APPROACHES TO THE SYNTHESIS OF QINGHAOSU

by

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A THESIS

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Accepted on behalf of the Faculty of the Graduate School by the Thesis Committee.

DEDICATION

To my wife, Sherry, who by her support, dedication, unselfish sacrifice and love has sustained me through a very difficult period of my life.

ACKNOWLEDGEMENT

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I. INTRODUCTION

A. Historical Background

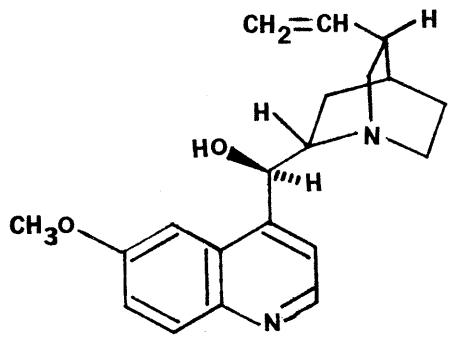
Over three thousand years ago a noted Chinese scholar, Huang Li, spoke of the "paroxysmal manifestations of chill and fever,"[1] the typical symptoms of the disease now known as malaria. In the fifth century B.C., Hippocrates described different kinds of fevers and showed that malaria was common during his time,[2] and in the fourth century B.C. records indicate that Rome had significant problems with malaria.[3] These historical writings show that malaria is in fact one of the oldest diseases known to mankind.

Although Qinghao and Chang Shan, Chinese medicinal herbs, have been used for over 2000 years for treating malaria,[4,5] it was the discovery of Peruvian or cinchona bark in the seventeenth century, that caused great excitement in the medical world. In 1632 Peruvian bark was brought to Spain, but it was not tried medicinally until 1639.[2] Of course, the active ingredient in cinchona bark is the well known anti-malarial drug quinine, which has been used extensively since the 17th century.

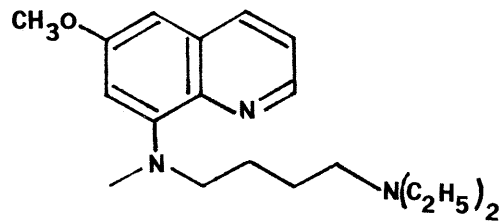
Although quinine (1) had been used for nearly 300 years, its structure was not determined until 1918.[6] The first synthesis of quinine was accomplished by Woodward and Doering in 1944.[7] However, these synthetic methods proved to be too elaborate and too expensive to be of much practical use.

Due to the great demand for cinchona bark, there was extensive harvesting of the cinchona tree, nearly resulting in its complete destruction. The Dutch were foresighted enough to relocate the tree to the island of Java, where it flourished. This relocation, however, became a problem when in World War II the Japanese maintained control of Java, thus gaining almost exclusive control of the world's quinine supply. Add to this the fact that several strains of malaria had shown resistance to quinine and the need for new synthetic anti-malarials was quite evident.

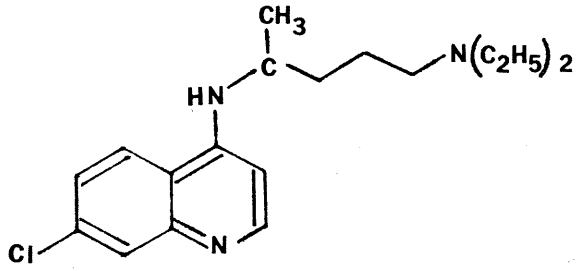
Between the first and second World Wars, Germany, Great Britian and the United States embarked on vigorous programs to develop new synthetic drugs. The Germans were first to synthesize successfully an active anti-malarial, that being plasmodin, later called pamaquine (2). Chloroquine (3) which was first developed in 1939 by the Bayer Co. of Germany,[8a] was initially rejected as being too toxic, but it has since become the most successful synthetic anti-malarial. The initial rejection of chloroquine could partially be attributed to the success



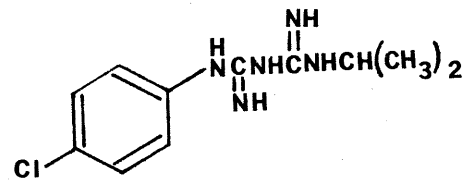
1 (quinine)



2 (pamaquine)



3 (chloroquine)



4 (chloroquanide)

Figure 1. Various anti-malarial compounds.

of the synthetic anti-malarial atabrine. Atabrine was introduced by Mauss and Mietzsch[8b] in 1933 and was one of the most popular drugs used for treating malaria during World War II.

In 1946, chloroquanide (4)[9] was developed in Great Britian, and shortly afterwards in 1947, paludrine, which is the hydrochloride salt of chloroquanide,[10] was synthesized in the United States. Both of these drugs were effective anti-malarials.[3]

With an arsenal of synthetic anti-malarials and various insecticides, there was hope that malaria could be totally eradicated. However, with the discovery of new strains of malaria which were resistent to these synthetic drugs and with the limited availability of many insecticides such as DDT man's fight against the age-old disease has been extended.[3] Malaria is still a leading cause of death in the world, especially in third world, underdeveloped countries of Africa and Southeast Asia. For instance, in 1974 it was reported that in Africa alone, malaria caused the death of about one million infants and children below the age of 14 years.[11a] It is also believed that there may be as many as 300 million cases of malaria per year worldwide.[11b] Therefore, the need for more anti- malarial drugs is again apparent.

In 1971 the antimalarial activity of the ancient Chinese medicinal herb Qinghao was rediscovered. Qinghao was shown to be especially active in the treatment of

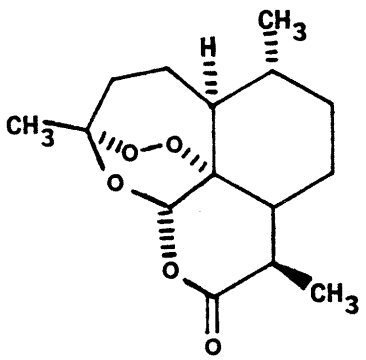


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Figure 2. The anti-malarial, qinghaosu.

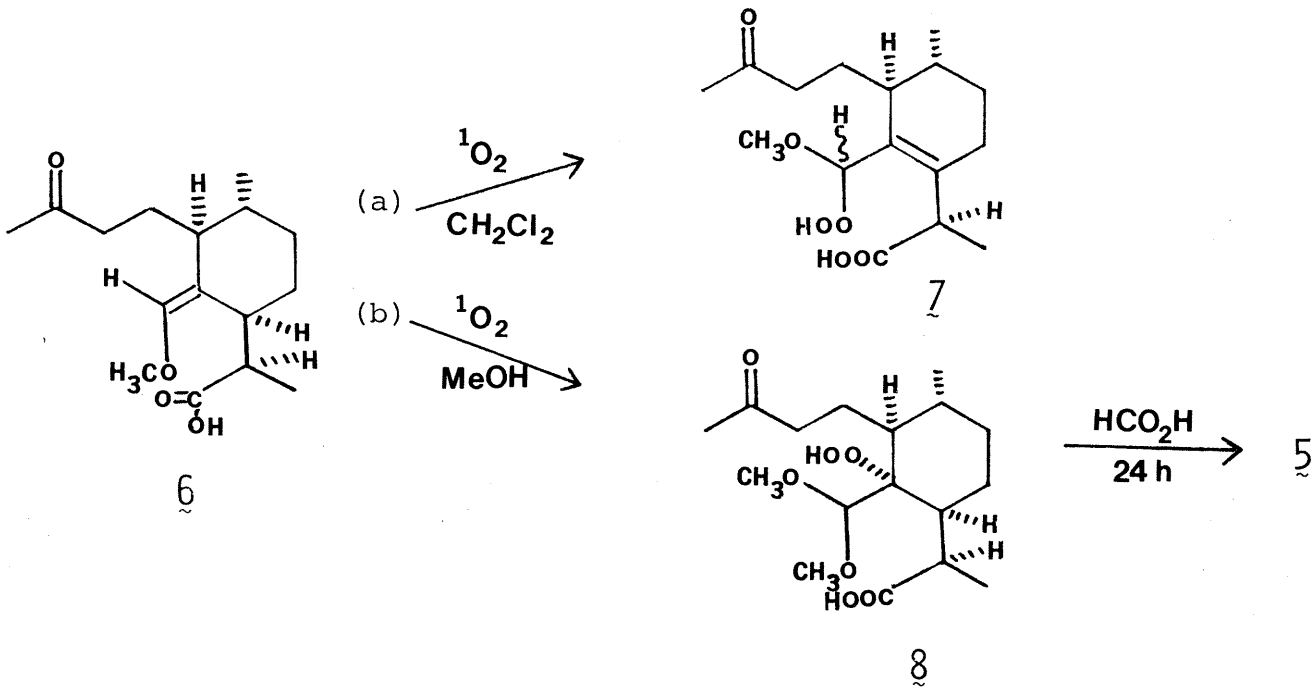
chloroquine-resistant strains of malaria. It would seem that man's search for a cure for an age-old disease has come full circle.

The active anti-malarial component of Qinghao was isolated from Artemisia annua L. in 1972,[4] and named qinghaosu (5). The structure and absolute configuration were established in 1978 using x-ray diffraction.[12]

Clinical trials for qinghaosu were conducted by the Chinese Coordinating Clinical Study Group on Qinghaosu, with more than 2000 cases of malaria being treated. Qinghaosu was used to treat both Plasmodium vivax malaria (1511 cases) and Plasmodium falciparum malaria (558 cases). In addition to these, 143 cases of chloroquine-resistant falciparum malaria and 141 cases of cerebral malaria were treated. All patients with P. falciparum and P. vivax malaria were reported as clinically cured, and good therapuetic effects were obtained in the remaining cases of malaria.[4]

B. The Original Synthesis of Qinghaosu.

In 1983, Schmid and Hofheinz reported the total synthesis of qinghaosu.[13] Beginning with (-)-isopulegol, Schmid and Hofheinz obtained the enol ether/carboxylic acid (6). Compound 6 was photo-oxygenated using singlet oxygen (methylene blue, CH_2Cl_2, room temperature) in an ene reaction to obtain the hydroperoxide 7.



Scheme I. Synthesis of qinghaosu.[13]

Compound 6 was converted to 7, to establish the double bond configuration of compound 6. Had the vinyl hydrogen and methoxy substituents been in the opposite configuration in 6, the double bond in 7 would have been in the other direction. This analysis was possible due to the cis-directing effects of methoxy groups on the ene reaction.[12a] When compound 6 was reacted with $^1O_2$ at -78°C (Scheme I(b)) in methylene blue and methanol, the hydroperoxide function was introduced at carbon 3 giving a mixture of products. It was assumed that 8 was the major product, and subsequent treatment of the crude mixture of oxygenation products with formic acid at 0°C for 24 hours in CH_2Cl_2 gave crystalline qinghaosu (5) in 30% yield.

II. STATEMENT OF THE PROBLEM

The object of this research was to develop new syntheses of bicyclic peroxides and to apply these new methods to the total synthesis of qinghaosu (Arteannuin A), a previously reported anti-malarial compound.[4] Qinghaosu has shown clinical activity in humans against chloroquine-resistant strains of malaria. The most challenging feature of qinghaosu, and the biologically active portion of the compound was the peroxide bridge.

Two routes to the bicyclic peroxide were studied:

(1) the ring opening of an epoxy ketone by peroxide followed by ring closure (Figure 3) and

(2) the intramolecular reaction of α-trimethylsilyl peroxy esters with a ketal to obtain ring closure (Figure 4).

The intent was to provide molecules with a biologically relevant piece of the target molecule which could themselves be evaluated as potential anti-malarials.

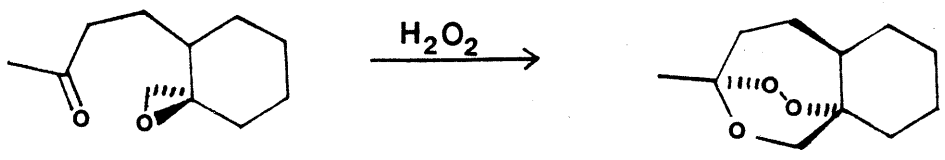


Figure 3. Conversion of an unsaturated oxirane to a cyclic peroxide.

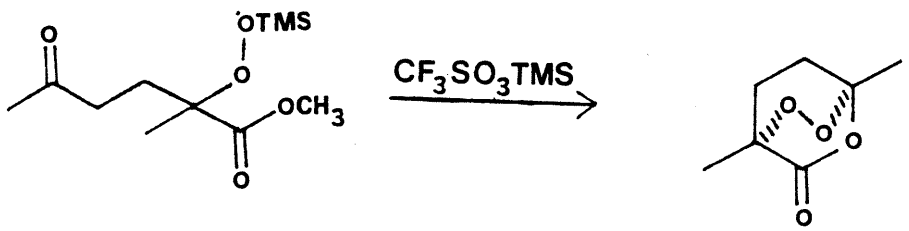
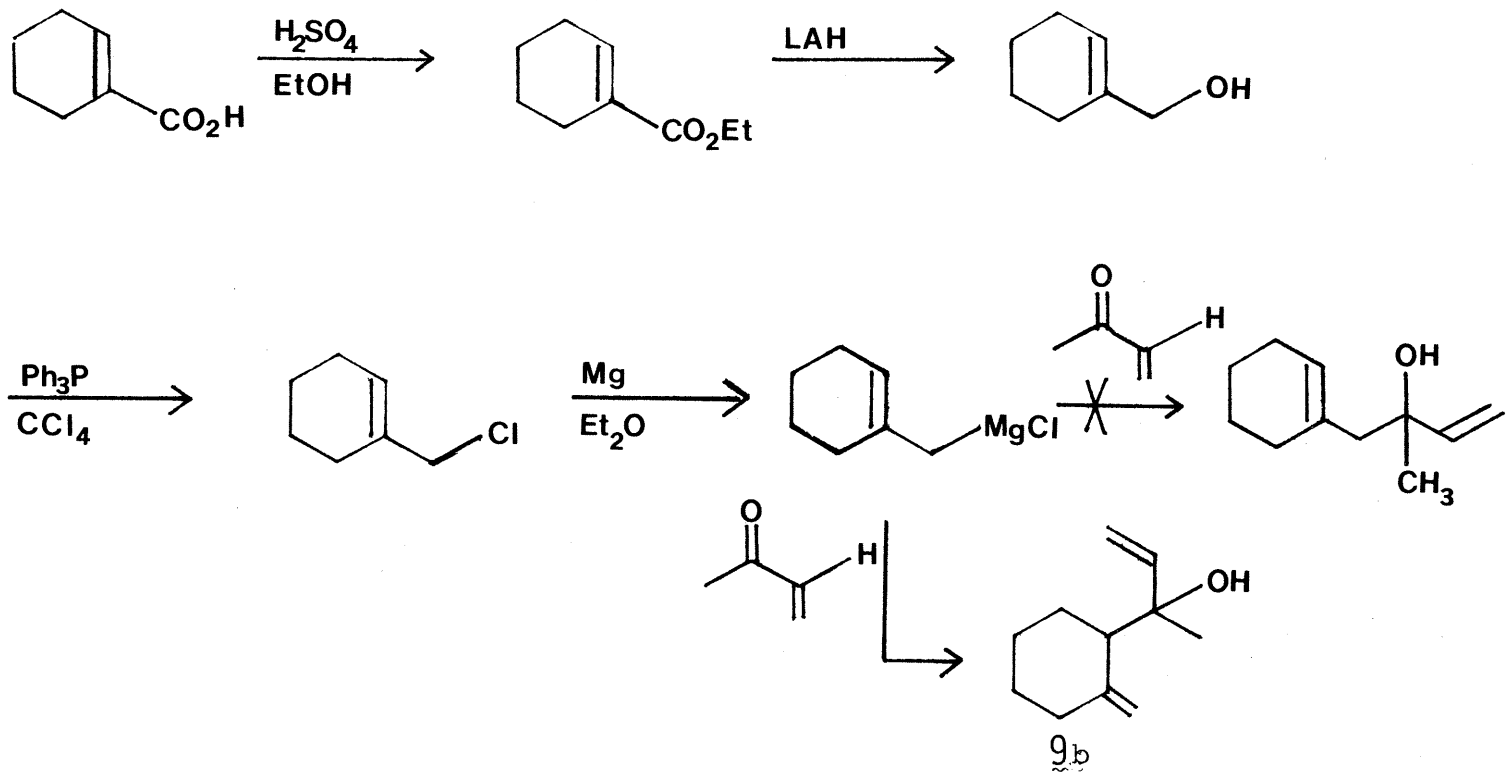


Figure 4. Conversion of keto-α-peroxy esters to 1,2,4-trioxan-5-one.

III. RESULTS AND DISCUSSION

Initial attempts to synthesize a bicyclic peroxide involved the esterification of commercially available 1-cyclohexene carboxylic acid and subsequent reduction to the alcohol using lithium aluminum hydride (LAH) (Scheme II). The allylic alcohol obtained in the previous reduction was converted to the halide and then to the corresponding Grignard reagent. Attempts to prepare both the chloride and bromide, using $SOCl_2$ and PBr_3, respectively, consistently resulted in allylic rearrangment. For these reasons triphenylphosphine (Ph_3P) and CCl_4 were utilized to prepare the chloride in good yield. Having obtained the desired halide and consequently the desired allylic Grignard reagent, attempts were made to add it to methyl vinyl ketone. However, rather than the desired Grignard reaction occurring to give an alcohol which could then undergo an alkoxide accelerated Cope rearrangement, the product was consistently alcohol 9b (Scheme II), as evidenced by ^1H NMR.

Failure of the Grignard of chloromethyl-1-cyclohexene to add to methyl vinyl ketone in the desired orientation necessitated investigation of an alternative route to the synthesis of the desired unsaturated ketone. Alkylation of

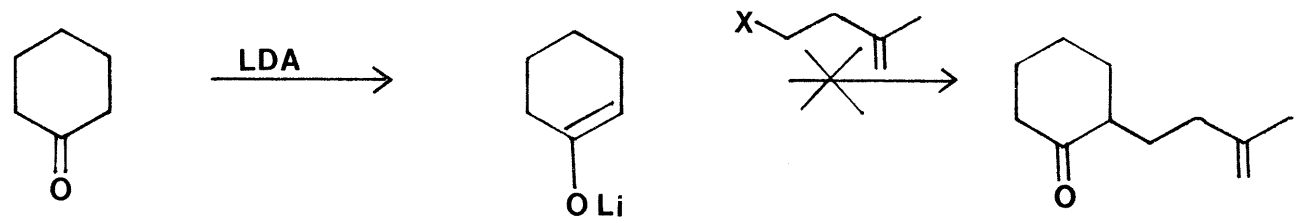


Scheme II. Proposed synthesis of 1-[2-hydroxy-2-methylbut-3-en-1-yl]-cyclohexene.

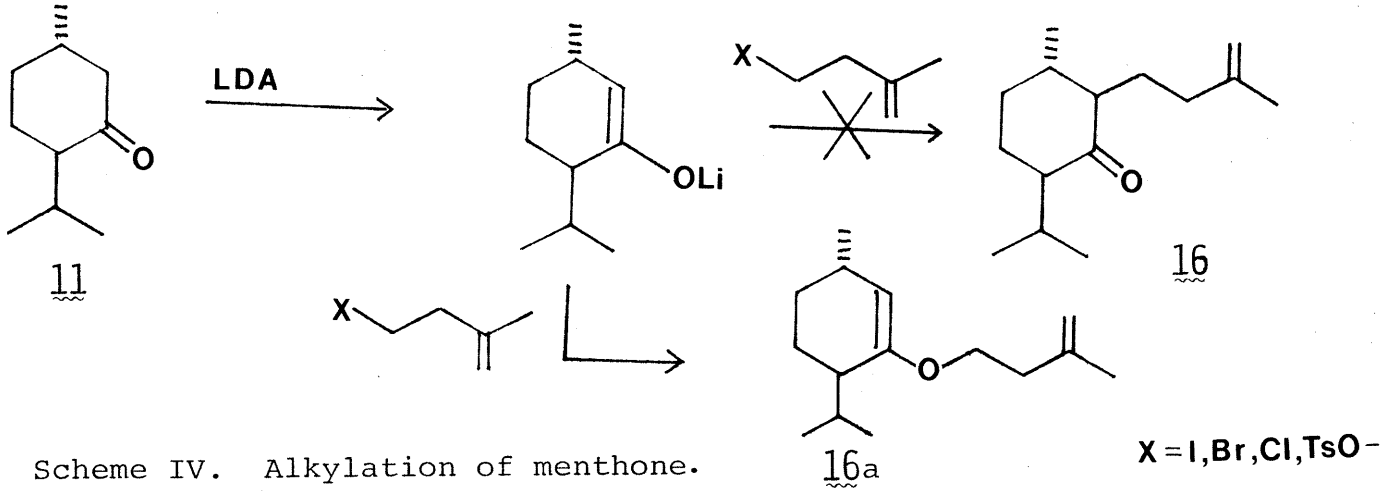
cyclohexanone was attempted by forming the enolate, lithium using diisopropyl amide in tetrahydrofuran (THF), and treating that with the appropriate halide (Scheme III). This reaction also failed to give the desired unsaturated ketone.

Having no success with cyclohexanone, the next system studied was that of menthone (11), which is readily available from chromic acid oxidation of menthol.[23] Alkylation of this unsymmetrical ketone required formation of the kinetic enolate, which was obtained by slowly adding the menthone to an excess of base (lithium diisopropylamide) in THF (Scheme IV). Again difficulties were encountered when trying to alkylate the enolate species. To make certain that the enolate was actually being formed and that addition was in fact possible, the trivial experiment of alkylating with n-butylbromide was done successfully.

Success with alkylation using n-butylbromide encouraged attempts to alkylate with the desired unsaturated alkyl substituent. When none of the alkyl halides resulted in an alkylation product, the alkyl tosylate was made and initial success was believed to have been obtained. However, closer examination of the ^{1}H NMR spectrum indicated that alkylation was not occurring at the α-carbon but rather at the oxygen atom. One would expect the methylene attached the oxygen in the tosylate to shift significantly upfield once attached to a carbon. However, the ^{1}H NMR showed that little or no shift occured, indicating it was still attached to oxygen.



Scheme III. Alkylation of cyclohexanone.

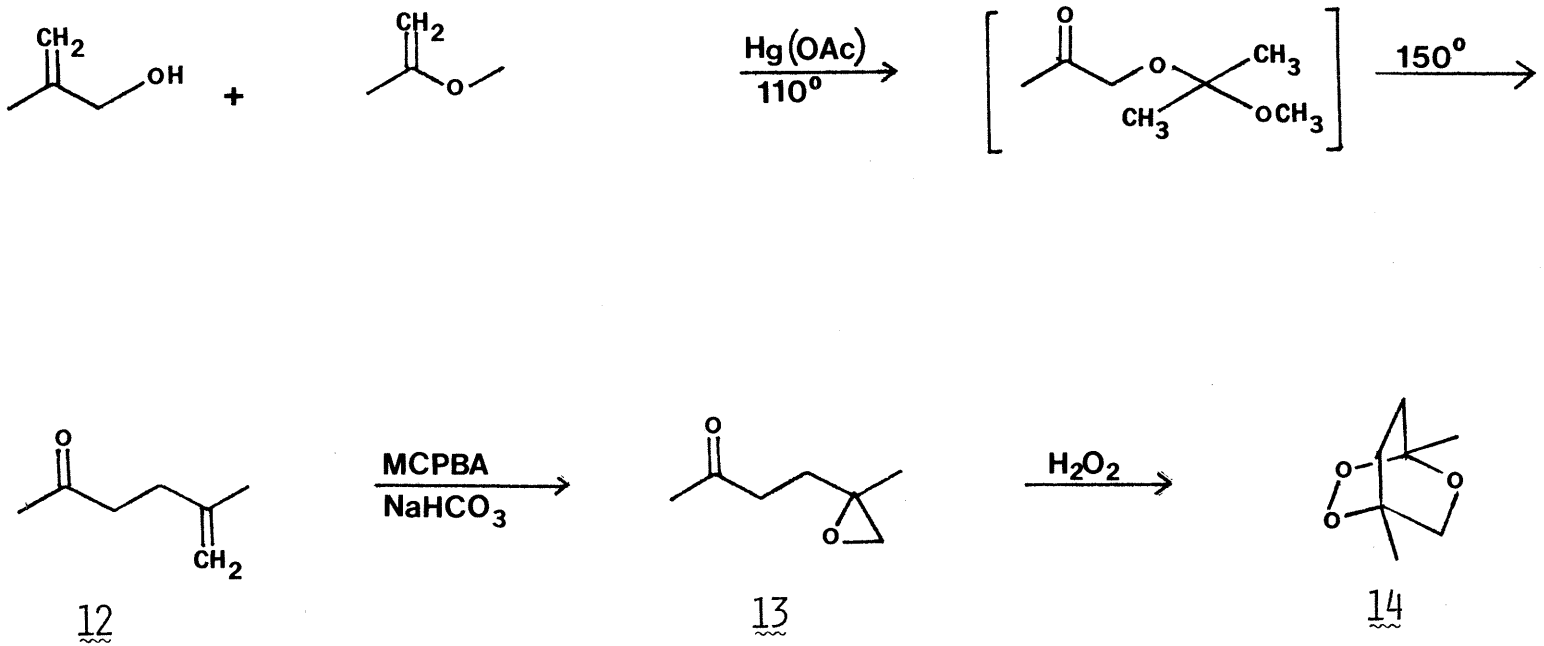


Scheme IV. Alkylation of menthone.

Discouraged by the failure to obtain the desired unsaturated ketones through a Grignard reaction or by alkylation, attention was turned to synthesizing the six-membered analoque of the bicyclic peroxide of 5, using a simpler unsaturated ketone system. These studies were done using a γ,δ-unsaturated ketone, as prepared by an unpublished method of McKenzie, following work of Saucy[15] and Carnduff.[16]

Methallyl alcohol was converted to 5-oxo-2-methylhex-1-ene (12) in a Claisen rearrangement by heating it in a sealed tube overnight at 150°C with 2-methoxypropene, mercuric acetate, and a small amount of hydroquinone to prevent polymerization. The olefin was cleanly epoxidized to 13 with m-chloroperbenzoic acid in a two-phase aqueous sodium bicarbonate-methylene chloride system. It was hoped that treatment of the epoxide with 90% hydrogen peroxide in THF would induce epoxide opening and subsequent ring closure to compound 14 (Scheme V). However, no epoxide opening was ever induced, not even with the addition of small amounts of magnesium sulfate.

At this point attention was turned to the possibility of forming an oxirane by transferring a methylene group to the carbonyl function of 12 and obtaining bicyclic ring formation in the manner shown in Scheme VI. It was believed that epoxidation of the γ,δ-unsaturated ketone 12 to the epoxide 13 and subsequent ozonolysis and trapping of the ozonide (15) would yield the bicyclic peroxide. Ozonolysis



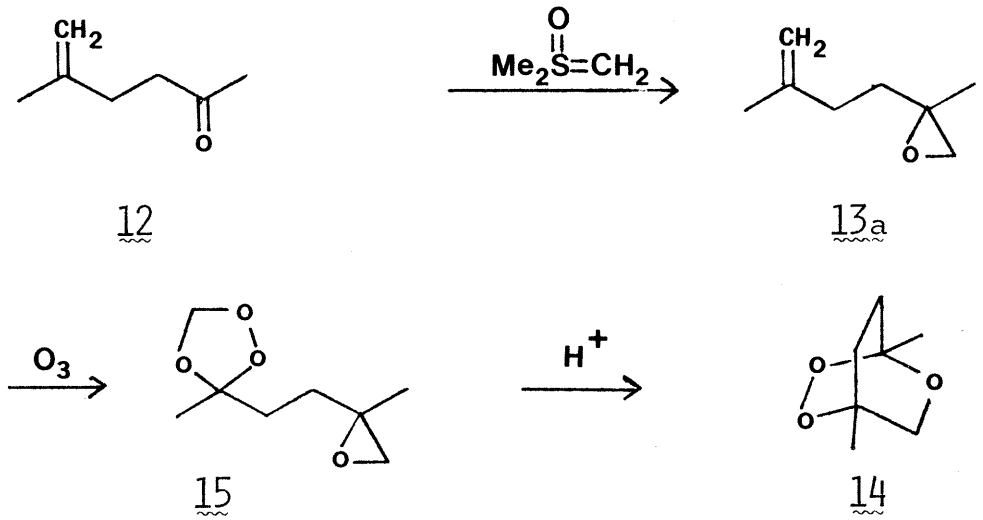
12 13 14

Scheme V. Proposed synthesis of 3,6-dimethyl-3,6-ethano-1,2,4-trioxane.

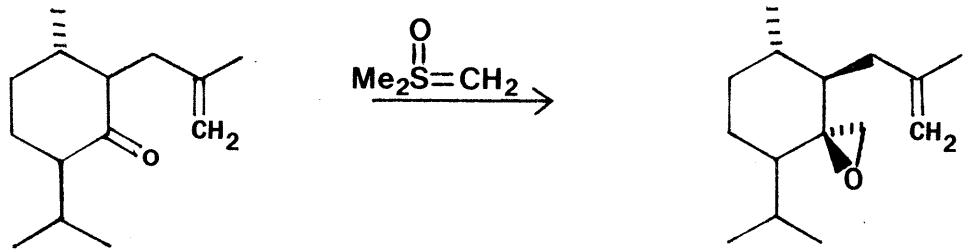
of olefins in alcohol solution yields a peroxy hemiketal and, the reaction attempted in Scheme VI is an analogous reaction. In the system shown in Scheme VI, stereochemistry presented no problems; however, due consideration was given to this eventual problem. In a system such as 16 (Scheme VII), which was one of the goals of this research, the stereochemistry would have to be considered. For this reason an epoxidation method was used which would be sensitive to steric effects and which would give the epoxide that was cis to the allylic side chain in compound 16.

The method chosen for forming an epoxide from 16, was that of Corey and Chaykovsky.[19] Since the epoxide cis to the allylic side chain of compound 16 was desired, then dimethylsulfoxonium methylide was used to deliver the methylene group in the equatorial position. It was necessary to have the epoxide cis to the allylic side chain, because using the epoxide with oxygen trans to the allylic side chain would eventually give 17 (Scheme VIII), which has the opposite configuration of the peroxide bridge found in the natural product (i.e. the cis peroxide).

Forming an oxirane from 12 was done in good yield (66%), and isolation of ozonide 15 was also accomplished in good yields (76%). However, attempts to initiate epoxide opening was a more difficult problem. A variety of both mineral and Lewis acids (HCl, H_2SO_4, $SnCl_4$, BF_3) was used to initiate the ring opening. However, these resulted in vigorous, exothermic reaction, giving only a



Scheme VI. Proposed synthesis of 3,6-dimethyl-3,6-ethano-1,2,4-trioxane through ozonolysis.



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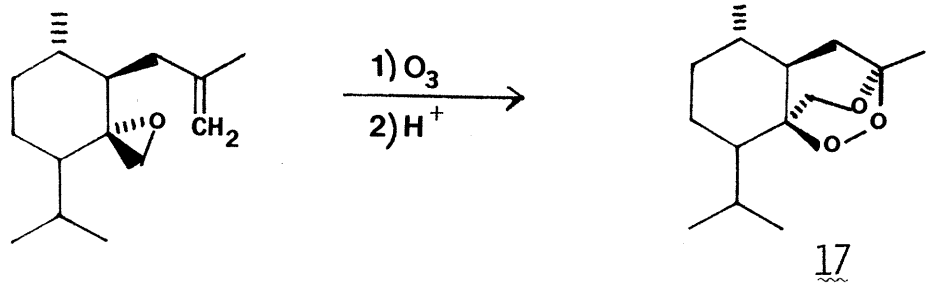
Scheme VII. Formation of cis-epoxide using dimethylsulfoxonium ylide.



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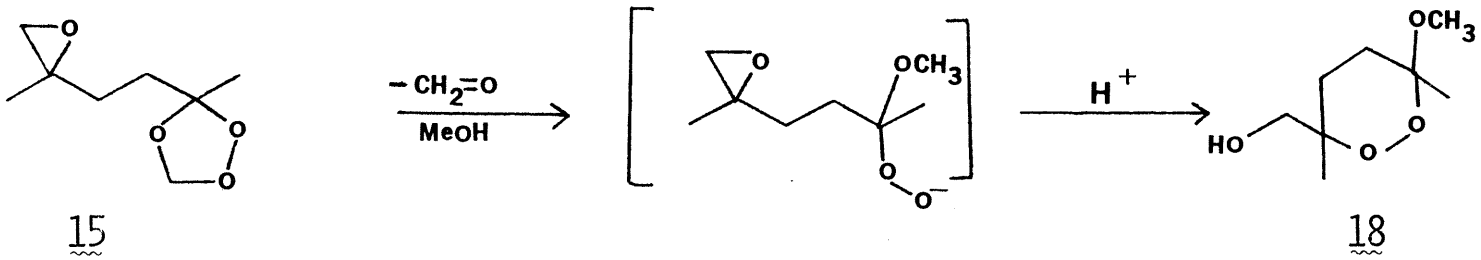
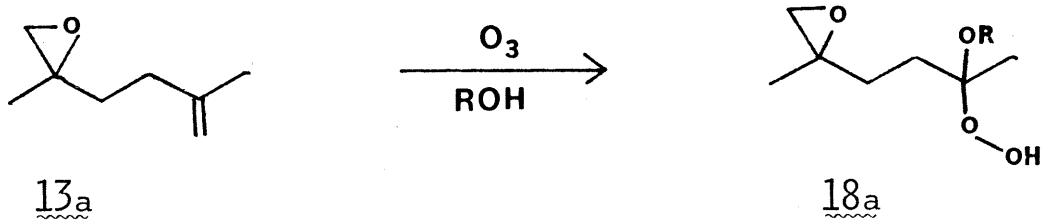
Scheme VIII. Conversion of trans-epoxide to cis-peroxide.



Scheme IX. Proposed mechanism of ozonide ring opening and peroxide ring closure.



R= CH_3-, CH_3CH_2-, CH_3CO-

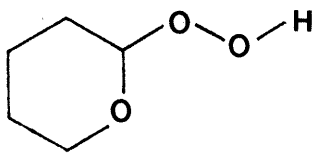
Scheme X. Trapping ozonides with various solvents.

black tar. The bicyclic peroxide was never isolated. Apparently the reaction took the course outlined in Scheme IX. The exact mechanism for this reaction was not elucidated, but to confirm our suspicions, we attempted the synthesis of some 1,2-dioxane compounds.

Following work done by Criegee[25] the olefinic-oxirane 13a was subjected to ozonolysis at -65°C in the appropriate solvent (CH_3OH, CH_3CH_2OH, or CH_2Cl_2/acetic acid), giving either an alkyloxy- or acyloxy- peroxide (Scheme X). It was hoped that subsequent treatment of these trapped peroxides with an acid would initiate epoxide opening and ring closure to the desired bicyclic peroxide or at least the analagous 1,2-dioxane. Although ^1H NMR indicated that some of the 1,2-dioxane may have been made, no evidence of the bicyclic peroxide could be found.

At this point there was some doubt whether ring formation through ozonolysis could be achieved at all. Therefore, a brief study in single ring closure was undertaken. Two systems were used for this study: 1-hexen-6-ol and 1-penten-5-ol. Both of these systems were subjected to ozonolysis at -60°C and gave good yields of the respective -hydroperoxy cyclic ethers shown in Figure 5 (90% of 19 and 51% of 20 respectively). However, subsequent attempts to obtain the bicyclic peroxides through ozonolysis and acid treatment gave no positive results.

At this point attention was turned to some work done by Jefford,[24] where TMS-triflate was used in an intermole-



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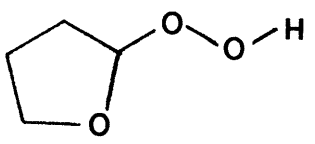

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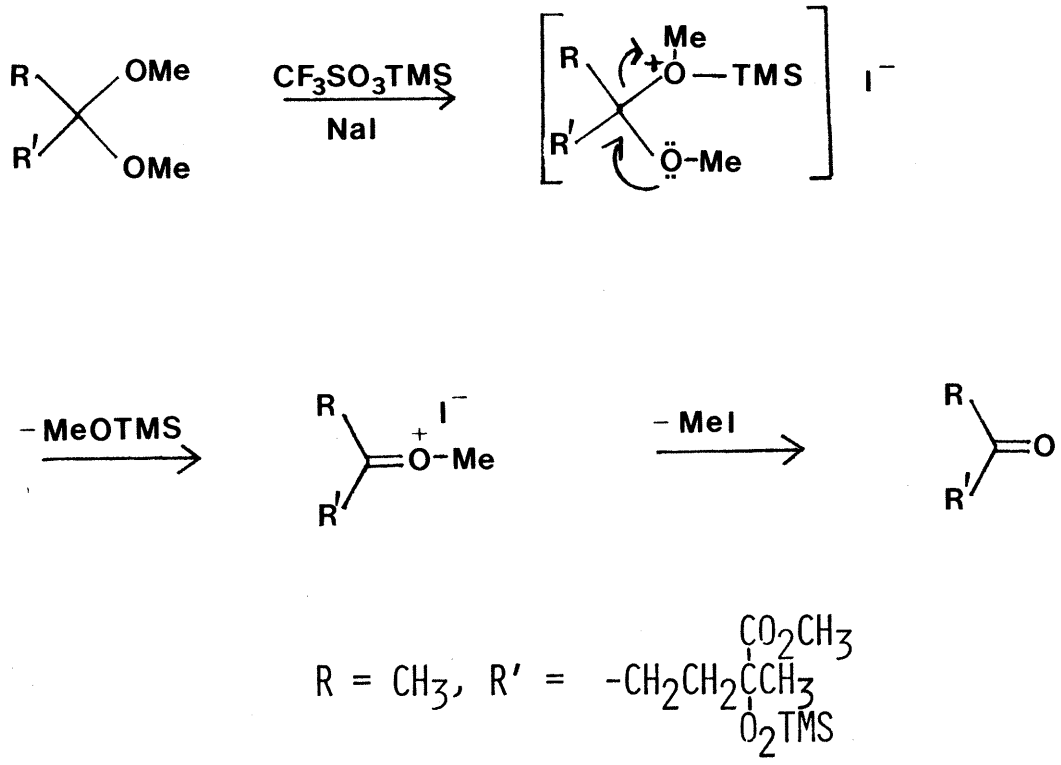
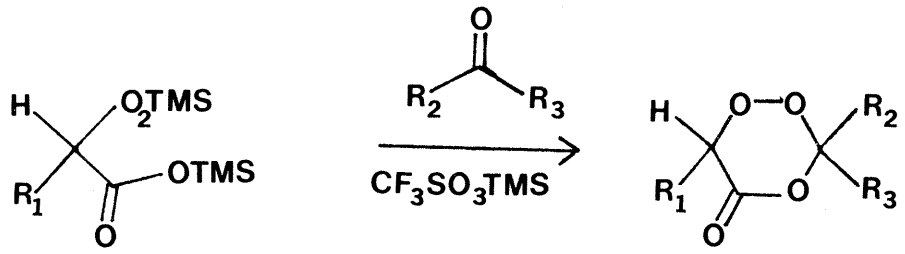
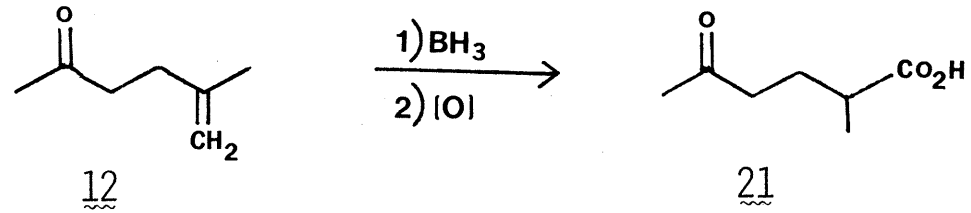
Figure 5. α-Hydroperoxy cyclic ethers.



Scheme XI. Proposed mechanism for TMS-triflate cleavage of ketals to ketones.



Scheme XII. Synthesis of 1,2,4-trioxan-5-ones.[24]

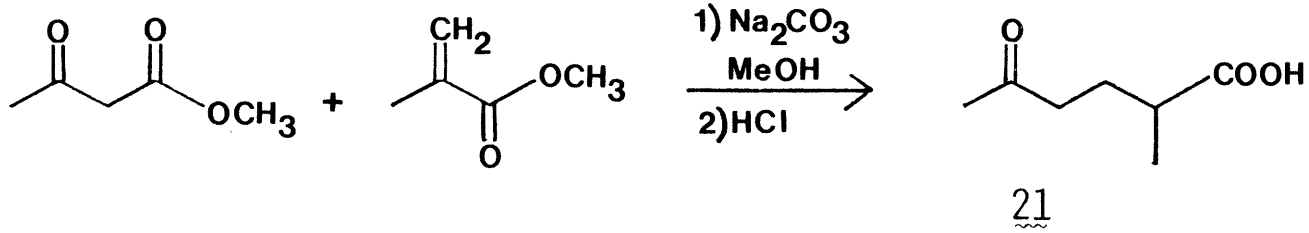


12 21

Scheme XIII. Preparation of 5-oxo-2-methylhexanoic acid.

cular reaction to cleave a TMS-peroxide bond and form a 1,2,4-trioxane (Scheme XII). We wondered whether this same reaction would work for an intramolecular ketal-ketene acetal, for Olah et al.[26] have shown that trichloromethylsilane/sodium iodide could be used to cleave dimethoxy acetals. We were interested in seeing whether trimethylsilyl trifluoromethanesulfonate (TMS-triflate) could be used with similar results, as the mechanisms of reaction would be quite similar (Scheme XI).

By using TMS-triflate as a catalyst, we were able to cleave the acetal function of dimethoxypropane to form acetone under anhydrous conditions. Therefore, the next project was the synthesis of a carboxylic acid-ketone system suitable for this study. Initially this was attempted through hydroboration of 12 to the ketoalcohol and subsequent oxidation to the carboxylic acid (Scheme XIII). However, it was discovered that compound 21 had already been synthesized by Akopyan[20] by a malonic ester synthesis. Using that method, a mixture of the acid/ester was obtained in good yield (50%). Initial formation of the ketal of 21 was attempted by reacting it with an ion exchange resin in MeOH; however, this met with failure, as did the reaction of 21 with dimethoxypropane or methyl orthoformate in the presence of H_2SO_4. Successful ketalization, as well as esterification of the ketone to 22, was accomplished by reaction of 21 with tetramethoxysilane and methanol in the presence of a catalytic amount of HCl (Scheme XIV), with a good yield (66%) resulting.



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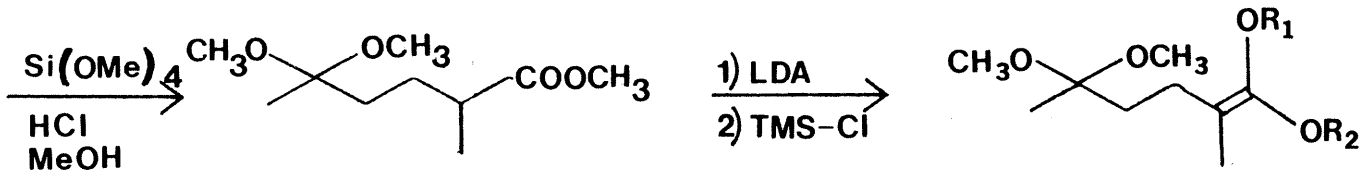
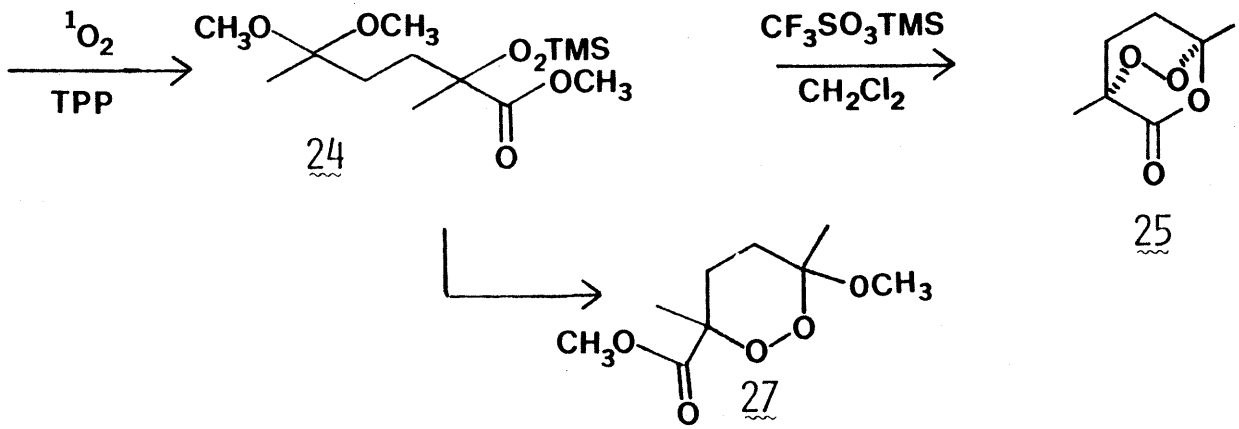


22

23a : R_1 = TMS, R_2 = CH_3

23b : R_1 = CH_3, R_2 = TMS



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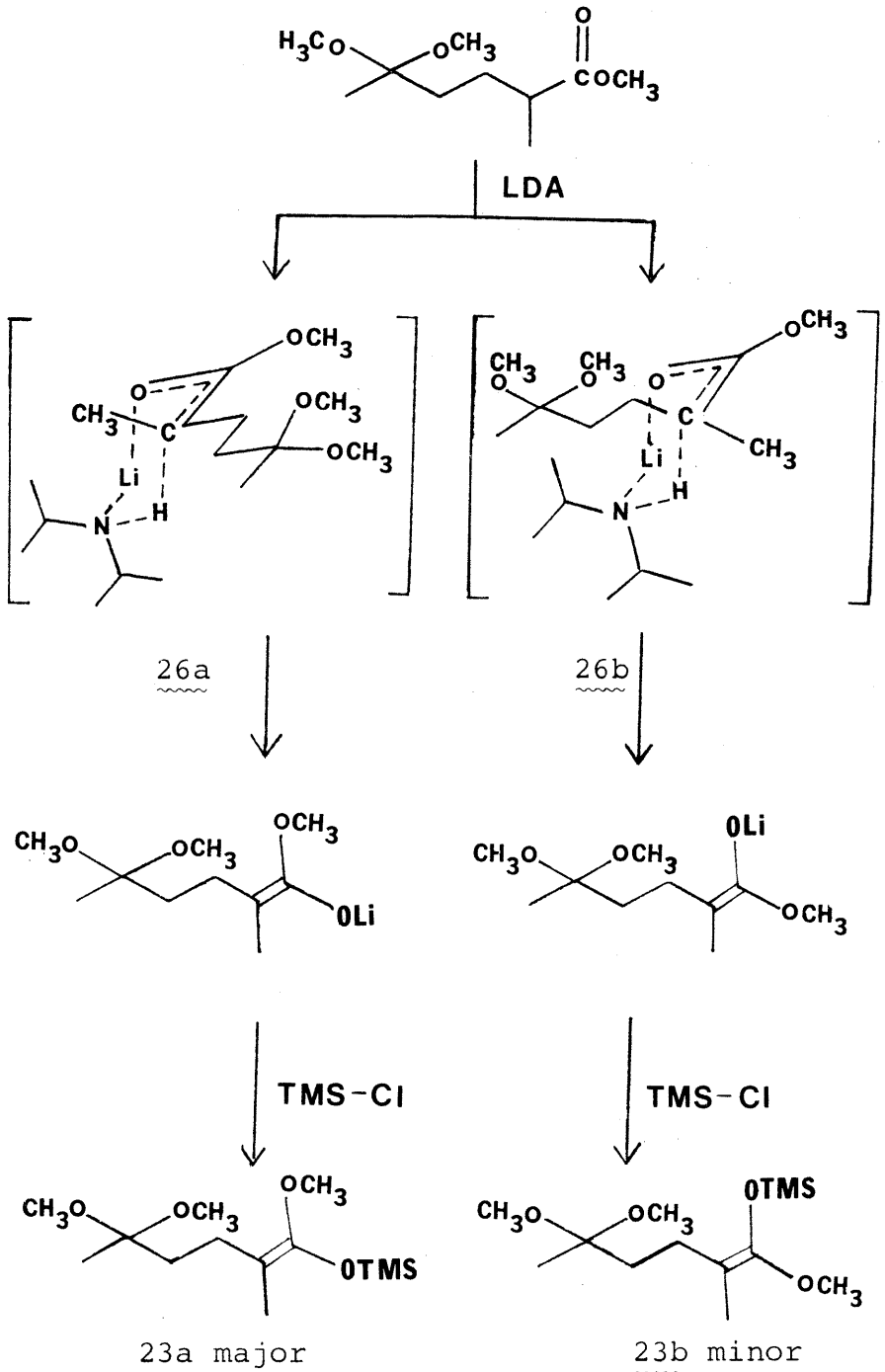
Scheme XIV. Proposed synthesis of 3,6-dimethyl-3,6-ethano-1,2,4-trioxan-5-one.

The next step in the synthesis of the bicyclic peroxide was the conversion of 22 to the keteneacetal. Addition of 22 to lithium disopropylamide in THF, and treatment of the enolate with chlorotrimethylsilane gave good yields (75%) of the ketene acetal in a 3:1 mixture of isomers. The findings of Ireland et al.[28] suggest, that it is most likely the E isomer which predominates. Ireland found that by using THF as the solvent, the reaction is kinetically controlled and the E isomer, which arises through a less sterically hindered transition state (Scheme XV), will predominate.

Jefford used a bis-TMS ketene acetal in the formation of the 1,2,4-trioxane;[24] however, we felt that the TMS-methyl keteneacetal could work as well. The photolysis experiment was conducted without attempting to separate the isomers 23a and 23b. Initially methylene blue was used as the sensitizer, with acetonitrile as the solvent. This however, failed to yield any of the TMS-peroxide 24 (Scheme XIV). Using tetraphenyl phorphine as the sensitizer in CH_2Cl_2 has resulted in formation of the TMS peroxide. This reaction requires more vigorous cooling due to the lower boiling point of CH_2Cl_2. As shown by Adam[22], the conversion of 23 to 24 goes by means of a 2+2 cycloaddition reaction with singlet oxygen.

It was difficult to obtain spectral data for compound 24 due to its tendency to undergo either acid- or base-catalyzed or thermal decomposition. A very likely decomposition product is the ketone shown in Scheme XVI.

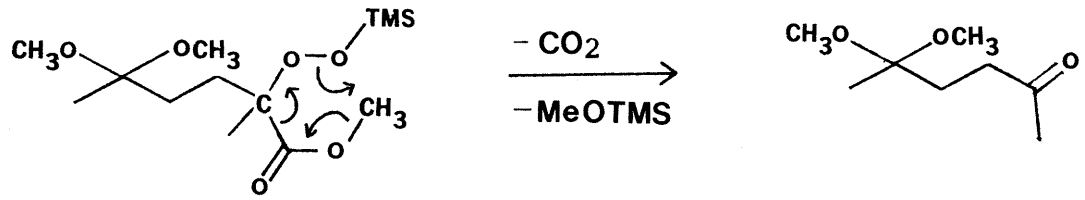


Scheme XV. Preparation of ketene acetals from methyl 5,5-dimethoxy-2-methylhexanoate.

The 2+2 cycloaddition reaction of 23 with singlet oxygen could also give the same methyl ketone shown in Scheme XVII.

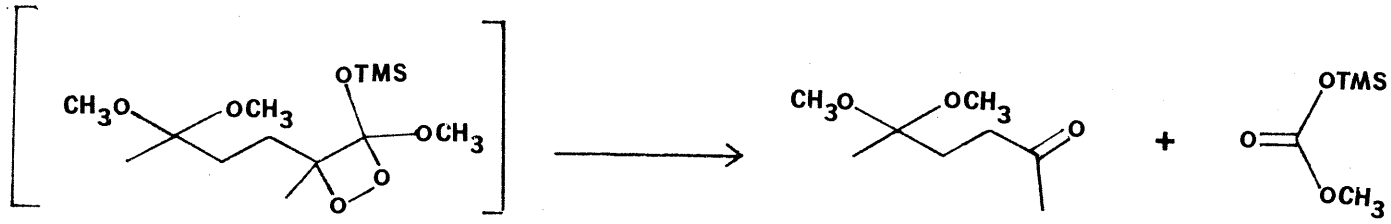
By using the crude reaction mixture without attempting to purify it, compound 24 was converted to 27 by reaction with trimethylsilyl trifluoromethanesulfonate at -78°C. After allowing the reaction to stir for approximately one hour, dry pyridine was added, and the mixture was poured into 10% solution of aqueous $NaHCO_3$ at 0°C. This was followed by ether extraction.

^1H NMR indicated that 27 was the major product rather than the bicyclic peroxide 25. Jefford allows the reaction with TMS-triflate to go for 4 hours, which might help assist the second ring in closing. Another possibility to assist the second ring in closing is the addition of a stronger nucleophile such as NaI. Addition of this stronger nucleophile would assist by helping to cleave the ketal as shown in Scheme XI.



24

Scheme XVI. Decarboxylation of α-TMS peroxy ester to methyl ketone.



Scheme XVII. Decomposition of 2+2 addition intermediate to methyl ketone and carbonate compounds.

IV. CONCLUSIONS

Currently the major portion of our research concentrates on obtaining the bicyclic 1,2,4 trioxan-5-one species. A possible route to this compound is through the bis-TMS ketal as opposed to using the TMS-methyl ketal (compound 23).

Based on the results obtained in the course of this research, it is obvious that the bicyclic peroxide is an elusive species. At the same time there are good indications that synthesis of such a compound is not hopeless, especially when one reflects on these results and combines these with outside findings. The fact that the peroxide ring can be formed with relative ease is extremely encouraging. This result, when combined with the fact that similar 1,2,4-trioxane rings were synthesized by Adam and Erden,[31] leads one to infer that these compounds should be stable enough to isolate.

V. EXPERIMENTAL

General Methods - Reactions were conducted under a nitrogen atmosphere (unless otherwise noted), and with magnetic stirring at room temperature (20-25°C). The phrase "solvent workup procedure" is used to indicate that the reaction was cooled to room temperature, diluted with water, and extracted three or more times with the indicated solvent. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and the resulting solution concentrated in vacuo by using a Buchi rotary evaporator. Ether solutions were washed with saturated brine prior to the aforementioned drying over magnesium sulfate.

Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared (IR) spectra were run on a Perkin-Elmer 1420 spectrophotometer as neat films. ^1H NMR spectra were recorded at 60 MHz on Varian EM-360A or at 200 MHz on a Nicolet NTR-200 instrument. Chemical shifts were determined in $CDCl_3$, (unless otherwise noted) and expressed in units (parts per million) downfield from the internal standard $(CH_3)_4Si$: (0.0). Thin-layer chromatography (TLC) was carried out on Whatman (catalog No. 4861-110) glass-backed

MK6F silica gel plates (200 m thickness). Gas-liquid chromatography (GLC) was conducted on a Hewlett-Packard 5710A flame ionization instrument equipped with capillary columns, either, 0.2 mm X 12.5 m crosslinked dimethyl silicone or 0.2 mm X 50.0 m crosslinked 5% phenylmethyl silicone column. Mass spectra (MS) were determined using the appropriate GC column on a Hewlett-Packard 5985A GC-MS instrument operating at 70 eV in the electron-impact mode. Anhydrous solvents were prepared via distillation from the appropriate drying agent as follows: tetrahydrofuran, sodium or potassium and benzophenone; methanol, magnesium/iodine; methylene chloride, phosphorus pentoxide; acetonitrile, phosphorus pentoxide; benzene, sodium; pyridine, calcium hydride. All other solvents were of "reagent" grade and were used directly as supplied. Elemental analyses were performed by Atlantic Microlab, Inc.

1-Chloromethylcyclohexene was prepared by the method of Calzada and Hooz.[30] In an argon atmosphere, 6.08 g (23.2 mmol) Ph_3P and 2.00 g (17.8 mmol) 1-hydroxymethyl-cyclohexene were mixed in 16 ml of dry CCl_4. The mixture was heated to reflux for one hour, cooled to room temperature, and 20 ml dry pentane was added. The mixture was stirred for 5 minutes and then filtered to remove triphenylphosphine oxide, the latter being washed with dry pentane. The filtrate and washings were combined and

concentrated on a rotary evaporator. Distillation of the residue (Kugelrohr) at 38 mm/80°C gave 1.67 g (72%) of a clear liquid: ^1H NMR ($CDCl_3$, 60 MHz) 1.22 - 2.11 (8 H, m, $(-CH_2-)_4$), 3.80 (2H, s, $-CH_2-Cl$), 5.65 (1H, b, = CH).

Preparation of 5-oxo-2-methylhexene (12).[15,16]

2-Methyoxypropene (7.88 g, 109. mmol), 2-methyl-2-propen-1-ol, (3.15 g, 43.7 mmol) and mercuric acetate (0.25 g, freshly recrystallized from ethanol) were stirred together at room temperature for 0.5 h. The solution was placed in a 75 ml stainless steel cylinder (Whitey No. HDF2-95), fitted with an inlet valve (Whitey 43M4-54) a relief valve (Napro 4CPA2-350), and a pressure gauge. Sixty milligrams of hydroquinone were added, and the apparatus was purged with prepurified nitrogen. It was pressurized to 150 psi with nitrogen and heated with constant agitation in an oil bath. The bath was heated slowly to 150°C and maintained at this temperature overnight. The cooled reaction mixture was removed from the depressurized cylinder, and the cylinder washed with diethyl ether. The reaction mixture and ether washings were combined and concentrated on a rotary evaporator. The resulting residue was distilled (Kugelrohr) at 40 mm/85°C [lit b.p. 100°C (185 mm)][29] to yield 4.49 g (88%) of a colorless oil: ^1H NMR (60 MHz, $CDCl_3$), δ 1.74 (3H, s, $CH_3C=C$), 2.16 (3H, s, CH_3C-O), 2.16-2.78

(4H, m, $-CH_2-CH_2-$), 4.58-4.86 (2H, m, $CH_2=$). I.R. (neat): ν = 1715, 1650, 1360, 1160, 890 cm^{-1}.

2-Methyl-2-(3-butanonyl)oxirane (13) was prepared following the procedure of Anderson and Veysoglu.[18] To a mixture of 30 ml of CH_2Cl_2, 1.00 g of 12 and 15 ml of 5% aqueous $NaHCO_3$ was added, slowly, with stirring (over a 10 minute period) 1.56 g of m-chloroperbenzoic acid (90%). The mixture was allowed to stir at room temperature until a faintly positive starch-iodide test was recorded (approximately 6 hours). The organic layer was separated and washed (3X) with 5% aqueous NaOH and dried over anhydrous Na_2SO_4 overnight. The dried organic layers were filtered and concentrated on a rotary evaporator. Further concentrations under reduced pressure (50 μm, room temperature) yielded 0.63 g (55%) of colorless oil: ^1H NMR (60 MHz, $CDCl_3$), δ1.30 (3H, s, $CH_3C=C$), 1.70-2.01 (2H, m, CH_2C-O), 2.15 (3H, s, $CH_3C=O$), 2.41-2.62 (2H, m, $CH_2-C=O$), 2.62 (2H, s, CH_2-O); IR(neat): ν = 1715, 1360, 1165, 895, 800 cm^{-1}.

2-Methyl-2-(2-methylbut-1-en-4-yl) oxirane (13a). Dimethylsulfoxonium methylide was prepared according to the procedure of Corey and Chaykovsky.[19] A solution of 1.50 g (16.4 mmol) of 12 in 5 ml of dry tetrahydrofuran was added with stirring to a solution of the ylide in 55 ml dry tetrahydrofuran (THF). The mixture was heated at

reflux overnight. The reaction mixture was extracted in a pentane solvent workup procedure, yielding 1.38 g of yellow oil. Kugelrohr distillation (40 mm, 70-75°C) of the residue yielded 1.11 g (66%) of colorless oil: ^1H NMR (60 MHz, $CDCl_3$), δ 1.31 (3H, s, CH_3-C=C), 1.55-190 (2H, m, CH_2-C-O), 1.74 (3H, s, CH_3-C-O), 1.90-2.33 (2H, m, -CH_2-C=), 2.56 (2H, s, CH_2-O) 4.66 (2H, s, CH_2=). IR (neat): ν = 3050 875,790 cm^1.

3-methyl-3-[2-(2-methyloxiranyl)ethyl]-1,2,4-trioxalane (15). Ozone (O_3) was bubbled through a mixture of 0.27g (2.0 mmol) of 13a in 2 ml of dry Ch_2Cl_2 at -78°C until a light blue color persisted in the reaction mixture. The reaction mixture was warmed to room temperature and concentrated on a rotary evaporator, yielding 0.26 (76%) of a viscous oil: ^1H NMR (60 MHz, $CDCl_3$), δ 1.30 (3H, s, CH_3-C=C), 1.42 (3H, s, CH_3-C-O), 1.65-2.30 (4H, m, -CH_2CH_2), 2.60 (2H, s, -Ch_2-O), 5.08 (2H, b, -O-CH_2O-).

General method for the preparation of 2-methyl-2-(3-hydroperoxy-3-alkoxybut-1-yl)oxiranes (18a). These compounds were prepared by following the method of Criegee.[25] Ozone (ca. O_3 6% in O_2) was bubbled through a mixture of 13a in the appropriate solvent (CH_3OH, CH_3CH_2OH or CH_2Cl_2/acetic acid) at -65°C, depending on the alkoxy group desired. When the

reaction mixture was a light blue color, ozone addition was ceased, and the reaction was warmed to room temperature and concentrated on a rotary evaporator. A methylene chloride solvent workup procedure was used yielding a viscous oil. Using 0.17g (1.35 mmol) of 13a in 4 ml of dry MeOH yielded 0.20 g (84%) of the desired peroxide 18a, R = OCH_3: ^1H NMR (60 MHz, $CDCl_3$), δ 1.00 (3H, s, CH_3-C=C), 1.44 (3H, s, Ch_3-C_2), 2.24 (2H, s, CH_2-O), 3.30 (3H, s, OCH_3). IR (neat): ν = 2940, 1360, 1230, 1175, 1070, 1055, 850.

Tetrahydro-2H-pyran-2-ylhydroperoxide (19). Ozone gas (ca. 6% O_3 in O_2) was bubbled through a solution of 0.60 g 5-hexene-1-ol in 6 ml of dry methanol at -60°C until a light blue color persisted. The solution was concentrated on a rotary evaporator. The residue was washed with a saturated solution of $NaHCO_3$ followed by H_2O and extracted with $CHCl_3$. The organic layers were combined and concentrated on a rotary evaporator, yielding 0.64 g (90%) of a clear oil: ^1H NMR (60 MHz, $CDCl_3$),δ 1.12-1.82 (6H, m, C-CH_2-CH_2-CH_2-C), 3.40-3.71 (2H, t, J = 9 Hz, CH_2-O) 4.70-5.17 (2H, m, -OH, -CHO_2).

Tetrahydro-2-furanylhydroperoxide (20). Compound 20 was prepared by the same procedure as 19 using 0.50 g of 4-penten-1-ol, yielding 0.31 g (51%) of a clear oil: ^1H NMR (60 MHz, $CDCl_3$), δ 1.60-2.20 (4H, m,

C-CH_2-CH_2-C), 3.93 (2H, t, J = 6 Hz, -CH_2-O-), 4.90-5.56 (2H, m, CHO_2 and OH).

5-Oxo-2-methylhexanoic acid (21), was prepared according to the procedure of Akopyan et al.[20] In 75 ml of dry methanol, 2.12 g (20.0 mmol) of Na_2CO_3 was suspended. To this suspension was added 25.00 g (250.0 mmol) of methyl methacrylate, and the mixture was heated to 65°C. To the heated mixture was added 23.20 g (200.0 mmol) of methyl acetoacetate. The reaction mixture was heated at reflux until the starting materials were consumed according to GC (approximately 12 hours). The reaction was cooled to room temperature, filtered and concentrated on a rotary evaporator. The residue was acidified in aqueous 50% HCl and refluxed until the Michael adduct was consumed according to GC. The reaction was again cooled to room temperature and HCl was removed on a rotary evaporator, leaving an oily residue with a white precipitate. The product was distilled (Kugelrohr) [lit. b.p. 105 - 110°C (20 μm)] at 10 mm/150°C, yielding 14.27 g (50%) of a clear liquid: ^1H NMR (60 MHz, $CDCl_3$), δ1.25 (3H, d, J = 6 Hz, CH_3-CO_2), 1.95 (2H, t, J = 7 Hz, -CH_2-CO), 2.22 (3H, s, CH_3C=O), 2.38-2.80 (3H, m, CH_2-CH-), 10.10 (1H, s, CO_2H).

Methyl 5,5-dimethoxy-2-methylhexanoate (22), was prepared according to the method of Zayar and Byrne.[21]

In 5.12 g (160 mmol) of dry methanol, 16.42 g (108 mmol) of tetramethylorthosilicate and 5.01 g (34.8 mmol) of 21 were mixed, and a catalytic amount of HCl gas was bubbled into the mixture and it was stirred at room temperature for 72 hours. The reaction mixture was made basic (to pH 8) using NaOMe. An initial distillation (Kugelrohr) at 10 mm/110°C was performed to remove excess $Si(OCH_3)_4$ and this was followed by a second distillation at 10 mm/150°C yielding 4.41 g (66%) of a clear liquid: ^1H MR (60 MHz, $CDCl_3$), δ 1.20 (3H, d, J = 8 Hz, CH_3-C), 1.25 (3H, s, CH_3-$C(OC)_2$), 1.45-2.75 (5H, m, CH_2-Ch_2-CH-), 3.14 (6H, s, -$(OCH_3)_2$), 3.64 (3H, s, CO_2CH_3).

Anal. Calcd for $C_{10}H_{20}O_4$: C, 59.09; H, 9.42. Found C, 58.93; H, 9.48.

1,5,5-Trimethoxy-2-methyl-1-trimethylsiyloxyhex-1-ene (23), was prepared by the method of Ainsworth et al.[27] A mixture of 9 ml (64 mmol) of diisopropylamine in 110 ml of dry tetrahydrofuran was cooled to 0°C, and 40 ml of n-butyl lithium (2.5 M) was added slowly with stirring, maintaining the temperature below 10°C. Immediately, 9.15 g (44.8 mmol) of 22 was added and the reaction mixture stirred at 0°C for 1.5 hours. 14 ml (110 mmol) of freshly distilled trimethylsilyl chloride was added slowly with stirring. This mixture was stirred at room temperature for 1 hour and then concentrated on a rotary evaporator (10mm, 100°C). The residue was distilled (Kugelrohr) at

100°C/50 μm and yielded 9.26 g (75%) of a clear liquid: ^{1}H NMR (200 MHz, $CDCl_3$), isomeric peaks in a 3:1 ratio: 0.13, 0.20 (9H, s, $OSi(CH_3)_3$), 1.52, 1.57 (2 H, m CH_2-C=), 3.13 (6H, s, $(OCH_3)_2$)), 3.36, 3.50 (3 H, s, OCH_3). Mass spectrum: m/z (relative intensity), 276 (26.8), 173 (38.1), 89 (59.3), 73 (55.5), 69 (100.0).

Anal. Calcd for $C_{13}H_{28}O_4Si$: C, 56.48; H, 10.21. Found: C, 56.51; H, 10.26.

Methyl 5,5-dimethoxy-2-methyl-2-trimethylsiylperoxy-hexanoate (24), was prepared according to the procedure of Adam et al.[22] In 100 ml of dry acetonitrile, 1.00 g (3.62 mmol) of 23 and 0.04 g of methylene blue (M. B.) were mixed. While bubbling O_2 into the mixture, it was irradiated with a 450-W mercury lamp, filtering being accomplished with a uranium glass sleeve. The mixture was irradiated for 5 hours and then cooled to room temperature and concentrated on a rotary evaporator. An alternative choice of solvent (CH_2Cl_2) and sensitizer (tetraphenyl phorphine) was used and required only 1.0 hour; however, more vigorous cooling was necessitated due to the lower boiling point of CH_2Cl_2. The yield was 58%. Mass spectrum: m/z (relative intensity), 308 (11.3), 307 (34.0), 233 (39.2), 89 (40.2), 59 (29.9), 43 (100).

Attempted synthesis of 3,6-dimethyl-3,6-ethano-1,2,4-trioxan-5-one (25). In 4 ml of dry CH_2Cl_2, 0.25 g

(0.81 mmol) of crude 24 was mixed and cooled to -78°C. To the cooled mixture 0.5 ml (2.6 mmol) of TMS-triflate was added, and the resulting mixture stirred for 4 hours while warming to -20°C. Dry pyridine (0.5 ml) was added, and the resulting solution was poured into a 10% aqueous $NaHCO_3$ solution and extracted with diethyl ether. The extracts were concentrated on a rotary evaporator. ^1H NMR of the crude product indicated that the likely product was a cyclic peroxide and not the desired 1,2,4 trioxane.

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