Tetrahedron: Asymmetry Vol. 1, No. 10, pp. 743-749, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

A SYNTHESIS OF AN OPTICALLY ACTIVE FORSKOLIN INTERMEDIATE VIA ALLENYL ETHER INTRAMOLECULAR CYCLOADDITION STRATEGY

Shigeru Nagashima and Ken Kanematsu*

Institute of Synthetic Organic Chemistry, Faculty of Pharmaceutical Sciences,
Kyushu University 62, Higashi-ku, Fukuoka 812, Japan

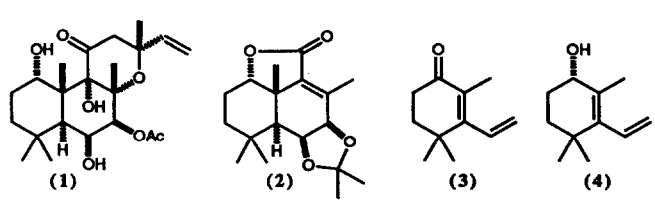
(*Received* 6 *September* 1990)

Abstract : An enantioselective route to the key intermediate of forskolin is described.

Forskolin (**1**), the major labdane diterpene isolated from the Indian plant *Coleus forskohlii*,[1] has a promising potential to be a novel drug useful for the treatment of diseases such as glaucoma,[2] congestive heart failure[3] and bronchial asthma.[4] It is an unique adenylate cyclase activator and is playing an invaluable role as a research tool in the understanding of cyclic AMP mediated physiological processes.[5] Coupling with its remarkable biological importance, this natural product is a challenging synthetic target owing to its unique structure with the presence of eight asymmetric centers, the high degree of functionalization.[6]

Recently, three different routes culminated successfully in the total synthesis of (±)-**1**, all of which, proceeding through the Ziegler intermediate (**2**).[7] Most recently, the first efficient enantioselective route to the key intermediate of forskolin has been reported by Corey's group.[8]

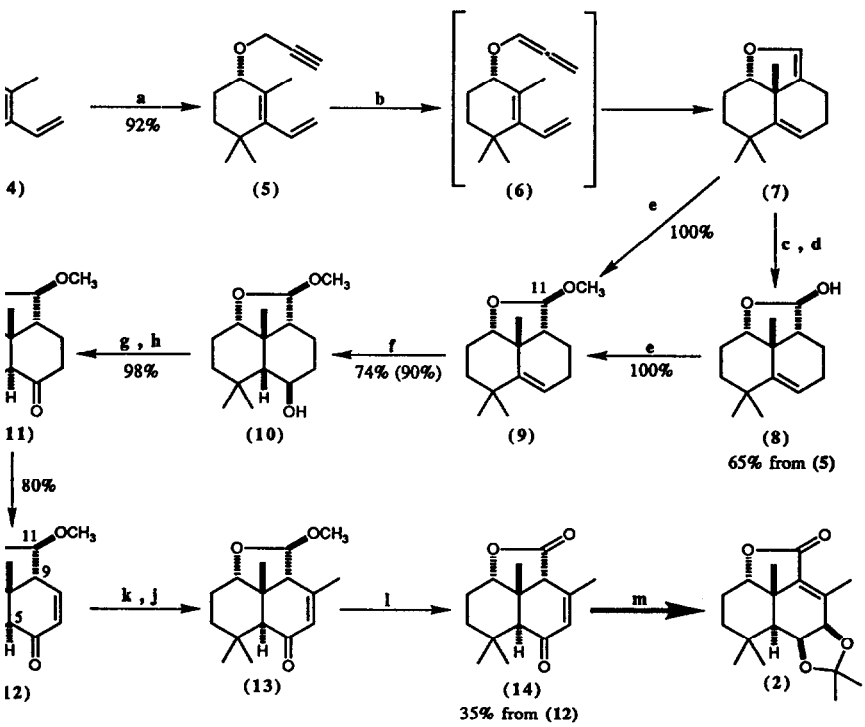
As part of our research program on the allene intramolecular cycloaddition reaction,[9] we developed the efficient synthetic route of a key intermediate of forskolin.[10] Now, we planned to take advantage of this methodology for construction of the optically active forskolin intermediate (**14**) as shown in Scheme.



(1) (2) (3) (4)

ylation of the dienol (4), obtained by enantioselective reduction of the dienone (3) by Corey's gave a 92% yield of propargyl ether (5), $[\alpha]_D^{26}$ -24.4 (c=3.0, $CHCl_3$), after silica gel hy (SGC) (Scheme). When the propargyl ether (5) was treated with *t*-BuOK (excess) in *t*-C for 1 h, adduct (7) was obtained as sole product, *via* the allenyl ether intermediate (6). the adduct (7) with 5% solution of 10-camphorsulfonic acid (CSA) in methanol at room or 30 min gave a quantitative yield of 9 ; the enantiomeric purity of 9 obtained this route was ca. onding to that of the starting alcohol (4). Successful elaboration of the enantioselective route vs. Treatment of 7 with 5% solution of CSA in tetrahydrofuran (THF)-H_2O (1:1) at room or 2 h gave a lactol (8),[12] mp 141-142°C, $[\alpha]_D^{26}$ -37.6 (c=1.0, $CHCl_3$), in 65% yield from 5 l a careful recrystallization from *n*-hexane. Treatment of 8 with 5% solution of CSA in methanol erature for 30 min gave a quantitative yield of 9, $[\alpha]_D^{25}$ -85.1 (c=1.0, $CHCl_3$).

be noted that the enantiomeric purity of 9 was shown to be >99% by 270 MHz ^1H NMR he presence of the chiral shift reagent (+)-[Eu(tfc)$_3$] (Aldrich Co.). Whereas two equal C_{11}-with baseline separation were observed with this shift reagent (25 mol%) and racemic (9), only a uld be detected with 9 which was prepared by the enantioselective route described above.



d **Conditions : a.** 60% NaOH, *n*-Bu_4NI (cat.), $CH{\equiv}CCH_2Br$, r.t. **b.** *t*-BuOK, *t*-BuOH, reflux **c.** 5% CSA in), r.t. **d.** recrystallization from *n*-hexane **e.** 5% CSA in MeOH, r.t. **f.** (i) BH_3-THF complex, THF, 0°C (ii) 0% H_2O_2, 0°C to r.t. **g.** PCC, Celite, CH_2Cl_2, 0°C **h.** 5% NaOMe in MeOH, reflux **i.** (i) LDA, THF, -78°C 8°C to r.t. **j.** 30% H_2O_2, pyridine, CH_2Cl_2, 0°C to r.t. **k.** (i) Me_2CuLi, Et_2O, -20°C (ii) PhSeCl, -20°C to r.t. *t*-CPBA, CH_2Cl_2, 0°C **m.** ref.7d

Hydroboration of **9** at 0°C for 20 h afforded a 74% yield of **10** (90% based on recovery of starting material), $[\alpha]_D^{27}$ -77.2 (c=1.0, $CHCl_3$). Treatment of the alcohol (**10**) with pyridinium chlorochromate (PCC) followed by epimerization with 5% solution of sodium methoxide in methanol (reflux) gave a 98% overall yield of ketone (**11**), $[\alpha]_D^{23}$ +60.9 (c=1.0, $CHCl_3$), after SGC. The ketone (**11**) was converted to the enone (**12**)[13] (80% overall), $[\alpha]_D^{22}$ -94.2 (c=1.3, $CHCl_3$), which was treated with lithium dimethyl cuprate, and the enolate was *in situ* selenenylation, followed by selenoxide elimination leading to **13**. The enone (**13**) was converted into the lactone (**14**), colorless crystals, mp 166-167°C, $[\alpha]_D^{27}$ -37.4 (c=0.4, $CHCl_3$), [lit.[8] mp 164-164°C, $[\alpha]_D^{23}$ -37.8 (c=0.4, $CHCl_3$)], in 35% overall yield from **12** after SGC.[14] According to Ziegler's method,[7d] **14** could be converted to the key intermediate (**2**) in four steps.

EXPERIMENTAL SECTION :

General. The Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. The ^1H NMR spectra were taken with a JMN-GSX500, JEOL GX-270, or Hitachi R-600 spectrometer with tetramethylsilane as an internal standard; chemical shifts are expressed in δ values. The ^{13}C NMR spectra were determined with a JEOL GX-270 with tetramethylsilane as an internal standard. IR spectra were obtained with a JASCO IR A-100 infrared spectrophotometer. Optical rotations were determined on a JASCO DIP-360 polarimeter. Mass spectra were determined on a JEOL-D300 equipped with a JMA 3100/3500 at an ionization voltage 30 eV. Elemental analysis were performed on Yanagimoto MT2 CHN recorder. For thin-layer chromatographic (TLC) analysis, Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.2mm) were used and column chromatography was done by using Merck Kieselgel 60 (70-200 mesh) as the stationary phase.

All reactions were carried out under an atomosphere of dry argon. All solvents were purified by distillation before use: ether and THF were distilled from sodium benzophenone ketyl.

(*S*)-(-)-2,4,4-Trimethyl-3-vinyl-2-cyclohexen-1-ol (4). - To a solution of **3** (2.35 g,14.3 mmol) and (*R*)-oxazaborolidine[11] (1.19 g, 4.3 mmol) in 8.6 ml of dry THF was added dropwise a solution of BH_3-THF in THF (8.6 ml, 8.6 mmol) over 9 h at 35°C. After the addition was complete, the reaction was quenched at 0°C with water, and the solvent was removed under the reduced pressure. The residue was extracted with ether. After the extract was concentrated, column chromatography on silica gel using hexane/ethyl acetate (10:1) as eluent gave **4** (2.26 g, 95%) as a colorless oil: IR (neat) 3310, 2945, 2860, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.23 (dd, J=17.5, 11.5 Hz, 1H), 5.29 (dd, J=11.5, 3.0 Hz, 1H), 4.99 (dd, J=17.5, 3.0 Hz, 1H), 3.94 (m, 1H), 1.81, (s, 3H), 1.71-1.05 (m, 5H), 1.03 (s, 3H), 1.00 (s, 3H); $[\alpha]_D^{23}$ -48.9 (c=3.1, $CHCl_3$); The enantiomeric excess was determined quantitatively by 500 MHz ^1H NMR analysis of the corresponding ester with (*S*)-(-)-MTPA: 83% ee; [lit.[11] $[\alpha]_D^{23}$ -53 (c=1.0, $CHCl_3$) (90% ee.)].

(*S*)-(-)-1-(2-Propynyloxy)-2,4,4-trimethyl-3-vinyl-2-cyclohexene (5). - To a solution of **4** (1.20 g, 7.2mmol) and *n*-BuNI (266 mg, 0.72 mmol) in 10 ml of aqueous sodium hydroxide (60%) was added propargyl bromide (1.92 ml, 21.6 mmol), and the mixture was then stirred at room temperature for 28 h. After the reaction mixture was diluted with ether, the organic layer was washed successively with water, 10% aqueous hydrogen chloride and brine, and dried over Na_2SO_4. The solvent was evaporated under reduced

pressure, and column chromatography on silica gel with hexane/ethyl acetate (20:1) as eluent afforded 5 (g, 92%) as a colorless oil: IR (neat) 3320, 2930, 2855, 1060 cm^{-1}; ^1H NMR($CDCl_3$) δ 6.21(dd, J=17.0, Hz, 1H), 5.27(dd, J=11.0, 2.4 Hz, 1H), 4.99(dd, J=17.0, 2.4 Hz, 1H), 4.19(d, J=2.4 Hz, 2H), 3.8 1H), 2.39(t, J=2.4 Hz, 1H), 2.05-1.25(m, 4H), 1.78(s, 3H), 1.00(s, 3H), 0.98(s, 3H); $[\alpha]_D^{26}$ -: (c=3.0, $CHCl_3$).

(-)-2β-Hydroxy-2aβ,3,4,6,7,8,8aβ,8bβ-octahydro-6,6,8bβ-trimethyl-2*H*-naphtho[1.8 furan (8). - A solution of **5** (329 mg, 1.61 mmol) and *t*-BuOK (998 mg, 8.89 mmol) in 5 ml of *t*-BuOH refluxed (83°C) for 1 h. After cooling, the reaction mixture was diluted with ether, washed successively saturated aqueous NH_4Cl and brine, and was dried over Na_2SO_4. The soluvent was removed *in vacuo* to **7** (330 mg, 100%) as a colorless oil: IR (neat) 2900, 2830, 1450, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.! 1H), 5.40(m, 1H), 4.25(t, J=7.2 Hz, 1H), 2.27(m, 2H), 1.03-0.85(m, 6H), 1.33(s, 3H), 1.26(s, 1.10(s, 3H); mass spectrum m/z 204(31, M^+), 189(100, M-CH_3).

Crude **7** (170 mg, 0.83 mmol) was dissolved in 5% solution of (±)-10-camphorsulfonic acid (CS/ THF-H_2O (1:1, 5ml), and the mixture was stirred at room temperature for 2 h. After dilution with ethe reaction mixture was washed successively with saturated aqueous $NaHCO_3$ and brine and dried over Na_2 The solvent was then removed under reduced pressure. The residue was subjected to a col chromatography on silica gel using hexane/ethyl acetate (1:1) as eluent to give **8** and recrystallized fro hexane to give optically pure **8** (120 mg, 65%) as colorless crystals: mp 141-142°C (*n*-hexane); IR (CH 3370, 2920, 1440, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.53(t, J=3.7 Hz, 1H), 5.17(d, J=6.1 Hz, 1H), 4.! J=3.0 Hz, 1H), 3.15(m, 1H), 2.17-2.10(m, 2H), 2.00-1.90(m, 1H), 1.89-1.71(m, 4H), 1.56(td, J=: 4.2 Hz, 1H), 1.24(dt, J=14.0, 3.7 Hz, 1H), 1.23(s, 3H), 1.09(s, 3H), 1.05(s, 3H); ^{13}C-NMR (CDC 144.62(s), 120.56(d), 99.26(d), 82.91(d), 56.52(d), 43.26(s), 35.52(s), 34.94(t), 31.42(q), 28.0 24.30(q), 22.53(t), 22.17(t), 16.82(t); mass spectrum, m/z 222(1, M^+), 204(31, M-H_2O), 189 (100 H_2O-CH_3); Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.50; H, 9.90; $[\alpha]_D^{26}$ -37.6 (c= $CHCl_3$).

(-)-2β-Methoxy-2aβ,3,4,6,7,8,8aβ,8bβ-octahydro-6,6,8bβ-trimethyl-2*H*-naphtho[1.8-furan (9). - **8** (120 mg, 0.54 mmol) was dissolved with 5% solution of CSA in methanol (5ml), anc mixture was stirred at room temperature for 30 min. After diluting with ether, the reaction mixture was wa successively with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was subjected to a column chromatography on silica gel u hexane/ethyl acetate (10:1) as eluent to give **9** (127 mg, 100%) as a colorless oil: IR (neat) 2925, 2850, 1 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.56(t, J=3.6 Hz, 1H), 4.69(d, J=5.4 Hz, 1H), 3.91(t, J= 3.0 Hz, 3.41(s, 3H), 2.30-1.25(m, 9H), 1.21(s, 3H), 1.09(s, 3H), 1.06(s, 3H); mass spectrium m/z 236(2,] 204(35, M-CH_3OH), 189(100, M-CH_3OH-CH_3); $[\alpha]_D^{25}$ -85.1 (c=1.0, $CHCl_3$).

(-)-2aβ,3,4,5,5aβ,6,7,8,8aβ,8bβ-Decahydro-5β-hydroxy-2β-methoxy-6,6,8bβ-trimeth 2*H*-naphtho[1.8-*bc*] furan (10). - To a solution of **9** (266 mg, 1.13 mmol) in 5 ml of dry THF added dropwise a solution of BH_3-THF in THF (3.4 ml, 3.4 mmol) at 0°C. After the reaction mixture stirred for 20 h at 0°C, the reaction was quenched at 0°C with water, and added with 10% sodium hydr

solution and 30% hydrogen peroxide solution. The resulting solution was further stirred for 2 h at room temperature and diluted with ethyl acetate. After organic layer was washed with brine and dried over Na_2SO_4, the solvent was removed *in vacuo*. The residue was subjected to a column chromatography on silica gel using hexane/ethyl acetate (2:1) as eluent afforded **9** (48 mg, 18%) and **10** (212 mg, 74%).

10: IR (neat) 3450, 2930, 2870, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.64(d, J=3.3 Hz, 1H), 3.92(m, 2H), 3.37(s, 3H), 2.00-1.66(m, 6H), 1.63(s, 1H), 1.56-1.25(m, 4H), 1.28(s, 3H), 1.09(s, 3H), 1.05(s, 3H); $[\alpha]_D^{27}$ -77.2 (c=1.0, $CHCl_3$).

(+)-5-Oxo-2aβ,3,4,5,5aα,6,7,8,8aβ,8bβ-decahydro-2β-methoxy-6,6,8bβ-trimethyl-2*H*-naphtho[1.8-*bc*] furan (11). - A solution of **10** (823 mg, 3.24 mmol) in 30 ml of dry dichloromethane was added 3 g of Celite and stirred with pyridinium chlorochromate (1.048 g, 4.86 mmol) for 2 h at 0°C. The reaction mixture was diluted with ether and filtered through a plug of Florisil (100-200 mesh). The solvent was removed under reduced pressure to afford the crude ketone as a colorless oil, which was used for the next reaction without further purification.

The ketone (814 mg, 3.23 mmol) obtained above dissolved in 5% solution of sodium methoxide in methanol (20 ml) and the resulting mixture was refluxed for 2 h. After cooling, the reaction mixture was diluted with ether, washed with saturated aqueous NH_4Cl and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was subjected to a column chromatography on silica gel using hexane/ethyl acetate (2:1) as eluent to give **11** (801 mg, 98% overall) as colorless crystals: mp 59°C (from *n*-heptane); IR (neat) 2940, 1715, 1105, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.81(d, J=2.8 Hz, 1H), 3.93(t, J=3.0 Hz, 1H), 3.40(s, 3H), 2.45(s, 1H), 2.40-2.09(m, 3H), 2.03(td, J=8.9, 2.8 Hz, 1H), 1.91-1.74(m, 3H), 1.48(td, J=12.0, 5.9 Hz, 1H), 1.18-1.10(m, 1H), 1.13(s, 3H), 1.08(s, 3H), 1.06(s, 3H); mass spectrum, m/z 252(1, M^+), 220(100, M-CH_3OH); HRMS calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1724; Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.54; H, 9.54; $[\alpha]_D^{23}$ +60.9 (c=1.0, $CHCl_3$).

(-)-5-Oxo-2β-methoxy-2aβ,5,5aα,6,7,8,8aβ,8bβ-octahydro-6,6,8bβ-trimethyl-2*H*-naphtho[1.8-*bc*] furan (12). - To a stirred solution of LDA (11.5 mmol) prepared from diisopropylamine (1.72 ml, 12.3 mmol) and *n*-BuLi (7.4 ml of 1.55 M solution in hexane, 11.5 mmol) in 5 ml of dry THF was added **11** (1.032 g, 4.1 mmol) in 5 ml of dry THF at -78°C. After 30 min, PhSeCl (3.926 g, 20.5 mmol) in 10 ml of dry THF was added rapidly, the reaction mixture was stirred for 2 h at room temperature and diluted with ether. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give the crude keto selenide which was used for the next reaction without further purification.

To a solution of the above selenide in 20 ml of dichloromethane containing 2 ml of pyridine was added dropwise 30% hydrogen peroxide (4 ml) at 0°C. The reaction mixture was stirred at room temperature for 2 h, diluted with dichloromethane, and was washed successively with saturated aqueous $NaHCO_3$, 10% hydrogen chloride solution, and brine. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was subjected to a column chromatograph on silica gel using hexane/ethyl acetate (10:1) as eluent to give **12** (819 mg, 80% overall) as a colorless oil: IR ($CHCl_3$) 2930, 1680, 1100, 985 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60(dd, J=9.9, 5.3 Hz, 1H), 5.91(dd, J=9.9, 1.3 Hz, 1H), 5.05(d, J=5.3 Hz, 1H), 3.99(t, J=2.7 Hz, 1H), 3.45(s, 3H), 2.67(s, 1H), 2.48(td, J=5.3, 1.3 Hz, 1H), 1.85-1.74(m, 2H), 1.56(td, J=13.0, 5.0 Hz, 1H),

1.26-1.13(m, 1H), 1.14(s, 3H), 1.13(s, 3H), 1.08(s, 3H); ^{13}C NMR ($CDCl_3$) δ 200.37(s), 140.00(d), 131.51(d), 106.59(d), 81.84(d), 59.96(d), 56.10(q), 55.28(d), 49.26(s), 35.86(t), 31.94(q), 31.18(s), 21.24(t), 20.83(q), 18.02(q); $[\alpha]_D^{22}$ -94.2 (c=1.3, $CHCl_3$).

(-)-5-Oxo-2aβ,5,5aα,6,7,8,8aβ,8bβ-octahydro-3,6,6,8bβ-tetramethyl-2*H*-naphtho[1.8-*bc*] furan-2-one (14). - To a solution of lithium dimethyl cuprate (0.08 mmol) prepared from CuI (160 mg, 0.84 mmol) and MeLi (2.5 ml of 0.63 M solution in ether, 1.6 mmol) in 4 ml of dry ether was added **12** (105 mg, 0.42 mmol) in 4 ml of dry ether at -18°C. After stirring for 2 h at -18°C, PhSeCl (402 mg, 2.1 mmol) in 4 ml of dry ether was added rapidly, the reaction mixture was stirred for 1 h at room temperature and poured into water, and extracted with ether. The extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* leaving a dark oily residue of the crude selenide. The crude selenide was dissolved in 5 ml of dichloromethane containing 1 ml of pyridine, added dropwise 2 ml of 30% hydrogene peroxide at 0°C. After stirring for 2 h at room temperature, diluted with dichloromethane, and washed successively with saturated aqueous $NaHCO_3$, 10% hydrogen chloride solution, and brine, and dried over Na_2SO_4, and the solvent removed *in vacuo*. Chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent gave **13** (79.8 mg, 72%) as a colorless oil: IR (neat) 2940, 1680, 1100, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.73(m, 1H), 5.00(d, J=5.1 Hz, 1H), 3.98(t, J=2.7 Hz, 1H), 3.47(s, 3H), 2.53(s, 1H), 2.31(d, J= 5.1 Hz, 1H), 1.88(m, 3H), 1.85-1.69(m, 2H), 1.54(td, J=12.6, 5.6 Hz, 1H), 1.18-1.12(m, 1H), 1.13(s, 3H), 1.10(s, 3H), 1.08(s, 3H); mass spectrum, m/z 264(1, M^+), 232(7, M-CH_3OH), 136(100).

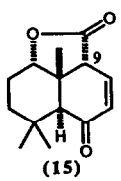
To a solution of **13** (79.8 mg, 0.30 mmol) in 2 ml of dichloromethane was added dropwise BF_3-Et_2O (16 μl, 0.17 mmol) at 0°C. The reaction mixture was added *m*-CPBA (86.3 mg, 0.4 mmol) and stirred for 2 h at room temperature. After diluting with ethyl acetate, the organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was evaporated *in vacuo*, and column chromatography on silica gel with hexane/ethyl acetate (4:1) as eluent afforded **14** (36.5 mg, 35% overall) as colorless crystals, which can be further purified by recrystallization from ether: mp 166-167°C; IR ($CHCl_3$) 2910, 1765, 1680, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.83(s, 1H), 4.29(t, J=2.9 Hz, 1H), 2.88(s, 1H), 2.44(s, 1H), 2.13(s, 3H), 2.05(ddt, J=15.1, 4.6, 2.9 Hz, 1H), 1.88(tdd, J=15.1, 4.6, 2.9 Hz, 1H), 1.50(td, J=13.8, 4.6 Hz, 1H), 1.25(s, 3H), 1.25(ddd, J=13.8, 4.6, 2.9 Hz, 1H), 1.17(s, 3H), 1.11(s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.98(s), 173.04(s), 148.25(s), 128.81(d), 82.39(d), 59.52(d), 54.30(d), 46.97(s), 35.44(t), 31.42(q), 30.89(s), 22.72(q), 20.80(t), 20.29(q), 18.12(q); mass spectrum, m/z 248(45, M+), 136(100); HRMS calcd for $C_{15}H_{20}O_3$ 248.14113, found 248.14112; $[\alpha]_D^{27}$ -37.4 (c=0.4, $CHCl_3$)[lit.[8] mp 164-164°C, $[\alpha]_D^{23}$ -37.8 (c=0.4, $CHCl_3$)].

ACKNOWLEDGEMENT :

This work was supported by the Grant-in-Aid for Scientific Research on Priority Areas No. 02453143 from the Ministry of Education, Science and Culture, Japanese Government.

REFERENCES AND NOTES :

1. Bhat, S.V.; Bajwa, B.S.; Dornauer, H.; de Souza, N.J.; Fehlhaber, H:-W. *Tetrahedron Lett.* **1977**, *18*, 1669.
2. Caprioli, J.; Sears, M. *Lancet* **1983**, 958.
3. Erhardt, P.W. *J. Med. Chem.* **1987**, *30*, 231.
4. Lichey, J.; Friedrich, T.; Priesnitz, M.; Biamino, G.; Usinger, P.; Huckauf, H. *Lancet* **1984**, 167.
5. For example, see : (a) Pfeuffer, E.; Dreher, R.-M.; Metzger, H.; Pfeuffer, T. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 3086. (b) May, D.C.; Ross, E.M.; Gilman, A.G.; Smigel, M.D. *J. Biol. Chem.* **1985**, *260*, 15829. (c) Smigel, M.D. *Ibid.* **1986**, *261*, 1976.
6. Colombo, M.I.; Somoza, C.; Zinczuk, J.; Bacigaluppo, J.A.; Ruveda, E.A. *Tetrahedron Lett.* **1990**, *31*, 39, and references cited therein.
7. (a) Ziegler, F.E.; Jaynes, B.H.; Saindane, M.T. *J. Am. Chem. Soc.* **1987**, *109*, 8115. (b) Hashimoto, S.; Sakata, S.; Sonegawa, M.; Ikegami, S. *Ibid.* **1988**, *110*, 3670. (c) Corey, E.J.; Jardine, P.D.S.; Rohloff, J.C. *Ibid.* **1988**, *110*, 3672. (d) First synthesis of **2**, see : Ziegler, F.E.; Jaynes, B.H.; Saindane, M.T. *Tetrahedron Lett.* **1985**, *26*, 3307.
8. Corey, E.J.; Jardine, P.D.S. *Ibid.* **1989**, *30*, 7297.
9. Hayakawa, K.; Aso, K.; Shiro, M.; Kanematsu, K. *J. Am. Chem. Soc.* **1989**, *111*, 5312.
10. Kanematsu, K.; Nagashima, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1028.
11. Corey, E.J.; Jardine, P.D.S.; Mohri, T. *Tetrahedron Lett.* **1988**, *29*, 6409.
12. **8** was converted to **15** in high yield with similar way, but conjugate methylation of **15**, with lithium dimethyl cuprate, did not occur, probably because of the presence of the acidic proton at C_9 in **15**.



(15)

13. The stereochemistry of **12** was confirmed by the observation of a positive NOE effect between the β-protons at C_1 and C_9, and the α-protons at C_5 and C_{11}.
14. Grieco, P.A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, *19*, 419.