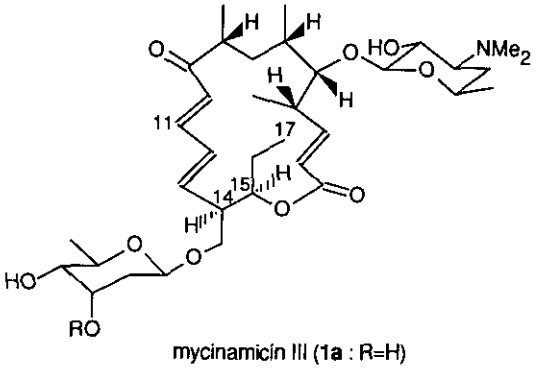
AN ENANTIOCONTROLLED ROUTE TO THE C_{11-17} SEGMENT OF MYCINAMICINS III AND IV

Seiichi Takano,* Yoshinori Sekiguchi, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract —— An enantiocontrolled route to the common C_{11-17} segment (**2**) of mycinamicins III (**1a**) and IV (**1b**) has been developed starting from the chiral α-hydroxyacetylene (**6**) obtained from (*E*)-4-benzyloxybut-2-en-1-ol (**3**).

In connection with a formal synthesis of protomycinolide IV,[1] we report here an enantiocontrolled route to the common C_{11-17} segment (**2**) of the macrolide antibiotics mycinamicins[2] III (**1a**) and IV (**1b**) starting with the chiral α-hydroxyacetylene[3,4] (**6**) obtained from 4-benzyloxybut-2-en-1-ol (**3**) by the Katsuki-Sharpless asymmetric epoxidation reaction followed by the base induced double elimination reaction *via* the epoxide intermediates (**4**) and (**5**).



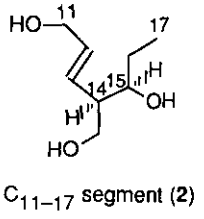
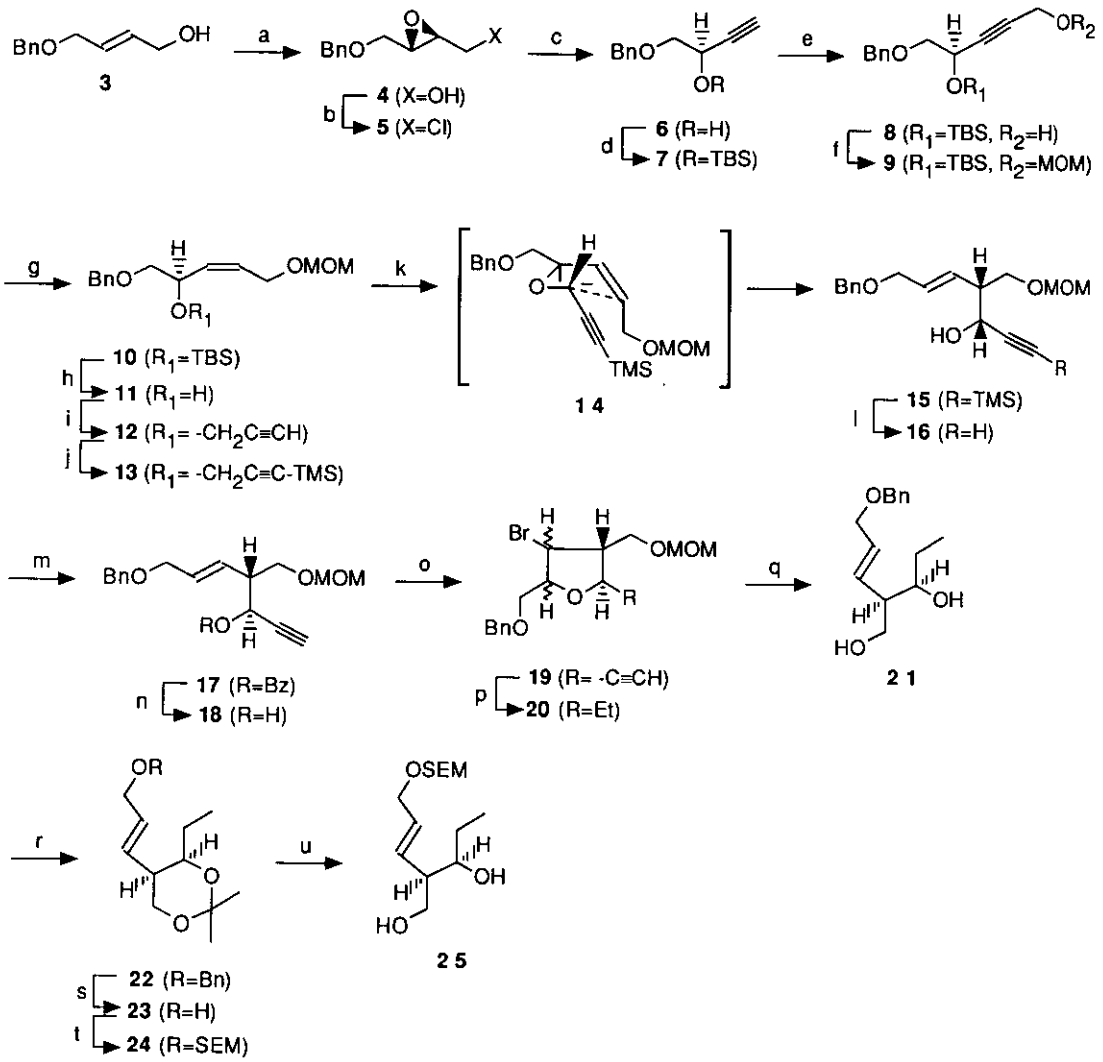


Figure 1

The acetylene alcohol[3,4] (**6**) was first converted into the one-carbon elongated (*Z*)-olefin alcohol (**11**) in a standard sequence of reactions *via* the silyl ether intermediates (**7**)~(**10**) without difficulties. This was then transformed into the propargyl ether (**13**) in 2 steps employing a modified Williamson synthesis using a complex of potassium fluoride and neutral alumina as catalyst[1,5] followed by silylation of the terminal acetylene group. The base induced [2,3]-Wittig rearrangement[1,6,7] of **13** proceeded in a complete diastereoselective manner to furnish a single product (**15**) having (*R*,*R*)-configuration in an excellent yield which may be generated *via* a 'folded envelope' transition state[6] (**14**). Optical purity of the product was determined to be ≥95% ee by ^{1}H nmr spectra (500 MHz) of the MTPA (*R*- and *S*-) esters. After desilylation of **15**, the configuration of the secondary hydroxy carbon center of the resulting **16** was inverted by employing the Mitsunobu reaction[8] to give the eneynol (**18**) having natural (14*R*,15*S*)-configuration after methanolysis of the resulting benzoate (**17**).

In order to discriminate the two unsaturated bonds, the eneynol (**18**) was first treated with *N*-bromosuccinimide (NBS) to protect the olefinic bond selectively by the formation of the bromo ether (**19**) as a mixture of epimers. The acetylenic group of the mixture was then hydrogenated to give the saturated ether (**20**) as a mixture of epimers. This was next exposed to zinc dust in the presence of hydrochloric acid to regenerate the olefinic bond to give rise to the benzyl ether (**21**) of the $C_{11\text{-}17}$ segment (**2**) with concomitant removal of the methoxymethyl group under the conditions.

To confirm the structure of **21**, it was transformed into the acetonide (**22**) whose benzyl group was then replaced by 2-trimethylsilylethoxymethyl (SEM) group[9] in two steps to give the SEM ether (**24**) *via* the primary alcohol (**23**). Finally, removal of the acetonide group from **24** afforded the SEM ether (**25**) of the $C_{11\text{-}17}$ segment (**2**) which has already been obtained by an entirely different procedure in the total synthesis of mycinolide IV, the aglycon of mycinamicins III (**1a**) and IV (**1b**), by Suzuki, Tsuchihashi and coworkers.[10,11]



Bn= -CH_2Ph; TBS= -$Si(Me)_2Bu^t$; TMS= -$SiMe_3$; MOM= -CH_2OMe; SEM= -$CH_2OCH_2CH_2SiMe_3$

Scheme 1

Reagents and conditions: a, diisopropyl (L)-tartrate, Ti(O-*i*-Pr)4, *t*-BuOOH; b, PPh_3, CCl_4, reflux; c, *n*-BuLi, THF, –30 °C; d, TBS-Cl, imidazole, DMF, room temperature; e, *n*-BuLi, (HCHO)n, THF; f, MOM-Cl, *i*-Pr_2NEt, CH_2Cl_2; g, H_2, Lindlar catalyst, hexane; h, (*n*-$Bu)_4NF$, THF; i, $CH{\equiv}CCH_2Br$, KF-Al_2O_3; j, EtMgBr, THF, then TBS-Cl; k, *n*-BuLi, THF, –78 °C; l, *n*-Bu_4NF, THF; m, $PhCO_2H$, *i*-PrOCON=NCO_2Pr-*i*, PPh_3; m, K_2CO_3, MeOH; o, NBS, $NaHCO_3$, THF; p, H_2, PtO_2, hexane; q, Zn, MeOH, conc. HCl (cat.); r, $MeC(OMe)_2Me$, PPTS, acetone; s, Na, liq. NH_3; t, SEM-Cl, *i*-Pr_2NEt, CH_2Cl_2; u, PPTS, MeOH.

EXPERIMENTAL SECTION

Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. Ir spectra were measured with a JASCO-IR-700 spectrophotometer. ^{1}H Nmr spectra were recorded on JEOL-JNM-FX90A (90 MHz) and JEOL-JNM-GX500 (500 MHz) spectrometers. Mass spectra were measured with a JEOL JMS-DX303 instrument. Reactions were carried out under argon.

(*R*)-4-Benzyloxy-3-*tert*-butyldimethylsilyloxy-1-butyne (7) ——

A mixture of the α-hydroxyacetylene[3,4,12] (**6**) (1.46 g, 8.31 mmol), *tert*-butyldimethylsilyl chloride (1.87 g, 12.46 mmol), and imidazole (1.98 g, 29.1 mmol) in DMF (10 ml) was stirred at room temperature for 14 h. After dilution with Et_2O, the mixture was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (80 g) using Et_2O-hexane (1:100 v/v) as eluent to give the silyl ether (**7**) (2.26 g, 94%) as a colorless oil; $[\alpha]_D^{23}$ –27.72° (*c* 1.01, $CHCl_3$). Ir (film) ν_{max}: 3320, 2120 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.33 (s, 5H), 4.62 (s, 2H), 4.56 (m, 1H), 3.58 (m, 2H), 2.42 (d, *J*=2.2 Hz, 1H), 0.95 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ms (m/z): 290 (M^+), 91 (100%). Exact Mass Calcd for $C_{17}H_{25}O_2Si$ (M^+-H): 289.1623. Found: 289.1615. *Anal.* Calcd for $C_{17}H_{25}O_2Si$: C 70.29, H 9.02. Found: C 70.51, H 8.84.

(*R*)-5-Benzyloxy-4-*tert*-butyldimethylsilyloxypent-2-yn-1-ol (8) ——

To a stirred mixture of the acetylene (**7**) (36.0 mg, 0.12 mmol) in THF (3 ml) was added *n*-butyllithium (1.6 M in hexane) (1.56 ml, 0.25 mmol) at 0 °C and, after 1 h, paraformaldehyde (11.2 mg) was added at the same temperature and the stirring was continued for 5 h. The mixture was treated with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using Et_2O-hexane (1:10~1:4 v/v) as eluent to give the alcohol (**8**) (17.7 mg, 45%, 64% based on consumed **7**) as a colorless oil and the starting material (**7**) (10.8 mg, 30%); $[\alpha]_D^{28}$ –15.66° (*c* 1.02, $CHCl_3$). Ir (film) ν_{max}: 3420 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ:

7.32 (s, 5H), 4.72-4.49 (m, 1H), 4.61 (s, 2H), 4.25 (br s, 2H), 3.56 (m, 2H), 1.75 (br s, 1H, exchangeable with D_2O), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ms (m/z): 199 (M^+-C_8H_9O), 91 (100%). Exact Mass Calcd for $C_{10}H_{19}O_2Si$ (M^+-C_8H_9O): 199.1154. Found: 199.1158.

(*R*)-5-Benzyloxy-4-*tert*-butyldimethylsilyloxy-1-methoxymethoxypent-2-ene (9) ——— A mixture of the alcohol (**8**) (288 mg, 0.90 mmol), (*i*-Pr)$_2$NEt (1.10 g, 6.30 mmol), and chloromethyl methyl ether (0.205 ml, 2.70 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 42 h. The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (15 g) using Et_2O-hexane (1:100 v/v) as eluent to give the ether (**9**) (323 mg, 99%) as a colorless oil; $[\alpha]_D^{30}$ –27.14° (*c* 1.01, $CHCl_3$). Ir (film) ν_{max}: 1250, 1145, 1100, 1045 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.33 (s, 5H), 4.78-4.49 (m, 1H), 4.69 (s, 2H), 4.60 (s, 2H), 4.24 (d, *J*=1.7 Hz, 2H), 3.57 (m, 2H), 3.36 (s, 3H), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ms (m/z): 334 (M^+-CH_2O), 91 (100%). Exact Mass Calcd for $C_{19}H_{30}O_3Si$ (M^+-CH_2O): 334.1965. Found: 334.1958.

(*R*)-(*Z*)-1-Benzyloxy-2-*tert*-butyldimethylsilyloxy-5-methoxymethoxypent-4-ene (10) ——— A suspension of the acetylene (**9**) (621.0 mg, 1.71 mmol) and Lindlar catalyst (18.6 mg) in hexane (5 ml) was hydrogenated under atmospheric pressure of hydrogen. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure. The residue was purified on a silica gel column (30 g) using Et_2O-hexane (1:20 v/v) to give the olefin (**10**) (599.3 mg, 96%) as a colorless oil; $[\alpha]_D^{28}$ –8.86° (*c* 1.11, $CHCl_3$). Ir (film) ν_{max}: 1255, 1150, 1100, 1050 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.31 (s, 5H), 5.78-5.32 (m, 2H), 4.72-4.49 (m, 1H), 4.61 (s, 2H), 4.54 (s, 2H), 4.24 (dd, *J*=12.6, 5.5 Hz, 1H), 4.02 (dd, *J*=12.6, 4.0 Hz, 1H), 3.57-3.22 (m, 2H), 3.35 (s, 3H), 0.88 (s, 9H), 0.07 (br s, 6H); ms (m/z): 335 (M^+-CH_3O), 91 (100%). Exact Mass Calcd for $C_{19}H_{31}O_3Si$ (M^+-CH_3O): 335.2042. Found: 335.2049. *Anal.* Calcd for $C_{20}H_{34}O_4Si$: C 65.53, H 9.35. Found: C 65.73, H 9.51.

(*R*)-(*Z*)-1-Benzyloxy-5-methoxymethoxypent-4-en-2-ol (11) ———

A solution of the silyl ether (**10**), (529.1 mg, 1.45 mmol) and tetra-*n*-butylammonium fluoride (1.0 M in THF) (1.45 ml, 1.45 mmol) in THF (5 ml) was stirred at room temperature for 1.2 h. The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (20 g) using Et_2O-hexane (1:4 v/v) as eluent to give the alcohol (**11**) (341 mg, 100%) as a colorless oil; $[\alpha]_D^{25}$ –26.88° (*c* 1.01, $CHCl_3$). Ir (film) ν_{max}: 3450 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.34 (s, 5H), 5.90-5.47 (m, 2H), 4.80-4.52 (m, 1H), 4.62 (s, 2H), 4.57 (s, 2H), 4.36-3.96 (m, 2H), 3.55-3.27 (m, 2H), 3.36 (s, 3H), 2.69 (d, *J*=2.9 Hz, 1H, exchangeable with D_2O); ms (m/z): 253 (M^++1), 91 (100%). Exact mass Calcd for $C_{14}H_{21}O_3$ (M^++1): 253.1440. Found: 253.1472. *Anal.* Calcd for $C_{14}H_{20}O_4$: C 66.65, H 7.99. Found: C 66.79, H 8.00.

(*R*)-(*Z*)-1-Benzyloxy-5-methoxymethoxy-2-propargyloxypent-4-ene (12) —— A suspension of the alcohol (**11**) (195 mg, 0.83 mmol), propargyl bromide (0.30 ml, 6.6 mmol), and KF-Al_2O_3 (2:3 v/v) (962 mg) in THF (20 ml) was stirred at room temperature for 25 h. After removal of the catalyst by filtration, the filtrate was evaporated and the residue was purified on a silica gel column (8 g) using Et_2O-hexane (1:10 v/v) as eluent to give the ether (**12**) (221 mg, 92%) as a colorless oil; bp 200 °C/1.0 Torr (Kugelrohr); $[\alpha]_D^{25}$ –80.19° (*c* 1.02, $CHCl_3$). Ir (film) ν_{max}: 3280, 2120 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.32 (s, 5H), 6.02-5.34 (m, 2H), 4.73-4.45 (m, 1H), 4.62 (s, 2H), 4.57 (s, 2H), 4.41-3.94 (m, 4H), 3.72-3.40 (m, 2H), 2.36 (s, 3H), 2.42 (t, *J*=2.4 Hz, 1H); ms (m/z): 289 (M^+-1), 91 (100%). Exact mass Calcd for $C_{17}H_{21}O_4$ (M^+-1): 289.1440. Found: 289.1422.

(*R*)-(*Z*)-1-Benzyloxy-5-methoxymethoxy-2-(3-trimethylsilylpropargyloxy)pent-3-ene (13) —— To a stirred solution of the acetylene (**12**) (221.3 mg, 0.76 mmol) in THF (5 ml) was added ethylmagnesium bromide (2.27 M in THF) (0.84 ml, 1.91 mmol) at 0 °C, then after 1.5 h at the same temperature, trimethylsilyl chloride (0.29 ml, 2.28 mmol) was added and the stirring was continued for 30 min at the same temperature. The mixture was treated with saturated aqueous NH_4Cl (5 ml) and extracted with Et_2O. The extract was washed with saturated aqueous

$NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (10 g) using Et_2O-hexane (1:10 v/v) as eluent to give the silylacetylene (**13**) (224.5 mg, 81%) as a colorless oil; $[\alpha]_D^{30}$ –70.82° (*c* 1.00, $CHCl_3$). Ir (film) ν_{max}: 2190 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.30 (s, 5H), 5.48-5.31 (m, 2H), 4.69-4.40 (m, 1H), 4.60 (s, 2H), 4.56 (s, 2H), 4.27-4.05 (m, 4H), 3.71-3.39 (m, 2H), 3.34 (m, 3H), 0.16 (br s, 9H); ms (m/z): 317 (M^+-$C_2H_5O_2$), 91 (100%). Exact Mass Calcd for $C_{18}H_{25}O_3Si$ (M^+-$C_2H_5O_2$): 317.1573. Found: 317.1568.

(3*R*,4*R*)-(*Z*)-7-Benzyloxy-4-methoxymethoxymethyl-1-trimethylsilylhept-5-en-1-yn-3-ol (15) —— To a stirred solution of the silylacetylene (**13**) (228.8 mg, 0.62 mmol) in THF (3 ml) was added *n*-butyllithium (0.54 ml, 0.86 mmol) at –78 °C, and the stirring was continued for 10 min. The mixture was treated with saturated aqueous $NaHCO_3$ (5 ml) and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (8 g) using Et_2O-hexane (1:4 v/v) as eluent to give the secondary alcohol (**15**) (215.5 mg, 97%) as a colorless oil; $[\alpha]_D^{27}$ +9.79° (*c* 1.02, $CHCl_3$). Ir (film) ν_{max}: 3425, 2175 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.33 (s, 5H), 5.90-5.72 (m, 2H), 4.70-4.44 (m, 1H), 4.62 (s, 2H), 4.52 (s, 2H), 4.11-3.95 (m, 2H), 3.82 (dd, *J*=9.8, 5.4 Hz, 1H), 3.66 (dd, *J*=9.8, 6.6 Hz, 1H), 3.37 (s, 3H), 2.83-2.47 (m, 2H, 1H exchangeable with D_2O), 0.17 (br s, 9H); ms (m/z): 347 (M^+-CH_3), 91 (100%). Exact Mass Calcd for $C_{19}H_{27}O_4Si$ (M^+-CH_3): 347.1679. Found: 347.1655.

(3*R*,4*R*)-(*E*)-7-Benzyloxy-4-methoxymethoxymethylhept-5-en-1-yn-3-ol (16) —— A mixture of the silylacetylene (**15**) (1.16 g, 3.21 mmol) and tetra-*n*-butylammonium fluoride (1.0 M in THF) (3.21 ml, 3.21 mmol) in THF (10 ml) was stirred at room temperature for 5 min. The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (30 g) using Et_2O-hexane (1:4 v/v) as eluent to give the eneyne (**16**) (882.1 mg, 95%) as a colorless oil; $[\alpha]_D^{28}$ +1.16° (*c* 1.03, $CHCl_3$). Ir (film) ν_{max}: 3420, 3290, 2125 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.33 (s, 5H), 6.05-5.07 (m, 2H), 4.71-4.44 (m, 1H), 4.62 (s, 2H), 4.52 (s,

2H), 4.12-3.96 (m, 2H), 3.82 (dd, *J*=9.8, 5.6 Hz, 1H), 3.66 (dd, *J*=9.8, 6.6 Hz, 2H), 3.37 (s, 3H), 2.87-2.53 (m, 2H, 1H exchangeable with D_2O), 2.50 (d, *J*=2.2 Hz, 1H); ms (m/z): 245 (M^+-$C_2H_5O_2$), 91 (100%). Exact Mass Calcd for $C_{15}H_{17}O_3$ (M^+-$C_2H_5O_2$): 245.1178. Found: 245.1171. ^1H nmr examination of MTPA (both enantiomers) esters of **16** showed optical homogeneity of the material: (*R*)-MTPA ester ($CDCl_3$) δ: 7.57-7.50 (m, 2H), 7.40-7.26 (m, 8H), 5.81 (dd, *J*=5.4, 2.4 Hz, 1H), 5.63 (m, 2H), 4.58 (d, *J*=6.7 Hz, 1H), 4.55 (d, *J*=6.7 Hz, 1H), 4.44 (s, 2H), 3.93 (d, *J*=2.4 Hz, 2H), 3.64 (dd, *J*=9.8, 7.3 Hz, 1H), 3.58 (s, 3H), 3.50 (dd, *J*=9.8, 5.5 Hz, 1H), 3.34 (s, 3H), 2.82 (m, 1H), 2.58 (d, *J*=2.5 Hz, 1H). (*S*)-MTPA ester ($CDCl_3$) δ: 7.56-7.50 (m, 2H), 7.41-7.27 (m, 8H), 5.81 (dd, *J*=5.5, 2.4 Hz, 1H), 5.77 (dt, *J*=15.9, 4.9 Hz, 1H), 5.70 (dd, *J*=15.9, 8.5 Hz, 1H), 4.61 (s, 2H), 4.46 (s, 2H), 3.98 (d, *J*=4.9 Hz, 2H), 3.69 (dd, *J*=9.8, 7.3 Hz, 1H), 3.60 (dd, *J*=9.8, 5.5 Hz, 1H), 3.52 (s, 3H), 3.63 (s, 3H), 2.91 (m, 1H), 2.54 (d, *J*=2.4 Hz, 1H).

(3*S*,4*R*)-(*E*)-3-Benzoyloxy-7-benzyloxy-4-methoxymethoxymethylhept-5-en-1-yne (17) ——— To a stirred solution of the secondary alcohol (**16**) (853.8 mg, 2.94 mmol) in THF (2 ml) were sequentially added benzoic acid (539.4 mg, 4.42 mmol), triphenylphosphine (1.31 g, 5.0 mmol), and diisopropyl azodicarboxylate (1.01 g, 5.0 mmol) at 0 °C and the stirring was continued for 10 min at the same temperature. After evaporation of the solvent under reduced pressure, the residue was purified on a silica gel column (140 g) using Et_2O-hexane (1:10 v/v) as eluent to give the benzoate (**17**) (972.3 mg, 84%) as a colorless oil; $[\alpha]_D^{30}$ –27.23° (*c* 1.20, $CHCl_3$). Ir (film) ν_{max}: 3280, 2140, 1725 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 8.15-7.96 (m, 2H), 7.80-7.37 (m, 3H), 7.50 (s, 5H), 5.96-5.77 (m, 3H), 4.61 (s, 2H), 4.48 (s, 2H), 4.05 (d, *J*=4.4 Hz, 2H), 3.75 (d, *J*=6.1 Hz, 2H), 3.32 (s, 3H), 3.07-2.72 (m, 1H), 2.52 (d, *J*=2.2 Hz, 1H); ms (m/z): 349 (M^+-C_2H_5O), 105 (100%). Exact Mass Calcd for $C_{22}H_{21}O_4$ (M^+-C_2H_5O): 349.1439. Found: 349.1444.

(3*S*,4*R*)-(*E*)-7-Benzyloxy-4-methoxymethoxymethylhept-5-en-1-yn-3-ol (18) ——— A suspension of the benzoate (**17**) (179.4 mg, 0.46 mmol) and K_2CO_3 (94.4 mg, 0.68 mmol) in MeOH (2 ml) was stirred at room temperature for 2 h. The mixture was diluted with Et_2O and water and the organic layer was separated. The

organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using Et_2O-hexane (1:2 v/v) as eluent to give the secondary alcohol (**18**) (131.4 mg, 100%) as a colorless oil; $[\alpha]_D^{27}$ –2.53° (*c* 1.01, $CHCl_3$). Ir (film) ν_{max}: 3430, 3300, 2120 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.33 (s, 5H), 6.00-5.45 (m, 2H), 4.64 (s, 2H), 4.61-4.39 (m, 1H), 4.51 (s, 2H), 4.08-3.93 (m, 2H), 3.86 (d, *J*=9.5 Hz, 1H), 3.69 (dd, *J*=9.5, 5.1 Hz, 1H), 3.39 (s, 3H), 3.25 (d, *J*=8.1 Hz, 1H, exchangeable with D_2O), 2.97-2.62 (m, 1H), 2.51 (d, *J*=2.2 Hz, 1H); ms (m/z): 245 (M^+-C_2H_5O), 91 (100%). Exact Mass Calcd for $C_{15}H_{17}O_3$ (M^+-C_2H_5O): 245.1178. Found: 245.1169.

(2*S*,3*R*,4*RS*,5*RS*)-5-Benzyloxymethyl-4-bromo-2-ethynyl-3-methoxymethoxymethyltetrahydrofuran (19) —— To a stirred suspension of the eneyne (**18**) (21.2 mg, 0.09 mmol) and $NaHCO_3$ (77.8 mg, 0.93 mmol) in THF (2 ml) was added NBS (19.8 mg, 0.11 mmol) and the stirring was continued for 1 h. The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using Et_2O-hexane (1:15 v/v) as eluent to give the bromo ether (**19**) (27.9 mg, 82%) as a colorless oil. Ir (film) ν_{max}: 3290, 2125 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.31 (s, 5H), 4.71-4.52 (m, 5H), 4.46-3.51 (m, 6H), 3.34 (s, 3H), 2.74 (m, 1H), 2.54 (d, *J*=2.2 Hz, 1H); ms (m/z): 325 (M^+-C_2H_5O), 323 (M^+-C_2H_5O), 91 (100%). Exact Mass Calcd for $C_{15}H_{16}O_3Br$ (M^+-C_2H_5O): 325.0262, 323.0283. Found: 325.0278, 323.0302.

(2*S*,3*R*,4*RS*,5*RS*)-5-Benzyloxymethyl-4-bromo-2-ethyl-3-methoxymethoxymethyltetrahydrofuran (20) —— A suspension of the acetylene (**19**) (22.9 mg, 0.06 mmol) in hexane (2 ml) was hydrogenated in the presence of PtO_2 (0.7 mg) under atmospheric pressure of hydrogen at room temperature for 1.5 h. After filtration using Celite pad, the filtrate was evaporated under reduced pressure and the residue was purified on a silica gel column (4 g) using Et_2O-hexane (1:7 v/v) as eluent to give the saturated product (**20**) (19.9 mg, 86%) as a colorless oil. Ir (film) ν_{max}: 1150, 1110, 1040, 965, 920, 740, 700 cm^{-1}; ^1H nmr ($CDCl_3$) δ:

7.33 (s, 5H), 4.62 (s, 4H), 4.21-3.48 (m, 7H), 3.35 (s, 3H), 2.49-2.12 (m, 1H), 1.88-1.49 (m, 2H), 1.00 (t, *J*=7.8 Hz, 3H); ms (m/z): 329 (M^+-C_2H_5O), 327 (M^+-C_2H_5O), 91 (100%). Exact Mass Calcd for $C_{15}H_{20}O_3Br$ (M^+-C_2H_5O): 329.0575, 327.0595. Found: 329.0567, 327.0572.

(4*R*,5*R*)-(*E*)-1-Benzyloxy-5-hydroxy-4-hydroxymethylhept-2-ene (21) [the Monobenzyl Ether of the C_{11-17} Segment (2)] ——— A suspension of the bromo ether (**20**) (383.0 mg, 1.03 mmol) and zinc dust (671.2 mg, 10.3 mmol) in MeOH (5 ml) containing 35% hydrochloric acid (0.1 ml) was refluxed for 2.5 h. After filtration, the filtrate was evaporated under reduced pressure and the residue was taken up into Et_2O. The ethereal layer, after filtration using Celite pad, was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated reduced pressure. The residue was purified on a silica gel column(10 g) to give the diol (**21**) (194.0 mg, 76%) as a colorless oil; $[\alpha]_D^{27}$ –8.65° (*c* 1.00, $CHCl_3$). Ir (film) ν_{max}: 3380 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.33 (s, 5H), 5.87-5.63 (m, 2H), 4.52 (s, 2H), 4.11-3.95 (m, 2H), 3.77 (d, *J*=5.6 Hz, 2H), 3.70 (m, 1H), 2.55-1.85 (m, 3H, 2H exchangeable with D_2O), 1.78-1.22 (m, 2H), 0.94 (t, *J*=7.8 Hz, 3H); ms (m/z): 174 (M^+-$C_3H_8O_2$), 91 (100%). Exact Mass Calcd for $C_{12}H_{14}O$ (M^+-$C_3H_8O_2$): 174.1044. Found: 174.1049.

(4*R*,5*R*)-(*E*)-5-(3-Benzyloxyprop-1-enyl)-4-ethyl-2,2-dimethyl-1,3-dioxane (22) ——— A mixture of the diol (**21**) (139.6 mg, 0.56 mmol), 2,2-dimethoxypropane (0.21 ml, 1.71 mmol), and pyridinium *p*-toluenesulfonate (PPTS) (7.0 mg, 0.03 mmol) in acetone (3 ml) was stirred at room temperature for 15 h. After evaporation of the solvent under reduced pressure, the residue was taken up into Et_2O and the ethereal layer was washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated reduced pressure. The residue was purified on a silica gel column (5 g) using Et_2O-hexane (1:15 v/v) as eluent to give the acetonide (**22**) (147.0 mg, 91%) as a colorless oil; $[\alpha]_D^{29}$ –22.50° (*c* 1.01, $CHCl_3$). Ir (film) ν_{max}: 1380, 1200, 1062, 980, 858, 742, 702 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.33 (s, 5H), 6.15 (dd, *J*=15.6, 9.3 Hz, 1H), 5.67 (dt, *J*=15.6, 6.1 Hz, 1H), 4.50 (s, 2H), 4.16 (dd, *J*=11.5, 2,9 Hz, 1H), 4.04 (d, *J*=6.1 Hz, 2H), 3.83 (td, *J*=6.8, 2.7 Hz, 1H), 3.72 (dd, *J*=11.5, 1.7 Hz, 1H),

2.09 (m, 1H), 1.70-1.20 (m, 2H), 1.47 (s, 3H), 1.43 (s, 3H), 1.03-0.70 (m, 3H); ms (m/z): 275 (M^+-CH_3), 91 (100%). Exact Mass Calcd for $C_{17}H_{23}O_3$ (M^+-CH_3): 275.1647. Found: 275.1627.

(4*R*,5*R*)-(*E*)-4-Ethyl-5-(3-hydroxyprop-1-enyl)-2,2-dimethyl-1,3-dioxan (23) —— To a stirred solution of the benzyl ether (**22**) (142.9 mg, 0.49 mmol) in a mixture of liquid NH_3 (30 ml) and THF (3 ml) was added Na (34 mg, 1.48 m atom) portionwise. After having faded blue color, MeOH (1 ml) was added to the mixture and ammonia was evaporated under atmospheric pressure. The residue diluted with CH_2Cl_2 was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using Et_2O-hexane (1:2 v/v) as eluent to give the primary alcohol (**23**) (54.9 mg, 56%) as a colorless oil; $[\alpha]_D^{28}$ –28.99° (*c* 1.03, $CHCl_3$). Ir (film) ν_{max}: 3420 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 6.12 (dd, *J*=15.6, 9.0 Hz, 1H), 5.72 (dt, *J*=15.6, 5.4 Hz, 1H), 4.31-4.01 (m, 1H), .414 (d, *J*=5.4 Hz, 2H), 3.84 (td, *J*=6.8, 2.4 Hz, 1H), 3.70 (dd, *J*=11.5, 2.0 Hz, 1H), 2.24-1.80 (m, 2H, 1H exchangeable with D_2O), 1.61-1.19 (m, 2H), 1.47 (s, 3H), 1.42 (s, 3H), 0.86 (t, *J*=7.8 Hz, 3H); ms (m/z): 185 (M^+-CH_3), 59 (100%). Exact Mass Calcd for $C_{16}H_{17}O_3$ (M^+-CH_3): 185.1178. Found: 185.1168.

(4*R*,5*R*)-(*E*)-4-Ethyl-2,2-dimethyl-5-[3-(2-trimethylsilyl)ethoxy-methoxyprop-1-enyl]-1,3-dioxane (24) —— A mixture of the primary alcohol (**23**) (54.1 mg, 0.27 mmol), 2-trimethylsilylethoxymethyl chloride (0.14 ml, 0.82 mmol), and (*i*-Pr)$_2$NEt (0.24 ml, 1.36 mmol) in CH_2Cl_2 (2 ml) was stirred at room temperature for 15 h. The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using Et_2O-hexane (1:15 v/v) as eluent to give the ether (**24**) (71.2 mg, 80%) as a colorless oil; $[\alpha]_D^{30}$ –20.74° (*c* 1.01, $CHCl_3$). Ir (film) ν_{max}: 1380, 1250, 1195, 1105, 1055, 855, 835 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 6.11 (dd, *J*=15.6, 9.2 Hz, 1H), 5.60 (dt, *J*=15.6, 6.1 Hz, 1H), 4.66 (s, 2H), 4.23-3.46 (m, 7H), 2.98 (m, 1H), 1.50-1.15 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H),

1.02-0.70 (m, 5H), 0.00 (s, 9H); ms (m/z): 315 (M^+-CH_3), 73 (100%). Exact Mass Calcd for $C_{16}H_{31}O_4Si$ (M^+-CH_3): 315.1992. Found: 315.1998.

(4*R*,5*R*)-(*E*)-5-Hydroxy-4-hydroxymethyl-1-(2-trimethylsilylethoxymethoxy)hept-2-ene (25) (the Suzuki-Tsuchihashi C_{11-17} Segment) -----

A mixture of the acetonide (**24**) (60.5 mg, 0.18 mmol) and PPTS (2.3 mg, 0.01 mmol) in MeOH (3 ml) was stirred at room temperature for 14 h. The mixture was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified on a silica gel column (5 g) using Et_2O-hexane (1:1~2:1 v/v) to give the diol (**25**) (48.8 mg, 98%) as a colorless oil; $[\alpha]_D^{30}$ −12.83° (*c* 0.97, $CHCl_3$). Ir (film) ν_{max}: 3400 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 5.79 (dd, *J*=15.9, 7.9 Hz, 1H), 5.74 (dt, *J*=15.9, 5.5 Hz, 1H), 4.70 (s, 2H), 4.11 (dd, *J*=12.2, 4.9 Hz, 1H), 4.07 (dd, *J*=12.2, 4.9 Hz, 2H), 3.85-3.71 (m, 3H), 3.63 (m, 2H), 2.35 (m, 1H), 2.25-2.09 (m, 2H, exchangeable with D_2O), 1.49 (quint, *J*=7.3 Hz, 2H), 0.98-0.92 (m, 5H), 0.03 (s, 9H); ms (m/z): 291 (M+1), 95 (100%).

ACKNOWLEDGEMENTS

We thank to the Ministry of Education, Science and Culture, Japan for partial financial support to this work and to the Japan Society for the Promotion of Science for Japanese Junior Scientist for a fellowship (to Y. S.).

REFERENCES

1. S. Takano, Y. Sekiguchi, Y. Shimazaki, and K. Ogasawara, preceding paper.
2. (a) M. Hayashi, M. Ohno, and S. Satoi, *J. Chem. Soc., Chem. Commun.*, 1980, 119. (b) S. Satoi, N. Muto, M. Hayashi, T. Fujii, and M. Otani, *J. Antibiot.*, 1980, **33**, 364. (c) M. Hayashi, H. Ohara, M. Ohno, H. Sakakibara, S. Satoi, K. Harada, and M. Suzuki, *ibid.*, 1981, **34**, 1075. (d) M. Hayashi, M. Ohno, K. Kinoshita, S. Satoi, M. Suzuki, and K. Harada, *ibid.*, 1981, **34**, 346. (e) M. Hayashi, K. Kinoshita, S. Satoi, and K. Nakatsu, *ibid.*, 1982, **35**, 1243.

3. S. Takano, K. Samizu, T. Sugihara, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1989, 1344.
4. S. Takano, T. Sugihara, K. Samizu, M. Akiyama, and K. Ogasawara, *Chem. Lett.*, 1989, 1781. An alternative synthesis, see: S. Takano, M. Akiyama, T. Sugihara, and K. Ogasawara, accompanied paper.
5. T. Ando, J. Yamawaki, T. Kawate, and S. Sumi, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 2504.
6. cf. T. Nakai and K. Mikami, *Chem. Rev.*, 1986, **86**, 885.
7. S. Takano, Y. Sekiguchi, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1987, 555.
8. O. Mitsunobu, *Synthesis*, 1981, 1.
9. B. H. Lipshuts and J. J. Tegrem, *Tetrahedron Lett.*, 1980, **21**, 3343.
10. K. Suzuki, T. Matsumoto, K. Tomooka, K. Matsumoto, and G. Tsuchihashi, *Chem. Lett.*, 1987, 113.
11. T. Matsumoto, H. Maeba, K. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, 1988, **29**, 3575.
12. Determined by ^{1}H nmr determination of MTPA (both enantiomers) esters, see: S. Takano, M. Takahashi, M. Yanase, Y. Sekiguchi, Y. Iwabuchi, and K. Ogasawara, *Chem. Lett.*, 1988, 1827.

Received, 8th November, 1991