DISSERTATION

INVESTIGATIONS INTO NOVEL APPLICATIONS OF THE KETONE-CATALYZED ASYMMETRIC EPOXIDATION AND PROGRESS TOWARD THE ASYMMETRIC TOTAL SYNTHESIS OF MERRILACTONE A

Submitted by
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In partial fulfillment of the requirements
for the Degree of Doctor of Philosophy
Colorado State University
Fort Collins, Colorado
Fall 2002

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY J. DAVID WARREN ENTITLED INVESTIGATIONS INTO NOVEL APPLICATIONS OF THE KETONE-CATALYZED ASYMMETRIC EPOXIDATION AND PROGRESS TOWARD THE ASYMMETRIC TOTAL SYNTHESIS OF MERRILACTONE A BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT OF DISSERTATION

INVESTIGATIONS INTO NOVEL APPLICATIONS OF THE KETONE-CATALYZED ASYMMETRIC EPOXIDATION AND PROGRESS TOWARD THE ASYMMETRIC TOTAL SYNTHESIS OF MERRILACTONE A.

The generation of enantiomerically pure compounds has been a constant challenge for organic chemists. The ability to synthesize a single enantiomer of a desired compound is of extreme importance for biologically active compounds. Oftentimes only one of a pair of enantiomers is biologically active, while the other is either inactive or deleterious. Enantioselective processes, especially those that are catalytic, have come to the forefront in today's synthetic laboratories, and catalytic asymmetric epoxidation reactions are no exception to this. Recently, an efficient asymmetric epoxidation method for simple, unfunctionalized olefins was reported using a fructose-derived ketone as catalyst and Oxone as oxidant. The use of this method for the asymmetric epoxidation of 2,2-disubstituted vinylsilanes has been investigated. The enantioselectivity of the reaction was found to be high in most cases. Following epoxidation, the substrates were desilylated to provide the corresponding 1,1-disubstituted terminal epoxides without loss optical purity.

The epoxidation of tryptophan derivatives has also been studied. It was found that these substrates do not readily participate in the asymmetric epoxidation, however limited results were obtained in the racemic epoxidation when the indole nitrogen of *N*-α-Boc-DL-tryptophan methyl ester was properly masked.

A novel ketone for use in the asymmetric epoxidation was also investigated. While the final target remained elusive, an interesting chelation effect was uncovered during the addition of organocerium and organolithium reagents to an advanced intermediate.

Finally, the total synthesis of the natural product merrilactone A was intensely studied. Merrilactone A has been shown to exhibit significant neurotrophic activity, such as greatly promoting neurite outgrowth in the primary cultures of fetal rat cortical neurons at concentrations from 10 μmol/L to 0.1μmol/L. It consists of a densely functionalized pentacyclic ring system featuring two fused γ-lactones and an oxetane ring. Key steps accomplished in the synthesis include a reagent-controlled stereoselective aldol reaction followed by substrate-controlled addition of vinyl lithium to the resulting β-hydroxyketone upon MOM protection of the newly formed alcohol.

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ACKNOWLEDGEMENTS

As I sit back and think about my adventures in graduate school, I can't help but realize that there is no way that I could have made this journey without the help of many, many friends. I have been fortunate enough to work with and around some of the brightest, most intelligent individuals anybody could ever ask for. Many of these people will remain unnamed, however that does not make them any less important. I would first like to thank my advisor, Professor Yian Shi, for always pushing me to be the best that I could possibly be, and for allowing me the freedom to explore "uncharted territory" in the lab. His method of mentorship, while challenging at times, breeds independent thinking and growth. I know that I would not be the person I am today without his guidance. Secondly, I would like to thank Professor Albert Meyers, his intense love and enthusiasm for chemistry is absolutely remarkable. I cherish the times that we were able to spend together. Whether inside or outside of an academic setting, I learned something every time we talked. I would also like to thank Professor Lou Hegedus for reminding me that there is life outside the lab, and that hard work always pays off. I will never forget the time we spent chasing river otters, or the numerous adventures that I was able to live through the pictures he frequently showed me. Additionally, I need to recognize perhaps the two most influential people in my young career, Drs. Larry Westrum and Ike Klundt. It was through their mentoring while I was an undergraduate that instilled in me a deep love and appreciation for Organic chemistry. I learned and grew more from them than they will ever know. I would also like to thank the many members of the Shi group that have helped me throughout my tenure at CSU. Mike Frohn, Jon Lorenz, Matt Hickey and Lianhe Shu, in particular. They made working in the lab that much more enjoyable, and their creative problem solving certainly got me out of many quandaries. To Julie, the many long discussions we had made life much more bearable, I can't even begin to thank you for all of the support you gave me when times were tough. Finally, to my parents, the unconditional love and support that you have given to me over the past five years is, without a doubt, the single most important thing that has brought me to this point in my life. I don't know how to even begin to express my gratitude; you mean more to me than you will ever know.

To my parents, Dave and Diana Manchak, with much love and appreciation

"The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strives valiantly; who errs and comes short again and again, who knows the great enthusiasms, the great devotions, and spends himself in a worthy cause; who at best, knows the triumph of high achievement; and who, at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those cold and timid souls who know neither victory nor defeat."

-Theodore Roosevelt

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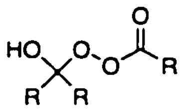
CHAPTER ONE

RECENT ADVANCES IN DIOXIRANE CHEMISTRY

1.1. INTRODUCTION

Dioxiranes, **1-1**, are the smallest members of the cyclic peroxide class of organic molecules. Their existence was first postulated by Bayer and Villiger in 1899 as a possible intermediate in the reaction which, today, bears their names.[1] Through the use of ^{18}O labeling, Doering[2] showed that the Bayer-Villiger reaction does not proceed through a dioxirane, but rather through the rearrangement of a Criegee-type[3] intermediate **1-2**. Although dioxiranes had been postulated as intermediates in a number of reactions, their existence was not proven until 1972 when Talbott and Thompson showed that perfluorodimethyl- and chlorodifluoromethyl(trifluororomethyl)dioxirane could be obtained by fluorine oxidation of the dilithium salt of the parent ketone hydrate at −80° to −30°C.[4] In 1974 Montgomery[5] reported that the ketone-catalyzed decomposition of Oxone likely involved a dioxirane intermediate, an observation which would play a significant role in the development of dioxiranes as reagents in organic synthesis. Through elegant kinetic and labeling studies, Edwards further demonstrated that dioxiranes were in fact involved in the ketone-catalyzed decomposition of Oxone.

1-1



1-2

A major discovery in the area of dioxirane chemistry was reported by Murray in 1985.[6] In his landmark paper, Murray described the isolation of dimethyldioxirane (DMDO) as a solution in acetone by distillation from a buffered acetone-Oxone mixture. Up until that time, dioxiranes had to be prepared *in situ*,[5,7-10] and thus were difficult to study. Isolation of dimethyldioxirane allowed for its full spectral characterization,[11,12] and gave chemists easy access to a relatively understudied oxidant. Unlike other oxidation reagents, reactions utilizing isolated dimethyldioxirane proceed under neutral pH, and produce no toxic byproducts, even with the most sensitive substrates (*vide infra*).

Given its remarkable story, dimethyldioxirane and its more reactive counterpart, methyl(trifluoromethyl)dioxirane (TFMDO), have been the subject of many excellent reviews.[13-23] An exhaustive review of the literature is not possible given the remarkable volume of papers published in this area, however, every attempt has been made to include those papers which further the synthetic utility or expose interesting reactivity of these reagents.

1.2. PREPARATIVE METHODS

The methods for preparation and isolation of dimethyldioxirane have been listed elsewhere,[6,24,25] however their importance warrants acknowledgment here. Isolated solutions of DMDO can be prepared by distillation of a buffered solution of Oxone in acetone,[6,25] with concentrations of 0.08 – 0.10 M obtained if an efficient condenser is used. In cases where more concentrated solutions are necessary, or when acetone is incompatible with the desired reaction, the dioxirane can be extracted into CH_2Cl_2 or $CHCl_3$ to give "acetone-free" solutions with concentrations of up to 0.35 M.[26,27] TFMDO can be isolated in the parent ketone using an analogous procedure with concentrations as high as 0.82 M.[28] Again, "acetone-free" solutions can be obtained using extraction procedures, if desired.[29]

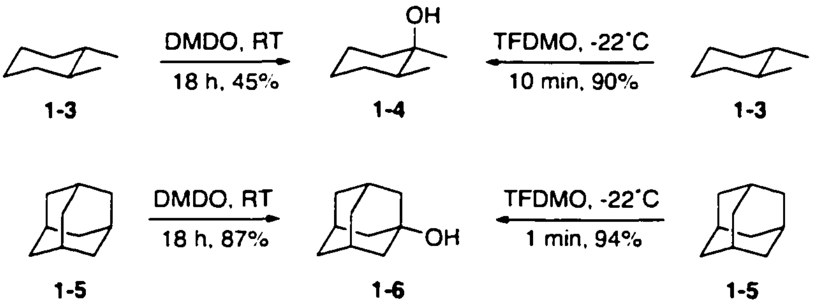
In situ formation of dioxiranes by reaction of Oxone and a ketone in a buffered biphasic solution is also a viable method for their preparation. The reactions can be run at neutral pH with an excess of ketone,[7-10,30-37] or at high pH with a catalytic amount of ketone (*vide infra*).[38]

1.3. C-H Insertions

1.3.1. Insertion into Unactivated C-H Bonds

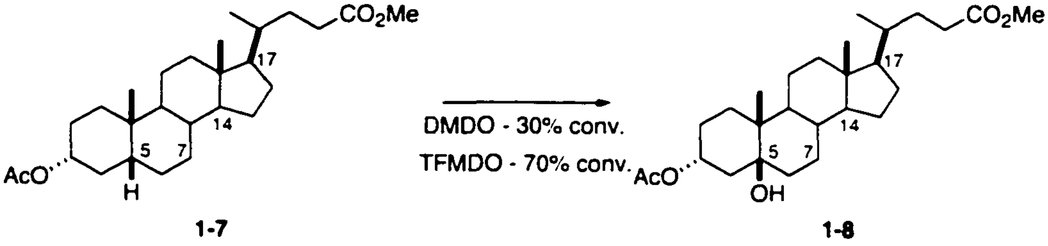
Possibly the most remarkable reaction carried out by dioxiranes is their ability to insert oxygen into unactivated C-H bonds.[39-44] Their high sensitivity to electronic and steric effects has induced the comparison to biological oxidants. Other oxidizing agents carry out the same reactions with large amounts of overoxidized side products. Thus the mild reaction conditions and ease of work-up provide for a markedly simple oxidation procedure in many cases.

Soon after the first isolation of DMDO, Murray reported that this oxidant inserted oxygen into C-H bonds of hydrocarbons to give alcohols or products derived from further oxidation of the alcohol, albeit under moderately forcing conditions.[45] Three years later, Curci reported that TFDMO carried out the same transformations in minutes at sub-ambient temperatures (Scheme 1.1).[46] In general, TFMDO reacts much faster than DMDO, enabling reactions to take place in minutes or hours rather than days. Furthermore the regio-, stereo-, and chemoselectivities of the two reagents are virtually the same.



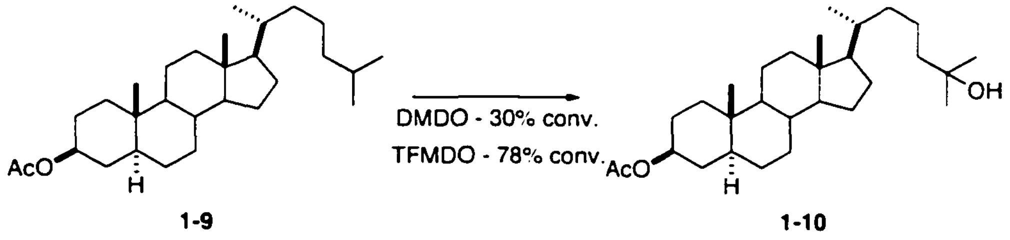
Scheme 1.1

Application of this methodology has been widespread. One of the most fascinating of these has been the oxyfunctionalization of steroids, since these compounds tend to be biologically active and their carboskeletons are relatively complex. Highly selective insertions can be carried out on similar C-H bonds due to small differences in their steric and electronic environment. For example, oxygenation of steroids in the coprostane series occurs at the pseudoequatorial C-5 bond exclusively (Scheme 1.2).[47] A slight perturbation of the electronic environment by the introduction of a C-7 acetoxy group reduces the reactivity of C-5 and gives sizeable amounts of C-14 and C-17 insertion products.[48]



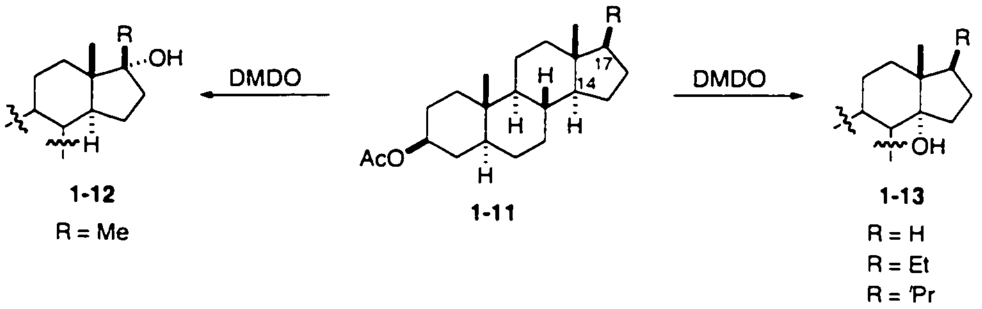
Scheme 1.2

Trans fusion of the A/B ring makes the C-5 hydrogen axial and less accessible to the oxidant, effectively rendering it unreactive. Insertions can then be selectively carried out elsewhere in the molecule. To this end, 3β-acetoxy-5α-cholestane **1-9** was allowed to react with either DMDO or TFMDO to give the 25-hydroxylated steroid **1-10** as the major product (Scheme 1.3).[49,50] Similar results were reported in the oxidation of brassinosteroid systems.[51-53]



Scheme 1.3

The high degree of selectivity in these cases is thought to arise not only from the preferential oxidation of a tertiary C-H bonds over secondary C-H bonds but also from the greater accessibility of the steroid side chain to the oxidant. Further evidence of this phenomenon comes from the oxidation of pregnane and androstane steroids.[54] Bovicelli reported that selectivity in the oxidation was greatly influenced by the C-17 side chain (Scheme 1.4). When there is no side chain, oxidation takes place at C-14, indicating that it is the least sterically-hindered tertiary carbon in the steroid skeleton. When a methyl group is introduced as a side chain, oxidation no longer occurs at C-14, but rather at C-17, since it is now the least-hindered tertiary position. Interestingly, replacement of the methyl group with either an ethyl or isopropyl group causes oxidation to revert back to C-14. The lack of reactivity of the tertiary C-H bond of the isopropyl side chain has been attributed to the shielding effect of the C-18 methyl group. Clearly the reaction is under both electronic and conformational control making it difficult to predict *a priori* the outcome in such complicated systems. Introduction of additional functionality into the carbon framework can effect both the conformational and electronic environment of the molecule in subtle ways giving rise to disparate selectivity.[55,56]



1-12
R = Me

1-11

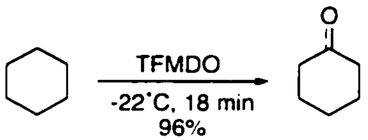
1-13
R = H
R = Et
R = ^{i}Pr

Scheme 1.4

1.3.2. Insertion into C-H Bonds with α Heteroatoms

The C-H bonds of alcohols are much more reactive than the C-H bonds of unfunctionalized carbons.[57] It is, therefore, not surprising to find that insertion into secondary C-H bonds is complicated by overoxidation of the alcohol product to the corresponding ketone. For example, exposure of cyclohexane **1-14** to 2 equivalents of TFMDO produces cyclohexanone **1-15** exclusively in 18 minutes at -22°C (Scheme

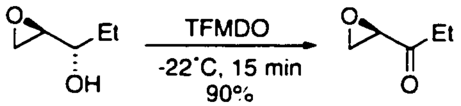
1.5).[46] The sensitivity of the dioxirane to electronic effects provides an avenue to isolate the ketone in high yield because the newly-formed carbonyl group deactivates the α position to further oxidation.



1-14 **1-15**

Scheme 1.5

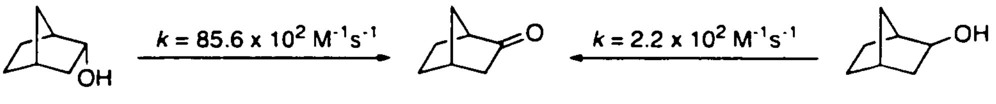
As is seen with nonsubstituted C-H bonds, the insertion takes place stereospecifically and stereochemistry on adjacent carbons is unaffected. Thus epoxy alcohol **1-16** was oxidized to the corresponding epoxy ketone **1-17** without any configurational loss in the epoxide (Scheme 1.6).[57]



1-16 **1-17**

Scheme 1.6

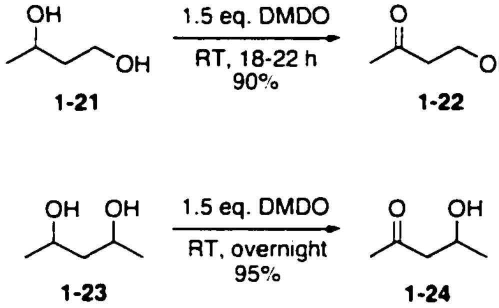
The delicate nature of the oxidant towards steric effects is clearly shown in the oxidation of norborneol to norcamphor **1-18**.[57] Oxidation of *endo*-norborneol **1-19** is about 40 times faster than the *exo*- stereoisomer **1-20** (Scheme 1.7).



1-19 **1-18** **1-20**

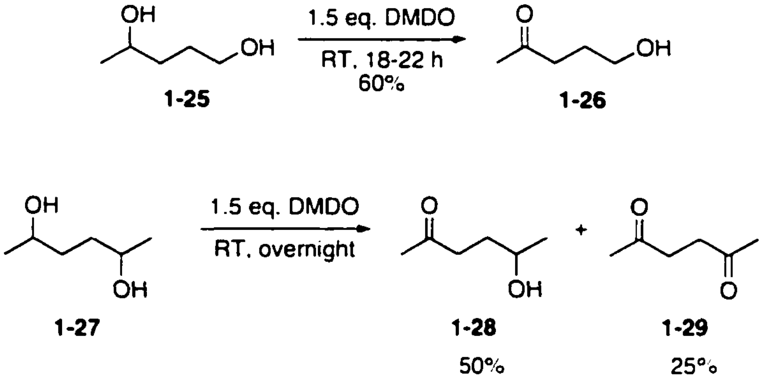
Scheme 1.7

One of the many advantages of alcohol oxidation using dioxiranes is that the reagents show extraordinary chemoselectivity. Secondary alcohols are selectively oxidized in the presence of primary ones. In the case of 1,2 and 1,3 diols, the newly-formed ketone deactivates the second alcohol, making it possible to isolate the hydroxy ketone in high yield, even if both alcohols are secondary (Scheme 1.8).[58,59]



Scheme 1.8

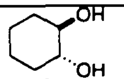
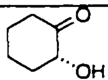
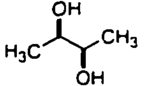
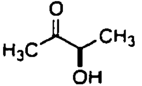
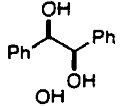
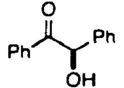
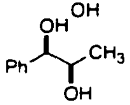
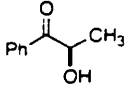
The deactivation is less severe in the case of 1,4 diols, and the corresponding hydroxy ketone is isolated along with higher amounts of overoxidized products (Scheme 1.9).



Scheme 1.9

When stereodefined alcohols are used, this procedure provides an efficient method for desymmeterization.[60] A significant drawback, however, is that the reaction is virtually random with unsymmetrical aliphatic diols, and the regioselectivity is practically nonexistent in this case (Table 1.1, entries 1-3). However, in certain cases, selectivity is observed (Table 1.1, entry 4).

Table 1.1. Oxidation of Optically Active 1,2-Diols with DMDO

Entry	**Substrate**	**ee (%)**	**Conv. (%)**	**Product**	**ee (%)**
1		95	>96		94
2		>98	92		>98
3		96	50		>92
4		89	94		86

An important extension of this methodology is the enantioselective oxidation of *vic*-diols by the fructose-derived ketone **1-30**.[61,62] In the case of *meso* diols, a desymmeterization can be effected, while racemic diols can be kinetically resolved (Table 1.2).

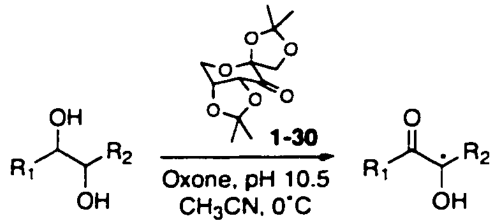
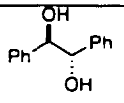
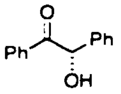
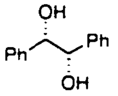
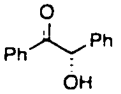
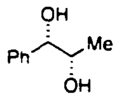
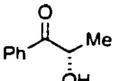
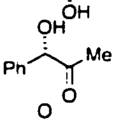
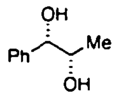
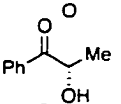
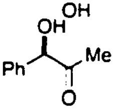
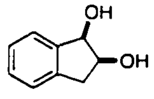
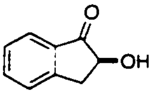
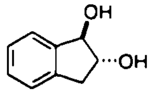
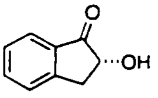


Table 1.2. Enantioselective Oxidation of *vic*-Diols by the Fructose Derived Dioxirane **1-30**

Entry	Substrate	Conv. (%)	Product	ee (%)
1	 *meso*	89		45
2	 *racemic*	51		65
3	 *threo*	20	 	69 44
4	 *erythro*	34	 	23 8
5	 *cis*	30		9
6	 *trans*	26		20

Analysis of the proposed transition state for this reaction shows a clear dependence on hydrogen bonding by the remote hydroxyl to the dioxirane. This type of interaction would be expected in such a polar transition state. Furthermore, the S-configured alcohol is more readily oxidized due to the inherent sterics of the dioxirane (Figure 1.1)

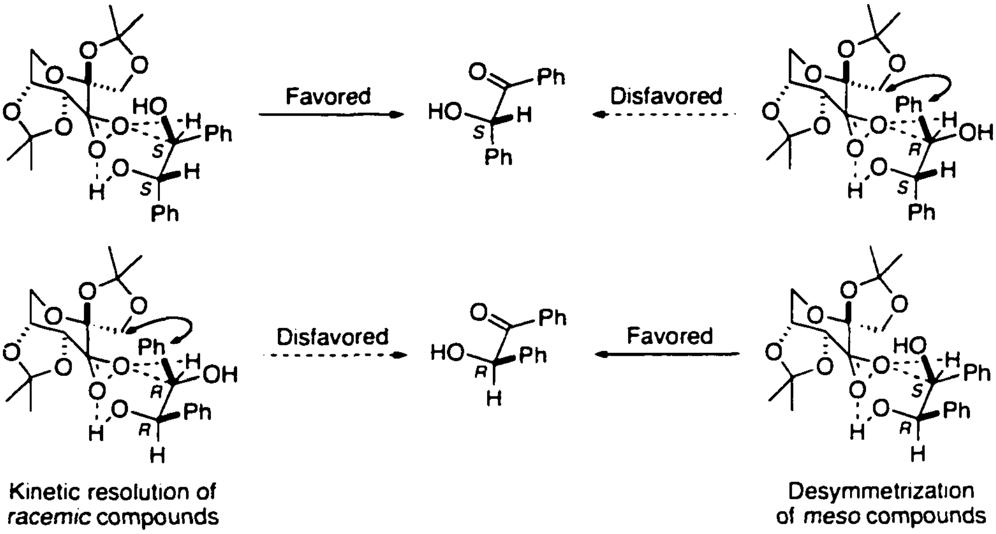
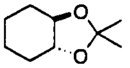
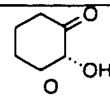
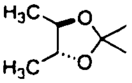
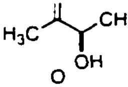
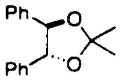
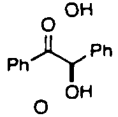
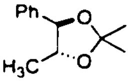
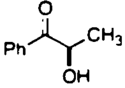


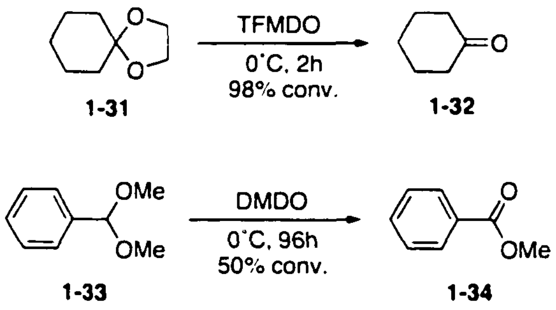
Figure 1.1. Proposed transition states for the enantioselective oxidation of *vic*-diols by ketone **1-30**

As might be expected, ethers can also activate C-H bonds toward insertion. Further application of the diol methodology shown above is seen in the oxidation of acetonides.[59,63,64] Interestingly, the product of the oxidation is the same as that for the corresponding diol (Table 1.3). The enantioselective oxidation of acetonides by the fructose-derived ketone **1-30** has also been disclosed, with reactivity similar to that of the unprotected alcohols.[62]

Table 1.3. Selective Oxidation of Optically Active Acetonides with TFMDO

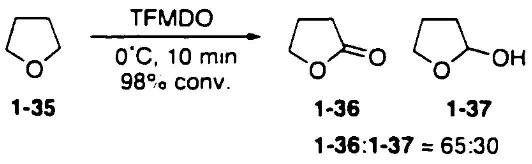
Entry	Substrate	ee (%)	Conv. (%)	Product	ee (%)
1		99	98		99
2		98	>98		98
3		97	93		97
4		92	90		92

In the absence of other reactive functionalities, acetals and ketals can be oxidized to give the corresponding ester or ketone.[65,66] This method is a much milder alternative to conventional oxidation reagents such as lead tetraacetate, singlet oxygen, hydroperoxides, or ozone, which are not very selective and generally give complex product mixtures. Other metal-catalyzed oxidations, including metal oxides in high oxidation states, LiOCl with a catalytic amount of Ru(II) complexes, and metal nitrates give the desired oxidation products, however they are often plagued with many side reactions. Compared with these methods, oxidations using dioxiranes have the distinct advantage of being operationally simple, with mild reaction conditions and increased product yields. Scheme 1.10 shows two such examples.



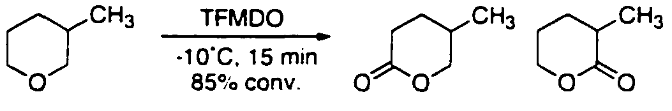
Scheme 1.10

Similarly, cyclic ethers can be oxidized to lactones.[65] In cases where the ether is symmetrical, yields of the lactone are quite high, giving mainly the hemiacetal as an underoxidized side product, Scheme 1.11.



Scheme 1.11

When the ether is not symmetrical, oxidation occurs primarily on the less sterically-hindered side. Of note is the oxidation of 3-methyltetrahydropyran **1-38** (Scheme 1.12). Strategic placement of the heteroatom perturbs the expected reactivity of 3°>2°>1° such that only the 2° C-H bond gets oxidized.

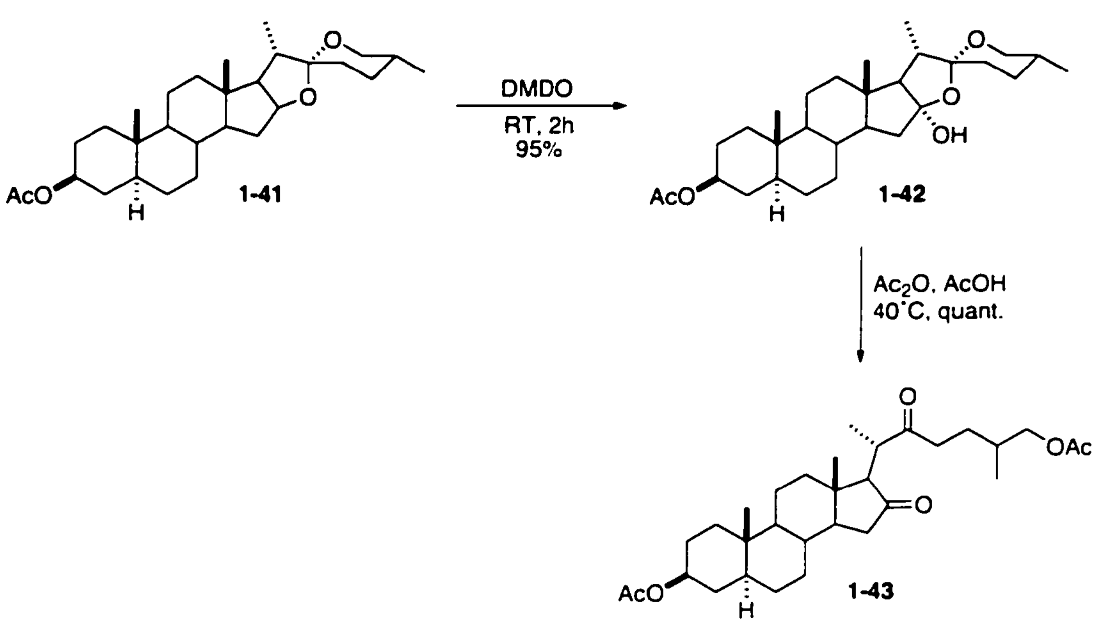


1-38 **1-39** **1-40**

1-39:**1-40** = 58:38

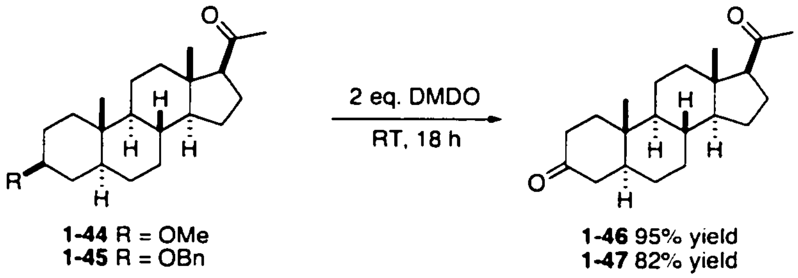
Scheme 1.12

This type of reactivity was exploited in the synthesis of functionalized cholestanes from sapogenins by selective oxyfunctionalization at the C16-H bond.[67] In the case of tigogenin acetate **1-41**, activation of C16 by the oxygen of the tetrahydrofuran ring allows for regiospecific oxidation to give intermediate **1-42** in 95% yield. The hemiacetal was then cleaved to give the 16,22-dioxo-27-acetoxycholestane derivative **1-43** in quantitative yield (Scheme 1.13).



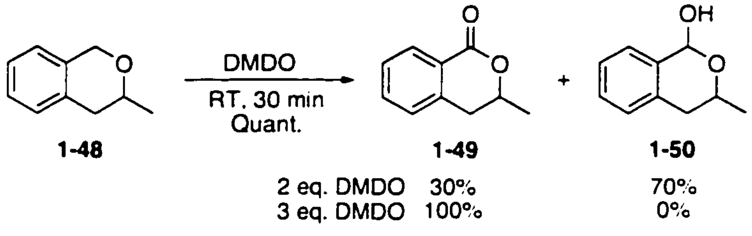
Scheme 1.13

C-H insertion into oxygen-activated bonds also provides the opportunity for a one pot transformation of methyl and benzyl ethers into ketones (Scheme 1-14).[68] In certain circumstances benzyl ethers can be cleaved without further oxidation to the ketone, giving a convenient deprotection procedure.[69,70]



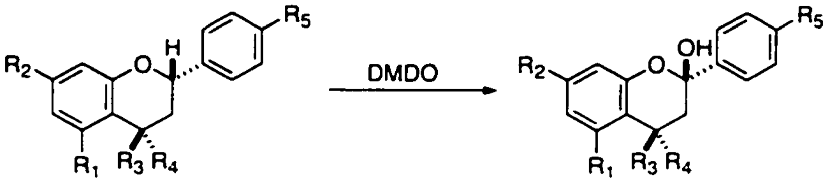
Scheme 1.14

An interesting extension of this methodology is the direct synthesis of isocoumarins from isochromans.[71] Remarkably, benzylethereal methylenes are oxidized in the presence of ethereal methynes (Scheme 1.15) Thus 3-methylisochroman **1-48** was oxidized quantitatively to 3-methyl-isocoumarin **1-49** using 3 equivalents of DMDO. When fewer than 3 equivalents was used, a mixture of the desired 3-methylisocoumarin and underoxidized 3,4-dihydro-3-methyl-H-2-benzopyran-1-ol **1-50** was found. Selectivity is presumed to arise from double activation of the methylene by the benzene ring and oxygen thus stabilizing the slightly positive transition state, *vide infra*. This method provides a unique approach to the synthesis of 3-alkyl substituted isocoumarins since no open-chain products were detected. When the 3-position is substituted with an aryl group, increasing amounts of open-chain products were found.[72]



Scheme 1.15

Further development of this idea led to the synthesis of anthocyanidins by oxidation of the benzylethereal carbon of flavonoids.[73] As shown in Scheme 1.16, 2,4-*cis*-flavane-4-acetate **1-51** was oxidized with DMDO at room temperature, furnishing the corresponding 2-hydroxy derivative **1-52** in 63% yield as the sole product. Similarly, flavan-5,7,4'-triacetate **1-53** was oxidized to the corresponding 2-hydroxy derivative **1-54** in 57% yield, further showing the utility of this reagent, as similar reagents impart oxyfunctionalization at the C-4 benzylic carbon.[73] Flavan 2-one **1-55** was oxidized to the 2-hydroxy-flavan-4-one **1-56** in only 27% yield, showing the suppressing effect of a carbonyl group on the reactivity of DMDO.



1-51 R_1, R_2, R_3, R_5 = H
R_4 = OAc

1-52 (63% yield)

1-53 R_1, R_2, R_5 = OAc
R_3, R_4 = H

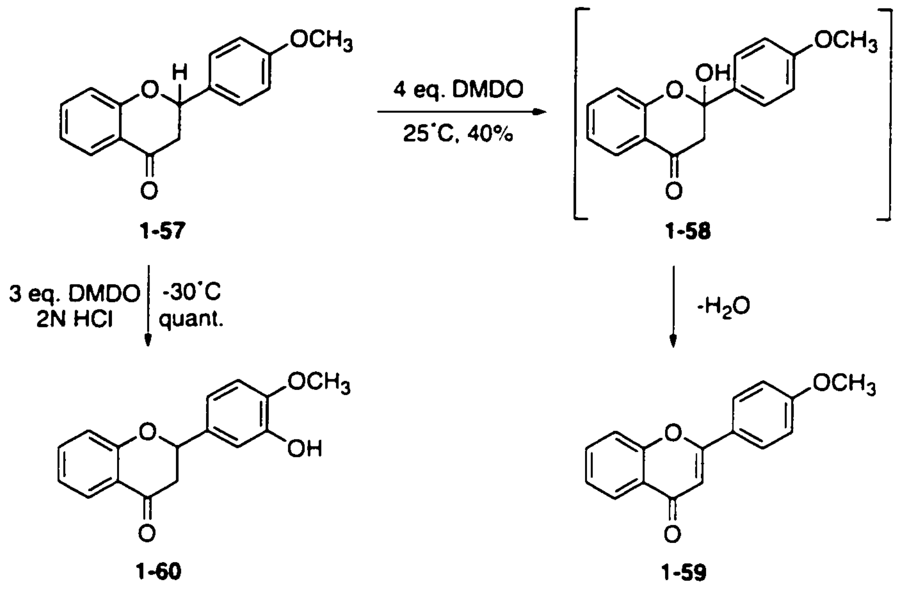
1-54 (57% yield)

1-55 R_1, R_2, R_5 = H
R_3, R_4 = O

1-56 (25% yield)

Scheme 1.16

Changing the substituents on the aryl rings of the flavone directs oxidation to the aromatic ring itself.[74] In this case, regio- and chemoselectivity strongly depends on the acidity of the reaction conditions. When 4'-methoxyflavone **1-57** was allowed to react with 4 equivalents of DMDO at 25°C under neutral conditions, oxidation occurred at the benzyl ethereal position giving **1-59** in 40% yield. When the pH was lowered by adding 2N HCl, reaction between 4'-methoxyflavone **1-57** and 3 equivalents DMDO at -30°C gave a quantitative yield of **1-60** (Scheme 1.17). Selectivity is most likely due to two factors: protonation of the benzyl ethereal oxygen deactivates the C-2 position, while protonated DMDO is much more electrophilic allowing for oxidation of the benzene ring.

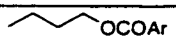
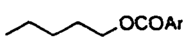
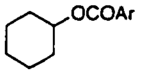
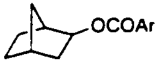
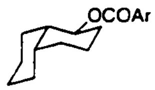


Scheme 1.17

1.3.3. Alternative Control of Regioselectivity

The regioselectivity of the insertion can also be influenced by functionality other than α-heteroatoms. For instance, in the reaction of linear, cyclic and bicyclic aliphatic esters with TFMDO, oxidation occurs at remote positions with a great deal of selectivity (Table 1.4).[75,76] Since oxidation of C-H bonds is an electrophilic process, reaction generally occurs at the most electron-rich C-H bond. Under normal conditions, this would mean that 3° C-H bonds get oxidized faster than 2° C-H bonds while 1° C-H bonds are unreactive. However, due to the electron-withdrawing nature of the ester, proximal C-H bonds are inductively deactivated causing an internal directing effect. The observed product distribution reflects the weakening of this effect with increasing distance along the aliphatic chain.

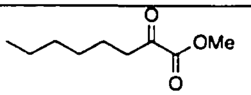
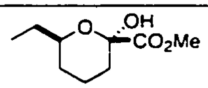
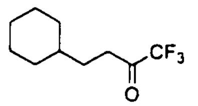
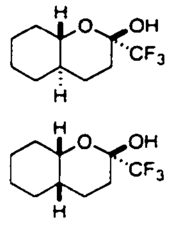
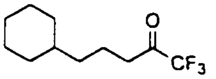
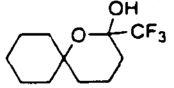
Table 1.4. Oxidation of *p*-Chlorophenyl Esters with TFMDO[a]

		Product Distribution (%)	
Entry	Substrate[b]	γ	δ
1		>98	0
2		12	88 (80)
3		40	60 (56)
4		2	98 (95)
5		>98 (97)	0

[a] Reactions were carried out at -20°C in CH_2Cl_2 for 48 h. [b] Substrate conversion was 100% in all cases; isolated yields are in parentheses.

An interesting approach to regioselective C-H insertions is the utilization of internal ketones as directing groups. This method involves the *in situ* generation of the dioxirane with subsequent insertion into the δ carbon.[77] By utilizing this method, 2° C-H bonds can be oxidized in the presence of 3° bonds, as long as the former is in the δ position. Oxidation of the δ C-H bond gives rise to a δ-hydroxy ketone which spontaneously cyclizes to give a hemiketal, thus preventing further oxidation at the δ site (Table 1.5)

Table 1.5. Selective Oxidation of the δ C-H Bond

Entry	Ketone	Product	Yield (%)
1			70
2		 (*trans/cis* = 4.8:1)	87
3			78

The mechanism of this reaction is thought to be concerted, proceeding through either a spiro or planar transition state (Figure 1.2). Analysis of the reaction products indicates the spiro transition state is favored (Table 1.5, entry 2).

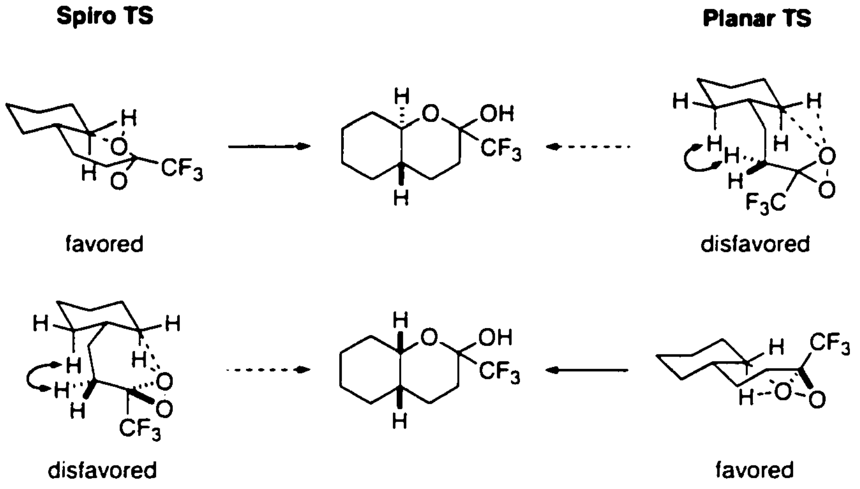
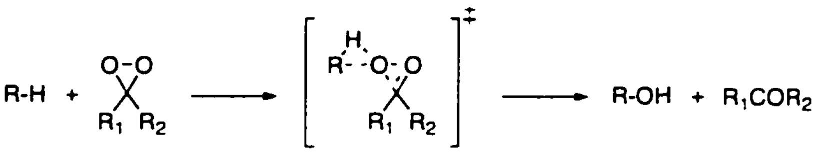


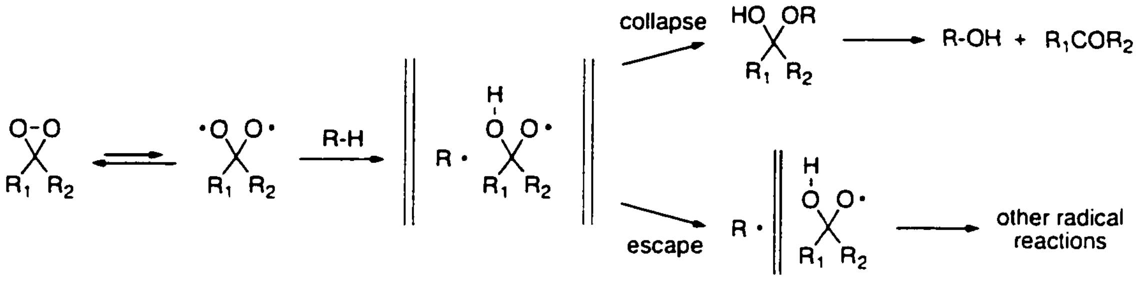
Figure 1.2 Proposed spiro and planar transition for intramolecular oxidation of a δ C-H bond

1.3.4. Mechanistic Considerations

The mechanism of dioxirane-mediated C-H insertion has been a hotly debated issue. Classically, two contrasting mechanisms have been proposed (Scheme 1.18): a concerted electrophilic oxygen insertion involving an "oxenoid" transition state,[46,78-80] and a radical mechanism involving hydrogen abstraction from the alkane by a ring-opened dioxymethane followed by a collapse of the radical pair in the solvent cage.[81-86]



Concerted electrophilic oxygen insertion mechanism



Radical mechanism

Scheme 1.18

Support for the concerted mechanism comes from the high degree of regio-[45,46,87,88] and stereoselectivity[78,89] observed in the reaction. Additional support comes from the second order kinetics observed, first order in both dioxirane and alkane.[45,46,90-92] Furthermore, both solvent[90] and primary isotope effects[45,46,93,94] indicate a concerted mechanism.

Evidence for a radical pathway was reported by Baumstark in 1989 for the oxidation of benzaldehyde with DMDO.[95] Additionally, the observation of alkyl bromide formation when the DMDO oxidation of alkanes is executed in the presence of CBrCl, lends support to the argument.[81] In these experiments, the formation of radical-based products can be inhibited by the addition of oxygen or other radical traps to the reaction medium.[81,96]

The possibility of a radical-based mechanism has been studied using computational methods, and was determined to be unlikely because the initial proton abstraction was calculated to be endothermic.[97] However, this mechanism cannot be completely ruled out based solely on these calculations.

In 1993, Bach proposed a unifying mechanism for hydrocarbon insertion reactions with a FMO model supported by *ab initio* molecular orbital calculations.[98] However, the studies were performed with water oxide (H_2O-O) as a model for the electrophilic oxidizing reagent. For this type of reaction, water oxide might be considered a somewhat remote model, and the competing diradical mechanism is unable to be studied with this method. In 1998, Houk reported a study on the mechanism of alkane oxidation using dioxirane and cyanodioxirane as models.[99] The results from this study support the concerted electrophilic oxygen insertion mechanism shown in Scheme 18. However, an asynchronous transition state having some diradical character was found for the oxygen insertion of dioxirane into C-H bonds (Figure 1.3). Although qualitatively like earlier models[46,98], Houk's transition state models have much more OH than CO bonding. Together with the polarized nature of the transition state, this suggests the reason why concerted oxygen insertion into tertiary CH bonds is highly favored. Additional computational studies have provided corroborating evidence that a concerted asynchronous transition state is highly likely.[100-102]

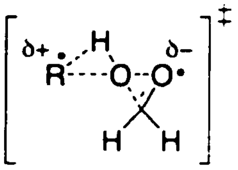


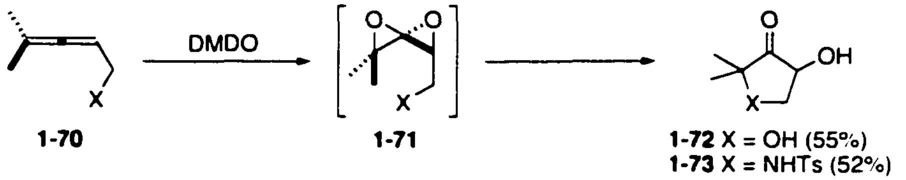
Figure 1.3 Houk's asynchronous mechanism

1.4. Epoxidation

1.4.1. Epoxidation with Isolated Dioxiranes

The development of a procedure for the isolation of Oxone-free dioxiranes ushered in a new era in epoxidation chemistry. The combination of convenient generation of reagent, neutral reaction conditions, and straightforward workup all contributed to the spectral identification and/or isolation of highly labile epoxides. [103-131] Furthermore, the diverse number of substrates that have been epoxidized by this method truly shows the utility of these reagents.[132-135] Among these include enamines,[136] enamides,[137,138] enecarbamates,[139,140] ylidenediketopiperazines,[141] polycyclic aromatic hydrocarbons,[142-148] benzene derivatives,[149-161]cyclic polyenes,[162-164] fullerenes,[165,166] substituted 2-methylene oxetanes,[167,168] and chalcones.[169]

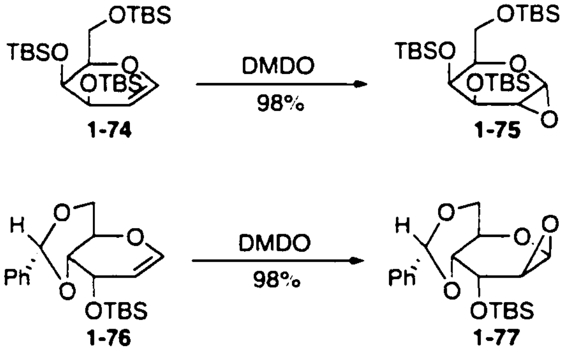
Both allenes[170-176] and cumulenes[177] are able to be epoxidized with isolated DMDO, and, in many cases, pendant functionality on the allene causes spontaneous cyclization, leading to a variety of interesting compounds (Scheme 1.20).



Scheme 1.20

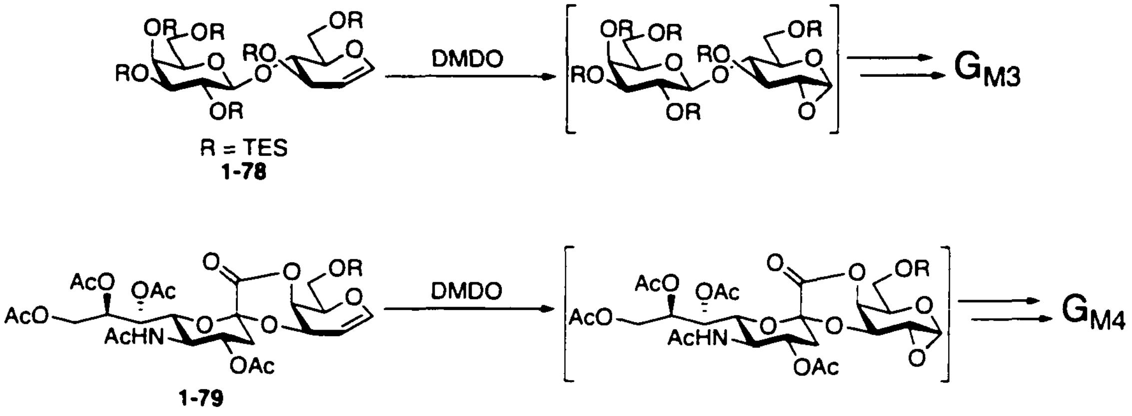
1.4.1.1. Epoxidation of Glycals

One of the most impressive uses for isolated dioxirane epoxidation, and one that truly shows the mildness under which the reaction takes place, is the epoxidation of glycals. Such reactions are noteworthy, not only because they provide direct access to 1,2-anhydrosugars directly from easily attainable starting materials, but also because they typically provide the hexose in high yield with excellent stereoselectivity. Such stereoselectivity arises from the substitution pattern on the glycal. For instance, in his initial report, Danishefsky reports that epoxidation of the galactal-derived system, **1-74**, gave only the α-oxirane **1-75**, while epoxidation of the allal derivative, **1-76**, gave only the β-oxirane **1-77**[178] (Scheme 1.20).



Scheme 1.20

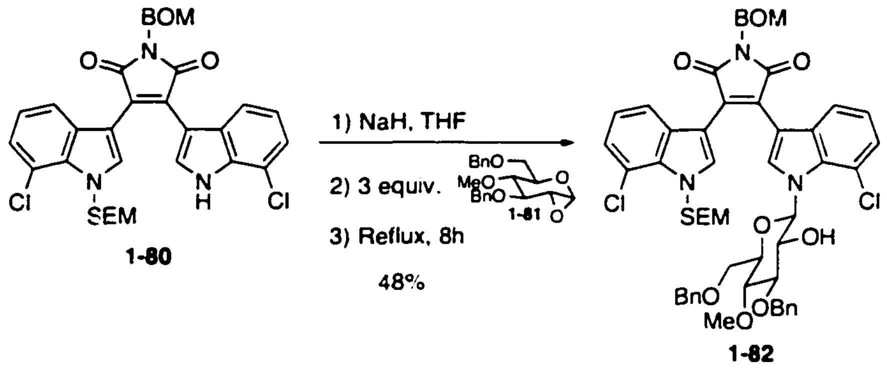
Danishefsky further demonstrated the utility of this method in his epoxidation of the highly-substituted disaccharides **1-78** and **1-79**, leading to the synthesis of gangliosides G_{M3}[179] and G_{M4},[180] respectively (Scheme 1.21).



Scheme 1.21

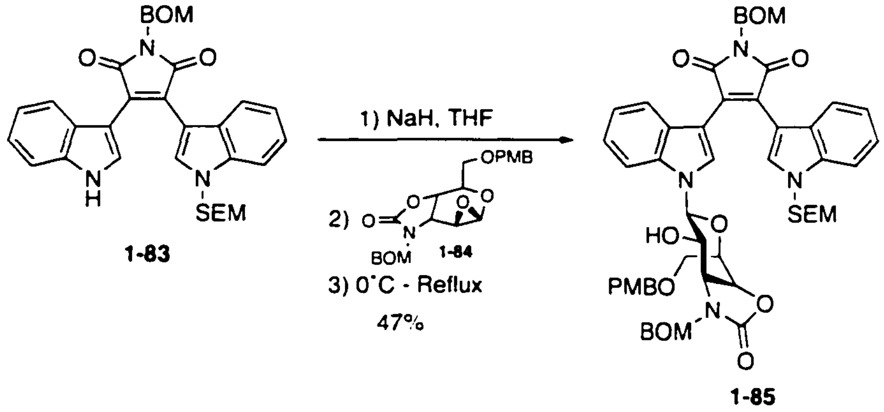
The 1,2-anhydrosugars obtained from epoxidation of glycals can be opened stereospecifically at the anomeric carbon with a variety of glycosyl acceptors yielding products with inverted stereochemistry.[181-192] Such reactions have been the basis for the synthesis of a multitude of natural glycosides[193-202], and have been utilized to generate oligosaccharides on solid support.[203-207]

Of these, an important example of this comes from Danishefsky's work on the synthesis of the antitumor agents Rebeccamycin[208] and Staurosporine.[209,210] He showed that indole **1-80** could be combined with α-1,2-anhydrosugar **1-81** to produce β-glucopyranoside **1-82**, which was further transformed into Rebeccamycin (Scheme 1.22).



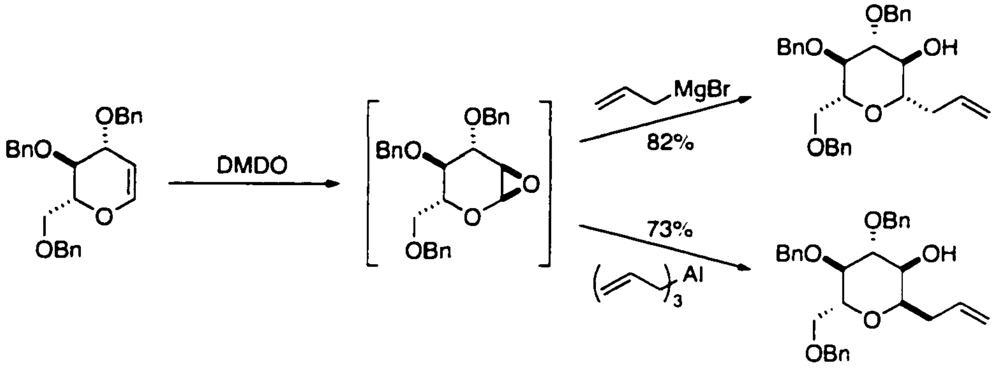
Scheme 1.22

Similarly, the β-1,2-anhydrosugar **1-84** was reacted with indole **1-83** to give the α-glucopyranoside **1-85**, which was used in studies leading to the total synthesis of Staurosporine[211] (Scheme 1.23).



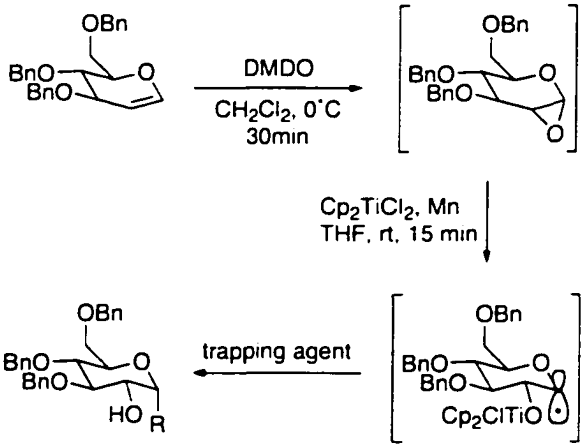
Scheme 1.23

Subsequent work in the area of nucleophilic opening of anhydrosugars by Craig[212] and Rainier,[213] led to the discovery that, by using aluminum or boron based nucleophiles, these epoxides can be stereospecifically opened to give C-glycosides having a cis relationship between the C-2 alkoxy group and the C-1 carbon-carbon bond, thus allowing for the synthesis of either α- or β-C-glycosides from a single glycosyl donor (Scheme 1.24).



Scheme 1.24

Conversely, Little has shown that reductive opening of the intermediate anhydrosugar with titanocene(III) chloride generates an anomeric radical, which can be treated with a variety of trapping agents, affording only the α-glycoside (Scheme 1.25).[214]

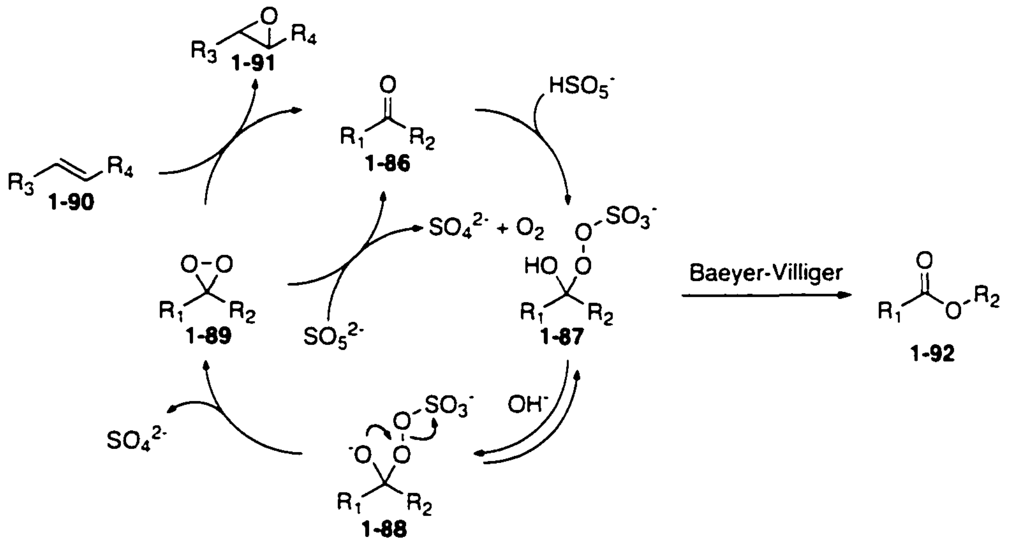


Scheme 1.25

1.4.2. Epoxidation with Dioxiranes Generated in Situ

1.4.2.1. Achiral ketones

One of the most important advances in dioxirane chemistry has been the discovery that they can be prepared and used *in situ*.[7] In general, the reaction involves reaction of Oxone and a ketone in a biphasic system consisting of water and an organic solvent in the presence of a phase transfer catalyst.[9] Since the oxidation of organic moieties regenerates the ketone, the reaction has catalytic potential (Scheme 1.25).



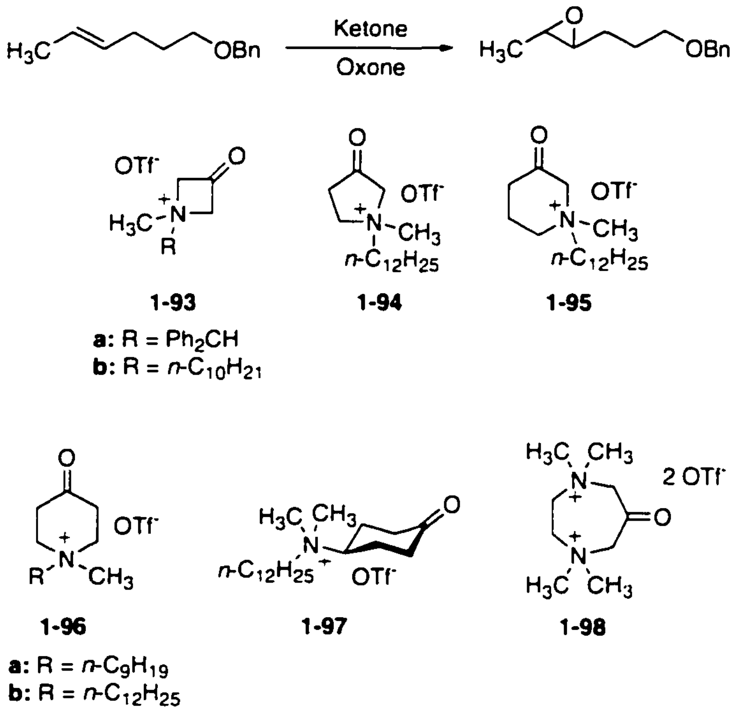
Scheme 1.25

Attack of the ketone by Oxone (monoperoxysulfate) yields the Crigee-type, tetrahedral intermediate **1-87**. Loss of a proton gives the highly reactive intermediate **1-88**, which then cyclizes, forming dioxirane **1-89**. The dioxirane can then react with an olefin, **1-90**, producing epoxide **1-91**, and regenerating the starting ketone. The fact that the epoxidation can be catalytic in the ketone has major implications in the use of chiral ketones to perform the transformation (*vide infra*).

Even though there is a catalytic cycle that can be drawn, the realization of a truly catalytic reaction suffered from two distinct problems: 1) Intermediate **1-87** can undergo a Baeyer-Villiger rearrangement to give ester **1-92** or 2) dioxirane **1-89** can undergo nonproductive decomposition by Oxone giving back the ketone.[21f] It was found that by buffering the reaction to a pH of 7.5, loss of ketone by Baeyer-Villiger oxidation could be minimized.[30] As to the problem of autodecomposition, Yang found that by using the more reactive TFMDO, lower catalyst loadings could be used, although stoichiometric amounts were still necessary.[32] Furthermore, Denmark reported that by controlling the rate of addition of Oxone into the reaction medium, the autodecomposition reaction could be suppressed.[33]

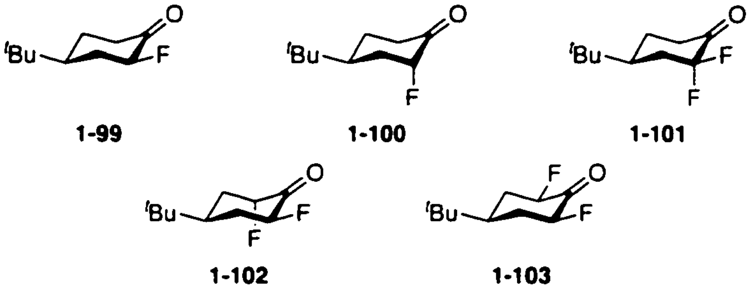
Additionally, carbonyl activation is crucial in regards to catalytic turnover. Ketones such as acetone,[9] 2-butanone,[21b] and cyclohexanone[31] are not electrophilic enough and must be present in large excess to get an efficient conversion. The use of TFMDO by Yang (*vide supra*) was an important advance in this area, and began an investigation into the requirements for effective catalytic turnover.

The use of substoichiometric amounts of ketone has been reported by Denmark in two interesting systems. The first employs the use of ammonium salts under biphasic conditions.[33,36] In this case the phase transfer catalyst and ketone precursor are contained within the same molecule. It was found that the lipophilicity of the ketone as well as proper placement of the internal phase transfer catalyst was critical for a successful catalyst. Among several catalysts tested (Scheme 1.26), the use of the 4-oxopiperidinium salts **1-96** gave the best results. Both **1-96a** and **1-96b** gave near quantitative conversion results when 2 equivalents of ketone were used. However **1-96b** showed remarkable activity when only 0.1 equivalents were used, near quantitative conversion in 24h.[15] By using the bis(ammonium) ketone **1-98**, complete conversion was obtained in a much shorter time period, 11h.[16]



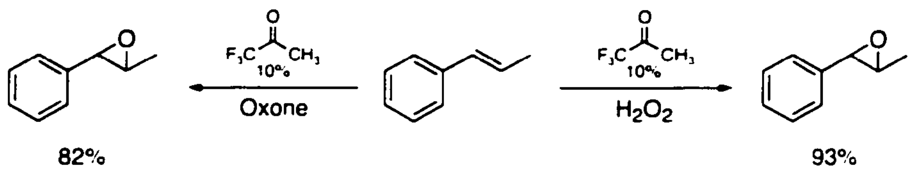
Scheme 1.26

Denmark further showed that catalytic epoxidation could be achieved with conformationally rigid α-fluorocyclohexanones under monophasic conditions (Scheme 27).[14] Perhaps more important was the observation that epoxidation efficiency was highly dependant on the orientation of the fluorine moiety. Although all of the catalysts were more efficient than 4-^{t}butylcyclohexanone, those with an equatorial fluorine were much better catalysts. When two equatorial fluorines were present, the catalyst was even more reactive.



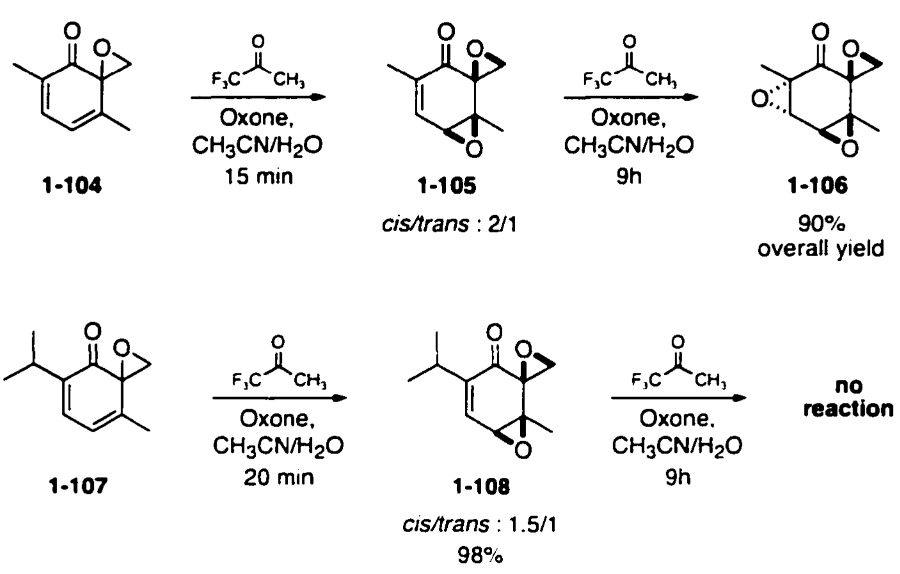
Scheme 1.27

In 1997 it was discovered that by running the reaction at a high pH, typically around 10.5, catalyst loadings could be reduced to substoichiometric amounts in the asymmetric epoxidation reaction using ketone **1-30** (*vide infra*).[217] This new method was quickly investigated for racemic epoxidation using acetone as catalyst.[38] Although excess catalyst was still necessary, the reaction proceeded much more rapidly. In 1999, the use of hydrogen peroxide (H_2O_2) was reported as an oxidant in the chiral ketone-catalyzed epoxidation reaction at high pH.[218] Shortly thereafter, this methodology was extended to include the use of trifluoroacetone.[219] Although acetone was still sluggish to react, trifluoroacetone could now be used in truly catalytic amounts (10-30 mol %). Interestingly, the use of Oxone, rather than H_2O_2 did not lower the activity of the catalyst when the reaction was run at high pH (Scheme 1.28).



Scheme 1.28

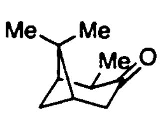
The use of TFMDO generated *in situ* in the synthesis of naturally-occurring compounds is beginning to rise.[220] For instance, Yang used this methodology in the synthesis of triepoxy analogs of Triptolide (Scheme 1.29).[221] Epoxidation of dienone **1-104** with *in situ* generated TFMDO gave only bisepoxide **1-105** in a 2:1 *cis:trans* ratio. Addition of additional reagent led to the formation of triepoxide, stereospecifically, i.e., the newly formed α,β epoxide was anti to that in the γ,δ position. Interestingly, when the same protocol was applied to isopropyldienone **1-107** only a 1.5:1 *cis:trans* ratio was obtained. However, use of additional reagent did not produce any of the expected triepoxide. Yang suggests that that steric hindrance of the isopropyl group prevents further epoxidation by TFMDO. Epoxidation was successful when isopropyl pyruvate was used as catalyst.



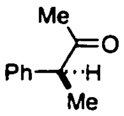
Scheme 1.29

1.4.2.2. Chiral ketones

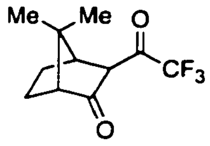
As shown above, the *in situ* generation of dioxiranes provides the framework for true catalysis. If the ketone employed is optically active, there exists an opportunity for the enantioselective epoxidation of prochiral olefins.[222] Particularly intriguing is the potential for the enantioselective epoxidation of unfunctionalized olefins. In 1984, Curci reported that by using (+)-isopinocamphone or (S)-(+)-3-phenylbutanone as catalysts ee's up to 12.5% could be achieved (Table 1.6).[223] In a subsequent report he notes that by incorporating a trifluoromethyl group into the ketone, it becomes much more active (Table 1.6).[224]



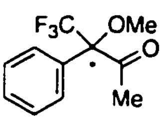
1-109



1-110

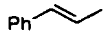
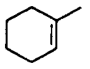
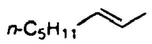
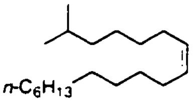


1-111

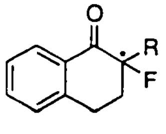


1-112

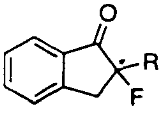
Table 1.6. Asymmetric Epoxidation of Olefins with Ketones **1-109**, **1-110**, **1-111**, & **112**

Entry	Substrate	Ketone	Yield (%)	ee (%)
1		**1-109**	60	12.5
2		**1-110**	85	9.5
3		**1-111**	82	13
4		**1-112**	77	18
5		**1-109**	90	10.4
6		**1-110**	92	12
7		**(S)-1-112**	80	20
8		**(S)-1-112**	80	16

The concept of carbonyl activation with electron-withdrawing groups was further illustrated by the 1-tetralone **1-113** and 1-indanone **1-114** -derived chiral ketones reported by Marples.[225] Although they were quite reactive, none of them provided optically active epoxides. This is explained by the lack of conformational rigidity in the saturated ring.

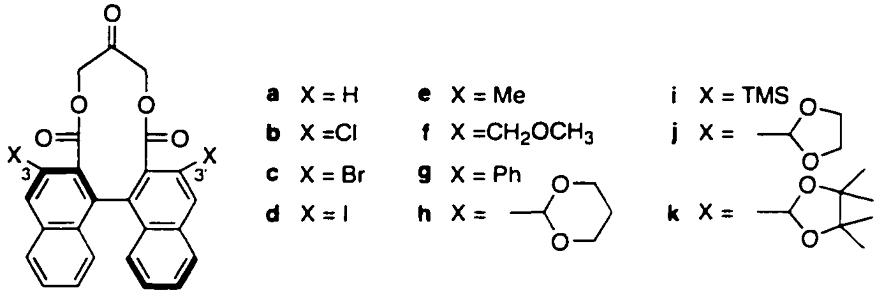


1-113



1-114

In 1996, Yang reported a completely new kind of chiral ketone.[226-228] Derived from 1,1'-binapthyl-2,2'-dicarboxylic acid, the 11-membered ring ketones **1-115a-k** were designed based on the following considerations: (a) The C_2 symmetry was introduced to limit the competing reaction modes of attack on the dioxirane. (b) The chiral element was placed away from the catalytic center with the intention of avoiding any substituents at the α-carbon, since α-carbons are prone to racemization, and steric hindrance at the α-carbon decreases the catalyst activity. (c) Two electron-withdrawing ester groups were introduced to activate the carbonyl.



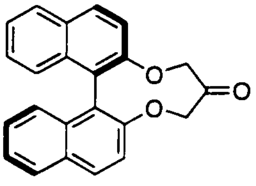
1-115

The first ketone of this sort, **1-115a**, displayed excellent stereoselectivity, as high as 87%, although a stoichiometric amount of catalyst was necessary.[226] Subsequent reports show that the placement of steric "sensors" in the 3 and 3' positions of napthalene provided for additional selectivity in the epoxidation (Table 1.7).[227,228] Additionally, only 10 mol% of the ketone was necessary, making the reaction truly catalytic.

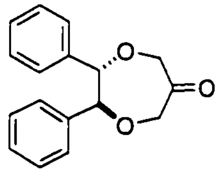
Table 1.7. Asymmetric Epoxidation of *trans*-Stilbene with Ketones **1-115 a-k**

Entry	Ketone	Yield (%)	ee (%)
1	**a**	91	47
2	**b**	95	76
3	**c**	92	75
4	**d**	90	32
5	**e**	93	56
6	**f**	92	66
7	**g**	50	55
8	**h**	95	71
9	**h (0°C)**	93	84
10	**i**	-	44
11	**j**	90	77
12	**k**	91	75

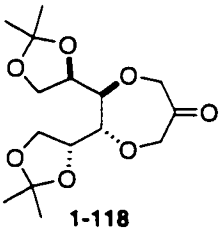
The success of Yang's C_2-symmetric ketone led other groups to disclose their results in this area.[17,229-231] Ketones **1-116 – 1-119** are particularly noteworthy. In these ketones, the ester groups have been replaced with ether groups in the hope that the carbonyl group would be brought closer to the chiral element. In each of these cases, a full equivalent of ketone was necessary to get any conversion. This is most likely due to the weaker electron-withdrawing capability of the ether moiety. Furthermore, bringing the chiral element closer to the carbonyl did not increase selectivity. In fact, a decrease in enantioselectivity was observed in each case.



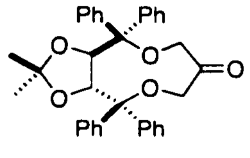
1-116



1-117

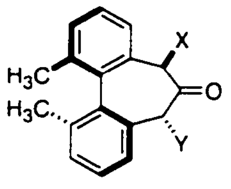


1-118



1-119

In 1999, Denmark reported a novel ketone that displayed both high reactivity and selectivity.[232] Based upon his earlier work demonstrating the value of fluorine at the α-position, ketone **1-120** was designed, which not only takes advantage of this, but also places a chiral element close to the reacting center. The influence of α-fluoro groups is clearly demonstrated here, as ketone **1-120a** gives only a 5% conversion for *trans*-β-methylstyrene while **1-120b** gives a 24% conversion. By switching to difluoroketone **1-120c**, a quantitative conversion was observed.



a X = Y = H
b X = H, Y = F
c X = Y = F

1-120

The ability of chiral ammonium salts (**1-121**) to promote the asymmetric epoxidation has also been studied. Ketones **1-122** and **1-123** were the first of this type to be reported.[33,36,232] Both ketones had low reactivity (Table 1.8, Entry 1), presumably due to the steric crowding around the carbonyl group.

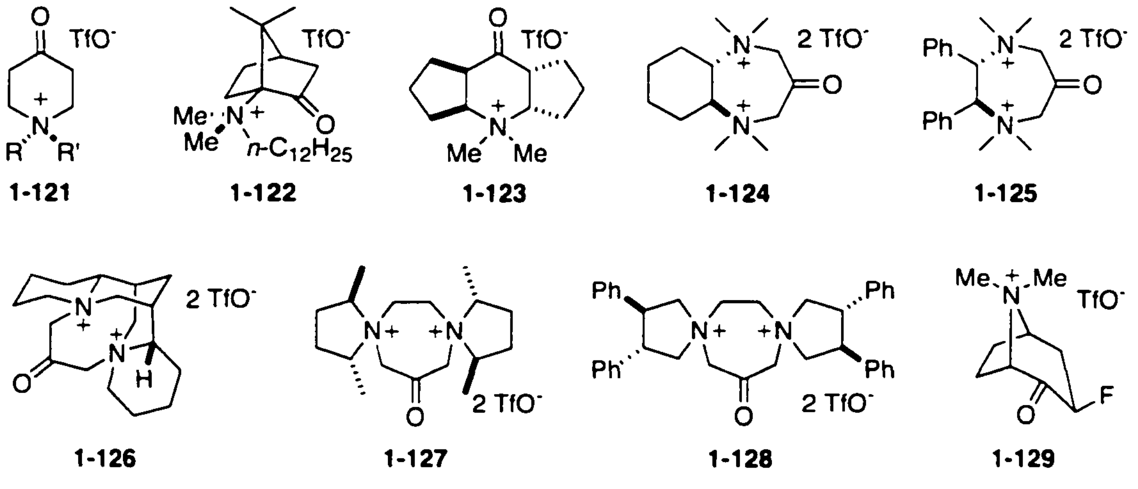


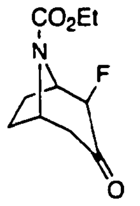
Figure 1.4 Denmark's ammonium salt based ketones

Incorporation of a second cationic ammonium species (ketones **1-124** - **1-127**) allowed for further catalyst activation as well as for suppression of the Baeyer-Villiger oxidation (*vide supra*). Although these catalysts were quite reactive, they did not display the enantioselectivity hoped for (Table 1.8, Entries 2-6). This has been attributed to the high degree of flexibility in the 7-membered ring. In an attempt to alleviate this problem, the rigid tropinone-derived ketone **1-129** was utilized. It was highly reactive, however, it still suffered from low enantioselectivity (Table 1.8, Entries 7 and 8).

Table 1.8. Asymmetric Epoxidation of Olefins with Denmark's Ammonium Ketones **1-123** – **1-129**

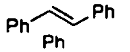
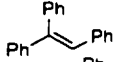
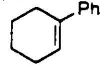
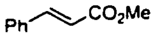
Entry	**Substrate**	**Ketone**	**Conv. (%)**	**ee (%)**
1		**1-123**	-	34
2		**1-124**	100	9
3		**1-125**	NR	-
4		**1-126**	54	40
5		**1-127**	95	8
6		**1-128**	100	10
7		**1-129**	100	35
8		**1-129**	-	58

In 1998, Armstrong reported a tropinone-derived ketone, **1-130**, which contained a carbamate on the bridgehead nitrogen in combination with an α-fluoro group.[33] The result was a highly reactive catalyst, with up to 83% ee reported for some cases (Table 1.9)

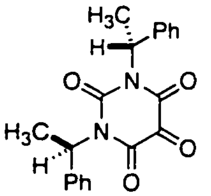


1-130

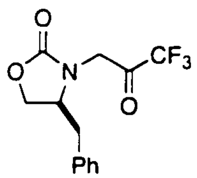
Table 9. Asymmetric Epoxidation of Olefins with Ketone **1-130**

Entry	Substrate	Yield (%)	ee (%)
1		88	76
2		100	73
3		100	83
4		33	64

Other types of ketones have been studied for their ability to promote the asymmetric epoxidation reaction, including *N,N*-dialkylalloxans **1-131**[234] and the oxazolidinone-derived ketone **1-132**.[235] Although **1-131** was a highly-active catalyst, no asymmetric induction was observed, undoubtedly because the chiral center was not close to the reaction center. Ketone **1-132** suffered from rapid Baeyer-Villiger decomposition; however, up to 34% ee could be obtained when 3 equivalents of ketone were used.

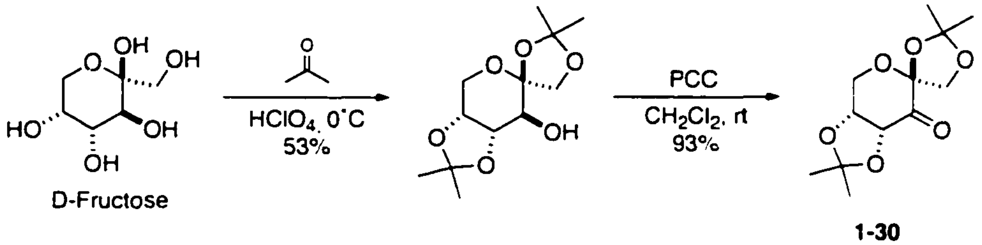


1-131



1-132

In 1996, the fructose-derived ketone **1-30** was developed as a highly selective epoxidation catalyst.[236] Synthesized in two steps from D-fructose by ketalization and oxidation[237,238] (Scheme 30), ketone **1-30** is a member of a class of ketones designed to contain the following general features: (1) The stereogenic centers are close to the reacting center, resulting in efficient stereochemical communication between substrate and catalyst. (2) The presence of fused ring(s) or a quaternary center α to the carbonyl group minimizes the epimerization of the stereogenic centers. (3) Approach of an olefin to the reacting dioxirane can be controlled by sterically blocking one face or using a C_2- or pseudo C_2-symmetric element. (4) Inductively withdrawing substituents are introduced to activate the carbonyl.



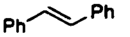
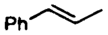
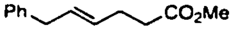
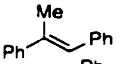
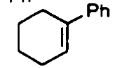
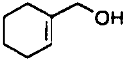
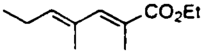
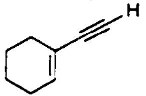
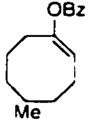
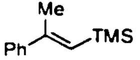
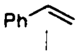
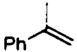
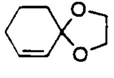
Scheme 1.30

Initially, the pH of the reaction was buffered to between 7-8 due to the rapid autodecomposition of Oxone at high pH. However, the reaction was hampered by decomposition of the ketone, presumably by Baeyer-Villiger oxidation resulting from intermediate **1-87** (Scheme 1.25). The decomposition was accompanied by a concomitant reduction of ee as the reaction proceeded. Therefore 3 equivalents of **1-30** and shorter reaction times were required to achieve both high enantioselectivity and conversion.

Analysis of the postulated mechanism indicated the Baeyer-Villiger reaction might be suppressed by raising the pH, since at a higher pH intermediate **1-88** would be favored, leading to a more efficient formation of dioxirane **1-89** (*vide supra*). Indeed, this was found to be true. At higher pH, the catalyst was much more stable, allowing for a reduction the amount used of both ketone and Oxone. With the new conditions the reaction could be run with 20-30 mol% ketone. Additionally, the enantioselectivity of the reaction was uniformly higher due to the suppression of both ketone decomposition and subsequent background reaction.

To test the generality of this asymmetric epoxidation, a variety of olefins were investigated using a catalytic amount of ketone **1-30** (typically 20-30 mol%). High enantioselectivities were obtained for a variety of *trans*- and trisubstituted olefins (Table 1.10, Entries 1-10). One drawback of this ketone was the low ee's observed for *cis*-disubstituted and terminal olefins (Table 1.10, Entries 11-13)

Table 1.10. Asymmetric epoxidation of representative olefins with ketone **1-30**

Entry	**Substrate**	**Yield (%)**	**ee (%)**	**Ref.**
1		85	98	238
2		94	96	238
3		68	92	238
4		89	96	238
5		94	98	238
6		93	94	239
7		89	94	240
8		78	93	241,242
9		82	95	243
10		74	94	244
11		90	24	238
12		81	28	238
13		43	61	238

To further probe structural requirements for chiral ketone catalysis, a number of related carbohydrate-based ketones were investigated (Figure 1.5).[245] The catalytic properties of these ketones was heavily influenced by the precise nature of the ketone structure. In general, ketones having the structure represented by **1-133** were superior, with **1-30** the most selective among these.

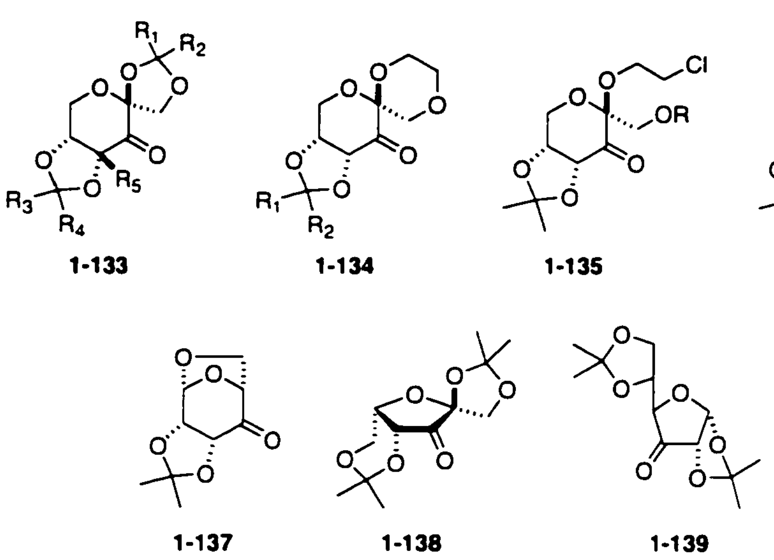
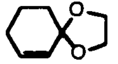
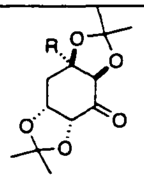
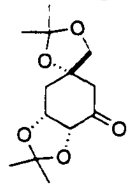
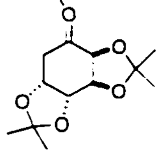


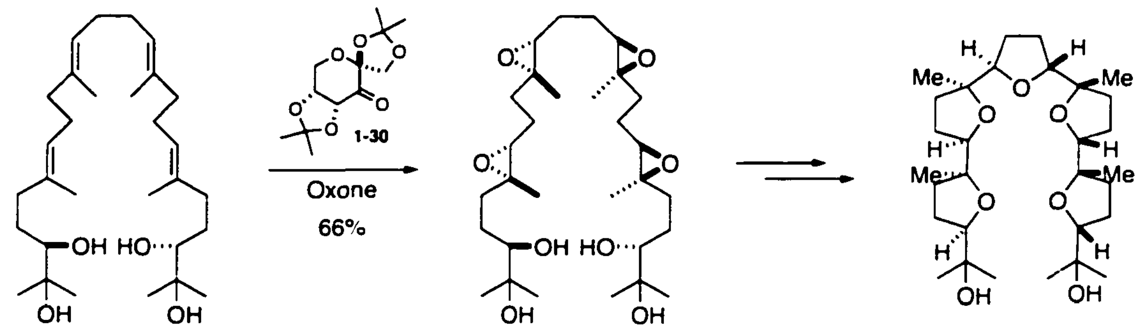
Figure 1.5

The success of the carbohydrate-based ketones, ketone **1-30** in particular, has generated a great deal of interest in the structural requirements for a good catalyst.[235,236-253] Ketone **1-30** consists of a fused ring and a quaternary carbon α to the carbonyl group, minimizing potential epimerization at these sites as well as placing the stereogenic centers close to the reacting center. Given the success of this ketone, a number of carbocyclic analogs were synthesized and tested to further probe the structural requirements for an efficient ketone catalyst. Table 1.11 lists a few of the more reactive ketones.

Table 1.11. Asymmetric epoxidation of representative olefins by carbocyclic Ketones

Entry	Ketone							Ref
		Conv (%)	ee (%)	Conv (%)	ee (%)	Conv (%)	ee (%)	
								
1	R = H	11	93	13	67	9	66	247,250
2	R = CO_2Me	66	95	90	67	56	66	247,250
3	R = CH_2OAc	95	90	96	65	82	68	247,250
4	R = CMe_2OH	91	96	79	69	55	45	247,250
5		33	66	36	26	28	36	249,254
6		30	50	40	24	-	-	255

The ability of ketone **1-30** to generate compounds of high optical purity was reported by Corey in the total synthesis of glabrescol **1-142**.[256,257] He found that tetraol **1-140** could be epoxidized in 66% yield to provide tetraepoxide **1-141** in an estimated 80% diastereomeric purity (Scheme 1.31). Remarkably, each olefin had been epoxidized with >20:1 *R*/*S* selectivity.



1-140 **1-141** **1-142**

80% diastereomeric purity

Scheme 1.31

Additionally, ketone **1-30** has been used in the synthesis of chiral, non-racemic unsymmetrical vinylallenes,[258] and arenes.[259]

1.4.3. Transition State Analysis

The geometry of the transition state of the dioxirane-mediated epoxidation has major implications in the stereochemical outcome of the reaction and for designing an effective ketone catalyst. The two possible extreme transition state geometries for the epoxidation of olefins with dioxiranes are spiro and planar (Figure 1.6).[20,227,228,236,238,260-267]

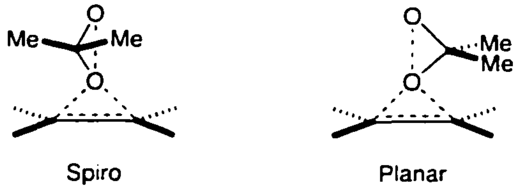


Figure 1.6. The spiro and planar transition states for dioxirane mediated epoxidation of olefins

Based on extensive experimental and computational data, it has been postulated that the spiro transition state is favored over the planar. One of the first pieces of experimental evidence in favor of the spiro transition state was reported in 1987 by Baumstark.[260,261] He observed that *cis*-hexenes were epoxidized 7-9 fold faster than the corresponding *trans*-hexenes, and that the addition of water to DMDO solutions in acetone gave increased reactivity. Analysis of the expected transition states suggests that the reaction proceeds though a spiro transition state (Figure 1.7). The lack of steric interactions between the methyl groups of the dioxirane and the R group of the alkene help to explain why *cis* olefins are epoxidized faster. Furthermore, the observed acceleration in the presence of water implicates a polarized transition state that benefits from hydrogen-bond donation from the surrounding solvent. This effect has also been seen in polar solvents, even those that do not possess hydrogen-bonding ability.[268] Acceleration of the reaction by hydrogen-bonding is not limited to the solvent. It has been found that substrates which are able to provide an internal hydrogen-bond also accelerate the reaction rate.[269-271]

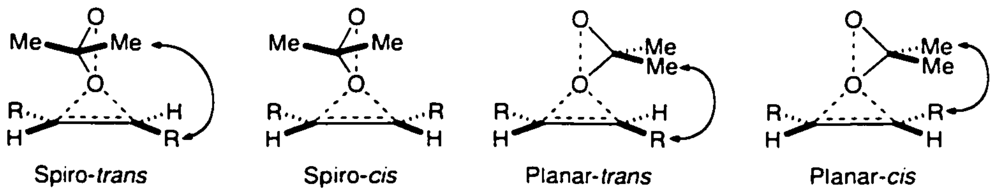


Figure 1.7. The spiro and planar transition states for the epoxidation of *trans*- and *cis*- olefins with dimethyldioxirane.

High level computational studies have also indicated that the epoxidation of alkenes passes through a spiro transition state, and further show the energetic benefits of hydrogen-bonding.[264,266,267,272,273] In a spiro transition state with dipolar character, the alkene can act as a donor and the dioxirane as an acceptor through a π-σ^* interaction. Such an interaction can explain the hydrogen-bond effect observed in the presence of allylic alcohols or when hydrogen-bonding solvents are used. Furthermore, back donation through a π^*-$p_{\text{lone pair}}$ interaction can only occur in the spiro transition state (Figure 1.8).[262,265,267,274] The higher reactivity of TFMDO can easily be explained using this model since the CF_3 group is able to stabilize the σ^* orbital of the dioxirane through negative hyperconjugation, thus lowering the frontier orbital energy gap.[264,275]

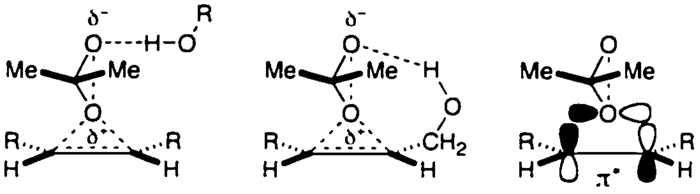


Figure 1.8. Spiro transition state models showing the benefits of a polar solvent, H-bond, and π^*-$p_{\text{lone pair}}$ interaction

The utilization of chiral dioxiranes has led to further insight into the nature of the transition state, since analysis of the stereochemistry of the resultant epoxide can indicate the path through which the reaction traveled. A few possible transition states for the reaction of a general trisubstituted olefin with ketone **1-30** are shown in Figure 1.9.[236,238] Steric repulsion disfavors transition states **B-G**, leaving spiro **A** and planar **H** as the two likely transition states. Fortunately the products arising from these are enantiomers, so simple the determination of the product configuration should be a good indication as to which transition state is favored. The stereochemistry of the products from nearly every example of *trans*-disubstituted and trisubstituted olefin studied with this ketone is consistent with the spiro transition state.

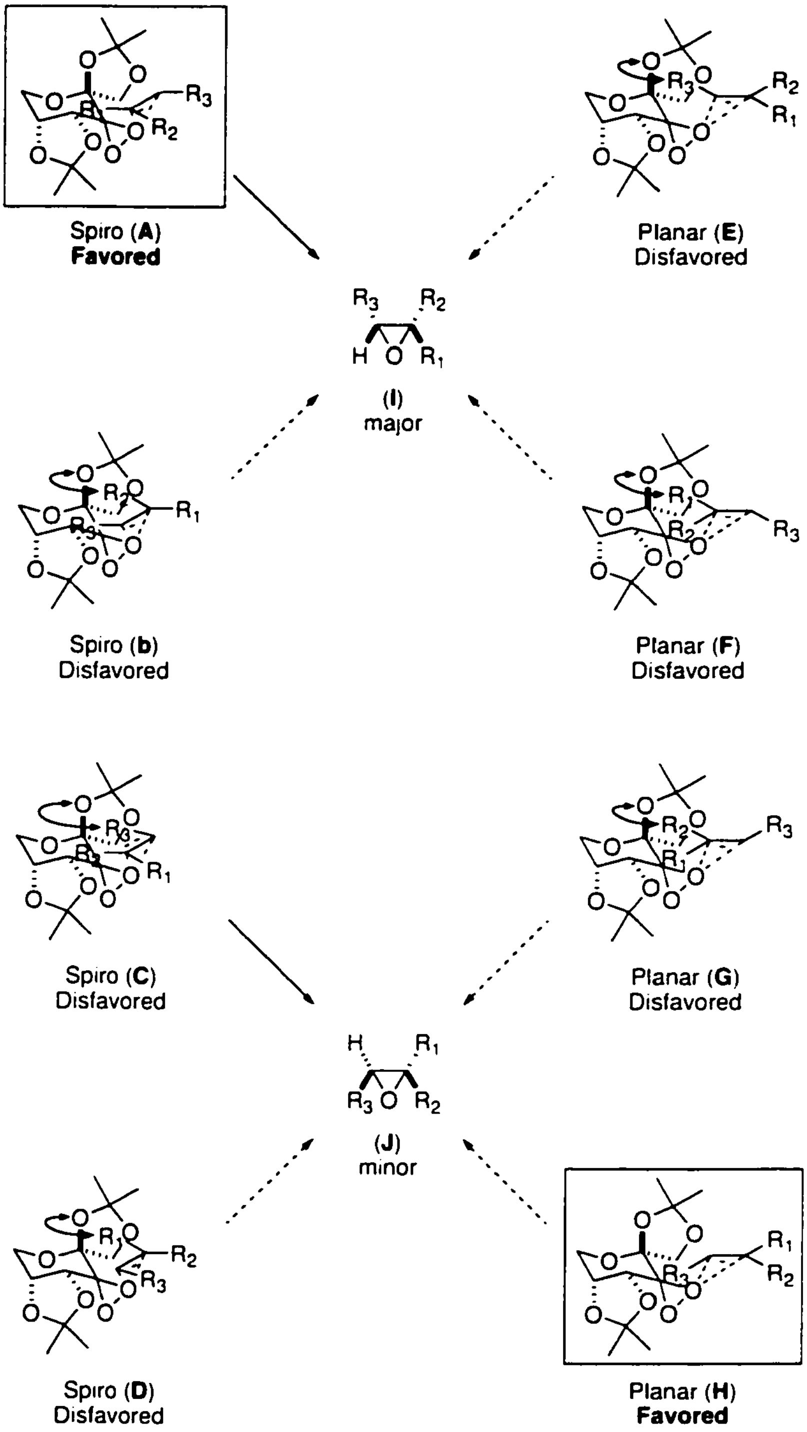
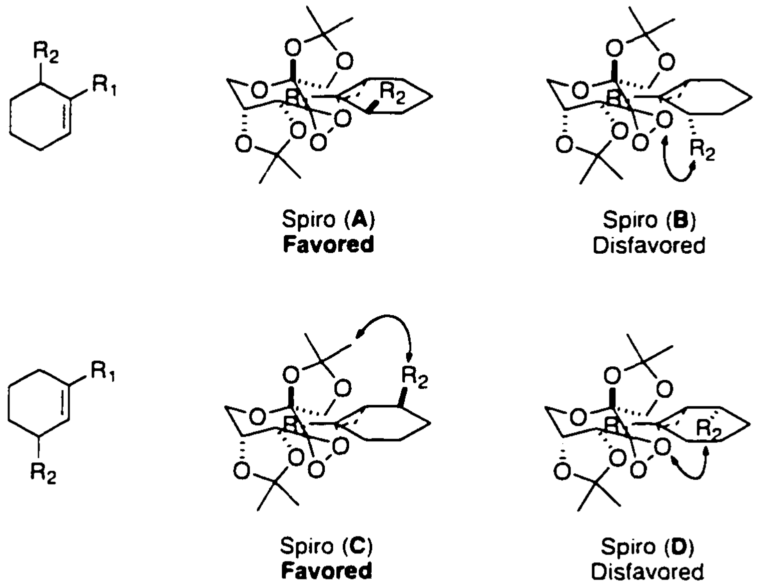


Figure 1.9. Spiro and planar transition state models for the reaction of the fructose derived dioxirane with a general olefin

Further analysis of the transition states suggested that a kinetic resolution of certain types of racemic olefins using chiral dioxiranes might be possible.[276,277] This was indeed found to be true for both 1,6- and 1,3-disubstituted cyclohexenes (Table 1.12).[276] Figure 1.10 shows the potential spiro transition states for each enantiomer of a generic 1,6- and 1,3-disubstituted cyclohexene. For a 1,6-disubstituted cyclohexene, transition state **A** is expected to be favored over **B** due to the steric interaction between R_2 and one of the oxygens in the dioxirane. The transition states for a 1,3-disubstituted cyclohexane show a similar situation, with **C** being favored over **D**.



Spiro (**A**)
Favored

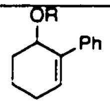
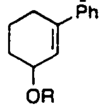
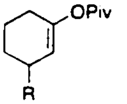
Spiro (**B**)
Disfavored

Spiro (**C**)
Favored

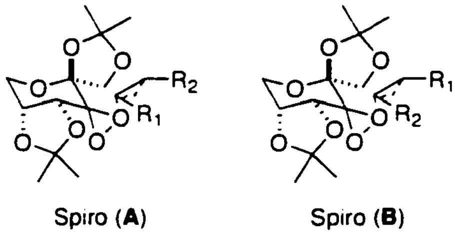
Spiro (**D**)
Disfavored

Figure 1.10. Spiro transition stated for 1,6-disubstuted and 1,3-disubstuted olefins

Table 1.12. Kinetic resolution of representative olefins by ketone **1-30** catalyzed asymmetric epoxidation

Entry	Substrate	Conv. (%)	Rec. S.M. ee (%)	Epoxide ee (%)	Epoxide (*trans/cis*)	k_{rel} (k_f/k_s)
						
1	R = TMS	49	96 (*S*)	95	>20	>100
2	R = CO_2Et	51	94 (*S*)	97	>20	70
						
3	R = TBS	70	99 (*R*)	81	4	11
4	R = Me	61	95 (*R*)	nd	6	14
						
5	R = OTMS	61	91 (*R*)	76	4	11
6	R = ^{t}Bu	54	99 (*R*)	84	>20	61

Analysis of the transition state helps to explain why *cis*-olefins are not epoxidized with high enantioselectivity by ketone **1-30**. Spiro transition states **A** and **B** are likely to be the two major competing pathways (Figure 1.11). The low ee obtained suggests that the ketone catalyst does not provide an adequate structural environment to differentiate between the two groups on the olefin.

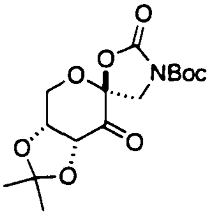


Spiro (**A**) Spiro (**B**)

Figure 1.11. Spiro transition states for *cis*-olefins

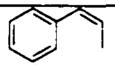
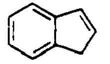
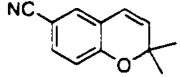
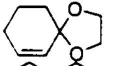
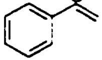
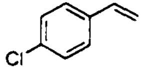
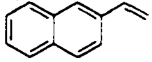
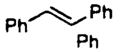
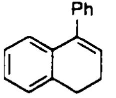
Recently, reports from the Shi lab described the reactivity of a new ketone, **1-143**, a nitrogen analog of ketone **1-30**. This ketone displayed remarkable selectivity in the epoxidation of conjugated *cis*-[278] (Table 1.13, entries 1-4) and terminal[279] olefins (Table

1.13, entries 6-8) The enantioselectivity for *trans-* and trisubstituted olefins was substrate dependant (Table 1.13, entries 9 and 10).

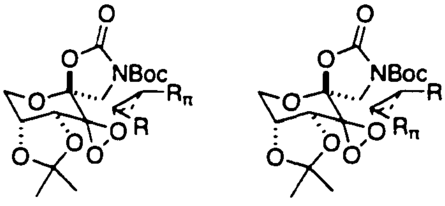


1-143

Table 1.13. Asymmetric epoxidation of olefins catalyzed by ketone **143**

Entry	Substrate	Yield (%)	ee (%)
1		87	91
2		88	83
3		61	91
4		82	91
5		61	97
6		>99	81
7		90	85
8		86	84
9		65	94
10		55	80

The high enantioselectivities observed with this catalyst are rather intriguing. Determination of the absolute configuration of some selected epoxides showed that groups with a π system preferred to be proximal to the spiro oxazolidinone, leading to spiro transition states **C** and **D** (Figure 1.12). It appears that spiro **C** is favored over **D** for substrates containing a π system, however a clear understanding of the reason for this awaits further study.



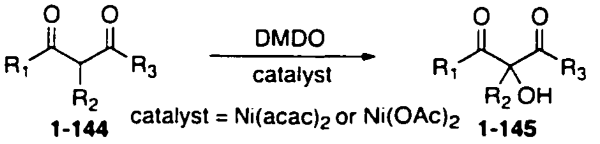
Spiro (**C**)
Favored

Spiro (**D**)
Disfavored

Figure 1.12. Spiro transition state for the epoxidation of olefins containing a π-system with ketone **1-143**

1.4.4. α-Oxidations

The oxidation of enol derivatives is emerging as a powerful way to generate α-hydroxy carbonyl compounds.[280-287] The use of DMDO to promote such transformations is becoming more widespread.[288-304] DMDO has been used to oxidize β-dicarbonyls **1-144**, in the presence of Ni(II) salts, giving the corresponding α-hydroxy compound **1-145**. Presumably the Ni(II) salt aids in the enolization of the diketone, which is then epoxidized (Scheme 1.32).[305]

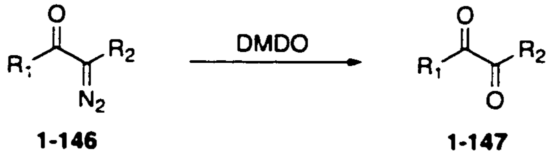


1-144

1-145

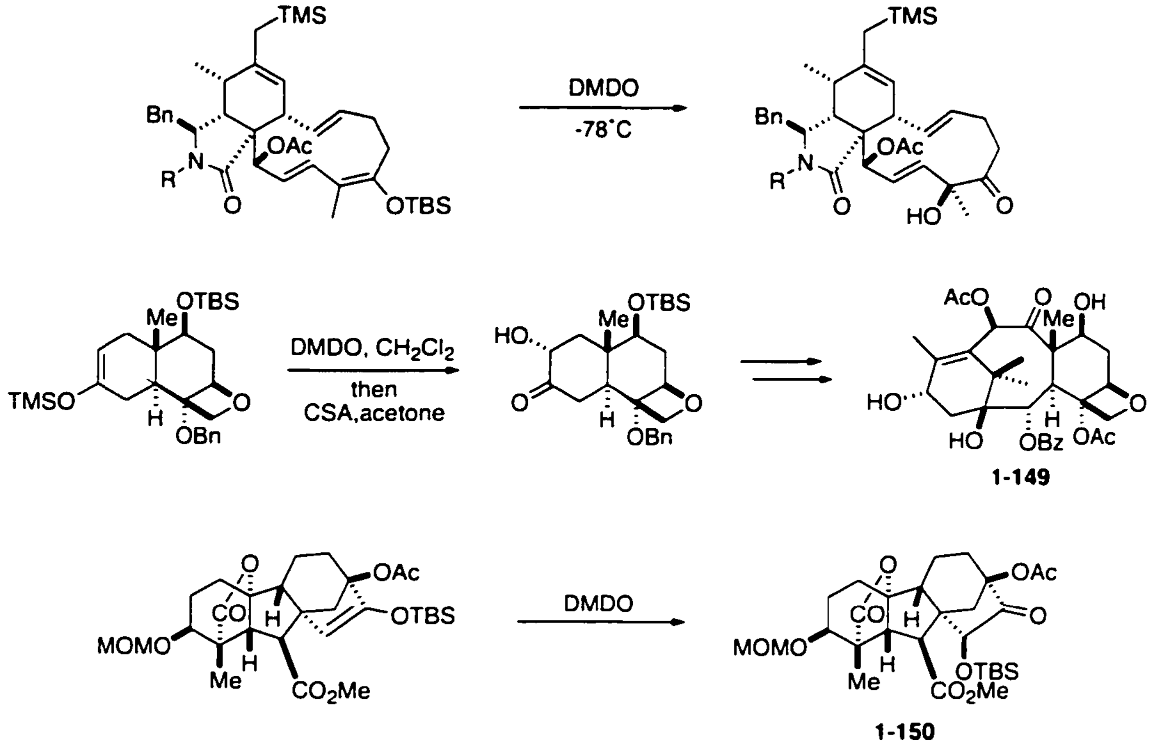
Scheme 1.32

In addition, α-diazo compounds **1-146** undergo oxidation with isolated DMDO to give α-dicarbonyl compounds **1-147** (Scheme 1.33).[306-312] Vicinal trioxo compounds[313] have been made using both this method and by the oxidation of either phosphoranylidenes[114] or α-bromo-β-dicarbonyls.[115]



Scheme 1.33

The epoxidation of silyl enol ethers has received a considerable amount of attention in the area of natural product synthesis.[116-120] In particular, this strategy has been employed in the diastereoselective installation of oxygen in the synthesis of 16,18-bis-*epi*-cytochalasin D[121] and bacattin III **1-149**,[122] and into the C-15 oxy substituent of the gibberelin skeleton **1-150** (Scheme 1.34).[123]

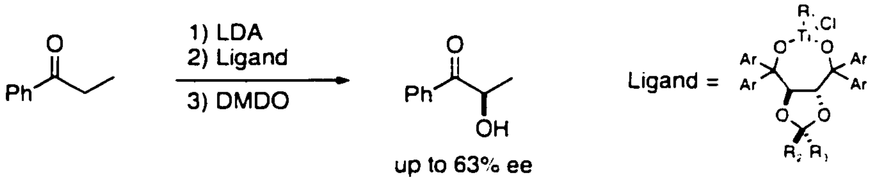


1-149

1-150

Scheme 1.34

When the enolate is rendered chiral, there is the potential for stereoselective oxidation. Through the use of a TADDOL-modified titanium enolate, up to 63% ee can be obtained upon epoxidation with DMDO (Scheme 1.35).[124,125]



Scheme 1.35

The enantioselective epoxidation of enol silyl ethers and esters provides a complimentary approach to the synthesis of enantiomerically enriched α-oxygenated ketones. Using the fructose-derived ketone **1-30** and Oxone as oxidant, epoxidation of these enol derivatives **1-151** led to the formation of oxy-substituted epoxides **1-152** or hydroxy ketones **1-153** with high enantioselectivity (Table 1.14).[243,326]

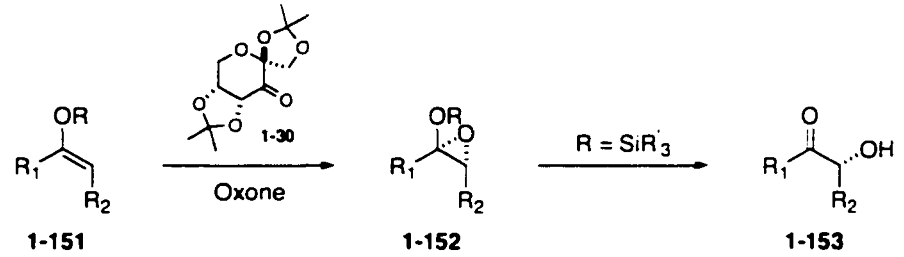
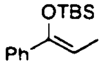
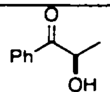
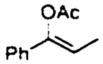
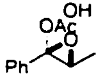
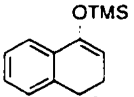
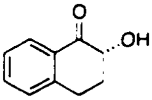
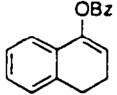
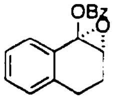
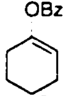
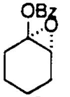
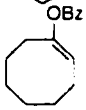
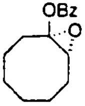
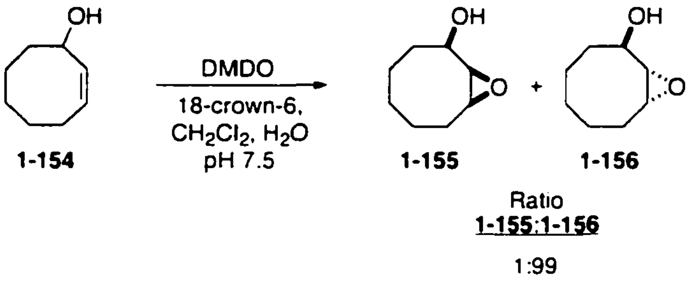


Table 1.14. Asymmetric epoxidation of enol silyl ethers and esters by ketone **1-30**

Entry	Substrate	Product	Yield (%)	ee (%)
1			80	90
2			66	91
3			70	83
4			92	88
5			82	93
6			82	95

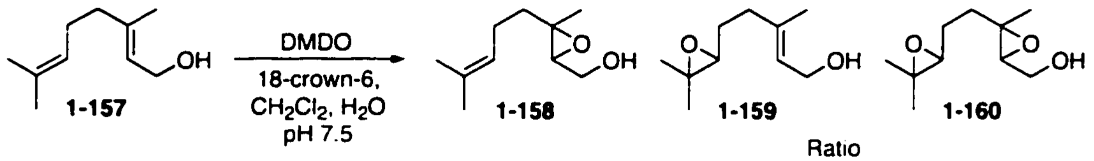
1.4.5. Regio- and Diastereoselectivity

One of the most interesting aspects of dioxirane-mediated epoxidation is the selectivity that is generally observed in the reaction. Not only is good regioselectivity seen, but often times excellent diastereoselectivity is observed as well. One of the earliest examples of this is the directing effect of allylic alcohols. In 1982, Curci showed that DMDO had a reactivity profile comparable to peroxoacids such as MCPBA.[8] For medium-ring allylic alcohols, epoxidation with either DMDO or MCPBA leads to the formation of primarily the *trans* epoxide (Scheme 1.36). Comparatively, epoxidation with *tert*-butyl hydroperoxide/vanadium(V) led to the formation of primarily the *cis* epoxide.



Scheme 1.36

Regioselectivity in the epoxidation of geraniol[8,327] **1-157**, and similar compounds,[328-330] was also investigated. At high conversions, bisepoxide **1-160** was the major product when DMDO was used as the oxidant. This was ascribed to the fact that an excess reagent was used. When the reaction was run to a lower conversion, production of bisepoxide **1-160** was reduced and the 6,7-epoxide **1-159** was the major product (Scheme 1.37). This is expected since DMDO is an electrophilic oxidant and the isolated ($\Delta^{6,7}$) C-C double bond is more electron-rich. The electrophilic nature of the oxidant can also be seen in the regioselective epoxidation of a number of polyene systems.[331,332]

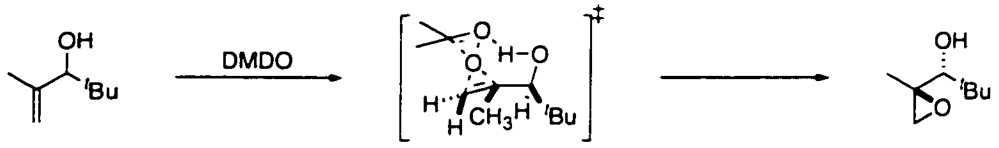


Conversion	Ratio 1-158:1-159:1-160
93%	2:30:68
40%	10:69:21

Scheme 1.37

The above reactivity profile is sensitive to solvent effects.[271,333,334] In hydrogen-bonding solvents such as MeOH, the dipolar transition states (*vide supra*) are equally stabilized by intermolecular hydrogen bonding with the solvent and therefore the most electron-rich olefin is epoxidized fastest. When the solvent is changed to CCl$_4$ this general stabilization is no longer present and so intramolecular hydrogen bonding with the allylic alcohol becomes the only method for stabilization of the transition state, leading to the higher formation of the 2,3-epoxide.

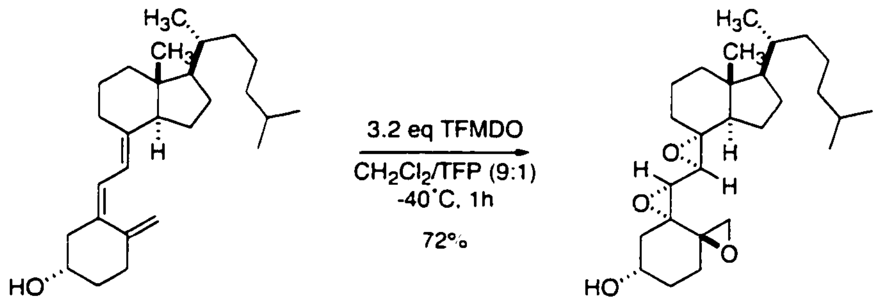
The ability of alcohols to provide transition state stabilization through hydrogen bond donation is thought to be one of the reasons high diastereoselectivity is observed in the epoxidation reaction.[270,334-336] Through hydrogen bonding, a highly-ordered transition state is likely, leading to high stereochemical communication between the incoming oxidant and the olefin. Adam found that epoxidation of allylic alcohol **1-161** with DMDO gave epoxide **1-163** as a 79:21 mixture of diastereomers, presumably by way of transition state **1-162** (Scheme 1.38). Recently, ammonium salts[147] and oxazolidine-substituted alkenes equipped with a free urea NH[148,149] were reported to show the same type of directing effect. In some cases, when large groups are placed on the olefin, allylic oxidation becomes competitive with epoxidation and products arising from C-H insertion are observed.[350]



1-161 **1-162** **1-163**

Scheme 1.38

In cases where there is no directing group, diastereoselectivity is still observed. The bias of the incoming oxidant can be influenced by the steric environment surrounding the olefin, leading to highly diastereoselective epoxidations.[351-367] Electrostatic effects can also play an important role in the diastereoselectivity observed.[20,269,363,368] One of the best examples showing the selectivity dioxiranes can display is the oxidation of vitamin D$_3$ **1-164** by TFMDO (Scheme 1.39).[369,370] Amazingly, triepoxide **1-165** was the only product isolated.



1-164 **1-165**

Scheme 1.39

The fact that DMDO, or TFMDO has been used in numerous stereoselective natural product syntheses is a tribute its ability to promote highly regio- and diastereoselective epoxidations. [371-394]

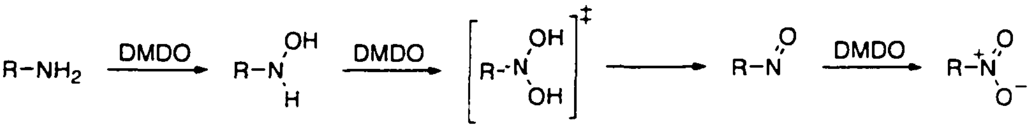
1.5. Oxidation of Heteroatoms

In contrast to other dioxiranes-mediated oxidation processes, oxidation of heteroatoms can be undertaken with other oxidizable groups in the molecule since they are faster than both epoxidation and C-H insertion. The *in situ* method for preparation of the dioxirane has enjoyed more success in this area than in others since the products of the oxidation are more stable to Oxone and are, in many cases, soluble in the monophasic aqueous reaction medium.

1.5.1. Nitrogen

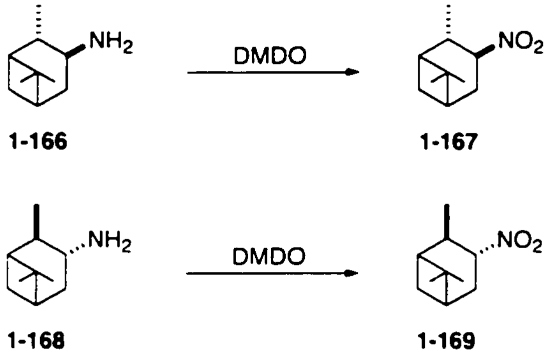
1.5.1.1. Primary Amines

Straight-chained aliphatic and aromatic primary amines can be oxidized with excess DMDO to their corresponding nitro compounds in high yield.[395-400] The reaction is believed to involve three separate oxygen transfers, and does not involve the tautomerization of the intermediate nitroso moiety (Scheme 1.40).



Scheme 1.40

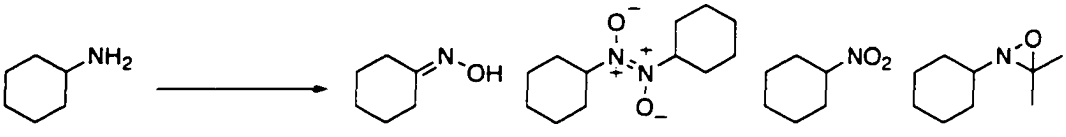
This mechanism is based on the observation that the oxidation of either enantiomer of isopinocampheylamine, **1-166** or **1-168**, gives the corresponding enantiomerically pure nitro derivative, **1-167** or **1-169** respectively (Scheme 1.41). If tautomerization were to take place, a diastereomeric mixture of the product would be expected. The putative stepwise mechanism of this reaction has been exploited by Giuliano, who reported that the oxidative deprotection of *O*-benzylhydroxyl amino groups is possible, yielding the corresponding nitro compound, in good yield.[401]



Scheme 1.41

Because these polar intermediates are reactive and can produce side products, the reaction must be run by the addition of the amine to excess oxidant in order for the desired process to compete effectively. If the dioxirane is added to the amine, or if there is substitution close to the nitrogen atom, alternative reaction manifolds can become important, leading to the formation of oximes, nitroso dimers, nitroallenes, nitrones, or oxaziridines.[402-404] The reaction is also sensitive to solvent effects, particularly in the *in situ* reaction. When the reaction is run under biphasic conditions, using CH_2Cl_2 as a cosolvent and cyclohexylamine **1-170** as substrate, the major product is nitroso dimer **1-172**, and is accompanied by oxime **1-171**, nitro compound **1-173**, and oxaziridine **1-174**.

However, when the oxidation is run under monophasic conditions, nitro compound **1-173** was the major product. Interestingly, under these conditions, none of the oxime **1-171** or oxaziridine **1-174** was observed (Scheme 1.42).



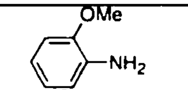
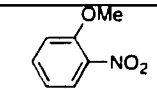
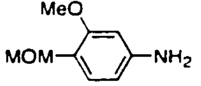
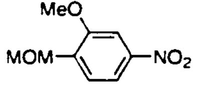
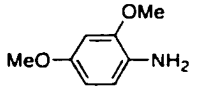
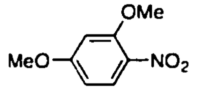
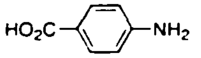
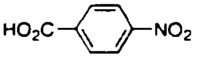
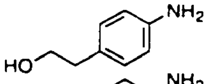
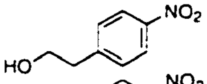
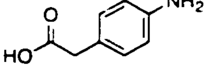
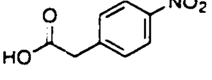
1-170 **1-171** **1-172** **1-173** **1-174**

equiv. of Oxone	cosolvent	products (%) 171	172	173	174
4.5	CH_2Cl_2	10	43	10	10
20	-	-	11	65	-

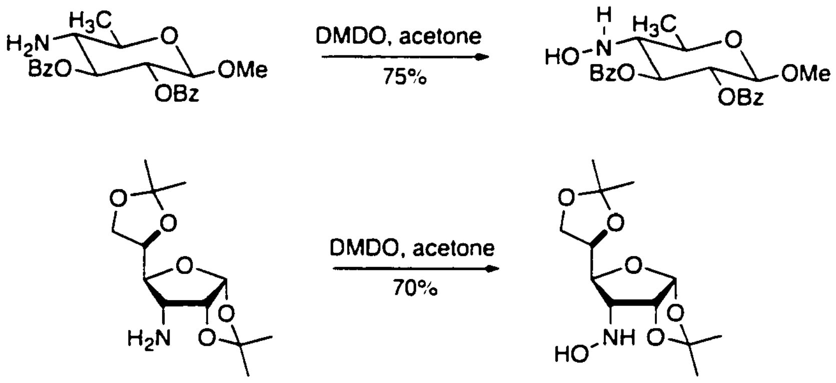
Scheme 1.42

The *in situ* protocol works particularly well for the oxidation of substituted anilines.[405-407] The amine functionality can be selectively oxidized to give the nitro compound in the presence of a wide variety of other potentially oxidizeable functional groups (Table 1.15)

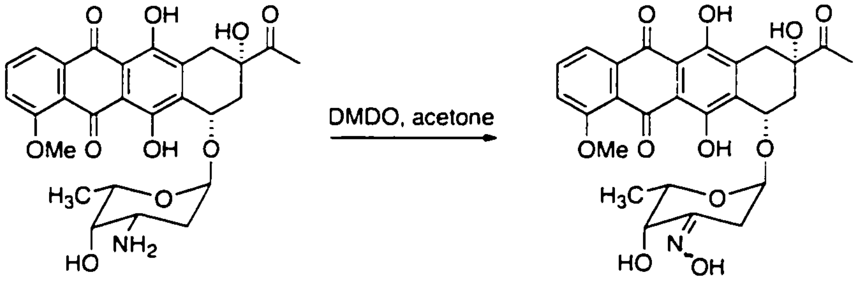
Table 1.15. Oxidation of substituted anilines with DMDO

Entry	Amine	Product	Yield (%)
1			100
2			78
3			85
4			73
5			73
6			81

Careful oxidation of some amino sugars can, in some cases, give the corresponding hydroxylamine (Scheme 1.43).[408,409] In these cases, it is likely that the strongly electron-deficient nature of the amine inhibits further oxidation to the oxime. However, this is not true for all amino sugars as oxidation of daunomycin **1-175** gave only the oxime **1-176** (Scheme 1.44).[408]



Scheme 1.43

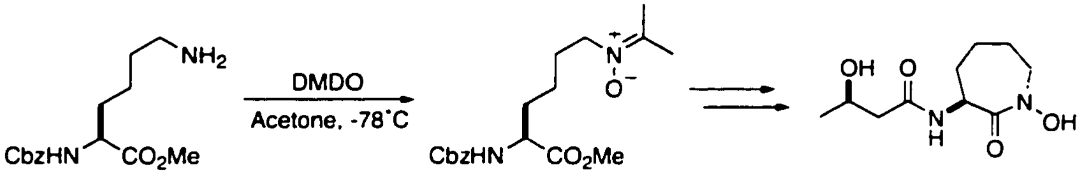


1-175

1-176

Scheme 1.44

The utility of 1° amine oxidation was displayed by Miller in his synthesis of cobactin T **1-179**.[410,411] Interestingly, oxidation of N^{α}-Cbz-L-lysine methyl ester **1-177** with DMDO at -78°C did not lead to the expected hydroxylamine, but instead gave the corresponding nitrone **1-178**. Further manipulation of the nitrone afforded cobactin T (Scheme 1.45)

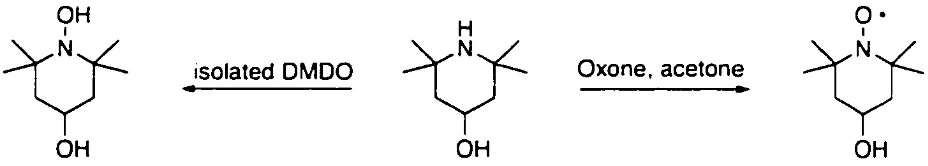


1-177 1-178 1-179

Scheme 1.45

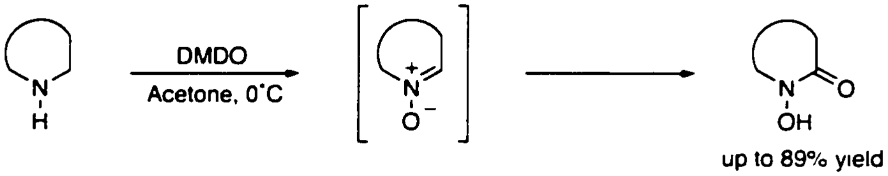
1.5.1.2. Secondary Amines

The oxidation of secondary amines can also be synthetically useful; however, as with primary amines, the outcome is highly procedure and substrate dependent. Careful oxidation of the amine with 1 equiv. of isolated DMDO at 0°C provides a general route to 2° hydroxylamines in good yield.[412-415] However, when the *in situ* protocol is applied, the excess oxidant present in the reaction mixture complicates matters, as overoxidation of the hydroxylamine to the corresponding nitroxide occurs (Scheme 1.46).[416,417]



Scheme 1.46

Cyclic secondary amines with α-hydrogens react quite differently. The hydroxylamine intermediate is oxidized to the nitrone, which gets further oxidized to the hydroxamic acid in good to high yield (Scheme 1.47).[418]



Scheme 1.47

1.5.1.3. Tertiary Amines

Aromatic and tertiary amines exhibit reactivity toward DMDO oxidation, with only a slight excess of the oxidant required to give near quantitative conversion to the N-oxide.[419-423] Figure 1.14 shows a variety of compounds accessible in this manner. Such compounds are receiving increased attention as potential hypoxia-selective cytotoxins in the clinical treatment of solid tumors.[424]

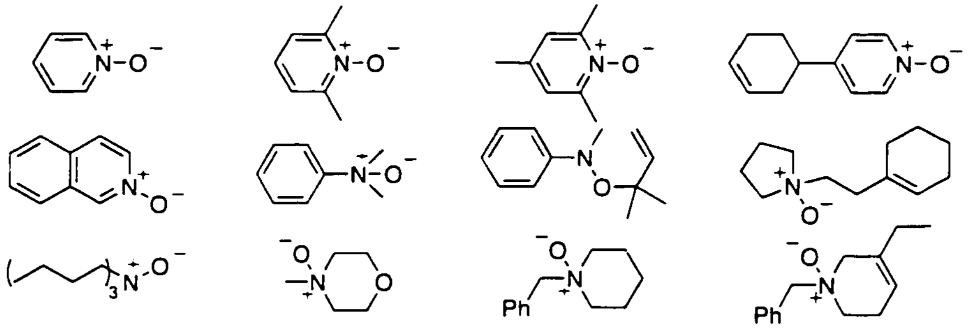
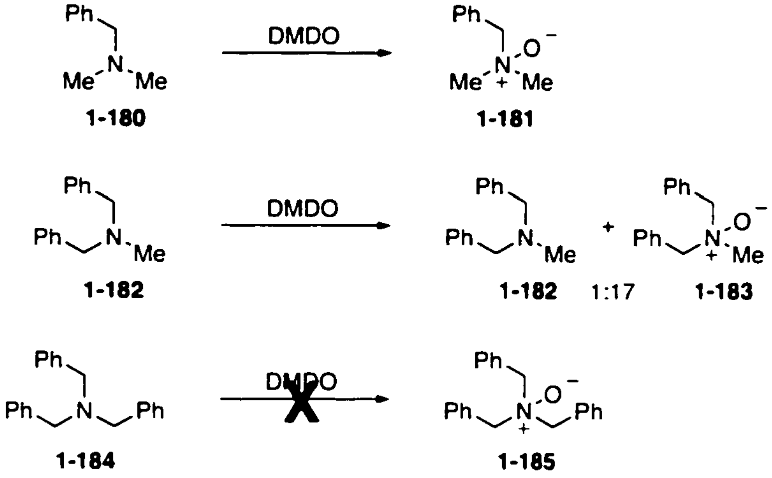


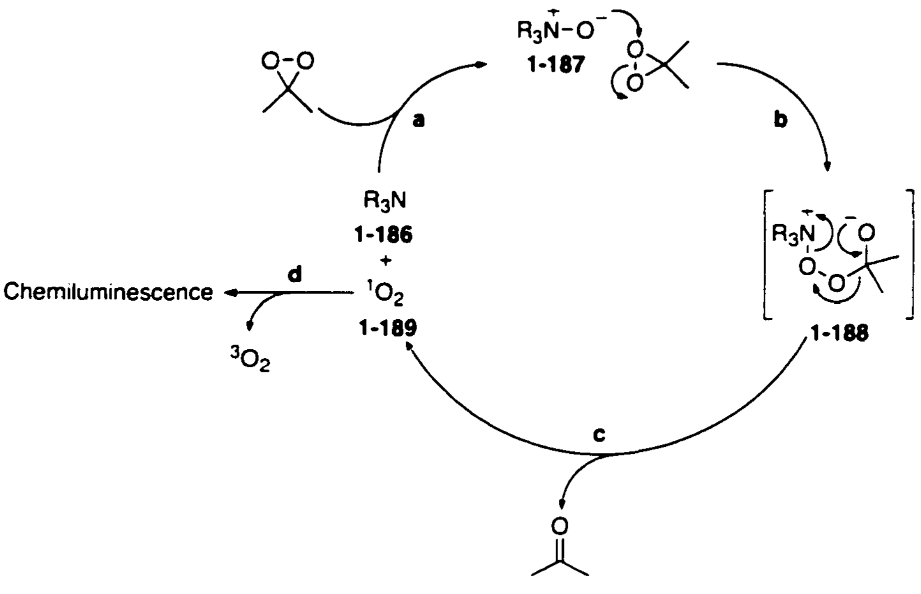
Figure 1.14 Tertiary and aromatic amine N-oxides available by DMDO oxidation

Some tertiary amines react only to partial conversion and then appear to be resistant to further oxidation, even when large excesses of DMDO are added.[420] For instance complete conversion to the *N*-oxide **1-181** was observed for *N,N*-dimethylbenzylamine **1-180**, while a 1:17 amine:*N*-oxide ratio was found for *N,N*-dibenzylmethylamine **1-182**. When tribenzylamine **1-184** was subjected to the reaction conditions, rapid consumption of the oxidant was observed, however no traces of the expected *N*-oxide **1-185** were found (Scheme 1.48).



Scheme 1.48

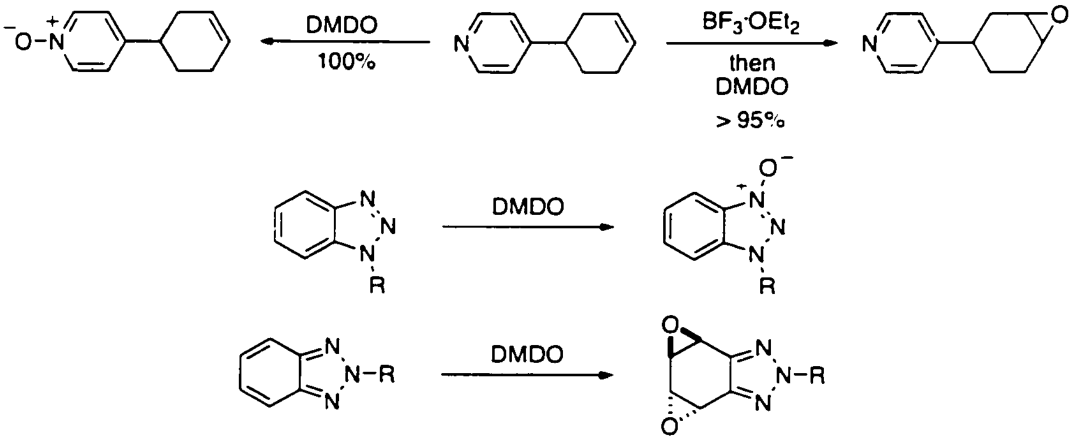
This phenomenon has been studied with DMAP[425] as well as a variety of heterocyclic and aliphatic tertiary amines.[426] and is consistent with the following mechanism (Scheme 1.49).



Scheme 1.49

After initial oxidation (**a**) of the amine **1-186**, the more nucleophilic *N*-oxide **1-187** can react with a second equivalent of DMDO leading to intermediate **1-188**. Spontaneous decomposition of the intermediate generates the starting amine **1-186**, acetone, and $^1O_2$ **1-189**. The $^1O_2$ can easily be detected as it decays to the more stable $^3O_2$, often times resulting in chemiluminescence. The driving force behind this DMDO decomposition pathway is the nucleophilicity of the *N*-oxide. The more nucleophilic the *N*-oxide, the faster the decomposition. As a result, each amine *N*-oxide has a characteristic equilibrium concentration that is dependent on its nucleophilicity. In the case of DMAP, the highest concentration of the *N*-oxide that can be obtained is 84%.[125] An interesting implication of this is that olefins elsewhere in the molecule are tolerated quite well since nitrogen oxidation is typically much faster than epoxidation.

Reversed chemoselectivity can be obtained by *in situ* protection of the amine followed by epoxidation. The amine can be protected as its ammonium salt,[427] or by the addition of BF_3•OEt_2 at -70°C before the addition of the oxidant.[428] Along the same lines, Katritsky found that oxidation of alkylbenzotriazoles is dependant on the position of the alkyl moiety. 1-alkylbenzotriazoles are converted to their N-oxides while 2-alkylbenzotriazoles are transformed into 2-alkyl-*trans*-4,5,6,7-diepoxy-4,5,6,7-tetrahydrobenzotriazoles (Scheme 1.50).[429]

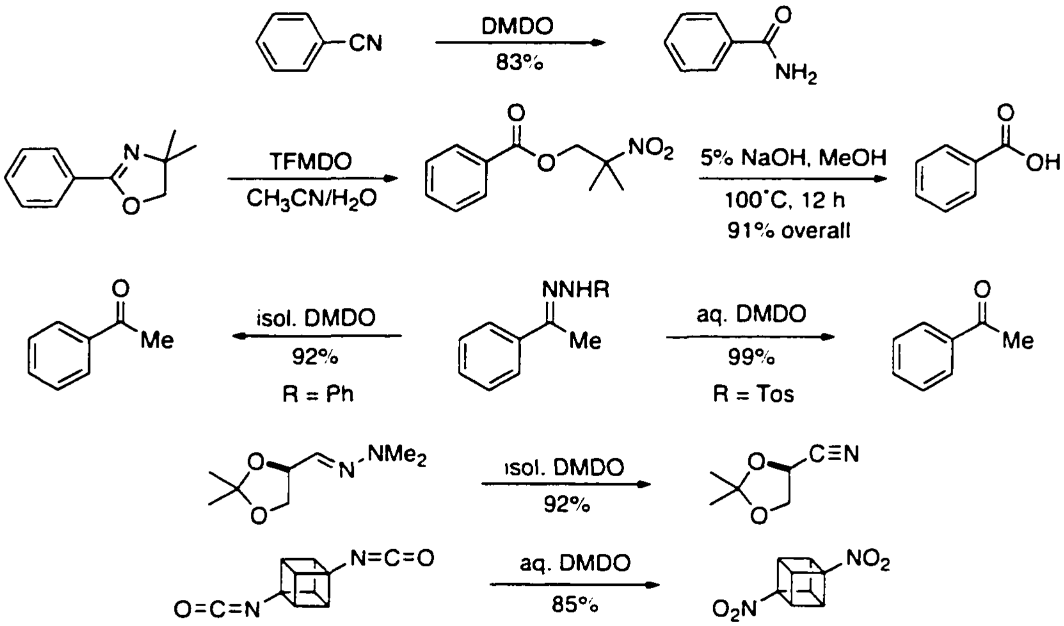


Scheme 1.50

1.5.1.4. Other Nitrogen Oxidations

The reaction of DMDO with nitrogen is not limited to amines. Several other nitrogen-containing functional groups are readily oxidized, and can display remarkable reactivity. Some of these transformations are shown in Scheme 1.51. A mild hydrolysis of nitriles ensues when they are exposed to *in situ* generated DMDO, leading to the formation of the corresponding amide.[430] A mild and efficient oxidative cleavage of aryl oxazolines to the parent carboxylic acid by *in situ* generated TFMDO can be achieved in

80-95% yield. Here, oxidative cleavage of the oxazoline by TFMDO gives an intermediate nitroester, which is then hydrolyzed under basic conditions to yield the carboxylic acid.[431]



Scheme 1.51

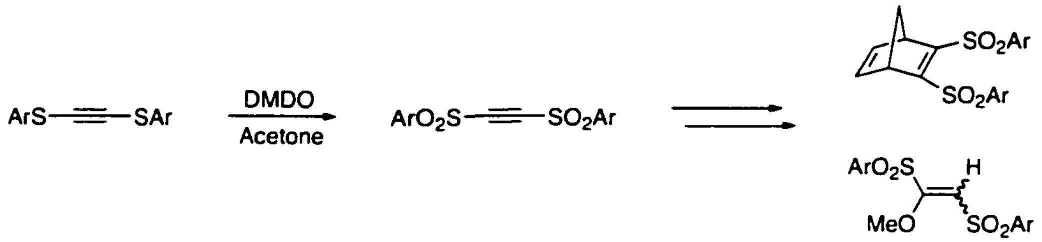
Aryl hydrozones can be oxidatively cleaved to the parent ketone using *in situ* generated DMDO[432] and aryl and alkyl hydrazones can be cleaved with isolated DMDO.[433] Additionally, *N,N*-dimethylhydrazones can be cleaved to their corresponding nitriles with either DMDO or TFMDO in isolated form.[434] Isocyanates can be directly converted to their analogous nitro compounds using wet DMDO.[435] Finally, σ^H adducts (Meisenheimer complexes) derived from carbanion addition to nitroarenes can be oxidized to either a phenol[436,437] or quinomethane[438] depending on the nature of the carbanion.

A ketone bound to a polystyrene-based solid support has also been prepared in an attempt to make a recyclable oxidation source.[439] When treated with Oxone and $NaHCO_3$, the dioxirane can oxidize anilines to nitro compounds and tertiary amines to the corresponding *N*-oxide. The spent reagent can be recycled, with only a gradual loss in activity, for up to five generations, at which time noticeable decomposition of the resin is observed.

1.5.2. Sulfur

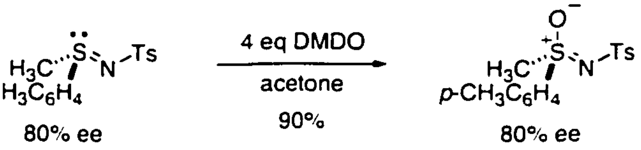
Sulfur oxidation has also received a great deal of attention, since, in many cases, selective reaction at sulfur in the presence of other potentially oxidizeable functional groups can occur. Additionally, as is typical with dioxirane oxidation, the reaction is mild, and operationally simple.

In this way ketene dithioacetals can be efficiently oxidized to their corresponding bis-sulfones with isolated DMDO. These are important since they can act as Michael acceptors and be used as synthetic equivalents for ethylenes and acetylenes in Diels-Alder and dipolar cycloaddition reactions.[440] Additionally, the previously unknown bis(arylsulphonyl)acetylenes were generated from the parent sulfide, and were highly active in both Diels-Alder and Michael reactions (Scheme 1.52).[237]



Scheme 1.52

Isolated DMDO provides an alternative to MCPBA or basic H_2O_2 for the oxidation of sulfilimines to sulfoximines.[441] Of particular interest is the fact that chiral sulfilimines can be oxidized without concomitant loss in enantiomeric excess (Scheme 1.53). Furthermore, DMDO has been shown to oxidize thiols to sulfinic acids,[442] sulfides to sulfoxides or sulfones[443–448], and thiophenes to their 1,1-dioxides.[449–452]



Scheme 1.53

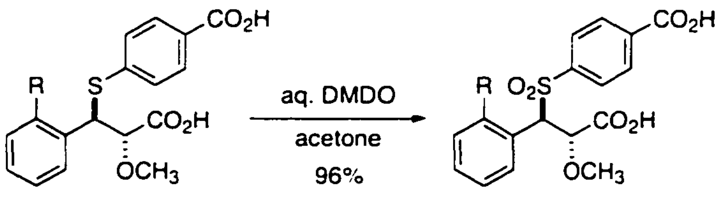
The oxidation of sulfides to optically active sulfoxides in the presence of an external source of chirality has been a major challenge in dioxirane chemistry. The greatest success in this area has been with the use of bovine serum albumin (BSA).[453,454] Using 1.3 – 5% BSA as a chiral additive, up to 89% ee could be obtained in the oxidation of sulfides using *in situ* derived dioxiranes (Table 1.16).

Table 1.16. Oxidation of sulfides with *in situ* generated DMDO, containing BSA

Entry	Sulphide	Time (min)	Yield (%)	ee (%)	Abs. config.
1	Ph-S-Me	180	98	7	(S)-(-)
2	*p*Tol-S-Me	60	77	32	(S)-(-)
3	Ph-S-^{i}Pr	120	56	79	(R)-(+)
4	Ph-S-^{i}Pr	5^a	67	89	(R)-(+)
5	Ph-S-^{t}Bu	120	70	73	(R)-(+)
6	Bz-S-Me	180	85	24	(S)-(-)

(a) TFMDO used as oxidant

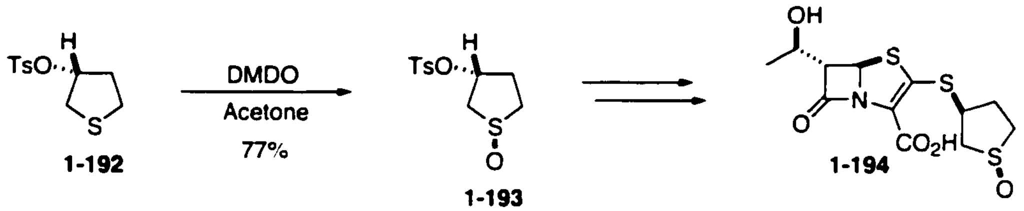
The exceptional reactivity of DMDO has been recognized by the pharmaceutical industry, as it was chosen as oxidant for the conversion of sulfide **1-190** to sulfone **1-191**, based on potential for scale-up as well as its environmentally benign character (Scheme 1.54).[455] Using wet DMDO, sulfone **1-191** was isolated in 96% yield and could be produced in kilogram quantities. Remarkably, no epimerization was detected, and also elimination of the sulfonyl acid moiety did not occur.



1-190 **1-191**

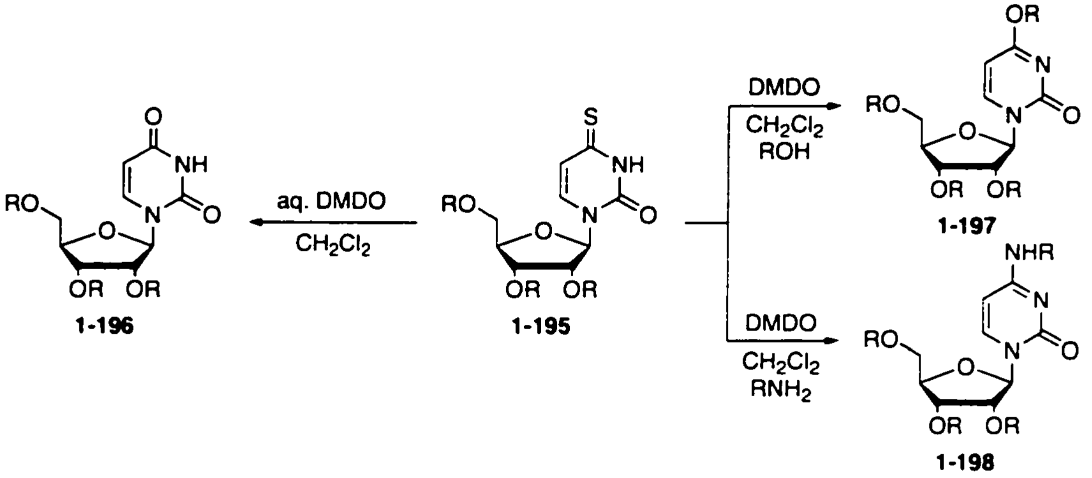
Scheme 1.54

Additionally, DMDO was the reagent of choice for the oxidation of sulfide **1-192** to sulfoxide **1-193**, a key intermediate in the Pfizer synthesis of penem antibiotic CP-70,429 **1-194** (Scheme 1.55).[456,457] It has also been used to generate a number of penicillin[458] and cephalosporin analogs.[459]



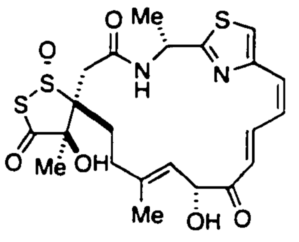
Scheme 1.55

Thionucleotides are thought to play an important role in the conformation of tRNA, and oxidation of these has received considerable attention, especially selective oxidation of the thioamide group. Several approaches to this problem have been reported, however these have shown varying degrees of success. One of the most common problems has been overoxidation. DMDO provides a convenient alternative, as oxidation of the thioamide moiety proceeds quite nicely.[460-464] The reaction can proceed in two ways, yielding two distinct products. For instance, treatment of 2',3',5'-tri-*O*-acetyl-4-thiouridine **1-195** with an aqueous DMDO solution in CH_2Cl_2 gave the corresponding 2',3',5'-tri-*O*-acetyl-4(3H)-uridine **1-196** in 95% yield.[460,463] However the same reaction carried out under anhydrous conditions in the presence of a nucleophile, such as an alcohol or amine gave the corresponding 4-alkoxyuridine **1-197** and cytidine **1-198** derivatives in good to moderate yields (Scheme 1.56). The reaction is believed to proceed through a sulfinic acid intermediate, with subsequent nucleophilic displacement.[461,462] When the nitrogen atom is removed (*i.e.* oxidation of a thione), formation of the sulfinic acid intermediate is not possible and oxidation proceeds to give a sulfine.[465]

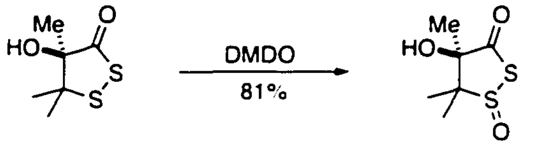


Scheme 1.56

The oxidation of sulfur-containing compounds has experienced growth, in part, due to the importance of these oxidized moieties in biologically active natural products. Perhaps the most spectacular example of this is Leinamycin **1-199**. The discovery of this unprecedented natural product has spurred intense study into polysulfide oxidation with DMDO.[466–469] Of particular interest is the dioxothiolane present in the natural product. Using the model 1,2-dithiolane-1-oxide **1-200**, Pattenden found that selective oxidation at the 3-position by DMDO gave the requisite 1,3-dioxo-1,2-dithiolane **1-201** (Scheme 1.57).[470–472]



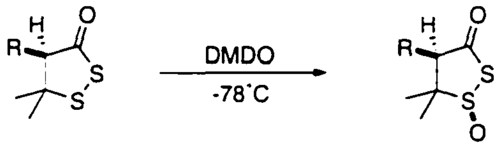
1-199



1-200 **1-201**

Scheme 1.57

A study on the diastereoselectivity of this transformation using a variety of 1,2-dithiolan-3-ones revealed that DMDO is much more selective than MCPBA, and can give up to 18:1 diastereoselectivity favoring the isomer shown (Scheme 1.58).[473]

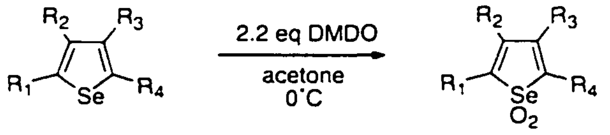


R	dr
NHBz	2:1
NHCbz	8:1
NHTs	15:1
NHBs	18:1

Scheme 1.58

1.5.3. Other Heteroatoms

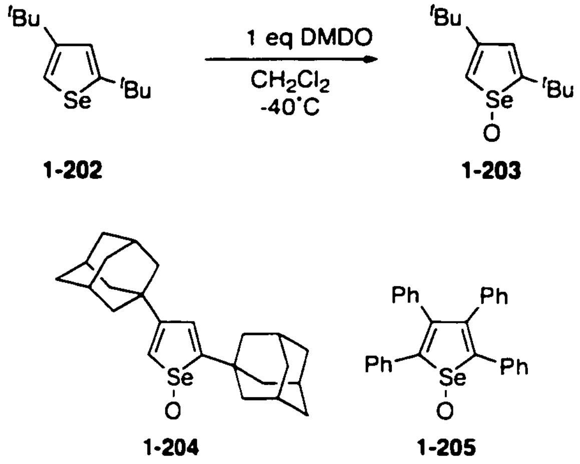
Not much has been reported on the use of DMDO to oxidize heteroatoms other than nitrogen and sulfur, with selenium receiving the most attention. Selenophene 1,1-dioxides are much more reactive than their thio analogues and, not surprisingly, their synthesis has been somewhat problematic. The most straightforward way to these highly reactive compounds it through oxidation of the parent selenophene. Prior to 1996, the only methods reported to accomplish this transformation were peracetic acid[474] and electrochemical oxidation[475] of dibenzoselenophene. At that time it was found that treatment of a variety of selenophenes with 2.2 equivalents DMDO led to the formation of the corresponding selenophene 1,1-dioxide in good to excellent yield (Scheme 1.59).[476,477] When only one equivalent of DMDO was used, nearly all of the starting selenophene was consumed, however none of the expected 1-oxide was isolated, presumably due to the lability of these compounds.



R_1	R_2	R_3	R_4	Yield (%)
C_6H_5	C_6H_5	C_6H_5	C_6H_5	97
Me	C_6H_5	C_6H_5	Me	97
4-MeC_6H_5	4-MeC_6H_5	4-MeC_6H_5	4-MeC_6H_5	89
t-Bu	H	*t*-Bu	H	97
-CH=CH-CH=CH-		H	H	71

Scheme 1.59

Selenophene 1-oxides can be isolated under certain circumstances. Oxidation of the sterically protected 2,4-di-^{t}butylselenophene **1-202** with 1 equiv. of DMDO in CH_2Cl_2 at –40°C led to near quantitative formation of its 1-oxide **1-203** (Scheme 1.60).[478] The stability of the selenophene 1-oxide is believed to be due to steric protection of the labile oxide by the large ^{t}butyl group. Oxidation of 2,4-di(1-adamantyl)- and tetraphenylselenophene led to near quantative formation of the corresponding 1-oxides **1-204** and **1-205**, further supporting this theory. There have been only scattered reports of selenium oxidation in non-aromatic systems, however, the steric element was necessary in all cases.[479]



1-202

1-203

1-204

1-205

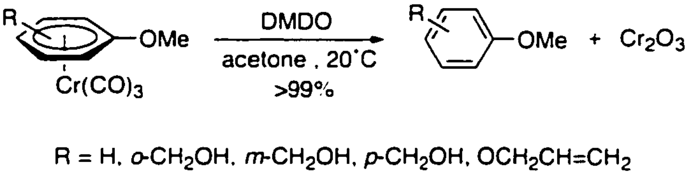
Scheme 1.60

DMDO can also oxidize alkyl iodides to their iodoso counterparts,[96,480,481] silanes to silanols,[482,483] phosphites to phosphates,[484,485] phosphine sulfides to phosphine oxides[486], and cyanoketophosphoranes to α-keto esters.[487]

1.6. Oxidation of Organometallic Species

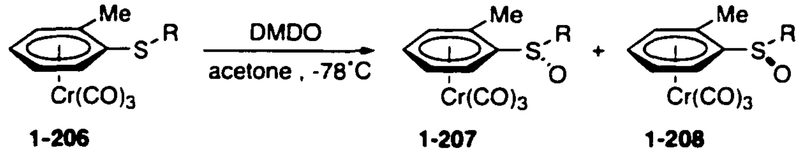
It appears that due to conflicting details in regards to the mechanism of action of DMDO, it was deemed too risky to apply the oxidation to organotransition metal complexes. Whether the oxidation would occur at the metal due to its' seemingly radical nature, or if typical organic reactions would occur on the bound ligands was unknown. Furthermore, it was unknown as to what effect the metal center would have on the selectivity of the oxidation on the bound ligand. The era of the DMDO oxidation of organometallic compounds was ushered in when it was found that stoichiometric amounts of DMDO quantitatively decarbonylated $Cp^*Re(CO)_3$ and $TpMo(CO)_3^-$ yielding the corresponding trioxo complexes Cp^*ReO_3 and $TpMoO_3^-$ respectively.[488] The mechanism of the reaction is not fully understood, however it is believed to proceed through a transient oxo(carbonyl)metal intermediate that is too labile to detect.

One of the more extensively studied reactions involves a Cr(III) arene complex. If the arene complex is relatively simple, then treatment with DMDO results in oxidative removal of the metal to give the free arene in good yield (Scheme 1.61).[489,490] However, in the case of thioanisole chromium tricarbonyl, the high reactivity of sulfur (*vide supra*) caused the oxidation to be transferred to the ligand, giving the corresponding sulfoxide complex.



Scheme 1.61

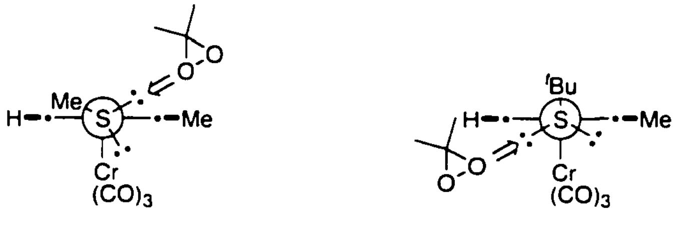
Of interest is the stereochemical outcome of the reaction, since two possible diastereomers can be formed (Scheme 1.62). It has been found that the diastereomeric outcome is a result of the conformation of the sulfide.[491]



	R	1-207 : 1-208	Yield (%)
1-206a	Me	9:1	78
1-206b	^{t}Bu	2:98	92

Scheme 1.62

In the case of the methyl-substituted sulfide **1-206a**, the preferred conformation **A** involves a staggered conformation of the sulfide lone pairs about the ring methyl group (Figure 1.15). Approach of the dioxirane from the opposite face of the metal results in diastereomer **1-207a**. On the other hand, the bulky ^{t}Bu group alters the staggered arrangement such that it is anti to the metal fragment, giving conformation **B**. Attack of the dioxirane, this time syn to the metal, leads to diastereomer **1-208b**.[491–493] Similar results are seen when the ring methyl group is changed to a methoxy group,[491–493] or when the metal is changed to tungsten, iron, ruthenium or rhenium.[494–499] Ligand-based thiol oxidation has not been limited to metallocene chemistry. In other systems, ligand-based oxidation of sulfur has provided sulfones.[500]

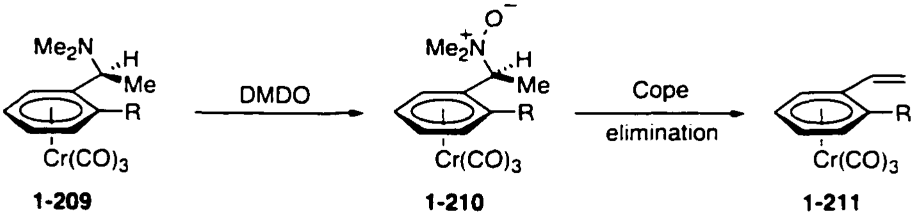


Conformation **A**

Conformation **B**

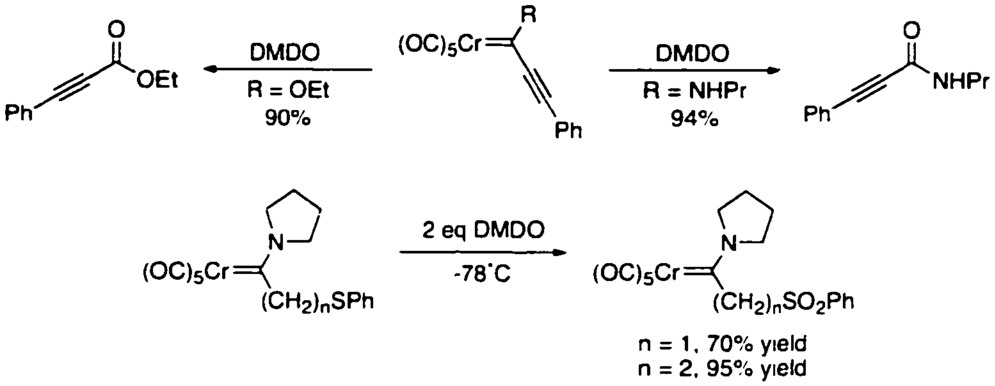
Figure 1.15. Approaches of DMDO to chromium-bound arene sulfides

The tricarbonylchromium (0) complex of *ortho*-substituted (S)-α-methylbenzyldimethylamines **1-209** has a very interesting reaction profile. Oxidation with excess DMDO led to formation of an amine oxide **1-210**, which underwent a Cope elimination to give vinyl compound **1-211** (Scheme 1.63).[501,502] When the *ortho* group was a heteroatom, such as sulfur or phosphorous, oxidation could occur there first followed by formation of the amine oxide and subsequent Cope elimination. Silanes, stannanes and olefins were completely unreactive as only the elimination product was observed.



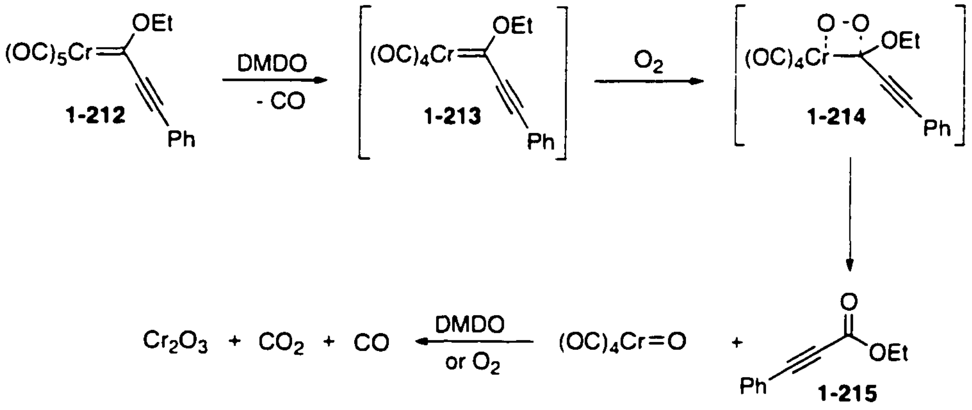
Scheme 1.63

In contrast to the arene complexes, the reaction of chromium carbene complexes with dioxiranes usually proceeds to cleave the metal-carbon bond and produce the organic moiety cleanly.[503] However, a remote sulfur atom is oxidized completely to the sulfone in preference to the oxidative removal of chromium (Scheme 1.64).[504] Also observed has been the preferred epoxidation of a conjugated enamine over oxidative removal of chromium.[505]



Scheme 1.64

There has been much speculation pertaining to the site of attack of DMDO on the carbene. Recent results have indicated the mechanism is likely to proceed *via* an initial decarbonylation at the metal site to give the highly unstable tetracarbonyl intermediate **1-213**, which is then cleaved by the action of O_2 by way of oxetane **1-214**, yielding ester **1-215** and a chromium tetracarbonyloxo species. Further oxidation of this species by either DMDO or O_2 leads to chromium(III) oxide, CO_2 and CO (Scheme 1.65).[509]



Scheme 1.65

Ligand-centered oxidation can also proceed by Si-H insertion yielding a silanol. A variety of metals can be utilized in this reaction, and mono-,[507-510] di-,[508,511] and trisilanols,[512] as well as dihydroxydisilanols,[513] can be made quite readily. The impressive electron-donating ability of the metal facilitates insertion, as DMDO rather than the more reactive TFMDO is usually all that is needed (in contrast to the C-H insertion reaction of organic moieties). Figure 1.16 shows a variety of silanols that can be obtained in this manner.

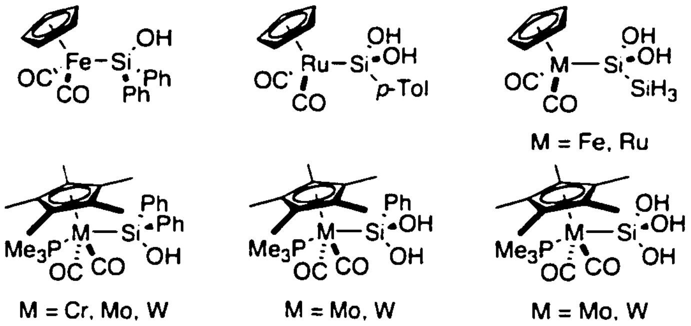
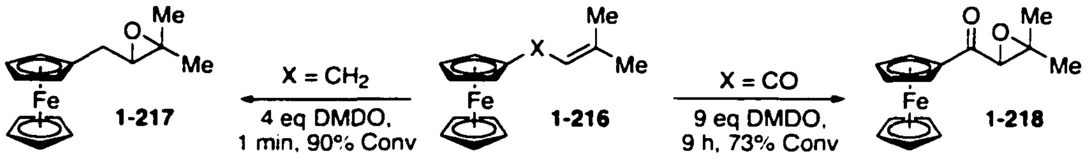


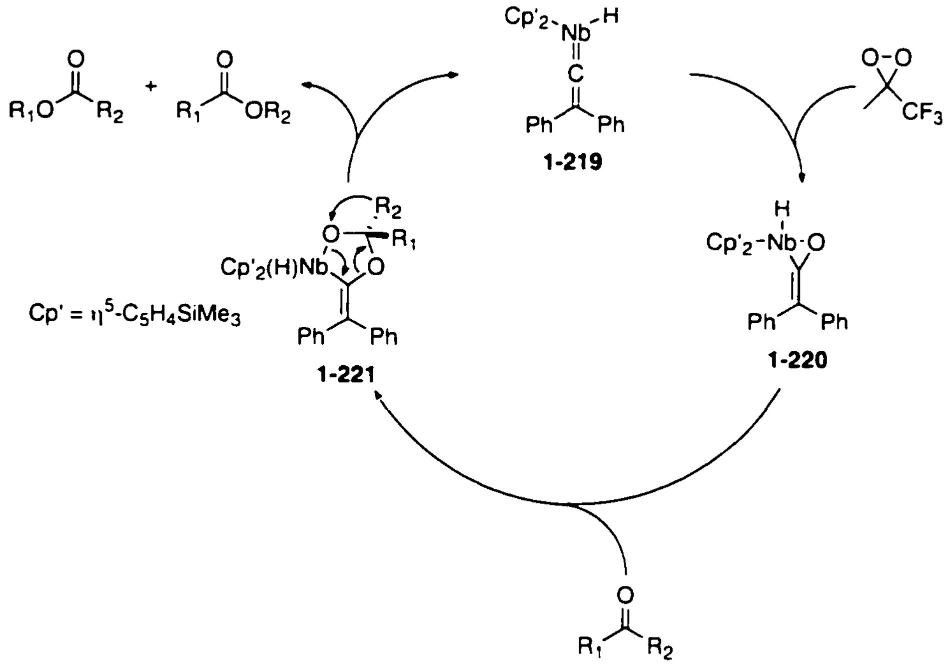
Figure 1.16. Silanols resulting from oxidation of metal-bound silanes

Epoxidations can also be carried out on the ligands of organometallic compounds, however the reactions are typically plagued with a variety of side reactions. For example, epoxidation of the olefin in the ferrocenyl complex **1-216** can proceed in fair to good yields (Scheme 1.66).[514] The electron-rich allylferrocenes typically react much faster and with less decomposition than their counterpart electron-poor acylferrocenes. A large excess of oxidant is needed to minimize side reactions due to electron transfer processes at the metal center, leading to paramagnetic iron-containing products. Similar results were obtained upon oxidation of substituted (tricarbonylcyclohexadiene)iron complexes,[515,516] as well as tris(pyrazolyl)borato-substituted alkenyltungsten complexes.[517]



Scheme 1.66

The use of TFDMDO as the terminal oxidant in a niobium-mediated Baeyer-Villiger type oxidation was reported in 1993.[518] Niobium ketene complex **1-220** was utilized as an oxygen atom transfer agent, converting ketones and aldehydes into esters and carboxylic acids. In the event, oxidation of the niobium alkylidene complex **1-219** with TFMDO gives rise to niobium ketene complex **1-220**. Reaction of **1-220** with a carbonyl compound generates dioxaniobicycle **1-221**. Selective migration of one of the R groups to the niobium-bound oxygen gives the oxygenated product and regenerates the alkylidene complex.



Scheme 1.67

The niobium center provides an electron-deficient oxygen for migration, then acts as a leaving group, similar to the carboxylate group in the peracid-induced Baeyer-Viliger reaction. Unlike the typical reaction, the migratory aptitude for the various R groups is 3° > Me > 1° ≥ 2° > Ar, whereas normal migratory aptitude is 3° > 2° ≈ Ar > 1° > Me. In **1-221**, the metallacycle ring lies in the equatorial place of the bent metallocene, and the C to O migration requires the migrating group to move about this plane, inducing a steric interaction with the ring $SiMe_3$ substituents. It is this interaction that is believed to counteract the usual electronic requirement of migration.[518] DMDO has also been utilized as a terminal oxidant for both salen- and metalloporphyrin- catalyzed epoxidations.[519-525]

1.7. Summary

Dioxiranes, either isolated or generated *in situ*, have proven to be exceptionally versatile oxidizing agents. The selectivity that these oxidants display has oftentimes drawn the comparison to biological oxidants. Their reactivity can be tempered by judicious choice of either oxidant (*i.e.* DMDO *vs.* TFMDO) or by careful placement of functionality on the molecule of interest. The utilization of chiral dioxiranes to perform enantioselective reactions has become an important part of their chemistry. Thus far, the most success in this area has been in the asymmetric epoxidation of unfunctionalized olefins.

1.8. References

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CHAPTER TWO

INVESTIGATIONS INTO NOVEL APPLICATIONS OF THE KETONE-CATALYZED ASYMMETRIC EPOXIDATION

2.1. INTRODUCTION AND BACKGROUND

The generation of enantiomerically pure compounds has been a constant challenge for organic chemists. The ability to synthesize a single enantiomer of a desired compound is of extreme importance for biologically active compounds. Oftentimes only one of a pair of enantiomers is biologically active, while the other is either inactive or deleterious. Enantioselective processes, especially those that are catalytic, have come to the forefront in today's synthetic laboratories,[1,2] and catalytic asymmetric epoxidation reactions are no exception to this.[3,4] Furthermore chiral, non-racemic epoxides have proven to be versatile synthons in organic synthesis. The inherent ring strain of epoxides allows them to react with a variety of nucleophiles, producing ring-opened products stereospecifically.[5] Historically, epoxidation reactions have been placed in two distinct categories: (1) epoxidation of allylic alcohols and (2) epoxidation of unfunctionalized olefins. The methodological study of epoxide formation has been the focus of intensive research efforts in the Shi group for several years, particularly the asymmetric epoxidation of unfunctionalized olefins.

2.1.1. Titanium (IV) Tartrate Catalysts

By far, the most recognized method for the epoxidation of allylic alcohols is that reported by Katsuki and Sharpless in 1980.[5,6] By using a system containing (+)- or (-)-diethyl tartrate (DET), titanium tetraisopropoxide and *tert*-butyl hydroperoxide (TBHP) in a non-polar solvent such as methylene chloride, they were able to achieve the unprecedented asymmetric epoxidation of di-, tri- and in limited cases tetrasubstituted allylic alcohols in good to excellent enantiomeric excess (ee); often greater than 95%. A major improvement in this reaction occurred in 1986, when it was found that the catalyst loading could be dropped to only 5-10 mol% if Molecular Sieves were added to the reaction mixture.[7]

Asymmetric induction arose *via* a highly-ordered transition state in which the oxygen of the alcohol was coordinated to the pre-formed titanium (IV)-DET conjugate (Figure 2.1). Oxygen transfer from TBHP to the olefin followed by subsequent displacement of the resulting alkoxide by more allylic alcohol and TBHP provided the desired epoxide. The facial selectivity may be controlled by the tartrate ligand used, allowing for the prediction of product stereochemistry. The predictive power of this reaction has been so great that oftentimes it is used to provide authentic samples for absolute configuration determination.

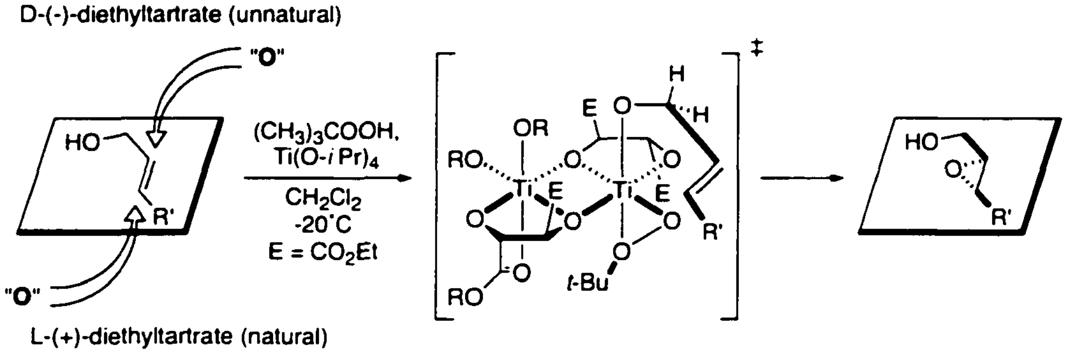
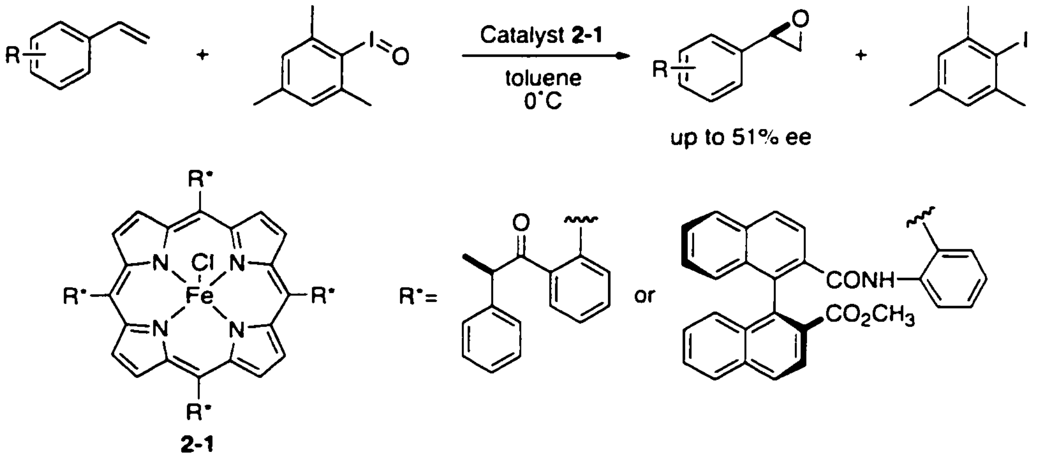


Figure 2.1 Transition state model for the Sharpless epoxidation

Although the Sharpless method may seem highly general, several problems arose if substrates other than allylic alcohols were used. If the alcohol moiety was moved just one carbon away (*i.e.* a homoallylic alcohol), the stereoselectivity dropped off dramatically. When the hydroxy group was completely removed, a total loss of stereoselectivity is observed. Additionally, as is the case for many asymmetric reactions, preexisting chirality can play a major role in the stereochemical outcome of this reaction. When a secondary allylic alcohol is used, its (R) or (S) absolute configuration can affect the *cis* or *trans* character of the epoxide formed. When the groups around the hydroxl become too large, a decrease or even total loss of selectivity is observed.[8] Finally, when 1,1-disubstuted olefins are employed, the chemical yields for the reaction drop, often well below 50%.

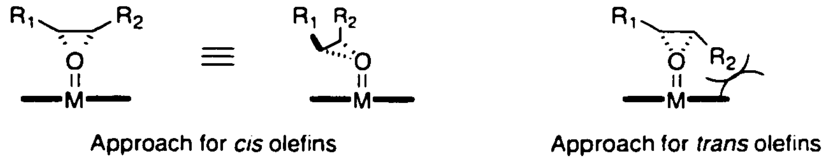
2.1.2. Metalloporphyrin-based Oxo Transfer Catalysts

Due to the remarkable interest in the Sharpless epoxidation and the recognition that it is not entirely a general method, intensive research was initiated to find a complementary reaction such that unfunctionalized olefins could be effectively epoxidized. The use of transition metal catalysts quickly became the method of choice to effect this transformation. One of the first examples of this was reported by Groves in 1983.[9] Using a chiral heme-like porphyrin catalyst based on the biological oxidant cytochrome P-450, epoxidation of unfunctionalized olefins occurred with modest enantioselectivity (Scheme 2.1). Styrene derivatives afforded the highest selectivity with these catalysts, however the highest ee was only 51%.



Scheme 2.1

In order to explain the selectivity observed, and to account for the general observation that *cis* olefins react faster than *trans*, a transition state in which oxygen atom transfer occurs *via* a side-on approach of the olefin to the iron-oxo intermediate has been proposed (Figure 2.2).[10] This approach is now widely accepted for both the metalloporphyrin- and metallosalen-catalyzed epoxidation reactions (*vide infra*).



Approach for *cis* olefins

Approach for *trans* olefins

Figure 2.2 Side-on approach model for oxygen transfer.

A major advance in this area was reported by Collman[11] in 1999. Through the use of a pseudo-C_2 symmetric porphyrin **2-2** he was able to epoxidize terminal olefins with good to modest selectivity (Figure 2.3). Since selectivity in these systems arises from a steric interaction between the olefin and the chiral "wings" of the catalyst, the ability to epoxidize terminal olefins with high selectivity is not unexpected.

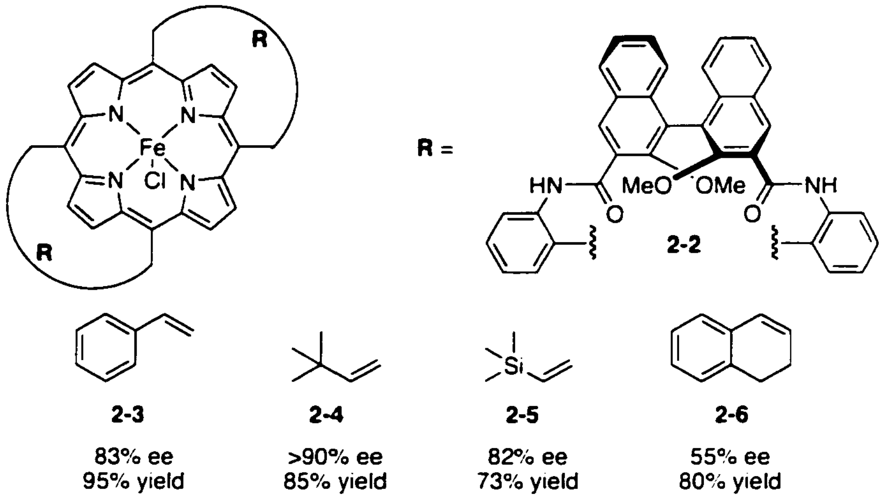
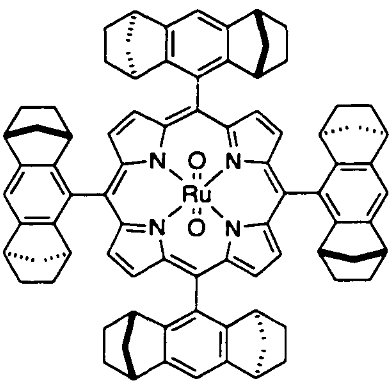


Figure 2.3 Collman's Porphyrin Catalyst

One advantage of the porphyrin-catalyzed epoxidation is that, in some cases, molecular oxygen can be used as terminal oxidant. In 1985, Groves showed that dioxoruthenium(VI)-porphyrin complexes catalyzed aerobic epoxidation. However an enantioselective version of this reaction was not available until Che[12] reported that the dioxoruthenium(VI)-porphyrin complex **2-7** catalyzed the epoxidation of *cis*-β-methylstyrene with good enantioselectivity under 8 atm of oxygen. Further work in this area by Che[13] has shown that the dichlororuthenium(VI)-porphyrin complex was much more reactive. In this case, the terminal oxidant was 2,6-dichloropyridine *N*-oxide.



2-7

Figure 2.4 Che's Porphyrin Catalyst

2.1.3. *Metallosalen-based Oxo Transfer Catalysts*

Metallosalen complexes [salen = *N,N'*-ethylenebis(salicylideneimine)] have a structure similar to metalloporphyrin complexes. It is their structural differences that account for their overall improved catalytic properties. The porphyrin ligand encircles a central metal ion and has peripheral sp^2 carbons, meaning all attached asymmetry is distal to the reacting metal. On the other hand, the salen ligand only partially surrounds a central metal ion and includes two sp^3 carbons in the ethylenediamine bridge. This allows for proximal placement of asymmetry, and translates to enhanced stereo-induction. Having similar properties, metallosalen and metalloporphyrin complexes oftentimes react in similar ways. The epoxidation of unfunctionalized olefins is no exception to this. It was known quite early that metallosalen complexes catalyze these reactions,[14-16] however the first asymmetric version was not known until 1990, when Jacobsen[17] and Katsuki[18] independently reported the epoxidation of conjugated olefins with metallosalen complexes. Catalysts such as **2-8** show remarkable selectivity for conjugated *cis*-di and tri-substuted olefins (80-95% ee), with "good" substrates as high as 98% ee (Figure 2.5).

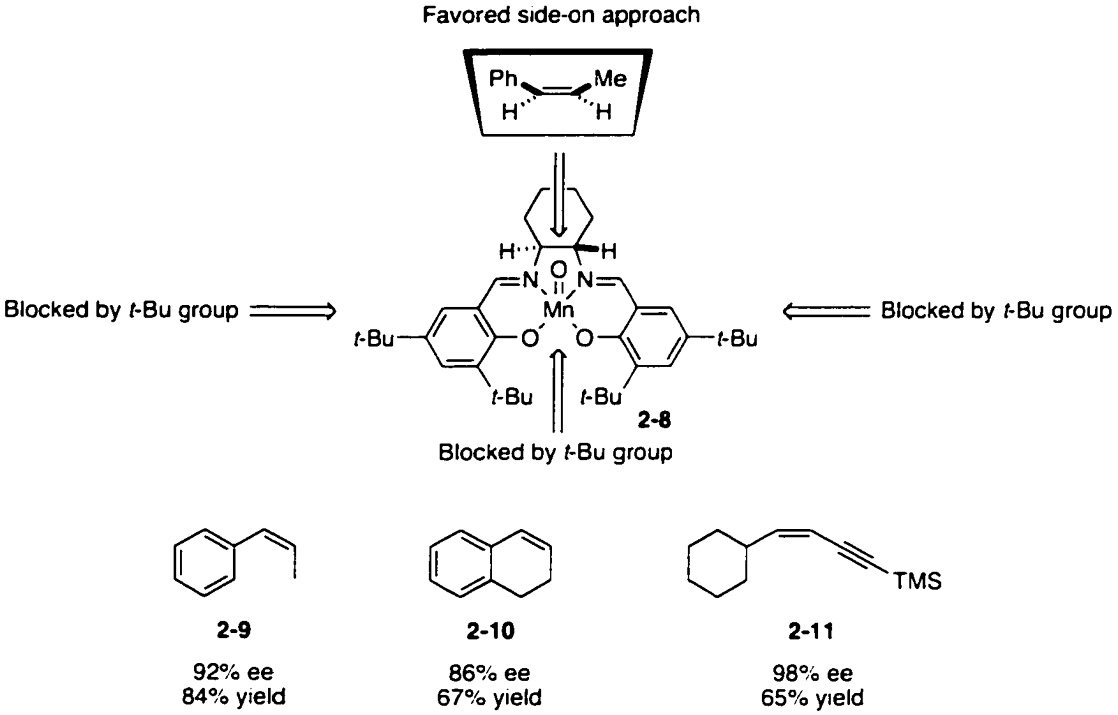


Figure 2.5 Jacobsen Epoxidation

Mechanistic studies[19] have indicated that this reaction proceeds through a radical intermediate which allows for carbon-carbon bond rotation between the radical and its vicinal carbon. As such, some conjugated *cis*-olefins isomerize, furnishing a mixture of the *cis*- and *trans*-epoxides. Enantiofacial distinction occurs *via* a side-on approach similar to that of metalloporphyrin catalysis, and is induced by the interaction of the incoming olefin with the chiral backbone of the salen ligand (Figure 2.5). With proper substitution, only one side-on pathway is operable.

2.1.4. Iminium Salt Catalysts

Recently a new method for the asymmetric epoxidation of olefins was disclosed. In these reactions imine or iminium salt catalysts were used as catalyst.[20-22] The active oxygen transfer agent is typically an oxaziridinium salt, used either in isolated form or generated *in situ* (Figure 2.6).[23,24]

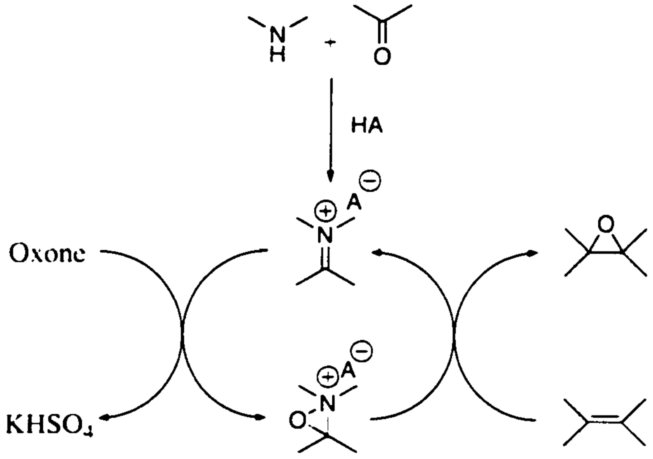
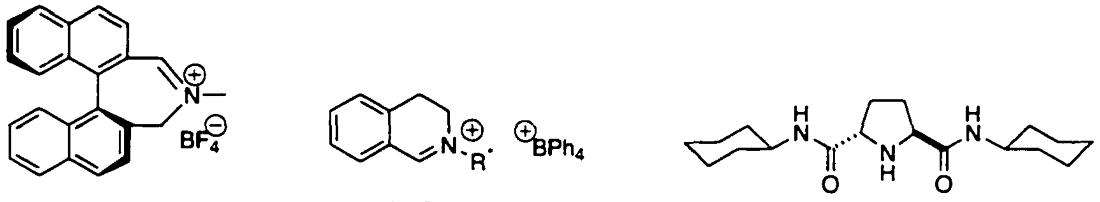


Figure 2.6 Oxaziridine Epoxidation of Olefins

Chiral, non-racemic iminium salts have been utilized as catalysts for this reaction (Figure 2.7).[25-32] In general, chemical yields were good, but enantioselectivity has yet to reach the levels of utility. The reasons for this trend are not fully understood, however these reagents have generated a great deal of interest from the synthetic community. Conceivably, these catalysts could include asymmetry on both the nitrogen and carbonyl moieties, potentially creating a chiral pocket. The use of a densely packed chiral pocket in metalloporphyrin catalysts has proven to be effective in the epoxidation of terminal olefins (*vide supra*), and it is hoped that this idea can be transferred to oxaziridine epoxidation.



2-11 up to 71% ee

2-12 up to 73% ee

2-13 up to 65% ee

Figure 2.7 Examples of Oxaziridinium Oxygen Transfer Catalysts

Recently, it has been found that amines themselves can catalyze olefin epoxidation in the presence of Oxone.[33] Mechanistic work has indicated that the reaction is most likely mediated by a chiral amine radical cation. While the enantioselectivity is not yet high for this reaction, the likelihood of finding a suitable catalyst is quite good, owing to the abundance of readily available chiral amines.

2.1.5. Ketone Catalysts

It has been known for some time that olefins can be epoxidized by ketones and potassium peroxomonosulfate (Oxone or Caroate).[34,35] Most commonly, acetone or 1,1,1-trifluoroacetone are used, making dimethyldioxirane (DMDO) or its trifluoro derivative. The reactive dioxirane can be isolated in its parent solvent, or it can be generated *in situ*. This second option generally involves a biphasic system using water and an organic solvent in the presence of a phase transfer catalyst. For asymmetric epoxidation, the *in situ* generation of dioxiranes has been utilized most frequently. In theory, the generation of a dioxirane and then its epoxidation of an olefin could be catalytic following the pathway shown (Figure 2.8). If a chiral ketone is used the opportunity exists for chirality to be transferred to the epoxide.

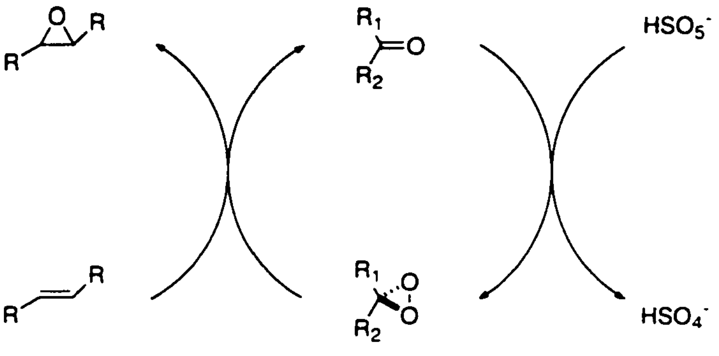
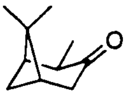


Figure 2.8 Ketone Catalyzed Epoxidation

2.1.5.1. Epoxidation with Chiral Non-Racemic Dioxiranes

In 1984, Curci[36] reported the first successful asymmetric epoxidation of olefins using chiral dioxiranes. He reports ee's of 6-12% in low yield with long reaction times, using ketones **2-15** and **2-16** (Figure 2.9). Although the ee's were low, they were the highest reported to date for the asymmetric epoxidation of unfunctionalized olefins. Very little was published on the dioxirane-mediated asymmetric epoxidation between 1984 and 1995.[37-42] At this time Curci[37] reported a more reactive and selective catalyst, **2-17**. This catalyst, as well as its enantiomer, gave ee's of only 20%, but the yields were much more respectable, 80-85%.



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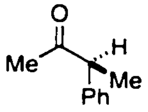

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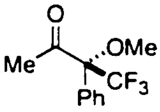


2-17

Figure 2.9 Curci's Ketone Catalysts

Also in 1995, Marples[39] published his attempts at asymmetric epoxidation using chiral ketones **2-18a** and **2-18b**, derived from tetralone and indanone (Figure 2.10).

Unfortunately there was no stereoinduction in the reaction. Marples explains this by noting the conformational mobility of the saturated ring. With little rigidity in the system, low induction would be expected.

2-18a **2-18b**

Figure 2.10 Marples' Ketone Catalysts

One year later, Yang[40] reported a series of ketone catalysts designed to take advantage of the information derived from both the chiral and achiral epoxidation of olefins with dioxiranes. It was found that the incorporation of electron-withdrawing groups increases the reactivity of the ketone and subsequent dioxirane. Bulky steric groups were attached to help communicate stereochemistry. From this information, Yang synthesized a series of biphenyl **2-19** and binapthyl **2-20** ketones (Figure 2.11). Each catalyst showed both improved chemical yield and ee for the epoxidation, the best being 87% ee for *trans*-stilbene. Later that year, Yang[41] improved these catalysts by attaching steric "sensors" designed to orient the substrate as it approaches the catalyst. The highest ee's, 84-95% for a variety of substrates, were observed when a 1,3-dioxane was used as the sensor, **2-21**.

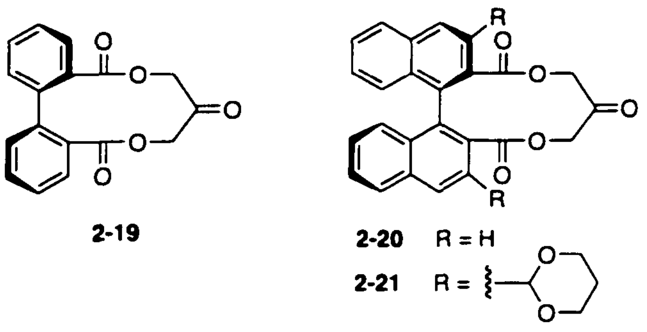
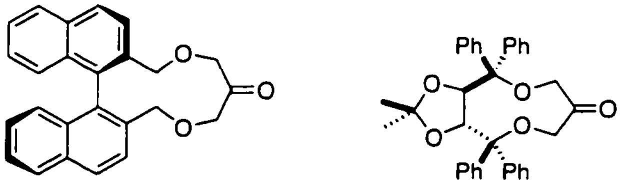


Figure 2.11 Yang's Ketone Catalysts

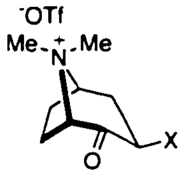
Several other groups have tried to develop C_2 symmetric catalysts similar to Yang's, however, only limited success has been seen. Both Song[43] and Adam[44] reported ketones in which the ester moiety has been converted to an ether. Song's ketone was derived from a chiral binapthol **2-22**, while Adam's ketone was derived from (+)-tartaric acid **2-23** (Figure 2.12). Neither group reported an increase in selectivity. In fact both observed a decrease in both ee and chemical yield compared to ketones **2-19**, **2-20**, and **2-21**.



2-22 **2-23**

Figure 2.12 Song's and Adam's Ketone Catalysts

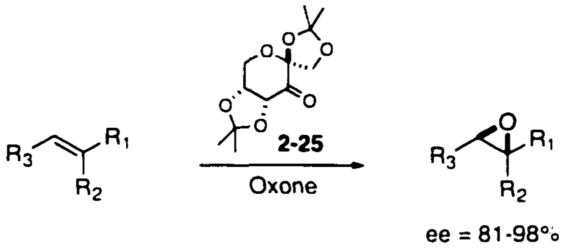
In 1997, Denmark[45] reported the effect of electronics on the rate of epoxidation. A series of fluorinated 4-*tert*-butylcyclohexanones were prepared and utilized in the epoxidation. The ketones which possessed an equatorial fluorine α to the carbonyl were better catalysts than those with an axial fluorine. This effect was even greater when two equatorial fluorines were present. To further illustrate the influence of an equatorially oriented fluorine, the tropanone derived ketone **2-24** was employed in the epoxidation *trans*-β-methylstyrene. When X was H, only a 21% conversion was observed. When X was changed to fluorine, the reaction went all the way to completion, giving a 35% ee.



2-24

Figure 2.13 Denmark's Tropanone Catalyst

In 1996, reports[46] from our laboratories were published describing a new type of ketone catalyst **2-25**. The catalyst was derived from D-fructose, and showed remarkable activity for the epoxidation of unfunctionalized *trans* olefins (Scheme 2.1). This type of ketone had many advantages; the stereogenic centers in the molecule were located near the center of the reaction, the carbons α to the carbonyl group were either quaternary or tied up in a ring thus minimizing epimerization, and they are easily synthesized from D-fructose. Using a known literature procedure,[47] the enantiomer of ketone **2-25** can be prepared from L-sorbose.



Scheme 2.1

2.1.5.2. Mechanism of the Dioxirane Mediated Asymmetric Epoxidation

Several papers[48-50] have appeared concerning the nature of the reactive intermediate in the epoxidation of olefins using Oxone and a ketone. One of the questions that needed to be answered concerned the actual epoxidation species. Two options quickly became apparent, dioxirane **2-26**, or the tetrahedral intermediate **2-27**.

2-26 **2-27**

Figure 2.14

The first paper dealing with this issue appeared in 1996.[48] On the basis of an ^{18}O labeling study Armstrong suggested that the open form **2-27** was the epoxidation agent. Using ^{18}O labeled 4-*tert*-butylcyclohexanone as the precursor to the catalyst, he performed a series of epoxidations looking for incorporation of the label into the epoxide. Finding no such incorporation, Armstrong concluded that intermediate **2-27** was the reactive species and not the dioxirane **2-26**. This study was quickly questioned on the basis of their poor 15% yield, and the reduced ability of their catalyst to distribute between the organic and aqueous layers to participate in the catalytic cycle. Subsequent reports found a substantial amount of background reaction, so it is very likely that the labeled ketone did not participate at all. Oxone itself is known to epoxidize olefins, but only at a slow rate in the absence of a ketone.[42]

In early 1997, Adam tried to clarify this issue by carrying out a competition study.[49] Knowing that the oxidation of an azomethine **2-28** with dioxirane **2-26** results in the formation of the corresponding nitrone **2-29** and/or aldehyde **2-30**, while oxidation with compounds such as **2-27** results in the exclusive formation of the corresponding oxaziridine **2-31**, the products of the competition could be analyzed to determine which pathway was used (Figure 2.15). Products from both pathways were observed, suggesting that a dioxirane is generated under the reaction conditions, but providing little clarification as to the reaction pathway for epoxidation.

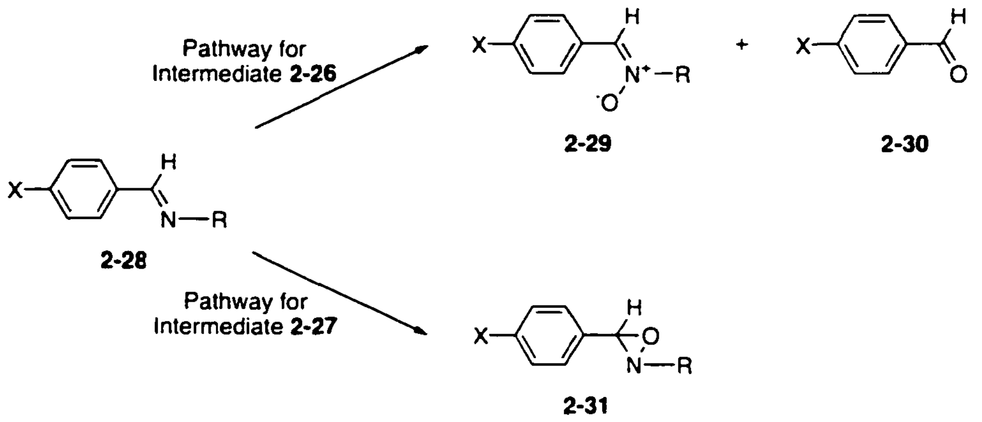
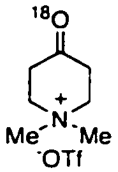


Figure 2.15 Adam's Competition Study

In late 1997, Denmark[50] provided concrete evidence for the participation of dioxiranes in the epoxidation of olefins. In an experiment similar to Armstrong's, Denmark used ^{18}O labeled 1,1-dimethyl-4-oxopiperidinium triflate **2-32** under phase transfer conditions to epoxidize 1-phenylcyclohexene in the presence of Oxone.



2-32

Figure 2.16 Catalyst for Denmark's ^{18}O Labeling Study

When one equivalent of ketone **2-32** containing 90% ^{18}O was used, 34% of the resulting epoxide contained the isotopic label. As the amount of ketone increased, the amount of ^{18}O incorporation also increased, suggesting that the dioxirane intermediate **2-26** was indeed involved. Even more convincing was that the epoxidation had proceeded in 90% yield, with very little background reaction. This study gave the most compelling evidence that dioxiranes are the reactive species in the epoxidation of olefins.

2.1.5.3. The Catalytic Cycle

In the initial report of the asymmetric epoxidation,[46] the reaction was run with 3 equivalents of ketone **2-25** in acetonitrile/water buffered to pH 7.8 with sodium bicarbonate. The large excess of ketone was necessary to obtain high ee's. It had been shown that intermediate **2-33**, formed after the attack by Oxone on the ketone, can undergo a Baeyer-Villiger rearrangement to yield a lactone, **2-36** or **2-37**, which can further degrade to acetone (Figure 2.17).[51] Since the reaction is typically done in an aqueous environment, it is difficult to isolate the degradation products since hydrolysis gives a water soluble product. In order to minimize decomposition of the catalyst and drive intermediate **2-33** toward the reactive dioxirane **2-35**, the pH of the reaction was raised. Not only was the catalyst more stable at the higher pH (10.5), the amount of Oxone used could actually be decreased (from 5 equiv. to 1.4 equiv.). With these improved conditions, it was possible to the lower the catalyst loading to 20-30 mole %, making the reaction truly catalytic.[52]

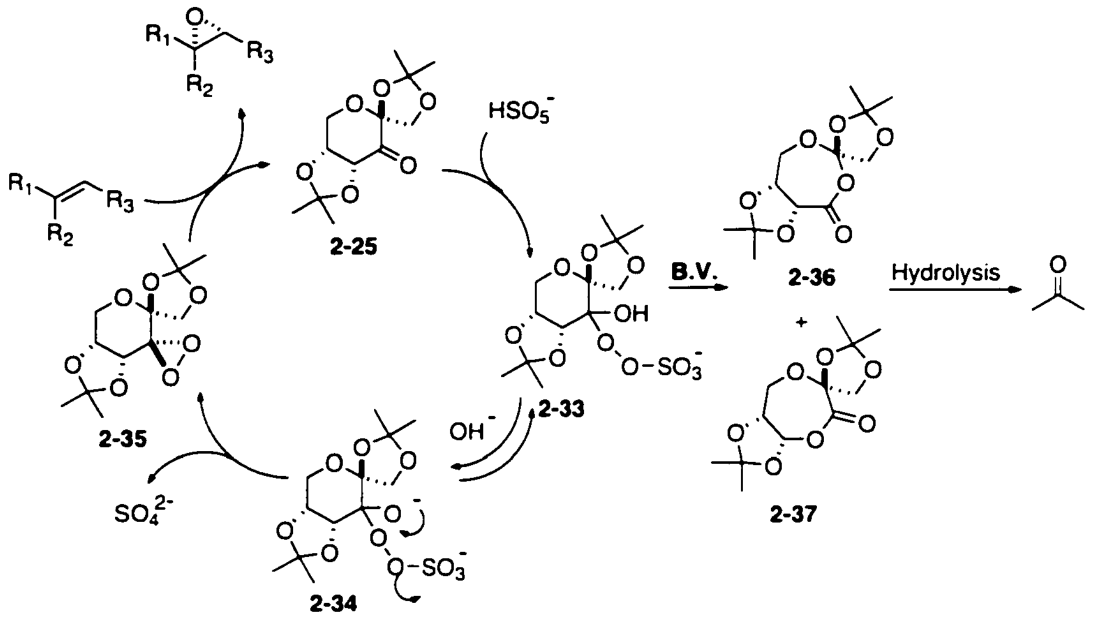


Figure 2.17 Proposed Catalytic Cycle

2.1.5.4. Prediction of Stereochemistry

The stereochemistry of the epoxide can easily be predicted based on the approach of the olefin to the dioxirane. There are two possible extreme orientations the olefin can approach, spiro and planar (Figure 2.18).

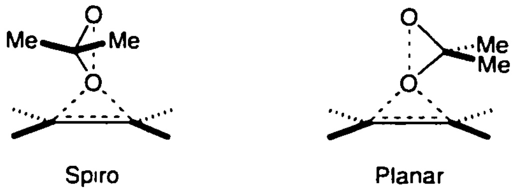


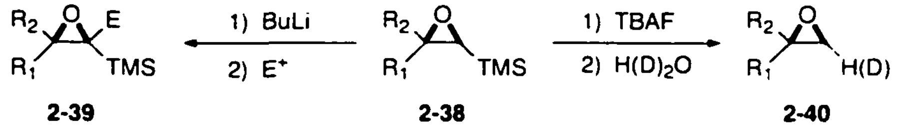
Figure 2.18 Spiro and Planar Transitions States

In the planar transition state the O-O bond is in the plane of the C-C π bond, whereas in the spiro transition state the O-O bond is orthogonal to the C-C π bond. A number of groups have performed theoretical calculations for the epoxidation of olefins, primarily ethylene, by dimethyldioxirane. In all reported cases, the spiro transition state had the lowest energy.[53-56] More importantly, the present experimental results suggest that the spiro transition state is the predominant pathway.

2.2. EPOXIDATION OF 2,2-DISUBSTITUTED VINYLSILANES

2.2.1. Background

α,β-Epoxysilanes are useful synthetic intermediates,[57] and new epoxides may be obtained from α,β-epoxysilanes by alkylation[58-60] or desilylation.[61-64] These methods proceed *via* an intermediate oxiranyl anion, which is then trapped by an electrophile, in the case of alkylation, or by a proton, in the case of desilylation (Scheme 2.2).



Scheme 2.2

The silicon group can also direct incoming nucleophiles, allowing for regioselective opening of the epoxide.[65-76] A variety of nucleophiles have been utilized in this reaction, and in nearly every case, ring opening occurs at the silicon-substituted carbon (Figure 2.19).

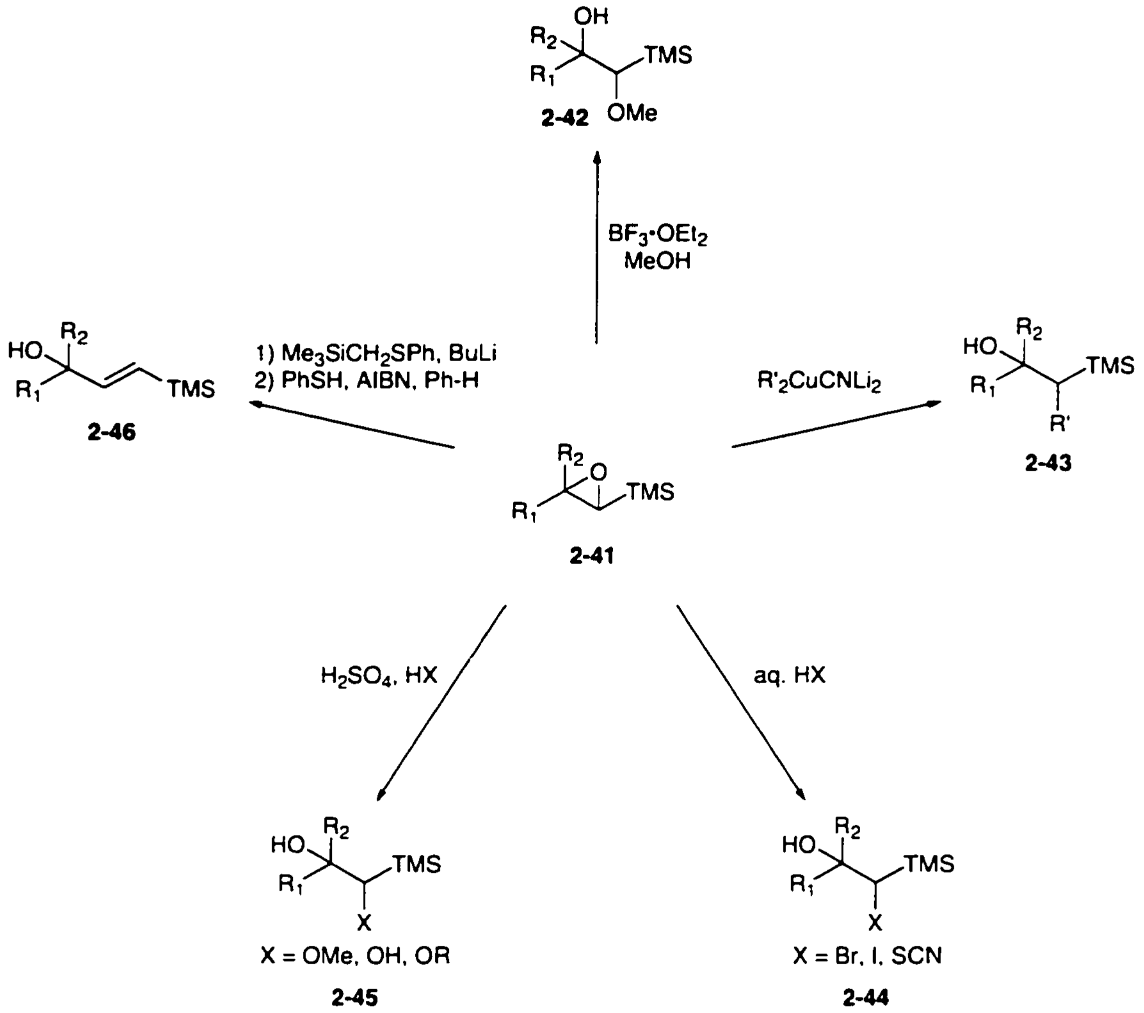
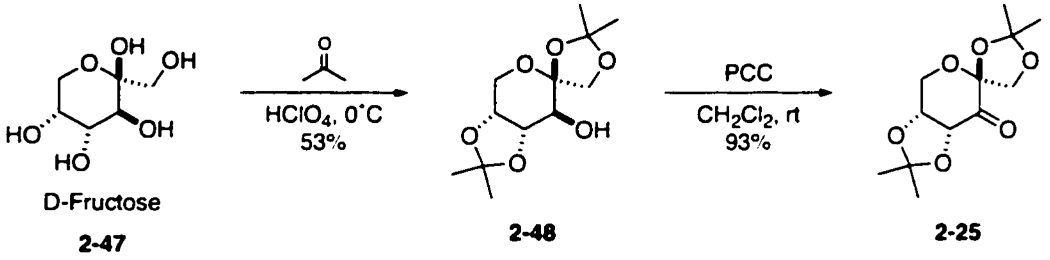


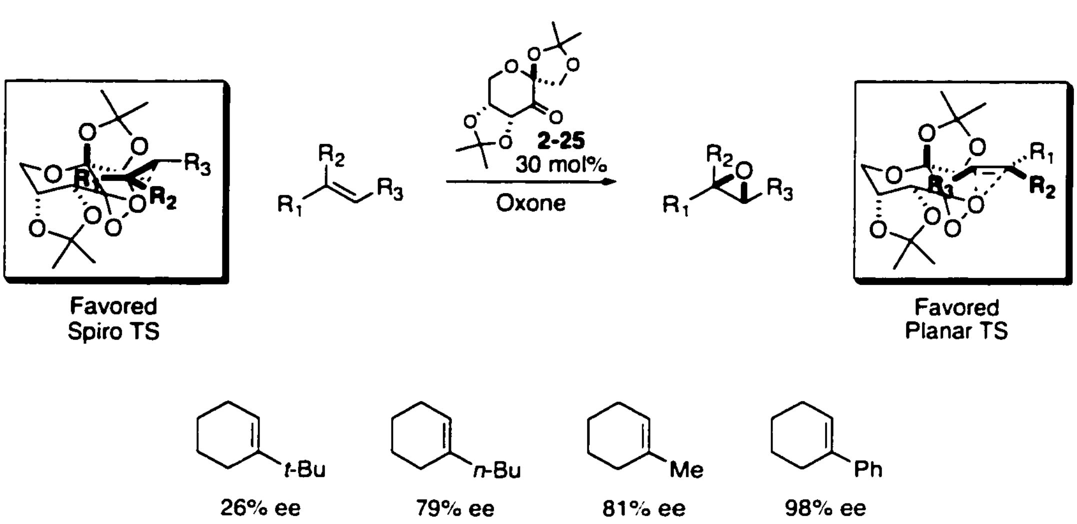
Figure 2.19 Nucleophilic Opening of α,β-Epoxy Silanes

Given the numerous applications of α,β-epoxy silanes, and the fact that the inherent chirality of such moieties can be transferred in subsequent reactions, it was important to generate them in an asymmetric fashion. The epoxidation of vinylsilanes presented an attractive approach to the synthesis of such compounds. Recently a highly enantioselective epoxidation method was reported[77-81] for *trans*- and trisubstituted olefins using the fructose derived ketone **2-25** as catalyst and Oxone as oxidant. This catalyst was easily prepared as shown in Scheme 2.3 and found to be highly substrate dependent.

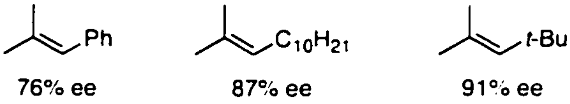


Scheme 2.3

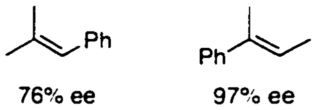
Assuming, as mentioned above, that there are only two competing pathways,[82] the spiro and planar (Figure 2.20), the effects of substitution on the olefin may be easy to predict. As the size of R_1 increases, the spiro transition state is disfavored due to the heightened steric interaction between the R group and the pyran ring of the catalyst. The net effect is to make the planar transition state more favorable, thus lowering the ee. It should be noted that there is not a total switch to the planar transition state, as this would presumably give the opposite enantiomer in high ee. Instead, the two transition states become more nearly equal in energy, allowing for little to no selectivity. In a similar way, as R_3 becomes larger, the planar transition state is disfavored due to the heightened steric interaction between the R group and the pyran ring. In this case the energy difference becomes greater, favoring the spiro transition state, and the selectivity rises. By combining the steric effects of both a small R_1 and a large R_3, the ee of the epoxide should be amplified due to the overwhelming predominance of the spiro transition state. This was indeed found to be the case.[77]



The effect of the size of R_1 on enantioselectivity
(Decreasing the size of R_1 results in a higher ee)



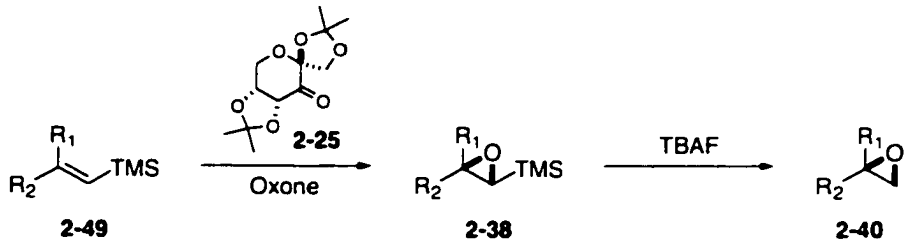
The effect of the size of R_3 on enantioselectivity
(Increasing the size of R_3 results in a higher ee)



The effect of the size of R_1 and R_3 on enantioselectivity
(Decreasing the size of R_1 and increasing the size of R_3 results in a higher ee)

Figure 2.21 The Effect of Sterics on Enantiomeric Excess

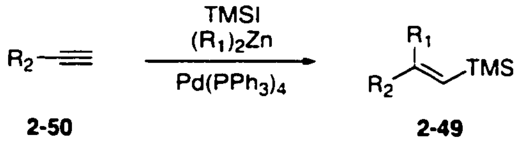
In an effort to expand the scope of this epoxidation method, it was found that 2,2-disubstuted vinylsilanes were quite complementary substrates, producing 2,2-disubstuted α,β-epoxysilanes with high enantioselectivity (Scheme 2.4). Additionally, it was found that upon desilylation, 1,1-disubstuted terminal epoxides could be obtained without loss in enantioselectivity, providing an efficient route to this class of compounds.[83]



Scheme 2.4

2.2.2. *Results*

Initial studies focused on the best method for synthesizing the desired vinylsilanes. It was quickly found the best route was the reported[84] palladium-catalyzed coupling of a terminal acetylene, dialkyl zinc and iodotrimethylsilane (Scheme 2.5). Although a wide variety of commercially available acetylenes participated in this coupling, only dimethyl-, diethyl-, and dibutylzinc gave products in satisfactory yield. Diphenylzinc was totally unreactive. Both dimethyl- and diethylzinc are commercially available, while dibutylzinc had to be prepared *in situ*.



Scheme 2.5

The putative mechanism for this reaction is shown in Figure 2.22. Initial loss of two ligands by palladium gives the highly reactive 14e$^-$ palladium(0) species, which undergoes oxidative addition into iodotrimethylsilane (TMSI) to give an intermediary silylpalladium(II) species. Silylpalladation of an acetylene leads to an σ-alkenyl-palladium(II) complex, which, in the presence of dialkylzinc, undergoes transmetallation generating a second σ-alkenylpalladium(II) complex. This then reductively eliminates to give the vinylsilanes and regenerates the initial palladium(0) species.

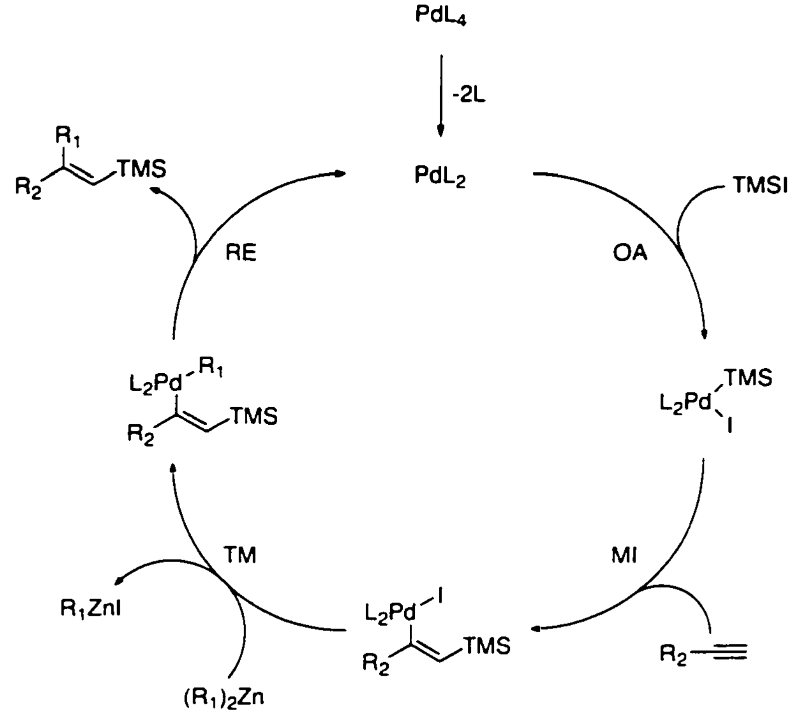
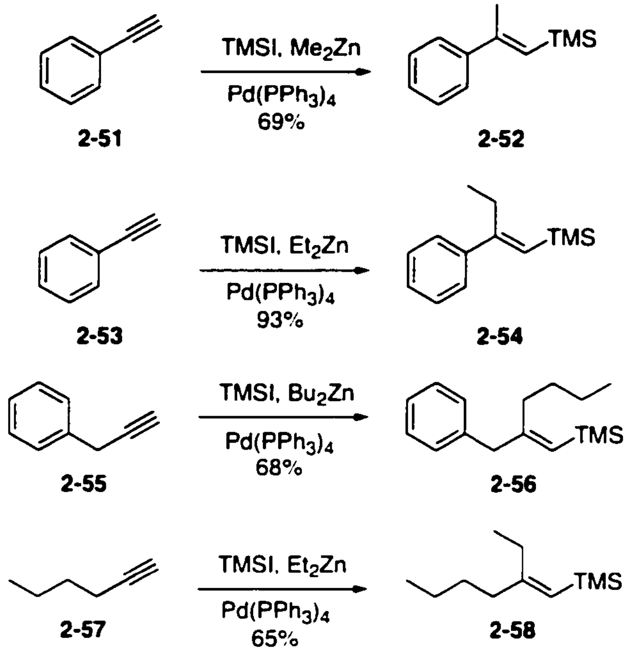


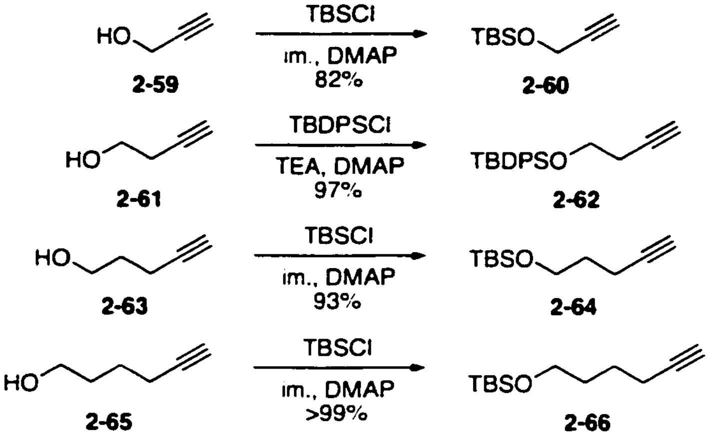
Figure 2.22 Proposed Catalytic Cycle for the Pd-Catalyzed Coupling of Acetylenes, Iodotrimethylsilane, and Dialkylzinc Reagents

This reaction proved to be operationally simple as most substrates subjected to the reaction conditions provided the desired products in good yield. The only problems arose when the acetylene contained either a carbon-based ether or an ester moiety. This is most likely due to selective reaction of the TMSI at these functional groups.[85,86] Scheme 2.6 shows the vinylsilanes that were synthesized directly from commercial acetylenes.



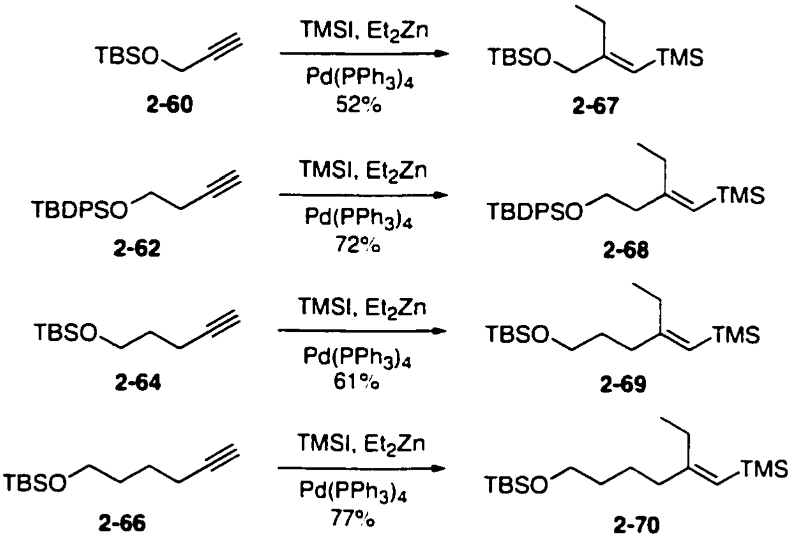
Scheme 2.6

To expand the substrate scope, oxygen functionality was incorporated into the R_1 position of the vinyl silane. Since free alcohols are not tolerated under the reaction conditions, it was necessary to protect the pendant hydroxyl group. To serve this purpose, silicon-based protecting groups were chosen, namely silyl ethers (Scheme 2.7). Silyl ethers have become one of the most widely-used protecting groups for the hydroxyl function.[87] This is most likely due to the ability to moderate their reactivity, both formation and cleavage, by careful selection of the substituents on the silicon atom. For our purposes, either the *t*-butyldimethylsilyl- or *t*-butyldiphenylsilyl ether was utilized (TBS or TBDPS, respectively).



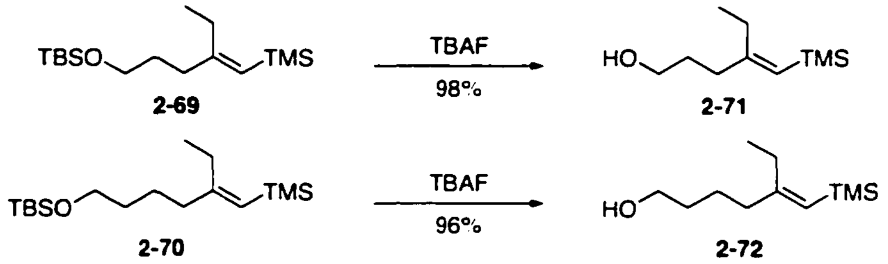
Scheme 2.7

These acetylenes were then subjected to the Pd-catalyzed coupling reaction. Reaction went smoothly in each case, with none of the desilylated products observed (Scheme 2.8).



Scheme 2.8

In order to further test the generality, and to determine the effect of a 1° alcohol in the epoxidation reaction,[88] two of the silyl protected substrates were subjected to removal of the protecting group (Scheme 2.9). Simple treatment of the silyl ether with tetrabutylammonium fluoride (TBAF) unveiled the 1° alcohol, which was left unprotected in the subsequent epoxidation step.

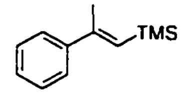
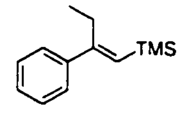
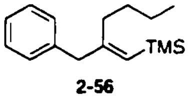
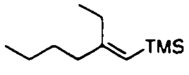
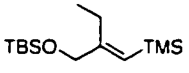
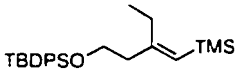
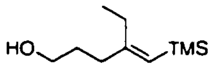
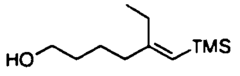


Scheme 2.9

With all the necessary substrates in hand, attention was turned to the asymmetric epoxidation. In all cases, the substrates proved to be somewhat unreactive, probably as a result of the increased steric bulk of the trimethylsilyl group in the R_1 position. Although good conversion could be obtained using less ketone (*e.g.* 0.3 equiv., Table 2.1, entry 7), higher conversions were obtained when more ketone (0.6 equiv.) was used.

In the dioxirane-mediated epoxidation, the spiro transition state is electronically favored as a result of a stabilizing interaction of an oxygen lone pair of the dioxirane with the π^* orbital of the olefin.[89] Earlier work indicated that the spiro transition state could be further favored by increasing the size of R_1 (*vide supra*). The sterically demanding silyl group should certainly be large enough to accomplish this. Gratifyingly, the enantioselectivity was high for these reactions (Table 2.1). In addition, there was no C-H insertion products detectable for any of the oxy-containing olefins.

Table 2.1. Asymmetric Epoxidation of Representative 2,2-Disubstituted Vinylsilanes[a]

Entry	Substrate	Yield (%)[b]	ee (%)	Config.
1	 **2-52**	74	94[c]	(*R*,*R*)[g,90]
2	 **2-54**	82	92[c]	(*R*,*R*)[h]
3	 **2-56**	66	93[d]	(*R*,*R*)[h]
4	 **2-58**	51	90[e]	(*R*,*R*)[h]
5	 **2-67**	67	84[e]	(*R*,*R*)[h]
6	 **2-68**	67	92[f]	(*R*,*R*)[h]
7	 **2-71**	80 71[i]	90[e] 93[e]	(*R*,*R*)[h] (*R*,*R*)[h]
8	 **2-72**	75	91[e]	(*R*,*R*)[h]

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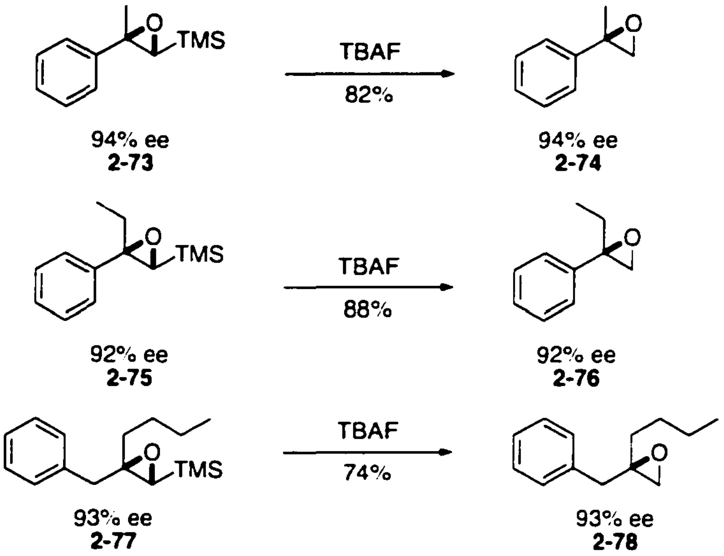
[a] All epoxidations were carried out at 0°C (bath temperature) with substrate (1 eq.), ketone (0.65 eq.), Oxone (1.35 eq.), and K$_2$CO$_3$ (5.8 eq.) in CH$_3$CN–dimethoxymethane-0.05 M Na$_2$B$_4$O$_7$•10 H$_2$O aqueous Na$_2$(EDTA) (4 x 10^{-4}) solution (1:2:2 v/v); the reactions were stopped after 3 h. [b] The epoxides were purified *via* flash chromatography and gave satisfactory spectroscopic characterization. [c] Enantioselectivity was determined by chiral HPLC (Chiracel OD) after desilylation. [d] Enantioselectivity was determined by chiral HPLC (Chiralpak AD) after desilylation. [e] Enantioselectivity was determined by ^{1}H NMR shift analysis of the epoxide directly with Eu(hfc)$_3$. [f] Enantioselectivity was determined by chiral HPLC (Chiralcel OD). [g] The absolute configuration was determined by comparison of the measured optical rotation with the reported one, after desilylation. [h] The absolute configuration was tentatively assigned by analogy based on the spiro reaction mode. [i] 0.3 eq. of ketone was used.

1,1-disubstituted terminal epoxides could be obtained with no loss in optical purity from the desilylation of the epoxysilanes using TBAF (Scheme 2.10). This presented an important advance in the generation of these compounds, as there was no efficient method for the stereoselective epoxidation of unfunctionalized 2,2-disubstituted olefins.



Scheme 2.10

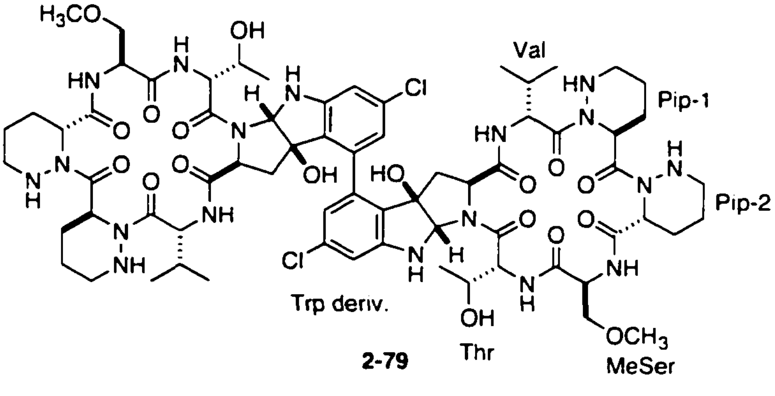
2.2.3. Conclusions

In summary, it was found that the epoxidation of 2,2-disubstituted vinylsilanes using the fructose-derived ketone **2-25** as catalyst and Oxone as oxidant is highly enantioselective. The silyl group enhances the selectivity by disfavoring the competing planar transition state through a steric effect. The availability of these enantiomerically enriched 2,2-disubstituted α,β-epoxysilanes provides opportunities for potential synthetic applications. For example, chiral 1,1-disubstituted terminal epoxides can be readily obtained from these epoxysilanes by desilylation.

2.3. Epoxidation of Indole Derivatives

2.3.1. Background

The natural product chloptosin **2-79**, a dimeric cyclohexapeptide, was recently isolated from the culture broth of a polyoxypeptin-producing strain of *Streptomyces*.[91] It induces the loss of viability in apoptosis-resistant AsPC-1 cells with an IC_{50} of 2.5 μg/mL after 24 h and in apoptosis-sensitive human pancreatic adenocarcinoma BxPC-3, human fibrocarcinoma HT1080, and human T cell Jurkat cells with IC_{50} values of 0.49, 0.07, and 0.20 μg/mL, respectively. Additionally, it inhibits the growth of AsPC-1, BxPC-3, HT1080, and Jurkat cells with IC_{50} values of 50, 12, 5.4, and 6.4 ng/mL respectively, assessed after 48 h of treatment. Furthermore, chloptosin strongly inhibits the growth of Gram-positive bacteria, such as *Staphylococcus*, *Micrococcus*, and *Bacillus* strains (MIC range 0.20-0.78 μg/mL), but not that of Gram-negative bacteria and was very effective against MRSA (MIC range of 0.025-1.56 μg/mL, MIC_{50} 0.78 μg/mL, MIC_{90} 0.78 μg/mL).



2-79

Figure 2.23 Chloptosin

Chloptosin is structurally related to himastatin **2-80**.[92-94] but is significantly different in its amino acid content (Figure 2.24). Most notable are the absence of an ester moiety and the presence of chlorine on the pyrroloindoline rings.

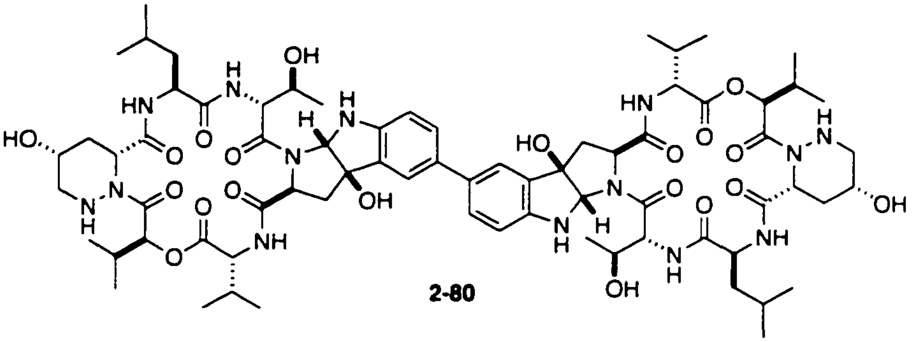
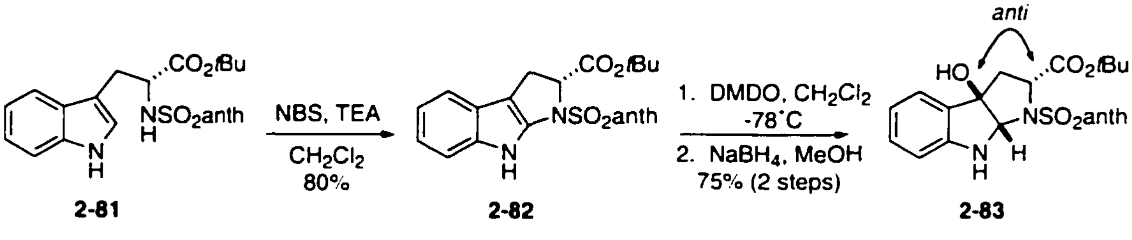


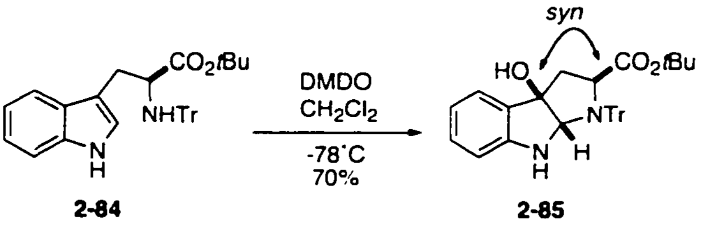
Figure 2.24 Himastatin

A total synthesis of himastatin was reported by the Danishefsky labs in 1998.[95,96] The major component of this synthesis was the construction of the 2,3,3a,8a-hexahydropyrrolo[2,3,*b*]indole moiety, **2-83**. Initial investigations into the assembly of this modified tryptophan derivative involved an oxidative cycloaromatization of the parent amino acid, followed by dimethyldioxirane (DMDO) epoxidation and subsequent ring opening (Scheme 2.11).[95]



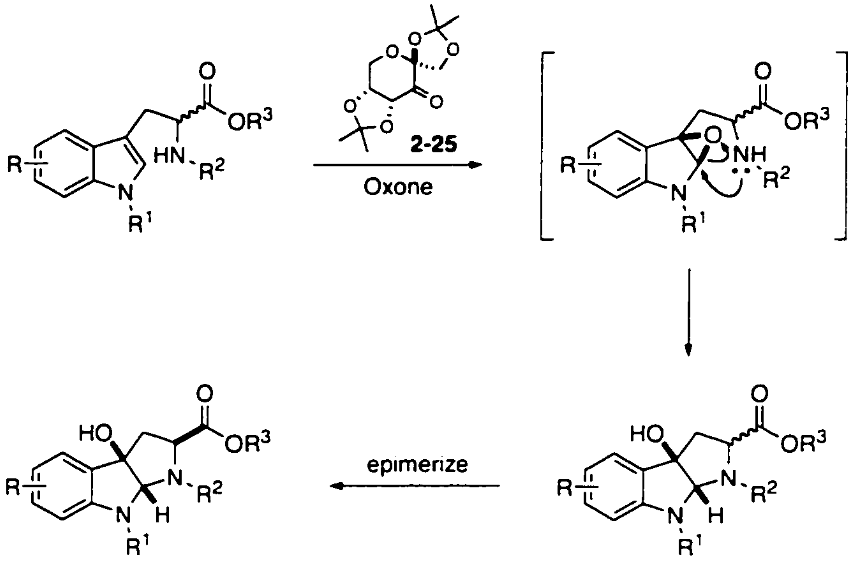
Scheme 2.11

Upon incorporation of this moiety into the synthesis, it was determined that the stereochemistry of the C_2-carboxamido group was incorrect, and a *syn* junction was required in the natural product. This was cleverly corrected by utilizing a stereospecific oxidative cyclization (Scheme 2.12).[96] Epoxidation of N-α-trityl-L-tryptophan *t*-butyl ester with DMDO gave the desired *syn-cis* hexahydropyrrolo[2,3,*b*]indole in 70% yield, apparently without the undesired *anti-cis* diastereomer. Danishefsky did not speculate as to the reason why this selectivity was observed, but it would be expected that the molecule assumes a rigid state at –78°C and the extant stereochemistry of the protected amino acid serves to direct the epoxidation. Incorporation of **2-85** into the synthesis gave the natural product.



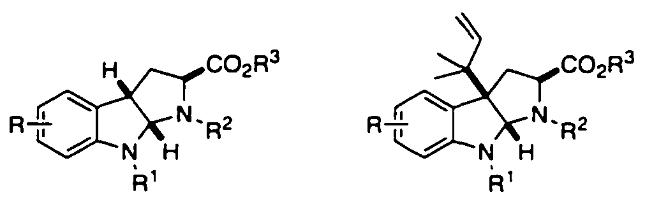
Scheme 2.12

It was the synthesis of the structurally-related indole derivative in chloptosin that drew our attention. The C_6-halosubstitution on the indole, as well as the necessity to be able to preferentially substitute the C_3 position in order to generate dimerization partners, led us to believe that a substantially different synthetic route was necessary. It was our plan to begin with a racemic tryptophan derivative, allowing for the most flexibility in synthesizing the appropriately functionalized indole. Epoxidation, followed by 5-*exo* cyclization[97,98] of the tryptophyl α-amino group onto the intermediate epoxyindole would give rise to the properly substituted pyrrolo[2,3,*b*]indoline system in much the same way that this moiety was generated in the himastatin synthesis. However, in the case of himastatin, an achiral oxidant could be used since the facial selectivity was determined by the substrate. If a racemic substrate were used, the epoxidation would have to be done stereospecifically, generating a mixture of *syn/anti* diastereomers. Epimerization of the pendent C_2-carboxamido group would then furnish the desired *syn-cis* relationship (Scheme 2.13).



Scheme 2.13

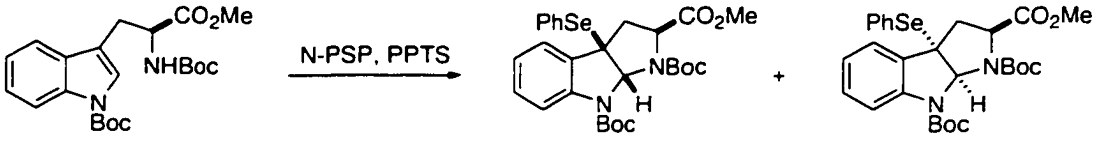
Although this approach to the synthesis of the 3a-hydroxyhexahydropyrrolo-[2,3,*b*]indole ring system has not been reported in the literature, the application of 5-*exo* cyclizations to form structurally similar systems has (Figure 2.25).[99-101] These systems contain the hexahydropyrrolo-[2,3,*b*]indole ring system but are substituted at the 3a (angular) position with either a hydrogen **2-86**,[100] or reverse prenyl moiety **2-87**.[101]



2-86 **2-87**

Figure 2.25

Although these compounds are differentially substituted at the angular position, their syntheses bear a remarkable similarity to our anticipated pathway. Compounds **2-89** and **2-90** are obtained *via* oxidative cyclization of tryptophan derivatives with N-phenylselenyl-phthalimide (N-PSP) to give the desired pyrroloindole as a roughly 9:1 mixture of *exo:endo* carboxylate isomers (Scheme 2.14). Given the product distribution, it is evident that the reaction is under kinetic control, since the *endo* product is known to be thermodynamically more stable than the *exo* product in related systems.[102]



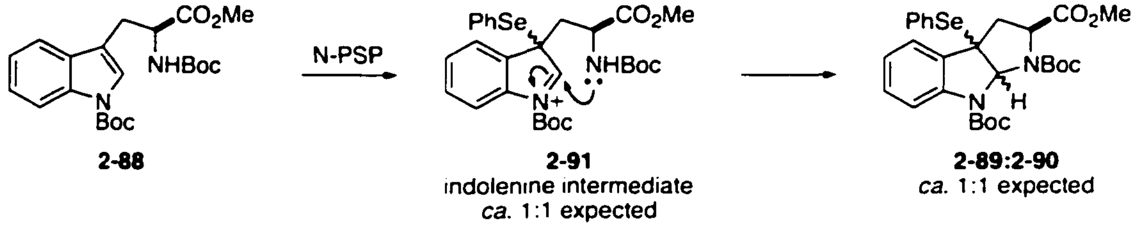
2-88

2-89
major
(*exo*)

2-90
minor
(*endo*)

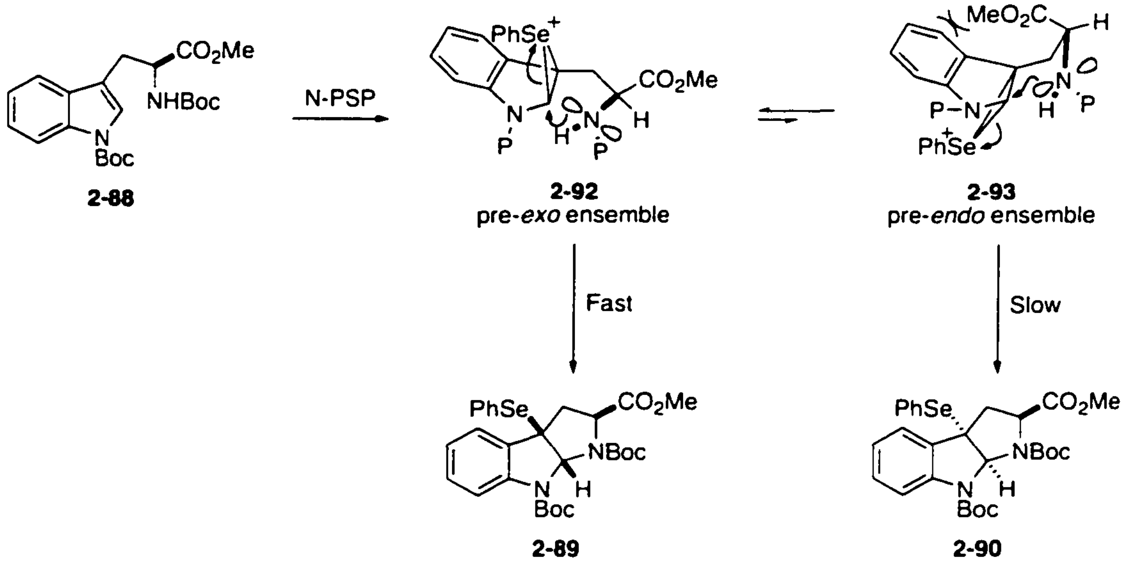
Scheme 2.14

The significance of this reaction is the mechanism of the cyclization, and how it relates to our proposed epoxidation/cyclization method. There are likely two competing processes.[101] The first involves the opening of a selenonium intermediate by the lone pair of the indole nitrogen, giving a discrete iminium species which is then quenched by attack from the pendant *N*-Boc amino group (Scheme 2.15). In this case the stereochemical outcome of the reaction would be, in essence, determined by the initial attack of the selenium species on C_3 of the indole. This scenario seems improbable, as it is not likely that formation of the indolenine cyclization intermediate could manifest a high degree of kinetic stereoselection.



Scheme 2.15

The second possible mechanism involves a "S_N2-like" opening of the selenonium intermediate directly by the pendant *N*-Boc amino group (Scheme 2.16). In this case the likelihood of kinetic selection is much greater. It is possible that the formation of the selenonium species is reversible and that the product distribution is a consequence of the energy differences in the diastereomeric transition state.

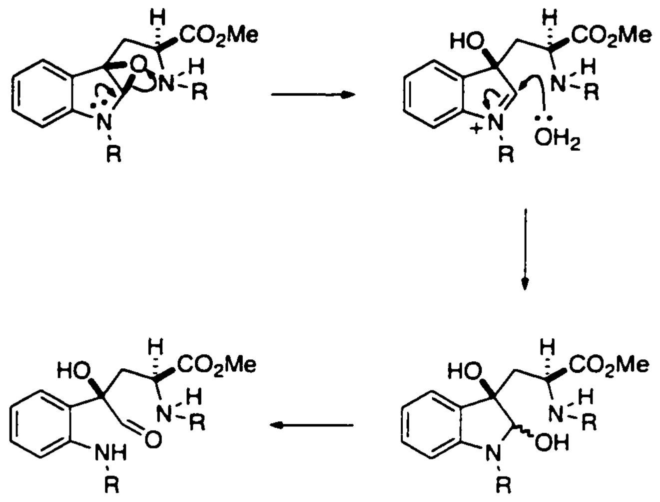


Scheme 2.16

Given these observations, it was felt that the 3a-hydroxyhexahydropyrrolo-[2,3,*b*]indole ring system could be prepared by application of our asymmetric epoxidation methodology. Additionally, since the reaction is run under moderately basic conditions, it was hoped that the C_2-carboalkoxy group would be epimerized during the reaction to provide the desired diastereomer.

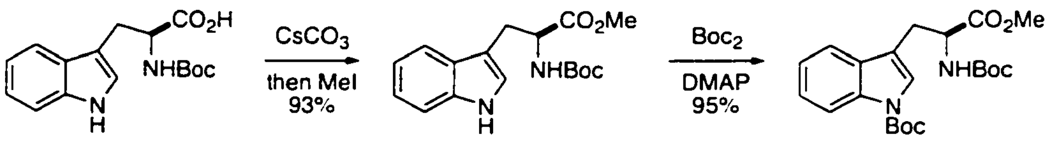
2.3.2. Results

Initial studies focused on the feasibility of the epoxidation/cyclization reaction, and quickly led to some important observations: (1) it is important that the side chain amino group be properly protected, as no reaction occurs when it is masked as either an *N*-acetyl or an *N*-benzyl amine. Additionally, protection with a highly electron-withdrawing group inhibits the nucleophilic epoxide opening. (2) The indole nitrogen must be properly protected. In this case, it was felt that a highly electron-withdrawing group was necessary. This would minimize the likelihood of epoxide opening *via* iminium ion formation, and diminish the possibility of N-oxide formation.[103] Since the reaction is done under aqueous conditions, it would be expected that, upon iminium ion formation, hydrolysis would ensue (Scheme 2.17).



Scheme 2.17

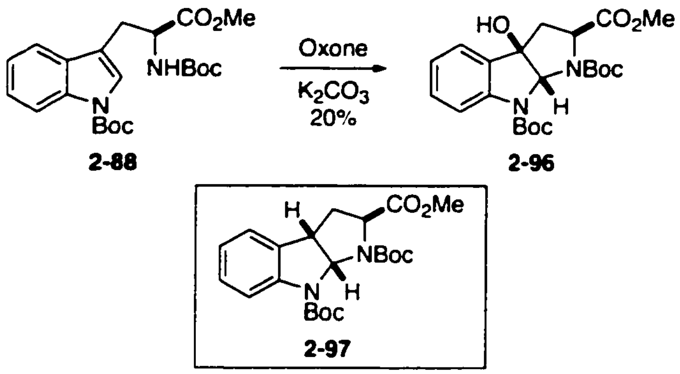
Initially, it was decided to see if a carbamate would serve as a suitable protecting group for both the side chain amino indole nitrogens. Thus N-α-Boc-L-tryptophan **2-94** was esterified utilizing the conditions reported by Wang[104] and then indole nitrogen **2-95** was protected as its N^{in}-Boc derivative **2-88** (Scheme 2.18).[105,106]



2-94 **2-95** **2-88**

Scheme 2.18

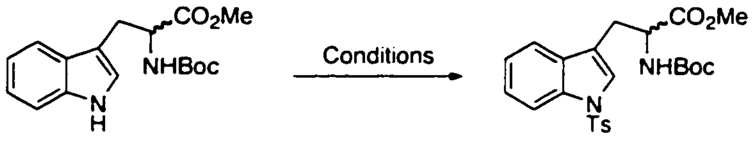
With this fully protected tryptophan in hand, racemic epoxidation was explored. Using the reported racemic epoxidation conditions,[107] the desired pyrroloindole **2-96** was obtained, albeit in poor yield (20%). The spectral data for this compound is nearly identical to a similar compound **2-97** containing an angular hydrogen rather than a hydroxyl group (Scheme 2.19).[108]



Scheme 2.19

Interestingly, **2-96** was isolated as a single *exo* diastereomer, suggesting either hydrolysis of the *endo* precursor occurs readily, or epimerization of the C_2-carboxyl group transpires under the reaction conditions. In either case, due to the low yield of cyclized product observed, it appears that hydrolysis "out-competes" cyclization in this system. It was, therefore, determined that the indole nitrogen be protected with a group having stronger electron-withdrawing abilities. Additionally, it was decided that racemic tryptophan should be used since epimerization of the C_2-carboxyl was our ultimate goal.

N-α-Boc-DL-tryptophan was prepared by the method of Garner[108] and then esterified using the previously described method to give N-α-Boc-DL-tryptophan methyl ester **2-98**. A series of protecting groups were then investigated to see if the use of a stronger electron-withdrawing group would curtail hydrolysis, making cyclization more competitive. Use of the strongly electron-withdrawing sulfonamide moiety as a protecting group for the indole nitrogen has been shown in the past,[109] and was chosen as a potential substrate. Generation of the *p*-toluenesulfonamide proved to be somewhat tricky. However the desired product could be obtained in 46% yield under the proper reaction conditions (Scheme 2.20).

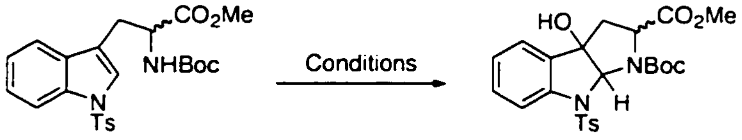


2-98 **2-99**

Entry	Conditions	Result
1	*p*TsCl, TEA, CH_2Cl_2	No reaction
2	*p*TsCl, NaOH, CH_2Cl_2, Bu_4NHSO_4	No reaction
3	*p*TsCl, DMF	No reaction
4	*p*TsCl, NaH, DMF	46% Yield

Scheme 2.20

Epoxidation of **2-99** proved to be difficult. None of the expected reaction products were obtained when either DMDO or ketone **2-25** was used as catalyst, in fact no identifiable products were found at all. When the more reactive 1,3-dichlorodimethyl-dioxirane was employed, only a small amount of what appeared to be the pyrroloindole was isolated (Scheme 2.21).

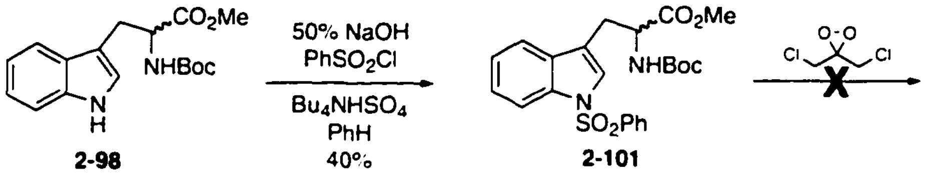


2-99 **2-100**

Entry	Conditions	Result
1	Dimethyldioxirane	No reaction
2	1,3-dichlorodimethyldioxirane	~14% yield
3	Ketone **2-25**	No reaction

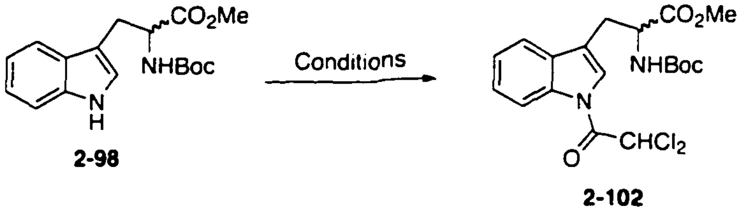
Scheme 2.21

Crich[100] reported that the use of a benzenesulfonate group as protection for the indole nitrogen gave particularly good results in his oxidative selenocyclization reaction (*vide supra*). With this in mind, the indole nitrogen was protected as its benzensulfonate[110] and subjected to the epoxidation conditions (Scheme 2.22). Unfortunately there was no reaction, even with 1,3-dichlorodimethyldioxirane.



Scheme 2.22

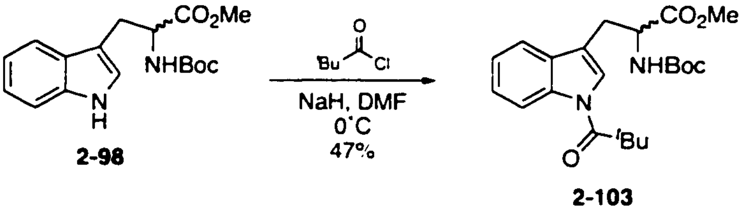
Concurrent with this effort, a second type of protecting group was investigated. In 1997 Rajeswaran[111] reported a novel method for the protection of the indole nitrogen. Treatment of simple indole with dichloroacetylchloride in dichloroethane (DCE) at reflux gave the dichloroacetylated indole in 88% yield. Unfortunately this protocol did not work with tryptophan; only starting material was recovered (Scheme 2.23).



Entry	Conditions	Result
1	$Cl_2HCCOCl$, DCE, Δ	No reaction
2	$Cl_2HCCOCl$, DCE, DMAP, Δ	No reaction
3	$Cl_2HCCOCl$, NaH, DMF	No reaction

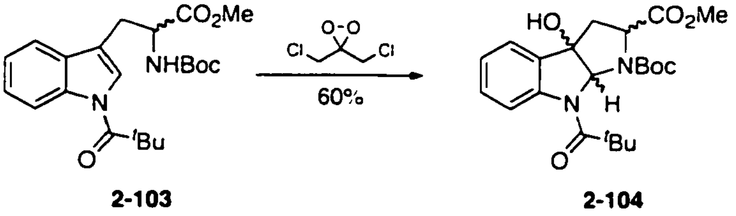
Scheme 2.23

Along the same lines, another acetate-type protecting group was investigated. Utilizing conditions reported by Nakatsuka, a pivaloate group could be placed on the indole nitrogen. Thus reaction of N-α-Boc-DL-tryptophan methyl ester with sodium hydride and trimethylacetylchloride at 0°C in DMF gave the protected N^{in} derivative as expected (Scheme 2.24).



Scheme 2.24

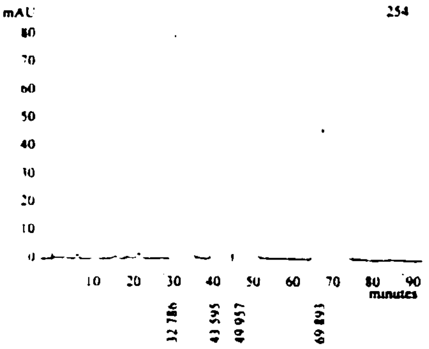
Epoxidation of **2-103** with DMDO was unsuccessful. However when the more reactive 1,3-dichlorodimethyldioxirane was used, the reaction proceeded to give the pyrroloindole **2-104** in a 1:1 ratio of *exo*:*endo* isomers (Scheme 2.25).



1:1 mixture of *exo*:*endo* isomers

Scheme 2.25

The diastereomers could not be separated by column chromatography, but were easily separable by HPLC. When a chiral column was used, complete enantio- and diastereomeric separation was possible (Figure 2.26). Unfortunately, when the asymmetric epoxidation conditions were applied, no reaction ensued and only starting material was recovered.



Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		24.6902	32.786	5444369
2		24.9605	43.595	5503975
3		25.3901	49.957	5598706
4		24.9593	69.893	5503719
	Totals	100.0001		22050768

Figure 2.26 HPLC Data Showing Enantio- and Diastereomeric Separation of **2-104**

Analysis of the preliminary results of this project indicated a potential problem. As a general observation in the epoxidation studies, it was found that placement of a large group in the R_3 position of a trisubstituted olefin raises the selectivity of the reaction (*vide supra*).[77] In this case, however, it appears that R_3 may be too big, effectively blocking the approach of the catalyst. Additionally, the large electron density present on the protecting group might complicate the situation. That is, there may be considerable electronic repulsion between the oxygen of the protecting group and the oxygens of the chiral ketal even further disfavoring catalyst approach (Figure 2.27).

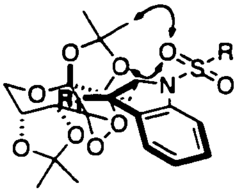


Figure 2.27

When the indole is protected with an acetate derivative, the oxygen is able to rotate away from the ketal to minimize the electronic repulsion. However, this places the alkyl moiety proximal to the ketal, increasing the steric problem (Figure 2.28).

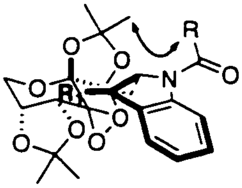
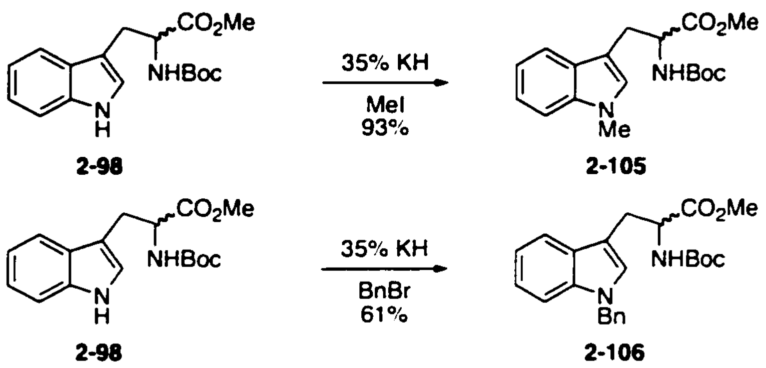


Figure 2.28

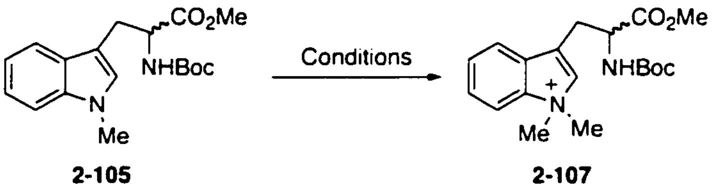
In an attempt to minimize this problem a new strategy was devised. It was originally believed that placement of an alkyl moiety on the nitrogen would be a problem as rapid N-oxidation might occur. This problem was addressed experimentally by investigation of both the N^{in}-methyl and N^{in}-benzyl derivatives.

Thus, N-α-Boc-DL-tryptophan methyl ester was protected with both methyl iodide and benzyl bromide according to the procedure reported by Snyder (Scheme 2.26).[112] Racemic epoxidation of the benzyl derivative resulted in immediate consumption of starting material. However, upon purification it was evident that the reaction conditions had only resulted in decomposition, and no identifiable products were obtained. Similar results were obtained with the methyl derivative.



Scheme 2.26

Since it was apparent that simple protection was not going to allow access to the desired pyrroloindoles, a different approach was taken. It was felt that if the indole nitrogen were quaternized the epoxidation problems might be circumvented. Unfortunately, these reactions could not be implemented due to the inability to quaternize the indole nitrogen (Scheme 2.27).



Entry	Reagent	Solvent	Result
1	MeOTf	CH_2Cl_2	Decomposition
2	MeI	Et_2O	No reaction
3	MeI	THF	No reaction

Scheme 2.27

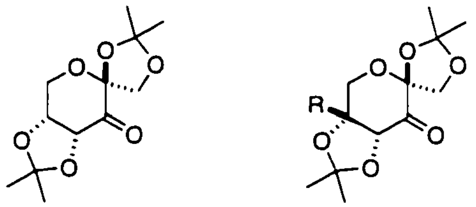
2.3.3. Conclusions

In summary, it was found that tryptophan derivatives could not be epoxidized efficiently under the original asymmetric epoxidation conditions. Limited results were obtained in the racemic epoxidation when the indole nitrogen of N-α-Boc-DL-tryptophan methyl ester was masked as either a *N*-Boc carbamate, *p*-toluenesulfonate, or trimethylacetate. Further study is necessary to see if these substrates can be epoxidized under the current conditions.

2.4. TOWARD THE SYNTHESIS OF A NOVEL KETONE FOR USE IN THE ASYMMETRIC EPOXIDATION REACTION

2.4.1. Background

The use of chiral ketones to affect the asymmetric epoxidation of unfunctionalized olefins has been the subject of great interest in recent years. In 1996 ketone **2-25** was reported as a good catalyst for the epoxidation of *trans*- and trisubstituted olefins.[46] In the continuing efforts to discover catalysts which are more general and demonstrate higher selectivity, ketone **2-108** was identified as a potential target (Figure 2.29).



2-25 **2-108**

Figure 2.29 Ketone Catalysts

Due to the structural similarities between ketones **2-25** and **2-108**, it was hoped that they would exhibit similar catalytic properties. However, with the addition of an R group β to the carbonyl, this new catalyst could conceivably give higher enantioselectivities. Analysis of the proposed transition state gives an indication as to why the selectivity is expected to be higher (Figure 2.30).

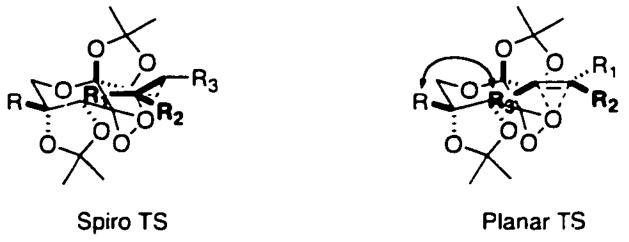
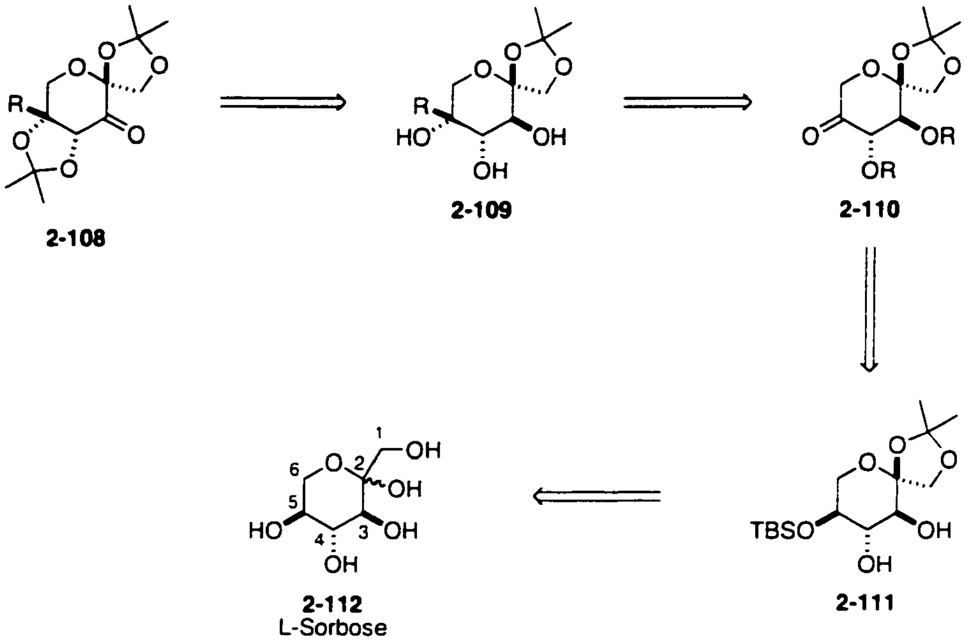


Figure 2.30 Spiro and Planar Transition States for Ketone **2-108**

In the favored spiro transition state the olefin approaches orthogonally to the dioxirane. As such, there is very little, if any, expected steric consequences by placement of a group β to the dioxirane. In the planar transition state the olefin approaches parallel to the dioxirane, placing R_1 in close proximity to the group on the β-carbon. The interaction between these two moieties generates a large steric repulsion, and as a result the planar transition state becomes even more disfavored.

It was envisioned that ketone **2-108** could be prepared from the readily available carbohydrate L-sorbose (Scheme 2.28). Retrosynthetically, ketone **2-108** comes from selective acetonization of triol **2-109** followed by oxidation of the remaining alcohol. Triol **2-109** can, in turn, come from selective nucleophilic addition to a ketone such as

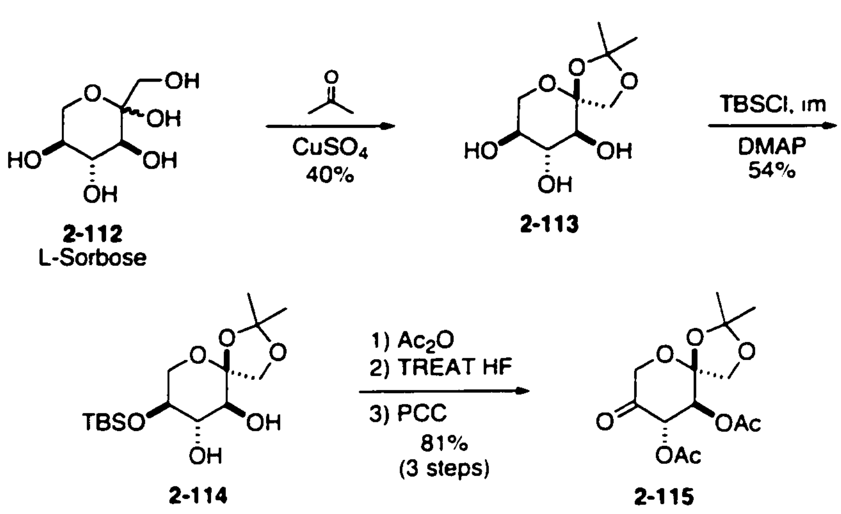
2-110, which can be obtained in 5 steps from L-sorbose, after acetonization, protection/deprotection and oxidation.



Scheme 2.28

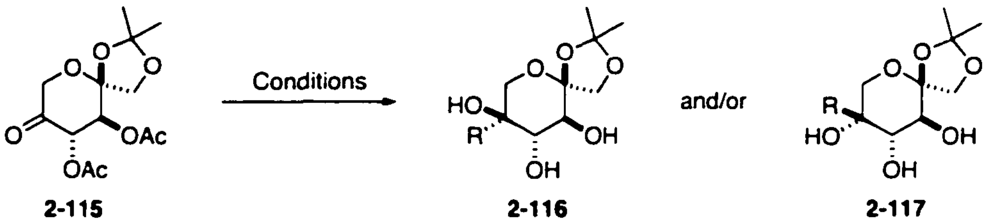
2.4.2. Results

The synthesis commenced with the mono ketalization of L-sorbose utilizing the method reported by Patil and Bose,[113,114] and selective TBS (TBS = $Me_2{}^tBuSi$) protection of the C_5 alcohol[115] furnishing diol **2-114** (Scheme 2.29). Acetylation of the remaining hydroxyls, followed by removal of the TBS ether and subsequent pyridinium chlorochromate (PCC) oxidation provided ketone **2-115**.



Scheme 2.29

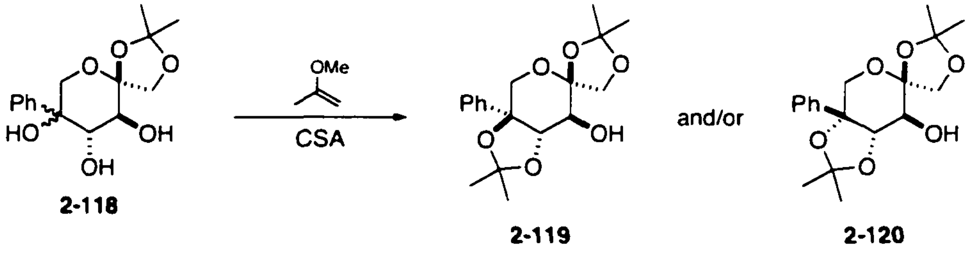
The C_2 and C_3 hydroxyls were protected as acetates so that treatment of ketone **2-115** with a nucleophile would result in addition to the ketone with concomitant removal of the acetates. It was surprising to find that treatment of ketone **2-115** with methylmagnesium chloride resulted only in very little reaction, with only unidentifiable products isolated along with unreacted starting material. The same was true when phenylmagnesium bromide was used. However, when the Grignard reagent was transformed into the less-basic organocerate,[116] reaction took place readily, and the desired triol was obtained in good yield. When phenyllithium was used as the nucleophile, the triol was also obtained. Interestingly, the two compounds were not identical. Each reaction had resulted in the formation of a separate diastereomeric product, without the formation of the other diastereomer (Scheme 2.30). This was not altogether unexpected, as these reagents are known to chelate oxygen functionality differently.[117-120] Based upon these previous models it was predicted that the organocerate would chelate better, leading to the incorrect diastereomer **2-116**.



Entry	Conditions	Result
1	MeMgBr	No Reaction
2	PhMgBr	No Reaction
3	PhMgBr/$CeCl_3$	**2-116**, 75%
4	PhLi	**2-117**, 69%

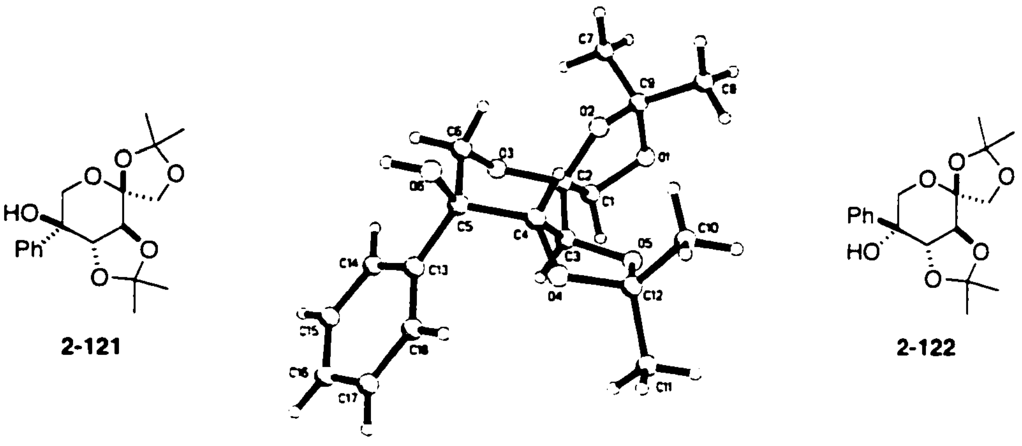
Scheme 2.30

Without absolute knowledge as to which diastereomer was the desired one, triols **2-116** and **2-117** were acetonized by treatment with 2-methoxypropene and (1R)-(-)-10-camphorsulfonic acid (CSA) (Scheme 2.31). Again, these compounds were similar in spectral properties, but it was quite evident that they were diastereomers. In order to clarify the identity of the diastereomers, it was felt that x-ray analysis of either the alcohol or ketone would be necessary.



Scheme 2.31

Oxidation of alcohols **2-119** and **2-120** provided perplexing results. Namely, none of the standard oxidation procedures worked, for either case. This was somewhat puzzling since oxidation of the parent ketone **2-25** was not a problem. Things were made clear when **2-119**, the acetonide from triol **2-116**, was crystallized. The x-ray structure showed that the acetonide had not formed between the C_4 and C_5 hydroxyls as expected; rather it had formed between the C_3 and C_4 hydroxyls (Figure 2.31). Furthermore, the stereochemistry at C_5 was revealed to be the undesired isomer, confirming the earlier prediction. The similarity in spectral data for **2-120**, the acetonide from triol **2-117**, and **2-119** suggested that the acetonide had formed between C_3 and C_4 as well, again explaining why oxidation of either tertiary hydroxyl group was unsuccessful.



2-121

2-121

2-122

Figure 2.31 Correct Structural Assignments and X-ray Structure of **2-121**

With the knowledge that the desired addition product arose from reaction of PhLi with **2-115**, and also that direct acetonization of **2-117** was not going to yield the desired product, attention was focused on how acetonide **2-120** could be accessed. The C_3 hydroxyl is likely to be more nucleophilic, and if this alcohol could be selectively reprotected, the desired acetonide might be accessible. Unfortunately, this was not the case as the C_3 alcohol of **2-117** could not be selectively protected.

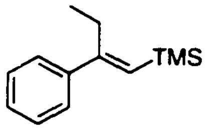
2.4.3. Conclusions

In summary, the synthesis of ketone **2-108**, a C_5-substituted analog of the fructose-derived ketone **2-25**, was investigated. An interesting chelation effect was uncovered during the addition of organocerium and organolithium reagents to ketone **2-115**. The addition of these reagents resulted in the selective formation of diastereomeric products. Acetonation of these products did not give the acetonide required for the ultimate generation of ketone **2-100**. Attempts to work around this problem were unsuccessful.

2.5. EXPERIMENTAL

General Methods. Oxone was purchased from Aldrich (the oxidation activity of the purchased Oxone occasionally varies with different batches). All glassware used for the epoxidation was carefully washed to be free of any trace metals, which are known to catalyze the decomposition of Oxone. Dioxane was freshly distilled from CaH under N_2. THF was distilled from sodium/benzophenone ketyl. Hexane was distilled prior to use. All other solvents were used without further purification. The 300 MHz ^{1}H NMR and 75.5 MHz ^{13}C NMR spectra were measured on a Varian-300 spectrometer in $CDCl_3$. Proton chemical shifts (δ) are given relative to internal $CHCl_3$ (7.26 ppm), and carbon chemical shifts are given relative to $CDCl_3$ (77.36 ppm). Infrared spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrometer. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ). Optical rotations were measured on an Autopol III automatic polarimeter in a 10 cm cell. Silica gel 60 (230-400 mesh) of E. Merck Co. was employed for all flash chromatography.

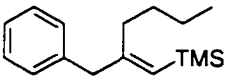
General Procedure for the Coupling Reaction with Me_2Zn and Et_2Zn:[84]



$C_{13}H_{20}Si$
Mol. Wt.: 204.38

To a 100 mL round bottomed flask was added $Pd(Ph_3)_4$ (0.04 mmol, 57.4 mg,), dioxane (5 mL), phenylacetylene **2-51** (2.5 mmol, 255 mg), and Et_2Zn (1 M in hexane, 2.5 mmol, 2.5 mL), under N_2. The mixture was stirred at room temperature for a period of 5 min and then iodotrimethylsilane (5.3 mmol, 0.75 mg) was added. Upon addition of the TMSI, a slight exothermic reaction occurred, and the solution turned from yellow/orange to red/brown. The mixture was allowed to react for an additional hour under N_2, and was then diluted with moist hexane (50 mL). Evaporation of the solvent *in vacuo* gave a dark brown oil. This was purified *via* flash chromatography (100% hexane) to yield (E)-2-phenyl-1-(trimethylsilyl)but-1-ene **2-52** (476 mg, 93%) as a clear, colorless oil. ^1H NMR ($CDCl_3$): δ 7.4-7.2 (m, 5H), 5.7 (s, 1H), 2.6 (q, J = 7.5 Hz, 2H), 0.94 (t, J = 7.5 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 159.4, 143.7, 128.5, 127.6, 126.6, 125.3, 28.2, 14.4, 0.6.

General Procedure for the Coupling Reaction with Bu_2Zn:[84]

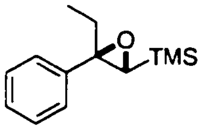


$C_{16}H_{26}Si$
Mol. Wt.: 246.46

To a flame-dried 100 mL round bottomed flask was added dry ZnI_2 (15 mmol, 4.78 g) and dioxane (10 mL), under N_2. The stirred mixture was cooled to 0°C (ice bath) and BuLi (2.5 M in hexane, 30 mmol, 12 mL) was added, dropwise, over a 30 min period. The resultant white slurry was then stirred at 0°C for 1 h and then warmed to 25°C, and stirred for 2 h. The precipitates were then filtered through a glass frit, and washed with dioxane (2 x 5 mL). The solution was then diluted with dioxane, to a total volume of 25 mL, making it approximately 0.6 M. The solution was then used for the coupling reaction without titration.

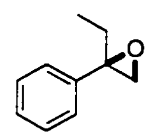
To a 100 mL round bottomed flask was sequentially added Pd(Ph$_3$)$_4$ (0.20 mmol, 232.5 mg), dioxane (20 mL), 3-phenyl-1-propyne **2-55** (10 mmol, 1.17 g), Bu$_2$Zn in dioxane (20 mL), and iodotrimethylsilane (21 mmol, 4.22 g) under N$_2$. The mixture was stirred at 25°C for 1 h and then diluted with moist hexane (200 mL). Evaporation of the solvent *in vacuo* yielded a light brown sludge. This was purified *via* flash chromatography (100% hexane) to yield (E)-2-benzyl-1-(trimethylsilyl)hex-1-ene **2-56** (253 mg, 68%) as a clear, colorless oil. ^{1}H NMR (CDCl$_3$): δ 7.37-7.18 (m, 5H), 5.25 (t, *J* = 1 Hz, 1H), 3.46 (s, 2H), 2.16-2.06 (m, 2H), 1.53-1.27 (m, 4H), 0.947 (t, *J* = 7.2 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (CDCl$_3$): δ 158.9, 140.5, 129.4, 128.6, 126.3, 46.3, 35.5, 31.7, 23.3, 14.5, 0.7; IR (NaCl): 3009, 2955, 2859, 1612, 1494, 1453, 1247, 836.6, 743 cm^{-1}.

General Epoxidation Procedure:[77]



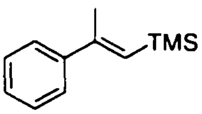
$C_{13}H_{20}OSi$
Mol. Wt.: 220.38

(E)-2-phenyl-1-(trimethylsilyl)but-1-ene **2-54** (0.20 g, 0.97 mmol) was dissolved in acetonitrile-dimethoxymethane (DMM) (15 mL, 1:2 v/v). Subsequently were added buffer (10 mL, 0.05 M solution of Na$_2$B$_4$O$_7$•10 H$_2$O in 4 x 10^{-4} M aqueous Na$_2$(EDTA)), tetrabutylammonium hydrogen sulfate (22 mg, 0.06 mmol), and ketone **2-25** (83 mg, 0.32 mmol). The mixture was cooled to 0° C (ice bath), and both a solution of Oxone (0.985 g, 1.6 mmol) in aqueous Na$_2$(EDTA) (4x10^{-4} M, 7.5 mL) and a solution of K$_2$CO$_3$ (0.925 g, 6.7 mmol) in water (7.5 mL) were added *via* syringe pump such that 6.5 mL of each solution was added over a 2 h period. After the 2 h addition period, the reaction was stirred an additional hour at 0° C, diluted with water (40 mL) and extracted with hexane (4x40 mL). The combined extracts were washed with brine (40 mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield a clear colorless oil. The oil was purified by flash chromatography [the silica gel was buffered with 1% Et_3N in hexane, hexane-ethyl acetate (1:0 to 4:1 v/v) was used as the eluent] to afford (E)-2-phenyl-1-(trimethylsilyl)but-1-ene oxide **2-75** as a colorless oil (180 mg, 82% yield). 1H NMR ($CDCl_3$): δ 7.3-7.2 (m, 5H), 2.26-2.14 (m, 1H), 2.16 (s, 1H), 1.64-1.51 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 1.28.5, 127.2, 126.1, 66.0, 62.7, 28.0, 10.2, -1.4; IR (NaCl): 3046, 3012, 2969, 1448, 1377, 1250, 838, 758, 700 cm^{-1}.



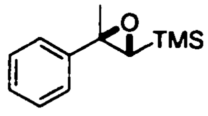
$C_{10}H_{12}O$
Mol. Wt.: 148.20

α-Ethylstyrene oxide (2-76): Colorless oil: $[\alpha]_D^{25}$ = -25.2 (*c* = 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$): **δ** 7.32-7.16 (m, 5H) 2.9 (d, *J* = 5.5 Hz, 1H), 2.67 (d, *J* = 5.5 Hz, 1H), 2.12 (dq, *J* = 14.6, 7.5 Hz, 1H), 1.74 (dq, *J* = 14.6, 7.5 Hz, 1H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 140.4, 128.5, 127.7, 126.4, 55.7, 28.6, 9.4.



$C_{12}H_{18}Si$
Mol. Wt.: 190.36

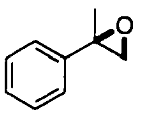
(E)-2-Phenyl-1-(trimethylsilyl)prop-1-ene (2-52): Colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.49-7.20 (m, 5H), 5.92 (q, *J* = 1 Hz, 1H), 2.22 (d, *J* = 1 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 152.0, 144.7, 128.4, 127.6, 125.8, 21.3, 0.4.



$C_{12}H_{18}OSi$
Mol. Wt.: 206.36

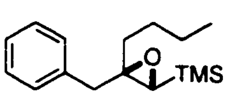
(E)-2-Phenyl-1-(trimethylsilyl)prop-1-ene Oxide (2-73, Table 2-1, entry 1): Colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.45-7.25 (m, 5H), 2.25 (s, 1H), 1.75 (s, 3H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 128.6, 127.3, 125.1, 63.0, 61.1, 21.3, -1.4; IR (KBR): 3061, 2957, 2900, 1603, 1493, 1447, 1379, 1250, 1112, 1063, 841, 757, 699 cm^{-1}.

General procedure for the removal of TMS:[121]



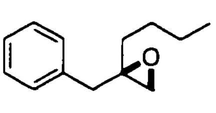
$C_9H_{10}O$
Mol. Wt.: 134.18

To a 10 mL round bottomed flask equipped with magnetic stir bar was placed (E)-2-phenyl-1-(trimethylsilyl)prop-1-ene oxide **2-73** (0.24 mmol, 50 mg) and THF (2.5 mL). The mixture was placed under a nitrogen atmosphere and tetrabutylammonium fluoride (1 M in THF, 0.5 mL, 0.5 mmol) was added dropwise. The resultant solution was stirred under a nitrogen atmosphere for a period of 2 h and then diluted with diethyl ether (10 mL). It was then extracted with water (3x10 mL), and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave a clear slightly yellow solution, which was purified *via* flash chromatography (hexane-ethyl acetate, 9:1 v/v) to yield α-methylstyrene oxide **2-74** as a clear, colorless oil (27 mg, 84%). $[\alpha]_D^{25}$ = +2.48 (*c* = 0.18, acetone); ^{1}H NMR ($CDCl_3$): δ 7.3-7.1 (m, 5H), 2.87 (d, *J* = 5.3 Hz, 1H), 2.69 (dd, *J* = 5.5, 0.7, 1H), 1.62 (d, *J* = 0.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$): δ 128.7, 127.8, 125.6, 57.4, 57.1, 22.2.



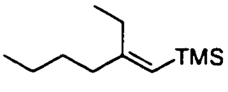
$C_{16}H_{26}OSi$
Mol. Wt.: 262.46

(E)-2-Benzyl-1-(trimethylsilyl)hex-1-ene Oxide (2-77, Table 2-1, entry 3): Colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.34-7.20 (m, 5H), 2.91, (dd, *J* = 3.7, 14.2 Hz, 2H), 2.14 (s, 1H), 1.58-1.24 (m, 6H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 129.8, 128.6, 126.7, 64.9, 58.1, 43.1, 33.0, 28.4, 14.4, -1.38; IR (NaCl): 3014, 2956, 1604, 1495, 1454, 1398, 840, 754, 699 cm^{-1}.



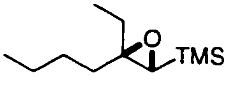
$C_{13}H_{18}O$
Mol. Wt.: 190.28

2-Benzylhex-1-ene Oxide (2-78): Colorless oil: $[\alpha]_D^{25}$ = -5.96 (*c* = 0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.33-7.20 (m, 5H), 2.89 (dd, *J* = 24, 14.2 Hz, 2H), 2.60 (dd, *J* = 14.3, 4.8 Hz, 2H), 1.64-1.25 (m, 6H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 130.0, 128.6, 126.8, 60.1, 52.2, 41.0, 34.0, 27.3, 23.1, 14.4; IR (NaCl): 3014, 2932, 2884, 2861, 1496, 1454, 700 cm^{-1}. Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.88; H, 9.57.



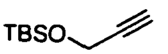
$C_{11}H_{24}Si$
Mol. Wt.: 184.39

(E)-2-Ethyl-1-(trimethylsilyl)hex-1-ene (2-58): Colorless oil: ^{1}H NMR ($CDCl_3$): δ 5.12 (t, *J* = 1.5 Hz, 1H), 2.2-2.0 (m, 4H), 1.5-1.2 (m, 4H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 162.1, 122.3, 38.4, 30.7, 29.3, 22.9, 14.4, 14.1, 0.71.



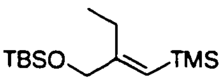
$C_{11}H_{24}OSi$
Mol. Wt.: 200.39

(E)-2-Ethyl-1-(trimethylsilyl)hex-1-ene Oxide (Table 2-1, entry 4): Colorless oil: $[\alpha]_D^{25}$ = +16.5 (*c* = 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 1H), 1.75-1.2 (m, 8H), 0.98 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 6.7 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 65.2, 58.7, 35.8, 27.3, 26.4, 23.2, 14.4, 10.3, -1.4; IR (NaCl): 2958, 1466, 1401, 1250, 879, 840, 753 cm^{-1}. Anal. Calcd. for $C_{11}H_{24}OSi$: C, 65.93; H, 12.07. Found: C, 66.16; H, 11.88.



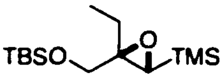
$C_9H_{18}OSi$
Mol. Wt.: 170.32

3-^{t}Butyldimethylsiloxyprop-1-yne (2-60): To a flame-dried 100 mL round bottomed flask, equipped with magnetic stir bar was placed propargyl alcohol **2-59** (21 mmol, 1.16 g), imidazole (32 mmol, 2.20 g), and dichloromethane (35 mL). The mixture was stirred under nitrogen for five min and then *tert*-butylchlorodimethylsilane (24 mmol, 3.62 g) and 4-(dimethylamino)pyridine (2.2 mmol, 0.26 g) were added sequentially. The reaction was stirred at room temperature for 1.5 h and an additional 10 mL of dichloromethane was then added. The solution was extracted with water (2 x 40 mL) and brine (1 x 40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (hexane-ethyl acetate, 9/1 v/v) gave 3-^{t}Butyldimethylsiloxyprop-1-yne **2-60** (2.94g, 82%) as a clear colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.29 (d, J = 2 Hz, 2H), 2.37 (t, J = 2 Hz, 1H), 0.89 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 82.7, 73.2, 51.9, 226.1, 18.6, -4.9; IR (NaCl): 3314, 2957, 2931, 2860, 1473, 1369, 1257, 1100, 1005, 838, 779, 662, 627 cm^{-1}.



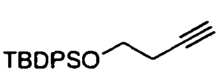
$C_{14}H_{32}OSi_2$
Mol. Wt.: 272.57

(E)- 2- (^{t}Butyldimethylsiloxymethyl)- 1- (trimethylsilyl)but- 1- ene (2-67): Colorless oil: ^{1}H NMR ($CDCl_3$): δ 5.49 (t, J = 1 Hz, 1H); 4.08 (d, J = 1 Hz, 2H), 2.12 (q, J = 7.6 Hz, 2H), 1.00 (t, J = 7.6 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 159.1, 120.7, 67.1, 26.3, 26.2, 18.8, 14.5, 0.6, -5.0; IR (NaCl): 2956, 2942, 2848, 1628, 1472, 1250, 1149, 1120, 1083, 895, 837, 775 cm^{-1}.



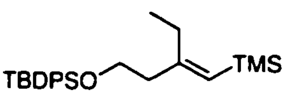
$C_{14}H_{32}O_2Si_2$
Mol. Wt.: 288.57

(E)- 2- (^{t}Butyldimethylsiloxymethyl)- 1- (trimethylsilyl)but- 1- ene Oxide (Table 2-1, entry 5): Colorless oil: $[\alpha]_D^{25}$ = +11.7 (c = 2.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.68 (d, J = 11 Hz, 1H), 3.52 (d, J = 11 Hz, 1H), 2.09 (d, J = 0.5 Hz, 1H), 1.81 (dqd, J = 14.5, 7.5, 0.5 Hz, 1H), 1.44 (dq, J = 14.5, 7.5 Hz), 0.99 (t, J = 7.5 Hz, 3H), 0.87, (s, 9H), 0.11 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 66.9, 95.50 55.7, 26.2, 24.18, 10.4, -1.5, -5.0, -5.1; IR (NaCl): 2956, 2930, 2857, 1463, 1412, 1361, 1251, 1104, 1006, 839, 777, 695, 668 cm^{-1}. Anal. Calcd. for $C_{14}H_{32}O_2Si_2$: C, 58.27; H, 11.18. Found: C, 58.46; H, 11.13.



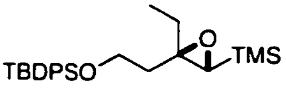
$C_{20}H_{24}OSi$
Mol. Wt.: 308.49

4-^{t}Butyldiphenylsiloxybut-1-yne (2-62): To a flame-dried 100 mL round bottomed flask, equipped with magnetic stir bar was placed 3-butyn-1-ol **2-61** (20 mmol, 1.42 g), triethylamine (14 mL), and dichloromethane (30 mL). The mixture was stirred under nitrogen for 5 min and then *tert*-butylchlorodiphenylsilane (22 mmol, 6.05 g) and 4-(dimethylamino)pyridine (2 mmol, 0.24 g) were added sequentially. The reaction was stirred at room temperature for 1.5 h and an additional 10 mL of dichloromethane was then added. The solution was extracted with water (2 x 40 mL) and brine (1 x 40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (hexane-ether, 9:1 v/v) gave 4-^{t}butyldiphenylsiloxybut-1-yne **2-62** (6.01g, 97%) as a clear colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.72-7.67 (m, 4H), 7.45-7.36 (m, 6H), 3.80 (t, J = 7 Hz, 2H) 2.47 (dt, J = 7, 2.7 Hz, 2H), 1.96 (t, J = 2.7 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 135.9, 130.0, 128.0, 69.6, 62.6, 32.0, 27.2, 23.0, 14.5; IR (NaCl): 3308, 3071, 2931, 2857, 1589, 1472, 1428, 1389, 1112, 918, 823, 738, 702, 639, 614, 505 cm^{-1}.



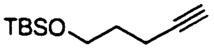
$C_{25}H_{38}OSi_2$
Mol. Wt.: 410.74

(E)- 4- (^{t}Butyldiphenylsiloxy)- 2- ethyl- 1- (trimethylsilyl)but-1-ene (2-68): Colorless oil: ^{1}H NMR ($CDCl_3$): δ 7.71-7.65 (m, 4H), 7.44-7.34 (m, 6H), 5.19, (t, J = 1 Hz, 1H), 3.75 (t, J = 7 Hz, 2H), 2.34 (dt, J = 7, 1 Hz, 2H), 2.10 (q, J = 7.5 Hz, 2H), 1.05 (s, 9H), 0.96 (t, J = 7.5 Hz, 3H), 0.09 (s, 9H); IR (NaCl): 3071, 2958, 2858, 1613, 1472, 1247, 1112, 840, 701 cm^{-1}.



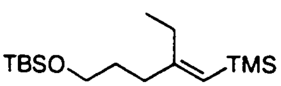
$C_{25}H_{38}O_2Si_2$
Mol. Wt.: 426.74

(E)- 4- (^{t}Butyldiphenylsiloxy)- 2- ethyl- 1- (trimethylsilyl)but-1-ene Oxide (Table 2-1, entry 6): Colorless oil: $[\alpha]_D^{25}$ = +5.97 (c = 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.68-7.62 (m, 4H), 7.43-7.32 (m, 6H), 3.72 (t, J = 7 Hz, 2H) 2.12 (s, 1H), 2.10-2.00 (m, 1H), 1.69-1.38 (m 3H), 1.03 (s, 9H), 0.96 (t, J = 7.5 Hz, 3H), 0.10 (s, 9H); IR (NaCl): 3071, 2957, 2857, 1589, 1428, 1250, 1112, 840, 702, 614 cm^{-1}. Anal. Calcd. for $C_{25}H_{38}O_2Si_2$: C, 70.36; H, 8.98. Found: C, 70.16; H, 8.90.



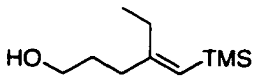
$C_{11}H_{22}OSi$
Mol. Wt.: 198.38

5-^{t}Butyldimethylsiloxypent-1-yne (2-64): Colorless oil: ^{1}H NMR ($CDCl_3$): δ 3.7 (t, J = 6 Hz, 2H), 2.27 (dt, J = 7.1, 2.7, Hz, 2H), 1.93 (t, J = 2.7 Hz, 1H), 1.72 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 84.6, 68.6, 61.8, 31.9. 26.3, 18.7, 15.2, -5.0; IR (NaCl): 3314, 2955, 2858, 1256, 1107, 980, 835, 776, 630 cm^{-1}.



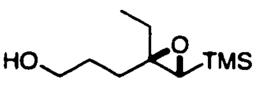
$C_{16}H_{36}OSi_2$
Mol. Wt.: 300.63

(E)- 5- (^{t}Butyldimethylsiloxy)- 2- ethyl- 1- (trimethylsilyl)pent-1-ene (2-69): Colorless oil: ^{1}H NMR ($CDCl_3$): δ 5.17 (t, J = 1 Hz, 1H), 3.60 (t, J = 6.5 Hz, 2H), 2.14 (q, J = 7.5 Hz, 2H), 2.11 (dt, J = 7.8, 1 Hz), 1.70-1.55 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H), 0.90 (s, 9H), 0.09, (s, 9H), 0.05 (s, 6H); ^{13}C NMR (CDCl$_3$): δ 161.3, 122.7, 63.2, 34.6, 31.6, 29.4, 26.3, 18.7, 14.1, 0.7, -4.9; IR (NaCl): 2955, 2910, 2858, 1613, 1472, 1248, 1106, 837, 775, 689 cm^{-1}.



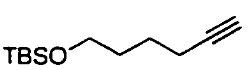
$C_{10}H_{22}OSi$
Mol. Wt.: 186.37

(E)-2-ethyl-1-(trimethylsilyl)pent-1-en-5-ol (2-71): To a solution of (E)-5-(^{t}Butyldimethylsiloxy)-2-ethyl-1-(trimethylsilyl)pent-1-ene **2-69** (5 mmol, 1.50 g) in THF (30 mL) was added a 1 M solution of TBAF in THF (6 mmol, 6 mL). The resulting solution was stirred at room temperature for 2 h and then diluted with diethyl ether (50 mL). The organic layer was extracted with water (2 x 50 mL) and brine (50 mL), dried (MgSO$_4$) and concentrated *in vacuo*, to yield a yellow oil. This was purified *via* flash chromatography (hexane-ethyl acetate, 4:1 v/v) to yield (E)-2-ethyl-1-(trimethylsilyl)pent-1-en-5-ol **2-71** (0.93 g, 99%) as a clear, colorless oil: ^{1}H NMR (CDCl$_3$): δ 5.19, (t, *J* = 1 Hz ,1H), 3.64 (q, *J* = 6 Hz, 2H), 2.145 (q, *J* = 7.5 Hz, 2H), 2.15 (dt, *J* = 7.6, 1 Hz, 2H), 1.74-1.64 (m, 2H), 1.63-1.55 (m, 1H) 1.01 (t, *J* = 7.5 Hz, 3H), 0.8 (s, 9H); ^{13}C NMR (CDCl$_3$): δ 161.1, 123.2, 63.2, 34.7, 31.3, 29.2, 25.9, 0.6; IR (NaCl): 3319, 2982, 1613, 1464, 1248, 1059, 838, 774, 689, 617 cm^{-1}.



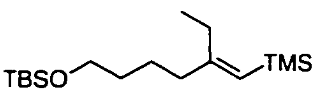
$C_{10}H_{22}O_2Si$
Mol. Wt.: 202.37

(E)-2-ethyl-1-(trimethylsilyl)pent-1-en-5-ol Oxide: Colorless oil: $[\alpha]_D^{25}$ = +21.5 (c = 1.83, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.65 (q, J = 6 Hz, 2H), 2.08 (d, J = 0.8 Hz, 1H), 2.01-1.91 (br s, 1H), 1.81-1.57 (m, 4H), 1.41 (dq, J = 14.6, 7.5 Hz, 2H), 1.00 (t, J = 7.5 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 65.1, 63.1, 58.9, 32.4, 28.2, 26.5, 10.5, -1.4; IR (NaCl): 3466, 2955, 1457, 1399, 1250, 1060, 841 cm^{-1}. Anal. Calcd. for $C_{10}H_{22}O_2Si$: C, 59.35; H, 10.96. Found: C, 59.50; H, 10.72.



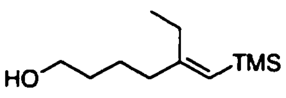
$C_{12}H_{24}OSi$
Mol. Wt.: 212.40

6-^{t}Butyldimethylsiloxyhex-1-yne (2-66): Colorless oil: ^1H NMR ($CDCl_3$): δ 3.63 (t, J = 6 Hz, 1H), 2.21 (dt, J = 6.8, 2.6 Hz, 2H), 1.94 (t, J = 2.6 Hz, 2H), 1.66-1.52 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 84.8, 68.6, 62.9, 32.1, 26.3, 25.3, 18.7, 18.6, -5.0; IR (NaCl): 3113, 2953, 2943, 2858, 1467, 1256, 1108, 1006, 974, 836, 776, 631 cm^{-1}.



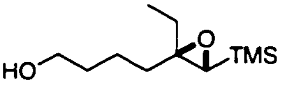
$C_{17}H_{38}OSi_2$
Mol. Wt.: 314.65

(E)-6-(^{t}Butyldimethylsiloxy)- 2-ethyl- 1- (trimethylsilyl)hex-1-ene (2-70): Colorless oil: ^1H NMR ($CDCl_3$): δ 5.15 (t, J = 1.1 Hz, 1H), 3.61 (t, J = 6.5 Hz, 2H), 2.12 (q, J = 7.5 Hz, 2H), 2.08 (dt, J = 7.3, 1.1 Hz, 2H), 1.57-1.38 (m, 4H), 1.00 (t, J = 7.5 Hz), 0.90 (s, 9H), 0.09 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 161.6, 122.6, 63.6, 38.3, 32.9, 29.2, 26.4, 24.5, 18.7, 14.1, 0.7, -4.9; IR (NaCl): 2954, 2858, 1613, 1472, 1248, 1107, 837, 775, 689 cm^{-1}.



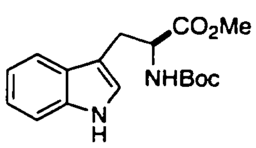
$C_{11}H_{24}OSi$
Mol. Wt.: 200.39

(E)-2-ethyl-1-(trimethylsilyl)hex-1-en-6-ol (2-72): Colorless oil: ^{1}H NMR ($CDCl_3$): δ 5.15 (s, 1H), 3.63 (dq, J = 6, 1Hz, 2H), 2.11 (q, J = 7.5 Hz, 2H), 2.08 (t, J = 6.6 Hz, 2H), 1.85-1.62 (br s, 1H), 1.61-1.41 (m, 4H), 0.99 (t, J = 7.5 Hz, 3H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 161.3, 122.8, 63.2, 38.2, 32.8, 29.2, 26.0, 24.5, 0.7; IR (NaCl): 3320, 2937, 1613, 1458, 1247, 1059, 867, 838, 690 cm^{-1}.



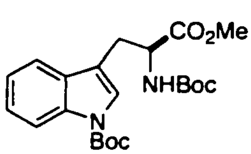
$C_{11}H_{24}O_2Si$
Mol. Wt.: 216.39

(E)-2-ethyl-1-(trimethylsilyl)hex-1-en-6-ol Oxide: Colorless oil: $[\alpha]_D^{25}$ = +18.5 (c = 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.61 (t, J = 6.5 Hz, 2H), 2.02 (d, J = 0.9 Hz, 1H), 1.95 (br s, 1H), 1.70-1.35 (m, 8H), 0.97 (t, J = 7.5 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 65.2, 62.9, 58.7, 35.6, 33.0, 26.4, 21.7, 10.3, -1.4; IR (NaCl): 3426, 2940, 1459, 1401, 1250, 1064, 879, 840, 754, 696, 610 cm^{-1}. Anal. Calcd. for $C_{11}H_{24}O_2Si$: C, 61.05; H, 11.18. Found: C, 61.00; H, 10.97.



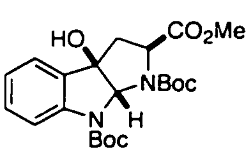
$C_{17}H_{22}N_2O_4$
Mol. Wt.: 318.37

N-α-Boc-L-Tryptophan Methyl Ester (2-95):[104] N-α-Boc-L-tryptophan **2-94** (5.0 g, 16.4 mmol) was dissolved in methanol (70 mL) and water (7 mL). The resulting solution was titrated to pH 7.0 with 20% aqueous cesium carbonate. The resulting mixture was evaporated to dryness and the residue was reevaporated twice from DMF (41 mL). The white cesium salt was then taken up in DMF (41 mL) and methyl iodide (2.55 g, 17.9 mmol) was added. The reaction was stirred at room temperature for 6 h, and then evaporated to dryness. Upon treatment of the crude slurry with water, the product solidified. The crude solid was taken into ethyl acetate, washed with water and dried. Concentration *in vacuo* gave the desired product as a white powder (4.87 g, 93%).



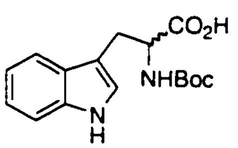
$C_{22}H_{30}N_2O_6$
Mol. Wt.: 418.48

N-α-Boc-N^{in}-Boc-L-Tryptophan Methyl Ester (2-88):[105,106] N-α-Boc-L-tryptophan methyl ester **2-95** (1.0 g, 3.1 mmol) was taken up in acetonitrile (8.4 mL) and di^{t}butyldicarbonate (720 mg, 3.3 mmol) and 4-dimethylaminopyridine (37 mg, 0.3 mmol) were sequentially added. The reaction was stirred at room temperature for 15 min and then extracted with ethyl acetate (2x). The combined organic layers were dried and concentrated to give the crude product as a clear, colorless oil. Purification by column chromatography (20% EtOAc/hex to 30% EtOAc/hex) gave the product as a clear, colorless oil which foamed under high vacuum (1.25 g, 95%).



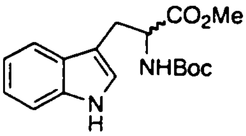
$C_{22}H_{30}N_2O_7$
Mol. Wt.: 434.48

Pyrrolo[2,3-*b*]indole (2-96): N-α-Boc-N^{in}-Boc-L-tryptophan methyl ester **2-88** (415 mg, 1 mmol) was dissolved in acetonitrile (5 mL) and dimethoxymethane (2.5 mL). To this was added tetrabutylammonium hydrogen sulfate (15 mg, 0.04 mmol), acetone (2.2 ml, 30 mmol) and 0.1M potassium carbonate (2 mL). Oxone (1.84 g, 3 mmol in 8 mL of 4×10^{-4}M EDTA solution) and potassium carbonate (1.84 g, 13.3 mmol in 8 mL of H_2O) were added *via* syringe pump such that the entire volume was delivered in 2.5 h. After addition of the Oxone was complete the reaction was extracted with EtOAc (3x). The combined extracts were washed with brine, dried, and concentrated to give a clear, colorless oil. Purification by column chromatography (30% EtOAc in hexane) gave the title compound as white crystals (86 mg, 20%). mp 71-78°C ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68-7.56 (m, 1H), 7.41-7.24 (m, 2H), 7.13-7.04 (m, 1H), 6.03 (s, 1H), 3.93 (dd, J = 9.6, 6.9 Hz, 1H), 3.74 (s, 3H), 3.05 (brs, 1H), 2.75 (dd, J = 12.6, 6.9 Hz, 1H), 2.44 (dd, J = 12.6, 9.6 Hz, 1H), 1.56, (s, 9H), 1.39 (s, 9H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 173.2, 152.8, 142.7, 136.8, 132.5, 130.8, 124.0, 123.4, 118.1, 83.8, 82.3, 81.6, 81.3, 59.5, 52.6, 38.7, 28.7, 28.6.



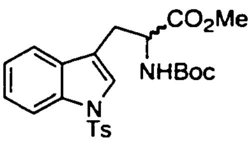
$C_{16}H_{20}N_2O_4$
Mol. Wt.: 304.34

N-α-Boc-DL-Tryptophan:[108] To an ice cold solution of DL-tryptophan (5.0 g, 24.5 mmol) in 1N NaOH (50 mL) was added a solution of di^{t}butyldicarbonate (6.4 g, 29.3 mmol) in dioxane (23 mL). The resulting mixture was stirred at 0°C for 45 min and then warmed to RT and stirred for an additional 4 h at which point TLC analysis (8:1:1 n-BuOH-H$_2$O-AcOH) showed complete reaction. The solvent was reduced to 1/2 its original volume *in vacuo*, and the resulting solution brought to 0°C and acidified to pH 2-3 by the slow addition of 1N potassium bisulfate. The solution was then extracted with EtOAc (3x). The combined organic layers were dried and concentrated to give the title compound as a sticky foam which was used without further purification (7.45 g, >99%).



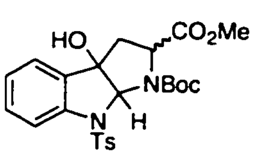
$C_{17}H_{22}N_2O_4$
Mol. Wt.: 318.37

N-α-Boc-DL-Tryptophan Methyl Ester (2-98):[108] N -α-Boc-DL-tryptophan (5.00 g, 16.4 mmol) was dissolved in methanol (70 mL) and water (7 mL). The resulting solution was titrated to pH 7.0 with 20% aqueous cesium carbonate (~19 mL). The resulting mixture was evaporated to dryness and the residue was reevaporated twice from DMF (41 mL). The white cesium salt was then taken up in DMF (41 mL) and methyl iodide (2.6 g, 17.9 mmol) was added. The reaction was stirred at room temperature for 6 h, and then evaporated to dryness. Upon treatment of the crude slurry with water, the product solidified. The crude solid was taken into ethyl acetate, washed with water and dried. Concentration *in vacuo* gave the desired product as a white powder (4.87 g, 93%). The product could be further purified by trituration with 1:1 hexane:EtOAc.



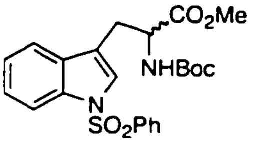
$C_{24}H_{28}N_2O_6S$
Mol. Wt.: 472.55

N-α-Boc-N^{in}-(p-toluenesulfonate)-DL-Tryptophan Methyl Ester (2-99):[100] To a solution of N-α-Boc-DL-tryptophan methyl ester **2-98** (250 mg, 0.78 mmol) in DMF (2 mL) under argon was added a NaH (60% suspension in mineral oil, 46.8 mg, 1.17 mmol). The resulting solution was stirred for 2 h under argon at which point a light green color persisted. p-Toluenesulfonyl chloride (185 mg, 0.97 mmol) was then added and an immediate color change to orange was observed. The resulting solution was stirred at RT for an additional 15 h then EtOAc (15 ml) was added and the solution was stirred an additional hour. Water was added and the organic layer was removed, washed with 5% $NaHCO_3$ and water, dried, and concentrated to give a sticky orange oil. Purification by column chromatography (20% EtOAc in toluene) gave the desired compound as a clear colorless oil that solidified upon standing (46%). mp 89-92°C ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.1 Hz, 1H), 7.37 (s, 1H), 7.31-7.21 (m, 2H), 7.20 (d, J = 8.1 Hz, 2H), 5.12 (m, 1H), 4.63 (dd, J = 13.2, 5.7 Hz, 1H), 3.62 (s, 3H), 3.20 (ddd, J = 28.2, 14.7, 5.7 Hz, 2H), 2.31 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.2, 155.2, 145.1, 135.3, 135.2, 131.1, 130.0, 126.9, 125.0, 124.6, 123.4, 119.7, 117.5, 113.9, 80.3, 53.8, 52.6, 28.6, 28.1, 21.8



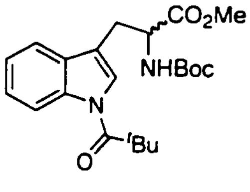
$C_{24}H_{28}N_2O_7S$
Mol. Wt.: 488.55

Pyrrolo[2,3-*b*]indole (2-100): To a stirred solution of N-α-Boc-N^{in}-(p-toluene sulfonate)-DL-tryptophan methyl ester (50 mg, 0.11 mmol) in acetonitrile (2.5 mL) at room temperature was added 1,3-dichlorodimethyldioxirane (14 mg, 0.11 mmol), tetrabutylammonium hydrogen sulfate (3 mg, 0.009 mmol), and 4 x 10^{-4}M aqueous Na_2-(EDTA) (1 mL). A finely ground mixture of Oxone (275 mg, 0.45 mmol) and sodium bicarbonate (120 mg, 1.4 mmol) was added in equal portions over 30 min. The reaction was then stirred an additional hour at room temperature and quenched by the addition of H_2O and EtOAc. The aqueous layer was extracted with an additional portion of EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to give a clear colorless oil. Purification by column chromatography (20-30% EtOAc-Hex) gave mostly starting material (40 mg) and a small amount of what appeared to be the desired product (7 mg, 14%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96-7.94 (m, 1H), 7.74-7.71 (m, 2H), 7.46-7.20 (m, 5H), 5.07-5.04 (m, 1H), 4.66 (m, 1H), 3.63 (s, 3H), 3.27-3.12 (m, 2H), 2.33 (s, 3H), 1.44 (s, 3H).



$C_{23}H_{26}N_2O_6S$
Mol. Wt.: 458.53

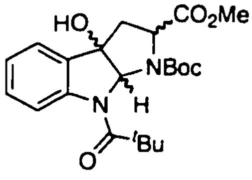
N-α-Boc-N^{in}-(benzenesulfonate)-DL-Tryptophan Methyl Ester (2-101):[110] To a room temperature solution of N-α-Boc-DL-tryptophan methyl ester **2-98** (250 mg, 0.78 mmol) and tetrabutylammonium hydrogen sulfate (26 mg, 0.08 mmol) in benzene (2.3 mL) was added sodium hydroxide (0.78 mL of a 50% aqueous solution). The resulting solution was stirred at room temperature for 5 min and a solution of benzenesulfonyl chloride (207 mg, 1.17 mmol) in benzene (1.2 mL) was added dropwise over 20 min. Upon complete addition, the reaction was stirred an additional 20 min and quenched with water. The organic phase was separated and filtered through a small plug of silica gel. The filtrate was dried ($MgSO_4$) and concentrated to give a clear, orange oil. Purification by column chromatography (3:2 Hex:EtOAc) gave the product as a slightly orange solid (133 mg, 40%). mp 126-128°C ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 7.2 Hz, 2H), 7.54-7.2 (m, 7H), 5.11 (m, 1H), 4.63 (dd, *J* = 12.9, 5.7 Hz, 1H), 3.61 (s, 3H), 3.20 (ddd, *J* = 27.6, 14.7, 5.4 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.2, 155.2, 138.3, 135.3, 134.0, 131.1, 129.5, 126.9, 125.2, 124.6, 123.5, 119.7, 117.8, 113.9, 80.4, 53.9, 53.6, 28.6, 28.1



$C_{22}H_{30}N_2O_5$
Mol. Wt.: 402.48

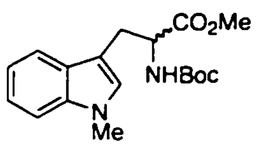
N-α-Boc-N^{in}-Trimethylacetyl-DL-Tryptophan Methyl Ester (2-103):[122] To a solution of N-α-Boc-DL-tryptophan methyl ester **2-98** (250 mg, 0.78 mmol) in DMF (1 mL) under argon was added a NaH (60% suspension in mineral oil, 40 mg, 1.7 mmol) at 0°C. The resulting solution was stirred for 15 min at 0°C then trimethylacetyl chloride (97.9 mg, 0.81 mmol) was added dropwise. After stirring at 0°C for 60 min, the mixture was poured into ice cold water and EtOAc, then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried, and concentrated to give a clear, colorless oil. Purification by column chromatography (20% EtOAc/Hex to 30% EtOAc/Hex) gave the title compound as a white powder (150 mg, 47%). ^{1}H NMR

(300 MHz, $CDCl_3$) δ 8.5 (d, *J* = 8.1 Hz, 1H), 7.57 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.39-7.22 (m, 2H), 5.22-5.12 (m, 1H), 4.77-4.66 (m, 1H), 3.70 (s, 3H), 3.24 (ddd, *J* = 30.0, 15.0, 5.6 Hz, 2H), 1.51 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 177.0, 172.5, 155.3, 137.2, 129.8, 125.7, 124.1, 123.7, 118.6, 117.7, 116.2, 80.4, 53.7, 52.8, 41.5, 29.0, 28.7, 28.2.



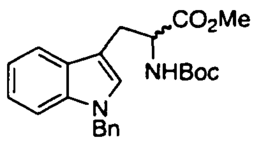
$C_{22}H_{30}N_2O_6$
Mol. Wt.: 418.48

Pyrrolo[2,3-*b*]indole (2-104): To a solution of N-α-Boc-N^{in}-trimethylacetyl-DL-tryptophan methyl ester **2-103** (50 mg, 0.12 mmol) in acetonitrile (2.5 ml) was added tetrabutylammonium hydrogen sulfate (3 mg, 0.008 mmol), 1,3-dichloroacetone (15 mg, 0.12 mmol), and $4x10^{-4}$M EDTA solution (1 mL). This was stirred at RT while a thoroughly mixed powder of Oxone (300 mg, 0.49 mmol) and sodium bicarbonate (130 mg, 1.5 mmol) was added portionwise over 30 min. The resulting solution was stirred an additional 1.5 h at RT and then quenched with water and EtOAc. The mixture was then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried and concentrated to give a clear, colorless oil. Purification by column chromatography (30% EtOAc in hexane) gave the product as a clear, colorless oil. NMR of the purified product indicates the presence of diastereomers in approximately a 1:1 ratio (30mg, 60%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 1H), 9.23 (s, 1H), 8.25 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.47-7.36 (m, 2H), 7.20-7.05 (m, 4H), 4.82 (dd, *J* = 9.9, 2.7, 1H), 4.35 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.87 (s, 3H), 3.56 (s, 3H), 2.12-2.82 (m, 2H), 2.75 (dd, *J* = 13.2, 2.4 Hz, 1H), 2.49 (dd, *J* = 12.9, 8.1 Hz, 1H), 1.63 (s, 9H), 1.62 (s, 9H), 1.41 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 177.3, 177.1, 173.9, 173.2, 171.1, 169.9, 150.0, 137.4, 137.3, 130.0, 129.9, 129.2, 128.5, 127.2, 125.6, 125.1, 124.5, 123.7, 123.5, 85.3, 85.1, 79.5, 56.0, 55.8, 53.2, 52.9, 40.2, 37.4, 38.1, 28.2, 28.0, 14.6; **IR** (NaCl): 3354, 2978, 1794, 1756, 1307 cm^{-1}.



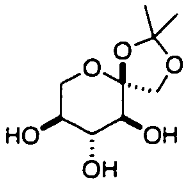
$C_{18}H_{24}N_2O_4$
Mol. Wt.: 332.39

N-α-Boc-N^{in}-Methyl-DL-Tryptophan Methyl Ester (2-105): Potassium hydride (35% dispersion in mineral oil, 89 mg, 0.78 mmol) was suspended in THF (1.3 mL) and cooled to –50°C. N-α-Boc-DL-tryptophan methyl ester **2-98** (250 mg, 0.78 mmol) was then added portionwise to the suspension and the resulting slurry was stirred under argon for 30 min at –50°C. At that point, methyl iodide (122 mg, 0.86 mmol) was added and the reaction was warmed to room temperature and stirred an additional 3 h. The reaction was quenched by the addition of water and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give the crude product as a white semi-solid. Purification by column chromatography (30% EtOAc/hex) gave the title compound as a white solid (243mg, 93%).

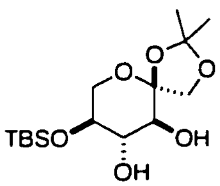


$C_{24}H_{28}N_2O_4$
Mol. Wt.: 408.49

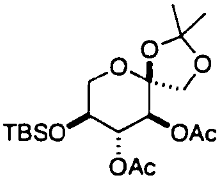
N-α-Boc-N^{in}-Benzyl-DL-Tryptophan Methyl Ester (2-106): Potassium hydride (35% dispersion in mineral oil, 89 mg, 0.78 mmol) was suspended in THF (1.3 mL) and cooled to –50°C. N-α-Boc-DL-tryptophan methyl ester **2-98** (250 mg, 0.78 mmol) was added portionwise to the suspension and the resulting slurry was stirred under argon for 30 min at –50°C. At that point, benzyl bromide (147 mg, 0.86 mmol) was added and the reaction was warmed to room temperature and stirred an additional 3 h. The reaction was quenched by the addition of water and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give the crude product as a white semi-solid. Purification by column chromatography (2% EtOAc in CH_2Cl_2) gave the title compound as a white solid (195 mg, 61%). mp 105-107°C ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 1H), 7.31-7.04 (m, 8H), 6.90 (s, 1h), 5.26 (s, 2H), 5.08 (m, 1H), 4.64 (dd, *J* = 13.5, 5.7 Hz, 1H), 3.61 (s, 3H), 3.27 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.9, 155.4, 137.7, 136.8, 129.0, 128.7, 127.9, 127.0, 122.2, 119.6, 119.2, 110.0, 109.7, 80.1, 60.7, 54.7, 52.5, 50.2, 28.7, 28.4.


$C_9H_{16}O_6$
Mol. Wt.: 220.22

1,2-O-Isopropylidene-α-L-sorbopyranose (2-113):[113,114] Anhydrous $CuSO_4$ (200 g, 1.25 mol) was added to freshly distilled acetone (1.4 L) in a flame-dried, 2 L, three-necked flask and stirred by mechanical stirrer for 1 h at room temperature. L-sorbose was then added (20 g, 111 mmol) and the slurry was heated to reflux (~50°C) and vigorously stirred for an additional five hs. Upon cooling, the slurry was filtered through a pad of Celite and concentrated to give a yellow oil. Crystallization occurred upon addition of diethyl ether. The crude compound was recrystallized from ether to yield the title compound as white needles (9.71g, 40%).

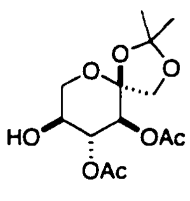

$C_{15}H_{30}O_6Si$
Mol. Wt.: 334.48

1,2-O- isopropylidene- 5- *O*- ^{t}butyldimethylsilyl-α-L-sorbopyranose (2-114): To a stirred solution of 1,2-*O*-isopropylidene-α-L-sorbopyranose **2-113** (7.5 g, 34.1 mmol) in anhydrous DMF (140 ml) was added DMAP (957 mg, 7.8 mmol) and imidazole (17.9 g, 263 mmol). The solution was stirred at room temperature for 5 min and then TBDMSCl (5.7 g, 37.8 mmol) was added. The reaction was placed under N_2 and stirred at room temperature for an additional 3 hrs when it was quenched by the addition of water. The product was extracted with $CHCl_3$ (3 x 40 ml), dried ($MgSO_4$), and concentrated to give a clear, colorless oil. Purification by flash chromatography (hexane-ethyl acetate, 4:1 v/v) gave the title compound as a thick oil (4.84 g, 43%). $[\alpha]_D^{25}$ = -37.5 (*c* = 10.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.11 (dd, *J* = 8.7, 1.5 Hz, 1H), 3.88 (dd, *J* = 8.7, 1.8 Hz, 1H), 3.54 (m, 4H), 3.33 (m, 1H), 3.15-3.05 (brm, 1H), 2.75-2.6 (brm, 1H), 1.46 (s, 3H) 1.39 (s, 1H), 0.84 (s, 9H), 0.07 (s, 3H), 0.5 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 112.3, 105.4, 76.7, 72.2, 71.4, 71.3, 64.0, 27.1, 26.6, 26.1, 18.4, -4.2, -4.3; IR (NaCl): 3431, 2934, 2892, 2859, 1466, 1377, 1255, 1188, 1116, 1078, 838 cm^{-1}.



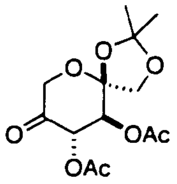
$C_{19}H_{34}O_8Si$
Mol. Wt.: 418.55

3,4- Di- *O*-acetyl-1,2-*O*-isopropylidine-5-*O*-^{t}butyldimethylsilyl-α-L-sorbopyranose: To a stirred solution of 1,2-*O*-isopropylidene-5-*O*-^{t}butyldimethylsilyl-α-L-sorbopyranose **2-114** (4.45 g, 13.2 mmol) in pyridine (5.4 ml) was added DMAP (370 mg, 3 mmol) and acetic anhydride (4.3 mL, 45.4 mmol). The mixture was placed under N_2 and stirred at room temperature for 3 hr and quenched by the addition of water. The product was extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated to give a clear yellow oil. Purification by flash chromatography (hex/EtOAc, 4:1 v/v) gave the title compound as a clear, colorless oil (4.84 mg, 87%). ^{1}H NMR ($CDCl_3$): δ 5.23 (dd, *J* = 10.2, 8.4, 1H), 4.88 (d, *J* = 9.9, 1H), 3.86 (d, *J* = 9.0 Hz, 1H), 3.77 (d, *J* = 9.0 Hz, 1H), 3.79-3.71 (m, 1H), 3.65 (d, *J* = 10.2 hz, 1H), 3.62-3.56 (m, 1H), 2.01 (s, 3H), 1.98 (s, 3H), 1.43, (s, 3H), 1.36 (s, 3H), 0.80 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (CDCl$_3$): δ 170.6, 169.8, 112.6, 104.0, 74.5, 72.0, 69.7, 69.6, 64.0, 26.9, 26.4, 25.8, 21.3, 21.0, 18.2, -4.6, -4.3; IR (NaCl): 2934, 1756, 1372, 1222, 1057 cm^{-1}.



$C_{13}H_{20}O_8$
Mol. Wt.: 304.29

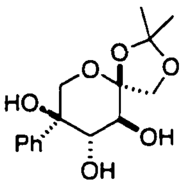
3,4-Di-*O*-acetyl-1,2-*O*-isopropylidine-α-L-sorbopyranose: To a stirred solution of 3,4-di-*O*-acetyl-1,2-*O*-isopropylidine-5-*O*-^{t}butyldimethylsilyl-α-L-sorbopyranose (4.62 g, 11.0 mmol) in THF (180 ml) was added triethylamine trihydrofluoride (TREAT•HF) (8.90 g, 55.0 mmol). The reaction was then stirred at room temperature for 18 hrs under N$_2$ and an additional portion of TREAT•HF (5.93 g, 36.7 mmol) was added. This was then stirred at room temperature for 10 hrs and quenched with water. Extraction with CHCl$_3$ (3 x 40 ml) followed by drying (MgSO$_4$) and concentration *in vacuo* gave the crude product as a yellow oil. Purification by flash chromatography (CHCl$_3$-CH$_3$OH, 100% to 4:1 v/v) gave the title compound as a clear, colorless oil (3.25 g 97%). ^{1}H NMR (CDCl$_3$): δ 5.13 (dd, *J* = 9.8, 8.7 Hz, 1H), 4.94 (d, *J* = 9.9 Hz, 1H), 3.89 (d, *J* = 9.3 Hz, 1H), 3.80 (d, *J* = 9.3 Hz, 1H), 3.81-3.63 (m, 3H), 3.0 (brs, 1H), 2.04 (s, 9H), 1.44 (s, 3H), 1.37 (s, 1H); ^{13}C NMR (CDCl$_3$): δ 171.9, 170.5, 112.6, 103.9, 75.5, 71.9, 69.4, 69.2, 63.6, 26.7, 26.3, 21.2, 21.0; IR (NaCl): 3464, 2990, 1742, 1374, 1224, 1048 cm^{-1}.



$C_{13}H_{18}O_8$
Mol. Wt.: 302.28

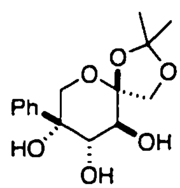
3,4- Di- *O*- acetyl- 1,2- *O*- isopropylidine- 5- keto- α- L- sorbopyranose (2-115): To a stirred solution of 3,4-di-*O*-acetyl-1,2-*O*-isopropylidine-α-L-sorbopyranose (3.25 g, 10.7 mmol) in CH$_2$Cl$_2$ (35 ml) was added freshly powdered 3Å molecular sieves (4.05 g). Pyridinium chlorochromate

(PCC) (5.82 g, 27 mmol) was then added as a solid over 10 min. The reaction was stirred at room temperature for 6 hr. Diethyl ether was added slowly and the brown slurry was filtered through a small pad of Celite. The brown solids were collected, washed with ether and filtered through the Celite. The brown filtrate was concentrated *in vacuo* to give a yellow/brown semisolid. Purification by flash chromatography (diethyl ether-hexane, 1:1 v/v) gave the title compound as a clear, colorless oil (2.55 g, 79%). Anal. Calcd. for $C_{13}H_{18}O_8$: C, 51.65; H, 6.00. Found: C, 51.51; H, 5.97; ^1H NMR ($CDCl_3$): δ 4.50 (d, J = 10.5 Hz, 1H), 5.36 (dd, J = 10.5, 0.9 Hz, 1H), 4.41 (dd, J = 15.3, 0.6 Hz, 1H), 4.06 (dd, J = 15.6, 0.6 Hz, 1H), 4.05 (dd, J = 9.6, 0.9 Hz, 1H), 3.94 (dd, J = 9.6, 0.9 Hz, 1H), 2.11 (d, J = 0.9 Hz, 3H), 2.09 (d, J = 0.9 Hz, 3H), 1.50 (s, 3H), 1.44 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 197.4, 170.0, 169.9, 113.4, 104.2, 75.2, 71.9, 69.6, 67.8, 26.6, 26.3, 21.0, 20.7; IR (NaCl): 3483 (hydrate), 2992, 2939, 1747, 1375, 1221, 1074, 976 cm^{-1}.



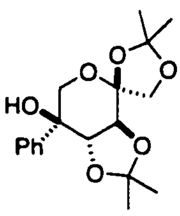
$C_{15}H_{20}O_6$
Mol. Wt.: 296.32

1,2-*O*-isopropylidine-5-β-phenyl-α-D-fructopyranose (2-116): Dry $CeCl_3$ (1.96 g, 7.94 mmol) was suspended in ether (20 ml) and cooled to -40°C in a N_2 atmosphere. PhMgBr (2.6 mL of a 3.0 M ether solution, 7.94 mmol) was added dropwise and the resulting slurry was stirred at -40°C for 1 h. A solution of 3,4-di-*O*-acetyl-1,2-*O*-isopropylidine-5-keto-α-L-sorbopyranose **2-115** in ether (10 mL) was then added dropwise and the mixture was stirred at –40°C for 5 hs and then warmed to room temperature. The mixture was quenched by the addition of methanol, and the solvent was removed *in vacuo* to yield a thick oil. This was passed through a short plug of silica gel to remove most of the Mg/Ce salts. Purification by flash chromatography (1:1 Et_2O:$CHCl_3$) gave the product as a white solid (274 mg, 75%). ^{1}H NMR ($CDCl_3$): δ 7.74-7.71 (m, 2H), 7.37-7.34 (m, 3H), 4.12 (d, J = 9.0 Hz, 1H), 4.07 (d, J = 11.7 Hz, 1H), 4.05 (d, J = 9.0 Hz, 1H), 3.99 (d, J = 9.6 Hz, 1H), 3.98 (d, J = 11.7 Hz, 1H), 3.25, (d, J = 9.6 Hz, 1H), 2.87-2.80 (brs, 1H), 2.65-2.45 (brs, 1H), 2.45-2.25 (brs, 1H), 1.56 (s, 3H), 1.46 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 140.7, 128.4, 127.8, 126.1, 112.4, 105.7, 76.5, 74.5, 72.0, 70.4, 68.9, 27.2, 26.6.



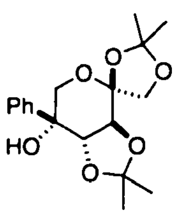
$C_{15}H_{20}O_6$
Mol. Wt.: 296.32

1,2-*O*-isopropylidine-5-α-phenyl-α-D-fructopyranose (2-117): To a stirred ethereal (20 mL) solution of 3,4-di-O-acetyl-1,2-O-isopropylidine-5-keto-α-L-sorbopyranose **2-115** (367 mg, 1.2 mmol) under N_2 at –78°C was added phenyl lithium (4.4 mL of a 1.8 M 70/30 cyclohexane/ether solution, 8.0 mmol). The reaction turned brown upon addition of the entire volume of PhLi. This was then stirred at –78°C for 6 hrs and then allowed to warm to room temperature overnight. The reaction was quenched by the addition of saturated aqueous ammonium chloride and then extracted with chloroform, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude product as an orange oil containing a white solid. Purification by flash chromatography (1:1 Et_2O:$CHCl_3$ to 1:1 MeOH:$CHCl_3$) gave the product as a white solid (249 mg, 69%). mp 157-158°C ^{1}H NMR ($CDCl_3$): δ 7.53-7.49 (m, 2H), 7.42-7.28 (m, 3H), 4.22 (d, J = 9.3 Hz, 1H), 4.21 (d, J = 9.0 Hz, 1H), 4.04 (d, J = 9.0 Hz, 1H), 3.93 (dd, J = 12.6, 1.5 Hz, 1H), 3.67 (dd, J = 9.6, 9.3 Hz, 1H), 3.57 (d, J = 12.6 Hz, 1H), 3.08 (d, J = 1.5 Hz, 1H), 2.79 (d, J = 2.7 Hz, 1H), 2.19, (d, J = 9.6 Hz, 1H), 1.52, (s, 3H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 140.4, 128.9, 128.2, 125.9, 112.5, 105.9, 76.5, 74.9, 72.4, 70.4, 69.0, 26.8, 26.8.



$C_{18}H_{24}O_6$
Mol. Wt.: 336.38

1,2,4,5-di-*O*-isopropylidine-5-β-phenyl-α-D-fructopyranose (2-121): To a stirred solution of 1,2-O-isopropylidine-5-β-phenyl-α-D-fructopyranose **2-116** (86 mg, 0.29 mmol) in CH_2Cl_2 (1.2 mL) was added 2-methoxypropene (0.18 ml, 1.88 mmol) and then a small quatity of (1S)-(+)-10-camphorsulfonic acid (cat.). The mixture was stirred at room temperature for 45 min. The reaction was quenched by the addition of triethylamine and the solvents were removed *in vacuo*. Purification by flash chromatography (4:1 $CHCl_3$:Et_2O) gave the product as a white solid (62 mg, 63%). The alcohol can be recrystalized from a mixture of 4:1 hexane/dichloromethane. mp 147-150°C ^1H NMR ($CDCl_3$): δ 7.68-7.64 (m, 2H), 7.39-7.27 (m, 3H), 4.31 (d, *J* = 9.9 Hz, 1H), 4.13 (d, *J* = 12.0 Hz, 1H), 4.05 (d, *J* = 9.3 Hz, 1H), 3.98 (d, *J* = 9.3 Hz, 1H), 3.84 (d, *J* = 12.0 Hz, 1H), 3.06 (d, *J* = 9.9 Hz, 1H), 2.52 (s, 1H), 1.54 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 139.5, 128.5, 128.3, 128.1, 112.4, 111.1, 105.0, 79.6, 76.0, 74.0, 71.6, 69.1, 27.3, 27.0, 26.9, 26.3; IR (NaCl): 3442, 2987, 1450, 1382, 1372, 1222, 905, 733, 701 cm^{-1}.



$C_{18}H_{24}O_6$
Mol. Wt.: 336.38

1,2,4,5-di-*O*-isopropylidine-5-α-phenyl-α-D-fructopyranose (2-122): To a stirred solution of 1,2-*O*-isopropylidine-5-α-phenyl-α-D-fructopyranose **2-117** (48 mg, 0.16 mmol) in CH_2Cl_2 (1.0 mL) was added 2-methoxypropene (0.1 ml, 1.04 mmol) and then a small quantity of (1S)-(+)-10-camphorsulfonic acid (cat.). The mixture was stirred at room temperature for 45 min. The mixture was quenched by the addition of triethylamine and the solvents were removed *in vacuo*. Purification by flash chromatography

(4:1 $CHCl_3$:Et_2O) gave the product as a clear, colorless oil (53 mg, 97%). ^1H NMR ($CDCl_3$): δ 7.58-7.54 (m, 2H), 7.42-7.29 (m, 3H), 4.56 (d, J = 9.3 Hz, 1H), 4.20, (d, J = 9.3 Hz, 1H), 4.13 (d, J = 9.3 Hz, 1H), 4.09 (d, J = 9.3, 1H), 3.75 (d, J = 12.6 Hz, 1H), 3.69 (dd, J = 12.6, 2.1 Hz, 1H), 2.65 (dd, J = 4.5, 2.1 Hz, 1H), 1.51, (s, 3H), 1.50 (s, 3H), 1.45 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 140.5, 128.9, 128.6, 126.0, 112.3, 110.6, 105.3, 76.5, 76.4, 72.4, 71.8, 70.5, 27.2, 27.1, 27.1, 26.3; IR (NaCl): 3448, 2987, 1372, 1224, 1028, 903 cm^{-1}.

2.6. REFERENCES

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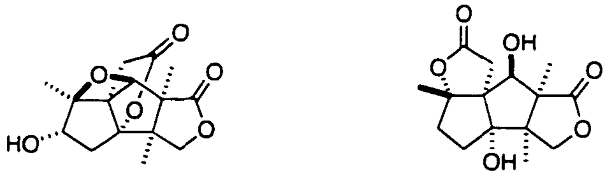
CHAPTER THREE

TOWARD THE ASYMMETRIC TOTAL SYNTHESIS OF MERRILACTONE A

3.1. INTRODUCTION AND BACKGROUND

Merrilactone A **3-1** is a novel sesquiterpene dilactone isolated from the methanol extracts of the pericarps of *Illicium merrillianum*, a plant indigenous to China and Myanmar.[1] It exhibits a significant neurotrophic activity, such as greatly promoting neurite outgrowth in the primary cultures of fetal rat cortical neurons at concentrations from 10 μmol/mL to 0.1μmol/mL. Neurotrophic factors are broadly defined as molecules that promote the growth and maintenance of neurons in *vitro* or in *vivo*.[2,3] The first-identified, and best-characterized neurotrophic factor is known simply as nerve growth factor (NGF).[2] NGF is a naturally occurring protein that functions to "promote the growth and survival of peripheral sympathetic and sensory neurons and basal forebrain cholinergic neurons".[4] It reduces cholinergic neuronal atrophy and improves spatial learning or memory retention in aged rats when given intraventricularly, and has potential implications for the treatment of Alzheimer's disease.[5,6] However, optimism toward the development of this as a potential therapeutic agent has been tempered by concerns as to the pharmacokinetics and bioavailability of such polypeptidal agents.[5] As such, the development of nonpeptidal neurotrophic agents as prospective therapeutics for neurodegenerative diseases is potentially of great significance. A total synthesis of merrilactone A, and possible analogues thereof, if successful, would provide a route by which novel therapeutic agents could be investigated.

Merrilactone A **3-1** consists of a densely functionalized pentacyclic ring system featuring two fused γ-lactones and an oxetane ring. Additionally, seven stereogenic centers, including five contiguous quaternary carbons, comprise the backbone of the molecule. It is structurally related to the anislactones, among which anislactone B[7] **3-2** is quite similar. The structure of merrilactone A was established by x-ray analysis,[1] and its absolute configuration was determined by the modified Mosher's method.[8]

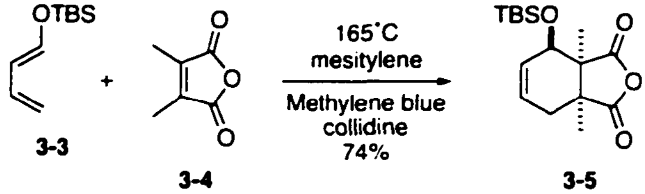


3-1 **3-2**

Figure 3.1 Merrilactone A, **3-1** and Anislactone B, **3-2**

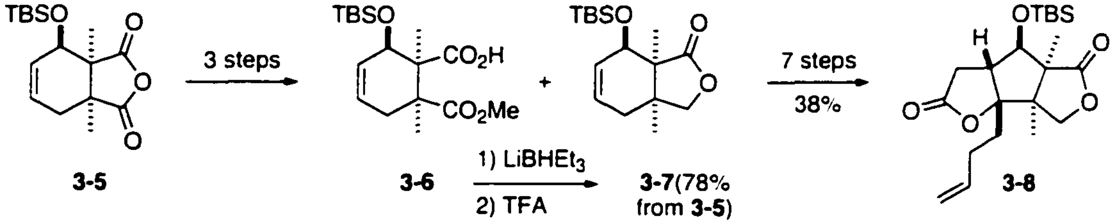
3.1.1. Previous Synthetic Approaches

To date, the only total synthesis of merrilactone A is the racemic approach reported by Danishefsky in 2002.[9] The synthesis was marked by the elegant incorporation of the two angular methyl groups utilizing an intermolecular Diels-Alder reaction (Scheme 3.1). The stereochemistry set in this initial reaction directs the formation of each subsequent stereogenic center with high diastereoselection.



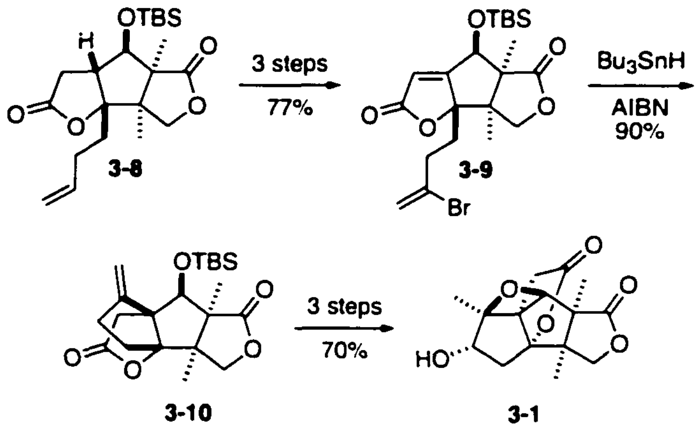
Scheme 3.1

Regioselective reduction of **3-5** to give the requisite lactone in **3-1** proved to be unsuccessful utilizing conventional borohydride reagents. Through a sequential ring-opening, reduction, and lactonization, **3-6** was obtained in 78% yield (Scheme 3.2). Subsequent conversion of **3-7** to bislactone **3-8** occurred in seven steps with an overall yield of 38%, setting two additional stereocenters in the process.



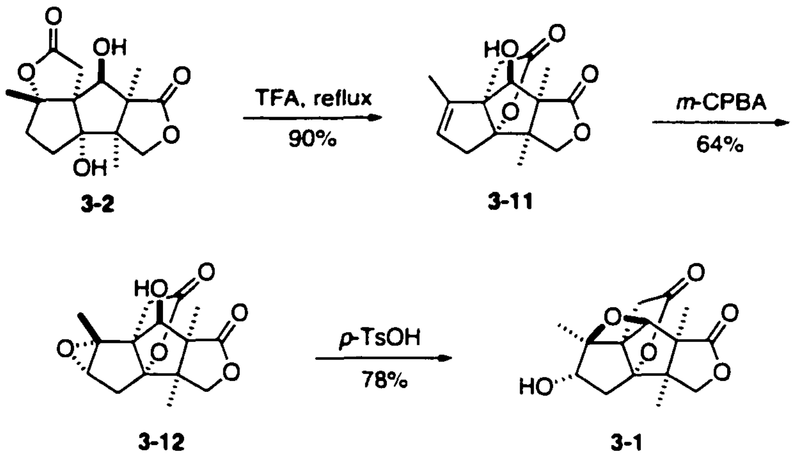
Scheme 3.2

Elaboration of **3-8** into merrilactone A **3-1** was accomplished in seven steps with an overall yield of 48% (Scheme 3.3). One of the key steps in this sequence involved a free radical cyclization of **3-9** to form the highly congested tetracycle **3-10**. In this reaction, concerns about a competitive reduction of the vinyl radical before cyclization were unfounded as the reaction proceeded in 90% yield. Merrilactone A was ultimately obtained from tetracycle **3-10** by isomerization of the exo methylene group followed by epoxidation and acid-induced homo-Payne rearrangement.



Scheme 3.3

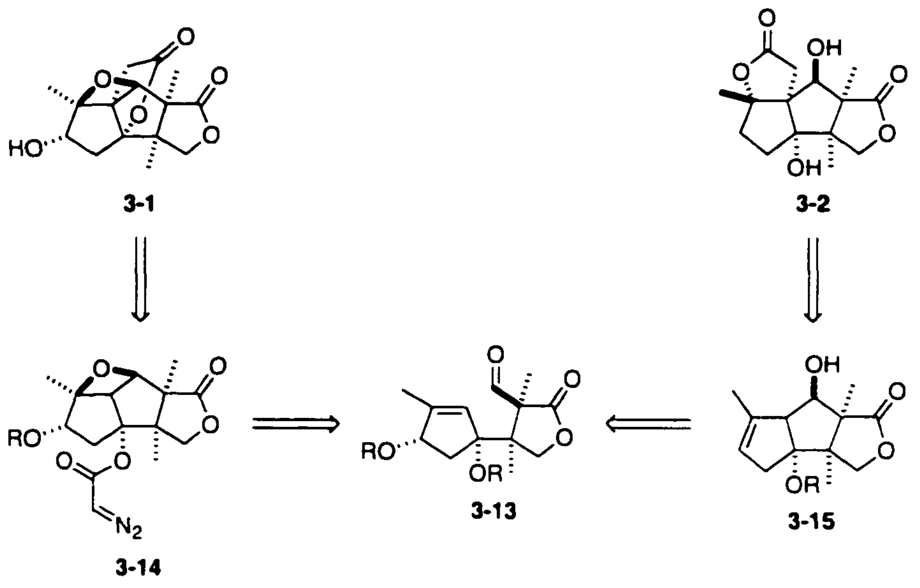
The acid-induced homo-Payne rearrangement reported by Danishefsky for the final step in his total synthesis of merrilactone A was also reported by Fukuyama,[10] who independently showed that this was a viable method for the chemical conversion of anislactone B to merrilactone A (Scheme 3.4). The limited amount of merrilactone A available for further study, coupled with the relatively abundant amount of anislactone B available from the plant source, prompted the current study. The key transformations involved a three-step procedure (dehydration, epoxidation and the aforementioned homo-Payne rearrangement).



Scheme 3.4

3.1.2. Synthetic Plan

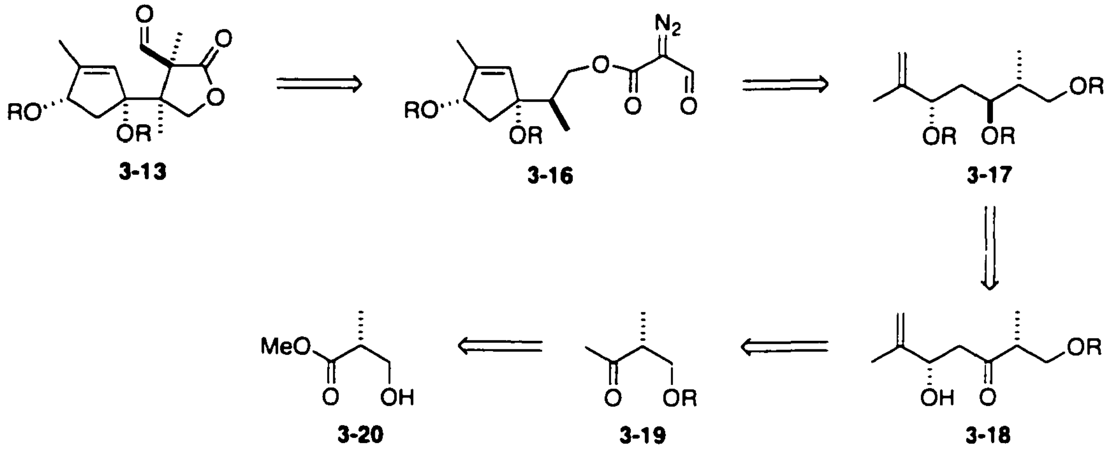
Interest in the synthesis of merrilactone A surfaced shortly after its structure was published. The important biological activity that it displayed as well as the pure challenge of synthesizing its densely oxygenated and sterically crowded core made merrilactone A an attractive target. Due to their structural similarities, it was believed that merrilactone A and anislactone B could be synthesized from a common intermediate **3-13** (Scheme 3.5). The fact that anislactone B could be accessed from such an advanced intermediate was appealing since it was anticipated, *a priori*, that it could also be transformed into merrilactone A in case the route failed at a later stage.



Scheme 3.5

It was anticipated that merrilactone A could be obtained from **3-13** by a Paterno-Büchi reaction,[11-13] followed by Corey-Myers diazoesterification[14] to give diazoester **3-14**. C-H insertion into the angular hydrogen by a rhodium-bound carbene[15-18] would, in turn furnish merrilactone A, upon deprotection of the alcohol. On the other hand, a modified Nozaki-Kishi reaction[19] would afford alcohol **3-15** which could be further elaborated to give anislactone B *via* oxidation and a similar rhodium carbene C-H insertion.

It was envisioned that lactone **3-13** could arise from a rhodium-bound carbene insertion into the activated methine in **3-16** followed by alkylation of the resulting β-ketoester (Scheme 3.6). It was further anticipated that formation of the cyclopentene in **3-16** would be accomplished by C-H insertion of an alkylidene carbene[20,21] generated *via* addition of Br_2 to the olefin in **3-17** followed by treatment of the putative intermediate dibromide with KHMDS. Directed reduction of the ketone in **3-18** with tetramethylammonium triacetoxyborohydride[22] would afford the anti 1,3-diol required by the natural product. The β-hydroxy ketone in **3-18** can be obtained from substrate-directed *anti* aldol addition[23,24] of the methyl ketone in **3-19** to methacrolein. Ketone **3-19** can be obtained from commercially available methyl-(R)-(-)-3-hydroxy-2-methyl propionate **3-20** by protection, Weinreb amide formation[25], and alkylation[26] with methyl magnesium bromide.



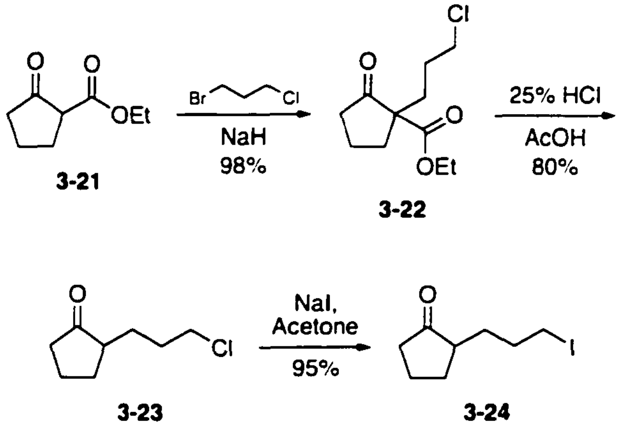
Scheme 3.6

3.2. Results and Discussion

3.2.1. Synthesis of a Model System

Before proceeding with the proposed scheme, it was deemed significant to establish that formation of the final ring system, *i.e.* **3-14** → **3-1**, could be accomplished *via* rhodium-mediated carbene insertion. To this end, the known [3.3.3]-bicyclic lactone **3-27** was targeted as a test substrate.[27] Since the C-H insertion is known to be stereospecific, only a racemic synthesis was necessary. The cyclization precursor can be accessed by Corey-Myers diazoesterification of alcohol **3-25**. This alcohol has been reported in the literature, and can be synthesized in four steps from β-keto ester **3-21**.[28-32]

Thus ethyl-2-oxocyclopentanecarboxylate **3-21** was alkylated with 1-bromo-3-chloropropane and subsequently decarboxylated to give 2-(3-chloropropyl)cyclopentanone **3-22** (Scheme 3.7).[33-35] Conversion of the chlorine in **3-23** to an iodide was accomplished using the classical Finkelstein reaction.[29,36]



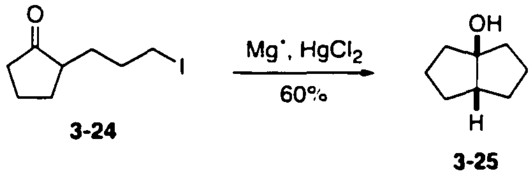
Scheme 3.7

With **3-24** in hand, cyclization to the targeted alcohol **3-25** was investigated. There are two related methods that accomplish this transformation. The first involves reaction of the alkyl iodide with SmI_2 to induce an intramolecular Barbier-type reaction, as described below. Pioneering studies by Kagan[37] in the early 1980's showed that SmI_2 could be used as a mild reducing agent for a number of organic functional groups, and that the intermolecular reaction of alkyl iodides with ketones under these conditions afforded the corresponding alcohol in good yield. Furthermore, reports from Molander[31,32] showed that this method was effective for intramolecular reactions as well.

In addition, he demonstrated that excellent selectivity for *cis* ring fusion could be obtained for certain substrates, including the desired [3.3.0] ring system.

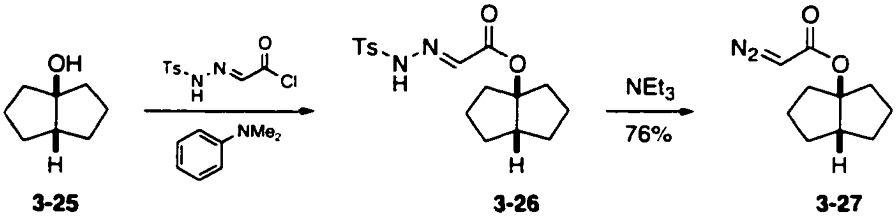
The second method involves the reaction of the alkyl iodide with magnesium, to induce an intramolecular Barbier reaction.[38] The Barbier reaction is a one step procedure for the preparation of alcohols from organohalides and carbonyl compounds by way of an intermediary organomagnesium species.[39] While the use of the Barbier reaction to form cycloalkanols had been known for some time,[40,41] it was not until 1982 that Crandall showed that the reaction could be used to form fused rings.[39] As is the case in the aforementioned SmI_2 reaction, the formation of *cis* fused rings is favored.

Reducing these methods to practice, treatment of **3-24** with either SmI_2 or Mg° afforded the desired bicyclo[3.3.0]octanol **3-25**. However, a much more reproducible reaction was obtained by utilizing the Crandall procedure (Scheme 3.8).



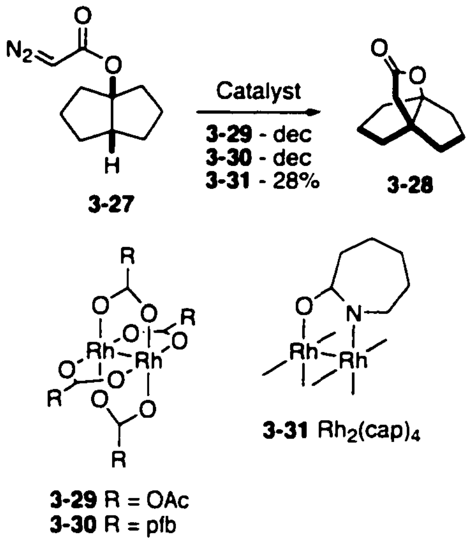
Scheme 3.8

Conversion of **3-25** into the **3-26**, the cyclization precursor, was accomplished using the diazoesterification method reported by Corey and Myers in 1984 (Scheme 3.9).[14] In the event, glyoxylic acid chloride *p*-toluenesulfonylhydrazone was added to a solution of **3-25** in methylene chloride. Dimethylaniline was added to promote formation of the corresponding ester, followed by triethylamine to decompose the hydrazone to diazoester **3-36**.



Scheme 3.9

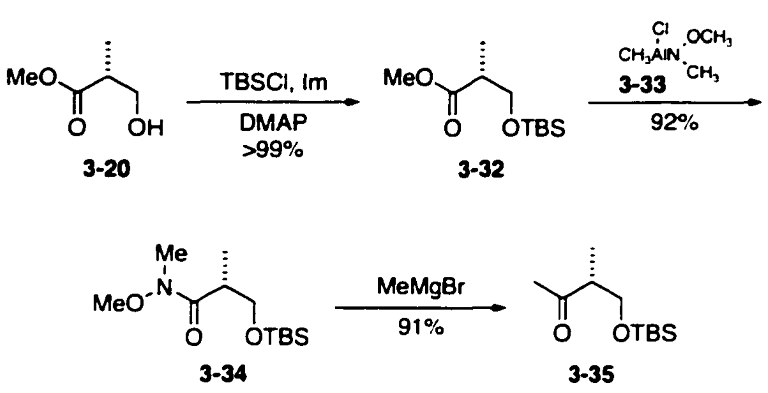
With diazoester **3-27** in hand, investigation began into which rhodium (II) catalyst would be required to achieve cyclization. The development of dirhodium (II) catalysts for intramolecular C-H insertion has seen great interest in recent years.[16-18,42-44] In particular, the dirhodium (II) carboxylates have been shown to be quite effective for a number of C-H insertion reactions. It was these catalysts that were investigated first. On treatment of diazoester **3-27** with $Rh_2(OAc)_4$ **3-29**[45,46] or Rh_2(perfluorobutyrate)$_4$ **3-30**,[47,48] only unidentifiable products were obtained. However, on treatment of **3-27** Rh_2(caprolactam)$_4$,[49] a 28% yield was obtained. While the yield was not high, this result demonstrated that the final C-H insertion was likely to succeed.[50]



Scheme 3.10

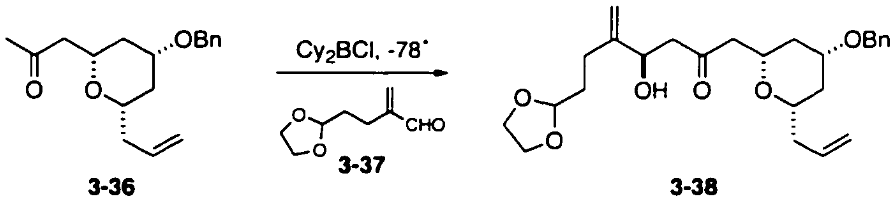
3.2.2. First Generation Synthesis of 3-16

Thus, the synthesis of **3-16** began by protecting the commercially available alcohol **3-20** as its TBS ether **3-32** in near quantitative yield (Scheme 3.11). Direct conversion of the ester to the Weinreb[25] amide by reaction with the *in situ* generated methyl-chloroaluminum amide **3-33** gave amide **3-34** in 92% yield. Alkylation[26] of the amide with methyl magnesium bromide gave the desired ketone **3-35** in 91% yield. It should be noted that this triad of reactions can be run without purification with virtually no loss in chemical yield.



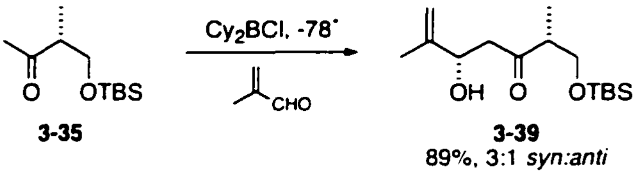
Scheme 3.11

With ketone **3-35** in hand, attention was then turned to the reaction of the dialkylboron enolate of **3-35** with methacrolein, affording β-hydroxy ketone **3-39**. Recently Patterson[51] and Evans,[52-54] reported that boron-mediated aldolization of β-oxygenated methyl ketones provides 1,5-*anti* stereoinduction, under substrate controlled conditions. A recent example of this was reported by Kozmin in his synthesis of the C_1-C_{15} fragment of leucascandrolide A.[55] Generation of the dicyclohexylboron enolate of ketone **3-36** followed by addition of aldehyde **3-37** at –78°C gave β-hydroxy ketone **3-38** in 74% yield with a dr >95:5 favoring the product shown (Scheme 3.12).



Scheme 3.12

The similarity of **3-36**, and other systems,[24,51,56,57] to **3-35** prompted an investigation as to whether or not a substrate directed aldol reaction between ketone **3-35** and methacrolein would proceed with high diastereoselectivity. Unfortunately this was not the case, as only a 3:1 diastereomeric ratio was observed, presumably in favor of the 1,4-*syn* product shown (Scheme 3.13). This was not altogether unexpected, as Patterson has reported that TBS protected β-hydroxyketones oftentimes give low selectivity.[51] Fortunately, reagent-directed aldol addition has been shown to be a viable alternative.[58-61]



Scheme 3.13

A good deal of work in this area has been reported by Patterson using (+)-(Ipc)$_2$BOTf.[23,56,58,62] Utilization of this reagent proved to be difficult, giving mainly decomposed starting material and otherwise unidentifiable products. By changing from the triflate to the chloride a much more efficient reaction took place. When the reaction was run at –78°C, using (+)-(Ipc)$_2$BCl (DIPCl), a 91% yield of the desired 1,4-syn hydroxyketone **3-39** was produced. The diastereoselectivity of the reaction was about 6.5:1 in favor of the desired diastereomer. By lowering the temperature to –90°C, the selectivity was improved to greater than 30:1, with little loss in chemical yield.[63] When the temperature was taken to –100°C, a 67:1 ratio could be obtained, however significant loss in chemical yield was observed (Table 3.1). Since **3-35** contains a stereocenter, the possibility exists for double stereodifferentiation.[64,65] In such a reaction the two reactants, being related asymmetrically, may either reinforce or oppose each other, consonant or dissonant double stereodifferentiation, respectively.[66] When (-)-DIPCl was utilized in the aldol reaction, a drastic drop in selectivity slightly favoring the anti-product was observed, indicating (+)-DIPCl is the "matched" reagent and gives consonant double stereodifferentiation (Table 3.1).

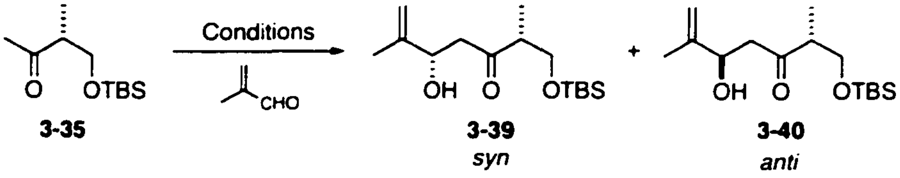
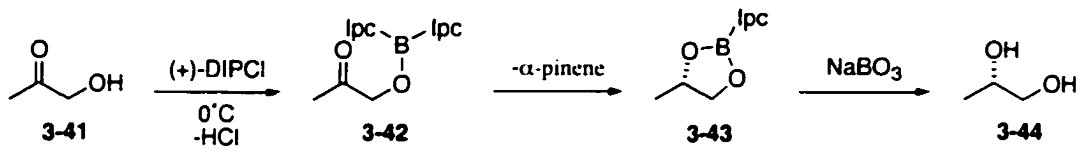


Table 3.1. Aldol Addition of Boron Enolates to Methacrolein

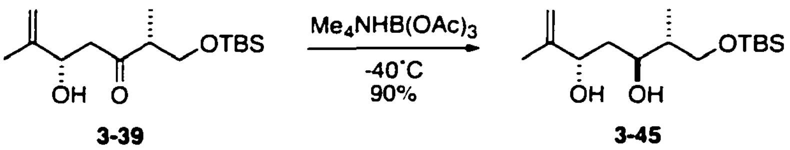
Entry	Conditions	Yield (%)	*syn/anti*
1	Cy_2BCl, -78°C	88	3/1
2	(+)-DIPCl, -78°C	91	6.5/1
3	(+)-DIPCl, -90°C	80	31/1
4	(+)-DIPCl, -100°C	35	67/1
5	(-)-DIPCl, -78°C	23	1/1.6

With good selectivity achieved in the aldol reaction, a 1,3-*anti* reduction of the ketone became the next major concern. Interestingly, Brown and Ramachandran[67] reported that this could be done by reduction of a β-hydroxyketone **3-41** with (+)-DIPCl at 0°C. Upon formation of the borinate ether **3-42**, a hydride is delivered by one of the attached pinanes, eliminating pinene to form boronate **3-43**. Perborate oxidation affords the pure diol **3-44** in 86-92% yield, with 84-92% ee (Scheme 3.14). This method has reportedly been extended to give an asymmetric enolboration-aldolization-reduction, effectively providing an aldol reaction with concomitant reduction of the β-hydroxy ketone to a 1,3-diol. In this case, the reduction proceeds with a high degree of *anti* selectivity. Since this appeared to apply directly to the synthesis in question, it was attempted. Unfortunately, none of the reduction product was observed. Apparently there has been a problem repeating the original experiments and efforts are currently being made to produce reproducible results.[68]



Scheme 3.14

Since the above-mentioned experiment failed, work reported by Evans was considered.[22] By using tetramethylammonium triacetoxyborohydride, acyclic β-hydroxy ketones can be reduced to their corresponding anti diols with high selectivity. Thus β-hydroxyketone **3-39** was reduced as described and gave what appeared to be diol **3-45** by IR and NMR (Scheme 3.15).



Scheme 3.15

The reduction is believed to proceed through a chair transition state as shown in Figure 3.2. The 1,3-diaxial interaction, R_2-OAc, destabilizes transition state T_S to a greater extent than the analogous 1,3-diaxial interaction HO^+-OAc, destabilizes the favored transition state T_A. It is important to note that hydride delivery occurs intramolecularly in this case, whereas external delivery would most likely give the 1,3-*syn* product.

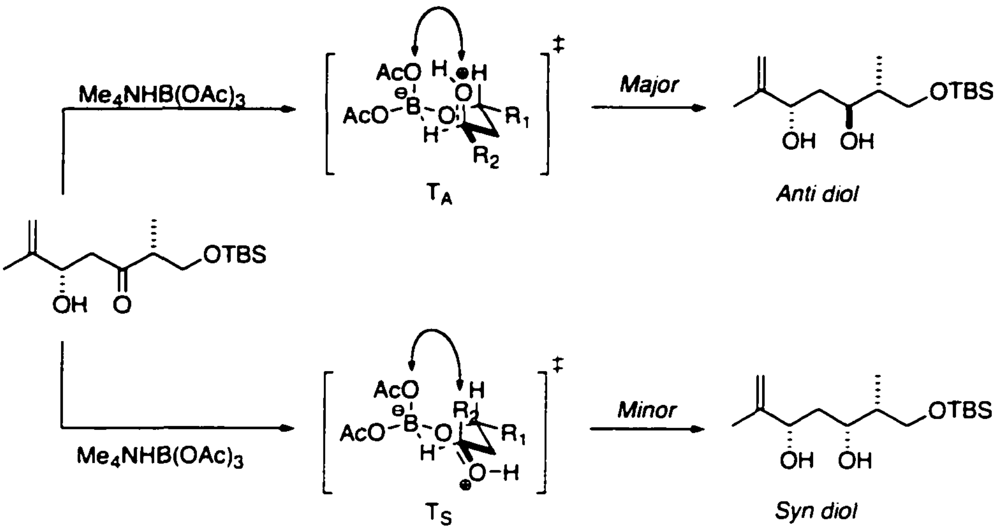


Figure 3.2. Proposed transition state for the stereoselective reduction of β-hydroxy ketones with tetramethylammonium triacetoxy borohydride.

With the diol in hand, it was necessary to finally establish that the diol was indeed *anti*. Fortunately, a simple experiment could be performed that would establish the relative stereochemistry of the two alcohols. Two papers appeared in the literature in 1990 that describe a method for determining the stereochemistry of 1,3 diol acetonides, one by Rychnovsky[69], and one by Evans.[70] The methods are essentially the same and use the chemical shifts of the acetonide gem-dimethyl groups in the ^{13}C NMR to determine the stereochemistry. If the diol is *anti*, both methyl carbons are expected to show up around 24 ppm. If it is *syn*, the methyl carbons show up differently at 19 and 30 ppm (Figure 3.3). When acetonation of the diol was performedthe peaks of interest showed up in the narrow range of 24.8 and 25.3 ppm, indicating that the *anti* diol had been formed.

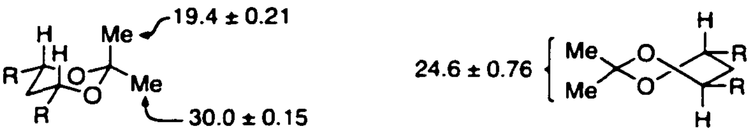
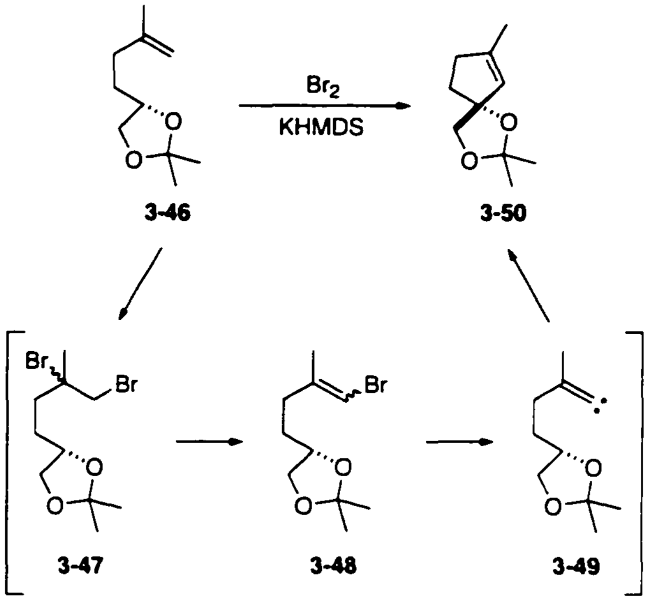


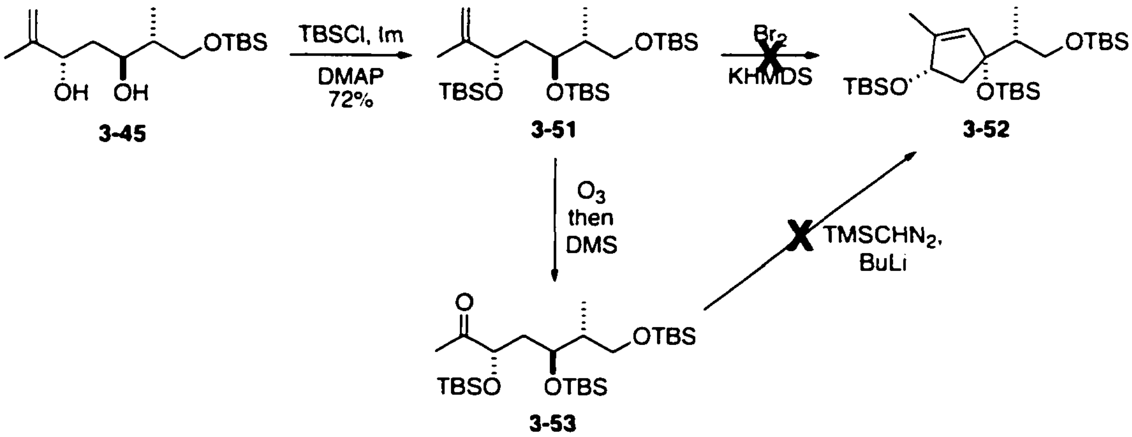
Figure 3.3. Average values for ^{13}C NMR Resonances of *Syn* and *Anti* Polypropionate Polyols.[70]

With the configuration of the diol now known to be *anti*, formation of the cyclopentene was investigated. The use of alkylidene carbenes to form cyclopentenes has been known for quite some time.[71-73] However, their use in large molecule synthesis had not been investigated until recently.[20,74-76] Typically, alkylidene carbenes are generated from ketones using diazophosphonates or (trimethylsilyl)diazomethane.[77,78] They can also be obtained by conversion of a ketone to a vinyl halide, followed by treatment with potassium bis(trimethylsilyl)amide (KHMDS), to effect an α-elimination.[75,79] Furthermore, simple alkenes can be brominated and then treated with KHMDS to accomplish the same transformation.[21,74] Of particular interest is Taber's report[21] on the use of this method in the synthesis of the spiro-fused cyclopentene **3-50** (Scheme 3.16). The cyclization involves initial bromination of **3-46** to give dibromide **3-47**, followed by elimination to form the vinyl bromide **3-48**. Deprotonation at the vinyl position, followed by α-elimination furnishes the alkylidene carbene **3-49**, which inserts into the methine C-H bond with retention of configuration, to afford **3-50**. It seemed as though this reaction set the precedent for the desired transformation.



Scheme 3.16

In order to minimize the use of different protecting groups in the synthesis, the hydroxyls in **3-45** were protected as TBS ethers, furnishing the fully protected triol **3-51** (Scheme 3.17). It was anticipated that the differential deprotection of the 1° TBS group could be accomplished after cyclization to afford the 1° alcohol necessary for subsequent C-H insertion (*i.e.* **3-16→3-13**).[80] Unfortunately, reaction of **3-51** with Br_2 and KHMDS yielded none of the expected cyclopentene **3-52**. Only starting material or decomposed materials were recovered. The observation of remaining starting material was puzzling since formation of the dibromide should not be reversible. Since equal moles of the alkene and Br_2 are added, it is likely that a full equivalent of Br_2 was not available for reaction. Under normal circumstances, the reaction is run in one pot, with the addition of Br_2 done at 0°, and then cooling the mixture to –78° before adding the KHMDS. To ensure that the dibromide formed completely, excess Br_2 was added and the reaction was worked up (to remove excess Br_2) before addition of the base. Complete consumption of the starting material was observed, however this still did not remedy the problem, as only decomposed products were isolated. Due to this difficulty, a second method to generate the alkylidene carbene was attempted, which involves the treatment of a ketone with (trimethylsilyl)diazomethane and BuLi.[30] Thus, the olefin in **3-51** was ozonized to give ketone **3-53**, and then subjected to these reaction conditions. The desired product, again was not obtained, only decomposition products.



Scheme 3.17

Analysis of the expected conformation of the carbene precursor gave a good indication as to why cyclization did not take place. It was expected that the TBS groups were aligned such that they were pointing away from each other, minimizing their steric interaction (Figure 3.4). In this conformation, the proximity of the desired methine is most likely not close enough to the carbene for insertion to occur, and due to the size of the pendant TBS groups, rotation to a point where they could react is restricted.

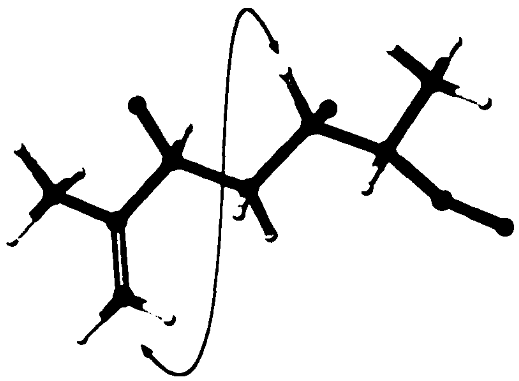


Figure 3.4. CAChe prediction for the conformation of the TBS protected triol. The TBS groups have been removed for clarity.

In order to get around this predicament, it became evident that a new protecting group strategy would have to be used. Since the TBS groups appeared to be too large, it was felt that incorporation of a substantially different group would be necessary. Protection of the diol as an acetonide, earlier used to determine the relative configuration of the diol, might allow the carbene and C-H group to be in much closer proximity (Figure 3.5), and was chosen as a target.

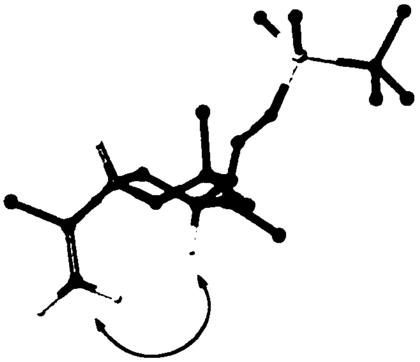
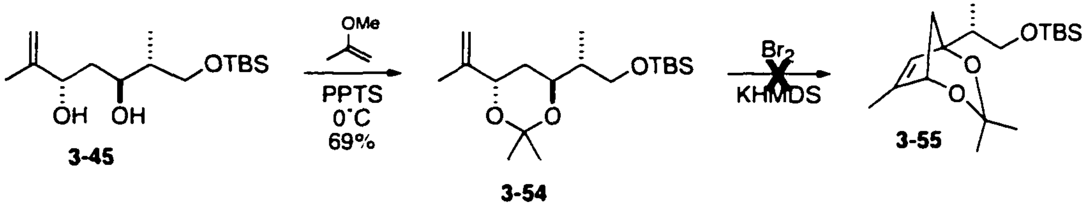


Figure 3.5. CAChe prediction for the conformation of the acetonide protected triol. Unnecessary hydrogens have been removed for clarity

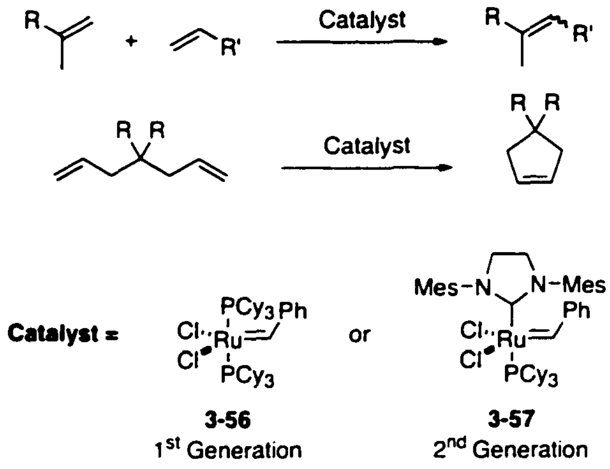
Thus diol **3-45** was protected as its acetonide **3-54** using 2-methoxypropene and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) (Scheme 3.18). Other methods gave either poor conversion or otherwise deleterious results. When the acetonide was subjected to cyclization conditions, none of the desired [3.2.1]-bicycle **3-55** was observed. It is unclear what the mode of decomposition is in either of these cases, but given the difficulty observed it was decided that this was not the proper solution to this problem.



Scheme 3.18

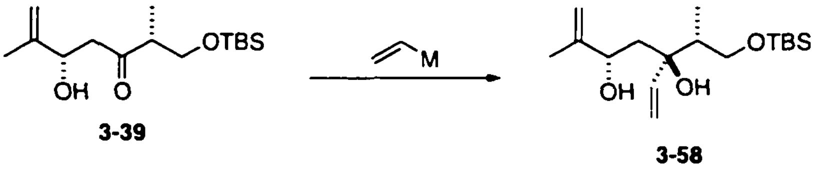
3.2.3. Second Generation Synthesis of 3-16

Since the carbene insertion did not give the desired results, an alternative route was considered. Since a great deal of effort had been invested to optimize the sequence to that point, it was hoped that a new route could be found that was somewhat related to the current one. One of the more increasingly popular methods for the formation of C-C double bonds is olefin metathesis (Scheme 3.19).[81-83] With the advent of Grubbs' second generation ruthenium catalyst containing the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligand **3-57**,[84,85] this method has provided an effective strategy for the formation of 5-membered rings *via* a ring-closing metathesis (RCM).[84] However, there remained a question of whether or not a vinyl group could be stereoselectively added to ketone **3-39** to provide the requisite diene.



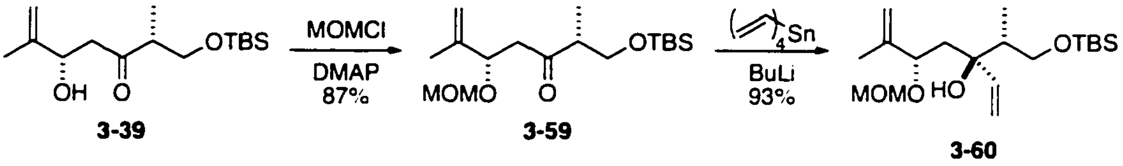
Scheme 3.19

The selective reduction performed earlier (Scheme 3.15) gave some indication that such a reaction would be possible. For this reaction, the vinyl group needed to be delivered in an intermolecular fashion, similar to the way the hydride was delivered in the reduction (Scheme 3.15). It was assumed that by coordination of an organometallic compound to the free hydroxyl group would allow for such a transformation to occur (Scheme 3.20). Reaction of ketone **3-39** with vinylmagnesium bromide under a variety of conditions indicated that the addition would be viable, however an unacceptable diastereomeric mixture (~1:1) was obtained in each case. It was speculated that by switching to a more oxophilic metal, such as lithium, the diastereomeric mixture could be greatly enhanced.



Scheme 3.20

To test this hypothesis, vinyllithium was next employed to add to ketone **3-39**. The diastereomeric ratio observed after addition was indeed enhanced, however it still was at an unacceptable level. In an attempt to further enhance the selectivity, the hydroxyl in **3-39** was protected as its methoxymethyl (MOM) ether (Scheme 3.21). Additionally, the natural aggregation of vinyllithium might play a destructive role in the stereoselectivity of the addition. In other words, aggregation inhibited efficient chelation by the hydroxyl group. To suppress this effect, vinyllithium was prepared *in situ*, *via* transmetalation from tributy(vinyl)tin.[86,87] In the event, *n*-butyllithium was added to a solution of tributyl(vinyl)tin in THF at −78° C followed by a THF solution of ketone **3-39**. Analysis of the crude reaction mixture showed that essentially only one diastereomer was present, and that the reaction had proceeded with high yield. In order to make the reaction more efficient, tetravinyltin was substituted, with no drop in selectivity or yield.[88,89]



Scheme 3.21

The reaction is believed to go through a highly ordered transition state in which chelation of the lithium by the two ethereal oxygens of the MOM group directs the vinyl group into the carbonyl in an efficient manner (Figure 3.6)

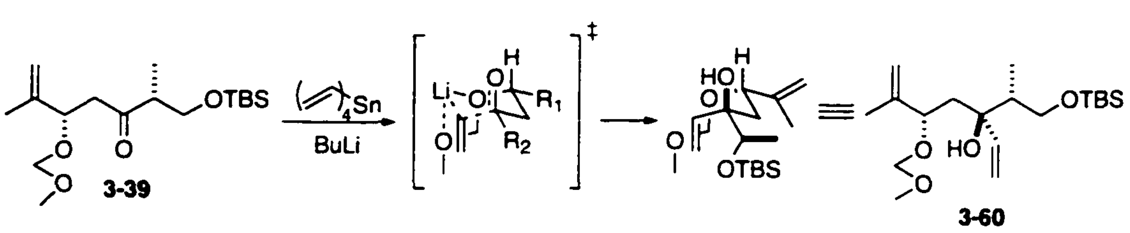
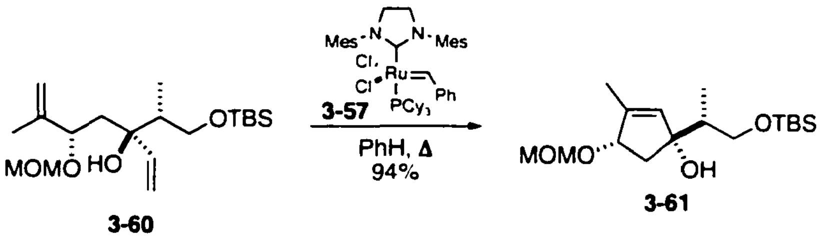


Figure 3.6. Assuming chelation of the lithium by the MOM group, the vinyl anion must come in as shown, approaching *via* the Bürgi-Dunitz angle.

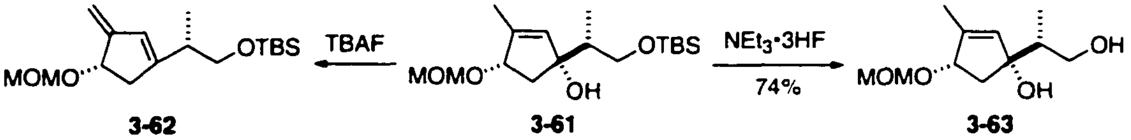
With diene **3-60** in hand, investigation into the RCM followed. It was believed that the alcohol in **3-60** did not need to be protected since Hoye showed that tertiary alcohols accelerated the reaction, in most cases.[90] Thus, reaction of the diene with Grubbs' 2nd generation catalyst gave the desired cyclopentenol **3-61** in 94% yield (Scheme 3.22). The choice of solvent and temperature proved to be quite important as reaction in methylene chloride at either room temperature or reflux yielded only recovered starting material. The reaction was successful when performed in benzene at room temperature. However long reaction times (>48 hr) were necessary to provide a useful conversion. Additionally, the use of the 1st generation catalyst **3-56** provided only marginal results.



Scheme 3.22

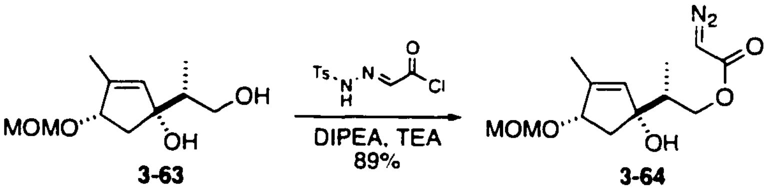
Deprotection of the primary silyl group proved to be more complicated than originally expected, owing to ready elimination of the allylic alcohol, or decomposition. Among the methods examined, treatment of **3-61** with triethylamine trihydrofluoride

(TREAT•HF) gave the best results (Scheme 3.23), with tetrabutylammonium fluoride (TBAF) and pyridine HF giving mainly elimination to **3-62** or decomposition reaction.



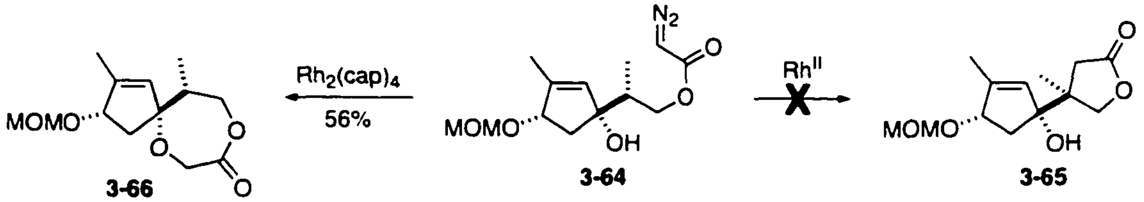
Scheme 3.23

Diazoesterification of **3-63** was attempted using the method reported by Corey and Myers.[14] In their initial report, they added Hünigs base to an ice-cold solution of the alcohol and the acid chloride. In the current system, it became apparent almost immediately that some form of decomposition was occurring causing the reaction to turn deep purple. This was confirmed when the reaction was quenched and a crude NMR spectrum was taken. Apparently the acid chloride had caused some form of elimination to occur. In order to assuage this problem, the order of addition was reversed; the acid chloride was added to an ice-cold solution of the alcohol and Hünigs base. Additionally, the workup was altered. The initial procedure called for washing the reaction with saturated aqueous citric acid, but given the sensitivity of the molecule to acidic conditions, this step was omitted. By utilizing the modified conditions, diazoester **3-64** was obtained in 89% yield (Scheme 3.24).



Scheme 3.24

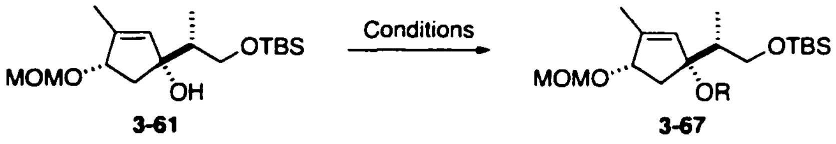
Diazoester **3-64** was then subjected to cyclization conditions. At the outset, it was not certain how the free hydroxyl group would affect the reaction. Alcohols are known to react with rhodium carbenoids, generating products resulting from O-H insertion.[91-94] However, Moody and Padwa[95,96] have shown that, by utilization of the proper catalyst, chemoselectivity can be observed. The investigation began with $Rh_2(OAc)_4$, and not unexpectedly, the reaction did not give the desired lactone as only unidentifiable products were isolated from the reaction mixture along with a small amount of starting material. By changing to the more reactive Rh_2(perfluorobutyrate)$_4$ the same problems were encountered and none of the starting material remained. Finally, an identifiable product was obtained by reaction of diazoester **3-64** with rhodium Rh_2(caprolactam)$_4$. Initially, it was thought that the lactone had been formed, but this expectation was tempered after close inspection of the spectral data. Most notable was the absence of an OH peak in the IR spectrum. Additionally, the methine signal in the ^{1}H NMR was still visible. It appeared as though O-H insertion had occurred to give **3-66** (Scheme 3.25). This was further confirmed by a ^{1}H-^{1}H COSY spectrum indicating that the connectivity was correct for O-H insertion, and HRMS also gave the correct molecular weight.



Scheme 3.25

It was concluded that the alcohol maybe detrimental to the C-H insertion pathway, and, in order for the desired insertion to occur, the hydroxyl would have to be protected.

Protection of **3-61** as a silyl ether, benzyl ether, methyl ether, or methoxymethyl ether could not be accomplished (Scheme 3.26). Presumably the sensitivity and steric hindrance prevent any alkylation or silylation of the tertiary hydroxyl.



Entry	Conditions	Result
1	TBSCl, NaH, DMAP	NR
2	TBSOTf, 2,6-lut.	Dec.
3	TESCl, NaH, DMAP	NR
4	BnBr, NaH, Bu$_4$NI	NR
5	MeI, DIPEA, DMAP	NR
6	MOMCl, NaI, DIPEA	NR

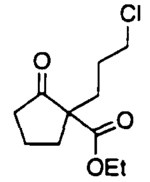
Scheme 3.26

3.2.4. Conclusions

In summary, the asymmetric total synthesis of merrilactone A, a sesquiterpene dilactone displaying neurotrophic activity, was investigated. Toward this goal, alcohol **3-61** was synthesized. Key steps accomplished in the synthesis include a reagent-controlled stereoselective aldol reaction followed by substrate-controlled addition of vinyl lithium to the resulting β-hydroxyketone **3-39**, upon MOM protection of the newly formed alcohol. Additionally, a model system was synthesized to study the probability of C-H insertion into the angular methine, of compound **3-14**.

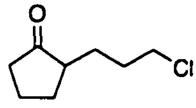
3.3. EXPERIMENTAL

General Methods. The 300 MHz ^{1}H NMR and 75.5 MHz ^{13}C NMR spectra were measured on a Varian-300 spectrometer in $CDCl_3$. Proton and carbon chemical shifts (δ) are given relative to $CHCl_3$, 7.26 ppm and 77.36 ppm respectively. Infrared spectra were recorded on a Perkin-Elmer 1600 Series FT-IR or a Nicolet Avatar 320 FT-IR spectrometer. Optical rotations were measured on an Autopol III automatic polarimeter in a 10 cm cell. Silica gel 60 (230-400 meshes) of E. Merck Co. was employed for all flash chromatography. Tetrahydrofuran (THF) and diethylether were distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane and benzene were distilled from calcium hydride immediately prior to use. Hexane was distilled prior to use. All other solvents were used without further purification. High resolution mass spectra were obtained from the mass spectrometry facility of Colorado State University.



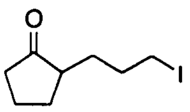
$C_{11}H_{17}ClO_3$
Mol. Wt.: 232.70

Ethyl-1-(3-chloropropyl)-2-oxocyclopentanecarboxylate (3-22):[33] To a stirred slurry of NaH (60% dispersion, 2.47g, 103 mmol) in dimethoxyethane (101 mL) was slowly added ethyl-2-oxocyclopentanecarboxylate (15.81 g, 101 mmol). When gas evolution had ceased, 1-bromo-3-chloropropane (14.84 g, 94.3 mmol) was added. The resulting solution was heated to reflux for 24 h, cooled, and filtered to remove solid NaBr. The solids were washed with ether and the filtrate and ether washings were concentrated. The resulting residue was poured into water, acidified with HCl, and extracted with ether. The extract was dried ($MgSO_4$) and concentrated to give a slightly yellow oil. Distillation produced the title compound as a clear, colorless oil (21.5 g, 98%).



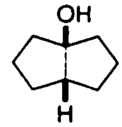
$C_8H_{13}ClO$
Mol. Wt.: 160.64

2-(3-chloropropyl)-cyclopentanone (3-23):[33] A solution of ethyl-1-(3-chloropropyl)-2-oxocyclo-pentanecarboxylate **3-22** (16.96 g, 73.0 mmol) in glacial acetic acid (23 mL) and 25% HCl (31 mL) was refluxed for 18 h, cooled and partitioned between water and ether. The organic phase was carefully washed with saturated aqueous $NaHCO_3$ until no gas evolution was observed, then water and brine. The extraxt was then dried ($MgSO_4$) and concentrated to give a yellow oil. Bulb to bulb distillation produced the title compound as a clear, colorless oil (9.38 g 80%).



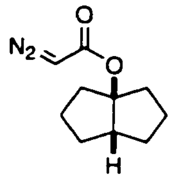
$C_8H_{13}IO$
Mol. Wt.: 252.09

2-(3-iodopropyl)-cyclopentanone (3-24):[29,32] To a solution of 2-(3-chloropropyl)-cyclopentanone **3-23** (3.86 g, 24.0 mmol) in acetone (47.9 mL) was added dry sodium iodide (7.14 g 47.6 mmol). The resulting solution was refluxed for 18 h, cooled and concentrated. The resulting solid was partitioned between water and ether and was washed with 10% $NaHSO_3$ and water, then dried ($MgSO_4$) and concentrated. Purification by column chromatography (10% Et_2O in Hexane) gave the title compound as a clear, colorless oil (2.97 g, 95%).



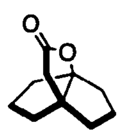
$C_8H_{14}O$
Mol. Wt.: 126.20

***Cis*-bicyclo[3.3.0]octan-1-ol:**[29,32] To a solution of magnesium turnings (350 mg, 14.4 mmol) in THF (28.8 mL) was added $MgCl_2$ (65 mg, 0.24 mmol) and the suspension was heated at reflux for 30 min. At that time, a solution of 2-(3-iodopropyl)-cyclopentanone **3-24** (2 g, 8 mmol) in THF (17.6 mL) was added dropwise over 20 min. The mixture was heated at reflux for 12 h and then quenched with water. The product was extracted with ether (2x) and the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated. Purification by column chromatography (20% Et_2O in hexane) gave the product as a slightly yellow oil (606 mg, 60%).



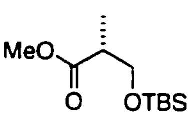
$C_{10}H_{14}N_2O_2$
Mol. Wt.: 194.23

***Cis*-bicyclo[3.3.0]octyl-1-diazoacetate (3-27):**[14] Glyoxylic acid chloride *p*-toluenesulfonylhydrazone (3.86 g, 14.8 mmol) was added to an ice-cooled solution of *cis*-bicyclo[3.3.0]octan-1-ol **3-25** (1.0 g, 7.9 mmol) in dichloromethane (45 mL) under an argon atmosphere. Dimethylaniline (1.8 mL, 14.4 mmol) was added and the dark green solution was stirred for 15 min prior to the injection of triethylamine (5.6 ml, 40.5 mmol). The resulting dark orange suspension was stirred for 10 min at 0°C and then for 15 min at room temperature before water (31.6 mL) was introduced and the mixture was concentrated *in vacuo*. Saturated aqueous cictric acid (63.2 mL) and 10% ethyl acetate-hexanes (63.2 mL) were added and the layers were separated. The organic layer was washed with citric acid solution (63.2 mL) and the combined aqueous layers were extracted with 10% ethyl acetate-hexanes (24.7 mL). This extract was washed with an equal volume of citric acid solution and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by column chromatography (20% Et_2O in hexane) gave the title compound as a yellow oil (1.17g, 76%). ^{1}H NMR ($CDCl_3$): δ 4.54 (s, 1H), 2.51-2.43 (m, 1H), 2.13-2.05, (m, 2H), 1.94-1.85 (m, 4H), 1.66-1.55 (m, 4H), 1.26-1.16 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 100.6, 50.6, 47.1, 39.7, 32.6, 26.0; IR (NaCl): 2952, 2867, 2107, 1690, 1371, 1177 cm^{-1}.



$C_{10}H_{14}O_2$
Mol. Wt.: 166.22

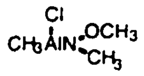
2-Oxatricyclo[3.3.3.0]undecan-3-one (3-28):[27,49,97] To a solution of rhodium(II) caprolactam (17 mg, 0.026 mmol) in dry dichloromethane (48 mL) was added a solution of *cis*-bicyclo[3.3.0]octyl-1-diazoacetate **3-27** (248 mg, 1.28 mmol) in dichloromethane (8 mL) *via* syringe pump over 20 h at room temperature. At the end of the addition the reaction was concentrated *in vacuo* and purified by column chromatography (10% EtOAc in hexane) to give a clear colorless oil (60 mg, 28%).



$C_{11}H_{24}O_3Si$
Mol. Wt.: 232.39

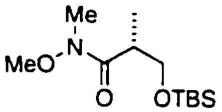
(R)-Methyl-3-(^{t}butyldimethylsiloxy)-2-methylpropionate (3-32): To a flame dried 50 mL flask was added methyl-(R)-(-)-3-hydroxy-2-methyl propionate (1.18 g, 10 mmol) and dichloromethane (17 mL). The flask was placed under an argon atmosphere and N,N-dimethylaminopyridine (122 mg, 1 mmol) and imidazole (1.09 g, 16 mmol) were added. The solution was stirred for 5 min at room temperature at which point the mixture was homogeneous. ^{t}Butyldimethylsilyl chloride (1.81 g, 12 mmol) was added in one portion, forming an immediate white precipitate. The mixture was stirred for 20 min at which point TLC (10% EtOAc/Hex) indicated no starting material remained. Water was added and the organic layer was removed and washed with a second portion of water, saturated NH_4Cl, and brine then dried and concentrated *in vacuo* to give a clear, colorless oil. Purification by column chromatography (10% EtOAc/Hex) gave the product (2.31 g, >99%) as a clear, colorless oil. $[\alpha]_D^{25} = -17.4$ ($c = 0.85$, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.77 (dd, J = 9.6, 6.9 Hz, 1H), 3.67 (s, 3H), 3.65 (dd, J = 9.6, 6.0 Hz, 1H), 2.70-2.59 (m, 1H), 1.13

(d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H) 0.03 (s, 3H); ^{13}C NMR (CDCl$_3$): δ 175.6, 65.6, 51.9, 42.9, 26.2, 18.6, 13.9, -5.0; IR (NaCl): 2954, 2858, 1744 cm^{-1}.



$C_3H_9AlClNO$
Mol. Wt.: 137.54

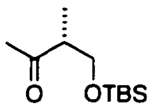
Methylchloroaluminum amide (3-33):[25] To a suspension of N,O-dimethylhydroxylamine hydrochloride (1.95g, 20 mmol) in benzene (20 mL) at 5°C was added a 2M solution of trimethylaluminum in toluene (10 mL) dropwise under argon. When the addition was complete, the mixture was warmed to room temperature and stirred for 1 h at which point the evolution of CH_4 was no longer evident. The solution was used immediately without further purification.



$C_{12}H_{27}NO_3Si$
Mol. Wt.: 261.43

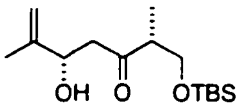
(R)-*N*-Methoxy-*N*-methyl-2-methyl-3-(^{t}butyldimethylsiloxy)-propionamide (3-34): To a stirred solution of methyl-(R)-(-)-3-(^{t}butyldimethylsiloxy)-2-methyl propionate **3-32** (2.3 g, 9.9 mmol) in benzene (99 mL) was added the entire amount of aluminum amide (~30 mL) *via* cannula. The resulting solution was heated at reflux for 3 h, at which point there was no longer starting material visible by TLC (30% EtOAc/Hex). Upon cooling, the reaction was slowly quenched with 5% HCl. The organic layer was drained off and the aqueous layer was washed (3x) with EtOAc. The combined organic layers were dried and concentrated to give a slightly yellow oil that was essentially pure by NMR analysis. The product was purified by passage through a short silica gel column (30% EtOAc/Hex), giving a clear, colorless oil (2.37 g, 92%). $[\alpha]_D^{25}$ = -15.2 (c = 1.62, CHCl$_3$): ^{1}H NMR (CDCl$_3$): δ 3.80 (dd, J = 9.5, 8.3 Hz, 1H), 3.68 (s, 1H), 3.50 (dd, J = 9.5, 6.2 Hz, 1H), 3.20-3.08 (brm, 1H), 3.16 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H) 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H);

^{13}C NMR (CDCl$_3$): δ 176.2, 66.05, 61.81, 38.43, 32.38, 26.25, 18.67, 14.19, -5.01; IR (NaCl): 2956, 2931, 2857, 1668, 1472 cm^{-1}.



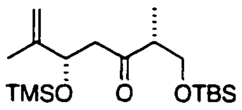
$C_{11}H_{24}O_2Si$
Mol. Wt.: 216.39

(R)-3-Methyl-4-(^{t}butyldimethylsiloxy)-2-butanone (3-35):[26] To a solution of (R)-*N*-methoxy-*N*-methyl-2-methyl-3-(^{t}butyldimethylsiloxy)-propionamide **3-34** (1g, 3.8 mmol) in THF (38 mL) at 0°C was added a 2.8 M solution of methylmagnesium bromide in THF (2.7 mL, 7.6 mmol). The resulting solution was stirred at 0°C for 3 h at which point the starting material was gone by TLC (30% EtOAc/hex). The reaction was poured into a saturated NH$_4$Cl solution and extracted with a 1:1 mixture of Et$_2$O and CH$_2$Cl$_2$. The organic layer was dried and concentrated to give a clear, colorless oil. Purification of the ketone by column chromatography (30% EtOAc/Hex) gave the title compound, (260 mg, 63%) as a clear, colorless oil. $[\alpha]_D^{25}$ = -28.7 (*c* = 2.69, CHCl$_3$); ^{1}H NMR (CDCl$_3$): δ 3.72 (dd, *J* = 9.9, 6.9 Hz, 1H), 3.64 (dd, *J* = 9.9, 5.4 Hz, 1H), 2.78-2.67 (m, 1H), 2.17 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (CDCl$_3$): δ 212.0, 65.77, 49.68, 29.97, 26.23, 18.62, 13.36, -5.07; IR (NaCl): 2955, 2930, 2858, 1718, 1257 cm^{-1}.



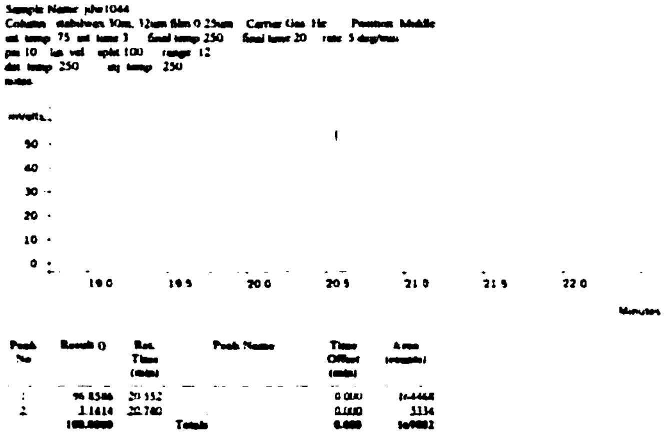
$C_{15}H_{30}O_3Si$
Mol. Wt.: 286.48

(2R,5S)- 5- hydroxy-2,6-dimethyl-1-(^{t}butyldimethylsiloxy)-hept-6-en-3-one (3-39): To a stirred solution of (+) chloro-diisopinocamphenylborane (962mg, 3 mmol) and triethylamine (0.48 mL, 3.4 mmol) in ether (24 mL) at 0°C was added a solution of (R)-3-methyl-4-(^{t}butyldimethylsiloxy)-2-butanone **3-35** (432 mg, 2 mmol) in ether (7.4 mL). The resulting white precipitate was stirred at 0°C for 15 min and then cooled to –90°C. A solution of freshly distilled methacrolein (0.22 mL, 2.6 mmol) in ether (7.4 mL) was then added slowly over 10 min. The reaction was stirred at –90°C for 5 h and then warmed to 0°C and diluted with water (12 mL) followed by the addition of sodium perborate monohydrate (293 mg, 2.9 mmol). The resulting solution was stirred at 0°C for 1 h. At that point, the organic layer was removed and the aqueous layer was saturated with solid potassium carbonate, and extracted with ethyl acetate (3x). The organic layers were combined, dried ($MgSO_4$), and concentrated to give a clear, colorless oil. Purification of the product by column chromatography (10% EtOAc/Hex-20% EtOAc/Hex) gave the title compound (458 mg, 80%) as a clear, colorless oil. $[\alpha]_D^{25}$ = -51.5 (*c* = 1.29, $CHCl_3$); HRMS FAB Calcd (M + 1) for $C_{15}H_{30}O_3Si$: 287.2042. Found: 287.2046. ^{1}H NMR ($CDCl_3$): δ 5.01 (s, 1H), 4.85 (s, 1H), 4.51 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.73 (dd, *J* = 9.9, 8.1 Hz, 1H), 3.66 (dd, *J* = 9.9, 5.4 Hz, 1H), 2.85-2.76 (m, 1H), 2.80 (dd, *J* = 17.7, 3.0 Hz, 1H), 2.69 (dd, *J* = 17.7, 9.3 Hz, 1H), 1.74 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 215.0, 145.9, 111.3, 71.2, 66.0, 49.4, 48.5, 26.2, 18.9, 13.1, -5.1; IR (NaCl): 3452, 2930, 2858, 1709, 1257 cm^{-1}.

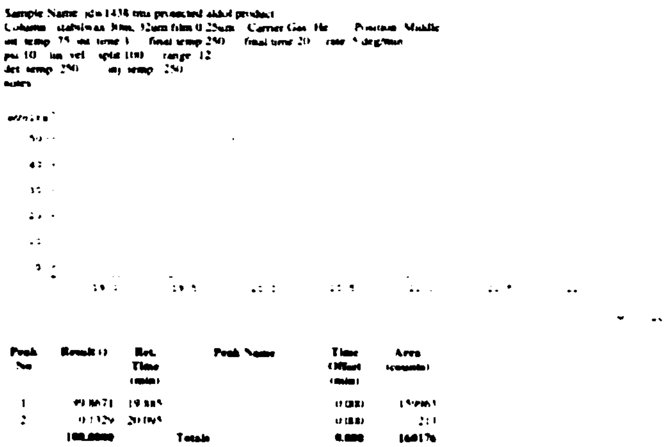


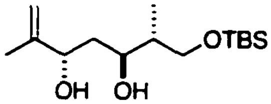
$C_{18}H_{38}O_3Si_2$
Mol. Wt.: 358.66

(2R,5S)- 2,6- dimethyl- 1- (^{t}butyldimethylsiloxy)- 5- (trimethylsiloxy)-hept-6-en-3-one: To a solution of (2R,5S)-5-hydroxy-2,6-dimethyl-1-(^{t}butyldimethylsiloxy)-hept-6-en-3-one **3-39** (10 mg, 35μmol) in CH_2Cl_2 (60 μL) was added DMAP (catalytic amt.), triethylamine (7 μL, 53 μmol), then TMSCl (6 μL, 42 μmol). An immediate reaction took place as evidenced by the formation of a white precipitate. After 3 min the reaction was diluted with water, and extracted with chloroform (3x). The combined organic layers were dried (Na_2SO_4) and concentrated to give a clear, colorless oil that was analyzed without purification. Injection on the GC showed a 97:3 ratio of diastereomers (major-20.55 min, minor-20.74 min).



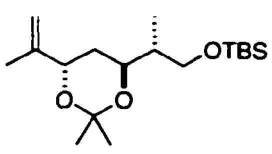
When a new bottle of (+)-DIPCl was used in the aldol reaction, the reaction provided an essentially diastereomerically pure compound.





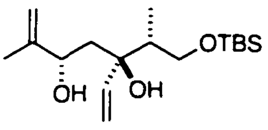
$C_{15}H_{32}O_3Si$
Mol. Wt.: 288.50

(3S,5S,6R)- 2,6- dimethyl- 7- (^{t}butyldimethylsiloxy)-hept-1-en-3,5-diol (3-45):[22] To a solution of tetramethylammonium triacetoxy-borohydride (551 mg, 2.1 mmol) in dry acetonitrile (1.2 mL) was added anhydrous acetic acid (2.1 mL) and the mixture was stirred for 30 min at room temperature. It was cooled to –40°C and a solution of (2R,5S)-5-hydroxy-2,6-dimethyl-1-(^{t}butyldimethylsiloxy)-hept-6-en-3-one **3-39** (75 mg, 0.26 mmol) in dry acetonitrile (0.38 mL) was added. The mixture was stirred at –40°C for 18 h, then quenched by the addition of 3 mL of 0.5 N aqueous sodium potassium tartrate and allowed to slowly warm to ambient temperature. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous layer was back extracted with dichloromethane (3x) and the combined organic layers were again washed with saturated aqueous sodium bicarbonate. This was repeated and the combined organic layers were dried ($MgSO_4$) and concentrated to give a clear, colorless oil. Purification by column chromatography (10-30% EtOAc/Hex) gave the title compound (68 mg, 90%) as a clear, colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.05 (s, 1H), 4.84 (s, 1H), 4.35 (dd, *J* = 5.4, 3.6 Hz, 1H), 3.84-3.76 (m, 1H), 3.82 (dd, *J* = 5.7, 2.7, 1H), 3.78 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.56 (dd, *J* = 10.0, 8.0 Hz, 2H), 1.84-1.73 (m, 1H), 1.70 (s, 3H), 0.86 (s, 9H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (CDCl$_3$): δ 147.7, 110.3, 75.5, 72.9, 69.4, 39.5, 38.8, 26.2, 29.2, 18.5, 13.8, -5.2, -5.1; IR (NaCl): 3430, 2956, 2929, 2857, 1409, 1101 cm^{-1}.



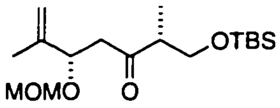
$C_{18}H_{36}O_3Si$
Mol. Wt.: 328.56

Acetonide (3-54): To a solution of (3S,5S,6R)-2,6-dimethyl-7-(^{t}butyl-dimethylsiloxy)-hept-1-en-3,5-diol **3-45** (200 mg, 0.7 mmol) in dichloromethane (3.6 mL) was added 2-methoxypropene (98 μL) and PPTS (5.6 mg, 0.02 mmol). The solution was stirred at 0°C for 4 h and the quenched by the addition of saturated, aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with an additional portion of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated to yield a clear, colorless oil. The crude product was purified by column chromatography (10% EtOAc/Hex) to give the desired product as a clear, colorless oil (157 mg, 69%). The reaction did not go to completion as 24 mg of the starting material was recovered. ^{13}C NMR ($CDCl_3$): δ 145.7, 110.5, 100.7, 70.1, 67.5, 64.5, 41.0, 35.1, 26.3, 25.3, 24.8, 19.0, 18.7, 12.6, -4.9, -5.0. DEPT analysis showed that the peaks at 24.8 and 25.3 were indeed methyl groups.



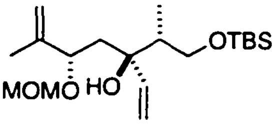
$C_{17}H_{34}O_3Si$
Mol. Wt.: 314.54

(3S,5R,6R)- 2,6- dimethyl- 5- vinyl- 7- (^{t}butyldimethylsiloxy)-hept-1-en-3,5-diol (3-58): A solution of (2R,5S)-5-hydroxy-2,6-dimethyl-1-(^{t}butyldimethylsiloxy)-hept-6-en-3-one **3-39** (286 mg, 1 mmol) in diethylether (26 mL) was taken to 0°C and vinyl magnesium bromide (1.0 M in THF, 3 mL, 3 mmol) was added dropwise. The resulting mixture was stirred at 0°C for 5 min and then at room temperature for 45 min. At that point, the reaction was partitioned between Et_2O and saturated NH_4Cl. The organic layer was drained off and the aqueous layer was washed with an additional portion of Et_2O. The combined organic layers were washed with NH_4Cl, brine and then dried ($MgSO_4$) and concentrated to give a clear, colorless oil. TLC analysis showed two spots that were heavily overlapped. Purification by column (10% Et_2O/Hex) gave a small bit of pure material (56 mg of each) from each spot and a good deal of mixed material (84 mg). Top spot: ^{1}H NMR ($CDCl_3$): δ 5.90 (dd, *J* = 17.1, 10.5 Hz, 1H), 5.43 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.22 (dd, *J* = 10.5, 1.8 Hz, 1H), 4.44 (dd, *J* = 10.8, 1.5 Hz, 1H), 3.62-3.57 (m, 2H), 2.41-2.30 (m, 1H), 1.79 (dd, *J* = 14.7, 1.5 Hz, 1H), 1.74 (s, 3H), 1.59 (dd, *J* = 14.7, 10.8 Hz, 1H), 0.90 (s, 9H), 0.79 (d, *J* = 7.5 Hz, 3H), 0.8 (s, 3H), 0.7 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 147.7, 140.1, 114.8, 110.4, 80.0, 72.1, 67.6, 43.6, 39.7, 26.2, 18.5, 18.4, 12.4, -5.3; Bottom spot: ^{1}H NMR ($CDCl_3$): δ 5.81 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.49 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.31 (dd, *J* = 10.8, 1.8 Hz, 1H), 4.72-5.15 (m, 1H), 4.80-4.63 (m, 1H), 4.26 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.94 (dd, *J* = 9.9, 3.3 Hz, 1H), 3.58 (dd, *J* = 9.9, 4.5 Hz, 1H), 1.91 (dd, *J* = 14.4, 10.2 Hz, 1H), 1.71 (s, 3H), 1.62-1.54 (m 1H), 1.41 (dd, *J* = 14.4, 1.5 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 147.7, 142.3, 114.9, 110.2, 80.0, 72.9, 67.4, 42.1, 41.6, 26.2, 18.9, 18.5, 12.2, -5.2, -5.3.



$C_{17}H_{34}O_4Si$
Mol. Wt.: 330.53

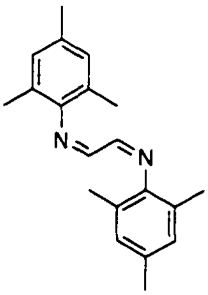
(2R,5S)- 5- (methoxymethyloxy)- 2,6- dimethyl- 1- (^{t}butyldimethylsiloxy)-hept-6-en-3-one (3-59): To an ice cold solution of (2R,5S)-5-hydroxy-2,6-dimethyl-1-(^{t}butyldimethylsiloxy)-hept-6-en-3-one **3-39** (1.09 g, 3.8 mmol) in dichloromethane (5 mL) was added Hünigs base (1.0 mL, 5.7 mmol), 4-dimethylaminopyridine (catalytic) and then methoxymethyl chloride (0.43 mL, 5.7 mmol). The solution was stirred at 0°C for 1 h, then warmed to ambient temperature and stirred an additional 12 h. At that point, the reaction was quenched by the addition of saturated NH_4Cl, extracted with CH_2Cl_2 (3x), dried and concentrated to give an orange oil. Purification by column chromatography (10% Et_2O/hexane) gave the desired compound as a clear, colorless oil (1.04 g, 87%). $[\alpha]_D^{25}$ = -84.0 (*c* = 2.50, $CHCl_3$); HRMS FAB Calcd (M + 1) for $C_{17}H_{34}O_4Si$: 331.2305. Found: 331.2308. ^{1}H NMR ($CDCl_3$): δ 5.01-4.99 (m, 1H), 4.93-4.90 (m, 1H), 4.57 (d, *J* = 6.3 Hz, 1H), 4.58-4.54 (m, 1H), 4.48 (d, *J* = 6.3 Hz, 1H), 3.71 (dd, *J* = 9.9, 7.2 Hz, 1H), 3.63 (*J* = 9.9, 5.4 Hz, 1H), 3.33 (s, 3H), 2.93 (dd, *J* = 16.5, 8.7 Hz, 1H), 2.86-2.71 (m, 1H), 2.52 (dd, *J* = 16.5, 3.6 Hz, 1H), 1.67 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H) 0.85 (s, 9H) 0.2 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 211.0, 143.5, 114.3, 94.2, 75.6, 65.8, 56.1, 49.7, 47.8, 26.2, 18.6, 17.7, 13.0, -5.1; IR (NaCl): 2955, 2930, 2886, 2858, 1717, 1152, 1098, 837 cm^{-1}.



$C_{19}H_{38}O_4Si$
Mol. Wt.: 358.59

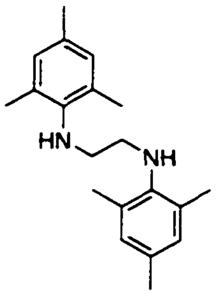
(2R,3R,5S)- 5- (methoxymethyloxy)- 2,6- dimethyl- 1- (^{t}butyl-dimethylsiloxy)-3-vinylhept-6-en-3-ol (3-60): A solution of tetravinyltin (268 mg, 1.2 mmol) in THF (14.2 ml) was cooled to –78°C. To this was added *n*-BuLi (2.6 M, 1.7 ml, 4.4 mmol), and the resulting solution was stirred at –78°C for 15 min. At that point a solution of (2R,5S)-5-(methoxymethyloxy)-2,6-dimethyl-1-(^{t}butyldimethylsiloxy)-hept-6-en-3-one **3-59** (936 mg, 3 mmol) in THF (4.7 ml) was added dropwise and the reaction was stirred an additional 45 min at –78°C then diluted with aq. NH_4Cl and slowly brought to ambient temperature. The aqueous layer was extracted with Et_2O and the organic layers combined, dried ($MgSO_4$) and concentrated to give a clear, colorless oil. Purification by column chromatography (10% Et_2O/hex) gave the title compound as a clear, colorless oil (950 mg, 93%). $[\alpha]_D^{25}$ = -29.0 (*c* = 1.26, $CHCl_3$); HRMS FAB Calcd (M + 1) for

$C_{19}H_{38}O_4Si$: 359.2618. Found: 359.2623. ^1H NMR ($CDCl_3$): δ 5.86 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.42 (dd, *J* = 17.1, 2.1 Hz, 1H), 5.24 (dd, *J* = 10.8, 2.1 Hz, 1H), 4.92-4.90 (m, 1H), 4.91-4.86 (m, 1H) 4.57 (d, *J* = 6.9 Hz, 1H), 4.45 (d, *J* = 6.9 Hz, 1H), 4.27 (dd, *J* = 10.2, 1.8 Hz, 1H), 3.66 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.56 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.38 (s, 3H), 2.04, (dd, *J* = 14.4, 10.2 Hz, 1H), 1.96-1.84 (m, 1H), 1.69-1.62 (m, 1H), 1.66 (s, 3H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 144.2, 142.7, 114.5, 114.2, 94.1, 78.5, 77.5, 65.5, 56.9, 44.9, 41.8, 26.3, 18.6, 17.5, 11.9, -4.9, -5.0; IR (NaCl): 3505, 2956, 2929, 2887, 2857, 1471, 1090, 1007, 837 cm^{-1}.



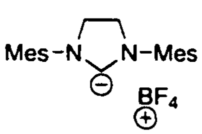
$C_{20}H_{24}N_2$
Mol. Wt.: 292.42

1,2-bis(2,4,6-trimethylphenylimino)ethane:[98] To a solution of 2,4,6-trimethylphenylamine (15.12 g, 111.8 mmol) in ethanol (250 mL) was added glyoxal (40% wt soln., 8.12 g, 55.9 mmol). The resulting bright yellow solution was stirred at room temperature for 14 h and then filtered. The yellow crystals were dried *in vacuo* giving the title compound (7.84 g). A second crop of crystals (2.04 g) precipitated from the EtOH/H_2O solution upon standing at room temperature over the course of 3 weeks. Additional crops were obtained by concentration of the mother liquor, cooling to 0°C and isolating the resultant bright yellow crystals by filtration. Total isolated yield: 13.39 g (82%). Spectral data for each crop matched the reported figures.



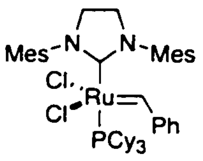
$C_{20}H_{28}N_2$
Mol. Wt.: 296.45

1,2-Bis(2,4,6-trimethylphenylamino)ethane:[99] To a suspension of 1,2-bis(2,4,6-trimethylphenylimino)ethane (7.30 g, 25 mmol) in methanol (250 mL) was added several crystals of bromocresol green (pH indicator) and the mixture was cooled to 0°C. Sodium cyanoborohydride (10g, 159 mmol) was added in one portion. Vigorous bubbling occurred and the solution turned a deep blue-green color (alkaline pH). After 10 min, concentrated HCl was added dropwise until the solution returned to its original, yellow color. Additional reduction occurred slowly, causing the mixture to become basic. The acidification process was repeated until the yellow color persisted. At that point, the reaction was warmed to ambient temperature and stirred for 1 hr then a solution of 2 M KOH was added dropwise until the mixture was weakly basic (pH 8-9). The mixture was diluted with water (300 mL) and extracted with Et_2O (3 x 500 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by column chromatography (20 % Et_2O/pentane) gave the title compound as a slightly yellow oil (7.13 g, 96 %). Spectral data for the purified product matched the reported figures.



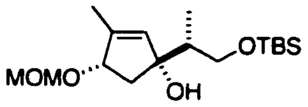
$C_{21}H_{27}BF_4N_2$
Mol. Wt.: 394.26

1,3-Dimesitylimidazolinium tetrafluoroborate:[100] To a 25 ml round-bottomed flask was added 1,2-bis(2,4,6-trimethylphenylamino)ethane (7.13 g, 24 mmol), ammonium tetraflouroborate (2.77 g, 26.4 mmol), and triethylorthoformate (4.39 mL, 26.4 mmol). The flask was equipped with a reflux condenser and submerged into a preheated oil bath at 120°C. The mixture was heated at reflux for 3 hr then cooled to ambient temperature. A tan solid precipitated, leaving a cloudy suspension. This mixture was recrystallized from anhydrous EtOH giving bright white crystals, which were washed with pentane and dried under vacuum giving the title compound (5.45 g, 58%). Spectral data for the purified product matched the reported figures.



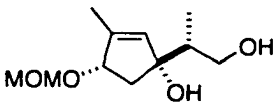
$C_{46}H_{66}Cl_2N_2PRu$
Mol. Wt.: 849.98

Tricyclohexylphosphine [1,3- bis- 2,4,6- trimethylphenyl)- 4,5-dihydroimidazol- 2- ylidene] [benzylidene] ruthenium (IV) dichloride (3-57):[100] To a suspension of 1,3-dimesitylimidazolinium tetrafluoroborate (587 mg, 1.5 mmol) in THF (10 mL) under argon was added a solution of potassium *tert*-butoxide (168 mg, 1.5 mmol) in THF (10 mL) *via* cannula. This mixture was immediately transferred by cannula to a second round-bottomed flask containing a solution of bis(tricyclohexylphosphine) benzylidine ruthenium (IV) dichloride (1.0 g, 1.2 mmol) in benzene (20 mL). The resulting mixture was refluxed at 80°C for 30 min and then cooled to ambient temperature. All manipulations from this point forward were carried out in air with reagent grade solvents. The solvents were removed *in vacuo*, leaving a red-brown solid residue. This was dissolved in 8:1 hexane/Et_2O and loaded onto a wide load of silica gel. Elution with the same solvent system slowly removed a pink-red colored band of the desired compound. Concentration of the product fractions *in vacuo* gave a cranberry red solid, which was dried under vacuum and provided the title compound (713 mg, 70%). Spectral data for the product matched the reported figures.



$C_{17}H_{34}O_4Si$
Mol. Wt.: 330.53

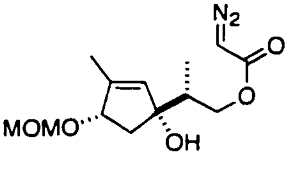
(1R,1'R,4S)- 1- [2'-^{t}butyldimethylsiloxy-1'-methylethyl]- 3-methyl- 4- (methoxymethyloxy)cyclopent- 2- en-1-ol (3-61): A stirred solution of (2R,3R,5S)-5-(methoxymethyloxy)-2,6-dimethyl-1-(^{t}butyldimethylsiloxy)-3-vinylhept-6-en-3-ol **3-57** (86 mg 0.25 mmol) in degassed benzene (1.25 ml) was placed under an argon atmosphere. To this was added tricyclohexylphosphine [1,3-bis-(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene] [benzylidene] ruthenium (IV) dichloride **3-57** (10.5 mg, 0.01 mmol)[84,85] and the mixture was heated to reflux and stirred under argon for 4 h and then exposed to atmospheric oxygen. After 2 h the solvent was removed and the remaining dark brown oil was purified directly *via* column chromatography (10% Et_2O/hex to 30% Et_2O/hex) to give the title compound as a clear, colorless oil. ^1H NMR ($CDCl_3$): δ 5.55-5.53 (m, 1H), 4.71, (d, J = 7.2 Hz, 1H), 4.66 (d, J = 7.2 Hz, 1H) 4.72-4.65 (m, 1H), 3.87 (dd, J = 10.2, 3.9 Hz, 1H), 3.60 (dd, J = 10.2, 6.9 Hz, 1H), 3.39 (s, 3H), 2.21 (dd, J = 13.5, 6.9 Hz, 1H), 2.01-1.89 (m, 1H), 1.87 (dd, J = 13.5, 3.9 Hz, 1H), 1.79, (s, 3H), 0.90 (s, 9H), 0.89-0.87 (m, 3H), 0.9 (s, 6H); IR (NaCl): 3485, 2954, 2930, 2884, 2857, 1255, 1048, 836 cm^{-1}.



$C_{11}H_{20}O_4$
Mol. Wt.: 216.27

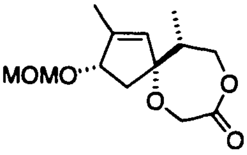
(1R,1'R,4S)- 1 - [2'- hydroxy -1' - methylethyl] -3 - methyl -4 - (methoxymethyl)-cyclopent-2-en-1-ol (3-63): To a stirred solution of (1R,1'R,4S)-1-[2'-^{t}butyldimethylsiloxy-1'-methylethyl]-3-methyl-4-(methoxymethyloxy)-cyclopent-2-en-1-ol **3-61** (1.16 g, 3.5 mmol) in THF (56 mL) at ambient temperature was added triethylamine trihydrofluoride (3 ml, 18.6 mmol). The reaction was stirred for 18 h, then concentrated and placed directly on a prepacked silica gel column buffered with 3% triethylamine in hexane. Elution with 75%

ethyl acetate in hexane afforded the title compound as a clear, slightly yellow oil (559 mg, 74%). HRMS FAB Calcd (M-H_2O) for $C_{11}H_{18}O_3$: 198.1256. Found: 198.1251. ^1H NMR ($CDCl_3$): δ 5.66-5.63 (m, 1H), 4.81 (d, *J* = 6.3 Hz, 1H), 4.76 (d, *J* = 6.3 Hz, 1H), 4.82-4.65 (m, 1H), 3.88 (dd, *J*= 11.1, 3.6, 1H), 3.77 (dd, *J* = 11.1, 7.5, 1H), 3.49 (s, 3H), 2.36 (dd, *J* = 14.4, 6.9 Hz, 1H), 2.15-1.95 (m, 1H), 2.04 (dd, *J* = 14.4, 4.2 Hz, 1H), 1.89 (s, 3H), 0.98 (d, *J* = 6.9, 3H); ^{13}C NMR ($CDCl_3$): δ 144.6, 133.5, 96.4, 87.7, 83.1, 66.7, 55.8, 43.0, 42.6, 14.4, 13.3. IR (NaCl): 3384, 1150, 1103, 1032 cm^{-1}.



$C_{13}H_{20}N_2O_5$
Mol. Wt.: 284.31

(1R,1'R,4S)- 1 - [2'- hydroxy -1' - methylethyl] -3 - methyl -4 - (methoxymethyl)-cyclopent-2-en-1-yl diazoacetate (3-64): To a solution of (1R,1'R,4S)-1-[2'-hydroxy-1'-methylethyl]-3-methyl-4-(methoxymethyl)-cyclopent-2-en-1-ol **3-63** (216 mg, 1.0 mmol) in dichloromethane (5.8 mL) at 0°C was added dimethylaniline (221 mg, 1.8 mmol) then glyoxylic acid chloride *p*-toluenesulfonylhydrazone (509 mg, 1.9 mmol). The resulting solution was stirred at 0°C for 10 min and then triethylamine (526 mg, 5.2 mmol) was added in one portion. The reaction was stirred for 10 min at 0°C and then warmed to room temperature and stirred an additional 15 min and quenched by the addition of water. The reaction was extracted with EtOAc (3x) and the combined organic layers were washed with water then dried ($MgSO_4$) and concentrated to a clear, orange oil. Purification by column chromatography (50% EtOAc/hex) gave the title compound as a yellow/orange oil (252 mg, 89%). IR (NaCl): 3459, 2943, 2886, 2112, 1693, 1398, 1360, 1034 cm^{-1}.



$C_{13}H_{20}O_5$
Mol. Wt.: 256.29

(3S, 6R, 11R)-3- (methoxymethyl)-2, 11-dimethyl-6, 9-dioxaspiro [4.6]undec-1-en-8-one (3-66): A solution of (1R,1'R,4S)-1-[2'-hydroxy- 1'- methylethyl]- 3-methyl-4-(methoxymethyl)-cyclopent-2-en-1-yl diazoacetate **3-64** (142 mg, 0.5 mmol) in CH_2Cl_2 (2.5 mL) was added to a refluxing solution of rhodium(II) caprolactam (3.3 mg, 0.005 mmol) in CH_2Cl_2 (10 mL) *via* syringe pump over 10 hr. At that point the reaction was cooled and concentrated. Purification by column chromatography (60% EtOAc/hex) gave the title compound as a clear, colorless oil (72 mg, 56%). HRMS FAB Calcd (M + 1) for $C_{13}H_{20}O_5$: 257.1389. Found: 257.1384. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (s, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.67 (d, 6.8 Hz, 1H), 4.71-4.66 (m, 1H), 4.31-4.24 (m, 2H), 4.21 (s, 2H), 3.39 (s, 3H), 2.38 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.17 (ddq, *J* = 13.6, 7.2, 6.4 Hz, 1H), 1.84, (s, 3H), 1.79 (dd, *J* = 13.6, 4.8 Hz, 1H), 1.03 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.0, 150.0, 127.8, 96.7, 91.0, 82.6, 70.2, 64.8, 55.9, 42.2, 41.4, 14.5, 12.9; IR (NaCl): 2939, 1740, 1221, 1150, 1092, 1047 cm^{-1}.

3.4. References

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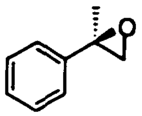
Appendix 1

Spectra for the Determination of Enantiomeric Excess of Epoxide Substrates

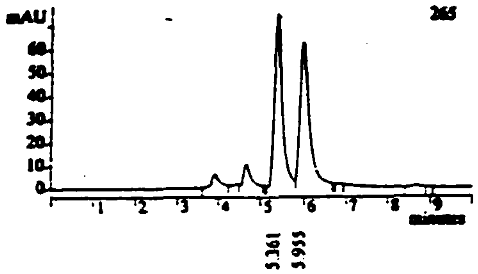
The spectra for the determination of enantiomeric excess of the epoxide substrates

α-Methylstyrene Oxide (Table 1, entry 1)



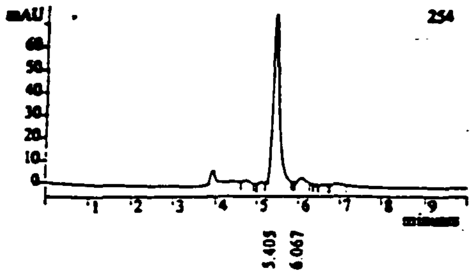
HPLC Conditions: **Column:** Chiralcel OD (Column No. OD00CE-GL031), Chiral Technologies Inc.
Eluent: Hexane/IPA (95/5) **Flow Rate:** 0.8 mL/min **Detection:** UV265

Racemate



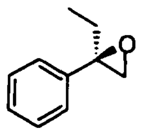
Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		49.1799	5.361	471235
2		50.8201	5.955	486952
	Totals	100.0000		958187

Chiral epoxide



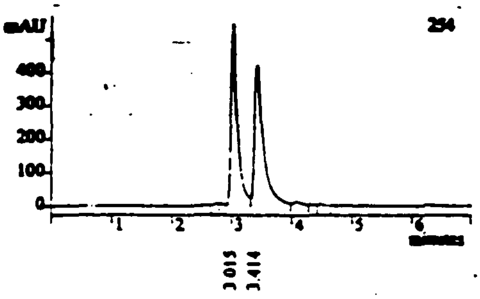
Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		97.2507	5.405	458381
2		2.7493	6.067	12959
	Totals	100.0000		471340

α-Ethylstyrene Oxide (Table 1, entry 2)



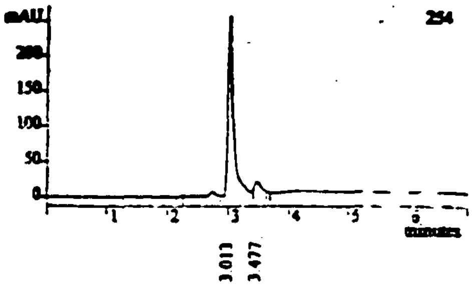
HPLC Conditions: **Column:** Chiralcel OD (Column No. OD00CE-GL031), Chiral Technologies Inc.
Eluent: Hexane/IPA (94/6) **Flow Rate:** 1.3 mL/min **Detection:** UV254

Racemate



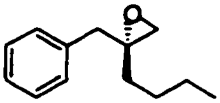
Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		48.3311	3.015	2123856
2		51.6689	3.414	2270536
	Totals	100.0000		4394392

Chiral epoxide



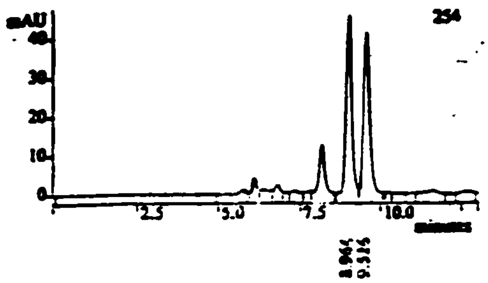
Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		95.9189	3.013	900702
2		4.0811	3.477	[illegible]322
	Totals	100.0000		9[illegible]9024

2-Benzyl-1-hexene Oxide (Table 1, entry 3)



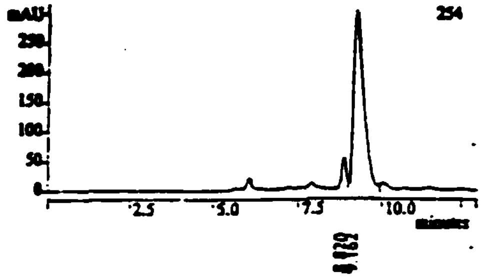
HPLC Conditions: **Column:** Chiralpak AD (Column No. AD00CE-IC048), Chiral Technologies Inc.
Eluent: Hexane/IPA (98/2) **Flow Rate:** 0.55 mL/min **Detection:** UV254

Racemate



Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		49.7801	8.964	295274
2		50.2199	9.526	297883
	Totals	100.0000		593157

Chiral epoxide



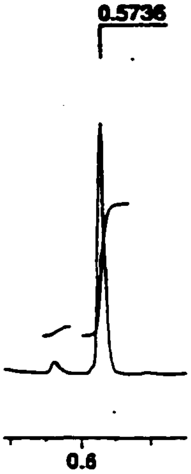
Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		3.3622	8.820	105870
2		96.6378	9.162	3042941
	Totals	100.0000		3148811

(R,R)-2-Ethyl-1-(trimethylsilyl)-1-hexene Oxide (Table 1, entry 4)

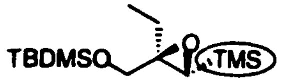
Enantioselectivity was determined by ^{1}H NMR shift analysis with Eu(hfc)$_3$ in CDCl$_3$

Racemate

Chiral epoxide

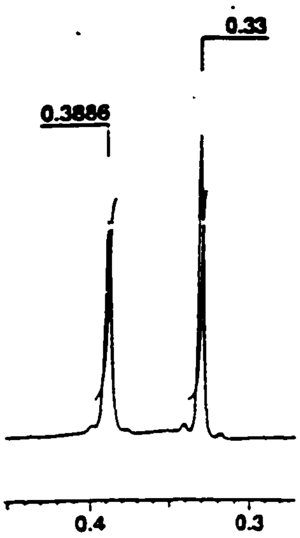


(R,R)-2-[(^{t}Butyldimethylsiloxy)methyl]-1-(trimethylsilyl)-1-butene Oxide (Table 1, entry 5)

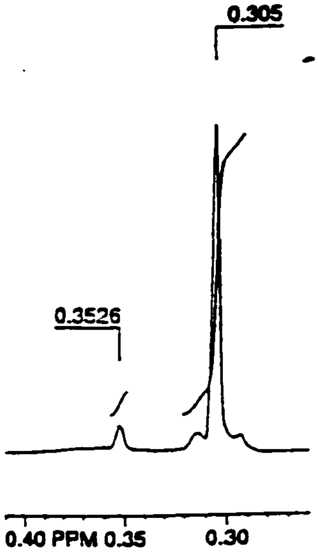


Enantioselectivity was determined by ^{1}H NMR shift analysis with Eu(hfc)$_3$ in CDCl$_3$

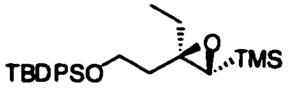
Racemate



Chiral epoxide

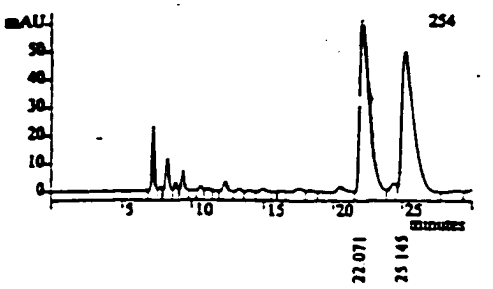


(R,R)-4-(^{t}Butyldiphenylsiloxy)-2-ethyl-1-(trimethylsilyl)-1-butene Oxide (Table 1, entry 6)



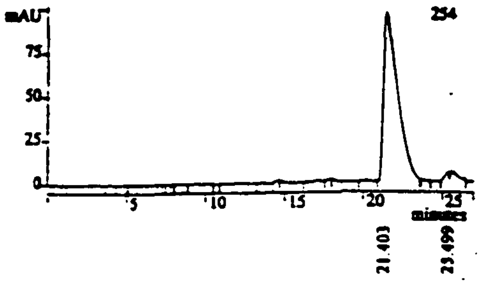
HPLC Conditions: **Column:** Chiralcel OD (Column No. OD00CE-GL031), Chiral Technologies Inc.
Eluent: Hexane **Flow Rate:** 0.5 mL/min **Detection:** UV254

Racemate



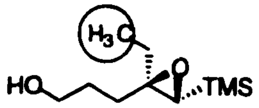
Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		51.1571	22.071	1611866
2		48.8429	25.145	1538952
	Totals	100.0000		3150818

Chiral epoxide



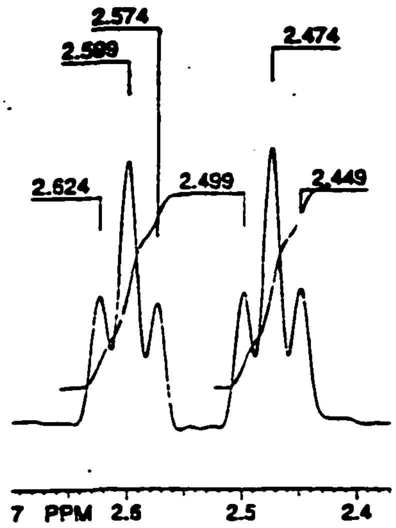
Peak No	Peak Name	Result ()	Ret. Time (min)	Area (counts)
1		95.8974	21.403	3061870
2		4.1026	25.499	130990
	Totals	100.0000		3192860

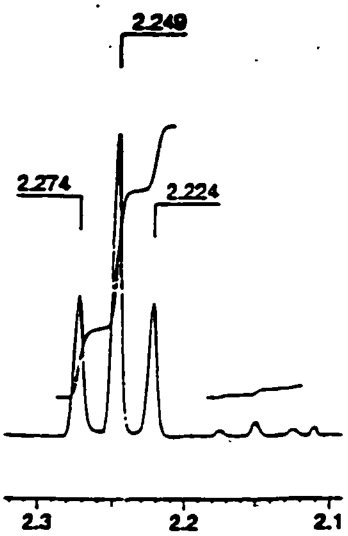
(R,R)-4-Ethyl-5-(trimethylsilyl)-4-penten-1-ol Oxide (Table 1, entry 7)



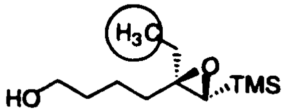
Enantioselectivity was determined by ^{1}H NMR shift analysis with Eu(hfc)$_3$ in CDCl$_3$

Racemate **Chiral epoxide**



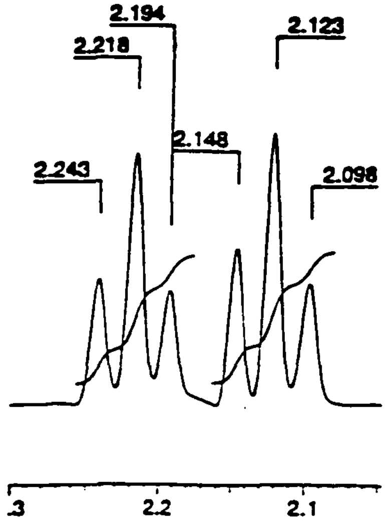


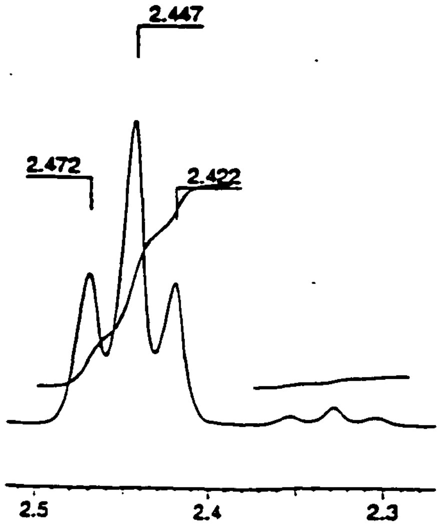
(R,R)-5-Ethyl-6-(trimethylsilyl)-5-hexen-1-ol Oxide (Table 1, entry 8)



Enantioselectivity was determined by ^{1}H NMR shift analysis with Eu(hfc)$_3$ in CDCl$_3$

Racemate **Chiral epoxide**





Appendix 2

X-ray Data for Acetonide 2-121

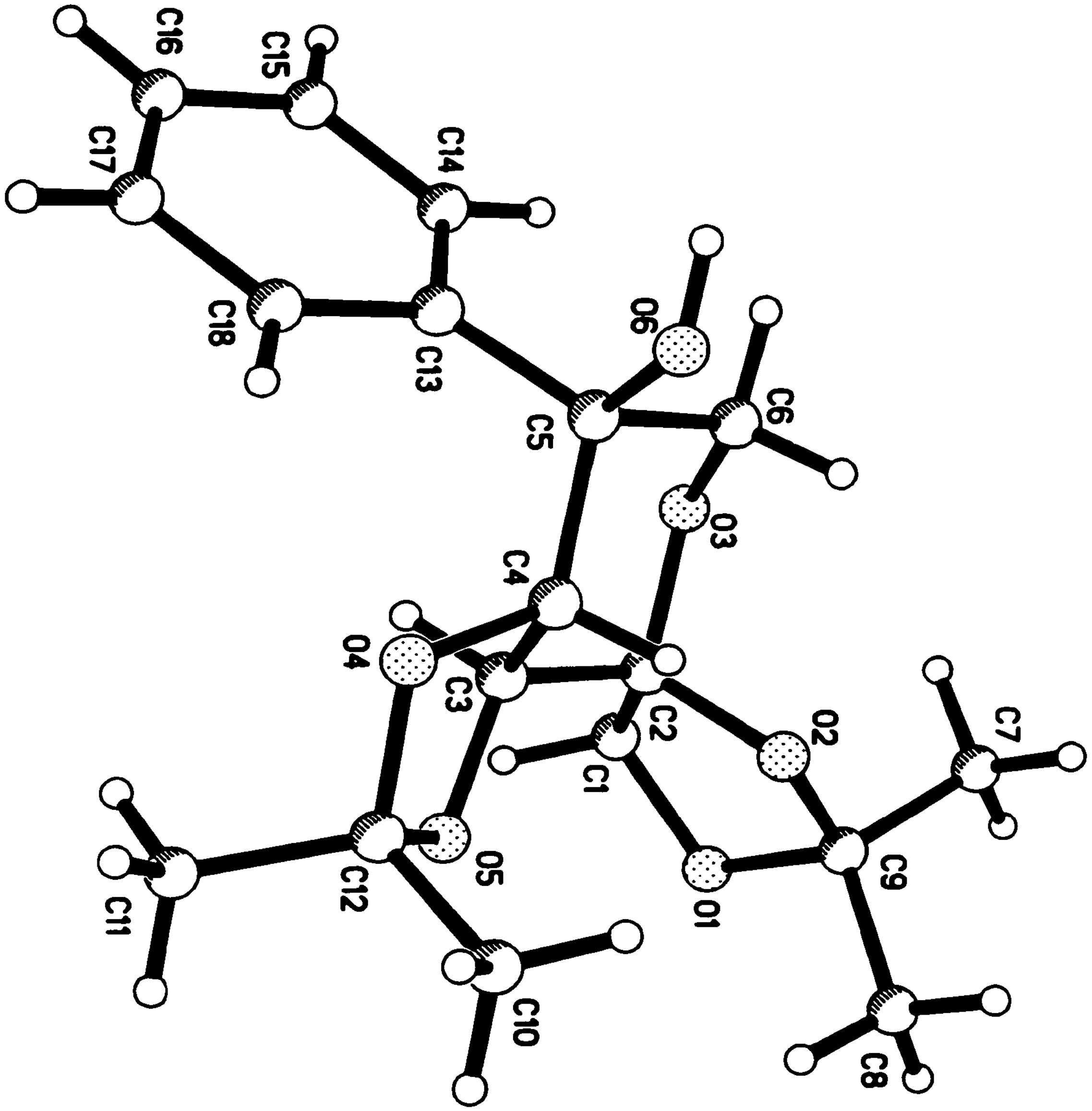

C16
C15
C17
C14
C18
C13
O6
C5
C6
O3
C4
O4
C3
C2
O2
C7
C1
C9
O5
O1
C12
C11
C10
C8

Table 1. Crystal data and structure refinement for D.Warren.

Identification code	ysccd12
Empirical formula	$C_{18}H_{24}O_6$
Formula weight	336.37
Temperature	170(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 7.3605(2) Å alpha = 90° b = 9.9460(3) Å beta = 90° c = 23.38360(10) Å gamma = 90°
Volume, Z	1711.86(7) $Å^3$, 4
Density (calculated)	1.305 Mg/m^3
Absorption coefficient	0.097 mm^{-1}
F(000)	720
Crystal size	0.10 x 0.20 x 0.40 mm
θ range for data collection	1.74 to 28.28°
Limiting indices	$-9 \le h \le 9$, $-12 \le k \le 13$, $-17 \le l \le 30$
Reflections collected	11546
Independent reflections	4151 (R_{int} = 0.0634)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4151 / 0 / 218
Goodness-of-fit on F^2	1.054
Final R indices [$I>2\sigma(I)$]	R1 = 0.0560, wR2 = 0.0957
R indices (all data)	R1 = 0.1142, wR2 = 0.1184
Absolute structure parameter	0.8(13)
Extinction coefficient	0.0061(12)
Largest diff. peak and hole	0.221 and -0.196 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	8232(2)	2482(2)	9188(1)	38(1)
O(2)	5827(2)	2766(2)	8603(1)	32(1)
O(3)	3890(2)	3668(2)	9308(1)	32(1)
O(4)	4688(2)	6424(2)	8017(1)	34(1)
O(5)	7223(2)	5424(2)	8421(1)	30(1)
O(6)	974(2)	5085(2)	8170(1)	36(1)
C(1)	7088(4)	3430(3)	9471(1)	35(1)
C(2)	5618(3)	3750(3)	9030(1)	29(1)
C(3)	5650(3)	5129(2)	8756(1)	26(1)
C(4)	4148(3)	5252(3)	8323(1)	27(1)
C(5)	2302(3)	5206(2)	8614(1)	29(1)
C(6)	2375(3)	3829(3)	8925(1)	33(1)
C(7)	6171(4)	598(3)	9058(1)	48(1)
C(8)	8272(4)	1410(3)	8273(1)	45(1)
C(9)	7132(4)	1778(3)	8783(1)	34(1)
C(10)	7058(4)	5543(3)	7393(1)	45(1)
C(11)	7479(4)	7640(3)	7998(1)	49(1)
C(12)	6620(3)	6273(3)	7944(1)	33(1)
C(13)	1846(3)	6400(3)	8996(1)	30(1)
C(14)	1187(4)	6244(3)	9547(1)	40(1)
C(15)	590(4)	7339(3)	9864(1)	48(1)
C(16)	677(4)	8611(3)	9638(1)	45(1)
C(17)	1380(4)	8801(3)	9096(1)	44(1)
C(18)	1937(4)	7713(3)	8775(1)	40(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(1)	1.426(3)	O(1)-C(9)	1.430(3)
O(2)-C(2)	1.406(3)	O(2)-C(9)	1.438(3)
O(3)-C(2)	1.431(3)	O(3)-C(6)	1.440(3)
O(4)-C(4)	1.423(3)	O(4)-C(12)	1.440(3)
O(5)-C(3)	1.428(3)	O(5)-C(12)	1.468(3)
O(6)-C(5)	1.431(3)	C(1)-C(2)	1.529(4)
C(2)-C(3)	1.513(3)	C(3)-C(4)	1.505(3)
C(4)-C(5)	1.522(3)	C(5)-C(13)	1.523(3)
C(5)-C(6)	1.551(3)	C(7)-C(9)	1.514(4)
C(8)-C(9)	1.504(4)	C(10)-C(12)	1.513(4)
C(11)-C(12)	1.504(4)	C(13)-C(14)	1.385(4)
C(13)-C(18)	1.406(4)	C(14)-C(15)	1.389(4)
C(15)-C(16)	1.372(4)	C(16)-C(17)	1.380(4)
C(17)-C(18)	1.380(4)		

C(1)-O(1)-C(9)	107.2(2)	C(2)-O(2)-C(9)	110.0(2)
C(2)-O(3)-C(6)	113.4(2)	C(4)-O(4)-C(12)	104.5(2)
C(3)-O(5)-C(12)	106.9(2)	O(1)-C(1)-C(2)	104.1(2)
O(2)-C(2)-O(3)	112.4(2)	O(2)-C(2)-C(3)	109.2(2)
O(3)-C(2)-C(3)	105.0(2)	O(2)-C(2)-C(1)	104.9(2)
O(3)-C(2)-C(1)	108.0(2)	C(3)-C(2)-C(1)	117.6(2)
O(5)-C(3)-C(4)	102.0(2)	O(5)-C(3)-C(2)	115.5(2)
C(4)-C(3)-C(2)	110.3(2)	O(4)-C(4)-C(3)	101.5(2)
O(4)-C(4)-C(5)	120.0(2)	C(3)-C(4)-C(5)	110.6(2)
O(6)-C(5)-C(4)	106.7(2)	O(6)-C(5)-C(13)	109.9(2)
C(4)-C(5)-C(13)	115.8(2)	O(6)-C(5)-C(6)	106.8(2)
C(4)-C(5)-C(6)	101.9(2)	C(13)-C(5)-C(6)	115.0(2)
O(3)-C(6)-C(5)	114.6(2)	O(1)-C(9)-O(2)	103.7(2)
O(1)-C(9)-C(8)	109.2(2)	O(2)-C(9)-C(8)	107.9(2)
O(1)-C(9)-C(7)	111.2(2)	O(2)-C(9)-C(7)	110.0(2)
C(8)-C(9)-C(7)	114.2(2)	O(4)-C(12)-O(5)	105.6(2)
O(4)-C(12)-C(11)	108.1(2)	O(5)-C(12)-C(11)	109.2(2)
O(4)-C(12)-C(10)	111.2(2)	O(5)-C(12)-C(10)	107.8(2)
C(11)-C(12)-C(10)	114.5(2)	C(14)-C(13)-C(18)	117.6(3)
C(14)-C(13)-C(5)	122.3(3)	C(18)-C(13)-C(5)	119.9(2)
C(13)-C(14)-C(15)	121.3(3)	C(16)-C(15)-C(14)	120.1(3)
C(15)-C(16)-C(17)	119.8(3)	C(18)-C(17)-C(16)	120.2(3)
C(17)-C(18)-C(13)	120.9(3)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [Å^2 x 10^3] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
O(1)	27(1)	48(1)	38(1)	4(1)	-4(1)	4(1)
O(2)	28(1)	34(1)	34(1)	-2(1)	-5(1)	6(1)
O(3)	25(1)	43(1)	29(1)	4(1)	3(1)	-2(1)
O(4)	19(1)	47(1)	34(1)	8(1)	2(1)	4(1)
O(5)	17(1)	42(1)	31(1)	8(1)	2(1)	2(1)
O(6)	18(1)	59(1)	32(1)	-6(1)	-3(1)	1(1)
C(1)	32(2)	42(2)	32(1)	3(1)	-1(1)	2(1)
C(2)	21(1)	39(2)	28(1)	0(1)	0(1)	-2(1)
C(3)	16(1)	36(2)	27(1)	-3(1)	0(1)	3(1)
C(4)	21(1)	37(2)	24(1)	1(1)	1(1)	2(1)
C(5)	18(1)	43(2)	25(1)	-2(1)	-2(1)	1(1)
C(6)	20(1)	45(2)	33(2)	-3(1)	1(1)	-3(1)
C(7)	46(2)	45(2)	52(2)	9(2)	3(2)	0(2)
C(8)	34(2)	52(2)	49(2)	-1(2)	4(1)	12(2)
C(9)	23(1)	38(2)	40(2)	6(1)	-3(1)	5(1)
C(10)	27(2)	73(2)	36(2)	7(2)	4(1)	5(2)
C(11)	36(2)	43(2)	69(2)	15(2)	-7(2)	-2(2)
C(12)	19(1)	47(2)	33(1)	8(1)	0(1)	6(1)
C(13)	17(1)	42(2)	31(1)	-4(1)	-1(1)	3(1)
C(14)	41(2)	47(2)	32(2)	-1(2)	2(1)	-5(1)
C(15)	49(2)	58(2)	36(2)	-14(2)	8(2)	-1(2)
C(16)	40(2)	49(2)	47(2)	-17(2)	-4(2)	9(2)
C(17)	37(2)	43(2)	51(2)	-1(2)	-2(1)	7(1)
C(18)	32(2)	50(2)	37(2)	2(2)	5(1)	8(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 1.

	x	y	z	U(eq)
H(6A)	-69(2)	5056(2)	8315(1)	54
H(1A)	7775(4)	4249(3)	9576(1)	42
H(1B)	6550(4)	3036(3)	9821(1)	42
H(3A)	5496(3)	5833(2)	9058(1)	32
H(4A)	4232(3)	4467(3)	8057(1)	33
H(6B)	1236(3)	3709(3)	9144(1)	39
H(6C)	2425(3)	3107(3)	8634(1)	39
H(7A)	5429(4)	135(3)	8771(1)	71
H(7B)	5389(4)	923(3)	9368(1)	71
H(7C)	7073(4)	-28(3)	9214(1)	71
H(8A)	7523(4)	927(3)	7994(1)	67
H(8B)	9280(4)	834(3)	8395(1)	67
H(8C)	8757(4)	2230(3)	8097(1)	67
H(10A)	8379(4)	5455(3)	7355(1)	68
H(10B)	6577(4)	6054(3)	7069(1)	68
H(10C)	6503(4)	4648(3)	7400(1)	68
H(11A)	8797(4)	7560(3)	7950(1)	74
H(11B)	7212(4)	8013(3)	8377(1)	74
H(11C)	6988(4)	8237(3)	7703(1)	74
H(14A)	1143(4)	5371(3)	9711(1)	48
H(15A)	120(4)	7208(3)	10238(1)	57
H(16A)	255(4)	9358(3)	9853(1)	54
H(17A)	1480(4)	9683(3)	8945(1)	53
H(18A)	2389(4)	7853(3)	8399(1)	48

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
2	0	0	762	767	12
4	0	0	130	117	6
6	0	0	323	321	8
8	0	0	152	148	7
1	1	0	328	341	2
2	1	0	752	730	6
3	1	0	345	335	4
4	1	0	464	449	4
5	1	0	0	29	1
6	1	0	87	87	6
7	1	0	199	195	4
8	1	0	79	79	8
9	1	0	19	25	19
0	2	0	18	21	8
1	2	0	92	94	1
2	2	0	171	173	2
3	2	0	172	167	2
4	2	0	62	67	5
5	2	0	207	203	3
6	2	0	209	218	4
7	2	0	0	1	1
8	2	0	78	82	8
9	2	0	41	19	19
1	3	0	219	210	2
2	3	0	286	290	2
3	3	0	351	342	3
4	3	0	41	46	9
5	3	0	27	43	26
6	3	0	101	94	5
7	3	0	123	116	6
8	3	0	96	88	9
9	3	0	61	62	14
0	4	0	38	41	6
1	4	0	324	327	2
2	4	0	73	77	2
3	4	0	222	222	2
4	4	0	99	107	3
5	4	0	35	42	18
6	4	0	206	215	4
7	4	0	73	88	13
8	4	0	53	52	52
9	4	0	8	22	7
1	5	0	52	47	3
2	5	0	126	122	2
3	5	0	22	9	11
4	5	0	180	176	2
5	5	0	0	12	1
6	5	0	369	375	4
7	5	0	8	27	7
8	5	0	0	57	1
0	6	0	158	143	3
1	6	0	0	12	1
2	6	0	85	87	3
3	6	0	203	209	3
4	6	0	22	11	21
5	6	0	57	50	7
6	6	0	72	62	10
7	6	0	89	101	13
8	6	0	39	31	38
1	7	0	209	213	2
2	7	0	192	199	2
3	7	0	0	20	1
4	7	0	112	112	5
5	7	0	0	15	1
6	7	0	97	90	8
7	7	0	19	36	18
8	7	0	0	59	1
0	8	C	547	537	5
1	8	0	149	149	3
2	8	0	62	69	6
3	8	0	150	144	4
4	8	0	121	121	5
5	8	0	101	78	6
6	8	0	38	37	25
7	8	0	91	67	11
1	9	0	45	46	13
2	9	0	218	219	3
3	9	0	155	153	4
4	9	0	145	144	5
5	9	0	67	57	11
6	9	0	34	1	33
7	9	0	105	69	24
0	10	0	203	196	9
1	10	0	55	54	13
2	10	0	21	70	21
3	10	0	0	14	1
4	10	0	38	26	21
5	10	0	21	34	20
6	10	0	64	53	14
1	11	0	0	34	1
2	11	0	50	31	19
3	11	0	0	30	1
4	11	0	0	24	1
5	11	0	44	22	43
0	12	0	117	94	13
1	12	0	0	42	1
2	12	0	46	4	27
3	12	0	0	32	1
1	13	0	12	2	12
1	0	1	648	649	6
2	0	1	1108	1106	10
3	0	1	284	279	4
4	0	1	93	94	4
5	0	1	14	7	13
6	0	1	254	242	4
7	0	1	159	156	4
8	0	1	164	164	4
9	0	1	0	1	1
-9	1	1	115	109	7
-8	1	1	103	114	6
-7	1	1	180	173	6
-6	1	1	159	158	4
-5	1	1	47	49	7
-4	1	1	283	272	3
-3	1	1	393	392	3
-2	1	1	477	498	3
-1	1	1	522	550	3
0	1	1	156	157	1
1	1	1	526	550	7
2	1	1	494	498	8
3	1	1	391	392	7
4	1	1	281	272	6
5	1	1	60	49	13
6	1	1	155	158	4
7	1	1	175	173	3
8	1	1	116	114	5
9	1	1	112	109	6
-9	2	1	60	75	13
-8	2	1	78	69	16
-7	2	1	116	115	7
-6	2	1	189	182	3
-5	2	1	185	183	4
-4	2	1	157	153	3
-3	2	1	227	226	2
-2	2	1	172	170	2
-1	2	1	314	325	4
0	2	1	622	651	4
1	2	1	313	325	6
2	2	1	169	170	2
3	2	1	232	226	2
4	2	1	150	153	3
5	2	1	178	183	4
6	2	1	185	182	4
7	2	1	109	116	6
8	2	1	69	69	7
9	2	1	82	76	8
-9	3	1	46	60	45
-8	3	1	103	96	8
-7	3	1	46	38	16
-6	3	1	136	143	4
-5	3	1	110	115	4
-4	3	1	133	132	3
-3	3	1	152	156	2
-2	3	1	81	84	4
-1	3	1	422	439	3
0	3	1	142	140	2
1	3	1	420	439	3
2	3	1	83	84	2
3	3	1	156	156	3
4	3	1	129	132	3
5	3	1	111	114	4
6	3	1	139	143	4
7	3	1	52	38	11
8	3	1	104	96	9
9	3	1	47	60	14
-9	4	1	0	8	1
-8	4	1	69	53	12
-7	4	1	58	64	18
-6	4	1	162	166	5
-5	4	1	58	67	6
-4	4	1	212	212	3
-3	4	1	90	84	2
-2	4	1	204	201	2
-1	4	1	192	196	2
0	4	1	537	544	3
1	4	1	195	196	2
2	4	1	203	201	2
3	4	1	83	84	3
4	4	1	211	212	2
5	4	1	55	67	8
6	4	1	151	166	4
7	4	1	56	64	13
8	4	1	58	53	15
9	4	1	81	8	19
-8	5	1	68	44	23
-7	5	1	91	93	9
-6	5	1	150	154	4
-5	5	1	145	145	6
-4	5	1	253	252	2
-3	5	1	211	210	2
-2	5	1	195	190	3
-1	5	1	142	142	2
0	5	1	159	165	2
1	5	1	141	142	2
2	5	1	196	190	5
3	5	1	211	210	2
4	5	1	258	252	4
5	5	1	139	145	3
6	5	1	156	154	6
7	5	1	95	93	6
8	5	1	55	44	18
-8	6	1	65	56	22
-7	6	1	82	93	12
-6	6	1	206	199	6
-5	6	1	99	95	6
-4	6	1	151	147	3
-3	6	1	130	133	2
-2	6	1	102	105	3
-1	6	1	55	56	3
0	6	1	107	108	2
1	6	1	62	56	4
2	6	1	106	105	2
3	6	1	129	133	2
4	6	1	149	147	3
5	6	1	95	95	5
6	6	1	188	199	7
7	6	1	102	93	10
8	6	1	41	56	41
-8	7	1	65	19	22
-7	7	1	86	89	10
-6	7	1	51	72	12
-5	7	1	51	71	13
-4	7	1	128	133	5
-3	7	1	45	52	8
-2	7	1	65	66	4
-1	7	1	157	154	2
0	7	1	93	84	5
1	7	1	155	154	3
2	7	1	67	66	4
3	7	1	55	52	6
4	7	1	124	133	4
5	7	1	85	71	11
6	7	1	86	72	9
7	7	1	97	89	10
8	7	1	0	19	1
-7	8	1	4	41	4
-6	8	1	70	71	9
-5	8	1	83	80	7
-4	8	1	114	112	5
-3	8	1	211	204	6
-2	8	1	88	87	4
-1	8	1	9	19	9
0	8	1	372	368	3
1	8	1	10	19	9
2	8	1	90	87	5
3	8	1	205	204	5
4	8	1	114	112	8
5	8	1	80	80	7
6	8	1	88	71	10
7	8	1	60	41	16
-7	9	1	68	51	15
-6	9	1	65	42	19
-5	9	1	45	48	44
-4	9	1	115	103	6
-3	9	1	85	87	6
-2	9	1	87	86	5
-1	9	1	83	73	5
0	9	1	109	114	10
1	9	1	81	73	9
2	9	1	92	86	5
3	9	1	79	87	6
4	9	1	104	103	6
5	9	1	45	48	16
6	9	1	35	42	34
7	9	1	59	51	21
-6	10	1	52	40	20
-5	10	1	30	45	30
-4	10	1	17	14	17
-3	10	1	18	51	18
-2	10	1	26	21	26
-1	10	1	0	34	1
0	10	1	0	3	1
1	10	1	37	34	36
2	10	1	23	21	23
3	10	1	7	51	7
4	10	1	0	14	1
5	10	1	37	45	29
6	10	1	0	40	1
-5	11	1	0	26	1
-4	11	1	63	82	30
-3	11	1	46	33	45
-2	11	1	33	45	32
-1	11	1	62	60	29
0	11	1	91	85	10
1	11	1	65	61	15
2	11	1	54	45	17
4	11	1	94	82	17
5	11	1	0	26	1
-3	12	1	17	20	16
-2	12	1	27	36	26
-1	12	1	0	38	1
0	12	1	49	51	23
1	12	1	7	38	7
2	12	1	25	36	24
3	12	1	30	20	29
-1	13	1	94	17	18
0	13	1	28	12	28
1	13	1	0	17	1
0	0	2	45	30	7
1	0	2	153	155	1
2	0	2	323	325	3
3	0	2	171	170	2
4	0	2	258	247	3
5	0	2	77	85	8
6	0	2	0	3	1
7	0	2	135	139	5
8	0	2	39	17	15
9	0	2	73	62	9
-9	1	2	70	59	18
-8	1	2	58	44	14
-7	1	2	137	142	6
-6	1	2	301	297	4
-5	1	2	266	257	3
-4	1	2	364	351	3
-3	1	2	313	308	3
-2	1	2	333	336	2
-1	1	2	574	587	3
0	1	2	1403	1356	13
1	1	2	571	587	5
2	1	2	335	336	6
3	1	2	320	308	6
4	1	2	358	351	7
5	1	2	274	257	7
6	1	2	303	297	4
7	1	2	143	142	4
8	1	2	72	44	7
9	1	2	48	59	14
-9	2	2	0	48	1
-8	2	2	109	102	12
-7	2	2	110	106	7
-6	2	2	112	114	6
-5	2	2	96	88	4
-4	2	2	203	198	2
-3	2	2	177	174	2
-2	2	2	0	7	1
-1	2	2	524	537	3
0	2	2	615	631	4
1	2	2	521	537	3
2	2	2	19	7	19
3	2	2	177	173	3
4	2	2	213	198	3
5	2	2	90	88	5
6	2	2	115	114	5
7	2	2	114	106	6
8	2	2	110	102	5
9	2	2	47	48	13
-9	3	2	0	39	1
-8	3	2	0	27	1
-7	3	2	186	185	7
-6	3	2	170	173	4
-5	3	2	158	156	3
-4	3	2	188	182	3
-3	3	2	293	291	3
-2	3	2	264	264	2
-1	3	2	133	129	3
0	3	2	211	219	1
1	3	2	134	129	1
2	3	2	264	264	3
3	3	2	288	291	3
4	3	2	192	182	5
5	3	2	155	156	4
6	3	2	172	173	4
7	3	2	177	185	5
8	3	2	24	27	24
9	3	2	38	39	22
-9	4	2	62	57	29
-8	4	2	76	79	12
-7	4	2	73	50	10
-6	4	2	258	257	5
-5	4	2	56	36	6
-4	4	2	130	129	3
-3	4	2	137	136	2
-2	4	2	274	269	3
-1	4	2	323	329	2
0	4	2	409	420	6
1	4	2	323	329	2
2	4	2	271	269	2
3	4	2	139	136	2
4	4	2	135	129	3
5	4	2	49	36	17
6	4	2	251	257	7
7	4	2	47	50	12
8	4	2	70	79	13
9	4	2	62	57	17
-8	5	2	80	45	16
-7	5	2	125	124	11
-6	5	2	114	113	5
-5	5	2	76	76	5
-4	5	2	174	175	2
-3	5	2	172	176	2
-2	5	2	215	214	2
-1	5	2	179	183	2
0	5	2	107	119	2
1	5	2	183	183	2
2	5	2	215	214	2
3	5	2	178	176	2
4	5	2	179	175	3
5	5	2	74	76	9
6	5	2	120	113	10
7	5	2	127	124	5
8	5	2	0	45	1
-8	6	2	0	18	1
-7	6	2	101	99	12
-6	6	2	122	130	5
-5	6	2	71	58	7
-4	6	2	55	66	8
-3	6	2	161	158	3
-2	6	2	144	145	2
-1	6	2	176	177	2
0	6	2	115	111	2
1	6	2	176	177	2
2	6	2	141	145	2
3	6	2	163	158	2
4	6	2	54	66	6
5	6	2	46	58	10
6	6	2	136	130	7
7	6	2	96	98	7
8	6	2	55	18	32
-8	7	2	19	37	18
-7	7	2	44	41	23
-6	7	2	52	53	13
-5	7	2	163	169	4
-4	7	2	54	48	9
-3	7	2	111	118	6
-2	7	2	143	143	3
-1	7	2	142	139	2
0	7	2	378	375	3
1	7	2	142	139	2
2	7	2	140	144	2
3	7	2	108	118	3
4	7	2	47	48	8
5	7	2	168	169	4
6	7	2	53	53	15
7	7	2	75	41	11
8	7	2	0	37	1
-7	8	2	92	114	10
-6	8	2	64	63	11
-5	8	2	41	46	14
-4	8	2	58	69	24
-3	8	2	40	29	10

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
-2	8	2	120	130	4
-1	8	2	177	177	3
0	8	2	80	75	9
1	8	2	181	177	3
2	8	2	126	129	4
3	8	2	33	29	11
4	8	2	76	69	7
5	8	2	57	47	13
6	8	2	81	63	10
7	8	2	116	114	9
-7	9	2	62	27	19
-6	9	2	95	96	9
-5	9	2	68	50	33
-4	9	2	119	112	5
-3	9	2	38	31	21
-2	9	2	135	131	4
-1	9	2	0	10	1
0	9	2	141	146	5
1	9	2	0	10	1
2	9	2	133	131	5
3	9	2	30	31	22
4	9	2	124	113	5
5	9	2	63	50	13
6	9	2	110	96	9
7	9	2	43	27	43
-6	10	2	34	38	33
-5	10	2	8	31	8
-4	10	2	76	65	9
-3	10	2	65	77	28
-2	10	2	68	68	7
-1	10	2	116	110	10
0	10	2	11	20	11
1	10	2	110	110	8
2	10	2	62	68	16
3	10	2	84	77	17
4	10	2	54	65	17
5	10	2	44	31	44
6	10	2	76	38	23
-5	11	2	26	34	25
-4	11	2	0	14	1
-3	11	2	43	17	42
-2	11	2	48	15	23
-1	11	2	46	36	21
0	11	2	83	81	11
1	11	2	0	36	1
2	11	2	0	15	1
3	11	2	73	17	21
4	11	2	0	14	1
5	11	2	80	34	24
-3	12	2	45	10	44
-2	12	2	15	34	14
-1	12	2	36	48	36
0	12	2	0	1	1
1	12	2	50	48	26
2	12	2	67	34	16
3	12	2	0	10	1
-1	13	2	60	70	42
0	13	2	0	11	1
1	13	2	105	70	11
1	0	3	19	17	6
2	0	3	220	220	2
3	0	3	435	442	3
4	0	3	276	261	3
5	0	3	449	424	5
6	0	3	50	41	10
7	0	3	101	105	7
8	0	3	208	200	4
9	0	3	63	64	11
-9	1	3	136	140	8
-8	1	3	0	48	1
-7	1	3	140	140	5
-6	1	3	235	235	4
-5	1	3	103	101	3
-4	1	3	223	222	2
-3	1	3	57	57	3
-2	1	3	462	479	3
-1	1	3	1220	1192	9
0	1	3	86	99	1
1	1	3	1208	1191	8
2	1	3	468	479	5
3	1	3	68	57	7
4	1	3	227	222	6
5	1	3	96	100	4
6	1	3	235	235	4
7	1	3	137	140	4
8	1	3	48	48	10
9	1	3	144	140	6
-9	2	3	65	80	21
-8	2	3	58	27	21
-7	2	3	37	33	36
-6	2	3	94	98	7
-5	2	3	157	161	3
-4	2	3	36	39	6
-3	2	3	401	397	3
-2	2	3	154	160	1
-1	2	3	541	561	4
0	2	3	895	924	7
1	2	3	544	561	5
2	2	3	152	160	4
3	2	3	396	398	7
4	2	3	50	39	12
5	2	3	158	161	5
6	2	3	100	98	5
7	2	3	39	33	11
8	2	3	0	27	1
9	2	3	85	79	9
-9	3	3	45	20	45
-8	3	3	65	32	20
-7	3	3	125	131	6
-6	3	3	110	116	4
-5	3	3	123	119	3
-4	3	3	12	18	11
-3	3	3	147	145	2
-2	3	3	250	245	3
-1	3	3	289	296	2
0	3	3	284	282	2
1	3	3	285	296	2
2	3	3	254	245	2
3	3	3	149	145	2
4	3	3	22	18	22
5	3	3	124	119	6
6	3	3	108	116	5
7	3	3	123	131	7
8	3	3	58	32	9
9	3	3	32	19	31
-9	4	3	67	43	27
-8	4	3	88	72	15
-7	4	3	38	51	37
-6	4	3	119	117	4
-5	4	3	112	119	4
-4	4	3	114	113	3
-3	4	3	99	98	2
-2	4	3	366	370	2
-1	4	3	173	169	2
0	4	3	190	184	2
1	4	3	172	169	3
2	4	3	364	370	3
3	4	3	92	99	3
4	4	3	111	112	3
5	4	3	117	119	4
6	4	3	121	117	5
7	4	3	56	51	10
8	4	3	85	72	11
9	4	3	52	43	22
-8	5	3	68	22	19
-7	5	3	73	78	16
-6	5	3	138	138	5
-5	5	3	66	64	6
-4	5	3	85	88	4
-3	5	3	91	86	2
-2	5	3	390	376	3
-1	5	3	190	194	4
0	5	3	198	192	2
1	5	3	188	194	3
2	5	3	388	376	3
3	5	3	93	85	3
4	5	3	93	88	4
5	5	3	55	64	6
6	5	3	131	138	4
7	5	3	79	78	8
8	5	3	49	22	49
9	5	3	78	53	24
-8	6	3	74	73	20
-7	6	3	99	93	12
-6	6	3	101	94	6
-5	6	3	125	124	7
-4	6	3	26	24	26
-3	6	3	175	179	3
-2	6	3	40	42	8
-1	6	3	80	81	3
0	6	3	399	390	3
1	6	3	72	81	3
2	6	3	43	42	7
3	6	3	179	179	3
4	6	3	0	24	1
5	6	3	130	124	5
6	6	3	78	94	7
7	6	3	114	93	6
8	6	3	79	73	19
-7	7	3	116	115	12
-6	7	3	180	184	5
-5	7	3	82	76	9
-4	7	3	74	69	7
-3	7	3	148	141	3
-2	7	3	43	38	8
-1	7	3	80	73	6
0	7	3	220	222	2
1	7	3	76	73	5
2	7	3	36	38	6
3	7	3	140	141	2
4	7	3	68	69	7
5	7	3	86	76	6
6	7	3	183	184	5
7	7	3	120	115	8
8	7	3	46	16	45
-7	8	3	53	46	24
-6	8	3	51	32	14
-5	8	3	101	100	6
-4	8	3	0	7	1
-3	8	3	175	181	4
-2	8	3	49	56	8
-1	8	3	67	74	5
0	8	3	50	31	7
1	8	3	74	74	4
2	8	3	58	56	5
3	8	3	178	181	4
4	8	3	0	7	1
5	8	3	103	100	24
6	8	3	37	32	26
7	8	3	75	46	13
-7	9	3	29	67	29
-6	9	3	69	60	10
-5	9	3	16	36	16
-4	9	3	72	84	8
-3	9	3	38	43	16
-2	9	3	54	70	10
-1	9	3	130	130	4
0	9	3	179	173	6
1	9	3	116	130	5
2	9	3	73	70	24
3	9	3	37	43	19
4	9	3	71	84	15
5	9	3	23	36	22
6	9	3	50	60	17
7	9	3	65	67	17
-6	10	3	50	29	17
-5	10	3	99	76	7
-4	10	3	71	80	9
-3	10	3	37	44	37
-2	10	3	54	64	9
-1	10	3	42	56	15
0	10	3	129	136	8
1	10	3	64	56	22
2	10	3	63	64	14
3	10	3	12	44	11
4	10	3	78	80	18
5	10	3	78	76	22
6	10	3	61	29	35
-5	11	3	0	30	1
-4	11	3	48	25	16
-3	11	3	29	57	29
-2	11	3	0	20	1
-1	11	3	103	100	9
0	11	3	43	47	25
1	11	3	94	100	10
2	11	3	19	20	18
3	11	3	42	57	41
4	11	3	63	25	30
5	11	3	29	30	29
-2	12	3	0	17	1
-1	12	3	0	11	1
0	12	3	23	43	22
1	12	3	0	11	1
2	12	3	46	17	32
3	12	3	0	30	1
-1	13	3	84	9	21
0	13	3	0	46	1
1	13	3	0	9	1
0	0	4	1601	1542	18
1	0	4	444	454	6
2	0	4	492	509	4
3	0	4	177	166	2
4	0	4	36	20	5
5	0	4	164	163	3
6	0	4	194	190	4
7	0	4	94	100	6
8	0	4	63	64	13
9	0	4	74	70	10
-9	1	4	54	19	31
-8	1	4	85	90	15
-7	1	4	18	42	18
-6	1	4	99	106	12
-5	1	4	55	58	6
-4	1	4	394	393	3
-3	1	4	320	313	3
-2	1	4	335	343	3
-1	1	4	950	953	7
0	1	4	457	485	3
1	1	4	951	953	7
2	1	4	337	343	5
3	1	4	321	313	3
4	1	4	400	394	4
5	1	4	70	58	5
6	1	4	113	106	5
7	1	4	12	42	11
8	1	4	93	90	6
9	1	4	36	19	20
-9	2	4	118	116	14
-8	2	4	51	67	25
-7	2	4	179	176	8
-6	2	4	196	188	5
-5	2	4	113	106	3
-4	2	4	170	167	3
-3	2	4	448	437	4
-2	2	4	345	351	3
-1	2	4	288	289	3
0	2	4	185	189	2
1	2	4	286	289	2
2	2	4	350	351	4
3	2	4	443	437	8
4	2	4	180	167	6
5	2	4	97	106	8
6	2	4	188	188	3
7	2	4	180	176	4
8	2	4	59	67	8
9	2	4	120	116	5
-9	3	4	42	38	42
-8	3	4	18	28	18
-7	3	4	26	65	26
-6	3	4	189	195	4
-5	3	4	20	24	20
-4	3	4	239	240	3
-3	3	4	401	394	3
-2	3	4	355	351	3
-1	3	4	685	696	5
0	3	4	838	843	6
1	3	4	695	696	5
2	3	4	357	351	3
3	3	4	394	394	3
4	3	4	245	241	3
5	3	4	34	24	15
6	3	4	188	195	4
7	3	4	76	65	6
8	3	4	39	28	13
9	3	4	26	38	26
-9	4	4	95	76	15
-8	4	4	0	50	1
-7	4	4	65	74	19
-6	4	4	68	68	9
-5	4	4	362	361	4
-4	4	4	33	32	10
-3	4	4	282	288	2
-2	4	4	66	71	2
-1	4	4	535	549	4
0	4	4	292	282	3
1	4	4	536	549	5
2	4	4	66	70	5
3	4	4	287	288	3
4	4	4	21	32	20
5	4	4	363	360	3
6	4	4	79	68	5
7	4	4	75	74	7
8	4	4	45	50	24
9	4	4	72	76	14
-8	5	4	21	29	20
-7	5	4	40	25	39
-6	5	4	157	159	5
-5	5	4	74	78	6
-4	5	4	145	146	3
-3	5	4	219	220	3
-2	5	4	57	59	4
-1	5	4	463	470	3
0	5	4	303	315	5
1	5	4	471	470	3
2	5	4	59	59	4
3	5	4	216	219	3
4	5	4	141	146	3
5	5	4	80	78	5
6	5	4	163	159	4
7	5	4	50	25	21
8	5	4	31	29	30
9	5	4	74	66	25
-8	6	4	59	16	25
-7	6	4	102	96	8
-6	6	4	65	67	9
-5	6	4	156	162	6
-4	6	4	104	99	5
-3	6	4	0	37	1
-2	6	4	37	45	8
-1	6	4	183	181	2
0	6	4	104	103	2
1	6	4	181	181	2
2	6	4	37	45	9
3	6	4	15	37	15
4	6	4	102	99	4
5	6	4	164	162	3
6	6	4	79	67	7
7	6	4	97	96	7
8	6	4	0	16	1
-7	7	4	63	59	31
-6	7	4	28	39	28
-5	7	4	97	94	6
-4	7	4	140	134	5
-3	7	4	64	64	7
-2	7	4	108	112	4
-1	7	4	173	170	3
0	7	4	17	12	17
1	7	4	168	170	2
2	7	4	114	112	3
3	7	4	70	63	5
4	7	4	133	134	4
5	7	4	99	94	6
6	7	4	40	39	15
7	7	4	80	59	11
8	7	4	86	27	17
-7	8	4	68	53	13
-6	8	4	27	33	27
-5	8	4	120	117	6
-4	8	4	48	29	12
-3	8	4	17	31	16
-2	8	4	18	24	17
-1	8	4	126	128	4
0	8	4	119	117	6
1	8	4	127	128	3
2	8	4	20	24	20
3	8	4	36	31	15
4	8	4	0	29	1
5	8	4	115	117	7
6	8	4	46	33	19
7	8	4	60	53	17
-6	9	4	53	54	28
-5	9	4	37	28	21
-4	9	4	126	128	5
-3	9	4	121	128	5
-2	9	4	38	49	11
-1	9	4	195	199	6
0	9	4	0	10	1
1	9	4	194	199	4
2	9	4	65	49	11
3	9	4	134	128	7
4	9	4	150	128	11
5	9	4	42	28	41
6	9	4	70	54	14
7	9	4	50	44	49
-6	10	4	55	52	16
-5	10	4	0	20	1
-4	10	4	0	50	1
-3	10	4	36	16	19
-2	10	4	34	42	15
-1	10	4	34	35	26
0	10	4	44	32	18
1	10	4	27	35	26
2	10	4	41	42	23
3	10	4	0	16	1
4	10	4	60	50	24
5	10	4	45	20	44
6	10	4	0	52	1
-5	11	4	50	52	16
-4	11	4	0	27	1
-3	11	4	49	30	49

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
-2	11	4	0	31	1
-1	11	4	61	47	13
0	11	4	0	20	1
1	11	4	59	47	16
2	11	4	0	31	1
3	11	4	0	30	1
4	11	4	75	27	21
-3	12	4	45	6	45
-2	12	4	26	39	25
-1	12	4	117	106	9
0	12	4	33	32	32
1	12	4	123	106	16
2	12	4	0	39	1
3	12	4	24	6	24
-1	13	4	68	58	26
0	13	4	0	20	1
1	13	4	45	58	44
1	0	5	356	377	7
2	0	5	397	394	4
3	0	5	224	214	2
4	0	5	33	18	6
5	0	5	172	172	3
6	0	5	253	259	4
7	0	5	84	93	8
8	0	5	42	14	21
9	0	5	54	62	18
-9	1	5	0	42	1
-8	1	5	51	62	27
-7	1	5	57	41	13
-6	1	5	162	161	5
-5	1	5	274	268	3
-4	1	5	159	164	2
-3	1	5	160	153	2
-2	1	5	294	289	4
-1	1	5	56	61	3
0	1	5	1150	1175	9
1	1	5	58	61	2
2	1	5	298	289	3
3	1	5	157	153	2
4	1	5	163	164	4
5	1	5	271	268	3
6	1	5	157	161	4
7	1	5	6	41	5
8	1	5	45	62	11
9	1	5	39	43	20
-9	2	5	116	104	15
-8	2	5	47	55	46
-7	2	5	133	147	9
-6	2	5	61	57	8
-5	2	5	110	114	4
-4	2	5	38	38	7
-3	2	5	83	92	4
-2	2	5	186	182	4
-1	2	5	287	296	2
0	2	5	531	557	4
1	2	5	285	296	2
2	2	5	187	182	3
3	2	5	95	92	3
4	2	5	37	38	8
5	2	5	110	113	4
6	2	5	43	57	10
7	2	5	148	147	4
8	2	5	46	56	11
9	2	5	102	104	6
-9	3	5	54	49	33
-8	3	5	82	86	19
-7	3	5	50	60	24
-6	3	5	150	160	6
-5	3	5	192	188	3
-4	3	5	206	200	2
-3	3	5	66	64	4
-2	3	5	221	213	3
-1	3	5	242	235	6
0	3	5	58	51	3
1	3	5	246	235	4
2	3	5	219	213	2
3	3	5	68	64	6
4	3	5	207	199	3
5	3	5	187	188	8
6	3	5	160	160	3
7	3	5	61	60	7
8	3	5	100	86	6
9	3	5	42	49	42
-9	4	5	40	52	40
-8	4	5	47	40	34
-7	4	5	77	75	10
-6	4	5	177	173	3
-5	4	5	87	97	4
-4	4	5	50	44	6
-3	4	5	193	201	3
-2	4	5	221	225	2
-1	4	5	226	221	3
0	4	5	120	117	2
1	4	5	227	221	3
2	4	5	217	225	3
3	4	5	193	201	2
4	4	5	42	44	7
5	4	5	100	97	4
6	4	5	167	173	3
7	4	5	66	75	7
8	4	5	53	40	10
9	4	5	24	52	23
-8	5	5	0	20	1
-7	5	5	62	47	13
-6	5	5	0	23	1
-5	5	5	79	84	6
-4	5	5	136	146	6
-3	5	5	87	85	4
-2	5	5	165	165	2
-1	5	5	143	144	2
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3	9	6	66	47	10
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3	11	6	0	9	1
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3	0	7	176	172	4
4	0	7	70	67	6
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6	0	7	257	254	5
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8	0	7	114	118	8
9	0	7	47	30	24
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3	1	7	158	162	3
4	1	7	224	215	3
5	1	7	118	123	4
6	1	7	210	206	5
7	1	7	76	88	14
8	1	7	47	52	46
9	1	7	57	50	12
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Table 6. Observed and calculated structure factors for 1

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7	2	7	112	116	7
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2	3	7	50	50	4
3	3	7	139	135	3
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8	3	7	73	70	12
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2	4	7	415	401	3
3	4	7	108	111	2
4	4	7	195	192	2
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6	4	7	147	146	4
7	4	7	15	34	14
8	4	7	0	4	1
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Table 6. Observed and calculated structure factors for 1

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7	6	9	21	43	20
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-3	11	11	18	33	17
-2	11	11	47	21	16
-1	11	11	17	15	16

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
0	11	11	0	19	1
1	11	11	34	15	33
2	11	11	0	21	1
3	11	11	42	33	42
-2	12	11	0	32	1
-1	12	11	20	15	20
0	12	11	45	14	18
1	12	11	0	15	1
2	12	11	58	32	47
0	0	12	17	9	17
1	0	12	178	173	3
2	0	12	56	53	5
3	0	12	91	92	3
4	0	12	218	216	3
5	0	12	136	127	6
6	0	12	69	47	7
7	0	12	48	41	17
8	0	12	0	7	1
-9	1	12	132	109	12
-8	1	12	91	73	25
-7	1	12	0	13	1
-6	1	12	111	102	5
-5	1	12	93	87	5
-4	1	12	106	108	4
-3	1	12	329	323	4
-2	1	12	244	245	3
-1	1	12	96	95	3
0	1	12	24	30	9
1	1	12	91	95	3
2	1	12	242	245	2
3	1	12	325	323	3
4	1	12	108	107	6
5	1	12	95	87	4
6	1	12	98	102	19
7	1	12	26	13	25
8	1	12	104	73	14
-8	2	12	48	28	25
-7	2	12	84	71	7
-6	2	12	103	100	6
-5	2	12	104	95	5
-4	2	12	172	163	4
-3	2	12	43	55	10
-2	2	12	166	168	2
-1	2	12	197	189	2
0	2	12	292	291	3
1	2	12	195	189	2
2	2	12	169	168	4
3	2	12	31	55	8
4	2	12	160	163	3
5	2	12	100	95	7
6	2	12	93	100	21
7	2	12	69	71	11
8	2	12	50	28	21
-8	3	12	0	18	1
-7	3	12	52	48	17
-6	3	12	81	86	7
-5	3	12	124	129	5
-4	3	12	270	267	3
-3	3	12	223	218	4
-2	3	12	192	190	4
-1	3	12	130	130	2
0	3	12	84	91	4
1	3	12	129	130	2
2	3	12	193	190	2
3	3	12	213	218	15
4	3	12	266	267	8
5	3	12	122	129	6
6	3	12	75	86	15
7	3	12	56	48	13
8	3	12	25	18	24
-8	4	12	53	47	23
-7	4	12	76	86	15
-6	4	12	80	75	8
-5	4	12	90	96	6
-4	4	12	66	66	5
-3	4	12	369	373	3
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-1	4	12	146	149	2
0	4	12	159	155	4
1	4	12	151	148	4
3	4	12	373	373	5
4	4	12	67	66	9
5	4	12	93	96	7
6	4	12	48	75	21
7	4	12	81	86	7
8	4	12	47	47	15
-8	5	12	73	24	21
-7	5	12	35	35	35
-6	5	12	0	39	1
-5	5	12	48	61	14
-4	5	12	158	163	4
-3	5	12	208	205	6
-2	5	12	108	108	5
-1	5	12	112	109	4
0	5	12	95	92	7
1	5	12	113	109	5
2	5	12	96	108	6
3	5	12	192	205	6
4	5	12	161	163	3
5	5	12	47	61	8
6	5	12	49	39	10
7	5	12	29	35	29
8	5	12	53	23	17
-7	6	12	46	53	20
-6	6	12	75	48	11
-5	6	12	15	22	15
-4	6	12	191	185	4
-3	6	12	24	27	23
-2	6	12	195	199	4
-1	6	12	147	148	8
0	6	12	128	121	10
1	6	12	155	148	7
2	6	12	202	199	5
3	6	12	25	27	25
4	6	12	184	185	5
5	6	12	36	22	13
6	6	12	60	48	8
7	6	12	50	53	12
-7	7	12	0	5	1
-6	7	12	80	47	11
-5	7	12	23	45	23
-4	7	12	83	89	7
-3	7	12	21	27	21
-2	7	12	66	54	8
-1	7	12	80	67	5
0	7	12	125	126	4
1	7	12	79	67	7
2	7	12	63	54	9
3	7	12	42	27	17
4	7	12	76	89	8
5	7	12	0	45	1
6	7	12	68	47	21
7	7	12	0	5	1
-6	8	12	0	37	1
-5	8	12	26	38	25
-4	8	12	108	103	6
-3	8	12	40	44	14
-2	8	12	0	38	1
-1	8	12	62	59	7
0	8	12	47	57	18
1	8	12	50	59	11
2	8	12	18	38	17
3	8	12	45	44	10
4	8	12	106	103	8
5	8	12	40	37	39
6	8	12	53	37	20
-5	9	12	43	36	19
-4	9	12	87	77	8
-3	9	12	0	8	1
-2	9	12	0	13	1
-1	9	12	51	46	13
0	9	12	20	32	19
1	9	12	50	46	15
2	9	12	37	13	27
3	9	12	37	8	37
4	9	12	90	78	11
5	9	12	43	36	36
6	9	12	66	23	33
-5	10	12	30	45	30
-4	10	12	35	32	35
-3	10	12	63	35	14
-2	10	12	66	51	10
-1	10	12	28	36	28
0	10	12	20	46	19
1	10	12	55	36	12
2	10	12	61	51	15
3	10	12	70	35	12
4	10	12	0	32	1
5	10	12	0	45	1
-3	11	12	62	11	39
-2	11	12	55	60	54
-1	11	12	30	36	29
0	11	12	61	42	13
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2	11	12	82	60	11
3	11	12	0	11	1
-1	12	12	0	22	1
0	12	12	75	29	20
1	12	12	46	22	46
1	0	13	411	394	3
2	0	13	431	426	4
3	0	13	150	145	3
4	0	13	114	112	3
5	0	13	0	9	1
6	0	13	0	3	1
7	0	13	0	23	1
8	0	13	92	88	10
-8	1	13	12	36	11
-7	1	13	52	59	14
-6	1	13	100	99	5
-5	1	13	148	150	4
-4	1	13	129	130	4
-3	1	13	220	212	3
-2	1	13	102	97	4
-1	1	13	120	113	3
0	1	13	415	421	3
1	1	13	115	113	3
2	1	13	99	97	3
3	1	13	223	212	3
4	1	13	128	130	3
5	1	13	150	150	3
6	1	13	103	99	5
7	1	13	38	59	32
8	1	13	36	36	35
-8	2	13	23	42	22
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-6	2	13	94	89	6
-5	2	13	69	70	7
-4	2	13	321	323	4
-3	2	13	169	170	3
-2	2	13	133	133	3
-1	2	13	167	174	2
0	2	13	31	29	7
1	2	13	176	174	2
2	2	13	130	133	3
3	2	13	169	170	3
4	2	13	330	323	4
5	2	13	77	70	7
6	2	13	83	89	8
7	2	13	101	93	8
8	2	13	67	42	14
-8	3	13	80	2	21
-7	3	13	0	18	1
-6	3	13	93	97	13
-5	3	13	119	115	6
-4	3	13	144	138	3
-3	3	13	282	286	4
-2	3	13	268	279	4
-1	3	13	96	104	3
0	3	13	106	100	3
1	3	13	103	104	2
2	3	13	271	279	8
3	3	13	285	286	5
4	3	13	127	138	6
5	3	13	116	116	6
6	3	13	95	97	8
7	3	13	0	18	1
8	3	13	45	2	44
-8	4	13	70	65	15
-7	4	13	49	44	17
-6	4	13	23	45	22
-5	4	13	193	203	4
-4	4	13	0	21	1
-3	4	13	259	255	3
-2	4	13	40	35	8
-1	4	13	84	78	3
0	4	13	34	32	15
1	4	13	80	78	6
2	4	13	37	35	15
3	4	13	254	255	5
4	4	13	6	21	6
5	4	13	199	203	5
6	4	13	33	45	32
7	4	13	48	44	11
8	4	13	62	65	13
-7	5	13	67	61	14
-6	5	13	91	99	8
-5	5	13	57	74	11
-4	5	13	97	102	5
-3	5	13	57	32	7
-2	5	13	170	173	4
-1	5	13	66	73	7
0	5	13	77	62	7
1	5	13	75	73	8
2	5	13	176	173	5
3	5	13	46	32	12
4	5	13	86	102	5
5	5	13	72	74	6
6	5	13	94	99	6
7	5	13	55	60	10
8	5	13	37	60	36
-7	6	13	42	28	26
-6	6	13	69	70	15
-5	6	13	65	55	11
-4	6	13	124	117	5
-3	6	13	178	172	4
-2	6	13	125	122	7
-1	6	13	81	78	7
0	6	13	268	249	11
1	6	13	85	78	7
2	6	13	123	122	6
3	6	13	167	171	5
4	6	13	124	117	6
5	6	13	31	55	31
6	6	13	61	70	8
7	6	13	41	28	16
-6	7	13	75	31	20
-5	7	13	53	52	11
-4	7	13	71	62	8
-3	7	13	154	145	5
-2	7	13	136	131	5
-1	7	13	100	108	6
0	7	13	192	174	4
1	7	13	103	108	6
2	7	13	131	131	6
3	7	13	147	145	5
4	7	13	71	62	25
5	7	13	65	52	11
6	7	13	49	31	20
7	7	13	14	43	14
-6	8	13	46	47	36
-5	8	13	11	8	10
-4	8	13	35	34	20
-3	8	13	92	88	7
-2	8	13	141	151	5
-1	8	13	129	127	4
0	8	13	0	3	1
1	8	13	121	127	5
2	8	13	150	151	5
3	8	13	83	88	7
4	8	13	31	35	31
5	8	13	19	8	19
6	8	13	65	47	24
-5	9	13	54	49	14
-4	9	13	53	41	13
-3	9	13	95	94	14
-2	9	13	0	31	1
-1	9	13	80	75	7
0	9	13	139	140	5
1	9	13	90	74	6
2	9	13	62	31	9
3	9	13	113	94	6
4	9	13	18	41	18
5	9	13	46	49	29
-4	10	13	42	45	20
-3	10	13	24	25	24
-2	10	13	18	26	18
-1	10	13	52	17	14
0	10	13	21	0	20
1	10	13	0	17	1
2	10	13	52	26	15
3	10	13	40	25	40
4	10	13	21	45	20
-3	11	13	66	47	14
-2	11	13	34	29	34
-1	11	13	47	6	17
0	11	13	53	34	29
1	11	13	0	6	1
2	11	13	28	29	28
3	11	13	72	47	14
0	12	13	91	92	16
0	0	14	120	121	5
1	0	14	0	1	1
2	0	14	27	16	9
3	0	14	37	34	7
4	0	14	0	11	1
5	0	14	21	31	21
6	0	14	41	30	13
7	0	14	0	1	1
8	0	14	61	58	25
-8	1	14	65	20	14
-7	1	14	100	73	7
-6	1	14	40	49	13
-5	1	14	102	110	5
-4	1	14	131	132	3
-3	1	14	237	233	3
-2	1	14	80	83	4
-1	1	14	122	120	4
0	1	14	258	259	3
1	1	14	121	121	2
2	1	14	78	83	4
3	1	14	240	233	3
4	1	14	134	132	3
5	1	14	115	110	4
6	1	14	52	49	35
7	1	14	71	73	11
8	1	14	52	20	26
-8	2	14	41	35	40
-7	2	14	127	131	6
-6	2	14	142	129	6
-5	2	14	142	141	4
-4	2	14	173	178	4
-3	2	14	113	116	4
-2	2	14	187	191	3
-1	2	14	88	88	3
0	2	14	327	325	3
1	2	14	84	88	3
2	2	14	184	191	2
3	2	14	115	116	3
4	2	14	170	178	5
5	2	14	149	141	5
6	2	14	139	129	6
7	2	14	134	131	7
8	2	14	0	35	1
-8	3	14	57	79	14
-7	3	14	61	75	11
-6	3	14	71	66	12
-5	3	14	94	92	5
-4	3	14	99	95	5
-3	3	14	302	306	4
-2	3	14	54	57	5
-1	3	14	136	134	3
0	3	14	82	88	3
1	3	14	136	135	4
2	3	14	52	57	8
3	3	14	308	306	6
4	3	14	110	95	6
5	3	14	95	92	7
6	3	14	70	65	10
7	3	14	71	76	11
8	3	14	87	79	10
-8	4	14	54	57	29
-7	4	14	0	27	1
-6	4	14	33	50	22
-5	4	14	218	221	5
-4	4	14	154	158	3
-3	4	14	282	284	3
-2	4	14	151	157	3
-1	4	14	131	128	5
0	4	14	195	195	4
1	4	14	126	128	5
2	4	14	155	157	5
3	4	14	270	284	5
4	4	14	158	158	5
5	4	14	213	221	5
6	4	14	48	50	18
7	4	14	43	28	20
8	4	14	68	57	11
-7	5	14	49	36	20
-6	5	14	67	59	11
-5	5	14	53	62	43
-4	5	14	80	72	5
-3	5	14	225	223	4
-2	5	14	98	89	11
-1	5	14	107	101	5
0	5	14	104	104	6
1	5	14	111	100	5
2	5	14	82	89	6
3	5	14	229	223	6
4	5	14	72	72	8
5	5	14	63	62	7
6	5	14	72	59	7
7	5	14	23	36	23
-7	6	14	57	51	16
-6	6	14	57	60	15
-5	6	14	55	59	12
-4	6	14	75	79	7
-3	6	14	67	69	8
-2	6	14	99	104	5
-1	6	14	136	141	5

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
0	6	14	147	156	5
1	6	14	143	141	21
2	6	14	109	104	6
3	6	14	63	69	9
4	6	14	77	79	15
5	6	14	42	59	21
6	6	14	44	60	20
7	6	14	51	51	17
-6	7	14	65	10	12
-5	7	14	80	74	15
-4	7	14	51	49	14
-3	7	14	72	82	7
-2	7	14	25	17	25
-1	7	14	36	38	12
0	7	14	155	166	6
1	7	14	39	39	38
2	7	14	53	17	10
3	7	14	77	82	18
4	7	14	46	49	16
5	7	14	79	74	18
6	7	14	29	10	28
-6	8	14	52	42	18
-5	8	14	9	16	8
-4	8	14	59	59	11
-3	8	14	35	30	35
-2	8	14	53	61	18
-1	8	14	56	23	16
0	8	14	13	12	12
1	8	14	35	23	18
2	8	14	66	61	11
3	8	14	0	29	1
4	8	14	48	59	18
5	8	14	0	16	1
6	8	14	61	42	33
-5	9	14	6	10	6
-4	9	14	0	25	1
-3	9	14	77	70	15
-2	9	14	14	19	13
-1	9	14	17	36	17
0	9	14	31	2	31
1	9	14	30	36	29
2	9	14	29	19	29
3	9	14	83	70	8
4	9	14	24	25	24
5	9	14	29	10	28
-4	10	14	63	44	12
-3	10	14	0	33	1
-2	10	14	67	63	11
-1	10	14	29	26	29
0	10	14	57	13	12
1	10	14	47	26	14
2	10	14	64	63	11
3	10	14	39	33	33
4	10	14	62	44	18
-3	11	14	36	36	36
-2	11	14	23	16	22
-1	11	14	42	17	23
0	11	14	18	7	18
1	11	14	37	17	36
2	11	14	16	16	16
3	11	14	0	36	1
1	0	15	86	78	3
2	0	15	100	103	4
3	0	15	71	62	4
4	0	15	90	90	6
5	0	15	158	167	3
6	0	15	17	35	17
7	0	15	0	27	1
8	0	15	70	52	69
-8	1	15	20	27	19
-7	1	15	74	71	11
-6	1	15	91	94	6
-5	1	15	16	27	16
-4	1	15	166	161	3
-3	1	15	119	127	5
-2	1	15	163	172	3
-1	1	15	114	108	3
0	1	15	46	46	7
1	1	15	107	108	3
2	1	15	176	172	3
3	1	15	124	127	4
4	1	15	161	161	3
5	1	15	0	27	1
6	1	15	98	94	7
7	1	15	72	71	11
8	1	15	0	27	1
-8	2	15	38	3	37
-7	2	15	20	12	19
-6	2	15	55	39	13
-5	2	15	120	119	5
-4	2	15	131	128	4
-3	2	15	102	106	4
-2	2	15	114	115	3
-1	2	15	89	89	4
0	2	15	63	56	4
1	2	15	87	89	4
2	2	15	113	115	3
3	2	15	97	106	14
4	2	15	138	128	9
5	2	15	105	119	11
6	2	15	0	39	1
7	2	15	0	12	1
8	2	15	55	4	18
-8	3	15	49	35	16
-7	3	15	58	23	17
-6	3	15	29	19	28
-5	3	15	46	52	10
-4	3	15	137	142	4
-3	3	15	134	128	3
-2	3	15	97	95	3
-1	3	15	146	145	3
0	3	15	55	57	4
1	3	15	139	145	3
2	3	15	90	95	6
3	3	15	139	128	5
4	3	15	147	142	5
5	3	15	52	52	13
6	3	15	48	19	15
7	3	15	0	23	1
8	3	15	47	35	19
-8	4	15	84	70	20
-7	4	15	0	31	1
-6	4	15	64	75	9
-5	4	15	58	52	9
-4	4	15	220	221	4
-3	4	15	113	123	4
-2	4	15	297	297	3
-1	4	15	75	77	5
0	4	15	104	95	5
1	4	15	67	77	7
2	4	15	307	297	5
3	4	15	118	123	5
4	4	15	220	221	5
5	4	15	53	52	18
6	4	15	63	74	28
7	4	15	54	31	24
8	4	15	83	70	10
-7	5	15	70	52	14
-6	5	15	12	34	12
-5	5	15	0	43	1
-4	5	15	96	105	5
-3	5	15	113	103	5
-2	5	15	130	126	4
-1	5	15	155	147	5
0	5	15	42	40	13
1	5	15	153	147	5
2	5	15	122	126	5
3	5	15	104	103	18
4	5	15	107	105	7
5	5	15	45	43	18
6	5	15	42	34	12
7	5	15	54	52	11
-7	6	15	89	66	10
-6	6	15	43	25	43
-5	6	15	71	62	10
-4	6	15	44	41	16
-3	6	15	38	32	15
-2	6	15	50	32	10
-1	6	15	96	95	7
0	6	15	67	56	33
1	6	15	87	95	10
2	6	15	26	32	26
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Table 6. Observed and calculated structure factors for 1

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0	0	20	92	100	6
1	0	20	106	104	4
2	0	20	67	59	5
3	0	20	147	148	3
4	0	20	107	105	7
5	0	20	0	21	1
6	0	20	21	5	20
7	0	20	46	5	45
-7	1	20	62	38	40
-6	1	20	58	54	13
-5	1	20	55	70	12
-4	1	20	60	49	7
-3	1	20	39	8	12
-2	1	20	128	121	4
-1	1	20	95	95	4
0	1	20	120	123	3
1	1	20	95	95	4
2	1	20	126	121	4
3	1	20	38	8	18
4	1	20	58	49	12
5	1	20	54	70	16
6	1	20	45	54	20
7	1	20	43	38	30
-7	2	20	101	87	11
-6	2	20	98	89	6
-5	2	20	48	57	10
-4	2	20	28	41	28
-3	2	20	0	14	1
-2	2	20	166	165	4
-1	2	20	195	198	6
0	2	20	33	0	33
1	2	20	189	198	6
2	2	20	152	165	5
3	2	20	0	14	1
4	2	20	54	41	13
5	2	20	47	57	17
6	2	20	108	89	12
7	2	20	114	87	9
-7	3	20	38	46	22
-6	3	20	47	23	14
-5	3	20	76	78	8
-4	3	20	114	114	5
-3	3	20	124	124	7
-2	3	20	59	57	15
-1	3	20	127	112	5
0	3	20	0	43	1
1	3	20	127	112	14
2	3	20	55	57	10
3	3	20	117	124	9
4	3	20	111	115	11
5	3	20	73	78	11
6	3	20	0	23	1
-6	4	20	51	27	14
-5	4	20	110	86	8
-4	4	20	99	100	6
-3	4	20	160	151	4
-2	4	20	85	88	8
-1	4	20	0	14	1
0	4	20	263	277	5
1	4	20	0	14	1
2	4	20	94	88	7
3	4	20	143	151	6
4	4	20	97	100	13
5	4	20	99	86	16
6	4	20	43	27	27
-6	5	20	76	50	9
-5	5	20	0	6	1
-4	5	20	93	81	7
-3	5	20	45	28	21
2	5	20	69	54	10
-1	5	20	22	19	22
0	5	20	133	123	6
1	5	20	21	19	20
2	5	20	60	54	22
3	5	20	47	28	15
4	5	20	90	81	9
5	5	20	0	6	1
6	5	20	57	50	18
-5	6	20	42	42	28
-4	6	20	70	56	11
-3	6	20	0	24	1
-2	6	20	70	56	31
-1	6	20	110	114	16
0	6	20	21	51	20
1	6	20	109	114	10
2	6	20	67	56	10
3	6	20	34	24	34
4	6	20	54	56	16
5	6	20	69	42	20
6	6	20	129	108	11
-5	7	20	45	51	45
-4	7	20	67	35	23
-3	7	20	46	19	18
-2	7	20	61	29	13
-1	7	20	51	49	15
0	7	20	36	15	34
1	7	20	81	49	10
2	7	20	18	29	18
3	7	20	0	19	1
4	7	20	0	35	1
5	7	20	36	51	36
4	8	20	66	57	15
-3	8	20	18	37	18
-2	8	20	65	45	12
-1	8	20	41	18	26
0	8	20	0	8	1
1	8	20	14	18	13
2	8	20	45	45	21
3	8	20	56	37	15
4	8	20	18	57	17
-2	9	20	0	36	1
-1	9	20	85	61	16
0	9	20	27	29	27

Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
1	9	20	70	61	12
2	9	20	24	36	23
3	9	20	73	79	19
0	10	20	71	48	20
1	10	20	43	27	43
1	0	21	148	145	6
2	0	21	246	250	4
3	0	21	134	142	5
4	0	21	100	98	9
5	0	21	79	63	10
6	0	21	134	124	8
7	0	21	0	9	1
-7	1	21	46	62	46
-6	1	21	49	61	17
-5	1	21	83	66	19
-4	1	21	117	120	5
-3	1	21	136	141	4
-2	1	21	39	37	10
-1	1	21	206	206	4
0	1	21	0	9	1
1	1	21	210	206	6
2	1	21	47	37	12
3	1	21	128	141	6
4	1	21	107	120	7
5	1	21	83	66	10
6	1	21	62	61	14
7	1	21	87	62	16
-7	2	21	41	59	41
-6	2	21	68	64	10
-5	2	21	50	51	13
-4	2	21	33	13	15
-3	2	21	0	26	1
-2	2	21	75	71	9
-1	2	21	216	227	4
0	2	21	61	56	8
1	2	21	221	227	5
2	2	21	81	71	7
3	2	21	53	26	13
4	2	21	0	13	1
5	2	21	46	51	27
6	2	21	84	65	11
-6	3	21	35	24	22
-5	3	21	22	21	22
-4	3	21	61	49	8
-3	3	21	37	31	14
-2	3	21	102	97	6
-1	3	21	127	126	6
0	3	21	70	56	15
1	3	21	116	126	6
2	3	21	107	97	9
3	3	21	0	31	1
4	3	21	70	49	12
5	3	21	35	21	34
6	3	21	33	24	32
-6	4	21	0	12	1
-5	4	21	53	62	12
-4	4	21	24	49	23
-3	4	21	104	106	6
-2	4	21	142	135	6
-1	4	21	142	135	7
0	4	21	40	18	40
1	4	21	136	135	7
2	4	21	136	136	6
3	4	21	104	106	7
4	4	21	55	49	19
5	4	21	19	62	19
6	4	21	24	12	24
-6	5	21	11	6	10
-5	5	21	0	32	1
-4	5	21	84	72	9
-3	5	21	87	93	9
-2	5	21	60	62	19
-1	5	21	77	82	9
0	5	21	221	211	13
1	5	21	67	82	10
2	5	21	55	62	12
3	5	21	107	93	7
4	5	21	67	72	13
5	5	21	44	32	43
6	5	21	43	6	43
-5	6	21	57	56	17
-4	6	21	55	56	15
-3	6	21	107	112	9
-2	6	21	57	57	13
-1	6	21	63	47	12
0	6	21	0	2	1
1	6	21	27	47	27
2	6	21	52	57	18
3	6	21	117	111	16
4	6	21	72	56	12
5	6	21	70	56	14
-4	7	21	73	64	13
-3	7	21	51	33	18
-2	7	21	0	16	1
-1	7	21	83	75	10
0	7	21	19	37	18
1	7	21	96	75	18
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3	7	21	41	33	40
4	7	21	66	64	14
5	7	21	88	75	18
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-2	8	21	99	86	10
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0	8	21	1	11	1
1	8	21	94	74	10
2	8	21	82	86	11
3	8	21	63	60	21
4	8	21	55	32	24
-2	9	21	32	27	31
-1	9	21	80	61	13
0	9	21	56	7	16
1	9	21	88	61	18
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1	0	22	100	103	4
2	0	22	62	64	14
3	0	22	75	84	8
4	0	22	138	124	7
5	0	22	54	0	23
6	0	22	29	36	28
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-5	1	22	26	21	26
-4	1	22	82	77	7
-3	1	22	98	97	5
-2	1	22	91	79	7
-1	1	22	119	115	6
0	1	22	34	60	14
1	1	22	118	115	5
2	1	22	72	79	24
3	1	22	100	97	7
4	1	22	65	77	16
5	1	22	0	21	1
6	1	22	43	25	23
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-5	2	22	106	102	7
-4	2	22	31	15	30
-3	2	22	42	45	13
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1	2	22	76	71	8
2	2	22	21	13	21
3	2	22	0	45	1
4	2	22	39	15	38
5	2	22	116	102	8
6	2	22	77	50	14
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-5	3	22	117	107	12
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-3	3	22	48	51	24
-2	3	22	19	16	19
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0	3	22	316	308	6
1	3	22	138	140	9
2	3	22	0	17	1
3	3	22	42	51	20
4	3	22	61	59	24
5	3	22	106	107	10
6	3	22	23	36	23
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-5	4	22	44	38	15
-4	4	22	29	34	28
-3	4	22	81	68	9
-2	4	22	12	21	11
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3	4	22	58	68	12
4	4	22	30	33	30
5	4	22	56	38	16
-5	5	22	73	72	37
-4	5	22	22	5	21
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-2	5	22	45	47	45
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0	5	22	21	34	21
1	5	22	122	114	7
2	5	22	63	47	11
3	5	22	49	40	16
4	5	22	0	5	1
5	5	22	76	72	13
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-4	6	22	70	62	25
-3	6	22	34	26	33
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2	6	22	67	56	11
3	6	22	11	25	10
4	6	22	67	62	14
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2	7	22	76	44	16
3	7	22	0	6	1
4	7	22	77	51	16
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1	0	23	66	77	10
2	0	23	113	109	15
3	0	23	58	51	13
4	0	23	97	97	8
5	0	23	23	6	23
6	0	23	0	18	1
-6	1	23	36	57	35
-5	1	23	0	23	1
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-3	1	23	79	92	10
-2	1	23	84	93	5
-1	1	23	73	73	7
0	1	23	35	36	20
1	1	23	73	73	7
2	1	23	94	93	8
3	1	23	93	92	10
4	1	23	86	83	21
5	1	23	0	23	1
6	1	23	71	57	13
-6	2	23	0	14	1
-5	2	23	0	16	1
-4	2	23	40	49	16
-3	2	23	75	71	8
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0	2	23	87	81	8
1	2	23	120	121	6
2	2	23	55	42	11
3	2	23	66	71	11
4	2	23	48	49	19
5	2	23	0	16	1
6	2	23	37	14	36
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-4	3	23	0	27	1
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-2	3	23	82	80	7
-1	3	23	115	137	18
0	3	23	123	122	12
1	3	23	126	136	6
2	3	23	82	80	10
3	3	23	79	83	10
4	3	23	41	27	25
5	3	23	89	81	11
6	3	23	92	108	17
-5	4	23	75	72	15
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-3	4	23	99	106	8
-2	4	23	83	87	20
-1	4	23	8	49	7
0	4	23	25	12	24
1	4	23	43	49	17
2	4	23	100	87	9
3	4	23	100	106	19
4	4	23	57	52	15
5	4	23	63	72	17
-5	5	23	110	103	9
-4	5	23	60	48	16
-3	5	23	24	13	23
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-1	5	23	49	43	32
0	5	23	59	18	16
1	5	23	40	43	20
2	5	23	73	72	10
3	5	23	25	13	24
4	5	23	68	48	12
5	5	23	105	103	10
-4	6	23	47	30	20
-3	6	23	53	55	18
-2	6	23	0	13	1
-1	6	23	82	79	10
0	6	23	34	10	33
1	6	23	91	79	15
2	6	23	29	13	29
3	6	23	75	55	11
4	6	23	30	30	29
-3	7	23	66	66	13
-2	7	23	56	52	16
-1	7	23	0	27	1
0	7	23	9	21	8
1	7	23	41	27	24
2	7	23	57	52	28
3	7	23	91	66	23
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0	8	23	13	16	13
1	8	23	47	45	47
2	8	23	0	42	1
0	0	24	84	88	11
1	0	24	26	13	26
2	0	24	47	30	13
3	0	24	102	98	10
4	0	24	53	40	15
5	0	24	0	28	1
6	0	24	68	58	23
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-5	1	24	41	25	25
-4	1	24	46	34	19
-3	1	24	59	15	21
-2	1	24	73	86	42
-1	1	24	126	135	5
0	1	24	43	27	12
1	1	24	141	135	10
2	1	24	71	86	10
3	1	24	25	16	24
4	1	24	30	34	30
5	1	24	9	25	8
6	1	24	66	41	23
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-4	2	24	0	33	1
-3	2	24	36	49	19
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-1	2	24	111	108	5
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2	2	24	125	123	7
3	2	24	40	49	40
4	2	24	59	33	24
5	2	24	14	46	14
6	2	24	75	61	20
-5	3	24	61	58	60
-4	3	24	61	36	10
-3	3	24	4	30	4
-2	3	24	50	31	16
-1	3	24	36	13	23
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1	3	24	27	13	27
2	3	24	46	31	45
3	3	24	49	30	17
4	3	24	58	36	17
5	3	24	67	58	15
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-2	4	24	30	56	30
-1	4	24	102	105	8
0	4	24	41	36	41
1	4	24	110	105	7
2	4	24	59	56	18
3	4	24	27	30	26
4	4	24	42	60	27
5	4	24	130	118	9
-5	5	24	69	53	20
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-3	5	24	0	27	1
-2	5	24	0	30	1
-1	5	24	44	24	19
0	5	24	129	117	14
1	5	24	0	24	1
2	5	24	22	30	21
3	5	24	29	27	29
4	5	24	35	60	35
-4	6	24	38	17	38
-3	6	24	0	3	1
-2	6	24	68	63	24
-1	6	24	15	17	14
0	6	24	0	1	1
1	6	24	36	17	35
2	6	24	78	63	11
3	6	24	38	3	38
4	6	24	0	17	1
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-1	7	24	28	57	27
0	7	24	42	21	27
1	7	24	61	57	25
2	7	24	79	75	12
3	7	24	51	29	33
0	8	24	0	27	1
1	0	25	33	9	32
2	0	25	110	95	8
3	0	25	8	28	7
4	0	25	26	55	26
5	0	25	26	8	26
-5	1	25	20	8	20
-4	1	25	42	4	41
-3	1	25	0	24	1
-2	1	25	69	63	12
-1	1	25	144	143	6
0	1	25	110	107	5
1	1	25	144	143	6
2	1	25	72	63	10
3	1	25	42	24	31
4	1	25	33	4	33
5	1	25	0	8	1
-5	2	25	81	67	17
-4	2	25	87	68	10
-3	2	25	0	18	1
-2	2	25	0	13	1
-1	2	25	115	115	7
0	2	25	97	101	8
1	2	25	123	115	6
2	2	25	0	13	1
3	2	25	0	18	1
4	2	25	88	68	11
5	2	25	61	67	16
-5	3	25	63	63	62
-4	3	25	47	27	16
-3	3	25	43	27	43
-2	3	25	127	127	7
-1	3	25	101	88	8
0	3	25	67	61	11
1	3	25	77	88	10
2	3	25	120	126	7
3	3	25	0	27	1
4	3	25	40	27	39
5	3	25	65	63	28
-5	4	25	87	97	21
-4	4	25	52	7	52
-3	4	25	27	14	26
-2	4	25	82	65	10
-1	4	25	97	67	9
0	4	25	0	14	1
1	4	25	40	67	23
2	4	25	74	65	11
3	4	25	32	14	32
-4	5	25	0	9	1
-3	5	25	43	12	42
-2	5	25	91	53	26
-1	5	25	60	45	13
0	5	25	64	51	13
1	5	25	39	45	31
2	5	25	73	53	12
3	5	25	17	12	17
4	5	25	0	9	1
-3	6	25	29	28	29
-2	6	25	68	54	32
-1	6	25	52	53	19
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Table 6. Observed and calculated structure factors for 1

h	k	l	10Fo	10Fc	10s
1	6	25	113	53	12
2	6	25	60	54	14
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-1	7	25	73	66	13
0	7	25	0	33	1
1	7	25	77	66	12
0	0	26	81	67	14
1	0	26	136	126	7
2	0	26	0	28	1
3	0	26	91	87	29
4	0	26	36	41	35
5	0	26	38	13	37
-5	1	26	36	41	35
-4	1	26	56	33	23
-3	1	26	33	42	33
-2	1	26	87	91	10
-1	1	26	52	70	16
0	1	26	22	25	22
1	1	26	64	70	11
2	1	26	96	91	9
3	1	26	41	42	41
4	1	26	42	33	31
5	1	26	15	41	14
-5	2	26	80	89	20
-4	2	26	0	7	1
-3	2	26	67	65	14
-2	2	26	30	33	30
-1	2	26	39	59	39
0	2	26	0	25	1
1	2	26	58	59	13
2	2	26	41	33	19
3	2	26	79	65	11
4	2	26	0	7	1
5	2	26	110	89	15
-4	3	26	104	68	10
-3	3	26	16	21	16
-2	3	26	18	22	18
-1	3	26	104	100	8
0	3	26	38	30	37
1	3	26	103	100	22
2	3	26	9	22	8
3	3	26	0	21	1
4	3	26	64	68	64
-4	4	26	35	24	34
-3	4	26	46	24	21
-2	4	26	63	75	13
-1	4	26	89	64	18
0	4	26	50	17	16
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