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STEREOCONTROLLED SYNTHESIS OF BOTH THE ENANTIOMERS OF PHASEIC ACID AND ITS METHYL ESTER, A PIVOTAL METABOLITE OF ABSCISIC ACID. †

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Abstract-----Both the enantiomers of phaseic acid **2a** and its methyl ester **2b** were synthesized in highly stereocontrolled manner starting from ethyl (1*R*,2*S*)-5,5-ethylenedioxy-2-hydroxycyclohexanecarboxylate **5** of 98.4% e.e. 6-Oxabicyclo[3.2.1]octenone **16** was employed as a key intermediate. Addition of a side chain to **16** was executed stereospecifically to give only the desired adduct **19**. This was transformed to optically pure phaseic acid **2a** and methyl phaseate **2b**.

INTRODUCTION

Since the structure-elucidation of abscisic acid **1** by Ohkuma and Addicott *et al*[1], chemical and biological studies on this plant hormone and related analogs have been pursued by many workers. Among them, one of the important discovery was the isolation and identification of several metabolites derived from **1**, such as phaseic acid **2a** and

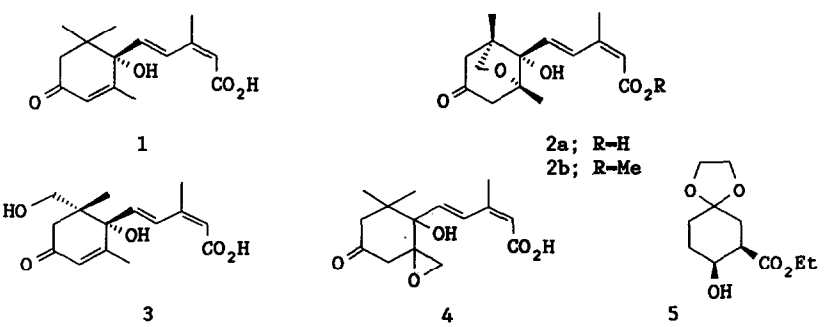

Fig.1

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†Synthesis of Mono- and Sesquiterpenoids
Part 17. Part 16, K.Mori and H.Takaishi, *Liebigs Ann. Chem.* in press.
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"Metabolite C" 3. MacMillan *et al* isolated phaseic acid 2a from *Phaseolus multiflorus* with abscisic acid-like activity[2a] and proposed its structure as depicted in 4[2b]. Later, Milborrow identified "Metabolite C" as the first oxidation metabolite in tomato stem using labeled 1[3], and determined its structure as 3[4]. Since "Metabolite C" 3 was easily isomerized to phaseic acid by heating, Milborrow revised the structure of phaseic acid from 4 to 2a[4]. Absolute configuration of 2a was later deduced by chemical correlation[5].

Although two syntheses of (±)-methyl phaseate 2b have been reported [6,7], and a chiral synthesis of unnatural (+)-2b was achieved by Oritani *et al* recently[8], none of those was stereoselective synthesis and the undesired epimer was produced predominantly. Moreover, in Oritani's chiral synthesis[8], only the unnatural enantiomer of 2b was obtained and its optical purity was supposed to be about 90% e.e., which might not be high enough for precise biological study. Thus, the synthesis of optically pure 2a, 2b should be significant and in connection with our continuing studies in the chiral synthesis of bioregulators, we started the synthesis of them.

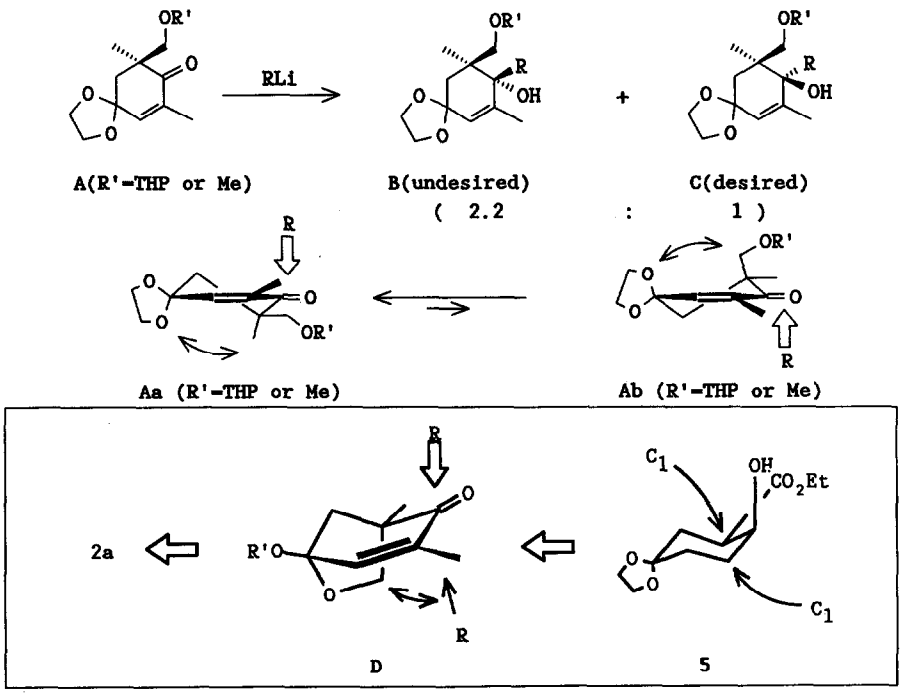


Fig.2 Conformational Analysis of Key Intermediate and Synthetic Plan.

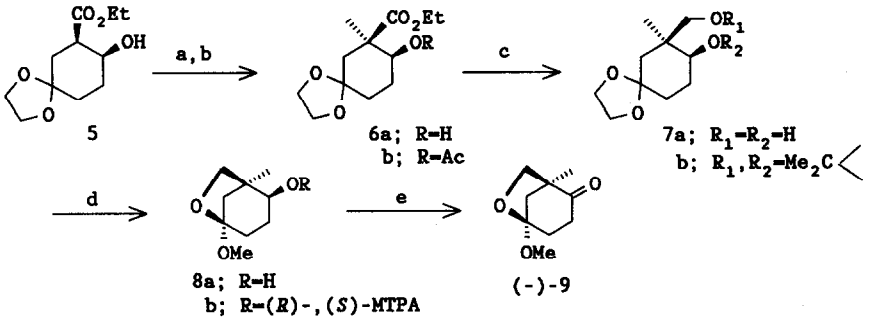
Here, we wish to describe the stereocontrolled synthesis of both the enantiomers of phaseic acid and its methyl ester, **2a** and **2b**, in highly optically pure form. We already reported the preparation of ethyl (1*R*,2*S*)-5,5-ethylenedioxy-2-hydroxycyclohexanecarboxylate **5** of 98.4%e.e. by the asymmetric reduction of the corresponding keto ester with baker's yeast[9], and its application to the syntheses of elemophilane sesquiterpenes[10,11]. In this synthesis, **5** was employed as an only chiral source for synthesizing both enantiomers.

SYNTHETIC PLAN

The crucial step of this synthesis is the stereoselective addition of a side chain unit to a cyclohexenone moiety. A flexible cyclohexenone **A** was employed as a substrate in Oritani's work, and the ratio of resulting two adducts, **B** and **C**, was 2.2/1, favoring the undesired epimer **B**. As shown in Fig.2, both conformers, **Aa** and **Ab**, possess 1,3-diaxial interaction between acetal oxygen and alkyl group. It is more severe in conformer **Ab**, however, because bulkier tetrahydropyranyloxymethyl group is axial. Thus, conformer **Aa** should be more stable and in fact, MM2 calculation[12] shows that even **Aa** with R'=Me is 1.7 kJ/mole more stable than **Ab**, that is, 65~70% of **A** is present as **Aa** form at 0°C and **Aa**/**Ab** = 1.9~2.3/1. Assuming that axial attack is favored by stereoelectronic control, **A** should give the undesired epimer **B** predominantly and it is essential to freeze the conformation into **Ab** type for giving the desired isomer **C**. Fortunately, less stable conformer contains axial hydroxymethyl equivalent and it may interact with acetal to give a cyclized derivative **D** , with a fixed conformation. Introduction of C-1 units and reduction of ester group of **5** are plausible to give **D**. Alkylation of the dianion of a cyclic hydroxyester was reported by Fráter and was shown to be antiselective[13]. In our case, however, the additional acetal group at C-5 position might affect the stereoselectivity of the alkylation, and this was first to be solved.

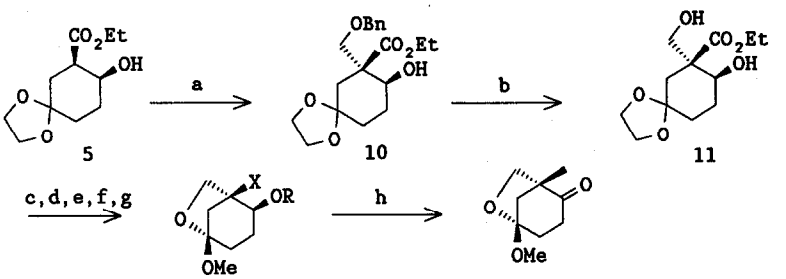
STEREOCHEMISTRY OF DIANION ALKYLATION

Alkylation of **5** with MeI under the similar condition reported by Fráter[13] gave almost pure anti-methylated product **6a** (70%). Stereochemistry of **6a** was determined as follows; **6a** was converted to its acetate **6b** and an acetonide **7b** *via* 3 steps. Half heights width (hhw) of proton attached to the carbon bearing secondary -OR in both **6b** and **7b** was less than 8 Hz and therefore, -OR is β-axial and methyl group must be α-axial to cyclohexane ring, that is, **6a** is anti-methylated product. The result showed that the additional acetal linkage enhances anti-selectivity. This isomer, **6a**, is useful for the synthesis of the



a; 2LDA,MeI/THF-HMPA, b; Ac_2O,DMAP/Py, c; $LiAlH_4$/THF,
d; *p*-TsOH(cat.)/MeOH, e; PDC,MS3A/CH_2Cl_2

SCHEME 1-a ; Preparation of Unnatural Enantiomer



a; 2LDA,BOMCl/THF-HMPA, b; H_2/Pd-C/EtOAc,3 atm, c; *p*-TsOH(cat.)/MeOH
d; Ac_2O,DMAP/Py, e; $LiAlH_4$/THF f; *p*-TsCl,DMAP/Py, g; $LiBEt_3H$/THF
h; PDC,MS3A/CH_2Cl_2

SCHEME 1-b ; Preparation of Natural Enantiomer

antipodes, but not for the natural **2a** and **2b**. Thus, it became necessar to introduce α-hydroxymethyl group. Using benzyloxymethyl chlorid (BOMCl) for the dianion alkylation, the desired isomer **10** was obtaine (~70%). Anti/syn ratio was estimated to be ~100/0 by 100MHz ^{1}H-NM analysis[14].

PREPARATION OF THE KEY INTERMEDIATE, BICYCLIC KETONE

Preparation of (-)-**9** was rather simple, namely, the acetate **6b** wa reduced with $LiAlH_4$ to give a diol **7a** (84% from **6a**)[15], which c treatment with *p*-TsOH in MeOH gave a bicyclic acetal-alcohol **8a** a crystals. Recrystallization afforded diastereomerically pure **8a**[16]

(72%). PDC oxidation[17] gave the desired ketone (-)-9 (89%).

As for the natural enantiomer, ethoxycarbonyl group had to be reduced to methyl group selectively. Reductive cleavage of the tosylate I derived from 10, however, gave unsatisfactory result†. The result prompted us to construct the rigid bicyclic system earlier than reductive cleavage of tosylate group.

Thus, 10 was hydrogenated over Pd-C to give a diol ester 11 (77%), which on treatment with *p*-TsOH in MeOH gave a bicyclic hydroxyester 12a (90%). Acetylation was followed by hydride reduction to give a diol 13 (95% from 12a)[15], which was tosylated under the similar manner as described before to give a monotosylate 14 (81%). In this case, Super-Hydride® reduction smoothly gave a single product 15a (83%) as crystals, probably because the bridged ring system prevented formation of a strained oxetane ring. The resulting alcohol 15a is a diastereomer of 8a and recrystallization also gave diastereomerically pure alcohol 15a[16]. Oxidation of 15a with PDC gave (+)-9 (89%). Thus, both the enantiomers of the bridged ketone 9 were available in highly optically pure form.

PREPARATION OF ENONE, ADDITION OF SIDE CHAIN UNIT AND COMPLETION OF SYNTHESIS

Phenylselenenylation of (+)-9 ($LiN(TMS)_2$,PhSeBr), methylation (NaH, MeI) and subsequent oxidative elimination *via* selenoxide (H_2O_2-$NaHCO_3$, THF) gave an enone precursor (+)-16 for crucial step (67% from (+)-9). This enone 16 was extremely labile to acid and even on a silica gel column, it decomposes to give a phenol derivative 17 via retro-aldol process. Addition of lithium salt of an acetylene 18 to the enone 16[8] gave an adduct (+)-19 with the desired stereochemistry as a sole product (90%). Thus, our prediction by conformational analysis was proved to be correct and the reaction proceeded with complete stereospecificity. Using Grignard reagent derived from 18, a rearranged product 20 was formed in addition to (+)-19. Desilylation of (+)-19 with Et_4NF gave a

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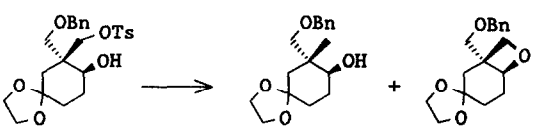
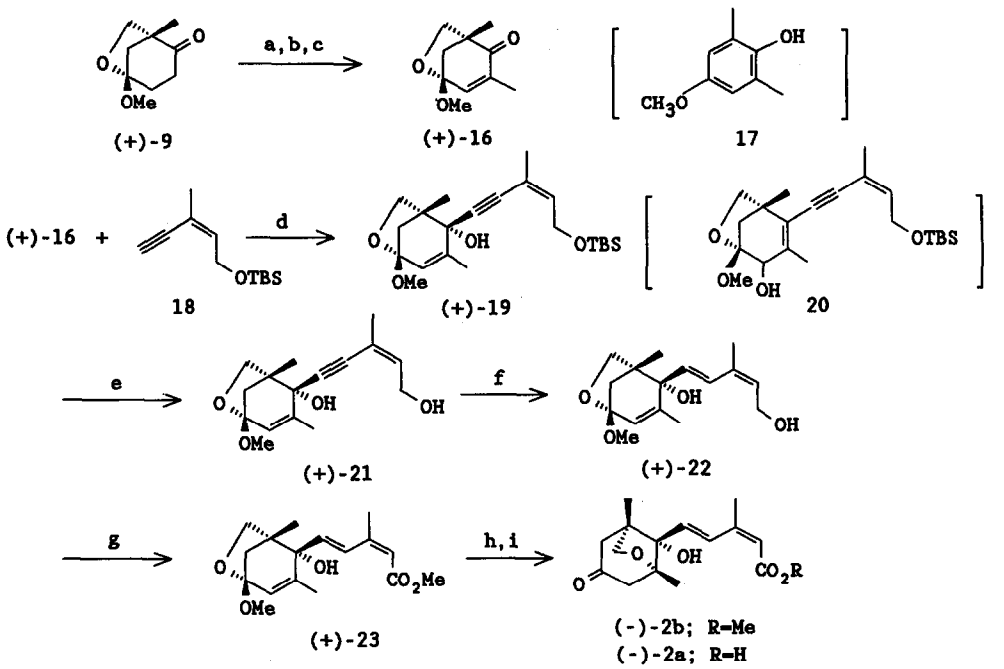
†Super-Hydride reduction of I yielded a mixture of two products. Major one, less polar isomer, was the unexpected oxetane III (47%) and the desired isomer II was a minor product (40%). Apparently, the oxetane ring was formed by intramolecular S_N2 displacement of tosylate with initially produced alkoxy-borane complex.



I II III



a; $(TMS)_2NLi$-PhSeBr/THF, b; NaH-MeI/THF, c; H_2O_2-$NaHCO_3$/THF, d; *n*-BuLi/THF
e; Et_4NF/CH_3CN, f; Red-Al®/THF, g; $MnO_2/CH_2Cl_2 \rightarrow MnO_2$-NaCN/MeOH-AcOH
h; aqHCl/THF, i; LiOH/THFaq

SCHEME 2 ; Stereospecific Addition of Acetylide and the Synthesis of (-)-Phaseic Acid

diol (+)-21 (96%). Reduction of (+)-21 with Red-Al® [18] gave an unstable (*Z,E*)-alcohol (+)-22 (69%). Oxidation of 22 by Corey's procedure[19] using MnO_2 and MnO_2-NaCN in MeOH-AcOH, afforded a methyl ester (+)-23 (74%). Finally, the ester 23 was treated with dil.HCl-THF to give (-)-methyl phaseate, (-)-2b (90%). In the same manner, (+)-methyl phaseate, (+)-2b was synthesized from (-)-9. Spectral data of synthetic (-)- and (+)-methyl phaseate were identical with those of authentic sample. Optical rotations of our (-)- and (+)-2b were as follows: (-)-2b; $[\alpha]_D^{17}$ -33.6°(c=0.93 or 0.1,$CHCl_3$). (+)-2b; $[\alpha]_D^{16}$ +33.0°(c=0.97, $CHCl_3$). Lit.; (+)-2b as >90% e.e.; $[\alpha]_D^{21}$ +27.5°(c=0.20,$CHCl_3$)[8]. (-)-2b from natural source; $[\alpha]_D^{20}$ -46°(c=0.1,$CHCl_3$)[20]. Mild alkaline hydrolysis of 2b afforded crystalline phaseic acid 2a. (-)-2a; m.p. 193~196°C (dec.), $[\alpha]_D^{16}$ -18.0°(c=0.10,MeOH). Lit.; m.p. 204~205°C[4],

$[\alpha]_D$ -3350°(MeOH)[2b]. (+)-2a; $[\alpha]_D^{21}$ +18.5°(c=0.11, MeOH). The optical purities of our synthetic samples were estimated to be ~100% e.e. by 300MHz ^{1}H-NMR analysis using chiral shift reagent, Eu(hfc)$_3$[21]. They were further supported by HPLC analysis using aminopropyl silica gel impregnated with a protein, ovomcoid, as a chiral stationary phase (ULTRON-ES-OVM®). The mixture of both enatiomers of phaseic acid completely separated into two peaks with about 5 min. difference of retention time.[22] Synthetic (-)-phaseic acid, natural enantiomer was shown to be more than 99.9% e.e.; smallest detectable peak (-0.03%) of the antipode was observed. While, (+)-enantiomer was proved to be nearly 100% e.e.; no antipode was detected. Although there have been much discrepancy on $[\alpha]_D$ values of phaseic acid 2a and methyl phaseate 2b between those reports, we believe that our synthesis clarified the exact values of pure methyl phaseate and phaseic acid.

In conclusion, both the enantiomers of phaseic acid 2a and methyl phaseate 2b were synthesized in optically pure form. The synthesis was accomplished in perfectly stereocontrolled manner using the bridged bicyclic enone 16 as a key intermediate. Overall yields for (+)- and (-)-2b were 8.4% and 5.1% through 14 and 17 steps from ethyl (1*R*,2*S*)-5,5-ethylenedioxy-2-hydroxycyclohexanecarboxylate 5 respectively.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils, as KBr disks for solids or with nujol for solids on a Jasco IRA-102 spectrometer. ^{1}H-NMR spectra were recorded with TMS and C_6D_5H (7.20 ppm) as an internal standard at 100MHz on a JEOL JNM FX-100 spectrometer or 400MHz and 300MHz on a Bruker AC-P300 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. UV spectra were measured on a HITACHI 300 spectrophotometer. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. Merck Kieselgel 60 was used for SiO_2 column chromatography. Neutral alumina (ICN) was used for Al_2O_3 column chromatography.

Ethyl (1*R*,2*S*)-5,5-ethylenedioxy-2-hydroxy-1-methylcyclohexanecarboxylate 6a

To an LDA solution prepared from diisopropylamine (15.8 ml,113 mmol) and *n*-BuLi (1.49 N,76 ml,113 mmol) in dry THF (70 ml) was added dropwise a soln of 5 (9.98 g,43.4 mmol) in dry THF (40 ml) at -70°C. After stirring for 1 h at -15°C, MeI (10.0 g,70.4 mmol) in HMPA (32 ml) was added at once, and the temperature was raised to 20°C. After stirring for 20 min at room temp, the reaction mixture was poured into sat NH_4Cl soln and extracted with ether(x5). The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (240 g). Elution with *n*-hexane-EtOAc (10:1~8:1) gave 7.46 g (71 %) of 6a, n_D^{17} 1.4716 ; $[\alpha]_D^{17}$ +26.1°(c=1.11,$CHCl_3$); ν_{max} 3530(s), 2970(s), 2950(s), 2900(s), 1710 (s), 1450(m), 1360(m), 1310(m), 1250(m), 1210(s), 1115(s), 1090(s), 1080(s),

985(s), 760(m), 695(m) cm^{-1}; δ(100MHz,$CDCl_3$) 1.30(3H,t,J=7Hz), 1.35(3H,s), 1.4~2.1 (4H,m), 2.28(1H,d,J=2Hz), 2.42(1H,d,J=2Hz), 3.44(1H,br), 3.7~4.0 (5H,m), 4.18(2H,q,J=7Hz). (Found: C,58.88; H,8.16 Calc. for $C_{12}H_{20}O_5$: C, 59.00; H,8.25%)

Ethyl (1*R*,2*S*)-2-acetoxy-5,5-ethylenedioxy-1-methylcyclohexanecarboxylate 6b

A mixture of 6a (7.39 g,30.3 mmol), Ac_2O (6 ml,63.6 mmol) and 4-*N*,*N*-dimethylaminopyridine (370 mg,3.0 mmol) in dry pyridine (30 ml) was stirred for 2 h at room temp. The reaction mixture was quenched with water and extracted with ether. The extract was washed with sat $CuSO_4$ soln (×3), water, sat $NaHCO_3$ soln, and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give 8.17 g (94 %) of 6b. This was pure enough (TLC, NMR, and IR) using for the next step. Analytical sample was obtained by SiO_2 chromatography, n_D^{16}1.4599; $[\alpha]_D^{16}$ +41.9° (c=1.02,$CHCl_3$); ν_{max}(film) 2990(s), 2900(s), 1740(s), 1440(m), 1370(s), 1240(s), 1190(m), 1120(m), 1090(s), 1060(m), 1035(m), 970(m), 950(m) cm^{-1}; δ(100MHz,$CDCl_3$) 1.22(3H,t,J=7Hz), 1.35(3H,s), 2.01(3H,s), 1.5~2.4(6H,m), 3.9~4.0(4H,m), 4.12(2H,dq,J=2 and 7Hz), 5.10(1H,br, hhw=8Hz). (Found: C,58.55; H,7.73 Calc. for $C_{14}H_{22}O_6$: C,58.73; H,7.75%)

(1*S*,2*S*)-4,4-Ethylenedioxy-2-hydroxymethyl-2-methylcyclohexanol 7a

To a stirred suspension of LAH (2.16 g,56.9 mmol) in dry THF (25 ml) was added a soln of 6b (8.14 g,28.5 mmol) in dry THF (25 ml) with ice-cooling. After stirring for 1 h at room temp, the reaction mixture was quenched with water (2 ml), 15% NaOH aq (2 ml), and water (6 ml). The precipitate was filtered through a celite pad and washed thoroughly with THF. The combined filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (100 g). Elution with *n*-hexane-EtOAc (3:2~1:2) gave 5.15 g (89 %) of 7a, n_D^{18} 1.4939; $[\alpha]_D^{18}$ +17.4°(c=1.13,$CHCl_3$); ν_{max}(film) 3400(s), 2950(s), 2880(s), 1440(m), 1360(m), 1090(m), 980(m), 945(m) cm^{-1}; δ(100MHz,$CDCl_3$) 1.04(3H,s), 1.3~2.2(6H,m), 2.51 (2H,br,hhw=4Hz), 3.57(1H,d,J=12Hz), 3.75(1H,d,J=12Hz), 3.5~3.8(1H,m), 3.95(4H,s). (Found: C,58.94; H,8.92 Calc. for $C_{10}H_{18}O_4$: C,59.38; H,8.97%)

(1*S*,2*S*,5*R*)-5-Methoxy-1-methyl-6-oxabicyclo[3.2.1]octan-2-ol 8a

A mixture of 7a (4.91 g,24.3 mmol) and *p*-TsOH·H_2O (460 mg) in dry MeOH (40 ml) was stirred for 1 h at room temp. To this was added solid $NaHCO_3$, and the reaction mixture was diluted with ether (200 ml). The precipitate was filtered through a celite pad and the filtrate was concentrated *in vacuo*. The residue was chromatograghed over SiO_2 (75 g). Elution with *n*-hexane-EtOAc (5:1~2:1) gave crystalline 8a (3.47 g). Recrystallization from *n*-hexane-*i*-Pr_2O gave 3.01 g (72 %) of pure 8a as needles; m.p. 31.0~32.0°C; $[\alpha]_D^{18}$ +50.0° (c=0.9,MeOH); ν_{max} (nujol) 3250(s), 2950(s), 2870(s), 1450(s), 1350(s), 1300(m), 1230(m), 1210(m), 1165(m), 1140(s), 1095(m), 1055(m), 1020(s), 935(m), 870(m), 800(m) cm^{-1}; δ(400MHz, $CDCl_3$) 1.11(3H,s), 1.35(1H,d,J=11.5Hz), 1.57(1H,br), 1.61~1.74(2H,m), 1.85~1.93(1H,m), 1.96~ 2.08(2H,m), 3.35(3H,s), 3.54(1H,dd,J=8.2 and 1.4Hz), 3.59~3.64(1H,m), 4.03(1H,dd,J=8.2 and 0.9Hz) HRMS *m/z* Found: 154.1039 Calc. for $C_9H_{14}O_2(M^+-H_2O)$: 154.0994

Ethyl (1*S*,2*S*)-1-benzyloxymethyl-5,5-ethylenedioxy-2-hydroxycyclohexanecarboxylate 10

To an LDA solution prepared from diisopropylamine (22 ml,157 mmol) and *n*-BuLi (1.49 N, 105 ml,157 mmol) in dry THF (90 ml) was added dropwise a soln of 5 (15.0 g,65.2 mmol) in dry THF (60 ml) at -70°C. After stirring for 1 h at -15°C, BOMCl (13 ml,93.5 mmol), distilled twice just before use, in HMPA (45 ml) was added at once, and the temperature was raised to 20°C. After stirring for 20 min at room temp, the reaction mixture was poured into sat NH_4Cl soln and extracted with ether (×5). The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (450 g). Elution with *n*-hexane-EtOAc (12:1~4:1) gave 16.1 g (70 %) of 10, ν_{max}(film) 2990(s), 2900 (s), 1740(s) 1440(m), 1370(s), 1240(s), 1190(m), 1120(m), 1090(s), 1060(m), 1035(m), 970 (m), 950(m); This was employed in the next step without further purification.

Ethyl (1*S*,2*S*)-5,5-ethylenedioxy-2-hydroxy-1-hydroxymethylcyclohexanecarboxylate 11

A mixture of 10 (47.0 g,134.3 mmol) and Pd-C (4 g) in EtOAc (80 ml) was shaken under H_2 (3 atm) until UV absorption disappeared on TLC. Pd-C was filtered off, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over SiO_2 (700 g). Elution with *n*-hexane-EtOAc (2:1~1:1) gave 26.9 g (77 %) of 11, n_D^{16} 1.4834; $[\alpha]_D^{16}$ +27.6°(c=1.09,$CHCl_3$); ν_{max}(film) 3470(s), 2950(s), 2900(s), 1710(s), 1445(m), 1365(m), 1170(m), 1110(s), 1050(s),

980(m), 950(m), 920(m) cm^{-1}; δ(100MHz,$CDCl_3$) 1.33(3H,t,J=7Hz), 1.68(1H,dd,J=12 and 5Hz), 2.17(1H,dd,J=12 and 3Hz), 1.5~2.2(4H,m), 3.5~4.1(7H,m), 3.77(2H,s), 4.25(2H,q,J=7Hz) (Found: C,54.88; H,7.66 Calc. for $C_{12}H_{20}O_6$: C,55.37; H,7.75%)

Ethyl (1*S*,2*S*,5*S*)-2-hydroxy-5-methoxy-6-oxabicyclo[3.2.1]octane-1-carboxylate 12a

A mixture of 11 (7.16 g,27.5 mmol) and *p*-TsOH·H_2O (520 mg) in dry MeOH (70 ml) was stirred for 8 h at room temp. To this was added solid $NaHCO_3$, and the reaction mixture was diluted with ether (350 ml). The precipitate was filtered through a celite pad and the filtrate was concentrated *in vacuo*. The residue was chromatograghed over SiO_2 (75 g). Elution with *n*-hexane-EtOAc (6:1~1:1) gave 5.14 g (81 %) of 12a and 0.8 g of recovered 11. In the same manner as described above, recovered 11 gave 0.53 g of 12a and total 5.67 g (90 %) of 12a was obtained; n_D^{15} 1.4757; $[\alpha]_D^{15}$ +4.0°(c=1.02,MeOH); ν_{max}(film) 3470(s), 2950(s), 1725(s), 1445(m), 1340(m), 1260(s), 1200(m), 1080(m), 1020(s), 980(s), 885(m), 845(m) cm^{-1}; δ(100MHz,$CDCl_3$) 1.30(3H,t,J=7Hz), 1.7~2.0(4H,m), 2.23(1H,d,J=11Hz), 2.32 (1H,d,J=11Hz), 2.81 (1H,d,J=3Hz), 3.42(3H,s), 3.77(1H,d,J=8Hz), 4.15(1H,d,J=8Hz), 4.21(2H,q,J=7Hz), 4.1~4.3(1H, m) (Found: C,57.12; H,7.73 Calc. for $C_{11}H_{18}O_5$: C,57.38; H,7.88%)

Ethyl (1*S*,2*S*,5*S*)-2-acetoxy-5-methoxy-6-oxabicyclo[3.2.1]octane-1-carboxylate 12b

A mixture of 12a (5.0 g,21.7 mmol), Ac_2O (10.4 ml,110 mmol) and 4-*N*,*N*-dimethylamino-pyridine (270 mg,2.2 mmol) in dry pyridine (30 ml) was stirred for 2 h at room temp. The reaction mixture was quenched with water and extracted with ether. The extract was washed with sat $CuSO_4$ soln (×3), water, sat $NaHCO_3$ soln, and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 5.8 g (98 %) of acetate 12b. This is pure enough (TLC, NMR, and IR) using for the next step. Analytical sample was obtained by SiO_2 chromatography. 12b; n_D^{15} 1.4612; $[\alpha]_D^{15}$ +2.1°(c=1.11,$CHCl_3$); ν_{max}(film) 2980(m), 1740(s), 1445(m), 1370(m), 1265(s), 1240 (s), 1200 (m), 1105(m), 1085(m), 1025(s), 980(m), 860(m) cm^{-1}; δ(100MHz,$CDCl_3$) 1.24(3H,t, J=7Hz), 1.7~2.2(5H,m), 2.06(3H,s), 2.47(1H,d,J=12Hz), 3.42(3H,s), 3.87(1H,d,J=8Hz), 3.93(1H, d,J=8Hz) 4.14(2H,dq,J=2 and 7Hz), 5.41(1H,br,hhw=7Hz). (Found: C,57.34; H,7.40 Calc. for $C_{13}H_{20}O_6$: C,57.07; H,7.29%)

(1*S*,2*S*,5*S*)-1-Hydroxymethyl-5-methoxy-6-oxabicyclo[3.2.1]octan-2-ol 13

To a stirred suspension of LAH (1.5 g,3.8 mmol) in dry THF (20 ml) was added a soln of 12b (5.8 g,21.3 mmol) in dry THF (20 ml) with ice-cooling. After stirring for 3 h at room temp, the reaction mixture was quenched with water (1.5 ml), 15% NaOH (1.5 ml), and water (4.5 ml). The precipitate was filtered through a celite pad and washed thoroughly with THF. The combined filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatograghed over SiO_2 (20 g). Elution with *n*-hexane-EtOAc (2:3~1:2) gave 3.9 g (97 %) of 13, n_D^{16} 1.4898; $[\alpha]_D^{16}$ -20.2°(c=1.01,MeOH); ν_{max}(film) 3420(s), 2950(s), 2880(m), 1450 (m), 1345(s), 1305(s), 1250(m), 1200(s), 1100(s), 1065(m), 1025(s), 965(m), 925(m), 870(m), 845 (m), 765(m) cm^{-1}; δ(100MHz,$CDCl_3$) 1.6~2.2(6H,m), 2.22(1H,t,J=5Hz), 2.73(1H,d,J=2Hz), 3.40 (3H,s), 3.61(2H,s), 3.76(2H,d,J=5Hz), 4.06(1H,br,hhw=6Hz) (Found: C,57.00; H,8.57 Calc. for $C_9H_{16}O_4$: C,57.43; H,8.57%)

(1*R*,2*S*,5*S*)-5-Methoxy-1-*p*-toluenesulfonyloxymethyl-6-oxabicyclo[3.2.1]octan-2-ol 14

To a soln of 13 (11.5 g,61.2 mmol) and 4-*N*,*N*-dimethylaminopyridine (2.24 g,18.3 mmol) in dry pyridine (50 ml) was added *p*-TsCl (15.2 g,79.7 mmol) at -10°C. The mixture was stirred for 7 h at -5°C. To the reaction mixture was added water (5 ml). After stirring for 30 min, the mixture was poured into water (300 ml) and extracted with ether. The extract was washed with sat $CuSO_4$ soln (×3), water, sat $NaHCO_3$ soln, and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (250 g). Elution with *n*-hexane-EtOAc (4:1~2:1) gave 17.0 g (81 %) of unstable tosylate 14, ν_{max}(film) 3450(m), 2950(m), 1595(m), 1450(m), 1355(s), 1305(m), 1230(m), 1190(s), 1175(s), 1100(s), 1030(s), 990(m), 960(s), 835 (m), 815(m), 760(m) cm^{-1}; δ(100MHz,$CDCl_3$) 1.58(1H,s), 1.7~1.9(6H,m), 2.47(3H,s), 3.34(3H,s), 3.72(2H,s), 3.80(1H,d,J=10Hz), 3.98(1H,br,hhw=7Hz), 4.37(1H,d,J=10Hz), 7.37(2H,d,J=8Hz), 7.79(2H,d,J=8Hz). This was employed for the next step without further purification.

(1*R*,2*S*,5*S*)-5-Methoxy-1-methyl-6-oxabicyclo[3.2.1]octan-2-ol 15a

To a soln of 14 (15.5 g,45.3 mmol) in dry THF (50 ml) was added dropwise Super-Hydride® (1 M,190 ml,190 mmol) with ice-cooling. After stirring for 2 h at room temp, the reaction mixture was quenched with water (1.5 ml), 3N NaOH (80 ml) and 35% H_2O_2 aq (70 ml), and

stirred for 1 h. The mixture was extracted with ether. The extract was washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (200 g). Elution with *n*-hexane-EtOAc (5:1~3:1) gave 6.50 g (83 %) of crystalline 15a. Recrystallization from *n*-hexane-*i*-Pr_2O gave 4.42 g (57 %) of pure 15a as fine needles, m.p. 42.5~43.0°C; $[\alpha]_D^{20}$ -28.5°(c=1.05,MeOH); ν_{max}(KBr) 3360(s), 2970(s), 2900(s), 1460(s), 1380(s), 1310(s), 1215(s), 1205(s), 1125(s), 1110(s), 1070(m), 1035(s), 1010(s), 970(s), 930(s), 875(m), 850(m), 770(m) cm^{-1}; δ(100MHz,$CDCl_3$) 1.12(3H,s), 1.7~2.0(7H,m), 3.38(3H,s), 3.63(1H,s), 3.6~3.7(1H,br). HRMS *m/z* Found: 154.0935 Calc. for $C_9H_{14}O_2(M^+-H_2O)$: 154.0994

5-Methoxy-1-methyl-6-oxabicyclo[3.2.1]octan-2-one 9

(a) (-)-isomer

To a stirred suspension of PDC (8.2 g,21.8 mmol) and finely powdered molecular sieves (8 g) in dry CH_2Cl_2 (20 ml) was added 8a (2.5 g,14.5 mmol) with ice-cooling. After stirring for 6 h at room temp, the reaction mixture was filtered through Florisil pad and the slurry was washed well with ether. The combined filtrate was concentrated *in vacuo*. The residue was chromatographed over SiO_2 (60 g). Elution with *n*-hexane-EtOAc (10:1~8:1) gave 2.2 g (89 %) of (-)-9, n_D^{18} 1.4705; $[\alpha]_D^{18}$ -48.0°(c=1.73,MeOH); ν_{max}(film) 2990(s), 2890(m), 1715(s), 1445 (m), 1350(m), 1315(m), 1290(s), 1235(m), 1205(s), 1140(s), 1110(m), 1075(m), 1040(s) 1025 (s), 1000(m), 935(s), 875(m), 790(m) cm^{-1}; δ(100MHz,$CDCl_3$) 1.17(3H,s), 1.6~2.8(6H,m) 3.45 (3H,s), 3.81(1H,d,J=8Hz), 3.94(1H,d,J=8Hz). (Found: C,63.47; H,8.29 Calc. for C_9H_{14} C,63.51; H,8.29%)

(b) (+)-isomer

In the same manner as described above, 15a (3.1 g,18.0 mmol) gave 2.74 g (89 %) of (+)-9, n_D^{20} 1.4689; $[\alpha]_D^{20}$ +49.2°(c=1.42,MeOH); The IR and NMR spectra were identical with those of (-)-9. (Found: C,63.06; H,8.19 Calc. for $C_9H_{14}O_3$: C,63.51; H,8.29%)

5-Methoxy-1,3-dimethyl-6-oxabicyclo[3.2.1]oct-3-en-2-one 16

(a) (-)-isomer

To a $(TMS)_2NLi$ solution prepared from $(TMS)_2NH$ (1.5 ml) and *n*-BuLi (1.49 N,4.7 ml,7.0 ml) in dry THF (8 ml) was added dropwise a soln of (-)-9 (1.0 g,5.9 mmol) in dry THF (8 ml) at -78°C. After stirring for 1 h at -78°C, PhSeBr (1.8 g,7.6 mmol) in dry THF (8 ml) was added dropwise. After stirring for 20 min, the reaction mixture was poured into water, and extracted with ether. The extract was washed with water, sat $NaHCO_3$ soln, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was roughly chromatographed over SiO_2. Elution with *n*-hexane-EtOAc (25:1~20:1) gave unstable phenylselenyl ketone. ν_{max}(film) 3060(w), 2970(s), 2930(s),2860(m), 1690(s), 1570(w), 1475(s), 1435(s), 1380(w), 1330(s), 1275(w), 1200(s), 1140(m), 1070(m), 1030(s), 940(m), 800(m), 740(s), 690(s) cm^{-1}; This was employed for the next step without further purification.

To a stirred suspension of NaH (0.74 g,18.5 mmol) in dry THF (10 ml) was added phenylselnyl ketone (ca. 5.9 mmol) in dry THF (10 ml) at 0°C. After that, CH_3I (2 ml,32.1 mmol) was added. After stirring for 5 h at 0°C, the reaction mixture was poured into sat NH_4Cl soln, and extracted with ether. The extract was washed with water, sat $NaHCO_3$ soln, and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (60 g). Elution with hexane-EtOAc (25:1~20:1) gave 1.85 g (93 % from (+)-9) of unstable (1*R*,3*RS*,5*S*)-5-Methoxy-1,3-dimethyl-3-phenylseleno-6-oxabicyclo[3.2.1]octan-2-one, ν_{max}(film) 3060(w), 2980 (s), 2940(s), 2870(m), 1695(s), 1435(m), 1340(m), 1280(m), 1205(s), 1160(m) 1120(m), 1090 (s), 1050(m), 1035(s), 1020(s), 940(m), 915(m), 745(s), 690(s) cm^{-1}. This was employed for the next step without further purification.

To a soln of selenyl ketone (1.85 g,5.46 mmol) and solid $NaHCO_3$ (1 g) in dry THF (20 ml) was added 35%H_2O_2 aq (1 ml) at 20°C. After stirring for 1 h at room temp, the reaction mixture was quenched with water and extracted with ether. The extract was washed with sat $Na_2S_2O_3$ soln, sat $NaHCO_3$ soln, and brine, dried (K_2CO_3), and concentrated *in vacuo*. The residue was chromatographed over alumina (grade IV, 30 g). Elution with *n*-hexane-EtOAc (40:1~30:1) gave 0.65 g (65 %) of (-)-16, n_D^{17}1.4831; $[\alpha]_D^{17}$ -79.8°(c=1.75,MeOH); ν_{max}(film) 2990(s), 2950(s), 2880(m), 1680(s), 1640(w), 1450(s), 1325(s), 1280(s), 1245(s), 1160(m), 1130(s), 1090(m), 1025(s), 1000(s), 950(m), 935(s), 820(m), 765(m) cm^{-1}; δ(100MHz,C_6D_6) 1.12(3H,s), 1.47(1H,d,J=10Hz), 1.72(3H,d,J=2Hz), 1.80(1H,dd,J=10 and 3Hz), 3.26(3H,s), 3.35(1H,d,J=8Hz), 3.43(1H,d,J=8Hz), 6.76(1H,dt,J=3 and 2Hz). HRMS *m/z* Found: 182.0923 Calc. for $C_{10}H_{14}O_3$: 182.0943

(b) (+)-isomer

In the same manner as described above, 1.5 g of (+)-9 gave 2.65 g (89 % from (+)-9) of unstable (1*S*,3*RS*,5*R*)-5-methoxy-1,3-dimethyl-3-phenylseleno-6-oxabicyclo[3.2.1]octan-2-one, which gave 1.07 g (76 %) of (+)-16, n_D^{20} 1.4866; $[\alpha]_D^{20}$ +78.1°(c=1.60,MeOH). The IR and NMR spectra were identical with those of (-)-16. HRMS *m/z* Found: 182.0921 Calc. for $C_{10}H_{14}O_3$: 182.0943

5-Methoxy-1,3-dimethyl-2-[(*Z*)-3-methyl-5-*t*-butyldimethylsilyloxy-3-penten-1-yn-1-yl]-6-oxabicyclo[3.2.1]oct-3-en-2-ol 19

(a) (-)-isomer

To a soln of 18 (0.75 g,3.57 mmol) in dry THF (5 ml) was addded dropwise *n*-BuLi (1.49 N, 2.3 ml,3.43 mmol) at -78°C. After stirring for 10 min at -78°C, (-)-16 (0.43 g,2.36 mmol) in dry THF (5 ml) was added dropwise at -78°C. After stirring for 10 min at -30°C, the reaction mixture was poured into sat NH_4Cl soln, and extracted with ether. The extract was washed with water, sat $NaHCO_3$ soln, and brine, dried (K_2CO_3), and concentrated *in vacuo*. The residue was chromatographed over alumina (grade III,30 g). Elution with *n*-hexane-EtOAc (30:1 ~15:1) gave 0.86 g (93 %) of (-)-19, n_D^{16} 1.4975; $[\alpha]_D^{16}$ -113.9°(c=1.01,MeOH); ν_{max} (film) 3450(s), 2970(s), 2910(s), 2880(s), 1650(w), 1460(m), 1450(m), 1330(s), 1255 (s), 1235(m), 1120(s), 1095(s), 1055(s), 1015(s), 950(m), 840(s), 780(s) cm^{-1}; δ(100MHz,C_6D_6) 0.16(6H,s), 1.05(9H,s), 1.27(3H,s), 1.70(3H,d,J=2Hz), 1.77(1H,s), 1.82 (3H,d,J=2Hz), 1.96(1H,dd, J=11 and 2Hz), 2.13(1H,d,J=11Hz), 3.40(3H,s), 3.55(1H,d,J=9Hz), 4.35(1H,d,J=9Hz), 4.46(1H,d, J=1Hz), 4.53(1H,d,J=1Hz), 5.7~6.0(2H,m). HRMS *m/z* Found: 392.2372 Calc. for $C_{22}H_{36}O_4$: 392.2383.

(b) (+)-isomer

In the same manner as described above, (+)-16 (1.00 g,5.49 mmol) gave 1.93 g (90 %) of (+)-19, n_D^{19} 1.4976; $[\alpha]_D^{19}$ +115.0°(c=1.03,MeOH). The IR and NMR spectra were identical with those of (-)-19. HRMS *m/z* Found: 392.2380 Calc. for $C_{22}H_{36}O_4$: 392.2383

2-[(*Z*)-5-Hydroxy-3-methyl-3-pentene-1-yn-1-yl]-1,3-dimethyl-5-methoxy-6-oxabicyclo-[3.2.1]oct-3-en-2-ol 21

(a) (-)-isomer

A mixture of (-)-19 (0.84 g,2.14 mmol) and Et_4NF (0.57 g,3.8 mmol) in CH_3CN (5 ml) was stirred for 5 h at room temp. To this was added sat $NaHCO_3$ soln (2 ml). After stirring for 20 min, the reaction mixture was poured into sat $NaHCO_3$ soln and brine (1:1), and extracted with EtOAc. The extract was washed with sat $NaHCO_3$ soln and brine, dried (K_2CO_3), and concentrated *in vacuo*. The residue was chromatographed over alumina (grade IV,20 g). Elution with *n*-hexane-EtOAc (5:1~3:1) gave 600 mg (quantitative) of (-)-21, $n_D^{16.5}$ 1.5236; $[\alpha]_D^{16.5}$ -242.4°(c=1.73,MeOH); ν_{max}(film) 3400(s), 3000(s), 2910(s), 1655(m), 1450(s), 1375(m), 1330 (s), 1295(m), 1235(s), 1125(s), 1090(s), 1010(br), 950(m), 820(m) cm^{-1}; δ(100MHz,C_6D_6) 1.34(3H,s), 1.72(3H,d,J=2Hz), 1.90(3H,d,J=2Hz), 1.96(1H,dd,J=11 and 2Hz), 2.13(1H,d,J=11Hz), 2.98(1H,s,hhw=4Hz), 3.42(3H,s), 3.59(1H,d,J=9Hz), 4.23(2H,br,hhw=14Hz), 4.40(1H,d,J=9Hz), 5.72(1H,tq,J=7 and 2Hz), 5.90(1H,dq,J=2 and 2Hz). HRMS *m/z* Found: 278.1494 Calc. for $C_{16}H_{22}O_4$: 278.1518

(b) (+)-isomer

In the same manner as described above, (+)-19 (1.74 g,4.44 mmol) gave 1.19 g (96 %) of (+)-21, n_D^{19} 1.5286; $[\alpha]_D^{19}$ +249.6°(c=2.36,MeOH). The IR and NMR spectra were identical with those of (-)-21. HRMS *m/z* Found: 278.1532 Calc. for $C_{16}H_{22}O_4$: 278.1518

2-[(1*E*,3*Z*)-5-Hydroxy-3-methyl-1,3-pentadien-1-yl]-1,3-dimethyl-5-methoxy-6-oxabicyclo[3.2.1]oct-3-en-2-ol 22

(a) (-)-isomer

To a soln of (-)-21 (570 mg,2.05 mmol) in dry THF (10 ml) was added dropwise Red-Al® (3.4 M,2.4 ml,8.16 mmol) at -10°C. After stirring for 2 h at 0°C, excess Red-Al® was destroyed with water. The reaction mixture was poured into sat NH_4Cl soln, and extracted with EtOAc. The extract was washed with sat $NaHCO_3$ soln and brine, dried (K_2CO_3), and concentrated *in vacuo*. The residue was roughly chromatographed over alumina (grade IV,20 g). Elution with *n*-hexane-EtOAc (3:1~2:1) gave 350 mg (61 %) of unstable (-)-22, ν_{max}(film) 3420 (s), 2970(s), 2900(m), 1650(m), 1450(m), 1375(m), 1330(m), 1230(m), 1120(s), 1090(m), 1010 (s), 930(m), 820(m) cm^{-1}; δ(100MHz,C_6D_6) 0.98(3H,s), 1.56(3H,d,J=1Hz), 1.72(1H,d,J=3Hz), 1.74(3H,s), 1.82(1H,d,J=3Hz), 3.43(3H,s), 3.54(1H,d,J=9Hz), 4.12(2H,br,hhw=14Hz), 4.31(1H,d, J=9Hz), 5.52(1H,brt,J=7Hz), 5.69(1H,d,J=16Hz), 5.96(1H,br), 6.75(1H,d,J=16Hz). This was

employed for the next step without further purification.
(b) (+)-isomer
In the same manner as described above, (+)-21 (1.08 g,3.88 mmol) gave 750 mg (69 %) of (+)-22. The IR and NMR spectra were identical with those of (-)-22.

Methyl (2*Z*,4*E*)-5-(2-hydroxy-5-methoxy-1,3-dimethyl-6-oxabicyclo[3.2.1]oct-3-en-2-yl)-3-methyl-2,4-pentadienoate 23.
(a) (-)-isomer
A mixture of (-)-22 (300 mg,1.07 mmol) and active MnO_2(1.2 g) in dry CH_2Cl_2 (5 ml) was stirred vigorously for 5 h at room temp. MnO_2 was filtered off and the filtrate was concentrated *in vacuo*. A mixture of this residue, active MnO_2 (1.3 g), NaCN (130 mg), and AcOH (0.05 ml) in dry MeOH (10 ml) was stirred for 5 h at room temp. MnO_2 was filtered off and MeOH was removed *in vacuo*. To the residue was added water and the mixture was extracted with ether (×5). The extract was washed with sat $NaHCO_3$ soln and brine, dried (K_2CO_3), and concentrated *in vacuo*. The residue was chromatographed over alumina (grade IV,5 g). Elution with *n*-hexane-EtOAc (10:1~8:1) gave 235 mg (71 %) of (-)-23, $n_D^{16.5}$ 1.5167; $[\alpha]_D^{16.5}$ -156.5° (c=0.65,MeOH); ν_{max}(film) 3500(s), 2960(s), 2900(m), 1715(s), 1635(m), 1605(s), 1450(s), 1380(m), 1330(s), 1230(s), 1160(s), 1125(s), 1020(s), 940(m), 820(m) cm^{-1}; δ(100MHz,C_6D_6) 0.98(3H,s), 1.38(3H,s), 1.68(3H,d,J=2Hz), 1.8~2.5(3H,m), 3.18(3H,s), 3.45(3H,s), 3.4~3.7(2H, m), 4.62(1H,d,J=2Hz), 5.75(1H,br,hhw=4Hz), 6.30(1H,d,J=16Hz), 8.65(1H,d,J=16Hz). HRMS *m/z* Found: 308.1687 Calc. for $C_{17}H_{24}O_5$: 308.1624
(b) (+)-isomer
In the same manner as described above, (+)-22 (580 mg,2.07 mmol) gave 470 mg (74 %) of (+)-23, n_D^{18} 1.5266; $[\alpha]_D^{18}$ +153.1°(c=2.15,MeOH). The IR and NMR spectra were identical with those of (-)-23. HRMS *m/z* Found: 308.1624 Calc. for $C_{17}H_{24}O_5$: 308.1670

Methyl (2*Z*,4*E*)-5-(8-hydroxy-1,5-dimethyl-3-oxo-6-oxabicyclo[3.2.1]octan-8-yl)-3-methyl-2,4-pentadienoate (Methyl phaseate) 2b
(a) (+)-methyl phaseate
A soln of (-)-23 (230 mg,0.75 mmol) in THF (5 ml) and 0.5 N HCl aq (5 ml) was stirred for 2 days. The reaction mixture was neutralized by adding sat $NaHCO_3$ soln, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (10 g). Elution with *n*-hexane-EtOAc (4:1~1:1) gave 210 mg (95 %) of 2b. Recrystallization gave 200 mg (90 %) of pure (+)-2b ((+)-methyl phaseate) as needles, m.p. 158.5~159.5°C; $[\alpha]_D^{16}$ +33.0°(c=0.97,$CHCl_3$); UV(MeOH) λ_{max} 265 nm (ε 18200); ν_{max}(KBr) 3460(s), 3000(w), 2970(m), 2910(w), 1715(s), 1690(s), 1635(w), 1600(m), 1460(w), 1430(w), 1375(m), 1230(s), 1165(s), 1065(w), 1045(m), 1020(m), 985(m), 920(w), 890(w), 850 (m), 815(w), 690(m) cm^{-1}; δ(300MHz, $CDCl_3$) 1.04(3H,s), 1.25(3H,s), 1.5~1.8(1H), 2.02(3H,d, J=1.1Hz), 2.48(1H,d,J=18.4Hz), 2.54(1H,dd,J=18.5 and 2.6Hz), 2.63(1H,d,J=18.4Hz), 2.65(1H, dd,J=18.5 and 1.4Hz), 3.73(3H,s), 3.78(1H,d,J=8.1Hz), 3.97(1H,dd,J=8.1 and 2.6Hz), 5.80(1H, s), 6.23(1H,d,J=15.8Hz), 8.17(1H,d,J=15.8Hz); ^{13}C-NMR(75MHz,$CDCl_3$) δ 15.7, 18.9, 21.0, 48.2, 51.3, 52.5, 52.7, 77.5, 82.3, 85.8, 118.8, 131.1, 131.8, 148.9, 166.4, 208.0. (Found: C,65.18; H,7.48 Calc. for $C_{16}H_{22}O_5$: C,65.29; H,7.53%)
(b) (-)-methyl phaseate
In the same manner as described above, (+)-23 (400 mg,1.3 mmol) gave 340 mg (90 %) of pure (-)-2b ((-)-methyl phaseate), m.p. 158.5~159.0°C; $[\alpha]_D^{17}$ -33.6°(c=0.93 or 0.1,$CHCl_3$). The IR, NMR, and UV data were identical with those of (+)-2b. (Found: C,65.40; H,7.53 Calc. for $C_{16}H_{22}O_5$: C,65.29; H,7.53%)

(2*Z*,4*E*)-5-(8-Hydroxy-1,5-dimethyl-3-oxo-6-oxabicyclo[3.2.1]octan-8-yl)-3-methyl-2,4-pentadienoic acid (Phaseic acid) 2a
(a) (+)-isomer
To a solution of (+)-2b (50 mg) in THF (2 ml) was added 0.1N LiOH aq (2 ml). After stirring for 2 days, the reaction mixture was diluted with sat. $NaHCO_3$ soln and extracted with ether. The extract was concentrated *in vacuo* to give 10 mg of recovered (+)-2b. The water layer was acidified by addition of dil. HCl aq and extracted with ether. The extract was concentrated *in vacuo* to give 20 mg of (+)-2a as amorphous solid. Recrystallization from $CHCl_3$ gave 10 mg of pure (+)-2a, m.p. 193~196°C (dec.); $[\alpha]_D^{21}$ +18.5°(c=0.11,MeOH); UV(MeOH) λ_{max} 262 nm (ε 16000); ν_{max}(KBr) 3460(s), 2950(s), 2770(w), 2680(w), 2590 (w), 1710(s), 1690 (s), 1630(s), 1600(s), 1450(m), 1410(m), 1380(m), 1280(s), 1255(s), 1200 (m), 1145(m), 1060 (m), 1020(s), 990(m), 955(m), 920(w), 890(w), 860(m), 820(w), 780(w), 725 (m), 690(w) cm^{-1};

δ(300Mz,$CDCl_3$) 1.04(3H,s), 1.25(3H,s), 2.06(3H,s), 2.50(1H,d,J=17.7Hz), 2.55(1H,dd,J=20 and 2.3Hz), 2.63(1H,d,J=18.3Hz), 2.67(1H,dd,J=20 and 1.5Hz), 3.79(1H,d,J=8.2Hz), 3.97(1H,dd, J=8.2 and 2.3Hz), 5.83(1H,s), 6.27(1H,d,J=15.8Hz), 8.12(1H,d,J=15.8Hz). δ(100MHz,$(CD_3)_2CO$) 1.02(3H,s), 1.20(3H,s), 2.0~3.0(7H,m), 3.63(1H,d,J=8Hz), 3.94(1H,dd,J=8 and 2Hz), 4.16(1H,s), 5.77(1H,s), 6.44(1H,d,J=16Hz), 8.18(1H,d,J=16Hz), 10.6(1H,br). (Found: C,63.88; H,7.19 Calc. for $C_{15}H_{20}O_5$: C,64.27; H,7.19%)

(b) (-)-isomer

In the same manner as described above, (-)-2b (50 mg) gave 10 mg of pure (-)-2a, m.p. 190~195°C (dec.); $[\alpha]_D^{16}$ -18.0°(c=0.10,MeOH). The IR, NMR and UV data were identical with those of (+)-2a. (Found: C,64.02; H,7.19 Calc. for $C_{15}H_{20}O_5$: C,64.27; H,7.19%)

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14. PDC oxidation of **10** followed by $NaBH_4$ reduction gave unseparable two isomers, **10** and its epimer. The signals of benzylic methylene proton showed clearly separated two singlet peaks, whereas that of **10** showed sharp one peak in 100MHz ^{1}H-NMR.
15. Direct hydride reduction of hydroxyesters, **6a** and **12a** gave substantial amount of by-products to reduce the yields of **7a** and **13** (~40%) presumably by initial formation of alkoxide ion. Two step conversion via the acetate gave much purer products in higher yields.
16. Determination of the optical purity of **8a** and **15a** was carried out by HPLC as follows: Each diastereomer, **8a** or **15a**, was converted to the corresponding (*R*)- and (*S*)-MTPA ester, **8b** or **15b**. HPLC analytical conditions; column normal phase, Nucleosil® 50-5, 4.6 mm × 25cm, eluent *n*-hexane-THF (10 : 1), flow rate 1.0 ml/min (30 kg/cm^2), detected at 254 nm; (*S*)-**8b**, Rt 23.8 min (99.5%) 22.6 min(0.5%), (*S*)-**15b**, Rt 19.1 min (99.3%) 17.7 min (0.7%). Therefore, the optical purities of **8a** and **15a** were determined to be **99.0% e.e.** and **98.6% e.e.** Moreover the diastereomeric excesses of **8a** and **15a** were determined to be **100% d.e.**

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21. Determination of the optical purities of (+)- and (-)-2b were carried out as follows: To a soln of (±)-2b (4 mg) in $CDCl_3$ (~0.35 ml) was added 6.5 mg of $Eu(hfc)_3$. The signals of methyl proton showed clearly separated two singlet peaks, whereas that of (+)- and (-)-2b showed sharp one peak in 300MHz ^{1}H-NMR. The chemical shifts of methyl group of (+)- and (-)-2b were 1.52 and 1.49 ppm respectively.
22. Hplc analysis was performed by Dr. M. Okamoto, Biochemical and Toxicological Laboratory, Sumitomo Chemical Industry Co. Detailed result including experimental will be published independently.