Towards the Synthesis of Calyculin A

by

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B.S. University of California -- Berkeley
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Department of Chemistry, July 3, 1992

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Professor Frederick D. Greene _____

Dedicated with love to my parents

Raymond and Shirley

and to my brothers

Michael and Steven

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ABSTRACT

Synthetic approaches towards various fragments of the marine natural product calyculin A are described. Attempts at the preparation of the C1-C9 tetraene making extensive use of Wittig and Horner-Emmons methodology are discussed in Chapter 1. Chapter 2 is concerned with the synthesis of the C26-C32 fragment in which the key step involves condensation of an amide with ethyl bromopyruvate to introduce the oxazole. Chapter 3 describes the work directed towards completion of the C33-C37 fragment featuring the hydrolytic opening of an imidate derived from a lactam followed by elaboration of the dimethylamino group. Final development of the methodology for the assembly of the C26-C37 fragment is discussed in Chapter 4, and the use of chiral isoxazolidines as auxiliaries in asymmetric synthesis as applied to the preparation of the C26-C32 portion is discussed in Chapter 5. Chapter 6 presents a discussion of our work on Calyculin A and chiral isoxazolidines as compared to research recently published by other groups.

Thesis Supervisor: Satoru Masamune
Title: Professor of Chemistry

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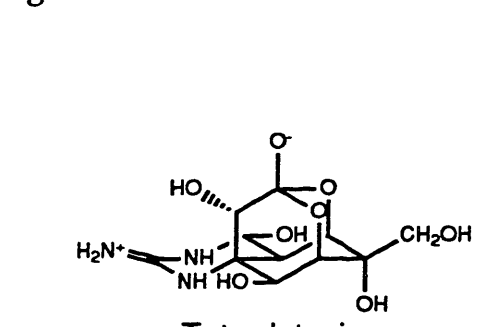
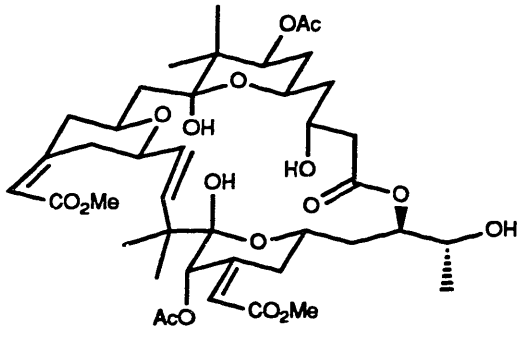
Introduction

0.1 Isolation of the Calyculins

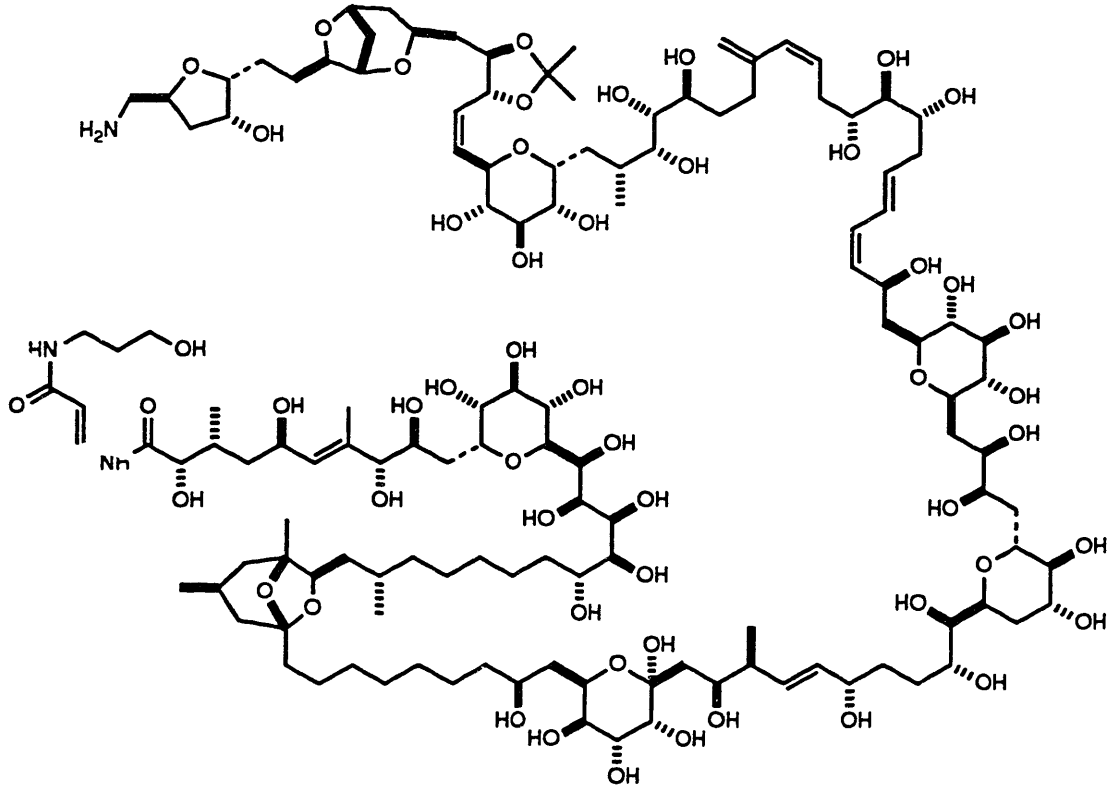
Figure 0.1



Tetrodotoxin
Spheroides rubripes
1



Bryostatin 7
Bugula neritina
2

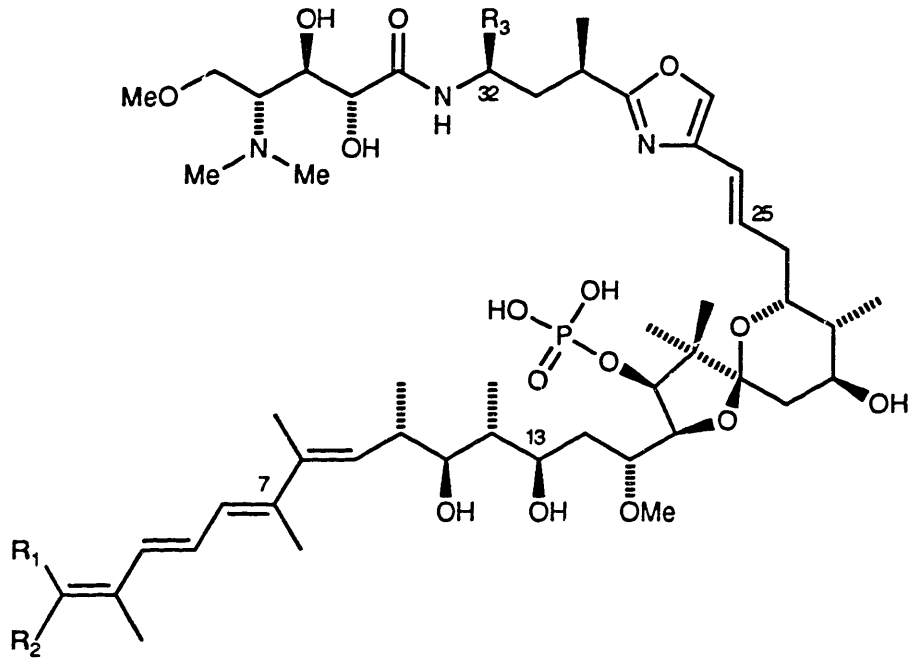


Palytoxin
Palythoa toxica
3

Marine organisms have proven to be important sources of natural products bearing unique structural and biological properties. Some

examples are shown in Figure 0.1 and are described accordingly. Tetrodotoxin, **1**, is the neurotoxin isolated from the blowfish, *Spheroides rubripes*, and is the active component of the so-called Haitian zombification powder.[1] Bryostatin 7, **2**, is a cytotoxin isolated from the sponge, *Bugula neritina*..[2] Palytoxin, **3**, is isolated from the coral, *Palythoa toxica*, and is believed to be the most potent non-peptidic, non-alkaloid toxin isolated from any marine organism.[3]

Figure 0.2



4: Calyculin A: R_1 = CN, R_2 = R_3 = H
5: Calyculin B: R_1 = R_3 = H, R_2 = CN
6: Calyculin C: R_1 = CN, R_2 = H, R_3 = Me
7: Calyculin D: R_1 = H, R_2 = CN, R_3 = Me
8: Calyculin E: 6,7 *Z* isomer of A
9: Calyculin F: 6,7 *Z* isomer of B
10: Calyculin G: 6,7 *Z* isomer of C
11: Calyculin H: 6,7 *Z* isomer of D

Between the years of 1986 and 1988, a novel family of four structurally related compounds was isolated from the biologically active extracts of the marine sponge, *Discodermia calyx*, and were characterized by NMR and x-

ray crystallographic techniques.[4,5,6,7] Furthermore, in 1990 an additional four members of this family were discovered.[8,9,10] These compounds were named calyculins A-H and their structures are shown in Figure 0.2.

Calyculin A, **4**, is the most abundant and the most biologically active member of the calyculin family, however it is present only in concentrations of about 150 mg/kg of wet sponge (Table 0.1).[4,6,9] The relatively low abundances of these compounds coupled with their diverse structural features and varied biological properties have made them desirable targets for many synthetic groups.[11-26]

Table 0.1[4,6,9]

Isolated Yields of the Calyculins from *Discodermia calyx*

Calyculin	mg/kg wet sponge	yield (%)
A	150	0.15
B	20	0.02
C	30	0.03
D	5	5×10^{-3}
E	1.8	1.8×10^{-3}
F	1.3	1.3×10^{-3}
G	0.9	9×10^{-4}
H	0.9	9×10^{-4}

0.2 Biological Properties of the Calyculins

Table 0.2

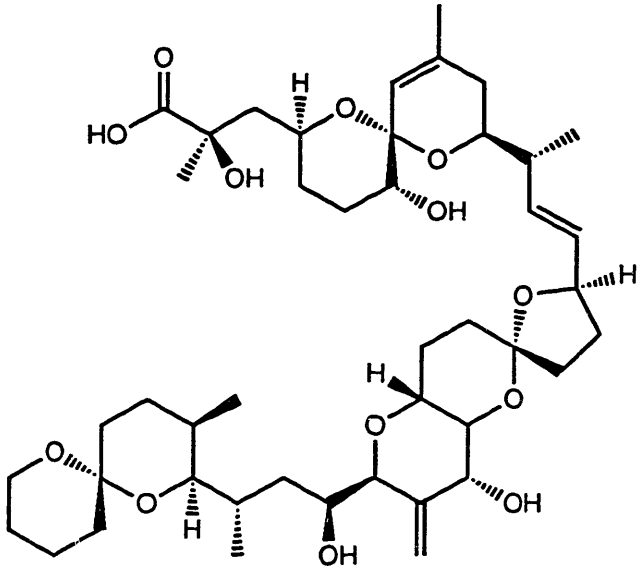
Minimum Inhibitory Dosages (ID) of Calyculins A-D

Calyculin	min ID (μg/mL)
A	0.01
B	0.01
C	0.005
D	0.005

Since 1986, the diverse biological properties of the calyculins have been the subject of intense scientific interest. The calyculins were first found

in the extracts of *Discodermia calyx* which inhibit the growth of fertilized starfish and sea urchin eggs.[5,27,28] The inhibitory doses (ID) of calyculins A-D as measured using methods developed by Ikegami[29] are listed in Table 0.2.

Figure 0.3



Okadaic Acid
12

After the initial assays and isolation, other biological properties of these novel compounds became apparent. One of the earliest of these to be discovered was the ability of calyculin A to inhibit the activity of various protein phosphatases.[27,30,31,32] This property was discovered when calyculin A, **4**, was found to inhibit the binding of okadaic acid, **5** (Figure 0.3), to protein phosphatases 1 and 2A present in homogenized mouse skin extracts. Although the binding of calyculin A to protein phosphatase 2A was found to be comparable to that of okadaic acid, calyculin A was found to bind 20-300 times more strongly to protein phosphatase 1.[27] The inhibitory concentrations (IC) of okadaic acid and calyculin A to various phosphatases are shown in Table 0.3.[27,30,33,34]

Table 0.3[27]

Inhibitory Concentrations (IC) of Okadaic Acid and Calyculin A to Various Phosphatases

Phosphatase	Okadaic Acid IC_{50} (nM)	Calyculin A IC_{50} (nM)	Substrates
Rabbit skeletal muscle type PP-1, catalytic subunit	60-200	2	myosin, LC20, phosphorylase a
Rabbit skeletal muscle type PP-2A, catalytic subunit	0.5-1.0	0.5-1.0	myosin, LC20, phosphorylase a
Chicken gizzard endogenous phosphatase of myosin B, crude	15-70	0.3-0.7	myosin, LC20, phosphorylase a
Chicken gizzard endogenous phosphatase of myosin B, partially purified	200	0.7	myosin, LC20, phosphorylase a
Bovine aortic polymolecular PP-2A	100		bovine heart myosin light chains, labeled by chick gizzard MLCK
Bovine brain PP-2B (calcineurin)	10,000		bovine heart myosin light chains, labeled by chick gizzard MLCK
Rabbit liver PP-2C	no effect at 10 μM		bovine heart myosin light chains, labeled by chick gizzard MLCK
Bovine semen and potato acid phosphatases	no effect at 10 μM	no effect at 1 μM	*p*-nitrophenyl phosphate
Alkaline phosphatases from bovine liver/ intestinalmucosa/ kidney and E. coli	no effect at 10 μM	no effect at 1 μM	*p*-nitrophenyl phosphate
Human placental cytoskeleton PtyP	no effect at 10 μM	no effect at 1 μM	enolase, poly(Glu-Tyr)

From the studies of calyculin A as a phosphatase inhibitor, much has been learned about cellular functions and the necessity of the phosphatase-kinase couple. For example, the 20 kDa myosin light chain prepared from chicken gizzards was phosphorylated as a result of increased kinase activity in the presence of calyculin A and in the absence of Ca^{2+}.[35] Furthermore, calyculin A has been shown to facilitate the opening of Ca^{2+} channels. This

effect is postulated to be regulated by an intracellular phosphorylation system.[36]

When cellular systems were treated with calyculin A a marked increase in protein phosphorylation within the cytosolic cellular fractions was observed. Specific species that were phosphorylated include vimetin and the 20 kDa myosin light chain. Furthermore, as observed by electron microscopy, addition of calyculin A to 3T3 cells induced a noticeable shape change in which the cell walls became rounded. This shape change was reversible on removal of calyculin A. In the shape altered cells, stress fibers, intermediate filaments, and microtubules were not noticeable. These observations lend support to the conjecture that cell shape is at least partially related to the phosphatase-kinase couple.[37]

As a final example of the ability of calyculin A to inhibit intracellular phosphatase activity, starfish oocytes were treated with calyculin A. The extract from these oocytes was shown to induce the phosphorylation of exogenously added H1 histone.[38] Therefore, from these results, there appears to be abundant evidence for the interference of calyculin A in phosphorylation-dephosphorylation systems.

As previously alluded to, calyculin A has also been shown to interact with Ca^{2+} levels in cellular systems. Evidence for this property is provided from the observation that calyculin A causes contractions in the smooth muscle of guinea pig taenia and rat aorta. The observation that these effects are independent of the external Ca^{2+} concentration, and that calyculin A actually facilitates the opening of voltage dependent Ca^{2+} channels in guinea pig taenia coli smooth muscle cells, further supports the above claim.[35,36]

Although these Ca^{2+} related effects are evident, they can be inhibited by protein kinase C inhibitor, H-7, and nifedipine.[39] Furthermore, the calyculin A induced muscular contractions can be decreased if the muscle strips are preincubated with endothelin-1 or phorbol 12-myristate 13-acetate.[40] These observations seem to lend support to the interrelation of the phosphatase-kinase couple and Ca^{2+} channels in cells. Consequently, with all of these drastic biological effects, it is not surprising that calyculin A has been shown to be an okadaic acid class tumor promoter when applied topically to mouse skin. The postulated mode of action of tumor promotion is initial binding of calyculin A to the okadaic acid receptor followed by inhibition of protein phosphatases. The result is increased kinase activity and inhibited protein dephosphorylation -- one of the essential processes necessary for tumor promotion.[28,32,41,42]

Calyculin A has also been shown to possess antitumor and antileukemic properties. This activity was noted in *in vitro* tests in which it was found to be active against L1210 mouse leukemia cells. Additionally, in *in vivo* tests, *Ehrlich ascites* tumor cells and P388 leukemia cells were implanted into mice and the mice were then treated with doses of calyculin A. In this *in vivo* study, the results were expressed as T/C % which is defined as: (mean survival time of the treated group)/(mean survival time of the control group) X 100. The results of these tests are shown in Tables 0.4 and 0.5, respectively.[5,7,8,28]

In light of the variety of biological properties of the calyculins reviewed here, it is interesting to note that calyculins E and F are being studied for yet one more function. Initial tests upon the isolation of these compounds revealed that they posess certain insecticidal attributes against the German cockroach and mosquito larvae.[8,10] With these results to

complete the list, the biochemical diversity of these *Discodermia calyx* isolates seems incontrovertible. Additionally, although the biological effects of these compounds renders them far too toxic for clinical use, the synthesis and study of calyculin fragments may reveal the structure/function requirements necessary to screen out some or all of their harmful effects. In this respect, synthetic organic chemistry remains unchallenged!

Table 0.4

***In Vitro* Activities of Calyculins A-D Against:**

	L1210 (ng/mL)	*A. pectin* (μg/mL)	*H. pulcher* (μg/mL)
Calyculin A	0.74	0.02	0.01
Calyculin B	0.88	0.02	0.01
Calyculin C	0.86	0.02	0.005
Calyculin D	1.5	0.05	0.005

Table 0.5

***In Vivo* Activities of Calyculin A**

	Dose (mg/kg)	Medium Life Span (day)	T/C (%)
Erlich	0.0075	17.0	141.7
	0.015	29.5	245.8
P388	0.0075	12.5	138.9
	0.015	13.0	144.4

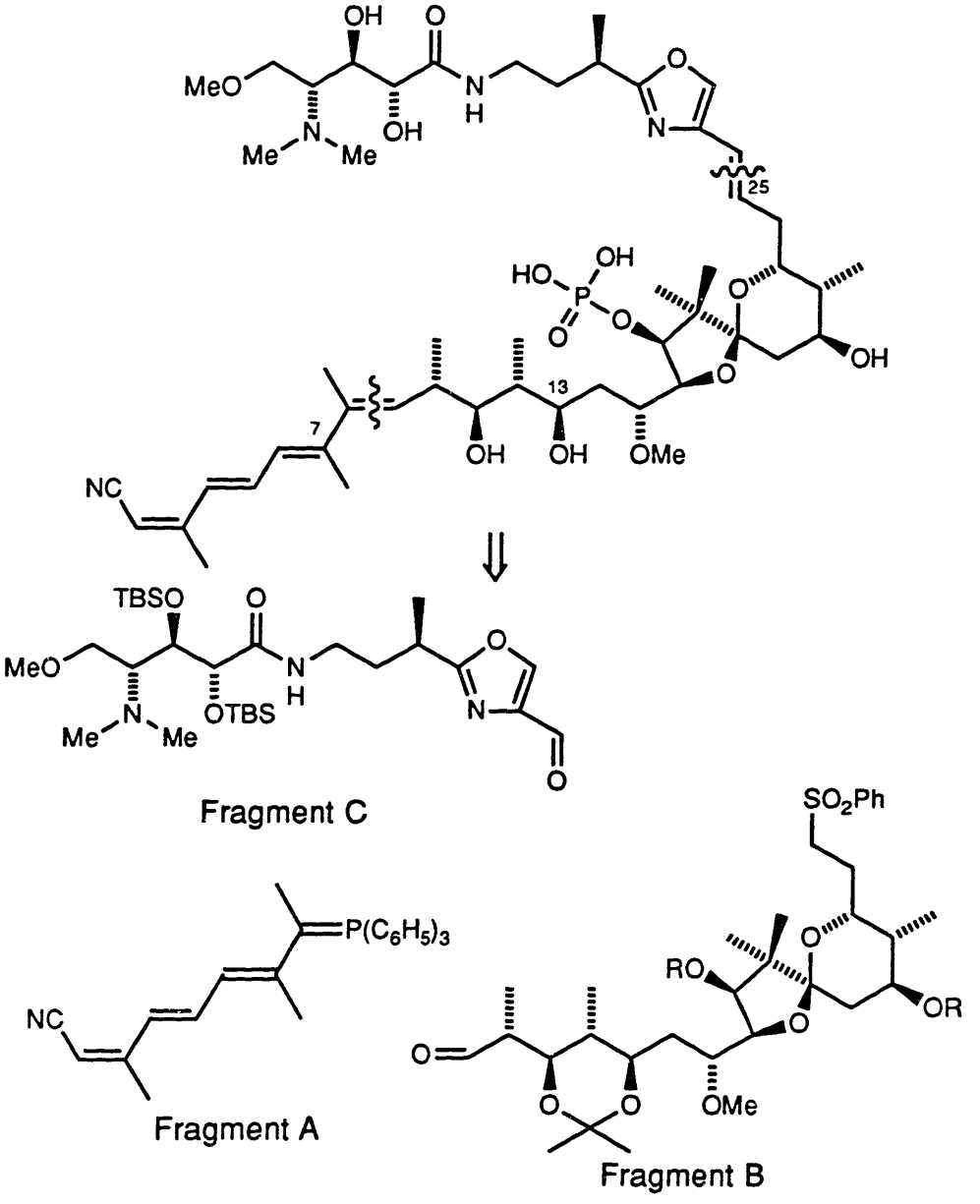
0.3 Structural Features of Calyculin A

When examining the structure of calyculin A, we find a diverse collection of functional groups bearing unique stereogenic relationships. Among these are an amino sugar fragment bearing the 4-amino-4-deoxy ribose configuration. The amino sugar is connected, *via* an amide bond, to a fragment possessing a 2,4 disubstituted oxazole. This portion is, in turn, attached to a 5,6 spiroketal unit bearing a phosphate moiety. Continuing along the skeleton, we find a polypropionate unit which, in turn, is joined

to a tetraene capped with a *Z* oriented nitrile. This illustrates the tremendous functional diversity of calyculin A contained within the relatively small space of a 37 carbon backbone, and, when considered alongside the biological properties, accentuates the appeal of this molecule to the synthetic organic chemist.

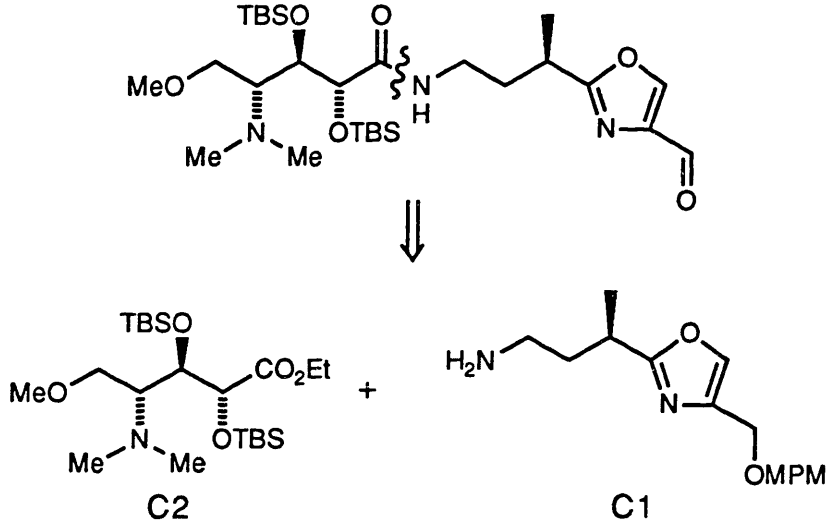
0.4 Retrosynthetic Analysis

Scheme 0.1



Our initial retrosynthetic analysis of calyculin A is shown in Scheme 0.1 and involves disconnections of the C8-C9 and the C25-C26 double bonds to yield fragments A, B, and C. Further disconnection of the amide bond, shown in Scheme 0.2, further divides fragment C into two distinct subfragments, C1 and C2.

Scheme 0.2



0.5 Chapter Summary

In this thesis, our early synthetic approaches to fragment A will be discussed in Chapter 1. Chapter 2 will be involved with the synthesis of fragment C1, and Chapter 3 will discuss the preparation of fragment C2.

Most synthetic projects run into unexpected problems, and the synthesis of calyculin A was no exception. The troubles referred to became apparent when two groups independently demonstrated that the absolute stereochemistry of the calyculins is opposite that shown in Figure 0.2.[42a] Therefore, our solutions to the preparation of natural calyculin A and the final preparation of fragment C will be discussed in Chapter 4.

Finally, the total synthesis of natural products often provides opportunities for the development of new chemical methodology. In this case, chiral isoxazolidines were used as auxiliaries in asymmetric alkylations. The results obtained from this study as well as a potential application to the preparation of fragment C1 will be discussed in Chapter 5.

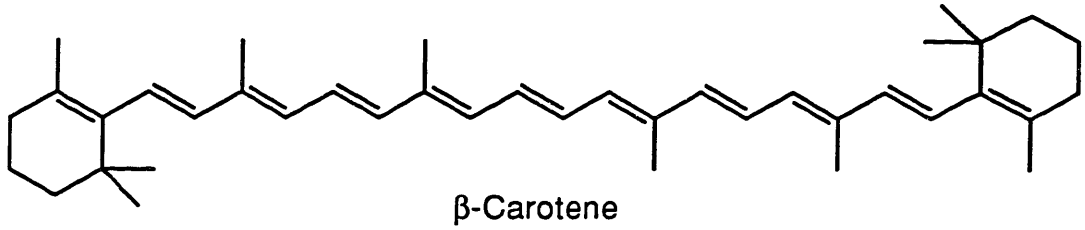
Chapter 1:

Approaches to Fragment A

1.1 Introduction

The ability to synthesize polyenes with specific substitution patterns around the double bonds has proven important in the synthesis of many naturally occurring compounds. The most notable of these syntheses is that of β-carotene, **13**[43,44,45] (Figure 1.1). During the evolution of polyene chemistry, many methods have been developed for the formation of double bonds in all configurations. Although many elegant olefin syntheses have subsequently been developed, few have proven as valuable to organic chemists as the Wittig reaction and the Horner-Emmons modification thereof. Therefore, we chose this methodology as our first approach to the synthesis of fragment A.

Figure 1.1



β-Carotene
13

1.2 Stepwise Approaches to Fragment A

Upon consideration of our initially proposed structure for fragment A (**14**, Scheme 1.2), we immediately recognized several problems. Among these were the possibility that the phosphorane would epimerize the center adjacent to the aldehyde in fragment B, and also whether we would be able to selectively introduce the *Z*-oriented nitrile.

Although it has been demonstrated that phosphoranes can epimerize α-stereogenic centers,[46] we decided in favor of taking this calculated risk.

However, even if epimerization proved to be of little consequence, the question of introduction of the Z oriented nitrile had to be addressed.

Upon searching the literature, we found that Still *et al.*, had developed a phosphonate reagent that preferentially formed Z-oriented esters when condensed with aldehydes (Scheme 1.1).[47] We postulated that if we could produce the corresponding cyano reagent, we might be able to obtain some Z selectivity on reaction with an appropriate ketone (Scheme 1.1). Therefore, with these two problems addressed, we proceeded to our synthetic strategy.

Scheme 1.1

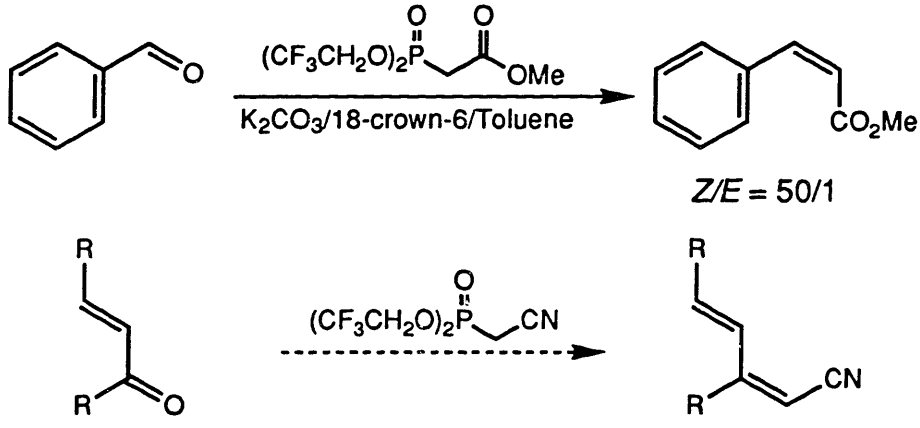
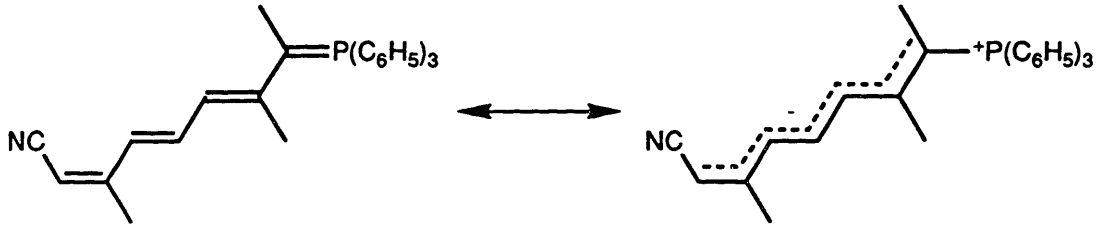


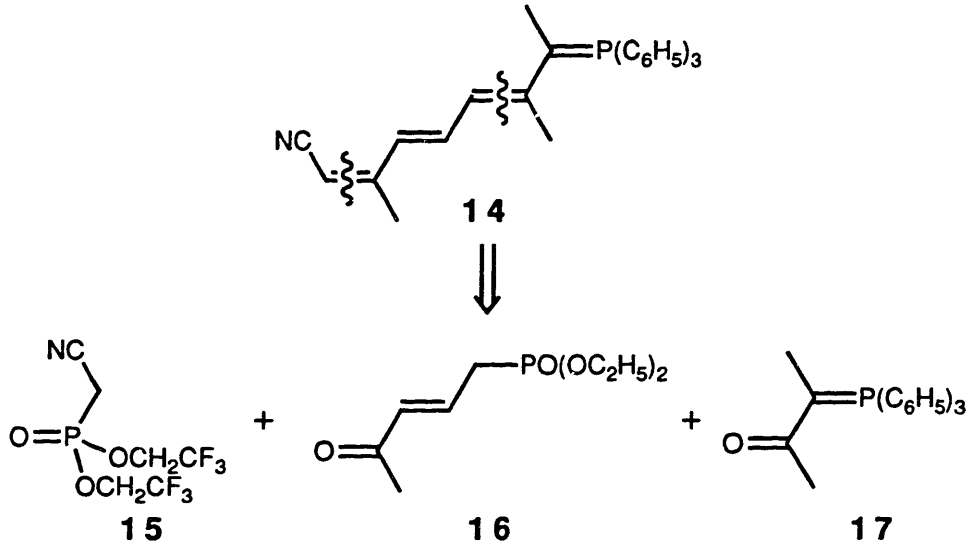
Figure 1.2



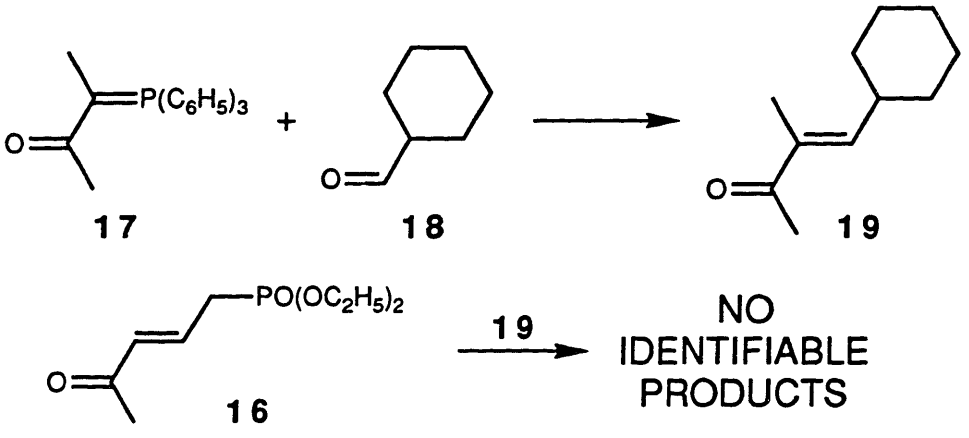
When considering fragment A, **14**, as a whole, we considered the possibility of loss of regiochemical integrity due to the dipolar nature of

phosphorus ylides (Figure 1.2). Therefore, we decided to build fragment A onto the final B-C fragment in the last three steps of the synthesis. Our retrosynthesis of fragment A, **14**, is shown in Scheme 1.2.

Scheme 1.2



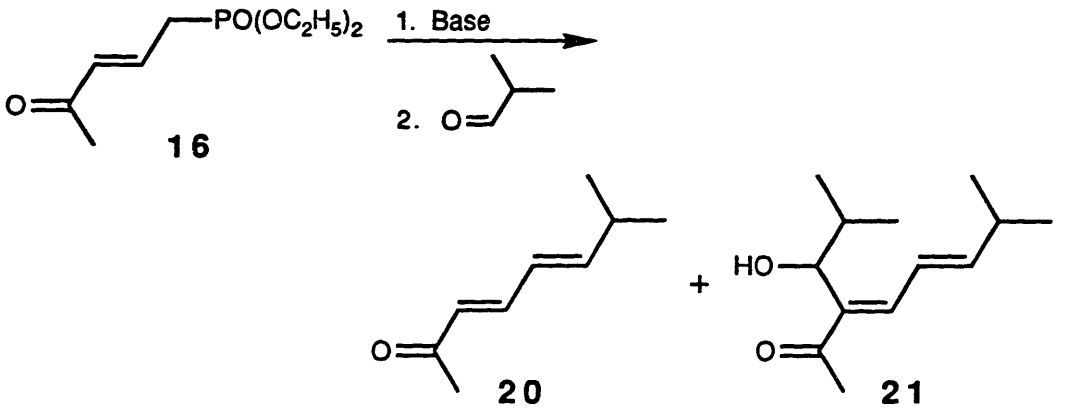
Scheme 1.3



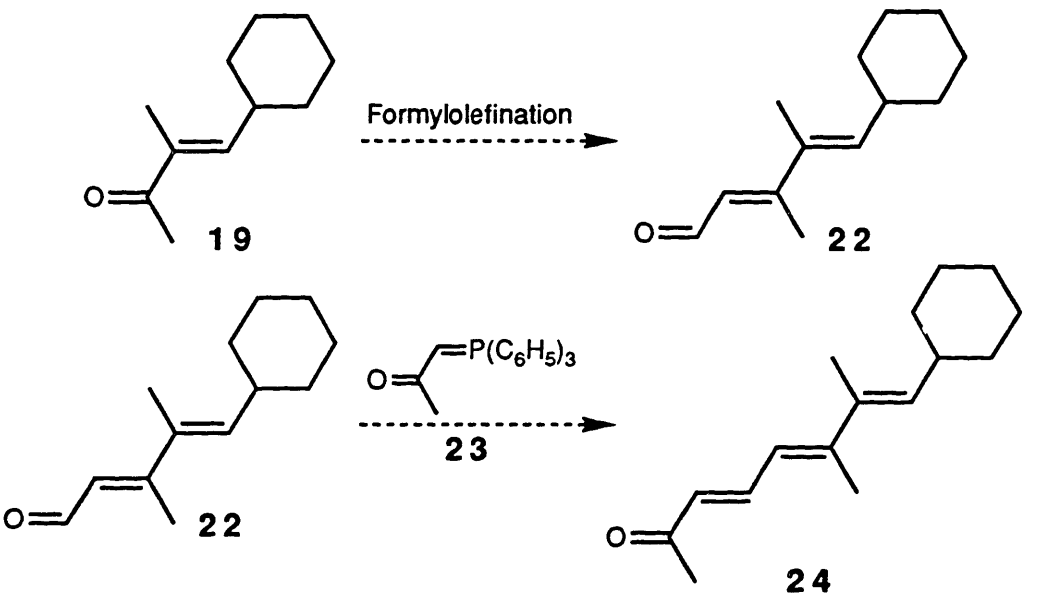
In practice, the application of this strategy utilizing cyclohexane carboxaldehyde, **18**, as a model for the B-C fragment, was not as straightforward as we would have liked. Our initial results are shown in

Scheme 1.3 and are described as follows. The phosphorane, **17**,[48] was condensed with cyclohexane carboxaldehyde, **18**, to produce a 70% yield of the enone, **19**. Unfortunately, when we attempted to couple the enone, **19**, with the phosphonate, **16**,[49] we observed no identifiable products.

Scheme 1.4



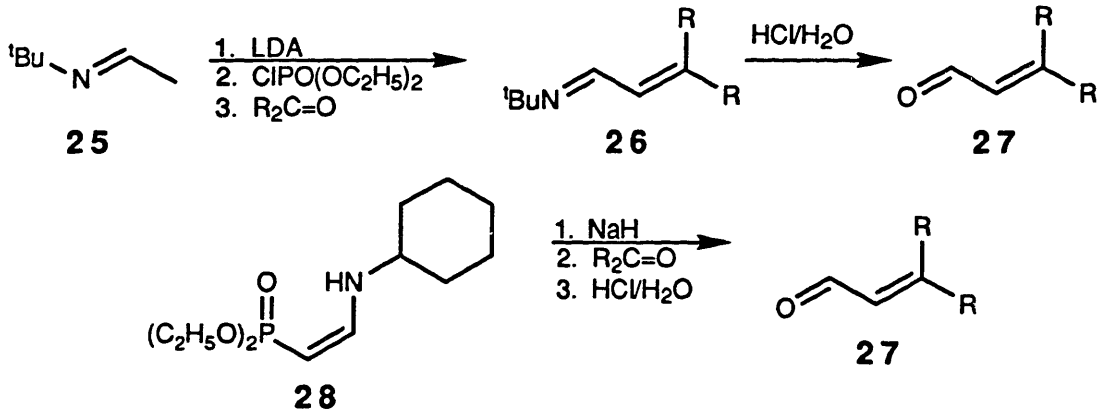
Scheme 1.5



In light of our disappointment regarding the reaction of the phosphonate, **16**, with the enone, **19**, we decided to test this phosphonate on

isobutyraldehyde in order to determine the actual utility of this compound. Surprisingly, we were only able to isolate a 14% yield of the desired product, **20**, along with substantially higher yields of compound **21** resulting from an additional aldol condensation (Scheme 1.4). With this result in hand, we decided that it would be better to replace the phosphonate, **16**, with two reagents in which the first effects a formylolefination on the enone, **19**, to produce the aldehyde, **22**. This aldehyde would then be treated with the phosphorane, **23**, to yield the desired conjugated ketone, **24** (Scheme 1.5).

Scheme 1.6

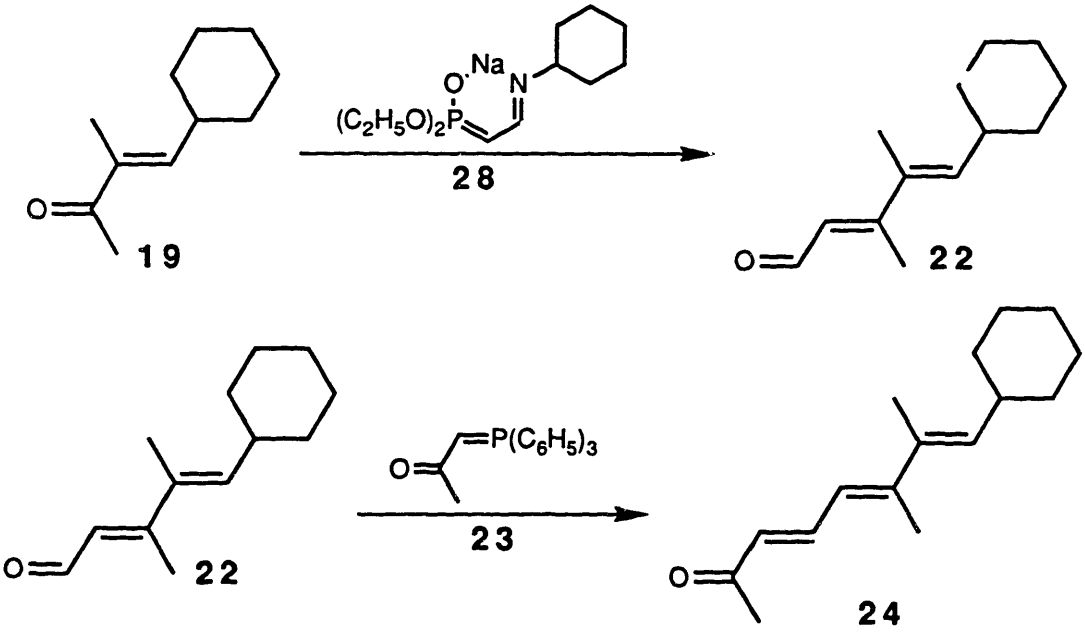


To date, two methods have been reported for the formyl-olefination of ketones using phosphonates (Scheme 1.6). The first, developed by Meyers *et al.*,[50] utilized a one-pot procedure in which ethylidene tert-butylimine, **25**, is condensed with diethylphosphorochloridate. The resulting phosphonate anion is condensed with a ketone to yield the conjugated imine, **26**. The aldehyde, **27**, is freed utilizing an acidic hydrolytic workup. The second procedure, developed by Nagata *et al.*,[51,52] utilizes the anion derived from diethyl 2-(cyclohexylamino)-vinyl-phosphonate, **28**. After condensation of this anion with a ketone, the aldehyde, **27**, is liberated during an acidic

hydrolytic workup.

Although the Meyers procedure failed to produce any reaction, we were able to obtain a 79% yield of our desired aldehyde, **22**, using Nagata's procedure. The fact that we obtained a 2.5 : 1 ratio of the *E* and *Z* isomers as shown by ^{1}H NMR and nOe studies was without consequence since treatment of this mixture with the phosphorane, **23**, in refluxing toluene produced a 62% yield of the desired product, **24**, as a single geometrical isomer as shown by ^{1}H NMR and nOe studies (Scheme 1.7). This presumably occurred as a result of the ability of stabilized ylides to participate in reversible Michael-type additions to conjugated carbonyls as shown in Scheme 1.8.[53,54,55]

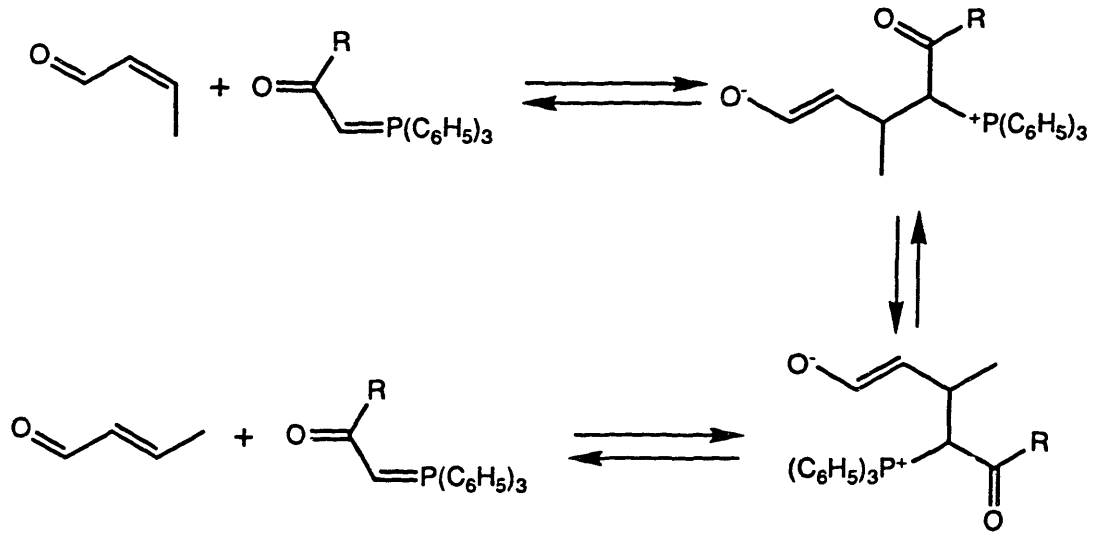
Scheme 1.7



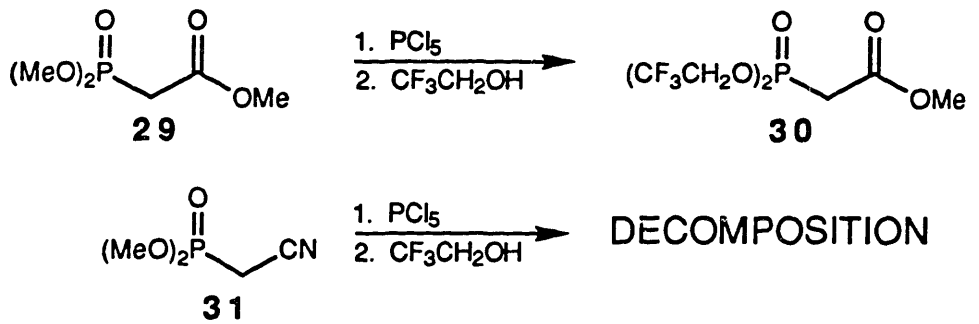
With the conjugated ketone, **24**, in hand, we were now ready to introduce the *Z* oriented nitrile. Consequently, we needed to develop an appropriate reagent to carry out this transformation. The phosphonate we

had designed for this purpose (**33**, Scheme 1.10) was based on a similar reagent developed by Still *et al.*[47] Although Still reported easily reproducible results for the preparation of his phosphonate, **30**, this procedure was not readily adapted to the preparation of our desired phosphonate, **33** (Scheme 1.9). Therefore, we began to explore alternate strategies to this compound.

Scheme 1.8



Scheme 1.9

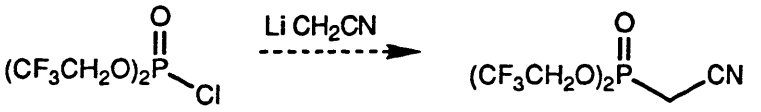


29 **30** **31**

In another approach to the phosphonate, **33**, we felt that we might be able to condense lithioacetonitrile with bis-trifluoroethyl

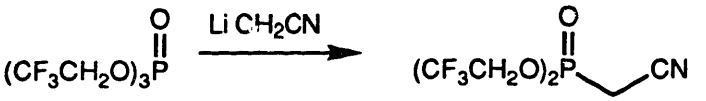
phosphorochloridate, **32**, (Scheme 1.10) prepared utilizing procedures described by Sellars *et al.*[56] However, due to the volatility and the subsequent difficulties involved in the isolation of bis-trifluoroethyl phosphorochloridate, we decided to search for an alternate but equivalent electrophile. In the experiments that followed, we were gratified to find that if we treated tris-trifluoroethylphosphate, **34**, with two equivalents of lithioacetonitrile we could produce a 15% yield of the desired phosphonate, **33** (Scheme 1.11).

Scheme 1.10



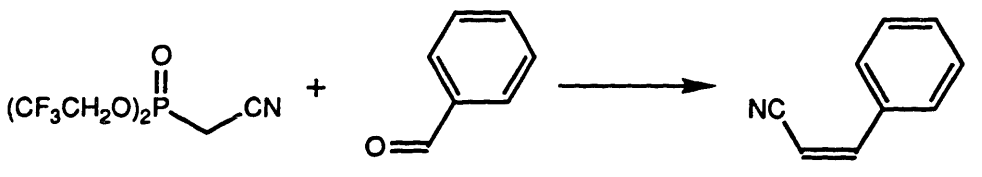
32 **33**

Scheme 1.11



34 **33**

Scheme 1.12



33 **35** **36**

Z/*E* = 18/1

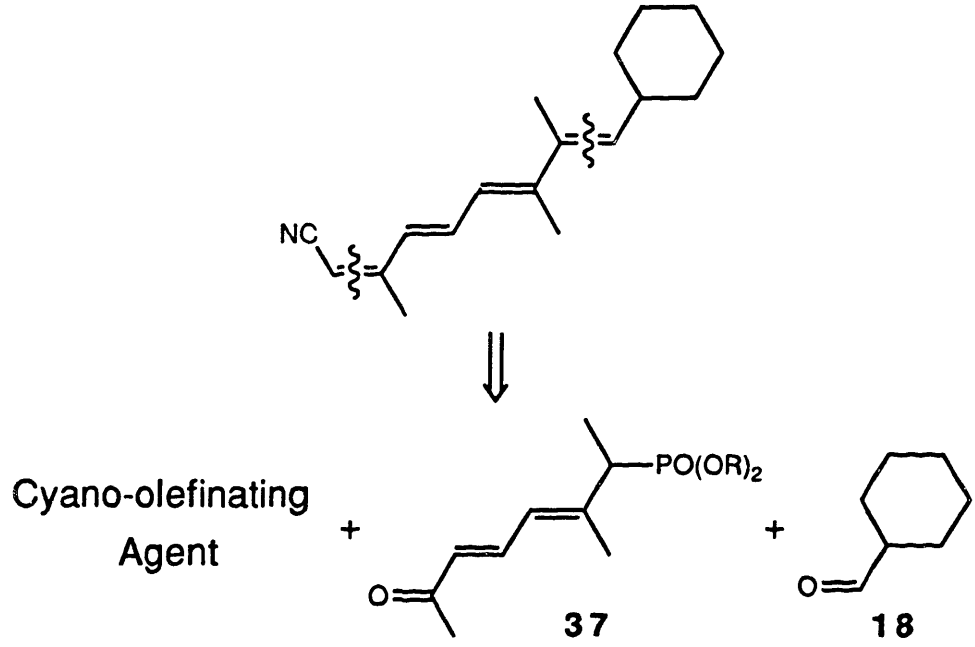
With our phosphonate, **33**, in hand, we were in a position to determine if this reagent would indeed perform *Z*-selective olefinations. Our initial study of the utility of **33** involved its reaction with benzaldehyde,

35, in order to form the anticipated *Z*-cinnamonitrile, **36**. As shown in Scheme 1.12, this reaction did, in fact, produce the desired product, **36**, as an 18 : 1 mixture of *Z* and *E* isomers as shown by ^{1}H NMR and nOe studies.

Although the initial olefination studies utilizing the phosphonate, **33**, were quite promising, we were disappointed to discover that this reagent would not react with ketones under any conditions. This was apparently due to the relatively non-nucleophilic nature of the phosphonate anion as a result of the inductive effect of the electronegative fluorine atoms. With this unfortunate result in addition to the extended length of the synthesis, we decided to re-examine our approach to fragment A.

1.3 Fragment A: More Convergent Approaches

Scheme 1.13



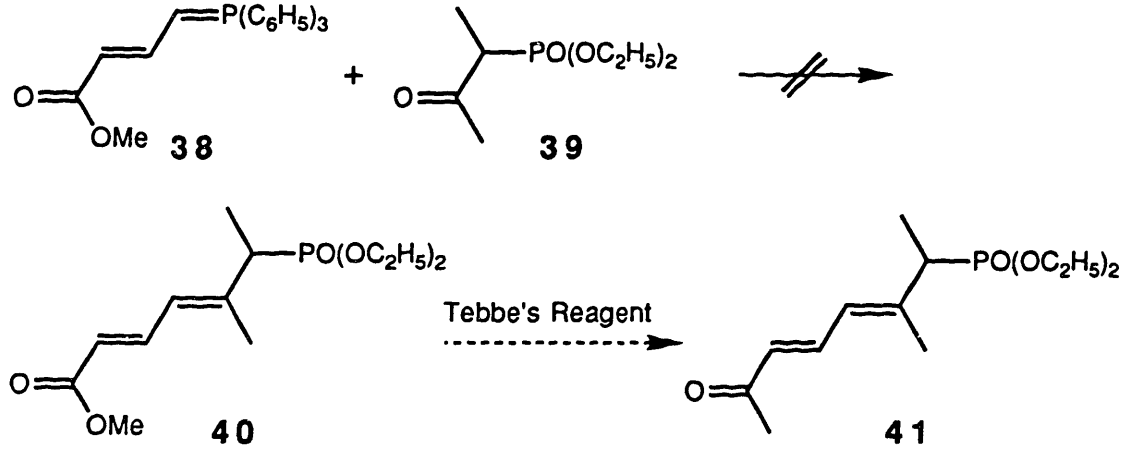
In re-evaluating of our strategy to fragment A, we recognized that at best our initial approach added four linear steps to the end of the synthesis

of calyculin A. With this consideration, we felt a more convergent approach would be in order. Therefore, as shown in Scheme 1.13, we decided to examine the utility of introducing the bulk of fragment A in the form of the phosphonate, **37**, and end the synthesis with an appropriately designed cyano-olefinating agent. We chose the second step in this sequence in spite of our disappointing result with the *Z* olefination because we felt that there were still options to be explored in the development of this methodology.

1.3.1 Two-Step Strategies

As illustrated in our retrosynthetic analysis (Scheme 1.13), we initially decided to continue our study of phosphonate chemistry. The specific phosphonate (**41**, Scheme 1.14) was to be prepared by the condensation of appropriate β-ketophosphonates with phosphoranes (Schemes 1.14 and 1.15).

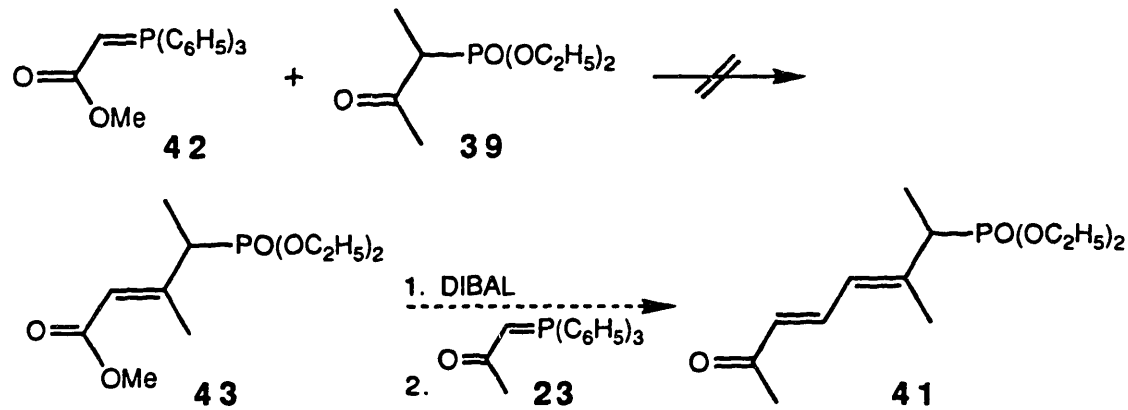
Scheme 1.14



As shown in Scheme 1.14, the phosphorane, **38**,[57] and the phosphonate, **39**,[58] were expected to condense to the phosphonate, **40**. Our

expectations that this reaction would proceed arose from the fact that acetonyl triphenylphosphorane condenses with diethyl formylmethyl phosphonate to yield a β,γ conjugated ketophosphonate.[49] The expected conjugated ester phosphonate, **40**, was then to be converted to the desired conjugated keto phosphonate, **41**, on treatment with Tebbe's reagent.[59] Unfortunately, we were unable to induce this reaction, presumably due to proton transfer from the phosphonate to the phosphorane. Therefore, after attempting the similar but more lengthy approach shown in Scheme 1.15, we decided to explore the strategy shown in Scheme 1.16.

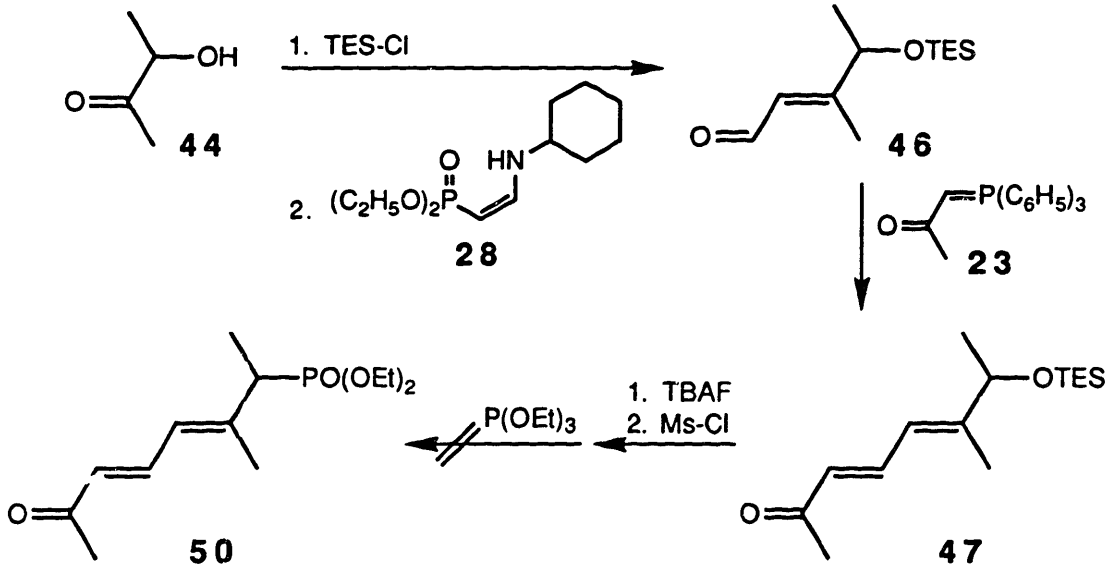
Scheme 1.15



As shown in Scheme 1.16, 3-hydroxy-2-butanone, **44**, was treated with triethylchlorosilane and the resulting silyloxy ketone, **45**, was converted to the conjugated aldehyde, **46** (46%, 2 steps), utilizing Nagata's reagent, **28**.[51,52] Condensation of **46** with the phosphorane, **23**, produced a 57% yield of the desired ketone, **47**. Subsequent treatment of **47** with tetrabutylammonium fluoride produced a 69% yield of the alcohol, **48**. Conversion of **48** to the corresponding chloride, **49**, was accomplished utilizing methane sulfonylchloride as described by Meyers *et al.*,[60] The crude chloride, **49**, was

expected to be transformed to the phosphonate, **50**, on treatment with triethylphosphite under Arbuzov conditions.[61] Unfortunately, as indicated by our experiments and as alluded to by Font *et al.*,[62] direct conversion of this type of conjugated ketone to a phosphonate or a phosphorane is not a promising strategy due to complications involving conjugate additions as well as enol phosphate formation.[63] With these disturbing revelations, we felt that the introduction of fragment A in two pieces was not the most promising approach. Therefore, as our last effort utilizing phosphorus chemistry in fragment A, we decided to study its introduction as a single piece.

Scheme 1.16

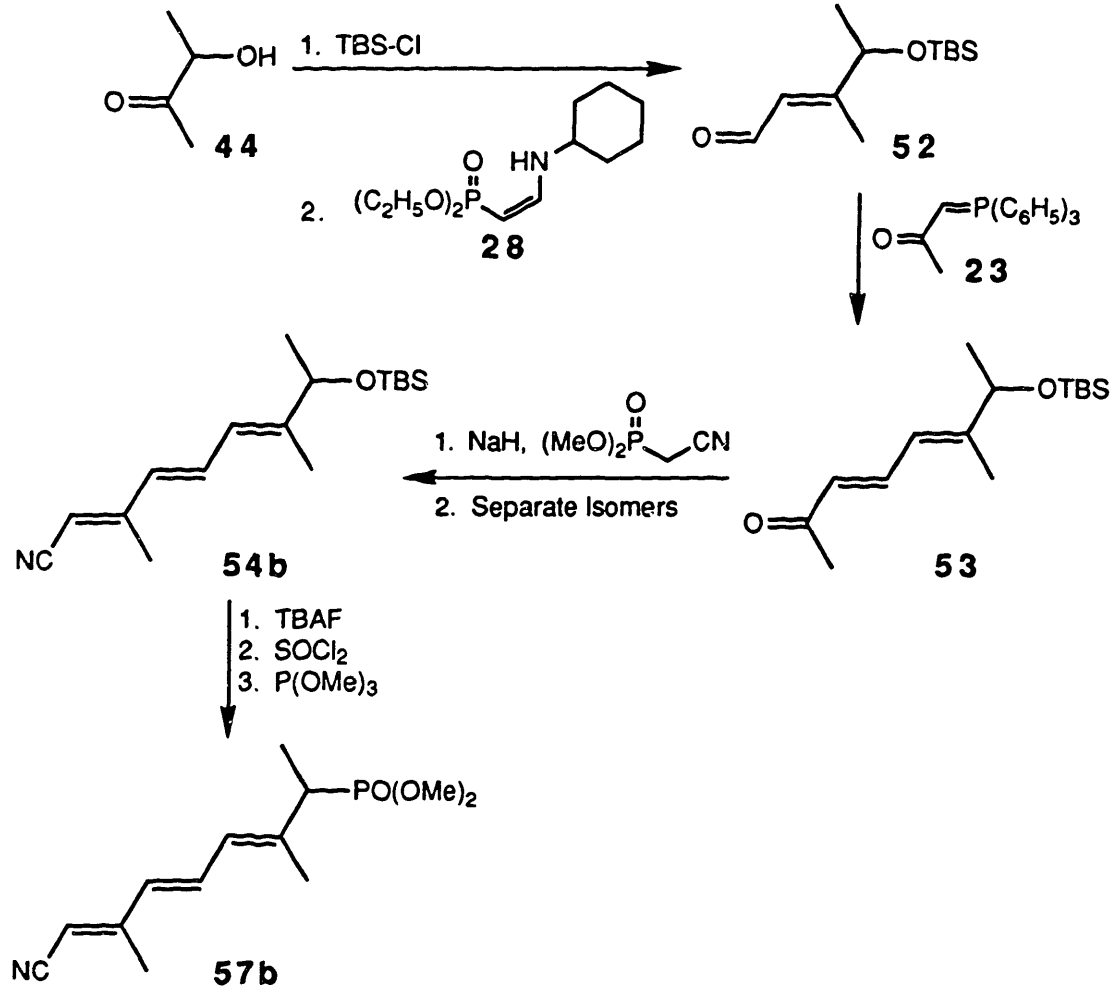


1.3.2 A One-Piece Fragment

In developing fragment A as a single piece, we felt the most direct approach was to convert the ketone, **47**, to the corresponding mixture of nitriles, separate the isomers, and learn whether we could, in fact, couple

the conjugated nitrile-phosphonate to an aldehyde. Unfortunately, at this point, we needed more starting material. Since we found that the triethylsilyloxy (TES) group was too labile to give high yields in some of our transformations, we proceeded from the beginning utilizing the more stable *tert*-butyldimethylsilyl (TBS) protecting group.

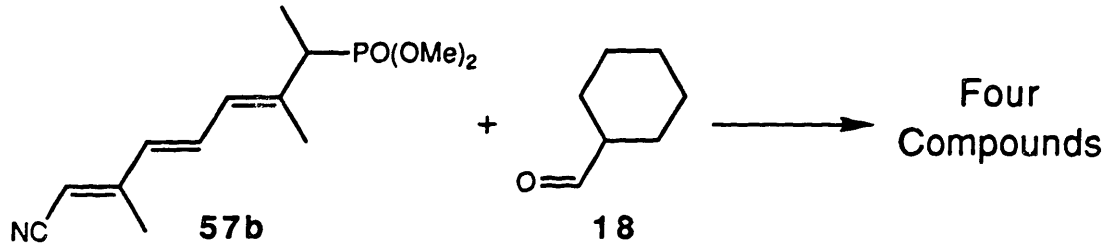
Scheme 1.17



As shown in Scheme 1.17, 3-hydroxy-2-butanone, **44**, was converted to the TBS ether, **51**, in 75% yield on treatment with *tert*-butyldimethylchlorosilane. The resulting silyloxy ketone, **51**, was then

converted, in 70% yield, to the aldehyde, **52**, utilizing Nagata's reagent, **28**.[51,52] Treatment of the aldehyde, **52**, with the phosphorane, **23**, produced a 76% yield of the ketone, **53**. Subsequent reaction of the ketone, **53**, with dimethyl cyanomethylphosphonate formed a 1 : 3.8 mixture of the *Z* and *E* isomers (**54a** and **54b**) of the fragment A skeleton, respectively. The isomers were separated on silica gel and the *E* isomer (**54b**) was used to model the final steps to the phosphonate as well as the Horner-Emmons coupling to the B-C fragment.

Scheme 1.18

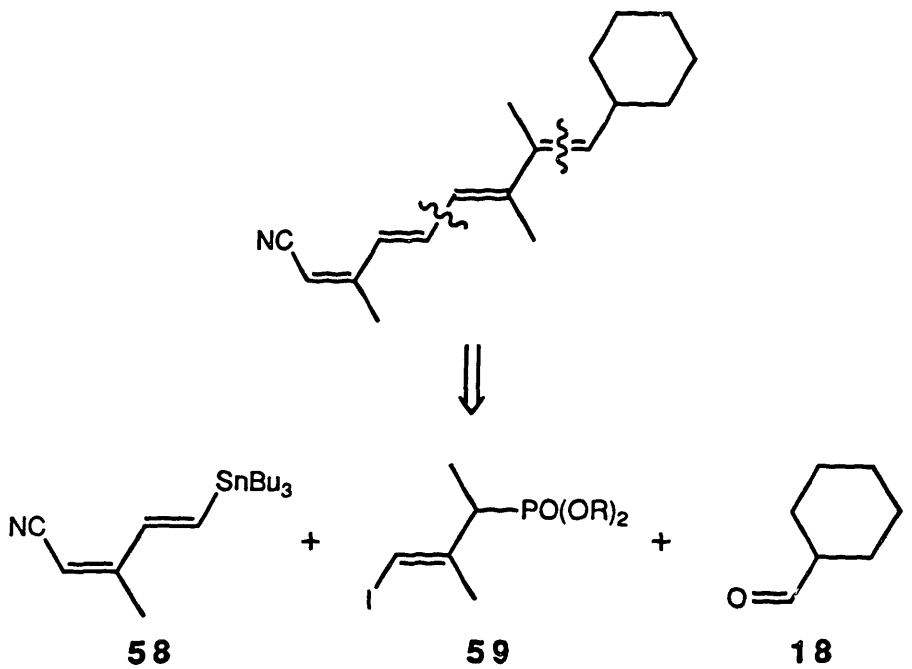


Conversion of the silyl ether, **54b**, to the alcohol, **55b**, was accomplished using tetrabutylammonium fluoride. Final conversion to the *E*-isomer of fragment A, **57b**, was expected to proceed *via* conversion of the alcohol to the chloride, **56b**, using methanesulfonyl chloride followed by treatment of the chloride with trimethyl phosphite. However, using 1-phenyl-1-buten-3-ol as a model system, we determined that conversion of **55b** to **56b** would best be accomplished using $SOCl_2$.[64] Unfortunately, although the chloride, **56b**, was formed in good yield (75%), we were unable to form the phosphonate, **57b**, in yields greater than 30%. However, in the hopes of optimizing these results at a later date, we proceeded to attempt its coupling to a model aldehyde (Scheme 1.18).

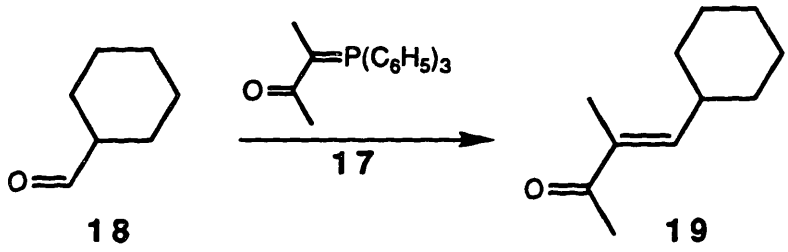
When attempting to couple our phosphonate, **57b**, to

cyclohexanecarboxaldehyde, **18**, we observed the formation of four isomeric compounds as shown by ^1H NMR and GC analysis. We believed these to result from isomerization about the C3-4 and C7-8 double bonds. This postulate was corroborated when the phosphonate, **57b**, was treated with base and quenched with H_2O thus forming four isomeric compounds as shown by ^1H NMR and GC analysis. In light of these results, the utility of Wittig and Horner-Emmons methodology in the preparation of fragment A seemed questionable. Consequently, we have proposed an alternate strategy involving a Stille coupling as outlined below (Scheme 1.19). This route to fragment A was investigated by Ms. Sandra A. Filla and has been found to be successful.

Scheme 1.19



1.4 Experimental Section



18 19

Ketone, 19

Cyclohexanecarboxaldehyde, **18**, (7.28 mL, 60.20 mmoles) and 1-acylethylidene triphenylphosphorane, **17**, (20 g, 60.24 mmoles) were heated to reflux in toluene (300 mL), under argon, for 65.5 hours. The toluene was removed under reduced pressure, and the residue was diluted with pentane (400 mL). The triphenylphosphine oxide was filtered off and the pentane was removed under reduced pressure. The residue was distilled through a 10 cm Vigreux column (P = 5 mm Hg) and the fraction boiling at 100°C was collected to yield the desired product as a colorless liquid (6.97 g, 70%).

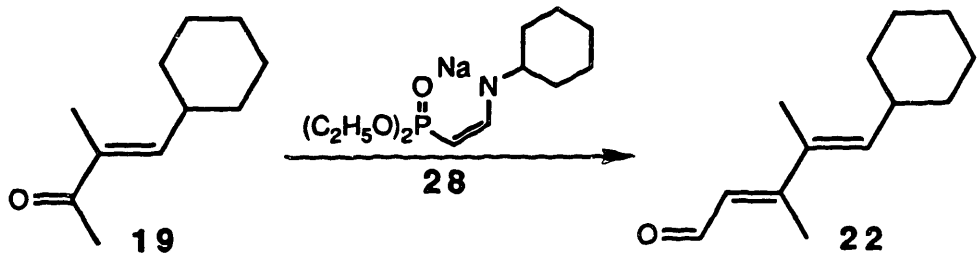
Physical Properties for **19**

R_f = 0.39 (10% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 6.4(m, 1H), 2.3-2.4(m, 1H), 2.26(s, 3H), 1.76(d, 3H, J = 2 Hz), 1.6-1.75(m, 5H), 1.05-1.4(m, 5H).

EI Mass Spec: m/e 166 $[M]^+$, 151, 123, 83, 43.

IR (neat) cm^{-1}: 2925, 2850, 1665, 1640, 1445, 1363, 1290, 1270, 1257, 1217, 1143, 998, 893.



Aldehyde, 22

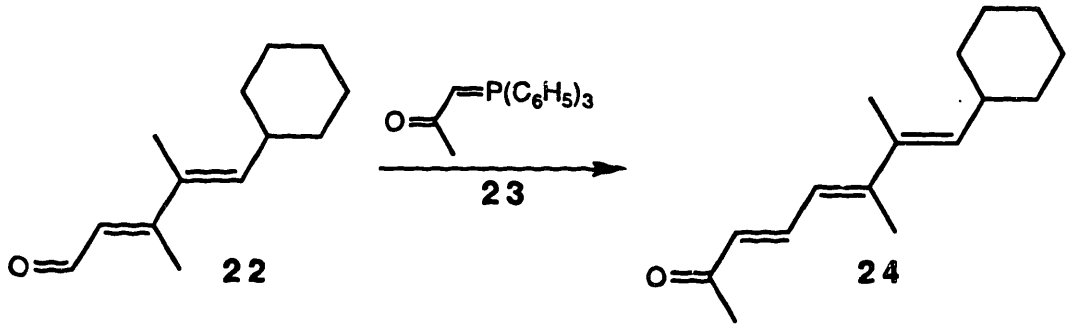
To a suspension of NaH (80%, 0.464 g, 15.33 mmoles) in THF (5mL), under argon, was slowly added a solution of diethyl 2-(cyclohexylamino)-vinyl-phosphonate, **28**, (4.00 g, 15.33 mmoles) in THF (5 mL). The mixture was stirred at ambient temperature for 15 minutes after which a solution of the ketone, **19**, (1.27 g, 7.67 mmoles) in THF (5 mL) was added over 15 minutes. The reaction was stirred for an additional 1.5 hours, after which it was diluted with ether (150 mL) and extracted with citric acid (5% in H_2O, 2 X 30 mL, 1 X 40 mL). The ether layer was then washed with brine (50 mL), dried over Na_2SO_4, concentrated, and the residue was purified on silica gel (10% ethyl acetate/hexane) to yield the desired product as a mixture of isomers (1.16 g, 79%).

Physical Properties for **22**

R_f = 0.30 (10% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): *Z* isomer: δ 9.62(d, *J* = 9.89 Hz, 1H), 5.84(m, 1H), 5.3(m, 1H), 2.28-2.42(m, 1H), 2.0(d, *J* = 2 Hz, 3 H), 1.78 (d, *J* = 2 Hz, 3H), 1.6-1.75(m, 5H), 1.05-1.4(m, 5H); *E* isomer: δ 10.12(d, *J* = 9.89 Hz, 1H), 6.06(m, 1H), 5.92(m, 1H), 2.28-2.42(m, 1H), 2.27(d, *J* = 2 Hz, 3H), 1.94(d, *J* = 2 Hz, 3H), 1.6-1.75(m, 5H), 1.05-1.4(m, 5H).

EI Mass Spec: m/e 192 $[M]^+$, 163, 149, 109, 83.



Ketone, 24

Acetonyltriphenylphosphorane, **23**, (1.91 g, 5.2 mmoles) and the aldehyde, **22**, (1.00 g, 5.2 mmoles) were heated to reflux in toluene (30 mL) for 30 hours under argon. The toluene was distilled off and the residue was diluted with pentane (100 mL). The triphenylphosphine oxide was filtered off and the pentane was removed under reduced pressure. The residue was purified on silica gel (3% ethyl acetate/hexane) to yield the desired product as a yellow solid (0.75 g, 62%).

Physical Properties for **24**

R_f = 0.22 (10% ethyl acetate/hexane).

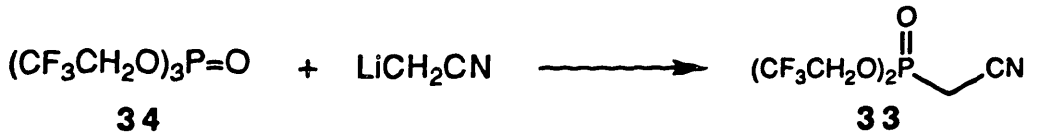
mp=50-51°C.

λ_{max} = 328 nm (measured)

λ_{max} = 329 nm (calculated).

^{1}H NMR (300 Hz, $CDCl_3$): δ 7.53-7.63(m, 1 H), 6.27(d, J = 15.3 Hz, 1H), 6.16(d, J = 18.4 Hz, 1H), 5.77(d, J = 12.2 Hz, 1H), 2.28-2.38(m, 1H), 2.27(s, 3H), 2.02(d, 3H, J = 2Hz), 1.83(d, J = 2 Hz, 3H), 1.6-1.75(m, 5H), 1.05-1.4(m, 5H).

EI Mass Spec: m/e 232 $[M]^+$, 217, 189, 109, 83.



34 **33**

Bis-Trifluoroethyl Cyanomethylphosphonate, 33

A 500 mL round bottomed flask was charged with THF (200 mL) and cooled to -78°C under a nitrogen atmosphere. n-BuLi (2.5 M in hexane, 58 mL, 0.145 mole) was added followed by CH_3CN (10 mL, 0.193 mole). The mixture was stirred at -78°C for 1 hour after which, a solution of tris-trifluoroethylphosphate, **34**, (24.1 g, 70.0 mmoles) in THF (100 mL) was added at a rate of 0.99 mL/minute. The addition was stopped when complete consumption of the precipitate was observed, and the reaction was quenched with 50% saturated NH_4Cl solution (80 mL). The mixture was warmed to room temperature and extracted with ether (300 mL). The ether layer was dried over Na_2SO_4, concentrated, and the residue was distilled (0.2 mm Hg, 100-103°C) to yield the product as a milky liquid (2.17 g, 15%).

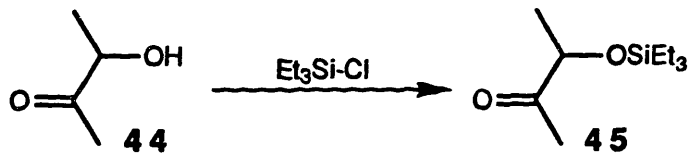
Physical Properties for **33**

^1H NMR (300 MHz, $CDCl_3$): δ 4.50(m, 4H), 3.18(d, 2H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 16.72(d), 63.3(m), 110.6(d), 122.03(dq).

EI Mass Spec: m/e 285 $[M]^+$, 266, 245, 83, 69.

IR (neat) cm^{-1}: 2980, 2925, 2260, 1460, 1420, 1395, 1300, 1175, 1095, 960, 890, 840.



44 45

Silyloxyketone, 45

Freshly distilled 3-hydroxy-2-butanone, **44**, (8.8 g, 0.1 mole) was dissolved in ether (200 mL). Imidazole (13.6 g, 0.2 mole) was added and the mixture was cooled to 0°C under argon. Triethychlorolsilane (25.0 mL, 0.15 mole) was added over 45 minutes after which the reaction was allowed to warm to room temperature. Stirring was continued for an additional 45 minutes after which the solids were filtered off and washed with ether. The combined ether phases were washed with 5% citric acid solution (3 X 100 mL), saturated $NaHCO_3$ solution (100 mL) and brine (100 mL). The ether phase was then dried over Na_2SO_4, filtered, and concentrated to a colorless liquid. Distillation of the liquid (92°C, 14 mm Hg) yielded the product as a colorless liquid (15.5 g, 77%).

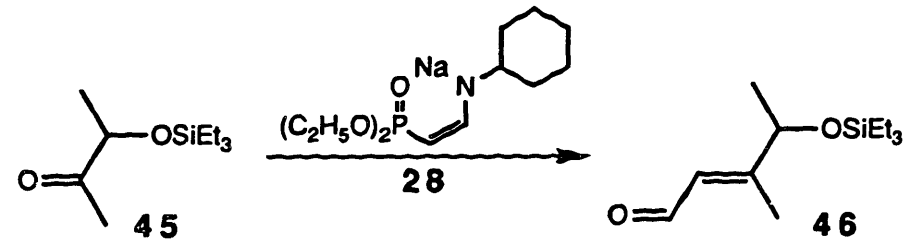
Physical Properties for **45**

R_f = 0.67 (20% ethyl acetate/hexane).

^1H NMR ($CDCl_3$, 300 MHz): δ 4.1(q, 1H), 2.15(s, 3H), 1.25(d, 3H), 0.95(t, 9H), 0.6(q, 6H).

EI Mass Spec: m/e 199 $[M - 2]^+$, 173, 159, 131, 115, 43.

IR (neat) cm^{-1}: 2920, 1725, 1460, 1415, 1350, 1235, 1120, 1055, 1000, 920, 780, 720.



Aldehyde, 46

To a suspension of NaH (80%, 0.225 g, 7.50 mmoles) in THF (4 mL) under nitrogen was added a solution of diethyl 2-(cyclohexylamino)-vinyl-phosphonate, **28**, (1.88g, 7.22 mmoles) in THF (3 mL). The mixture was stirred at room temperature for 30 minutes after which a solution of the silyloxyketone, **45**, (0.999 g, 4.95 mmoles) in THF (3 mL) was added. The reaction was stirred for 20 minutes after which it was diluted with ether (50 mL) and washed with 5% citric acid (3 X 10 mL). The ether phase was dried over Na_2SO_4, filtered, and concentrated to a yellow residue. Elution of the residue down silica gel (5% ethyl acetate/hexane) yielded the product as a light yellow oil (0.675 g, 60%).

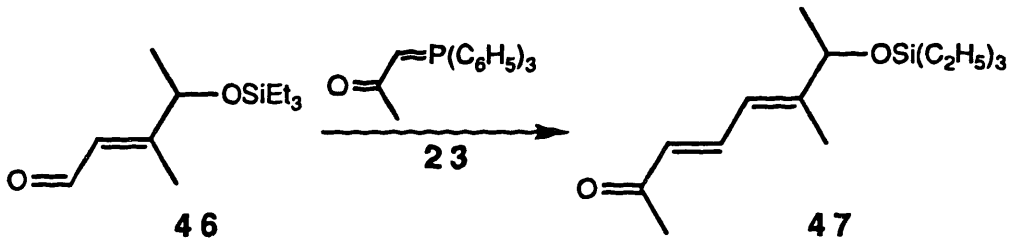
Physical Properties for **46**

R_f = 0.53 (20% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 10.04(d, J = 7.72 Hz, 1H), 6.1(m, 1H), 4.26(q, J = 6.40, 1H), 2.12(d, J = 1.14 Hz, 3H), 1.28(d, J = 6.57 Hz, 3H), 0.9(t, J = 7.86 Hz, 9H), 0.6(q, J = 7.67 Hz, 6H).

EI Mass Spec: m/e 226 $[M - 1]^+$, 199, 131, 115, 97, 43.

IR (neat) cm^{-1}: 2920, 1680, 1460, 1410, 1380, 1235, 1190, 1085, 815.



46 47

Ketone, 49

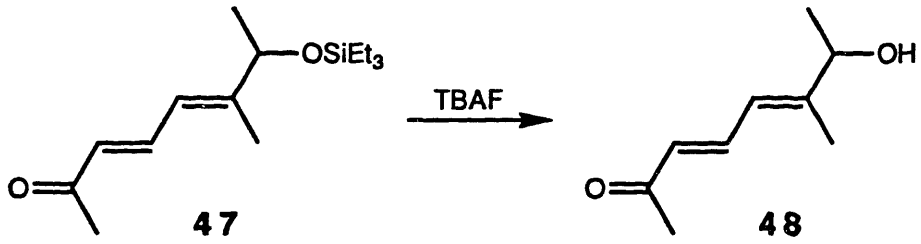
Acetonyltriphenylphosphorane, **23**, (2.08 g, 6.5 mmoles) and the aldehyde, **46**, (1.49 g, 6.5 mmoles) were heated to reflux in benzene (20 mL) for 48 hours under argon. The reaction was concentrated under reduced pressure and the residue was diluted with hexane (25 mL). The triphenylphosphine oxide was filtered off and the hexane was removed under reduced pressure. The residue was purified on silica gel (4% ethyl acetate/hexane) to yield the desired product as a yellow oil (0.99 g, 57%).

Physical Properties for **47**

R_f = 0.49 (20% ethyl acetate/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43(m, 1H), 6.23(d, J = 11.65 Hz, 1H), 6.14(d, J = 15.43 Hz, 1H), 4.25(q, J = 6.5 Hz, 1H), 1.87(s, 3H), 2.28(s, 3H), 1.25(d, J = 6.43 Hz, 3H), 0.9(t, J = 7.86 Hz, 9H), 0.6(q, J = 7.67 Hz, 6H).

EI Mass Spec: m/e 268 $[M]^+$, 253, 115.



47 48

Hydroxyketone, 48

The ketone, **47**, (0.996 g, 3.72 mmoles) was dissolved in THF (20 mL) and cooled to 0°C under argon. Tetrabutylammonium fluoride (1M in THF, 7.44 mmoles) was slowly added to the mixture. The reaction was stirred at 0°C for 5 minutes after which, the reaction mixture was partitioned between ether (50 mL) and saturated $NaHCO_3$ solution (50 mL). The ether was washed with saturated $NaHCO_3$ solution (2 X 25 mL) and brine (25 mL), after which it was dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel (25% ethyl acetate/hexane) to yield the product as a light yellow oil (0.393 g, 69%).

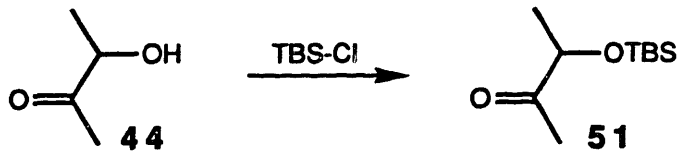
Physical Properties for **48**

R_f = 0.34 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.44(dd, 2H), 6.26(d, 1H), 6.17(d, 1H), 4.33(q, 1H), 2.30(s, 3H), 1.90(d, 3H), 1.33(d, 3H).

EI Mass Spec: m/e 154 $[M]^+$, 136, 111, 43.

IR (neat) cm^{-1}: 3340, 2960, 1660, 1350, 1225, 1075.



Silyloxyketone, 51

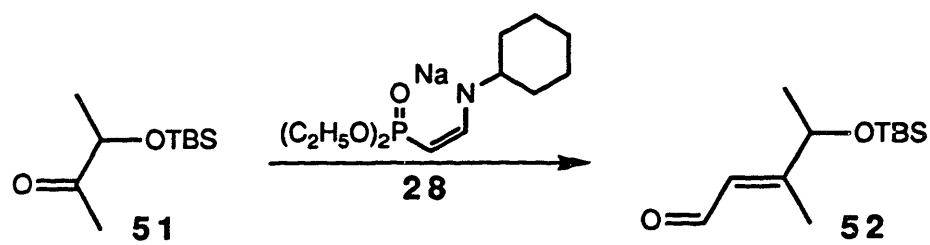
Freshly distilled 3-hydroxy-2-butanone, **44**, (17.80g, 0.202 mole) and imidazole (16.85g, 0.248 mole) were dissolved in ether (350 mL) and cooled to 0°C under nitrogen. A solution of *tert*-butyldimethylchlorosilane (37.36 g, 0.248 mole) in ether (150 mL) was added over 45 minutes. The reaction was warmed to room temperature and stirred for 16 hours, after which the solids were filtered off and the filtrate was concentrated. Distillation of the residue (14 mm Hg, 70-73°C) yielded the product as a cloudy liquid (30.4 g, 75%).

Physical Properties for **51**

R_f = 0.74 (20% ethyl acetate/hexane).

^1H NMR (250 MHz, $CDCl_3$): δ 4.10(q, 1H), 2.18(s, 3H), 1.28(d, 3H), 0.90(s, 9H), 0.06(s, 6H).

IR (neat) cm^{-1}: 2900, 1725, 1470, 1360, 1255, 1120, 1060, 1000, 920, 830, 770, 660.



Aldehyde, 52

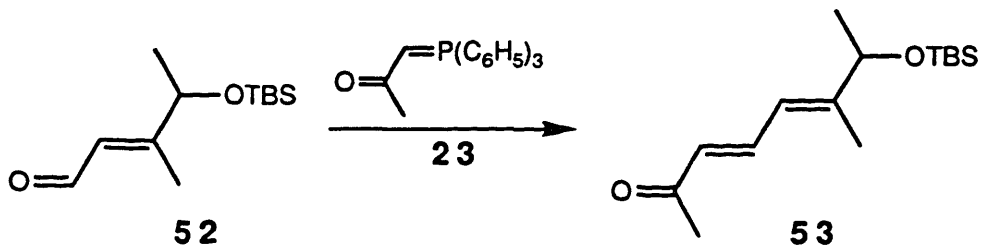
NaH (80%, 4.60 g, .153 mole) was suspended in THF (50 mL) at room temperature under argon. A solution of diethyl 2-(cyclohexylamino)-vinyl-phosphonate, **28**, (40 g, 0.153 mole) in THF (50 mL) was added over 30

minutes. The resulting mixture was stirred for an additional hour after which, the silyloxyketone, **51**, (25.0 g, 0.123 mole) in THF (50 mL) was added over 1 hour. The reaction was stirred for an additional 40 minutes after which, it was quenched with saturated NH_4Cl solution (150 mL). Ether (500 mL) was added and the layers were separated. The ether layer was washed with 5% citric acid solution (3 X 150 mL) and brine (2 X 100 mL). The organic phase was dried over Na_2SO_4, filetered and concentrated, and the residue was distilled (0.1 mm Hg, 82-83°C) to yield the product as a colorless liquid (19.48 g, 70%).

Physical Properties for **52**

R_f = 0.55 (20% ethyl acetate/hexane).

^1H NMR (250 MHz, $CDCl_3$): δ 10.03(d, 1H), 6.08(d, 1H), 4.25(q, 1H), 2.11(d, 3H), 1.27(d, 3H), 0.90(s, 9H), 0.03(d, 6H).



52 **53**

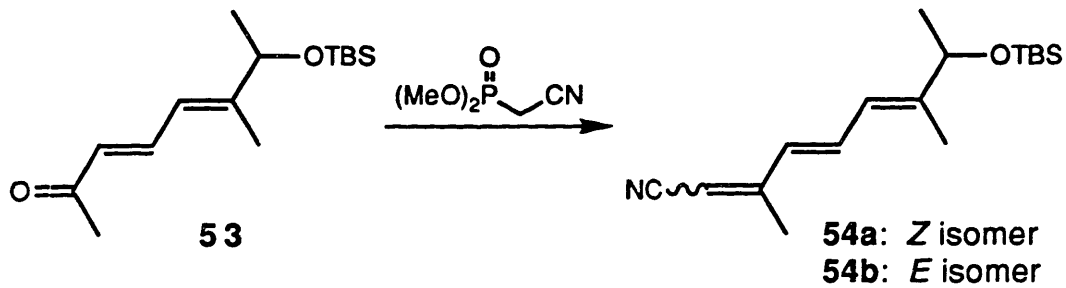
Ketone, 53

Acetonyltriphenylphosphorane, **28**, (11.65 g, 37.0 mmoles) and the aldehyde, **52**, (8.35 g, 37.0 mmoles) and were heated to reflux in benzene (100 mL) under argon for 24 hours. The solvent was removed and the residue was washed with hexane. The solids were filtered off and the filtrate was concentrated. The residue was purified on silica gel (4% ethyl acetate/hexane) to yield the product as a yellow liquid (7.57 g, 76%).

Physical Properties for 53

R_f = 0.52 (20% ethyl acetate/hexane).

^1H NMR (250 MHz, $CDCl_3$): δ 7.41(dd, 1H), 6.20(d, 1H), 6.12(d, 1H), 4.23(q, 1H), 2.27(s, 3H), 1.86(d, 3H), 1.22(d, 3H), 0.87(s, 9H), 0.03(d, 6H).



Z/E Nitrile, 54a/54b

NaH (80%, 0.935 g, 31.2 mmoles) was suspended in THF (20 mL) at room temperature under argon. A solution of dimethyl cyanomethylphosphonate (4.63 g, 31.1 mmoles) in THF (20 mL) was added over 20 minutes. The mixture was stirred for an additional 20 minutes after which, a solution of the ketone, **53**, (7.57 g, 28.25 mmoles) was added over 45 minutes. The reaction was stirred for 3 hours after which a solution of the anion of dimethyl cyanomethylphosphonate (prepared from dimethyl cyanomethylphosphonate (3 g), NaH (80%, 0.608 g), and THF (20 mL)) was added over 10 minutes. The reaction was stirred for an additional 10 minutes after which, it was quenched with saturated NH_4Cl solution (50 mL). Ether (100 mL) was added and the layers were separated. The organic phase was washed with saturated NH_4Cl solution (50 mL) and brine (2 X 25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated, and the residue was separated into its two components by repetitive flash

chromatography (silica gel, 9% ethyl acetate/hexane) to yield the *Z*-isomer (1.352 g, 16%), **54a**, and the *E*-isomer (5.099 g, 62%), **54b**.

Physical Properties for **54a**

R_f = 0.62 (20% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 6.82(dd, 1H), 6.74(d, *J* = 15.14 Hz, 1H), 6.19(d, *J* = 10.29 Hz, 1H), 5.07(s, 1H), 4.24(q, *J* = 6.43 Hz, 1H), 2.04(s, 3H), 1.81(s, 3H), 1.21(d, *J* = 6.43 Hz, 3H), 0.87(s, 9H), 0.06(d, *J* = 8.78 Hz, 6H).

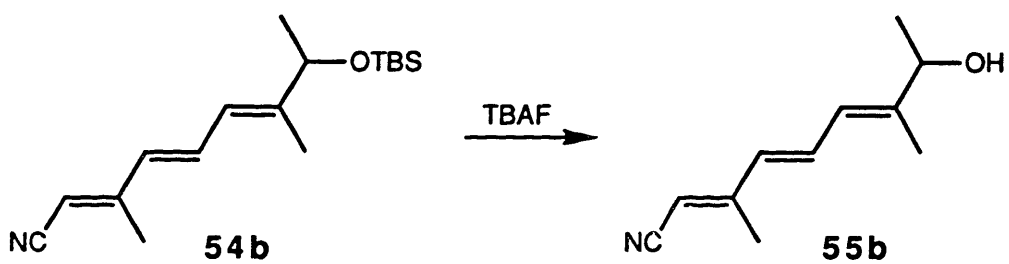
IR (neat) cm^{-1}: 3040, 2940, 2850, 2700, 1720, 1635, 1600, 1567, 1460, 1440, 1360, 1308, 1250, 1217, 1150, 1075, 980, 960, 825, 770, 657.

Physical Properties for **54b**

R_f = 0.64 (20% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 6.80(dd, 1H), 6.24(d, *J* = 15.14 Hz, 1H), 6.15(d, *J* = 11.07 Hz, 1H), 5.18(s, 1H), 4.23(q, *J* = 6.43, 1H), 2.20(s, 3H), 1.82(s, 3H), 1.23(d, *J* = 6.43 Hz, 3H), 0.89(s, 9H), 0.03(d, *J* = 8.83 Hz, 6H).

IR (neat) cm^{-1}: 3040, 2930, 2850, 2700, 1720, 1635, 1600, 1570, 1460, 1440, 1385, 1358, 1250, 1150, 1080, 955, 825, 770, 658.



Hydroxynitrile, 55b

The nitrile, **54b**, (1.0 g, 3.44 mmoles) was dissolved in THF (20 mL) and cooled to 0°C under argon. Tetrabutylammonium fluoride (1M in THF,

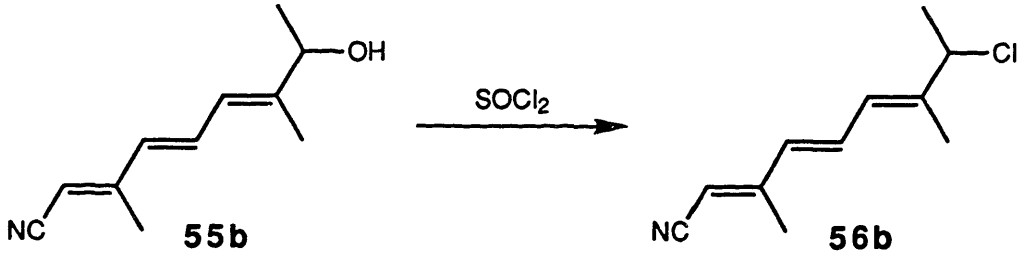
7 mL) was slowly added and the mixture was stirred at 0°C for 3 hours, after which the reaction was quenched with saturated $NaHCO_3$ solution (50 mL). The aqueous mixture was extracted with ether (3 X 50 mL), and the combined ether layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified on silica gel (35% ethyl acetate/hexane) to yield the product as a light brown oil (0.612 g, 99%).

Physical Properties for **55b**

R_f = 0.48 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 6.78(dd, 1H), 6.26(d, 1H), 6.17(d, 1H), 5.18(s, 1H), 4.30(q, 1H), 2.19(s, 3H), 1.84(s, 3H), 1.30(d, 3H).

EI Mass Spec: m/e 177 $[M]^+$, 162, 134, 43.



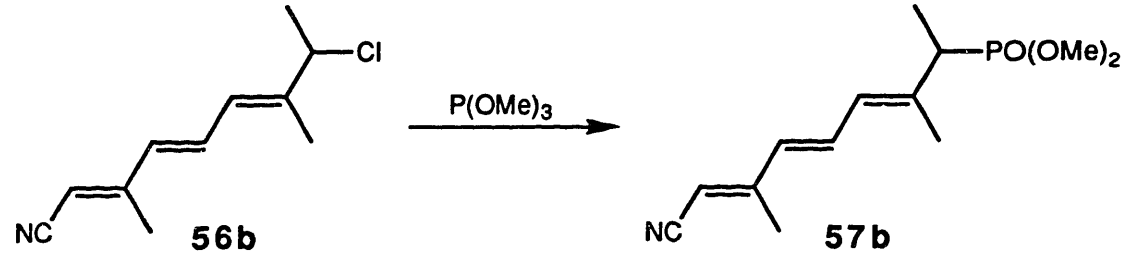
Chloride, 56b

The hydroxynitrile, **55b**, (53.2 mg, 0.30 mmoles) was dissolved in THF (0.5 mL) and cooled to 0°C under argon. 2,6-Lutidine (80 mL, 0.688 mmoles) was added followed by $SOCl_2$ (50 mL, .685 mmoles). The reaction was stirred at 0°C for 3 hours, after which it was quenched with saturated NH_4Cl solution (2 mL). The aqueous mixture was washed with ethyl acetate (5 mL), and the ethyl acetate was washed with saturated $CuSO_4$ solution (2 mL) and brine (2 X 2 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to yield the pure product (44.6 mg, 76%).

Physical Properties for **56b**

R_f = 0.54 (20% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 6.73(dd, 1H), 6.29(d, *J* = 15.14 Hz, 1H), 6.16(d, *J* = 10.85 Hz, 1H), 5.20(s, 1H), 4.61(q, *J* = 6.69 Hz, 1H), 2.18(s, 3H), 1.93(s, 3H), 1.61(d, *J* = 7.00 Hz, 3H).



Phosphonate, 57b

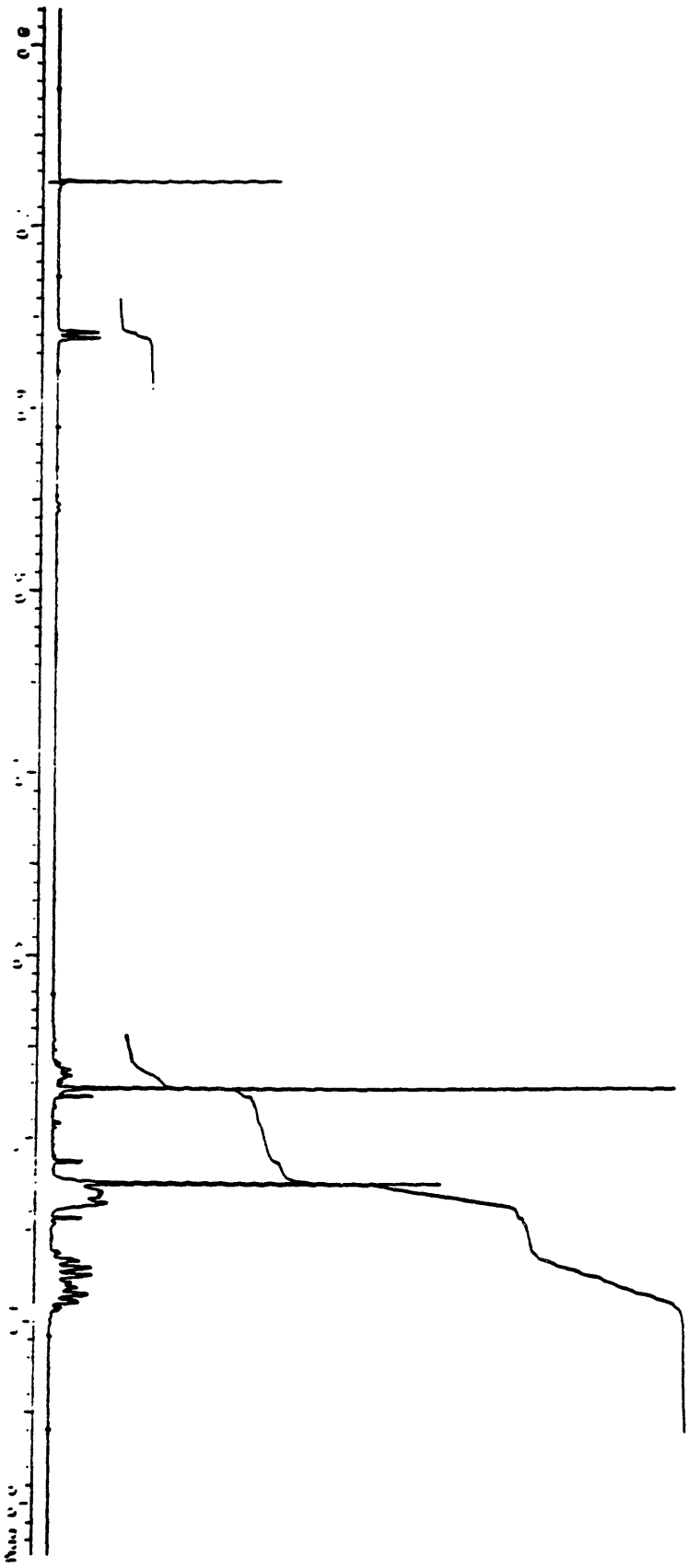
The chloride, **56b**, (44.6 mg, 0.23 mmoles) was heated to reflux in trimethyl phosphite (0.5 mL) under argon for 24 hours. The excess phosphite was removed under vacuum and the residue was purified on silica gel (ethyl acetate) to yield the product as a yellow oil (25.9 mg, 42%).

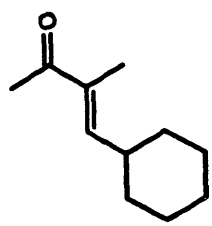
Physical Properties for **57b**

R_f = 0.35 (ethyl acetate).

^1H NMR (300 MHz, $CDCl_3$): δ 6.80(m, 1H), 6.25(dd, 1H), 6.10(dd, 1H), 5.18(s, 1H), 3.75(dd, 6H), 2.73(dq, 1H), 2.18(s, 3H), 1.96(dd, 3H), 1.37(dd, 3H).

1.5 NMR Spectra





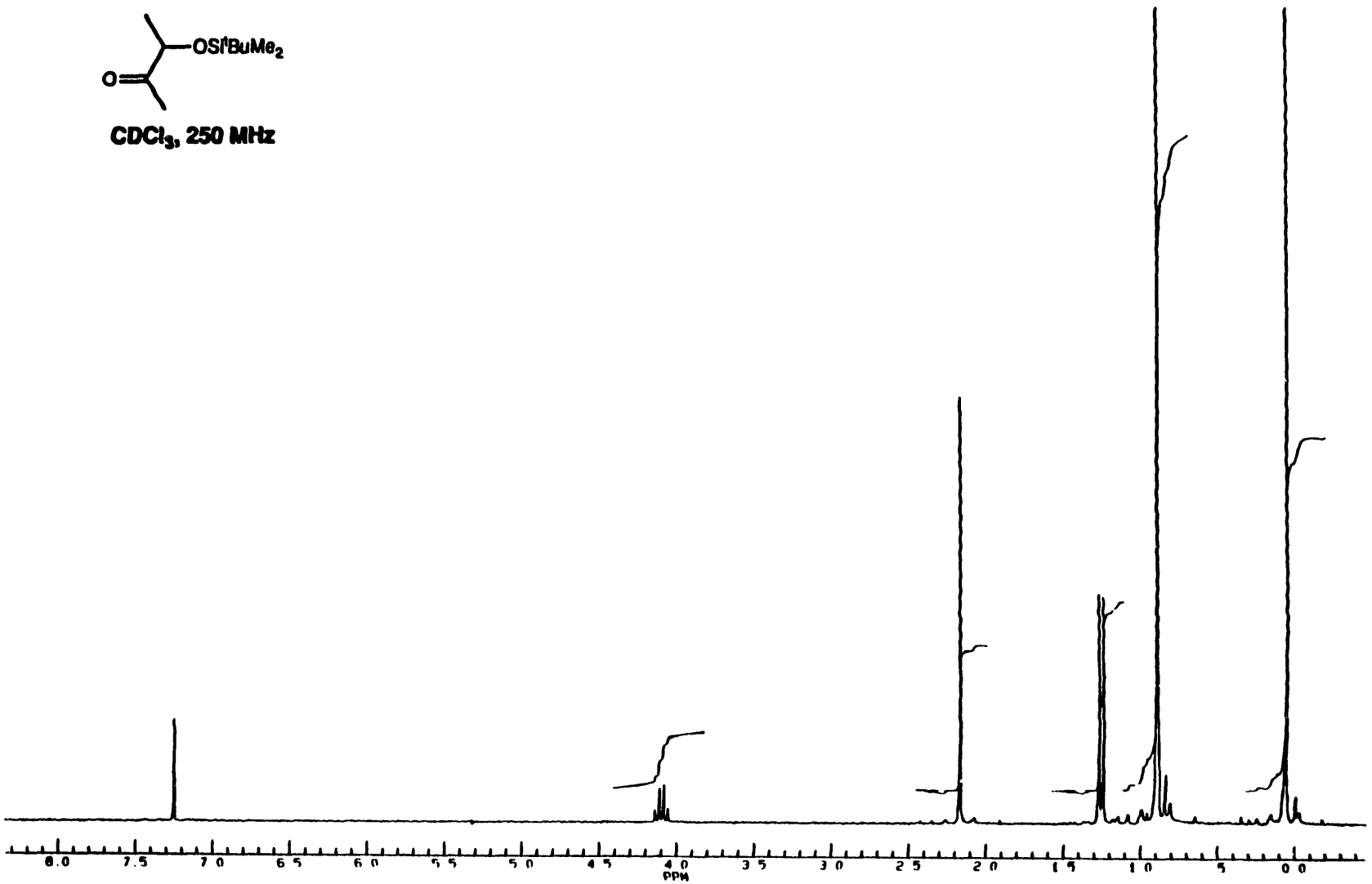
$CDCl_3$, 300 MHz

CDCl3, 300 MHz
PPM 0.0

(CF3CH2O)2P(=O)CH2CN
CDCl3, 300 MHz
10 PPM
9
8
7
6
5
4
3
2
1

CDCl3, 300 MHz
OSiEt3
OSiEt3

CDCl3, 300 MHz
O
OSiEt3
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm


OSi^{t}BuMe$_2$
O
CDCl$_3$, 250 MHz
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

CDCl3, 300 MHz
NC
OSitBuMe2

CDCl3, 300 MHz
NC
OSi'BuMe2

NC
Cl
$CDCl_3$, 300 MHz
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM 0.0

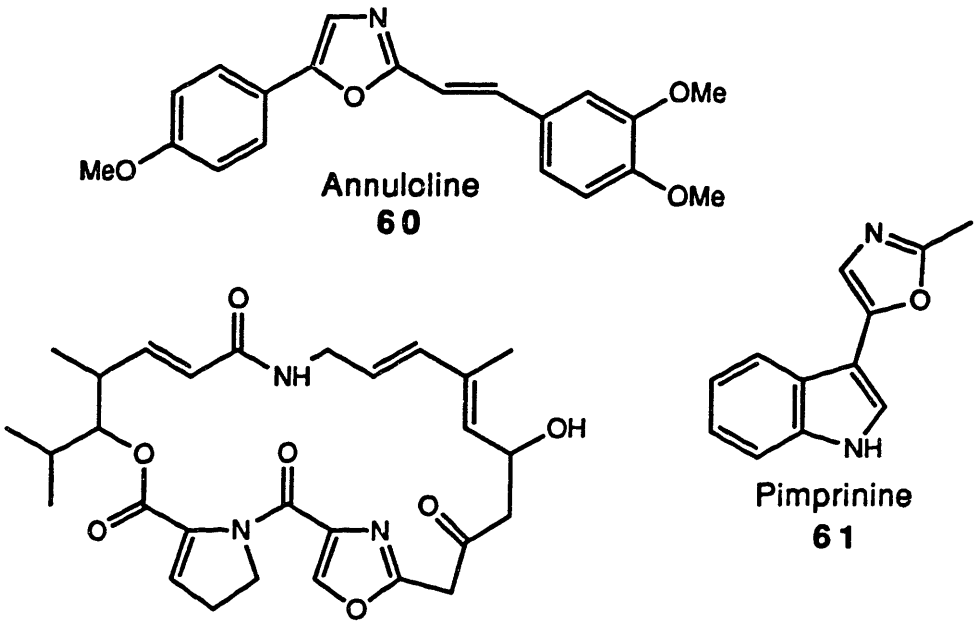
NC
PO(OMe)2
CDCl3, 300 MHz

Chapter 2:

Fragment C1

2.1 Introduction

Figure 2.1



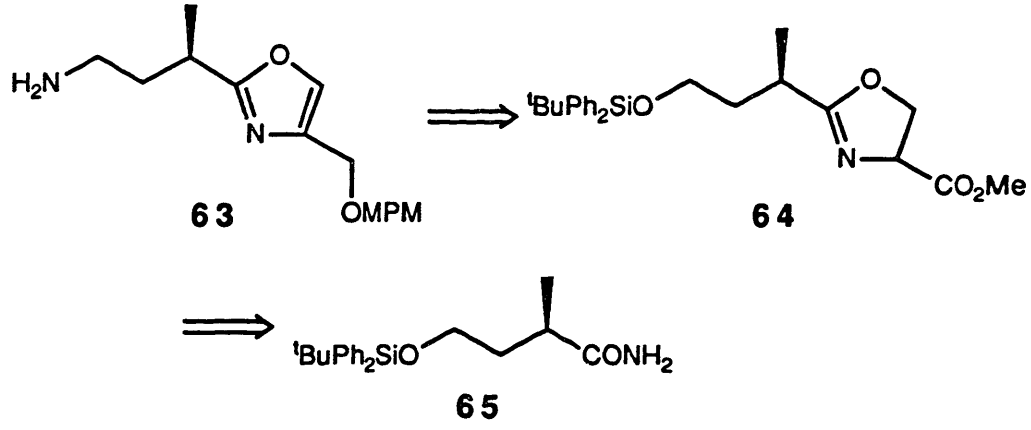
The presence of oxazoles in many biologically active naturally occurring compounds has generated much interest among synthetic organic chemists. Consequently, oxazole bearing synthetic targets have included annuloline, **60**,[65,66] pimprinine, **61**,[67] and ostreogrycin A, **62**[68,69,70] (Figure 2.1). Unfortunately, the harshness of conditions required for the preparation of oxazoles has generally provided low to good yields.[71,72] Additionally, relatively few examples exist in which stereogenic centers are present α to the ring. Synthetically speaking, it is for these reasons that oxazoles have been attractive targets to organic chemists and have enticed us to develop a new protocol for their preparation. Since, at the time of this research, the absolute stereochemistry of calyculin A was unknown, this

protocol was applied to the preparation of fragment C1 with stereochemistry subsequently shown to be enantiomeric to that of the natural product.

2.2 Retrosynthetic Analysis

Our retrosynthetic analysis of fragment C1, **63**, is shown in Scheme 2.1. We originally envisioned the oxazole, **63**, arising from the corresponding oxazoline, **64**.[73,74] We then imagined deriving the oxazoline, **64**, from the imidate of the corresponding amide, **65**, on treatment with serine methyl ester.[75] Since little is known about the application of this methodology to amides bearing α stereogenic centers, we felt we would have the added advantage of being able to determine the enantiomeric purity of the α center, through NMR analysis of the diastereomers, if we trapped the imidate with enantiomerically pure serine methyl ester.

Scheme 2.1

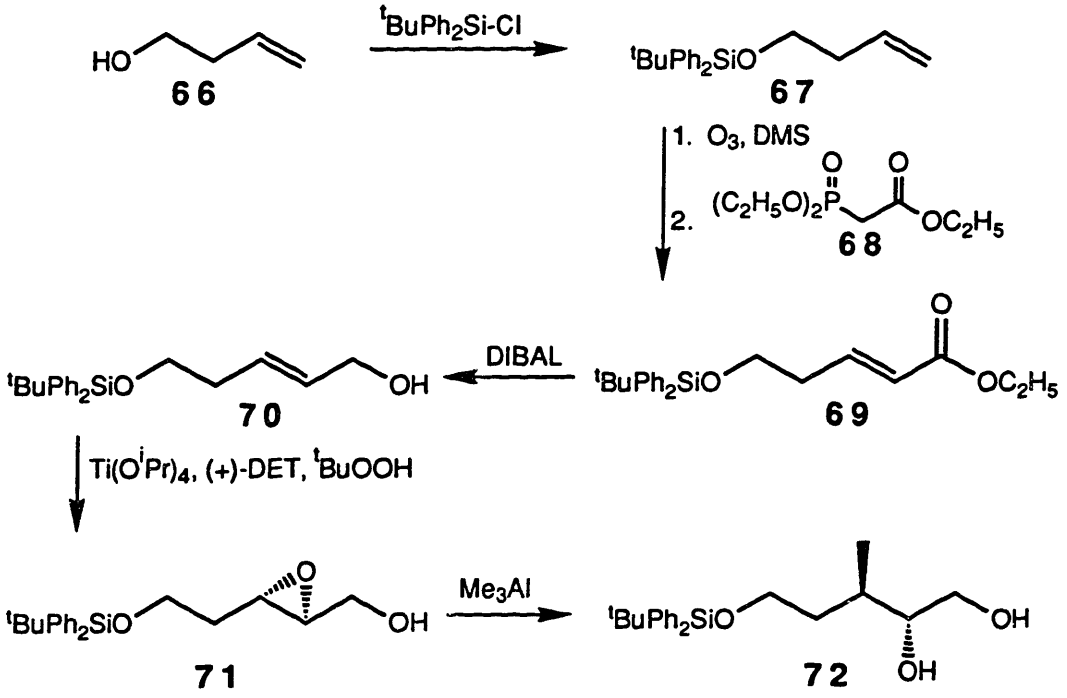


2.3 Preparation of the Amide, 65

The first phase of our amide synthesis brought us to the 1,2-diol, **72**, shown in Scheme 2.2. Treatment of 3-buten-1-ol, **66**, with *tert*-butyl diphenylchlorosilane produced a quantitative yield of the protected alcohol,

67. The olefin was then ozonolyzed and the resulting aldehyde was homologated, on treatment with triethyl phosphonoacetate, 68, to the α,β-unsaturated ester, 69, utilizing the Masamune conditions for the Horner-Emmons modification of the Wittig reaction[76] (75%, two steps). The ester, 69, was then reduced to the allylic alcohol, 70, in quantitative yield on treatment with DIBAL, and the allylic alcohol, 70, was converted to the epoxy alcohol, 71, in 86% yield utilizing the Sharpless asymmetric epoxidation.[77]

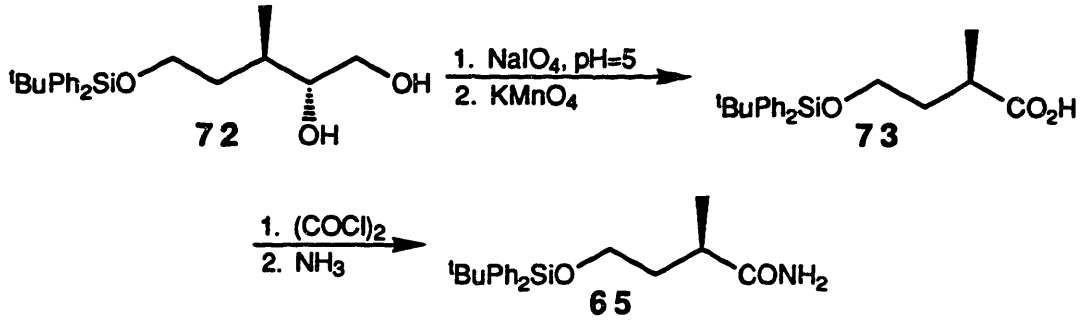
Scheme 2.2



At this stage, we were unable to determine the enantiomeric purity of our intermediate due to a lack of resolution of the peaks in the ^{1}H and ^{19}F NMR spectra of the corresponding Mosher ester. However, when we introduced the methyl group with regioselective opening of the epoxide to the diol, 72 (91% yield),[78,79] we found a > 40 : 1 mixture of 1,2 to 1,3 diols as

well as an enantiomeric purity of > 20 : 1 as shown by ^{19}F NMR analysis of the corresponding bis-Mosher ester.

Scheme 2.3

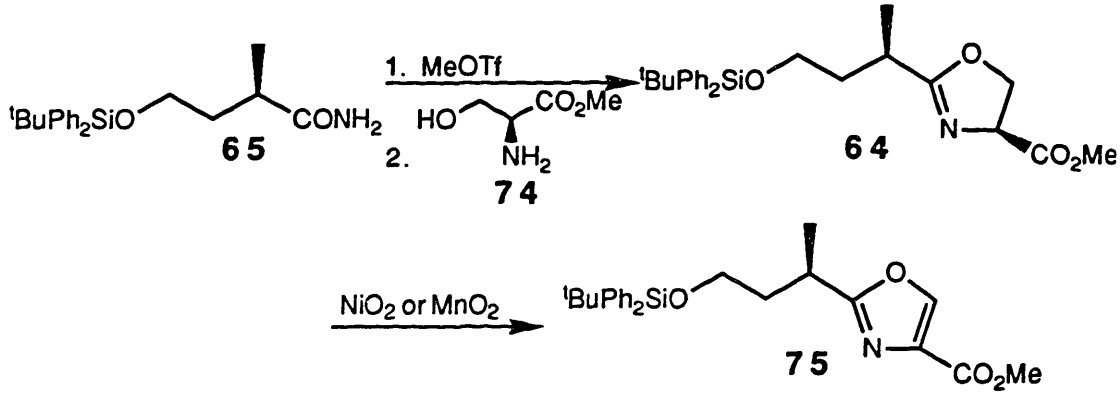


At this point we were ready to convert the diol, **72**, to the amide, **65**, as shown in Scheme 2.3. The diol, **72**, was treated with $NaIO_4$[79] and the resulting aldehyde was oxidized to the acid, **73**, with $KMnO_4$[80] (95%, two steps). Unfortunately, on reduction of the acid, **73**, to the corresponding alcohol with $BH_3 \cdot Me_2S$[81] and analysis of the corresponding Mosher ester by ^1H NMR we found that significant epimerization of the stereogenic center had occurred. Fortunately, we were able to avoid this problem by running the two step procedure buffered at pH = 5. With the epimerization problem solved, we converted the acid, **73**, to the corresponding acid chloride on treatment with oxalyl chloride. *In situ* treatment of the crude acid chloride with liquid ammonia yielded the amide, **65**, in quantitative yield over two steps. Additionally, we were able to show, *via* HPLC analysis, that the enantiomeric purity of the amide remained > 20 : 1.[82] Furthermore, through recrystallization from hexane, we were able to enhance the optical purity of the amide, **65**, to > 99 : 1. With the amide in hand, we were ready to explore the preparation of the oxazole.

2.4 Preparation of the Oxazole

Our original approach to the oxazole (Scheme 2.4) involved treatment of the amide, **65**, with methyl triflate and reaction of the resulting imidate with serine methyl ester, **74**, to yield the oxazoline, **64**, in 90% yield.[75] The oxazoline was then oxidized to the oxazole, **75**, in 42% yield on heating to reflux in benzene in the presence of NiO_2 or MnO_2.[73,74] Due to (1) the relatively low yields from the oxidation, (2) our observed epimerization when optically pure serine methyl ester was used, and (3) the fact that oxazolines bearing α-stereogenic centers are completely racemized when heated to 40°C for 16 hours,[83,84] we elected to explore alternate strategies for the preparation of oxazoles.

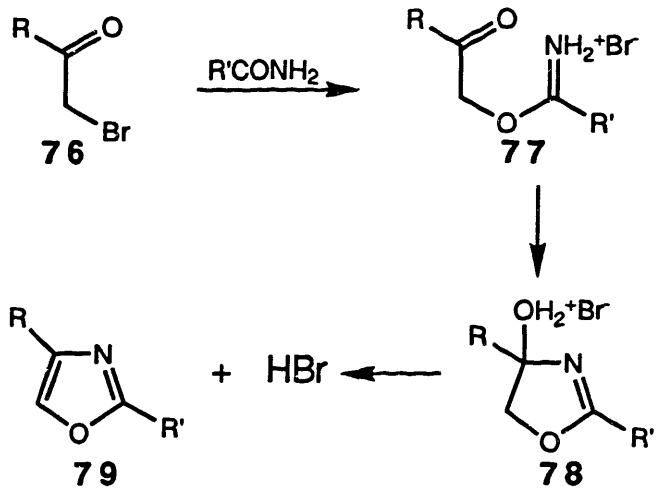
Scheme 2.4



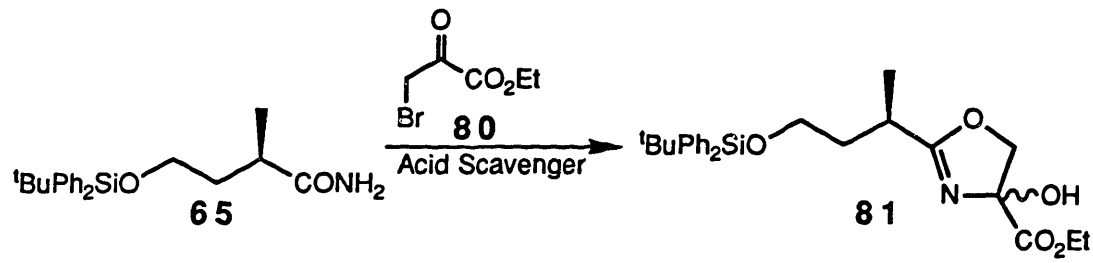
It has been well documented that when heated with α-bromoketones to 140°C in the absence of solvent, amides yield 2,4-disubstituted oxazoles in relatively low yields.[85,86] The proposed mechanism, shown in Scheme 2.5, involves initial displacement of the bromide by the amide oxygen forming the imidate-type species, **77**. Cyclization then forms the 4-hydroxyoxazoline, **78**, which dehydrates under acidic conditions to the oxazole, **79**.

In order to apply this type of methodology to our synthesis, we had to address two points -- (1) the previously mentioned fact that oxazolines bearing α-stereogenic centers are completely racemized on heating to 40°C for 16 hours, and (2) the fact that our amide bears an acid unstable silyl ether. We felt, however, that both of these problems could be overcome if we utilized a polar aprotic solvent in the presence of an acid scavenger.

Scheme 2.5



Scheme 2.6



Initially, we set out to determine if we could form the intermediate 4-hydroxyoxazoline, **81**, by treating our amide, **65**, with ethyl bromopyruvate, **80**, as shown in Scheme 2.6. Our study involved a variety of solvents and acid scavengers, the results of which are shown in Table 2.1. Consequently,

we found that heating our amide and ethyl bromopyruvate to reflux in acetonitrile in the presence of cyclopentene oxide as an acid scavenger, we were able to produce an 81% yield of the desired 4-hydroxyoxazoline, **81**, with an 18% yield of recovered amide, **65**. What was now required was a means of dehydrating our oxazoline to the desired oxazole, **82**.

Table 2.1

Conditions for Hydroxyoxazoline Formation

Solvent	Acid Scavenger	Temp	Pyruvate	81	65
Toluene	K_2CO_3 (3eq)	Reflux	1.1 eq	----	----
EtOH	K_2CO_3 (3eq)	Reflux	1.1 eq	----	----
CH_3CN	K_2CO_3 (3eq)	Reflux	1.1 eq	61%	14%
CH_3CN	K_2CO_3 (10eq)	Reflux	3 eq	57%	----
CH_3CN	$NaHCO_3$ (10eq)	Reflux	2 eq	28%	----
CH_3CN	K_2CO_3 (10eq)	50°C	2 eq	24%	----
CH_3CN/EtOH 1/1	K_2CO_3 (10eq)	Reflux	2 eq	----	----
CH_3CN	K_2CO_3 (10eq)	Reflux	6 eq	29%	----
CH_3CN	 (2.5eq)	Reflux	2 eq	81%	18%

Scheme 2.7

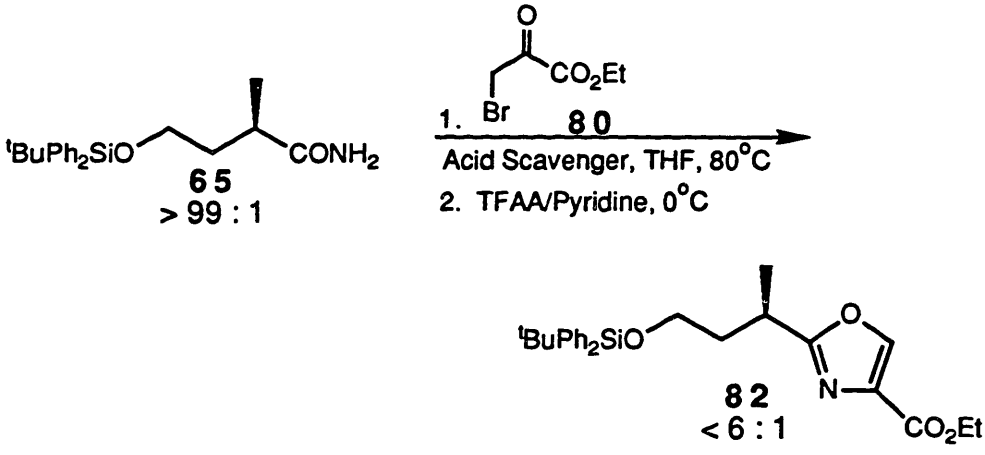
Table 2.2

Conditions for Dehydration of the Hydroxyoxazoline to the Oxazole

Reagent	Solvent	Temp	Yield
AcOH	AcOH	Reflux	----
AcOH	AcOH	RT	----
$POCl_3$	$POCl_3$	RT to 50°C	----
PPE	$CHCl_3$	Reflux	----
P_2O_5/Ac_2O	$CHCl_3$	RT	----
TFAA/Pyridine	THF	RT	76%

Our search for suitable conditions to effect the dehydration of the 4-hydroxyoxazoline, **81**, to the desired oxazole, **82**, shown in Scheme 2.7, led us through a variety of conditions shown in Table 2.2. As it turned out, the only conditions which did not cause complete decomposition of the 4-hydroxyoxazoline were trifluoroacetic anhydride (TFAA) in the presence of pyridine. These conditions afforded a 76% yield of the desired oxazole, **82**. With this result, we were ready to combine these two steps into a one-pot process.

Scheme 2.8

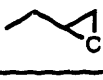
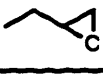


While optimizing the one-pot oxazole preparation shown in Scheme 2.8, we tried a variety of conditions, all of which included running the first phase of the reaction at reflux temperatures and using, in the second phase, four equivalents of TFAA and eight equivalents of pyridine. The results of our study, shown in Table 2.3, demonstrated that little change in the yield occurred when we switched from the more strained cyclopentene oxide to the less strained epoxy butane. This result was advantageous in that the latter epoxide is much less expensive. Unfortunately, as we learned by

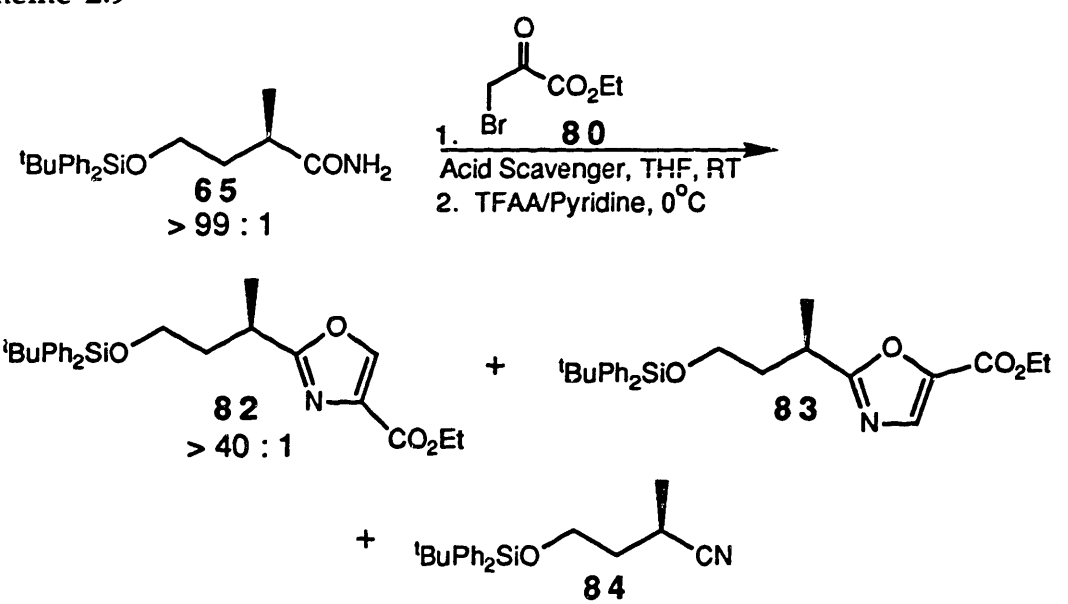
removal of the silyl group and subsequent formation of the Mosher ester, this reaction sequence was causing significant epimerization. This came as no surprise as we were running these reactions at elevated temperatures.[83,84] Therefore, we set out in search of more mild conditions.

Table 2.3

Conditions for the Hydroxyoxazoline Formation Step in Scheme 2.8

Solvent	Scavenger	Pyruvate (eq)	Yield
CH_3CN	 (2.5eq)	2	31%
THF	 (2.5eq)	2	63%
THF	 (3.5eq)	3	70%
THF	 (3.5eq)	3	73%
THF	 (2.5eq)	3	76%

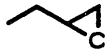
Scheme 2.9



In varying the conditions for our oxazole synthesis, we found that, in addition to running the reaction at room temperature, the choice of acid scavenger was critical for the success of this reaction -- specifically, the more reactive the epoxide, the less the degree of epimerization. Additionally, after embarking on this study, we found two significant side products, the quantities of which were also controlled by the choice of epoxide. These products were the 2,5-disubstituted oxazole, **83**, and the nitrile, **84** (Scheme 2.9). The 2,5-disubstituted oxazole, **83**, is believed to arise from initial attack of ethyl bromopyruvate by the amide nitrogen. The nitrile, **84**, is believed to arise from dehydration of the amide. This study, the results of which are shown in Table 2.4, eventually led to a 63% yield of the desired oxazole, **82**, in enantiomerically pure form when epoxy cyclopentene[87] was used as the acid scavenger. Additionally, although the undesired 2,5-oxazole, **83**, was not formed, we were unable to suppress a 35% yield of the nitrile, **84**.

Table 2.4

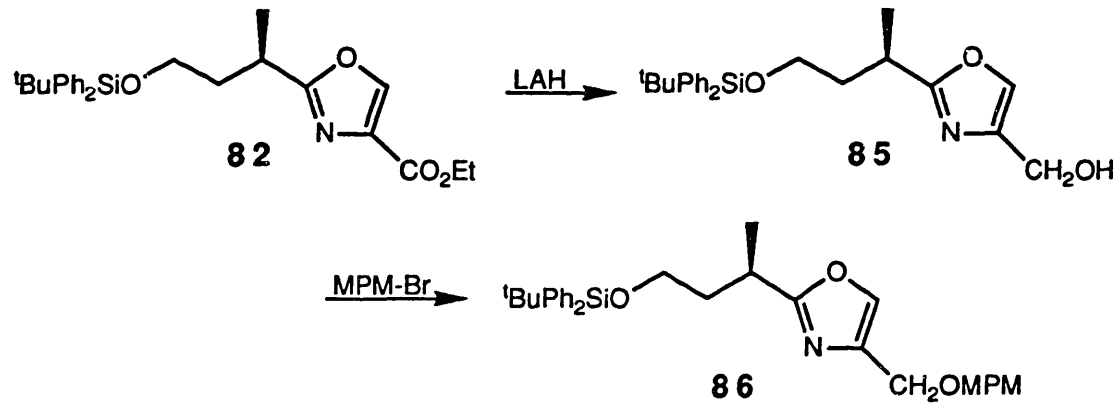
Final Conditions for the One-Pot Oxazole Formation (Scheme 2.9)

Scavenger	Pyruvate	Time	82	83	84	Ratio
 (7eq)	5eq	18 Hours	56%	0.5%	-----	6 : 1
 (7eq)	5eq	14 Hours	71%	1%	-----	10 : 1
 (7eq)	5eq	7 Hours	20%	----	55%	> 40 : 1
 (7eq)	5eq	16 Hours	43%	----	49%	> 40 : 1
 (10eq)	5eq	16 Hours	30%	----	50%	-----
 (7eq)	5eq	32 Hours	-----	----	95%	-----
 (16eq)	5eq	17 Hours	63%	----	35%	> 40 : 1

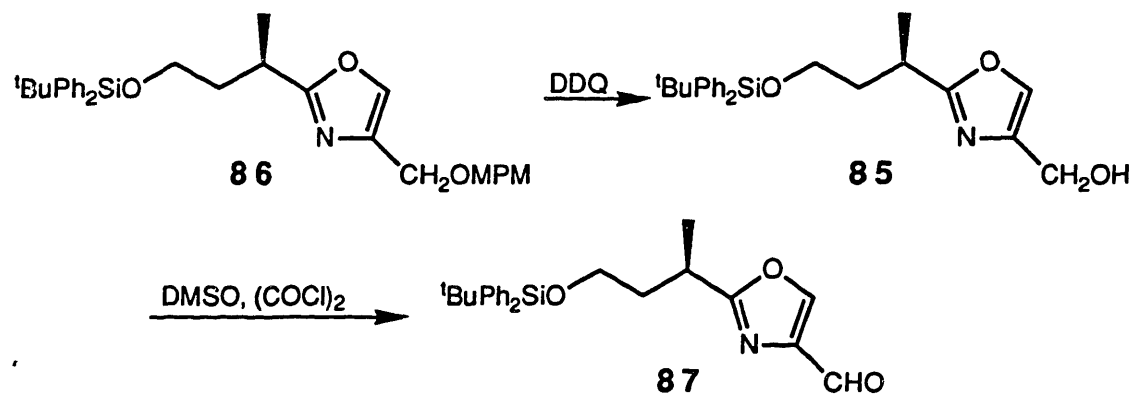
2.5 Completion of the C1 Fragment

With the yield of the oxazole formation optimized with the exclusion of epimerization, we were ready to complete the synthesis of the C1 fragment. Beginning with the intermediate, **82**, reduction of the ester functionality with LAH afforded a 96% yield of the alcohol, **85**. Subsequent protection of the alcohol with MPM-Br produced a 95% yield of the desired MPM ether, **86**, as shown in Scheme 2.10.

Scheme 2.10



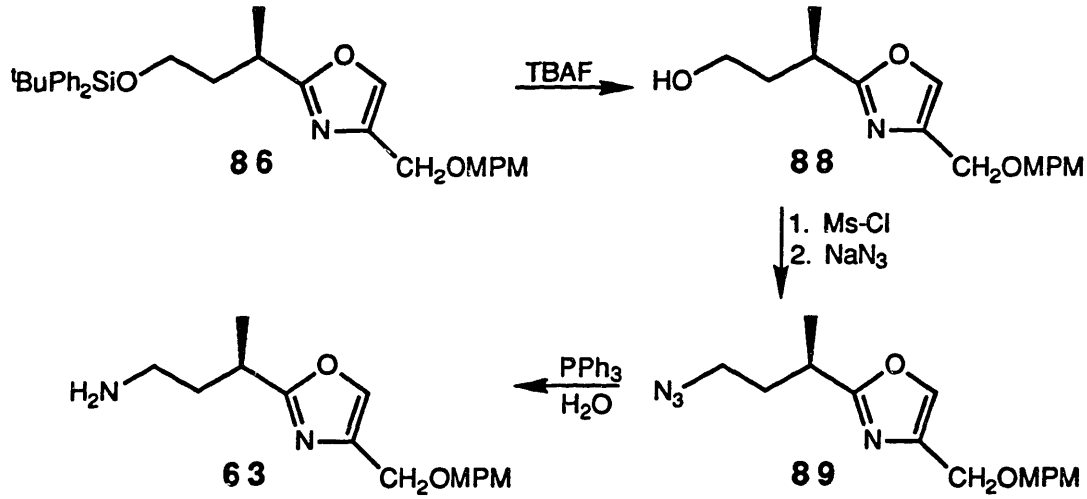
Scheme 2.11



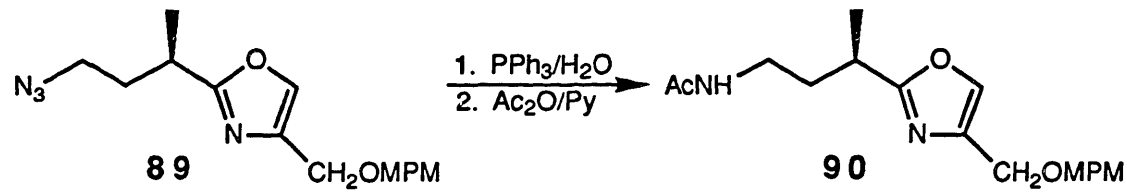
At this stage, we felt it prudent to see if the MPM group could be cleaved and if the alcohol could be oxidized to the corresponding aldehyde

in preparation for the Julia-Lythgoe coupling[88,89,90] to be used in the coupling of the B and C fragments. As shown in Scheme 2.11, treatment of the MPM ether with DDQ[91,92] produced a 92% yield of the alcohol, **85**. The alcohol was then converted, in 99% yield, to the desired aldehyde, **87**, utilizing Swern conditions.[93]

Scheme 2.12



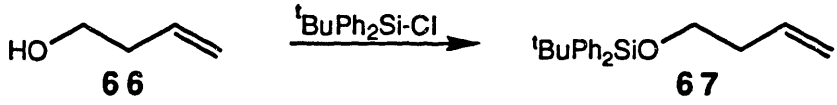
Scheme 2.13



Continuing on with the MPM ether, **86**, treatment with TBAF produced the alcohol, **88**, in quantitative yield. The alcohol, **88**, was then treated with methanesulfonyl chloride to yield the mesylate which was converted, *in situ*, to the azide, **89**, on reaction with sodium azide (98% yield, two steps). Reduction of the azide, **89**, with triphenylphosphine/H_2O produced an 83% yield of the amine, **63** (Scheme 2.12).[94] Although the yield

of the amine was quite good, we were able to show that the reduction actually proceeded in much greater yield by converting the azide, **89**, to the acetamide, **90**, in 97% over the two step process (Scheme 2.13). With these results, we have postulated that the 83% yield of the amine, **63**, was due to loss of product during chromatography as well as possible air oxidation of the amine itself. In any event, we had now completed the synthesis of fragment C1 and could now proceed to the preparation of fragment C2.

2.6 Experimental Section



66 **67**

Silyl Ether, 67

At room temperature under argon, *tert*-butyldiphenylchlorosilane (41.0 mL, 157.01 mmoles) was slowly added to a solution of 3-butene-1-ol, **66**, (11.1 g, 153.93 mmoles) and imidazole (23.1 g, 338.65 mmoles) in methylene chloride (120 mL). After stirring for 15 hours, the reaction was quenched with pH = 7 buffer. The products were extracted three times with ethyl acetate, and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the product was purified on silica gel (2% ethyl acetate/hexane) to yield the product (47.8 g, 100%) as a colorless oil.

Physical Properties for **67**

R_f = 0.83 (30% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.66-7.69(m, 4H), 7.34-7.45(m, 6H), 5.83(ddd, J = 17.1, 10.2, 6.8 Hz, 1H), 5.05(ddd, J = 17.1, 3.4, 1.4 Hz, 1H), 5.02(dd, J = 10.2, 1.4 Hz, 1H), 3.71(t, J = 6.7 Hz, 2H), 2.32(qt, J = 6.7 and 1.1 Hz, 2H), 1.05(s, 9H).

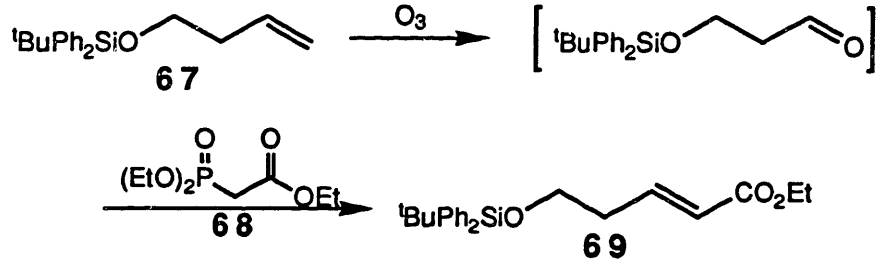
^{13}C NMR (300 MHz, $CDCl_3$): δ 135.63, 135.46, 134.03, 129.58, 127.62, 116.37, 63.55, 37.25, 26.90, 19.26.

FAB Mass Spec: m/e 311 $[M + 1]^+$,253, 135, 105.

Exact Mass: $[M + 1]^+$ = 311.18312 (calculated)

$[M + 1]^+$ = 311.1829 (measured).

IR ($CHCl_3$) cm^{-1}: 2975-3020 (m, br), 2900-2960 (s, br), 2870 (s), 2830 (s), 1950 (w), 1456 (m), 1449 (m), 1410 (m), 1375 (m), 1348 (m), 1165-1200 (s, br), 1052-1105 (s, br), 980 (m), 970 (m), 895 (s).



67 68 69

α,β-Unsaturated Ester, 69

A solution of the olefin, **67**, (11.20 g, 33.09 mmoles) in methylene chloride-methanol (10 : 1, 200 mL) was cooled to -78°C and ozone was bubbled into the solution until saturated (solution turned blue). Me_2S (3.65 mL, 49.64 mmoles) and $(^iPr)_2NEt$ (8.65 mL, 49.64 mmoles) were then added. The resulting solution was slowly warmed to room temperature and quenched with pH = 7 buffer. The products were extracted three times with CH_2Cl_2, and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residual oil was diluted with acetonitrile (60 mL). The resulting solution was added dropwise to a solution of triethyl phosphonoacetate, **68**, (8.54 mL, 43.02 mmoles), LiCl (2.0 g, 43.02 mmoles), and DBU (5.44 mL, 36.40 mmoles) in acetonitrile (40 mL) at

0°C under argon. The resulting solution was stirred for 15 minutes at room temperature and quenched with pH = 7 buffer. The products were extracted three times with ethyl acetate, and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the product was purified on silica gel (2% ethyl acetate/hexane) to yield the desired product (9.53 g, 75% yield) as a colorless oil.

Physical Properties for 69

R_f = 0.53 (13% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.64-7.67(m, 4H), 7.35-7.46(m, 6H), 6.98(dt, *J* = 15.7, 7.1 Hz, 1H), 5.83(dt, *J* = 15.7, 1.5 Hz, 1H), 4.17(q, *J* = 7.1 Hz, 2H), 3.74(t, *J* = 6.4 Hz, 2H), 2.41(qd, *J* = 6.5, 1.4 Hz, 2H), 1.27(t, *J* = 7.1 Hz, 3H), 1.02(s, 9H).

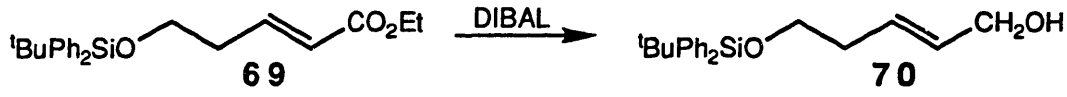
^{13}C NMR (300 MHz, $CDCl_3$): δ 166.45, 145.78, 135.57, 133.63, 129.71, 127.69, 123.07, 62.34, 60.16, 35.47, 26.85, 19.21, 14.29.

FAB Mass Spec: m/e 383 $[M + 1]^+$, 325, 327, 135.

Exact Mass: $[M + 1]^+$ = 383.20425 (calculated)

$[M + 1]^+$ = 383.2038 (measured).

IR ($CHCl_3$) cm^{-1}: 3005 (s), 2960 (s), 2940 (s), 2860 (s), 1720 (s), 1655 (s), 1585 (w), 1510 (m), 1480 (m), 1470 (m), 1430 (m), 1390 (m), 1380 (m), 1160-1250 (s, br), 1040 (s), 984 (m), 930 (m).



69 **70**

Allylic Alcohol, 70

A solution of the ester, **69**, (12.13 g, 31.71 mmoles) in ether (240 mL) was cooled to -78°C under argon and a solution of DIBAL (46.5 mL, 69.76

mmoles, 1.5M in toluene) was added dropwise over 30 minutes. After an additional hour at -78°C, the reaction was added, *via* cannula, to an ether (100 mL)-saturated Rochelle's salt (100 mL) solution maintained at 0°C. After the addition the resulting mixture was stirred for 1 hour at room temperature, after which two layers formed. The products were extracted three times with ether, and the combined extracts were washed with 10% HCl, saturated $NaHCO_3$ solution, and brine. The resulting solution was dried over $MgSO_4$ and concentrated to dryness yielding the pure allylic alcohol (10.69 g, 99%) as a colorless oil.

Physical Properties for **70**

R_f = 0.41 (33% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.65-7.69(m, 4H), 7.35-7.45(m, 6H), 5.67(m, 2H), 4.06(m, 2H), 3.71(t, *J* = 6.5 Hz, 2H), 1.30(m, 2H), 1.16(m, 1H), 1.05(s, 9H).

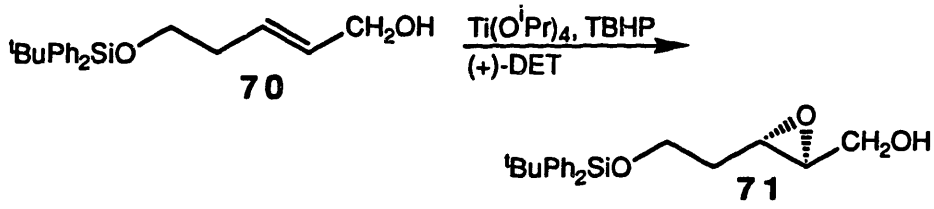
^{13}C NMR (300 MHz, $CDCl_3$): δ 135.60, 133.96, 131.01, 129.62, 129.54, 127.64, 63.75, 63.50, 35.61, 26.89, 19.25.

FAB Mass Spec: m/e 323 $[M - 17]^+$, 199, 135.

Exact Mass: $[M - OH]^+$ = 323.18312 (calculated)

$[M - OH]^+$ = 323.1828 (measured).

IR ($CHCl_3$) cm^{-1}: 3695 (m), 3610 (m), 3010 (s), 2960 (s), 2917 (s), 2860 (s), 2397 (m), 2325 (m), 2315 (m), 1715-1750 (w, br), 1690 (w), 1605 (w), 1595 (w), 1514 (s), 1480 (m), 1425 (s), 1380-1390 (m, br), 1180-1240 (s, br), 1075-1120 (s, br), 995 (m), 970 (s), 920 (s).



Epoxide, 71

4Å molecular sieves (22 g) were suspended in methylene chloride (190 mL) and cooled to -30°C under argon. (+)-DET (0.651 mL, 3.81 mmoles), and $Ti(O^iPr)_4$ (0.944 mL, 3.17 mmoles) were added and the mixture was stirred for 5 minutes. TBHP (6.4M solution in toluene, 9.91 mL, 63.42 mmoles) was added dropwise and the resulting mixture was stirred at -30°C for 30 minutes. A solution of the allylic alcohol, **70**, (10.78 g, 31.71 mmoles) in CH_2Cl_2 (50 mL) was added dropwise and the resulting mixture was stirred at -30°C for 20 hours, after which it was warmed to 0°C. Water (20 mL) was then added followed by a 30% aqueous solution of NaOH-NaCl (3.8 mL). The resulting suspension was stirred at room temperature for 1 hour and the organic layer was separated. The aqueous layer was washed three times with CH_2Cl_2, and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (14% ethyl acetate/hexane) to furnish the epoxide, **71**, as a colorless oil (9.93g, 88%).

Physical Properties for **71**

R_f = 0.30 (33% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.62-7.69(m, 4H), 7.34-7.45(m, 6H), 3.90(ddd, *J* = 12.4, 5.4, 2.4 Hz, 1H), 3.80(m, 2H), 3.60(ddd, *J* = 12.4, 6.9, 4.3 Hz, 1H), 3.13(td, *J* = 5.8, 2.5 Hz, 1H), 2.97(ddd, *J* = 4.4, 2.5, 2.5 Hz, 1H), 1.92(dd, *J* = 6.8, 6.3 Hz, 1H), 1.81(dd, *J* = 11.8, 6.2 Hz, 2H), 1.04(s, 9H).

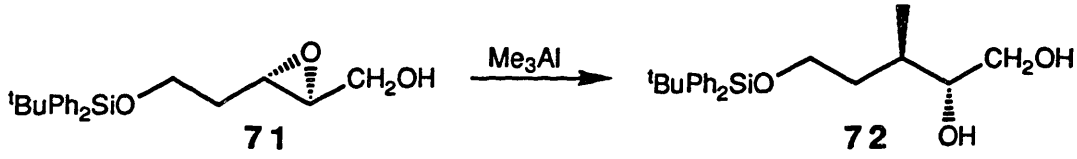
^{13}C NMR (300 MHz, $CDCl_3$): δ 135.56, 133.61, 129.72, 127.73, 61.69, 60.78, 58.61, 53.73, 34.82, 26.86, 19.19.

FAB Mass Spec: m/e 357 $[M + 1]^+$, 269, 199, 135.

Exact Mass: $[M + 1]^+$ = 357.188599 (calculated)

$[M + 1]^+$ = 357.1887 (measured).

IR ($CHCl_3$) cm^{-1}: 3680 (w), 3600 (m), 3010 (s), 2960 (s), 2917 (s), 2860 (s), 2397 (m), 2325 (m), 2315 (m), 1715-1750 (w, br), 1690 (w), 1605 (w), 1595 (w), 1514 (s), 1505 (s), 1480 (m), 1425 (s), 1380-1390 (m, br), 1180-1240 (s, br), 1075-1120 (s, br), 995 (m), 970 (s), 920 (s).



71 72

Diol, 72

A solution of the epoxide, **71**, (9.81 g, 27.51 mmoles) in pentane (200 mL) was cooled to 0°C and Me_3Al (2.0M in hexane, 41.3 mL, 82.53 mmoles) was added dropwise over 15 minutes. After 2 hours at 0°C, the reaction was carefully quenched with 10% HCl. The resulting mixture was stirred at room temperature for 15 minutes. The products were extracted three times with ethyl acetate and the combined extracts were washed with saturated $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the solvent was removed and the product was purified on silica gel (20% ethyl acetate/hexane) to give the diol, **72**, (9.30g 91%) as a colorless oil. The products comprised a diastereomeric mixture of > 20 : 1, as determined by 300-MHz ^1H NMR of the corresponding bis-MTPA ester and a > 40 : 1 mixture of 1,2 and 1,3 diols, as determined by GLC analysis.

Physical Properties for 72

R_f = 0.20 (40% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.68-7.71(m, 4H), 7.39-7.49(m, 6H), 3.64(s, 1H), 3.52-3.82(m, 5H), 2.41(s, 1H), 1.57-1.85(m, 3H), 1.07(s, 9H), 0.90(d, *J* = 6.9 Hz, 3H).

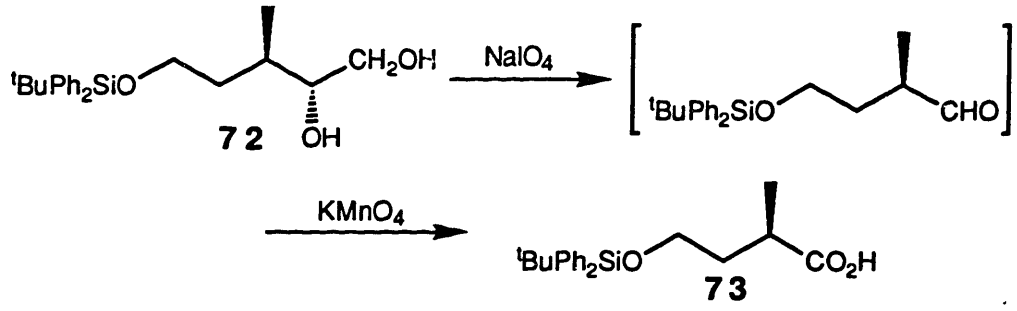
^{13}C NMR (300 MHz, $CDCl_3$): δ 135.59, 133.19, 129.83, 127.79, 76.10, 64.97, 62.27, 35.79, 34.06, 26.84, 19.11, 16.54.

FAB Mass Spec: m/e 373 $[M + 1]^+$, 297, 199, 135, 117, 99.

Exact Mass: $[M + 1]^+$ = 373.219899 (calculated)

$[M + 1]^+$ = 373.2196 (measured).

IR ($CHCl_3$) cm^{-1}: 3560, 3350, 2900, 1450, 1410, 1375, 1075.



Acid, 73

The diol, **72**, (2.01 g, 5.395 mmoles) was dissolved in ^tBuOH (30 mL) and pH = 5 buffer (30 mL). $NaIO_4$ (1.73 g, 8.093 mmoles) was added and the mixture was stirred at room temperature for 40 minutes. $KMnO_4$ (1.0M aqueous solution, 14 mL) was then added and the reaction was stirred for an additional 10 minutes, after which the reaction was titrated with saturated Na_2SO_3 solution until the purple color was gone. The resulting brown precipitate was dissolved by titration with 10% HCl. The products were then extracted three times with ethyl acetate and the combined extracts were

washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (9% ethyl acetate/hexane) to yield the acid (1.84 g, 95%) as a colorless solid. Upon reduction of the acid ($Me_2S{\cdot}BH_3$, ether) and formation of the corresponding MTPA ester, the enantiomeric purity of the acid was found to be > 20 : 1.

Physical Properties for 73

R_f = 0.29 (33% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.65-7.68(m, 4H), 7.37-7.46(m, 6H), 3.71(m, 2H), 2.74(ddd, *J* = 13.8, 7.1, 7.1 Hz, 1H), 2.02(m, 1H), 1.65(ddd, *J* = 13.8, 7.8, 6.0 Hz, 1H), 1.19(d, *J* = 7.1 Hz, 3H), 1.04(s, 9H).

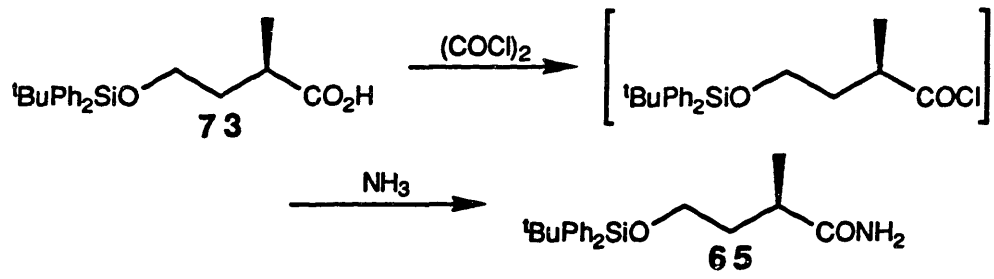
^{13}C NMR (300 MHz, $CDCl_3$): δ 182.38, 135.54, 133.69, 129.58, 127.62, 61.56, 36.09, 35.87, 26.81, 19.14, 16.82.

FAB Mass Spec: m/e 357 $[M + 1]^+$, 339, 299, 221, 199, 135.

Exact Mass: $[M + 1]^+$ = 357.188599 (calculated)

$[M + 1]^+$ = 357.1889 (measured).

IR ($CHCl_3$) cm^{-1}: 3530 (w), 2900-3330 (m, br), 3030 (w), 2960 (s), 2935 (s), 2890 (s), 2860 (s), 1710 (s), 1590 (w), 1475 (m), 1430 (m), 1390 (m), 1375 (w), 1240-1305 (m, br), 1090-1230 (m, br), 995 (m), 900 (m).



Amide, 65

Oxalyl chloride (0.31 mL, 3.54 mmoles) was added dropwise to a solution of the acid, **73**, (840 mg, 2.36 mmoles) in dry benzene (10 mL) at 0°C under argon. The reaction was stirred for 1 hour at room temperature after which, *N,N*-dimethylformamide (1 drop) was added. After an additional 1 hour, the solution was diluted with THF (15 mL) and transferred, *via* cannula, to a solution of NH_3(l) (5 mL) in THF (10 mL) at -78°C under argon. The mixture was warmed to room temperature and the excess NH_3 was allowed to evaporate over 4 hours. After dilution with ethyl acetate, saturated NH_4Cl solution was added and the products were extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to dryness to yield the pure amide (840 mg, 100%) as a colorless solid. The products comprised a > 20 : 1 mixture enantiomers, as determined by HPLC.[82] After three recrystallizations from hexane, the optical purity was > 99 : 1.

Physical Properties for **65**

R_f = 0.25 (50% ethyl acetate/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64-7.67(m, 4H), 7.35-7.46(m, 6H), 5.49(s, 1H), 5.42(s, 1H), 3.71(m, 2H), 2.58(m, 1H), 1.87(ddd, *J* = 13.5, 8.2, 5.3 Hz, 1H), 1.64(ddd, *J* = 13.5, 6.5, 6.5 Hz, 1H), 1.14(d, *J* = 7.1 Hz, 3H), 1.06(s, 9H).

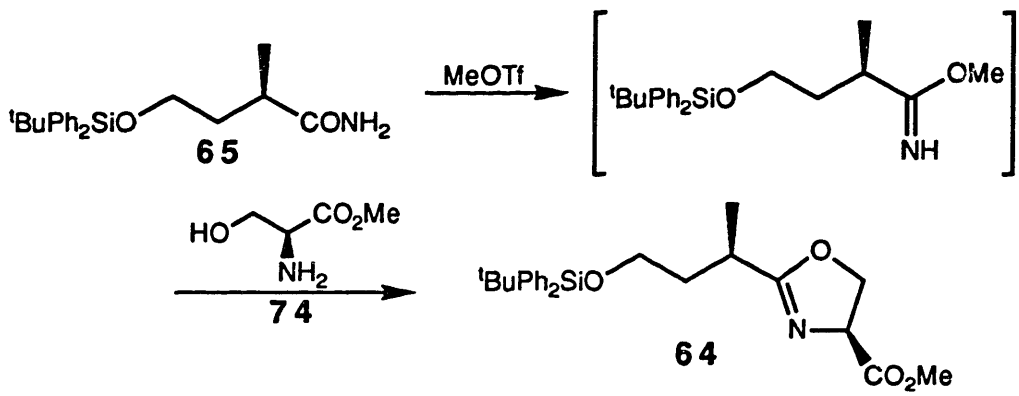
^{13}C NMR (300 MHz, $CDCl_3$): δ 179.15, 135.50, 133.67, 129.70, 127.70, 61.66, 36.85, 36.67, 26.92, 19.21, 17.51.

EI Mass Spec: m/e 340 $[M - 15]^+$, 298, 220, 198.

Exact Mass: $[M - CH_3]^+$ = 340.17328 (calculated)

$[M - CH_3]^+$ = 340.1732 (measured).

IR ($CHCl_3$) cm^{-1}: 3540 (m), 3420 (m), 2980 (s), 2940 (s), 2890 (s), 2860 (s), 1685 (s, br), 1595 (s), 1475 (m), 1445 (w), 1395 (m), 1370 (w), 1280 (m, br), 1070-1125 (s, br), 995 (m), 975 (m), 895 (m).



Oxazoline, 64

A solution of the amide, **65**, (73.9 mg, 0.208 mmole) in CH_2Cl_2 (3 mL) was cooled to 0°C under argon and methyl triflate (1.02M in CH_2Cl_2, 0.4 mL, 0.416 mmole) was added. After 48 hours at room temperature, the solution was cooled to 0°C and *l*-serine methyl ester hydrochloride, **74**, (47.7 mg, 0.250 mmole) was added followed by triethylamine (53 mL, 0.312 mmole). The mixture was stirred at room temperature for 20 hours, after which triethylamine (53 mL, 0.312 mmole) was added. The reaction was stirred an additional 10 hours and quenched with water. The products were extracted three times with ethyl acetate and the combined extracts were washed with

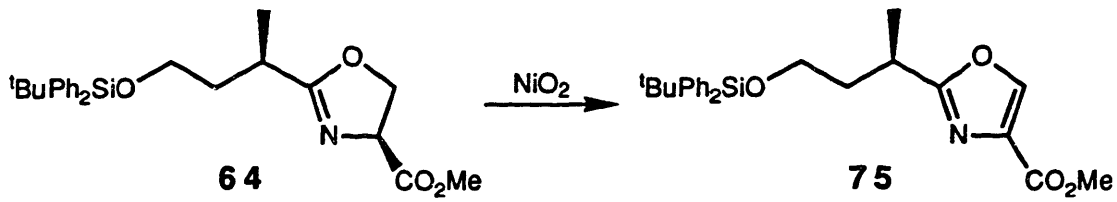
brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (25% ethyl acetate/hexane) to give the oxazoline (82.5 mg, 90%) as a colorless oil.

Physical Properties for 64

R_f = 0.60 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.62-7.65(m, 4H), 7.33-7.44(m, 6H), 4.64(ddd, *J* = 10.8, 7.7, 3.0 Hz, 1 H), 4.40(td, *J* = 8.2, 3.0 Hz, 1 H), 4.29(dd, *J* = 10.8, 8.2 Hz, 1 H), 3.72(s, 3H), 3.68(m, 2H), 2.78(sept, *J* = 7.0 Hz, 1H), 1.98(sept of d, *J* = 6.6, 2.2 Hz, 1H), 1.67(sept of d, *J* = 6.6, 1.6 Hz, 1H), 1.16(d, *J* = 7.0 Hz, 3H), 1.01(s, 9H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 174.4, 172.1, 135.8, 134.0, 129.7, 127.8, 77.2, 69.1, 67.9, 61.3, 52.4, 36.4, 36.3, 29.9, 29.7, 26.6, 19.0, 17.3.



64 75

Oxazole, 75

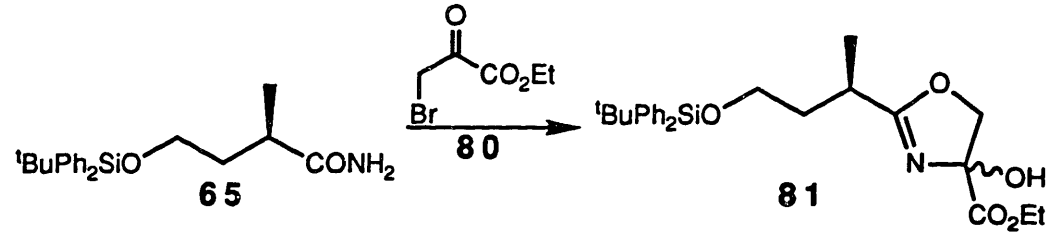
NiO_2 (421 mg, 200 wt%) was suspended in a solution of the oxazoline, 64, (231.3 mg, 0.526 mmole) in dry benzene (20 mL), and the mixture was heated to reflux for 2 hours. NiO_2 (460 mg) was then added and heating was continued until no oxazoline was detected by TLC (about 6 hours). After cooling to room temperature, the mixture was filtered through a Celite pad, the solids were washed with ethyl acetate, and the combined organic phases were concentrated to dryness. Purification of the residue on silica gel (9%

ethyl acetate/hexane) gave the oxazole, **75**, (97.2 mg, 42%) as a colorless oil, and the amide, **65**, (15.1 mg, 8%) as a colorless solid.

Physical Properties for **75**

R_f = 0.52 (33% ethyl acetate/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09(s, 1H), 7.57-7.66(m, 4H), 7.29-7.40(m, 6H), 3.89(s, 3H), 3.66(dd, *J* = 6.4, 5.9 Hz, 2H), 3.31(sext, *J* = 7.0 Hz, 1H), 2.11(sext, *J* = 6.6 Hz, 1H), 1.83(sext, *J* = 6.6 Hz, 1H), 1.31(d, *J* = 7.0 Hz, 3H), 1.00(s, 9H).



4-Hydroxyoxazoline, 81

The amide, **65**, (0.502 g, 1.410 mmole) was dissolved in acetonitrile (10 mL) at room temperature under argon. Cyclopentene oxide (0.308 mL, 3.526 mmoles) was added followed by ethyl bromopyruvate, **80**, (0.354 mL, 2.821 mmoles). The resulting solution was heated to reflux for 3 hours, after which the reaction was concentrated to dryness. Purification of the residue on silica gel (25% acetone/hexane) gave the 4-hydroxyoxazoline, **81**, (0.536 g, 81%) as a colorless oil and the amide, **65**, (90.3 mg, 18%) as a colorless solid.

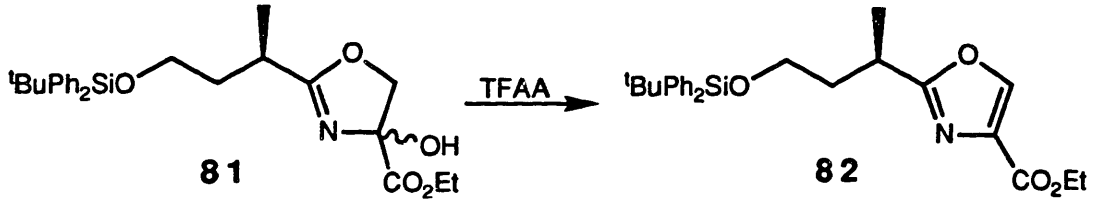
Physical Properties for **81**

R_f = 0.36 (20% acetone/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64-7.67(m, 4H), 7.34-7.45(m, 6H), 4.54(d, *J* = 9.9 Hz, 1H), 4.22(qd, *J* = 7.2, 1.5 Hz, 2H), 4.15(dd, *J* = 9.9, 1.0 Hz, 1H), 4.04(m,

1H), 3.70(m, 2H), 2.83(sext, J = 7.1 Hz, 1H), 2.02(m, 1H), 1.70(ddd, J = 13.4, 6.2, 6.2 Hz, 1 H), 1.22(td, J = 7.2, 1.5 Hz, 3H), 1.22(d, J = 7.1 Hz, 3H), 1.04(s, 9H).

IR ($CHCl_3$) cm^{-1}: 3475, 2930, 1725, 1625, 1450, 1415, 1355, 1200, 1075, 855.



Oxazole, 82

A solution of the 4-hydroxyoxazoline, **81**, (70.8 mg, 0.151 mmole) in THF (2 mL) was cooled to 0°C under argon. Pyridine (98 mL, 1.208 mmole) was added followed by trifluoroacetic anhydride (85 mL, 0.604 mmole) and the reaction was stirred at 0°C for 15 minutes. The reaction was then quenched with pH = 7 buffer and the products were extracted three times with ethyl acetate. The combined organic extracts were with washed saturated $CuSO_4$ solution (2 X 1 mL), saturated $NaHCO_3$ solution (1 mL), and brine (1 mL). After drying over $MgSO_4$, The solvent was removed and the residue was purified on silica gel (7% ethyl acetate/hexane) to give the oxazole (57.7 mg, 85%) as a colorless oil.

Physical Properties for **82**

R_f = 0.46 (20% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 8.09(s, 1H), 7.60-7.66(m, 4H), 7.32-7.44(m, 6H), 4.38(q, J = 6.9 Hz, 2H), 3.67(m, 2H), 3.34(m, 1H), 2.15(m, 1H), 1.83(m, 1H), 1.37(t, J = 6.9 Hz, 3H), 1.33(d, J = 6.9 Hz, 3H), 1.03(s, 9H).

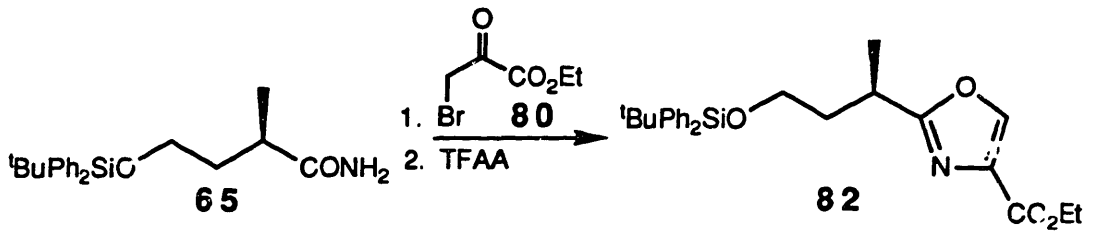
^{13}C NMR (300 MHz, $CDCl_3$): δ 169.19, 161.41, 143.30, 135.51, 133.74, 133.67, 129.55, 127.60, 61.27, 60.96, 37.31, 30.45, 26.82, 19.14, 18.29, 14.29.

EI Mass Spec: m/e 436 $[M - 15]^+$, 394, 288, 179.

Exact Mass: $[M - CH_3]^+$ = 436.19441 (calculated)

$[M - CH_3]^+$ = 436.1941 (measured).

IR (neat) cm^{-1}: 3160, 3060, 2930, 1780, 1740, 1580, 1470, 1425, 1370, 1310.



Oxazole, 82

The amide, **65**, (500 mg, 1.4061 mmole) was dissolved in THF at room temperature under argon. Epoxycyclopentene (0.80 mL, 10.00 mmoles) was added followed by ethyl bromopyruvate, **80**, (0.882 mL, 7.030 mmoles). The resulting solution was stirred at room temperature for 5 hours, after which epoxycyclopentene (0.33 mL, 4.12 mmoles) was added. Stirring was continued for an additional 5 hours, after which epoxycyclopentene (0.33 mL, 4.12 mmoles) was added. After 5 more hours, a final addition of epoxycyclopentene (0.33 mL, 4.12 mmoles) was made. The reaction was stirred for 8 hours, after which it was cooled to 0°C. Pyridine (0.910 mL, 11.249 mmoles) was added followed by TFAA (0.794 mL, 5.624 mmoles) and the resulting solution was stirred at 0°C for 10 minutes. The reaction was quenched with pH = 7 buffer and washed three times with ethyl acetate. The combined extracts were washed twice with saturated $CuSO_4$ solution, saturated $NaHCO_3$ solution, and brine. After drying over $MgSO_4$, the

solvent was removed and the residue was purified on silica gel (6% ethyl acetate/hexane) to give the oxazole, **82**, (0.400 g, 63%) and the nitrile, **84**, (0.166 g 35%) as colorless oils.

Physical Properties for **82**

R_f = 0.46 (20% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$) δ 8.09(s, 1H), 7.60-7.66(m, 4H), 7.32-7.44(comp m, 6H), 4.38(q, *J* = 6.9 Hz, 2H), 3.67(m, 2H), 3.34(m, 1H), 2.15(m, 1H), 1.83(m, 1H), 1.37(t, *J* = 6.9 Hz, 3H), 1.33(d, *J* = 6.9 Hz, 3H), 1.03(s, 9H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 169.19, 161.41, 143.30, 135.51, 133.74, 133.67, 129.55, 127.60, 61.27, 60.96, 37.31, 30.45, 26.82, 19.14, 18.29, 14.29.

EI Mass Spec: m/e 436 $[M - 15]^+$, 394, 288, 179.

Exact Mass: $[M - CH_3]^+$ = 436.19441 (calculated)

$[M - CH_3]^+$ = 436.1941 (measured).

IR (neat) cm^{-1}: 3160, 3060, 2930, 1780, 1740, 1580, 1470, 1425, 1370, 1310.

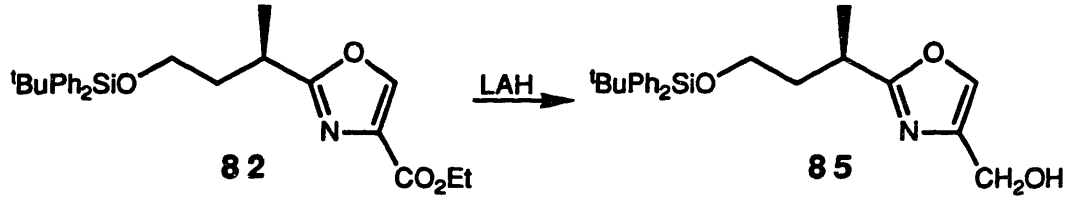
Physical Properties for **84**

R_f = 0.46 (10% acetone/hexane).

^1H NMR (300 MHz, $CDCl_3$) δ 7.62-7.70(m, 4H), 7.36-7.47(m, 6H), 3.79(m, 2H), 2.96(m, 1H), 1.69-1.91(m, 2H), 1.32(d, *J* = 7.1 Hz, 3H), 1.06(s, 9 H).

EI Mass Spec: m/e 280 $[M - 57]^+$, 208, 181, 91.

IR (neat) cm^{-1}: 3080, 2945, 2850, 2225, 1585, 1460, 1425, 1385, 1100.



Alcohol, 85

$LiAlH_4$ (81.1 mg, 2.106 mmoles) was suspended in ether (10 mL) and cooled to 0°C under argon. The oxazole, **82**, (460.9 mg, 1.053 mmole) was dissolved in ether (25 mL) and added, *via* cannula, to the $LiAlH_4$. The mixture was stirred at 0°C for 20 minutes, after which it was quenched with $Na_2SO_4 \cdot 10H_2O$. The resulting mixture was stirred at room temperature for 1 hour, after which it was filtered through a Celite pad. Concentration of the filtrate produced the pure alcohol (412.3 mg, 96%) as a colorless oil.

Physical Properties for **85**

R_f = 0.30 (60% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.61-7.67(m, 4H), 7.45(s, 1H), 7.33-7.45(m, 6H), 4.55(d, *J* = 5.5 Hz, 2H), 3.69(m, 2H), 1.03(s, 9H), 3.25(sext, *J* = 6.9 Hz, 1H), 2.11(m, 2H), 1.81(m, 1H), 1.30(d, *J* = 6.9 Hz, 3H).

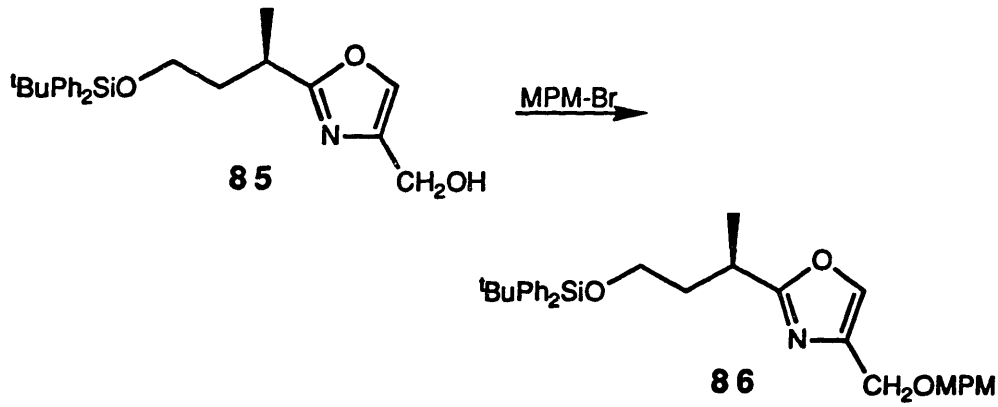
^{13}C NMR (300 MHz, $CDCl_3$): δ 168.91, 139.75, 135.52, 134.30, 133.76, 129.54, 127.59, 61.36, 56.84, 37.49, 30.33, 26.83, 19.16, 18.32.

EI Mass Spec: m/e 409 M^+, 394, 352, 274, 199, 136.

Exact Mass: M^+ = 409.20732 (calculated)

M^+ = 409.2069 (measured).

IR (neat) cm^{-1}: 3350, 3060, 2920, 1560, 1470, 1425, 1100.



MPM-Ether, 86

KH (35%, 230 mg, 2.064 mmoles) was suspended in THF (10 mL) and 18-Crown-6 (cat. amount) was added. The mixture was cooled to 0°C under argon, and a solution of the alcohol, **85**, (600.7 mg, 1.474 mmole) in THF (20 mL) was added. After 15 minutes at 0°C, *p*-methoxybenzyl bromide (0.31 mL, 2.064 mmoles) was added. The reaction was stirred at room temperature for 4 hours, cooled to 0°C, and carefully quenched with water. The products were extracted three times with ethyl acetate, and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (6% ethyl acetate/hexane) to give the desired product (744 mg, 95%) as a colorless oil.

Physical Properties for **86**

R_f = 0.24 (15% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.60-7.66(m, 4H), 7.45(t, *J* = 0.98 Hz, 1H), 7.30-7.43(m, 6H), 1.02(s, 9H), 7.27(dm, *J* = 8.8 Hz, 2H), 6.87(dm, *J* = 8.8 Hz, 2H), 4.53(s, 2H), 4.39(d, *J* = 0.98 Hz, 2H), 3.80(s, 3H), 3.69(d, *J* = 6.3 Hz, 2H), 3.24(m, 1H), 2.12(m, 1H), 1.80(m, 1H), 1.30(d, *J* = 7.0 Hz, 3H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 168.59, 159.24, 137.41, 135.47, 133.72, 133.65, 129.96, 129.50, 127.53, 113.76, 72.29, 63.71, 61.28, 55.19, 37.39, 30.23, 26.78, 19.12, 18.31.

EI Mass Spec: m/e 514 $[M - 15]^+$, 472, 393, 259, 121.

Exact Mass: $[M - CH_3]^+$ = 514.24136 (calculated)

$[M - CH_3]^+$ = 514.2409 (measured).

IR (neat) cm^{-1}: 3060, 2910, 2850, 1610, 1565, 1510, 1460, 1425, 1245, 1170, 1100, 815, 730, 690.

Alcohol, 85

The MPM-ether, **86**, (61.9 mg, 0.117 mmole) was dissolved in CH_2Cl_2/water (20/1, 1 mL) at room temperature under argon. DDQ (29.1 mg, 0.129 mmole) was added and the reaction was stirred for 15 hours. After quenching with saturated $NaHCO_3$ solution, the products were extracted four times with CH_2Cl_2. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (33% ethyl acetate/hexane) to yield the alcohol (43.2 mg, 92%) as a colorless oil.

Physical Properties for **85**

R_f = 0.30 (60% ethyl acetate/hexane).

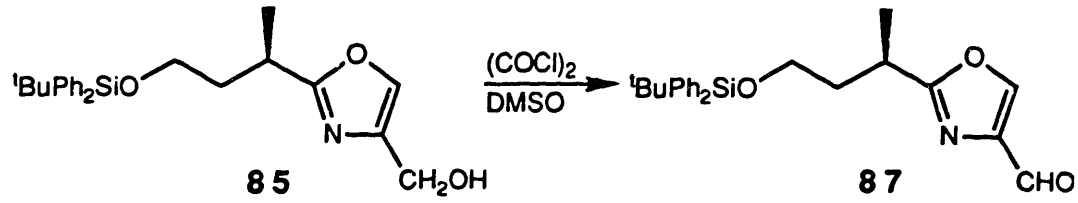
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.67(m, 4H), 7.45(s, 1H), 7.33-7.45(m, 6H), 4.55(d, *J* = 5.5 Hz, 2H), 3.69(m, 2H), 3.25(sext, *J* = 6.9 Hz, 1H), 2.11(m, 2H), 1.81(m, 1H), 1.30(d, *J* = 6.9 Hz, 3H), 1.03(s, 9H).

EI Mass Spec: m/e 409 M^+, 394, 352, 274, 199, 136.

Exact Mass: M^+ = 409.20732 (calculated)

M^+ = 409.2069 (measured).

IR (neat) cm^{-1}: 3350, 3060, 2920, 1560, 1470, 1425, 1100.



85 87

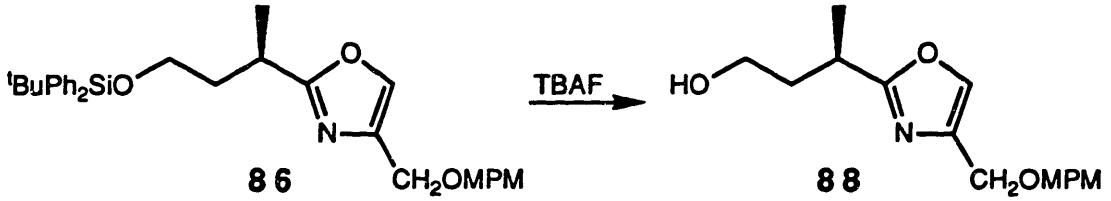
Aldehyde, 87

Oxalyl chloride (18.4 mL, 0.212 mmole) was dissolved in CH_2Cl_2 (1 mL) and cooled to -78°C under argon. DMSO (30 mL, 0.424 mmole) was added, dropwise, and the reaction was stirred for at -78°C for 5 minutes. A solution of the alcohol, **85**, (43.2 mg, 0.106 mmole) in CH_2Cl_2 (2 mL) was added, *via* cannula, and the resulting milky solution was stirred for 20 minutes at -78°C. Triethylamine (0.132 mL, 0.954 mmole) was added, and the reaction was stirred for 10 minutes at -78°C. After warming to room temperature, the reaction was quenched with water and the products were extracted three times with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to dryness. The residue was purified on silica gel (14% ethyl acetate/hexane) to give the aldehyde (42.4 mg, 99%) as a colorless oil.

Physical Properties for 87

R_f = 0.50 (50% ethyl acetate/hexane).

^1H NMR (250 MHz, $CDCl_3$): δ 9.88(s, 1H), 8.12(s, 1H), 7.60-7.65(m, 4H), 7.32-7.45(m, 6H), 3.70(m, 2H), 3.34(sext, *J* = 7.1 Hz, 1H), 2.14(ddt, *J* = 13.7, 6.2, 6.2 Hz, 1H), 1.85(ddt, *J* = 12.7, 6.3, 6.3 Hz, 1H), 1.35(d, *J* = 7.1 Hz, 3H), 1.03(s, 9H).



Alcohol, 88

The silyl ether, **86**, (744 mg, 1.404 mmol) was dissolved in THF (8 mL) at room temperature under argon. Tetrabutylammonium fluoride (1.0M in THF, 2.8 mL, 2.808 mmole) was added and the reaction was stirred for 6 hours. The solvent was removed and the product purified on silica gel (75% ethyl acetate/hexane) to give the alcohol (418.9 mg, 100%) as a colorless oil.

Physical Properties for 88

R_f = 0.24 (80% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.50(t, *J* = 0.95 Hz, 1H), 7.29(dm, *J* = 8.7 Hz, 2H), 6.88(dm, *J* = 8.7 Hz, 2H), 4.52(s, 2H), 4.40(d, *J* = 0.95 Hz, 2H), 3.80(s, 3H), 3.68(t, *J* = 5.9 Hz, 2H), 3.19(m, 1H), 2.74(s, 1H), 1.84-2.08(m, 2H), 1.36(d, *J* = 7.1 Hz, 3H).

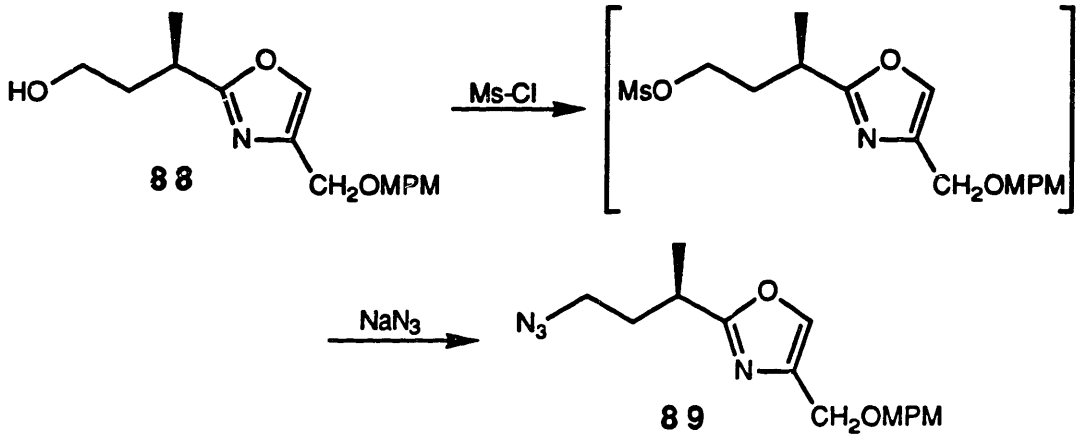
^{13}C NMR (300 MHz, $CDCl_3$): δ 168.49, 159.30, 137.26, 135.81, 129.88, 129.51, 113.81, 72.38, 63.55, 60.25, 55.24, 37.54, 31.09, 18.46.

FAB Mass Spec: m/e 292 $[M + 1]^+$, 155, 121.

Exact Mass: $[M + 1]^+$ = 292.15488 (calculated)

$[M + 1]^+ = 292.1547$ (measured).

IR (neat) cm^{-1}: 3400, 2940, 1613, 1570, 1510, 1460, 1300, 1245, 1170, 1075, 813.



Azide, 89

The alcohol, **88**, (136.2 mg, 0.467 mmole) was dissolved in CH_2Cl_2 (1.6 mL), cooled to 0°C under argon, and triethylamine (0.19 mL, 1.401 mmole) was added. Methanesulfonyl chloride (54.4 μL, 0.700 mmole) was then added and the reaction was stirred at 0°C for 30 minutes. The solvent was removed under reduced pressure and the residue was dissolved in DMF (4.7 mL). NaN_3 was added and the reaction was stirred at room temperature under argon for 30 hours. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 X 10 mL). The combined organics were washed with brine (5 mL) and dried over Na_2SO_4. Concentration of the organics and purification of the residue on silica gel (25% ethyl acetate/hexane) gave the azide, **89**, (128.1 mg, 87%) as a colorless oil.

Physical Properties for 89

R_f = 0.50 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.51(t, *J* = 0.94 Hz, 1H), 7.29(dm, *J* = 8.3 Hz, 2H), 6.88(dm, *J* = 8.3 Hz, 2H), 4.55(s, 2H), 4.41(d, *J* = 0.94 Hz, 2H), 3.80(s, 3H), 3.33(td, *J* = 7.0, 2.9 Hz, 2H), 3.11(m, 1H), 2.10(ddd, *J* = 13.4, 8.1, 6.7 Hz, 1H), 1.86(ddd, *J* = 13.4, 7.4, 5.9 Hz, 1H), 1.36(d, *J* = 7.5 Hz, 3H).

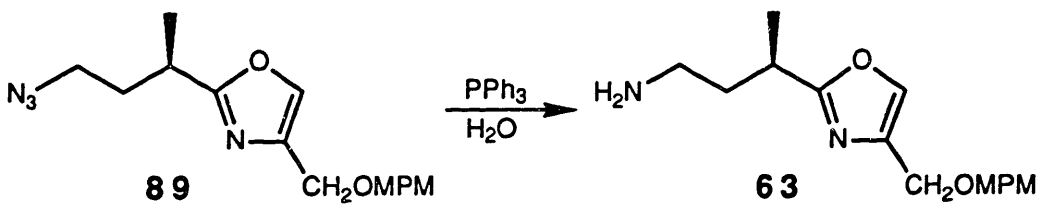
^{13}C NMR (300 MHz, $CDCl_3$): δ 166.97, 159.04, 137.51, 135.61, 129.69, 129.24, 113.53, 72.07, 63.44, 54.92, 48.87, 33.66, 30.85, 18.12.

FAB Mass Spec: m/e 317 $[M+1]^+$, 274, 180.

Exact Mass: $[M + 1]^+$ = 317.16137 (calculated)

$[M + 1]^+$ = 317.1610 (measured).

IR (neat) cm^{-1}: 2940, 2040, 1610, 1570, 1510,1455, 1360, 1300, 1245, 1170, 1075, 1030, 810.



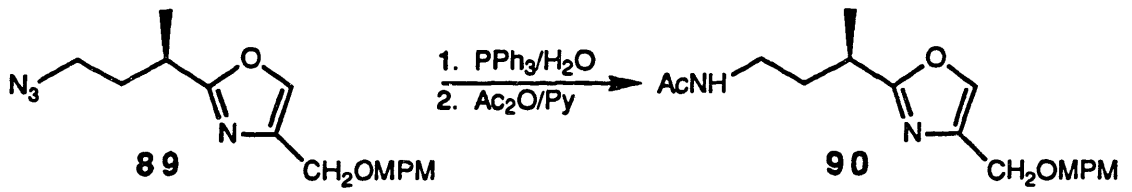
Amine, 63

The azide, **89**, (120.1 mg, 0.405 mmole) was dissolved in THF (8 mL) and PPh_3 (127.8 mg, 0.486 mmole) was added. The mixture was stirred at room temperature under argon for 10 hours, after which water (72.9 μL, 4.05 mmoles) was added. After stirring for an additional 12 hours, the reaction was concentrated to dryness and the residue was purified on silica gel (CH_2Cl_2/Et_3N 100/1 then $CH_2Cl_2/MeOH/Et_3N$ 9/1/0.1 then

CH_2Cl_2/MeOH/H_2O/Et_3N 75/22/3/1) to yield the amine (98.0 mg, 83%) as a colorless oil.

Physical Properties for 63

^1H NMR (250 MHz, C_6D_6): δ 7.24(s, 1H), 7.20(d, *J* = 6.67 Hz, 2H), 6.77(d, *J* = 6.74 Hz, 2H), 4.41(s, 2H), 4.40(s, 2H), 3.28(s, 3H), 2.94(sext, *J* = 7.47 Hz, 1H), 2.44(dd, *J* = 6.97 Hz, 2H), 1.79(sext, *J* = 8.07 Hz, 1H), 1.44(sext, *J* = 6.40 Hz, 1H), 1.17(d, *J* = 7.12 Hz, 3H), 0.88(s, 2H).



Acetamide, 90

The azide, 89, (125.0 mg, 0.396 mmole) was dissolved in THF (8 mL) and PPh_3 (124.5 mg, 0.475 mmole) was added. The mixture was stirred at room temperature under argon for 10 hours after which, water (71.2 μL, 3.956 mmoles) was added. After stirring for an additional 12 hours, pyridine (500 μL) was added followed by Ac_2O (100 μL). Stirring was continued for an additional 30 minutes, after which the reaction was concentrated to dryness and the residue was purified on silica gel (ethyl acetate) to yield the acetamide (125.3 mg, 97%) as a colorless oil.

Physical Properties for 90

R_f = .15 (ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51(s, 1H), 7.25(m, 2H), 6.85(m, 2H), 6.00(s, 1H), 4.52(s, 2H), 4.39(d, *J* = .98 Hz, 2H), 3.78(s, 3H), 3.35(m, 1H), 3.18(m, 1H), 3.09(m, 1H), 1.91(m, 2H), 1.90(s, 3H), 1.33(d, *J* = 7.01 Hz, 3H).

FAB Mass Spec: m/e 333 $[M+1]^+$, 153, 121.

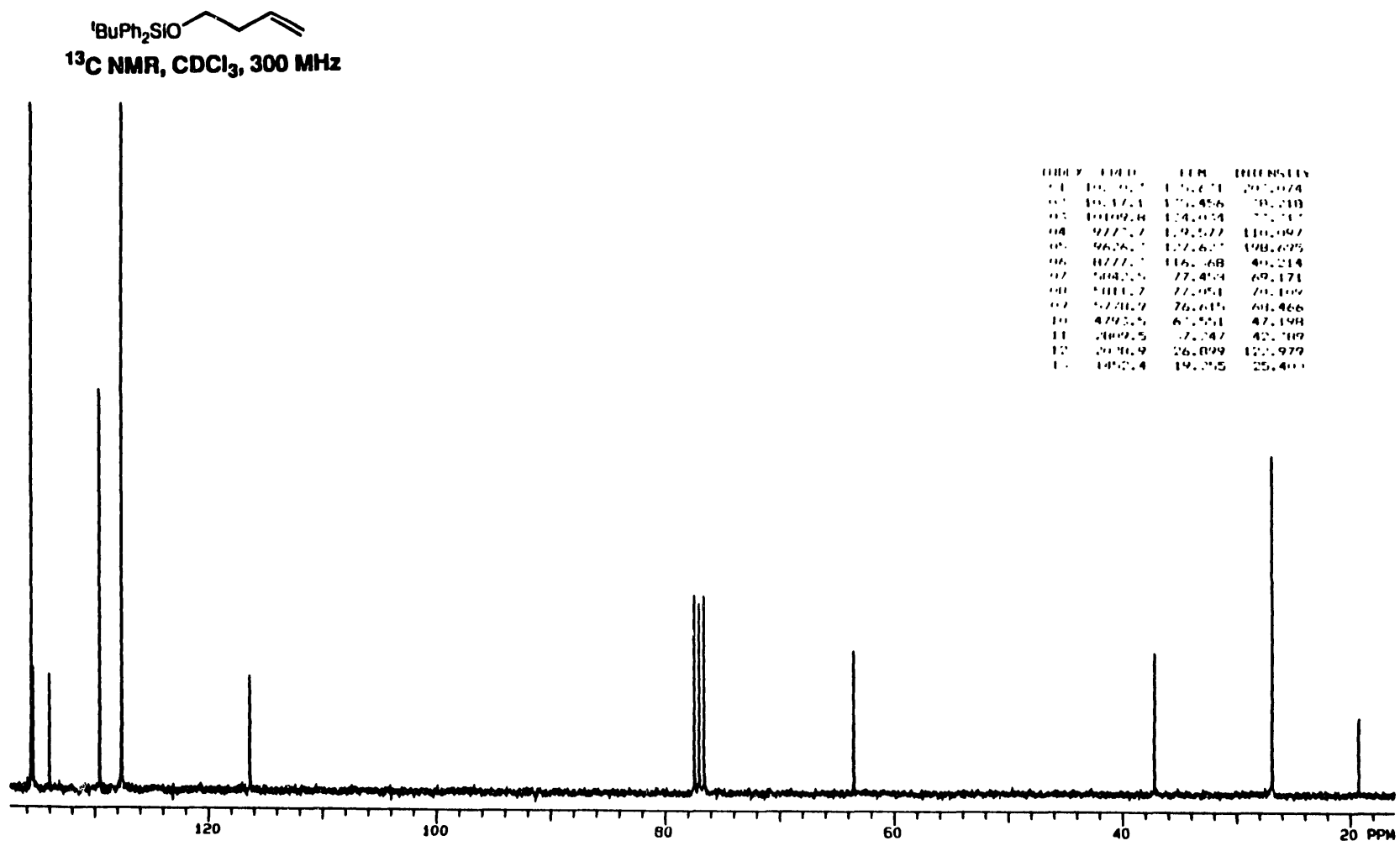
Exact Mass: $[M + 1]^+$ = 333.18143 (calculated)

$[M + 1]^+$ = 333.1812 (measured).

IR (neat) cm^{-1}: 3300, 3040 2925, 1650, 1620, 1550,1520, 1450, 1360, 1240, 1170, 1070, 1025, 810.

2.7 NMR Spectra

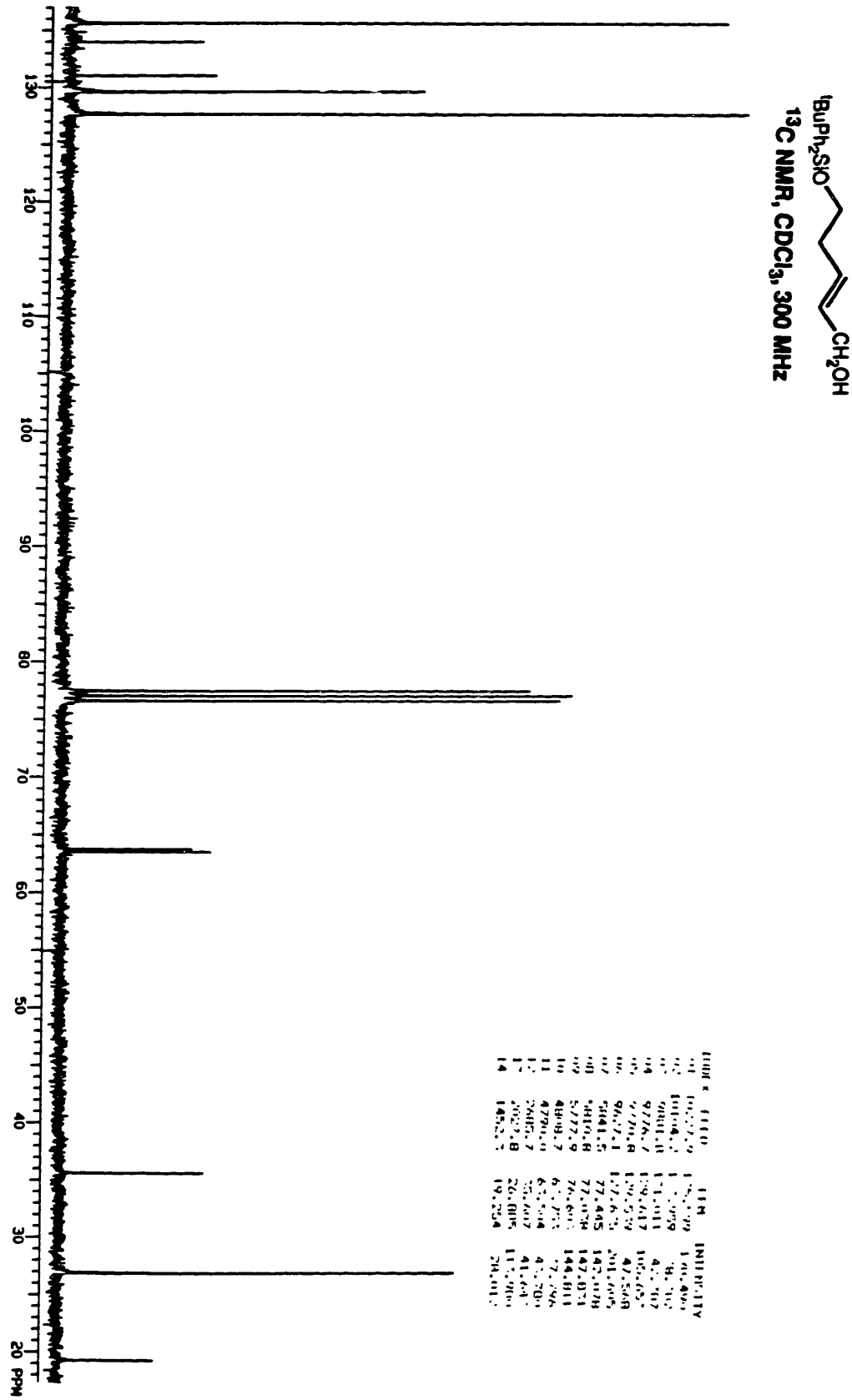
$^tBuPh_2SiO$
$CDCl_3$, 300 MHz
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


tBuPh2SiO
13C NMR, CDCl3, 300 MHz
120
100
80
60
40
20 PPM

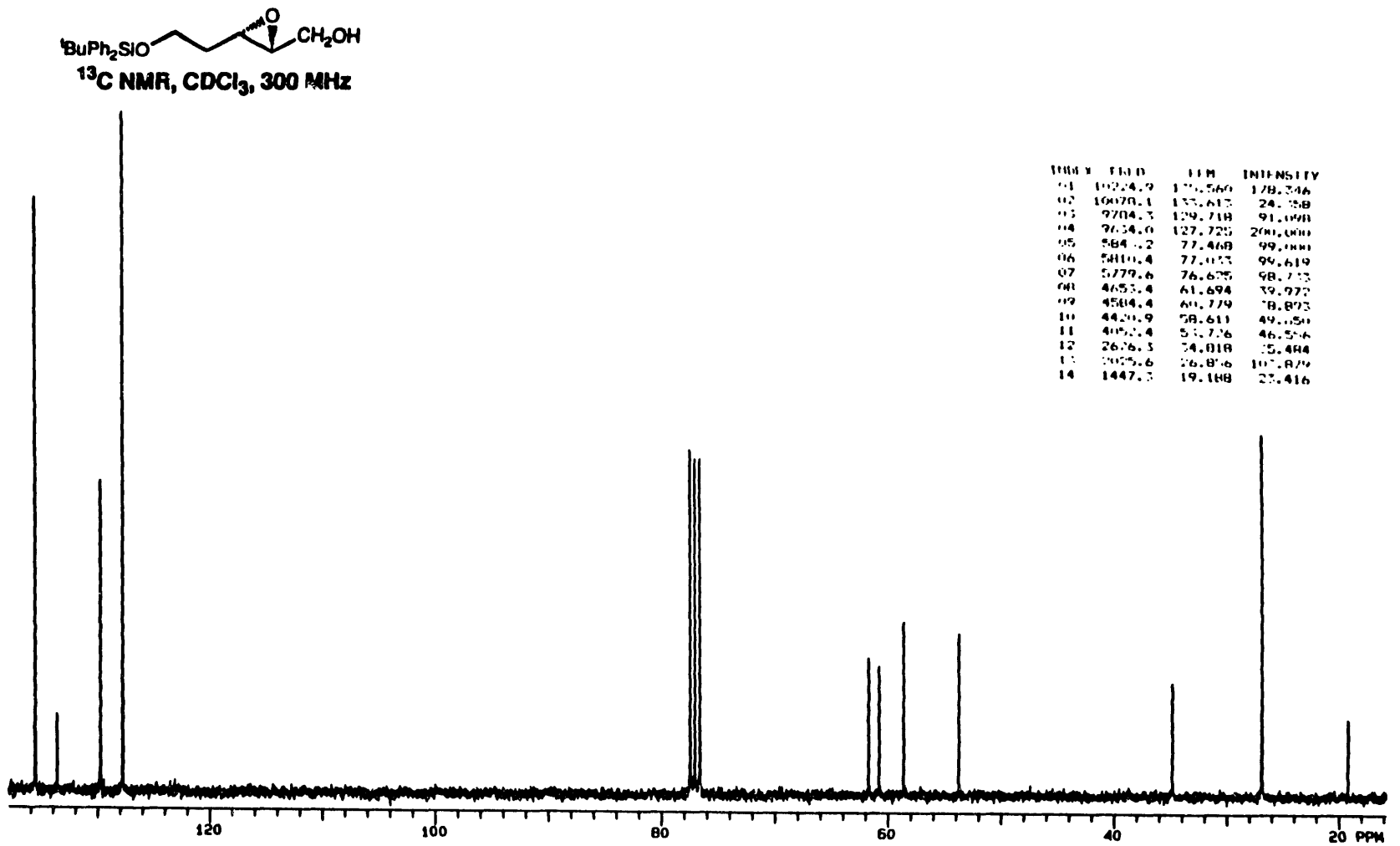
tBuPh2SiO
CO2Et
CDCl3, 300 MHz

$^{t}BuPh_2SiO$
CO_2Et
^{13}C NMR, $CDCl_3$, 300 MHz
160
140
120
100
80
60
40
20 PPM

tBuPh2SiO
CH2OH
CDCl3, 300 MHz
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm


tBuPh2SiO
CH2OH
13C NMR, CDCl3, 300 MHz
130
120
110
100
90
80
70
60
50
40
30
20
PPM

$^tBuPh_2SiO$
O
CH_2OH
$CDCl_3$, 300 MHz
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

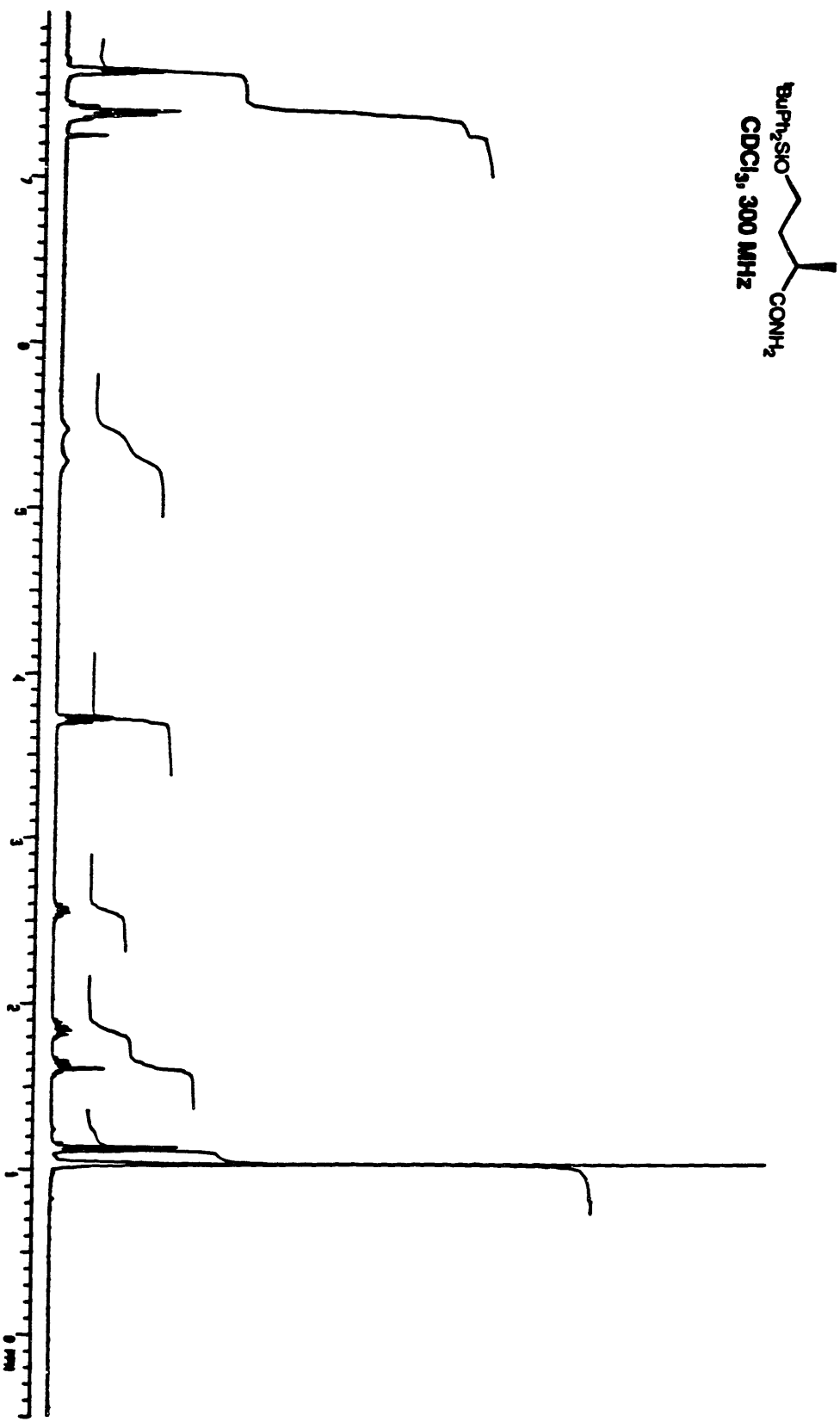

tBuPh2SiO
CH2OH
13C NMR, CDCl3, 300 MHz
120
100
80
60
40
20 PPM

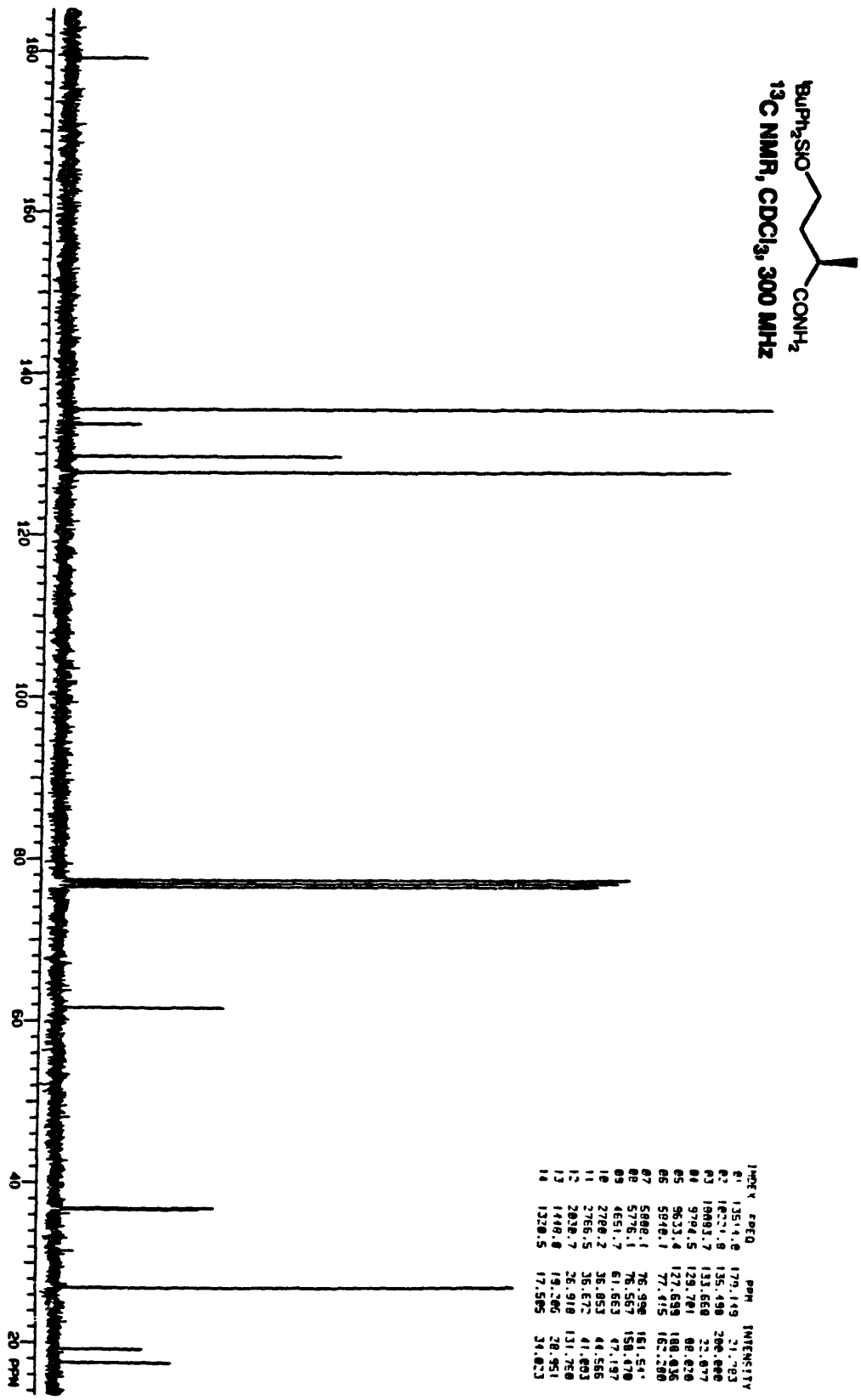
CDCl3, 300 MHz
tBuPh2SiO
OH
CH2OH

^{t}BuPh$_2$SiO
OH
CH$_2$OH
^{13}C NMR, CDCl$_3$, 300 MHz
120
100
80
60
40
20 PPM

$^tBuPh_2SiO$
$CDCl_3$, 300 MHz
CO_2H
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

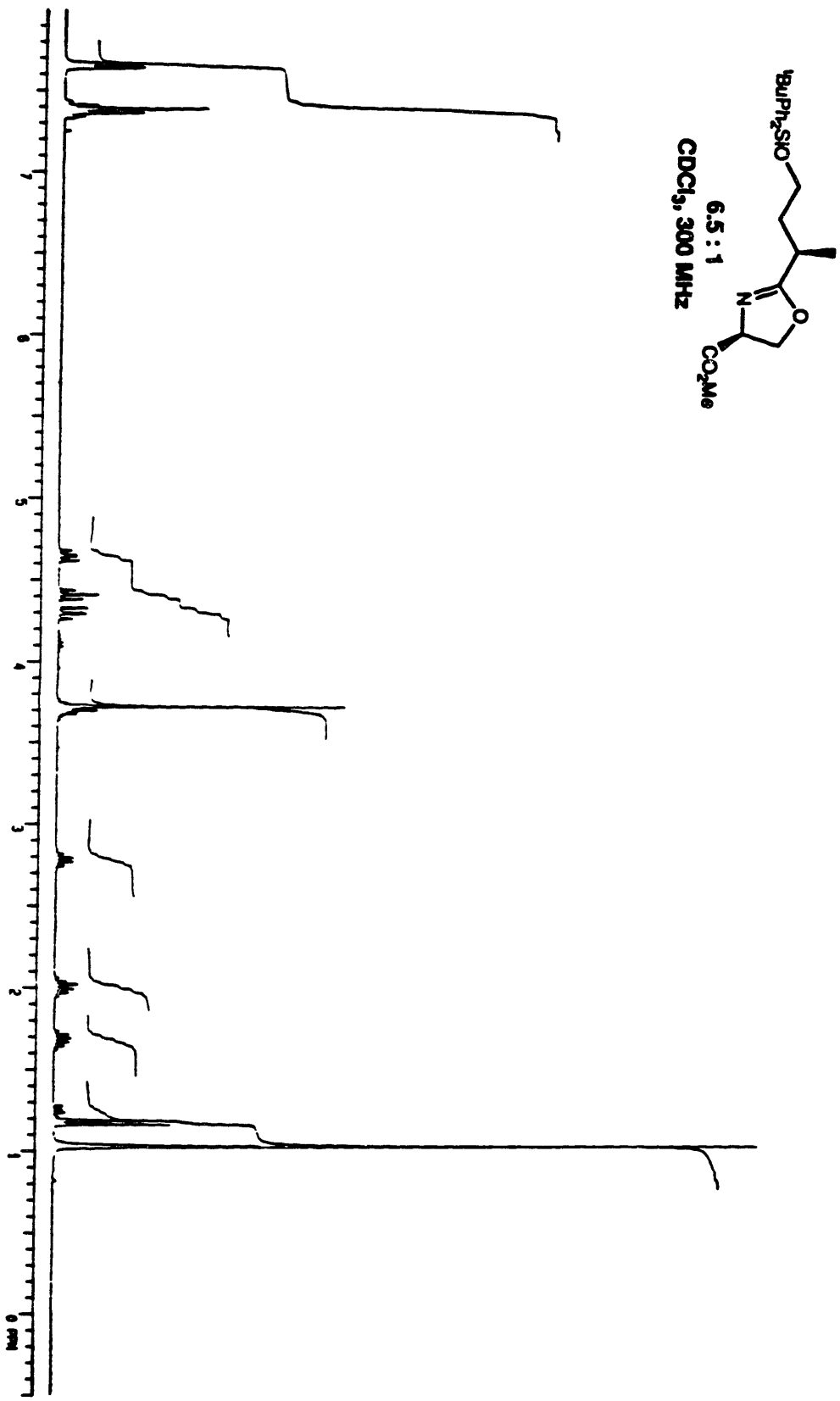
^{13}C NMR, $CDCl_3$, 300 MHz
^{t}BuPh$_2$SiO
CO$_2$H
180
160
140
120
100
80
60
40
20
PPM


tBuPh2SiO
CONH2
CDCl3, 300 MHz


tBuPh2SiO
CONH2
13C NMR, CDCl3, 300 MHz
160
140
120
100
80
60
40
20
PPM

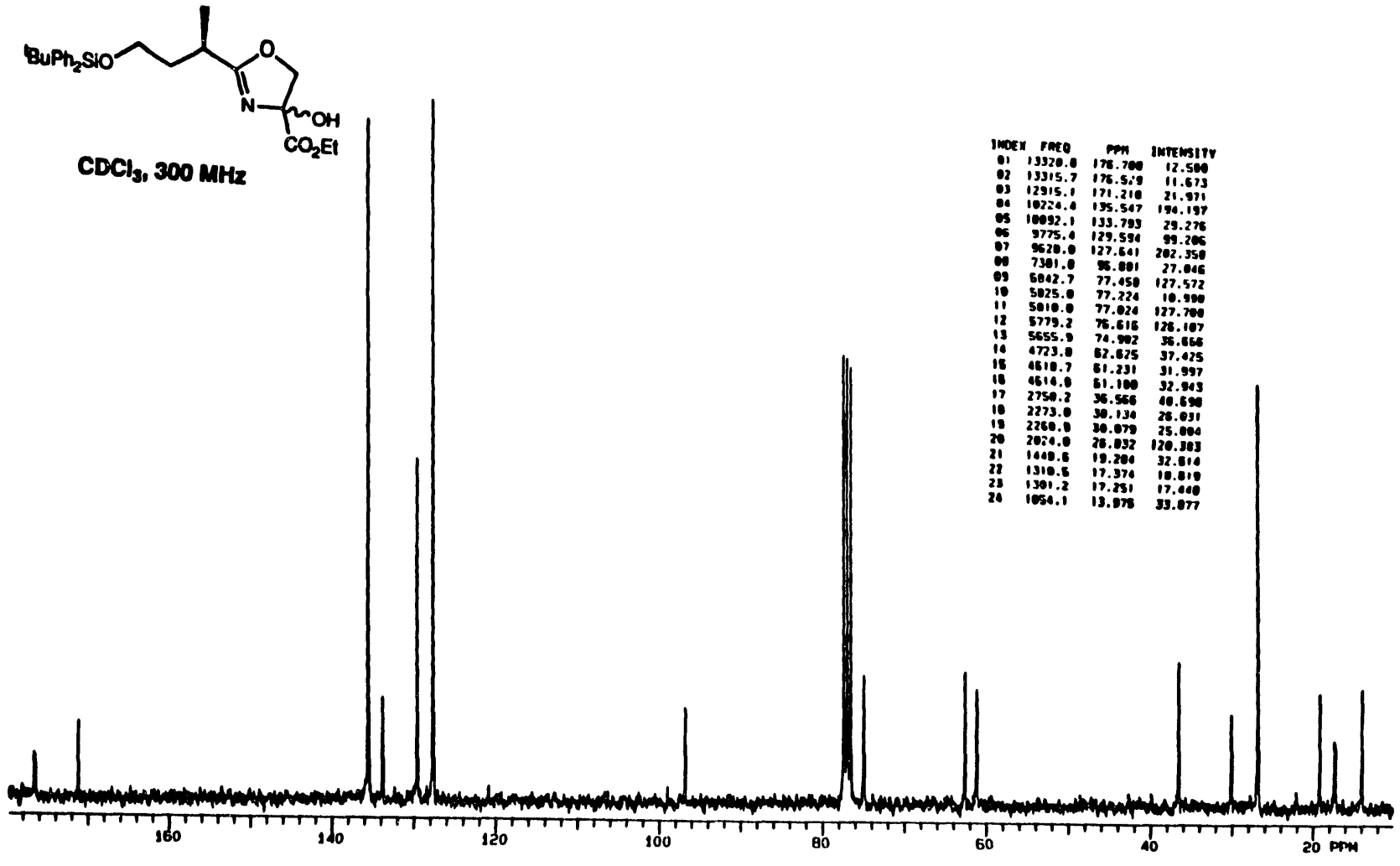
Racemic
$CDCl_3$, 300 MHz
$^tBuPh_2SiO$
N
O
CO_2Me

tBuPh2SiO
Racemic
CDCl3, 300 MHz
CO2Me
N
O
INDEX FREQ PPM INTENSITY
01 13155.1 174.327 23.960
02 12985.3 172.070 10.372
03 10241.0 135.722 104.644
04 10110.1 133.976 19.513
05 9789.4 129.727 98.983
06 9641.1 127.761 200.000
07 5946.0 77.470 53.905
08 5813.4 77.010 57.403
09 5781.2 76.610 52.957
10 5289.9 69.848 39.568
11 5123.6 67.896 27.915
12 4922.8 61.260 26.171
13 4760.8 52.155 35.564
14 2760.5 36.623 29.002
15 2741.5 36.330 26.767
16 2253.2 29.859 28.679
17 2241.1 29.698 21.157
18 2087.2 26.599 136.616
19 1427.7 18.915 35.679
20 1396.0 17.817 27.259
21 1382.1 17.255 23.700


6.5 : 1
CDCl3, 300 MHz
CO2Me
N
O
tBuPh2SiO

tBuPh2SiO
N
O
CO2Me
6.5 : 1
CDCl3, 300 MHz
INDEX FREQ PPM INTENSITY
01 13152.4 174.291 23.327
02 12982.3 172.038 10.100
03 10230.0 135.602 167.245
04 10106.0 133.959 22.687
05 9796.4 129.697 80.578
06 9630.4 127.725 200.000
07 9463.3 77.433 40.041
08 9011.0 77.095 46.673
09 8778.7 76.577 39.000
10 8706.4 69.958 63.398
11 8122.8 67.004 41.363
12 4620.1 61.220 47.027
13 3947.5 52.311 31.523
14 2758.0 36.294 44.709
15 2230.1 29.650 33.960
16 2080.2 28.550 130.261
17 1424.9 18.883 25.595
18 1290.5 17.222 49.794

CDCl3, 300 MHz
tBuPh2SiO
N
O
OH
CO2Et
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

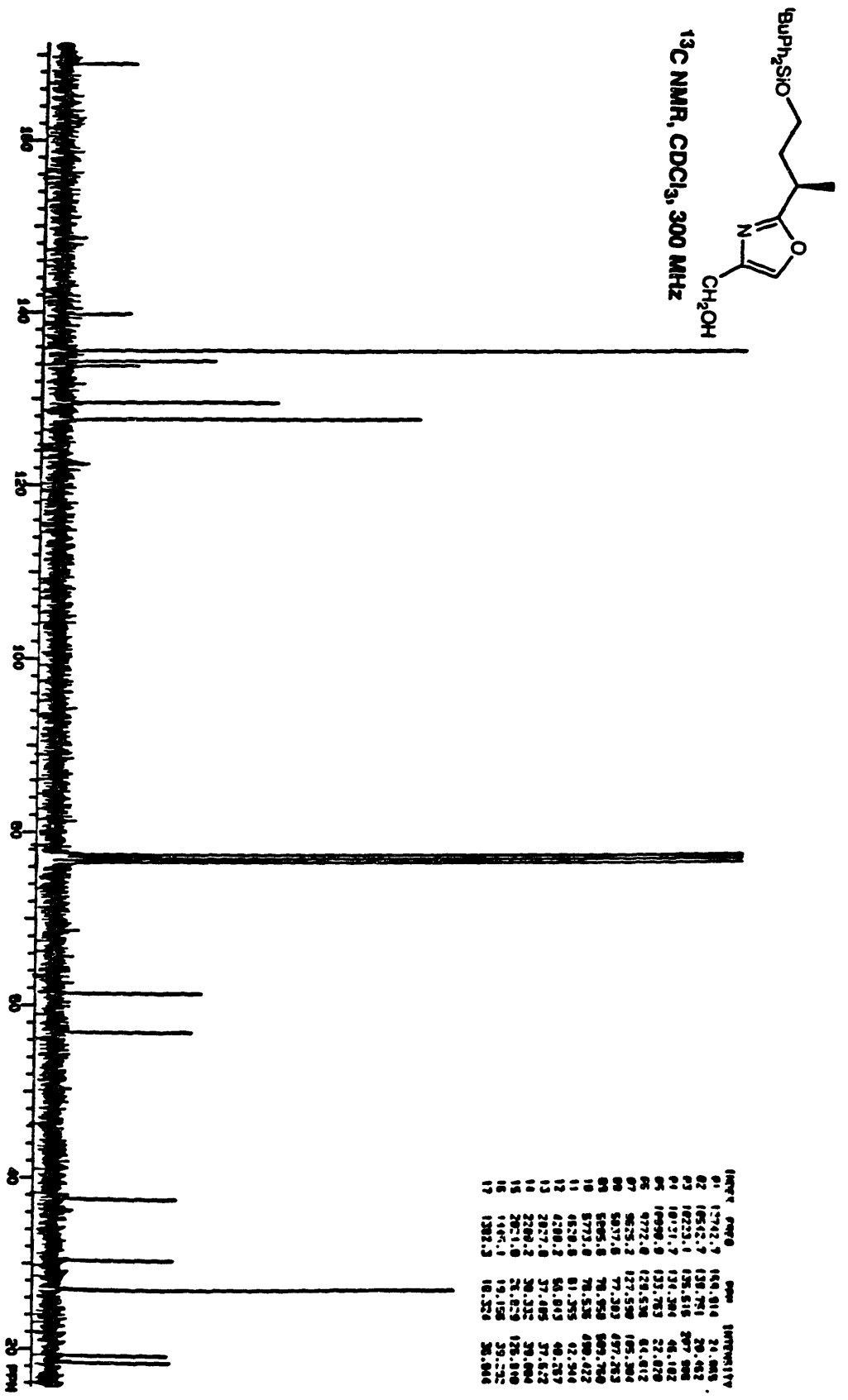


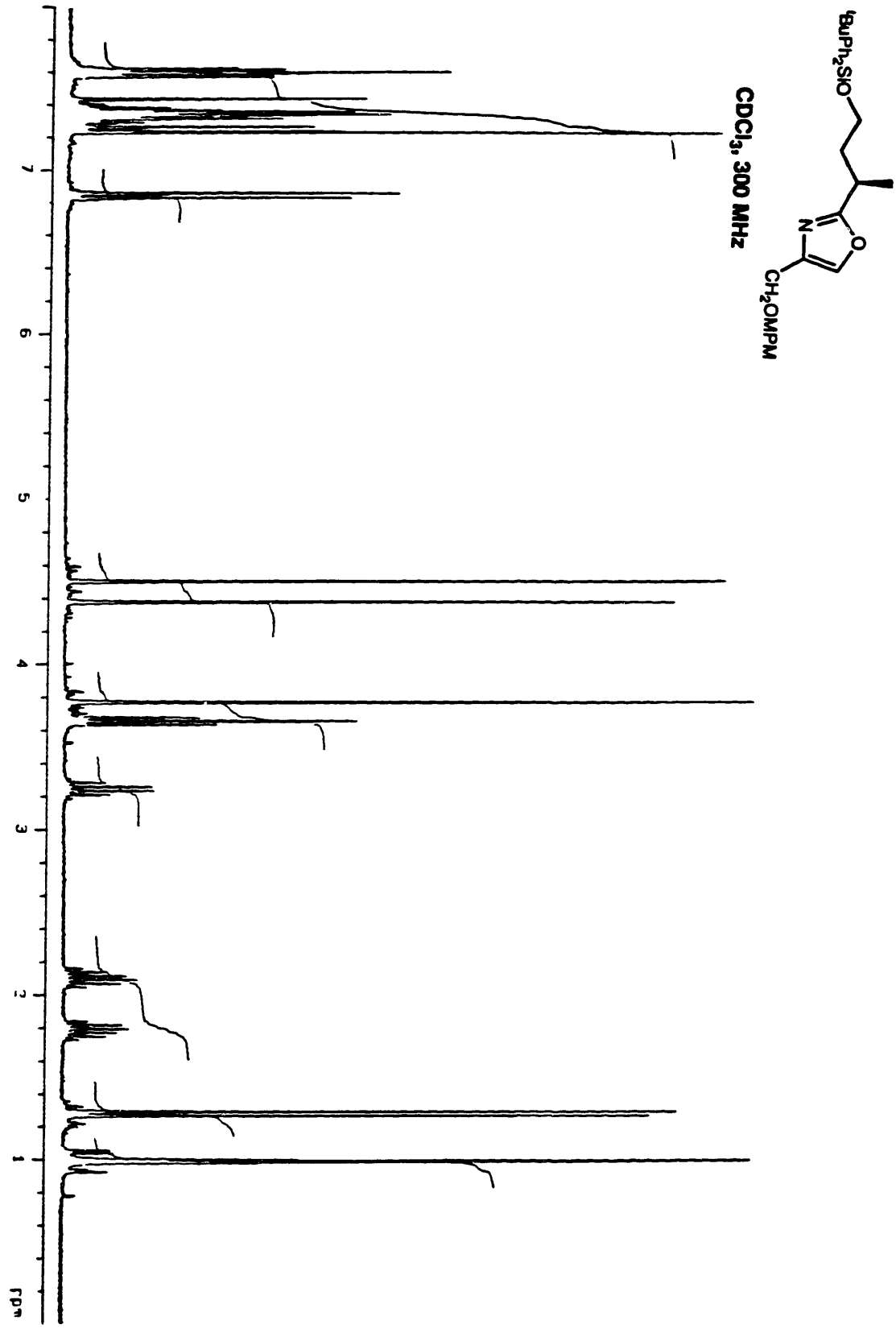
INDEX	FREQ	PPM	INTENSITY
01	13320.8	176.700	12.500
02	13315.7	176.579	11.673
03	12915.1	171.218	21.971
04	10224.4	135.547	194.197
05	10092.1	133.793	29.276
06	9775.4	129.594	99.206
07	9620.0	127.641	202.350
08	7381.0	98.881	27.046
09	6842.7	77.458	127.572
10	5825.0	77.224	10.990
11	5810.0	77.024	127.700
12	5779.2	76.616	126.107
13	5655.9	74.982	36.666
14	4723.0	62.675	37.425
15	4610.7	61.231	31.997
16	4614.0	61.100	32.943
17	2750.2	36.566	40.690
18	2273.0	30.134	26.031
19	2260.8	30.079	25.004
20	2024.0	26.932	120.383
21	1440.6	19.204	32.814
22	1310.5	17.376	18.819
23	1301.2	17.251	17.440
24	1054.1	13.978	33.077

$^tBuPh_2SiO$
N
O
CO_2Et
$CDCl_3$, 300 MHz
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0 PPM
0.0

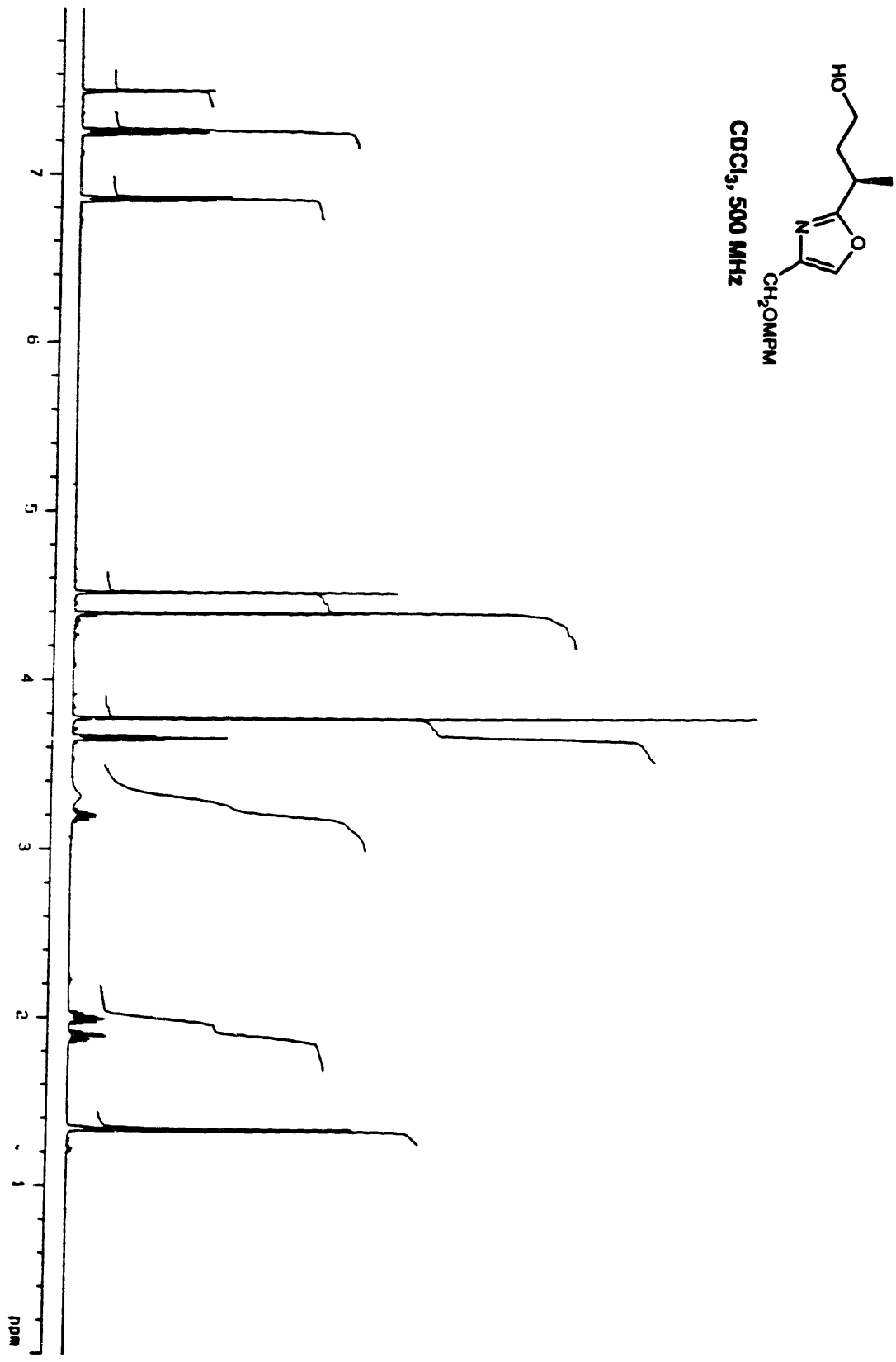
^{13}C NMR, $CDCl_3$, 300 MHz
$^tBuPh_2SiO$
N
O
CO_2Et
160
140
120
100
80
60
40
20 PPM

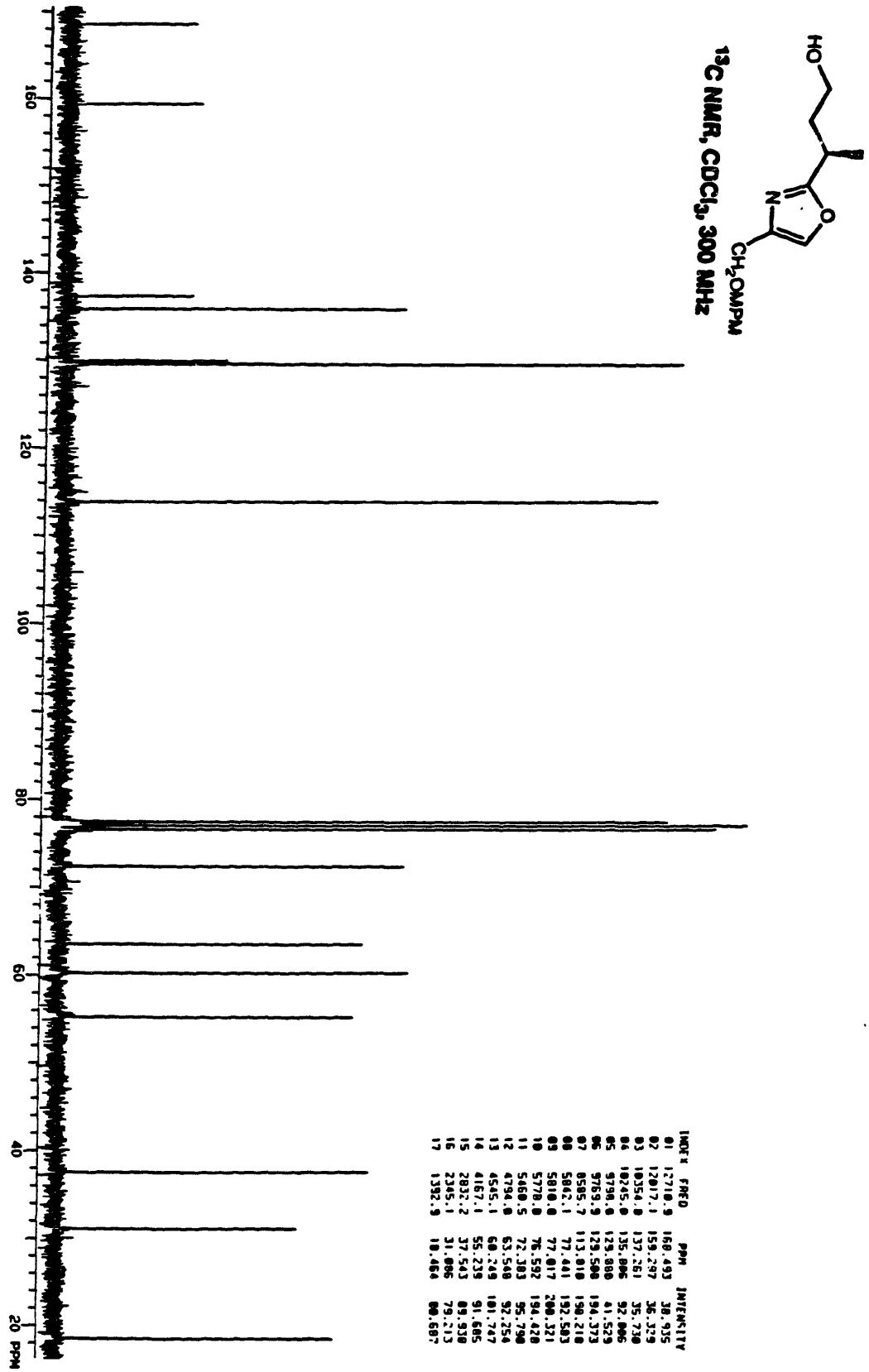
CDCl3, 300 MHz
tBuPh2SiO
N
O
CH2OH
0.0
1.0 PPM
2.0
3.0
4.0
5.0
6.0
7.0
8.0


^{13}C NMR, $CDCl_3$, 300 MHz
$^tBuPh_2SiO$
N
O
CH_2OH

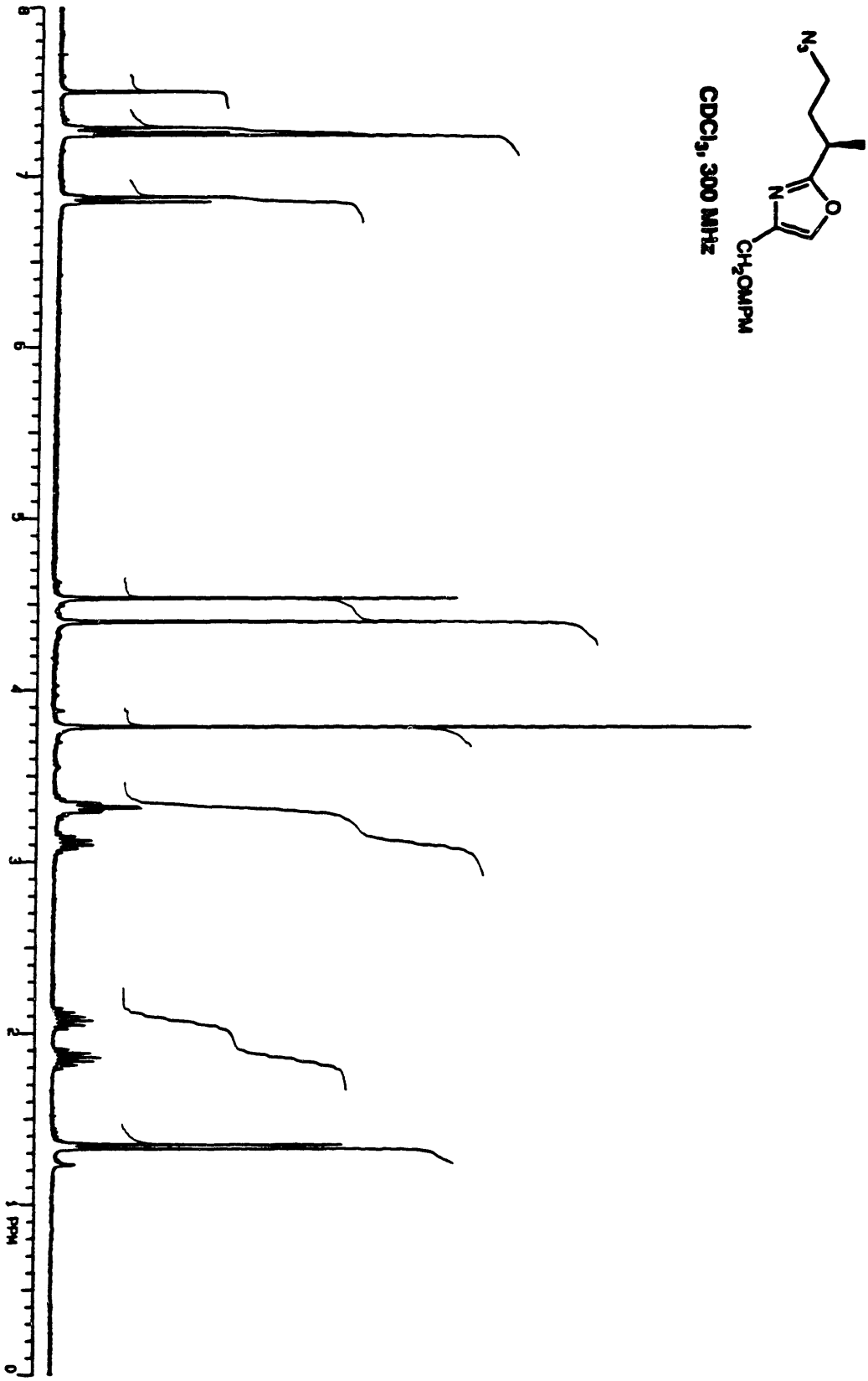

CDCl3, 300 MHz
tBuPh2SiO
N
O
CH2OMPM
ppm
7
6
5
4
3
2
1

^{13}C NMR, CDCl$_3$, 300 MHz
^{t}BuPh$_2$SiO
N
O
CH$_2$OMPM
160
140
120
100
80
60
40
20
PPM


CDCl3, 500 MHz
HO
N
O
CH2OMPM
PPM
1
2
3
4
5
6
7

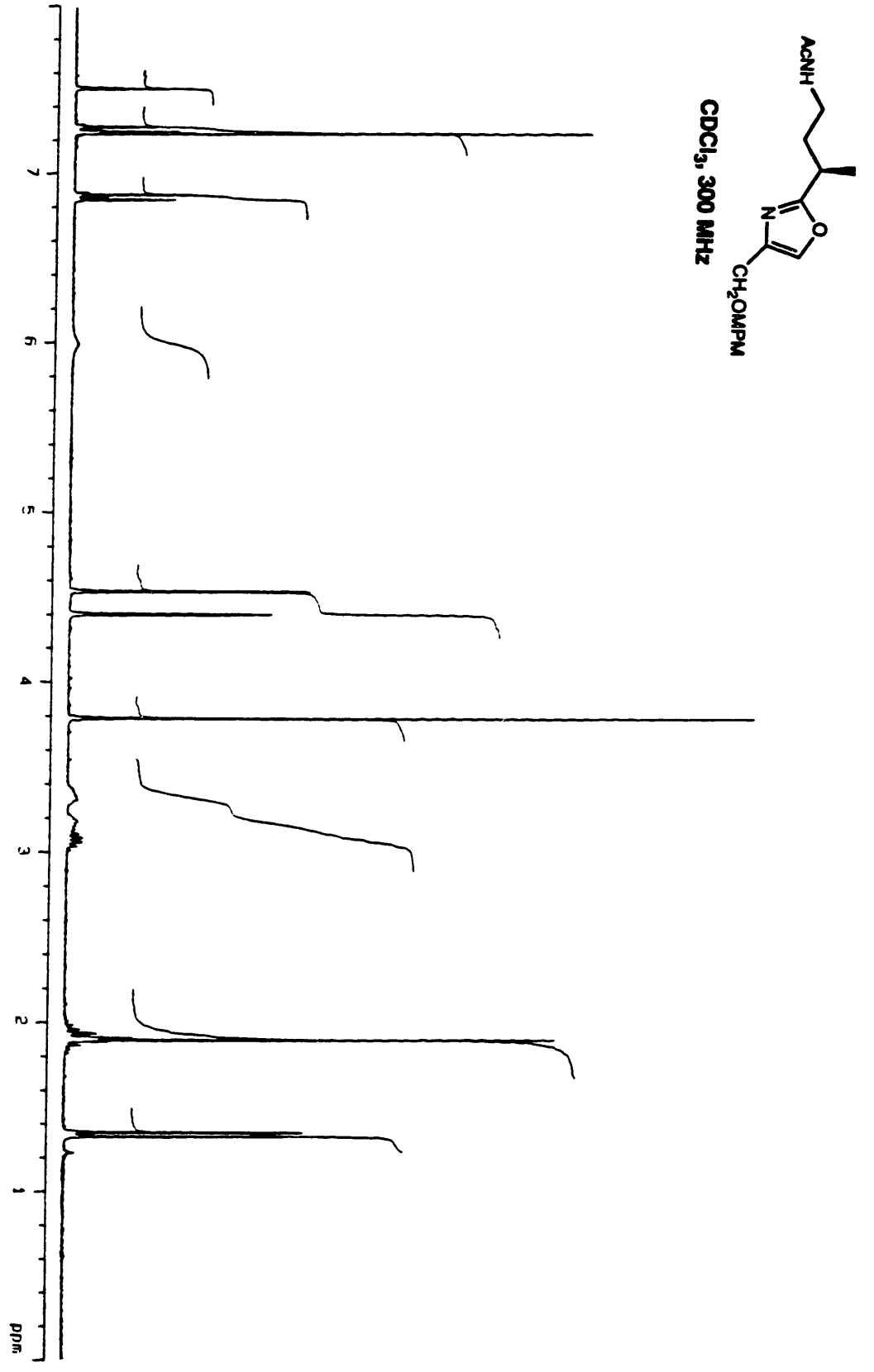


INDEX	FREQ	PPM	INTENSITY
01	12710.9	160.493	38.935
02	12017.1	159.297	36.329
03	10354.0	137.261	35.730
04	10245.0	135.896	92.006
05	9798.0	129.880	41.529
06	9769.9	129.508	194.373
07	8585.7	113.818	196.210
08	5842.1	77.441	192.583
09	5810.0	77.017	200.321
10	5778.0	76.592	194.420
11	5468.5	72.303	95.790
12	4794.0	63.568	92.254
13	4595.1	60.249	101.747
14	4187.1	55.239	91.685
15	2832.2	37.543	89.930
16	2395.1	31.896	79.213
17	1392.9	18.464	80.687


CDCl3, 300 MHz
CH2OMPM
N3
N
O
ppm
0
1
2
3
4
5
6
7
8

^{13}C NMR, $CDCl_3$, 300 MHz
CH_2OMPM
N_3
N
O
160
140
120
100
80
60
40
20
PPM

C_6D_6, 250 MHz
CH_2OMPM

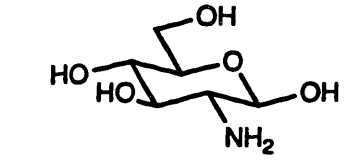

AcNH
N
O
CH2OMPM
CDCl3, 300 MHz
7
6
5
4
3
2
1
ppm

Chapter 3:

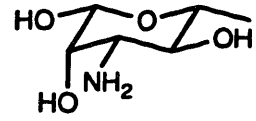
Fragment C2

3.1 Introduction

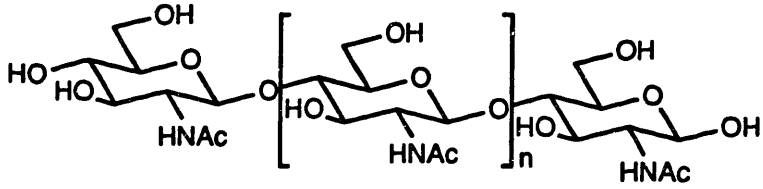
Figure 3.1



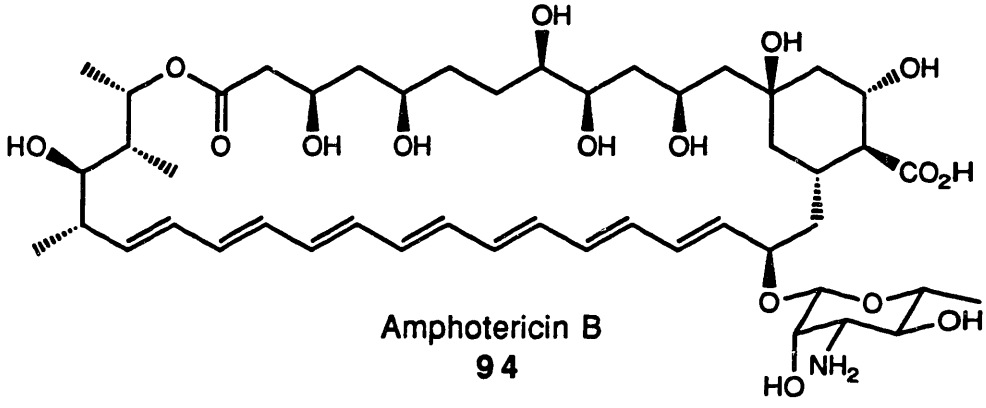
2-Amino-2-Deoxyglucose
Glucosamine
91



3-Amino-3-Deoxyrhammose
Mycosamine
92



Chitin
93



Amphotericin B
94

Amino sugars have presented themselves in the chemistry of natural products through a variety of ways. They appear as components of biopolymers such as glucosamine, **91**, in chitin, **93**,[95,96,97] and as side groups such as mycosamine, **92**, in amphotericin B, **94**,[98,99,100] (Figure 3.1). Consequently, both amino sugars and natural products containing subfragments of similar structure have gained much attention from synthetic organic chemists. In the case of calyculin A, this similarity is apparent when comparing fragment C2 to 4-amino-4-deoxyribonic acid.

Strategies used to synthesize carbohydrates and their derivatives include the utilization of chiral pool starting materials such as amino acids, as well as the derivitization of readily available carbohydrates. In our search for an efficient method for the preparation of fragment C2, we have explored three major strategies. These strategies will be discussed in this chapter.

3.2 Strategy 1: D-Serine as the Starting Material

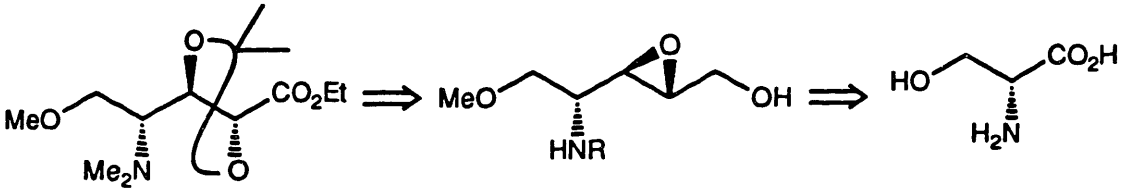
Upon examining the structure of fragment C2, D-serine can immediately be identified as a viable starting material for its preparation. This section will describe our study of this strategy.

3.2.1 Retrosynthetic Analysis

In our initial retrosynthetic analysis for fragment C2, **95** (Scheme 3.1), we envisioned the target arising from the epoxy alcohol, **96**, *via* a Payne rearrangement[101] followed by standard protecting group methodology. The epoxy alcohol, **96**, was envisioned to arise from a Wittig homologation of the aldehyde derived from reduction of *d*-serine, **97**, followed by a Sharpless asymmetric epoxidation.[77]

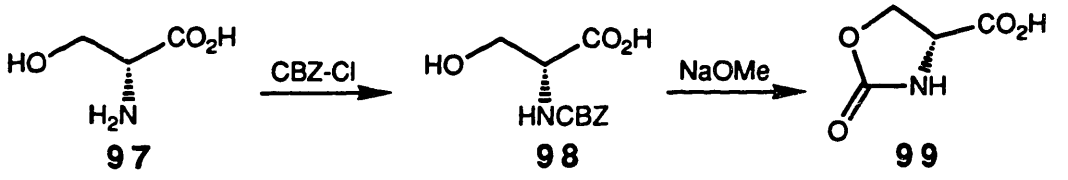
Although the use of D-serine, **97**, had the advantage of possessing the amine functionality with its necessary stereochemistry there were some problems inherent to this strategy. Among these problems were finding a protecting group for the amine which was fully compatible with the reaction sequence, and also performing a Sharpless asymmetric epoxidation in the presence of this functional group. In spite of these potential drawbacks, we initially approached the preparation of fragment C2, **95**, utilizing this strategy.

Scheme 3.1

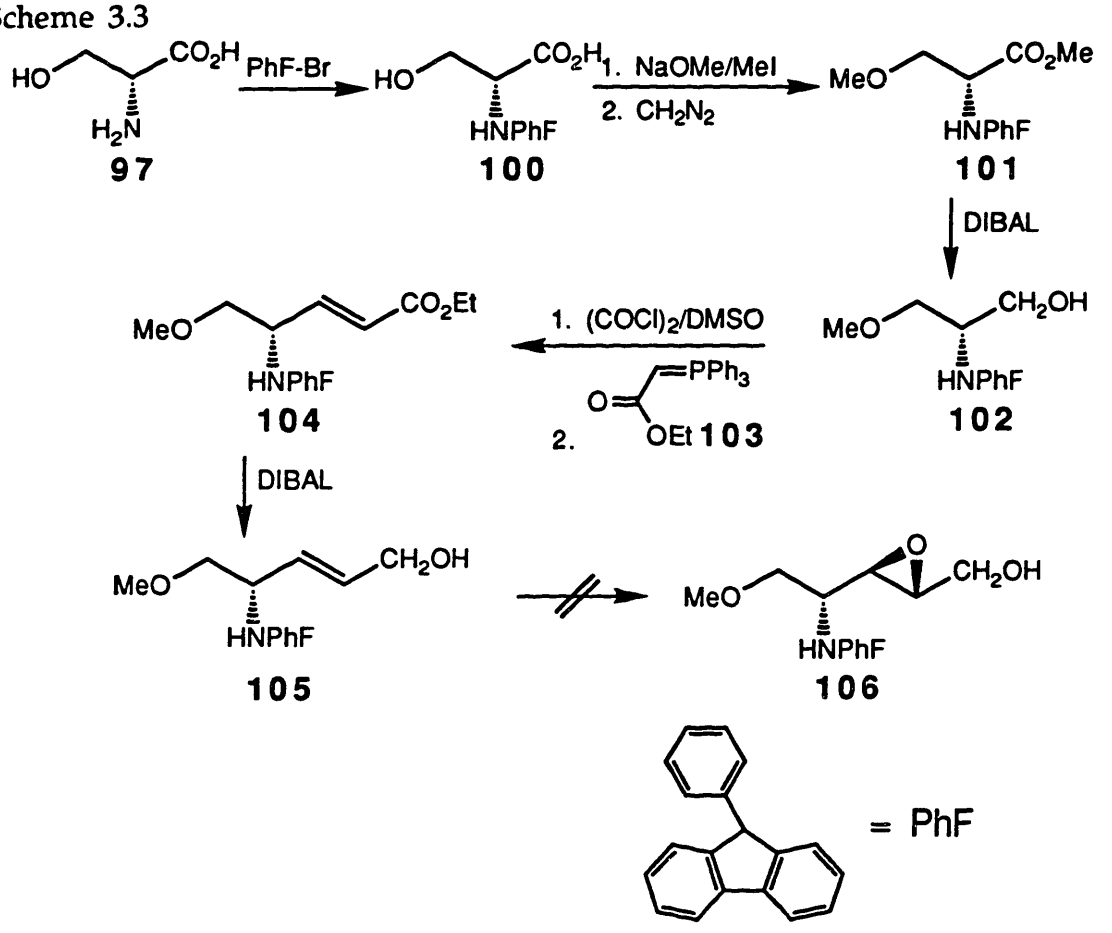


3.2.2 D-Serine Results

Scheme 3.2



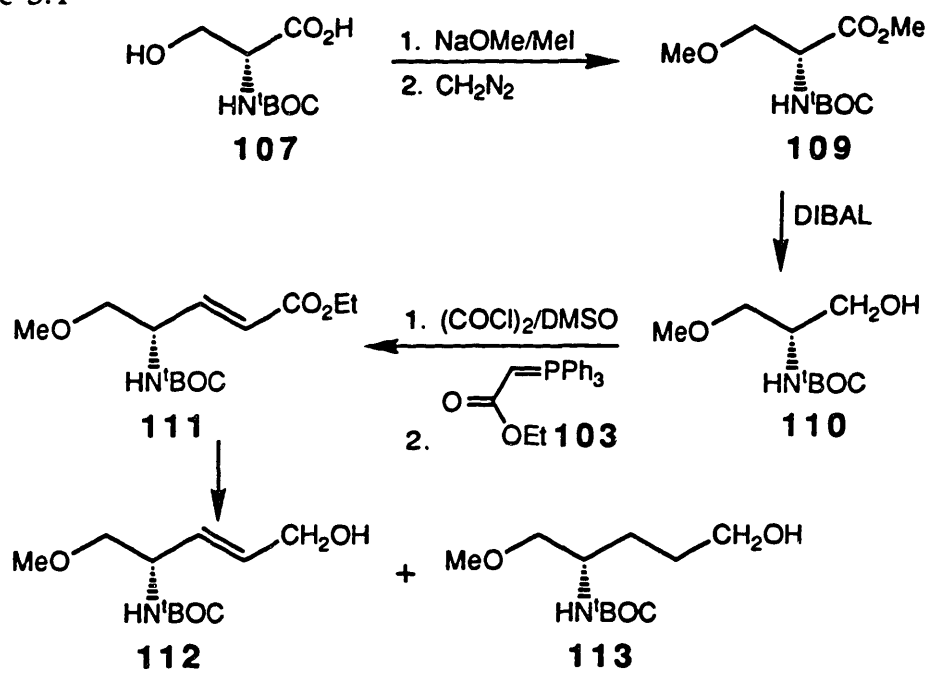
Scheme 3.3



Using D-serine, **97**, as the starting material for fragment C2, **95**, our first task was to see that the amine was suitably protected. Although similar chemistry was known with N-^{t}BOC-serine, we decided to begin our study with the CBZ protecting group.

Formation of N-CBZ-D-serine, **98**, was easily achieved in 55% yield. Unfortunately, we were unable to methylate the oxygen using conditions developed by Benoiton for N-^{t}BOC-serine,[102] possibly due to formation of the oxazolidone, **99** (Scheme 3.2). Therefore, still desiring a protecting group containing a chromophore, we turned to the 9-phenylfluorenyl protecting group.[103]

Scheme 3.4



As shown in Scheme 3.3, treatment of D-serine, **97**, with 9-phenylfluorenylbromide[103] afforded the protected amino acid (63% yield). Treatment of the resulting 9-phenyl fluorenyl-D-serine, **100**, with sodium

methoxide and methyl iodide,[102] followed by diazomethane yielded **101** (45% yield, two steps). The ester was then reduced to the alcohol, **102**, on treatment with DIBAL (50% yield). Ireland's Swern-Wittig combination[104] was then applied to produce the desired α,β-unsaturated ester, **104** (79% yield). Reduction to the allylic alcohol, **105**, was then accomplished on treatment with DIBAL (97% yield). Unfortunately, at this stage, all attempts to form **106** failed. This was presumably due to the size of the 9-phenylfluorenyl protecting group. The construction of space filling molecular models demonstrated that this protecting group completely covered the double bond thus blocking the approach of any reactive agents.

In lieu of extending the length of this relatively inefficient strategy by adding deprotection and reprotection steps, we opted to utilize D-serine, **97**, with one more protecting group as shown in Scheme 3.4. ^{t}BOC-D-serine, **107**, was converted, in 48% yield, to the methyl ether, **108**. The ether was then converted to the methyl ester, **109**, in 79% yield on treatment with diazomethane. Reduction to the alcohol, **110**, was accomplished in 95% on reaction with DIBAL, and the subsequent Swern-Wittig combination[104] produced a 49% yield of the α,β-unsaturated ester, **111**. Unfortunately, at this stage, we were unable to reduce the ester to the allylic alcohol, **112**, in any yield greater than 20%. The major product was consistently the fully reduced alcohol, **113**. Therefore, due to the relatively low yields and protecting group problems, we chose to abandon this strategy in favor of one in which the amine is introduced at a later stage in the synthesis.

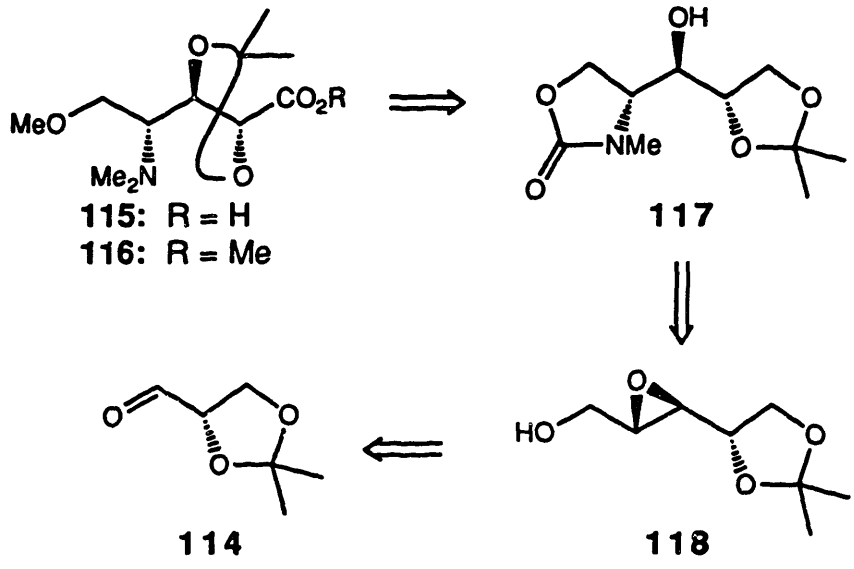
3.3 Strategy 2: (*S*)-Isopropylidine Glyceraldehyde as the Starting Material

When re-evaluating our strategy towards fragment C2, we realized that instead of building from left to right using D-serine, **97**, we could build

from right to left utilizing (*S*)-isopropylidine glyceraldehyde, **114**. This section will describe our exploration of this strategy.

3.3.1 Retrosynthetic Analysis

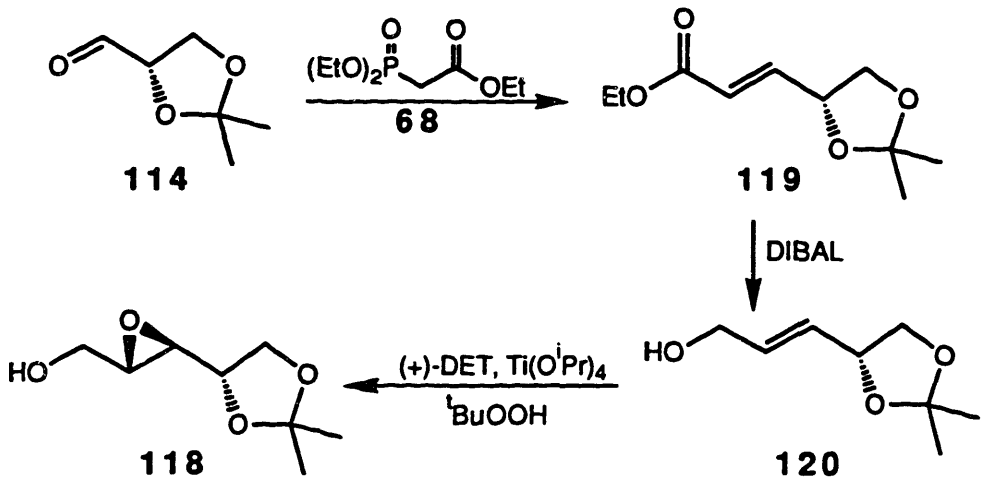
Scheme 3.5



As shown in Scheme 3.5. We had envisioned obtaining fragment C2 in the form of the acid, **115**, or the methyl ester, **116**, from the carbamate, **117**. The carbamate, **117**, was to be derived from the epoxy alcohol, **118**, which is readily available from (*S*)-isopropylidine glyceraldehyde, **114**. The main advantage inherent in this route is a well documented strategy for the incorporation of the amine functionality at a late stage in the synthesis.[106] The main disadvantage involves problems associated with performing oxidations in the presence of amines. Fortunately, such oxidations had been ducumented utilizing platinum catalysts[108] and we decided to procede with this strategy.

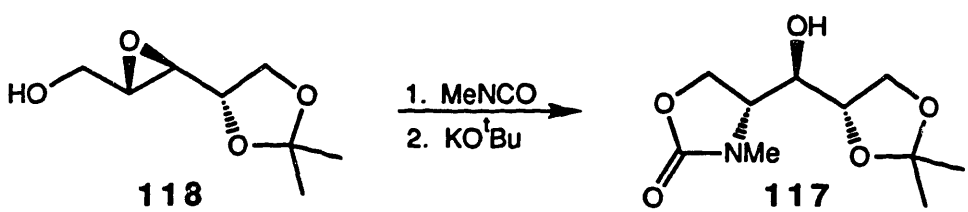
3.3.2 The Carbamate, 117

Scheme 3.6



En route to the carbamate, **117**, we first needed to obtain the epoxide, **118**. As shown in Scheme 3.6, this was accomplished beginning with (*S*)-isopropylidine glyceraldehyde, **114**.[105] Treatment of **114** with triethylphosphonoacetate, **68**, produced the α,β-unsaturated ester, **119**, in 73% yield. Reduction of the ester with DIBAL produced a 96% yield of the allylic alcohol, **120**. Finally, conversion of the allylic alcohol, **120**, to the epoxide, **118**, was accomplished in 87% yield utilizing the Sharpless asymmetric epoxidation.[77]

Scheme 3.7

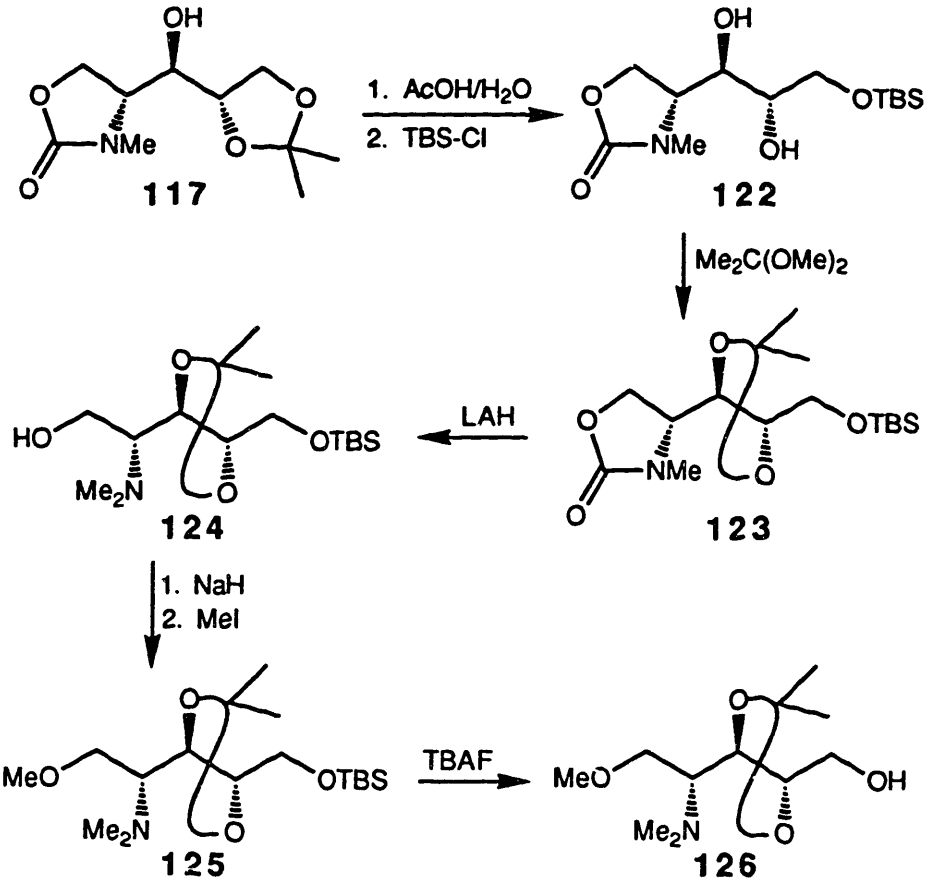


As shown in Scheme 3.7, preparation of the carbamate, **117**, was accomplished by conversion of the epoxy alcohol, **118**, to the open chain

methyl carbamate, **121** (87% yield), on treatment with methyl isocyanate.[106] Treatment of **121** with potassium *tert*-butoxide[107] effected cyclization with ring opening of the epoxide to form the cyclic carbamate, **117**, in 78% yield.

3.3.3 Attempts at the Completion of Fragment C2

Scheme 3.8



As shown in Scheme 3.8, the acetonide, **117**, was hydrolyzed with aqueous acetic acid, and the crude triol was selectively silylated at the primary position with *tert*-butyldimethylchlorosilane. This two step sequence produced the diol, **122**, in 93% overall yield.

Conversion of the diol, **122**, to the acetonide, **123**, was accomplished in 97% yield on treatment with 2,2-dimethoxypropane in the presence of

catalytic camphorsulphonic acid. The dimethyl amine, **124**, was then formed in 90% yield on reduction of the carbamate with LAH. The resulting primary alcohol was then converted to the methyl ether, **125**, in 72% yield on treatment with MeI and NaH. Finally, the silyl group was removed in 94% yield on treatment with tetrabutylammonium fluoride, thus forming the primary alcohol, **126**.

Scheme 3.9

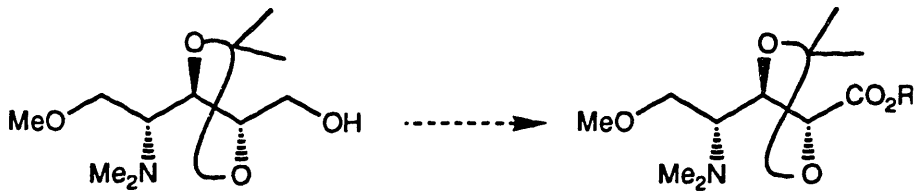
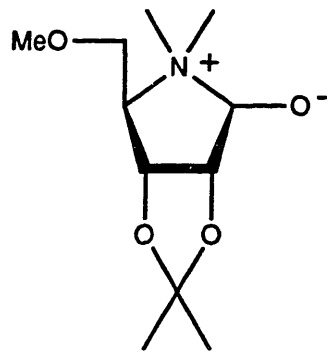


Figure 3.2



At this stage, the completion of fragment C2 rested on our ability to convert the amino alcohol, **126**, to the corresponding amino acid, **115**, or amino ester, **116**, as shown in Scheme 3.9. One method used for the oxidation of amino sugars to amino uronic acids involves the use of molecular oxygen in the presence of a platinum catalyst.[108] Unfortunately,

when we applied this method to our dimethylamino alcohol, we found that the reaction conditions demethylated the amine.[109,110] With this disappointing result, we set out to try a variety of other oxidation methods.

When we attempted the Swern oxidation,[93] our initial results seemed promising in that the crude product mixture could be converted back to starting material on treatment with $NaBH_4$. However, the reaction never proceeded beyond 50% completion and the highly polar nature of the product made purification by chromatography impossible even in the most polar solvent systems. Consequently, we saw an even greater need for an oxidation that would give a clean reaction in near quantitative yields. Therefore, we studied the recently reviewed TPAP oxidation,[111] the use of PDC,[112] the SO_3/pyridine/DMSO oxidation,[113] and the use of the Dess-Martin periodinane reagent.[114] Unfortunately, none of these methods produced the desired product as observed by the crude ^1H NMR spectra. Furthermore, no reaction was observed when $AgCO_3$/Celite[115] was used. However, when DCC/DMSO[116] was used, we observed a set of completely new peaks in the ^1H NMR. Unfortunately, the reaction was not clean enough to allow any definitive conclusions. Therefore, we attempted the use of acetic anhydride/DMSO[117] and the use of TFAA/DMSO.[118] Where the former only acylated the alcohol, the latter produced a compound which could be purified by maintaining the crude reaction mixture under vacuum for long periods of time. The yields were approximately 50% and no aldehyde peaks were apparent in the ^1H NMR. However, the spectrum was consistent with **127** (Figure 3.2) in which the amine had added to the aldehyde to produce an ammonium salt.[119] This is also consistent with our ability to reduce the product back to the alcohol, **126**. Unfortunately, we were unable to oxidize this product to the acid, **115**. Furthermore, treatment

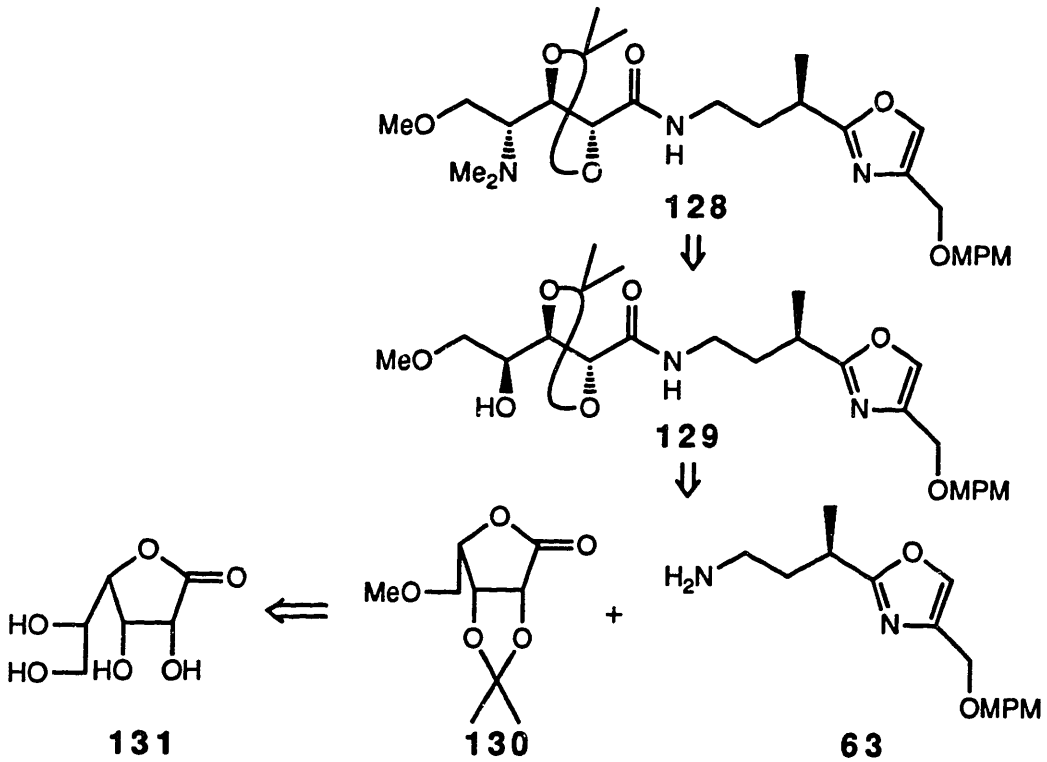
of **127** with *N*-iodosuccinimide in methanol[120] failed to give the methyl ester, **116**. Therefore, we felt it was time to reevaluate our synthetic strategy.

3.4 Strategy 3: D-Gulonolactone as the Starting Material

Our first strategy to fragment C2 demonstrated that the introduction of the amine at a late stage was necessary, and the second strategy showed that a late stage oxidation would not work. With these results, we chose to incorporate a starting material that was already in the proper oxidation state for fragment C2. This starting material was D-gulonolactone, **131**, and had the added advantage of possessing two of the three necessary stereocenters. With the understanding that the third stereocenter required inversion, we began an exploration of this strategy. This section will describe our results.

3.4.1 Retrosynthetic Analysis

Scheme 3.10

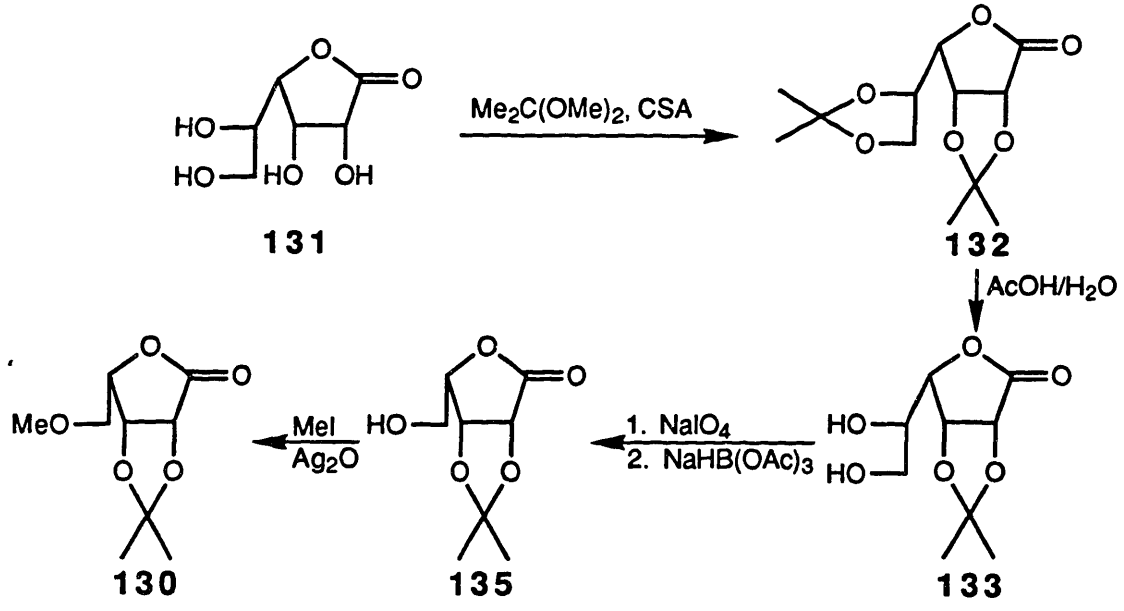


As shown in Scheme 3.10, we envisioned the completion of fragment C, **128**, by inverting the alcohol on **129** with a nitrogen nucleophile and elaborating the nitrogen to the dimethylamino group. The alcohol, **129**, was to come from ring opening of the lactone, **130**, with fragment C1, **63**. The lactone, **130**, was available in five steps from D-gulonolactone, **131**.[121,122]

3.4.2 The Lactone

Our preparation of the lactone, **130**, shown in Scheme 3.11, began with the convertion of D-gulonolactone, **131**, to its bis-acetonide, **132** (80% yield), on treatment with dimethoxypropane and camphorsulphonic acid. The bis-acetonide, **132**, was then hydrolyzed to the diol, **133**, in 87% yield as described by Jones.[121] The diol, **133**, was then converted to the aldehyde, **134**, on treatment with $NaIO_4$, and the aldehyde was reduced to the alcohol, **135**, with $NaHB(OAc)_3$ (79%, two steps). Methylation to **130** was accomplished on treatment with methyl iodide and silver oxide (83% yield).[122]

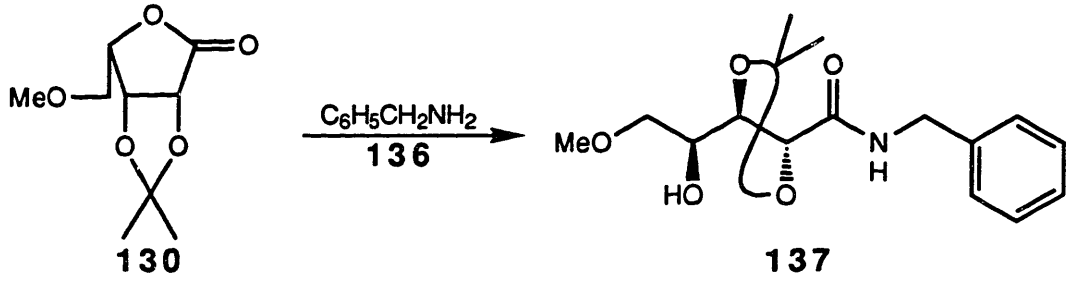
Scheme 3.11



3.4.3 The Hydroxyamide

At this stage, we were ready to study the coupling of fragment C1 with the lactone, **130**. In the interest of optimizing the coupling conditions before using fragment C1, **63**, we decided to study the final stages with benzylamine, **136**, as a model. As shown in Scheme 3.12, heating the lactone, **130**, benzylamine, **136**, and a catalytic amount of Hünig's base to reflux in methanol[123] produced a 96% yield of the model hydroxyamide, **137**. With substantial quantities of this compound in hand, we were ready to study the completion of fragment C.

Scheme 3.12



3.4.4 Attempted Completion of Fragment C

Scheme 3.13

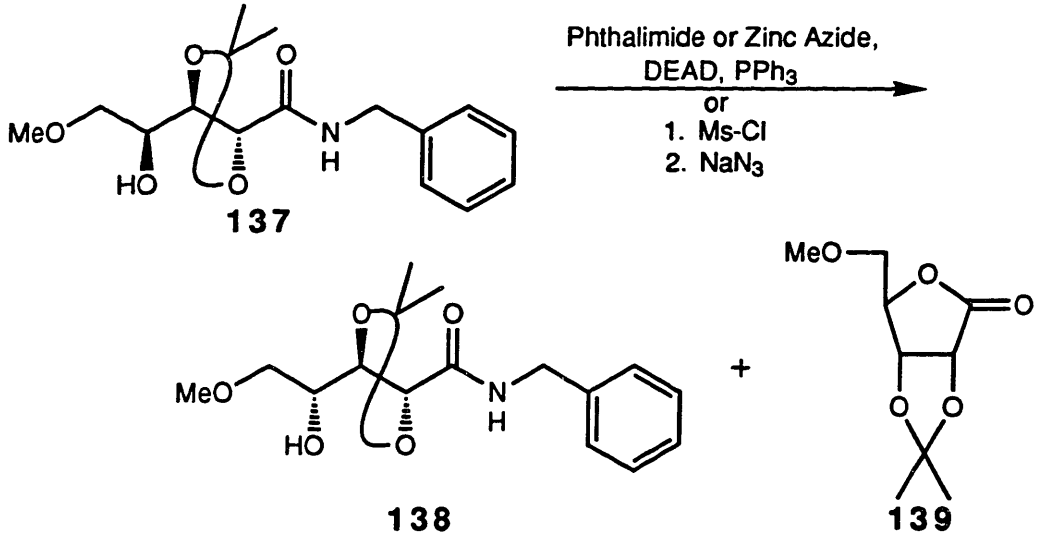
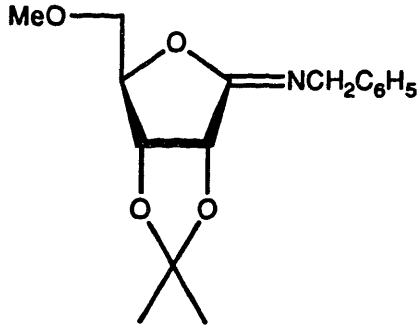


Figure 3.3

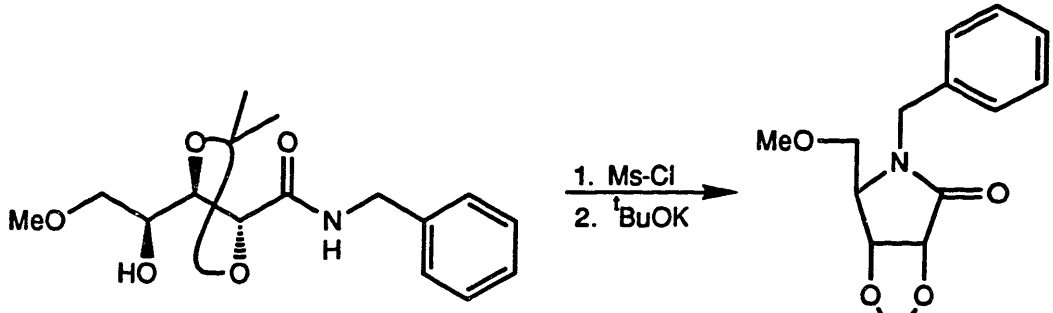


141

Completion of the synthesis was expected to proceed either through the direct displacement of the hydroxyl group with a nitrogen nucleophile such as phthalimide or by initial conversion of the alcohol to the corresponding mesylate followed by displacement with azide. However, when we treated the alcohol with phthalimide or zinc azide under Mitsunobu conditions,[124,125] we were disappointed to find an 83% combined yield of the hydroxyamide, **138**, and the lactone, **139**, in a 3 : 1 ratio, respectively (Scheme 3.13). It is important to note that the hydroxyamide, **138**, and the lactone, **139**, possess the inverted configuration at C4 when compared to the starting hydroxyamide, **137**, and the lactone, **131**, respectively. Furthermore, although we were able to convert the hydroxyamide, **137**, into the mesylate, **140**, we observed the same mixture of products obtained under Mitsunobu conditions when we attempted to displace the mesylate with azide. These results can be explained by the imidate, **141** (Figure 3.3), which forms when the amide oxygen displaces the leaving group to form a 5,5 cis-fused system with inversion of the center at C4. Hydrolysis then affords the observed products. This effect, believed to result from the acetonide holding the ends of the molecule in close proximity, caused us to re-evaluate the utility of this group.

3.4.5 The Acetonide: Turning Problems to Advantages

Scheme 3.14

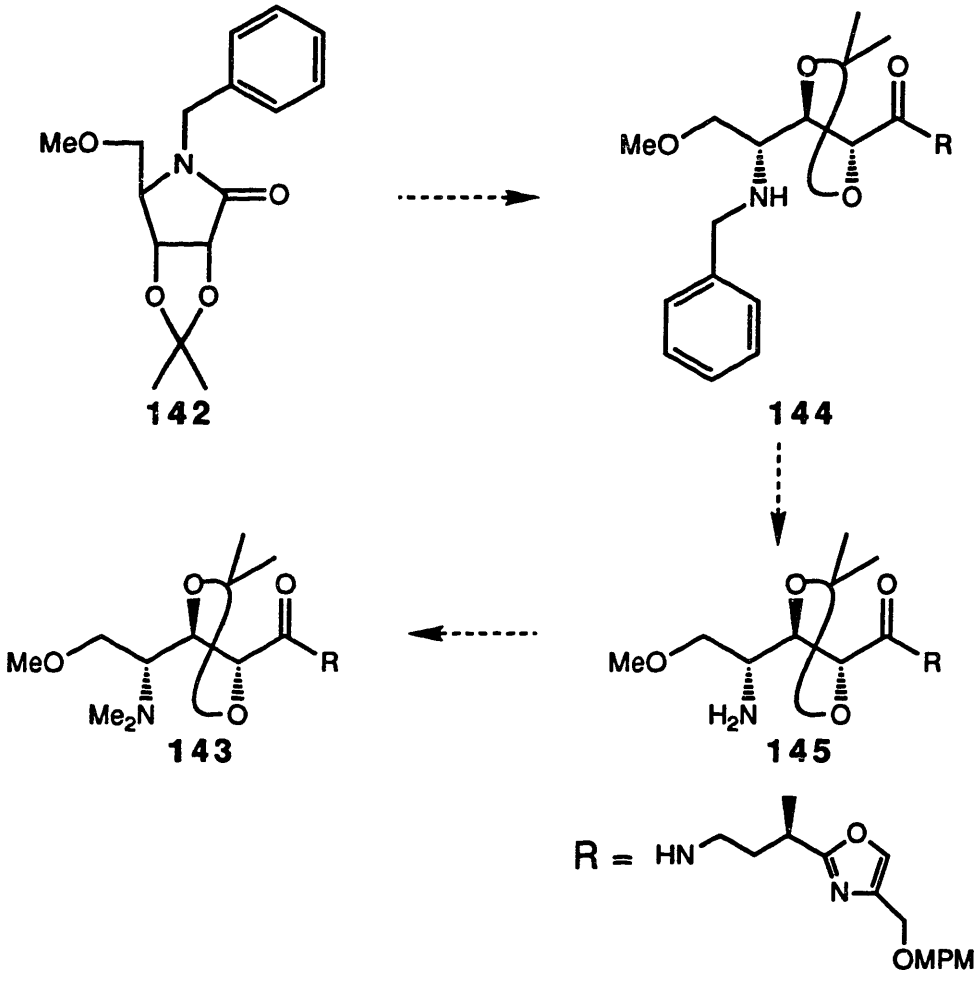


137 **142**

When considering the ability of the acetonide to hold the side groups of the hydroxyamide, **137**, in close proximity thus making intramolecular reactions with inversion of stereochemistry inevitable, we considered the possibility of inducing the nitrogen of the amide to displace a leaving group. This would provide two advantages. The first is that the nitrogen would be introduced at the correct site with the correct stereochemistry, and the second is that all of the stereocenters included in fragment C2 would be established. As shown in Scheme 3.14, when exploring this possibility, we found that converting the hydroxyamide, **137**, to the corresponding mesylate, **140**, followed by treatment of the crude mesylate with potassium *tert*-butoxide cleanly produced an 87% yield of the desired lactam, **142**.[126]

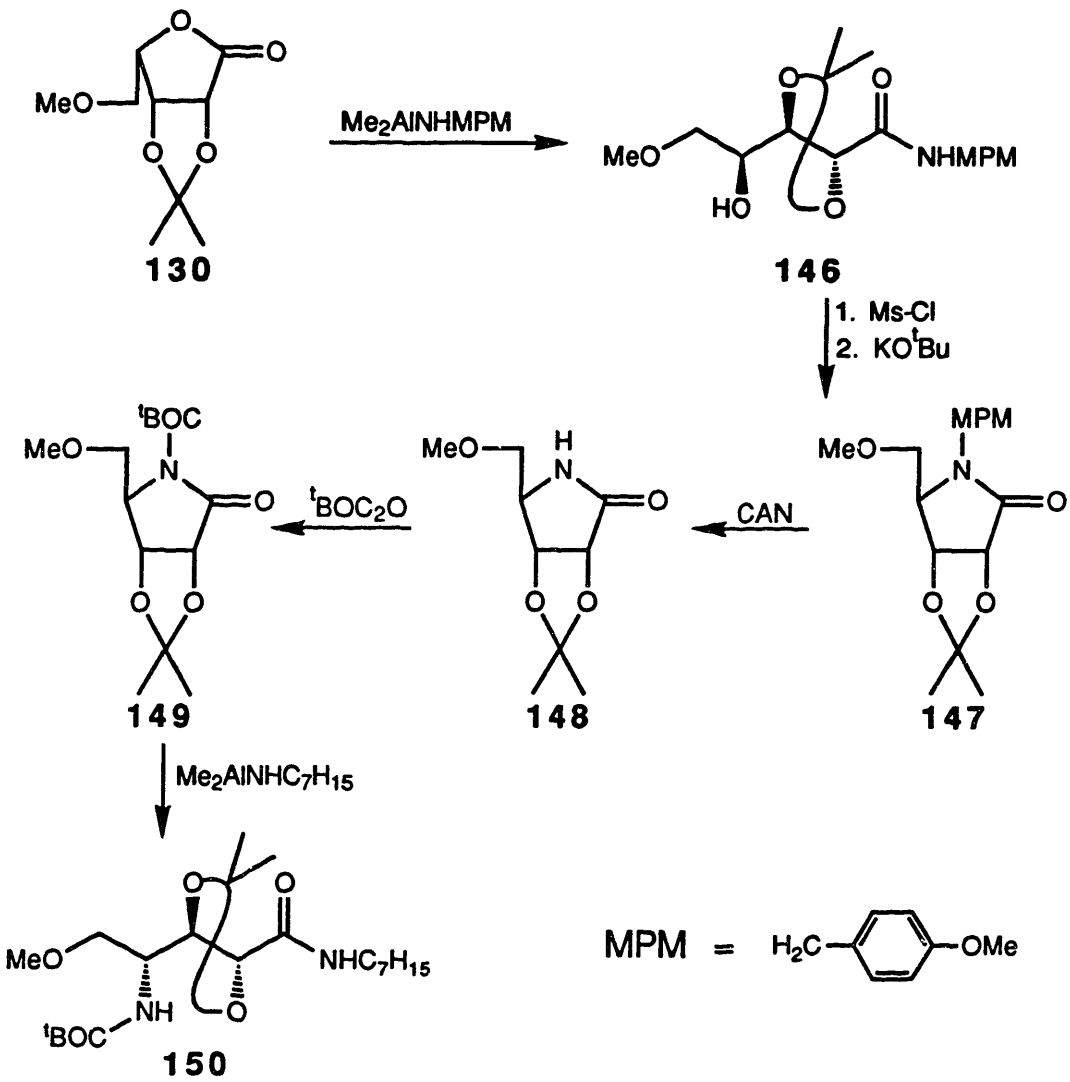
At this stage, all that remained for the completion of fragment C, **143**, was to open the lactam, **142**, to the benzylamino amide, **144**, remove the benzyl group to form the amino amide, **145**, and methylate the amine (Scheme 3.15). Unfortunately, all attempts to open the lactam failed. We felt, however, that if we could remove some electron density from the nitrogen thus stabilizing the anion, we would be able to avoid this problem.

Scheme 3.15



In developing a strategy utilizing electron withdrawing protecting groups on the lactam nitrogen, we went back and opened the lactone, **130**, to the *p*-methoxy benzylamide, **146**,[127,128,129] in 99% yield (Scheme 3.16). This hydroxyamide was then carried through to the MPM-protected lactam, **147**, in 87% yield over two steps. The MPM group was then removed with ceric ammonium nitrate (CAN)[130] to form the lactam, **148**, which was then treated with ^{t}BOC anhydride[131] to provide the ^{t}BOC-protected lactam, **149**. This lactam was easily opened with the Weinreb reagent derived from heptylamine[127,128,129] to form the ^{t}BOC protected amino amide, **150**.

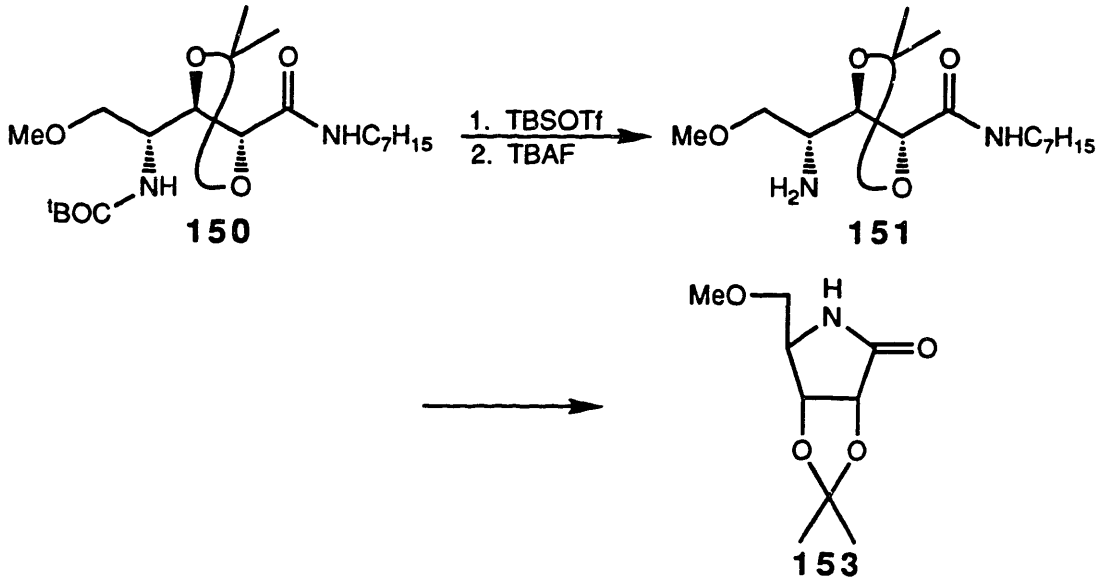
Scheme 3.16



Successful completion of our strategy now relied on the removal of the ^{t}BOC protecting group followed by methylation of the amine. As shown in Scheme 3.17, the ^{t}BOC group was removed in 81% yield on treatment with TBSOTf followed by tetrabutylammonium fluoride (TBAF).[132] To our disappointment, all attempts to convert the primary amine, **151**, to the dimethylamine, **152**, resulted in cyclization to the lactam, **153**.

At this stage, we realized our synthesis was becoming far too elaborate considering the size of the fragment. Therefore, we began to re-evaluate our options and needs with respect to protecting groups. Additionally, we decided to search for alternative methods used to open lactams.

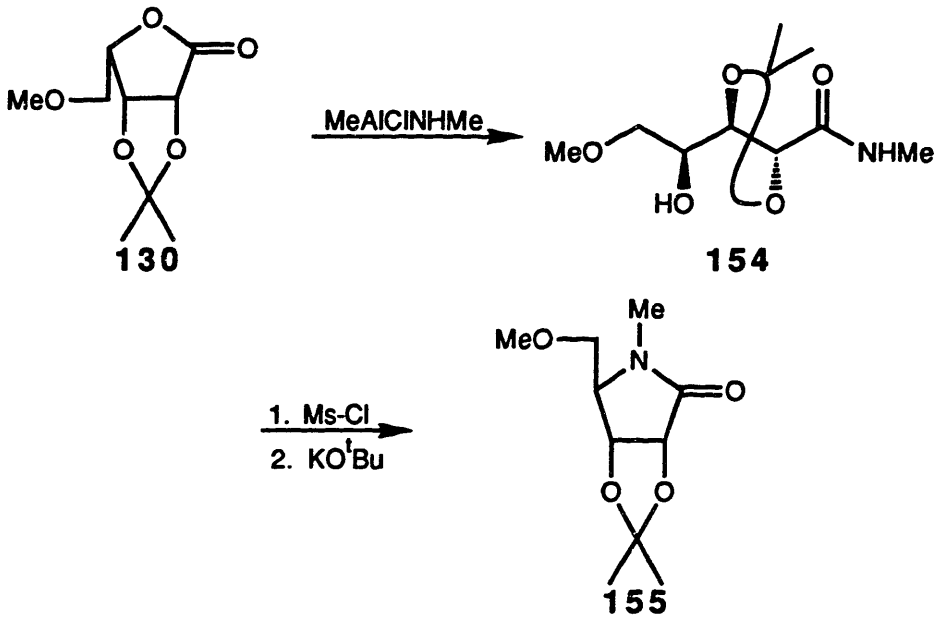
Scheme 3.17



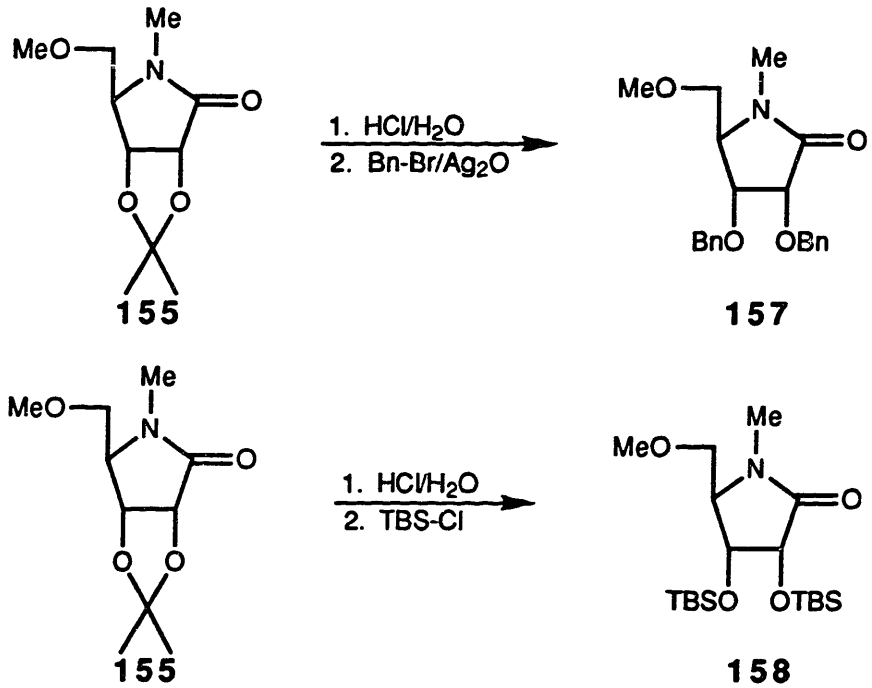
3.4.6 Protecting Groups and the Lactam

When considering how to shorten our synthetic strategy while enhancing its efficiency, we felt it would be advantageous to introduce one of the methyl groups to the nitrogen at a relatively early stage. Therefore, as shown in Scheme 3.18, we converted the lactone, **130**, to the hydroxy amide, **154**, in 99% yield utilizing the Weinreb reagent derived from methylamine hydrochloride.[129] Cyclization of the resulting hydroxy amide, **154**, to the methyl lactam, **155**, was effected on treatment with methanesulfonyl chloride followed by potassium *tert*-butoxide (84%, two steps) as previously described.

Scheme 3.18



Scheme 3.19

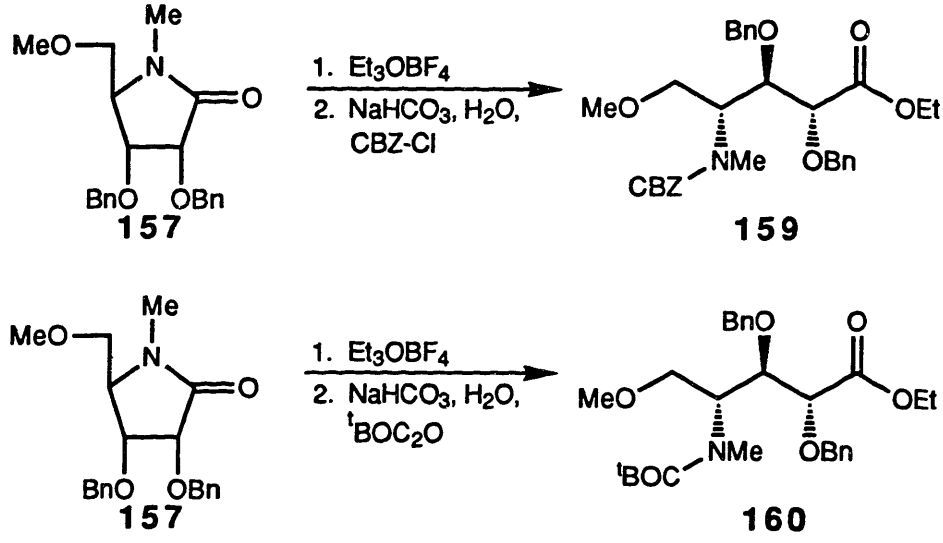


Realizing that the presence of the acetonide was preventing us from efficiently opening the lactam, we decided to explore alternative protecting

groups for the diol. Therefore, as shown in Scheme 3.19, we removed the acetonide under acidic hydrolytic conditions and reprotected the diol, **156**, as the bis-benzyloxy lactam, **157**, (83% yield, 2 steps) and the bis-*tert*-butyldimethylsilyloxy lactam, **158**, (95% yield, 2 steps).

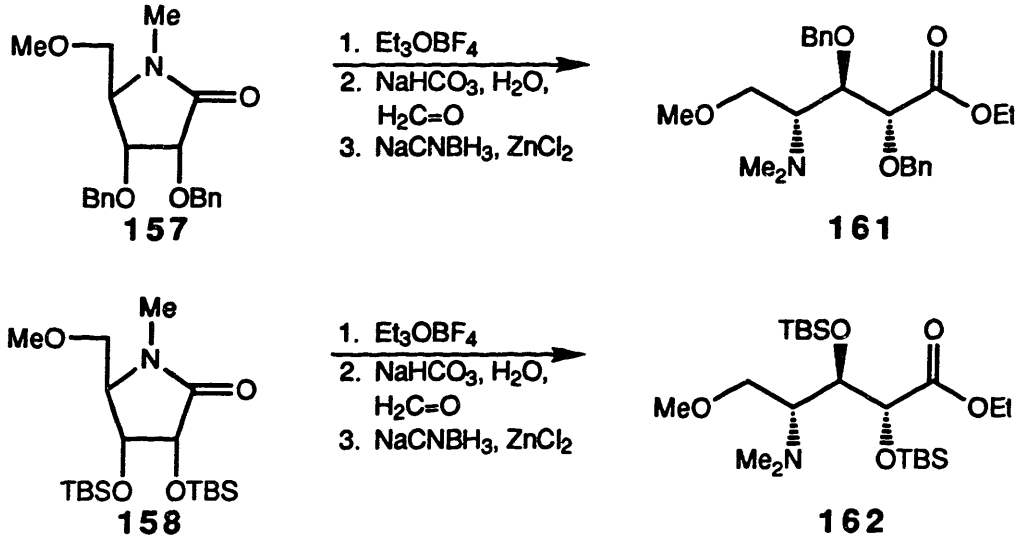
3.4.7 Ring Opening of the Lactam

Scheme 3.20



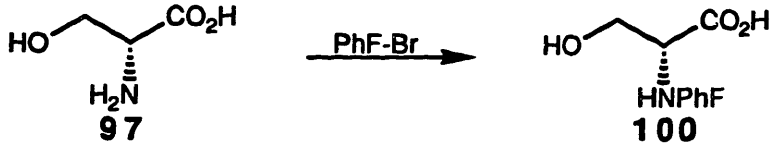
Exploring the ring opening reactions of lactams, we began our study with the bis-benzyloxy lactam, **157**. We felt that if we could form an imidate from this lactam, mild basic hydrolysis of this imidate would yield an amino ester[132a] which could be trapped with various electrophiles.[133] As shown in Scheme 3.20, treatment of the bis benzyloxy lactam, **157**, with the Meerwein reagent[134] cleanly formed the imidate in the presence of 2,6-di-tert-butylpyridine. Furthermore, basic hydrolysis of the imidate in the presence of CBZ-Cl or ^{t}BOC anhydride provided the CBZ protected amino ester, **159**, (75% yield, 2 steps) or the ^{t}BOC protected amino ester, **160**, (72% yield, 2 steps) respectively.

Scheme 3.21



Although it is well known that carbamates can be reduced to methyl groups using strong reducing agents, the likelihood of being able to perform this reaction on the protected amino esters, **159** or **160**, seemed quite low. However, we felt that if the amino ester was trapped in the form of an imine, reduction of the imine to the amine could be accomplished with no consequence to the ester functionality. Therefore, as shown in Scheme 3.21, we converted the bis-benzyloxy lactam, **157**, to the imidate on treatment with the Meerwein reagent,[134] and hydrolyzed the crude imidate under basic conditions in the presence of formaldehyde to form the imine. The imine was then reduced, *in situ*, to the bis-benzyloxy dimethylaminoester, **161**, in 79% yield over three steps with the zinc chloride modification of the $NaCNBH_3$ reduction.[135] Additionally, this reaction sequence was easily adapted to the bis-*tert*-butyldimethylsilyloxy lactam, **158**, thus providing, in 69% yield over three steps, the bis-*tert*-butyldimethylsilyloxy aminoester, **162**. With these results, we had completed fragment C2 and were now ready to study its coupling with fragment C1.

3.5 Experimental Section



***N*-(9-Phenylfluorenyl)-D-Serine, 100**

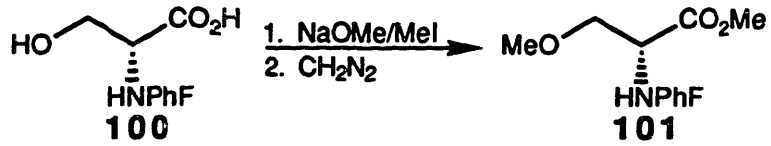
D-Serine (2.10 g, 20 mmoles) was suspended in CH_2Cl_2 (35 mL) at room temperature under argon. Trimethylchlorosilane (8.8 mL, 70 mmoles) was added and the mixture was heated to reflux for 20 minutes. The reaction was allowed to cool, after which a solution of triethylamine (9.76 mL) in CH_2Cl_2 (20 mL) was added. The reaction was stirred for an additional 45 minutes, cooled to 0°C, and a solution of methanol (1.22 mL, 30 mmoles) in CH_2Cl_2 (5 mL) was added. The mixture was allowed to warm to room temperature, after which triethylamine (2.79 mL) was added followed by 9-phenylfluorenyl bromide (6.42 g, 20 mmoles) and $Pb(NO_3)_2$ (6.42 g, 20 mmoles). The reaction was stirred under argon for 2 days, after which methanol (5 mL) was added. The mixture was stirred for 15 minutes and the solvent was removed under reduced pressure. The residue was partitioned between THF (100 mL), 5% citric acid solution (100 mL), and ether (100 mL). The layers were separated and the organic phase was washed with 1M NaOH solution (2 X 50 mL) and water (2 X 50 mL). The combined aqueous layers were neutralized with glacial acetic acid and washed with 50% THF/ethyl acetate (2 X 100 mL). The organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the pure product (4.35 g, 63%) as a light brown solid.

Physical Properties for 100

R_f = 0.17 (ethyl acetate).

^{1}H NMR (250 MHz, $CDCl_3$): δ 7.60-7.70(m, 2H), 7.15-7.40(m, 11H), 3.10-3.55(m, 2H), 2.60(t, 1H).

EI Mass Spec: m/e 345 $[M]^+$, 314, 300, 268, 241.



***N*-(9-Phenylfluorenyl)-*O*-Methyl-D-Serine Methyl Ester, 101**

NaH (80%, 1.20 g, 40 mmoles) was suspended in THF (74 mL) under argon and methanol (6 mL) was added. The mixture was stirred at room temperature for 10 minutes, after which 40 mL of the solution was transferred to a solution of *N*-(9-phenylfluorenyl)-D-serine (3.45 g, 10 mmoles) in THF (100 mL). The mixture was stirred at room temperature under argon for 1 hour, after which a solution of methyl iodide (1 mL, 16 mmoles) in THF (10 mL) was added. The reaction was stirred for 1 hour, after which the remainder of the NaOMe solution was added followed by a solution of methyl iodide (2 mL, 32 mmoles) in THF (10 mL). The reaction was stirred for 18 hours, after which the solvent was removed under reduced pressure. The residue was dissolved in water (50 mL) and the aqueous mixture was washed with ether (25 mL) and acidified with solid citric acid. The aqueous phase was then washed with ethyl acetate (3 X 25 mL). The ethyl acetate was washed with 10% $Na_2S_2O_3$ solution (3 X 25 mL). The combined aqueous phases were washed with ethyl acetate (25 mL) and the combined ethyl acetate phases were washed with 10% $Na_2S_2O_3$ solution (25 mL) and brine (2 X 25 mL). The ethyl acetate was dried over Na_2SO_4 and concentrated to a light brown foam which was immediately taken up in

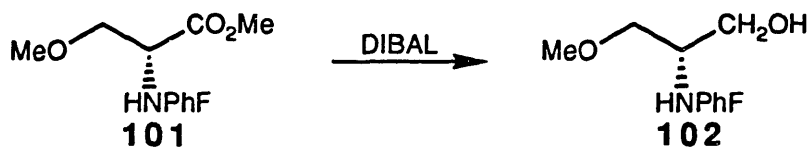
ether (100 mL). An ethereal solution of diazomethane was then added until no more gas evolved. The reaction was quenched with glacial acetic acid and the ether was washed with saturated $NaHCO_3$ solution (2 X 50 mL) and brine (2 X 50 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified on silica gel (25% ethyl acetate/hexane) to yield the desired product (1.67 g, 45%) as a light yellow crystalline solid.

Physical Properties for **101**

R_f = 0.45 (25% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.65-7.7(m, 2H), 7.2-7.45(m, 11H), 3.42(dd, 1H), 3.30(s, 3H), 3.28(dd, 1H), 3.20(s, 3H), 3.07(m, 1H), 2.88(m, 1H).

EI Mass Spec: m/e 373 $[M]^+$, 328, 314, 241.



101 **102**

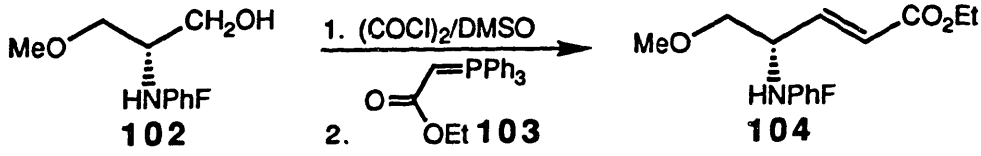
Alcohol, 102

N-(9-Phenyfluorenyl)-*O*-methyl-D-serine methyl ester (0.95 g, 2.55 mmoles) was dissolved in ether (10 mL) and cooled to -78°C under argon. DIBAL (1M in hexane, 5 mL, 5 mmoles) was added dropwise and the reaction was warmed from -78°C to room temperature over 3.5 hours. The reaction was quenched with methanol (10 mL) and combined with ethyl acetate (50 mL). The ethyl acetate was washed with 1N HCl (3 X 20 mL) and saturated $NaHCO_3$ solution (20 mL), after which it was dried over Na_2SO_4, filtered, and concentrated to yield the product (0.445 g, 50%) as a yellow oil.

Physical Properties for **102**

R_f = 0.21 (25% ethyl acetate/hexane).

^1H NMR (250 MHz, $CDCl_3$): δ 7.65-7.75(m, 2H), 7.15-7.45(m, 11H), 3.20(dd, 1H), 3.10(s, 3H), 3.06(dd, 1H), 2.96(dd, 1H), 2.84(dd, 1H), 2.69(broad s, 1H), 2.34(m, 1H), 1.55(broad s, 1H).



Ester, 104

To a solution of $(COCl)_2$ (0.135 mL, 1.54 mmoles) in CH_2Cl_2 (13 mL) at -78°C under argon was added DMSO (0.222 mL, 3.13 mmoles). The resulting mixture was stirred at -78°C for 10 minutes, after which a solution of the alcohol, **102**, (0.45 g, 1.30 mmoles) in CH_2Cl_2 (10 mL) was added. The mixture was stirred at -78°C for 2 hours, after which triethylamine (0.90 mL, 6.46 mmoles) was added. Stirring was continued at -78°C for 1 hour, after which a solution of (carbethoxymethylene)triphenylphosphorane, **103**, (1.30 g, 3.73 mmoles) in CH_2Cl_2 (5 mL) was added. The mixture was allowed to warm to room temperature over 20 hours, after which it was poured onto brine (100 mL) and washed with CH_2Cl_2 (2 X 100 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue on silica gel (15% ethyl acetate/hexane) yielded the product (0.425 g, 79%) as a colorless oil.

Physical Properties for **104**

R_f = 0.45 (25% ethyl acetate/hexane).

^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23(t, 3H), 2.80(broad s, 1H), 2.95(m, 2H), 3.15(s, 3H), 3.23(m, 1H), 4.05(q, 2H), 5.27(d, 1H), 6.38(dd, 1H), 7.1-7.5(m, 11H), 7.55-7.7(m, 2H).

104 **105**

Alcohol, 105

The ester, **104**, (0.42 g, 1.02 mmoles) was dissolved in ether (10 mL) and cooled to -78°C under argon. DIBAL (1M in hexane, 3 mL, 3 mmoles) was added dropwise and the mixture was warmed from -78°C to room temperature over 2.5 hours. The reaction was then transferred, *via* cannula, to saturated Rochelle's salt solution (50 mL) and stirred at room temperature for 15 minutes. The mixture was washed with CH_2Cl_2 (3 X 50 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the pure product (0.37 g, 97%) as a light yellow oil.

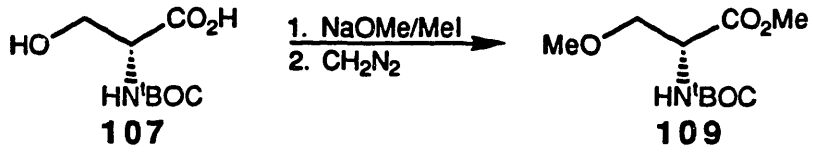
Physical Properties for **105**

R_f = 0.10 (25% ethyl acetate/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.7(d, 1H), 7.6(d, 1H), 7.15-7.45(m, 11H), 4.8-5.1(m, 2H), 3.52(m, 2H), 3.27(t, 1H), 3.25(s, 3H), 1.55(broad s, 1H), 3.00(m, 2H), 2.85(broad s, 1H).

EI Mass Spec: m/e 326 $[M - 33]^+$, 241.

IR (neat) cm^{-1}: 3400, 3060, 2900, 1600, 1450, 1200.



107 **109**

***N*-^{t}BOC-*O*-Methyl-D-Serine Methyl Ester, 109**

NaH (80%, 6 g, 0.2 mole) was suspended in THF (370 mL) under argon and methanol (30 mL) was added. The mixture was stirred at room temperature for 30 minutes, after which 200 mL of the solution was transferred to a solution of *N*-^{t}BOC-D-serine (10.25 g, 50 mmoles) in THF (500 mL). The mixture was stirred at room temperature under argon for 1 hour, after which a solution of methyl iodide (5 mL, 80 mmoles) in THF (50 mL) was added. The reaction was stirred for 1 hour, after which the remainder of the NaOMe solution was added followed by a solution of methyl iodide (10 mL, 0.16 mole) in THF (50 mL). The reaction was stirred for 18 hours, after which the solvent was removed under reduced pressure. The residue was dissolved in water (250 mL), and the aqueous layer was washed with ether (125 mL) and acidified, at 0°C, with solid citric acid. The aqueous phase was then washed with ethyl acetate (3 X 125 mL) and the combined ethyl acetate phases were washed with 20% $Na_2S_2O_3$ solution (3 X 125 mL). The combined aqueous phases were washed with ethyl acetate (125 mL) and the combined organic phases were washed with 20% $Na_2S_2O_3$ solution (125 mL) and concentrated. The residue was then dissolved in water (150 mL) and washed with CH_2Cl_2 (150 mL). The CH_2Cl_2 was dried over Na_2SO_4 and concentrated to a viscous oil. The oil was dissolved in ethyl acetate (100 mL) and an ethereal solution of diazomethane was added until no more gas evolved. The reaction was quenched with glacial acetic acid, after which it was washed with saturated $NaHCO_3$ solution (2 X 50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered, and

concentrated under reduced pressure. The residue was purified on silica gel (25% ethyl acetate/hexane) to yield the product (4.40 g, 38%) as a colorless oil.

Physical Properties for **109**

R_f = 0.36 (25% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 5.36(broad m, 1H), 4.42(broad m, 1H), 3.79(dd, 1H), 3.75(s, 3H), 3.59(dd, 1H), 3.35(s, 3H), 1.45(s, 9H).

109 **110**

Alcohol, 110

N-^{t}BOC-*O*-methyl-D-serine methyl ester (0.244 g, 1.05 mmoles) was dissolved in ether (2 mL) and cooled to -78°C under argon. DIBAL (1M in toluene, 2.6 mL, 2.6 mmoles) was added dropwise and the reaction was warmed from -78°C to room temperature over 18 hours. The reaction was then transferred, *via* cannula, to saturated Rochelle's salt solution (10 mL). The resulting mixture was stirred at room temperature for 40 minutes, after which the layers were separated and the aqueous phase was washed with ethyl acetate (10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the pure product (0.203 g, 95%) as a yellow oil.

Physical Properties for **110**

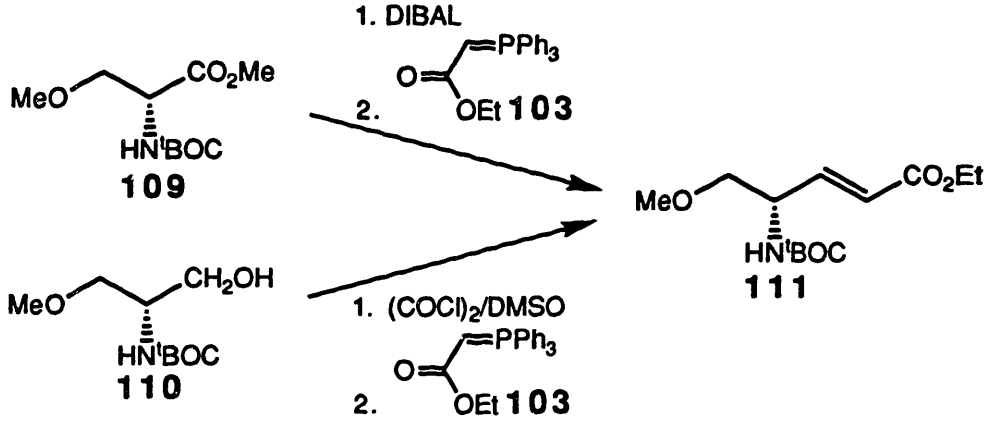
R_f = 0.29 (50% ethyl acetate/ether).

^1H NMR (250 MHz, $CDCl_3$): δ 5.15(broad s, 1H), 3.76(broad m, 2H), 3.55(m,

2H), 3.35(s, 3H), 2.65(broad m, 1H), 1.60(s, 1H), 1.45(s, 9H).

EI Mass Spec: m/e 205 [M]+, 174, 160, 132, 118, 104, 74, 57.

IR (neat) cm^{-1}: 3400, 2950, 1680, 1500, 1330.



Ester, 111

From **109**:

N-^{t}BOC-*O*-methyl-D-serine methyl ester (0.91 g, 3.90 mmoles) was dissolved in ether (10 mL) and cooled to -78°C under argon. DIBAL (1M in toluene, 10 mL, 10 mmoles) was added to the mixture over 10 minutes and the reaction was stirred at -78°C for 3 hours. The reaction was transferred, *via* cannula, to saturated Rochelle's salt solution (50 mL) pre-cooled to 0°C, and the mixture was stirred at room temperature for 1 hour. Ethyl acetate (20 mL) was then added and the layers were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and (carbethoxymethylene)triphenylphosphorane, **103**, (1.35 g, 3.90 mmoles) was added. The reaction was stirred at room temperature under argon for 36 hours and concentrated to dryness. Purification of the residue on silica gel (20% ethyl acetate/hexane) gave the product (0.58 g, 55%) as a colorless oil.

From **110**:

To a solution of $(COCl)_2$ (0.51 mL, 5.76 mmoles) in CH_2Cl_2 (50 mL) at -78°C under argon was added DMSO (0.86 mL, 12.13 mmoles). The resulting mixture was stirred at -78°C for 10 minutes, after which a solution of the alcohol, **110**, (0.995 g, 4.85 mmoles) in CH_2Cl_2 (36 mL) was added. The mixture was stirred at -78°C for 2 hours, after which triethylamine (3.54 mL, 25.38 mmoles) was added. Stirring was continued at -78°C for 1 hour, after which a solution of (carbethoxymethylene)triphenylphosphorane, **103**, (5 g, 14.35 mmoles) in CH_2Cl_2 (25 mL) was added. The mixture was allowed to warm to room temperature over 21 hours, after which it was poured onto brine (200 mL) and extracted with CH_2Cl_2 (2 X 200 mL). The CH_2Cl_2 was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue on silica gel (20% ethyl acetate/hexane) yielded the product (0.58 g, 44%) as a colorless oil.

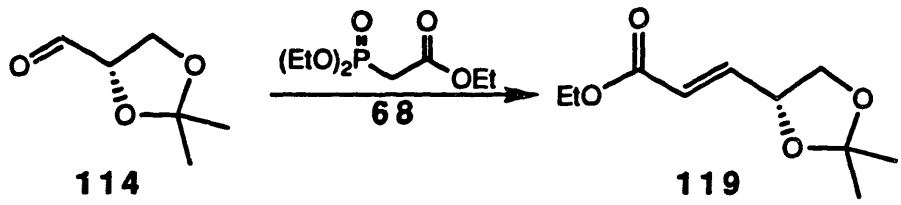
Physical Properties for **111**

R_f = 0.31 (25% ethyl acetate/hexane).

^1H NMR (250 MHz, $CDCl_3$): δ 6.90(dd, 1H), 5.95(dd, 1H), 4.97(broad s, 1H), 4.44(broad s, 1H), 4.15(q, 2H), 3.48(d, 2H), 3.31(s, 3H), 1.42(s, 9H), 1.25(t, 3H).

EI Mass Spec: m/e 200 $[M]^+$, 172, 157, 128, 57.

IR (neat) cm^{-1}: 2980, 2940, 1720, 1660, 1520, 1365.



114 119

Ester, 119

Triethyl phosphonoacetate (2.013 g, 7.684 mmoles) was dissolved in THF (20 mL). The resulting solution was added to a suspension of NaH (80%, 0.279 g, 9.313 mmoles) in THF (20 mL) at room temperature under argon. After stirring for 20 minutes, the phosphonate solution was added to a solution of (*S*)-isopropylidine glyceraldehyde (0.896 g, 6.892 mmoles) in THF (60 mL) over 10 minutes. The mixture was stirred at room temperature under argon for 20 minutes, after which the reaction was diluted with ether (150 mL) and washed with saturated NH_4Cl solution (50 mL), $NaHCO_3$ solution (50 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated to dryness. Purification on silica gel (15% ethyl acetate/hexane) gave the product as a colorless oil (1.1202 g, 73%).

Physical Properties for **119**

R_f = 0.55 (25% ethyl acetate/hexane).

$[\alpha]_D$ = -39.4 c = 3.39 ($CHCl_3$, observed)

= -41.8 c = 3.28 ($CHCl_3$, literature).

^1H NMR (250 MHz, $CDCl_3$): δ 6.87(m, 1H), 6.08(m, 1H), 4.65(m, 1H), 4.18(m, 3H), 3.66(dd, 1H), 1.43(s, 3H), 1.38(s, 3H), 1.28(t, 3H).

IR (neat) cm^{-1}: 2980, 2940, 2870, 1720, 1660, 1450, 1370, 1300.

119 120

Allylic Alcohol, 120

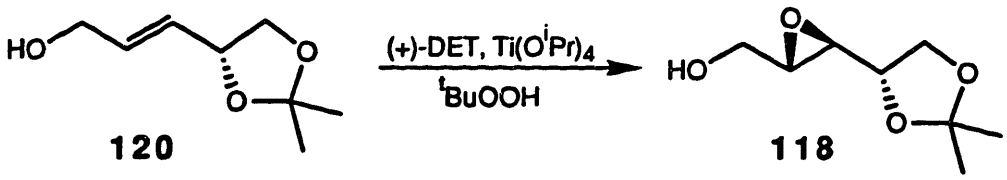
The ester, **119**, (2.318 g, 11.60 mmoles) was dissolved in CH_2Cl_2 (45 mL) and cooled to 0°C under argon. DIBAL (1M in toluene, 25 mL, 25 mmoles) was added and the reaction was stirred at 0°C for 20 minutes, after which it was transferred to saturated Rochelle's salt solution (50 mL) at 0°C. The resulting mixture was stirred at room temperature for 1.5 hours, after which the layers were separated and the aqueous phase was washed with ethyl acetate (2 X 20 mL). The combined organics were dried over Na_2SO_4 and concentrated to dryness. The residue was passed through a 1 inch plug of silica gel (50% ethyl acetate/hexane). Concentration of the filtrate yielded the product as a colorless oil (1.761 g, 96%).

Physical Properties for **120**

R_f = 0.28 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 5.95(m, 1H), 5.71(m, 1H), 4.53(m, 1H), 4.16(m, 2H), 4.08(dd, 1H), 3.59(dd, 1H), 1.42(s, 3H), 1.38(s, 3H).

IR ($CDCl_3$) cm^{-1}: 3620, 2995, 2940, 2880, 1450, 1370, 1215, 1150, 1050.



120 118

Epoxide, 118

Activated 4Å powdered molecular sieves (0.155 g) were suspended in CH_2Cl_2 (11 mL) and cooled to -20°C. (+)-Diethyl tartrate (32.2 mL, 0.189 mmole) was added followed by $(^iPrO)_4Ti$ (46.7 mL, 0.157 mmole). *tert*-Butyl hydroperoxide (3M in isooctane, 2.1 mL, 6.287 mmoles) was added dropwise and the resulting mixture was stirred at -20°C for 30 minutes. A solution of the alcohol, **120**, (0.497 g, 3.144 mmoles) in CH_2Cl_2 (2 mL) was added dropwise and the mixture was stirred at -20°C under argon for 23 hours, after which the reaction was warmed to 0°C and water (0.89 mL) was added. The mixture was then warmed to room temperature over 30 minutes and a solution of NaOH (30% in saturated NaCl, 0.18 mL) was added. The mixture was stirred for 25 minutes, the layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 X 25 mL). The combined organics were dried over Na_2SO_4, concentrated, and the residue was purified on silica gel (70% ethyl acetate/hexane) to yield the product as a colorless oil (0.471 g, 86%).

Physical Properties for **118**

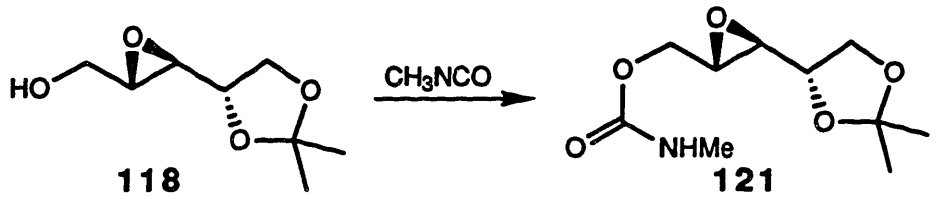
R_f = 0.37 (70% ethyl acetate/hexane).

$[\alpha]_D$ = +36.0 c = 0.145 ($CHCl_3$, observed)

= +38.6 c = 0.145 ($CHCl_3$, literature).

^1H NMR (300 MHz, $CDCl_3$): δ 4.16(dd, 1H), 3.97(m, 3H), 3.72(m, 1H), 3.13(m, 2H), 1.70(t, 1H), 1.47(s, 3H), 1.40(s, 3H).

IR ($CDCl_3$) cm^{-1}: 3580, 2900, 1440, 1360, 1235, 1200, 1140, 1045.



118 121

Epoxycarbamate, 121

The epoxide, **118**, (0.471 g, 2.708 mmoles) was dissolved in benzene (10 mL) and methyl isocyanate (0.18 mL, 3.054 mmoles) was added. The reaction was warmed to 50°C for 3 days, after which methanol (2 mL) was added. Stirring was continued at 50°C for 1 hour, after which the reaction was concentrated and the residue was purified on silica gel (50% ethyl acetate/hexane) to yield the product as a colorless oil (0.545 g, 87%).

Physical Properties for **121**

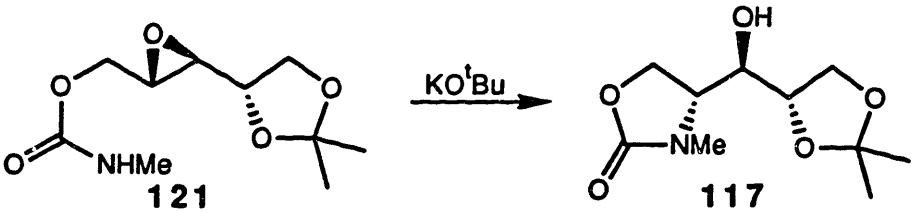
R_f = 0.47 (70% ethyl acetate/hexane).

$[\alpha]_D$ = +35.4 c = 0.04247 ($CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ 4.67(broad s, 1H), 4.41(dd, 1H), 4.80(dd, 1H), 3.90(m, 3H), 3.19(m, 1H), 2.95(m, 1H), 2.78(d, 3H), 1.43(s, 3H), 1.34(s, 3H).

EI Mass Spec: m/e 216 $[M - 15]^+$, 99, 71, 58, 43.

IR ($CHCl_3$) cm^{-1}: 3440, 2960, 1715, 1500, 1360, 1180.



121 117

Oxazolidinone, 117

The epoxycarbamate, **121**, (3.316 g, 14.354 mmoles) was dissolved in THF (66 mL) and cooled to -10°C under argon, after which potassium *tert*-

butoxide (0.58M in THF, 27.20 mL, 15.79 mmoles) was added. The reaction was stirred at -10°C for 30 minutes, after which it was quenched with saturated NH_4Cl solution (50 mL). The reaction was partitioned with ethyl acetate (150 mL) and the aqueous layer was washed with ethyl acetate (150 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by recrystallization from ethyl acetate/hexane to yield the product as colorless needles (2.578 g, 78%).

Physical Properties for **117**

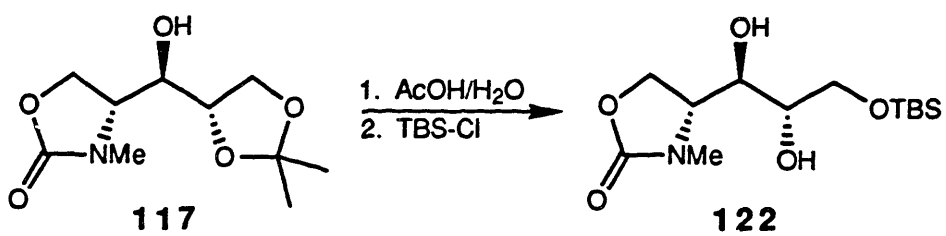
R_f = 0.24 (70% ethyl acetate/hexane).

$[\alpha]_D$ = -6.17 c = 0.02041 ($CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ 4.48(dd, 1H), 4.33(dd, 1H), 4.17(dd, 1H), 4.03(m, 2H), 3.90(m, 2H), 3.83(m, 1H), 2.90(s, 3H), 1.41(s, 3H), 1.33(s, 3H).

EI Mass Spec: m/e 216 $[M - 15]^+$, 131, 100, 73, 56.

IR ($CHCl_3$) cm^{-1}: 3350, 2960, 1735, 1420, 1050.



117 **122**

Diol, 122

The oxazolidinone, **117**, (0.100 g, 0.434 mmole) was dissolved in acetic acid (0.63 mL) and water (0.89 mL) was added. The reaction was heated to 50°C for 6 hours, after which it was concentrated to dryness. After 24 hours under vacuum, the residue was taken up in DMF (4 mL). Imidazole (118 mg, 1.735 mmoles) was added and the mixture was cooled to -10°C under

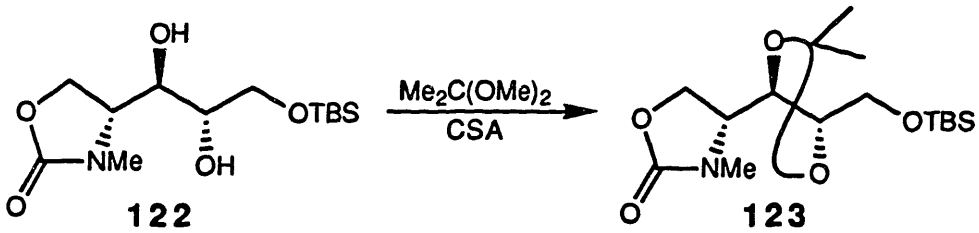
argon. A solution of *tert*-butyldimethylchlorosilane (82.7 mg, 0.548 mmole) in DMF (2 mL) was added and the reaction was warmed from -10°C to room temperature over 2.5 hours. The reaction was then partitioned between water (20 mL) and ethyl acetate (40 mL). The aqueous phase was washed with ethyl acetate (40 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated to dryness. The residue was purified on silica gel (ethyl acetate) to yield the product as a white crystalline solid (0.122 g, 93%).

Physical Properties for **122**

R_f = 0.53 (ethyl acetate).

^1H NMR (300 MHz, $CDCl_3$): δ 4.43(dd, 1H), 4.30(dd, 1H), 4.07(m, 1H), 3.84(m, 2H), 3.71(m, 2H), 3.49(m, 1H), 2.85(s, 3H), 2.61(d, 1H), 0.88(s, 9H), 0.07(s, 6H).

IR ($CDCl_3$) cm^{-1}: 3550, 3350, 2910, 1730, 1450, 1240.



Acetonide, 123

The diol, **122**, (0.122 g, 0.399 mmole) was dissolved in CH_2Cl_2 (5 mL). 2,2-dimethoxypropane (0.24 mL, 1.993 mmoles) was added followed by camphorsulfonic acid (10 mg). The mixture was stirred at room temperature under argon for 1 hour, after which it was diluted to 10 mL with CH_2Cl_2. The reaction was then washed with saturated $NaHCO_3$ solution (10 mL). The organics were dried over Na_2SO_4 and concentrated to dryness. The residue was purified by filtration through a 1 inch plug of

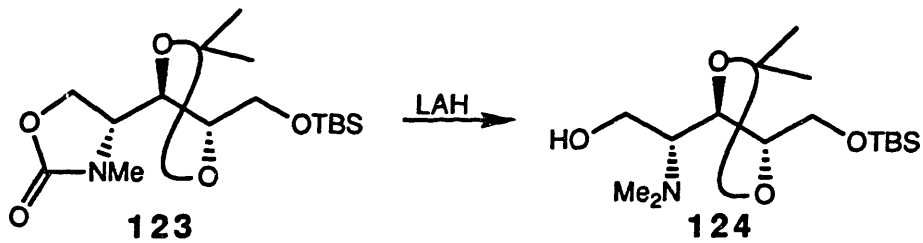
silica gel (70% ethyl acetate/hexane) to yield the product as a colorless crystalline solid (0.133 g, 97%).

Physical Properties for **123**

R_f = 0.62 (70% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 4.43(m, 2H), 4.31(m, 2H), 4.04(m, 1H), 3.78(dd, 1H), 3.50(dd, 1H), 2.93(s, 3H), 1.48(s, 3H), 1.39(s, 3H), 0.91(s, 9H), 0.10(s, 6H).

IR ($CDCl_3$) cm^{-1}: 2900, 1740, 1420, 1245, 1030.



123 **124**

Amino Alcohol, 124

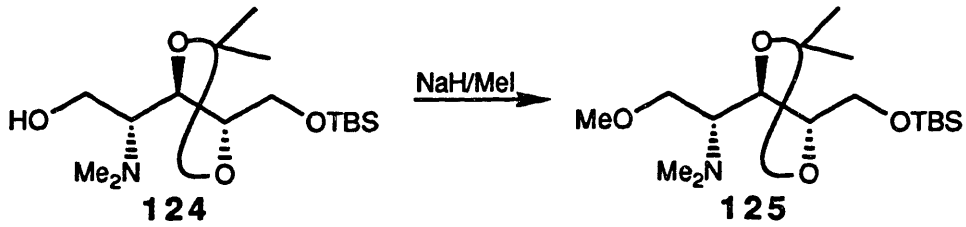
The acetonide, **123**, (11.947 g, 34.628 mmoles) was dissolved in ether (200 mL). $LiAlH_4$ (4.342 g, 114.274 mmoles) was suspended in ether (150 mL). Both solutions were cooled to -10°C under argon, after which the acetonide was added, dropwise, to the $LiAlH_4$. The reaction was allowed to warm from -10°C to room temperature over 4 hours after which, it was quenched by slowly adding $Na_2SO_4 \cdot 10H_2O$ until no more gas evolution was observed. After 1 hour, the solids were filtered off and washed with ether. The combined filtrates were concentrated to dryness to yield the product requiring no further purification (10.947 g, 95%).

Physical Properties for **124**

R_f = 0.29 (70% ethyl acetate/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.33(dd, 1H), 4.18(dd, 1H), 3.74(m, 3H), 3.60(dd, 1H), 2.94(m, 1H), 2.75(broad s, 1H), 2.29(s, 6H), 1.40(s, 3H), 1.32(s, 3H), 0.88(s, 9H), 0.06(s, 6H).

IR ($CDCl_3$) cm^{-1}: 3520, 2910, 1445, 1360, 1240.



124 125

Methyl Ether, 125

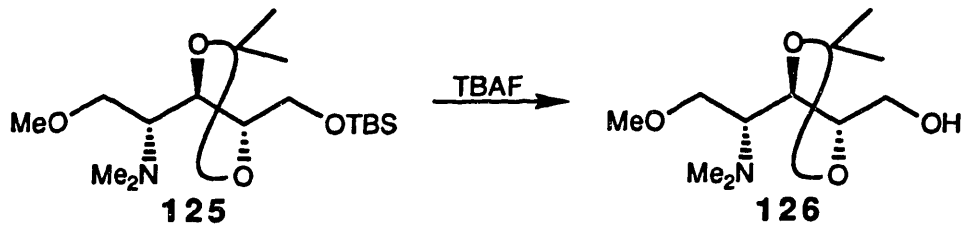
NaH (35%, 27.8 mg, 0.405 mmole) was suspended in THF (1.5 mL) and a solution of the amino alcohol, **124**, (67.5 mg, 0.203 mmole) in THF (2 mL) was added. The mixture was stirred at room temperature under argon for 10 minutes, after which methyl iodide (13.8 mL, 0.222 mmole) was added. Stirring was continued for 1.5 hours, after which the reaction was quenched with methanol (0.10 mL) and partitioned between ethyl acetate (15 mL) and brine (5 mL). The layers were separated and the organic phase was dried over Na_2SO_4 and concentrated. The residue was purified on silica gel (25% ethyl acetate/hexane) to yield the product as a colorless oil (50.5 mg, 72%).

Physical Properties for **125**

R_f = 0.31 (25% ethyl acetate/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17(m, 2H), 3.89(dd, 1H), 3.72(dd, 1H), 3.61(dd, 1H), 3.52(dd, 1H), 3.33(s, 3H), 2.95(m, 1H), 2.34(s, 6H), 1.43(s, 3H), 1.32(s, 3H), 0.90(s, 9H), 0.06(s, 6H).

IR ($CDCl_3$) cm^{-1}: 2900, 1450, 1360, 1240.



125 126

Amino Alcohol, 126

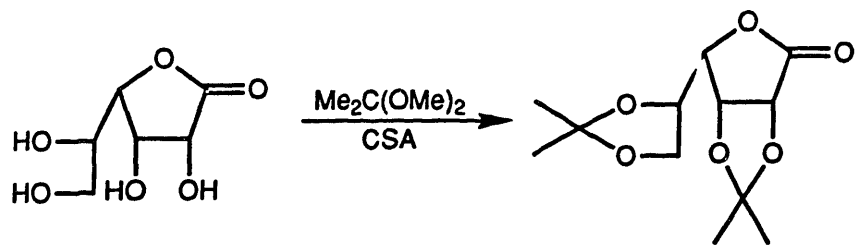
The methyl ether, **125**, (0.146 g, 0.419 mmole) was dissolved in THF (5 mL) and tetrabutylammonium fluoride (1M in THF, 0.46 mL, 0.46 mmole) was added. The reaction was stirred for 15 minutes at room temperature under argon, after which it was filtered through silica gel (ethyl acetate) and concentrated to dryness. The resulting oil was purified on silica gel (70% ethyl acetate/hexane) to yield the desired product (91.7 mg, 94%).

Physical Properties for **126**

R_f = 0.26 (70% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 6.36(broad s, 1H), 4.29(m, 2H), 3.65(m, 4H), 3.33(s, 3H), 2.97(m, 1H), 2.39(s, 6H), 1.37(s, 3H), 1.32(s, 3H).

IR ($CDCl_3$) cm^{-1}: 3150, 2910, 1445, 1235, 1210, 1040.



131 132

2,3-5,6-Di-*O*-Isopropylidine-D-Gulono-1,4-Lactone, 132

D-Gulono-1,4-lactone (1.001 g, 5.623 mmoles) was suspended in CH_2Cl_2 (50 ml) and camphorsulfonic acid (0.101 g, 0.435 mmole) was added followed by 2,2-dimethoxy propane (7 mL, 57 mmoles). The mixture was

stirred at room temperature under argon for 24 hours, after which it was washed with saturated $NaHCO_3$ solution (50 mL). The aqueous phase was washed with CH_2Cl_2 (50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The resulting residue was purified on silica gel (40% ethyl acetate/hexane) to yield the desired product (1.162 g, 80%).

Physical Properties for **132**

R_f = 0.60 (50% ethyl acetate/hexane).

$[\alpha]_D$ = -57.8 c = 2.8 (acetone).

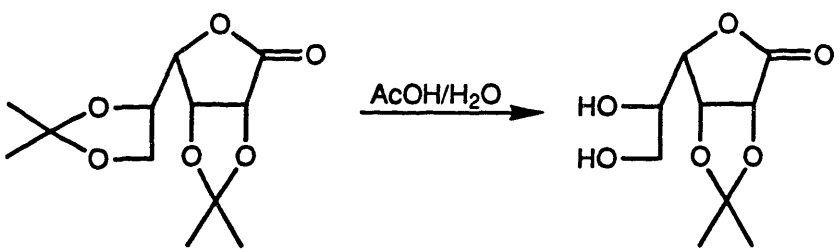
m. p. = 151-152°C.

^1H NMR (300 MHz, $CDCl_3$): δ 4.81(d, 1H), 4.71(m, 1H), 4.40(m, 2H), 4.20(m, 1H), 3.80(m, 1H), 1.52(s, 6H), 1.37(s, 3H), 1.35(s, 3H).

EI Mass Spec: m/e 243 $[M - 15]^+$, 185, 157, 125, 101, 59, 43.

Exact Mass: $[M - CH_3]^+$ = 243.08686 (calculated)

$[M - CH_3]^+$ = 243.0867 (measured).



132 **133**

Diol, 133

2,3-5,6-Di-*O*-isopropylidine-D-gulono-1,4-lactone (49.4 mg, 0.192 mmole) was dissolved in acetic acid (0.30 mL) and water (44 mL) was added. The mixture was warmed to 45°C for 5.5 hours, after which it was concentrated to dryness under vacuum. The residue was purified on silica

gel (ethyl acetate) to yield the desired product (36.3 mg, 87%).

Physical Properties for **133**

R_f = 0.39 (ethyl acetate).

$[\alpha]_D$ = -76.1 c = 2.79 (acetone).

m. p. = 140-141°C.

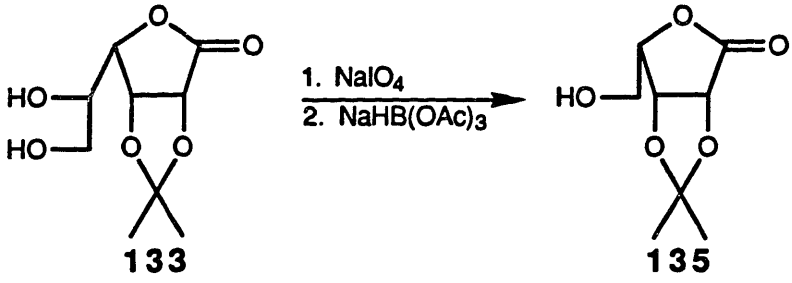
^1H NMR (300 MHz, acetone): δ 4.95(m, 2H), 4.59(dd, 1H), 4.20(m, 1H), 3.93(m, 1H), 3.77(m, 1H), 3.70(m, 2H), 1.37(s, 3H), 1.35(s, 3H).

EI Mass Spec: m/e 203 $[M - 15]^+$, 187, 159, 143, 125, 116, 83.

Exact Mass: $[M - CH_3]^+$ = 203.05556 (calculated)

$[M - CH_3]^+$ = 203.0555 (measured).

IR (nujol mull) cm^{-1}: 3250, 1775, 1455, 1370, 1080.



133 **135**

Alcohol, 135

The diol, **133**, (1.017 g, 4.665 mmoles) was dissolved in water (40 mL) and $NaIO_4$ (1.002 g, 4.704 mmoles) was added. The mixture was stirred at room temperature for 30 minutes, after which it was saturated with NaCl. The resulting mixture was washed with ethyl acetate (15 X 40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under vacuum. To the residue was added benzene (40 mL), acetic acid (4 mL), and $NaHB(OAc)_3$ (1.003 g, 4.730 mmoles). The mixture was

stirred at room temperature under argon for 45 minutes, after which it was concentrated to dryness. The residue was dried, azeotropically, with toluene (2 X 50 mL) and methanol (3 X 50 mL), and finally purified on silica gel (70% ethyl acetate/hexane) to yield the desired product (0.697 g, 79%).

Physical Properties for 135

R_f = 0.63 (ethyl acetate).

$[\alpha]_D$ = -90 c = 1.00 (acetone).

m. p. = 97-98°C.

^1H NMR (250 MHz, $CDCl_3$): δ 4.88(m, 2H), 4.59(m, 1H), 4.00(m, 2H), 2.00(dd, 1H), 1.49(s, 3H), 1.40(s, 3H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 173.44, 114.54, 79.18, 76.22, 76.15, 60.90, 26.67, 25.76.

EI Mass Spec: m/e 173 $[M - 15]^+$, 149, 129, 83, 59, 43.

Exact Mass: $[M - CH_3]^+$ = 173.0450 (calculated)

$[M - CH_3]^+$ = 173.0452 (measured).

IR ($CHCl_3$) cm^{-1}: 3600, 1795, 1375, 1175, 1110.

135 130

Methyl Ether, 130

The alcohol, **135**, (0.010 g, 0.531 mmole) was dissolved in methyl iodide (2 mL) and Ag_2O (0.399 g) was added followed by anhydrous $CaSO_4$

(0.147 g). The resulting suspension was stirred at room temperature under argon for 7.5 hours, after which it was filtered through Celite and concentrated to dryness. The residue was purified on recrystallization desired product (0.089 g, 83%).

Physical Properties for **130**

R_f = 0.47 (50% ethyl acetate/hexane).

$[\alpha]_D$ = -80 c = 0.50 (acetone).

m. p. = 83-85°C.

^1H NMR (300 MHz, $CDCl_3$): δ 4.84(s, 2H), 4.63(m, 1H), 3.77(m, 2H), 3.46(s, 3H), 1.49(s, 3H), 1.41(s, 3H).

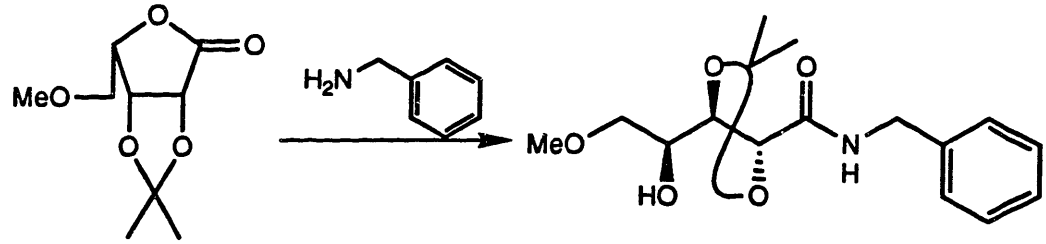
^{13}C NMR (300 MHz, $CDCl_3$): δ 173.34, 114.30, 77.98, 76.02, 75.95, 70.16, 59.45, 26.73, 25.89.

EI Mass Spec: m/e 187 $[M - 15]^+$, 143, 85, 71, 45.

Exact Mass: $[M - CH_3]^+$ = 187.06065 (calculated)

$[M - CH_3]^+$ = 187.0607 (measured).

IR ($CDCl_3$) cm^{-1}: 1795, 1455, 1375, 1085, 870.



130 **137**

Benzyl Amide, 137

The lactone, **130**, (0.103 g, 0.510 mmole) was dissolved in methanol (10 mL) and benzylamine (60 μL, 0.550 mmole) was added, followed by Hünig's

base (57 μL, 0.328 mmole). The reaction was heated to reflux under argon for 14 hours, after which the mixture was concentrated to dryness and the residue was purified on silica gel (70% ethyl acetate/hexane) to yield the product as a colorless oil (0.149 g, 94%).

Physical Properties for 137

R_f = 0.33 (70% ethyl acetate/hexane).

$[\alpha]_D$ = +45.79 c = 1.865 (acetone).

^1H NMR (300 MHz, $CDCl_3$): δ 7.29(m, 5H), 6.90(broad m, 1H), 4.59(d, 1H), 4.45(m, 3H), 4.13(m, 1H), 3.45(m, 2H), 3.45(s, 3H), 2.34(d, 1H), 1.50(s, 3H), 1.35(s, 3H).

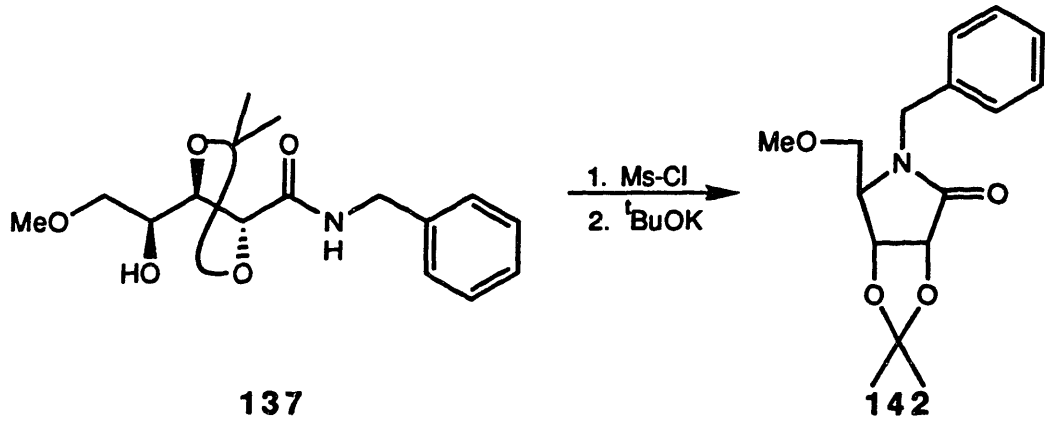
^{13}C NMR (300 MHz, $CDCl_3$): δ 170.06, 138.04, 128.88, 127.90, 127.68, 109.88, 77.05, 75.79, 73.97, 67.20, 59.03, 42.88, 26.36, 24.23.

EI Mass Spec: m/e 309 $[M]^+$, 294, 277, 264, 235, 205, 177, 91.

Exact Mass: $[M]^+$ = 309.15762 (calculated)

$[M]^+$ = 309.1574 (measured).

IR (neat) cm^{-1}: 3440, 3020, 2980, 2940, 1675, 1530, 1455, 1375.



137 142

Lactam, 142

The hydroxyamide, **137**, (158.5 mg, 0.512 mmole) and triethylamine (0.215 mL, 1.536 mmoles) were dissolved in CH_2CL_2 (2 mL) and cooled to 0°C under argon. Methanesulfonyl chloride (60 μL, 0.768 mmole) was added and the reaction was stirred at 0°C for 30 minutes. The solvent was then removed under reduced pressure and the residue was diluted with THF (13 mL) and filtered through Celite under argon. The resulting solution was cooled to -40°C and potassium *tert*-butoxide (0.6M ion THF, 1.8 mL, 1.075 mmoles) was added. After warming to room temperature over of 1 hour, the reaction was quenched with pH = 7 buffer. The products were extracted with ethyl acetate (3 X 10 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (60% ethyl acetate/hexane) to give the product (129.8 mg, 87%) as a colorless oil.

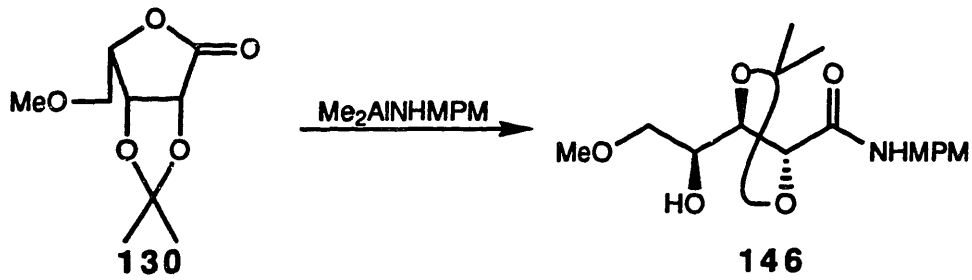
Physical Properties for **142**

R_f = 0.23 (30% acetone/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.25-7.33(m, 5H), 4.86(1/2 ABq, J_{AB} = 15.2 Hz, 1H), 4.76(1/2 ABq, J_{AB} = 5.6 Hz, 1H), 4.55(1/2 ABq, J_{AB} = 5.6 Hz, 1H), 4.16(1/2 ABq, J_{AB} = 15.2 Hz, 1H), 3.57(dd, J = 2.6 Hz, 1H), 3.38(d, J = 2.6 Hz, 2H), 3.23(s,

3H), 1.44(s, 3H), 1.38(s, 3H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 172.2, 135.1, 128.7, 128.0, 127.7, 111.8, 77.7, 76.4, 69.4, 60.6, 59.0, 44.2, 26.9, 25.5.



130 146

Hydroxyamide, 146

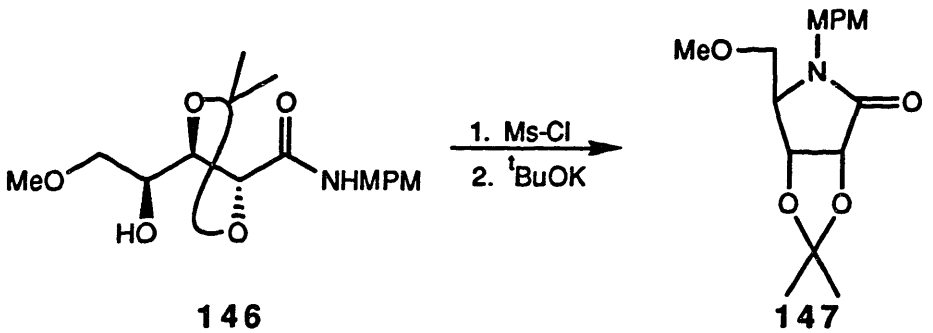
p-Methoxybenzylamine (0.172 mL, 1.315 mmoles) was dissolved in benzene (2 mL) and cooled to 0°C under argon. Trimethylaluminum (2.0M in hexane, 0.657 mL, 1.315 mmoles) was added dropwise, and the mixture was stirred for 30 minutes at room temperature. The resulting solution was added, *via* cannula, to a solution of the lactone, **130**, (221.6 mg, 1.096 mmole) in benzene (2 mL) at 0°C. The resulting mixture was stirred for 3 hours at room temperature, after which it was cooled to 0°C and quenched with saturated Rochelle's salt solution (2 mL). After stirring for 30 minutes at room temperature, the products were extracted with ethyl acetate (3 X 5 mL), and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue purified on silica gel (66% ethyl acetate/hexane) to give the product (369.8 mg, 99%) as a colorless oil.

Physical Properties for **146**

R_f = 0.25 (66% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.24(d, *J* = 6.8 Hz, 2H), 6.87(d, *J* = 6.8 Hz, 2H),

6.86(m, 1H), 4.61(d, J = 7.9 Hz, 1H), 4.48(dd, J = 7.9, 2.6 Hz, 1H), 4.41(d, J = 5.8 Hz, 2H), 4.17(m, 1H), 3.80(s, 3H), 3.50(m, 2H), 3.39(s, 3H), 2.30(d, J = 7.1 Hz, 1H), 1.53(s, 3H), 1.38(s, 3H).



146 147

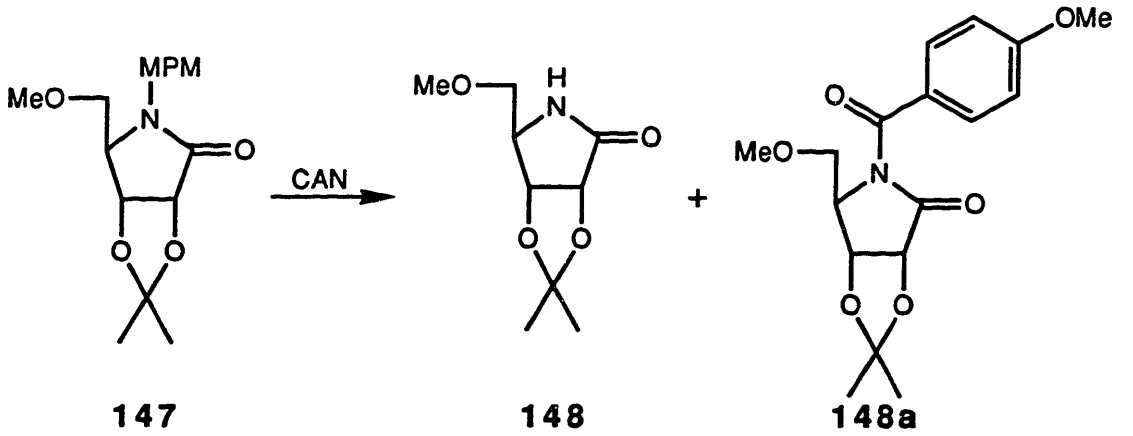
MPM-Lactam, 147

The hydroxyamide, **146**, (322.8 mg, 0.951 mmole) and triethylamine (0.4 mL, 2.853 mmoles) were dissolved in CH_2Cl_2 (4 mL) and cooled to 0°C under argon. Methanesulfonyl chloride (0.111 mL, 1.427 mmoles) was added and the reaction was stirred at 0°C for 30 minutes. The solvent was removed and the residue was diluted with THF (15 mL) and filtered through Celite under argon. The resulting solution was cooled to -40°C and potassium *tert*-butoxide (0.6M in THF, 3.2 mL, 1.902 mmoles) was added. After warming to room temperature over 1 hour, the reaction was quenched with pH = 7 buffer. The products were extracted with ethyl acetate (3 X 10 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (60% ethyl acetate/hexane) to yield the desired product (266.7 mg, 87%) as a colorless oil.

Physical Properties for **147**

R_f = 0.31 (30% acetone/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.19(d, *J* = 8.7 Hz, 2H), 6.86(d, *J* = 8.7 Hz, 2H), 4.87(1/2 ABq, J_{AB} = 15.0 Hz, 1H), 4.73(d, *J* = 5.4 Hz, 1H), 4.51(d, *J* = 5.4 Hz, 1H), 4.05(1/2 ABq, J_{AB} = 15.0Hz, 1 H), 3.80(s, 3H), 3.54(dd, *J* = 2.6 Hz, 1H), 3.38(d, *J* = 2.6 Hz, 2H), 3.24(s, 3H), 1.43(s, 3H), 1.36(s, 3H).



147 **148** **148a**

Lactam, 148

The *p*-methoxybenzyl lactam, **147**, (141 mg, 0.439 mmole) was dissolved in acetonitrile/water (3/1, 7 mL) and cooled to 0°C. Ceric ammonium nitrate (CAN, 962 mg, 1.751 mmoles) was added over 30 minutes. The reaction was stirred for an additional 6 hours at 0°C, after which water was added and the products were extracted with ethyl acetate (3 X 10 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue purified on silica gel (33% ethyl acetate/hexane) to give the desired product, **148**, (66.3 mg, 75%) and the imide, **148a**, (34.6 mg, 24%) as colorless oils.

Physical Properties for **148**

R_f = 0.22 (9% ethyl acetate/hexane).

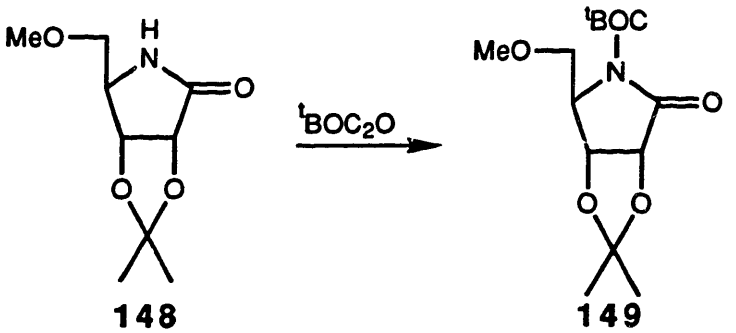
^1H NMR (300 MHz, $CDCl_3$): δ 7.43(s, 1H), 4.59(ABq, J_{AB} = 5.8Hz, $\Delta\nu_{AB}$ = 12.1 Hz, 2H), 3.79(dd, J = 3.6 Hz, 1H), 3.44(qd, J = 9.8, 3.6 Hz, 2H), 3.35(s, 3H), 1.47(s, 3H), 1.37(s, 3H).

Physical Properties for **148a**

R_f = 0.80 (9% ethyl acetate/hexane).

^1H NMR (250 MHz, C_6D_6): δ 7.83(d, J = 8.8 Hz, 2H), 6.60(d, J = 8.8 Hz, 2H), 4.76(d, J = 5.4 Hz, 1H), 4.66(dd, J = 2.1 Hz, 1H), 4.25(d, J = 5.4 Hz, 1H), 3.64(dd, J = 9.8, 2.5 Hz, 1H), 3.11(s, 3H), 2.92(dd, J = 9.8, 1.9 Hz, 1H), 2.78(s, 3H), 1.44(s, 3H), 1.17(s, 3H).

IR ($CHCl_3$) cm^{-1}: 2980 (m), 2930 (s, br), 2838 (m), 1755 (s, br), 1670 (s, br), 1600 (s), 1575 (m), 1500 (w), 1455 (m), 1380 (m), 1375 (m), 1365 (m), 1350 (m), 1313 (s), 1280-1300 (s, br), 1240-1260 (s, br), 1167 (s), 1150 (m), 1078-1110 (m, br), 1025 (m), 1010 (m), 960 (w).



148 **149**

^{t}BOC-Lactam, 149

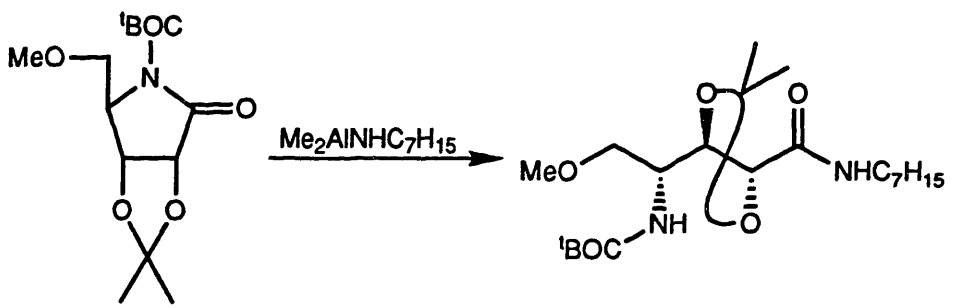
The lactam, **148**, (64.8 mg, 0.322 mmole), triethylamine (45 mL, 0.322 mmole), and DMAP (40 mg, 0.322 mmole) were dissolved in CH_2Cl_2 (3 mL)

at room temperature under argon. A solution of $(^tBOC)_2O$ (164 mg, 0.741 mmole) in CH_2Cl_2 (2 mL) was added and the reaction was stirred at room temperature for 2 hours. The solvent was the removed and the residue was purified by on silica gel (25% ethyl acetate/hexane) to give the product (96.3 mg, 99%) as an oil which solidified on standing.

Physical Properties for **149**

R_f = 0.23 (25% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 4.68(d, *J* = 5.3 Hz, 1H), 4.52(d, *J* = 5.3 Hz, 1H), 4.27(s, 1H), 3.67(dd, *J* = 9.8, 2.4 Hz, 1H), 3.58(d, *J* = 9.8 Hz, 1H), 3.31(s, 3H), 1.59(s, 9H), 1.45(s, 3H), 1.37(s, 3H).



149 **150**

^{t}BOC-Aminoamide, 150

A solution of heptylamine (33.5 mL, 0.226 mmole) in benzene (1 mL) was cooled to 0°C under argon and trimethylaluminum (2.0M in hexane, 0.113 mL, 0.226 mmole) was added. After stirring for 1 hour at room temperature, this solution was added, *via* cannula, to a solution of the ^{t}BOC-lactam, **149**, (56.7 mg, 0.188 mmole) in benzene (1 mL) at 0°C. The resulting mixture was stirred for 3 hours at room temperature, after which it was cooled to 0°C and carefully quenched with saturated Rochelle's salt

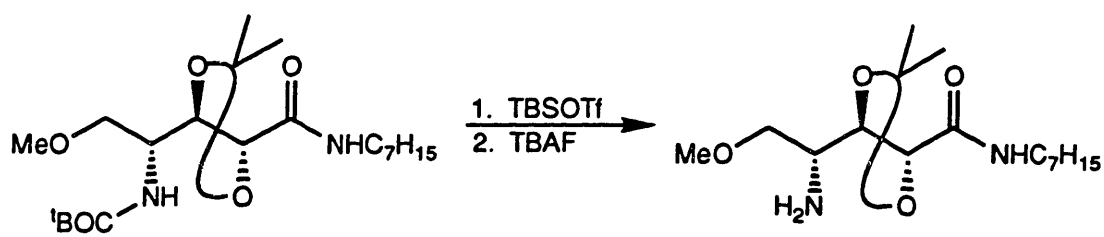
solution. After stirring for 30 minutes at room temperature, the products were extracted with ethyl acetate (3 X 5 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (25% ethyl acetate/hexane) to give the desired product (63.2 mg, 81%) as a colorless oil.

Physical Properties for 150

R_f = 0.38 (40% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 6.62(t, *J* = 5.1 Hz, 1H), 4.94(d, *J* = 8.4 Hz, 1H), 4.53(dd, *J* = 11.3, 6.6 Hz, 1H), 4.49(d, *J* = 6.6 Hz, 1H), 4.00(m, 1H), 3.63(dd, *J* = 9.7, 5.1 Hz, 1H), 3.50(dd, *J* = 9.7, 4.4 Hz, 1H), 3.35(s, 3H), 3.16-3.48(m, 2H), 1.53(s, 3H), 1.43(s, 9H), 1.37(s, 3H), 1.27-1.53(m, 10H), 0.88(t, *J* = 6.9 Hz, 3H).

^1H NMR (300 MHz, C_6D_6): δ 6.49(t, *J* = 5.1 Hz, 1H), 5.37(d, *J* = 8.7 Hz, 1H), 4.59(dd, *J* = 6.8 Hz, 1H), 4.51(d, *J* = 6.8 Hz, 1H), 4.46(m, 1H), 3.72(dd, *J* = 9.6, 5.5 Hz, 1H), 3.66(dd, *J* = 9.6, 4.6 Hz, 1H), 3.13-3.22(m, 2H), 3.12(s, 3H), 1.49(s, 9H), 1.34(s, 3H), 1.09(s, 3H), 1.09-1.35(m, 10H), 0.88(t, *J* = 6.9 Hz, 3H).



150 **151**

Aminoamide, 151

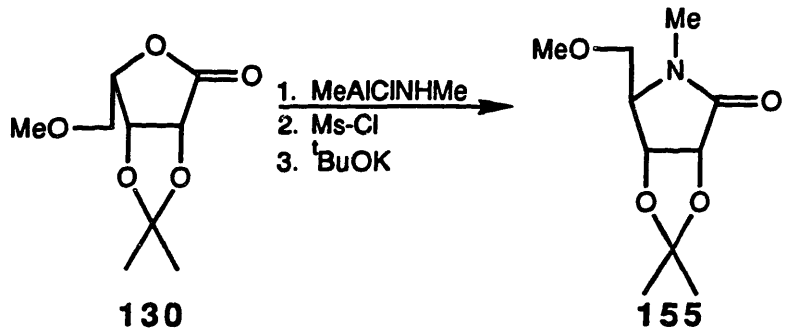
The ^{t}BOC-aminoamide, **150**, (14.6 mg, 0.035 mmole) and 2,6-lutidine (8.2 mL, 0.105 mmole) were dissolved in CH_2Cl_2 (1 mL) at room temperature under argon. ^{t}BuMe$_2$SiOTf (12.1 μL, 0.053 mmole) was added and the

reaction was stirred for 15 minutes. The reaction was quenched with saturated NH_4Cl solution (2 mL) and the products were extracted ether (3 X 2 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was dissolved in THF (1 mL). Tetrabutylammonium fluoride (1M in THF, 39 μL, 0.039 mmole) was added and the reaction was stirred for 30 minutes at room temperature under argon. After quenching with saturated NH_4Cl solution (3 mL), the reaction was washed with chloroform (3 X 3 mL) and the combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (ethyl acetate then 10% methanol/chloroform) to give the product (10.1 mg, 91%) as a 5 : 1 mixture of aminoamide, **151**, and lactam, **148**, as determined by 300-MHz ^1H NMR.

Physical Properties for **151**

R_f = 0.13 (2% methanol chloroform).

^1H NMR (300 MHz, C_6D_6): δ 6.53(m, 1H), 4.58(d, *J* = 7.2 Hz, 1H), 4.33(dd, *J* = 9.4, 7.2 Hz, 1H), 3.72(dd, *J* = 8.9, 2.8 Hz, 1H), 3.56(dd, *J* = 8.9, 7.0 Hz, 1H), 3.38(m, 1H), 3.23(m, 1H), 3.11(s, 3H), 3.01(m, 1H), 2.61(s, 2H), 1.37(s, 3H), 1.14(s, 3H), 1.11-1.25(m, 10H), 0.87(t, *J* = 7.0 Hz, 3H).



Methyl Lactam, 155

$MeNH_2 \cdot HCl$ (140.8 mg, 2.163 mmoles) was suspended in benzene (2 mL) and cooled to 0°C under argon. Trimethylaluminum (2.0M in hexane, 1.04 mL, 2.163 mmoles) was added, dropwise, over a period of 10 minutes. After stirring for 30 minutes at room temperature, the resulting solution was added, *via* cannula, to a solution of lactone, **130**, (208.2 mg, 1.030 mmole) in benzene (4 mL) at room temperature under argon. The resulting mixture was stirred for 3 hours, after which it was cooled to 0°C and carefully quenched with saturated Rochelle's salt solution. After stirring for 1 hour, the products were extracted with ethyl acetate (4 X 5 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed to give the hydroxyamide, **154**, (238.1 mg, 99% yield) as a white solid which was immediately dissolved in CH_2Cl_2 (3 mL). Triethylamine (0.430 mL, 3.090 mmoles) was added and the mixture was cooled to 0°C under argon. Methanesulfonyl chloride (0.12 mL, 1.545 mmoles) was then added and the reaction was stirred at 0°C for 30 minutes. The solvent was then removed and the residue was diluted with THF (22 mL) and filtered through Celite under argon. The resulting solution was cooled to -40°C and potassium *tert*-butoxide (1.41M in THF, 3 mL, 4.120 mmoles) was added. After warming to room temperature over 1 hour, the reaction was quenched with pH = 7 buffer (30 mL). The products were

extracted with ethyl acetate (3 X 15 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the product was purified on silica gel (80% ethyl acetate/hexane) to give the methyl lactam (184.3 mg, 84%) as a colorless oil.

Physical Properties for **154**

R_f = 0.14 (ethyl acetate).

^1H NMR (300 MHz, $CDCl_3$): δ 6.82(s, 1H), 4.57(d, J = 7.8 Hz, 1H), 4.45(dd, J = 7.8, 2.6 Hz, 1H), 4.11(ddd, J = 6.7, 6.0, 2.6 Hz, 1H), 3.50(ABX, J_{AB} = 9.7 Hz, J_{AX} = 6.7 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 14.8 Hz, 2H), 3.83(s, 3H), 2.85(d, J = 4.7 Hz, 3H), 2.33(d, J = 6.9 Hz, 1H), 1.58(s, 3H), 1.39(s, 3H).

Physical Properties for **155**

R_f = 0.32 (ethyl acetate).

^1H NMR (300 MHz, $CDCl_3$): δ 4.63(d, J = 5.8 Hz, 1H), 4.53(d, J = 5.8 Hz, 1H), 3.61(t, J = 2.7 Hz, 1H), 3.52(ABX, J_{AB} = 10 Hz, J_{AX} = 3.2 Hz, J_{BX} = 2.7 Hz, $\Delta\nu_{AB}$ = 15 Hz, 2H), 3.33(s, 3H), 2.87(s, 3H), 1.42(s, 3H), 1.37(s, 3H).

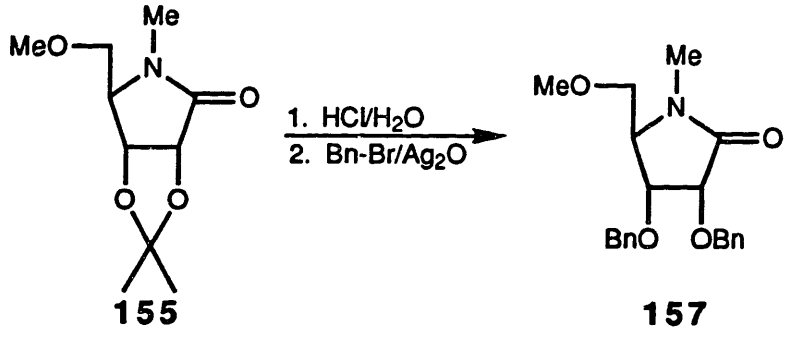
^{13}C NMR (300 MHz, $CDCl_3$): δ 171.48, 111.60, 77.31, 76.10, 69.42, 63.52, 59.17, 27.78, 26.87, 25.54.

EI Mass Spec: m/e 200 $[M - 15]^+$, 170, 142, 85, 69, 45.

Exact Mass: $[M - CH_3]^+$ = 200.09228 (calculated)

$[M - CH_3]^+$ = 200.0921 (measured).

IR ($CHCl_3$) cm^{-1}: 2995, 2937, 1700, 1450, 1400, 1375, 1120, 1070.



155 157

Dibenzyl Lactam, 157

The methyl lactam, **155**, (74.8 mg, 0.348 mmole) was dissolved in THF (2 mL) and concentrated HCl (1.5 mL) was added. The reaction was stirred at room temperature for 2 hours, after which it was concentrated to dryness. The residue was azeotropically dried with benzene (3 X 5 mL) and kept under vacuum for 24 hours. The residue was then dissolved in DMF (1 mL) and Ag_2O (367 mg, 5 equiv by wt) was added. Benzyl bromide (0.29 mL, 2.436 mmoles) was added to the resulting suspension and the reaction was stirred at room temperature under argon for 20 hours. The reaction was then filtered through Celite and the solids were washed with $CHCl_3$. The combined organics were diluted with ether/hexane (4/1, 5 mL) and saturated NH_4Cl solution (5 mL) was added. The products were extracted with ether/hexane (4/1, 3 X 5 mL) and the combined organics were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (80% ethyl acetate/hexane) to give the desired product (102.8 mg, 83%) as an oil.

Physical Properties for **157**

R_f = 0.40 (ethyl acetate).

^1H NMR (300 MHz, $CDCl_3$): δ 7.44(d, J = 6.8 Hz, 2H), 7.30(d, J = 7.1Hz, 2H), 7.06-7.19(m, 6H), 5.04(ABq, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 85.2 Hz, 2H), 4.48(ABq, J_{AB}

= 11.7 Hz, $\Delta\nu_{AB}$ = 79.8 Hz, 2H), 4.07(d, J = 5.5 Hz, 1H), 3.80(dd, J = 5.5, 3.6 Hz, 1 H), 3.37(q, J = 3.6 Hz, 1H), 2.86(d, J = 3.6 Hz, 2H), 2.82(s, 3H), 2.57(s, 3H).

^{1}H NMR (300 MHz, C_6D_6): δ 7.40-7.44(m, 2H), 7.27-7.36(m, 8H), 4.89(ABq, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 55.3 Hz, 2H), 4.60(ABq, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 48.7 Hz, 2H), 4.11(d, J = 5.8 Hz, 1H), 3.97(dd, J = 5.8, 2.9 Hz, 1H), 3.59(q, J = 3.1 Hz, 1H), 3.48(dd, J = 10.3, 3.3 Hz, 1H), 3.29(dd, J = 10.3, 2.8 Hz, 1H), 3.27(s, 3H), 2.86(s, 3H).

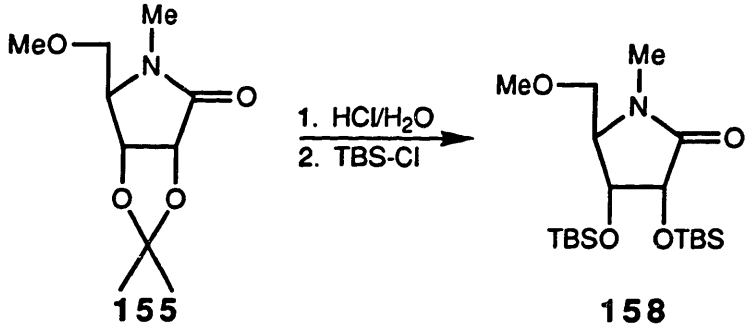
^{13}C NMR (300 MHz, $CDCl_3$): δ 171.17, 137.86, 137.71, 128.25, 128.16, 127.97, 127.82, 127.70, 127.53, 74.97, 74.51, 72.26, 72.03, 69.71, 63.33, 59.01, 27.56.

FAB Mass Spec: m/e 356 $[M + 1]^+$, 326, 278, 264, 248, 181.

Exact Mass: $[M + 1]^+$ = 356.18618 (calculated)

$[M + 1]^+$ = 356.1864 (measured).

IR (neat) cm^{-1}: 3060, 3025, 2900, 1700, 1450, 1400, 1350, 1260, 1190, 1100, 1155, 730, 690.



155 **158**

Bis-TBS Lactam, 158

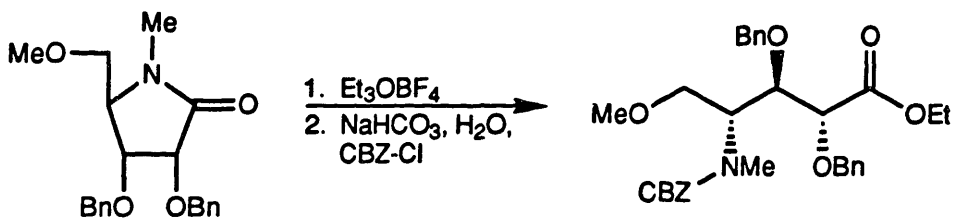
The methyl lactam, **155**, (447.1 mg, 2.077 mmole) was dissolved in THF (5 mL) and concentrated HCl (5 mL) was added. The reaction was stirred at room temperature for 3 hours, after which the solvent was removed and the residue was azeotropically dried with benzene (5 X 5 mL)

and kept under vacuum for 24 hours. The residue was dissolved in CH_2Cl_2 (7 mL) and imidazole (710 mg, 10.385 mmoles) was added followed by *tert*-butyldimethylchlorosilane (940 mg, 6.231 mmoles). After 24 hours, the mixture was quenched with pH = 7 buffer (10 mL). The products were extracted with ethyl acetate (3 X 10 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the product purified on silica gel (15% ethyl acetate/hexane) to give the product (797.7 mg, 95% yield) an oil.

Physical Properties for **158**

R_f = 0.40 (33% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 4.23(d, *J* = 5.1 Hz, 1H), 4.14(dd, *J* = 5.1, 1.9 Hz, 1H), 3.47(d, *J* = 1.1 Hz, 1H), 3.46(s, 1H), 3.35(m, 1H), 3.34(s, 3H), 2.84(s, 3H), 0.93(s, 9H), 0.88(s, 9H), 0.18(s, 3H), 0.14(s, 3H), 0.091(s, 3H), 0.086(s, 3H).



157 **159**

CBZ-Aminoester, 159

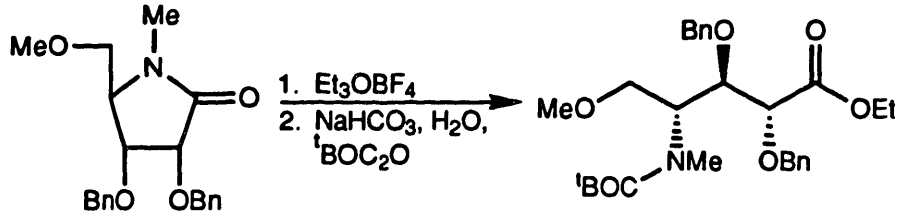
The dibenzyl lactam, **157**, (38.9 mg, 0.199 mmole) was dissolved in CH_2Cl_2 (1 mL) and 2,6-di-*tert*-butylpyridine (49 μL, 0.398 mmole) was added followed by Et_3OBF_4 (1M in CH_2Cl_2, 0.40 mL, 0.398 mmole). The reaction was stirred at room temperature under argon for 6 hours, after which the solvent was removed and the residue was dissolved in ether (1.5 mL). CBZ-Cl (46 μL, 0.597 mmole) was added followed by saturated $NaHCO_3$ solution

(1.5 mL). The mixture was stirred for 1 hour, after which ethyl acetate (5 mL) and brine (5 mL) were added. The products were extracted with ethyl acetate (3 X 5 mL) and the combined organics were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (15% ethyl acetate/hexane) to give the desired product (43.8 mg, 75%) and the starting lactam (9.9 mg, 25%) as oils.

Physical Properties for 159

R_f = 0.62 (40% ethyl acetate/hexane).

^1H NMR (250 MHz, $CDCl_3$): δ 7.27-7.37 (m, 15H), 5.09 (s, 2H), (4.01, 4.28, isomers, m, 4H), (4.33, 4.79, isomers, m, 5H), (3.50, 3.82, isomers, m, 2H), (3.21, 3.27, isomers, s, s, 3H), (2.82, 2.85, isomers, s, s, 3H), (1.18, 1.24, isomers, t, t, J = 7.1 Hz, J = 7.2 Hz, 3H), .



157 160

^{t}BOC-Aminoester, 160

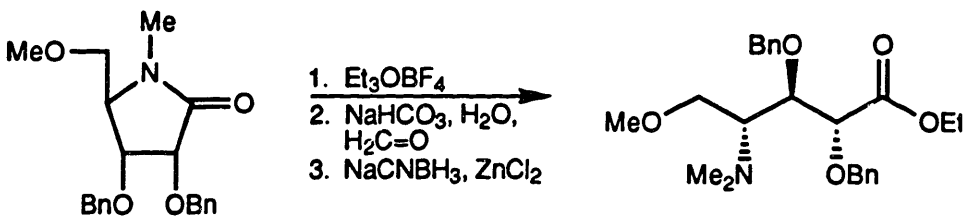
The dibenzyl lactam, **157**, (37.7 mg, 0.106 mmole) and 2,6-di-*tert*-butylpyridine (48 μL, 0.212 mmole) were dissolved in CH_2Cl_2 (1 mL) and Et_3OBF_4 (1M in CH_2Cl_2, 0.21 mL, 0.212 mmole) was added. The mixture was stirred at room temperature under argon for 24 hours. The solvent was removed, and the residue was dissolved in ether (2 mL). $(^tBOC)_2O$ (47.1 mg, 0.212 mmole) was added followed by saturated $NaHCO_3$ solution (1 mL). The mixture was stirred for 1.5 hours, after which ethyl acetate (5 mL) and

brine (5 mL) were added. The products were extracted with ethyl acetate (3 X 5 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (15% ethyl acetate/hexane) to give the product, **160**, (38.5 mg, 72%) and the lactam, **157**, (7.3 mg, 19%) as oils.

Physical Properties for **160**

R_f = 0.64 (50% ethyl acetate/hexane).

^1H NMR (250 MHz, $CDCl_3$): δ 7.27-7.39 (comp m, 10H), (4.71, 4.81, isomers, m, 2H), (4.40, 4.52, isomers, m, 2H), (4.01, 4.25, isomers, m, 5H), (3.56, 3.84, isomers, m, 2H), 3.28 (s, 3H), 2.77 (s, 3H), (1.40, 1.43, isomers, s, s, 9H), (1.23, 1.31, isomers, m, 3H).



157 **161**

Dimethylaminoester, 161

The dibenzyl lactam, **157**, (30 mg, 0.084 mmole) and 2,6-di-*tert*-butylpyridine (38 μL, 0.168 mmole) were dissolved in CH_2Cl_2 (1 mL), and Et_3OBF_4 (1M in CH_2Cl_2, 0.17 mL, 0.168 mmole) was added. The reaction was stirred at room temperature under argon for 16 hours, after which the solvent was removed. Aqueous formaldehyde (37%, 28 μL, 0.336 mmole) was added followed by saturated $NaHCO_3$ solution (0.8 mL) and methanol (1 mL).

$ZnCl_2$ (37 mg, 0.252 mmole) was dissolved in MeOH (1 mL) added, *via*

cannula, to a solution of $NaCNBH_3$ (33.6 mg, 0.504 mmole) in MeOH (1 mL). The mixture was stirred at room temperature under argon for 5 minutes, after which it was added, *via* cannula, to the above reaction. The resulting mixture was stirred for 4 hours and quenched with 0.1N KOH (1 mL). The products were extracted with ethyl acetate (3 X 5 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the product was purified on silica gel (25% ethyl acetate/hexane) to give the dimethylaminoester, **161**, (27.6 mg, 79%) and the dibenzyl lactam, **157**, (3.4 mg, 11%) as oils.

Physical Properties for **161**

R_f = 0.38 (33% ethyl acetate/hexane).

^1H NMR (250 MHz, C_6D_6): δ 7.41(d, J = 6.6 Hz, 2H), 7.33(d, J = 7.1 Hz, 2H), 7.06-7.21(m, 6H), 4.91(1/2 ABq, J_{AB} = 12.1 Hz, 1H), 4.73(1/2 ABq, J_{AB} = 11.4 Hz, 1H), 4.56(d, J = 1.7 Hz, 1 H), 4.46(1/2 ABq, J_{AB} = 12.1 Hz, 1H), 4.42(1/2 ABq, J_{AB} = 11.4 Hz, 1H), 4.11(dd, J = 10.1, 1.7 Hz, 1H), 4.05(q, J = 7.1 Hz, 2H), 3.67(dd, J = 9.8, 2.4 Hz, 1H), 3.54(dd, J = 9.8, 7.1 Hz, 1H), 3.41(ddd, J = 9.8, 7.1, 2.4 Hz, 1H), 3.05(s, 3H), 2.36(s, 6H), 1.02(t, J = 7.1 Hz, 3H).

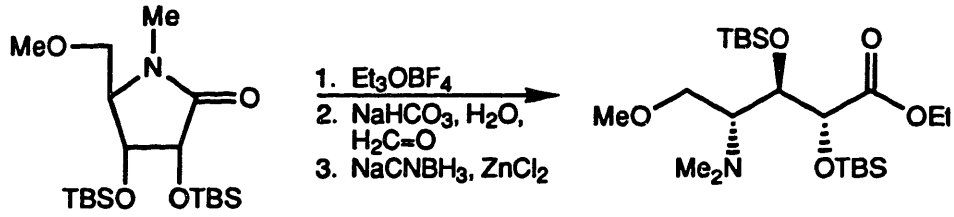
^{13}C NMR (300 MHz, $CDCl_3$): δ 170.04, 139.32, 138.98, 128.45, 128.38, 128.07, 128.03, 127.54, 80.72, 78.94, 73.03, 73.00, 69.78, 62.31, 60.16, 58.38, 42.15, 14.36.

FAB Mass Spec: m/e 416 $[M + 1]^+$, 370, 308, 102.

Exact Mass: $[M + 1]^+$ = 416.24370 (calculated)

$[M + 1]^+$ = 416.2440 (measured).

IR (neat) cm^{-1}: 3090, 3065, 3035, 2980, 2935, 2875, 2835, 1750, 1745, 1498, 1455, 1390, 1368, 1346, 1280, 1190, 1110, 1025, 760, 690.



158 **162**

Dimethylaminoester, 162

The bis-TBS lactam, **158**, (73.7 mg, 0.183 mmole) and 2,6-di-*tert*-butylpyridine (0.125 mL, 0.549 mmole) were dissolved in CH_2Cl_2 (2 mL), and Et_3OBF_4 (1M in CH_2Cl_2, 0.55 mL, 0.549 mmole) was added. The mixture was stirred at room temperature under argon for 24 hours, after which the solvent was removed. Aqueous formaldehyde (37%, 60 μL, 0.732 mmole) was added followed by saturated $NaHCO_3$ solution (1 mL), and methanol (1 mL).

$ZnCl_2$ (81.8 mg, 0.549 mmole) was dissolved in MeOH (1 mL) and added *via* cannula to a solution of $NaCNBH_3$ (77.4 mg, 1.098 mmoles) in MeOH (.5 mL). The mixture was stirred at room temperature under argon for 5 minutes, after which the mixture was added, *via* cannula, to the above reaction. The resulting mixture was stirred for 4 hours and quenched with 0.1N KOH (5 mL). The products were extracted with ethyl acetate (3 X 5 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the product was purified on silica gel (2% ethyl acetate/hexane) to give the dimethylaminoester, **162**, (58.1 mg, 69%) and the bis-TBS lactam, **158**, (18.6 mg, 25%) as oils.

Physical Properties for **162**

R_f = 0.73 (20% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 4.30(d, *J* = 1.5 Hz, 1H), 4.07(q, *J* = 7.3 Hz, 2H), 4.02(dd, *J* = 10.1, 1.5 Hz, 1H), 3.53(m, 2H), 3.29(s, 3H), 3.11(ddd, *J* = 10.1, 8.2, 4.0

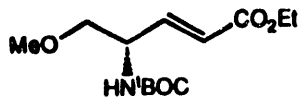
Hz, 1H), 2.24(s, 6H), 1.27(t, J = 7.3 Hz, 3H), 0.94(s, 9H), 0.89(s, 9H), 0.11(s, 3H), 0.10(s, 3H), 0.07(s, 3H), 0.06(s, 3H).

^{1}H NMR (300 MHz, C_6D_6): δ 4.66(d, J = 1.5 Hz, 1H), 4.32(dd, J = 10.1, 1.5 Hz, 1H), 4.00(m, 2H), 3.58(d, J = 5.1 Hz, 2H), 3.36(m, 1H), 3.09(s, 3H), 2.39(s, 6H), 1.08(s, 18H), 1.02(t, J = 3.4 Hz, 3H), 0.25(s, 6H), 0.15(s, 3H), 0.13(s, 3H).

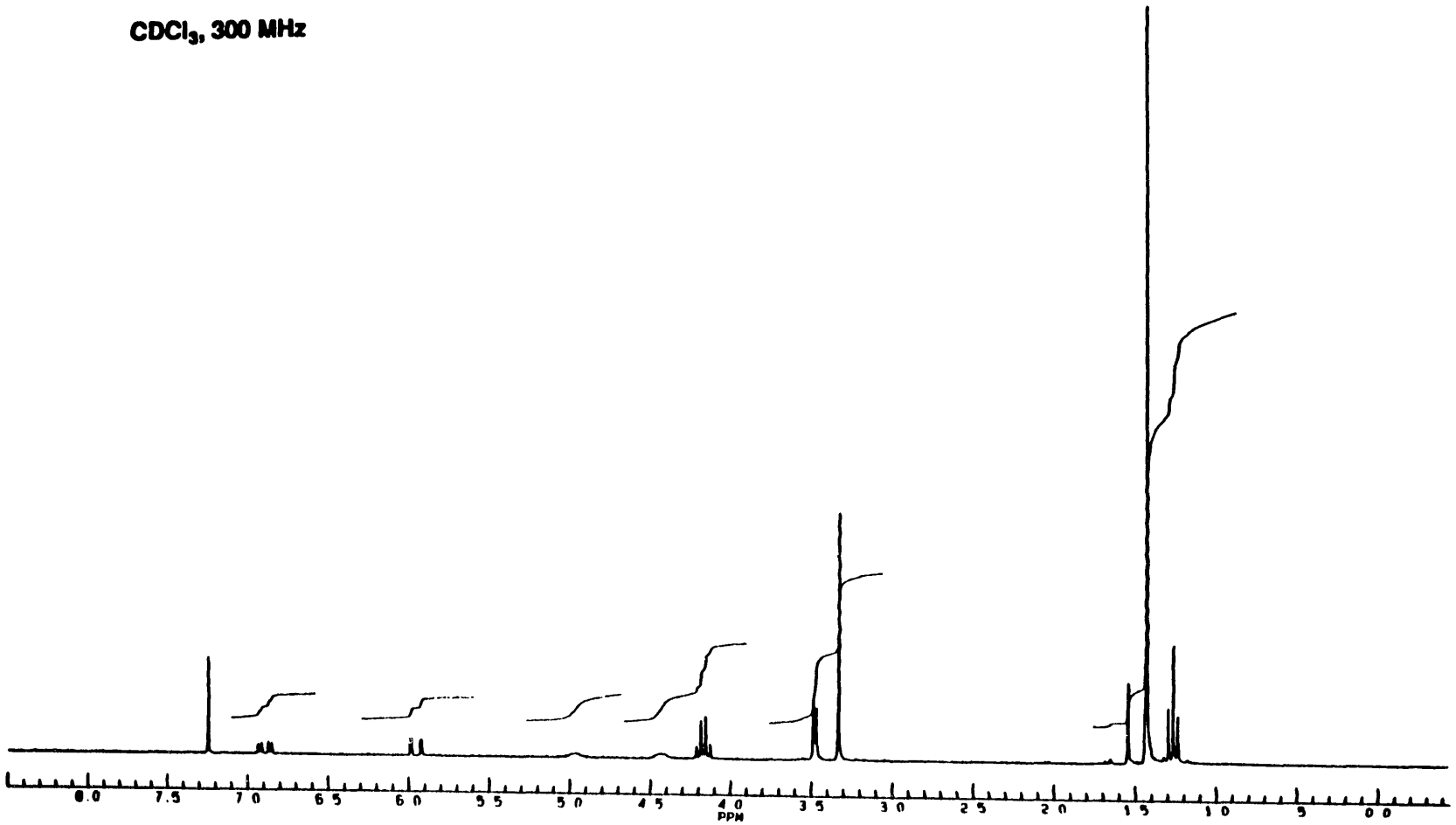
^{13}C NMR (300 MHz, $CDCl_3$): δ 171.2, 77.2, 75.6, 74.6, 70.7, 61.4, 60.0, 58.4, 41.8, 26.0, 25.8, 18.4, 18.0, 14.2, -3.9, -4.8, -5.0, -5.3.

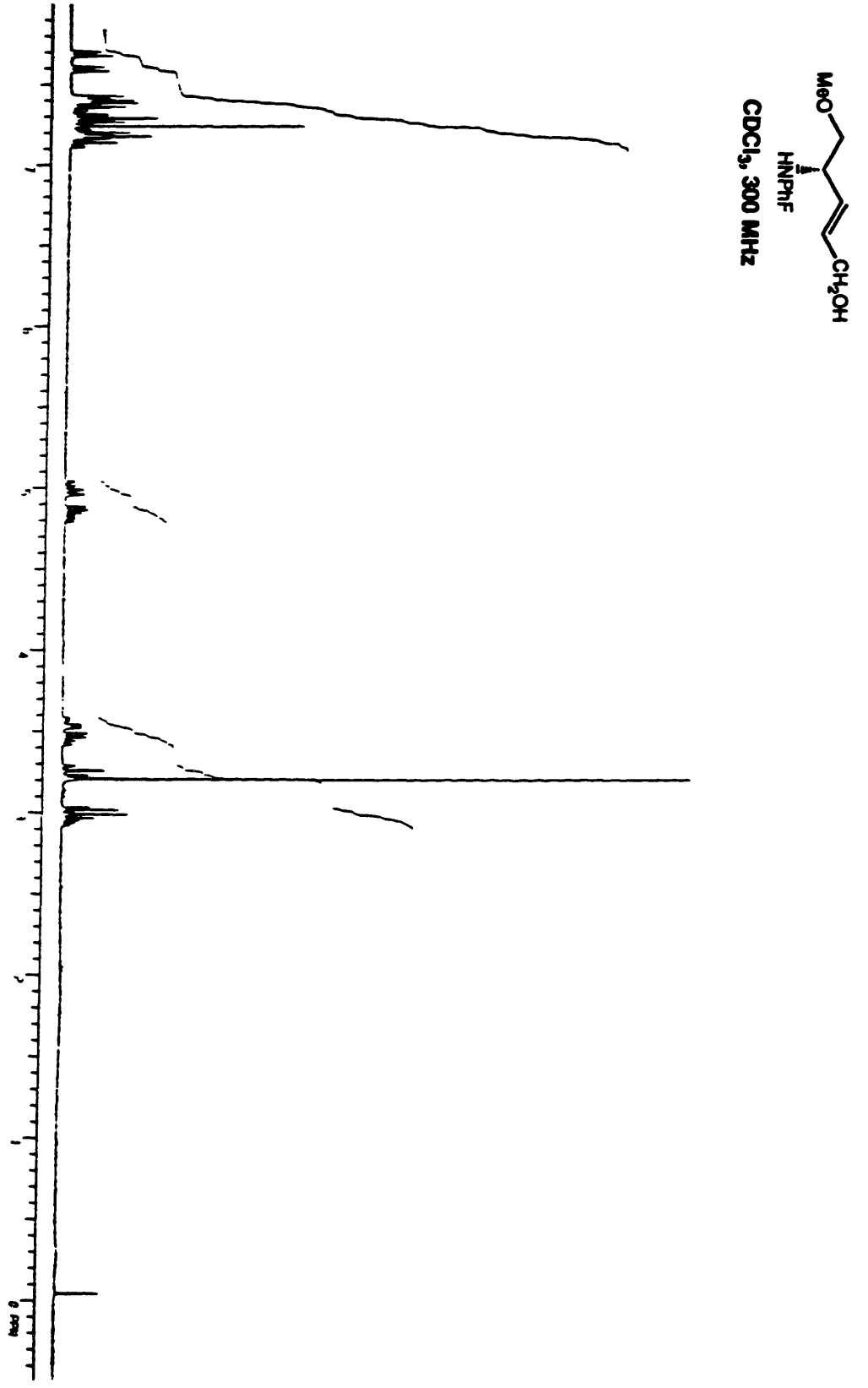
3.6 NMR Spectra

MeO
CO2Me
HNBOC
CDCl3, 300 MHz

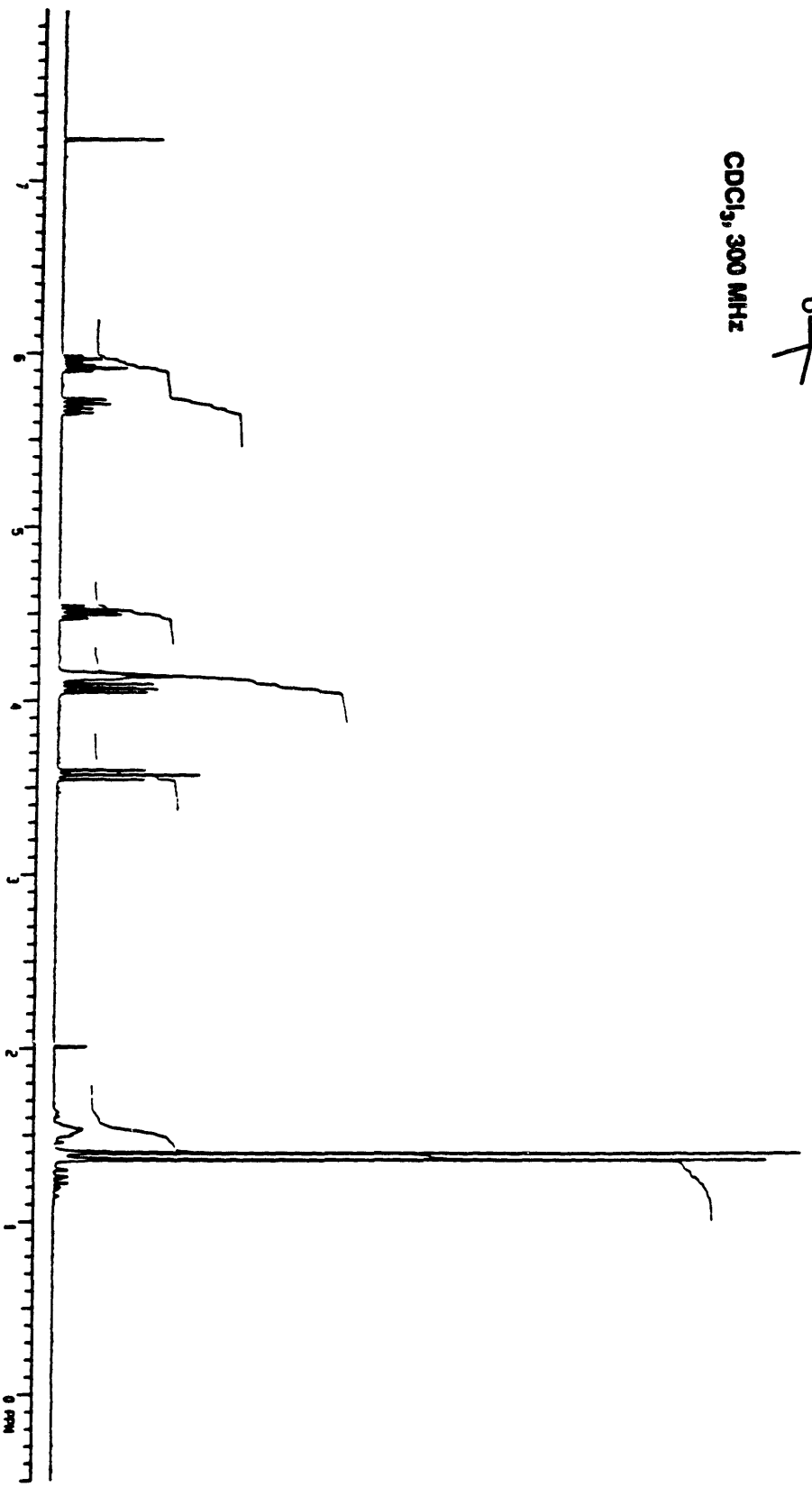


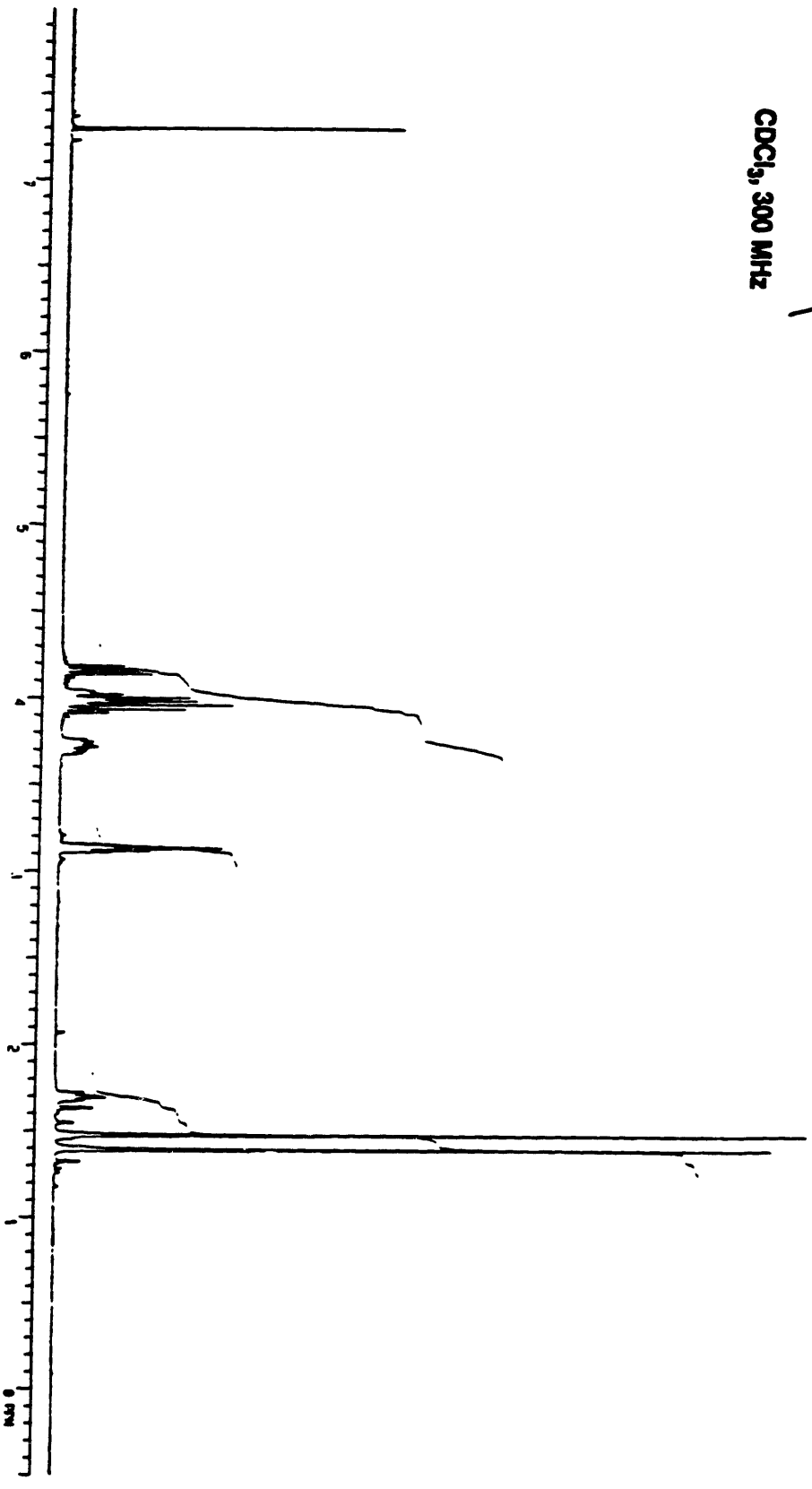
$CDCl_3$, 300 MHz

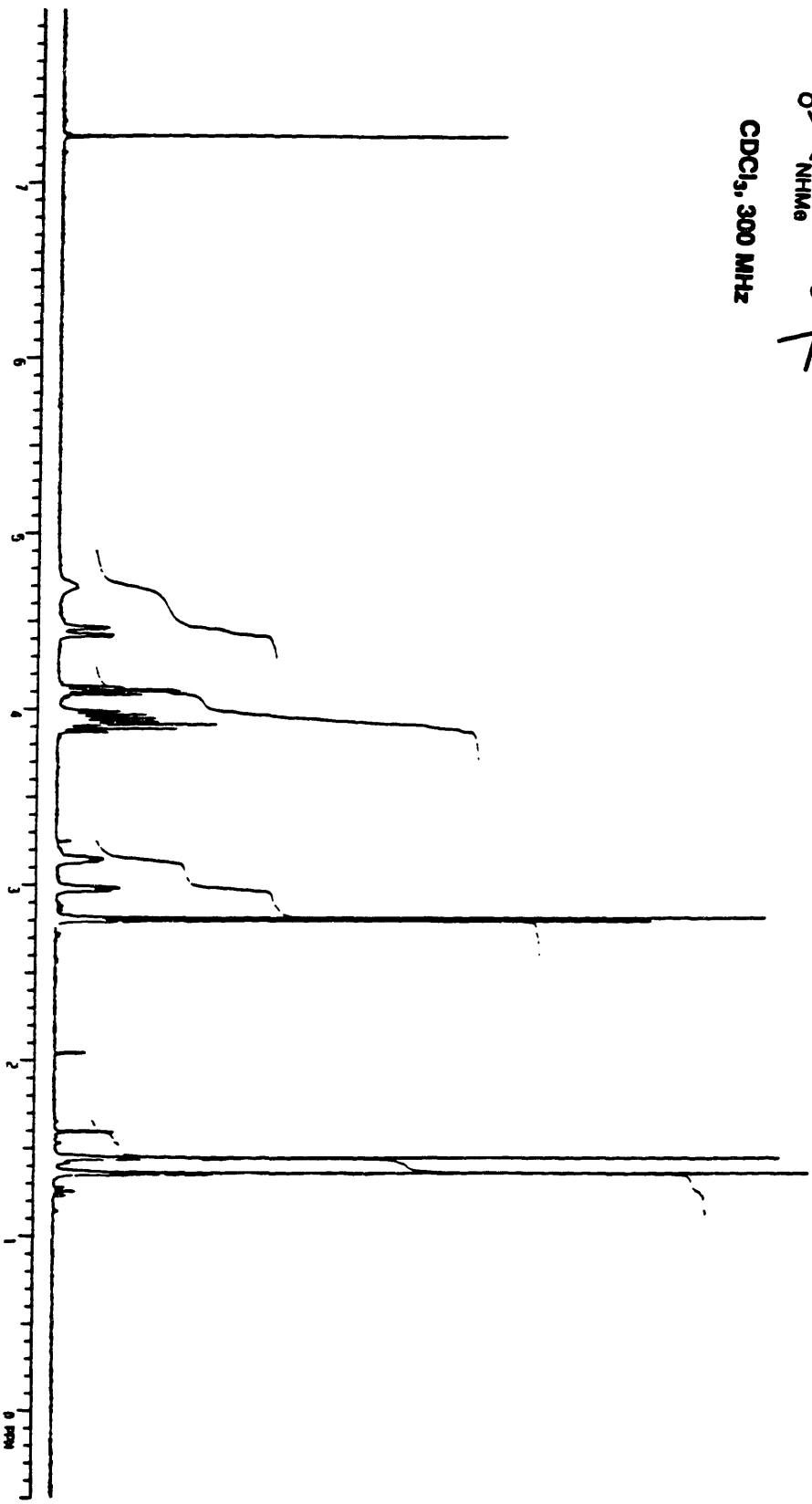



MeO
HNPhF
CH2OH
CDCl3, 300 MHz

CDCl3, 300 MHz
EtO
O
O
O
PPM 0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0

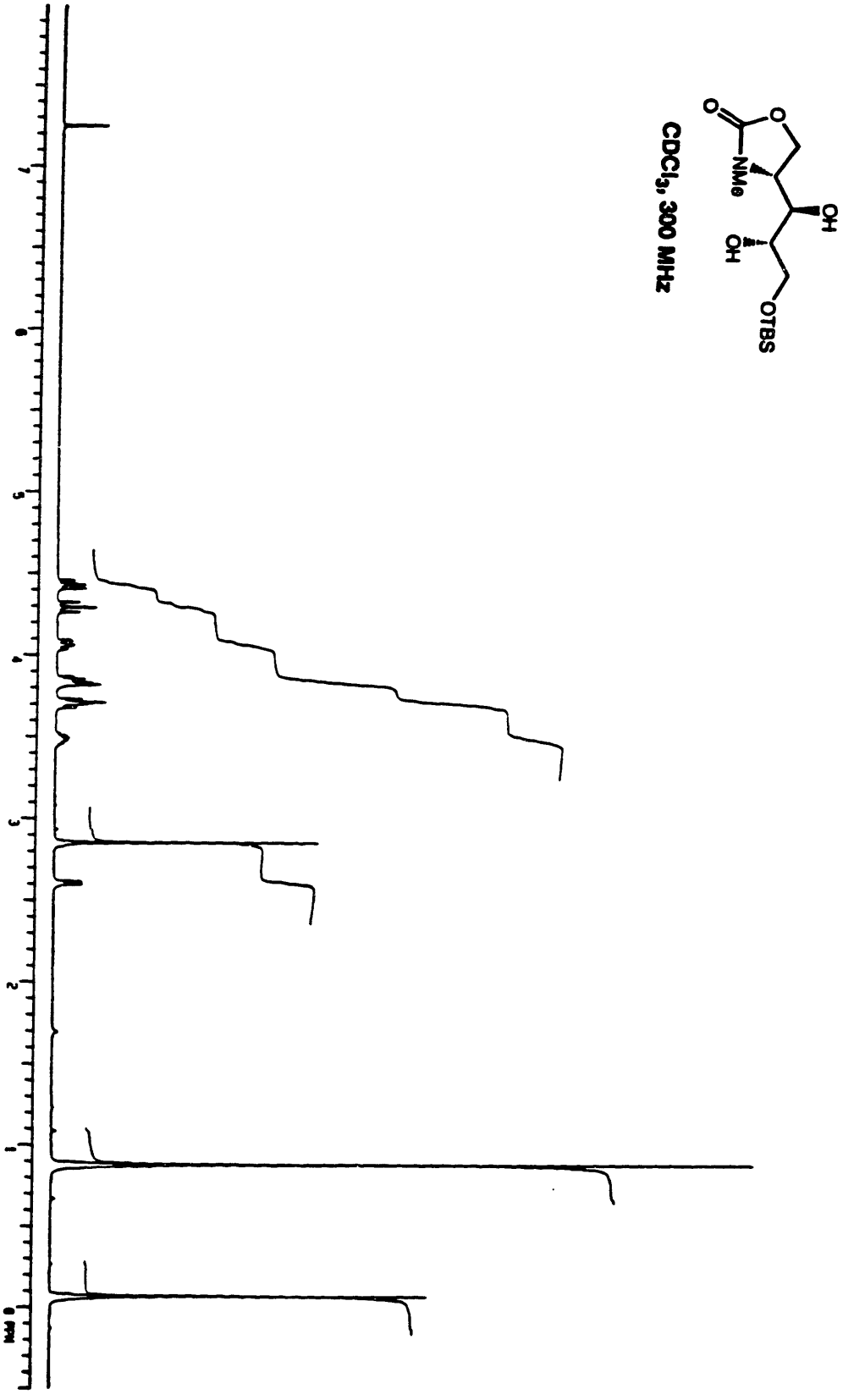

CDCl3, 300 MHz
OH
O
O


CDCl3, 300 MHz
HO
O
O
O
O
PPM
1
2
5
6
7


NHMe
CDCl3, 300 MHz

CDCl3, 300 MHz
NMe
OH
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

DMSO, 300 MHz
NMe
OH
OH
OH
O
O
O


CDCl3, 300 MHz
NMe
OH
OH
OTBS

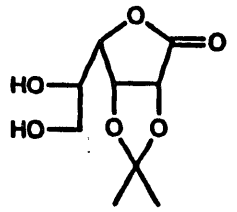
CDCl3, 300 MHz
NMe
OTBS

HO
Me2N
O
O
OTBS
CDCl3, 300 MHz
PPM 0

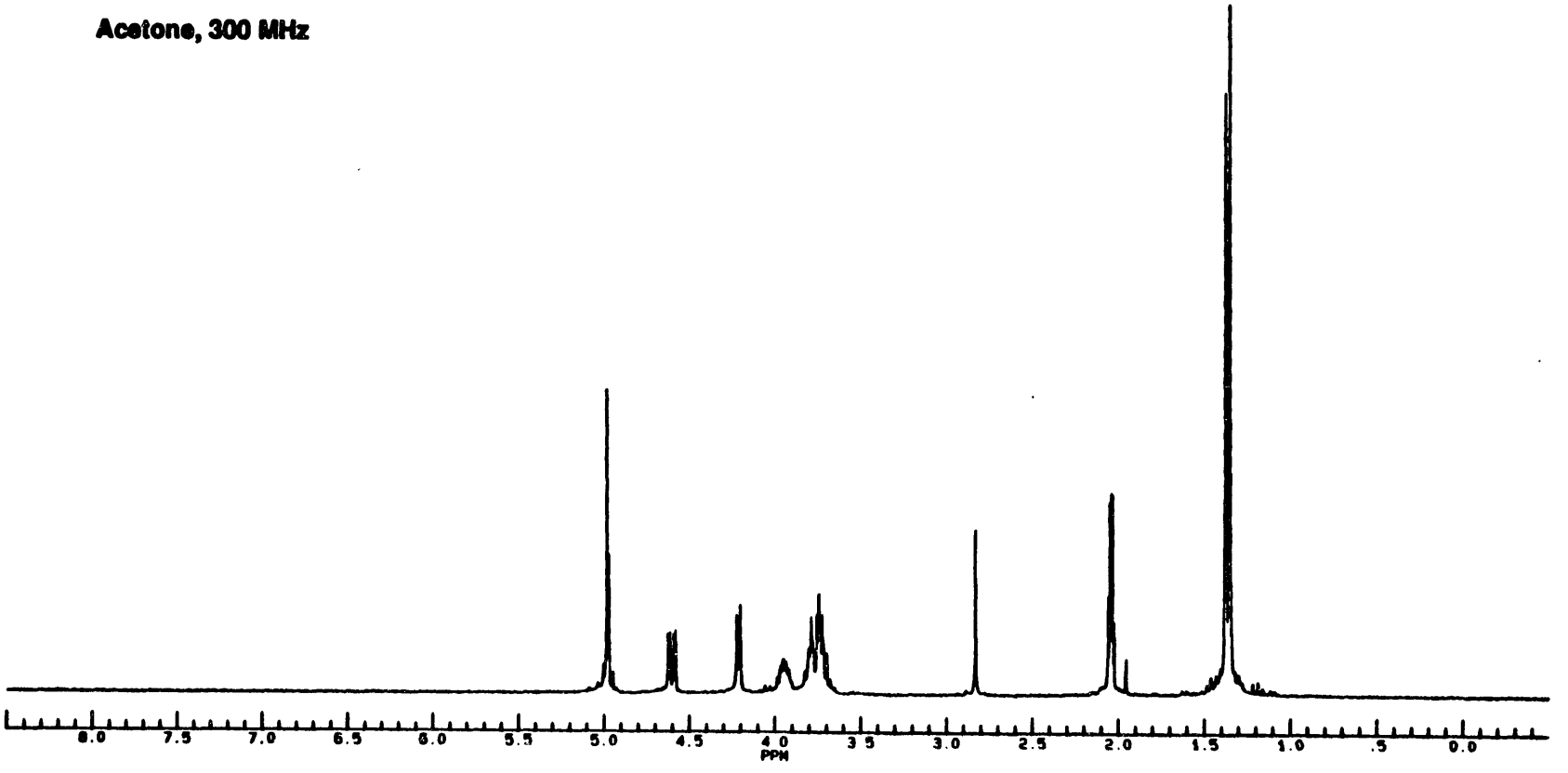
MeO
Me2N
O
OTBS
CDCl3, 300 MHz

CDCl3, 300 MHz
MeO
Me2N
OH
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

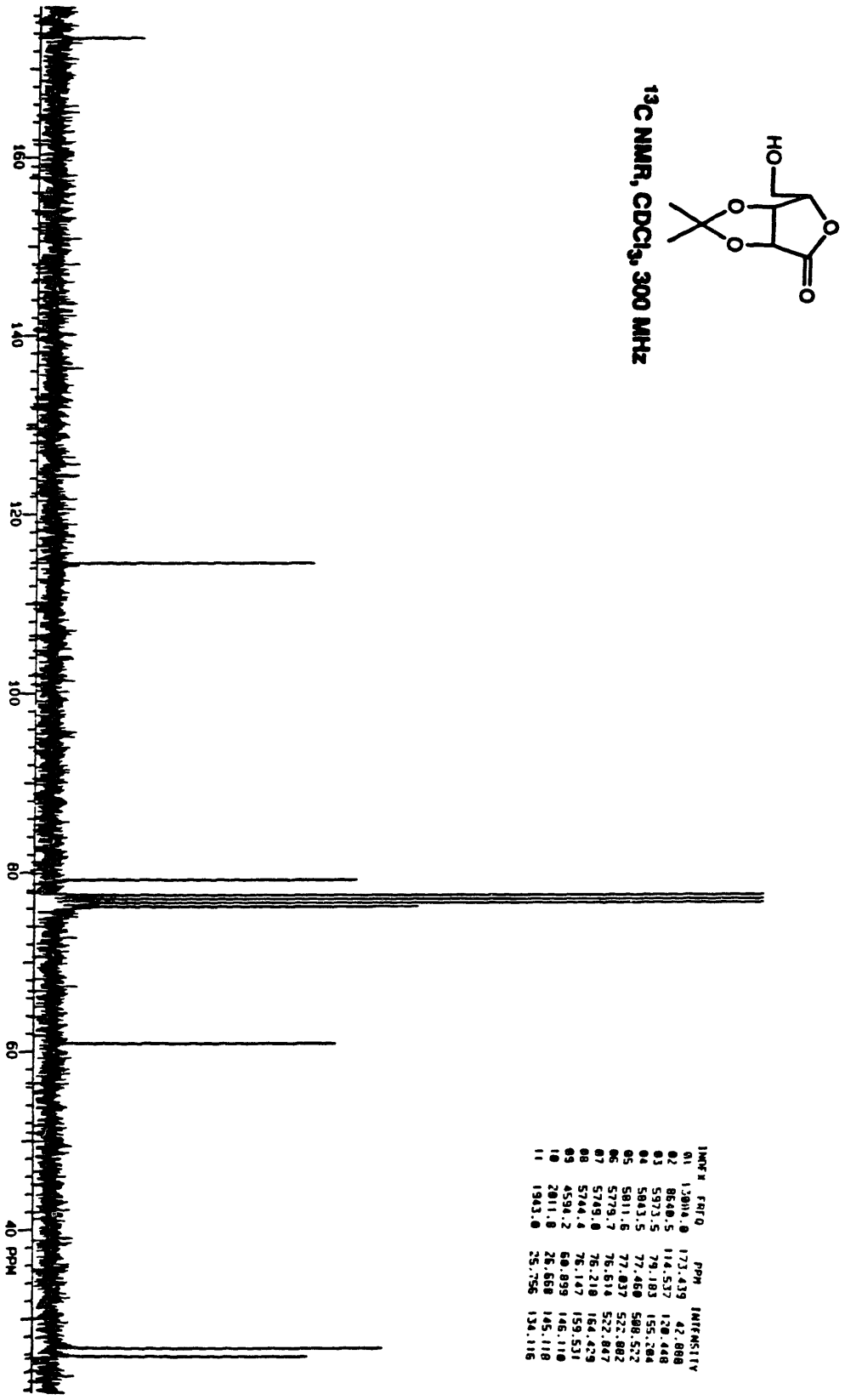
CDCl3, 300 MHz
PPM
0.0 PPM



Acetone, 300 MHz



CDCl3, 300 MHz
HO
O
O
O
O
0
1
2
3
4
5
6
7



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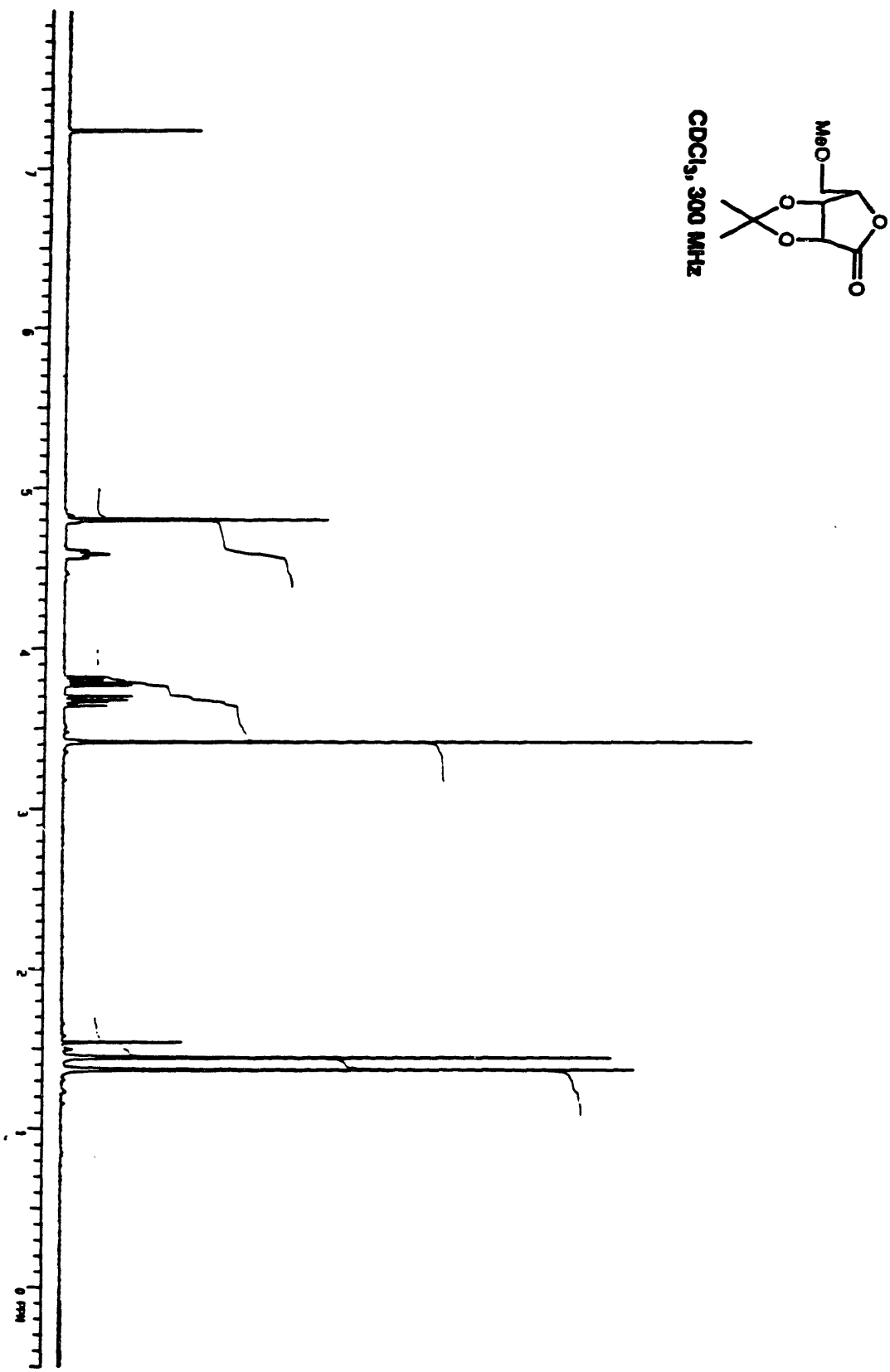
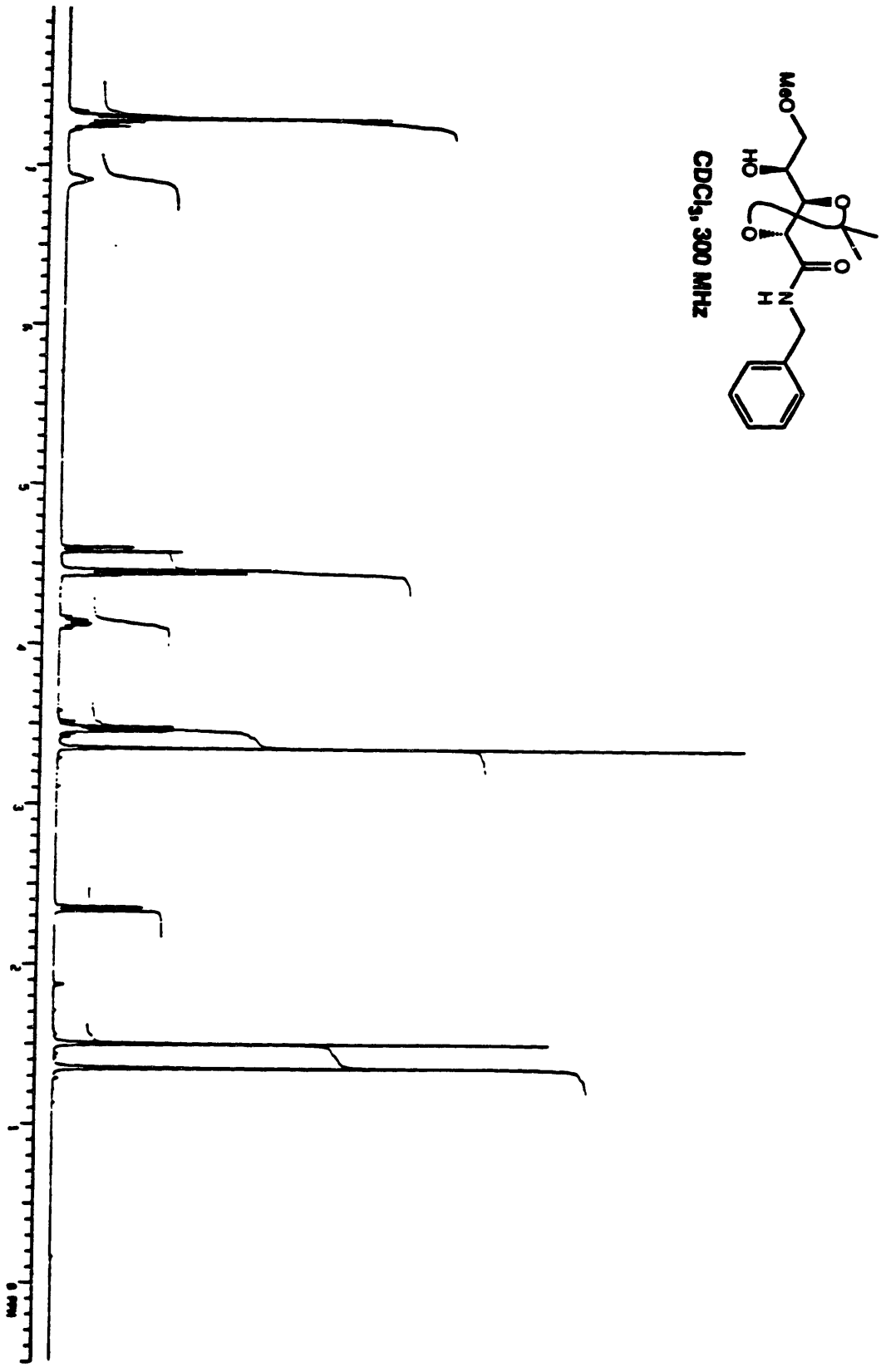
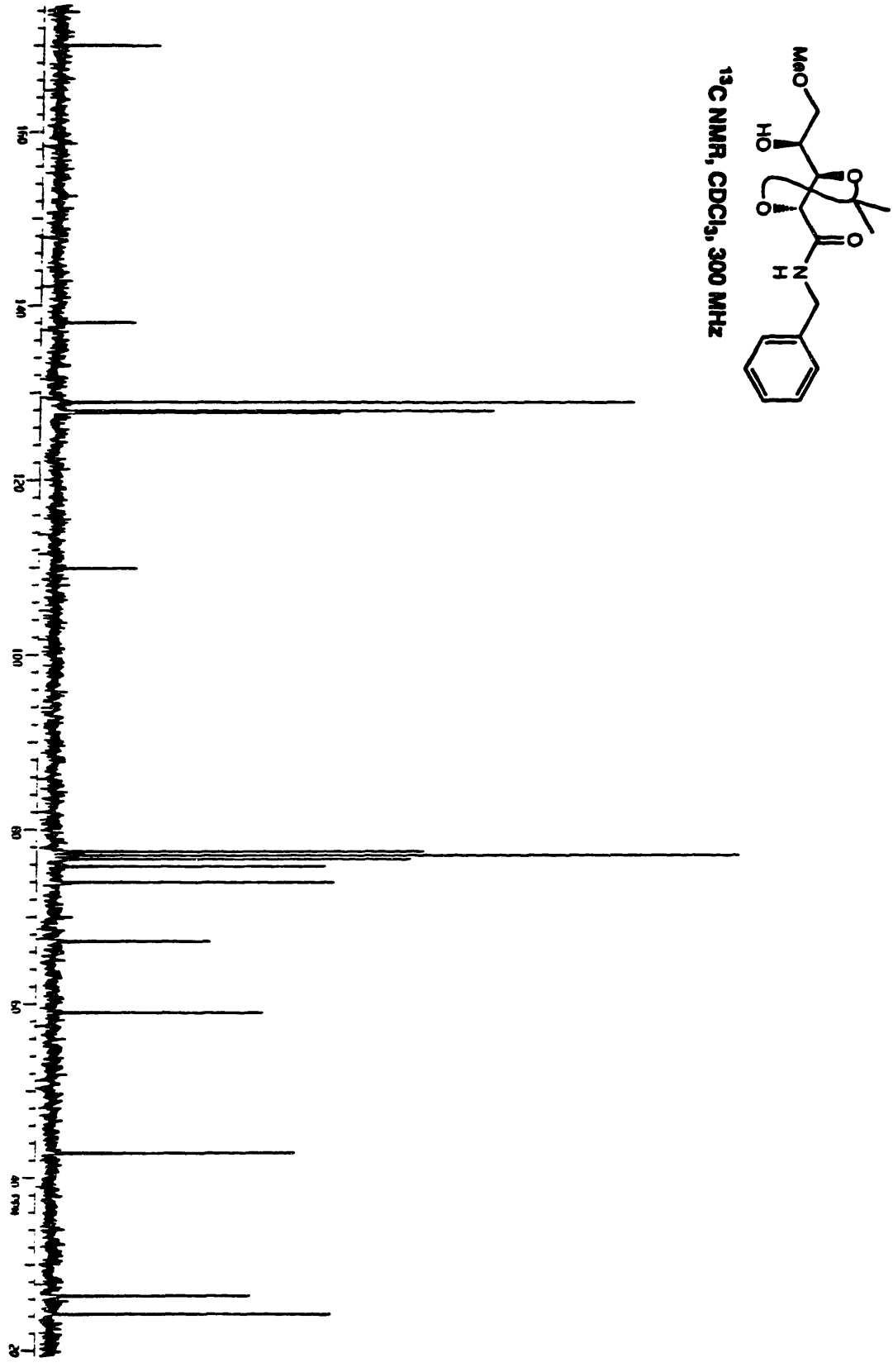
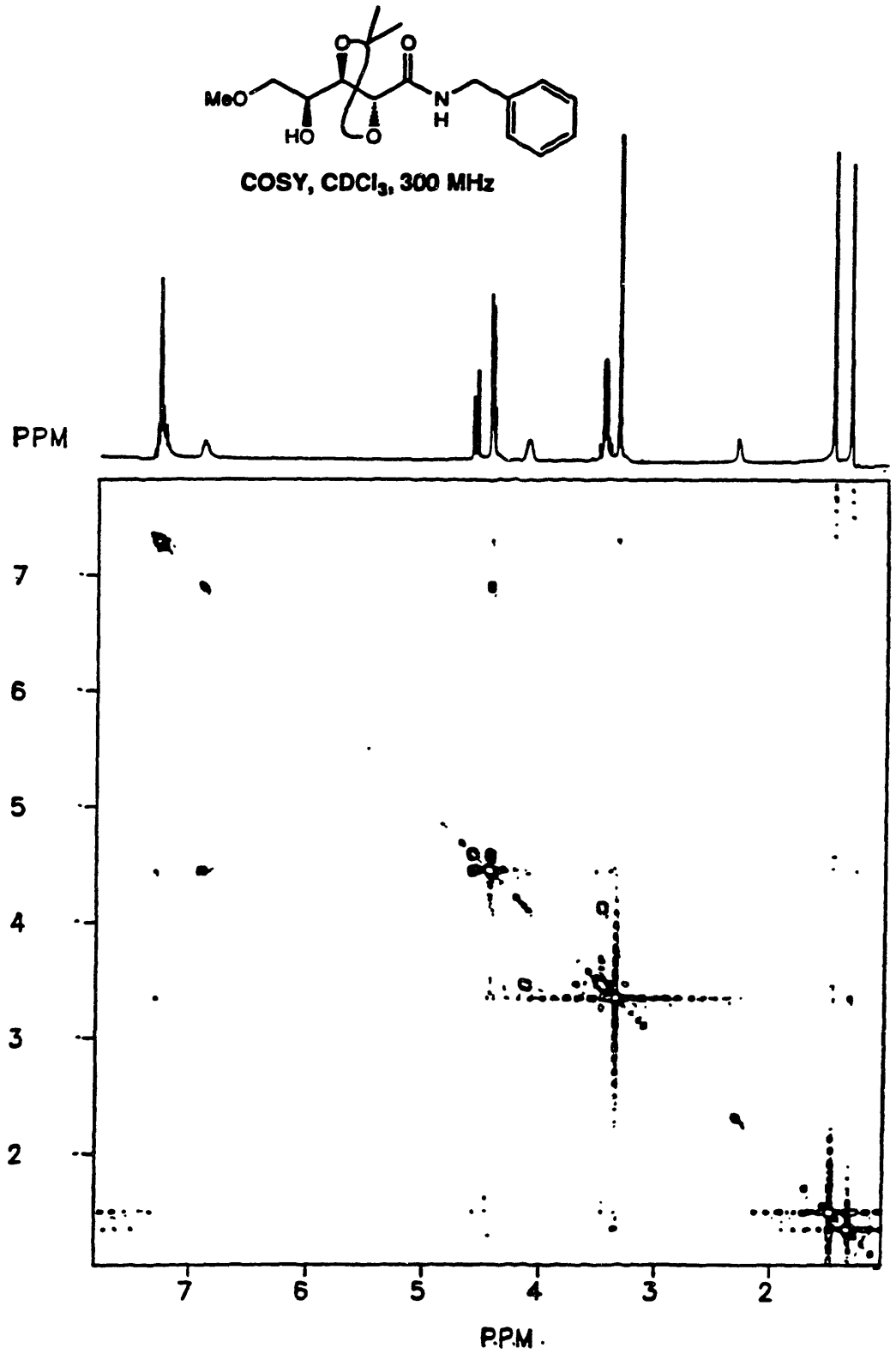
03	5973.5	79.183	155.284
04	5843.5	77.460	508.522
05	5811.6	77.037	522.082
06	5779.7	76.614	522.847
07	5749.0	76.210	164.429
08	5744.4	76.147	159.531
09	4594.2	60.959	146.110
10	2011.8	26.668	145.110
11	1963.0	25.756	134.116

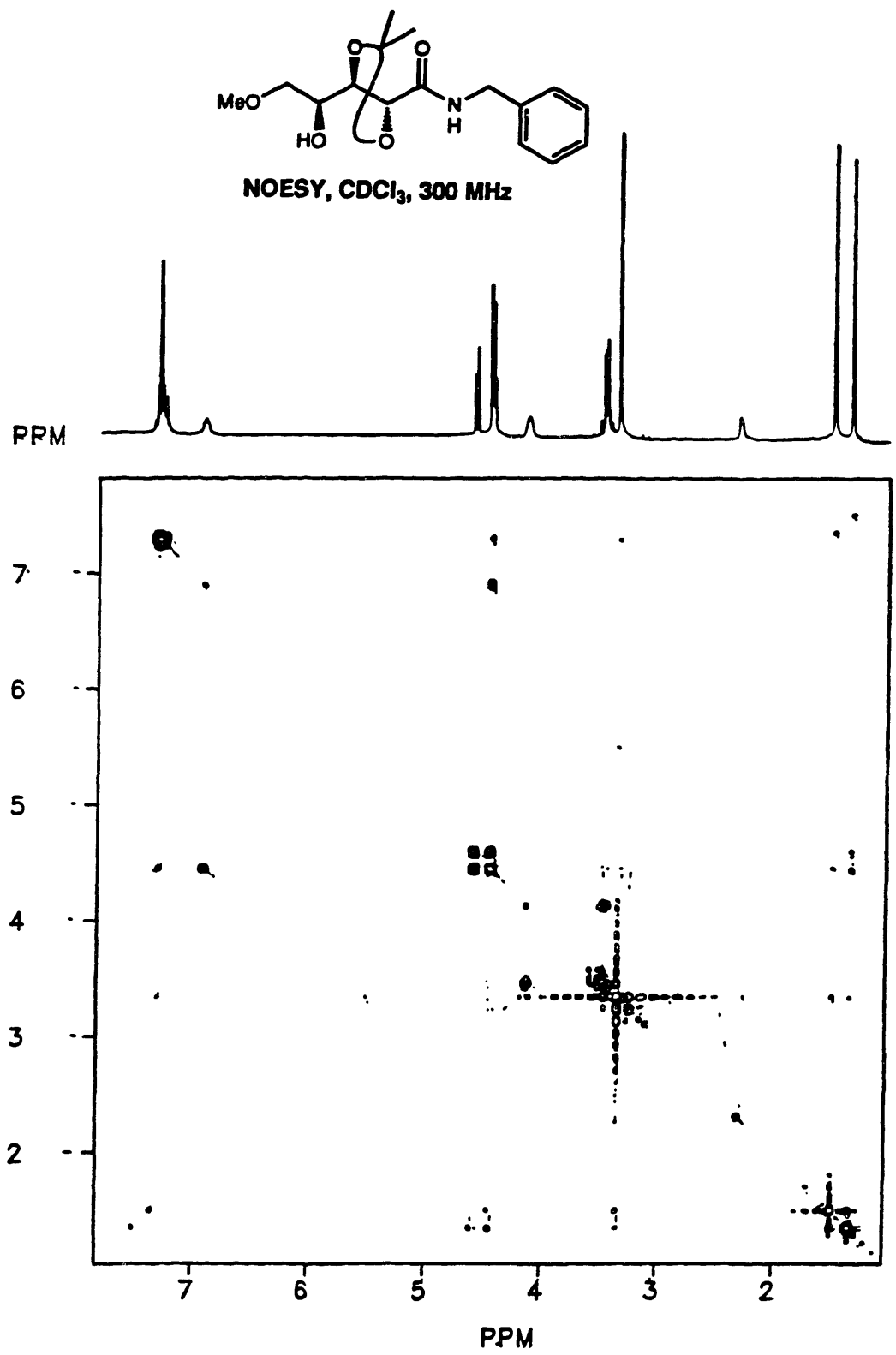

CDCl3, 300 MHz
MeO
O
O
O
O

MeO
O
O
O
O
^{13}C NMR, $CDCl_3$, 300 MHz
180
140
120
100
80
60
40
PPM
INDEX FREQ PPM INTENSITY
01 13976.6 123.340 31.669
02 9622.5 114.296 80.042
03 9083.0 77.900 146.079
04 9011.3 77.431 596.079
05 8989.5 77.010 559.065
06 8777.4 76.580 555.092
07 8734.0 76.019 170.192
08 8726.4 75.967 181.196
09 8593.1 76.154 159.359
10 8488.9 58.451 96.100
11 2815.9 25.731 97.743
12 1953.1 25.890 128.653


CDCl3, 300 MHz
MeO
HO
O
O
H
N
O

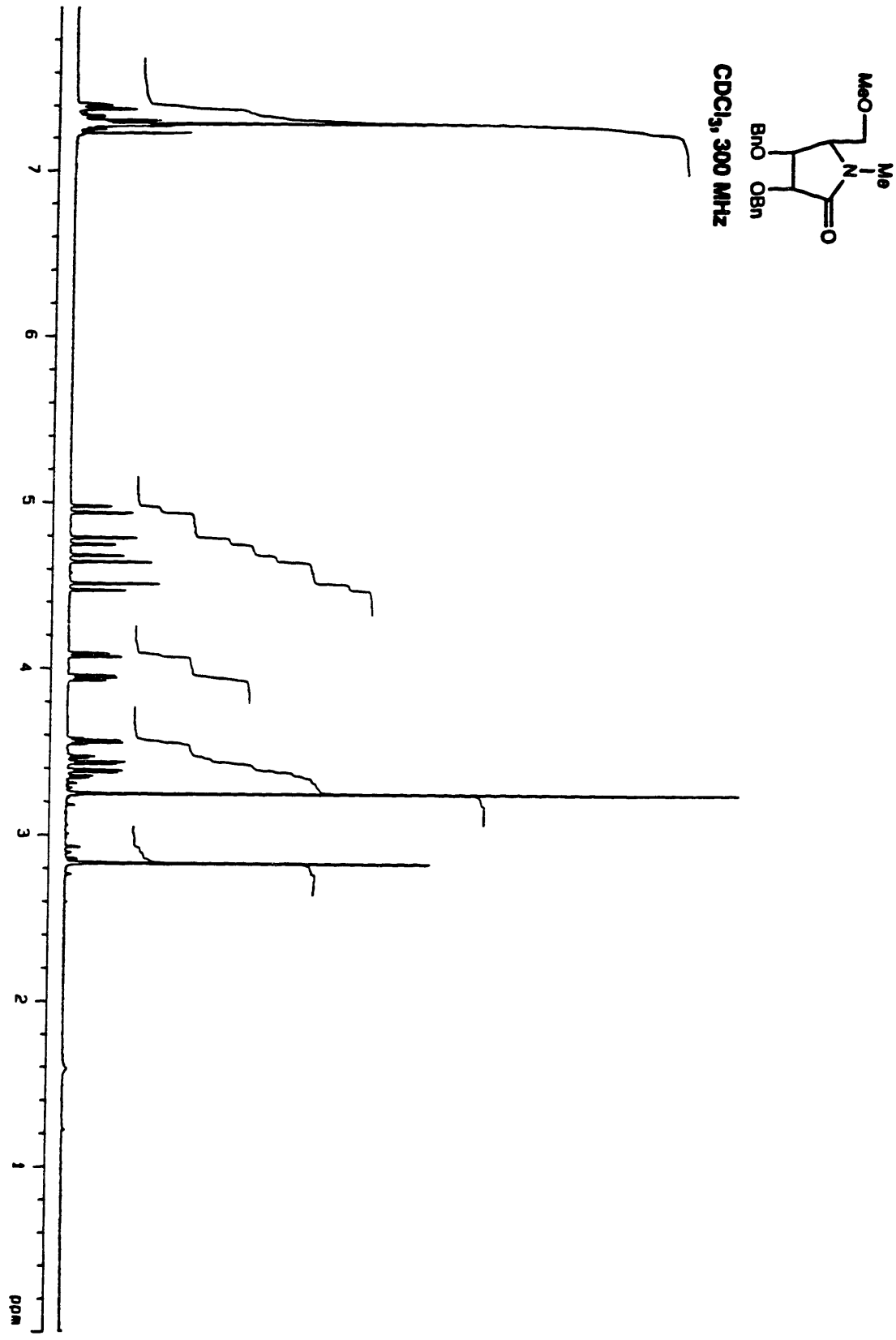

MeO
HO
O
O
O
H
N
^{13}C NMR, CDCl$_3$, 300 MHz


MeO
HO
O
O
N
H
O
COSY, CDCl3, 300 MHz
PPM
7
6
5
4
3
2
7
6
5
4
3
2
PPM


MeO
HO
O
O
N
H
NOESY, CDCl3, 300 MHz
PPM
7
6
5
4
3
2
7
6
5
4
3
2
PPM

CDCl3, 300 MHz
MeO
Me
N
O
O
O
PPM
0
2
4
6
8

^{13}C NMR, $CDCl_3$, 300 MHz
MeO
Me
O
O
N
O
160
140
120
100
80
60
40 PPM
INDEX FREQ PPM INTENSITY
01 13936.1 171.478 56.334
02 8419.0 111.601 127.924
03 5841.9 77.448 163.214
04 5831.9 77.307 102.393
05 5810.0 77.017 166.227
06 5777.7 76.588 168.149
07 5740.4 76.099 201.831
08 5236.0 69.410 93.969
09 4791.6 63.516 144.799
10 4463.7 59.169 147.926
11 2095.6 27.779 142.930
12 2027.1 26.871 143.471
13 1926.5 25.537 166.705


MeO
Me
N
BnO
OBn
O
CDCl3, 300 MHz
ppm
1
2
3
4
5
6
7

INDEX	FRQ	PPM	INTENSITY
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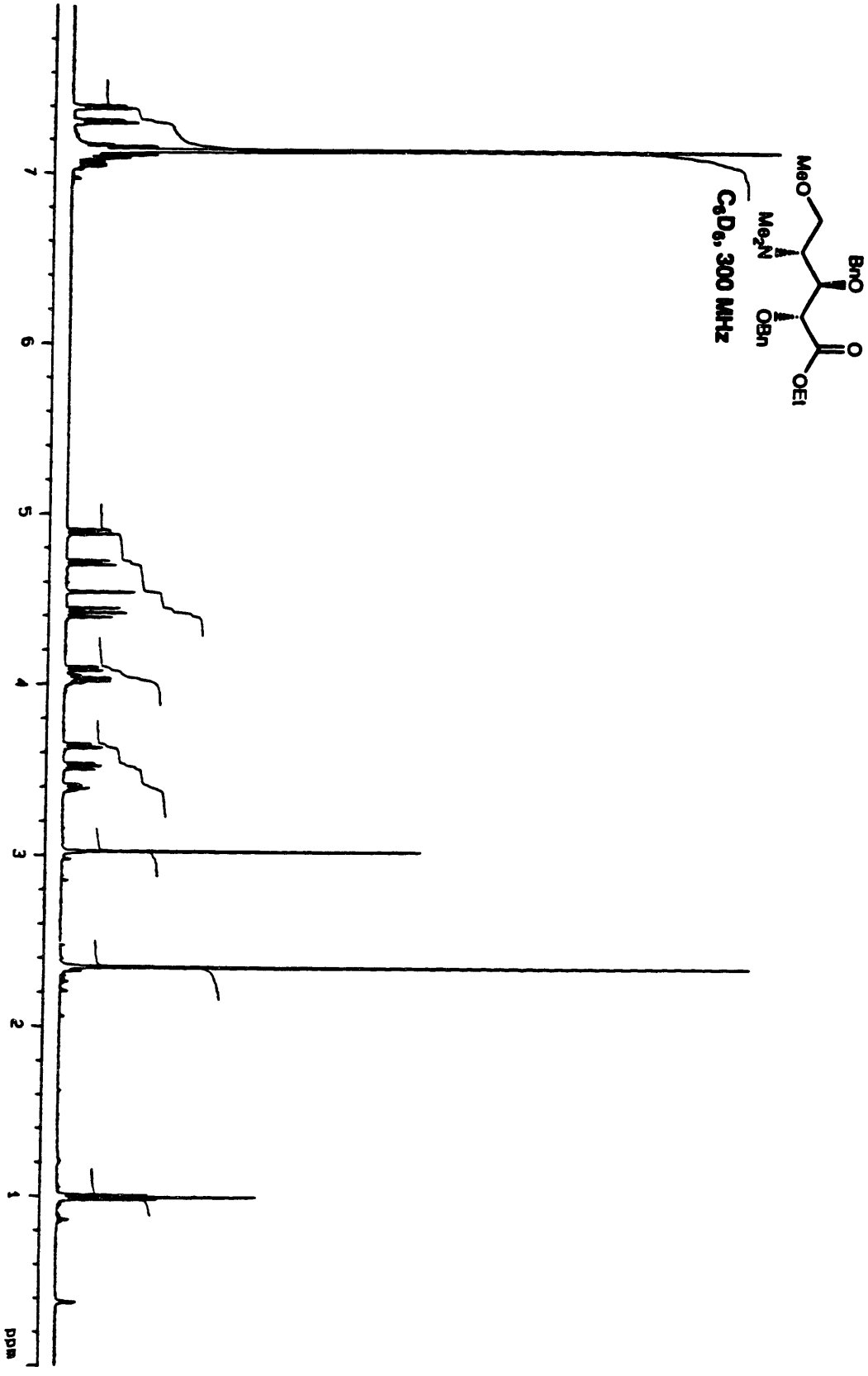
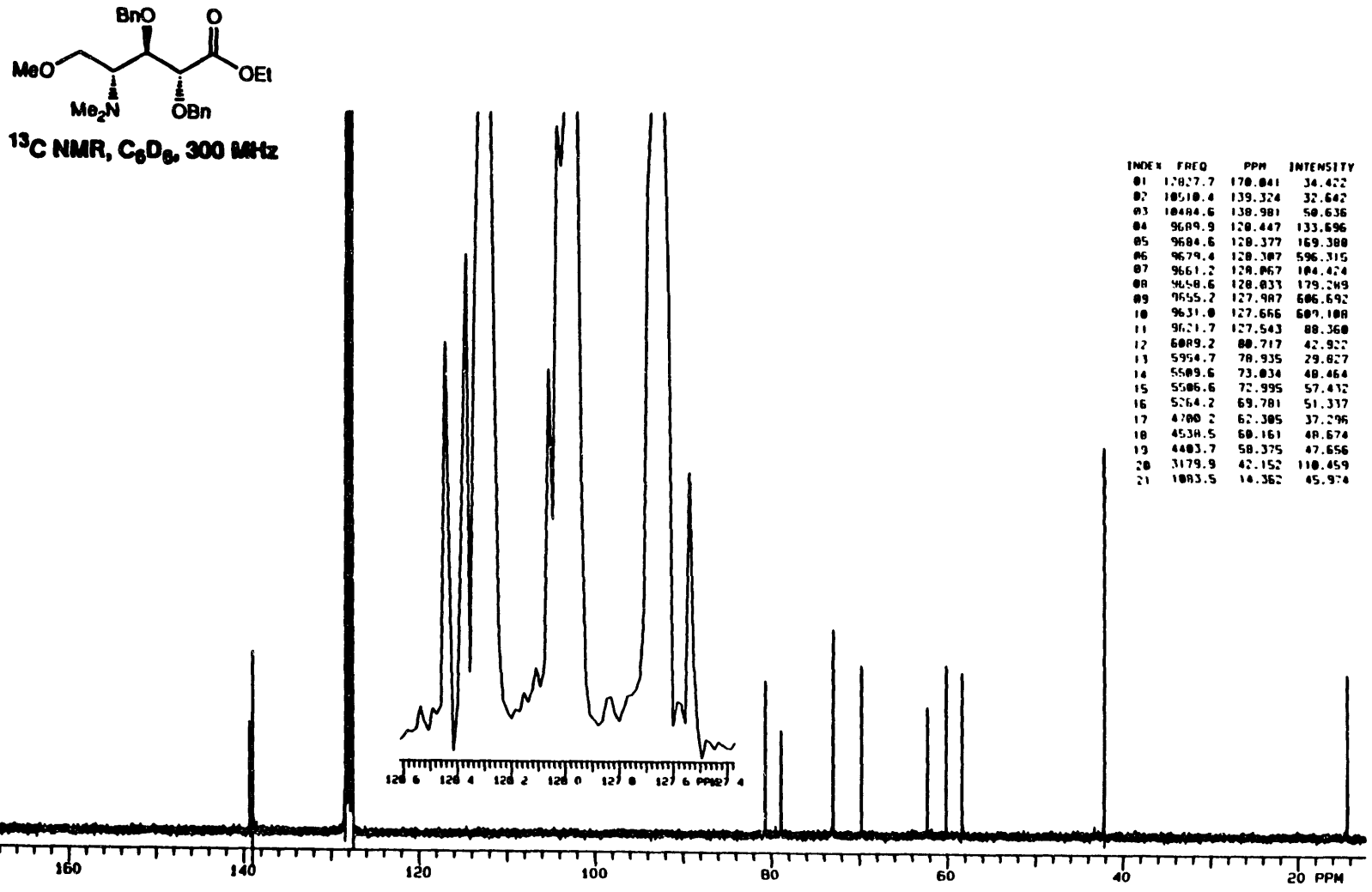
02	10359.9	137.859	49.118
03	10188.7	137.710	34.397
04	9674.7	128.246	193.960
05	9697.9	128.156	200.382
06	9654.0	127.971	177.643
07	9642.3	127.816	159.457
08	9633.2	127.695	79.819
09	9620.5	127.528	90.433
10	5841.1	77.420	132.530
11	5809.1	77.004	136.533
12	5777.0	76.579	131.582
13	5655.8	74.972	79.805
14	5621.2	74.513	60.340
15	5451.0	72.258	90.971
16	5414.0	72.032	81.230
17	5258.8	69.709	54.989
18	4777.6	63.331	79.396
19	4451.6	59.009	67.108
20	2078.0	27.556	59.393

MeO
Me
N
O
TBSO
OTBS
CDCl3, 300 MHz
PPM


MeO
BnO
O
Me2N
OBn
OEt
C6D6, 300 MHz
7
6
5
4
3
2
1
ppm

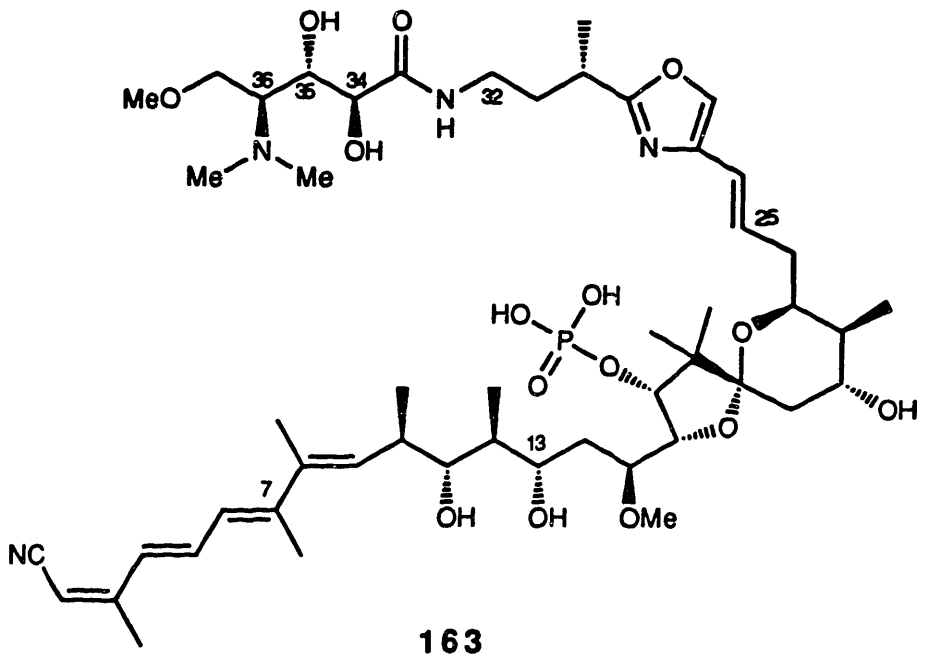

BnO
O
MeO
OEt
Me2N
OBn
13C NMR, C6D6, 300 MHz
INDEX FREQ PPM INTENSITY
01 17827.7 170.041 34.422
02 10510.4 139.324 32.642
03 10484.6 138.981 50.636
04 9689.9 128.447 133.696
05 9684.6 128.377 169.388
06 9679.4 128.307 596.315
07 9661.2 128.067 104.424
08 9658.6 128.033 179.269
09 9655.2 127.987 606.692
10 9631.0 127.666 609.108
11 9621.7 127.543 88.360
12 6089.2 80.717 42.922
13 5954.7 78.935 29.827
14 5509.6 73.034 48.464
15 5506.6 72.995 57.432
16 5264.2 69.781 51.317
17 4700.2 62.305 37.296
18 4530.5 60.161 48.674
19 4403.7 58.375 47.656
20 3179.9 42.152 110.459
21 1083.5 14.362 45.974
160
140
120
100
80
60
40
20 PPM

MeO
TBSO
Me2N
OTBS
O
OEt
CDCl3, 300 MHz
ppm
0
1
2
3
4
5
6
7

Chapter 4:
The Absolute Stereochemistry of Calyculin A and the Synthesis of Fragment C

4.1 Introduction

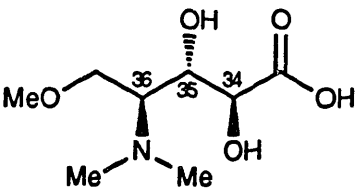
Figure 4.1



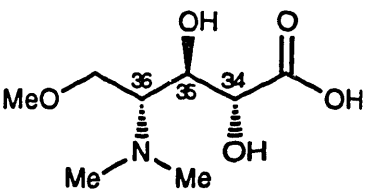
163

Up to this point, our preparation of fragment C of calyculin A was proceeding as expected. We had worked out strategies for the preparation of fragments C1 and C2, and were beginning to study the final coupling to fragment C. Unfortunately, while this work was in progress, two independent publications[18,136] appeared which demonstrated that natural calyculin A, **163**, bears the absolute stereochemistry shown in Figure 4.1. This structure is enantiomeric to that drawn in the original report, although the authors indicated that the absolute configuration was not determined.[4]

Figure 4.2



164



165

The relative stereochemistry had been determined utilizing NMR and x-ray crystallographic techniques,[4] and we had no reason to approach the synthesis of calyculin A with stereochemistry other than that depicted in Fusetani's original publications. However, in late 1991 Fusetani and coworkers reported the degradation of a mixture of calyculins followed by the subsequent isolation of the C33-C37 fragment, **164** (Figure 4.2).[136] This fragment produced a positive Cotton effect at 207 nm in the CD spectrum indicating the *S* configuration at C34.[136] At the same time, Hamada and coworkers reported the synthesis of the C33-C37 fragment of calyculin bearing the (34*R*, 35*R*, 36*R*) configuration, **165** (Figure 4.2), and demonstrated that its optical rotation was opposite to that of the same fragment isolated from the degradation of natural calyculin.[18] Both of these results conclusively demonstrated that the absolute stereochemistry of the calyculins was opposite to that depicted in previous publications.

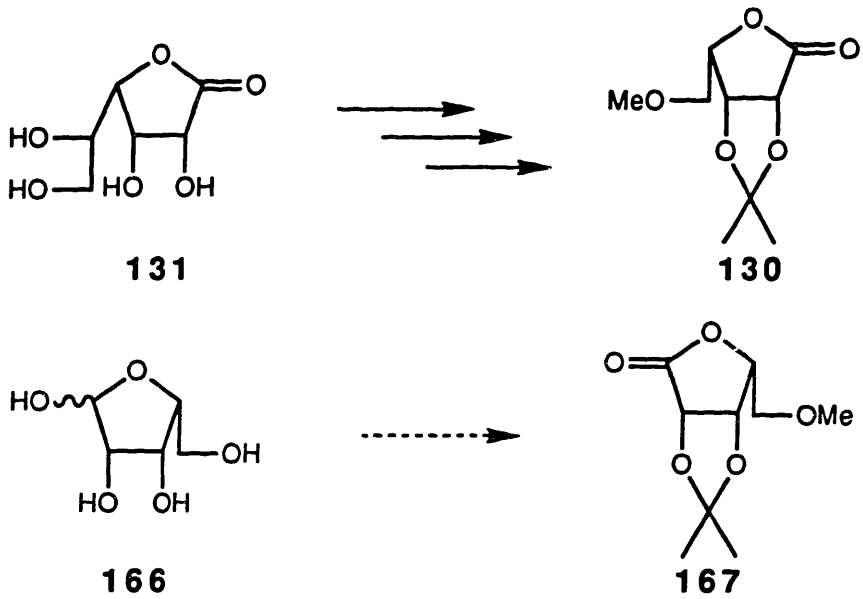
In light of these results and in spite of the fact that we were close to completing the synthesis of the enantiomer of calyculin A, we chose to go back and prepare the fragments with the correct stereochemistry. In fact, all of the methodology we had developed could be applied to the synthesis of natural calyculin with the exception of one point in the preparation of fragment C2. Although D-gulononlactone, **131**, was a convenient starting material for the enantiomer, L-gulonolactone was not commercially available in any affordable quantities. This chapter will discuss the synthesis of fragments C1 and C2 *en route* to the preparation of natural calyculin A.

4.2 The Lactone, 167

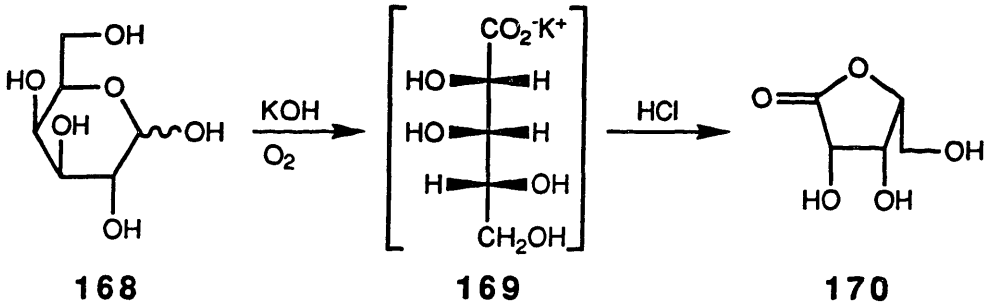
When considering that lactone, **130**, derived from D-gulonolactone, **131**, is a derivative of L-lyxonolactone, we might consider arriving at the

lactone, **167**, from D-lyxose, **166** (Scheme 4.1). Unfortunately, the cost of D-lyxose, **166**, precludes consideration of this strategy. Fortunately, it has been well documented that aldoses can be oxidatively degraded by one carbon unit to aldonic acid salts. On acidification, these salts can be converted to lactones.[137,138] Thus, D-galactose, **168**, was oxidized to potassium-D-lyxonate, **169**, on warming in aqueous KOH saturated with O_2. Heating to reflux a suspension of potassium-D-lyxonate, **169**, in isopropanol saturated with HCl gave D-lyxonolactone, **170** (65% yield, two steps, Scheme 4.2).[138]

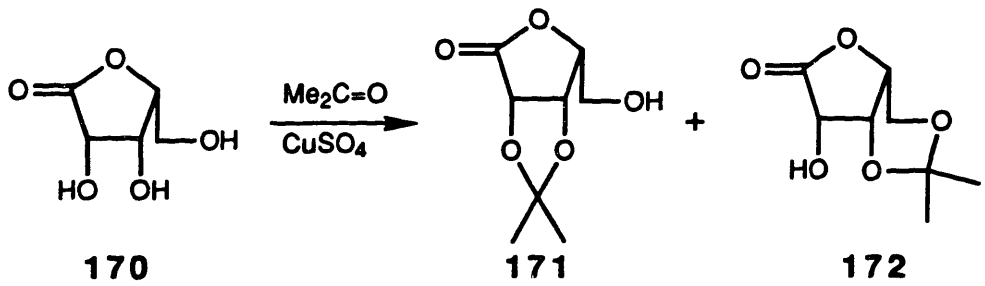
Scheme 4.1



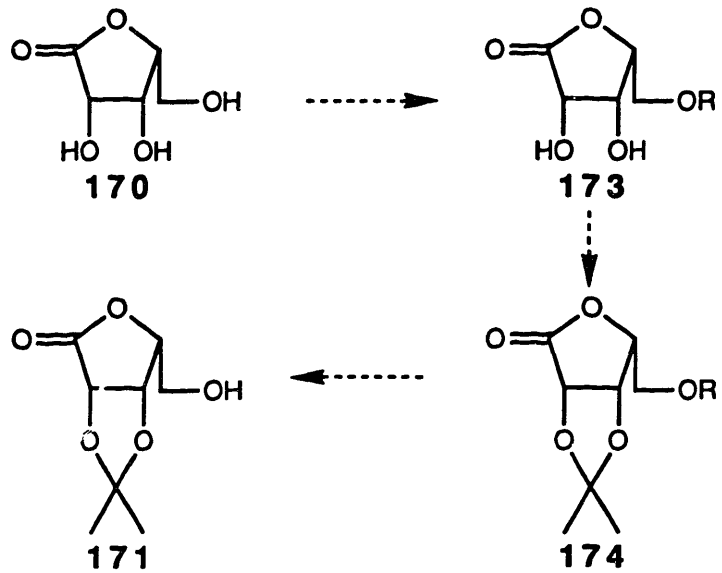
Scheme 4.2



Scheme 4.3



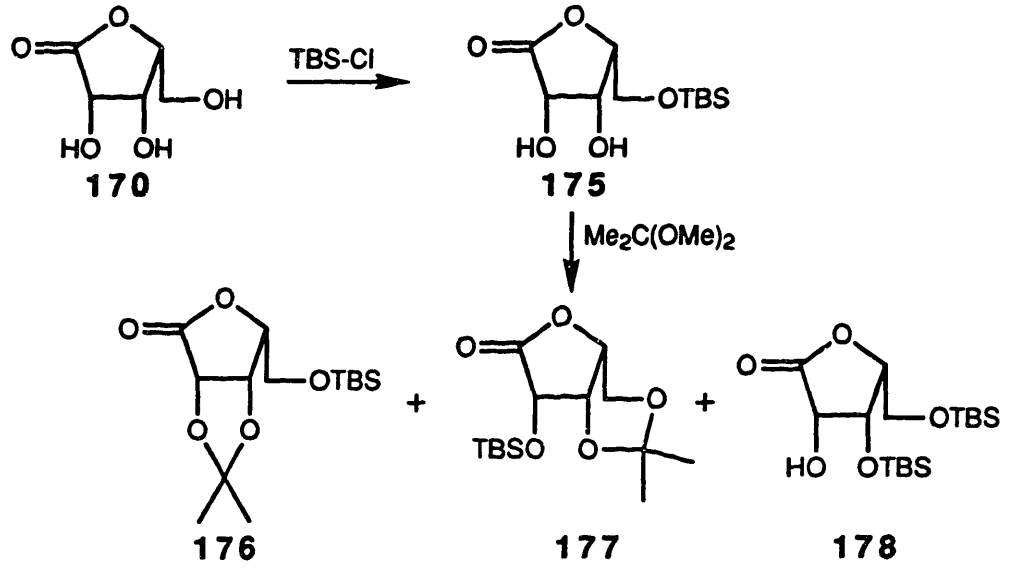
Scheme 4.4



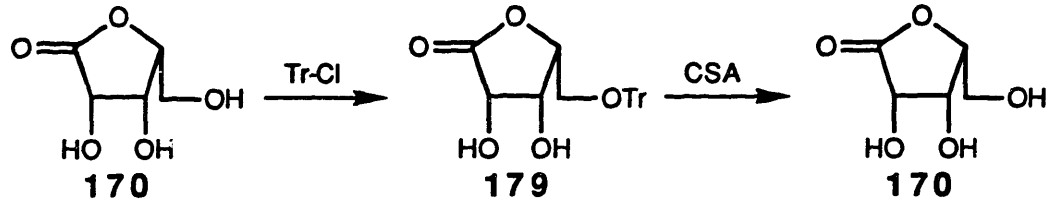
At this stage, completion of the preparation of lactone **167** centered around the selective formation of the 2,3-acetonide, **171**, followed by methylation of the primary alcohol. It has been reported that D-lyxonolactone, **170**, can be converted to a 3 : 1 mixture of the 2,3-acetonide, **171**, and the 3,5-acetonide, **172**, on treatment with acetone in the presence of anhydrous copper sulfate (Scheme 4.3).[139,140] We felt, however, that it was more efficient to initially protect the primary alcohol, form the acetonide, and then deprotect the primary alcohol (Scheme 4.4). The main advantage

to this three step procedure was the elimination of a need to separate the 2,3-acetonide, **171**, from its 3,5-isomer, **172**.

Scheme 4.5



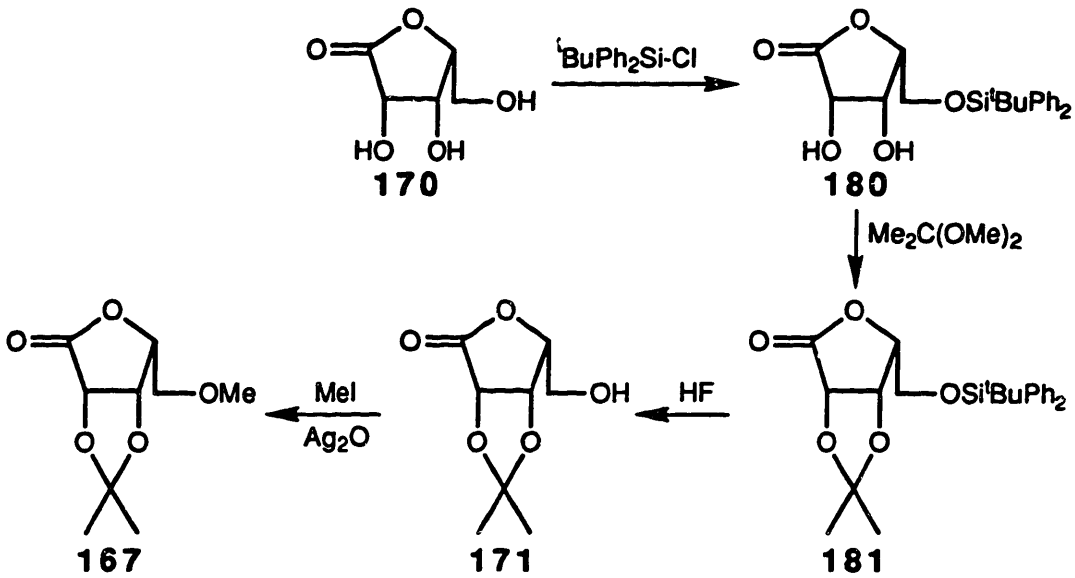
Scheme 4.6



In our development of the three step sequence shown in Scheme 4.4, we found that we could selectively protect the primary alcohol as its *tert*-butyldimethylsilyl ether, **175**, in 95% yield (Scheme 4.5). Unfortunately, when we attempted to form the acetonide, **176**, utilizing 2,2-dimethoxypropane and catalytic camphorsulfonic acid, we observed formation of the desired acetonide, **176**, in only 29% yield, accompanied by

177 (30% yield) and 178 (6.5% yield). These products presumably arose from initial scrambling of the silyl group.

Scheme 4.7



Although our initial results were discouraging, we chose to examine this strategy with a variety of protecting groups. When attempting this strategy with the trityl ether, **179**, we found that our conditions for acetonide formation cleanly cleaved the trityl group (Scheme 4.6). However, as shown in Scheme 4.7, when we converted D-lyxonolactone, **170**, to the *tert*-butyldiphenylsilyl ether, **180** (99% yield), we found that formation of the acetonide, **181**, could be accomplished in 96% yield as described above. Removal of the silyl group on treatment with HF/pyridine/THF[141] produced the alcohol, **171**, in 81% yield. Finally, conversion of the alcohol, **171**, to the methyl ether, **167**, was achieved in 83% yield using methyl iodide and silver oxide.[122] With this material in hand, we could proceed with the preparation of the desired enantiomers of fragments C1 and C2.

4.3 Fragments C1 and C2

With the lactone, **167**, in hand, we could now proceed to the preparation of fragments C1, **190**, and C2, **194**. The final syntheses of these fragments will be discussed in this section.

4.3.1 Fragment C1, 190

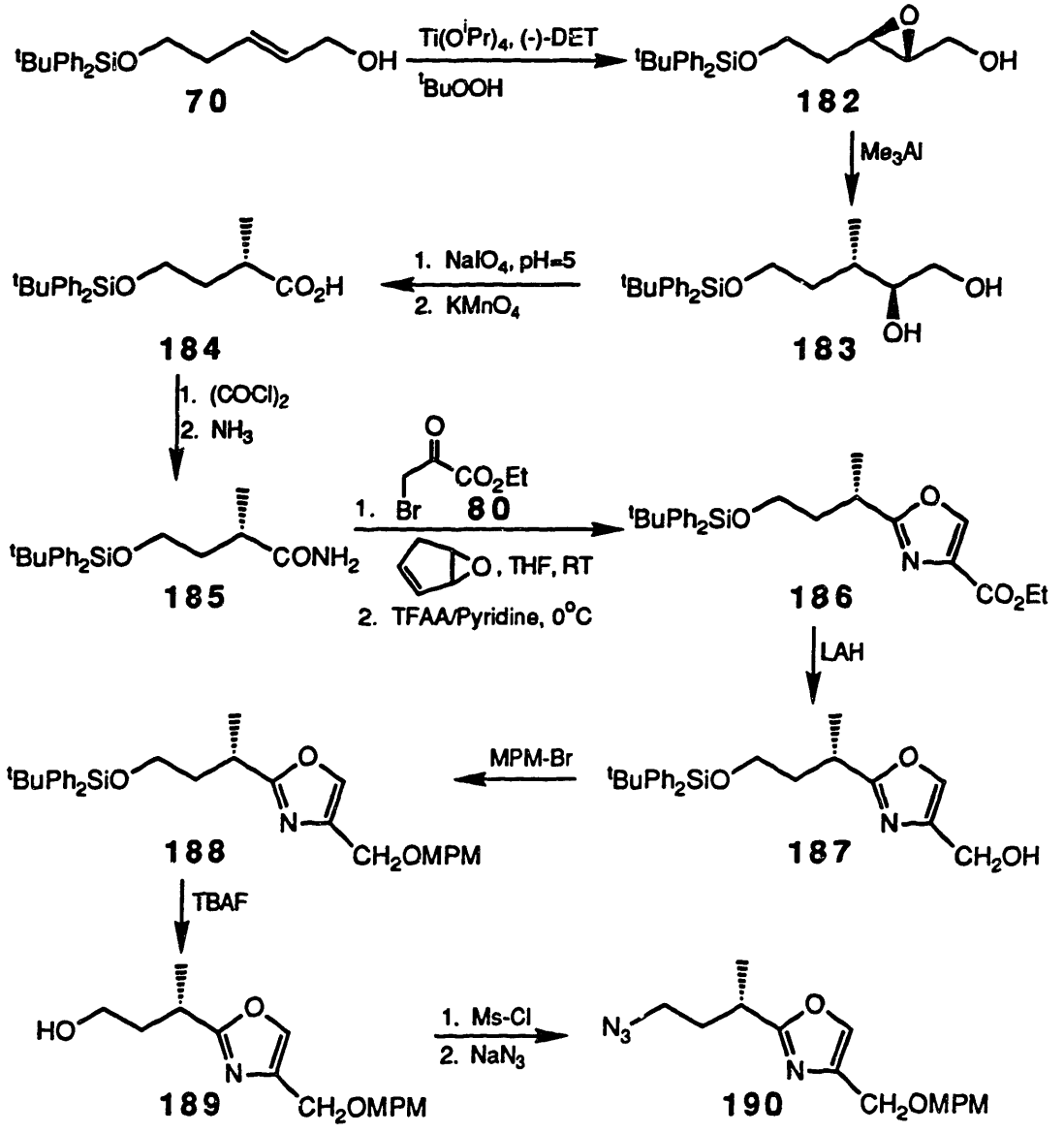
Using the same methodology as described in Chapter 2, with the exception of the opposite Sharpless epoxidation, fragment C1 was prepared as summarized below (Scheme 4.8).

The alcohol, **70**, was converted to the epoxide, **182**, in 88% yield utilizing the Sharpless asymmetric epoxidation.[77] The epoxide, **182**, was then converted to the diol, **183**, on treatment with trimethylaluminum (91% yield),[78,79] and the diol was converted to the acid, **184**, by sequential treatment with $NaIO_4$ and $KMnO_4$[79,80] (95% yield, 2 steps). The amide, **185**, was then formed by converting the acid, **184**, to the acid chloride with oxalyl chloride followed by condensation with ammonia (100% yield, 2 steps).

The oxazole, **186**, was prepared by condensing the amide, **185**, with ethyl bromopyruvate followed by dehydration with trifluoroacetic anhydride. The alcohol, **187**, was then formed on reduction of the ester with LAH (96% yield), and subsequently converted to its MPM ether, **188**, on treatment with MPM-Br and KH (95% yield).

Final elaboration of the oxazole, **188**, to fragment C1, **190**, was accomplished by initial cleavage of the silyl ether with tetrabutylammonium fluoride (100% yield). The alcohol, **189**, was then converted to the azide, **190**, on treatment with methane sulfonylchloride followed by sodium azide (98% yield, 2 steps) to complete the synthesis of fragment C1.

Scheme 4.8



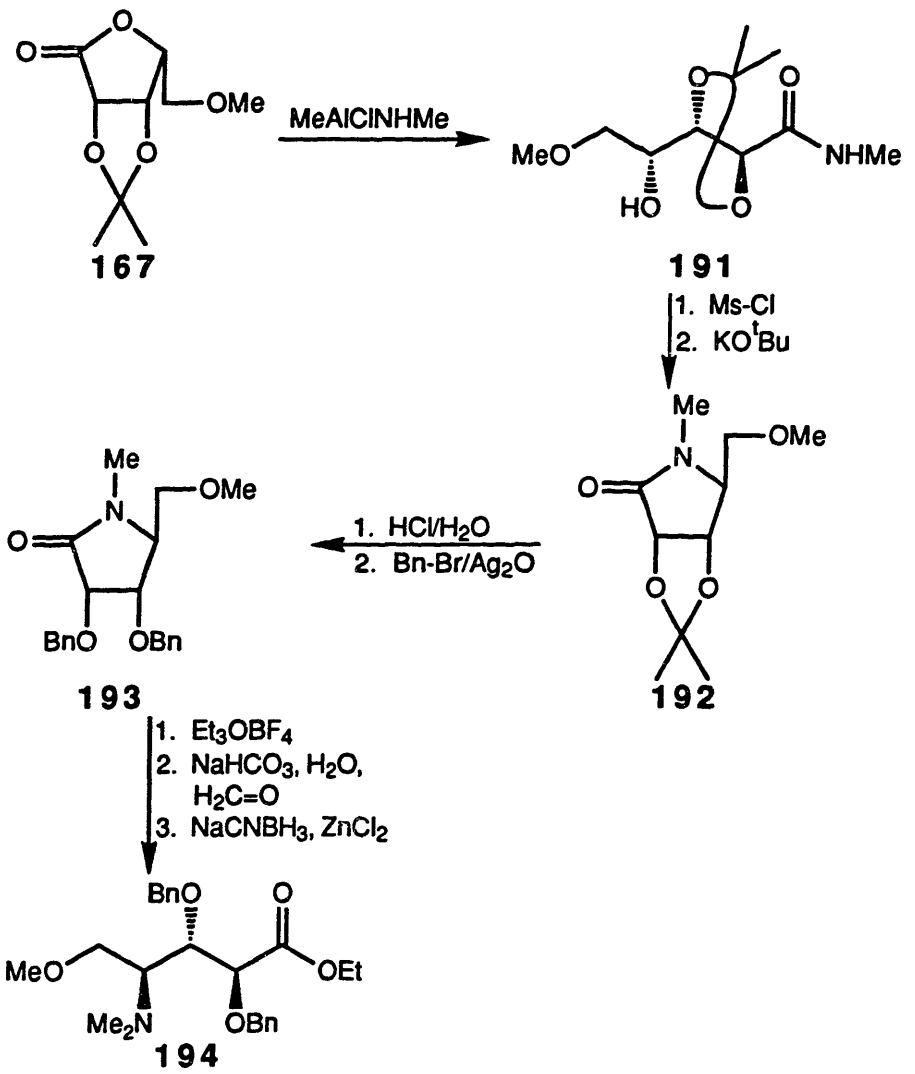
4.3.2 Fragment C2, 194

Using the same methodology as in Chapter 3, fragment C2 was prepared from the lactone, **167**, as summarized below (Scheme 4.9).

The lactone, **167**, was opened to the hydroxyamide, **191**, (99% yield) utilizing chemistry developed in the Weinreb group.[129] Cyclization of the

hydroxyamide, **191**, to the lactam, **192**, was accomplished in 84% on initial conversion to the mesylate followed by treatment with base.

Scheme 4.9

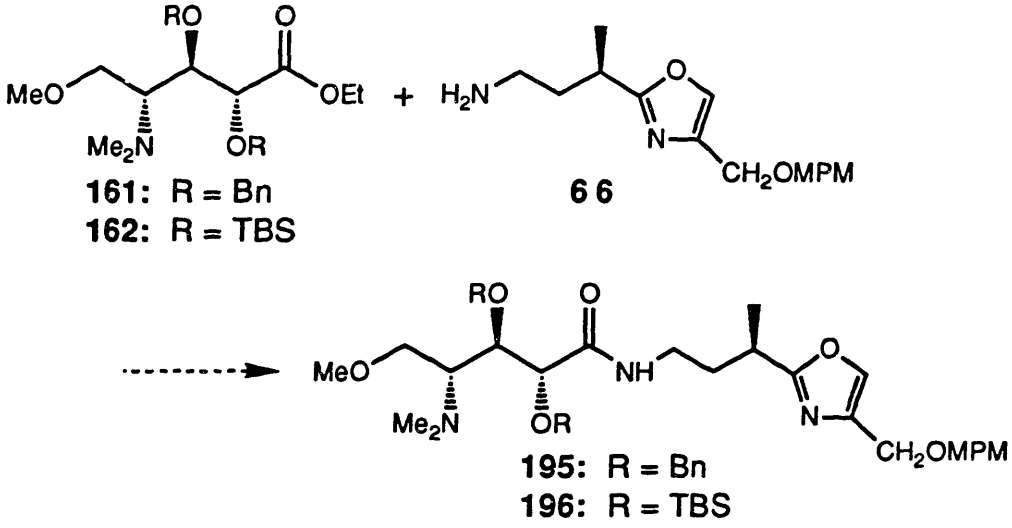


At this stage, the acetonide, **192**, was hydrolyzed under acidic conditions, and the resulting diol was reprotected as the corresponding dibenzyl ether, **193**. Completion of fragment C2, **194**, was accomplished by converting the lactam, **193**, to its imidate on treatment with the Meerwein reagent.[134] Basic hydrolysis of this imidate in the presence of formaldehyde

then trapped the resulting amino ester as its iminium salt. This iminium salt was then reduced to the amine, **194**, utilizing the zinc chloride modification of the $NaCNBH_3$ reduction.[135] With these results, we had completed the synthesis of fragment C2 and were now ready to complete fragment C.

4.4 Fragment C

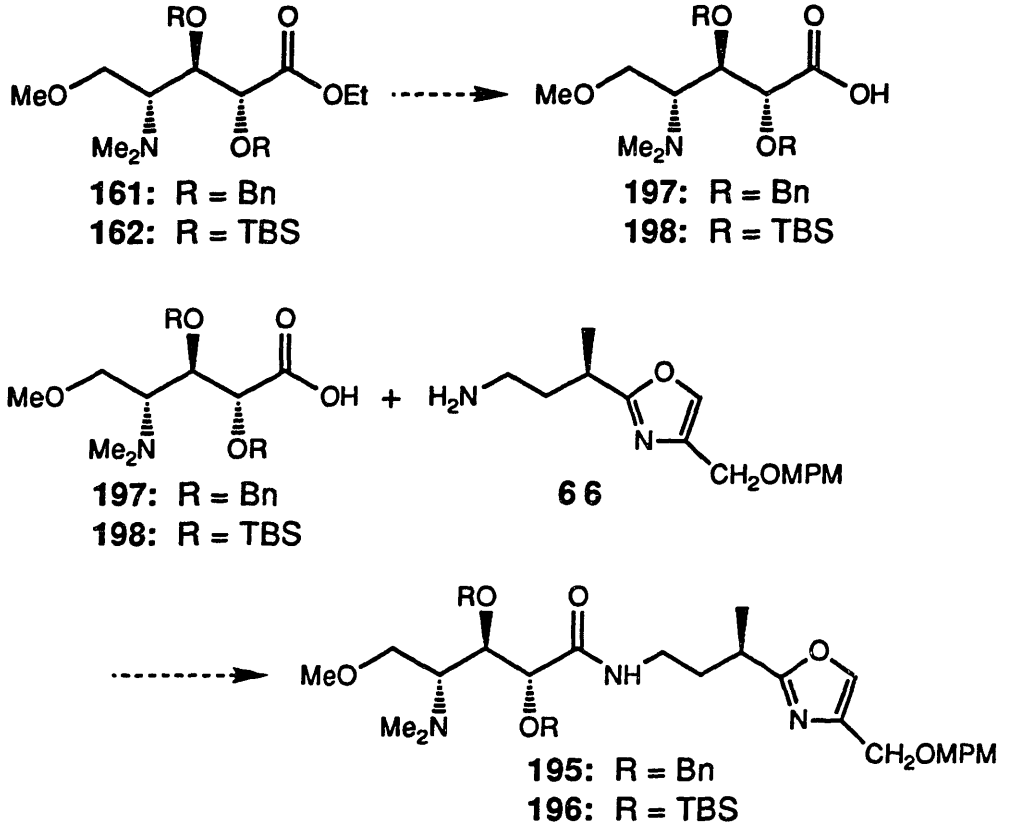
Scheme 4.10



When considering the coupling of fragment C1 and C2, we chose to utilize the corresponding enantiomers as models for the natural system. Our approach was to involve the exploration of two strategies. The first of these was the direct coupling of the amine, **66**, with either the dibenzyl amino ester, **161**, or the bis-*tert*-butyldimethylsilyl amino ester, **162**, to form the appropriate amide, **195** or **196** (Scheme 4.10). The second strategy involved the hydrolysis of either the dibenzyl amino ester, **161**, or the bis-*tert*-butyldimethylsilyl amino ester, **162**, followed by use of DCC methodolgy in the coupling of either amino acid **197** or **198** with the amine, **66**, to form

the respective amides, **195** or **196** (Scheme 4.11). This section will discuss these strategies and the problems we encountered in their exploration.

Scheme 4.11

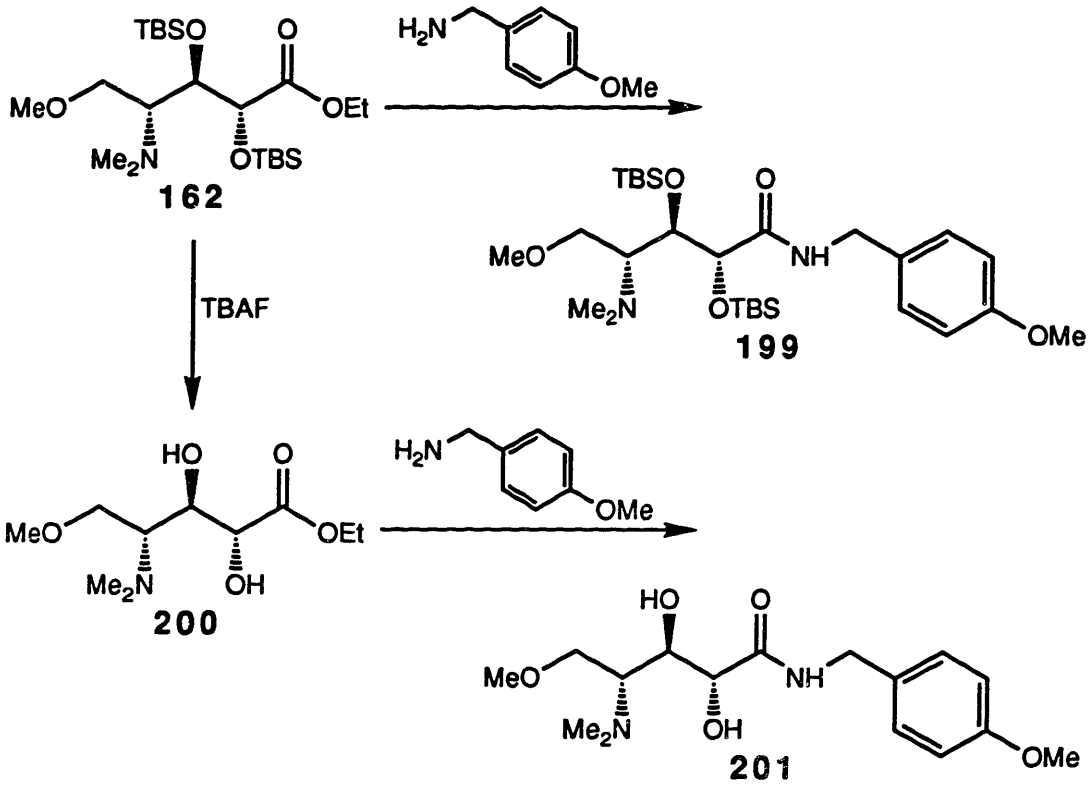


4.4.1 Direct Coupling

We began our study of the direct coupling of fragments C1 and C2 with the bis-*tert*-butyldimethylsilyl protected amino ester, **162**. With *p*-methoxy benzylamine as a model for **66**, we found that the best yield we could obtain in the formation of the amide, **199** (Scheme 4.12), was 10% even after heating the reaction to reflux for two days. However, we found that if we first removed the *tert*-butyldimethylsilyl groups to form the diol, **200**, we could increase the yield of the amide, **201**, to 55% over the same two

day period. With these disappointing results, we decided to explore the possibility of first hydrolyzing the amino ester to the amino acid and then utilizing DCC methodology in the coupling of fragments C1 and C2.

Scheme 4.12

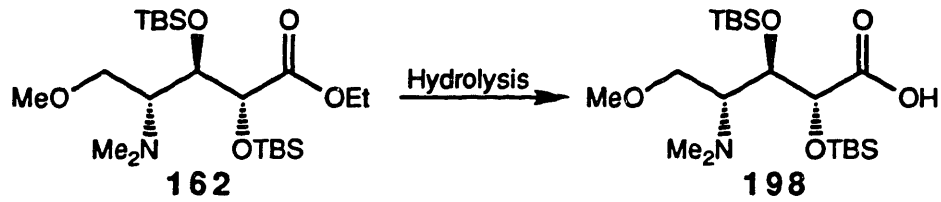


4.4.2 DCC Methodology

Our approach using DCC methodology involved initial hydrolysis of the amino ester to an amino acid, and then effecting the coupling of the two fragments. In this study, we began with the bis-*tert*-butyldimethylsilyl amino ester, **162**. Unfortunately, as shown in Scheme 4.13 and Table 4.1, the hydrolysis of amino ester **162** to amino acid **198** was not as straightforward as we had anticipated, and the best isolated yield remained at 55%. These results are not meant to imply that the hydrolysis would not proceed beyond

50%. The hydrolysis did, in fact, go to completion. The problem arose on isolation of the amino acid when one of the two protecting groups was cleaved. This led us to believe that the silyl protected amino ester was unsuitable and we should explore the dibenzyl protected derivative, **161**.

Scheme 4.13



162 **198**

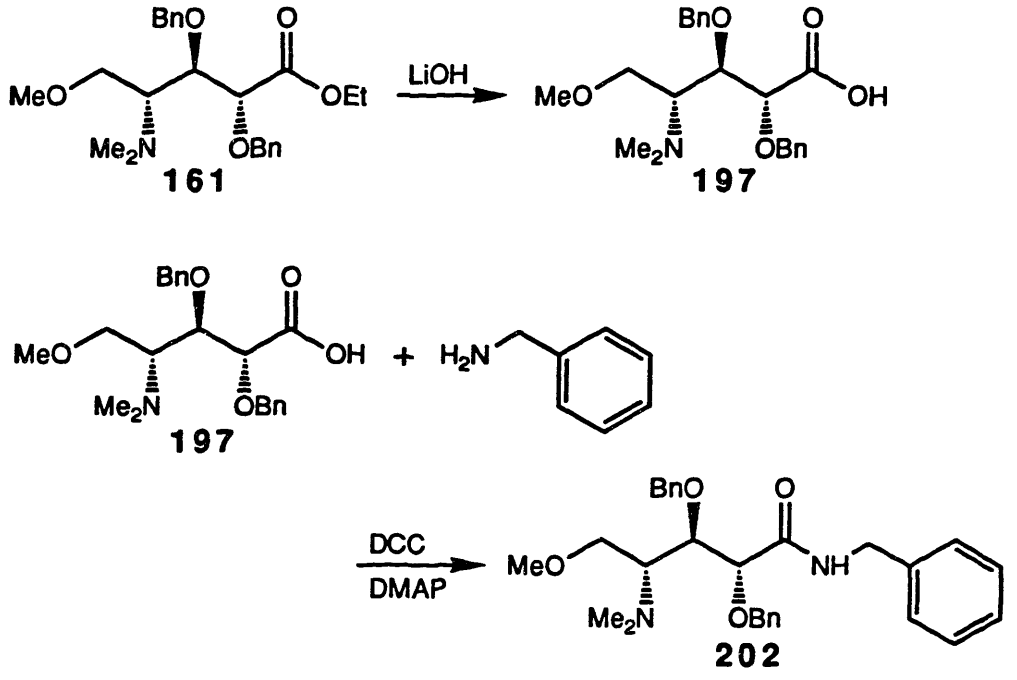
Table 4.1

Hydrolysis of bis-TBS Protected Amino Ester

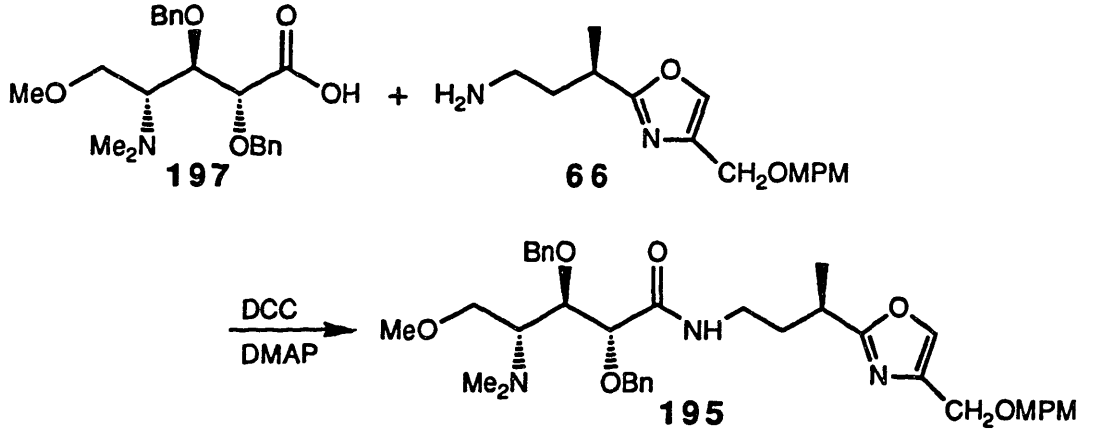
Hydrolysis Conditions	Yield
2 equiv. LiOH THF/MeOH/H_2O 2/2/1 2 days, 40-50°C	50%
8 equiv. ^tBuOK 2 equiv. H_2O Et2O, 16 hours, RT	55%
2 equiv. LiOH THF/H_2O 3/1	Very Slow
2 equiv. LiOH $^tBuOH/H_2O$	Very Slow

As shown in Scheme 4.14, hydrolysis of the amino ester, **161**, provided the corresponding amino acid, **197**, in 97% yield and requiring no further purification. Furthermore, employing benzylamine as a model for fragment C1, we were able to effect coupling with **197** to give the amide, **202**, in >90% yield on treatment with DCC/DMAP. Applying these conditions to fragments C1 and C2, we obtained a 69% yield of fragment C, **195** (Scheme 4.15) thus completing my contribution to the synthesis of calyculin A.

Scheme 4.14

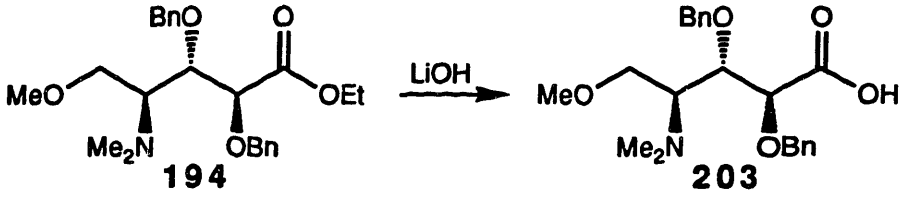


Scheme 4.15

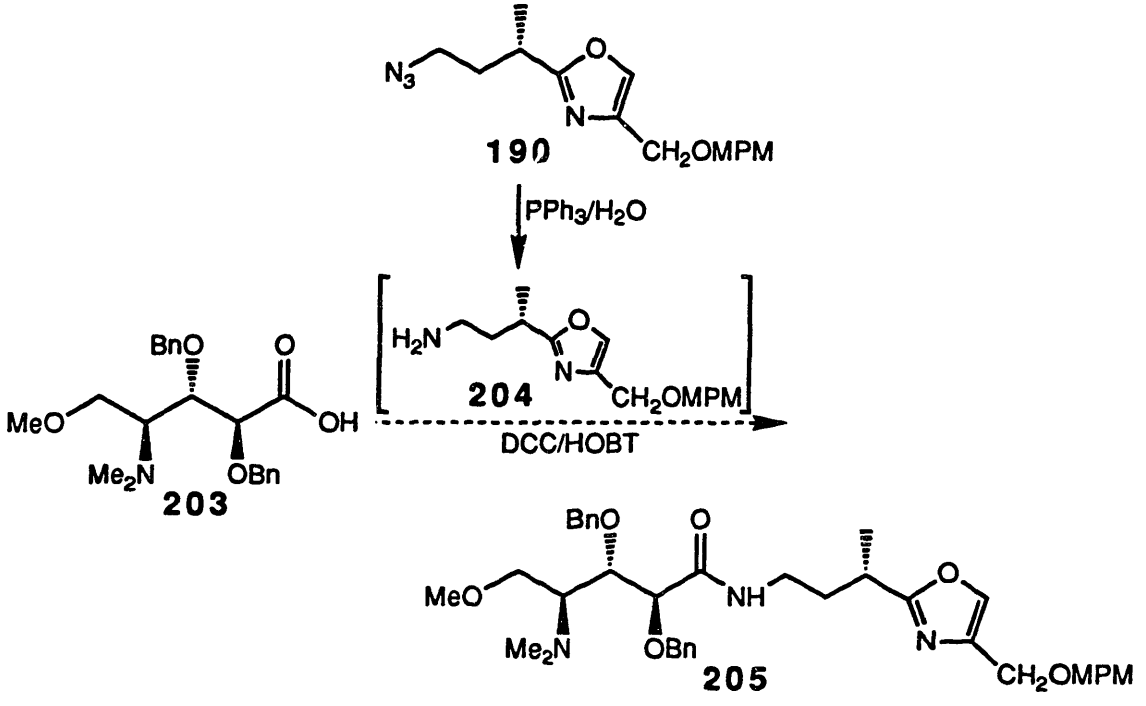


With the strategy to fragment C developed, the final preparation of the natural enantiomer is being completed by Dr. Lian-Yong Chen. In this capacity, and with knowledge of the instability of the amine, **66**, conversion of the azide, **190**, to the amine, **204**, followed by an *in situ* coupling with the amino acid, **203**, is being pursued.

Scheme 4.16

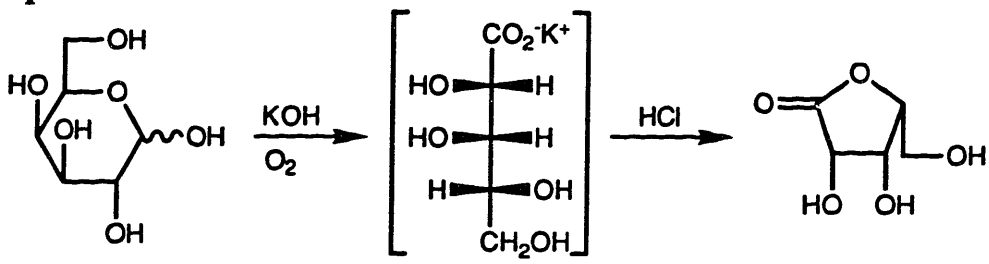


Scheme 4.17



As shown in Scheme 4.16, the ester, **194**, was hydrolyzed to the acid, **203**, on treatment with aqueous lithium hydroxide (97% yield). At this stage, the acid is to be treated with the crude amine, **204**, in the presence of DCC and HOBT[142,143,144] to give the natural enantiomer of fragment C of calyculin A, **205**, in its final form. With the positive results we had obtained for the unnatural enantiomer of fragment C, no problems are anticipated with this strategy and those remaining on the project should soon be able to complete the syntheis of this intriguing natural product.

4.5 Experimental Section



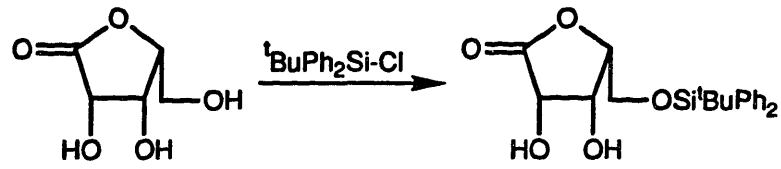
168 **169** **170**

D-Lyxonolactone, 170

KOH (28.0g, 0.499 mole) was dissolved in MeOH (250 mL) and H_2O (60 mL) and warmed to 35°C. O_2 was bubbled into the solution through 2 stainless steel HPLC solvent filters and a solution of D-galactose (30.0g, 0.167 mole) in H_2O (60 mL) was added over 9 hours with mechanical stirring. O_2 was bubbled into the mixture for an additional 2 hours, after which air was bubbled in through the same apparatus for 2 days. The resulting mixture was then poured into MeOH (500 mL) and the suspension was stirred at room temperature for 1 day. The solids were filtered off and suspended in isopropanol (150 mL). HCl was bubbled into the suspension for 40 minutes, after which the reaction was heated to reflux. The resulting solution was immediately filtered, cooled, and concentrated to dryness. Recrystallization of the residue from isopropanol provided D-lyxonolactone (16.0 g, 65%) as a white crystalline solid.

Physical Properties for **170**

^1H NMR (300 MHz, D_2O): δ 4.59(d, J = 4.73 Hz, 1H), 4.47(ddd, J = 4.41, 4.56, 9.46 Hz, 1H), 4.42(dd, J = 2.93, 4.89 Hz, 1H), 3.79(dd, J = 4.56, 12.55 Hz, 1H), 3.74(dd, J = 7.01, 12.55 Hz, 1H).



170 **180**

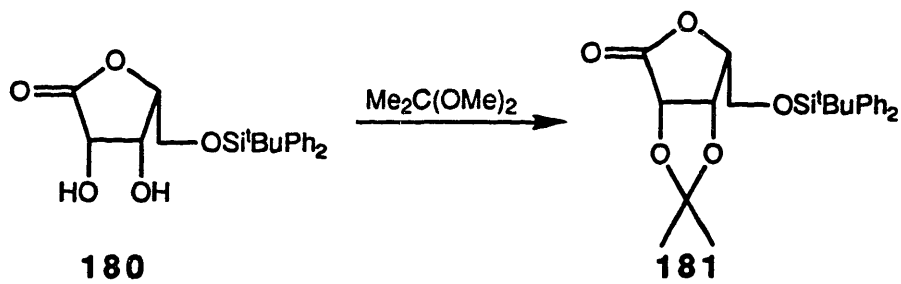
Silyl ether, 180

D-Lyxonolactone, **170**, (2.001 g, 13.523 mmoles) and imidazole (1.933 g, 28.398 mmoles) were dissolved in DMF (20 mL) and $^tBuPh_2SiCl$ (3.69 mL, 14.20 mmoles) was added. The reaction was stirred at room temperature under argon for 15 hours, after which it was poured onto H_2O (100 mL). The resulting mixture was washed with CH_2Cl_2 (4 X 20 mL) and the combined extracts were dried over $MgSO_4$. Concentration of the resulting solution provided the pure silyl ether (5.168 g, 99%) as a colorless solid.

Physical Properties for **180**

R_f = 0.26 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.65(m, 4H), 7.42(m, 6H), 4.52(m, 1H), 4.41(m, 2H), 4.06(d, *J* = 5.22 Hz, 2H), 3.22(broad s, 1H), 3.00(broad s, 1H), 1.04(s, 9H).



180 **181**

Acetonide, 181

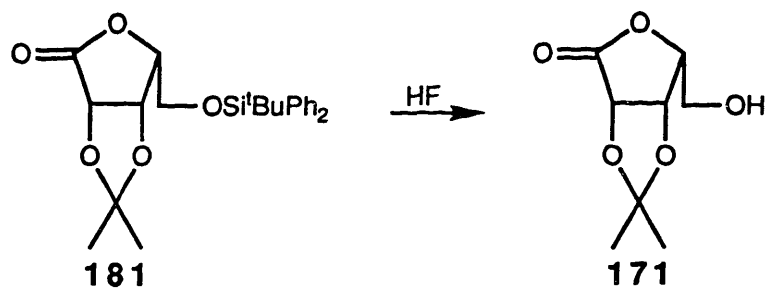
The silyl ether, **180**, (0.112 g, 0.289 mmole) was dissolved in CH_2Cl_2 (1 mL) and camphorsulfonic acid (6.7 mg, 0.029 mmole) was added followed by 2,2-dimethoxypropane (0.356 mL, 2.891 mmoles). The reaction was stirred at

room temperature under argon for 2.5 hours, after which it was washed with saturated $NaHCO_3$ solution (1 mL). The aqueous layer was washed with CH_2Cl_2 (1 mL) and the combined organics were dried over MgSO4 and concentrated to dryness. Purification of the residue on silica gel (15% ethyl acetate/hexane) gave the acetonide (0.118 g, 96%) as a colorless viscous oil.

Physical Properties for **181**

R_f = 0.46 (25% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.67(m, 4H), 7.39(m, 6H), 4.77(d, *J* = 5.38 Hz, 1H), 4.75(d, *J* = 5.21 Hz, 1H), 4.55(dt, *J* = 3.10, 6.52 Hz, 1H), 3.98(s, 1H), 3.95(d, *J* = 0.98, 1H), 1.35(s, 6H), 1.03(s, 9H).



181 **171**

Alcohol, 171

The acetonide, **181**, (0.836 g, 1.962 mmole) was dissolved in THF (8.40 mL) and a solution of (HF/py)/py/THF (1/2.9/10, 8.40 mL) was added. The reaction was stirred at room temperature under argon for 2 hours, after which it was filtered through silica gel (ethyl acetate). The resulting solution was concentrated to dryness and the residue was washed with hexane. The resulting solids were dried under vacuum to provide the pure alcohol (0.299 g, 81%) as a colorless solid.

Physical Properties for **171**

R_f = 0.63 (ethyl acetate).

$[\alpha]_D$ = +90 c = 1.0 (acetone).

m. p. = 97-98°C.

^1H NMR (250 MHz, $CDCl_3$): δ 4.88(m, 2H), 4.59(m, 1H), 4.00(m, 2H), 2.00(dd, 1H), 1.49(s, 3H), 1.40(s, 3H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 173.44, 114.54, 79.18, 76.22, 76.15, 60.90, 26.67, 25.76.

EI Mass Spec: m/e 173 $[M - 15]^+$, 149, 129, 83, 59, 43.

Exact Mass: $[M - CH_3]^+$ = 173.0450 (calculated)

$[M - CH_3]^+$ = 173.0452 (measured).

IR ($CHCl_3$) cm^{-1}: 3600, 1795, 1375, 1175, 1110.

171 **167**

Methyl Ether, 167

The alcohol, **171**, (0.010 g, 0.531 mmole) was dissolved in methyl iodide (2 mL) and Ag_2O (0.399 g) was added followed by anhydrous $CaSO_4$ (0.147 g). The resulting suspension was stirred at room temperature under argon for 7.5 hours, after which it was filtered through Celite and concentrated to dryness. The residue was purified on on recrystallization from hexane to give the desired product (0.089 g, 83%).

Physical Properties for 167

R_f = 0.47 (50% ethyl acetate/hexane).

$[\alpha]_D$ = +80 c = 0.5 (acetone).

m. p. = 83-85°C.

^1H NMR (300 MHz, $CDCl_3$): δ 4.84(s, 2H), 4.63(m, 1H), 3.77(m, 2H), 3.46(s, 3H), 1.49(s, 3H), 1.41(s, 3H).

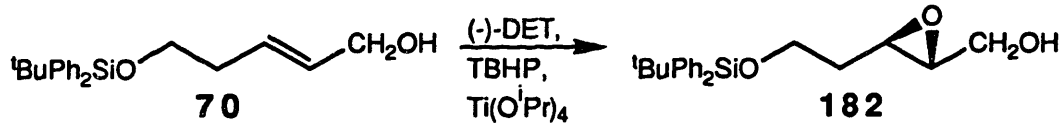
^{13}C NMR (300 MHz, $CDCl_3$): δ 173.34, 114.30, 77.98, 76.02, 75.95, 70.16, 59.45, 26.73, 25.89.

EI Mass Spec: m/e 187 $[M - 15]^+$, 143, 85, 71, 45.

Exact Mass: $[M - CH_3]^+$ = 187.06065 (calculated)

$[M - CH_3]^+$ = 187.0607 (measured).

IR ($CDCl_3$) cm^{-1}: 1795, 1455, 1375, 1085, 870.



70 182

Epoxide, 182

4Å molecular sieves (22 g) was suspended in CH_2Cl_2 (190 mL) and cooled to -30°C under argon. (-)-DET (0.651 mL, 3.805 mmoles), and $Ti(O^iPr)_4$ (0.944 mL, 3.171 mmoles) were added and the mixture was stirred for 5 minutes. TBHP (6.4M solution, 9.91 mL, 63.42 mmoles) was added dropwise and the resulting mixture was stirred at -30°C for 30 minutes. A solution of the allylic alcohol, 70, (11.29 g, 31.71 mmole) in CH_2Cl_2 (50 mL) was added dropwise and the resulting mixture was stirred at -30°C for 20 hours, after which it was warmed to 0°C. Water (20 mL) was then added followed by a 30% aqueous solution of NaOH-NaCl (3.8 mL). The resulting suspension was stirred at room temperature for 1 hour and the organic layer

was separated. The aqueous layer was extracted three times with CH_2Cl_2, and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (15% ethyl acetate/hexane) to furnish the epoxide (9.93g, 88%) as a colorless oil.

Physical Properties for **182**

R_f = 0.30 (33% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.62-7.69 (m, 4H), 7.34-7.45(m, 6H), 3.90(ddd, *J* = 12.4, 5.4, 2.4 Hz, 1H), 3.80 (m, 2 H), 3.60(ddd, *J* = 12.4, 6.9, 4.3 Hz, 1H), 3.13(td, *J* = 5.8, 2.5 Hz, 1H), 2.97(ddd, *J* = 4.4, 2.5, 2.5 Hz, 1H), 1.92(dd, *J* = 6.8, 6.3 Hz, 1H), 1.81(dd, *J* = 11.8, 6.2 Hz, 2H), 1.04(s, 9H).

^{13}C NMR (300 MHz, $CDCl_3$): δ 135.56, 133.61, 129.72, 127.73, 61.69, 60.78, 58.61, 53.73, 34.82, 26.86, 19.19.

FAB Mass Spec: m/e 357 $[M + 1]^+$, 269, 199, 135.

Exact Mass: $[M + 1]^+$ = 357.188599 (calculated)

$[M + 1]^+$ = 357.1887 (measured).

IR ($CHCl_3$) cm^{-1}: 3680 (w), 3600 (m), 3010 (s), 2960 (s), 2917 (s), 2860 (s), 2397 (m), 2325 (m), 2315 (m), 1715-1750 (w, br), 1690 (w), 1605 (w), 1595 (w), 1514 (s), 1505 (s), 1480 (m), 1425 (s), 1380-1390 (m, br), 1180-1240 (s, br), 1075-1120 (s, br), 995 (m), 970 (s), 920 (s) .

182 183

Diol, 183

A solution of the epoxide, **182**, (9.81 g, 27.51 mmol) in pentane (200 mL) was cooled to 0°C and trimethylaluminum (2.0M in hexane, 41.3 mL, 82.53 mmoles) was added dropwise over 15 minutes. After 2 hours at 0°C, the reaction was carefully quenched with 10% HCl. The resulting mixture was stirred at room temperature for 15 minutes. The products were extracted three times with ethyl acetate and the combined extracts were washed with saturated $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the solvent was removed and the product was purified on silica gel (20% ethyl acetate/hexane) to give the diol, **183**, (9.30g 91%) as a colorless oil. The products comprised a diastereomeric mixture of 40 : 1, as determined by 300-MHz ^1H NMR of the corresponding bis-MTPA ester and a > 40 : 1 mixture of 1,2 and 1,3 diols, as determined by GLC analysis.

Physical Properties for **183**

R_f = 0.20 (40% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.68-7.71(m, 4H), 7.44(m, 6H), 3.6(s, 1H), 3.52-3.82(m, 5H), 2.41(s, 1H), 1.57-1.85(m, 3H), 1.07(s, 9H), 0.90(d, J = 6.9 Hz, 3H).

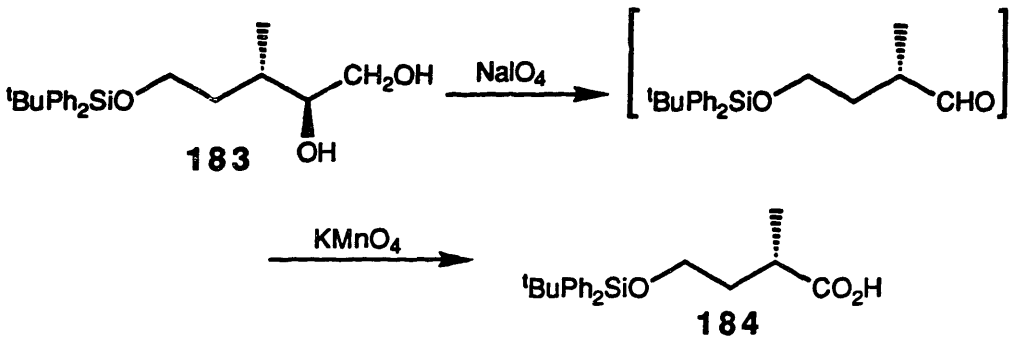
^{13}C NMR (300 MHz, $CDCl_3$): δ 135.59, 133.19, 129.83, 127.79, 76.10, 64.97, 62.27, 35.79, 34.06, 26.84, 19.11, 16.54.

FAB Mass Spec: m/e 373 $[M + 1]^+$, 297, 199, 135, 117, 99.

Exact Mass: $[M + 1]^+$ = 373.219899 (calculated)

$[M + 1]^+$ = 373.2196 (measured).

IR ($CHCl_3$) cm^{-1}: 3560, 3350, 2900, 1450, 1410, 1375, 1075.



Acid, 184

The diol, **183**, (2.01 g, 5.395 mmoles) was dissolved in ^{t}BuOH (30 mL) and pH = 5 buffer (30 mL). $NaIO_4$ (1.73 g, 8.093 mmoles) was added and the mixture was stirred at room temperature for 40 minutes. $KMnO_4$ (1.0M aqueous solution, 14 mL) was then added and the reaction was stirred for an additional 10 minutes, after which the reaction was titrated with saturated Na_2SO_3 until disappearance of the purple color was observed. The resulting brown precipitate was dissolved on titration with 10% HCl. The products were then extracted three times with ethyl acetate and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (10% ethyl acetate/hexane) to yield the acid (1.84 g, 95%) as a colorless solid. Upon reduction of the acid ($Me_2S{\cdot}BH_3$, ether) and formation of the corresponding MTPA ester, the enantiomeric purity of the acid was found to be 40 : 1.

Physical Properties for **184**

R_f = 0.29 (33% ethyl acetate/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65-7.68(m, 4H), 7.37-7.46(m, 6H), 3.71(m, 2H), 2.74(ddd, *J* = 13.8, 7.1, 7.1 Hz, 1H), 2.02(m, 1H), 1.65(ddd, *J* = 13.8, 7.8, 6.0 Hz, 1H), 1.19(d, *J* = 7.1 Hz, 3H), 1.04(s, 9H).

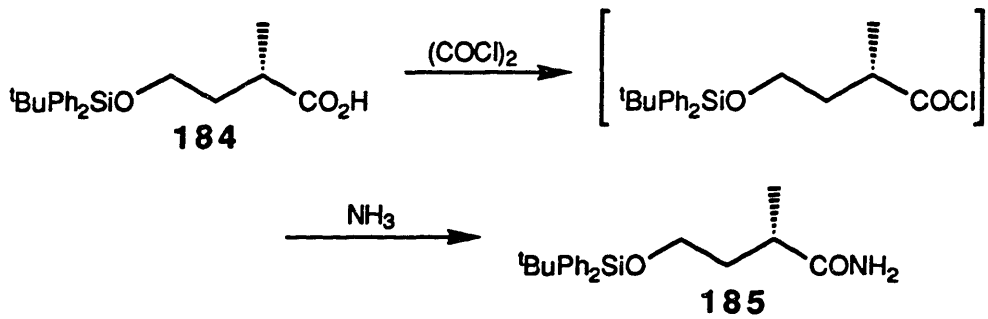
^{13}C NMR (300 MHz, $CDCl_3$): δ 182.38, 135.54, 133.69, 129.58, 127.62, 61.56, 36.09, 35.87, 26.81, 19.14, 16.82.

FAB Mass Spec: m/e 357 $[M + 1]^+$, 339, 299, 221, 199, 135.

Exact Mass: $[M + 1]^+$ = 357.188599 (calculated)

$[M + 1]^+$ = 357.1889 (measured).

IR ($CHCl_3$) cm^{-1}: 3530 (w), 2900-3330 (m, br), 3030 (w), 2960 (s), 2935 (s), 2890 (s), 2860 (s), 1710 (s), 1590 (w), 1475 (m), 1430 (m), 1390 (m), 1375 (w), 1240-1305 (m, br), 1090-1230 (m, br), 995 (m), 900 (m).



Amide, 185

Oxalyl chloride (0.31 mL, 3.54 mmoles) was added dropwise to a solution of the acid, **184**, (840 mg, 2.36 mmoles) in benzene (10 mL) at 0°C under argon. The reaction was stirred for 1 hour at room temperature, after which *N,N*-dimethylformamide (1 drop) was added. After an additional 1 hour, the solution was diluted with THF (15 mL) and transferred, *via* cannula, to a solution of NH_3(l) (5 mL) in THF (10 mL) at -78°C under argon. The mixture was warmed to room temperature and the excess NH_3 was allowed to evaporate over 4 hours. After dilution with ethyl acetate, saturated NH_4Cl solution was added and the products were extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to dryness to yield the pure amide (840 mg,

100%) as a colorless solid. The products comprised a > 20 : 1 mixture enantiomers as determined by chiral HPLC. Furthermore, after 3 recrystallizations from hexane, the optical purity of the amide was increased to > 99 : 1.

Physical Properties for **185**

R_f = 0.25 (50% ethyl acetate/hexane).

$[\alpha]_D$ = +11.9 c = 2.01 ($CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ 7.64-7.67(m, 4H), 7.35-7.46(m, 6H), 5.49(s, 1H), 5.42(s, 1H), 3.71(m, 2H), 2.58(m, 1H), 1.87(ddd, *J* = 13.5, 8.2, 5.3 Hz, 1H), 1.64(ddd, *J* = 13.5, 6.5, 6.5 Hz, 1H), 1.14(d, *J* = 7.1 Hz, 3H), 1.06(s, 9H).

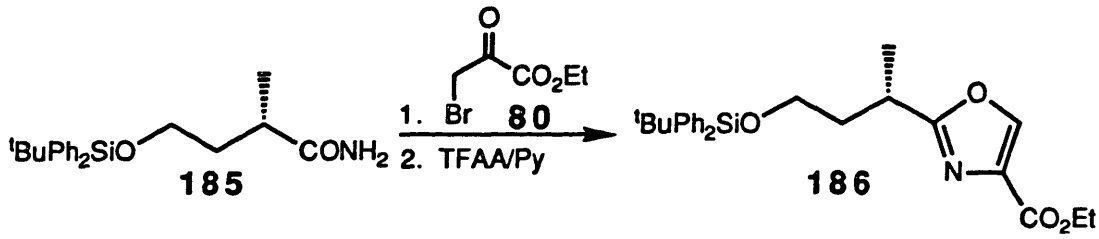
^{13}C NMR (300 MHz, $CDCl_3$): δ 179.15, 135.50, 133.67, 129.70, 127.70, 61.66, 36.85, 36.67, 26.92, 19.21, 17.51.

EI Mass Spec: m/e 340 $[M - 15]^+$, 298, 220, 198.

Exact Mass: $[M - CH_3]^+$ = 340.17328 (calculated)

$[M - CH_3]^+$ = 340.1732 (measured).

IR ($CHCl_3$) cm^{-1}: 3540 (m), 3420 (m), 2980 (s), 2940 (s), 2890 (s), 2860 (s), 1685 (s, br), 1595 (s), 1475 (m), 1445 (w), 1395 (m), 1370 (w), 1280 (m, br), 1070-1125 (s, br), 995 (m), 975 (m), 895 (m).



Oxazole, 186

The amide, **185**, (500 mg, 1.406 mmoles) was dissolved in THF at room temperature under argon. Epoxycyclopentene (0.80 mL, 10.00 mmoles) was added followed by ethyl bromopyruvate (0.882 mL, 7.030 mmoles). The resulting solution was stirred at room temperature for 5 hours, after which epoxycyclopentene (0.33 mL, 4.12 mmoles) was added. Stirring was continued for an additional 5 hours after which a further portion of epoxycyclopentene (0.33 mL, 4.12 mmoles) was added. After 5 more hours, a final addition of epoxycyclopentene (0.33 mL, 4.12 mmoles) was made. The reaction was stirred for 8 hours, after which it was cooled to 0°C. Pyridine (0.910 mL, 11.249 mmoles) was added followed by TFAA (0.794 mL, 5.624 mmoles) and the resulting solution was stirred at 0°C for 10 minutes. The reaction was quenched with pH = 7 buffer and washed three times with ethyl acetate. The combined extracts were washed twice with saturated $CuSO_4$ solution, saturated $NaHCO_3$ solution, and brine. After drying over $MgSO_4$, the solvent was removed and the residue was purified on silica gel (6% ethyl acetate/hexane) to give the oxazole (0.400 g, 63%) and the nitrile (0.166 g 35%) as colorless oils.

Physical Properties for **186**

R_f = 0.46 (20% ethyl acetate/hexane).

$[\alpha]_D$ = +9.9 c = 2.23 ($CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09(s, 1H), 7.60-7.66(m, 4H), 7.32-7.44(m, 6H), 4.38(q, *J* = 6.9 Hz, 2H), 3.67(m, 2H), 3.34(m, 1H), 2.15(m, 1H), 1.83(m, 1H), 1.37(t, *J* = 6.9 Hz, 3H), 1.33(d, *J* = 6.9 Hz, 3H), 1.03(s, 9H).

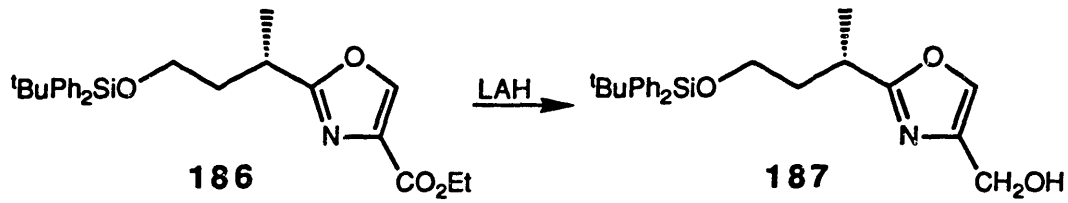
^{13}C NMR (300 MHz, $CDCl_3$): δ 169.19, 161.41, 143.30, 135.51, 133.74, 133.67, 129.55, 127.60, 61.27, 60.96, 37.31, 30.45, 26.82, 19.14, 18.29, 14.29.

EI Mass Spec: m/e 436 $[M - 15]^+$, 394, 288, 179.

Exact Mass: $[M - CH_3]^+$ = 436.19441 (calculated)

$[M - CH_3]^+$ = 436.1941 (measured).

IR (neat) cm^{-1}: 3160, 3060, 2930, 1780, 1740, 1580, 1470, 1425, 1370, 1310.



186 187

Alcohol, 187

$LiAlH_4$ (81.1 mg, 2.106 mmoles) was suspended in ether (10 mL) and cooled to 0°C under argon. The oxazole, **186**, (460.9 mg, 1.053 mmoles) was dissolved in ether (25 mL) and added *via* cannula to the $LiAlH_4$. The mixture was stirred at 0°C for 20 minutes, after which it was quenched with $Na_2SO_4 \cdot 10H_2O$. The resulting mixture was stirred at room temperature for 1 hour, after which it was filtered through a Celite pad. Concentration of the filtrate produced the pure alcohol (412.3 mg, 96%) as a colorless oil.

Physical Properties for **187**

R_f = 0.30 (60% ethyl acetate/hexane).

$[\alpha]_D$ = +14.0 c = 1.87 ($CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.67(m, 4H), 7.45(s, 1H), 7.33-7.45(m, 6H), 4.55(d, *J* = 5.5 Hz, 2H), 3.69(m, 2H), 3.25(sext, *J* = 6.9 Hz, 1H), 2.11(m, 2H), 1.81(m, 1H), 1.30(d, *J* = 6.9 Hz, 3H), 1.03(s, 9H).

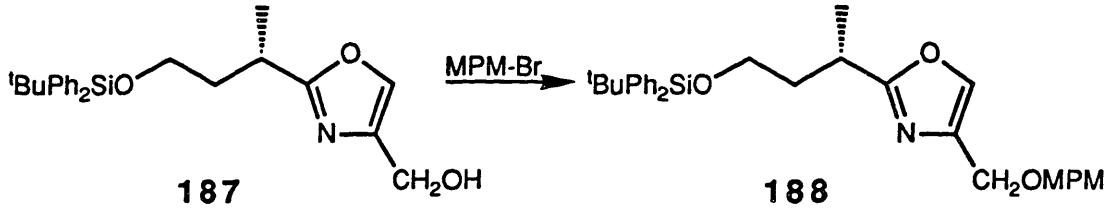
^{13}C NMR (300 MHz, $CDCl_3$): δ 168.91, 139.75, 135.52, 134.30, 133.76, 129.54, 127.59, 61.36, 56.84, 37.49, 30.33, 26.83, 19.16, 18.32.

EI Mass Spec: m/e 409 M^+, 394, 352, 274, 199, 136.

Exact Mass: M^+ = 409.20732 (calculated)

M^+ = 409.2069 (measured).

IR (neat) cm^{-1}: 3350, 3060, 2920, 1560, 1470, 1425, 1100.



187 188

MPM Ether, 188

KH (35%, 230 mg, 2.064 mmoles) was suspended in THF (10 mL) and 18-Crown-6 (cat. amount) was added. The mixture was cooled to 0°C under argon, and a solution of the oxazole, **187**, (600.7 mg, 1.474 mmol) in THF (20 mL) was added. After 15 minutes at 0°C, *p*-methoxybenzyl bromide (0.31 mL, 2.064 mmoles) was added. The reaction was stirred at room temperature for 4 hours, cooled to 0°C, and carefully quenched with water. The products were extracted three times with ethyl acetate, and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed residue was purified on silica gel (10% ethyl acetate/hexane) to give the desired product (744 mg, 95%) as a colorless oil

Physical Properties for 188

R_f = 0.24 (15% ethyl acetate/hexane).

$[\alpha]_D$ = +8.9 c = 2.06 ($CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ 7.60-7.66(m, 4H), 7.45(t, *J* = 0.98 Hz, 1H), 7.30-7.43(m, 6H), 7.27(dm, *J* = 8.8 Hz, 2H), 6.87(dm, *J* = 8.8 Hz, 2H), 4.53(s, 2H), 4.39(d, *J* = 0.98 Hz, 2H), 3.80(s, 3H), 3.69(d, *J* = 6.3 Hz, 2H), 3.24(m, 1H), 2.12(m, 1H), 1.80(m, 1H), 1.30(d, *J* = 7.0 Hz, 3H), 1.02(s, 9H).

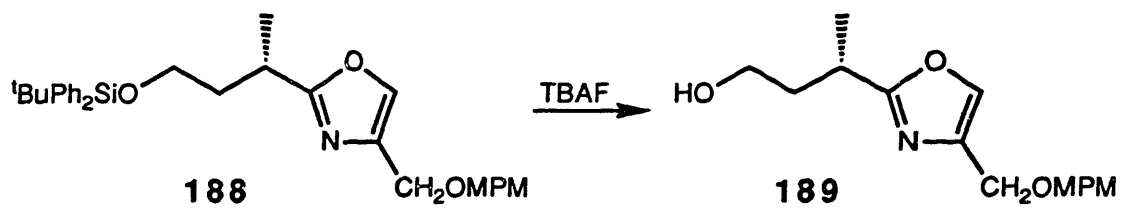
^{13}C NMR (300 MHz, $CDCl_3$): δ 168.59, 159.24, 137.41, 135.47, 133.72, 133.65, 129.96, 129.50, 127.53, 113.76, 72.29, 63.71, 61.28, 55.19, 37.39, 30.23, 26.78, 19.12, 18.31.

EI Mass Spec: m/e 514 $[M - 15]^+$, 472, 393, 259, 121.

Exact Mass: $[M - CH_3]^+$ = 514.24136 (calculated)

$[M - CH_3]^+$ = 514.2409 (measured).

IR (neat) cm^{-1}: 3060, 2910, 2850, 1610, 1565, 1510, 1460, 1425, 1245, 1170, 1100, 815, 730, 690.



188 189

Alcohol, 189

The MPM ether, **188**, (744 mg, 1.404 mmoles) was dissolved in THF (8 mL) at room temperature under argon. Tetrabutylammonium fluoride (1.0M in THF, 2.8 mL, 2.808 mmoles) was added and the reaction was stirred for 6 hours. The solvent was removed and the product was purified on

silica gel (75% ethyl acetate/hexane) to give the alcohol (418.9 mg, 100%) as a colorless oil.

Physical Properties for 189

R_f = 0.24 (80% ethyl acetate/hexane).

$[\alpha]_D$ = +17.1 c = 2.03 ($CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ 7.50(t, *J* = 0.95 Hz, 1H), 7.29(dm, *J* = 8.7 Hz, 2H), 6.88(dm, *J* = 8.7 Hz, 2H), 4.52(s, 2H), 4.40(d, *J* = 0.95 Hz, 2H), 3.80(s, 3H), 3.68(t, *J* = 5.9 Hz, 2H), 3.19(m, 1H), 2.74(s, 1H), 1.84-2.08(m, 2H), 1.36(d, *J* = 7.1 Hz, 3H).

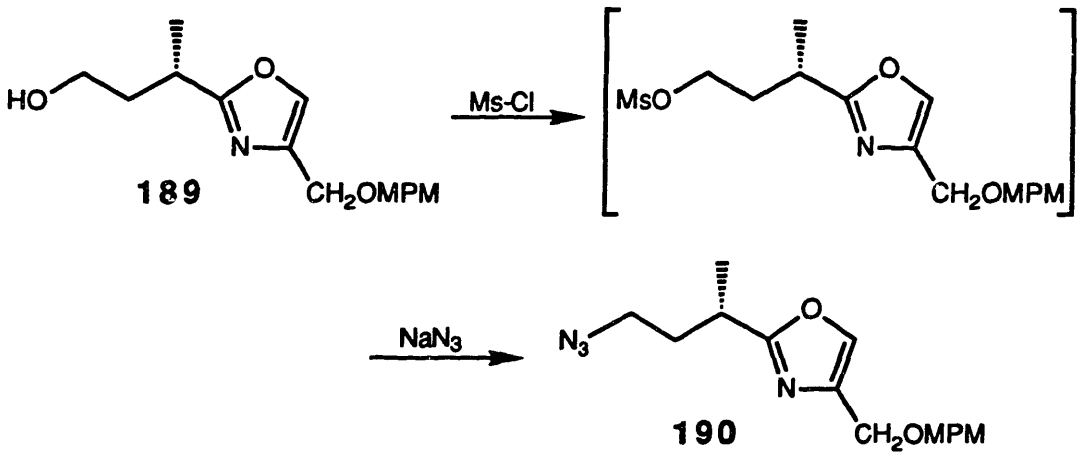
^{13}C NMR (300 MHz, $CDCl_3$): δ 168.49, 159.30, 137.26, 135.81, 129.88, 129.51, 113.81, 72.38, 63.55, 60.25, 55.24, 37.54, 31.09, 18.46.

FAB Mass Spec: m/e 292 $[M + 1]^+$, 155, 121.

Exact Mass: $[M + 1]^+$ = 292.15488 (calculated)

$[M + 1]^+$ = 292.1547 (measured).

IR (neat) cm^{-1}: 3400, 2940, 1613, 1570, 1510, 1460, 1300, 1245, 1170, 1075, 813.



Azide, 190

The alcohol, **189**, (136.2 mg, 0.467 mmole) was dissolved in CH_2Cl_2 (1.6 mL), cooled to 0°C under argon, and triethylamine (0.19 mL, 1.401 mmole) was added. Methanesulfonyl chloride (54.4 μL, 0.700 mmole) was then added and the reaction was stirred at 0°C for 30 minutes. The solvent was removed under reduced pressure and the residue was dissolved in DMF (4.7 mL). NaN_3 was added and the reaction was stirred at room temperature under argon for 30 hours. The reaction was quenched with H_2O (10 mL) and washed with ethyl acetate (3 X 10 mL). The combined organics were washed with brine (5 mL) and dried over Na_2SO_4. Concentration of the organics and purification of the residue on silica gel (25% ethyl acetate/hexane) gave the azide (128.1 mg, 87%) as a colorless oil.

Physical Properties for **190**

R_f = 0.50 (50% ethyl acetate/hexane).

$[\alpha]_D$ = +30.1 c = 1.90 ($CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ 7.51(t, *J* = 0.94 Hz, 1H), 7.29(dm, *J* = 8.3 Hz, 2H), 6.88(dm, *J* = 8.3 Hz, 2H), 4.55(s, 2H), 4.41(d, *J* = 0.94 Hz, 2H), 3.80(s, 3H), 3.33(td,

J = 7.0, 2.9 Hz, 2H), 3.11(m, 1H), 2.10(ddd, J = 13.4, 8.1, 6.7 Hz, 1H), 1.86(ddd, J = 13.4, 7.4, 5.9 Hz, 1H), 1.36(d, J = 7.5 Hz, 3H).

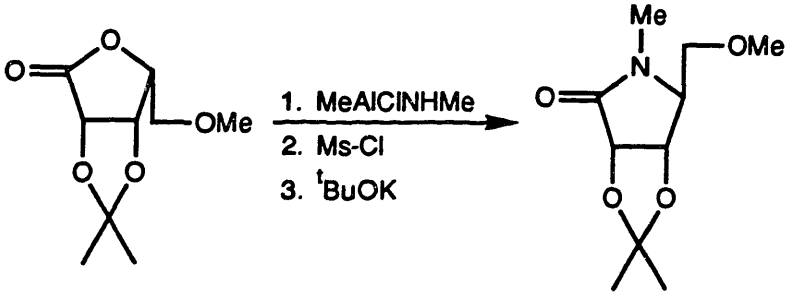
^{13}C NMR (300 MHz, $CDCl_3$): δ 166.97, 159.04, 137.51, 135.61, 129.69, 129.24, 113.53, 72.07, 63.44, 54.92, 48.87, 33.66, 30.85, 18.12.

FAB Mass Spec: m/e 317 $[M+1]^+$, 274, 180.

Exact Mass: $[M + 1]^+$ = 317.16137 (calculated)

$[M + 1]^+$ = 317.1610 (measured).

IR (neat) cm^{-1}: 2940, 2040, 1610, 1570, 1510,1455, 1360, 1300, 1245, 1170, 1075, 1030, 810.



167 **192**

Methyl Lactam, 192

$MeNH_2 \cdot HCl$ (140.8 mg, 2.163 mmoles) was suspended in benzene (2 mL) and cooled to 0°C under argon. Trimethylaluminum (2.0M in hexane, 1.04 mL, 2.163 mmoles) was added, dropwise, over a period of 10 minutes. After stirring for 30 minutes at room temperature, the resulting solution was added, *via* cannula, to a solution of the lactone, **167**, (208.2 mg, 1.030 mmoles) in benzene (4 mL) at room temperature under argon. The resulting mixture was stirred for 3 hours, after which it was cooled to 0°C and carefully quenched with saturated Rochelle's salt solution. After stirring for 1 hour, the products were extracted with ethyl acetate (4 X 5 mL)

and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed to give the hydroxyamide, **191**, (238.1 mg, 99%) as a white solid which was immediately dissolved in CH_2Cl_2 (3 mL). Triethylamine (0.430 mL, 3.090 mmoles) was added and the mixture was cooled to 0°C under argon. Methanesulfonyl chloride (0.12 mL, 1.545 mmoles) was then added and the reaction was stirred at 0°C for 30 minutes. The solvent was removed and the residue was diluted with THF (22 mL) and filtered through Celite under argon. The resulting solution was cooled to -40°C and potassium *tert*-butoxide (1.41M in THF, 3 mL, 4.120 mmoles) was added. After warming to room temperature over 1 hour, the reaction was quenched with pH = 7 buffer (30 mL). The products were extracted with ethyl acetate (3 X 15 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the product was purified on silica gel (80% ethyl acetate/hexane) to give the methyl lactam (184.3 mg, 84%) as a colorless oil.

Physical Properties for **191**

R_f = 0.14 (ethyl acetate).

^1H NMR (300 MHz, $CDCl_3$): δ 6.82(s, 1H), 4.57(d, J = 7.8 Hz, 1H), 4.45(dd, J = 7.8, 2.6 Hz, 1H), 4.11(ddd, J = 6.7, 6.0, 2.6 Hz, 1H), 3.50(ABX, J_{AB} = 9.7 Hz, J_{AX} = 6.7 Hz, J_{BX} = 5.8 Hz, $\Delta\nu_{AB}$ = 14.8 Hz, 2H), 3.83(s, 3H), 2.85(d, J = 4.7 Hz, 3H), 2.33(d, J = 6.9 Hz, 1H), 1.58(s, 3H), 1.39(s, 3H).

Physical Properties for **192**

R_f = 0.32 (ethyl acetate).

$[\alpha]_D$ = +30.5 c = 2.37 ($CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.63(d, J = 5.8 Hz, 1H), 4.53(d, J = 5.8 Hz, 1H), 3.61 (t, J = 2.7 Hz, 1H), 3.52(ABX, J_{AB} = 10 Hz, J_{AX} = 3.2 Hz, J_{BX} = 2.7 Hz, $\Delta\nu_{AB}$ = 15 Hz, 2H), 3.33(s, 3H), 2.87(s, 3H), 1.42(s, 3H), 1.37(s, 3H).

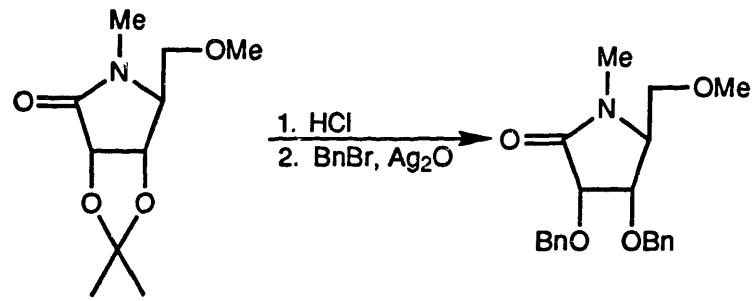
^{13}C NMR (300 MHz, $CDCl_3$): δ 171.48, 111.60, 77.31, 76.10, 69.42, 63.52, 59.17, 27.78, 26.87, 25.54.

EI Mass Spec: m/e 200 $[M - 15]^+$, 170, 142, 85, 69, 45.

Exact Mass: $[M - CH_3]^+$ = 200.09228 (calculated)

$[M - CH_3]^+$ = 200.0921 (measured).

IR ($CHCl_3$) cm^{-1}: 2995, 2937, 1700, 1450, 1400, 1375, 1120, 1070.



192 193

Dibenzyl Ether, 193

The methyl lactam, **192**, (74.8 mg, 0.348 mmole) was dissolved in THF (2 mL) and concentrated HCl (1.5 mL) was added. The reaction was stirred at room temperature for 2 hours, after which it was concentrated to dryness. The residue was azeotropically dried with benzene (3 X 5 mL) and kept under vacuum for 24 hours. The residue was then dissolved in DMF (1 mL) and Ag_2O (367 mg, 5 equiv by wt) added. Benzyl bromide (0.29 mL, 2.436 mmoles) was added to the resulting suspension and the reaction was stirred at room temperature under argon for 20 hours. The reaction was then filtered through Celite and the solids were washed with $CHCl_3$. The

combined organics were diluted with ether/hexane (4/1, 5 mL) and saturated NH_4Cl solution (5 mL) was added. The products were extracted with ether/hexane (4/1, 3 X 5 mL) and the combined organics were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was purified on silica gel (80% ethyl acetate/hexane) to give the desired product (102.8 mg, 83%) as an oil.

Physical Properties for **193**

R_f = 0.40 (ethyl acetate).

$[\alpha]_D$ = -113.9 c = 1.92 ($CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ 7.44(d, J = 6.8 Hz, 2H), 7.30(d, J = 7.1Hz, 2H), 7.06-7.19(m, 6H), 5.04(ABq, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 85.2 Hz, 2H), 4.48(ABq, J_{AB} = 11.7 Hz, $\Delta\nu_{AB}$ = 79.8 Hz, 2H), 4.07(d, J = 5.5 Hz, 1H), 3.80(dd, J = 5.5, 3.6 Hz, 1H), 3.37(q, J = 3.6 Hz, 1H), 2.86(d, J = 3.6 Hz, 2H), 2.82(s, 3H), 2.57(s, 3H).

^1H NMR (300 MHz, C_6D_6): δ 7.40-7.44(m, 2H), 7.27-7.36(m, 8H), 4.89(ABq, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 55.3 Hz, 2H), 4.60(ABq, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 48.7 Hz, 2H), 4.11(d, J = 5.8 Hz, 1H), 3.97(dd, J = 5.8, 2.9 Hz, 1H), 3.59(q, J = 3.1 Hz, 1H), 3.48(dd, J = 10.3, 3.3 Hz, 1H), 3.29(dd, J = 10.3, 2.8 Hz, 1H), 3.27(s, 3H), 2.86(s, 3H).

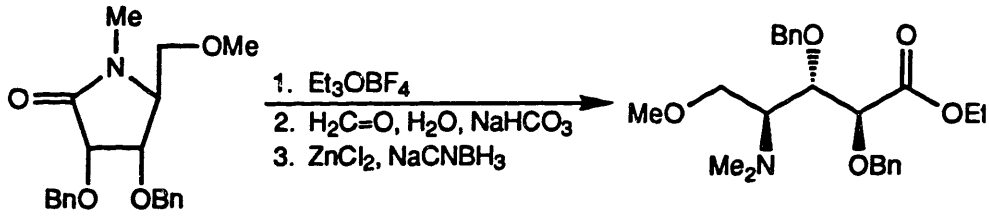
^{13}C NMR (300 MHz, $CDCl_3$): δ 171.17, 137.86, 137.71, 128.25, 128.16, 127.97, 127.82, 127.70, 127.53, 74.97, 74.51, 72.26, 72.03, 69.71, 63.33, 59.01, 27.56.

FAB Mass Spec: m/e 356 $[M + 1]^+$, 326, 278, 264, 248, 181.

Exact Mass: $[M + 1]^+$ = 356.18618 (calculated)

$[M + 1]^+$ = 356.1864 (measured).

IR (neat) cm^{-1}: 3060, 3025, 2900, 1700, 1450, 1400, 1350, 1260, 1190, 1100, 1155, 730, 690.



193 **194**

Amino ester, 194

The dibenzyl ether, **193**, (30 mg, 0.084 mmole) and 2,6-di-*tert*-butylpyridine (38 μL, 0.168 mmole) were dissolved in CH_2Cl_2 (1 mL) and Et_3OBF_4 (1M in CH_2Cl_2, 0.17 mL, 0.168 mmole) was added. The reaction was stirred at room temperature under argon for 16 hours, after which the solvent was removed. Aqueous formaldehyde (37%, 28 μL, 0.336 mmole) was added followed by saturated $NaHCO_3$ (0.8 mL) and methanol (1 mL).

$ZnCl_2$ (37 mg, 0.252 mmole) was dissolved in MeOH (1 mL) and added, *via* cannula, to solution of $NaCNBH_3$ (33.6 mg, 0.504 mmole) in MeOH (1 mL). The mixture was stirred at room temperature under argon for 5 minutes, after which it was added, *via* cannula, to the above reaction. The resulting mixture was stirred for 4 hours and quenched with 0.1N KOH (1 mL). The products were extracted with ethyl acetate (3 X 5 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed and the product was purified on silica gel (25% ethyl acetate/hexane) to give the amino ester, **194**, (27.6 mg, 79%) and the dibenzyl ether, **193**, (3.4 mg, 11%) as oils.

Physical Properties for **194**

R_f = 0.38 (33% ethyl acetate/hexane).

$[\alpha]_D$ = -59.7 c = 1.75 (acetone).

^{1}H NMR (250 MHz, C_6D_6): δ 7.41(d, J = 6.6 Hz, 2H), 7.33(d, J = 7.1 Hz, 2H), 7.06-7.21(m, 6H), 4.91(1/2 ABq, J_{AB} = 12.1 Hz, 1H), 4.73(1/2 ABq, J_{AB} = 11.4 Hz, 1H), 4.56(d, J = 1.7 Hz, 1H), 4.46(1/2 ABq, J_{AB} = 12.1 Hz, 1H), 4.42(1/2 ABq, J_{AB} = 11.4 Hz, 1H), 4.11(dd, J = 10.1, 1.7 Hz, 1H), 4.05(q, J = 7.1 Hz, 2H), 3.67(dd, J = 9.8, 2.4 Hz, 1H), 3.54(dd, J = 9.8, 7.1 Hz, 1H), 3.41(ddd, J = 9.8, 7.1, 2.4 Hz, 1H), 3.05(s, 3H), 2.36(s, 6H), 1.02(t, J = 7.1 Hz, 3H).

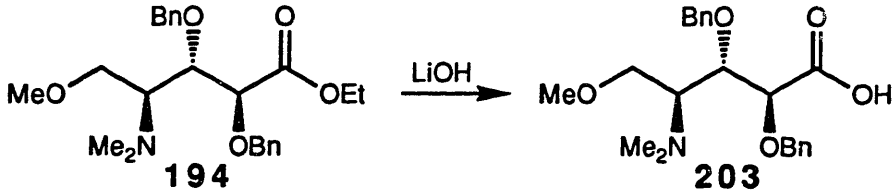
^{13}C NMR (300 MHz, $CDCl_3$): δ 170.04, 139.32, 138.98, 128.45, 128.38, 128.07, 128.03, 127.54, 80.72, 78.94, 73.03, 73.00, 69.78, 62.31, 60.16, 58.38, 42.15, 14.36.

FAB Mass Spec: m/e 416 $[M + 1]^+$, 370, 308, 102.

Exact Mass: $[M + 1]^+$ = 416.24370 (calculated)

$[M + 1]^+$ = 416.2440 (measured).

IR (neat) cm^{-1}: 3090, 3065, 3035, 2980, 2935, 2875, 2835, 1750, 1745, 1498, 1455, 1390, 1368, 1346, 1280, 1190, 1110, 1025, 760, 690.



194 203

Acid, 203

The ester, **194**, (135 mg, 0.325 mmole) was dissolved in THF/H_2O (3/1, 1 mL) and LiOH·H_2O (30 mg, 0.714 mmole) was added. The reaction was stirred for 3 days at room temperature, after which it was acidified to pH = 3 with 1N HCl. The product was extracted with ethyl acetate (10 X 2 mL) and the combined extracts were dried over $MgSO_4$. Concentration under reduced pressure provided the pure acid (122 mg, 97%) as a white foam.

Physical Properties for **202**

R_f = 0.29 (10% MeOH/CH_2Cl_2)

^{1}H NMR (300 MHz, C_6D_6): δ 7.45(d, *J* = 7.8 Hz, 2H), 7.28(d, *J* = 7.2 Hz, 2H), 5.05(d, *J* = 12 Hz, 1H), 4.68(m, 3H), 4.50(dd, *J* = 12, 10.8 Hz, 2H), 4.17(m, 1H), 4.08(d, *J* = 12.6 Hz, 1H), 3.64(dd, *J* = 11.4, 8.4 Hz, 1H), 2.96(s, 3H), 2.40(s, 6H).

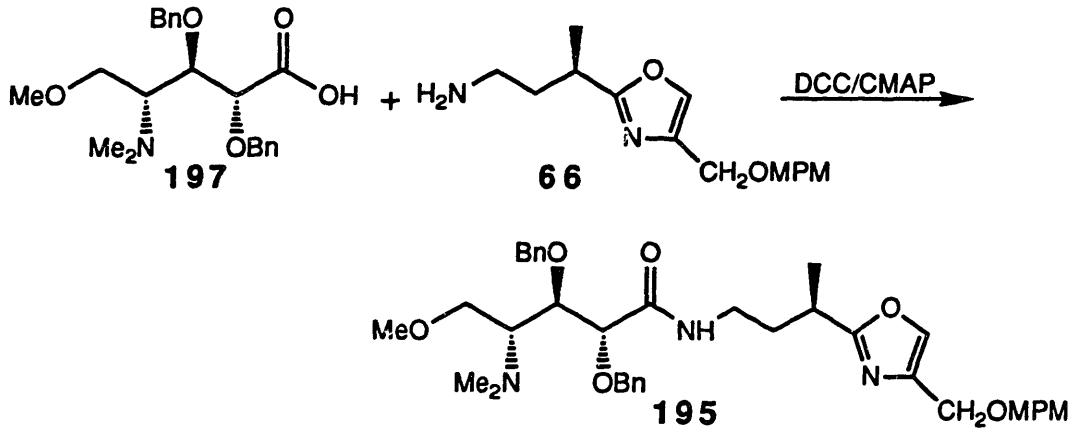
^{13}C NMR (300 MHz, C_6D_6): δ 173.74, 138.90, 138.62, 128.60, 128.52, 128.18, 127.90, 127.42, 78.85, 78.76, 72.50, 71.64, 67.81, 65.09, 58.29, 41.86.

FAB Mass Spec: m/e 388 $[M + 1]^+$, 307, 154, 136.

Exact Mass: $[M + 1]^+$ = 388.212399 (calculated)

$[M + 1]^+$ = 388.2121 (measured).

IR ($CHCl_3$) cm^{-1}: 2980, 3000-2400, 1740, 1604, 1460, 1200, 1110, 1020.



Fragment C Enantiomer, 195

To a solution of the amine, **66**, (27.5 mg, 0.095 mmole) in CH_2Cl_2 (1 mL) was added DMAP (9.0 mg, 0.074 mmole) and DCC (17.2 mg, 0.083 mmole), and the reaction was cooled to 0°C under argon. A solution of the acid, **197**, (22.0 mg, 0.057 mmole) in CH_2Cl_2 (0.5 mL) was added, *via* cannula, and the reaction was stirred at 0°C for 30 minutes and 11 hours at room temperature. The reaction was then diluted with ether (5 mL) and the

precipitate was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was purified on silica gel (5% methanol/CH_2Cl_2) to give the product (25.9 mg, 69%) as a colorless oil.

Physical Properties for **195**

R_f = 0.20 (5% methanol/CH_2Cl_2).

^1H NMR (500 MHz, C_6D_6): δ 7.03-7.31(m, 13H), 6.76(m, *J* = 8.79 Hz, 2H), 6.74(broad m, 1H), 4.66(d, *J* = 11.24 Hz, 1H), 4.57(d, *J* = 11.73 Hz, 1H), 4.47(d, *J* = 11.73 Hz, 1H), 4.44(d, *J* = 1.47 Hz, 1H), 4.40(d, *J* = 11.73 Hz, 1H), 4.38(s, 2H), 4.35(s, 2H), 4.27(dd, *J* = 1.46, 10.26 Hz, 1H), 3.65(dd, *J* = 2.45, 10.26 Hz, 1H), 3.55(dd, *J* = 6.84, 10.26 Hz, 1H), 3.41(ddd, *J* = 2.94, 2.44, 6.84 Hz, 1H), 3.36(septet, *J* = 3.36 Hz, 1H), 3.27(s, 3H), 3.10(sextet, *J* = 5.87 Hz, 1H), 3.04(s, 3H), 2.85(d sextets, *J* = 6.35, 7.82 Hz, 1H), 2.37(s, 6H), 1.84(d sextets, *J* = 5.5, 8.0 Hz, 1H), 1.61(sextet, *J* = 1.61 Hz, 1H), 1.12(d, 6.5 Hz, 3H).

^{13}C NMR (500 MHz, C_6D_6): δ 169.81, 167.83, 159.73, 139.38, 138.83, 138.56, 135.62, 130.79, 129.56, 114.06, 80.97, 80.51, 73.62, 73.31, 72.33, 69.55, 64.44, 62.74, 58.38, 54.74, 42.29, 37.10, 35.34, 31.75, 18.46.

FAB Mass Spec: m/e 660 $[M + 1]^+$, 121, 102, 91.

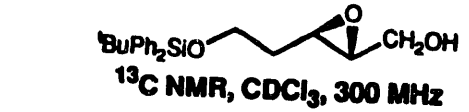
Exact Mass: $[M + 1]^+$ = 660.36488 (calculated)

$[M + 1]^+$ = 660.3653 (measured).

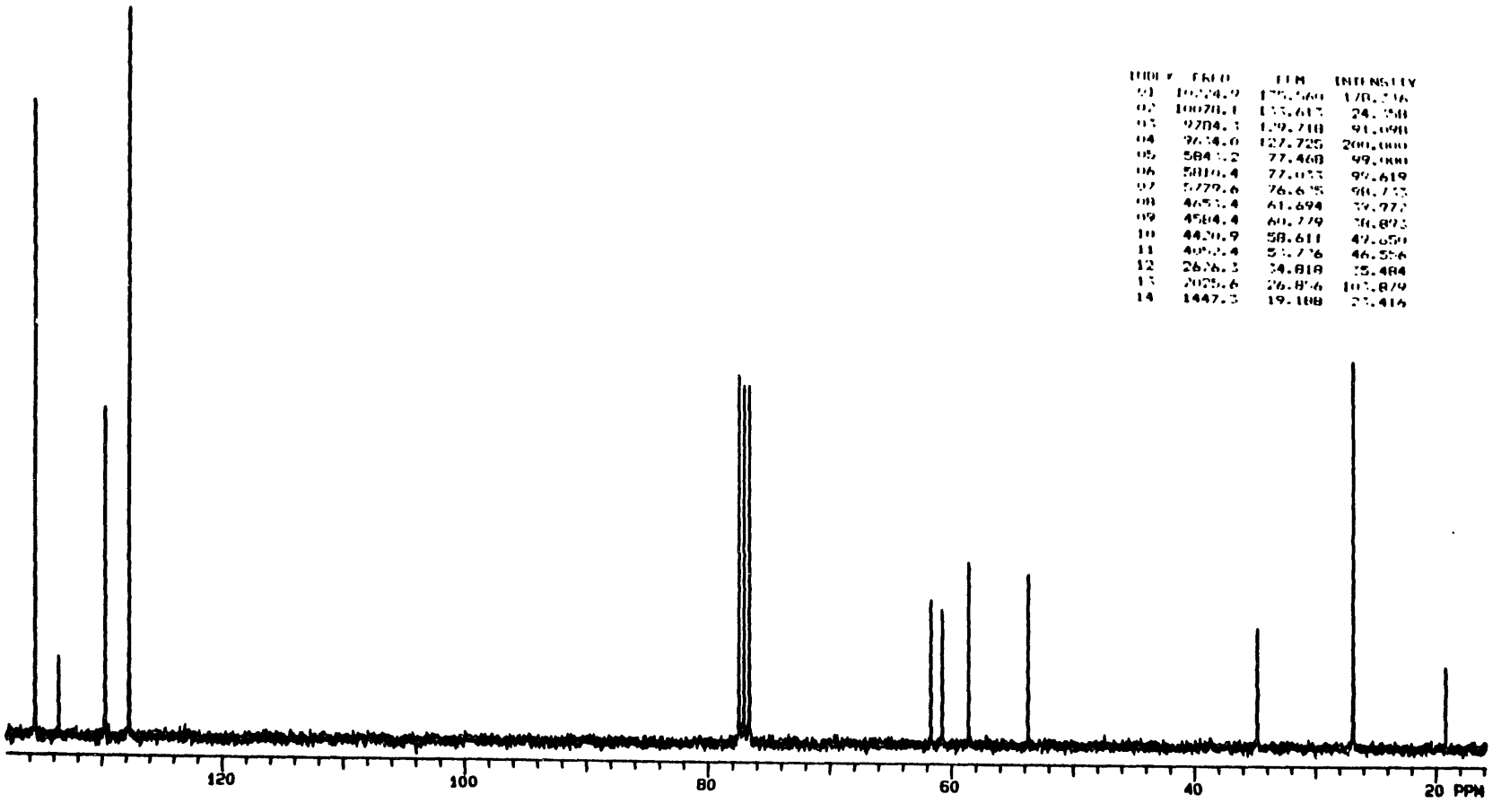
IR (C_6D_6) cm^{-1}: 3430, 3030, 2930, 2860, 1675, 1510, 1245, 1080, 1030, 725, 687.

4.6 NMR Spectra

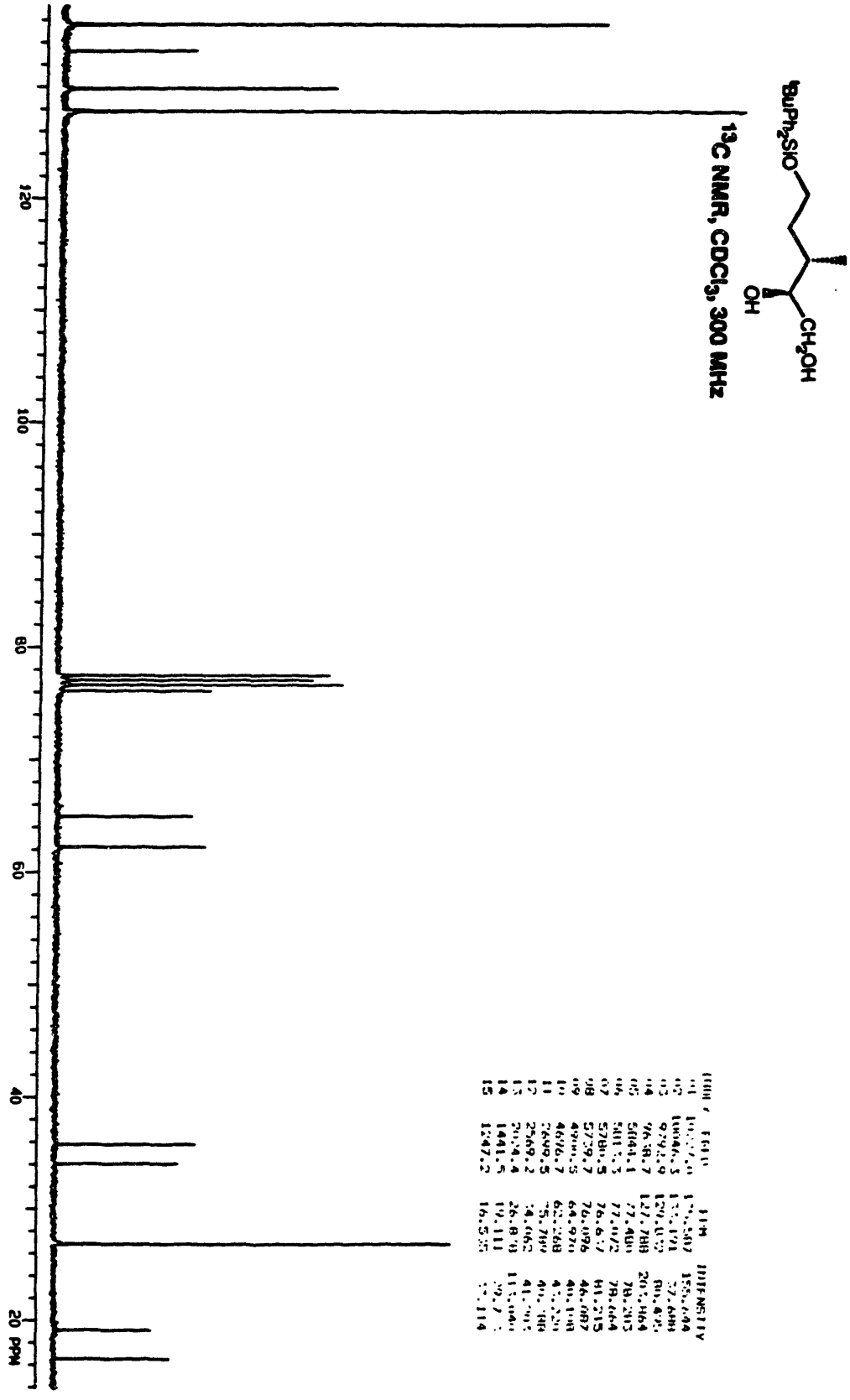
tBuPh2SiO
O
CH2OH
CDCl3, 300 MHz
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm



^{13}C NMR, $CDCl_3$, 300 MHz

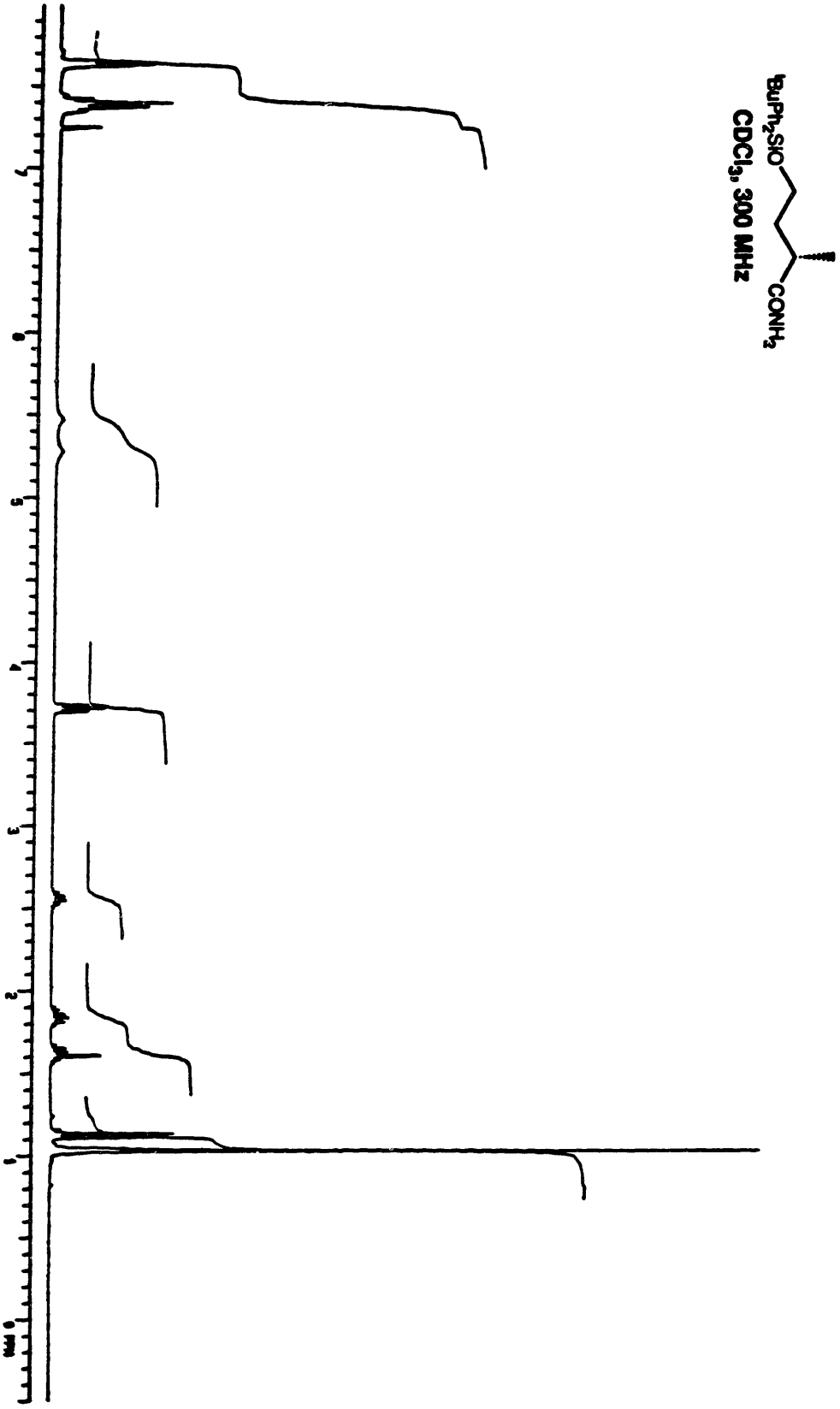


CDCl3, 300 MHz
tBuPh2SiO
OH
CH2OH


tBuPh2SiO
OH
CH2OH
13C NMR, CDCl3, 300 MHz
120
100
80
60
40
20 PPM

tBuPh2SiO
CO2H
CDCl3, 300 MHz
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

tBuPh2SiO
CO2H
13C NMR, CDCl3, 300 MHz
180
160
140
120
100
80
60
40
20
PPM


$^tBuPh_2SiO$
$CONH_2$
$CDCl_3$, 300 MHz

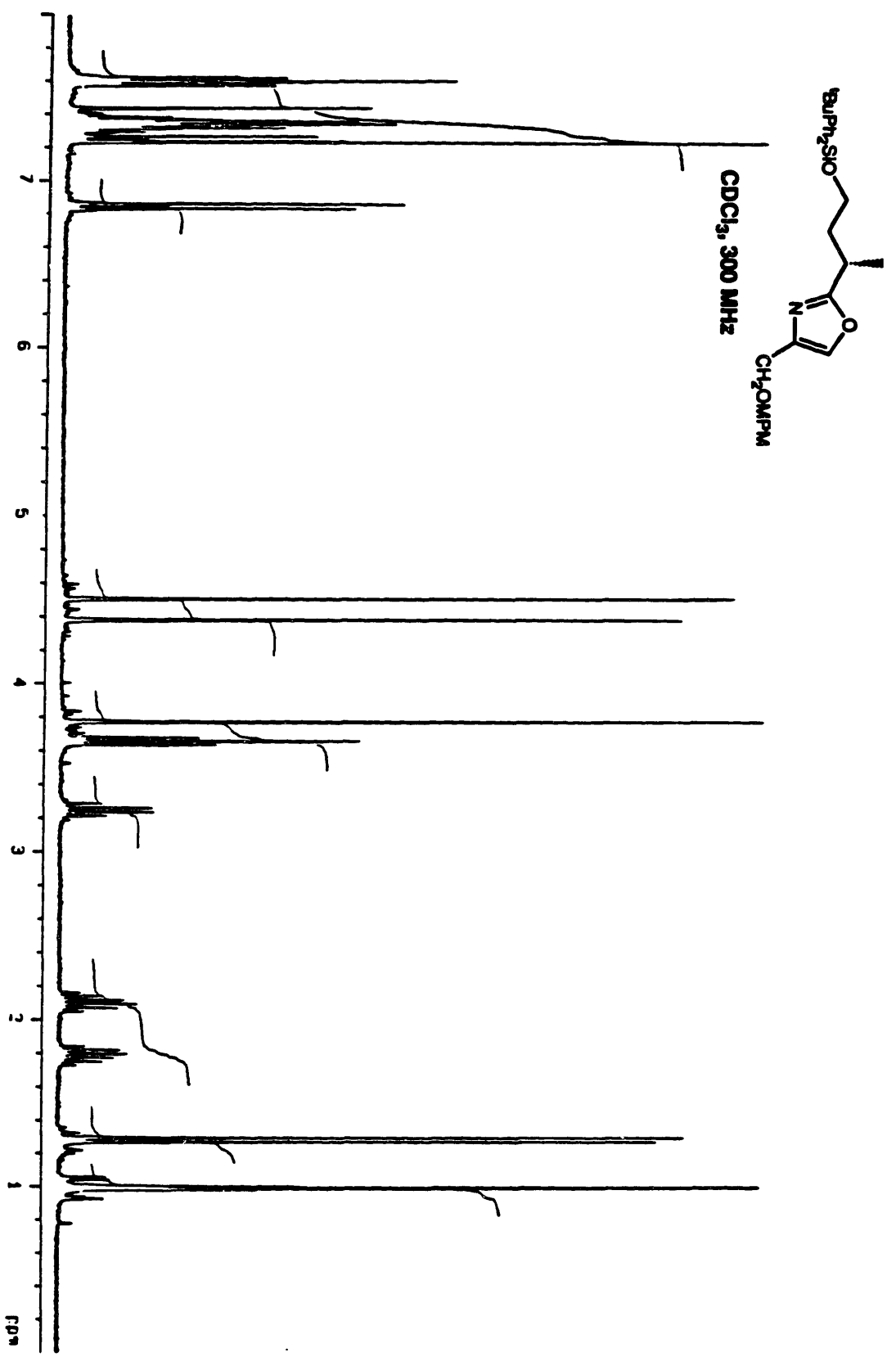
tBuPh2SiO
CONH2
13C NMR, CDCl3, 300 MHz
160
140
120
100
80
60
40
20 PPM

$CDCl_3$, 300 MHz
$^tBuPh_2SiO$
N
O
CO_2Et
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0 PPM
0.0

^{13}C NMR, $CDCl_3$, 300 MHz
^{t}BuPh$_2$SiO
N
O
CO$_2$Et
160
140
120
100
80
60
40
20
PPM

$CDCl_3$, 300 MHz
$^tBuPh_2SiO$
N
O
CH_2OH
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

^{13}C NMR, $CDCl_3$, 300 MHz
$BuPh_2SiO$
CH_2OH
N
O


CDCl3, 300 MHz
tBuPh2SiO
N
O
CH2OMPM
ppm
1
2
3
4
5
6
7

^{13}C NMR, $CDCl_3$, 300 MHz
^{t}BuPh$_2$SiO
N
O
CH$_2$OMPM
160
140
120
100
80
60
40
20
PPM

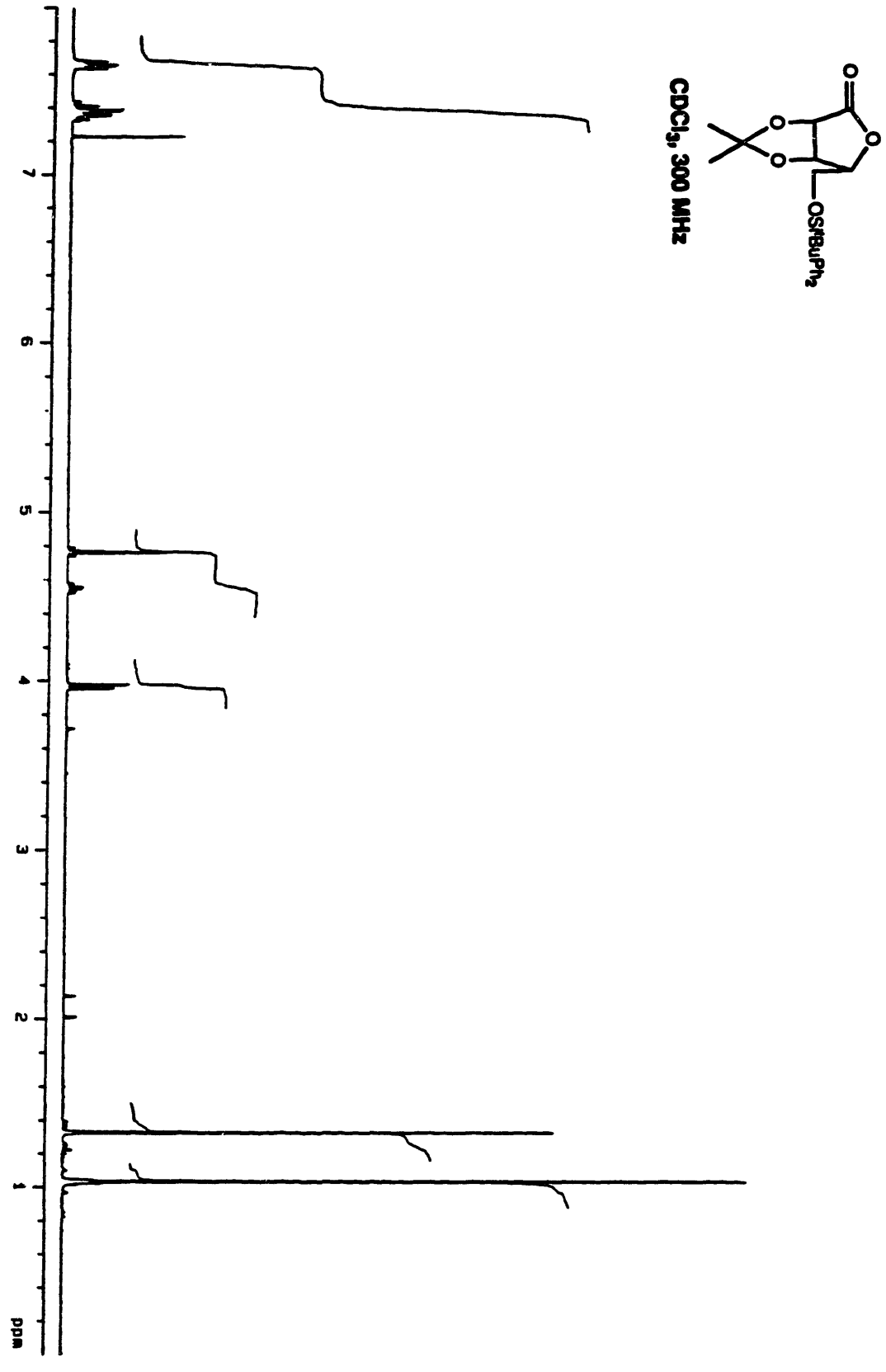
CDCl3, 500 MHz
HO
N
O
CH2OMPM
7
6
5
4
3
2
1
ppm

INDEX	FREQ	PPM	INTENSITY
01	12710.9	168.493	38.935
02	12017.1	159.297	36.329
03	10354.0	137.261	35.730
04	10245.0	135.806	92.006
05	9750.0	129.880	41.529
06	9769.9	129.500	194.373
07	8505.7	113.010	190.210
08	5842.1	77.441	152.583
09	5810.0	77.017	200.321
10	5770.0	76.592	194.428
11	5460.5	72.383	95.790
12	4794.0	63.548	92.254
13	4545.1	60.245	101.747
14	4187.1	55.239	91.685
15	2832.2	37.543	89.930
16	2345.1	31.086	79.113
17	1392.9	18.454	80.687

CDCl3, 300 MHz
PPM

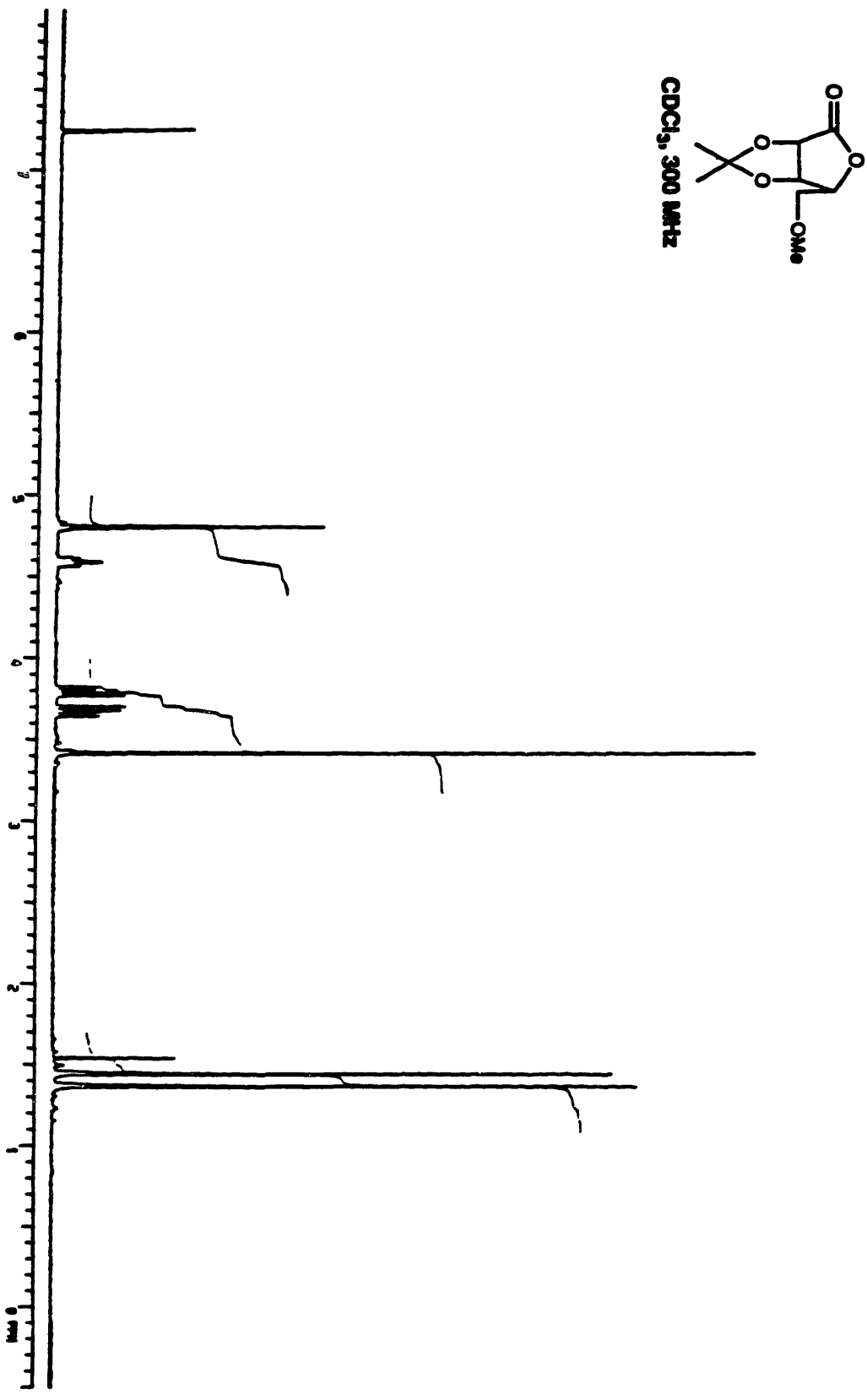
^{13}C NMR, $CDCl_3$, 300 MHz
CH_2OMPM
N_3
O
N
160
140
120
100
80
60
40
20
ppm

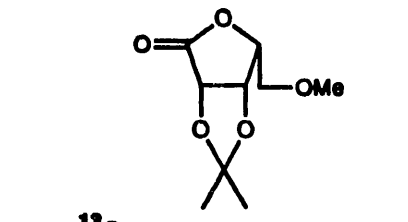
CDCl3, 300 MHz
HO
OH
OSiBuPh2
ppm
1
2
3
4
5
6
7
8


CDCl3, 300 MHz
OSiBuPh2
ppm
7
6
5
4
3
2
1

CDCl3, 300 MHz
O
O
O
O
OH

INDEX	FREQ	PPM	INTENSITY
01	13044.0	173.439	42.808
02	8548.5	114.537	128.448
03	5971.5	79.183	155.284
04	5843.5	77.480	508.522
05	5811.6	77.037	522.802
06	5779.7	76.614	522.847
07	5749.0	76.210	164.429
08	5744.4	76.147	158.531
09	4594.2	60.899	146.110
10	2811.8	36.958	145.118
11	1943.8	25.756	134.116

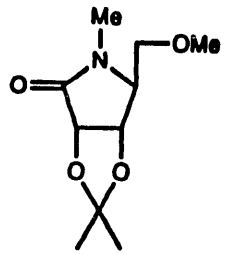

CDCl3, 300 MHz
OMe



^{13}C NMR, $CDCl_3$, 300 MHz

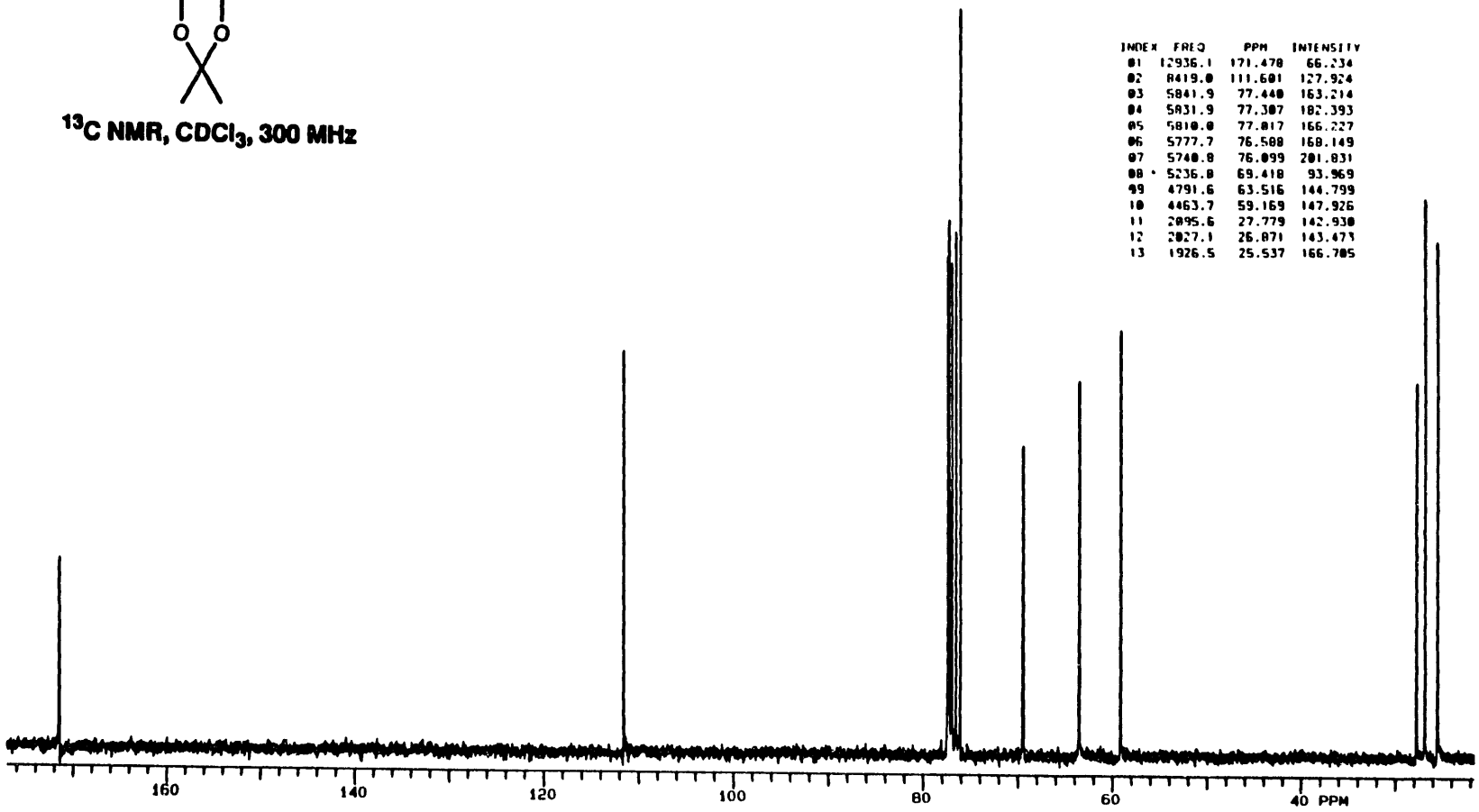
INDEX	FREQ	PPM	INTENSITY
01	13076.6	173.340	31.669
02	8622.5	114.290	80.042
03	5883.8	77.984	146.879
04	5841.3	77.431	646.074
05	5809.5	77.010	650.065
06	5777.4	76.584	656.092
07	5734.8	76.019	170.192
08	5729.4	75.947	181.396
09	5293.1	70.164	159.359
10	4484.9	59.451	96.100
11	2016.6	26.731	97.743
12	1953.1	25.890	120.663

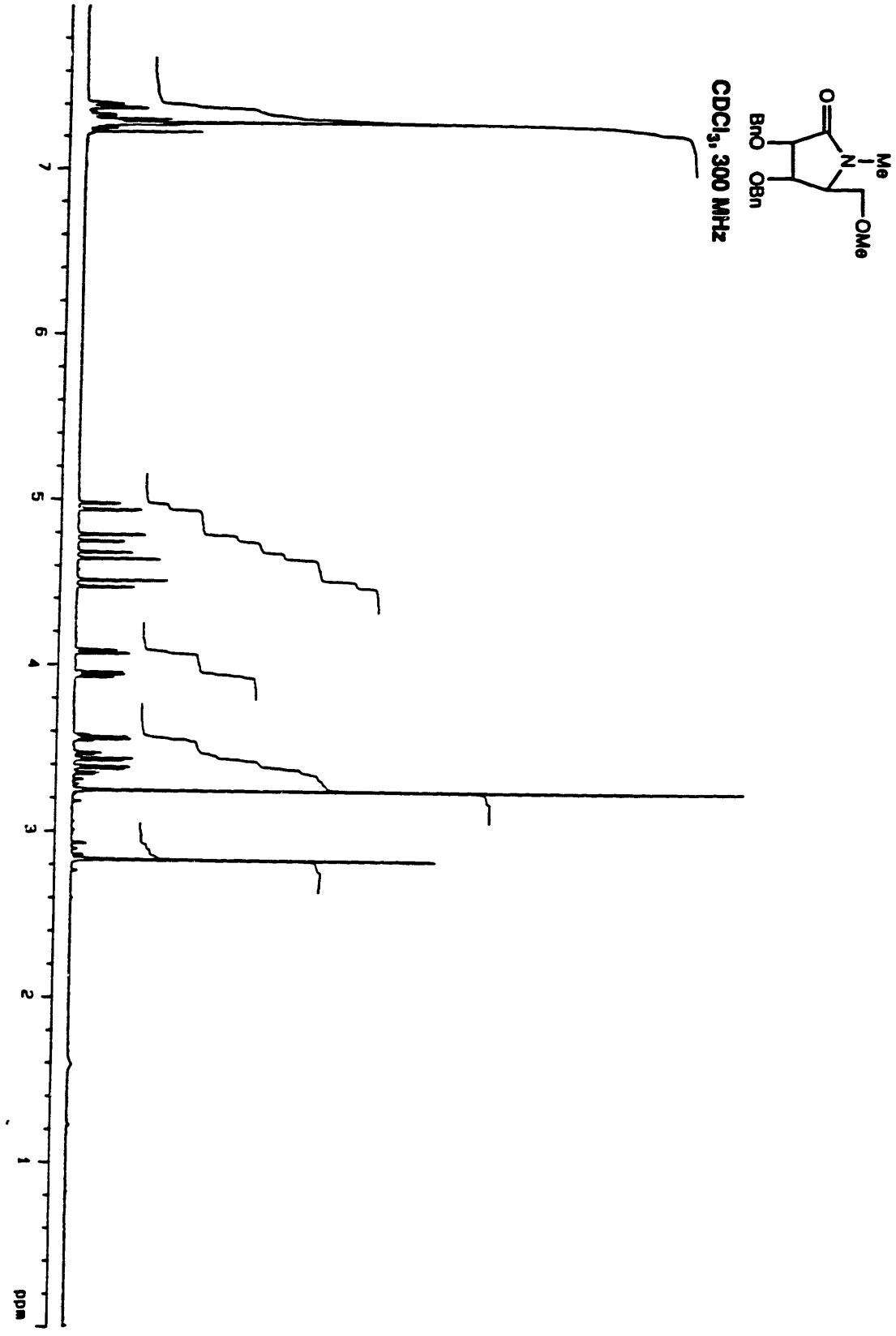
CDCl3, 300 MHz
Me
OMe
O
O
O
N
PPM
0
2
3
4
5
6
8

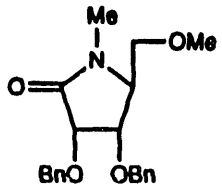


^{13}C NMR, $CDCl_3$, 300 MHz

INDEX	FREQ	PPM	INTENSITY
01	12936.1	171.478	66.234
02	8419.0	111.601	127.924
03	5841.9	77.440	163.214
04	5831.9	77.307	182.393
05	5810.0	77.017	166.227
06	5777.7	76.588	168.149
07	5740.8	76.099	201.831
08	5236.8	69.418	93.969
09	4791.6	63.516	144.799
10	4463.7	59.169	147.926
11	2095.6	27.779	142.930
12	2027.1	26.871	143.473
13	1926.5	25.537	166.705

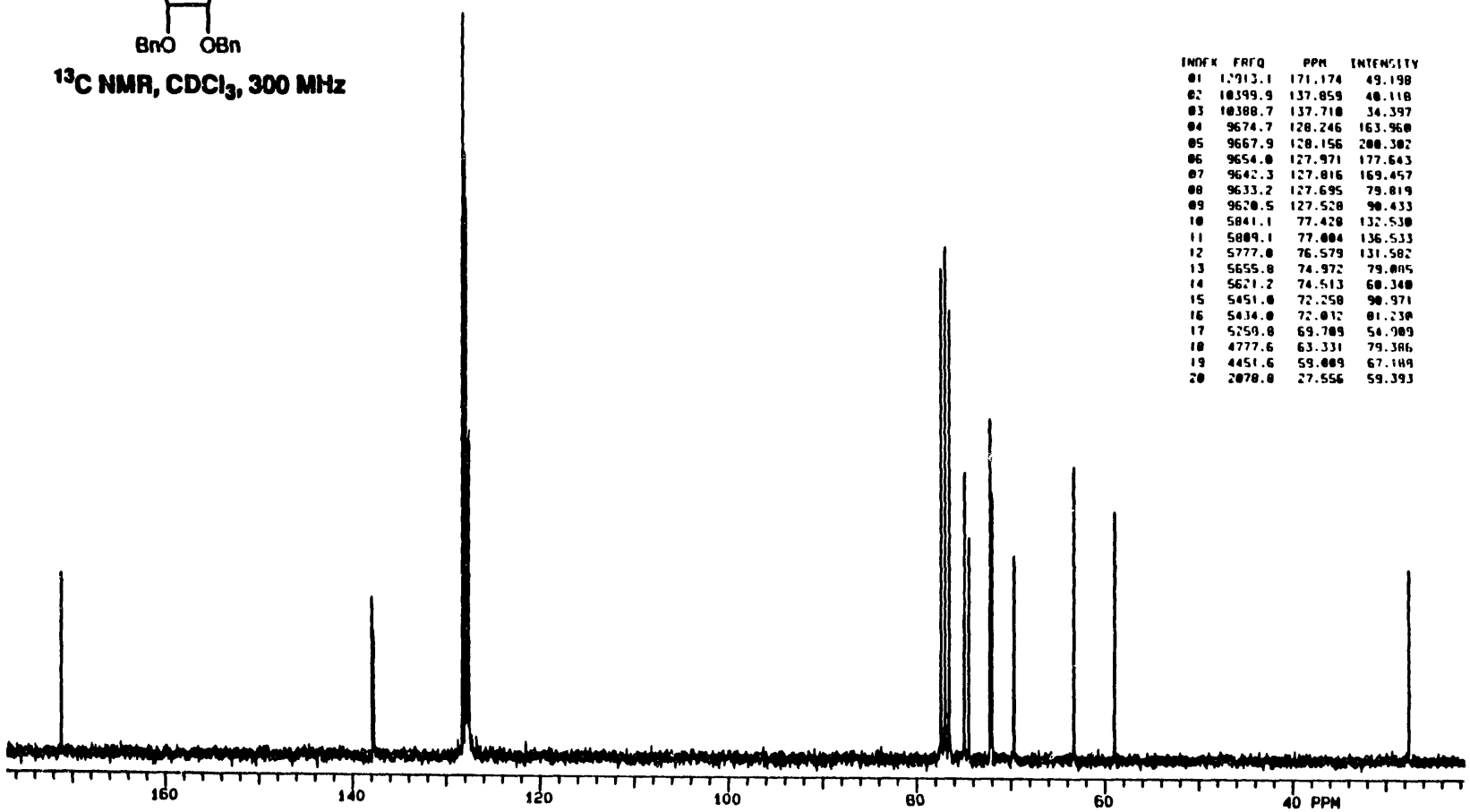


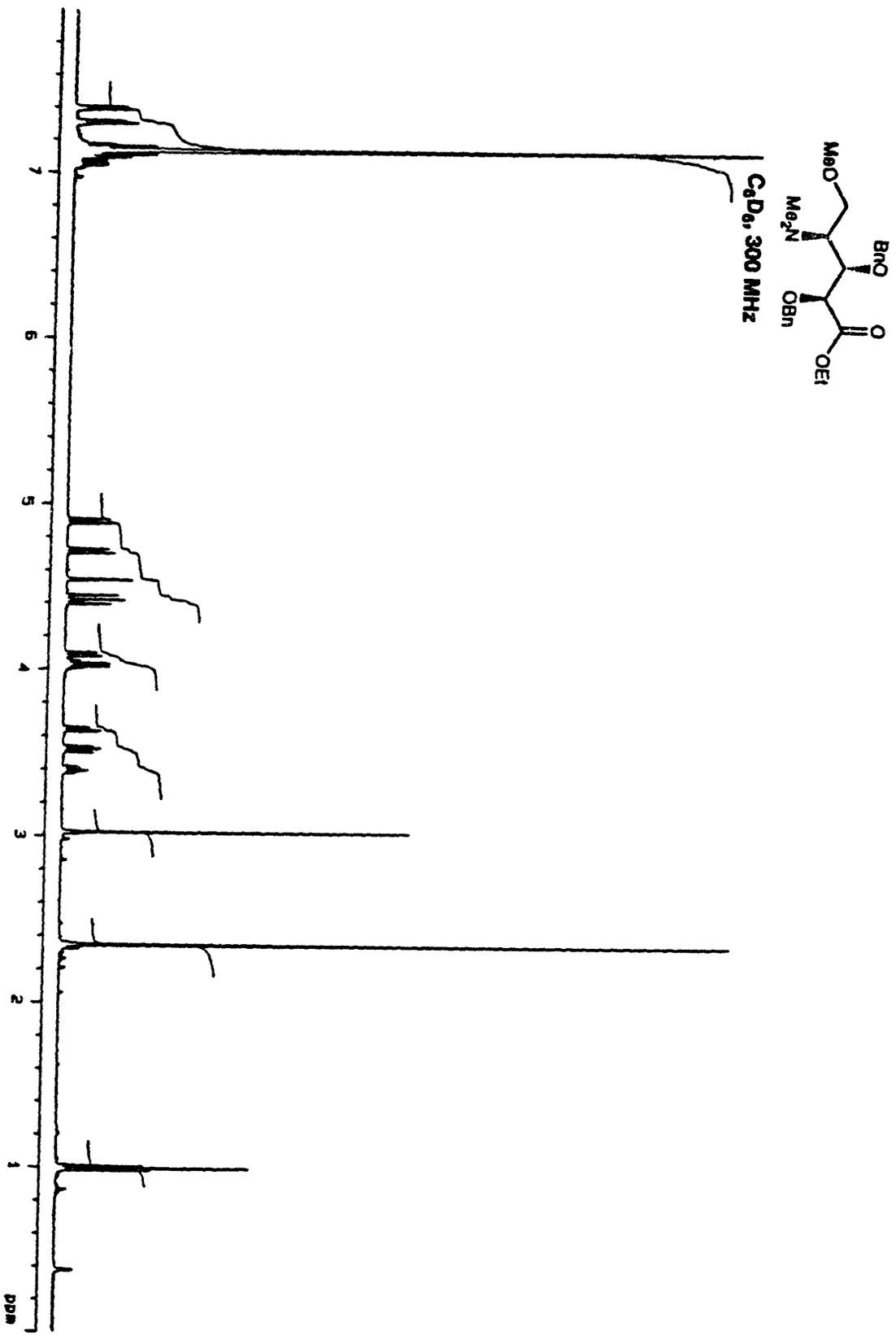

CDCl3, 300 MHz
BnO
OBn
O
N
Me
OMe
ppm

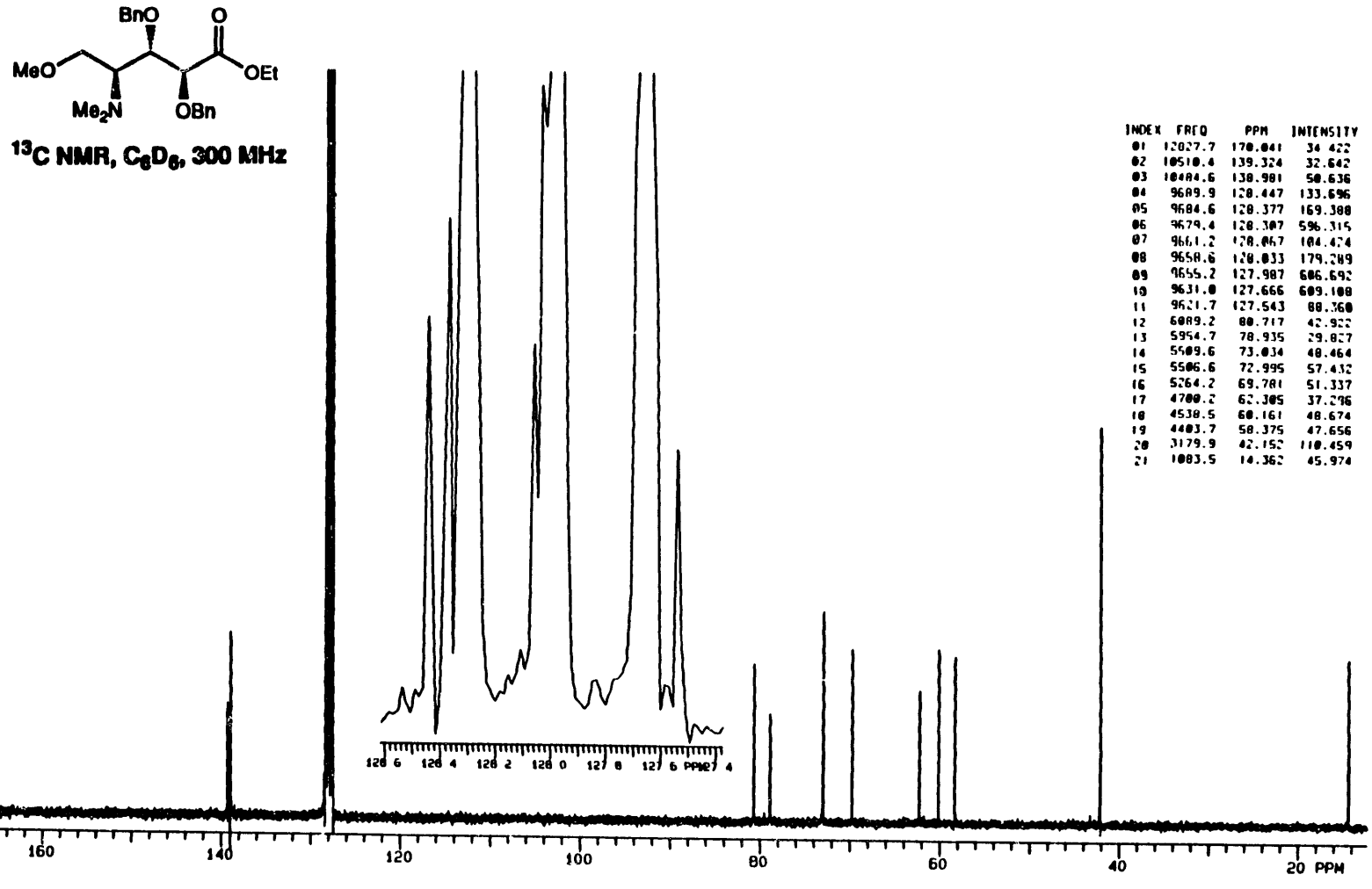


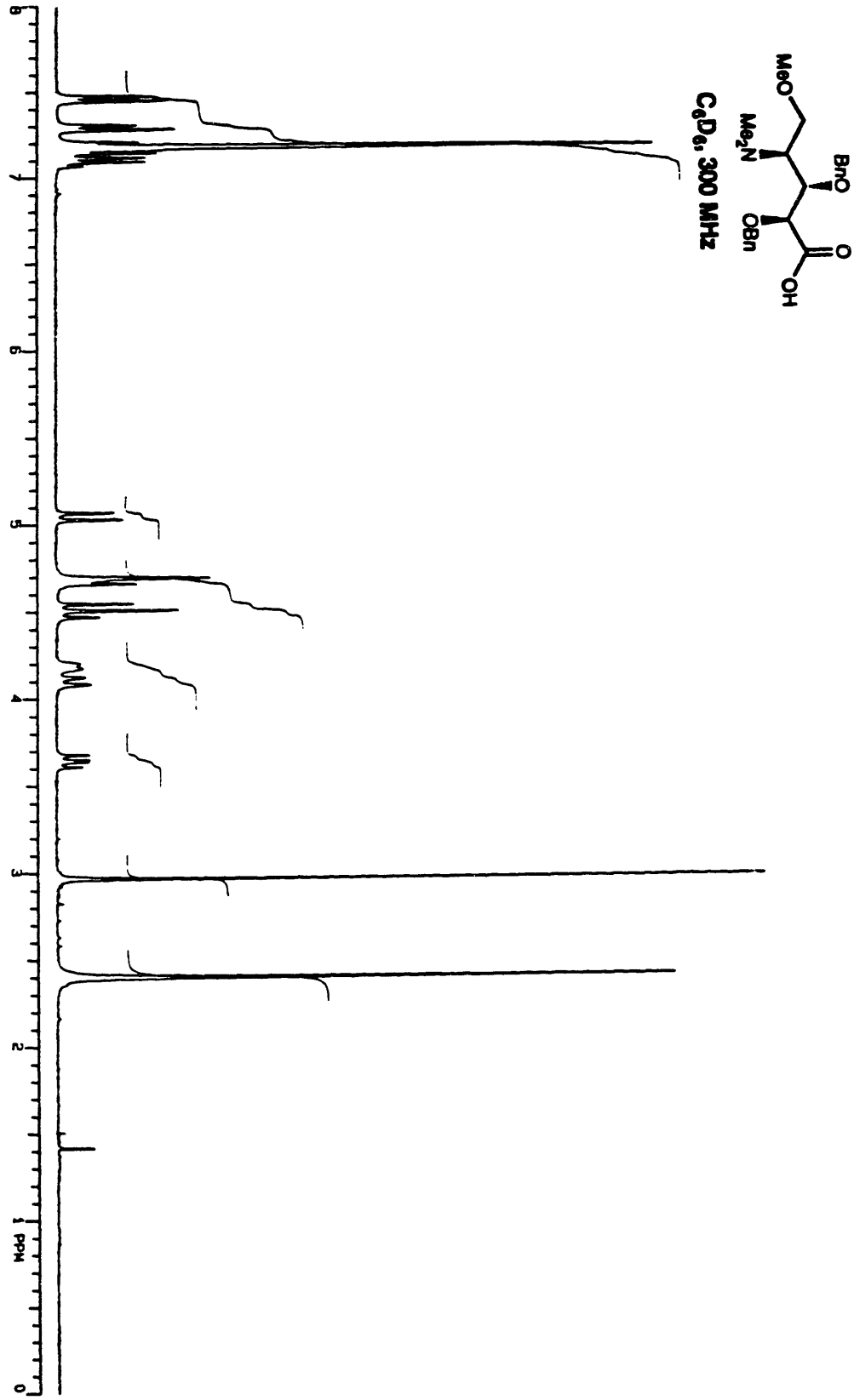
^{13}C NMR, $CDCl_3$, 300 MHz

INDEX	FREQ	PPM	INTENSITY
01	10913.1	171.174	49.198
02	10399.9	137.859	40.118
03	10388.7	137.710	34.397
04	9674.7	128.246	163.960
05	9667.9	128.156	200.302
06	9654.0	127.971	177.643
07	9642.3	127.816	169.457
08	9633.2	127.695	79.819
09	9620.5	127.528	90.433
10	5841.1	77.420	132.530
11	5809.1	77.004	136.533
12	5777.0	76.579	131.582
13	5655.8	74.972	79.005
14	5621.2	74.513	60.340
15	5451.0	72.258	90.971
16	5434.0	72.032	81.230
17	5250.8	69.709	54.909
18	4777.6	63.331	79.386
19	4451.6	59.009	67.149
20	2078.8	27.556	59.393




MeO
BnO
Me2N
OBn
O
OEt
C6D6, 300 MHz
7
6
5
4
3
2
1
ppm


BnO
O
MeO
OEt
Me2N
OBn
13C NMR, C6D6, 300 MHz
INDEX FREQ PPM INTENSITY
01 12027.7 170.041 34.422
02 10510.4 139.324 32.642
03 10484.6 138.981 50.636
04 9689.9 128.447 133.696
05 9684.6 128.377 169.388
06 9679.4 128.307 596.315
07 9661.2 128.067 184.474
08 9658.6 128.033 179.289
09 9655.2 127.987 606.692
10 9631.0 127.666 609.108
11 9621.7 127.543 88.360
12 6089.2 80.717 42.922
13 5954.7 78.935 29.827
14 5509.6 73.034 48.464
15 5506.6 72.995 57.432
16 5264.2 69.781 51.337
17 4700.2 62.305 37.296
18 4538.5 60.161 48.674
19 4403.7 58.375 47.656
20 3179.9 42.152 110.459
21 1083.5 14.362 45.974
160
140
120
100
80
60
40
20 PPM


MeO
Me2N
BnO
OBn
O
OH
C6D6, 300 MHz
ppm

MeO
BnO
O
Me2N
OBn
OH
13C NMR, C6D6, 300 MHz
160
140
120
100
80
60 PPM
40

MeO
BnO
Me2N
OBn
O
N
H
N
O
CH2OMPM
C6D6, 500 MHz
7
6
5
4
3
2
1
ppm

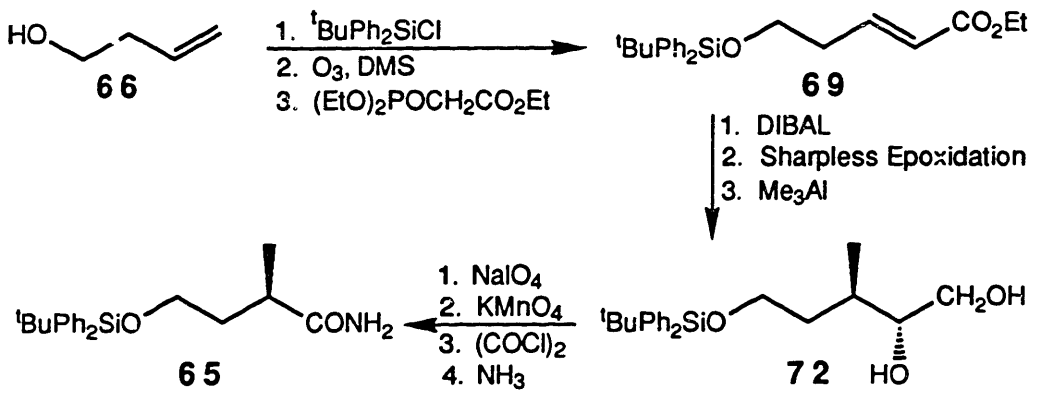
MeO
Me2N
BnO
OBn
O
N
H
N
O
CH2OMPM
13C NMR, C6D6, 500 MHz
ppm

Chapter 5:
Isoxazolidines as Chiral Auxiliaries in Asymmetric Synthesis and their Potential Use in the Preparation of Fragment C1 of Calyculin A

5.1 Introduction

As shown in Scheme 5.1, our original preparation of the amide intermediate, **65**, to fragment C1 involved initial silylation of the homoallylic alcohol, **66**, followed by ozonolysis and Horner-Emmons olefination.[76] The resulting α,β-unsaturated ester,**69**, was then reduced with DIBAL, epoxidized,[77] and the epoxide was opened with trimethylaluminum to the diol, **72**.[78,79] The diol was then oxidatively cleaved to an aldehyde,[79] and the aldehyde was oxidized to the acid.[80] Finally, the acid was converted to the acid chloride and subsequently condensed with ammonia to produce the amide, **65**. This sequence represents a ten-step synthesis of a fragment bearing only five essential carbons and one stereogenic center. We did not find this very efficient, and set out to develop an alternate strategy.

Scheme 5.1

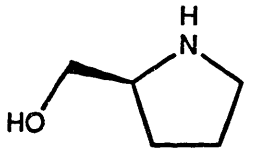


5.2 The Design of a Chiral Auxiliary

Chiral auxiliaries have found great utility in organic synthesis, and the search more effective and versatile chiral auxiliaries has been a formidable challenge to organic chemists over recent years.[145] In our search for a better preparation of amide **65**, an intermediate in the synthesis of

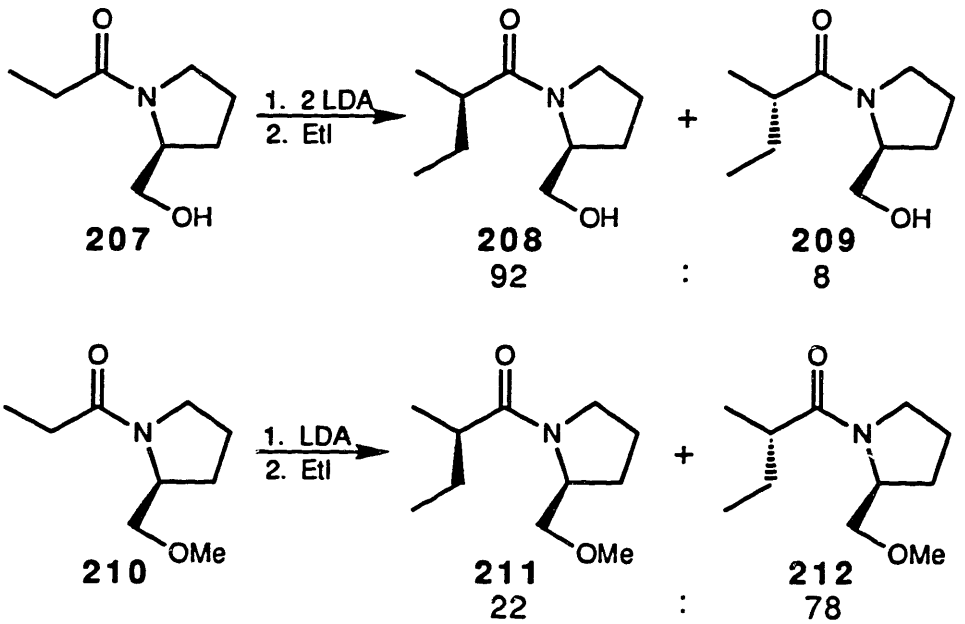
fragment C1, we became aware of prolinol, **206** (Figure 5.1), a chiral auxiliary that had been studied by Evans in 1980.[146]

Figure 5.1



206

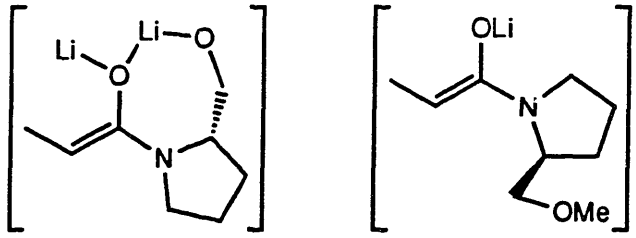
Scheme 5.2



As shown in Scheme 5.2, Evans demonstrated that alkylation of *N*-propionyl prolinol, **207**, on treatment with two equivalents of LDA followed by ethyl iodide provides a 92 : 8 ratio of diastereomers. What we found even more interesting was that when the methyl ether, **210**, was used, diastereomeric induction occurred to the extent of 22 : 78 in the opposite direction. These results can possibly be explained as follows using the two enolate structures, **213** and **214**, shown in Figure 5.2. If, on treatment with

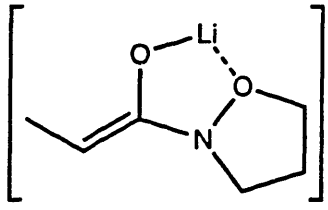
base, the enolate of **207** forms the lithium bridged 5-7 fused bicyclic ring system, **213**, we would expect this relatively hindered system to be blocked from the back side and allow approach of an electrophile from the front. If, on the other hand, the methyl ether, **210**, forms the enolate, **214**, in which the lithium does not coordinate to the ether oxygen, we would expect more shielding from the front and a greater ease of approach by an electrophile from the rear. The lower diastereoinduction can be accounted for by the greater freedom of rotation around the nitrogen-carbonyl bond.

Figure 5.2



213 **214**

Figure 5.3



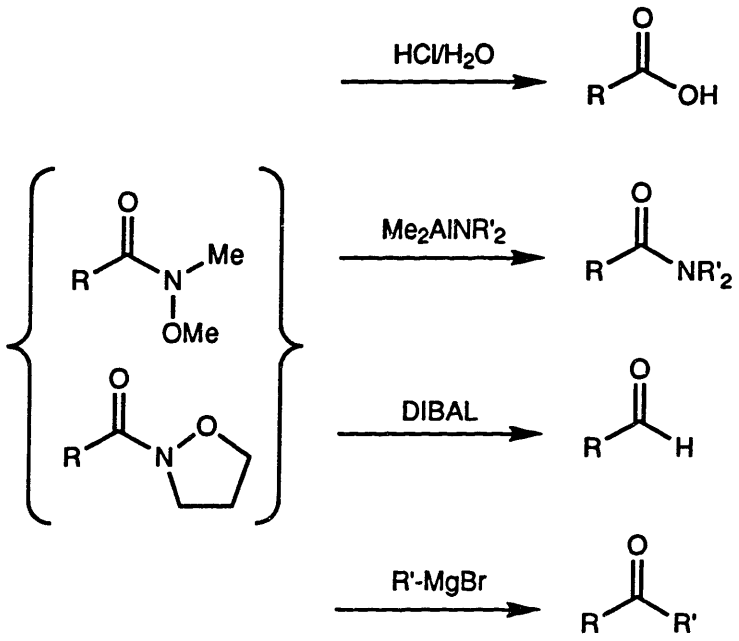
215

When considering the two structures in Figure 5.2, we postulated that we might be able to improve upon Evans' results by adding an extra coordination site to the proline ring. Thus, by replacing the methylene group adjacent to the nitrogen with an oxygen, we felt that formation of the 5-5 cis-fused lithium-bridged enolate, **215** (Figure 5.3), would be favored. Therefore, we decided to study the utility of isoxazolidines as chiral

auxiliaries for asymmetric synthesis.

5.3 Reactions of Isoxazolidides

Scheme 5.3

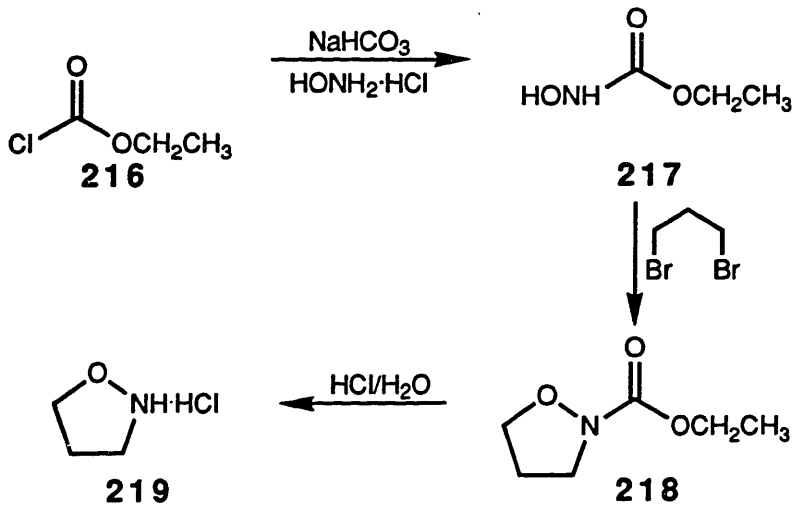


When considering the development of any new methodology, it is important to be aware of its potential versatility. Therefore, we went to the literature to learn what transformations were possible with isoxazolidides, and their related *N*-methyl-*N*-methoxyamides. Our search, summarized in Scheme 5.3, showed that these species can easily be hydrolyzed to acids under acidic conditions, converted to other amides utilizing Weinreb conditions,[127,128,129] converted to aldehydes on treatment with DIBAL,[147,148] and transformed into ketones using alkyllithium or Grignard reagents.[147,148,149,150] Therefore, as indicated in the literature, these compounds are quite versatile and present avenues into many functional groups desired from a synthetic standpoint. With these promising data, we

next needed to determine if isoxazolides could be alkylated α to the carbonyl group.

5.4 Preparation and Alkylation of Isoxazolidides

Scheme 5.4

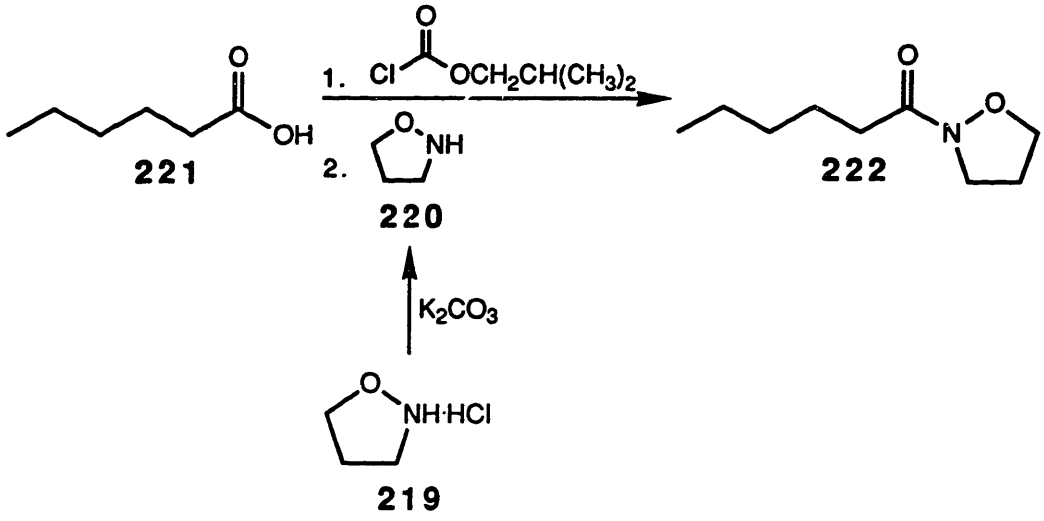


Before we could study the alkylation of isoxazolidides, we needed to obtain quantities of isoxazolidine hydrochloride, **219**. The preparation, described by King,[151] is shown in Scheme 5.4 and proceeded as follows. Ethylchloroformate, **216**, was converted to the *N*-hydroxyurethane, **217**, on treatment with hydroxylamine hydrochloride and sodium bicarbonate. The urethane was then converted to *N*-ethoxycarbonyl isoxazolidide, **218**, on treatment with 1,3-dibromopropane in the presence of potassium carbonate. Finally, isoxazolidine hydrochloride, **219**, was formed upon acid hydrolysis of **218**. With isoxazolidine hydrochloride in hand, we were now ready to form isoxazolidides and study the alkylation of these species.

As shown in Scheme 5.5, isoxazolidine hydrochloride, **219**, was converted to its free base, **220**, and subsequently acylated[152] with hexanoic acid, **221**, to give a 95% yield of the isoxazolidide, **222**. At this point, we now

needed to develop conditions for the alkylation of **222**.

Scheme 5.5



Scheme 5.6

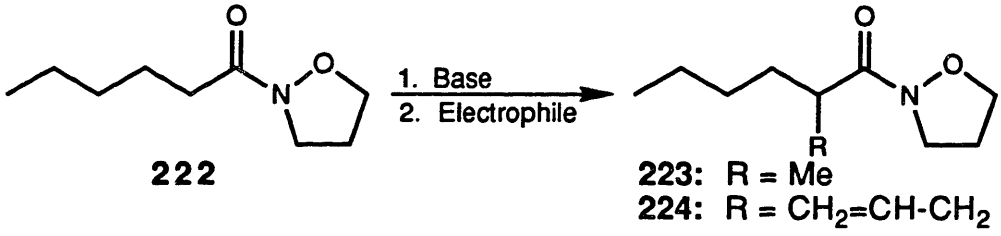


Table 5.1

Alkylation and Allylation of Isoxazolidide 222

Solvent	Base	Electrophile	Product	Yield (%)
THF	LDA	MeI	**223**	0
THF	$(TMS)_2NLi$	MeI	**223**	98
THF	$(TMS)_2NLi$	CH_2=CH-CH_2Br	**224**	56
Et_2O	$(TMS)_2NLi$	CH_2=CH-CH_2Br	**224**	0
THF	$(TMS)_2NLi$	CH_2=CH-CH_2Br/ HMPA	**224**	92

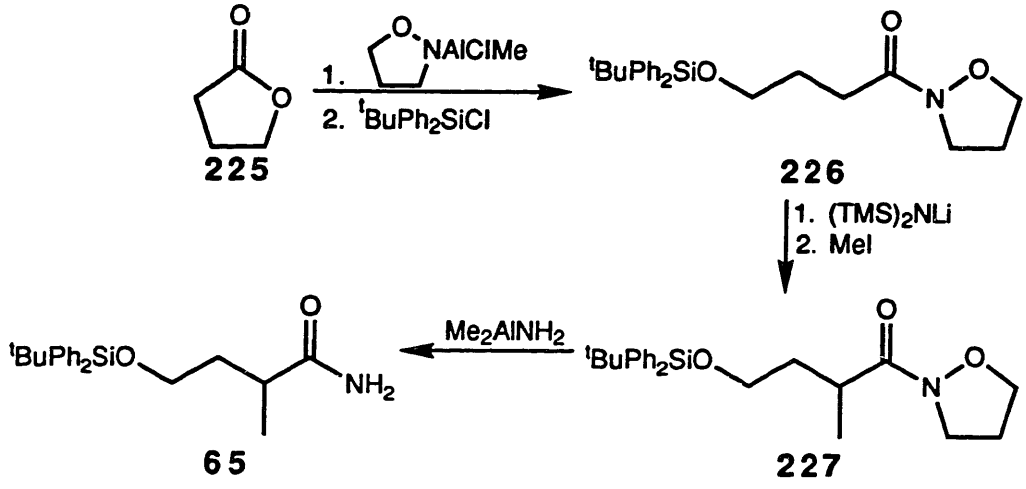
The results from our initial study of the alkylation and allylation of isoxazolidide **222** (Scheme 5.6) are shown in Table 5.1 and are described as

follows. All reactions were run at -78°C over a three hour reaction period. Initially, we attempted deprotonation of **222** with LDA. Under these conditions, we found no reaction. However, when we deprotonated **222** with lithium hexamethyldisilazide, we were able to affect methylation with methyl iodide in near quantitative yield. In the case of allylation with allyl bromide, the reaction was not as straightforward, and we were able to effect a 92% yield of the desired product only after adding one equivalent of HMPA to the reaction mixture. In any event, with these observations, we felt that further study into the application of this methodology to the synthesis of fragment C1 was warranted.

5.5 The Application of Isoxazolidides to Fragment C1

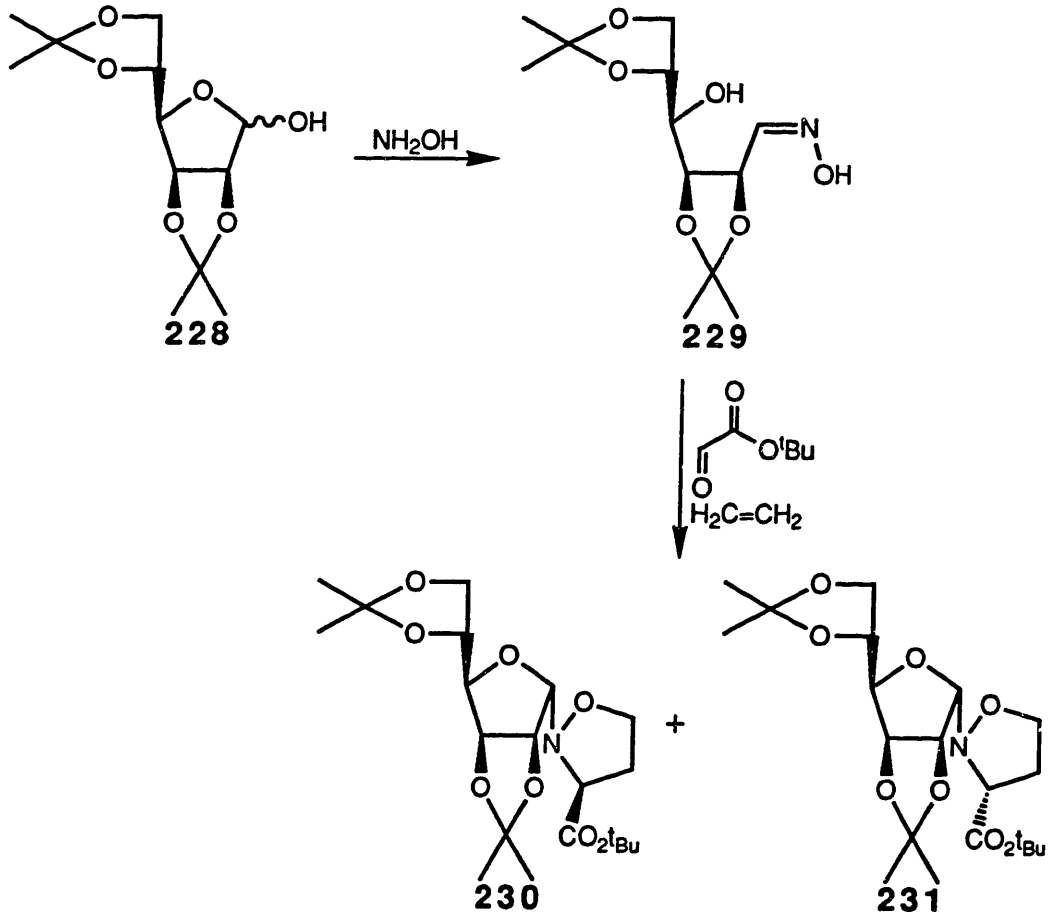
With the methodology for the methylation of isoxazolidides established, it was now time to determine if this methodology could be applied to a racemic synthesis of the amide, **65**. This strategy, shown in Scheme 5.7, proceeded as follows. Butyrolactone, **225**, was treated with the Weinreb reagent[127,128,129] derived from isoxazolidine hydrochloride, **219**, and the crude hydroxyisoxazolidide was treated with *tert*-butyldiphenylchlorosilane to provide the silyl ether, **226**, in 75% over two steps. The silyl ether, **226**, was then deprotonated with lithium hexamethyldisilazide and methylated on treatment with methyl iodide to yield the isoxazolidide, **227**. Treatment of this isoxazolidide with the Weinreb reagent[127,128,129] derived from trimethylaluminum and ammonia provided a 60% yield of amide **65** in racemic form. This four-step sequence provided us with a better overall yield than our previous ten-step synthesis and we were now ready to explore the utility of chiral isoxazolidines in asymmetric synthesis.

Scheme 5.7



5.6 Chiral Isoxazolidines

Scheme 5.8

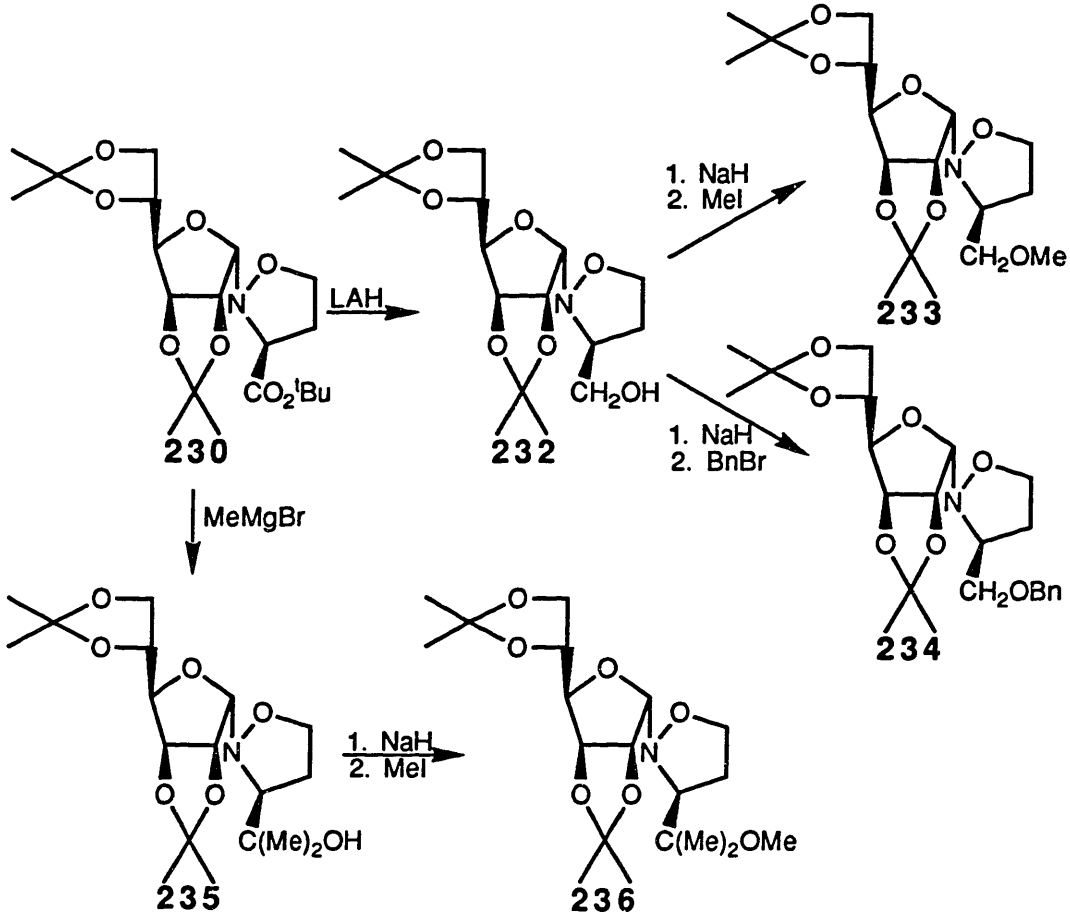


The ability of sugars to induce asymmetry in chemical reactions has been known since as early as 1890 in the Kiliani-Fischer extension of hexoses to higher carbohydrates.[153,154,155] With this in mind, it is not surprising that Vasella developed a synthesis of chiral isoxazolidines using mannose as a chiral auxiliary.[156] The specific synthesis is shown in Scheme 5.8 and is described as follows. 2,3:5,6-(*O*)-Diisopropylidine-*d*-mannofuranose, **228**,[157] was converted to its oxime, **229**, in 65% yield on treatment with hydroxylamine. The oxime, **229**, was then treated with *tert*-butylglyoxalate at 80°C under 1000 psi of ethylene to provide a 98% yield of isoxazolidine glycosides **230** and **231** in a ratio of 3 : 1. The mechanism of this reaction presumably involves initial condensation of the oxime with the glyoxalate followed by a (3 + 2) dipolar cycloaddition. Successive recrystalizations easilly separated the products to provide a 47% yield of diastereomerically pure **230**.

At this stage, Vasella chose to separate the isoxazolidine from the sugar under acidic hydrolytic conditions to study its activity as an unnatural aminoacid in various proteins. Our needs, however, directed us to further derivatize the glycoside, **230**, in order to develop a useful set of chiral auxiliaries. Our extension of Vasella's synthesis is shown in Scheme 5.9 and proceeded as follows. The *tert*-butyl ester, **230**, was reduced to the primary alcohol, **232**, in quantitative yield on treatment with $LiAlH_4$. The resulting alcohol, **232**, was converted to the methyl ether, **233** (98% yield), or the benzyl ether, **234** (99% yield), on treatment with NaH followed by methyl iodide or benzyl bromide, respectively. Alternatively, the *tert*-butyl ester, **230**, was converted to the tertiary alcohol, **235**, in 95% yield on treatment with MeMgBr. Subsequently, the tertiary alcohol, **235**, was converted to the corresponding methyl ether, **236**, in 68% yield on treatment with NaH

followed by methyl iodide. This series of reactions provided us with five easily attainable isoxazolidine derivatives which, after hydrolysis from the sugar, could be used in our studies on asymmetric induction. In the interest of simplicity, we began with the ether derivatives, **233**, **234**, and **236**.

Scheme 5.9

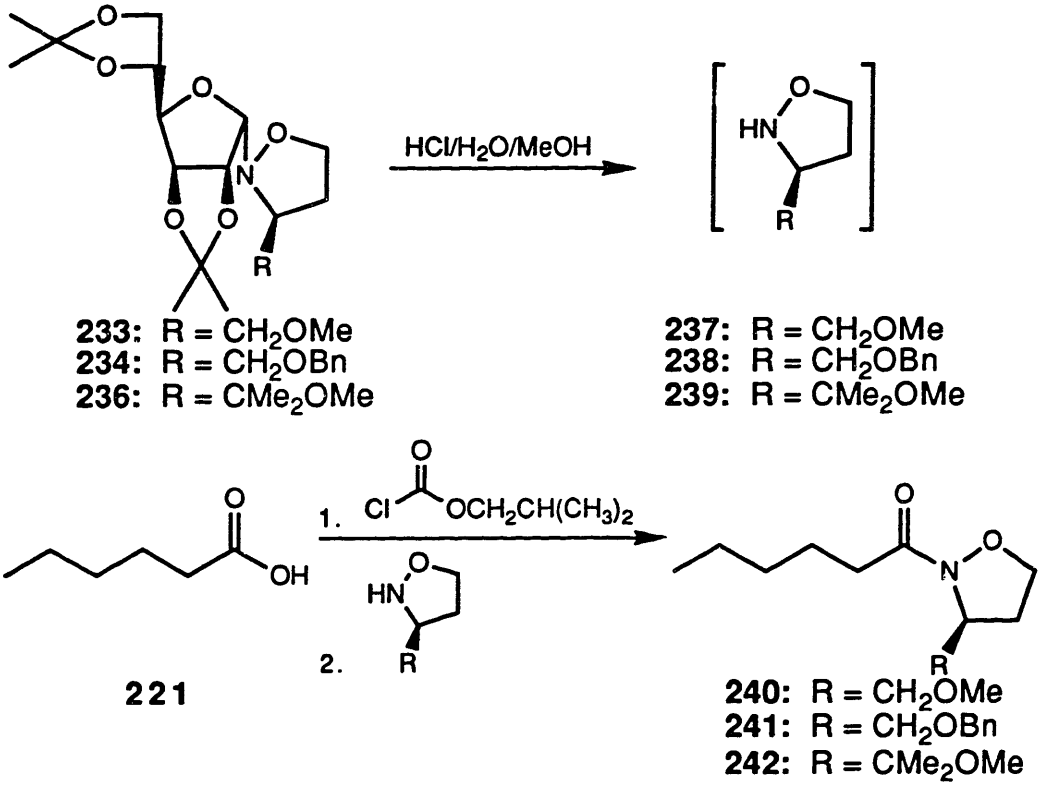


5.7 Asymmetric Alkylations

Although the tert-butyl ester isoxazolidine was easily isolated on hydrolysis of the glycosidic bond,[156] our derivatives underwent rapid decomposition under these conditions. Therefore, it was not feasible, at this time, to isolate the pure isoxazolidines, and we proceeded with acylation of

these compounds using their crude reaction isolates (42-55% from glycosides, Scheme 5.10). Once we had isolated the isoxazolidides, we began our study of their utility as chiral auxiliaries.

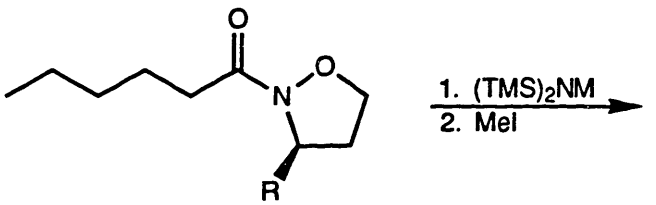
Scheme 5.10



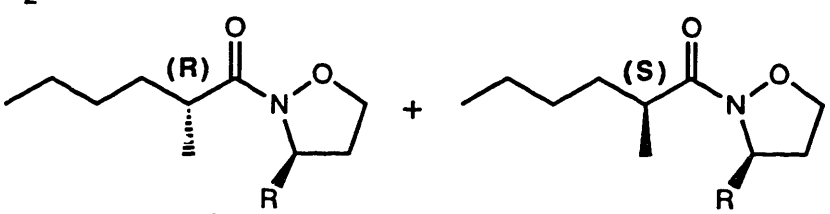
The general alkylation reaction we studied involved the use of a hexamethyldisilazide base for enolate formation followed by treatment with methyl iodide (Scheme 5.11). The results of this study are shown in Table 5.2 and are described as follows. Our initial experiments involved the use of lithium as the counterion. Under these conditions, we found that Et_2O was not as good a solvent as THF, and the addition of HMPA to the reaction was not advantageous. Furthermore, changing the counterion did not help the reaction and our best results were obtained at -95°C and provided a 93% de.

This result represents a significant improvement over the results Evans obtained utilizing prolinol as a chiral auxiliary.[148] We were disappointed, however, to find that larger side groups on the isoxazolidide provided lower diastereomeric excesses. In all cases, the configuration was determined by converting the methylated isoxazolidides to their corresponding methyl ketones and comparing the measured optical rotations with literature values.

Scheme 5.11



240: R = CH_2OMe
241: R = CH_2OBn
242: R = CMe_2OMe



243: R = CH_2OMe
244: R = CH_2OBn
245: R = CMe_2OMe

246: R = CH_2OMe
247: R = CH_2OBn
248: R = CMe_2OMe

The observation of lower diastereomeric induction with larger R groups was not surprising when considering the possible enolate structure shown in Figure 5.4. When considering this structure, it is easy to imagine that a smaller R group would allow for easier formation of the tricoordinate lithium cation and greater shielding of the front side of the enolate. On the other hand, if a larger R group is used, it is not unreasonable that the greater steric requirements would cause the side chain to not coordinate to the

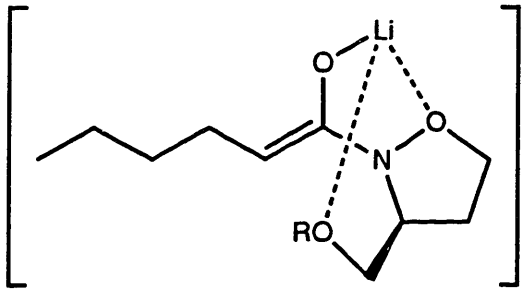
lithium. This would decrease the shielding of the front side of the enolate and cause a lower degree of diastereomeric induction. As this appeared to be the case, the best R group on the isoxazolidine ring was determined to be CH_3OCH_2 and we were ready to apply this technology towards the preparation of amide **65**.

Table 5.2

Results for Isoxazolidine Induced Diastereoinduction

Isoxazolidide	M	Solvent	Temp	Yield (%)	%de	Configuration
240	Li	THF	-78	84	90	R
240	Li	THF/HMPA	-78	85	81	R
240	Li	Et_2O/HMPA	-78	66	83	R
240	Li	THF	-95	97	93	R
240	MgBr	THF	-78	NR	---	---
240	Na	THF	-78	83	88	R
240	K	THF	-78	79	89	R
241	Li	THF	-78	85	69	R
242	Li	THF	-78	78	75	R

Figure 5.4



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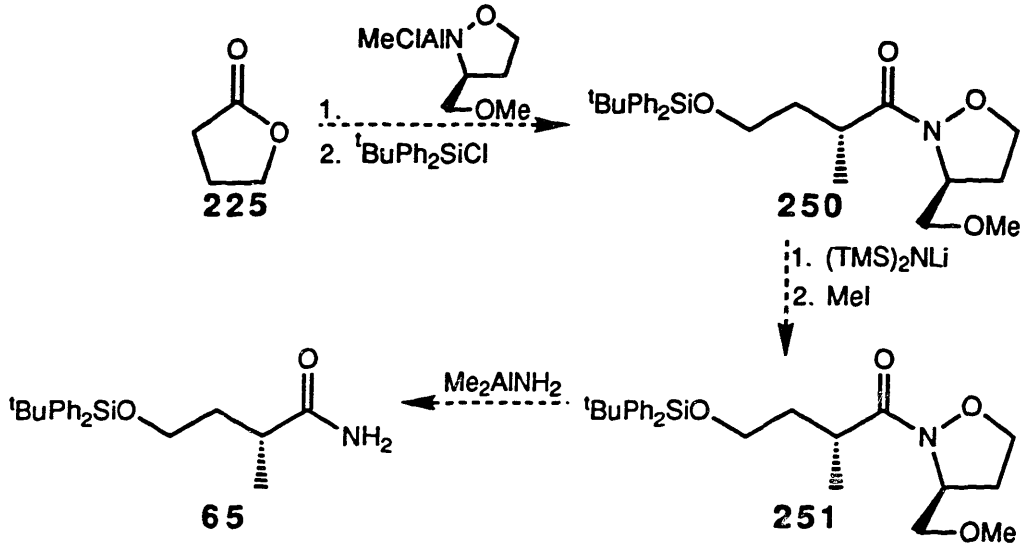
5.8 Potential Application of Chiral Isoxazolidines to Fragment C1

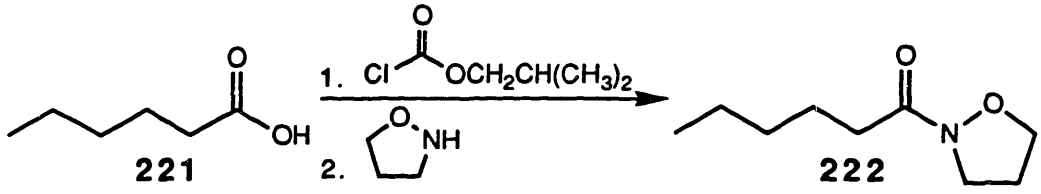
The strategy for applying the use of chiral isoxazolidines to the synthesis of fragment C1 is shown in Scheme 5.12. This strategy has not yet been carried out due to the problems we have encountered in isolating the

pure isoxazolidines from the hydrolysis of the corresponding glycosides. Additionally, due to our need for large quantities of fragments C1 and C2, this project was temporarily discontinued. However, in view of the potential generality of this technology, it is hoped that this problem will be quickly solved and the value of these chiral auxiliaries fully demonstrated.

Scheme 5.12



5.9 Experimental Section



Isoxazolidide, 222

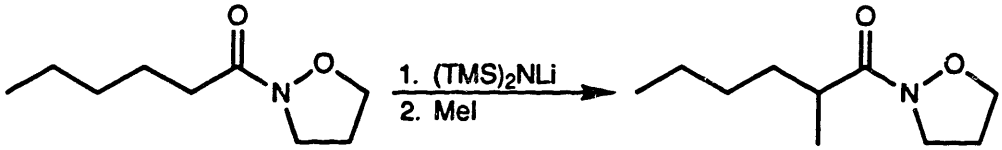
Isoxazolidine hydrochloride, **219**, (1.00 g, 9.17 mmoles) was suspended in THF (20 mL) and water (0.80 mL) was added. The mixture was stirred for 5 minutes under argon, after which K_2CO_3 (2.50 g) was added. The resulting mixture was stirred for 2 hours after which K_2CO_3 (0.50 g) was added. After stirring for an additional 30 minutes, the solids were allowed to settle.

Hexanoic acid, **221**, (1.15 mL, 9.17 mmoles) was dissolved in THF (40 mL) and *N*-methylmorpholine (1.00 mL, 9.17 mmoles) was added. The solution was cooled to -20°C under argon and isobutyl chloroformate (1.20 mL, 9.17 mmoles) was added. After stirring for 1 minute, the isoxazolidine solution prepared above was added *via* cannula. The reaction was allowed to stir at -20°C for 1 hour, after which it was warmed to room temperature and concentrated to dryness. Ethyl acetate (75 mL) was added to the residue and the mixture was washed with 5% citric acid solution (50 mL). The aqueous phase was washed with ethyl acetate (75 mL) and the combined organic phases were washed with 5% citric acid solution (50 mL) and saturated $NaHCO_3$ solution (2 X 50 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated. Distillation of the residue (P = 1 mm Hg, T = 117-120°C) gave the product (1.10 g, 70%) as a colorless liquid.

Physical Properties for **222**

R_f = 0.07 (15% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 3.92(t, *J* = 6.76 Hz, 2H), 3.69(dd, *J* = 7.3 Hz, 2H), 2.40(dd, *J* = 7.37 Hz, 2H), 2.28(quintet, *J* = 6.93 Hz, 2H), 1.62(m, 2H), 1.30(m, 4H), 0.88(t, *J* = 6.90 Hz, 3H).



222 **223**

Methyl Isoxazolidide, 223

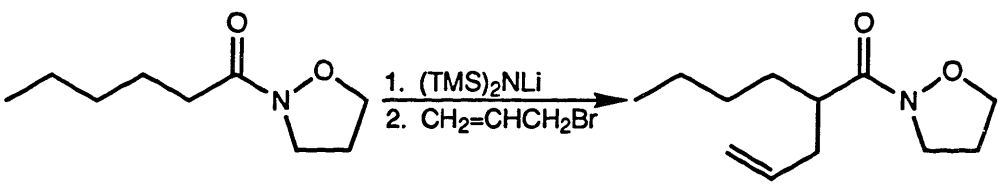
$(TMS)_2NH$ (147μL, 0.698 mmole) was dissolved in THF (4 mL) and cooled to -78°C under argon. n-BuLi (2.46M in hexane, 260 μL, 0.640 mmole)

was added and the mixture was stirred at -78°C for 30 minutes. Isoxazolidide **222** (100 μL, 0.581 mmole) was added and the mixture was stirred at -78°C for 1 hour, after which methyl iodide (200 μL) was added. The reaction was maintained at -78°C for 1 hour, after which it was allowed to warm to -20°C over 2 hours. After an additional hour at -20°C, the reaction was quenched with saturated NH_4Cl solution (1 mL) and washed with ethyl acetate (10 mL). The ethyl acetate was dried over $MgSO_4$, and concentrated to dryness. Purification on silica gel (50% ethyl acetate/hexane) yielded the desired product as a colorless oil (105 mg, 98%).

Physical Properties for **223**

R_f = 0.49 (15% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 3.92(dt, *J* = 2.06, 6.76 Hz, 2H), 3.69(m, 2H), 2.85(m, 1H), 2.27(quintet, *J* = 7.06 Hz, 2H), 1.63(m, 1H), 1.38(m, 1H), 1.26(m, 4H), 1.07(d, *J* = 6.86 Hz, 3H), 0.85(t, *J* = 6.86 Hz, 3H).



222 **224**

2-Allyl Hexanoic Isoxazolidide, 224

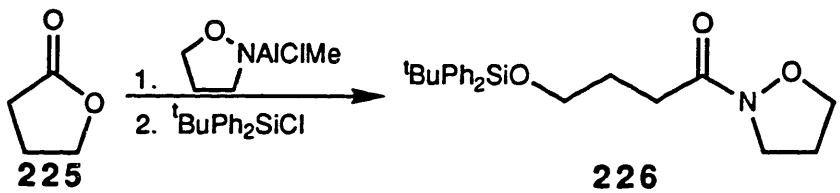
$(TMS)_2NH$ (147 μL, 0.698 mmole) was dissolved in THF (4 mL) and cooled to -78°C under argon. n-BuLi (2.46M in hexane, 260 μL, 0.640 mmole) was added and the mixture was stirred at -78°C for 30 minutes. Isoxazolidide **222** (100 μL, 0.581 mmole) was added and the mixture was stirred at -78°C for 1 hour, after which HMPA (100 μL, 0.581 mmole) was added followed by

allyl bromide (277 μL, 3.197 mmoles). The reaction was warmed from -78 to -20°C over 1.5 hours, after which it was quenched with saturated NH_4Cl solution (1 mL) and washed with ethyl acetate (10 mL). The ethyl acetate was washed with water (2 X 2 mL), dried over $MgSO_4$, and concentrated to dryness. Purification on silica gel (50% ethyl acetate/hexane) yielded the desired product (113 mg, 92%) as a colorless oil.

Physical Properties for **224**

R_f = 0.30 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 5.74(m, 1H), 5.00(dd, *J* = 17.13, 21.80 Hz, 2H), 3.93(dt, *J* = 1.82, 6.93 Hz, 2H), 3.72(m, 2H), 2.95(broad m, 1H), 2.31(m, 3H), 2.19(m, 1H), 1.62(m, 1H), 1.43(m, 1H), 1.27(m, 4H), 0.86(t, *J* = 6.86 Hz, 3H).



225 **226**

***tert*-Butyldiphenylsilyloxy Isoxazolidide, 226**

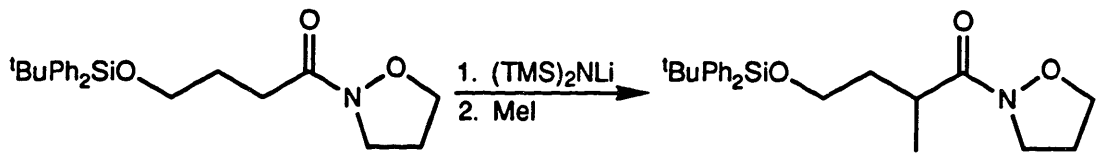
Isoxazolidine hydrochloride, **219**, (0.880 g, 8.077 mmoles) was suspended in C_6H_6 (17.6 mL) and cooled to 0°C under argon. Trimethylaluminum (2M in hexanes, 4.04 mL, 8.08 mmoles) was added and the reaction was stirred at room temperature for 1.5 hours. Butyrolactone, **225**, (0.310 mL, 4.039 mmoles) was added and the reaction was stirred at room temperature for 2 hours, after which it was cooled to 0°C. After quenching with saturated Rochelle's salt solution (2 mL), the mixture was washed with ethyl acetate (3 X 5 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was

dissolved in CH_2Cl_2 (10 mL) and imidazole (0.495 g, 7.271 mmoles) was added. $^tBuPh_2SiCl$ (0.945 mL, 3.635 mmoles) was added and the reaction was stirred at room temperature under argon for 1 hour. The resulting mixture was washed with water (10 mL), dried over $MgSO_4$, and concentrated to dryness. The residue was purified on silica gel (50% ethyl acetate/hexane) to give the desired product (1.212 g, 76%) as a colorless oil.

Physical Properties for 226

R_f = 0.40 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.63(m, 4H), 7.37(m, 6H), 3.89(t, *J* = 6.68 Hz, 2H), 3.69(t, *J* = 6.20 Hz, 2H), 3.67(t, *J* = 7.50 Hz, 2H), 2.53(t, *J* = 7.50 Hz, 2H), 2.26(m, *J* = 7.66 Hz, 2H), 1.87(m, *J* = 7.82 Hz, 2H), 1.02(s, 9H).



226 **227**

Methyl *tert*-Butyldiphenylsilyloxy Isoxazolidide, 227

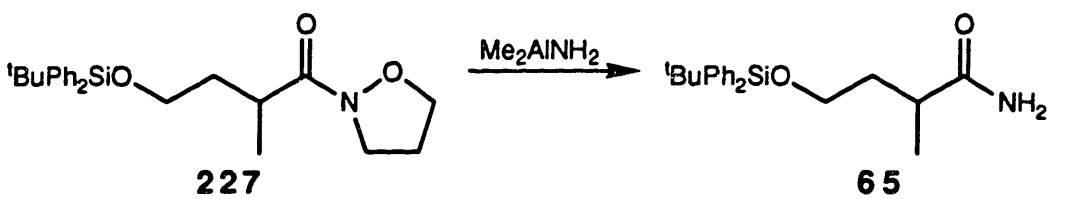
$(TMS)_2NH$ (0.2945 mL, 1.396 mmoles) was dissolved in THF (3.75 mL) and cooled to -78°C under argon. n-BuLi (2.40M in hexane, 0.582 mL, 1.396 mmoles) was added and the reaction was stirred for 30 minutes. The *tert*-butyldiphenylsilyloxy isoxazolidide, **225**, (0.504 mL, 1.269 mmoles) was dissolved in THF (0.75 mL) and added, *via* cannula, to the $(TMS)_2NLi$. The reaction was stirred at -78°C for 1 hour, after which MeI (0.435 mL, 6.980 mmoles) was added. Stirring was continued for an additional 1.5 hours, after which the reaction was allowed to warm to -20°C over 2 hours. The reaction was then quenched with saturated NH_4Cl solution (5 mL), washed

with ethyl acetate (2 X 10 mL), dried over $MgSO_4$, and concentrated to dryness. Purification of the residue on silica gel (50% ethyl acetate/hexane) provided the desired product (0.500g, 96%) as a colorless oil.

Physical Properties for 227

R_f = 0.43 (50% ethyl acetate/hexane)

^1H NMR (300 MHz, $CDCl_3$): δ 7.65(m, 4H), 7.36(m, 6H), 3.90(m, *J* = 6.45 Hz, 2H), 3.68(m, *J* = 6.39 Hz, 4H), 3.16(m, 1H), 2.25(m, *J* = 2.50 Hz, 7.06 Hz, 2H), 1.98(m, *J* = 6.39 Hz, 1H), 1.58(m, *J* = 6.93 Hz, 1H), 1.10(d, *J* = 6.93 Hz, 3H), 1.03(s, 9H).



227 65

Racemic Amide, 65

Trimethylaluminum (2M in hexane, 0.14 mL, 0.285 mmole) was added to a solution of NH_3 (0.32M in CH_2Cl_2, 1.20 mL, 0.381 mmole) and stirred at room temperature under argon for 15 minutes. The methyl *tert*-butyldiphenylsilyloxy isoxazolidide, **227**, (39.1 mg, 0.095 mmole) was dissolved in C_6H_6 (1.50 mL) and added, *via* cannula, to the Me_2AlNH_2 solution. The reaction was stirred at 55°C for 6 hours, after which it was cooled to 0°C and quenched with saturated Rochelle's salt solution (2 mL). The mixture was stirred at room temperature for 20 minutes, after which it was washed with ethyl acetate (3 X 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification on silica gel (50% ethyl acetate/hexane) gave the amide (20.3 mg, 60%) as a colorless solid.

Physical Properties for 65

R_f = 0.25 (50% ethyl acetatehexane).

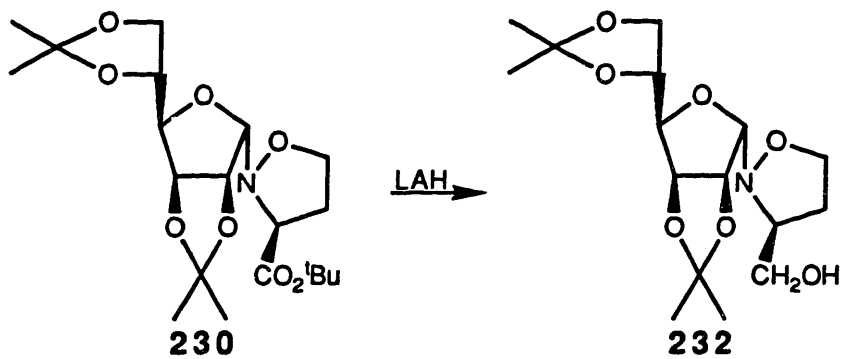
^1H NMR (300 MHz, $CDCl_3$): δ 7.64-7.67(m, 4H), 7.35-7.46(m, 6H), 5.49(s, 1H), 5.42(s, 1H), 3.71(m, 2H), 2.58(m, 1H), 1.87(ddd, *J* = 13.5, 8.2, 5.3 Hz, 1H), 1.64(ddd, *J* = 13.5, 6.5, 6.5 Hz, 1H), 1.14(d, *J* = 7.1 Hz, 3H), 1.06(s, 9H).

EI Mass Spec: m/e 340 $[M - 15]^+$, 298, 220, 198.

Exact Mass: $[M - CH_3]^+$ = 340.17328 (calculated)

$[M - CH_3]^+$ = 340.1732 (measured).

IR ($CHCl_3$) cm^{-1}: 3540 (m), 3420 (m), 2980 (s), 2940 (s), 2890 (s), 2860 (s), 1685 (s, br), 1595 (s), 1475 (m), 1445 (w), 1395 (m), 1370 (w), 1280 (m, br), 1070-1125 (s, br), 995 (m), 975 (m), 895 (m).



230 **232**

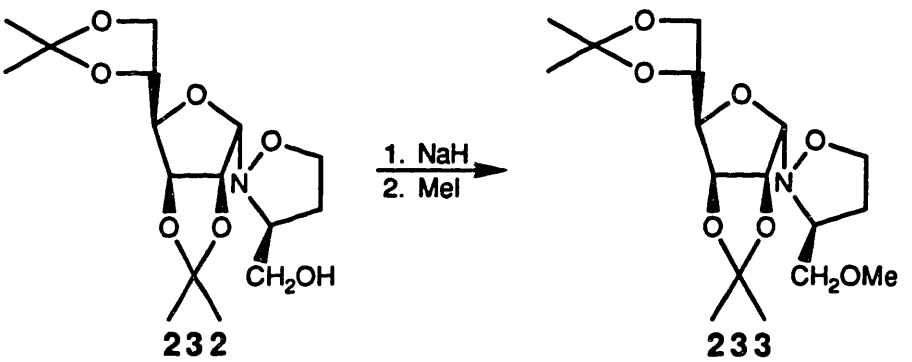
Hydroxymethylisoxazolidine Mannoside, 232

The isoxazolidine mannoside, **230**, (5.00 g, 12.05 mmoles) was dissolved in THF (10 mL) under argon and added, *via* cannula, to a suspension of $LiAlH_4$ (915 mg, 24.10 mmoles) in THF (40 mL) at 0°C. The reaction was stirred for 30 minutes at 0°C under argon, after which it was quenched with $Na_2SO_4 \cdot 10H_2O$. The mixture was stirred at room temperature for 1 hour, filtered, and concentrated to dryness yielding the desired product (4.11 g, 99%) as a colorless solid requiring no purification.

Physical Properties for 232

R_f = 0.14 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 4.98(d, *J* = 5.87 Hz, 1H), 4.83(dd, *J* = 3.91, 6.26 Hz, 1H), 4.45(s, 1H), 4.38(dd, *J* = 6.13, 11.74 Hz, 1H), 4.14(dd, *J* = 3.74, 6.78 Hz, 1H), 3.84-3.62(m, 4H), 3.42-3.62(m, 3H), 2.35(m, 1H), 2.17(dd, *J* = 5.05, 7.37 Hz, 1H), 1.99(m, 1H), 1.47(s, 3H), 1.42(s, 3H), 1.36(s, 3H), 1.34(s, 3H).



232 233

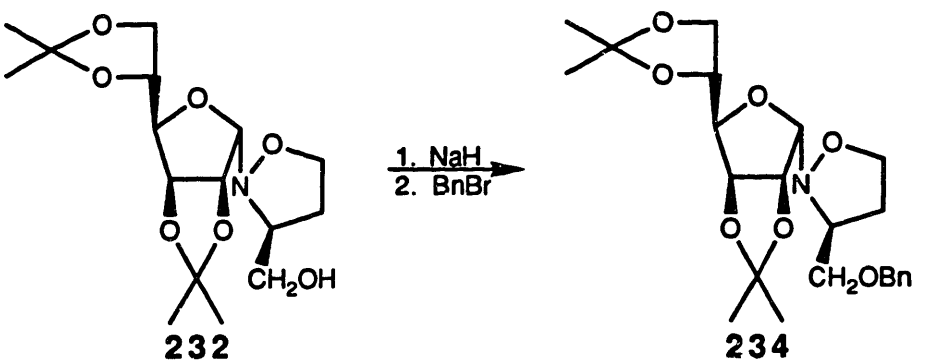
Methoxymethylisoxazolidine Mannoside, 233

NaH (80%, 208 mg, 6.96 mmoles) was suspended in THF (20 mL) and cooled to 0°C under argon. A solution of the hydroxymethylisoxazolidine mannoside, **232**, (2.00 g, 5.80 mmoles) in THF (10 mL) was added, *via* cannula, and the resulting mixture was stirred at 0°C for 30 minutes. Methyl iodide (0.38 mL, 6.38 mmoles) was added and the reaction was allowed to warm to room temperature over 5 hours. After quenching with pH = 7 buffer (30 mL), the product was extracted with ethyl acetate (2 X 30 mL). The ethyl acetate layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified on silica gel (50% ethyl acetate/hexane) to yield the desired product (2.06 g, 99%) as a thick syrup.

Physical Properties for **233**

R_f = 0.49 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 4.97(d, *J* = 6.15 Hz, 1H), 4.82(dd, *J* = 3.65, 6.15 Hz, 1H), 4.41(s, 1H), 4.37(m, 1H), 4.18(dd, *J* = 3.65, 7.43 Hz, 1H), 4.07(ddd, *J* = 4.46, 5.58, 8.45 Hz, 2H), 3.93(m, 2H), 3.65(m, 1H), 3.38(dd, *J* = 6.45, 9.43 Hz, 1H), 3.36(s, 3H), 3.25(dd, *J* = 6.02, 9.43 Hz, 1H), 2.33(m, 1H), 2.03(m, 1H), 1.47(s, 3H), 1.43(s, 3H), 1.37(s, 3H), 1.33(s, 3H).



232 **234**

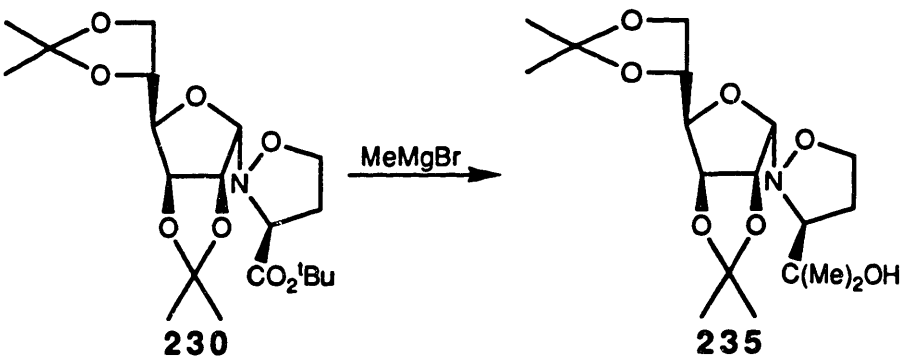
Benzyloxymethyisoxazolidine Mannoside, 234

NaH (80%, 0.104 g, 3.471 mmoles) was suspended in THF (15 mL) and cooled to 0°C under argon. The hydroxymethylisoxazolidine mannoside, **232**, (1.001 g, 2.893 mmoles) was dissolved in THF (5 mL) and added, *via* cannula, to the NaH. The mixture was stirred at 0°C for 30 minutes, after which benzyl bromide (0.378 mL, 3.182 mmoles) was added. The reaction was stirred at room temperature for 22 hours, after which it was quenched with pH = 7 buffer (30 mL) and washed with ethyl acetate (3 X 20 mL). The combined organics were dried over $MgSO_4$ and concentrated to dryness. The residue was purified on silica gel (25% ethyl acetate/hexane) to give the desired product (1.255 g, 99%) as a colorless oil.

Physical Properties for 234

R_f = 0.71 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.31(m, 5H), 4.95(d, *J* = 6.03 Hz, 1H), 4.80(dd, *J* = 3.75, 6.20 Hz, 1H), 4.53(AB, *J* = 12.06 Hz, 2H), 4.41(s, 1H), 4.35(m, 1H), 4.16(dd, *J* = 3.59, 7.50 Hz, 1H), 4.06(dd, *J* = 6.20, 8.64 Hz, 1H), 4.00(dd, *J* = 4.73, 8.48 Hz, 1H), 3.90(m, 2H), 3.68(m, 1H), 3.46(dd, *J* = 6.68, 9.45 Hz, 1H), 3.30(dd, *J* = 6.85, 9.29 Hz, 1H), 2.32(m, 1H), 2.04(m, 1H), 1.46(s, 3H), 1.38(s, 3H), 1.35(s, 3H), 1.32(s, 3H).



230 **235**

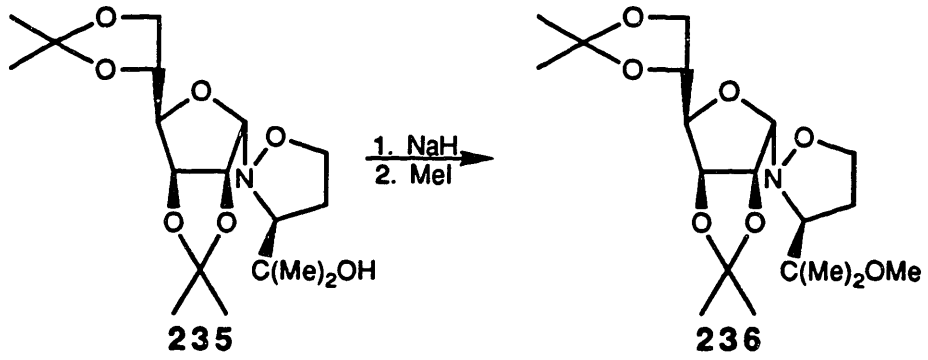
Dimethylhydroxymethylisoxazolidine Mannoside, 235

The isoxazolidine mannoside, **230**, (5.00 g, 12.05 mmoles) was dissolved in ether (100 mL) and cooled to 0°C under argon. MeMgBr (3M in ether, 12.05 mL, 36.15 mmoles) was added, dropwise, and the solution was stirred at 0°C for 1 hour. The reaction was then quenched with pH = 7 buffer (100 mL) and water (100 mL) was added. The resulting mixture was washed with ethyl acetate (2 X 100 mL). The ethyl acetate was dried over $MgSO_4$, filtered, and concentrated to dryness yielding the desired product (4.27 g, 95%) as a thick syrup requiring no further purification.

Physical Properties for 235

R_f = 0.31 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 5.00(d, *J* = 6.12 Hz, 1H), 4.83(dd, *J* = 3.67, 6.10 Hz, 1H), 4.38(m, 2H), 4.14(dd, *J* = 3.46, 7.55 Hz, 1H), 4.08(dd, *J* = 6.16, 8.62 Hz, 1H), 3.93-4.01(m, 3H), 3.35(dd, *J* = 4.83, 7.30 Hz, 1H), 2.30(m, 2H), 2.03(s, 1H), 1.47(s, 3H), 1.41(s, 3H), 1.36(s, 3H), 1.34(s, 3H), 1.22(s, 3H), 1.16(s, 3H).



235 236

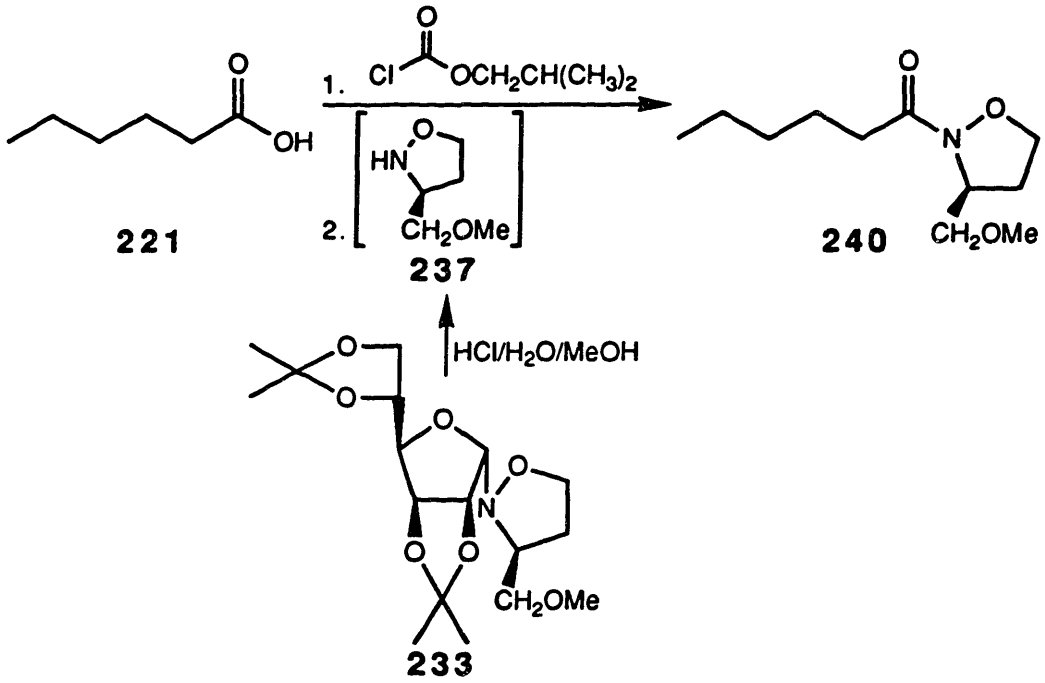
Dimethylmethoxymethylisoxazolidine Mannoside, 236

NaH (80%, 161 mg, 5.37 mmoles) was suspended in THF (10 mL) at room temperature under argon. A solution of the dimethylmethoxymethylisoxazolidine mannoside, **235**, (1.67 g, 4.48 mmoles) in THF (10 mL) was added, *via* cannula, and the resulting mixture was stirred at room temperature for 45 minutes. Methyl iodide (0.28 mL, 4.48 mmoles) was added and the reaction was stirred at room temperature for 2 days. After quenching with pH = 7 buffer (25 mL), the product was extracted with ethyl acetate (2 X 25 mL). The ethyl acetate layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified on silica gel (15% ethyl acetate/hexane) to yield the desired product (1.18 g, 68%) as a thick syrup and recovered starting material (0.30 g, 18%).

Physical Properties for 236

R_f = 0.74 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 5.00(d, *J* = 6.03 Hz, 1H), 4.81(dd, *J* = 3.49, 6.03 Hz, 1H), 4.37(m, 1H), 4.33(s, 1H), 4.15(dd, *J* = 3.59, 7.50 Hz, 1H), 4.05(ABX, *J* = 6.19, 8.80, 4.56 Hz, 2H), 3.96(m, 1H), 3.90(m, 1H), 3.47(dd, *J* = 3.26, 8.97 Hz, 1H), 3.20(s, 3H), 2.47(m, 1H), 2.35(m, 1H), 1.47(s, 3H), 1.42(s, 3H), 1.36(s, 3H), 1.33(s, 3H), 1.19(s, 3H), 1.07(s, 3H).



5-(*S*)-Methoxymethylisoxazolidide, 240

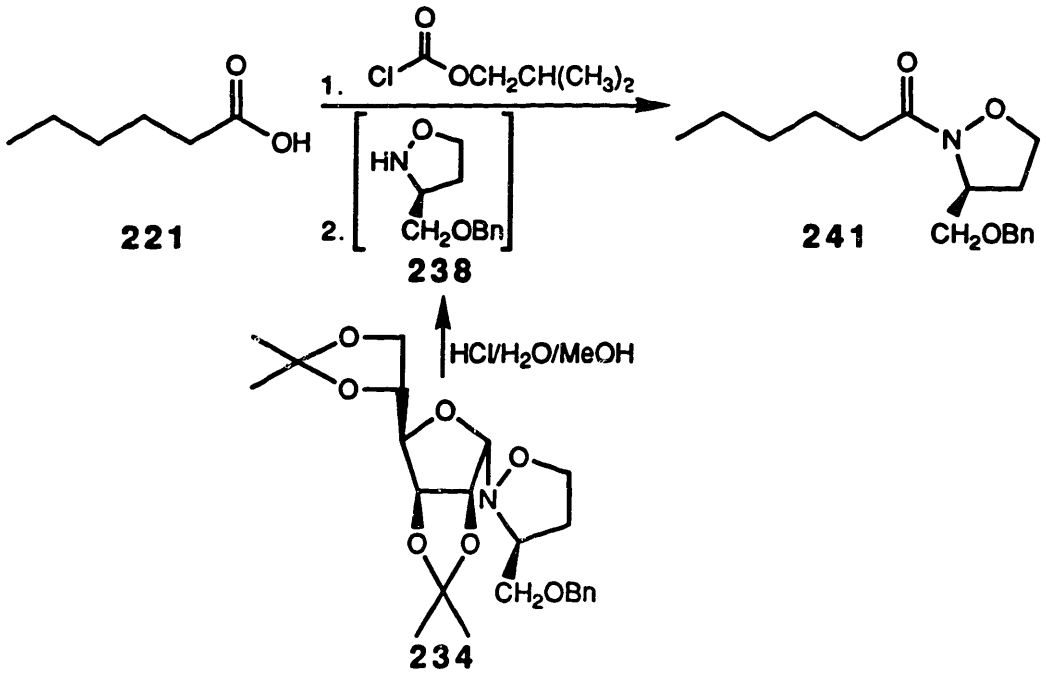
The methoxymethylisoxazolidine mannoside, **233**, (1.016 g, 2.831 mmoles) was dissolved in MeOH (15 mL) and concentrated HCl (1.5 mL) was added. The reaction was stirred at room temperature for 6 hours, after which it was quenched with saturated $NaHCO_3$ solution (30 mL). NaOH (1 pellet) was dissolved in the mixture and the resulting solution was washed with ethyl acetate (3 X 30 mL). The combined ethyl acetate layers were dried

over $MgSO_4$, concentrated to dryness, and dissolved in THF (5 mL). Hexanoic acid, **221**, (355 μL, 2.83 mmoles) was dissolved in THF (10 mL) and *N*-methylmorpholine (311 μL, 2.83 mmoles) was added. The mixture was cooled to -20°C under argon and isobutyl chloroformate (367 μL, 2.83 mmoles) was added. After 1 minute, the isoxazolidine solution was added, *via* cannula, and the reaction was stirred at -20°C for 1 hour. The reaction was then warmed to room temperature, concentrated, and combined with ethyl acetate (15 mL). The ethyl acetate was washed with 5% citric acid solution (2 X 10 mL) and saturated $NaHCO_3$ solution (2 X 10 mL), after which it was dried over $MgSO_4$, concentrated to dryness, and purified on silica gel (50% ethyl acetate/hexane) to yield the desired product (0.256 g, 42%) as a colorless liquid.

Physical Properties for **240**

R_f = 0.47 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 4.50(m, 1H), 4.11(dt, *J* = 3.59, 7.91 Hz, 1H), 3.70(dt, *J* = 7.17, 7.99 Hz, 1H), 3.55(dd, *J* = 4.89, 9.62 Hz, 1H), 3.39(dd, *J* = 6.36, 9.46 Hz, 1H), 3.37(s, 3H), 2.45(m, 1H), 2.35(m, 2H), 2.23(m, 1H), 1.60(m, 2H), 1.30(m, 4H), 0.87(m, 3H).



5-(*S*)-Benzyloxymethylisoxazolidide, 241

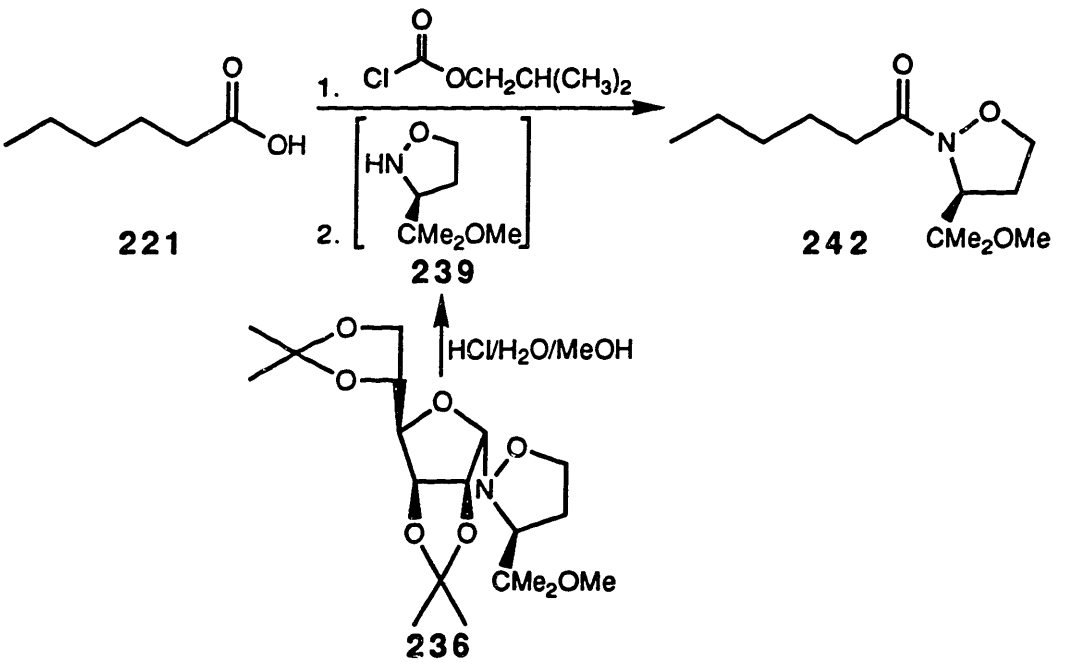
The benzyloxymethylisoxazolidine mannoside, **234**, (1.180 g, 2.713 mmoles) was dissolved in MeOH (16 mL) and 10% HCl was added. The reaction was stirred at room temperature for 6 hours, after which it was quenched with saturated $NaHCO_3$ solution (30 mL). NaOH (1 pellet) was added and the reaction was washed with ethyl acetate (3 X 30 mL). The combined organics were dried over $MgSO_4$, concentrated to dryness and the residue was dissolved in THF (5 mL). Hexanoic acid, **221**, (0.340 mL, 2.713 mmoles) was dissolved in THF (15 mL). *N*-methylmorpholine (0.298 mL, 2.713 mmoles) was added and the mixture was cooled to -20°C under argon. Isobutylchloroformate (0.352 mL, 2.713 mmoles) was added and the reaction was stirred for 1 minute. The isoxazolidine solution was added, *via* cannula, and the reaction was stirred at -20°C for 1 hour, after which it was warmed to room temperature and concentrated to dryness. After adding ethyl acetate (20 mL), the mixture was washed with 5% citric acid solution (2 X 10 mL) and saturated $NaHCO_3$ solution (2 X 10 mL). The combined

organic phases were dried over $MgSO_4$ and concentrated to dryness. Purification of the residue on silica gel (25% ethyl acetate/hexane) provided the desired product (0.579 g, 73% yield) as a colorless oil.

Physical Properties for **241**

R_f = 0.58 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 7.31(m, 5H), 4.54(m, 3H), 4.10(dt, *J* = 3.75, 7.82 Hz, 1H), 3.72(m, 1H), 3.66(dd, *J* = 4.89, 9.62 Hz, 1H), 3.45(dd, *J* = 6.85, 9.62 Hz, 1H), 2.34(m, 4H), 1.61(m, 2H), 1.31(m, 4H), 0.87(m, 3H).



5-(*S*)-Dimethylmethoxymethyl Isoxazolidide, 242

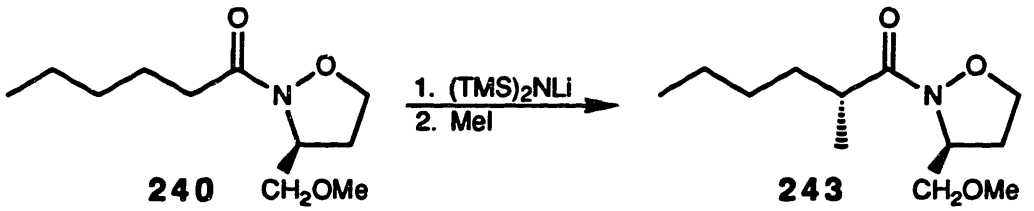
The dimethylmethoxymethylisoxazolidine mannoside, **236**, (1.184 g, 3.059 mmoles) was dissolved in MeOH (18 mL) and concentrated HCl (1.8 mL) was added. The reaction was stirred at room temperature for 6 hours after which, it was quenched with saturated $NaHCO_3$ solution (30 mL).

NaOH (1 pellet) was dissolved in the mixture and the resulting solution was extracted with ethyl acetate (3 X 30 mL). The ethyl acetate was dried over $MgSO_4$, concentrated, and dissolved in THF (5 mL). Hexanoic acid, **221**, (383 μL, 3.06 mmoles) was dissolved in THF (10 mL) and *N*-methylmorpholine (336 μL, 3.06 mmoles) was added. After cooling to -20°C under argon, isobutyl chloroformate (397 μL, 3.06 mmoles) was added. After 1 minute, the isoxazolidine solution was added, *via* cannula, and the reaction was stirred at -20°C for 1 hour. The reaction was then warmed to room temperature, concentrated, and combined with ethyl acetate (15 mL). The ethyl acetate was washed with 5% citric acid solution (2 X 10 mL) and saturated $NaHCO_3$ solution (2 X 10 mL), after which it was dried over $MgSO_4$, concentrated to dryness, and purified on silica gel (50% ethyl acetate/hexane) to yield the desired product (0.412 g, 55%) as a colorless liquid.

Physical Properties for **242**

R_f = 0.68 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 4.41(dd, *J* = 5.70, 9.29 Hz, 1H), 4.12(dt, *J* = 1.96, 8.08 Hz, 1H), 3.55(dt, *J* = 7.82, 10.27 Hz, 1H), 3.24(s, 3H), 2.56(m, 1H), 2.41(m, 1H), 2.35(m, 1H), 2.21(m, 1H), 1.62(m, 2H), 1.32(m, 4H), 1.20(s, 3H), 1.15(s, 3H), 0.89(m, 3H).



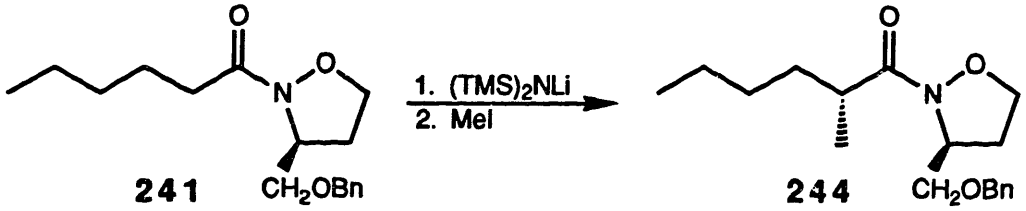
5-(*S*)-Methoxymethyl-2'-(*R*)-Methylhexanoyl Isoxazolidide, 243

$(TMS)_2NH$ (33.7 μL, 0.160 mmole) was dissolved in THF (0.5 mL) and cooled to -78°C under argon. n-BuLi (2.40M in hexane, 67 μL, 0.160 mmole) was added and the mixture was stirred at -78°C for 30 minutes. Hexanoic isoxazolidide **240** (29.8 μL, 0.145 mmole) was added and the mixture was stirred at -78°C for 1 hour, after which it was cooled to -95°C. Methyl iodide (50 μL, 0.803 mmole) was added and the reaction was stirred at -95°C for 3 hours, after which it was allowed to warm to -78°C over 1 hour. The reaction was quenched with saturated NH_4Cl solution (1 mL), warmed to room temperature, and extracted with ethyl acetate (3 mL). The ethyl acetate layer was dried over $MgSO_4$, and concentrated to dryness. Purification of the residue on silica gel (50% ethyl acetate/hexane) yielded the desired product (34.2 mg, 97%, 93% de) as a colorless liquid.

Physical Properties for **243**

R_f = 0.51 (50% ethyl acetate/hexane).

^1H NMR (300 MHz, $CDCl_3$): δ 4.51(m, 1H), 4.13(dt, *J* = 3.65, 7.91 Hz, 1H), 3.72(m, 1H), 3.59(dd, *J* = 4.56, 9.63 Hz, 1H), 3.42(dd, *J* = 6.58, 9.63 Hz, 1H), 3.39(s, 3H), 2.88(m, 1H), 2.40(m, 1H), 2.27(m, 1H), 1.62(m, 1H), 1.34(m, 5H), 1.14(d, *J* = 6.89 Hz, 3H), 0.88(m, 3H).



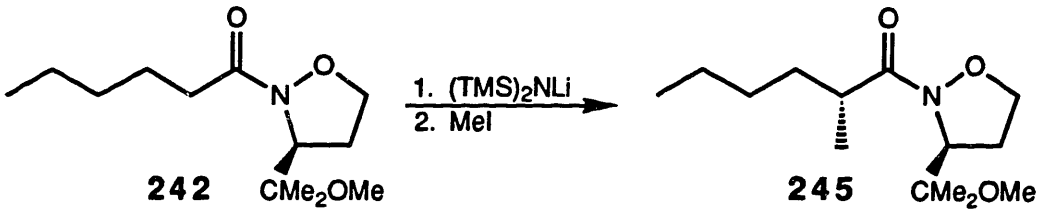
5-(*S*)-Benzyloxymethyl-2'-(*R*)-Methylhexanoyl Isoxazolidide, 244

$(TMS)_2NH$ (33.7 μL, 0.160 mmole) was dissolved in THF (0.5 mL) and cooled to -78°C under argon. n-BuLi (2.40M in hexane, 67 μL, 0.160 mmole) was added and the mixture was stirred at -78°C for 30 minutes. Hexanoic isoxazolidide **241** (30 μL, 0.145 mmole) was dissolved in THF (0.25 mL) and added, *via* cannula, to the $(TMS)_2NLi$. The mixture was stirred at -78°C for 1 hour, after which methyl iodide (50 μL, 0.803 mmole) was added. The reaction was stirred at -78°C for 3 hours, after which it was quenched with saturated NH_4Cl solution (1 mL) and washed with ethyl acetate (3 mL). The ethyl acetate layer was dried over $MgSO_4$, and concentrated to dryness. Purification on silica gel (50% ethyl acetate/hexane) yielded the desired product (37.7 mg, 85%, 69% de) as a colorless liquid.

Physical Properties for 244

R_f = 0.70 (50% ethyl acetate/hexane)

^1H NMR (300 MHz, $CDCl_3$): δ 7.31(m, 5H), 4.55(m, 3H), 4.11(dt, *J* = 3.75, 7.82 Hz, 1H), 3.71(dd, *J* = 7.17 Hz, 1H), 3.68(dd, *J* = 4.80, 9.62 Hz, 1H), 3.45(dd, *J* = 6.85, 9.62 Hz, 1H), 2.39(m, 2H), 2.37(m, 1H), 2.29(m, 1H), 1.61(m, 2H), 1.30(m, 4H), 0.87(m, 3H).



5-(*S*)-Dimethylmethoxymethyl-2'-(*R*)-Methylhexanoyl Isoxazolidide, 245

$(TMS)_2NH$ (33.7 μL, 0.160 mmole) was dissolved in THF (0.5 mL) and cooled to -78°C under argon. n-BuLi (2.40M in hexane, 67 μL, 0.160 mmole) was added and the mixture was stirred at -78°C for 30 minutes. Hexanoic isoxazolidide **242** (35.2 μL, 0.145 mmole) was added and the mixture was stirred at -78°C for 1 hour. Methyl iodide (50 μL, 0.803 mmole) was added and the reaction was stirred at -78°C for 3 hours, after which it was quenched with saturated NH_4Cl solution (1 mL) and washed with ethyl acetate (3 mL). The ethyl acetate layer was dried over $MgSO_4$, filtered, and concentrated to dryness. Purification on silica gel (50% ethyl acetate/hexane) yielded the product (29.1 mg, 78%, 75% de) as a colorless liquid.

Physical Properties for **245**

R_f = 0.81 (50% ethyl acetate/hexane)

^1H NMR (300 MHz, $CDCl_3$): δ 4.45(dd, *J* = 5.47, 9.43 Hz, 1H), 4.13(dt, *J* = 2.44, 8.22 Hz, 1H), 3.57(dt, *J* = 7.67, 9.96 Hz, 1H), 3.25(s, 3H), 2.94(m, 1H), 2.44(m, 1H), 2.23(m, 1H), 1.64(m, 1H), 1.29(m, 5H), 1.20(s, 3H), 1.17(d, *J* = 6.92 Hz, 3H), 1.14(s, 3H), 0.88(t, *J* = 6.76 Hz, 3H).

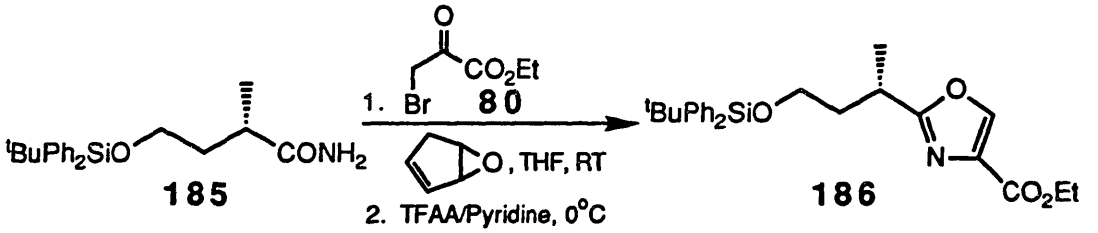
Chapter 6:
Summary and Discussion

6.1 Introduction

Chapter 1 discussed our early attempts at the preparation of fragment A of calyculin A. Chapters 2 and 3 described the preparation of fragments which would lead to the enantiomer of calyculin A, and chapter 4 illustrated our preparation of the natural enantiomers of these fragments as well as their coupling to form fragment C. Finally, Chapter 5 described progress towards the development of a new and potentially useful chiral auxiliary. However, at no point in these chapters was there a comparison of our research to work recently published by other groups. Therefore, this chapter will present such arguments specifically pertaining to the preparation of the oxazole in fragment C1, the preparation of fragment C2, and the usefulness of isoxazolidines as chiral auxiliaries when compared to other proven compounds.

6.2 The Oxazole

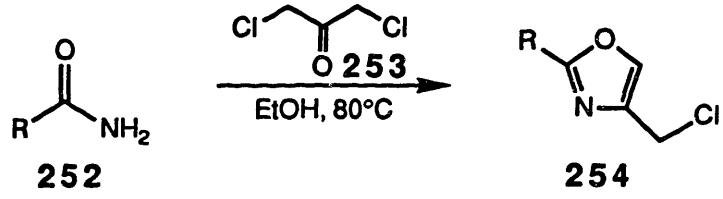
Scheme 6.1



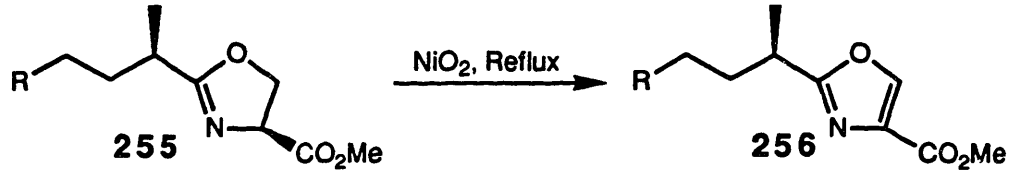
Our oxazole preparation, shown in Scheme 6.1, incorporates the condensation of the amide, **185**, with ethyl bromopyruvate, **80**, followed by dehydration of the corresponding 4-hydroxyoxazoline with trifluoroacetic anhydride and pyridine (see chapter 2). As it turns out, of all the work on calyculin that has been published to date,[16,17,21,25] our synthesis is the only

one exploiting this methodology. The remainder of this section will describe work published by Armstrong,[17] Smith,[16] Hamada,[21] and Evans.[25]

Scheme 6.2



Scheme 6.3

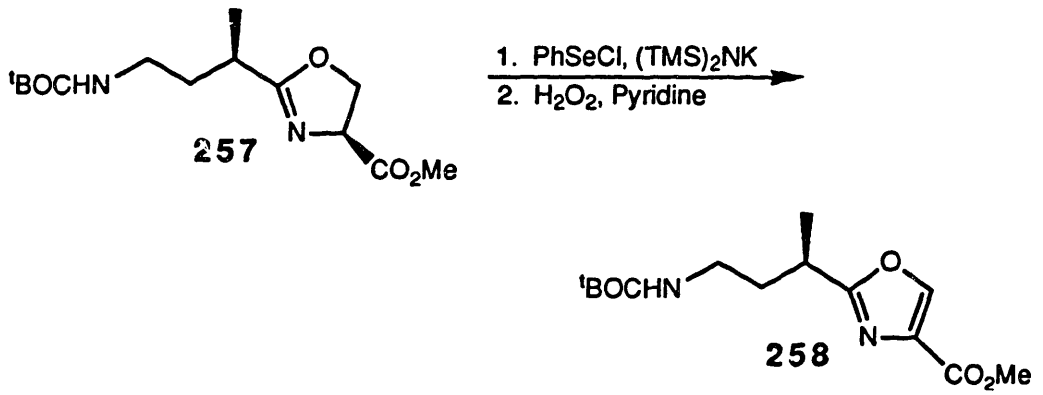


The only reported method for the preparation of the oxazole that resembles ours is that of Armstrong.[17] His strategy, shown in Scheme 6.2, involves the condensation of an amide, **252**, with 1,3-dichloroacetone, **253**. The other three groups[16,21,25] all report similar strategies towards this functional group and incorporate the dehydrogenation of an oxazoline, **255**, to an oxazole, **256** (Scheme 6.3). Although these two general strategies seem quite different, they both involve the application of elevated temperatures to oxazolines. The oxazoline from Armstrong's method is an intermediate in the condensation of the amide with 1,3-dichloroacetone (see Scheme 2.5) while those reported by the others are prepared and isolated. The problems involving elevated temperatures on oxazolines are apparent from our observation that the NiO_2 procedure induces some epimerization. Further support of this observation was found in literature claims that oxazolines, when heated to 40°C for 16 hours, lose all stereochemical integrity.[83,84]

With this in mind, it is surprising that Evans and Smith reported no study of epimerization during this reaction. Hamada reported no observed epimerization during the NiO_2 reaction, but his group carried out this transformation at room temperature. This result was particularly surprising when considering our observed lack of reaction under these conditions.

There is one more method reported for the formation of the oxazole. This is an alternate approach utilized by Evans[25] for large scale preparations and involves selenium chemistry (Scheme 6.4). Although Evans reports no study of epimerization during this reaction, it is likely that the stereochemical integrity of the α-center remains intact due to the greater acidity of the proton α to the ester.

Scheme 6.4

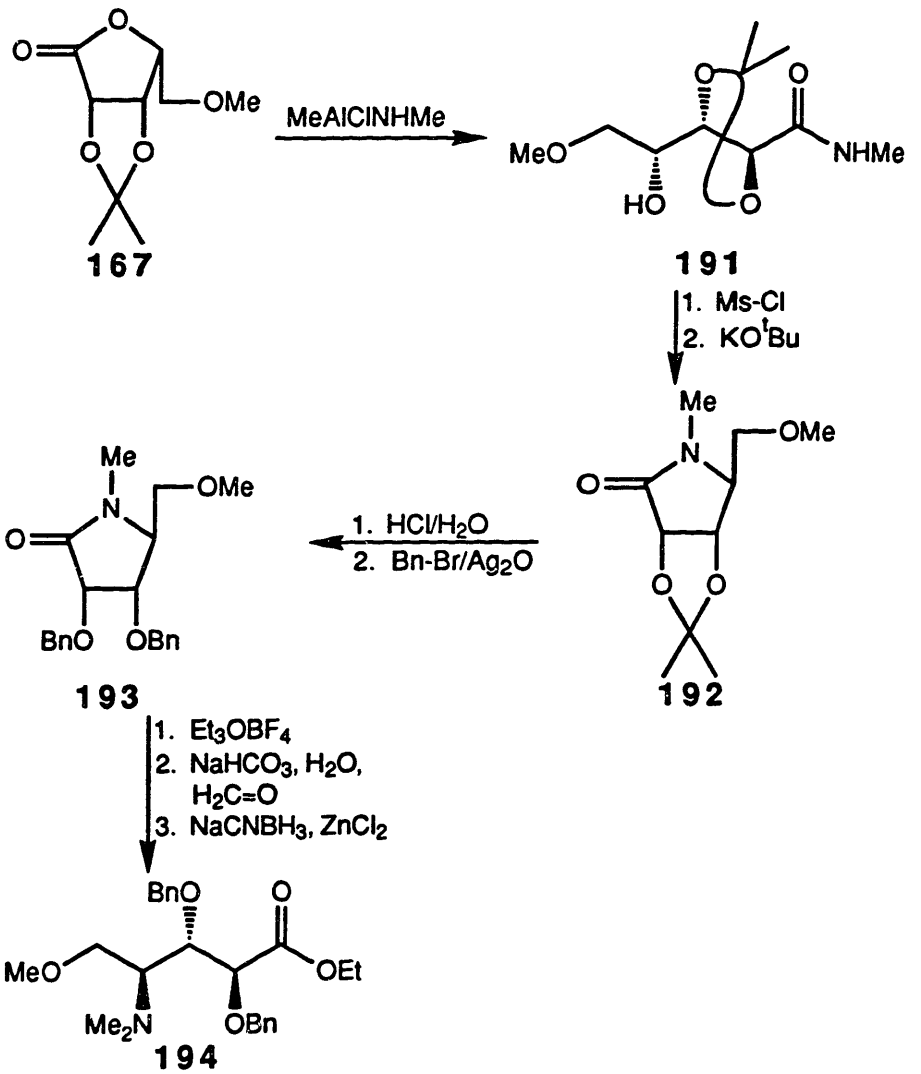


6.3 Fragment C2

Our preparation of fragment C2 incorporates the derivatization of D-lyxonolactone, **170**, a readily available chiral pool starting material bearing two correct stereocenters and one requiring inversion, to the literature compound **167**[122] (see Scheme 4.7). This strategy is comprised of four one-pot reaction sequences from **167** (Scheme 6.5) in which no stereogenic

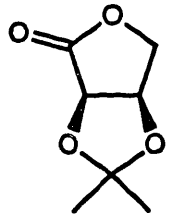
centers need be created. Consequently, our preparation is highly competitive with four published routes to analogous compounds. These routes, the starting materials of which are shown in Figure 6.1, include Smith's ten-step synthesis from 2,3-*O*-isopropylidine-D-erythronolactone, **259**,[16] Hamada's nine-step synthesis from 4-hydroxymethylbutyrolactam, **260**,[18] an eight-step synthesis from *N*-methylglycine, **261**, by Evans,[25] and Koskinen's six-step synthesis from the serine-derived aldehyde, **262**.[19] All of these strategies require the introduction of one or more stereogenic centers.

Scheme 6.5

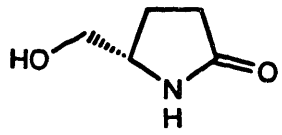


167 **191** **192** **193** **194**

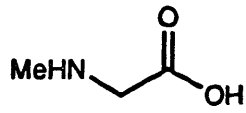
Figure 6.1



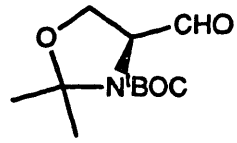
259



260



261

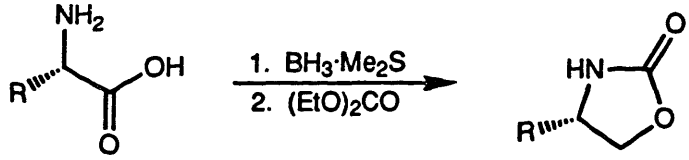


262

6.4 Isoxazolidine Chemistry

Although Chapter 5 dealt extensively with our study of isoxazolidines as chiral auxiliaries in asymmetric synthesis, no comparison was made with Evans' extremely successful oxazolidinone auxiliaries.[158] The Evans auxiliaries are convenient in that they are easily prepared by reduction of aminoacids followed by treatment with diethyl carbonate (Scheme 6.6).[159]

Scheme 6.6



Although the formation of oxazolidinones is much easier than formation of chiral isoxazolidines (see Schemes 5.8 and 5.9), our auxiliaries potentially have advantages over Evans'. For example, the Evans auxiliaries can only be acylated by reaction with acid chlorides or other similarly reactive derivatives, but not esters. On the other hand, isoxazolidines avoid this problem in that they are fully compatible with Weinreb methodology.[127,128,129] Other advantages include the ability to directly cleave the auxiliary with alkyllithium, Grignard, or Weinreb reagents.[147,148,149,150] These factors alone illustrate the complementarity of

these two methodologies in spite of the slightly lower diastereomeric inductions of isoxazolidines (93% vs >99%).

6.5 Conclusion

This thesis has extensively dealt with strategies, both successful and not, directed toward the synthesis of fragments of calyculin A, as well as the introduction of new methodology. Our strategies have distinct advantages over other reported routes to analogous compounds and illustrate the application of contemporary organic chemistry to the solution of relatively complex synthetic problems. With these problems solved, the completion of the total synthesis of calyculin A should not be far off.

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