[Chem. Pharm. Bull. 32(9)3417—3427(1984)]

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

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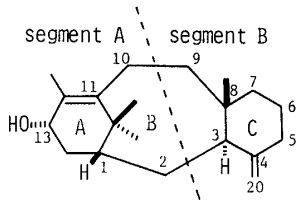
(Received January 12, 1984)

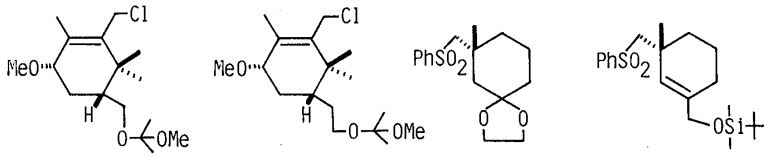
Two kinds of chiral segments, *i.e.* segment B-I (**4**) and segment B-II (**5**), which are potentially versatile building-blocks for construction of the right half of taxane-type diterpenoids, were synthesized from 3-methyl-2-cyclohexen-1-one (**6**) *via* optical resolution of the (2*S*,3*S*)-2,3-butanediol ketal derivatives (**8**, **15**).

Keywords——taxane-type diterpenoid; optical resolution with (2*S*,3*S*)-2,3-butanediol ketal; CD of cyclopropyl ketone; HPLC for optical resolution; π-allylpalladium complex

In the previous paper,[1] we reported syntheses of two chiral segments, *i.e.* segment A-I (**2**) and segment A-II (**3**), which were potentially versatile building-blocks for construction of the left half of taxane-type diterpenoids, *e.g.* 13α-hydroxy-taxa-4(20),11-diene (**1**). As a continuation of this work, we have investigated synthetic methods for two other chiral segments, *i.e.* segment B-I (**4**) and segment B-II (**5**), which should be useful for construction of the right half of **1**. This paper deals with the synthesis of these two chiral segments (**4**, **5**) from 3-methyl-2-cyclohexen-1-one (**6**), involving optical resolution during the reaction procedure. As mentioned in the previous paper,[1] segment A (*e.g.* **2**, **3**) and segment B (*e.g.* **4**, **5**) were obtained in principle by splitting the C_2–C_3 and C_9–C_{10} bonds of **1**. Segment B has been designed to comprise the C ring with the 8-CH_3 group and the C-9 residue,[2] having the same C-8 absolute configuration as in **1**. In regard to the C-9 substituent, we have chosen a



13α-hydroxy-taxa-4(20),11-diene (**1**)



segment A-I (**2**) segment A-II (**3**) segment B-I (**4**) segment B-II (**5**)

Chart 1

phenylsulfone group, since it should then be possible to avoid the occurrence of self-condensation during the coupling reaction with segment A under basic conditions. Furthermore, the phenylsulfone group is readily removable either by reduction[3] or by oxidation[4] after C_9–C_{10} bond formation in the course of the synthetic approach to **1**.

Synthesis of Segment B-I (4)

Treatment of 3-methyl-2-cyclohexen-1-one (**6**)[5] with sodium hydride and dimethyloxosulfonium methylide in dimethyl sulfoxide (DMSO)[6] provided a volatile cyclopropyl ketone (**7**) in 65% yield. The optical resolution of this ketone was carried out in the following manner. The ketone (**7**) was subjected to ketalization with (2*S*,3*S*)-2,3-butanediol[7] in the presence of pyridinium *p*-toluenesulfonate (PPTS) in benzene to afford a diastereomeric mixture (**8**) in good yield. The mixture (**8**) was separated by recycled high-performance liquid chromatography (HPLC) to give two diastereoisomers, **8a** and **8b**. The separated diastereoisomers (**8a** and **8b**) were then each treated with PPTS in aqueous acetone to obtain the individual parent cyclopropyl ketones, **7a** and **7b**. The spectral properties [infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR) and mass (MS) spectra] of **7a** and **7b** coincided with those of the above-described racemic cyclopropyl ketone (**7**), while the optical properties [specific rotations and circular dichroism (CD) spectra] of **7a** and **7b** showed that these cyclopropyl ketones were enantiomeric. Their absolute configurations were determined from their CD spectra, **7a**: $[\theta]_{285}$ +5300 (pos. max.) and **7b**: $[\theta]_{285}$ −5300 (neg. max.), on the basis of the octant rule[8] as applied to the cyclopropyl ketone moieties. Of these enantiomers, **7a** (8*S* isomer) was found to be suitable for further conversion to segment B-I (**4**), which has the same C-8 configuration as the target compound **1**.

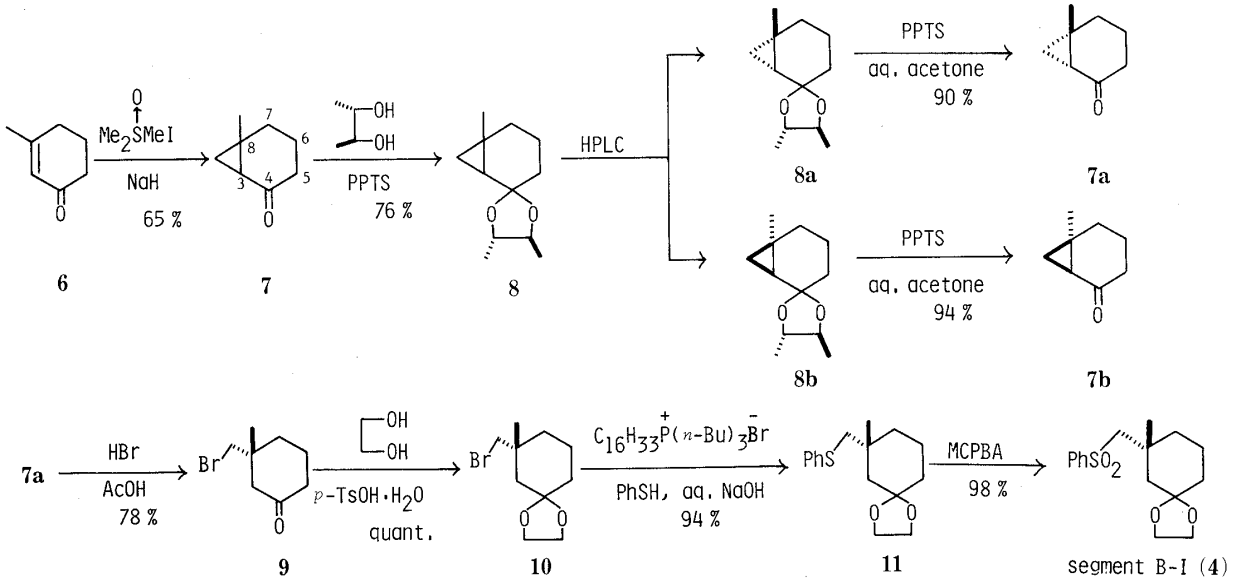


Chart 2

The optically active cyclopropyl ketone (**7a**) was treated with 30% hydrogen bromide in acetic acid to yield the bromoketone (**9**), which, after quantitative ketalization (to give **10**), was converted in high yield to the phenylsulfide (**11**) by treatment with thiophenol and aqueous sodium hydroxide in benzene in the presence of 0.5 mol eq of phase-transfer catalyst (hexadecyltributylphosphonium bromide[9]). Oxidation of the phenylsulfide (**11**) with *m*-chloroperbenzoic acid (MCPBA) furnished segment B-I (**4**) in 98% yield.

The structure of segment B-I (**4**) was substantiated by its spectral properties. The IR spectrum showed absorption bands of the phenyl and sulfone groups, whereas the ultraviolet (UV) spectrum showed an absorption maximum attributable to the phenylsulfone residue.

The ^{1}H-NMR spectrum showed signals due to the *tert*-methyl group at C-8, the methylene protons adjacent to the sulfone group, the ehtylene ketal protons, and the phenyl protons. The overall yield for the synthesis of the optically active segment B-I (**4**) from 3-methyl-2-cyclohexen-1-one (**6**) was 15%.

Segment B-I (**4**) may be synthesized from **6** through the following alternative route. Hydrocyanation and subsequent acidic hydrolysis of **6** yielded the keto-acid (**13**), which, after protection of the carbonyl function by ordinary ethylene ketalization, was esterified with diazomethane to give the ketal-methyl ester (**14**). In order to effect the optical resolution, **14** was converted to a diastereomeric mixture of the (2*S*,3*S*)-2,3-butanediol ketal derivative (**15**) in 93% yield by successive acidic hydrolysis, ketalization, and $LiAlH_4$ reduction. The complete separation of the diastereomeric mixture (**15**) was achieved by HPLC to furnish **15a** and **15b**. The C-8 absolute configurations of the diastereomers were determined in the following manner. Acidic hydrolysis of both ketals, **15a** and **15b**, gave high yields of the individual keto-alcohols, **16a** and **16b**, which were enantiomeric. The spectral data (IR, ^{1}H-NMR, MS) for the two compounds were superimposable, whereas the specific rotations and the CD spectra of the two were enantiomeric, **16a**: $[\theta]_{287}$ +1900 (pos. max.) and **16b**: $[\theta]_{287}$ −1900 (neg. max.). Since the preferred conformations for **16a** and **16b** were presumed to be as depicted in i and ii, respectively, the keto-alcohol showing a positive CD maximum was assigned the 8*R* structure (**16a**) and the other giving a negative CD curve was assigned the 8*S* structure (**16b**).

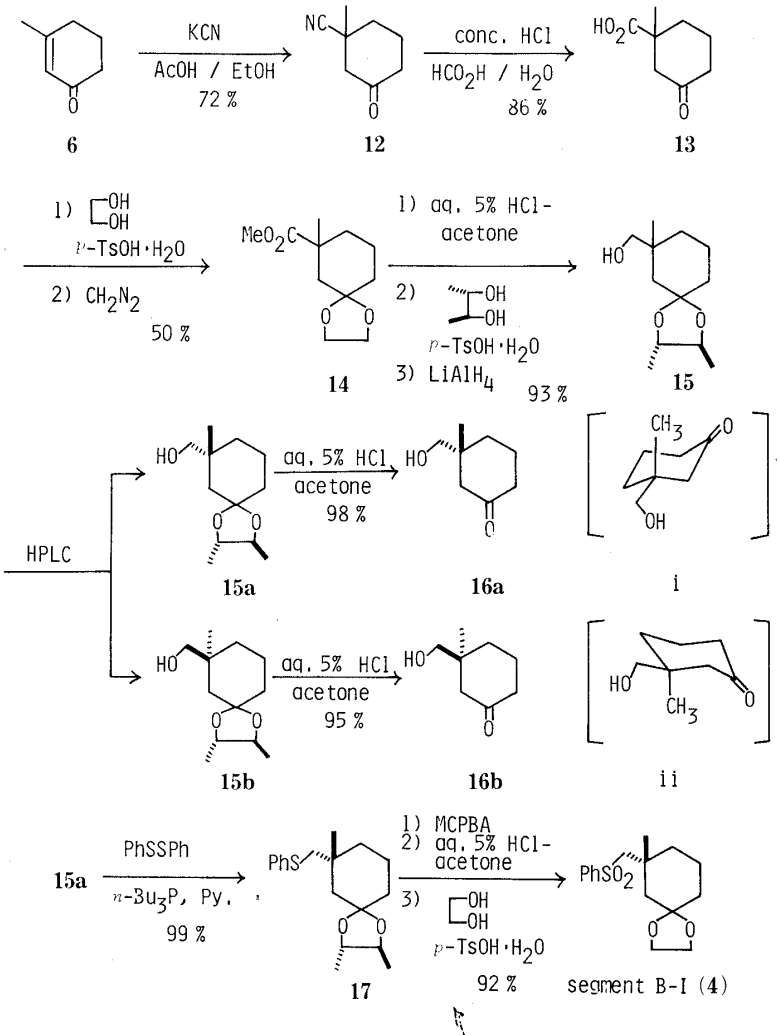


Chart 3

The butanediol ketal (**15a**) with the 8*R* configuration was then converted to segment B-I (**4**). Treatment of **15a** with diphenyl disulfide and tri-*n*-butylphosphine in pyridine quantitatively provided the phenylsulfide (**17**). Oxidation of **17** with MCPBA and subsequent ketal exchange furnished the desired segment B-I (**4**) in 92% yield from **17**. The overall yield of segment B-I (**4**) from the starting compound (**6**) was 12%, but this procedure was found to be more suitable for the larger-scale synthesis (more than 100 g) of segment B-I (**4**) than the above-described route *via* the cyclopropyl ketone (**7**).

Synthesis of Segment B-II (5)

Segment B-I (**4**) appeared to be suitable for construction of the 20-nor-4-oxo-type taxane skeleton. We next synthesized optically active segment B-II (**5**), which contained all the carbons necessary for construction of the right half of the taxane skeleton, from the above-described optically active keto-alcohol (**16a**). Acetylation and subsequent methylenation of **16a** furnished a 1:3 mixture of two epoxides (**18**) in 95% yield. Without separation, the epoxide mixture was treated with trimethylsilyl trifluoromethanesulfonate (TMS-OTf)[10] and 2,6-lutidine in toluene to afford a regioisomeric mixture of allylic alcohols (**19**) in 84% yield. The composition of the mixture (**19**), $\Delta^3 : \Delta^4 = 1 : 2.5$, was assumed on the basis of the ^{1}H-NMR signals due to the olefinic protons at C-3 and C-4. Since the attempted separation of **19** failed, the regioisomeric mixture was subjected to pyridinium chlorochromate (PCC) oxidation and the resulting α,β-unsaturated aldehyde mixture was separated to furnish **20a** and **20b** in 1:2.5 ratio.

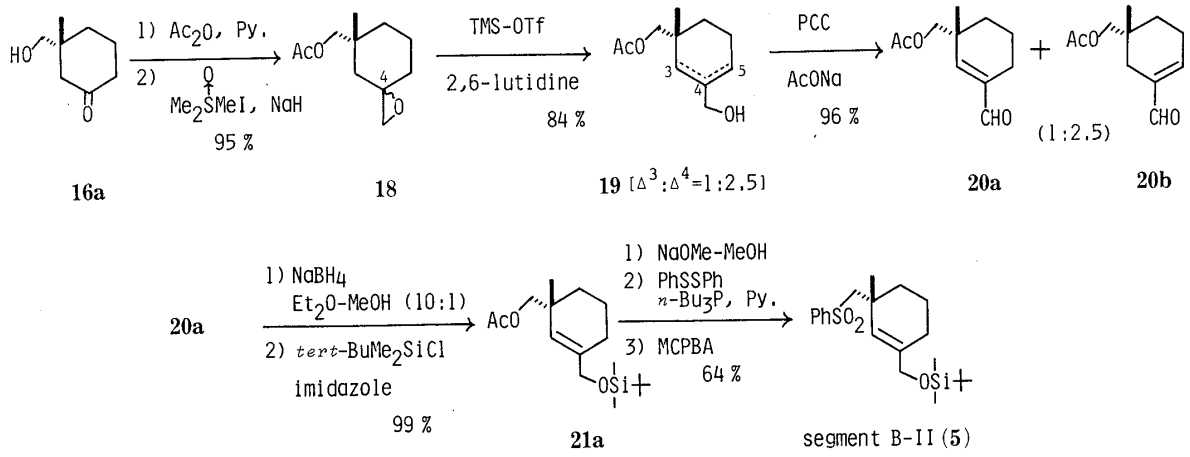


Chart 4

The IR and UV spectra of **20a** and **20b** showed absorption bands attributable to the α,β-unsaturated aldehyde moiety. The ^{1}H-NMR spectra of both compounds showed signals due to the *tert*-methyl group at C-8 (δ 1.13 in **20a**, δ 0.96 in **20b**) and the olefinic protons (1H at δ 6.43, m, $W_{h/2} = 3$ Hz in **20a**; 1H at δ 6.72, m, $W_{h/2} = 10$ Hz in **20b**) which led us to assign the individual double bonds as Δ^3 for **20a** and Δ^4 for **20b**.

$NaBH_4$ reduction followed by silylation of **20a** quantitatively provided **21a**, which, on successive treatments with methanolic sodium methoxide (alkaline hydrolysis), diphenyl disulfide and tri-*n*-butylphosphine (sulphenylation), and MCPBA (oxidation), was converted to the desired final product segment B-II (**5**) in 64% yield from **21a**. The structure of segment B-II (**5**) was substantiated by its spectral properties. The IR spectrum showed phenyl and sulfone group absorption bands, whereas the UV spectrum showed the absorption maximum due to the phenylsulfone group. The ^{1}H-NMR spectrum showed signals due to the *tert*-methyl group at C-8, the phenylsulfone group attached to the methylene function at C-8, the silyl ether group, the methylene having the silyloxy moiety attached to C-4, and the olefinic proton

at C-3. The overall yield of optically active segment B-II (**5**) from **16a** was 14%.

The Δ^4 compound (**20b**) was converted to the above-described regioisomeric mixture (**19**), containing the Δ^3 isomer as the major component, increase the amount of material available for the synthesis of segment B-II (**5**) in the following manner.

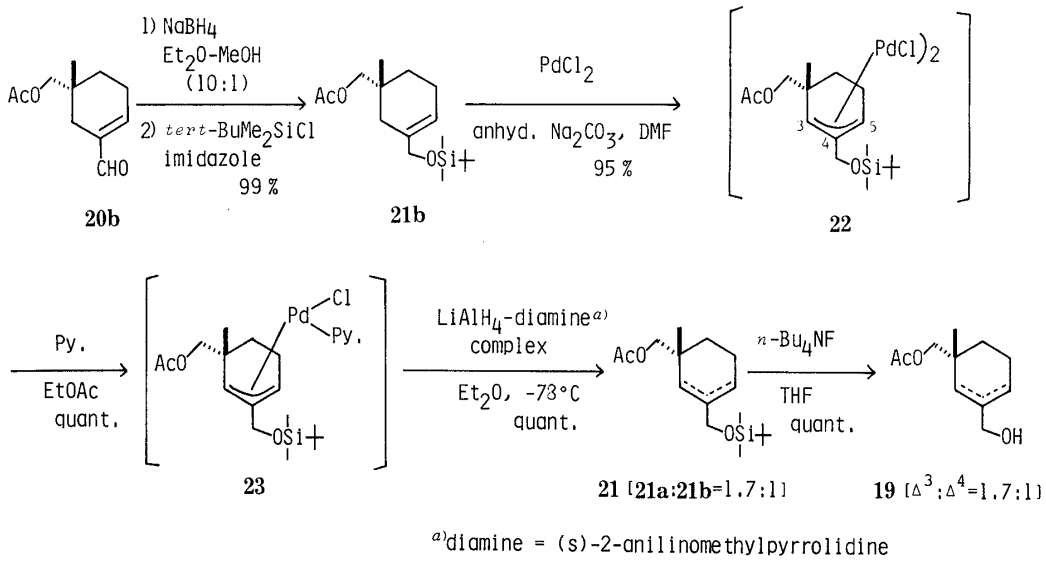


Chart 5

$NaBH_4$ reduction followed by silylation of **20b** as carried out above (from **20a** to **21a**) furnished **21b**, which, on treatment with palladium chloride in the presence of anhydrous sodium carbonate in dimethyl formamide (DMF),[11] was converted to the dichloro-bis(π-allyl)dipalladium complex (**22**) in 95% yield. Further treatment of **22** with 2 mol eq of pyridine in ethyl acetate[12] quantitatively provided the monomeric π-allylpalladium complex with a pyridine ligand (**23**). We next examined reduction of these two kinds of π-allylpalladium complex (**22**, **23**) with various metal hydride reagents to find the optimal reduction conditions for obtaining **21** containing the Δ^3 compound (**21a**) as the principal product (Table I).

TABLE I. Hydride Reduction of π-Allylpalladium Complex (**22**, **23**)

	Reagent	Solvent[a]	Eq.[b]	Temp. (°C)	**21a**:**21b**[c]	Yield (%)
	$LiAlH_4$	THF	7.2	−78	1.1:1	100
22	$LiAl(O\text{-}tert\text{-}Bu)_3H$	THF	1.8	r.t. (20)	No reaction (10 h)[d]	
			3.7	−23	Very slow (10 h)	
				−78	<10%[d]	
			7.2	r.t. (20)	1:1.4	100
				−23	1:1.3	100
				−78	1.1:1	100
	$LiAlH_4$–diamine complex	Et_2O	7.2	−78	1.2:1[e]	100
23	$LiAlH_4$–diamine complex	Et_2O	2.0	−78	1.7:1	100

a) Substrate (10 mg)/solvent (1.25 ml).
b) Molar equivalent of the reagent to the substrate.
c) Determined by GLC and ^{1}H-NMR.
d) The starting material (**22**) was recovered.
e) The acetate was reductively hydrolyzed.

Initially we presumed on stereochemical grounds that the hydride attack on these π-allylpalladium complexes (**22**, **23**) would occur predominantly at C-5, resulting in the formation of the Δ^3- isomer (**21a**) as the principal product. However, as shown in Table I, no significant regioselectivity was achieved in the reduction of **22** under various reaction conditions, except in the case of the $LiAlH_4$–(s)-2-anilinomethylpyrrolidine complex reduction,[13] in which the Δ^3 isomer (**21a**) was obtained in a slightly greater amount ($\Delta^3 : \Delta^4 = 1.2 : 1$). When this $LiAlH_4$–diamine reduction was applied to **23**, the ratio of Δ^3 and Δ^4 in **21** was improved to 1.7 : 1. The quantitative conversion of **21** to **19**, which retained the Δ^3/Δ^4 ratio, was effected by treatment with tetra-*n*-butylammonium fluoride (*n*-Bu_4NF) in tetrahydrofuran. The regioisomeric mixture (**19**) thus obtained was again used for the synthesis of segment B-II (**5**) as described above.

We have synthesized two optically active forms of segment B, *i.e.* segment B-I (**4**) and segment B-II (**5**), starting from 3-methyl-2-cyclohexen-1-one (**6**). We are currently investigating the construction of optically active 13α-hydroxytaxa-4(20),11-diene (**1**) by the use of segment A-I (**2**),[1] segment A-II (**3**),[1] segment B-I (**4**), and segment B-II (**5**).

Experimental

The following instruments were used to obtain physical data: specific rotations, JASCO DIP-181 digital polarimeter; IR spectra, Hitachi 260-30 infrared spectrometer; UV spectra, Hitachi 330 spectrophotometer; CD spectra, JASCO ORD/UV-5 spectrometer; ^{1}H-NMR spectra, Hitachi R-22 (90 MHz) NMR spectrometer (with tetramethylsilane (TMS) as an internal standard unless otherwise specified); MS and high resolution MS, JEOL JMS-D300 mass spectrometer or JEOL JMS-01SG-2 mass spectrometer. For gas liquid chromatography (GLC), a Hitachi 163 or 663 gas chromatograph with a hydrogen flame ionization detecter (FID) detector, was used and a Waters ALC-100 (column: μ-Porasil) machine or a Waters System 500A (column: PrepPAK 500/SILICA) machine was used for HPLC. Silica gel (Merck, 0.05—0.2 mm or 0.04—0.063 mm) and precoated thin layer chromatography (TLC) plates (Merck, Silica gel 60 F_{254}) were used for column and TLC and detection of spots on TLC plates was done by spraying 1% $Ce(SO_4)_2$–10% H_2SO_4 with subsequent heating or by spraying a 2,4-dinitrophenylhydrazine reagent or a bromocresol green reagent. All reactions were carried out under a nitrogen or an argon atmosphere.

Preparation of the Cyclopropyl Ketone (7) from 3-Methyl-2-cyclohexen-1-one (6)——A suspension of 60% NaH (4.60 g, 115 mmol) in DMSO (200 ml) was treated with dimethyloxosulfonium methylide (23.5 g, 107 mmol) and the mixture was stirred at room temperature for 30 min. The reaction mixture was then mixed with a solution of **6** (12.6 g, 115 mmol) in DMSO (20 ml) and the whole was stirred at room temperature for a further 1.5 h. The reaction mixture was poured into ice–water and the whole was extracted with Et_2O. The Et_2O extract was washed with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure furnished the product (13.9 g), which was purified by column chromatography (SiO_2, 750 g, *n*-hexane–EtOAc = 5 : 1) to furnish **7** (9.30 g, 65%). **7**, colorless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3000, 1686. ^{1}H-NMR (CCl_4, δ): 0.81 (1H, dd, J=4, 8 Hz, 3-H), 1.21 (3H, s, *tert*-CH_3), 1.2—2.5 (8H, m). High resolution MS (*m/z*): Calcd for $C_8H_{12}O$: 124.089. Found: 124.089. MS *m/z* (%): 124 (M^+, 13), 67 (100).

Preparation of the Butanediol Ketal (8) from the Cyclopropyl Ketone (7)——A solution of **7** (4.60 g, 37.0 mmol) in benzene (50 ml) was treated with (2*S*,3*S*)-2,3-butanediol (4.40 ml, 48 mmol) and PPTS (one microspatula-full) and the whole mixture was heated under reflux for 1.5 h with azeotropic removal of water. After cooling, the reaction mixture was poured into ice-water and the whole was extracted with EtOAc. The EtOAc extract was washed scuccesively with aq. sat. $NaHCO_3$ and aq. sat. NaCl, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (6.35 g), which was purified by column chromatography (SiO_2, 300 g, *n*-hexane–EtOAc = 20 : 1) to furnish **8** (a diastereomeric mixture, 5.50 g, 76%) together with **7** (recovered, 0.80 g, 18%).

HPLC Separation of 8 Giving 8a and 8b——The diastereomeric mixture **8** (700 mg) was separated by HPLC using a Waters System 500A machine (PrepPAK 500/SILICA ($\times$2), *n*-hexane–EtOAc = 50 : 1, flow rate 200 ml/min, recycle ($\times$3), RI detector) to furnish **8a** (180 mg), **8b** (142 mg), and a mixture of **8a** and **8b** (320 mg). **8a**, colorless oil, $[\alpha]_D^{23}$ −23° (c = 1.4, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3060, 1110, 1097. ^{1}H-NMR (CCl_4, δ): 0.1—1.1 (3H, ABC, cyclopropyl protons), 1.09 (3H, s, *tert*-CH_3), 1.17 (3H, d, J=6 Hz), 1.22 (3H, d, J=6 Hz), 3.2—3.9 (2H, m) (–O–CH(CH_3)–CH(CH_3)–O–). High resolution MS (*m/z*): Calcd for $C_{12}H_{20}O_2$: 196.146. Found: 196.144. MS *m/z* (%): 196 (M^+, 5), 127 (100). **8b**, colorless oil, $[\alpha]_D^{23}$ +58° (c = 3.8, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3060, 1112, 1095. ^{1}H-NMR (CCl_4, δ): 0.1—1.1 (3H, ABC, cyclopropyl protons), 1.07 (3H, s, *tert*-CH_3), 1.17 (6H, d, J=6 Hz), 3.1—3.9 (2H, m, –O–CH(CH_3)–CH(CH_3)–O–). High resolution MS (*m/z*): Calcd for $C_{12}H_{20}O_2$: 196.146. Found: 196.144. MS *m/z* (%): 196 (M^+, 5), 127 (100).

Acidic Hydrolysis of 8a and 8b Giving 7a and 7b——A solution of **8a** (180 mg) in a mixture of acetone (2.0 ml) and water (0.5 ml) was treated with PPTS (one microspatula-full) and the mixture was heated under reflux for 30 min. After cooling, the reaction mixture was poured into ice-water and the whole was extracted with Et_2O. Work-up of the Et_2O extract in the usual manner gave the product (110 mg), which was purified by column chromatography (SiO_2, 5 g, *n*-hexane–EtOAc = 5 : 1) to furnish **7a** (103 mg, 90%). In the same way, **8b** (250 mg) was hydrolyzed to furnish **7b** (149 mg 94%). **7a**, colorless oil, $[\alpha]_D^{23}$ −6.9° (*c* = 2.3, $CHCl_3$). CD (*c* = 0.67, MeOH): $[\theta]_{285}^{26}$ +5300 (pos. max.). High resolution MS (*m/z*): Calcd for $C_8H_{12}O$: 124.089. Found: 124.089. **7b**, colorless oil, $[\alpha]_D^{23}$ +7.0° (*c* = 1.2, $CHCl_3$). CD (*c* = 0.30, MeOH): $[\theta]_{285}^{26}$ −5300 (neg. max.). High resolution MS (*m/z*): Calcd for $C_8H_{12}O$: 124.089. Found:124.089. The IR (CCl_4), ^{1}H-NMR (CCl_4), and mass spectra of **7a** and **7b** were superimposable on those of **7**.

Hydrogen Bromide Treatment of 7a Giving the Bromoketone (9)——A solution of **7a** (149 mg, 1.20 mmol) in benzene (4 ml) was treated with 30% HBr–AcOH (0.40 ml, 1.50 mmol) and the mixture was stirred at room temperature for 15 min, then poured into aq. sat. $NaHCO_3$. The whole was extracted with EtOAc. The EtOAc extract was washed with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent gave the product (235 mg), which was purified by column chromatography (SiO_2, 10 g, *n*-hexane–EtOAc = 5 : 1) to furnish **9** (190 mg, 78%). **9**, colorless oil, Beilstein test: positive, $[\alpha]_D^{23}$ −5.8° (*c* = 9.0, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1714, 664. ^{1}H-NMR (CCl_4, δ): 1.08 (3H, s, *tert*-CH_3), 1.4—2.5 (8H, m), 3.29 (2H, s, –CH_2Br). High resolution MS (*m/z*): Calcd for $C_8H_{13}{}^{81}BrO$: 206.013. Found 206.011. Calcd. for $C_8H_{13}{}^{79}BrO$: 204.015. Found: 204.014. MS *m/z* (%): 206 ($C_8H_{13}{}^{81}BrO$, 7), 204 ($C_8H_{13}{}^{79}BrO$, 7), 109 (100).

Ketalization of 9 Giving 10——A solution of **9** (190 mg) in benzene (10 ml) was treated with ethylene glycol (0.3 ml) and *p*-TsOH·H_2O (one microspatula-full) and the mixture was heated under reflux for 30 min with azeotropic removal of water. After cooling, the reaction mixture was poured into ice-water and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner furnished **10** (230 mg, quant.). **10**, colorless oil, Beilstein test: positive, $[\alpha]_D^{23}$ −0.7° (*c* = 7.9, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1108, 661. ^{1}H-NMR (CCl_4, δ): 1.05 (3H, s, *tert*-CH_3), 1.2—1.8 (8H, m), 3.41 (2H, s, –CH_2Br), 3.84 (4H, s, –O–CH_2CH_2–O–). High reoslution MS (*m/z*): Calcd for $C_{10}H_{17}{}^{81}BrO_2$: 250.039. Found: 250.039. Calcd for $C_{10}H_{17}{}^{79}BrO_2$: 248.041. Found: 248.041. MS *m/z* (%): 250 ($C_{10}H_{17}{}^{81}BrO_2$, 2), 248 ($C_{10}H_{17}{}^{79}BrO_2$, 2), 99 (100).

Preparation of the Phenylsulfide (11) from 10——A solution of **10** (174 mg, 0.70 mmol) in benzene (1.5 ml) was treated with aq. 2 N NaOH (2.0 ml), hexadecyltributylphosphonium bromide (200 mg, 0.35 mmol) and thiophenol (0.30 ml, 2.92 mmol) and the mixture was heated under reflux for 72 h. After cooling, the reaction mixture was poured into ice-water and the whole was extracted with EtOAc. The EtOAc extract was washed repeatedly with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (325 mg), which was purified by column chromatography (SiO_2, 12 g, *n*-hexane–EtOAc = 10 : 1) to furnish **11** (183 mg, 94%). **11**, colorless oil, $[\alpha]_D^{23}$ −31° (*c* = 3.7, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{22}O_2S$: C, 69.03; H, 7.96; S, 11.52. Found: C, 68.89; H, 7.99; S, 11.71. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3060, 1581, 1080, 685. UV λ_{max}^{EtOH} nm (ε): 254 (9800). ^{1}H-NMR (CCl_4, δ): 1.04 (3H, s, *tert*-CH_3), 1.1—1.9 (8H, m), 2.94, 3.01 (2H, ABq, *J* = 13 Hz, –CH_2SPh), 3.80 (4H, s, –O–CH_2CH_2–O–), 6.7—7.4 (5H, m, phenyl protons). MS *m/z* (%): 278 (M^+, 21), 99 (100).

Preparation of Segment B-I (4) from 11——A stirred mixture of **11** (3.20 g, 11.5 mmol) in CH_2Cl_2 (100 ml) and aq. 5% $NaHCO_3$ (100 ml) was treated with 80% MCPBA (4.95 g, 23.0 mmol) in small portions and the mixture was stirred for 1 h, then treated with aq. 10% $Na_2S_2O_3$. The whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave the product (4.46 g), which was purified by column chromatography (SiO_2, 90 g, *n*-hexane–EtOAc = 2 : 1) to furnish segment B-I (**4**, 3.50 g, 98%). Segment B-I (**4**), colorless viscous oil, $[\alpha]_D^{26}$ −24° (*c* = 4.7, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14; S, 10.33. Found: C, 61.82; H, 7.06; S, 10.47. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3070, 1575, 1320, 1150. UV λ_{max}^{EtOH} nm (ε): 215 (9200). ^{1}H-NMR (CCl_4, δ): 1.30 (3H, s, *tert*-CH_3), 2.99, 3.37 (2H, ABq, *J* = 14 Hz, –CH_2SO_2Ph), 3.7—4.4 (4H, m, –O–CH_2CH_2–O–), 7.4—8.0 (5H, m, phenyl protons). MS *m/z* (%): 310 (M^+, 6), 99 (100).

Hydrocyanation of 6 Giving the Cyanoketone (12)——A solution of **6** (55 g, 0.50 mol) in abs. EtOH (500 ml) and AcOH (45 ml) was treated with KCN (66 g, 1.00 mol) and the mixture was heated under reflux with stirring for 2.5 h. After cooling, 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 gave the product, which was purified by distillation under reduced pressure (bp 146—148 °C, 20 mmHg) to furnish **12** (49.1 g, 72%) and **6** (recovered, 11.8 g, 21%). **12**, colorless oil, bp 146—148 °C (20 mmHg). *Anal.* Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.92; H, 8.26; N, 10.34. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2215, 1725. ^{1}H-NMR (CCl_4, δ): 1.44 ($CDCl_3$, δ): 1.30 (3H, s, *tert*-CH_3), 1.4—2.8 (8H, m), 9.02 (1H, br s, COOH). MS *m/z* (%): 156 (M^+, 43), 41 (100).

Acidic Hydrolysis of 12 Giving the Keto-Acid (13)——A stirred solution of **12** (55 g, 0.40 mol) in HCOOH (200 ml)–conc. HCl (100 ml)–water (30 ml) was heated under reflux for 16 h. After cooling, the reaction mixture was poured into aq. sat. NaCl and the whole was extracted with $CHCl_3$. The organic phase was then extracted with aq. sat. $NaHCO_3$ and the aq. sat. $NaHCO_3$ phase was separated and acidified with aq. 5% HCl. The whole aqueous mixture was extracted again with $CHCl_3$ and the $CHCl_3$ extract was washed with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure furnished **13** (54 g, 86%). **13**, colorless oil. *Anal.* Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.41; H, 7.73. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—2200 (br), 1760, 1720, 1705. ^{1}H-NMR

($CDCl_3$,δ): 1.30 (3H, s, *tert*-CH_3), 1.4—2.8 (8H, m), 9.02 (1H, br s, COOH). MS *m/z* (%): 156 (M^+, 43), 41 (100).

Ketalization Followed by Methylation of 13 Giving 14——A solution of **13** (11.4 g, 73 mmol) in benzene (70 ml) was treated with ethylene glycol (4.6 ml, 88 mmol) and *p*-TsOH·H_2O (100 mg) and the mixture was heated under reflux for 1 h with azeotropic removal of water. After cooling, the reaction mixture was treated with excess ethereal diazomethane. The reaction mixture was concentrated under reduced pressure to give the product (16.2 g), which was purified by column chromatography (SiO_2, 500 g, *n*-hexane–EtOAc = 5 : 1) to furnish **14** (7.75 g, 50%). **14**, colorless oil. *Anal.* Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.68; H, 8.64. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730, 1160. ^{1}H-NMR (CCl_4, δ): 1.14 (3H, s, *tert*-CH_3), 0.9—2.3 (8H, m), 3.60 (3H, s, $COOCH_3$), 3.6—4.1 (4H, m, –O–CH_2CH_2–O–). MS *m/z* (%): 214 (M^+, 8), 99 (100).

Preparation of the Butanediol Ketal (15) from 14——A solution of **14** (12.0 g, 56 mmol) in aq. 5% HCl (20 ml)–acetone (100 ml) was heated under reflux for 1 h. After cooling, the reaction mixture was poured into ice-water and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave the ketone product (9.5 g). The ketone (9.5 g) was dissolved in benzene (100 ml) and the solution was treated with (2*S*,3*S*)-2,3-butanediol (6 ml) and *p*-TsOH·H_2O (100 mg). The whole mixture was heated under reflux for 1 h with azeotropic removal of water. After cooling, the reaction mixture was poured into ice-water and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave the butanediol ketal (13.5 g). A solution of this ketal (13.5 g, 56 mmol) in tetrahydrofuran (100 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.6 g, 42 mmol) in tetrahydrofuran (150 ml) and the whole was stirred for 1 h. The reaction mixture was ice-cooled and treated successively with EtOAc (2 ml), water (0.8 ml), aq. 4 N NaOH (1.8 ml), and water (2 ml). After warming to room temperature, the reaction mixture was stirred for a further 1 h. The white precipitate was removed by filtration and washed repeatedly with EtOAc. The combined organic phase (filtrate and washings) was dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (12.2 g), which was purified by column chromatography (SiO_2, 150 g, *n*-hexane–EtOAc = 3 : 1) to furnish **15** (11.1 g, 93%).

HPLC Separation of 15 Giving 15a and 15b——The diastereomeric mixture **15** (50 mg) was separated by HPLC using a Waters ALC-100 machine (column: μ-Porasil, 1 ft × 2, *n*-hexane–$CHCl_3$ = 1 : 2, flow rate 5.0 ml/min, RI detector) to furnish **15a** (23 mg) and **15b** (23 mg). **15a**, colorless oil, $[\alpha]_D^{20}$ +12° (*c* = 0.8, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.16; H, 10.22. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640, 3480, 1100. ^{1}H-NMR ($CDCl_3$, δ): 0.94 (3H, s, *tert*-CH_3), 1.22 (6H, d, *J* = 6 Hz), 3.2—3.8 (2H, m) (–O–CH(CH_3)–CH(CH_3)–O–), 2.23 (1H, br s, OH, exchangeable with D_2O), 3.41 (2H, br s, –C<u>H</u>$_2$OH). MS *m/z* (%): 214 (M^+, 7), 183 (100). **15b**, colorless oil, $[\alpha]_D^{20}$ +3.5° (*c* = 2.6, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 66.96; H, 10.21. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620, 3460, 1095. ^{1}H-NMR ($CDCl_3$, δ): 0.94 (3H, s, *tert*-CH_3), 1.23 (6H, d, *J* = 6 Hz), 3.2—3.8 (2H, m) (–O–CH(CH_3)–CH(CH_3)–O–), 2.22 (1H, br s, OH, exchangeable with D_2O), 3.33, 3.51 (2H ABq, *J* = 12 Hz, –C<u>H</u>$_2$OH). MS *m/z* (%): 214 (M^+, 8), 183 (100).

Acidic Hydrolysis of 15a and 15b Giving 16a and 16b——A solution of **15a** (50 mg) in acetone (3.0 ml) was treated with aq. 5% HCl (0.6 ml) and the mixture was heated under reflux for 15 min. After cooling, the reaction mixture was poured into ice-water and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner furnished **16a** (32 mg, 98%). In the same manner, **15b** (120 mg) was hydrolyzed to furnish **16b** (75 mg, 95%). **16a**, colorless oil, $[\alpha]_D^{20}$ +14° (*c* = 0.8, $CHCl_3$). *Anal.* Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.57; H, 10.19. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3625 (free), 3430 (intermolecularly bonded), 1705. The OH band at 3430 cm^{-1} disappeared in the spectrum of the 0.024 M CCl_4 solution, while the intensity of the sharp band at 3625 cm^{-1} was increased. CD (*c* = 0.75, MeOH): $[\theta]_{287}^{20}$ +1900 (pos. max.); (*c* = 4.53, CCl_4): $[\theta]_{295}^{16}$ +855 (pos. max.). ^{1}H-NMR (CCl_4, δ): 0.94 (3H, s, *tert*-CH_3), 1.3—2.5 (8H, m), 3.29 (2H, br s, –C<u>H</u>$_2$OH). MS *m/z* (%): 142 (M^+, 9), 111 (100). **16b**, colorless oil, $[\alpha]_D^{20}$ −13° (*c* = 3.9, $CHCl_3$). *Anal.* Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.35; H, 10.22. CD (*c* = 1.23, MeOH): $[\theta]_{287}^{20}$ −1900 (neg. max.); (*c* = 4.45, CCl_4): $[\theta]_{295}^{16}$ −855 (neg. max.). The IR (CCl_4), ^{1}H-NMR (CCl_4), and MS data for **16b** were identical with those for **16a**.

Preparation of the Phenylsulfide (17) from 15a——A solution of **15a** (3.40 g, 16 mmol) in pyridine (9.0 ml) was treated with diphenyl disulfide (4.50 g, 21 mmol) and tri-*n*-butylphosphine (6.0 ml, 24 mmol) and the mixture was stirred at 60 °C for 23 h, then poured into ice-water. The whole was extracted with EtOAc. The EtOAc extract was washed with 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 (5.8 g), which was purified by column chromatography (SiO_2, 100 g, *n*-hexane and then *n*-hexane–EtOAc = 30 : 1) to furnish **17** (4.85 g, 99%) **17**, colorless oil, $[\alpha]_D^{21}$ −31° (*c* = 2.8, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3060, 1739, 1580, 1100, 692. UV λ_{max}^{EtOH} nm (ε): 256 (9000). ^{1}H-NMR (CCl_4, δ): 1.02 (3H, s, *tert*-CH_3), 1.07 (3H, d, *J* = 6 Hz), 1.14 (3H, d, *J* = 6 Hz), 3.2—3.7 (2H, m) (–O–CH(CH_3)–CH(CH_3)–O–), 2.85, 3.12 (2H, ABq, *J* = 12 Hz, –CH_2SPh), 6.8—7.5 (5H, m, phenyl protons). High resolution MS (*m/z*): Calcd for $C_{18}H_{26}O_2S$: 306.165. Found: 306.165. MS *m/z* (%): 306 (M^+, 56), 183 (100).

Preparation of Segment B-I (4) from 17——A solution of **17** (4.85 g, 16 mmol) in CH_2Cl_2 (50 ml) was treated with aq. sat. $NaHCO_3$ (80 ml) and 80% MCPBA (8.0 g, 37 mmol) and the mixture was stirred at room temperature for 1 h, then treated with aq. 10% $Na_2S_2O_3$. The whole was extracted with EtOAc. Usual work-up of the EtOAc extract gave the sulfone product (5.84 g). A mixture of the sulfone product (5.84 g), aq. 5% HCl (20 ml), and acetone (30 ml) was heated under reflux for 1.5 h. After cooling, the reaction mixture was poured into ice-water and the whole was

extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave the ketone product (4.63 g). A solution of this ketone product (4.63 g) in benzene (70 ml) was treated with ethylene glycol (5.0 ml) and *p*-TsOH·H_2O (20 mg) and the mixture was heated under reflux for 30 min with azeotropic removal of water. After cooling, the reaction mixture was poured into ice-water and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave the product (5.20 g), which was purified by column chromatography (SiO_2, 100 g, *n*-hexane–EtOAc = 2 : 1) to furnish segment B-I (**4**, 4.54 g, 92%). Segment B-I obtained here was identical with the above-prepared segment B-I (**4**) by $[\alpha]_D$, IR (CCl_4), and ^{1}H-NMR (CCl_4) comparisons.

Preparation of the Epoxides (18) from 16a——A solution of **16a** (1.65 g, 11.6 mmol) in pyridine (5.0 ml) was treated with Ac_2O (5.0 ml) and the mixture was allowed to stand at room temperature for 2 h, then poured into ice-water. The whole was extracted with EtOAc. Usual work-up of the EtOAc extract gave the acetate (2.13 g). A suspension of 50% NaH (1.11 g, 23.1 mmol) in DMSO (38 ml) was treated with dimethyloxosulfonium methylide (5.60 g, 25.5 mmol). This mixture was stirred at room temperature for 70 min and treated with a solution of the above acetate (2.13 g) in DMSO (7.5 ml), then the whole was stirred at room temperature for a further 30 min. The reaction mixture was poured into ice-water and the whole was extracted with EtOAc. The EtOAc extract was washed repeatedly with aq. sat. NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the product (2.85 g), which was purified by column chromatography (SiO_2, 100 g, *n*-hexane–EtOAc = 4 : 1) to furnish **18** (2.18 g, 95%). **18**, colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3030, 1740, 1240, 918, 908. ^{1}H-NMR (CCl_4, δ): 0.96 (9/4H, s), 1.03 (3/4H, s) (*tert*-CH_3), 1.99 (3H, s, OAc), 2.35, 2.40 (1/2H,,ABq, J = 5 Hz), 2.44 (3/2H, s) (epoxide protons), 3.76 (1/2H, s), 3.79, 3.95 (3/2H, ABq, J = 11 Hz) (–CH_2OAc). High resolution MS (*m/z*): Calcd for $C_{11}H_{18}O_3$: 198.125. Found: 198.125. MS *m/z* (%): 198 (M^+, 1), 43 (100).

TMS-OTf Treatment of 18 Giving 19——A solution of TMS-OTf (719 mg, 3.23 mmol) and 2,6-lutidine (0.38 ml, 3.23 mmol) was diluted with toluene to give a total volume of 10.0 ml. The reagent solution thus prepared (9.50 ml, 3.04 mmol) was added dropwise to a solution of **18** (607 mg, 3.07 mmol) in toluene (20 ml) over a period of 10 min at −78 °C. After being stirred for a further 10 min, the reaction mixture was allowed to warm gradually to room temperature, then it was stirred for a further 20 min, and poured into ice-water. The whole was extracted with EtOAc and the EtOAc extract was treated with aq. 5% HCl (to remove the TMS protecting group of the product), 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 (653 mg), which was purified by column chromatography (SiO_2, 50 g, *n*-hexane–EtOAc = 2 : 1) to furnish **19** (505 mg, 84%). GLC analysis (15% PEGS 3 mm × 2 m, column temp. 200 °C, N_2 flow rate 20 ml/min) disclosed that **19** obtained here was a 1 : 2.5 mixture of two regioisomers. **19**, colorless oil. IR ν_{max}^{film} cm^{-1}: 3410, 1732, 1240. ^{1}H-NMR (CCl_4, δ): 0.94 (15/7H, S), 0.99 (6/7H, s) (*tert*-CH_3), 2.00 (3H, s, OAc), 2.24 (1H, br s, OH, exchangeable with D_2O), 3.5—4.1 (2H, m, –CH_2OAc), 3.86 (2H, br s, =C–C$\underline{H}_2$OH), 5.31 (2/7H, m, $W_{h/2}$ = 4 Hz, 3-H), 5.57 (5/7H, m, $W_{h/2}$ = 8 Hz, 5-H). High resolution MS (*m/z*): Calcd for $C_{11}H_{18}O_3$: 198.125. Found: 198.125. MS *m/z* (%): 198 (M^+, 2), 125 (100).

PCC Oxidation of 19 Giving 20a and 20b——A solution of **19** (996 mg, 5.03 mmol) in CH_2Cl_2 (35 ml) was treated with anhydrous NaOAc (619 mg, 7.55 mmol) and PCC (1.60 g, 7.55 mmol) and the mixture was stirred at room temperature for 45 min. After dilution with ether (200 ml), the reaction mixture was passed through a Florisil column (120 g). Removal of the solvent from the eluate under reduced pressure gave the product (1.01 g), which was purified by column chromatograph (SiO_2, 50 g, *n*-hexane–EtOAc = 5 : 1) to furnish **20a** (272 mg, 28%) and **20b** (679 mg, 69%). **20a**, colorless oil, $[\alpha]_D^{19}$ +33° (*c* = 1.7, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2865, 2800, 2710, 1743, 1690, 1641, 1230, 1040. UV λ_{max}^{MeOH} nm (ε): 229 (14000). ^{1}H-NMR (CCl_4, δ): 1.13 (3H, s, *tert*-CH_3), 2.03 (3H, s, OAc), 2.0—2.2 (2H, m, 5-H_2), 3.83, 3.96 (2H, ABq, J = 11 Hz, –CH_2OAc), 6.43 (1H, m, $W_{h/2}$ = 3 Hz, 3-H), 9.32 (1H, s, CHO). High resolution MS (*m/z*): Calcd for $C_{11}H_{16}O_3$: 196.110. Found: 196.111. MS *m/z* (%): 196 (M^+, 4), 124 (100). **20b**, colorless oil, $[\alpha]_D^{19}$ +14° (*c* = 2.9, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2880, 2800, 2710, 1740, 1687, 1641, 1240, 1035. UV λ_{max}^{MeOH} nm (ε): 231 (14000). ^{1}H-NMR (CCl_4, δ): 0.96 (3H, s, *tert*-CH_3), 2.01 (3H, s, OAc), 2.1—2.5 (4H, m, 3-H_2, 6-H_2), 3.80 (2H, s, –CH_2OAc), 6.72 (1H, m, $W_{h/2}$ = 10 Hz, 5-H), 9.38 (1H, s, CHO). High resolution MS (*m/z*): Calcd for $C_{11}H_{16}O_3$: 196.110. Found: 196.111. MS *m/z* (%): 196 (M^+, 2), 43 (100).

Preparation of 21a from 20a——An ice-cooled solution of **20a** (111 mg, 0.57 mmol) in Et_2O–MeOH (10 : 1, 60 ml) was treated with $NaBH_4$ (23 mg, 0.62 mmol) and the mixture was stirred for 30 min, then poured into ice-water. The whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave the product (111 mg), which was dissolved in DMF (1.0 ml) and treated with imidazole (150 mg, 2.22 mmol) and *tert*-Bu$(CH_3)_2$SiCl (200 mg, 1.32 mmol). The whole mixture was stirred at room temperature for 10 min, then poured into 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 gave the product (286 mg), which was purified by column chromatography (SiO_2, 15 g, *n*-hexane–EtOAc = 5 : 1) to furnish **21a** (174 mg, 99%). **21a**, colorless oil, $[\alpha]_D^{19}$ +27° (*c* = 1.1, $CHCl_3$). *Anal.* Calcd for $C_{17}H_{32}O_3Si$: C, 59.90; H, 10.32. Found: C, 60.02; H, 10.34. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1741, 1245. ^{1}H-NMR (CCl_4, δ):[14] 0.00 (6H, s, –Si(C$\underline{H}_3$)$_2$-*tert*-Bu), 0.89 (9H, s, –Si$(CH_3)_2$-*tert*-Bu), 0.96 (3H, s, *tert*-CH_3), 1.91 (3H, s, OAc), 3.65, 3.79 (2H, ABq, J = 11 Hz, –CH_2OAc), 3.87 (2H, br s, –C$\underline{H}_2$OSi(C$\underline{H}_3$)$_2$-*tert*-Bu), 5.25 (1H, m, $W_{h/2}$ = 4 Hz, 3-H). MS *m/z* (%): 255 (M^+-*tert*-Bu, 15), 117 (100).

Preparation of Segment B-II (5) from 21a——A solution of **21a** (290 mg, 0.93 mmol) in MeOH (1.5 ml) was

treated with 28% NaOMe–MeOH (0.30 ml) and the mixture was left to stand at room temperature for 1 h, then poured into ice-water. The whole was extracted with EtOAc. The porudct (250 mg), obtained by usual work-up of the EtOAc extract, was dissolved in pyridine (2.0 ml). This solution was treated with diphenyl disulfide (600 mg, 2.75 mmol) and *n*-Bu_3P (0.76 ml, 3.05 mmol), and the mixture was stirred at 60 °C for 3 h. After cooling, the reaction mixture was poured into water and the whole was extracted with EtOAc. Work-up of the EtOAc extract in the usual manner gave the product (380 mg), which was purified by column chromatography (SiO_2, 20 g, *n*-hexane and then *n*-hexane–EtOAc = 20 : 1) to furnish the sulfide (323 mg). An ice-cooled mixture of the sulfide (323 mg) in CH_2Cl_2 (45 ml) and aq. 5% $NaHCO_3$ (45 ml) was treated with MCPBA (470 mg, 2.19 mmol) in small portions with stirring and the whole was stirred for a further 20 min. After addition of aq. sat. $Na_2S_2O_3$, the reaction mixture was extracted with EtOAc and the EtOAc extract was worked up in the usual manner to give the product (416 mg). Column chromatography (SiO_2, 40 g, *n*-hexane–EtOAc = 5 : 1) of the product furnished segment B-II (**5**, 235 mg, 64%). Segment B-II (**5**), colorless oil, $[\alpha]_D^{21}$ +15° (*c* = 0.7, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{34}O_3SSi$: C, 63.91; H, 8.68; S, 8.13. Found: C, 64.05; H, 8.71; S, 8.12. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3060, 1321, 1252, 1153, 1083. UV λ_{max}^{MeOH} nm (ε): 218 (12000). ^{1}H-NMR (CCl_4, δ):[14] 0.00 (6H, s, $-Si(C\underline{H}_3)_2$-*tert*-Bu), 0.87 (9H, s, $-Si(CH_3)_2$-*tert*-Bu), 1.27 (3H, s, *tert*-CH_3), 2.92 (2H, s, $-C\underline{H}_2SO_2Ph$), 3.84 (2H, br s, $-C\underline{H}_2OSi(CH_3)_2$-*tert*-Bu), 5.38 (1H, m, $W_{h/2}$ = 5 Hz, 3-H), 7.2—7.9 (5H, m, phenyl protons). MS *m/z* (%): 379 ($M^+ - CH_3$, 2), 337 (M^+ – *tert*-Bu, 100).

Preparation of 21b from 20b——An ice-cooled solution of **20b** (250 mg, 1.28 mmol) in Et_2O–MeOH (10 : 1, 12 ml) was treated with $NaBH_4$ (50 mg, 1.32 mmol) and the mixture was stirred for 1 h then poured into ice-water. The whole was then extracted with EtOAc and the EtOAc extract was worked up in the usual manner to give the product (253 mg). A solution of the product (253 mg) in DMF (2.0 ml) was treated with imidazole (300 mg, 4.44 mmol) and *tert*-$Bu(CH_3)_2SiCl$ (400 mg, 2.64 mmol) and the mixture was stirred at room temperature for 10 min, then poured into water. The whole was extracted with EtOAc. Usual work-up of the EtOAc extract gave the product (510 mg), which was purified by column chromatography (SiO_2, 15 g, *n*-hexane–EtOAc = 5 : 1) to furnish **21b** (393 mg, 99%). **21b**, colorless oil, $[\alpha]_D^{17}$ +5.3° (*c* = 2.5, $CHCl_3$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1741, 1245. ^{1}H-NMR (CCl_4, δ):[14] 0.00 (6H, s, $-Si(C\underline{H}_3)_2$-*tert*-Bu), 0.84 (9H, s, *tert*-Bu), 0.88 (3H, s, *tert*-CH_3), 1.90 (3H, s, OAc), 3.67 (2H, s, $-CH_2OAc$), 3.81 (2H, br s, $-C\underline{H}_2OSi(CH_3)_2$-*tert*-Bu), 5.40 (1H, m, $W_{h/2}$ = 8 Hz, 5-H). High resolution MS (*m/z*): Calcd for $C_{17}H_{32}O_3Si$: 312.212. Found: 312.213. MS *m/z* (%): 312 (M^+, 1), 255 (M^+ – *tert*-Bu, 12), 121 (100).

Preparation of 22 from 21b——A solution of **21b** (100 mg, 0.32 mmol) in DMF (1.8 ml) was treated with $PdCl_2$ (205 mg, 1.17 mmol) and anhydrous Na_2CO_3 (124 mg, 1.17 mmol) and the mixture was sirred at 70 °C for 24 h. The reaction mixture was further treated with $PdCl_2$ (100 mg, 0.57 mmol) and anhydrous Na_2CO_3 (60 mg, 0.57 mmol) and stirred at 70 °C for 24 h. After cooling, the reaction mixture was poured into aq. 5% HCl and the whole was extracted with EtOAc. The EtOAc extract was 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 (150 mg), which was purified by column chromatography (SiO_2, 10 g, *n*-hexane–EtOAc = 3 : 1) to furnish the dichloro-bis(π-allyl)dipalladium complex (**22**, 138 mg, 95%) as a yellow oil.

Hydride Reduction of 22——A solution of **22** (10 mg, 0.011 mmol) in a suitable solvent (1.25 ml) was treated with metal hydride under various conditions as shown in Table I. The ratio of **21a** and **21b** in each reaction was determined by GLC analysis (15% PEGS 3 mm × 2 m, column temp. 200 °C, N_2 flow rate 20 ml/min, with a FID detector).

Preparation of 21 from 22 *via* 23——A solution of **22** (883 mg, 1.95 mmol) in EtOAc (20 ml) was treated with pyridine (0.31 ml, 3.89 mmol) and the mixture was left to stand for 1 h. Removal of the solvent under reduced pressure gave the π-allylpalladium complex with a pyridine ligand (**23**, 1.035 g). A solution of (*S*)-2-anilinomethylpyrrolidine (1.03 g, 5.85 mmol) in Et_2O (31 ml) was added dropwise to a suspension of $LiAlH_4$ (148 mg, 3.89 mmol) in Et_2O (40 ml), and the mixture was stirred at room temperature for 1 h. The $LiAlH_4$–diamine complex[13] thus prepared was treated with a solution of **23** (1.035 g) in Et_2O (22 ml) at −78 °C and the whole was stirred for 15 min. The reaction mixture was allowed to warm to room temperature, then it was treated with water (50 ml) and the organic phase was separated. The aqueous phase was extracted with Et_2O. The combined organic phase was washed with 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 (860 mg), which was purified by column chromatography (SiO_2, 15 g, *n*-hexane–EtOAc = 3 : 1) to furnish **21** (**21a** : **21b** = 1.7 : 1, 650 mg, quant.) as a colorless oil. The ratio of **21a** and **21b** in **21** thus prepared was determined from the olefinic proton signal intensities (3-H, 5-H) in the ^{1}H-NMR spectrum (CCl_4) of **21**.

Preparation of 19 from 21——A solution of **21** (644 mg, 2.06 mmol) in tetrahydrofuran (3.0 ml) was treated with 1.0 M *n*-Bu_4NF–tetrahydrofuran (5.0 ml, 5.0 mmol) and the mixture was stirred at room temperature for 1.5 h. Removal of the solvent from the reaction mixture under reduced pressure gave the product (1.0 g), which was purified by column chromatography (SiO_2, 10 g, *n*-hexane–EtOAc = 2 : 1) to furnish **19** (408 mg, quant.) as a colorless oil. The ^{1}H-NMR spectrum of **19** obtained here indicated that **19** consisted of **19a** and **19b** in 1.7 : 1 ratio as judged from the olefinic proton signal intensities (3-H, 5-H).

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 (58110006).

References and Notes

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