ASYMMETRIC SYNTHESIS OF KEY SYNTHETIC INTERMEDIATES OF *ASPIDOSPERMA* AND *HUNTERIA* TYPE INDOLE ALKALOIDS

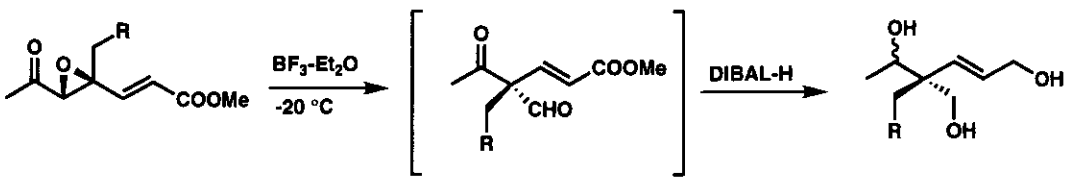
Kunisuke Okada,* Kazumasa Murakami, Hideo Tanino, Hisae Kakoi, and Shoji Inoue

Faculty of Pharmacy, Meijo University, Tenpaku, Nagoya 468, Japan

Abstract - Chiral synthon (**6**), prepared from α,β-epoxy ketone (**4**) *via* 1,2 acyl migration reaction as a key step, was converted to lactones (**7**) and (**8**), the key intermediates for *Aspidosperma* and *Hunteria* type indole alkaloids.

Condensation of tryptamine with the C9 unit having a chiral quaternary carbon center has been shown quite useful for synthesizing *Aspidosperma* and *Hunteria* type indole alkaloids.[1,2] Construction of quaternary building block (**3**) *via* 1,2-acyl migration of the optically active α,β-epoxy ketone (**1** to **2**)[3] was studied to establish an enantioselective synthesis of chiral synthon (**6**) corresponding to the C9 unit. Acyl migration in optically active epoxy ketone (**4**) {90% ee; $[\alpha]_D^{25}$ -9.41° (c 0.90, $CHCl_3$)} was found to occur in the presence of boron trifluoride etherate at -20 ℃ with inversion of the configuration at the migration terminus with high degree of concertedness. The keto aldehyde (**5**) thus obtained was reduced with diisobutyl-aluminum hydride (DIBAL-H) to give the C9 triol (**6**).[4] (Scheme 1)

Scheme 1



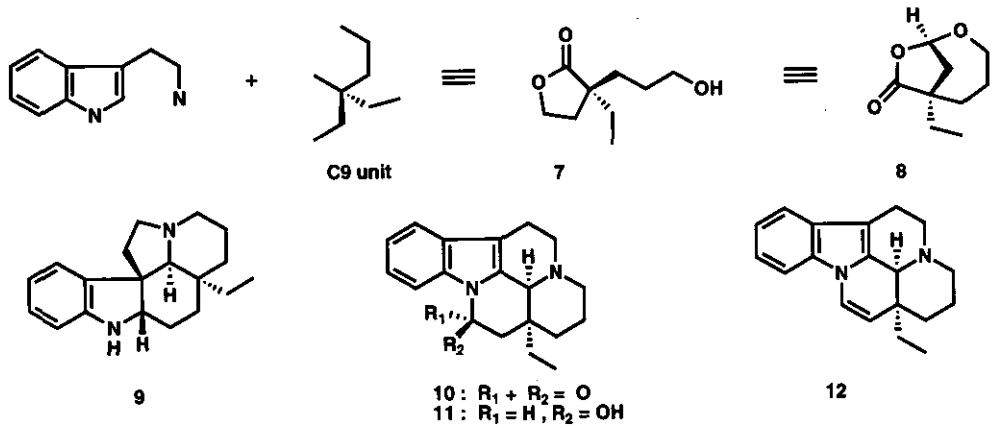
1: R=H
4: R=Me

2: R=H
5: R=Me

3: R=H
6: R=Me

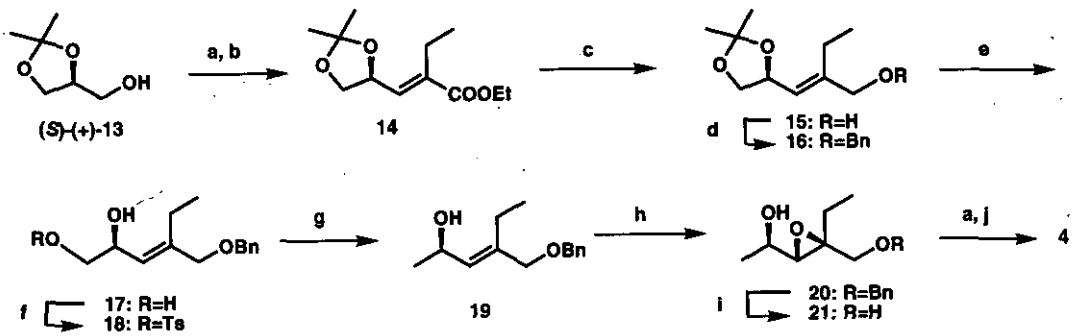
Now, we describe here a conventional synthesis of the starting material (**4**) and a method for the conversion of C9 triol (**6**) to lactone (**7**) and bicyclic lactone (**8**), known key intermediates[1] for the synthesis of *Aspidosperma* and *Hunteria* type indole alkaloids such as (-)-aspidospermidine (**9**), (-)-eburnamonine (**10**), (+)-eburnamine (**11**), and (-)-eburnamenine (**12**) as depicted in Chart 1, is presented and discussed in the following.

Chart 1



The synthesis of chiral epoxy ketone (**4**) starting from (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (**13**) through optical active epoxy alcohol (**20**) was achieved conventionally in 11 steps (overall yield 50.2%) as summarized in Scheme 2.

Scheme 2

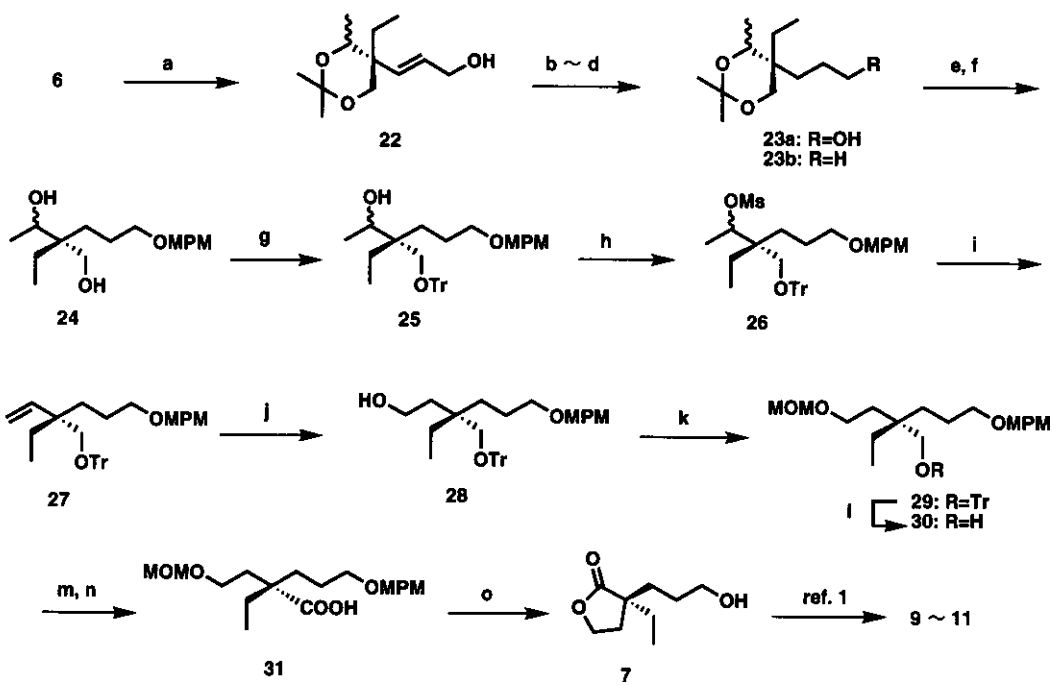


a) Swern oxidn; b) $Ph_3P=C(C_2H_5)COOEt$; c) DIBAL-H; d) NaH /BnBr; e) 80% AcOH; f) TsCl / py; g) LAH; h) *m*-CPBA; i) H2 / Pd-C; j) $Ph_3P=CHCOOMe$

Thus, treatment of **4** with BF_3-Et_2O in CH_2Cl_2 at -20 ℃ for 1.5 h followed by direct reduction of the resulting migration product (**5**) with DIBAL-H (5.0 mol equiv.) in CH_2Cl_2 at -20 ℃ in the presence of powdered $NaHCO_3$ yielded triol (**6**) in 70.0% yield, after purification on a silica gel column.

As a first step on the synthesis of lactone (**7**) from triol (**6**) (Scheme 3), **6** was converted to **22** by treatment with 2,2-dimethoxypropane in the presence of camphorsulfonic acid (CSA) in dimethylformamide (DMF) at 90 ℃ for 15 min in nearly quantitative yield.

Scheme 3

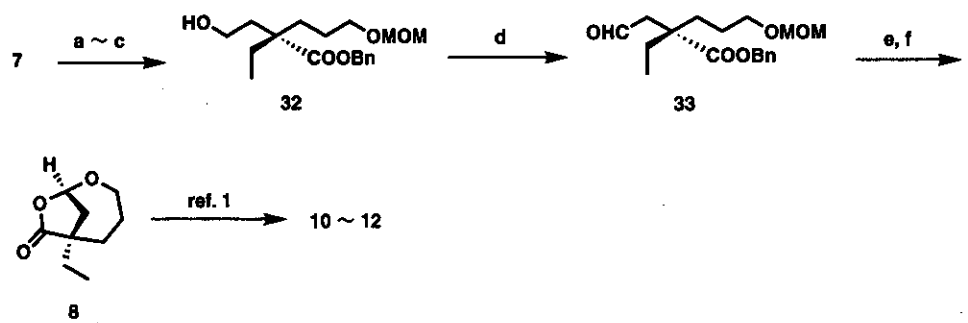


a) 2,2-dimethoxypropane / CSA; b) PCC; c) H_2 / 10% Pd-C; d) $NaBH_4$; e) NaH / MPMCl; f) 1N HCl; g) TrCl / py; h) MsCl / py; i) DBU; j) BH_3-THF / H_2O_2, NaOH; k) MOMCl / DIPEA; l) 80% AcOH; m) SO_3-py / DMSO / TEA; n) $NaClO_2$; o) 1N HCl

The transformation of **22** to dihydro derivative (**23a**)[5] was carried out in 58.0% overall yield as follows: i) oxidation with pyridinium chlorochromate (PCC) in CH_2Cl_2, ii) catalytic hydrogenation in ethyl acetate [10% palladium on carbon (Pd-C), H_2 atmosphere], and iii) reduction with $NaBH_4$ in MeOH. Protection of the primary alcohol of **23a** by treatment with 4-methoxybenzyl chloride (MPMCl) and NaH in DMF followed by selective deprotection of the acetonide moiety generated diol (**24**) (87.8% yield), which was further transformed to mesylate (**26**) [methanesulfonyl chloride (MsCl) / pyridine (py), room temperature] through trityl ether (**25**) [trityl chloride (TrCl) / py, 90 ℃, 1 h] in 81.9% yield in two steps. Removal of the methanesulfonyl group of **26** was completed by heating with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene for 30 h to give olefin (**27**) {$[\alpha]_{D25}$ +4.63° (c 1.00, $CHCl_3$)} in 93.2% yield. The hydroboration of **27** in the conventional way produced C2 alcohol (**28**){$[\alpha]_{D25}$ +6.24°(c 0.87, $CHCl_3$)} in

70.9% yield, which was protected by the methoxymethyl group [methoxymethyl chloride (MOMCl), diisopropylethylamine (DIPEA) in CH_2Cl_2, 0 ℃, 30 min], affording **29** (98.7%). This was followed by deprotection of the trityl group (80% acetic acid, 60 ℃, 30 min), to give C1 alcohol (**30**) {$[\alpha]_D^{25}$ +6.87° (c 0.92, $CHCl_3$)} in 82.1% yield. Transformation of the hydroxymethyl group of **30** to carboxylic acid was done in 95.5% yield by stepwise oxidation as follows: i) SO_3-pyridine complex, dimethyl sulfoxide (DMSO), and triethylamine (TEA) in CH_2Cl_2, ii) $NaClO_2$ in *t*-butyl alcohol. Treatment of the resulting carboxylic acid (**31**) with 1N HCl-MeOH (60 ℃, 1 h) gave rise to the desired lactone (**7**)[1b] {$[\alpha]_D^{25}$ +1.65° (c 0.35, $CHCl_3$)} in 80.0% yield after purification on tlc, whose spectral data were found superimposable on those of the authentic compound. Lactone (**7**) has been used for the synthesis of (-)-aspidospermidine (**9**), (-)-eburnamonine (**10**), and (+)-eburnamine (**11**), respectively.[1]

Scheme 4



a) 1. MOMCl / DIPEA; b) 1.5N KOH; c) BnBr; d) SO_3-py / DMSO / TEA; e) H_2 / 10% Pd-C; f) 4N HCl

Further transformation from lactone (**7**) to bicyclic lactone (**8**) was conducted as follows (Scheme 4): after protection of the C3 primary alcohol of **7** with MOM group, the lactone was hydrolized with a mixture of 1.5N KOH aqueous solution and MeOH (80 ℃, 2.5 h). The reaction mixture was neutralized with carbon dioxide, and then concentrated and dried under vacuum. The residue was treated with benzyl bromide (BnBr) in DMF to afford benzyl ester (**32**) in 59.3% overall yield from **7**. The C2 primary alcohol of **32** thus obtained was oxidized with SO_3-pyridine complex-DMSO-TEA to give aldehyde (**33**). The hydrogenolysis of **33** (H_2/10% Pd-C in ethyl acetate) and lactonization (4N HCl in dioxane=1:1) furnished the desired bicyclic lactone (**8**)[1a] {$[\alpha]_D^{25}$ +4.60° (c 0.30, $CHCl_3$)} in 72.9% yield after recrystallization from ether (mp 82.5~84 ℃), the spectral data of which were completely identical with those of the authentic compound, which has been transformed to (-)-eburnamonine (**10**), (+)-eburnamine

(**11**), and (-)- eburnamenine (**12**).[1] Further study on triol (**6**) and its derivatives is in progress.

EXPERIMENTAL

Melting point is uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Infrared (ir) spectra were recorded with a JASCO IR-A spectrophotometer. ^{1}H-Nmr spectra were measured with a JNM-GX 270 or a JNM-GX 400 spectrometer . The chemical shifts were expressed in ppm (δ) downfield from tetramethylsilane as internal standard. The following abbreviations were used: singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), multiplet (m), and broad (br). Mass (ms) spectra were obtained with Hitachi M-80 (EI) or JEOL HX-110 (FAB) spectrometer. Column chromatography was performed on Kanto Chemical silica gel (over 100 mesh) or Wakogel C-300 (flash column chromatography). Tlc was carried out on Kieselgel 60F254 plates (Art. 5744, Merck). Unless otherwise noted, all reaction mixtures were dried, after work up, over anhydrous Na_2SO_4.

Compound (14)

To a stirred solution of $(COCl)_2$ (3.85 ml, 44.13 mmol) in dry CH_2Cl_2 (75 ml) at -78 ℃ was added DMSO (6.70 ml, 94.42 mmol) and the mixture was stirred for 10 min at -78 ℃. After addition of a solution of (*S*)-(+)-**13** (4.67 ml, 37.81 mmol) in dry CH_2Cl_2 (50 ml) at -78 ℃, the mixture was stirred for 15 min at -78 ℃. After addition of TEA (21 ml, 150.7 mmol) at -78 ℃, the mixture was further stirred for 1 h at -78 ℃ to room temperature. To the resulting mixture were added dry CH_2Cl_2 (50 ml) and (α-ethylcarboethoxymethylene)-triphenylphosphorane (17.0 g, 45.2 mmol) and the mixture was stirred at room temperature for 1 h. After dilution with CH_2Cl_2, the mixture was washed with water and brine, dried, and then concentrated under reduced pressure. The residual oil was purified by flash column chromatography on silica gel with *n*-hexane-AcOEt (7:1 v/v) as eluent to give **14** (8.63 g, 99.6%) as an oil; $[\alpha]_D^{25}$ +14.52° (c 1.25, $CHCl_3$); ir (film): 1710, 1235, 1060 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 1.03 (3H, t, J=7.7 Hz), 1.30 (3H, t, J=7.0 Hz), 1.41 (3H, s), 1.45 (3H, s), 2.35 (2H, m), 3.63 (1H, t, J=8.0 Hz), 4.17 (1H, dd, J=8.0, 7.8 Hz), 4.21 (2H, q, J=7.0 Hz), 4.85 (1H, m), 6.63 (1H, d, J=8.4 Hz); HRms *m/z*: calcd for $C_{12}H_{21}O_4$ $[MH]^+$ 229.1440, found 229.1460.

Compound (15)

To a solution of **14** (10.0 g, 43.83 mmol) in dry CH_2Cl_2 (30 ml) at -15 ℃ under nitrogen was slowly

added 1.0M DIBAL-H in *n*-hexane (87.6 ml, 87.6 mmol) and the mixture was stirred for 20 min at -15 ℃. After dilution with CH_2Cl_2 (500 ml), the solution was stirred with 0.5N HCl (80 ml) for 10 min at -15 ℃. The organic layer was separated and successively washed with saturated aq. $NaHCO_3$ and brine, dried, and concentrated. The residue was purified by flash column chromatography on silica gel with *n*-hexane-AcOEt (3:2 v/v) as eluent to afford **15** (7.82 g, 95.9%) as an oil; $[\alpha]_{D}^{25}$ +6.25° (c 0.76, $CHCl_3$); ir(film): 3400 (br), 1220, 1050 cm^{-1} ; ^{1}H-nmr δ: 1.03 (3H, t, J=7.4 Hz), 1.40 (3H, s), 1.43 (3H, s), 2.15 (2H, m), 3.55 (1H, t, J=8.0 Hz), 4.07 (1H, dd, J=8.0, 7.8 Hz), 4.08 (2H, s), 4.83 (1H, m), 5.44 (1H, d, J=8.7 Hz); HRms *m/z*: calcd for $C_{10}H_{19}O_3$ $[MH]^+$ 187.1334, found 187.1323.

Compound (16)

To a solution of **15** (3.0 g, 16.13 mmol) in dry DMF (30 ml) was added NaH (60% dispersion in mineral oil, 0.84 g, 21.0 mmol) at 0 ℃. After beeing stirred for 30 min at the same temperature, BnBr (2.37 ml, 20.0 mmol) was added dropwise to the reaction mixture and the mixture was stirred at room temperature for 1 h. After beeing diluted with AcOEt (500 ml), the mixture was washed with 0.5N HCl, water (5 times), and brine, dried, and concentrated. The residue was purified by flash column chromatography on silica gel with *n*-hexane-AcOEt (7:1 v/v) as eluent to give **16** (4.33 g, 96.0%) as an oil; $[\alpha]_{D}^{25}$ +8.08° (c 0.96, $CHCl_3$); ir (film): 1375, 1220, 1050 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 1.02 (3H, t, J=7.7 Hz), 1.40 (3H. s), 1.43 (3H, s), 2.17 (2H, m), 3.54 (1H, t, J=8.0 Hz), 3.97 (2H, s), 4.07 (1H, dd, J=8.0, 7.8 Hz), 4.48 (2H, s), 4.89 (1H, m), 5.48 (1H, d, J=8.4 Hz), 7.29~7.34 (5H, m); HRms *m/z*: calcd for $C_{17}H_{25}O_3$ $[MH]^+$ 277.1804, found 277.1808.

Compound (17)

A solution of **16** (4.31 g, 15.61 mmol) in 80% AcOH (50 ml) was heated at 80 ℃ for 2 h. After cooling, the reaction mixture was concentrated. The residue was dissolved in AcOEt (100ml) and the solution was washed with saturated aq. $NaHCO_3$ and brine, dried, and concentrated. The residue was purified by flash column chromatography on silica gel with *n*-hexane-AcOEt (1:2 v/v) as eluent to give **17** (3.60 g, 97.7%) as an oil; $[\alpha]_{D}^{25}$ +10.62° (c 0.82, $CHCl_3$); ir (film): 3360 (br), 1465, 1070 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 1.01 (3H, t, J=7.7 Hz), 2.16 (2H, m), 3.50 (2H, m), 3.94 (2H, s), 4.48 (2H, s), 4.50 (1H, m), 5.42 (1H, d, J=8.7 Hz), 7.25~7.37 (5H, m); HRms *m/z*: calcd for $C_{14}H_{20}O_3Na$ $[MNa]^+$ 259.1310, found 259.1275.

Compound (18)

To a solution of **17** (2.79 g, 11.82 mmol) in pyridne (30 ml) was added *p*-toluenesulfonyl chloride (*p*-TsCl, 98% purity, 2.76 g, 14.20 mmol) at 0 ℃ and the mixture was allowed to stand at room temperature for 12 h. After dilution with AcOEt (300 ml), the mixture was washed with 1N HCl (twice), saturated aq. $NaHCO_3$, and brine, dried, and concentrated. The residue was purified by flash column chromatography on silica gel with *n*-hexane-AcOEt (3:1 v/v) as eluent to give **18** (3.15 g, 68.3%) as an oil; $[\alpha]_D^{25}$ +27.13° (c 1.06, $CHCl_3$); ir (film): 3400 (br), 1360, 1070 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 0.98 (3H, t, J=7.7 Hz), 2.10 (2H, m), 2.43 (3H, s), 3.92 (2H, s), 3.96 (2H, m), 4.46 (2H, s), 4.67 (1H, m), 5.34 (1H, d, J=8.7 Hz), 7.26～7.38 (7H, m), 7.80 (2H, d, J=8.4 Hz); HRms *m/z*: calcd for $C_{21}H_{26}O_5SNa$ $[MNa]^+$ 413.1399, found 413.1390.

Compound (19)

Tosylate (**18**) (1.79 g, 4.590 mmol) was treated with 1.0 M lithium aluminum hydride (LAH) solution in tetrahydrofuran (THF) (4.6 ml, 4.6 mmol) in CH_2Cl_2 (50 ml) at room temperature for 1 h. After dilution with CH_2Cl_2, the mixture was stirred vigorously with 1N HCl at 0 ℃ for 15 min. The organic layer was separated and washed with water, saturated aq. $NaHCO_3$, and brine, dried, and concentrated. The residue was purified by silica gel flash column chromatography with *n*-hexane-AcOEt (2:1 v/v) as eluent to give **19** (0.982 g, 97.0%) as an oil; $[\alpha]_D^{25}$ +6.66° (c 1.00, $CHCl_3$); ir (film): 3360 (br), 1450, 1370, 1065 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 1.02 (3H, t, J=7.4 Hz), 1.26 (3H, d, J=6.4 Hz), 2.16 (2H, m), 3.94 (2H, s), 4.48 (2H, s), 4.65 (1H, m), 5.47 (1H, d, J=8.7 Hz), 7.25～7.36 (5H, m); HRms *m/z*: calcd for $C_{14}H_{20}O_2$ $[M]^+$ 220.1462, found 220.1450.

Compound (20)

To a solution of **19** (7.72 g, 35.09 mmol) in dry CH_2Cl_2 (220 ml) was added *m*-CPBA (80% purity, 9.84 g, 45.62 mmol) at 0 ℃. After stirring for 1 h at 0 ℃, the mixture was diluted with CH_2Cl_2 and successively washed with saturated aq. $Na_2S_2O_3$, water, saturated aq. $NaHCO_3$, and brine, dried, and concentrated. The residue was purified by flash column chromatography on silica gel with *n*-hexane-AcOEt (2:1 v/v) as eluent to give **20** (7.77 g, 93.8 %) as an oil; $[\alpha]_D^{25}$ +4.12° (c 0.74, $CHCl_3$); ir(film):

3400 (br), 1450, 1070 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 1.00 (3H, t, J=7.7 Hz), 1.28 (3H, d, J=6.4 Hz), 1.58 (1H, dq, J=15.4, 7.7 Hz), 1.81 (1H, dq, J=15.4, 7.7 Hz), 2.87 (1H, d, J=8.1 Hz), 3.48 (1H, d, J=11.5 Hz), 3.55 (1H, d, J=11.5 Hz), 3.72 (1H, m), 4.52 (1H, d of AB, J=12.1 Hz), 4.58 (1H, d of AB, J=12.1 Hz), 7.28~7.38 (5H, m); HRms *m/z*: calcd for $C_{14}H_{21}O_3$ $[MH]^+$ 237.1491, found 237.1477.

Compound (21)

To a solution of **20** (1.52 g, 6.441 mmol) in a mixture of AcOEt-MeOH-H_2O-AcOH (6:2:2:1 v/v, 15 ml) was added 10% Pd-C (1.52 g). After stirring at room temperature for 1 h under hydrogen atmosphere, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give a residual oil, which was subjected to flash column chromatography on silica gel. Elution with *n*-hexane-AcOEt (1:4 v/v) affoded **21** (0.928 g, 99.0%) as an oil; $[\alpha]_{D}^{25}$ -21.50° (c 0.91 $CHCl_3$); ir (film): 3360 (br), 1460, 1375, 1060 cm^{-1}; ^{1}H-nmr (CD_3COOD) δ: 1.01 (3H, t, J=7.7 Hz), 1.27 (3H, d, J=6.2 Hz), 1.61 (1H, dq, J=15.4, 7.7 Hz), 1.75 (1H, dq, J=15.4, 7.7 Hz), 3.12 (1H, d, J=8.4 Hz), 3.69 (1H, d, J=12.6 Hz), 3.75 (1H, d, J=12.6 Hz), 3.80 (1H, m); HRms *m/z*: calcd for $C_7H_{14}O_3$ $[MH]^+$ 147.1021, found 147.1027.

Epoxy ketone (4)

To a srirred solution of $(COCl)_2$ (6.13 ml, 70.27 mmol) in dry CH_2Cl_2 (70 ml) at -78 ℃ was added DMSO (11.2 ml, 157.8 mmol) and the mixture was stirred for 10 min at -78 ℃. After addition of a solution of **21** (4.77 g, 32.65 mmol) in dry CH_2Cl_2 (47 ml) at -78 ℃, the mixture was stirred for 15 min at the same temperature. After addition of TEA (36.5 ml, 261.9 mmol) at -78 ℃, the mixture was further stirred for 5 min at -78 ℃ and 1 h at room temperature. To the reaction mixture was added (carbomethoxy-methylene)triphenylphosphorane (32.7 g, 97.80 mmol) and the mixture was stirred for 12 h at room temperature. After evaporation of the solvent under reduced pressure, the residue was taken up into AcOEt. The solution was washed with water and brine, dried, and concentrated under reduced pressure to give a residue, which was subjected to flash column chromatography on silica gel. Elution with *n*-hexane-AcOEt (3:1 v/v) affoded **4** (5.89 g, 91.1%) as an oil; $[\alpha]_{D}^{25}$ -9.41° (c 0.90, $CHCl_3$); ir (film): 1720, 1660, 1310, 1160, 1070 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 1.02 (3H, t, J=7.4 Hz), 1.63 (1H, dq, J=14.8, 7.4 Hz), 1.76

(1H, dq, J=14.8, 7.4 Hz), 2.27 (3H, s), 3.46 (1H, s), 3.76 (3H, s), 6.10 (1H, d, J=15.4 Hz), 6.91 (1H, d, J=15.4 Hz); HRms *m/z*: calcd for $C_{10}H_{15}O_4$ $[MH]^+$ 199.0970, found 199.0964.

Triol (6)

To a stirred solution of **4** (457.7 mg, 2.312 mmol) in dry CH_2Cl_2 (13 ml) was slowly added BF_3-Et_2O complex (0.34 ml, 2.76 mmol) at -20 ℃ and the mixture was stirred for 1.5 h. After addition of dry powdered $NaHCO_3$ (2.0 g, 23.8 mmol), the mixture was stirred vigorously at -20 ℃ for 10 min. To the mixture was added 1.0M DIBAL-H in *n*-hexane (11.56 ml, 11.56 mmol) dropwise. After stirring at -20 ℃ for 15 min, 4N HCl-MeOH (1.73 ml, 6.92 mmol) was added to the mixture, which was further stirred at -20 ℃ for 5 min and then allowed to stand at room temperature. After evaporation of the solvent under reduced pressure, the residue was taken up into CH_2Cl_2 and the mixture was then filtered through Celite. The filtrate was concentrated under reduced pressure to give an oil which was subjected to column chromatography on silica gel. Elution with CH_2Cl_2-MeOH (10:1 v/v) gave a diastereomeric mixture (1:1) of **6** (281.4 mg, 70.0%) as an oil, ir (film): 3360 (br), 1380, 1040 cm^{-1}; ms *m/z*: 174 $[M]^+$, which was separated by silica gel tlc. Less polar isomer: ^{1}H-Nmr ($CDCl_3$) δ: 0.78 (3H, t, J=7.4 Hz), 1.11 (1H, dq, J=14.8, 7.4 Hz), 1.15 (3H, d, J=6.4 Hz), 1.37 (1H, dq, J=14.8, 7.4 Hz), 3.68 (1H, d, J=11.2 Hz), 3.82 (1H, d, J=11.2 Hz), 3.90 (1H, q, J=6.4 Hz), 4.18 (2H, d, J=4.4 Hz), 5.65～5.66 (2H, m). More polar isomer: ^{1}H-Nmr ($CDCl_3$) δ: 0.82 (3H, t, J=7.4 Hz), 1.23 (1H, d, J=6.4 Hz), 1.32 (1H, dq, J=14.8, 7.4 Hz), 1.48 (1H, dq, J=14.8, 7.4 Hz), 3.72 (1H, d, J=11.2 Hz), 3.83 (1H, d, J=11.2 Hz), 3.92 (1H, q, J=6.4 Hz), 4.18 (2H, d, J=5.4 Hz), 5.61 (1H, d, J=16.1 Hz), 5.82 (1H, dt, J=16.1, 5.4 Hz).

Compound (22)

The mixture of **6** (85.4 mg, 0.491 mmol), 2,2-dimethoxypropane (0.30 ml, 2.44 mmol), and CSA (3.1 mg, 0.013 mmol) in DMF (2.6 ml) was heated at 90 ℃ for 15 min under N_2 atmosphere. After cooling, the mixture was diluted with AcOEt (50 ml) and the solution was successively washed with H_2O (5 times) and brine, dried, and concentrated. The residue was dissolved in a mixture of AcOH-CH_2Cl_2-MeOH (1:15:4 v/v) and the mixture was warmed at 30 ℃ for 1 h. After addition of CH_2Cl_2 (100 ml), the solution was washed with saturated aq. $NaHCO_3$ and brine, dried, and concentrated under reduced pressure to give a residue which was subjected to column chromatography on silica gel. Elution with CH_2Cl_2-MeOH (10:1

v/v) afforded a diastereomeric mixture (1:1) of **22** (104.1 mg, 99.6%) as an oil, ir (film): 3400, 1380, 1200, 970 cm^{-1}; HRms *m/z*: calcd for $C_{12}H_{23}O_3$ $[MH]^+$ 215.1647, found 215.1626, which was separated by silica gel tlc. Less polar isomer: ^{1}H-Nmr ($CDCl_3$) δ: 0.87 (3H, t, J=7.8 Hz), 1.05 (3H, d, J=6.4 Hz), 1.35～1.50 (2H, m), 1.40 (3H, s), 1.46 (3H, s), 3.71 (2H, s), 3.89 (1H, q, J=6.4 Hz), 4.14 (2H, d, J=5.7 Hz), 5.41 (1H, d, J=16.5 Hz), 5.60 (1H, dt, J=16.5, 5.7 Hz). More polar isomer: ^{1}H-Nmr ($CDCl_3$) δ: 0.81 (3H, t, J=7.8 Hz), 1.03 (3H, d, J=6.4 Hz), 1.20～1.55 (2H, m), 1.40 (3H, s), 1.46 (3H, s), 3.65 (1H, d, J=11.7 Hz), 3.78 (1H, d, J=11.7 Hz), 3.89 (1H, q, J=6.4 Hz), 4.19 (2H, d, J=5.4 Hz), 5.84 (1H, dt, J=16.1, 5.4 Hz), 5.92 (1H, d, J=16.1 Hz).

Compound (23a)

To a solution of **22** (1.47 g, 6.869 mmol) in CH_2Cl_2 (35 ml) was added PCC (2.97 g, 13.78 mmol) and the mixture was stirred at room temperature for 1 h. After dilution with AcOEt (100 ml), the mixture was stirred vigorously for 30 min and passed through a short column of silica gel. The column was washed with AcOEt. Evaporation of the eluent gave a crude aldehyde which was hydrogenated by using 10% Pd-C (1.2 g) in AcOEt (30 ml) under H_2 atmosphere for 30 min. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was taken up into MeOH (30 ml) and treated with $NaBH_4$ (0.6 g, 15.86 mmol) for 10 min at room temperature. The reaction mixture was quenched with H_2O and neutralized with 1N HCl. After evaporation of the solvent, the residue was dissolved in AcOEt and the solution was washed with saturated aq. $NaHCO_3$ and brine, dried, and concentrated. The residue was purified by flash column chromatography on silica gel with *n*-hexane-AcOEt (2:1 v/v) as eluent to afford a diastereomeric mixture (1:1) of **23a** (860.9 mg, 58.0%) as an oil, ir (film): 3400 (br), 1380, 1200, 1100, 1060 cm^{-1}; HRms *m/z*: calcd for $C_{12}H_{25}O_3$ $[MH]^+$ 217.1804, found 217.1783, which was separated by silica gel tlc. Less polar isomer: ^{1}H-Nmr ($CDCl_3$) δ: 0.86 (3H, t, J=7.7 Hz), 1.07 (3H, d, J=6.4 Hz), 1.11～1.35 (4H, m), 1.38 (3H, s), 1.43 (3H, s), 1.61 (1H, m), 1.81 (1H, m), 3.54 (1H, d, J=11.8 Hz), 3.62～3.69 (3H, m), 3.95 (1H, q, J=6.4 Hz). More polar isomer: ^{1}H-Nmr ($CDCl_3$) δ: 0.90 (3H, t, J=7.4 Hz), 1.07 (3H, d, J=6.4 Hz), 1.10～1.34 (3H, m), 1.38 (3H, s), 1.42 (3H, s), 1.48～1.57 (2H, m), 1.86 (1H, dq, J=14.8, 7.4 Hz), 3.55～3.64 (4H, m), 3.94 (1H, q, J=6.4 Hz).

Compound (24)

To a solution of **23a** (830.9 mg, 3.847 mmol) in DMF (25 ml) was added NaH (60% dispersion in mineral oil, 0.457 g, 11.43 mmol) and stirred for 30 min at 0 ℃. After addition of MPMCl (98% purity, 1.0 ml, 7.23 mmol) at 0 ℃, the mixture was stirred at room temperature for 1 h and then diluted with AcOEt (300 ml). The solution was washed with 1N HCl, H_2O (5 times), and brine, dried, and concentrated. The residue was taken up into 1N HCl-MeOH (28 ml) and allowed to stand at room temperature for 1 h. After neutralization with powdered $NaHCO_3$ at 0 ℃, the mixture was concentrated under reduced pressure. The residue was partitioned between H_2O and AcOEt. The aqueous layer was thoroughly extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was purified by flash column chromatography on silica gel with *n*-hexane-AcOEt (2:3 v/v) as eluent to give a diastereomeric mixture (1:1) of **24** (1.00 g, 87.8%) as an oil; ir (film): 3360 (br), 1610, 1510, 1240 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 0.79, and 0.84 (3H, t, J=7.7 Hz), 1.05～1.37 (2H, m), 1.20 and 1.22 (3H, d, J=6.4 Hz), 1.40～1.69 (4H, m), 3.40～3.57 (3H, m), 3.70 and 3.71 (1H, d, J=11.4 Hz), 3.80 (3H, s), 3.85 (1H, m), 4.43 and 4.44 (2H, s), 6.87 (2H, d, J=8.7 Hz), 7.26 (2H,d, J=8.7 Hz); HRms *m/z*: calcd for $C_{17}H_{29}O_4$ $[MH]^+$ 297.2066, found 297.2090.

Compound (25)

A mixture of **24** (0.997 g, 3.368 mmol) and TrCl (98% purity, 1.88 g, 6.609 mmol) in pyridine (920 ml) was heated at 90 ℃ for 1 h. After cooling, the mixture was concentrated. The residue was taken up into CH_2Cl_2 and the solution was washed with 0.5 N HCl, H_2O, saturated aq. $NaHCO_3$, and brine, dried, and concentrated. The residue was purified by flash column chromatography on silica gel with *n*-hexane-AcOEt (4:1 v/v) to give a diastereomeric mixture (1:1) of **25** (1.51 g, 83.3 %) as an oil; ir (film): 3520 (br), 1620, 1520, 1250, 700 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 0.67 and 0.78 (3H, t, J=7.7 Hz), 0.92 (3H, d, J=6.4 Hz), 1.08～1.75 (6H, m), 3.04 (1H, d, J=9.4 Hz), 3.17 and 3.19 (1H, d, J=9.4 Hz), 3.31 and 3.44 (2H, t, J=6.7 Hz), 3.68～3.78 (1H, m), 3.78 (3H, s), 4.36 and 4.44 (2H, s), 6.84 and 6.85 (2H, d, J=8.7 Hz), 7.18 and 7.44 (17H, m); HRms *m/z*: calcd for $C_{17}H_{27}O_4$ $[M\text{-}Tr]^+$ 295.1907, found 295.1905.

Compound (26)

A mixture of **25** (1.50 g, 2.788 mmol) and MsCl (2.1 ml, 27.13 mmol) in dry pyridine (30 ml) was allowed to stand at room temperature for 1.5 h. After evaporation of the solvent followed by addition of CH_2Cl_2 (200 ml), the resulting solution was washed with 0.5 N HCl, H_2O, saturated aq. $NaHCO_3$, and brine, dried, and concentrated. The residue was purified by flash column chromatography on silica gel with *n*-hexane-AcOEt (3:1 v/v) as eluent to afford a diastereomeric mixture (1:1) of **26** (1.69 g, 98.3%) as an oil; ir (film): 1610, 1510, 1170 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 0.72 and 0.75 (3H, t, J=7.7 Hz), 1.31 and 1.33 (3H, d, J=6.7 Hz), 1.25～1.60 (6H, m), 2.86 and 2.88 (3H, s), 2.96 (1H, d, J=12.1 Hz), 3.00 (1H, d, J=12.1 Hz), 3.34 (2H, m), 3.78 (3H, s), 4.37 and 4.40 (2H, s), 4.89 (1H, q, J=6.7 Hz), 6.84 and 6.85 (2H, d, J=8.7 Hz), 7.19～7.44 (17H, m); HRms *m/z*: calcd for $C_{17}H_{25}O_3$ [M-Tr-MsOH]$^+$ 277.1803, found 277.1823.

Compound (27)

A mixture of **26** (1.635 g, 2.654 mmol) and DBU (4.0 ml, 26.75 mmol) in toluene (30 ml) was heated under reflux for 30 h. After cooling, the mixture was diluted with CH_2Cl_2 and washed with 1N HCl, saturated aq. $NaHCO_3$, and brine, dried, and concentrated. The residue was purified by silica gel flash column chromatography with *n*-hexane-AcOEt (5:1 v/v) to give **27** (1.286 g, 93.2%) as an oil;$[\alpha]_{D}^{25}$ +4.63° (c 1.00, $CHCl_3$); ir (film): 1610, 1510, 1240, 1090, 690 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 0.61 (3H, t, J=7.4 Hz), 1.25～1.54 (6H, m), 2.94 (2H, s), 3.35 (3H, t, J=6.7 Hz), 3.79 (3H, s), 4.38 (2H, s), 4.84 (1H, d, J=16.5 Hz), 5.04 (1H, d, J=11.1 Hz), 5.67 (1H, dd, J=16.5, 11.1 Hz), 6.85 (2H, d, J=8.7 Hz), 7.18～7.45 (17H, m); HRms *m/z*: calcd for $C_{17}H_{25}O_3$ [M-Tr]$^+$ 277.1803, found 277.1804.

Compound (28)

To a stirred, ice-cooled solution of **27** (479.3 mg, 0.922 mmol) in dry THF (3 ml) was added 1.0 M BH_3-THF (0.6 ml, 0.6 mmol) and the mixture was stirred at room temperature for 19 h. To the above mixture were successively added H_2O (0.9 ml), 3N NaOH (1.2 ml), and 30% aq. H_2O_2 (1.2 ml) and the mixture was stirred for 2 h at room temperature. After acidification with 1N HCl, the mixture was diluted with AcOEt, which was washed with saturated aq. $NaHCO_3$, and brine, dried, and concentrated. The residue

was subjected to silica gel column chromatography with *n*-hexane-AcOEt (3:2 v/v) as eluent to give **28** (351.7 mg, 70.9%) as an oil; $[\alpha]_{D}^{25}$ +6.24° (c 0.87, $CHCl_3$); ir (film): 3400 (br), 1620, 1510, 1450, 1245, 1085, 700 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ : 0.68 (3H, t, J=7.4 Hz), 1.33～1.38 (6H, m), 1.60 (2H, t, J=6.1 Hz), 2.88 (2H, s), 3.36 (2H, t, J=6.0 Hz), 3.46 (2H, m), 3.78 (3H, s), 4.40 (2H, s), 6.85 (2H, d, J=8.7 Hz), 7.21～7.44 (17H, m); HRms *m/z*: calcd for $C_{17}H_{27}O_4$ $[M\text{-}Tr]^+$ 295.1907, found 295.1904.

Compound (29)

An ice-cooled mixture of **28** (311.7 mg, 0.579 mmol), MOMCl(0.13 ml, 1.71 mmol) and DIPEA (0.5 ml, 2.87 mmol) in dry CH_2Cl_2 (0.5 ml) was stirred for 30 min under N_2 atmosphere. After dilution with CH_2Cl_2, the mixture was washed with saturated aq. $NaHCO_3$ and brine, dried, and concentrated. The residue was purified by column chromatography on silica gel with *n*-hexane-AcOEt (4:1 v/v) as eluent to give **29** (332.6 mg, 98.7%) as an oil; $[\alpha]_{D}^{25}$ +6.58° (c 0.89, $CHCl_3$); ir (film): 1620, 1450, 1240, 1090, 700 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 0.67 (3H, t, J=7.4 Hz), 1.32～1.37 (6H, m), 1.66 (2H, t, J=6.1 Hz), 2.83 (2H, s), 3.28 (3H, s), 3.36 (4H, m), 3.78 (3H, s), 4.39 (2H, s), 4.51 (2H, s), 6.85 (2H, d, J=8.7 Hz), 7.21～7.45 (17H, m); HRms *m/z*: calcd for $C_{19}H_{31}O_5$ $[M\text{-}Tr]^+$ 339.2170, found 339.2178.

Compound (30)

A solution of **29** (292.6 mg, 0.503 mmol) in 80% aq. AcOH (7 ml) was heated at 60 ℃ for 1.5 h. After cooling, the mixture was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography with *n*-hexane-AcOEt (3:2 v/v) as eluent to affod **30** (140.4 mg, 82.1%) as an oil; $[\alpha]_{D}^{25}$ +6.87° (c 0.92, $CHCl_3$); ir (film): 3450 (br), 1610, 1510, 1240, 1030, cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 0.80 (3H, t, J=7.4 Hz), 1.24～1.37 (4H, m), 1.50～1.60 (2H, m), 1.58 (2H, t, J=6.0 Hz), 3.36 (3H, s), 3.42 (2H, t, J=6.7 Hz), 3.59 (2H, t, J=6.0 Hz), 3.80 (3H, s), 4.43 (2H, s), 4.61 (2H, s), 6.87 (2H, d, J=8.4 Hz), 7.25 (2H, d, J=8.4 Hz); HRms *m/z*: calcd for $C_{19}H_{33}O_5$ $[MH]^+$ 341.2328, found 341.2343.

Compound (31)

To a solution of **30** (16.8 mg, 0.0494 mmol) in a mixture of DMSO (0.5 ml), TEA (0.2 ml), and dry

CH_2Cl_2 (0.2 ml) was added SO_3-pyridine complex (98% purity, 63.0 mg, 0.388 mmol) and the mixture was stirred at room temperature for 20 min. The reaction mixture was poured into ice water and the aqueous phase was thoroughly extracted with AcOEt. The extract was washed with 0.1 N HCl, H_2O (5 times), saturated aq. $NaHCO_3$, and brine, dried, and concentrated. The residue was treated with a mixture of 2-methyl-2-butene (0.02 ml, 0.189 mmol), NaH_2PO_4-$2H_2O$ (7.7 mg, 0.049 mmol), *t*-butyl alcohol (0.4 ml), and $NaClO_2$ (85% purity, 8.4 g, 0.173 mmol) at room temperature. After stirring for 1 h, the mixture was acidified with 1N HCl at 0 ℃. The aqueou phase was thoroughly extracted with CH_2Cl_2 and the extract was washed with brine, dried, and concentrated. The residual oil was purified by silica gel column chromatography with *n*-hexane-AcOEt (3:2 v/v) as eluent to afford the carboxylic acid (**31**) (16.7 mg, 95.5%) as an oil; $[\alpha]_{D}^{25}$ +7.29° (c 1.32, $CHCl_3$); ir (film): 3400 (br), 1715, 1610, 1510, 1460, 1250, 1100, 1030 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 0.84 (3H, t, J=7.4 Hz), 1.56～1.66 (4H, m), 1.91 (2H, brt, J=7.1 Hz), 3.33 (3H, s), 3.43 (2H, t, J=6.0 Hz), 3.53 (2H, t, J=7.1 Hz), 3.80 (3H, s), 4.42 (2H, s), 4.56 (2H, s), 6.87 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz); HRms *m/z*: calcd for $C_{19}H_{31}O_6$ $[MH]^+$ 355.2121, found 355.2132.

Lactone (7)

A solution of **31** (60.2 mg, 0.170 mmol) in 1N HCl-MeOH (2 ml) was heated at 60 ℃ for 1 h. After cooling, the mixture was neutralized with powdered $NaHCO_3$ (0.2 g) portion wise and concentrated under reduced pressure. The residue was extracted with AcOEt and the extract was washed with brine, dried and concentrated. The residual oil was purified by silica gel column chromatography with *n*-hexane-AcOEt (4:5 v/v) as eluent to give **7** (23.4 mg, 80.0 %) as an oil; $[\alpha]_{D}^{25}$ +1.65° (c 0.35, $CHCl_3$); ir (film): 3400 (br), 1760, 1460, 1380, 1190, 1015 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 0.95 (3H, t, J=7.3 Hz), 1.52～1.70 (6H, m), 2.15 (2H, t, J=7.4 Hz), 3.64 (2H, m), 4.26 (2H, t, J=7.4 Hz); HRms *m/z*: calcd for $C_9H_{17}O_3$ $[MH]^+$ 173.1178, found 173.1157.

Compound (32)

To a solution of **7** (23.0 mg, 0.134 mmol) in CH_2Cl_2 (0.8 ml) was added DIPEA (0.12 ml, 0.689 mmol) and MOMCl (0.63 ml, 0.375 mmol) at 0 ℃. The mixture was stirred at room temperature for 2 h. After

dilution with CH_2Cl_2, the solution was successively washed with 0.5 N HCl, saturated aq. $NaHCO_3$, and brine, dried and concentrated. The residue was subjected to silica gel column chromatography with *n*-hexane-AcOEt (1:1 v/v) as eluent to give the MOM-ether lactone {(26.8 mg, 92.7%) as an oil; ^{1}H-nmr ($CDCl_3$) δ: 0.95 (3H, t, J=7.3 Hz), 1.50~1.74 (6H, m), 2.15 (2H, t, J=7.3 Hz), 3.35 (3H, s), 3.52 (2H, m), 4.25 (2H, t, J=6.8 Hz), 4.60 (2H, s)}, which was successively treated with 1.5N aq. KOH-MeOH (4:1 v/v) (1 ml) at 80 ℃ for 2.5 h. After cooling, the mixture was neutralized with CO_2 (dry ice) and concentrated under reduced pressure. The residue was dried *in vacuo* and then mixed with dry K_2CO_3 powder (10 mg). The mixture was suspended in anhydrous DMF (1 ml) and treated with benzyl bromide (0.044 ml, 0.368 mmol) at room temperature for 1 h under N_2 atmosphere. After dilution with AcOEt, the mixture was filtered through Celite, and the filtrate was washed with H_2O (5 times) and brine, dried, and concentrated. The residue was purified by silica gel column chromatography with *n*-hexane-AcOEt (1:1 v/v) as eluent to afford **32** (24.6 mg, 64.0%) as an oil; ^{1}H-nmr ($CDCl_3$) δ: 0.80 (3H, t, J=7.3 Hz), 1.47 (2H, dq, J=13.2, 4.4 Hz), 1.66 (4H, m), 1.89 (2H, dt, J=7.0, 3.3 Hz), 3.35 (3H, s), 3.47 (2H, t, J=6.6 Hz), 3.62 (2H, t, J=7.0 Hz), 4.58 (2H, s), 5.12 (2H, s), 7.30~7.38 (5H, m).

Compound (33)

To a solution of **32** (24.6 mg, 0.08 mmol) in a mixture of DMSO (0.8 ml), TEA (0.3 ml), and CH_2Cl_2 (0.3 ml) was added SO_3-pyridine complex (126.3 mg, 0.794 mmol) and the mixture was stirred for 20 min at room temperature. The resulting mixture was poured into water and the aqueous phase was thoroughly extracted with AcOEt. The combined organic phases were washed with 0.5N HCl, saturated aq. $NaHCO_3$, and brine, dried, and concentrated. The residue was subjected to column chromatography on silica gel. Elution with *n*-hexane-AcOEt (3:1 v/v) afforded **33** (21.3 mg, 87.1%) as an oil; ^{1}H-nmr ($CDCl_3$) δ: 0.82 (3H, t, J=7.4 Hz), 1.42~1.51 (2H, m), 1.68~1.80 (4H, m), 2.68 (2H, d, J=2.0 Hz), 3.32 (3H, s), 3.54 (2H, t, J=6.4 Hz), 4.56 (2H, s), 5.14 (2H, s), 7.34 (5H, m), 9.75 (1H, t, J=2.0 Hz).

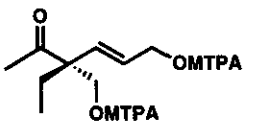
Bicyclic lactone (8)

A mixture of **33** (7.8 mg, 0.025 mmol) and 10% Pd-C (7.8 mg) in AcOEt (2 ml) was stirred under H_2 atmosphere for 30 min. The catalyst was filtered off and the filtrate was concentrated under reduced

pressure. The residue was dissolved in a mixture of 2N HCl-dioxane (1:1 v/v) and the solution was allowed to stand at room temperature for 15 h. Evaporation of the solvent gave a residue which was purified by silica gel tlc with *n*-hexane-AcOEt (2:1 v/v) to give **8** (recrystallized from ether, 3.1 mg, 72.9%); mp: 82.5~84.0 ℃; $[\alpha]_{D}^{25}$ +4.60° (c 0.30, $CHCl_3$); ir (film): 1770, 1345, 1255, 1110 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 0.93 (3H, t, J=7.0 Hz), 1.50~2.00 (6H, m), 2.22 (1H, d, J=14.1 Hz), 2.34 (2H, ddd, J=14.1, 6.1, 1.0 Hz), 3.80~4.10 (2H, m), 5.83 (1H, dd, J=6.1, 1.0 Hz); HRms *m/z*: calcd for $C_9H_{15}O_3$ $[MH]^+$ 171.1020, found 171.1043.

REFERENCES AND NOTES

1. a) S. Takano, M. Yonaga, M. Morimoto, and K. Ogasawara, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 305. b) M. Node, H. Nagasawa, and K. Fuji, *J. Org. Chem.*, 1990, **55**, 517 and references cited therein. c) A. I. Meyers, J. Romine, and A. J. Robichaud, *Heterocycles*, 1990, **30**, 339. d) M. Ihara, M. Takahashi, N. Taniguchi, K. Yasui, H. Niitsuma, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 525.
2. a) M. Asaoka and H. Takei, *Heterocycles*, 1989, **29**, 243. b) G. Palmisano, P. D'Anniballe, and M. Santagostino, *Tetrahedron*, 1994, **50**, 9487.
3. K. Okada, T. Katsura, H. Tanino, H. Kakoi, and S. Inoue, *Chem. Lett.*, **1994**, 157 and references cited therein.
4. Triol (**6**) was converted into di-MTPA ester (**34**) by the following sequences: i) (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPACl) / py, ii) pyridinium dichromate / CH_2Cl_2.
   The optical purity of **34** was determined by a ^{1}H-nmr to be 76% ee based on two singlets appeared at 2.05 and 2.02 ppm with integral ratio of 88:12. Optical yield on the acyl migration reaction, in this case, was 84.4%.



34

5. Direct catalytic hydrogenation of **22** produced undesired product (**23b**, 50%) and alcohol (**23a**, 40%).

Received, 30th April, 1996