SYNTHETIC STUDIES DIRECTED TOWARDS THE
INDOLE ALKALOID (±)-ARISTOTELINE

by

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We accept this thesis as conforming to
the required standard

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ABSTRACT

This thesis describes some synthetic studies directed towards (±)--aristoteline (8), a naturally occurring indole alkaloid possessing a novel molecular structure. An efficient, stereoselective synthesis of the ketal carbamate (116) and attempts to transform this material into (8) are reported.

The synthesis of the intermediate diketal ether (35) was accomplished as follows. Treatment of 9-methyl-5(10)-octalin-1,6-dione with 2,2-dimethyl-1,3-propanediol in the presence of p-toluenesulfonic acid (as catalyst) produced the corresponding diketal compound. Subjection of the latter material to a hydroboration-oxidation sequence, using borane-dimethylsulfide complex and hydrogen peroxide, afforded two alcohols in a ratio of approximately 9:1. The relative stereochemistry of these alcohols was determined by chemical correlation with compounds of known structure and stereochemistry. The preparation of the diketal ether (35) was completed by the etherification of the major product from the hydroboration-oxidation sequence with β-methoxyethoxymethyl chloride.
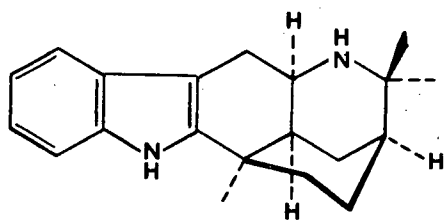
The elaboration of the diketal ether (35) into the α,β-unsaturated ester (61) was accomplished in two steps. Thus, treatment of compound (35) with 2-methylcyclohexanone in the presence of a catalytic amount of p-toluenesulfonic acid produced a mixture of the corresponding monoketal compounds. This crude mixture was allowed to react with the potassium salt of triethyl phosphonoacetate giving the α,β-unsaturated ester (61) as a 1:1 mixture of geometric isomers.

Hydrogenation of compound (61) using platinum oxide catalyst produced a mixture (64:36, respectively) of two saturated esters, the desired α-face epimer (72) and its diastereomer. The sterochemical disposition of these compounds was deduced by chemical correlation with compounds of known stereochemistry in conjunction with ^{1}H nmr spectral analysis.
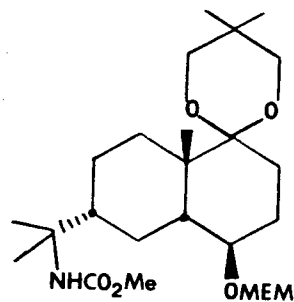
The synthesis of the ketal carbamate (116) was completed in three steps from the saturated ester (72). Treatment of the latter compound with lithium diisopropylamide and methyl iodide afforded the corresponding α,α-dimethylester. The ester functionality was then cleaved using a mixture of potassium tert-butoxide in anhydrous dimethylsulfoxide. The resulting carboxylic acid was elaborated into the ketal carbamate (116) through the use of a novel and efficient modification of the Curtius reaction.

Unfortunately, the conversion of the ketal carbamate (116) into (±)-aristoteline (8), via an intramolecular cyclization, was unsuccessful. All attempts to selectively remove the methoxyethoxymethyl (MEM) ether moiety from (116) met with failure.
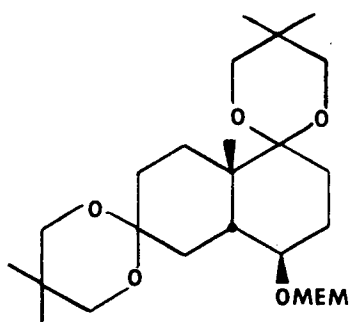
In an attempt to circumvent this problem a modified approach for the completion of the synthesis of (8) was initiated. The ketal carbamate (116) was treated with excess titanium tetrachloride resulting in the removal of both the ketal group and the ether functionality. Oxidation of the resulting alcohol, with a chromium trioxide-pyridine complex, afforded the carbamate dione (128). Unfortunately, attempts to deprotect the amino group of (128), and subsequently elaborate the desired product into (8), via a reductive amination, were unsuccessful.
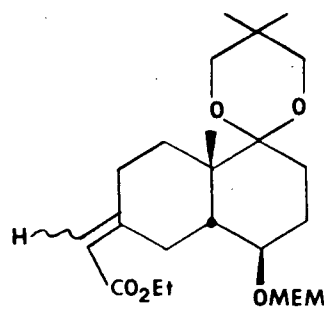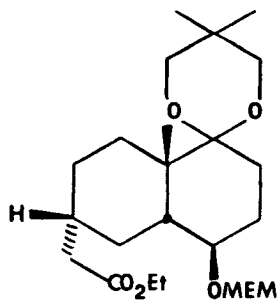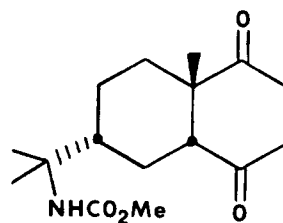
(8)

(116)

(35)

(61)

(72)

(128)

MEM = CH₂OCH₂CH₂OCH₃

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ACKNOWLEDGEMENTS

INTRODUCTION

I. <u>General Comments</u>

Perhaps one of the greatest demonstrations of the efficacy of modern organic chemistry is expressed through its application in the form of organic synthesis. All of us, in our day to day existence, make use of a virtually countless number of synthetic items. Since modern society demands an ever increasing number of these novel and diverse synthetic materials, often the impetus for the development of new synthetic methods is provided through this challenge. Thus, the rapid development of this branch of the field of chemical science is witnessed by the overwhelming number of publications detailing new synthetic procedures.

Most of these new methods for accomplishing a given chemical transformation are initially applied to a series of organic molecules which are relatively simple in structure. In this way, the utility of a given procedure is demonstrated and a general idea of its efficiency and limitations is documented. Before any of these methods may be regarded as generally applicable, however, they should be first tested in the synthesis of a variety of complex organic compounds. In these more elaborate and highly functionalized molecules, an appreciation of the compatability of a new synthetic method, its reaction conditions and the necessary reagents, with the additional complications of molecular

complexity may be evaluated more realistically.

In a broader sense, in fact, many of the most fundamental concepts which underlie organic chemistry as a whole meet with their most crucial trials when they are applied during the course of the synthesis of intricate organic molecules. These complex chemical systems are omnipresent in nature and many of these naturally occurring substances have proven to be useful in a wide variety of ways. The use of natural products as medicinals, for example, dates back to man's earliest records.[1] Frequently, however, the physiologically active substances isolated from nature are present in only very small quantities and their isolation usually requires rather elaborate and time consuming techniques. Thus, it is often through their total syntheses that many of these compounds eventually become available in useful quantities.

Of the large number of known physiologically active natural products, a great many belong to the family of the indole alkaloids. These compounds comprise a very large family of natural products (approximately 700 are now known) and they have been actively investigated for decades.[2,3,4] Some typical examples are reserpine (1), isolated from the Indian snake root plant Rauwolfia serpentina and used for the treatment of mental disorders and strychnine (2), the cardiac stimulant isolated from Strychnos nux vomica. The first total syntheses of both reserpine (1)[5] and strychnine (2)[6] were completed by the late R.B. Woodward's group in 1958 and 1954, respectively.

(1)

(2)
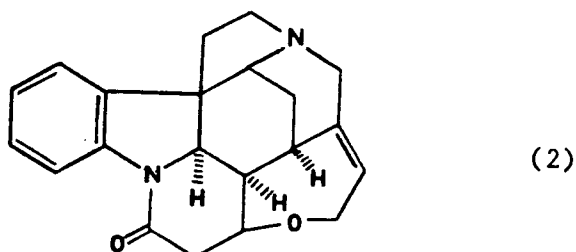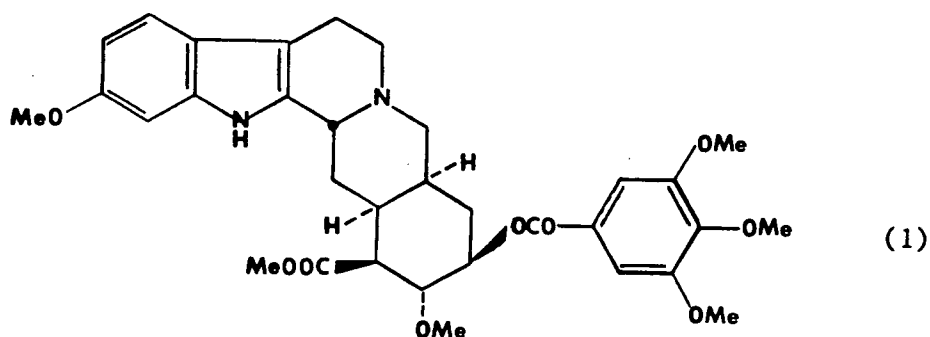
Synthetic approaches to the indole alkaloid family of compounds, not surprisingly, have been numerous and most of the major structural types of this class of natural products have been successfully prepared synthetically. For example, the recent synthesis of vinblastine (3), a complex bisindole alkaloid which is currently finding use clinically as an antitumor agent, serves as an interesting illustration of the synthetic challenges being met in this area.[7]

(3)
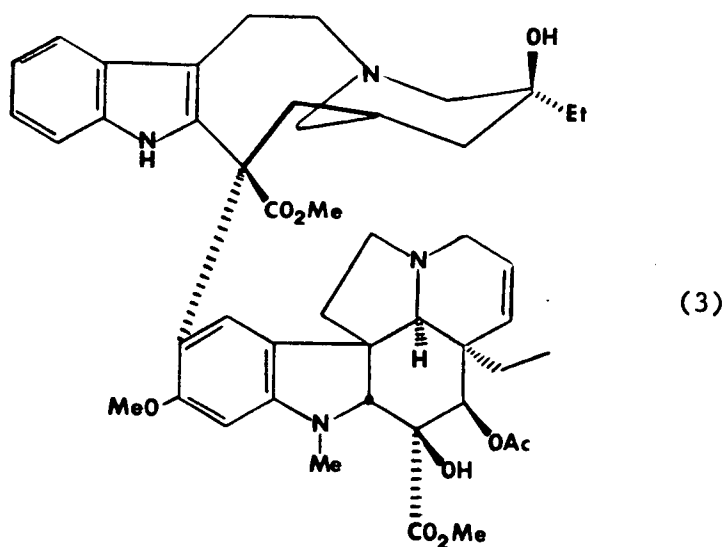
Naturally occurring indole alkaloids are found in a large number of flowering plants and they display a multiformity of structural types.[8] For the most part, though, they may be classified into four major groups based on their carbon skeletons. These four classifications are illustrated by corynantheine (4) (corynanthe type), tabersonine (5) (aspidosperma type), geissoschizoline (6) (strychnos type) and coronaridine (7) (iboga type).
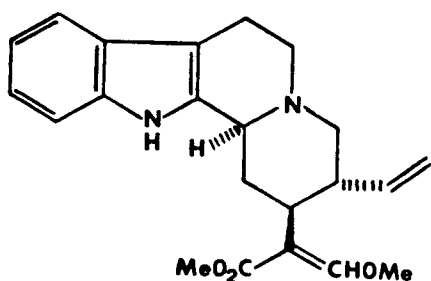
(4)
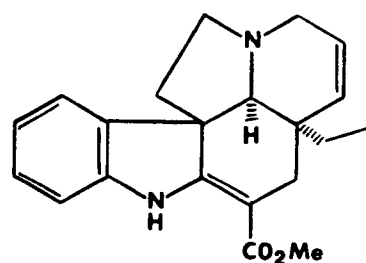
(5)
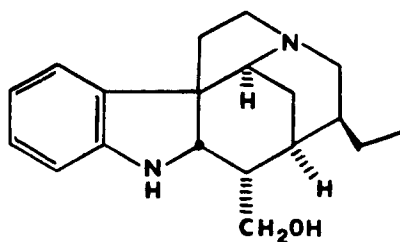
(6)
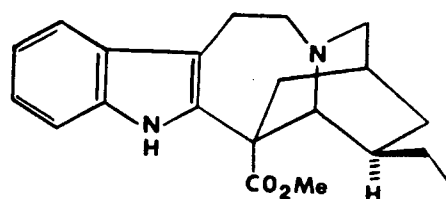
(7)

In 1975 the structural elucidation of a novel indole alkaloid, aristoteline (8), was reported.[9] Aristoteline was found to possess an as yet unknown type of carbon skeleton which had not been observed
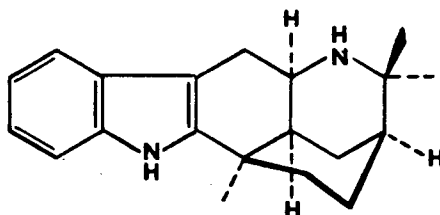
(8)

in any previously isolated indole alkaloids. Thus, this compound repre-
sented the first member of a new class of indole alkaloid and, in the
short time since its structure was determined, three other alkaloids
belonging to this group have been isolated. Aristotelone (9) has been
found in _Aristotelia_ _chilensis_ which also contains aristoteline (8).[10]
Aristone (10) and aristotelinine (11), both belonging to this new class,
are also present in _Aristotelia_ _chilensis_.[11]
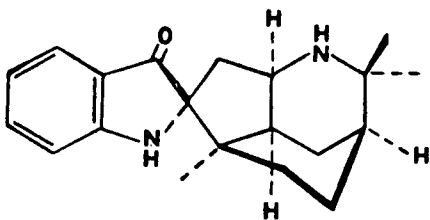
(9)
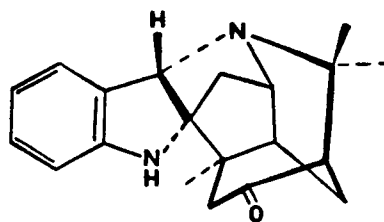
(10)
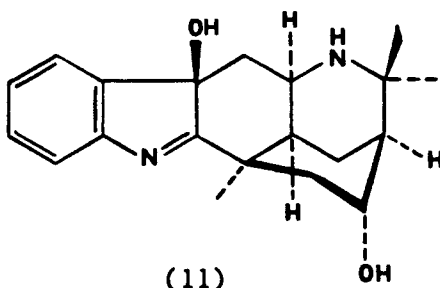
(11)

Although this class of indole alkaloids provides an interesting synthetic challenge, as yet there have been no reported synthetic approaches to this family of compounds.

II. The Isolation and Structural Elucidation of Aristoteline

Aristoteline (8) was first isolated from the New Zealand wineberry plant Aristotelia serrata and, later, it was also found to occur in Aristotelia chilensis. This alkaloid, which was extracted from the roots and stems of the wineberry plant in a yield of approximately 0.07% (from dried plant material), was the main alkaloid present, making up approximately 40% of the total alkaloids.

Microanalysis of crystalline aristoteline (8), crystallized from methanol (mp 164 °C, $[\alpha]_D^{20}$ + 16 °), indicated a molecular formula of $C_{20}H_{26}N_2$, as did the high resolution mass spectrum. The compound gave a negative Ehrlich test, yet its uv spectrum resembled that of an indole. Since both the ^{13}C nmr and ^1H nmr spectra were consistent with the presence of a 2,3-disubstituted indole system, and since both showed the absence of olefinic functionality, aristoteline (8) had to have three rings in addition to the indole nucleus. The ir spectrum of the alkaloid displayed a distinct NH stretching absorption and, since equilibration of the compound with D_2O removed two broad one-proton resonances in the ^1H nmr spectrum (δ 7.59 and 0.96), both of the nitrogen atoms in the molecule were secondary. This finding was further supported by the fact that the equilibrated material produced a molecular

ion of the pure alkaloid. In addition, treatment of the alkaloid under mild acetylation conditions gave a crystalline N-acetyl derivative which exhibited mp 268-270 °C. The acetylated derivative retained the indolic NH functionality as judged from its ^{1}H nmr and uv spectra.

The ^{1}H nmr spectrum of aristoteline (8) showed three 3-proton singlets (methyl groups) at high field. Two of these were shifted downfield to a similar extent upon the addition of either trifluoroacetic acid or a europium shift reagent. The chemical shift of the third methyl singlet, however, was affected to a far lesser extent under both conditions. This finding suggested that aristoteline (8) probably had geminal methyl groups attached to a carbon atom adjacent to the non-indolic nitrogen atom. According to these observations, the third methyl group appeared to be remote from this nitrogen atom. Since the mass spectrum of the molecule displayed an intense M-CH_3 ion at m/e = 279 mass units, a methyl group attached to a carbon atom α to a nitrogen atom was indeed likely. The mass spectrum of (8) also showed a strong ion corresponding to the loss of C_3H_7N from the molecular ion, along with the appearance of the appropriate metastable ion. These facts, when considered in conjunction with the ^{1}H nmr data, definitely supported the presence of geminal methyl groups α to the non-indolic nitrogen atom.

A broad, one-proton absorption in the ^{1}H nmr spectrum of (8) at δ 3.6 was assigned to a proton attached to another carbon atom α to the non-indolic nitrogen atom. This proton shifted downfield on N-acetylation and was coupled to two other protons resonating at δ2.58 and 3.05.

The latter two protons were assigned as being due to a methylene group attached to the indole nucleus. The aforementioned data supported the partial structure shown below.
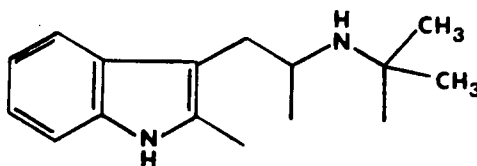
Treatment of a methanolic solution of aristoteline (8) with hydrogen bromide gave the hydrobromide salt of the alkaloid as large colorless prisms. Subjection of this material to a single crystal, x-ray crystallographic analysis produced the complete structure and absolute stereochemistry of aristoteline (8).
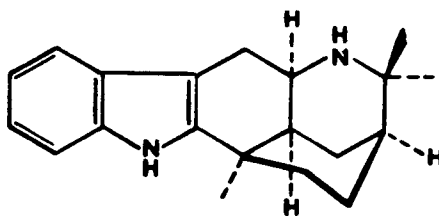
III. The Objective

Aristoteline (8) represents the first member of a new class of indole alkaloids. Since this class of alkaloids presents a new and interesting synthetic challenge, the objective of the research described

in this thesis was to explore and develop synthetic routes which would

hopefully lead to the eventual total synthesis of aristoteline (8).

Thus, the work described herein should, in the future, lay the ground-

work leading to the synthesis of this hitherto unexplored class of in-

dole alkaloids.

DISCUSSION

I. General Considerations

One of the most fundamental approaches employed in the development of a viable total synthesis of a complex organic compound involves a methodology which has recently been given the name "retero-synthetic analysis".[12,13] The latter term refers to the commonly used practice of reducing the synthesis of a complex molecule into a series of successively less complex intermediates. Each of these has the capability (in theory, if not always in practice) of being converted into the next more complex intermediate in the series, usually through the use of carefully selected synthetic procedures which have been developed and refined previously. In this way, one eventually arrives at a starting material for the synthesis which is both relatively simple in structure and readily available, and one which, in theory, can ultimately be converted into the desired product by the aforementioned series of transformations. Although this type of analysis is not without its critics[14], the technique has proven its generality many times in the past.

The application of a retero-synthetic analysis to (±)-aristoteline (8) led to the series of intermediates illustrated in Scheme I. The following discussion describes how this scheme was developed and the progress which has been made toward its completion.

On examining the structure of the natural product, it can readily be realized that this material should be directly available from the

(8)

(12)

(14)

(13)

(15)

(16)

(18)

(17)

SCHEME 1

(21)

13 Steps
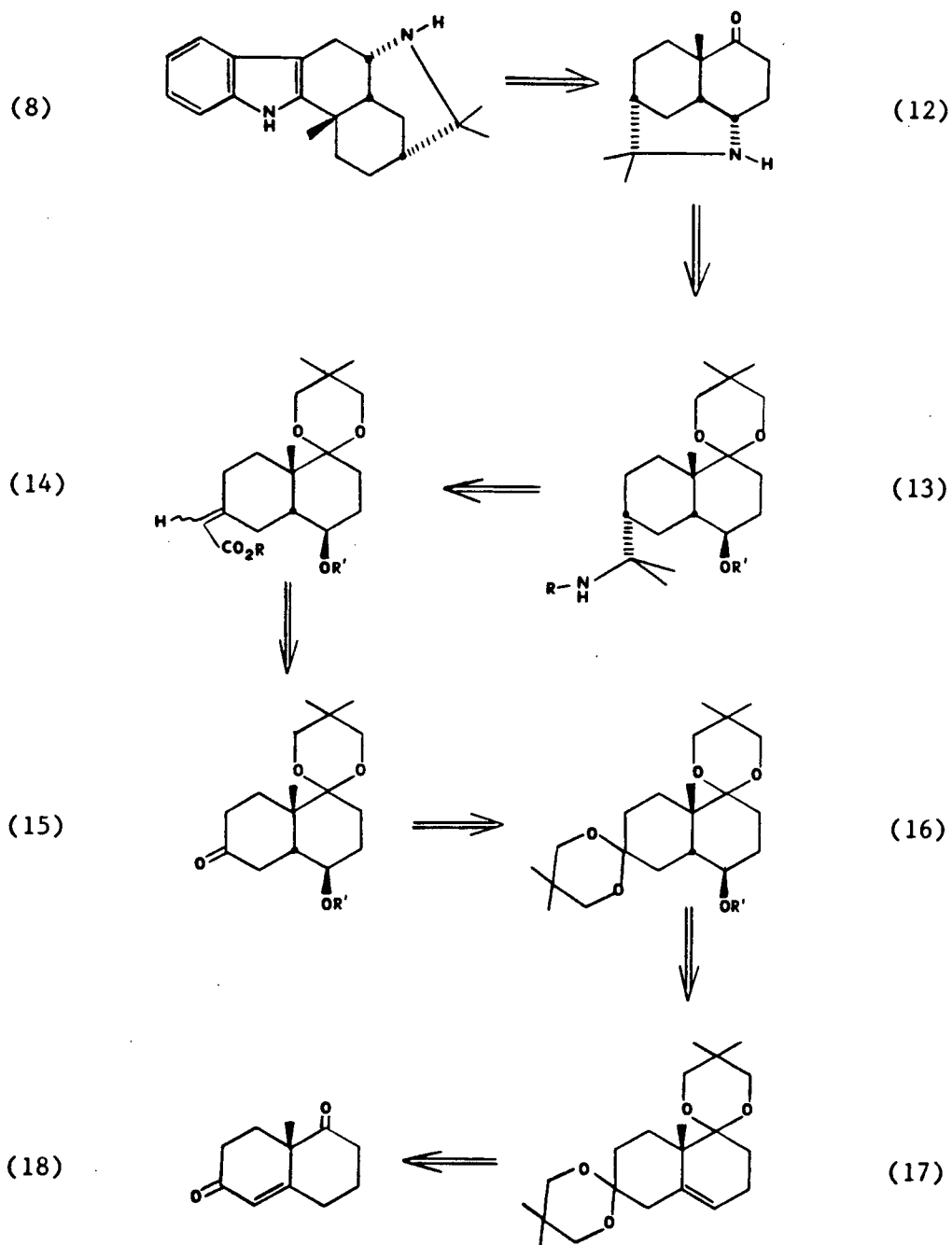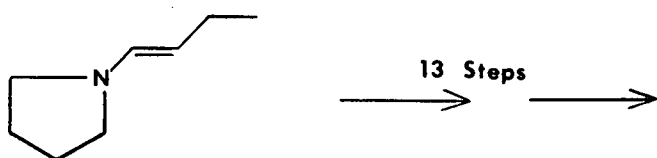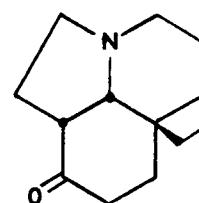
(22)

FISCHER
INDOLE

R = OCH₃ (23a)
= H (23b)

1) LAH
2) acetylation
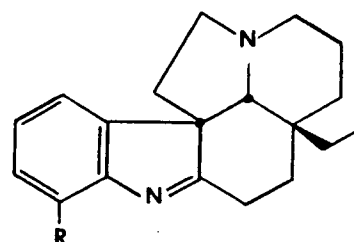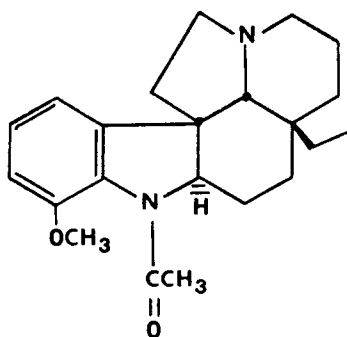
(20)

KBH₄
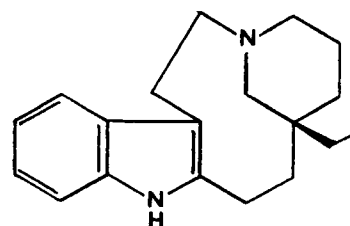
(19)

tricyclic ketone (12) via a Fischer indole synthesis[15]. The preparation of indole alkaloids through the use of the Fischer indole synthesis, performed on appropriately functionalized ketones, has been exploited in the past. For example, Stork et al published the first total synthesis of quebrachamine (19) [via (23b)] and aspidospermine (20) [via (23a)] from the tricyclic ketone (22).[16] Ban et al[17] and Stevens et al[18] have also reported syntheses of the ketone (22) employing quite different synthetic routes from that used by Stork.

Ban's group has also published an elegant synthesis of epiibogamine (26) from the isoquinuclidine (25) via a Fischer indole synthesis.[19]
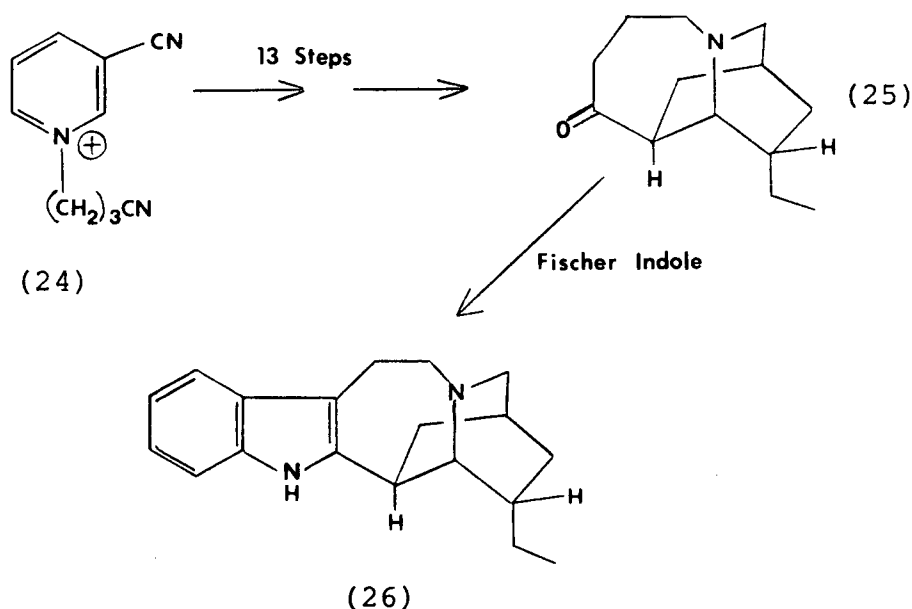
Thus, with this initial reduction in the complexity of the task,

the target molecule of our synthetic efforts became the tricyclic ketone

(12). An examination of a molecular model of this substance led to the

idea that perhaps one efficient method of producing the desired tri-

cyclic system would involve an intramolecular cyclization of compound

(13) (R' = Ts or Ms) to produce the tricyclic ketal (27). The latter

would be expected to yield the tricyclic ketone (12) by acid catalyzed

cleavage of the ketal.

(13)

Base →

(27)

Base

(13a)

(13b)
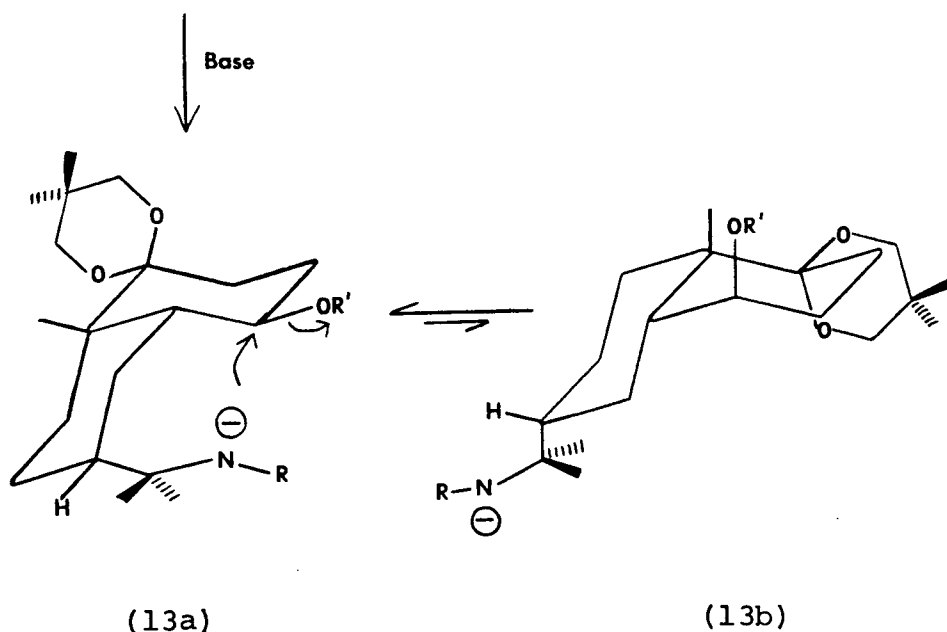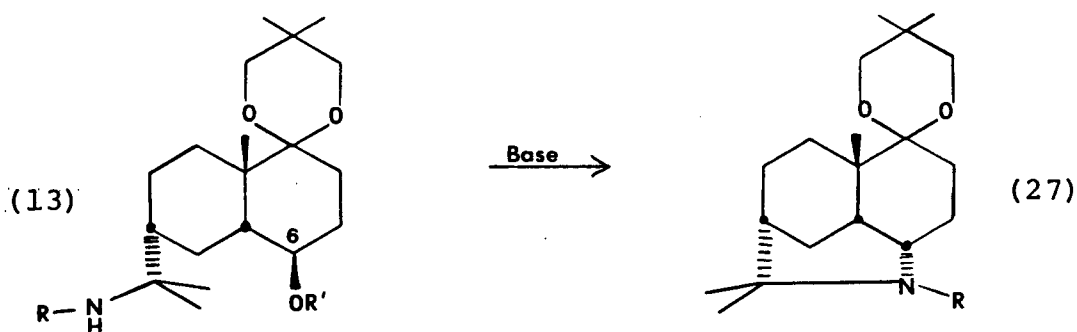
Ring closures involving the interaction of a nucleophilic nitrogen atom with a carbon atom substituted with a suitable leaving group are well known. In addition, it was expected that compound (13) could attain a conformation [resembling (13a)] in which a process of this type should be facilitated by virtue of the proximity of the two centers in question. Thus, it was felt that the construction of compound (13), functionalized with a reliable leaving group (e.g. tosylate, R' = Ts) affixed at C_6 in the required stereochemical orientation, would provide the tricyclic ketal (27) via a base-promoted cyclization.

Obviously, if the ring closure to produce the desired tricyclic system was to be successful, the stereochemical orientation of the nitrogen containing appendage, attached at C_3, was crucial. The synthetic scheme called for the introduction of the desired stereochemistry at C_3 through the hydrogenation of the α,β- unsaturated ester (14). Again, careful examination of a molecular model of this compound suggested that the hydrogenation reaction should give predominantly the desired epimer, since the convex side (β face) of the molecule is, for steric reasons, far more accessible to a heterogeneous catalyst than the concave side (α face).

(14)   (28)
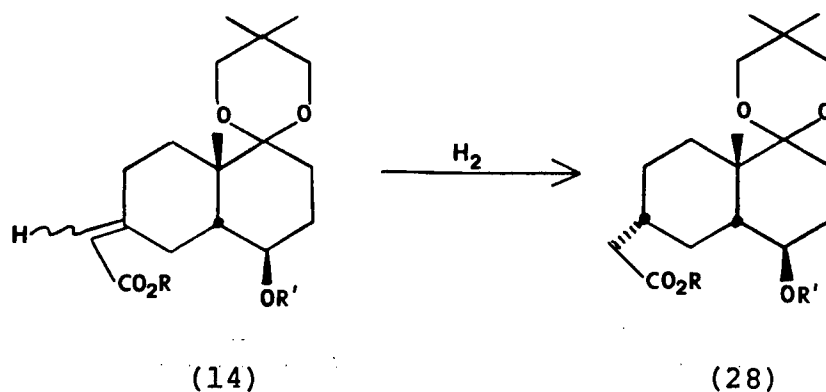
The elaboration of the predicted product, the saturated ester (28), into compound (13), was envisaged as a potentially straightforward process. Dialkylation of the saturated ester (28) to give a gem-dimethyl system α to the ester functionality, followed by the saponification of the resulting product (29), should produce the carboxylic acid (30). The latter compound, it was hoped, could then be converted into the desired nitrogen containing system by way of the well known Curtius reaction.[20]

(28)   (29)   (30)
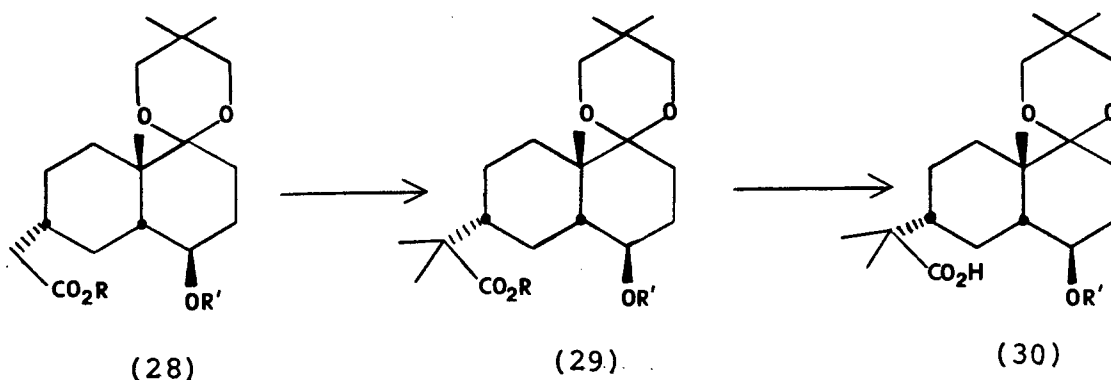
Of the wide variety of procedures which may be employed to generate α,β-unsaturated esters, perhaps the most widely used is the Wittig reaction or one of the many modifications thereof.[21,22] This type of reaction is both very general and, more often than not, proceeds to afford high yields of unsaturated carbonyl compounds. Therefore, it was felt that the α,β-unsaturated ester (14) would be most efficiently obtained from the corresponding ketone (15), utilizing a Wittig-type procedure.

(15)   (14)
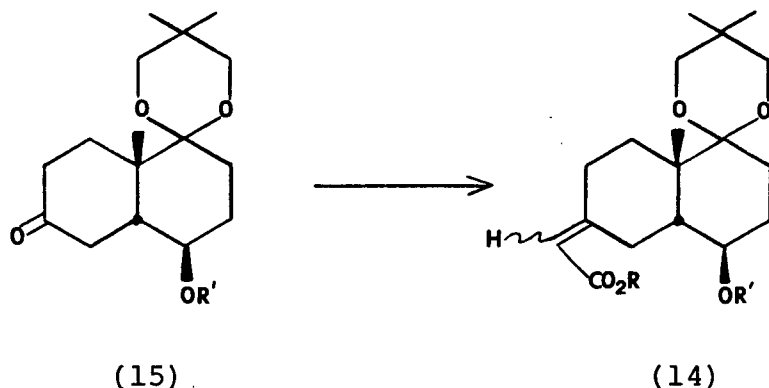
The synthesis of the monoketone (15) was to be completed by the selective deprotection of the A ring ketone of the diketal compound (16), where R' is a suitable alcohol protecting group (vide infra). This scheme rested on the observation that the A ring ketal was considerably less sterically encumbered than the ketal at C_9 in the B ring and, for this reason, it was considered likely that the less-hindered ketal group could be hydrolyzed selectively.

(16)   (15)
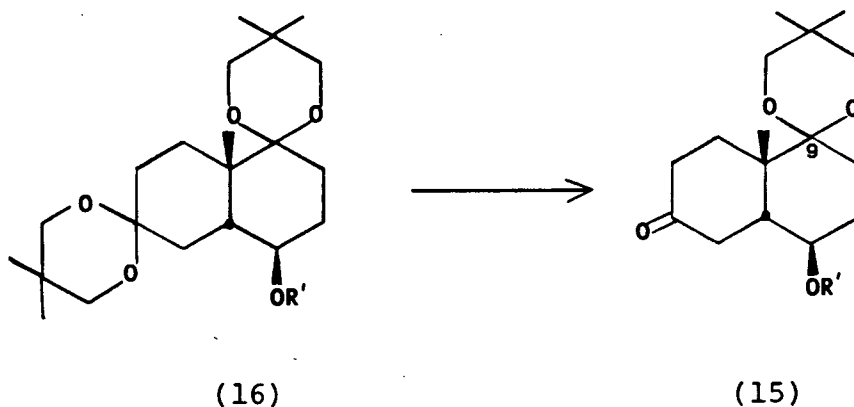
Finally, the synthetic plan for the synthesis of the diketal compound (16) began from the readily available 9-methyl-5(10)-octalin-1,6--

dione (18)[23]. Diketalization of this dione should produce the corresponding diketal olefin (17). Hydroboration of this material would be expected to occur from the β face of the molecule, since the approach of a borane complex from the α side of the molecule would be sterically more hindered, mainly due to the axially orientated oxygen atoms of the two ketal functionalities.

(18)   (17)   (31)
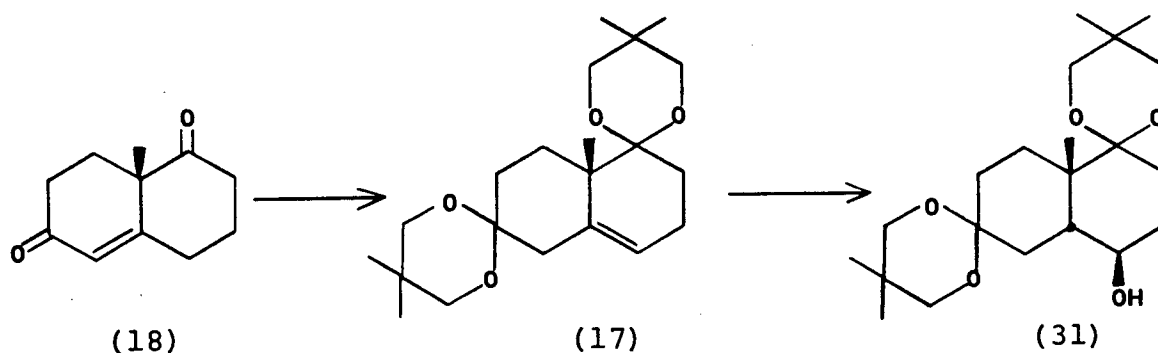
The hydroboration-oxidation of similarly situated olefins in other bicyclic systems has been used in the past to regioselectively introduce an oxygen functionality at C_6.[24] For example, compound (32) was converted into a mixture of the alcohols (33) and (34) in a yield of 62%.[25]

(32)   (33)   (34)
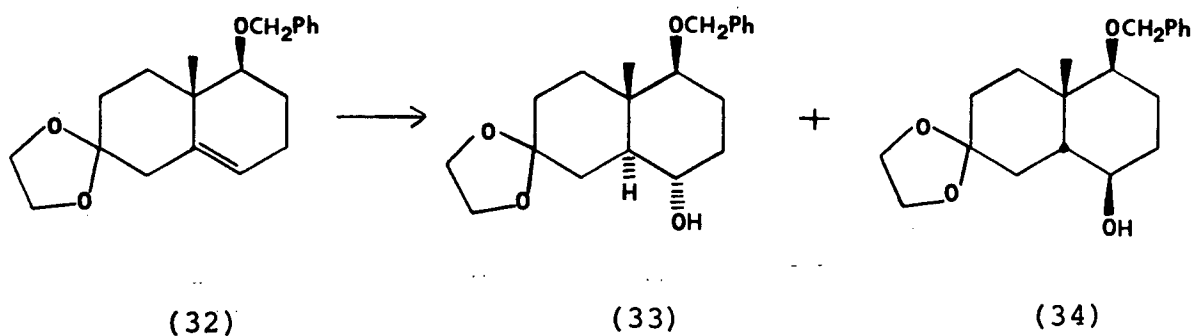
In the case of the diketal olefin (17), it was expected that the hydroboration reaction would proceed both regio- and stereoselectively to produce the diketal alcohol (31) as the predominant product. This expectation was based on the observation that the diketal olefin (17) was subject to hind rance provided by both the axially orientated oxygen atoms at C_3 and C_9. A borane reagent was therefore expected to approach the olefin from the side of the molecule (β face) cis to the angular methyl group.

The preparation of the diketal compound (16) could then be completed by the protection of the alcohol functionality in the diketal alcohol (31) with a suitable protecting group. A wide variety of protecting groups are available for the protection of hydroxyl groups.[26]

(31)   (16)
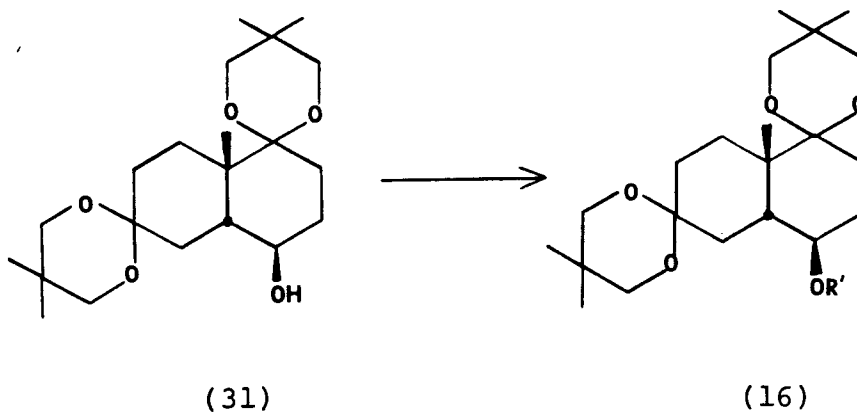
The recently introduced MEM (β-methoxyethoxymethyl) ether was selected since this protecting group was both devoid of chirality and was reportedly formed and removed in high yield.[27] In addition, the MEM ether was expected to be stable to the reaction conditions that were anticipated during the course of the synthesis.

Armed with the synthetic scheme outlined above, we began our empir-

ical studies directed toward the preparation of the target molecule, the tricyclic ketone (12).

II. The Synthesis of the Diketal Ether (35)

The starting material used for the preparation of the diketal ether (35), 9-methyl-5(10)-octalin-1,6-dione (18), was prepared according to a literature procedure[23] from 2-methyl-1,3-cyclohexanedione, in a yield of 51-55%[†]. The dione (18) was recrystallized, dried under reduced pressure and subjected to standard ketalization conditions using dry benzene as the solvent, a catalytic amount of p-toluenesulfonic acid, and approximately ten equivalents of 2,2-dimethyl-1,3-propanediol producing the diketal olefin (17) in 72% yield. This material underwent substantial decomposition when subjected to column chromatography (silica gel) if its duration on the column was lengthy (large scale purifications).[28]

(18)   (17)   (35)
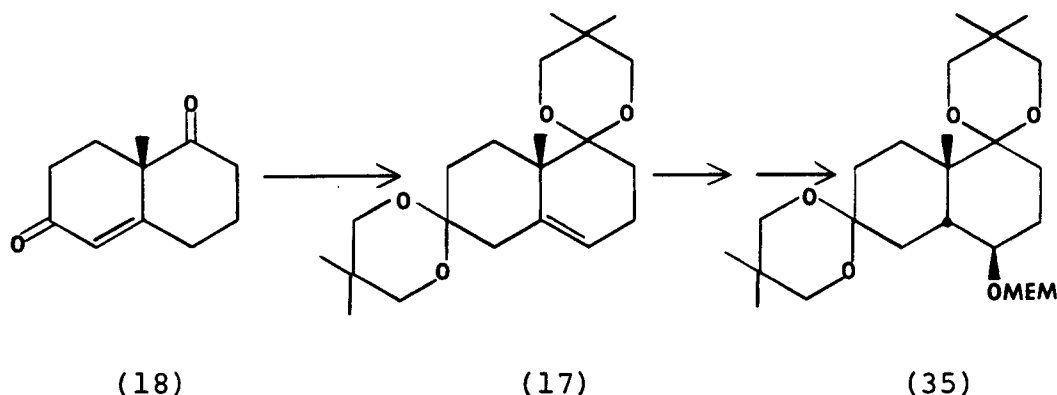
[†]In our hands, the yield of 9-methyl-5(10)-octalin-1,6-dione was consistently between 51% and 55%. Marshall et al have reported a yield of 76%.[23]

The ^{1}H nmr spectrum of this material showed five tertiary methyl groups (δ 0.71, 0.86, 1.02, 1.16 and 1.18), a complex eight-proton multiplet† between δ 3.24 and 3.88, due to the ketal methylenes, and a one-proton, broad singlet at δ 5.26–5.40 for the olefinic proton. In the ^{13}C nmr spectrum, the olefinic carbons, C_5 and C_6, appeared at δ138.21 and 120.41, respectively.

The diketal olefin (17) was hydroborated with excess borane-di-methyl sulfide complex[29] in hexane (room temperature, 20 h) and, after the oxidation of the intermediate organoborane species†† with alkaline hydrogen peroxide, a mixture of two alcohols was obtained in a ratio of approximately 9:1. On steric grounds, it was expected that the major product isolated from the hydroboration reaction would be the desired cis-fused alcohol (31). Therefore, it seemed reasonable to propose that the minor product was the trans-fused alcohol (36), resulting from the

---

†A detailed analysis of the complex ^{1}H nmr pattern produced by the methylene protons of this type of ketal has been described.[30]

††A white solid was isolated from the hydroboration reaction, before oxidation, as a precipitated, amorphous material which proved to be the organoboronic acid (37); mp 160–161 °C.
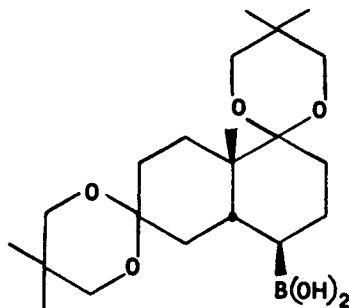
(37)

attack of the hydroborating reagent from the more hindered (β face) side of the olefin. However, since the hydroboration step determined the stereochemistry at both C_5 and C_6 and, since the stereochemical orientation at <u>both</u> these centres was crucial to the successful development of our synthetic plan, it was decided to ascertain whether or not these assignments were indeed correct.
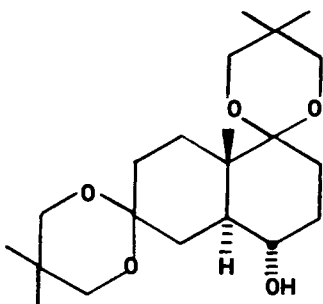
(36)

There has been a considerable amount of research in the steroid field directed toward the correlation of the chemical shifts of angular methyl protons with the stereochemistry of the AB ring junction in both the <u>cis</u> and <u>trans</u>-fused systems.[31-33] In all the cases studied, the <u>cis</u>-fused system exhibited an angular methyl resonance at lower field than the coresponding <u>trans</u>-fused case. For example, the angular methyl group on the AB ring junction of $5\beta,14\alpha$-androstane <u>(38)</u> resonates at $\delta 0.925$ whereas the signal due to the angular methyl group of $5\alpha,14\alpha$-androstane <u>(39)</u> appears at δ 0.792.

δ 0.925

(38)

δ 0.792

(39)
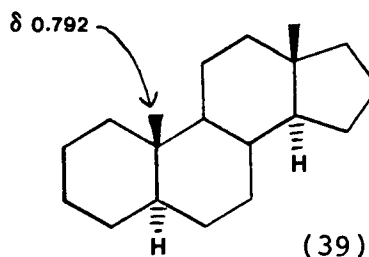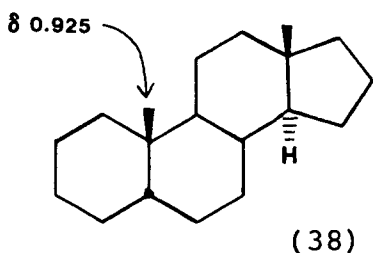
Generally speaking, the same tendency is found in bicyclic systems as well. For example, in the cis-fused ketone (40), the angular methyl group gives rise to a singlet at δ 0.95 in the ^{1}H nmr spectrum, whereas in the trans-fused system (41), the corresponding resonance is found at δ 0.80.[34]

δ 0.95

(40)

δ 0.80

(41)
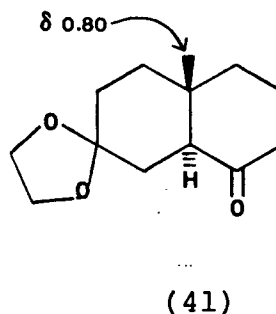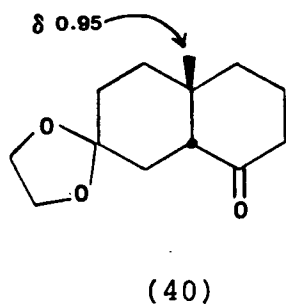
The major product (mp 162-163 °C) isolated (84%) from the hydroboration of the diketal olefin (17) exhibited a three-proton singlet at δ1.21 in the ^{1}H nmr spectrum. This signal was attributed to the angular methyl group. The minor product (mp 189-191 °C), isolated in 9% yield, displayed a three-proton singlet at δ 0.94, also assigned to the angular methyl group.

Although the preceding ^{1}H nmr data, as well as the expected course of the hydroboration reaction based on steric arguments, supported the initial assignments, it was decided to seek direct chemical evidence confirming our assignments. This was done for three reasons. Firstly, the steroid studies alluded to earlier were not strictly applicable to bicyclic systems. Secondly, although we were quite confident of the assignments for the angular methyl resonances in the ^{1}H nmr spectra (see Section VII), the molecules in question each possessed five tertiary methyl groups, all resonating between δ 0.68 and 1.21. Clearly, the specific angular methyl group assignments would have to be considered somewhat tentative. Finally, at the time that our work was being carried out, the literature contained an apparent exception to general observation that, in cis-fused bicyclic systems, the angular methyl group resonates at lower field than in the corresponding trans-fused system. Thus, J.E. McMurry reported[35] that the angular methyl group in the cis-fused compound (42) exhibited a three-proton singlet at δ 1.08 in its ^{1}H nmr spectrum. The coresponding trans-fused system (43) showed a tertiary methyl group at δ 1.23.[†]

δ 1.08 ⟶ δ 1.23 ⟶
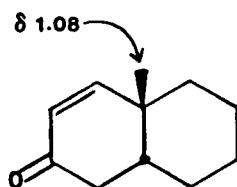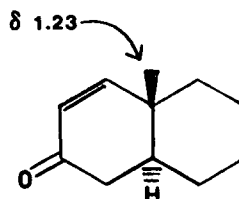
(42)   (43)

[†]Later, after our studies in this area were complete, D.L. Boger at Harvard University conclusively demonstrated that these assignments were in error.[36]

It appeared that a rather straightforward chemical means of proving the stereochemistry of the products resulting from the hydroboration of (17) could be achieved as follows. Oxidation of the major product, tentatively assigned as the cis-fused compound (31), under non-epimerizing conditions, should afford the cis-fused ketone (44) if this assignment was correct. The latter material should epimerize, under basic conditions, to furnish the thermodynamically more stable trans-fused ketone (45).

(31)   (44)   (45)
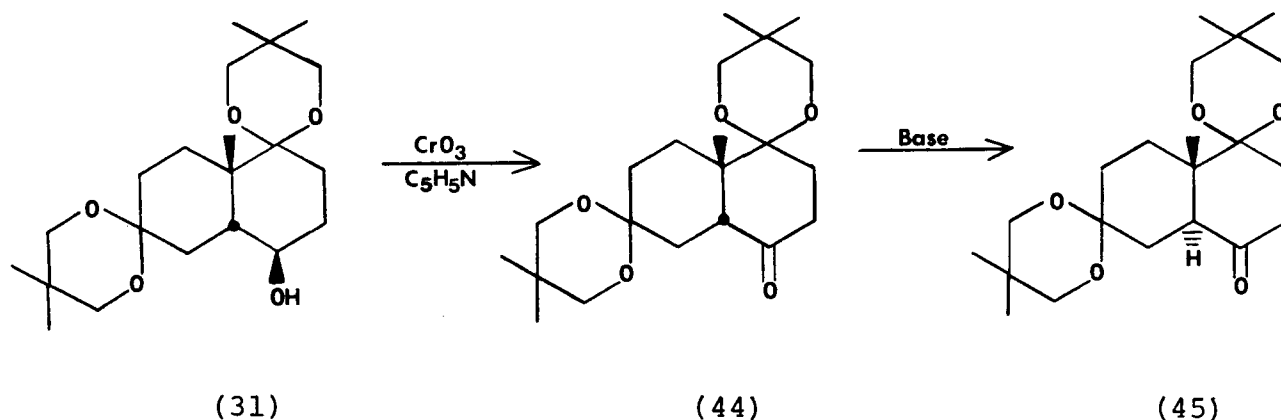
The Collins oxidation (treatment of an alcohol with a chromium trioxide-pyridine complex in methylene chloride) is a well known method used for the oxidation of secondary alcohols to the corresponding ketone under essentially neutral conditions.[37] Grieco, for example, oxidized the alcohol (46) with Collins reagent, furnishing the ketone (47), in 96% yield.[38] The latter compound is thermodynamically less stable than the corresponding trans-fused system.

(46)

(47)
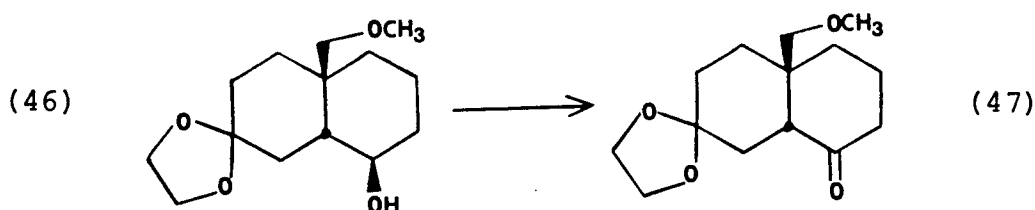
Accordingly, the major product isolated from the hydroboration--oxidation of (17) was oxidized with chromium trioxide-pyridine complex in methylene chloride to afford a single product in 77% yield. This material showed a saturated carbonyl absorption at 1705 cm^{-1} in the ir spectrum. The ^{1}H nmr spectrum of this compound exhibited a two-proton multiplet between δ 2.72 and 3.06, for the protons on C_7, and the signal due to the angular methyl group appeared at δ 0.86.

Surprisingly, the ketone isolated from the Collins oxidation of (31) was recovered unchanged when treated with base (sodium methoxide), even after prolonged periods of time. In addition, when the minor product from the hydroboration-oxidation of (17) was oxidized under conditions identical with those employed for the major alcohol, the same ketone (91%) was obtained as the sole product. For reasons which were not readily apparent, one of the ketonic products obtained from the oxidations described above was epimerizing, under the reaction conditions or during work-up, to the trans-fused ketone (45).

In an attempt to circumvent this problem, the pyruvate ester (48) was prepared (pyridine, pyruvoyl chloride) from the diketal alcohol which had tentatively been assigned the cis-fused stereochemistry as

(31)   (48)
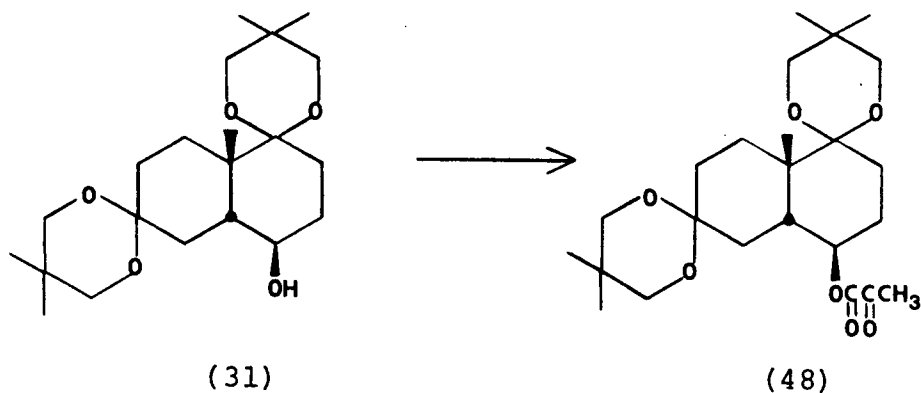
shown in (31). A recent article[39] by Binkley had reported that the photolysis of pyruvate esters provided the corresponding ketone in high yield, under conditions which were completely neutral. For example, Binkley reported that menthol (49) was converted (88% yield) into menthone (50) using this method.

(49)   (50)
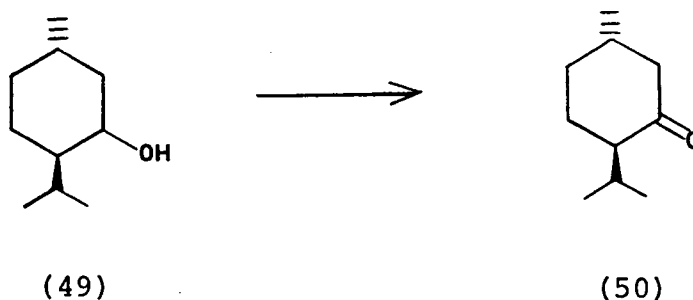
The pyruvate ester (48) showed a carbonyl absorption at 1728 cm^{-1} in the ir spectrum and, in the ^{1}H nmr spectrum, the methyl group of the pyruvate ester moiety gave rise to a singlet at δ 2.43. Unfortunately, when this material was subjected to photolysis (benzene, 1.1 h, ambient temperature) a complex mixture (tlc) of products was formed and this oxidation approach was abandoned.

Since these attempts to ascertain the stereochemistry of the two compounds isolated from the hydroboration of the diketal olefin (17) had not been successful, it was decided to correlate these compounds with the known octalones (51)[40] and (52)[41]. Thus, it was felt that the

(51)   (52)
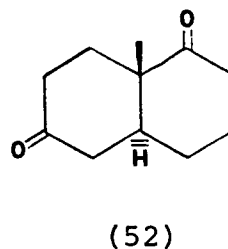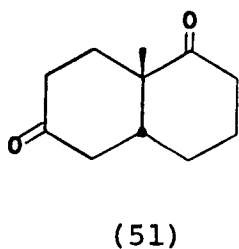
corresponding tosylate (53) of the desired cis-fused diketal alcohol (31) could be converted, by hydride reduction, into the bicyclic diketal (54). The latter material would afford, via acidic hydrolysis of the ketal groups, the known octalone (51) (see Scheme 2).
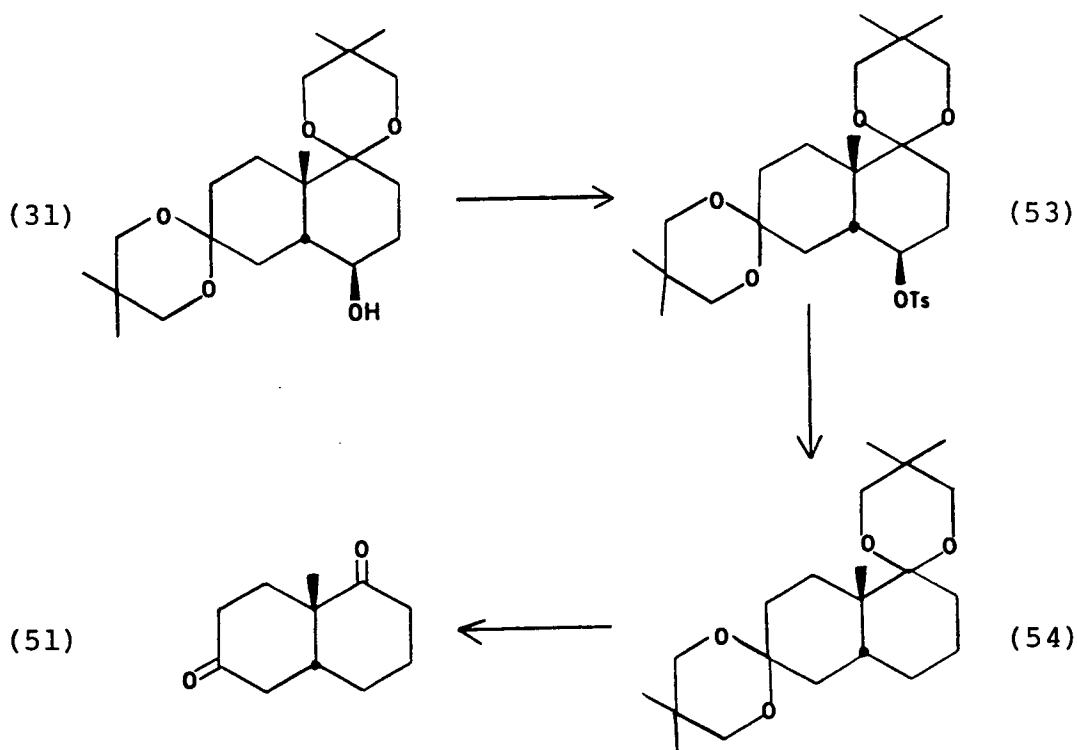
SCHEME 2

H.C. Brown[42,43] has demonstrated that the displacement of certain "leaving groups", notably chloride, bromide, mesylate and tosylate, may be achieved very efficiently with lithium triethylborohydride ("superhydride"). For example, the tosylate (55) was converted into cyclooctane (56) in 81% yield using the reagent.

(55)   (56)
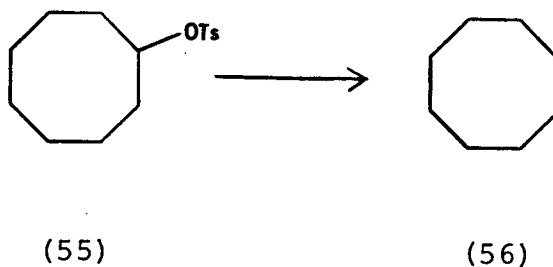
Therefore, the preparation of the diketal tosylate (53) was under-taken. Reaction of the diketal alcohol (31) with excess p-toluenesul-fonyl chloride in pyridine (ambient temperature, 24 h) provided the tosylate (53) in 88% yield. Treatment of the latter substance with lithium triethylborohydride in tetrahydrofuran gave a mixture of two compounds, in a ratio of 5:2 (glc). The major product was identified as the olefin (57), mp 134.5-135.5 °C. The ^{1}H nmr spectrum of this material showed five tertiary methyl groups (δ 1.18, 1.12, 1.00, 0.90, 0.70), an eight-proton multiplet (δ 3.20-3.88) for the ketal methylenes, and a two-proton multiplet (olefinic protons) between δ 5.28 and 5.68.

(57)
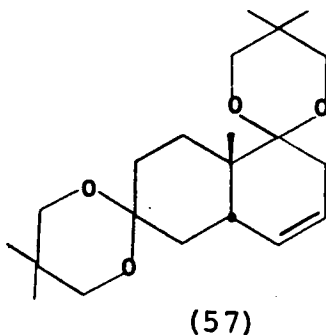
The minor product (mp 128-130 °C) initially created some confusion.

Thus, although its molecular weight (352 mass units) was identical with that of the desired bicyclic diketal (54), the ^{1}H nmr spectrum of this compound was anomalous and could not be reconciled with that expected of the desired material (54). Furthermore, this material proved to be very difficult to obtain in pure form since it consistently co-crystallized with the major product (57). Purification of this compound could be effected by preparative tlc but the efficiency of this method was low due to the similarity of the affinities of this material and the olefin (57) to silica gel. For these reasons, as well as for the fact a more effective preparation of (57) was found (vide infra), this compound was not investigated further.

These results suggested that an E$_2$ type of elimination of the tosylate anion was occurring in preference to its direct displacement. The displacement of the tosylate, in an S$_N$2 fashion, required that the attacking species (hydride ion) approach from the concave side (α face) of the molecule. Molecular models of the tosylate (53) clearly showed that steric hindrance would make such a process quite difficult [cf. (53a), (53b)]. On the other hand, the elimination pathway, involving

(53a)   (53b)
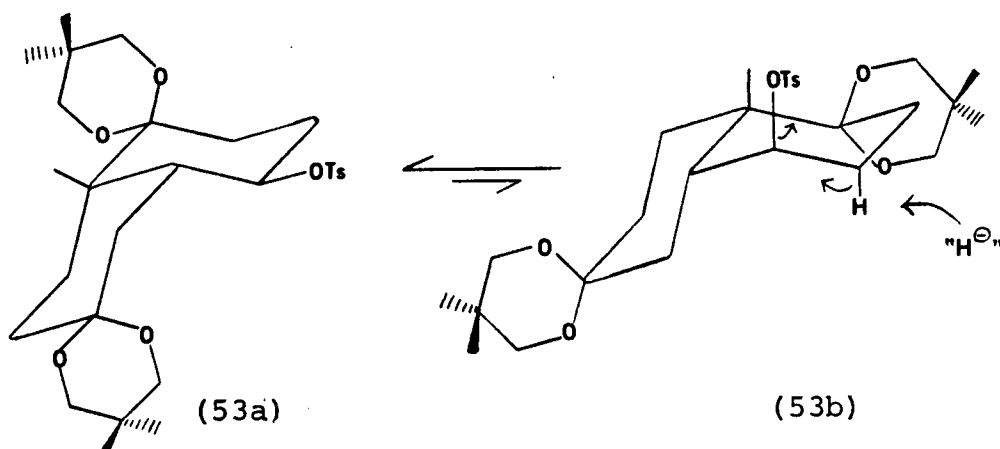
the abstraction of a proton from C_7, would presumably be less sterically encumbered.

Since the direct displacement of the tosylate did not appear to be a facile mode of reaction for (53), a more efficient preparation of the olefin (57) was sought. It was expected that the conversion of (57) into the desired bicyclic diketal (54) could be accomplished via the hydrogenation of the double bond in (57).

(57)   (54)
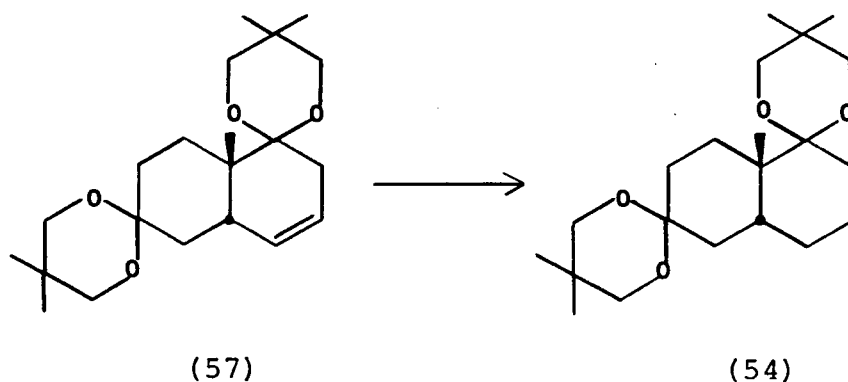
It was found that the treatment of a solution (dimethyl sulfoxide--benzene) of (53) with potassium tert-butoxide in the presence of 18--Crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) at 55 °C (0.5 h) produced the olefin (57) in good yield.[44,45] The latter compound was further characterized by the hydrolysis of the two ketal moieties (hydrochloric acid-acetone), thus affording the diketo olefin (58). The olefinic protons of (58) appeared as a two-proton multiplet at δ 5.84 in

(53)   (57)

(57)   (58)
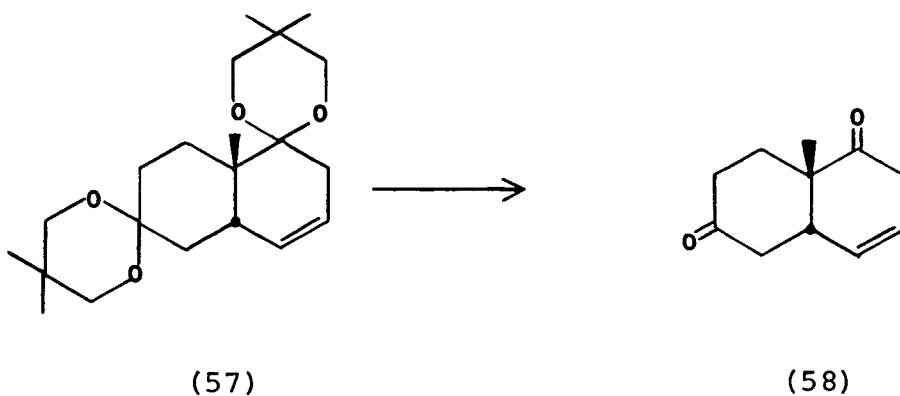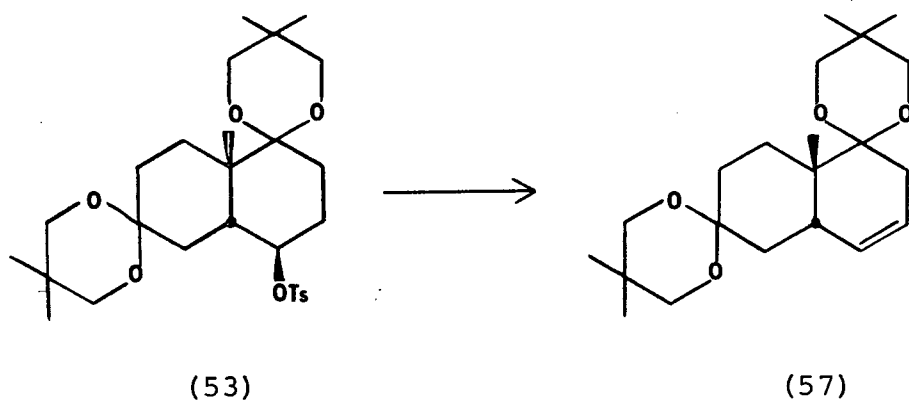
the ^{1}H nmr spectrum and the ir spectrum of this material showed a carbonyl absorption at 1710 cm^{-1}.

Hydrogenation of the olefin (57) over 10% palladium-on-carbon in ethyl acetate produced the bicyclic diketal (54) in 88% yield. The ^{1}H nmr spectrum of this material (mp 123.5-125 °C) showed an absence of any olefinic protons. The ketal methylenes of (54) gave rise to an eight-proton multiplet between δ 3.16 and 3.80, and the five tertiary methyl groups resonated at δ 1.18, 1.11, 0.98, 0.90 and 0.68.

(57)   (54)   (17)
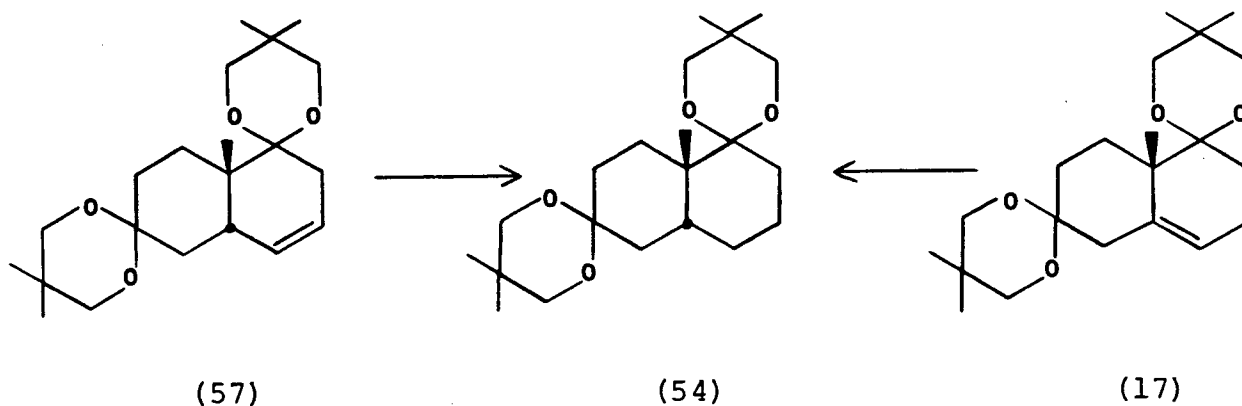
Compound (54) was also directly available from the diketal olefin (17) by hydrogenation over palladium (96% yield). As discussed previously (vide supra), the β face of the diketal olefin (17) was thought to be considerably more hindered than the α side. Since hydrogenation of (17) gave the bicyclic diketal (54) as the sole product, this proposal was certainly consistent with the above result.

Hydrolysis of (54) in acetone containing 1N hydrochloric acid afforded the dione (51) (88% yield), which exhibited mp 62-65 °C (lit.[40] mp 64.5-65.5 °C). This material was identical in all respects with an authentic sample of the dione (51) which was prepared by the hydrogenation of 9-methyl-5(10)-octalin-1,6-dione (18) (93%) at room temperature for 16 h. The overall series of transformations is summarized in Scheme 3.

For the purpose of direct comparison (^{1}H nmr, ir) of the cis-fused dione (51) with the corresponding trans isomer (52), an authentic sample of the latter substance was prepared. Hydrolysis of the monoketal ketone (59)[†] with aqueous hydrochloric acid-acetone gave the dione (52)

[†]This material was kindly supplied by Dr. D.J. Herbert, Department of Chemistry, University of British Columbia.

(18)

(51)

(17)

(54)

(31)

(57)

(53)
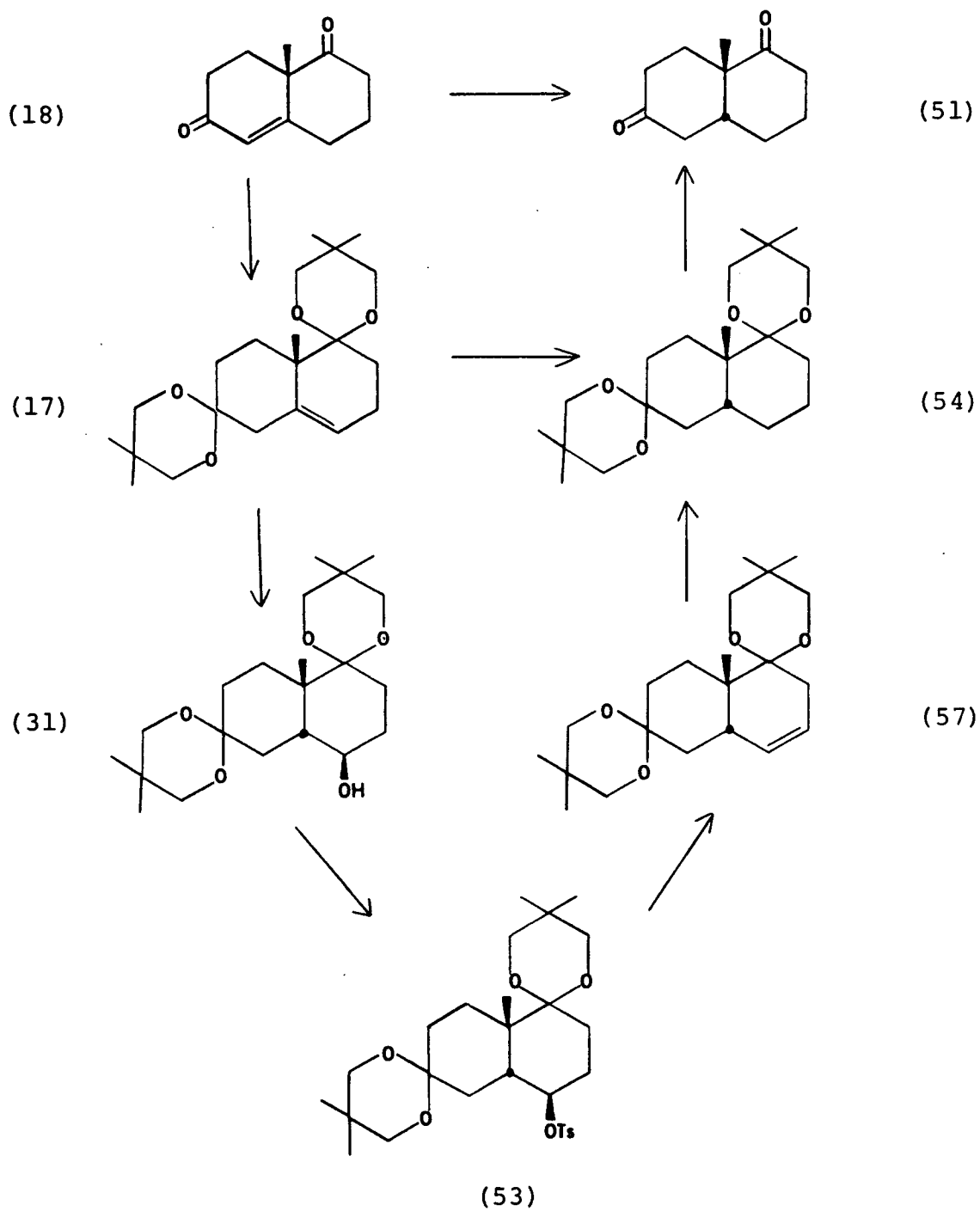
SCHEME 3

in 83% yield. This material, which was clearly different from the cis-fused dione (51) as judged by glc, ^{1}H nmr and ir analyses, exhibited mp 55-56 °C (lit.[41] mp 56-57 °C).

(59)   (52)
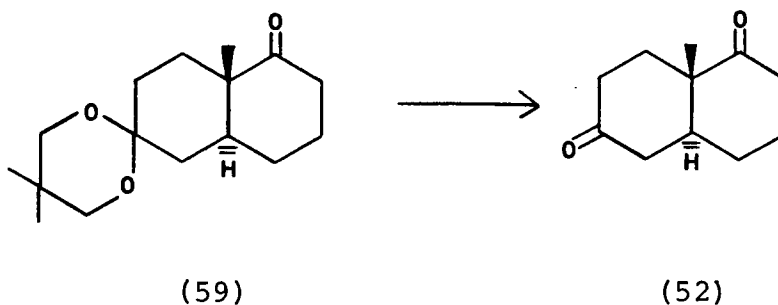
The results summarized above fully substantiated our tentative assignment of the major product from the hydroboration of the diketal olefin (17) as the cis-fused alcohol (31). The latter compound was characterized further by its conversion into the dione alcohol (60). This material was isolated (97% yield) from the acid catalyzed hydrolysis (2N hydrochloric acid-acetone) of (31). Compound (60), exhibiting mp 108-109 °C, showed a hydroxyl absorption at 3430 cm^{-1} and a saturated carbonyl absorption at 1706 cm^{-1} in its ir spectrum. The ^{1}H nmr

(31)   (60)
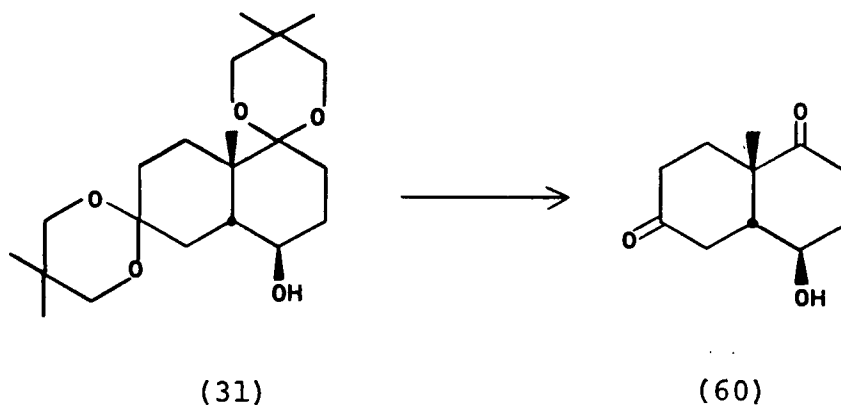
spectrum of this material exhibited a three-proton singlet at δ 1.47

(angular methyl group), a one-proton doublet (J = 4 Hz) at δ 3.00, due to the hydroxyl proton, and a one-proton, seven-line signal (dddd, J = 8,8,4 and 4 Hz) at δ 3.89 due to the proton at C_6. When the hydroxyl proton was replaced by deuterium (D_2O exchange), the ^{1}H nmr resonance for the hydroxyl proton disappeared and the signal at δ 3.89, due to C_6H, collapsed to a symmetrical six-line signal (ddd, J = 8,8 and 4 Hz).

Since the initial stereochemical assignment regarding the cis-fused alcohol (31) proved to be correct, an epimerization (of the ketone product) must have occurred when (31) had been subjected to oxidation with Collins reagent (vide supra). This anomalous result seemed worthy of re-investigation. When the oxidation of the alcohol (31) was re-peated under conditions similar to those used previously (chromium trioxide-pyridine complex), the cis-fused ketone (44) was isolated (93%) as the sole product! This material showed a saturated carbonyl absorp-

(31)   (44)
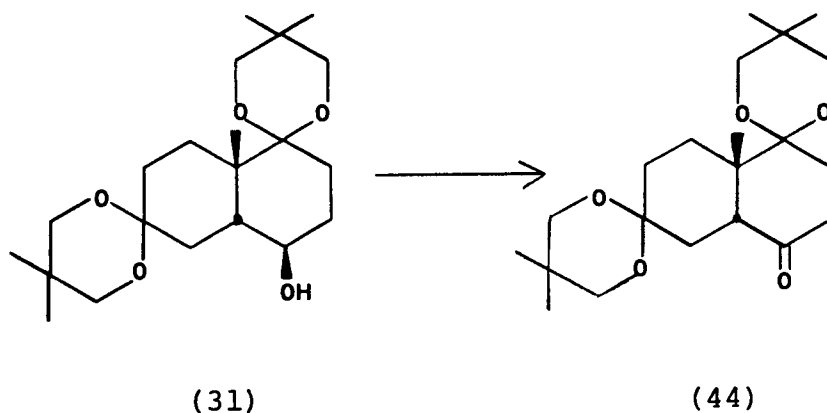
tion at 1705 cm^{-1} in the ir spectrum and, in the ^{1}H nmr spectrum, the angular methyl group produced a three-proton singlet at δ 1.22.

The only difference between the two procedures used for the oxida-

tion of (31) involved the work-up of the reactions. In the experiment in which the trans-fused ketone (45) was isolated, the work-up procedure involved flushing the crude reaction mixture through a short column of neutral alumina. Elution of the column with ethyl acetate, followed by the evaporation of the solvents from the eluent, afforded the trans-fused ketone (45) (77%). In the experiment which resulted in the isolation of the cis-fused ketone (44), the work-up of the reaction involved simple filtration of the crude reaction mixture, followed by an aqueous work-up of the resulting filtrate. The cis-fused ketone (44) thus isolated was unaffected when passed through a column of basic alumina (ethyl acetate eluent) and was only partially epimerized upon treatment with sodium methoxide in methanol at 70 °C (3 h).

The reason(s) for these apparently contradictory results remain a mystery. Since the only experimental differences in the oxidations described above involved the respective work-up procedures, it is probable the epimerization of (44) occurred at this point. The mechanism of this transformation, however, is obscure and any rationalizations toward this end would be idle speculation.

Treatment of the diketal ketone (44) with sodium methoxide in methanol at room temperature for four days, gave the epimerized compound (45) in essentially quantitative yield. This material (mp 146-148 °C) was identical (^{1}H nmr, ir) with the previously prepared ketone (45).

(44)   (45)
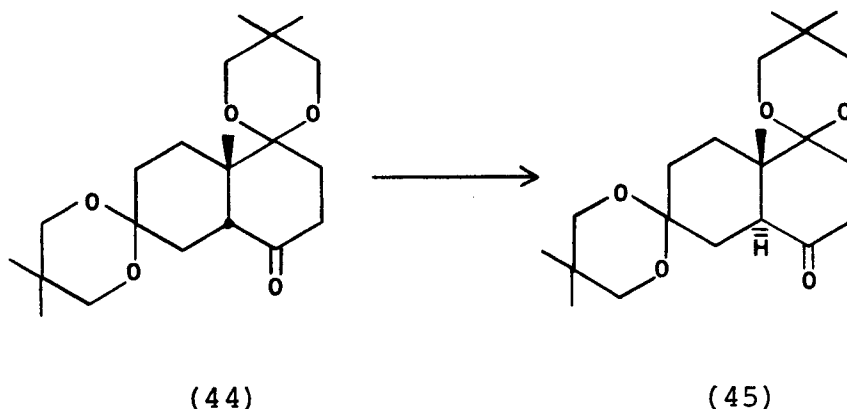
The synthesis of the diketal ether (35) was completed by protection

of the alcohol (31) as the β-methoxyethoxymethyl ether (MEM ether).

The alcohol (31) was first treated with potassium hydride in tetrahy-

drofuran containing approximately 10% hexamethylphosphoramide.   The

resulting alkoxide was allowed to react with β-methoxyethoxymethyl

chloride (MEM chloride) affording the desired ether (35) in 89% yield.

The ^{1}H nmr spectrum of compound (35) displayed a three-proton singlet at

δ 3.40 (due to the methoxy methyl group of the MEM moiety) and a two-

proton AB quartet at δ 4.85 (-OCH$_2$O-).   The ^{13}C nmr spectrum of (35)

showed a triplet (J = 162 Hz) at δ 95.69 (-OCH$_2$O-).

(31)   (35)
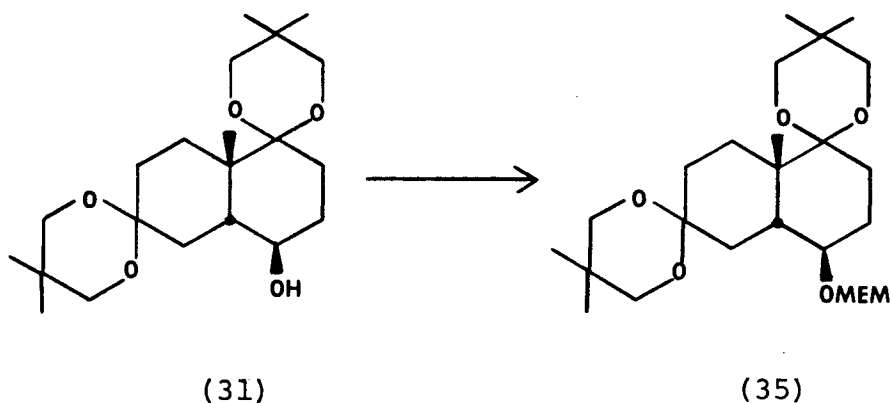
III. <u>Synthesis of the α,β-Unsaturated Ester (61)</u>

In accord with our synthetic plans, it was envisaged that the diketal ether (35) could be transformed into the α,β-unsaturated ester (61) via the monoketone (62). The latter, potentially available from the ether (35) by selective A ring ketal cleavage, would then be converted into the α,β-unsaturated ester (61) by means of a Horner-Emmons reaction.[46]

(35)   (62)   (61)
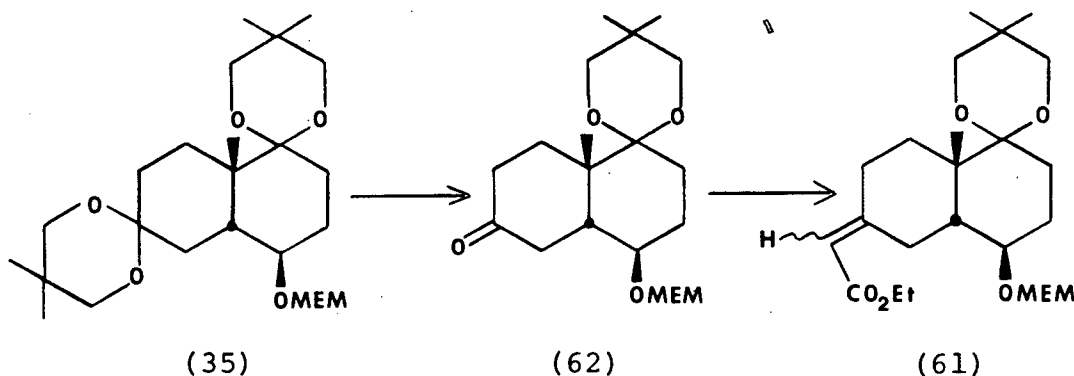
Unfortunately, the initial attempts to selectively remove the A ring ketal in (35) met with only moderate success. Treatment of the diketal ether (35) with 5% acetic acid in acetone (ambient temperature, 5 h) afforded a mixture of the monoketones (63) and (62), in a ratio of approximately 2:1, respectively. These compounds were almost indistinguishable by tlc, but the ^{1}H nmr spectrum of the mixture clearly indicated that the major component was the undesired material (63). Thus, the ^{1}H nmr spectrum of this material showed six singlets in the high-field region (tertiary methyl groups), three of which were considerably more intense than the other three. The more intense signals

appeared at δ 1.31, 1.00 and 0.88, while the three less intense signals

appeared at δ 1.40, 1.20 and 0.72. On the basis of the observation that

the methyl groups of the B ring ketal functionality consistently gave

rise to singlets at δ 1.18 ± 0.02 and δ 0.70 ± 0.02 (see section VII),

the minor isomer was assigned structure (62), the desired keto ketal.
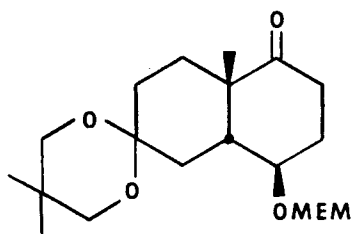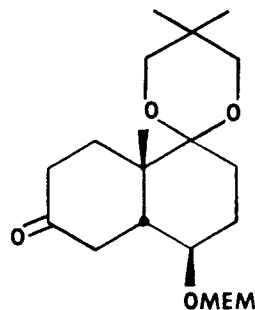
(63)   (62)

Other acidic cleavage conditions, including dilute aqueous hydro-

chloric acid-acetone and 0.05 N perchloric acid-tetrahydrofuran mix-

tures, gave results essentially identical with those obtained previ-

ously.

These results demonstrated that the acid catalyzed hydrolysis of

the B ring ketal in (35) was a more facile process than the correspond-

ing A ring ketal cleavage. In addition, based on the poor resolution of

the two monoketones (62) and (63) by tlc, it appeared that the separa-

tion of these two compounds by column chromatography would also prove to

be problematic. For these reasons, the exploration of a potentially

more efficient route to the α,β-unsaturated ester (61) was initiated.

It was envisaged that exposure of the diketal ether (35) to mildly

acidic hydrolysis conditions would produce the dione (64), still re-

taining the somewhat acid sensitive MEM protecting group. This material

should afford the α,β-unsaturated ester (65) when subjected to a Horner-Emmons reaction.[46,47] It was expected that the B ring ketone

(35)   (64)   (65)
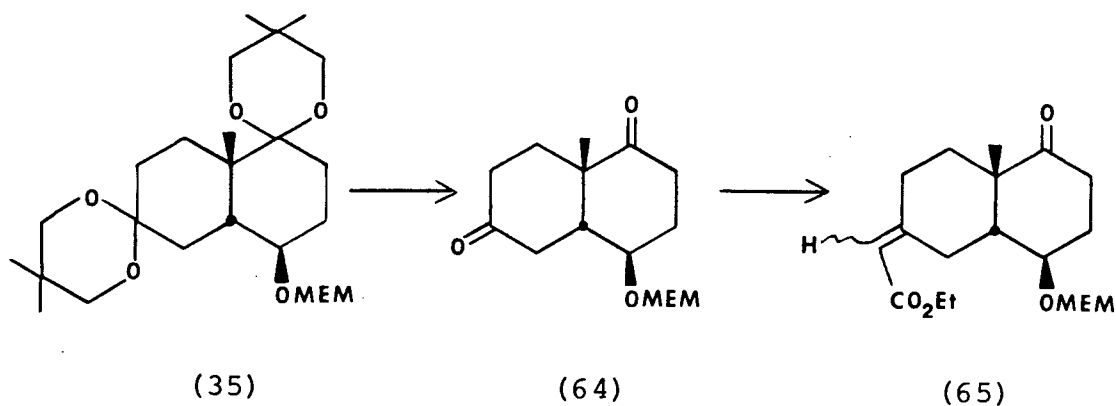
would be considerably less reactive than the A ring carbonyl since the introduction of an α,β-unsaturated ester at this position would be retarded by strain (A[1,3]) in the transition state.[48] The synthesis of (61) could then be completed by the re-ketalization of the B ring ketone in (65) as depicted below.

(65)   (61)
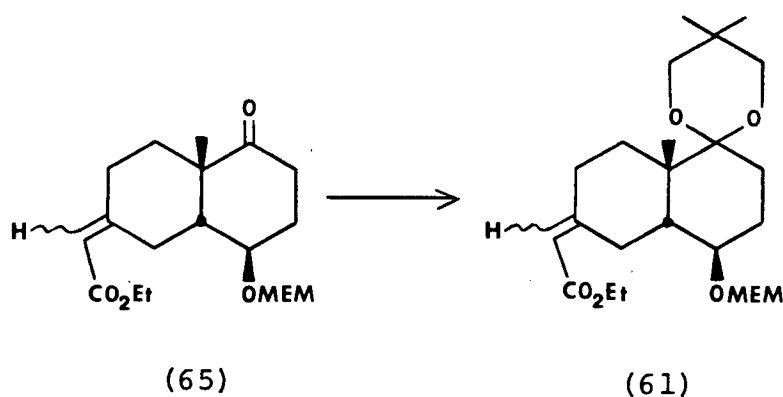
Accordingly, the diketal ether (35) was treated with 1N hydrochloric acid in acetone at ambient temperature, thus affording the dione

(64) in 92% yield. This material exhibited a saturated carbonyl absorption at 1705 cm^{-1} in the ir spectrum. The ^{1}H nmr spectrum of (64) displayed a three-proton signlet at δ 3.38 (methoxy methyl) and a two-proton singlet AB quartet (J = 6 Hz) at δ 4.83 (-OC$\underline{H}_2$O-), indicating that the MEM protecting group had survived the hydrolysis conditions.

The dione (64) reacted smoothly with three equivalents of the potassium salt of triethyl phosphonoacetate in 1,2-dimethoxyethane (6 h, ambient temperature) giving the α,β-unsaturated ester (65) in good yield. Compound (65) was obtained as a 1:1 mixture of geometric isomers

(64)   (65)
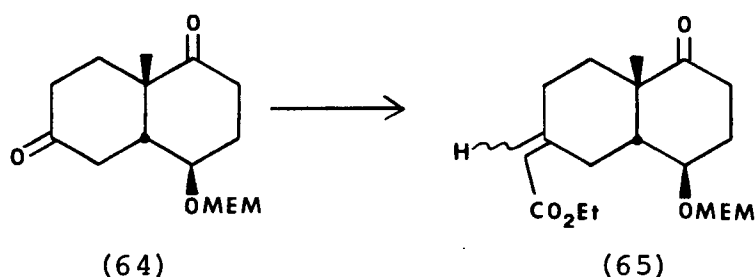
which were separable by preparative tlc. One of the geometric isomers of (65) showed a strong absorption at 221 nm (ε = 15,200) in the uv spectrum and absorptions at 1708 and 1646 cm^{-1} in the ir spectrum. The ^{1}H nmr spectrum of this material exhibited a three-proton triplet (J = 7 Hz) at δ 1.29, a two-proton quartet (J = 7 Hz) at δ 4.16 and a one-proton singlet (olefinic proton) at δ 5.66, indicating the presence of an α,β-unsaturated ethyl ester.

The other isomer of (65) showed resonances in the ^{1}H nmr spectrum at δ 1.29 (a three-proton triplet, J = 7 Hz), δ 4.18 (a two-proton quartet, J = 7 Hz) and at δ 5.69 (a one-proton singlet). The angular

methyl group and the methoxy methyl group appeared at identical chemical

shifts (δ 1.34 and 3.38, respectively) in both isomers.

When the α,β-unsaturated ester (65) was exposed to "standard"

ketalization conditions (2,2-dimethyl-1,3-propanediol and p-toluenesul-

fonic acid in benzene), the desired substance (61) was, unfortunately,

not obtained. Instead, the ether cleaved compound (66), as a mixture of

geometric isomers, was isolated in 89% yield.

(65)   (66)
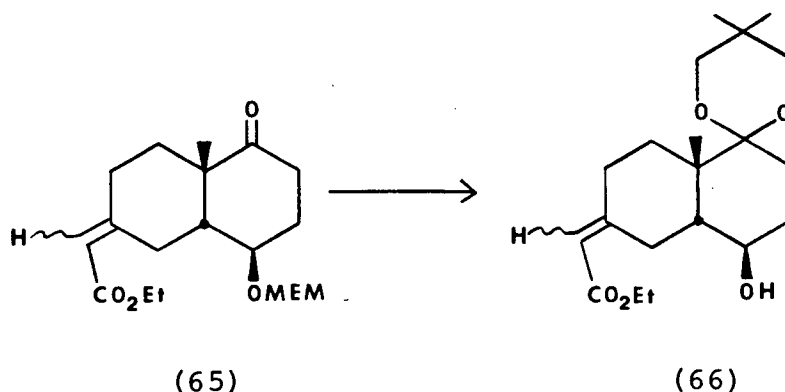
The two isomers of compound (66) were clearly distinguishable by

tlc. Separation of the mixture by preparative tlc (50% ethyl acetate in

cyclohexane) gave a pure sample of each isomer. One of the isomers (mp

110-112 °C) showed an absorption at 222 nm (ϵ = 12,900) in the uv spec-

trum. The ir spectrum of this material exhibited absorptions at 3500

cm^{-1} (hydroxyl group) and at 1695 and 1648 cm^{-1} (unsaturated ester).

The ^{1}H nmr spectrum substantiated the loss of the MEM group and the

presence of the ketal moiety (two three-proton singlets at δ 0.70 and

1.18).

The other isomer of compound (66) also displayed a hydroxyl group

absorption (3450 cm^{-1}) and absorptions characteristic of an α,β-unsatur-

ated ester (1710 and 1642 cm^{-1}) in its ir spectrum. The ^{1}H nmr spectrum

of this material showed three high-field singlets (methyl groups) at δ0.72, 1.21 and 1.28, and a broad, one-proton singlet at δ5.70 (olefinic proton).

Since the MEM protecting group was obviously not stable to the ketalization conditions described above, a milder method for replacing the ketal group was sought. One alternative would be to treat the α,β-- unsaturated ester (65) with ethylene glycol (as solvent) containing a catalytic amount of p-toluenesulfonic acid. This reaction could be performed at room temperature, thereby avoiding the elevated temperature (80 °C) used in the "standard" ketalization conditions.

Unfortunately, compound (65) afforded only the MEM cleaved ethylene ketal (67) under the reaction conditions described above (24 h). The

(65)   (67)
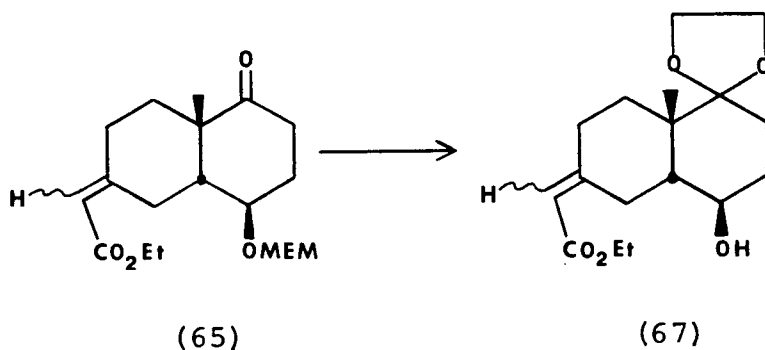
two isomers of compound (67) were separated by preparative tlc (25% ethyl acetate in cyclohexane). One of the isomers (mp 163-167 °C) exhibited an absorption at 3600 cm^{-1} (hydroxyl group) and absorptions at 1703 and 1641 cm^{-1} (unsaturated ester) in the ir spectrum. The protons of the ethylene ketal group gave rise to a four-proton singlet at δ3.96 in the ^{1}H nmr spectrum. The uv spectrum of this substance showed an absorp-

tion at 223 nm ($\varepsilon = 11,300$).

The other geometric isomer of (67) (mp 177-178 °C) showed an absorption at 224 nm ($\varepsilon = 11,060$) in its uv spectrum and absorptions at 3500 cm^{-1} (broad, hydroxyl group) and at 1687 and 1642 cm^{-1} (unsaturated ester) in its ir spectrum. The ^{1}H nmr spectrum of this substance showed a three-proton singlet at δ 1.14 (angular methyl group), a broad, one-proton resonance between δ 3.91 and 4.28 (hydroxyl proton) and a broad, one-proton singlet at δ 5.80 (olefinic proton).

Results very similar to those described above were obtained when other acid catalysts were used in conjunction with ethylene glycol in attempts to ketalize (65). For example, the use of a catalytic amount of either hydrochloric acid or boron trifluoride-etherate[49] resulted in the cleavage of the MEM ether during the course of the ketalization reaction.

Another procedure used for the ketalization of ketones involves a trans-ketalization procedure, in which the ketone is treated with a large excess of another ketal in the presence of an acid catalyst. This type of procedure has been used advantageously by Sir Derek Barton to effect the ketalization of acid sensitive molecules which proved to be unstable under the usual ketalization conditions.[50] For example, compound (68) was converted into the acetal (69) using diethylene ortho-carbonate.[51]

(68)   (69)
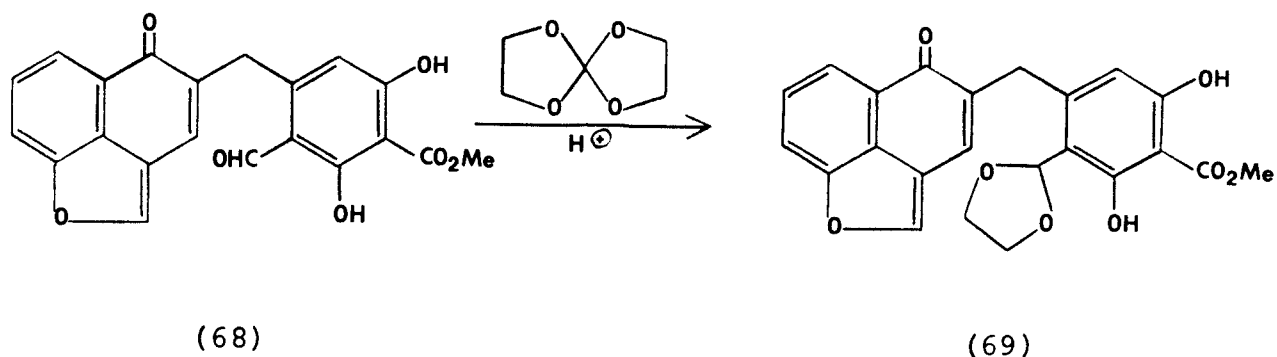
In an analogous fashion, (65) was treated with 2-ethyl-2,5,5-tri-methyl-1,3-dioxane (70) (as solvent) containing a catalytic amount of p-toluenesulfonic acid (60 °C, 4 days) to produce a rather complex mixture of products. This mixture was separated by preparative tlc, affording the desired α,β-unsaturated ester (61) (27%), as well as the α,β-unsaturated ester (66) (34%) and recovered starting material (23%).

(65)   (61)   (66)
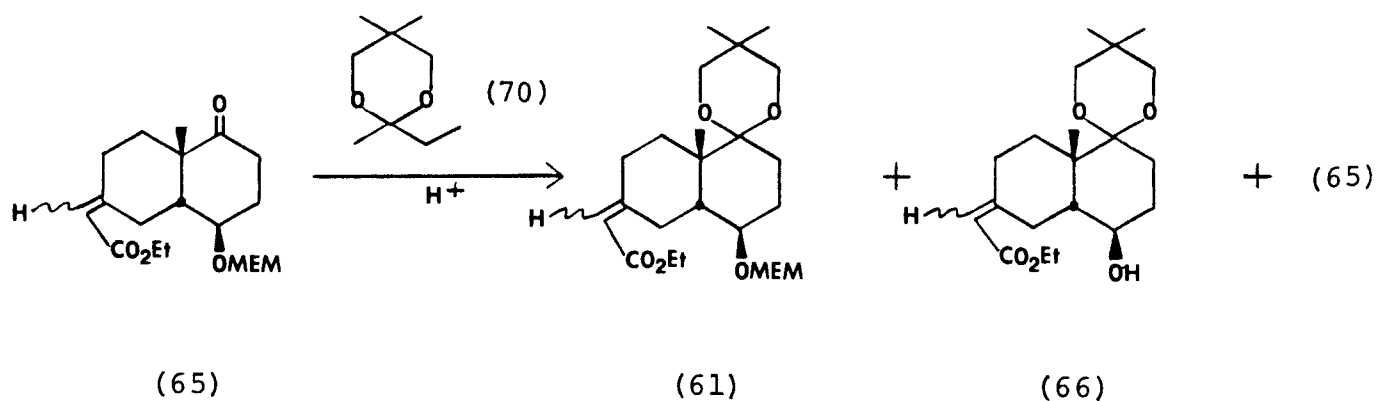
The desired material, compound (61), was isolated as a mixture of geometric isomers which were indistinguishable by tlc and glc analyses. One of these isomers could be obtained in pure form by fractional crys-

tallization of the mixture from ether-hexane. This material exhibited mp 57-58.5 °C, and gave an absorption at 223 nm ($\varepsilon = 7700$) in the uv spectrum and absorptions at 1705 and 1645 cm^{-1} in the ir spectrum, characteristic of an α,β-unsaturated ester functionality. The ^1H nmr spectrum of this substance showed signals due to three tertiary methyl groups (δ 1.30, 1.18 and 0.70) and the α,β-unsaturated ethyl ester moiety was evidenced by resonances at δ 1.26 (three-proton triplet, J = 7 Hz), δ 4.11 (two-proton quartet, J = 7 Hz) and δ 5.58 (one-proton singlet, olefinic proton). The MEM protecting group gave characteristic ^1H nmr resonances at δ 3.40 (methoxy methyl) and at δ 4.78, for the two protons α to two oxygen atoms, as an AB quartet (J = 7 Hz). The ketal methylenes, C_6H, and the remaining protons of the MEM group appeared as a broad multiplet, integrating for nine protons, between δ 3.12 and 3.94.

Although the procedure discussed above did provide the desired α,β-- unsaturated ester (61), the reaction was not clean and the yield (27%) of the desired material was far too low to be considered synthetically useful. For these reasons, it was decided to re-investigate the selective cleavage of the A ring ketal in (35) in the hopes of discovering a more efficient route to the α,β-unsaturated ester (61). Since a molecular model of (35) suggested that the A ring ketal group of this material was considerably more open (less hindered) than the B ring ketal, a method for selectively removing the A ring ketal exploiting this differ-
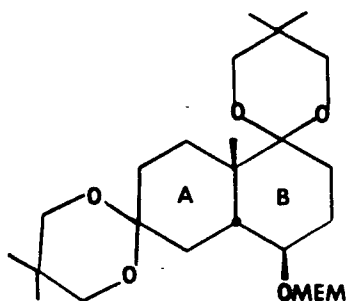
(35)

ence in steric encumberance seemed an attractive possibility.

With this consideration in mind, the diketal ether (35) was stirred

with dry methyl ethyl ketone containing p-toluenesulfonic acid to effect

trans-ketalization to the solvent. Under these conditions (0 °C, 18 h),

a 2:1 ratio of the monoketones (62) and (63), respectively, was obtained

in 91% yield. This ratio was the reverse of that obtained via the acid

catalyzed hydrolysis of the diketal ether (35) (vide supra).

(35)   (62)   (63)
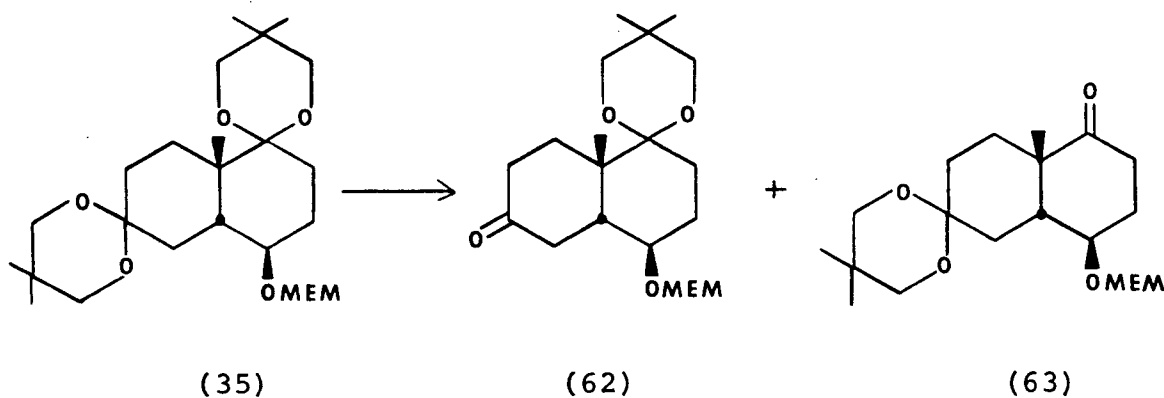
The ratio of the ketones (62) and (63) was based on an ^{1}H nmr

spectrum of a pure mixture of these compounds. As discussed previously,

the tertiary methyl signals at δ 1.40, 1.20 and 0.72 were assigned to

the monoketone (62). In order to ascertain whether or not this assign-

ment was correct, a pure sample of one of the monoketones was necessary. By equilibration of a pure sample of one of the monoketones (62) or (63) with methanol-d_1, in the presence of sodium methoxide, it would be possible to differentiate between these two materials by determining the number of deuterium atoms incorporated into the given monoketone.

A pure sample of compound (63) (mp 64-65 °C) was obtained by subjection of the mixture of compounds (62) and (63) to preparative tlc. This substance exhibited a saturated carbonyl absorption at 1703 cm^{-1} in the ir spectrum. The ^{1}H nmr spectrum of (63) showed signals due to three tertiary methyl groups at δ 1.31, 1.00 and 0.88. The MEM ether group exhibited characteristic absorptions at δ 3.40 (methoxy methyl) and at δ 4.87 (two protons, -OC$\underline{H}_2$O-), an AB quartet (J = 8 Hz).

The deuteration of (63) was accomplished by treatment of this material with methanol-d_1 containing a small amount of sodium methoxide. The resulting solution was refluxed gently for 30 h, thus affording (71) as the sole product. This material exhibited a molecular ion peak at m/e 372 (low resolution ms) indicating the incorporation of two deuterium atoms. There was no indication of any material corresponding to the introduction of four deuterium atoms, which would have been the expected result if compound (62) were to be treated under similar conditions.[52]

(63)   (71)
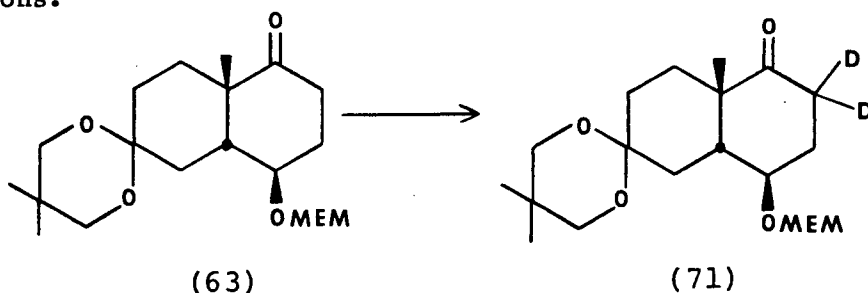
Since the exchange diketalization of the diketal ether (35) with

methyl ethyl ketone had produced the desired monoketone (62) and the

undesired isomer (63) in a ratio of 2:1, respectively, it was hoped that

a more sterically demanding ketone (as solvent) would produce the de-

sired material in a still more selective fashion. Accordingly, a sol-

ution of the diketal ether (35) in freshly distilled 2-methylcyclo-

hexanone, containing a small amount of p-toluenesulfonic acid as cata-

lyst, was stirred for 17 h at ambient temperature. Under these condi-

tions, the monoketones (62) and (63) were isolated (82%) in a ratio of

approximately 3.5:1, respectively. The solvent, 2-methylcyclohexanone,

was recovered from the crude product by distillation under reduced

pressure.

The use of 2,6-dimethylcyclohexanone as the solvent, under reaction

conditions similar to those described above, produced approximately the

same ratio of the monoketones (62) and (63). Under these conditions,

however, the reaction was considerably slower, requiring approximately

120 h at ambient temperature to proceed to completion (tlc).

Since a reasonably efficient method for the preparation of the

desired monoketone (62) was now in hand, it was envisaged that the α,β--

unsaturated ester (61) could be produced in good yield via the reaction

of the monoketone mixture [(62) and (63)] with an appropriate Horner-

Emmons reagent. In practice, the monoketone mixture was not purified.

Instead, the crude product resulting from the reaction of the diketal

ether (35) with 2-methylcyclohexanone as described above, was treated

directly with three equivalents of the potassium salt of triethyl phos-

phonoacetate (19 h, ambient temperature). Under these conditons, the desired material (61) was isolated in a 73% overall yield from the diketal ether (35), after column chromatography.

(35)   (61)
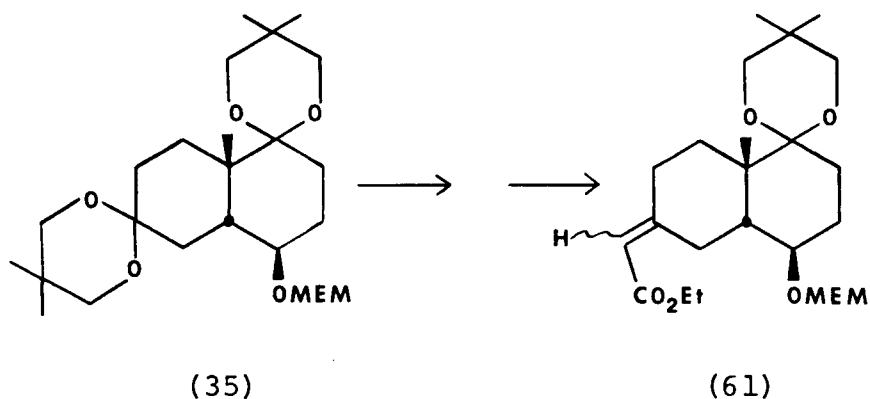
The undesired monoketone (63), containing a small amount of re-covered (62), was also isolated from the reaction described above in a yield of approximately 20%. This mixture could be recycled through its conversion (92% yield) into the diketal alcohol (31) using "standard" ketalization conditions.

The overall series of transformations described in this section are summarized in Scheme 4, shown below.

(35)

(63)

via (31)

(64)

+

(62)

(65)

(61)
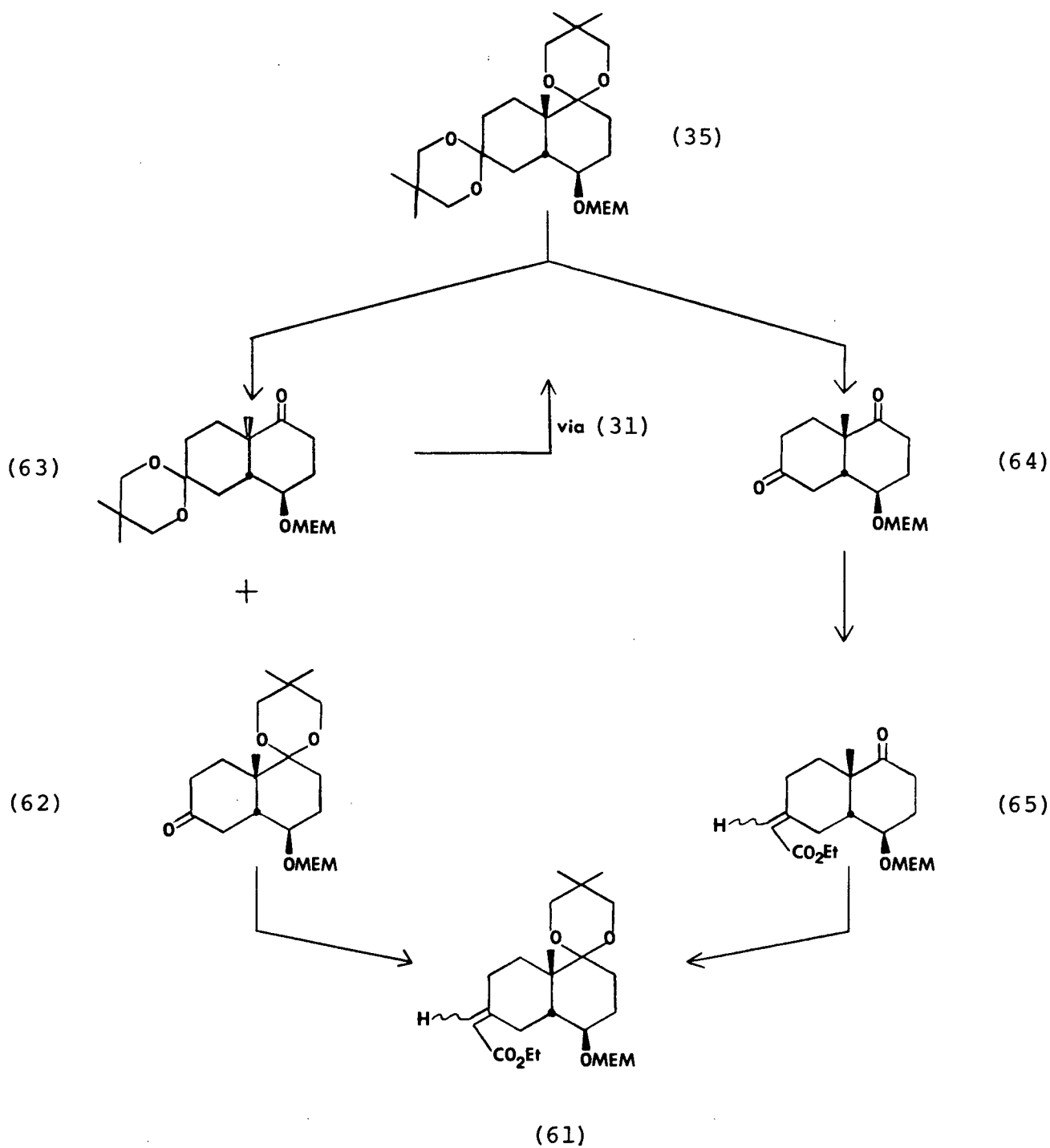
SCHEME 4

IV. The Introduction and Proof of the Stereochemistry at C_3

With a satisfactory synthetic route to the α,β-unsaturated ester (61) in hand, the next step of the synthetic scheme called for the introduction of the required stereochemistry at C_3. It was envisaged that this objective could be accomplished through the hydrogenation of the double bond in compound (61). An examination of a molecular model of (61) suggested that the convex side (β face) of the molecule was considerably more open (less hindered) to a heterogeneous catalyst than the concave side of the molecule. It was expected, therefore, that the hydrogenation of (61) would afford the desired saturated ester (72) in a stereoselective fashion.

The initial attempts to hydrogenate compound (61) (10% palladium--on-carbon, ethanol), at atmospheric pressure and room temperature, produced several products (as judged by tlc), all of which were considerably more polar than the starting material. The ^{1}H nmr spectrum of the crude mixtures isolated from these reactions indicated that, in addition to the hydrogenation of the double bond, the ketal functionality had been removed under the reaction conditions.

When platinum oxide was used as the catalyst, however, the hydrogenation of compound (61) (ethyl acetate as solvent) afforded two compounds (91% yield) in a ratio of 6:4 (glc). This mixture was separated by column chromatography (silica gel, 33% ethyl acetate in benzene as eluent) affording a pure sample of each compound.

The major product, tentatively assigned as the desired saturated ester (72), exhibited an absorption at 1737 cm^{-1} in its ir spectrum due

to the saturated ester moiety. The ^{1}H nmr spectrum of this material showed three 3-proton singlets (δ 0.68, 1.04 and 1.16) due to the tertiary methyl groups, a three-proton triplet (J = 7.5 Hz, δ 1.24) and a two-proton quartet (J = 7.5 Hz, δ 4.09) due to the ethyl ester, and a two-proton AB quartet centred at δ 4.70 ($-OC\underline{H}_2O-$). The ^{13}C nmr spectrum of this compound exhibited a triplet (J = 162 Hz) at δ 93.61 ($-O\underline{C}H_2O-$) and two singlets at δ 102.48 (C_9) and 173.06 (ester carbonyl).

(61)   (72)   (76)
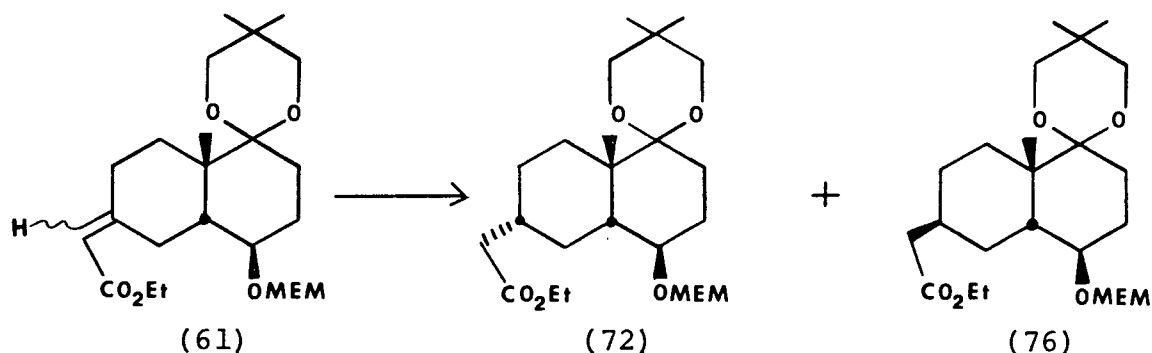
The minor product, tentatively assigned structure (76), displayed an absorption at 1730 cm^{-1} in its ir spectrum indicative of a saturated ester functionality. In the ^{1}H nmr spectrum this substance exhibited two high-field singlets at δ 0.68 (three protons) and at δ 1.13 (six protons) accounting for the three tertiary methyl groups. Resonances appearing at δ 1.21 (three-proton triplet, J = 7 Hz) and at δ 4.06 (two-proton quartet, J = 7 Hz) indicated the presence of an ethyl ester moiety. Signals characteristic of the MEM ether group appeared at δ 3.33 (methoxy methyl, three-proton singlet) and at δ 4.74 ($-OC\underline{H}_2O-$, two-proton AB quartet, J = 7 Hz).

Although the spectral data of the two compounds described above was in accord with that expected for the saturated esters (72) and (76), respectively, it was not possible to definitively assign the structures

of either of these materials solely on the basis of their respective
spectral data.   In order to secure these assignments, the following
scheme was devised.   It was envisaged that the corresponding tosylate
(73) of the desired ester (72) would undergo an intramolecular cycliz-
ation [cf. (73a)], upon treatment with a suitable base, to provide the
tricyclic system (74).   On the other hand, it was expected that the

(72)

(73)

Base

(74)

(73a)
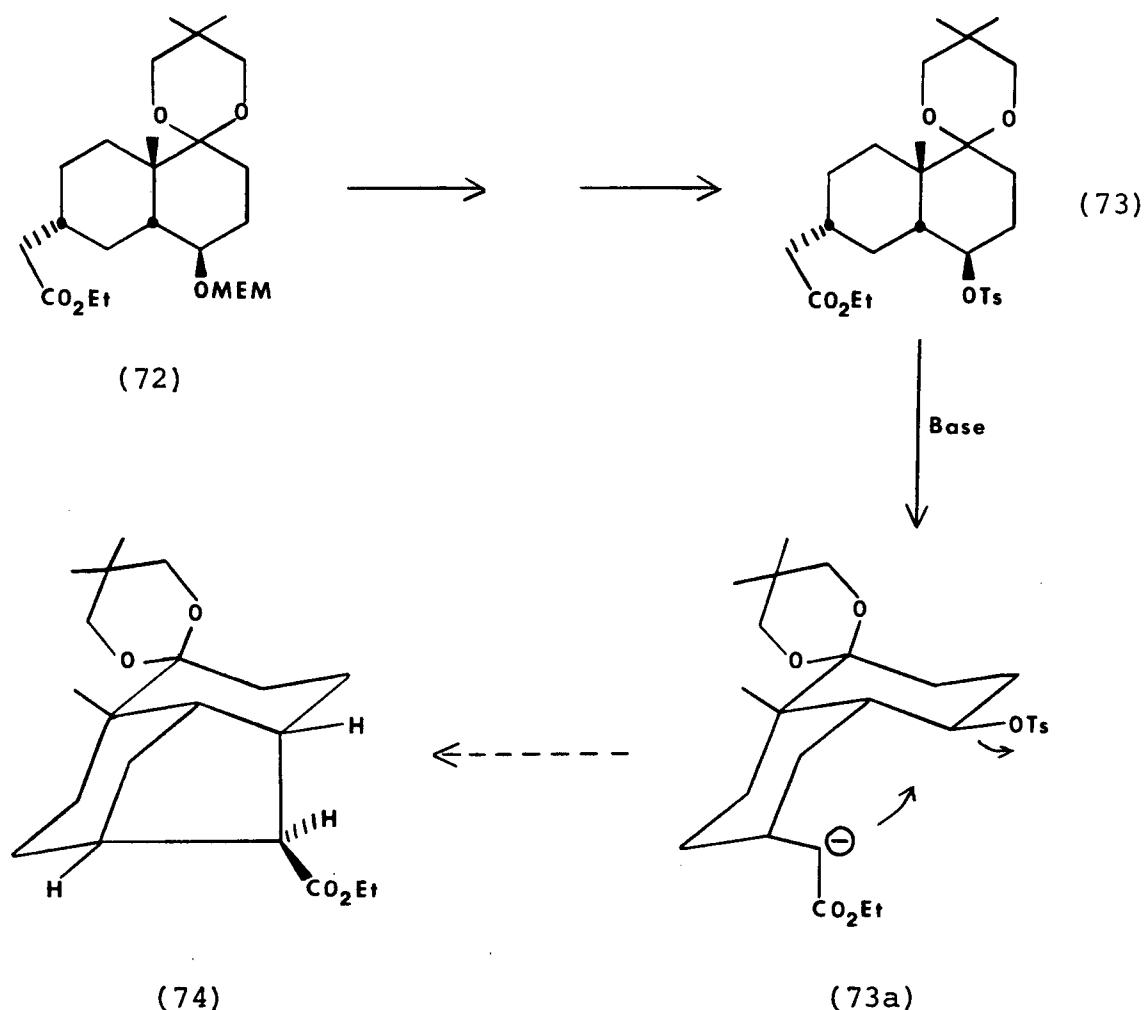
corresponding tosylate (75) of the undesired epimer, saturated ester

(76), would not undergo intramolecular alkylation upon treatment with an appropriate base, since compound (75) could not attain a conformation in which an internal cyclization was possible. Both of the tosylates (73) and (75) were potentially available from the corresponding saturated esters (72) and (76), respectively, via removal of the MEM ether protecting group, followed by the tosylation of the resulting alcohols (77) and (78).

(72) ; R=β-H   (77)   (73)

(76) ; R=α-H   (78)   (75)

Unfortunately, treatment of the minor product (76), resulting from the hydrogenation of (61), with titanium tetrachloride[27,53,54] in methylene chloride (0 °C, 45 min) did not produce the desired ketal alcohol (78). The ^{1}H nmr spectrum of the isolated crude product clearly showed that both the MEM ether functionality and the ketal group had been cleaved under the reaction conditions. This problem was eventually circumvented by treating compound (76) with p-toluenesulfonic acid under "standard" (2,2-dimethyl-1,3-propanediol, benzene) ketalization conditions. Under these reaction conditions (reflux, 45 min) two products were formed (tlc). Purification of the crude product by preparative tlc (40% ethyl acetate in benzene) gave a major product (higher R_f) and a

minor product (lower R_f), in a ratio of approximately 3:1, respectively.

The major product (75%) exhibited absorptions at 3480 (hydroxyl group) and 1735 cm^{-1} (saturated ester) in its ir spectrum. In its ^{1}H nmr spectrum, this compound showed singlets at δ 0.70 (three protons) and 1.18 (six protons), a broad, one-proton singlet at δ 1.68 (hydroxyl proton), and a one-proton, six-line signal (ddd, J = 10,10 and 5.5 Hz) centred at δ 3.78 (C_6H). All of the signals characteristic of a MEM ether were absent. The spectral data summarized above indicated that this compound was the desired ketal alcohol (78).

The minor product (22%) showed absorptions at 3452 (hydroxyl group), 1720 (shoulder, ester carbonyl) and 1702 cm^{-1} (ketone carbonyl) in the ir spectrum. In the mass spectrum of this substance, the molecular ion (m/e = 268) appeared as an extremely weak signal while the signal corresponding to a loss of water from the molecular ion (m/e = 250) was the base peak. The ^{1}H nmr spectrum of this compound exhibited only one high-field singlet at δ 1.21 (three protons, angular methyl) and a one--proton singlet at δ 1.77 (hydroxyl proton). This material evidently was the keto alcohol (79), obtained from compound (76) by cleavage of both the MEM ether group and the ketal functionality.

Treatment of the ketal alcohol (78) with p-toluenesulfonyl chloride in pyridine (ambient temperature, 13 h) afforded the corresponding tosylate (75) (81%). This compound [mp 148-149 °C (dec.)] exhibited a saturated ester absorption at 1720 cm^{-1} in its ir spectrum. In its ^{1}H nmr spectrum this material showed two singlets due to the tertiary methyl groups at δ 0.68 (three protons) and 1.13 (six protons), a three--

proton triplet at δ 1.26 (J = 7 Hz, ester methyl), and a two-proton quartet at δ 4.11 (J = 7 Hz, ester methylene). The ketal methylenes appeared as a four-proton multiplet between δ 3.14 and 3.70, and the proton at C_6 appeared as a six-line signal (ddd, J = 11,11 and 5.5 Hz) at δ 4.78. The tosylate group gave rise to signals at δ 2.40 (three-proton singlet, aromatic methyl) and at δ 7.31 and 7.80 (two 2-proton doublets, J = 8 Hz, aromatic protons).

(76)   (79)

                                          +

(75)   (78)
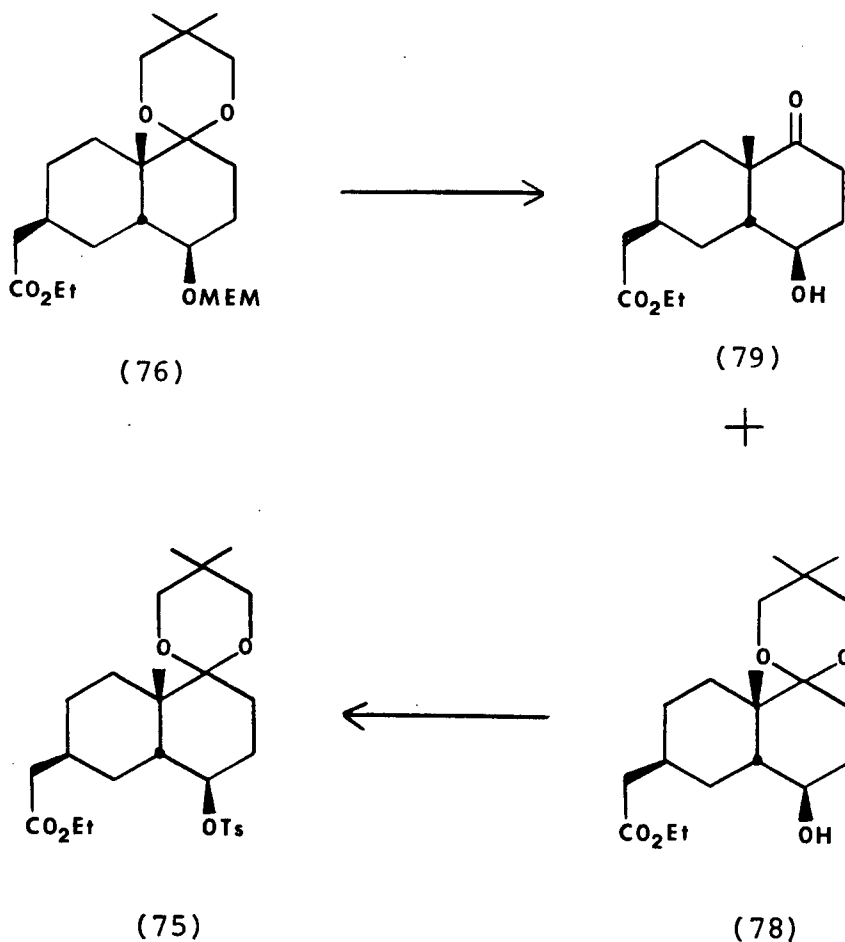
The major product isolated from the hydrogenation of compound (61), tentatively assigned as the desired saturated ester (72) (vide

supra), was converted into the corresponding tosylate (73) under conditions similar to those outlined above. Thus, treatment of compound (72) with p-toluenesulfonic acid, under "standard" ketalization conditions, afforded a mixture of the ketal alcohol (77) and the keto alcohol (80).[†] Separation of this mixture was effected by preparative tlc using 33% ethyl acetate in benzene as the developing solvent.

The ketal alcohol (77) (54%) exhibited absorptions at 3495 (hydroxyl group) and 1728 cm^{-1} (ester carbonyl) in the ir spectrum. The ^1H nmr spectrum of this material showed three tertiary methyl singlets (δ 0.68, 1.12 and 1.15), a three-proton triplet (δ 1.22, J = 7 Hz) due to the methyl group of the ethyl ester, and a two-proton quartet (δ 4.09, J = 7 Hz), assigned to the methylene group of the ethyl ester functionality. The hydroxyl proton appeared as a one-proton singlet at δ 3.68.

The minor product, keto alcohol (80) (30%), displayed absorptions at 3605 (hydroxyl group), 1723 (shoulder, ester carbonyl), and 1708 cm^{-1} (ketone carbonyl) in its ir spectrum. The ^1H nmr spectrum of compound (80) exhibited a three-proton triplet (J = 7 Hz) at δ 1.20 and a two-proton quartet (J = 7 Hz) at δ 4.07 due to the ethyl ester functionality. The angular methyl group appeared as a three-proton singlet at δ 1.38.

[†]The product distribution obtained from this reaction varied significantly even when attempts were made to duplicate the conditions described herein. Often, a larger proportion of the keto alcohol (80) was isolated accompanied by several side products.

The hydroxyl group proton exhibited a one-proton singlet at δ 1.82 and the proton attached to C_6 appeared as a broad, one-proton singlet at δ 3.87.

The tosylate (73) was prepared from the ketal alcohol (77) via treatment of the latter substance with p-toluenesulfonyl chloride in pyridine (17 h, ambient temperature). Compound (73), isolated in 80% yield after preparative tlc, showed an absorption at 1722 cm^{-1} in its ir spectrum (ester carbonyl). In its ^1H nmr spectrum, this material exhibited a three-proton singlet (δ 1.01) due to the angular methyl group and two additional three-proton singlets (δ 0.68, 1.13) due to the ketal methyls. The ethyl ester moiety gave rise to signals at δ 1.24 (methyl group, three-proton triplet, J = 7 Hz) and at δ 4.07 (methylene group, two-proton quartet, J = 7 Hz). Resonances at δ 2.42, 7.31 and 7.56, a three-proton singlet and two 2-proton doublets (J = 8 Hz), respectively, substantiated the presence of the tosylate functionality. The ketal methylene groups appeared as a four-proton multiplet between δ 3.12-3.80 and the proton attached to C_6 exhibited a broad, one-proton singlet at δ 4.49.

(72)

(80)

+

(73)

(77)
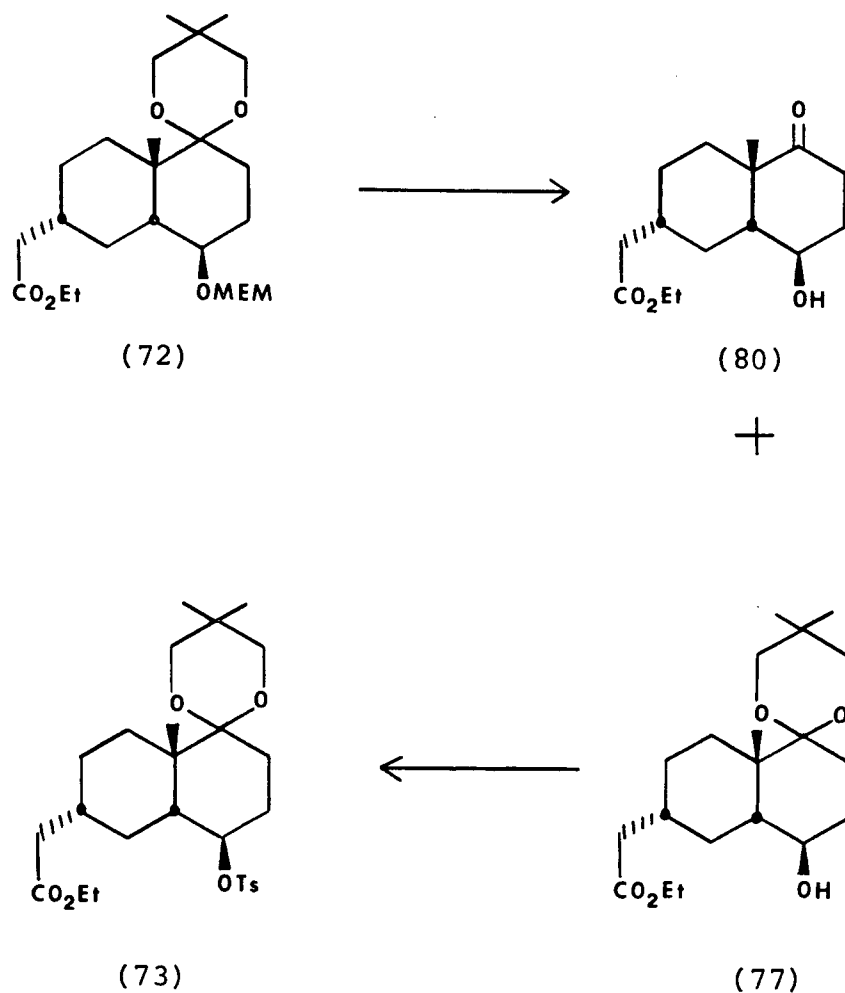
In order to demonstrate that the major product resulting from the hydrogenation of the α,β-unsaturated ester (61) was, in fact, the desired ester (72), the intramolecular cyclization (vide supra) of the tosylate (73) was attempted. Accordingly, compound (73) was added to a cold (-78 °C) solution containing excess lithium diisopropylamide in tetrahydrofuran. The resulting solution was warmed to room temperature and stirred for several hours. Unfortunately, only the starting material (73) (>90%) was recovered from the reaction mixture (tlc, ^{1}H nmr

analyses). Attempts to cyclize compound (73) at elevated temperature (50 °C), using lithium diisopropylamide as the base, also resulted only in the recovery of the starting material.

At this stage, it appeared possible that the (tentative) structural assignments made with respect to the hydrogenation products (72) and (76) were incorrect. However, surprisingly, treatment of the epimeric tosylate (75) with lithium diisopropylamide under conditions identical with those described above also failed to produce the tricyclic system (74). Here again, the starting material was recovered unchanged.

In a synthesis of the triterpene lupeol (81), Stork et al cyclized the ester (82) producing the ring closed material (83).[55] The experimental conditions used in this transformation involved the treatment of compound (82) with sodium bis(trimethylsilyl)amide in benzene solution.

(82)

(83)

(81)
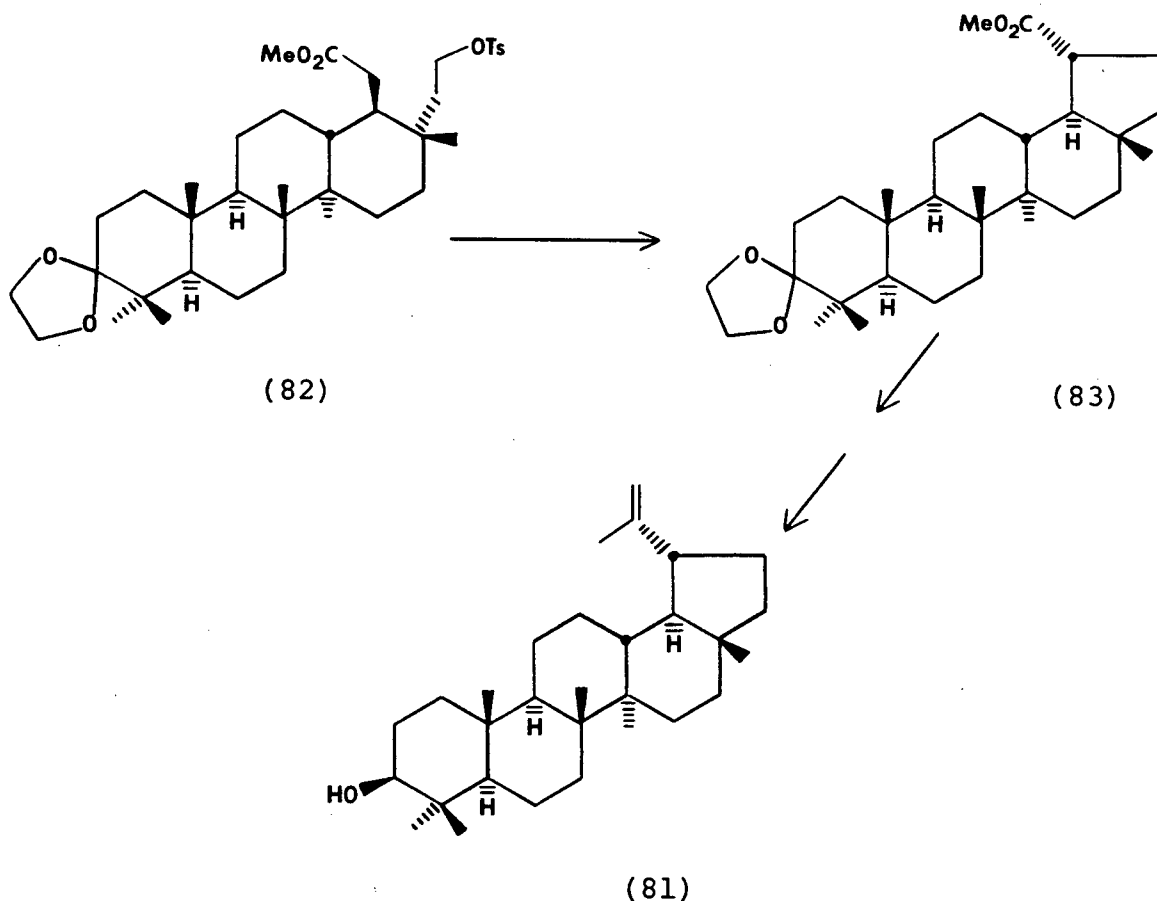
Piers and co-workers had also used similar conditions to effect the
intramolecular cyclization of compound (85).[56]   Thus, treatment of
compound (85) with sodium bis(trimethylsilyl)amide (room temperature, 40
min) furnished (-)-ylangocamphor (84), in 84% yield.

(85)   (84)
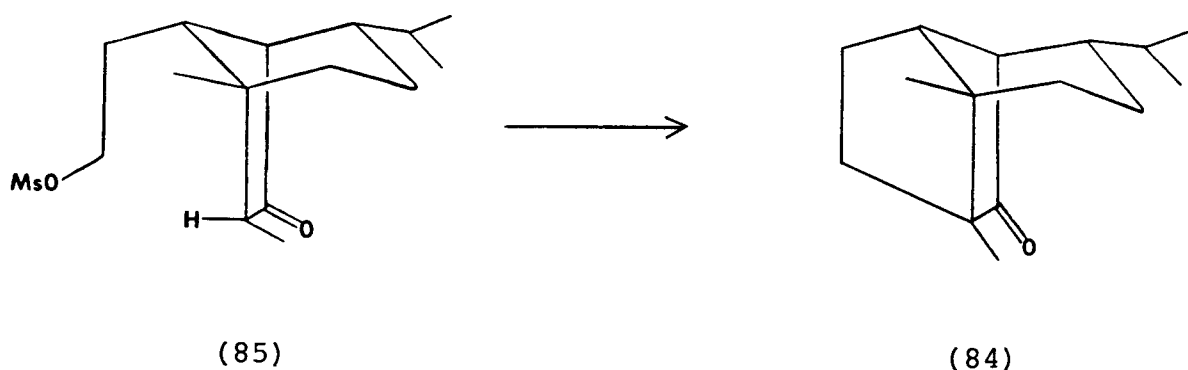
Accordingly, the tosylates (73) and (75) were each treated with
excess sodium bis(trimethylsilyl)amide in benzene at room temperature.
Both tosylates failed to undergo the desired reaction (tlc) at this
temperature (2 h) and, unfortunately, when the reaction mixtures were
heated to reflux (1 h) none of the desired tricyclic compound (74) was
isolated from either of the tosylates (73) or (75). Under these condi-
tions the starting materials were not recovered, however, and these
reactions led only to intractable material.

It was not clear why the desired tosylate (73) had failed to under-go the expected cyclization reaction to form compound (74). It appeared a priori that this system was, in fact, quite well suited to cyclize as proposed. An examination of a molecular model of (73), as well as geometric considerations[57], both failed to suggest any reason for our lack of success.

Examination of the ^{1}H nmr spectra of the tosylates (73) and (75) suggested that the tentative structural assignments were indeed correct. Thus, the spectra of these two compounds exhibited a potentially meaning-ful difference in the appearance of the resonances due to the protons attached at C_6. In compound (75), tentatively assigned as the undesired epimer, the proton at C_6 gave rise to a symmetrical six-line signal (ddd, J = 11, 11 and 5.5 Hz) at δ 4.78. This is a coupling pattern which is typical[58] of an axially orientated proton on a cyclohexane ring which is coupled to two adjacent axial protons (usually equally, as is the case here) and to one adjacent equatorial proton (in this instance at C_7). The diaxial couplings gave rise to two large splittings (approx-imately 11 Hz) and the axial-equatorial coupling produced a smaller splitting of 5.5 Hz. The ^{1}H nmr spectrum of (75) was thus consistent with the conformation of this material [cf. (75a)] which was predicted, on the basis of conformational analysis, to be the most stable chair-chair arrangement.[59]

(75a)
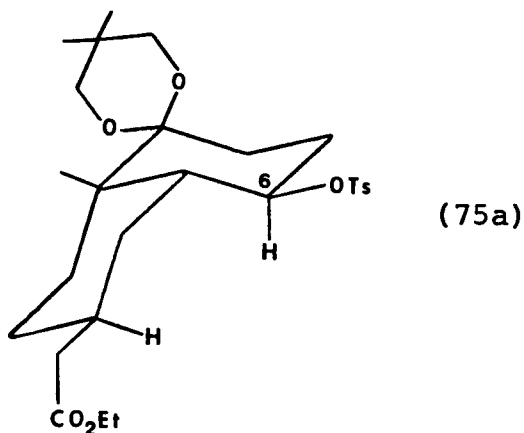
The epimeric material, compound (73), on the other hand, exhibited a broad ($w_{1/2}$ = 6 Hz), one-proton singlet at δ 4.49 due to the proton at C_6. The lack of similarity of this resonance with that of the corresponding proton in compound (75) strongly suggested that the conformations of these two materials were quite dissimilar. However, on the basis of conformational analysis, it was predicted that this material would exist preferentially in a conformation [cf. (73a)] that was very similar to that proposed for the isomeric material, compound (75). In this conformation one 1,3-diaxial interaction was present as opposed to three similar interactions in conformation (73b).

(73a)   (73b)
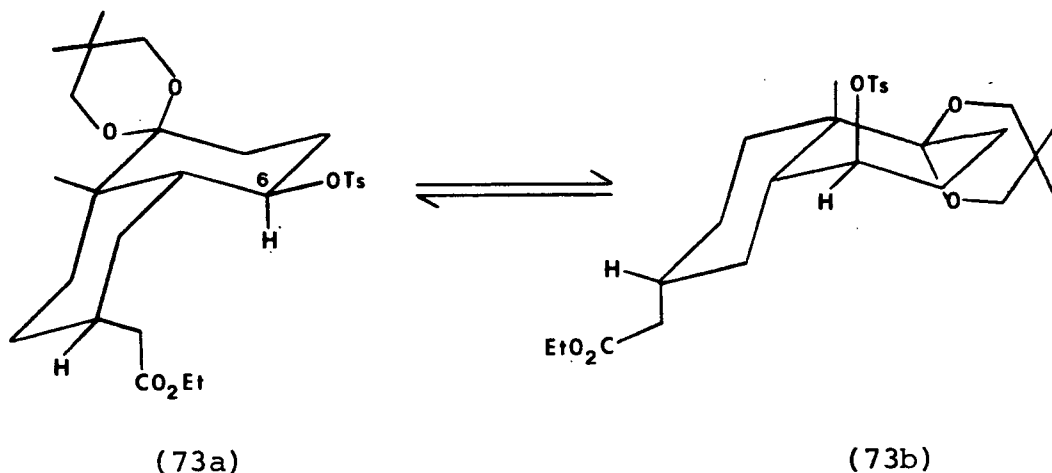
To complicate matters further, if compound (73) did, in fact, exist preferentially in a conformation resembling (73b), as the above data suggested, then it would be expected that the C_6 proton (which is equatorial in this case) would resonate at lower field than the corresponding proton (axially orientated) in compound (75).[58] In point of fact, the opposite was the case.

The ^{1}H nmr spectrum (270 MHz) of the ketal alcohol (78), tentatively assigned as possessing a β-oriented carboethoxymethyl group at

C_3, exhibited a resonance at $\delta 3.78$ due to the C_6 proton. This signal also appeared as a six-line multiplet (ddd, J = 10, 10 and 5.5 Hz) consistent with the resonance in the corresponding tosylate (75). In the epimeric alcohol (77), however, the C_6 proton (resonating at approximately $\delta 3.50$) was not separated (even at 270 MHz) from the resonances due to the ketal methylenes. Thus, although the shape of this resonance could not be observed, it did appear, as before, at higher field than the resonance due to the corresponding proton in the epimeric material (78).
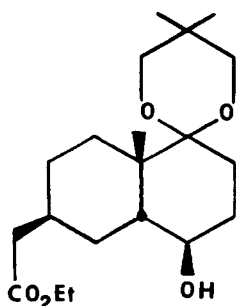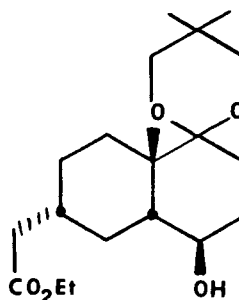
(78)   (77)

During the period of time that the attempted intramolecular cyclization reactions were being studied, another study of the tosylates (73) and (75) was being conducted. This investigation involved the study of the spin-lattice relaxation[60,61] rates of some selected protons in both the tosylates (73) and (75) conducted with the hope of gaining some insight concerning the conformational preferences of these materials, and of obtaining information regarding the tentative assignment of the stereochemistry at C_3. At this juncture a brief explanation of the phenomenon of spin-lattice relaxation is in order. A more detailed

discussion of this process, including the experimental procedure involved, has been published[60] and is beyond the scope of the present discussion.

The study of spin-lattice relaxation involves the excitation and subsequent transfer of energy (magnetic) between a given proton (or set of protons) which is being observed and the surrounding molecular lattice. The mechanism responsible for this relaxation (a "dipole-dipole" interaction) is such that it is dominated by interproton interactions. Thus, it is the nearest neighbour protons which are by far the largest contributors to the relaxation of a given proton. Since this effect is distance dependent, varying as the inverse sixth power of the distance between the nuclei, the protons which are in the closest proximity to each other relax most rapidly.

The experiment consists of the acquisition and subsequent analysis of a series of partially relaxed spectra from which the spin-lattice relaxation time (T_1-value) of a proton of interest may be measured. The values obtained from such measurements, proton T_1-values, reflect the environment and the orientation of a given proton with respect to its surrounding neighbours. These relaxation times have been shown to be sensitive to "through-space" interactions (in disaccharides) between protons of a given molecule which are separated from each other by several carbon atoms but are held in proximity to each other by virtue of molecular geometry.[62] Therefore, it is sometimes possible to obtain a direct measure of the relative spatial dispositions of protons on a given molecule and hence to deduce the geometry of the molecule in question. A rather simple example which demonstrates the use of this

technique is provided by the relaxation measurements performed on vinyl acetate (86).[63] The geminal protons (H_2 and H_3), which have the smallest internuclear separation, were found to relax much more rapidly than the vinylic proton H_1. In addition, H_2 relaxes more quickly than does H_3 due to the proximity of the former to H_1 (cis relationship).

(26.9 sec)   (86.2 sec)

$$H_2\diagdown C = C \diagup H_1$$

(35.8 sec)

(86)
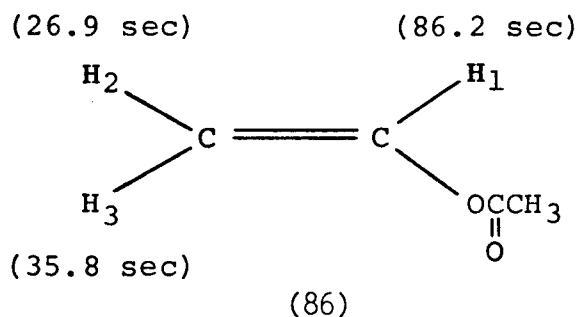
In the context of the work described in this thesis, it was felt that this technique could provide pertinent insight relating to the molecules which were tentatively assigned as the tosylates (73) and (75). In the expected preferred conformation of compound (75) [cf. (75a)], the rate of relaxation of the C_6 proton was expected to be influenced primarily by only the equatorially orientated (gauche relationship) proton at C_7. In the epimeric material (73), a quite different situation prevailed regardless of whether this compound existed preferentially in a conformation resembling (73a) or (73b). If this substance preferred a conformation like (73a), the C_6 proton would be held in close proximity to the methylene group α to the ester functionality. The latter protons would thus be expected to contribute substantially to the rate of relaxation experienced by C_6H. In the diastereomeric material (75) this mode of relaxation would not be available since the ester containing side chain (at C_3) would be positioned such that it

was a considerable distance from the entire B-ring.

If compound (73) preferred a conformation resembling (73b), on the other hand, the proton at C_6 would still be anticipated to undergo a more rapid rate of relaxation than the corresponding proton in (75). In this conformation the relaxation of the C_6 proton would be affected by three neighbouring protons (at C_5 and C_7), all of which are held in a gauche relationship to C_6H. Thus, regardless of the conformational disposition of compound (73), it was envisaged that the T_1-value measured for C_6H would be considerably smaller than that determined for the proton at C_6 in compound (75).

As a result of these considerations, it was hoped that it would be possible to establish whether or not our tentative stereochemical assignments for these compounds were in fact correct. The ^{1}H nmr spectrum (270 MHz) of each of the tosylates (73) and (75) exhibited a clearly distinguishable resonance for the proton at C_6. Thus, in each case, observation of this proton during the relaxation experiment[†] was straightforward. Unfortunately, the T_1-values determined for the C_6 protons in compounds (73) and (75) were, within the limits of experimental error, identical.

The failure of this technique to provide evidence which could aid in the differentiation between the epimers (73) and (75) was rather disappointing. However, while spin-lattice relaxation phenomena are usually interpretable in most relatively simple systems, often, in more complex compounds, there are many poorly understood interconnecting

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[†]These experiments were conducted by Dr. L.D. Colebrook, Concordia University,on sabbatical leave at the University of British Columbia.

relaxation pathways which can make a simple evaluation of the results quite difficult.

Since the studies discussed above did not result in the confirmation of the tentative assignments regarding the stereochemistry at C_3, another approach of a different tenor was developed to solve this quandary. It is well known that alkali metal-ammonia reductions of α,β-unsaturated carbonyl compounds produce, as a rule, the thermodynamically more stable product in those cases where two epimeric products are possible.[64,65] Although there are known exceptions[66,67] to this generalization, albeit very few, the vast majority of α,β-unsaturated carbonyl compounds which have been reduced with alkali metals in ammonia adhere to it.

On the basis of the foregoing information, it was anticipated that lithium-ammonia reduction[68] of the α,β-unsaturated ester (61) would produce the alcohol (89). Clearly, compound (89) [cf. (89a)] would be expected to be thermodynamically more stable than the epimeric material (90) [cf. (90a)] on the basis of conformational analysis. Compound

(89a)   (90a)
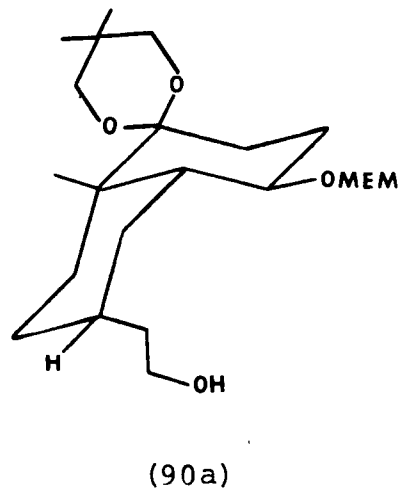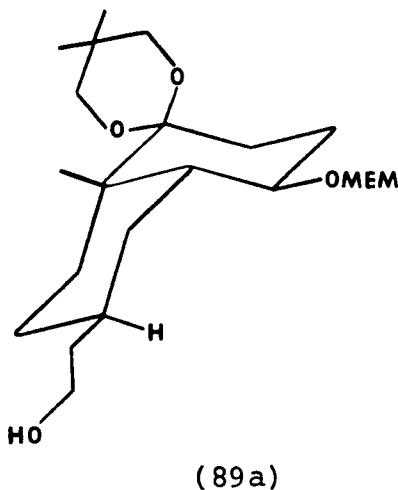
(89) should also be the product resulting from the reduction of the undesired saturated ester (76) with a suitable metal hydride reducing agent (e.g. lithium aluminum hydride).

(61)   (89)   (76)
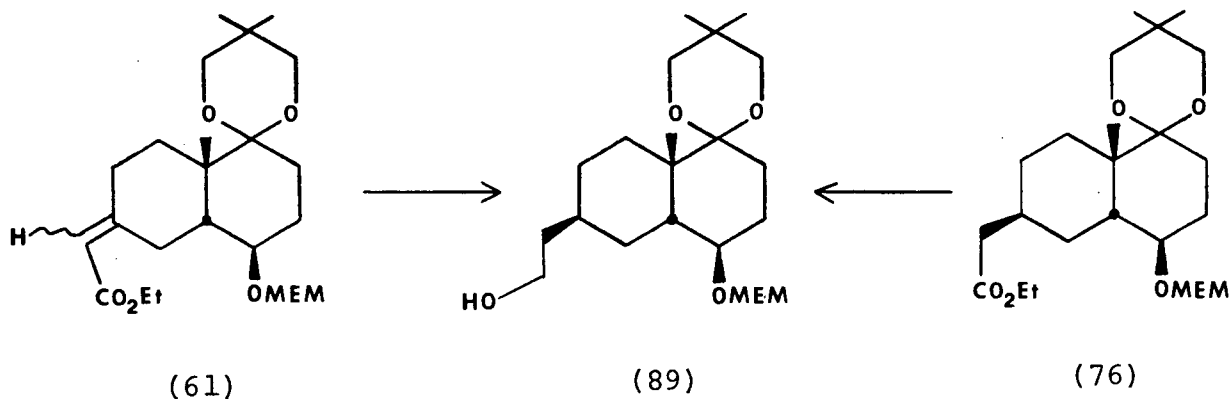
Conversely, the desired saturated ester (72) was expected to furnish the epimeric alcohol (90) upon reduction with a suitable metal hydride reagent. These conversions were thus expected to provide tangible evidence as to the tentative stereochemical assignments made for the epimeric saturated esters (72) and (76).

(72)   (90)
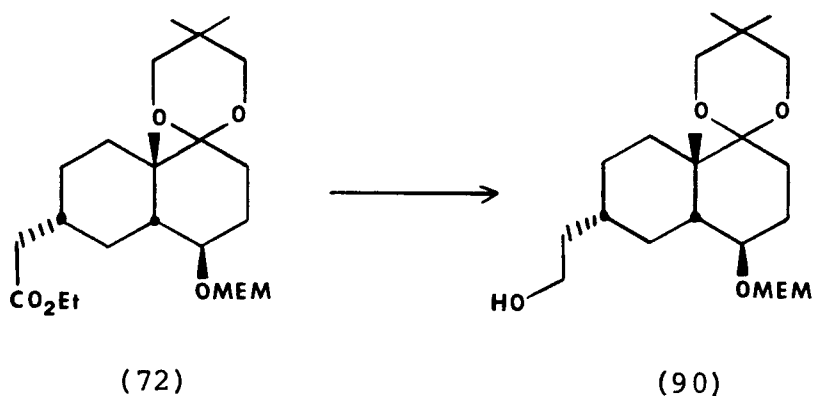
Reduction of compound (61) was accomplished by the treatment of a solution of this material (ammonia, ether and ethanol) with lithium

metal at -78 °C. A single product, alcohol (89), was obtained from the reaction mixture in 84% yield. This substance showed a broad hydroxyl group absorption at 3480 cm^{-1} in its ir spectrum. The ^{1}H nmr spectrum of this material exhibited a broad, one-proton singlet at δ 2.12 (hydroxyl proton) and demonstrated the absence of olefinic protons and of all the resonances due to the ethyl ester moiety. The three tertiary methyl groups gave rise to signals at δ 0.68 (three-proton singlet) and at δ 1.15 (six-proton singlet).

Treatment of the saturated ester (76) with lithium aluminum hydride in anhydrous ether (-78 °C, 1 h) afforded the alcohol (89) as the sole product of the reduction (99%). This material was identical in all respects with the compound isolated (as described above) from the lithium-ammonia-ethanol reduction of the α,β-unsaturated ester (61).

Reduction of the saturated ester (72), under conditions similar to those outlined above (lithium aluminum hydride, ether, -78 °C), gave the epimeric alcohol (90) as a colorless gum (100%). The spectral data obtained from this substance clearly showed that this material was different from the alcohol (89). Infrared analysis of this material showed a broad hydroxyl group absorption at 3490 cm^{-1} and, in the ^{1}H nmr spectrum, the angular methyl group gave rise to a three-proton singlet at δ 1.04.

The results described above provided ample evidence for the fact that the tentative assignments made for the structure of the saturated esters (72) and (76) (vide supra) were, in fact, correct. These compounds were further characterized by their conversion into the keto ethers (92) and (91), whose preparations are outlined below.

Acid-catalyzed hydrolysis of the saturated ester (72) with 1N hydrochloric acid in acetone (ambient temperature, 1 h) afforded the keto ether (92) (77%). The ir spectrum of this material (purified by preparative tlc) showed the presence of both an ester group and a keto functionality (1732 and 1705 cm^{-1}, respectively). As expected, the ^{1}H nmr spectrum of compound (92) revealed only one tertiary methyl resonance, a three-proton singlet at δ 1.35 (angular methyl group). The MEM ether protons (-OCH$_2$CH$_2$O-) and C$_6$H gave rise to a complex multiplet between δ 3.48 and 3.86.

(72)   (92)
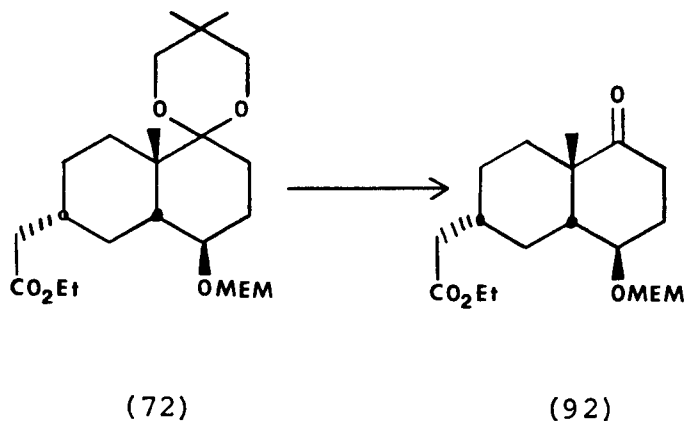
Hydrolysis of the saturated ester (76), under conditions identical with those described above (1N hydrochloric acid-acetone, room temperature, 1 h), yielded the keto ether (91) (82%) as the sole product. The ir spectrum of the latter compound showed absorptions at 1730 (ester carbonyl group) and at 1708 cm^{-1} (keto functionality). In its ^{1}H nmr spectrum, compound (91) exhibited a resonance due to the angular methyl group at δ 1.21 (a three-proton singlet). The proton attached to C$_6$ produced a signal at δ 4.16 which was coincident with the two-proton

quartet (J = 7 Hz) due to the methylene group of the ethyl ester func-
tionality.

(76)   (91)
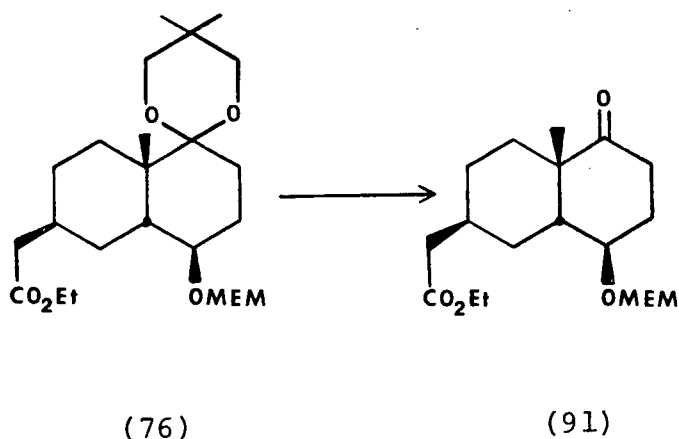
At this point, the focus of our attention was directed once again
toward the hydrogenation of the α,β-unsaturated ester (61). As men-
tioned previously, the hydrogenation of (61) using platinum oxide as
catalyst in ethyl acetate afforded a disappointingly low ratio of the
desired saturated ester (72) to the epimeric compound (76) (6:4, respec-
tively). Somewhat unexpectedly, variation of the reaction conditions
(catalyst, solvent, hydrogen pressure and temperature) failed to improve
this ratio by more than approximately 10%. A fairly wide variety of
combinations of catalysts (10% palladium-on-carbon, platinum oxide, 5%
palladium-on-barium sulfate, tris(triphenylphosphine)rhodium chloride,
5% ruthenium-on-alumina) and solvents (ethyl acetate, hexane, ethanol,
5% potassium hydroxide in ethanol, cyclohexane, benzene, tetrahydro-
furan and 8% triethylamine in tetrahydrofuran) were evaluated. Varia-
tions of both the ratio of catalyst to substrate, as well as substrate
concentration, failed to alter the product distribution significantly.
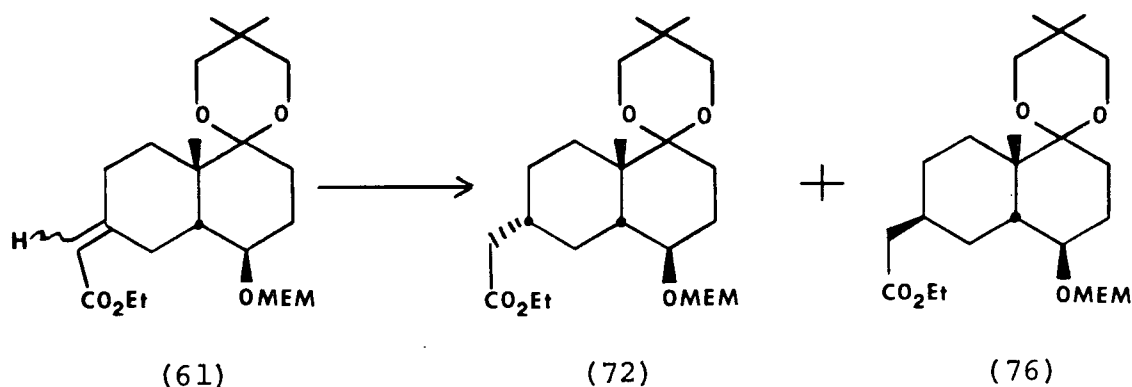
The conditions which were found to be the most selective (determined by glc) were 5% palladium-on-barium sulfate in hexane (atmospheric pressure, ambient temperature) which provided (72) and (76) in a ratio of 34:66, respectively, and 5% ruthenium-on-alumina in ethanol containing 5% potassium hydroxide (atmospheric pressure, ambient temperature) which afforded (72) and (76) in a ratio of 69:31, respectively. In practice, however, the conditions which were used routinely were platinum oxide in tetrahydrofuran (50 psi, ambient temperature), since these conditions provided a ratio [(72):(76) = 66:34] similar to that obtained in the ruthenium catalyzed case and the catalyst was more readily available.

Interestingly, it was found that under the finally chosen conditions (platinum oxide, tetrahydrofuran, 50 psi), one of the geometric isomers of (61), obtained as a pure solid by fractional crystallization of the mixture of isomers (vide supra), afforded the saturated esters (72) and (76) in a ratio of 85:15, respectively. Thus, for some obscure

reason(s), one geometric isomer of (61) was more accessible to hetero-
geneously catalyzed hydrogenation from the α face than was the other
geometric isomer. By inference, the latter material displayed virtually
no selectivity when hydrogenated under the aforementioned conditions.

During the course of these studies a major complication became
evident. It was found that only selected batches of catalyst (platinum
oxide) gave rise to reproducible hydrogenation of compound (61). With
other lots, varying degrees of side product formation occurred. The
major side product formed in these reactions was the keto ether (92)
which appeared to result from ketal cleavage of the desired saturated
ester (72) under the hydrogenation conditions. The epimeric (and un-
desired) saturated ester (76), seldom underwent noticeable decomposition
even under reaction conditions in which the desired saturated ester
(72) was almost entirely converted into compound (92). A satisfactory
explanation for this rather unusual behavior was not found.

Another attempt to increase the efficiency of the production of the
desired saturated ester (72) was carried out as follows. It was hoped
that the preparation and subsequent hydrogenation of the endocyclic
olefins (93) and (94) might give rise to a greater proportion of the
desired material (72) than that obtained from compound (61).

Thus, a mixture of these compounds, which were inseparable by glc
and tlc, was prepared by the treatment of the α,β-unsaturated ester
(61) (a 1:1 mixture of isomers) with a 1:1 complex of lithium diisopro-
pylamide and hexamethylphosphoramide (-78 °C, 1.25 h) in tetrahydro-
furan[69], followed by protonation of the resultant mixture of enolate
anions. Purification of the resulting crude product by preparative tlc

gave (62% yield) the olefins (93) and (94), in a ratio of approximately

3:1, respectively. The major product was tentatively assigned structure

(93). This assignment was based on literature precedent[70,71,72] and

also on the observation that the protons on C_2 would be kinetically more

acidic than those on C_4. This was believed to be the case since the

latter protons were judged to be considerably more hindered than those

attached to C_2.

(61)   (93)   (94)
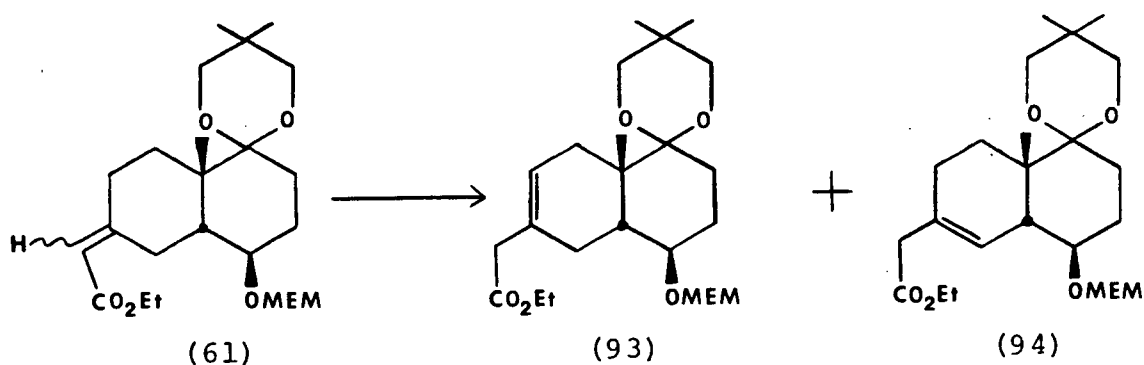
Interestingly, treatment of one of the geometric isomers of (61)

(vide supra) with lithium diisopropylamide-hexamethylphosphoramide,

under conditions identical with those outlined above, afforded the

olefin (93) as the sole product (80% yield). The ir spectrum of this

material showed an absorption due to a saturated ester group at 1730

cm^{-1}. In the ^1H nmr spectrum the protons α to the ester functionality

appeared as a two-proton singlet ($\delta 2.94$) and the olefinic proton pro-

duced a broad, one-proton resonance at $\delta 5.49$.

The hydrogenation (platinum oxide, tetrahydrofuran) of either the

mixture of olefins (93) and (94), or compound (93) alone, was substan-

tially slower than the hydrogenation of compound (61) under similar

conditions. Analysis of the crude material isolated from these reactions (glc, tlc) showed that the saturated esters (72) and (76) were formed in a ratio of approximately 1:1. These products were accompanied by several, more polar side products.

The lack of pronounced stereoselectivity encountered in the hydrogenation reactions described in this section was rather disappointing. These results tended to suggest that the β face (convex side) of the α,β-unsaturated ester (61), as well as the olefins (93) and (94), were somewhat more hindered than was anticipated a priori. An alternative rationalization, however, is perhaps worthy of consideration. It is conceivable that an attractive ("haptophilic")[73] interaction between the MEM ether moiety[†] and the surface of the catalyst may have altered the expected course of the hydrogenation reaction. Thus, if the MEM ether group was "held" on the catalysts surface in such a fashion so as to allow hydrogen (adsorbed on the surface of the catalyst) to attack the olefin from the concave side (α face) of the molecule, then the undesired saturated ester (76) would be produced.

This type of interaction has previously been proposed as a rationalization for anomalous ("contra-steric") hydrogenation results in other systems.[75,76] For example, McMurry[77] found that while the hydrogenation

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[†] It is of passing interest to note that the MEM ether moiety has been found to exert powerful (and unusual) directing effects on the stereochemistry of some carbonyl reductions.[74]

(platinum oxide) of compound (87) occurred exclusively from the less
hindered side of the molecule, the corresponding alcohol (88) produced a
mixture of products (55:45) favoring the addition of hydrogen from the
more hindered side of the molecule.
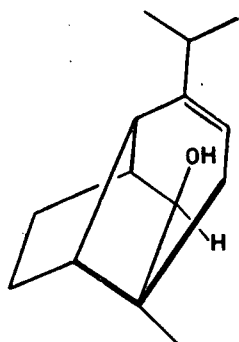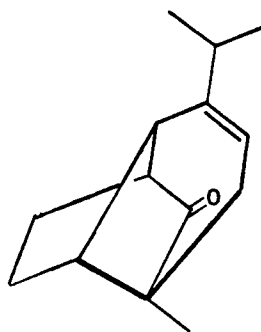
(88)   (87)

V. Attempted Synthesis of the Tricyclic Ketone (12) via Intramolecular Cyclization

The synthetic scheme envisaged for the conversion of the saturated
ester (72) into the tricyclic ketone (12) is illustrated in Scheme 5.
Dialkylation of compound (72) should afford the α,α-dimethyl ester (95)
which, in turn, was to be transformed into the amino compound (13) (R' =
MEM) by the saponification of (95), followed by subjection of the
resultant acid to a Curtius reaction[20]. Compound (13) would then be
converted into the corresponding tosylate, after cleaving the MEM ether
moiety, and subsequently cyclized and deprotected to afford the tri-
cyclic system (12).

(72)   →   (95)

(12)   ←   (13)
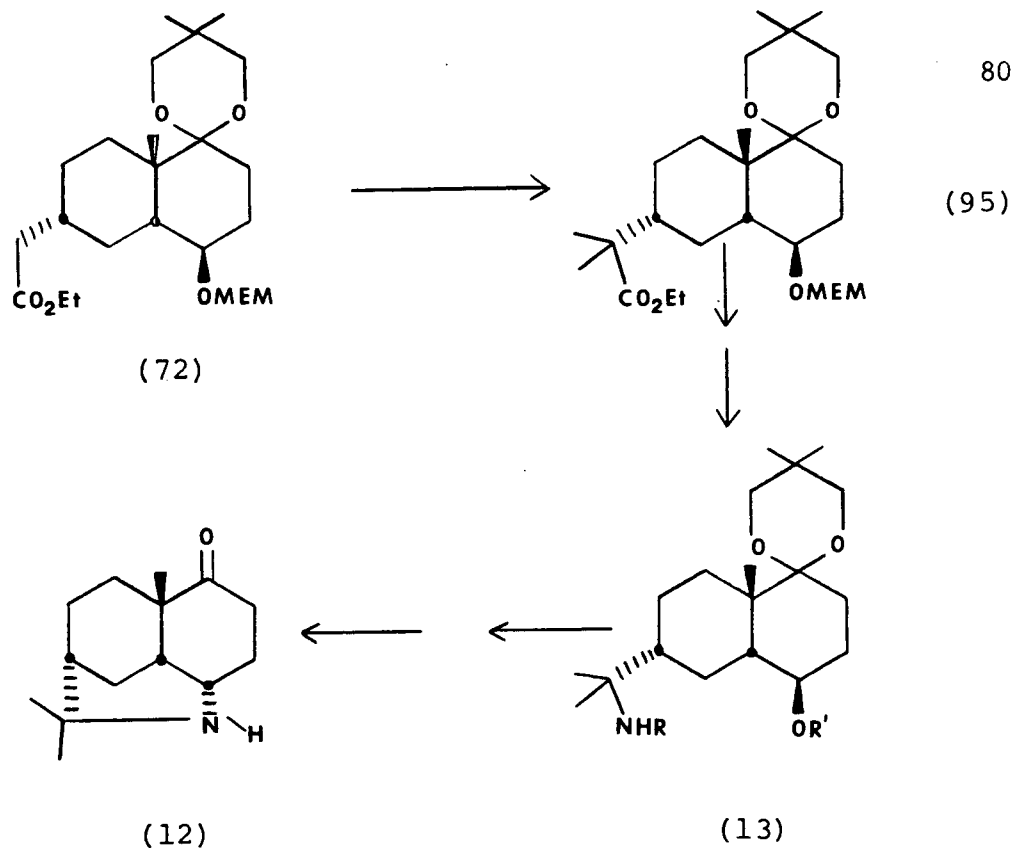
SCHEME 5

However, at this stage another possible synthetic approach to the dialkylated ester (95), employing the α,β-unsaturated ester (61) as starting material, was considered. Schlessinger et al had demonstrated that the deconjugative alkylation of α,β-unsaturated esters, producing α,α-dialkyl-β,γ-unsaturated esters, often proceeds in excellent yields.[69] For example, ethyl crotonate (96) afforded (94% overall) the dialkylated material (97) employing this methodology.

(96)   →   (97)
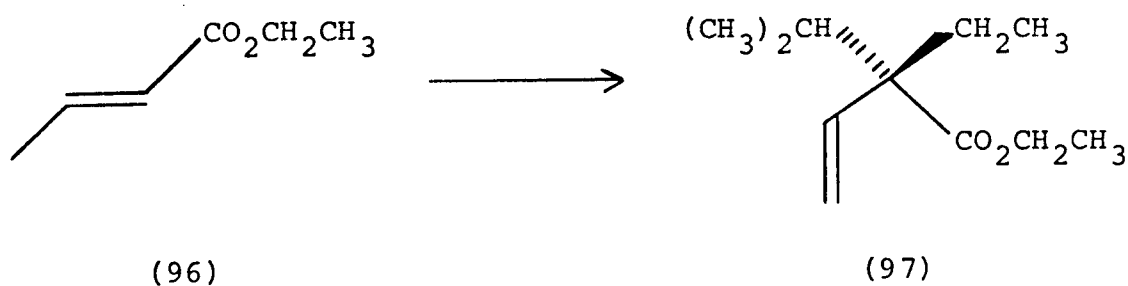
Thus, it was anticipated that the α,β-unsaturated ester (61) could be transformed into the α,α-dimethyl-β,γ-unsaturated compound (98) [and/or (99)]. This substance, it was hoped, could then be hydrogenated to produce the desired dialkylated ester (95). This methodology potentially provided both simplicity as well as an opportunity to attempt to increase the stereoselectivity of the production of the desired epimer (α face at C_3) in the hydrogenation step.

Accordingly, the α,β-unsaturated ester (61) was treated successively with two equivalents of lithium diisopropylamide-hexamethylphosphoramide complex and excess methyl iodide (tetrahydrofuran, -78 °C to 0 °C). The crude product was purified by preparative tlc giving, in low yield, what appeared to be a mixture of the monoalkylated compounds (100) and (101). This mixture was treated under conditions similar to those

(61)   (98)   +   (99)

(95)
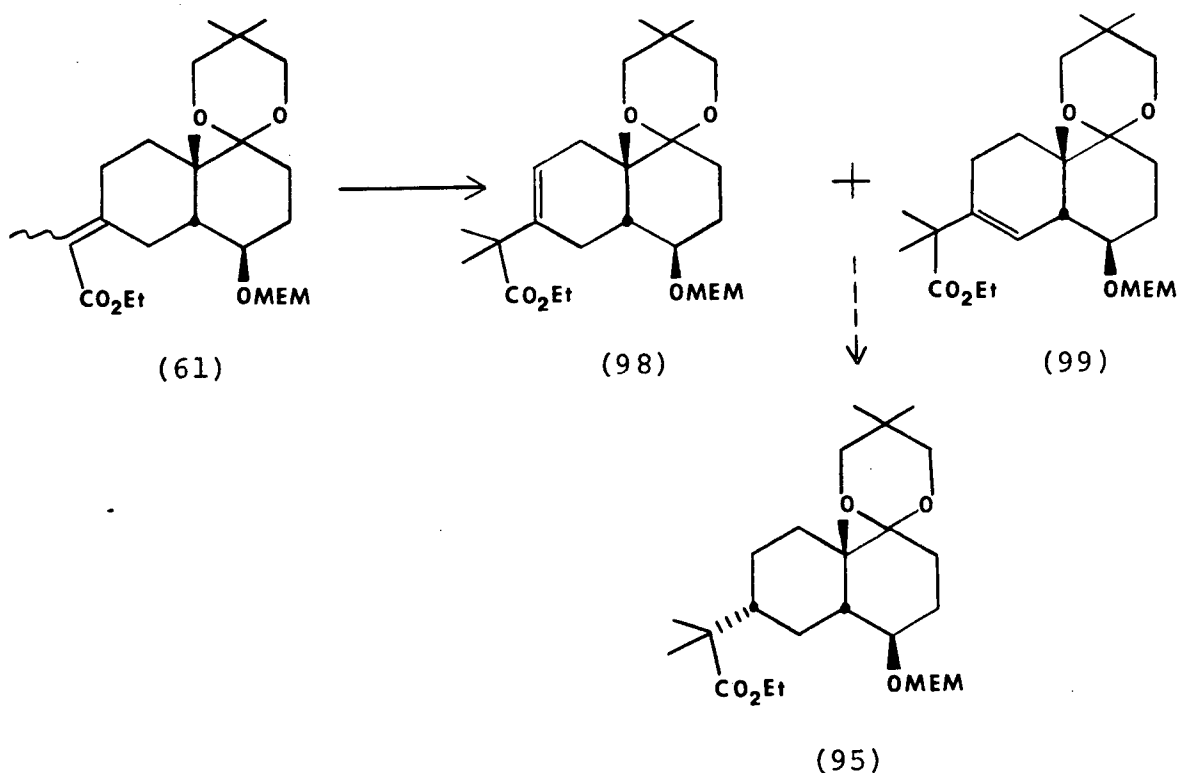
described above affording (62% yield) the desired dialkylated system as a mixture of compounds (98) and (99) (approximately 5:1 ratio). These compounds were indistinguishable on the basis of their respective spectral data.

(100)   (101)
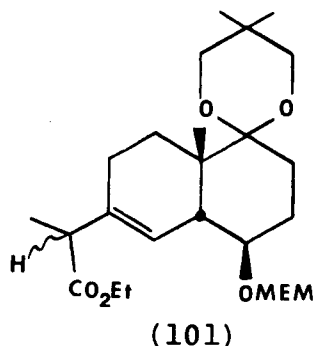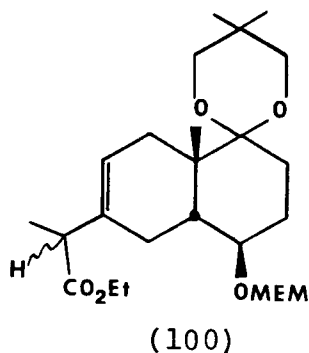
Unfortunately, in our hands all attempts to hydrogenate this mixture resulted only in the recovery of the starting material. Presumably, with the additional steric encumbrance due to the geminal dimethyl groups on the side chain, the endocyclic double bond was effectively inert to hydrogenation under the conditions employed.

This possible route toward the dialkylated ester (95) was not investigated further, in part because the overall yield of the alkylation procedure was low. In addition, the failure of these compounds to undergo hydrogenation precluded further studies in this direction.

At this juncture, it was decided to return to the original plan for the synthesis of the dialkylated material (95). This transformation was accomplished as follows. Treatment of the saturated ester (72) with excess lithium diisopropylamide (tetrahydrofuran, -78 °C, 1 h), followed by methyl iodide in hexamethylphosphoramide (-20 °C, 30 min; 0 °C, 30 min), afforded the dialkylated ester (95) in essentially quantitative

yield. The ir spectrum of this substance showed an absorption at 1725 cm^{-1} due to the ester carbonyl group. Five tertiary methyl groups were evident in the ^1H nmr spectrum, three as three-proton singlets (δ 0.70, 1.05 and 1.18) and the remaining two as a six-proton singlet at δ 1.07.

Attempts to saponify the dialkylated ester (95) with 1N potassium hydroxide in methanol (52 h, reflux) were unsuccessful and the starting material was recovered quantitatively. Several other methods aimed at producing the dialkylated acid (102) were also investigated. These included the use of potassium tert-butoxide in ether-water solution[78] (ambient temperature, 15 h) and treatment of (95) with lithium thio-methoxide in hexamethylphosphoramide[79] (80 °C, 2 h), both of which have been used in the past to cleave hindered esters. In our hands neither of these methods produced the desired product (102) in any appreciable quantity.
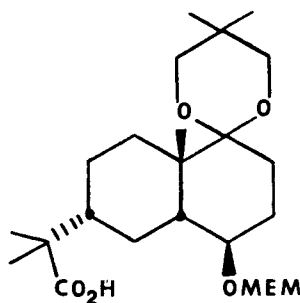
(102)

When the dialkylated ester (95) was treated with potassium tert-butoxide in dry dimethyl sulfoxide[80] (ambient temperature, 1.75 h), however, all the starting material disappeared with the concomitant formation of a very polar product (baseline by tlc). Neutralization of the reaction mixture (0.25 N hydrochloric acid), followed by routine aqueous work-up, afforded only the keto acid (103), in moderate yield.

This material displayed a broad absorption (3400-2450 cm^{-1}) in its ir

spectrum due to the carboxylic acid functionality. That the ketal group

had been removed under these conditions was substantiated by the ^{1}H nmr

spectrum of (103) which showed only three tertiary methyl signals at δ 1.08,

1.11 and 1.35 (angular methyl).

(95)   (103)
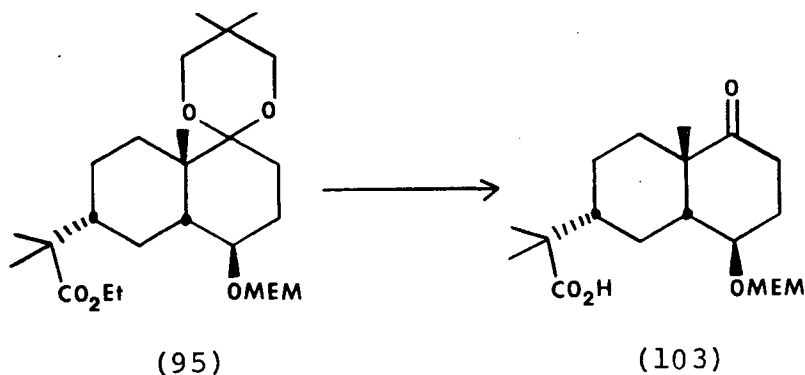
Clearly, the ketal cleavage must have occurred during the neutral-

ization step since the hydrolysis conditions used were quite basic in

nature. After considerable experimentation, it was found that if the

neutralization was performed under different conditions than those

described above, the desired carboxylic acid (102), mp 124-125 °C, was

obtained in a yield of 88%. These conditions entailed cooling (0 °C)

the reaction mixture, followed by the neutralization of the excess base

through the portion-wise addition of acidic ion exchange resin. The

resulting cold suspension was then immediately filtered to remove the

acidic exchange resin. Under these conditions, there was no detectable

ketal cleavage.

In the ir spectrum of the carboxylic acid (102), the carboxylic

acid functionality gave rise to absorptions at 3450-2400 (broad) and at

1695 cm^{-1}. The ^{1}H nmr spectrum of this material displayed signals

accounting for five tertiary methyl groups as three 3-proton singlets

(δ 0.70, 1.06 and 1.18) and one six-proton singlet at δ 1.11.

The elaboration of the carboxylic acid (102) into the nitrogen containing material (13) (see Scheme 5) was to be attempted through the use of a Curtius degradation sequence[20] or a related modification thereof.[81,82] Thus, the plan involved the conversion of the carboxylic acid (102) into the corresponding isocyanate (106), via the intermediacy of the acid chloride (104) and the acyl azide (105), as indicated in the accompanying equation.

(102)

(104)

(106)

(105)
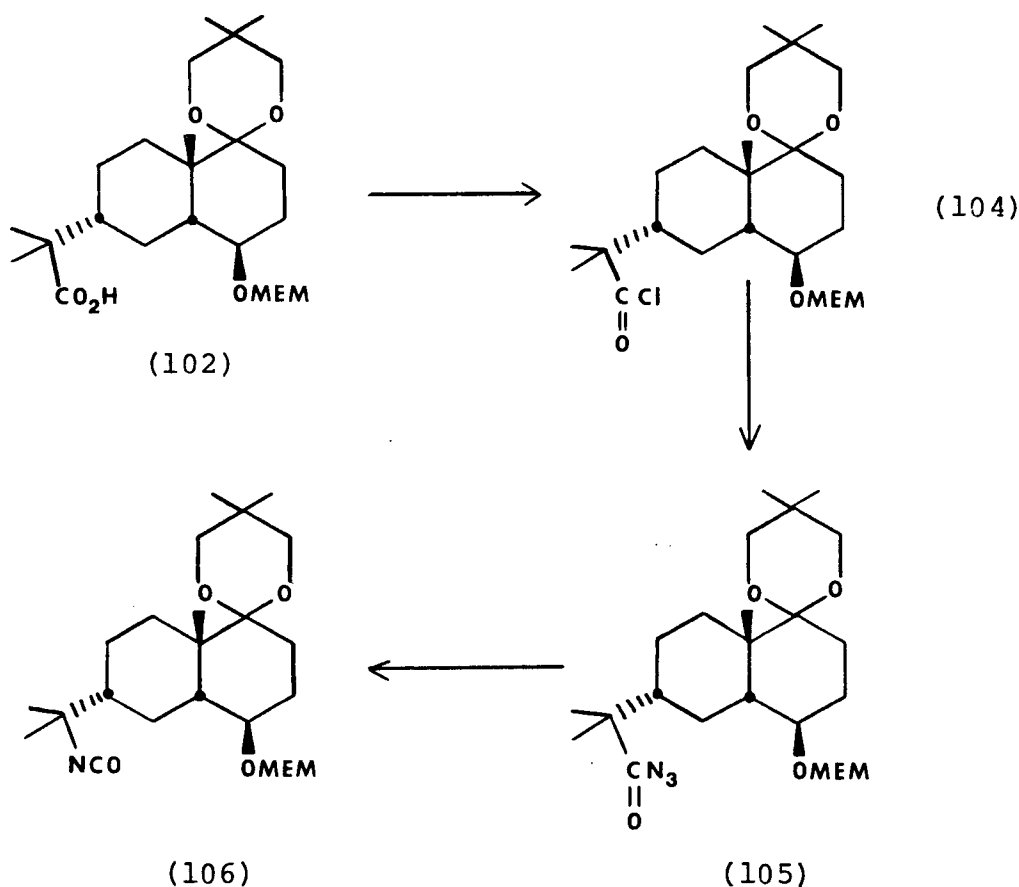
The first step of this proposed sequence involved the formation of

the acid chloride (104). Acid chlorides may be prepared from the parent acid in a variety of ways. Reagents such as thionyl chloride[83] and phosphorus pentachloride[84] have largely been replaced by reagents requiring less vigorous reaction conditions such as triphenylphosphine-carbon tetrachloride[85], phosgene[86], and oxalyl chloride[87]. The latter reagent was chosen for our purposes since the yield of acid chloride produced using the reagent is often very good and, since the gaseous biproducts formed (carbon monoxide and carbon dioxide) leave the reaction mixture, the equilibrium is driven to the side of the desired acyl chloride.

Oxalyl chloride may be used to form acid chlorides in a number of different ways. These involve the use of the reagent alone[88,89] in a solution (usually benzene) containing the given acid or in the presence of pyridine in a solution containing either the parent acid[89,90] or its sodium[91,92] or potassium[93] salt.

In the case of the carboxylic acid (102), the use of oxalyl chloride alone was avoided due to the inherently acidic nature of this method and the incompatibility of compound (102) with even traces of acid. However, even the reaction of this reagent with the latter compound in the presence of pyridine (ambient temperature, 3 h), afforded the desired acyl chloride (104) in only moderate yield. Infrared analysis of the crude product demonstrated the presence of unreacted starting material (102) (3300-2450 and 1700 cm^{-1}), as well as the desired acid chloride (1785 cm^{-1}). This material was subsequently allowed to react with sodium azide (0 °C, 1.5 h) in acetone-water and the resulting product, which showed an acyl azide absorption at 2155 cm^{-1} in the ir

spectrum, was then refluxed (2 h) in benzene. The crude material thus obtained was a mixture of several products (tlc). This mixture contained some material possessing an isocyanate functionality (ir absorption at 2280 cm^{-1}). However, the presence of carbonyl containing material was also indicated (broad ir band at 1700-1780 cm^{-1}). Attempts to trap the isocyanate (106), assumed to be present in the mixture (ir analysis), by reaction with methyl lithium[94,95] (0 °C, 10 min) led only to intractable material.

The sodium salt of compound (102) [obtained from aqueous sodium hydroxide (1 equivalent) by lyophilization] was treated with oxalyl chloride (benzene) containing a small amount of pyridine and the material thus obtained was allowed to react with sodium azide (as above). A solution of the resultant crude product in benzene was refluxed (3 h), producing a mixture quite similar to that described above (tlc, ir).

Since the preparation of the acid chloride (104), and subsequently the isocyanate (106), was not being accomplished efficiently under the conditions outlined above, some alternative procedures were investigated. The first of these involved the attempted conversion of the silyl ester (107) into the desired acyl chloride (104). Wissner et al had recently reported[96] the synthesis of acid chlorides from the corresponding tert-butyldimethylsilyl esters, in excellent yields, using a complex of oxalyl chloride and dimethylformamide.

Accordingly, the silyl ester (107) was prepared (99% yield) from the carboxylic acid (102) via treatment of the latter compound with tert-butyldimethylsilyl chloride in dry dimethylformamide containing

imidazole (60 °C, 17 h). Compound (107) displayed a carboxyl group absorption at 1715 cm^{-1} in its ir spectrum. In the ^{1}H nmr spectrum, this substance exhibited resonances at δ 0.26 (six-proton singlet) and at δ 0.95 (nine-proton singlet) due to the methyl groups and the tert-- butyl group, respectively, attached to the silicon atom.

(107)
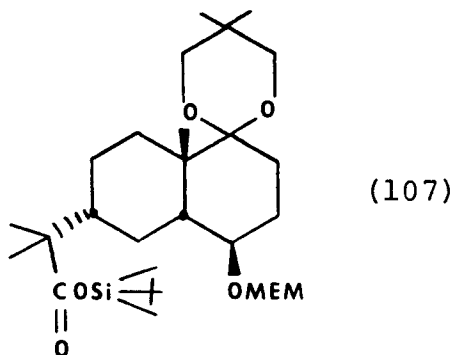
This material was allowed to react with dimethylformamide-oxalyl chloride (room temperature, 3 h) in methylene chloride and the resultant material was treated with excess sodium azide (ambient temperature, 3.5 h) in acetone. The crude product isolated from this reaction showed a weak azide absorption at 2150 cm^{-1} in the ir spectrum. Unfortunately, when this material was refluxed in xylene (2.5 h) several products were formed (tlc). The ir spectrum of the crude material showed the disappearance of the azide band and the appearance of a weak isocyanate absorption (2275 cm^{-1}) but also exhibited a strong carbonyl absorption at 1710 cm^{-1}.

Since the synthesis of the acyl chloride (104), by any of the methods outlined above, was not being accomplished efficiently, the preparation of the hydrazide (108) was attempted. It is well known that hydrazides may be converted into the corresponding acyl azides by the treatment of the former substances with sodium nitrite (or an organic

nitrite) in acidic solutions.[97] Alternatively, azides may be prepared

from hydrazides through the treatment of the latter materials with

nitrosyl chloride at low temperature.[98] In the context of these syn-

thetic studies, it was clear that due to the sensitivity of the inter-

mediate compounds to acidic conditions, only the latter methodology was

appropriate. This type of sequence has recently been used[99] to advan-

tage in preparing azides in other acid sensitive molecules.

(95)   (108)
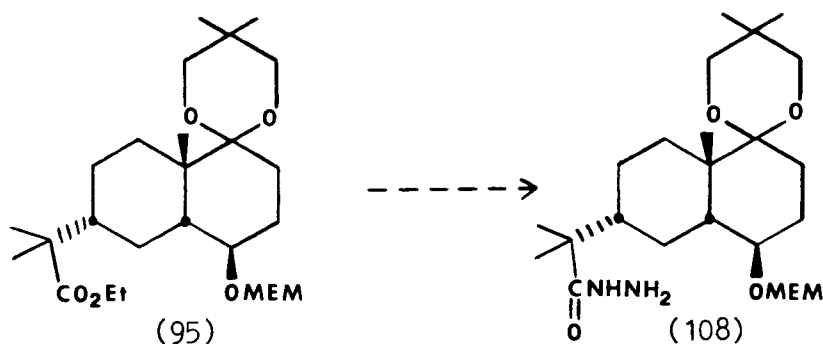
Thus, it was felt that the preparation of the hydrazide (108),

potentially available from the dialkylated ester (95), would provide an

alternative route to the desired azide (105). Unfortunately, subjection

of the dialkylated ester (95) to hydrazinolysis conditions (excess

anhydrous hydrazine in methanol, ambient temperature, 90 h) resulted

only in the recovery of the starting material. Even at elevated temp-

eratures (65 °C, 24 h) compound (95) failed to undergo the desired

transformation. Although the preparation of hydrazides is usually an

uncomplicated process, in this case, perhaps due to the hindered nature

of the ester carbonyl (vide supra), the starting material was inert

under the given reaction conditions.

Another approach which was briefly investigated involved the

attempted preparation of the isocyanate (106) from the mixed anhydride

(109). Weinstock[100] developed this modification of the Curtius reaction

explicitly for use with acid sensitive substrates. In a recent modi-

fication of this method, Overman et al[101] prepared a series of sensitive

N-acylamino-1,3-dienes in good overall yield.

CO₂Et OMEM	COCOEt OMEM ‖ ‖ O O	NCO OMEM
(102)	(109)	(106)
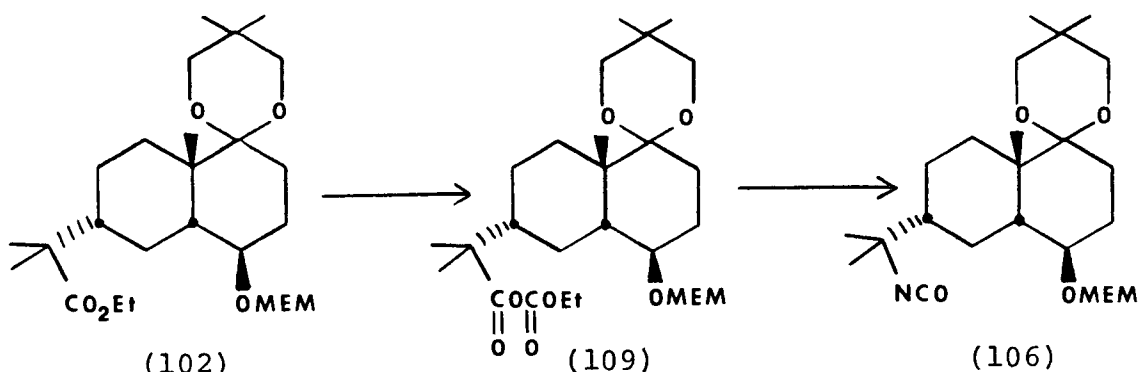
Thus, the carboxylic acid (102) was treated with ethyl chloro-

formate and N,N-diisopropylamine in acetone (0 °C, 5 h) and the resul-

tant material was treated with excess sodium azide in acetone-water

(ambient temperature, 20 h). The crude mixture thus obtained was dis-

solved in dry p-xylene and the solution was refluxed (3 h). Examin-

ation of the crude product by ir spectral analysis showed that it con-

tained both an isocyanate moiety (ir absorption at 2280 cm^{-1}) and a

carbonyl group (ir absorption at approximately 1705 cm^{-1}). By tlc, this

material was found to contain a considerable amount of the starting

material (102).

Although the presence of recovered starting material (102) in the

crude product could be due simply to its incomplete reaction, it was

suspected that this material resulted from the attack of azide ion at

the "wrong" carbonyl of the mixed anhydride (109). Mixed anhydrides of

this type predominantly react with nucleophiles (e.g. azide ion) at the

more reactive carbonyl group (labelled α) originating from the parent

acid. In the case of compound (109), however, this centre was ster-
ically very hindered due to the presence of the adjacent geminal methyl
groups. It was felt that this arrangement could tend to discourage
nucleophilic attack at this carbonyl group. Attack of azide ion at the
other carbonyl group (β) would generate the carboxylate of (102) which
would be expected to protonate during work-up regenerating the starting
material (102).

$$
\begin{array}{ccccccc}
 & O & & O & & & \\
 & \| & & \| & & & \\
R & C & O & C & O & R' \\
 & \alpha & & \beta & & &
\end{array}
$$
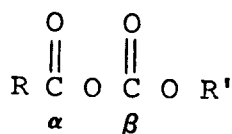
Another modification of the Curtius reaction, reported by Yamada
and co-workers[102] in 1972, made use of a novel reagent, diphenylphos-
phoryl azide. Yamada demonstrated that, with this reagent, the direct

$$
\begin{array}{c}
C_6H_5O \\
 \diagdown \quad \overset{O}{\underset{\uparrow}{P}} - N_3 \\
C_6H_5O \diagup
\end{array}
$$
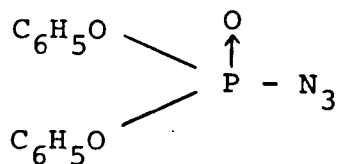
transformation of a carboxylic acid to a carbamate (urethane) was possible.
For example, benzoic acid (110) was converted into the corresponding
tert-butyl carbamate (111) in a yield of 74%.

(110)   (111)
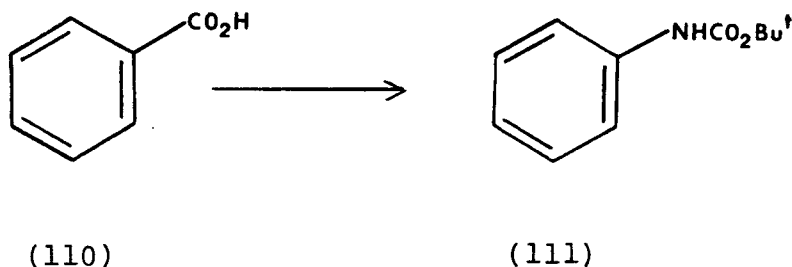
This method was experimentally far less complex than the standard
Curtius reaction and it provided the given amine as the carbamate deriva-
tive.[103] For the purposes of the synthetic scheme under investigation
here, the latter attribute of this technique was of considerable impor-
tance.   According to the synthetic plan (see Scheme 5), the tosylate
derivative (13) (R' = Ts) was to be prepared from the corresponding MEM
ether (R' = MEM) via cleavage of the ether protecting group followed by
the tosylation of the resulting alcohol (R' = H). Obviously, the selec-
tive tosylation of the alcohol, in the presence of a free amine (R = H),
could prove to be quite difficult if not impossible.   It is also per-
tinent to note that Yamada's procedure was conducted under essentially
neutral conditions and thus it was expected that both the acid sensitive
MEM ether group and the extremely acid labile ketal functionality of
compound (102) would survive these reaction conditions.
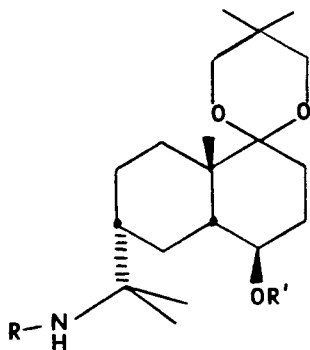
(13)

In order to determine whether or not this was the case, it was decided to treat the carboxylic acid (112) with Yamada's reagent. In this way, the compatibility of the reaction conditions with the ketal group and the MEM ether functionality could be evaluated on an expendable compound which was formally available (via saponification) from the "undesired" saturated ester (76).

(76)   (112)   (113)
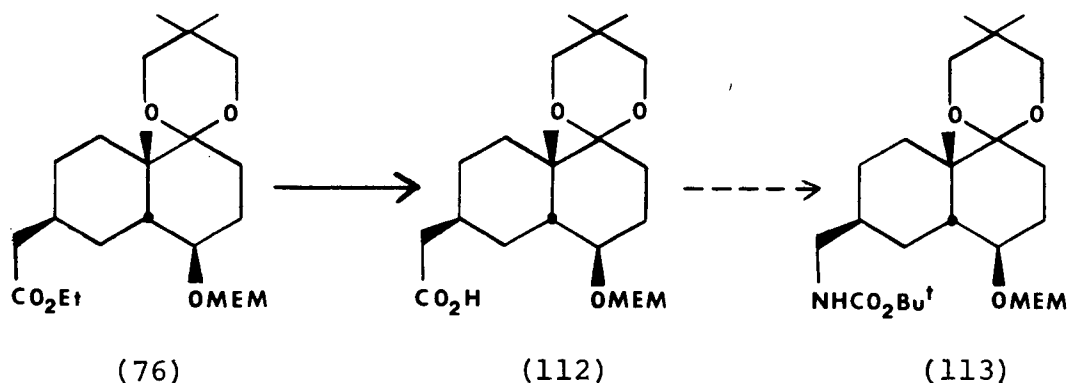
Accordingly, the saturated ester (76) was treated with 1N potassium hydroxide in methanol (reflux, 2 h) furnishing the carboxylic acid (112) in 54% yield. That this material contained a carboxylic acid functionality was shown by a broad absorption between 3500 and 2390 cm^{-1} (hydroxyl group) and by a sharp signal at 1713 cm^{-1} (carbonyl group) in the ir spectrum. The ^1H nmr spectrum of this substance demonstrated the absence of an ester functionality and exhibited a broad, one-proton singlet (δ 8.78-9.20) for the carboxylic acid proton.

The carboxylic acid (112) was allowed to react with freshly distilled diphenylphosphoryl azide[†] and triethylamine in dry tert-butyl alcohol (relux, 18 h). Purification of the crude product by preparative

---

[†]Prepared from diphenyl phosphorochloridate and sodium azide, bp 170 °C (0.8 mm) [lit.[102] bp 157 °C (0.17 mm)]. This material slowly discolors when stored at ambient temperature.

tlc gave the tert-butyl ester (114) (19%) and an inseparable mixture (approximately 40%) which appeared to contain the desired carbamate (113) as well as a small amount of an unidentified side product. The ir spectrum of this mixture showed a distinct NH absorption at 3350 cm^{-1} and the ^{1}H nmr spectrum exhibited resonances at δ 6.13 (broad, one—proton singlet, -NH-) and between δ 3.0 and 4.0, indicating the MEM ether and the ketal group were present. The mass spectrum of this material showed a strong signal at m/e = 485, consistent with compound (113).

The side product, compound (114), showed an ester carbonyl absorption at 1722 cm^{-1} in the ir spectrum. In the ^{1}H nmr spectrum, this material exhibited resonances attributed to three tertiary methyl groups at δ 0.70 (three-proton singlet) and at δ 1.18 (six-proton singlet). The tert-butyl group gave rise to a nine-proton singlet at δ 1.43. The MEM ether group displayed characteristic resonances at δ 3.37 (three—proton singlet, methoxy methyl group) and at δ 4.72 and 4.78 (two 2—proton doublets, J = 8 Hz, AB quartet, -OCH$_2$O-).

(112)   (113)   (114)
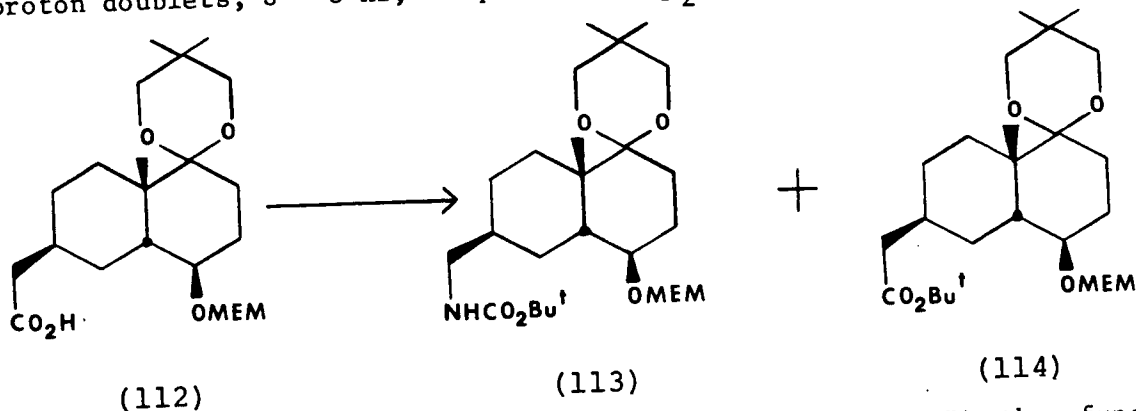
The results outlined above suggested that both the MEM ether functionality and the ketal moiety were stable to the reaction conditions involved with the use of Yamada's reagent[102]. However, the yield of the

reaction employing compound (112) as the substrate was quite low and the appearance of the tert-butyl ester side product (presumably arising from the reaction of tert-butyl alcohol with the intermediate acyl azide species) was somewhat discouraging. With the carboxylic acid (102), however, the formation of the corresponding tert-butyl ester, as a side reaction, was unlikely. If the intermediate acyl azide (105) was formed as expected, this material was anticipated to be too hindered (based on the results obtained from both the attempted hydrazide formation and the formation of the acyl azide via the Weinstock modification[100]) to react with the solvent (tert-butyl alcohol) to any appreciable degree.
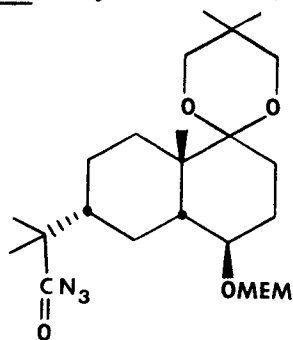
(105)

Thus, the carboxylic acid (102) was treated with freshly distilled diphenylphosphoryl azide and triethylamine in dry tert-butyl alcohol (reflux, 27 h). Surprisingly, when the resulting crude product was purified by preparative tlc, the isocyanate (106) was isolated in 45% yield. This material, which was a stable, colorless gum, exhibited a characteristic absorption for an isocyanate moiety (2265 cm^{-1}) in the ir spectrum. The ^{1}H nmr spectrum showed three tertiary methyl groups at δ 0.70 and 1.20 (two three-proton singlets, ketal methyl groups) and at δ 1.07 (three-proton singlet, angular methyl group). The geminal methyl groups, α to the isocyanate moiety, were characteristically

shifted downfield with respect to the starting material (102), giving

rise to a six-proton singlet at δ 1.28.

(102)   (106)   (116)
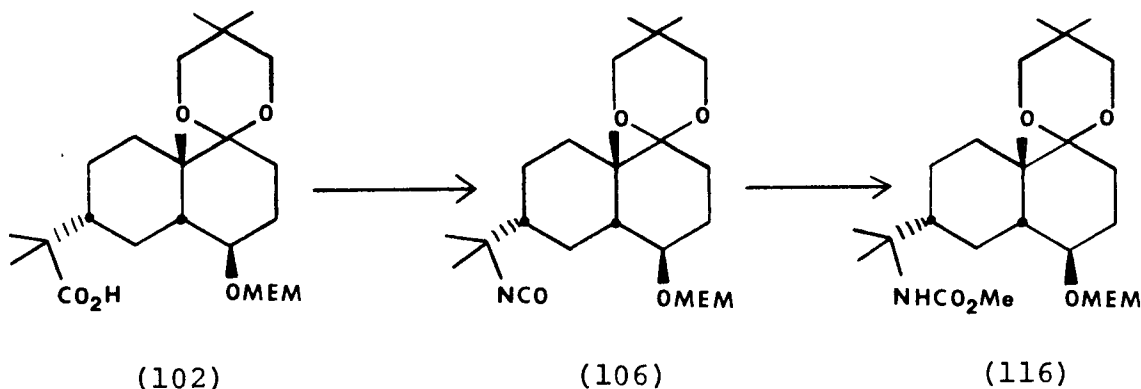
Treatment of the isocyanate (106) with dry methanol (reflux, 24 h)

afforded the ketal carbamate (115) in quantitative yield. This sub-

stance showed absorbances due to the carbamate moiety at 3440 cm^{-1} (NH)

and at 1722 cm^{-1} (carbonyl group) in the ir spectrum. The ^{1}H nmr

spectrum of this compound exhibited two low field, three-proton singlets

at δ 3.41 (methoxy methyl of the MEM ether group) and at δ 3.62 (carbo-

methoxy group). The proton on the nitrogen atom of the carbamate func-

tionality appeared as a broad, one-proton singlet at δ 4.60.

These results suggested that the isocyanate group in compound

(106) was sterically too encumbered to react with the solvent (tert-

butyl alcohol) to produce the expected tert-butyl urethane. As men-

tioned previously, it seemed likely that the geminal dimethyl groups

α to the isocyanate functionality were effectively shielding this group

from reacting. Even with the use of a sterically less demanding alcohol

(e.g. methanol), the reaction of this material to form the corresponding

carbamate was quite slow. This data is in accord with published reports[104]

indicating that primary alcohols react with isocyanates approximately

200 times faster than tertiary alcohols.

The successful preparation of the ketal carbamate (116), albeit an encouraging result, was tempered by the fact that the yield (45%) of this material was low. In Yamada's communication[102] on the use of diphenylphosphoryl azide, it was suggested that the formation of the carbamate product proceeds via the intermediacy of the corresponding acyl azide. Furthermore, the formation of the latter was proposed as occurring through an intermediate such as that depicted below [cf. (I)]. It seemed attractive to question whether or not the predominant intermediate might not actually be the mixed phosphate anhydride (II).

$$R - \overset{\overset{\displaystyle O}{\|}}{C} - O - \overset{\overset{\displaystyle O^{\ominus}}{|}}{\underset{\underset{\displaystyle N_3}{|}}{P}} - (OPh)_2 \qquad\qquad R - \overset{\overset{\displaystyle O}{\|}}{C} - O - \overset{\overset{\displaystyle O}{\uparrow}}{P} - (OC_6H_5)_2$$

$$(I) \qquad\qquad\qquad\qquad\qquad (II)$$
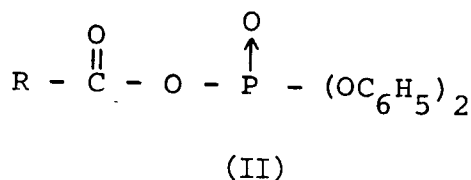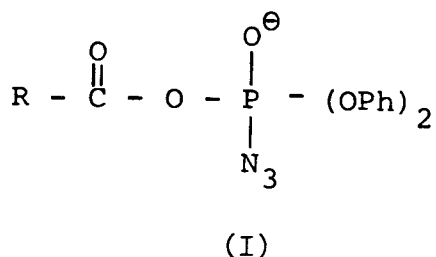
This general type of anhydride was not unknown[105] and it was felt that this type of compound might meet our synthetic needs from two points of view. Firstly, the formation of this type of derivative from compound (102) could be effected under basic conditions. It was felt that, considering the demonstrated lability of this system [cf. (102)] to acid, these conditions might well give rise to superior yields of a derivatized acid as compared to those involving the possibility of the presence of even trace amounts of acidic materials (e.g. acyl chloride preparations). Secondly, it was hoped that this type of mixed anhydride, as opposed to that produced using Weinstocks' modification[100],

would react with a nucleophile (e.g. azide ion) preferentially at carbon rather than phosphorus.

In this regard, it is of interest to note that the cyclic system (117) was found to react with primary amines predominantly at carbon but, with alcohols, almost exclusively at phosphorus.[105] On the other

$$HO_2C \diagup\diagdown P \xrightarrow[\text{}]{} OR' \quad \xleftarrow{R'OH} \quad \diagdown P \diagup \quad \xrightarrow{R'NH_2} \quad R'HNC \diagup\diagdown P -$$
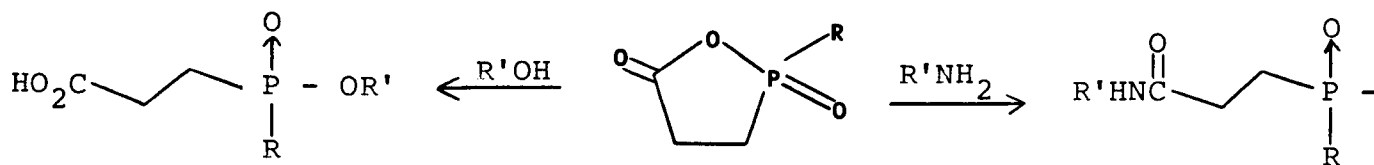
(117)

hand, Masamune et al[106] had reported that the reaction of this type of mixed anhydride, with Tl (I) thiolates, afforded the corresponding thiol esters in excellent yield. For example, cholic acid (118) gave the 2--methylpropane-2-thiol ester (119) in an overall yield of 86%.
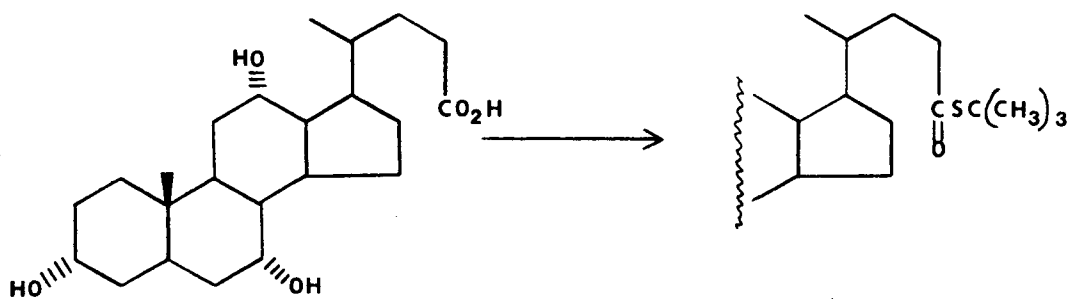
(118)   (119)

Thus, in the hopes of increasing the yield of the ketal carbamate (116), the following series of transformations were carried out. A solution of the carboxylic acid (102) in dry tetrahydrofuran was treated

with dry triethylamine (2.3 equivalents), followed by two equivalents of diethyl phosphorochloridate (ambient temperature, 4 h). The crude product was dissolved in hexamethylphosphoramide and the resulting solution was added to a solution-suspension of excess sodium azide in hexamethylphosphoramide (ambient temperature, 15 h). A solution of.the resulting acyl azide (ir absorption at 2155 cm^{-1}) in dry toluene was refluxed for 3 h. Finally, the crude material obtained from the toluene solution was dissolved in methanol containing a small amount of DBN[†] (1,5-diazabicyclo[4.3.0]non-5-ene), and the resulting solution was refluxed for 90 min. The isolated crude product (97%) was pure by tlc, ^{1}H nmr, and glc, and proved to be the desired ketal carbamate (116).

In order to complete the synthesis of the tricyclic ketone (12), the removal of the MEM ether protecting group, followed by the conversion of the resulting alcohol (120) into a suitable leaving group (e.g. tosylate), was necessary. With the molecule thus functionalized, a base promoted intramolecular cyclization should form the tricyclic compound (122). Hydrolysis of both the ketal group and the carbamate functionality should then furnish the desired ketone (12) (Scheme 6).

Following this plan, studies aimed at selectively removing the MEM ether were initiated. This task was anticipated to be problematic since the ketal group present in several of the intermediates leading to compound (116) had been found to be very labile in acid. Indeed, this

---

[†]Without a catalytic amount of DBN, the reaction of the crude isocyanate (106) (ir absorption at 2280 cm^{-1}) with methanol was very slow (incomplete after 22 h at room temperature).

(116)

(120)

(121)

(122)

(12)
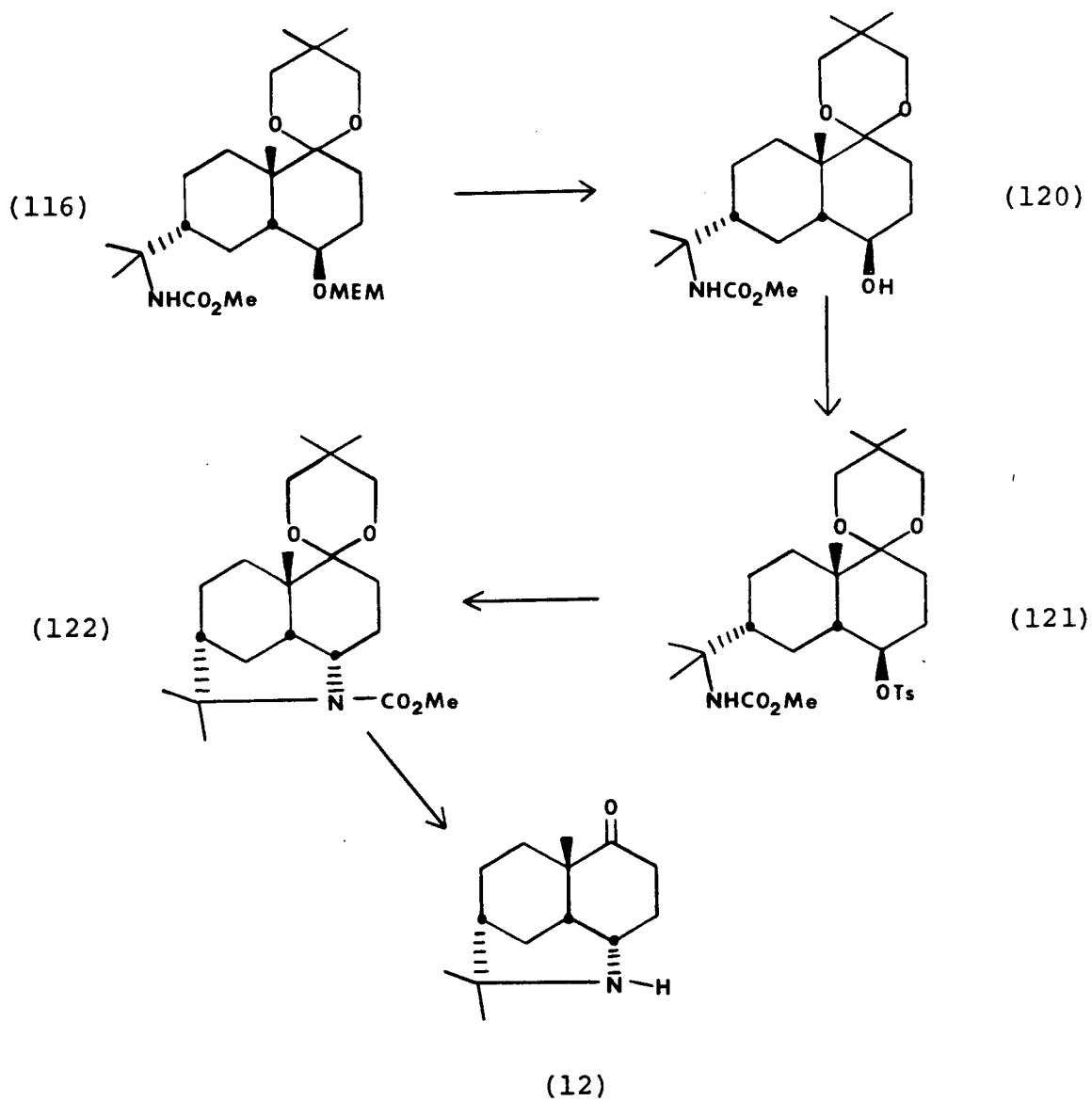
SCHEME 6

concern proved justified, for when the ketal carbamate (116) was treated under a wide variety of acidic conditions, the desired alcohol (120) was not obtained.

Exposure of the ketal carbamate (116) to titanium tetrachloride[27,53] (-20 °C, 0.5 h), for example, afforded the keto carbamate (123) and the carbamate alcohol (124), in a ratio of 4:1, respectively. There was no evidence to indicate that any of the desired material (120) had been produced.

(116)   (123)   (124)
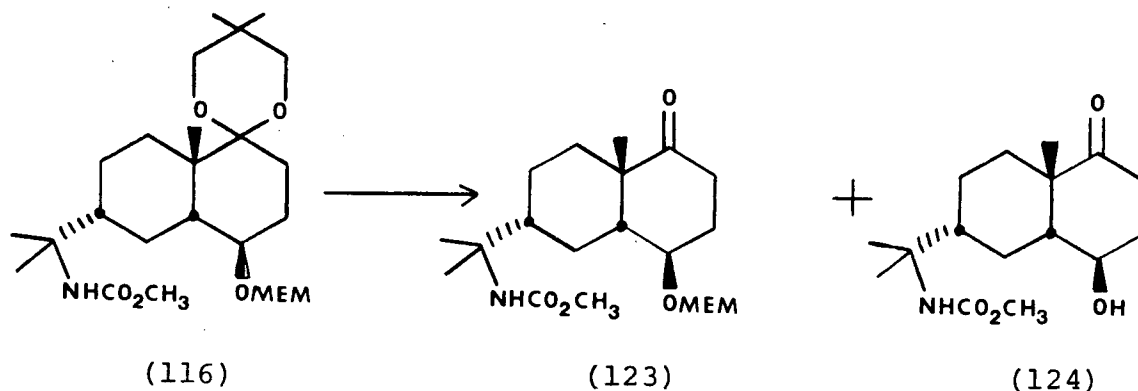
The keto carbamate (123) exhibited absorptions in its ir spectrum at 3447 and 1723 cm^{-1} (NH and the carbonyl group of the carbamate functionality, respectively) and at 1701 cm^{-1} (keto group). In the ^1H nmr spectrum the gem-dimethyl group gave rise to two three-proton singlets (δ 1.17 and 1.20). All of the resonances characteristic of the ketal group were absent.

The ir spectrum of the carbamate alcohol (124) showed absorptions due to the hydroxyl group (3620 cm^{-1}), the carbamate functionality (3450 and 1720 cm^{-1}), and the keto group (1706 cm^{-1}). The ^1H nmr spectrum of this material exhibited signals due to the carbamate functionality at δ 3.60 (three-proton singlet, methoxy methyl group) and at δ 4.53 (a broad, one-proton singlet, -NH-). The lack of any resonances character-

istic of the MEM ether group or the ketal functionality was clearly evident.

The use of other acidic reagents were all uniformly unsuccessful in selectively removing the MEM ether group from compound (116). The use of anhydrous stannic chloride[27] (0 °C, 1.2 h) in methylene chloride, for example, selectively removed the ketal functionality affording the keto carbamate (123) as the only detectable product in high yield.

In the hopes of maintaining a protected ketone functionality at C_9, during the acid catalyzed cleavage of the MEM ether moiety, a trans-ketalization reaction on the ketal carbamate (116) was attempted. This type of strategy had been employed by Kishi[99] during the course of the total synthesis of saxitoxin (127). Kishi found that the replacement of the acid labile ketal group (63%) (by trans-ketalization using propanedithiol) in compound (125), forming the thioketal compound (126), allowed the use of acidic reaction conditions employed in subsequent steps which otherwise had cleaved the ketal functionality.

(125)   (126)   (127)

R = NHCONH$_2$
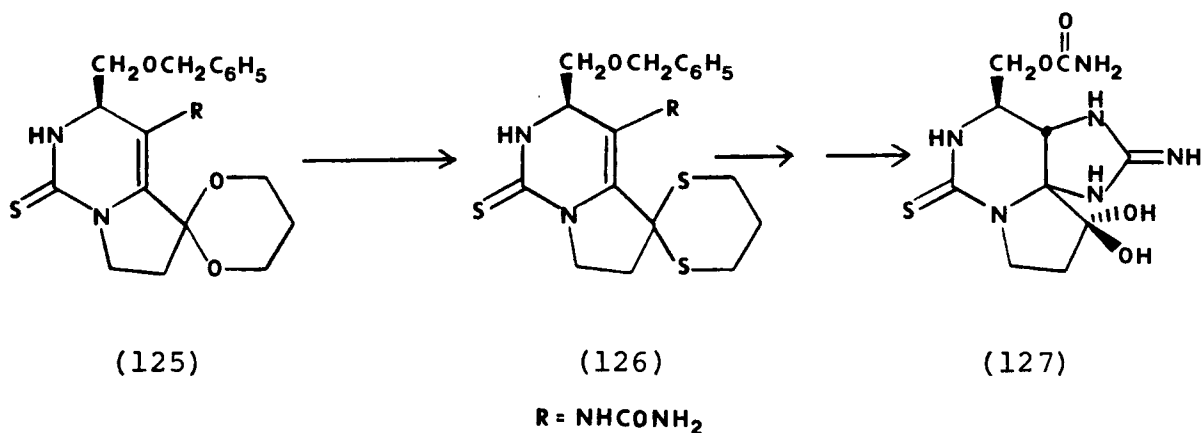
Accordingly, the ketal carbamate (116) was treated with excess

propanedithiol in dry acetonitrile containing a catalytic amount of boron trifluoride etherate (ambient temperature, 41 h). Unfortunately, the only compound isolated (85%) from the crude product (which was pure by tlc and glc analyses) was the keto carbamate (123).

(116)   (123)
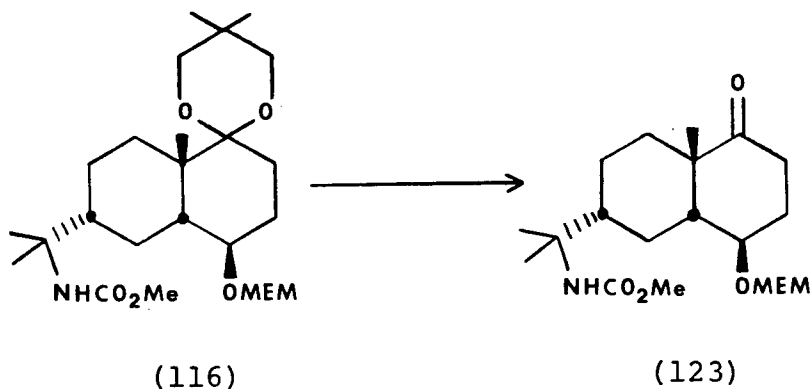
Overall, these results suggested, in no uncertain terms, that the feasibility of selectively removing the MEM ether moiety in compound (116) was very doubtful. In all the reaction procedures which were studied, the ketal moiety was removed quantitatively whereas the MEM ether group was usually maintained. In those cases where the ether protecting group was successfully removed, the concomitant loss of the ketal functionality appeared to be unavoidable. Thus, we were forced to attempt to complete the synthesis of the tricyclic ketone (12) utilizing a different methodology (vide infra). The series of transformations described in this section, leading to the ketal carbamate (116), are illustrated in Scheme 7.

(72)

(95)

(106)

(102)

(116)
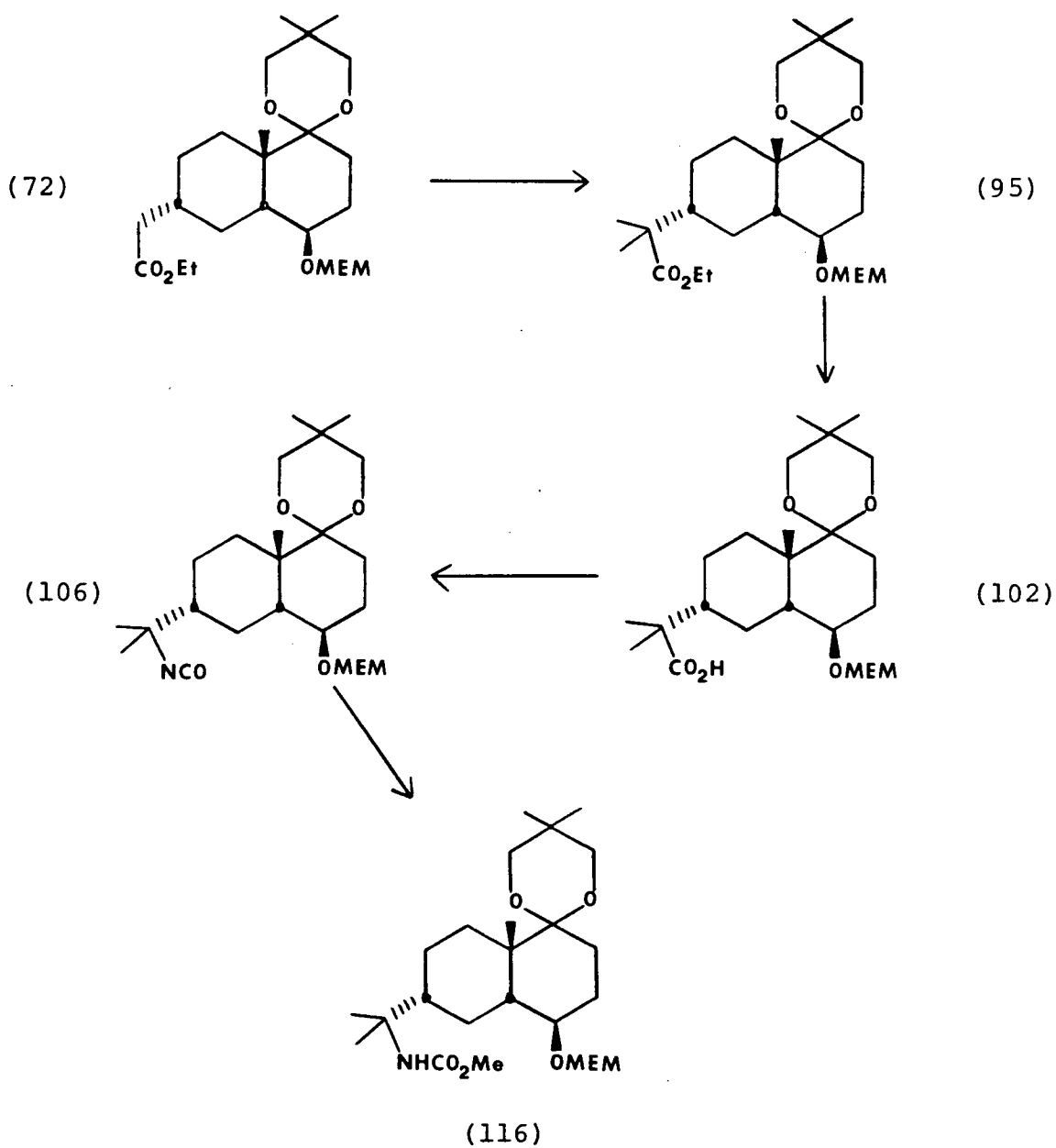
SCHEME 7

VI. Attempted Synthesis of the Tricyclic Ketone (12) via

Reductive Amination

An alternative synthetic pathway which was envisaged for the com-
pletion of the synthesis of the tricyclic ketone (12) is shown schemat-
ically below (Scheme 8). On the basis of the results obtained during
the attempted removal of the MEM ether group of the ketal carbamate
(116), it was anticipated that the treatment of this material under
acidic conditions more vigorous than those used previously would afford
the carbamate alcohol (124) as the predominant product. The carbamate
alcohol (124), it was hoped, could then be oxidized to furnish the
carbamate dione (128). Treatment of this material under conditions
necessary to cleave the urethane functionality would provide the amino
dione (129). It was felt that this substance could then be transformed
directly into the desired tricyclic ketone (12) by way of a reductive
amination.

It is pertinent to note that the (theoretically) possible epimer-
ization of the carbamate (128), to form the undesired trans ring fused
system (131), was not expected to be a complication. An examination of
a molecular model of each of the molecules in question clearly indicated
that the cis-fused system, compound (128), was the thermodynamically
more stable of the two compounds. On the basis of conformational analy-
sis, one would expect the dione (128), containing an equatorially ori-
ented substituent at C_3 [cf. (128a)], to be more stable than the dione
(131), possessing a bulky side chain (at C_3) in an axial orientation
[cf. (131a)].

(116)

(124)

(129)

(128)

(130)

(12)

SCHEME 8

(128)

(131)

(128a)

(131a)
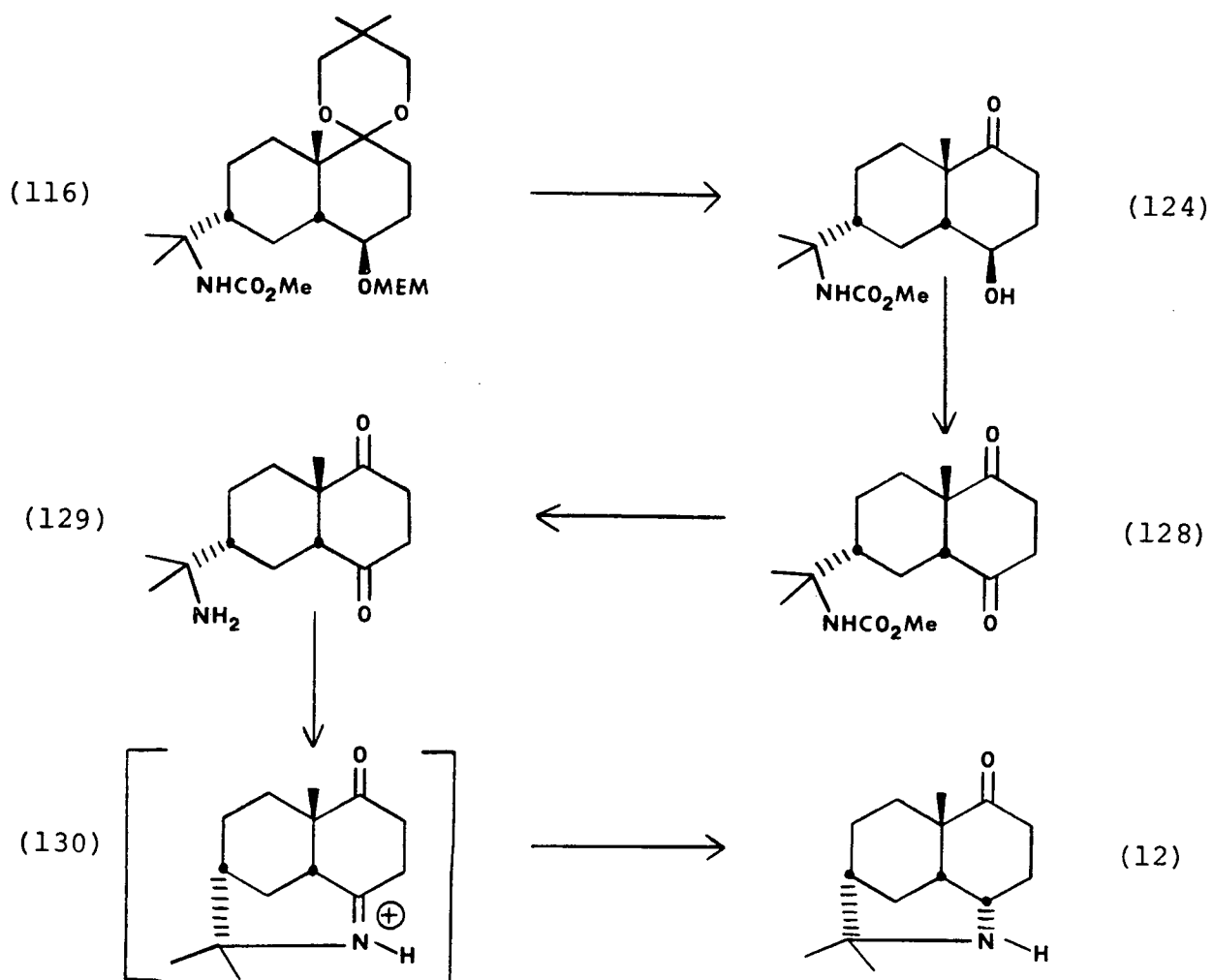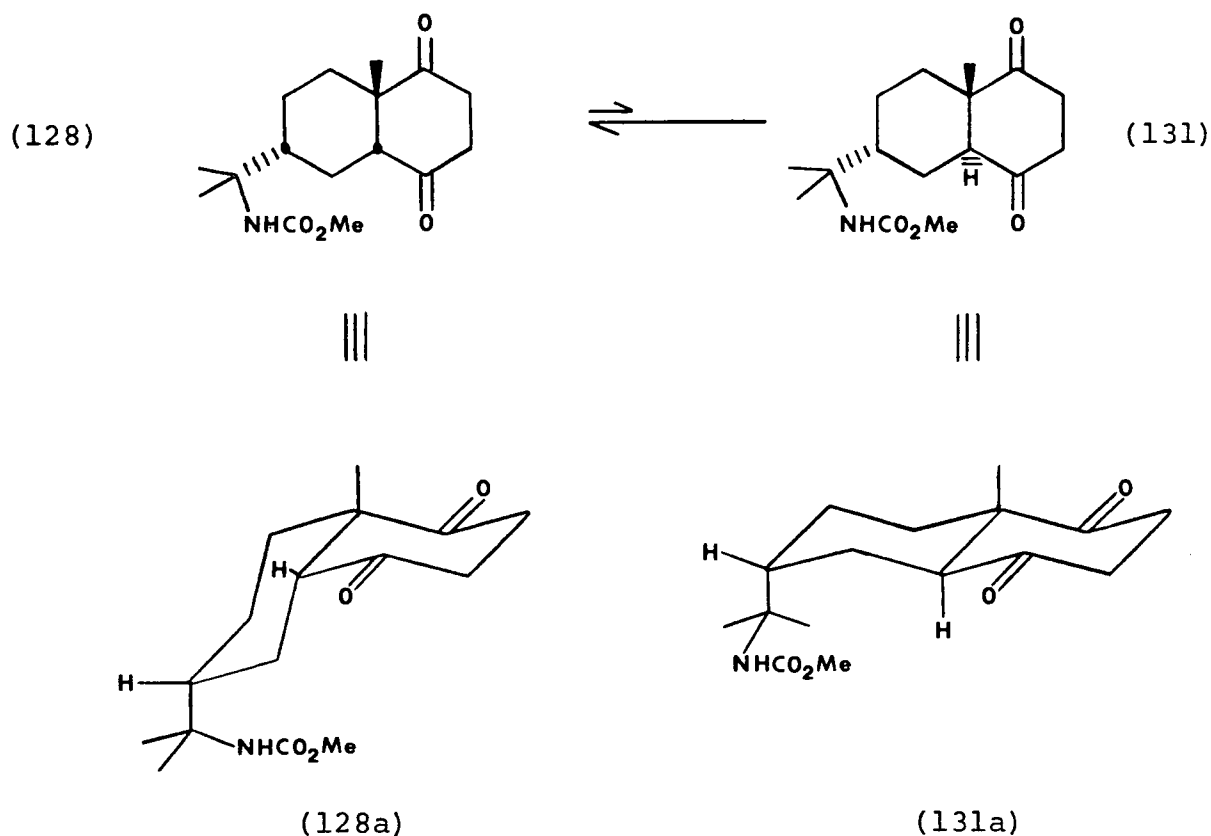
The conversion of compound (129) into the tricyclic ketone (12) was visualized as occurring through a reductive amination [via (130)] using sodium cyanoborohydride.[107,108] This transformation, it was hoped, would occur in a regio- and stereoselective fashion. Thus, although both the keto functionalities of the amino dione (129) were theoretically capable of reacting (intramolecularly) with the amino group, it was anticipated that the keto group at C_6 would react preferentially.

This expectation was based on the fact that, geometrically, the formation of an intermediate iminium species at C_9 could occur only with difficulty. A molecular model of this intermediate species suggested that this material was indeed severely strained.

That this transformation would occur stereoselectively was based on an examination of a molecular model of compound (130), the expected intermediate iminium species, which suggested that approach of the reducing agent (e.g. cyanohydridoborate anion) would, for steric reasons, be from the convex side (β face) of the molecule. Furthermore, the reduction of ketones at pH 6-7 with sodium cyanoborohydride has been shown[107] to be very slow whereas iminium species are reduced rapidly under these conditions. Thus, the keto group at C_9 in compound (129) was not expected to be reduced using this methodology.

Intramolecular reductive aminations have been used successfully in the past during the course of various total syntheses.[107,109] For example, in a synthesis of the alkaloid nicotine (134), Borch et al[107] converted the ketoaldehyde (132) into compound (133) (47%) utilizing this technique. And, more recently, Kende and co-workers[110] used a reductive amination procedure as the key step [cf. (135) to (136)] in an elegant total synthesis of dendrobine (137).

(132)   (133)   (134)

(135)

(136)

35%

(137)
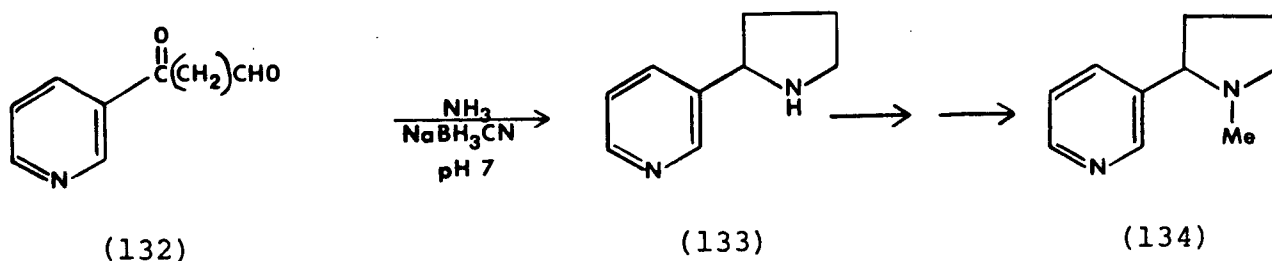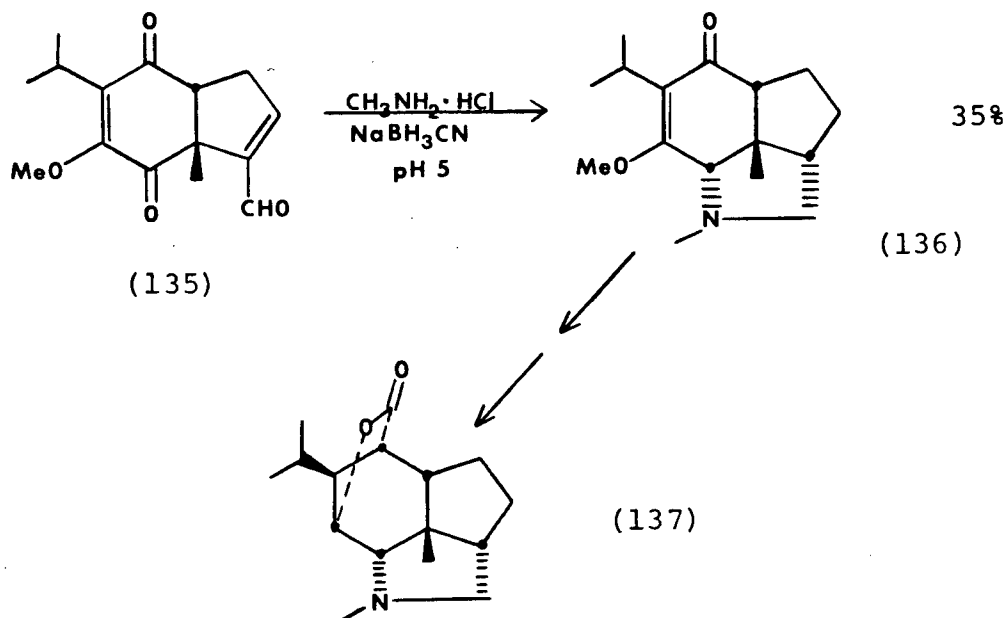
The scheme outlined above (Scheme 8) was thus attractive from two points of view. Firstly, the proposed conversion of the ketal carbamate (116) into the tricyclic ketone (12) was envisaged as a potentially straightforward sequence of events involving relatively simple experimental conditions and reagents. Secondly, the overall number of steps involved in the transformation was not increased in number from that of the original plan (see Scheme 6).

Accordingly, the ketal carbamate (116) was treated with excess titanium tetrachloride (1.5 h, 0 °C) in methylene chloride affording (80%) the carbamate alcohol (124), which was identical in all respects to the material prepared previously. Oxidation of this material with Collins reagent[37] (a chromium trioxide-pyridine complex in methylene chloride) for 30 min at ambient temperature furnished the carbamate dione (128) in 81% yield.

In the ir spectrum of the carbamate dione (128), the carbonyl

groups gave rise to a strong absorption at 1715 cm^{-1} and the carbamate group displayed an absorption at 3450 cm^{-1}. The ^{1}H nmr spectrum of this substance exhibited resonances at δ 1.14, 1.18, and 1.21 (three--proton singlets, tertiary methyl groups), at δ 3.59 (three-proton singlet, methoxy methyl group), and at δ 4.65 (a broad, one-proton singlet, NH proton).

Unfortunately, in our hands, all attempts to deprotect the amino group in compound (128) were unsuccessful. Treatment of the carbamate dione (128) under a variety of conditions failed to furnish the desired amino dione (129). Compound (128) proved to be exceptionally stable and was recovered even after treatment with 6N hydrochloric acid in dioxane (2 h, 100 °C). The use of reagents such as trimethylsilyl iodide[111,112] (22 h, ambient temperature), trichlorosilane-triethylamine[113,114] (46 h, room temperature), and excess lithium iodide-dimethylformamide[115] (18 h, reflux), all of which have been used to cleave carbamates, were also ineffective. Treatment of compound (128) under conditions (30% hydrogen bromide in acetic acid, 3 h, reflux) which were recently used by Overman et al[116] to effect the cleavage of an unusually stable carbamate, led only to intractable material.

These results were rather discouraging and prompted the consideration of an alternative route to the amino dione (129), as shown in the equations below. Thus, it was envisaged that the carboxylic acid (102) could be converted into the desired amino dione (129) using a methodology similar to that used to prepare the ketal carbamate (116) (vide

supra). That is, successive treatment of the acid (102) with diethyl phosphorochloridate, sodium azide, and refluxing toluene, would produce the intermediate isocyanate (106). This material, it was hoped, could be converted, without isolation, into the keto amine (139) by exposure of the crude isocyanate (106) to aqueous acidic conditions.

(102)   (106)   (139)

Alternatively, the isocyanate (106) potentially could be transformed into the amino dione (129) in two steps via the ketal amine (138) and the keto amine (139). Specifically, treatment of the isocyanate (106) under aqueous basic conditions was expected to afford the ketal amine (138) which could then be converted into the keto amine (139) through the removal of both the MEM ether group and the ketal functionality under conditions similar to those used previously.

(106)   (138)   (139)

Although these proposed conversions have not been examined in detail, some preliminary results have been obtained. For example, it was found that the treatment of the crude isocyanate (106) (see p. 98) under acidic hydrolysis conditions (1N hydrochloric acid in tetrahydrofuran, 2 h, reflux) gave rise to a considerable number of products, as judged by tlc. However, subjection of the isocyanate (106) to basic hydrolysis conditions (2N sodium hydroxide in p-dioxane, 3 h, reflux) afforded the ketal amine (138) in 83% yield.

The mass spectrum of (138) showed characteristic ions at m/e 398 ($M^{\oplus}$ - CH$_3$) and at m/e 58 (C$_3$H$_8$N$^{\oplus}$, base peak), both resulting from α-cleavage adjacent to the nitrogen atom. The ir spectrum of this substance displayed an absorption at 3450 cm^{-1} due to the amino group. In the ^{1}H nmr spectrum the geminal methyl groups α to the nitrogen atom and the angular methyl group gave rise to a nine-proton singlet at δ 1.04. The protons attached to the nitrogen atom appeared as a two-proton singlet at δ 1.95.

It was anticipated that treatment of this material (138) with titanium tetrachloride, under conditions similar to those used for the conversion of the ketal carbamate (116) into the carbamate alcohol (124), would furnish the keto amine (139). However, treatment of this substance with titanium tetrachloride in methylene chloride (five equivalents, 1 h, 0 °C) gave rise only to intractable material.

Although no further experimental studies have been performed directed toward the completion of the synthesis of the tricyclic ketone (12), it is appropriate at this juncture to comment on the direction that further studies in this area might take. One possible solution to

(106)

(140), R = $CH_2C_6H_5$

(141), R = $C(CH_3)_3$

1) $TiCl_4$
2) $CrO_3 \cdot 2C_5H_5N$

(129)

(142), R = $CH_2C_6H_5$

(143), R = $C(CH_3)_3$

(12)
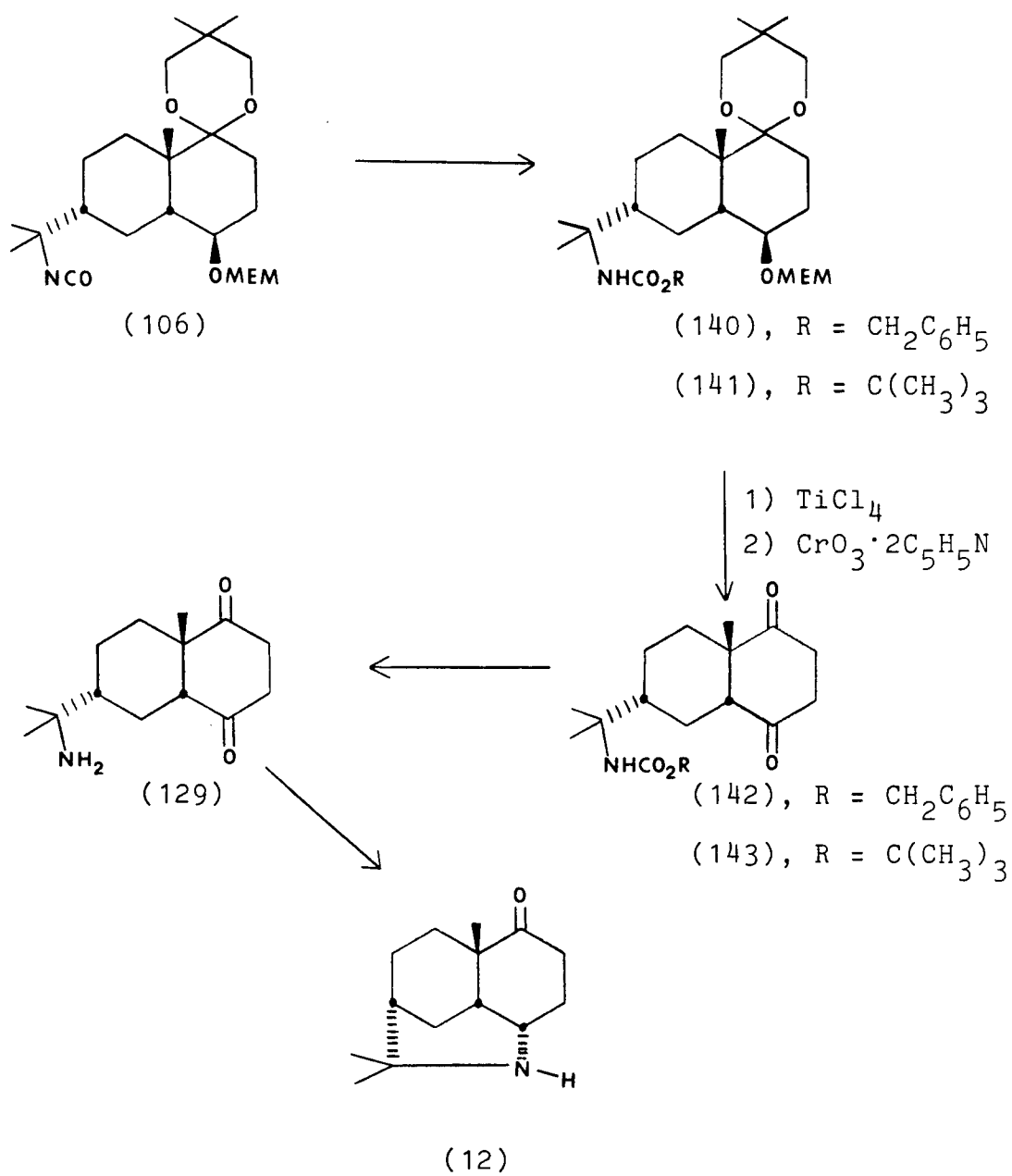
SCHEME 9

the difficulties encountered in the preparation of the amino dione (129), for example, would involve the preparation of compound (140) or (141) (see Scheme 9). These substances would be expected to be convertible to the amino dione (129) in two steps. Thus, treatment of either (140) or (141) under acidic conditions (e.g. titanium tetrachloride), followed by the oxidation of the resulting crude product (cf. Collins oxidation), would be anticipated to produce compounds (142) or (143), respectively. The latter compounds, due to the relative ease of removal of the amino protecting groups[117], would be expected to produce the desired amino dione (129) under quite mild conditions. Assuming that the transformation of compound (129) into the tricyclic ketone (12) would proceed uneventfully, this route would provide a convenient completion of the synthesis of (12).

VII. ^{1}H nmr Assignments

This section of the discussion is included to provide an explanation of the basis on which some of the ^{1}H nmr resonances were assigned. As mentioned previously (section II), on several occasions during the course of the research described herein, it was important to be able to distinguish the resonance due to the angular methyl group from those of the ketal moiety(ies). It was found that this objective could be accomplished through the comparison of several different molecules of a given structural series. For example, a comparison of the tertiary methyl group shifts in a series of compounds all bearing two ketal functionalities (at C_3 and C_9), but possessing different substituents at

C_5, C_6 and C_7, showed that the these resonances were subject to only small changes in position (see Table 1). In this group of compounds the angular methyl group resonated at δ 1.16 $\pm$ 0.05 and the A-ring ketal methyl groups at δ 0.85 $\pm$ 0.05 and δ 1.00 $\pm$ 0.08. The B-ring ketal methyl groups gave rise to signals at δ 0.71 $\pm$ 0.06 and δ 1.17 $\pm$ 0.02.

In this series of compounds, the three-proton singlet due to the angular methyl group usually appeared as an appreciably more intense signal than those due to the ketal methyl groups. It seemed likely that this phenomenon was a result of a lesser degree of long range coupling experienced by the angular methyl group as opposed to that felt by the ketal methyl groups[30]. Thus, the angular methyl resonances were initially assigned on this basis. However, further support for these assignments was later obtained from the examination of the ^{1}H nmr spectrum of the monoketone (62). The angular methyl group of this material gave rise to a three-proton singlet at δ 1.40 and the ketal methyl groups produced resonances at δ 0.72 and 1.20. It seemed clear that the absence of the A-ring ketal in this compound might well affect the shift of the angular methyl group but was extremely unlikely to affect the ketal methyl groups which are remote from C_3.

(62)
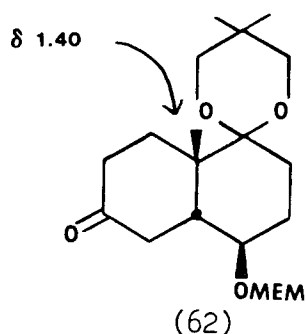
In addition to the considerations discussed above, an examination

of the chemical shifts of the compounds listed in Table 2 supports the
angular methyl group and B-ring ketal methyl assignments. The compounds
which are considered in Table 2 lack an A-ring ketal functionality (at
C_3) and, instead, possess β face substitutents at this position. It is
clear that both this series of compounds and the diketal series (Table
1) also share a common conformation (see Section IV). Thus, it was
expected that the angular methyl group shifts and the shifts of the
tertiary methyl groups of the B-ring ketal moiety would be very similar.
This is in fact the case.

It should also be noted that, in the remaining two series of com-
pounds tabluated (Tables 3 and 4), the B-ring ketal methyl group shifts
are essentially invariant and are in full accord with the assignments
discussed above. Specifically, the compounds in Table 3 (α substituted
at C_3) exhibit the expected shifts due to the ketal methyls (δ 0.70 $\pm$
0.02, 1.18 $\pm$ 0.03) and show angular methyl shifts consistently at lower
field than those in Tables 1 and 2. The series of compounds in Table 4
(sp^2 at C_3) also display predictable shifts for the B-ring ketal methyls
and exhibit angular methyl group shifts consistently at higher field
(δ 1.35 $\pm$ 0.05) than those tabulated in Tables 1 and 2.

In those cases where, by coincidence, other tertiary methyl groups
resonate in close proximity to either one of the ketal methyls or the
angular methyl group, no specific assignment has been made. For ex-
ample, compound (95) [entry 5, Table 3] exhibits resonances at δ 1.05 (a
three-proton singlet) and at δ 1.07 (a six-proton singlet) which are too
similar in position to assign and are thus denoted as "tertiary methyls".

Thus, on the basis of the shifts tabulated in Tables 1 through 4,

the assignments of many of the tertiary methyl signals in the ^{1}H nmr
spectra of the compounds discussed in this dissertation have been made.
Since this deductive form of resonance assignment does not constitute a
proof, the assignments herein must be considered tentative.

TABLE 1: Chemical Shifts (δ) of Methyl Group Protons in the Bicyclic Diketal Series
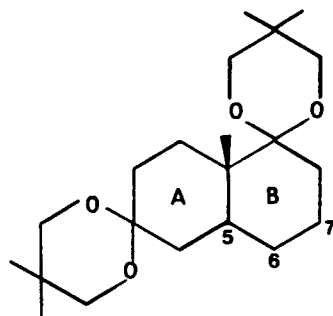
Entry	Substituents			Angular Methyl Group	Ketal Methyl Groups				Compound Number
	C_5	C_6	C_7		A Ring		B Ring		
1.			H_2	1.18*	0.86	1.02	0.71	1.16	(17)
2.	β-H	β-OH	H_2	1.21*	0.85	1.02	0.69	1.17	(31)
3.	β-H	β-OMEM	H_2	1.18*	0.88	0.96	0.70	1.16	(35)
4.	β-H		H_2	1.22	0.80	1.08	0.74	1.18	(44)
5.	β-H	β-OCOCOCH$_2$	H_2	1.22*	0.84	0.92	0.70	1.18	(48)
6.	β-H	H_2	H_2	1.11	0.90	0.98	0.68	1.18	(54)
7.	β-H			1.12*	0.90	1.00	0.70	1.18	(57)

*Signal intensity stronger than remaining signals.

TABLE 2: Chemical Shifts (δ) of Methyl Groups Protons in the Bicyclic

Monoketal Series (β-C$_3$ Substituted)

Entry	Substituents C$_3$	C$_6$	Angular Methyl Group	Ketal Methyl Groups		Compound Number
1.	β-CH$_2$CO$_2$Et	β-OTs	1.13	0.68	1.13	(75)
2.	β-CH$_2$CO$_2$Et	β-OMEM	1.13	0.68	1.13	(76)
3.	β-CH$_2$CO$_2$Et	β-OH	1.18	0.70	1.18	(78)
4.	β-CH$_2$CH$_2$OH	β-OMEM	1.15	0.68	1.15	(89)
5.	β-CH$_2$CO$_2$H	β-OMEM	1.18	0.70	1.18	(112)
6.	β-CH$_2$CO$_2$Bu^t	β-OMEM	1.18	0.70	1.18	(114)

TABLE 3: Chemical Shifts (δ) of Methyl Group Protons in the Bicyclic

Monoketal Series (α-C$_3$ Substituted)
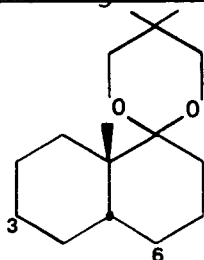
Entry	Substituents C$_3$	C$_6$	Angular Methyl Group	Ketal Methyl Groups		Additional Tertiary Methyl Groups	Compound Number
1.	α-CH$_2$CO$_2$Et	β-OMEM	1.04	0.68	1.16		(72)
2.	α-CH$_2$CO$_2$Et	β-OTs	1.01	0.68	1.13		(73)
3.	α-CH$_2$CO$_2$Et	β-OH	1.12	0.68	1.15		(77)
4.	α-CH$_2$CH$_2$OH	β-OMEM	1.04*	0.68	1.16		(90)
5.	α-C(CH$_3$)$_2$CO$_2$Et	β-OMEM	1.05†	0.70	1.18	1.07†	(95)
6.	α-C(CH$_3$)$_2$CO$_2$H	β-OMEM	1.06††	0.70	1.18	1.11††	(102)
7.	α-C(CH$_3$)$_2$NCO	β-OMEM	1.07	0.70	1.20	1.28	(106)
8.	α-C(CH$_3$)$_2$CO$_2$Si	β-OMEM	1.07	0.71	1.19	1.07	(107)
9.	α-C(CH$_3$)$_2$NHCO$_2$-CH$_3$	β-OMEM	1.06	0.72	1.20	1.24	(116)
10.	α-C(CH$_3$)$_2$NH$_2$	β-OMEM	1.04	0.70	1.19	1.04	(138)

*Signal intensity stronger than remaining signals.

†,†† These assignments may be exchanged.

TABLE 4: Chemical Shifts (δ) of Methyl Group Protons in the Bicyclic

Monoketal Series (sp^2-C_3)
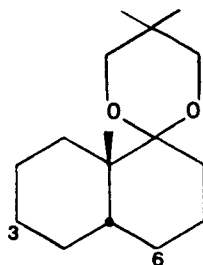
| Entry | Substituents | | Angular Methyl Group | Ketal Methyl Groups | | Compound Number |
	C_3	C_6				
1.	$=0$	β-OMEM	1.40	0.72	1.20	(62)
2.	$\diagup CO_2Et$	β-OH	1.32	0.70	1.18	(66) *
3.	$\diagup CO_2Et$	β-OH	1.34	0.72	1.21	(66) *
4.	$\diagup CO_2Et$	β-OMEM	1.30	0.70	1.18	(61)

*These compounds are geometric isomers.

EXPERIMENTAL

General Information

Melting points, determined with a Fisher-Johns melting point apparatus, and boiling points are uncorrected. Ultraviolet (uv) spectra were obtained with a Cary 15 spectrophotometer using methanol as solvent. Infrared spectra were recorded on Perkin-Elmer model 710 and model 710B infrared spectrophotometers. The proton magnetic resonance (^{1}H nmr) spectra were taken in deuterochloroform solution on Varian Associates Spectrometers, models T-60, HA-100 and XL-100 and on a 270 MHz unit composed of an Oxford Instruments 63.4 KG superconducting magnet and a Nicolet 16K computer attached to a Bruker TT-23 console. Signal positions are given in parts per million (δ) with tetramethylsilane as an internal reference; the multiplicity, integrated peak areas and proton assignments are indicated in parentheses. Protons attached to a bicyclic system are assigned by carbon number according to the diagram below. The methyl group attached to the bicyclic system at C_{10} is denoted
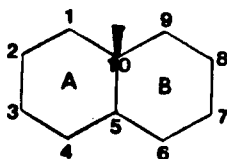
"angular". The carbon magnetic resonance (^{13}C nmr) spectra were taken in deuterochloroform solution on a Varian CFT-20 Spectrometer. Signal positions are given in parts per million (δ) with tetramethylsilane as an internal reference; where available the multiplicity and carbon assignments are indicated in parentheses. Gas-liquid chromatography

(glc) was carried out on a Hewlett Packard HP 5832 A gas chromatograph. The following columns were used: (A) 6 ft x 0.125 in, 5% OV-210 on Gas-Chrom Q (100/120 mesh); (B) 6 ft x 0.125 in, 5% OV-17 on Gas-Chrom Q (100/120 mesh). The column used and the column temperature are indicated in parentheses. A flow rate of 30 ml/min of helium gas was employed for all analyses. Column chromatography was performed using neutral silica gel (E. Merck, Silica Gel 60). Thin layer chromatography (tlc) was carried out on 20 x 5 cm glass plates coated with 0.7 mm of neutral silica gel (E. Merck, silica gel 60) or with commercial silica gel plates (Eastman Chromatogram Sheet Type 13181). Preparative thin layer chromatograpy was carried out with 20 x 20 cm glass plates coated with 0.7 mm of neutral silica gel (E. Merck, silica gel 60). The high resolution mass spectra were recorded with a Kratos/AEI MS50 or a Kratos/AEI MS902 mass spectrometer. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

All the reactions described herein were performed under an atmosphere of dry argon (or, in some instances, nitrogen) unless otherwise specified.

The solvents used were dried and purified as described below. Tetrahydrofuran and dimethoxyethane were distilled from sodium benzophenone ketyl in the appropriate solvent under argon.[118] Methanol and ethanol were distilled from their respective magnesium alkoxides. Benzene was distilled from calcium hydride and stored over $4\overset{o}{A}$ molecular sieves. Dichloromethane was distilled from phosphorous pentoxide and stored over $3\overset{o}{A}$ molecular sieves. Hexamethylphosphoramide was distilled from barium oxide and stored over 13X molecular sieves. Anhydrous ether was obtained commercially.

Preparation of the Diketal Olefin (17)
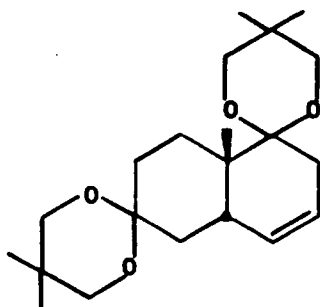
To 175 ml of freshly distilled benzene was added 5.0 g (48 mmol) of 2,2-dimethyl-1,3-propanediol and the resulting solution was heated to reflux for 0.5 h with azeotropic removal of water utilizing a Dean-Stark trap. The solution was then cooled to room temperature and 865 mg (4.8 mmol) of recrystallized 9-methyl-5(10)-octalin-1,6-dione[23] was added, followed by 91 mg (0.48 mmol) of p-toluenesulfonic acid monohydrate. After the reaction mixture had been refluxed for 5 h (Dean-Stark trap), it was cooled to room temperature, poured into saturated aqueous sodium bicarbonate (150 ml) and diluted with ether (250 ml). The layers were separated, the aqueous layer was extracted with ether (100 ml) and the combined ether solution was washed successively with five portions of water and one portion of brine. Removal of the solvents in vacuo, after drying over anhydrous sodium sulfate, gave the crude product as a yellow gum. When this material was dissolved in a small amount of methanol (approximately 10 ml) and the resulting solution was cooled in a freezer, 1.6 g of a pale yellow amorphous solid was isolated. Recrystallization of this solid (methanol) gave 1.03 g (61%) of water white prisms which proved to be the desired diketal olefin (17), pure by nmr, tlc and glc (column A, 160 °C). Chromatography of the residue on 50 g

of silica gel (elution of the column with 17% ethyl acetate in benzene)

gave a further 187 mg (11%) of the diketal olefin (17). The recrystal-

lized diketal olefin (17), mp 137-139 $^\circ$C, exhibited the following spec-

tral data: ir (CHCl$_3$) v_{max} 1092 cm^{-1}; ^{1}H nmr δ 0.71, 1.16 (2s, 3H each,

B ring ketal methyls),0.86, 1.02 (2s, 3H each, A ring ketal methyls),

1.18 (s, 3H, angular methyl), 3.24-3.88 (m, 8H, ketal methylenes), 5.26-

5.40 (broad s, 1H, C$_6$H); ^{13}C nmr δ 98.26 (C$_3$), 99.93 (C$_9$), 120.41 (C$_6$),

138.21 (C$_5$). Anal. calcd. for C$_{21}$H$_{34}$O$_4$: C 71.96, H 9.78; found: C

71.78, H 9.94.

Hydroboration of the Diketal Olefin (17):

Preparation of the Diketal Alcohols (31) & (36)
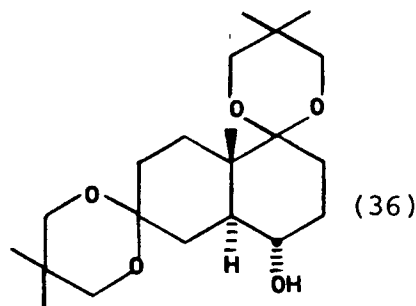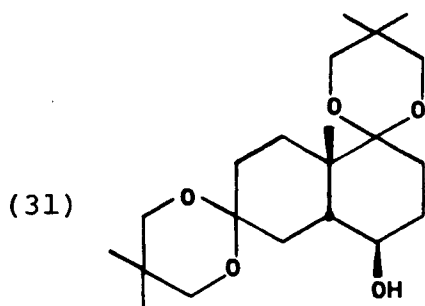
To a stirred ice-cold solution of 1.21 g (3.3 mmol) of the diketal

olefin (17) in 75 ml of n-hexane was added, dropwise, 3 ml (29 mmol) of

borane-methyl sulfide complex. The solution was allowed to warm to room

temperature and was stirred for 20 h. The reaction mixture was cooled

in an ice-water bath and absolute ethanol (10 ml), followed by 3N sodium

hydroxide (10 ml), was added slowly. Aqueous hydrogen peroxide (30%,

2.6 ml) was added to the mixture, the cooling bath was removed, and the

reaction mixture was warmed to a gentle reflux in a fume hood (approxi-

mately 10 minutes). After the solution had been cooled to room temper-
ature, it was poured into water (100 ml) and the resultant mixture was
diluted with ether (150 ml). The aqueous layer was then isolated,
extracted with ether (50 ml), and the combined organic phases were
washed successively with water and brine and dried over anhydrous sodium
sulfate. Concentration of the dried solution to 20 ml in volume fol-
lowed by cooling in a freezer gave 818 mg (64%) of the desired alcohol
(31) as an amorphous solid which was homogeneous by glc (column A, 175
^{o}C) and tlc analyses. The residual crude product obtained from the
mother liquor was purified by column chromatography on 60 g of silica
gel. Elution of the column with 33% ethyl acetate in benzene afforded
88 mg of the starting material (17), a further 250 mg (20%) of the
desired alcohol (31) and 91 mg (9%) of the trans-fused alcohol (36).

An analytical sample of the desired alcohol (31), mp 162-163 ^{o}C,
was obtained by recrystallization from methylene chloride-hexane and
gave the following spectral data: ir (CHCl$_3$) ν_{max} 3450 cm^{-1}; ^{1}H nmr δ
0.69, 1.17 (2s, 3H each, B ring ketal methyls), 0.85, 1.02 (2s, 3H each,
A ring ketal methyls), 1.21 (s, 3H, angular methyl), 3.20-3.86 (m, 8H,
ketal methylenes), 3.90-4.23 (broad m, 1H, C$_6$H); ^{13}C nmr δ 97.86 (C$_3$),
100.21 (C$_9$). Anal. calcd. for C$_{21}$H$_{36}$O$_5$: C 68.45, H 9.85; found: C
68.21, H 9.72.

The minor product, the trans-fused alcohol (36), was recrystallized
from ethyl ether and exhibited mp 189-191 ^{o}C; ir (CHCl$_3$) ν_{max} 3620,
1105 cm^{-1}; ^{1}H nmr δ 0.68, 1.13 (2s, 3H each, B ring ketal methyls),
0.90, 1.00 (2s, 3H each, A ring ketal methyls), 0.94 (s, 3H, angular

methyl), 3.18-3.78 (m, 9H, ketal methylenes, -OC$\underline{H}_2$C$\underline{H}_2$O-, & C$_6\underline{H}$); ^{13}C

nmr δ 97.88 (C$_3$), 99.44 (C$_9$). Anal. calcd. for C$_{21}$H$_{36}$O$_5$: C 68.45,

H 9.85; found: C 68.19, H 10.02.

Preparation of the Diketo Alcohol (60)
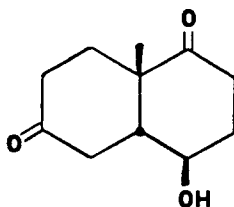
To a sitrred mixture of 2 ml of acetone and 2 ml of 2$\underline{N}$ hydrochloric

acid was added 200 mg (0.54 mmol) of the diketal alcohol (31) at room

temperature. The reaction mixture was stirred for 2 h and poured into

aqueous sodium bicarbonate. The resulting mixture was thoroughly ex-

tracted with methylene chloride and the combined organic extracts were

washed successively with water and brine and dried over anhydrous sodium

sulfate. Removal of the solvent under reduced pressure gave a yellow

gum which crystallized on standing, mp 103-106 $^{\circ}$C. The crude solid was

recrystallized from chloroform-hexane yielding 104 mg (97%) of the

diketo alcohol (60) as a white solid which exhibited mp 108.5-109 $^{\circ}$C:

ir (CHCl$_3$) ν_{max} 3430, 1706 cm^{-1}; ^{1}H nmr δ 1.47 (s, 3H, angular methyl),

3.00 (d, 1H, J = 4 Hz, -O$\underline{H}$), 3.89 (dddd, 1H, J = 8,8,4 & 4 Hz, C$_6\underline{H}$).

Anal. calcd. for C$_{11}$H$_{16}$O$_3$: C 67.32, H 8.22; found: C 67.16, H 8.09.

Preparation of the Diketal Ketone (45)
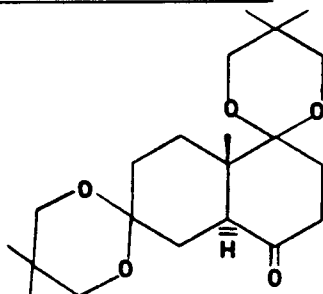
A)   By Oxidation-Epimerization of the cis-Fused Diketal Alcohol (31)

To a solution of 0.13 ml (1.6 mmol) of dry pyridine in 4 ml of dry methylene chloride was added 82 mg (0.82 mmol) of chromium trioxide. The resulting mixture was stirred for 15 min and a solution of 49 mg (0.135 mmol) of the dry diketal alcohol (31) in 5 ml of methylene chloride was added in one portion. The reaction mixture was stirred at room temperature for 15 min and poured onto a short column of activity I, neutral alumina (approx. 10 g). Elution of the column with ethyl acetate, followed by evaporation of the solvent in vacuo, gave 53 mg of a clear, viscous oil. Trituration of the oil with hexane gave 38 mg (77%) of the diketal ketone (45), as a pure (tlc, ^{1}H nmr) white solid. Recrystallization of the isolated solid from hexane gave an analytical sample exhibiting mp 147-148 °C: ir (CHCl$_3$) ν_{max} 1705, 1097 cm^{-1}; ^{1}H nmr δ 0.72, 1.16 (2s, 3H each, B ring ketal methyls), 0.83, 0.98 (2s, 3H each, A ring ketal methyls), 0.86 (s, 3H, angular methyl), 2.72-3.06 (m, 2H), 3.20-3.82 (m, 8H, ketal methylenes). Exact mass calcd. for C$_{21}$H$_{34}$O$_5$: 366.2406; found: 366.2410.

B)   By Oxidation of the trans-Fused Diketal Alcohol (36)

To a stirred, ice cold solution of 0.32 ml (4.0 mmol) of pyridine

and 15 ml of methylene chloride was added 198 mg (2.0 mmol) of dry

chromium trioxide. After aproximately 15 min the solution was warmed to

room temperature and the mixture was stirred for 45 min yielding a dark

red, homogeneous solution. A solution of the trans-fused alcohol (36)

(121 mg, 0.33 mmol), in 10 ml of methylene chloride, was added and,

after 25 min, the reaction mixture was filtered. The residual solid was

washed with ether, dissolved in 5% aqueous sodium hydroxide and the

resulting solution was extracted with ether. The filtrate was combined

with the ether extracts and the resulting solution was washed with 5%

aqueous sodium hydroxide, water and brine. Evaporation of the solvent

from the dried (anhydrous sodium sulfate) solution, followed by tri-

turation of the residual material with hexane, gave 110 mg (91%) of the

diketal ketone (45) as a pure (tlc, glc, ^{1}H nmr) solid. This material

(mp 146-147 $^\circ$C) was identical with the diketal ketone (45) prepared

according to the procedure above (ir, ^{1}H nmr).

Preparation of the Pyruvate Ester (48)
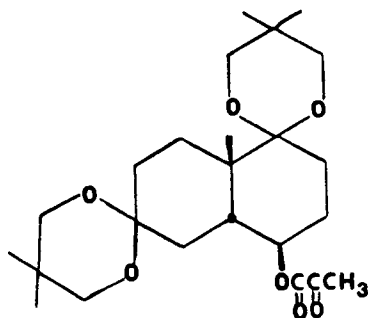
To a cold (0 $^\circ$C) solution of 0.2 ml (2.5 mmol) of pyridine and 356

mg (0.97 mmol) of the cis-fused diketal alcohol (31) in 30 ml of dry

benzene was added a solution of 145 mg (1.4 mmol) of pyruvoyl chloride[t]

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[t]This material was prepared according to the procedure of Ottenheijm et al[119] from pyruvic acid and dichloromethyl methyl ether.

in 2 ml of benzene. Stirring was continued for 25 min, the reaction

mixture was filtered and the filtrate was evaporated yielding a color-

less oil. Dissolution of this crude oil in ether, followed by cooling,

gave 83 mg (19%) of the desired ester (48) as a white amorphous solid,

mp 148-151 °C. Chromatography (45 g silica gel, 20% ethyl acetate in

benzene used as eluting solvent) gave a further 174 mg (41%) of the

pyruvate ester (48), as well as 100 mg of recovered starting material

(31).

Recrystallized (ether-chloroform) pyruvate ester (48), mp 156-157 °C,

gave the following spectral data: ir (CHCl$_3$) ν_{max} 1728, 1110, 1085 cm^{-1};

^{1}H nmr δ 0.70, 1.18 (2s, 3H each, B ring ketal methyls), 0.84, 0.92

(2s, 3H each, A ring ketal methyls), 1.22 (s, 3H, angular methyl), 2.43

(s, 3H, -OCOCOCH$_3$), 3.20-3.84 (m, 8H, ketal methylenes), 5.20-5.52 (m,

1H, C$_6$H). Exact mass calcd. for C$_{24}$H$_{38}$O$_7$: 438.2617; found: 438.2612.
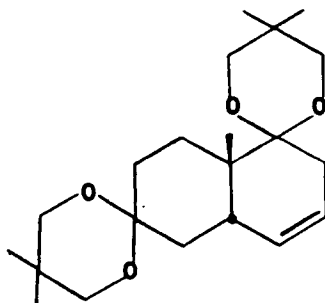
Preparation of the Diketal Tosylate (53)
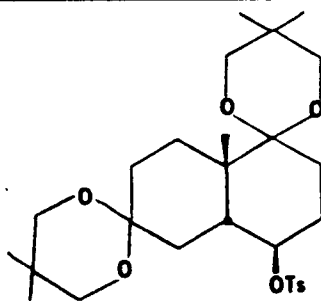
The diketal alcohol (31) (818 mg, 2.2 mmol) was dissolved in 20 ml

of pyridine and the solution was cooled in an ice-water bath. Recrys-

tallized p-toluenesulfonyl chloride, 4.24 g (22 mmol), was added, in

portions with stirring, and the reaction mixture was warmed to room

temperature. After 24 h the mixture was cooled in an ice-water bath,

ice was added and the resultant mixture was stirred for thirty minutes.

The solution was poured into ether (50 ml) and the organic phase was

washed successively with saturated aqueous sodium bicarbonate, water and

brine. The dried (sodium sulfate) ethereal solution was evaporated to

yield a crude solid which, when recrystallized from acetone, gave 700 mg

(61%) of pure (tlc, ^{1}H nmr) diketal tosylate (53) as a white amorphous

solid. The material obtained from the mother liquor was chromatographed

on 50 g of silica gel. Elution of the column with 25% ethyl acetate in

benzene gave a further 317 mg (27%) of the desired product (53). An

analytical sample of the diketal tosylate (53), prepared by recrystal-

lization from acetone, exhibited mp 123-125 $^{\circ}$C (dec); ir (CHCl$_3$) ν_{max}

1170, 1085 cm^{-1}; ^{1}H nmr δ 0.68 (s, 3H, ketal methyl), 0.93 (s, 6H, ketal

methyls), 1.15 (s, 6H, ketal methyl and angular methyl), 2.42 (s, 3H,

aromatic methyl), 3.20-3.74 (m, 8H, ketal methylenes), 5.02-5.30 (broad

m, 1H, C$_6$H), 7.32, 7.84 (2d, 2H each, J = 8 Hz, aromatic protons).

Anal. calcd. for C$_{28}$H$_{42}$O$_7$S: C 64.34, H 8.10; found: C 64.29, H 8.20.

Preparation of the Diketal Olefin (57)

To a solution of 143 mg (0.27 mmol) of the diketal tosylate (53) in

5 ml of dry dimethyl sulfoxide and 1 ml of dry benzene was added 217 mg

(0.82 mmol) of 18-Crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) and 82 mg (0.73 mmol) of potassium tert-butoxide. This mixture was warmed, with stirring, to 55 $^\circ$C and stirred for 30 min. The resulting dark brown solution was poured into water, the aqueous layer was thoroughly extracted with ether and the combined ether extracts were washed successively with dilute aqueous hydrochloric acid, water and brine. Evaporation of the solvent from the dried (sodium sulfate) extracts under reduced pressure, followed by crystallization of the crude product from hexane, gave 58 mg (60%) of the desired diketal olefin (57) as an amorphous solid, mp 123-129 $^\circ$C. The mother liquor (33 mg) consisted of two compounds (glc, tlc), the desired olefin (57) and an unidentified side product in a ratio of 6:4, respectively.

An analytical sample of the olefin (57), prepared by recrystallization of a portion the crude material from hexane, exhibited mp 134.5-135.5 $^\circ$C; ir (CHCl$_3$) ν_{max} 1087 cm^{-1}; ^{1}H nmr δ 0.70, 1.18 (2s, 3H each, B ring ketal methyls), 0.90, 1.00 (2s, 3H each, A ring ketal methyls), 1.12 (s, 3H, angular methyl), 3.20-3.88 (m, 8H, ketal methylenes), 5.28-5.68 (m, 2H, C$_6$H & C$_7$H). Anal. calcd. for C$_{21}$H$_{34}$O$_4$: C 71.96, H 9.78; found: C 72.08, H 9.70.

Preparation of the Diketo Olefin (58)
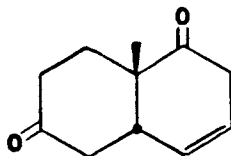
The diketal olefin (57) (46 mg, 0.26 mmol) was dissolved in 2 ml of acetone and 2 ml of 2 $\underline{N}$ hydrochloric acid was added dropwise with stirring at room temperature. The stirring was continued for 2 h and the reaction mixture was poured into aqueous sodium bicarbonate and the resulting solution was thoroughly extracted with ether. The combined ethereal extracts were washed (water and brine) and dried over anhydrous sodium sulfate. Removal of the solvents $\underline{in}$ $\underline{vacuo}$ gave 15 mg (64%) of a pale yellow oil which was pure by tlc and ^{1}H nmr analyses. The diketo olefin (58) gave the following spectral data: ir (CHCl$_3$) ν_{max} 1710 cm^{-1}; ^{1}H nmr δ 1.30 (s, 3H, angular methyl), 3.02 (unresolved d, 2H, J = 4 Hz, C$_8$Hs), 5.84 (m, 2H, C$_6$H & C$_7$H). $\underline{Exact}$ $\underline{mass}$ calcd. for C$_{11}$H$_{14}$O$_2$: 178.0994; found: 178.0996.
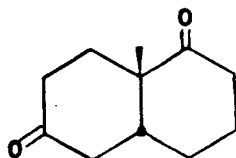
Preparation of the Bicyclic Diketal (54)
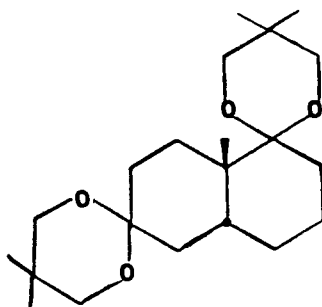
A)   By Catalytic Hydrogenation of the Diketal Olefin (57)

To a solution of the diketal olefin (57) (25 mg, 0.07 mmol) in 7 ml

of ethyl acetate was added 10 mg of 10% palladium-on-carbon. The mix-

ture was hydrogenated at atmospheric pressure and room temperature for

1.75 h. The resulting mixture was filtered through celite and the

filtrate was evaporated in vacuo yielding a colorless oil which crystal-

lized on standing. This material was recrystallized from ether giving

22 mg (88%) of pure bicyclic diketal (54), which exhibited mp 123.5-125

^{o}C; ir (CHCl$_3$) ν_{max} 1095 cm^{-1}; ^{1}H nmr δ 0.68, 1.18 (2s, 3H each, B ring

ketal methyls), 0.90, 0.98 (2s, 3H each, A ring ketal methyls), 1.11 (s,

3H, angular methyl), 3.16-3.80 (m, 8H, ketal methylenes). Anal. calcd.

for C$_{21}$H$_{36}$O$_4$: C 71.55, H 10.29; found: C 71.70, H 10.15.

B)   By Catalytic Hydrogenation of the Diketal Olefin (17)

A solution of 165 mg (0.47 mmol) of the diketal olefin (17) in 10

ml of ethyl acetate containing 50 mg of 10% palladium-on-carbon, was

hydrogenated at atmospheric pressure and room temperature for 16 h. The

resulting suspension was filtered through celite and the filtrate was

evaporated under reduced pressure giving 160 mg (96%) of a pure (tlc,

glc), colorless oil which crystallized on standing (mp 113-117 ^{o}C).

Recrystallation of the isolated solid from ether gave an analytical

sample of the bicyclic diketal (54), mp 122.5-125 ^{o}C, which was identic-

al (tlc, glc, ^{1}H nmr, mp, mixture mp) with the material previously pre-

pared (see part A).

Preparation of the Dione (51)

A) By Hydrolysis of the Bicyclic Diketal (54)

To a stirred solution of the bicyclic diketal (54) (87 mg, 0.25 mmol) in 5 ml of acetone was added 5 ml of 1N hydrochloric acid. The reaction mixture was warmed to 50 $^{\circ}$C and maintained at this temperature for 5 h. The solution was cooled to room temperature, poured into water and the resulting solution was extracted with two portions of ether. The combined organic phase was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvents gave a pale yellow oil which crystallized when triturated with hexane, yielding 39 mg (88%) of pure (tlc, glc, column B, 150 $^{\circ}$C) dione (51), as a white solid, mp 62-65 $^{\circ}$C (lit.[40] mp 64.5-65.5 $^{\circ}$C); ir (CHCl$_3$) ν_{max} 1703 cm^{-1}; ^{1}H nmr δ 1.36 (s, 3H, angular methyl).

B) By Hydrogenation of 9-Methyl-5(10)-Octalin-1,6-Dione

To a solution of 343 mg (1.9 mmol) of 9-methyl-5(10)-octalin-1,6-dione[23] in 20 ml of ethyl acetate was added 32 mg of 10% palladium-on-carbon. The mixture was hydrogenated at room temperature and atmospheric pressure for 16 h. The resulting mixture was filtered through celite and the filtrate was evaporated yielding a yellow oil which crystallized upon standing (mp 51-57 $^{\circ}$C). Recrystallization of the

crude solid from ether-hexane gave 320 mg (93%) of a water-white solid, mp 63-65.5 °C (lit.[40] mp 64.5-65.5 °C), which was pure by tlc and glc (column B, 150 °C). This material was identical (tlc, ^{1}H nmr) with the previously prepared dione (51) (see part A). A mixed melting point of the isolated solid with the previously prepared material was not depressed.

Preparation of the trans-fused Dione (52)
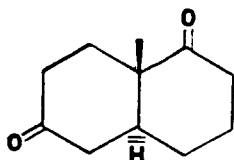
The monoketal ketone (59)[†] (143 mg, 0.54 mmol) was dissolved in 3 ml of acetone and 3 ml of 1N hydrochloric acid was added with stirring at room temperature. After 2 h had elapsed, the reaction mixture was diluted with water and the resultant solution was extracted with two portions of ether. The combined ethereal extracts were washed successively with three portions of water and one portion of brine and dried over anhydrous sodium sulfate. Removal of the solvents in vacuo gave a colorless oil which crystallized when cooled in an ice bath. The isolated solid, the trans-fused dione (52), weighed 81 mg (83%). Recrystallization of this material from ether-hexane gave a white solid, exhi-

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[†]This compound was kindly supplied by Dr. D.J. Herbert, Department of Chemistry, University of British Columbia.

biting mp 55-56 $^\circ$C (lit.[41] mp 56-57 $^\circ$C), which was clearly different from

the dione (51) as judged by glc (column B, 150 $^\circ$C), tlc and ^{1}H nmr

analyses. ^{1}H nmr δ 1.30 (s, 3H, angular methyl).

Preparation of the cis-Fused Diketal Ketone (44)
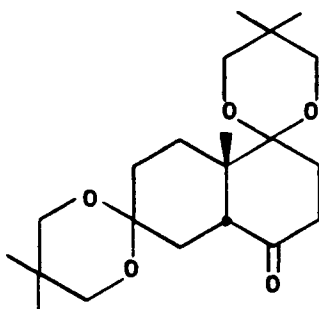
To a stirred, cold (0 $^\circ$C) solution of 0.34 ml (4.17 mmol) of pyri-

dine in 10 ml of methylene chloride was added 210 mg (2.1 mmol) of dry

chromium trioxide. After 15 min the solution was warmed to room temper-

ature and the stirring was continued for 45 min. To the resulting dark

red solution was added a solution of 128 mg (0.35 mmol) of the diketal

alcohol (31) in 10 ml of methylene chloride. After 25 min the reaction

mixture was filtered and the solid residue was washed with two portions

of ether and dissolved in 5% aqueous sodium hydroxide. The resultant

solution was extracted with ether and the combined ether solution was

added to the filtrate. This solution was washed successively with three

portions of 5% aqueous sodium hydroxide, two portions of water and brine

and dried over anhydrous sodium sulfate. Evaporation of the solvent

gave 145 mg of a pale yellow solid (mp 138-148 $^\circ$C) which was recrystal-

lized from methylene chloride-hexane giving 118 mg (93%) of pure cis-

fused diketal ketone (44), mp 150.5-151.5 $^\circ$C; ir (CHCl$_3$) ν_{max} 1705, 1100

cm^{-1}; ^1H nmr δ 0.74, 1.18 (2s, 3H each, B ring ketal methyls), 0.80, 1.08 (2s, 3H each, A ring ketal methyls), 1.22 (s, 3H, angular methyl), 2.88 (ddd, 1H, J = 13.5,6.5 & 1.5 Hz), 3.14-3.84 (m, 9H, ketal methylenes and C_5H). _Anal._ calcd. for $C_{21}H_{34}O_5$: C 68.82, H 9.35; found: C 68.82, H 9.30.

Epimerization of the cis-Fused Diketal Ketone (44)

Approximately 5 mg of metallic sodium was added to 8 ml of anhydrous methanol and the resulting suspension was stirred until all the sodium had reacted. A solution of the cis-fused diketal ketone (44) (11 mg, 0.03 mmol) in 4 ml of anhydrous methanol was added and the mixture was stirred at room temperature for four days. The reaction mixture was poured into water and the resulting solution was thoroughly extracted with ether. The combined ether extracts were washed successively with water and brine and dried with anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave a pale yellow gum which was crystallized from hexane, yielding 10 mg (91%) of the desired trans-fused ketone (45), as a pure solid exhibiting mp 146-148 °C. This material was identical in all respects with the trans-fused ketone (45) which had been prepared previously (see page 128).
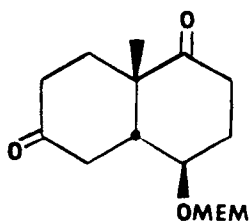
Preparation of the Diketal Ether (35)
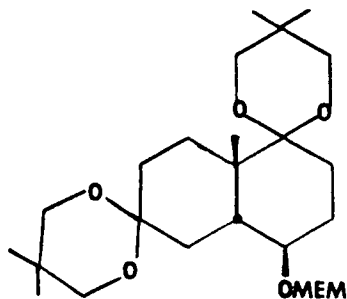
A solution of 7.02 g (15.4 mmol) of the diketal alcohol (31) in 300 ml of tetrahydrofuran and 40 ml of hexamethylphosphoramide was cooled in an ice-water bath. Two equivalents of potassium hydride (23% suspension, 6.6 ml) were added and the reaction mixture was stirred for fifteen minutes. The mixture was then warmed to a gentle reflux (steam bath) over ten minutes, allowed to reflux for fifteen minutes, then cooled in an ice-water bath. An opaque, milky solution resulted when MEM-chloride (β-methoxyethoxymethyl chloride) (2.6 ml, 23 mmol) was added dropwise. The resulting mixture was stirred at room temperature until no starting material was in evidence by tlc (approximately 1.5 h). Neutral alumina (50 g, activity IV) and water (25 ml) were added slowly and successively. After the resultant mixture had been stirred vigorously for ten minutes, it was filtered. The filtrate was diluted with 50 ml of saturated aqueous sodium bicarbonate and the resulting solution was extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous sodium sulfate. Removal of the solvent gave a clear gum which was dissolved in hot n-hexane. When the resultant solution was cooled, 6.0 g (69%) of the desired diketal ether (35) was obtained as a pure [tlc, glc (column A, 175 $^\circ$C)] white amorphous solid. Chromatography of the material obtained from the mother liquor on 200 g of silica gel (elution of the column with 25% ethyl acetate in benzene) gave an additional 1.71 g (20%) of the desired product (35). An analytical sample, prepared by recrystallization of a small amount of this material from n-hexane, exhibited mp 101.5-103 $^\circ$C; ir (CHCl$_3$) ν_{max} 1110 cm^{-1}; ^{1}H nmr δ 0.70, 1.16 (2s, 3H each, B ring

ketal methyls), 0.88, 0.96 (2s, 3H each, A ring ketal methyls), 1.18 (s,

3H, angular methyl), 3.40 (s, 3H, -OC$\underline{\text{H}}_3$), 3.98 (broad s, 1H, C$_6$H), 4.80,

4.91 (2d, 2H, J = 7 Hz, -OCH$_2$O-, AB quartet); ^{13}C nmr δ 95.69 (t, J =

162 Hz, -O$\underline{\text{C}}$H$_2$O-), 97.98 (C$_3$), 100.13 (C$_9$). <u>Anal.</u> calcd. for C$_{25}$H$_{44}$O$_7$:

C 68.45, H 9.85; found: C 68.19, H 10.02.

Preparation of the Dione Ether (64)

To a solution of 95 mg (0.21 mmol) of the diketal ether <u>(35)</u> in 7

ml of acetone was added 7 ml of 1 $\underline{\text{N}}$ hydrochloric acid with stirring at

room temperature. After 2.4 h had elapsed, the reaction mixture was

poured into cold, saturated aqueous sodium bicarbonate and the resultant

mixture was extracted with ether. The combined ether extracts were

washed, successively, with water and brine and dried over anhydrous

magnesium sulfate. Evaporation of the solvent gave 54 mg (92%) of a

colorless gum which was pure by tlc, ^{1}H nmr and glc (columns A & B, 190 ^{o}C)

analyses. This material exhibited ir (film) ν_{max} 1705, 1100, 1030

cm^{-1}; ^{1}H nmr δ 1.43 (s, 3H, angular methyl), 3.38 (s, 3H, -OC$\underline{\text{H}}_3$), 3.50-

3.92 (m, 5H, -OC$\underline{\text{H}}_2$C$\underline{\text{H}}_2$O- & C$_6$H), 4.79, 4.87 (2d, 2H, J = 6 Hz, -OC$\underline{\text{H}}_2$O-,

AB quartet). <u>Exact</u> <u>mass</u> calcd. for C$_{15}$H$_{24}$O$_5$: 284.1624; found: 284.1645.

Preparation of the α,β-Unsaturated Ester (65)
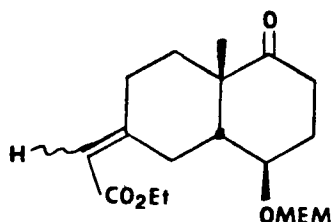
To a solution of 925 mg (2.0 mmol) of the diketal ether (35) in 15 ml of acetone was added 15 ml of 1N aqueous hydrochloric acid. The solution was stirred at room temperature for 2.25 h and then poured into cold saturated aqueous sodium bicarbonate (60 ml). The resulting solution was extracted thoroughly with methylene chloride and the combined organic extracts were washed with water and brine and dried over sodium sulfate. The solvent was then evaporated in vacuo giving 545 mg of a colorless oil which was dried overnight under high vacuum.

This material was dissolved in 20 ml of dry 1,2-dimethoxyethane and the resulting solution was cooled in an ice-water bath. A cold (0 °C) solution[†] (10 ml, 3.0 mmol) of the potassium salt of triethyl phosphonoacetate in 1,2-dimethoxyethane was added dropwise. The cooling bath was removed and the reaction mixture was stirred for 6 h at room temperature. The solution was poured into water and thoroughly extracted with


[†]The potassium salt of triethyl phosphonoacetate was prepared as follows: 17 ml of 1,2-dimethoxyethane and 1 ml of a 21% suspension of potassium hydride in mineral oil was cooled to 0 °C and 1.15 ml (5.8 mmol) of triethyl phosphonoacetate was added dropwise and the mixture was stirred for 15 min giving a clear, pale yellow solution.

ether. The combined ethereal extracts were washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a pale yellow oil which was dissolved in ethyl acetate and passed through a short column of silica gel (appoximately 20 g) giving 646 mg of crude product. Purification of this material by preparative tlc, using 25% cyclohexane in ethyl acetate as eluting solvent, yielded 580 mg (81%) of the desired α,β-unsaturated ester (65), a 1:1 mixture [nmr, glc (column A, 200 $^\circ$C)] of geometric isomers, as a colorless gum. A pure sample of one of the geometric isomers of the α,β-unsaturated ester (65) was obtained by preparative tlc (35% cyclohexane in ethyl acetate eluent; triple development) and exhibited: uv λ_{max} 221 nm (ϵ=15,212); ir (film) ν_{max} 1708, 1646, 1050 cm^{-1}; ^{1}H nmr δ 1.29 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$), 1.34 (s, 3H, angular methyl), 3.38 (s, 3H, -OCH$_3$), 4.16 (q, 2H, J = 7 Hz, -OCH$_2$CH$_3$), 4.84 (s, 2H, -OCH$_2$O-), 5.66 (s, 1H, olefinic proton). Exact mass calcd. for C$_{19}$H$_{30}$O$_6$: 354.2043; found: 354.2050.

By comparing the ^{1}H nmr spectra of the pure geometric isomer with that of the pure mixture, the ^{1}H nmr resonances due to the other isomer could be assigned as follows: ^{1}H nmr δ 1.29 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$), 1.34 (s, 3H, angular methyl), 3.38 (s, 3H, -OCH$_3$), 4.18 (q, 2H, J = 7 Hz, -OCH$_2$CH$_3$), 4.80 (s, 2H, -OCH$_2$O-), 5.69 (s, 1H, olefinic proton).

Preparation of the α,β-Unsaturated Ester (66)
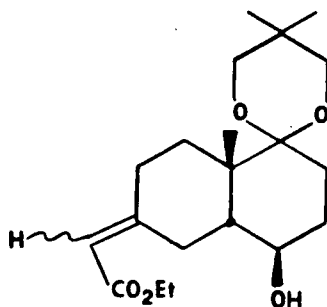
A solution consisting of 60 mg (0.17 mmol) of α,β-unsaturated ester (65), 100 mg (0.96 mmol) of 2,2-dimethyl-1,3-propanediol, approximately 4 mg (0.02 mmol) of p-toluenesulfonic acid monohydrate and, 25 ml of freshly distilled benzene was refluxed for 5.5 h with azeotropic removal of water utilizing a Dean-Stark trap. The reaction mixture was cooled to room temperature and poured into aqueous sodium bicarbonate. The resulting solution was extracted thoroughly with ether and the combined organic extracts were washed (water, brine) and dried over anhydrous sodium sulfate. Removal of the solvents under reduced pressure gave a yellow gum which was purified by preparative tlc (50% ethyl acetate in cyclohexane eluent). Two compounds, both of the geometric isomers of the α,β-unsaturated ester (66), were thus isolated.

The first, which solidified on standing (26 mg, 44%), was recrystallized from carbon tetrachloride-hexane and exhibited mp 110-112 °C; uv λ_{max} 222 nm ($\varepsilon = 12{,}893$); ir (CHCl$_3$) ν_{max} 3500 (broad), 1695, 1648 cm^{-1}; ^{1}H nmr δ 0.70, 1.18 (2s, 3H each, ketal methyls), 1.25 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$), 1.32 (s, 3H, angular methyl), 4.12 (q, 2H, J = 7Hz, -OCH$_2$CH$_3$), 4.14 (s, 1H, -OH), 5.74 (broad s, 1H, olefinic proton). Anal. calcd. for C$_{20}$H$_{32}$O$_5$: C 68.15, H 9.15; found: C 68.23, H 9.18.

The second geometric isomer (27 mg, 45%) gave the following spectral data: ir (film) ν_{max} 3450 (broad), 1710, 1642 cm^{-1}; ^{1}H nmr δ 0.72, 1.21 (2s, 3H each, ketal methyls), 1.28 (t, 3H, J = 8 Hz, -OCH$_2$CH$_3$), 1.34 (s, 3H, angular methyl), 4.16 (q, 2H, J = 8 Hz, -OCH$_2$CH$_3$), 5.70 (broad s, 1H, olefinic proton). Exact mass calcd. for C$_{20}$H$_{32}$O$_5$: 352.2250; found: 352.2262.

Preparation of the α,β-Unsaturated Ester (67)
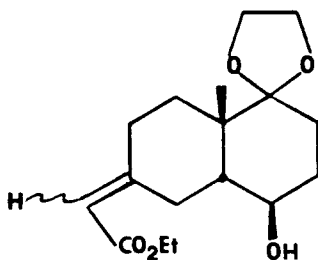
The α,β-unsaturated ester (67) (62 mg, 0.18 mmol) was dissolved in 3 ml of ethylene glycol and 0.02 ml (0.16 mmol) of freshly distilled boron trifloride etherate was added with stirring. The mixture was stirred at room temperature for 24 h, poured into aqueous sodium bicarbonate and the resulting solution was thoroughly extracted with ether. The combined ether extracts were washed successively with water and brine and dried over anydrous sodium sulfate. Evaporation of the solvents under reduced pressure gave a brown oil which was purified by preparative tlc (25% ethyl acetate in cyclohexane) giving both the geometric isomers of the α,β-unsaturated ester (67).

One of these isomers (R_f = 0.3, 42%), which solidified on standing, mp 163-167 °C, gave the following analytical data: uv λ_{max} 223 (ε = 11,324); ir (CHCl$_3$) ν_{max} 3600, 1703, 1641 cm^{-1}; ^{1}H nmr δ 1.13 (s, 3H, angular methyl), 1.28 (t, 3H, J = 8 Hz, -OCH$_2$CH$_3$), 3.96 (s, 4H, ketal protons), 4.16 (q, 2H, J = 8 Hz, -OCH$_2$CH$_3$), 5.71 (broad s, 1H, olefinic proton). Exact mass calcd. for C$_{17}$H$_{26}$O$_5$: 310.1780; found: 310.1773.
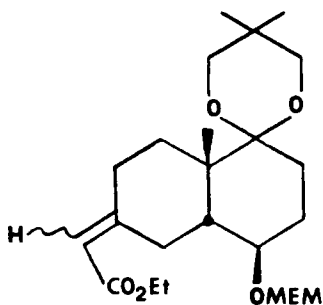
The other geometric isomer (R_f = 0.2, 48%) exhibited mp 177-178 °C; uv λ_{max} 224 (ε = 11,064); ir (CHCl$_3$) ν_{max} 3500 (broad), 1687, 1642 cm^{-1}; ^{1}H nmr δ 1.14 (s, 3H, angular methyl), 1.28 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$), 3.91-4.28 (broad s, 1H, -OH), 3.95 (s, 4H, ketal protons),

4.18 (q, 2H, J = 7 Hz, $-O\underline{CH}_2CH_3$), 5.80 (broad s, 1H, olefinic proton).

<u>Exact</u> <u>mass</u> calcd. for $C_{17}H_{26}O_5$: 310.1780; found: 310.1786.

Preparation of the α,β-Unsaturated Ester (61)

A) From the Diketal Ether (35)

To 75 ml of dry 2-methylcyclohexanone was added 5.54 g (12.1 mmol) of the diketal ether (35) followed by 210 mg (1.1 mmol) of p-toluenesulfonic acid monohydrate. This solution was stirred at room temperature for three days, at which time only a trace of the starting material was present by tlc. The reaction mixture was poured into aqueous sodium bicarbonate and the resultant mixture was extracted with two portions ether. The combined ethereal extracts were washed with water and brine and dried over anhydrous sodium sulfate. The solvent was removed <u>in</u> <u>vacuo</u> to afford a pale yellow oil which consisted primarily of the monoketal ethers (62) and (63) in a ratio of 3.5:1, respectively (glc). A solution of this oil in 50 ml of 1,2-dimethoxyethane was added to a cold (0 °C) solution of the potassium salt of triethyl phosphonoacetate (32 mmol).[†] The resulting solution was stirred for 0.5 h at 0 °C. The

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[†]The potassium salt of triethyl phosphonoacetate was prepared as follows: to a cold (0 °C) solution of 6.6 ml (32 mmol) of a 21% suspension of potassium hydride in mineral oil and 200 ml of dry 1,2-dimethoxyethane was added 7.2 ml (36 mmol) of triethyl phosphonoacetate and the resulting solution was stirred for 15 min.

ice-water bath was removed and the reaction mixture was stirred for 19 h at room temperature. The solution was poured into cold water and diluted with ether. The aqueous layer was extracted with a further portion of ether, the combined organic extracts were washed (water, brine) and the dried (sodium sulfate) solution was evaporated giving 11.0 g of crude product. Chromatography (400 g silica gel, 33% ethyl acetate in benzene as eluting solvent) of this material gave 3.91 g (73%) of the α,β-unsaturated ester (61), a 1:1 mixture of geometric isomers (nmr), as a viscous, colorless gum and 0.9 g (20%) of the monoketal ether (63), containing a small amount of recovered (62).

Selective crystallization of a portion of the α,β-unsaturated ester (61) from ether-hexane afforded a pure sample of one of the geometric isomers as colorless prisms, mp 57-58 $^{\circ}$C; uv λ_{max} 223 nm (ε = 7684); ir (CHCl$_3$) ν_{max} 1705, 1645, 1147, 1105, 1040 cm^{-1}; ^{1}H nmr δ 0.70, 1.18 (2s, 3H each, ketal methyls), 1.26 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$), 1.30 (s, 3H, angular methyl), 3.40 (s, 3H, -OCH$_3$), 4.11 (q, 2H, J = 7 Hz, -OCH$_2$CH$_3$), 4.73, 4.82 (2d, 2H, J = 7 Hz, -OCH$_2$O-, AB quartet), 5.58 (s, 1H, olefinic proton). Anal. calcd. for C$_{24}$H$_{40}$O$_7$: C 65.43, H 9.15; found: C 65.56, H 9.19.

By comparing the ^{1}H nmr spectrum of the isomer isolated as a pure solid with that of the pure mixture of geometric isomers, the spectral data due to the geometric isomer not isolated in pure form could be assigned as as follows: [1]H nmr δ 0.70, 1.18 (2s, 3H each, ketal methyls), 1.24 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$), 1.30 (s, 3H, angular methyl), 3.36 (s, 3H, -OCH$_3$), 3.91 (q, 2H, J = 7 Hz, -OCH$_2$CH$_3$), 4.62, 4.74 (2d, J = 8 Hz, -OCH$_2$O-, AB quartet), 5.70 (broad s, 1H, olefinic proton).

B)   From the α,β-Unsaturated Ester (65)

A solution of the α,β-unsaturated ester (65) (202 mg, 0.57 mmol) in

12 ml of freshly distilled 2-ethyl-2,5,5-trimethyl-1,3-dioxane (70)[†] was

treated with 32 mg (0.17 mmol) of p-toluenesulfonic acid monohydrate.

The mixture was heated to 60 °C and stirred at this temperature for 4

days. The reaction mixture was cooled to room temperature, diluted with

ether and the resulting solution was washed successively with two por-

tions of aqueous sodium bicarbonate, two portions of water and one

portion of brine. The ether was removed under reduced pressure and the

residual solution, containing the crude product and (70), was passed

through a short column of neutral alumina (activity IV) using petroleum

ether (bp 30-60 °C) as eluting solvent. After all the solvent (70)

had been eluted (glc) from the column, ethyl acetate, in gradually

increasing proportions, was added to the eluting solvent. The column

was flushed with solvent until all the crude product (tlc) had been

eluted and the combined product containing fractions were concentrated

in vacuo. The crude product contained four compounds (tlc) which were

separated by preparative tlc (40% ethyl acetate in cyclohexane as devel-

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[†]This material was prepared as follows: to a solution of dry butanone
(40 g, 0.56 mol) in 400 ml of dry benzene was added 2,2-dimethyl-1,3--
propanediol (125 g, 1.2 mol) and a catalytic amount of p-toluene-
sulfonic acid. The resulting solution was refluxed under a Dean-Stark
trap for four hours, cooled to room temperature and poured into aqueous
sodium bicarbonate. The resulting mixture was thoroughly extracted with
ether and the combined organic extracts were washed (water, brine) and
dried (sodium sulfate). Evaporation of the solvents under reduced pres-
sure, followed by fractional distillation of the residue (74°C/56 mm),
gave 2-ethyl-2,5,5-trimethyl-1,3-dioxane (70) as a pure [glc (column A,
70 °C), ^{1}H nmr], colorless liquid.

oping solvent) yielding 46 mg (23%) of recovered starting material (65), 36 mg (34% total) of each of the geometric isomers of the α,β-unsaturated ester (66) (both of which were idential in all respects with previously prepared material, see p. 142) and 68 mg (27%) of the desired α,β-unsaturated ester (61). The latter proved to be identical (ir, ^{1}H nmr) with the material prepared previously (see Part A).

Preparation of the Monoketones (62) and (63)

(62)

(63)
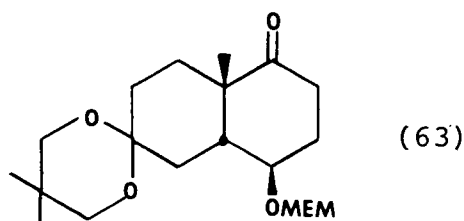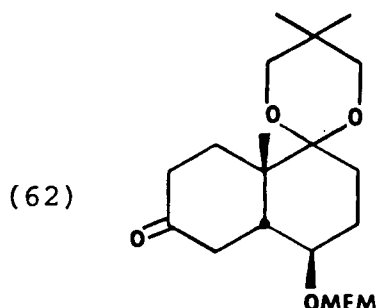
To a solution of 19 mg (0.04 mmol) of the diketal ether (35) in 10 ml of dry methyl ethyl ketone was added 4 mg (0.02 mmol) of p-toluene-sulphonic acid. The solution was cooled to 0 °C and stirred for 18 h. The reaction mixture was poured into dilute aqueous sodium bicarbonate and the resulting solution was thoroughly extracted with ether. The combined ether extracts were washed successively with water and brine and dried over anhydrous sodium sulfate. Removal of the solvents gave a viscous oil which was subjected to preparative tlc (33% ethyl acetate in cyclohexane) giving 14 mg (91%) of a 2:1 mixture (glc, ^{1}H nmr) of the monoketones (62) and (63), respectively. A pure sample of monoketone (63) was obtained by preparative tlc (triple development using 25% ethyl acetate in cyclohexane). This material crystallized after prolonged

storage at -6 $^{\circ}$C; recrystallization from chloroform-hexane gave the monoketone (63) as white needles, mp 64-65 $^{\circ}$C; ir (CHCl$_3$) ν_{max} 1703, 1090, 1035 cm^{-1}; ^{1}H nmr δ 0.88, 1.00 (2s, 3H each, ketal methyls), 1.31 (s, 3H, angular methyl), 2.58-3.02 (m, 1H, C$_8$H), 3.40 (s, 3H, -OCH$_3$), 4.83, 4.91 (2d, 2H, J = 8 Hz, -OCH$_2$O-, AB quartet). Anal. calcd. for C$_{20}$H$_{34}$O$_6$: C 64.84, H 9.25; found: C 65.05, H 9.35.

The ^{1}H nmr spectral data of the major component, monoketone (62), obtained via a comparison of the ^{1}H nmr spectra of the pure mixture with that of the pure monoketone (63), is as follows: ^{1}H nmr δ 0.72, 1.20 (2s, 3H each, ketal methyls), 1.40 (s, 3H, angular methyl), 3.34 (s, 3H, -OCH$_3$), 4.63, 4.78 (2d, 2H, J = 7 Hz, -OCH$_2$O-, AB quartet).

Deuteration of the Monoketone (63)

The monoketone (63) (32 mg, 0.08 mmol) was dissolved in 4 ml of methanol-d$_1$ and a small amount of sodium methoxide was added. The resulting solution was gently refluxed for 30 h, cooled to room temperature and poured into water. The resulting mixture was extracted with two portions of ether and the combined ether solution was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvents gave 30 mg of the deuterated ketone (71), which exhibited a molecular ion peak at m/e 372 (low resolution mass spectrometry) corresponding to the introduction of 2 deuterium atoms. The ^{1}H nmr spectral data of this material was as follows: ^{1}H nmr δ 0.88, 1.00 (2s, 3H each, ketal methyls), 1.31 (s, 3H, angular methyl), 3.40 (s, 3H, -OCH$_3$), 4.83, 4.91 (2d, 2H, J = 8 Hz, -OCH$_2$O-, AB quartet).

Ketalization of the Monoketals (63) and (62)

To a solution of 190 mg (0.51 mmol) of a 65:35 mixture (glc, nmr)

of the monoketals (63) and (62), respectively, and 530 mg (5.0 mmol) of

2,2-dimethyl-1,3-propanediol in 30 ml of benzene was added 10 mg (0.05

mmol) of p-toluenesulfonic acid monohydrate. The solution was refluxed

under a Dean-Stark trap for 4 h and subsequently cooled to room temper-

ature. Dilution of the mixture with ether, followed by washing the

resulting solution with aqueous sodium bicarbonate, water and brine,

gave a clear, yellow solution which was dried over anhydrous sodium

sulfate. Removal of the solvents under reduced pressure yielded a pale

yellow gum. Crystallization of this material from methylene chloride-

hexane afforded 95 mg (48%) of the diketal alcohol (31) as a pure solid.

Concentration of the mother liquor followed by the purification of the

resulting residue by preparative tlc (30% ethyl acetate in benzene),

gave a further 88 mg (44%) of the diketal alcohol (31). This material

(mp 161-163 °C) was identical in all respects with the diketal alcohol

(31) which was prepared previously (see page 125).

Hydrogenation of the α,β-Unsaturated Ester (61)

To a solution of 525 mg (1.2 mmol) of the α,β-unsaturated ester

(61) in tetrahydrofuran was added 50 mg of platinum oxide. The mixture

was hydrogenated at 50 psi and room temperature. After the reaction was

complete (tlc, 2 h), the mixture was filtered through celite. Evapor-

ation of the solvent from the filtrate gave a viscous colorless gum

which was composed of two compounds (tlc) in a ratio of 66:34 [glc

column A, 220 °C)]. The crude product was subjected to column chromatography on 40 g of silica gel using 25% ethyl acetate in cyclohexane as eluting solvent, yielding 176 mg (34%) of the saturated ester (76) and 332 mg (63%) of the desired product, saturated ester (72).

The undesired epimer, saturated ester (76), gave the following analytical data: ir (film) ν_{max} 1730, 1100, 1032 cm^{-1}; ^{1}H nmr δ 0.68 (s, 3H, ketal methyl), 1.13 (s, 6H, ketal methyl & angular methyl), 1.21 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$), 3.33 (s, 3H, -OCH$_3$), 4.06 (q, 2H, J = 7 Hz, -OCH$_2$CH$_3$), 4.69, 4.79 (2d, 2H, J = 7 Hz, -OCH$_2$O-, AB quartet); ^{13}C nmr δ 94.70 (-OCH$_2$O-), 99.85 (C$_9$), 172.71 (-CO$_2$C$_2$H$_5$). <u>Exact mass</u> calcd. for C$_{24}$H$_{42}$O$_7$: 442.2930; found: 442.2946.

The desired epimer, saturated ester (72), gave the following analytical data: ir (film) ν_{max} 1737, 1118, 1045 cm^{-1}, ^{1}H nmr δ 0.68, 1.16 (2s, 3H each, ketal methyls), 1.04 (s, 3H, angular methyl), 1.24 (t, 3H, J = 7.5 Hz, -OCH$_2$CH$_3$), 2.06-2.52 (m, 4H, -CH$_2$CO$_2$C$_2$H$_5$, C$_3$H and C$_5$H), 3.35 (s, 3H, -OCH$_3$), 4.09 (q, 2H, J = 7.5 Hz, -OCH$_2$CH$_3$), 4.64, 4.77 (2d, 2H, J = 7.5 Hz, -OCH$_2$O-, AB quartet); ^{13}C nmr δ 93.61 (t, J = 162 Hz, -OCH$_2$O-), 102.48 (C$_9$), 173.06 (-CO$_2$C$_2$H$_5$). <u>Exact mass</u> calcd. for C$_{24}$H$_{42}$O$_7$: 442.2930; found: 442.2948.

<u>Deprotection of the Saturated Ester (76):</u>

<u>Preparation of the Ketal Alcohol (78) and the Keto Alcohol (79)</u>

(78)

(79)

To a solution of 155 mg (0.35 mmol) of the saturated ester <u>(76)</u> in 20 ml of dry benzene was added 182 mg (1.75 mmol) of recrystallized 2,2—dimethyl-1,3-propanediol followed by 25 mg (0.13 mmol) of p-toluene-sulfonic acid. The solution was refluxed in an apparatus fitted with a Dean-Stark separator for 45 min. The mixture was cooled to room temper-ature, poured into aqueous sodium bicarbonate and thoroughly extracted with ether. The combined organic extracts were washed with water (3 portions) and brine and dried over anhydrous sodium sulfate. Evapor-ation of the solvents <u>in vacuo</u>, followed by purification of the crude product by preparative tlc (40% ethyl acetate in benzene developer), afforded 93 mg (75%) of the ketal alcohol <u>(78)</u>, as well as 21 mg (22%) of the ketal cleaved product, the keto alcohol <u>(79)</u>.

The ketal alcohol <u>(78)</u> displayed the following spectral character-istics: ir (film) ν_{max} 3480 (broad), 1735, 1103 cm^{-1}; ^{1}H nmr δ 0.70 (s, 3H, ketal methyl), 1.18 (s, 6H, ketal methyl & angular methyl), 1.24 (t, 3H, J = 7 Hz, -OCH$_2$C$\underline{H}_3$), 1.68 (broad s, 1H, -O$\underline{H}$), 3.18-3.78 (m, 4H, ketal methylenes), 3.78 (ddd, 1H, J = 10, 10 & 5.5 Hz, C$_6$H), 4.14 (q, 2H, J = 7 Hz, -OC$\underline{H}_2$CH$_3$). <u>Exact mass</u> calcd. for C$_{20}$H$_{34}$O$_5$: 354.2406;

found: 354.2391.

The keto alcohol (79) gave the following spectral data: ir $(CHCl_3)$ ν_{max} 3452 (broad), 1720 (shoulder), 1702 cm^{-1}; ^{1}H nmr δ 1.21 (s, 3H, angular methyl), 1.28 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), 1.77 (s, 1H, $-O\underline{H}$), 4.08-4.40 (m, 1H, C_6H), 4.16 (q, 2H, J = 7 Hz, $-OC\underline{H}_2CH_3$). Exact mass calcd. for $C_{15}H_{24}O_4$: 268.1674; found: 268.1676.

Preparation of the Ketal Tosylate (75)
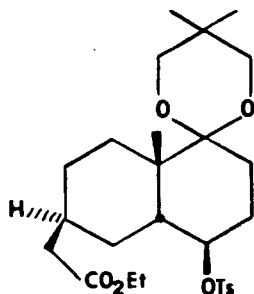
To a cold solution (0 °C) of 62 mg (0.18 mmol) of the ketal alcohol (78) in 5 ml of dry pyridine was added 300 mg (1.6 mmol) of recrystallized p-toluenesulfonyl chloride with stirring. The reaction mixture was warmed to room temperature and stirred for 13 h. The mixture was diluted with ether and the resulting solution was washed with aqueous sodium bicarbonate, water and brine. After the solution had been dried over anhydrous sodium sulfate, the solvents were removed in vacuo. The crude product (98 mg) thus obtained was purified by preparative tlc (25% ethyl acetate in cyclohexane) affording 72 mg (81%) of the ketal tosylate (75) as a cream colored solid (mp 142-143 °C). Recrystallization of this material from acetone gave pure white needles of the ketal tosylate (75), which exhibited mp 148-149 °C (dec); ir $(CHCl_3)$ ν_{max} 1720 cm^{-1}; ^{1}H nmr δ 0.68 (s, 3H, ketal methyl), 1.13 (s, 6H, ketal methyl &

angular methyl), 1.26 (t, 3H, J = 7 Hz, $-OCH_2CH_3$), 2.40 (s, 3H, aromatic

methyl), 3.14-3.70 (m, 4H, ketal methylenes), 4.11 (q, 2H, J = 7 Hz,

$-OCH_2CH_3$), 4.78 (ddd, 1H, J = 11,11 & 5.5 Hz, C_6H), 7.31, 7.80 (2d, 2H

each, J = 8 Hz, aromatic protons). <u>Exact mass</u> calcd. for $C_{27}H_{40}O_7S$:

508.2494; found: 508.2501.

Deprotection of the Saturated Ester (72):

Preparation of the Ketal Alcohol (77) and the Keto Alcohol (80)
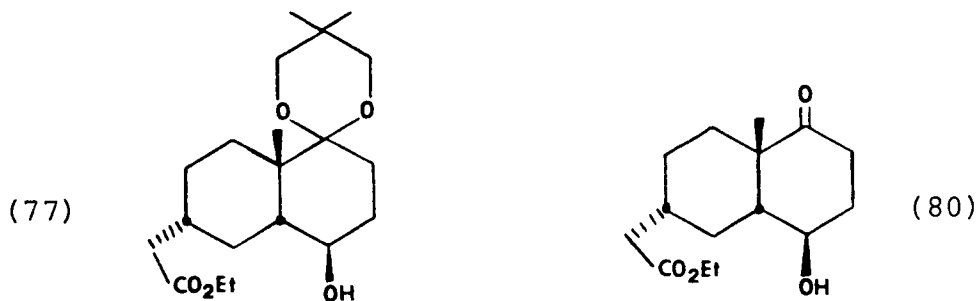
A solution consisting of 200 mg (0.45 mmol) of the saturated ester

(72), 235 mg (2.3 mmol) of dry, recrystallized 2,2-dimethyl-1,3-propan-

ediol, 25 mg (0.13 mmol) of p-toluenesulfonic acid and 30 ml of dry

benzene was refluxed for 45 min using an apparatus fitted with a Dean-

Stark trap. After the reaction mixture had been cooled to room temper-

ature, it was diluted with ether. The resulting solution was washed

with aqueous sodium bicarbonate (two portions). The ether layer was

isolated and washed with water and brine and dried over anhydrous sodium

sulfate. Purification of the crude product by preparative tlc (33%

ethyl acetate in benzene as developing solvent) gave 86 mg (54%) of the

ketal alcohol (77) as a pale yellow gum and 36 mg (30%) of the keto

alcohol (80).

The ketal alcohol (77) gave the following spectral data: ir (film)

ν_{max} 3495 (broad), 1728, 1095 cm^{-1}; ^{1}H nmr δ 0.68, 1.15 (2s, 3H each, ketal methyls), 1.12 (s, 3H, angular methyl), 1.22 (t, 3H, J = 7 Hz, -OCH$_2$C$\underline{H}_3$), 3.11-3.83 (m, 5H, ketal methylenes & C$_6$H), 3.68 (s, 1H, -O$\underline{H}$), 4.09 (q, 2H, J = 7 Hz, -OC$\underline{H}_2$CH$_3$). <u>Exact</u> <u>mass</u> calcd. for C$_{20}$H$_{34}$O$_5$: 354.2406; found: 354.2408.

The keto alcohol (80) had the following spectral characteristics: ir (CHCl$_3$) ν_{max} 3605, 1723 (shoulder), 1708 cm^{-1}; ^{1}H nmr δ 1.20 (t, 3H, J = 7 Hz, -OCH$_2$C$\underline{H}_3$), 1.38 (s, 3H, angular methyl), 1.82 (s, 1H, -O$\underline{H}$), 2.72-3.18 (m, 1H, C$_8$H), 3.87 (broad s, 1H, C$_6$H), 4.07 (q, 2H, J = 7 Hz, -OC$\underline{H}_2$CH$_3$). <u>Exact</u> <u>mass</u> calcd. for C$_{15}$H$_{24}$O$_4$: 268.1675; found: 268.1674.

<u>Preparation of the Ketal Tosylate (73)</u>
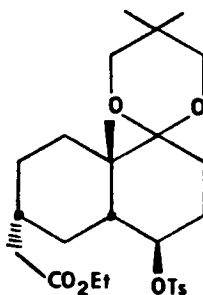
To a solution of 85 mg (0.24 mmol) of the ketal alcohol (77) in 5 ml of dry pyridine was added, at 0 °C with stirring, 460 mg (2.4 mmol) of recrystallized p-toluenesulfonyl chloride. The reaction mixture was warmed to room temperature and stirred at this temperature for 17 h. The mixture was cooled to 0 °C and ice was added to the reaction mixture. After the resultant mixture had been stirred until all the ice had melted, the solution was diluted with ether and the organic layer was isolated and washed with aqueous sodium bicarbonate, water and brine. The dried (sodium sulfate) solution was evaporated under reduced

pressure to give a pale yellow gum (one component by tlc). Purification of this material by preparative tlc (25% ethyl acetate in benzene) gave 98 mg (80%) of the ketal tosylate (73). The latter gave the following spectral data: ir (film) ν_{max} 1722 cm^{-1}; ^{1}H nmr δ 0.68, 1.13 (2s, 3H each, ketal methyls), 1.01 (s, 3H, angular methyl), 1.24 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$), 2.42 (s, 3H, aromatic methyl), 3.12-3.80 (m, 4H, ketal methylenes), 4.09 (q, 2H, J = 7 Hz, -OCH$_2$CH$_3$), 4.49 (broad s, 1H, C$_6$H), 7.31, 7.56 (2d, 2H each, J = 8 Hz, aromatic protons). Exact mass calcd. for C$_{27}$H$_{40}$O$_7$S: 508.2494; found: 508.2455.

Preparation of the Keto Ether (92)
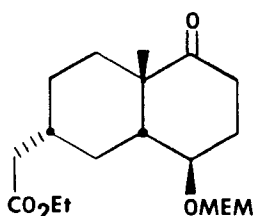
The saturated ester (72), 32 mg (0.07 mmol), was dissolved in 5 ml of acetone and 5 ml of 1N hydrochloric acid was added with stirring. The solution was stirred at room temperature for 1 h, poured into saturated aqueous sodium bicarbonate and the resulting mixture was thoroughly extracted with ether. The combined organic phase was washed with three portions of water and one portion of brine and dried over anhydrous sodium sulfate. Removal of the solvents in vacuo afforded 20 mg (77%) of the keto ether (92) as a colorless oil which was pure by tlc, ^{1}H nmr and glc (column A, 190 ^{o}C) analyses. This material exhibited the following analytical data: ir (film) ν_{max} 1732, 1705, 1115, 1050 cm^{-1};

^{1}H nmr δ 1.25 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$), 1.35 (s, 3H, angular methyl),

3.42 (s, 3H, -OCH$_3$), 3.48-3.86 (m, 5H, C$_6$H & -OCH$_2$CH$_2$O-), 4.14 (q, 2H,

J = 7 Hz, -OCH$_2$CH$_3$), 4.82, 4.88 (2d, 2H, J = 7 Hz, -OCH$_2$O-, AB quartet).

Exact mass calcd. for C$_{19}$H$_{32}$O$_6$: 356.2199; found: 356.2191.

Preparation of the Keto Ether (91)
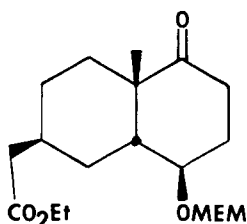
To a solution of 48 mg (0.11 mmol) of the saturated ester (76) in 5

ml of acetone was added, with stirring at room temperature, 5 ml of 1N

hydrochloric acid. The solution was stirred for 1 h and poured into

saturated aqueous sodium bicarbonate. Thorough extraction of the re-

sulting mixture with ether, followed by washing (water, brine) and

drying (sodium sulfate) of the combined organic phase, gave 32 mg (82%)

of the keto ether (91) after the solvents had been removed under reduced

pressure. The product, a colorless oil, was pure by tlc, ^{1}H nmr and glc

(column A, 190 ^{o}C) analyses. The following spectral data was obtained

from this material: ir (film) ν_{max} 1730, 1708, 1108, 1048 cm^{-1}; ^{1}H nmr δ

1.21 (s, 3H, angular methyl), 1.25 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$), 3.42 (s,

3H, -OCH$_3$), 3.48-3.86 (m, 4H, -OCH$_2$CH$_2$O-), 4.12 (m, 1H, C$_6$H), 4.16 (q,

3H, J = 7 Hz, -OCH$_2$CH$_3$), 4.85, 4.91 (2d, 2H, J = 7 Hz, -OCH$_2$O-, AB

quartet). Exact mass calcd. for C$_{19}$H$_{32}$O$_6$: 356.2199; found: 356.2187.

Preparation of the Alcohol (89)
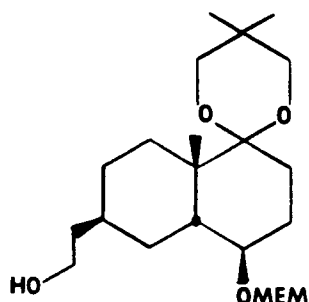
A) By Reduction of the Saturated Ester (76)

A suspension containing 20 mg (0.5 mmol) of 95% lithium aluminum hydride in 10 ml of anhydrous ether was cooled to -78 °C. To this cold solution was added, dropwise with stirring, 105 mg (0.24 mmol) of the saturated ester (76) dissolved in 8 ml of anhydrous ether. After 1 h the reaction mixture was warmed to 0 °C and 4 ml of ethyl acetate was added followed by 5 ml of water. The mixture was warmed to room temperature, filtered through celite and the filtrate was diluted with water and ether. The layers were separated and the organic phase was washed successively with two portions of water and one portion of brine. The dried (sodium sulfate) organic extracts were evaporated in vacuo affording 94 mg (99%) of the alcohol (89) which was pure by tlc and glc (column A, 220 °C) analyses. This material exhibited the following spectral properties: ir (film) ν_{max} 3480 (broad), 1105, 1035 cm^{-1}; ^{1}H nmr δ 0.68 (s, 3H, ketal methyl), 1.15 (s, 6H, angular methyl & ketal methyl), 2.12 (broad s, 1H, -OH), 2.54 (dd, 1H, J = 3 & 11 Hz, C$_5$H), 3.12-3.81 (m, 9H, ketal methylenes, -OCH$_2$CH$_2$O-, & C$_6$H), 3.34 (s, 3H, -OCH$_3$), 3.87 (ddd, 1H, J = 11, 11 & 5 Hz, C$_6$H), 4.66, 4.80 (2d, 2H, J = 7 Hz, -OCH$_2$O-, AB quartet). Exact mass calcd. for C$_{22}$H$_{40}$O$_6$: 400.2825; found: 400.2855.

B)   By Birch-type Reduction of the α,β-Unsaturated Ester (61)

Freshly distilled ammonia (from lithium metal), 30 ml, was added to

a cold solution (-78 °C) consisting of 78 mg (0.18 mmol) of the α,β--

unsaturated ester (61), 15 ml of anhydrous ether and 10 ml of absolute

ethanol. Lithium wire was added, in finely cut portions, until a blue

color remained in solution between additions for 10-15 min. The reac-

tion was quenched by the portion-wise addition of ammonium chloride.

The ammonia was allowed to evaporate and the residue was diluted with

water and ether. The ether layer was isolated and subsequently washed

with water and brine and dried over anhydrous sodium sulfate. Removal

of the solvents under reduced pressure afforded 60 mg (84%) of the

alcohol (89) as a colorless gum which was pure by ^{1}H nmr, tlc and glc

(column A, 220 °C) analyses. This material was identical in all respects

with the material prepared previously (see Part A).

Preparation of the Alcohol (90)
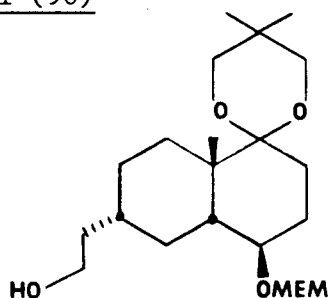
To a cold (-78 °C) suspension of 20 mg (0.5 mmol) of 95% lithium

aluminum hydride in 10 ml of anhydrous ether was added, dropwise with

stirring, 60 mg (0.14 mmol) of the saturated ester (72) dissolved in 5

ml of anhydrous ether. The temperature was maintained at -78 °C for one

hour then the solution was warmed to 0 °C. Ethyl acetate (5 ml), followed by water (4 ml), was added to the reaction mixture and the solution was warmed to room temperature. The mixture was filtered through celite, the filtrate was diluted with water, and thoroughly extracted with ether. The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate and evaporated yielding 57 mg (100%) of the alcohol (90) as a pure [tlc, glc (column A, 220 °C)], colorless gum; ir (film) v_{max} 3490 (broad), 1100, 1035 cm^{-1}; ^1H nmr δ 0.68, 1.16 (2s, 3H each, ketal methyls), 1.04 (s, 3H, angular methyl), 2.33 (m, 2H, C_3H & C_5H), 3.12-3.80 (m, 11H, $-C\underline{H}_2OH$, $-OC\underline{H}_2C\underline{H}_2O-$, ketal methylenes & C_6H), 3.35 (s, 3H, $-OC\underline{H}_3$), 4.68, 4.78 (2d, 2H, J = 7 Hz, $-OC\underline{H}_2O-$, AB quartet). Exact mass calcd. for $C_{22}H_{40}O_6$: 400.2825; found: 400.2859.

Preparation of the β,γ-Unsaturated Ester (93)
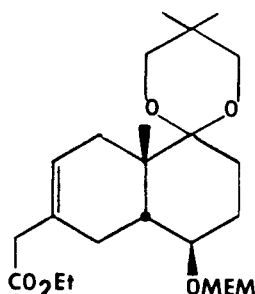
To a cold (-78 °C) solution containing 150 mg (0.34 mmol) of the α,β-unsaturated ester (61) (crystalline isomer) in 5 ml of dry tetrahydrofuran was added 1.03 ml (1.75 M, 0.85 mmol) of a cold (0 °C) solution of lithium diisopropylamide-hexamethylphosphoramide (1:1) in tetrahydrofuran. The resulting solution was stirred at -78 °C for 3 h. Water (approximately 1 ml) was added to the reaction mixture and the

mixture was warmed to room temperature. The solution was poured into ether and the resultant solution was diluted with water. The aqueous layer was thoroughly extracted with ether and the combined organic phase was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvents in vacuo gave 129 mg of a yellow gum [100% by glc (column A, 180 °C)]. Purification of this material by preparative tlc (25% ethyl acetate in cyclohexane) afforded 120 mg (80%) of the β,γ--unsaturated ester (93) as a pale yellow gum; ir (film) ν_{max} 1730, 1100, 1038 cm^{-1}; ^{1}H nmr δ 0.70, 1.19 (2s, 3H each, ketal methyls), 1.10 (s, 3H, angular methyl), 1.24 (t, 3H, J = 7 Hz, $-OCH_2C\underline{H}_3$), 2.94 (s, 2H, $-C\underline{H}_2CO_2C_2H_5$), 3.18-3.90 (m, 9H, ketal methylenes, $-OC\underline{H}_2C\underline{H}_2O-$, & C_6H), 3.38 (s, 3H, $-OC\underline{H}_3$), 4.13 (q, 2H, J = 7 Hz, $-OC\underline{H}_2CH_3$), 4.70, 4.81 (2d, 2H, J = 7 Hz, $-OC\underline{H}_2O-$, AB quartet), 5.49 (broad s, 1H, C_2H). Exact mass calcd. for $C_{24}H_{40}O_7$: 440.2774; found: 440.2769.

Preparation of the Dialkylated Ester (95)
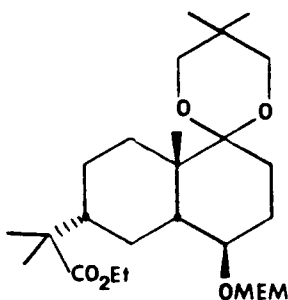
A solution containing 251 mg (0.57 mmol) of the saturated ester (72) in 3 ml of dry tetrahydrofuran was cooled to -78 °C and 2.0 ml (1.1 mmol) of a cold (0 °C), 0.54 M solution of lithium diisopropylamide in tetrahydrofuran was added dropwise. The resulting solution was stirred at -78 °C for one hour and 0.07 ml (1.1 mmol) of methyl iodide in 0.5 ml

of hexamethylphosphoramide was added dropwise. The reaction mixture was warmed to -20 $^{\circ}$C (0.5 h) and subsequently warmed to 0 $^{\circ}$C and stirred at this temperature for 0.5 h. Lithium diisopropylamide (2.6 ml, 0.54 $\underline{M}$, 1.4 mmol) was added to the reaction mixture at -78 $^{\circ}$C and, after the resultant solution had been stirred for 1 h, it was warmed to -20 $^{\circ}$C (30 min). A solution of 0.14 ml (2.3 mmol) of methyl iodide in 5 ml of hexamethylphosphoramide was added to the reaction mixture at -78 $^{\circ}$C, the mixture was warmed to -20 $^{\circ}$C (30 min) and then warmed to 0 $^{\circ}$C for 1.5 h. The reaction mixture was poured into water and the resulting solution was thoroughly extracted with ether. The combined ether extracts were washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvents gave 307 mg of a pale brown gum. Preparative tlc (25% ethyl acetate in benzene) purification of the crude product gave 264 mg (99%) of the pure dialkylated ester (95) as a color-less gum; ir (film) v_{max} 1725, 1105, 1035 cm^{-1}; ^{1}H nmr δ 0.70, 1.18 (2s, 3H each, ketal methyls), 1.05 (s, 3H, tertiary methyl), 1.07 (s, 6H, tertiary methyls), 1.24 (t, 3H, J = 8 Hz, -OCH$_2$C$\underline{H}_3$), 2.26-2.48 (m, 2H, C$_3$H & C$_5$H), 3.10-3.78 (m, 9H, ketal methylenes, -OC$\underline{H}_2$C$\underline{H}_2$O-, & C$_6$H), 3.40 (s, 3H, -OC$\underline{H}_3$), 4.12 (q, 2H, J = 8 Hz, -OC$\underline{H}_2$CH$_3$), 4.72, 4.78 (2d, 2H, J = 7 Hz, -OC$\underline{H}_2$O-, AB quartet). Exact mass calcd. for C$_{26}$H$_{46}$O$_7$: 470.3243; found: 470.3204.

Preparation of the Carboxylic Acid (102)
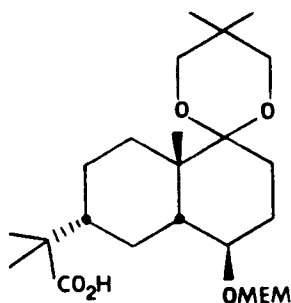
To a solution of 143 mg (0.3 mmol) of the dialkylated ester (95) in 1 ml of dry dimethyl sulfoxide was added 5 ml of a 1M̲ solution of potassium tert̲-butoxide in dry dimethyl sulfoxide, with stirring at room temperature. The resulting dark brown solution was stirred for 1.75 h, cooled to 0 °C and 2 ml each of methanol and water was added. Acidic ion exchange resin (Amberlite IR-120) was added, in portions with vigorous stirring, until a neutral pH was reached (pH paper). The resulting cold mixture was immediately filtered (sintered glass) and the resin was washed with several portions of ether. The filtrate was diluted with water and the ether layer was isolated and washed successively with water and brine. The dried (sodium sulfate) organic phase was evaporated yielding 158 mg of a yellow gum. This material was purified by preparative tlc (ethyl acetate) affording 118 mg (88%) of a pale yellow gum which crystallized on standing. Recrystallization of a portion of this material from ether-hexane gave an analytical sample of the carboxylic acid (102), which exhibited mp 124-125 °C; ir (CHCl$_3$) ν_{max} 3450-2400 (broad), 1695, 1110, 1040 cm^{-1}; ^{1}H nmr δ 0.70, 1.18 (2s, 3H each, ketal methyls), 1.06 (s, 3H, tertiary methyl), 1.11 (s, 6H, tertiary methyls), 2.20-2.54 (m, 2H, C$_3$H & C$_5$H), 3.10-3.84 (m, 9H, ketal methylenes, -OCH$_2$CH$_2$O-, & C$_6$H), 3.40 (s, 3H, -OCH$_3$), 4.73, 4.78 (2d, 2H, J = 7

Hz, $-OCH_2O-$, AB quartet). <u>Anal.</u> calcd. for $C_{24}H_{42}O_7$: C 65.13, H 9.57; found: C 65.19, H 9.64.

<u>Preparation of the Silyl Ester (107)</u>
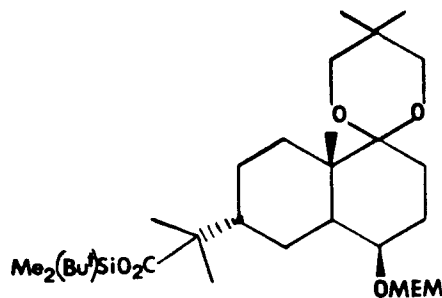
To a solution of the carboxylic acid <u>(102)</u> (150 mg, 0.27 mmol) in 3 ml of dry dimethylformamide was added 102 mg (0.67 mmol) of <u>tert</u>-butyl-dimethylsilyl chloride in 1 ml of dry dimethylformamide. To this solution was added 92 mg (1.4 mmol) of imidazole with stirring. The resulting solution was warmed to 60 $^{\circ}$C and stirred for 17 h at this temperature. The reaction mixture was cooled to room temperature, poured into water and the resultant solution was thoroughly extracted with ether. The combined ether extracts were washed with aqueous sodium bicarbonate, water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure, followed by subjection of the resultant oil to high vacuum at 50 °C (24 h), afforded 187 mg (99%) of a pure [tlc, ^{1}H nmr, glc (column A, 180 $^{\circ}$C)], colorless gum; ir (film) ν_{max} 1715, 1105, 1041 cm^{-1}; ^{1}H nmr δ 0.26 (s, 6H, $-Si(CH_3)_2-$), 0.71, 1.19 (2s, 3H each, ketal methyls), 0.95 (s, 9H, $-SiC(CH_3)_3$), 1.07 (s, 9H, angular methyl & $-C(CH_3)_2CO-$), 3.00-3.86 (m, 9H, ketal methylenes, $-OCH_2CH_2O-$, & C_6H), 3.42 (s, 3H, $-OCH_3$), 4.76 (s, 2H, $-OCH_2O-$). <u>Exact</u> <u>mass</u> calcd. for $C_{30}H_{56}O_7Si$: 556.3795; found: 556.3756.

Preparation of the Acid (112)
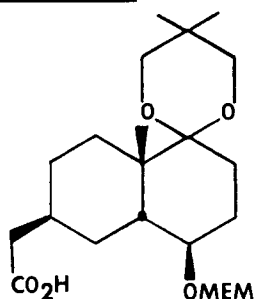
To a solution of 130 mg (0.29 mmol) of the saturated ester (76) in 1 ml of methanol was added 6 ml of a 1M solution of potassium hydroxide in methanol. The resulting solution was refluxed for 2 h, cooled to room temperature and poured into water. This mixture was cooled to 0 °C and neutralized (pH paper) with acidic ion exchange resin (Amberlite IR-120). The mixture was filtered and the exchange resin was washed with ether. The aqueous layer of the filtrate was extracted with ether and the combined organic phase was washed with water and brine. Evaporation of the dried (anhydrous sodium sulfate) solvents under reduced pressure gave 66 mg (54%) of a pale yellow gum which was pure by tlc and ^{1}H nmr. This material exhibited the following spectral data: ir (film) ν_{max} 3500-2390 (broad), 1713, 1110, 1042 cm^{-1}; ^{1}H nmr δ 0.70 (s, 3H, ketal methyl), 1.18 (s, 6H, ketal & angular methyls), 3.16-4.02 (m, 9H, ketal methylenes, -OC$\underline{H}_2$C$\underline{H}_2$O-, & C$_6\underline{H}$), 3.39 (s, 3H, -OC$\underline{H}_3$), 4.75, 4.85 (2d, 2H, J = 7 Hz, -OC$\underline{H}_2$O-, AB quartet), 8.78-9.20 (broad s, 1H, -CO$_2\underline{H}$). Exact mass calcd. for C$_{22}$H$_{38}$O$_7$: 414.2618; found: 414.2621.

Reaction of the Acid (112) with Diphenylphosphoryl Azide:

Preparation of the Ester (114)
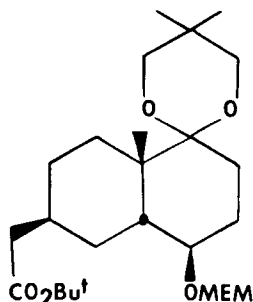
To a solution of 66 mg (0.16 mmol) of the acid (112) in 1.5 ml of dry tert-butyl alcohol was added 0.038 ml (0.17 mmol) of freshly distilled diphenylphosphoryl azide and 0.024 ml (0.17 mmol) of dry triethylamine. The resulting solution was refluxed for 18 h, cooled to room temperature and poured into water. This solution was thoroughly extracted with ether and the combined organic phase was washed with water and brine. The ether extracts were dried over anhydrous sodium sulfate and evaporated in vacuo yielding the crude product as a brown gum. This material was purified by preparative tlc (25% ethyl acetate in benzene) affording 14 mg (19%) of the ester (114) as a pure [tlc, ^{1}H nmr, glc (column A, 175 $^\circ$C)], colorless gum and 31 mg of a mixture which contained some of the desired carbamate (113) as judged by ir, ms and ^{1}H nmr analyses.

The ester (114) gave the following spectral data: ir (film) ν_{max} 1722, 1100, 1042 cm^{-1}; ^{1}H nmr δ 0.70 (s, 3H, ketal methyl), 1.18 (s, 6H, ketal & angular methyls), 1.43 (s, 9H, -C(CH$_3$)$_3$), 3.12-3.98 (m, 9H, ketal methylenes, -OCH$_2$CH$_2$O-, & C$_6$H), 3.37 (s, 3H, -OCH$_3$), 4.72, 4.78 (2d, 2H, J = 8 Hz, -OCH$_2$O-, AB quartet). Exact mass calcd. for C$_{26}$H$_{46}$O$_7$: 470.3243; found: 470.3211.

Preparation of the Isocyanate (106)
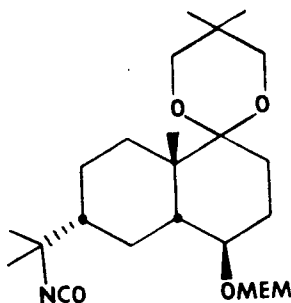
To a solution of 29 mg (0.066 mmol) of the carboxylic acid (102) dissolved in 1 ml of dry tert-butyl alcohol was added 0.5 ml (0.074 mmol, 0.15 $\underline{M}$) of a solution of freshly distilled diphenylphosphoryl azide in dry tert-butyl alcohol. The resulting solution was refluxed for 27 h. The mixture was cooled to room temperature and the solvent was evaporated yielding a light brown solid. This material was dissolved in chloroform, filtered and the solvent evaporated from the filtrate yielding 40 mg of a colorless gum. Purification of this material by preparative tlc (17% ethyl acetate in benzene) gave 13 mg (45%) of the isocyanate (106) as as colorless gum. The latter exhibited ir (film) ν_{max} 2265, 1105, 1035 cm^{-1}; ^{1}H nmr δ 0.70, 1.20 (2s, 3H each, ketal methyls), 1.07 (s, 3H, angular methyl), 1.28 (s, 6H, -C(C$\underline{H}_3$)$_2$NCO), 2.26-2.64 (m, 2H, C$_3$H & C$_5$H), 3.20-3.86 (m, 9H, ketal methylenes, -OC$\underline{H}_2$C$\underline{H}_2$O-, & C$_6$H), 3.41 (s, 3H, -OC$\underline{H}_3$), 4.75, 4.81 (2d, 2H, J = 7 Hz, -OC$\underline{H}_2$O-, AB quartet). Exact mass calcd. for C$_{24}$H$_{41}$NO$_6$: 439.2933; found: 439.2933.

Preparation of the Ketal Carbamate (116)
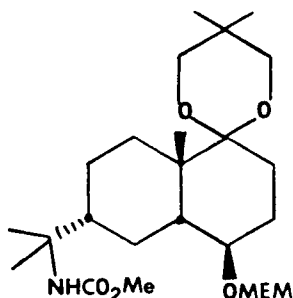
To a solution containing 525 mg (1.19 mmol) of the carboxylic acid (102), 0.39 ml (2.8 mmol) of dry triethylamine and 15 ml of dry tetrahydrofuran was added two equivalents (0.33 ml) of diethyl phosphorochloridate, dropwise at room temperature. The resulting cloudy solution was stirred for 4 h, filtered rapidly through celite and the filtrate was concentrated in vacuo. The residual material was dissolved in dry hexamethylphosphoramide (10 ml) and the resultant solution was added to a solution-suspension comprised of 1.1 g (16.9 mmol) of dry, recrystallized sodium azide in 20 ml of dry hexamethylphosphoramide. The resulting mixture was stirred for 15 h at room temperature and poured into cold, dilute aqueous sodium bicarbonate. This mixture was thoroughly extracted with ether and the combined ethereal extracts were washed with water and brine and dried over sodium sulfate. Evaporation of the solvents, followed by subjection of the residue to high vacuum for approximately 1 h, gave a pale yellow oil. This material displayed characteristic acyl azide absorptions in the ir spectrum at 1712 and 2155 cm^{-1}.

The oil was dissolved in 20 ml of dry toluene and the resultant solution was heated at reflux for 3 h. The solution was cooled to room temperature and the solvent was removed in vacuo yielding a viscous,

pale yellow oil. This material exhibited an intense absorption (2280 cm^{-1}) in its ir spectrum characteristic of an isocyanate functionality and showed a complete absence of any absorptions characteristic of an acyl azide.

Dry methanol (20 ml), containing one drop of 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN), was added to the oil and the resulting solution was stirred at room temperature for 1.75 h, followed by 1.5 h at reflux. Evaporation of the solvent gave 611 mg of an almost colorless, viscous gum. This material was placed under high vacuum for 24 h affording 545 mg (97%) of the ketal carbamate (116) which was pure by ^{1}H nmr, tlc and glc (column A, 180 °C; column B, 190 °C) analyses. The latter compound exhibited the following spectral data: ir (CHCl$_3$) ν_{max} 3440, 1722, 1110, 1040 cm^{-1}; ^{1}H nmr δ 0.72, 1.20 (2s, 3H each, ketal methyls), 1.06 (s, 3H, angular methyl), 1.24 (s, 6H, $-C(C\underline{H}_3)_2NHCO_2CH_3$), 2.24-2.56 (m, 2H, C$_3$H & C$_5$H), 3.12-4.00 (m, 9H, ketal methylenes, $-OC\underline{H}_2C\underline{H}_2O-$, & C$_6$H), 3.41 (s, 3H, $-OCH_2CH_2OC\underline{H}_3$), 3.62 (s, 3H, $-CO_2C\underline{H}_3$), 4.60 (broad s, 1H, $-N\underline{H}CO_2CH_3$), 4.74, 4.80 (2d, 2H, J = 7 Hz, $-OC\underline{H}_2O-$, AB quartet). Exact mass calcd. for C$_{25}$H$_{45}$NO$_7$: 471.3196; found: 471.3213.

Preparation of the Carbamate Alcohol (124)
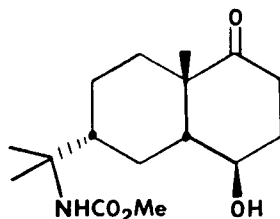
A solution of 263 mg (0.56 mmol) of the ketal carbamate (116) in 10

ml of dry methylene chloride was cooled to 0 °C. A solution of titanium tetrachloride in methylene chloride (0.37 ml, 1.5 M) was added and the resulting mixture was stirred for 1.5 h. Concentrated ammonium hydroxide (10 drops) was added and the reaction mixture was poured into aqueous sodium bicarbonate. This solution was extracted with five portions of methylene chloride and the combined organic extracts were washed successively with water and brine. The dried (sodium sulfate) solution was concentrated under reduced pressure giving a pale yellow gum. Subjection of this material to high vacuum for 16 h at ambient temperature, afforded 172 mg (80%) of the carbamate alcohol (124) as an off-white foam which was pure by tlc, ^{1}H nmr and glc (column A, 190 °C) analyses. The carbamate alcohol (124) gave the following spectral data: ir (CHCl$_3$) ν_{max} 3620, 3450, 1720, 1706, 1509 cm^{-1}; ^{1}H nmr δ 1.16, 1.21 (2s, 3H each, -C(CH$_3$)$_2$NH-), 1.41 (s, 3H, angular methyl), 3.60 (s, 3H, -OCH$_3$), 3.96 (broad s, 1H, C$_6$H), 4.53 (broad s, 1H, -NH-). Exact mass calcd. for C$_{16}$H$_{27}$NO$_4$: 297.1940; found: 297.1938.

Attempted trans-Ketalization of the Ketal Carbamate (116):
Preparation of the Keto Carbamate (123)
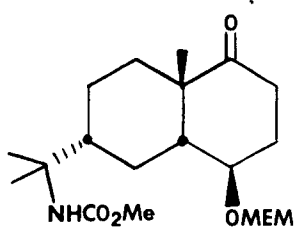
To a solution of 23 mg (0.049 mmol) of the ketal carbamate (116) in 4 ml of dry acetonitrile was added 0.073 ml (0.73 mmol) of 1,3-propane-

dithiol followed by 0.1 equivalents of freshly distilled boron trifluoride etherate in dry acetonitrile (0.1 ml, 0.07 $\underline{M}$). The reaction mixture was stirred at ambient temperature in a fume cupboard for 41 h. The solution was poured into 2% aqueous sodium hydroxide and the resulting solution was thoroughly extracted with ether. The combined ethereal extracts were washed successively with 2% aqueous sodium hydroxide, water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvents under reduced pressure afforded 16 mg (85%) of the keto carbamate (123) as the sole product [glc (column A, 190 °C) tlc, ^{1}H nmr]. This substance exhibited the following spectral data: ir (CHCl$_3$) ν_{max} 3447, 1723, 1701, 1505, 1100, 1045 cm^{-1}; ^{1}H nmr δ 1.17, 1.20 (2s, 3H each, -C(C$\underline{H}_3$)$_2$NH-), 1.33 (s, 3H, angular methyl), 3.42 (s, 3H, -OCH$_2$CH$_2$OC$\underline{H}_3$), 3.50-3.98 (m, 5H, -OC$\underline{H}_2$C$\underline{H}_2$O- & C$_6$H), 3.62 (s, 3H, -NHCO$_2$C$\underline{H}_3$), 4.51 (broad s, 1H, -N$\underline{H}$-), 4.81, 4.88 (2d, 2H, J = 7 Hz, -OC$\underline{H}_2$O-, AB quartet). $\underline{Exact}$ $\underline{mass}$ calcd. for C$_{20}$H$_{35}$NO$_6$: 385.2464; found: 385.2449.

Preparation of the Carbamate Dione (128)
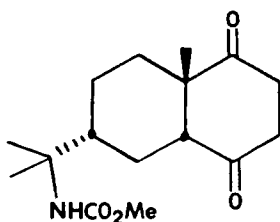
To a cold (0 °C) solution containing 10 ml of dry methylene chloride and 0.26 ml (3.2 mmol) of dry pyridine was added 160 mg (1.6 mmol) of chromium trioxide. The resulting red solution was stirred at 0 °C for 15 min and subsequently warmed to room temperature and stirred for a

further 45 min. A solution of the carbamate alcohol (128) (79 mg, 0.26

mmol) in 4 ml of methylene chloride was added in one portion and the

reaction mixture was stirred at room temperature for 30 min. The solu-

tion was filtered through glass wool and the solid residue was washed

with two portions of ether. The residue was dissolved in 5% aqueous

sodium hydroxide and the resulting solution was thoroughly extracted

with ether. The ethereal extracts were then combined with the filtrate

and the resultant solution was washed successively with 5% aqueous

sodium hydroxide, water and brine. The dried (sodium sulfate) organic

phase was evaporated under reduced pressure yielding 64 mg (81%) of the

desired dione (128) as a pure [tlc, glc (columns A & B, 190 °C)], color-

less gum; ir (CHCl$_3$) ν_{max} 3450, 1715 cm^{-1}; ^{1}H nmr δ 1.14, 1.18, 1.21

(3s, 3H each, tertiary methyls), 3.59 (s, 3H, -OC$\underline{H}_3$), 4.65 (broad s, 1H,

-N$\underline{H}$CO$_2$CH$_3$). <u>Exact</u> <u>mass</u> calcd. for C$_{16}$H$_{25}$NO$_4$: 295.1781; found: 295.1761.

Preparation of the Ketal Amine (138)
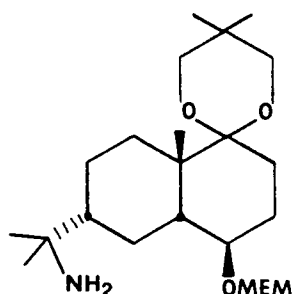
To a stirred solution of the carboxylic acid (102) (125 mg, 0.28

mmol) in dry tetrahydrofuran (8 ml) at room temperature, was added dry

triethylamine (0.086 ml, 0.62 mmol) followed by a solution of diethyl

chlorophosphate (0.073 ml, 0.48 mmol) in 1 ml of tetrahydrofuran. The

solution was stirred at room temperature for 4 h and then rapidly fil-

tered through celite. The filtrate was concentrated in vacuo and the resulting oil was dissolved in dry hexamethylphosphoramide (4 ml). This solution was immediately added to a slurry of dry sodium azide (0.26 g, 3.9 mmol) in 10 ml of hexamethylphosphoramide and the reaction mixture was stirred at room temperature for 16 h. Cold (0 °C), dilute aqueous sodium bicarbonate was then added and the resulting mixture was thoroughly extracted with ether. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent gave the acyl azide (105) as a pale yellow oil [ir (film) ν_{max} 2155, 1712, 1116, 1040 cm^{-1}].

A solution of the crude acyl azide (105) in 10 ml of dry toluene was heated at reflux for 3 h. The reaction mixture was cooled and the solvent was removed affording 115 mg of the isocyanate (106) as a viscous, pale yellow oil [ir (film) ν_{max} 2264, 1108, 1040 cm^{-1}].

A portion of the crude isocyanate (106) (47 mg, 0.11 mmol) was dissolved in 2 ml of p-dioxane and 3 ml of 2N aqueous sodium hydroxide was added. The resulting solution was heated at reflux for 3 h and then cooled to room temperature. The reaction mixture was poured into water and the resulting mixture was thoroughly extracted with ether. The combined ether layers were washed with water, with brine and dried over anhydrous sodium sulfate. Removal of the solvent afforded 34 mg (83%) of the ketal amine (138) as a colorless gum. An analytical sample of this material, obtained by preparative tlc (30% cyclohexane in ethyl acetate), exhibited ir (film) ν_{max} 3450, 1116, 1040 cm^{-1}; ^{1}H nmr δ 0.70 (s, 3H, ketal methyl), 1.04 (s, 9H, angular methyl & $-C(\underline{CH}_3)_2NH_2$), 1.19 (s, 3H, ketal methyl), 1.95 (s, 2H, $-N\underline{H}_2$), 3.08-3.86 (m, 9H, ketal

methylenes, $-OC\underline{H}_2C\underline{H}_2O-$, & C_6H), 3.40 (s, 3H, $-OC\underline{H}_3$), 4.74, 4.80 (2d, 2H,

J = 7 Hz, $-OC\underline{H}_2O-$, AB quartet). <u>Exact</u> <u>mass</u> calcd. for $C_{23}H_{43}NO_5$: 413.3141;

found: 413.3164.

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It has been said that 99% pure by glc means:

> "when the substance was introduced into a certain
> glc column, in certain conditions of gas flow and
> temperature, 99% of the integrated response of a
> recorder to that portion of the substance or its
> impurities or decomposition products that reached
> and affected the detecting device in the time
> available was exhibited as a single peak."

J.W. Cornforth in a Robert Robinson lecture entitled "The Logic of Working
with Enzymes", [Quart. Rev., 1, 1973].