UNIVERSITY OF ILLINOIS

December 21, 1992

THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

David S. Hays

ENTITLED Studies Towards Dioxirane Mediated Catalytic Asymmetric Epoxidations of Olefins

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE DEGREE OF Bachelor of Science in Chemistry

Instructor in Charge

APPROVED:

HEAD OF DEPARTMENT OF Chemistry

O-1364

Studies Towards Dioxirane Mediated Catalytic Asymmetric Epoxidations of Olefins

by

David S. Hays

Thesis

for the
Degree of Bachelor of Science
in
Chemistry

College of Liberal Arts and Sciences
University of Illinois
Urbana, Illinois

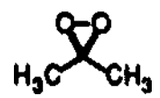
1992

Table of Contents

Introduction

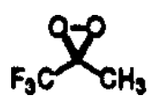
The asymmetric epoxidation of olefins has remained a significant challenge to synthetic organic chemists. The catalytic method developed by Sharpless,[1] while extremely efficient and capable of achieving high, reproducible enantioselectivities, is lacking in generality in that an allylic alcohol moiety must be present. More recently, Jacobsen has demonstrated high enantioselectivities utilizing a Mn^{III} salen complex as the catalytic species and bleach as the oxidant in the epoxidation of Z-olefins.[2] E-olefins were found to give much lower selectivities. Many stoichiometric methods have been reported which have utilized reagents such as chiral organic peracids,[3] chiral oxaziridines,[4] and chiral molybdenum diperoxide complexes.[5] The enantiomeric excess in these reactions was at best 51%. Thus, the development of a catalytic asymmetric epoxidation procedure for unfunctionalized E-olefins would be a valuable addition to synthetic organic chemistry.

A class of reagents which has recently found utility within the field of synthetic chemistry is that of dioxiranes.[6] Two such reagents are shown in Figure 1. Dimethyl dioxirane **1** and methyl(trifluoromethyl)dioxirane **2** have been shown to be mild, stereospecific reagents[7] for the oxidation of olefins to their corresponding epoxides.



Dimethyldioxirane

1



Methyl(trifluormethyl)dioxirane

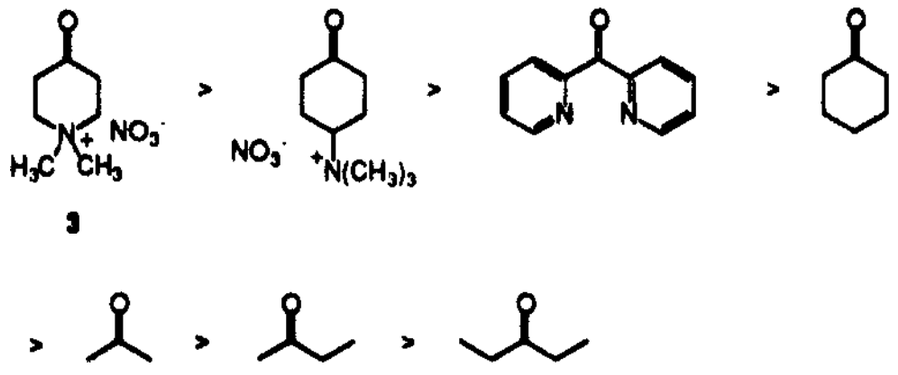
2

Figure 1. Two Examples of Dioxiranes.

The existence of dioxiranes was first proposed in 1899 by Baeyer and Villiger as an intermediate in the reaction that now bears their names.[8] Much later, the formation of dioxiranes was reported in an ozone-olefin reaction,[9] and theoretical studies were carried out to support their existence.[10] These studies led Murray in 1979 to propose dimethyldioxirane as the possible oxidizing species which forms under "Baeyer-Villager conditions" in the presence of acetone and peracetic acid. This new species was found to be capable of oxidizing hexenes to their respective epoxides, albeit in modest yields. A significant finding came when dioxirane was detected by mass-spectrometry in the low-temperature gas-phase ozonolysis of ethylene.[11] Studies since 1979 have pointed to the presence of dioxiranes in the photooxygenation of diazoalkanes,[12] but this proposal has been met with controversy.[13]

A new chapter in the history of dioxiranes was begun when Montgomery[14] found that certain ketones catalyze a number of reactions involving peroxomonosulfate ion in an unexpected manner. Peroxomonosulfate is obtained commercially from Aldrich as OXONE® (produced in the United States by Du Pont) and is known alternatively as Caro's salt or caroate. Its formula is best represented as $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, and it is a stable salt. Its corresponding acid (Caro's acid), however, has been reported to detonate.[15] The ionization constants for Caro's acid have been found to be $pK_1 < 0$ and $pK_2 = 9.4$.[16] The potassium salt was used by Baeyer and Villiger in their pioneering study.[8]

Montgomery studied the peroxomonosulfate oxidation of chloride ion and Polar Blue, as well as the decomposition of peroxomonosulfate ion. He found that the rates for these three reactions are dramatically increased by the presence of certain ketones. The rate data for three of these keones is shown in Table I, and the overall trend he found was:



3

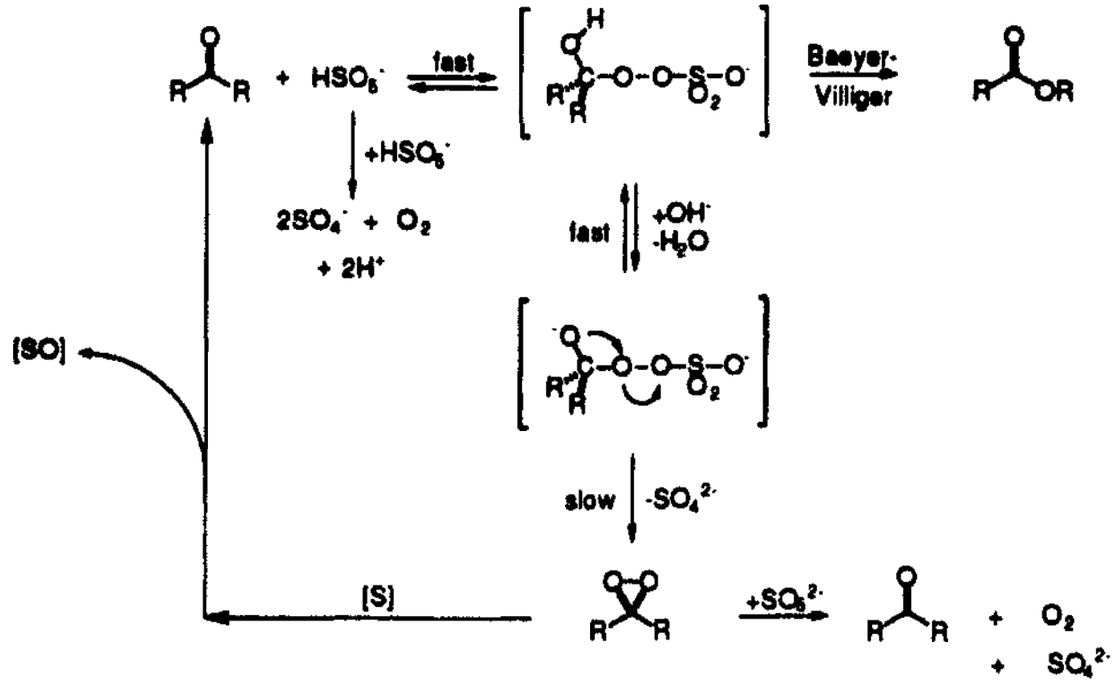
Table I. Data for Three Ketone-Catalyzed Peroxomonosulfate Reactions studied by Montgomery.

	relative rates of reactions		
ketone	decomposition of peroxomonosulfate	chloride oxidation	Polar Blue oxidation
none	<0.1	<0.1	<0.1
acetone	1.0	1.0	1.0
cyclohexanone	9.4	6.1	8.8
1,1-dimethyl-1-4-oxopiperidinium nitrate (3)	1400	1300	930

An excellent linear free energy plot was obtained for the rates of these three reactions, suggesting a common intermediate. Montgomery proposed that this intermediate is a dioxirane formed via nucleophilic attack of peroxomonosulfate ion on the ketone. He also found that the rate of the reaction is strongly dependent on pH. The observed trend suggests that the presence of a quaternary ammonium moiety greatly accelerates the reactions.

Later, Edwards and Curci carried out ^{18}O labeling studies and kinetic studies which provided evidence for the involvement of dioxiranes in the peroxomonosulfate decomposition reaction.[7,17] In these studies, the epoxidation of olefins using a caroate/ketone system was achieved for the first time. The mechanism which was proposed is shown in Scheme 1. As can be seen, the outcome of the reaction is predicted to be highly pH dependent. Montgomery found that near pH 9, the Baeyer-Villiger pathway can become significant with ketones such as cyclohexanone.[14] At high pH, the peroxomonosulfate self-decomposition pathway and the reaction of dioxirane with peroxosulfate ion will become significant, in agreement with Montgomery's findings.

Scheme I



Further evidence for the formation of dioxiranes in the caroate/ketone system was supplied by Adam.[18] In this study, thianthrene-5-oxide was used as a mechanistic probe. Curci later unambiguously identified dimethyl dioxirane 1 in the aqueous acetone/caroate mixture via ^{17}O and ^{13}C NMR.[19]

The synthetic utility of the ketone/caroate sytstem was demonstrated when Curci described three new approaches to olefin epoxidation:[20]

A) A stock solution of potassium peroxomonosulfate is added dropwise to the olefin in acetone solution at 0 °C and pH 7.5. This method is applicable to water soluble olefins.

B) A stock solution of potassium peroxomonosulfate is added dropwise to the olefin in a biphasic mixture of benzene and aqueous buffer (pH 7.5) at 6 - 8 °C. 18-Crown-6 is used as a phase transfer catalyst (PTC). This method is for water insoluble olefins.

C) This method is the same as "B," but CH_2Cl_2 replaces benzene and tetrabutylammonium hydrogen sulfate replaces 18-crown-6.

All reactions were performed using a pH stat.

An alternative epoxidation procedure was later detailed by Murray.[21] In this method, the dioxirane which is formed from a caroate/ketone system is isolated in a solution of the parent ketone using a multiple cold trap distillation apparatus. This solution can be titrated and used as the oxidizing reagent. Dioxiranes from several ketones were prepared and characterized by spectroscopic methods. Recently, Murray reported a procedure for the isolation of non-volatile dioxiranes which does not involve a distillation step.[22] Surprisingly, the dioxiranes of three chiral ketones (including that from menthone) were prepared in this manner, but their potential as asymmetric catalysts was not investigated.

Because of their mild properties, isolated dioxiranes have found their way into several syntheses of complicated sturctures. Danishefsky has utilized isolated dimethyldioxirane in the direct epoxidation of glycals,[23] which were in turn used as precursers to 2-deoxy-ß-glycosides.[24] Isolated methyl(trifluoromethyl)dioxirane **2** has been shown to be a much more active epoxidizing agent than dimethyldioxirane **1**,[25] and it has recently been used in the epoxidations of some polycyclic aromatic hydrocarbons to achieve high yields.[26]

A current topic of debate concerning dioxiranes is the geometry of the transition structure during the oxygen transfer event. Two limiting models have been proposed (Figure 2). The Curci/Edwards model[6a] predicts that all five atoms are coplanar (the "butterfly model"), similar to the model proposed by Bartlet[27] for the oxidation of olefins by peracids. The Baumstark model is a spiro-fused bicyclic system and is supported by kinetic studies concerning the oxidation of *cis* versus *trans* olefins[28]. Recently, a computational study by Bach, et al. has been reported concerning the transition state geometry for the

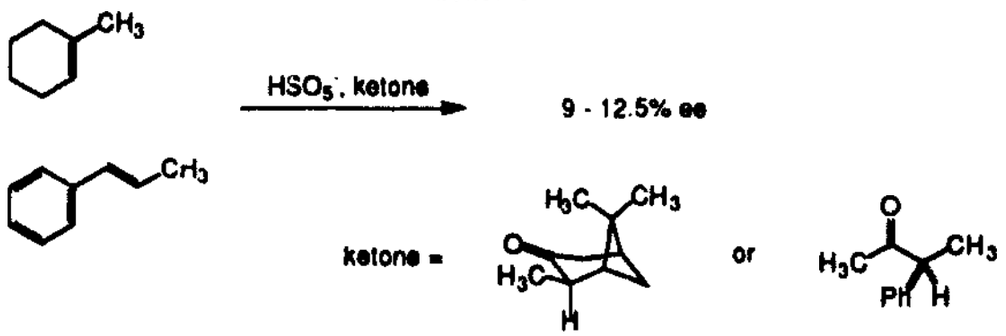
dimethyldioxirane/ethylene system.[29] Their calculations support the spiro model, but they warn that an unsymmetrical approach is often less than or equal to the symmetrical approach in energy for many similar reactions. Such a reaction pathway may be discovered in the dioxirane/ethylene system. The resolution of this issue will undoubtedly provide valuable aids in the design of chiral catalysts.

"Butterfly" (Curci/Edwards) "Spiro" (Baumstark)

Figure 2. Two Proposed Transition Structures for a Dioxirane/Olefin Reaction.

There have been three reports in the literature of asymmetric oxidation using chiral dioxiranes. Curci obtained ee's of 9 - 12.5% in the systems shown (Scheme 2)[30] using his method "C" as described above. He also mentions unpublished work in a later paper in which ee's of 24% were achieved using 4,4,4-trifluoro-3-phenyl-3-methoxy-2-butanone.[6a] More recently, Colonna and Gaggero have reported ee's of 89% in the oxidation of sulfides to sulfoxides using in situ generated dioxiranes with bovine serum albumin as a chiral auxiliary.[31]

Scheme 2



Project Goals

Although dioxiranes have become recognized as mild, selective oxidants within the field of synthetic organic chemistry, their potential as catalytic asymmetric epoxidizing agents has yet to be fully explored. The one reported study of asymmetric induction in such a transformation was able to obtain only low enantioselectivity. This leads one to believe that through rational design, an efficient, selective chiral ketone may possibly be synthesized and exploited for its use in asymmetric epoxidations of olefins. In this report, preliminary studies towards this goal are described. They include:

1) The synthesis of a suitable test olefin for our studies;

2) The identification of the most important parameters in Curci's method "C" (described above) with respect to our test olefin. These parameters will be adjusted so that the minimal amount of acetone provides a ca. 80-% conversion to epoxide;

3) A systematic survey of commercially available ketones to identify important structural features. Our test olefin and optimized conditions will be used, and the epoxidation efficiencies will be compared with that of acetone.

4) On the basis of this survey of structure/reactivity, achiral catalysts will be synthesized to provide models of future chiral catalysts. These will take the form of ketones bearing quaternary ammonium moieties.

Results and Discussion

Synthesis of Test Olefin (7)

With the long-term goal of achieving catalytic asymmetric epoxidations of E-olefins mediated by dioxiranes, a suitable test olefin had to be designed and prepared. Such a *trans* olefin should possess the following features:

a) it should be easily prepared from readily available starting materials;

b) the substituents on the olefin should be alkyl groups, only, so that any selectivity which arises may be attributed only to steric interactions;

c) it should be lipophilic in order to mimic most synthetically useful olefins in our two-phase reaction medium

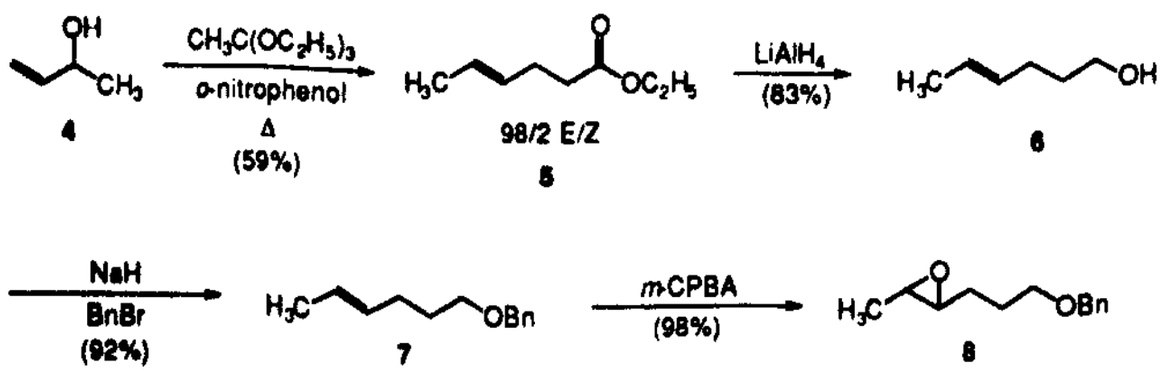
d) its epoxide enantiomers should be easily resolved using chiral HPLC or GC;

e) it should possess a UV chromophore; and,

f) both olefin and epoxide should be non-volatile and stable to workup and chromatography.

The model compound we chose was 6-(Phenylmethyloxy)-2(E)-hexene (7, Scheme 3). 3-Buten-2-ol **4** was either prepared[32] or obtained as the commercial product. Treatment with triethyl orthoacetate afforded the ester **5** in an E/Z ratio of 98/2. Reduction with $LiAlH_4$ and protection as the benzyl ether afforded the desired olefin **7**. An authentic sample of the corresponding epoxide **8** was prepared by treatment with *m*-CPBA.

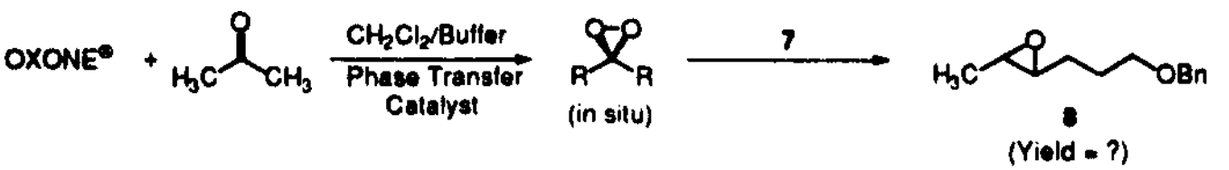
Scheme 3



Optimization of Reaction Conditions with Acetone Catalysis

When dioxiranes have been employed as epoxidizing agents using Curci's method "C,"[20] a large excess of OXONE® and/or ketone is typically used. To our knowledge, an optimaztion study on these parameters has never been reported. If an efficient catalytic asymmetric epoxidation protocol is to be developed, variables such as pH, stoichiometry, and rate of addition of OXONE® must be optimized, with the ultimate goal of minimizing the equivalents of catalyst. The first study undertaken was thus designed to optimize these parameters on our test olefin **7** using acetone as a catalyst in a biphasic aqueous buffer/CH_2Cl_2 medium (Scheme 4). In order that an effective comparison with alternative catalysts could be made in future studies, the goal was to find the minimum amount of acetone required such that a ca. 80% conversion to epoxide **8** was achieved.

Scheme 4



The first variable investigated was the stoichiometry of OXONE®, and the results from this study are shown in Table II, entries 1,2,3 and 7,8. It can be seen that, with the other variables held constant, the number of equivalents of oxidizing agent has little or no effect on the outcome of the reaction, provided at least ten equivalents are used. It appears that by adding more OXONE® stock solution, we are simply diluting the reaction with respect to acetone, PTC, and olefin. This allows the self-decomposition pathway of peroxomonosulfate (Scheme 1) to predominate, and the effect of adding more oxidizing agent is nullified.

The next variable investigated was the stoichiometry of PTC, tetrabutylammonium hydrogen sulfate. The results from this study are shown in Table II, entries 1,4, and 6. These data show that the conversion to epoxide under our conditions cannot be improved by adding more PTC, provided at least 0.1 equivalents are used.

The stoichiometry of acetone was next investigated, as shown in Table II, entries 1 and 5. In going from 1 equivalent of acetone to 10 equivalents, the reaction gives nearly quantitative conversion. The equivalents of acetone was therefore left as the sliding variable in achieving the target conversion of 80%.

Table II. Summary of Optimization Studies for Acetone Catalyzed Epoxidations of 7

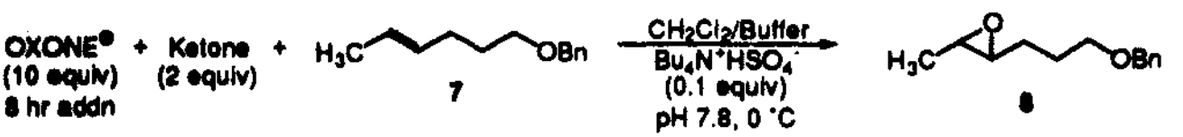
entry	OXONE® (equiv)	acetone (equiv)	Bu_4HSO_4 (equiv)	OXONE® add'n time (min)	epoxide/ olefin (recovered)	epoxide/ olefin (GC)
1	10	1	0.1	10	42 : 58	50 : 50
2	20	1	0.1	20	37 : 63	-
3	42	1	0.1	43	44 : 56	44 : 56
4	10	1	0.25	10	46 : 54	45 : 55
5	10	10	0.1	10	99 : 1	100 : 0
6	10	1	1.0	10	41 : 59	32 : 68
7	10	1	0.1	120	58 : 42	60 : 40
8	20	1	0.1	240	53 : 47	55 : 45
9	10	2	0.1	120	63 : 37	63 : 37
10	10	2	0.1	240	85 : 15	88 : 12
11	**10**	**2**	**0.1**	**480**	**87 : 13**	**88 : 12**
12	10	1	0.1	480	71 : 29	75 : 25
13	5	1	0.1	240	49 : 51	52 : 48

It was found that the rate of addition of OXONE® stock solution has a drastic effect on the outcome of the reaction, as shown in entries 1, 7, and 9, 10, 11 of Table II. Figure 3 shows a study by Forbes in these laboratories in which the concentration of peroxomonosulfate ion in aqueous solution maintained at pH 7.8 on a pH stat is monitored by iodometric titration versus time. It can be seen that after 4 hours, the concentration of oxidizing species has leveled off at 0.075 M, but it is notable that some peroxomonosulfate ion is still present. In accordance with Scheme 1, the bimolecular OXONE® self-decompositon reaction is the only pathway available at pH 7.8 and explains the behavior shown in the figure. By adding the OXONE® solution more slowly, we are minimizing this bimolecular decompostion pathway and maximizing the productive pathway of epoxidation.

A pH study was carried out by Forbes in these laboratories. Determining the optimum pH for the reaction is crucial because at high pH, only decomposition of OXONE® will occur. The Baeyer-Villiger pathway is also expected to be pH dependent. (Scheme 1) The results of this study are shown in Figure 4. It can be seen that the maximum conversion is achieved at a pH of 7.8 to 8.0.

The final variables were now fine-tuned to select entry 11 in Table 2 as our chosen conditions for the systematic survey of ketone structures (Scheme 5).

Scheme 5



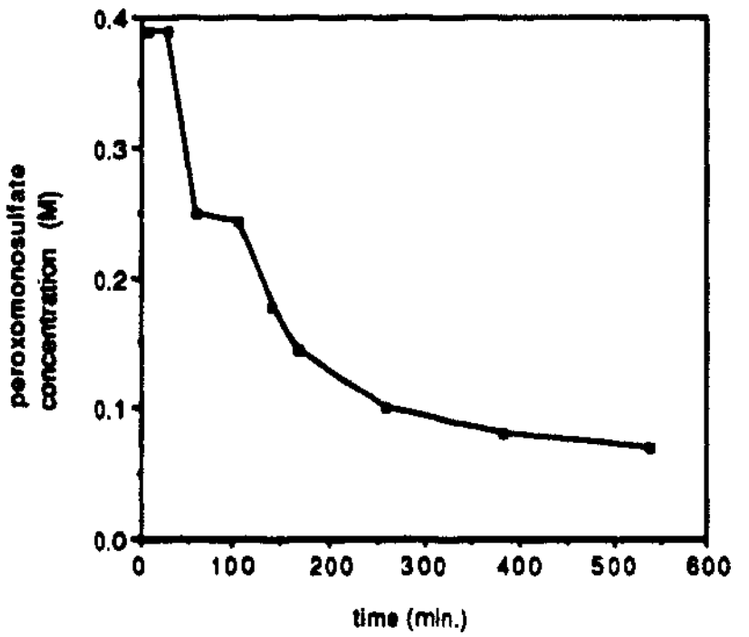


Figure 3. Peroxomonosulfate Self-Decomposition at pH 7.8.

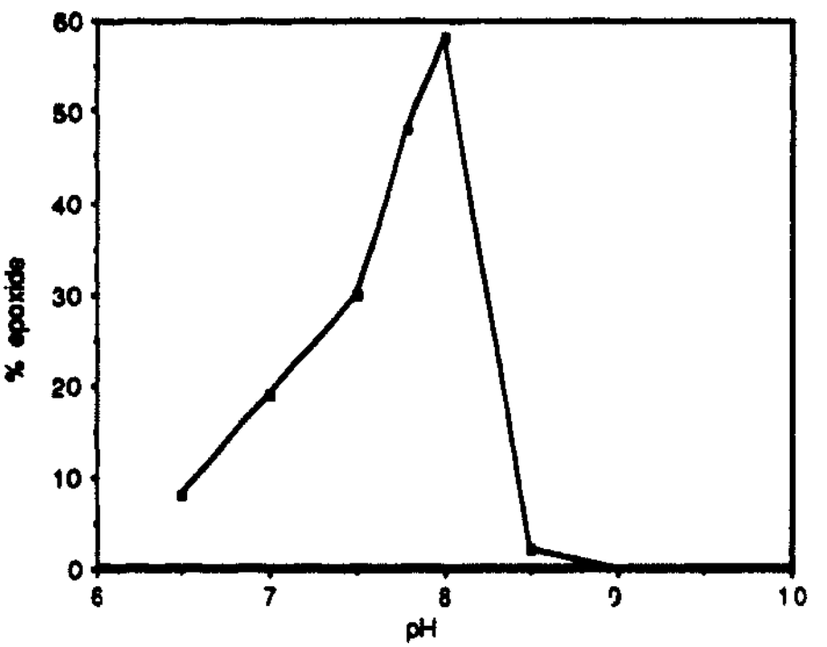


Figure 4. Percent Conversion to Epoxide Versus pH

Structure/Reactivity Survey of Commercially Available Ketones

Although several dioxiranes have been prepared and characterized, only acetone and trifluoroacetone have found widespread use as dioxirane precursors within the realm of synthetic organic chemistry.[6] Barring Montgomery's work[14] (Table I) on three ketone catalyzed peroxomonosulfate reactions, there has been no systematic study of ketone structure versus oxidation efficiency, specifically of epoxidation efficiency. If the rational design of an efficient chiral catalyst is to be achieved, such structure/reactivity data must be obtained. Thus, the next study we performed was a systematic survey of commercially available ketones to identify important structural characteristics for the epoxidation of our test olefin 7 under the conditions determined above.

The data from this study are given in Table III and Figure 5.

Table III. Summary of Survey of Ketone Structure/Reactivity in Epoxidation of 7

ketone	water solubility of ketone	24 hr epoxide/olefin ratio (recovered)
acetone	miscible	75 : 25
2-butanone	27%, 20 °C	40 : 60
3-pentanone	5%, 20 °C	5 : 95
trifluoroacetone		29 : 71
hexafluoroacetone		2 : 98
cyclobutanone		2 : 98
cyclopentanone	30%, 25 °C	3 : 97
cyclohexanone	8-9%, 20 °C	67 : 33
none	-	2 : 98

In going from acetone to 2-butanone to 3-pentanone, it can be seen in Table III that the efficiency and rate of epoxidation drops. Bulky groups and groups that donate electron density to the carbonyl are expected to stabilize the carbonyl. In addition, water solubility decreases in going down the series.

Acetone is seen to be a better catalyst than trifluoroacetone in Table III and Figure 5. Curci found that isolatated methyl(trifluoromethyl)dioxirane 2 is a more efficient oxidant than dimethyl dioxirane 1.[25] However, in our system, the competition between formation of dioxirane and OXONE® self-decomposition is present. This is not the case when isolated dioxiranes are used. It is believed that formation of the hydrate with trifluoroacetone is the cause of this observation. This is especially manifested in the case of hexafluoroacetone which gives only background epoxidation.

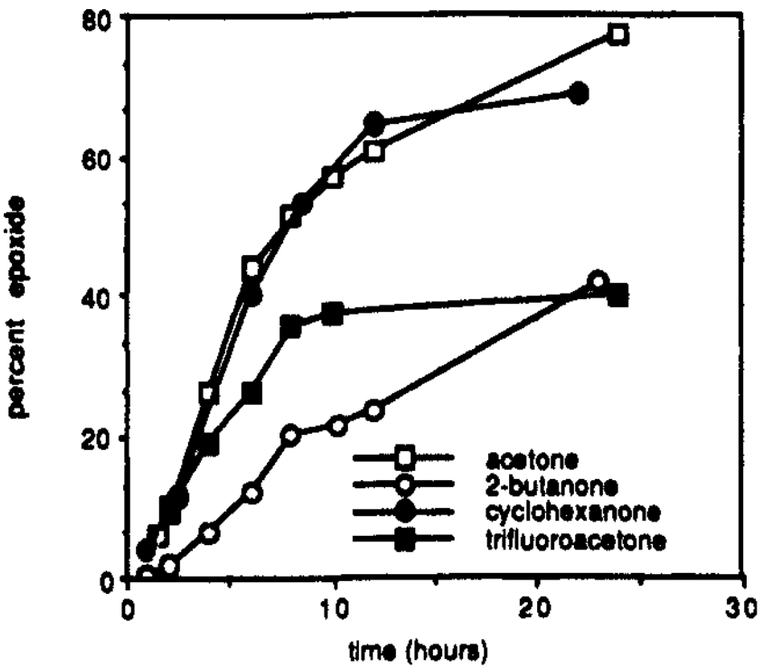


Figure 5. Rates of Epoxidation in Structure/Reactivity Survey

In considering the cyclic structures, cyclohexanone is the least water soluble of the three which were investigated, yet it is the most efficient cyclic catalyst. Cyclobutanone has been demonstrated to form the Baeyer-Villiger product under our conditions.[7] Edwards found that cyclohexanone is 50 times faster than cyclopentanone in the catalysis of peroxomonosulfate decompostions, with analogy being made to the trend for $NaBH_4$ reduction of these ketones.[7] In comparing cyclopentanone with cyclohexanone, Prelog found that the equilibrium constant for formation of the cyanohydrin from cyclohexanone and cyclopentanone is 1000 and 48 respectively.[33]

The following conclusions concerning ketone structure can be made:

1) Some water solubility of the ketone must be present. This is equivalent ot saying that the partition coefficient for the ketone in water/CH_2Cl_2 must be large enough such that enough ketone is present in the water layer at any given time to react with peroxomonosulfate ion. Otherwise, the rate of OXONE® self-decomposition will greatly exceed that of dioxirane formation. The trend observed in the aliphatic ketones supports this conclusion.

2) The equilibrium constant for the formation of the hydrate must be small enough such that at any given time, there is enough unhydrated ketone present in the water layer to react with peroxomonosulfate ion. Otherwise, the rate of OXONE® self-decomposition will greatly exceed that of dioxirane formation. This equilibrium is expected to lie towards the hydrate if the carbonyl carbon is particularly electron deficient or if ring strain is such that an sp^3 center is greatly favored over an sp^2 center. This factor is believed to be the cause of the observed acetone/trifluouroacetone/hexafluoroacetone trend.

3) The general factors which control nucleophilic attack on carbonyl carbons are expected to be operative during the bimolecular attack of peroxomonosulfate ion on the ketone. Thus, bulky groups and groups which stabilize the carbonyl by donation of electron density are expected to cause less susceptibility to nucleophilic attack. In addition to solubility factors, this may be the cause of the trend observed in the aliphatic ketone series, as Montgomery found the same trend with respect to three aqueous oxidation reactions. The general trend for the propensity of cyclic systems to undergo a transition from an sp^2 to an sp^3 center is manifested in the observation that cyclohexanone is a better catalyst than cyclopentanone.

4) The formation of the Baeyer-Villiger product must be suppressed. This is an irreversible pathway which takes the ketone out of the catalytic cycle. This pathway is expected to be a problem in strained cyclic systems such as cyclobutanone.

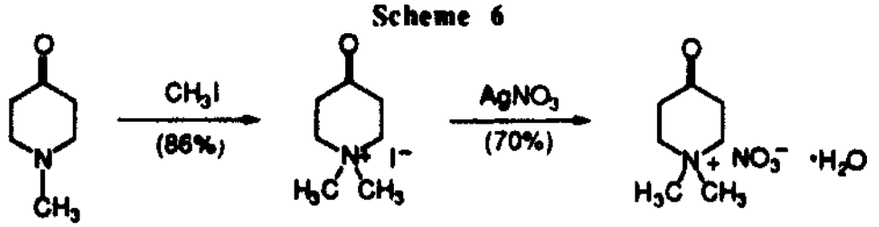
From this study, we can conclude that a six-membered ring ketone is a good candidate for a chiral template. By adjusting solubility properties, we can optimize effect 1. It also appears that in a six-membered ring system, attack by peroxomonosulfate ion is both rapid and energetically feasible such that competition with OXONE® self-decomposition is favorable. Finally, it appears that the Baeyer-Villiger pathway is not a dominating factor.

Synthesis of 4-Oxo-piperidinium Salts

Montgomery found that certain six-membered ring ketones bearing quaternary ammonium salts showed remarkable rates of catalytic oxidation of chloride ion and catalytic destruction of peroxymonosulfate ion with respect to acetone.[14] These reactions were later shown by Edwards and Curci to proceed through dioxiranes.[7] Since quaternary ammonium salts are commonly used as phase transfer catalysts, PTC properties may be built in to a chiral ketone, and the necessary solubility properties may be obtained by varying the alkyl substituents on nitrogen. Lepoivre et al.[34] studied the hydration of N-alkyl piperidinium compounds and demonstrated that the carbonyl group was highly activated towards nucleophilic attack with respect to the corresponding neutral species. Thus, such ketones appear to be a rich source of efficient catalysts for the reaction at hand, and a study concerning the synthesis of 4-oxopiperidinium compounds **13**, **14**, and **15** and the investigation of their catalytic properties was undertaken.

Montgomery did not publish the synthesis of compound 3, but it was readily obtained by treatment of the commercially available piperidone 9 with methyl iodide (Scheme 6) to yield the N,N-dimethyl piperidinium species 10. Ion exchange with silver nitrate in aqueous solution afforded the corresponding nitrate 3 which crystallizes as the hydrtate.[35]

Scheme 6



9 10 3

The analogs 15 could not be prepared by simple alkylation of the methyl piperidone 9, as decomposition results. This was also shown by a previous worker in these laboratories. However, they could be prepared as shown in Scheme 7. The primary amine 11 was combined in a Michael reaction with methyl acrylate to afford the diester 12. This was treated with NaH to afford the product of a Dieckmann condensation 13 as the ß-keto ester, which was subsequently decarboxylated using the general procedure of McElvain and Rorig[36] to afford the N-alkyl piperidone 14. The desired quaternary ammonium salts 15 were then obtained by treatment with suitable methylating agents.

Investigation of 4-Oxo-piperidinium Salts

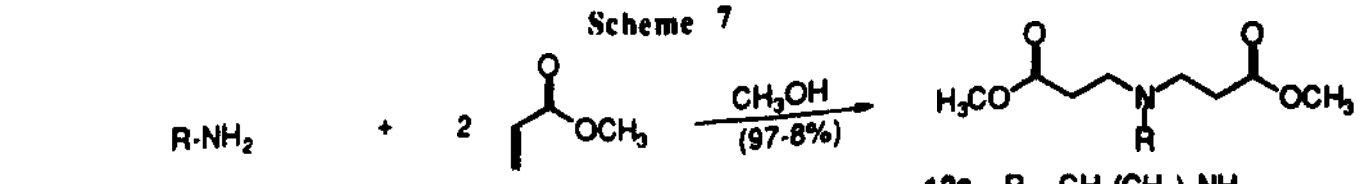
With the 4-oxo-piperidinium salts in hand, the investigation of their potential as catalysts in the epoxidation reaction was carried out. The results of this study are shown in Table IV and Figure 6. It is important to note that the primary difference among the piperidinium salts is solubility properties and emulsifying abilities.

Table IV. Summary of Epoxidations Catalyzed by 4-Oxo-piperidinium Salts

entry	ketone	OXONE® (equiv)	ketone (equiv)	OXONE® add'n time (hrs)	epoxide/ olefin (12 hrs)	[a]epoxide/ olefin (recovered)	[a]epoxide/ olefin (GC)
1	acetone	10	1	12	37 : 63	71 : 29	70 : 30
2	3	10	2	8	1 : 99	1 : 99	1 : 99
3	15a	10	2	8	98 : 2	100 : 0	-
4	15a	10	1	8	43 : 57	44 : 56	-
5	15a	10	1	12	81 : 19	-	82 : 18
6	15b	10	1	8	98 : 2	100 : 0	
7	15b	10	0.1	8	77 : 23	-	94 : 6
8	15b	1	0.1	8	15 : 85	14 : 86	19 : 81
9	15c[b]	10	0.1	8	1 : 99	-	4 : 96

[a] Data for time = 24 hours; [b] Synthesized and investigated by Forbes in these laboratories.

Scheme 7



11a R = $CH_3(CH_2)_5NH_2$

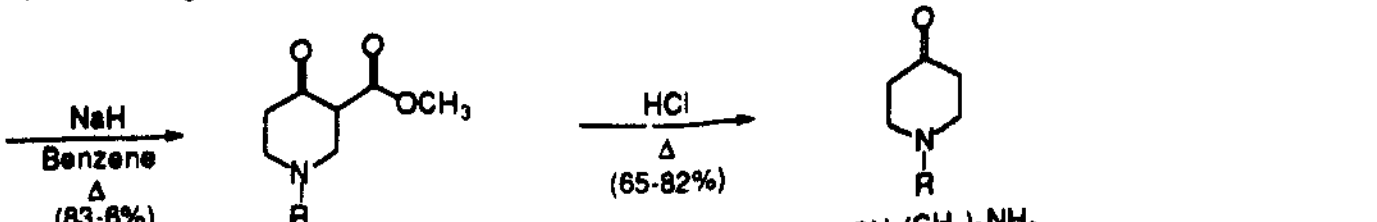
11b R = $CH_3(CH_2)_{11}NH_2$

11c R = $CH_3(CH_2)_{17}NH_2$

12a R = $CH_3(CH_2)_5NH_2$

12b R = $CH_3(CH_2)_{11}NH_2$

12c R = $CH_3(CH_2)_{17}NH_2$



13a R = $CH_3(CH_2)_5NH_2$

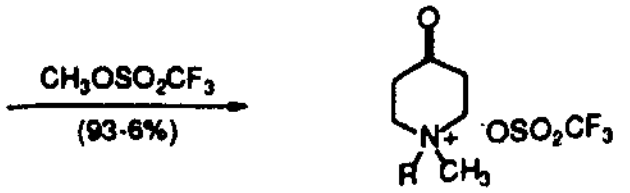
13b R = $CH_3(CH_2)_{11}NH_2$

13c R = $CH_3(CH_2)_{17}NH_2$

14a R = $CH_3(CH_2)_5NH_2$

14b R = $CH_3(CH_2)_{11}NH_2$

14c R = $CH_3(CH_2)_{17}NH_2$



15a R = $CH_3(CH_2)_5NH_2$

15b R = $CH_3(CH_2)_{11}NH_2$

15c R = $CH_3(CH_2)_{17}NH_2$

The order of efficiency of these catalysts was found to be:

$$R = C_{12}H_{25} > R = C_6H_{13} > R = C_{18}H_{37} \approx R = CH_3$$

The octadecyl variant was shown by Forbes in these laboratories to provide substantial epoxidation when the reaction is run at room temperature rather than 0 °C (as done in this study), probably due to its insolubility in cold water/CH_2Cl_2.

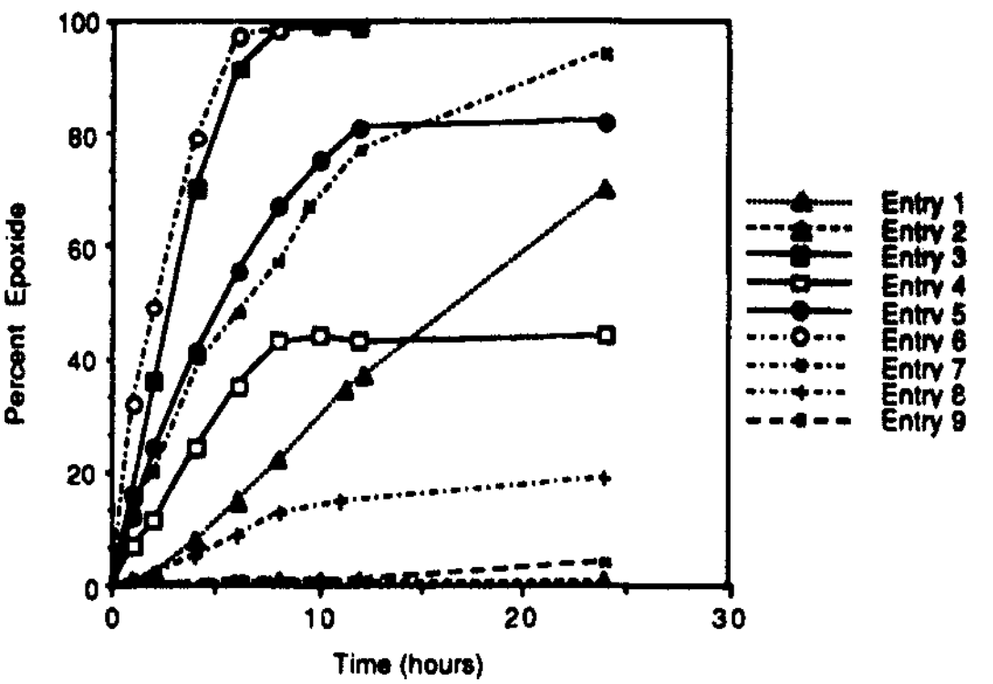


Figure 6. Rates of Epoxidation for Piperidinium Catalyzed Reactions

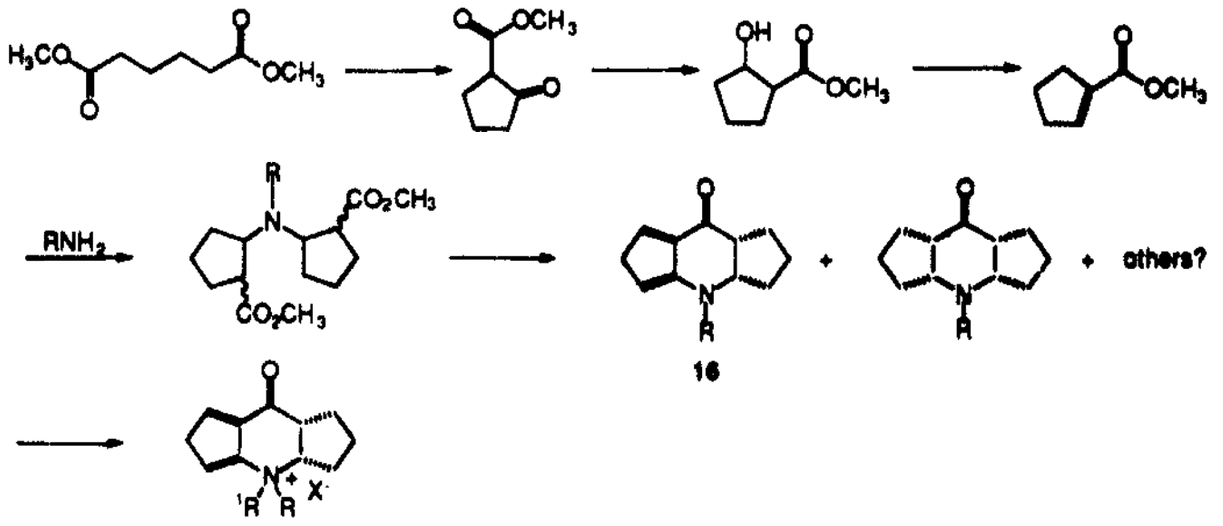
The most efficient catalyst studied in this series was the R = dodecyl version **15b** of the piperidinium salts. This catalyst was able to be used sub-stoichiometrically (10 mol %) to achieve a 94% conversion to epoxide. An attempt to minimize the amount of Oxone® to 1 equivalent was fruitless, confirming that the decomposition of peroxymonosulfate is still operative. A major drawback of these catalysts is that they do not appear to be easily recoverable. Upon work-up, little or no catalyst is transferred to the organic layer.

Conclusion

As of yet, we have not demonstrated asymmetric epoxidation by potassium peroxomonosulfate catalyzed by a chiral ketone. However, important structural features of a potential catalyst have come to light. The catalyst will most likely be based on a 4-oxo-piperidinium salt. Such a template has been shown in this work to be a much more efficient catalyst than acetone. Moreover, the required phase transfer properties for our water/CH_2Cl_2 medium are manifested in the quaternary ammonium moiety. It has been shown in this study that a model compound bearing methyl and dodecyl substituents on the nitrogen **15b** may be used substoichiometrically (10 mol %) under our chosen conditions to achieve high conversion to epoxide (94%).

Synthesis of a chiral ketone **16** for use as a catalyst based on the 4-oxo-piperidinium structure is currently underway by Forbes in these laboratories. MM-2 calculations indicate that this cis ring fused C_2 symmetric diastereomer is the most stable isomer. A potential route is currently being pursued and is given in Scheme 8. Future studies will revolve around synthesis and resolution of such a compound, optimization of the counterion and the solvent, and investigations of the transition structure.

Scheme 8



Experimental

General Experimental

^1H and ^{13}C spectra were recorded on Varian XL-200 (200 MHz ^1H, 50.3 MHz ^{13}C), General Electric QE-300 (300 MHz ^1H, 75.5 MHz ^{13}C), or Varian Unity-400 (400 MHz ^1H, 100.6 MHz ^{13}C) in deuteriochloroform ($CDCl_3$) with chloroform (7.26 ppm ^1H, 77.0 ppm ^{13}C) as an internal reference. Data are reported in the following order: chemical shifts in ppm (δ); multiplicities are indicated br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants, *J*, are reported (Hz); integration is provided; and assignment is indicated. Assignments of individual resonances are supported by DEPT spectra in some instances. Infrared spectra were recorded on a IBM FTIR-32 spectrophotometer. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67-100%), m (medium 40-o6%), w (weak 20-40%), and b (broad). Mass spectra were obtained by the University of Illinois Mass Spectrometry Center on a Varian MAT CH-5 spectrometer with ionization voltages of 70 and 10 eV. Low resolution fast atom bombardment (FAB) spectra were obtained on a VG / AB-SE spectrometer. Data are reported in the form *m/e* (intensity relative to base = 100). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 plates, thickness 0.25 mm. Visualization was accomplished by UV light, potassium permanganate solution, para-anisaldehyde solution, iodine, or phosphomolybdic acid reagent. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: dichloromethane (CH_2Cl_2), pentane, hexane: $CaCl_2$; ethyl acetate (EtOAc): K_2CO_3; *tert*-butyl methyl ether (TBME): $CaSO_4/FeSO_4$. Column chromatography was performed by the method of Still[37] with 32-63 μm silica gel (Woelm). Analytical gas chromatography (GC) was performed on a Hewlett Packard 5890 gas chromatograph with a built in flame ionization detector (FID). The column used for separation was a Hewlett Packard Ultra 2 phenyl methyl silicone 50 m x 0.2 mm x 0.33 μm capillary column. Retention times and peak ratios were measured on a Hewlett Packard 3393A Integrator. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Bulb-to-bulb distillations were done on a Büchi GKR-50 Kugelrohr, and boiling points correspond to uncorrected, air bath temperatures.

All reactions were performed under a dry nitrogen atomsphere in oven- and/or flame-dried glassware, except for the OXONE® reactions. "Brine" refers to a satruated solution of NaCl.

All OXONE® epoxidations were carried out using a Brinkman pH stat apparatus which consists of a Brinkman pH-meter E512, a Brinkman Impulsomat 473, and a Brinkman Dosimat E412.

Reagents, Suppliers, and Purification

Acetic acid, glacial	Baker
Acetone	Fisher, distilled from K_2CO_3
Acetone-d_6	Cambridge Isotope Laboratories
Ammonium Chloride	Fisher
Benzene	Fisher, distilled from CaH_2
Benzyl Bromide	Aldrich, distilled from $MgSO_4$
3-Buten-2-ol	Denmark Group Sample, distilled
Calcium Hydride	Alfa
Chloroform-d	Cambridge Isotope Laboratories
m-Chloroperoxybenzoic Acid (MCPBA)	Fluka, recrystallized
Dichloromethane	Aldrich, distilled from CaH_2
Diethyl ether	Fisher, dried with CaH_2, distilled from Na/benzophenone
Dodecylamine	Aldrich, distilled from KOH
Hydrochloric Acid	Fisher
Lithium Aluminum Hydride	Johnson Matthey
Hexylamine	Aldrich, distilled from CaH_2
Iodomethane	Aldrich, distilled
Potassium Carbonate	EM Science
Magnesium Sulfate	EM Science
Methanol	Fisher, ditilled from Mg
Methyl Acrylate	Univ. of Illinois Marvel Storeroom, washed with base, distilled from $CaCl_2$[38]
Methyl Magnesium Bromide	Aldrich
1-Methyl-4-piperidone	Aldrich, distilled
Methyl Trifluoromethanesulfonate	Aldrich, distilled
OXONE®	Aldrich
Sodium Bicarbonate	Fisher
Sodium Chloride	EM Science
Sodium Hydride	Aldrich, 60% dispersion
Sodium Hydroxide	EM Science

Tetrabutylammonium Hydrogen Sulfate	Aldrich
Tetrabutylammonium Iodide	Aldrich
Tetrahydrofuran (THF)	Aldrich, distilled from Na/benzophenone

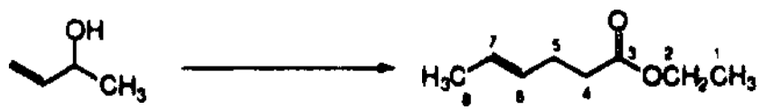
Experimental Procedures

Synthesis of Test Olefin

3-Buten-2-ol (4) [DH-I-58]

This was prepared according to the method of Claisen.[32]

Ethyl 4-hexenoate (5) [DH-I-73][39]



4 5

Triethyl orthoacetate (37.1 g, 229 mmol, 1.10 equiv) was placed in a 100 mL three-neck round bottom flask equipped with thermometer, glass stopper, magnetic stirrer, and a reflux condenser on which was mounted a Claisen head equipped with a 10 mL dropping funnel and a short path condenser with thermometer. With the reflux condenser off, the allylic alcohol 4 (18.0 mL, 208 mmol) was added dropwise over 1 hour. After an additional hour, no additional ethanol was being produced. The reflux condenser was turned on, and the solution was refluxed for 3 hours (135 °C internal temperature). After cooling to room temperature, the solution was poured into 100 mL diethyl ether and washed with 1 N NaOH (1 x 60 mL), H_2O (2 x 60 mL), and brine (1 x 60 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was taken up in THF (20 mL) and stirred with 10% aqueous HCl (20 mL) for 20 minutes to hydrolyze the remaining triethyl orthoacetate. The organic layer was drawn off, washed with H_2O (2x) and brine (1x), and dried ($MgSO_4$). It was filtered, concentrated, and fractionally distilled in vacuo to afford 16.7 g (59%) of 5 as a colorless oil with an E/Z ratio of 98/2 (GC, 130 °C, (5 min), 10 °C/min, 200 °C (10 min)).

Analytical Data for 5

bp: 72-74 °C (25 torr) (head temperature)

^{1}H NMR: (300 MHz, $CDCl_3$)

5.52-5.38 (m, 2 H, HC(6), HC(7)), 4.12 (q, J = 7.1, 2H, $H_2C(2)$), 2.37-2.26 (m 4 H, $H_2C(4)$, $H_2C(5)$), 1.63 (d, J = 5.3, 3 H, $H_3C(8)$), 1.24 (t, J = 7.1, 3 H, $H_3C(1)$).

TLC: R_f 0.46 (5/1 hexanes/EtOAc)

4-Hexen-1-ol (6) [DH-1-76][39]

5 6

A solution of ethyl 4-hexenoate 5 (16.0 g, 113 mmol) in diethyl ether (45 mL) was added to an ice-cold suspension of lithium aluminum hydride (4.27 g, 113 mmol, 1.00 equiv) in diethyl ether (200 mL) over 45 minutes. After stirring for 2 hours at 0 °C, the reaction was quenched by careful addition of ethyl acetate (10.2 mL). The lithium salts were precipitated out by sequential addition of H_2O (4.3 mL), NaOH (6 N, 4.3 mL), and H_2O (12.8 mL). The white salts were filtered out, and the reulting solution was dried ($MgSO_4$) and concentrated in vacuo. The resulting slightly yellow oil was fractionally distilled in vacuo to afford 9.38 g (83%) of 6 as a colorless oil.

Analytical Data for 6

bp: 74-76 °C (25 torr) (head temperature)

^{1}H NMR: (300 MHz, $CDCl_3$)

5.50-5.39 (m, 2 H, HC(4), HC(5)), 3.63 (t, J = 6.5, 2 H, $H_2C(1)$), 2.09-2.03 (m, 2 H, $H_2C(3)$), 1.69-1.55 (m, 6 H, $H_3C(6)$, $H_2C(3)$, HO).

TLC: R_f 0.48 (hexanes/EtOAc 1/1)

6-(Phenylmethyloxy)-2(E)-hexene (7) [DH-I-50]

The alcohol **6** (4.30 g, 42.9 mmol) was added dropwise to a suspension of oil-free sodium hydride (1.13 g, 47.2 mol, 1.10 equiv) in THF (50 mL). The mixture was stirred for 7 hours, at which time the white, foamy suspension was treated with tetrabutylammonium iodide (0.887 g, 2.40 mmol, 0.056 equiv) and benzyl bromide (5.10 mL, 42.9 mmol, 1.00 equiv). After stirring an additional 2 1/4 hours, the mixture was partitioned beweened ethyl acetate (150 mL) and saturated NH_4Cl (150 mL). The organic layer was drawn off, and the aqueous layer was washed with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (1 x), dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was fractionally distilled in vacuo to afford 7.57 g (93%) of **7** as a slightly yellow oil. It was further purified by flash column chromatography (hexanes/EtOAc 30/1) and bulb to bulb distillation in two equal portions to afford **7** as an analytically pure, colorless oil.

Analytical Data for **7**

bp: 91-92 °C (0.2 torr) (head temperature)

^{1}H NMR: (300 MHz, $CDCl_3$)

7.37-7.28 (m, 5 H, HC(2', 3', 4', 5', 6')), 5.57-5.43 (m, 2 H, HC(2, 3)), 4.52 (s, 2 H, H_2C(7)), 3.49 (t, J=6.6, 2 H, H_2C(6)), 2.13- 2.06 (m, 2 H, H_2C(5)), 1.74-1.65 (m, 5 H, H_3C, H_2C(1,4)).

^{13}C NMR: (75.5 MHz, $CDCl_3$)

138.61 (C(1')), 130.67 (C(3)), 128.28 (C(3',5')), 127.58 (C(2',6') or (C(4')), 127.42 (C(2',6') or (C(4')), 125.18 (C(2)), 72.81 (C(7)), 69.77(C(6)), 29.55 (C(4)) or (C(5)), 29.11 (C(4)) or (C(5)), 17.90 (C(1)).

IR: (Thin film)

3088 (w), 3063 (w), 3029 (m), 2936 (s), 2855 (s), 2793 (w), 1495 (w), 1453 (s), 1364 (m), 1308(w), 1204 (w), 1103 (s), 1028 (m), 967 (s), 735 (s).

MS: (10 eV)

190 (M^+, 94), 161 (20), 108 (11), 107 (74), 106 (27), 99 (100), 98 (32), 92 (30), 91 (46), 83 (14), 82 (86), 81 (83), 69 (20), 57 (12), 55 (14), 43 (15).

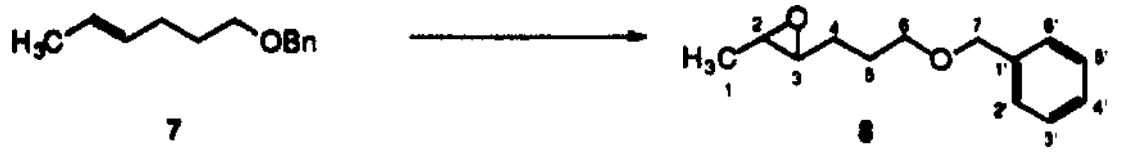
TLC: R_f 0.27 (hexanes/EtOAc 12/1)

Analysis: $C_{13}H_{18}O$ (MW 190.28)

Calcd:	C, 82.06	H, 9.53
Found:	C, 82.08	H, 9.52

Independent Synthesis of Epoxide

trans-2-Methyl-1-(prop-3-yloxybenzyl)oxirane (8) [DH-I-52]



The olefin 7 (0.160 g, 0.841 mmol) was dissolved in CH_2Cl_2, and the solution was cooled on ice. A solution of *m*-CPBA (0.160 g, 0.927 mmol, 1.10 equiv) in CH_2Cl_2 (5 mL) was added with stirring. The reaction was allowed to warm up to room temperature and was stirred as such for 12 hours. The solution was washed with saturated $NaHCO_3$ (1 x 15 mL) and H_2O (1 x 15 mL), and the combined aqueous layers were back extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by flash column chromatography (1/8 EtOAc/hexanes) to afford 0.170 g of 8 as a colorless oil (98%).

Analytical Data for 8 from *m*-CPBA synthesis

^{1}H NMR: (300 MHz, $CDCl_3$)

7.35-7.26 (m, 5 H, HC(2', 3', 4', 5', 6')), 4.51 (s, 2 H, H_2C(7)), 3.55-3.48 (m, 2 H, H_2C(6)), 2.77-2.72 (dq, J_d = 2.1, J_q = 5.1, 1 H, HC(2)), 2.68-2.63 (m, 1 H, HC(3)), 1.80-1.56, 4 H, H_2C(4), H_2C(5)), 1.28 (d, J = 5.2, 3 H, H_3C(1))

^{13}C NMR: (75.5 MHz, $CDCl_3$)

138.42 (C(1')), 128.33 (C(3', 5')), 127.61 (C(2',6') or C(4')), 127.52 (C(2',6') or C(4')), 72.88 (C(7)), 69.73 (C(6)), 59.44 (C(3)), 54.59 (C(2)), 28.80 (C(4)), 26.19 (C(5)), 17.62 (C(1)).

IR: (Thin film)

3063 (w), 3031 (w), 2928 (m), 2857 (m), 1495 (m), 1482 (w), 1453 (m), 1379 (m), 1362 (m), 1204 (w), 1102 (s), 1028 (m), 934 (m), 860 (m), 739 (m).

TLC: R_f 0.40 (hexanes/EtOAc 4/1)

The epoxide product **8** from an OXONE® reaction was further purified by column chromatography and bulb to bulb distillation to afford a colorless oil. Its spectroscopic data was found to agree with that from the independent m-CPBA synthesis.

Analytical Data for 8 from Oxone Epoxidation

bp: 135 °C (0.2 torr) (air bath temperature)

^{1}H NMR: (300 MHz, $CDCl_3$)

7.37-7.25 (m, 5 H, HC(2', 3', 4', 5', 6')), 4.51 (s, 2 H, $H_2C(7)$), 3.57-3.45 (m, 2 H, $H_2C(6)$), 2.78-2.72 (dq, J_d = 2.2, J_q = 5.2, 1 H, HC(2)), 2.68-2.63 (m, 1 H, HC(3)), 1.85-1.31 (m, 4 H, $H_2C(4,5)$, 1.28 (d, J = 5.2, 3 H, $H_3C(1)$).

^{13}C NMR: (75.5 MHz, $CDCl_3$)

138.50 (C(1')), 128.37 (C(3', 5')), 127.63 (C(2',6') or C(4')), 127.56 (C(2',6') or C(4')), 72.90 (C(7)), 69.77 (C(6)), 59.44 (C(3)), 54.59 (C(2)), 28.84 (C(4)), 26.25 (C(5)), 17.68 (C(1)).

IR: (Thin film)

3031 (w), 2928 (m), 2859 (s), 1495 (w), 1482 (w), 1453 (m), 1379 (m), 1362 (m), 1204 (w), 1102 (s), 1028 (m), 1007 (w), 934 (m), 860 (m), 739 (s).

MS: (10 eV)

188 (20), 187 (36), 173 (22), 120 (25), 108 (10), 107 (88), 97 (13), 91 (38), 82 (77), 71 (100), 69 (14), 67 (15), 57 (10).

TLC: R_f 0.40 (hexanes/EtOAc 4/1)

Analysis: $C_{13}H_{18}O_2$ (MW 190.28)

Calcd:	C, 75.69	H, 8.79
Found:	C, 75.61	H, 8.83

Synthesis of Quaternary Ammonium Salts

4-Oxo-1,1-dimethylpiperidinium iodide (10) [DH-I-83][40]

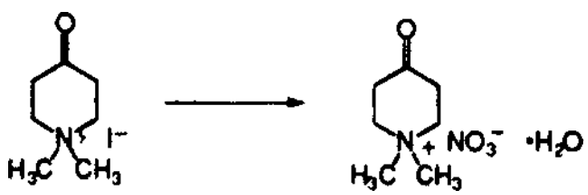
9 **10**

Methyl iodide (4.39 mL, 70.5 mmol, 1.06 equiv) was added in one portion to a stirred solution of N-methylpiperidone 9 (8.2 mL, 66.5 mmol) in diethyl ether (150 mL). After 10 minutes, a white precipitate appeared. The reaction was stirred at at room temperature for 2 hours, and then at reflux for 20 hours. The crystals were collected by filtration and dried under vacuum to afford 14.5 g (86%) of **10** as a white solid.

Analytical Data for **10**

^{1}H NMR was found to agree with the nitrate analog.[35]

4,4-Dihydroxy-1,1-dimethylpiperidinium nitrate (3) [DH-I-86]



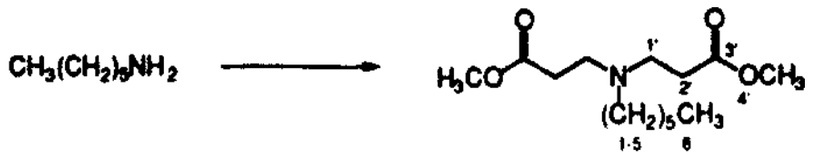
10 **3**

To a solution of silver nitrate (4.16 g, 24.5 mmol, 1.05 equiv) in water (30 mL) was added the piperidinium iodide **10** (6.00 g, 23.5 mmol) portionwise over 5 minutes. The reaction was stirred for 2 hours, at which time the mixture was passed through a pad of Celite to remove the AgI. The water was evaporated in vacuo until a precipitate appeared. This crop was collected by filtration and washed with cold MeOH, and a second crop was obtained by complete evaporation of the filtrate and filtration as above to afford 3.44 g (70%) of **3** as a slightly brown solid.

Analytical Data for **3**

^{1}H NMR was found to agree with the ^{1}H NMR spectrum of the known material.[35]

N-Hexyl-N-[2-(methoxycarbonyl)ethyl]β-alanine methyl ester (12a) [DH-I-100]



11a **12a**

The general procedure of McElvain and Rorig was followed.[36] Methyl acrylate (9.79 mL, 109 mmol, 2.20 equiv) was added in one portion to a stirred solution of hexylamine **11a** (6.53 mL, 49.4 mmol) in MeOH (6.5 mL) at 0 °C. The reaction was allowed to warm up to room temperature, and it was stirred as such for 24 hours. The methanol and excess methyl acrylate were removed on a rotary evaporator, and the residue was passed through a pad of silica (1/1 EtOAc/hexanes) to afford 13.1 g (97%) of **12a** as a colorless oil.

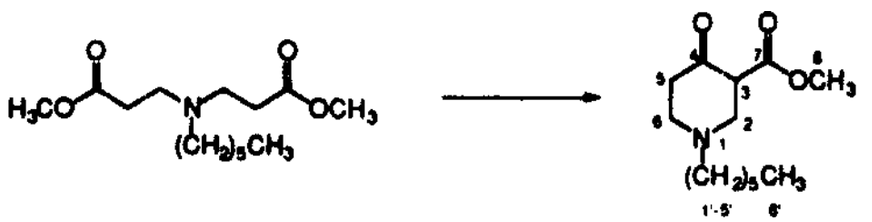
Analytical Data for **12a**

^{1}H NMR: (400 MHz, $CDCl_3$)

3.66 (s, 6 H, $H_3C(4')$), 2.75 (br t, J = 7.2, 4 H, $H_2C(2')$), 2.43 (t, J = 7.1, 4 H, $H_2C(1')$), 2.38 (t, J = 7.4, 2 H, $H_2C(1)$), 1.41-1.38 (br m, 2 H, $H_2C(2)$), 1.29-1.24 (br m, 6 H, $H_2C(3,4,5)$), 0.87 (br t, J = 6.6, 3 H, $H_3C(6)$).

TLC: R_f 0.55 (1/1 EtOAc/hexanes)

1-(1-Hexyl)-3-carbomethoxy-4-piperidone (13a) [DH-II-8]



12a **13a**

The general method of McElvain and Rorig.[36] was followed. To a stirred suspension of oil-free NaH (2.57 g, 107 mmol, 2.25 equiv) in benzene (75 mL) was added the diester **12a** (13.0 g, 47.6 mmol). The mixture was warmed to 32 °C until the reaction initiated as evidenced by the evolution of H_2. After 30

minutes, the evolution of H_2 had decreased, and the reaction was heated to reflux for 7 hours. The reaction was quenched by cooling on ice and carefully adding 6.1 mL of glacial acetic acid. The hydrate of acetic acid was precipitated out by the addition of 5.9 mL of H_2O. The mixture was filtered through a pad of celite, dried (K_2CO_3), filtered, and concentrated in vacuo. The resulting residue was passed through a pad of silica (1/2 EtOAc/Hexanes) and concentrated in vacuo to afford 9.94 g (86%) of **13a** as a slightly yellow oil.

Analytical Data for 13a

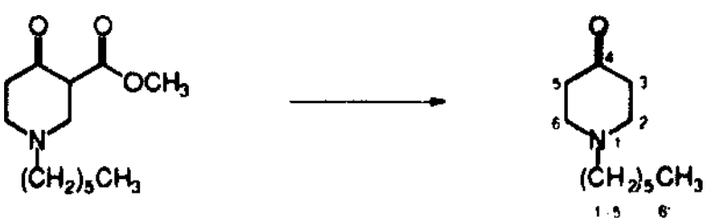
bp: 165 °C (0.2 torr) (air bath temperature)

^{1}H NMR: (300 MHz, $CDCl_3$)

3.70 (s, 3 H, $H_3C(8)$), 3.05 (s, 2 H, $H_2C(2)$), 2.58 (t, 2 H, $H_2C(5)$), 2.41-2.30 (m, 4 H, $H_2C(6)$, $H_2C(1')$), 1.50-1.38 (br m, 2 H, $H_2C(2')$), 1.25 (br s, 6 H, $H_2C(3',4',5')$), 0.88-0.78 (br m, 2 H, $H_3C(6')$).

TLC: R_f 0.52 (hexanes/EtOAc 1/1)

1-(ß-Hexyl)-4-piperidone (14a) [DH-II-9]



13a **14a**

The general procedure of McElvain and Rorig was followed.[36] The ß-keto ester **13a** (11.0 g, 45.4 mmol) was dissolved in 2.4 N aqueous HCl (30 mL) and heated to reflux for 16 1/2 hours. The solution was made slightly basic by addition of saturated $NaHCO_3$, at which time the solution began to get cloudy. Solid NaCl was added to salt out the product. The aqueous phase was extracted with TBME (8x), and NaCl was added until the aqueous layer ceased to become cloudy. The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo. The residue was passed through a pad of silica (2/1 EtOAc/hexanes) and distilled bulb to bulb in vacuo to afford 4.92 g (65%) of **14a** as a colorless oil.

Analytical Data for 14a

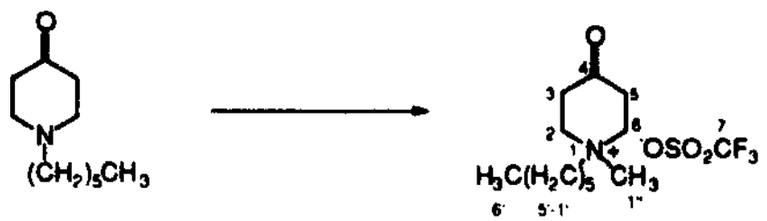
bp: 120 °C (0.2 torr) (air bath temperature)

^{1}H NMR: (300 MHz, $CDCl_3$)

2.73 (t, J = 6.1 4 H, $H_2C(3,5)$), 2.47-2.40 (m, 6 H, $H_2C(2,6,1')$), 1.53-1.49 (m, 2 H, $H_2C(2')$), 1.34-1.29 (m, 6 H, $H_2C(3',4',5')$), 0.88 (t, J = 6.6, 3 H $H_3C(6)$).

TLC: R_f 0.30 (hexanes/EtOAc 1/1)

4-Oxo-1-hexyl-1-methylpiperidinium Trifluoromethanesulfonate (15a) [DH-II-12]



14a **15a**

To an ice cold solution of the N-hexyl-piperidone **14a** (1.50 g, 8.18 mmol) in CH_2Cl_2 (36 mL) was added methyl trifloromethanesulfonate (1.31 mL, 11.6 mmol, 1.42 equiv) in one portion. The reaction was allowed to warm up to room temperature and was stirred as such for 4 hours. The product was concentrated in vacuo to afford white crystals which were recrystallized (hexanes/EtOAc) to afford 2.64 g (93%) of **15a** as a white solid.

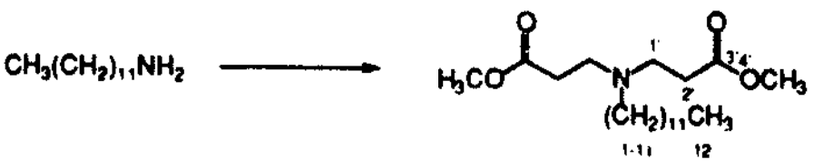
Analytical Data for 15a

mp: 115-116 °C

^{1}H NMR: (400 MHz, acetone-d_6)

4.04 (t, J = 6.7, 4 H, $H_2C(3,5)$), 3.81-3.77 (m, 2 H, $H_2C(1')$), 3.50 (s, 3 H, $H_3C(1'')$), 2.97-2.84 (br m, 4 H, $H_2C(2,6)$), 2.02-1.96 (m, 2 H, $H_2C(2')$), 1.50-1.32 (m, 6 H, $H_2C(3',4',5')$), 0.89 (t, J = 7.1, 3 H, $H_3C(6')$).

N-Dodecyl-N-[2-(methoxycarbonyl)ethyl]ß-alanine methyl ester(12b) [DH-II-15]



11b **12b**

To an ice cold solution of dodecylamine **11b** (9.27 g, 50.0 mmol) in MeOH (7 mL) was added methyl acrylate (9.91 mL, 110 mmol, 2.20 equiv) in one portion. The reaction was allowed to warm up to room temperature and was stirred as such for 24 hours. The product was concentrated in vacuo, divided into two equal portions, and passed through pads of silica (1/2 EtOAc/hexanes) to afford 17.5 g (98%) of **12b** as a colorless oil. A small portion was further purified by flash column chromatography and bulb to bulb distillation to afford analytically pure material.

Analytical Data for **12b**

bp: 250 °C (0.2 torr) (air bath temperature)

^{1}H NMR: (400 MHz, $CDCl_3$)

3.66 (s, 6 H, $H_3C(4')$), 2.75 (br t, J = 7.0, 4 H, $H_2C(2')$), 2.43 (br t, J = 7.1, 4 H, $H_2C(1')$), 2.38 (br t, J = 7.2, 2 H, $H_2C(1)$), 1.41-1.36 (br s, 2 H, $H_2C(2)$), 1.25 (br s, 18 H, $H_2C(3\text{-}11)$), 0.87 (br t, J = 6.7, 3 H, $H_3C(12)$).

^{13}C NMR: (100.6 MHz, $CDCl_3$)

172.92 (C(3')), 53.62 (C(1)), 51.34 (C(4')), 49.05 (C(1')), 32.33 (C(2')), 31.75 (CH_2), 29.51 (CH_2), 29.48 (CH_2), 29.41 (CH_2), 29.19 (CH_2), 27.18 (CH_2), 26.93 (CH_2), 25.53 (CH_2), 13.95 (CH_3).

IR: (Thin film)

2924 (s), 2853 (s), 1740 (s), 1462 (s), 1437 (s), 1356 (m), 1323 (m), 1200 (s), 1172 (s), 1045 (m), 891 (w), 841 (w), 785 (w), 722 (w).

MS: (10 eV)

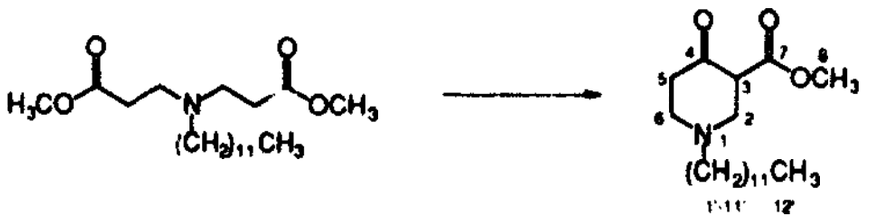
357 (M^+, 5), 284 (23), 203 (13), 202 (100).

TLC: R_f 0.26 (EtOAc/hexanes 1/3)

Analysis: $C_{20}H_{39}NO_4$ (MW 357.54)

Calcd:	C, 67.19	H, 10.99	N, 3.92
Found:	C, 66.91	H, 10.92	N, 3.90

1-(1-Dodecyl)-3-carbomethoxy-4-piperidone (13b) [DH-II-20]



12b **13b**

The general procedure of McElvain and Rorig was followed.[36] To a stirred suspension of oil-free NaH (2.57 g, 107 mmol, 2.25 equiv) in benzene (75 mL) was added the diester **12b** (17.0 g, 47.5 mmol) as follows. About 1 mL was added, and the mixture was heated to 40 °C. 200 μL of MeOH were added to initiate the reaction, as evidenced by a slight reflux with the evolution of hydrogen. The remainder of the diester was added at such a rate as to maintain a gentle reflux. The reaction was then heated to reflux for 4 hours and quenched by the addition of glacial acetic acid (6.1 mL). The hydrate of acetic acid was precipitated out by the addition of 5.9 mL of H_2O. The mixture was passed through a pad of Celite, dried (K_2CO_3), and concentrated in vacuo. The resulting residue was divided into two equal portions and passed through a pad of silica (1/2 EtOAc/hexanes) to afford 12.87 g (83%) of **13b** as a slightly yellow oil which crystallizes in the freezer. A small portion was further purified by flash column chromatography (hexanes/EtOAc 3/1) to afford the analytically pure material.

Analytical Data for **13b**

^{1}H NMR: (400 MHz, $CDCl_3$)

3.75 (s, 3 H, $H_3C(8)$), 3.14 (br s, 2 H, $H_2C(2)$), 2.63-2.56 (br m, 2 H, $H_2C(5)$), 2.49-2.44 (br m, 4 H, $H_2C(6,1')$). 1.53-1.51 (br m, 2 H, $H_2C(2')$), 1.28-1.25 (br m, 18 H, $H_2C(3'-11')$), 0.87 (br t, J = 6.8, 3 H, $H_3C(12')$).

^{13}C NMR: (100.6 MHz, $CDCl_3$)

204.00 (C(4)), 171.20 (CO), 170.20 (CO), 169.15 (CO), 96.50 (C(3) enol), 57.90, 56.94, 56.20 (C(3)), 54.96, 53.28, 52.08 (C(8)), 51.20 (C(8)), 49.63, 49.21, 40.57, 31.76, 29.51, 29.49, 29.47, 29.44, 29.35, 29.26, 29.20, 27.37, 27.20, 27.13, 22.53, 13.98 (C(12')).

IR: (Thin film)

2915 (s), 2855(s), 2811(s), 1750 (m), 1725(m), 1667 (s), 1626 (s), 1443 (s), 1418 (m), 1360 (s), 1308 (s), 1235 (s), 1194 (s), 1136 (s), 1071 (m), 1051 (m), 995 (w), 961 (m), 884 (m), 816 (s), 722 (w).

MS: (70 eV)

325 (M+, 2.4), 170 (100), 138 (51), 43 (12), 42 (21), 41 (11).

TLC: R_f 0.30 (EtOAc/hexanes 1/1)

Analysis: $C_{19}H_{35}NO_3$ (MW 325.50)

Calcd:	C, 70.11	H, 10.84	N, 4.30
Found:	C, 70.06	H, 10.86	N, 4.32

N-(1-Dodecyl)-4-piperidone (14b) [DH-II-21]

13b 14b

The general procedure of McElvain and Rorig was followed.[36] The β-keto ester 13b was added to 50 mL aqueous HCl (2.4 N). Upon heating, the white solid dissolved to give a cloudy solution. The reaction was refluxed for 15 hours. The solution was brought to pH 8 by addition of saturated $NaHCO_3$ which caused a white solid to precipitate out. The aqueous layer was extracted with TBME (3 x 150 mL), and the combined organic layers were dried (K_2CO_3), filtered through a pad of Celite, and concentrated in vacuo. The resulting residue was passed through a pad of silica (EtOAc) and distilled bulb to bulb to afford 8.04 g (82%) of 14b as a colorless oil which crystallized on cooling. A small portion was further purified by flash column chromatography and bulb to bulb distillation to afford analytically pure material.

Analytical Data for 14b

bp: 155 °C (0.2 torr) (air bath temperature)

^{1}H NMR: (300 MHz, $CDCl_3$)

2.74 (br s, 4 H, $H_2C(3,5)$), 2.46 (br s, 6 H, $H_2C(2,6,1')$), 1.52 (br s, 2 H, $H_2C(2')$), 1.29-1.19 (m, 18 H, $H_2C(3'\text{-}11')$), 0.88 (t, J = 6.6, 3 H, $H_3C(12')$).

^{13}C NMR: (100.6MHz, $CDCl_3$)

209.23 (C(4)), 57.48 (C(2,6)), 53.01 (C(1')), 41.10 (C(3,5)), 31.77, 29.51, 29.29, 29.47, 29.44, 29.40, 29.21, 27.37, 27.33, 22.54, 13.99 (C(12')).

IR: (Thin film)

2926 (s), 2853 (s), 2807 (m), 1723 (s), 1466 (m), 1412 (w), 1325 (w), 1375 (m), 1350 (m), 1221 (m), 1132 (m), 1084 (w), 1009 (w), 762 (w), 722 (w).

MS: (70 eV)

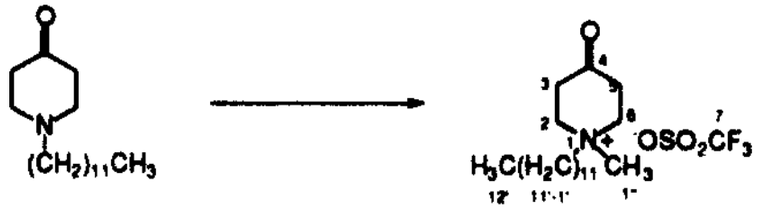
267 (M^+, 1.3), 113 (7), 112 (100), 91 (11), 43 (9), 42 (16), 41 (8).

TLC: R_f 0.38 (EtOAc/hexanes 3/1)

Analysis: $C_{17}H_{33}NO$ (MW 267.46)

Calcd:	C, 76.34	H, 12.44	N, 5.24
Found:	C, 76.35	H, 12.49	N, 5.19

4-Oxo-1-(1-dodecyl)-1-methylpiperidinium Trifluoromethanesulfonate (15b) [DH-II-23]



14b **15b**

To an ice cold solution of the N-(1-dodecyl)piperidone **14b** (4.00 g, 15.0 mmol) in CH_2Cl_2 (65 mL) was added methyl trifloromethanesulfonate (2.39 mL, 21.1 mmol, 1.41 equiv) in one portion. After 10 minutes, a white precipitate appeared which dissolved upon warming to room temperature. The reaction was stirred at room temperature for 4 hours. The product was concentrated in vacuo to afford white crystals which were recrystallized (hexanes/EtOAc 2/1) to afford 6.22 g (96%) of analytically pure **15b** as a white solid.

Analytical Data for 15b

mp: 168-169 °C

^{1}H NMR: (400 MHz, d_6-acetone)

4.05 (t, J = 6.6, 4 H, $H_2C(3,5)$), 3.80 (m, 2 H, $H_2C(1')$), 3.51 (s, 3 H, $H_3C(1'')$), 2.95-2.84 (m, 4 H, $H_2C(2,6)$), 2.01 (m, 2 H, $H_2C(2')$), 1.49-1.38 (br m, 4 H, $H_2C(3',4')$), 1.28 (br s, 14 H, $H_2C(5'$-$11')$), 0.87 (t, J = 6.8 3 H, $H_3C(12')$).

^{13}C NMR: (100.6 MHz, d_6-acetone)

199.81 (C(4)), 121.13 (d, J = 322, F_3C), 63.17 (C(1')), 58.93 (C(2,6)), 47.46 (C(1'') or CH_2), 34.78 (C(3,5)), 31.61 (CH_2), 29.34 (CH_2), 29.24 (CH_2), 29.12 (CH_2), 29.06(CH_2), 28.83 (CH_2), 25.93 (CH2), 22.31 (CH_2), 21.95 (CH_2), 13.37 (CH_3).

IR: (KBr))

2921 (s), 2851 (s), 1730 (s), 1468 (m), 1264 (s), 1225 (s), 1165 (s), 1032 (s).

MS: (FAB magic bullet)

282.3 (M^+, 57).

Analysis: $C_{19}F_3H_{36}NO_4S$ (MW 431.56)

Calcd:	C, 52.88	H, 8.41	N, 3.25
Found:	C, 52.92	H, 8.40	N, 3.28

General Procedure for OXONE® Epoxidations

In a 250 mL or 300 mL three neck round bottom flask were placed phosphate buffer (20 mL, pH 7.8), CH_2Cl_2 (17.5 mL), olefin 7 (0.333 g, 1.75 mmol), ketone (as indicated), and tetrabutylammonium hydrogen sulfate (0.0594 g, 0.175 mmol, 0.1 equiv, unless otherwise noted) (except when ketones bearing quaternary ammonium moieties were used). The mixture was cooled on ice, hooked up to the pH-stat, and addition of OXONE® solution was achieved via a syringe pump. The OXONE® stock solution was prepared as a ca. 0.4 M, 1 L aqueous solution stabilized by 0.43 mM EDTA·2Na and titrated by the standard iodometric method (its concentration drops ca. 11% over 9 weeks when stored at ambient temperature). The pH of the reaction was maintained at 7.8 ± 0.2 by automatic addition of 2 N aqueous KOH. The reaction was stirred vigorously at 0-5 °C for 14 hours and then allowed to warm up to room temperature for a total reaction time of 24 hours. The progress of the reaction was monitored at ca. 2 hour intervals by gas chromatography. After 24 hours, the organic layer was drawn off, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and

concentrated in vacuo. The resulting residue was separated into olefin 7 and epoxide 8 components by flash column chromatography (1/8 EtOAc/hexanes). The identity of each component was confirmed by ^1H NMR (200 MHz).

References

(1) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am Chem Soc.* **1987**, *109*, 5765. (b) Reviews: Pfenninger, A. *Synthesis* **1986**, 89. (c) Rossiter, B. E. *Asymmetric Synthesis*; Academic Press, Inc.: Orlando, 1985; Vol. 5, p 193. (d)Finn, M. G.; Sharpless, K. B. *Ibid.*, p. 247. (e) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

(2) Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703-6704, and references therein.

(3) (a) Ewins, R. C.; Henbest, H. B.; McKervey, M. A. *J. Chem. Soc, Chem. Commun.* **1967**, 1085. (b) Pirkle, W.; Rinaldi, R. *J. Org. Chem.* **1977**, *42*, 2020.

(4) Davis, F. A.; Harakal, M. E.; Awad, S. B. *J. Am. Chem. Soc.* **1983**, *105*, 3123.

(5) (a) Kagan, H. B.; Mimoun, H.; Mark, C.; Shuring, V. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 485. (b) Tani, K.; Hanafusa, M.; Otsuka, S. *Tetrahedron Lett .* **1979**, *20*, 3017.

(6) Adam, W.; Curci, R; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205-211.

(7) Edwards, J. O.; Pater, R. H.; Curci, R.; Di Furia, F. *Photochem. and Photobiology* **1979**, *30*, 63-70.

(8) Baeyer, A.; Villiger, V. *Ber. Deut. Chem. Ges.* **1899**, *32*, 3625.

(9) Lovas, F. J.; Suenram, R. D. *Chem. Phys. Lett.* **1977**, *51*, 453-456.

(10) Wadt, W. R.; Goddard, W. A. *J. Am. Chem. Soc.* **1975**, *97*, 3004-3021.

(11) Martinez, R. I.; Huie, R. E.; Herron, J. T. *Chem Phys Lett.* **1977**, *51*, 457.

(12) Sander, W. W. *J. Org. Chem.* **1988**, *53*, 121.

(13) Ishiguro, K.; Hirano, Y.; Sawaki, Y. *J. Org. Chem.* **1988**, *53*, 5397.

(14) Montgomery, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 7820-7821.

(15) Edwards, J. O. *Chem. and Eng. News* **1955**, *33*, 3336.

(16) Ball, D. L.; Edwards, J. O. *J. Am. Chem. Soc.* **1956**, *78*, 1125-1129.

(17) Gallopo, A. R.; Edwards, J. O. *J. Org. Chem.* **1981**, 46, 1684-1688.

(18) Adam, W.; Haas, W.; Sieker, G. *J. Am. Chem. Soc.* **1984**, *106*, 5020-5022.

(19) Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1987**, *52*, 699-700.

(20) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758-4760.

(21) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847-2853.

(22) Murray, R. W.; Singh, Megh, Jeyaraman, R. *J. Am. Chem. Soc.* **1992**, *114*, 1346-1351.

(23) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666.

(24) Gervay, J.; Danishefsky, S. *J. Org. Chem.* **1991**, *56*, 5448-5451.

(25) (a) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3890-3891.
(b) Mello, R.; Fiorentino, M.; Fusco C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749-6757.
(c) Troisi, L.; Cassidie, L. L.; Mello, R.; Curci, R. *Tetrahedron Lett.* **1989**, *30*, 257.

(26) Mello, R.; Ciminale, F.; Fiorentino, M.; Fusco, C.; Prencipe, T.; Curci, R. *Tetrahedron Lett.* **1990**, *31*, 6097-6100.

(27) Bartlett, P. D. *Rec. Chem. Prog.* II, **1950**, 47.

(28) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311-3314.

(29) Bach, R. D.; Andrés, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1992**, *114*, 7207-7217.

(30) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, *155*, 155-156.

(31) Colonna, S.; Gaggero, N. *Tetrahedron Lett.* **1989**, *30*, 6233-6236.

(32) Claisen, *Ber.* **1926**, *59*, 2348.

(33) Prelog, V.; Kobelt, M. *Helv. Chim. Acta.* **1949**, *32*, 1187.

(34) Van Luppen, J. J.; Lepoivre, J. A.; Dommisse, R. A.; Alderweireldt, F. C. *Orgn. Mag. Res.* **1979**, *12*, 399.

(35) Wilde, R. G. *Postdoctoral Report*; Univ. of Illinois: Urbana, IL, 1989.

(36) McElvain, S. M.; Rorig, K. *J. Am. Chem. Soc.* **1948**, *70*, 1820-1828.

(37) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(38) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1980; p 325.

(39) Dappen, M. S. *Ph.D. Thesis*; Univ. of Illinois: Urbana, IL.

(40) Cardwell, H. M. E.; McQuillen, F. J. *J. Chem. Soc.* **1949**, 708-715.