Synthesis of (+)-Methyl Phaseate and Its Isomer from (−)-β-Pinene

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The total synthesis of (+)-methyl phaseate (2b) and its epimer (25) is described. The known β-ketoester (8), which was prepared from (−)-β-pinene (4), was converted to a key intermediate (5) *via* a 1,4-dioxoester (7). The reaction of 5 with a lithium reagent of the acetylene TBDMS ether (6) in THF–HMPA at −70°C afforded the desired acetylene alcohol (17) and its epimer (18) in high yields. 17 was transformed into (+)-methyl phaseate (2b). From this synthetic work, the absolute configuration of natural (−)-phaseic acid (2a) was confirmed.

As the result of a wide chemical study of the natural plant hormone abscisic acid (**1**, ABA),[1] some metabolites[2] of **1** have been so far isolated from higher plants. Among them, (−)-phaseic acid (**2a**) as a typical metabolite was first isolated from the immature seed of *Phaseolus multiflorus* by MacMillan *et al.*,[3] and the occurrence of **2a** has been now verified in several other plants.[4] The metabolite (**2a**) is estimated to be biosynthetically derived from the first oxidation product of ABA (**1**), metabolite C (**3**), which is easily converted to **2a** or **2b** by heating or methylation.[5] The unique biological activity of **2a** in connection with ABA (**1**), especially the stomatal closing effect on plants, seems very interesting.[6] The relative stereochemistry of (−)-**2a** was proved by Milborrow[7] and Sakan *et al.*[8] as shown in Fig. 1, and this result was also supported by our synthetic study.[9] After completing the total synthesis of (±)-methyl phaseate (**2b**) and its isomers, we have undertaken the chiral synthesis of **2b**.

In this paper, we describe the total synthesis of an enantiomer (+)-**2b**, from readily available, inexpensive (−)-β-pinene (**4**) to confirm the absolute configuration of natural (−)-**2a**.[10]

The retrosynthetic plan is shown in Scheme 1. We divided target molecule **2b** into its cyclohexane moiety and side chain unit, which could possibly be synthesized from the substituted cyclohexenone (**5**) and acetylenic *t*-butyldimethylsilyl (TBDMS) ether (**6**), respec-

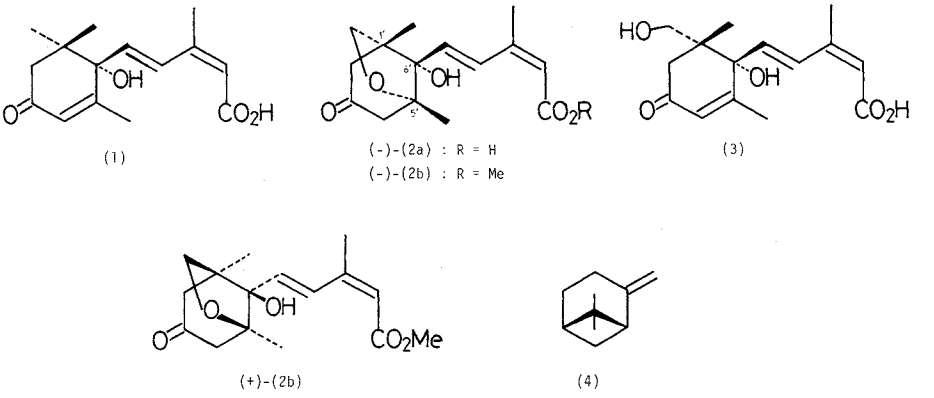
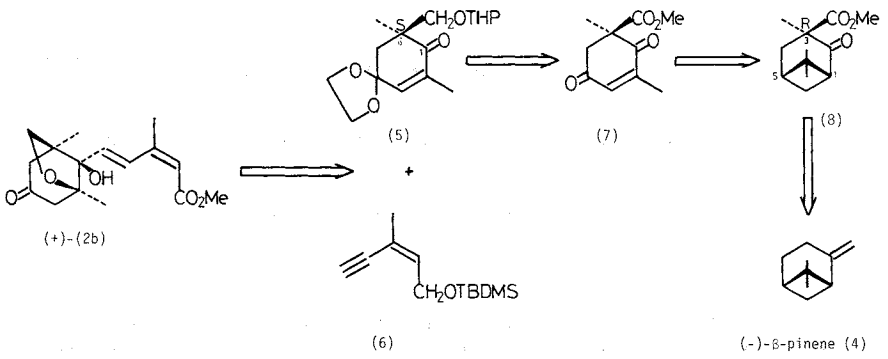
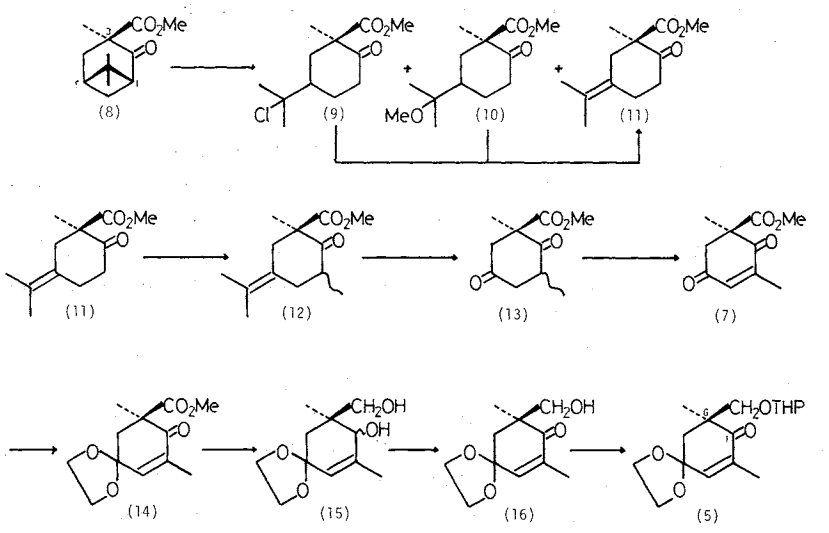


Fig. 1.



Scheme 1.



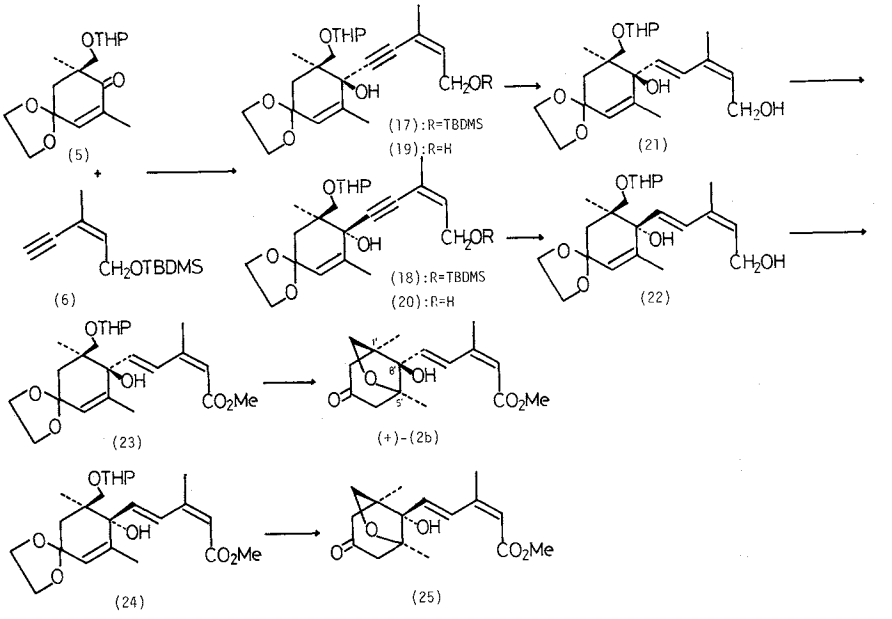
Scheme 2.

tively. The central problem in this synthesis was to secure the chiral oxoacetal (**5**) possessing a quaternary carbon center. The oxoacetal (**5**) seemed to be derived from the 1,4-dioxoester (**7**), which could be expected to be synthesized by acidic cyclobutane ring opening of the oxoester (**8**) followed by functionalization. The absolute configuration (1*R*, 3*R*, 5*R*) of the oxoester (**8**) has already been established.[11] Therefore, we undertook to transfer the chirality of 3*R* in **8** to that of 6*S* in **5**.

The β-oxoester **8**, which was synthesized from (−)-β-pinene (**4**) in 3 steps by Torii's method,[11] was subjected to acid catalyzed cleavage of the cyclobutane ring with dry HCl gas in methanol to give a mixture of three oxoesters, chloro ester (**9**), methoxy ester (**10**) and the expected isopropylidene ester (**11**), in a ratio of 2 : 2 : 1 in an almost quantitative yield. Although the desired ketoester (**11**) could be separated by silica gel chromatography, the mixture was directly subjected to a treatment with silica gel in chloroform[13] to afford the isopropylidene oxoester (**11**) in a 67% overall yield from **8**. Methylation of **11** with lithium diisopropylamide (LDA) and methyl iodide in tetrahydrofuran (THF) at −78 ~ 0°C provided methyl ketone **12** as an epimeric mixture. In order to elaborate the oxygen function at the C(5) position, **12** was treated with ozone in methanol at −70°C and followed by a subsequent reductive work up with dimethyl sulfide to give 1,4-dioxoester (**13**) in a good yield. Dehydrogenation of the cyclohexane ring of **13**

was accomplished by Sharpless's method as follows[14]: the dioxoester (**13**) was reacted with phenylselenenyl chloride in ethyl acetate, and the resulting selenide was immediately oxidized with hydrogen peroxide in the presence of pyridine to afford an enone (**7**) as the sole product in a 79% yield from **13**. Spectral data supported the proposed structure for compound (**7**). Next, selective monoacetalization of **7** with methyl orthoformate and ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid in ether gave a monoacetal (**14**). Lithium aluminum hydride reduction of **14** afforded crystalline diol **15**, which was found to decompose easily to a highly polar substance during purification (*e.g.* recrystallization, silica gel chromatography). Therefore, the crude diol was directly oxidized with MnO_2 in methylene chloride to give the hydroxy oxoacetal (**16**) in a 78% overall yield from **7**. The primary hydroxyl group of **16** was protected with 2,3-dihydropyran in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS)[15] to convert to the tetrahydropyranyl ether (**5**), whose spectral data were identical with those of racemic **5**.[16]

The remaining task in the present study was the introduction of a side chain unit into the C-1 ketone group in **5**. We found that the reaction of **5** with the Grignard reagent of acetylene TBDMS ether (**6**) was not satisfactory because it proceeded slowly and a considerable amount of starting acetal **5** was recovered. On the other hand, while the reaction of **5** with the lithium derivative of **6** in THF at −20°C afforded a 1:2.2 mixture of the desired alcohol **17** (30%) and the undesired one **18** (67%), replacement of the solvent with a THF-hexamethylphosphoramide (HMPA) mixture at −70°C improved the selectivity (**17**/**18**=48:52, 94%). Also, these isomer (**17** and **18**) could be easily separated by simple silica gel chromatography; *Rf* values for **17** and **18** were 0.21 and 0.42, respectively, using hexane–EtOAc (4:1). The stereochemistry of **17** and **18** was determined by their ^{1}H-NMR spectra. Thus, the 6′-CH_3 peak of **18** was observed to be shifted to a lower field than that of **17**. This result shows that the 6′-CH_3 group of **18** had a *cis* relationship to the 1′-*tert* hydroxyl group. This difference in the chemical shift of the 6′-CH_3 protons for each isomer was also the case for the corresponding derivatives shown below. By mechanistic assum-



Scheme 3.

ptions, if oxoacetal **5** could adopt a more energetically favorable conformation with the bulky equatorial THPoxy methyl group, it is considered that major isomer **18** resulted from axial attack at C-1 in **5** by the lithium derivative of **6**.[17] This estimation was also confirmed by converting **17** to methyl phaseate **2b**. A practical hydrolysis of the TBDMSoxy group of **17** was accoplished with NaOH in methanol to provide the acetylene diol **19** quantitatively. In order to construct the 2*Z*,4*E*-pentenediol framework, **19** was reduced with Red-Al in THF[18] to convert the dienol **21**. The unstable dienal, which had been obtained by MnO_2 oxidation of **21**, was oxidized with MnO_2 in the presence of NaCN and acetic acid in methanol[19] to give the methyl ester (**23**) . At the last stage, methyl ester **23** was treated with dil. HCl in aq. THF to afford (+)-methyl phaseate (**2b**) {$[\alpha]_D^{21}$ +27.5° (c=0.20, $CHCl_3$)} in 51% overall yield from **17**. Also, (+)-methyl epiphaseate (**25**) was synthesized from **18** in the same way. The spectral data of synthetic (+)-methyl phaseate (**2b**) and its isomer (**25**) were identical with those of racemic (**2b**) and (**25**).[9] The optical purity of the synthetic sample (**2b**) was determined to be >94% *e.e.* by ^{1}H-NMR analysis, using the chiral shift reagent, Eu(hfc)$_3$. The optical rotation of natural phaseic acid (**2a**) has been reported to be of an extraordinarily large value ($[\alpha]_{589}$ −3350°) by MacMillan *et al.*,[3] but Koshimizu *et al.* showed a value of $[\alpha]_D^{20}$ −46° (c=0.1, $CHCl_3$) for the methyl ester (**2b**) of natural phaseic acid (**2a**).[20] Although our synthetic enantiomer ((+)−**2b**) showed a somewhat smaller optical rotation value than that of the natural compound, the stereochemistry of natural (−)-methyl phaseate (**2b**), from this synthetic work, was shown to be of (1′*R*, 5′*R*, 8′*S*) form. In this way, the absolute configuration of natural phaseic acid (**2a**) was confirmed.

Experimental

Melting points (mp) and boiling points (bp) are uncorrected. Infrared (IR) spectra were recorded on a JASCO IR-810 infrared spectrometer. Nuclear magnetic resonance (NMR) spectra were measured on a JEOL JNM-FX-100 spectrometer with TMS as an internal standard. 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 × 3 mm stainless steel column packed with 10% silicone SE-30 on chromosorb W (N_2 flow rate: 30 ml/min).

(−)-(*1R*)-*Methyl 5-isopropylidene-1-methyl-2-oxocyclohexane-1-carboxylate* (**11**). To a stirred solution of **8** (210 mg, 1 mmol) in methanol (10 ml) was bubbled dry HCl gas at room temperature under nitrogen. The mixture was stirred overnight and then concentrated *in vacuo* to leave an oil, which was diluted with ether. The ethereal solution was successively washed with saturated $NaHCO_3$ solution, water and brine, and dried over $MgSO_4$. Removal of the solvent left an oil, which consisted of **9** (*Rf* 0.26), **10** (*Rf* 0.14) and **11** (*Rf* 0.48) by TLC analysis (hexane–EtOAc 4 : 1). This mixture was employed in the next step without further purification.

9. IR ν_{max} (film) cm^{-1}: 1742, 1718, 1460, 1240, 1222, 1122, 1105. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, s), 1.62 (6H, s), 3.75 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 20.8, 27.0, 30.4, 36.9, 37.1, 44.4, 52.4, 56.7, 72.4, 173.2, 208.9. *Anal.* Found: C, 58.65: H, 7.89; Cl, 14.56. Calcd. for $C_{12}H_{19}O_3Cl$: C, 58.42; H, 7.76; Cl, 14.37%. **10**. IR ν_{max} (film) cm^{-1}: 2820, 1737, 1705, 1455, 1248, 1230, 1103, 980. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, s), 1.16 (3H, s), 1.47 (3H, s), 3.21 (3H, s), 3.74 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 20.8, 22.1, 26.6, 36.4, 37.7, 40.6, 48.8, 52.2, 57.2, 76.1, 173.6, 209.5. *Anal.* Found: C, 63.88; H, 9.21. Calcd. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15%.

This crude product was dissolved in $CHCl_3$ (10 ml) and to this solution was added SiO_2 (4.1 g). The suspension was stirred at 65°C for 12 h under Ar and then filtered. The filtrate was concentrated *in vacuo* to leave an oil, which was purified by preparative TLC (hexane–EtOAc (4 : 1)) to give **11** (141 mg, 67% from 8).

11. $[\alpha]_D^{21}$ −28.7° (c=0.40, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1740, 1720, 1675, 1458, 1440, 1245, 1218, 1133, 1075. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (s), 1.72 (3H, br. s), 1.76 (3H, br. s), 2.19 (1H, d, J=15 Hz), 3.19 (1H, d, J=15 Hz), 3.69 (3H, s) ^{13}C-NMR ($CDCl_3$) δ: 20.4, 20.7, 28.4, 39.4, 39.7, 52.1, 57.3, 124.3, 127.1, 173.3, 208.2. *Anal.* Found: C, 68.39; H, 8.72. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63%.

(*1R*)-*Methyl 5-isopropylidene-1,3-dimethyl-2-oxocyclohexane-1-carboxylate* (**12**). To a stirred solution of diisopropylamine (0.88 ml, 6.2 mmol) and trace amount of 2,2′-dipyridyl in THF (10 ml) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (3.9 ml, 6.2 mmol) at −70°C under nitrogen and the mixture was stirred for 30 min. A solution of **11** (1.0 g, 4.8 mmol) in THF (3 ml)

was added dropwise to a stirred LDA solution at −78°C, and the mixture was stirred for 30 min before the reaction temperature was gradually raised to −30°C. Methyl iodide (0.45 ml, 7.2 mmol) was added to this solution, the reaction temperature was gradually raised to −5°C, and the mixture was stirred at −5~0°C for 1.5 hr. 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 over $MgSO_4$. Removal of the solvent gave an oil, which was purified by preparative TLC (hexane–ether (9 : 1)) to give **12** (744 mg, 94% based on the consumed starting ketone (**11**)) as a diastereomeric mixture (*ca.* 3 : 2, ^{1}H-NMR analysis). Also **11** (256 mg) was recovered. **12**. IR ν_{max} (film) cm^{-1}: 1745, 1730, 1718, 1658, 1460, 1378, 1233, 1135. ^{1}H-NMR ($CDCl_3$) δ: 1.09, 1.11 (total 3H, each d, J=6.5 Hz), 1.30, 1.37 (total 3H, each s), 1.72, 1.78 (total 12H, each br. s), 3.67, 3.70 (total 3H, each s). *Anal.* Found: C, 69.44; H, 9.19. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99%.

(1R)-Methyl 1,3-dimethyl-2,5-dioxo-cyclohexane-1-carboxylate (**13**). A solution of **11** (140 mg, 0.67 mmol) in methanol (10 ml) was treated with O_3 at −78°C until the characteristic blue color was obtained. The excess O_3 was flushed with O_2 and then N_2. Me_2S (0.1 ml) was added with stirring. The mixture was allowed to warm to room temperature and stirring was continued overnight. After removing the solvent, the residue was purified by preparative TLC (hexane–ether (1 : 1)) to give **13** (103 mg, 84%). IR ν_{max} (film) cm^{-1}: 1743, 1720, 1268, 1250, 1230, 1138, 1120. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (d, J=6.3 Hz), 1.21 (d, J=6.4 Hz, total 3H), 1.39, 1.45 (total 3H, each s), 3.72, 3.75 (total 3H, each s). *Anal.* Found: C, 60.35; H, 7.08. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12%.

(−)-(1S)-Methyl 1,3-dimethyl-2,5-dioxo-3-cyclohexene-1-carboxylate (**7**). A mixture of **13** (3.64 g, 18.4 mmol) and phenylselenenyl chloride (3.87 g, 20.2 mmol) in ethyl acetate (120 ml) was stirred at room temperature for 6 hr, and then water was added. After being separated, the organic layer was concentrated *in vacuo* to leave an oil, which was dissolved in CH_2Cl_2 (85 ml) containing pyridine (3.7 ml). To a vigorously stirred solution of this was added aqueous hydrogen peroxide (15%, 44 ml, *ca.* 190 mmol) with ice-bath cooling. The mixture was stirred for 2 hr and diluted with ether. The solution was washed with sat. $CuSO_4$ solution, water and brine, and dried over $MgSO_4$. Removal of the solvent left an oil, which was passed through silica gel column (ether) to give **7** (2.86 g, 79%). **7**. $[\alpha]_D^{21}$ −38.6° (c=0.58, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 1745, 1705, 1690, 1625, 1258, 1170, 1140, 1116, 923, 850. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, s), 2.04 (3H, d, J=1.5 Hz), 2.67 (1H, d, J=17 Hz), 3.32 (1H, dd, J=17, 1.2 Hz), 3.72 (3H, s), 6.56 (1H, dd, J=1.5, 1.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 16.9, 20.6, 47.3, 53.1, 56.3, 137.7. 150.1, 171.5, 194.6, 195.8. UV λ_{max} (EtOH) nm (ε) 242 (6600). *Anal.* Found: C, 61.03; H, 6.23. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17%.

(−)-(1S)-Methyl 5,5-ethylenedioxy-1,3-dimethyl-2-oxo-2-cyclohexene-1-carboxylate (**14**). To a stirred mixture of **7** (1.28 g, 6.53 mmol), methyl orthoformate (0.83 g, 7.82 mmol) and ethylene glycol (0.81 g, 13.0 mmol) in ether (15 ml) was added *p*-toluenesulfonic acid (124 mg, 0.65 mmol). The mixture was stirred for 12 hr at room temperature under nitrogen and then poured into a sat. $NaHCO_3$ solution. The resulting mixture was extracted with ether. The extracts was washed with water and brine, and dried over $MgSO_4$. Removal of solvent gave a crude acetal (**14**, 1.50 g), which was employed in the next step without further purification. A pure sample of compound (**14**) was obtained by preparative TLC (hexane–EtOAc (4 : 1)). $[\alpha]_D^{21}$ −32.5° (c=0.53, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 2895, 1743, 1690, 1640, 1125, 1090, 1037, 995, 950. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, s), 1.86 (3H, d, J=1.5 Hz), 2.12 (1H, d, J=14 Hz), 2.68 (1H, dd, J=14, 1.7 Hz), 3.69 (3H, s), 3.97~4.02 (4H, m), 6.35 (1H, dd, J=1.7, 1.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 15.9, 21.5, 43.4, 52.3, 52.7, 64.6, 64.9, 102.9, 137.0, 140.2, 173.5, 196.8. UV λ_{max} (EtOH) nm (ε) 233 (8330). *Anal.* Found: C, 59.77; H, 7.15, Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71%.

(−)-(6S)-4,4-Ethylenedioxy-6-hydroxymethyl-2,6-dimethyl-2-cyclohexen-1-one (**16**) To a stirred suspension of $LiAlH_4$ (420 mg, 11.1 mmol) in ether (25 ml) was added dropwise a solution of crude acetal **14** (1.5 g, 6.25 mmol) in ether (5 ml) at 0°C under nitrogen. The mixture was stirred at room temperature for 3.5 hr and then heated under reflux for 1 hr. The reaction was quenched by the addition of water, and the mixture was then filtered. The filter cake was washed thoroughly with methylene chloride. The combined organic layer was dried over $MgSO_4$ and evaporated to give a crystalline solid (**15**, 1.40 g), which was directly employed in the next step without further purification. To a solution of this crude alcohol (**15**, 1.40 g, *ca.* 6.54 mmol) in methylene chloride (20 min) was added active MnO_2 (14 g), and the mixture was then shaken for 5 hr at room temperature under nitrogen. The mixture was filtered through a Celite pad, and the filtrate was evaporated to give an oil, which was purified by silica gel column chromatograpy (hexane–EtOAc (1 : 1)) to give **16** (1.08 g, 78% from **7**). $[\alpha]_D^{21}$ −28.3° (c=0.18, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3400, 2890, 1678, 1090, 1018, 965. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, s), 1.81 (3H, d, J=1.5 Hz), 1.98 (1H, dd, J=14, 1.2 Hz), 2.34 (1H, d, J=14 Hz), 2.76 (OH, dd, J=7.8, 5.4 Hz), 3.47 (1H, dd, J=11, 5.4 Hz), 3.72 (1H, dd, J=11, 7.8 Hz), 4.04 (4H, m), 6.38 (1H, dd, J=1.5, 1.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 15.9, 21.6, 41.9, 47.3, 64.7, 65.0, 69.4, 104.1, 136.6, 140.3, 198.2. UV λ_{max} (EtOH) nm (ε): 231 (8200). *Anal.* Found: C, 62.36; H, 7.75. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%.

(6S)-4,4-Ethylenedioxy-2,6-dimethyl-6-tetrahydropyranyloxymethyl-2-cyclohexen-1-one (**5**). To a stirred solution of **16** (680 mg, 3.21 mmol) and 2,3-dihydropyran (539 mg, 6.42 mmol) in methylene chloride (12 ml)

was added pyridinium *p*-toluenesulfonate (100 mg, 0.39 mmol). The mixture was stirred at room temperature for 7 hr and then diluted with ether. The organic solution was washed with sat. $NaHCO_3$ solution, water and brine, and dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was purified by preparative TLC (benzene–EtOAc (5 : 1)) to give **5** (911 mg, 96%). IR ν_{max} (film) cm^{-1}: 1678, 1350, 1133, 1120, 1085, 1063, 1035, 1020, 970, 905, 865, 815. ^{1}H-NMR ($CDCl_3$) δ: 1.20, 1.22 (total 3H, each s), 1.80 ~ 1.81 (3H, s), 1.85 ~ 2.04 (1H, m), 2.55, 2.63 (total 1H, each d, J = 14 Hz), 3.16, 3.49 (total 1H, each d, J = 9 Hz), 4.02 (4H, m), 3.71, 4.03 (total 1H, each d, J = 9 Hz), 4.56 ~ 4.59 (1H, br. s), 6.34 ~ 6.37 (1H, br. t). *Anal.* Found: C, 64.61; H, 8.33. Calcd. for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16%.

(Z)-3-Methyl-2-penten-4-yn-1-ol t-butyldimethylsilyl ether (**6**). To a stirred solution of 3-methyl-2-penten-4-yn-1-ol (2.1 g, 21.9 mmol) and *t*-butyldimethylsilyl chloride (4.0 g, 26.5 mmol) in THF (20 ml) was added a mixture of triethylamine (2.7 g, 26.7 mmol) and 4-dimethylaminopyridine (271 mg, 2.22 mmol) in THF (5 ml) at 0°C under nitrogen. The mixture was stirred at 0°C for 30 min and then at room temperature for 2.5 hr. The reaction mixture was poured into cold water and the organic layer was separated. The aqueous layer was extracted with hexane, and the combined organic layer was washed with water and brine, and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was distilled under reduced pressure to afford **6** (4.0 g, 87%). Bp 94 ~ 96°C (13 ~ 15 mmHg). IR ν_{max} (film) cm^{-1}: 3302, 2852, 2100, 1638, 1255, 1105, 1060, 838, 775. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.90 (9H, s), 1.88 (3H, m), 3.14 (1H, s), 4.38 (2H, dd, J = 6.4, 1.3 Hz), 5.86 (1H, t, J = 6.4 Hz). *Anal.* Found: C, 68.40; H, 10.46. Calcd. for $C_{12}H_{22}OSi$: C, 68.51; H, 10.54%.

(1′R,6′S)-(Z)-5-(4′,4′-Ethylenedioxy-1′-hydroxy-2′,6′-dimethyl-6′-tetrahydropyranyloxymethyl-2′-cyclohexen-1′-yl)-3-methyl-2-penten-4-yn-1-ol t-butyldimethylsilyl ether (**17**) and *(1′S,6′S)-(Z)-5-(4′,4′-ethylenedioxy-1′-hydroxy-2′,6′-dimethyl-6′-tetrahydropyranyloxymethyl-2′-cyclohexen-1′-yl)-3-methyl-2-penten-4-yn-1-ol t-butyl dimethylsilyl ether* (**18**).

(a) To a stirred solution of **6** (1.89 g, 9.00 mmol) in THF (30 ml) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (5.4 ml, 8.64 mmol) at −13°C under argon. After stirring for 45 min, the reaction mixture was cooled to −20°C, and **5** (890 mg, 3.03 mmol) in THF (3 ml) was added to the stirred mixture. The mixture was stirred for 1 hr at −20°C and then at room temperature for 1 hr. After quenching with aq. NH_4Cl solution, the resulting mixture was extracted with ether. The extract was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was purified by silica gel column chromatography (hexane–EtOAc (4 : 1)) to give **17** (460 mg, 30%) and **18** (1.02 g, 67%).

(b) To a stirred solution of **6** (220 mg, 1.05 mmol) in THF (2 ml) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (0.66 ml, 1.05 mmol) at −73°C under argon. HMPA (0.4 ml) was added to this solution, and the reaction mixture was warmed to 0°C for 45 min and then cooled to −73°C. **5** (100 mg, 0.34 mmol) in THF (0.5 ml) was added to the mixture at −73°C, and the mixture was stirred at −73°C for 1.5 hr. By this procedure, **17** (77 mg, 45%) and **18** (83 mg, 48%) were obtained. **17**. IR ν_{max} (film) cm^{-1}: 3430, 2850, 1665, 1635, 1118, 1085, 1050, 1030, 835, 770. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (9H, s), 1.23, 1.25 (total 3H, each s), 1.86 (3H, s), 1.96 (3H, s), 3.93 (4H, m), 4.36 (2H, br. d, J = 6.1 Hz), 4.66, 4.87 (total 1H, each br. s), 5.35 (1H, br. s), 5.75 (1H, dt, J = 6.1, 1.5 Hz). *Anal.* Found: C, 66.50; H, 9.17. Calcd. for $C_{28}H_{46}O_6Si$: C, 66.37; H, 9.15%. **18**. IR ν_{max} (film) cm^{-1}: 3500, 2860, 1670, 1630, 1120, 1093, 1055, 1030, 835, 775. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (9H, s), 1.23, 1.28 (total 3H, each s), 1.83 (3H, s), 1.91 (3H, m), 3.06 (1H, d, J = 9.3 Hz), 3.91 (4H, m), 4.34 (2H, br. d, J = 6.1 Hz), 4.69 (1H, s), 5.30 (1H, s), 5.75 (1H, dt, J = 6.1, 1.5 Hz). *Anal.* Found: C, 66.57; H, 9.12. Calcd. for $C_{28}H_{46}O_6Si$: C, 66.37; H, 9.15%.

(1′R,6′S)-(Z)-5-(4′,4′-Ethylenedioxy-1′-hydroxy-2′,6′-dimethyl-6′-tetrahydropyranyloxymethyl-2′-cyclohexen-1′-yl)-3-methyl-2-penten-4-yn-1-ol (**19**). To a stirred solution of **17** (380 mg, 0.75 mmol) in methanol (3.2 ml) was added 5% NaOH solution (1.1 ml) at 0°C under nitrogen. The mixture was stirred at 0°C for 30 min and then at room temperature overnight. The solution was concentrated *in vacuo* and water was added to the residue. The mixture was extracted with EtOAc. The extracts was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by preparative TLC (hexane–EtOAc (1 : 2)) to give **19** (290 mg, 99%). IR ν_{max} (film) cm^{-1}: 3410, 1670, 1638, 1120, 1090, 1020. ^{1}H-NMR ($CDCl_3$) δ: 1.25, 1.26 (total 3H, each s), 1.88 (3H, m), 1.95 (3H, m), 3.93 (4H, m), 4.27 (2H, d, J = 6.1 Hz), 4.64 (1H, br. s), 5.35 (1H, br. s), 5.88 (1H, dt, J = 6.8, 1.5 Hz). *Anal.* Found: C, 67.57; H, 8.14. Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22%.

(1′S,6′S)-(Z)-5-(4′,4′-Ethylenedioxy-1′-hydroxy-2′,6′-dimethyl-6′-tetrahydropyranyloxymethyl-2′-cyclohexen-1′-yl)-3-methyl-2-penten-4-yn-1-ol (**20**). As in the preceding case, the TBDMS ether (**18**, 300 mg, 0.59 mmol) was converted to **20** (228 mg, 98%). IR ν_{max} (film) cm^{-1}: 3480, 1675, 1638, 1123, 1095, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.24, 1.28 (total 3H, each s), 1.87 (3H, m), 1.91 (3H, m), 3.91 (4H, m), 4.66, 4.74 (total 1H, each br. s), 5.32 (1H, br. s), 5.88 (1H, m). *Anal.* Found: C, 67.72; H, 8.13. Calcd. for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22%.

(1′R,6′S)-(2Z,4E)-5-(4′,4′-Ethylenedioxy-1′-hydroxy-2′,6′-dimethyl-6′-tetrahydropyranyloxymethyl-2′-cyclohexen-1′-yl)-3-methyl-2,4-pentadienol (**21**). To a stirred solution of **19** (250 mg, 0.64 mmol) in THF (3.0 ml) was

added dropwise a mixture of a 3.4 M solution of Red-Al (0.63 ml, 2.13 mmol) in toluene and THF (1 ml) under nitrogen at 0°C, and the mixture was stirred for 30 min at the same temperature. The mixture was stirred for 4 hr at room temperature, then treated with sat. NH_4Cl solution, and filtered. The filtrate was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent gave a residual oil, which was purified by preparative TLC (hexane–EtOAc (1 : 1), twice) to afford **21** (228 mg, 91%). IR ν_{max} ($CHCl_3$) cm^{-1}: 3450, 1663, 1120, 1090, 1025, 978, 950, 903, 868, 810. ^{1}H-NMR ($CDCl_3$) δ: 1.05, 1.09 (total 3H, each s), 1.72 (3H, m), 1.86 (3H, m), 3.91 (4H, m), 5.38 (1H, m), 5.59 (1H, t, J=6.3 Hz), 5.68 (1H, d, J=16 Hz), 6.72 (1H, d, J=16 Hz). *Anal.* Found: C, 64.38; H, 9.36. Calcd. for $C_{22}H_{34}O_6 \cdot H_2O$: C, 64.06; H, 8.80%.

(1′S,6′S)-(2Z,4E)-5-(4′,4′-Ethylenedioxy-1′-hydroxy-2′,6′-dimethyl-6′-tetrahydropyranyloxymethyl-2′-cyclohexen-1′-yl)-3-methyl-2,4-pentadienol (**22**). As in the preceding case, the diol (**20**, 240 mg, 0.61 mmol) was converted to the dinediol (**22**, 214 mg, 89%). IR ν_{max} ($CHCl_3$) cm^{-1}: 3500, 3440, 1675, 1120, 1090, 1030, 978, 968, 903, 870, 810. ^{1}H-NMR ($CDCl_3$) δ: 1.26, 1.32 (total 3H, each s), 1.67 (3H, m), 1.86 (3H, br. s), 3.92 (4H, m), 4.30 ~ 4.33 (2H, br. d), 4.51 ~ 4.56 (1H, br. d), 5.36 (1H, br. s), 5.58 (1H, t, J=6.6 Hz), 5.80, 5.89, 6.73, 6.79 (total 2H, each d, J=16 Hz). *Anal.* Found: C, 64.54; H, 8.41%. Calcd. for $C_{22}H_{34}O_6 \cdot H_2O$: C, 64.06; H, 8.80%.

(1′R,6′S)-(2Z,4E)-Methyl 5-(4′,4′-ethylenedioxy-1′-hydroxy-2′,6′-dimethyl-6′-tetrahydropyranyloxymethyl-2′-cyclohexen-1′-yl)-3-methyl-2,4-pentadienoate (**23**). To a solution of **21** (450 mg, 1.14 mmol) in CH_2Cl_2 (15 ml) was added active MnO_2 (7.8 g). The mixture was shaken under nitrogen at room temperature for 3 hr and then filtered. The filtrate was concentrated *in vacuo* to give an oil (360 mg), which was dissolved in methanol (30 ml). To this solution was added active MnO_2 (3.6 g), NaCN (239 mg, 4.88 mmol) and AcOH (84 μl, 1.47 mmol), and the mixture was shaken under nitrogen at room temperature overnight. The mixture was filtered and the filtrate was concentrated *in vacuo* to give a residual oil, which was treated with water. The mixture was extracted with EtOAc, the extract was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent afforded an oil, which was purified by preparative TLC (hexane–EtOAc (1 : 1)) to give **23** (340 mg, 71% from 21). IR ν_{max} ($CHCl_3$) cm^{-1}: 3470, 1720, 1638, 1605, 1240, 1162, 1090, 1035. ^{1}H-NMR ($CDCl_3$) δ: 1.06, 1.11 (total 3H, each s), 1.73 (3H, br. s), 1.99 (3H, m), 3.70 (3H, s), 3.92 (4H, m), 4.60, 4.67 (total 1H, br. s), 5.41 (1H, m), 5.69 (1H, br. s), 6.03 (1H, d, J=16 Hz), 7.82 (1H, d, J=16 Hz). *Anal.* Found: C, 65.12: H, 7.85. Calcd. for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11%.

(1′S,6′S)-(2Z,4E)-Methyl 5-(4′,4′-ethylenedioxy-1′-hydroxy-2′,6′-dimethyl-6′-tetrahydropyranyloxymethyl-2′-cyclohexen-1′-yl)-3-methyl-2,4-pentadienoate (**24**). As in the preceding case, the diol **22**, 124 mg, 0.31 mmol) was converted to **24** (96 mg, 72% from **22**). IR ν_{max} ($CHCl_3$) cm^{-1}: 3500, 1716, 1680, 1632, 1600, 1238, 1160, 1125, 1090, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.27, 1.33 (total 3H, each s), 1.68 (3H, m), 2.00 (3H, m), 3.69 (3H, s), 3.93 (4H, m), 4.48, 4.60 (total 1H, each br. s), 5.38 (1H, br. s), 5.68 (1H, br. s), 6.15, 6.25, 7.85, 7.91 (total 2H, each d, J=16 Hz). *Anal.* Found: C, 64.94; H, 8.37. Calcd. for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11%.

(+)-*(1′S,5′S,8′R)-(2Z,4E)-Methyl phaseate* (**2b**). To a stirred solution of **23** (160 mg, 0.38 mmol) in THF (2 ml) was added a 5% HCl solution (0.5 ml) under nitrogen at 0°C. The mixture was stirred at 0°C for 1 hr and then at room temperature for 7 hr. To the reaction mixture was added $NaHCO_3$ powder, and the mixture was stirred for several minutes. The mixture was diluted with water, and the resulting mixture was extracted with EtOAc. The extract was washed with water and brine, and dried over $MgSO_4$. Removal of the solvent gave a crystalline product, which was purified by preparative TLC (CH_2Cl_2–MeOH (20 : 1)) to afford (+)-**2b** (92 mg, 83%). mp 159 ~ 160.5°C (hexane–EtOAc). $[\alpha]_D^{21}$ +27.5° (c=0.2, $CHCl_3$). IR ν_{max} (KBr) cm^{-1}: 3440, 2890, 1720, 1690, 1640, 1605, 1378, 1237, 1165, 1045, 1020, 983. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, s), 1.25 (3H, s), 2.02 (3H, d, J=1.5 Hz), 2.21 (OH), 2.52 (2H, br. s), 2.64 (2H, br. s), 3.73 (3H, s), 3.78 (1H, d, J=8.1 Hz), 3.98 (1H, dd, J=8.1, 1.7 Hz), 5.80 (1H, br. s), 6.24 (1H, d, J=16 Hz), 8.17 (1H, d, J=16 Hz), ^{13}C-NMR ($CDCl_3$) δ: 15.8, 19.0, 21.1, 48.4, 51.2, 52.7, 52.9, 75.8, 82.4, 85.9, 118.8, 131.5, 131.9, 149.1, 166.3, 203.5. UV λ_{max} (EtOH) nm (ε): 265 (17000). *Anal.* Found: C, 65.25; H, 7.60. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53%.

(+)-*(1′S,5′S,8′S)-(2Z,4E)-Methyl epiphaseate* (**25**). As with the case for **23**, the methyl ester (**24**, 96 mg) was converted to **25** (56 mg, 84%), mp 167 ~ 169°C (hexane-EtOAc). $[\alpha]_D^{21}$ +39.8° (c=0.40, $CHCl_3$). IR ν_{max} (KBr) cm^{-1}: 3450, 1663, 1120, 1090, 1025, 978, 950, 903, 868, 810. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, s), 1.12 (3H, s), 2.07 (3H, d, J=1.1 Hz), 2.25 (1H, dd, J=17, 1.8 Hz), 2.42 (1H, dd, J=17, 1.8 Hz), 2.49 (OH), 2.83 (1H, d, J=17 Hz), 2.85 (1H, dd, J=17, 2.8 Hz), 3.73 (3H, s), 3.79 (1H, dd, J=9.0, 2.8 Hz), 3.85 (1H, d, J=9.0 Hz), 5.78 (1H, br. s), 6.34 (1H, d, J=16 Hz), 7.97 (1H, d, J=16 Hz). ^{13}C-NMR ($CDCl_3$) δ: 18.3, 21.4, 21.5, 46.5, 50.7, 51.0, 51.1, 76.6, 81.7, 84.3, 117.5, 127.4, 136.7, 149.9, 166.7, 209.9. UV λ_{max} (EtOH) nm (ε) 265 (19400). *Anal.* Found: C, 65.23; H, 7.58. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53%.

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