AN ABSTRACT OF THE THESIS OF

Michael Paul Prisbylla for the degree of Doctor of Philosophy

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Title: THE SYNTHESIS OF TRISPORIC ACIDS

Abstract approved: Redacted for Privacy

Dr. James D. White

A total synthesis of the fungal hormones, trisporic acids A and B, is described, starting from α-methyltetronic acid 34. A Robinson annelation of 34 with ethyl vinyl ketone affords the lactone 33. Treatment of 33 with N-bromosuccinimide gave 97, which was hydrolyzed to the lactol 103. The reaction of 103 with diazomethane produced aldehyde 28.

A Wittig reaction of 103 and the ylide 51 afforded (±)-(7E, 9E)-trisporic acid A in 16% yield. The phosphonium bromide 58 was prepared by a Wadsworth-Emmons condensation of 54 with valeraldehyde to give the trans adduct 55, which was reduced with lithium aluminum hydride to 56. Treatment of 56 with phosphorus tribromide gave 57, which was converted with triphenylphosphine to 58.

A Wittig reaction of 103 and 29 furnished, after hydrolysis, (±)-(7E, 9E)-trisporic acid B (3). Treatment of 3 with diazomethane afforded a 5% yield of (±)-(7E, 9E)-trisporic acid B methyl ester, 12.

The Synthesis of Trisporic Acids

by

Michael Paul Prisbylla

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Typed by Opal Grossnicklaus for Michael Paul Prisbylla

To my parents

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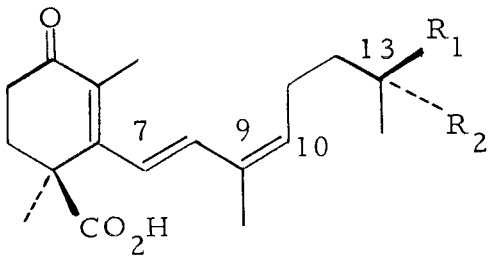
THE SYNTHESIS OF TRISPORIC ACIDS

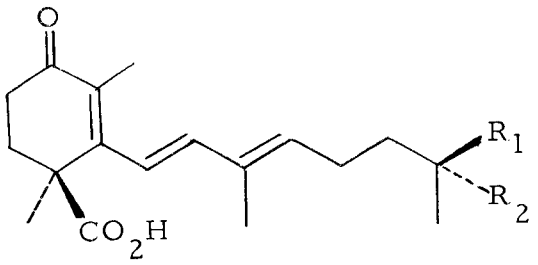
I. INTRODUCTION: THE TRISPORIC ACIDS

Fungi belonging to the class Mucorales, including the genera Mucor, Phycomyces, and Blakeslea, have in common a mechanism of sexuality which appears to be truly primitive (1). It has become clear that their sexual development is mediated by hormones known as the trisporic acids (1-5, Figure 1) (2, 3). Of these, 9-cis-trisporic acid B, 1, is the most active and is considered to be the



1 $R_1, R_2 = O$ 9-cis-TRISPORIC ACID B

2 $R_1 = H, R_2 = OH$ 9-cis-TRISPORIC ACID C



3 $R_1, R_2 = O$ 9-trans-TRISPORIC ACID B

4 $R_1 = H, R_2 = OH$ 9-trans-TRISPORIC ACID C

5 $R_1, R_2 = H$ 9-trans-TRISPORIC ACID A

Figure 1. Trisporic Acids (stereochemistry implied) (4).

the "true" hormone (3). Sexual development of the two mating types, plus and minus, is superficially the same, and is in response to the same hormone. However, simultaneous and cooperative metabolism in both mating types is essential for hormone production (3).

Recently neutral metabolites, which are produced in low yield, have been isolated when the mating types are grown separately (3, 5). These substances derived from β-carotene (2) have been named pro-hormones, P^+ and P^- (6-10, Figure 2). They are, demonstrably,

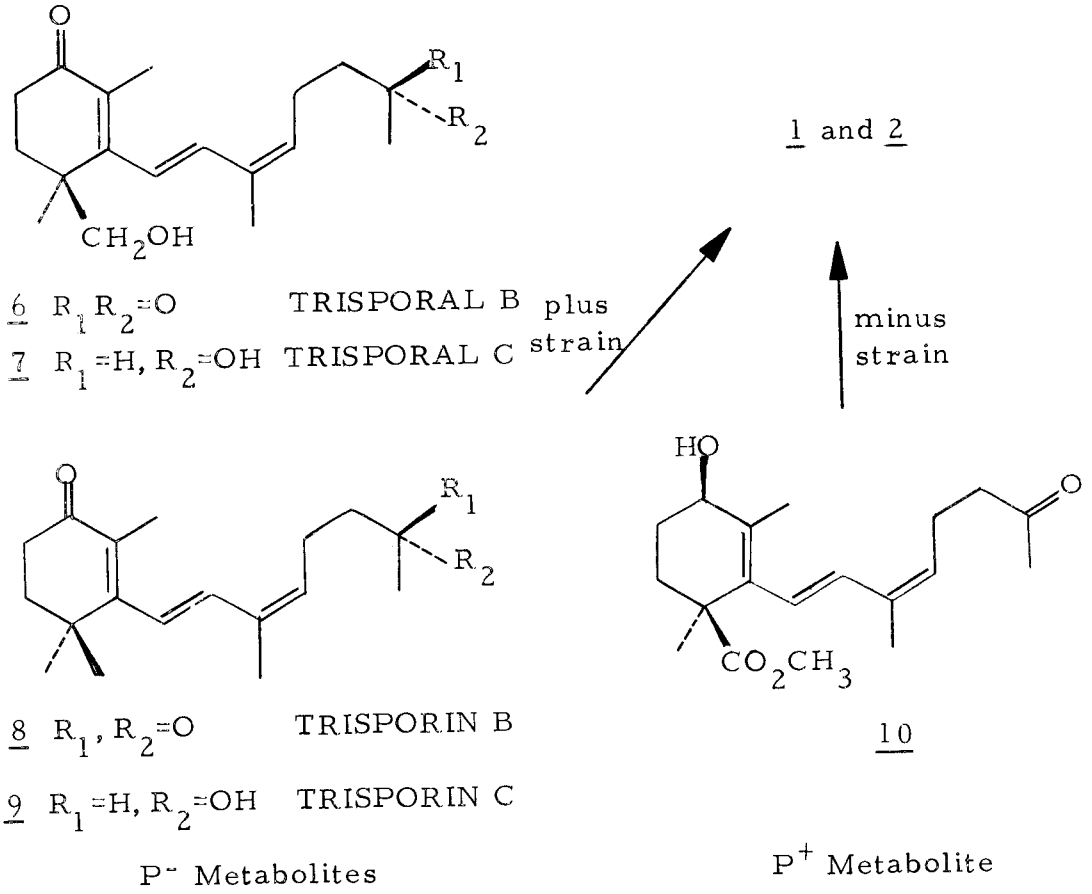
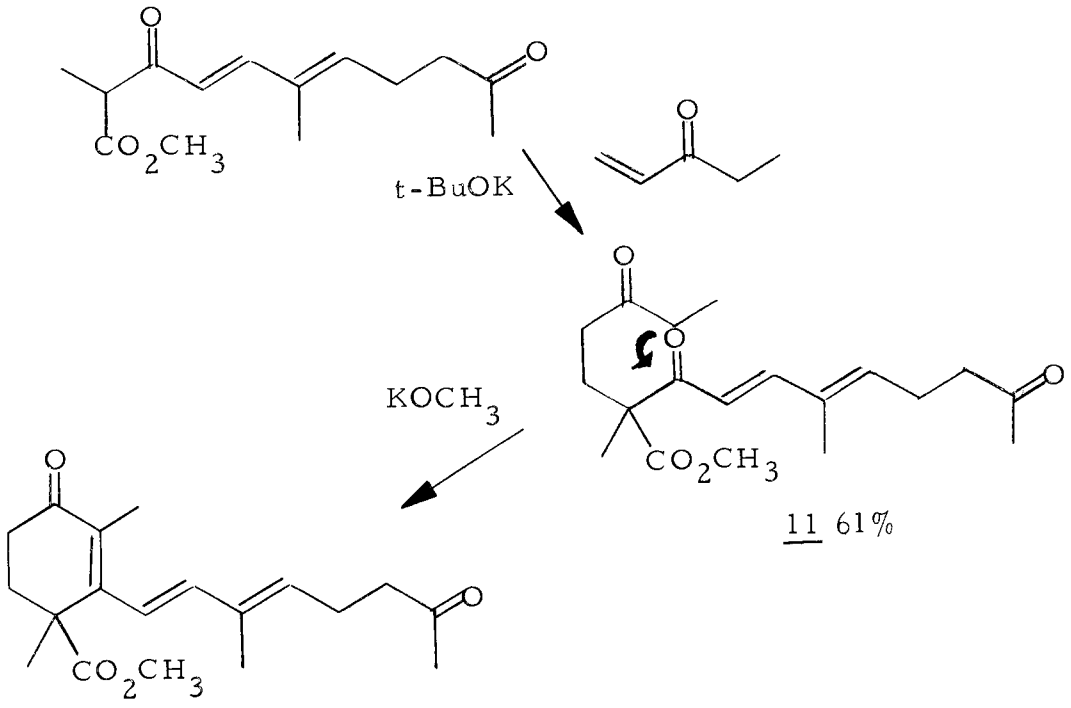


Figure 2

precursors of the trisporic acids and are effective precisely to the extent that they may be converted into the corresponding trisporic acid (3). The prohormones of one mating type are converted by their sexual partner into trisporic acids at zygophore induction, thus indicating a direct chemical link between the mating process in different strains.

The first synthesis of a methyl trisporate was reported by Edwards and co-workers (6). Their synthesis of the active (2, 3, 7) (±)-(7E, 9E)-trisporic acid B methyl ester was predicated upon the construction of an acyclic precursor 11 which would then undergo intramolecular aldol cyclization to give the desired product 12.

Scheme 1

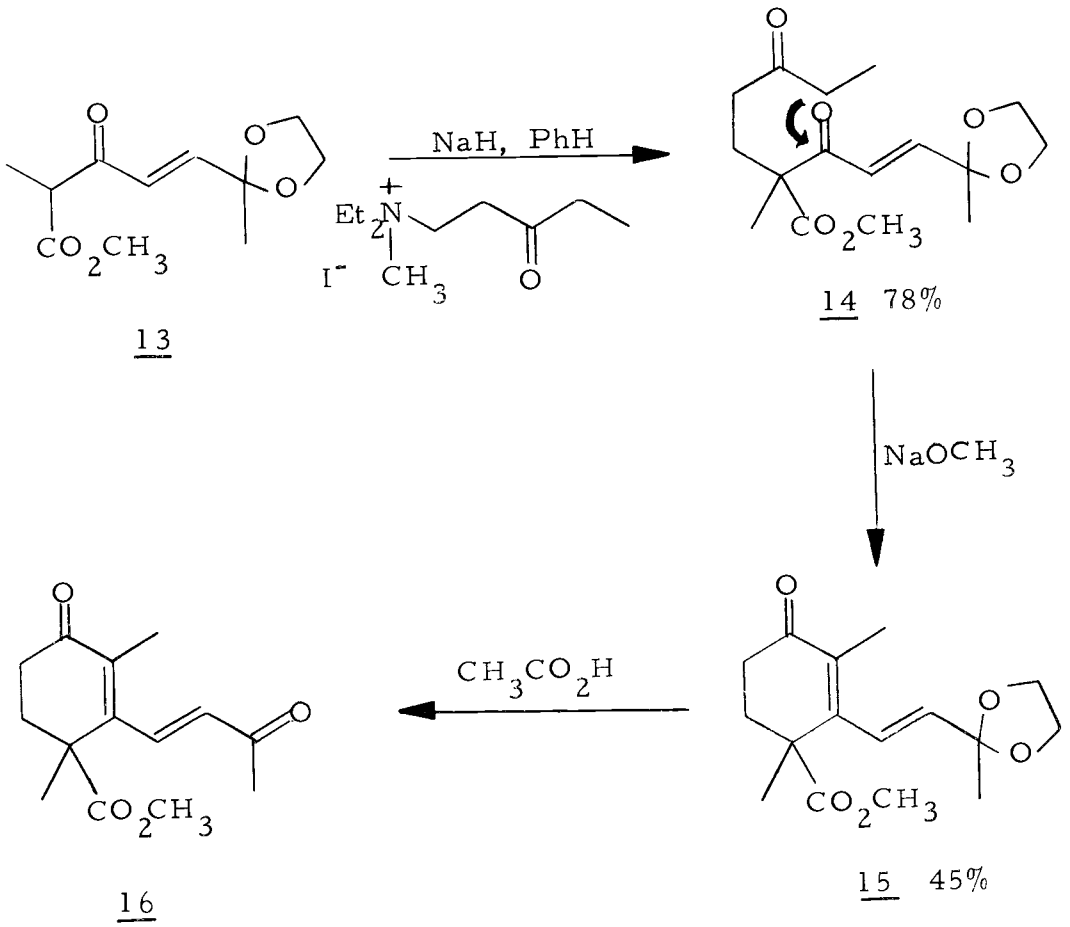


11 61%

12 10%

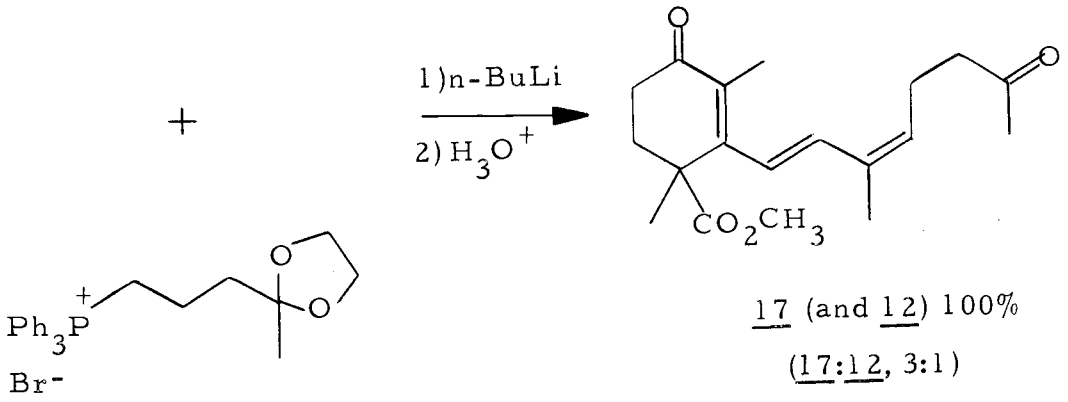
An alternate synthesis of methyl trisporate B reported by Isoe, Hayase, and Sakan (8) was based upon the formation of the C-9, 10 double bond from 16 and is shown, in part, in Scheme 2. The cyclohexenone moiety, 16, was constructed by Michael addition of 13 to ethyl vinyl ketone and a subsequent aldol cyclization of 14 to 15. This synthesis provides a method for chain elongation to give 9-cis and 9-trans isomers of methyl trisporate B, 17 and 12, respectively.

Scheme 2



13 14 78% 15 45% 16

16

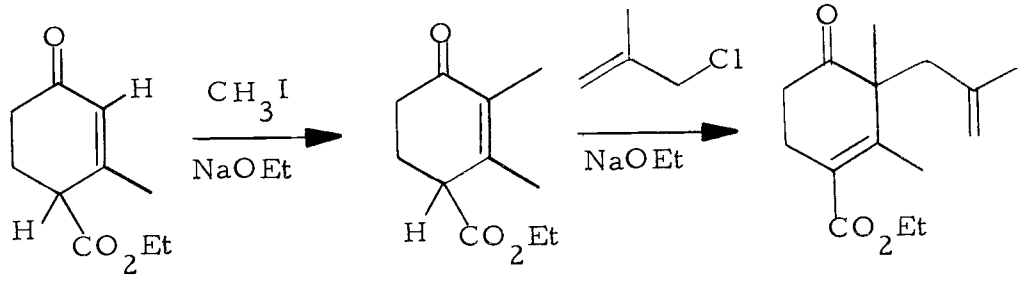


17 (and 12) 100%

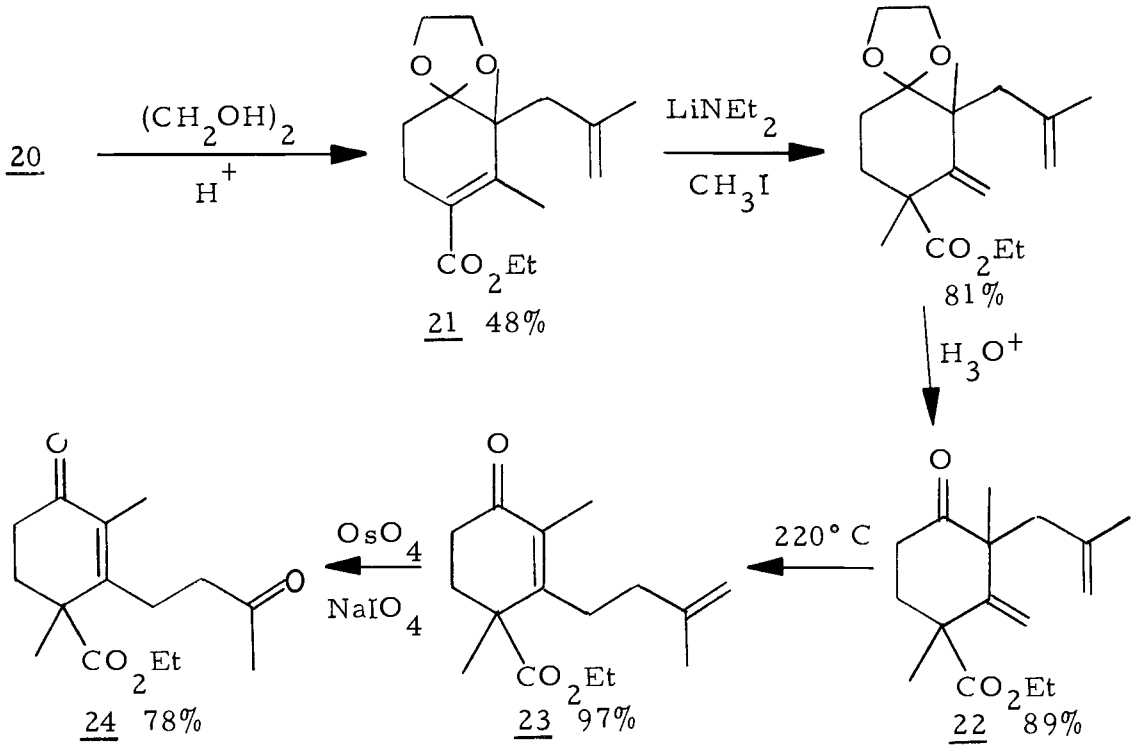
(17:12, 3:1)

A totally different synthetic approach was developed by White and Sung (9). This route, summarized in Scheme 3, utilized the sequential alkylation of Hagemann's ester 18, with first a methyl group to give 19, and then a methallyl group, to produce 20. Ketalization of 20 afforded 21, which was alkylated alpha to the ester function and deketalized to yield 22. The latter underwent a smooth Cope rearrangement to 23. Oxidative cleavage of the terminal olefin afforded 24, an intermediate for possible entry to the trisporic acids.

Scheme 3

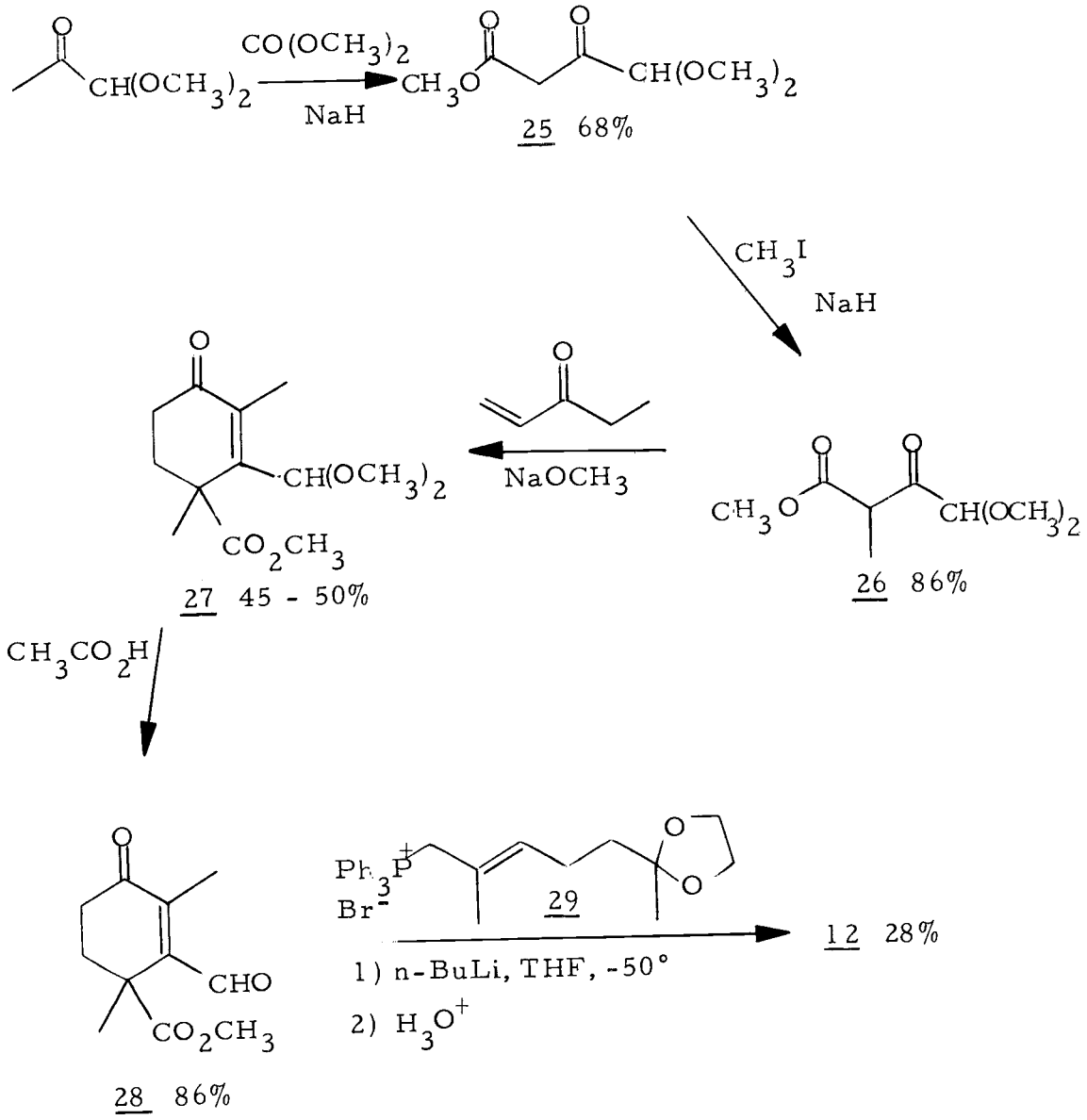


18 19 20



Secrist and co-workers (10) have recently reported a synthesis of 12, via formation of the C-7, 8 double bond, as outlined in Scheme 4. These workers followed previous syntheses in utilizing the Robinson annelation sequence to provide the highly functionalized cyclohexenone moiety 28. Thus, the treatment of pyruvaldehyde dimethyl acetal with sodium hydride and dimethyl carbonate afforded the β-ketoester 25, which was methylated with sodium hydride and methyl iodide to provide 26. Treatment of 26 with one equivalent of sodium methoxide and excess ethyl vinyl ketone gave 27 directly. Mild hydrolysis produced the aldehyde 28, which was reacted with the ylide from 29 to afford 12 in 28% yield.

Scheme 4



An analysis of these earlier approaches to the trisporic acids indicates that the Robinson annelation sequence, as used here, suffers from low yields and necessary purifications, while the alkylation sequence starting from Hagemann's ester is burdened with the problems of dealing with rather complex mixtures of alkylation products.

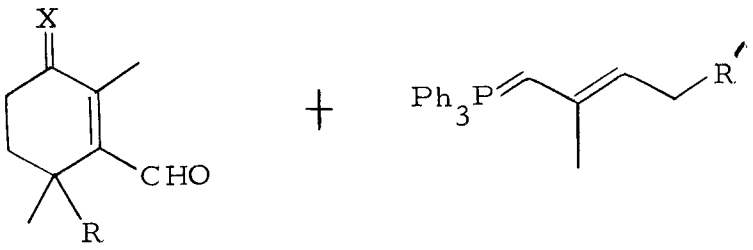
Thus, efficient synthesis of the cyclohexenone moiety of the trisporic acids still remained a substantial challenge.

At the beginning of this work, it appeared that formation of the C-7, 8 double bond via a Wittig reaction would lend itself to a stereocontrolled reaction giving, perhaps solely, the trans isomer. This stereochemical preference is based upon the known propensity for Wittig reactions to occur exclusively in a trans manner when the reactants contain extensive conjugation (11, 12). Coupled with the fact that ylides derived from allylic phosphonium salts are configurationally stable (12), this leads to the expectation that 7-trans-9-trans and 7-trans-9-cis-trisporic acids can be synthesized in pure form.

II. DISCUSSION AND RESULTS

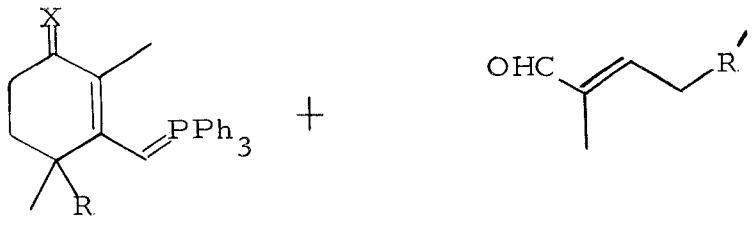
The intention of forming the C-7, 8 double bond in the trisporic acids via a Wittig reaction dictates two possible modes of coupling. Keeping in mind the reservations discussed in Chapter I, they are shown below in Figure 3.

I



30

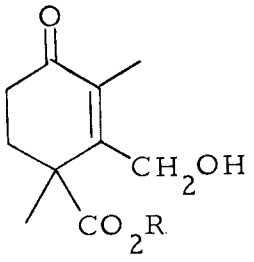
II



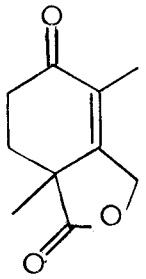
31

Figure 3.

Retrosynthetic analysis suggests that a suitable precursor to the cyclohexene moieties 30 and 31 is the alcohol 32, or more precisely, the lactone 33. These two precursors are essentially C-7 functionalized derivatives of Hagemann's ester. For reasons described previously, we wished to avoid the alkylation of Hagemann's ester, and so a new approach was devised, utilizing a different Robinson annelation sequence.



32

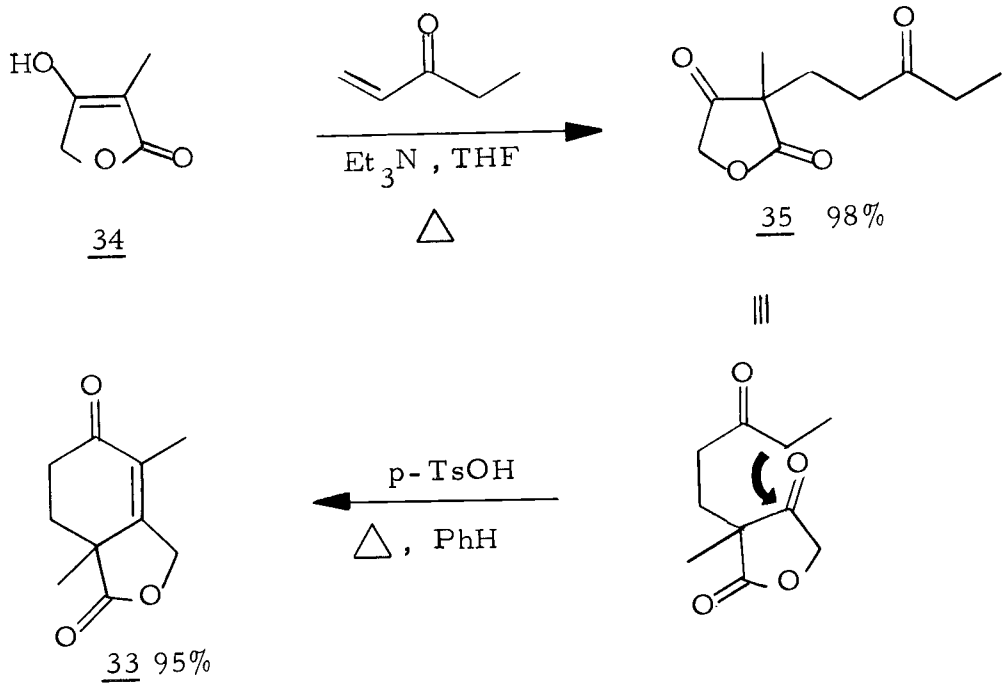


33

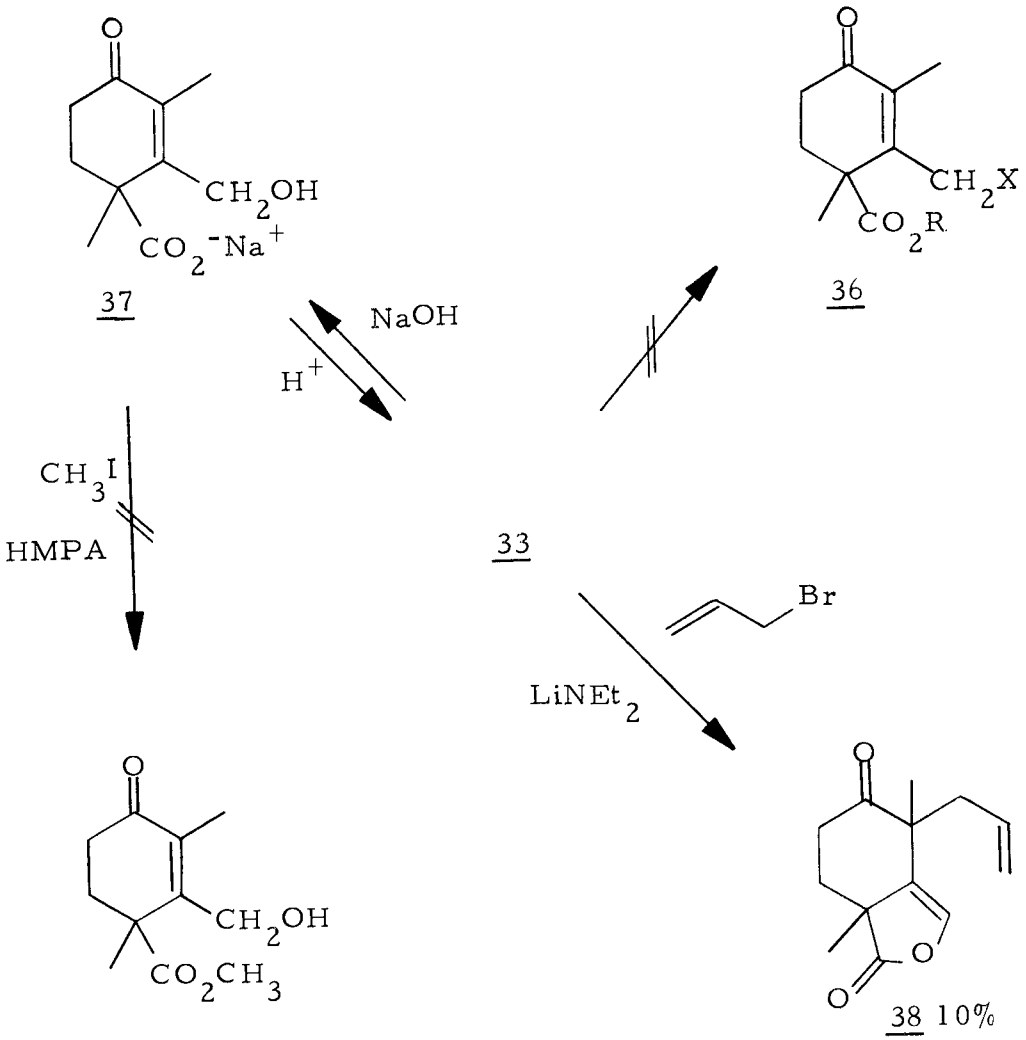
1. Robinson Annelation Sequence

Analysis of the lactone portion of 33 reveals that it may be derived from the known α-methyltetronic acid (34) (13). Treatment of 34 with ethyl vinyl ketone and a catalytic amount of triethylamine (14, 15, 16, 17) gave the Michael adduct (18) 35 (98%), which was subsequently cyclized in an acid-catalyzed aldol reaction (17) to give the crystalline lactone 33, in 95% yield. Thus, the apparent difficulties of the Robinson annelation sequence mentioned previously seem to have been resolved in this approach in that the cyclohexenone moiety found in the trisporic acids may be cleanly obtained in high yield (93% from 34).

Scheme 6



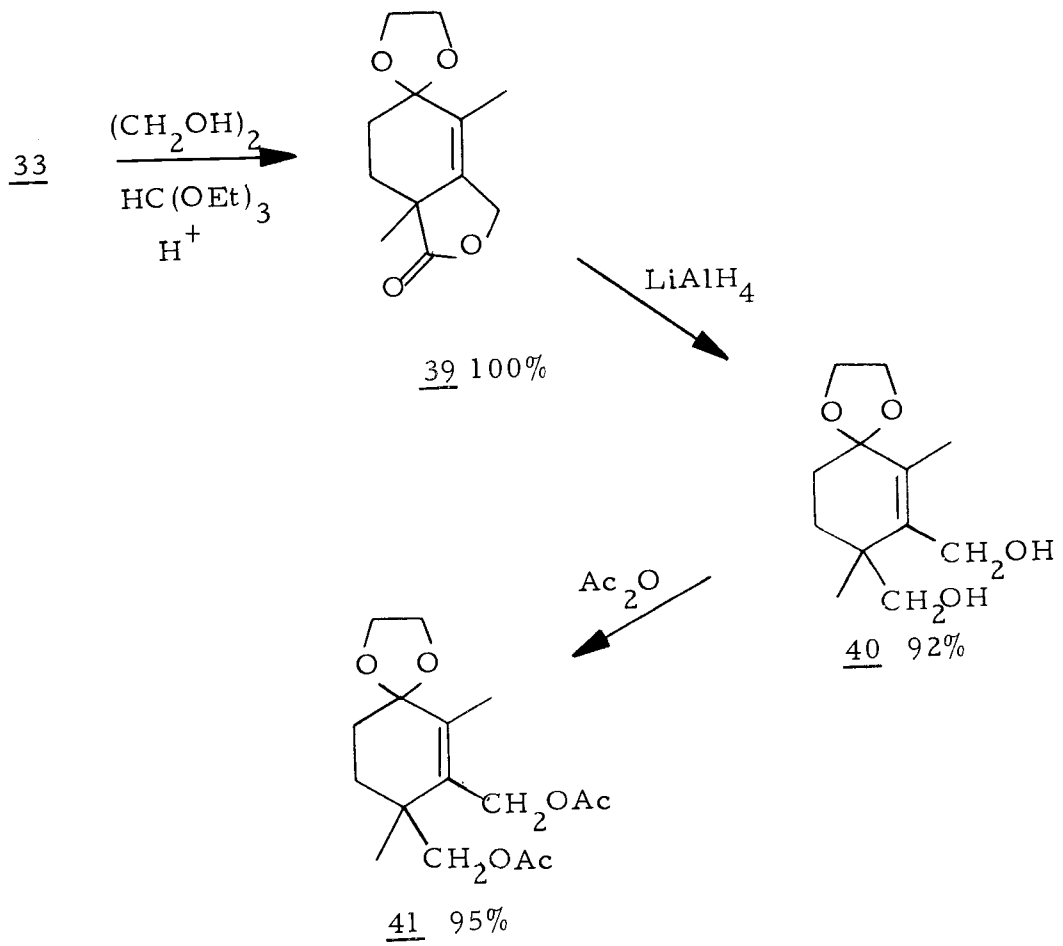
With the desired keto-lactone 33 in hand, attempts were made to produce the allylic halide 36. However, all reaction conditions (hydrogen bromide gas, methanol; hydrogen chloride gas, ethanol; thionyl chloride, then ethanol), led only to recovered starting material. The lactone does appear to give 37 upon addition of sodium hydroxide (by thin layer chromatography), but recloses upon aqueous workup (19). Alkylation of the carboxylate 37 (20) again gave only recovered starting material. Treatment of 33 with allyl bromide and lithium diethylamide gave alkylation alpha to the ketone, as in 38. Modification of reaction conditions (lithium dicyclohexylamide or sec-butylithium) were of no benefit.

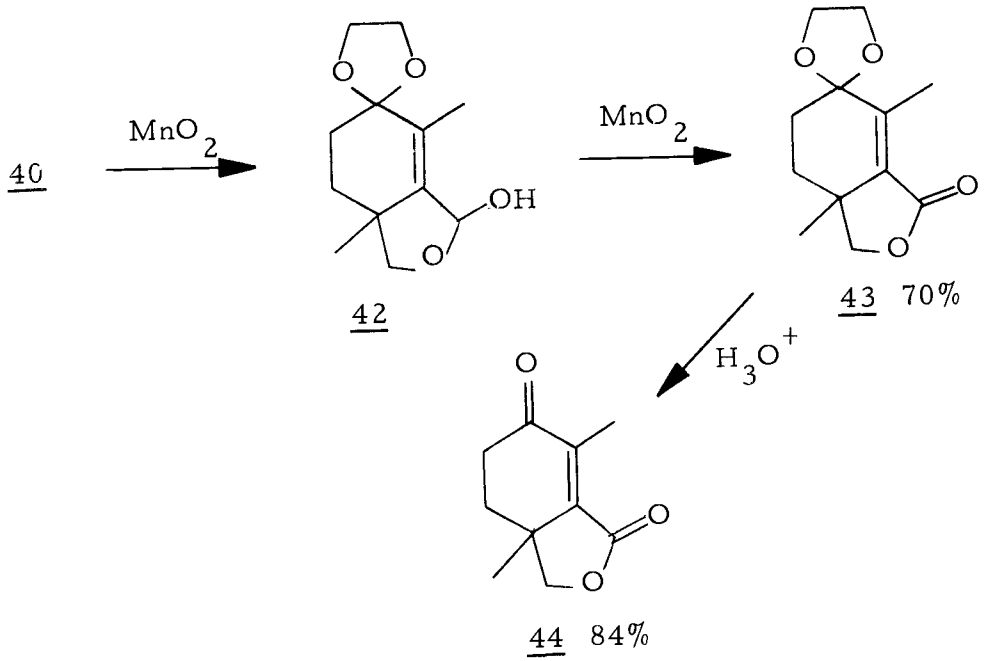


The uncooperative behavior of 33, in failing to yield a useful intermediate, led to the conclusion that the lactone moiety must be modified. Compound 33 was ketalized to give 39 in quantitative yield (Scheme 7) by the use of ethylene glycol, triethylorthoformate, and a trace of p-toluenesulfonic acid at room temperature (21). This method was found to be much milder than the normal ketalization procedure (Dean-Stark trap, acid, refluxing benzene), which gave a mixture of products. Allylic ketals of this type are known to be

easily cleaved, even under conditions where saturated ketals are inert (9). In fact, the ketal 39 was unstable to chromatography (silica gel, ether), undergoing facile hydrolysis to 33, and hence it was used directly. Reduction of 39 to diol 40 was accomplished by the use of lithium aluminum hydride in ether (92%). The diol could not be purified, but the diacetate 41 was prepared and fully characterized, confirming the identity of 40.

Scheme 7

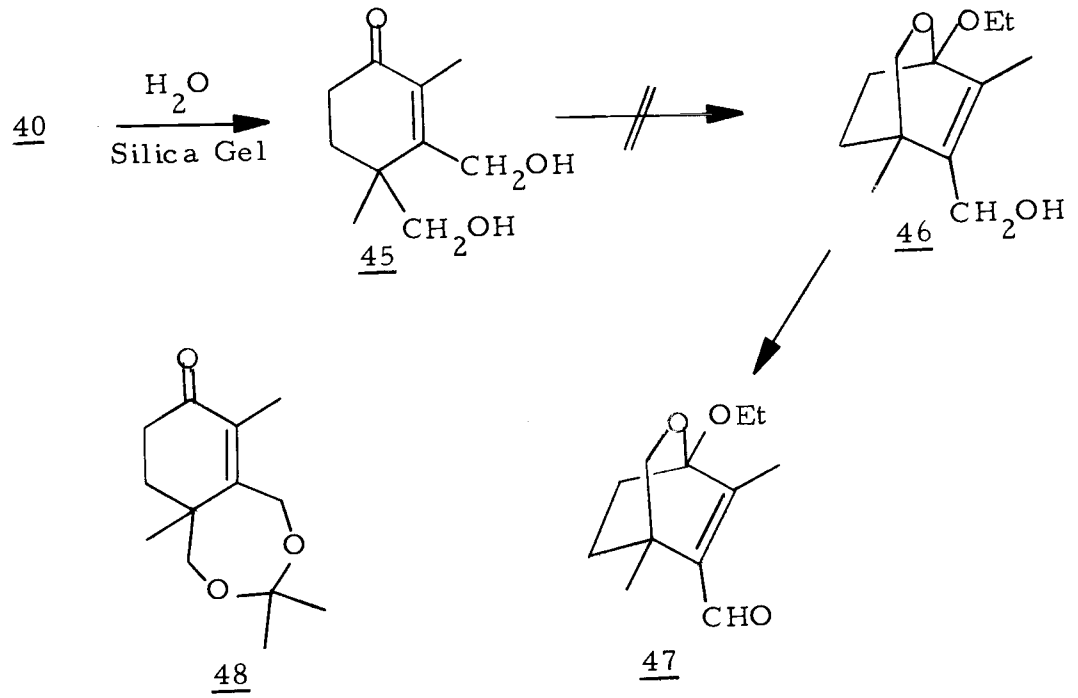




Oxidation of 40 with activated manganese dioxide is patterned after the method of Wenkert (22), and proceeds to give the crystalline lactone 43 in 70% yield. The oxidization occurs through the hemiacetal 42, as shown by isolation of mixtures of 42 and 43 after incomplete reaction times, insufficient oxidant, or by following the reaction by thin layer chromatography (silica gel, ether). Due to purification difficulties, the hemiacetal was not isolated, but was oxidized to the lactone 43. The ketal function of 43 was stable to chromatography, but could be cleaved with aqueous dioxane and p-toluenesulfonic acid to give the lactone 44 (84%).

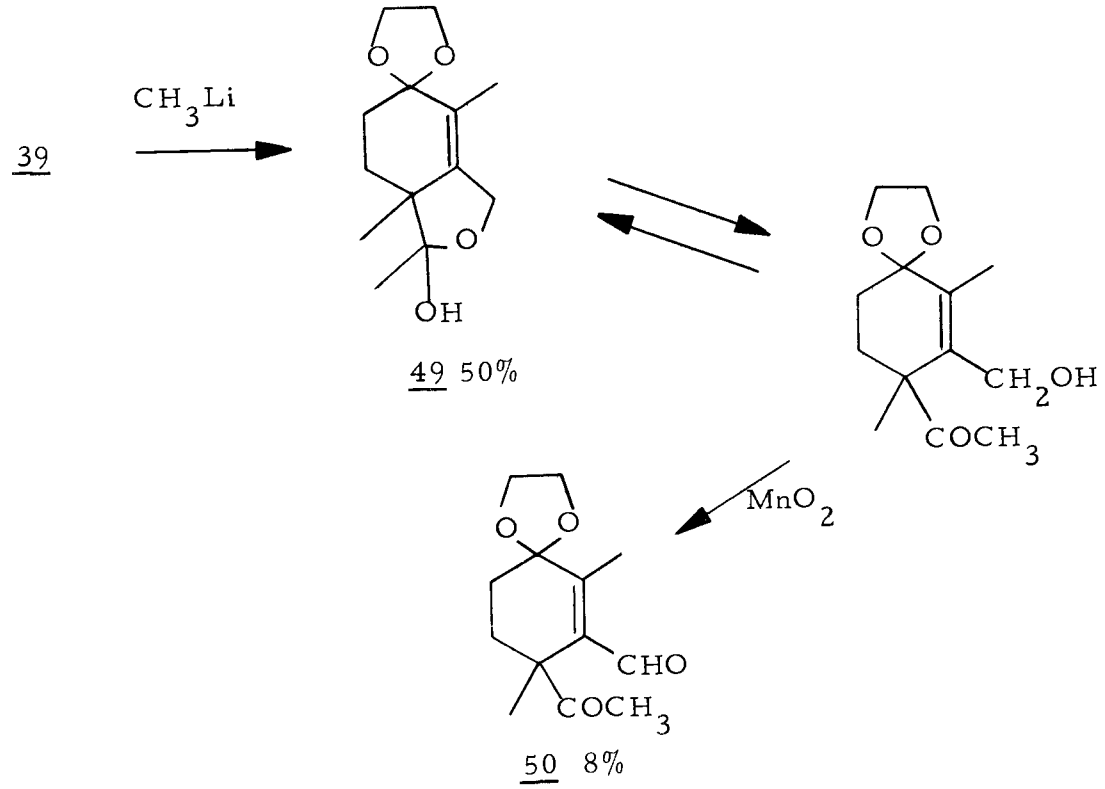
Since activated manganese dioxide is known to be specific for oxidation of allylic alcohols (22, 23), an attempt was made to modify 40 so that a free allylic alcohol and a protected primary alcohol would be obtained, as in 46. Oxidation of 46 with activated manganese

dioxide would produce 47.

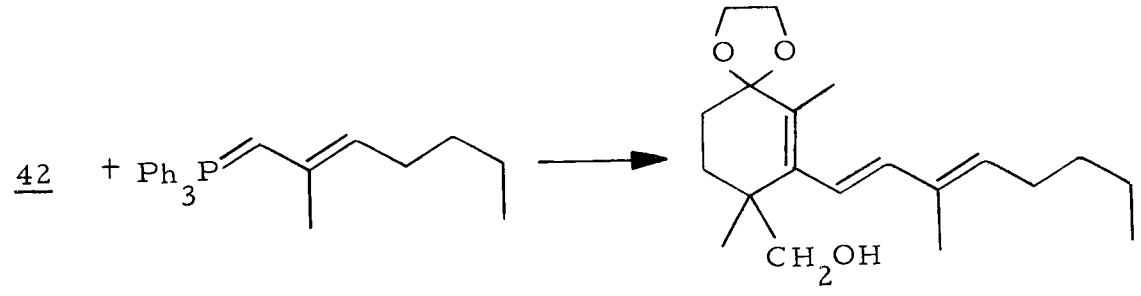


Hydrolysis of the ketal (p-toluenesulfonic acid, water) in 40 gave 45 in poor yield. The latter rapidly turned dark. Attempted trans-ketalization (refluxing acetone, p-toluenesulfonic acid), gave a mixture of 45 and probably 48. The removal of the ketal function was finally accomplished by treatment with wet ether and silica gel. However, this approach was ultimately to no avail, since attempted conversion of 45 (p-toluenesulfonic acid, ethanol, triethylorthoformate) to 46 gave a complex and inseparable mixture. The aldehyde 50 was obtained by addition of methyl lithium to 39 affording 49 (50%), which was subsequently oxidized with activated manganese dioxide. However, the poor yield and unreproducibility in the methyl lithium reaction, coupled with difficulties in the conversion of 50 to

a more useful derivative led to the abandonment of this scheme and development of the alternate approach below.

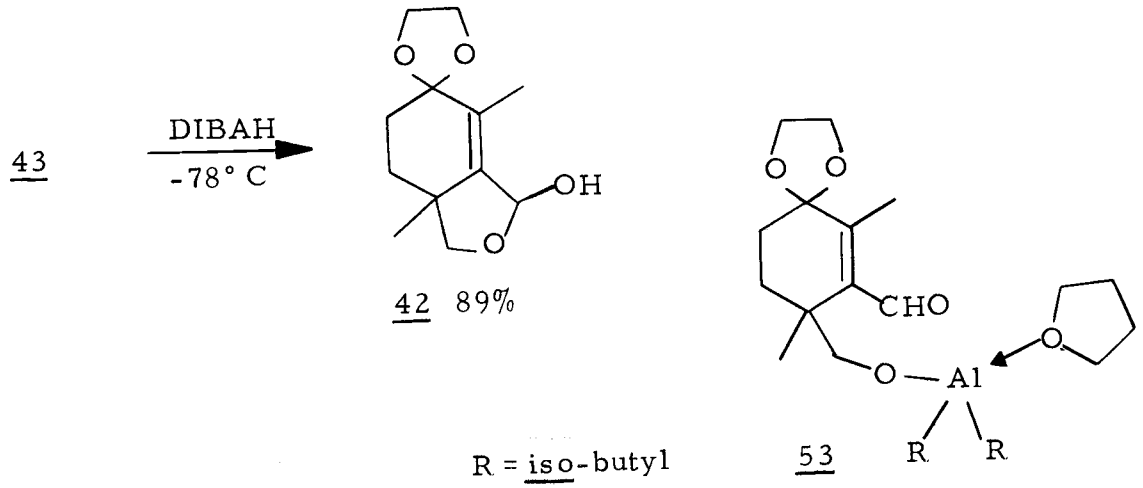


It is well documented that ylides of allylic phosphonium salts react with α,β-unsaturated aldehydes (11). Also known is the fact that hemiacetals will undergo Wittig reactions (24). This suggested the possibility of coupling 42 and 51 directly, to afford 52.



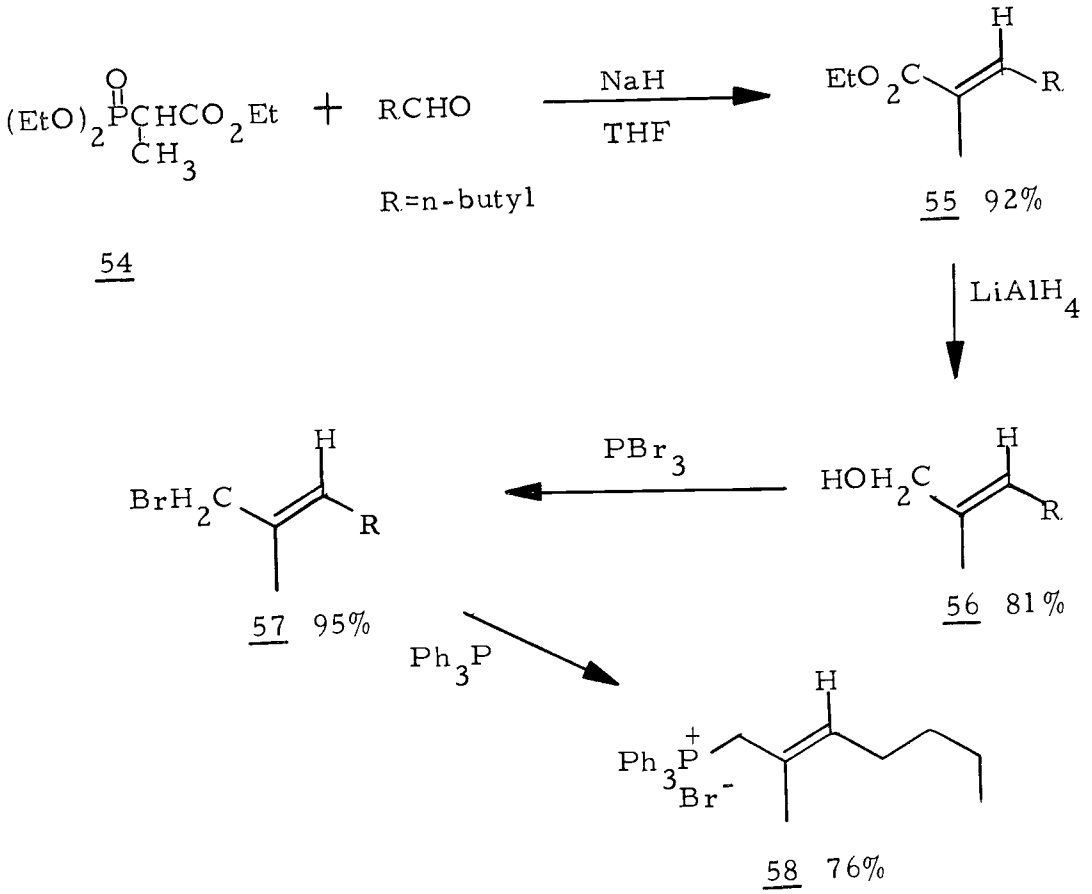
51 52

Hemiacetal 42, was generated by reduction of the lactone 43 with di-iso-butylaluminum hydride (25) in dry toluene at -78° C. When the reduction was carried out in dry tetrahydrofuran at -78° C a mixture of 40, 42 and 43 was obtained, indicating that the hemiacetal opens in a polar solvent to give an intermediate such as 53, which is further reduced.



The phosphonium salt 58, was constructed as outlined in Scheme 8. A Wadsworth-Emmons reaction of 54 with valeraldehyde gave the α,β-unsaturated ester 55 in 92% yield as a single isomer. Assignment of the trans geometry follows from literature precedent (26, 27). Reduction of 55 with lithium aluminum hydride afforded the alcohol 56 (81%). Treatment of 56 with phosphorus tribromide gave the bromide 57 (95%), which was converted to the phosphonium salt 58 by treatment with triphenylphosphine in benzene at room temperature (28).

Scheme 8



54

55 92%

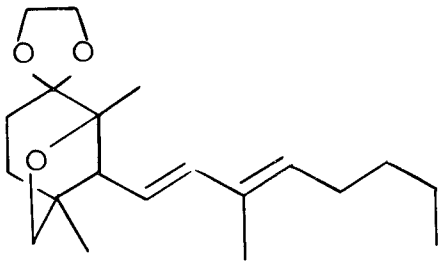
56 81%

57 95%

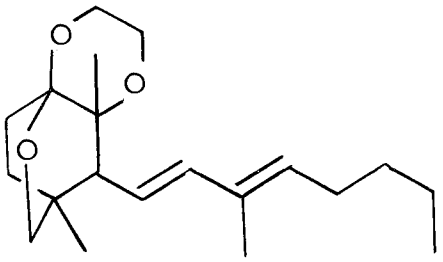
58 76%

The reaction of 42 and 51 (sodium hydride, dimethyl sulfoxide) (26) produced a new compound which was isolated in 40% yield. The fact that this product was not the desired 52 was established by the lack of an alcohol stretching absorption in the infrared spectrum. Since adduct formation was assured by its mass spectrum (M^+ 320), an analysis of the NMR spectrum, which showed signals for a vinyl hydrogen (δ 6.14 with a coupling constant of 16 Hz), three methyl singlets and an ether methylene (δ 1.06, 1.27, 1.80 and 3.77 respectively), allowed the assignment of two possible structures, 59 and 60. A clear distinction between these two isomers could not

be made.

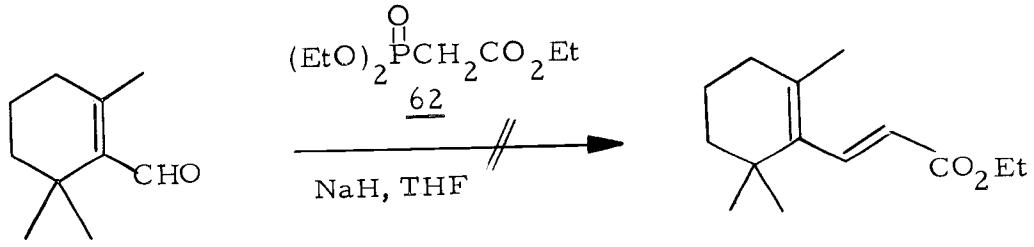


59

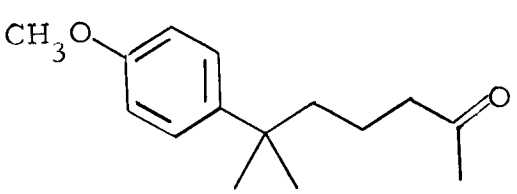


60

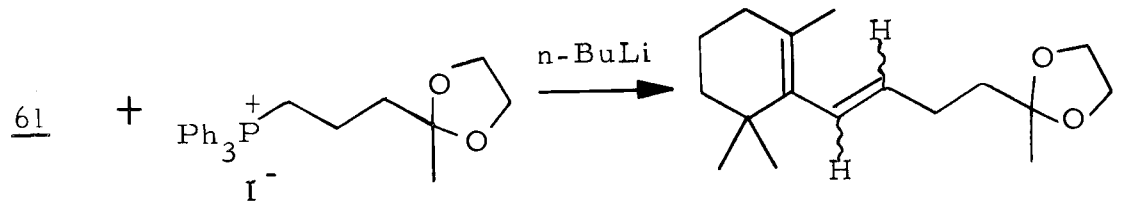
The question as to when the rearrangement process occurs may be answered by consideration of a model study conducted with β-cyclocitral 61. This aldehyde gave no reaction with the stabilized ylide 51, nor with the phosphonate 62 (29). The condensation product 65 was obtained as a mixture of isomers with the ylide from 64 (30). It was also determined that 51 does not react with unhindered methyl ketones, such as 63.



61

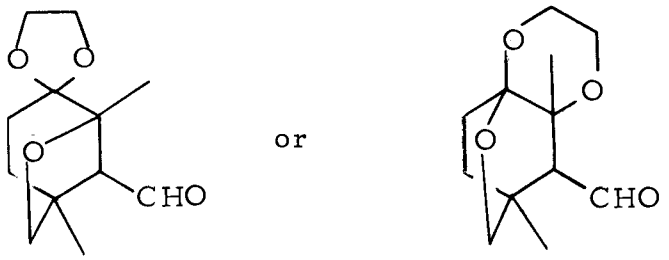


63



61 + Ph_3P^+ I^- (64) → (65)

These results indicate that the hemiacetal 42 undergoes rearrangement prior to Wittig reaction to give 66 or 67, which then reacts with the ylide 51 producing 59 or 60.



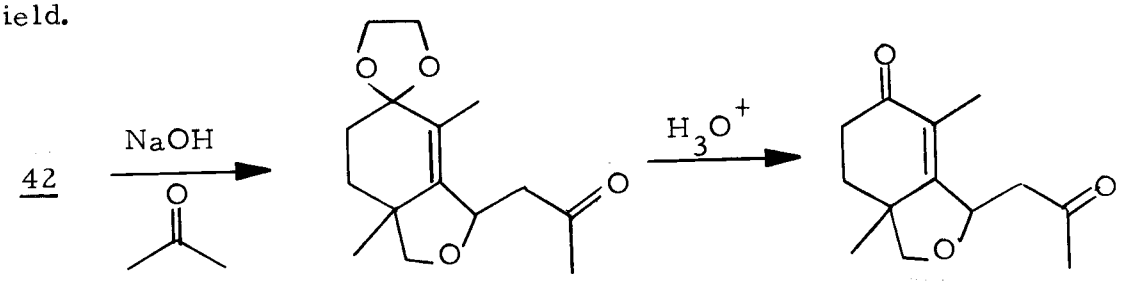
66 or 67

Removal of the ethylene glycol protecting group (p-toluenesulfonic acid, water or refluxing acetone, p-toluenesulfonic acid) from 59 or 60 could not be accomplished. Attention was therefore directed toward the chemistry of hemiacetal intermediate 42.

2. Chain Extension Reactions

The hemiacetal 42 appeared to be a promising intermediate, even though the Wittig reaction (42 + 51 → 52) had failed to produce the desired product. In particular, the availability of the phosphonium salt 64 made chain extension seem plausible. The intermediate for

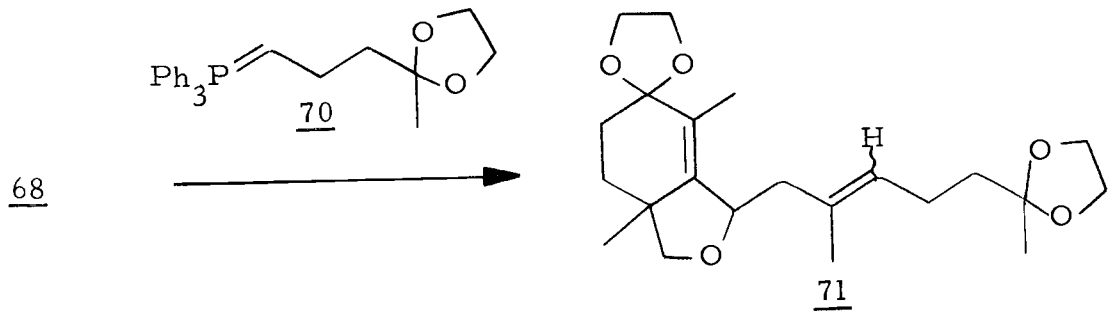
this chain elongation thus becomes the methyl ketone 68. The latter is essentially the product of a crossed-aldol reaction between the hemiacetal 42 and acetone (31), and was obtained in approximately 68% when treated with aqueous sodium hydroxide in acetone. Analysis of the NMR (-COC$\underline{H}_3$, δ 2.24 and 2.20; =C-C$\underline{H}_3$, δ 1.56 and 1.24) revealed that 68 is actually produced as a diastereomeric mixture. Cleavage of the ketal function afforded 69, as a single isomer in 94% yield.

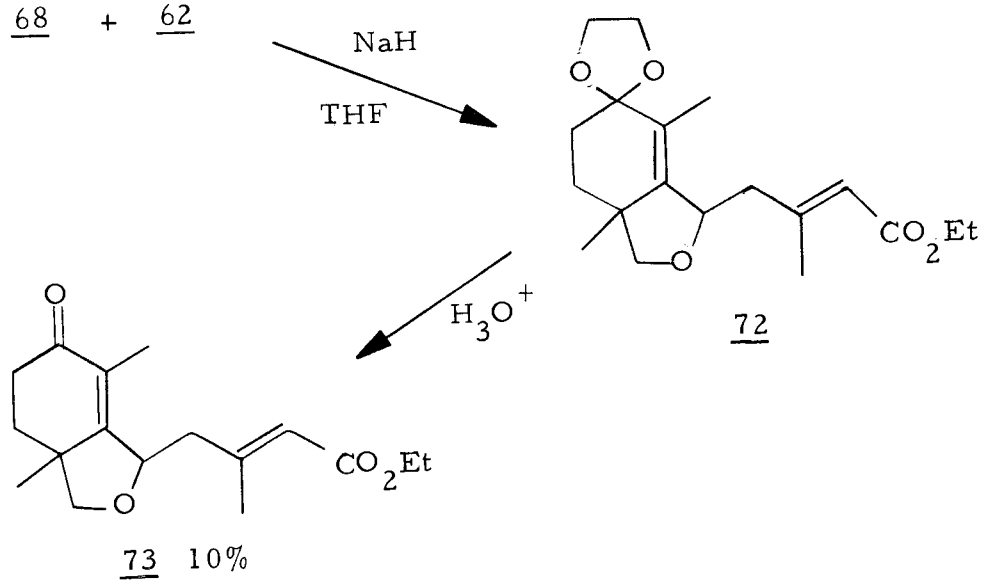


68 68%

69 94%

The reaction of 68 with the ylide 70 derived from 64 (sodium hydride, dimethyl sulfoxide) gave a complex mixture rather than the expected 71. However, reaction of 68 with the anion of diethyl carbethoxymethylphosphonate afforded a mixture which appeared upon spectroscopic examination to contain 72. The ketal 72 is of interest because it contains the carbon skeleton of trisporone, a degradation product of the trisporols (3, 8, 32). In order to purify this substance, the ketal function was cleaved, affording 73 in approximately 10% yield from 68. The use of two equivalents of 62 was of no advantage, in that an even more complex mixture of products was obtained.





72

73 10%

These results directed our attention to the diketone 69. Isoe et al., reported in their synthesis of methyl trisporate B (8) that 70 reacted solely with the methyl ketone of 16 (See Scheme 2). The possibility of a selective Wittig reaction between 69 and 70 is intriguing, although remote. In fact, the reaction of 69 and 70 (tetrahydrofuran, dry-ice acetone bath), gave a mixture which could not be separated, nor its NMR spectrum interpreted. Also, there was no adduct formed when the anion of 62 was reacted with 69.

During cleavage of the ketal function of 68, (68→69), it was noted

that the mixture of diastereomers of 68 was converted to a single isomer of 69. Two possible pathways for this epimerization of the C-7 center, under the acidic conditions, are shown below in Figure 4. Path a shows the isomerization process occurring via the enol 74, whereas pathway b posits the intermediacy of alcohol 75.

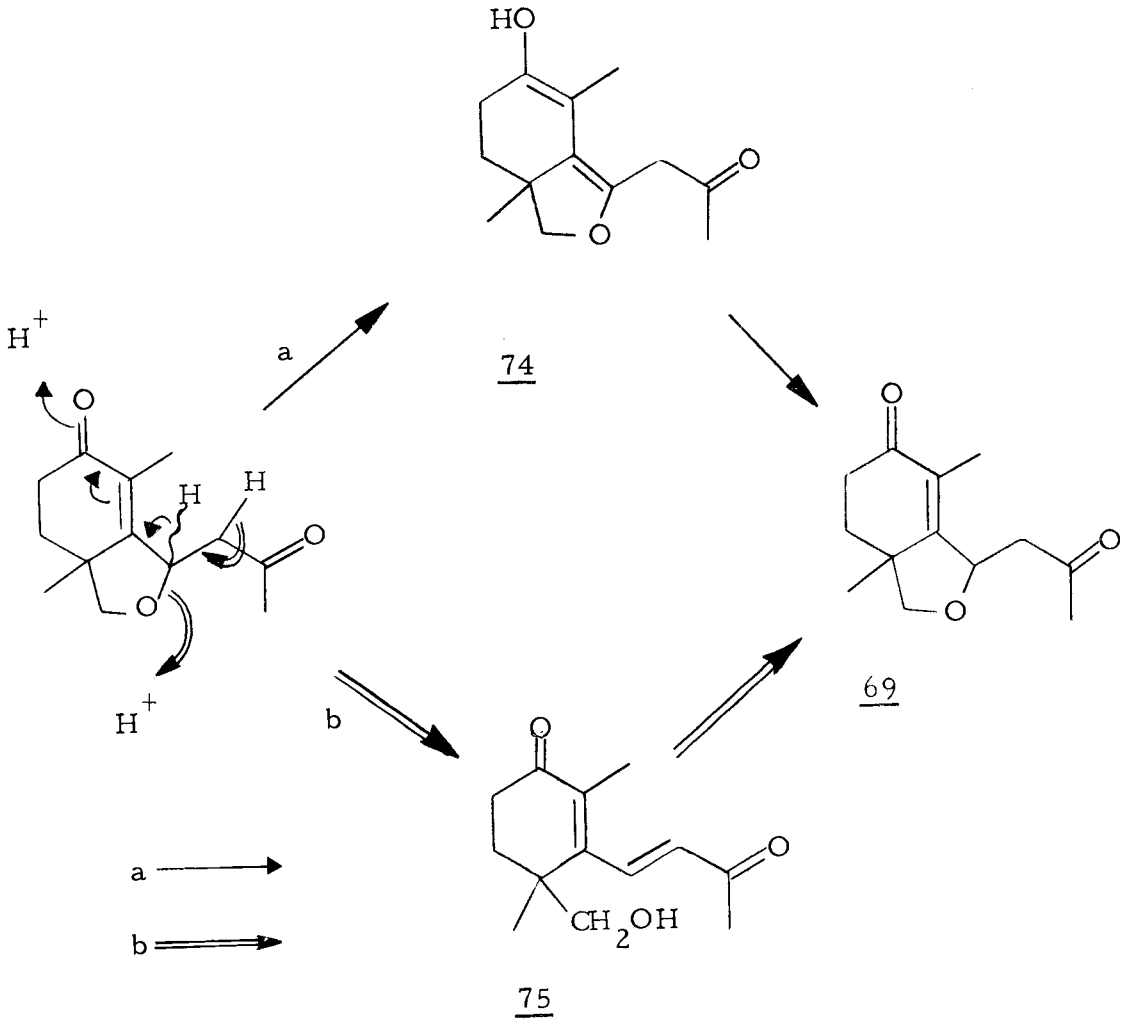
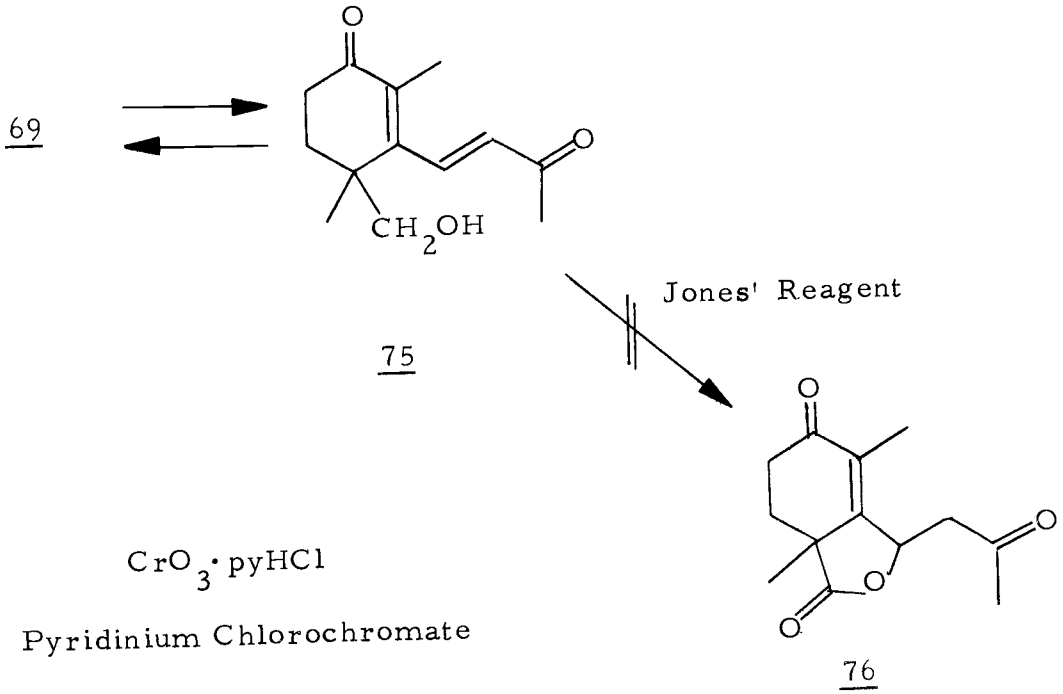


Figure 4.

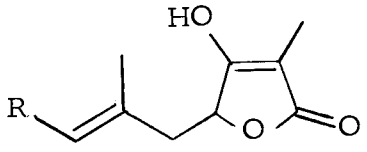
If this epimerization process occurs via pathway b, the alcohol function should lend itself to oxidation. Oxidation of 75 would produce 76, the equivalent of 16. Treatment of 69 with Jones' reagent (33) in acetone, however, afford only unidentified fragments along with a small amount of recovered starting material, while Corey's reagent (34), pyridinium chlorochromate, failed to give any reaction.



The consistent formation of complex mixtures and/or low yields of products in the chain extensions of 68 and 69 forced the conclusion that the entire side chain must be incorporated as an intact unit. A more promising approach, based on this strategy, is described in the following section.

3. A Dianion Approach

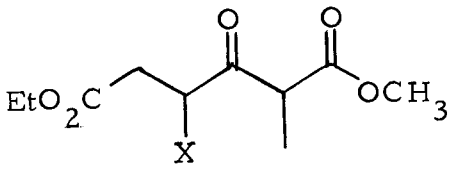
The earlier successful synthesis of γ-lactone 33 (Scheme 6) via the Robinson annelation sequence made the γ-substituted tetronic acid 77 a very attractive intermediate. Tetronic acids have been prepared by cyclization of acetoacetates of lactic acid (35), via the closure of γ-bromo-β-ketoesters (13, 36, 37, 38), and by a method due to Schlessinger (39) in which α-hydroxy thioesters are converted into γ-hydroxy-β-ketoesters and cyclized under acidic conditions.



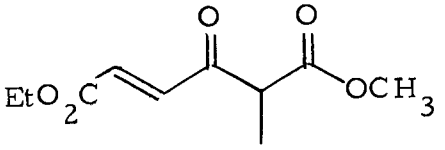
77

$R=CH_2(CH_2)_2CH_3$
$R=CH_2CH_2COCH_3$

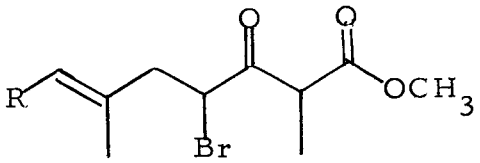
The cyclization of acetoacetates developed by Lacey (35) is confined to the preparation of α-acyl or α-unsubstituted tetronic acids and hence is of little use here. Also, it must be noted that γ-bromo-β-ketoesters such as 78 (X=Br), undergo a facile elimination of hydrogen bromide (rather than cyclization), affording unsaturated compounds such as 80 (38). Presumably, the same would be true for 79 (X=OH). This elimination process puts the cyclization of an intermediate such as 81 on questionable ground, and makes an alternate synthesis of γ-substituted tetronic acids desirable.



78 X=Br
79 X=OH

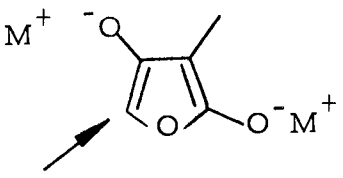


80



81

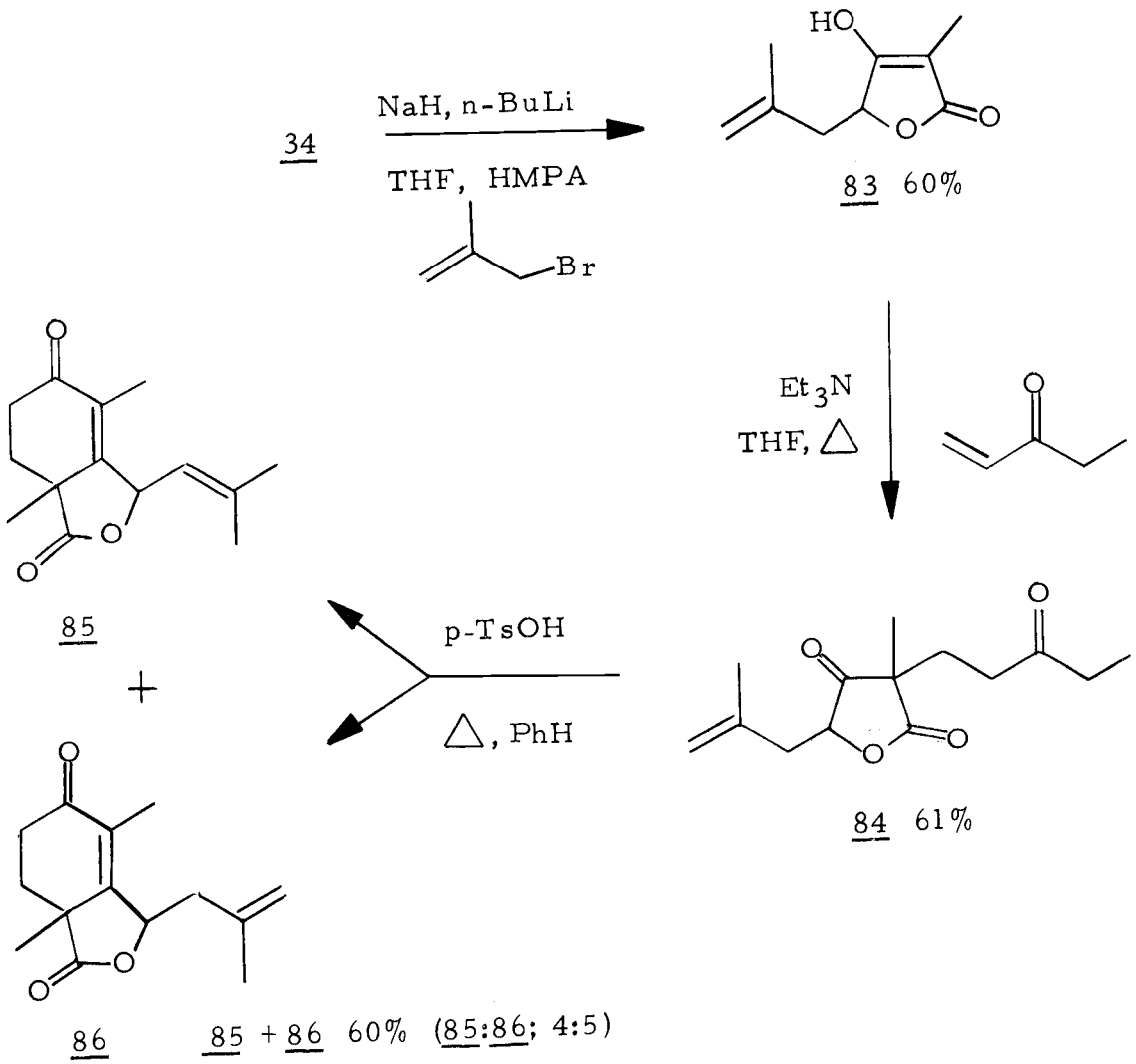
Weiler has recently reported the γ-alkylation of β-ketoesters in tetrahydrofuran via the corresponding dianions (40). Extension of this concept to tetronic acids would yield γ-substituted derivatives directly. The dianion of α-methyltetronic acid 82, has indeed been reported to give γ-alkylation in good yields with benzyl chloride in liquid ammonia (41). In general, however, alkylations of β-ketoesters proceed in low yields under these conditions, due to incomplete dianion formation and subsequent competition of amide ion for the alkyl halide (42).



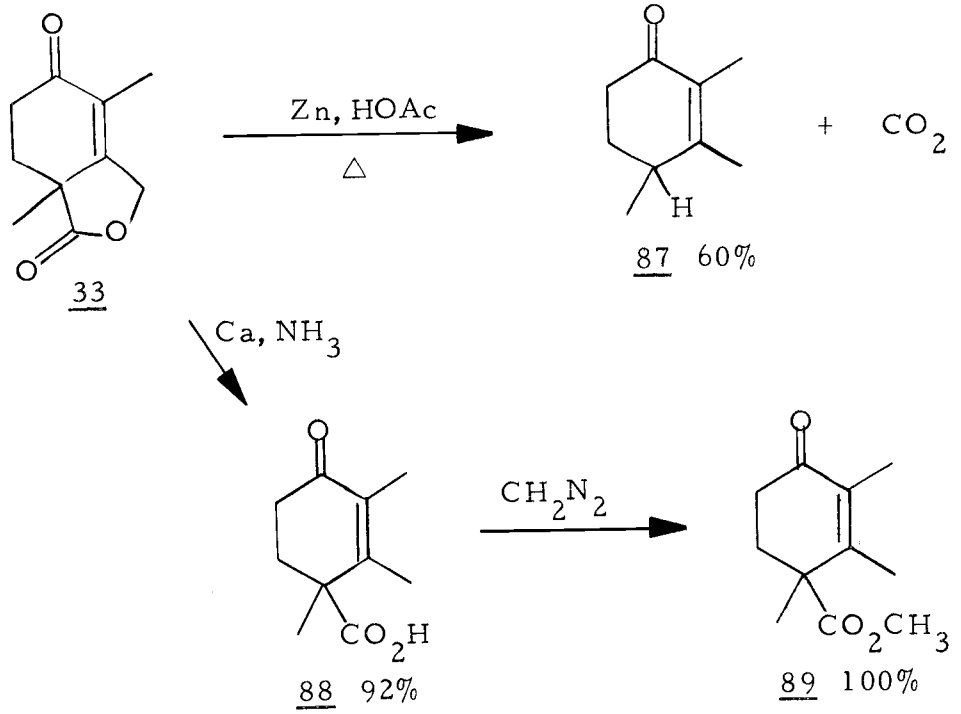
Predicted Site of Alkylation 82

The reaction conditions described by Weiler, except with added hexamethylphosphoramide (HMPA), led to γ-alkylation of 34 in the presence of methallyl bromide, producing 83 in good yield (Scheme 9). Treatment of 83 with ethyl vinyl ketone afforded the Michael adduct 84 (61%). Acid-catalyzed cyclization of 84 furnished the desired lactones 85 and 86 in 60% yield. The ratio of 86 to 85 was determined by NMR analysis to be 5:4.

Scheme 9



The model sequence developed above looked promising for the introduction of the various side chains found in the trisporic acids. However, in order to be useful, the γ-lactone function required modification. A careful examination of 33 reveals that it is a γ-acyloxy-α,β-unsaturated ketone. Although an acetoxy group in this structural environment can be reductively cleaved, treatment of 33 with chromous chloride gave no reaction (43, 44, 45). The action of zinc powder in refluxing glacial acetic acid produced only 87 (60%), presumably through decarboxylation of the corresponding acid. Reduction using calcium metal in liquid ammonia (46) did give the desired acid 88 in 92% yield, which was esterified with ethereal diazomethane to afford 89 (100%). Attempted esterification of 88 with boron trifluoride ethereate in refluxing methanol (47) led to a mixture of 87, 88 and 89.



Dreiding models indicate that the preferred conformation of the lactone 33 has the C-1 methyl group in an axial position, as in Figure 5. The difference in the ease of reduction of 33 is consistent with the fact that the chromous chloride reductions are known to be subject to stereoelectronic control (the only reductions of γ-acetoxy-α, β-unsaturated ketones reported with this reagent are cases where the acetoxy substituent is axial)(45, 48) while the calcium ammonia reductions of related systems are not (46).

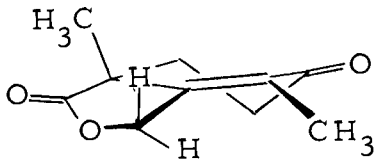
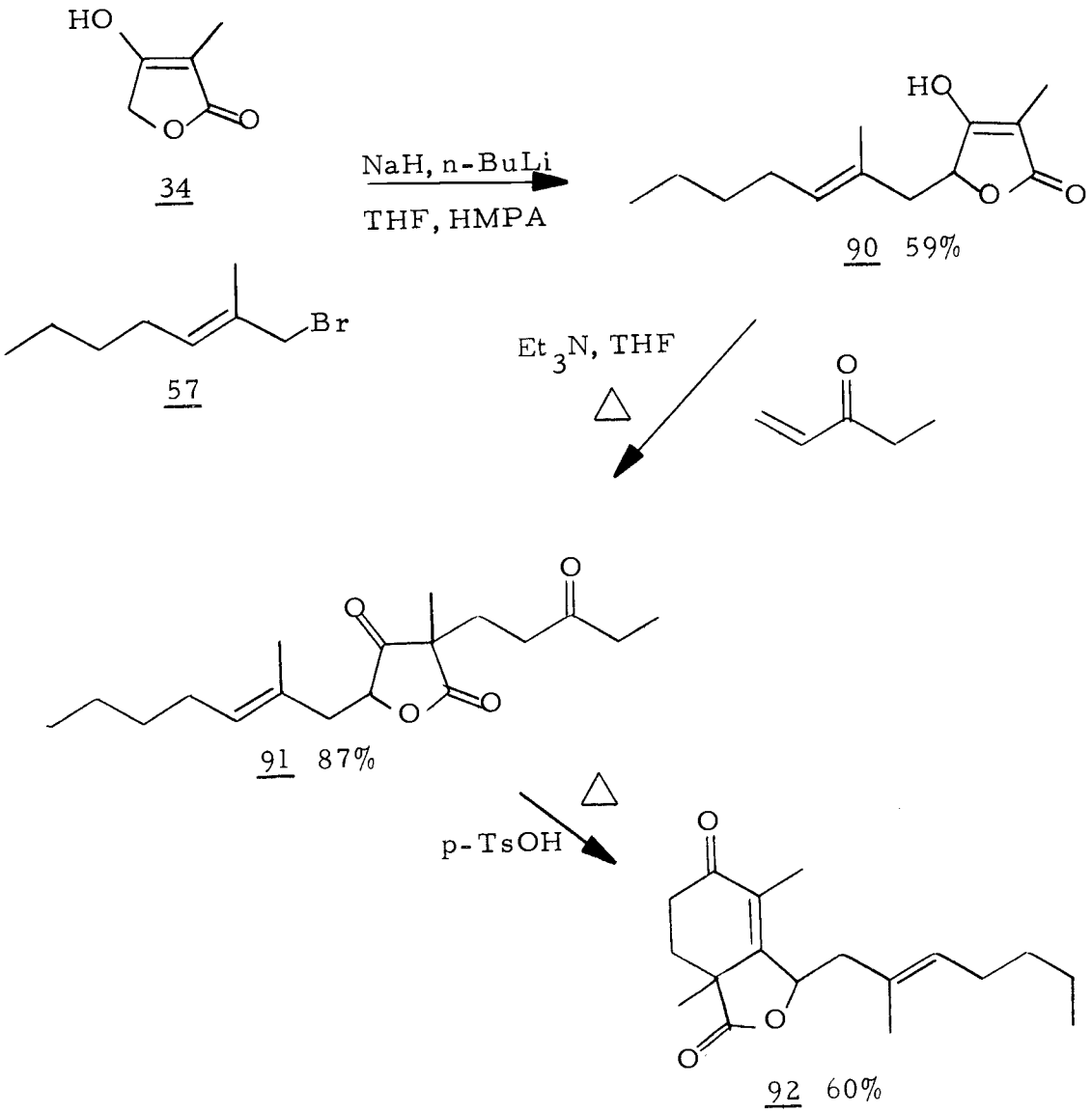


Figure 5.

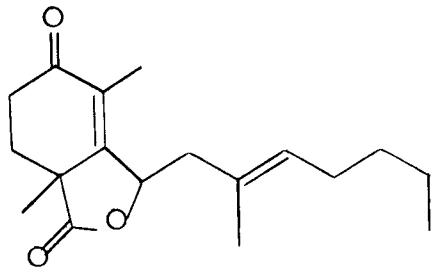
With the conditions for transformation of lactone 33 to ester 89 established, 34 was alkylated with the previously described allylic bromide 57 to give the γ-substituted tetronic acid 90 in 59% yield. The Michael adduct 91 was obtained in 87% yield, and subsequent cyclization afforded 92 in 61% yield, as outlined in Scheme 10.

Scheme 10

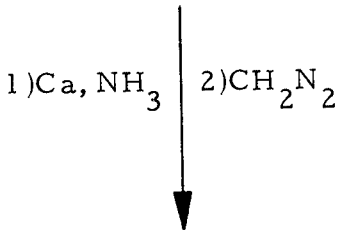


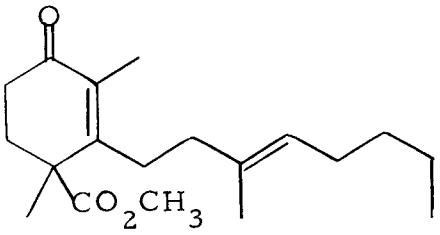
With a small quantity of γ-lactone 92 in hand, the dissolving-metal reduction was performed using an excess of calcium (46), and the resulting product was treated with ethereal diazomethane. Contrary to expectations based on the model study, the desired product

93 (7, 8-dihydrotrisporic acid A methyl ester), was but a minor component of a complex mixture. The major products appeared to be the ketone 94 and the alcohol 95.

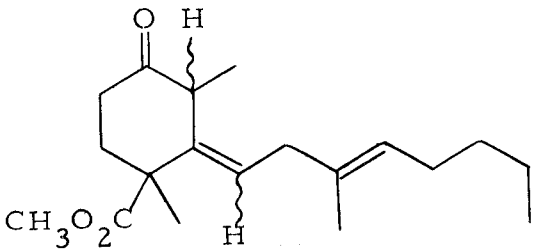


92

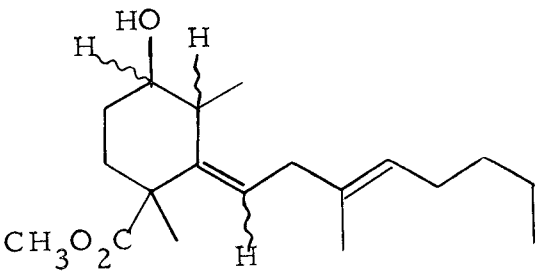




93



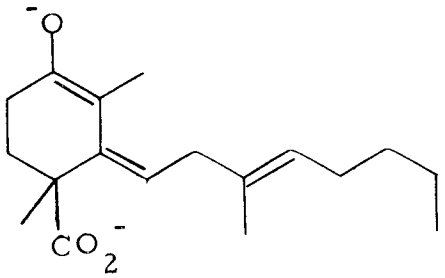
94



95

The assignment of structure to 93 is based upon singlets in the NMR spectrum (δ 3.64 ester $C\underline{H}_3$ and 1.85 vinyl $C\underline{H}_3$), and its mass spectrum (M^+, 306). The enone 93 also shows an UV active spot upon analysis by thin layer chromatography. The structures of ketone 94 and the alcohol 95, which were separated from 93 by preparative thin layer chromatography, are based upon IR (3410 cm^{-1}; 95, ; 1710 cm^{-1}, 94; 1725 and 1250 cm^{-1}, 94 and 95), NMR (δ 3.70 ester $C\underline{H}_3$, 94 and 95), and mass spectral information (306 and 308, M^+ for 94 and 95, respectively).

The formation of 94 indicates that increased substitution at C-7 decreases the stability of the α, β-unsaturated enone system, while stabilizing the exo-trisubstituted olefin. Also, it appears that kinetic protonation of the enolate 96, upon quenching the reaction, occurs alpha to the ketone. That this position does bear a large fraction of the negative charge may be ascertained from the predominate alpha alkylation of similar enolates (49).



96

The above results indicated that the β, γ-unsaturated ketone 94 is the initial reduction product from 92. It then becomes apparent

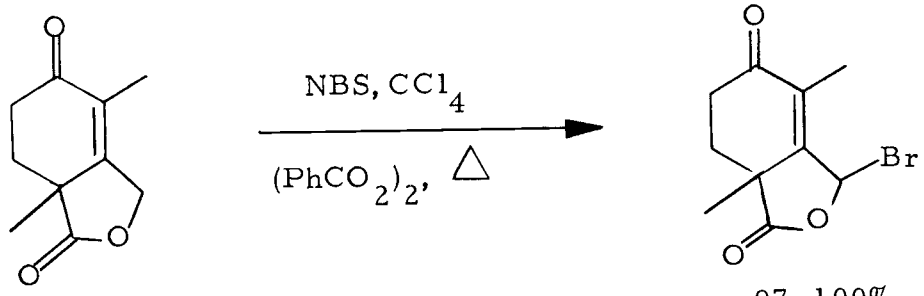
that the desired α, β-unsaturated product 93, was formed via isomerization during the workup procedure (acidification with 10% sulfuric acid). Alcohol 95 may be accounted for by over-reduction of 94, a supposition which has basis in the reduction of related α-acetoxy ketones under similar conditions (46). Further proof for the structure of alcohol 95 (as opposed to its endocyclic isomer) came from the lack of reaction with activated manganese dioxide, hence it is not an allylic alcohol. Also, attempted dehydrogenation of 94 with dichlorodicyanobenzoquinone gave no reaction.

Although the lactone 92 could be prepared in good yield, the production of large amounts was inconvenient due to the rather lengthy chromatographic separations required. Thus, further investigation of this sequence was not pursued although, in principle, this approach to the trisporic acids appears to be a viable one.

4. Approaches from Bromo-Lactone 97

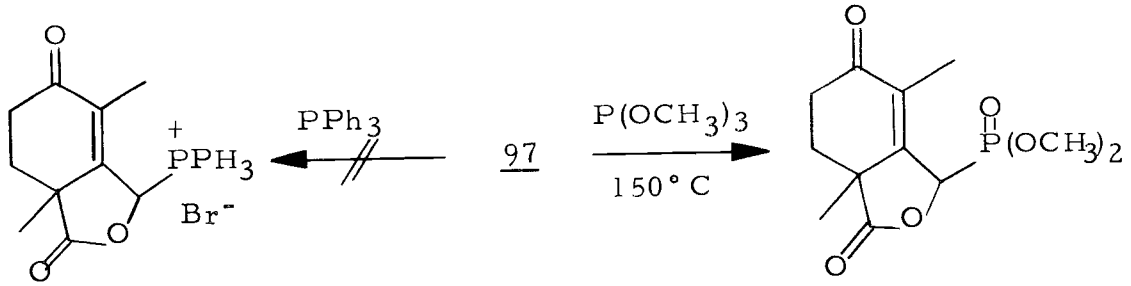
The ease with which the lactone 33 may be prepared makes its use in a synthetic scheme highly advantageous. An intersting possibility for its further transformation to the trisporic acids is conversion to the bromo-lactone 97. Treatment of α, β-unsaturated-γ-butylrolactones with N-bromosuccinimide (NBS), is known to afford the γ-bromo derivatives efficiently (13, 50). Thus, the reaction of 33 with N-bromosuccinimide and a trace of benzoylperoxide afforded

97, in a quantitative yield.



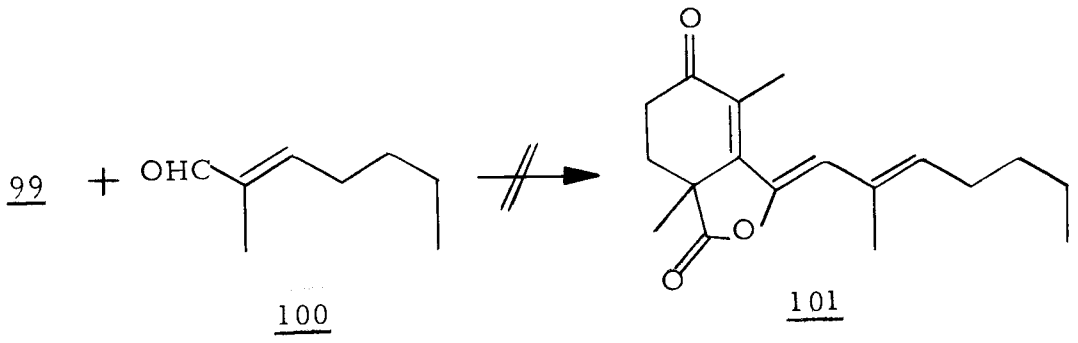
33 97 100%

With the acquisition of this bromo-lactone, a coupling between the cyclohexene moiety and various side-chains via a Wittig reaction seemed feasible. The conversion of 97 to its phosphonium salt 98 could not be accomplished (13), but the phosphonate 99 could be made by treatment of 97 with trimethylphosphite at 150° C. The phosphonate, although prepared in only 32% yield, is rather interesting in that it shows an unusual five bond coupling between phosphorus and hydrogen, $J_{PCCCCH} = 4$ Hz (51).

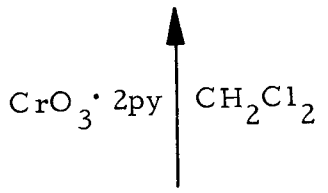


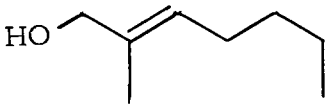
98 99 32%

Unfortunately, the attempted condensation of phosphonate 99 with the α,β-unsaturated aldehyde 100, prepared by Collin's (52) oxidation of 56, gave no adduct. The reaction of 99 with valeraldehyde afforded 102 in only 10% yield. Thus, it was concluded that 99 is an unsuitable reagent for a Wadsworth-Emmons reaction.

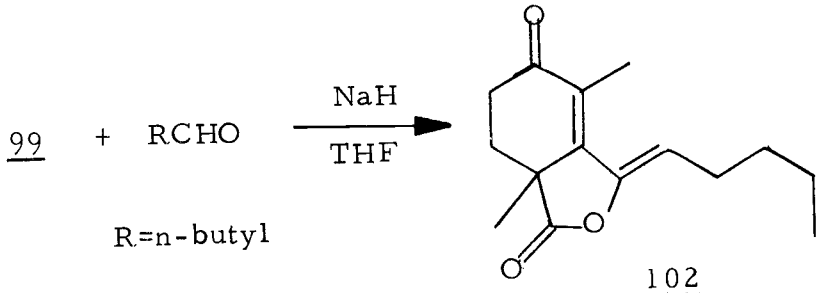


100 101



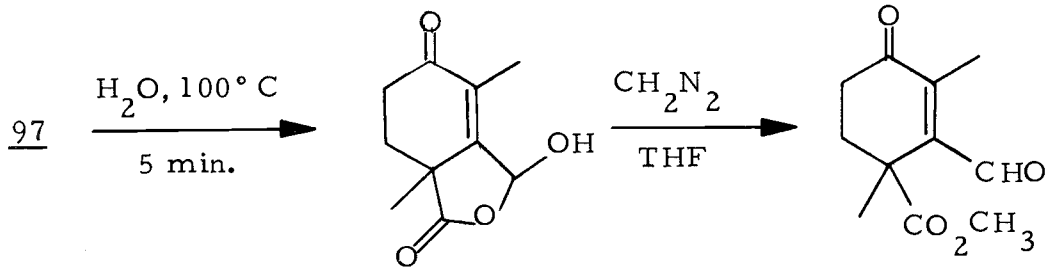


56



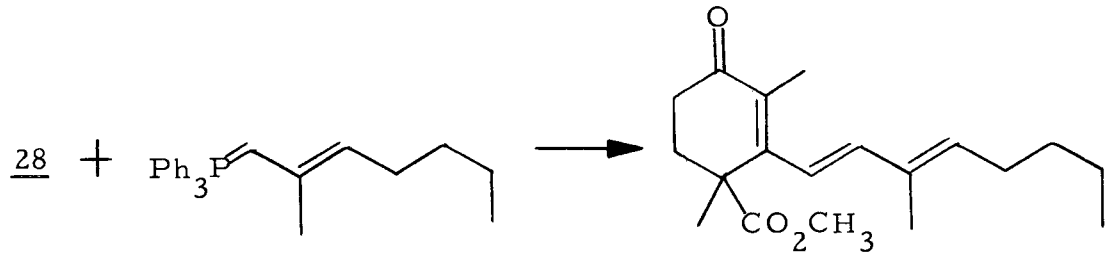
102

The synthesis of hydroxy-lactones from bromo-lactones analogous to 97 has been carried out previously (53) and, in fact, the conversion of 97 to the lactol 103 was accomplished upon its dissolution in hot water. The aldehyde 28 was obtained in 56% yield when the lactol was treated with ethereal diazomethane.

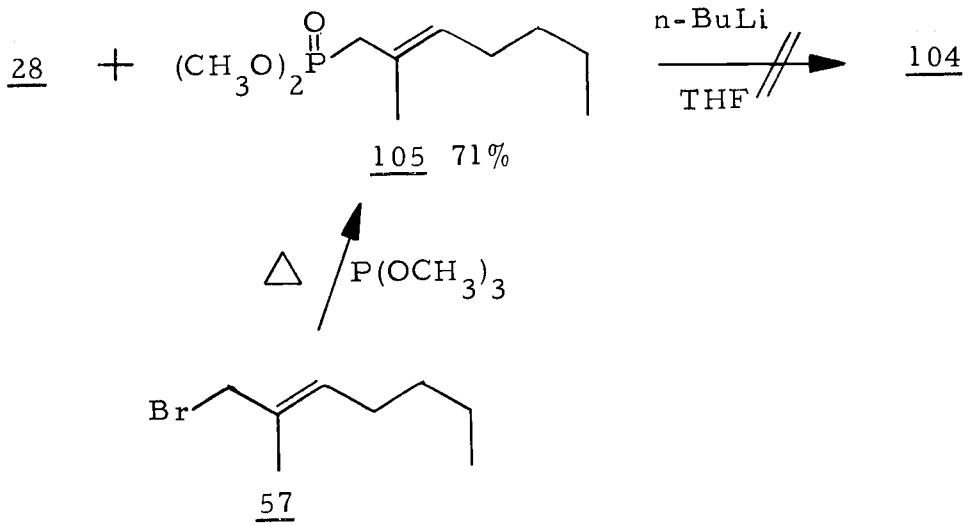


103 80% 28 56%

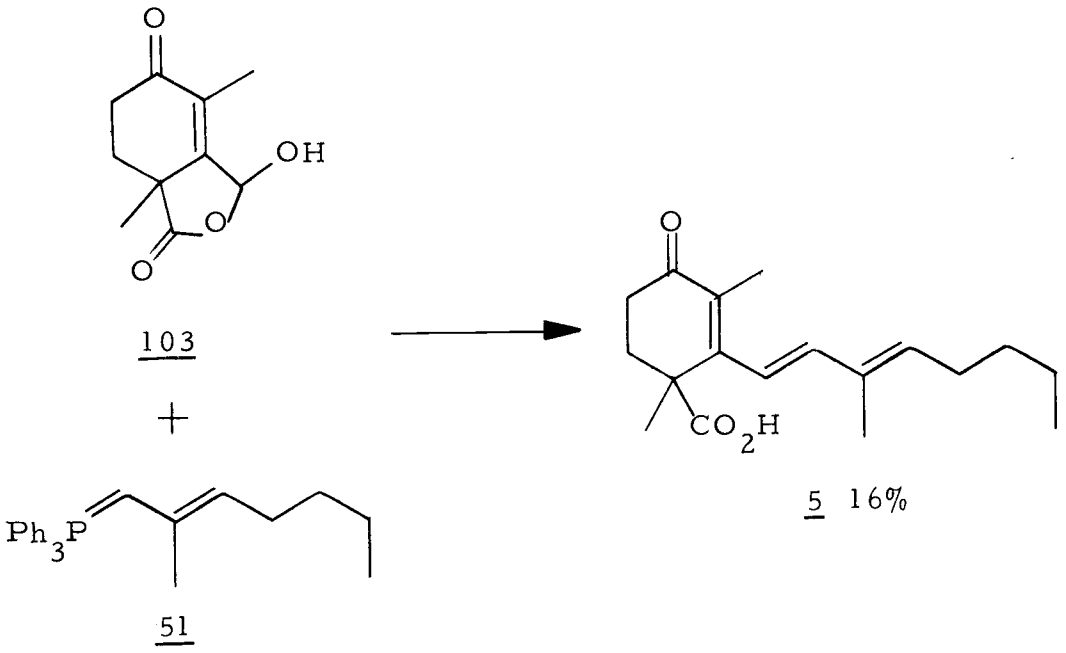
The synthesis of 28 constitutes a formal total synthesis of methyl trisporate B 12, since this conversion has been accomplished by Secrist et al. (10). The coupling of 28 with the ylide 51 afford (±)-(7E, 9E)-trisporic acid A methyl ester 104 in 29% yield. A reaction between 28 and phosphonate 105 (6), prepared from the bromide 57, gave only polymeric material.



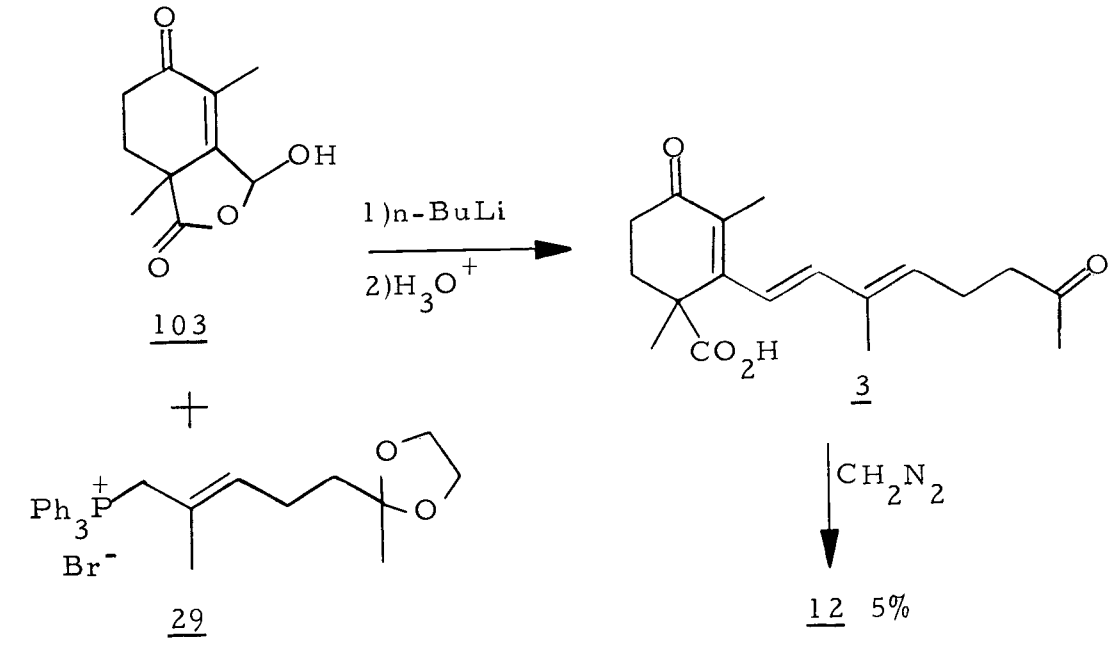
51 104 29%



Extension of this scheme to a synthesis of the labile trisporic acid A required condensation of 51 with the lactol 103 directly. Reaction of the lactol with two equivalents of the ylide 51, afforded (±)-(7E, 9E)-trisporic acid A in 16% yield after chromatography. In a similar manner, the lactol 103 was treated with two equivalents of the ylide derived from 29 (10, 29) giving, after cleavage of the ketal, (±)-(7E, 9E)-trisporic acid B, 3 (M^+, 304). However, purification of this acid proved difficult due to recovered lactol 103. The conversion of 3 and 103 to the methyl esters 12 and 28, which was accomplished by treatment with ethereal diazomethane, confirmed the structural assignment of 3. Preparative thin layer chromatography afforded pure (±)-(7E, 9E)-trisporic acid B methyl ester, 12, in a 5% yield.



103 + 51 → 5 16%



103 + 29 → 3 → 12 5%

5. Conclusion

The main objective of this work has been accomplished, namely the total synthesis of trisporic acids A and B and their methyl esters. The synthesis was achieved along the lines delineated in Figure 3, I (Chapter II). An objective was also realized in the efficient synthesis of the parent cyclohexenone moiety found in the trisporic acids. This cyclohexenone, functionalized as in lactol 103, may be generated in four steps (34→35→33→97→103) in approximately 70% overall yield from 34. In addition, this sequence requires little purification of intermediates, that being recrystallization of lactol 103. Although the final Witting reaction occurs in low yield, this is partly compensated by the ease in which the reactants are generated.

EXPERIMENTAL

General

Infrared spectra (IR) were obtained with a Perkin-Elmer 137 or 727B infrared spectrophotometer. Ultraviolet spectra (UV) were obtained with a Carey 15 spectrophotometer. Nuclear magnetic resonance spectra (NMR) were obtained with either a Varian EM-360, EM-360A, or HA-100 spectrometer and are reported in δ units with tetramethylsilane (TMS) as the internal standard. Coupling constants (J) are given in Hertz; s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, etc. Mass spectra and exact mass determinations were obtained using a CEC-103B spectrometer, using an ionizing potential of 70 eV. Preparative thin layer chromatography (TLC) plates were obtained from Brinkman or Analtech and were prepared from silica gel GF-254. Column chromatography was performed using neutral silica gel (Activity II). All boiling points (bp) and melting points (mp) are uncorrected. Dry tetrahydrofuran (THF) was obtained by distillation, under nitrogen, from lithium aluminum hydride. Hexamethylphosphoramide (HMPA) and dimethyl sulfoxide (DMSO) were dried by distillation from calcium hydride at reduced pressure. Other solvents were purified using standard procedures.

4-Hydroxy-2-methyl-3-oxo-(3-oxopentyl)butanoic Acid γ-Lactone (35)

To 14.00 g (123 mmol) of α-methyltetronic acid (34) in 270 ml of dry THF was added 1.25 g (12.3 mmol) of triethylamine. Heating produced a light yellow solution, after which 15.77 g (188 mmol, 1.50 equivalents) of ethyl vinyl ketone was added and the solution was refluxed for six hours. The solvent was removed under reduced pressure and the residue taken up into ether and washed with brine. The ethereal layer was dried ($MgSO_4$), filtered, and the solvent removed to give 23.80 g (98%) of 35: bp 96-100° C (0.05 mm); IR (film) 1800, 1750, 1705 cm^{-1}; NMR ($CDCl_3$) δ 4.80 (2H, s), 2.52 (2H, t, J=7 Hz), 2.44 (2H, q, J=7 Hz), 2.03 (2H, t, J=7 Hz), 1.31 (3H, s), 1.01 (3H, t, J=7 Hz); mass spectrum m/e 198.088 (M^+, calc for $C_{10}H_{14}O_4$ 198.089).

4,8-Dimethyl-1,5-dioxo-2-oxabicyclo[4.3.0]non-4(9)-ene (33)

The tetronic acid 35 (13.60 g, 68.80 mmol) was refluxed in 150 ml of dry benzene containing 736 mg of p-toluenesulfonic acid for 36 h, with water removal via a Dean-Stark trap. Ether was added, and the cooled solution was washed with saturated aqueous sodium bicarbonate and then brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give 11.80 g (95%) of 33. The crystalline

material was washed with ether or chromatographed using ether as eluent to give pure 33: mp 58-60° C, IR ($CHCl_3$) 1780, 1680 cm^{-1}; NMR ($CDCl_3$) δ 5.01 (2H, m, J=1 Hz), 2.72-2.52 (2H, m), 2.23 (2H, m), 1.74 (3H, m, J=1 Hz), 1.51 (3H, s); mass spectrum m/e 180.078 (M^+, calc for $C_{10}H_{12}O_3$ 180.079).

7-Allyl-7, 9-dimethyl-3, 6-dioxo-2-oxabicyclo[4. 3. 0]non-1(8)-ene (38)

The lactone 33 (204 mg, 1.14 mmol) in 2 ml of dry THF was added dropwise to a solution of lithium diethylamide (1.14 mmol) in 2 ml of dry THF containing 0.25 ml of HMPA at -78° C (dry ice-acetone bath) and the mixture was stirred for 10 minutes. Then 0.100 ml (1.14 mmol) of allyl bromide was added and the solution was allowed to warm and stirred overnight. Water was added and the resulting solution extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed. Preparative TLC gave 23 mg (10%) of 38: IR ($CHCl_3$) 1785, 1710 cm^{-1}; NMR ($CDCl_3$) δ 6.73 (1H, s, isomer A vinyl H), 6.40 (1H, s, isomer B vinyl H), 6.0-5.0 (ABX system isomers A and B), 1.66 (3H, s, isomer B), 1.57 (3H, s, isomer A), 1.36 (3H, s, isomer A), 1.24 (3H, s, isomer B); mass spectrum m/e 220.109 (M^+, calc for $C_{13}H_{16}O_3$ 220.110).

4, 8-Dimethyl-5, 5-ethylenedioxy-1-oxo-2-oxabicyclo[4. 3. 0]non-4(9)-ene (39)

The lactone 33 (5. 04 g, 28. 0 mmol) was stirred for 32 h in 100 ml of anhydrous ether containing 10 ml of triethylorthoformate (freshly distilled), 10 ml of ethylene glycol (dried with Molecular Sieve) and a trace of p-toluenesulfonic acid. The solvent was removed under reduced pressure and the residue taken up into 300 ml of methylene chloride and washed with 50 ml of saturated aqueous sodium bicarbonate and 50 ml of brine, dried ($MgSO_4$), filtered and solvent removed to give 6. 26 g (100%) of 39: Recrystallization of a small portion (carbon tetrachloride, then hexane) gave colorless crystals of 39: mp 114-116° C; IR ($CHCl_3$) 1780, 1150, 1090, 1070 cm^{-1}; NMR ($CDCl_3$) δ 4. 85 (2H, s), 4. 06 (4H, bs), 1. 90 (4H, bs), 1. 70 (3H, s), 1. 35 (3H, s); mass spectrum m/e 224. 105, 99, 86 (M^+, calc for $C_{12}H_{16}O_4$ 224. 105).

1, 1-Ethylenedioxy-2, 4-dimethyl-3, 4-dihydroxymethyl-2-cyclohexene (40)

The lactone 39 (3. 20 g, 14. 2 mmol) was taken up in 50 ml dry THF and added dropwise over a period of 30 minutes to an ice-cold suspension of lithium aluminum hydride (562 mg, 14. 8 mmol) in 50 ml of dry ether. The solution was stirred for 30 minutes and excess lithium aluminum hydride was destroyed carefully with water. The

solution was filtered, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give 2.93 g (92%) of 40: IR (film) 3500 (broad OH), 1160, 1120, 1080 cm^{-1}; NMR ($CDCl_3$) δ 4.30 (s, allylic $-C\underline{H}_2-OH$), 3.9-3.1 ($-C\underline{H}_2-OH$, $-O-C\underline{H}_2-C\underline{H}_2-O-$), 2.30 (s, $-O\underline{H}$, exchanges upon addition of D_2O), 1.66 (s, vinyl $C\underline{H}_3$), 0.87 (s, $C\underline{H}_3$); mass spectrum m/e 228.136 (M^+, calc for $C_{12}H_{20}O_4$ 228.136).

1,1-Ethylenedioxy-2,4-dimethyl-3,4-diacetoxymethyl-2-cyclohexene (41)

The diol 40 (750 mg, 3.30 mmol) in 12 ml of anhydrous ether, was added to 0.93 ml of acetic anhydride (1.0 g, 3.0 equiv), and 0.85 ml of pyridine (0.83 g, 3.2 equiv), initially at 0° C. The solution was allowed to warm to room temperature and stirred for 32 h. Ether was added and the solution washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford 994 mg (95%) of 41: IR (film) 1750, 1180, 1160, 1080 cm^{-1}; NMR ($CDCl_3$) δ 4.68 (2H, s, $=C-C\underline{H}_2-OAc$), 4.20-3.90 (6H, m, $-O-C\underline{H}_2-C\underline{H}_2-O-$ and $-C\underline{H}_2-OAc$), 2.03 (6H, s), 1.90-1.65 (7H, m, $=C-CH_3$ and $-C\underline{H}_2-C\underline{H}_2$), 1.06 (3H, s); mass spectrum m/e 312.158 (M^+, calc for $C_{16}H_{24}O_5$ 312.157).

4, 8-Dimethyl-5, 5-ethylenedioxy-3-oxo-2-oxabicyclo[4. 3. 0]non-4(9)-ene (43)

The diol 40 (2. 80 g, 12. 2 mmol) was stirred in 40 ml of anhydrous ether with 12 g (four weight equivalents) of activated manganese dioxide. After 48 h the solution was filtered over a Celite pad, (the Celite was washed with dry methanol), and then reacted with an additional four weight equivalents of activated manganese for four days. The solution was again filtered over Celite, the Celite was washed with 50 ml of ether, and then with 2 x 25 ml of dry methanol. This gave 1. 92 g (70%) of 43: mp 76-77° C; IR (film) 1760, 1680, 1170, 1142 cm^{-1}; NMR ($CDCl_3$) δ 4. 20 (6H, complex multiplet), 2. 05 (3H, s), 2. 0-1. 65 (4H, m), 1. 25 (3H, s); mass spectrum m/e 224. 106, 99, 86, (M^+, calc for $C_{12}H_{16}O_4$ 224. 105).

4, 8-Dimethyl-3, 5-dioxo-2-oxabicyclo-[4. 3. 0]non-4(9)-ene (44)

The ketal 43 (201 mg, 0. 805 mmol) was stirred in 5 ml of 20% aqueous dioxane with 19 mg of p-toluenesulfonic acid for 43 h. Ether was added and the solution was washed with 10 ml of saturated aqueous sodium bicarbonate and brine (25 ml), dried ($MgSO_4$), filtered and the solvent removed. Chromatography (ether) gave 135 mg (84%) of 44: mp 56-58° C; IR ($CHCl_3$) 1760, 1680, 1210 cm^{-1}; NMR ($CDCl_3$) δ 4. 26 (1H, d, J=8 Hz), 4. 01 (1H, d, J=8 Hz), 2. 66 (2H, m), 2. 14

(3H, s), 2.10 (2H, m), 1.42 (3H, s); mass spectrum m/e 180.081 (M^+, calc for $C_{10}H_{12}O_3$ 180.079).

3,4-Dihydroxymethyl-2,4-dimethyl-2-cyclohexen-1-one (45)

A small amount of ketal 40 was stirred with ca 2 g of silica gel in wet ether overnight. The solution was filtered, dried ($MgSO_4$), filtered again and the solvent removed to afford 45: NMR ($CDCl_3$) δ 4.33 (2H, s), 3.92 (1H, d, J=12 Hz), 3.36 (1H, d, J=12 Hz), 2.50 (2H, s), 1.90 (3H, s), 1.10 (3H, s), 4.4-3.4 (2H, broad, disappears upon addition of D_2O).

5,5-Ethylenedioxy-1-hydroxy-1,4,8-trimethyl-2-oxabicyclo[4.3.0]non-4(9)-ene (49)

Methyl lithium (0.14 ml, 0.24 mmol, 1.8 M in hexane) was added to 54 mg (0.24 mmol) of 39 in 5 ml of dry pentane-ether (2:1) at -78° C. The solution was allowed to warm to room temperature and stirred for 30 minutes. Water was added and the product isolated by extraction into ether. The combined ethereal extracts were dried ($MgSO_4$), filtered and the solvent removed in vacuo to give 39 mg (50%) of 49: IR (film) 3500, 1660 cm^{-1}; NMR ($CDCl_3$) δ 4.38 (2H, s), 4.03 (4H, bs), 2.73 (1H, exchanges with D_2O), 1.96 (2H, s), 1.60 (3H, s) 1.40-1.13 (2H, m), 1.40 (3H, s), 1.10 (3H, s).

4-Acetyl-2, 4-dimethyl-1, 1-ethylenedioxy-3-formyl-2-cyclohexene (50)

The hemiketal 49 (50 mg, 0.21 mmol) was stirred in 10 ml of anhydrous ether with 250 mg (5 weight equivalents) of activated manganese dioxide for 48 h. The solution was filtered over a Celite pad and the pad was washed with ether. The ether was removed *in vacuo* and the residue purified by preparative TLC (ether) to give 4 mg (8%) of 50: IR ($CHCl_3$) 1710, 1680 cm^{-1}; NMR ($CDCl_3$) δ 10.08 (1H, s), 4.3-4.0 (4H, bm), 2.16 (3H, s), 2.05 (3H, s), 2.0-1.46 (4H, m), 1.30 (3H, s); mass spectrum m/e 238.120, 99, 86: (M^+, calc for $C_{13}H_{18}O_4$ 238.121).

4, 8-Dimethyl-5, 5-ethylenedioxy-3-hydroxy-2-oxabicyclo[4.3.0]non-4(9)-ene (42)

To 153 mg (0.681 mmol) of 43 in 4 ml of dry toluene at -78° C, was added in one portion 0.60 ml (0.68 mmol) of di-isobutylaluminum hydride (20% by weight in hexane). The solution was stirred for 15 minutes at -78° C and then 0.5 ml of water was added. The product was extracted with ether (4 x 25 ml) and the combined ethereal layers were dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure to give 138 mg (89%) of 42 as a mixture of stereoisomers: IR (film) 3500, 1160, 1125, 1080 cm^{-1}; NMR ($CDCl_3$) δ 5.8 (1H, m), 4.20-3.80 (6H, m), 3.42 (1H, d, J=8 Hz), 2.00-1.80 (m, $-CH_2-\overset{O}{\overset{\|}{C}}-$),

1.78 (s, vinyl $C\underline{H}_3$, isomer A), 1.70 (s, vinyl $C\underline{H}_3$, isomer B), 1.75-1.50 (m, $-C\underline{H}_2-CH_2-$), 1.48 (s, $C\underline{H}_3$, isomer A), 1.17 (s, $C\underline{H}_3$, isomer B); mass spectrum m/e 226.120, 99, 86, (M^+, calc for $C_{12}H_{18}O_4$ 226.121).

Ethyl trans-2-Methyl-2-heptenoate (55)

Diethyl 1-carbethoxyethylphosphonate (54) (20.15 g, 84.66 mmol) in 10 ml of dry THF was added to a suspension of 4.10 g (85.45 mmol) of sodium hydride (50% mineral oil dispersion, washed with 30-60° petroleum ether), in 150 ml of dry THF and stirred at room temperature, under nitrogen, for 1.5 h. Valeraldehyde (7.28 g, 84.66 mmol) in 10 ml of dry THF was added dropwise to the clear solution and, after addition was complete, the mixture was stirred for an additional 3 h. Water was added and the solution extracted with ether (3 x 100 ml). The combined ethereal layers were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed in vacuo. Distillation gave 13.2 g (92%) of 55: bp 69-71° C (3.0 mm); IR (film) 1720 cm^{-1}; NMR ($CDCl_3$) δ 6.79 (1H, t), 4.22 (2H, q, J=7 Hz), 2.20-2.07 (2H, m), 1.86 (3H, s), 1.60-1.20 (4H, m), 1.30 (3H, t, J=7 Hz), 0.94 (3H, m); mass spectrum m/e 170.132 (M^+, calc for $C_{10}H_{18}O_2$ 171.131).

trans-2-Methyl-2-hepten-1-ol (56)

Ester 55 (13.21 g, 77.17 mmol) in 10 ml of anhydrous ether was added dropwise to a suspension of lithium aluminum hydride, (2.93 g, 77.17 mmol) in 150 ml of anhydrous ether at 0° C. The solution was stirred for 1.5 h. Excess lithium aluminum hydride was destroyed by careful addition of water at 0° C. The precipitated aluminum salts were dissolved in 100 ml of 10% sulfuric acid and the aqueous layer was decanted. The ethereal layer was washed with saturated aqueous sodium bicarbonate (25 ml), brine (50 ml), dried ($MgSO_4$), filtered, and the solvent was removed in vacuo. Distillation of the residual oil gave 8.01 g (81%) of 56: bp 40-42° C (0.05 mm); IR (film) 3450 cm^{-1}; NMR ($CDCl_3$) δ 5.42 (1H, t), 4.02 (2H, s), 2.12 (1H, s, disappears upon addition of D_2O), 2.24-1.90 (2H, m), 1.69 (3H, s), 1.60-1.20 (4H, m), 0.93 (3H, m); mass spectrum m/e 128.120 (M^+, calc for $C_8H_{16}O$ 128.120).

trans-1-Bromo-2-methyl-2-heptene (57)

Freshly distilled phosphorus tribromide (0.25 ml, 2.6 mmol) was added to 1.00 g (7.80 mmol) of 56 in 8 ml of anhydrous ether at room temperature. The solution was stirred for 1.5 h, then diluted with ether and poured into cold water. The aqueous layer was extracted with ether (100 ml). The combined ethereal extracts were

washed with brine, dried ($MgSO_4$), filtered, and the solvent removed to yield 1.43 g (95%) of 57: IR (film) 1660, 1450, 1200 cm^{-1}; NMR ($CDCl_3$) δ 5.67 (1H, t), 4.03 (2H, s), 1.80 (3H, s), 1.56-1.18 (4H, m), 0.90 (3H, m); the mass spectrum showed no peak corresponding to the molecular ion.

trans-2-Methyl-2-heptenyltriphenylphosphonium Bromide (58)

The crude bromide 57, (2.18 g, 11.45 mmol) was stirred in 50 ml of dry benzene containing 3.26 g (12.44 mmol) of triphenylphosphine (recrystallized and dried) (53). The crude product was recrystallized (acetone/ether), and vacuum-dried over refluxing benzene in the presence of phosphorus pentoxide to give 3.97 g (76%) of 58: mp 164.5-167° C, NMR ($CDCl_3$) δ ca 7.80 (15H, bm), 5.36 (1H, m), 4.65 (2H, d, J=14 Hz), 2.04-1.80 (2H, m), 2.2-2.0 (4H, m), 1.50 (3H, bd), 0.82 (3H, m). This material did not give an acceptable combusion analysis.

Reaction of 42 with 51

Sodium hydride (102 mg, 2.13 mmol, 50% mineral oil dispersion) was heated to 65° C in 5 ml of dry DMSO for 1 h. The solution was cooled and 913 mg (2.13 mmol) of 58 in 2 ml of dry DMSO was added dropwise. Then 138 mg (0.610 mmol) of crude hemiacetal 42 was added in 3 ml dry THF and the solution stirred for 60 h. Water

was added and the product was extracted with pentane. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. Preparative TLC (ether/hexane 3:1), gave 80 mg (40%) of a product identified as 59 or 60: IR (film) 2980, 1140, 1080 cm^{-1}; NMR ($CDCl_3$) δ 6.14 (1H, d, J=16 Hz), *ca* 5.33 (m, vinyl H), 5.30 (d, J=16 Hz), 4.20-3.80 (6H, m), 3.77 (s, -O-C$\underline{H}_2$-), 1.80 (s, vinyl C$\underline{H}_3$), 1.27 (s, -O-C-C$\underline{H}_3$), 1.06 (s, C$\underline{H}_3$), 0.88 (m, C$\underline{H}_3$); mass spectrum 320.237 (M^+, calc for $C_{20}H_{32}O_3$, 320.235).

3-Acetonyl-4,8-dimethyl-5,5-ethylenedioxy-2-oxabicyclo[4.3.0]non-4(9)-ene (68)

The hemiacetal 42 (479 mg, 2.10 mmol) was added in one portion to a solution containing 3 ml of ethanol, 2 ml of acetone, 2 ml of water and 266 mg of sodium hydroxide. The solution was stirred at room temperature for 64 h. Saturated aqueous ammonium chloride was added and the product extracted with ether. The combined ethereal layers were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. Distillation gave 380 mg (68%) of 68 as a mixture of stereoisomers: bp 75° C (bath temperature) (0.07 mm); IR (film) 1725, 1080, 1040 cm^{-1}; NMR ($CDCl_3$) δ 4.80 (m, O-C$\underline{H}$-CH_2COCH_3, isomers A and B), 4.18-3.96 (m, -O-C$\underline{H}_2$-C$\underline{H}_2$-O), 3.80 (d, J=8 Hz), 3.32 (d, J=8 Hz), 2.75 (d, CH-C$\underline{H}_2$-COCH_3, isomer A), 2.70 (d, CH-C$\underline{H}_2$-COCH_3, isomer B), 2.24 (s, -COC$\underline{H}_3$, isomer A), 2.20 (s, -COC$\underline{H}_3$, isomer B), 2.05-1.82 (m, -CH_2-C$\underline{H}_2$-C<O/O>), 1.74-1.50

(m, -C<u>H</u>$_2$-CH$_2$-C$\begin{matrix}O\\ \diagup\\ \diagdown\\ O\end{matrix}$), 1.56 (s, vinyl C<u>H</u>$_3$, isomer A), 1.24 (s, vinyl C<u>H</u>$_3$, isomer B), 1.26 (s, C<u>H</u>$_3$, isomers A and B); mass spectrum m/e 266.151 (M^+, calc for $C_{15}H_{22}O_4$, 266.152).

3-Acetonyl-4,8-dimethyl-5-oxo-2-oxabicyclo[4.3.0]non-4(9)-ene (69)

Ketal 68 (80 mg, 0.30 mmol) was stirred in 5 ml of 20% aqueous dioxane for 4 h with a trace of p-toluenesulfonic acid. Ether was added and the aqueous layer removed. The ethereal layer was washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), filtered, and the solvent removed <u>in vacuo</u> to give 63 mg (94%) of 69: IR ($CHCl_3$) 1720, 1675 cm^{-1}; NMR ($CDCl_3$) δ 5.10 (1H, t, J=6 Hz, -C<u>H</u>-CH$_2$-), 3.92 (1H, d, J=8 Hz), 3.46 (1H, d, J=8 Hz), 2.83 (2H, d, J=6 Hz, -CH-C<u>H</u>$_2$), 2.62-2.46 (2H, m), 2.28 (3H, s), 1.93-1.80 (2H, m), 1.69 (3H, s), 1.38 (3H, s); mass spectrum m/e 222.124 (M^+, calc for $C_{13}H_{18}O_3$ 222.126).

Ethyl 3-Methyl-4-(4,8-dimethyl-5-oxo-2-oxabicyclo[4.3.0]non-4(9)-enyl)but-2-enoate (73)

Ketal 68 (181 mg, 0.68 mmol), was treated with one equivalent (0.68 mmol) of the anion of diethyl 1-carbethoxymethylphosphonate, prepared from 33 mg (0.68 mmol) of sodium hydride (50% mineral oil dispersion) and 153 mg (0.68 mmol) of diethyl 1-carbethoxymethylphosphonate (62), at room temperature for one hour. Water

was added and the solution extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed in vacuo. The residue thus obtained was stirred in 5 ml of 25% aqueous dioxane with a trace of p-toluenesulfonic acid overnight. Ether was added and the resulting solution was washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), filtered and the solvent removed. Preparative TLC, using ether as eluent, afforded 22 mg (10%) of 73: NMR ($CDCl_3$) δ 5.84 (1H, s), 4.76 (1H, bd), 4.14 (2H, q, J=7 Hz), 3.92 (1H, d, J=8 Hz), 3.46 (1H, d, J=8 Hz), 2.80-2.40 (4H, m), 2.28 (3H, s), 2.0-1.8 (2H, m), 1.72 (3H, s), 1.35 (3H, s), 1.26 (3H, t, J=7 Hz); mass spectrum m/e 292, M^+.

2-Methyl-4-(2-methyl-2-propenyl)tetronic Acid (83)

To 96 mg (2.0 mmol) of sodium hydride (50% mineral oil dispersion washed with dry pentane) in 3 ml of dry THF was added 228 mg (2.0 mmol) of α-methyltetronic acid (34) in 2 ml of a 1:1 mixture of dry THF and dry HMPA. The solution was stirred at room temperature for 20 minutes, cooled to 0° C (ice bath), and 1.0 ml (2.0 mmol) of 2.0 M n-butyllithium was added dropwise. The resulting paste was stirred for 20 minutes and then 270 mg (2.0 mmol) of methallyl bromide in 1 ml of dry THF was added. The ice-bath was removed and the solution was stirred for 2 h. Water and then 10%

sulfuric acid was added, and the product was extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed to give 83 in good yield. Preparative TLC (ethyl acetate/ethanol/acetic acid, 90:10:2) of a small portion gave pure 83: IR ($CHCl_3$) ca 3000 (broad OH), 1730, 1650 cm^{-1}; NMR ($CDCl_3$) δ 9.15 (1H, bs, variable with temperature), 4.86 (3H, bm, =C-CH-O-, ABX and $C=CH_2$), 2.76 (1H, d, J=16, ABX), 2.22 (1H, dd, J=8, 16 Hz, ABX), 1.79 (3H, s), 1.72 (3H, s); mass spectrum m/e 168.077 (M^+, calc for $C_9H_{12}O_3$ 168.079).

2,6-Dimethyl-4-hydroxy-3-oxo-2-(3-oxopentyl)hept-6-enoic Acid γ-Lactone (84)

The crude tetronic acid 83 (85 mg, 0.51 mmol) was refluxed in 3 ml of dry THF containing four drops of triethylamine and 77 mg (0.92 mmol; 1.8 equivalents) of ethyl vinyl ketone. The solution was cooled, ether was added, and the solution was washed with brine, dried ($MgSO_4$), filtered and the solvent removed to give 78 mg (61%) of 84: IR (film) 1795, 1750, 1705 cm^{-1}; NMR ($CDCl_3$) δ 4.96 (3H, bm), ca 2.50 (6H, m), 2.03 (2H, t, J=7 Hz), 1.80 (3H, s), 1.27 (3H, s), 1.03 (3H, t, J=7 Hz); mass spectrum m/e 252.137 (M^+, calc for $C_{14}H_{20}O_4$ 252.136).

4, 8-Dimethyl-1, 5-dioxo-2-oxa-3-(2-methyl-1-propenyl)bicyclo[4. 3. 0]non-4(9)-ene (85)

and

4, 8-Dimethyl-1, 5-dioxo-2-oxa-3-(2-methyl-2-propenyl)bicyclo[4. 3. 0]non-4(9)-ene (86)

Approximately 78 mg (ca 0. 310 mmol) of crude 84 was heated at reflux in dry benzene containing a trace of p-toluenesulfonic acid for 36 h. Water was removed via a Dean-Stark trap. The solution was cooled, ether was added, and the solution was washed with saturated aqueous sodium bicarbonate, brine, dried ($MgSO_4$), filtered, and the solvent removed in vacuo. Preparative TLC (ether/hexane, 70:30) gave 43 mg (60%) of a mixture of 85 and 86: IR ($CHCl_3$) 1785, 1675 cm^{-1} (both isomers); NMR (CCl_4) δ 5. 70 (1H, d, J=10 Hz, (85)), 5. 25 (1H, d, J=10 Hz, (85)), 5. 18 (1H, t, J=6 Hz, (86)), 4. 92 (2H, bs, -C=C$\underline{H}_2$, (86)), 2. 50 (2H, d, J=6 Hz, (86)), 1. 88 (vinyl C$\underline{H}_3$, α to C=O, both isomers), 1. 70 (vinyl C$\underline{H}_3$), 1. 61 (vinyl C$\underline{H}_3$), 1. 52 (C$\underline{H}_3$, both isomers); mass spectrum m/e 234. 127 (M^+, calc for $C_{14}H_{18}O_3$ 234. 126).

2, 3, 4-Trimethylcyclohex-2-enone (87)

The lactone 33 (48 mg, 0. 27 mmol) in 4 ml of glacial acetic acid was heated at reflux for 23 h with 205 mg of zinc powder. The excess zinc was removed by filtration, and the residue was taken up

into water and extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. Preparative TLC (hexane/ether, 60:40) gave 21 mg (60%) of 87: IR ($CHCl_3$) 1660 cm^{-1}; NMR ($CDCl_3$) ca 2.6-1.6 (5H, m), 1.94 (3H, s), 1.77 (3H, s), 1.19 (3H, d, J=7 Hz); mass spectrum m/e 138.104 (M^+, calc for $C_9H_{14}O$ 138.104).

Methyl 1, 2, 3-Trimethyl-4-oxocyclohex-2-enyl-1-carboxylate (89)

Calcium metal (155 mg, 3.88 mmol) was dissolved in ca 5 ml of liquid ammonia and stirred for 15 minutes. Then 360 mg (2.0 mmol) of lactone 33 in 4 ml of dry THF was added, and the solution was stirred for 25 minutes. The reaction was quenched with ammonium chloride. Water was added, followed by 10% sulfuric acid, and the mixture was extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed to give 335 mg (92%) of crude 88. The acid was treated with ethereal diazomethane to afford 355 mg (91% from the lactone) of crude ester 89. Preparative TLC (ether/hexane, 1:1) of a small portion gave pure 89: IR (film) 1730, 1670, 1250 cm^{-1}; NMR ($CDCl_3$) δ 3.73 (3H, s), 2.58-1.80 (4H, m), 1.88 (3H, s), 1.80 (3H, s), 1.44 (3H, s); mass spectrum m/e 196.111 (M^+, calc for $C_{11}H_{16}O_3$ 196.110).

2-Methyl-4-(2-methyl-2-heptenyl)tetronic Acid (90)

The tetronic acid 34 (129 mg, 1.1 mmol) in 2 ml of a 1:1 mixture of dry THF and dry HMPA was added to 54 mg (1.1 mmol) of sodium hydride (50% mineral oil dispersion, washed with dry pentane) in 1 ml of THF under nitrogen at room temperature. The solution was stirred for 1 h and 0.56 ml (1.1 mmol) of 2.0 M n-butyllithium was added dropwise. The solution stirred for 30 minutes, cooled to 0° C (ice bath), and 215 mg (1.13 mmol) of bromide 57 in 2 ml of dry THF was added. The solution was allowed to warm to room temperature and stirred for 3 h. Water (10 ml) and then 10% sulfuric acid were added, and the product extracted with ether (3 x 25 ml). The combined ethereal layers were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed. Column chromatography (ethyl acetate/hexane/acetic acid, 60:30:2) gave 151 mg (59%) of 90: IR ($CHCl_3$) 3100 (broad OH), 1735, 1705, 1660 cm^{-1}; NMR ($CDCl_3$) δ 7.50 (1H, bs, variable with temperature), 5.29 (1H, bt), 4.81 (1H, d, J=8 Hz, ABX), 2.68 (1H, d, J=16 Hz, ABX), 2.20 (1H, dd, J=8, 16 Hz, ABX), 2.0 (2H, m), 1.72 (3H, s), 1.57 (3H, s), 1.50-1.12 (4H, m), 0.88 (3H, m); mass spectrum m/e 224.140 (M^+, calc for $C_{13}H_{20}O_3$ 224.141).

2, 6-Dimethyl-4-hydroxy-3-oxo-2-(3-oxopentyl)undec-6-enoic Acid γ-Lactone (91)

The tetronic acid 90 (151 mg, 0.67 mmol) was heated at reflux for 4 h in dry THF containing 88 mg (1.0 mmol; 1.5 equivalents) of ethyl vinyl ketone and 5 drops of triethylamine (distilled from potassium hydroxide). The solution was cooled, water was added, and the product extracted with ether (3 x 25 ml). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to give 182 mg (87%) of 91: IR (film) 1795, 1750, 1710 cm^{-1}; NMR ($CDCl_3$) δ 5.30 (1H, bt), 5.10-4.80 (1H, m), 2.70-2.30 (6H, m), 2.2-1.9 (4H, m), 1.68 (3H, s), 1.48-1.20 (4H, m), 1.24 (3H, s), 1.02 (3H, t, J=7 Hz), 0.88 (3H, m); mass spectrum m/e 308.201 (M^+, calc for $C_{18}H_{28}O_4$ 308.199).

4, 8-Dimethyl-1, 5-dioxo-2-oxa-3-(2-methyl-2-heptenyl)bicyclo[4.3.0] non-4(9)-ene (92)

The adduct 91 (180 mg, 0.58 mmol) was refluxed in dry benzene containing 74 mg of p-toluenesulfonic acid for 48 h with water removal via a Dean-Stark trap. The solution was cooled, ether was added, and the mixture was washed with saturated aqueous sodium bicarbonate, brine, dried ($MgSO_4$), filtered and the solvent removed. Column chromatography followed by preparative TLC (ether/hexane, 60:40) gave 105 mg (61%) of 92; IR ($CHCl_3$) 1775, 1665 cm^{-1}; NMR ($CDCl_3$)

δ 5.34 (1H, bt), 5.22 (1H, t, J=7 Hz), 2.74-2.42 (4H, m), 2.26-1.90 (4H, m), 1.75 (6H, s), 1.58 (3H, s), 1.48-1.30 (4H, m), 0.90 (3H, m); mass spectrum m/e 290.188 (M^+, calc for $C_{18}H_{26}O_3$ 290.188).

Preparation of (93), (94) and (95)

To 67 mg (1.70 mmol) of calcium metal dissolved in ca 5 ml of liquid ammonia was added 115 mg (0.40 mmol) of the lactone (92) in 2 ml of dry THF. The solution was stirred for 20 minutes. The reaction was quenched with ammonium chloride, and the ammonia was allowed to evaporate. Water followed by 10% sulfuric acid, was added and the solution was extracted with ether (5 x 20 ml). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed. The residue was taken up in to 5 ml of ether and treated with an excess of ethereal diazomethane. The excess diazomethane was destroyed by the careful addition of acetic acid. Ether was added and the resulting solution was washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), filtered, and the solvent removed in vacuo to afford a mixture of 93, 94 and 95. These substances were separated by preparative TLC (ether/hexane, 70:30).

Compound 93: NMR ($CDCl_3$) δ 3.64 (s, ester CH_3), 1.85 (s, vinyl CH_3); mass spectrum m/e 306.221 (M^+, calc for

$C_{19}H_{30}O_3$ 306.219).

Compound 94: IR (film) 1725, 1710, 1250 cm^{-1}; NMR ($CDCl_3$) δ 3.70 (s, ester CH_3); mass spectrum m/e 306.219 (M^+, calc for $C_{19}H_{30}O_3$ 306.219).

Compound 95: IR (film) 3410, 1725, 1250 cm^{-1}; NMR ($CDCl_3$) δ 3.70 (s, ester (CH_3); mass spectrum m/e 308.234 (M^+, calc for $C_{19}H_{32}O_3$ 308.235).

3-Bromo-4,8-dimethyl-1,5-dioxo-2-oxabicyclo[4.3.0]non-4(9)-ene (97)

The keto-lactone 33, (360 mg, 2.0 mmol) was heated at reflux in 25 ml of dry carbon tetrachloride containing 360 mg (2.0 mmol) of N-bromosuccinimide (recrystallized and dried) (54) and a trace of benzoyl peroxide for 3 h. The solution was cooled, filtered, and the solvent removed *in vacuo* to give 516 mg (100%) of 97. Recrystallization from benzene/hexane afforded the crystalline 97: m.p. decomp 88-134° C; IR (Nujol) 1790, 1675 cm^{-1}; NMR ($CDCl_3$) δ 7.02 (1H, s), 2.74-2.60 (2H, m), 2.20-2.00 (2H, m), 1.83 (3H, s), 1.80 (3H, s); mass spectrum m/e 257.991 (M^+, calc for $C_{10}H_{11}O_3$ (79) Br 257.989).

Dimethyl 7,9-Dimethyl-3,6-dioxo-2-oxabicyclo-[4.3.0]non-7-enylphosphonate (99)

The bromo-lactone 97 (393 mg, 1.5 mmol) was heated with 3 ml of trimethylphosphite at 150° C (bath temperature) for 1 h. Excess

trimethylphosphite was removed in vacuo and the crude material was chromatographed, eluting with ethyl acetate, to give 140 mg (32%) of 99: IR (film) 1800, 1680, 1275, 1030 (broad) cm^{-1}; NMR ($CDCl_3$) δ 5.39 (1H, d, J=12 Hz), 3.97 (3H, d, J=12 Hz), 3.89 (3H, d, J=12 Hz), 2.87 (3H, d, J=4 Hz), 2.80-2.20 (2H, m), 2.20-2.00 (2H, m), 1.73 (3H, s); mass spectrum m/e 288.076 (M^+, calc for $C_{12}H_{17}O_6P$ 288.076).

trans-2-Methyl-2-hepten-1-al (100)

The alcohol 56 (245 mg, 1.9 mmol) in 1 ml dry methylene chloride was added in one portion to 3.3 g (12 mmol, 6.5 equivalents) of Collin's reagent (51) in 20 ml of dry methylene chloride. The solution was stirred for 15 minutes and then filtered over a Celite pad. The filtrate was diluted with ether and washed with saturated aqueous sodium bicarbonate (20 ml), 10% sulfuric acid (20 ml), and brine. The solution was dried ($MgSO_4$), filtered, and the solvent removed to give 216 mg (89%) of 100: NMR ($CDCl_3$) δ 9.43 (1H, s), 6.46 (1H, t), 1.81 (3H, s), 1.5-1.1 (4H, m), 0.93 (3H, m); mass spectrum m/e 126.105 (M^+, calc for $C_8H_{14}O$ 126.104).

4,8-Dimethyl-1,5-dioxo-3-pentylidenyl-2-oxabicyclo[4.3.0]non-4(9)-ene (102)

The phosphonate 99 (350 mg, 1.2 mmol) in 2 ml of dry THF was

added to 60 mg (1.2 mmol) of sodium hydride (50% mineral oil dispersion), and the resultant solution was stirred for 1 h at 0° C (ice-bath). Then 133 ul (1.2 mmol) of valeraldehyde was added and the solution was stirred at room temperature for 2 h. Water was added and the solution extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed. Chromatography (hexane/ethyl acetate, 2:1) afforded 33 mg (ca 10%) of slightly impure 102: IR ($CHCl_3$) 1790, 1660 cm^{-1}; NMR ($CDCl_3$) δ 5.45 (1H, t), 1.94 (3H, s), 1.48 (s, $-C-CH_3$), 0.92 (m, $-CH_2-CH_3$); mass spectrum m/e 248.141 (M^+, calc for $C_{15}H_{20}O_3$ 248.141).

4,8-Dimethyl-1,5-dioxo-3-hydroxy-2-oxabicyclo[4.3.0]non-4(9)-ene (103)

The bromo-lactone 97 (502 mg, 1.9 mmol), was heated to 100° C (bath temperature) in 10 ml of water for five minutes, during which the starting material dissolved and the solution became strongly acidic. The solution was cooled, diluted with 20 ml of water, and extracted with ether (5 x 20 ml). The combined ethereal extracts were washed with brine, dried ($Mg SO_4$), filtered and the solvent removed to give 331 mg (86%) of crude 103. Recrystallization from ethyl acetate/benzene/hexane gave colorless 103: mp decomp with gas evolution 146-178° C; IR (Nujol) 1740, 1670 cm^{-1}; NMR (acetone-d_6) δ 7.25 (1H, bs, exchanges upon addition of D_2O), 6.43 (1H, s),

1.78 (3H, s), 1.50 (3H, s); mass spectrum m/e 196.072 (M^+, calc for $C_{10}H_{12}O_4$ 196.074).

Methyl 1,3-Dimethyl-2-formyl-4-oxocyclohex-2-enyl-1-carboxylate (28)

The crude lactol 103, prepared from 258 mg (1 mmol) of 97, was treated with excess ethereal diazomethane in 8 ml of dry THF. The excess diazomethane was quenched with acetic acid. Water was added, followed by saturated aqueous sodium bicarbonate, and the solution was extracted with ether (4 x 20 ml). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed in vacuo. Crystallization from ether/pentane gave 118 mg (56%) of pure 28: mp 72-74° C (lit. (10) mp 80-81° C); IR ($CHCl_3$) 1735, 1675 cm^{-1}; NMR ($CDCl_3$) δ 10.32 (1H, s), 3.70 (3H, s), 2.76-1.76 (4H, m), 2.15 (3H, s), 1.52 (3H, s); mass spectrum m/e 210.091 (M^+, calc for $C_{11}H_{14}O_4$ 210.089).

Methyl (±)-(7E,9E)-Trisporate A (104)

To 254 mg (0.56 mmol) of phosphonium salt 58 in 5 ml of dry THF was added 234 µl (0.56 mmol) of 2.4 M n-butyllithium at room temperature. The resulting deep red solution was stirred for 20 minutes (10). The solution was cooled to -78° C (dry ice-acetone bath) and 118 mg (0.56 mmol) of 28 in 2 ml of dry THF was added

dropwise. The solution was stirred for 1 h, quenched with 5 ml of water, acidified (10 ml 10% sulfuric acid), and the product was extracted with ether (3 x 20 ml). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed. Preparative TLC (ether/pentane, 60:40) under nitrogen in the dark gave 50 mg (29%) of (±) methyl trisporate A (104): IR (film) 1723, 1659, 1595, 1245 cm^{-1}; NMR ($CDCl_3$) δ 6.37 (1H, d, J=16 Hz), 6.25 (1H, d, J=16 Hz), 5.64 (1H, bt), 3.70 (3H, s), 1.96 (3H, s), 1.80 (3H, s), 1.53 (3H, s), 0.91 (3H, m); UV $\lambda_{max}^{CH_3OH}$ 320 nm; mass spectrum m/e 304.205 (M^+, calc for $C_{19}H_{28}O_3$ 304.204).

Dimethyl trans-2-Methyl-2-heptenylphosphonate (105)

The crude bromide 57 (1.42 g, 7.50 mmol) and 1.00 g (8.06 mmol) of trimethylphosphite were heated together for 1 h at 130° C (bath temperature). The solution was cooled and then concentrated. Distillation gave 1.17 g (71%) of 105: bp 74° C (0.05 mm); IR (film) 1460, 1250 cm^{-1}; NMR ($CDCl_3$) δ 5.36 (1H, m), 3.75 (6H, d, J=12 Hz), 2.57 (2H, d, J=22 Hz), 2.20-1.84 (2H, m), 1.78 (3H, d, J=4 Hz), 1.50-1.30 (4H, m), 0.89 (3H, m); mass spectrum m/e 220.125 (M^+, calc for $C_{10}H_{21}O_3P$ 220.123).

(±)-(7E, 9E)-Trisporic Acid A (5)

To 906 mg (2.00 mmol) of the phosphonium salt 58 in 5 ml of dry THF was added 0.84 ml (2.0 mmol) of 2.4 M n-butyllithium at room temperature, and the resulting deep red solution was stirred for 20 minutes (10). The solution was cooled to -78° C (dry ice-acetone bath) and 196 mg (1.00 mmol) of lactol 103 in 2 ml of THF was added dropwise. The solution was stirred for 1 h, quenched with water (10 ml), acidified with 10% sulfuric acid (10 ml), and the product was extracted with ether (5 x 20 ml). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed. Preparative TLC (ethyl acetate/hexane/acetic acid, 50:50:2) under nitrogen in the dark gave 46 mg (16%) of (±) trisporic acid A (5): IR ($CHCl_3$) 2950 (broad OH), 1705, 1660, 1600, 1200 cm^{-1}; NMR ($CDCl_3$) δ 9.15 (1H, bs, variable with temperature), 6.46 (1H, d, J=16 Hz), 6.29 (1H, d, J=16 Hz), 5.67 (1H, bt), 1.96 (3H, s), 1.81 (3H, s), 1.52 (3H, s), 0.91 (3H, m); UV $\lambda_{max}^{CH_3OH}$ 322 nm; mass spectrum m/e 290.186 (M^+, calc for $C_{18}H_{26}O_3$ 290.188).

Methyl (±)-(7E, 9E)-Trisporate B (12)

To 1.24 g (2.0 mmol) of phosphonium salt 29 (10, 29) in 8 ml of dry THF was added 0.84 ml (2.0 mmol) of 2.4 M n-butyllithium at room temperature, and the resulting deep-red solution was stirred

for 20 minutes (10). The solution was cooled to -78° C (dry-ice acetone bath) and 196 mg (1.0 mmol) of lactol 103 in 2 ml of dry THF was added dropwise. The solution was stirred at -78° C for 1 h, quenched with water and acidified with 10% sulfuric acid (5 ml). The products were extracted with ether (5 x 20 ml). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed. The crude material thus obtained was stirred in 5 ml of THF and 4 ml of 5% sulfuric acid for 12 h, and the product extracted with ether (5 x 20 ml). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed. Attempted preparative TLC (hexane/ethyl acetate/acetic acid 60:60:3) under nitrogen in the dark afforded a mixture of 3 and 103.

Compound 3: UV $\lambda_{max}^{CH_3OH}$ 322 nm; mass spectrum m/e 304.167 (M^+, calc for $C_{18}H_{24}O_4$ 304.167).

Separation was accomplished by conversion to methyl esters 12 and 28, and subsequent preparative TLC (hexane/ethyl acetate 1:1) under nitrogen in the dark. This afforded 15 mg (5%) of 12: IR ($CHCl_3$) 1720, 1655 cm^{-1}; NMR ($CDCl_3$) δ 6.30 (2H, s), 5.56 (1H, m), 3.68 (3H, s), 2.16 (3H, s), 1.94 (3H, s), 1.82 (3H, s), 1.51 (3H, s); UV $\lambda_{max}^{CH_3OH}$ 322 nm (lit. (6) $\lambda_{max}^{CH_3OH}$ 322 nm) mass spectrum m/e 318.184 (M^+, calc for $C_{19}H_{26}O_4$ 318.183).

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