(q, 2 H, CH_2), 4.11 (s, 1 H, OH), 3.92 (t, 2 H, CH_2OH), 2.90 (t, 2 H, CH_2S) ppm.

Oxidation. This reaction was performed identically to the elimination except that the 60% hydroxide solution was replaced with 5% sodium hypochlorite.

Acknowledgment. We gratefully acknowledge the financial support of this research by the Army Research Office (DAAG29-82-K-0181).

Registry No. 1, 693-30-1; PEG, 25322-68-3; octyl bromide, 111-83-1; 2-(methylthio)ethyl chloride, 542-81-4; tergitol NP-13, 9016-45-9; potassium acetate, 127-08-2; thiodiglycol monoacetate, 2020-50-0; [(2-hydroxyethyl)thio]ethene, 3090-56-0; phenylacetonitrile, 140-29-4; 2-mercaptoethanol, 60-24-2; vinyl acetate, 108-05-4.

Stereoselective Synthesis of Trisporic Acids A and B, Their Methyl Esters, and Trisporols A and B, Hormones and Prohormones of Mucoraceous Fungi[1]

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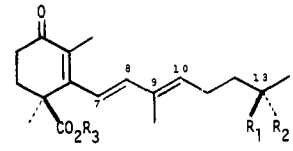
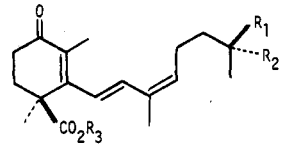
Syntheses of (9*E*)- and (9*Z*)-trisporic acids A (**1** and **4**) and B (**2** and **5**) and the corresponding methyl esters (**7**, **10**, **8**, and **11**, respectively) were accomplished via the Wittig reaction of lactol **52** with an appropriate phosphorane. The lactol was prepared by means of a Robinson annulation of α-methyltetronic acid with ethyl vinyl ketone to give **36**, followed by allylic bromination and hydrolysis. Methyl O^4,4-dihydrotrisporate B (**17**) was also synthesized by this route, confirming the structural and stereochemical assignment previously made to this prohormone of *Blakeslea trispora*. Trisporols A (**92**) and B (**13**) were obtained by a variant of this pathway, in which γ alkylation of the dianion **62** with the appropriate *Z* allylic bromide was followed by Robinson annulation with ethyl vinyl ketone. Bioassay of the synthesized hormones and prohormones with mating strains of *Mucor mucedo* showed that trisporic acids of the A series are inactive, whereas the B acids and their esters are active with both strains. Trisporols A and B and methyl O^4,4-dihydrotrisporate are strain-specific in their ability to induce zygophore formation.

Heterothallic fungi of the order Mucorales propagate through the union of sexually differentiated mating types.[2] The development of oppositely sexed ("plus" and "minus") mating strains as well as the mating process which leads to zygospore formation is mediated by a family of C_{18} isoprenoid substances consisting inter alia of (9*E*)-trisporic acids A (**1**), B (**2**), and C (**3**), their 9*Z* isomers **4**, **5**, and **6**, and the corresponding methyl esters **7**–**12**.[3] Extensive biological studies by van den Ende,[4] Sutter,[5] and Gooday[6] lend credence to the view that these carotenoid-derived substances both regulate the first stages of sexual development and stimulate the production of zygophores (sex cells) in organisms such as *Phycomyces blakesleeanus*, *Mucor mucedo*, and *Blakeslea trispora*. Further studies have demonstrated that certain prohormones or "pheromones", which are specific to each mating strain,[7] are transmitted to the sexual partner and converted to trisporic acids at the stage of zygophore induction.[8] These prohormones include trisporols B (**13**) and C (**14**),[9] trisporins B (**15**) and C (**16**),[10] and a substance tentatively



1, $R_1=R_2=R_3=H$
2, $R_1,R_2=O$, $R_3=H$
3, $R_1=OH$, $R_2=R_3=H$
7, $R_1=R_2=H$, $R_3=CH_3$
8, $R_1=R_2=O$, $R_3=CH_3$
9, $R_1=OH$, $R_2=H$, $R_3=CH_3$
54 $R_1,R_2=OCH_2CH_2O$, $R_3=H$
56 $R_1,R_2=OCH_2CH_2O$, $R_3=CH_3$



4, $R_1=R_2=R_3=H$
5, $R_1,R_2=O$, $R_3=H$
6, $R_1=R_3=H$, $R_2=OH$
10, $R_1=R_2=H$, $R_3=CH_3$
11, $R_1,R_2=O$, $R_3=CH_3$
12, $R_1=H,R_2=OH$, $R_3=CH_3$
55, $R_1,R_2=OCH_2CH_2O$, $R_3=H$
57, $R_1,R_2=OCH_2CH_2O$, $R_3=CH_3$

assigned structure **17**.[9,10] As an illustration of this cooperative behavior, it was shown that trisporins and trisporols, which are produced only by minus cultures of *B. trispora*, were converted by the oppositely sexed plus strain into **5** and **6**, whereas **17** from the plus type was trans-

(1) Abstracted from the Ph. D. Thesis of M. P. P., Oregon State University, 1977.
(2) Hesseltine, C. W.; Ellis, J. J. In "The Fungi"; Ainsworth, G. C., Sparrow, F. K., Sussman, A. S., Eds.; Academic Press: New York, 1971; pp 187–217.
(3) Bu'Lock, J. D.; Jones, B. E.; Winskill, N. *Pure Appl. Chem.* **1976**, *47*, 191.
(4) van den Ende, H. In "The Filamentous Fungi"; Smith, J. E.; Berry, D. R., Eds.; Wiley: New York, 1978; Vol. 3, p 257.
(5) (a) Sutter, R. P. In "Eucaryotic Microbes as Model Developmental Systems"; O'Day, D. H., Horgen, P. A., Eds.; Marcel Dekker: New York, 1977; p 251. (b) Sutter, R. P.; Whitaker, J. P. *Naturwissenschaften* **1981**, *68*, 147. (c) Sutter, R. P.; Whitaker, J. P. *J. Biol. Chem.* **1981**, *256*, 2334.
(6) Gooday, G. W. *Annu. Rev. Biochem.* **1974**, *43*, 35.
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(8) (a) Werkman, B. A.; van den Ende, H. *J. Gen. Microbiol.* **1974**, *82*, 273. (b) Sutter, R. P. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 127.
(9) Bu'Lock, J. D.; Jones, B. E.; Winskill, N. *J. Chem. Soc., Chem. Commun.* **1974**, 708.
(10) Nieuwenhuis, M.; van den Ende, H. *Arch. Microbiol.* **1975**, *102*, 167.

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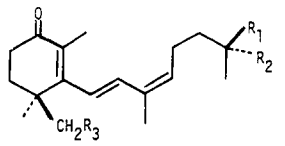
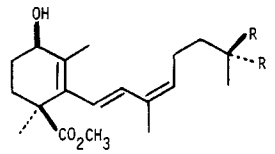


13, R_1,R_2=O, R_3=OH
14, R_1=H, R_2=R_3=OH
15, R_1,R_2=O, R_3=H
16, R_1=R_3=H, R_2=OH
92, R_1=R_2=H, R_3=OH



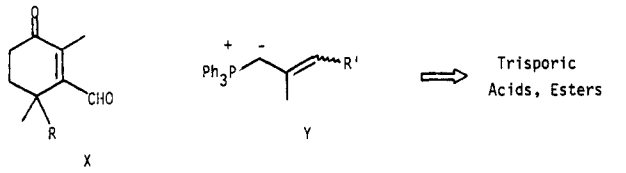
17, R,R=O
58, R,R=OCH_2CH_2O

formed into these same trisporic acids by minus cultures. The very small quantities of these hormones and prohormones available from natural sources make their acquisition through chemical synthesis imperative for physiological studies of the reproductive process in these Mucoraceous fungi. Further impetus for a stereoselective route to these metabolites came from the fact that the 9*E* and 9*Z* isomers are generally difficult to separate, with the consequence that the apparently different responses evoked by the natural materials remained clouded. Although routes to specific trisporic acid derivatives, notably methyl (7*E*,9*E*)-trisporate B (**8**), have been described previously,[11] no general stragegem embracing the entire set of structures in this family has been reported. Moreover, in view of the fact that the methyl trisporates undergo decomposition when saponification is attempted, it was obligatory to devise a route to the acids that avoided this feature. Herein, we describe stereoselective syntheses of (9*E*)- and (9*Z*)-trisporic acids and esters of the A and B series, the (9*Z*)-trisporols of the same series,[12] and methyl (9*Z*)-O^4,4-dihydrotrisporate B (**17**) by a route that confirms the structural assignment previously made to this prohormone.[13] We also report the results of bioassays with these synthetic (racemic) materials that clarify their role in zygophore induction with plus and minus strains of *Mucor mucedo*.

Results

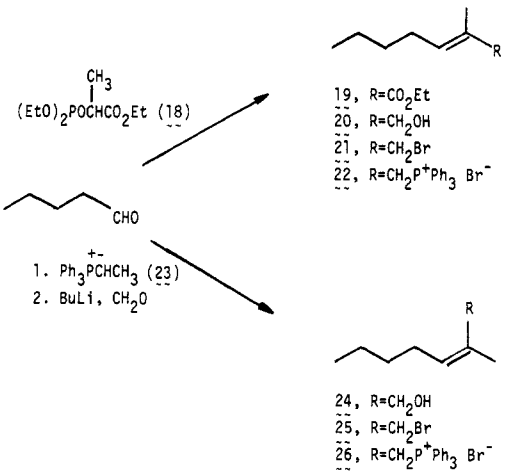
Wittig Route to Trisporic Acids and Esters. Our choice of a convergent approach to the trisporic acid system was influenced by the need to accommodate both *E* and *Z* configuration at the 9,10 double bond as well as the 13-keto function of the B series. A Wittig reaction of a cyclohexenone moiety with an appropriate side chain appeared to offer an attractive plan for linking two segments represented generically as X and Y.[11c] With this in prospect, the trisporic A and B acid side chains were prepared in the form of phosphonium salts in both *E* and *Z* configurations.

The *E* salt **22** required for **1** was synthesized by a Horner–Emmons reaction of *n*-valeraldehyde with phosphonate **18**, which gave geometrically pure **19** in 91% yield.



X Y

The ester was reduced to alcohol **20**, and the latter was brominated to **21** and then treated with triphenylphosphine to afford **22** in high overall yield.[14] Alterna-

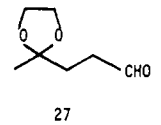


19, R=CO_2Et
20, R=CH_2OH
21, R=CH_2Br
22, R=$CH_2P^+Ph_3$ Br^-

24, R=CH_2OH
25, R=CH_2Br
26, R=$CH_2P^+Ph_3$ Br^-

tively, a Wittig reaction of *n*-valeraldehyde with ethylidenetriphenylphosphorane (**23**), followed by treatment of the intermediate oxidoylide with formaldehyde,[15] afforded (2*Z*)-2-methylheptenol (**24**), which was brominated at −30 °C with phosphorus tribromide and lithium bromide in the presence of collidine. These conditions gave **25** contaminated with a small amount of its double-bond isomer **21**, which was separated chromatographically. Conversion of **25** to the phosphonium salt **26** was readily accomplished in ether.

Synthesis of the *E* and *Z* side chain precursors in the B series began from ethyl levulinate, which was transformed to aldehyde **27** by ketalization, reduction with lithium aluminum hydride, and oxidation.[11a] A pair of reaction sequences parallel to those employed with valeraldehyde gave the *E* and *Z* alcohols **28** and **29**, from which the corresponding bromides **30** and **31** and phosphonium salts **32** and **33** were obtained.



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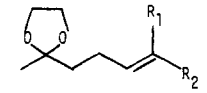


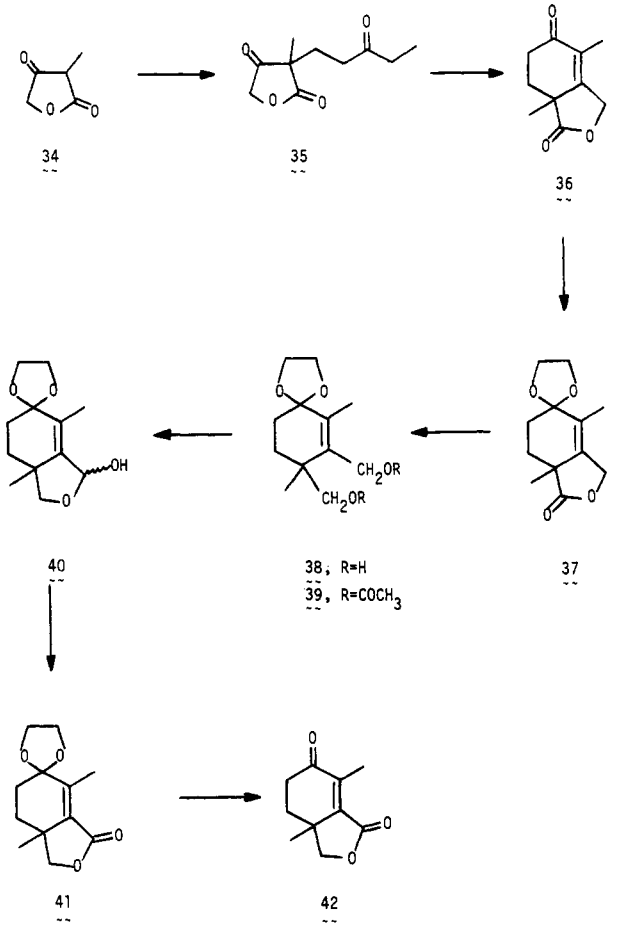
28, R_1=CH_3, R_2=CH_2OH
29, R_1=CH_2OH, R_3=CH_3
30, R_1=CH_3, R_2=CH_2Br
31, R_1=CH_2Br, R_2=CH_3
32, R_1=CH_3, R_2=$CH_2P^+Ph_3$ Br^-
33, R_1=$CH_2P^+Ph_3$ Br^-, R_2=CH_3

In devising a route to a cyclohexenone synthon for coupling with these preformed side chains, we sought a strategem that would accommodate not only the free trisporic acids and their methyl esters but also the reduced variants found in the trisporols as well. When an earlier approach from Hagemann's ester foundered on our inability to control the regioselectivity of alkylation reactions

(11) (a) Edwards, J. A.; Schwarz, V.; Fajkos, J.; Maddox, M. L.; Fried, J. H. *J. Chem. Soc. D* **1971**, 292. (b) Isoe, S.; Hayase, Y.; Sakan, T. *Tetrahedron Lett.* **1971**, 3691. (c) Secrist, J. A.; Hickey, C. H.; Norris, R. E. *J. Org. Chem.* **1977**, *42*, 525.
(12) Prisbylla, M. P.; Takabe, K.; White, J. D. *J. Am. Chem. Soc.* **1979**, *101*, 762.
(13) Takabe, K.; White, J. D. *Tetrahedron Lett.* **1983**, *24*, 3709.
(14) Polyachenko, L. N.; Davydova, L. P.; Mishchenko, V. V.; Samokhvalov, G. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1973**, *43*, 409.
(15) (a) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 226. (b) Bhalerao, U. T.; Rapoport, H. *Ibid.* **1971**, *93*, 4835.

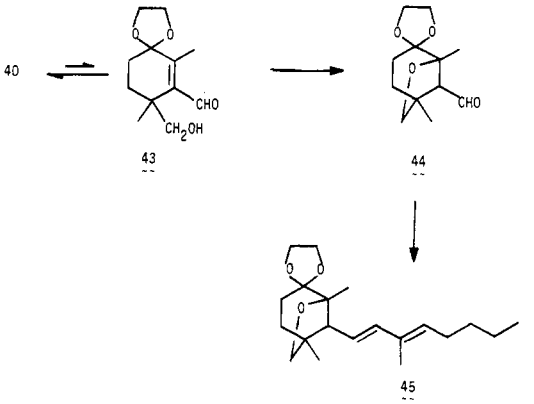
in this system,[16] we turned to an alternative scheme that eventually provided **52** as a compliant partner in Wittig reactions with **22**, **26**, **32**, and **33**.

The successful routes that have been forged to the methyl trisporates uniformly fabricate the cyclohexenone moiety through intramolecular aldol condensation of a 1,5-diketone.[11] This precedent prompted us to consider a variant beginning from α-methyltetronic acid (**34**), and, to this end, a highly expedient synthesis of **36** was explored through a Robinson annulation of **34** with ethyl vinyl ketone (EVK). In practice, the sequence was most conveniently effected in two steps: treatment of **34** with EVK in the presence of triethylamine afforded **35** (98%) and the latter, when exposed to *p*-toluenesulfonic acid in refluxing benzene, gave **36** (95%).

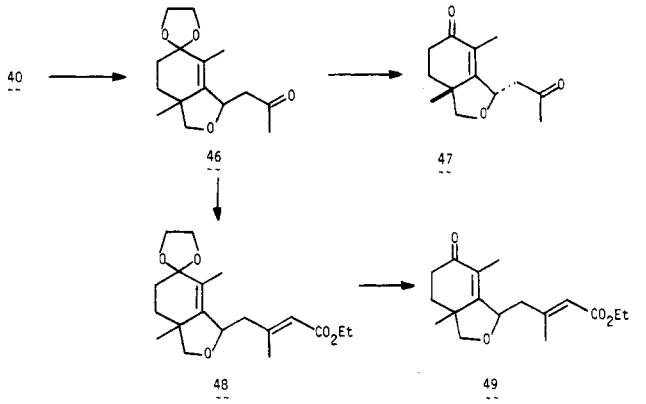


In order to modify **36**, and thereby permit attachment of the trisporate side chains, this γ-lactone was converted (quantitatively) to ketal **37** with ethylene glycol and triethyl orthoformate. The ketal was reduced to diol **38** (90%), which was characterized as its diacetate **39** (96%). Oxidation of **38** with manganese dioxide afforded the crystalline lactone **41** in 70% yield via the cyclic hemiacetal **40**, and the lactone was converted cleanly to **42** upon acidic hydrolysis. Although it was not possible to intercept **40** en route from **38** to **41**, the hemiacetal could be obtained in excellent yield by reduction of **41** with diisobutylaluminum hydride.

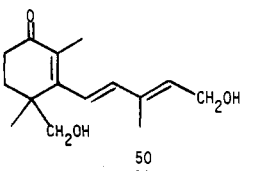
The hope that **40** would serve as a substrate in Wittig reactions with the phosphonium salts in hand was quickly dashed with the outcome of its condensation with **22**. Instead of the expected trisporol A derivative, a product which clearly lacked an alcohol function was obtained. After careful scrutiny of the ^{1}H NMR spectrum, it was deduced that this substance possessed structure **45**, a conclusion that can be reconciled with the assumption that **43** undergoes cyclization to **44** prior to the Wittig reaction.



In spite of the errant behavior of **40** with **22**, the hemiacetal underwent a smooth aldol condensation with acetone to give **46** (68%) as a mixture of two diastereomers. The latter was hydrolyzed in nearly quantitative yield to a single diketone **47**. The epimerization that accompanies



hydrolysis of **46** to give a stereochemically homogeneous product could proceed via reversible β-elimination or enolization of the cyclohexenone in **47**. Our failure to observe any trace of a dienone or alcohol function in the course of this process is tentative evidence for the latter pathway. On this basis, it was considered likely that enolate formation from **47** would preclude use of the methyl ketone as a locus for olefination, a surmise which proved correct when the anion of ethyl (diethylphosphono)acetate failed to react with this diketone. However, the same phosphonate did react with **46** to give **48**, which was hydrolyzed to keto ester **49** in low yield. The latter is of interest due to its similarity to trisporone (**50**), a metabolite of *B. trispora* that is thought to arise by biological degradation of **17**.[5b]



Although it was not possible to gain access to the trisporols via a Wittig reaction with **40**, the simplicity inherent in the preparation of **36** encouraged us to pursue an approach to the trisporic acids from this system. For this plan, an oxidation was required at the methylene carbon of the γ-lactone and, to our delight, treatment of **36** with *N*-bromosuccinimide gave the bromo lactone **51** as a

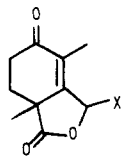
(16) White, J. D.; Sung, W. L. *J. Org. Chem.* **1974**, *39*, 2323.

Table I. Wittig Reactions of 52 with Phosphonium Ylides

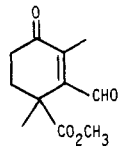
entry	phosphonium salt[a]	reactn temp, °C	reactn time, h	product(s) (ratio)	yield, %
1	22	−78	2.0	1	56
2	26	−78	2.0	4 + 1 (46:54)	69
3	26	0	0.5	4 + 1 (55:45)	58
4	32	−78	2.0	54	61
5	33	−78	1.0	55 + 54 (53:47)	53

[a] The ylide was generated from the phosphonium salt with *n*-BuLi at −35 °C for 22 and 32 and at −78 °C for 26 and 33.

crystalline mixture of cis/trans isomers in quantitative yield. Hydrolysis of 51 to 52 was accomplished with hot



51, X=Br
52, X=OH



53

water and, upon exposure of this crystalline lactol to ethereal diazomethane, 53 was formed in good overall yield. The latter corresponds to a substance prepared independently by Secrist et al. in the course of their synthesis of 8.[11c] With 52 and 53 in hand, it was a straightforward exercise to test their suitability as precursors to the trisporic acids and methyl esters, respectively. The Wittig reactions of 22, 26, 32, and 33 with 52 and 53 were explored in detail, and the results of this study are summarized in Table I.

It is apparent from a comparison of yields that the lactol 52 is a considerably better substrate in the Wittig reaction than the aldehyde 53. Thus, for synthesis of methyl (9*E*)-trisporates A (7) and B (8), it was more expedient to proceed through the corresponding acids 1 and 2 followed by treatment with ethereal diazomethane than directly from 53. However, in the Wittig reaction of 52 with the *Z* ylides from 26 and 33, a mixture of stereoisomers at the 9,10 double bond was produced, the ratio of which was influenced primarily by the duration of the reaction. Hence, by diminishing the reaction time it was possible to improve stereoselectivity at the expense of yield (10 min at 0 °C gave an 80:20 *Z*/*E* ratio). A similar observation was made in the Wittig reactions of 53, where variable amounts of isomerization at the trisubstituted double bond were noted with the *Z* ylides. In all cases, the olefination products from 52 and 53 were found to possess the expected *E* configuration at the 7,8 double bond.[17]

Completion of the syntheses of the B series required hydrolysis of the ethylene ketal in 54–56, and this was conveniently effected with dilute hydrochloric acid at 0 °C. The resulting trisporic acids and methyl esters were shown to be identical by comparison of ultraviolet, infrared, and nuclear magnetic resonance spectra with natural materials kindly furnished by Professor Richard P. Sutter. Analysis of the NMR spectra of the trisporic acids and their esters brought to light an informative relationship between the vinyl proton chemical shifts and the configuration of the 9,10 linkage in these structures. As seen from Table II, the C-7 and C-8 proton resonances in the *Z* series differ by as much as 0.5 ppm, with the latter shifted downfield, whereas in the *E* series these protons occupy a nearly equivalent magnetic environment. This

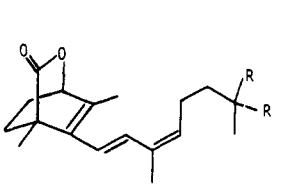
Table II. Vinyl Proton Resonances for (9*E*)- and (9*Z*)-Trisporic Acids and Related Compounds

compd	C-9,10 confign	chemical shift (ppm) H_7[a]	H_8[a]	H_{10}[b]
1	*E*	6.29	6.46	5.67
2	*E*	6.19	6.40	5.61
4	*Z*	6.33	6.84	5.53
5	*Z*	6.37	6.83	5.45
7	*E*	6.25	6.37	5.64
8	*E*	6.14	6.32	5.25
10	*Z*	6.32	6.76	5.48
11	*Z*	6.34	6.76	5.50
13	*Z*	6.20	6.68	5.42
17	*Z*	6.08	6.39	5.33
54	*E*	6.19	6.40	5.61
56	*E*	6.14	6.32	5.55
58	*Z*	6.08	6.39	5.33
92	*Z*	6.16	6.62	5.51

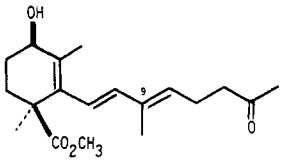
[a] These protons appear as doublets (J = 16.5 Hz). [b] These protons appear as triplets (J = 7 Hz).

diagnostic was employed to determine product ratios in Wittig reactions with 26 and 33.

With 57 in hand, it proved to be a simple matter to prepare 17. Thus, reduction of 57 with sodium borohydride afforded hydroxy ester 58 which, in contact with potassium *tert*-butoxide, underwent lactonization to 59.



59, R,R = OCH_2CH_2O
60, R,R = O



61

This result permits assignment of configuration to the reduction product as shown. Hydrolysis of 58 with 80% aqueous acetic acid yielded (±)-17 with spectral properties in agreement with those reported for the natural pheromone from the plus mating strain of *B. trispora*. An analogous reduction of 56 furnished the 9*E* isomer of 58, and subsequent hydrolysis gave 61, whose spectral properties clearly differed from those of the natural substance.

Tetronic Acid Dianion Route to Trisporols. The double-bond isomerization that accompanied the Wittig reaction of 52 with ylides from 26 and 33, together with the difficulty of separating pure trisporates of 9*Z* configuration, prompted a search for an alternative strategy for uniting the two components of these structures. Literature precedence for the γ-alkylation of β-keto ester dianions[18] suggested that a similar protocol might be applicable to a tetronic acid such as 34,[19] so that the species 62 would

62

permit attachment of the appropriate trisporate side chain prior to annulation of the cyclohexenone moiety. It was recognized, of course, that resonance in 62 includes a hybrid that embodies a furanoid nucleus, and that this contributor should reinforce electrophilic attack at the desired position.[20]

(17) Barlow, L.; Pattenden, G. *J. Chem. Soc., Perkin Trans 1* **1976**, 1029.

(18) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

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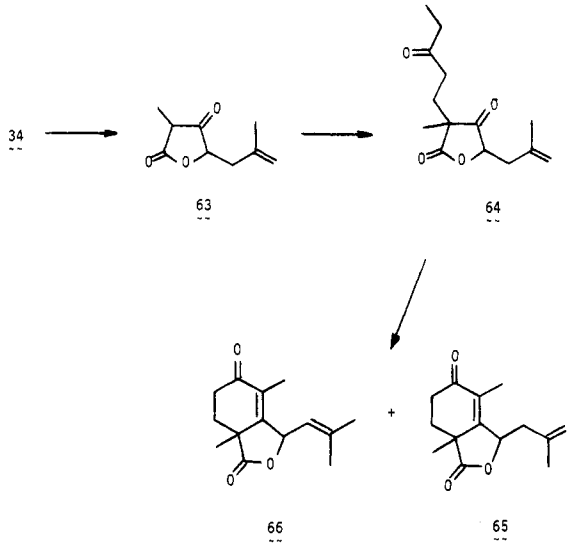
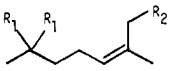
The dianion **62** was generated from **34** by treatment first with sodium hydride in THF–HMPA and then with *n*-butyllithium, and its reactivity was tested with methallyl bromide.[21] The γ-alkylated tetronic acid **63** was obtained



in 60% yield, and a subsequent Michael reaction with EVK furnished **64** as a pair of stereoisomers. Acid-catalyzed aldol condensation of this diketone afforded a 1:1 mixture of **65** and its isomer **66**, arising from migration of the terminal olefin to the more stable trisubstituted position, in 60% yield.

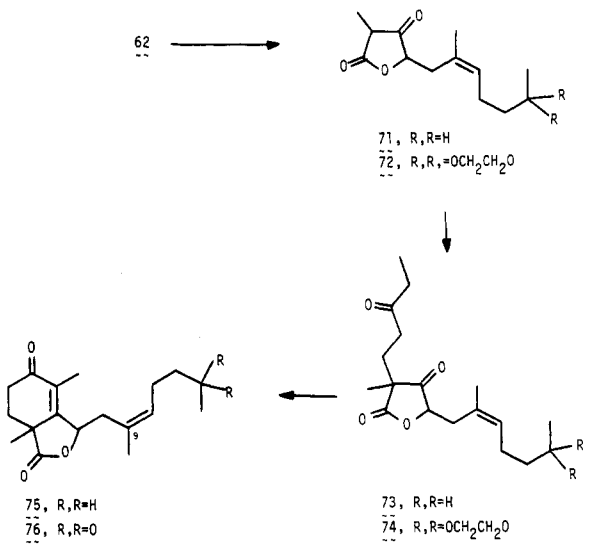
Extension of this model sequence to syntheses of (9*Z*)-trisporols A and B required geometrically pure allylic bromides **25** and **31**, for which the previous preparation from alcohols **24** and **29** was not satisfactory. Consequently, an indirect method, adapted from the procedure of Stork et al., was employed.[22] This entailed conversion of **24** and **29** to their respective *p*-toluenesulfonates **67** and **68** with methyllithium and *p*-toluenesulfonyl chloride,



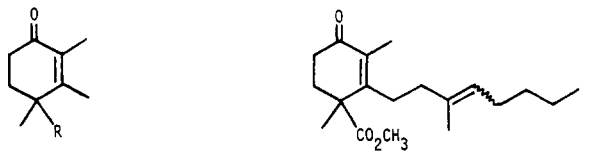
67, R_1,R_1=H, R_2=OTs
68, R_1,R_1=OCH_2CH_2O, R_2=OTs
69, R_1,R_1=H R_2=Cl
70, R_1, R_1=OCH_2CH_2O, R_2=Cl

followed by displacement with lithium chloride in DMF. The allylic chlorides **69** and **70** obtained by this means were stereochemically homogeneous and, upon exposure to lithium bromide in DMF, they gave **25** and **31** in high yield. Alkylation of **62** with these bromides afforded **71** and **72** in 65% and 63% yields, respectively. This convergent sequence was made even more concise when it was found that isolation of **71** and **72** was unnecessary, since the monoanion that remained after alkylation provided the locus for the subsequent Robinson annelation with EVK. This tandem sequence therefore *assembled the entire trisporic acid system in one pot.* For practical reasons, the final step involving cyclization of **73** and **74** was effected separately, since this reaction proceeded more cleanly under acid catalysis. In the case of **74**, condensation was accompanied by ketal hydrolysis to give **76**.

Unfortunately, although **75** and **76** can be regarded as progenitors of the corresponding trisporic acids, no means



could be found for effecting the conversion of these stable lactones to the trienone acids. Attempts to bring about elimination or, more plausibly, saponification followed by dehydration led to decomposition. As an alternative, a dissolving metal reduction of **75** and **76** was envisioned that would afford the 7,8-dihydrotrisporic acids, from which the natural substances might be available by dehydrogenation. The favorable prospects for this indirect approach were heightened by the finding that keto acid **77** was obtained



in 92% yield upon treatment of **36** with calcium in liquid ammonia. This acid was conveniently characterized as its methyl ester **78**, prepared with diazomethane. However, when a similar reduction of **75** or its 9*E* isomer (prepared from **21**) was attempted and the crude mixture esterified with diazomethane, **79** was obtained only in low yield and was accompanied by products (hydroxy esters) from over reduction.

Although these results appear to preclude access to trisporic acids from structures such as **75** and **76**, these compounds proved to be suitable intermediates for preparation of the trisporols. Thus ketalization of **75** and **76** with ethylene glycol in the presence of triethyl orthoformate gave **80** and the bis ketal **81**, respectively. Reduction of these lactones with lithium aluminum hydride furnished the diols **82** and **83** which, without purification, were hydrolyzed in aqueous acetic acid to give ketones **84** and **85** in 60% and 53% yields (from **75** and **76**, respecitively). Attempts to effect dehydration of the secondary alcohol in **84** and **85** were without success, and it was, therefore, necessary to devise a circuitous route to install the 7,8 unsaturation in these structures. Treatment of **84** and **85** with acetic anhydride in pyridine resulted in selective acetylation of the primary alcohol functions of these diols to produce **86** and **87**; subsequent exposure to methanesulfonyl chloride in pyridine then furnished **88** and **89** in good overall yield. Elimination of these mesylates took place upon warming to 80 °C in Me_2SO,[23] and

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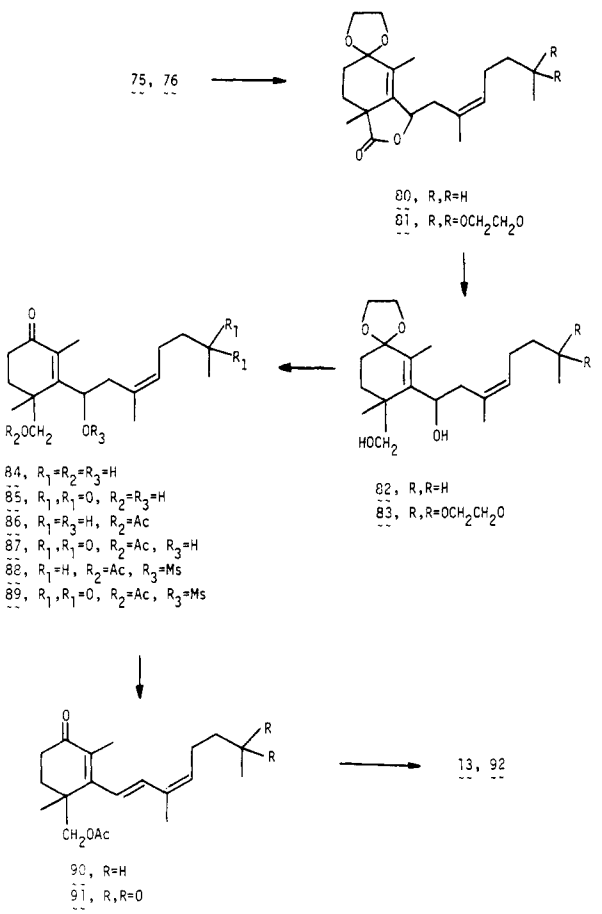

the resulting acetates **90** and **91** were finally saponified to give (9*Z*)-trisporol A (**92**) and the corresponding trisporol B (**13**). The spectral properties of the latter were in precise agreement with those reported by Bu'Lock et al.[9] and, upon oxidation with Jones' reagent, **13** gave (9*Z*)-trisporic acid B (**5**). Trisporol A appears not to have been isolated from nature as yet.

Bioassay of Synthetic Hormones and Prohormones. The biological activity of the synthesized hormones and prohormones was measured by observing zygophore induction separately in plus and minus strains of *M. mucedo*. Solutions of the synthetic substances in water were applied to an agar plate on which an inoculum of the plus or minus strain of *M. mucedo* had been incubated. After a further incubation period (7–16 h), the number of zygophores in the vicinity of the applied hormone was counted. In each case, control plates containing both plus and minus mating strains and the pure strain without hormone were run simultaneously. In general, zygophores induced by the synthetic materials were easily distinguished from zygophores produced during normal growth and from immature sporangiophores. The induced zygophores were larger, nonseptate, and nonbranching and were invariably localized in the area containing the hormone. Where ambiguity existed, a further incubation period caused maturation of the sporangiophores which then produced sporangia.

The data summarized in Table III lead to several conclusions. First, trisporic acid A of both 9*E* (**1**) and 9*Z* (**4**) configuration is inactive. Second, both configurational isomers of trisporic acid B (**2**, **5**) and both isomers of methyl trisporate B (**8**, **11**) are effective in promoting zygophores with both plus and minus mating strains. The plus strain appears to be more responsive to the B trisporic acids (**2** and **5**) than to their methyl esters (**8** and **11**), whereas the minus strain shows no obvious discrimination. Third, trisporols A (**92**) and B (**13**) are active only on the plus strain, the minus cultures of *M. mucedo* showing no response to these prohormones. Also, trisporol B possesses approximately twice the activity of its A congener. Finally, prohormone **17** was found to induce zygophores only in the minus type, the plus strain being completely unaffected by this compound.

Thus, a clear-cut mating strain specificity is exhibited in the biological activity of the synthesized prohormones. This is in accord with the reported properties of the natural substances.[9] No such strain specificity is observed with the synthetic trisporic acids or their methyl esters.

Table III. Induction of Zygophores in *Mucor mucedo* by Trisporic Acids, Their Methyl Esters, and Trisporols

compd	dose (μg)	average no. of zygophores[a] (+) strain	(−) strain
1	100	0	0
2	20	40.5	13.8
2	1	26.8	6.0
4	100	0	0
5	10	46.5	13.8
5	1	11.0	8.0
8	20	31.8	18.8
8	1	2.8	6.5
11	10	22.8	11.8
11	1	4.5	5.8
13	50	*b*	0
13	20	63.8	0
13	1	22.8	0
17	50	0	*b*
17	20	0	16.0
17	1	0	4.3
92	50	*b*	0
92	20	30.3	0
92	1	12.0	0

[a] Determined microscopically per unit area. [b] Not measured.

Experimental Section

Infrared spectra (IR) were obtained with a Perkin-Elmer Model 137 or 727B infrared spectrophotometer. Ultraviolet spectra (UV) were measured with a Cary Varian Model 15 spectrophotometer. Nuclear magnetic resonance spectra (NMR) were obtained with a Varian Model EM-360A, HA-100, or FT-80 spectrometer. Chemical shifts are reported in δ units with tetramethylsilane (Me_4Si) as the internal standard. Coupling constants (*J*) are given in hertz; s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet, etc. Mass spectra and exact mass determinations were obtained with a CEC-110 spectrometer, at an ionizing potential of 70 eV. Preparative and analytical thin-layer chromatography (TLC) was carried out with Brinkman or Analtech plates coated with silica gel GF-254. Column chromatography was performed with 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 sodium benzophenone ketyl. Hexamethylphosphoramide (HMPA) and dimethyl sulfoxide (Me_2SO) were dried by distillation from calcium hydride at reduced pressure. Other solvents were purified by using standard procedures. Organic extracts were dried over magnesium sulfate, unless otherwise noted. Elemental analyses were carried out by Dr. Susan Rottschaefer, Department of Chemistry, University of Oregon, and by Micro-Tech Laboratories, Inc., Skokie, IL.

Ethyl (*E*)-2-Methyl-2-heptenoate (19). Diethyl (1-carbethoxyethyl)phosphonate (**18**) (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) in 150 mL of dry THF, and the mixture was stirred at room temperature 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 × 100 mL). The combined ethereal layers were washed with brine, dried, and filtered. The solvent was removed in vacuo, and the residue was

distilled to give 13.21 g (91%) of **19**: bp 69–71 °C (3.0 mm); IR (film) 1720 cm^{-1}; NMR ($CDCl_3$) δ 6.79 (1 H, br t), 4.22 (2 H, q, J = 7 Hz), 2.20–2.07 (2 H, m), 1.86 (3 H, s), 1.60–1.20 (4 H, m), 1.30 (3 H, t, J = 7 Hz), 0.94 (3 H, m); mass spectrum, m/z 170.132 (M^+, calcd for $C_{10}H_{18}O_2$ 170.131).

(*E*)-2-Methyl-2-hepten-1-ol (20). A solution of **19** (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, and 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) and brine (50 mL) and dried. The solvent was removed in vacuo, and the residual oil was distilled to give 8.01 g (81%) of **20**: bp 40–42 °C (0.05 mm); IR (film) 3450 cm^{-1}; NMR ($CDCl_3$) δ 5.42 (1 H, br t), 4.02 (2 H, s), 2.12 (1 H, s, disappears upon addition of D_2O), 2.24–1.90 (2 H, m), 1.69 (3 H, s), 1.60–1.20 (4 H, m), 0.93 (3 H, m); mass spectrum, m/z 128.120 (M^+, calcd for $C_8H_{16}O$ 128.120).

(*E*)-1-Bromo-2-methyl-2-heptene (21). Freshly distilled phosphorus tribromide (0.25 mL, 2.6 mmol) was added to 1.00 g (7.80 mmol) of **20** 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), and the extract was, washed with brine, dried, and filtered. The solvent was removed to yield 1.43 g (95%) of virtually pure **21**: IR (film) 1660, 1450, 1200 cm^{-1}; NMR ($CDCl_3$) δ 5.67 (1 H, br t), 4.03 (2 H, s), 1.80 (3 H, s), 1.56–1.18 (4 H, m), 0.90 (3 H, m). This material was used without further purification.

((*E*)-2-Methyl-2-heptenyl)triphenylphosphonium Bromide (22). The bromide **21** (2.18 g, 11.45 mmol) was stirred in 50 mL of dry benzene containing 3.26 g (12.44 mmol) of freshly crystallized triphenylphosphine. The product was collected, recrystallized from acetone–ether, and vacuum-dried at 80 °C in the presence of phosphorus pentoxide to give 3.97 g (76%) of **22**: mp 164.5–167 °C, NMR ($CDCl_3$) δ 7.80 (15 H, br m), 5.36 (1 H, m), 4.65 (2 H, d, J = 14 Hz), 2.04–1.80 (2 H, m), 2.2–2.0 (4 H, m), 1.50 (3 H, br d), 0.82 (3 H, m). Anal. Calcd for $C_{26}H_{30}BrP$: C, 68.72; H, 6.61; Br, 17.62. Found: C, 69.04; H, 6.56; Br, 17.38.

(*Z*)-1-Bromo-2-methyl-2-heptene (25). To a solution of 737 mg (5.75 mmol) of **24**,[15b] 773 mg (8.63 mmol) of lithium bromide, and 1.06 g (8.63 mmol) of collidine in 30 mL of ether at −30 °C, was added 273 μL (2.89 mmol) of phosphorus tribromide in 1 mL of ether. The mixture was allowed to warm to room temperature and stirred for 10 h, after which it was poured into ice–water and extracted with ether (3 × 20 mL). The extract was washed with brine, dried, and filtered, and the filtrate was concentrated. The residual oil was chromatographed on silica gel and eluted with petroleum ether (30–60 °C) to give 769 mg (70%) of **25** as an oil: IR (film) 3030, 1660, 1205, 840 cm^{-1}; NMR (CCl_4) δ 5.33 (1 H, t, J = 7 Hz), 3.90 (2 H, s), 1.82 (3 H, s), 2.27–1.67 (2 H, m), 1.57–1.10 (4 H, m), 0.91 (3 H, t, J = 7 Hz); mass spectrum, m/z 178.034, 180.033 (calcd for $C_7H_{15}{}^{79}Br$ and $C_7H_{15}{}^{81}Br$ 178.035, 180.033).

((*Z*)-2-Methyl-2-heptenyl)triphenylphosphonium Bromide (26). A mixture of 229 mg (1.20 mmol) of **25** and 355 mg (1.35 mmol) of triphenylphosphine in 4 mL of ether was stirred under nitrogen for 72 h. The resulting precipitate was removed by filtration to give 382 mg of virtually pure **26**. A further 40 mg of **26** was obtained from the filtrate upon standing for 72 h, giving a total of 422 mg (78%) of **26** as an amorphous solid: IR (KBr) 3040, 1580, 1425, 1105 cm^{-1}; NMR (acetone-d_6) δ 8.24–7.76 (15 H, m), 5.53 (1 H, m), 4.81 (2 H, d, J = 16 Hz), 1.72 (3 H, d, J = 2 Hz), 1.53 (2 H, m), 1.30–0.98 (4 H, m), 0.74 (3 H, t, J = 7 Hz). This material was partially converted to **22** upon attempted crystallization.

(*E*)-1-Bromo-6,6-(ethylenedioxy)-2-methyl-2-heptene (30). To a solution of 523 mg (2.81 mmol) of **28**,[11c] 270 mg (3.09 mmol) of lithium bromide, and 337 mg (3.09 mmol) of collidine in 8 mL of ether at −30 °C was added a solution of 103 μL of freshly distilled phosphorus tribromide in 0.5 mL of ether. The mixture was allowed to warm to 0 °C, stirred for 15 min, and then poured into ice–water. The mixture was extracted with ether (3 × 20 mL), and the ethereal extract was washed with brine and dried. After filtration, the solution was concentrated, and the residual oil was placed on a column of silica gel. Elution with n-hexane–ethyl acetate (2:1) afforded 303 mg (43%) of pure **30**: IR (film) 1660, 1210, 1065 cm^{-1}; NMR (CCl_4) δ 5.67 (1 H, t, J = 7 Hz), 3.89 (2 H, s), 3.87 (4 H, s), 1.76 (3 H, br s), 1.23 (3 H, s). Anal. Calcd for $C_{10}H_{17}BrO_2$: C, 48.19; H, 6.83; Br, 32.13. Found: C, 47.84; H, 6.81; Br, 31.77.

[(*E*)-6,6-(Ethylenedioxy)-2-methyl-2-heptenyl]triphenylphosphonium Bromide (32). A solution of 303 mg (1.22 mmol) of **30** and 360 mg (1.36 mmol) of triphenylphosphine in 3.5 mL of ether was stirred at 30 °C for 88 h. The precipitate was filtered off and washed with ether to give 350 mg (56%) of **32** as an amorphous solid: IR (KBr) 2790, 1585, 1439, 1110, 1055 cm^{-1}; NMR (acetone-d_6) δ 8.22–7.50 (15 H, m), 5.55 (1 H, m), 4.82 (2 H, d, J = 15 Hz), 3.87 (4 H, s), 2.55 (3 H, m), 1.56 (3 H, br s), 1.20 (3 H, s). This substance was used promptly for subsequent Wittig reactions.

(*Z*)-6,6-(Ethylenedioxy)-2-methyl-2-heptenol (29). To a stirred solution of ethylidenetriphenylphosphorane, prepared from 3.60 g (9.68 mmol) of ethyltriphenylphosphonium bromide in THF at −78 °C and 4.41 mL of a 2.2 M hexane solution of n-butyllithium, was added 1.40 g (9.68 mmol) of **27**[11a] in 10 mL of THF. The mixture was stirred at −78 °C for 15 min, and a further 4.41 mL of 2.2 M n-butyllithium in hexane was added over 30 min. The resulting deep red solution was allowed to warm to −10 °C and 725 mg (22.9 mmol) of p-formaldehyde was added. This mixture was stirred at 0 °C for 2 h and at room temperature for 18 h and was then poured into ice–water and extracted with ether (3 × 30 mL). The ethereal extract was dried and concentrated to leave an oil which was chromatographed on silica gel. Elution with n-hexane–ethyl acetate (1:1) gave 1.14 g (63%) of **29**: IR (film) 3400, 1650, 1055, 1000, and 860 cm^{-1}; NMR (CCl_4) δ 5.28 (1 H, t, J = 7 Hz), 4.10 (2 H, s), 3.92 (4 H, s), 2.66 (1 H, s), 1.78 (3 H, s), 1.30 (3 H, s); mass spectrum, m/z 186. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.71; H, 9.60.

(*Z*)-1-Bromo-6,6-(ethylenedioxy)-2-methyl-2-heptene (31). To a solution of 587 mg (3.16 mmol) of **29**, 425 mg (4.74 mmol) of lithium bromide and 581 mg (4.74 mmol) of collidine in 11 mL of ether at −35 °C was added 150 μL (1.58 mmol) of phosphorus tribromide. The solution was allowed to warm to room temperature and was stirred for 1.5 h. The reaction mixture was poured into ice–water and extracted with ether (3 × 20 mL). The ethereal extract was dried and concentrated, and the residual oil was chromatographed on silica gel. Elution with n-hexane–ethyl acetate (3:1) yielded 340 mg (43%) of **31**: IR (film) 1660, 1205, 1055 cm^{-1}; NMR (CCl_4) δ 5.38 (1 H, t, J = 7 Hz), 3.93 (2 H, s), 3.88 (4 H, s), 1.83 (3 H, s), 1.26 (3 H, s); mass spectrum, m/z 248.250. Anal. Calcd for $C_{10}H_{17}BrO_2$: C, 48.19; H, 6.83; Br, 32.13. Found: C, 47.91; H, 6.94; Br, 31.84.

[(*Z*)-6,6-(Ethylenedioxy)-2-methyl-2-heptenyl]triphenylphosphonium Bromide (33). A solution of 68 mg (0.28 mmol) of **31** and 82 mg (0.31 mmol) of triphenylphosphine in 1.2 mL of ether was stirred at 30 °C for 65 h. The resulting precipitate was filtered off and washed with ether to furnish 117 mg (78%) of **33**: IR (KBr) 3030, 1580, 1430, 1105, 1050 cm^{-1}; NMR (acetone-d_6) δ 8.23–7.50 (15 H), 5.56 (1 H, m), 4.85 (2 H, d, J = 15 Hz), 3.84 (4 H, s), 1.74 (3 H, br s), 1.08 (3 H, s). This substance was used promptly for subsequent Wittig reactions.

4-Hydroxy-2-methyl-3-oxo-2-(3-oxopentyl)butanoic Acid γ-Lactone (35). To 14.00 g (123 mmol) of α-methyltetronic acid (**34**)[19] and 1.25 g (12.3 mmol) of triethylamine in 250 mL of THF was added 15.77 g (188 mmol) of ethyl vinyl ketone, and the yellow solution was refluxed for 6 h. The solvent was removed under reduced pressure, and the residue was taken up into ether and washed with brine. The ethereal layer was dried and filtered, and the solvent was 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 (2 H, s), 2.52 (2 H, t, J = 7 Hz), 2.44 (2 H, q, J = 7 Hz), 2.03 (2 H, t, J = 7 Hz), 1.31 (3 H, s), 1.01 (3 H, t, J = 7 Hz); mass spectrum, m/z 198.088 (M^+, calcd for $C_{10}H_{14}O_4$ 198.089).

4,8-Dimethyl-1,5-dioxo-2-oxabicyclo[4.3.0]non-4(9)-ene (36). A solution of 13.60 g (68.60 mmol) of **35** in 150 mL of benzene containing 736 mg of p-toluenesulfonic acid was refluxed for 36 h with water removal via a Dean–Stark trap. Ether was added to the cooled solution which was washed with saturated aqueous sodium bicarbonate and dried. The solvent was removed in vacuo to give 11.80 g (95%) of crystalline **36**. This material was chro-

matographed, with ether as eluent, to give an analytical sample of **36**: mp 58–60 °C; IR ($CHCl_3$) 1780, 1680 cm^{-1}; NMR ($CDCl_3$) δ 5.01 (2 H, m, J = 1 Hz), 2.72–2.52 (2 H, m), 2.23 (2 H, m), 1.74 (3 H, m, J = 1 Hz), 1.51 (3 H, s); mass spectrum, m/z 180.078 (M^+, calcd for $C_{10}H_{12}O_3$ 180.079). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.64; H, 6.64. Found: C, 66.58; H, 6.81.

4,8-Dimethyl-5,5-(ethylenedioxy)-1-oxo-2-oxabicyclo-[4.3.0]non-4(9)-ene (37). A solution of 5.04 g (28.0 mmol) of **36** in 100 mL of anhydrous ether containing 10 mL of triethyl orthoformate, 10 mL of ethylene glycol, and a crystal of *p*-toluenesulfonic acid was allowed to stand for 32 h. The solvent was removed under reduced pressure, and the residue was taken up into 300 mL of methylene chloride, which was washed with 50 mL of saturated aqueous sodium bicarbonate and 50 mL of brine and dried. Removal of the solvent afforded 6.26 g (100%) of crystalline **37**. Recrystallization of an analytical sample from carbon tetrachloride and then hexane gave **37**: mp 114–116 °C; IR ($CHCl_3$) 1780, 1150, 1090, 1070 cm^{-1}; NMR ($CDCl_3$) δ 4.85 (2 H, s), 4.06 (4 H, br s), 1.90 (4 H, br s), 1.70 (3 H, s), 1.35 (3 H, s); mass spectrum, m/z 224.105 (M^+, calcd for $C_{12}H_{16}O_4$ 224.105). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.26; H, 7.14. Found: C, 64.03; H, 6.97.

1,1-(Ethylenedioxy)-2,4-dimethyl-3,4-bis(hydroxymethyl)-2-cyclohexene (38). A solution of 3.20 g (14.3 mmol) of **37** in 50 mL of THF was added dropwise over 0.5 h to an ice-cold suspension of 562 mg (14.8 mmol) of lithium aluminum hydride in 50 mL of ether. The mixture was stirred for 0.5 h, and excess lithium aluminum hydride was destroyed by careful addition of water. The solution was filtered and dried, and the solvent was removed in vacuo to give 2.93 g (90%) of **38**: IR (film) 3500 (br), 1160, 1120, 1080 cm^{-1}; NMR ($CDCl_3$) δ 4.30 (2 H, s), 3.9–3.1 (6 H, m), 2.30 (1 H, s, disappears upon addition of D_2O), 1.66 (3 H, s), 0.87 (3 H, s); mass spectrum, m/z 228.136 (M^+, calcd for $C_{12}H_{20}O_4$ 228.136).

1,1-(Ethylenedioxy)-2,4-dimethyl-3,4-bis(acetoxymethyl)-2-cyclohexene (39). A solution of 750 mg (3.30 mmol) of **38** in 12 mL of ether was added to 0.93 mL (1.0 g, 3.0 equiv) of acetic anhydride and 0.85 mL (0.83 g, 3.2 equiv) of pyridine at 0 °C. The mixture was allowed to warm to room temperature and stirred for 32 h. Ether was added, and the solution was washed with saturated aqueous sodium bicarbonate and brine and dried. The solvent was removed in vacuo to afford 994 mg (96%) of **39**: IR (film) 1750, 1180, 1160, 1080 cm^{-1}; NMR ($CDCl_3$) δ 4.68 (2 H, s), 4.20–3.90 (6 H, m), 2.03 (6 H, s), 1.90–1.65 (7 H, m), 1.06 (3 H, s); mass spectrum, m/z 312.158 (M^+, calcd for $C_{16}H_{24}O_6$ 312.157).

4,8-Dimethyl-5,5-(ethylenedioxy)-3-oxo-2-oxabicyclo-[4.3.0]non-4(9)-ene (41). A mixture of 2.80 g (12.2 mmol) of **38** and 12 g of activated manganese dioxide in 40 mL of ether was stirred for 48 h. The solution was filtered through Celite and then treated with an additional 12 g of activated manganese dioxide for 4 days. The solution was again filtered through Celite, and the Celite was washed with 50 mL of ether and with 2 × 25 mL of methanol. Removal of the solvents gave 1.92 g (70%) of **41** which crystallized on standing: mp 76–77 °C; IR (film) 1760, 1680, 1170, 1142 cm^{-1}; NMR ($CDCl_3$) δ 4.20 (5 H, m), 2.05 (3 H, s), 2.0–1.65 (4 H, m), 1.25 (3 H, s); mass spectrum, m/z 224.106 (M^+, calcd for $C_{12}H_{16}O_4$ 224.105).

4,8-Dimethyl-3,5-dioxo-2-oxabicyclo[4.3.0]non-4(9)-ene (42). A mixture of 201 mg (0.805 mmol) of **41** in 5 mL of 20% aqueous dioxane containing 19 mg of *p*-toluenesulfonic acid was stirred for 43 h. Ether was added, and the solution was washed with 10 mL of saturated aqueous sodium bicarbonate and brine (25 mL) and dried. The solvent was removed, and the residue was chromatographed on silica. Elution with ether gave 135 mg (84%) of **42**: mp 56–58 °C; IR ($CHCl_3$) 1760, 1680, 1210 cm^{-1}; NMR ($CDCl_3$) δ 4.26 (1 H, d, J = 8 Hz), 4.01 (1 H, d, J = 8 Hz), 2.66 (2 H, m), 2.14 (3 H, s), 2.10 (2 H, m), 1.42 (3 H, s); mass spectrum, m/z 180.081 (M^+, calcd for $C_{10}H_{12}O_3$ 180.179). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.64; H, 6.64. Found: C, 66.85; H, 6.76.

4,8-Dimethyl-5,5-(ethylenedioxy)-3-hydroxy-2-oxabicyclo[4.3.0]non-4(9)-ene (40). To 153 mg (0.681 mmol) of **41** in 4 mL of toluene at −78 °C was added in one portion of 0.60 mL (0.68 mmol) of diisobutylaluminum hydride (20% by weight in hexane). The solution was stirred for 15 min at −78 °C, and 0.5 mL of water was added. The mixture was extracted with ether (4 × 25 mL), the ethereal extract was dried, and the solvent was removed under reduced pressure to give 138 mg (89%) of **40** as a pair of cis/trans stereoisomers: IR (film) 3500, 1160, 1125, 1080 cm^{-1}; NMR ($CDCl_3$) δ 5.80 (1 H, m), 4.20–3.80 (6 H, m), 3.42 (1 H, d, J = 8 Hz), 2.00–1.80 (2 H, m), 1.78 (3 H, s, isomer A), 1.70 (3 H, s, isomer B), 1.75–1.50 (2 H, m), 1.48 (3 H, s, isomer A), 1.17 (3 H, s, isomer B); mass spectrum, m/z 226.120 (M^+, calcd for $C_{12}H_{18}O_4$ 226.121).

Wittig Reaction of 22 with 40. A suspension of 102 mg (2.13 mmol) of sodium hydride (50% mineral oil dispersion) in 5 mL of Me_2SO was heated at 65 °C for 1 h. The solution was cooled to 0 °C, and 913 mg (2.13 mmol) of **22** in 2 mL of Me_2SO was added dropwise. After 15 min, 138 mg (0.610 mmol) of **40** in 3 mL of THF was added, and the solution was stirred for 60 h. Water was added, and the mixture was extracted with pentane. The extract was washed with brine and dried, and the solvent was removed in vacuo. Preparative TLC of the residual oil with ether/hexane (3:1) as eluent gave 80 mg (40%) of **45**: IR (film) 2980, 1140, 1080 cm^{-1}; NMR ($CDCl_3$) δ 6.14 (1 H, d, J = 16 Hz), 5.33 (1 H, m), 5.30 (1 H, dd, J = 8, 16 Hz), 4.20–3.80 (6 H, m), 3.77 (2 H, s), 1.80 (3 H, s), 1.27 (3 H, s), 1.06 (3 H, s), 0.88 (3 H, t, J = 7 Hz); mass spectrum, m/z 320.237 (M^+, calcd 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 (46). The hemiacetal **40** (479 mg, 2.10 mmol) was added in one portion to a solution of 266 mg (6.65 mmol) of sodium hydroxide in 3 mL of ethanol, 2 mL of acetone, and 2 mL of water. The solution was stirred at room temperature for 64 h, and saturated aqueous ammonium chloride was added. The mixture was extracted with ether, the combined ethereal extract was dried, and the solvent was removed in vacuo. Distillation of the residual oil gave 380 mg (68%) of **46** as a mixture of two stereoisomers: bp 75 °C (0.07 mm); IR (film) 1725, 1080, 1040 cm^{-1}; NMR ($CDCl_3$) δ 4.80 (1 H, m, isomers A and B), 4.18–3.96 (4 H, m), 3.80 (1 H, d, J = 8 Hz), 3.32 (1 H, d, J = 8 Hz), 2.75 (2 H, d, J = 7 Hz, isomer A), 2.70 (2 H, d, J = 7 Hz, isomer B), 2.05–1.82 (2 H, m), 1.74–1.50 (2 H, m), 1.56 (3 H, s, isomer A), 1.24 (3 H, s, isomer B), 1.26 (6 H, s, isomers A and B); mass spectrum, m/z 266.151 (M^+, calcd for $C_{15}H_{22}O_4$ 266.152).

***trans*-3-Acetonyl-4,8-dimethyl-5-oxo-2-oxabicyclo[4.3.0]-non-4(9)-ene (47).** A solution of 80 mg (0.30 mmol) of **46** in 5 mL of 20% aqueous dioxane containing a crystal of *p*-toluenesulfonic acid was stirred for 4 h. Ether was added, and the aqueous layer was removed. The ethereal solution was washed with saturated aqueous sodium bicarbonate and dried. The solvent was removed in vacuo to give 63 mg (94%) of **47**: IR ($CHCl_3$) 1720, 1675 cm^{-1}; NMR ($CDCl_3$) δ 5.10 (1 H, t, J = 6 Hz), 3.92 (1 H, d, J = 8 Hz), 3.46 (1 H, d, J = 8 Hz), 2.83 (2 H, d, J = 6 Hz), 2.62–2.46 (2 H, m), 2.28 (3 H, s), 1.93–1.80 (2 H, m), 1.69 (3 H, s), 1.38 (3 H, s); mass spectrum, m/z 222.124 (M^+, calcd 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 (49). To a solution containing 1 equiv (0.68 mmol) of the anion of diethyl (1-carbethoxyethyl)-phosphonate, prepared from 33 mg (0.68 mmol) of sodium hydride (50% mineral oil dispersion) and 153 mg (0.68 mmol) of diethyl (1-carbethoxyethyl)phosphonate **18** in THF, was added 181 mg (0.68 mmol) of **46**. After mixture was stirred at room temperature for 1 h, water was added, and the solution was extracted with ether. The ethereal extract was washed with brine and dried, and the solvent was removed in vacuo. The material (**48**) thus obtained was taken up in 5 mL of 25% aqueous dioxane containing a trace of *p*-toluenesulfonic acid, and the mixture was stirred overnight. Ether was added, and the resulting solution was washed with saturated aqueous sodium bicarbonate and dried. The solvent was removed, and the residual oil was subjected to preparative TLC, using ether as eluent, to afford 22 mg (10%) of **49**: NMR ($CDCl_3$) δ 5.84 (1 H, s), 4.76 (1 H, br d), 4.14 (2 H, q, J = 7 Hz), 3.92 (1 H, d, J = 8 Hz), 3.46 (1 H, d, J = 8 Hz), 2.80–2.40 (4 H, m), 2.28 (3 H, s), 2.0–1.8 (2 H, m), 1.72 (3 H, s), 1.35 (3 H, s), 1.26 (3 H, t, J = 7 Hz); mass spectrum, m/z 292.166 (M^+, calcd for $C_{17}H_{24}O_4$ 292.167).

3-Bromo-4,8-dimethyl-1,5-dioxo-2-oxabicyclo[4.3.0]non-4-(9)-ene (51). A mixture of 360 mg (2.0 mmol) of **36**, 356 mg (2.0 mmol) of *N*-bromosuccinimide, and a trace of benzoyl peroxide in 25 mL of carbon tetrachloride was refluxed for 3 h. The cooled

solution was filtered, and the solvent was removed in vacuo. Recrystallization of the residue from benzene–hexane afforded 516 mg (100%) of **51**: mp 88–134 °C dec; IR (Nujol) 1790, 1675 cm^{-1}; NMR ($CDCl_3$) δ 7.02 (1 H, s), 2.74–2.60 (2 H, m), 2.20–2.00 (2 H, m), 1.83 (3 H, s), 1.80 (3 H, s); mass spectrum, *m/z* 257.991 (M^+, calcd for $C_{10}H_{11}O_3{}^{79}Br$ 257.989).

4,8-Dimethyl-1,5-dioxo-3-hydroxy-2-oxabicyclo[4.3.0]non-4(9)-ene (52). A suspension of 502 mg (1.9 mmol) of **41** in 10 mL of water was heated at 100 °C for 5 min, during which the starting material dissolved and the solution became strongly acidic. The cooled solution was diluted with 20 mL of water and extracted with ether (5 × 20 mL). The combined ethereal extracts were washed with brine and dried. The solvent was removed, and the residue was recrystallized from ethyl acetate–benzene–hexane to give 331 mg (89%) of **52**: mp 146–178 °C, dec with gas evolution; IR (Nujol) 1740, 1670 cm^{-1}; NMR (acetone-d_6) δ 7.25 (1 H, br s, disappears upon addition of D_2O), 6.43 (1 H, s), 1.78 (3 H, s), 1.50 (3 H, s). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.46; H, 6.33.

Addition of excess ethereal diazomethane to 197 mg (1.0 mmol) of **52** in 8 mL of THF, followed by a quench with acetic acid, filtration, and removal of solvent, gave a solid which was crystallized from ether–pentane to provide 118 mg (56%) of **53**: mp 72–74 °C (lit.[11c] mp 80–81 °C).

Methyl (7*E*,9*E*)-Trisporate A (7). To 93.7 mg (0.207 mmol) of **22** in 1.4 mL of THF at 0 °C was added 93 μL (0.207 mmol) of 2.2 M *n*-butyllithium in hexane, and the resulting deep red solution was stirred for 10 min. The solution was cooled to −78 °C, and 21.3 mg (0.108 mmol) of **52** in 0.6 mL of THF was added. The mixture was allowed to warm to 0 °C, stirred for 40 min, and then quenched with water, followed by 2.5% sulfuric acid. The solution was extracted with ether (3 × 15 mL), and the ethereal extract was washed with brine and dried. This solution was concentrated, and an excess of ethereal diazomethane was added. After 2 h, glacial acetic acid was added, followed by saturated, aqueous sodium bicarbonate, and the ethereal layer was separated and dried. The solvent was removed, and the residual oil was subjected to preparative TLC (ether–pentane, 60:40) under nitrogen in the dark to give 22.1 mg (67%) of **7**: IR (film) 1723, 1659, 1595, 1245 cm^{-1}; NMR ($CDCl_3$) δ 6.37 (1 H, d, *J* = 16 Hz), 6.25 (1 H, d, *J* = 16 Hz), 5.64 (1 H, br t), 3.70 (3 H, s), 1.96 (3 H, s), 1.80 (3 H, s), 1.53 (3 H, s), 0.91 (3 H, m); UV $\lambda_{max}{}^{MeOH}$ 320 nm; mass spectrum, *m/z* 304.205 (M^+, calcd for $C_{19}H_{28}O_3$ 304.204).

(7*E*,9*E*)-Trisporic Acid A (1). To 96.3 mg (0.21 mmol) of **22** in 1.4 mL of THF at −35 °C was added 96.5 μL (0.21 mmol) of 2.2 M *n*-butyllithium in hexane, and the resulting deep red solution was stirred for 15 min. The solution was cooled to −78 °C, and 20.8 mg (0.105 mmol) of **52** in 0.4 mL of THF containing 0.14 mL of HMPA was added. The solution was stirred for 2 h and then allowed to warm to 0 °C. The mixture was quenched with water (0.5 mL) and acidified with 2.5% sulfuric acid. The mixture was extracted with ether (3 × 15 mL), and the extract was washed with brine and dried. The solvent was removed, and the residue was subjected to preparative TLC (ethyl acetate–hexane–acetic acid, 50:50:2) under nitrogen in the dark to give 17.0 mg (56%) of **1**: IR ($CHCl_3$) 2950 (br), 1705, 1660, 1600, 1200 cm^{-1}; NMR ($CDCl_3$) δ 9.15 (1 H, br s, variable with temperature), 6.46 (1 H, d, *J* = 16 Hz), 6.29 (1 H, d, *J* = 16 Hz), 5.67 (1 H, br t), 1.96 (3 H, s), 1.81 (3 H, s), 1.52 (3 H, s), 0.91 (3 H, m); UV $\lambda_{max}{}^{MeOH}$ 322 nm; mass spectrum, *m/z* 290.186 (M^+, calcd for $C_{18}H_{26}O_3$ 290.188).

Methyl (7*E*,9*E*)-Trisporate B (8). To 103 mg (0.201 mmol) of **32** in 1.5 mL of THF at 0 °C was added 91 μL (0.201 mmol) of 2.2 M *n*-butyllithium in hexane, and the mixture was stirred for 10 min. The deep red solution was cooled to −78 °C, and 21.5 mg (0.109 mmol) of **52** in 0.56 mL of THF was added. The mixture was allowed to warm to 0 °C and stirred for 40 min and was then quenched with water and acidified with 2.5% sulfuric acid. The mixture was extracted with ether, and the extract was dried and concentrated and was treated with an excess of ethereal diazomethane. After decomposition of the excess diazomethane with acetic acid, the ethereal solution was washed with saturated, aqueous sodium bicarbonate and dried. Removal of the solvent in vacuo followed by preparative TLC of the residual oil (elution with hexane–ethyl acetate, 1:1) gave 27.0 mg (68%) of **56**: IR (film), 1730, 1680, 1595, and 965 cm^{-1}; NMR (CCl_4) δ 6.32 (1 H, d, *J* = 16 Hz), 6.14 (1 H, d, *J* = 16 Hz), 5.55 (1 H, t, *J* = 7 Hz), 3.88 (4 H, s), 3.65 (3 H, s), 1.90 (3 H, s), 1.82 (3 H, s), 1.49 (3 H, s), 1.26 (3 H, s).

A solution of this material is 2.5 mL of THF and 2.4 mL of 5% hydrochloric acid was stirred at 0 °C for 5 h. The solution was extracted with ether, and the extract was washed with saturated, aqueous sodium bicarbonate and dried. Removal of the solvent in vacuo and preparative TLC of the residue (elution with hexane–ethyl acetate, 1:1) under nitrogen in the dark furnished 21.2 mg (93%) of **8**: IR ($CHCl_3$) 1720 (br), 1655 cm^{-1}; NMR ($CDCl_3$) δ 6.30 (2 H, s), 5.56 (1 H, m), 3.68 (3 H, s), 2.16 (3 H, s), 1.94 (3 H, s), 1.82 (3 H, s), 1.51 (3 H, s); UV $\lambda_{max}{}^{CH_3OH}$ 322 nm (lit.[11a] 322 nm); mass spectrum, *m/z* 318.184 (M^+, calcd for $C_{19}H_{26}O_4$ 318.183).

(7*E*,9*E*)-Trisporic Acid B (2). To 98.1 mg (0.192 mmol) of **32** in 1.4 mL of THF at −35 °C was added 87 μL (0.192 mmol) of 2.2 M *n*-butyllithium in hexane, and the mixture was stirred for 10 min. The deep red solution was cooled to −78 °C, and 20.2 mg (0.102 mmol) of **52** in 0.42 mL of THF containing 0.14 mL of HMPA was added. The mixture was stirred for 2 h, was allowed to warm to 0 °C, and was stirred for an additional 0.5 h before quenching with 0.5 mL of water. After acidification with 2.5% sulfuric acid, the mixture was extracted with ether (3 × 10 mL), and the extract was washed with brine and dried. The ether was removed, and the residue was purified by preparative TLC (ethyl acetate–hexane–acetic acid, 60:40:2) to give 21.7 mg (61%) of **54**: IR (film) 3150, 1730, 1660, 1590, 960 cm^{-1}; NMR (CCl_4) δ 10.32 (1 H, br s), 6.40 (1 H, d, *J* = 16 Hz), 6.19 (1 H, d, *J* = 16 Hz), 5.61 (1 H, t, *J* = 7 Hz), 3.91 (4 H, s), 1.91 (3 H, s), 1.82 (3 H, s), 1.49 (3 H, s), 1.26 (3 H, s).

A solution of 17.2 mg (4.94 mmol) of **54** in 2 mL of THF and 2.0 mL of 5% hydrochloric acid was stirred at 0 °C for 5 h under nitrogen in the dark. To this mixture was added 20 mL of brine, and the solution was extracted with ether (3 × 15 mL). The ethereal extract was washed with brine and dried, and the ether was removed to afford 14.3 mg (95%) of **2**: IR (film) 3150, 1725, 1660, 1595, 965 cm^{-1}; NMR (CCl_4) δ 6.39 (1 H, d, *J* = 16 Hz), 6.19 (1 H, d, *J* = 16 Hz), 5.52 (1 H, br t, *J* = 7 Hz), 2.09 (3 H, s), 1.89 (3 H, s), 1.82 (3 H, s), 1.48 (3 H, s); mass spectrum, *m/z* 304.167 (M^+, calcd for $C_{18}H_{24}O_4$ 304.167).

(7*E*,9*Z*)-Trisporic Acid A (4). To 93.1 mg (0.205 mmol) of **26** in 1.4 mL of THF at −78 °C was added 93.3 μL (0.205 mmol) of 2.2 M *n*-butyllithium in hexane, and the mixture was stirred for 1 h. To this deep red solution was added 20.1 mg (0.102 mmol) of **52** in 0.42 mL of THF containing 0.14 mL of HMPA. The mixture was stirred for 2 h, allowed to warm slowly to 0 °C, and quenched with 10 mL of water. Extraction with ether, followed by drying and removal of the solvent, gave 14.4 mg (49%) of a 46:54 mixture of **4** and **1**. Preparative TLC (ethyl acetate–hexane–acetic acid, 50:50:2) gave pure **4**: IR (film) 3200, 1720, 1700, 1595, 965 cm^{-1}; NMR (CCl_4) δ 6.84 (1 H, d, *J* = 16 Hz), 6.33 (1 H, d, *J* = 16 Hz), 5.53 (1 H, t, *J* = 7 Hz), 1.94 (3 H, s), 1.88 (3 H, s), 1.53 (3 H, s); mass spectrum, *m/z* 290.189 (M^+, calcd for $C_{18}H_{26}O_3$ 290.188).

Methyl (7*E*,9*Z*)-Trisporate A (10). To 93.3 mg (0.206 mmol) of **26** was added 93.6 μL (0.206 mmol) of 2.2 M *n*-butyllithium in hexane, and the mixture was stirred for 15 min. The deep red solution was cooled to −78 °C, and 21.5 mg (0.109 mmol) of **52** in 0.42 mL of THF containing 0.14 mL of HMPA was added. The mixture was allowed to warm to 0 °C and stirred for 25 min. Extraction with ether, followed by washing of the extract with brine, drying, and removal of the solvent, gave a residue which was taken up into 2.5 mL of ether and treated with ethereal diazomethane at 0 °C. After decomposition of the excess diazomethane with acetic acid, filtration, and removal of solvents, 19.4 mg (58%) of a 55:45 mixture of **10** and **7** was obtained. Pure **10** was isolated by preparative TLC (ethyl acetate–hexane, 1:2): IR (film) 1730, 1665, 1595, 965 cm^{-1}; NMR (CCl_4) δ 6.76 (1 H, d, J = 16 Hz), 6.32 (1 H, d, *J* = 16 Hz), 5.48 (1 H, m), 3.65 (3 H, s), 1.93 (3 H, s), 1.89 (3 H, s), 1.53 (3 H, s), 0.94 (3 H, t, *J* = 7 Hz); mass spectrum, *m/z* 304.204 (M^+, calcd for $C_{19}H_{28}O_3$ 304.204).

(7*E*,9*Z*)-Trisporic Acid B (5). To 106 mg (0.21 mmol) of **33** in 1.4 mL of THF at −78 °C was added 94 μL (0.21 mmol) of 2.2 M *n*-butyllithium in hexane, and the mixture was stirred for 30 min. The solution was warmed to −45 °C, stirred for 5 min and then was cooled to −78 °C again as 20.5 mg (0.104 mmol) of

52 in 0.42 mL of THF containing 0.14 mL of HMPA was added. The mixture was stirred for 1 h, gradually warmed to 0 °C, and quenched with 10 mL of water. Extraction with ether, followed by washing of the extract, drying, and removal of the solvent, gave 19.3 mg of impure **55**. This was immediately dissolved in 2 mL of THF containing 2 mL of 5% hydrochloric acid, and the mixture was stirred at 0 °C for 4 h. Extraction with ether and removal of the solvent gave 11.8 mg (47%) of a 53:47 mixture of **5** and **2**. Pure **5** was obtained by preparative TLC (ethyl acetate–hexane–acetic acid, 60:40:2): IR (film) 3150, 1720, 1655, 1595, 965 cm^{-1}; NMR (CCl_4) δ 6.83 (1 H, d, J = 16 Hz), 6.37 (1 H, d, J = 16 Hz), 5.45 (1 H, m), 2.05 (3 H, s), 1.91 (3 H, s), 1.26 (3 H, s), 1.51 (3 H, s); mass spectrum, m/z 304.168 (M^+, calcd for $C_{18}H_{24}O_4$ 304.167).

Methyl (7*E*,9*Z*)-Trisporate B (11). To 102 mg (0.20 mmol) of **33** in 1.4 mL of THF at −78 °C was added 92 μL (0.20 mmol) of 2.2 M *n*-butyllithium in hexane, and the mixture was stirred for 1 h. To this deep red solution was added 21.5 mg (0.109 mmol) of **52** in 0.42 mL of THF containing 0.14 mL of HMPA. The mixture was stirred for 1.5 h and allowed to warm to 0 °C. Extraction with ether, followed by drying and removal of the solvent, gave an oil which was dissolved in 3 mL of ether and treated with an excess of ethereal diazomethane at 0 °C. Filtration and removal of the solvent gave 17.1 mg (43%) of a mixture of **56** and **57**. A solution of this material in 1.5 mL of THF and 1.5 mL of 5% hydrochloric acid was stirred at 0 °C for 5.5 h under nitrogen. The mixture was extracted with ether, and the extract was washed with saturated aqueous sodium bicarbonate and dried. Removal of the solvent gave 14.8 mg (98%) of a 47:53 mixture of **11** and **8**. This material was subjected to preparative TLC (elution with hexane–ethyl acetate) under nitrogen in the dark to give pure **11**: UV λ_{max}^{EtOH} 325 nm; IR (film) 1730, 1660, 1595, 965 cm^{-1}; NMR (CCl_4) δ 6.76 (1 H, d, J = 16 Hz), 6.34 (1 H, d, J = 16 Hz), 5.50 (1 H, m), 3.68 (3 H, s), 2.10 (3 H, s), 1.92 (3 H, s), 1.86 (3 H, s), 1.54 (3 H, s); mass spectrum, m/z 318.183 (M^+, calcd for $C_{19}H_{26}O_4$ 318.183).

Methyl (7*E*,9*Z*)-O^4,4-Dihydrotrisporate B (17). To a stirred solution of 82.9 mg (0.229 mmol) of **57** in 5 mL of a 1:1 mixture of dimethoxyethane and *tert*-butyl alcohol at 0 °C was added 93.5 mg of sodium borohydride. The mixture was allowed to warm to room temperature, stirred for 22 h, then poured into water (10 mL), and extracted with ether. The extract was dried and concentrated to give an oil which was chromatographed on silica. Elution with hexane–ethyl acetate (1.5:1) furnished 42.5 mg (51%) of **58**: IR (film) 3450, 1730, 960, 860 cm^{-1}; NMR (CCl_4) δ 6.3. (1 H, d, J = 16 Hz), 6.08 (1 H, d, J = 16 Hz), 5.33 (1 H, t, J = 7 Hz), 4.03 (1 H, m), 3.87 (4 H, s), 3.62 (3 H, s), 1.90 (3 H, s), 1.87 (3 H, s), 1.10 (3 H, s), 1.04 (3 H, s); mass spectrum, m/z 364.

A solution of 39.8 mg (0.109 mmol) of **58** in 1.5 mL of a mixture of acetic acid and water (4:1) was allowed to stand at room temperature for 4.5 h. The solution was poured into cold, saturated aqueous sodium bicarbonate and extracted with ether. The extract was dried and concentrated to a small volume which was placed on a column of silica. Elution with hexane–ethyl acetate (1.5:1) gave 9.0 mg (26%) of **17**: IR (film) 3450, 1730 cm^{-1}; NMR (CCl_4) δ 6.20 (1 H, d, J = 16 Hz), 6.06 (1 H, d, J = 16 Hz), 5.61 (1 H, m), 4.05 (1 H, m), 3.64 (3 H, s), 2.14 (3 H, s), 1.93 (3 H, s), 1.75 (3 H, s), 1.30 (3 H, s); mass spectrum, m/z 320.198 (M^+, calcd for $C_{19}H_{28}O$ 320.198).

Keto Lactone 60. A solution of 20.0 mg (0.055 mmol) of **58** in 2.5 mL of *tert*-butyl alcohol containing a catalytic quantity of potassium *tert*-butoxide was stirred at room temperature for 22 h. The reaction mixture was worked up, and the crude **59** was hydrolyzed in aqueous acetic acid as described for **58** to give 15.8 mg (91%) of **60**: IR (film) 1755, 1715 cm^{-1}; NMR (CCl_4) δ 6.09 (1 H, d, J = 16 Hz), 5.95 (1 H, d, J = 16 Hz), 5.44 (1 H, br t, J = 7 Hz), 4.87 (1 H, t, J = 4 Hz), 2.10 (3 H, s), 1.99 (3 H, s), 1.82 (3 H, s), 1.37 (3 H, s); mass spectrum, m/z 288.172 (M^+, calcd for $C_{18}H_{24}O_3$ 288.173).

2-Methyl-4-(2-methyl-2-propenyl)tetronic Acid (63). To 96 mg (2.0 mmol) of sodium hydride (50% mineral oil dispersion which had been washed with pentane) in 3 mL of THF was added 338 mg (2.0 mmol) of α-methyltetronic acid (**34**)[19] in 2 mL of a 1:1 mixture of THF and HMPA. The solution was stirred at room temperature for 20 min and cooled to 0 °C (ice bath), and 1.0 mL (2.0 mmol) of 2.0 M *n*-butyllithium was added dropwise. The resulting pasty mixture was stirred for 20 min, and 270 mg (2.0 mmol) of methallyl bromide in 1 mL of THF was added. The ice bath was removed, and the solution was stirred for 2 h. Water, followed by 10% sulfuric acid, was added, and the mixture was extracted with ether. The ethereal extract was washed with brine and dried, and the solvent was removed to give 202 mg (60%) of slightly impure **63**. A purified sample of **63** was obtained by preparative TLC (ethyl acetate–ethanol–acetic acid, 90:10:2): IR ($CHCl_3$) 3000 (br), 1730, 1650 cm^{-1}; NMR ($CDCl_3$) δ 9.15 (1 H, br s, variable with temperature), 4.86 (3 H, br m), 2.76 (1 H, d, J = 16 Hz), 2.22 (1 H, dd, J = 8, 16 Hz), 1.79 (3 H, s), 1.72 (3 H, s); mass spectrum, m/z 168.077 (M^+, calcd for $C_9H_{12}O_3$ 168.079).

2,6-Dimethyl-4-hydroxy-3-oxo-2-(3-oxopentyl)hept-6-enoic Acid γ-Lactone (64). A solution of 85 mg (0.51 mmol) of **63** in 3 mL of THF containing 4 drops of triethylamine and 77 mg (0.92 mmol; 1.8 equiv) of ethyl vinyl ketone was refluxed for 3.5 h. Ether was added to the cooled solution, and the extract was washed with brine and dried. The solvent was removed to give 78 mg (61%) of **64**: IR (film) 1795, 1750, 1705 cm^{-1}; NMR ($CDCl_3$) δ 4.96 (3 H, br m), 2.50 (6 H, m), 2.03 (2 H, t, J = 7 Hz), 1.80 (3 H, s), 1.27 (3 H, s), 1.03 (3 H, t, J = 7 Hz); mass spectrum, m/z 252 (M^+). This material was used without purification for conversion to **65** and **66**.

4,8-Dimethyl-1,5-dioxo-3-(2-methyl-1-propenyl)-2-oxabicyclo[4.3.0]non-4(9)-ene (65) and 4,8-Dimethyl-1,5-dioxo-3-(2-methyl-2-propenyl)-2-oxabicyclo[4.3.0]non-4(9)-ene (66). A solution of 78 mg (0.310 mmol) of **64** in 5 mL of benzene containing a trace of *p*-toluenesulfonic acid was refluxed for 36 h with removal of water via Dean–Stark trap. The solution was cooled, ether was added, and the ethereal extract was washed with saturated aqueous sodium bicarbonate and dried. The solvent was removed in vacuo, and the residual oil was subjected to preparative TLC (ether–hexane, 70:30) to give 43 mg (60%) of a mixture of **65** and **66**: IR ($CHCl_3$) 1785, 1675 cm^{-1}; NMR (CCl_4) δ 5.70 (1 H, d, J = 10 Hz, **65**), 5.25 (1 H, d, J = 10 Hz, **65**), 5.18 (1 H, t, J = 6 Hz, **66**), 4.92 (2 H, br s, **66**), 2.50 (2 H, d, J = 6 Hz, **66**), 1.88 (3 H, s, **65** and **66**); mass spectrum, m/z 234.127 (M^+, calcd for $C_{14}H_{18}O_3$ 234.126).

(*Z*)-1-Chloro-6,6-(ethylenedioxy)-2-methyl-2-heptene (70). To a stirred solution of 359 mg (1.93 mmol) of **29** in 2 mL of ether containing 0.7 mL of HMPA at 0 °C was added dropwise 1.2 mL of 1.8 M methyllithium in ether, followed by a solution of 386 mg (2.03 mmol) of *p*-toluenesulfonyl chloride in 2 mL of ether. After addition was complete, 82 mg (1.93 mmol) of lithium chloride was added, and the mixture was stirred for 19 h at room temperature. To this mixture was added 5 mL of ether followed by 5 mL of water, and the separated organic layer was washed with water and dried. Removal of the solvent yielded 372 mg of slightly impure **70** which was chromatographed on silica. Elution with hexane–ether (3:1) gave 323 mg (82%) of **70**: IR (film) 1275, 1055, 940, 860, 800 cm^{-1}; NMR (CCl_4) δ 5.37 (1 H, t, J = 7 Hz), 4.02 (2 H, s), 3.87 (4 H, s), 1.81 (3 H, s), 1.24 (3 H, s). Anal. Calcd for $C_{10}H_{17}ClO_2$: C, 58.68; H, 8.31; Cl, 17.36. Found: C, 58.42; H, 8.44; Cl, 17.02.

A mixture of 1.975 g (9.65 mmol) of **70** and 3.012 g (29.28 mmol) of sodium bromide in 35 mL of DMF was stirred at room temperature for 5 h. To this solution was added 10 mL of ether, followed by 10 mL of water, and the ethereal extract, after being washed several times with water, was dried. Removal of the solvent gave 2.189 g (91%) of **31**, identical with the substance prepared from **29** with phosphorus tribromide (vide supra).

(*Z*)-1-Chloro-2-methyl-2-heptene (69). This compound was prepared from **24** in a manner exactly analogous to that employed for the synthesis of **70** from **29**. It was converted to **25** by the procedure described above for the conversion of **70** to **31**.

(2′*Z*)-2-Methyl-4-(2′-methyl-2′-heptenyl)tetronic Acid (71). To 178 mg (3.73 mmol) of sodium hydride (that had been washed free of mineral oil) in 6 mL of THF at 0 °C was added a solution of 393 mg (3.44 mmol) of **34** in 5 mL of a 1:1 mixture of THF and HMPA. The mixture was stirred for 40 min at room temperature and was cooled again to 0 °C as 1.56 mL of 2.2 M *n*-butyllithium in hexane was added. After being stirred at room temperature for 30 min, this mixture was cooled to −35 °C, and 657 mg (3.44 mmol) of **25** in 6 mL of THF was added. This solution was warmed to room temperature and stirred for 15 h, after which it was cooled to 0 °C, and water, followed by 5% sulfuric acid,

was added. The mixture was extracted with ether, and the extract was washed with brine and dried. The ether was removed, and the residual oil was purified by column chromatography on silica gel. Elution with ethyl acetate–hexane–acetic acid (100:50:0.5) gave 501 mg (65%) of **71**: IR (film) 1725, 1650, 840 cm^{-1}; NMR (CCl_4) δ 10.8 (1 H, br s), 5.31 (1 H, t, J = 7 Hz), 4.79 (1 H, m), 1.77 (3 H, s), 1.74 (3 H, s), 0.90 (3 H, m); mass spectrum, m/z 224.140 (M^+, calcd for $C_{13}H_{20}O_3$ 224.141).

Keto Lactone 75. A solution of 466 mg (2.08 mmol) of **71**, 350 mg (4.16 mmol) of ethyl vinyl ketone, and 160 mg of triethylamine in 20 mL of THF was stirred for 27 h at 30 °C. The volatiles were removed under reduced pressure, and the residue was taken up into ether. This solution was washed with brine and dried, and the ether was removed to afford 621 mg (97%) of fairly pure **73**: IR (film) 1790, 1705, 1645 cm^{-1}; NMR (CCl_4) δ 5.33 (1 H, t, J = 7 Hz), 4.80 (1 H, m), 1.79 (3 H, s), 1.21 (3 H, s). This material was used for the next reaction without further purification.

A solution of 234 mg (0.77 mmol) of **73** in 25 mL of benzene containing 41 mg of *p*-toluenesulfonic acid was refluxed (water was removed by a Dean–Stark trap) for 20 h. The mixture was cooled to room temperature, and saturated aqueous sodium bicarbonate was added. The mixture was extracted with ether, and the extract was washed with brine and dried. After removal of the solvent, column chromatography gave 165 mg (75%) of **75**: IR (film) 1780, 1670 cm^{-1}; NMR (CCl_4) δ 5.37 (1 H, t, J = 7 Hz), 5.10 (1 H, t, J = 6 Hz), 1.85 (3 H, s), 1.72 (3 H, s), 1.55 (3 H, s), 0.91 (3 H, m). Anal. Calcd for $C_{18}H_{25}O_3$: C, 74.45; H, 9.02. Found: C, 73.97; H, 8.84.

(2*Z*)-2-Methyl-4-[6′,6′-(ethylenedioxy)-2′-methyl-2′-heptenyl]tetronic Acid (72). To 35.7 mg (1.48 mmol) of sodium hydride (that had been washed free of mineral oil) in 2.5 mL of THF at 0 °C was added a solution of 157 mg (1.38 mmol) of **34** in 2.5 mL of a 1:1 mixture of THF and HMPA. The mixture was stirred for 50 min at room temperature and was cooled to 0 °C as 0.62 mL of 2.2 M *n*-butyllithium in hexane was added. After 30 min of stirring at room temperature, the mixture was cooled to −45 °C and 341 mg (1.37 mmol) of **31** in 2.5 mL of THF was added. The mixture was allowed to warm gradually to room temperature and stirred for 24 h before dilution with 1 mL of water and acidification with 2.5% sulfuric acid. The mixture was extracted with ether, and the extract was washed with brine and dried. The ether was removed, and the residue was purifed by column chromatography on silica. Elution with ethyl acetate–hexane–acetic acid (50:50:2) gave 244 mg (63%) of **72**: IR (film) 1730, 1650, 1060, 860 cm^{-1}; NMR (CCl_4) δ 5.31 (1 H, t, J = 7 Hz), 4.80 (1 H, m), 3.86 (4 H, s), 1.75 (3 H, s), 1.72 (3 H, s), 1.23 (3 H, s); mass spectrum, m/z 282.147 (M^+, calcd for $C_{15}H_{22}O_5$ 282.147).

Keto Lactone 76. A solution of 301 mg (1.07 mmol) of **72**, 190 mg (2.26 mmol) of ethyl vinyl ketone, and 90 mg of triethylamine in 10 mL of THF was refluxed for 6 h. The volatiles were removed at reduced pressure, and ether and brine were added to the residue. The organic layer was separated, washed with brine, and dried. Removal of the solvent gave 367 mg (94%) of **74**: (IR) film 1800, 1760, 1720, 1060 cm^{-1}; NMR (CCl_4) δ 5.35 (1 H, t, J = 7 Hz), 4.80 (1 H, m), 3.85 (4 H, s), 1.78 (3 H, s), 1.22 (6 H, s), 1.00 (3 H, t, J = 7 Hz); mass spectrum, m/z 366.205 (M^+, calcd for $C_{20}H_{30}O_6$ 366.204.

A solution of 939 mg (2.56 mmol) of **74** in 80 mL of benzene containing 170 mg of *p*-toluenesulfonic acid was refluxed (water and removed by a Dean–Stark trap) for 27 h. Saturated aqueous sodium bicarbonate was added, and the mixture was extracted with ether. The organic layer was washed with brine and dried, and the solvent was removed. Column chromatography of the residue on silica gel, eluting with ethyl acetate–hexane (1:2), gave 559 mg (71%) of **76**: IR (film) 1780, 1715, 1670 cm^{-1}; NMR (CCl_4) δ 5.42–5.00 (2 H, m), 2.06 (3 H, s), 1.83 (3 H, s), 1.73 (3 H, s), 1.58 (3 H, s); mass spectrum, m/z 304.166 (M^+, calcd for $C_{18}H_{24}O_4$ 304.167). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 69.68; H, 7.89.

Methyl 1,2,3-Trimethyl-4-oxocyclohex-2-ene-1-carboxylate (78). To a solution of 155 mg (3.88 mmol) of calcium metal in 5 mL of liquid ammonia was added a solution of 360 mg (2.0 mmol) of **36** in 4 mL of THF. The mixture was stirred for 25 min, and the reaction was quenched with ammonium chloride. Water was added, followed by 10% sulfuric acid, and the mixture was extracted with ether. The ethereal extract was washed with brine and dried, and the solvent was removed to give 335 mg of **77**. This acid was treated with excess ethereal diazomethane to afford 355 mg (91%) of slightly impure **78**. A purified sample was obtained by preparative TLC, eluting with ether–hexane (1:1): IR (film) 1730, 1670, 1250 cm^{-1}; NMR ($CDCl_3$) δ 3.73 (3 H, s), 2.58–1.80 (4 H, m), 1.88 (3 H, s), 1.80 (3 H, s), 1.44 (3 H, s); mass spectrum, m/z 196.111 (M^+, calcd for $C_{11}H_{16}O_3$ 196.110).

Dihydroxy Ketone 84. A solution of 183 mg (0.63 mmol) of **75**, 1.0 mL of ethylene glycol, 1.0 mL of ethyl orthoformate, and 49 mg of *p*-toluenesulfonic acid in 4 mL of ether was kept at room temperature for 35 h. To this solution was added saturated aqueous sodium bicarbonate, and the mixture was extracted with ether. The extract was washed with brine and dried, and the ether was removed to afford crude **80**: IR (film) 1780 cm^{-1}; NMR (CCl_4) δ 3.80 (4 H, m).

This material was dissolved in 10 mL of THF and was added to an ice-cooled suspension of 400 mg of lithium aluminum hydride in 9 mL of ether at 0 °C. The mixture was stirred for 20 h at room temperature and then cooled to 0 °C as water was added carefully. The mixture was filtered, the filtrate was dried, and the ether was removed in vacuo to give crude **82**, which was taken up into 7 mL of a 4:1 mixture of acetic acid and water. After standing at room temperature for 5 h, the mixture was poured into cold, saturated aqueous sodium bicarbonate, and the mixture was extracted with ether. The extract was washed with brine and dried, and the ether was removed to afford a viscous oil. Column chromatography of this oil gave 111 mg (60%) of **84**: IR (film) 3400, 1650 cm^{-1}; NMR (CCl_4) δ 5.35 (1 H, t, J = 7 Hz), 4.82 (1 H, m), 3.74 (1 H, d, J = 10 Hz), 3.56 (1 H, d, J = 10 Hz), 1.83 (3 H, s), 1.81 (3 H, s), 1.36 (3 H, s), 0.92 (3 H, t, J = 6 Hz). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.69; H, 10.01. In addition, 51 mg of unreacted **75** was recovered.

Acetate 86. A solution of 100 mg (0.38 mmol) of **84** in 5 mL of ether was added to 399 mg (3.9 mmol) of acetic anhydride and 343 mg (4.3 mmol) of pyridine in 5 mL of ether at 0 °C. The mixture was warmed slowly to room temperature, stirred for 36 h, and poured into cold, saturated aqueous sodium bicarbonate. The mixture was extracted with ether, and the extract was washed with saturated aqueous copper sulfate and dried. The solvent was removed, and the residue was purified by column chromatography on silica. Elution with hexane–ethyl acetate (3:1) gave 104 mg (83%) of **86**: IR (film) 3490, 1740, 1670, 1040 cm^{-1}; NMR (CCl_4) δ 5.27 (1 H, m), 4.73 (1 H, m), 4.57 (1 H, dd, J = 3, 11 Hz), 3.93 (1 H, d, J = 11 Hz), 1.94 (3 H, s), 1.81 and 1.79 (3 H, s), 1.44 and 1.40 (3 H, s), 0.90 (3 H, t, J = 6 Hz); mass spectrum, m/z 336.230 (M^+, calcd for $C_{20}H_{32}O_4$ 336.229).

Mesylate 88. To a solution of 74.7 mg (0.222 mmol) of **86** in 1.0 mL of pyridine at 0 °C was added dropwise 80 mg of methanesulfonyl chloride. The solution was stirred for 30 min at 0 °C, then was warmed to room temperature, and stirred for 13 h. The mixture was poured into ice–water and extracted with ether, and the extract was washed with saturated aqueous copper sulfate and dried. The ether was removed, and the residue was purified by column chromatography (elution with ether–hexane, 3:2) to yield 71.4 mg (78%) of **88**: IR (film) 1740, 1670, 1370, 1230, 1170 cm^{-1}; NMR (CCl_4) δ 5.62–5.18 (2 H, m), 4.03 (2 H, br s), 2.88 (3 H, s), 2.03 (3 H, s), 1.99 and 1.94 (3 H, s), 1.81 and 1.72 (3 H, s), 1.36 (3 H, s), 0.91 (3 H, t, J = 6 Hz); mass spectrum, m/z 414 (M^+).

Trisporol A (92). A solution of 47.5 mg (0.115 mmol) of **88** in 3 mL of Me_2SO was heated at 80 °C for 1 h. After all of the starting material had been consumed as determined by disappearance of the methyl resonance of the mesylate group in the NMR spectrum, the mixture was cooled to room temperature, poured into water, and extracted with ether. The extract was washed with brine and dried, and the ether was removed to give an oil which was purified by preparative TLC. Elution with hexane–ethyl acetate (1:2) gave 17.6 mg (48%) of trisporol A acetate (**90**).

To a solution of 17.0 mg of **90** in 1.0 mL of ethanol at 0 °C was added 0.3 mL of 0.5 M aqueous potassium carbonate. The mixture was stirred for 2.5 h at 0 °C and then for 5 h at room temperature. Water and ether were added to the mixture which was extracted with ether. The extract was washed and dried, the ether was removed, and the residue was purified by preparative TLC. Elution with hexane–ethyl acetate (2:1) gave 9.7 mg (32%) of **92**:

IR (film) 3450, 1660, 1600, 965 cm^{-1}; NMR (CCl_4) δ 6.62 (1 H, d, J = 16 Hz), 6.16 (1 H, d, J = 16 Hz), 5.51 (1 H, m), 3.68 (1 H, d, J = 11 Hz), 3.38 (1 H, d, J = 11 Hz), 1.82 (6 H, s), 1.12 (3 H, s); mass spectrum, m/z 276.207 (M^+, calcd for $C_{18}H_{28}O_2$ 276.208).

Dihydroxy Diketone 85. A solution of 559 mg (1.84 mmol) of **76**, 3.0 mL of ethylene glycol, 3.0 mL of triethyl orthoformate, and 134 mg of *p*-toluenesulfonic acid in 12 mL of ether was left at room temperature for 37 h. Saturated aqueous sodium bicarbonate was added, and the mixture was extracted with ether. The extract was washed with brine and dried, and the ether was removed to afford crude diketal **81**: IR (film) 1770, 1060 cm^{-1}; NMR (CCl_4) δ 3.77 (4 H, s), 3.90 (4 H, m). This material in 30 mL of THF was added to an ice-cooled suspension of 987 mg of lithium aluminum hydride in 27 mL of ether at 0 °C, and the mixture was stirred for 22 h at room temperature. Water was carefully added to the mixture, which was then filtered. The filtrate was dried, and the ether was removed to afford crude **83**: IR (film) 3450, 1060 cm^{-1}; NMR (CCl_4) δ 3.67 (4 H, s), 3.73 (4 H, s). This diol was taken up into 10 mL of a 4:1 mixture of acetic acid and water, and the solution was left at room temperature for 4.5 h. The mixture was poured into cold saturated aqueous sodium bicarbonate and extracted with ether. The extract was washed with brine and dried, and the ether was removed. Column chromatography of the residue gave 315 mg (56%) of **85**: IR (film) 3450, 1710, 1660, 1050 cm^{-1}; NMR (CCl_4) δ 5.15 (1 H, m), 4.84 (1 H, m), 3.77 (1 H, d, J = 10 Hz), 3.56 (1 H, d, J = 10 Hz), 2.11 (3 H, s), 1.84 (3 H, s), 1.78 (3 H, s), 1.33 (3 H, s). Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.66; H, 8.87.

Acetate 87. A solution of 291 mg (0.94 mmol) of **85** in 8 mL of ether was added to a solution of 667 mg (6.58 mmol) of acetic anhydride and 588 mg (7.44 mmol) of pyridine in 5 mL of ether at 0 °C. The mixture was warmed to room temperature, stirred for 22 h, and poured into cold, saturated aqueous sodium bicarbonate. The mixture was extracted with ether, and the extract was washed with saturated aqueous copper sulfate and dried. The solvent was removed, and the residue was subjected to column chromatography on silica. Elution with hexane–ethyl acetate (1:1) gave 262 mg (79%) of **87**: IR (film) 3500, 1740, 1670, 1240, 1040 cm^{-1}; NMR (CCl_4) δ 5.16 (1 H, t, J = 7 Hz), 4.73 (1 H, m), 4.58 (1 H, d, J = 11 Hz), 3.95 (1 H, d, J = 11 Hz), 3.32 (1 H, br s), 2.07 (3 H, s), 1.94 (3 H, s), 1.81 (3 H, s), 1.78 (3 H, s), 1.45 (3 H, s); mass spectrum, m/z 350.208 (M^+, calcd for $C_{20}H_{30}O_5$ 350.209).

Mesylate 89. To an ice-cold solution of 184 mg (0.53 mmol) of **87** in 5.5 mL of pyridine was added 375 mg of methanesulfonyl chloride. The reaction mixture was warmed to room temperature, stirred for 12 h, and poured into ice–water. The mixture was extracted with ether, and the extract was washed with saturated aqueous copper sulfate and dried. After the ether was removed, column chromatography of the residue on silica and elution with ethyl acetate–hexane (2:1) gave 212 mg (94%) of **89**: IR (film) 1740, 1715, 1680, 1070, 1040, 900 cm^{-1}; NMR (CCl_4) δ 5.60–5.20 (2 H, m), 4.06 (2 H, br s), 2.94 (3 H, s), 2.10 (3 H, s), 2.06 (3 H, s), 2.03 (3 H, s), 1.82 (3 H, s), 1.40 (3 H, s); mass spectrum, m/z 332 ($M^+ - CH_3SO_3H$).

Trisporol B Acetate (91). A solution of 32.5 mg (0.085 mmol) of **89** in 4 mL of Me_2SO was heated at 80 °C for 2 h and then was poured into water. The mixture was extracted with ether, and the extract was washed with brine and dried. The ether was removed to afford a viscous liquid which was subjected to preparative TLC on silica. Elution with ethyl acetate–hexane (55:45) gave 8.6 mg (34%) of **91**: UV λ_{max}^{EtOH} 301 nm (ϵ 11 100); IR (film) 1740, 1710, 1660, 1240, 1040, 965 cm^{-1}; NMR (CCl_4) δ 6.64 (1 H, d, J = 16 Hz), 6.11 (1 H, d, J = 16 Hz), 5.45 (1 H, t, J = 7 Hz), 4.22 (1 H, d, J = 11 Hz), 3.89 (1 H, d, J = 11 Hz), 2.08 (3 H, s), 2.00 (3 H, s), 1.88 (3 H, s), 1.19 (3 H, s); mass spectrum, m/z 332.200 (M^+, calcd for $C_{20}H_{28}O_4$ 332.199).

Trisporol B (13). To a solution of 34.5 mg (0.104 mmol) of **91** in 3.0 mL of ethanol at 0 °C was added 0.9 mL of 0.5 M aqueous potassium carbonate, and the mixture was stirred for 1 h. The solution was warmed to room temperature, stirred for a further 12 h, and poured into water. The mixture was extracted with ether, and the extract was washed with brine and dried. The ether was removed, and the residue was purified by column chromatography to give 16.4 mg (54%) of **13**: UV λ_{max}^{EtOH} 301 nm (ϵ 23 000); IR (film) 3450, 1710, 1650, 1600, 960 cm^{-1}; NMR (CCl_4) δ 6.68 (1 H, d, J = 16 Hz), 6.20 (1 H, d, J = 16 Hz), 5.42 (1 H, t, J = 7 Hz), 3.69 (1 H, d, J = 10 Hz), 3.39 (1 H, d, J = 10 Hz), 3.10 (1 H, br s), 2.10 (3 H, s), 1.89 (3 H, s), 1.82 (3 H, s), 1.12 (3 H, s); mass spectrum, m/z 290.187 (M^+, calcd for $C_{18}H_{26}O_3$ 290.188).

Oxidation of 13. To a solution of 12.0 mg (0.041 mmol) of **13** in 0.5 mL of acetone at 0 °C was added 3 drops of Jones' reagent, and the solution was stirred for 10 min. Excess oxidant was consumed by the addition of one drop of isopropyl alcohol, and the mixture was then poured into water and extracted with ether. The extract was washed with brine and dried, and the ether was removed to afford 8.3 mg of **5**, identical with material prepared from **33**.

Bioassay of Synthetic Trisporic Acids, Their Methyl Esters, and Trisporols. Plus and minus mating strains of *M. mucedo* were inoculated on agar containing 300 ppm of 2-[(4-chlorophenyl)thio]triethylamine hydrochloride (CPTA) in 90-mm Petri dishes and incubated for 203 days. Freshly prepared stock solutions of the hormones at ca. 10 mg in 5 mL of water were diluted 2-, 5-, 10-, and 100-fold, and 50 μL of each solution were placed in each of four holes cut ca. 1 cm in front of the hyphal margin on each dish. The *M. mucedo* was then incubated in the presence of the hormones at room temperature for 14 h, and, after a further 7–16 h, the plates were examined at 60–100× magnification with a dissecting microscope. A mating control containing both plus and minus strains and a control containing each strain with no hormone added was run simultaneously. Zygophores per unit area in each well were counted by using the 16-square grid of the microscope and were easily distinguished from immature sporangiophores by the orange-tipped hyphal.

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