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THE UNIVERSITY OF ALBERTA

I. SYNTHESIS OF GRANDISOL

II. TOWARDS THE SYNTHESIS OF ACTINOBOLAMINE

by

© LOIS MARGARET BROWNE

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

Department of Chemistry

Edmonton, Alberta

Fall, 1972

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled I. SYNTHESIS OF GRANDISOL II. TOWARDS THE SYNTHESIS OF ACTINOBOLAMINE submitted by LOIS MARGARET BROWNE in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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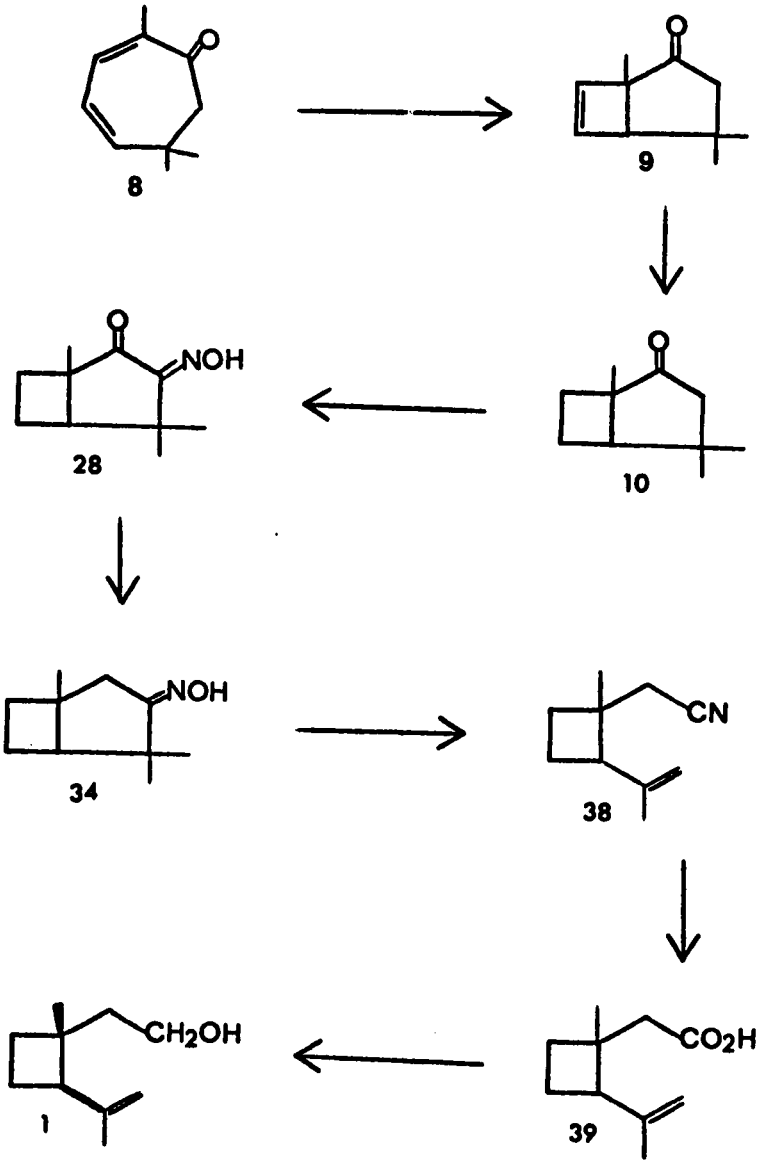
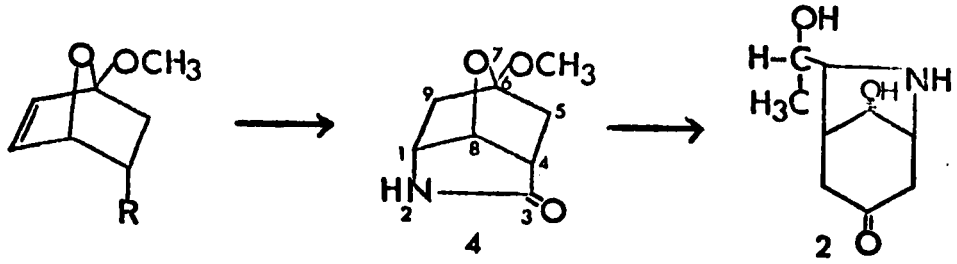
A B S T R A C T

The boll weevil, Anthonomus grandis Boheman, is a major pest of cotton. The pheromone complex emitted by the male boll weevil has been used as a general, nontoxic method of surveying and controlling the insect population. The stereoselective synthesis of one component of the



pheromone complex, grandisol (1), has been achieved in seven steps from eucarvone, (8), as outlined above. Irradiation of eucarvone gave a bicyclic ketone 9 which was readily converted to ketone 10 by hydrogenation. Treatment of ketone 10 with amyl nitrite and potassium t-amylate afforded the oximinoketone 28. Transformation to oxime 34 by mild Huang-Minlon reduction, followed by Beckmann rearrangement of the oxime with phosphorus pentachloride gave seconitrile 38. Hydrolysis to secoacid 39 then reduction of 39 afforded grandisol, 1.

In studies towards the synthesis of actinobolamine (2), Diels-Alder reactions of 2-methoxyfuran with several dienophiles were carried out. An adduct with an endo substituent on the side opposite to the bridgehead methoxyl could possibly be transformed to the tricyclic compound 4, which is a potential precursor to actinobolamine. Such an adduct has been prepared.



A C K N O W L E D G E M E N T S

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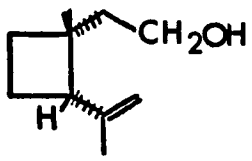
INTRODUCTION

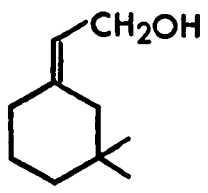
Pollution of our environment and ecological imbalance caused by insecticides has stimulated interest in the use of insect sex attractants (pheromones) as a general, nontoxic method of surveying and controlling insect populations.[1a-c]

The boll weevil, Anthonomus grandis Boheman, is a major pest of cotton. The pheromone complex[2] emitted by live male boll weevils causes a response in female boll weevils in the field[3] as well as in laboratory assays.[4] In addition, the pheromone complex evokes an aggregating response of both sexes in the field.[5]

The components of this complex have been isolated and identified by Tumlinson and co-workers.[6a,b] They are the four terpenoid compounds grandisol, 1, (Z)-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol, 2, (Z)-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde, 3, and (E)-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde, 4.



1



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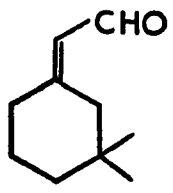

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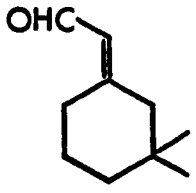


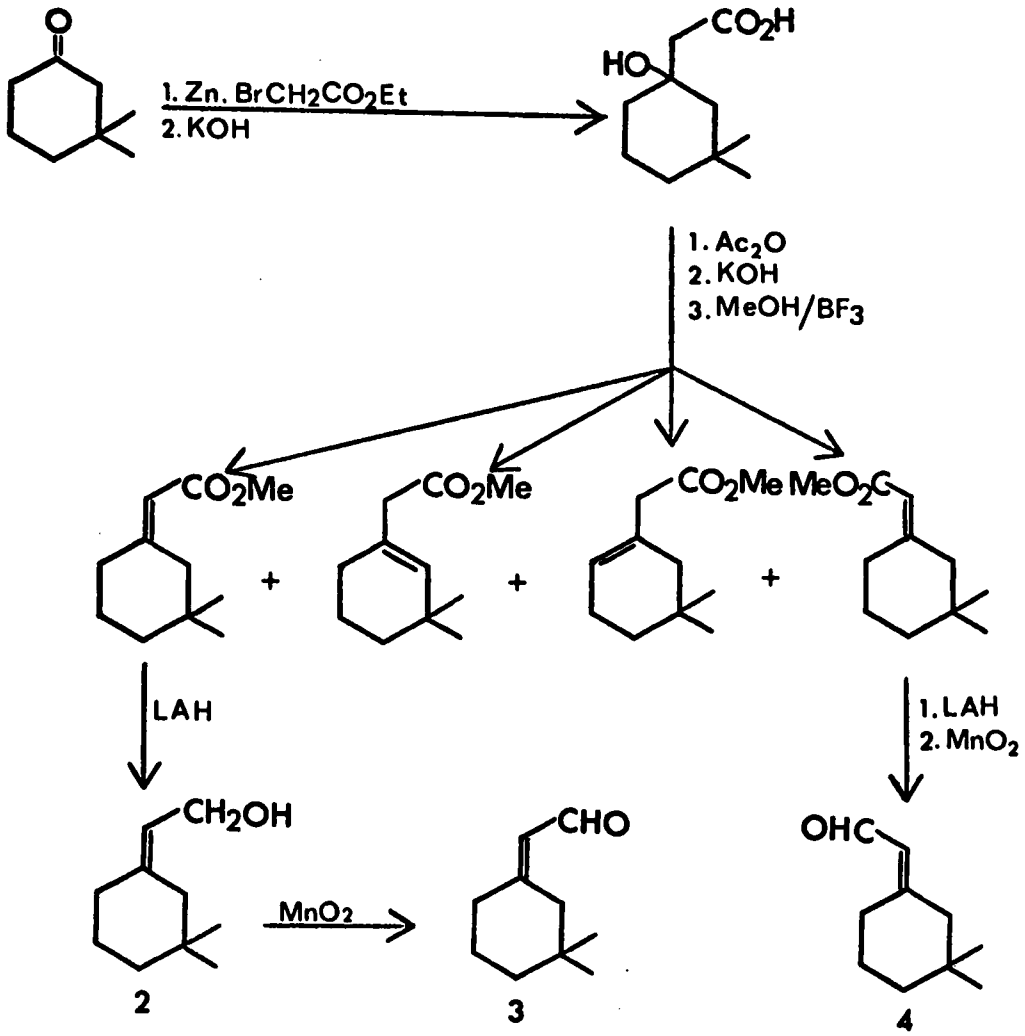
4

The practical value in using the sex attractant as a means of control compared to other methods has led several

research groups to seek an economical synthesis of its components.

Compounds 2, 3, and 4 have been synthesized by two different routes. Tumlinson and co-workers[6a,b] (see Chart 1) used a Reformatsky reaction of ethyl bromoacetate with 3,3-dimethylcyclohexanone followed by saponification to yield 2-(1-hydroxy-3,3-dimethylcyclohexyl)acetic acid. The hydroxy acid was dehydrated with acetic anhydride and

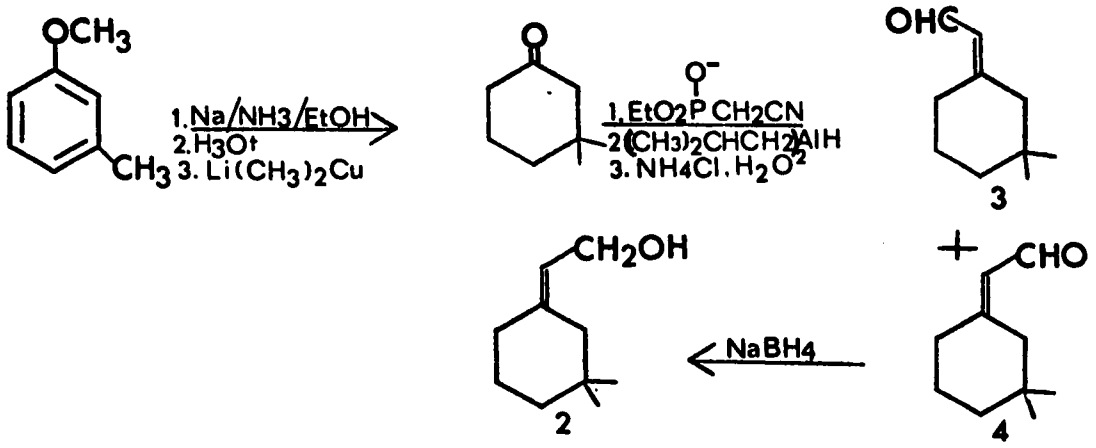
Chart 1



the unsaturated acids esterified with methanol to give a mixture of four unsaturated esters. The unsaturated esters were separated and reduced to the respective (Z)- and (E)-unsaturated alcohols with lithium aluminum hydride. Selective oxidation with active manganese dioxide gave the (Z)- and (E)- aldehydes, respectively. The disadvantage of this synthesis is the tedious separation of the ester mixture either by preparative glc or careful distillation through a spinning band column.

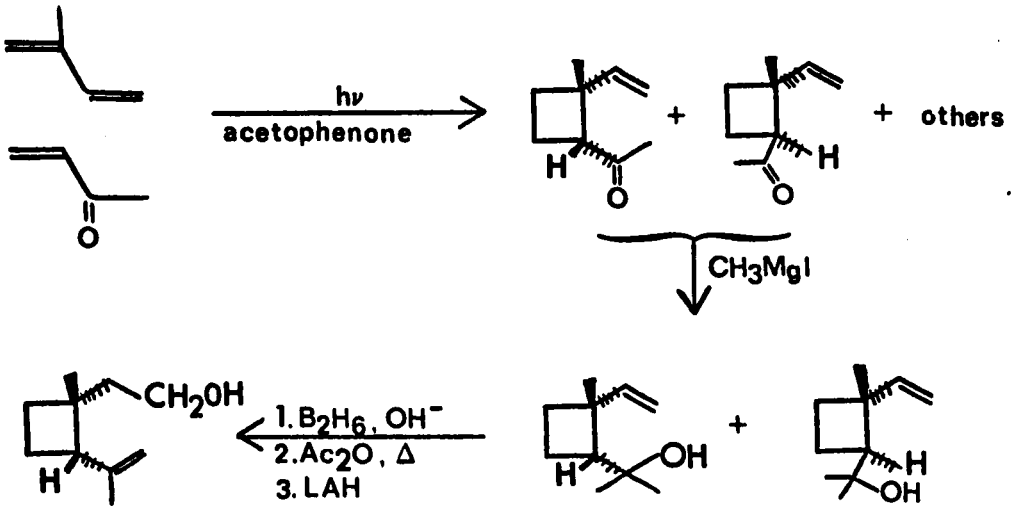
More recently Babler and Mortell[7] (see Chart 2) prepared 3,3-dimethycyclohexanone by Birch reduction of m-methylanisole, followed by hydrolysis and conjugate addition of lithium dimethylcopper. A modified Wittig reaction between the dimethylcyclohexanone and diethyl cyanomethylphosphonate gave a high yield of an inseparable mixture of α,β-unsaturated nitriles. The unsaturated nitriles were reduced to the corresponding aldehydes, 3 and 4, by use of one equivalent of diisobutylaluminum hydride. This facile route leads to 60% overall yields of unsaturated aldehydes 3 and 4. The attractiveness of the pheromone complex is reduced when (E)-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol is present. In this synthetic sequence the mixture of (Z)- and (E)- aldehydes must be separated prior to reduction with sodium borohydride of the (Z)-aldehyde to form (Z)-alcohol 2.

Chart 2



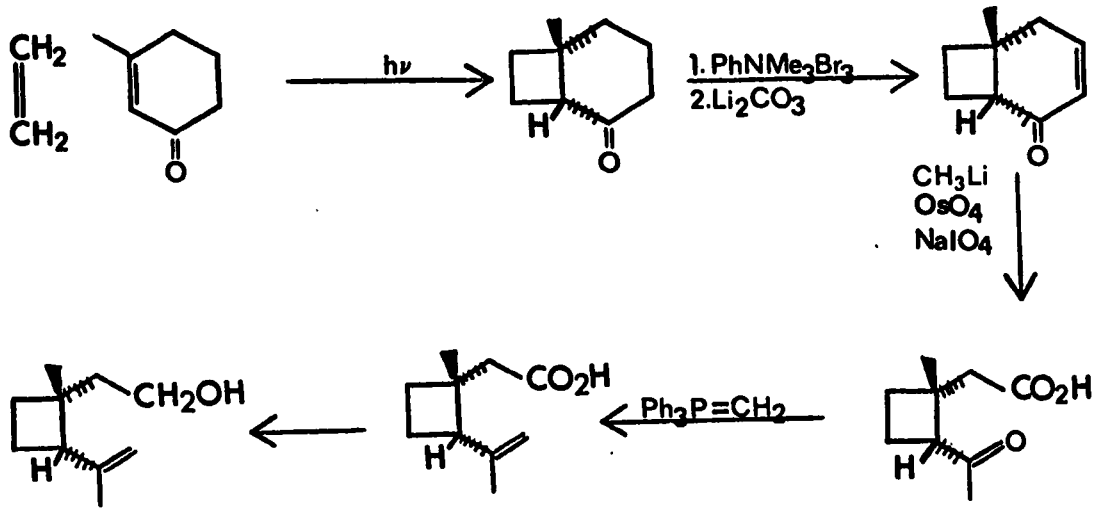
Grandisol, 1, has been synthesized nonselectively[5a,b] and stereoselectively[6,8]. In a nonselective synthesis (see Chart 3), Tumlinson and co-workers[5a,b] prepared grandisol and its trans isomer by photocycloaddition of isoprene and methyl vinyl ketone to obtain an epimeric mixture of 2-methyl-2-vinylcyclobutyl methyl ketones as well as several other products. Grignard addition of methylmagnesium iodide gave a mixture of alcohols which were separated by preparative glc. Hydroboration of the separated alcohol afforded a diol, which was acetylated and the ester pyrolyzed with refluxing acetic anhydride. Reduction with lithium aluminum hydride afforded grandisol, 1. The low yield and difficult isolation procedure in the photocyclization step of this route demanded a more selective synthesis.

Chart 3



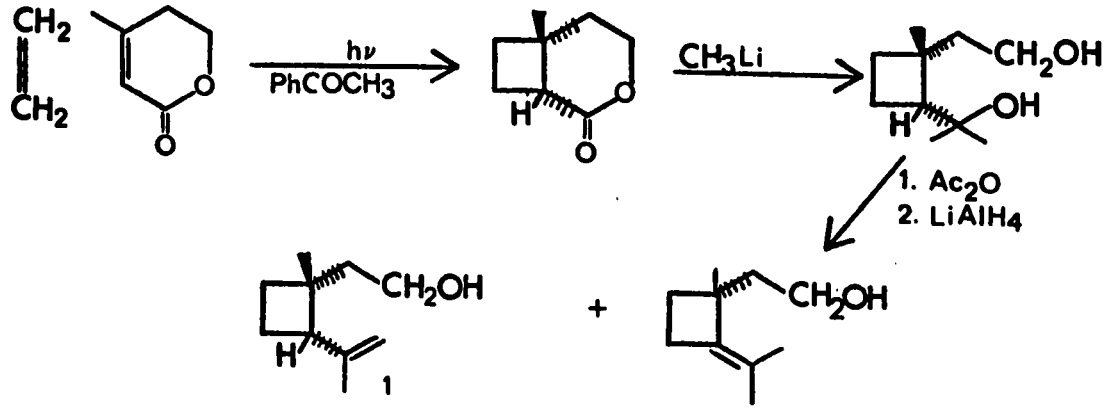
Because of the two asymmetric centers on the four-membered ring structure of grandisol, a stereoselective synthesis is challenging. Siddall and co-workers[8a,b] (see Chart 4) used a photochemical cycloaddition of 3-methyl-cyclohex-2-enone with ethylene to form 6-methylbicyclo-[4.2.0] octan-2-one in which the stable form is cis rather than trans. This compound was brominated with phenyl-trimethylammonium tribromide, then dehydrobrominated with lithium carbonate. Treatment of the resulting conjugated ketone with methyl lithium, followed by careful ring opening of the cis olefinic alcohol by osmium tetroxide catalyzed sodium periodate oxidation gave a single cis keto-acid. Alkenylation with methylene triphenylphosphorane, then reduction yielded grandisol as a racemate.

Chart 4

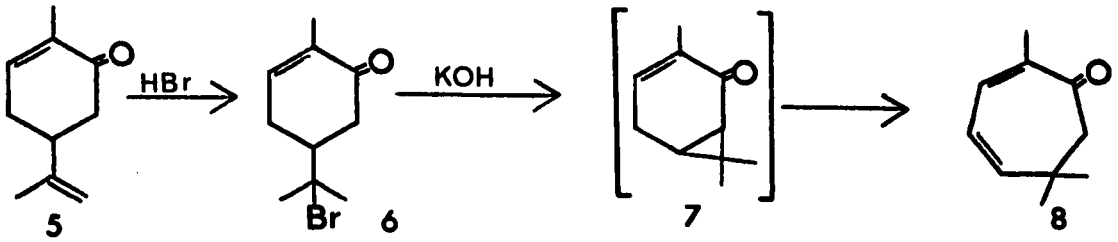


Gueldner and co-workers[8,9] (see Chart 5) very recently published details of a synthesis which utilizes a sensitized photocycloaddition of ethylene to dehydrated mevalonic acid lactone to form 6-methyl-3-oxabicyclo[4.2.0]-octan-2-one as the major product. Treatment of the bicyclic compound with methyl lithium followed by dehydration with acetic anhydride and reduction gave a mixture of isomeric compounds, one of which was racemic grandisol. These isomeric olefinic alcohols could be separated by careful distillation on a spinning band column.

Chart 5

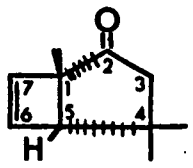


This thesis describes a method of preparing grandisol, 1, in seven steps from eucarvone. The latter compound is easily prepared in good yield from the commercially available carvone[10a,b]. Addition of hydrobromic acid to carvone affords carvone hydrobromide, 6. Subsequent treatment with base causes rearrangement of the hydrobromide to eucarvone, 8, through the intermediate carenone, 7.



D I S C U S S I O N

During our initial survey of possible synthetic routes to grandisol we noticed that a photolysis product of eucarvone, 1,4,4-trimethylbicyclo[3.2.0]hept-6-en-2-one, 9, has a carbon skeleton similar to that of grandisol, 1. The photolysis product has not only the correct arrangement of carbon atoms but the stereochemistry of the C-1 methyl and the C-5 hydrogen has the desired cis relationship. Hydrogenation of this compound gives 1,4,4-trimethylbicyclo[3.2.0]heptan-2-one, 10, which is an attractive synthetic intermediate.



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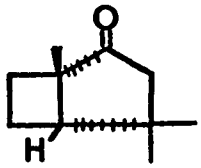
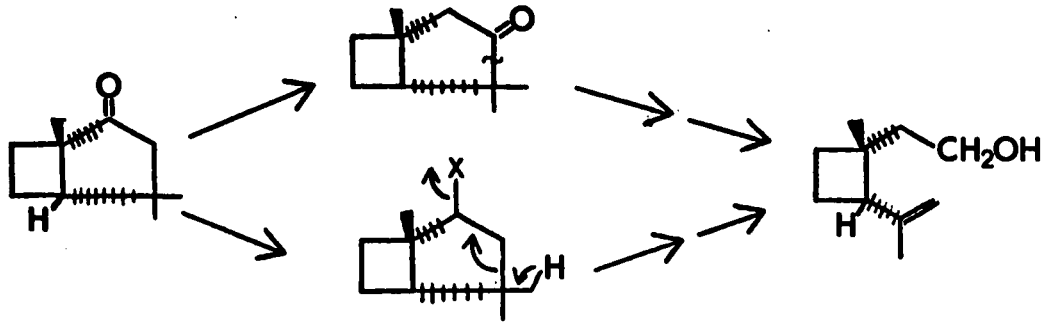
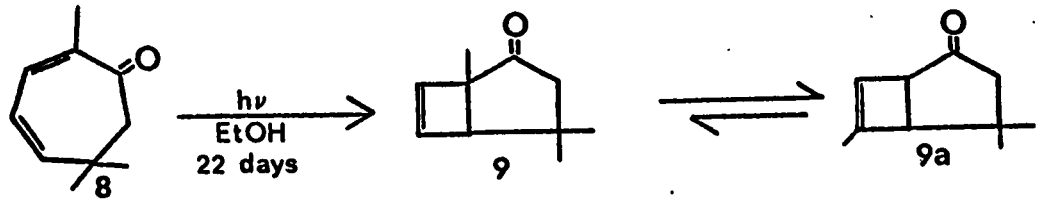


10

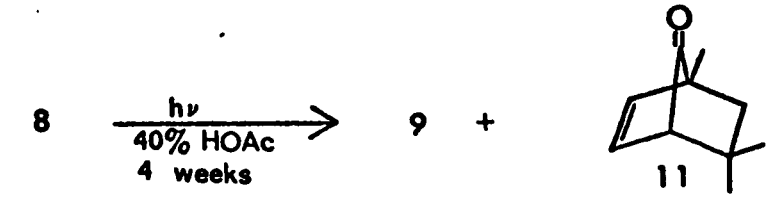
The bicyclic ketone 10 could in theory be modified to grandisol by either of the following pathways: (i) ketone transposition from C-2 to C-3, followed by cleavage of the C-3, C-4 bond; (ii) transformation of the C-2 carbonyl to a leaving group, followed by a "Grob-type" fragmentation. Thus we undertook the synthesis of the key intermediate from the readily available 2,4-cycloheptadienone, eucarvone, 8[10a,b].



Several studies on the photoisomerization of eucarvone have appeared. Buchi and Burgess[11] irradiated an alcohol solution of eucarvone for 22 days and isolated isomers 9 and 9a in 36% yield. This was the first example of a photolytic 1,3-acyl migration of β,γ-unsaturated

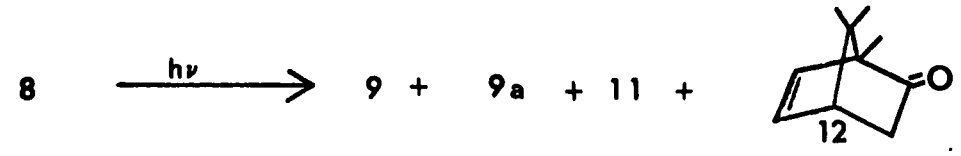


ketones. Later, Hurst and Whitham[12a,b], obtained equal amounts of 9 and another product, 11, by irradiating eucarvone in 40% aqueous acetic acid.

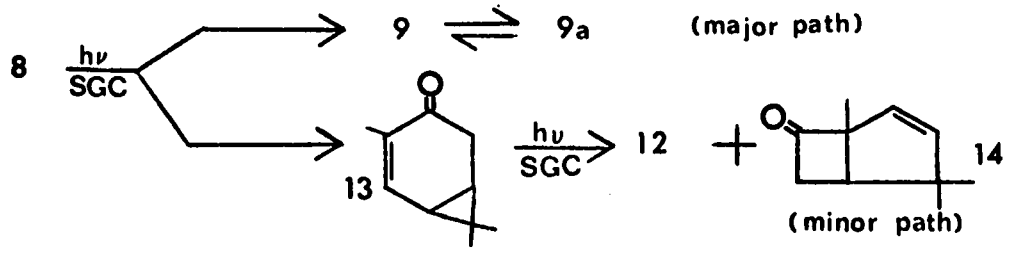


Shuster, Nash and Kantor[13] detected a fourth product, dehydrocamphor, 12. They used several different solvents for photoisomerization of eucarvone. In each case com-

pounds 9, 9a, 11, and 12 were formed; the relative ratios were solvent dependent and compound 9 always predominated.

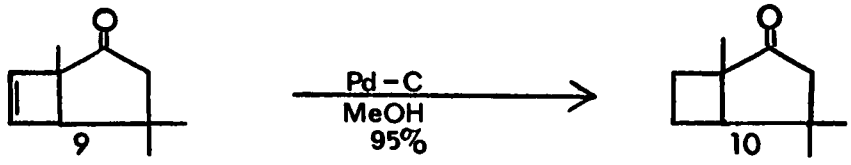


Shuster and Sussman[14] showed by competitive photolysis of eucarvone that the rate of disappearance of eucarvone increases in polar relative to non-polar solvents but that the material balance in terms of the four photoproducts was lower in polar media. They also showed that conversion of eucarvone to compound 9 could be effected with high energy triplet sensitizers, but the efficiency of the reaction was not different from that on direct photolysis. Hart and Takino[15a,b] have studied the irradiation of eucarvone adsorbed on silica gel--cyclohexane (SGC) or in trifluoroethanol solution (TFE). In either of these strongly polar media the photoisomerization is greatly accelerated. Two new products, compound 13 and 14, were isolated. The authors propose that two non-interchangeable reaction pathways arising predominately from singlet states account for the products observed.



We have irradiated eucarvone in several solvent systems: methanol, trifluoroethanol (TFE), SGC, ethylene glycol, and ethylene glycol-TFE. In TFE or SGC product isolation was difficult as the crude photolysis mixture tended to polymerize. In methanol, ethylene glycol and ethylene glycol-TFE (100:1), compound 9 could be isolated in 20-25%, 30-37%, and 50-52% yields, respectively. The photolysis of eucarvone in ethylene glycol-TFE proceeded cleanly and gave reasonable yields of bicyclic ketone 9 by fractional distillation. This has become our preferred route to compound 9.

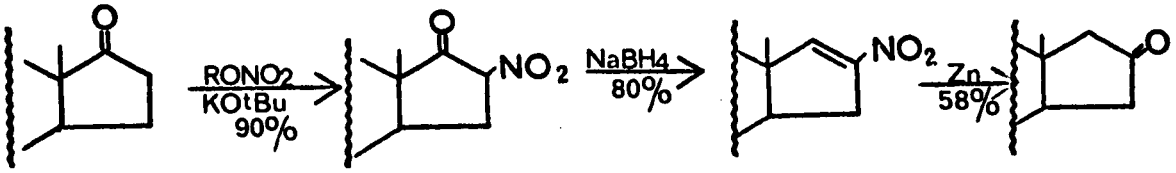
Hydrogenation of compound 9 over 20% palladium--charcoal in methanol gave compound 10 in 95% yield. The spectral data obtained from the synthetic material are identical with the reported values[11].



Having prepared the desired bicyclic ketone in satisfactory yield, the problem became that of transposing the ketone function from C-2 to C-3. Methods used previously for this purpose in steroidal and terpenoid systems have been summarized[16] and several compendia of ketone transposition methods are available[17a,b]. Unfortunately, some of the better methods are applicable only in certain situations, for example, methods involving formation of a

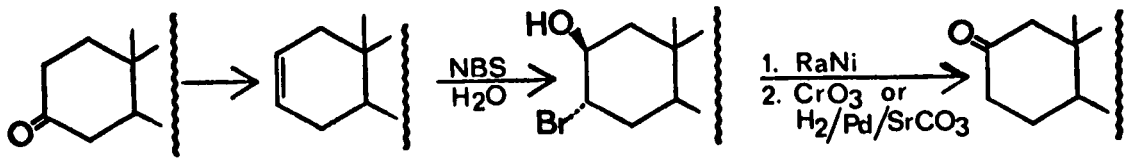
diosphenol could not be adapted to our synthetic sequence. Thus of the numerous routes available, the following methods were considered for transposition of the ketone.

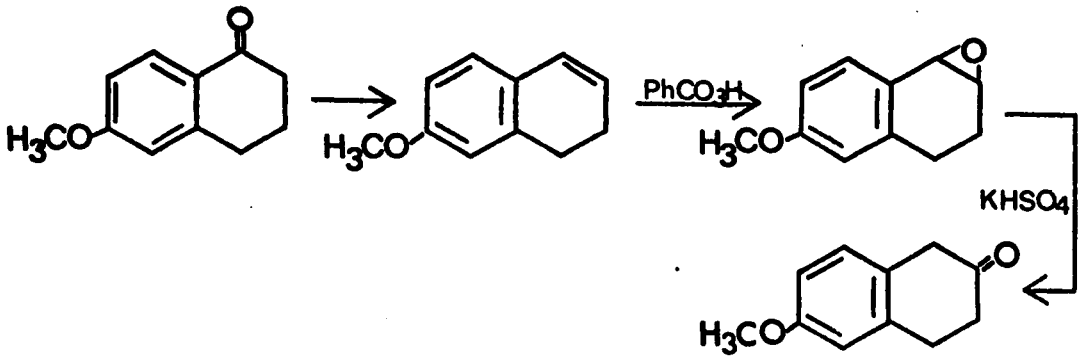
Hassner, Larkin and Dowd[18] have shifted the position of the ketone carbonyl via reduction of 2-nitroketones.



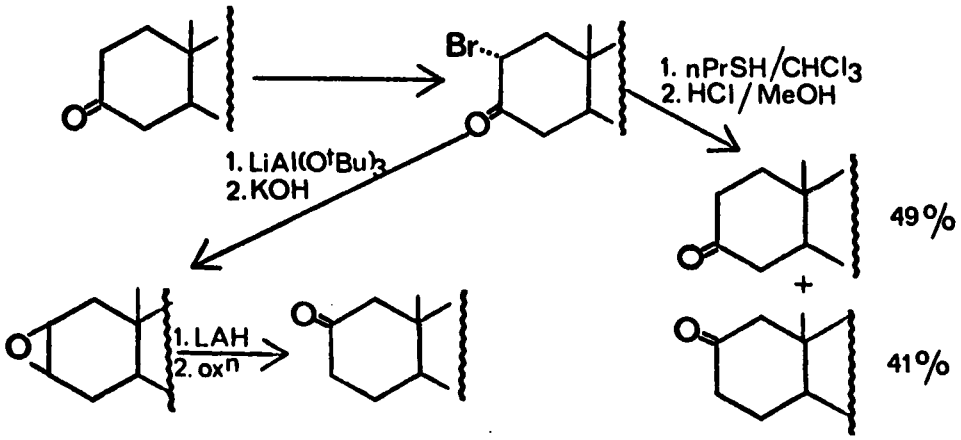
The scope of this method is limited since sterically hindered systems such as 2,2-dimethyl-5-nitrocyclopentanone give very low yields (10%) of nitro olefin.

Another route, studied by Klimstra and co-workers[19] and Clarke and Daum[20], involved addition of hypobromous acid to an olefin, followed by selective removal of bromine. On the other hand, Nagata and Terasawa[21] formed an epoxide which was rearranged to a ketone on aqueous acidic workup. While the cases cited give only desired ketone, in general modificaiton of an olefin to a ketone need not be selective and mixtures of positional isomers may be obtained.

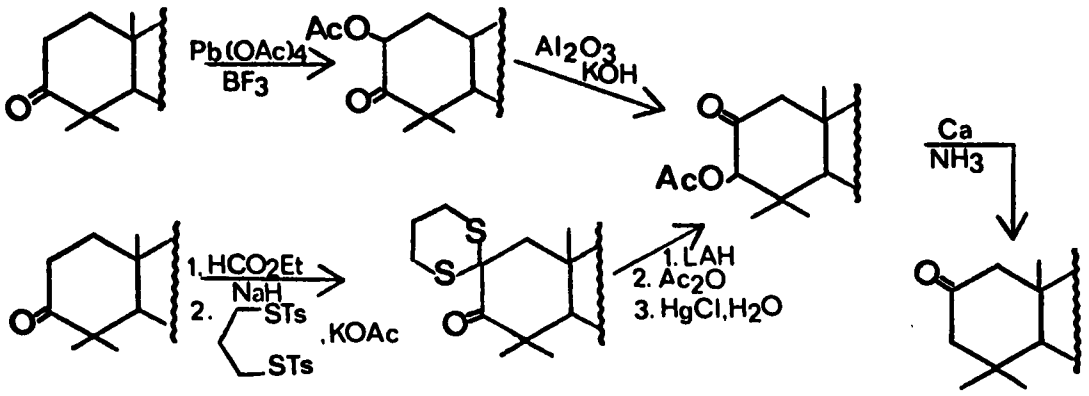




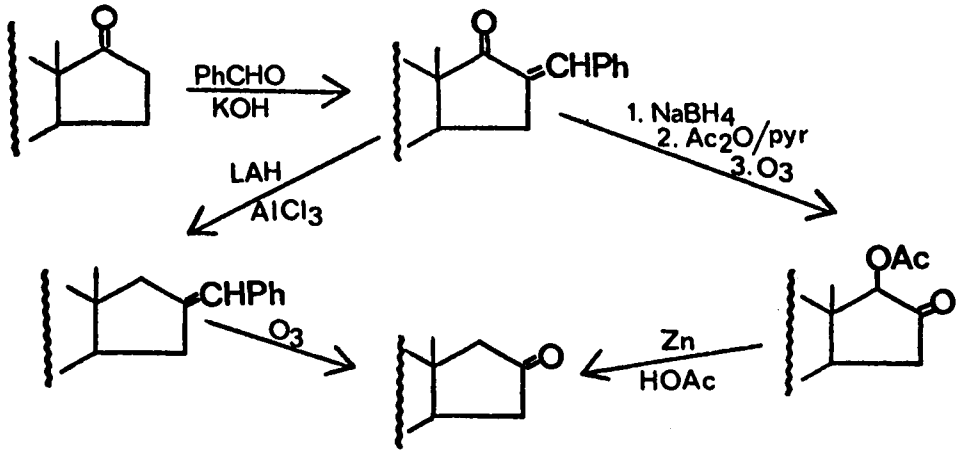
Shifting the keto function to an adjacent methylene via an α-bromoketone has been accomplished by Djerassi and Gurst[22] and by Clarke[23]. This method may also give mixtures of positional isomers.



Formation of an α-acetoxyketone followed by isomerization in basic media has been used by Ayer and Law[24], Levisalles and co-workers[25], and Elks and co-workers[26a,b] to move the ketone to adjacent carbon. The success of the method depends upon the thermodynamic stability of the isomeric acetoxyketones. Marshall and Roebke[27] have altered the scheme for use with acid-sensitive, oxidative-sensitive molecules.

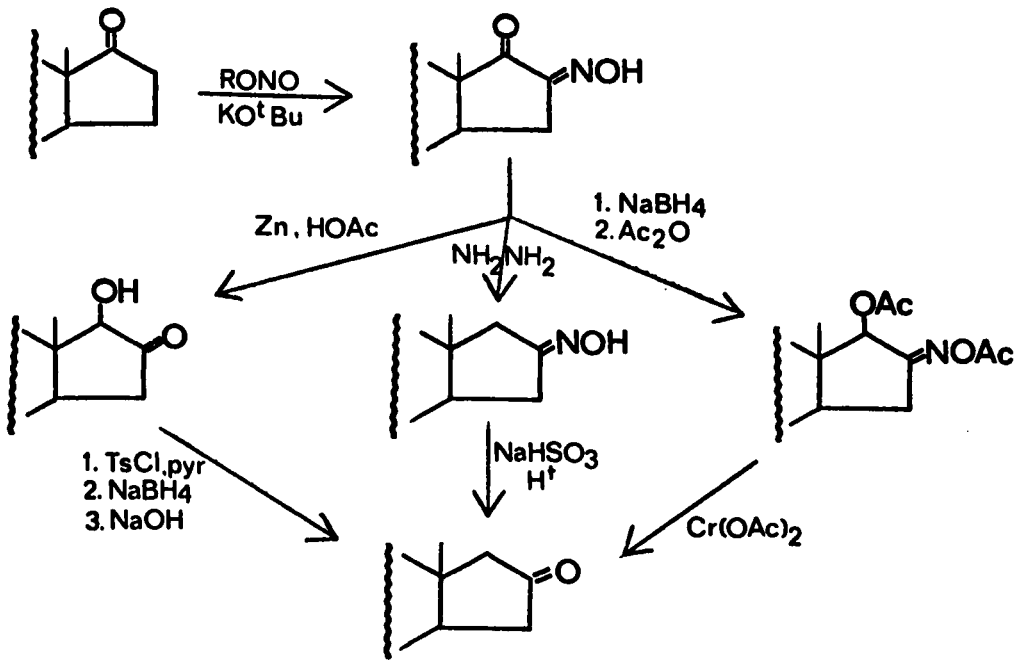


A more discriminative method has been developed by Meakins and co-workers[16,28] and Fetizone[29], in which the position of the ketone is changed through a benzylidene ketone. The reduction step in this procedure may give mixtures.



Another method of ketone transposition involves an intermediate oximinoketone. Stodola[30] and co-workers and Varech and Jacques[31] transformed the oximinoketone by a modified Clemmensen reduction to an α-ketol, which was then converted to the ketone. The possible equilibration

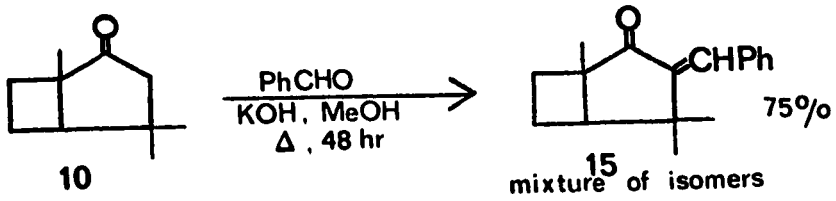
to a mixture of α-ketols was overcome by Just and Lin[32], and Elad and Ginsburg[33]. Mild Huang-Minlon reduction of the oximinoketone gave the oxime which was converted to the ketone by hydrolysis. In another variation Corey and Richman[34] altered the oximinoketone to an acetoximino acetate which on treatment with chromous acetate gave the desired ketone.



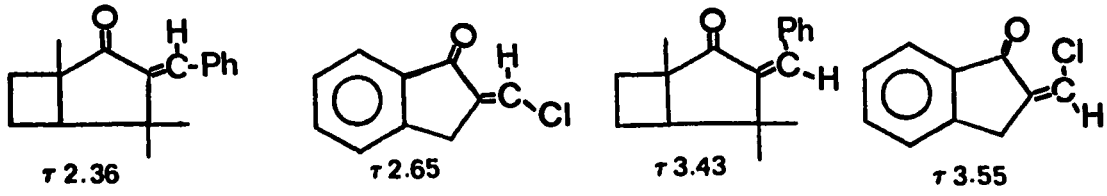
Of the methods considered for transposition of the ketone, we felt the most promising involved the benzylidene ketone, the acetoxyketone, and the oximinoketone. Thus we tried these methods to transpose the ketone of 1,4,4-trimethylbicyclo[3.2.0]heptan-2-one from C-2 to C-3.

Heating the bicyclic ketone 10 with benzaldehyde and potassium hydroxide for 48 hours gave in 75% yield the

benzylidene ketone 15 as a mixture of isomers (nmr). The ir spectrum shows absorption bands characteristic of an α,β-unsaturated ketone at 1710 and 1610 cm^{-1}, while the uv spectrum shows an absorption maximum at 290 nm (ε = 21,900) consistent with a benzylidene ketone.

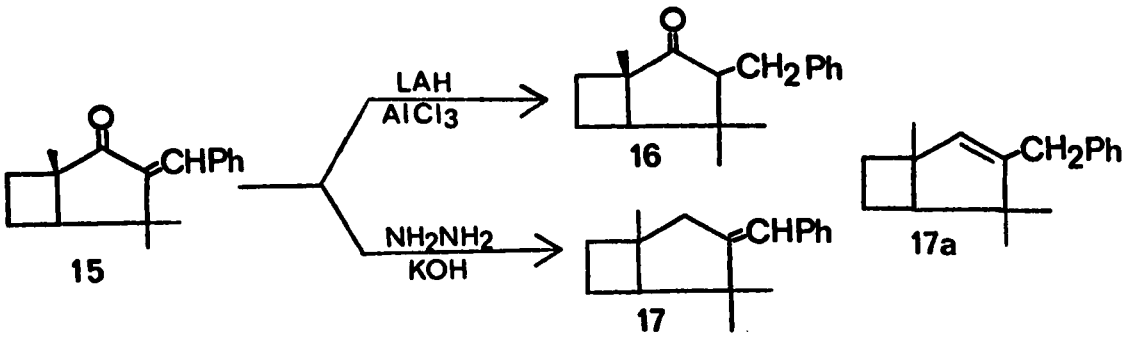


An attempt was made to separate the isomers. Chromatography over alumina gave first an oil which was a 3:1 mixture of cis:trans benzylidene ketone (nmr), followed by a crystalline compound, mp 57-59°, which was the cis benzylidene ketone 10a. Assignment of the stereochemistry was based on comparisons of the chemical shifts of the olefinic protons of our compounds with that reported for 2-chloromethylidene-1-indanone[35].



Reduction of the mixture of the benzylidene ketone with lithium aluminum hydride--aluminum chloride[28] under a variety of conditions gave rise to several products

The major component was the benzyl ketone 16, (ir: 1730 (C=O) cm^{-1})), nmr: no olefinic protons) resulting from 1,4-addition of hydride to the α,β-unsaturated ketone. Usually α,β-unsaturated ketones are reduced to olefins by lithium aluminum hydride--aluminum chloride[36a,b], but in some cases saturated ketones have been obtained[37].



Reduction of benzylidene ketone 15 by the Nagata-Itazaki[38] modification of the Wolff-Kishner reaction gave a 58% yield of the desired benzylidene compound 17 as an oil. This compound gives the correct analysis for $C_{17}H_{22}$ and its nmr spectrum shows three methyl groups at τ 8.95 (3H) and 8.73 (6H). No isomeric benzyl olefin 17a was produced as the nmr of the crude reaction product did not show signals in the region expected for a vinyl proton (τ 4.4-5.0) or a benzylic allylic methylene group (<τ 7.4).

The uv spectrum of the benzylidene compound 17 is unusual. Generally this type of compound absorbs at 250-255 nm with an extinction coefficient of 20,000; for example,

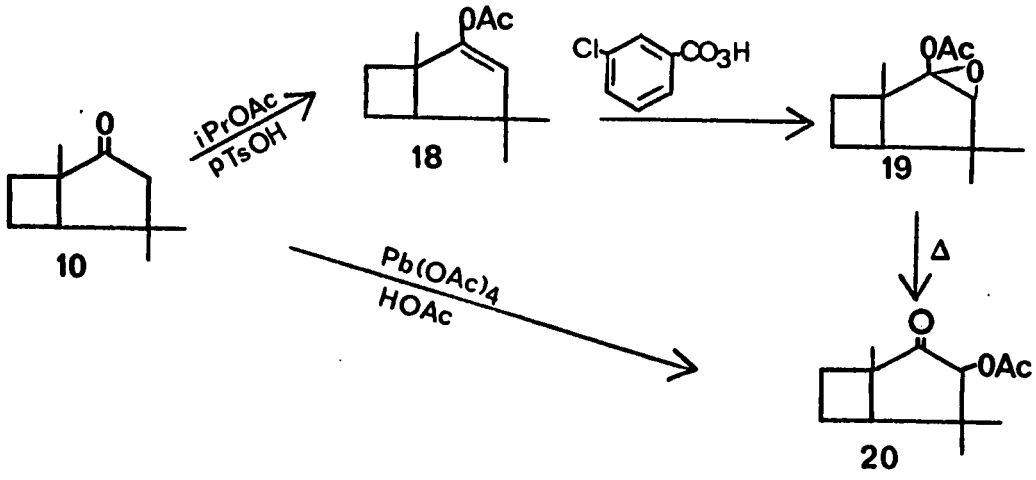
16-benzylidene-5α-androstane has λ_{max} 256 nm (ε = 22,050)[16]. Compound 17 has λ_{max} 249 (ε = 2,150) suggesting that steric crowding by the gem-dimethyl group at C-4 is relieved by twisting, resulting in non-coplanarity of the chromophoric group. Similar results have been observed for substituted biphenyls as well as cis- and trans-stilbenes[39].

The benzylidene compound 17 did not undergo reaction when subjected to low-temperature ozonolysis. However, ozonolysis of compound 17 in acetic acid at room temperature gave a low recovery of a crystalline compound, mp 138.5-140°, of unknown structure. The compound, which is insoluble in sodium bicarbonate solution, has the following spectral properties. (i) The infrared spectrum has carbonyl absorption at 1730 (sh) and 1695 cm^{-1}. (ii) The nmr spectrum has no signal lower than τ 7.8. There are two singlets (2H) at τ 8.14 and 8.17 superimposed on a broad multiplet and three methyl singlets at τ 8.72, 8.74 and 8.98. (iii) The mass spectrum shows measured ions at m/e 194 ($C_{12}H_{18}O_2$, M+), 166 ($C_{10}H_{14}O_2$, M+ - C_2H_4), and 121 (C_9H_{13}, M+ - $C_3H_5O_2$). (iv) The uv spectrum shows only end absorption. The ozonolysis product was acetylated with acetic anhydride in pyridine. The acetylated compound does not show hydroxyl absorption in the infrared, but shows carbonyl absorptions at 1775 and 1720 cm^{-1}.

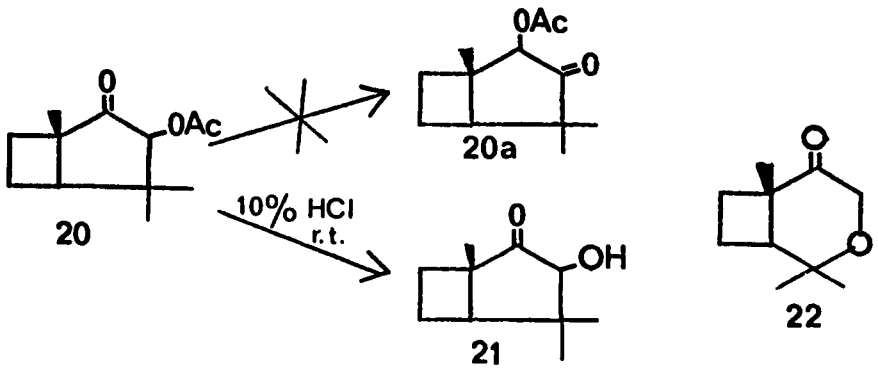
Other methods of oxidative cleavage ($KMnO_4/NaIO_4$[40],

$RuCl_3/NaOCl$[41]) were unsuccessful. Unreacted benzylidene compound was recovered intact. Attempted conversion to a diol by prolonged treatment with osmium tetroxide--hydrogen peroxide[42] gave unreacted 17. Presumably the lack of reactivity of compound 17 is due to steric hindrance of the carbon-carbon double bond.

Thwarted in this approach, we attempted ketone transposition through the α-acetoxyketone route. The enol acetate 18 was prepared in 59% yield by treating ketone 10 with iso-propenyl acetate. Epoxidation with m-chloroperbenzoic acid gave 79% of the acetoxy epoxide 19 which on heating rearranged to the acetoxyketone 20[43]. Alternatively, treatment of ketone 10 with lead tetraacetate[44] in refluxing acetic acid for four days gave a 89% yield of α-acetoxyketone 20. This compound absorbs at 1760, 1750 and 1235 cm^{-1} in the infrared. In addition, the nmr spectrum shows three methyl singlets (τ 9.20, 8.84, 8.77), an acetoxy methyl (τ 7.83), and a low-field methine (τ 4.36, COCHOAc).



Experiments designed to give the isomeric α-acetoxyketone 20a were unsuccessful. Under a variety of conditions (alumina[24], tetramethylammonium acetate[43], methanolic sulfuric acid[45]) α-acetoxyketone 20 was recovered, suggesting that of the two isomers, 20 and 20a, the former is the thermodynamically more stable. Very mild hydrolysis conditions (HCl, room temp, 24 h) led to formation of α-hydroxyketone 21 (ir: 3540 (OH), 1745 (C=O) cm^{-1}) while more drastic conditions (H_2SO_4, MeOH, reflux, 24 h or HI/HOAc[46]) gave several compounds.



The hydrolysis of compound 20 using sulfuric acid--methanol at 65° seemed promising at first. The mixture appeared to be composed of two compounds (tlc, alumina, chloroform). We speculated that one of the components was compound 22 since the nmr spectrum of the reaction mixture shows a singlet at τ 6.4. This signal might be caused by a methylene of the group $COCH_2O$. The mixture was separated by

dry column chromatography. The more polar compound was shown by spectral data to be α-hydroxyketone 21. The less polar component was a mixture as shown by its nmr spectrum. This was confirmed by glc analysis (Zonyl E-7, temp program, 180 ml/min) which showed the less polar component contained three compounds. The reaction mixture was not investigated further.

Attempted reduction of the α-acetoxyketone 20 to an alcohol by a modified Wolff-Kishner reaction led to a low recovery of a mixture of compounds. Attempted reduction through the p-toluenesulfonylhydrazone derivative of the α-acetoxyketone 20 was unsuccessful.

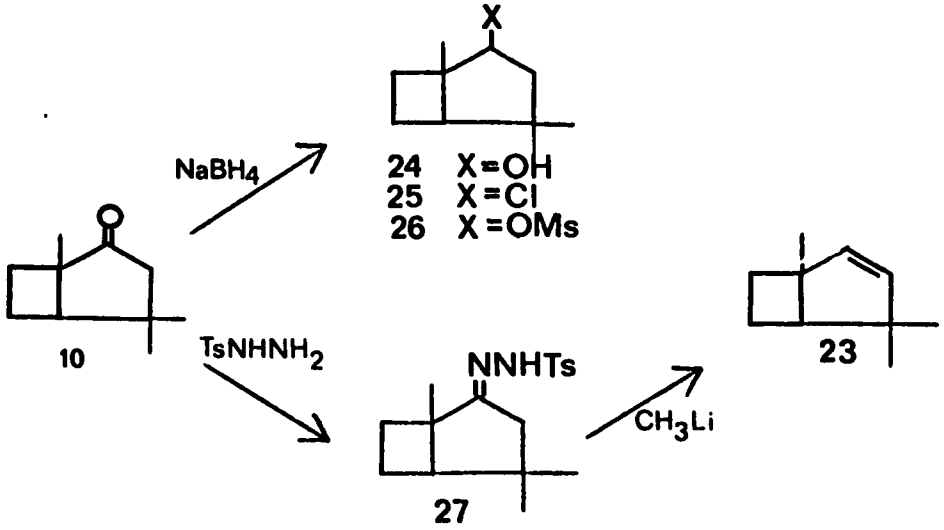
Because the α-acetoxyketone could not be converted to its isomer successfully, we felt that it might be possible to transpose the ketone through the intermediate olefin 23. Treatment of ketone 10 with sodium borohydride gave, in 95% yield, the alcohol 24. This compound, which is a semi-solid (mp 46-54°) gives the correct analysis for $C_{10}H_{18}O$, and shows hydroxyl absorption bands at 3640, 3480 and 1065 cm^{-1} in its infrared spectrum. The nmr spectrum displays three methyl singlets (τ 8.80, 3H; 9.31, 6H), a hydroxyl proton (τ 7.76), and a carbinol proton (τ 6.23, t, J = 9Hz) coupled to two methylene protons (τ 8.33, d, J =9Hz).

The alcohol 24 was resistant to dehydration by a variety of methods. Treatment with thionyl chloride in

methylene chloride[49] or with thionyl chloride in pyridine[50] gave a new compound (tlc, silica gel, benzene). This compound does not show hydroxyl absorption in the infrared spectrum, and the nmr spectrum shows signals similar to that of the starting alcohol. It seems likely that the chloro compound 25 has been formed, i.e., that the alcohol undergoes substitution rather than elimination under these reaction conditions.

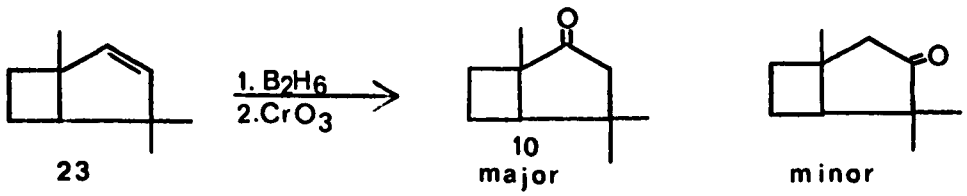
The alcohol was converted to the mesylate 26 by treatment with methanesulfonyl chloride in pyridine. The ir spectrum of compound 26 does not show hydroxyl absorption, whereas the nmr spectrum shows a low-field methine (τ 5.32, CHOMs) and a mesyl methyl (τ 7.10). The mesylate was recovered when allowed to reflux with ethanolic sodium ethoxide or when stirred with potassium t-butoxide in dry dimethyl sulfoxide[51].

Heating alcohol 24 with iodine[52] or anhydrous oxalic acid[53] gave a low recovery of a mixture of compounds.



The olefin 23 was obtained by another route. Ketone 10 was converted to the tosylhydrazone 27, then treated with methyl lithium to give the olefin 23[54]. The low yield (39%) of compound 23 may be, in part, attributed to its volatility (bp 115-120°, 760 mm). The ir spectrum of olefin 23 shows absorption at 1610 cm^{-1}. The nmr spectrum displays a singlet (τ 4.63) for two equivalent olefinic protons, as well as three methyl singlets (τ 8.83, 9.03, 9.05).

Compound 23 did not undergo Markownikoff hydration by Brown's solvomercuration method[55], unreacted olefin being recovered. Hydroboration[56] of compound 23 followed by two-phase oxidation[57] gave a mixture of ketones, which was shown by glc to be a 3 to 2 mixture of positional isomers, the major isomer being ketone 10.



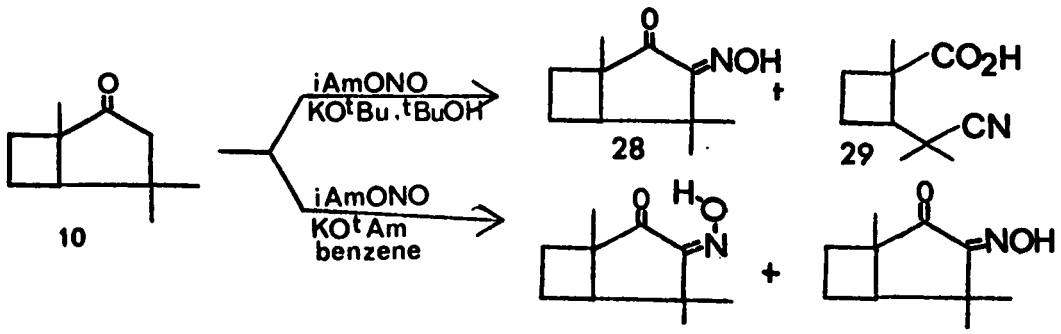
23 10 major minor

In search of a more promising ketone transposition method, we pursued the oximinoketone route. Initially formation of the oximinoketone 28 presented problems. Treatment of ketone 10 with n-butyl nitrite under acid catalysis[58] for 12 hours gave only starting ketone, whereas use of i-amyl nitrite with potassium t-butoxide in anhydrous t-butyl alcohol[59] led to formation of the oximino-

ketone. When the reaction was carried out on a larger scale, however, very low yields of oximinoketone were obtained. The major compound formed during the reaction was the acid nitrile, 29, (mp 189-192°) which arose from a Beckmann cleavage reaction. The ir spectrum shows a broad carboxyl band (3400-2500 cm^{-1}), a nitrile band (2220 cm^{-1}) and a carbonyl band (1710 cm^{-1}). In order to determine at which stage of the reaction cleavage occurred, the following experiments were carried out. Oximinoketone 28 was recovered quantitatively after being stirred with dilute hydrochloric acid for one hour. On the other hand, a mixture of oximinoketone and acid nitrile was obtained when compound 28 was stirred in a solution of potassium hydroxide in anhydrous t-butyl alcohol for 24 hours. It thus appeared that cleavage occurred during the reaction and not during the reaction work-up. Manipulation of the experimental conditions enabled us to form oximinoketone 28 in good yield. Thus treatment of ketone 10 with dry i-amyl nitrite and either freshly sublimed potassium t-butoxide or potassium t-amylate in anhydrous benzene[60] gave, in 89% yield, oximinoketone 28 as a mixture of isomers (ir, nmr).

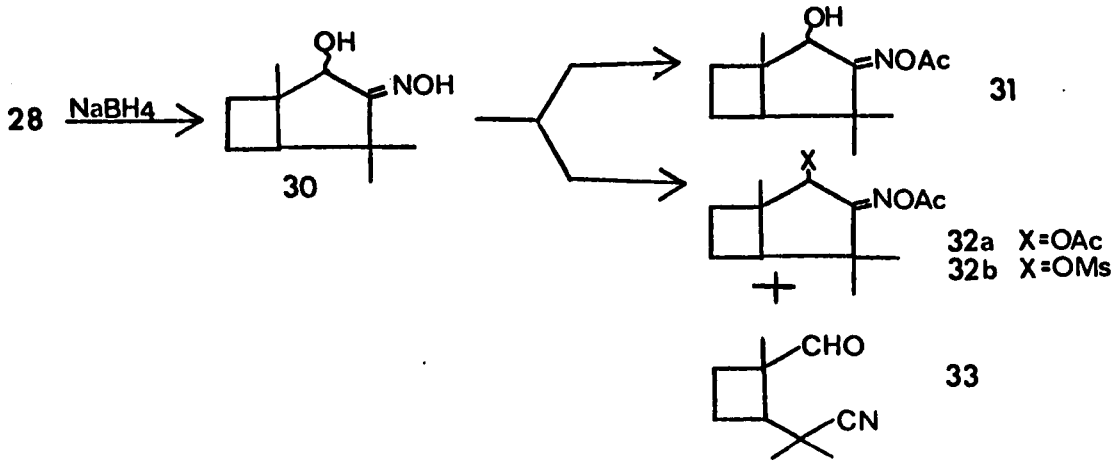
The ir spectrum of the oximinoketone mixture shows absorptions at 3560, 3360 (NOH), 1740, 1690 (C=O), 1630 and 1580 (C=N) cm^{-1}. An attempt was made to separate the

isomers. Chromatography over silicic acid gave first a crystalline mixture of the two isomers, followed by a crystalline oximinoketone, mp 128-131.5°. This isomer, which was present in largest amount, shows absorption bands at 3560, 3360 (NOH), 1740 (C=O), and 1630 (C=N) cm^{-1} in its infrared spectrum. This is consistent with an intermolecularly hydrogen-bonded oximinoketone. The nmr spectrum shows signals for the oximino proton (τ 0.15) as well as three methyl groups (τ 8.59, 3H; 8.75, 6H).



In an attempt to utilize Corey's ketone transposition method[34], the oximinoketone was reduced quantitatively with sodium borohydride to the oximino alcohol, 30. The ir spectrum of this crystalline compound (mp 69-72.5°) shows absorption bands at 3580, 3300 and 1070 (br, NOH, OH) and 1680 (w, C=N) cm^{-1}. Mild acetylation of 30 afforded a crystalline acetoximino alcohol 31 (mp 89.5-90.5°). The ir spectrum of the acetoximino alcohol shows absorption bands at 3550, 3450, 1070 (OH), 1755 (C=O), and 1660 (C=N) cm^{-1}. More vigorous acetylation gave a mixture of acet-

oximino acetate 32a (ir: no OH; 1770, 1745 cm^{-1} (C=O) cm^{-1}) and another compound which was probably the cyanoaldehyde 33 (ir: 2730, 1720 CHO, 2230 cm^{-1} (C≡N) cm^{-1}; nmr τ -0.33 CHO). Attempted mesylation of the acetoximino alcohol gave a mixture of the acetoximino mesylate 32b and the cyanoaldehyde. Although the latter compound was not isolated, fragmentation to form the cyanoaldehyde is not unusual. Such a reaction is well documented for α-hydroxyoximes, α-ketooximes, α-ketoetheroximes and similar compounds[61].



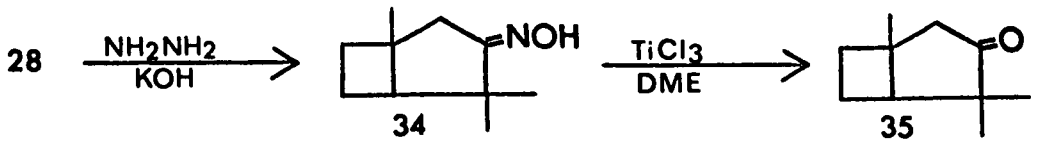
Since neither the acetoximino acetate nor the acetoximino mesylate could be prepared in good yield, reductive deoximation was attempted on the acetoximino alcohol, 31. Compound 31 was treated with chromous acetate and the reaction product was analyzed by glc--mass spectroscopy. A mixture of eight compounds was obtained. Three minor compounds had the desired molecular ion (m/e 152),

and one of these had the same retention time as ketone 10. The major compound formed was probably the cyanoaldehyde 33 as shown by the ir and nmr spectra of the reaction mixture. The low yield of ketone produced by this reaction precluded its use in our synthetic sequence.

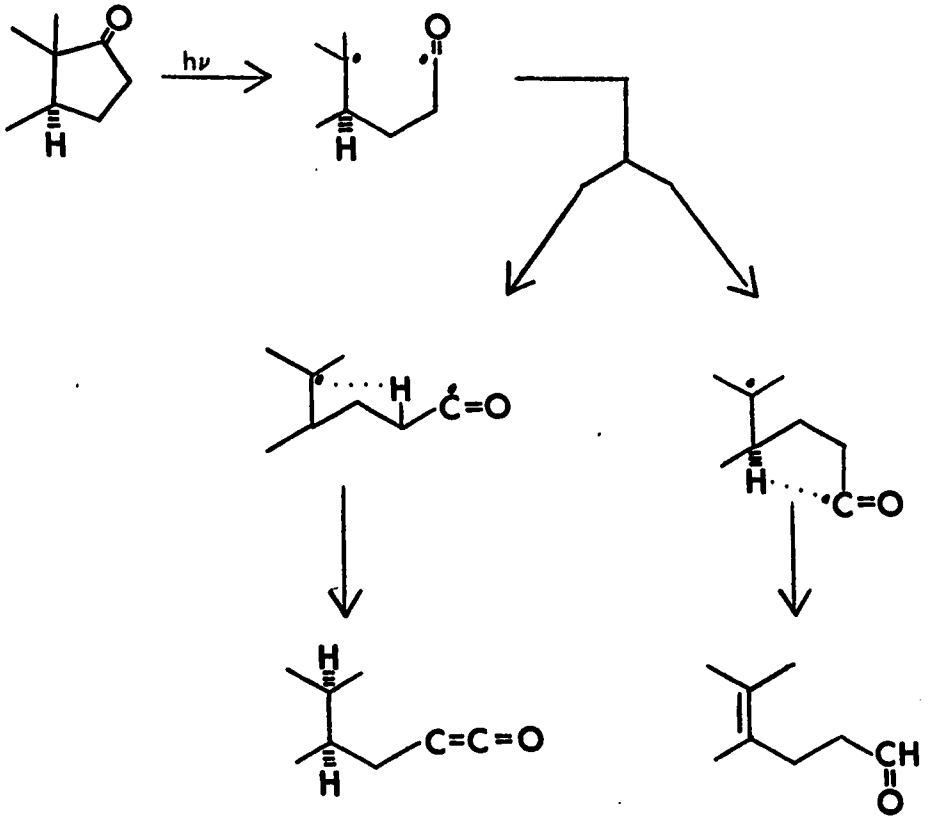
Utilization of the Wolff-Kishner reaction enabled us to remove the carbonyl group in the oximinoketone. Heating the oximinoketone with excess hydrazine[33] led to isolation of a small quantity of oxime 34, however use of just one and one-half equivalents of hydrazine hydrate with excess base[32] gave a crystalline oxime (mp 118-119.5°) in 82% yield. This compound analyzes correctly for $C_{10}H_{17}NO$. Its ir spectrum shows oxime absorption at 3580 and 3290, as well as C=N absorption at 1670 cm^{-1}. The nmr spectrum displays a low-field, D_2O exchangeable proton (τ 0.80, NOH), geminal methylene protons as a set of doublets (τ 7.07, 7.73, J = 19Hz) and three methyl signals (τ 8.70, 3H; 8.93, 6H).

Several methods were investigated in an attempt to convert oxime 34 to the ketone. Hydrolysis with levulinic acid[62a], sodium bisulfite[62b], or treatment with thallium trinitrate[62c] gave low yields of ketone. However, ketone 35 was formed in high yield when the oxime was treated with titanium trichloride[62d] in dimethoxyethane. The ketone analyzes correctly for $C_{10}H_{16}O$ and forms a 2,4-

dinitrophenylhydrazone derivative (mp 169-171.5°). It shows carbonyl absorption at 1735 cm^{-1} in the infrared. The nmr spectrum of ketone 35 displays two singlets for non-equivalent geminal methylene protons (τ 7.68, 7.70) and three methyl groups (τ 8.67, 9.05, 9.10).

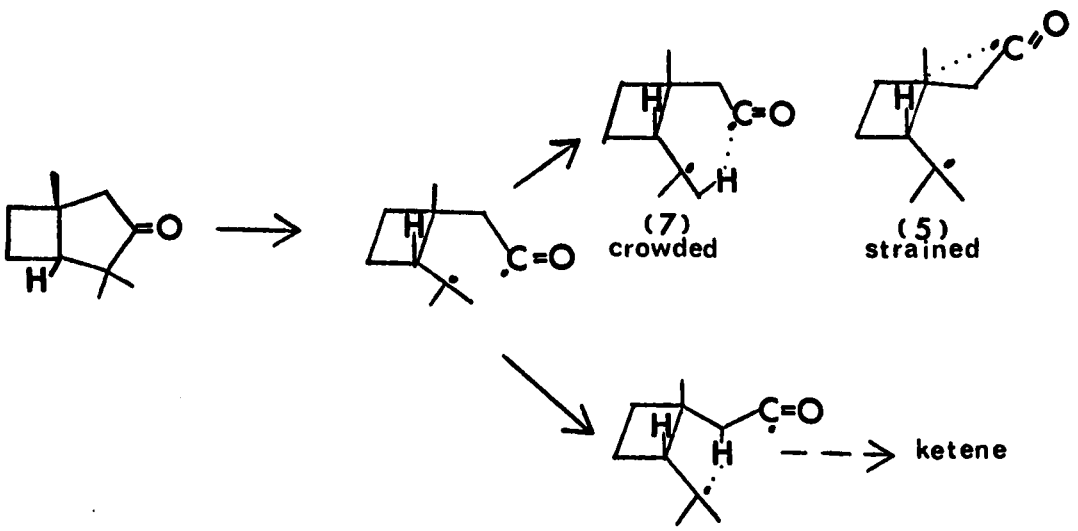


With ketone 35 in hand, we considered several methods of effecting cleavage of the C-3 C-4 bond. Photolytic cleavage reactions in saturated ketones are well known[63,64]. The reaction can formally be represented as



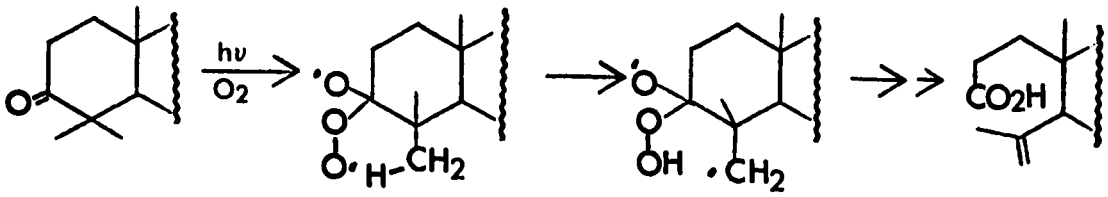
fission of the CO-C bond on the side of the carbonyl group where the most substituted radical will be generated, followed by stereoselective intramolecular disproportionation to form a ketene and/or an unsaturated aldehyde. The formation of an unsaturated aldehyde is observed largely in non-protic solvents.

Examination of a molecular model of ketone 35 showed that formation of a ketene should be favored over formation of an unsaturated aldehyde. Thus the photochemical cleavage of ketone 35 did not seem promising.

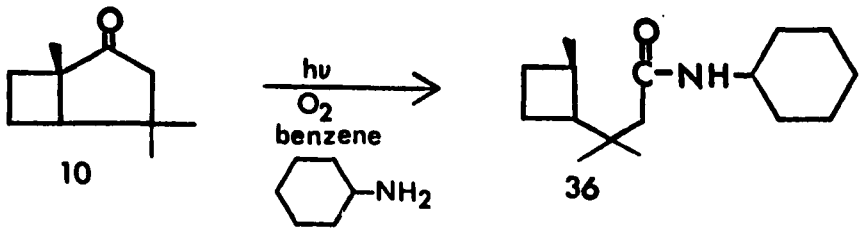


An alternative reaction is the photo-oxidation of cyclic ketones to unsaturated carboxylic acids[64]. When 3-keto-4,4-dimethyl isoprenoids are irradiated while oxygen is continuously passed through the solution, an unsaturated acid can be isolated after 24 hours. The proposed

mode of formation assumes that the cyclic ketone in the photoexcited state reacts with an oxygen molecule to form a hydroxy--hydroperoxy diradical. The diradical undergoes intramolecular rearrangement in a stereoselective manner to yield an unsaturated acid.

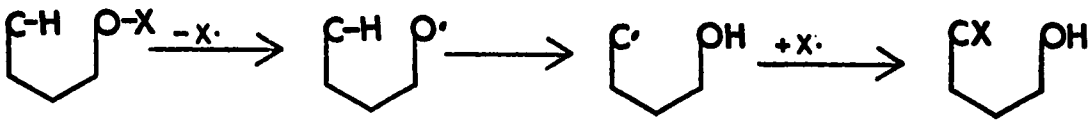


Any ketone with at least one hydrogen on a β-carbon and cisoid arrangement of oxygen and hydrogen should undergo the cleavage reaction. These requirements are met by ketone 10 and ketone 35. Because ketone 10 was more readily available than ketone 35, it was used as a model compound for the photo-oxidation reaction. An oxygen-saturated solution of ketone 10 containing cyclohexylamine was irradiated for 24 hours. The photolysis mixture was separated into acidic and neutral fractions. The acidic fraction (20%) contained a mixture of many compounds. The neutral fraction (70%) contained mainly one compound which was isolated by chromatography. It is a saturated amide, mp 53-56°, (ir: 3430 (NH), 1670, 1650 (C=O, amide I, amide II) cm^{-1}; nmr: no olefinic protons) and was assigned structure 36 on the basis of its spectral properties.



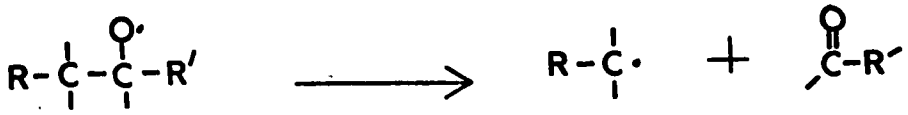
While photo-oxidative cleavage has been used in synthesis of 3-ketosteroids[65], yields are generally poor; the other products formed are those arising from ketene formation. Since one of our objectives was to achieve the synthesis of grandisol in good yield, this route did not seem especially promising.

It has been shown that molecules which meet certain structural and geometrical requirements can undergo specific intramolecular free-radical attack at unactivated C-H bonds. A number of reactions of this type have been reviewed[66a-d], and have become synthetically important. They include the photolysis of nitrite esters (the Barton reaction)[67], photolysis of hypohalites[68], treatment of an alcohol with bromine and silver oxide[69], and treatment of an alcohol either thermally or photolytically with lead tetraacetate[70]. The key step in each of these reactions is an intramolecular 1,5-hydrogen transfer through a six-membered cyclic transition state. This transfer corresponds to specific attack on a hydrogen atom attached to a δ-carbon. In this type of reaction the distance between reacting centers must not be too great (<2.8 Å).

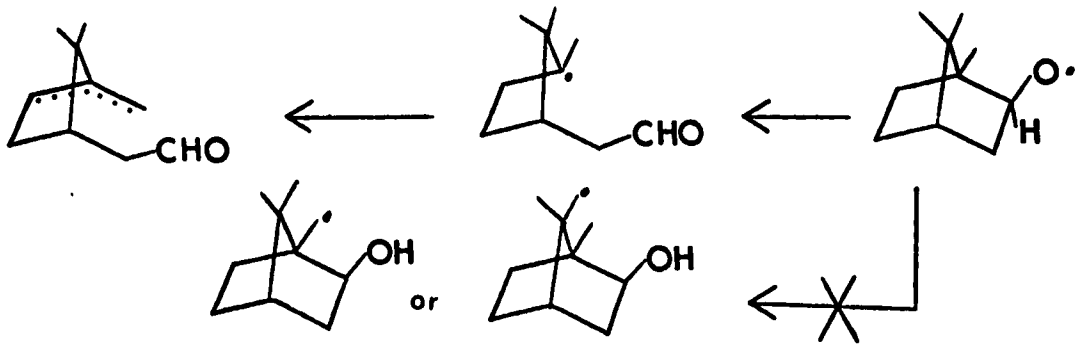


X=NO, Halogen, $Pb(OAc)_3$

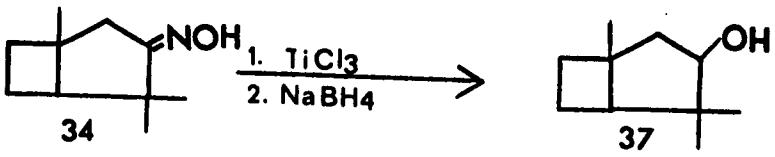
No products resulting from 1,4-hydrogen abstraction have been observed. In compounds which may undergo only 1,4-hydrogen abstraction because of structural or steric reasons, an alternate reaction occurs: β-cleavage of the oxy-radical to form a carbonyl compound and an appropriately substituted alkyl moiety.



For example, in isoborneol[71], the distance between the δ-methyl group and oxygen is large, thus the alkoxy radical undergoes fragmentation.



These "Barton-type" reactions could have synthetic utility in our case because reaction of the appropriate alcohol derivative should favor cleavage over 1,5-hydrogen abstraction.



34 37

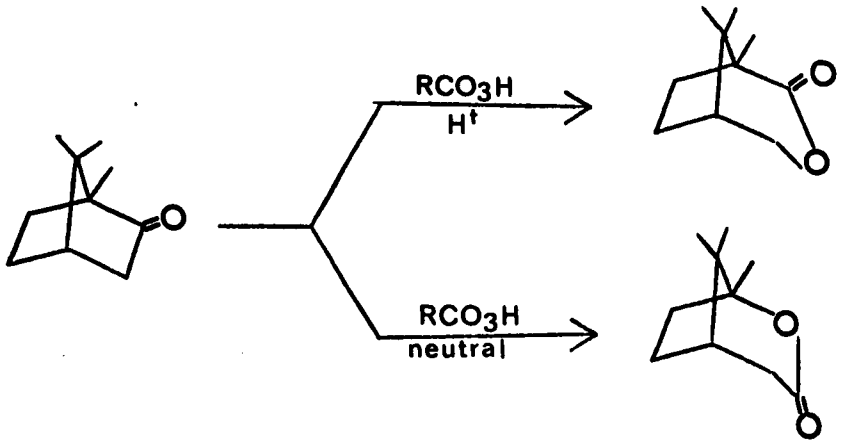
Alcohol 37 was prepared in two steps from oxime 34 without isolation of the intermediate ketone. Thus treatment of oxime 34 with titanium trichloride, followed by sodium borohydride reduction gave alcohol 37 in 95% overall yield. Alcohol 37, which is a liquid (n_D 1.4675) shows absorptions characteristic of an α-branched secondary alcohol at 3370 and 1060 cm^{-1} in its infrared spectrum. The nmr spectrum shows a carbinol proton as a quartet (τ 5.85, J = 7, 11Hz), a hydroxyl proton (τ 7.76) and three methyl singlets (τ 8.77, 8.90, 9.05).

Although we feel that a derivative of alcohol 37 may undergo cleavage, no such reaction was attempted since at about the same time successful cleavage of the C-3 C-4 bond was obtained as described on page 40.

One final route to cleavage of the C-3 C-4 bond should be considered: that arising through a rearrangement reaction. Three such reactions could lead to synthetically useful intermediates in our case, notably, the Baeyer-Villiger rearrangement[72a,b], the Schmidt reaction[73a,b], and the abnormal Beckmann rearrangement[74a-d].

In the Baeyer-Villiger reaction, treatment of a

cyclic ketone with a peracid gives a lactone. Normally the group which migrates is that which is best able to support a positive charge. It is apparent that oxidation of an unsymmetrical cyclic ketone can lead to two isomeric lactones. Often reaction conditions may influence product distribution. For example, camphor gives rise to different products when oxidations are carried out in neutral and acidic media[75].

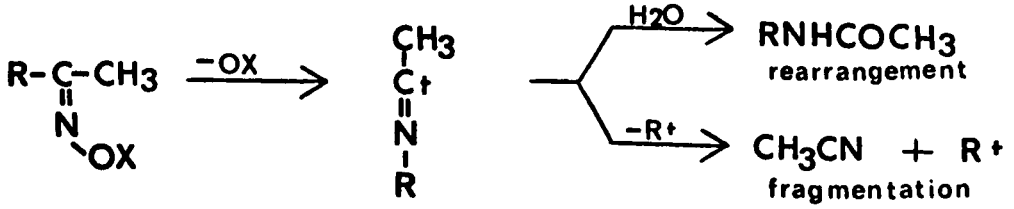


However, when 4,4-dimethyl-3-ketosteroids are subjected to Baeyer-Villiger reaction conditions, loss of a methyl group from C-4 results giving a monomethyl lactone[76a-c]. This interesting modification limits the utility of the Baeyer-Villiger oxidation as a possible step in our synthesis of grandisol.

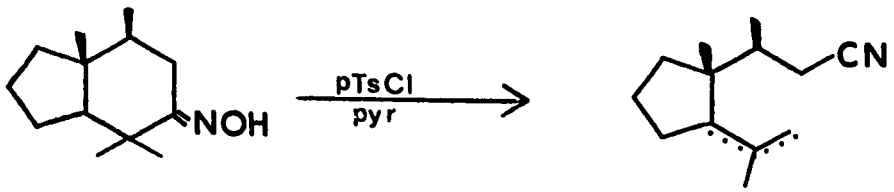
When an unsymmetrical, cyclic ketone is treated with hydrazoic acid, two isomeric lactams may be produced and under certain conditions both products of the Schmidt

reaction are formed. Whenever one of the groups attached to the carbonyl group gives rise to a stable carbonium ion, fragmentation producing a nitrile may result[77].

The Beckmann rearrangement reaction of oximes usually gives results similar to the Schmidt reaction. In general, a lactam is formed when a cyclic oxime is treated with phosphorus pentachloride, concentrated sulfuric acid or a number of other Lewis or proton acids. The group which migrates is the one trans to the hydroxyl group. It is known, however, that unsymmetrical cyclic ketoximes can form both possible lactams and it may be that the oxime undergoes isomerization under the reaction conditions before the migration takes place. The so-called "abnormal Beckmann rearrangement", a fragmentation reaction, may occur with ketoximes, particularly in cases where a stable carbonium ion may be formed. There is evidence in some cases that the mechanism involves first rearrangement and then amide formation or cleavage, i.e., that the product is determined after formation of a common intermediate. Variation of experimental conditions can direct the reaction course.



This fragmentation reaction has found synthetic utility in the triterpenoid field[78], and more recently, a Beckmann fragmentation was a key step towards the synthesis of hydrazulenes[79].



We felt that the abnormal Beckmann rearrangement was the method of choice to effect bond cleavage in our synthetic sequence. Initial experiments to this end were disappointing. Treatment of oxime 34 with p-toluenesulfonyl chloride in refluxing pyridine, thionyl chloride, phosphorus pentachloride, or phosphorus pentoxide gave varying mixtures. The ir spectrum of the mixtures showed two nitrile absorptions (2260, 2220 cm^{-1}) and carbonyl absorption of a lactam (1655 cm^{-1}). Therefore it seemed important to establish the stereochemistry of the oxime.

Several methods utilizing nmr have been suggested for the determination of the stereochemistry of oximes[80a-d]. In the method of Karabatsos and co-workers[80a], nmr spectra were obtained in carbon tetrachloride and in benzene. The magnitude of the benzene-induced changes in chemical shifts were taken as an indication of configuration. They observed that $\Delta\nu(\Delta\nu = \nu_{benzene} - \nu_{CCl_4})$ for protons trans to

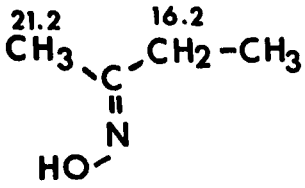
the oxime hydroxyl is greater than the Δν value for the same proton when cis to the hydroxyl.

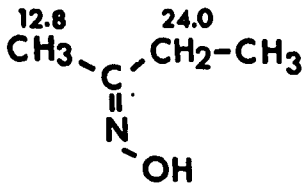
The nmr spectra of oxime 34 in benzene and carbon tetrachloride show that only one isomer is present. Since the assignment of configuration by solvent effects requires comparison of changes in chemical shifts for the same protons in both isomers, this method was not informative in our case.

Fox and co-workers[80b] obtained nmr spectra of oximes in benzene solution. The addition of small amounts of concentrated hydrochloric acid vapor to an nmr sample caused the α-protons cis to the hydroxyl to shift to higher field, while the trans α-protons were shifted to lower field.

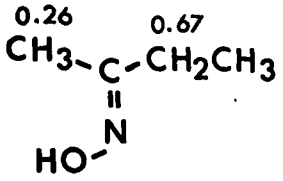
When hydrogen chloride is added to a benzene solution of oxime 34, the nmr spectrum shows no change. Addition of excess hydrogen chloride resulted in salt formation.

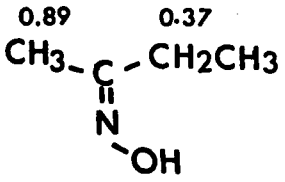
Tris(dipivalomethanato)europiumIII [$Eu(DPM)_3$] has recently been used to effect paramagnetic-induced shifts in the nmr spectra of oximes. Wolkowski[80c] obtained nmr spectra in carbon tetrachloride and carbon tetrachloride--$Eu(DPM)_3$. Results were reported as $\Delta E\nu$ ($\Delta E\nu = \delta_{Eu} - \delta_{CCl_4}$) ppm after extrapolation to an equimolar ratio of $Eu(DPM)_3$ to oxime. He found that cis α-protons are more strongly shifted than trans α-protons, for example the values for cis- and trans-2-butanone oxime are shown below.





He proposes that the proton to oxygen distance is a predominant factor in the induced shifts while the nitrogen lone pair plays an insignificant role. On the other hand, Berlin and Rengaraju[80d] obtained nmr spectra in deuterochloroform and deuterochloroform--Eu(DPM)$_3$. Results were reported as $\Delta\delta$ ($\Delta\delta = \delta_{Eu} - \delta_{CDCl_3}$) ppm. They found that all protons of the <u>trans</u> forms are more deshielded than the corresponding protons of the <u>cis</u> forms, for example, value of <u>cis</u>- and <u>trans</u>-2-butanone oxime are shown below.





They suggest that co-ordination occurs through the nitrogen lone pair and that the difference in magnitude of deshielding of <u>trans</u> and <u>cis</u> forms is a steric effect.

Addition of Eu(DPM)$_3$ to an nmr sample of oxime <u>34</u> initially gave poor spectra. However, when a lower temperature (10°) and longer contact time (one hour after addition of shift reagent) was employed the following

results were observed. The gem-dimethyl group shifts 0.99 ppm downfield, whereas the methylene protons shift 2.00, 2.04 ppm downfield. In view of the contradictory results of Wolkowski and Berlin and Rengaraju, we are reluctant to assign the stereochemistry of the oxime on the basis of these methods. Presumably the complex is binding on the side of the methylene group, but whether it coordinates with oxygen or with the nitrogen is uncertain.

A trans stereochemistry of oxime 34 ((E) to the gem-dimethyl group) is desirable for cleavage of the C-3 C-4 bond. On the intuitive assumption that we indeed had the desired stereoisomer, experimental conditions which would effect the cleavage were sought. When oxime 34 was stirred with phosphorus pentachloride in anhydrous benzene--ether (1:1), seconitrile 38 was formed as the major product (glc--mass spectroscopy). If the solvents were not rigorously dry, another compound of uncertain structure was formed instead. The compound has the following spectral properties:

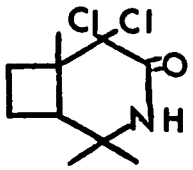
(i) The ir spectrum shows sharp absorption bands at 3300 (NH), 1670 (C=O) cm^{-1}.

(ii) The nmr spectrum shows a broad signal at τ 2.65 and three methyl singlets (τ 8.33, 8.48, 8.80).

(iii) The mass spectrum shows an ion at m/e 220 with measured mass for $C_9H_{12}NO^{35}Cl_2$. This was obviously not the molecular ion since it had an even

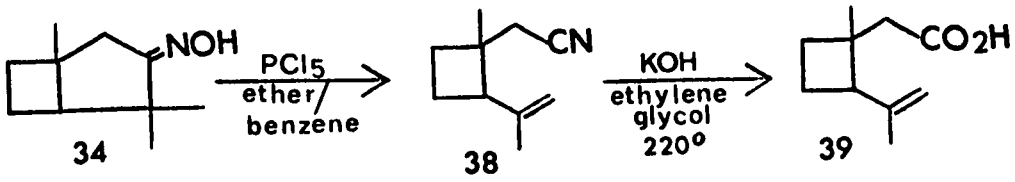
number of hydrogens. Chemical ionization mass spectrometry shows that the molecular ion is m/e 235.

A structure consistent with the spectral evidence is shown below. It could arise by chlorination of the lactam formed on Beckmann rearrangement of oxime 34.



Phosphorus pentachloride has previously been reported to chlorinate alpha to the carbonyl of a ketone[81], for example, 2,2-dimethyl-3-pentanone forms 2-chloro-4,4-dimethyl-3-pentanone upon treatment with phosphorus pentachloride.

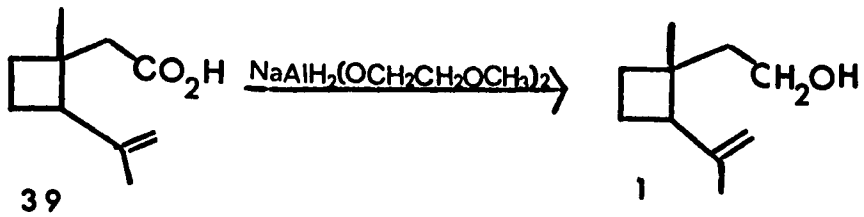
Seconitrile 38, obtained by Beckmann cleavage of oxime 34, was not purified but hydrolyzed with potassium hydroxide to secoacid 39.



The secoacid had been prepared previously be Sidall and co-workers[8b]. The ir spectrum of compound 39 shows absorption bands at 3300-2500 (COOH), 1710 (C=O), and 1650, 890

($C=CH_2$) cm^{-1}. The nmr spectrum displays the acidic proton at τ 0.4, two vinyl protons (τ 5.16, 5.34), a vinylic methyl group (τ 8.33), and a methyl group (τ 8.67). The spectral data obtained corresponds to that reported[8b].

Reduction of secoacid 39 with sodium bis(2-methoxyethoxy) aluminum hydride gave grandisol, 1. The spectra of the synthetic product, compound 1, are identical with published spectra[6b], and are presented on pp 47.

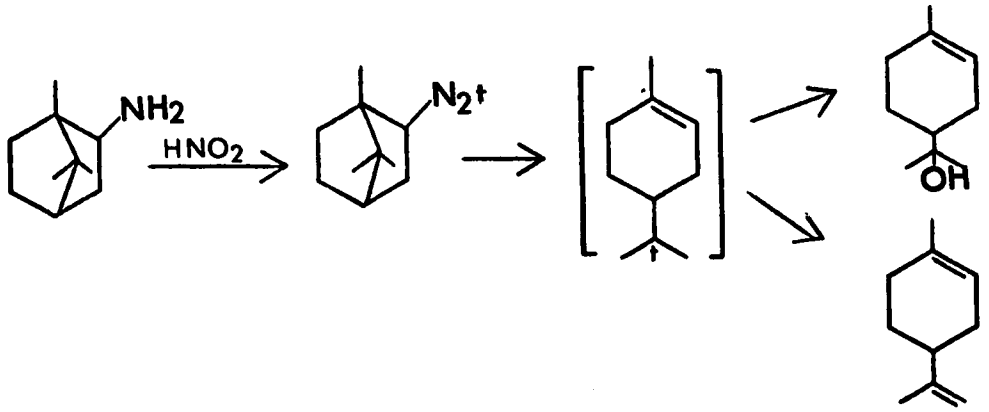


39 1

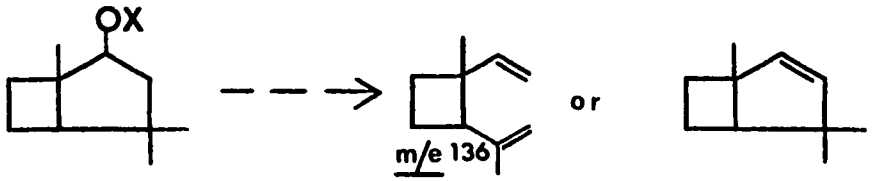
As mentioned at the beginning of the discussion, one way of modifying ketone 10 to grandisol would be transformation of the C-2 carbonyl to a leaving group followed by a fragmentation reaction[82a,b]. While this synthetic sequence was not completed, some preliminary experiments were directed towards this plan and are reported here.

When alcohol derivatives with both α and γ branching are subjected to solvolysis, they may undergo fragmentation to give an olefin and a carbonium ion. The carbonium ion then undergoes further elimination or substitution depending on the reaction conditions.

These fragmentation reactions occur to the greatest extent for tertiary substrates, but even with favorable substrates fragmentation is not always observed. Thus cis- and trans-3,3,5-trimethylcyclohexyl tosylate does not give rise to fragmentation upon solvolysis[83]. However, fragmentation does occur in strained compounds, for example, endo-bornyl amine forms α-terpineol and limonene on deamination[84].

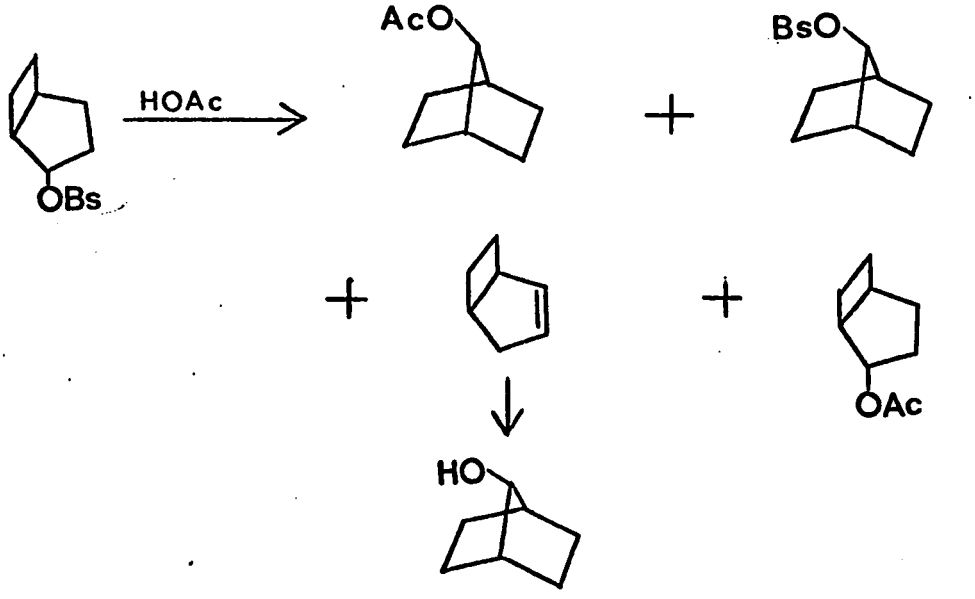


We felt that solvolysis of a derivative of alcohol 34 might favor cleavage over elimination as shown below.



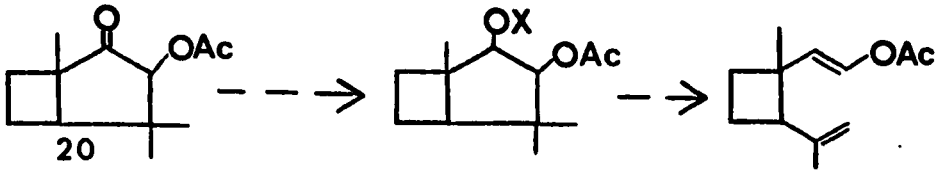
The mesylate 26, prepared by treating alcohol 24 with methanesulfonyl chloride in pyridine was solvolyzed

in refluxing acetic acid containing sodium acetate. The reaction product was analyzed by glc--mass spectroscopy. Of the twelve compounds present in the reaction mixture, only one minor compound had a molecular ion of m/e 136. Several major components (4) had molecular ions of m/e 154, isomeric with alcohol 24. It therefore seems that solvolysis of mesylate 26 gives rise mainly to rearrangement products. Other workers have obtained similar results. Winstein and co-workers[85] studied the solvolysis of a similar compound, 2-brosyloxybicyclo[3.2.0]heptane. They found that this ester acetolyzes with extensive rearrangement, the major product being 7-acetoxybicyclo[2.2.1]heptane.



Perhaps a better molecule for fragmentation would be that derived from α-acetoxyketone 20. Solvolysis of such a compound could give the desired fragmentation pro-

duct.

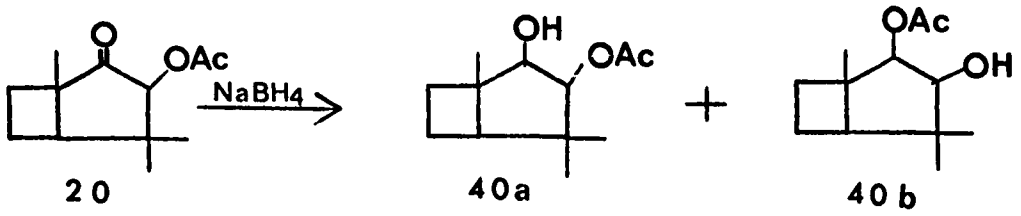


This fragmentation scheme has an advantage over that previously proposed. The fragmentation product has a functional group on the correct carbon for modification of the compound to grandisol.

We therefore investigated such a reaction pathway. Reduction of α-acetoxyketone 20 with sodium borohydride gave a mixture of two acetoxyalcohols as shown by nmr spectroscopy (two acetyl singlets τ 7.87, 7.93). Varying the reaction time (15 min to 4 h) or solvent composition (DME/H_2O: 4/1 to 50/1) did not alter the product composition. Conditions could not be found which would allow separation of the mixture (tlc, glc).

To determine whether the mixture contained positional isomers or epimeric acetoxyalcohols, the following experiment was carried out. Two-phase oxidation[57] of the acetoxyalcohols gave two acetoxyketones, 20 and 20a, as shown by glc and nmr spectroscopy (methine proton singlets τ 4.37, 4.74). Thus sodium borohydride reduction of α-acetoxyketone 20 gave a mixture of positionally isomeric acetoxyalcohols, 40a and 40b. Similar results have been

reported for sodium borohydride reduction of steroidal α-acetoxyketones[86].

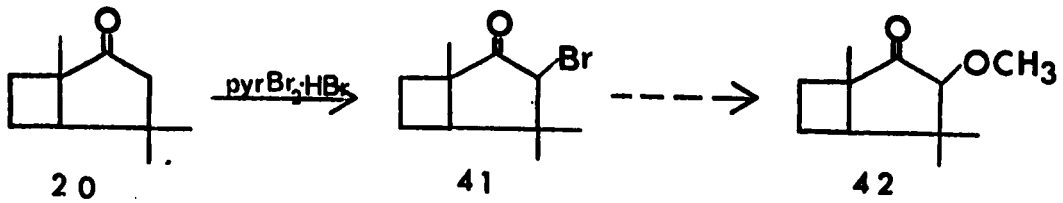


20 40a 40b

Reduction of acetoxyketone 20 either catalytically or with sodium cyanoborohydride led to recovery of compound 20 intact.

Replacement of the acetoxyl group of compound 20 with a methoxyl group should alleviate the formation of positional isomers during reduction. α-Methoxyketone 42 was an attractive intermediate, and should be available from an α-bromoketone.

The α-bromoketone 41 was prepared in high yield by bromination of ketone 10 with pyridinium bromide perbromide. This compound analyzes correctly for $C_{10}H_{15}OBr$. The ir spectrum of compound 41 shows carbonyl absorption at 1750 cm^{-1} and the nmr spectrum shows a lowfield methine singlet (τ 4.93) as well as three methyl singlets (τ 8.72, 8.86, 9.14). This data is consistent with an α-bromoketone. However, attempts to prepare the α-methoxyketone have not been successful. Efforts along this line were discontinued when the oxime fragmentation route proved successful.



The synthetic sequence employed to synthesize grandisol is summarized below.

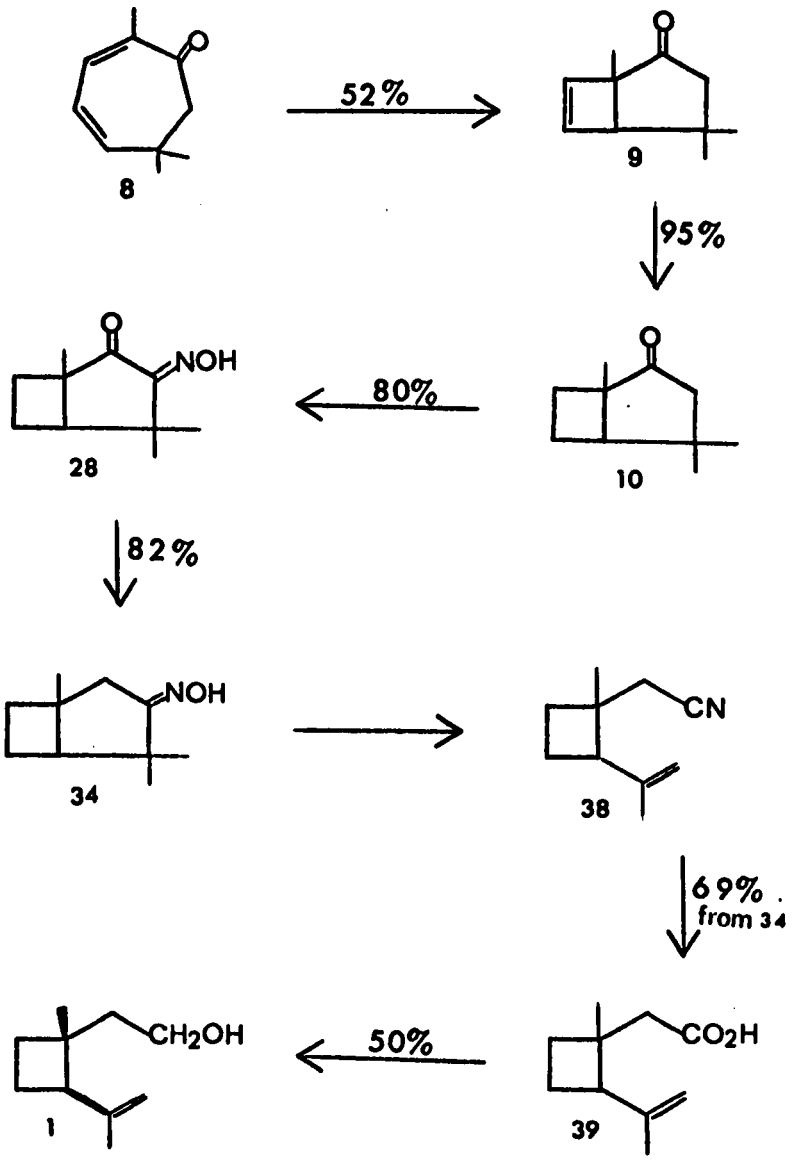
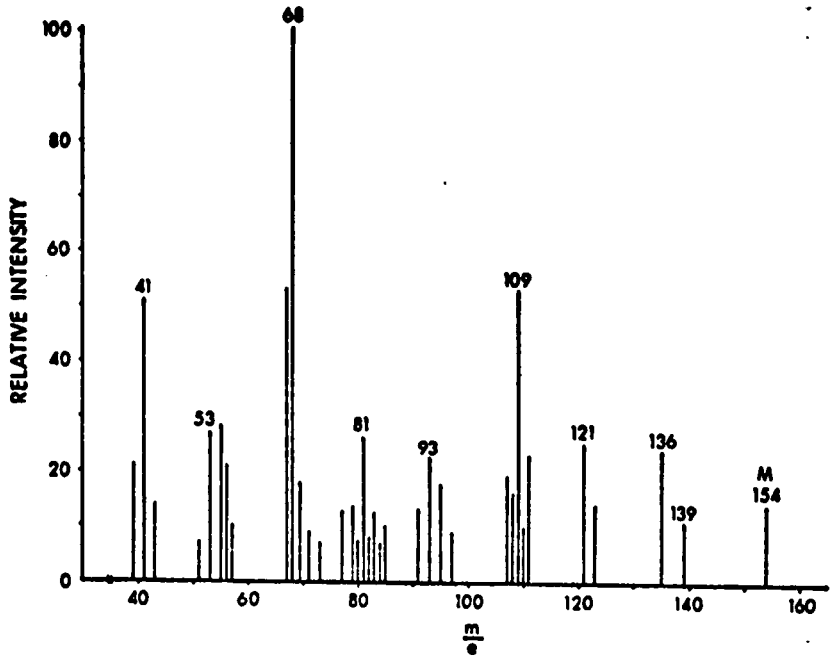
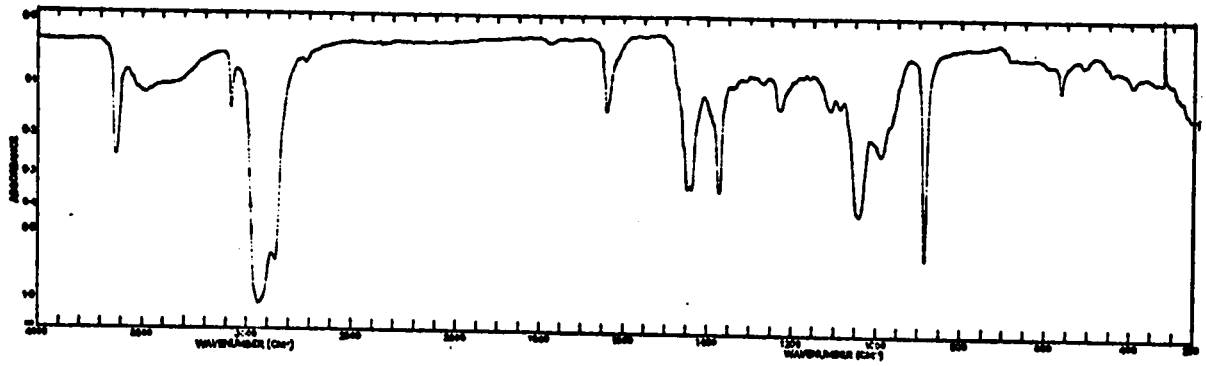


Figure 1

Mass spectrum (MS-9), infrared spectrum (CCl_4) and nuclear magnetic resonance spectrum (CCl_4) of synthetic grandisol, 1.


RELATIVE INTENSITY
100
80
60
40
20
0
41
53
68
81
93
109
121
136
139
M
154
40
60
80
100
120
140
160
m/e



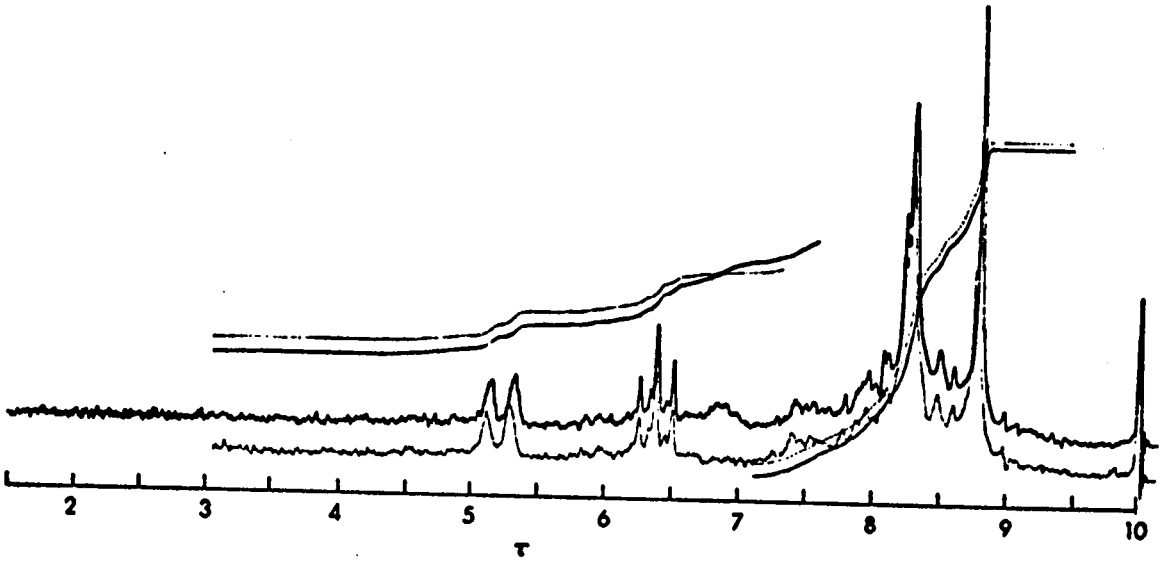
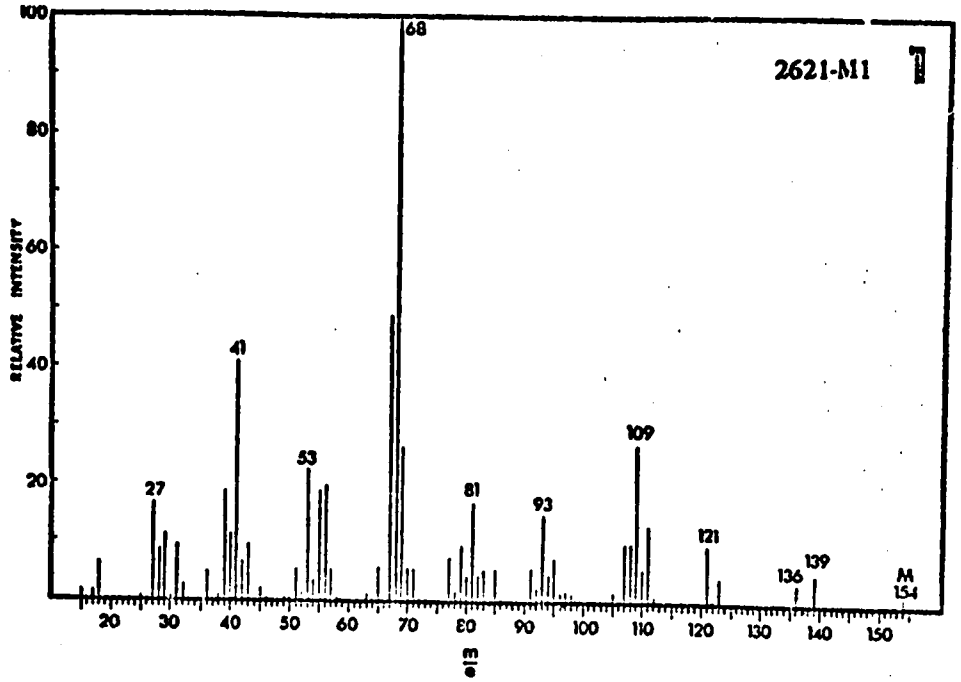
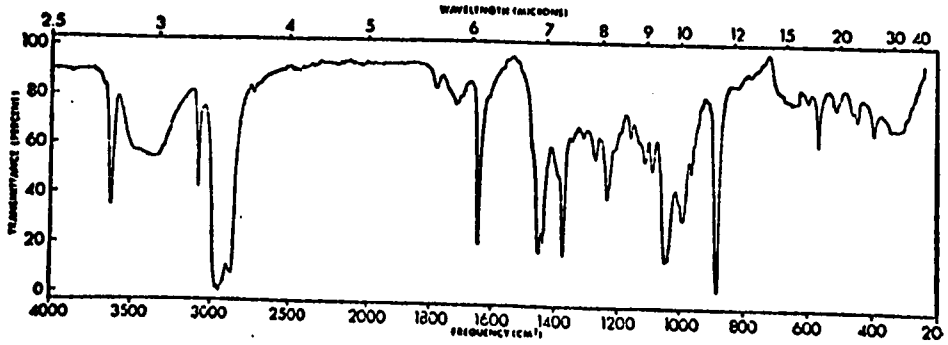
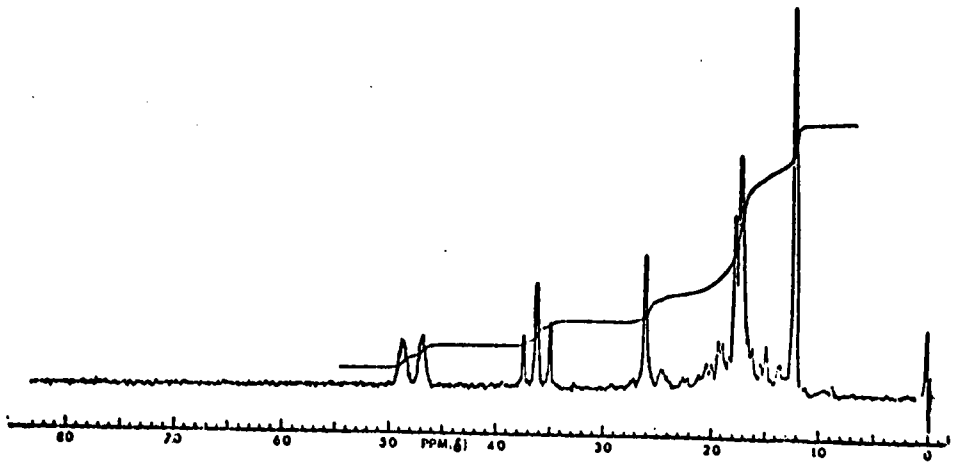

2
3
4
5
6
7
8
9
10
τ

Figure 2

Mass spectrum, infrared spectrum and nuclear magnetic resonance spectrum of grandisol, 1.[6b]


2621-M1
RELATIVE INTENSITY
m/e
68
41
27
53
81
93
109
121
136
139
M
154


WAVELENGTH (MICRONS)
FREQUENCY (CM⁻¹)


PPM (δ)

E X P E R I M E N T A L

Solutions were dried over anhydrous magnesium sulfate unless otherwise specified.

R_f value = distance moved by compound / distance moved by solvent.

Melting points were determined on a Fischer-Johns or Leitz-Wetzlar hot-stage melting point apparatus and are uncorrected.

Microanalyses were performed by the Microanalytical Laboratory of this department.

Infrared spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrophotometer, a Unicam SP1000 grating infrared spectrophotometer, or a Perkin-Elmer Model 421 dual grating infrared spectrophotometer.

Nuclear magnetic resonance spectra were measured using a Varian Associates Model A-60 spectrometer or a Varian Model HR-100 spectrometer with tetramethylsilane as internal standard. Deuterium exchangeable protons are noted in text as D_2O.

Mass spectra were recorded on an A.E.I. Model MS-9 mass spectrometer or an A.E.I. Model GC/MS mass spectrometer with a WB separator.

Chemical ionization spectra were recorded on an A.E.I. Model MS-12 mass spectrometer with a chemical ionization source and ammonia as internal standard.

Preparation of eucarvone, 8[10a,b]

Carvone (100 g) was added dropwise to a stirred, cooled solution of hydrobromic acid in glacial acetic acid (500 g, 30% HBr in glacial HOAc). The rate of addition was adjusted such that the temperature of the solution was maintained between 8 and 12°. When addition was complete (approximately 0.5 h), the cooling bath was removed and stirring was continued a further 15 min. The solution was poured into water (800 ml). The lower organic layer was separated, and the aqueous layer was extracted with ether. The organic fractions were combined, washed twice with water, neutralized ($NaHCO_3$), washed with water, dried (Na_2SO_4), then added dropwise to a stirred, cooled solution of potassium hydroxide (75 g) in methanol (300 ml). After addition was complete, the solution was concentrated on a steam bath, then poured onto a sulfuric acid (50 ml)-crushed ice (1 l.) mixture. Water was added to dissolve the inorganic salts. The upper oily layer was separated and the aqueous layer extracted with ether. The organic fractions were combined, washed with saturated sodium bicarbonate solution, water, and dried (Na_2SO_4). The solution was concentrated and the residual oil fractionated using a spinning band apparatus to give 65 g, 65% eucarvone, 8.

bp 82° (7 mm); n_D^{24} 1.5050 [lit.[10a,b] bp 82.5-84° (8 mm);

n_D^{20} 1.5080].

$ir_{(neat)}$: 1660 cm^{-1} (C=C-C=O).

Photolysis studies of eucarvone, 8

Eucarvone in various solvents (0.08-1.1 M) was irradiated in a pyrex vessel with an immersible mercury vapor lamp (Hanovia 250 W) for varying lengths of time, the reaction being monitored by glc. After the appropriate workup the crude photolysis mixture was fractionated using a spinning band apparatus. Results for the solvents studied are presented below.

Photolysis of Eucarvone in Various Solvents

Solvent	Time	Glc (No. compd)	Yield of Compound 9
Methanol	7 d	5[a]	21-33%
TFE	12.5 h	5	none
SGC	3 d	5	none
Ethylene glycol	5 d	4[b]	30-35%
Ethylene glycol-TFE	7 d	3[b]	50-52%

a 10' x 1/4" PDEAS, 150°, 60 ml/min.

b 20' x 3/8" Carbowax 20M, 200°, 60 ml/min.

1,4,4-Trimethylbicyclo[3.2.0]hept-6-en-2-one, 9[15a,b]

A stirred solution of eucarvone (13.0 g) in ethylene glycol (500 ml) and trifluoroethanol (50 ml) was irradiated in a pyrex vessel with an immersible mercury vapor

lamp (250W, Hanovia med pres) for seven days. The photolysis mixture was diluted with water (500 ml), then continuously extracted with pentane for 48 hours. The pentane solution was dried, concentrated in vacuo at room temperature, and the residual oil was fractionated through a 40 cm spinning band column giving unsaturated ketone, 9.

bp 90-91° (35 mm); n_D^{23} 1.4561 [lit[11] bp 110-111° (45 mm), n_D^{25} 1.4556].

$ir_{(neat)}$: 1740 cm^{-1} (C=O).

$nmr_{(CCl_4)}$: τ 3.67 (d, 1, J = 2.5Hz, cis C=CH), 3.90 (d, 1, J = 2.5Hz, cis C=CH), 7.20 (d, 1, J = 17Hz, gem CH_2), 7.44 (s, 1, CH), 8.26 (d, 1, J = 17Hz, gem CH_2), 8.78 (s, 3, CH_3), 8.92 (s, 3, CH_3), 9.05 (s, 3, CH_3).

2,4-dinitrophenylhydrazone derivative mp 162-163° [lit[11] 161.5-162.5°].

1,4,4-Trimethylbicyclo[3.2.0]heptan-2-one, 10[11]

Unsaturated ketone 9 (5.8 g) was hydrogenated over 30% palladized charcoal (0.1 g) in methanol (100 ml) at room temperature and atmospheric pressure. After one equivalent of hydrogen had been consumed, the mixture was filtered and concentrated. The residual clear liquid (one compound by glc analysis (10% PDEAS, 10' x 1/4", column temp 150°, flow rate 60 ml/min) was used in subsequent steps without further purification. Yield of saturated ketone 10 was 5.6 g (95%).

n_D^{24} 1.4585 [lit.[11] n_D^{25} 1.4556].

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C,

78.73; H, 10.35.

$ir_{(neat)}$: 1735 cm^{-1} (C=O).

$nmr_{(CCl_4)}$: τ 8.78 (s, 3, $C\underline{H}_3$), 8.97 (s, 3, $C\underline{H}_3$), 9.10 (s, 3, $C\underline{H}_3$).

mass spectrum: m/e 152.1201 calcd for $C_{10}H_{16}O$, 152.1194 meas (67), 137(9), 124(29), 109(89), 95(97), 82(100), 81 (42), 69(70), 67(57), 55(28), 41(97), 39(37).

2,4-dinitrophenylhydrazone derivative mp 148.5-150.5° [lit[11] 147.5-148°].

3-Benzylidene-1,4,4-trimethylbicyclo[3.2.0]heptan-2-one, 15

A stirred solution of ketone 10 (1.4 g), benzaldehyde (3 ml), sodium hydroxide (0.9 g), methanol (45 ml) and water (25 ml) was heated on a steam bath for 48 h. The reaction mixture was cooled, diluted with water and extracted with methylene chloride. The organic fraction was dried and concentrated to an oil (0.6 g), which was purified by chromatography over alumina (BDH). Elution with petroleum ether (bp 65°) gave an oil which was a mixture of cis- and trans-benzylidene ketones. Further elution with pet. ether gave cis-benzylidene ketone as a crystalline compound (mp 57-59°); total yield 1.65 g (75%).

Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.68; H, 8.18.

$uv_{(95\%\ EtOH)}$: 290 nm (ε = 21,900), 226 nm (ε = 11,650).

$ir_{(CHCl_3)}$: 1710 (C=O), 1610 (C=C) cm^{-1}.

nmr$_{(CDCl_3)}$: cis-15 τ 2.36 (s, 1, cis COC=CH), 2.70 (s, 5, ArH), 8.12 (m, 5), 8.70 (s, 3, CH_3), 8.75 (s, 3, CH_3), 9.07 (s, 3, CH_3). trans-15 τ 3.43 (s, trans COC=CH), 8.72 (s, CH_3), 8.82 (s, CH_3), 8.95 (s, CH_3).

mass spectrum: m/e 240.1514 calcd for $C_{17}H_{20}O$, 240.1516 meas (100), 225(35), 212(51), 197(46), 184(25), 170(29), 169(30), 155(32), 143(37), 129(80), 128(56), 115(33), 97(51), 95(83), 91(73), 77(40), 69(48), 41(88), 39(40).

3-Benzyl-1,4,4-trimethylbicyclo[3.2.0]heptan-2-one, 16

Benzylidene ketone 15 (0.5 g) in ether (20 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (0.2 g) and aluminum chloride (0.98 g) in ether (70 ml). After addition was complete, the mixture was refluxed for 24 hours, then cooled. Excess hydride was destroyed by cautious addition of 3N sodium hydroxide, then water. The ether fraction was separated, dried and concentrated. The crude product was chromatographed over alumina (BDH). Elution with petroleum ether (bp 65°) gave benzyl ketone 16, as an oil (0.29 g, 56.5%). η_D^{24} 1.5230.

Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.10; H, 9.07.

ir$_{(film)}$: 1730 (C=O), 1600, 1500 cm^{-1}.

nmr$_{(CDCl_3)}$: τ 2.75 (s, 5, ArH), 8.78 (s, 3, CH_3), 9.13 (s, 3, CH_3), 9.22 (s, 3, CH_3).

mass spectrum: m/e 242.1617 calcd for $C_{17}H_{22}O$, 242.1678 meas (21), 173(100), 146(12), 131(12), 123(9), 97(84), 91(43), 69(10), 55(9), 43(12), 41(28).

3-Benzylidene-1,4,4-trimethylbicyclo[3.2.0]heptane, 17

Benzylidene ketone 15 (0.21 g), 85% hydrazine hydrate (29 ml), hydrazine dihydrochloride (0.73 g) and triethylene glycol (174 ml) were heated at 120° for two hours. Potassium hydroxide pellets (1.1 g) were added and the temperature was slowly raised to 230°, allowing the low boiling material to distil. The reaction mixture was held at that temperature for 1.5 h then cooled, diluted with water and extracted with petroleum ether. The pet ether fraction was washed with water, dried, concentrated and the residual oil substilled, bp 100° (0.5 mm). Yield 0.11 g (58%).

Anal. Calcd for $C_{17}H_{22}$: C, 90.20; H, 9.80. Found: C, 89.87; H, 9.77.

uv_{max}^{MeOH}: 249 nm (ε = 2,150).

$ir_{(film)}$: 1610 (conj C=C), 1500 cm^{-1}.

$nmr_{(CDCl_3)}$: τ cr at 2.83 (m, 6, ArH and ArCH=C), 8.52 (s, 2, CH_2C=C), 8.73 (s, 6, CH_3), 8.95 (s, 3, CH_3).

mass spectrum: m/e 226.1721 calcd for $C_{17}H_{22}$, 226.1715 meas (6), 198(9), 145(100), 129(11), 91(39).

Attempted oxidative cleavage of the benzylidene compound 17

Ozone was bubbled through a solution of compound

17 in the solvent shown until a blue color indicated the presence of excess ozone. The reaction mixture was allowed to stand at varying temperatures for varying lengths of time. Excess ozone was removed and the reaction mixture subjected to an oxidative workup. In most cases only unreacted benzylidene compound was recovered.

Conditions Used for Ozonolysis

Solvent	Time(h)	Temp	Result
ethyl acetate	1.5	-10	recovered benzylidene
methylene chloride	4.5	-70	recovered benzylidene
acetic acid	6	24	low recovery of a mixture

Ozone was bubbled slowly through a solution of benzylidene compound 17 (0.250 g) in acetic acid (10 ml) for six hours. Excess ozone was removed and the acid solution diluted with water, then neutralized ($NaHCO_3$). The aqueous solution was continuously extracted with ether. The ether fraction was dried and concentrated to a solid (0.082 g). The solid which was mainly one compound (tlc, silica gel, benzene) was recrystallized from ethyl acetate mp 138.5-140°.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.23; H, 9.49.

$ir_{(CHCl_3)}$: 3300-2500 (br OH), 1730 sh, 1695 (C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: no protons below τ 2, no exchangeable protons,

τ 8.14 (s, 1), 8.17 (s, 1), 8.72 (s, 3, $C\underline{H}_3$), 8.74 (s, 3, $C\underline{H}_3$), 8.98 (s, 3, $C\underline{H}_3$).

mass spectrum: m/e 194.1308 calcd for $C_{12}H_{18}O_2$, 194.1309 meas (2), 166.0994 calcd for $C_{10}H_{14}O_2$, 166.0999 meas (60), 151 (29), 121.1017 calcd for C_9H_{13}, 121.1023 meas (68), 107(29), 105(21), 93(27), 91(37), 82(100), 81(66), 79(26), 77(20), 69(21), 67(52), 41(44), 39(26).

The above compound (0.005 g), acetic anhydride (10 drops) and pyridine (5 drops) were caused to react at room temperature for 24 hours. Excess solvents were removed by azeotropic distillation with toluene to give 0.007 g acetylated compound.

$ir_{(CHCl_3)}$: 1775, 1720 (C=O of an acyclic anhydride) cm^{-1}.

$nmr_{(CDCl_3)}$: unchanged from above.

Benzylidene compound 17, solvent and oxidizing reagent were allowed to stand at room temperature for various periods. Excess oxidizing agent was destroyed and the reaction mixture worked up in the appropriate manner. In all cases unreacted benzylidene was recovered.

Conditions Used for Oxidative Cleavage

Reagent	Solvent	Time(h)	Result
$KMnO_4/NaIO_4$ [40]	butanol	2	recovered benzylidene
$KMnO_4/NaIO_4$	pyridine	20	recovered benzylidene
$RuCl_3/NaOCl$ [41]	methylene chloride	2	recovered benzylidene
OsO_4/H_2O_2 [42]	acetone	46	recovered benzylidene

2-Acetoxy-1,4,4-trimethylbicyclo[3.2.0]hept-2-ene, 18

A mixture of ketone 10 (1.0 g), isopropenyl acetate (1.4 g), and p-toluenesulfonic acid (catalytic amount) was allowed to reflux overnight, then excess acetone was removed by distillation. The mixture was cooled, diluted with ether, washed successively with saturated sodium bicarbonate solution, brine, dried, concentrated, and distilled to give 0.7 g (59%) enol acetate 18: bp 50-52° (1.5 mm).

η_D^{21} 1.4594.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.48; H, 9.14.

$ir_{(neat)}$: 1775 (C=O), 1640 (C=C) cm^{-1}.

$nmr_{(CCl_4)}$: τ 4.56 (s, 1, C=C$\underline{H}$), 7.93 (s, 3, OCOC$\underline{H}_3$), 8.17 (m, 5), 8.92 (s, 3, C$\underline{H}_3$), 9.00 (s, 6, C$\underline{H}_3$).

mass spectrum: m/e 194.1307 calcd for $C_{12}H_{18}O_2$, 194.1300 meas (1), 147(46), 124(100), 109(43), 94(14), 91(12), 67 (11).

2,3-Epoxy-2-acetoxy-1,4,4-trimethylbicyclo[3.2.0]heptane, 19

A mixture of enol acetate 18 (0.7 g), m-chloroperbenzoic acid (0.65 g) and anhydrous ether (15 ml) was allowed to stand at room temperature 72 hours. The reaction mixture was washed successively with 10% sodium bisulfite solution and saturated sodium bicarbonate solu-

tion, then dried, concentrated, and distilled to give 0.6 g (79%) acetoxy epoxide, 19.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.14; H, 8.74.

$ir_{(neat)}$: 1770 (C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 6.48 (s, 1, OCH), 7.92 (s, 3, $OCOCH_3$), 8.79 (s, 3, CH_3) 8.94 (s, 6, CH_3); 20% of an isomeric acetoxy epoxide: 6.33 (s, OCH), 7.87 (s, $OCOCH_3$), 8.68 (s, CH_3), 8.84 (s, CH_3).

mass spectrum: m/e 210.1256 calcd for $C_{12}H_{18}O_3$, 210.1252 meas (16), 168(37), 139(13), 100(19), 95(11), 81(11), 72(57), 69(54), 55(11), 43(100), 41(45).

3-Acetoxy-1,4,4-trimethylbicyclo[3.2.0]heptan-2-one, 20

The acetoxy epoxide 19 (0.24 g) was heated in an oil bath at 220° for three hours, then substilled to give 0.15 g (62.5%) acetoxy ketone 20: bp 80° (0.2 mm). η_D^{24} 1.4607.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 67.89; H, 9.50. Found: C, 68.16; H, 9.53.

$ir_{(neat)}$: 1760 (C=O), 1750 (C=O), 1235 ($OCOCH_3$) cm^{-1}.

$nmr_{(CCl_4)}$: τ4.36 (s, 1, CHOAc), 7.83 (s, 3, $OCOCH_3$), 8.77 (s, 3, CH_3), 8.84 (s, 3, CH_3), 9.20 (s, 3, CH_3).

mass spectrum: m/e 210.1256 calcd for $C_{12}H_{18}O_3$, 210.1250 meas (5), 167(16), 139(10), 100(10), 72(50), 71(14), 43 (100), 41(31).

Formation of acetoxyketone 20 using lead tetraacetate

A mixture of ketone 10 (3.95 g), lead tetraacetate (14.0 g), acetic acid (40 ml), and 1,2,2-trichloroethane (80 ml) was allowed to reflux for four days. The mixture was cooled and ethylene glycol (2 ml) was added to destroy excess lead tetraacetate. The mixture was then washed successively with water and sodium hydroxide solution (5%). The aqueous fraction was backwashed with ether. The organic fractions were combined, dried, concentrated and distilled to give 4.85 g (89%) acetoxy ketone 20: bp 65-71° (0.05 mm).

Attempted isomerization of α-Acetoxyketone, 20

Isomerization of the α-acetoxyketone 20 was tried by several methods, as summarized in the following chart.

Isomerization of α-Acetoxyketone 20

Solvent	Catalyst	Temp	Time	Result
ether	alumina[24]	r.t.	12 h	recovered 20
acetone	$N^+Me_4OAc^-$[43]	r.t.	7 d	recovered 20
methanol	6N H_2SO_4[45]	r.t.	2 d	recovered 20*
methanol	10% HCl	reflux	2 h	recovered 20*
methanol	6N H_2SO_4	reflux	1 d	mixture of several compounds
acetic acid	HI[46]	reflux	1 h	mixture of several compounds

*after acetylation

3-Hydroxy-1,4,4-trimethylbicyclo[3.2.0]heptan-2-one, 21

α-Acetoxyketone (0.41 g), 10% hydrochloric acid (20 ml), and methanol (10 ml) were stirred at room temperature for 24 hours. Methanol was removed in vacuo and the reaction mixture extracted with methylene chloride. The methylene chloride fraction was dried and concentrated to give 0.29 g (81%) of α-hydroxyketone, 21.

$ir_{(CHCl_3)}$: 3540 (OH), 1745 (C=O) cm^{-1}.

$nmr_{(CCl_4)}$: τ 5.50 (s, 1, C<u>H</u>OH), 5.82 (s, 1, O<u>H</u>, D_2O), 8.80 (s, 3, C<u>H</u>$_3$), 8.88 (s, 3, C<u>H</u>$_3$), 9.17 (s, 3, C<u>H</u>$_3$).

mass spectrum: m/e 168.1150 calcd for $C_{10}H_{16}O_2$, 168.1150 meas (14), 100(45), 95(18), 80(15), 72(38), 69(100), 53(21), 43(33), 41(82), 39(26).

Sulfuric acid catalyzed hydrolysis of α-acetoxyketone 20

α-Acetoxyketone 20 (0.5 g), methanol (4 ml) and 6N sulfuric acid (4 ml) were allowed to reflux for 20 hours. The mixture was cooled, diluted with water and extracted with methylene chloride. The methylene chloride fraction was washed with saturated sodium bicarbonate solution, dried and concentrated to an oil (0.470 g). The tlc of the oil showed the presence of two components (alumina, chloroform). The two components were separated by dry column chromatography over alumina. The more polar compound was α-hydroxyketone 21 (ir, nmr). The less polar material was a mixture of three compounds (glc, Zonyl E-7 20' x 3/8",

temp program, 180 ml/min; nmr).

Attempted reduction of α-acetoxyketone 20

Wolff Kishner Reduction

α-Acetoxyketone (0.5 g), hydrazine dihydrochloride (1.7 g), 85% hydrazine hydrate (8.4 ml), and triethylene glycol (150 ml) were heated at 105° for 0.5 h, then potassium hydroxide pellets (2.9 g) were added cautiously and the temperature increased allowing the low boiling material to distill. The reaction mixture was held at 165° for two hours, then cooled, diluted with water and continuously extracted with pentane for 24 hours. The pentane extract was washed with water, dried, and concentrated to an oil (0.11 g), which was shown to be a mixture of four compounds by tlc (silica gel; methylene chloride--methanol, 20:1).

Tosylhydrazone Formation

α-Acetoxyketone (0.192 g), p-toluenesulfonylhydrazine (0.186 g), sulfuric acid (2 drops), and methanol (5 ml) were allowed to reflux under a nitrogen atmosphere overnight. The reaction mixture was cooled, concentrated, diluted with water and extracted with ether. The ether extract was dried and concentrated to an oil, which was shown to be a mixture of six compounds by tlc (silica gel; benzene).

1,4,4-Trimethylbicyclo[3.2.0]heptan-2-ol, 24

Ketone 10 (1.62 g), sodium borohydride (0.4 g), and methanol (100 ml) were allowed to stir at room temperature for four hours. The mixture was diluted with water, acidified (HCl), and extracted with methylene chloride. The methylene chloride extract was dried and concentrated. A 1.53 g (93%) yield of compound 24 was obtained after sublimation (80°, 760 mm): mp 46-54°.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.61; H, 11.50.

$ir_{(CHCl_3)}$: 3640, 3480, 1065 (OH) cm^{-1}.

$nmr_{(CCl_4)}$: τ 6.23 (t, 1, J = 9Hz, C<u>H</u>OH), 7.76 (s, 1, O<u>H</u>, D_2O), 8.33 (d, 2 J = 9Hz, $C\underline{H}_2$CHOH), 8.80 (s, 3, $C\underline{H}_3$), 9.31 (s, 3, $C\underline{H}_3$).

mass spectrum: m/e 154.1358 calcd for $C_{10}H_{18}O$, 154.1361 meas (10), 139(80), 126(43), 111(100), 97(24), 95(50), 93 (30), 85(47), 84(39), 83(37), 71(44), 69(66), 67(30), 55 (49), 43(43), 41(86).

Attempted dehydration of alcohol 24

a) Treatment with thionyl chloride[49,50]

Alcohol 24 (0.250 g), thionyl chloride (2 ml), and methylene chloride[49] were stirred at room temperature for four days. The reaction mixture was diluted with water and the methylene chloride layer separated. The methylene chloride fraction was washed with water, dried and concen-

trated. The oil obtained (0.141 g) was 2-chloro-1,4,4-trimethylbicyclo[3.2.0]heptane, 25, (tlc, alumina, benzene R_f 0.87; alcohol 24 R_f 0.20).

$ir_{(CHCl_3)}$: no OH absorption

$nmr_{(CCl_4)}$: τ 6.13 (t, 1 J = 8.5Hz, CHCl), 8.79 (s, 3, CH_3), 9.12, (s, 6, CH_3).

Similar results were obtained when alcohol 24 was treated with thionyl chloride in pyridine[50].

b) De-mesylation

Alcohol 24 (0.250 g), methanesulfonyl chloride (1 ml) and pyridine (2 ml) were reacted at 0° for 24 hours. The reaction mixture was diluted with 5% sodium hydroxide solution, and extracted with methylene chloride. The methylene chloride fraction was washed with dilute hydrochloric acid, water, dried and concentrated to give compound 26 (0.217 g).

$ir_{(neat)}$: no OH absorption.

$nmr_{(CDCl_3)}$: τ 5.32 (t, 1 J = 9Hz, CHOMs), 7.10 (s, 3, OSO_2CH_3), 8.69 (s, 3, CH_3), 9.05 (s, 6, CH_3).

Compound 26 was stirred with ethanolic sodium ethoxide overnight, then allowed to reflux for one hour. The solution was concentrated to one-half volume, diluted with water, and extracted with ether. The ether fraction was dried and concentrated to give 0.200 g unreacted mesylate 26.

Compound 26 (0.200 g) and potassium t-butoxide (0.1 g) in anhydrous dimethyl sulfoxide (1 ml) were stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with pentane. The pentane fraction was washed with water, dried and concentrated to give only unreacted mesylate 26 (0.140 g).

c) Treatment with iodine[52]

Alcohol 24 (0.25 g), iodine (1 crystal) and benzene (10 ml) were allowed to reflux for 48 hours. The reaction mixture was cooled, washed with water, 5% sodium hydroxide solution, dried, and concentrated. Only unreacted alcohol 24 (0.09 g) was recovered.

d) Treatment with anhydrous oxalic acid[53]

Alcohol 24 (0.24 g) and anhydrous oxalic acid (0.12 g) were heated at 220° for 0.5 hour. The mixture was cooled and diluted with ether. The ether solution was washed with sodium bicarbonate, dried and concentrated to give 0.17 g of a mixture of compounds (tlc, alumina, benzene).

1,4,4-Trimethylbicyclo[3.2.0]hept-2-ene, 23

Tosylhydrazone derivative 27

Ketone, 10 (5.0 g), p-toluenesulfonylhydrazine (6.3 g), and methanol (100 ml) were allowed to reflux for 24 hours. Excess methanol was distilled, the reaction mix-

ture cooled, and the tosylhydrazone which crystallized was collected (3.2 g). The mother liquors were concentrated and the residue was chromatographed over silicic acid. Elution with chloroform--methanol (100:1) gave 4.3 g tosylhydrazone 27. Total yield: 7.5 g (69.5%), mp 111-113°.

ir$_{(CHCl_3)}$: 3520, 3440 (NH), 1660 (C=N) cm^{-1}.

nmr$_{(CDCl_3)}$: τ 2.10 (d, 2 J = 8.5Hz, ArH), 2.70 (d, 2 J = 8.5Hz, ArH), 2.41 (s, 1, NH), 7.60 (s, 3, $ArCH_3$), 7.73 (s, 2, CH_2), 8.78 (s, 3, CH_3), 9.06 (s, 3, CH_3), 9.30 (s, 3, CH_3).

mass spectrum: m/e 320.1558 calcd for $C_{17}H_{24}N_2O_2{}^{32}S$, 320.1558 meas(3), 292(14), 165(42), 151(8), 136(60), 134(20), 121(29), 109(100), 108(25), 95(15), 93(41), 91(54), 81(25), 79(23), 77(20), 69(20), 62(30), 41(51).

Bamford-Stevens reaction

Methyl lithium (1.5M, 25 ml) was added to a cooled solution of tosylhydrazone 27 (2.0 g), in ether (50 ml). The mixture was allowed to stand at room temperature 2 days, then was diluted with ice-water, acidified (HCl), and the upper ether layer separated. The aqueous layer was extracted with ether. The ether fractions were combined, washed successively with water, saturated sodium bicarbonate solution, brine, and dried. The solution was concentrated and the residual liquid distilled to give 0.33 g olefin 23: bp 115-120 (760 mm).

$ir_{(CHCl_3)}$: 1610 (C=C) cm^{-1}.

$nmr_{(CCl_4)}$: τ 4.63 (s, 2, cis-C<u>H</u>=C<u>H</u>), 8.83 (s, 3, C<u>H</u>$_3$), 9.03 (s, 3, C<u>H</u>$_3$), 9.05 (s, 3, C<u>H</u>$_3$).

Hydration of olefin 23

Oxymercuration-demercuration[55]

Olefin 23 (0.14 g) in tetrahydrofuran (0.5 ml) was added dropwise to a stirred suspension of mercuric acetate (0.32 g), water (1 ml) and tetrahydrofuran (1 ml). Stirring was continued for 24 hours, then sodium hydroxide solution (3M, 1 ml) and sodium borohydride solution (0.5M in 3M NaOH, 1 ml) was added. The reaction mixture was saturated with salt, filtered, the upper tetrahydrofuran layer separated, washed with brine, dried, and concentrated to give only unreacted olefin 23.

Hydroboration[56]

Borane in tetrahydrofuran (1M, 3 ml) was added dropwise to a stirred, cooled solution (0-5°) of olefin 23 (0.3 g) in anhydrous tetrahydrofuran (15 ml). After addition was complete, the reaction mixture was allowed to warm to room temperature, and maintained at that temperature for 2.5 hours. The solution was cooled (0-5°), sodium hydroxide solution (3M, 3 ml) and hydrogen peroxide (30%, 3 ml) were added cautiously and the mixture allowed to stir overnight. The mixture was diluted with water, the organic

fraction separated, and the aqueous layer extracted with ether. The organic fractions were combined, washed with brine, dried, and concentrated to give 0.194 g of a mixture of alcohols.

$ir_{(CHCl_3)}$: 3740, 3480 (OH) cm^{-1}.

Ice-cold chromic acid solution[57] (0.5 ml) was added to a cooled solution (0-5°) of alcohols (0.17 g) in ether (5 ml). The mixture was stirred vigorously for 5 minutes, then a further 0.5 ml of chromic acid solution was added. After stirring 15 minutes more, the layers were separated. The aqueous fraction was extracted with ether. The organic fractions were combined and washed with sodium hydroxide solution (1.5 M), water, brine, dried, and concentrated to give a mixture of ketones.

$ir_{(neat)}$: 1750 (C=O) cm^{-1}.

Glc analysis of the product showed a 2:3 mixture of two compounds, the major compound had the same retention time as ketone 10 (15% Carbowax 20M, 5' x 1/8", 100°, 60 ml/min).

3-Oximino-1,4,4-trimethylbicyclo[3.2.0]heptan-2-one, 28

Acid catalysis

Anhydrous hydrogen chloride was bubbled through a solution of ketone 10 (1.0 g) in anhydrous ether (50 ml). The gas flow was stopped, n-butyl nitrite (0.7 g) was added, then anhydrous HCl was bubbled through the solution for 15 minutes. The orange solution was allowed to stand at

room temperature overnight. The solution was concentrated to an oil which contained only starting ketone 10 as shown by glc analysis (10% PDEAS, 10' x 1/4", 150°, 60 ml/min).

Basic catalysis

Isoamyl nitrite (1.2 g) was added dropwise to a stirred solution of ketone 10 (0.8 g) and potassium tert-butoxide (1.2 g) in anhydrous tert-butyl alcohol (15 ml) in a nitrogen atmosphere. The red solution was allowed to stir for 20 hours, then was diluted with water, washed with ether, acidified (HCl), and extracted with ether. The ether fraction was dried and concentrated to an oil (0.63 g). Crystallization from ether gave oximinoketone 28, (0.25 g, 26%). The mother liquor was concentrated and a portion (0.16 g) chromatographed over silica gel (6 g). Elution with chloroform gave a crystalline compound (0.085 g), 1-methyl-2(1-methyl-1-cyanoethyl)cyclobutyl carboxylic acid, 29: mp 189-192°.

$ir_{(CHCl_3)}$: 3400-2500 (COOH), 2220 (C≡N), 1710 (C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 8.86 (s, 3, $C\underline{H}_3$), 8.72 (s, 3, $C\underline{H}_3$), 8.57 (s, 3, $C\underline{H}_3$), 7.83 (s, 4, $C\underline{H}_2$), -1.95 (s, 1, $COO\underline{H}$ D_2O).

mass spectrum: 181.1103 calcd for $C_{10}H_{15}NO_2$, 181.1102 meas (5), 155(9), 135(11), 126(14), 109(29), 95(30), 87(21), 69(100), 55(24), 41(86).

3-Oximino-1,4,4-trimethylbicyclo[3.2.0]heptan-2-one, 28

Ketone 10 (5.1 g) in anhydrous benzene (10 ml) was added dropwise to a stirred, cooled solution of potassium t-amylate (7.5 g, 75 ml of 0.85 N KO^{t}Am in benzene)[60] in anhydrous benzene, followed by dropwise addition of i-amyl nitrite (3.75 g, distilled and stored over molecular sieve 5A) in anhydrous benzene (10 ml). The purple solution was stirred at room temperature for 24 hours. The solution was cooled, and diluted with 5% aqueous HCl. The upper organic layer was separated and washed with saturated sodium bicarbonate solution. The aqueous fraction was neutralized ($NaHCO_3$) and extracted with methylene chloride. The organic fractions were combined, washed with brine, dried, and concentrated to an oil. The oil was chromatographed over silicic acid (200 g) using a quartz column and an ultraviolet light to minitor the separation. Elution with chloroform (400 ml) gave a crystalline mixture of oximinoketones (1.2 g). Further elution with chloroform gave a crystalline oximinoketone (3.6 g); mp 128-131.5°. Total yield of oximinoketone was 4.8 g (80%).

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73.
Found: C, 65.92; H, 8.14; N, 7.55.

$ir_{(CHCl_3)}$: a) 3560, 3360 (NOH), 1740 (C=O), 1630 (C=N) cm^{-1}; b) 3200 (NOH), 1690 (C=O), 1580 (C=N) cm^{-1}.

$nmr_{(CDCl_3)}$: a) τ 0.15 (br s, 1, NO$\underline{H}$, D_2O), 8.59 (s, 3, C$\underline{H}_3$),

8.75 (s, 6, $C\underline{H}_3$); b) τ 8.65 (s, 3, $C\underline{H}_3$), 8.79 (s, 3, $C\underline{H}_3$), 8.82 (s, 3, $C\underline{H}_3$).

mass spectrum: a) m/e 181.1103 calcd for $C_{10}H_{15}NO_2$, 181.1100 meas(21), 164(22), 136(33), 109(45), 97(74), 95(25), 94(14), 81(13), 69(23), 68(13), 67(16), 55(100), 53(19), 41(83), 39(36); b) m/e 181.1103 calcd for $C_{10}H_{15}NO_2$, 181.1104 meas (19), 164(9), 136(31), 109(26), 98(25), 97(100), 95(14), 69(28), 67(3), 55(63), 41(63), 39(30).

Oximinoketone 28 (0.096 g), t-butyl alcohol (2 ml), and 10% aqueous hydrochloric acid (10 ml) were allowed to stir at room temperature for one hour. The solution was extracted with methylene chloride, dried, and concentrated to give oximinoketone 28 (0.090 g).

Oximinoketone 28 (0.060 g), potassium hydroxide (1 pellet), and anhydrous t-butyl alcohol (10 ml) were stirred at room temperature for 24 hours. The solution was diluted with water and extracted with methylene chloride. The methylene chloride fraction was dried and concentrated to give oximinoketone 28 (0.040 g). The aqueous fraction was acidified and extracted with methylene chloride. The methylene chloride fraction was dried and concentrated to give a mixture of oximinoketone 28 and acid nitrile 29 (0.020 g).

3-Oximino-1,4,4-trimethylbicyclo[3.2.0]heptan-2-ol, 30

Sodium borohydride (0.050 g) in water (2 ml) was

added dropwise to a stirred solution of oximinoketone 28 (0.226 g) in dimethoxyethane (8 ml). After addition was complete, stirring was continued for 30 minutes. The solution was diluted with water, carefully acidified (HCl), neutralized ($NaHCO_3$), and extracted with methylene chloride. The organic fraction was dried and concentrated to give 0.545 g (100%) of a crystalline oximino alcohol, 21: mp 69-72.5°.

Anal. Calcd for $C_{10}H_{16}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.11; H, 9.25; N, 7.97.

$ir_{(CHCl_3)}$: 3580, 3300, 1070 (NOH, OH), 1680 (w, C=N) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 5.65 (s, 1, C<u>H</u>OH), 8.60 (s, 3, C<u>H</u>$_3$), 8.65 (s, 3, C<u>H</u>$_3$), 8.84 (s, 3, C<u>H</u>$_3$); a small quantity of another epimer was present as shown by signal at τ 5.50 (C<u>H</u>OH).

mass spectrum: <u>m/e</u> (M+-OH) 166.1231 calcd for $C_{10}H_{16}NO$, 166.1235 meas(16), 122(13), 114(12), 109(13), 97(45), 95 (22), 87(43), 81(27), 69(100), 55(37), 53(21), 43(23).

<u>3-Acetoximino-1,4,4-trimethylbicyclo[3.2.0]heptan-2-ol, 31</u>

Oximinoalcohol 30 (0.1 g), benzene (1 ml), pyridine (1 drop), and acetic anhydride (0.14 g) were heated in an oil bath at 65° for one hour. The mixture was concentrated by azeotropic distillation with benzene, dried <u>in vacuo</u> to give acetoximino alcohol 31: mp 89.5-90.5°.

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.91; H, 8.52; N, 6.11.

ir$_{(CHCl_3)}$: 3550, 3450, 1070 (OH), 1755 (C=O), 1660 (C=N) cm^{-1}.

nmr$_{(CDCl_3)}$: τ 5.45 (s, 1, C<u>H</u>OH), 6.20 (s, 1, O<u>H</u>, D_2O), 7.82 (s, 3, OCOC<u>H</u>$_3$), 8.63 (s, 6, C<u>H</u>$_3$), 8.80 (s, 3, C<u>H</u>$_3$).

mass spectrum: <u>m/e</u> (M+=OAc) 182.1181 calcd for $C_{10}H_{16}NO_2$, 182.1179 meas(2), 165(6), 150(6), 148(6), 139(7), 136(24), 122(41), 109(39), 107(28), 97(60), 95(34), 82(30), 81(86), 69(100), 68(50), 67(27), 60(36), 55(46), 53(23), 45(32), 43(54), 41(59).

<u>Attempted formation of acetoximino acetate, 32a</u>

Oximino alcohol <u>30</u> (0.125 g), acetic anhydride (0.2 g), pyridine (0.16 g), and benzene (2 ml) were heated in an oil bath (65°) for 0.5 hour. Excess solvents were removed by azeotropic distillation with benzene and the residual oil (0.153 g) was dried <u>in vacuo</u>. This oil was a mixture of two compounds (tlc: silica gel, chloroform--methanol). The ir and nmr spectra were consistent with a mixture of acetoximino acetate <u>32a</u> and cyanoaldehyde <u>33</u>.

ir$_{(CHCl_3)}$: 2730 (CHO), 2230 (CN), 1720 (C=O), 1770, 1745 (C=O) cm^{-1}.

nmr$_{(CDCl_3)}$: τ -0.33 (s, C<u>H</u>O), 8.68 (s, C<u>H</u>$_3$), 8.70 (s, C<u>H</u>$_3$); 4.06 (s, C<u>H</u>OAc), 7.82 (s, OCOC<u>H</u>$_3$), 7.85 (s, OCOC<u>H</u>$_3$), 8.62 (s, C<u>H</u>$_3$), 8.77 (s, C<u>H</u>$_3$).

Attempted formation of acetoximino mesylate, 32b

Acetoximino alcohol 31 (0.122 g), pyridine (2 drops), methanesulfonyl chloride (0.098 g), and benzene (1 ml) were allowed to stand at 0° overnight. Excess solvent was removed by azeotropic distillation with benzene and the residue (0.150 g) was dried in vacuo. The ir and nmr spectra of the residue are consistent with a mixture of acetoximino mesylate 32b, cyanoaldehyde 33, and acetoximino alcohol 31.

Attempted reduction of acetoximino alcohol 31 with chromous acetate[34]

Acetoximino alcohol (0.4 g), tetrahydrofuran (6.4 ml), chromous acetate (1.6 g), and water (2 ml) were heated at 65° in a nitrogen atmosphere for 36 hours. The mixture was allowed to cool, diluted with water, filtered, and extracted with methylene chloride. The methylene chloride fraction was washed with 10% hydrochloric acid, saturated sodium bicarbonate, water, then dried and concentrated. Analysis of the residual oil by glc--mass spectrometry showed a mixture of eight compounds; three minor compounds had a molecular ion of 152. The ir and nmr spectra are consistent with impure cyano aldehyde.

$ir_{(CHCl_3)}$: 2730, 2230, 1720; 1770, 1745 cm^{-1}.

$nmr_{(CCl_4)}$: τ -0.33 (s, C<u>H</u>O), 8.68 (s, C<u>H</u>$_3$), 8.70 (s, C<u>H</u>$_3$).

Attempted reduction of oximinoketone, 28[33]

Oximinoketone (0.291 g), hydrazine hydrate (85%, 1 ml), and diethylene glycol (50 ml) were heated at 70° overnight, then at 145° for two hours. The mixture was allowed to cool, diluted with water, acidified (HCl), and extracted with pentane. The pentane fraction was dried, concentrated (0.164 g), and chromatographed over alumina (10 g). Elution with chloroform gave crystalline oxime 34 (0.057 g, 21%).

3-Oximino-1,4,4-trimethylbicyclo[3.2.0]heptane, 34

A mixture of oximinoketone 28 (0.760 g), hydrazine hydrate (85%, 0.238 ml), potassium hydroxide (0.3 g), and ethylene glycol (15 ml) was heated at 150° for four hours. The reaction mixture was allowed to cool, diluted with water, acidified (HCl), neutralized ($NaHCO_3$), and extracted with pentane. The pentane fraction was washed with brine, dried, and concentrated to give 0.570 g (81.5%) crystalline oxime 34: mp 118-119.5°.

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.53; H, 10.36; N, 8.56.

$ir_{(CHCl_3)}$: 3580, 3290 (NOH), 1670 (C=N) cm^{-1}.

$nmr_{(CCl_4)}$: τ 0.80 (s, 1, NO$\underline{H}$, D_2O), 7.07 (d, 1 J = 19Hz, gem $C\underline{H}_2$), 7.73 (d, 1 J = 19Hz, gem $C\underline{H}_2$), 8.70 (s, 3, $C\underline{H}_3$), 8.93 (s, 6, $C\underline{H}_3$).

Observed Chemical Shift (τ) on Addition of $Eu(DPM)_3$ to Oxime 34 (0.0167 g) in CCl_4 (1 ml)

mg $Eu(DPM)_3$	CH_2		CH_3	$C(CH_3)_2$
0	7.07	7.73	8.70	8.93
5.3	6.63	7.28	7.98	8.55
11.3	5.80	6.46	7.83	8.23
16.1	5.08	5.73	7.22	8.00

mass spectrum: m/e 167.1310 calcd for $C_{10}H_{17}NO$, 167.1315 meas(7), 153(13), 152(38), 150(35), 138(15), 125(38), 124(57), 122(40), 109(24), 94(13), 93(14), 92(13), 81(21), 79(23), 77(12), 69(74), 68(20), 55(32), 53(24), 41(100).

1,4,4-Trimethylbicyclo[3.2.0]heptan-3-one, 35

Oxime 34 (0.430 g), dimethoxyethane (8 ml), water (4 ml) and titanium trichloride (1.5 eq, 3.1 ml) were allowed to reflux 15 minutes. The cooled solution was diluted with water and extracted with methylene chloride. The methylene chloride fraction was washed with sodium bicarbonate solution, dried and concentrated by distillation at atmospheric pressure.

η_D^{22} 1.4590.

$ir_{(neat)}$: 1735 (C=O) cm^{-1}.

$nmr_{(CCl_4)}$: τ 7.68 (s, 1, $C\underline{H}_2CO$), 7.70 (s, 1, $C\underline{H}_2CO$), 8.67 (s, 3, $C\underline{H}_3$), 9.05 (s, 3, $C\underline{H}_3$), 9.10 (s, 3, $C\underline{H}_3$).

mass spectrum: m/e 152.1201 calcd for $C_{10}H_{16}O$, 152.1203 meas(2), 73(73), 67(100), 45(96), 42(19), 41(20).

2,4-Dinitrophenylhydrazone derivative: mp 169-171.5°.

N-Cyclohexyl-3-methyl-3(2'-methylcyclobutyl)butanamide, 36

Ketone 10 (1.0 g), cyclohexylamine (freshly distilled from barium oxide, 0.5 ml), and anhydrous benzene (150 ml) was irradiated in a pyrex vessel with an immersible mercury vapor lamp (250 W, Hanovia med pres) for 24 hours. During this time, oxygen was continuously bubbled through the photolysis mixture. The solution was concentrated. The residue was dissolved in methanolic ether and separated into neutral (0.5 g) and acidic (0.2 g) fractions. The acidic material was a mixture of several compounds (tlc, alumina, chloroform--methanol). The neutral material showed several compounds (tlc, alumina, benzene), one being present in major amount. The neutral fraction was chromatographed over aluminum oxide (BDH, 20 g). Elution with benzene gave 0.26 g of crystalline compound 36: mp 53-56°.

Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.31; H, 11.44; N, 5.40.

$ir_{(CHCl_3)}$: 3430 (NH), 1670 sh, 1650 (C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 4.6 (br s, 1) 6.3 (br m, 1), 8.08 (s, 2, $C\underline{H}_2CO$) 8.92 (s, 3, $C\underline{H}_3$), 9.05 (s, 6, $C\underline{H}_3$).

mass spectrum: m/e 251(5), 235(20), 209(4), 194(4), 182(6),

141(73), 126(6), 111(11), 98(14), 83(36), 69(39), 60(100), 55(47), 42(14), 41(52).

1,4,4-Trimethylbicyclo[3.2.0]heptan-3-ol, 37

Oxime 34 (0.320 g), dimethoxyethane (6 ml), water (3 ml), and titanium trichloride (2.3 ml) were heated at 110° for 15 minutes. The reaction mixture was cooled, diluted with water, and extracted with methylene chloride. The methylene chloride fraction was washed with saturated sodium bicarbonate solution, dried, and the methylene chloride removed by distillation. Sodium borohydride (0.1 g), sodium hydroxide (2M, 1 ml), and water (1 ml) was added to the reaction mixture. After 24 hours the solution was diluted with water, acidified (HCl), neutralized ($NaHCO_3$), and extracted with methylene chloride. The methylene chloride fraction was dried and concentrated to give alcohol 37 (0.287 g, 97%).

η_D^{22} 1.4675.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76.

Found: C, 77.57; H, 12.02.

$ir_{(neat)}$: 3370, 1060 (OH) cm^{-1}.

$nmr_{(CCl_4)}$: τ 5.85 (q, 1 J = 7, 11Hz, CHOH), 7.76 (s, 1, OH, D_2O), 8.77 (s, 3, CH_3), 8.90 (s, 3, CH_3), 9.05 (s, 3, CH_3).

mass spectrum: m/e 154.1358 calcd for $C_{10}H_{18}O$, 154.1360 meas(4), 136(16), 126(32), 111(46), 95(13), 93(15), 85(26),

83(26), 71(37), 70(100), 69(30), 55(26), 43(40), 41(40).

Attempted Beckmann Cleavage of oxime 34

Oxime 34 (0.250 g) in ether--benzene (4 ml; 1:1) was added dropwise to a stirred solution of phosphorus pentachloride (0.320 g) in ether--benzene (4 ml; 1:1). The mixture was stirred at room temperature for 24 hours, then diluted with water. The organic phase was separated and the aqueous phase was extracted with methylene chloride. The combined organic fractions were washed with sodium bicarbonate solution, dried and concentrated. Crystallization from ethyl acetate afforded 0.220 g of a crystalline compound of unknown structure: mp 186-187°.

Anal. Calcd for $C_{10}H_{15}NO^{35}Cl_2$: C, 50.85; H, 6.40.
Found: C, 50.00; H, 6.74.

$ir_{(CHCl_3)}$: 3300, 3150, 1670 (C=O), 1655, 1365, 1350, 1340, 890 cm^{-1}.

$nmr_{(CDCl_3)}$: τ 2.65 (br m, 1), 8.33 (s, 3, $C\underline{H}_3$), 8.48 (s, 3, $C\underline{H}_3$), 8.80 (s, 3, $C\underline{H}_3$).

mass spectrum: m/e 220.0296 calcd for $C_9H_{12}NO^{35}Cl_2$, 220.0291 meas(17), 157(5), 141(7), 115(11), 79(5), 69(100), 53(7), 41(26).

Chemical ionization: $(M+ + NH_4^+)$ 253, (M^+) 235, 220.

2-Isopropenyl-1-methylcyclobutane acetic acid, 39

Oxime 34 (0.473 g) in anhydrous benzene (5 ml) and

anhydrous ether (5 ml) was added dropwise to a cooled, stirred suspension of phosphorus pentachloride (0.560 g) in anhydrous benzene (5 ml) and anhydrous ether (5 ml). After addition was complete, the mixture was stirred at room temperature for six hours. The reaction mixture was diluted with cold sodium bicarbonate solution and the organic layer separated. The aqueous fraction was washed with methylene chloride. The organic fractions were combined, dried, and excess solvents removed by distillation through a 20 cm column packed with glass helices. The product was analyzed by glc--mass spectroscopy (Zonyl E-7, 10' x 3/8", 170°, 120 ml/min). Four products were formed. The major component has a molecular ion of m/e 149. The three minor components had apparent molecular ions of m/e 152, 149, 168. The ir and nmr spectra of the reaction mixture showed seconitrile 38 to be the major product.

$ir_{(CHCl_3)}$: 2250 (CN), 1650, 890 ($C=C\underline{H}_2$) cm^{-1}.

$nmr_{(CCl_4)}$: τ 5.10 (m, 1, $C=C\underline{H}_2$), 5.23 (m, 1, $C=C\underline{H}_2$), 8.33 (br s, 3, $C=C-C\underline{H}_3$), 8.64 (s, 3, $C\underline{H}_3$).

Impure seconitrile 38, potassium hydroxide (0.300 g) and ethylene glycol (10 ml) were heated at 200° for 24 hours. The mixture was cooled, diluted with water, and washed with methylene chloride to remove non-acidic material. The aqueous fraction was acidified (HCl) and extracted with methylene chloride. The methylene chloride fraction was

separated into strong acid and non-acidic material by extraction with sodium bicarbonate. The acidic material was recovered from the sodium bicarbonate solution by acidification (HCl), extraction with methylene chloride, and removal of solvent. Secoacid 39 (0.324 g, 69%) was obtained as an oil, bp 108-110° (0.5 mm).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59.

Found: C, 70.47; H, 9.48.

$ir_{(CCl_4)}$: 3300-2500 (COOH), 1710 (C=O), 1650, 890 ($C=CH_2$) cm^{-1}.

$nmr_{(CCl_4)}$: τ 0.4 (1, m, COO$\underline{H}$, D_2O), 5.16 (m, 1, C=C$\underline{H}_2$), 5.34 (m, 1, C=C$\underline{H}_2$), 8.33 (br s, 3, C=C-C$\underline{H}_3$), 8.67 (s, 3, C$\underline{H}_3$).

mass spectrum: 168.1150 calcd for $C_{10\ 16}O_2$, 168.1146 meas (5), 153(5), 125(29), 109(16), 108(92), 95(13), 93(23), 91(13), 81(28), 69(26), 68(100), 67(62), 55(10), 53(18), 43(26), 41(28), 39(16).

Cis-2-isopropenyl-1-methylcyclobutaneethanol (Grandisol), 1

Secocarboxylic acid 39 (0.11 g) in anhydrous benzene (2 ml) was added dropwise to a stirred solution of sodium dihydrobis(2-methoxyethoxy)aluminate (0.24 g) in refluxing benzene (10 ml). The solution was allowed to reflux one hour, then excess benzene (6 ml) was removed by distillation. The solution was cooled, and unreacted hydride destroyed with 10% sulfuric acid. The aqueous frac-

tion was extracted with methylene chloride. The combined organic fractions were washed with sodium bicarbonate solution, dried, and concentrated. Molecular distillation of the concentrate gave 0.05 g, 50% of grandisol, 1.

ir$_{(CCl_4)}$: 3620, 3500 (OH), 1640, 885 (C=C) cm^{-1}.

nmr$_{(CCl_4)}$: τ 5.18 (m, 1, C=C$\underline{H}_2$), 5.37 (m, 1, C=C$\underline{H}_2$), 6.43 (t, 2 J = 7.5Hz, C$\underline{H}_2$C$\underline{H}_2$OH), 6.92 (br s, 1, O$\underline{H}$, D_2O), 8.33 (br s, 3, C=CC$\underline{H}_3$), 8.83 (s, 3, C$\underline{H}_3$).

mass spectrum: m/e 154.1358 calcd for $C_{10}H_{18}O$, 154.1354 meas(13), 139(11), 136(23), 121(25), 110(23), 109(53), 93(22), 81(26), 69(18), 68(100), 67(53), 56(21), 55(28), 53(27), 41(21), 39(26).

Solvolysis of compound 26

Compound 26 (0.69 g), anhydrous sodium acetate (0.27 g) and glacial acetic acid (15 ml) were allowed to reflux for 24 hours. The mixture was diluted with water, neutralized to pH 6 (KOH), and extracted with methylene chloride. The methylene chloride fraction was washed with sodium bicarbonate solution, brine, dried, and concentrated to give 0.291 g of a mixture of compounds. Analysis by glc--mass spectroscopy (Zonyl E-7, 10' x 3/8", temp program, 45 ml/min) shows a mixture of 12 compounds. The compounds, listed in order of increasing retention time, have the following apparent molecular ions: i) m/e 134, ii) m/e 172, iii) m/e 152, iv) m/e 154, v) m/e 154, vi) m/e 154,

vii) m/e 154, viii) m/e 194, ix) m/e 134, x) m/e 194, xi--xii) m/e 136.

Sodium borohydride reduction of α-acetoxyketone 20

Sodium borohydride (0.025 g) in water (1 ml) was added dropwise to a stirred solution of α-acetoxyketone 20 (0.1 g) in dimethoxyethane (4 ml). The reaction mixture was stirred at room temperature for four hours, then diluted with water, acidified (dil HCl), and extracted with methylene chloride. The methylene chloride fraction was dried and concentrated to give a 3:2 mixture of acetoxyalcohols (0.120 g).

$ir_{(CHCl_3)}$: 3620, 3500 (OH), 1750, 1740 (C=O) cm^{-1}.

$nmr_{(CCl_4)}$: major compound τ 5.17 (d, 1 J = 5.5Hz), 5.82 (d, 1 J = 5.5Hz), 6.88 (br s, 1, O$\underline{H}$, D_2O), 7.94 (s, 3, OCOC$\underline{H}_3$), 8.83 (s, 3, C$\underline{H}_3$), 9.02 (s, 3, C$\underline{H}_3$), 9.10 (s, 3, C$\underline{H}_3$);

minor compound τ 5.00 (d, 1 J = 5.5Hz), 6.30 (d, 1 J = 5.5Hz), 6.88 (br s, O$\underline{H}$, D_2O), 7.87 (s, 3, OCOC$\underline{H}_3$), 8.75 (s, 3, C$\underline{H}_3$), 8.97 (s, 3, C$\underline{H}_3$), 9.07 (s, 3, C$\underline{H}_3$).

This mixture could not be separated by tlc (alumina or silica gel) or by glc (15% Carbowax 20M, 20% SE-30, 3% OV-17, 10% QF-1, 20% Zonyl E-7).

Oxidation of isomeric acetoxyalcohols[57]

The mixture of α-acetoxy alcohols (0.080 g) in

anhydrous ether (2 ml) was cooled in an ice bath and ice-cold chromic acid solution[57] (0.4 ml) was added dropwise with stirring. The mixture was stirred vigorously for ten minutes, then diluted with water. The aqueous layer was separated and extracted with ether. The combined ether fractions were washed successively with sodium bicarbonate solution, water, brine, and dried. Concentration in vacuo gave a mixture of acetoxyketones.

$ir_{(CHCl_3)}$: 1760, 1750 (C=O) cm^{-1}.

$nmr_{(CCl_4)}$: τ 4.37 (s, 1, C<u>H</u>OAc), 7.85 (s, 3, OCOC<u>H</u>$_3$), 8.78 (s, 3, C<u>H</u>$_3$), 8.93 (s, 3, C<u>H</u>$_3$), 9.05 (s, 3, C<u>H</u>$_3$);

τ 4.74 (s, 1, C<u>H</u>OAc), 7.90 (s, 3, OCOC<u>H</u>$_3$), 8.93 (s, 3, C<u>H</u>$_3$), 8.99 (s, 6, C<u>H</u>$_3$).

<u>3-Bromo-1,4,4-trimethylbicyclo[3.2.0]heptan-2-one, 41</u>

Ketone <u>10</u>, (0.5 g), pyridinium hydrobromide perbromide (0.92 g), acetic acid (5 ml), and chloroform (10 ml) were stirred at room temperature for three hours. The mixture was diluted with ice-water, neutralized ($NaHCO_3$), and extracted with methylene chloride. The methylene chloride fraction was washed with dilute hydrochloric acid, sodium bicarbonate solution, brine, dried, and concentrated to give α-bromoketone <u>41</u>. Compound <u>41</u> was purified by distillation. Yield 0.5 g, (76%). bp 74° (0.25 mm). η_D^{23} 1.5016.

Anal. Calcd for $C_{10}H_{15}OBr$: C, 51.97; H, 6.54; Br, 34.57.

Found: C, 52.00; H, 6.53; Br, 33.23.

$ir_{(CHCl_3)}$: 1750 (C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 4.93 (s, 1, C<u>H</u>Br), 8.72 (s, 3, C<u>H</u>$_3$), 8.88 (s, 3, C<u>H</u>$_3$), 9.14 (s, 3, C<u>H</u>$_3$).

mass spectrum: 230.0306 calcd for $C_{10}H_{15}O^{79}Br$, 230.0310 meas(18), 151(13), 124(14), 123(100), 109(16), 97(13), 95 (27), 83(18), 82(21), 81(33), 69(70), 68(25), 67(33), 53(25), 51(19), 41(51), 39(30).

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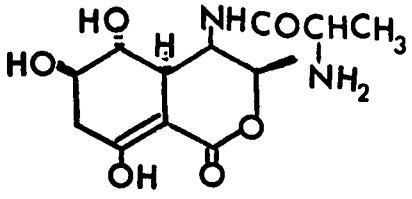
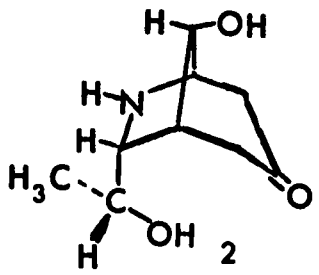
II. TOWARDS THE SYNTHESIS OF ACTINOBOLAMINE

I N T R O D U C T I O N

The antibiotic actinobolin was first described by Haskell and Bartz[1]. The compound, isolated from an antibiotic beer cultured by Streptomycetes griseoviridus var. atrofaciens possesses broad spectrum antibiotic activity and has demonstrated value as a chemotherapeutic agent in certain types of neoplastic diseases[2a-c]. In 1967, Munk and co-workers, using a computer program as an aid to evaluate the structural implications of experimental data, determined that the structure of actinobolin was as shown for compound 1[3a,b]. Acid hydrolysis of actinobolin gives a basic fragment, actinobolamine, 2[4].

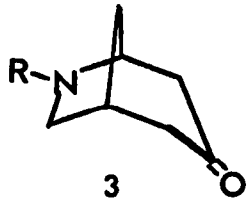


1



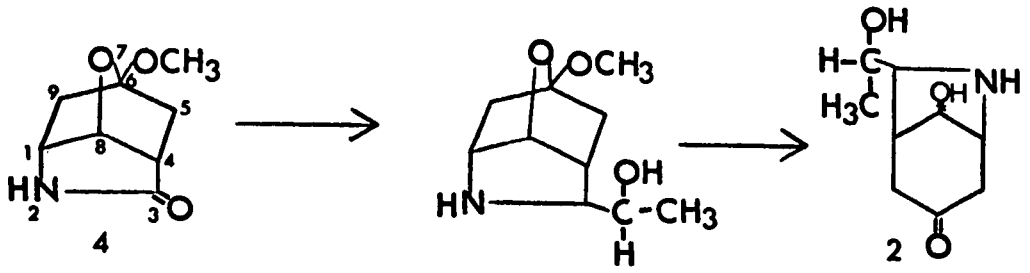
2

To date no synthesis of actinobolin or actinobolamine has been reported, although two similar reports of the synthesis of 6-azabicyclo[3.2.1]octan-3-one, 3, have appeared[5a,b].

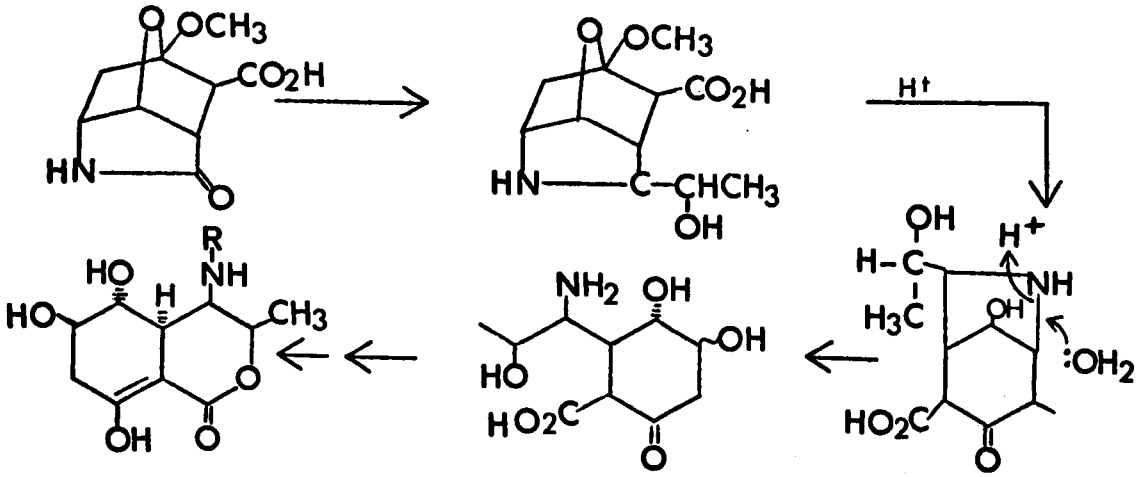


3

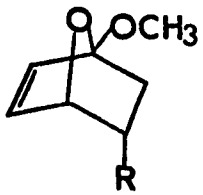
An attractive intermediate towards the synthesis of actinobolamine 2 is the tricyclic compound 4, 6-methoxy-3-oxo-2-aza-7-oxatricyclo[4.2.1.$0^{4,8}$] nonane. This compound could be transformed to actinobolamine by addition of a two carbon unit at C-3 followed by acid hydrolysis.



The stereochemical outcome upon acid hydrolysis of the tricyclic system 4 should be such that in the product four of the five consecutive asymmetric centers will necessarily have the correct configuration. In addition, if the tricyclic compound 4 contains a potential carboxyl group at C-5, it would be a possible precursor to actinobolin, 1.



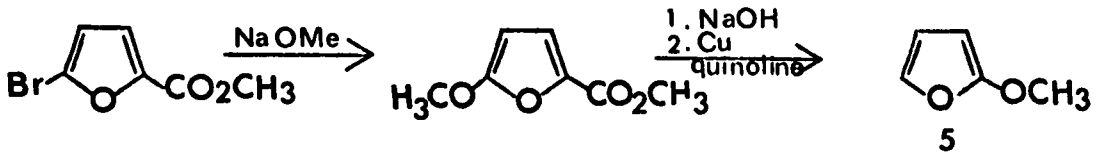
One route to the tricyclic compound 4 is through a Diels-Alder reaction of 2-methoxyfuran. The adduct must have an endo substituent on the side opposite to the bridgehead methoxyl, i.e., a compound of the following general structure.



This thesis will describe our attempts to obtain such an adduct of 2-methoxyfuran. As well some preliminary efforts directed towards the formation of the tricyclic compound 4 will be reported.

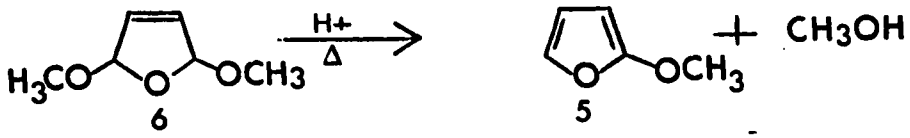
D I S C U S S I O N

The diene, 2-methoxyfuran 5, has previously been prepared by two different routes[6,7]. Amstutz and Petfield[6a] treated methyl 5-bromo-2-furoate with sodium methoxide to form methyl 5-methoxy-2-furoate. Subsequent saponification followed by decarboxylation gave 2-methoxyfuran in 10 to 36% yield. Wilson and co-workers[7a,b] have obtained com-



5

pound 5 in 51% yield by acid-catalyzed pyrolysis of 2,5-dihydro-2,5-dimethoxyfuran.



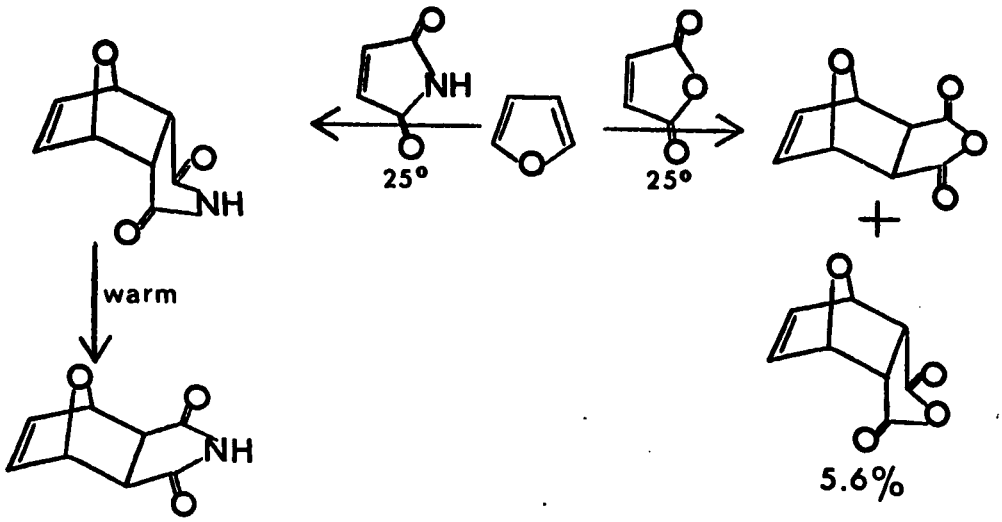
6 5

We prepared diene 5 by acid-catalyzed pyrolysis of commercially available 2,5-dihydro-2,5-dimethoxyfuran.

Initially the diene was elusive. The distillate from the pyrolysis reaction contained starting material, 2,5-dihydro-2,5-dimethoxyfuran, and products, methanol and 2-methoxyfuran. Attempted separation by distillation generally led to polymerization. However, if both the bath temperature and the rate of addition of compound 6 were controlled such that the temperature of the distillate did

not rise above 90°, this problem was avoided. No starting material was present in the distillate. It was found that 2-methoxyfuran is sensitive to acid and to oxygen. If all the methanol was not removed, compound 5 polymerized when stored in a nitrogen atmosphere in the cold. Therefore we found it most expedient to use freshly prepared 2-methoxyfuran.

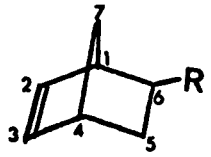
Certain generalities concerning the Diels-Alder reaction of furans[8] may be drawn from the results of the numerous investigations in this area. Furan and a dienophile undergo a [4+2] cycloaddition reaction to form a bicyclic molecule. Less reactive furans, where longer reaction times and higher temperatures are required, give rise to exo adducts. In contrast, with more active dienes and in reactions at lower temperatures, predominately endo adducts are formed. However, the reaction is seldom stereospecific as demonstrated by Stockmann[9]. He showed by hypoiodite tritration of the Diels-Alder product, that the exo-furan--maleic anhydride adduct contained 5 to 6% of the endo isomer. Other workers have obtained similar results with the furan--maleimide system[10]. Endo addition is favored kinetically but the adduct usually isomerizes to the thermodynamically more stable exo adduct.

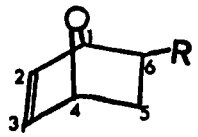


2-Methoxyfuran is not much more reactive a diene than furan itself. Adducts with such highly reactive dienophiles as maleic anhydride[7a], fumaronitrile[7a], and dimethyl acetylene dicarboxylate[11] have been reported, but the stereochemistry of the products was not clarified. No adducts of 2-methoxyfuran with monosubstituted dienophiles have been reported.

The stereochemistry of Diels-Alder adducts can be derived from an analysis of their nmr spectra. Laszlo and R. Schleyer[12] have studied the nmr spectra of a series of norbornene derivatives. The coupling constants observed for the compounds studied are summarized on column two of the following table. Gagnaire and Payo-Subiza[13] have studied the nmr spectra of 7-oxanorbornene and derivatives. The coupling constants observed are summarized in column three of the following table.

Observed Coupling Constants of Norbornene and 7-Oxanorbornene Derivatives



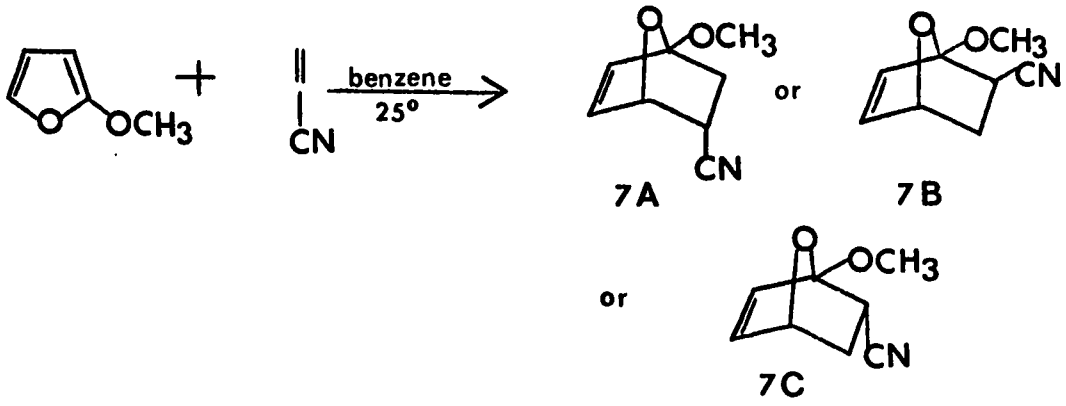


Vicinal Protons (exo=x, endo=n)	Observed Coupling (cps)[12]	(cps)[13]
$J_{2,3}$	5.0 - 6.0	--
$J_{1,2}$ ($J_{3,4}$)	2.4 - 3.0	--
$J_{4,5x}$	3.0 - 5.0	4.2 - 5.0
$J_{4,5n}$ ($J_{1,6n}$)	0	0
$J_{5x,6x}$ (R=H)	7.5 - 9.2	11 - 11.4
$J_{5n,6n}$	5.8 - 7.7	7
$J_{5x,6n}$	2.1 - 5.8	0 - 3.2
Geminal Protons	Observed Coupling	
$J_{5x,5n}$	12.3 - 13.2	--

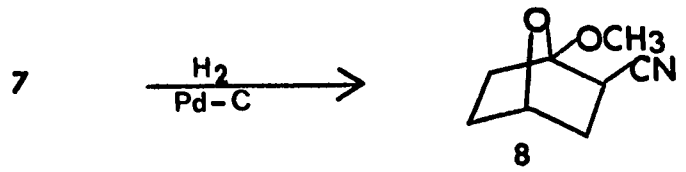
The multiplicity of the bridgehead proton (H-1, H-4) should indicate the stereochemistry of the Diels-Alder adduct. The nmr spectrum of an adduct containing an exo-substituent should show the bridgehead proton as a doublet (small coupling to vic-olefinic proton, zero coupling to vic-endo-proton). On the other hand, the nmr spectrum of an adduct containing an endo-substituent should display the

bridgehead proton as a doublet of doublets (small coupling to vic-olefinic proton, large coupling to vic-exo-proton). The stereochemistry of the Diels-Alder adducts of 2-methoxyfuran was assigned on this basis.

We have reacted 2-methoxyfuran with several mono- and α,α-disubstituted dienophiles. When 2-methoxyfuran, 5, was reacted with acrylonitrile in anhydrous benzene at room temperature, a crystalline compound, mp 78.5-79.5°, was isolated after four days. The ir spectrum of the compound shows non-conjugated nitrile absorption at 2245 cm^{-1} and C=C absorption at 1610 cm^{-1}. The nmr spectrum shows the bridgehead proton as a doublet of doublets at τ 5.04 (J = 2,4.5Hz), whereas the proton geminal to the cyano group appears as a quartet at τ 7.34 (J = 4.5, 8Hz). This data is consistent with the formation of compound 7A, 7B, or 7C.



In order to determine which stereoisomer had formed, the 2-methoxyfuran--acrylonitrile adduct was hydrogenated over 5% palladized charcoal.



The crystalline compound obtained (mp 87.5-88°) shows non-conjugated nitrile (2245 cm^{-1}) in its infrared spectrum. The nmr spectrum shows no olefinic protons. The bridge-head proton is a multiplet at τ 5.48, whereas the proton geminal to the nitrile appears as a quartet at τ 7.07.

Fraser[14] has studied the chemical shift values of a series of bicyclic Diels-Alder adducts and their hydrogenated products. He found that on hydrogenation the "absorption frequency of protons (exo) which lie above the plane of the double bond are shifted upfield whereas a downfield shift is experienced by protons (endo) which lie in the plane of the double bond".

In our case, the proton geminal to the cyano group resonates at τ 7.34 in the methoxyfuran--acrylonitrile adduct. Hydrogenation causes a downfield shift in the nmr spectrum to τ 7.07 for this proton. Thus the structure of the hydrogenated compound is 8 and the 2-methoxyfuran--acrylonitrile adduct must have structure 7B. Further support for this structure assignment is available from spin-spin decoupling experiments of the methoxyfuran--acrylonitrile adduct. Double irradiation at 497Hz (τ 5.03) does not change the quartet at τ 7.34. This eliminates the pos-

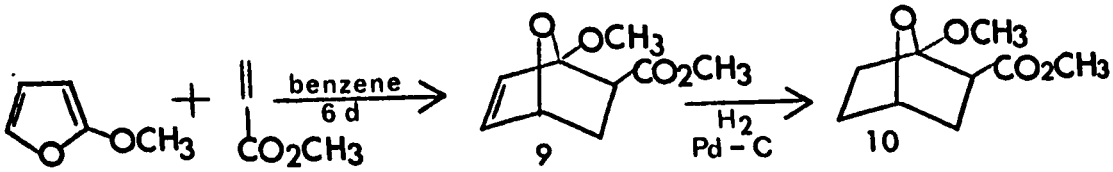
sible structure 7A, since the quartet observed for the proton geminal to the cyano group should collapse to a doublet in this compound.

We had hoped that a mono-substituted dienophile with a bulkier activating group than nitrile, might change the orientation such that the functional group in the adduct would be on the side remote from the methoxyl group. When 2-methoxyfuran was reacted with methyl acrylate at room temperature, a product could be isolated after six days. The ir spectrum of the product shows ester carbonyl absorption at 1740 cm^{-1} and an isolated double bond at 1615 cm^{-1}. The nmr spectrum displays two olefinic protons (τ 3.44, 3.76), two methoxyl singlets (τ 6.37, 6.45), the bridgehead proton as a doublet of doublets (τ 5.20), and a lowfield methine (τ 7.03 quartet). As well, a small amount (less than 10%) of another stereoisomer is present.

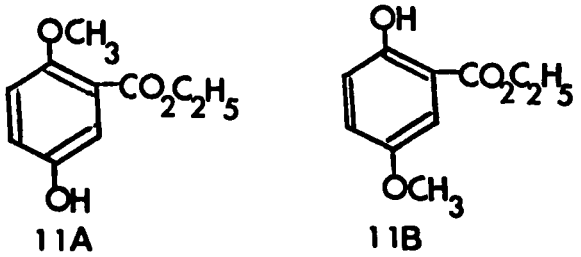
Hydrogenation of the methoxyfuran--methyl acrylate adduct led to isolation of a single stereoisomer. The nmr spectrum of this compound shows a multiplet at τ 5.58 for the bridgehead proton, two methoxyl singlets (τ 6.24, 6.43) and a lowfield methine (τ 6.80).

In the nmr, the proton geminal to the carbomethoxyl group of the adduct shifts to lower field upon hydrogenation (from τ 7.03 to 6.80). Thus the stereochemistry of the hydrogenated adduct was assigned as shown for com-

pound 10 and that of the Diels-Alder product as shown for compound 9.



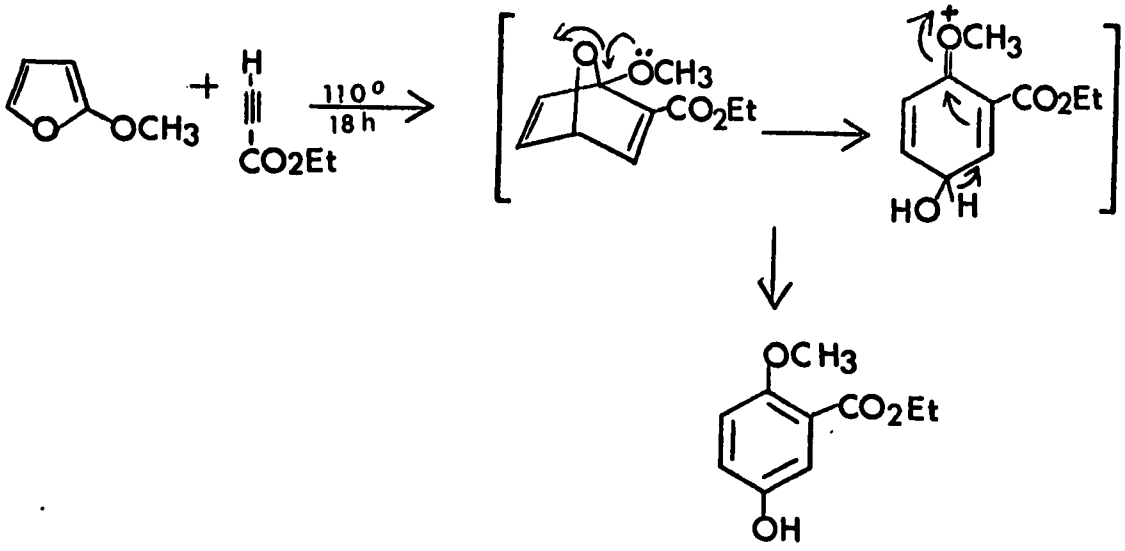
Very little Diels-Alder adduct was formed after several weeks when 2-methoxyfuran was treated at room temperature with benzyl acrylate, ethyl propiolate or propiolamide. However, when compound 5 was reacted with excess ethyl propiolate at 110° for 18 hours a mixture of products was obtained (glc). The major component was isolated by preparative glc (SE-30). The ir spectrum shows absorption bands of a hydroxyl group (3600, 3350 cm^{-1}), a methoxyl (2840 cm^{-1}) and an ester carbonyl (1720 cm^{-1}). The nmr spectrum displays an ethyl group (τ 8.67 t, 5.68 q), a methoxyl (τ 6.23), a hydroxyl (τ 4.00), and three aromatic protons (τ 2.75, 3.10, 3.16). This is consistent with the formation of either compound 11A or compound 11B.



11A 11B

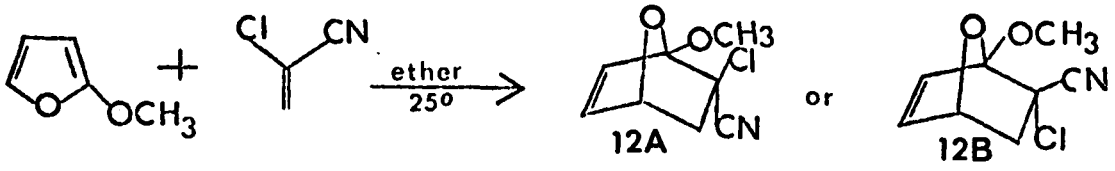
Saponification of the methoxyfuran--ethyl propiolate mixture led to isolation of a crystalline acid, mp 150-152°. The melting point reported for 2-methoxy-5-hydroxy-

benzoic acid is 155-156°, whereas that reported for 5-methoxy-2-hydroxybenzoic acid is 145-146°[15]. Esterification of the crystalline acid with diazomethane gave a single methyl ester (ir, nmr). It seems, therefore, that the acid obtained upon saponification of the Diels-Alder reaction mixture was 2-methoxy-5-hydroxybenzoic acid. Thus reaction of 2-methoxyfuran and ethyl propiolate gave compound 11a which was formed by aromatization of the Diels-Alder adduct. Aromatization of adducts of substituted furans have been used as a method to synthesize substituted aromatic compounds[16].

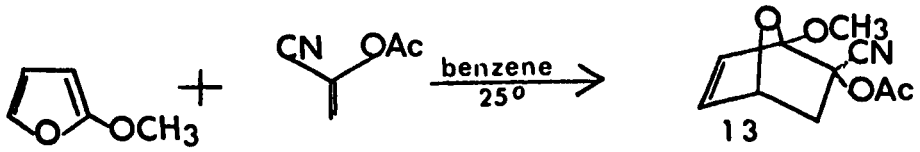


Methoxyfuran also reacted with α,α-disubstituted dienophiles. When compound 5 is treated with α-chloroacrylonitrile at room temperature, a crystalline adduct, mp 62-63°, is formed after two days. The ir spectrum of the adduct shows absorption bands for a methoxyl group (2850 cm^{-1}) and nitrile (2250 cm^{-1}). The nmr spectrum dis-

plays two olefinic protons (τ 2.60, 3.60), a bridgehead proton (τ 5.01, d of d), a methoxyl group (τ 6.23) and two methylene protons (τ 6.86, 7.96). The multiplicity of the bridgehead proton is consistent with either structure 12A or 12B.

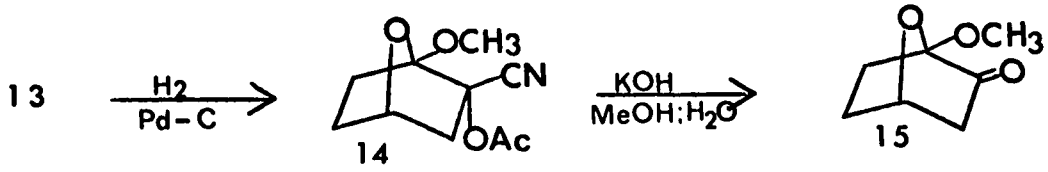


In compound 12 the geminal chloro and nitrile groups had the "undesired" orientation. We thought that transformation of these groups to a carbonyl might allow us to functionalize the bicyclic compound at C-5. Since adducts of α-acetoxyacrylonitrile are readily hydrolyzed to ketones, this dienophile was reacted with 2-methoxyfuran. After one month, a crystalline adduct had formed. The multiplicity of the bridgehead proton in the nmr spectrum of the adduct (τ 5.05, d of d) established the formation of compound 13.



Catalytic hydrogenation of the methoxyfuran--acetoxyacrylonitrile adduct gave compound 14. The chemical shift of the acetoxyl methyl in the nmr appears at τ 7.84, 0.09 ppm downfield from that observed for compound

13 (τ 7.93). Using Fraser's correlation[14], we assign the stereochemistry as shown for compound 14 and compound 13.



Hydrolysis of compound 14 gave a high yield of 1-methoxy-7-oxabicyclo[2.2.1]heptan-2-one, 15. The bicyclic ketone shows carbonyl absorption at 1760 cm^{-1} in its infrared. The nmr spectrum displays the bridgehead proton as a broad triplet (τ 5.26), a methoxyl methyl (τ 6.50), and methylene protons vicinal to a carbonyl (τ 7.52, 7.70).

Prolonged treatment of ketone 15 with pyrrolidine did not give an enamine. Attempted formation of an α-ketoacid by reacting ketone 15 with methyl magnesium carbonate[17] was unsuccessful.

All products of methoxyfuran with mono- or α,α-disubstituted dienophiles gave products in which a substituent(s) was vicinal to the bridgehead methoxyl. These results can be rationalized if one considers the mechanism of the Diels-Alder reaction[18a-c]. It is generally conceded[18a] that the Diels-Alder reaction is a concerted reaction which is controlled by orbital symmetry[18b]. However, these considerations have not given a completely satisfactory explanation for the orientation phenomena of unsymmetrical dienes and dienophiles. Recently, Deslong-

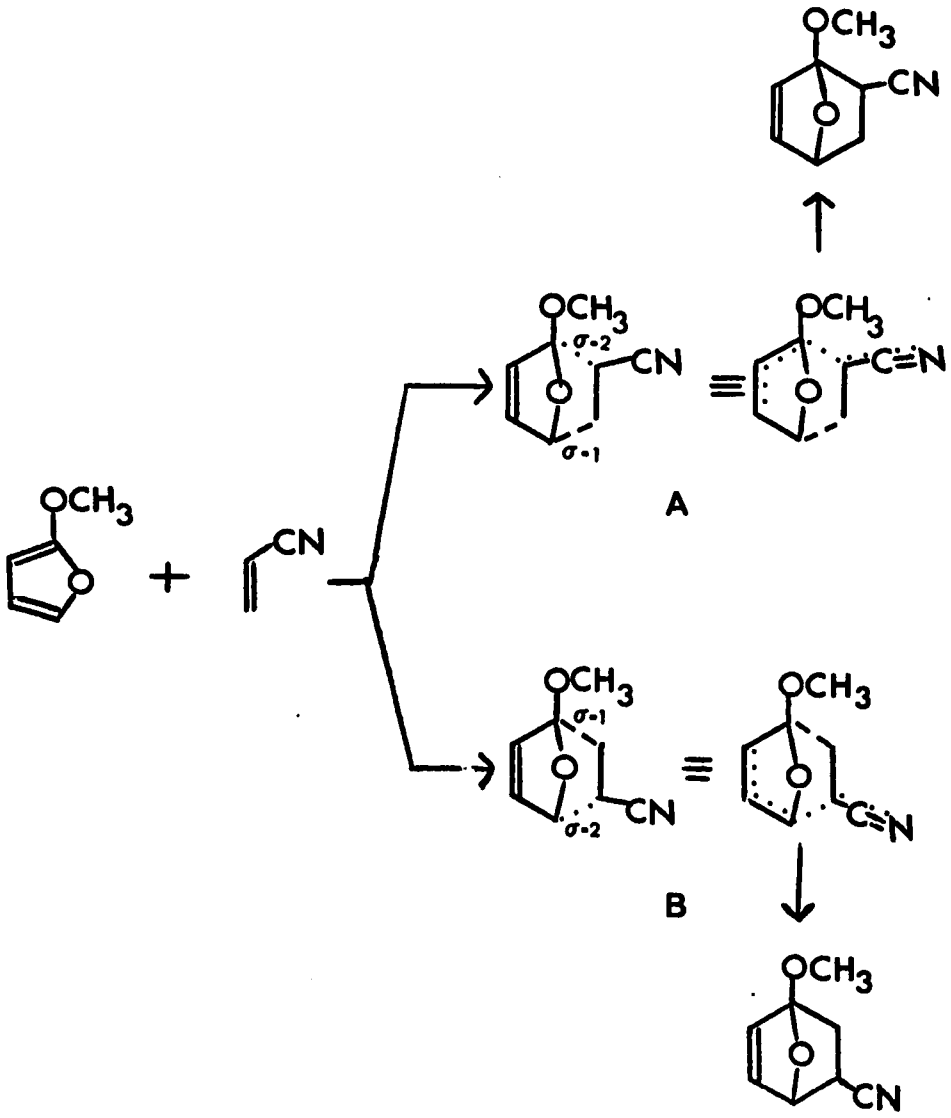
champs[18c] has set forth a set of postulates which allow one to predict the orientation of the adducts from unsymmetrical dienes and dienophiles, and which lead to a correct explanation of the orientation observed.

"The proposition is: a) The Diels-Alder reaction is a one-step process but with an unsymmetrical transition state. This simply means that in the transition state, one bond (σ-1) is almost completely formed while the other bond (σ-2) is in the process to be formed.

b) The lowest energetic transition state will be the one which will permit the largest electronic delocalization only on the bond in the process to be formed (σ-2). Thus, substituents both in the dienophile and in the diene will have a role to play in deciding which carbons will be involved in the σ-2 bond and consequently will determine the lowest transition state."

The application of such simple principles enable us to predict the stereochemical orientation of the Diels-Alder reaction with 2-methoxyfuran. For example, two transition states (A and B) are possible for the 2-methoxyfuran--acrylonitrile adduct. The transition state A is lower in energy than transition state B, because in the former the methoxyl is able to stabilize the σ-2 bond. Thus the predicted orientation of the adduct is that derived from transition state A. Indeed this was the orientation observed

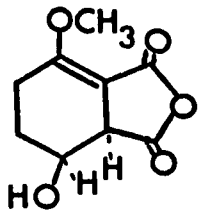
for the 2-methoxyfuran--acrylonitrile adduct.



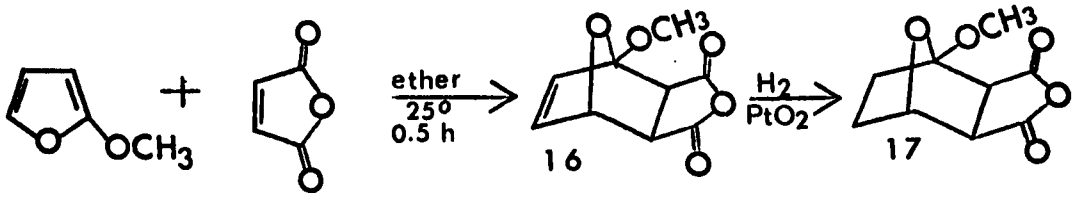
In order to obtain a Diels-Alder adduct of 2-methoxyfuran with an endo substituent at C-5 it appeared that diene 5 must be reacted with an α,β-disubstituted dienophile. Reaction of 2-methoxyfuran with maleic anhydride at room temperature readily gave the exo adduct, 16. The ir spectrum shows anhydride absorption bands at 1870 and 1800 cm^{-1}. The nmr spectrum shows two olefinic protons

(τ 3.25, d of d; 3.47, d), the bridgehead proton as a doublet (τ 4.89, J = 2Hz), a methoxyl group (τ 6.50) and two methine protons (τ 6.45, d; 6.71, d). When the methoxyfuran--maleic anhydride adduct was formed at lower temperature (-70 for 12 h, then 0°), a mixture of starting material, endo adduct, and exo adduct was obtained (nmr). It was not possible to isolate the endo adduct or to form it in large amounts.

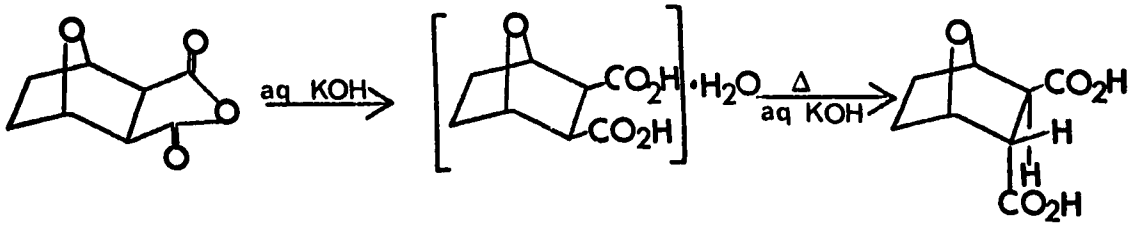
The adduct was subjected to catalytic hydrogenation. If the catalyst (platinum oxide) contained traces of acid, a mixture of compounds was obtained. Chromatography of the mixture (silicic acid) led to isolation of a crystalline compound, mp 129-130°. This compound was assigned the structure shown below on the basis of the following spectral evidence. It has molecular formula $C_9H_{10}O_5$ as determined by exact mass measurement of its molecular ion (m/e 198) in the mass spectrum. Its infrared spectrum shows hydroxyl absorption (3540 cm^{-1}), methoxyl (2840 cm^{-1}), anhydride carbonyl (1830, 1800 sh, 1760, 1750 sh cm^{-1}), and olefin (1630 cm^{-1}). The uv maximum at 245 (ε = 34,500) is similar to that reported for ethyl 3-methoxybut-2-enoate (λ_{max} 245 nm, log ε = 4.44)[19]. The nmr spectrum displays a carbinol proton (τ 5.48, broad d J = 3Hz) coupled to H-2 (τ 6.66, d J = 3Hz), a methoxyl group (τ 6.05) and a hydroxyl group (τ 7.16, exchangeable with D_2O).



However, when the platinum oxide was prewashed with sodium bicarbonate solution, compound 17 was formed in high yield (ir: 1870, 1800 cm^{-1}, anhydride. nmr: τ 5.25, H-4; 6.46, $OC\underline{H}_3$; 6.68, H-2, H-3).

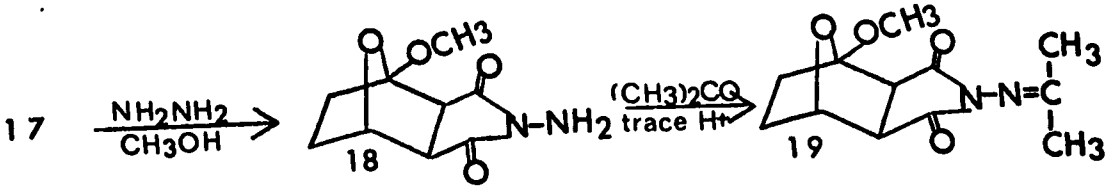


Previous workers have shown that exo-cis-acids undergo isomerization in hot alkali to give trans-acids[10].



In our case opening of the anhydride ring of compound 17 with a nucleophile, followed by epimerization with base could possibly lead to a product with the desired endo configuration at C-3. Therefore compound 17 was reacted with refluxing methanolic hydrazine. After 15 minutes, two compounds were obtained which were separated by chro-

matography over silicic acid. The major component isolated crystallized from acetone, mp 154-155.5°. The molecular formula $C_{12}H_{16}N_2O_4$ was determined by exact mass measurement of the molecular ion m/e 252 in the mass spectrum. The ir spectrum of the compound shows absorption bands at 1770, 1700, 1630 cm^{-1}. The nmr spectrum shows a bridgehead proton (τ 5.42, m), a methoxyl group (τ 6.37, s), and two methyl singlets (τ 7.77, 8.17). When the major component obtained from chromatography was crystallized from ethyl acetate rather than acetone, the compound melted at 136-138°. The molecular formula $C_9H_{12}N_2O_4$ was determined by exact mass measurement of the molecular ion m/e 212. The ir spectrum shows absorption bands for NH (3340, 3270 cm^{-1}) and carbonyl (1770, 1700 cm^{-1}). The nmr spectrum displays a bridgehead proton (τ 5.23), a broad, D_2O exchangeable two proton singlet (τ 5.63), a methoxyl group (τ 6.50), and two methine protons (τ 6.93). The spectral data presented are consistent with the formation of an amino imide 18 and a propylidene amino imide 19.

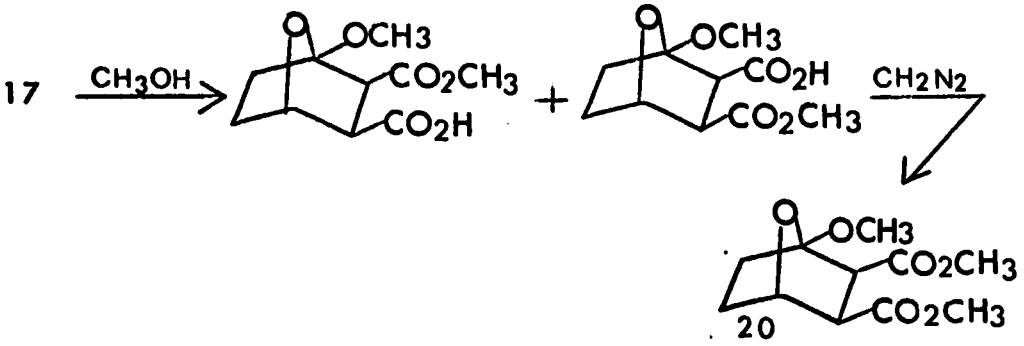


Other workers have obtained similar results with α,α-dimethylglutaric anhydride and α-pyridylhydrazine[20].

Attempted ring opening and subsequent epimeriza-

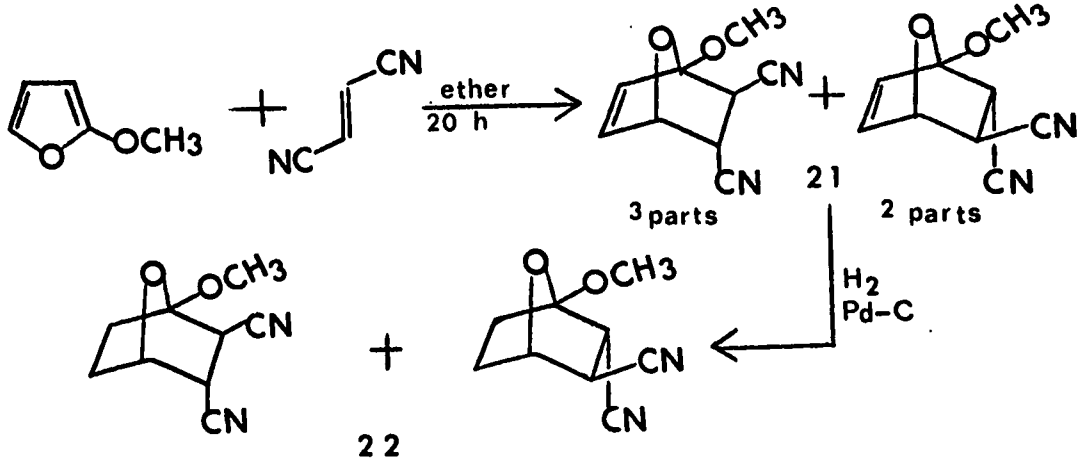
tion of compound 18 by treatment with hot alkali gave only an intractable mixture.

When anhydride 17 was reacted in refluxing methanol for 1.5 hours, two half-acid half-esters were obtained (nmr). The two compounds were positional isomers since treatment of the mixture with diazomethane gave one dimethyl ester, 20. The ir spectrum of the dimethyl ester shows carbonyl absorption at 1735 cm^{-1}. The nmr spectrum displays a bridgehead proton (τ 5.00), three methoxyl methyls (τ 6.33, 6.35, 6.50) and two methine protons (τ 6.61, 6.98, d J = 10Hz). The multiplicity of the methine protons (two doublets J = 10Hz) established the exo-cis-configuration for the dimethyl ester.



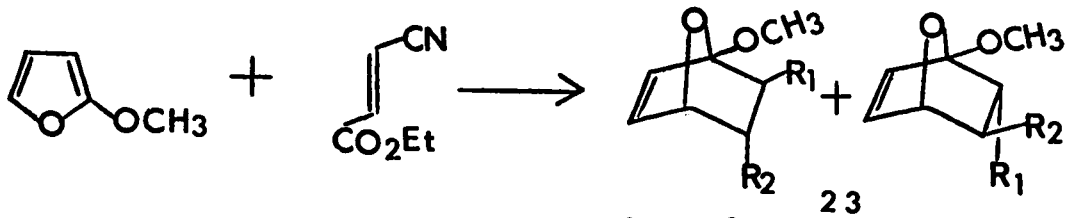
Several other disubstituted dienophiles have been used to prepare Diels-Alder adducts. When 2-methoxyfuran was reacted with diethyl fumarate at room temperature only traces of adduct were detected (nmr) after three days. However, reaction of fumaronitrile and compound 5 proceeded readily and a crystalline adduct, 21, was isolated.

The adduct appeared to be a single compound (tlc: silica gel, chloroform), but the nmr spectrum showed it was a mixture (2:1) of stereoisomers (two H-4 protons, τ 4.69, d of d; τ 4.89, d). Catalytic hydrogenation with palladized charcoal gave a crystalline mixture of stereoisomers, 22, (mp 145-147°) which could not be separated by fractional crystallization or chromatography (single spot tlc: silica gel, chloroform; alumina, benzene--chloroform).



β-Carboethoxyacrylonitrile, readily prepared from maleic anhydride[21], reacted slowly with 2-methoxyfuran. After standing one week at 25° the reaction mixture had reached an equilibrium (nmr) of starting reagents and two adducts (ratio 1:1). However, heating the mixture at 70° for three days led to the formation of a single adduct. In this compound the functional group at C-5 (CN or $CO_2CH_2CH_3$) has the exo configuration (23B or 23D). The nmr spectrum of the adduct shows the C-4 proton as a doublet

(τ 4.84, J = 2Hz) which is coupled to the olefinic proton at C-3. The Diels-Alder adducts were formed in several solvents: anhydrous benzene, anhydrous ether, acetone, acetonitrile, and neat. The reaction course was monitored by nmr. In all cases, an equilibrium mixture of starting material (small amount) and two adducts ratio (1:1) was observed.



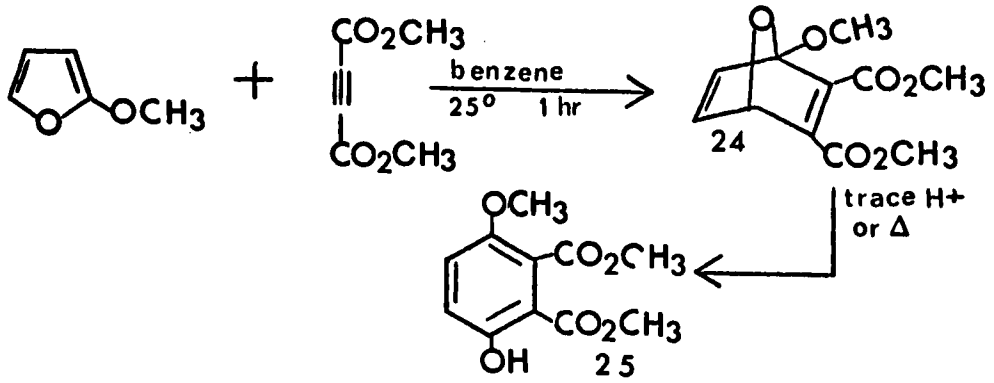
23

A $R_1 = CN$, $R_2 = CO_2Et$ or C $R_1 = CO_2Et$, $R_2 = CN$

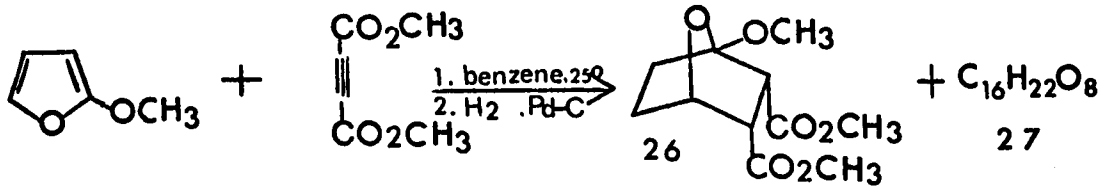
B $R_1 = CN$, $R_2 = CO_2Et$ or D $R_1 = CO_2Et$, $R_2 = CN$

Catalytic hydrogenation of the mixture 23 followed by chromatography over alumina did not allow separation of the stereoisomers.

2-Methoxyfuran reacted readily with dimethyl acetylene dicarboxylate at room temperature[11]. The adduct 24, which is a high boiling liquid can be isolated after one hour. The nmr spectrum of the compound shows olefinic protons (τ 2.25, d of d; 3.00, d), a bridgehead proton (τ 4.46, d) a methoxyl and two methyls of esters (τ 6.13, 6.22, 6.41). The adduct was very sensitive to traces of acid, readily aromatizing to form dimethyl 3-hydroxy-6-methoxyphthalate, 25, mp 112-114° (reported 118-119°)[11].



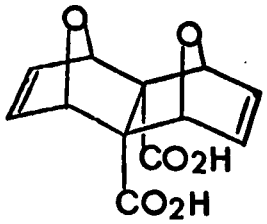
If excess diene 5 was present, two products were formed. No attempt was made to separate the compounds at this point. The mixture was hydrogenated in the presence of palladized charcoal. Two compounds, an oil and a crystalline compound 27, mp 136.5-137.5°, were isolated.



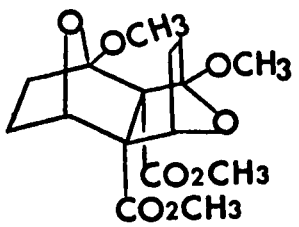
Compound 26 analyzes correctly for $C_{11}H_{16}O_6$. The ir spectrum shows ester carbonyl absorption at 1750 cm^{-1}. The nmr spectrum displays a low-field proton (τ 5.52, m, H-4), a methoxyl and two esters methyl groups (τ 6.33, 6.37, 6.52). Preliminary attempts to saponify the ester groups were unsuccessful, and no further experiments in this sequence were performed.

The crystalline compound 27 isolated from the hydrogenation of the furan--dimethyl acetylene dicarboxy-

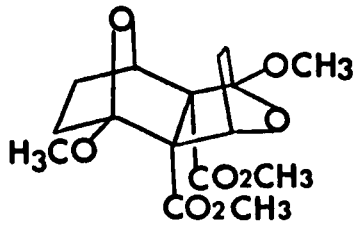
late adduct analyzes for $C_{16}H_{22}O_8$. Its infrared spectrum shows carbonyl absorption at 1750 cm^{-1}. The nmr spectrum shows two low-field protons (τ 4.91, m; 5.60, m), two methoxyl and two ester methyls (τ 6.28, 6.36, 6.58, 6.62). Deslongchamps and Kallos[22] have shown that one Diels-Alder product of furan and acetylene dicarboxylic acid is a di-adduct with the exo-exo configuration.



Compound 27 is probably a saturated di-adduct of methoxyfuran--dimethyl acetylene dicarboxylate, but an exo-exo or an endo-endo configuration is unlikely since the nmr spectrum displays two bridgehead protons with different chemical shift values. An exo-endo configuration could account for this difference.

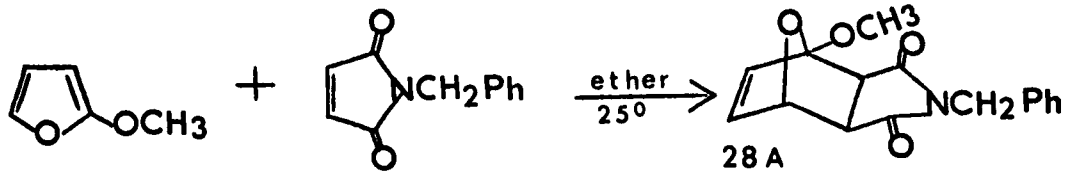


or

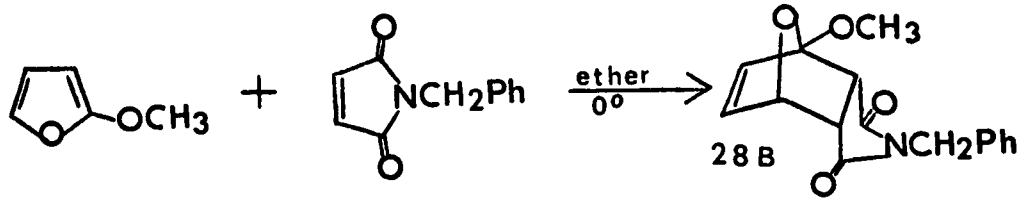


N-Benzylmaleimide[23] reacted with 2-methoxyfuran at 0° in acetone or at 25° in ether to form a crystalline

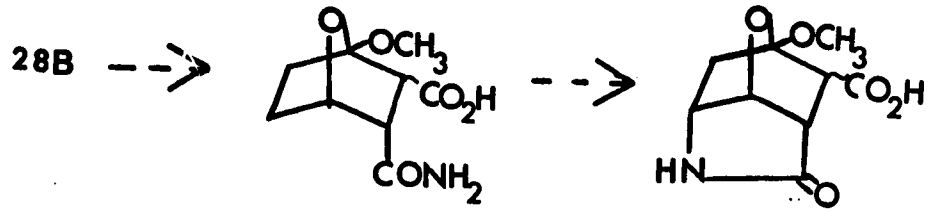
adduct, 28A, mp 108.5-110.5°. The nmr spectrum of the compound displays the bridgehead proton as a doublet (τ 4.87, J = 2Hz) indicating that it has the exo configuration.



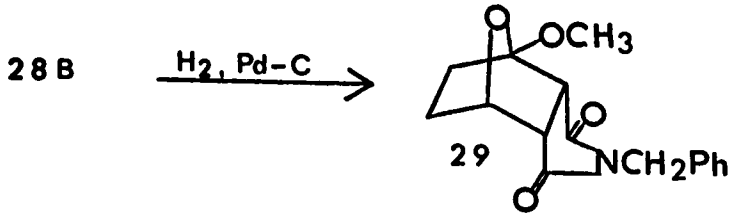
On the other hand, when 2-methoxyfuran, N-benzylmaleimide, and ether were kept at 0° for several days, a quantitative yield of a crystalline adduct, 28B, mp 94.5-96°, was obtained. The nmr spectrum shows the bridgehead proton as a doublet of doublets (τ 4.97, J = 2,5Hz) establishing the endo configuration for this adduct.



Having finally isolated an adduct which contained a C-5 endo substituent, we pursued two routes to the tricyclic compound 4. One route involved hydrogenation to a saturated adduct, hydrolysis of the imide ring to form a one-half amide, one-half acid, and finally carbon--nitrogen bond formation by nitrene insertion into a C-H bond[24a,b].

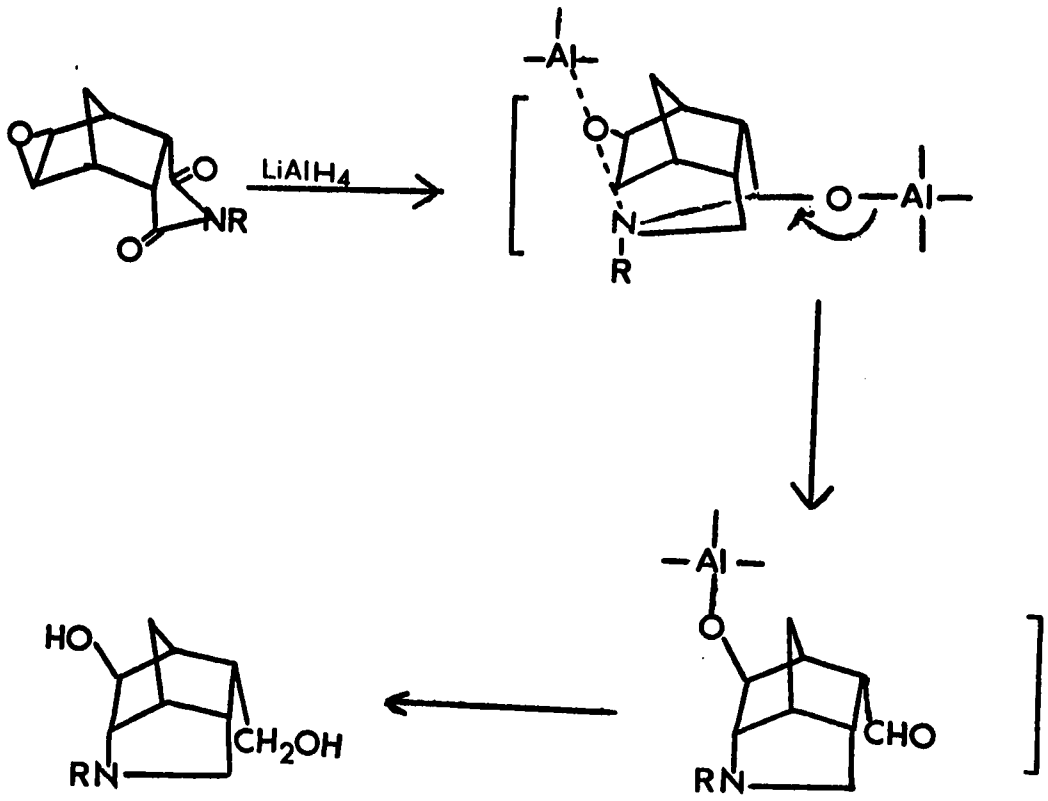


When compound 28B was subjected to catalytic hydrogenation, a high yield of a crystalline saturated analogue, 29, mp 68°, was obtained. This compound analyzes correctly for $C_{16}H_{17}NO_4$. Its ir spectrum shows absorption bands for methoxyl (2850 cm^{-1}) and imide carbonyl (1765, 1708 cm^{-1}).

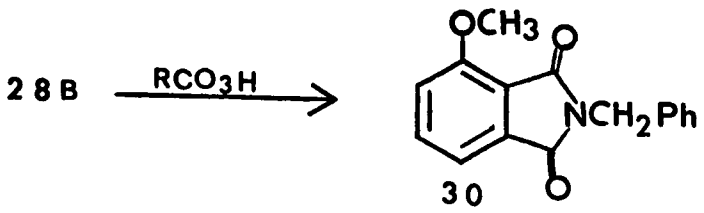


Attempted hydrolysis with potassium hydroxide led to a mixture of products. Conditions could not be found which allowed formation of a hydrolysis product which had the methoxyl group intact (nmr).

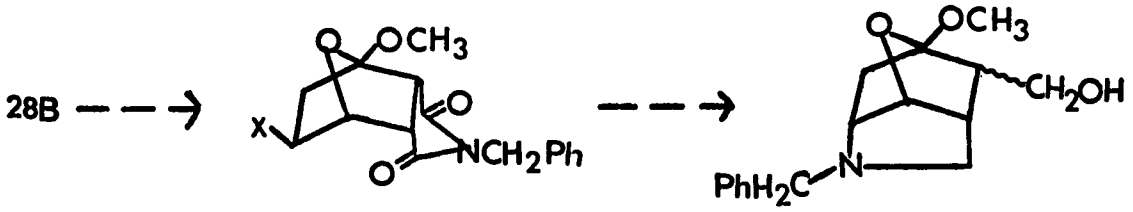
Gray and Heitmeier[25] have reported that a concerted, reductive cleavage of the imide ring occurs when exo-5,6-epoxynorbornane-endo-2,3-dicarboximide is reduced with lithium aluminum hydride. The epoxynorbornane dicarboximides were readily prepared in excellent yields by epoxidation of the norbornene precursor with commercial peracetic acid in acidic media[26].



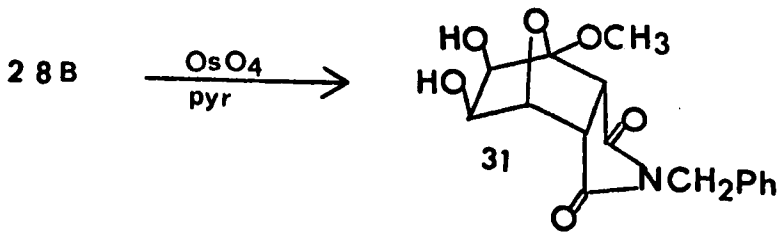
When compound 28B was treated with m-chloroperbenzoic acid, monoperphthalic acid, or under neutral conditions with peroxybenzimidic acid[27], or buffered pertrifluoroacetic acid[28], a mixture of five compounds was obtained (silica gel, chloroform--methanol, 50:1). The major component of the mixture was N-benzyl-3-methoxyphthalimide, 30, (ir: 2850, OCH_3; 1765 and 1710, imide carbonyl; 1610 and 1500 cm^{-1}, aromatic. nmr: τ 2.64, ArH; 5.18, $ArCH_2$; 6.01, OCH_3). We were unable to detect any of the desired epoxide product in the reaction mixture.



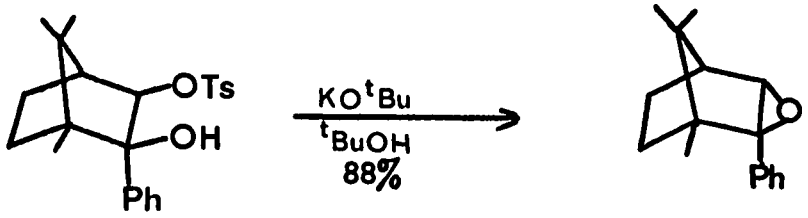
We attempted several other reactions which would introduce a potential leaving group at C-3 of compound 28B. Such a compound should also undergo reductive cleavage with lithium aluminum hydride to give a tricyclic compound.



Attempted hydration by Brown's oxymercuration--demercuration method[29] gave an intractable tar. Treatment of compound 28B with acetyl hypobromite[30] gave a mixture (nmr: no OCH_3). However, a crystalline diol, mp 130-131.5°, was formed when compound 28B was treated with osmium tetroxide in pyridine.

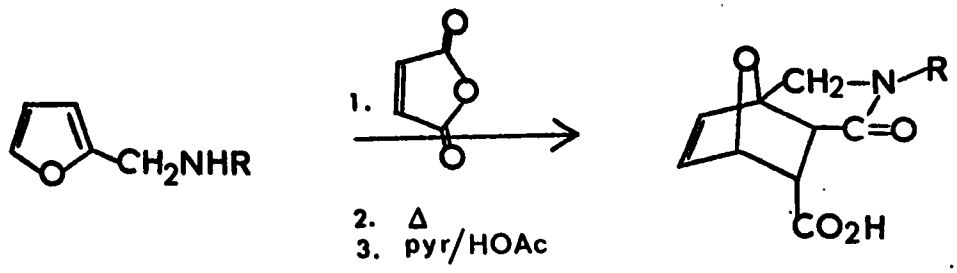


The diol has the correct molecular formula, $C_{16}H_{17}NO_6$, as shown by the exact mass measurement of the molecular ion (m/e 319) in its mass spectrum. The ir spectrum of compound 31 shows absorption bands for hydroxyl (3550 cm^{-1}) and imide carbonyl (1760 and 1700 cm^{-1}). The nmr spectrum displays five aromatic protons (τ 2.65, s), a benzyl methylene (τ 5.39, s), a one proton doublet (τ 5.55 H-4, J = 4Hz), a methoxyl group (τ 6.33, s), and two hydroxyl protons (τ 7.0, broad, D_2O exchangeable). Formation of this compound was encouraging since Hartshorn and co-workers[31] have reported the formation of epoxides by syn elimination from cis diol monotosylates.

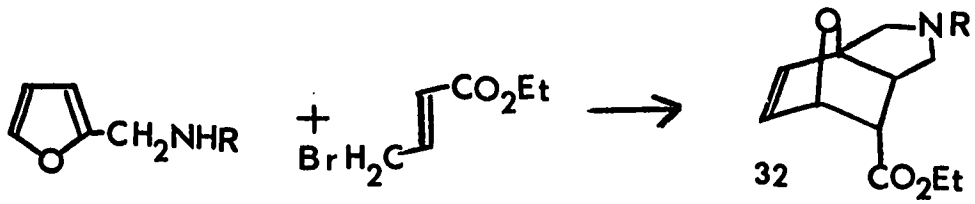


At this point, our work towards the synthesis of tricyclic compound 4 was interrupted in order that we might concentrate on the grandisol synthesis described in Part 1.

Recently, the formation of 3-oxo-5,7a-endoxo-tetrahydro isoquinoline-4-endo-carboxylic acid by an intramolecular Diels-Alder reaction of (2-furfuryl)-aniline and maleic anhydride followed by acid catalyzed isomerization has been reported[32].



A similar result has been obtained in our research laboratory. When (2-furfuryl)-aniline was reacted with ethyl 4-bromocrotonate, a crystalline Diels-Alder adduct 32, containing an endo carboethoxy group was isolated[33].



The synthesis of the tricyclic compound 4 remains incomplete. However, the synthetic sequence involving reductive cleavage of an epoxy imide with lithium aluminum hydride appears promising. In addition, the intramolecular Diels-Alder adduct, 32, could be adapted to the synthetic scheme for the total synthesis of actinobolamine and actinobolin.

EXPERIMENTAL

Solutions were dried over anhydrous magnesium sulfate unless otherwise specified.

R_f value = distance moved by compound / distance moved by solvent.

Melting points were determined on a hot-stage Fischer-Johns or Leitz-Wetzlar melting point apparatus and are uncorrected.

Microanalyses were performed by the Microanalytical Laboratory of this department.

Infrared spectra were recorded on a Perkin-Elmer Model 337 or a Unicam Model SP 1000 grating infrared spectrophotometer, or a Perkin-Elmer Model 421 dual grating infrared spectrophotometer.

Nuclear magnetic resonance spectra were measured on a Varian Associates Model A-60 spectrometer or a Varian Associates Model HR-100 spectrometer with tetramethylsilane as internal standard. Deuterium exchangeable protons are noted in text as D_2O.

Mass spectra were recorded on an AEI Model MS-9 mass spectrometer or an AEI MS-12 mass spectrometer.

2-Methoxyfuran, 5

Dibutyl phthalate (25 ml) and β-naphthalenesulfonic acid were placed in a three necked flask equipped

with a gas-inlet tube, an addition funnel, and a 30 cm column packed with steel wool which was connected to a condenser for distillation. The pyrolysis media was pre-heated to 250-270° under a steady stream of nitrogen. 2,5-Dihydro-2,5-dimethoxyfuran (45 g) was added at such a rate that the temperature of the distillate did not rise above 90°. When the pyrolysis was finished, methanol was completely removed by distillation through a 20 cm column packed with glass helices. The residue was distilled as quickly as possible to give 18 g (45%) of 2-methoxyfuran, 5.

bp: 110-111° (760 mm) [lit. 110-112° (750 mm)][6].

$ir_{(CCl_4)}$: 3140, 3120 (w doublet), 3020, 2850 (OCH_3), 1600 1500, (C=C of aromatic system) cm^{-1}.

$nmr^{34}_{(CDCl_3)}$: τ 3.17 (d of d 1 J = 1.5, 2.5Hz, H-5), 3.80 (d of d 1 J = 2.5, 3.5Hz, H-4), 4.89 (dofd, 1, J = 1.5, 3.5Hz, H-3), 6.16 (s, 3, OCH_3).

6-Exo-cyano-1-methoxy-7-oxabicyclo[2.2.1]hept-2-ene, 7

2-Methoxyfuran (5 g), acrylonitrile (5 g) and anhydrous benzene (20 ml) were stirred at room temperature for four days. The solution was concentrated to give an oil (7 g, 97%), which crystallized on standing.

mp: 78.5-79.5°.

Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27.

Found: C, 63.55; H, 6.00; N, 9.33.

$ir_{(CCl_4)}$: 2840 (OCH_3), 2245 (CN), 1610, 700 (C=C) cm^{-1}.

nmr$_{(CDCl_3)}$: τ 3.41 (d of d, 1 J = 2,6Hz, H-3), 3.73 (d, 1 J = 6Hz, H-2), 5.04 (d of d, 1 J = 2, 4.5Hz, H-4), 6.39 (s, 3, OCH_3), 7.34 (q, 1, J = 4.5 8Hz, H-6n), 7.60 (m, 1, H-5n), 8.02 (q, 1 J = 8, 12Hz, H-5x).

mass spectrum: m/e 151(1), 136(1), 122(1), 111(1), 109(1), 98(100), 83(77), 65(8), 55(29), 53(48), 52(32), 51(15), 39(21).

2-Exo-cyano-1-methoxy-7-oxabicyclo[2.2.1]heptane, 8

Compound 7 (2.5 g), 5% palladized charcoal (0.1 g) and ethyl acetate (40 ml) were stirred under hydrogen at atmospheric pressure until 500 ml of hydrogen was absorbed. The catalyst was filtered, washed with ethyl acetate and the reaction mixture concentrated to give 1.6 g (60%) of a crystalline product, mp 87.5-88°.

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.49; H, 7.02, N, 8.91.

ir$_{(CCl_4)}$: 2840 (OCH_3), 2245 (CN) cm^{-1}.

nmr$_{(CDCl_3)}$: τ 5.48 (m, 1, H-4), 6.43 (s, 3, OCH_3), 7.07 (q, 1, H-2n).

mass spectrum: m/e 153.0789 calcd for $C_8H_{11}NO_2$, 153.0789 meas (11), 125 (14), 124(82), 121(30), 112(38), 110(45), 109(33), 100(25), 99(43), 94(27), 93(48), 85(20), 80(25), 74(39), 69(100), 68(37), 67(32), 66(52), 59(37), 55(71), 43(64), 41(55), 39(37).

6-Exo-carbomethoxy-1-methoxy-7-oxabicyclo[2.2.1]hept-2-ene, 9

2-Methoxyfuran (0.65 g), methyl acrylate (0.57 g) and anhydrous benzene (10 ml) were stirred at room temperature. After six days the soltuion was concentrated to an oil (0.30 g, 24%). The sample was purified by molecular distillation (bath temperature 80-90°, 0.05 mm).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57.

Found: C, 58.42; H, 6.62.

$ir_{(CHCl_3)}$: 2860 (OCH_3), 1740 (C=O), 1615 (C=C) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 3.44 (d of d, 1 J = 2, 6Hz, H-3), 3.76 (d, 1 J = 6Hz, H-2), 5.20 (d of d, 1 J = 2, 4.5Hz, H-4), 6.37 (s, 3, OCH_3), 6.45 (s, 3, OCH_3), 7.03 (d of d, 1 J = 4, 9.5Hz, H-6n), 7.60 (m, 1, H-5x), 8.33 (d of d, 1 J = 4, 11Hz, H-5n).

mass spectrum: m/e 184.0736 calcd for $C_9H_{12}O_4$, 184.0730 meas (1), 166(4), 136(2), 135(10), 121(2), 120(2), 98(39) 85(12), 83(35), 58(8), 55(100), 45(6), 44(6), 39(6).

2-Exo-carbomethoxy-1-methoxy-7-oxabicyclo[2.2.1]heptane, 10

Compound 9 (0.085 g), 30% palladized charcoal (catalytic amount) and ethyl acetate were stirred under hydrogen at atmospheric pressure until 15 ml of hydrogen was consumed. The catalyst was filtered and the solution concentrated to an oil (0.078 g, 91%).

$ir_{(CHCl_3)}$: 2860 (OCH_3), 1740 (C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 5.58 (m, 1, H-4), 6.24 (s, 3, OCH_3), 6.43 (s, 3, OCH_3), 6.80 (m, 1, H-2n).

mass spectrum: m/e 186.0892 calcd for $C_9H_{14}O_4$, 186.0887 meas (42), 155(44), 154(61), 143(26), 142(34), 141(25), 132(55), 127(62), 126(55), 122(82), 113(30), 111(90), 109 (76), 100(58), 95(64), 85(70), 81(45), 67(100), 59(66), 55(80), 43(48), 41(97), 39(51).

Ethyl 2-methoxy-5-hydroxybenzoate, 11A

2-Methoxyfuran (10.1 g) and ethyl propiolate (25 g) were heated in an autoclave at 110° for 18 hours. The resulting oily product was distilled at reduced pressure (bp 135-150°, 8 mm). Glc analysis (SE-30, 10' x 1/4", 210°, 60 ml/min) showed the presence of two components. The two components were separated by preparative glc. The component present in minor amount was not identified. The major compound was ethyl 2-methoxy-5-hydroxybenzoate.

$ir_{(CHCl_3)}$: 3600, 3350 (OH), 2840 (OCH_3), 1720 (C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 2.75 (d, 1 J = 2.5Hz, ArH), 3.10 (d, 1 J = 2.5Hz, ArH), 3.16 (s superimposed on d, 1, ArH), 4.00 (s, 1, OH), 5.68 (q, 2 J = 7Hz, CH_2CH_3), 6.23 (s, 3, OCH_3) 8.67 (t, 3 J = 7Hz, CH_2CH_3).

mass spectrum: m/e 196(52), 151(100), 149(74), 137(12), 136(13), 121(19), 109(10), 108(17), 95(10), 93(18), 80(10), 65(19), 53(12), 52(15), 51(10), 39(14).

The mixture obtained from the Diels-Alder reaction (1.6 g) was allowed to reflux with 5% ethanolic potassium hydroxide (ethanol / water: 1/1, 50 ml) for 16 hours. After cooling, the solution was washed with ether, acidified (HCl) and extracted with ether. The ether extract was dried and concentrated to give 2-methoxy-5-hydroxybenzoic acid, mp 150-152° [lit. 154-155°][15].

$ir_{(nujol)}$: 3420 (OH), 3300-2500 (COOH), 1710 (C=O) cm^{-1}.

$nmr_{(acetone\ -d_6)}$: no signals <τ 2, cr at τ 2.52 (t, 1 J = 2Hz, Ar<u>H</u>), 3.05 (d, 2, J = 2Hz, Ar<u>H</u>), 6.00 (s, 3, $OC\underline{H}_3$).

mass spectrum: <u>m/e</u> 168(100), 153(24), 151(20), 139(16), 136(14), 125(16), 122(14), 121(54), 109(31), 108(19), 107 (12), 97(32), 95(30), 93(13), 81(50), 80(14), 79(18), 69 (12), 65(18), 63(20), 53(28), 51(16), 50(12), 39(21).

2-Methoxy-5-hydroxybenzoic acid was dissolved in ether and a solution of diazomethane was added dropwise until the yellow color of excess diazomethane persisted. The solution was concentrated to yield methyl 2-methoxy-5-hydroxybenzoate, mp 80-82° [lit 83-84°][15].

$ir_{(CHCl_3)}$: 3600, 3350 (OH), 2840 (OCH_3), 1735 (C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 2.53 (d, 1 J = 2.5Hz, Ar<u>H</u>), 2.94 (d, 1 J = 2.5Hz, Ar<u>H</u>), 3.00 (s, superimposed on d, 1, Ar<u>H</u>), 3.85 (br s, 1, O<u>H</u>), 6.05 (s, 3, $OC\underline{H}_3$), 6.12 (s, 3, $OC\underline{H}_3$).

mass spectrum: <u>m/e</u> 182(98), 167(14), 151(100), 148(86), 136(24), 121(32), 108(34), 93(43), 65(32), 53(28), 52(25).

6-Chloro-6-cyano-1-methoxy-7-oxabicyclo[2.2.1]hept-2-ene, 12

2-Methoxyfuran (1.1 g), α-chloroacrylonitrile (1 g) and anhydrous ether (25 ml) were stirred at room temperature for 72 hours. The solution was concentrated to an oil (1.5 g) which crystallized on standing in the cold, mp 62-63°.

Anal. Calcd for $C_8H_8NO_2Cl$: C, 51.76; H, 4.34; N, 7.55, Cl, 19.10.

Found: C, 51.69; H, 4.12; N, 7.64; Cl, 19.33.

$ir_{(CHCl_3)}$: 2850 (OCH_3), 2250 (w, CN) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 2.60 (d of d, 1 J = 2.5, 6Hz, H-3), 3.60 (d, 1 J = 6Hz, H-2), 5.01 (d of d, 1 J = 2.5, 5Hz, H-4), 6.23 (s, 3, OCH_3), 6.86 (d of d, 1 J = 5, 13Hz, H-5x), 7.96 (d, 1 J = 13Hz, H-5n).

6-Acetoxy-6-cyano-1-methoxy-7-oxabicyclo[2.2.1]hept-2-ene, 13

α-Acetoxyacrylonitrile (20.2 g), 2-methoxyfuran (18.0 g) and anhydrous benzene (100 ml) was allowed to stand at room temperature. The reaction was monitored by nmr. After one month the reaction was complete. The solution was concentrated and the crystalline adduct collected, mp 101-102.5°.

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70.

Found: C, 57.20; H, 5.53; N, 6.92.

$ir_{(nujol)}$: 2850 (OCH_3), 2240 (w, CN), 1735 (C=O) cm^{-1}.
$nmr_{(CDCl_3)}$: τ 3.20 (d of d, 1 J = 2, 6Hz, H-3), 3.65 (d, 1 J = 6Hz, H-2), 5.05 (d of d, 1 J = 2, 5Hz, H-4), 6.32 (s, 3, OCH_3), 6.90 (d of d, 1 J = 5, 14Hz, H-5x), 7.93 (s, 3, $OCOCH_3$), 8.16 (d, 1 J = 14Hz, H-5n).
mass spectrum: 209(1), 98(39), 83(28), 69(2), 55(12), 43(100), 42(10).

2-Acetoxy-2-cyano-1-methoxy-7-oxabicyclo[2.2.1]heptane, 14

A mixture of compound 13 (1.0 g), 30% palladized charcoal (0.05 g) and ethyl acetate (25 ml) was stirred under hydrogen at atmospheric pressure until 110 ml (100%) of hydrogen was absorbed. The catalyst was filtered and the solution concentrated to give 1.0 g, 97%, of crystalline compound 14, mp 118.5-120°.
Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63.
Found: C, 56.64; H, 6.08; N, 6.75.
$ir_{(nujol)}$: 2850 (OCH_3), 2240 (w, CN), 1750 (C=O) cm^{-1}.
$nmr_{(CDCl_3)}$: τ 5.44 (t, 1, H-4), 6.38 (s, 3, OCH_3), 7.84 (s, 3, $OCOCH_3$).
mass spectrum: 211(1), 169(4), 168(30), 141(6), 125(8), 113(7), 97(14), 92(4), 74(4), 71(16), 59(10), 55(11), 43 (100).

1-Methoxy-7-oxabicyclo[2.2.1]heptan-2-one, 15

Compound 14 (0.98 g), 2% aqueous potassium hydroxide

(100 ml), and methanol (5 ml) were stirred at room temperature for three hours. The solution was diluted with water and extracted with ether. The ether extract was dried and concentrated to give 0.59 g (90%) of ketone 15.

$ir_{(CHCl_3)}$: 2850 (OCH_3), 1760 (C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 5.26 (t, 1, H-4), 6.50 (s, 3, OCH_3), 7.52 (d of d, 1 J = 1.5, 6Hz, H-3x), 7.70 (s, 1, H-3n).

Attempted formation of an enamine from ketone 15

A solution of ketone 15 (0.59 g), pyrrolidine (0.31 g), and benzene was placed in a 100 ml flask equipped with a Dean-Stark separator and a condenser. The solution was allowed to reflux for 24 hours, then cooled and concentrated. The residual oil (0.47 g) was a mixture of three components, the major component being starting ketone 15. Analysis of the mixture by nmr did not show the formation of an enamine (no signal for a vinyl proton downfield from τ 6).

Attempted formation of an α-keto acid from ketone 15

Ketone 15 (0.17 g), methyl magnesium carbonate (2M, 12 ml), and methanol were allowed to reflux in a nitrogen atmosphere for 20 hours. The reaction mixture was cooled, poured into ice-cold aqueous hydrochloric acid. The solution was continuously extracted with methylene chloride. The methylene chloride fraction was dried and

concentrated to give 0.1 g of an intractable mixture.

3-Methoxy-exo-cis-3,6-endoxo-Δ^4-tetrahydrophthalic anhydride, 16

To a stirred solution of maleic anhydride (4 g) in anhydrous ether (50 ml) was added a solution of 2-methoxyfuran (4 g) in anhydrous ether (10 ml). Within 0.5 hours, a crystalline adduct formed. Yield: 6.2 g (78%). mp: 110-113° [lit 117-119° dec][7a].

Anal. Calcd for $C_9H_8O_5$: C, 55.11; H, 4.11.

Found: C, 54.95; H, 4.39.

$ir_{(CHCl_3)}$: 2850 (OCH_3), 1870, 1800 (anhydride C=O) cm^{-1}

$nmr_{(CDCl_3)}$: τ 3.25 (d of d, 1 J = 2, 6Hz, H-3), 3.47 (d, 1 J = 6Hz, H-2), 4.89 (d, 1 J = 2Hz, H-4), 6.45 (d, 1 J = 7Hz), 6.50 (s, 3, OCH_3), 6.71 (d, 1 J = 7Hz).

mass spectrum: m/e 196(1), 134(1), 124(4), 109(6), 98(100), 83(85), 55(42), 54(68), 44(8), 39(10).

Attempted hydrogenation of compound 16

Compound 16 (3.5 g), platinum oxide (0.35 g) and ethyl acetate (100 ml) were stirred under hydrogen until 400 ml of hydrogen was absorbed. The solution was filtered and concentrated to give 3.4 g of a mixture of compounds. Chromatography over silicic acid gave 6-methoxy-3-hydroxy-$\Delta^{1,6}$-tetrahydrophthalic anhydride, mp 129-130°.

λ_{max}^{MeOH}: 245 nm (ε = 34,500).

$ir_{(nujol)}$: 3540 (OH), 2840 (OCH_3), 1830, 1800 sh, 1760, 1750 sh (anhydride C=O), 1630 (C=C) cm^{-1}.

$nmr_{(acetone\text{-}d_6)}$: τ 5.48 (br d, 1 J = 3Hz, H-4), 6.05 (s, 3, OCH_3), 6.26 (d, 1 J = 3Hz, H-3), 7.16 (br s, 1, OH, D_2O).

mass spectrum: m/e 198.0528 calcd for $C_9H_{10}O_5$, 198.0528 meas (70), 180(19), 155(24), 154(58), 138(18), 126(36), 97(28), 83(53), 82(100), 65(20), 55(35), 53(26), 52(55), 43(39), 41(20), 39(65).

3-Methoxy-exo-cis-3,6-endoxohexahydrophthalic anhydride, 17

A solution of compound 16 (0.75 g), platinum oxide (prewashed with sodium bicarbonate and dried, 0.07 g) and ethyl acetate (40 ml) was hydrogenated under 30 lb pressure until no further uptake of hydrogen was observed. The catalyst was filtered and the solution concentrated to an oil (0.8 g) which crystallized on standing, mp 178-180°.

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09.

Found: C, 54.84; H, 5.22.

$ir_{(CHCl_3)}$: 2850 (OCH_3), 1870, 1800 (anhydride C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 5.25 (m, 1, H-4), 6.46 (s, 3, OCH_3), 6.68 (d, 2 J = 2Hz, H-2, H-3).

mass spectrum: m/e 198(17), 154(25), 126(38), 122(31), 111(45), 109(57), 101(100), 99(45), 98(64), 95(38), 94(38) 85(45), 84(28), 83(28), 82(31), 81(38), 67(64), 55(93), 41(53).

N-Amino-3-methoxy-exo-cis-3,6-endoxohexahydrophthalimide, 18

Compound 17 (0.66 g) in absolute ethanol (10 ml) was added dropwise to a refluxing solution of hydrazine hydrate (85%, 0.25 ml) in anhydrous ethanol (10 ml). After addition was complete, the reaction mixture was allowed to reflux for 20 minutes. The solution was cooled and concentrated to give a mixture of two compounds (tlc: silica gel, chloroform--methanol 25:1). Chromatography over silicic acid led to isolation of the major compound which was crystallized from acetone (compound 19) mp 154-155.5°.

λ_{max}^{MeOH}: 215 nm (ε = 5,550).

$ir_{(CHCl_3)}$: 1770, 1700 (imide C=O), 1630 (C=N), 1380, 1360 ($C(CH_3)_2$).

$nmr_{(CDCl_3)}$: τ 5.42 (m, 1, H-4), 6.37 (s, 3, OCH_3), 6.86 (s, 2, H-2, H-3), 7.77, (s, 3, CH_3), 8.17 (s, 3, CH_3).

mass spectrum: m/e 252.1110 calcd for $C_{12}H_{16}N_2O_4$, 252.1111 meas (95), 237(25), 195(72), 193(64), 185(45), 164(46), 154(99), 153(35), 136(34), 126(95), 125(33), 111(66), 100 (100), 99(100), 98(56), 94(91), 81(100), 58(90), 41(100).

The compound isolated by chromatography was crystallized from ethyl acetate (compound 18) mp 136-138°.

$ir_{(CHCl_3)}$: 3340, 3270 (NH_2), 1770, 1700 (imide carbinyl cm^{-1}.

nmr$_{(CDCl_3)}$: τ 5.23 (m, 1, H-4), 5.63 (br s, 2, NH_2, D_2O), 6.50 (s, 3, OCH_3), 6.93 (s, 2, H-2, H-3).

mass spectrum: m/e 212.0797 calcd for $C_9H_{12}N_2O_4$, 212.0797 meas (32), 181(13), 153(44), 139(33), 122(34), 114(93), 111(61), 100(76), 99(100), 98(78), 95(41), 85(32), 84(51), 81(68), 67(56), 66(32), 59(56), 55(63), 53(54), 44(40), 41(70).

Attempted hydrolysis of Compound 18

Compound 18 (0.05 g) in ethanol (30 ml) was added to a solution of barium hydroxide (0.5 g) and water (10 ml). The mixture was allowed to reflux for 24 hours. The mixture was cooled, saturated with dry ice, and the insoluble barium carbonate removed by filtration through celite. The filtrate was diluted with water and extracted with methylene chloride. The methylene chloride solution was dried and concentrated to give 0.03 g of an intractable mixture.

Dimethyl 3-methoxy-exo-cis-3,6-endoxohexahydrophthalate, 20

Compound 17 (1.35 g) was dissolved in anhydrous methanol (50 ml) and the solution allowed to reflux for 1.5 hours. The solution was cooled and concentrated to give a mixture of half-acid, half-methyl ester (1.32 g; two components tlc: alumina, chloroform--methanol, 25:1).

ir$_{(CHCl_3)}$: 3500 (OH), 2850 (OCH_3), 1710 (C=O) cm^{-1}.

nmr$_{(CDCl_3)}$: τ 5.00 (m, 1, H-4), 6.33 (s, 3, OCH_3), 6.35 (s, 3, OCH_3), 6.50 (s, 3, OCH_3), 6.61 (d, 1 J = 10Hz, H-2 or H-3), 6.98 (d, 1 J = 10Hz, H-2 or H-3).

The mixture (0.5 g) was dissolved in anhydrous methanol and ethereal diazomethane solution was added in excess. The solution was concentrated to give (0.49 g) of a dimethyl ester, 20, mp 100-102°.

ir$_{(CHCl_3)}$: 2850 (OCH_3), 1735 (C=O) cm^{-1}.

3-Methoxy-3,6-endoxo-Δ^4-tetrahydrophthalonitrile, 21

2-Methoxyfuran (1.00 g), fumaronitrile (1.25 g) and anhydrous ether (20 ml) were stirred at room temperature. After 19 hours, the crystalline precipitate formed was collected (single component, tlc: silica gel, chloroform). The spectral data showed that compound 21 was a mixture of stereoisomers.

ir$_{(CHCl_3)}$: 2850 (OCH_3), 2240 (CN), 1590 (C=C) cm^{-1}.

nmr$_{(acetone\text{-}d_6)}$: τ 3.18 (d of d, J = 2, 6Hz, H-3), 3.25 (d, J = 6Hz, H-2), 4.69 (d of d, 1 J = 2, 4.5Hz, H-4), 4.89 (d, J = 2Hz, H-4), 6.37 (d, J = 4.5Hz), 6.47 (two overlapping s, 6, OCH_3), 6.85 (m).

3-Methoxy-3,6-endoxohexahydrophthalonitrile, 22

Compound 21 (0.09 g), 30% palladized charcoal (catalytic amount) and ethyl acetate were stirred under

hydrogen at atmospheric pressure until no further hydrogen was absorbed. The catalyst was removed and the solution concentrated to give (0.08 g, 87%) of a crystalline product, mp 145-147°. Analysis by tlc (silica gel: chloroform, R_f = 0.48. alumina: benzene--chloroform, 3:2, R_f = 0.52) indicated one component but spectral data showed a mixture of stereoisomers.

$ir_{(CHCl_3)}$: 2850 (OCH_3), 2250 (CN) cm^{-1}.

$nmr_{(pyridine - d_5)}$: τ 5.24 (t, H-4), 5.42 (br s, H-4), 6.54 (two overlapping s, 6, OCH_3).

β-Carboethoxyacrylonitrile--2-Methoxyfuran adduct, 23

2-Methoxyfuran (3.6 g), β-carboethoxyacrylonitrile[21] (2.8 g), and benzene were stirred at room temperature for 184 hours. The solution was concentrated to an oil. Analysis by nmr showed a mixture of stereoisomers. (τ 4.84, 4.93, 2 H-4; 6.40, 6.43, 2 OCH_3; 5.79, 8.72, 5.84, 8.75, 2 CH_2CH_3)

2-Methoxyfuran (0.9 g), β-carboethoxyacrylonitrile (1.0 g), and benzene were heated at 60° in a nitrogen atmosphere for 64 hours. The solution was concentrated to an oil. Analysis by nmr showed mainly one stereoisomer (Compound 23B or 23D).

$nmr_{(CDCl_3)}$: τ 3.26 (d, 1 J = 2, 5Hz, H-3), 3.45 (d, 1 J = 5Hz, H-2), 4.84 (d, 1 J = 2Hz, H-4), 6.40 (s, 3, OCH_3), 5.79 (q, 2 J = 7Hz, CH_2CH_3), 8.68 (t, 3 J = 7Hz, CH_2CH_3).

Attempted hydrogenation of Compound 23

Compound 23 (5.0 g), 30% palladized charcoal, and ethyl acetate (75 ml) were hydrogenated under 30 lb pressure until no further hydrogen was absorbed. The catalyst was removed by filtration and the solution concentrated. Analysis of the reaction mixture by nmr showed β-carboethoxypropionitrile and two hydrogenated adducts (2 OCH_3). Chromatography over alumina did not lead to separation of the hydrogenated adducts.

Dimethyl 3-methoxy-3,6-endoxo-$\Delta^{1,4}$-dihydrophthalate, 24

2-Methoxyfuran (2.4 g), dimethyl acetylene dicarboxylate (3.6 g), and anhydrous benzene were stirred at room temperature for one hour. The solution was concentrated and purified by distillation (120°, 0.1 mm). $nmr_{(CDCl_3)}$: τ 2.25 (d of d, 1 J = 2, 5.5Hz, H-3), 3.00 (d, 1 J = 5.5Hz, H-2), 4.46 (d, 1 J = 2Hz, H-4), 6.13 (s, 3, OCH_3), 6.22 (s, 3, OCH_3), 6.41 (s, 3, OCH_3). mass spectrum: m/e 240.0634 calcd for $C_{11}H_{12}O_6$, 240.0637 meas (37), 211(41), 210(100), 178(25), 150(25), 149(31), 137(24), 65(22), 53(38).

Formation of Compound 27

2-Methoxyfuran (4.5 g), dimethyl acetylene dicarboxylate (9.0 g) and ether were stirred at room temperature overnight. The solution was concentrated, dissolved

in ethyl acetate containing 30% palladized charcoal and hydrogenated under 22 lb pressure until no further hydrogen was absorbed. The catalyst was removed by filtration and the solution concentrated. Crystalline compound 27, mp 136.5-137.5° separated from the oil.

Anal. Calcd for $C_{16}H_{22}O_8$: C, 56.14; H, 6.48.

Found: C, 56.38; H, 6.53.

$ir_{(CHCl_3)}$: 2850 (OCH_3), 1750 (C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 4.91 (m, 1), 5.60 (m, 1), 6.28 (s, 3, OCH_3), 6.36 (s, 3, OCH_3), 6.58 (s, 3, OCH_3), 6.62 (s, 3, OCH_3).

mass spectrum: m/e 342.1315 calcd for $C_{16}H_{22}O_8$, 342.1310, meas (7), 283(36), 278(47), 251(31), 246(47), 218(50), 193(23), 191(49), 190(40), 177(44), 163(46), 159(30), 149 (24), 135(24), 131(36), 121(23), 105(30), 103(24), 91(38), 85(27), 79(29), 77(38), 71(39), 65(66), 59(100), 55(55).

Dimethyl 3-methoxy-cis-endo-3,6-endoxohexahydrophthalate, 26

Compound 24 (1.00 g), 30% palladized charcoal (0.1 g), and ethyl acetate were stirred under hydrogen at atmospheric pressure until no further hydrogen was absorbed. The solution was filtered and concentrated to an oil. Distillation (120°, 0.2 mm) gave 0.9 g (89%) of compound 26.

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60.

Found: C, 54.07, H, 6.51.

$ir_{(CHCl_3)}$: 2850 (OCH_3), 1750 (C=O) cm^{-1}.

nmr$_{(CDCl_3)}$: τ 5.52 (m, 1, H-4), 6.33 (s, 3, OCH_3), 6.37 (s, 3, OCH_3), 6.52 (s, 3, OCH_3).

N-Benzyl 3-methoxy-exo-cis-3,6-endoxo-Δ^4-tetrahydrophthalimide, 28A

2-Methoxyfuran (5.9 g), N-benzylmaleimide[23] (10.1 g), and acetone (300 ml) were kept at 0° for several days. Removal of solvent gave 17.0 g (100%) of crystalline compound 28A, mp 108.5-110.5°.

Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.39; H, 5.26; N, 4.84.

ir$_{(Nujol)}$: 2830 (OCH_3), 1765, 1695 (imide C=O) cm^{-1}.

nmr$_{(CDCl_3)}$: τ 2.65 (m, 5, ArH), 3.34 (d of d, 1 J = 2, 6Hz, H-3), 3.50 (d, 1 J = 6Hz, H-2), 4.87 (d, 1 J = 2Hz, H-4), 5.32 (s, 2, NCH_2Ph), 6.41 (s, 3, OCH_3), 7.01 (d, 1 J = 8Hz, H-5 or H-6), 7.11 (d, 1 J = 8Hz, H-5 or H-6).

mass spectrum: m/e 285.1001 calcd for $C_{16}H_{15}NO_4$, 285.0996 meas (1), 257(2), 187(35), 106(19), 98(100), 91(15), 83(24).

N-Benzyl 3-methoxy-endo-cis-3,6-endoxo-Δ^4-tetrahydrophthalimide, 28B

2-Methoxyfuran (5.3 g), N-benzylmaleimide (9.5 g), and anhydrous ether (250 ml) were kept at 0° for several days. The product which crystallized from solution was collected, mp 94-95.5° (15.0 g, 97%).

Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91.

Found: C, 67.38; H, 5.15; N, 5.00.

$ir_{(nujol)}$: 1760, 1700 (imide C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 2.73 (s, 5, ArH), 2.89 (d, 1 J = 2Hz, H-3), 2.91 (s, 1, H-2), 4.97 (d of d, 1 J = 2, 5Hz, H-4), 5.76 (s, 2, NCH_2Ph), 6.37 (d of d, 1 J = 7, 8Hz, H-5), 6.50 (s, 3, OCH_3), 6.74 (d, 1 J = 8Hz, H-6). Double irradiation at 507 cps (τ 4.93) collapses τ 6.37 to a doublet.

mass spectrum: m/e 285(7), 267(21), 187(100), 149(22), 130(23), 109(48), 105(43), 98(49), 90(32), 55(22).

N-Benzyl 3-methoxy-endo-cis-3,6-endoxohexahydrophthalimide, 29

Compound 28B (0.35 g), 30% palladized charcoal (catalytic amount), and ethyl acetate were stirred under hydrogen at atmospheric pressure until no further hydrogen was absorbed. The solution was filtered and concentrated to give 0.35 g (98%) of compound 29, mp 68°.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87.

Found: C, 67.10; H, 6.19; N, 5.15.

$ir_{(nujol)}$: 2850 (OCH_3), 1765, 1708 (imide C=O) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 2.67 (m, 5, ArH), 5.40 (s superimposed on m, 3, NCH_2Ph, H-4), 6.50 (s, 3, OCH_3).

mass spectrum: m/e 287.1158 calcd for $C_{16}H_{17}NO_4$, 287.1152 meas (68), 227(13), 200(12), 189(38), 154(21), 132(13), 126 (34), 124(31), 111(25), 100(25), 99(70), 91(100), 81(26), 67(25), 65(26), 55(20), 53(22).

Attempted Epoxidation of Compound 28B

Compound 28B in solvent was added dropwise to a stirred solution of peracid in solvent. After the appropriate reaction time, excess peracid was destroyed with sodium bisulfite solution and the reaction product isolated. The following table summarizes the results.

Attempted Epoxidation of Compound 28B

Peracid	Solvent	Temp	Time	Result
m-chloroperbenzoic	ether	0°	2 h	5 compounds (tlc)
monoperphthalic	$CHCl_3$	0°	48 h	4 compounds (tlc)
peroxybenzimidic	methanol	25°	48 h	3 compounds (nmr)
peroxytrifluoroacetic Na_2HPO_4	CH_2Cl_2	0°	3 h	5 compounds (nmr)

One compound isolated from the reaction mixture by fractional crystallization was N-benzyl 2-methoxyphthalimide, mp 153-155°.

$ir_{(CHCl_3)}$: 2850 (OCH_3), 1765, 1700 (imide C=O), 1610, 1500 (aromatic C=C) cm^{-1}.

$nmr_{(CDCl_3)}$: τ 2.64 (m, 8, ArH), 5.18 (s, 2, NCH_2Ph), 6.01 (s, 3, OCH_3).

mass spectrum: m/e 267.0895 calcd for $C_{16}H_{13}NO_3$, 267.0890 meas (100), 249(40), 244(37), 221(25), 135(20), 104(30), 91(48), 77(22), 76(24).

Attempted Solvomercuration of Compound 28B[29]

Compound 28B (0.8 g), mercuric acetate solution (3M, tetrahydrofuran--water, 1:1), were stirred at room temperature for 24 hours. No color change had occurred. Addition of sodium hydroxide solution (3M, 3 ml), sodium borohydride (0.05 g), then salt and separation of the organic fraction gave on concentration an intractable tar.

Treatment of Compound 28B with acetyl hypobromite[30]

Acetyl hypobromite solution[30] (17.5 ml) was added all at once to a cooled (0°) solution of compound 28B (0.5 g) in carbon tetrachloride (10 ml). The reaction mixture was stirred for 50 minutes, then was washed with sodium bisulfite solution. The organic layer was separated and concentrated to give a mixture of products (no methoxyl in nmr).

N-Benzyl 3-methoxy-4,5-dihydroxy-endo-cis-3,6-endoxohexahydrophthalimide, 31

Compound 28B (1.1 g), pyridine (15 ml) and osmium tetroxide (1.0 g) were stirred at room temperature for four days. A mixture of sodium bisulfite (1.8 g), pyridine (20 ml) and water (30 ml) was added all at once and the solution stirred for 30 minutes. The mixture was continuously extracted with methylene chloride. The methylene chloride fraction was dried and concentrated to give a diol, mp 130-131.5°.

ir$_{(CHCl_3)}$: 3550 (OH), 1760, 1700 (imide C=O) cm^{-1}.
nmr$_{(CDCl_3)}$: τ 2.65 (s, 5, ArH), 5.39 (s, 2, NCH$_2$Ph), 5.55 (m, 1, H-4), 6.33 (s, 3, OCH$_3$), 7.0 (br s, 2, OH, D$_2$O).
mass spectrum: m/e 319.1056 calcd for $C_{16}H_{17}NO_6$, 319.1062 meas(1), 247(38), 188(30), 110(22), 91(100).

Attempted formation of 2-methoxyfuran--dimethyl fumarate adduct

2-Methoxyfuran (2.5 g), diethyl fumarate (4.2 g) and anhydrous benzene were stirred at room temperature for 72 hours. The solution was concentrated to an oil. The nmr spectrum of the oil showed only the presence of 2-methoxyfuran and diethylfumarate.

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