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TOTAL SYNTHESIS OF (+)-METHYL TRISPORATE B, FUNGAL SEX HORMONE

SHUNYA TAKAHASHI, TAKAYUKI ORITANI and KYOHEI YAMASHITA

Department of Agricultural Chemistry, Faculty of Agriculture,
Tohoku University, Sendai 981, Japan

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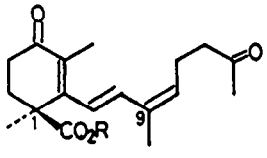
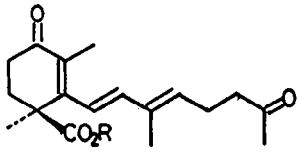
ABSTRACT---The enantioselective synthesis of (+)-methyl trisporates B (2 and 4) has been described. The chiral enedione 11, which was prepared by asymmetric aldol condensation of the prochiral triketone 12, was converted to α-hydroxyketone 9 via the oxobenzoate 10. Cleavage of acyloin moiety in 9 with lead tetraacetate led to the β-ionone type derivative 6. Regioselective Wittig reaction of 6 with the ylide 7, followed by deprotection, afforded (+)-(7E,9Z)-methyl trisporate B (2) and its 9E-isomer (4). From this synthetic work, the absolute configuration of natural trisporic acids B (1 and 3) was confirmed.

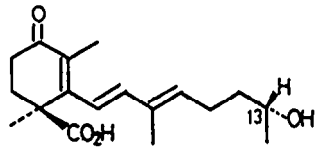
Trisporic acids (1, 3 and 5), which were isolated from mated cultures of fungi Mucor mucedo and Blakeslea trispora, are fungal sexual hormones[1] and have been shown to be biosynthetically formed from β-carotene by way of retinal.[2] These acids not only regulate sexual reproduction but are also known to cause a marked increase in the carotene content of B. trispora and promote steroid biosynthesis.[3] By further extensive studies, several congeners including biologically active prohormone had been so far isolated from the same fungi.[4] The absolute configuration of these acids at C-1 was estimated to be (1S) by a biosynthetic study and CD spectrum analysis.[5] The (13R)-configuration of trisporic acid C (5) has been established by degradation.[6]



1: R=H 2: R=Me



3: R=H 4: R=Me

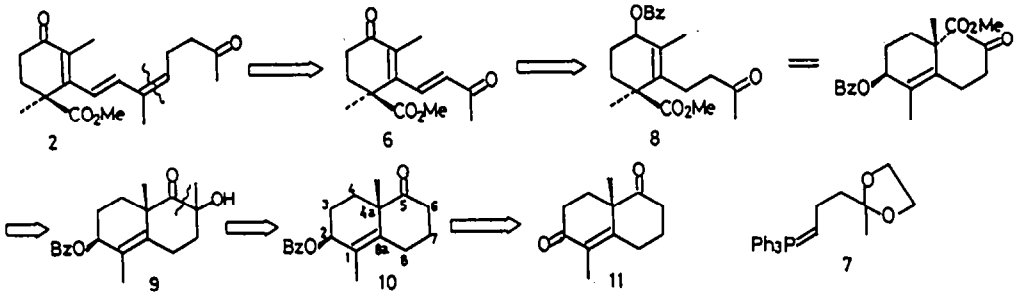


5 (also 9Z)

These intriguing biological activities have attracted many organic chemists.[7] The first synthesis of (±)-(7E,9E)-methyl trisporate B (4) by J. A. Edwards et al. revised the earlier stereochemical assignment at C-9 of trisporic acids[7a] and then many synthetic studies of racemic trisporic acids had been so far reported.[7] However their chiral forms have not yet been synthesized. In this paper, we describe the details of the chiral synthesis of (+)-methyl trisporates B (2 and 4) to confirm the absolute configuration of C-1.[8] As the

stereochemistry of **2** has been shown to be (1S)[5] we chose the chiral (+)-(8aS)-enedione (**11**) as the starting material. Our synthetic strategy is outlined in Scheme 1.

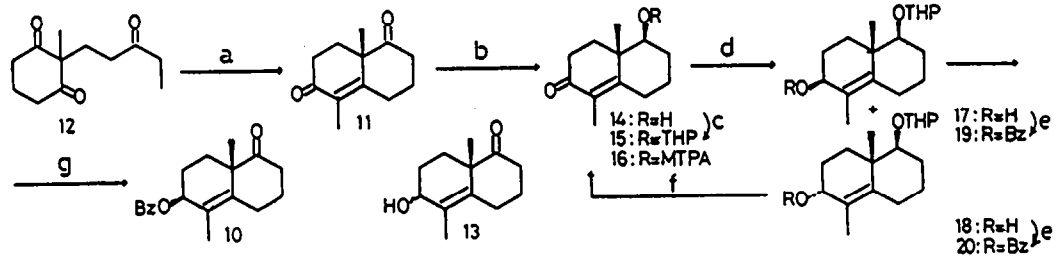
Scheme 1



Wittig reaction of the dioxoester (±)-**6** with the phosphonium ylide (**7**) has already been reported to produce (±)-methyl trisporates B (**2** and **4**).[7b] So, in order to accomplish the synthesis of (+)-methyl trisporates B (**2** and **4**), we planned to synthesize **6** in chiral form. In elaboration of side chain in **6**, the presence of keto group in the cyclohexene ring is an obstacle. Thus the oxoester **8**, in which the ring ketone is modified to benzoate ester, would be visualized as a synthetic precursor of **6**. Compound **8** may be derived by oxidative cleavage of the acyloin **9**, which would be synthesized from chiral enedione **11** via oxobenzoate **10**.

Our synthetic work began with the preparation of (-)-2,3,4,4a,5,6,7,8-octahydro-1,4a-dimethyl-5-oxo-2-naphthyl benzoate (**10**) from optical active enedione **11**. (Scheme 2).

Scheme 2



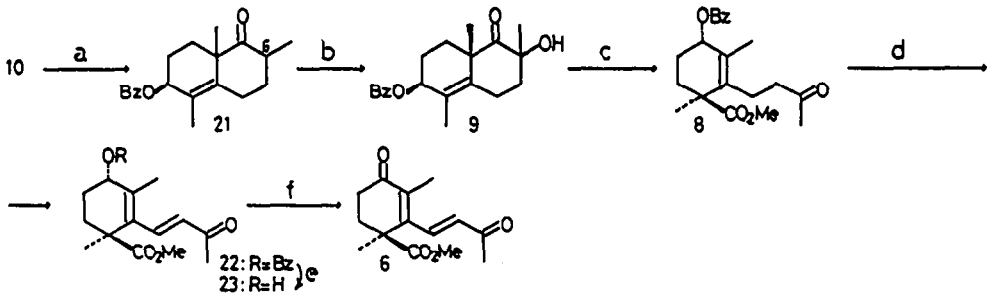
(a) L-phenylalanine, d-CSA, DMF; (b) $NaBH_4$, EtOH; (c) DHP, PPTS, CH_2Cl_2;
(d) LAH, ether, -75°C; (e) BzCl, Pyr; (f) MnO_2, CH_2Cl_2;
(g) (1) p-TsOH, MeOH; (2) PCC, CH_2Cl_2

The chiral starting material **11** had already been synthesized from the triketone **12** using L-proline pyrrolidine amide by Yamada *et al.*[9] however, the optical purity of the resulting enedione **11** was 63% enantiomeric excess (e.e.). Also, Uda *et al.* reported the synthesis of Wieland-Miesher ketone analogues bearing an angular protected hydroxymethyl group in high chemical and optical yields by the use of chiral amino acid and d-camphorsulfonic acid (d-CSA) in dimethylformamide (DMF).[10] Thus, we adopted Uda's method to synthesize **11**. The triketone **12** was treated with L-phenylalanine and d-CSA in DMF to give the (+)-enedione **11** in a good yield. The optical purity of **11** was determined by the α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA)[11] **16** of the hydroxyenone as follows. As the preparation of oxoallylalcohol **13** by regioselective reduction of **11** was unsuccessful, we employed the stepwise procedure to obtain the oxobenzoate **10**.

The saturated carbonyl group of **11** was selectively reduced with sodium borohydride in ethanol to afford the hydroxyenone **14** in a 90% yield.[12] The optical purity of **14** was determined to be more than 94% e.e. by the ^{1}H-NMR analysis of its MTPA ester **16**. The hydroxyl group of **14** was protected with 2,3-dihydropyran in the presence of pyridinium p-toluenesulfonate (PPTS)[13] in methylene chloride to convert into the THP-ether **15** almost quantitatively. The unsaturated carbonyl group of **15** was stereoselectively reduced with lithium aluminum hydride in ether at -75 °C to provide a mixture of β- and α-alcohols (**17** and **18**) (ca. 9:1 ratio), which was separated into each isomer by silica gel chromatography. On the other hand, the use of the other reducing agent (e.g. DIBAL-H, L-Selectride etc.) lowered the selectivity. The stereochemistry of these alcohols could be estimated by the precedent[14] and also assigned by an ^{1}H-NMR analysis of their benzoate derivatives (**19** and **20**), which were prepared from each alcohol (**17** and **18**) by treatment with benzoyl chloride in pyridine respectively. The ^{1}H-NMR spectrum of **19** showed peaks at δ 1.14 (3H, s) and 5.50 (1H, brt, $W_{h/2}$ = 14 Hz), whilst **20** showed 1.07 (3H, s) and 5.39 ppm (1H, brs, $W_{h/2}$ = 6 Hz). These results indicate the β-pseudoequatorial orientation of the hydroxyl group of the major product **17**. Though the inversion of **18** into **19** by Mitsunobu method[15] was unsuccessful, the minor alcohol **18** could be returned to the starting enone **14** by oxidation with MnO_2 in methylene chloride quantitatively. The THP-oxy group of **17** was hydrolyzed with small excess of p-toluenesulfonic acid (p-TsOH) in methanol to give the hydroxybenzoate, which was oxidized with pyridinium chlorochromate (PCC)[16] in methylene chloride to afford the oxobenzoate (**10**) as white crystal in a 81% yield from **17**.

Next, our attention turned to the functionalization of oxobenzoate (**10**) toward the β-ionone type derivative (**6**). (Scheme 3).

Scheme 3



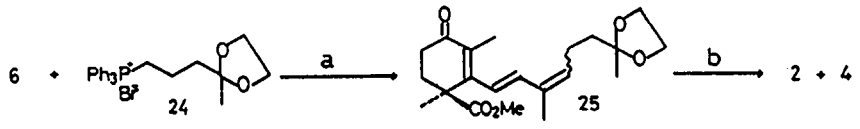
(a) LDA, CH_3I, -78~0°C; (b) NaH, $(EtO)_3P$, O_2, t-BuOH, THF, DMF; (c) LTA, benzene, MeOH; (d) (1) PhSeCl; H^+; (2) H_2O_2, CH_2Cl_2; (e) NaOH, MeOH; (f) MnO_2, CH_2Cl_2

Methylation of **10** with lithium diisopropyl amide (LDA) and methyl iodide in tetrahydrofuran (THF) at -78 °C provided the methyl ketone (**21**) as an epimeric mixture in an 87% yield (ratio, ca. 1:1, by ^{1}H-NMR analysis). The construction of a quaternary carbon center by hydroxylation at C-6 position of **21** was achieved by autooxidation according to Gardner et al..[17] Thus, the methyl ketone **21** was treated with t-BuONa in THF and DMF to convert the corresponding sodium enolate, which was treated with oxygen in the presence of triethyl phosphite at -20 °C to afford the acyloin **9** as a stereoisomeric mixture in an 88% yield. As these isomers could not be separated, the mixture was, without separation, subjected to ring cleavage. In order to elaborate the β-ionone framework, **9** was treated with lead tetraacetate in benzene-methanol[18] to give methyl ketone **8** in a 77% yield. Dehydrogenation of the side chain of **8** was accomplished

by Sharpless's procedure[19] as follows. The methyl ketone 8 was reacted with phenylselenenyl chloride in the presence of a catalytic amount of conc. HCl in ethyl acetate to give crude selenide, which was oxidized with 15% hydrogen peroxide (H_2O_2) to afford an (E)-olefin 22 as a sole product in a 57% yield from 8. Selective hydrolysis of the benzoyloxy group of 22 with sodium hydroxide in methanol yielded the allylic alcohol 23, which was oxidized with MnO_2 in methylene chloride to provide a desired diketone 6 in an 85% yield from 22. The spectral data of (+)-6 was consistent with those of reported racemic 6.[7b] Also, the optical purity of 6 was determined to be more than 94% e.e. by ^{1}H-NMR analysis using a chiral shift reagent (Eu(hfc)$_3$).

At this stage, the synthesis of methyl trisporates B (2 and 4) was formally complete,[7b] but the absolute configuration of the target molecule (2 and 4) had not been confirmed. Therefore, following Isoe's procedure,[7b] 6 was converted to 2 and 4. (Scheme 4).

Scheme 4



(a) n-BuLi, THF, -20°C; (b) HCl

A regioselective Wittig reaction of 6 with the ylide generated from 3-(2-methyl-1,3-dioxolan-2-yl)propyltriphenylphosphonium bromide 24[20] and n-BuLi in THF at -20°C gave a mixture of trisporate acetals (25),(9Z:9E = ca. 3:1 by ^{1}H-NMR analysis), which was separated into each component by preparative TLC and then each acetal was treated with dil. HCl in aq. THF to afford (+)-methyl trisporate B (2, $[\alpha]_D^{21}$ +16.7°) and its 9E isomer (4, $[\alpha]_D^{21}$ +21.7°). The spectral data for synthetic samples (2 and 4) were identical with the reported one.[1,7] The optical rotation of natural methyl trisporate B, which is estimated to be a mixture of the (9Z) and (9E) forms, has been reported to be $[\alpha]_D^{21}$ +39°.[1a] Though the optical rotation of synthetic methyl esters (2 and 4) is small relative to those of natural product, the absolute configuration of natural trisporic acids at C-1 was synthetically established.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a JASCO IR-810 infrared spectrometer. ^{1}H-NMR (100 MHz) spectra were measured on a JEOL JNM-FX-100 spectrometer with TMS as an internal standard. High resolution mass spectra were obtained with a JEOL JMS DX-300 mass spectrometer. Thin-layer chromatography (TLC) was performed on a silica gel (Merck 60 PF_{254}, 0.5 mm thickness). Optical rotations were measured on a Jasco DIP-4 spectrometer. Gas chromatographic (GLC) analyses were performed on a Yanaco G-3800 instrument with a flame ionization detector, using a 2 m x 3 mm stainless steel column packed with 10% silicone SE-30 on chromosorb W (N_2 flow rate: 30 ml/min).

(+)-(8aS)-3,4,8,8a,Tetrahydro-5,8a-dimethyl-1,6(2H,7H)-naphthalenedione (11). To a stirred solution of 12 (12.4 g, 59 mmol) in DMF (312 ml) was added L-phenylalanine (9.8 g, 59 mmol) and d-CSA (6.9 g, 30 mmol). The mixture was stirred at room temperature for 94 h and then at 40~50 °C for 21 h under argon. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with sat. $NaHCO_3$ soln., water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel chromatography (CH_2Cl_2:EtOAc = 15:1) to give 11 (9.7 g, 86%) as an oil. $[\alpha]_D^{21}$ +124° (c = 0.96, $CHCl_3$). IR ν_{max} ($CHCl_3$) cm^{-1}:1710, 1670, 1610. ^{1}H-NMR ($CDCl_3$) δ : 1.43 (3H, s), 1.82 (3H, d, J = 1.22 Hz), 1.68~3.10 (10H, m). This oil was crystallized in hexane at ice bath cooling to give needles, mp 46~47 °C.

(+)-(4aS,5S)-4,4a,5,6,7,8-Hexahydro-5-hydroxy-1,4a-dimethyl-2(3H)-naphthalenone (14).
To a stirred solution of 11 ($[\alpha]_D^{21}$ +124° (c = 0.96, $CHCl_3$), 783 mg, 4.1 mmol) in ethanol (4.7 ml) was added dropwise a solution of $NaBH_4$ (42 mg, 1.1 mmol) in ethanol (10 ml) at ice bath cooling under nitrogen. After an additional stirring for 5 min the excess hydride was decomposed by addition of acetic acid (0.1 ml). The reaction mixture was concentrated in vacuo and the residue was treated with CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with water and brine, and dried ($MgSO_4$). Evaporation of the solvent followed by silica gel chromatography (CH_2Cl_2:EtOAc = 2:1) of the residue afforded 14 (712 mg, 90%) as an oil. $[\alpha]_D^{21}$ +165° (c = 3.27) (lit.[12] $[\alpha]_D$ +162.6° (c = 2.17)). IR ν_{max} (film) cm^{-1}: 3430, 1660, 1605, 1060, 990. ^{1}H-NMR ($CDCl_3$) δ:1.19 (3H, s), 1.77 (3H, s), 1.27~2.77 (11H, m), 3.45 (1H, m).

(4aS,5S)-4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-5-tetrahydropyranyloxy-2(3H)-naphthalenone (15).
To a stirred solution of 14 (6.8 g, 35 mmol) and 2,3-dihydropyran (5.8 g, 69 mmol) in CH_2Cl_2 (100 ml) was added PPTS (1.8 g, 7.1 mmol). The mixture was stirred at room temperature under nitrogen for 4.5 h and then diluted with ether. The ethereal solution was washed with sat. $NaHCO_3$ soln., water and brine, dried ($MgSO_4$) and evaporated. Chromatography of the residual oil on silica gel with hexane-EtOAc (3:1) gave 15 (9.5 g, 98%) as an oil. IR ν_{max}(film) cm^{-1}: 1670, 1610, 1135, 1120, 1030, 1000, 905. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H x 2, s), 1.78 (3H x 2, s), 1.38~2.76, (30H, m), 3.17~3.62 (4H, m), 3.76~4.16 (2H,m), 4.59 (1H, brs), 4.74 (1H, brs), 3.89 (1H x 2, m). Anal. Found: C, 72.94; H, 9.69. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41%.

(2S,4aS,5S)- and (2R,4aS,5S)-2,3,4,4a,5,6,7,8-Octahydro-1,4a-dimethyl-5-tetrahydropyranyloxy-2-naphthols (17 and 18).
To a stirred suspension of $LiAlH_4$ (1.42 g, 37 mmol) in ether (150 ml) was added dropwise a solution of 15 (9.2 g, 33 mmol) in ether (10 ml) at -75 °C under nitrogen. The mixture was stirred at the same temperature for 1 h and then 2.8 ml of sat. NH_4Cl soln. was added to the reaction mixture. The mixture was filtered and the filter cake was washed with ether exhaustively. The combined filtrate and washings were concentrated in vacuo. The residue was chromatographed over silica gel (hexane:EtOAc = 4:1) to give 17 (8.3 g) as an oil and 18 (0.9 g) as a solid (99% yield).
17: IR ν_{max}($CHCl_3$) cm^{-1}: 3400, 1657, 1135, 1118, 1030, 1005, 900. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H x 2, s), 1.72 (3H x 2, s), 1.20~2.09 (32H, m), 2.30~2.60 (2H, m), 3.07~3.62 (4H, m), 3.80~4.14 (2H x 2, brs), 4.55 (1H, brs), 4.69 (1H, brs). Anal. Found: C, 72.52; H, 10.09. Calcd. for $C_{17}H_{28}O_3$: C, 72.86; H, 10.06%.
18: mp: 120~122°C. IR ν_{max}($CHCl_3$) cm^{-1}: 3400, 1658, 1135, 1118, 1035, 1008, 985. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H x 2, s), 1.76 (3H x 2, s), 1.21~2.10 (32H, m), 2.30~2.60 (2H, m), 3.07~3.57 (4H, m), 3.80~4.10 (2H x 2, brs), 4.60 (1H, brs), 4.72 (1H, brs). Anal. Found: C, 72.79; H, 10.33. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06%.

Oxidation of 18 with MnO_2.
To a solution of 18 (560 mg, 2 mmol) in CH_2Cl_2 (3 ml) was added MnO_2 (4.5 g) and the mixture was shaken under nitrogen at room temperature for 7 h and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to give an oil, which was purified by silica gel chromatography (CH_2Cl_2) to afford 15 (550 mg, 99%).

(2S,4aS,5S)-2,3,4,4a,5,6,7,8-Octahydro-1,4a-dimethyl-5-tetrahydropyranyloxy-2-naphthyl benzoate (19).
To a stirred solution of 17 (8.3 g, 30 mmol) in pyridine (40 ml) was added benzoyl chloride (5.0 g, 36 mmol) at ice bath cooling under nitrogen and the mixture was stirred for 12 h. The reaction mixture was poured into ice-water and the mixture was vigorously stirred. The resulting mixture was extracted with ether. The ethereal solution was washed with sat. $CuSO_4$ soln., sat. $NaHCO_3$ soln., water and brine, and dried ($MgSO_4$). Evaporation of the solvent gave a residual oil, which was chromatographed on alumina with CH_2Cl_2 to give 19 (11.2 g, 98%) as an oil. IR ν_{max}($CHCl_3$) cm^{-1}: 3070, 1718, 1603, 1585, 1270, 1115, 1030, 715. ^{1}H-NMR ($CDCl_3$) δ : 1.14 (3H x 2, s), 1.66 (3H x 2, s), 1.26~2.07 (30H, m), 2.30~2.62 (2H, m), 3.13~3.57 (4H, m), 3.80~4.01 (1H x 2, m), 4.57 (1H, brs), 4.71 (1H, brs), 5.50 (1H x 2, brt, $W_{h/2}$ = 14 Hz), 7.33~7.63 (3H x 2), 8.02~8.11 (2H x 2). Anal. Found: C, 74.91; H, 8.22. Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39%.

(2R,4aS,5S)-2,3,4,4a,5,6,7,8-Octahydro-1,4a-dimethyl-5-tetrahydropyranyloxy-2-naphthyl benzoate (20).
To a stirred solution of 18 (45 mg, 0.16 mmol) in pyridine (1 ml) was added

dropwise benzoyl chloride (22 μl, 0.19 mmol) at ice bath cooling under nitrogen and the mixture was stirred for 3 h. **20** (60 mg, 98%) was obtained under condition similar to those described above. IR ν_{max}(CHCl$_3$) cm^{-1}: 3060, 1718, 1605, 1585, 1270, 1110, 1070, 1030, 715. ^{1}H-NMR (CDCl$_3$) δ: 1.07 (3H x 2, s), 1.69 (3H x 2, s), 1.19∿2.10 (30H, m), 2.36∿2.64 (2H, m), 3.16∿3.54 (4H, m), 3.80∿4.10 (1H x 2, m), 4.65 (1H, brs), 4.77 (1H, brs), 5.39 (1H x 2, brs, $W_{h/2}$ = 5.7 Hz), 7.33∿7.68 (3H x 2), 8.02∿8.12 (2H x 2). Anal. Found: C, 75.11; H, 8.48. Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39%.

(-)-(2S,4aS)-2,3,4,4a,5,6,7,8-Octahydro-1,4a-dimethyl-5-oxo-2-naphthyl benzoate (10).
To the strirred solution of the benzoate **19** (521 mg, 1.36 mmol) in aq. methanol (20 ml) was added p-TsOH (51 mg, 0.27 mmol) at room temperature and the mixture was stirred for 6 h. To the mixture was added powdered $NaHCO_3$ and the resulting mixture was concentrated *in vacuo*. The residue was treated with water-EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine, dried ($MgSO_4$). Evaporation of the solvent gave the alcohol, which was used in the next reaction without further purification. A pure sample was obtained by silica gel chromatography (hexane:EtOAc = 4:1). mp 108.5∿109.5°C. IR ν_{max}(KBr) cm^{-1}: 3520, 3420, 1713, 1697, 1598, 1580, 1278, 1260, 1110, 990, 710. ^{1}H-NMR (CDCl$_3$) δ: 1.12 (3H, s), 1.68 (3H, s), 1.28∿2.20 (10H, m), 2.40∿2.66 (1H, m), 3.32 (1H, m), 5.50 (1H, brt, $W_{h/2}$ = 12.8 Hz), 7.33∿7.56 (3H), 9.01∿8.11 (2H). Anal. Found: C, 75.72; H, 8.35. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05%.
This crude alcohol (ca. 400 mg) was dissolved in CH_2Cl_2(3 ml) and this solution was added to a stirred suspension of PCC (440 mg, 2.04 mmol) in CH_2Cl_2(2 ml) under nitrogen. The mixture was stirred for 2.5 h at room temperature, diluted with ether, and passed through a column of florisil. The column was washed with ether. The filtrate and washings were combined and concentrated under reduced pressure. The oily residue was purified by silica gel chromatography (hexane:EtOAc = 4:1) to give **10** (329 mg, 81%), which crystallized on standing in a refrigerator. Recrystallization from hexane-ether gave white plates. mp 39∿40°C. $[\alpha]_D^{21}$ -37.2° (c = 1.00, $CHCl_3$). IR ν_{max} (KBr) cm^{-1}: 3000, 1712, 1272, 1110, 1003, 723, ^{1}H-NMR (CDCl$_3$) δ: 1.38 (3H, s), 1.72 (3H, brs), 1.40∿2.90 (10H, m), 5.44 (1H, brs, $W_{h/2}$ = 14.3 Hz), 7.34∿7.57 (3H), 8.01∿8.11 (2H). Anal. Found: C, 76.30; H, 7.53. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43%.

(2S,4aS,6RS)-2,3,4,4a,5,6,7,8-Octahydro-1,4a-dimethyl-5-oxo-2-naphthyl benzoate (21).
To a stirred solution of diisopropylamine (0.283 ml, 2.02 mmol) and trace amount of 2,2'-dipyridyl in THF (18 ml) was added dropwise a 1.6 M solution of n-BuLi in hexane (1.3 ml, 2.02 mmol) at -70°C under nitrogen. The mixture was stirred for 30 min. A solution of **10** (464 mg, 1.56 mmol) in THF (3 ml) was added dropwise to a stirred LDA solution at -70°C and the mixture was stirred for 30 min, and then the reaction temperature was gradually raised to -40°C. Methyl iodide (0.194 ml, 3.11 mmol) was added to the above solution and then the reaction temperature was gradually raised to -10°C and the mixture was stirred at -10∿0°C for 1.1 h. The reaction was quenched with aq. NH_4Cl solution and the resulting mixture was extracted with ether. The extract was washed with water and brine and dried ($MgSO_4$). Evaporation of the solvent gave a residual oil, which was purified with silica gel chromatography (hexane:EtOAc = 6:1) to give **21** (425 mg, 87%) as a diastereomeric mixture (ratio, ca. 1:1, ^{1}H-NMR analysis) and **10** (49 mg).
21: IR ν_{max} (film) cm^{-1}: 3070, 1715, 1603, 1270, 1113, 715. ^{1}H-NMR (CDCl$_3$) δ: 1.05 (3H, d, J = 6.6 Hz), 1.07 (3H, d, J = 6.4 Hz), 1.30 (3H, s), 1.40 (3H, s), 1.71 (3H x 2, brs), 1.30∿2.93 (18H, m), 5.38∿5.50 (1H x 2), 7.39∿7.65 (3H x 2), 8.01∿8.11 (2H x 2). Anal. Found: C, 77.24; H, 8.00. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74%.

(2S,4aS,6RS)-2,3,4,4a,5,6,7,8-Octahydro-6-hydroxy-1,4a,6-trimethyl-5-oxo-2-naphthyl benzoate (9).
To a stirred solution of NaH (55 mg, 1.36 mmol) in the presence of triethyl phosphite (0.22 ml, 1.28 mmol) in a mixture of t-BuOH (0.58 ml) and DMF (3 ml) was added dropwise the methyl ketone **21** (327 mg, 1.05 mmol) in THF (3 ml) at -18∿-20°C under nitrogen and then O_2 was passed through the above solution for 3 h at the same temperature. AcOH (0.3 ml) was added to the reaction mixture at -15°C with vigorous stirring and then the resulting mixture was poured into water. The mixture was extracted with ether, and the extract was washed with aq. $NaHCO_3$ soln., water and brine, dried ($MgSO_4$). Evaporation of the solvent gave an oil, which was purified with silica gel chromatography (hexane:EtOAc = 4:1) to afford **9** (303 mg, 88%) as a diastereomeric mixture and **21** (9 mg).
9: IR ν_{max} ($CHCl_3$) cm^{-1}: 3490, 1715, 1270, 1110, 713. ^{1}H-NMR (CDCl$_3$) δ: 1.25 (3H, s), 1.39 (3H, s), 1.41 (3H, s), 1.50 (3H, s), 1.71 (3H x 2, brs), 1.60∿2.88 (18H, m), 5.46 (1H x 2), 7.35∿7.69 (3H x 2), 8.01∿8.17 (2H x 2). Anal. Found: C, 73.19; H, 7.40; Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37%.

(1S,4S)-Methyl 4-benzoyloxy-1,3-dimethyl-2-(3-oxobutyl)-2-cyclohexenecarboxylate (8).
To a stirred solution of 9 (218 mg, 0.66 mmol) in a mixture of benzene (12 ml) and methanol (3 ml) was added lead tetraacetate (884 mg, 1.99 mmol) in a 5 portions at room temperature under nitrogen and then the mixture was stirred at 40°C for 4h and concentrated in vacuo. The residue was treated with water and the mixture was extracted with ether. The extract was washed with aq. $NaHCO_3$ soln., water and brine, and dried ($MgSO_4$). Evaporation of the solvent gave a residual oil, which was chromatographed on silica gel (benzene:EtOAc = 4:1) to give 8 (183 mg, 77%) as an oil.
8: $[\alpha]_D^{21}$ -119° (c = 0.53, $CHCl_3$). IR ν_{max}($CHCl_3$) cm^{-1}: 3070, 1730, 1718, 1270, 1070, 1110, 715. ^{1}H-NMR ($CDCl_3$) δ:1.40 (3H, s), 1.72 (3H, s), 2.15 (3H, s), 1.70~2.70 (8H, m), 3.68 (3H, s), 5.48 (1H, brt), 7.35~7.66 (3H), 8.00~8.10 (2H). Anal. Found: C, 70.22; H, 7.55. Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31%.

(1S,4S)-Methyl 4-benzoyloxy-1,3-dimethyl-2-(3-oxo-1E-butenyl)-2-cyclohexene-1-carboxylate (22).
To a stirred solution of 8 (122 mg, 0.34 mmol) and phenylselenenyl chloride (79 mg, 0.41 mmol) in EtOAc (5.6 ml) was added 2 drops of conc. HCl soln. at room temperature and the mixture was stirred for 1.6 h, and then concentrated in vacuo. The residue was purified with preparative TLC (hexane:EtOAc = 3:1) to give crude selenide (107 mg) and 8 (23 mg). This crude selenide (107 mg, ca. 0.21 mmol) was dissolved in a mixture of CH_2Cl_2 (1.2 ml) and pyridine (39 μl). To an above solution was added dropwise 15% H_2O_2 solution (475 μl, ca. 2.1 mmol) with vigorous stirring in an ice bath and the mixture was stirred for 30 min at the same temperature. The cooling bath was removed and stirring was continued at room temperature for 2 h. The mixture was poured into water and the resulting mixture was extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$). Evaporation of the solvent gave an oil, which was purified with preparative TLC (hexane:EtOAc = 2:1) to afford 22 (69 mg, 57% from 8) $[\alpha]_D^{21}$ -40.2° (c = 0.13, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3060, 1717, 1690, 1595, 1590, 1263, 1250, 1105, 975, 710. ^{1}H-NMR δ: 1.47 (3H, s), 1.95 (3H, s), 1.57~2.20 (4H, m), 2.30 (3H, s), 3.70 (3H, s), 5.62 (1H, brt), 6.08 (1H, d, J = 17 Hz), 7.38 (1H, d, J = 17 Hz), 7.36~7.60 (3H), 8.01 (2H). UV λ_{max} (EtOH) nm (ε): 281 (10100), 230 (12100). Anal. Found: C, 70.06; H, 7.11. Calcd. for $C_{21}H_{24}O_5$: C, 70.76; H, 6.79%.

(+)-(S)-Methyl 1,3-dimethyl-4-oxo-2-(3-oxo-1E-butenyl)-2-cyclohexene-1-carboxylate (6).
To a stirred solution of 22 (31 mg, 0.087 mmol) in methanol (3 ml) was added 5% NaOH solution (0.31 ml) in ice bath under nitrogen. The mixture was stirred at the same temperature for 2 h and then at room temperature for an additional 1.5 h. The resulting mixture was concentrated in vacuo and the residue was treated with water-EtOAc. Organic layer was separated and aqueous layer was extracted with EtOAc exhaustively. The organic layer was combined and washed with water and brine, dried ($MgSO_4$). Evaporation of the solvent gave a crude alcohol 23 (22 mg). 23: IR ν_{max} ($CHCl_3$) cm^{-1}: 3420, 1725, 1660, 1635, 1603, 1595, 1255, 975. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, s), 1.50~2.00 (5H, m), 2.02 (3H, brs), 2.27 (3H, s), 3.67 (3H, s), 4.17 (1H, brs), 6.01 (1H, d, J = 17 Hz), 7.36 (1H, d, J = 17 Hz). Anal. Found: C, 66.66; H, 8.08. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99%.
The above crude alcohol 23 (22 mg, 0.087 mmol) was dissolved in CH_2Cl_2 (3 ml) and active MnO_2 (220 mg) was added to this solution. The mixture was shaken under nitrogen at room temperature for 2.5 h and then filtered through a pad of Celite, which was washed with EtOAc exhaustively. The filtrate and washings were combined and concentrated in vacuo. The oily residue was purified by preparative TLC (hexane:EtOAc = 2:1) to give 6 (18 mg, 83% from 22) as a light yellow oil. $[\alpha]_D^{21}$ +14.0° (c = 1.00, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1730, 1695, 1672, 1610, 1595, 1250, 978. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, s), 1.95 (3H, s), 2.33 (3H, s), 1.78~2.64 (4H, m), 3.72 (3H, s), 6.23 (1H, d, J = 17 Hz), 7.36 (1H, d, J = 17 Hz). UV λ_{max} (EtOH) nm (ε): 291 (11100), 217 (6100). Anal. Found: C, 67.08; H, 7.54. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

(+)-(7E,9Z)-Methyl trisporate B (2) and (+)-(7E,9E)-methyl trisporate B (4).
To a stirred suspension of 24 (156 mg, 0.33 mmol) in THF (2 ml) was added dropwise a 1.6 M solution of n-BuLi in hexane (0.2 ml, 0.31 mmol) at -18°C under argon and then the mixture was stirred for 45 min. To the above solution was added dropwise a solution of 6 (32 mg, 0.13 mmol) in THF (1 ml) at -20~-18°C with stirring and then the mixture was stirred for 1 h. The mixture was poured into cold NH_4Cl solution and the resulting mixture was extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$). Evaporation of the solvent gave an yellow oil, which was purified with preparative TLC (cyclohexane:EtOAc = 3:1) to give 25 (33 mg, (9Z):(9E) = ca. 3:1, ^{1}H-NMR analysis, 71%) and 6 (7 mg). The acetals 25 were separated by preparative TLC ($CHCl_3$:acetone = 40:1) into each isomer, which was respectively treated with dil. HCl in THF, and then purified by preparative TLC (hexane:EtOAc = 1:1) under nitrogen in

the dark to afford 2 and 4.
2: $[\alpha]_D^{21}$ +16.7° (c = 0.44, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1730, 1663, 1595, 1355, 1250, 970. ^1H-NMR ($CDCl_3$) δ: 1.56 (3H, s), 1.86 (3H, s), 1.96 (3H, s), 2.16 (3H, s), 2.00∿2.64 (8H, m), 3.70 (3H, s), 5.51 (1H, brt, J = 6.4 Hz), 6.38 (1H, d, J = 16 Hz), 6.80 (1H, d, J = 16 Hz). UV λ_{max} (EtOH) nm: 327, 232. High MS. Found: M^+ 318.18218. Calcd. for $C_{19}H_{26}O_4$: M^+ 318.18298. GLC t_R: 26.7 min (column temp., 200 C).
4: $[\alpha]_D^{21}$ +21.7° (c = 0.23, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1730, 1663, 1598, 1355, 1250, 970. ^1H-NMR ($CDCl_3$) δ: 1.51 (3H, s), 1.81 (3H, s), 1.94 (3H, s), 2.16 (3H, s), 2.00∿2.62 (8H, m), 3.68 (3H, s), 5.56 (1H, brt, J = 6.1 Hz), 6.28 (2H, s). UV λ_{max} (EtOH) nm: 321, 232. High MS. Found: M^+ 318.18280. Calcd. for $C_{19}H_{26}O_4$: M^+ 318.18298. GLC t_R: 33.4 min (column temp. 200 °C).

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