control. The stereochemistry of the products has been explained to result from secondary orbital interactions between the diene-dienophile pair. One of the biggest advantages of Danishefsky's diene is that the functionality in the products can be easily transformed into a variety of other functional groups and this has been used advantageously in a number of natural product syntheses.[13] For example, its first use was in the total synthesis of *dl*-vernolepin **12**,[13b] a known tumor inhibitor (Scheme 1.4). The diene **5** was reacted with **9** to afford the bicyclic adduct **10,** which was not isolated. Instead the crude product was treated with *p*-toluenesulfonic acid, which hydrolysed the

trimethylsilyl ether and eliminated the methoxy group to give **11** in fair yield (60%). This compound was then converted to *dl*-vernolepin in 17 steps.

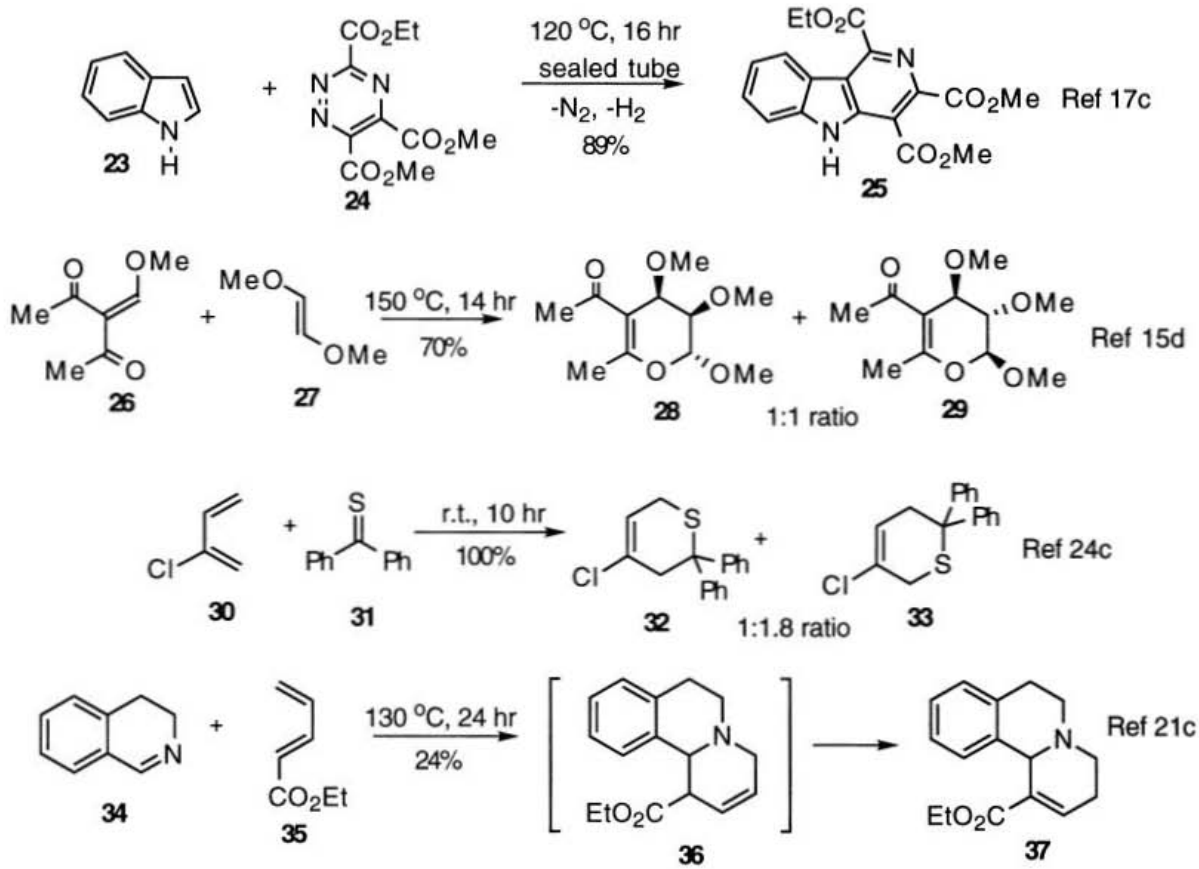


Scheme 1.4 Synthesis of *dl*-vernolepin.[13b]

While normal electron demand Diels-Alder reactions have been well studied and have demonstrated great synthetic utility, inverse electron demand reactions are less common. A typical inverse electron demand reaction involves an electron-deficient diene which reacts with an electron-rich dienophile. It can be seen in Figure 1.2 that there is a small dienophile-HOMO diene-LUMO energy difference in this situation. The majority of the known reactions of this type are, in fact, hetero-Diels-Alder reactions[14-24] and the heteroatomic addend can be the diene (**13-17**) or the dienophile (**18-22**). Some examples are shown in Scheme 1.5. Some reactions of this type of system are outlined in Scheme 1.6.



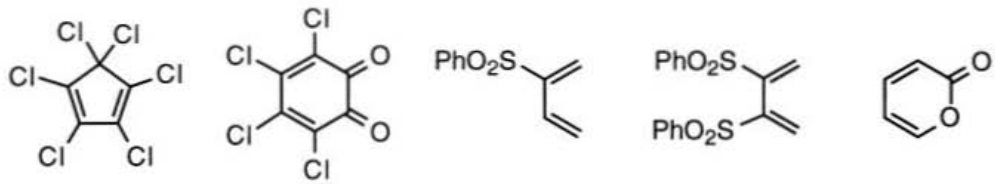
Scheme 1.5 Common acyclic heteroatomic dienes and dienophiles



Scheme 1.6 Examples of heteroatomic Diels-Alder reactions

The focus of this work is to develop electron-deficient dienes which can be used in the synthesis of carbocyclic adducts. Many of the known purely carbon containing

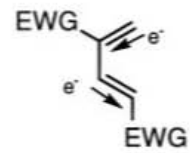
dienes that have been used in inverse electron demand Diels-Alder reactions result in products which, as yet, have not found broad synthetic utility. Some known examples of electron-deficient dienes are shown in Scheme 1.6, and of these, 2-pyrone **42** and its substituted derivatives appear to be synthetically the most useful.[29g]



38[25] **39**[26] **40**[27] **41**[28] **42**[29]

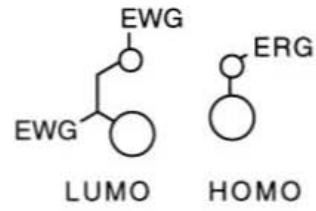
Scheme 1.7 Examples of carbon containing electron-deficient 1,3-dienes

The first class of dienes that was chosen to be studied was those bearing electron withdrawing groups in the 1 and 3 positions, *i.e.*, **43**. These dienes might be expected to be quite reactive in the inverse electron demand Diels-Alder reaction by virtue of the



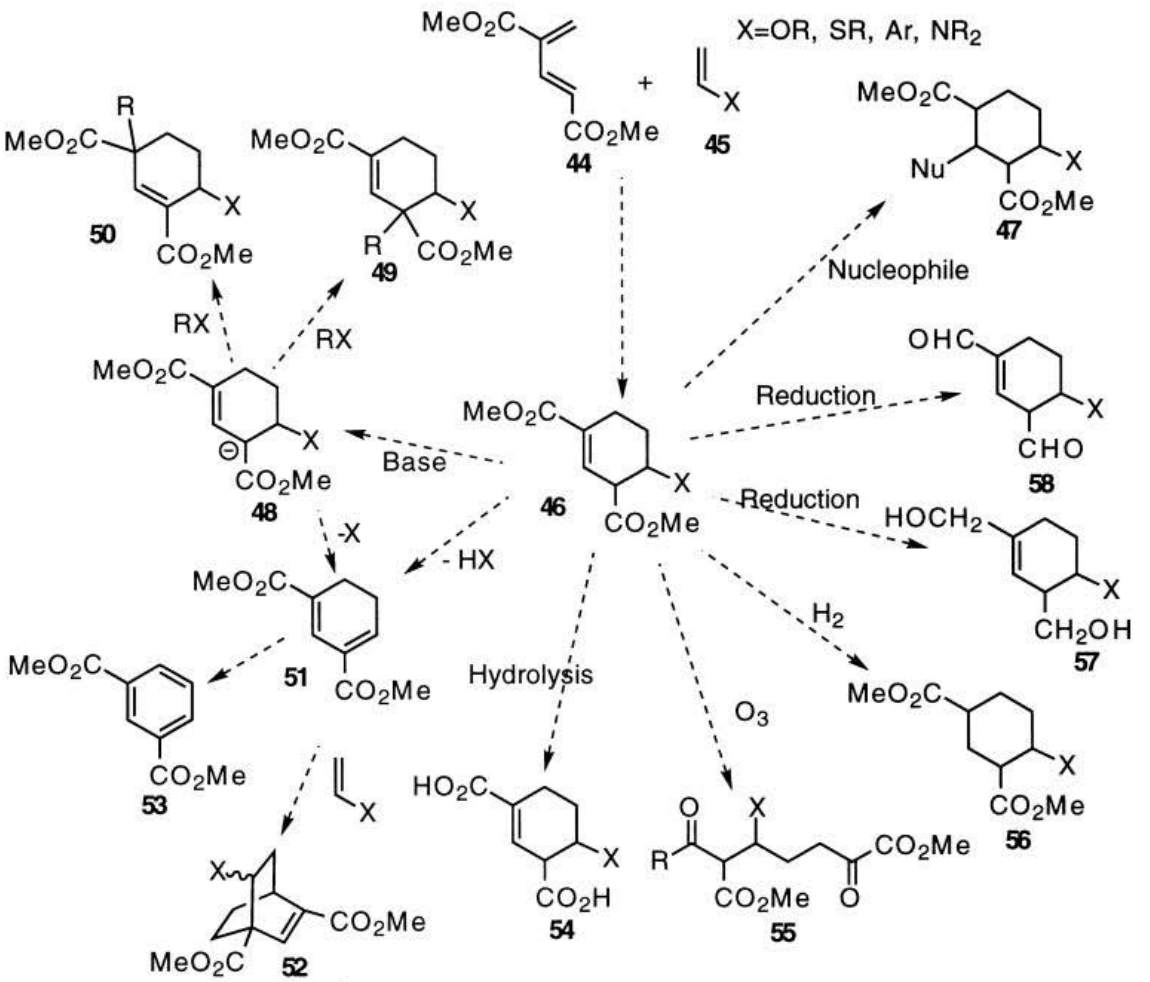
43

position of the substituents. As in the case of Danishefsky's diene, the two electron withdrawing groups might be expected to work in tandem to electronically bias the two ends of the diene. This would be in an opposite sense to Danishefsky's diene (Scheme 1.8) by withdrawing electron density rather than donating it into the diene. A monosubstituted, electron-rich dienophile might be expected to approach this formal electronic complement to Danishefsky's diene in a selective orientation and should result in predictable regiochemical outcomes in its Diels-Alder reactions. The expected



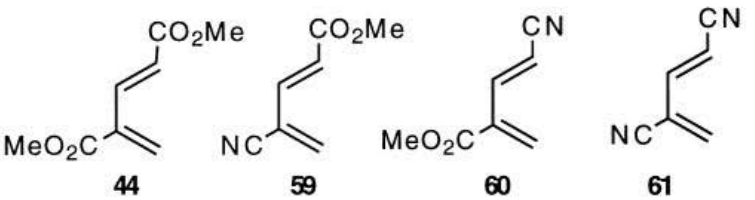
Scheme 1.8 Frontier orbital coefficients of an electron-deficient diene and an electron-rich dienophile

products would incorporate functionality different in nature from an adduct of Danishefsky's diene. These different functional groups could then be synthetically transformed in a number of ways. Possible synthetic transformations of the anticipated Diels-Alder adducts of diene **44** and a monosubstituted electron-rich dienophile **45** are shown in Scheme 1.8. For example, the unsaturated ester in **46** could be attacked by a nucleophile in a Michael addition to give a 1,2,3,4-tetrasubstituted cyclohexane derivative **47**. Alternatively, the saturated ester could be deprotonated, and then it could act as a nucleophile **48** to give **49** and/or **50**. The stabilized anion **48** could also undergo elimination to afford diene **51**. Diene **51** might also be accessible by acid catalyzed elimination of HX from **46**. This diene may be an interesting objective because, like **44**, it is a diene with electron withdrawing groups at the 1 and 3 positions thus regenerating an electron-deficient diene moiety. Since diene **51** is cyclic, it must be in the reactive *s-cis* form and may be able to undergo further inverse electron demand Diels-Alder reactions, providing bicyclic adducts such as **52**. Alternatively, aromatization of the new diene would yield an isophthalate ester **53**. Hydrolysis, reduction and oxidative cleavage reactions of adduct **46** to give products **54-58** are also possible.



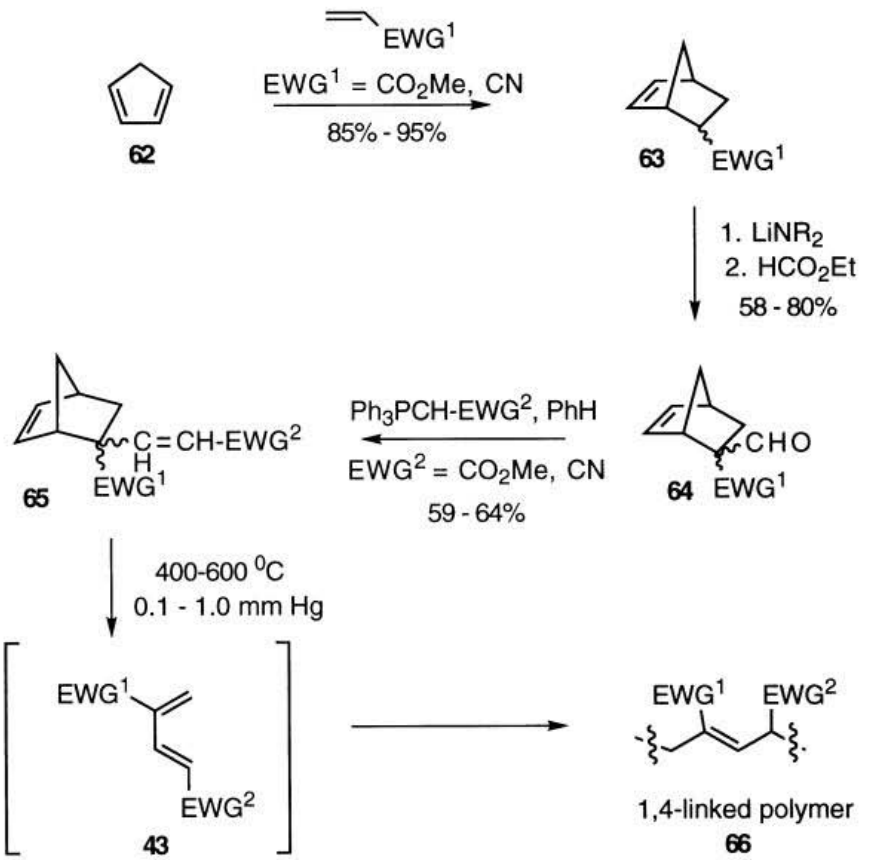
Scheme 1.9 Potential synthetic transformations of Diels-Alder adducts of **44**

The first report of 1,3-electron-deficient-1,3-butadienes was in 1981 by Ahn and Hall,[30a] polymer chemists, who reported the synthesis of compounds **44, 59-61** (Scheme 1.10) by the general method outlined in Scheme 1.11. The synthesis involves a Diels-



Scheme 1.10 Electron-deficient 1,3-butadienes

Alder reaction between cyclopentadiene and methyl acrylate or acrylonitrile,[30b] formylation of the adduct **63** by a lithium amide base and ethyl formate, followed by a Wittig reaction at the aldehyde. The products **65** were subjected to flash vacuum thermolysis, which brought about a retro-Diels-Alder reaction to give the starting

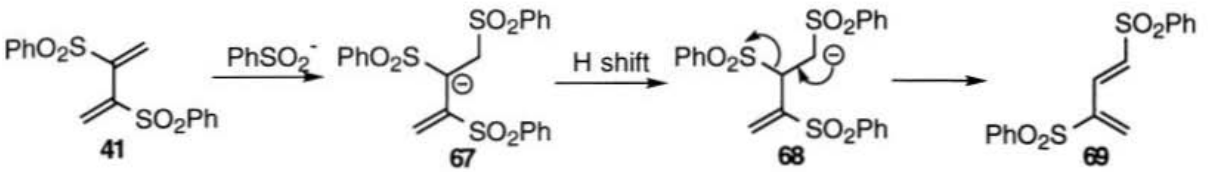


Scheme 1.11 First synthesis of compounds **44, 59-61**.[30]

cyclopentadiene and the desired electron-deficient butadienes. Compounds **59** and **61** were isolated in their pure form but were stable only as solutions in. Compounds **44** and **60** polymerized on thermolysis and could not be isolated in their pure form. The investigators reasoned that these compounds may be liquids under the reaction conditions and would therefore oligermize and polymerize easily in the liquid state. Since the focus

of this research was on the properties of the resulting polymers, the potential Diels-Alder properties of **44**, **59-61** were not investigated and no report on these systems has since appeared. It was concluded on the basis of NMR experiments that the polymerizations occurred in a 1,4 fashion. The diagnostic resonance in the ^1H NMR ($CDCl_3$) of the polymers was a doublet observed between δ 6.6-6.2 and was due to the proton attached to the double bond of the polymer. This type of polymerization indicates that the dienes may be reactive in a Diels-Alder fashion in that the 1 and 4 positions are the reactive sites in the molecules. An important implication of Hall's findings is that the dienes of interest are not particularly stable and cannot be readily isolated in their pure form. Therefore, approaches to the synthesis of these compounds should be designed to involve their generation in the presence of appropriate dienophiles for the Diels-Alder reaction to take place.

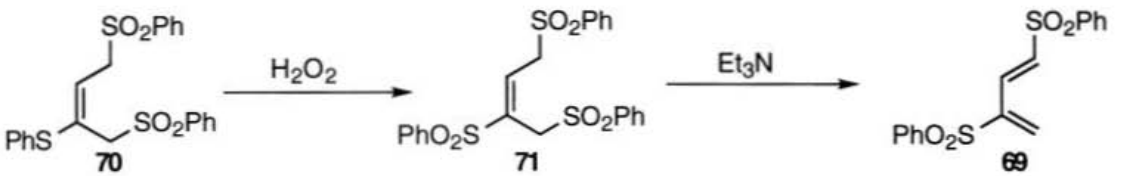
The problem of instability/high reactivity was encountered in the synthesis of another electron-deficient 1,3-diene in work published by Padwa in the late eighties and early nineties.[28a-c] Padwa's interest in this area was the use of 2,3-bis(phenylsulfonyl)-1,3-butadiene **41** (Scheme 1.7) in the Diels-Alder reaction. His calculations indicated that the *s-trans* conformer of this diene is energetically preferred.[28a] Consequently, it does not undergo Diels-Alder reactions readily. Conditions required to convert this to the higher energy *s-cis* conformer resulted in cycloaddition reaction products that had the two sulfone functional groups positioned 1,3 to one another. The authors rationalized this by invoking an isomerization of **41** to the more stable 1,3-bis(phenylsulfonyl)-1,3-butadiene **69** *via* the following mechanism (Scheme 1.12).[28b] This rearrangement requires the



Scheme 1.12 Isomerization of diene **41** to **69**

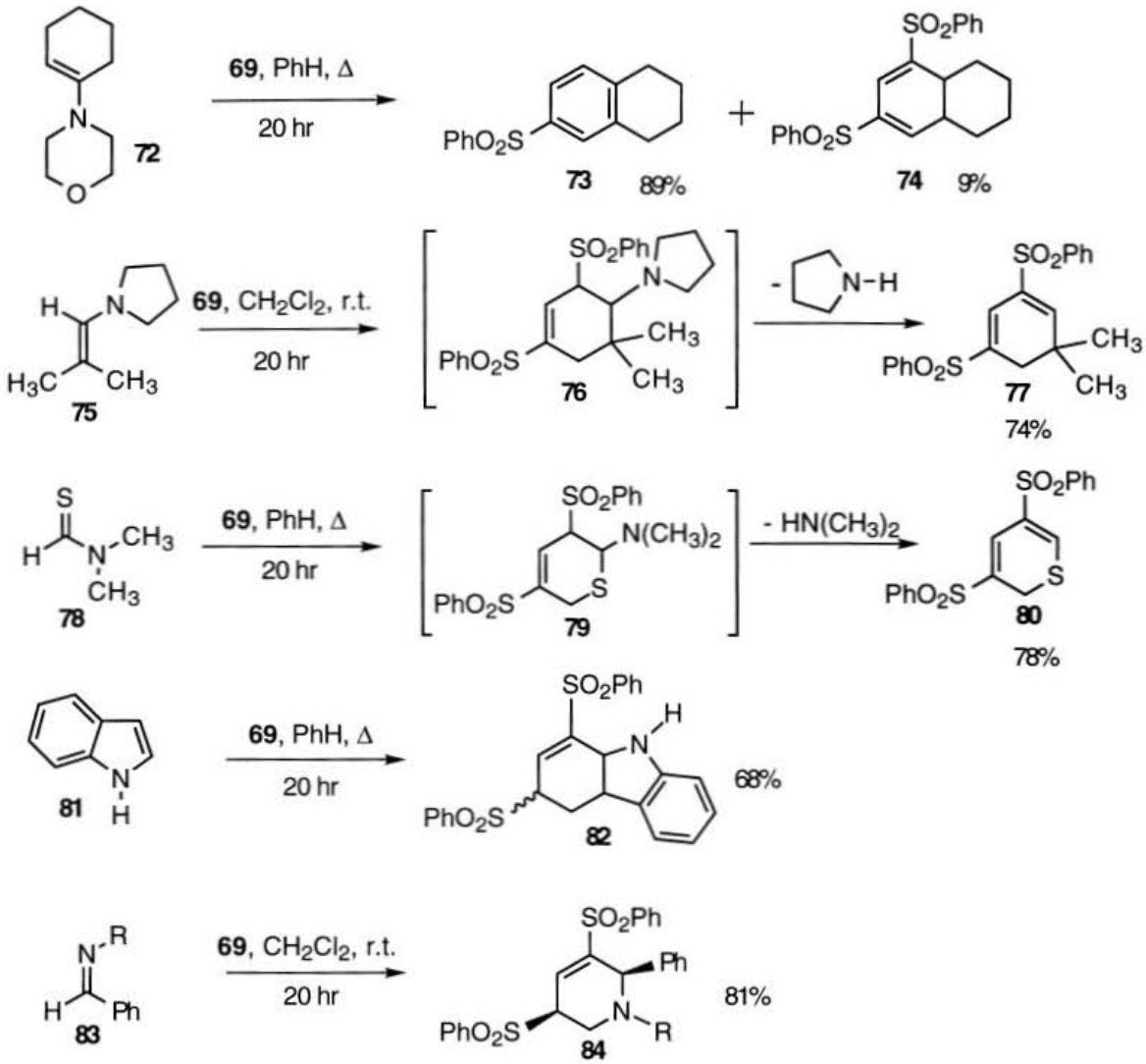
presence of the benzene sulfinate anion which was postulated to be present under the reaction conditions.

Molecular modeling[28a] of the 1,3-bis(sulfone) indicated that the *s-cis* form is lower in energy than the *s-trans* form and that the LUMO is considerably lower in energy (-1.39 eV) than that of the 2,3-isomer (-0.29 eV). The *s-cis* form is required for any Diels-Alder reaction to occur so its greater stability over the *s-trans* form and the lower LUMO energy make the 1,3-bis(sulfone) **69** a very reactive diene. This is indeed the case, but it is so reactive that it was found to dimerize readily in its pure form. It was therefore necessary to generate it in the presence of a series of dienophiles by the peroxide oxidation of **70** followed by elimination of benzene sulfinate (Scheme 1.13).



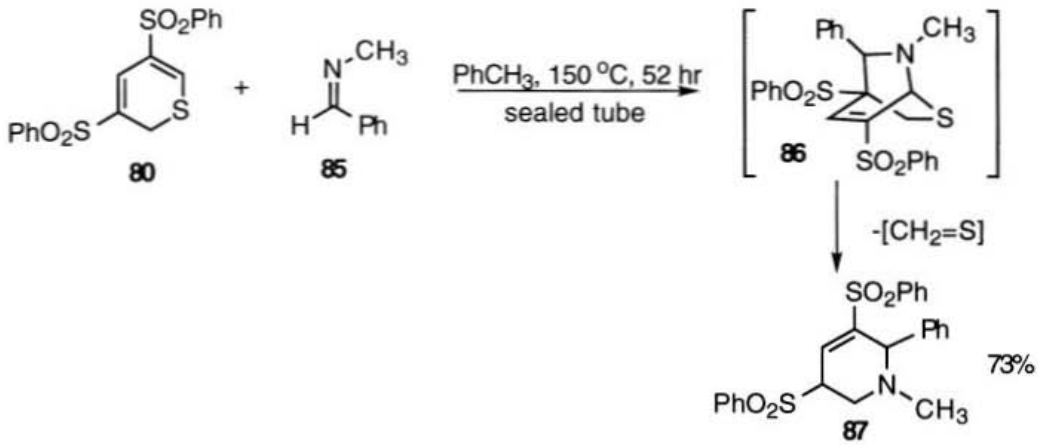
Scheme 1.13 *In situ* generation of diene **69**

The diene **69** was found to be reactive towards a variety of electron-rich dienophiles to give cycloaddition products in good yields (Scheme 1.14).[28b,c] However, the direct cycloaddition products were not isolated due to subsequent isomerization and/or elimination reactions. Nevertheless, Diels-Alder reactions with a variety of electron-rich dienophiles were strongly indicated.



Scheme 1.14 Diels-Alder reactions of diene **69**

An interesting result was obtained with compound **80** when it was subjected to a second Diels-Alder reaction as outlined in Scheme 1.15.[28b] It acted for a second time as an electron-deficient diene demonstrating the potentially iterative nature of these systems.



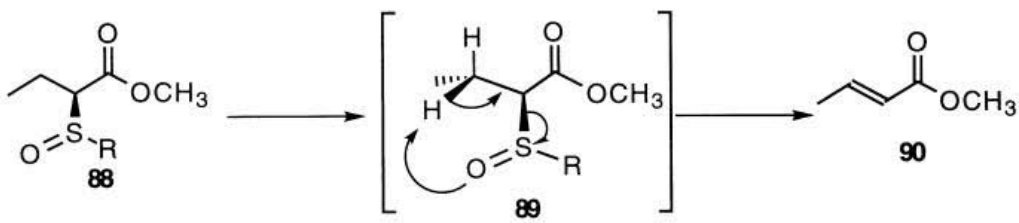
Scheme 1.15 Further Diels-Alder reaction of compound **80**.[28b]

Padwa has not pursued this work further in the recent literature, but the results appear to be promising and may prove to be applicable to the 1,3-electron-deficient-1,3-butadiene systems currently under investigation and, eventually, a broad range of related electron-deficient dienes.

Chapter 2

Synthesis of the Electron-Deficient Diene

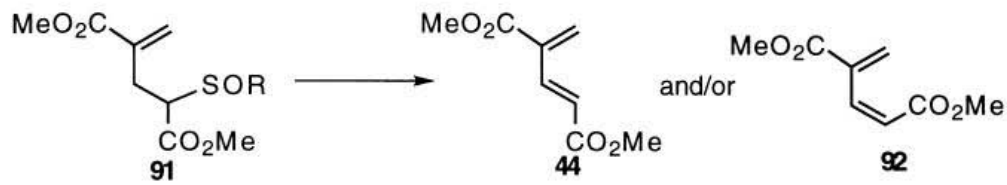
Diene **44** was selected for initial study. The first obstacle to the synthesis of **44** was the report[30a] that it could not be isolated in its pure form. Therefore, methods of generating **44** *in situ* were considered. The ideal masked diene should be easily prepared, and the diene should be generated under fairly mild conditions to avoid decomposition of either the starting materials or of any products. Since the diene contains two ester groups, introduction of α,β-unsaturation to a carbonyl group was considered. Traditionally, this type of oxidation has been achieved by a bromination-dehydrobromination approach[31] or the use of dehydrogenation reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[32] selenium dioxide,[32b,33] palladium (II),[34] pyridine-*N*-oxide-acetic anhydride,[35] periodic acid,[36] palladium on carbon[37] and sulfur.[38] These approaches often require the use of rather harsh conditions, the yields are often poor and reproducibility is frequently difficult. The use of sulfoxide eliminations has proven to be an effective, mild method for the synthesis of α,β-unsaturated carbonyl compounds when the sulfoxide group is present α to the carbonyl.[39-42] Thermolysis of the sulfoxide gives a stereospecific *syn* elimination of a sulfenic acid as in Scheme 2.1.[39]



Scheme 2.1 Mechanism of sulfoxide elimination

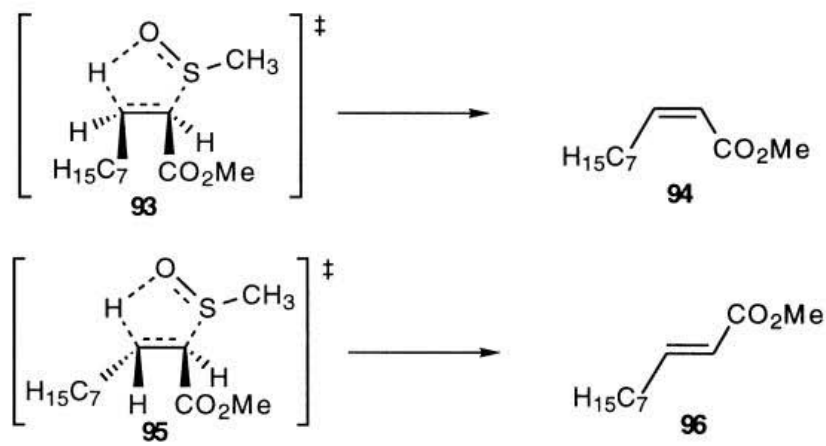
An analogous procedure using a selenoxide instead of a sulfoxide has also shown synthetic utility.[43] However, the toxicity and expense of selenium compounds made this route a less attractive option than the sulfoxide.

The sulfoxide **91** that was chosen for this study is an open chain compound and there is a possibility that the elimination can result in an *E* or *Z* alkene as the product to give **44** and/or **92** (Scheme 2.2). It has been demonstrated, however, that for compounds



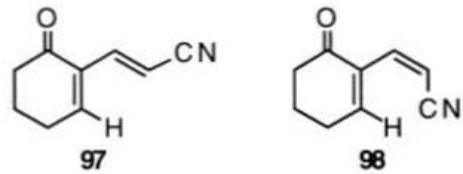
Scheme 2.2 Potential products of sulfoxide elimination from **91**

with only one substituent β to the sulfoxide, as in compound **91**, the *E* isomer is formed exclusively.[39] For example, thermolysis of ethyl 2-(methylsulfinyl)decanoate **93** resulted in exclusive formation of the *E* alkene.[39a] Comparison of the possible transition states that lead to the *E* and *Z* isomers explains this selectivity (Scheme 2.3). The steric interactions in the transition state **93**, which leads to the *Z* isomer **94**, are greater than for the *E* transition state **95**, and the desired *E* isomer **96** is preferentially obtained. This is



Scheme 2.3 Transition states of sulfoxide elimination from ethyl 2-(methylsulfinyl)decanoate

advantageous for this study because the *Z* isomer **92** will likely be less reactive in a Diels-Alder manner due to unfavourable intramolecular steric interactions. This has been demonstrated by results obtained in a related project in this laboratory.[44] Compounds **97** and **98** are obtained by a Horner-Wadsworth-Emmons reaction and it was found that **97** is

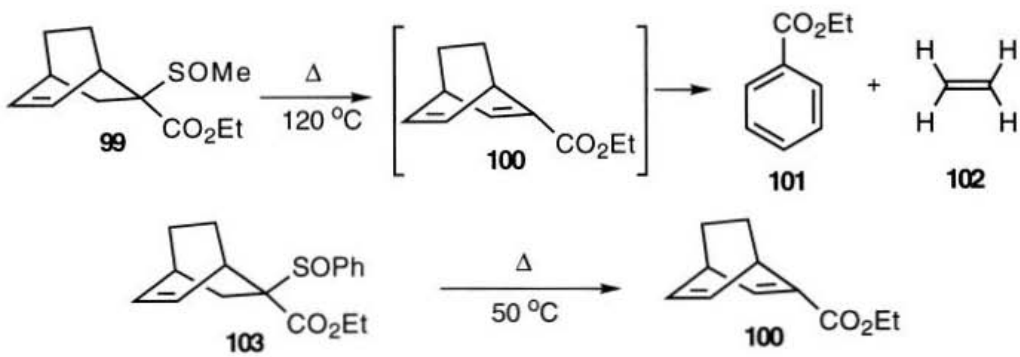


97 **98**

Scheme 2.4 Electron deficient dienes related to **44**

more reactive than **98** in Diels-Alder cycloadditions. The decreased reactivity of the *Z* isomer may be due to an intramolecular steric interaction in the planar *s-cis* conformer of **98** between the nitrile and the hydrogen of the ring double bond. This interaction may be twisting the molecule out of the planar *s-cis* conformation required for a Diels-Alder reaction to occur.

Previous studies have shown that when the substituent on the sulfoxide is a phenyl group, the temperature of elimination is significantly lower than for the corresponding alkyl sulfoxide.[39-40] For example, thermolysis of ethyl 2-(methylsulfinyl)bicyclo-[2.2.2]oct-5-ene-2-carboxylate **99** at 120 °C resulted in elimination of the sulfoxide and a



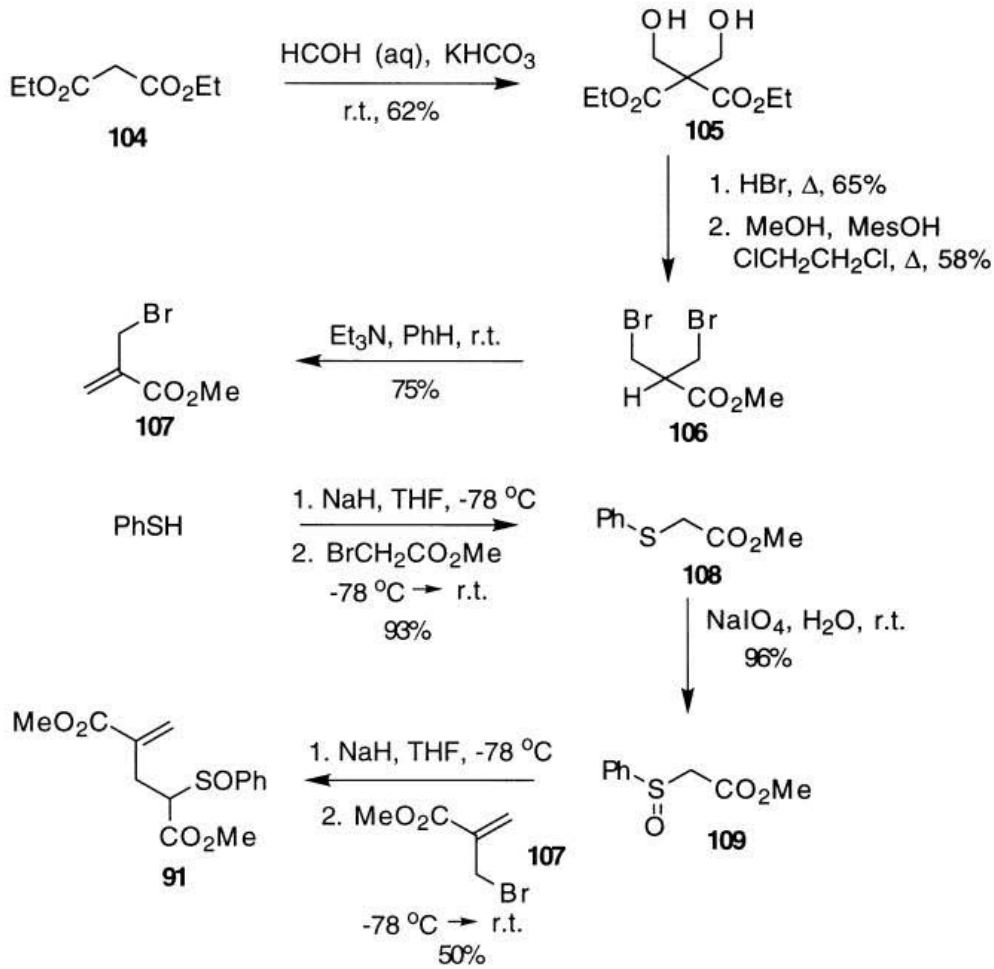
99 **100** **101** **102**

103 **100**

Scheme 2.5 Effect of sulfoxide substituent on elimination reaction

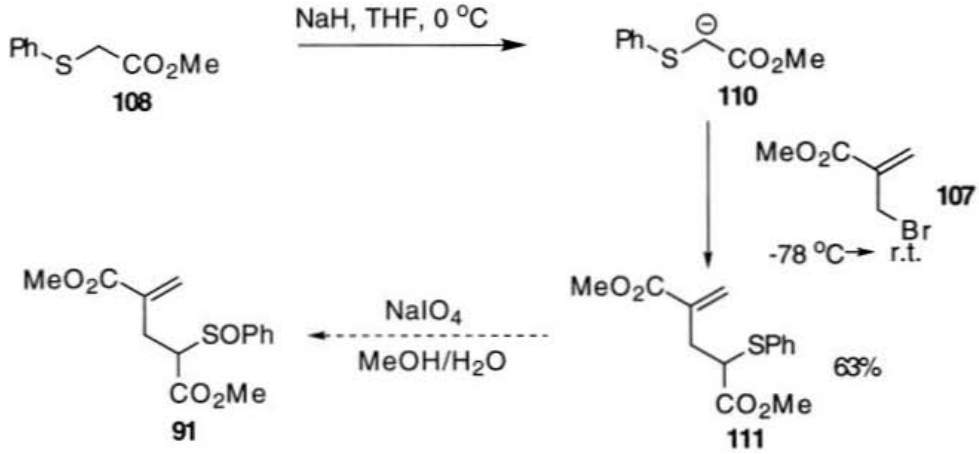
retro-Diels-Alder reaction to give ethene and ethyl benzoate (Scheme 2.5).[39a] However, the use of the phenylsulfinyl group in **103** lowered the elimination temperature to 50 °C to give the desired ethyl bicyclo[2.2.2]octa-2,5-diene-2-carboxylate **100**. This effect has been explained by a number of related factors[40] including greater stability of a phenylsulfinyl anion than an alkylsulfinyl anion, the increased basicity of the sulfoxide oxygen in the phenyl sulfoxide and that the carbon-sulfur bond which must be broken in the phenyl sulfoxide is weaker than in the corresponding alkyl sulfoxide. Thus, the phenylsulfinyl group was chosen to be incorporated into the diene precursor **91**.

The convergent synthesis of the diene precursor is outlined in Scheme 2.6. Treatment of diethyl malonate with potassium bicarbonate and two equivalents of aqueous formaldehyde afforded diethyl bis(hydroxymethyl)malonate **105** in 62% yield.[45] Refluxing this compound in concentrated hydrobromic acid resulted in bromination of both alcohols, two-fold ester hydrolysis and a single decarboxylation to give 3-bromo-2-(bromomethyl)propanoic acid in fair yield (65%).[46] Subsequent reesterification was accomplished upon treatment with methanol and methanesulfonic acid to give **106** in 58% yield.[46] Dehydrobromination of the resultant ester with triethylamine provided the required methyl 2-(bromomethyl)propenoate **107** in 75% yield.[46] The observed yields for these reactions were found to be equal to or slightly better (within 5%) than the reported literature yields.



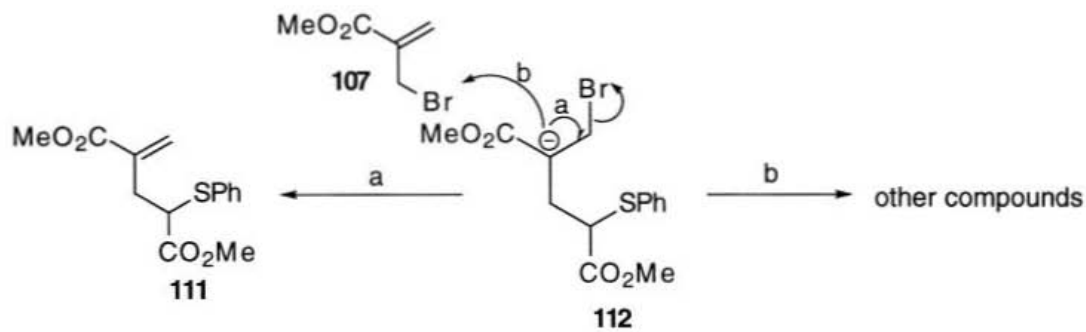
Scheme 2.6 Synthesis of diene precursor **91**

The other fragment of the diene precursor containing the sulfoxide functionality was synthesized by deprotonation of thiophenol with sodium hydride and nucleophilic attack on methyl bromoacetate providing the thioether **108** in excellent yield (93%), similar to the literature value. An initial approach to the synthesis of the diene precursor (Scheme 2.7) was to deprotonate the ester **108** with sodium hydride and to add the enolate



Scheme 2.7 Attempted synthesis of **91** *via* **111**

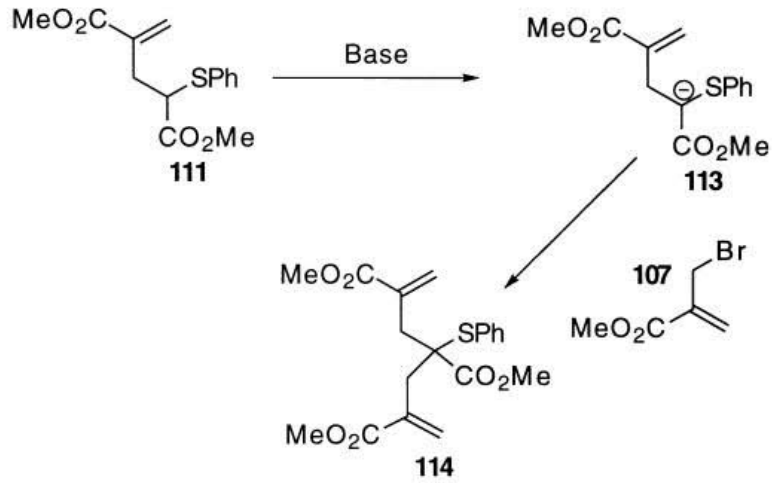
to a solution of the electrophile **107**. Unfortunately, this approach resulted in a complex mixture. Michael addition to the conjugated ester of **107** by the stabilized enolate may have competed with the desired substitution. Although the new enolate **112** resulting from Michael addition can eliminate bromine to give the desired product, it could also react with the electrophile **107** in another Michael addition or an S_N2 reaction to displace



Scheme 2.8 Possible reactions of enolate **112**

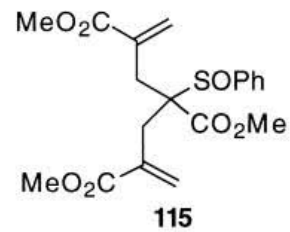
bromine (Scheme 2.8). Inverse addition of the enolate of **110** to a solution of the electrophile **107** gave the diene precursor **111** in only fair yield (63%). The main byproduct was the result of the addition of two molecules of electrophile to the sulfide

108 to give **114** in 10% yield. Compound **111** must be deprotonated in the reaction mixture by excess sodium hydride or by the enolate **110**. This new enolate **113** can then react with another molecule of electrophile **107** to give the byproduct **114**. In addition, the subsequent oxidation of the thioether **111** to the corresponding sulfoxide was not



Scheme 2.9 Byproduct of the synthesis of **111**

adequately achieved due to solubility problems. This approach was not pursued further. Instead the oxidation of **108** with sodium periodate[47] to the sulfoxide **109** was accomplished in excellent yield (96%) before incorporation into the diene precursor. This yield also matched that reported in the literature. An inverse addition was used again in this case to give the desired product **91** in 50% yield. Again, a byproduct **115** derived from two-fold addition of the electrophile was isolated in 16% yield.



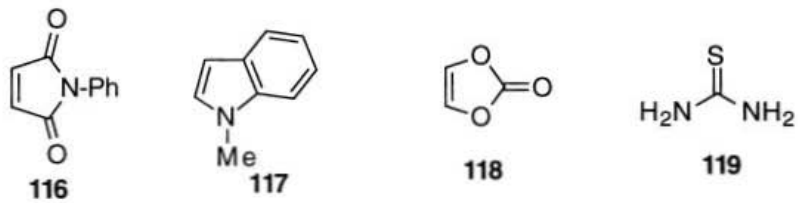
Scheme 2.10 Byproduct of synthesis of compound **91**

With a small amount of the diene precursor in hand, it was essential to determine the temperature at which the sulfoxide elimination occurred. The first evidence that the desired diene **44** is produced from **91** was observed in the mass spectrum of **91**. A peak at *m/z* 296 for the sulfoxide **91** was not present in the mass spectrum. This peak was not expected to be present in the spectrum considering the rather harsh ionization conditions typically employed in mass spectral analysis. However, a peak corresponding to the diene **44** was observed (*m/z* 178) and the fragmentation pattern of this compound can be traced in the mass spectrum. More evidence for the generation of the diene was obtained with an NMR tube experiment with a sample of the sulfoxide in deuterated benzene. The sample was heated in a thermostated bath for thirty minutes and analyzed by NMR to determine if a reaction was taking place. If no elimination had occurred, the temperature of the bath was increased by ~10 °C with NMR monitoring after thirty minutes until a reaction was observed. The reaction was followed by the disappearance of the doublet of doublets at δ 3.9 in the NMR spectrum corresponding to the proton α to the sulfoxide of one of the two diastereoisomers. The elimination appeared to occur very slowly at 40 °C, but rapidly at 78 °C. The crude NMR spectrum was very complex but there was evidence that **44** was present and observable in the spectrum. A number of pairs of doublets appeared in the double bond region with coupling constants in the range of 15-17 Hz, which is typical for an *E* 1,2-disubstituted double bond. As the sulfoxide elimination selectively produces the *E* isomer of the double bond, that range of coupling constants was expected to be observed in the NMR spectrum of **44**. In addition, two new singlets were present at δ 5.4 and δ 5.7 which could be attributed to the CH_2 of the terminal alkene of **44**.

Subsequent NMR tube reactions with the sulfoxide in the presence of sulfenic acid traps, *i.e.*, trimethylphosphite,[41b,c] pyridine,[41a] and calcium carbonate,[39a] were performed to determine if any difference in the sulfoxide elimination could be observed.

The temperature of elimination did not appear to be affected and the same rate of elimination appeared to be occurring in each case. Proton signals in the double bond region, which were observed in the NMR spectrum with no sulfenic acid trap were consistently observed in each of these spectra as well. It did appear, however, that the NMR spectra of the calcium carbonate and trimethylphosphite cases were cleaner than in the case of the sulfoxide alone or with the addition of pyridine. TLC analysis also indicated that the added trimethylphosphite gave a cleaner reaction mixture. These sulfenic acid traps, especially calcium carbonate and trimethylphosphite, must be investigated more thoroughly for use in actual Diels-Alder reactions.

Preliminary investigations of Diels-Alder reactions with some common dienophiles, e.g. *N*-phenylmaleimide **116**, *N*-methylindole **117**, vinylene carbonate **118** and thiourea **119**, were performed in NMR tubes with deuterated benzene as the solvent.

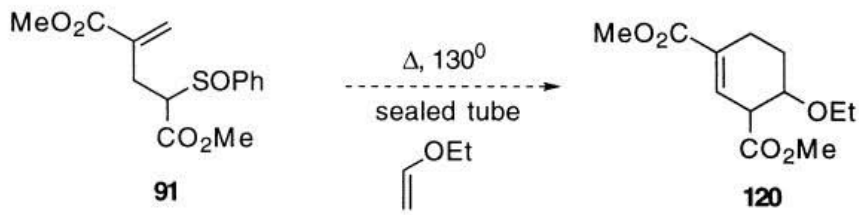


Scheme 2.11 Dienophiles attempted in Diels-Alder reactions with **91**

These reactions were done in the absence of sulfenic acid traps. The results from these experiments appeared to be promising with some changes occurring in the ^{1}H NMR spectra. In each of these experiments, the signals corresponding to the carbon chain of the sulfoxide disappeared within one hour at 78 °C. Some of the pairs of doublets that were observed in the previous NMR tube experiments that may be attributed to **44** were also observed. In addition, multiplets appeared at 2.3 ppm and 2.0 ppm which may have been due to cycloaddition reactions with the dienophiles. However, these signals were also observed in the earlier NMR tube experiments with the sulfoxide alone and with

$CaCO_3$ indicating that they may have been due to dimerization or polymerization of the diene itself. Complete or partial consumption of the dienophiles was not observed in the NMR spectra because each was used in excess of the diene precursor. Since the scale was so small in these experiments, no products were isolated or characterized.

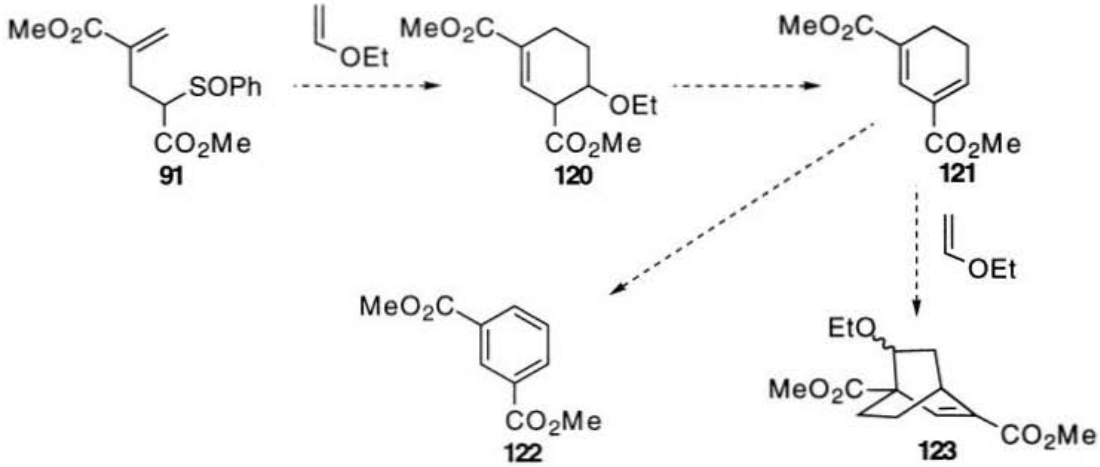
Another experiment was attempted based on work on a similar project in our laboratory[44] with the diene precursor heated to 130 °C overnight in a sealed tube with ethyl vinyl ether as the solvent, again in the absence of acid traps. The crude mixture was analyzed by TLC and NMR after removal of the excess ethyl vinyl ether under vacuum.



Scheme 2.12 Attempted reaction of **91** with ethyl vinyl ether

A complex mixture was obtained but the presence of triplets at 1.0-1.3 ppm and quartets at 3.4-3.7 ppm in the NMR spectrum indicated some form of incorporation of the ethoxy group of the ethyl vinyl ether. This may have been the result of Diels-Alder reactions. However, several products were produced in the reaction and none of these compounds could be isolated and characterized to determine their structures. It is suspected that the conditions employed were much too harsh since the earlier NMR tube experiments indicated that the elimination occurs at a much lower temperature than was used here. The sulfenic acid produced by the reaction may have been affecting the products to give a complex mixture particularly at this high temperature. The potential products of the Diels-Alder reactions attempted to this point contain functionality which can readily react with the acid generated and result in a mixture of products. For example, as outlined in Scheme 2.13, the ethoxy group could be protonated by the acid and eliminate ethanol to

give another form of the 1,3-electron deficient diene **121**. This could conceivably aromatize to give **122**, or it could react with another molecule of dienophile to give the bicyclic compound **123**. As with Padwa's work on the bis(sulfone) (Scheme 1.14)[28], this may prove to be a useful reaction sequence in the future, providing entry into novel bicyclic compounds. However, milder conditions must be investigated first to determine

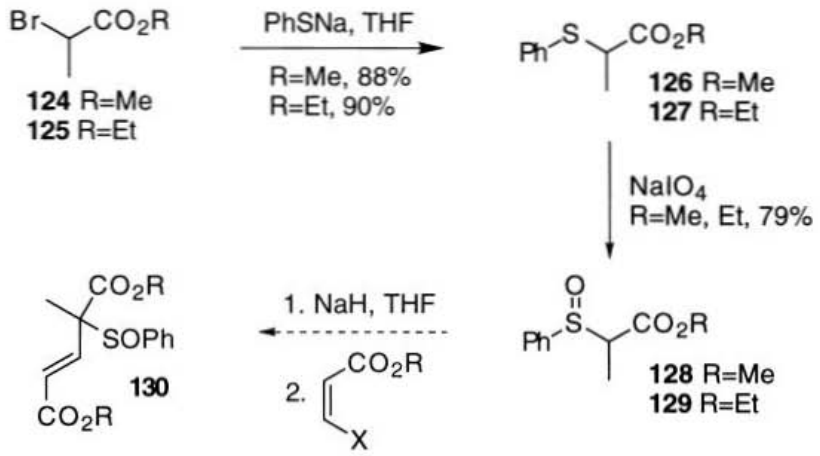


Scheme 2.13 Possible reactions of **91** in ethyl vinyl ether

the minimum requirements for the desired reaction. In addition, benzenesulfenic acid has also been shown to react with vinyl ethers in an electrophilic addition to the double bond[42] and this side-reaction may explain the incorporation of the ethoxy group in the crude mixture. The variety of potential products and the difficult chromatographic separation of the mixture made characterization of the reaction impossible and the presence of these potential products could not be determined.

Preliminary studies of a second diene precursor were also performed and the synthesis is outlined in Scheme 2.14. Since a major byproduct of the earlier precursor syntheses was the two-fold alkylation of sulfoxide **109**, the use of the isomeric sulfoxides **128** (R=Me) and **129** (R=Et) which cannot undergo this side reaction were investigated.

Similar methodology to that developed for **91** was employed for these compounds. Deprotonation of thiophenol and addition to methyl or ethyl 2-bromopropanoate resulted in the corresponding sulfides in excellent yield (88% and 90% respectively). This was

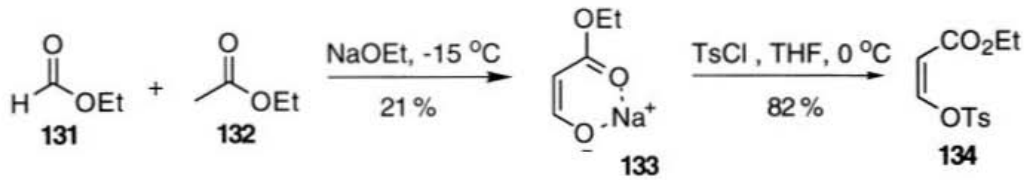


Scheme 2.14 Synthesis of second diene precursor **130**

followed by periodate oxidation, which proceeded in good yield (79% for both) with some starting material recovered (16% for methyl and 19% for ethyl). The sulfoxide must be handled with some caution due to the possibility that the sulfenic acid may eliminate in this compound before it is incorporated into the diene precursor. Not surprisingly, attempts to purify these compounds by distillation under vacuum resulted in rapid decomposition at approximately 80 °C. However, column chromatography led to facile separation of the sulfide from the much more polar sulfoxide. The sulfoxides **128/129** were obtained as a ~1:1 mixture of two diastereomers and no attempt was made to separatethese isomers.

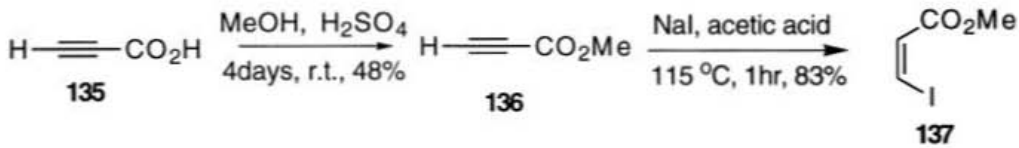
The electrophilic portion of the second diene precursor was synthesized in two ways. The first involved the sodium ethoxide induced condensation of ethyl formate with ethyl acetate to give the sodium salt of ethyl 3-oxopropanoate **133** in 21% yield.[48] The ethyl esters were used in this case because attempts to utilize the methyl esters resulted in

none of the desired product. Addition of *p*-toluenesulfonyl chloride to a suspension of the salt resulted in only the (*Z*)-enol tosylate **134** in good yield (82%). This selectivity may be rationalized by a template effect of the sodium cation with both the ester and the oxygen of the enol maintaining the salt in the *Z* form **133**.



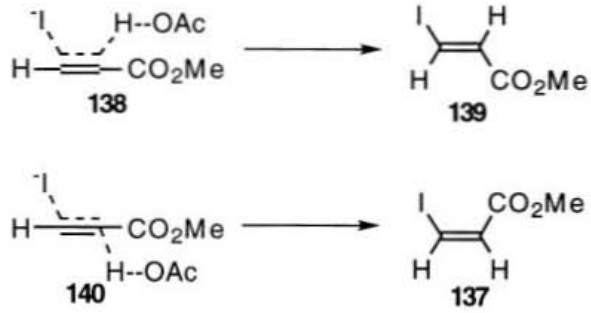
Scheme 2.15 Synthesis of enol tosylate **134**

The other form of the electrophile synthesized was obtained starting from the esterification of propynoic acid[49] and treatment of the resultant ester with sodium iodide in acetic acid to give selectively the (*Z*) isomer of methyl 3-iodopropenoate **137**[50a] in



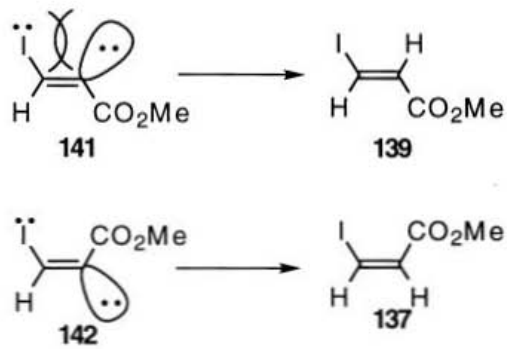
Scheme 2.16 Synthesis of (*Z*)-methyl 3-iodopropenoate **137**

good yield (83%) from methyl propynoate. In a related literature study on hydro-halogenations,[50b] it was reasoned that this selectivity may result from a transition state in which the halogen and the acetic acid are on opposite sides of the triple bond to diminish steric interactions (Scheme 2.17). The authors also argue that the vinyl anion electron pair, which results from addition of the halide to the triple bond, may exert a



Scheme 2.17 Rationalization of stereoselectivity of hydroiodination reaction

stereoelectronic effect (Scheme 2.18). The halide and the electron pair will repel one another if on the same side as in the intermediate **141** (which will give the *E* isomer) but not if on opposite sides **142** (which will give the *Z* isomer). Since the more stable form of the intermediate is **142**, the *Z* isomer is obtained selectively.



Scheme 2.18 Rationalization of stereoselectivity of hydroiodination reaction

As shown in Scheme 2.14, the second diene precursor may be generated by the deprotonation of the sulfoxide by sodium hydride followed by addition to the appropriate electrophile **134** or **137**. This reaction has been attempted but has not been successfully accomplished and starting materials were recovered. The problem with this conjugate addition reaction may be the steric bulk of the tertiary nucleophiles derived from **128/129**.

Further investigation involving different reaction conditions will be required to determine if this is indeed the case.

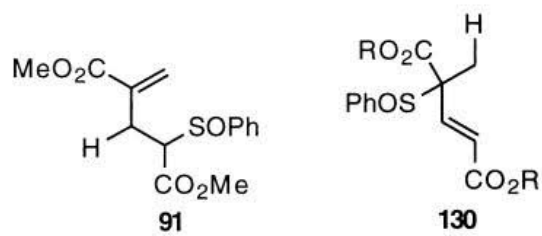
At this point, a decision was made to suspend investigation in this area. Although none of the desired inverse electron demand Diels-Alder reactions were accomplished, the synthetic methodology to two direct precursors of diene **44** was established and there are clear indications that **44** is indeed formed under relatively mild conditions. The optimization of reaction conditions, modification of the synthetic approach and the achievement of some inverse electron demand Diels-Alder reactions will be the objectives of future investigation.

Chapter 3

Conclusions of Diels-Alder Work

The synthesis of a sulfoxide presursor **91** to diene **44** has been developed from readily available starting materials. This compound must be further studied to optimize the synthesis and to determine the ideal conditions required to generate the diene. Generation of the diene in the presence of dienophiles must be performed to determine if it is reactive in a Diels-Alder manner. Sulfenic acid traps, especially trimethyl phosphite and calcium carbonate, may prove to be useful in maintaining neutral reaction conditions and preventing unwanted side reactions.

The synthesis of the second sulfoxide precursor **130** must be completed and this compound studied. It may prove to be a more useful precursor to the diene if it can be synthesized in a yield greater than that achieved with compound **91**. However, in sulfoxide eliminations removal of the methyl proton in **130** proceeds more slowly than removal of the allyl proton as in **91**.[39f] This may require a higher temperature for the elimination

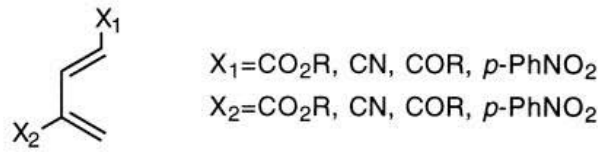


Scheme 3.1 Two direct precursors to diene **44**

to take place, but may make the sulfoxide more stable during isolation and storage. In addition, the rate of diene reaction may also be more controlled by an adjustment in the rate of generation. This will be investigated when the synthesis has been completed.

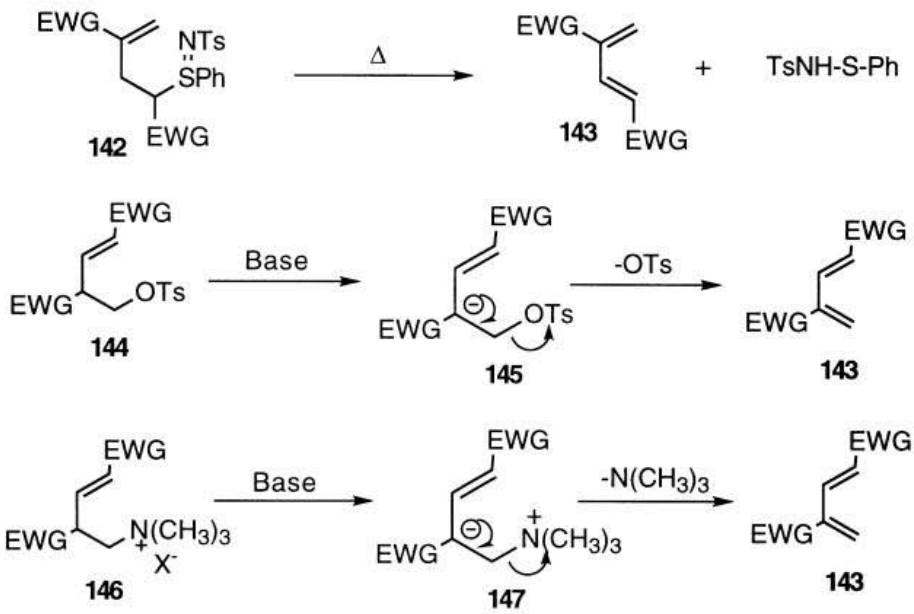
The methodology developed for compounds **91** and **130** may be applied to diene precursors substituted with other electron withdrawing groups. A series of these types of

dienes can be envisioned by replacing one or both of the methyl esters with nitrile, aldehyde, ketone and *ortho*- or *para*-nitrophenyl functional groups.



Scheme 3.2 Possible electron deficient 1,3-butadienes

Alternative methods of *in situ* generation of the diene are also under consideration including *via* the *N*-*p*-toluenesulfonylsulfilimines **142**, the tosylate **144** and the tertiary amine **146**. The sulfonimido compound **142** is analogous to the sulfoxide and benefits from a lower temperature of elimination to the unsaturated compound.[54a] Although this



Scheme 3.3 Alternate precursors to the electron deficient dienes

is closely related to the sulfoxide elimination, it has not been as widely used and very little discussion has appeared in the literature. It is known that the elimination goes

through a similar transition state as the sulfoxide elimination and is as stereoselective, giving the *E* alkene.[54b] The more labile nature of the sulfonimido group to elimination may prove to be useful in this case. These compounds are typically prepared from oxidation of the corresponding sulfide with Chloramine T (TsNClNa).[54c] For **144** and **146**, deprotonation α to the ester may lead to elimination of the tosylate or the trialkyl amine and generation of the diene under more desirable conditions than the sulfoxide elimination provides. However, it is not known if the elimination in these cases will be steroselective to result in the desired *E* double bonds.

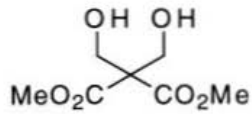
The possible Diels-Alder reactions of this family of butadienes will be studied with electron rich, electron neutral and electron deficient dienophiles to determine the extent to which Diels-Alder methodology may be applied to these electron deficient dienes. A related project[44] has revealed that these types of electron deficient dienes are reactive with a variety of dienophiles, and the study of those particular dienes is ongoing. The results to this point have been very encouraging and may prove to be applicable to this project as well. Further study of this potentially important class of dienes may reveal reactivity and adducts that have previously been unavailable and thereby broaden the scope of the Diels-Alder reaction in total synthesis.

Chapter 4

Experimental for Diels-Alder Work

General procedures. Reactions were performed under ambient atmosphere, unless otherwise stated. All commercial chemicals were obtained from Aldrich and used as obtained without further purification. Tetrahydrofuran was freshly distilled over sodium/benzophenone. Thin layer chromatography was performed on E. Merck 60 F_{254} precoated silica plates. Flash column chromatography was performed according to the procedure of Still[51] using silica gel 60 (E. Merck, 230-400 mesh). Melting points (m.p.) were obtained on a Fisher-Johns apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a GE GN-300NB spectrometer at 300.117 MHz and 75.475 MHz, respectively, in $CDCl_3$ unless otherwise specified. Chemical shifts are in ppm relative to internal standards: TMS (tetramethylsilane) for ^{1}H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C NMR. Individual peaks are reported as chemical shift, multiplicity (s=singlet, d=doublet, dd=doublet of doublets, dt=doublet of triplets, t=triplet, q=quartet, m=multiplet), number of hydrogens and coupling constant. Reported multiplicities are apparent multiplicities. The assignments are based on ^{1}H-^{13}C HETCOR (2-D heteronuclear), APT (attached proton test) and nOe (nuclear Overhauser effect) experiments. The nOe measurements were made from sets of interleaved ^{1}H experiments (16k) of 8 transients cycled 12 to 16 times through the list of frequencies to be saturated. The decoupler was gated on in CW mode for 6 seconds with sufficient attanuation to give a 70-90% reduction in intensity of the irradiated peak. Frequency changes were preceded by a 60 second delay. Four scans were used to equilibrate spins before data acquisition, but a relaxation delay was not applied between scans at the same frequency. The nOe difference spectra were obtained from zero-filled 32k data tables to which a 1-2 Hz exponential line-broadening function had been applied. The nOe data are reported as follows: irradiated signal (enhanced signal, enhancement). Infrared spectra (IR) were recored on a Mattson Polaris FT instrument. Peaks are reported in cm^{-1} with the following intensities: s=strong, m=medium, w=weak, br=broad. Low resolution (LRMS) and high resolution mass spectra (HRMS) were measured on a V. G. Micromass 7070HS instrument. MS data are reported as *m/z* and intensity (% of base peak).

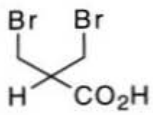
Diethyl 2,2-bis(hydroxymethyl)propanedioate 105:[45]



Potassium bicarbonate (8.00 g, 79.9 mmol) and aqueous formaldehyde solution (166 g of 37% solution, 2 mol) were stirred in a 500 mL round bottomed flask at 20 °C in a water bath and diethyl 1,3-propanedioate (160 g, 1 mol) was added dropwise while maintaining the reaction temperature between 25-30 °C. Stirring was continued for one hour and the mixture was transferred to a separatory funnel. Saturated $(NH_4)_2SO_4$ solution (300 mL) was added, and the mixture extracted with diethyl ether (300 mL). The organic portion was dried with Na_2SO_4, filtered into a 1 L three-necked flask, and the solvent was removed by distillation until the temperature of the solution reached 45-50 °C. The distillation apparatus was removed and replaced with a thermometer adapter equipped with a piece of glass tubing that reached below the surface of the oily residue and closed by a piece of rubber tubing and a screw clamp. Air was then drawn through another neck of the flask by means of an aspirator and the screw clamp was adjusted such that the pressure was maintained at 20-30 mm Hg and the viscous liquid splattered on the upper part of the flask (This sped the crystallization process). The flask was then warmed to 40 °C until crystallization began and for an additional 30 minutes. Isopropyl ether (500 mL) was added and the mixture was warmed to 50 °C to dissolve the product. The solution was then transferred to a 1L Erlenmeyer flask and stirred in an ice water bath until the product precipitated. The suspension was refrigerated, filtered by suction and the product dried at room temperature for 24 hours then in a vacuum desiccator over sulfuric acid for a further 24 hours to yield 136 g (616 mmol, 62%) of a colourless solid that was suitable for use in the next step. The product could be recrystallized from isopropyl ether to give colourless needles: m.p. 48-49 °C (lit. [45] m.p. 50-52 °C); IR 3558 cm^{-1} (br), 2989 cm^{-1}

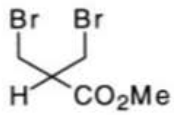
(m), 2942 cm^{-1} (m), 2910 cm^{-1} (w), 1722 cm^{-1} (s), 1300 cm^{-1} (s), 1266 cm^{-1} (s); ^1H NMR δ 4.26 (q, 2H, *J*=7.1 Hz), 4.11 (s, 2H), 2.80 (br s, 1H), 1.29 (t, 3H, *J*=7.1 Hz); ^{13}C NMR δ 169.5, 64.2, 61.9, 60.9, 14.0; LRMS *m/z* 221 (0.12, M+1), 127 (49), 99 (36).

3-Bromo-2-(bromomethyl)propanoic acid 143:[46]



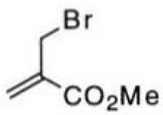
Diethyl 2,2-bis(hydroxymethyl)propanedioate **105** (110 g, 500 mmol) and concentrated hydrobromic acid (900 mL) were combined in a 2 L round bottomed flask and a portion of the aqueous acid was distilled by vigorously refluxing the mixture for six hours. The residue was then cooled at -15 °C overnight, and the precipitated crystals were removed by suction filtration. The product was dried by suction for six hours and then in a vacuum desiccator over active Drierite for six days to give 58.3 g (237 mmol, 47%) of a tan solid. Further concentration of the filtrate followed by cooling and filtration of the precipitate resulted in a second crop of the product (22.23 g, 90.42 mmol, 18%). The crude product (combined yield 65%) was suitable for use in the next step without further purification. The product could be recrystallized from water to give colourless needles: m.p. 101-102 °C (lit.[46] m.p. 98-101 °C); IR 1726 cm^{-1} (s); ^1H NMR δ 3.78 (AA'BB' portion of AA'BB'X system, 4H), 3.26 (X portion of AA'BB'X system, 1H); ^{13}C NMR δ 175.3, 48.3, 29.8; LRMS *m/z* 248 (1.8, $[^{81}Br^{81}Br]M^+$), 246 (3.6, $[^{81}Br^{79}Br]M^+$), 244 (1.8, $[^{79}Br^{79}Br]M^+$), 167 (28), 165 (28), 153 (21), 151 (21), 85 (26).

Methyl 3-bromo-2-(bromomethyl)propanoate 106:[46]



A solution of 3-bromo-2-(bromomethyl)propanoic acid **143** (61.50 g, 250.0 mmol), methanol (32 mL, 0.78 mol), and methanesulfonic acid (0.2 mL) in 1,2-dichloroethane (75 mL) were heated at reflux for 24 hours. The reflux condenser was equipped with a $CaCl_2$ drying tube to exclude atmospheric water. The mixture was cooled to room temperature, diluted with dichloromethane (200 mL) and neutralized with cold 1M $NaHCO_3$ solution. The organic portion was dried with Na_2SO_4, the solvent was removed and the residue distilled under vacuum (77-78 °C/1.0 mm Hg, lit. [46] b.p. 60-62 °C/0.4 mm Hg) to give a colourless oil (38.92 g, 149.8 mmol, 58%): IR 2956 cm^{-1} (s), 2847 cm^{-1} (w), 1738 cm^{-1} (s), 1441 cm^{-1} (s), 1355 cm^{-1} (s), 1307 cm^{-1} (s), 1169 cm^{-1} (s); ^1H NMR δ 3.78 (s, 3H), 3.75 (AA'BB' portion of AA'BB'X system, 4H), 3.20 (X portion of AA'BB'X system, 1H); ^{13}C NMR δ 169.7, 52.4, 48.3, 30.4; LRMS *m/z* 262 (1.5, $^{81}Br^{81}Br$-M^+), 260 (2.97, $^{81}Br^{79}Br$-M^+), 258 (1.63, $^{79}Br^{79}Br$-M^+), 229 (3), 201 (10), 181 (29), 179 (33), 167 (38), 165 (39), 121 (25), 119 (26), 99 (18), 95 (10), 93 (12).

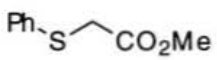
Methyl 2-(bromomethyl)propenoate 107:[46]



Methyl 3-bromo-2-(bromomethyl)propanoate **106** (10.80 g, 41.56 mmol) was stirred vigorously in anhydrous benzene (25 mL) at room temperature while triethylamine (3.92 g, 38.8 mmol) in benzene (25 mL) was added dropwise. The dropping funnel was equipped with a $CaCl_2$ drying tube to exclude atmospheric water. The mixture was

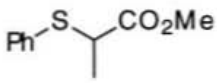
stirred for one hour at room temperature, refluxed for one hour and then allowed to cool. The precipitated solid was removed by filtration, extracted twice with anhydrous benzene (10 mL) and the combined filtrates were concentrated by rotary evaporation. Vacuum distillation (50-55 °C/2 mm Hg, lit. [46] b.p. 35-37 °C/1.3 mm Hg) of the residue yielded 5.23 g (29.2 mmol, 75%) of a colourless oil: IR 3022 cm^{-1} (s), 2955 cm^{-1} (m), 1726 cm^{-1} (s), 1633 cm^{-1} (m); ^1H NMR δ 6.34 (d, 1H, *J*=0.6 Hz), 5.96 (dt, 1H, *J*=0.6, 0.9 Hz), 4.18 (d, 2H, *J*=0.9 Hz), 3.82 (s, 3H); ^{13}C NMR δ 165.0, 137.1, 129.0, 52.1, 29.1; LRMS *m/z* 180 (35, ^{81}Br-M^+), 178 (34, ^{79}Br-M^+), 149 (25), 147 (25), 121 (23), 119 (24), 99 (100).

Methyl 2-(phenylthio)acetate 108:



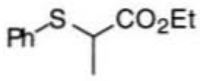
Thiophenol (27.54 g, 250.0 mmol) was added to a suspension of sodium hydride (7.50 g of 80% dispersion, 250 mmol) in THF (500 mL) under nitrogen at -78 °C, then the mixture was warmed to room temperature and stirred for one hour. The resultant white slurry was then cooled to -78 °C, and methyl bromoacetate (38.24 g, 250.0 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for two hours. Water (100 mL) was added, and the product was extracted into CH_2Cl_2 (2 x 200 mL). The organic extracts were washed with brine, dried (Na_2SO_4) and the solvent removed to give a pale brown oil. Vacuum distillation (99-102 °C/1.0 mm Hg, lit.[52] b.p. 93-95 °C/0.6 mm) yielded 42.35 g (232.4 mmol, 93%) of a colourless oil: IR 3002 cm^{-1} (m), 2956 cm^{-1} (m), 1737 cm^{-1} (s), 1584 cm^{-1} (m), 1292 cm^{-1} (s); ^1H NMR δ 7.41-7.22 (m, 5H), 3.69 (s, 3H), 3.64 (s, 2H); ^{13}C NMR δ 170.0, 134.8, 129.7, 128.9, 126.8, 61.3, 52.4, 36.3; LRMS *m/z* 182 (47, M^+), 123 (100), 109 (13).

Methyl 2-(phenylthio)propanoate 126:



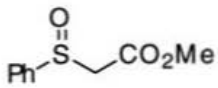
Thiophenol (13.20 g, 120.0 mmol), sodium hydride (4.80 g of 60% dispersion, 120 mmol) and methyl 2-bromopropanoate (20.00 g, 120.0 mol) were reacted as described for **108**. Vacuum distillation (118 - 120 °C/1.0 mm Hg) yielded 20.62 g (105.1 mmol, 88%) of a colourless oil: IR 3003 cm^{-1} (s), 2955 cm^{-1} (s), 2950 cm^{-1} (m), 1730 cm^{-1} (s), 1583 cm^{-1} (w); ^1H NMR δ 7.47-7.28 (m, 5H), 3.80 (q, 1H, *J*=7.1 Hz), 3.67 (s, 3H), 1.48 (d, 3H, *J*=7.1 Hz); ^{13}C NMR δ 173.0, 144.9, 133.0, 128.9, 128.0, 52.2, 45.2, 17.4; LRMS *m/z* 196 (36, M^+), 137 (100), 109 (41).

Ethyl 2-(phenylthio)propanoate 127:



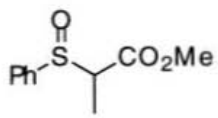
Thiophenol (12.17 g, 110.0 mmol), sodium hydride (4.42 g of 60% dispersion, 110 mmol) and ethyl 2-bromopropanoate (20.00 g, 110.0 mmol) were reacted as described for **108**. Vacuum distillation (84-87 °C/1.0 mm Hg, lit.[53] b.p. 159-161 °C/23.5 mm Hg) yielded 20.95 g (99.62 mmol, 90%) of a colourless oil: IR 2989 cm^{-1} (s), 2935 cm^{-1} (m), 1726 cm^{-1} (s), 1584 cm^{-1} (w); ^1H NMR δ 7.48-7.28 (m, 5H), 4.11 (q, 2H, *J*=7.2 Hz), 3.79 (q, 1H, *J*=7.1 Hz), 1.48 (d, 3H, *J*=7.1 Hz), 1.18 (t, 3H, *J*=7.2 Hz); ^{13}C NMR δ 172.6, 133.2, 133.0, 128.8, 127.9, 61.2, 45.3, 17.4, 14.0; LRMS *m/z* 210 (30, M^+), 137 (100), 109 (25).

Methyl 2-(phenylthio)acetate-S-oxide 109:



Sodium periodate (12.33 g, 57.64 mmol, 1.05 eq.) was dissolved in distilled water (150 mL), methyl 2-(phenylthio)acetate **108** (10.00 g, 54.90 mmol) was added and the emulsion was stirred vigorously for 15 hours at room temperature. The product was then extracted into CH_2Cl_2 (3x100 mL), dried (Na_2SO_4), and the solvent removed to give a pale yellow oil which solidified on standing. Vacuum distillation (142-143 °C/1 mm Hg) yielded 10.46g (52.79 mmol, 96%) of a colourless oil which solidified in the distillation flask. Recrystallization from diethyl ether gave colourless plates: m.p. 54-55 °C (lit.[52] m.p. 53-55 °C, lit. b.p. 130-131 °C/0.5 mm Hg); IR 3061 cm^{-1} (m), 2995 cm^{-1} (s), 2957 cm^{-1} (s), 2900 cm^{-1} (w), 1742 cm^{-1} (s), 1287 cm^{-1} (s), 1087 cm^{-1} (s); ^1H NMR δ 7.64-7.52 (m, 5H), 3.85 (d, 1H, *J*=13.7 Hz), 3.71 (s, 3H), 3.69 (d, 1H, *J*=13.7 Hz); ^{13}C NMR δ 165.1, 142.9, 131.7, 129.3, 123.9, 61.4, 52.6; LRMS *m/z* 198 (27, M^+), 125 (100), 97 (28).

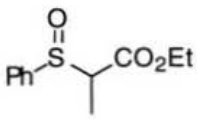
Methyl (*RR*,*SS*)- and (*RS*,*SR*)-2-(phenylthio)propanoate-*S*-oxide 128:



Sodium periodate (22.89 g, 107.0 mmol, 1.05 eq.) and methyl 2-(phenylthio)propanoate **126** (20.00 g, 102.0 mmol) in 250 mL water were reacted as described for **109.** Column chromatography of the resultant pale yellow oil (6:1 CH_2Cl_2:EtOAc) gave starting material (3.14 g, 16.0 mmol, 16%) and the product (18.19 g, 88.00 mmol, 79%) as a colourless oil: IR 3065 cm^{-1} (w), 2994 cm^{-1} (s), 2925 cm^{-1} (s), 2855 cm^{-1} (s), 1737 cm^{-1} (s), 1086 cm^{-1} (s); ^1H NMR δ 7.70-7.52 (m, 5H), 3.68, 3.67 (2s, 3H), 3.84, 3.51 (q, 1H,

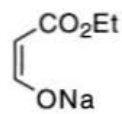
J=7.1 Hz), 1.47, 1.32 (d, 3H, *J*=7.1 Hz); ^{13}C NMR δ 168.9, 168.2, 141.8, 140.3, 131.8, 131.6, 129.1, 129.0, 125.0, 124.5, 65.47, 63.6, 52.6, 52.4, 9.3, 8.7; LRMS *m/z* 212 (12, M^+), 126 (43), 125 (73), 110 (62), 109 (38), 97 (21), 87 (18).

Ethyl (*RR*,*SS*)- and (*RS*,*SR*)-2-(phenylthio)propanoate-*S*-oxide 129:



Sodium periodate (10.68 g, 49.93 mmol, 1.05 eq.) and ethyl 2-(phenylthio)propanoate **127** (10.00 g, 47.55 mmol) in 200 ml of water were reacted as described for **109**. Column chromatography of the resultant pale yellow oil (6:1 CH_2Cl_2:EtOAc) gave starting material (1.87 g, 8.89 mmol, 19%) and the product (8.45 g, 37.34 mmol, 79%) as a colourless oil: IR 3069 cm^{-1} (w), 2992 cm^{-1} (s), 2939 cm^{-1} (m), 1738 cm^{-1} (s), 1088 cm^{-1} (s); ^{1}H NMR δ 7.66-7.50 (m, 5H), 4.12 (m, 2H), 3.81, 3.49 (q, 1H, *J*=7.2 Hz), 1.32, 1.49 (d, 3H, *J*=7.2 Hz), 1.201, 1.198 (t, 3H, *J*=6.8 Hz); ^{13}C NMR δ 167.7, 140.4, 131.7, 131.6, 129.1, 128.9, 125.1, 124.6, 65.7, 63.6, 61.7, 61.7, 14.0, 9.6, 8.8; LRMS *m/z* 226 (10, M^+), 126 (49), 125 (64), 110 (21), 109 (17), 101 (38), 97 (17).

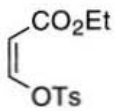
(*Z*) Sodium salt of ethyl 3-oxopropanoate 133:[48]



Sodium (11.5 g, 0.500 mol) was suspended in diethyl ether (150 mL) in a 250 mL three-necked flask equipped with a $CaCl_2$ drying tube, and absolute ethanol (25 g, 0.50 mol) was added dropwise. The resultant mixture was refluxed overnight and then cooled to -15 °C. Ethyl formate (90 g, 1.2 mol) was added followed by ethyl acetate (44 g, 0.50 mol) and the suspension was diluted with 100 mL of diethyl ether. The mixture was

allowed to warm to room temperature and stirring was continued for six hours. The suspension was cooled to 0 °C, the precipitate was filtered off, and the filter cake eluted several times with diethyl ether. The salt was dried under vacuum (1.0 mm Hg) at 75 °C for three hours to yield a white powder (14.59 g, 105.6 mmol, 21%).

Ethyl (*Z*)-3-[(4-methylphenylsulfonyl)oxy]propenoate 134:[48b]

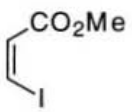


The sodium salt of ethyl 3-oxopropanoate **133** (5.00 g, 36.2 mmol) was suspended in THF (100 mL) at 0 °C as *p*-toluenesulfonyl chloride (6.90 g, 36.2 mmol) in THF (30 mL) was added dropwise over one hour. The dropping funnel was equipped with a $CaCl_2$ drying tube to exclude atmospheric water. The reaction was stirred for an additional hour then diluted with diethyl ether (100 mL), washed with water (2x20 mL), dried over $MgSO_4$, and the solvent was removed to give 8.07 g (29.8 mmol, 82%) of a colourless solid. Recrystallization from petroleum ether gave colourless crystals: m.p. 76.5-77.5 °C (lit.[48b] m.p. 78-78.5 °C); IR 3065 cm^{-1} (w), 3039 cm^{-1} (m), 2987 cm^{-1} (m), 1721 cm^{-1} (s), 1659 cm^{-1} (s), 1598 cm^{-1} (m), 1388 cm^{-1} (s), 1265 cm^{-1} (s), 1170 cm^{-1} (s); ^1H NMR δ 7.84 (d, 2H, *J*=8.3 Hz), 7.37 (d, 2H, *J*=8.3 Hz), 6.94 (d, 1H, *J*=7.0 Hz), 5.31 (d, 1H, *J*=7.0 Hz), 4.13 (q, 2H, *J*=7.1 Hz), 2.46 (s, 3H), 1.23 (t, 3H, *J*=7.1 Hz); ^{13}C NMR δ 162.7, 145.9, 144.4, 132.2, 130.0, 127.9, 106.3, 60.5, 21.7, 14.1; LRMS *m/z* M^+ peak not observed, 225 (4), 155 (64), 91 (100); HRMS calcd. for $C_{12}H_{14}SO_5$ 270.0561, found 270.0564.

Methyl propynoate 136:[49]

A chilled mixture of methanol (33.0 g, 1.03 mol) and concentrated sulfuric acid (6 g) was added portionwise to chilled propynoic acid (20.0 g, 0.286 mol). After sitting for four days at room temperature the solution was refluxed for thirty minutes and cooled. The mixture was poured portionwise into saturated $(NH_4)_2SO_4$ solution, which was then extracted with diethyl ether (4x150 mL). The combined organic extracts were washed with 10% $KHCO_3$, water, dried with Na_2SO_4, and the solvent removed to give a pale brown oil (13.11 g). Distillation (95-105 °C/760 mm Hg, lit.[49] b.p. 103-105 °C) of this residue yielded 11.55 g (13.74 mmol, 48%) of a colourless oil which was sufficiently pure for the next step. IR 3298 cm^{-1} (s), 3039 cm^{-1} (s), 2957 cm^{-1} (s), 2844 cm^{-1} (w), 2126 cm^{-1} (s), 1711 cm^{-1} (s), 1271 cm^{-1} (s); ^1H NMR δ 3.81 (s, 3H), 2.95 (s, 1H); ^{13}C NMR δ 153.1, 74.9, 74.3, 52.9; LRMS *m/z* this sample boils at such a low point that LRMS could not be obtained

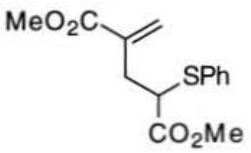
Methyl (*Z*)-3-iodopropenoate 137:[50a]



Methyl propynoate **136** (5.17 g, 61.5 mmol), sodium iodide (14.75 g, 98.40 mmol, 1.6 eq.), and acetic acid (23.64 g, 393.6 mmol, 6.4 eq.) were combined, and the suspension was stirred at 115 °C for one hour under nitrogen. The hot mixture was then poured into 200 mL of water in a separatory funnel. The reaction flask was washed with 10 mL of water and 60 mL of diethyl ether, which were added to the separatory funnel. The layers were separated, the aqueous portion was extracted with diethyl ether (60 mL) and the combined organic phases were washed with saturated $NaHCO_3$ solution, 1M $Na_2S_2O_3$

solution, brine (20 mL of each) and were then dried with $MgSO_4$. Removal of the solvent at reduced pressure followed by vacuum distillation (71-73 °C/1.0 mm Hg, lit.[50a] b.p. 30-40 °C/0.03 mm Hg) yielded a colourless oil (10.82 g, 51.04 mmol, 83%): IR 3000 cm^{-1} (w), 2954 cm^{-1} (m), 2844 cm^{-1} (w), 1726 cm^{-1} (s), 1599 cm^{-1} (s), 1166 cm^{-1} (s); ^1H NMR δ 7.49 (d, 1H, *J*=8.9 Hz), 6.92 (d, 1H, *J*=8.9 Hz), 3.79 (s, 3H); ^{13}C NMR δ 164.9, 129.4, 95.2, 51.6; LRMS *m/z* 212 (98, M^+), 181 (100), 153 (38), 127 (90), 85 (46).

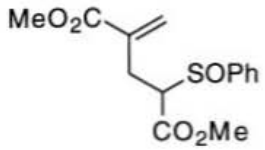
Dimethyl 2-methylene-4-(phenylthio)-1,5-pentanedioate 111:



Methyl 2-(phenylthio)acetate **108** (2.03 g, 11.1 mmol) was added to a stirred suspension of sodium hydride (0.45 g of 60% dispersion, 11 mmol) in THF under nitrogen at -78 °C, and the resultant slurry was warmed to room temperature and stirred for one hour. The cloudy, yellow reaction mixture was then cooled to 0 °C and was added to a THF solution of methyl 2-(bromomethyl)-2-propenoate **107** (3.00 g, 16.8 mmol, 1.5 eq.) at 0 °C dropwise *via* cannula. The mixture was allowed to warm to room temperature and stir for one hour. Cold saturated NH_4Cl solution was then added dropwise, and the product was extracted into CH_2Cl_2. The organic portion was washed with water and brine, dried over Na_2SO_4, and the solvent was removed to give a yellow oil. Column chromatography on silica gel with CH_2Cl_2 as the eluent provided 1.97 g (7.03 mmol, 63%) of the desired product as a colourless oil: IR 3017 cm^{-1} (s), 2954 cm^{-1} (m), 1729 cm^{-1} (s), 1631 cm^{-1} (w), 1440 cm^{-1} (s), 1163 cm^{-1} (s); ^1H NMR δ 7.50-7.20 (m, 5H), 6.26 (s, 1H), 5.66 (d, 1H, *J*=0.8 Hz), 4.00 (dd, X portion of ABX system, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 2.83 (2 x dd, AB portion of ABX system, 2H); ^{13}C NMR δ 171.9, 166.7, 136.1, 132.9, 128.9,

128.6, 128.1, 52.2, 52.0, 49.1, 34.7; LRMS *m/z* 280 (8, M^+), 248 (57), 216 (66), 189 (35), 161 (80), 149 (30), 139 (27), 128 (19), 121 (100), 111 (21), 110 (33), 109 (59).

Dimethyl 2-methylene-4-(phenylthio)-1,5-pentanedioate-S-oxide 91:

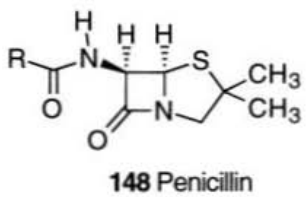


Methyl 2-(phenylthio)acetate-S-oxide **109** (2.21 g, 11.2 mmol) was added to a stirred suspension of sodium hydride (0.45 g of 60% dispersion, 11 mmol) in THF under nitrogen at -78 °C and the resultant slurry was allowed to warm to room temperature and stir for one hour. The clear, yellow reaction mixture was then cooled to 0 °C and was added dropwise *via* cannula to a THF solution of methyl 2-(bromomethyl)-2-propenoate **107** (3.00 g, 16.8 mmol, 1.5 eq.) at 0 °C. The mixture was allowed to warm to room temperature and stir for one hour. Saturated NH_4Cl solution was added dropwise and the product was extracted into CH_2Cl_2 (3x50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed to give a pale yellow oil. Column chromatography on silica gel using 4:1 CH_2Cl_2:EtOAc as the eluent afforded 1.66 g (5.60 mmol, 50%) of a colourless oil: IR 3063 cm^{-1} (w), 3019 cm^{-1} (m), 2955 cm^{-1} (s), 2846 cm^{-1} (w), 1726 cm^{-1} (s), 1656 cm^{-1} (m), 1440 cm^{-1} (s), 1173 cm^{-1} (s), 1088 cm^{-1} (s); ^1H NMR δ 7.65-7.53 (m, 5H), 6.28, 6.24 (s, 1H), 5.76, 5.70 (d, 1H, *J*=0.9 Hz), 4.90, 4.75 (m, 1H), 2.90 (m, 2H); ^{13}C NMR δ 167.7, 166.5, 166.4, 141.6, 140.9, 135.4, 135.0, 131.8, 131.7, 129.4, 129.1, 129.0, 128.9, 124.7, 124.6, 69.7, 67.1, 52.4, 52.2, 52.1, 52.0, 28.7, 28.4; LRMS *m/z* M^+ not observed, 221 (1.5), 219 (1.4), 218 (7), 171 (24), 170 (12), 139 (40), 126 (18), 125 (33), 111 (100), 110 (39), 109 (29), 97 (11), 83 (16), 79 (15), 78 (36), 77 (50), 69 (12), 68 (12), 66 (15), 65 (19), 59 (34), 53 (21), 52 (22), 51 (59), 50 (27), 45 (14), 41 (12), 39 (28).

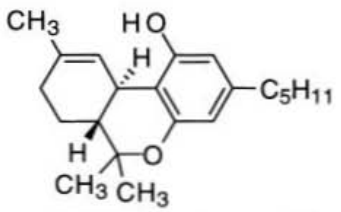
Chapter 5

Introduction to Protoberberine Synthesis

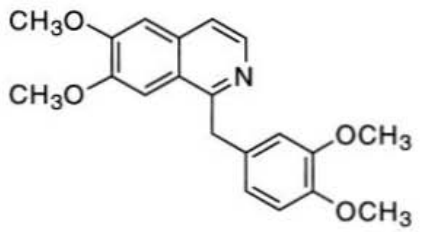
The synthesis of natural products is one of the greatest challenges to the synthetic organic chemist. The attraction for many to this field has been the intellectual challenge of the multistep synthesis and the prospect of making a compound better than Nature is able to produce it. Natural product synthesis has become a much more practical endeavor rather than mainly an intellectual pursuit. These compounds are becoming increasingly important as the pharmaceutical industry searches for more efficacious drugs for a variety of medicinal applications.[55] Some examples of natural products that are of pharmaceutical interest are the penicillins (antibiotics) **148**,[56] Δ^9-tetrahydrocannabinol (antiemetic) **149**,[57] papaverine (smooth muscle relaxant) **150**,[58] theophylline



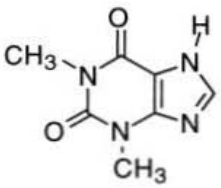
148 Penicillin



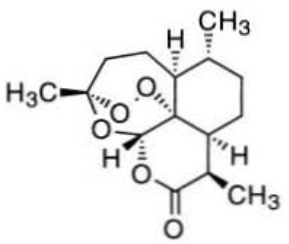
149 Tetrahydrocannabinol



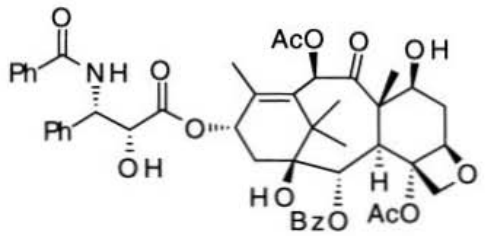
150 Papaverine



151 Theophylline



152 Artemesinin



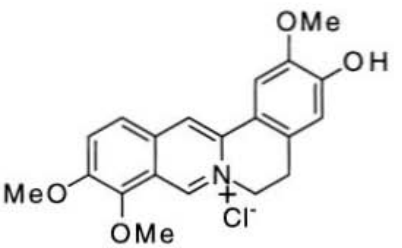
153 Taxol

Scheme 5.1 Natural products of pharmaceutical interest

(bronchodilator) **151**,[59] artemesinin (antimalarial) **152**[60-62] and taxol (anticancer) **153**.[63-66] Many natural products, such as the penicillins **148**, are isolated from their natural sources because the total synthesis[56a-c] is not as efficient or as inexpensive as the isolation procedure.[56d] Other compounds, such as **149-151**, are commercially

synthesized out of convenience or necessity. For example, theophylline **151** is readily synthesized from dimethylurea and ethyl cyanoacetate[59a-c] more efficiently than it is extracted from its natural source.[59d] Tetrahydrocannabinol **149** and papaverine **150**, on the other hand are synthesized[57a-d,58a-c] because they are not found in their natural sources in large quantities.[57e,58d] For some compounds which have more recently been found to be clinically useful, particularly those which are as structurally complex as artemisinin **152** and taxol **153**, the total synthesis has not yet been accomplished efficiently. Artemisinin is still isolated from its natural source and taxol has been isolated from natural sources but is now more efficiently obtained by semisynthesis from a compound found in greater quantities in the same plants.[61,65] These are not viable long term options for widespread use because **152** and **153** are not found in sufficiently large quantities. In these cases, total synthesis must be accomplished in order to obtain enough of the compound to study and use clinically. In fact, a number of different approaches to the synthesis of artemisinin[62] and taxol[66] have recently been reported but none of these methods have as yet been used commercially.

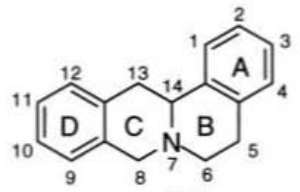
Another compound which is isolated in very small quantities from natural sources is jatrorrhizine **154**, a member of the protoberberine alkaloids.[67-71] The protoberberine



154 Jatrorrhizine

alkaloids are characterized by the skeleton **155** and over one hundred of these alkaloids have been isolated, mainly from plants found in China and India.[71] Substitution at nearly

every position around the skeleton has been observed for different members of the protoberberine family. The vast majority of naturally occurring protoberberines have four



155

Scheme 5.2 Characteristic skeleton of the protoberberine alkaloids

O-substituents (usually OH, OMe, OCH_2O) and these are typically present at the 2 and 3 positions and either the 9 and 10 or the 10 and 11 positions.*

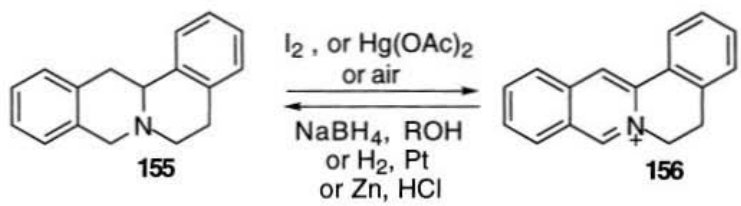
Jatrorrhizine is highly coloured (for example, the natural form is the chloride salt which is deep yellow) and has been found as a minor constituent in one of the dyes used in an ancient publication of the Diamond Sutra, a scripture of the Buddhist religion. That printing of the Diamond Sutra is the oldest known printed text, dating back to the year 868,[72] and jatrorrhizine appears to be acting as a preservative of the paper in the text. Jatrorrhizine has been found in a variety of traditional medicine preparations used as analgesics, sedatives, antiseptics and as cures for bleeding disorders and eye diseases.[73] More stringent research in laboratories has demonstrated anti-malarial activity,[74b,c] uterine tissue stimulation[74d] and intercalation into DNA and RNA,[74e] suggesting potential use against cancer.

No total synthesis of jatrorrhizine has appeared in the literature to date, and it is currently isolated from its natural sources especially from plant cell culture.[75] This procedure affords only milligram quantities after an exhaustive extraction and separation

* Compounds of the protoberberine series with the 10,11-substitution pattern have in a few instances been referred to generically as pseudoberberines. It appears to be an older term that is currently not in widespread use except in the names of a few of these alkaloids, for example, see compound **158**. In this discussion, the term protoberberine will apply to both the 9,10- and the 10,11-substitution patterns.

procedure[74b,75] so the total synthesis of jatrorrhizine from readily available starting materials was undertaken.

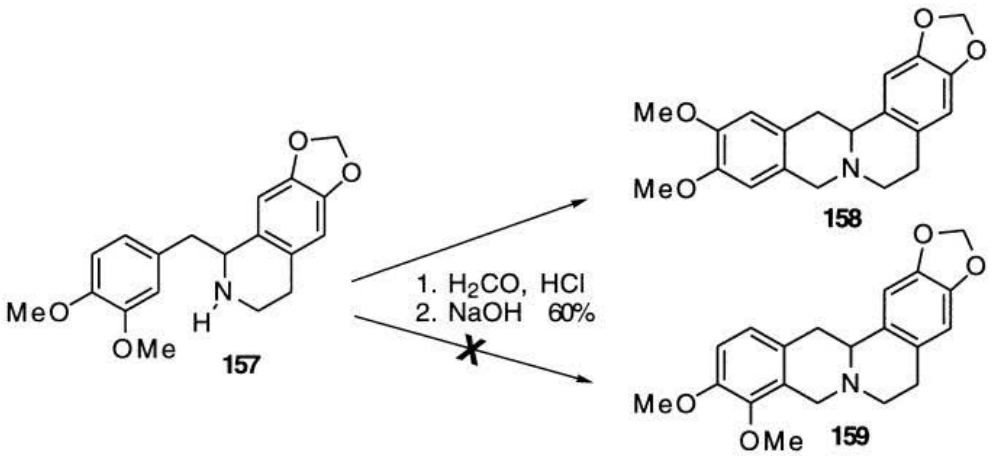
Other members of this family of alkaloids have been synthesized,[71] but each approach appears to be inadequate for jatrorrhizine for different reasons (*vide infra*). Prior approaches to the synthesis of the protoberberine skeleton have most often been directed to the tetrahydroprotoberberines in which the B- and C-rings are saturated as in structure **155**. These are readily converted to the analogous quaternary protoberberine salts **156** upon oxidation by I_2, $Hg(OAc)_2$, or in air (Scheme 5.3).[76] The reverse reaction is readily accomplished by $NaBH_4$ in alcoholic solvents, hydrogenation over platinum



Scheme 5.3 Interconversion of quaternary protoberberine salts with tetrahydroprotoberberines[76,77]

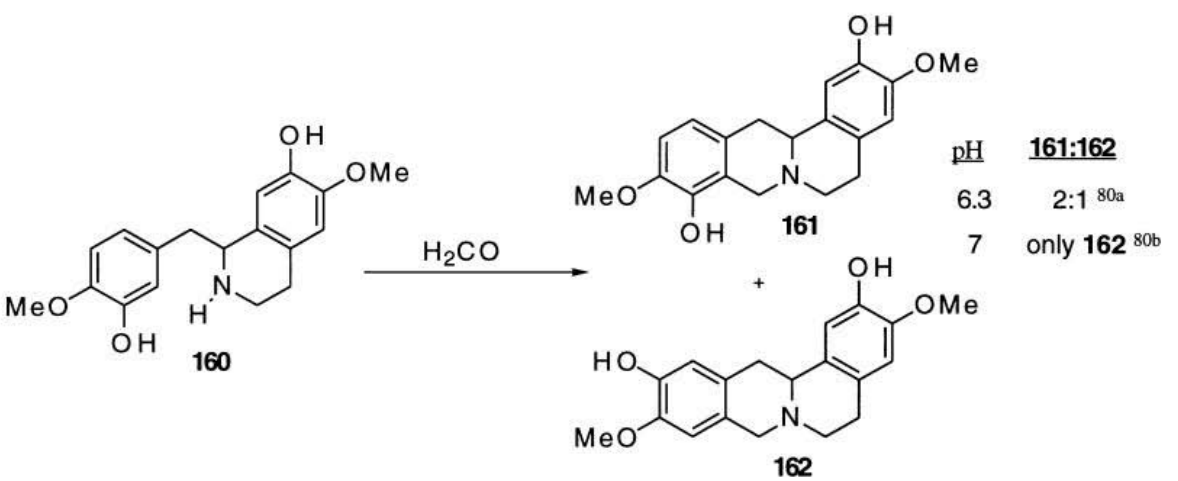
catalysts or reduction by zinc in hydrochloric acid.[77] Bearing these commonly performed conversions in mind, the following discussion of the previous syntheses of these alkaloids will, for most cases, be limited to the syntheses of the tetrahydroprotoberberines **155**.

The classical approach to the synthesis of protoberberine alkaloids has been the closure of the C-ring *via* a Mannich condensation of **157** with formaldehyde in acid as in Scheme 5.4.[78] This reaction is more specifically referred to as the Pictet-Spengler reaction[79] when used to synthesize isoquinoline systems. In the example shown in Scheme 5.4, this approach gave tetrahydropseudoberberine **158** as the product and not "tetrahydroberberine" **159** (*i.e.*, canadine).[78a] Compound **158** is the isomer which was



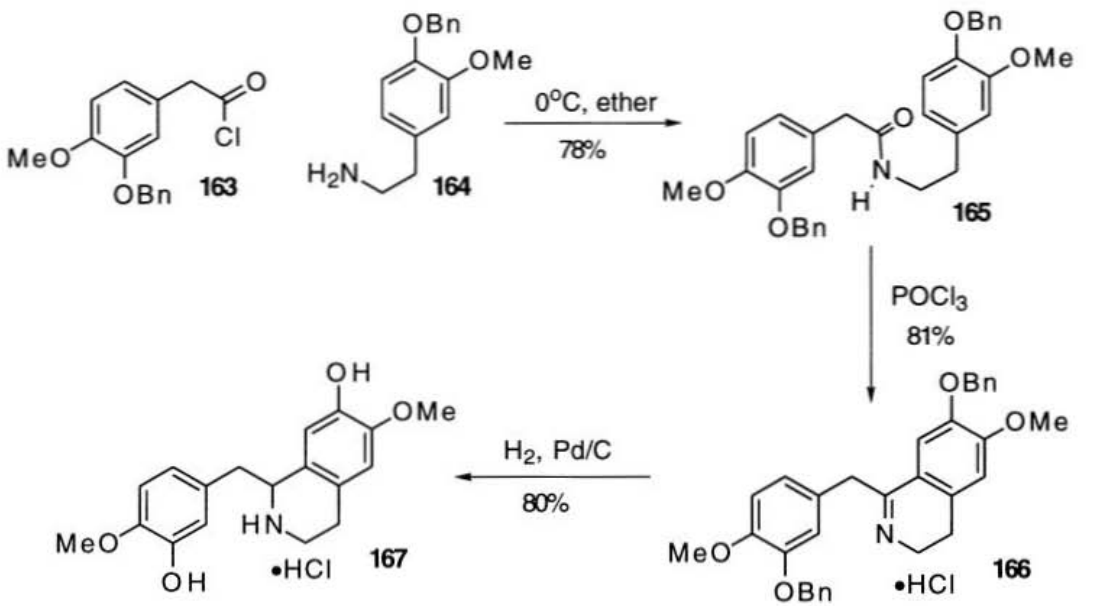
Scheme 5.4 Pictet-Spengler reaction in protoberberine synthesis[78a]

expected to be produced in this reaction because compound **159**, canadine, is more sterically crowded about the D-ring than is **158**. However, when the D-ring was a phenol as in **160** (Scheme 5.5), a more equal mixture was obtained due to the increased activation of the position *ortho* to the hydroxyl group.[80] Thus, the unexpected and more sterically crowded isomer **161** was more readily produced. The hydroxyl group in the A-ring had no effect on the reaction because the same substitution pattern in the products was



Scheme 5.5 Effect of pH and phenol substituent on Pictet-Spengler reaction[80]

obtained when an alkoxy rather than a hydroxyl group was present. The ratio of products depends on the acidity of the reaction mixture. At pH 6.3, the ratio of scoulerine **161** to coreximine **162** is 2:1,[80a] but at pH 7, in the presence of formaldehyde and no acid, only **162** was reported.[80b] To apply this methodology to jatrorrhizine, a separation of isomers would be required and the phenol required in the D-ring to obtain the 9,10-substitution pattern would need to be methylated in the desired product by diazomethane or by base followed by MeI. In addition, compounds **157** and **160** were obtained by the process outlined in Scheme 5.6.[81] The acid chloride **163** and the amine **164** were reacted to give the amide **165**. Alternatively, the analogous carboxylic acid or ester have been fused with the amines to give the required amides. The amide was then subjected to a Bischler-Napieralski reaction (**165** → **166**) followed by catalytic hydrogenation of the resultant

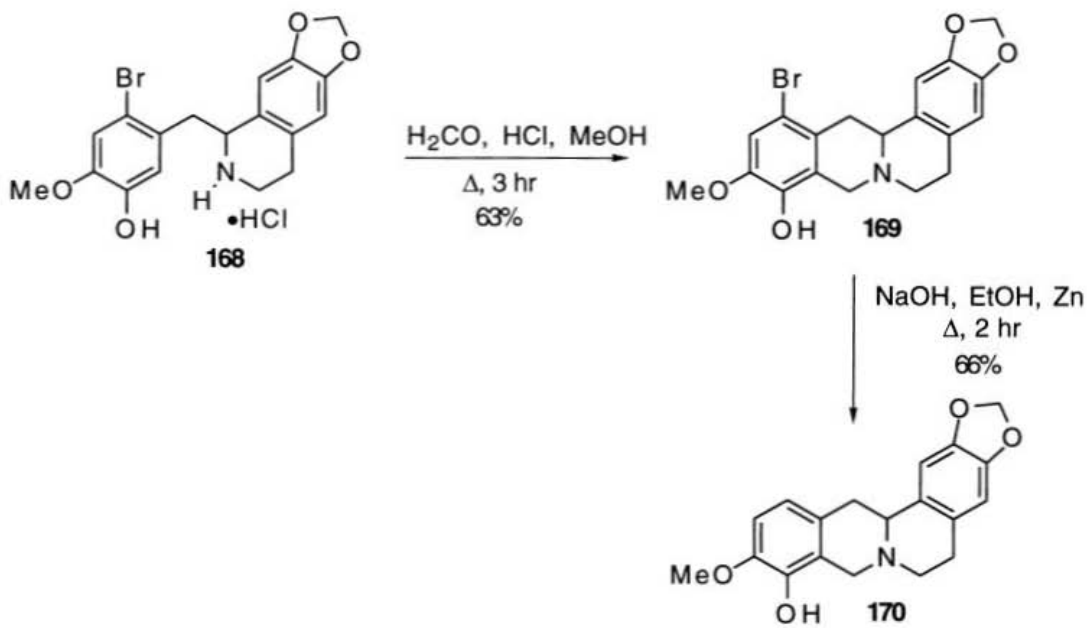


Scheme 5.6 Synthesis of compound **167** [81]

dihydroisoquinoline salt **166** and hydrogenolysis of the benzyl ethers.[81a] Although the sequence depicted in Scheme 5.6 proceeded with good yields, a number of dehydrating

agents other than $POCl_3$ have been used for the Bischler-Napieralski step,[84] and determining the optimum reagent and reaction conditions can be difficult.[84] These factors made this approach less than appealing for the synthesis of jatrorrhizine.

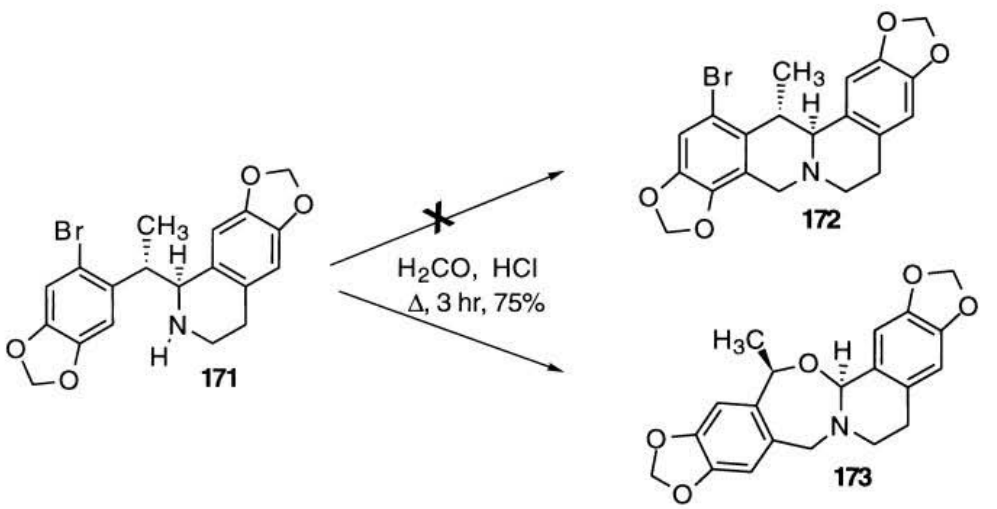
A more regiospecific approach to the synthesis of the desired 9,10-D-ring substitution pattern *via* the Pictet-Spengler reaction is to block one of the two possible sites of ring closure with a bromine atom.[82] In this way, 12-bromonandinine **169** was synthesized from **168** as outlined in Scheme 5.7.[82a] The bromine atom is then removed by standard methods, such as $LiAlH_4$, hydrogenolysis with palladium on carbon or by zinc metal and hydroxide, as in this case, to give the tetrahydroprotoberberine



Scheme 5.7 Bromine as a protecting group in the Pictet-Spengler reaction[82a]

nandinine **170**. The presence of the bromine atom tends to lower the yields for the Pictet-Spengler reaction as bromine deactivates the aromatic ring. As in the Pictet-Spengler reaction depicted in Scheme 5.5, this reaction occurs by the contribution of the hydroxyl group *ortho* to the site of cyclization. Therefore, subsequent methylation of the phenolic

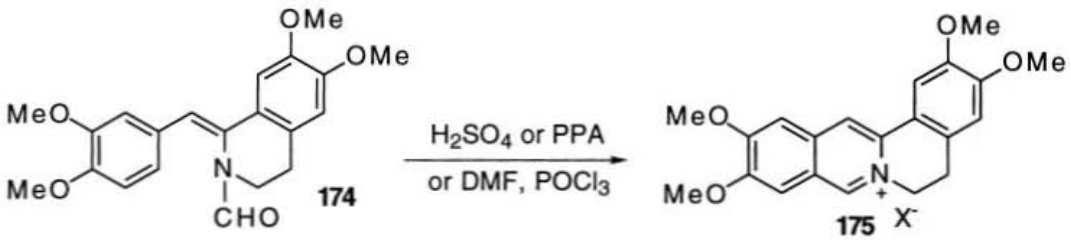
product would be required if this approach was taken towards jatrorrhizine. In addition, the use of bromine as a protecting group has failed in at least one case, and the expected ring closure of **171** to **172** (Scheme 5.8) did not occur.[83] Instead, the benzoxazepino-isoquinoline **173** was confirmed as the product by x-ray crystallography. The failure of



Scheme 5.8 Failure of bromine directed Pictet-Spengler reaction[83]

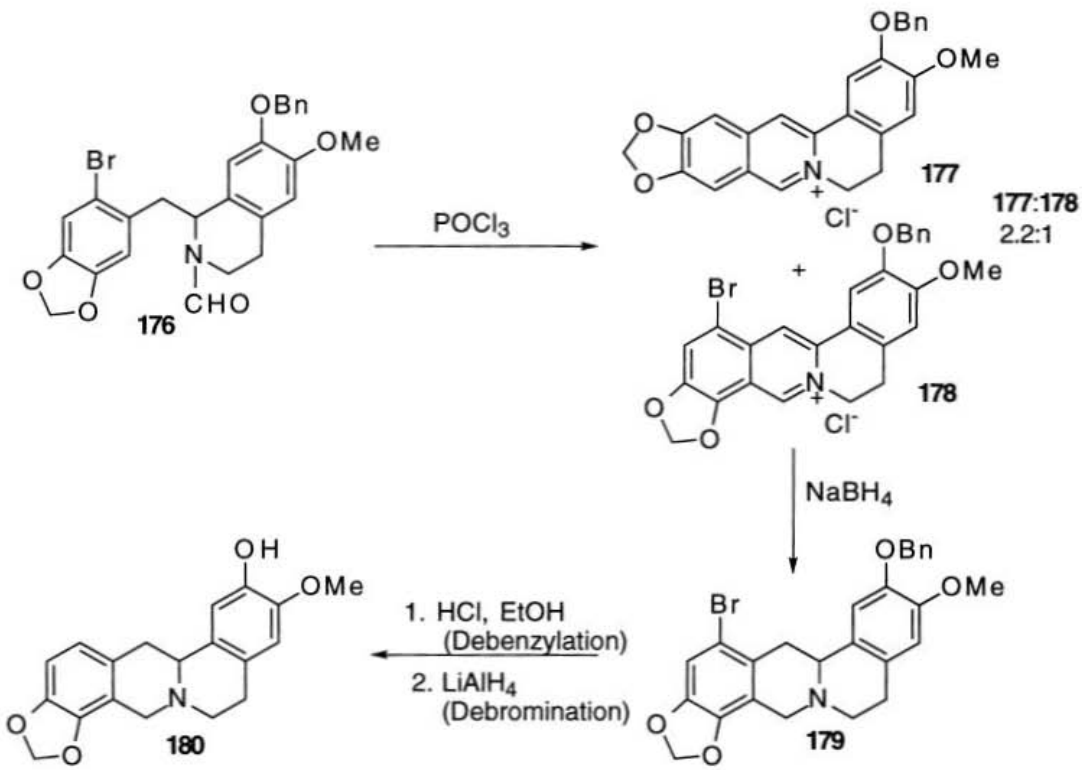
this reaction to give the desired compound may in part have been due to the absence of an hydroxyl activating group as in Schemes 5.5 and 5.7. However, the methodology has been shown to fail and furthermore it was hoped that the use of bromine as a protecting group could be avoided as this would add two steps to the total synthesis (bromination and subsequent debromination). Therefore, this approach was not pursued for the synthesis of jatrorrhizine.

The C-ring of the protoberberines has also been closed by the Bischler-Napieralski reaction,[84] as outlined in Scheme 5.9, to give the aromatic protoberberine **175** directly.[85] This reaction is highly regioselective but results in the exclusive formation of



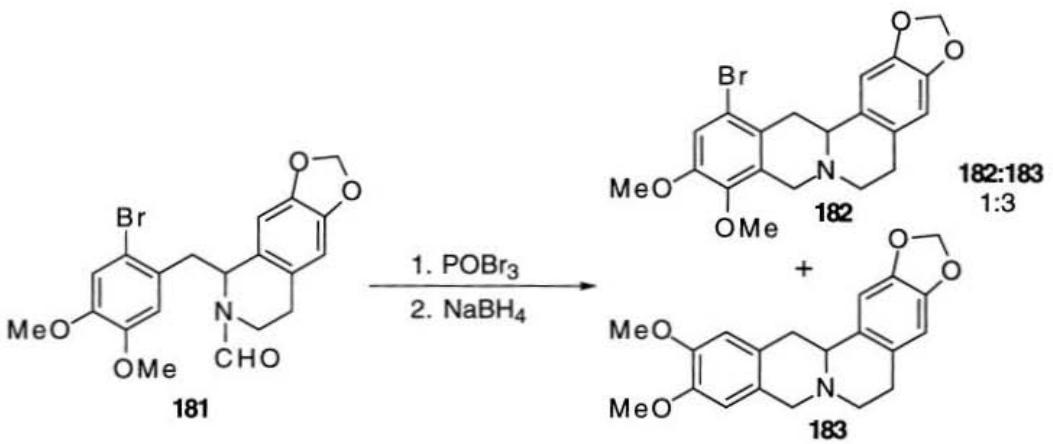
Scheme 5.9 Closure of the C-ring by a Bischler-Napieralski reaction[85]

the 10,11-substituted protoberberines not the 9,10 substitution pattern required for jatrorrhizine. Bromine protection was attempted in the Bischler-Napieralski reaction to direct the regiochemical outcome as outlined in Scheme 5.10 for the synthesis of cheilanthifoline **180**.[86a] In this case, the enamine double bond present in **174** is not present in **176** but the aromatic product is still obtained under the reaction conditions.



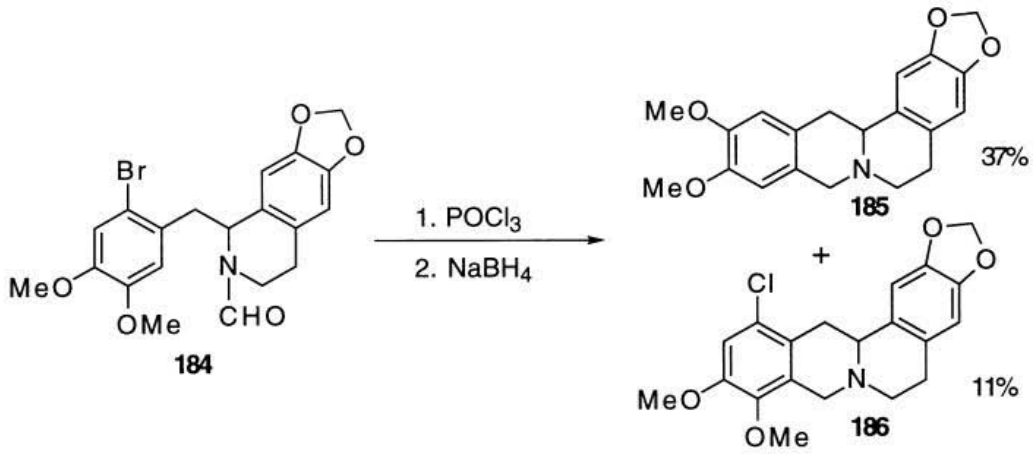
Scheme 5.10 Attempted bromine protection in Bischler-Napieralski reaction[86a]

These unsaturated protoberberines **177/178** were then individually reduced to the tetrahydroprotoberberines by borohydride reduction. The bromine atom has proven to be less effective as a directing group here than in the Pictet-Spengler methods. The ring closure is directed to give the 10,11-substitution pattern **177** in the product so strongly that the bromine atom used as a directing group tends to be eliminated. This approach has resulted in more extensive removal of the bromine atom to provide a mixture of the expected 12-bromocanadine **182** and the 10,11-substituted tetrahydro-ψ-berberine **183** in a 1:3 mixture as in Scheme 5.11.[86b] Complete replacement of the bromine atom has also



Scheme 5.11 Failure of the bromine-directed Bischler-Napieralski reaction[86b]

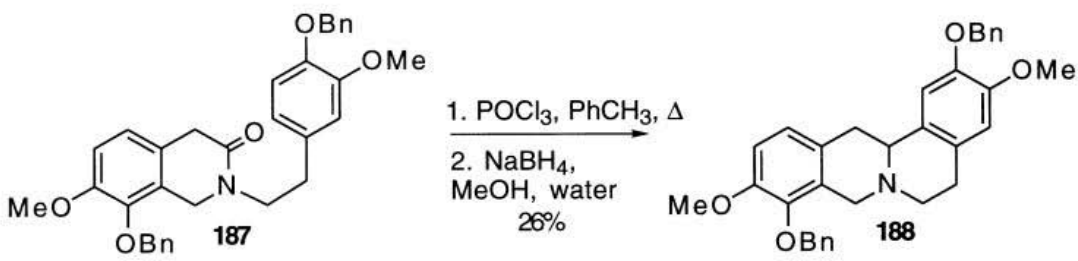
been observed with a different dehydrating agent. The reaction outlined in Scheme 5.12 was first reported to give only the debrominated compound **185**.[86c] Reinvestigation of this reaction by another group[86b] indicated, as outlined in Scheme 5.12, that the debrominated **185** was obtained as well as **186** in which the bromine atom was



Scheme 5.12 Failure of bromine protection[86b]

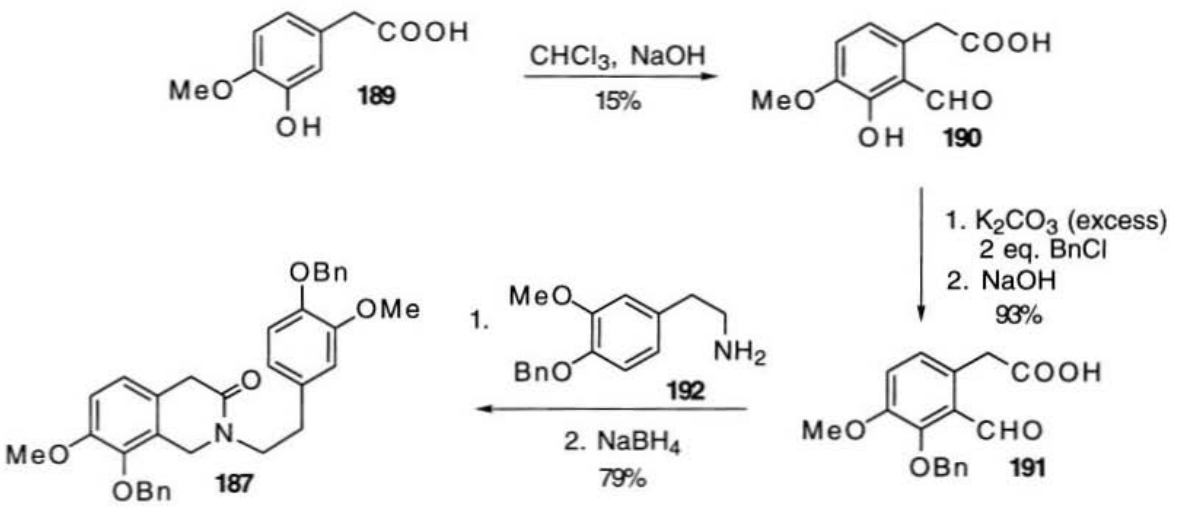
replaced by a chlorine atom. All attempts to replace this chlorine atom with hydrogen failed, further demonstrating the difficulties that can be encountered with these types of reactions. Again, to avoid the possibilities that a separation of isomers may be required and that a stalwart chlorine may become incorporated in the product as in **186**, this approach was not pursued for the synthesis of jatrorrhizine.

Variants of the Bischler-Napieralski reaction have most often been used to close the B-ring of the protoberberine skeleton as in Scheme 5.13.[80a] This sequence does indeed provide the substitution pattern required for jatrorrhizine by fixing the D-ring



Scheme 5.13 Bischler-Napieralski reaction in closure of B-ring[80a]

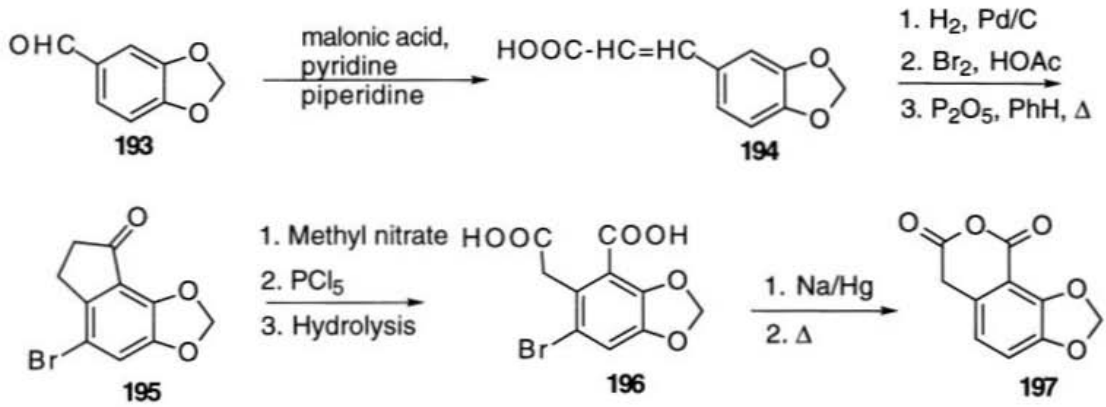
substitution pattern early in the synthesis but in poor yield (26%) based on **187**.[80a] Although this yield is considerably lower than the typical yields for this reaction, it serves to demonstrate the variation in results that is often observed in the Bischler-Napieralski reaction.[84] The synthesis of **187** itself is an additional weakness of this methodology. Obtaining this 1,2,3,4-tetrasubstituted pattern required for the D-ring of the protoberberine by classical methods is typically inefficient for compounds used in all of the variants of the Bischler-Napieralski methodology. For example, compound **190** was obtained *via* a Reimer-Tiemann reaction in low yield (15%) followed by protection of the phenolic hydroxyl (Scheme 5.14). The aldehyde **191** was then condensed with the amine **192** to give an imine, which was reduced with borohydride resulting in the tricyclic



Scheme 5.14 Synthesis of 1,2,3,4 tetrasubstituted compound for Bischler-Napieralski reaction[80a]

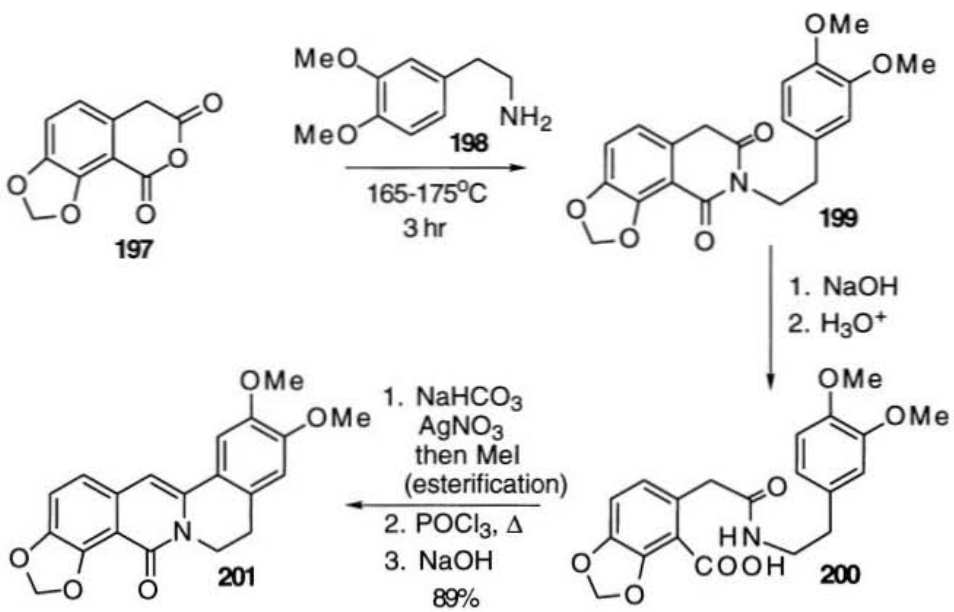
lactam **187** in only 11% yield in three steps from **189**. This overall yield is very low for three steps so was not considered efficient for the present synthesis.

Another approach to this substitution pattern involves the use of bromine as a protecting group to direct the site of reaction as outlined in Scheme 5.15 to give the



Scheme 5.15 Synthesis of 1,2,3,4 tetrasubstituted compound for Bischler-Napieralski reaction[88a]

homophthalic anhydride **197**.[88a] This material was then used in a Bischler-Napieralski reaction as outlined in Scheme 5.16 to give the oxyprotoberberine **201**. These

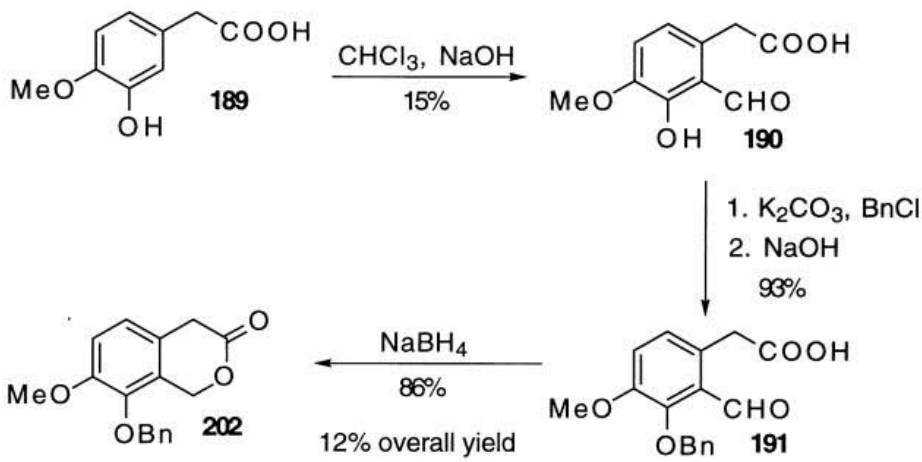


Scheme 5.16 Use of homophthalic anhydride **197** in protoberberine synthesis[88b]

compounds can then be reduced by standard methods, such as $LiAlH_4$, to the tetrahydro-protoberberines.[88c] Few yields were reported for the series of reactions in Schemes 5.15

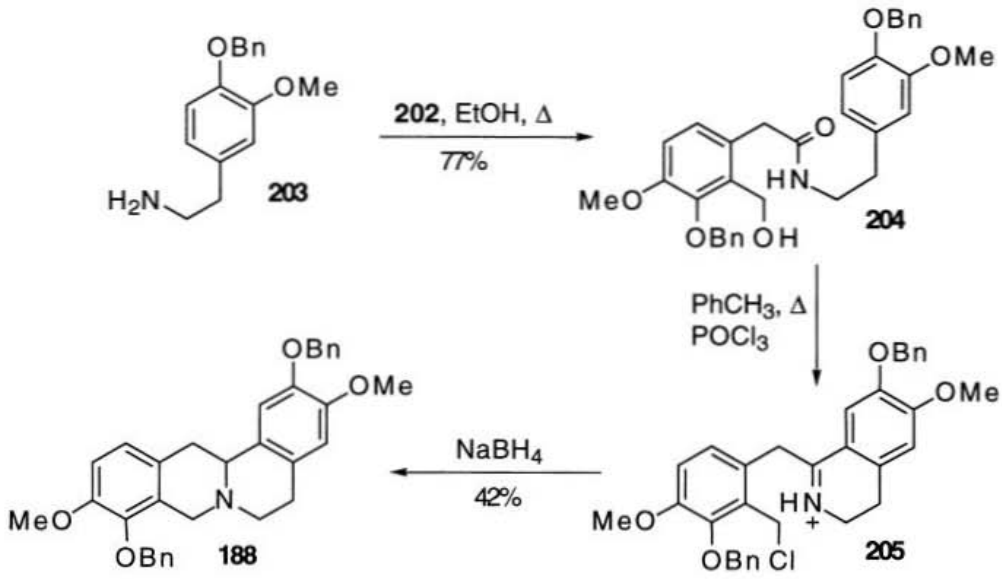
and 5.16, but the synthesis of **197** involves far too many steps for it to be useful synthetically.

Alternatively, a lactone (such as 8-benzoxy-7-methoxyisochroman-3-one **202**) can be used instead of the homophthalic anhydrides **197** to give the tetrahydroprotoberberines directly.[80a, 89-91] However, the classical approaches to these 1,2,3,4-tetrasubstituted lactones offer no significant advantage as these are almost as inefficiently synthesized as the homophthalic anhydrides. In the first case (Scheme 5.17),[80a] the same low yield (15%) Reimer-Tiemann reaction described in Scheme 5.14 was used to formylate the aromatic ring *ortho* to the phenolic hydroxyl group, and the phenol **190** was subsequently benzylated as described in Scheme 5.14. The formyl substituent was then converted to a



Scheme 5.17 Classical approach to 1,2,3,4-tetrasubstituted lactones[80a]

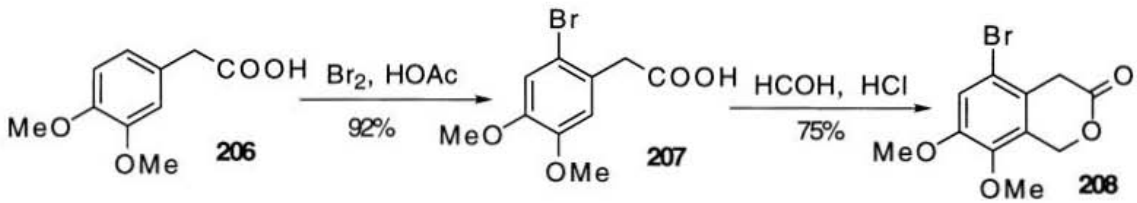
hydroxymethyl group by borohydride reduction with simultaneous lactone **202** formation. Because of the low yield obtained in the first step, the overall yield for this sequence is only 12%. Lactone **202** was then used in the synthesis of **188** by the sequence outlined in Scheme 5.18.[80a] The lactone **202** was heated with amine **203** to give the amide **204**,



Scheme 5.18 Use of lactone **202** in tetrahydroprotoberberine synthesis[80a]

which was treated with phosphorus oxychloride to close the B-ring to the dihydro-isoquinoline salt **205**. Borohydride reduction of the dihydroisoquinoline ring resulted in an intramolecular ring closure between the nitrogen and the chloromethyl group, which was produced by the action of phosphorus oxychloride.

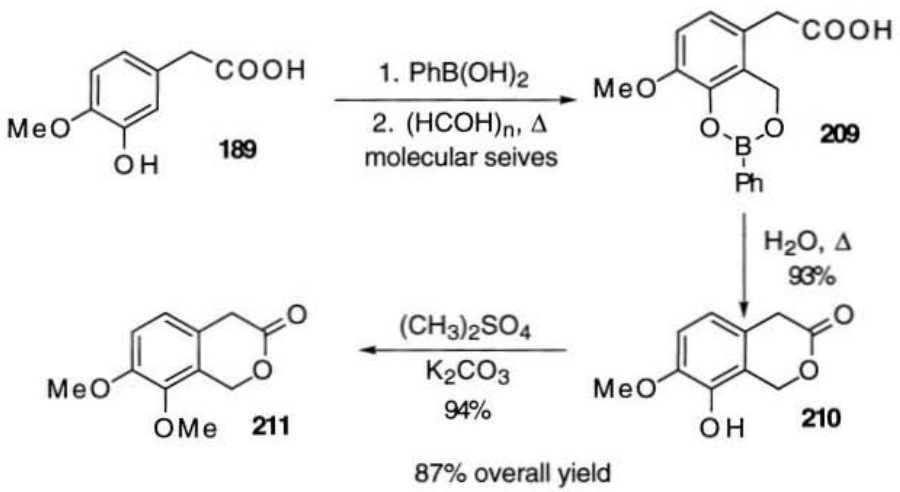
An alternative approach to the 1,2,3,4-tetrasubstituted lactones is once again the use of bromine as a protecting group as shown in Scheme 5.19.[89b] 3,4-Dimethoxy-phenylacetic acid **206** was brominated and then converted to 5-bromo-7,8-dimethoxy-isochroman-3-one **208** by the introduction of an hydroxymethyl group in the required



Scheme 5.19 Synthesis of 1,2,3,4-tetrasubstituted lactones *via* bromine protection[89b]

position of the aromatic ring. Although the isochromanone **208** was obtained in good yield from **206** (69% overall), we hoped that the use of bromine as a protecting group would not be required because, as previously mentioned, this would add two steps to the total synthesis (bromination with subsequent debromination).

The synthesis of these tetrasubstituted lactones was greatly improved by the use of phenylboronic acid and paraformaldehyde to introduce a hydroxymethyl group adjacent to the phenolic hydroxyl in much better yield (Scheme 5.20).[90] The hydroxyl group is required for the formation of the intermediate boronate **209**, which is not isolated, and the isochromanone **210** is obtained directly from **189** in excellent yield (93%). This has been



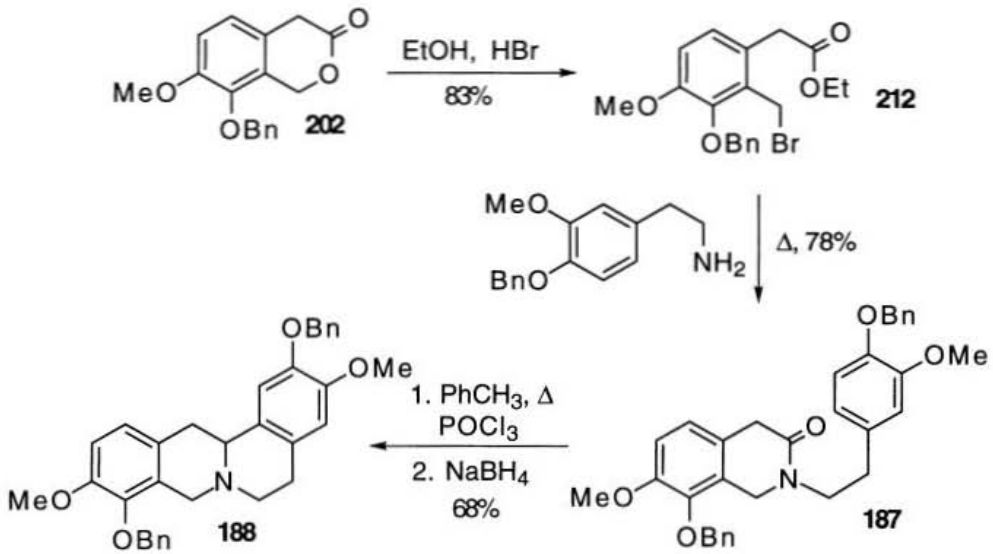
87% overall yield

Scheme 5.20 Improved approach to 1,2,3,4-tetrasubstituted lactones[90]

followed by methylation or benzylation of the phenol to obtain the desired substitution pattern for the protoberberines. The resultant lactones can then be used in total syntheses as in Scheme 5.18.

A modification of the lactone approach to the protoberberine alkaloids has also been developed.[91] The lactones have been converted to so-called "bromoesters" **212** by the action of ethanolic hydrobromic acid (Scheme 5.21). The bromoesters are then

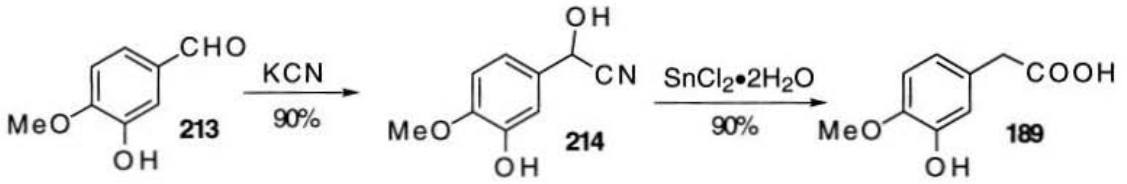
reacted with the appropriate amine to give a tricyclic amide **187** which, as in Scheme 5.13, is treated with phosphorus oxychloride to complete the B-ring followed by



Scheme 5.21 Use of bromoester **212** in tetrahydroprotoberberine synthesis[91a,b]

borohydride reduction to **188**. The yield for this ring closure reaction (**187** → **188**) is more typically observed in the Bischler-Napieralski reaction than the much lower yield observed in Scheme 5.13. This "bromoester" modification results in a slight improvement in the yield of **188** over the yield obtained in Scheme 5.18, giving a 44% yield *via* the "bromo-ester" rather than a 32% yield directly from the lactone.[80a]

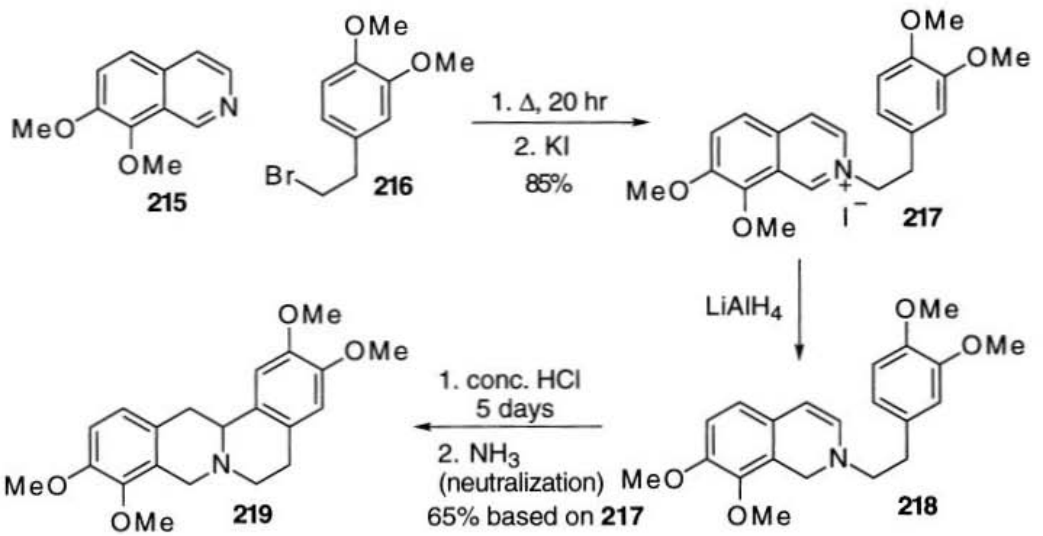
The shortcoming of all of these lactone syntheses is that the starting material in each of these approaches is not commercially available but is synthesized from isovanillin **213** by the steps outlined in Scheme 5.22.[92] Although the yield for each step is excellent (90% for each step), the sequence requires the use of the highly toxic potassium cyanide



Scheme 5.22 Synthesis of (3-hydroxy-4-methoxyphenyl)acetic acid **189**[92]

followed by hydrolysis of the cyanohydrin **214** to the corresponding carboxylic acid **189**. The toxicity of the cyanide was not the primary concern, but the subsequent problems that have been encountered with the lactone routes outlined here did not justify its use.

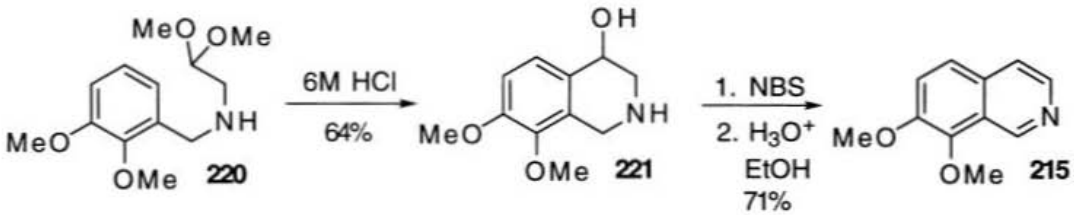
An alternative route to the 9,10-substituted protoberberines has been to start with an isoquinoline with the required substitution pattern. Perhaps the simplest approach to the protoberberine alkaloids uses such an intermediate and involves the closure of the B-ring *via* a dihydroisoquinoline intermediate **218** (Scheme 5.23).[88c,93] This reaction is



Scheme 5.23 Protoberberine synthesis *via* dihydroisoquinoline intermediate **218**[93a]

accomplished with a mineral acid, such as concentrated HCl,[88c,93a] or a mixture of phosphoric and formic acids,[93b,c] in moderate yield from **218**, but it is the synthesis of the

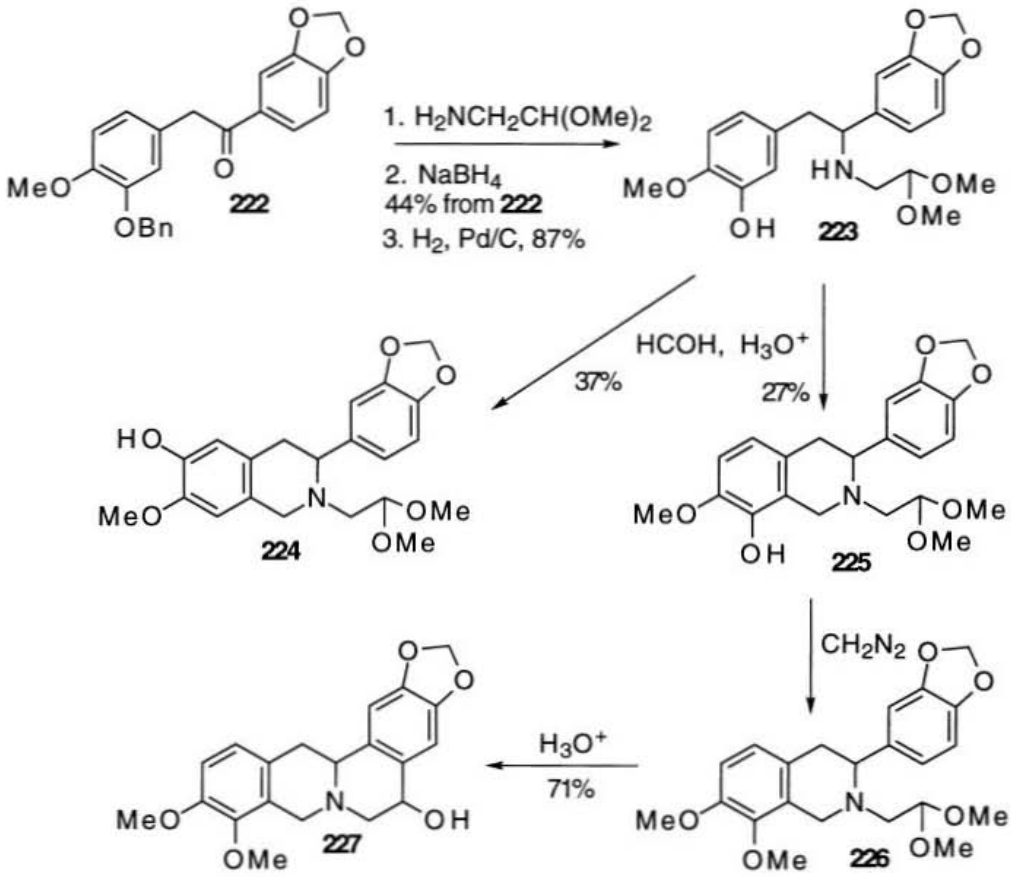
isoquinoline **215** that is the inefficient step. Compound **215** is obtained by the Pomerantz-Fritsch reaction (Scheme 5.24),[94] which is a ring closure reaction of the acetal **220** in acid to give the 7,8-dimethoxyisoquinoline **215**.[93a] This reaction is regiospecific for the required substitution pattern because there is only one site at which the ring closure may occur. Although this compound is obtained in moderate overall yield (45%) from readily available starting materials (2,3-dimethoxybenzaldehyde and aminoacetaldehyde dimethyl acetal followed by hydrogenation of the resultant imine), we



Scheme 5.24 Synthesis of isoquinoline **215** *via* Pomerantz-Fritsch reaction[93a]

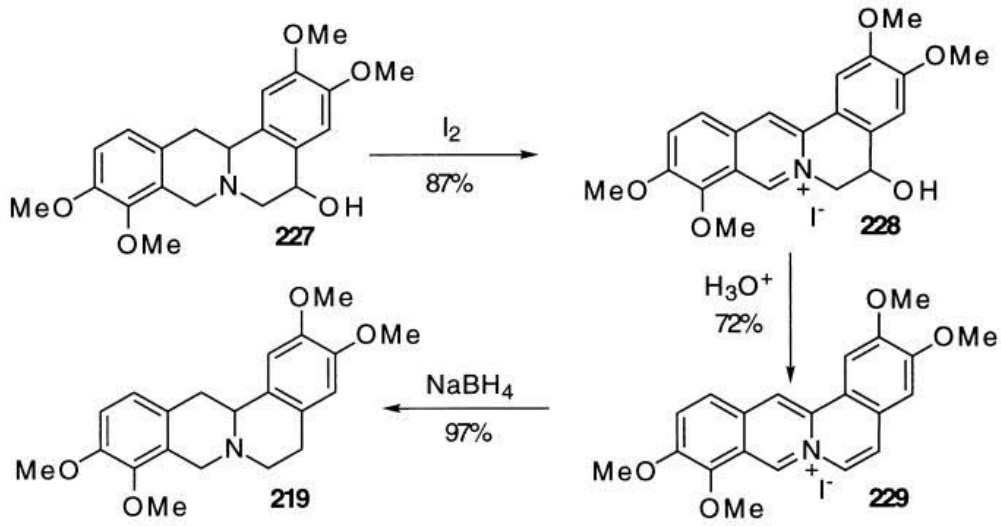
hoped that the isoquinoline portion could be synthesized more efficiently and in better yield than in this procedure.

The Pomerantz-Fritsch reaction has also been used as the final step in the synthesis of the protoberberine skeleton (Scheme 5.25).[95] The 9,10-substitution pattern of the protoberberine is obtained by the *ortho*-hydroxyl activated Mannich condensation of **223** to **225** (as previously discussed) which, in this synthesis, gives a mixture of the 10,11- and the 9,10-substitution pattern in a ratio of 1.3:1 (**224**:**225**). In this report, the Pomerantz-Fritsch reaction results in the 5-hydroxytetrahydroprotoberberine **227**, which can be converted to berberastine iodide **228**[95b] by treating with iodine to aromatize the C-ring. These compounds have been reacted with acid to eliminate water and give the fully aromatic dehydroprotoberberine **229** followed by reduction with sodium borohydride or catalytic hydrogenation (Scheme 5.26) to the tetrahydroprotoberberine **219**.[95b] The lack



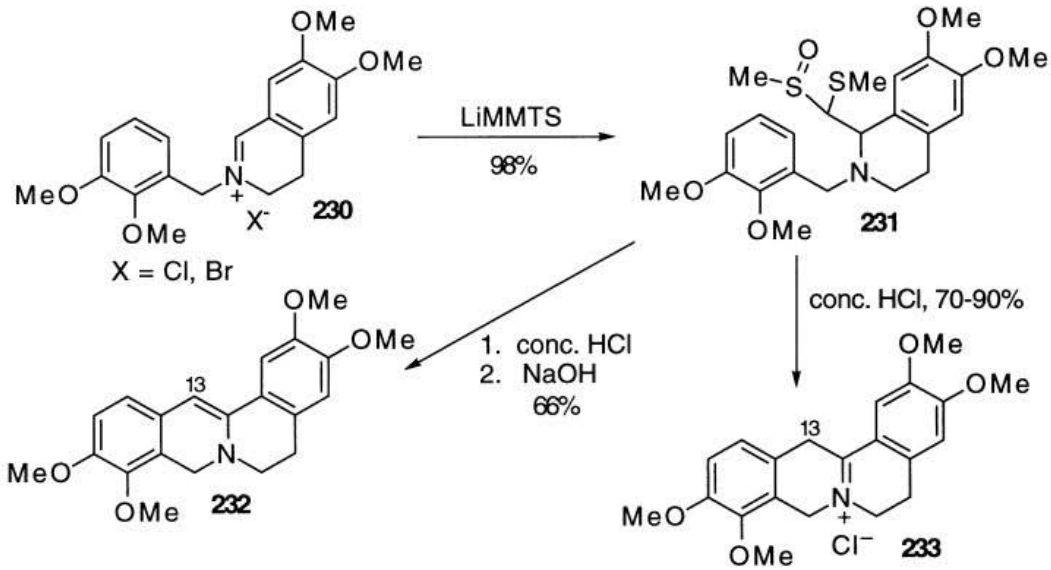
Scheme 5.25 Use of Pomerantz-Fritsch reaction in protoberberine synthesis[95a]

of selectivity of the Mannich reaction for the 9,10-substitution pattern (**223** → **225**) and the steps required to convert the 5-hydroxyprotoberberine to the protoberberine (Scheme 5.26) made this sequence seem inadequate for jatrorrhizine.



Scheme 5.26 Conversion of 5-hydroxyprotoberberine to tetrahydroprotoberberine[95b]

One approach to the protoberberine alkaloids that can be considered as the sulfur analog of the Pomerantz-Fritsch reaction is outlined in Scheme 5.27.[96] This reaction

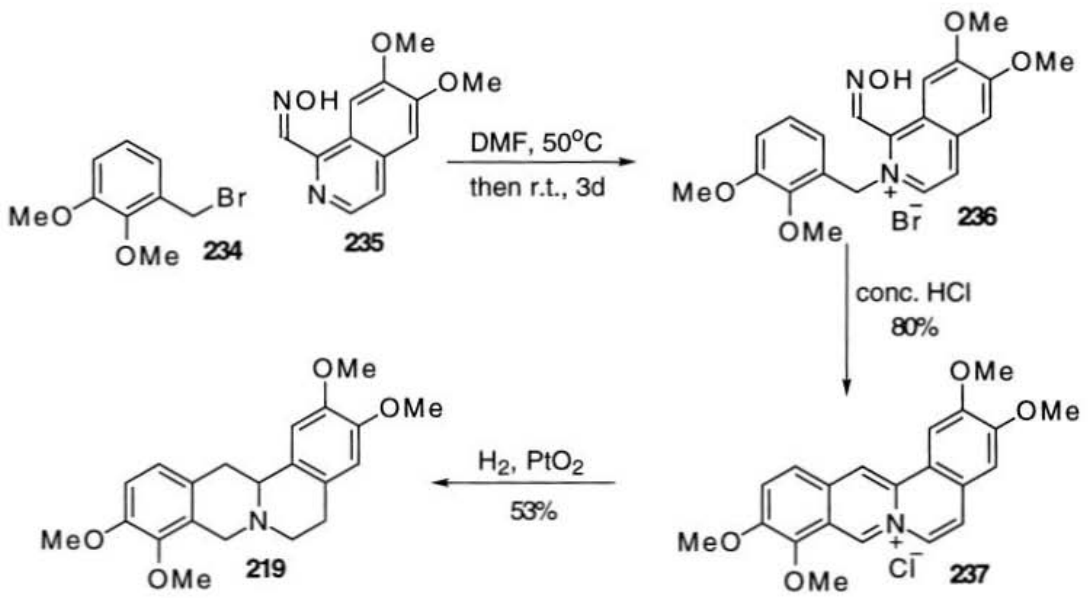


Scheme 5.27 Synthesis of protoberberines *via* Pomerantz-Fritsch type reaction[96]

results in the 9,10-substitution pattern because, as in Scheme 5.24, there is only one site

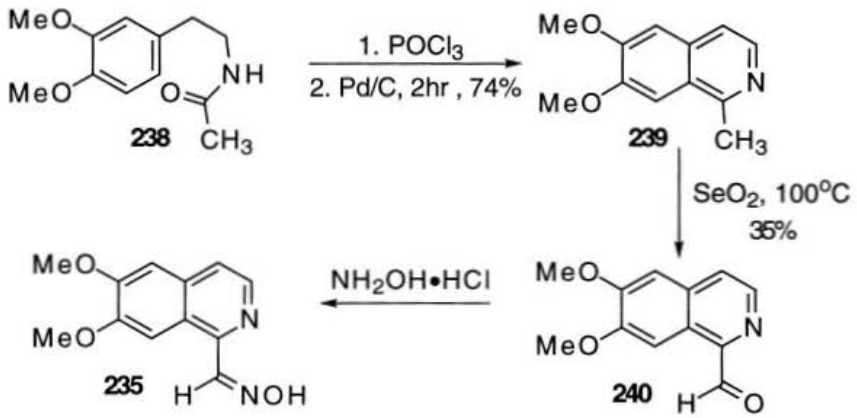
available for the ring closure to occur. Carbon 13 of the protoberberine skeleton was introduced to the dihydroisoquinoline portion of **230** *via* the lithium salt of methyl methylthiomethylsulfoxide (MMTS). The ring closures were accomplished by heating in concentrated HCl, and compounds **232** and **233** were individually reduced by $NaBH_4$ to the tetrahydroprotoberberines. The C-ring of each of these compounds could also be oxidized directly to the aromatic protoberberine as in Scheme 5.3 rather than reduced. In this report, one of the tetrahydroprotoberberines was aromatized in the C-ring by iodine in 95% yield.

Another strategy that is very similar to this involves the use of an isoquinoline-1-carboxaldehyde oxime **235** as in Scheme 5.28.[97] The substitution pattern in the D-ring is again specific for the 9,10-substitution pattern based on a readily available starting material **234**, which gives rise to only one site available for the final ring closure. Quaternization of the isoquinoline **235** and the bromide **234** gives a salt **236**, which is cyclised in acid to the dehydroprotoberberine **237**. This is then reduced by a standard



Scheme 5.28 Protoberberine synthesis *via* isoquinoline-1-carboxaldehyde oxime[97a]

method to the tetrahydroprotoberberine.[97a] The 53% yield reported for the catalytic hydrogenation is very low compared to other reactions of this type[77c] and no explanation was given for this result. The drawback of this approach is the synthesis of the isoquinoline-1-carboxaldehyde **235** (Scheme 5.29), which is obtained in poor yield (35%) by selenium dioxide oxidation of the 1-methylisoquinoline **239**.[97a,b] The aldehyde

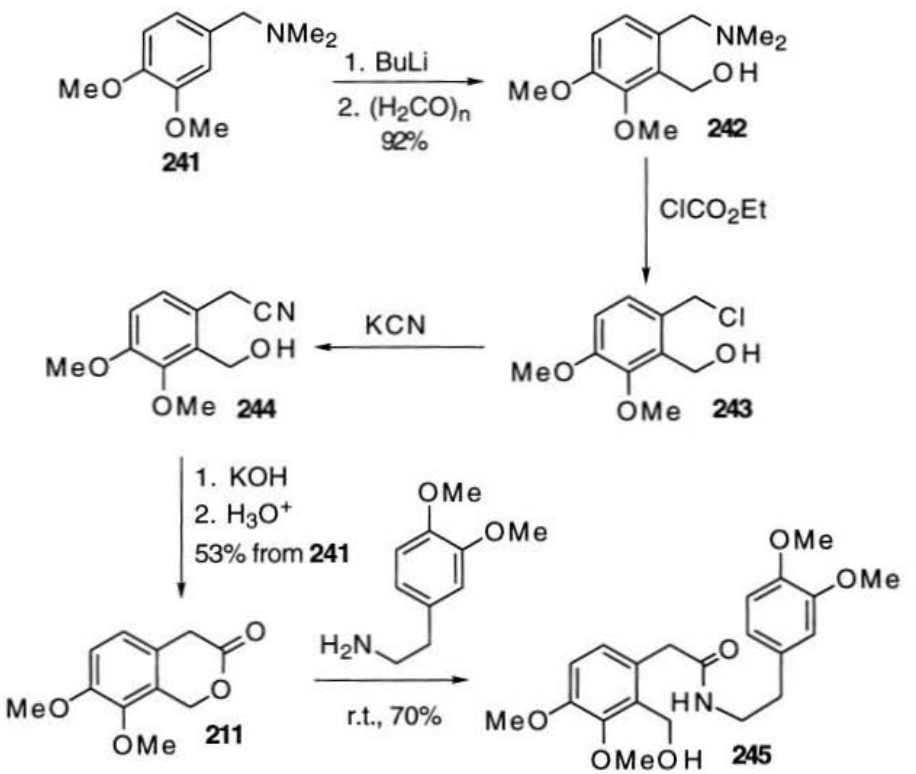


Scheme 5.29 Synthesis of isoquinoline-1-carboxaldehyde oxime **235**[97a]

240 is then converted to the oxime **235** by hydroxylamine hydrochloride for use in the protoberberine synthesis. Initially, the aldehyde **240** was used in the total synthesis,[98] but the yields were greatly improved from 30% to 80% by the use of the oxime **235**.

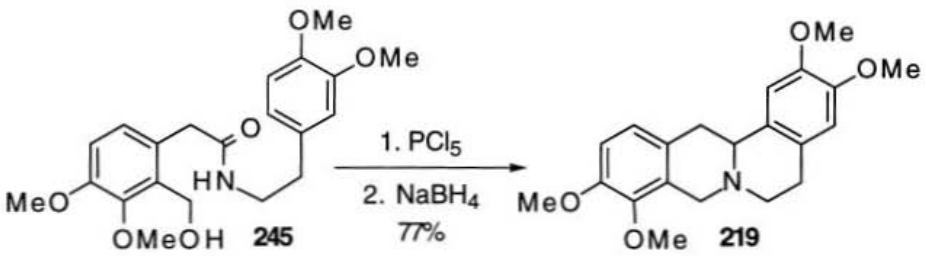
The syntheses discussed to this point have, for the most part, been classical approaches to the protoberberine alkaloids, and many of the key reactions have been accomplished in low and/or variable yield under the same experimental conditions. The required 1,2,3,4-tetrasubstituted starting materials that have proven to be the inadequacy of past attempts at protoberberine syntheses may be more readily obtained by more modern synthetic strategies. Aromatic lithiation reactions[99] have provided entry into a number of these sterically crowded aromatic compounds, which have either not been synthesized or are synthesized by lengthy routes (for example see Scheme 5.13). One

approach that utilizes this metalation methodology is outlined in Scheme 5.30.[100] *Ortho*-lithiation of the readily available *N,N*-dimethyl-3,4-dimethoxybenzylamine **241** occurred exclusively at the 2-position, and addition of paraformaldehyde to the anion resulted in the hydroxymethyl compound **242**. The next three steps were done without isolation of the intermediates. Treatment of the dimethylamino compound **242** with ethyl chloroformate resulted in the chloride **243**, which was converted to the nitrile **244** by the addition of potassium cyanide. Basic hydrolysis to the corresponding acid followed by acidic workup gave the isochroman-3-one **211** in fair overall yield. As outlined in



Scheme 5.30 *Ortho*-lithiation approach to protoberberine alkaloids[100]

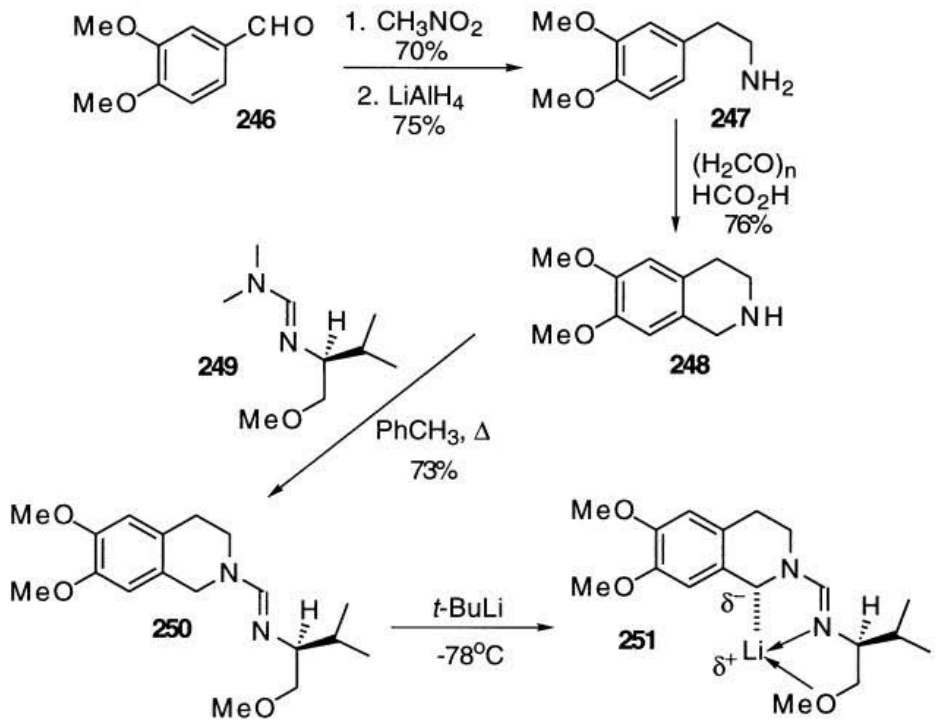
Schemes 5.30 and 5.31, this compound was then used in the same manner as previously synthesized lactones (Scheme 5.18). Addition of the 3,4-dimethoxyphenethylamine resulted in the amide **245**. This was subjected to cyclodehydration, in this case by



Scheme 5.31 Cyclodehydration of **245** to tetrahydroprotoberberine **219**

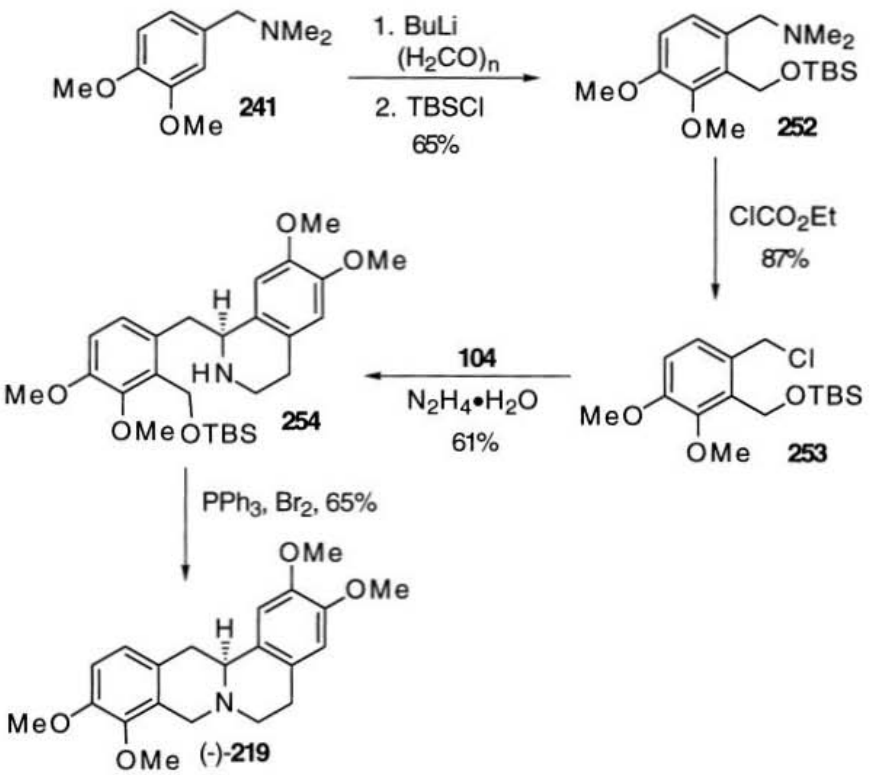
phosphorus pentachloride, followed by borohydride reduction to the tetrahydroprotoberberine **219**. Although the tetrahydroprotoberberines are obtained in acceptable overall yield (in this example, 28% from the amine **241**), the route to the isochroman **211** is not particularly efficient.

Another aromatic lithiation approach is outlined in Scheme 5.33, and it utilizes the chiral formamidine synthesized in Scheme 5.32.[101] Condensation of 3,4-dimethoxybenzaldehyde (veratraldehyde) **246** with nitromethane and $LiAlH_4$ reduction of the resultant nitrostyrene gave the phenethylamine **247** in fair overall yield.[102] A Pictet-Spengler reaction gave the expected 6,7-dimethoxytetrahydroisoquinoline **248** in good yield. The chiral auxiliary **249** was introduced into the strategy to give compound **250**. The chiral formamidine introduced in compound **250** was used to direct the deprotonation of the isoquinoline ring and provide the anion **251** selectively. The other portion of the protoberberine was synthesized by a similar method to that outlined in Scheme 5.30.



Scheme 5.32 Synthesis of chiral formamidine for *ortho*-lithiation reaction[101,102]

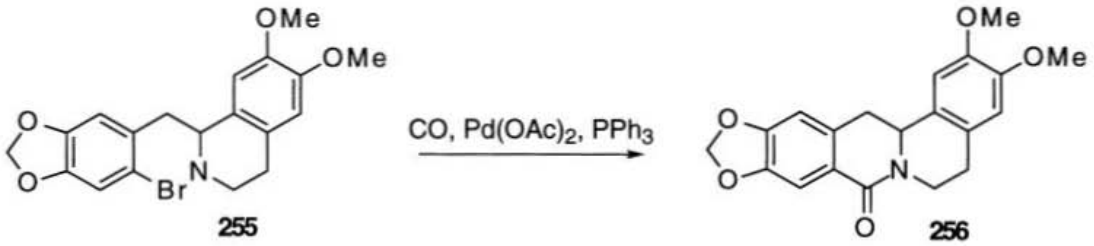
Ortho-lithiation of **241** and introduction of the hydroxymethyl group *via* paraformaldehyde were accomplished in the same manner. However, in this case the final goal was not a lactone, so the alcohol was protected as the *t*-butyldimethylsilyl ether followed by conversion of the dimethylamine group to the chloride **253**. This was attacked by the anion **251** and then the chiral auxiliary was removed by hydrazine hydrate to give **254** stereoselectively. The tetrahydroprotoberberine **219** was completed by conversion of the silyl ether to the bromide, intramolecular closure of the C-ring and



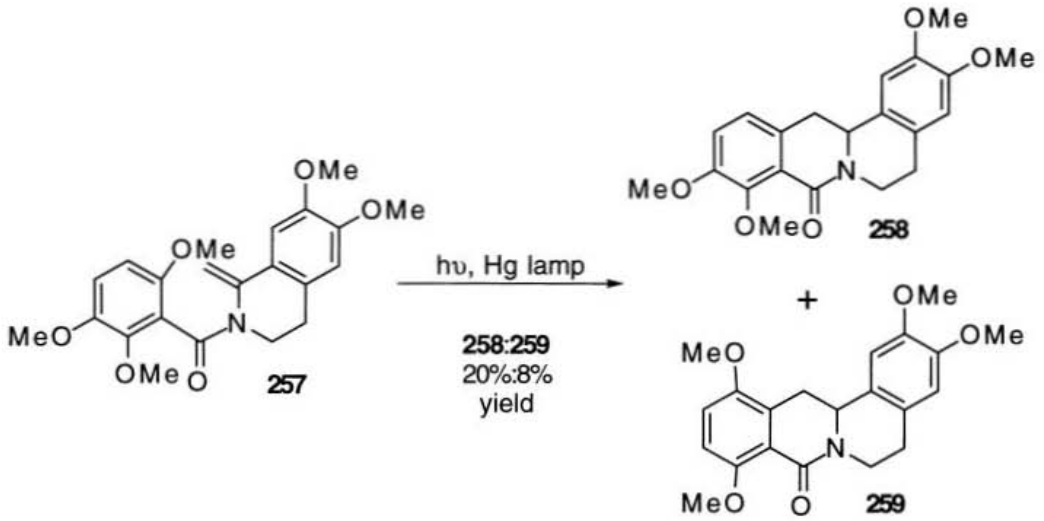
Scheme 5.33 Chiral *ortho*-lithiation approach to protoberberine synthesis[101]

neutralization of the HBr produced in the reaction. Thus, the total asymmetric synthesis of (-)-tetrahydropalmatine **219** was accomplished in 22% yield and 88% enantiomeric excess (94:6 mixture of enantiomers). As jatrorrhizine is aromatic in the C-ring, this chiral approach is not necessary for the purpose of our study. However, this synthesis of **219** demonstrates the utility of aromatic lithiation reactions in the synthesis of 1,2,3,4-tetrasubstituted compounds and their potential for use in the synthesis of a number of the protoberberine alkaloids.

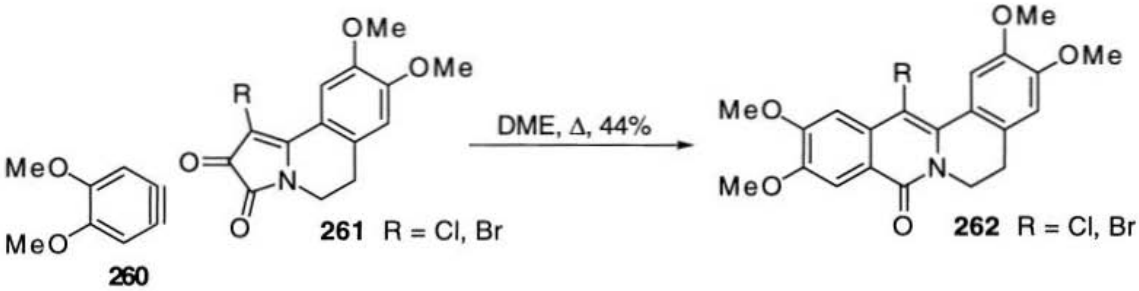
Other approaches to the protoberberine alkaloids that have appeared include palladium catalysed insertion of carbon monoxide (Scheme 5.34),[103] cycloaddition reactions by photolysis (Scheme 5.35)[104] and *via* benzyne (Scheme 5.36)[105] or benzocyclobutene (Scheme 5.37)[106] intermediates.



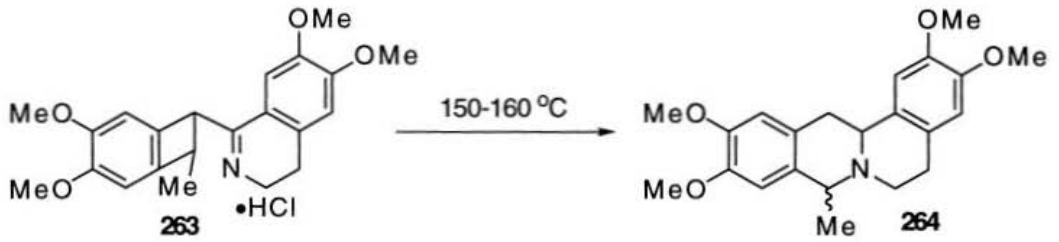
Scheme 5.34 Synthesis of protoberberines *via* carbon monoxide insertion[103]



Scheme 5.35 Synthesis of protoberberines *via* photolysis[104b]



Scheme 5.36 Synthesis of protoberberines *via* benzyne intermediate[105]



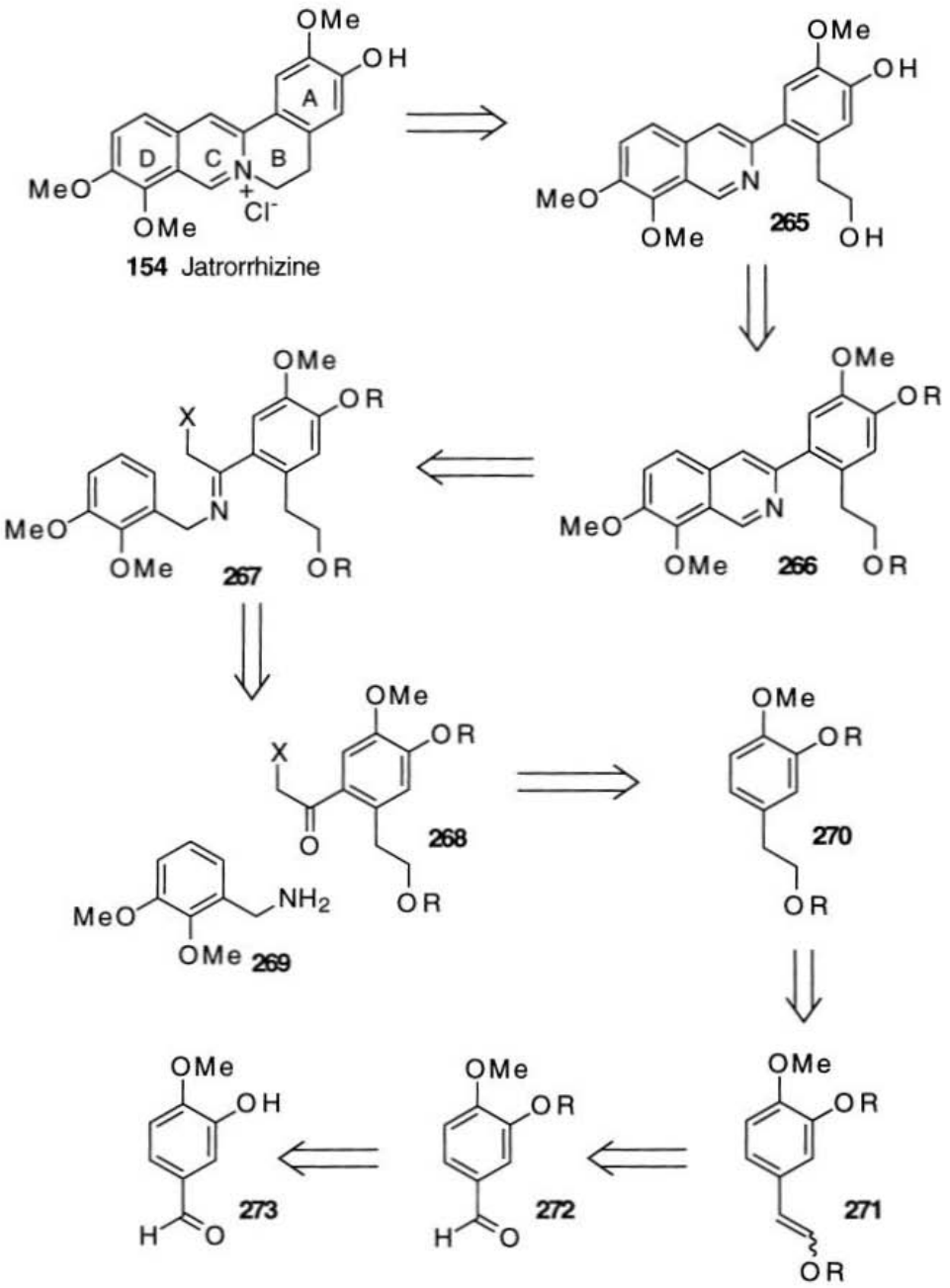
Scheme 5.37 Synthesis of protoberberines *via* benzocyclobutene intermediate[106a]

These do not appear to be generally applicable to the synthesis of other protoberberines as they often demonstrate an inherent lack of selectivity for the substitution pattern desired for jatrorrhizine. They therefore remain rather specific approaches to only certain members of this large family of alkaloids. Faced with the limitations of previous approaches to the syntheses of these alkaloids a new approach was considered for the first total synthesis of jatrorrhizine.

Chapter 6

Progress Towards the Total Synthesis of Jatrorrhizine

The first retrosynthetic analysis of jatrorrhizine that was considered is outlined in Scheme 6.1. Completion of the B ring by intramolecular ammonium salt formation between the isoquinoline portion of the molecule and a chloroethyl group on the A ring

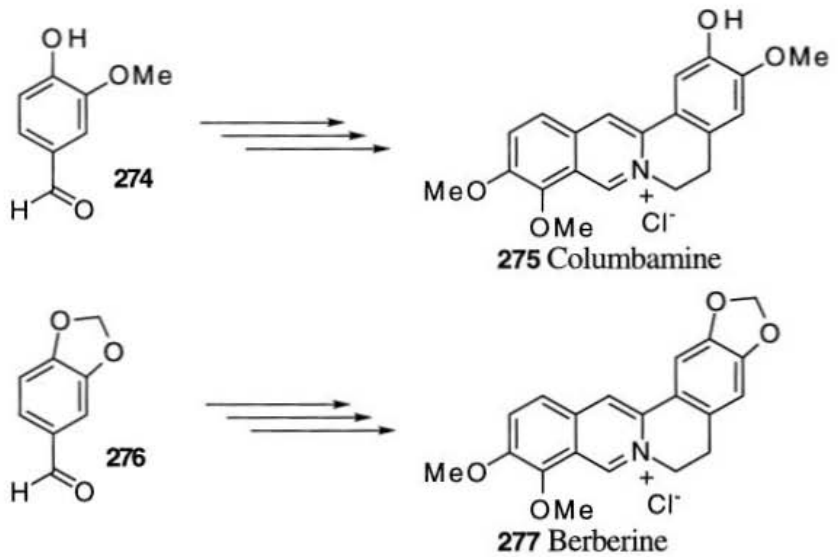


Scheme 6.1 Retrosynthetic analysis of jatrorrhizine

could be accomplished upon chlorination of the parent alcohol **265**. The hydroxyl protons of the primary alcohol and the phenol in **265** may adversely affect some of the prerequisite reactions, so must be protected, i.e., **266**. It was felt that compound **266** could be obtained from the imine **267** by an electrophilic substitution reaction where X is an appropriate leaving group. The aromatic ring in **267** that will become the D-ring of the final product is substituted with three electron-donating groups and should be quite activated to electrophilic substitution.[108] The ring closure may require a subsequent aromatization reaction if the oxidation to the fully aromatic **266** does not occur under the reaction conditions. The imine **267** could potentially be derived from condensation of the ketone **268** with 2,3-dimethoxybenzylamine **269**, a commercially available compound. The ketone **268** may be obtained by a Friedel-Crafts acetylation of **270** using an X-substituted acyl halide, e.g. bromoacetyl bromide. Alternatively, acetyl chloride itself could be used followed by incorporation of the leaving group X. This aromatic ring is also very electron rich so should be quite activated towards Friedel-Crafts reactions. We felt that this ring would be more activated than the arenes of the two benzyl protecting groups. Compound **270** may be synthesized *via* saturation of compound **271** obtained by a Wittig or some other olefination reaction of aldehyde **272**. The aldehyde **272** can be acquired by the protection of commercially available 3-hydroxy-4-methoxybenzaldehyde **273**, commonly known as isovanillin. The benzyl ether protecting group was selected as these are formed readily with alcohols and are very stable to the majority of reaction conditions.[107]

This retrosynthetic analysis can readily be applied to the synthesis of other protoberberine alkaloids. For example, substitution of 3-methoxy-4-hydroxy-benzaldehyde (vanillin) **274** for 3-hydroxy-4-methoxybenzaldehyde **273** would provide the substitution pattern required on the A ring for columbamine **275**. Berberine **277** could be synthesized by the use of 3,4-methylenedioxybenzaldehyde (piperonal) **276**. More

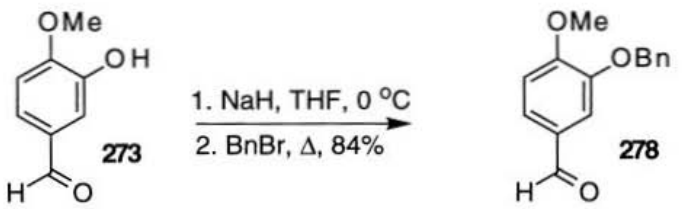
variations in the substitution pattern of the A and D rings can be readily made with other commercially and synthetically available compounds. Berberine **277** is commercially available because it is found in greater quantities in its natural source than other



Scheme 6.2 Potential syntheses of other protoberberines

protoberberine alkaloids. Therefore, the synthesis of berberine will not be considered here. Discussion here will be limited to the synthesis of jatrorrhizine.

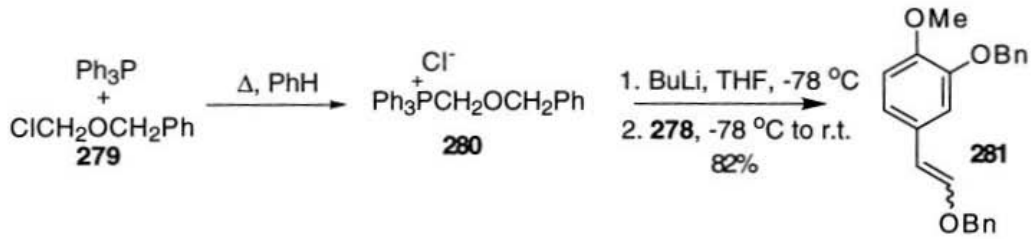
3-Hydroxy-4-methoxybenzaldehyde **273** was deprotonated by sodium hydride



Scheme 6.3 Benzylation of isovanillin

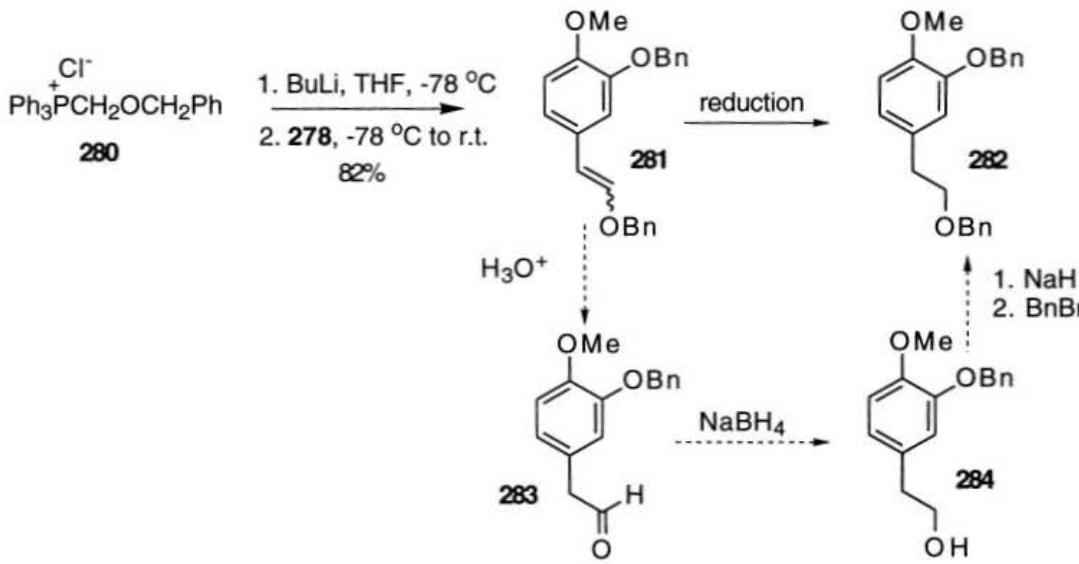
and benzylated with benzyl bromide in 84% yield.[107] The resulting aldehyde **278** was then reacted with the ylid derived from the phosphonium salt **280**, which was prepared by

the reaction of benzyl chloromethyl ether **279**[109] and triphenylphosphine. A 2:1 mixture of alkenes (*E*)-**281** and (*Z*)-**281** was obtained from the Wittig reaction[110] in 82%



Scheme 6.4 Wittig reaction of **278**

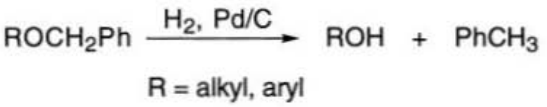
combined yield. This ratio, which was determined by integration of the olefinic signals in the ^{1}H NMR spectrum of **281**, is typical for reactions with this type of unstabilized ylid under these conditions.[110] This type of Wittig reaction has been used to obtain a single carbon homologation of an aldehyde after hydrolysis of the enol ether **281** with acid to give **283** as outlined in Scheme 6.5.[111] In our work, reduction of the enol ether provided the required protected alcohol more efficiently than a single carbon homologation of the



Schme 6.5 Synthesis of compound **282**

aldehyde to give **283**, followed by reduction to the alcohol **284** and benzylation of the resultant primary alcohol.

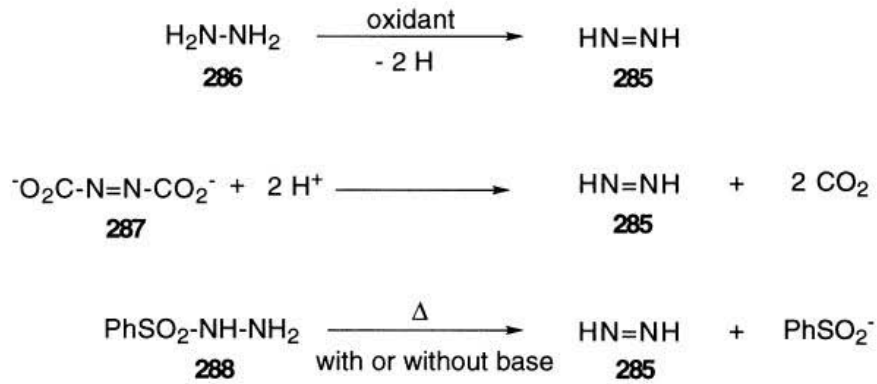
The reduction of the enol ether had the potential to be troublesome if a catalytic hydrogenation approach was utilized. Catalytic hydrogenation of an alkene is typically performed in the presence of palladium on carbon under an atmosphere of hydrogen gas. These conditions will also cleave benzyl ethers to give the parent alcohol and toluene Scheme 6.6.[112-113] Since the compound being studied contains two benzyl ethers as well



Scheme 6.6 Catalytic hydrogenolysis of benzyl ether

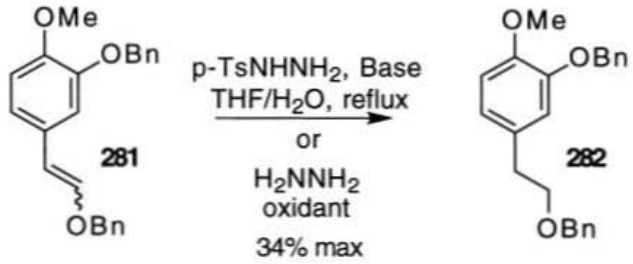
as the alkene, there are seven potential products resulting from reduction of the alkene and/or removal of one or both of the benzyl groups. Reduction of the alkene should proceed at a rate faster than removal of the benzyl groups and a certain degree of selectivity was expected.[112] Initial experiments with palladium on carbon did not appear to be promising and mixtures of products were observed by NMR and TLC analysis of the reactions. Various palladium catalysts have been developed that show greater selectivity for particular functional groups.[113] These were considered, most notably palladium on barium sulfate or on strontium carbonate, which mediate preferential hydrogenation of enol ethers.[113] Rhodium and ruthenium catalysts are also known to preferentially hydrogenate double bonds rather than hydrogenolyse benzyl ethers.[113] Nevertheless, all hydrogenation catalysts do have the potential to cause debenzylation so at this point experimental study of this hydrogenation moved away from a catalytic approach and instead focused on the use of diimide, a hydrogen donor.[114-117]

Diimide **285** is a neutral, transient species most commonly generated by the oxidation of hydrazine **286**, the decomposition of potassium azodicarboxylate **287** or the base-catalyzed thermal cleavage of *p*-toluenesulfonylhydrazide **288** as outlined in Scheme 6.7.[114] Diimide has found synthetic use in cases in which catalytic hydrogenation proved



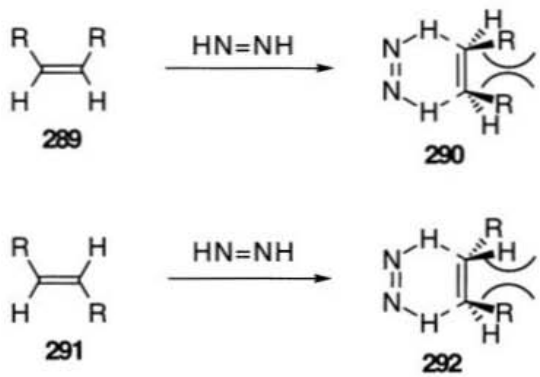
Scheme 6.7 Generation of diimide

to be unsatisfactory. These include situations where the molecule contains a sulfide, as this functional group poisons hydrogenation catalysts and renders them ineffective.[115] Diimide also has greater steric demands than palladium catalyzed hydrogenation, and this has been used to provide hydrogenations with greater stereocontrol.[116] The other situation in which diimide has been used effectively is in the presence of other functional groups that may be reduced by hydrogenation, such as carbonyls, nitriles, halogens or benzyl ethers as in the reduction to be studied.[117] A wide variety of conditions to generate diimide were investigated, in particular the alkaline catalyzed decomposition of *p*-toluenesulfonyl-hydrazide **288** and the oxidation of hydrazine **286** as outlined in Scheme 6.8. However, in no case did the conversion exceed 34% even in the presence of



Scheme 6.8 Reduction of **281** by diimide

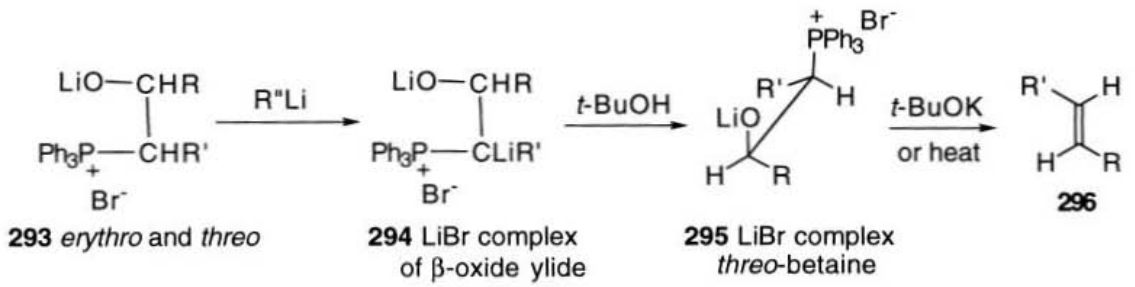
a large excess of diimide. Previous studies have shown that the mechanism of the reduction proceeds through a six-membered cyclic transition state with "synchronous hydrogen transport" from the diimide to the alkene.[114b,c] Inspection of the structure of the transition state as in Scheme 6.7 indicates that for the *Z* isomer **290**, there are greater steric interactions than in the transition state for the *E* isomer **292**. This results in a greater rate of reduction for *E* alkenes than for *Z* alkenes. Since the product of the



Scheme 6.8 Transition states of diimide reduction for *E* and *Z* alkenes[114b]

Wittig reaction is a 2:1 mixture of the *E*:*Z* isomers of **281**, reduction by diimide will proceed slowly on one third of the mixture. This was, in fact, demonstrated in one set of experiments where an alkene mixture was subjected to three successive diimide reductions. It was found that the *E* isomer was more selectively reduced than the *Z*

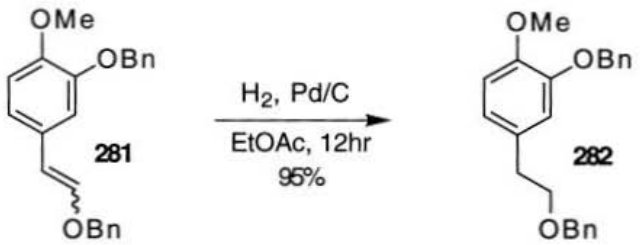
isomer until no *E* isomer remained after the third reaction. One approach at this stage could be to convert the *Z* isomer to the more readily reduced *E* isomer. A number of methods exist for the conversion of *Z* alkenes to the more stable *E* alkenes.[118] Attempts to achieve this with iodine[118d-g] resulted in a complex mixture of products, so this approach was not pursued further. Another approach could be to alter the Wittig reaction to give enhanced selectivity for the *E* alkene and many such modifications are known.[110] These include replacement of triphenylphosphine with a trialkylphosphine[119] or *P*-phenyl-dibenzophosphole,[120] the use of an alkyllithium base[121] and the addition of lithium salts.[122] Perhaps the most popular method is the Schlosser modification[110,123] in which the ylid is formed as a lithium halide complex **293** and reacted with the aldehyde at low temperature. Addition of base followed by stereoselective reprotonation of the anion **294** generates the *threo*-betaine **295**. Warming the solution then causes the cleavage of the betaine intermediate to triphenylphosphine oxide and the *E*-alkene **296** selectively.



Scheme 6.9 Schlosser modification of Wittig reaction

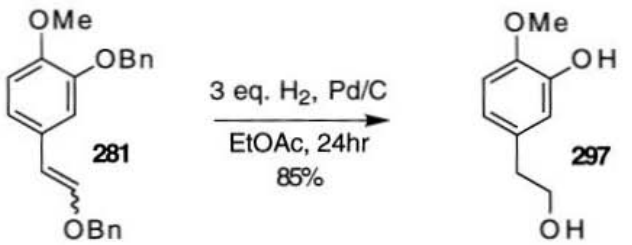
While the use of such modifications was considered, another aspect of the diimide reduction indicated that this still might not be the most effective strategy. Previous studies have shown that hydrogenation by diimide is not particularly effective on polarized double bonds.[113b,c] Since alkene **281** is an enol ether, this does not bode well for the diimide reduction. Although the starting alkene **281** is separable from the alkane

282 by chromatography, this option was deemed to be unsatisfactory and the hydrogenation over palladium catalysts was reinvestigated. It was found that in very carefully performed reactions using palladium on carbon and precisely one equivalent of hydrogen, the enol ether **281** was selectively reduced providing **282** in excellent yield (95%). There was no evidence of hydrogenolysis of either of the benzyl ethers. The use



Scheme 6.10 Hydrogenation of the alkene **281**

of three equivalents of hydrogen resulted in complete hydrogenation of the double bond and hydrogenolysis of both benzyl ethers to give **297** (Scheme 6.11). Benzyl ethers can occasionally be resistant to cleavage,[107] but are relatively labile to hydrogenolysis in this

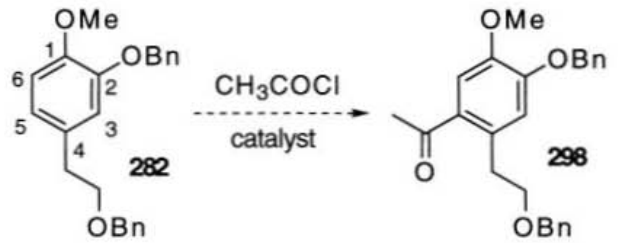


Scheme 6.11 Reduction and debenzylation of **281** by hydrogenation

compound. This suggested that removal in the final stages of the synthesis may proceed without significant difficulty.

The next step of the synthetic scheme was a Friedel-Crafts acylation of the central aromatic ring. Acylation should occur at the 5-position because this is the most reactive

position of the ring.[108] Although each of the positions available for substitution can be viewed as activated, formation of the 1,2,4,5-substituted compound is more favourable



Scheme 6.12 Expected site of Friedel-Crafts acylation of **282**

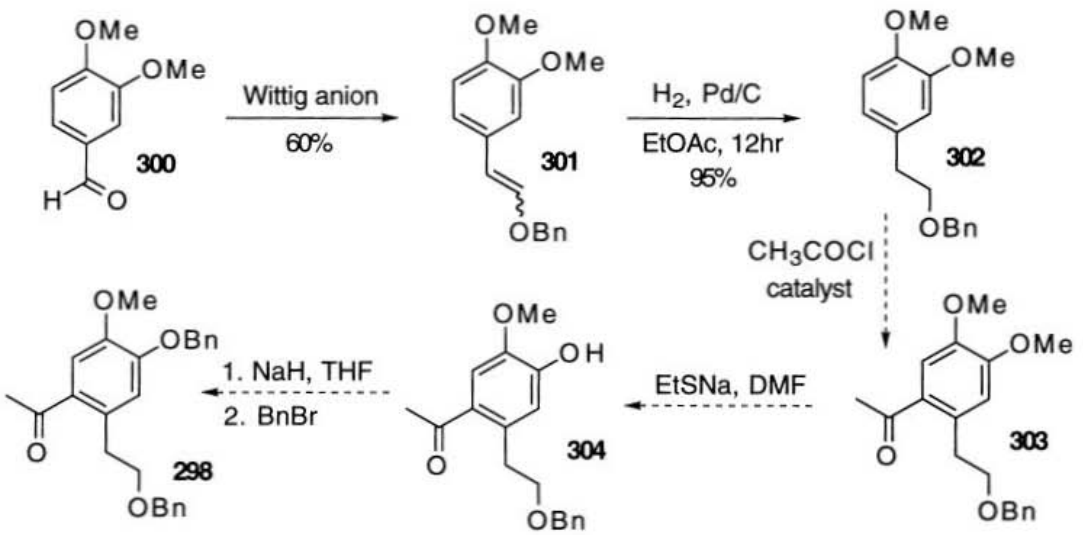
than any other possible substitution pattern based on steric grounds. Friedel-Crafts reactions using $AlCl_3$ or $FeCl_3$ in CH_2Cl_2 or CS_2 with bromoacetyl bromide or acetyl chloride were attempted under a variety of conditions. Unfortunately, the desired acylation did not occur as expected. Either no reaction occurred or multiple acylations took place to give an intractable mixture. An interesting product that was isolated from one experiment with $FeCl_3$ in CS_2 resulted from replacement of both benzyl groups by acetyl groups giving compound **299** in 12% yield. Friedel-Crafts catalysts readily cleave methyl ethers,

Scheme 6.13 An unexpected compound isolated from attempted acylation of **282**

especially those *ortho* to the position of acylation,[124] but benzyl ether cleavage is not as commonly observed. $FeCl_3$ has been used to selectively remove benzyl ethers in the

presence of methyl ethers,[125] but in this case the presence of acetyl chloride results in the diacetate derivative **299**. This benzyl ether cleavage with $FeCl_3$ was kept in mind in case hydrogenolytic deprotection of the benzyl groups in the planned penultimate step of the total synthesis should prove troublesome.

In an attempt to limit the number of aromatic sites available in the substrate, **302** was investigated as a potential intermediate. Compound **302** was synthesized in the same manner as **282**, via the enol ether **301** but the starting material was 3,4-dimethoxy-benzaldehyde (veratraldehyde) **300** rather than benzylated isovanillin **278**. Introduction of an acetyl group at position 5 of **302** would afford **303** as in Scheme 6.14. This type of compound has been shown to be suitable for the selective removal of the methyl ether

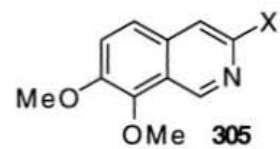


Scheme 6.14 Acylation of **302** and selective demethylation

para to the acetyl group with EtSNa in DMF.[126] Subsequent benzylation of the phenol would again provide the desired dibenzyl-protected intermediate **298**. Friedel-Crafts reactions with this compound also resulted in mixtures of products. A different alcohol protecting group, such as a *t*-butyldimethylsilyl ether (TBDMS) or *o*-nitrobenzyl ether,[127]

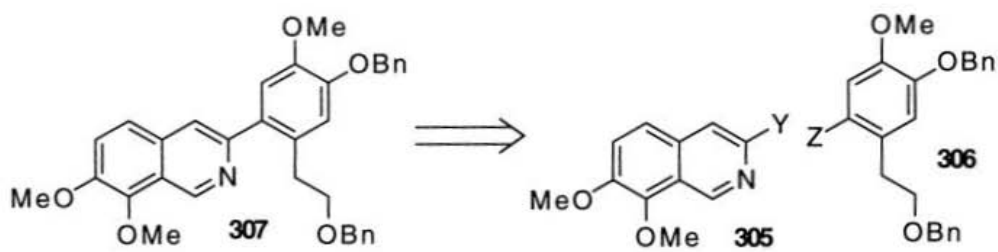
could have simplified the Friedel-Crafts reaction by limiting the number of sites available for acylation. The TBDMS ether is relatively stable to mild Friedel-Crafts reaction conditions, and the nitrobenzyl ether is less activated to electrophilic substitution by virtue of the electron withdrawing nitro group. However, it was felt that the benzyl protecting groups should remain since it was not known exactly what conditions would be required in the remaining reactions, and benzyl ethers are highly stable to a very wide variety of reaction conditions.[127]

At this point the synthetic strategy was reexamined. The initial retrosynthetic analysis incorporates the critical isoquinoline ring closure (**267** → **266**) fairly late in the synthesis so it was decided that the new strategy should include completion of this reaction at an earlier stage. Synthesis of an isoquinoline substituted at the 3-position **305** with an appropriate group would afford a substrate suitable for a biaryl coupling reaction.



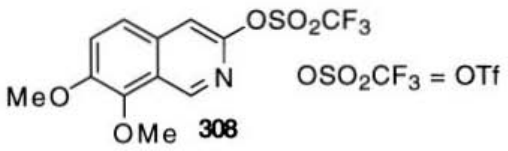
305

Biaryl coupling methodology has become a very powerful and widespread synthetic tool, and a variety of coupling partners and catalysts have been developed.[128-133] Thus, the other fragment **282** of the final compound that had been synthesized could still be useful



Scheme 6.15 Biaryl coupling methodology approach to jatrorrhizine

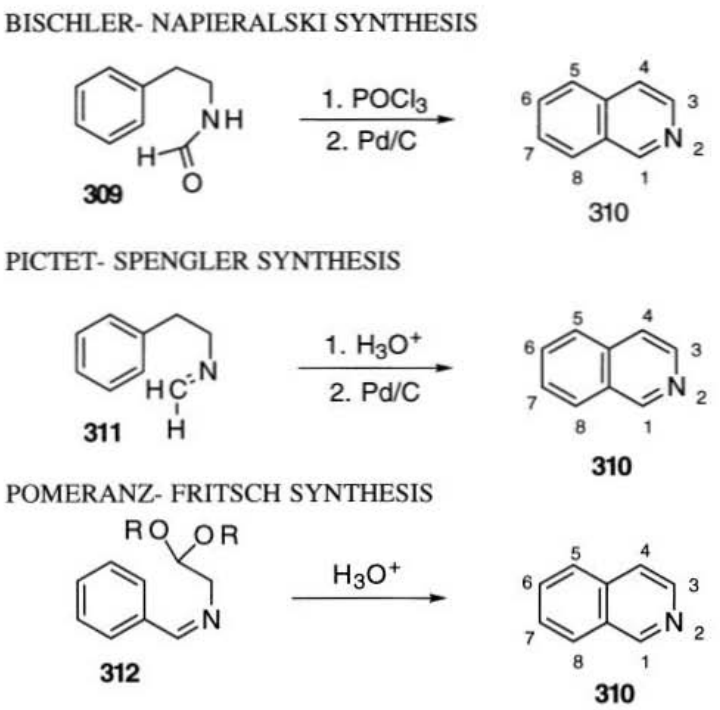
and the total synthesis would be more convergent. The isoquinoline that was chosen to be pursued is substituted in the 3-position with the trifluoromethanesulfonoxy (triflate, OTf) group, which has recently been shown to be a very effective leaving group in a variety of



308 OSO_2CF_3 = OTf

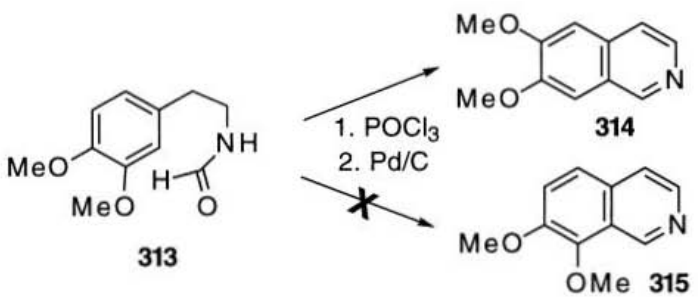
biaryl coupling reactions.[133] Other phenol derivatives, such as mesylates,[129a,b] phosphates,[129c] carbamates,[133a] alkoxy[129d] and tetrazolyls,[129e] have been used in these reactions, but the triflate has demonstrated greater utility than these types of compounds.[133] A similar heteroatomic moiety had been shown to be stable and useful in biaryl coupling reactions.[134] It is not known if **308** has been used in biaryl coupling reactions but 1-trifluoromethanesulfonoxyisoquinoline and 2-trifluoromethanesulfonoxy-quinoline have been used previously in cross coupling reactions.

Classically, isoquinoline syntheses have been performed in one of three ways: the Bischler-Napieralski,[84] the Pictet-Spengler[79] and the Pomerantz-Fritsch[94] reactions, which are outlined in Scheme 6.16. Each of these reactions is facilitated by an activated aromatic ring system, especially an electron-donating substituent *para* to the desired site of ring closure. Such a substituent is indeed present in the case being studied. The Bischler-Napieralski reaction is the most frequently used method of isoquinoline synthesis and involves the cyclodehydration of *N*-acyl β-phenethylamines **313** to 3,4-dihydroisoquinolines. The most commonly used reagents to affect this transformation are



Scheme 6.16 Classical approaches to the synthesis of isoquinolines

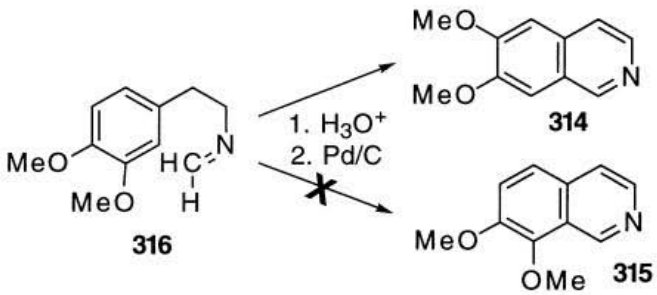
phosphorus pentoxide and phosphorus oxychloride in dry, inert solvents, such as chloroform, benzene or xylene. Reduction or dehydrogenation of these partially saturated heterocyclic systems gives the 1,2,3,4-tetrahydroisoquinoline or the isoquinoline, respectively. However, the desired compound is a 7,8-dimethoxy substituted isoquinoline and this substitution pattern is difficult to obtain with the Bischler-Napieralski reaction.



Scheme 6.17 Bischler-Napieralski approach to substituted isoquinolines

The favoured product for this type of reaction is the 6,7-dimethoxy substituted isoquinoline **314** as outlined in Scheme 6.17.

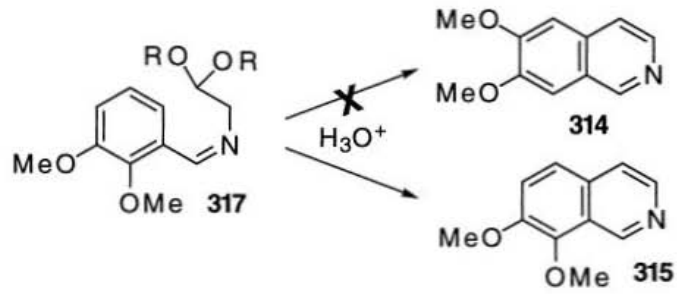
The Pictet-Spengler reaction consists of the condensation of β-phenethylamines with carbonyl compounds in acid to give 1,2,3,4-tetrahydroisoquinolines (Scheme 6.18). This transformation is most commonly achieved by the action of hydrochloric acid or sulfuric acid and the fully aromatic compound can be obtained by dehydrogenation.



Scheme 6.18 Pictet-Spengler approach to substituted isoquinolines

However, the desired substitution pattern is difficult to obtain with this type of reaction as well and the product obtained is the same 6,7-dimethoxyisoquinoline ring as in the Bischler-Napieralski reaction.

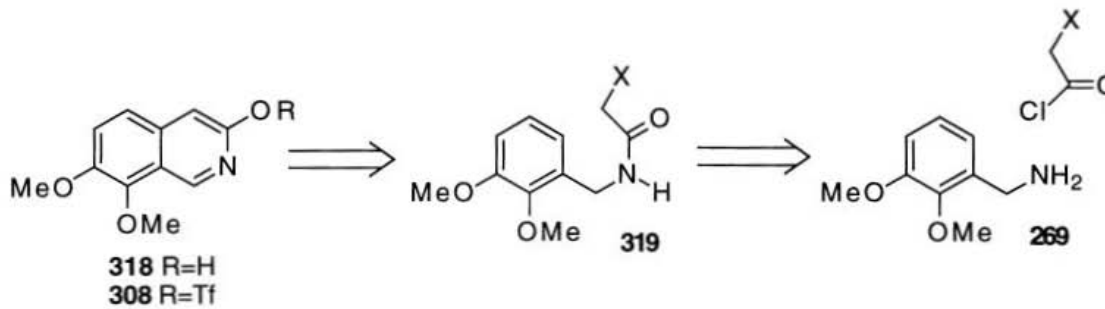
The Pomerantz-Fritsch reaction involves the cyclization of benzalaminoacetals **317** in acid to give fully aromatic isoquinolines directly (Scheme 6.19). This reaction is commonly performed in different concentrations of sulfuric acid or in mixtures of sulfuric acid with reagents such as hydrogen chloride, phosphorus pentoxide or phosphorus oxychloride. The Pomerantz-Fritsch reaction is generally better than the Bischler-Napieralski or the Pictet-Spengler reactions for preparing 7,8-disubstituted isoquinolines, such as **315**. This is because there is only one site of cyclization, and it results in the



Scheme 6.19 Pomerantz-Fritsch approach to substituted isoquinolines

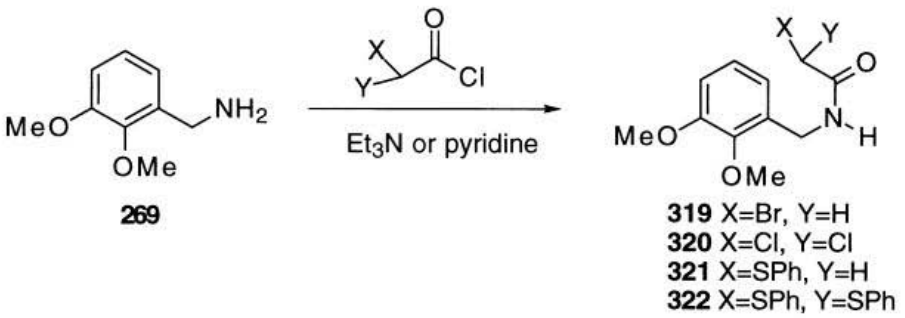
desired 1,2,3,4-tetrasubstituted product. Unfortunately, the desired product is usually obtained in lower than 50% yield.

With these limitations to the classical methods of isoquinoline synthesis, other methods of effecting the ring closure were investigated. The target heteroatomic portion at this stage was the isoquinolinol **318**, and it was anticipated that this structure could result from the closure of the heteroatomic ring by an electrophilic substitution reaction as in Scheme 6.20. The aromatic ring of **319** possesses two methoxy groups and the alkyl group so it is very electron rich and should be very reactive to aromatic substitution reactions.[108] Substitution at the desired position would result in a sterically hindered 1,2,3,4-substituted aromatic ring, which may not be obtained via an intermolecular reaction since every position on the ring is very activated. To ensure the correct



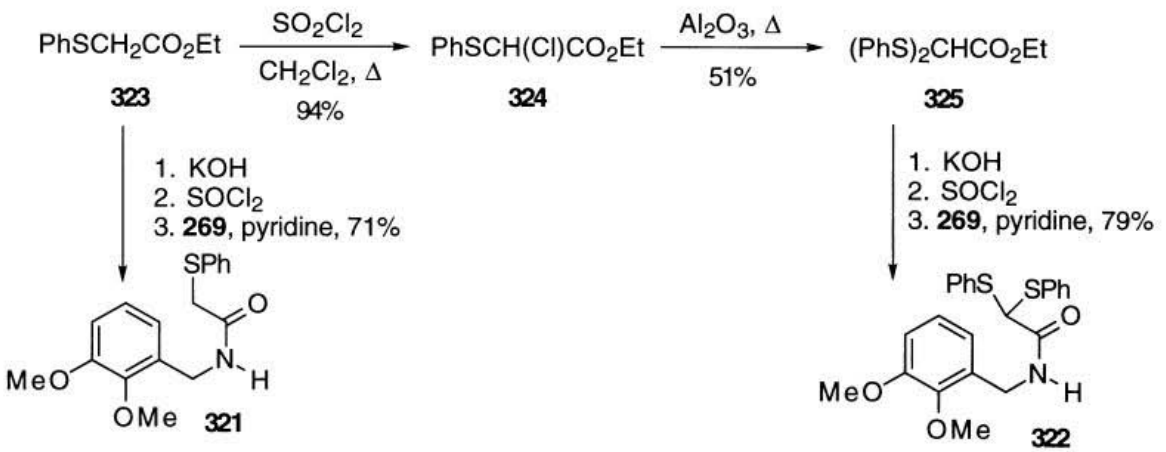
Scheme 6.20 Retrosynthetic analysis of **308**

regiochemistry, an intramolecular approach was utilized. A series of amides **319** - **322** (Scheme 6.21) were synthesized[139] with different leaving groups (X and Y) for the aromatic substitution reaction. The halogenated amides **319** and **320** were synthesized



Scheme 6.21 Potential precursors to **318**

from the amine **269** and commercially available acid chlorides. As outlined in Scheme 6.22, amide **321** was synthesized by the basic hydrolysis of **323** and conversion of the resulting acid salt to the acid chloride with thionyl chloride. The acid chloride was then added to the amine **269** and pyridine without purification. Amide **322** was

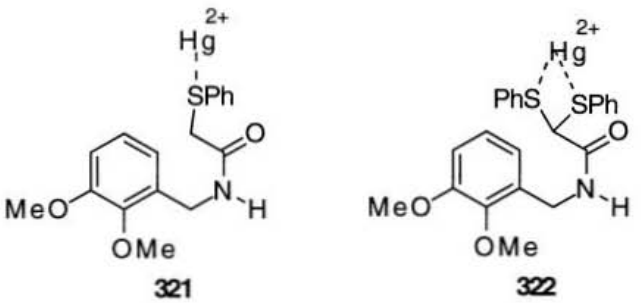


Scheme 6.22 Synthesis of amides **321** and **322**

similarly synthesized via compound **325** as outlined in Scheme 6.22.

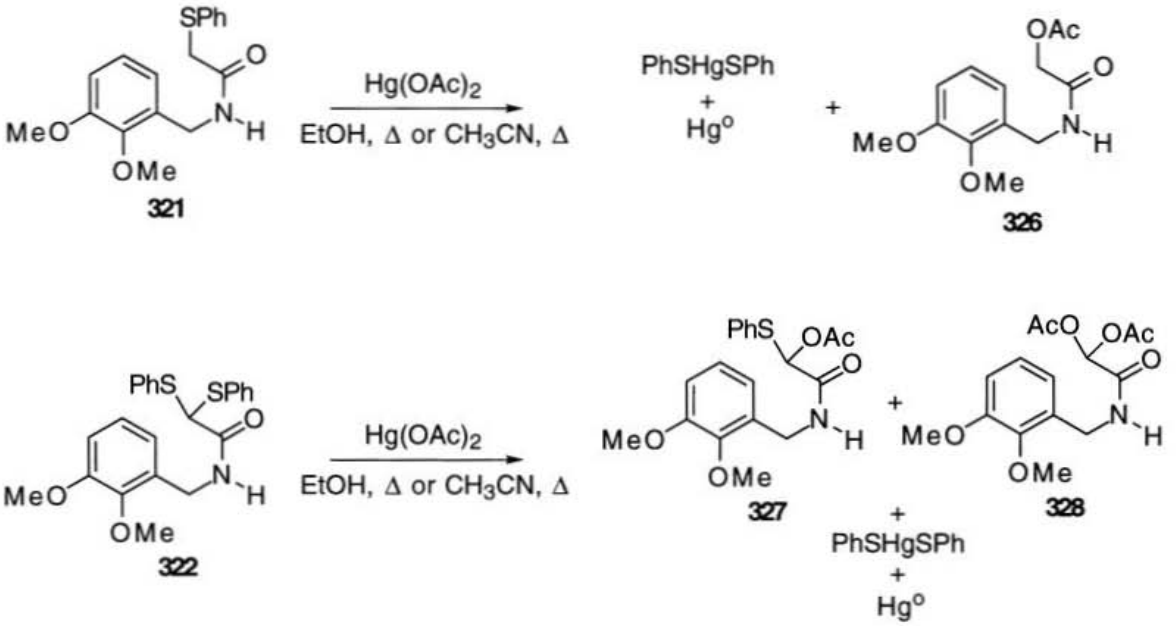
The halogenated amides **319** and **320** were subjected to a variety of Friedel-Crafts type reactions, utilizing polyphosphoric acid at different temperatures and $AlCl_3$ or $FeCl_3$ in a number of typical solvents (e.g. ether, dichloromethane, hexanes, heptane, decalin, nitrobenzene). The desired reaction did not appear to be occurring, and starting material was recovered quantitatively or intractable tars were obtained.

The phenylthio substituted amides **321** and **322** were utilized in a novel attempt to accomplish the desired ring closure *via* an as yet unknown sulfur analog of the Pomerantz-Fritsch reaction. It was felt that complexation of the soft sulfur atoms with soft metal salts[140] such as those of mercury or silver (Scheme 6.23) would make the carbon *alpha* to the amide carbonyl sufficiently electrophilic to be attacked by the highly activated aromatic ring. Reactions were attempted with mercury (II) acetate in refluxing



Scheme 6.23 Complexation of mercury (II) with **321** and **322**

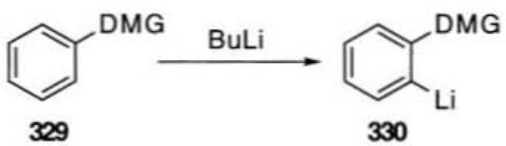
ethanol or acetonitrile, and, although each attempt resulted in a complex mixture, curious results were obtained in each reaction performed. As outlined in Scheme 6.24, precipitates of mercury(II) thiophenolate were observed, liquid mercury was produced, and some substitution of acetate for the phenylthio group was observed in every case.



Scheme 6.24 Products of mercury (II) salt reactions with **321** and **322**

None of the desired bicyclic compound was obtained from any of these reaction mixtures, and the work on these reactions was not pursued further.

Another approach to the synthesis of the isoquinoline is the use of a directed *ortho* metalation (DoM) outlined in Scheme 6.25.[99] This methodology has become particularly



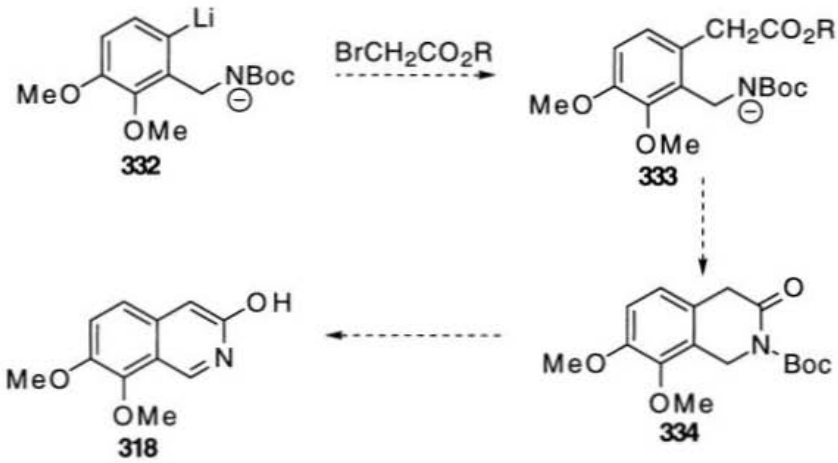
Scheme 6.25 Directed *ortho*-metalation methodology[99]

useful for the regiospecific synthesis of 1,2-, 1,2,3- and 1,2,3,4-substituted aromatics, which often can not be obtained by traditional electrophilic substitution reactions. A variety of directed metalation groups (DMG's) have been investigated[99] that direct alkyllithium bases to deprotonate at the aromatic position adjacent to that group. A good

coordinating site for the alkyllithium base is required for regiospecific deprotonation, and the substituent must be resistant to nucleophilic attack by the base. A heteroatom must be present to satisfy these requirements and confer DMG character to an aromatic substituent. Some DMG's that have shown synthetic utility include NH-*t*-Boc, $CONR_2$, CH_2NR_2 and OR, where R is usually CH_3. Compound **331** was synthesized from amine **269** in excellent yield (89%)[141] as in Scheme 6.26 to determine its usefulness as a DoM substrate. If the protected benzylamine is a useful DMG, the addition of two equivalents of butyllithium would remove the carbamate proton and the aromatic proton adjacent to

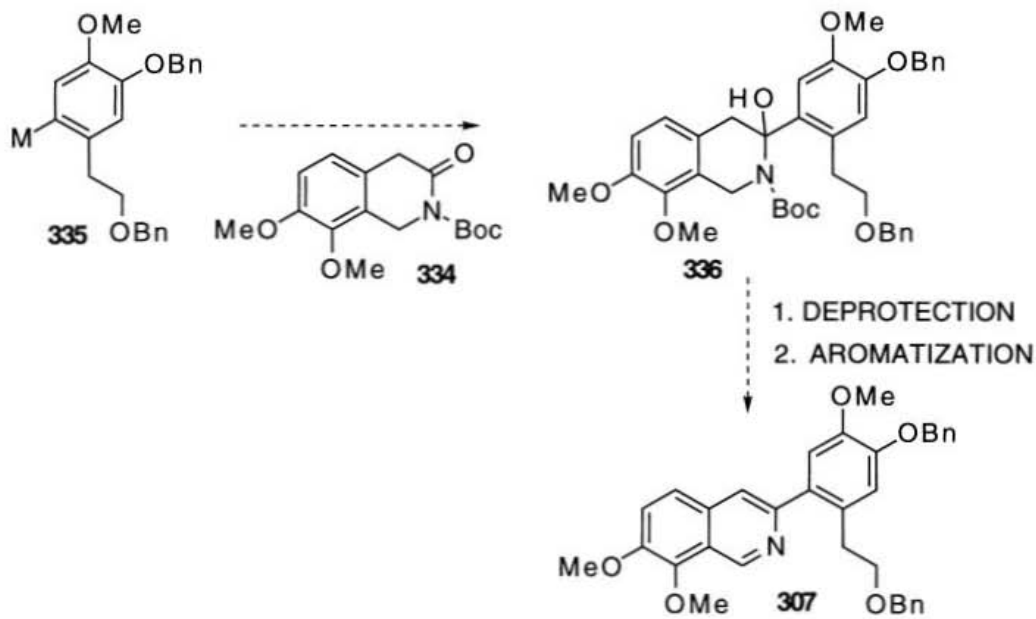
Scheme 6.26 DoM methodology applied to **331**

the alkylamine to give the dianion **332**. Metalation could be directed by the NH-*t*-Boc or the methoxy group, but the NH-*t*-Boc has been shown to direct the metalation selectively in the presence of methoxy groups.[99b] The NH-*t*-Boc group is not attacked by the base in a nucleophilic manner due to the presence of the negative charge on the nitrogen and the bulky nature of the *t*-Boc group.[99a] Upon lithiation, quenching the aromatic anion with ethyl bromoacetate could then introduce the functionality required to obtain the cyclic amide **334**. This lactam may form under the reaction conditions or a further elaboration may be required to effect the ring closure. The fully aromatic structure **318** could then be



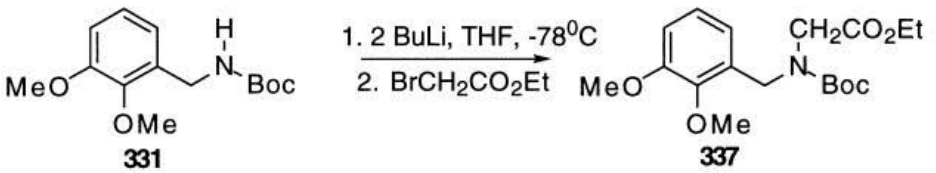
Scheme 6.27 DoM approach to synthesis of **318**

obtained by removal of the *t*-Boc group[141] followed by an aromatization reaction. Alternatively, this amide **334** may be a suitable substrate for a nucleophilic attack by an organometallic compound **335** derived from **282** as in Scheme 6.28. However, all attempts at performing *ortho*-metalations on **331** showed that the desired reaction did not



Scheme 6.28 Alternate synthesis of **307** using **334**

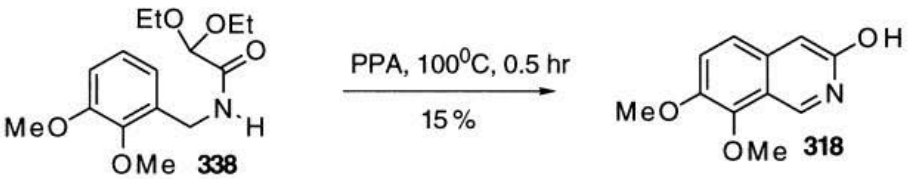
take place. Starting material **331** and small quantities of the *N*-alkylated compound **337** were isolated. The aromatic lithiation may simply not have occurred or any aromatic



Scheme 6.29 Product isolated from attempted lithiation of **331**

anion that was formed may have been re-protonated by the acidic α-protons of ethyl bromoacetate.

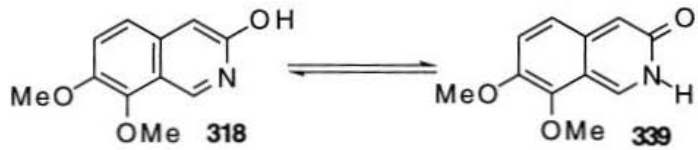
During these investigations, a previous synthesis of the desired compound **318** by a Pomerantz-Fritsch reaction of the diethoxyamide **338** in polyphosphoric acid was found.[142a] Virtually no experimental details were described, but the reaction was said to give the required compound **318** in "modest yield." This method was used and the



Scheme 6.30 Synthesis of **318**

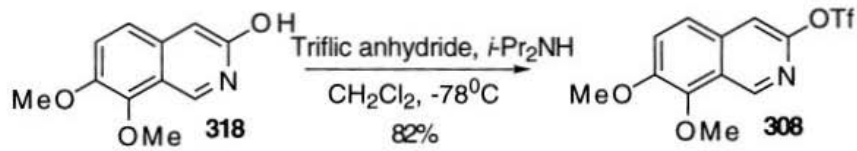
desired isoquinolinol was obtained in 15% yield after extensive extraction of the polyphosphoric acid mixture.

Previous research has shown that this type of isoquinolinol exists as two different tautomers, the lactim **318** and the lactam **339** (Scheme 6.31), depending upon the solvent



Scheme 6.31 Tautomerization between **318** and **339**

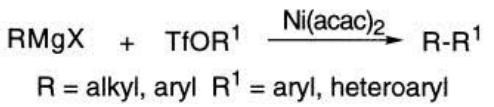
and temperature.[143] Neither the lactim nor the lactam proton is observed in the NMR spectrum at room temperature. Variable temperature NMR in $CDCl_3$ demonstrated that the lactim form **318** is predominant at low temperature, with a broad singlet appearing at 14.5 ppm when cooled to -60 °C. Therefore, triflation of **318** was performed in CH_2Cl_2



Scheme 6.32 Triflation of **318**

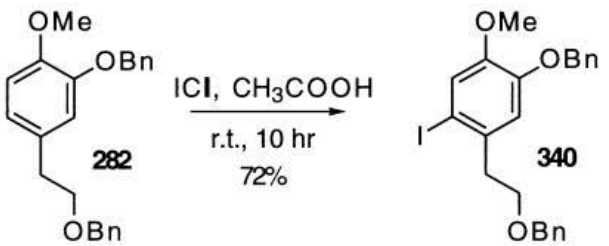
at -78 °C (Scheme 6.32) similar to work done previously[144] to afford **308**.

With the desired triflate in hand, the other portion of the final product was required in a form that could be used in a biaryl coupling reaction. The most common types of compounds used in biaryl coupling reactions with triflates are organometallic reagents, based on metals such as tin,[132] magnesium[133] and zinc,[134] as well as organoboron[135,136] and organosilicon[137] reagents. Organotin compounds (Stille coupling) and zinc compounds have been well studied and have received widespread use in synthesis, but the first of these to be chosen for study was a magnesium based approach. Organomagnesium (Grignard) reagents have recently been shown to couple to triflates with catalysis by $Ni(acac)_2$[133a] as outlined in Scheme 6.33, so a halogen was



Scheme 6.33 Coupling of Grignard reagent with triflate

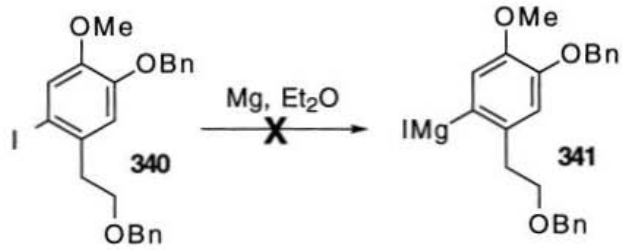
required in the 5-position of the central aromatic ring of **282**. The dibenzyl protected compound **282** was converted to the 5-iodo derivative **340**, as in Scheme 6.34, by the action of iodine monochloride, a mild aromatic iodination reagent.[145] In contrast to the attempted acylations discussed earlier, this reaction occurred selectively at the expected



Scheme 6.34 Iodination of **282**

location in good yield (72%) with no evidence of iodination at any other positions on the aromatic rings. The position of iodination was determined by a nuclear Overhauser effect (nOe) NMR experiment. Minor byproducts of the reaction appeared to result from debenzylation of the product and the starting material.

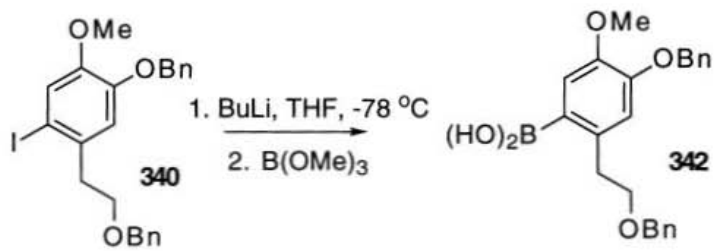
In the Grignard reaction, formation of the organomagnesium reagents from alkyl and aryl iodides generally occur readily due to the higher reactivity of these compounds over the corresponding bromides, chlorides or fluorides.[146] Treatment of compound **340** with magnesium, however, resulted in no reaction (Scheme 6.35), presumably due to the commonly observed problem of inhibited Grignard formation in the presence of methoxy groups. The alkoxy groups, as well as hydroxy and amino groups, coat and inactivate the



Scheme 6.35 Attempted formation of Grignard reagent **341**

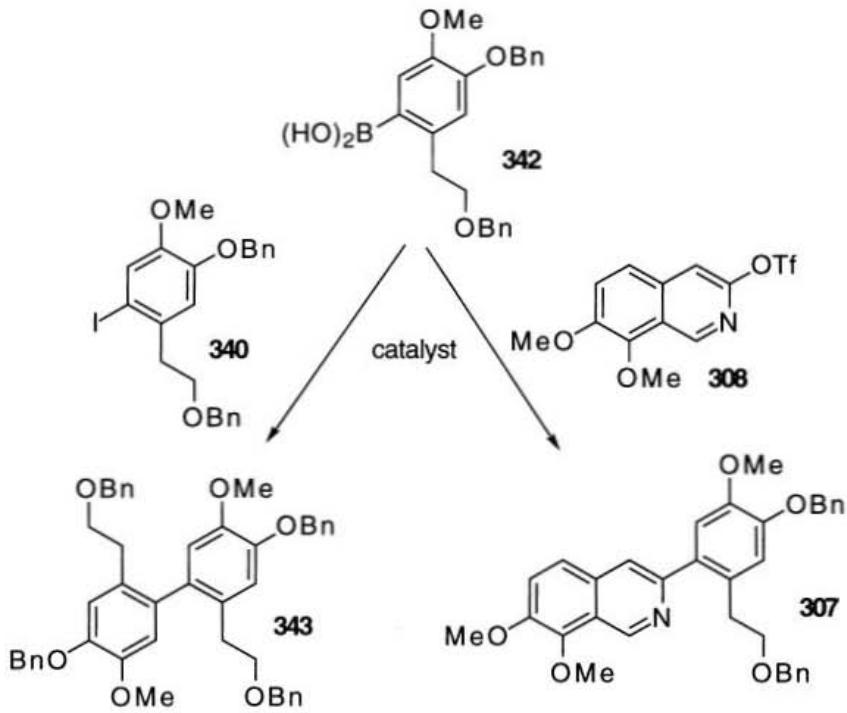
magnesium metal to prevent reaction.[147] The use of catalytic iodine[148a-c] and entrainment reagents[148d,e] in an effort to activate the magnesium to react with the substrate were not effective at generating the Grignard reagent so other biaryl couplings were considered.

Results in another project in the laboratory[149] using an aryl triflate - aryl boronic acid coupling methodology (Suzuki-type coupling)[135,136] have given favorable results, and this approach was studied next. Boronic acids and boronate esters have recently become useful in these coupling reactions for a number of reasons. The coupling reaction is compatible with a number of electrophilic functional groups, the boron compounds are relatively stable, and the inorganic byproduct of the reaction is readily eliminated in water. The aryl boronic acids are most often synthesized via the corresponding aryl lithium,[135f] which should form readily with the iodinated compound **340** due to the ease of metallating iodides with butyllithium. This metal-halogen exchange reaction was



Scheme 6.36 Conversion of iodide **340** to boronic acid **342**

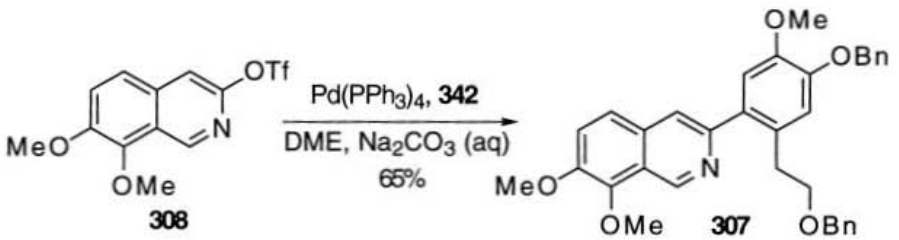
achieved and quenching with trimethyl borate followed by an acidic workup gave the crude boronic acid (Scheme 6.36). Boronic acids decompose during column chromatography so rigorous purification is typically not performed.[150] For this synthesis, a slight excess of the crude compound was used in the biaryl coupling reactions. Complete conversion of the iodide to the boronic acid must be ensured prior to the coupling reaction because boronic acid - iodide couplings proceed at a faster rate than boronic acid - triflate couplings.[136a] Since the crude boronic acid is used in the coupling reaction any iodide that remains will compete with the triflate in the reaction, and, as outlined in Scheme 6.37, the product will be a mixture of the homocoupled compound **343** and the desired heterocoupled compound **307**. However, consumption of the iodide



Scheme 6.37 Potential coupling products of boronic acid **342**

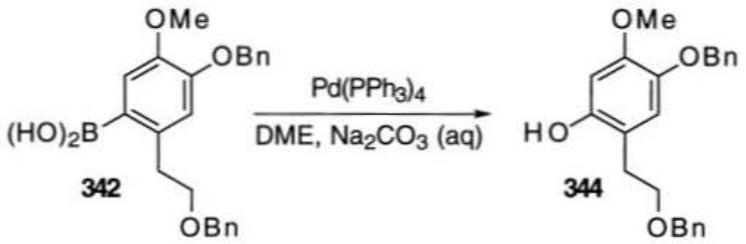
was readily followed by TLC analysis of the lithiation reaction mixture so this byproduct was easily avoided.

Coupling of the aryl triflate - aryl boronic acid is generally done with palladium catalysts and a variety have been shown to be effective in different cases.[135,136] The most commonly used catalyst is tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$),[151] and this was chosen to be investigated first. The desired triflate - crude boronic acid coupling was accomplished in refluxing 1,2-dimethoxyethane (DME) in the presence of



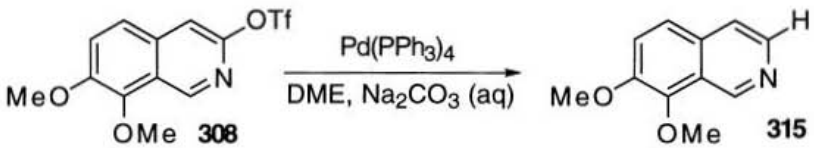
Scheme 6.38 Biaryl coupling of **308** with **342**

aqueous Na_2CO_3[136a,b] to give a 65% yield of **307**. Although this reaction was accomplished once on a small scale, attempts to repeat the biaryl coupling reaction were not successful. Possible reasons for this are unanticipated problems with performing the reaction on a larger scale or decomposition of the catalyst. The tetrakis(triphenyl-phosphine)palladium(0) catalyst is known to decompose on exposure to oxygen. An unfortunate result of these attempts was the consumption of the required starting materials **342** and **308**. The boronic acid **342** was found to be converted to the phenol **344**, (Scheme 6.39) and the triflate **308** underwent reductive elimination of the trifluoro-methylsulfonoxy group to the deoxygenated compound **315** (Scheme 6.40). The reaction



Scheme 6.39 Byproduct of biaryl coupling reaction

of boronic acid to phenol has been reported to occur[152] when the cross-coupling reaction is very slow, and it has been shown that varying degrees of homocoupling occur as well.[152] The formation of the homocoupled compound **336** could not be confirmed in this case, but the phenol **344** was isolated and characterized. Triflate homocoupling has also been reported,[153] but this product could not be detected in the reaction mixture.

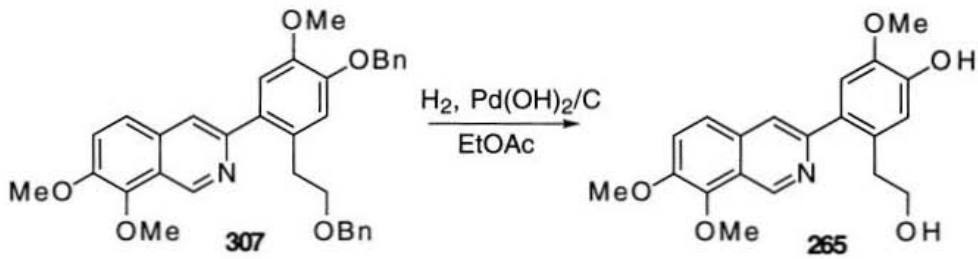


Scheme 6.40 Byproduct of biaryl coupling reaction

Reductive elimination of triflates has been used as an approach to the removal of a phenol group[154] but, in this case, results in the loss of the functionality required in the isoquinoline ring for the biaryl coupling reaction. Because compound **308** was the limiting reagent, the loss of this isoquinoline moiety proved to be a significant setback to the synthesis of greater quantities of **307**. However, a small quantity of **307** was obtained from the successful biaryl coupling reaction and this was utilized for the remaining reactions.

Cleavage of the benzyl protecting groups of **307** was required to afford the alcohol functionalities of **265**. This reaction can be accomplished by hydrogenolysis under an

atmosphere of hydrogen in the presence of palladium on carbon but this can proceed with difficulty depending on the substrate. Although the hydrogenolysis of **282** with Pd/C mentioned previously suggested that the debenzylation at this stage might proceed with a minimum of difficulty, a more effective and reliable catalyst for benzyl ether cleavage is palladium hydroxide on carbon, known as Pearlman's catalyst.[155] The use of this catalyst did result in the clean removal of both benzyl groups of **307**, as illustrated in Scheme 6.41. This reaction was performed on a small scale only (20 mg), and it was not possible

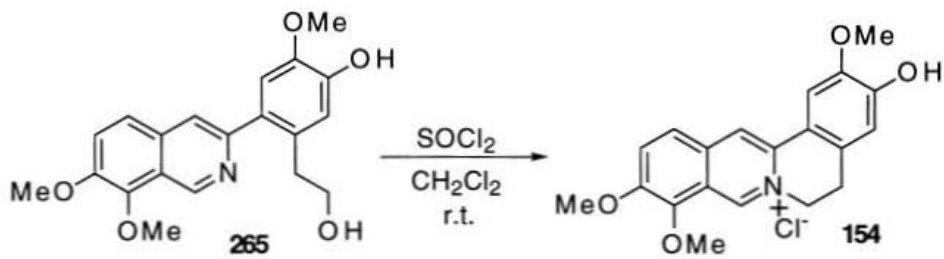


307 265

Scheme 6.41 Hydrogenolysis of **307**

to determine an accurate yield for the product.

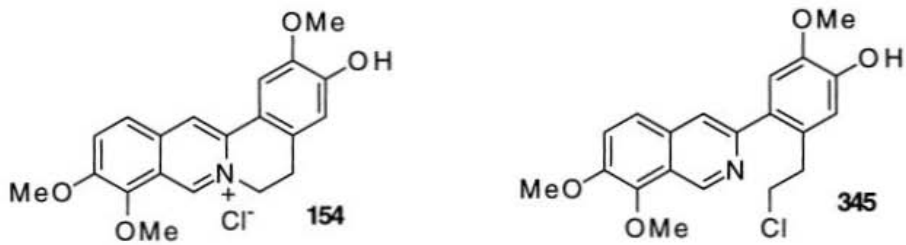
The final step in the synthetic sequence is the conversion of the primary alcohol group in **265** to a chloride. It was hoped that the required ring closure reaction would occur under the reaction conditions. As described in Scheme 6.42, compound **265** was dissolved in CH_2Cl_2, and an excess of thionyl chloride was added. The solution instantly turned from a very pale yellow colour to a bright yellow. This suggested that the



265 154

Scheme 6.42 Completion of B-ring of jatrorrhizine

conversion to the quaternary jatrorrhizine chloride, which is bright yellow, had been accomplished. TLC analysis (EtOAc) indicated that the starting material **265** ($R_f = 0.47$) was consumed, and the product of the reaction appeared as a baseline spot on the TLC plate, as would be expected in this solvent system for a quaternary ammonium salt. This spot fluoresced a bright yellow colour under long wave UV light (365 nm), as previously reported for jatrorrhizine. Again, this reaction was done on a very small scale (~2 mg), and the amount of product was insufficient to characterize unequivocally as jatrorrhizine. An attempt was made to measure IR and ^{1}H NMR spectra. Comparison of the IR spectrum with that reported for authentic jatrorrhizine[75d] suggested that jatrorrhizine was present in the sample. The major signals in both spectra correlate well but the sample was not sufficiently pure to confirm complete correlation. Comparison of the ^{1}H NMR spectrum with the reported proton NMR spectrum[70] also suggested that jatrorrhizine is indeed present in the sample, but the quantity was so small that the signals are somewhat obscured by impurities (water, grease), non-deuterated NMR solvent and baseline noise. In addition, the product appears to be a mixture perhaps of the quaternary ammonium salt and the corresponding primary chloride **345**. Evidence for the latter was a second proton signal corresponding to the 1-position of an isoquinoline ring in the ^{1}H NMR. The presence of a mixture may be explained by an equilibrium between **154** and **345** but no



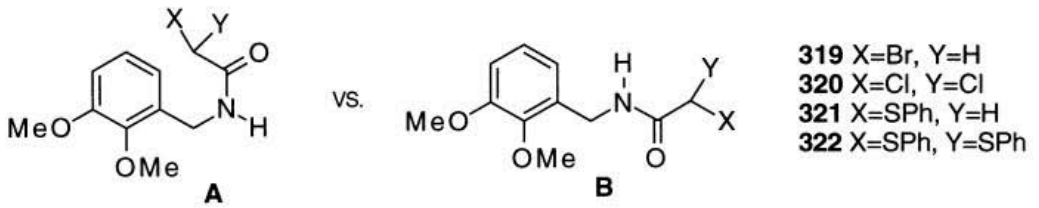
Scheme 6.43 Jatrorrhizine **154** and the primary chloride **345**

precedent has been found for this type of equilibrium. The proton shifts are slightly different than those reported in the paper originally quoting ^{1}H NMR data,[70] but that spectrum was performed in 2:1 DMSO-d_6:CD_3OD whereas the present spectrum was taken in $CDCl_3$. The lower boiling $CDCl_3$ was used for this sample to ease retrieval of the sample if this became necessary. However, the IR data and the NMR data for one component corresponds to the data previously reported for jatrorrhizine suggesting the total synthesis may have been accomplished, albeit in very low yield.

Chapter 7

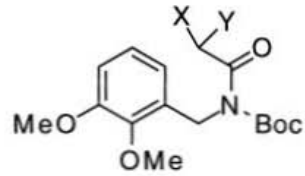
Conclusions of Jatrorrhizine Synthesis

Although not complete, significant progress has been made towards the first total synthesis of jatrorrhizine from readily available starting materials. The critical steps in this approach are the Pomerantz-Fritsch reaction to obtain the isoquinolinol **308** and the Suzuki-type biaryl cross coupling reaction to obtain **307**. Although the isoquinolinol has been obtained and used in the synthesis, the yield is unacceptably low to be considered synthetically practical. This step of the synthesis must be improved. Of particular interest will be the amides **319-322**, especially the sulfur containing amides **321** and **322** as well as the aromatic lithiation reactions. The curious results obtained with **321** and **322** (Scheme 6.24) will be analyzed more closely with a focus on variations in temperature, solvent and the mercury salt. In addition, the halogenated amides **319** and **320** will be reinvestigated. It is possible that the problem with these aromatic substitution reactions is the conformation of the amides themselves. The cisoid form **A** is required for the desired reaction to occur, but these amides may be in the transoid form **B** and therefore may not



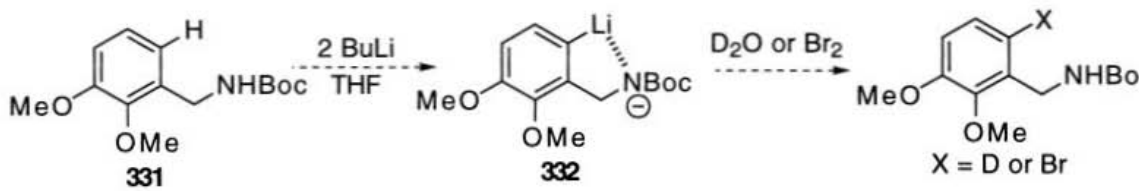
Scheme 7.1 Conformations of amides **319-322**

react intramolecularly but intermolecularly. The use of a bulky group on the nitrogen of the amide may force these compounds into the **A** form thus permitting the desired reaction to occur. Instead of amides **319-322**, the analogous series of Boc substituted amides **346-349** may prove to be more useful in these aromatic substitution reactions.



346 X=Br, Y=H
347 X=Cl, Y=Cl
348 X=SPh, Y=H
349 X=SPh, Y=SPh

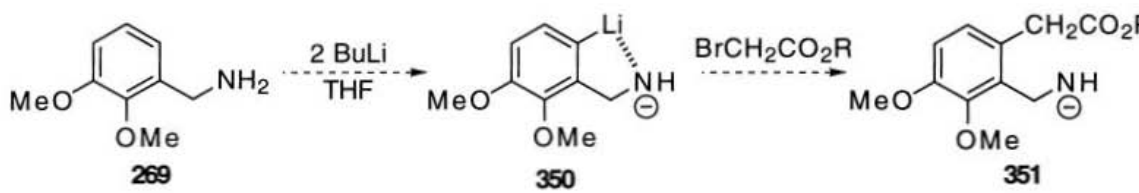
The aromatic lithiation reactions will also be studied, particularly a closer examination of the Boc protected amine **331** and the use of the free amine **269** (Scheme 7.1). Reinvestigation of the Boc amine **331** must be performed to determine if the aromatic lithiation is occurring. This can be accomplished by adding two equivalents of butyllithium then quenching the reaction mixture with deuterium oxide or bromine. If an aromatic proton is removed, the quench will replace the proton with a deuterium or bromine atom. A simple ^{1}H NMR spectrum will show if aromatic substitution has



331 **332**

Scheme 7.2 Aromatic lithiation and quench of **331**

occurred, and the position of substitution could be easily determined. The amine **269** itself may be an adequate directed metalating group and the use of two equivalents of



269 **350** **351**

Scheme 7.3 Use of **269** in *ortho*-metallation reaction

butyllithium may generate the desired dianion required for 1,2,3,4-tetrasubstitution. The quench described for the Boc amine in Scheme 7.2 will also be investigated for this compound. As outlined in Scheme 6.27, the ring closure to the lactam may occur under the reaction conditions or a further elaboration may be required. However, the protons of the bromoacetate may prove to be too acidic for this purpose and may simply reprotonate the dianion. This may require a new approach, such as the Reformatsky reaction outlined in Scheme 7.4. *Ortho*-lithiation of the amine **269** (or the Boc amine **331**) followed by bromination would afford **352**, a suitable substrate for a Reformatsky reaction. The

Scheme 7.4 Reformatsky reaction approach to isoquinolines

Reformatsky reagent **353** is generated by the addition of activated zinc metal to the corresponding bromoester. This organozinc reagent displaces the halide of the aromatic ring under the catalysis of zerovalent nickel or palladium catalysts.[156] The success of this reaction will rely on the completion of the desired aromatic lithiation. Again the formation of the lactam ring may or may not occur under these reaction conditions.

The biaryl coupling reaction must also be further investigated to determine the reason that this reaction could not be successfully repeated. Since subsequent attempts to repeat the experiment were scaled up from the first reaction, variations in the temperature of the reaction may have occurred in the failed attempts. This will be investigated as well as the choice of catalyst.

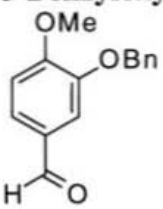
Although the total synthesis of jatrorrhizine has not been accomplished, a direct precursor **265** has been synthesized. Further study is required to improve on this new method of synthesizing this important class of alkaloids.

Chapter 8

Experimental for Jatrorrhizine Synthesis

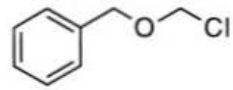
For general experimental information, see the **General procedures** section of Chapter 4, page 37.

3-Benzyloxy-4-methoxybenzaldehyde 278:



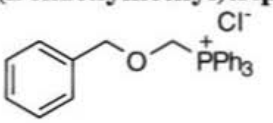
3-Hydroxy-4-methoxybenzaldehyde (isovanillin) **273** (10.00 g, 65.72 mmol) was stirred with sodium hydride (2.62g of 60% dispersion in mineral oil, 65.7 mmol) at -78 °C in THF. The resultant slurry was allowed to warm to room temperature to allow complete deprotonation of the starting material. The reaction was then returned to the acetone-dry ice bath and tetrabutylammonium iodide (0.24 g, 0.66 mmol, 0.01 eq.) was added, followed by benzyl bromide (13.55 g, 78.86 mmol, 1.2 eq.). Stirring was continued at -78 °C for one hour. The mixture was warmed to room temperature and then heated at reflux for four hours. The reaction was cooled to room temperature. Water (50 mL) was added, and the product was extracted into dichloromethane (2x100 mL). The combined organic fractions were washed with brine (50 mL) and dried over Na_2SO_4, and the solvent was removed to give a brown solid. Column chromatography (CH_2Cl_2) gave the product as a colourless solid (13.37 g, 55.20 mmol, 84%), which could be recrystallized from a 4:1 mixture of pentane/hexanes to yield colourless needles: m.p. 61-62 °C (lit. m.p. 62-63 °C);[157] IR 3057 cm^{-1} (s), 3030 cm^{-1} (s), 2990 cm^{-1} (s), 1687 cm^{-1} (s), 1586 cm^{-1} (s), 1510 cm^{-1} (s), 1435 cm^{-1} (s), 1269 cm^{-1} (s); ^1H NMR δ 9.82 (s, 1H), 7.48-7.00 (m, 8H), 5.19 (s, 2H), 3.96 (s, 3H); ^{13}C NMR δ 190.8, 155.0, 148.6, 136.2, 129.9, 128.6, 128.1, 127.4, 126.9, 111.3, 110.7, 70.8, 56.2; LRMS *m/z* 242 (3, M^+), 92 (7), 91 (100), 65 (12), 51 (7), 39 (7).

Benzyloxychloromethane 279:[55a]



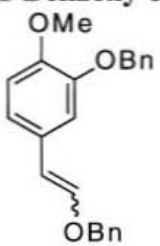
A suspension of paraformaldehyde (16.51 g, 550.0 mmol as CH_2O) in benzyl alcohol (54.07 g, 500.0 mmol) was stirred with a mechanical stirrer in a 250 mL three-necked flask cooled with a water bath. A Claisen adapter equipped with a thermometer and a $CaCl_2$ drying tube was placed in one neck of the flask, and a thermometer adapter holding a Pasteur pipette was placed in another. Anhydrous HCl gas was introduced through the pipette under the surface of the mixture as a fine stream of bubbles for two hours. The flow of gas was regulated such that the temperature of the reaction mixture was maintained between 20-25 °C. The resultant cloudy white mixture was transferred to a separatory funnel, and the layers were allowed to separate overnight. The lower layer was drawn off, and the upper layer was diluted with pentane (200 mL) and dried over $MgSO_4$ with stirring for three hours at 0 °C. The drying agent was removed by filtration, calcium chloride (~0.5 g) was added to prevent decomposition, and the solvent was removed. The colourless, residual oil (77.55 g, 495.2 mmol, 99%) was sufficiently pure to be suitable for use in the next step. Vacuum distillation (62-64 °C/2 mm Hg, lit.[55a] b.p. 70-71 °C/3 mm Hg) of the oil from fresh calcium chloride gave a colourless oil: IR 3041 cm^{-1} (s), 2953 cm^{-1} (m), 2887 cm^{-1} (m), 1497 cm^{-1} (m), 1455 cm^{-1} (m), 1386 cm^{-1} (m), 1316 cm^{-1} (m), 1242 cm^{-1} (m), 1117 cm^{-1} (s); ^1H NMR δ 7.40-7.25 (m, 5H), 5.52 (s, 2H), 4.75 (s, 2H); ^{13}C NMR δ 135.5, 128.6, 128.4, 127.9, 81.7, 71.3; LRMS *m/z* 158 (2, ^{37}Cl-M^+), 156 (5, ^{35}Cl-M^+), 128 (3), 126 (8), 91 (100), 65 (12), 39 (11).

(Benzoxymethyl)triphenylphosphonium chloride 280:



A solution of benzoxychloromethane **279** (10.0 g, 63.85 mmol) in 100 mL of benzene was added to triphenylphosphine (16.75 g, 63.85 mmol) in 100 mL of benzene and the mixture was refluxed for twelve hours. The reaction was cooled to room temperature. The colourless solid that formed (14.32 g, 34.18 mmol, 54%) was filtered off and washed with a minimum of chilled benzene. Concentration of the filtrate to ~100 mL yielded a second crop of crystals which was identical with the first crop by NMR (11.02 g, 26.31 mmol, 41%, combined yield 95%): IR 2936 cm^{-1} (s), 1601 cm^{-1} (s), 1455 cm^{-1} (s), 1099 cm^{-1} (s); ^{1}H NMR δ 7.85-7.27 (m, 20H), 6.06 (d, $^{2}J_{H-P}$=4.28 Hz, 2H), 5.02 (s, 2H); ^{13}C NMR δ 135.6, 135.0, 133.8 (d, $^{2}J_{C-P}$=10.4 Hz), 130.1 (d, $^{3}J_{C-P}$=2.4 Hz), 128.6, 128.2, 128.0, 116.2 (d, $^{1}J_{C-P}$=86.1 Hz), 75.9 (d, $^{3}J_{C-P}$=12.8 Hz), 62.8 (d, $^{1}J_{C-P}$=69.6 Hz); ^{31}P NMR δ 18.85; LRMS *m/z* (M^{+} peak not observed), 263 (20), 262 (100), 261 (15), 185 (11), 184 (15), 183 (66), 126 (10), 108 (38), 107 (15), 91 (78).

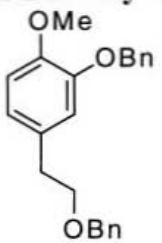
1-Benzoxy-5-(2-benzoxyethenyl)-2-methoxybenzene 281:



A suspension of the phosphonium salt **280** (17.29 g, 41.28 mmol, 2 eq.) in THF (300 mL) was stirred at -78 °C as butyllithium (25.8 mL of a 1.6 M solution in hexanes, 41 mmol, 2 eq.) was added dropwise by syringe. The solution immediately turned a deep maroon colour, and was to stirred for 15 minutes at -78 °C. A solution of **278** (5.00 g, 20.6 mmol) in THF (100 mL) at -78 °C was added to the deprotonated Wittig salt by cannula. The

mixture was stirred for one hour, warmed to room temperature and stirred overnight. Water was added to the reaction mixture, and the products were extracted into dichloromethane (2x150 mL). The combined organic fractions were washed with water (50 mL) and brine (50 mL) and dried over Na_2SO_4. The solvent was removed to give a brown oily solid. Column chromatography (8:1 hexanes:ethyl acetate) yielded a colourless solid (5.85 g, 16.9 mmol, 82%), which could be recrystallized from CH_2Cl_2:hexanes to give colourless needles. Recrystallization from diisopropyl ether afforded nearly pure (*E*)-**281**: m.p. 123-125 °C; IR (*E/Z* mixture) 3029 cm^{-1} (s), 2976 cm^{-1} (s), 1640 cm^{-1} (s), 1513 cm^{-1} (s), 1262 cm^{-1} (s), 1136 cm^{-1} (s), 1024 cm^{-1} (s); (*E*)-**281** ^1H NMR δ 7.46-6.79 (m, 13H), 6.88 (d, 1H, *J*=12.9 Hz), 5.87 (d, 1H, *J*=12.9 Hz), 5.12 (s, 2H), 4.83 (s, 2H), 3.86 (s, 3H); ^{13}C NMR δ 148.2, 148.1, 146.5, 137.2, 136.7, 129.1, 128.5, 128.5 128.0, 127.8, 127.5, 127.2, 118.3, 112.1, 111.2, 106.5, 71.8, 71.1, 56.1; (*Z*)-**281** ^1H NMR δ 7.46-6.79 (m, 13H), 6.18 (d, 1H, *J*=7.0 Hz), 5.17 (d, 1H, *J*=7.0 Hz), 5.09 (s, 2H), 4.93 (s, 2H), 3.87 (s, 3H); ^{13}C NMR δ 147.8, 147.6, 146.5, 144.9, 137.3, 137.2, 128.9, 128.5, 128.4, 127.8, 127.6, 127.2, 121.4, 114.1, 111.5, 106.0, 74.7, 70.7, 56.0; LRMS (*E/Z* mixture) *m/z* 346 (9, M^+), 255 (8), 227 (4), 195 (3), 167 (2), 121 (3), 92, (12), 91 (100), 65 (21).

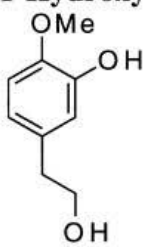
1-Benzoxy-5-(2-benzoxyethyl)-2-methoxybenzene 282:



A solution of **281** (2.50 g, 7.22 mmol) in ethyl acetate (250 mL) was stirred under an atmosphere of hydrogen in the presence of a catalytic amount of palladium on carbon for 12 hours at room temperature until the appropriate amount of H_2 (162 mL, 7.22 mmol)

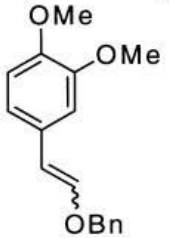
was taken up. The suspension was then filtered through a plug of Celite® and the filter cake was washed several times with ethyl acetate. The combined solutions were dried with $MgSO_4$, and the solvent was removed to give 2.47 g (7.09 mmol, 95%) of a colourless solid, which could be recrystallized from hexanes to give colourless needles: m.p. 57-58 °C; IR 3034 cm^{-1} (s), 2974 cm^{-1} (m), 2935 cm^{-1} (w), 1515 cm^{-1} (m), 1263 cm^{-1} (m), 1228 cm^{-1} (m), 1205 cm^{-1} (s), 1156 cm^{-1} (m), 1028 cm^{-1} (m); ^1H NMR δ 7.44-6.77 (m, 13H), 5.10 (s, 2H), 4.48 (s, 2H), 3.85 (s, 3H), 3.61 (t, 2H, *J*=7.0 Hz), 2.82 (t, 2H, *J*=7.0 Hz); ^{13}C NMR δ 148.1, 147.9, 138.4, 137.2, 131.6, 128.4, 128.3, 127.7, 127.6, 127.5, 127.3, 121.5, 115.1, 111.8, 72.9, 71.3, 71.0, 56.1, 35.8; LRMS *m/z* 348 (4, M^+), 227 (2), 180 (2), 167 (2), 151 (4), 137 (2), 135 (2), 123 (2), 108 (2), 107 (2), 92 (8), 91 (100), 77 (2), 65 (8), 51 (2), 39 (3).

1-Hydroxy-5-(2-hydroxyethyl)-2-methoxybenzene 297:



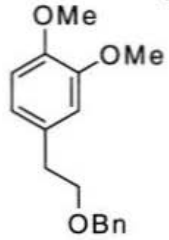
Compound **281** (0.50 g, 1.4 mmol) in EtOAc (50 mL) with catalytic Pd/C and H_2 (94 mL, 4.2 mmol, 3 eq.) were reacted as described for the synthesis of **281** for 24 hours to give 0.20 g (1.2 mmol, 85%) of a colourless solid: m.p. 65-66 °C; IR 3688 cm^{-1} (s), 3615 cm^{-1} (s), 3550 cm^{-1} (m), 3030 cm^{-1} (m), 2940 cm^{-1} (s), 1575 cm^{-1} (s), 1516 cm^{-1} (s), 1422 cm^{-1} (m), 1272 cm^{-1} (m), 1202 cm^{-1} (s); ^1H NMR δ 6.81-6.69 (m, 3H), 5.62 (s, 1H), 3.87 (s, 3H), 3.82 (br t, 2H), 2.78 (t, *J*=6.5 Hz, 2H), 1.41 (br s, 1H); ^{13}C NMR δ 145.7, 145.2, 131.6, 120.4, 115.1, 110.8, 63.7, 56.0, 38.6; LRMS *m/z* 168 (22, M^+), 138 (11), 137 (100), 122 (23), 94 (37), 78 (10), 77 (22), 66 (21), 65 (23), 55 (14), 52 (13), 51 (23), 41 (11), 39 (36), 31 (21).

4-(2-Benzoxyethenyl)-1,2-dimethoxybenzene 301:



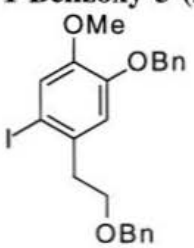
The phosphonium salt **280** (30.99 g, 73.98 mmol, 2 eq.), butyllithium (46.2 mL of a 1.6 M solution in hexanes, 74 mmol, 2 eq.), and 3,4-dimethoxybenzaldehyde (6.15 g, 37.0 mmol) were reacted as described for compound **281**. Column chromatography with 6:1 hexanes:EtOAc gave the product as a colourless oil that solidified on refrigeration (6.02 g, 22.3 mmol, 60%). The product coiuld be recrystallized from hexanes to give colourless plates of nearly pure (*E*)-**301**: m.p. 42-43 °C; IR (*E/Z* mixture) 3027 cm^{-1} (s), 2939 cm^{-1} (m), 2840 cm^{-1} (m), 1723 cm^{-1} (s), 1682 cm^{-1} (s), 1589 cm^{-1} (s), 1512 cm^{-1} (s), 1465 cm^{-1} (s), 1271 cm^{-1} (s), 1157 cm^{-1} (s), 1010 cm^{-1} (m); (*E*)-**301** ^1H NMR δ 7.39-6.22 (m, 8H), 6.97 (d, *J*=12.9 Hz, 1H), 5.93 (d, *J*=12.9 Hz, 1H), 4.88 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR δ 149.0, 147.4, 146.5, 136.8, 129.1, 128.5, 128.0, 127.5, 117.6, 111.4, 108.3, 106.7, 71.8, 55.9, 55.8; (*Z*)-**301** ^1H NMR δ 7.39-6.22 (m, 8H), 6.23 (d, *J*=7.0 Hz, 1H), 5.23 (d, *J*=7.0 Hz, 1H), 4.96 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H); ^{13}C NMR δ 148.4, 147.1, 146.5, 144.8, 137.1, 129.0, 128.5, 127.2, 120.8, 111.5, 110.9, 106.1, 74.7, 55.7, 55.6; LRMS (*E/Z* mixture) *m/z* 270 (12, M^+), 180 (11), 179 (90), 151 (52), 148 (24), 137 (12), 136 (10), 107 (13), 91 (100), 77 (19), 65 (35), 63 (10), 51 (17), 39 (23).

4-(2-Benzoxyethyl)-1,2-dimethoxybenzene 302:



Compound **301** (3.00 g, 11.1 mmol) in EtOAc (250 mL) with catalytic Pd/C and H_2 (249 mL, 11.1 mmol) was reacted as described for compound **282** to give 2.87 g (10.5 mmol, 95%) of a colourless oil: IR 2939 cm^{-1} (s), 2863 cm^{-1} (s), 1703 cm^{-1} (s), 1592 cm^{-1} (s), 1511 cm^{-1} (s), 1465 cm^{-1} (s), 1267 cm^{-1} (s), 1215 cm^{-1} (s), 1096 cm^{-1} (s); ^1H NMR δ 7.33-6.77 (m, 8H), 4.53 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.68 (t, 2H, *J*=7.0 Hz), 2.88 (t, 2H, *J*=7.0 Hz); ^{13}C NMR δ 148.7, 147.4, 138.4, 131.6, 128.3, 127.6, 127.5, 120.7, 112.2, 111.1, 73.0, 71.4, 55.9, 55.8, 35.9; LRMS *m/z* 272 (14, M^+), 152 (10), 151 (100), 91 (56), 65 (14).

1-Benzoxy-5-(2-benzoxyethyl)-4-iodo-2-methoxybenzene 340:



Compound **282** (1.16 g, 3.33 mmol) was dissolved in glacial acetic acid (100 mL) and a solution of iodine monochloride (0.54 g, 3.3 mmol) in glacial acetic acid (15 mL) was added dropwise. The resultant dark brown solution was stirred overnight then diluted with CH_2Cl_2 (200 mL), extracted with 2M NaOH (100 mL), 1M $Na_2S_2O_5$ (2x50 mL) then brine (50 mL). The organic portion was dried with Na_2SO_4, and the solvent was removed to give a pale brown oil. Column chromatography (CH_2Cl_2) afforded 1.14 g (2.40 mmol, 72%) of a pale yellow oil, which solidified on standing and could be

recrystallized from hexanes to give colourless needles: m.p. 67-68 °C; IR 3036 cm^{-1} (s), 2977 cm^{-1} (m), 1504 cm^{-1} (w), 1227 cm^{-1} (s), 1206 cm^{-1} (s); ^1H NMR δ 7.40-7.24 (m, 11H), 6.83 (s, 1H), 5.02 (s, 2H), 4.45 (s, 2H), 3.76 (s, 3H), 3.56 (t, 2H, *J*=6.9 Hz), 2.91 (t, 2H, *J*=6.9 Hz); ^{13}C NMR δ 148.7, 148.3, 138.3, 136.7, 133.9, 128.5, 128.3, 122.1, 115.7, 89.0, 72.9, 71.0, 69.8, 56.2, 40.5; nOe data δ 6.83 (5.02, 5.4%; 3.56, 1.0%; 2.91, 2.0%), 3.56 (6.83, 2.8%; 4.45, 3.5%; 2.91, 2.3%), 2.91 (6.83, 8.2%; 3.56, 3.3%); LRMS *m/z* 474 (46, M^+), 256 (12), 165 (63), 92 (33), 91 (100), 77, (10), 65 (34), 63 (11), 51 (11), 39 (16).

_N_-(2,3-Dimethoxybenzyl)-2-bromoacetamide 319:

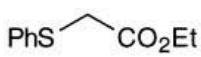
A solution of bromoacetyl bromide (2.61 g, 12.0 mmol) in benzene (50 mL) was stirred at room temperature as a solution of 2,3-dimethoxybenzylamine (2.00 g, 12.0 mmol) and triethylamine (1.21 g, 12.0 mmol) in benzene (20 mL) was added dropwise. The cloudy, white suspension was stirred for two hours, and it was diluted with CH_2Cl_2 (100 mL), washed with 2M HCl, water, and brine (30 mL each). The organic portion was dried with Na_2SO_4, and the solvent was removed to give a beige solid. The crude product was passed through a short plug of silica gel eluted with 1:1 EtOAc:petroleum ether to give a colourless solid (2.91 g, 10.1 mmol, 84%), which was recrystallized from water to give colourless, silky needles: m.p. 101-102 °C; IR 3423 cm^{-1} (w), 3040 cm^{-1} (w), 3016 cm^{-1} (s), 1666 cm^{-1} (s), 1484 cm^{-1} (s), 1210 cm^{-1} (s), 1088 cm^{-1} (w); ^1H NMR δ 7.06-6.83 (m, 4H, 3 ArH and one NH), 4.49 (d, 2H, *J*=5.8 Hz), 3.90 (s, 3H), 3.89 (s, 2H), 3.88 (s, 3H); ^{13}C NMR δ 165.0, 152.6, 147.3, 130.8, 124.2, 121.4, 112.3, 60.8, 55.8, 39.9, 29.2;

LRMS *m/z* 289 (7, ^{81}Br-M$^+$), 287 (7, ^{79}Br-M$^+$), 209 (12), 208 (100), 191 (12), 176 (11), 167 (11), 166 (22), 150 (14), 137 (10), 136 (11), 91 (13), 65 (11).

2,2-dichloro-*N*-(2,3-Dimethoxybenzyl)acetamide 320:

Dichloroacetyl chloride (0.88 g, 6.0 mmol), 2,3-dimethoxybenzylamine (1.00 g, 5.98 mmol) and triethylamine (0.61 g, 6.0 mmol) were reacted and purified as described for **319** to give a colourless solid (1.46 g, 5.25 mmol, 88%), which was recrystallized from water to give colourless, silky needles: m.p. 126.5-127.5 °C; IR 3425 cm^{-1} (s), 3022 cm^{-1} (s), 2978 cm^{-1} (w), 1692 cm^{-1} (s), 1524 cm^{-1} (w), 1484 cm^{-1} (m), 1237 cm^{-1} (m), 1207 cm^{-1} (m), 1088 cm^{-1} (w); ^{1}H NMR δ 7.07-6.86 (m, 4H, 3 ArH and one NH), 5.93 (s, 1H), 4.51 (d, 2H, *J*=5.8 Hz), 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR δ 163.7, 152.6, 147.2, 130.1, 124.3, 121.2, 112.4, 66.4, 60.8, 55.7, 40.1; LRMS *m/z* 281 (2.5, ^{37}Cl^{37}Cl-M$^+$), 279 (14.5, ^{37}Cl^{35}Cl-M$^+$), 277 (21.3, ^{35}Cl^{35}Cl-M$^+$), 244 (32), 243 (13), 242 (100), 206 (24), 166 (18), 151 (18), 137 (11), 136 (34), 106 (11), 91 (31), 77 (12), 65 (20), 51 (10), 39 (11), 32(13), 28 (61); HRMS calcd. for $C_{11}H_{13}Cl_2NO_3$ 277.0272, found 277.0272.

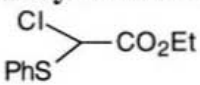
Ethyl 2-(phenylthio)acetate 323:



Sodium hydride (6.00 g of 60% dispersion in mineral oil, 250 mmol) was stirred at -78 °C in THF and thiophenol (27.54 g, 250.0 mmol) was added. The gray suspension was allowed to warm to room temperature and stirred for one hour. The resultant white slurry was returned to -78 °C. Ethyl bromoacetate (41.75 g, 250.0 mol) was added, and the mixture was warmed to room temperature and stirred for 2 hours. Saturated aqueous

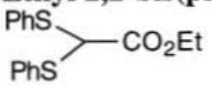
NH_4Cl (50 mL) was added and the minimum amount of water needed to dissolve the remaining salts was added. The product was extracted into CH_2Cl_2 (2x100 mL), and the combined organic extracts were washed with brine and dried with Na_2SO_4. The solvent was removed, and vacuum distillation (114-115 °C/1 mm Hg, lit.[53] b.p. 118 °C/1 mm Hg) afforded the product (44.13 g, 224.8 mmol, 90%) as a colourless liquid: IR 3012 cm^{-1} (m), 2968 cm^{-1} (m), 1732 cm^{-1} (s), 1579 cm^{-1} (m), 1289 cm^{-1} (s); ^1H NMR δ 7.42-7.22 (m, 5H), 4.16 (q, 2H, *J*=7.1 Hz), 3.63 (s, 2H), 1.21 (t, 3H, *J*=7.1 Hz); ^{13}C NMR δ 169.6, 135.0, 129.9, 128.9, 126.9, 61.5, 36.7, 14.0; LRMS *m/z* 196 (45, M^+), 123 (100), 109 (13), 77 (15), 65 (13), 51 (16), 45 (55).

Ethyl 2-chloro-2-(phenylthio)acetate 324:[158]



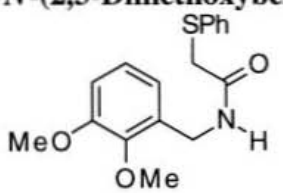
Ethyl 2-(phenylthio)acetate (10.00 g, 50.95 mmol) in CH_2Cl_2 (150 mL) was stirred at reflux as a solution of sulfuryl chloride (7.22 g, 53.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise over two hours. The resultant yellow solution was refluxed for another hour then cooled to room temperature. The reaction was allowed to stand overnight. The solvent was removed and vacuum distillation (112-114 °C/1mm Hg) of the residue gave the product as a pale yellow oil (11.04 g, 47.85 mmol, 94%): IR 3011 cm^{-1} (s), 1745 cm^{-1} (s), 1474 cm^{-1} (w), 1441 cm^{-1} (w), 1243 cm^{-1} (s), 1174 cm^{-1} (s), 1023 cm^{-1} (m); ^1H NMR δ 7.61-7.38 (m, 5H), 5.53 (s, 1H), 4.24 (q, 2H, *J*=7.1 Hz), 1.28 (t, 3H, *J*=7.1 Hz); ^{13}C NMR δ 165.8, 137.3, 134.1, 129.2, 129.6, 64.8, 62.9, 13.9; LRMS *m/z* 232 (11, ^{37}Cl-M^+), 230 (33, ^{35}Cl-M^+), 159 (35), 157 (100), 123 (11), 122 (14), 121 (58), 109 (27), 78 (14), 77 (41), 69 (10), 65 (22), 51 (34), 50 (11), 45 (38), 29 (58).

Ethyl 2,2-bis(phenylthio)acetate 325:[159]



Ethyl 2-chloro-2-(phenylthio)acetate (11.04 g, 47.85 mmol) was adsorbed onto neutral Al_2O_3 (40 g) and heated at 80 °C for 24 hours under an atmosphere of nitrogen. The product was then eluted from the alumina by washing with CH_2Cl_2 (4x100 mL). The solvent was removed, and vacuum distillation (178-180 °C/1 mm Hg, lit.[159] b.p. 165-167 °C/1 mm Hg) of the residue yielded the product (3.72 g, 23.9 mmol, 51%) as a yellow oil. Slight decomposition was observed in the NMR spectrum at this high temperature so an analytically pure sample was obtained by column chromatography (1:1 petroleum ether:CH_2Cl_2) to give the product as a colourless oil: IR 3069 cm^{-1} (s), 2979 cm^{-1} (m), 1730 cm^{-1} (s), 1583 cm^{-1} (w), 1481 cm^{-1} (m), 1440 cm^{-1} (m), 1283 cm^{-1} (s), 1143 cm^{-1} (m), 1025 cm^{-1} (m); ^1H NMR δ 7.51-7.30 (m, 10 H), 4.85 (s, 1H), 4.14 (q, 2H, *J*=7.1 Hz), 1.17 (t, 3H, *J*=7.1 Hz); ^{13}C NMR δ 168.5, 133.3, 132.7, 129.0, 128.6, 62.1, 58.3, 13.9; LRMS *m/z* 304 (8, M^+), 195 (34), 149 (32), 121 (100), 109 (24), 77 (40), 51 (26), 45 (30).

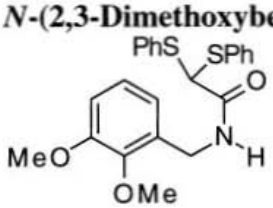
***N*-(2,3-Dimethoxybenzyl)-2-(phenylthio)acetamide 321:**



Ethyl 2-(phenylthio)acetate (3.12 g, 15.9 mmol) was suspended in 40 mL of water as KOH (0.89 g, 16 mmol) in water (40 mL) was added dropwise. The mixture rapidly became one phase, and it was allowed to stir at room temperature for two hours. The solvent was removed to give a colourless solid, which was dried at 50 °C under vacuum for three hours. The solid was suspended in ether (30 mL), and the mixture was maintained at 10 °C as thionyl chloride (1.42 g, 12.0 mmol) in ether (15 mL) was added

dropwise. The resultant cloudy suspension was refluxed for thirty minutes, cooled to room temperature, then poured into a vigorously stirred solution of 2,3-dimethoxy-benzylamine (2.00 g, 12.0 mmol) in triethylamine (1.21 g, 12.0 mmol) and benzene (20 mL) at room temperature. The yellow suspension was refluxed for thirty minutes, allowed to cool then poured onto ice and extracted with benzene (2x150 mL). The combined organic extracts were washed with water and brine (50 mL each) then dried with Na_2SO_4. Removal of the solvent and chromatography (4:1 CH_2Cl_2:EtOAc) yielded the product as a colourless solid (2.68 g, 8.44 mmol, 71%), which could be recrystallized from EtOAc:hexanes to give colourless needles: m.p. 107-108 °C; IR 3398 cm^{-1} (w), 3032 cm^{-1} (s), 2967 cm^{-1} (w), 1665 cm^{-1} (s), 1482 cm^{-1} (s), 1278 cm^{-1} (m), 1086 cm^{-1} (m); ^1H NMR δ 7.26-6.68 (m, 9H, 8 ArH and one NH), 4.44 (d, 2H, *J*=5.9 Hz), 3.83 (s, 3H), 3.78 (s, 3H), 3.62 (s, 2H); ^{13}C NMR δ 167.5, 152.4, 147.0, 134.5, 131.1, 129.1, 128.2, 126.5, 124.0, 120.9, 111.9, 60.5, 39.0, 37.4; LRMS *m/z* 317 (12, M^+), 209 (11), 208 (100), 166 (11), 151 (18), 136 (26), 123 (13), 91 (23), 45 (13).

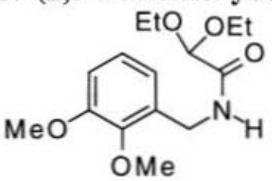
_N_-(2,3-Dimethoxybenzyl)-2,2-bis(phenylthio)acetamide 322:



Ethyl 2,2-bis(phenylthio)acetate (4.76 g, 15.7 mmol), KOH (0.88 g, 16 mmol), thionyl chloride (1.42 g, 12.0 mmol), 2,3-dimethoxybenzylamine (2.00 g, 12.0 mmol) and triethylamine (1.21 g, 12.0 mmol) were reacted as for compound **321**. Column chromatography (2:1 petroleum ether:EtOAc) yielded the product as a colourless solid (4.03 g, 9.47 mmol, 79%) which was recrystallized from EtOAc to give colourless needles: m.p. 116-116.5 °C; IR 3391 cm^{-1} (w), 3029 cm^{-1} (s), 2940 cm^{-1} (w), 1672 cm^{-1} (s), 1514 cm^{-1} (m), 1482 cm^{-1} (s), 1279 cm^{-1} (m), 1086 cm^{-1} (m); ^1H NMR δ 7.42-7.23

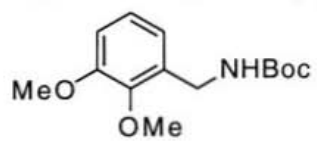
(m, 14H, 13 ArH and one NH), 4.36 (d, 2H, *J*=5.9 Hz), 3.85 (s, 3H), 3.78 (s, 3H); ^{13}C NMR δ 166.9, 152.5, 147.1, 132.7, 132.4, 130.8, 129.1, 128.3, 124.1, 121.2, 112.0, 60.6, 58.0, 55.7, 39.3; LRMS *m/z* 425 (17, M^+), 316 (11), 259 (18), 232 (12), 231 (25), 207 (12), 206 (100), 178 (11), 151 (12), 136 (17), 123 (26), 121 (15), 110 (13), 109 (12), 91 (23), 77 (12), 45 (13).

_N_-(2,3-Dimethoxybenzyl)-2,2-diethoxyacetamide 338:[142]



Ethyl diethoxyacetate (5.00 g, 28.4 mmol), KOH (1.59 g, 28.4 mmol), thionyl chloride (3.38 g, 28.4 mmol), 2,3-dimethoxybenzylamine (4.00 g, 23.9 mmol) and triethylamine (2.42 g, 23.9 mmol) were reacted as for **321**. Column chromatography (2:1 EtOAc:petroleum ether) of the residual oil afforded 5.01 g (16.8 mmol, 70%) of the product as a pale yellow oil: IR 3424 cm^{-1} (m), 3030 cm^{-1} (s), 2940 cm^{-1} (m), 1688 cm^{-1} (s), 1516 cm^{-1} (s), 1484 cm^{-1} (s), 1279 cm^{-1} (s), 1088 cm^{-1} (s); ^1H NMR δ 7.05-6.86 (m, 4H, 3 ArH and one NH), 4.82 (s, 1H), 4.49 (d, 2H, *J*=6.0 Hz), 3.87 (s, 3H), 3.87 (s, 3H), 3.65 (m, 4H), 1.23 (t, 6H, *J*=7.0 Hz); ^{13}C NMR δ 167.6, 152.6, 147.2, 131.4, 124.2, 121.3, 112.0, 98.5, 62.4, 60.7, 55.8, 38.3, 15.1; LRMS *m/z* 297 (2, M^+), 136 (10), 103 (100), 91 (11), 75 (60), 47 (59), 29 (13), 28 (16).

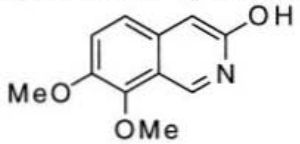
_N_-(*tert*-Butoxycarbonyl)-2,3-dimethoxybenzylamine 331:



A solution of 2,3-dimethoxybenzylamine (1.47 g, 8.79 mmol) in $CHCl_3$ (50 mL) was stirred at room temperature under an atmosphere of nitrogen as a solution of di-*tert*-

butyldicarbonate (2.11 g, 9.66 mmol, 1.1 eq) in $CHCl_3$ (20 mL) was added dropwise. The resultant pale yellow solution was stirred for two hours at room temperature, and the solvent was removed to give a yellow solid, which was recrystallized from hexanes to afford colourless needles (2.10 g, 7.85 mmol, 89%): m.p. 64-65 °C; IR 3454 cm^{-1} (w), 3028 cm^{-1} (s), 2937 cm^{-1} (w), 1707 cm^{-1} (s), 1513 cm^{-1} (m), 1483 cm^{-1} (s), 1244 cm^{-1} (s), 1168 cm^{-1} (s), 1080 cm^{-1} (m); ^1H NMR δ 6.84-7.04 (m, 3H), 4.99 (broad s, 1H), 4.33 (d, 2H, *J*=6.0 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 1.44 (s, 9H); ^{13}C NMR δ 155.8, 152.5, 147.0, 132.6, 124.1, 121.0, 111.7, 79.2, 60.6, 55.7, 40.0, 28.4; LRMS *m/z* 267 (10, M^+), 210 (28), 166 (79), 152 (26), 151 (33), 136 (27), 57 (100), 41 (42).

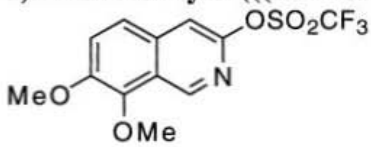
7,8-Dimethoxy-3-hydroxyisoquinoline 318:[88a]



Polyphosphoric acid (100 mL) was prepared in a 250 mL three-necked round-bottomed flask equipped with a mechanical stirrer and heated at 100 °C. Compound **338** (1.00 g, 3.36 mmol) was added dropwise, and the resultant brown mixture was stirred for 30 minutes. The hot reaction mixture was then poured onto ice (200 mL). The dark brown solution was saturated with NaCl and extracted with CH_2Cl_2 (8x500 mL). The combined extracts were dried with Na_2SO_4, and the solvent removed to give an orange solid. Column chromatography (4:1 EtOAc:MeOH) gave the desired product as a yellow solid (0.10 g, 0.49 mmol, 15%), which could be recrystallized from ethanol to give yellow needles: 128-129 °C (lit.[88a] m.p. 130-132 °C); IR 3376 cm^{-1} (w), 2930 cm^{-1} (s), 2855 cm^{-1} (w), 1693 cm^{-1} (s), 1592 cm^{-1} (m), 1500 cm^{-1} (m), 1460 cm^{-1} (m), 1264 cm^{-1} (s), 1247 cm^{-1} (m), 1047 cm^{-1} (w); ^1H NMR δ 8.97 (s, 1H), 7.37 (d, 1H, *J*=9.2 Hz), 7.31 (d, 1H, *J*=9.2 Hz), 6.93 (s, 1H), 4.05 (s, 3H), 3.94 (s, 3H); ^{13}C NMR δ 161.0, 145.0, 144.9, 144.0, 140.8, 138.2, 123.9, 121.2, 118.3, 104, 61.4, 57.7; LRMS *m/z* 205 (100, M^+), 190

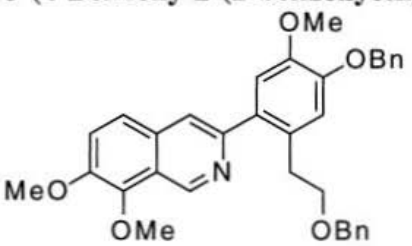
(59), 162 (39), 147 (22), 134 (29), 119 (18), 116 (12), 91 (13), 63 (16), 32 (13); HRMS calcd. for $C_{11}H_{11}NO_3$ 205.0739, found 205.0734

7,8-Dimethoxy-3-(((trifluoromethyl)sulfonyl)oxy)isoquinoline 308:



Compound **318** (0.20 g, 0.97 mmol) was stirred in CH_2Cl_2 at -78 °C as diisopropylamine (0.25 mL, 1.9 mmol, 2 eq.) was added. The solution was stirred at -78 °C for 30 minutes, triflic anhydride (0.32 mL, 1.9 mmol, 2 eq.) was added dropwise by syringe, and the mixture was stirred for one hour and then allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2 and extracted with water until the washings were neutral. The organic portion was then washed with brine and dried (Na_2SO_4), and the solvent was removed to give a brown solid. Column chromatography (CH_2Cl_2) afforded an orange solid (0.27 g, 0.80 mmol, 82%), which is very nearly pure triflate: m.p. 83-84 °C; IR 2992 cm^{-1} (s), 2936 cm^{-1} (w), 2847 cm^{-1} (w), 1596 cm^{-1} (s), 1563 cm^{-1} (s), 1421 cm^{-1} (s), 1278 cm^{-1} (s), 1140 cm^{-1} (s); ^1H NMR δ 9.33 (s, 1H), 7.62 (d, 1H, *J*=9.1 Hz), 7.59 (d, 1H, *J*=9.1 Hz), 7.50 (s, 1H), 4.09 (s, 3H), 4.03 (s, 3H); ^{13}C NMR δ 151.6, 149.4, 147.3, 144.0, 133.6, 124.3, 122.6, 121.7, 118.7 (q, $^1J_{C\text{-}F}$=320 Hz), 110.18, 61.69, 57.02; LRMS *m/z* 337 (69, M^+), 204 (73), 177 (13), 176 (100), 161 (26), 116 (47), 89 (14), 69 (16), 63 (15).

3-(4-Benzoxy-2-(2-benzoxyethyl)-5-methoxyphenyl)-7,8-dimethoxyisoquinoline 307:

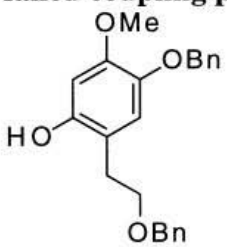


Compound **340** (0.11 g, 0.23 mmol, 1.5 eq.) was stirred in THF at -78 °C as butyllithium (0.19 mL of 1.6 M soln. in hexanes, 0.30 mmol, 2 eq.) was added dropwise by syringe. The solution was stirred at -78 °C for 15 minutes then trimethyl borate (0.05 mL, 0.45 mmol, 3 eq.) was added dropwise *via* syringe. The solution was warmed to room temperature and stirred for twenty minutes, then 100 mL each of 10% HCl and ether were added. The organic layer containing the boronic acid was washed with water, then the solution was dried with $MgSO_4$. The solvent was then removed to give a black solid, which was used without further purification.

The triflate **308** (0.050 g, 0.15 mmol) was dissolved in ~4 mL dimethoxyethane (DME), $Pd(PPh_3)_4$ was added, followed by 2M Na_2CO_3 (1 mL). The mixture was brought to reflux, and the crude boronic acid in DME (1 mL) was added. The black colour instantly disappeared, and the orange solution was refluxed for 18 hr. The mixture was then treated with ethyl acetate (5 mL) and extracted with 1 M NaOH (10 mL) then brine (10 mL). The organic portion was dried with $MgSO_4$. The solvent was removed, and column chromatography (6:1 CH_2Cl_2:EtOAc) afforded the product as a colourless solid (0.051 g, 0.095 mmol, 65%): IR 3033 cm^{-1} (s), 2941 cm^{-1} (m), 2862 cm^{-1} (w), 1606 cm^{-1} (m), 1514 cm^{-1} (m), 1465 cm^{-1} (m), 1373 cm^{-1} (m), 1264 cm^{-1} (m), 1138 cm^{-1} (m), 1108 cm^{-1} (m), 1069 cm^{-1} (m), 1026 cm^{-1} (m); ^1H NMR δ 9.56 (s, 1H), 7.61-6.91 (m, 15 H), 5.18 (s, 2H), 4.37 (s, 2H), 4.10 (s, 3H), 4.02 (s, 3H), 3.90 (s, 3H), 3.55 (t, 2H, *J*=7.2 Hz), 2.97 (t, 2H, *J*=7.2 Hz); LRMS *m/z* 535 (0.8, M^+), 444 (9), 428 (23), 427 (28), 426

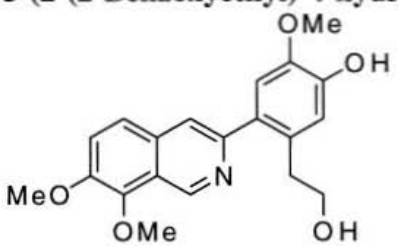
(12), 352 (8), 323 (6), 322 (8), 338 (18), 336 (10), 308 (8), 307 (7), 293 (3), 292 (4), 278 (5), 264 (4), 262 (3), 222 (3), 92 (7), 91 (100), 77 (6), 65 (9), 32 (5).

Isolation of 4-Benzoxy-2-(2-benzoxyethyl)-1-hydroxy-5-methoxybenzene 344 from failed coupling procedure:



After the usual workup procedure for coupling reactions (*vide supra*), column chromatography (CH_2Cl_2) afforded the phenol **344** in ~40% yield as a pale yellow solid: m.p. 42-43 °C; IR 3290 cm^{-1} (br), 3034 cm^{-1} (s), 2929 cm^{-1} (w), 2868 cm^{-1} (w), 1640 cm^{-1} (w), 1510 cm^{-1} (s), 1454 cm^{-1} (w), 1366 cm^{-1} (w), 1251 cm^{-1} (m), 1214 cm^{-1} (s), 1119 cm^{-1} (w), 1049 cm^{-1} (w); ^1H NMR δ 7.89 (s, 1H), 7.41-7.25 (m, 10H), 6.58 (s, 1H), 6.56 (s,1H), 5.03 (s, 2H), 4.57 (s, 2H), 3.84 (s, 3H), 3.72 (t, 2H), 2.78 (t, 2H); ^{13}C NMR δ 150.60, 149.98, 141.39, 137.69, 136.76, 128.57, 128.37, 128.07, 127.81, 127.67, 127.50, 118.48, 117.48, 102.30, 73.72, 72.61, 72.51, 55.93, 32.57; nOe data δ 7.89 (6.56, 1.3%; 2.78, 1.5%), 3.84 (7.89, 7%; 6.56, 22%; 5.03, 8%; 4.57, 7%; 3.72, 7%; 2.78, 8%), 3.72 (7.89, 9%; 5.03, 8%; 4.57, 13%; 3.84, 7%; 2.78, 13%), 2.78 (7.89, 13%; 6.58, 14%; 5.03, 7%; 4.57, 8%; 3.84, 8%; 3.72, 14%); LRMS *m/z* 364 (0.45, M^+), 273 (4), 181 (2), 166 (3), 165 (5), 137 (2), 92 (8), 91 (100), 77 (2), 69 (3), 65 (8), 51 (2), 39 (3).

3-(2-(2-Benzoxyethyl)-4-hydroxy-5-methoxyphenyl)-7,8-dimethoxyisoquinoline 265:



Compound **307** (0.02 g) was dissolved in EtOAc (10 mL), and a catalytic amount of $Pd(OH)_2$ on carbon was added. The suspension was stirred under an atmosphere of H_2 for 24 hr. The suspension was then filtered through a plug of Celite®, and the filter plug was reextracted several times with EtOAc. The solution was then dried with $MgSO_4$ and the solvent was removed. Column chromatography (EtOAc) of the residue afforded the product as a pale yellow solid: m.p. 173-174 °C; ^{1}H NMR δ 9.54 (s, 1H), 7.74 (s, 1H), 7.62 (d, 1H, *J*=9.0 Hz), 7.55 (d, 1H, *J*=9.0 Hz), 6.97 (s, 1H), 6.94 (s, 1H), 5.68 (s, 1H), 4.10 (s, 3H), 4.03 (s, 3H), 3.99 (t, 2H, *J*=5.5 Hz), 3.93 (s, 3H), 2.83 (t, 2H, *J*=5.5 Hz), primary OH not observed; LRMS *m/z* 355 (29, M^+), 338 (59), 337 (64), 336 (96), 326 (21), 325 (100), 324 (24), 323 (50), 322 (28), 310 (37), 308 (34), 294 (23), 280 (18), 266 (24), 251 (21), 222 (20), 206 (12), 168 (13), 147 (13), 139 (12), 131 (12), 126 (14), 124 (11), 117 (12), 44 (16), 32 (25), 31 (12).

Diels-Alder References

1. Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

2. (a) Desimoni, G.; Tacconi, G.; Bario, A.; Pollini, G. P. In *Natural Product Synthesis through Pericyclic Reactions*; ACS Monograph; American Chemical Society: Washington, D.C., **1984**; Chapter 5. (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold. R., Ed.; Springer Verlag: New York, **1986**; 261. (c) Paquette, L. A. In *Asymmetric Synthesis;* Morrison, J. D., Ed.; Academic Press: New York, **1984**; Vol. 3, Chapter 4. (d) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; Wiley-Interscience: New York, **1990**.

3. (a) Wheeler, J. *J. Chem. Soc.* **1929**, 378-393. (b) Wheeler, J.; Wood,W. *J. Chem. Soc.* **1930**, 1819-1828.

4. (a) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779-807. (b) Houk, K. N.; Lin, Y.-T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554-556. (c) Dolbier, Jr., W. R.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471-477.

5. (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876-889. (b) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092-4094. (c) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923-3941. (d) Eisenstein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron* **1977**, *33*, 523-531. (e) Alston, P. V.; Ottenbrite, R. M. *J. Org. Chem.* **1975**, *40*, 1111-1116.

6. (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, **1970**. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions;* Wiley-Interscience: Chichester, **1978**; Chapter 4. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361-369. (d) Herndon, W. C. *Chem. Rev.* **1972**, *72*, 157-179.

7. (a) Townshend, R. E.; Ramunni, G.; Segal, G.; Hehre, W. J.; Salem, L. *J. Am. Chem. Soc.* **1976**, *98*, 2190-2192. (b) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381-7396.

8. Koizumi, T.; Arai, Y.; Takayama, H.; Kuriyama, K.; Shiro, M. *Tetrahedron Lett.* **1987**, *28,* 3689-3692.

9. Sustmann, R.; Schubert, R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11,* 840.

10. (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974,** *96*, 7807-7808. (b) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979,** *101*, 6996-6999. (c) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400-406. (d) Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444-4451. (e) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Raimondi, L. *J. Org. Chem.* **1992**, *57*, 3605-3609. (f) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749-1760.

11. Danishefsky, S.; Kitahara, T.; Schuda, P. *Org. Syn. Coll. Vol. 7,* **1990**, 312-315.

12. Danishefsky's diene is commercially available from the Aldrich Chemical Company, Inc. at a cost of $100.30 CDN for 5 grams (1996 catalogue).

13. (a) Danishefsky, S. *Aldrichimica Acta* **1986**, *19*, 59-69. (b) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977,** *99*, 6066-6073.

(c) Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. *J. Am. Chem. Soc.* **1978**, *100*, 6536-6538. (d) Danishefsky, S; Hirama, M. *J. Am. Chem. Soc.* **1977**, *99*, 7740-7741. (e) Waldmann, H.; Braun, M.; Weymann, M.; Gewehr, M. *Tetrahedron* **1993**, *49*, 397-416.

14. For reviews of the inverse electron demand Diels-Alder reaction of hetero dienes: (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869-2939. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781-793. (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Organic Chemistry Monograph Series, Vol. 47; Academic Press: New York, **1987**. (d) Kametani, T.; Hibino, S. In *Advances in Heterocyclic Chemistry;* Katritzky, A. R., Ed.; Academic Press: New York, **1987**; Vol. 42, pp 246-335. (e) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087-3128.

15. (a) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1984**, *25*, 721-724. (b) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 3373-3377. (c) Schmidt, R. R.; Maier, M. *Tetrahedron Lett.* **1982**, *23*, 1789-1792.

16. (a) Serckx-Poncin, B.; Hesbain-Frisque, A. M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261-3264. (b) Krishan, K.; Singh, A.; Singh, B.; Kumar, S. *Synth. Commun.* **1984**, *14*, 219-225.

17. (a) Cheng, Y.-S.; Ho, E.; Mariano, P. S.; Ammon, H. L. *J. Org. Chem.* **1985**, *50*, 5678-5686. (b) Nomura, Y.; Takeuchi, Y.; Tomoda, S.; Ito, M. M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2779-2785. (c) Benson, S. C.; Gross, J. L.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 3257-3269.

18. (a) Hartke, K.; Kissel, T.; Quante, J.; Henssen, G. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 953-954. (b) Gillmann, T.; Hartke, K. *Chem. Ber.* **1986**, *119*, 2859-2867.

19. (a) L'Abbe, G.; Dekerk, J.-P.; Declercq, J.-P.; Germain, G.; van Meerssche, M. *Tetrahedron Lett.* **1979**, *20*, 3213-3216. (b) Hall, Jr., H. K.; Miniutti, D. L. *Tetrahedron Lett.* **1984**, *25*, 943-946.

20. Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968-6969.

21. (a) Jung, M. E.; Shishido, K.; Light, L.; Davis, L. *Tetrahedron Lett.* **1981**, *22*, 4607-4610. (b) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949-975. (c) Bohlmann, F.; Habeck, D.; Poetsch, E.; Schumann, D. *Chem. Ber.* **1967**, *100*, 2742-2756.

22. (a) Herczegh, P.; Zsely, M.; Bognar, R.; Szilagyi, L. *Tetrahedron Lett.* **1986**, *27*, 1509-1512. (b) Peled, M.; Ginsburg, D. *Heterocycles* **1981**, *15*, 1187-1193. (c) Johnson, M. D.; Moody, C. J. *J. Chem. Soc. Perkin Trans. I* **1985**, 71-74. (d) Gavina, F.; Gil, P.; Palazon, B. *Tetrahedron Lett.* **1979**, *20*, 1333-1336.

23. Ideses, R.; Shani, A.; Klug, J. T. *Chem. Ind. (London)* **1982**, 409-410.

24. (a) Tamaru, Y.; Satomi, H.; Kitao, O.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 2561-2564. (b) Katada, T.; Eguchi, S.; Sasaki, T. *J. Org. Chem.* **1986**, *51*, 314-320. (c) Ohno, A.; Ohnishi, Y.; Tsuchihashi, G. *Tetrahedron* **1969**, *25*, 871-876.

25. (a) Mazzocchi, P. H.; Stahly, B.; Dodd, J.; Rondan, N. G.; Domelsmith, L. N.; Rozeboom, M. D.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6482-6490.

(b) Papadopoulos, M.; Jenner, G. *Tetrahedron Lett.* **1982**, *23*, 1889-1892. (c) Dondoni, A.; Fogagnolo, M.; Mastellari, A.; Pedrini, P.; Ugozzoli, F. *Tetrahedron Lett.* **1986**, *27*, 3915-3918. (d) Burry, L. C.; Bridson, J. N.; Burnell, D. J. *J. Org. Chem.* **1995**, *60*, 5931-5934.

26. (a) Pyle, J. L.; Shaffer, A. A.; Cantrell, J. S. *J. Org. Chem.* **1981**, *46*, 115-118. (b) Pyle, J. L.; Lunsford, R. L.; Cantrell, J. S. *J. Org. Chem.* **1979**, *44*, 2391-2395.

27. (a) Bäckvall, J. E.; Rise, T. F. *Tetrahedron Lett.* **1989**, *30*, 5347-5348. (b) Bäckvall, J. E.; Juntunen, S. K. *J. Am. Chem. Soc.* **1987**, *109*, 6396-6403. (c) Bäckvall, J. E.; Juntunen, S. K. *J. Org. Chem.* **1988**, *53*, 2398-2400. (d) Bäckvall, J. E.; Plobeck, N. A.; Juntunen, S. K. *Tetrahedron Lett.* **1989**, *30*, 2589-2592.

28. (a) Padwa, A.; Harrison, B., Norman, B. H. *Tetrahedron Lett.* **1989**, *30,* 3259-3262. (b) Padwa, A.; Gareau, Y.; Harrison, B.; Norman, B. H. *J. Org. Chem.* **1991**, *56,* 2713-2720. (c) Padwa, A.; Gareau, Y.; Harrison, B.; Rodriguez, A. *J. Org. Chem.* **1992**, *57*, 3540-3545. (d) Maskyama, Y.; Sato, H.; Kurusu, Y. *Tetrahedron Lett.* **1985**, *26*, 67-68.

29. (a) For a review on 2-pyrone chemistry, see Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111-9171. (b) Markó, E. I.; Evans, G. R.; Declercq, J.-P. *Tetrahedron* **1994**, *50*, 4557-4574. (c) Markó, E. I.; Evans, G. R. *Tetrahedron Lett.* **1994**, *35*, 2771-2774. (d) Posner, G. H.; Carry, J.-C.; Lee, J. K.; Bull, D. S.; Dai, H. *Tetrahedron Lett.* **1994**, *35*, 1321-1324. (e) Posner, G. H.; Eydoux, F.; Lee, J. K; Bull, D. S. *Tetrahedron Lett.* **1994**, *35*, 7541-7544. (f) Posner, G. H.; Dai, H.; Bull, D. S.; Lee, J. K; Eydoux, F.; Ishihara, Y.; Welsh, W.; Pryor, N.; Petr, Jr., S. *J. Org. Chem.* **1996**, *61*, 671-676. (g) For the use of 2-hydroxypyrone in the total synthesis of taxol, see Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634-644.

30. (a) Ahn, K.-D.; Hall, H. K. *J. Polymr. Sci., Polymr. Chem. Ed.* **1981,** *19*, 629-644. (b) Ponticello, I. S. *J. Polymr. Sci., Polymr. Chem. Ed.* **1979,** *17*, 3499-3508.

31. (a) McEntee, M. E.; Pinder, A. R. *J. Chem. Soc.* **1957**, 4419-4426. (b) Joly, R.; Warnant, J.; Nominée, G.; Bertin, D. *Bull. Soc. Chim. Fr.* **1958**, 366-367. (c) Hussey, C. W. T.; Pinder, A. R. *J. Chem. Soc.* **1961**, 3525-3532. (d) Hussey, C. W. T.; Pinder, A. R. *J. Chem. Soc.* **1962**, 1517-1518. (e) Garbisch, Jr., E. W. *J. Org. Chem.* **1965**, *30*, 2109-2120. (f) Miller, B.; Wong, H.-S. *Tetrahedron* **1972**, *28*, 2369-2376. (g) Green, A. E.; Muller, J. C.; Ourisson, G. *Tetrahedron Lett.* **1972**, *13*, 3375-3378. (h) Slotter, P. L.; Hill, K. A. *J. Org. Chem.* **1973**, *38*, 2576-2578. (i) Bordwell, F. C.; Wellmen, K. M. *J. Org. Chem.* **1963**, *28*, 2544-2550. (j) Smith, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855-1869.

32. (a) Kasturi, T. R.; Pettit, G. R.; Jaeggi, K. A. *J. Chem. Soc., Chem. Commun.* **1967**, 644-646. (b) Marx, J. N.; Cox, J. H.; Norman, L. R. *J. Org. Chem.* **1972**, *37*, 4489-4491. (c) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153-195. (d) Cainelli, G.; Cardillo, G.; Umani Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1973**, 94-95.

33. Jerusi, R. A. *Sel. Org. Transform.* **1970**, *1*, 301-326.

34. (a) Theissen, R. J. *J. Org. Chem.* **1971**, *36*, 752-757. (b) Bierling, B.; Kirsche, K.; Oberender, H. *J. Prakt. Chem.* **1972**, *314*, 170-180.

35. Cohen, T.; Shaw, C. K.; Jenkins, J. A. *J. Org. Chem.* **1973**, *38*, 3737-3739.
36. Thomas, A. F.; Ozainne, M. *J. Chem. Soc., Chem. Commun.* **1973**, 746.

37. Trolliet, M.; Longeray, R.; Dreux, J. *Bull. Soc. Chim. Fr.* **1974**, 1484-1486.

38. Pettit, G. R.; Fessler, D. C.; Paull, K. D.; Hofer, P.; Knight, J. C. *J. Org. Chem.* **1970**, *35*, 1398-1404.

39. (a) For a review of the sulfoxide elimination, see Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887-4902. (b) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363-382. (c) Trost, B. M.; Salzmann, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6840-6842. (d) Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 7923. (e) Iwai, K.; Kawai, M.; Kosugi, H.; Uda, H. *Chem. Lett.* **1974**, 385-388. (f) Trost, B. M.; Leung, K. K. *Tetrahedron Lett.* **1975**, *16*, 4197-4200.

40. (a) Andersen, K. K.; Edmonds, W. H.; Biasotti, J. B.; Strecker, R. A. *J. Chem. Soc.* **1966**, *31*, 2859-2862. (b) Shelton, J. R.; Davis, K. E. *Int. J. Sulfur Chem.* **1973**, *8*, 197-204. (c) Emerson, D. W.; Korniski, T. J. *J. Org. Chem.* **1969**, *34*, 4115-4118.

41. (a) Kamiya, T.; Teraji, T.; Saito, Y.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron Lett.* **1973**, *14*, 3001-3004. (b) Hatfield, L. D.; Fisher, J.; José, F. L.; Cooper, R. D. G. *Tetrahedron Lett.* **1970**, 4897-4900. (c) Cooper, R. D. G.; José, F. L. *J. Am. Chem. Soc.* **1970**, *92*, 2575-2576.

42. (a) Ager, I.; Barton, D. H. R.; Lucente, G.; Sammes, P. G. *J. Chem. Soc., Chem. Comm.* **1972**, 601. (b) Barton, D. H. R.; Greig, D. G. T.; Lucente, G.; Sammes, P. G.; Taylor, M. V.; Cooper, C. M.; Hewitt, G.; Underwood, W. G. E. *J. Chem. Soc., Chem. Comm.* **1970**, 1683-1684.

43. (a) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434-5447 and references therein. (b) Sharpless, K. B.; Gordon, K. M.; Lauer, R. F.; Patrick, D. W.; Singer, S. P.; Young, M. W. *Chem. Scr.* **1975**, *8A*, 9-13.
(c) Williams, J. R.; Leber, J. D. *Synthesis* **1977**, 427-428.

44. Pi, Zulan, Master's Thesis, **1996**, Memorial University of Newfoundland.

45. Block, Jr., P. *Org. Syn. Coll. Vol. 5*, **1973**, 381-383.

46. Cassady, J. M.; Howie, G. A.; Robinson, J. M.; Stamos, I. K. *Org. Syn. Coll. Vol. 7,* **1990**, 319-323.

47. Johnson, C. R.; Keiser, J. E. *Org. Syn. Coll. Vol. 5,* **1973**, 791-793.

48. (a) Ramaswamy, S. Ph.D. Thesis, University of British Columbia, **1982**, pp 215-217.
(b) Deuschel, v. W. *Helv. Chim. Acta.* **1952**, *35*, 1587.

49. Moureu, C.; Bongrand, J. C. *Ann. Chim.* **1920**, *9*, 47-58.

50. (a) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816-1819.
(b) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709-713.

51. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *53*, 2923-2925.

52. Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffman, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7373-7379.

53. Minamida, I.; Ikeda, Y.; Uneyama, K.; Tagaki, W.; Oae, S. *Tetrahedron* **1968**, *24*, 5293-5309.

54. (a) Tsujihara, K.; Furukawa, N.; Oae, S. *Tetrahedron*, **1971**, *27*, 4921-4930.
(b) Tsujihara, K.; Harada, K; Furukawa, N.; Oae, S. *Tetrahedron*, **1971**, *27*, 6101-6108.
(c) Tsujihara, K.; Furukawa, N.; Oae, K.; Oae, S. *Bull. Chem. Soc. Jap*. **1969**, *42*, 2631-2635.

Jatrorrhizine References

55. (a) Kinghorn, A. D.; Balandrin, M. F., Eds. *Human Medicinal Agents from Plants*, ACS Symposium Series 534; American Chemical Society: Washington, DC, **1993**. (b) Pettit, G. R.; Pierson, F. H.; Herald, C. L., Eds. *Anticancer Drugs from Animals, Plants, and Microorganisms*; Wiley-Interscience: Toronto, **1994**. (c) Huang, K. C. *The Pharmacology of Chinese Herbs*; CRC Press: Boca Raton, Florida, **1993**. (d) Tyler, V. E.; Brady, L. R.; Robbers, J. E. "Alkaloids." In *Pharmacognosy*; Lea & Febiger: Philadelphia, **1988**; 9th Edition.

56. (a) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1962**, *84*, 2983-2990. (b) Holden, K. G. "Total Synthesis of Penicillins, Cephalosporins, and Their Nuclear Analogs." In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, **1982**; Vol. 2, Chapter 2. (c) Heusler, K. "Total Synthesis of Penicillins and Cephalosporins." In *Cephalosporins and Penicillins: Chemistry and Biology*; Flynn, E. H., Ed.; Academic Press: New York, **1972**; Chapter 6. (d) Lemke, P. A., Brannon, D. R. "Microbial Synthesis of Cephalosporin and Penicillin Compounds." In *Cephalosporins and Penicillins: Chemistry and Biology*; Flynn, E. H., Ed.; Academic Press: New York, **1972**; Chapter 9. (e) *The Organic Chemistry of β-Lactams*, Georg, G. I., Ed.; VCH: New York, **1992**.

57. (a) Inoue, S.; Kosugi, C.; Lu, Z. G.; Sato, K. *Nippon Kagaku Kaishi* **1992**, 45-52. (b) Razdan, R. K. "The Total Synthesis of Cannabinoids." In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons, Inc.: New York, **1981**; Vol. 4, pp 185-262. (c) Mechoulam, R.; McCallum, N. K.; Burstein, S. *Chem. Rev.* **1976**, *76*, 75-112. (d) Mechoulam, R.; Braun, P.; Gaoni, Y. *J. Am. Chem. Soc.* **1967**, *89*, 4552-4554. (e) Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1964**, *86*, 1646-1647. (f) Sallan, S. E.; Cronin, C.; Zelen, M.; Zinberg, N. E. *N. Engl. J. Med.* **1980**, *302*, 135-138. (g) Chang, A. E.; Shiling, D. J.; Stillman, R. C.; Goldberg, N. H.; Seipp, C. A.; Barofsky, I.; Rosenberg, S. A. *Cancer* **1981**, *47*, 1746-1751. (h) Poster, D. S.; Penta, J. S.; Bruno, S.; Macdonald, J. S. *J. Am. Med. Assoc.* **1981**, *245*, 2047-2051.

58. (a) Goldberg, A. A. *Chem. Prod. Chem. News* **1954**, *17*, 371-374. (b) Braz, G. I.; Chizhov, A. K. *Soviet Pharm. Res.* **1958**, *3*, 90-93. (c) Pictet, A.; Gams, A. *Compt. Rend.* **1909**, *149*, 210-212. (d) Pictet, A.; Gams, A. *Chem. Ber.* **1909**, *42*, 2943-2952. (e) Hifnawy, M. S.; Muhtadi, F. J. *Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic Press: New York, **1988**; Vol. 17, pp 367-447.

59. (a) Traube, W. *Chem. Ber.* **1900**, *33*, 3035-3067. (b) Grinberg, F. *J. Appl. Chem. USSR* **1940**, *13*, 1461-1463. (c) Gebner, B.; Krebs, L. *J. Gen. Chem. USSR* **1946**, *16*, 179-186. (d) Cohen, J. L. *Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic Press: New York, **1975**, Vol. 4, pp 466-493.

60. (a) Klayman, D. L. "*Artemisia annua*: From Weed to Respectable Antimalarial Plant." In *Human Medicinal Agents from Plants*, ACS Symposium Series 534; Kinghorn, A. D.; Balandrin, M. F., Eds.; American Chemical Society: Washington, DC, **1993**; Chapter 17. (b) Klayman, D. L. *Science* **1985**, *228*, 1049-1055.

61. (a) Van Geldre, E.; Vergauwe, A.; Van den Eeckhout, E. *Plant Mol. Biol.* **1997**, *33*, 199-209. (b) Jung, M. *Curr. Med. Chem.* **1994**, *1*, 35-49. (c) Zaman, S. S.; Sharma, R. P. *Heterocycles* **1991**, *32*, 1593-1637. (d) Luo, X.-D.; Shen, C. C. *Med. Res. Rev.* **1987**, *7*,

29-52. (e) Klayman, D. L.; Lin, A. J.; Acton, N.; Scovill, J. P.; Hoch, J. M.; Milhous, W. K.; Theoharides, A. D.; Dobek, A. S. *J. Nat. Prod.* **1984**, *47*, 715-717.

62. (a) Zhou, W.-S.; Xu, X.-X. *Acc. Chem. Res.* **1994**, *27*, 211-216. (b) Avery, M. A.; Gao, F.; Chong, W. K. M.; Jennings-White, C. *Trends in Organic Chemistry* **1993**, *4*, 413-468. (c) Avery, M. A.; Chong, W. K. M.; Mehrotra, S.; Jennings-White, C. *J. Am. Chem. Soc.* **1992**, *114*, 974-979.

63. (a) Kingston, D. G. I. "Taxol, an Exciting Anticancer Drug from *Taxus brevifolia*: An Overview." In *Human Medicinal Agents from Plants*, ACS Symposium Series 534; Kinghorn, A. D.; Balandrin, M. F., Eds.; American Chemical Society: Washington, DC, **1993**; Chapter 10. (b) Grocholova, R.; Petr, J.; Jilek, F. *J. Experimental Zoo.* **1997**, *277*, 49-56. (c) Kostrubsky, V. E.; Lewis, L. D.; Wood, S. G.; Sinclair, P. R.; Wrighton, S. A.; Sinclair, J. F. *Tox. Appl. Pharm.* **1997**, *142*, 79-86.

64. (a) Jenkins, P. *Chem. Britain* **1996**, 43-46. (b) Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M. *Taxane Anticancer Agents, Basic Science and Current Status*, ACS Symposium Series 583; American Chemical Society: Washington, DC, **1995**. (c) Farina, V., Ed. *The Chemistry and Pharmacology of Taxol and Its Derivatives*; Elsevier: New York, **1995**. (d) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Ang. Chemie, Int. Ed. Eng.* **1994**, *33*, 15-44. (e) Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemporary Organic Synthesis* **1994**, *1*, 47-75. (f) Suffness, M. *Ann. Rep. Med. Chem.* **1993**, *28*, 305-314. (g) Paquette, L. A. "Studies Directed Towards the Total Synthesis of Taxanes." In *Studies in Natural Product Chemistry*; Rahman, A-ur., Ed.; Elsevier Science Publ.: Amsterdam, **1992**; Vol. 11, pp 3-69. (h) Kingston, D. G. I. *Pharmac. Ther.* **1991**, *52*, 1-34.

65. (a) Ellis, D. D.; Zeldin, E. L.; Brodhagen, M.; Russin, W. A.; McCown, B. H. *J. Nat. Prod.* **1996**, *59*, 246-250. (b) Cragg, G. M.; Snader, K. M. *Cancer Cells* **1990**, *3*, 233-235. (c) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327.

66. (a) Toivola, R. J.; Koskinen, A. M. P. *Synlett* **1996**, 1159-1161. (b) Delaloge, F.; Prunet, J.; Pancrazia, A.; Lallemand, J. Y. *Tetrahedron Lett.* **1997**, *38*, 237-240. (c) Frost, C.; Linnane, P.; Magnus, P.; Spyvee, M. *Tetrahedron Lett.* **1996**, *37*, 9139-9142. (d) Patel, R. N.; Banerjee, A.; Szarka, L. J. *J. Am. Oil Chem. Soc.* **1996**, *73*, 1363-1375. (e) Bauta, W. E.; Booth, J.; Deluca, M.; Diorazio, L.; Donohoe, T. J.; Frost, C.; Magnus, P.; Mendoza, J.; Pye, P.; Tarrant, J. G.; Thom, S.; Ujjainwalla, F. *Tetrahedron* **1996**, *52*, 14081-14102. (f) Magnus, P.; Booth, J.; Diorazio, L.; Donohoe, T. J.; Lynch, V.; Magnus, N.; Mendoza, J.; Pye, P.; Tarrant, J. G. *Tetrahedron* **1996**, *52*, 14103-14146. (g) Magnus, P.; Diorazio, L.; Donohoe, T. J.; Giles, M.; Pye, P.; Tarrant, J.; Thom, S. *Tetrahedron* **1996**, *52*, 14147-14176. (h) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813-2817. (i) Gennari, C.; Vulpetti, A.; Donghi, M.; Mongelli, N.; Vanotti, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1723-1725. (j) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624-633. (k) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Clairborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634-644. (l) Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Clairborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645-652. (m) Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.*

1995, *117*, 653-659. (n) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723-1726. (o) Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Clairborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630-634. (p) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K. *J. Chem. Soc., Chem. Commun.* **1994**, 295-296. (q) Nicolaou, K. C.; Clairborne, C. F.; Nantermet, P. G.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1994**, *116*, 1591-1592. (r) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597-1598. (s) Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599-1600.

67. Chemical Abstracts name 5,6-dihydro-3-hydroxy-2,9,10-trimethoxydibenzo[a,g]-quinolizinium chloride [3621-38-3]

68. Siwon, J.; Verpoorte, R.; van Essen, G. F. A.; Baerheim Svendson, A. *Planta Medica* **1980**, *38*, 24-32.

69. Ghosh, R.; Mukherjee, K.; Roychowdury, P.; Klayman, D. L. *Acta Cryst. Sec. C* **1993**, *49*, 1665-1667.

70. Hussain, R. A.; Kim, J.; Beecher, C. W. W.; Kinghorn, A. D. *Heterocycles* **1989**, *29*, 2257-2260.

71. (a) Bhakuni, D. S.; Jain, S. "Protoberberine Alkaloids." In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press, Inc.: New York, **1986**; Vol. 28, Chapter 2. (b) Pandey, G. D.; Tiwari, K. P. *Heterocycles* **1980**, *14*, 59-82. (c) Shamma, M.; Moniot, J. L. "The Protoberberines and Retroprotoberberines." In *Isoquinoline Alkaloids Research: 1972-1977*; Plenum Press: New York, **1978**; Chapter 19. (d) Shamma, M. "The Protoberberines and Retroprotoberberines." In *The Isoquinoline Alkaloids: Chemistry and Pharmacology, Organic Chemistry*: A Series of Monographs; Blomquist, A. T., Wasserman, H., Eds.; Academic Press, Inc.: New York, **1972**; Vol. 25, Chapter 16. (e) Pelz, K. *Chem. Listy*, **1963**, *57*, 1107-1127. (f) Manske, R. H. F.; Ashford, W. R. "The Protoberberine Alkaloids." In *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F.; Holmes, H. L., Eds.; Academic Press Inc.: New York, **1954**; Vol. 4, Chapter 29. (g) Kondo, Y. *Heterocycles* **1976**, *4*, 197-219. (h) Kametani, T. "The Total Synthesis of Isoquinoline Alkaloids." In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons, Inc.: New York, **1977**; Vol. 3, Chapter 1.

72. Hopkirk, P. *Foreign Devils on the Silk Road*; Butler and Tanner, Ltd.: London, **1980**; p 174.

73. (a) Keys, J. D. *Chinese Herbs*; Charles E. Tuttle Co.: Tokyo, **1976**; pp 179-180. (b) Sabir, M. *Bulletin of Islamic Medicine*, National Council for Culture, Arts and Letters, Kuwait, **1981**; Vol. 1, pp 431-438.

74. (a) *Merck Index*, 11th Edition; Merck and Co., Inc.: Rahway, N.J., **1989**; p 5142. (b) Vennerstrom, J. L.; Klayman, D. L. *J. Med. Chem.* **1988**, *31*, 1084-1085.

(c) Partridge, S. J.; Russell, P. F.; Anderson, M. M.; Wright, C. W.; Phillipson, J. D.; Kirby, G. C.; Warhurst, D. C.; Schiff, Jr., P. L. *J. Pharm. Pharmacol. (Suppl.)* **1990**, *42*, 97P. (d) Farnsworth, N. R.; Bingel, A. S.; Cordell, G. A.; Crane, F. A.; Fong, H. S. *J. Pharm. Sci.* **1975**, *64*, 535-598. (e) Smékal, E.; Kubova, N. *Stud. Biophys.* **1984**, *101*, 121-123. (f) Misik, V.; Bezakova, L.; Malekova, L.; Kostalova, D. *Planta Medica* **1995**, *61*, 372-373.

75. (a) Chuang, W. C.; Young, D. S.; Liu, L. K. *J. Chrom.* **1996**, *755*, 19-26. (b) Liu, Y. M.; Sheu, S. J. *J. Chrom.* **1992**, *623*, 196-199. (c) Cava, M. P.; Reed, T. A. *J. Org. Chem.* **1967**, *32*, 1640-1641. (d) Cava, M. P.; Reed, T. A.; Beal, J. L. *Lloydia* **1965**, *28*, 73-83. (e) Spath, E.; Duschinsky, R. *Chem. Ber.* **1925**, *58*, 1939-1946. (f) Spath, E.; Quietensky, H. *Chem. Ber.* **1925**, *58*, 2267-2279.

76. (a) Shamma, M.; Jones, C. D. *J. Am. Chem. Soc.* **1970**, *92*, 4943-4949. (b) Elliott, Jr., I. W. *J. Heterocyclic Chem.* **1967**, *4*, 639-640. (c) Takemoto, T.; Kondo, Y. *J. Pharm. Soc. Japan* **1962**, *82*, 1408.

77. (a) Cava, M. P.; Nomura, K.; Talapatra, S. K.; Mitchell, M. J.; Schlessinger, R. H.; Buck, K. T.; Beal, J. L.; Douglas, B.; Raffauf, R. F.; Weisbach, J. A. *J. Org. Chem.* **1968**, *33*, 2785-2789. (b) Meise, W. *Justus Liebigs Ann. Chem.* **1971**, *748*, 55-58. (c) Augustine, R. L. *Catalytic Hydrogenation*; Marcel Decker, Inc.: New York, **1965**; pp 104-107.

78. (a) Haworth, R.; Perkin, Jr., W. H.; Rankin, J. *J. Chem. Soc.* **1924**, *125*, 1686-1701. (b) Buck, J.; Perkin, Jr., W. H. *J. Chem. Soc.* **1924**, *125*, 1675-1686.

79. Whaley, W. M.; Govindachari, T. R. "The Pictet-Spengler Synthesis of Tetrahydroisoquinolines and Related Compounds." In *Organic Reactions*; Adams, R. *et al.*, Eds.; John Wiley & Sons, Inc.: New York, **1951**; Vol. 6, Chapter 3.

80. (a) Battersby, A. R.; Southgate, R.; Staunton, J.; Hirst, M. *J. Chem. Soc. (C)* **1966**, 1052-1057. (b) Kametani, T.; Fukumoto, K.; Agui, H.; Yagi, H.; Kigasawa, K.; Sugahara, H.; Hiiragi, M.; Hayasaka, T.; Ishimaru, H. *J. Chem. Soc. (C)* **1968**, 112-118. (c) Kametani, T.; Honda, T.; Ihara, M. *J. Chem. Soc., Chem. Comm.* **1970**, 1253-1254. (d) Chiang, H.-C.; Brochmann-Hanssen, E. *J. Org. Chem.* **1977**, *42*, 3190-3194.

81. (a) Battersby, A. R.; Binks, R.; Francis, R. J.; McCaldin, D. J.; Ramuz, H. *J. Chem. Soc.* **1964**, 3600-3610. (b) Jain, M. K. *J. Chem. Soc.* **1962**, 2203-2206.

82. (a) Kametani, T.; Noguchi, I.; Saito, K.; Kaneda, S. *J. Chem. Soc. (C)* **1969**, 2036-2038. (b) Kametani, T.; Honda, T.; Ihara, M. *J. Chem. Soc. (C)* **1971**, 3318-3321. (c) Kametani, T.; Ihara, M. *J. Chem. Soc. (C)* **1967**, 530-532. (d) Kametani, T.; Iida, H.; Honda, T.; Ihara, M. *J. Heterocyclic Chem.* **1970**, *7*, 491-493.

83. Natarajan, S.; Pai, B.; Rajaraman, R.; Swaminathan, C.; Nagarajan, K.; Sudarsanam, V.; Rogers, D.; Quick, A. *Tetrahedron Lett.* **1975**, *16*, 3573-3576.

84. Whaley, W. M.; Govindachari, T. R. "The Preparation of 3,4-Dihydroisoquinolines and Related Compounds by the Bischler-Napieralski Reaction." In *Organic Reactions*; Adams, R. *et al.*, Eds.; John Wiley & Sons, Inc.: New York, **1951**; Vol. 6, Chapter 2.

85. (a) Quang Thuan, N. T.; Gardent, J. *C. R. Acad. Sc. Paris C.* **1968**, *267*, 1340-1342. (b) Quang Thuan, N. T.; Gardent, J. *Bull. Soc. Chim. Fr.* **1966**, *6*, 2401-2402.

86. (a) Tani, C.; Takao, S.; Endo, H.; Oda, E. *J. Pharm. Soc. Japan* **1973**, *93*, 268-271. (b) Rajaraman, R.; Pai, B. R.; Premila, M. S.; Suguna, H. *Ind. J. Chem.* **1977**, *15B*, 876-879. (c) Haworth, R. D.; Perkin, Jr., W. H. *J. Chem. Soc.* **1925**, *127*, 1448-1453. (d) Pai, B. R.; Natarajan, S.; Manikumar, G.; Rajaraman, R.; Suguna, H. *J. Org. Chem.* **1978**, *43*, 1992-1994.

87. (a) Baxter, I.; Swan, G. A. *J. Chem. Soc.* **1965**, 4014-4024. (b) Onda, M. *J. Pharm. Soc. Japan* **1954**, *74*, 915-917. (c) Battersby, A. R.; Binks, R.; Francis, R. J.; McCaldin, D. J.; Ramuz, H. *J. Chem. Soc.* **1964**, 3600-3610. (d) Jain, M. K. *J. Chem. Soc.* **1962**, 2203-2206.

88. (a) Haworth, R. D.; Perkin, Jr., W. H.; Stevens, T. S. *J. Chem. Soc.* **1926**, *127*, 1764-1769. (b) Haworth, R. D.; Perkin, Jr., W. H. *J. Chem. Soc.* **1926**, *127*, 1769-1784. (c) Huffman, J. W.; Miller, E. G. *J. Org. Chem.* **1960**, *25*, 90-92.

89. (a) For a review, see Pandey, G. D.; Tiwari, K. P. *Heterocycles* **1981**, *16*, 449-485. (b) Pandey, G. D.; Tiwari, K. P. *Curr. Sci.* **1980**, *49*, 216-218.

90. (a) Cushman, M.; Dekow, F. W. *J. Org. Chem.* **1979**, *44*, 407-409. (b) Nagata, W.; Itazaki, H.; Okada, K.; Wakabayashi, T.; Shibata, K.; Tokutake, N. *Chem. Pharm. Bull.* **1975**, *23*, 2867-2877.

91. (a) Pandey, G. D.; Tiwari, K. P. *Ind. J. Chem.* **1980**, *19B*, 272-275. (b) Pandey, G. D.; Tiwari, K. P. *Heterocycles* **1979**, *12*, 1327-1330. (c) Pandey, G. D.; Tiwari, K. P. *Curr. Sci.* **1979**, *48*, 1032-1033.

92. Grewe, R.; Fischer, H. *Chem. Ber.* **1963**, *96*, 1520-1528.

93. (a) Sainsbury, M.; Brown, D. W.; Dyke, S. F.; Hardy, G. *Tetrahedron* **1969**, *25*, 1881-1895. (b) Battersby, A. R.; Binks, R.; Uzzell, P. S. *Chem. Ind.* **1955**, 1039. (c) Battersby, A. R.; Le Count, D. J.; Garratt, S.; Thrift, R. I. *Tetrahedron* **1961**, *14*, 46-53. (d) Brown, D. W.; Dyke, S. F. *Tetrahedron* **1966**, *22*, 2429-2435.

94. Gensler, W. J. "The Synthesis of Isoquinolines by the Pomerantz-Fritsch Reaction." In *Organic Reactions*; Adams, R. *et al.*, Eds.; John Wiley & Sons, Inc.: New York, **1951**; Vol. 6, Chapter 4.

95. (a) Dyke, S. F.; Tiley, E. P. *Tetrahedron* **1975**, *31*, 561-568. (b) Dyke, S. F.; Brown, D. W.; Sainsbury, M.; Hardy, G. *Tetrahedron* **1971**, *27*, 3495-3502. (c) Brown, D. W.; Dyke, S. F.; Hardy, G.; Sainsbury, M. *Tetrahedron Lett.* **1968**, 5177-5178. (d) Vicente, T.; Martínez de Marigorta, E.; Domínguez, E.; Carrillo, L.; Badia, D. *Heterocycles* **1993**, *36*, 2067-2071. (e) Tellitu, I.; Badia, D., Domínguez, E.; Carrillo, L. *Heterocycles* **1996**, *43*, 2099-2112.

96. Kiparissides, Z.; Fichtner, R. H.; Poplawski, J.; Nalliah, B. C.; MacLean, D. B. *Can. J. Chem.* **1980**, *58*, 2770-2779.

97. (a) Bradsher, C. K.; Dutta, N. L. *J. Org. Chem.* **1961**, *26*, 2231-2234. (b) Bradsher, C. K.; Dutta, N. L. *J. Am. Chem. Soc.* **1960**, *82*, 1145-1147. (c) Dutta, N. L.; Bradsher, C. K. *J. Org. Chem.* **1962**, *27*, 2213-2214. (d) Andrew, H. F.; Bradsher, C. K. *Tetrahedron Lett.* **1966**, 3069-3071. (e) Augstein, W.; Bradsher, C. K. *J. Org. Chem.* **1969**, *34*, 1349-1352.

98. Bradsher, C. K.; Jones, J. H. *J. Org. Chem.* **1958**, *23*, 430-431.

99. (a) Snieckus, V. S. *Chem. Rev.* **1990**, *90*, 879-933. (b) Gschwend, H. W.; Rodriguez, H. R. "Heteroatom-Facilitated Lithiations." In *Organic Reactions*; Dauben, W. *et al.*, Eds.; John Wiley & Sons, Inc.: New York, **1979**; Vol. 26, Chapter 1.

100. Narasimhan, N. S.; Mali, R. S.; Kulkarni, B. K. *Tetrahedron* **1983**, *39*, 1975-1982.

101. Matulenko, M. A.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 573-580.

102. (a) Marsden, R.; MacLean, D. B. *Can. J. Chem.* **1984**, *62*, 1392-1399. (b) Roblot, F.; Hocquemiller, R.; Cave, A. *Bull. Soc. Chim. Fr.* **1990**, *127*, 258-267.

103. (a) Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43*, 1684-1687. (b) Pandey, G. D.; Tiwari, K. P. *Synth. Comm.* **1979**, *9*, 895-900. (c) Pandey, G. D.; Tiwari, K. P. *Tetrahedron* **1981**, *37*, 1213-1214.

104. (a) Ninomiya, I.; Naito, T. "Application of Enamide Cyclization in Alkaloid Synthesis." In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, **1983**; Volume XXII, pp 223-241. (b) Ninomiya, I.; Naito, T.; Takasugi, H. *J. Chem. Soc., Perkin Trans. I* **1975**, 1720-1724. (c) Lenz, G. *J. Org. Chem.* **1974**, *39*, 2839-2845. (d) Ninomiya, I.; Takasugi, H.; Naito, T. *Heterocycles* **1973**, *1*, 17-20.

105. Cobas, A.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 6765-6769.

106. (a) Kametani, T.; Fukumoto, T. *Heterocycles* **1975**, *3*, 29.

107. (a) Greene, T. *Protective Groups in Organic Synthesis*; Wiley-Interscience: Toronto, **1981**; pp 29-31, 97-98. (b) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, *17*, 3535-3536. (c) Augustine, R. L. *Catalytic Hydrogenation*; Marcel Decker, Inc.: New York, **1965**; pp 135-136.

108. (a) Olah, G. A. "Definition and Scope." In *Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: London, **1963**; Vol. I, Chapter II, pp 91-115. (b) Gore, P. H. "Aromatic Ketone Synthesis." In *Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: London, **1963**; Vol. III, Chapter XXXI. (c) Ingold, C. K. "Aromatic Substitution." In *Structure and Mechanism in Organic Chemistry*, 2nd Ed.; George Banta Company, Inc.: New York, **1969**; Chapter VI. (d) Gore, P. H. *Chem. Rev.* **1955**, *55*, 233-281. (e) Pearson, D. E.; Buehler, C. A. *Synthesis* **1972**, 533-542.

109. (a) Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckman, Jr., R. K.; Medwid, J. B. *Org. Syn. Coll. Vol. 6*, **1988**, 101-103. (b) Hill, A. J.; Keach, D. T. *J. Am. Chem. Soc.* **1926**, *48*, 257-261.

110. (a) Johnson, A. W. "The Wittig Reaction I. Scope and Applications." In *Ylides and Imines of Phosphorus*; Johnson, A. W., Ed.; John Wiley & Sons, Inc.: New York, **1993**; Chapter 8. (b) Johnson, A. W. "The Wittig Reaction II. Mechanism and Stereochemistry." In *Ylides and Imines of Phosphorus*; Johnson, A. W., Ed.; John Wiley & Sons, Inc.: New York, **1993**; Chapter 9. (c) Schlosser, M. "The Stereochemistry of the Wittig Reaction." In *Topics in Stereochemistry*; Eliel, E. L.; Allinger, N. L., Eds.; Wiley-Interscience: New York, **1970**; Vol. 5, pp 1-30. (d) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.

111. (a) Warren, S. *Chem. Ind.* **1980**, 824-828. (b) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150-6151. (c) For the application of this reaction to the synthesis of methyl ketones, see Coulson, D. R. *Tetrahedron Lett.* **1964**, 3323-3326.

112. Bindra, J. S.; Grodski, A. *J. Org. Chem.* **1978**, *43*, 3240-3241.

113. Augustine, R. L. *Catalytic Hydrogenation*; Marcel Decker, Inc.: New York, **1965**.

114. (a) Dewey, R. S.; van Temelen, E. E. *J. Am. Chem. Soc.* **1961**, *83*, 3729. (b) Miller, C. E. *J. Chem. Ed.* **1965**, *42*, 254-259. (c) Hünig, S.; Müller, H.-R.; Thier, W. *Ang. Chemie, Int. Ed. Eng.* **1965**, *4*, 271-280. (d) Hoffman, Jr., J. M.; Schlessinger, R. H. *J. Chem. Soc., Chem. Comm.* **1971**, 1245-1246. (e) Friedman, L.; Litle, R. L.; Reichle, W. R. *Org. Syn. Coll. Vol. #5* **1973**, 1055-1057. (f) Corey, E. J.; Mock, W. L.; Pasto, D. J. *Tetrahedron Lett.* **1961**, 347-352. (g) Hünig, S.; Müller, H.-R.; Thier, W. *Tetrahedron Lett.* **1961**, 353-357.

115. Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105-2114.

116. Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575-2584.

117. Hart, D. J.; Hong, W.-P.; Hsu, L.-Y. *J. Org. Chem.* **1987**, *52*, 4665-4673.

118. (a) Sonnet, P. E. *Tetrahedron* **1980**, *36*, 557-604. (b) Wyman, G. M. *Chem. Rev.* **1955**, *55*, 625-657. (c) Marvel, C. S. In *Organic Chemistry*, 2nd Edition; Gilman, H., Ed.; John Wiley & Sons, Inc.: New York, **1943**; Vol. 1, p 453. (d) Roelofs, W.; Comeau, A.; Hill, A.; Milicevic, G. *Science* **1971**, *174*, 297-299. (e) Crombie, L.; Tayler, J. L. *J. Chem. Soc.* **1957**, 2760-2766. (f) Ruggli, P.; Staub, A. *Helv. Chim. Acta* **1937**, *20*, 37-52.

119. (a) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821-5823. (b) Vedejs, E.; Marth, C. F.; Ruggeri, R. *J. Am. Chem. Soc.* **1988**, *110*, 3940-3948.

120. Vedejs, E.; Marth, C. F. *Tetrahedron Lett.* **1987**, *28*, 3445-3448.

121. (a) Schlosser, M.; Schaub, B.; De Oliveira-Neto, J.; Jeganathan, S. *Chimia* **1986**, *40*, 244-245. (b) Anderson, R. J.; Henrick, C. A. *J. Am. Chem. Soc.* **1975**, *97*, 4327-4334.

122. (a) Schlosser, M.; Christmann, K.-F. *Ang. Chemie, Int. Ed. Eng.* **1964**, *3*, 636. (b) Bergelson, L. D.; Shemyakin, M. M. *Pure Appl. Chem.* **1964**, *9*, 271-283.

123. (a) Schlosser, M.; Christmann, K.-F. *Justus Liebigs Ann. Chem.* **1967**, *708*, 1-35. (b) Schlosser, M.; Christmann, K.-F.; Piskala, A. *Chem. Ber.* **1970**, *103*, 2814-2820.

124. (a) Gore, P. H. "Aromatic Ketone Synthesis." In *Friedel-Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: London, **1963**; Vol. III, Chapter XXXI, p 9. (b) Auwers, K.; Rietz, E. *Chem. Ber.* **1907**, *40*, 3514-3521. (c) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275-4277.

125. Park, M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, *28*, 3823-3824.

126. (a) Dodge, J. A.; Stocksdale, M. G.; Fahey, K. J.; Jones, C. D. *J. Org. Chem.* **1995**, *60*, 739-741. (b) Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Tetrahedron* **1982**, *38*, 3687-3692. (c) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327-1328.

127. Greene, T. *Protective Groups in Organic Synthesis*; Wiley-Interscience: Toronto, **1981**; pp 10-113.

128. Knight, D. W. "Coupling Reactions Between sp^2 Carbon Centers." In *Comprehensive Organic Transformations*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**; Vol. 3, Chapter 2.3.

129. (a) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176-185. (b) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1066-1069. (c) Hayashi, T.; Katsuro, Y.; Okamoto, Y.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 4449-4452. (d) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246-2247. (e) Johnstone, R. A. W.; McLean, W. N. *Tetrahedron Lett.* **1988**, *29*, 5553-5556.

130. Kalinin, V.N. *Synthesis* **1992**, 413-432.

131. (a) Robl, J. A. *Synthesis* **1991**, 56-58. (b) Crisp, G. T.; Papadopoulos, S. *Aust. J. Chem.* **1989**, *42*, 279-285. (c) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478-5486.

132. (a) Farina, V.; Roth, G. P. *Adv. Metal-Organic Chem.* **1996**, *5*, 1-53. (b) Mitchell, T. N. *Synthesis* **1992**, 803-815. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508-524.

133. (a) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066-4068. (b) Tamao, K.; Komada, S.; Nakajima, I.; Kumada, M.; Minato, A.; Suzuki, K. *Tetrahedron* **1982**, *38*, 3347-3354. (c) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669-679. (d) For a review of the chemistry of triflates, see Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85-126.

134. (a) Erdik, E. *Tetrahedron* **1992**, *48*, 9577-9648. (b) Quesnelle, C.; Familoni, O. B.; Snieckus, V. *Synlett* **1994**, 349-350. (c) Koch, K.; Chambers, R. J.; Biggers, M. S. *Synlett* **1994**, 347-348. (d) Manabe, K.; Okamura, K.; Date, T; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 2705-2708. (e) Manabe, K.; Okamura, K.; Date, T; Koga, K. *J. Org. Chem.* **1993**, *58*, 6692-6700. (f) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. *Synlett* **1990**, 47-48.

135. (a) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213-222. (b) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419-422. (c) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178-184.

(d) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. M. *J. Chem. Soc., Chem. Comm.* **1994**, 2395. (e) Gillmann, T.; Weeber, T. *Synlett* **1994**, 649-650. (f) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763-3768. Boronic acids were prepared by essentially this procedure. (g) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207-210.

136. (a) Fu, J.-m.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665-1668. (b) Huth, A.; Beetz, I.; Schumann, I. *Tetrahedron* **1989**, *45*, 6679-6682. (c) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201-2208. (d) Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221-223. (e) Shieh, W.-C.; Carlson, J. A. *J. Org. Chem.* **1992**, *57*, 379-381.

137. Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845-853.

138. Snieckus, V. *Pure Appl. Chem.* **1994**, *66*, 2155-2158.

139. Challis, B. C.; Butler, A. R. "Substitution at an Amino Nitrogen." In *The Chemistry of the Amino Group*; Patai, S., Ed.; Interscience: New York, **1968**; pp 279-290. Beckwith, A. L. J. "Synthesis of Amides." In *The Chemistry of Amides*; Zabicky, J., Ed.; Interscience: New York, **1970**; Chapter 2.

140. Ho, T.-L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, **1977**.

141. (a) Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Nat. Acad. Sci. USA* **1972**, *69*, 730-732. (b) Greene, T. *Protective Groups in Organic Synthesis*; Wiley-Interscience: Toronto, **1981**; pp 232-233.

142. (a) Kanojia, R. M.; Press, J. B.; Lever, Jr., O. W.; Williams, L.; McNally, J. J.; Tobia, A. J.; Falotico, R.; Moore, Jr., J. B. *J. Med. Chem.* **1988**, *31*, 1363-1368. (b) Fukumi, H.; Kurihara, H. *Heterocycles* **1978**, *9*, 1197-1206.

143. (a) Evans, D. A.; Smith, G. F.; Wahid, M. A. *J. Chem. Soc. (B)*, **1967**, 590-595. (b) McCorkindale, N. J.; McCulloch, A. W. *Tetrahedron* **1971**, *27*, 4653-4666.

144. Farina, V.; Baker, S. R.; Sapino, Jr., C. *Tetrahedron Lett.* **1988**, *29*, 6043-6046.

145. McCleland, C. W. "Iodine Monochloride." In *Synthetic Reagents*; Pizey, J. S., Ed.; Ellis Horwood Limited: Chichester, **1983**; Vol. 5, Chapter 2.

146. Lai, Y.-H. *Synthesis* **1981**, 585-604.

147. Field, L. *J. Am. Chem. Soc.* **1956**, *78*, 92-97.

148. (a) Gilman, H.; Peterson, J. M.; Schulze, F. *Recl. Trav. Chim. Pays-Bas* **1928**, *47*, 19-27. (b) Gilman, H.; Heck, L. L. *Bull. Soc. Chim. Fr.* **1929**, *45*, 250-254. (c) Gilman, H.; Kirby, R. H. *Recl. Trav. Chim. Pays-Bas* **1935**, *54*, 577-583. (d) Pearson, D. E.; Cowan, D.; Beckler, J. D. *J. Org. Chem.* **1959**, *24*, 504-509. (e) Pettit, G. R.; Baumann, M. F.; Rangammal, K. N. *J. Med. Pharm. Chem.* **1962**, *5*, 800-808.

149. Bala, Y. and Bodwell, G., unpublished results.

150. (a) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763-3768. (b) Washburn, R. M.; Levens, E.; Albright, C. F.; Billig, F. A.; Cernak, E. S. "Preparation, Properties and Uses of Benzeneboronic Acid." In *Metal-Organic Compounds*, Advances in Chemistry Series No. 23, Sittig, M., Chairman; American Chemical Society: Washington, DC, **1959**; pp 102-128.

151. Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121-124.

152. (a) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346-2351. (b) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33-41.

153. (a) Jutand, A.; Mosleh, A. *Synlett* **1993**, 568-570. (b) Jutand, A.; Négri, S.; Mosleh, A. *J. Chem. Soc., Chem. Comm.* **1992**, 1729-1730.

154. (a) Peterson, G. A.; Kunng, F.-A.; McCallum, J. S.; Wulff, W. D. *Tetrahedron Lett.* **1987**, *28*, 1381-1384. (b) Cacchi, S.; Ciattini, P. G.; Morera, E.; Otar, G. *Tetrahedron Lett.* **1986**, *27*, 5541-5544. (c) Chen, Q.-Y.; He, Y.-B.; Yang, Z.-Y. *J. Chem. Soc., Chem. Comm.* **1986**, 1452-1453. (d) Subramanian, L. R.; Martinez, A. G.; Fernandez, A. H.; Alvarez, R. M. *Synthesis*, **1984**, 481-485. (e) Clark, F. R. S.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. I* **1975**, 121-125.

155. Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663-1664.

156. (a) Erdik, E. *Tetrahedron* **1992**, *48*, 9577-9648. (b) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273-281. (c) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1977**, *132*, C17-C19.

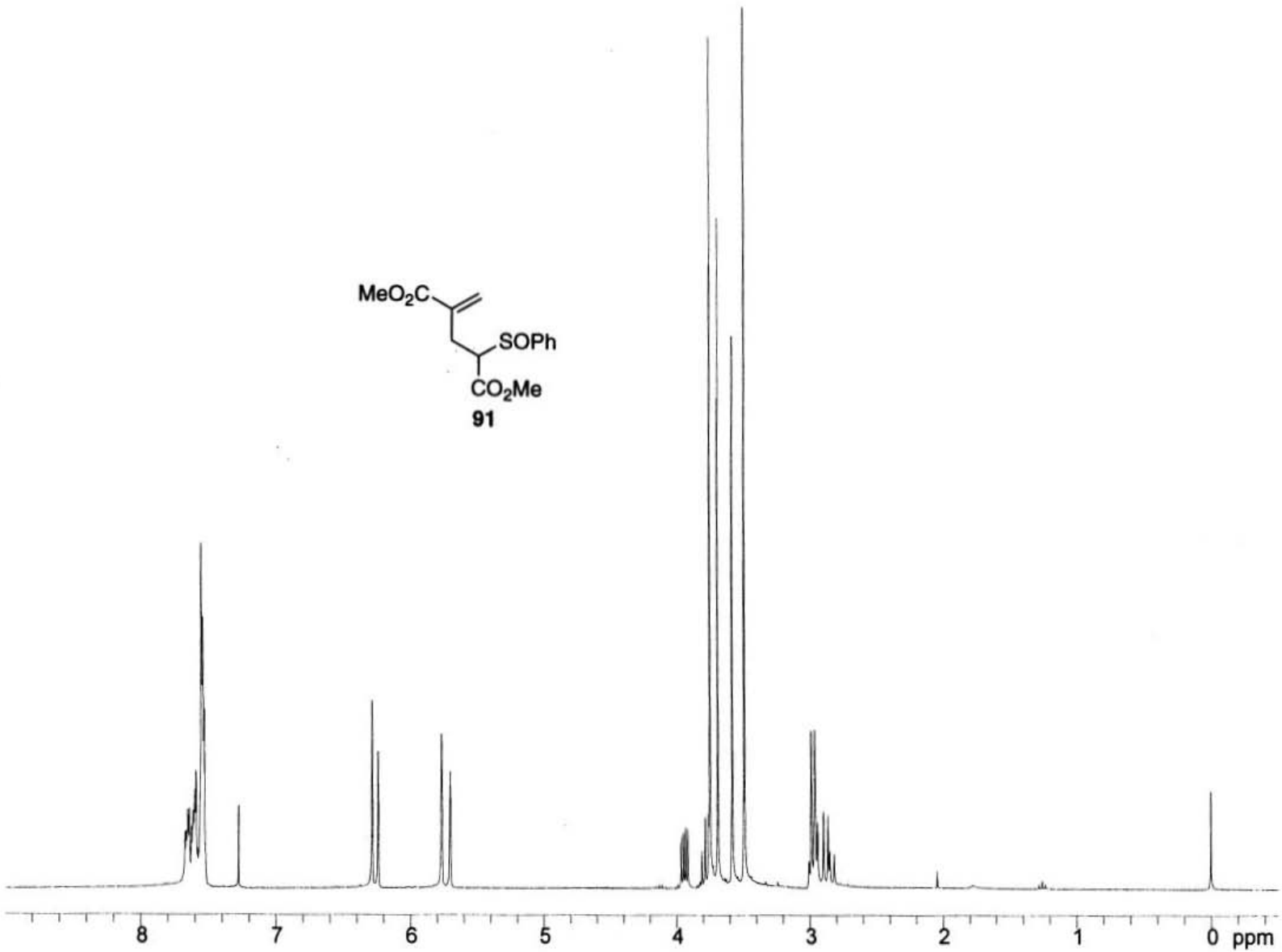
157. Spath, E.; Orechoff, A.; Kuffner, F. *Chem. Ber.* **1934**, *67*, 1214-1217.

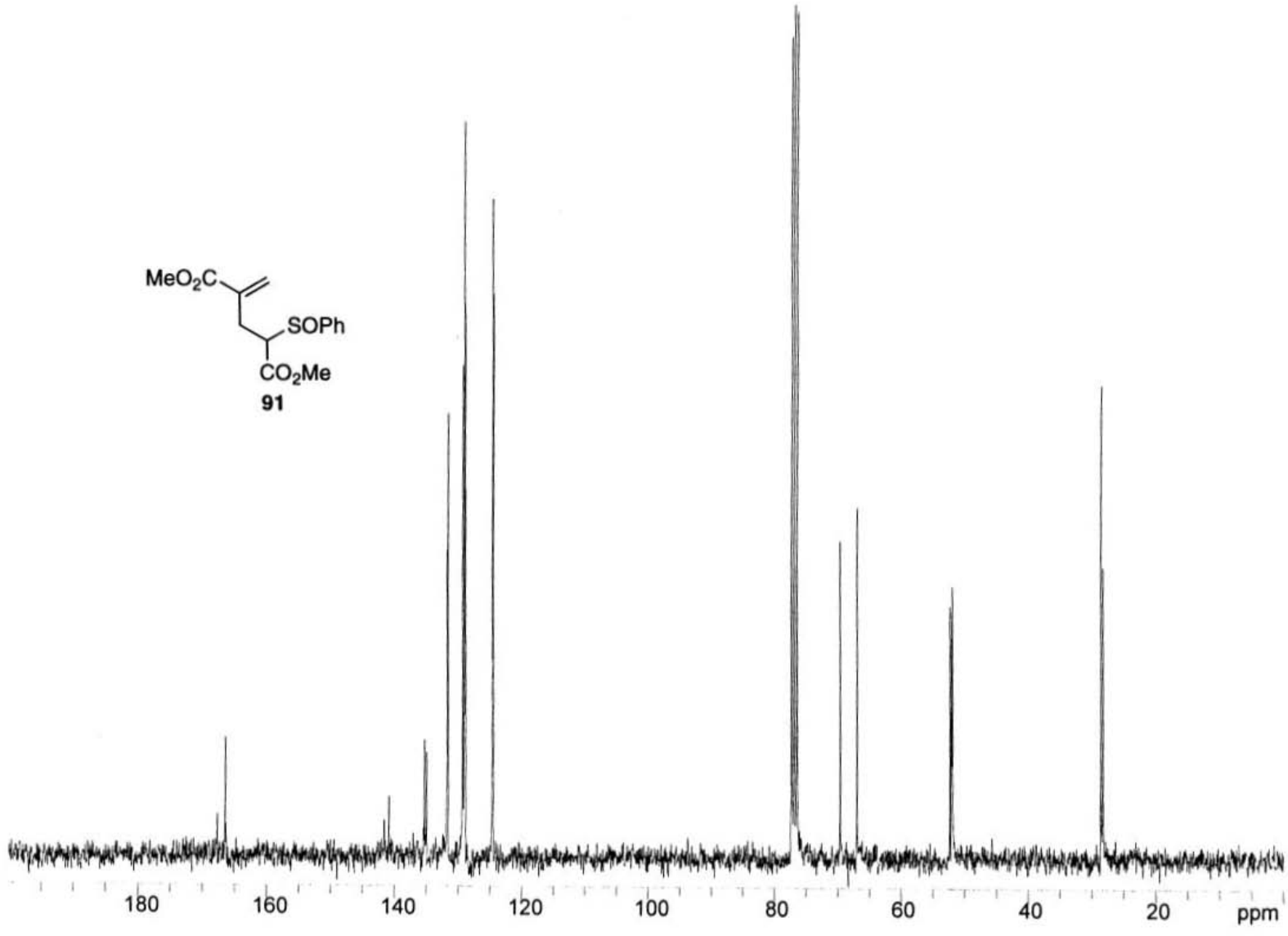
158. Bordwell, F. G.; Pitt, B. M. *J. Am. Chem. Soc.* **1955**, *77*, 572-577.

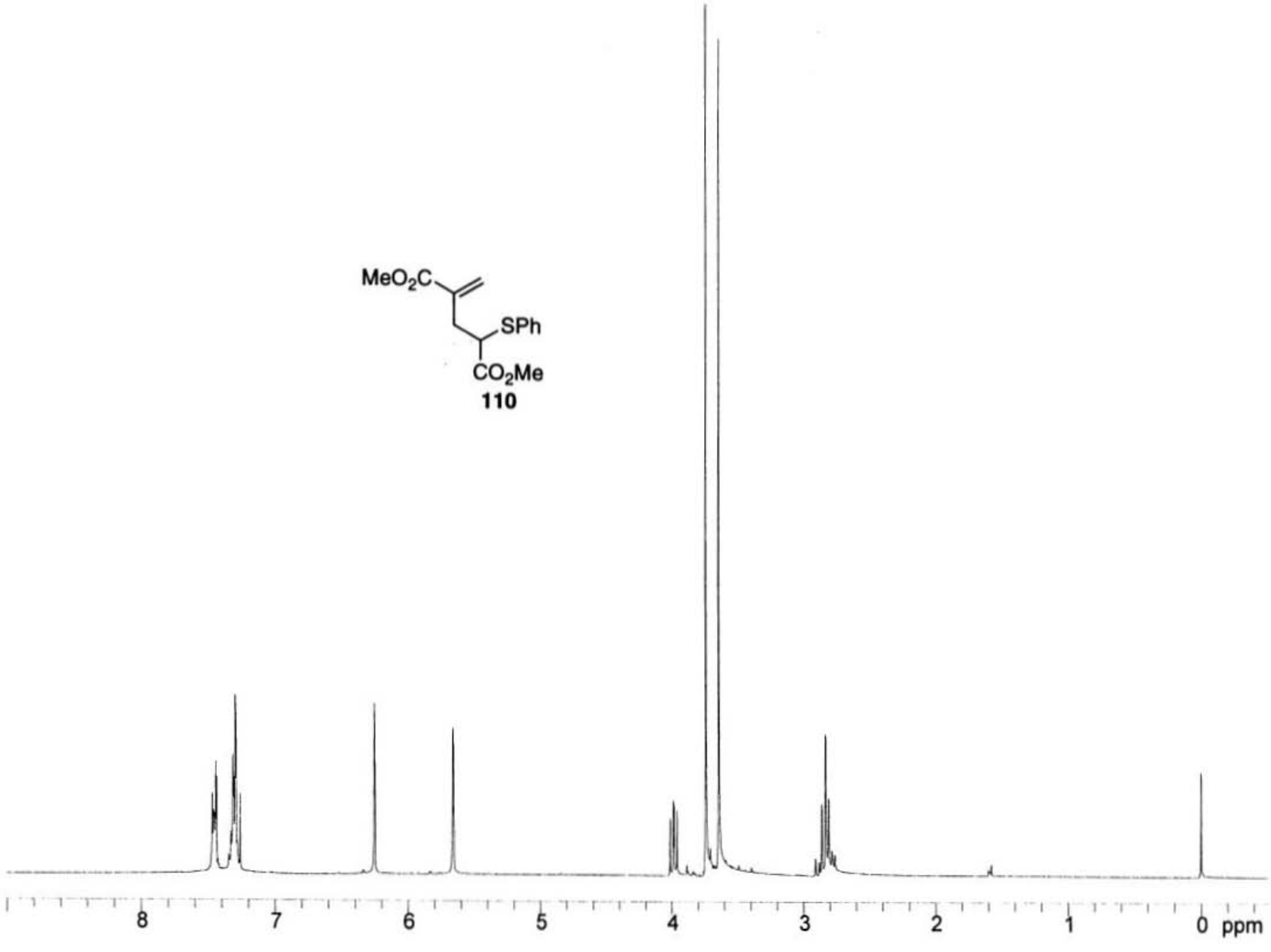
159. Campbell, M. M.; Jigajinni, V. B.; MacLean, K. A.; Wightman, R. H. *Tetrahedron Lett.* **1980**, *21*, 3305-3306.

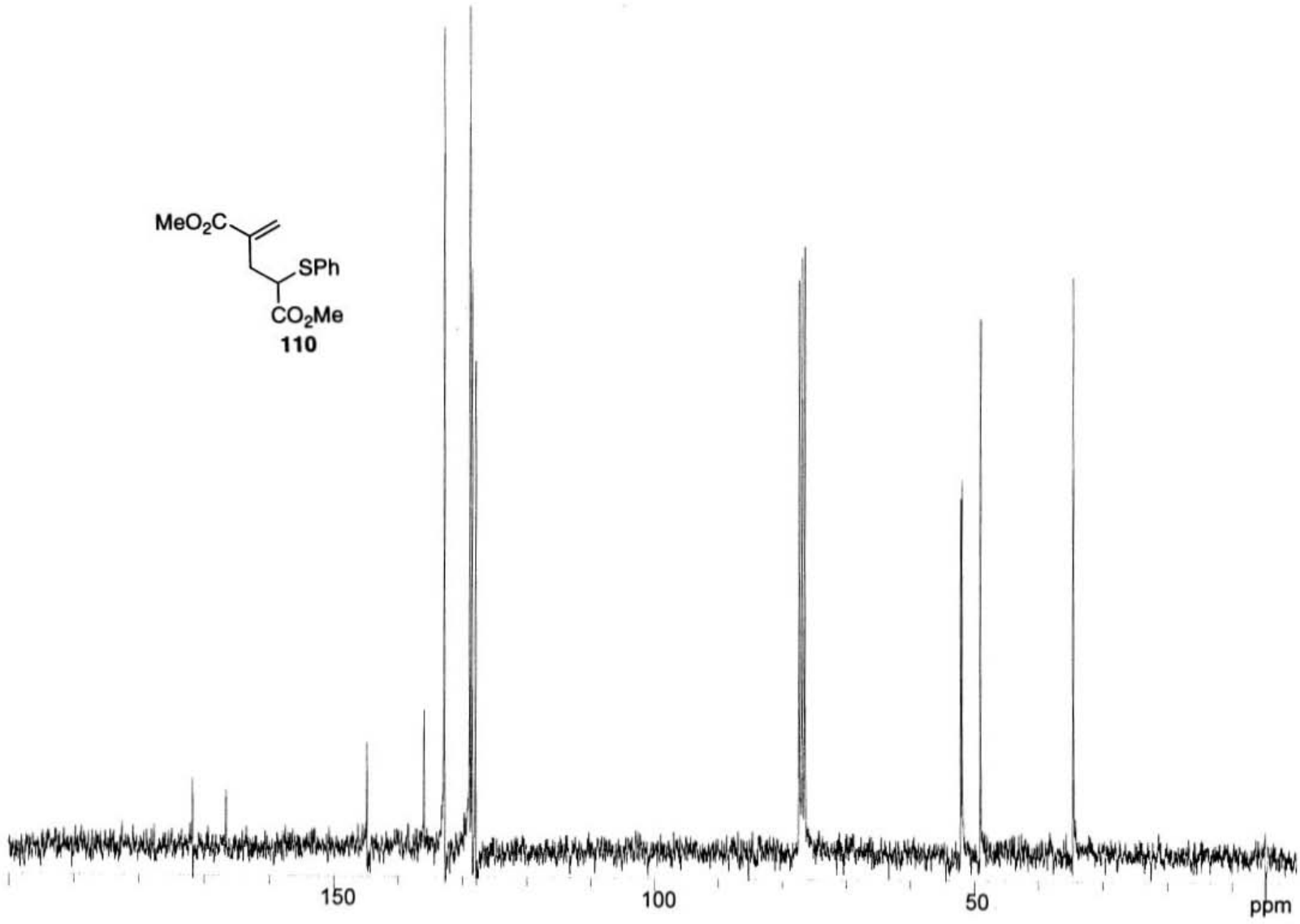
Appendix

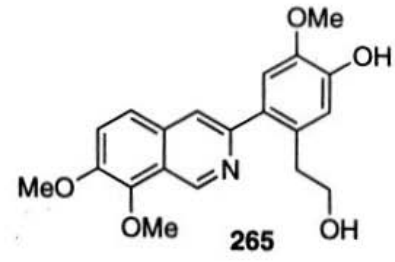
The ^{1}H and ^{13}C spectra of new compounds are arranged in the order in which the compounds appear in the text. For instrumental details, see **General Procedures** of Chapter 4 - Diene Experimental, page 38.


MeO2C
SOPh
CO2Me
91
8
7
6
5
4
3
2
1
0 ppm

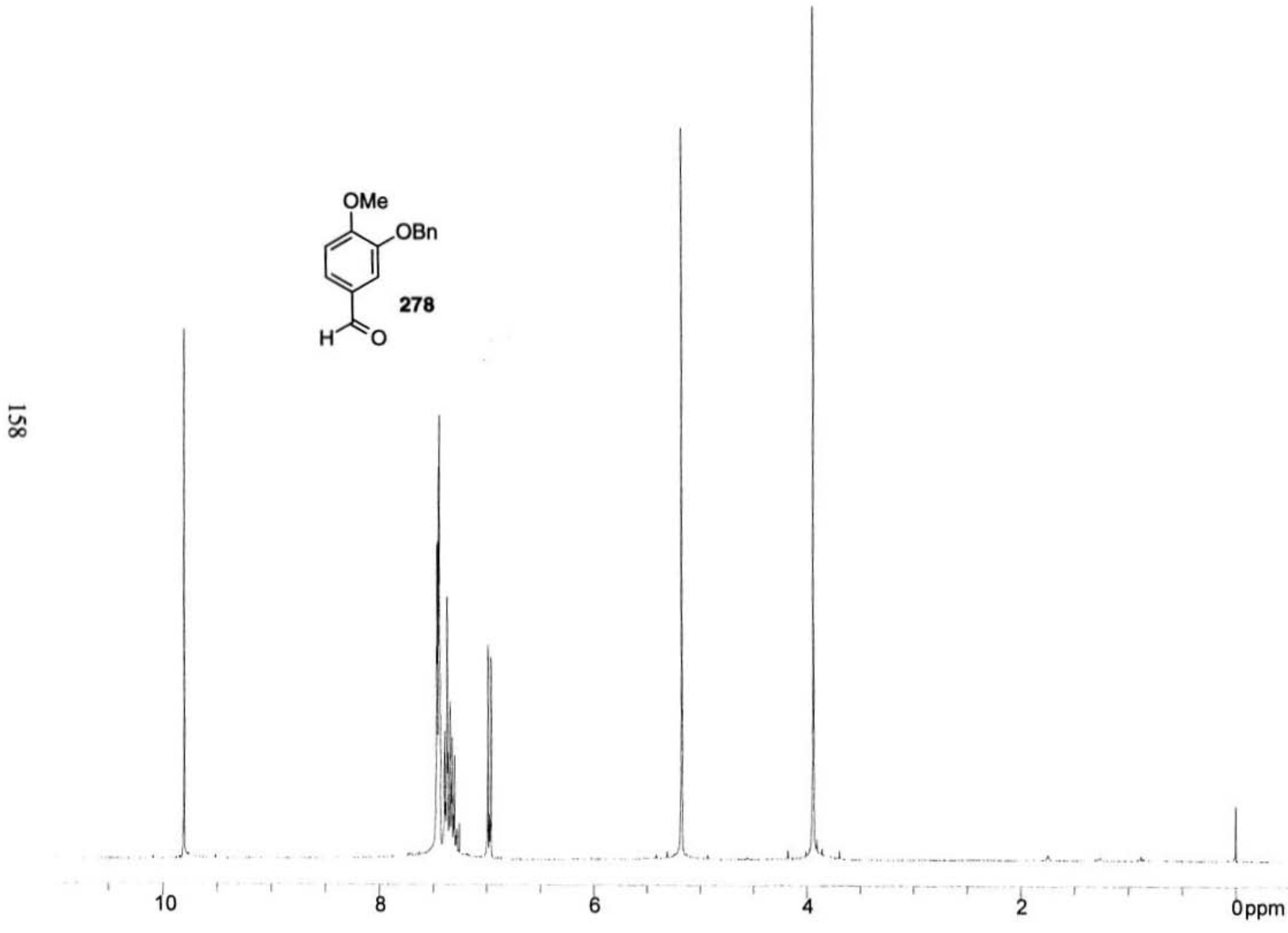

MeO2C
SOPh
CO2Me
91
180
160
140
120
100
80
60
40
20
ppm

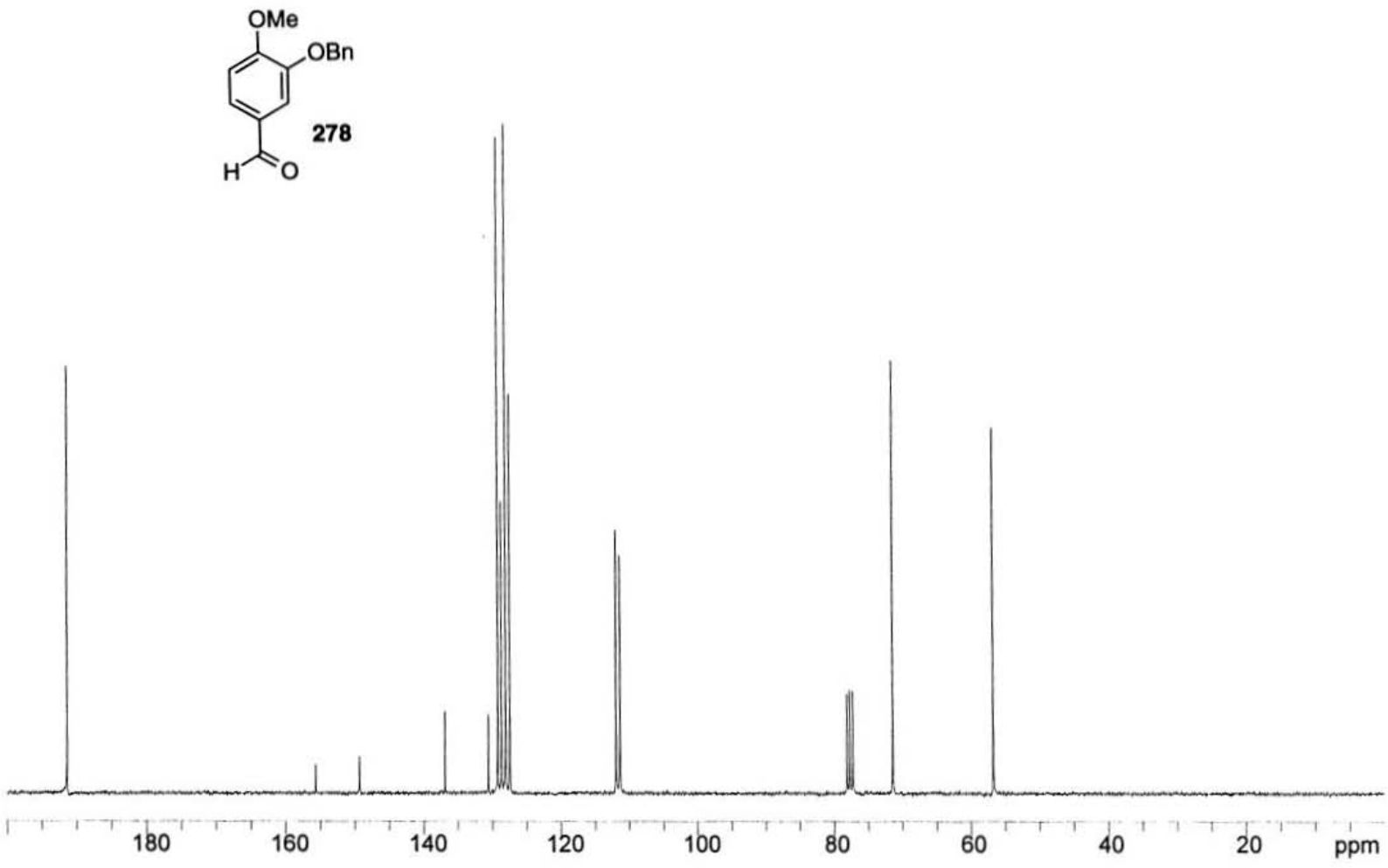

MeO2C
SPh
CO2Me
110
8
7
6
5
4
3
2
1
0 ppm

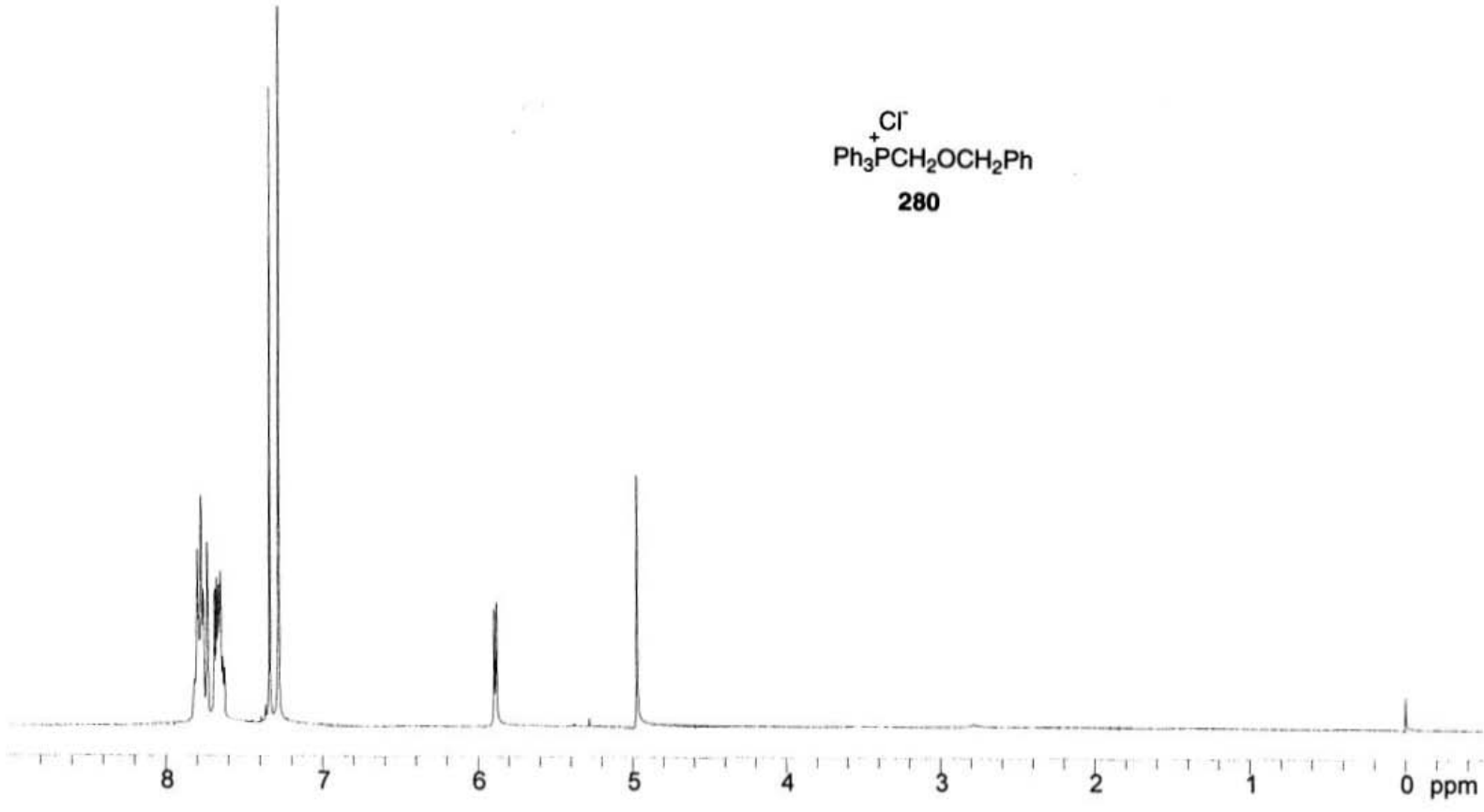

MeO2C
SPh
CO2Me
110
150
100
50
ppm

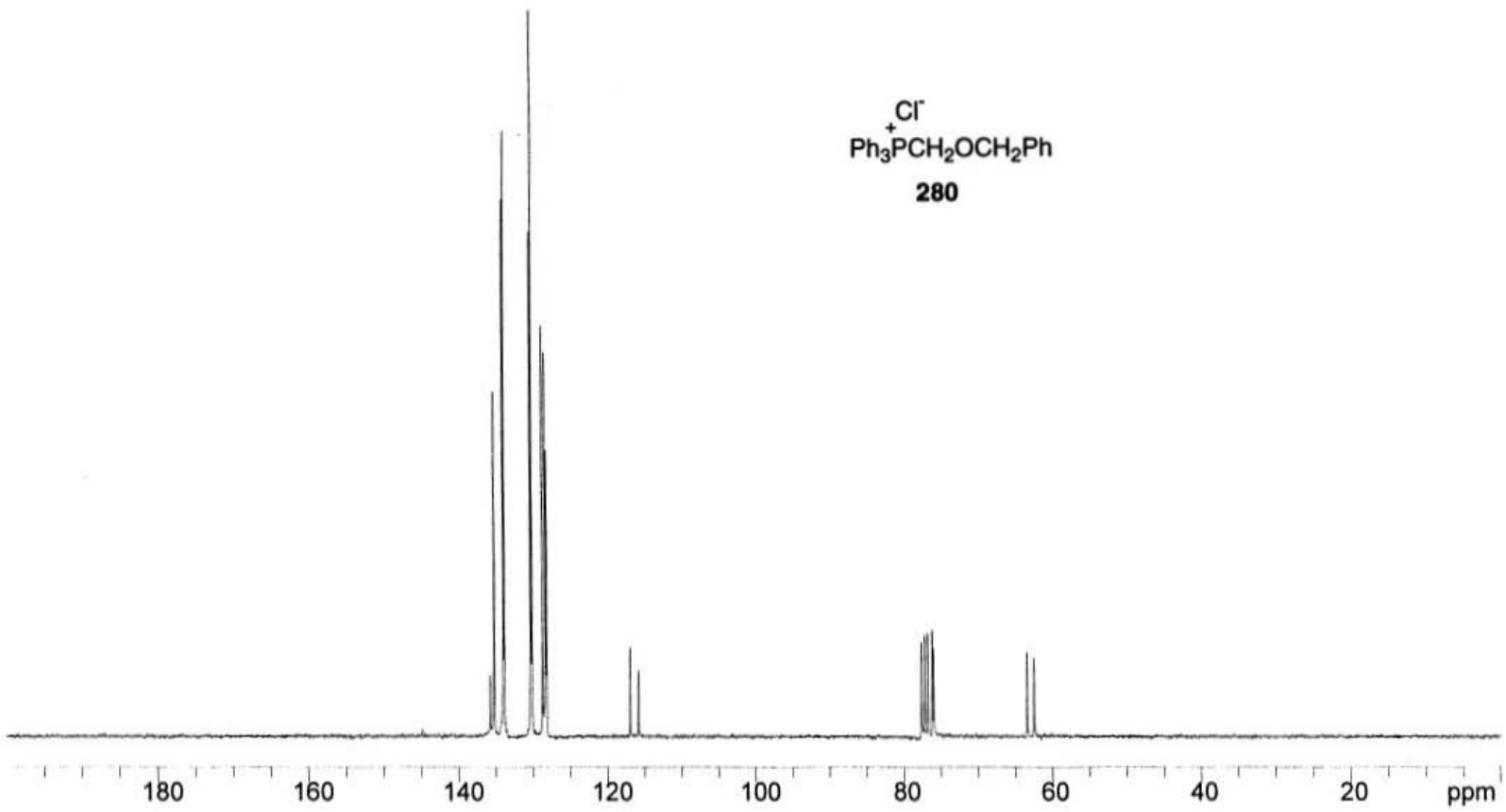


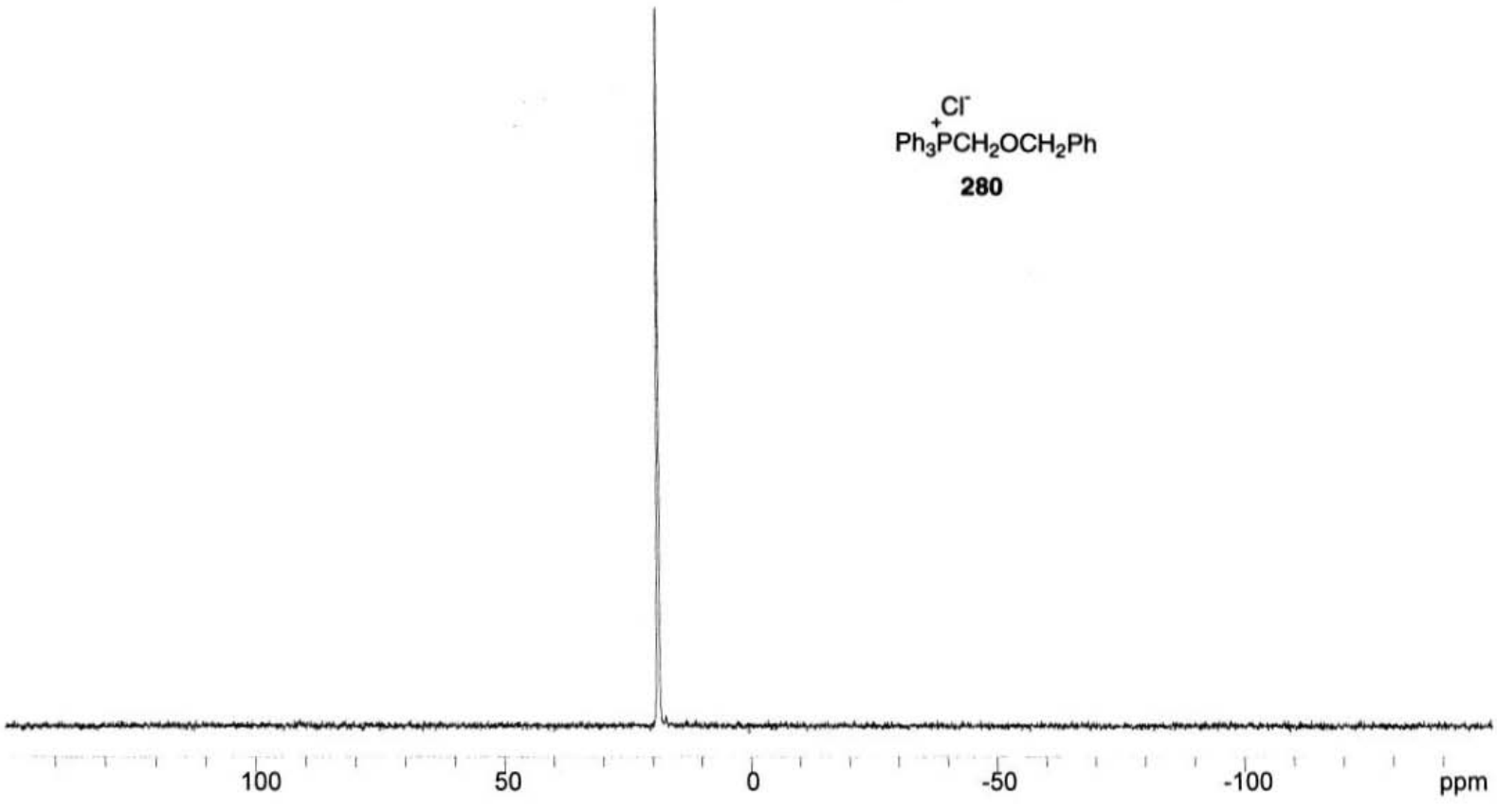
265

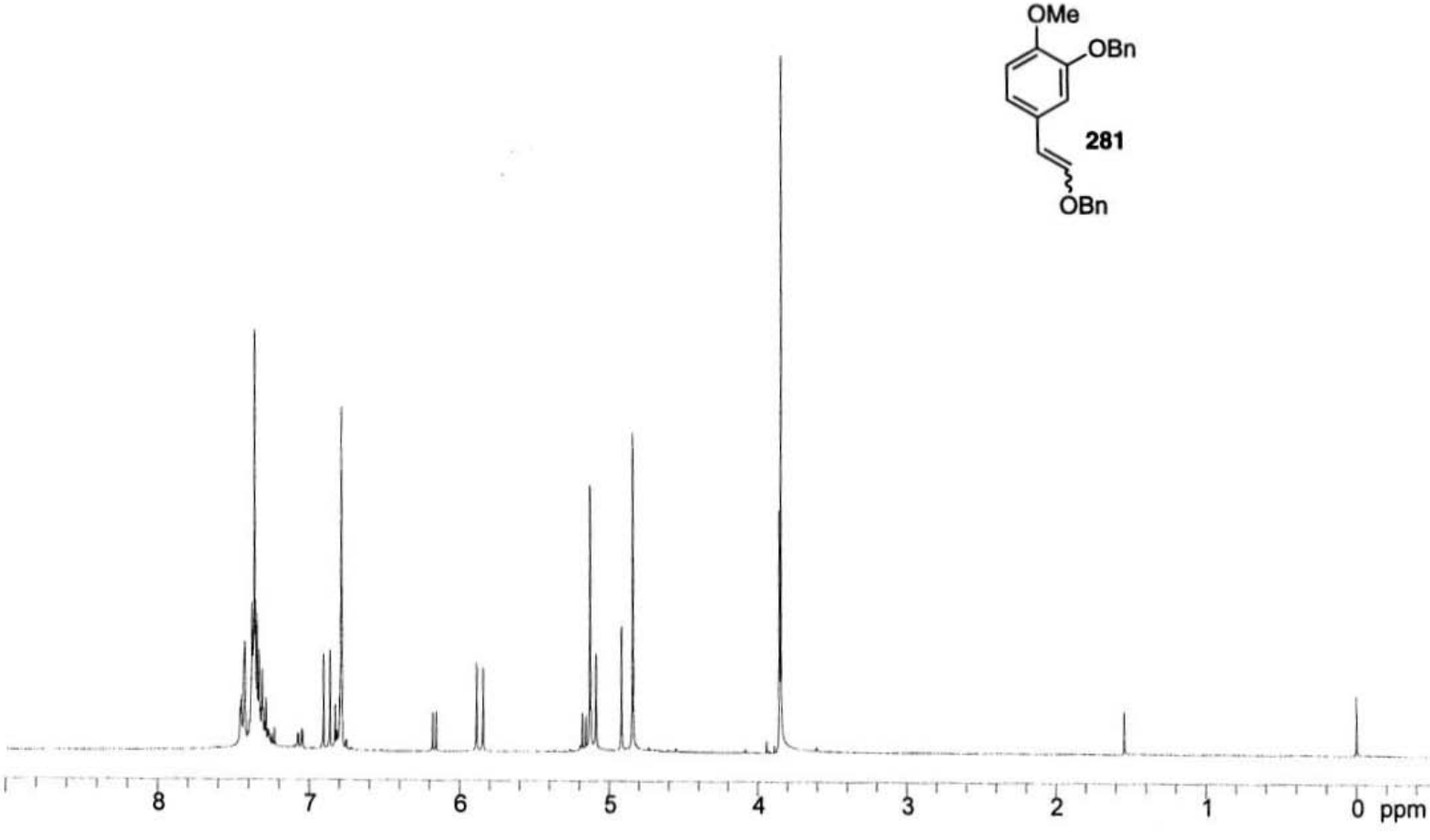

OMe
OBn
278
H
O
10
8
6
4
2
0ppm

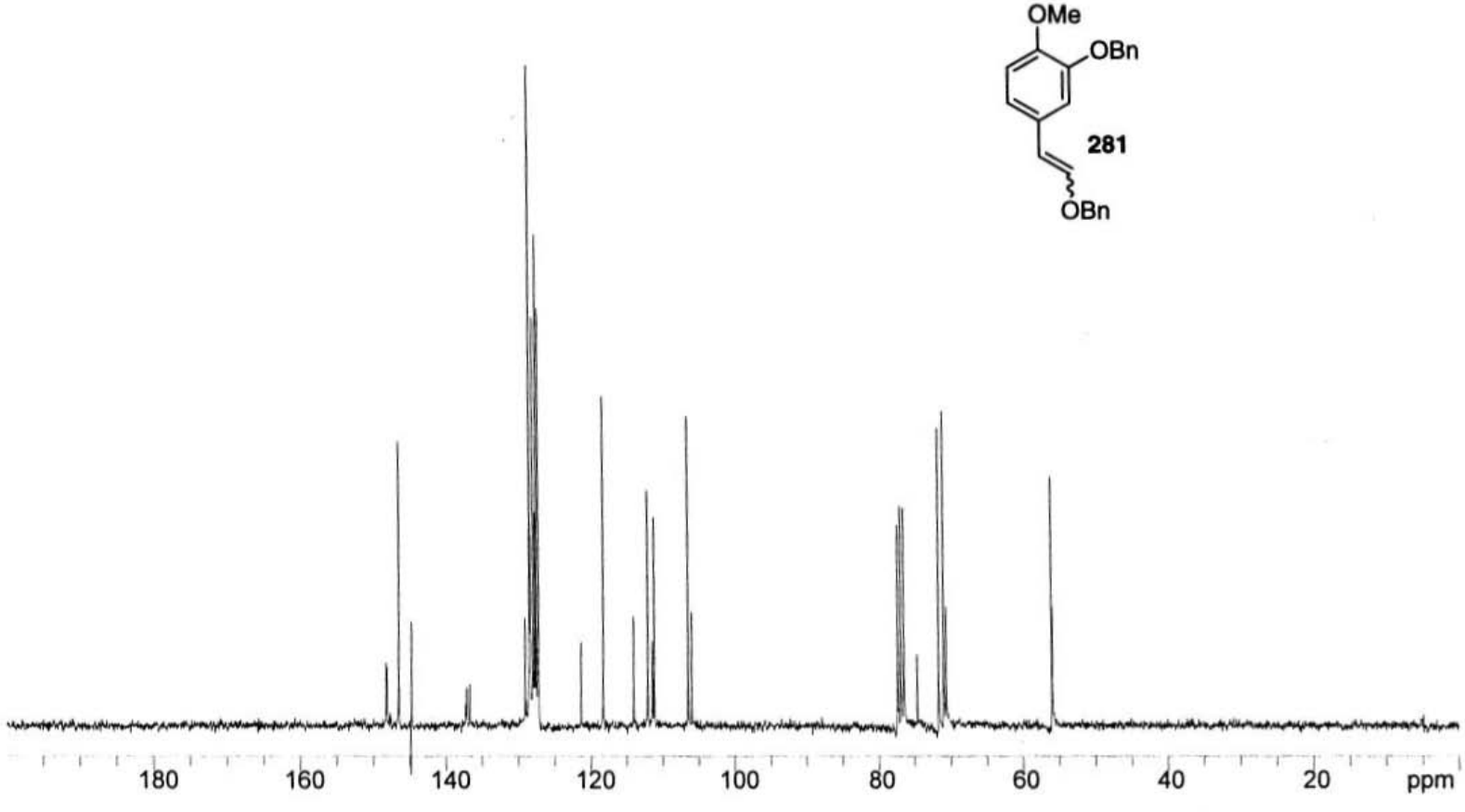

OMe
OBn
278
H
O
180
160
140
120
100
80
60
40
20
ppm


Cl⁻
+
Ph3PCH2OCH2Ph
280
8
7
6
5
4
3
2
1
0 ppm

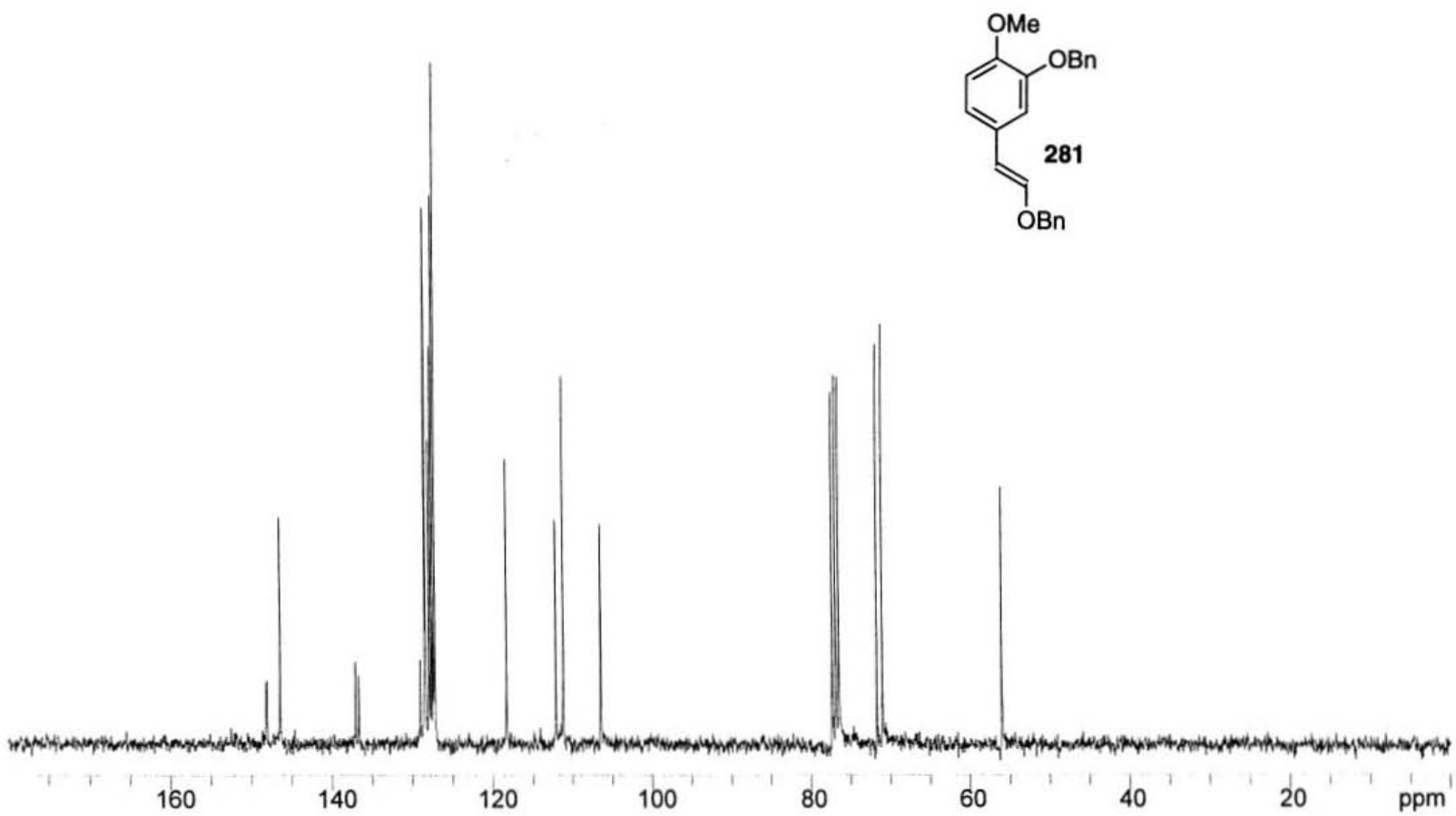

Cl⁻
+
Ph3PCH2OCH2Ph
280
180
160
140
120
100
80
60
40
20
ppm

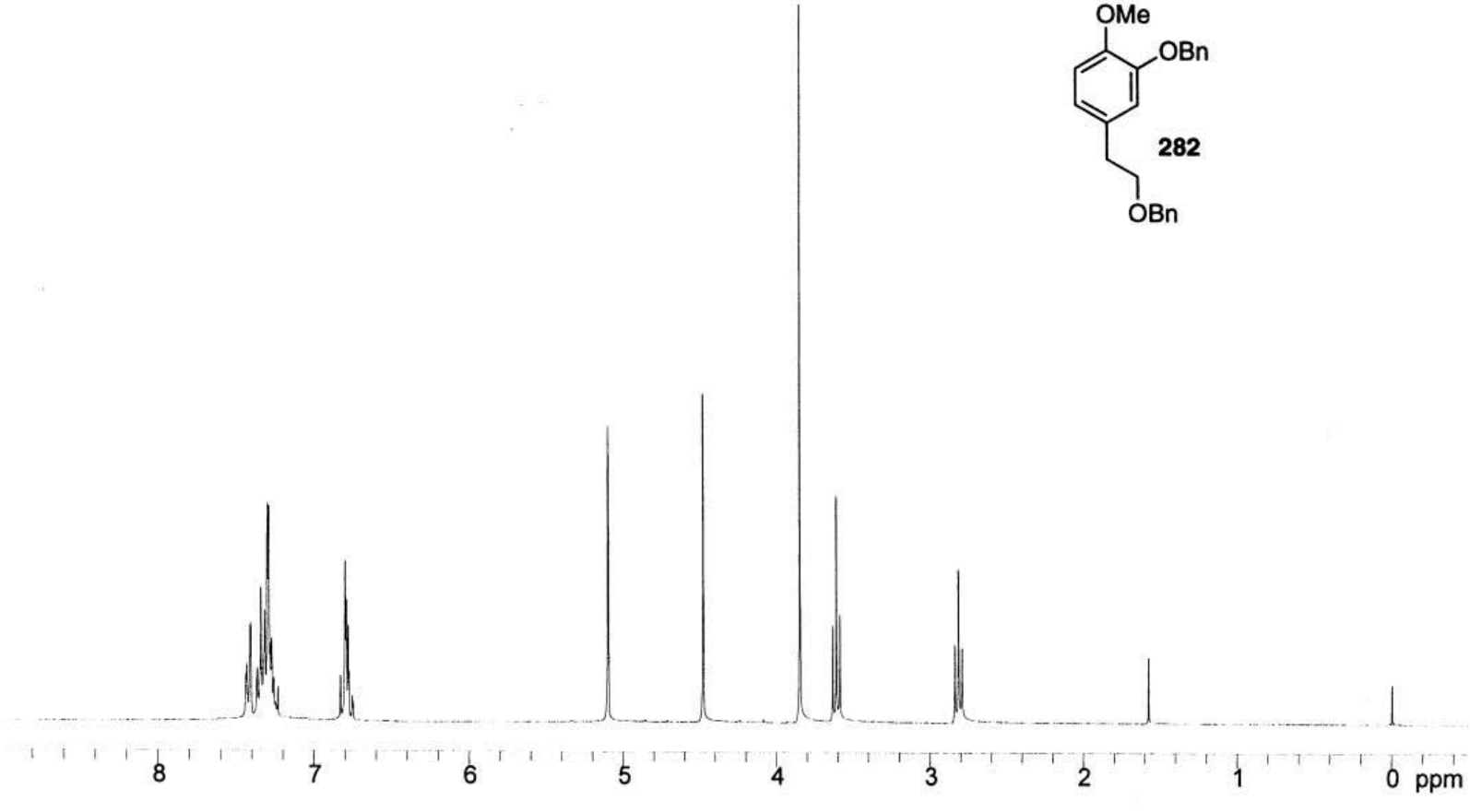

Cl⁻
+
Ph3PCH2OCH2Ph
280
100
50
0
-50
-100
ppm

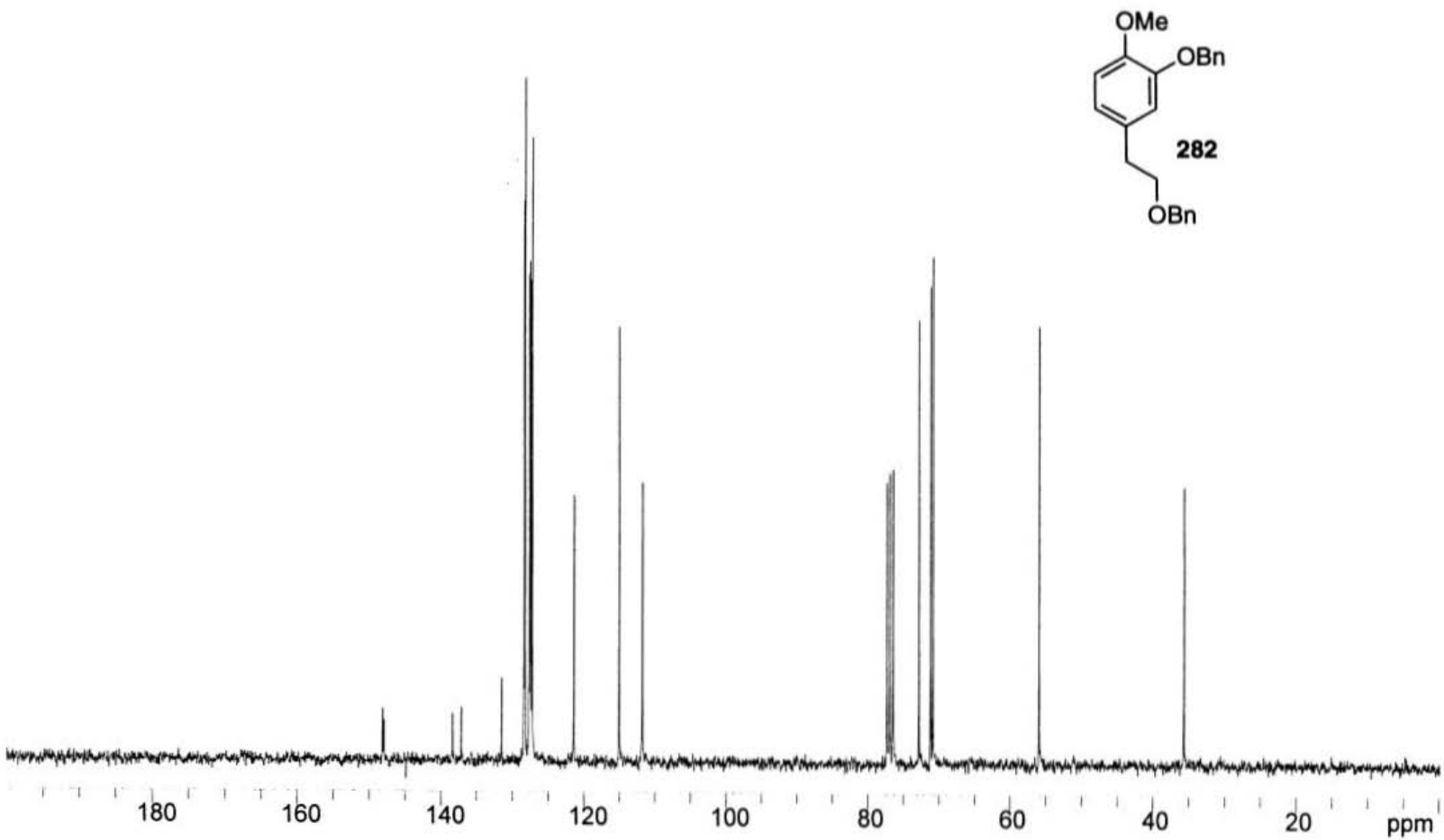

OMe
OBn
281
OBn
8
7
6
5
4
3
2
1
0 ppm

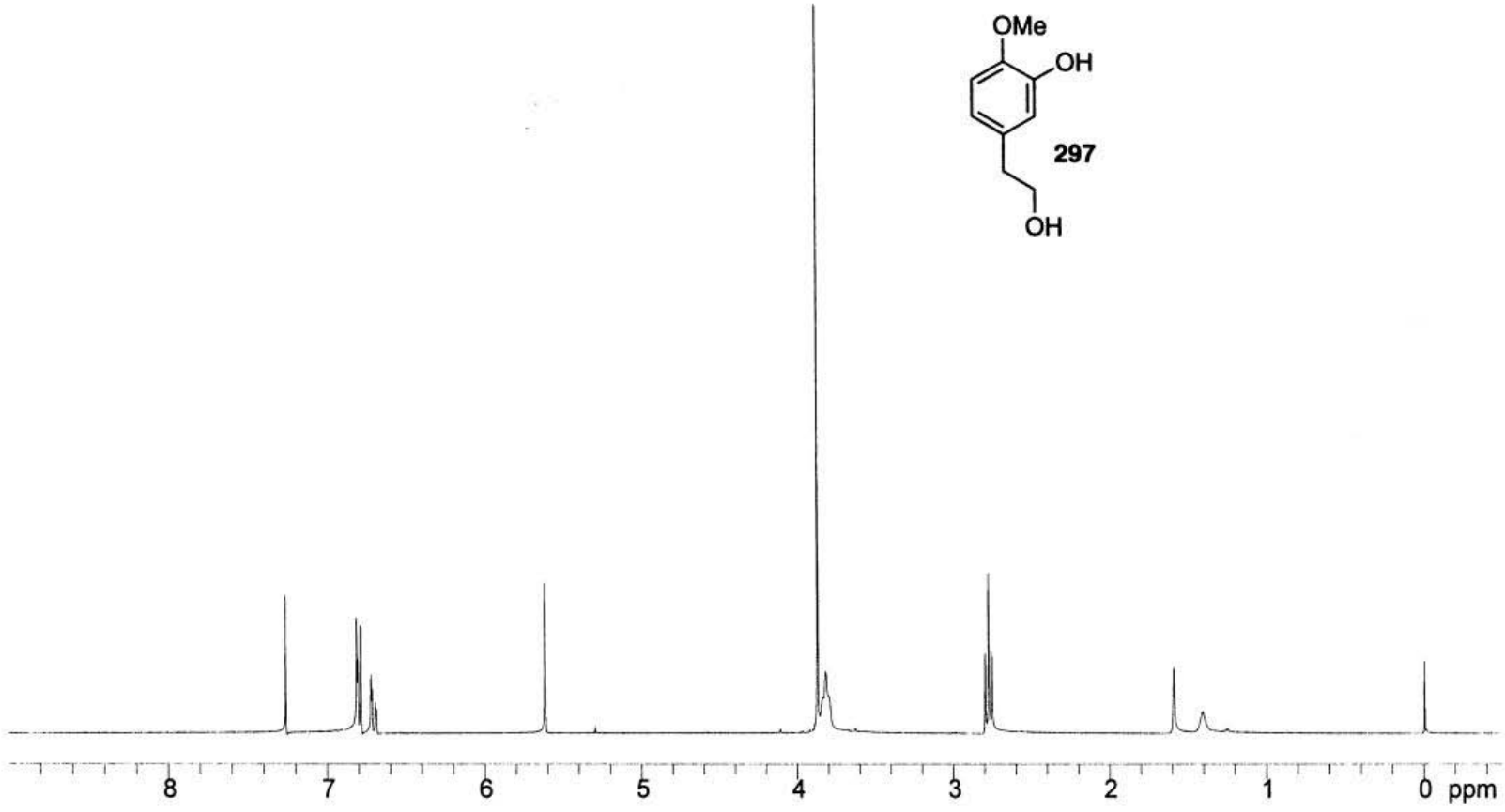

OMe
OBn
281
OBn
180
160
140
120
100
80
60
40
20
ppm

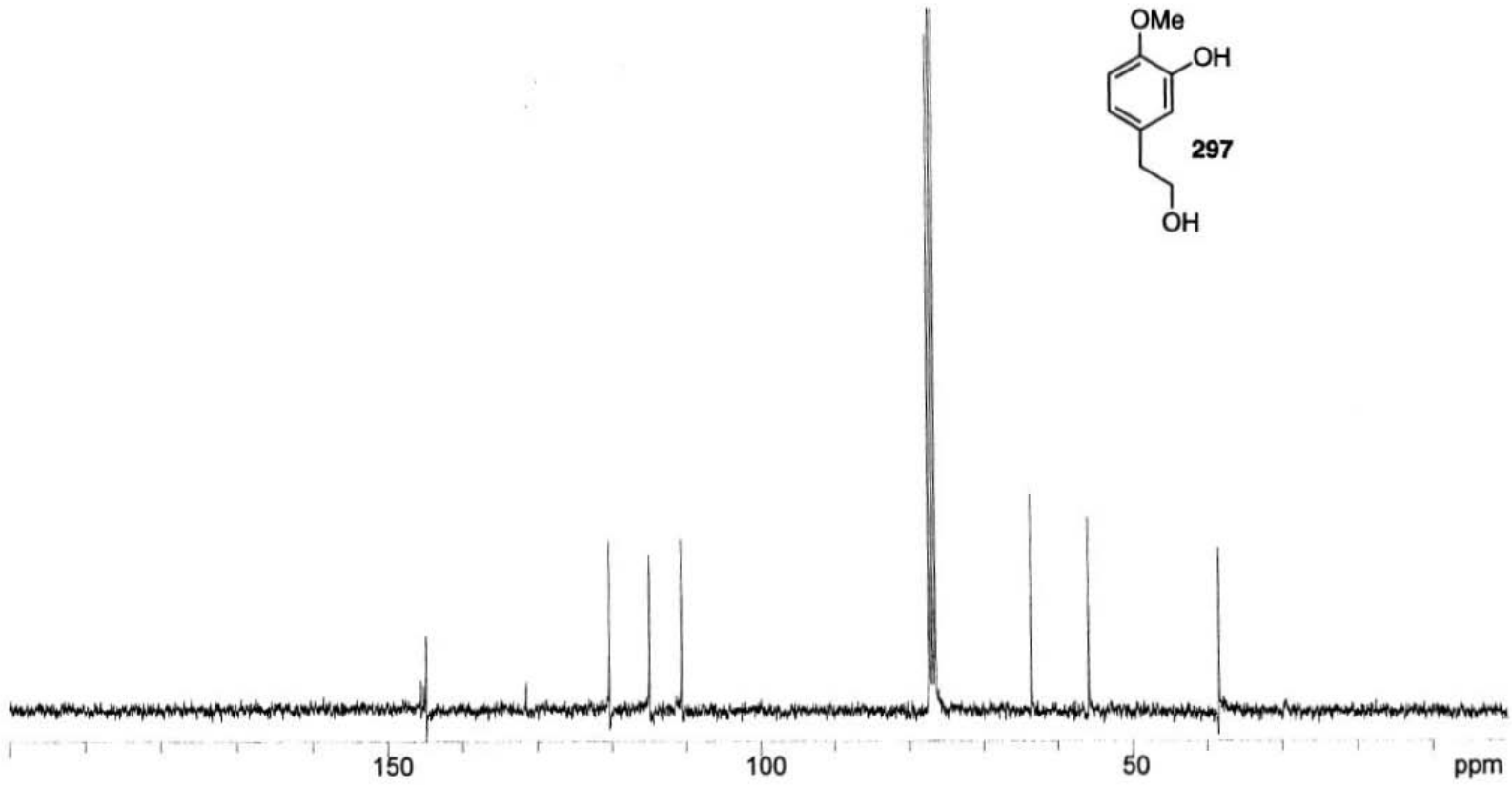
OMe
OBn
281
OBn
0 ppm

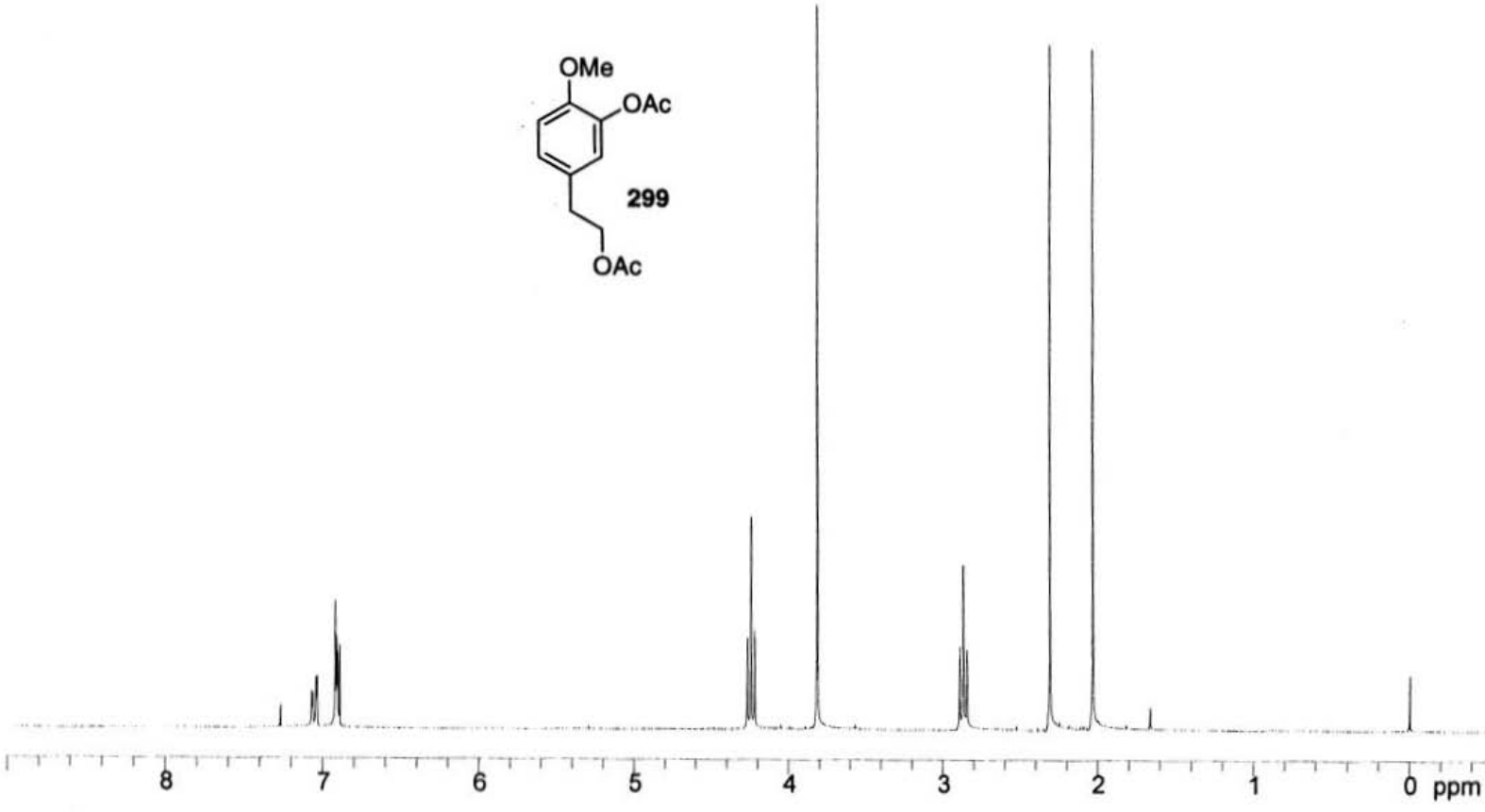

OMe
OBn
281
OBn
160
140
120
100
80
60
40
20
ppm

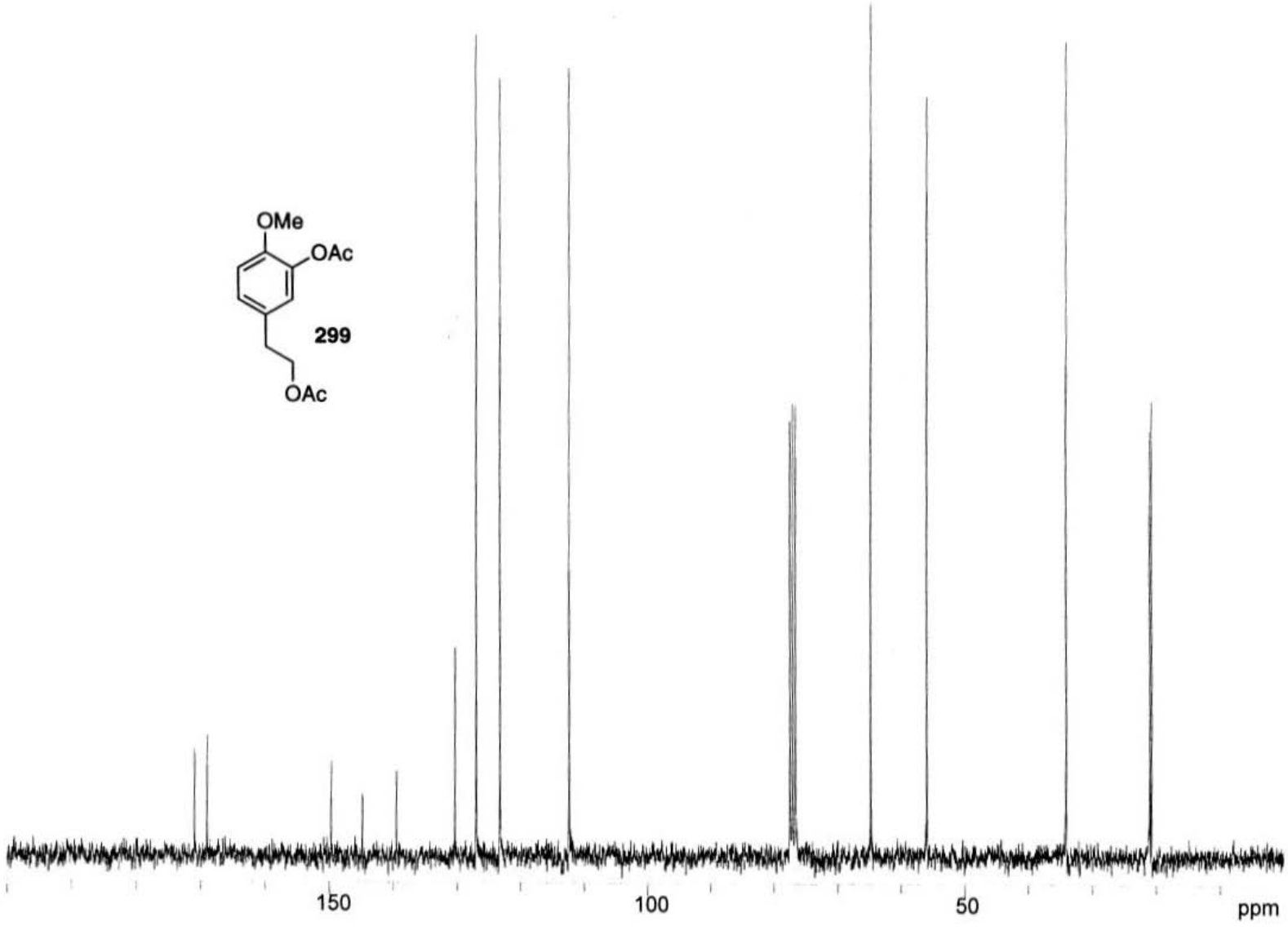

OMe
OBn
282
OBn
8
7
6
5
4
3
2
1
0 ppm

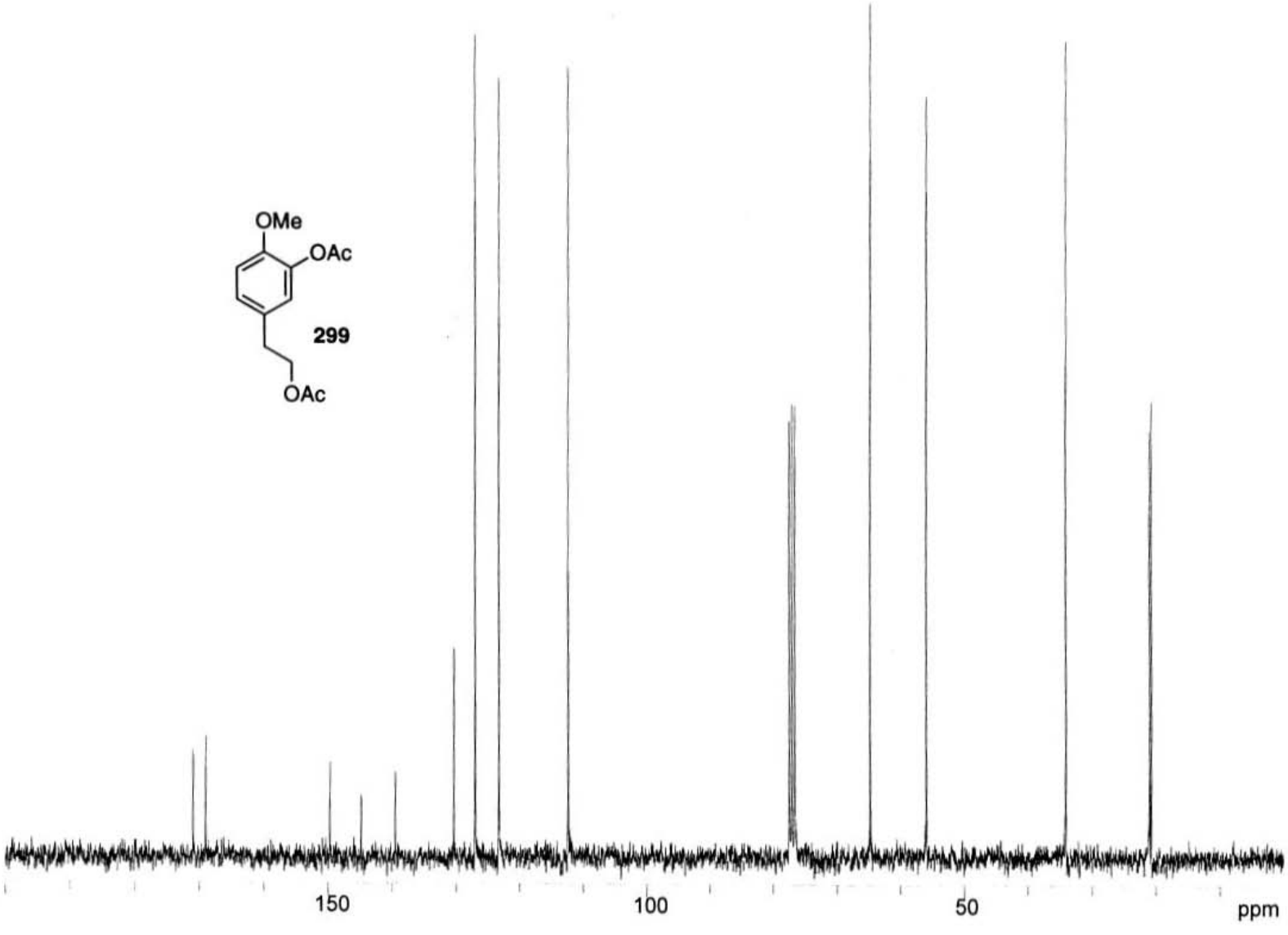

OMe
OBn
282
OBn
180
160
140
120
100
80
60
40
20
ppm

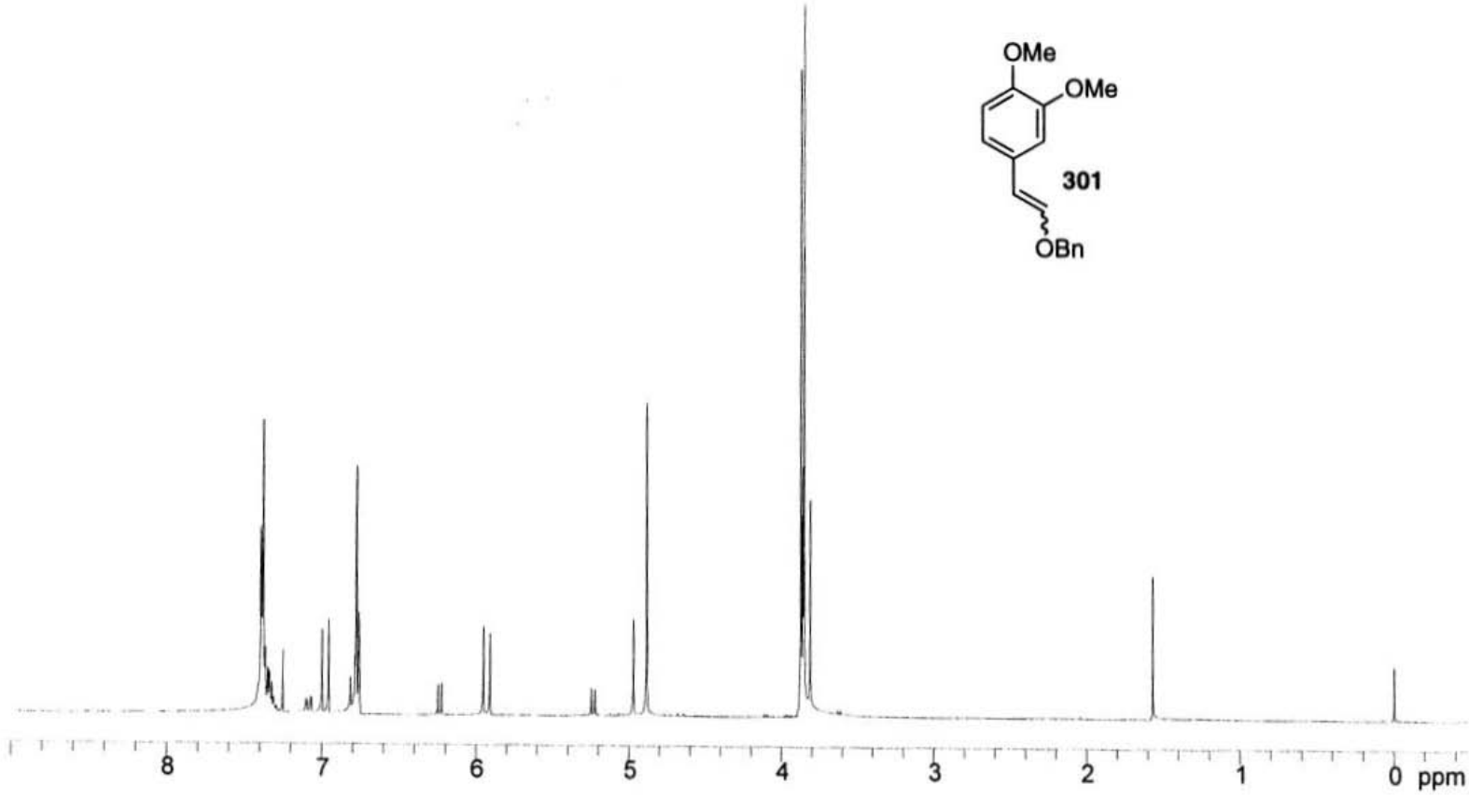

OMe
OH
297
OH
8
7
6
5
4
3
2
1
0 ppm

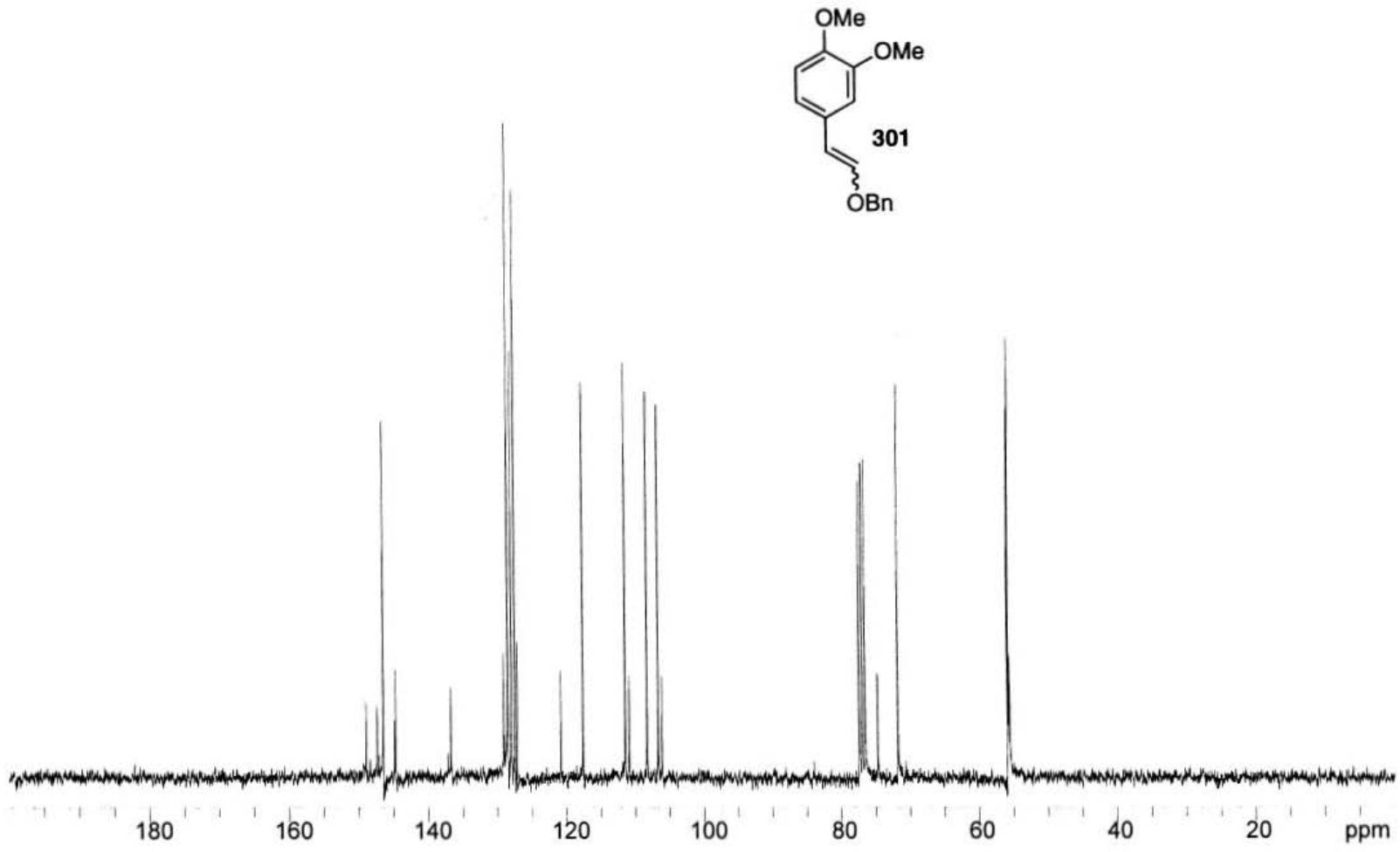

OMe
OH
297
OH
150
100
50
ppm

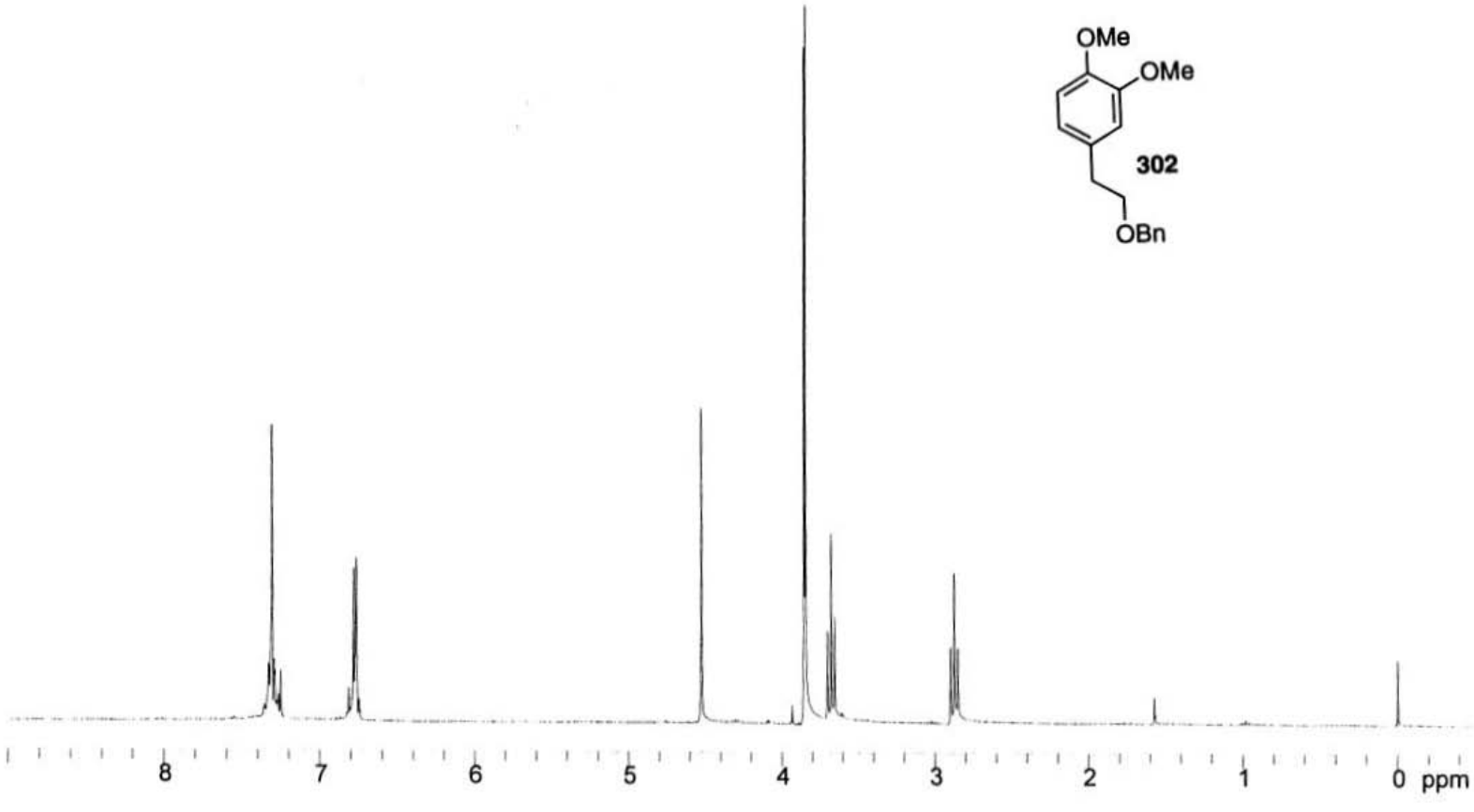

OMe
OAc
299
OAc
8
7
6
5
4
3
2
1
0 ppm


OMe
OAc
299
OAc
150
100
50
ppm

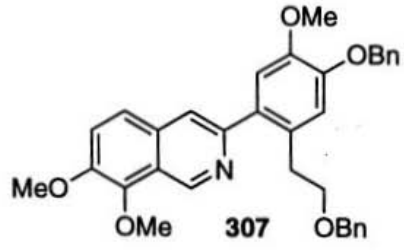

OMe
OAc
299
OAc
150
100
50
ppm


OMe
OMe
301
OBn
8
7
6
5
4
3
2
1
0 ppm

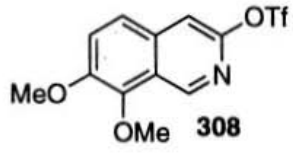

OMe
OMe
301
OBn
180
160
140
120
100
80
60
40
20
ppm


OMe
OMe
302
OBn
8
7
6
5
4
3
2
1
0 ppm

OMe
OMe
302
OBn
ppm
20
40
60
80
100
120
140
160
180



307

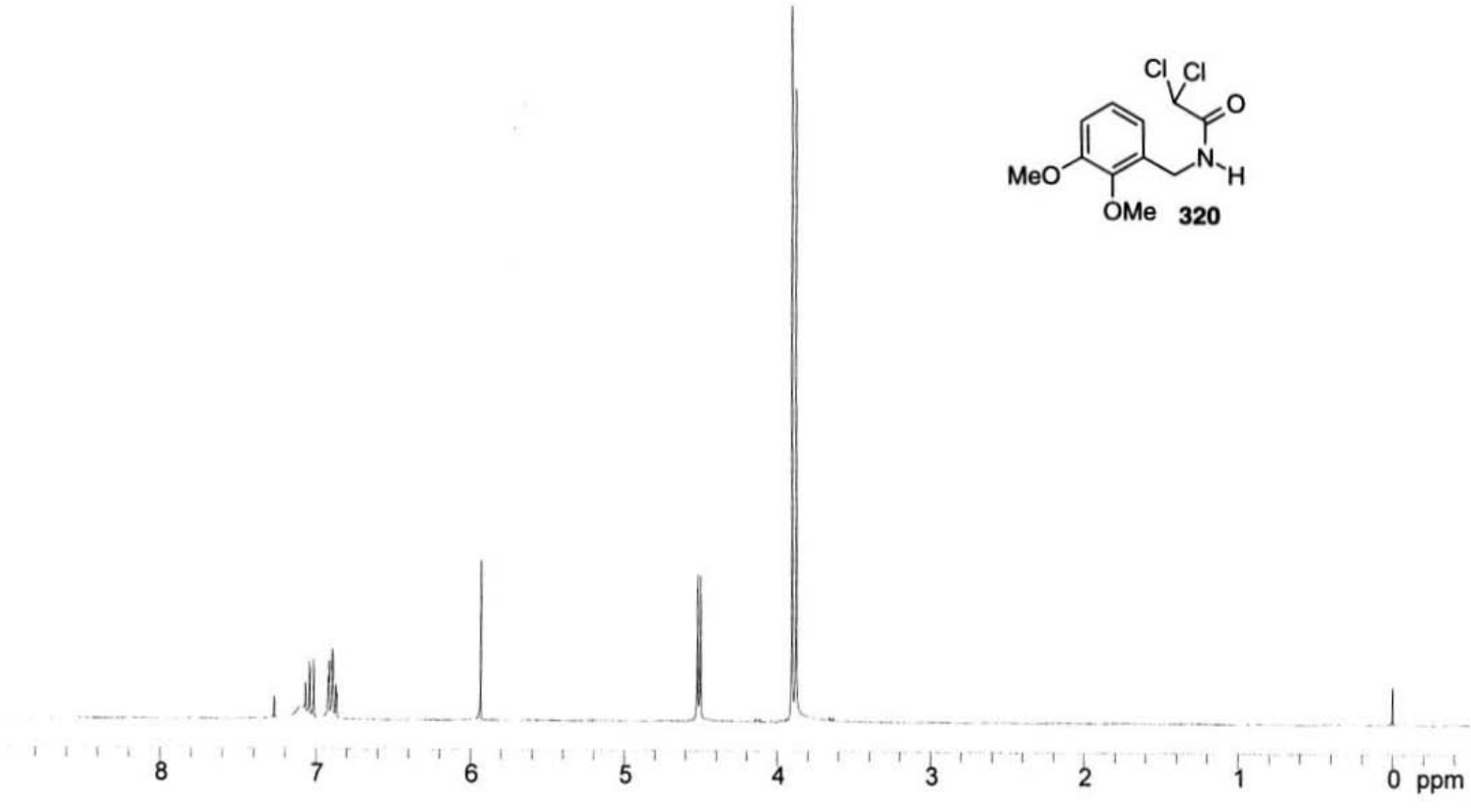


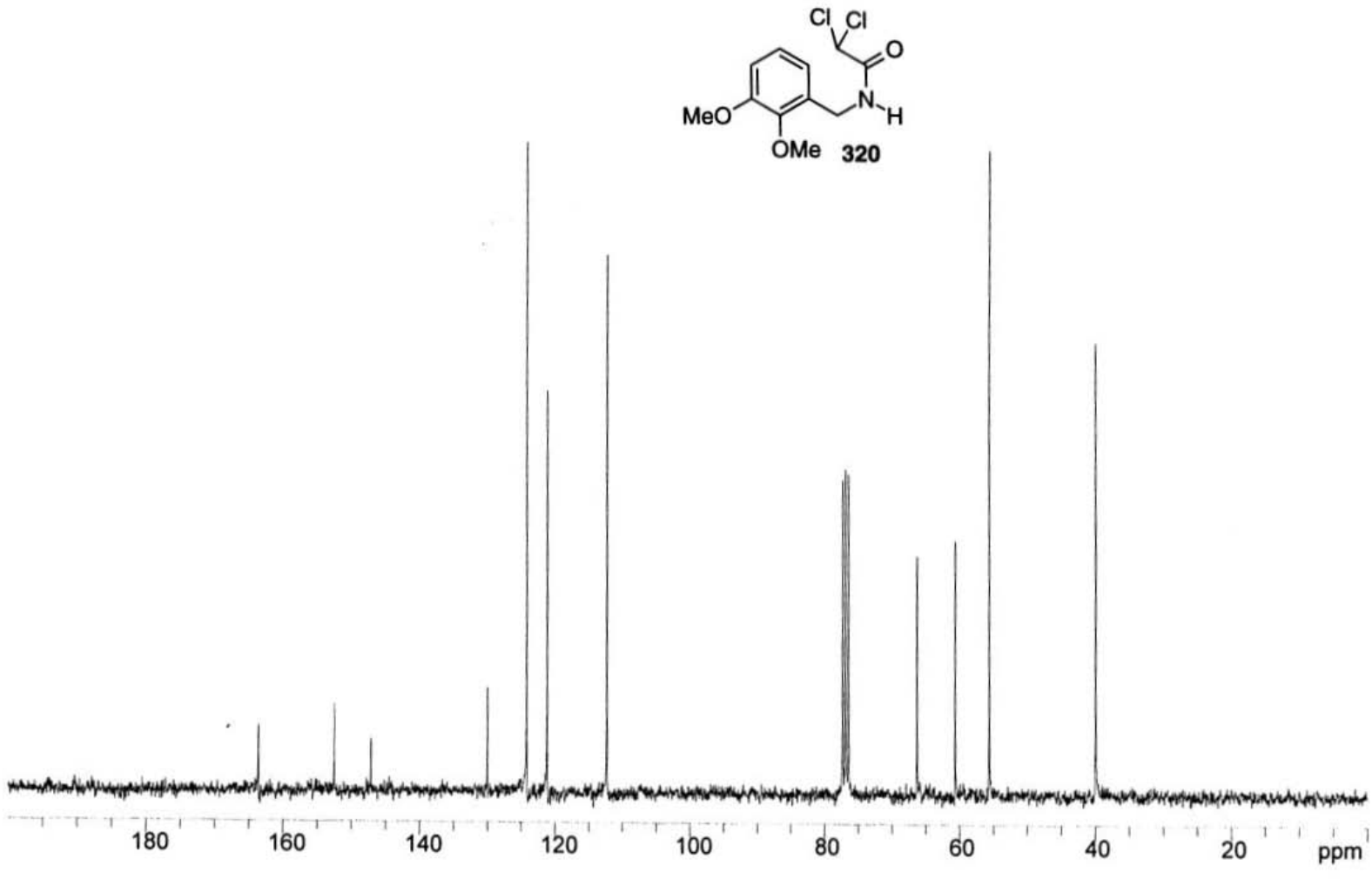
308

OTf
N
OMe
MeO
308
ppm
20
40
60
80
100
120
140
160
180

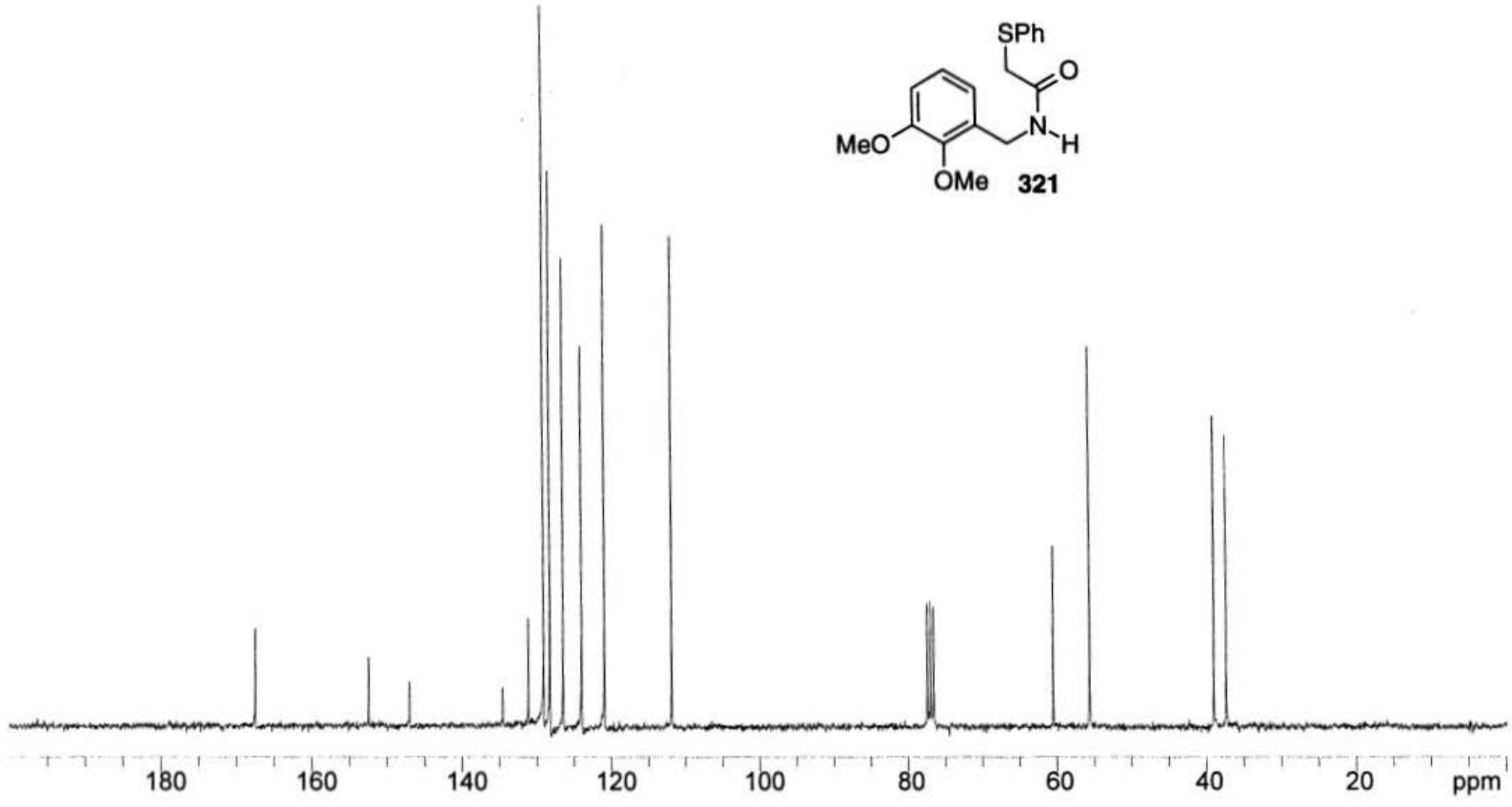
Br
O
N
H
OMe
MeO
319
0 ppm
1
2
3
4
5
6
7
8

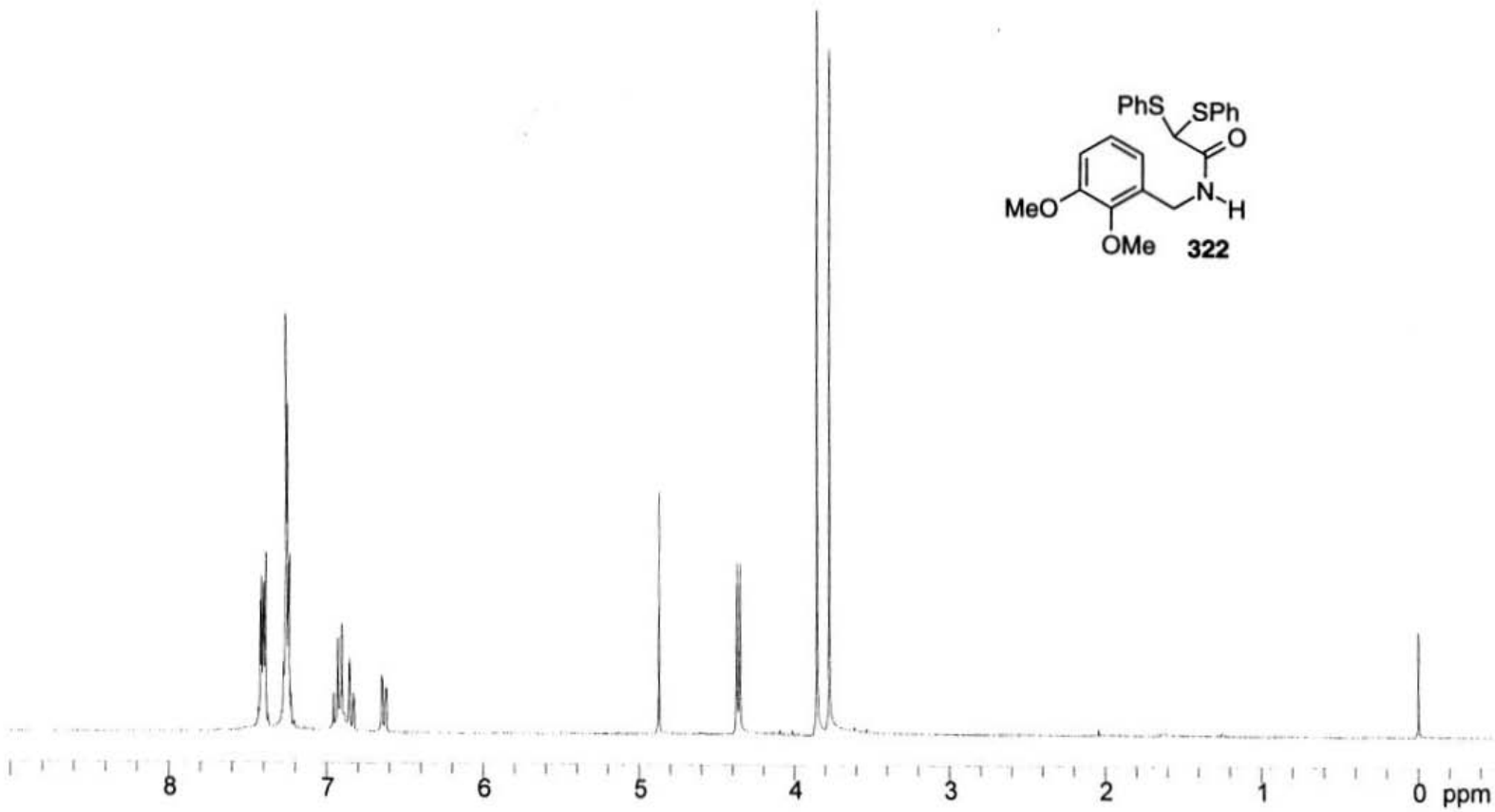
Br
O
N
H
OMe
MeO
319
ppm
20
40
60
80
100
120
140
160
180

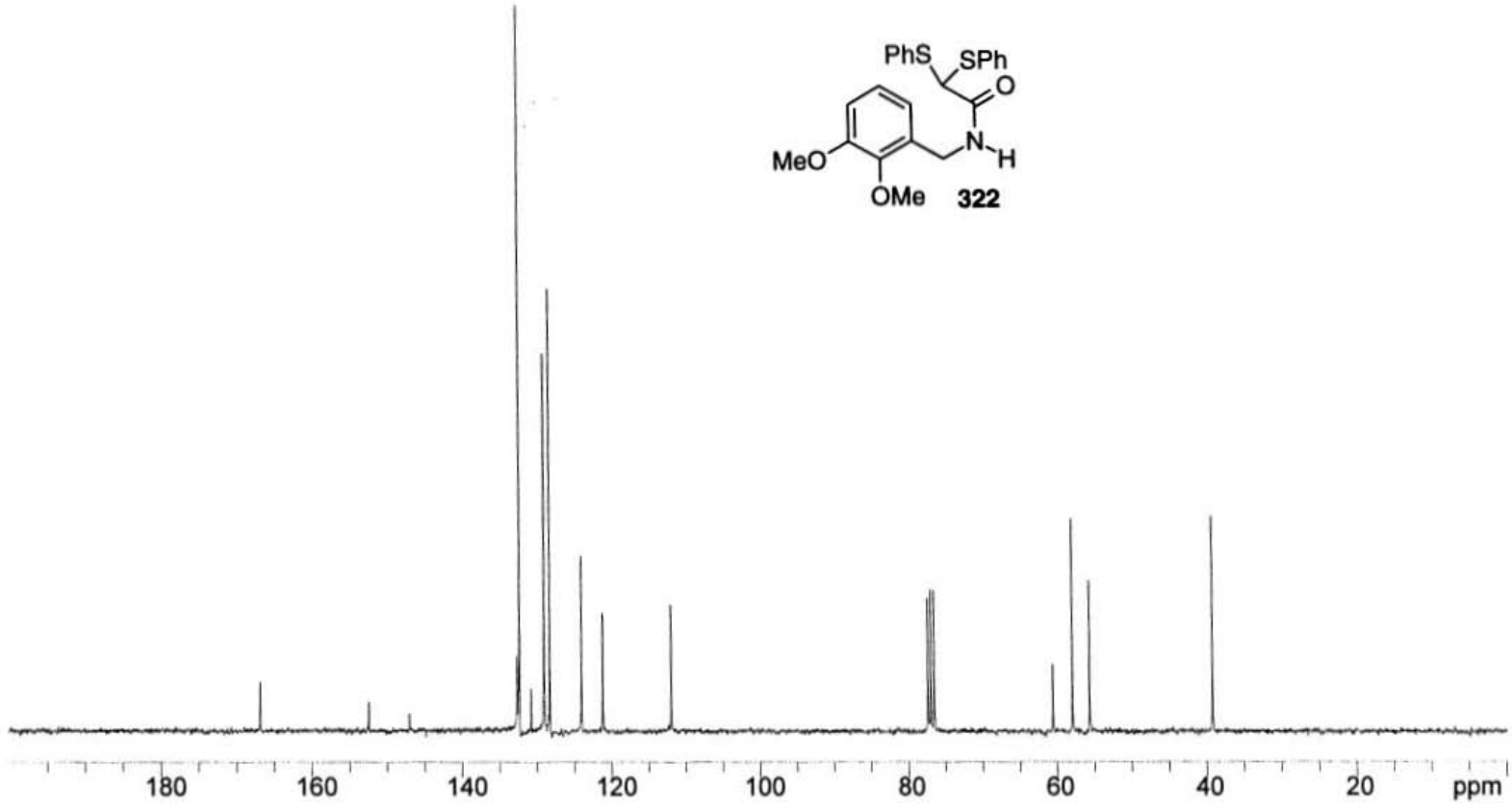

Cl
Cl
O
N
H
MeO
OMe
320
8
7
6
5
4
3
2
1
0 ppm

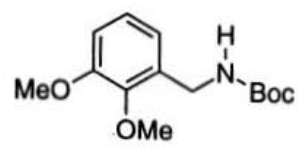

Cl
Cl
O
N
H
MeO
OMe
320
180
160
140
120
100
80
60
40
20
ppm

SPh
O
N
H
OMe
MeO
321
8
7
6
5
4
3
2
1
0 ppm

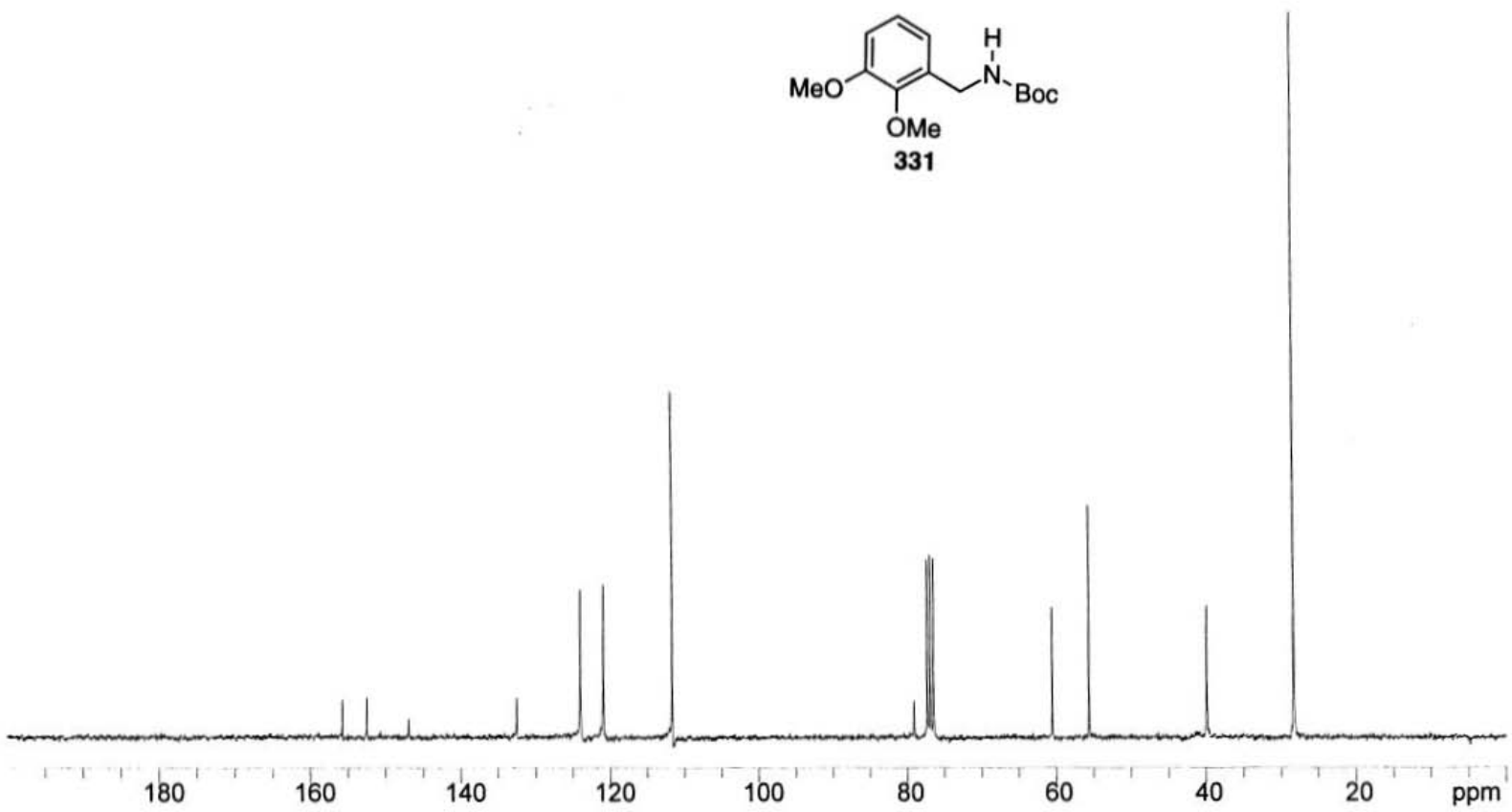

SPh
O
N
H
MeO
OMe
321
180
160
140
120
100
80
60
40
20
ppm


PhS
SPh
O
N
H
MeO
OMe
322
8
7
6
5
4
3
2
1
0 ppm


PhS
SPh
O
N
H
MeO
OMe
322
180
160
140
120
100
80
60
40
20
ppm

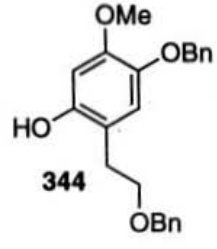


331

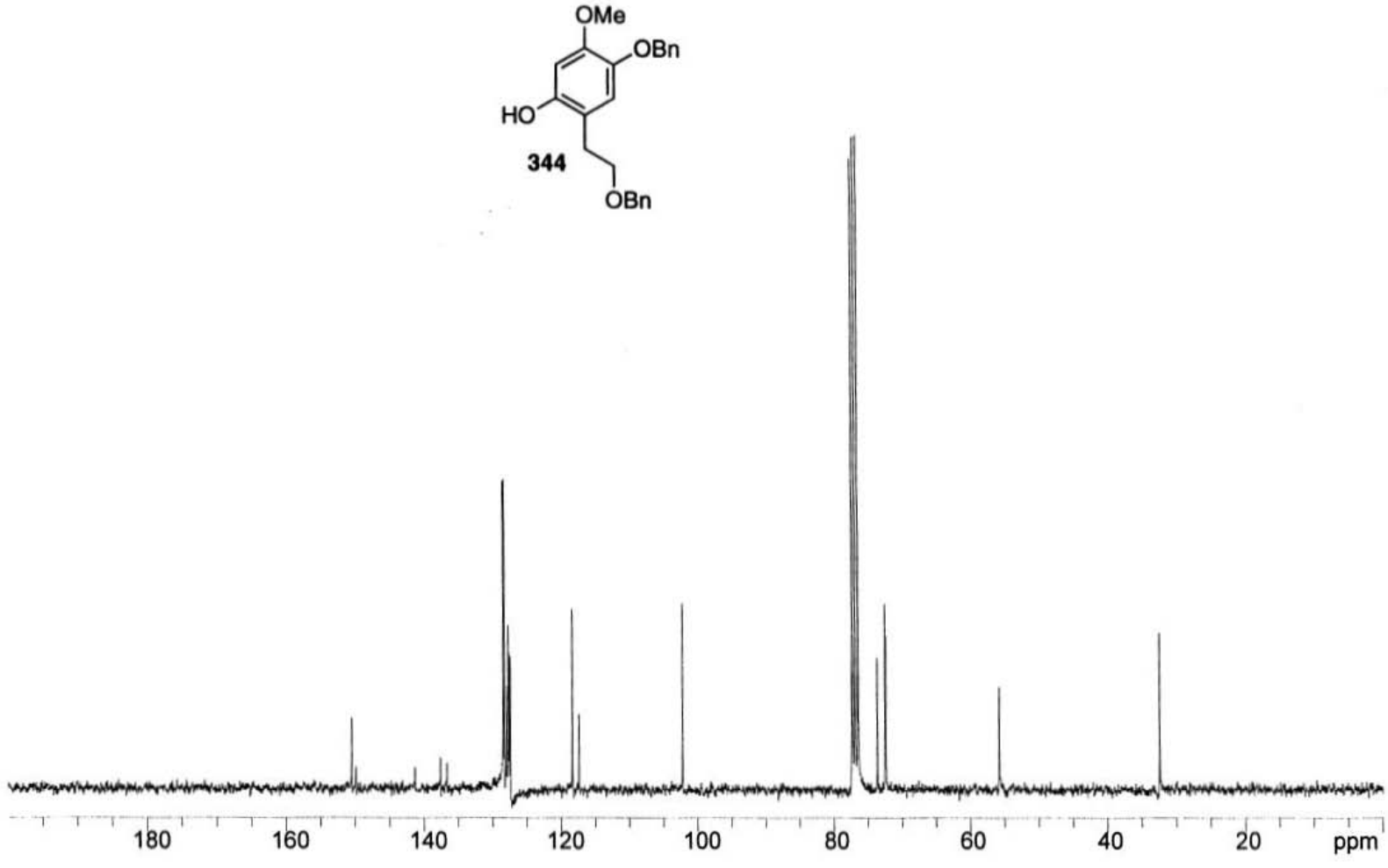

MeO
OMe
H
N
Boc
331
180
160
140
120
100
80
60
40
20
ppm

OBn
OMe
340
OBn
I
8
7
6
5
4
3
2
1
0 ppm

OMe
OBn
340
OBn
I
ppm
20
40
60
80
100
120
140
160
180



344


OMe
OBn
HO
344
OBn
180
160
140
120
100
80
60
40
20
ppm