W. F. Hain for skilled technical assistance. This work was supported in part by U.S. Public Health Service Grant GM-2907.

Registry No.—I, 60803-65-8; Ia, 60803-66-9; Ib, 60803-67-0; II, 60803-69-2; IIa, 60803-70-5; IIb, 23361-38-8; III, 60803-72-7; IIIa, 60803-73-8; IIIb, 60828-33-3; β-(4-bromobenzyl) aspartate, 60828-77-5; *N*-Boc-serine, 3262-72-4; 4-bromobenzyl bromide, 589-15-1; dicydohexylamine, 101-83-7; *O*-(4-chlorobenzyl)threonine 4-chlorobenzyl ester hydrogen oxalate, 60803-75-0; chlorobenzyl alcohol, 873-76-7; H_2N-Phe, 63-91-2; H-Asp-Phe-OH, 13433-09-5; H-Ser-Phe-OH, 16875-28-8; H-Thr-Phe-OH, 16875-27-7.

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A Convenient Total Synthesis of (±)-(7*E*,9*E*)-Trisporic Acid B Methyl Ester

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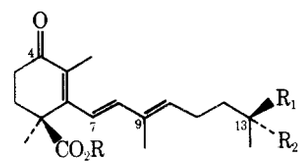
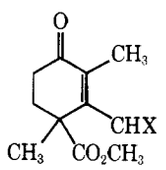
A brief converging total synthesis of the title compound is reported, utilizing as the key step a Michael-aldol sequence on the β-keto ester **4b** to form the highly functionalized cyclohexenone **2b.**

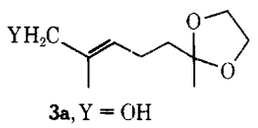
The sexual cycle of the fungi *Blakeslea trispora* and *Mucor mucedo* is mediated by a series of hormones, the trisporic acids (**1a–c,** R = H).[2] These hormones are derived biosynthetically from β-carotene,[3] and recently several prohormones have been isolated with lower oxidation levels at C-4 and the carboxylic acid carbon,[4] indicating that these are the sites of last modification in the biosynthesis. Synthetic efforts have thus far resulted in two syntheses of methyl trisporate B (**1b,** R = CH_3) and/or C (**1c,** R = CH_3),[5,6] and some work has recently been carried out on the utilization of Hagemann's ester for the formation of a potential intermediate in trisporic acid synthesis.[7] We wish to describe a convenient converging synthesis of the methyl ester of (±)-(7*E*,9*E*)-trisporic acid B (**1b,** R = CH_3), which is also a fully active compound.[4]



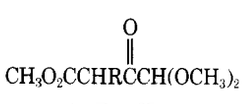
1a, $R_1 = R_2 = H$
b, $R_1 = R_2 = O$ (and 9-cis)
c, $R_1 = H$; $R_2 = OH$ (and 9-cis)



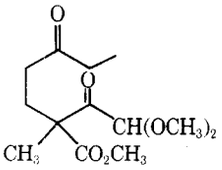
2a, X = O
b, $X = (OCH_3)_2$



3a, Y = OH
b, Y = Br
c, $Y = {}^+PPh_3{}^-$



4a, R = H
b, $R = CH_3$



5

The striking feature of this molecule is certainly the cyclohexenone moiety, suggesting a Michael-aldol sequence for its formation. We felt that the potential power of this sequence dictated its use, but contrary to previous work,[5,6] we wished to carry out the formation of the ring as quickly as possible, before the appendage at C-6 was attached. With this in mind we chose as our target molecules the aldehyde **2a** and the phosphonium salt **3c,** which we planned to join via a Wittig reaction. The choice of **2a** and **3c** provides us with two molecules each of which should be available in a few steps, thus portending a very direct overall route.

Analysis of the aldehyde **2a** indicates that the most effective means of applying the Michael-aldol sequence is to form the six-membered ring by joining a four-carbon unit to a two-carbon unit. Treatment of pyruvaldehyde dimethyl acetal with sodium hydride and dimethyl carbonate afforded the β-keto ester **4a,**[8] which was methylated with sodium hydride and methyl iodide to provide **4b.**[8] At this point there were several options available to us for the conversion to **2b.** In principle the Michael adduct might be first isolated, and then cyclized to **2b** under mild conditions, or the entire Michael-aldol sequence might be carried out at one time with a somewhat stronger base. The highly functionalized nature of **4b** suggested the former approach as the more promising one. Treatment of a solution of **4b** in methanol containing a catalytic amount of sodium methoxide with ethyl vinyl ketone did indeed afford **5,** which could be cyclized under various conditions to **2b.** More conveniently, however, the best procedure turned out to involve treatment of a solution of **4b** in methanol containing 1 equiv of sodium methoxide at room temperature with ethyl vinyl ketone over 3 h. This method provided **2b** directly in 45–50% yield, with no contamination by **5.** In this procedure methyl vinyl ketone also worked well as the Michael

acceptor. Unmasking of the aldehyde **2a** was accomplished by mild acidic hydrolysis of **2b.**

Synthesis of the phosphonium salt **3c** was accomplished starting with the alcohol **3a,** available conveniently in three steps from 6-methyl-5-hepten-2-one.[9,10] Addition of PBr_3 to a solution of **3a** and 2,4,6-collidine gave the unstable allylic bromide **3b,** which was immediately dissolved in ether and heated at reflux with triphenylphosphine overnight to afford the colorless salt **3c.**

On the basis of precedent in the vitamin A literature,[11] which indicates that in areas of extended conjugation the Wittig reaction will introduce a trans double bond exclusively, it was expected that the reaction of **2a** and the ylide of **3c** would provide only the 7*E* isomer. In addition, molecular models indicated that the 7*Z* isomer would have increased steric constraints owing to the methyl at C-5 and the quaternary carbon at C-1. Thus, the ylide generated from **3c** was condensed with aldehyde **2a** and the ketal functionality removed in situ by the addition of 5% HCl. Isolation by preparative TLC gave the pure methyl ester of (±)-(7*E*,9*E*)-trisporic acid B, in 28% yield for the two steps. Examination of a wide variety of conditions provided no improvement in the yield for these steps, though individually both half molecules gave excellent yields in other Wittig reactions. The synthetic material gave a correct exact mass and showed identical spectral properties with the natural product.[5,6] The facile conversion of methyl trisporate B to C has been reported.[6]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus, and are corrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 467 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian A-60A spectrometer; chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded with an AEI-MS9 spectrometer at 70 eV.

Toluene was dried by distillation from CaH_2; tetrahydrofuran and diethyl ether were dried by distillation from sodium and benzophenone; methanol was dried by distillation from magnesium methoxide; hexane was distilled and stored over molecular sieves. Sodium hydride was weighed directly into the reaction vessels as a 50% dispersion in mineral oil, and then washed four times with toluene to remove the oil.

Methyl 4,4-Dimethoxy-3-oxobutyrate (4a). To a suspension of 15.6 g (0.65 mol) of NaH in 150 ml of toluene was added 58.5 g (0.65 mol) of dimethyl carbonate, and the mixture heated to reflux with mechanical stirring. A solution of 38.5 g (0.326 mol) of pyruvaldehyde dimethyl acetal in 40 ml of toluene was added over 1 h, and the mixture heated at reflux for a total of 6 h. The solution was cooled to ambient temperature and 75 ml of acetic acid added slowly, followed by 200 ml of water. The organic layer was separated, and the aqueous layer washed with benzene. The combined organic layer was washed with water, dried, and evaporated in vacuo. The residue was vacuum distilled to afford 39.2 g (68%) of the β-keto ester: bp 66–67 °C (0.75 mm) [lit.[8] bp 76 °C (5 mm)]; IR (neat) 1752, 1729 cm^{-1}; NMR ($CDCl_3$) δ 3.40 [s, 6, $(OCH_3)_2$], 3.56 (s, 2, $-CH_2-$), 3.71 (s, 3, CO_2CH_3), 4.55 [s, 1, $CH(OCH_3)_2$].

Methyl 4,4-Dimethoxy-2-methyl-3-oxobutyrate (4b). To a suspension of 4.34 g (0.181 mol) of NaH in 150 ml of toluene was added 31.9 g (0.181 mol) of ester **4a** in 30 ml of toluene dropwise, with mechanical stirring. After addition was complete the mixture was brought to reflux for 0.5 h and cooled to ambient temperature. To the salt was added 51 g (0.36 mol) of CH_3I dropwise, and the mixture heated at 90 °C for 3 h. After cooling the NaI was filtered off and washed with toluene, and the filtrate washed with water, dried, and evaporated in vacuo. Distillation of the residue afforded 29.56 g (86%) of the colorless monomethylated product: bp 77–78 °C (1.5 mm) [lit.[8] bp 88 °C (5 mm)]; IR (neat) 1751, 1727 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (d, 3, J = 7 Hz, CH_3CH), 3.38 [s, 6, $CH(OCH_3)_2$], 3.69 (s, 3, CO_2CH_3), 3.83 (q, 1, J = 1 Hz, $CHCH_3$), 4.65 [s, 1, $CH(OCH_3)_2$].

Methyl 2-Dimethoxymethyl-1,3-dimethyl-4-oxocyclohex-2-enyl-1-carboxylate (2b). To a stirred solution of 31 g (0.163 mol) of ester **4b** in 150 ml of methanol containing 0.18 mol of sodium methoxide was added 18 g (0.214 mol) of ethyl vinyl ketone dropwise over a period of several hours, and the solution stirred at ambient temperature overnight. Addition of 150 ml of water was followed by evaporation of the methanol and extraction several times with CH_2Cl_2. The organic extracts were dried, the solvent removed in vacuo, and the residue briefly vacuum distilled to remove nonvolatile and colored materials. Direct crystallization utilizing ether–petroleum ether afforded 10.9 g (26%) of colorless crystals, mp 59–60 °C. Chromatography of the mother liquors on silica gel eluting with 1:1 ether–petroleum ether, allows the isolation of additional pure material, the total yield generally being in the neighborhood of 45–50%: IR (KBr) 1733, 1675, 1615 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (s, 3, $CH_3CCO_2CH_3$), 1.83 (s, 3, $CH_3C{=}C$), 1.75–2.63 (m, 4, $-CH_2CH_2-$), 3.31 and 3.38 [2 s, 6, $(OCH_3)_2$], 3.68 (s, 3, CO_2CH_3), 5.03 [s, 1, $CH(OCH_3)_2$].

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.94; H, 7.81. Found: C, 61.16; H, 7.96.

Methyl 1,3-Dimethyl-2-formyl-4-oxocyclohex-2-enyl-1-carboxylate (2a). A solution of the acetal **2b** (1.105 g, 4.32 mmol) in 15 ml of 1:1:1 water–methanol–acetic acid was allowed to stand at ambient temperature for 12 h. After evaporation of the methanol in vacuo the solution was poured slowly into an excess of 5% aqueous sodium bicarbonate and extracted several times with ether. The ether extracts were dried and evaporated to give a quantitative yield of the aldehyde as a pale yellow syrup. Crystallization from ether–petroleum ether afforded 0.78 g (86%) of pure aldehyde as pale yellow crystals: mp 80–81 °C; IR (KBr) 1732, 1677 cm^{-1} (br); NMR ($CDCl_3$) δ 1.49 (s, 3, $CH_3CCO_2CH_3$), 2.21 (s, 3, $CH_3C{=}C$), 1.76–2.79 (m, 4, $-CH_2CH_2-$), 3.68 (s, 3, CO_2CH_3), 10.29 (s, 1, CHO).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 62.58; H, 6.74.

(*E*)-6,6-Ethylenedioxy-2-methyl-2-heptenyltriphenylphosphonium Bromide (3c). To a stirred solution of 558 mg (3.0 mmol) of alcohol **3a**[10] and 726 mg (6.0 mmol) of 2,4,6-collidine in 5 ml of 1:1 ether–hexane at 0 °C protected from moisture was added 543 mg (2.0 mmol) of PBr_3 in 1 ml of hexane dropwise over 0.5 h. Stirring was continued for an additional 1 h, and the reaction mixture worked up by the addition of water and extraction several times with ether. The ether extracts were dried, solvent was removed in vacuo, and the crude allylic bromide **3b** and 600 mg (2.3 mmol) of triphenylphosphine were immediately dissolved in 5 ml of ether and heated at reflux for 16 h. Filtration and washing with ether yielded 551 mg (36% overall) of phosphonium salt **3c:** mp 166–172 °C; IR (KBr) 3045, 2785, 1614 cm^{-1}; NMR ($CDCl_3$) δ 1.23 [s, 3, $CH_3C(-O-)O-$], 1.50 (br d, 3, $CH_3C{=}C$), 1.4–2.4 (m, 4, CCH_2CH_2C), 3.87 (s, 4, $-OCH_2CH_2O-$), 4.57 (d, 2, J = 14.5 Hz, $CH_2P^+Ph_3$), 5.42 (br t, 1, $C{=}CH$), 7.73 (m, 15, Ph_3). This compound proved difficult both to purify and analyze, and would not give a molecular ion in the mass spectrum. Since it was obtained in reasonable purity after filtration, the salt was dried and used directly.

(±)-Methyl (7*E*,9*E*)-Trisporate B. To a stirred suspension of powdered phosphonium salt **3c** (364 mg, 0.712 mmol) in 5 ml of THF under N_2 at ambient temperature was added *n*-BuLi (0.57 ml of a 2.15 M solution) dropwise, the salt gradually dissolving to yield a deep red solution of the ylide. After 0.25 h the ylide was cooled to −50 °C and a solution of aldehyde **2a** (149.5 mg, 0.712 mmol) in 1.5 ml of THF added dropwise via syringe. Stirring was continued for 1 h at −50 °C, when TLC analysis (1:1 ether–petroleum ether) showed no aldehyde present, and then 5 ml of 5% HCl was added, and the solution stirred at 0 °C for 1 h. Addition of 5 ml of water was followed by evaporation of the THF in vacuo and extraction several times with ether. The ether extracts were dried, solvent removed in vacuo, and the residue immediately subjected to preparative thin layer chromatography under N_2 in the dark (elution with 3:2 ether–petroleum ether). Isolation of the appropriate band gave 63 mg (28%) of (±)-trisporic acid B methyl ester, spectrally identical with the natural material (IR, UV, NMR); mass spectrum calcd *m/e* 318.1831, obsd *m/e* 318.1836.

Acknowledgment. We wish to thank S. Scott Stewart for carrying out certain experiments bearing on this work, Dr. P. L. Fuchs of Purdue University for helpful discussions, and the Ohio State University Department of Chemistry for its generous support.

Registry No.—**1b,** 60760-98-7; **2a,** 60705-21-7; **2b,** 60705-22-8; **3a,** 21488-96-0; **3b,** 60705-23-9; **3c,** 60705-24-0; **4a,** 60705-25-1; **4b,** 60705-26-2; dimethyl carbonate, 616-38-6; pyruvaldehyde dimethyl acetal, 6342-56-9; CH_3I, 74-88-4; ethyl vinyl ketone, 1629-58-9; PBr_3, 7789-60-8; triphenylphosphine, 603-35-0.

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Rearrangement of α-Bromocamphoric Anhydride. 2. Competitive Mechanisms in the Formation of Laurolenic Acid[1,2a-c]

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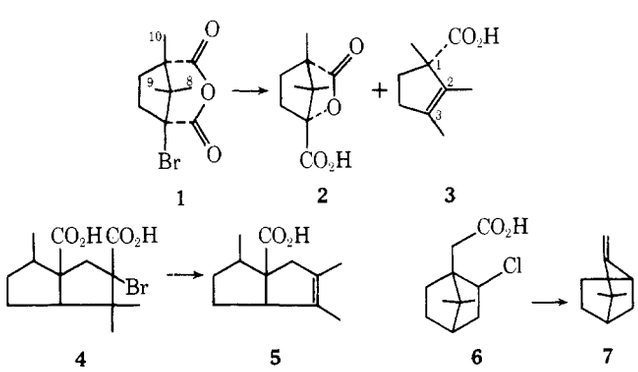
α-Bromocamphoric anhydride (1) is converted by aqueous sodium carbonate into camphanic acid (2) and the rearranged product laurolenic acid (3). L(+)-α-Bromocamphoric anhydride-*8,8,8-d*$_3$ was prepared from L(−)-camphor-*8,8,8-d*$_3$ by oxidation with selenium dioxide and then hydrogen peroxide, followed by bromination. Rearrangement of this labeled anhydride produces L(−)-laurolenic acid in which 71% of the CD_3 group is located at the 1 position and 29% is at the 3 position. In conjunction with earlier work, these results indicate that the rearrangement is not unimechanistic, but follows at least two competitive pathways. One of these involves loss of the carboxyl γ to the bromine by a path which is concerted with migration of the 8-methyl to the initially brominated carbon. Another process involves loss of the α-carboxyl, but the present results do not determine whether or not this is also concerted with the stereoselective 8-methyl migration. Even if it is, concerted γ-decarboxylation predominates over concerted α-decarboxylation. Optically and isotopically pure L(−)-camphor-*8,8,8-d*$_3$ was prepared in 41% overall yield from L(−)-8-apoisoborneol-7-carboxylic acid lactone by lithium aluminum deuteride reduction to L(+)-8-hydroxyisoborneol-*8,8-d*$_2$ (**17**-d_2), selective preparation of the 8-benzoate, Jones oxidation and saponification to afford L(−)-8-hydroxycamphor-*8,8-d*$_2$ (**25**-d_2), treatment with phosphorus tribromide to produce the 8-bromo ketone, and tri-*n*-butyltin deuteride reduction. Small amounts of the 2,8-dibenzoate **20** and the 2-monobenzoate **21** are by-products of the benzoylation, the latter being converted to carboxy ester **29** in the oxidation step. Conversion of the undeuterated diol **17** to ketol **25** by selective 8-tritylation, Sarett oxidation, and hydrolysis of keto trityl ether **23** is also described. 2-Hydroxy- and 2-keto-8-*p*-toluenesulfonates **22** and **26** are both converted by lithium aluminum hydride into cyclic ether **30**, which is also produced by attempted tosylation of **17** at room temperature.

One of the most striking molecular rearrangements of organic chemistry is the solvolytic conversion of α-bromocamphoric anhydride (1) to laurolenic acid (3), first reported by Fittig and Woringer in 1885.[3] This unsaturated acid accompanies the major unrearranged product, camphanic acid (2),



in about 15% yield when the solvolysis is conducted at pH 11,[4] and its formation involves the unusual combination of bromide loss, 1,2-methyl migration, and decarboxylation of an α- or γ-bromo acid. Other examples of potentially analogous reactions are extremely rare, but include the rearrangement of bromonorcedrenedicarboxylic acid (an α-bromo acid, **4** → **5**)[5] and of 2-chloro-1-apocamphaneacetic acid (a γ-bromo acid, **6** → **7**).[6] A few related base-catalyzed rearrangements of α-bromo acids not accompanied by decarboxylation are also known.[7]

Some time ago we became interested in the mechanism of this peculiar reaction, particularly in the stereoselectivity of methyl migration and in the regioselectivity of decarboxylation. Owing to the particular juxtaposition of functional groups in the camphoric acid system, the latter is not intuitively obvious as it is in the cases of **4** and **6**. In an earlier paper we reported the results of research showing that the methyl migration which occurs during formation of laurolenic acid is completely stereoselective and therefore concerted with bromide loss, and that neither an α-lactone (or its mechanistic equivalent), a carbene, nor camphanic acid is involved in the rearrangement.[1] It is also known that the rearrangement product is at least 96% optically pure[8] and has the same configuration at C-1 as does the bromo anhydride from which it is derived.[1,8-10] These results limit the mechanistic possibil-