Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 2, pp. 247-254, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $6.00+0.00

0957-4166(94)E0022-3

Stereocontrolled Synthesis of the B-Ring Moiety of Sesbanimide Alkaloids: Formal Chiral Synthesis of Sesbanimides A and B

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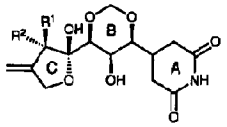
Abstract: Stereoselective synthesis of the key intermediate for sesbanimide A and sesbanimide B was achieved by employing a chelation controlled aldol reaction of a tetronic acid derivative with (*R*)-2,3-cyclohexylideneglyceraldehyde as a key step.

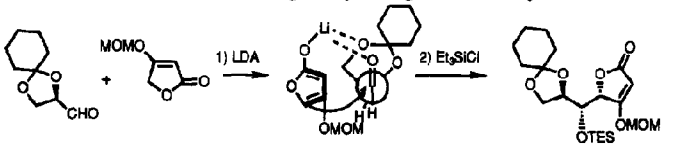
Sesbanimide A (**1**) and sesbanimide B (**2**) have been isolated from the seeds of *Sesbania drummondii*[1] and *Sesbania punicea*[2] and have been shown to be potent antitumor compounds. Owing to the interesting biological activity and novel structural features of the Sesbania alkaloids, and also in order to elucidate their structure-activity relationships, a number of syntheses and synthetic approaches to optically active forms have been published[3] by several groups employing D-glucose,[4] D-xylose,[5] L-sorbitol,[5,6] and (*R*)-glyceraldehyde[7] as chiral starting materials. (Figure 1)



1 sesbanimide A $R^1 = H$, $R^2 = Me$
2 sesbanimide B $R^1 = Me$, $R^2 = H$

Figure 1.

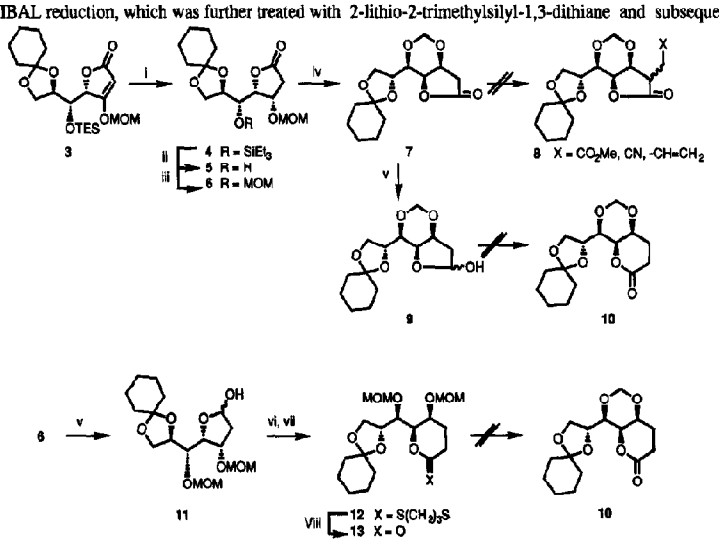
Recently we reported[8] the chelation controlled aldol reaction of a tetronic acid derivative with (*R*)-glyceraldehyde to give the anti, syn-adduct (**3**) stereoselectively as shown in Scheme 1. As an extension of this work, we have investigated the stereoselective synthesis of sesbanimide A and sesbanimide B, and report here a stereocontrolled construction of their B-ring moiety leading to the formal synthesis of these alkaloids.



Scheme 1.

Reduction of the silyl ether (**3**) over rhodium on alumina under 7 atm of hydrogen in ethyl acetate in the presence of a catalytic amount of sodium hydrogen carbonate afforded the γ-lactone (**4**) as the single stereoisomer, in 98% yield, which on exposure to 2% hydrochloric acid in tetrahydrofuran at 0°C for 2h furnished the alcohol (**5**) in quantitative yield. After protection of the hydroxyl group of **5** as the methoxymethyl ether (**6**) $[\alpha]_D$ +25.3 (c=1.1, $CHCl_3$), a construction of the B-ring was carried out under the Linderman's reaction conditions[9] with the use of boron trifluoride etherate in toluene to give the tricyclic

compound (7) $[\alpha]_D$ +52.2 (c=1.0, $CHCl_3$), in 72% yield. Thus, the synthesis of the B-ring moiety of sesbanimide was achieved stereoselectively with the desired chirality. In order to prepare the imide moiety of sesbanimide, ring expansion of the γ-lactone into a δ-lactone and the introduction of a methylamine unit to **7** were required. Although the alkylations of the γ-lactone (7) with methyl bromoacetate, allyl bromide, or iodoacetonitrile in the presence of a base, such as lithium diisopropylamide, potassium *tert*-butoxide, or sodium hydride in an appropriate solvent were first investigated under various reaction conditions, none of the desired product (**8**) could be isolated from these reactions. We therefore turned our attention to the conversion of the γ-lactone (**7**) into the δ-lactone (**10**) before introduction of a methylamine moiety, however the treatment of the lactol (**9**), prepared from the γ-lactone (7) by diisobutylaluminum hydride (DIBAL) reduction, with 2-lithio-2-trimethylsilyl-1,3-dithiane, prepared from 2-trimethylsilyl-1,3-dithiane and *n*-butyllithium, afforded none of the desired product. Based on these results, we thought that the ring expansion should be attempted before 1,3-dioxane formation. Thus, the γ-lactone (**6**) was converted into the lactol (**11**) by DIBAL reduction, which was further treated with 2-lithio-2-trimethylsilyl-1,3-dithiane and subsequently

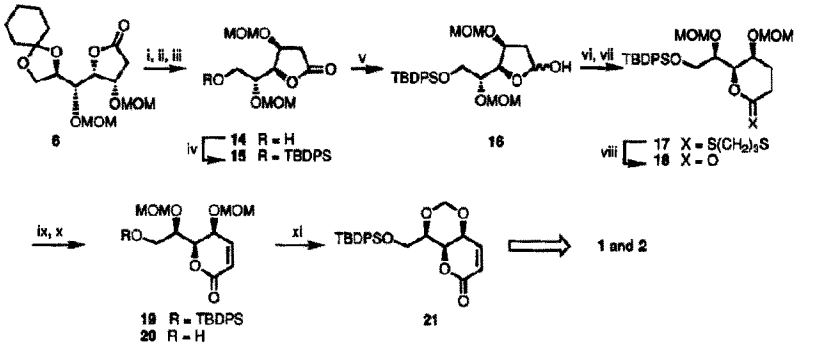


Scheme 2: i) H_2 (7 atm), Rh on alumina, AcOEt, r.t. (98%) ; ii) 2% HCl, 0°C, THF (100%); iii) MOMCl, $^iPr_2NEt$, CH_2Cl_2, reflux (97%); iv) BF_3 OEt_2, 0°C, toluene (65%); v) DIBAL, -78°C, THF (99%); vi) *n*-BuLi, 2-TMS-1,3-dithiane, -78°C, THF; vii) CSA, THF, r.t. (98% from 11); viii) $NaIO_4$, 80% MeCN, r.t. (80%).

with camphorsulfonic acid to give the thioacetal (**12**). Hydrolysis of 12 with sodium periodate in 80% aqueous acetonitrile provided the δ-lactone (**13**), whose attempted 1,3-dioxane formations under the Linderman's reaction conditions with slight modifications, however, all failed. (Scheme 2)

Since the presence of the cyclohexylidene group seems to cause trouble in the above reactions, we decided to remove the cyclohexylidene acetal before conversion of the γ-lactone into the δ-lactone. The cyclohexylidene acetal of **6** was selectively deblocked by treatment with 60% aqueous trifluoroacetic acid in tetrahydrofuran at 0°C to give the glycol, which, without purification was subjected to a glycol cleavage reaction with sodium periodate, and subsequently reduced with sodium borohydride to provide the primary

alcohol (**14**) in 63% yield from **6**. Silylation of **14** with *tert*-butyldiphenylsilyl chloride afforded the silyl ether (**15**) $[\alpha]_D$ -7.4 (c=0.3, $CHCl_3$), in 92% yield. Ring expansion of the γ-lactone was achieved in the usual manner as follows. Reduction of **15** with DIBAL gave the lactol (**16**), which on reaction with 2-lithio-2-trimethylsilyl-1,3-dithiane, followed by acid treatment afforded the thioacetal (**17**) in 83% yield. Hydrolysis of **17** into the δ-lactone (**18**) was accomplished by treatment with sodium periodate in 80% aqueous acetonitrile at 0°C in quantitative yield. The δ-lactone (**18**) was then converted into the α,β-unsaturated lactone (**19**) $[\alpha]_D$ +81.8 (c=0.8, $CHCl_3$), by treatment with phenylselenenyl chloride in the presence of LDA in tetrahydrofuran, followed by oxidative elimination with 30% hydrogen peroxide in 87% yield. Finally the unsaturated lactone (**19**) was transformed under the Linderman's procedure to the 1,3-dioxane derivative (**21**) $[\alpha]_D$ -8.2 (c=0.7, $CHCl_3$), in 83% yield, whose proton NMR and IR spectra were identical with those of the racemate[10] (Scheme 3).



Scheme 3: i) 60% TFA, 0°C, THF; ii) $NaIO_4$, 0°C, H_2O-ether (1:1); iii) $NaBH_4$, 0°C, MeOH (63% from **6**); iv) TBDPSCl, Et_3N, DMAP, CH_2Cl_2 (92%); v) DIBAL, -78°C, THF (90%) ; vi) *n*-BuLi, 2-TMS-1,3-dithiane, -78 to -15 °C, THF; Vii) CSA, 0°C, THF (83% from 16); viii) $NaIO_4$, 0°C, 80% MeCN (100%); ix) LDA, -78 °C, THF-HMPA then PhSeBr; x) 30% H_2O_2, 0°C, THF, AcOH (cat) (87% from **19**); xi) BF_3OEt_2, 0°C, CH_2Cl_2 (83%).

The optical purity of the α,β-unsaturated lactone (**19**) was also confirmed by direct comparison with the authentic specimen, derived from the optically pure primary alcohol (**20**), recently prepared by us[11] as an intermediate for the synthesis of antitumor antibiotics, goniofufurone and goniopypyrone. The synthetic procedure for **19** described here seems to be superior in a large scale preparation to the previous work,[11] which involved the unstable compound as an intermediate. Since this lactone (**21**) had already been transformed[10] into sesbanimide A and sesbanimide B, this synthesis constitutes their formal chiral synthesis.

Thus, we could disclose the formal chiral synthesis of sesbanimide A and B. It is noteworthy that the three contiguous asymmetric centers of sesbanimide have been introduced with high stereoselectivity and correct configuration by using a chelation controlled aldol reaction of a tetronic acid derivative with (*R*)-glyceraldehyde. This strategy should provide the emerging synthetic methodology for solving complex stereochemical problems.

Experimental

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 Spectrophotometer. ^{1}H-NMR spectra were obtained for solution in $CDCl_3$ on a JEOL PMX GSX 270 instrument, and chemical shifts are reported on the δ scale from internal

tetramethylsilane. *J* values are given in Hz. Mass spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter.

(3*S*,4*R*,5*R*,6*R*)-6,7-Cyclohexylidenedioxy-5-triethylsiloxy-3-methoxymethoxyheptan-4-olide (4): A solution of **3** (200 mg, 0.47mmol) in ethyl acetate (2 ml) was hydrogenated over 5% rhodium on alumina (50 mg) in the presence of sodium hydrogen carbonate (50 mg, 0.60 mmol) for 8h under medium pressure (7.0 atm) of hydrogen. The catalyst was filtered off and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (5:1, v/v) afforded the γ-lactone (**4**)(197 mg, 98%) as a colorless oil. $[\alpha]_D$ -6.1 (c=2.9, $CHCl_3$). IR ($CHCl_3$) 1780 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.60-0.75 (6H, m, 3×CH_2CH_3), 0.97 (9H, t, J=7.9 Hz, 3×CH_2CH_3), 1.25-1.61 (10H, m, C_6H_{10}), 2.66 (1H, dd, *J*=6.1 and 17.1 Hz, 2-H), 2.75 (1H, dd, *J*=4.9 and 17.1 Hz, 2-H), 3.39 (3H, s, OCH_3), 3.87 (1H, dd, *J*=6.7 and 7.3 Hz, 7-H), 4.01 (1H, dd, *J*=6.7 and 7.3 Hz, 7-H), 4.11 (1H, dt, *J*=5.5 and 6.7 Hz, 6-H), 4.29 (1H, t, *J*=5.5 Hz, 5-H), 4.44 (1H, dd, *J*=5.5 and 10.4 Hz, 4-H), 4.44-4.52 (1H, m, 3-H), 4.65 and 4.69 (each 1H, each d, *J*=7.3 Hz, OCH_2O). MS *m/z* 430 (M^+)(Found 430.2391. Calcd for $C_{21}H_{38}O_7Si$ 430.2386). Anal. Calcd for $C_{21}H_{38}O_7Si \cdot 0.1C_6H_{12}$: C, 59.07; H, 9.04. Found: C, 59.04; H, 9.11.

(3*S*,4*R*,5*R*,6*R*)-6,7-Cyclohexylidenedioxy-5-hydroxy-3-methoxymethoxyheptan-4-olide (5): To a stirred solution of **4** (1.0 g, 2.33 mmol) in tetrahydrofuran (10 ml) was added 2% hydrochloric acid (2 ml) at 0°C and the resulting mixture was further stirred at ambient temperature overnight. After the solution was neutralized by treatment with sodium hydrogen carbonate, the solvent was evaporated off and the residue was extracted with ethyl acetate. The extract was dried over Na_2SO_4 and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (2:1, v/v) afforded the alcohol (**5**)(735 mg, 100%) as a colorless oil. $[\alpha]_D$ -3.5 (c=0.8, $CHCl_3$). IR ($CHCl_3$) 1780 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.28-1.60 (10H, m, C_6H_{10}), 2.68-2.85 (2H, m, 2-H), 2.98-3.08 (1H, br s, OH), 3.41 (3H, s, OCH_3), 3.93 (1H, dd, *J*=1.2 and 7.9 Hz, 5-H), 4.02 (1H, dd, *J*=4.9 and 8.6 Hz, 7-H), 4.13 (1H, dd, *J*=5.5 and 8.6 Hz, 7-H), 4.15-4.24 (1H, m, 6-H), 4.64-4.75 (1H, m, 3-H), 4.71 (2H, br s, OCH_2O), 4.78 (1H, dd, *J*=1.2 and 6.1 Hz, 4-H). MS *m/z* 316 (M^+)(Found 316.1526. Calcd for $C_{15}H_{24}O_7$ 316.1526.) Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 57.17; H, 7.92.

(3*S*,4*R*,5*R*,6*R*)-6,7-Cyclohexylidenedioxy-3,5-bis(methoxymethoxy)heptan-4-olide (6): To a stirred solution of **5** (2.0 g, 6.33 mmol) in dichloromethane (20 ml) in the presence of *N,N*-diisopropylethylamine (3.4 ml) was added chloromethyl methyl ether (1.9 ml, 25.3 mmol) at 0°C and the resulting mixture was heated at reflux for overnight. The solution was diluted with dichloromethane and the mixture was washed with saturated ammonium chloride solution, and dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (6:1, v/v) afforded the ether (**6**)(2.2 g, 97%) as a colorless oil. $[\alpha]_D$ +25.3 (c=1.1, $CHCl_3$). IR ($CHCl_3$) 1780 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40-1.60 (10H, m, C_6H_{10}), 2.72 (2H, d, *J*=7.3 Hz, 2-H_2), 3.38 (6H, s, 2×OCH_3), 4.00-4.22 (4H, m, 5-H, 6-H, and 7-H_2), 4.52 (1H, q, *J*=6.7 Hz, 3-H), 4.67-4.73 (4H, m, 4-H, OCH_2O, and $OCHHO$), 4.89 (1H, d, *J*=6.7 Hz, $OCHHO$). MS *m/z* 360 (M^+)(Found 360.1776. Calcd for $C_{17}H_{28}O_8$ 360.1783). Anal. Calcd for $C_{17}H_{28}O_8$: C, 56.65; H, 7.83. Found: C, 56.69; H, 8.04.

(3*S*,4*R*,5*R*,6*R*)-6,7-Cyclohexylidenedioxy-3,5-methylenedioxyheptan-4-olide (7): To a stirred solution of the ether (**6**)(50 mg, 0.14 mmol) in dry toluene (1.5 ml) was added boron trifluoride etherate (0.05 ml, 0.41 mmol) at 0°C under argon and the mixture was further stirred for 20 min at the same temperature. The solution was treated with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to leave a residue, which was subjected to column

chromatography on silica gel. Elution with hexane-ethyl acetate (4:1, v/v) afforded the lactone (7)(28 mg, 72%) as a colorless oil. $[\alpha]_D$ -52.2 (c=1.0, $CHCl_3$). IR ($CHCl_3$) 1790 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30-1.72 (10H, m, C_6H_{10}), 2.56 (1H, d, *J*=17.1 Hz, 2-H), 2.75 (1H, dd, *J*=4.3 and 17.1 Hz, 2-H), 3.88-4.13 (3H, m, 4-H, 5-H, and 6-H), 4.29-4.38 (2H, m, 7-H_2), 4.63 (1H, dd, *J*=3.1 and 4.3 Hz, 3-H), 4.85 and 5.05 (each 1H, each s, OC*H*HO). MS *m/z* 284 (M^+)(Found 284.1253. Calcd for $C_{14}H_{20}O_6$ 284.1259).

5(*R*)-[(2*R*,3)-Cyclohexylidenedioxy-1(*R*)-methoxymethoxypropyl]-5-hydroxy-3(*S*)-methoxymethoxytetrahydrofuran (11): To a stirred solution of the lactone (6)(140 mg, 0.39 mmol) in tetrahydrofuran (40 ml) was added 0.93M solution of diisobutylaluminum hydride in hexane (0.84 ml, 0.78 mmol) at -78°C under argon and the mixture was further stirred for 3h at the same temperature. A mixture of methanol water (1:1)(2 ml) was added to the solution and the resulting solution was further stirred for 20 min. An insoluble material was filtered off and the filtrate was concentrated to give a residue, which was taken up with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (3:1, v/v) afforded the lactol (**11**)(133 mg, 95%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.30-1.72 (10H, m, C_6H_{10}), 2.00-2.17 (1H, m, 2-H), 2.23-2.30 (1H, m, 2-H), 3.40 and 3.45 (each 1.5H, each s, OCH_3), 3.38 and 3.42 (each 1.5H, each s, OCH_3), 3.97-4.42 (6H, m, 3-H, 4-H, 5-H, 6-H, and 7-H_2), 4.68 (2H, br s, OCH_2O), 4.79 and 4.95 (each 1H, each d, *J*=6.7 Hz, OC*H*HO), 5.38-5.40 (0.5H, m, 1-H), 5.62-5.72 (0.5H, br s, 1-H). MS *m/z* 362 (M^+)(Found 362.3258. Calcd for $C_{17}H_{30}O_8$ 362.3253). This compound was used without further purification in the next step.

(4*S*,5*R*,6*R*,7*R*)-7,8-Cyclohexylidenedioxy-4,6-bis(methoxymethoxy)octan-5-olide (13): To a stirred solution of 2-trimethylsilyl-1,3-dithiane (3.2 ml, 16.6 mmol) in tetrahydrofuran (50 ml) was added 1.61M solution of *n*-butyllithium in hexane (10 ml, 16.6 mmol) at 0°C and the mixture was stirred at room temperature for 2h. The solution was cooled to -78°C. A solution of the lactol (**11**)(300 mg, 0.83 mmol) in tetrahydrofuran (3 ml) was added to this solution at the same temperature and the resulting solution was further stirred for 4h, then treated with saturated ammonium chloride solution. The solvent was evaporated and the residue was taken up with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to leave a residue, which was dissolved into tetrahydrofuran. To this solution was added D-camphor-10-sulfonic acid (38 mg, 1.66 mmol) at ambient temperature and the mixture was further stirred overnight. After addition of sodium hydrogen carbonate, the solution was concentrated to leave a residue, which was extracted with ethyl acetate. Evaporation of the solvent afforded the acetal (**12**) which without purification was used in the next step. The compound (12) was dissolved into 80% aqueous acetonitrile (2 ml) and sodium periodate (177 mg, 0.83 mmol) was added to this solution. The resulting solution was stirred at room temperature for 2h. An insoluble material was precipitated, which was filtered off and the precipitate was washed with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (2:1, v/v) afforded the δ-lactone (**13**)(214 mg, 69% from **6**) as a colorless oil. $[\alpha]_D$ +2.0 (c=1.3, $CHCl_3$). IR ($CHCl_3$) 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30-1.65 (10H, m, C_6H_{10}), 1.93-2.02 (1H, m, 3-H), 2.23-2.33 (1H, m, 3-H), 2.57 (1H, ddd, *J*=4.9, 7.9, and 18.3 Hz, 2-H), 2.72 (1H, ddd, *J*=7.9, 9.2, and 18.3 Hz, 2-H), 3.41 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.97 (1H, dd, *J*=7.3 and 7.9 Hz, 8-H), 4.08 (1H, dd, *J*=6.1 and 7.9 Hz, 8-H), 4.10-4.24 (3H, m, 5-H, 6-H, and 7-H), 4.32 (1H, dd, *J*=2.5 and 6.7 Hz, 4-H), 4.70 and 4.73 (each 1H, each d, *J*=6.7 Hz, OC*H*HO), 4.78 and 4.85 (each 1H, each d, *J*=6.7 Hz, OC*H*HO). MS *m/z* 374 (M^+)(Found 374.1937. Calcd for $C_{18}H_{30}O_8$ 374.1939).

(3*S*,4*R*,5*R*)-6-Hydroxy-3,5-bis(methoxymethoxy)hexan-4-olide (14): A solution of the ether (**6**)(150 mg, 0.42 mmol) in tetrahydrofuran (1 ml) and 60% aqueous trifluoroacetic acid (5.0 ml) was stirred at 0°C for 1h. After neutralization with saturated sodium hydrogen carbonate solution, the mixture was extracted with dichloromethane. The extract was washed with water, dried over Na_2SO_4 and concentrated to leave a residue, which was taken up with ether-water (5 ml, 1:1). To this solution was added sodium periodate (178 mg, 0.84 mmol) at 0°C and the precipitated insoluble materials were filtered off. The filtrate was diluted with ethyl acetate, washed with brine and dried over Na_2SO_4. Removal of the solvent gave a residue, which was dissolved into methanol (5 ml) and sodium borohydride (32 mg) was added to this solution at 0°C. After the stirring had been continued for 1h, the mixture was treated with brine and extracted with ethyl acetate. The extract was dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate afforded the primary alcohol (**14**)(66 mg, 63% from **6**) as a colorless oil. $[\alpha]_D$ +46.9 (c=0.9, $CHCl_3$). IR ($CHCl_3$) 1780 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.70 (1H, dd, *J*=6.1 and 18.3 Hz, 2-H), 2.74 (1H, dd, *J*=4.9 and 18.3 Hz, 2-H), 2.77-2.87 (1H, m, OH), 3.39 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 3.65-3.87 (2H, m, 6-H_2), 4.02-4.09 (1H, m, 5-H), 4.48-4.57 (1H, m, 3-H), 4.62 (1H, dd, *J*=5.5 and 6.7 Hz, 4-H), 4.64 and 4.69 (each 1H, each d, *J*=7.3 Hz, OCH*H*O), 4.75 and 4.82 (each 1H, each d, *J*=6.7 Hz, OCH*H*O). Anal. Calcd for $C_{10}H_{18}O_7$: C, 48.00; H, 7.25. Found: C, 47.72; H, 7.48.

(3*S*,4*R*,5*R*)-6-*tert*-Butyldiphenylsiloxy-3,5-bis(methoxymethoxy)hexan-4-olide (15): A solution of the primary alcohol (**14**)(62 mg, 0.25 mmol) and *tert*-butyldiphenylsilyl chloride (0.13 ml, 0.50 mmol) in dichloromethane (0.5 ml) in the presence of triethylamine (0.07 ml, 0.50 mmol) and a catalytic amount of *N*,*N*-dimethylaminopyridine was stirred for 2h at room temperature. The mixture was diluted with dichloromethane and dried over Na_2SO_4. Evaporation of the solvent afforded a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (3:1, v/v) afforded the silyl ether (**15**)(111 mg, 92%) as a colorless oil. $[\alpha]_D$ -7.4 (c=0.3, $CHCl_3$). IR ($CHCl_3$) 1780 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.06 (9H, s, *tert*-Bu), 2.67 (1H, dd, *J*=5.5 and 17.7 Hz, 2-H), 2.75 (1H, dd, *J*=4.9 and 17.7 Hz, 2-H), 3.29 (6H, s, 2×OCH_3), 3.81 (1H, dd, *J*=4.3 and 11.0 Hz, 6-H), 3.88 (1H, dd, *J*=4.9 and 11.0 Hz, 6-H), 4.04 (1H, dt, *J*=4.3 and 4.9 Hz, 5-H), 4.43 (1H, dt, *J*=4.9 and 5.5 Hz, 3-H), 4.50 and 4.57 (each 1H, each d, *J*=7.3 Hz, OCH*H*O), 4.63 and 4.76 (each 1H, each d, *J*=6.7 Hz, OCH*H*O), 4.86 (1H, t, *J*=4.9 Hz, 4-H), 7.36-7.70 (10H, m, aromatic protons). Anal. Calcd for $C_{26}H_{36}O_7Si$: C, 63.91; H, 7.43. Found: C, 63.85; H, 7.58.

2(*R*)-[2-*tert*-Butyldiphenylsiloxy-1(*R*)-methoxymethoxyethyl]-5-hydroxy-3(*S*)-methoxymethoxy-tetrahydrofuran (16): To a stirred solution of the lactone (**15**)(226 mg, 0.46 mmol) in tetrahydrofuran (3 ml) was added diisobutylaluminum hydride (1.0 ml, 0.93 mmol) at -78°C under argon and the resulting mixture was further stirred at the same temperature for 1h. A mixture of methanol-water (1:1)(2 ml) was added to the solution and the resulting solution was further stirred for 20 min. An insoluble material was filtered off and the filtrate was concentrated to give a residue, which was taken up with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (2:1, v/v) afforded the lactol (**16**)(203 mg, 90%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.05 (9H, s, *tert*-Bu), 2.00-2.20 (3H, m, 2-CH_2 and OH), 3.29 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.75-4.00 (3H, m, 5-H and 6-H_2), 4.20-4.36 (2H, m, 3-H and 4-H), 4.48 and 4.59 (each 1H, each d, *J*=6.7 Hz, OCH*H*O), 4.80 and 4.85 (each 1H, each d, *J*=6.7 Hz, OCH*H*O), 5.40 (0.5H, d, *J*=4.3 Hz, 1-H), 5.63-5.70 (0.5H, br s, 1-H), 7.36-7.70 (10H, m, aromatic protons). Anal. Calcd for $C_{26}H_{38}O_7Si$: C, 63.65; H, 7.81. Found: C, 63.93; H, 7.81.

2(*R*)-[2-*tert*-Butyldiphenylsiloxy-1(*R*)-methoxymethoxyethyl]-3(*S*)-methoxymethoxy-4,5-dihydro-6-trimethylenedithio-2*H*-pyran (17): To a stirred solution of 2-trimethylsilyl-1,3-dithiane (0.39 ml, 2.0 mmol) in tetrahydrofuran (3.5 ml) was added 1.61M *n*-butyllithium in hexane solution (1.3 ml, 2.0 mmol) at -20°C under argon and the solution was further stirred for 30 min. This solution was cooled to -78°C and a solution of the lactol (**16**)(50 mg, 0.10 mmol) in tetrahydrofuran (0.5 ml) was added to this solution at the same temperature. The resulting solution was allowed to warm to -15°C and further stirred for 2h at the same temperature. After treatment with saturated ammonium chloride solution, the mixture was extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4 and concentrated to leave a residue, which was dissolved into tetrahydrofuran (2 ml). D-Camphor-10-sulfonic acid (12 mg, 0.05 mmol) was added to this solution and the resulting mixture was stirred for 1h at 0°C. The mixture was treated with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (4:1, v/v) afforded the thioacetal (**17**)(50 mg, 83%) as a colorless oil. $[\alpha]_D$ -29.5 (c=2.3, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.07 (9H, s, *tert*-Bu), 1.84-2.02 (2H, m, 2-H_2 and 3-H_2), 2.06-2.17 (2H, m, $SCH_2CH_2CH_2S$), 2.57-2.65 (2H, m, 2×SC*H*H), 3.13-3.19 (1H, m, SC*H*H), 3.24 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 3.42-3.53 (1H, m, SCH*H*), 3.71 (1H, br s, 5-H), 3.83-3.96 (3H, m, 6-H and 7-H), 4.39-4.44 (1H, m, 4-H), 4.40 and 4.59 (each 1H, each d, *J*=7.3 Hz, OCH*H*O), 4.75 and 4.89 (each 1H, each d, *J*=6.7 Hz, OCH*H*O), 7.35-7.75 (10H, m, aromatic protons). MS *m/z* 592 (M^+)(Found 592.2346. Calcd for $C_{30}H_{44}O_6S_2Si$ 592.2347).

(4*S*,5*R*,6*R*)-7-*tert*-Butyldiphenylsiloxy-4,6-bis(methoxymethoxy)heptan-5-olide (18): A solution of the thioacetal (**17**)(10 mg, 0.02 mmol) in 80% aqueous acetonitrile (0.5 ml) in the presence of sodium periodate (14 mg, 0.07 mmol) was stirred at 0°C for 30 min. After filtration of the insoluble material, the filtrate was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (3:1, v/v) afforded the δ-lactone (**18**)(8.5 mg, 100%) as a colorless oil. $[\alpha]_D$ -6.6 (c=1.7, $CHCl_3$). IR ($CHCl_3$) 1780 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.05 (9H, s, *tert*-Bu), 1.89-2.01 (1H, m, 3-H), 2.16-2.27 (1H, m, 3-H), 2.50-2.72 (2H, m, 2-H_2), 3.26 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.85 (1H, dd, *J*=3.7 and 11.6 Hz, 7-H), 3.92 (1H, dd, *J*=2.4 and 11.6 Hz, 7-H), 3.94-4.01 (1H, m, 6-H), 4.07-4.10 (1H, m, 5-H), 4.45 and 4.59 (each 1H, each d, *J*=7.3 Hz, OCH*H*O), 4.66 (1H, dd, *J*=1.8 and 7.3 Hz, 4-H), 4.69 and 4.76 (each 1H, each d, *J*=6.7 Hz, OCH*H*O), 7.35-7.72 (10H, m, aromatic protons). Anal. Calcd for $C_{27}H_{38}O_7Si \cdot 0.1H_2O$: C, 64.26; H, 7.63. Found: C, 64.12; H, 7.77.

(4*S*,5*R*,6*R*)-7-*tert*-Butyldiphenylsiloxy-4,6-bis(methoxymethoxy)hept-2-en-5-olide (19): To a stirred solution of lithium diisopropylamide [prepared from diisopropylamine (0.02 ml, 0.16 mmol) and 1.61M *n*-butyllithium in hexane solution (0.09 ml, 0.14 mmol)] in tetrahydrofuran (0.5 ml) was added a solution of the lactone (**18**)(24 mg, 0.05 mmol) in tetrahydrofuran (0.5 ml) at -78°C. After the stirring had been continued for 1h at the same temperature, hexamethylphosphoric triamide (0.05 ml) was added to the solution and the resulting mixture was further stirred for 10 min. A solution of phenylselenenyl bromide (34 mg, 0.15 mmol) in tetrahydrofuran (0.5 ml) was added to the solution at -78°C and the mixture was stirred for 2h at the same temperature. The solution was treated with saturated ammonium chloride solution and concentrated to leave a residue, which was dissolved in tetrahydrofuran (0.5 ml). To this solution was added 30% hydrogen peroxide (0.03 ml) and one drop of acetic acid at 0°C and the mixture was stirred for 10 min at the same temperature. The mixture was treated with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which

was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (4:1, v/v) afforded the unsaturated lactone (**19**)(21 mg, 87%) as a colorless oil. $[\alpha]_D$ +81.8 (c=0.8, $CHCl_3$). IR ($CHCl_3$) 1730 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.06 (9H, s, *tert*-Bu), 3.23 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.79 (1H, dd, *J*=3.7 and 11.6 Hz, 7-H), 3.96 (1H, dd, *J*=2.4 and 11.6 Hz, 7-H), 4.06-4.11 (2H, m, 4-H and 6-H), 4.38 and 4.54 (each 1H, each d, *J*=6.7 Hz, OCH*H*O), 4.71 and 4.79 (each 1H, each d, *J*=6.7 Hz, OCH*H*O), 4.73 (1H, dd, *J*=2.4 and 7.3 Hz, 5-H), 6.16 (1H, d, *J*=9.8 Hz, 2-H), 7.00 (1H, dd, *J*=6.1 and 9.8 Hz, 3-H), 7.35-7.75 (10H, m, aromatic protons). Anal. Calcd for $C_{27}H_{36}O_7Si$: C, 64.77; H, 7.25. Found: C, 64.80; H, 7.37.

(4*S*,5*R*,6*R*)-7-*tert*-Butyldiphenylsiloxy-4,6-methylenedioxyhept-2-en-5-olide (21): To a stirred solution of the unsaturated lactone (**19**)(97 mg, 0.19 mmol) in dichloromethane (2 ml) was added dropwise boron trifluoride etherate (0.07 ml, 0.58 mmol) at 0°C and the resulting mixture was stirred for 1h at the same temperature. After treatment with saturated ammonium chloride solution, the mixture was extracted with dichloromethane. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (4:1, v/v) afforded the lactone (**21**)(69 mg, 83%) as colorless prisms, m.p. 92-93°C (from hexane-ether). $[\alpha]_D$ -8.2 (c=0.7, $CHCl_3$). IR ($CHCl_3$) 1725 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.05 (9H, s, *tert*-Bu), 3.87-3.94 (2H, m, 6-H and 7-H), 4.08 (1H, dd, *J*=9.2 and 11.6 Hz, 7-H), 4.15 (1H, dd, *J*=2.4 and 6.1 Hz, 4-H), 4.32 (1H, br s, 5-H), 4.79 and 5.10 (each 1H, each d, *J*=6.1 Hz, OCH*H*O), 6.27 (1H, d, *J*=9.8 Hz, 2-H), 6.90 (1H, dd, *J*=6.1 and 9.8 Hz, 3-H), 7.35-7.72 (10H, m, aromatic protons). MS *m/z* 367 (M^+-57)(Found 367.1008. Calcd for $C_{20}H_{19}O_5Si$ 367.1002). Anal. Calcd for $C_{24}H_{28}O_5Si$: C, 67.90; H, 6.65. Found: C, 67.70; H, 6.67.

Acknowledgment: We are indebted to Professor P. A. Grieco, Indiana University, U.S.A. for a gift of the spectral data of the α,β-unsaturated lactone (**21**).

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(*Received in Japan* 22 *November* 1993)