[Chem. Pharm. Bull. 32(4)1294—1302(1984)]

Chemical Transformation of Terpenoids. VI.[1] Syntheses of Chiral Segments, Key Building-Blocks for the Left Half of Taxane-Type Diterpenoids

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(Received July 15, 1983)

By the use of a bromomethyl-cyclohexane derivative (**7**), which was synthesized from *d*-camphor (**5**), as the starting compound, two kinds of chiral segments, *i.e.* segment A-I (**3**) and segment A-II (**4**), were synthesized. These segments are potentially versatile building blocks for construction of the left half of taxane-type diterpenoids.

Keywords——*d*-camphor; taxane-type diterpenoid; chiral segment; taxa-4(20),11-diene; base dehydrobromination; sodium liquid ammonia reduction; selenium dioxide oxidation

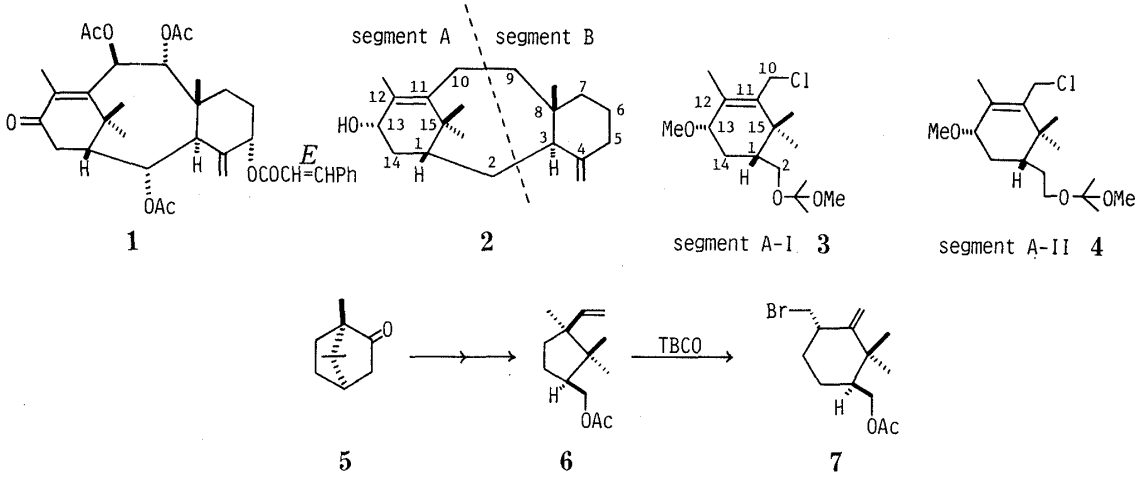
Taxane-type diterpenoids occur fairly widely in Taxaceous plants as Taxus alkaloids, and various kinds of derivatives, *e.g.* taxinine (**1**),[2] have hitherto been chemically characterized. Since the taxane-type diterpenoids possess a strained tricyclo[9.3.1.$0^{3,8}$]pentadecane skeleton, they represent interesting targets for synthetic studies.[3] Furthermore, anti-tumor and anti-leukemia active taxane-type diterpenoids, *e.g.* taxol and cephalomannine, have been isolated recently.[4]

As a continuation of our transformation studies on terpenoids,[1,5] we have been undertaking synthetic studies of optically active taxane-type diterpenoids. This and the forthcoming papers deal with our synthetic approaches to those diterpenoids. We have chosen 13α-hydroxy-taxa-4(20),11-diene (**2**) as the target compound.

Our synthetic strategy comprises construction of the desired carbon skeleton (**2**) by combination of two optically active segments, segment A (left half) and segment B (right half), obtained in principle by splitting the C_2–C_3 and C_9–C_{10} bonds of **2**. In this paper, we describe the synthesis of two kinds of optically active segment A, *i.e.* segment A-I (**3**)[6] and its homolog segment A-II (**4**), from the bromomethyl-cyclohexane derivative (**7**)[5b] which was previously synthesized from *d*-camphor (**5**) *via* ring-enlargement reaction of the vinyl-cyclopentane derivative (**6**) by the use of 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO).

Synthesis of Segment A-I (3)[7]

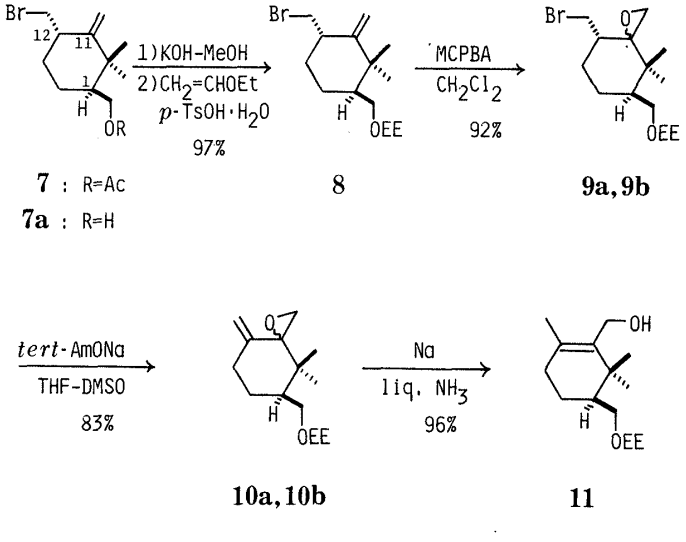
Treatment of the bromomethyl-cyclohexanecarbinol (**7a**), which was prepared by alkaline hydrolysis of the above-mentioned bromomethyl-cyclohexanecarbinyl acetate (**7**),[5b] with ethyl vinyl ether in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) provided the ethoxyethyl ether (**8**) in excellent yield. Epoxidation of **8** with 1.5 molar equivalents of *m*-chloroperbenzoic acid (MCPBA) furnished a 1 : 1 mixture of two epoxides (**9**) in 92% yield. Although these two epoxides (**9a**, **b**) could be separated by repeated silica gel column chromatography, the individual C_{11} configurations were not determined. Dehydrobromination of **9a** and **9b** with sodium tertiary amylate (*tert*-AmONa) in tetrahydrofuran (THF)–dimethyl sulfoxide (DMSO) furnished the corresponding α,β-unsaturated epoxides **10a** and **10b** in high yields. Subsequent reduction of both **10a** and **10b** with sodium



1 2 segment A-I 3 segment A-II 4

5 6 7

Chart 1



7 : R=Ac
7a : R=H

8 9a,9b

10a,10b 11

EE=ethoxyethyl

Chart 2

and liquid ammonia provided the same allylic alcohol (**11**) in high yields (81% from **9a** and 75% from **9b**). The allylic alcohol (**11**) could also be conveniently prepared from the epoxide mixture (**9**) by a similar procedure in 80% overall yield. The structure of **11** was substantiated by its physicochemical properties, *e.g.* hydroxyl and the double bond absorption bands in its infrared (IR) spectrum, and signals assignable to the olefinic methyl group (12-CH_3) and the allylic primary carbinyl methylene function (11-CH_2OH) in its proton nuclear magnetic resonance (^{1}H-NMR) spectrum. We also investigated the optimal reaction conditions for the dehydrobromination of **9** to yield **10** and the results are summarized in Table I.

Conversion from **10** to **11** was accomplished by diisobutylaluminum hydride reduction at -78 °C in *n*-hexane, but the yield was unsatisfactory.

Acetylation of **11** (giving **11a**) followed by oxidation with 2 equivalents of selenium dioxide (SeO_2) in dioxane–pyridine furnished the 13α-hydroxylated product (**12**) in 92% yield. The structure of **12** was substantiated by its IR and ^{1}H-NMR spectra; the latter showed a two-proton singlet due to the acetoxymethylene protons (11-CH_2OAc) and a one-proton triplet-like signal at δ 3.83 ($W_{h/2}=8$ Hz) assignable to 13β-H. The 13*S* configuration of **12** was supported by the following considerations: i) the half-band width of the 13-H signal was 8 Hz

TABLE I. Dehydrobromination of **9**[a]

Base (eq)	Solvent	Temp. (°C)	Time	Yield (%)
tert-AmONa (5.0)	THF–DMSO (2:1)	70	15 min	83
(1.5)	—	80	22 h	67
DBU[b] (2.3)	—	100	4 h	39
(4.6)	Benzene	80	42 h	33
2,6-Lutidine (10)	—	80	24 h	[c]
DBU–2,6-lutidine (2.0:2.0)	Toluene	80	48 h	65
2,4,6-Collidine (10)	—	80	24 h	[c]
DBU–2,4,6-collidine (0.5:10)	—	80	24 h	30

a) Each reaction was carried out by using 100 mg of **9** as the starting compound and the yield was calculated on the basis of **10**, which was obtained by purification of the reaction product by silica gel column chromatography.
b) DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.
c) No reaction; the starting material was recovered.

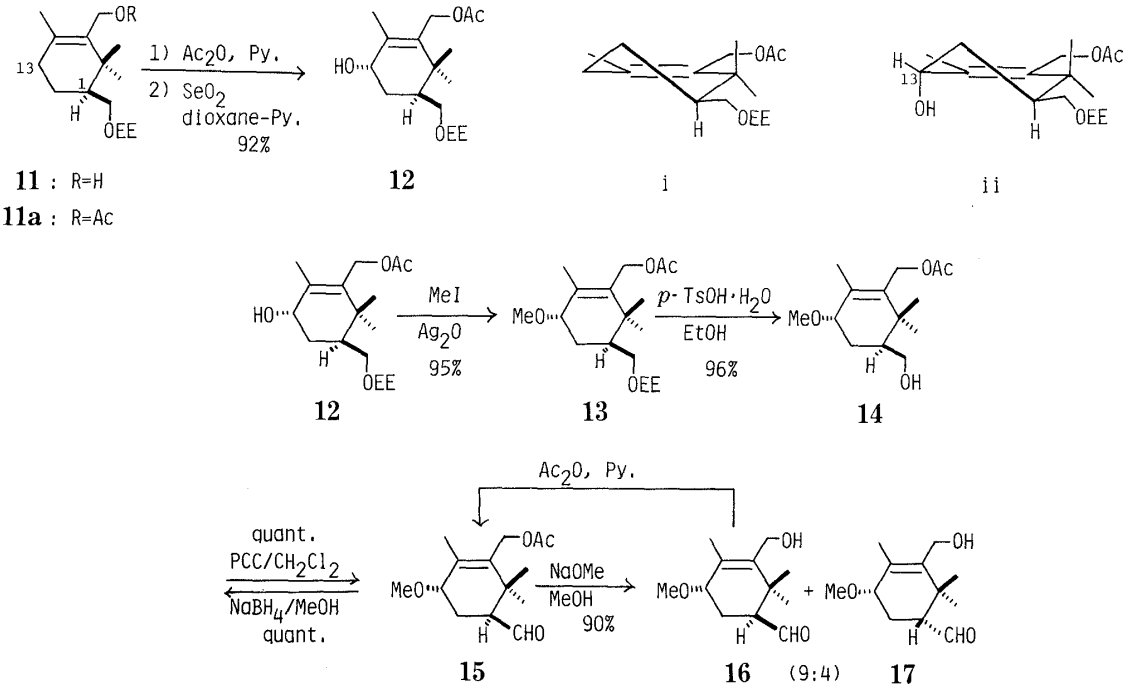


Chart 3

(t-like), which is consistent with the conformation ii, and ii) the predominant conformation of **11a** was considered to be i and the SeO_2 oxidation[8] of i was presumed to proceed from the less-hindered α side to afford ii.

Methylation of **12** with methyl iodide and silver oxide[9] furnished the methyl ether (**13**), which was then treated with *p*-TsOH·H_2O in 95% ethanol to remove the ethoxyethyl group to afford the carbinol (**14**) in excellent yield from **12**. Pyridinium chlorochromate (PCC) oxidation[10] of **14** quantitatively gave the aldehyde (**15**), which reverted to the parent carbinol (**14**) quantitatively upon sodium borohydride reduction. Thus, the C_1 configuration in **14** was shown to be retained during the PCC oxidation.

Treatment of the aldehyde (**15**) with methanolic sodium methoxide at room temperature provided a mixture of deacetylated products, **16** and **17**, in a ratio of 9:4. Acetylation of the major product (**16**) quantitatively provided the parent aldehyde (**15**); thus, the C_1 configuration in **16** was shown to be the same as in **15**. The minor product (**17**) possessed hydroxyl and aldehyde functions as shown by its IR spectrum. The ^{1}H-NMR spectrum of **17** showed

signals assignable to the secondary methoxyl group, the allylic primary carbinyl group, and the secondary aldehyde group. Thus, **17** was shown to be the C_1 epimer of the major aldehyde (**16**). Since a mixture of **16** and **17** in the same ratio (9 : 4) was also formed upon similar treatment of **16** with methanolic sodium methoxide as carried out for **15**, **16** could be converted in turn to **17**, which possesses the same C_1 configuration as that in the target compound **2**.

Since the aldehyde (**17**) having the desired C_1 configuration was successfully synthesized from the bromomethyl-cyclohexane derivative (**7**), **17** was then converted to segment A-I (**3**) as described below.

Acetylation (giving **17a**) followed by sodium borohydride reduction of **17** almost quantitatively furnished **18**, which corresponded to the C_1 epimer of **14**. Treatment of **18** with isopropenyl methyl ether and phosphorus oxychloride[11] gave the methoxyisopropyl ether (**18a**), which, on subsequent alkaline hydrolysis, was converted to an allylic carbinol (**18b**). The allylic carbinol (**18b**) was then, without further purification, treated with lithium chloride-mesyl chloride (MsCl)-2,4,6-collidine[12] to furnish segment A-I (**3**) in 98% yield from **18**. Segment A-I (**3**) showed a positive Beilstein test. The IR spectrum of **3** lacked the hydroxyl absorption band, but showed the double bond and the chloride absorption bands. The ^{1}H-NMR spectrum of segment A-I (**3**) showed signals due to the methoxyisopropyloxymethyl group at the C_1, two tertiary methyl groups, one olefinic methyl group, and one secondary methoxyl group, and one allylic methylene function having a chlorine atom. These physical data substantiated the structure of segment A-I (**3**).

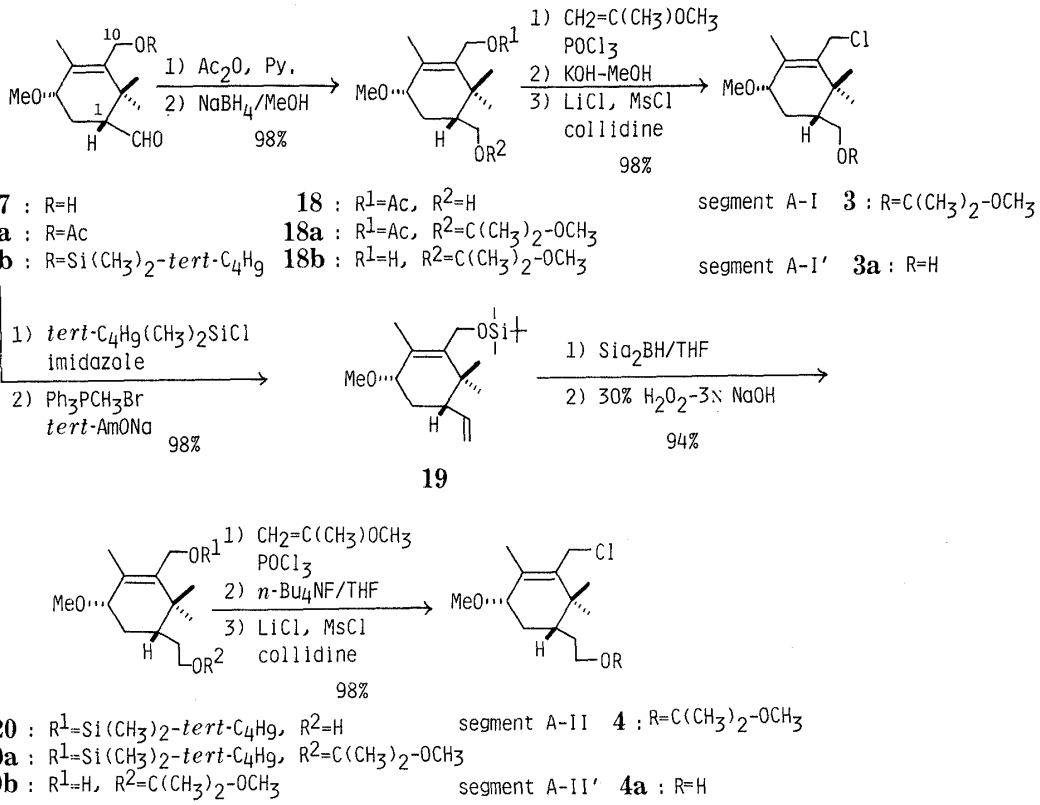


Chart 4

Synthesis of Segment A-II (4)

Segment A-II (**4**), a homolog of segment A-I (**3**), was synthesized from the above-mentioned aldehyde (**17**). Treatment of **17** with *tert*-butyldimethylsilyl (TBDMS) chloride and imidazole[13] furnished the TBDMS ether (**17b**), which, on treatment with methyltriphenyl-

phosphonium bromide and *tert*-AmONa, was converted to the vinyl derivative (**19**) in 98% yield. Hydroboration wirth disiamyl borane and subsequent oxidation with hydrogen peroxide of **19** furnished the homo-alcohol (**20**) in excellent yield. After conversion of **20** to the methoxyisopropyl ether (**20a**), desilylation of **20a** with tetra-*n*-butylammonium fluoride (*n*-Bu_4NF)[14] (giving **20b**) and subsequent chlorination with lithium chloride-MsCl-2,4,6-collidine provided segment A-II (**4**) in 98% yield from **20**.

Segment A-II (**4**) showed a positive Beilstein test and the structure was supported by its physicochemical properties. Thus, the IR spectrum of **4** showed the double bond and the chloride absorption bands and the ^{1}H-NMR spectrum showed signals ascribable to the methoxyisopropyl protecting group together with signals due to two tertiary methyl groups, one olefinic methyl group, one secondary methoxyl group, and one chloromethyl group attached to the double bond. Since the methoxyisopropyl protecting groups of segment A-I (**3**) and segment A-II (**4**) are labile and readily removed even at room temperature, the structures of **3** and **4** were further confirmed by examination of the physicochemical properties of the individual deprotected derivatives, segment A-I′ (**3a**) and segment A-II′ (**4a**).

As mentioned above, segment A-I (**3**) and segment A-II (**4**), which are considered to be versatile synthons for construction of the left half of taxane-type diterpenoids, have been synthesized from *d*-camphor (**5**) *via* the bromomethyl-cyclohexane derivative (**7**) in 15 and 14% overall yields from **7**. Synthetic studies on the optically active right half synthon (segment B) will be reported in a forthcoming paper.

Experimental

The following instruments were used to obtain physical data: specific rotations, JASCO DIP-181 digital polarimeter; IR spectra, Hitachi 260-30 infrared spectrometer; ^{1}H-NMR spectra, Hitachi R-22 (90 MHz) NMR spectrometer (with TMS as an internal standard); mass spectra (MS) and high resolution MS, JEOL JMS-D300 mass spectrometer or JEOL JMS-01SG-2 mass spectrometer. Silica gel (Merck, 0.05—0.2 mm or 0.04—0.063 mm) and pre-coated TLC plates (Merck, silica gel 60 F_{254}) were used for column and thin-layer chromatography (TLC) and detection of spots on TLC plates was done by spraying 1% $Ce(SO_4)_2$–10% H_2SO_4 and subsequent heating. All reactions were carried out under a nitrogen or an argon atmosphere.

Alkaline Hydrolysis of 7 Giving 7a——A solution of **7** (2.47 g, 8.5 mmol) in 10% KOH–MeOH (15 g, 27 mmol) was allowed to stand at room temperature for 1.5 h. The reaction mixture was poured into ice-water and the whole was extracted with EtOAc. The EtOAc extract was washed with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure furnished **7a** (2.11 g, quant.). **7a**, colorless oil, $[\alpha]_D^{14}$ +63° (c=2.1, $CHCl_3$) *Anal.* Calcd for $C_{11}H_{19}BrO$: C, 53.45; H, 7.75; Br, 32.33. Found: C, 53.20; H, 7.84; Br, 32.21. IR ν_{max}^{film} cm^{-1}: 3320 (br), 3095, 1630, 900. ^{1}H-NMR (CCl_4, δ): 0.96, 1.19 (3H each, both s, *tert*-CH_3 ×2), 3.2—3.9 (4H, m, –C<u>H</u>$_2$Br, –C<u>H</u>–C<u>H</u>$_2$–O–), 4.56, 4.83 (1H each, both br s, >C=C<u>H</u>$_2$). MS m/z (%): 248 ($C_{11}H_{19}{}^{81}BrO$, 1), 246 ($C_{11}H_{19}{}^{79}BrO$, 1), 135 (100).

Ethoxyethylation of 7a Giving 8——A solution of **7a** (2.11 g, 8.5 mmol) in CH_2Cl_2 (20 ml) was treated with ethyl vinyl ether (1.2 ml, excess) and *p*-TsOH·H_2O (2 mg) and the reaction mixture was stirred under ice-cooling for 30 min, then poured into aq. sat. $NaHCO_3$. The separated organic phase was taken, washed with aq. sat. NaCl, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (2.82 g), which was purified by column chromatography (SiO_2, 80 g, benzene–EtOAc=20:1) to furnish **8** (2.64 g, 97%). **8**, colorless oil, $[\alpha]_D^{19}$ +60° (c=1.3, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{27}BrO_2$: C, 56.42; H, 8.53; Br, 25.03. Found: C, 56.57; H, 8.73; Br, 25.16. IR ν_{max}^{film} cm^{-1}: 3080, 1626, 890. ^{1}H-NMR (CCl_4, δ): 0.97, 1.15 (3H each, both s, *tert*-CH_3 ×2), 1.14 (3H, t, J=7 Hz, –OCH$_2$C<u>H</u>$_3$), 1.26 (3H, d, J=6 Hz, –O–CH(C<u>H</u>$_3$)–O–), 3.0—3.8 (6H, m, –C<u>H</u>$_2$Br, –C<u>H</u>–C<u>H</u>$_2$–O–, –OC<u>H</u>$_2$CH$_3$), 4.53 (1H, q, J=6 Hz, –O–C<u>H</u>(CH$_3$)–O–), 4.54, 4.83 (1H each, both br s, >C=C<u>H</u>$_2$). MS m/z (%): 275 ($C_{15}H_{27}{}^{81}BrO_2$–C_2H_5O, 18), 273 ($C_{15}H_{27}{}^{79}BrO_2$–C_2H_5O, 18), 107 (100).

Epoxidation of 8 Giving 9——A solution of **8** (1.07 g, 3.35 mmol) in CH_2Cl_2 (20 ml) was treated with 80% MCPBA (1.10 g, 5.10 mmol) and the whole mixture was stirred at room temperature for 1 h. After decomposition of the excess peracid by addition of aq. sat. Na_2SO_3, the organic phase was successively washed with aq. sat. $NaHCO_3$ and aq. sat. NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (1.10 g), which was purified by column chromatography (SiO_2, 50 g, *n*-hexane–EtOAc=10:1) to furnish **9a** (559 mg, 50%) and **9b** (473 mg, 42%). **9a**, colorless oil, $[\alpha]_D^{17}$ +10° (c=3.6, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{27}BrO_3$: C, 53.73; H, 8.12; Br, 23.83. Found: C, 53.79; H, 8.26; Br, 24.12. IR ν_{max}^{film} cm^{-1}: 3045, 1135, 1098, 935. ^{1}H-NMR (CCl_4, δ): 0.82, 1.00 (3H each, both s, *tert*-CH_3 ×2), 1.14 (3H, t, J=7 Hz, –O–CH$_2$C<u>H</u>$_3$), 1.22 (3H, d, J=5 Hz, –O–CH(C<u>H</u>$_3$)–O–), 2.7—3.7

(8H, m, $-CH_2Br$, $-CH-CH_2-O-$, $-OCH_2CH_3$, $>C(O)-CH_2$), 4.55 (1H, q, $J=5$ Hz, $-O-CH(CH_3)-O-$). MS *m/z* (%): 321 ($C_{15}H_{27}{}^{81}BrO_3-CH_3$, 1), 319 ($C_{15}H_{27}{}^{79}BrO_3-CH_3$, 1), 73 (100). **9b**, colorless oil, $[\alpha]_D^{17}$ +55° (*c*=3.2, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{27}BrO_3$: C, 53.73; H, 8.12; Br, 23.83. Found: C, 53.72; H, 8.28; Br, 23.89. IR ν_{max}^{film} cm^{-1}: 3045, 1135, 1095, 883. ^{1}H-NMR (CCl_4, δ): 0.81, 0.99 (3H each, both s, *tert*-$CH_3\times2$), 1.14 (3H, t, $J=7$ Hz, $-O-CH_2CH_3$), 1.22 (3H, d, $J=5$ Hz, $-O-CH(CH_3)-O-$), 2.4—3.8 (8H, m, $-CH_2Br$, $-CH-CH_2-O-$, $-OCH_2CH_3$, $>C(O)-CH_2$), 4.56 (1H, q, $J=5$ Hz, $-O-CH(CH_3)-O-$). MS *m/z* (%): 321 ($C_{15}H_{27}{}^{81}BrO_3-CH_3$, 3), 319 ($C_{15}H_{27}{}^{79}BrO_3-CH_3$, 3), 73 (100).

Dehydrobromination of 9a and 9b——A solution of *tert*-AmONa [prepared from 50% NaH (65 mg, 1.35 mmol) and *tert*-AmOH (0.18 ml, 1.65 mmol)] in THF (1.0 ml) was treated with a solution of **9a** (91 mg, 0.27 mmol) in THF (0.5 ml), and the whole was stirred at room temperature for 5 min. The reaction mixture was treated with DMSO (0.5 ml), then stirred at 70 °C for 30 min, and poured into ice-water. The whole was extracted with EtOAc. The EtOAc extract was washed with aq. sat. NaCl and dried over $MgSO_4$. The product (90 mg) obtained by removal of the solvent under reduced pressure was purified by column chromatography (SiO_2, 5 g, *n*-hexane–EtOAc=10:1) to furnish **10a** (58 mg, 85%). Through the same reaction procedure, **9b** (83 mg) was converted to **10b** (52 mg, 82%). **10a**, colorless oil, $[\alpha]_D^{26}$ +2.7° (*c*=0.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3070, 3040, 1646, 906. ^{1}H-NMR (CCl_4, δ): 0.83, 0.97 (3H each, both s, *tert*-$CH_3\times2$), 1.16 (3H, t, $J=7$ Hz, $-OCH_2CH_3$), 1.22 (3H, d, $J=5$ Hz, $-O-CH(CH_3)-O-$), 2.44, 2.80 (2H, ABq, $J=6$ Hz, $>C(O)-CH_2$), 3.1—3.8 (4H, m, $-CH-CH_2-O-$, $-OCH_2CH_3$), 4.57 (1H, q, $J=5$ Hz, $-O-CH(CH_3)-O-$), 4.71, 4.79 (1H each, both br s, $>C=CH_2$). High resolution MS (*m/z*): Calcd for $C_{15}H_{26}O_3$: 254.188. Found: 254.188. MS *m/z* (%): 254 (M^+, 1), 73 (100). **10b**, colorless oil, $[\alpha]_D^{26}$ +51° (*c*=0.2, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3080, 3040, 1649, 905. ^{1}H-NMR (CCl_4, δ): 0.84 (6H, s, *tert*-$CH_3\times2$), 1.14 (3H, t, $J=7$ Hz, $-OCH_2CH_3$), 1.21 (3H, d, $J=5$ Hz, $-O-CH(CH_3)-O-$), 2.19, 2.78 (2H, ABq, $J=6$ Hz, $>C(O)-CH_2$), 2.8—3.8 (4H, m, $-CH-CH_2-O-$, $-OCH_2CH_3$), 4.54 (1H, q, $J=5$ Hz, $-O-CH(CH_3)-O-$), 4.64, 4.87 (1H each, both br s, $>C=CH_2$). High resolution MS (*m/z*): Calcd for $C_{15}H_{26}O_3$: 254.188. Found: 254.188. MS *m/z* (%): 254 (M^+, 3), 73 (100).

Na-Liq. NH_3 Reduction of 10a and 10b Giving 11——A stirred solution of Na (100 mg) in liq. NH_3 (20 ml) was treated at −78 °C with a solution of **10a** (57 mg) in THF (0.5 ml) and the mixture was stirred for a further 30 min. After decomposition of excess Na with MeOH, the reaction mixture was extracted with EtOAc. The EtOAc extract was washed with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (57 mg), which was purified by column chromatography (SiO_2, 5 g, *n*-hexane–EtOAc=2:1) to furnish **11** (55 mg, 96%). Through the same reaction procedure, **10b** (52 mg) was reduced to provide **11** (48 mg, 92%). **11**, colorless oil, $[\alpha]_D^{15}$ −39° (*c*=2.7, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{28}O_3$: C, 68.42; H, 10.13. Found: C, 68.17; H, 10.00. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3615, 3480, 1645. ^{1}H-NMR (CCl_4, δ): 0.87, 1.12 (3H each, both s, *tert*-$CH_3\times2$), 1.16 (3H, t, $J=7$ Hz, $-OCH_2CH_3$), 1.23 (3H, d, $J=5$ Hz, $-O-CH(CH_3)-O-$), 1.72 (3H, s, 12-CH_3), 3.0—3.8 (4H, m, $-CH-CH_2-O-$, $-OCH_2CH_3$), 4.00 (2H, s, $=C-CH_2OH$), 4.59 (1H, q, $J=5$ Hz, $-O-CH(CH_3)-O-$). MS *m/z* (%): 256 (M^+, 2), 148 (100).

Preparation of 11 from 9——A solution of the epoxide mixture (**9**, 5.00 g, 14.9 mmol) in THF (15 ml) was treated with a solution of *tert*-AmONa [prepared from 50% NaH (3.60 g, 75 mmol) and *tert*-AmOH (10.0 ml, 91 mmol)] in THF (25 ml), and the mixture was stirred at room temperature for 5 min. After addition of DMSO (20 ml), the reaction mixture was stirred at 70 °C for 15 min. After cooling, the whole mixture was poured into ice-water and extracted with EtOAc. Work-up of the EtOAc extract as described above gave the product (4.32 g), which was purified by column chromatography (SiO_2, 250 g, *n*-hexane–EtOAc=10:1) to furnish **10** (3.15 g). A solution of **10** (3.15 g, 12.4 mmol) in THF (6.0 ml) was added dropwise to a stirred mixture of Na (0.6 g, 26 mmol) and liq. NH_3 (40 ml) at −78 °C, and the whole mixture was stirred for a further 30 min. After addition of MeOH, the reaction mixture was extracted with EtOAc. Work-up of the EtOAc extract as described above gave the product (3.08 g), which was purified by column chromatography (SiO_2, 150 g, *n*-hexane–EtOAc=2:1) to furnish **11** (3.05 g, 96%).

Diisobutylaluminum Hydride Reduction of 10 Giving 11——A solution of 1.16 M iso-Bu_2AlH in *n*-hexane (5.2 ml, 6.03 mmol) was treated with **10** (300 mg, 1.18 mmol) at −78 °C and the mixture was stirred for 2.5 h. The temperature was allowed to rise gradually to room temperature, then the reaction mixture was stirred for a further 2 h. The reaction was quenched by addition of aq. 5% H_2SO_4, then extracted with EtOAc. The EtOAc extract was successively washed with aq. sat. $NaHCO_3$ and aq. sat. NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (300 mg), which was purified by column chromatography (SiO_2, 20 g, *n*-hexane–EtOAc=2:1) to furnish **11** (121 mg, 40%).

Preparation of 12 from 11 by Acetylation Followed by SeO_2 Oxidation——A solution of **11** (560 mg, 2.19 mmol) in pyridine (5.0 ml) was treated with Ac_2O (2.0 ml). The reaction mixture was left to stand at room temperature overnight, then poured into ice-water, and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave the acetate (**11a**) (635 mg, 2.13 mmol). A solution of **11a** (635 mg) in dioxane (45 ml) and pyridine (0.35 ml, 4.33 mmol) was treated with SeO_2 (480 mg, 4.32 mmol) and the whole mixture was stirred at 80 °C for 2.5 h. After cooling, the reaction mixture was treated with aq. sat. $NaHCO_3$ and the whole was extracted with EtOAc. The

EtOAc extract was washed with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (816 mg), which was purified by column chromatography (SiO_2, 30 g, *n*-hexane–EtOAc = 2 : 1) to furnish **12** (633 mg, 92%). **12**, colorless oil, $[\alpha]_D^{25}$ −75° (*c* = 1.1, $CHCl_3$). *Anal.* Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 64.76; H, 9.81. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 3450, 1735, 1235. ^{1}H-NMR (CCl_4, δ): 0.83, 1.11 (3H each, both s, *tert*-CH_3 × 2), 1.15 (3H, t, *J* = 7 Hz, –$OCH_2\underline{C}H_3$), 1.27 (3H, d, *J* = 5 Hz, –O–CH($C\underline{H}_3$)–O–), 1.78 (3H, s, 12-CH_3), 1.98 (3H, s, OAc), 3.0—4.0 (4H, m, –$\underline{C}H$–$C\underline{H}_2$O–, –$OC\underline{H}_2CH_3$), 3.38 (1H, m, $W_{h/2}$ = 8 Hz, 13-H), 4.51 (2H, s, =$\underline{C}$–$C\underline{H}_2$OAc), 4.61 (1H, q, *J* = 5 Hz, –O–$C\underline{H}$(CH_3)–O–). MS *m/z* (%): 241 (M^+ − 73, 1), 73 (100).

Methylation of 12 Giving 13——A solution of **12** (500 mg, 1.59 mmol) in dimethylformamide (DMF) (5.0 ml) was treated with CH_3I (5.0 ml, excess) and Ag_2O (3.00 g, excess). The reaction mixture was stirred in the dark at room temperature for 24 h, then filtered to remove the insoluble material, which was washed repeatedly with EtOAc. The combined filtrate and washings were washed successively with aq. 15% $Na_2S_2O_3$ and aq. sat. NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (520 mg), which was purified by column chromatography (SiO_2, 10 g, *n*-hexane–EtOAc = 2 : 1) to furnish **13** (496 mg, 95%). **13**, colorless oil, $[\alpha]_D^{25}$ −30° (*c* = 1.3, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.61; H, 10.00. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735, 1235, 1085. ^{1}H-NMR (CCl_4, δ): 0.82, 1.08 (3H each, both s, *tert*-CH_3 × 2), 1.16 (3H, t, *J* = 7 Hz, –$OCH_2C\underline{H}_3$), 1.24 (3H, d, *J* = 5 Hz, –O–CH($C\underline{H}_3$)–O–), 1.71 (3H, s, 12-CH_3), 1.96 (3H, s, OAc), 3.30 (3H, s, –OCH_3), 4.50 (2H, s, =$\underline{C}$–$C\underline{H}_2$OAc), 4.61 (1H, q, *J* = 5 Hz, –O–$C\underline{H}$(CH_3)–O–). MS *m/z* (%): 268 (M^+ − AcOH, 12), 255 (M^+ − 73, 10), 73 (100).

Acidic Hydrolysis of 13 Giving 14——A solution of **13** (496 mg, 1.51 mmol) in aq. 95% EtOH (15 ml) was treated with *p*-TsOH · H_2O (180 mg, 0.95 mmol) and the mixture was stirred at room temperature for 1.5 h. After quenching of the reaction with aq. sat. $NaHCO_3$, the reaction mixture was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave the product (403 mg), which was purified by column chromatography (SiO_2, 25 g, *n*-hexane–EtOAc = 3 : 2) to furnish **14** (372 mg, 96%). **14**, colorless oil, $[\alpha]_D^{25}$ −57° (*c* = 1.0, $CHCl_3$). *Anal.* Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.50; H, 9.41. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630, 3430, 1735, 1235. ^{1}H-NMR (CCl_4, δ): 0.80, 1.09 (3H each, both s, *tert*-CH_3 × 2), 1.72 (3H, s, 12-CH_3), 1.98 (3H, s, OAc), 2.39 (1H, br s, –OH, exchangeable with D_2O), 3.33 (3H, s, –OCH_3), 4.51 (2H, s, =$\underline{C}$–$C\underline{H}_2$OAc). MS *m/z* (%): 241 (M^+ − CH_3, 1), 196 (100).

PCC Oxidation of 14 Giving 15——A solution of **14** (409 mg, 1.60 mmol) in CH_2Cl_2 (10 ml) was treated with PCC (520 mg, 2.41 mmol) and the mixture was stirred at room temperature for 2 h. After dilution with ether (100 ml), the reaction mixture was passed through a Florisil (13 g) column. Removal of the solvent from the eluate under reduced pressure furnished **15** (405 mg) quantitatively. **15**, colorless oil, $[\alpha]_D^{25}$ −59° (*c* = 0.8, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2815, 2725, 1735, 1720, 1229, 1082. ^{1}H-NMR (CCl_4, δ): 0.98, 1.30 (3H each, both s, *tert*-CH_3 × 2), 1.73 (3H, s, 12-CH_3), 1.98 (3H, s, OAc), 2.44 (1H, d-like, *J* = *ca.* 12 Hz, 1-H), 3.31 (3H, s, –OCH_3), 4.51 (2H, s, =$\underline{C}$–$C\underline{H}_2$OAc), 9.87 (1H, d, *J* = 1 Hz, –CHO). High resolution MS (*m/z*): Calcd for $C_{14}H_{22}O_4$: 254.152. Found: 254.153. MS *m/z* (%): 254 (M^+, 1), 194 (100).

$NaBH_4$ Reduction of 15 Regenerating 14——An ice-cooled solution of **15** (100 mg, 0.39 mmol) in MeOH (1.5 ml) was treated with $NaBH_4$ (15 mg, 0.39 mmol). The reaction mixture was stirred for 5 min, then poured into ice-water, and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner furnished **14** (101 mg) quantitatively.

NaOMe Treatment of 15 Giving 16 and 17——A solution of **15** (350 mg) in MeOH (2.0 ml) was treated with 10% NaOMe–MeOH (2.0 ml). The reaction mixture was left to stand at room temperature for 30 min, then poured into ice-water, and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave the product (310 mg), which was purified by column chromatography (SiO_2, 15 g, *n*-hexane–EtOAc = 2 : 1) to furnish **16** (180 mg, 62%) and **17** (80 mg, 28%). **16**, colorless oil, $[\alpha]_D^{20}$ −66° (*c* = 1.0, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620, 3440, 2810, 2720, 1715, 1079. ^{1}H-NMR (CCl_4, δ): 0.97, 1.37 (3H each, both s, *tert*-CH_3 × 2), 1.78 (3H, s, 12-CH_3), 2.44 (1H, d-like, *J* = *ca.* 12 Hz, 1-H), 2.53 (1H, br s, –OH, exchangeable with D_2O), 3.31 (3H, s, –OCH_3), 4.00 (2H, br s, =$\underline{C}$–$C\underline{H}_2$OH), 9.83 (1H, d, *J* = 1 Hz, –CHO). High resolution MS (*m/z*): Calcd for $C_{12}H_{20}O_3$: 212.141. Found: 212.140. MS *m/z* (%): 212 (M^+, 1), 194 (100). **17**, colorless oil, $[\alpha]_D^{25}$ +21° (*c* = 0.9, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620, 3440, 2820, 2720, 1715, 1085. ^{1}H-NMR (CCl_4, δ): 1.10, 1.20 (3H each, both s, *tert*-CH_3 × 2), 1.78 (3H, s, 12-CH_3), 2.10 (1H, m, 1-H), 2.26 (1H, br s, –OH, exchangeable with D_2O), 3.28 (3H, s, –OCH_3), 3.51 (1H, t-like, 13-H), 4.04 (2H, s, =$\underline{C}$–$C\underline{H}_2$OH), 9.69 (1H, d, *J* = 3 Hz, –CHO). High resolution MS (*m/z*): Calcd for $C_{12}H_{20}O_3$: 212.141. Found: 212.142. MS *m/z* (%): 212 (M^+, 1), 181 (100).

Acetylation of 16 Giving 15——A solution of **16** (100 mg) in pyridine (0.5 ml) was treated with Ac_2O (0.3 ml). The reaction mixture was left to stand at room temperature for 5 h, then poured into ice-water, and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner furnished **15** (116 mg, 97%).

NaOMe Treatment of 16——A solution of **16** (150 mg) in MeOH (1.0 ml) was treated with 10% NaOMe–MeOH (1.0 ml) and the mixture was allowed to stand at room temperature for 30 min. Work-up of the reaction mixture as described above gave the product (140 mg), which was purified by column chromatography (SiO_2, 7 g, *n*-hexane–EtOAc = 2 : 1) to furnish **16** (94 mg, 63% recovered) and **17** (41 mg, 27%).

Conversion of 17 Giving 18——A solution of **17** (70 mg, 0.33 ml) in pyridine (0.3 ml) was treated with Ac_2O (0.2 ml). The reaction mixture was left to stand at room temperature for 2 h, then poured into ice-water, and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner furnished **17a** (83 mg), which

was dissolved in MeOH (1.5 ml). The MeOH solution was then treated with $NaBH_4$ (10 mg, 0.26 mmol) and the reaction mixture was stirred for 5 min, then poured into ice-water. The whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner furnished **18** (83 mg, 98%). **18**, colorless oil, $[\alpha]_D^{25}$ $-6°$ ($c=3.1$, $CHCl_3$). *Anal.* Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.57; H, 9.50. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640, 3460, 1735, 1230, 1095. ^{1}H-NMR (CCl_4, δ): 0.93, 1.06 (3H each, both s, *tert*-$CH_3 \times 2$), 1.70 (3H, s, 12-CH_3), 1.98 (3H, s, OAc), 2.31 (1H, br s, –OH, exchangeable with D_2O), 3.37 (3H, s, $-OCH_3$), 3.0—3.7 (3H, m, $-\underset{|}{C}H-C\underline{H}_2OH$, 13-H), 4.50 (2H, br s, $=\underset{|}{C}-C\underline{H}_2OAc$).

Synthesis of Segment A-I (3) from 18——A solution of **18** (144 mg, 0.56 mmol) in isopropenyl methyl ether (1.0 ml) was treated with $POCl_3$ (trace) at room temperature for 10 min. After addition of Et_3N (3 drops), the reaction mixture was concentrated under reduced pressure to furnish **18a** (184 mg). A solution of **18a** in 2 N KOH–MeOH (1.0 ml) was stirred at room temperature for 30 min, then poured into ice-water and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave **18b** (160 mg). An ice-cooled mixture of **18b** (160 mg, 0.56 mmol) in dimethoxyethane (DME) (1.2 ml), 2,4,6-collidine (0.12 ml, 0.91 mmol) and anhydrous LiCl (48 mg, 1.12 mmol) was treated with mesyl chloride (MsCl) (0.09 ml, 1.16 mmol) and DMF (0.60 ml), and the mixture was stirred for 2.5 h. The reaction mixture was poured into ice-water and the whole was extracted with ether. The ether extract was washed successively with aq. sat. $CuNO_3$, aq. sat. NaCl, aq. sat. $NaHCO_3$, and aq. sat. NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure furnished segment A-I (**3**, 167 mg, 98%). Segment A-I (**3**), colorless oil, Beilstein test (+). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1640, 1382, 1373, 1100, 691. ^{1}H-NMR (CCl_4, δ): 0.90, 1.18 (3H each, both s, *tert*-$CH_3 \times 2$), 1.27 (6H, s, $-O-C(C\underline{H}_3)_2-OCH_3$), 1.76 (3H, s, 12-$CH_3$), 3.08 (3H, s, $-O-C(CH_3)_2-OC\underline{H}_3$), 3.29 (3H, s, $-OCH_3$), 3.87, 4.00 (2H, ABq, $J=11$ Hz, $=\underset{|}{C}-C\underline{H}_2Cl$).

Acidic Treatment of Segment A-I (3) Giving Segment A-I′ (3a)——A solution of **3** (121 mg) in aq. 95% EtOH (5 ml) was treated with *p*-TsOH·H_2O (30 mg) and stirred at room temperature for 30 min. After addition of aq. sat. $NaHCO_3$, the reaction mixture was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner furnished segment A-I′ (**3a**, 83 mg, 92%). **3a**, colorless oil, Beilstein test (+), $[\alpha]_D^{15}$ $+21°$ ($c=0.8$, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630, 3410, 1635, 1105, 695. ^{1}H-NMR (CCl_4, δ): 0.97, 1.14 (3H each, both s, *tert*-$CH_3 \times 2$), 1.78 (3H, s, 12-CH_3), 3.34 (3H, s, $-OCH_3$), 3.1—3.9 (3H, m, $-\underset{|}{C}H-C\underline{H}_2O-$, 13-H), 3.93, 4.01 (2H, ABq, $J=11$ Hz, $=\underset{|}{C}-C\underline{H}_2Cl$). High resolution MS (*m/z*): Calcd for $C_{12}H_{21}{}^{37}ClO_2$: 234.120. Found: 234.122. Calcd for $C_{12}H_{21}{}^{35}ClO_2$: 232.123. Found: 232.122. MS *m/z* (%): 234 ($C_{12}H_{21}{}^{37}ClO_2$, <1), 232 ($C_{12}H_{21}{}^{35}ClO_2$, <1), 198 (100).

Preparation of 19 from 17——A solution of **17** (2.30 g, 10.8 mmol) in DMF (10 ml) was treated with imidazole (2.06 g, 30.2 mmol) and *tert*-$Bu(CH_3)_2SiCl$ (2.28 g, 15.1 mmol). The reaction mixture was stirred at room temperature for 1 h, then poured into ice-water, and the whole was extracted with EtOAc. The EtOAc extract was washed successively with aq. 5% HCl, aq. sat. $NaHCO_3$, and aq. sat. NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure furnished **17b** (3.65 g), which was dissolved in THF (22 ml). This solution was treated with a methylenetriphenylphosphorane-THF solution [prepared from Ph_3PCH_3Br (7.71 g, 21.6 mmol), 50% NaH (930 mg, 19.4 mmol), *tert*-AmOH (5.30 ml, excess), and THF (45 ml)]. The reaction mixture was stirred at room temperature for 15 min, then poured into ice-water, and the whole was extracted with EtOAc. The EtOAc extract was washed with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (10.5 g), which was purified by column chromatography (SiO_2, 20 g, *n*-hexane–EtOAc = 5 : 1) to furnish **19** (3.44 g, 98%). **19**, colorless oil, $[\alpha]_D^{21}$ $+46°$ ($c=2.6$, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3060, 1632, 1250, 1095, 1050, 910, 831. ^{1}H-NMR (CCl_4, δ)[15]: 0.00 (6H, s, $-O-Si(C\underline{H}_3)_2$-*tert*-Bu), 0.82 (12H, s, $-O-Si(CH_3)_2$-*tert*-$C_4\underline{H}_9$, *tert*-CH_3), 0.93 (3H, s, *tert*-CH_3), 1.62 (3H, s, 12-CH_3), 3.20 (3H, s, $-OCH_3$), 3.58 (1H, m, 13-H), 3.93, 4.16 (2H, ABq, $J=12$ Hz, $=\underset{|}{C}-C\underline{H}_2O-$), 4.8—5.1 (2H, AB in ABC, $-CH=C\underline{H}_2$), 5.5—6.0 (1H, C in ABC, $-C\underline{H}=CH_2$). High resolution MS (*m/z*): Calcd for $C_{19}H_{36}O_2Si$: 324.248. Found: 324.248. MS *m/z* (%): 324 (M^+, 4), 179 (100).

Hydroboration-Oxidation of 19 Giving 20——An ice-cooled solution of **19** (3.44 g, 10.6 mmol) in THF (25 ml) was treated dropwise with a disiamylborane–THF solution [prepared from 2-methyl-2-butene (10.2 ml, 96 mmol), $NaBH_4$ (2.74 g, 72 mmol), BF_3–Et_2O (6.0 ml, 48 mmol), and THF (36 ml)] over a period of 30 min, and the whole solution was stirred for a further 30 min. While the temperature was held at 10 °C, the reaction mixture was treated with water (20 ml) to decompose excess disiamylborane. After treatment with aq. 3 N NaOH (20 ml), the reaction mixture was treated with aq. 30% H_2O_2 (25 ml) at 20 °C and stirred further for 10 min. The reaction mixture was then poured into ice-water and the whole was extracted with EtOAc. The EtOAc extract was washed successively with aq. sat. Na_2SO_3, aq. 5% HCl, aq. sat. $NaHCO_3$, and aq. sat. NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (3.86 g), which was purified by column chromatography (SiO_2, 200 g, *n*-hexane–EtOAc = 3 : 1) to furnish **20** (3.40 g, 94%). **20**, colorless oil, $[\alpha]_D^{16}$ $+43°$ ($c=1.1$, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640, 3480, 1250, 850. ^{1}H-NMR (CCl_4, δ)[15]: 0.00 (6H, s, $-O-Si(C\underline{H}_3)_2$-*tert*-Bu), 0.83 (9H, s, $-O-Si(CH_3)_2$-*tert*-$C_4\underline{H}_9$), 0.80, 0.96 (3H each, both s, *tert*-$CH_3 \times 2$), 1.60 (3H, s, 12-CH_3), 2.10 (1H, br s, –OH, exchangeable with D_2O), 3.20 (3H, s, $-OCH_3$), 3.3—3.7 (3H, m, $-CH_2C\underline{H}_2OH$, 13-H), 3.93, 4.06 (2H, ABq, $J=12$ Hz, $=\underset{|}{C}-C\underline{H}_2O-$). High resolution MS (*m/z*): Calcd for $C_{19}H_{38}O_3Si$: 342.259. Found: 342.259. MS *m/z* (%): 342 (M^+, 1), 197 (100).

Synthesis of Segment A-II (4) from 20——A solution of **20** (3.00 g, 8.77 mmol) in isopropenyl methyl ether (15 ml) was treated with $POCl_3$ (trace) and the mixture was allowed to stand at room temperature for 30 min. After addition of Et_3N (3 drops), the reaction mixture was concentrated under reduced pressure to furnish **20a** (3.63 g). A

solution of **20a** (3.63 g) in THF (10 ml) was treated with a 1.0 M n-Bu_4NF–THF solution (20 ml, 20.0 mmol) and the mixture was stirred at room temperature for 2.5 h. After treatment with pyridine (5 drops), the reaction mixture was concentrated under reduced pressure to give the product (*ca.* 10 g), which was purified by column chromatography (Florisil, 100 g, ether) to furnish **20b** (2.63 g). An ice-cooled mixture of **20b** (2.63 g), DME (9 ml), DMF (9 ml), 2,4,6-collidine (2.42 ml, 18.4 mmol), and anhydrous LiCl (745 mg, 17.5 mmol) was treated with MsCl (1.36 ml, 17.5 mmol) and the reaction mixture was stirred for 2 h, then poured into ice-water. The whole was extracted with ether. The ether extract was washed successively with aq. sat. $CuNO_3$, aq. sat. NaCl, aq. sat. $NaHCO_3$, and aq. sat. NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure furnished segment A-II (**4**, 2.74 g, 98%). Segment A-II (**4**), colorless oil, Beilstein test (+). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1640, 1100, 691. ^{1}H-NMR (CCl_4, δ): 0.91, 1.12 (3H each, both s, *tert*-$CH_3 \times 2$), 1.28 (6H, s, $-O-C(CH_3)_2OCH_3$), 1.78 (3H, s, 12-CH_3), 3.12 (3H, s, $-O-C(CH_3)_2OCH_3$), 3.30 (3H, s, $-OCH_3$), 3.1—3.8 (3H, m, $-CH_2CH_2-O-$, 13-H), 3.94, 4.09 (2H, ABq, J = 12 Hz, $=C-CH_2Cl$).

Acidic Treatment of Segment A-II (4) Giving Segment A-II′ (4a)——A solution of **4** (100 mg) in aq. 95% EtOH (5 ml) was treated with p-$TsOH \cdot H_2O$ (22 mg) and stirred at room temperature for 30 min. After addition of aq. sat. $NaHCO_3$, the reaction mixture was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner furnished segment A-II′ (**4a**, 74 mg, 96%). Segment A-II′ (**4a**), colorless oil, Beilstein test (+), $[\alpha]_D^{23}$ +110° (c = 1.8, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3400, 1090, 680. ^{1}H-NMR (CCl_4, δ): 0.91, 1.11 (3H each, both s, *tert*-$CH_3 \times 2$), 1.78 (3H, s, 12-CH_3), 3.02 (1H, br s, –OH, exchangeable with D_2O), 3.30 (3H, s, $-OCH_3$), 3.2—3.9 (3H, m, $-CH_2CH_2OH$, 13-H), 3.94, 4.09 (2H, ABq, J = 12 Hz, $=C-CH_2Cl$). High resolution MS (m/z): Calcd for $C_{13}H_{23}{}^{37}ClO_2$: 248.136. Found: 248.136. Calcd for $C_{13}H_{23}{}^{35}ClO_2$: 246.139. Found: 246.139. MS m/z (%): 248 ($C_{13}H_{23}{}^{37}ClO_2$, 2), 246 ($C_{13}H_{23}{}^{35}ClO_2$, 7), 211 (100).

Acknowledgement The authors are grateful to the Ministry of Education, Science and Culture of Japan for financial support in the form of a Grant-in-Aid for Special Project Research (57118007).

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