Practical Synthesis of 1,3-*O*-Di-*tert*-butylsilylene-Protected D- and L-Erythritols as a Four-Carbon Chiral Building Block

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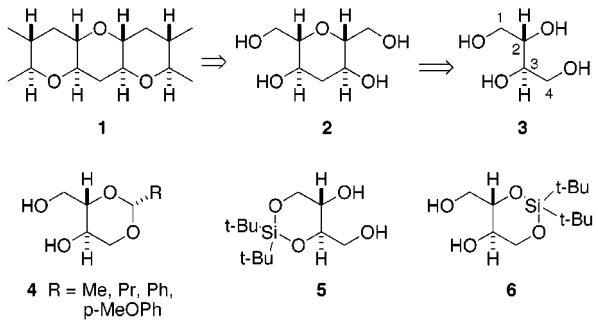
Received July 13, 2001

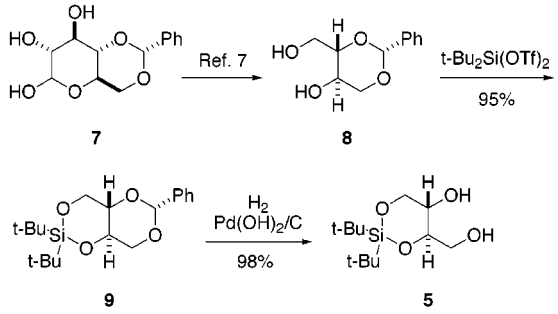
Marine polycyclic ether toxins consist of bioactive agents whose skeletons incorporate regular oxygenated heterocycles,[1] and their unique ladder architectures and potent biological activities have attracted the attention of numerous synthetic chemists. The highly symmetrical *trans*-fused polycyclic ether skeleton consisting of six-membered rings has led researchers to believe that an iterative or convergent approach might be the best way to synthesize these molecules.[2,3] As part of our program toward these ring systems, we have developed a five-step iterative approach to *trans*-fused polytetrahydropyrans **1** based on a combination strategy of alkylation of an oxiranyl anion and a 6-*endo* cyclization.[2b] To apply this strategy to the synthesis of natural toxins, we required a four-carbon building block, erythritol (**3**), for the preparation of a tetrasubstituted tetrahydropyran **2** (Scheme 1). Regioselective cyclic protection of the two hydroxyl groups at the C(1)- and C(3)-positions or the C(2)- and C(4)-positions of erythritol provides enantiomeric 1,3-*O*-protected D- or L-erythritol, respectively. However, as erythritol belongs to a *meso*-compound, its use as a chiral four-carbon building block is very limited compared to threitol and its derivatives.[4]

1,3-*O*-Alkylidene-L-erythritols [2-substituted (2*R*,4*S*,5*R*)-5-hydroxy-1,3-dioxane-4-methanols] **4** with R = Me,[5] Pr,[6] Ph,[7] or *p*-MeOPh[8] have been employed as useful chiral

Scheme 1



Scheme 2



building blocks as well as their carboxaldehyde analogues,[9] and interestingly, a 2-butylidene derivative, coruscol A, was recently isolated from a *Penicillium* sp. as a natural product.[10] Although acetals **4** can be easily prepared from D-glucose, synthesis of its enantiomer requires expensive L-glucose as reported in the synthesis of glycosidase inhibitor salacinol.[11] Furthermore, the acetal functional group in **4** would not tolerate acidic reaction conditions such as *p*-toluenesulfonic acid in methanol, which may be employed for the synthesis of **2**. In this paper, we report a simple and efficient synthesis of both enantiomers of 1,3-*O*-silylene-protected D- and L-erythritols (**5** and **6**) that are more acid stable than 1,3-*O*-alkylidene derivatives.

According to the reported procedure,[7] 1,3-*O*-benzylidene-L-erythritol (**8**) was prepared from 4,6-*O*-benzylidene-D-glucose (**7**) by $NaIO_4$ oxidation in the presence of $NaHCO_3$ followed by $NaBH_4$ reduction (Scheme 2). Cyclic protection of the primary and secondary hydroxyl groups with di-*tert*-butylsilyl bis(trifluoromethanesulfonate)[12] gave

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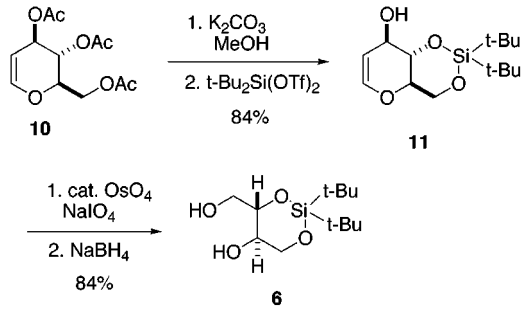
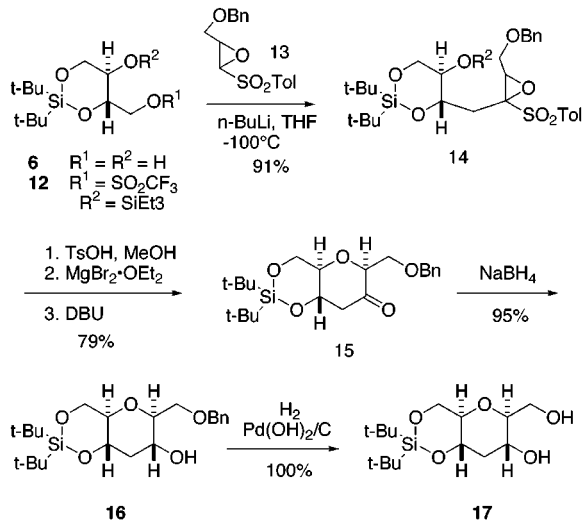
10.1021/jo0107103 CCC: $20.00 © 2001 American Chemical Society
Published on Web 11/20/2001

Scheme 3



Scheme 4



silylene acetal **9** in 95% yield. Selective deprotection of benzylidene acetal by hydrogenolysis using palladium hydroxide on carbon in ethyl acetate−acetic acid afforded 1,3-*O*-di-*tert*-butylsilylene-D-erythritol **5** [(4*R*,5*S*)-2-di-*tert*-butyl-5-hydroxy-1,3-dioxa-2-silacyclohexane-4-methanol] in 98% yield.

Its enantiomeric diol **6** was prepared from the commercially available tri-*O*-acetyl-D-glucal (**10**) (Scheme 3). Deacetylation and the following regioselective cyclic silylation were performed in a one-pot procedure. Methanolysis of **10** with a catalytic amount of K_2CO_3 followed by removal of methanol gave D-glucal, which was then dissolved in DMF and 2,6-lutidine and treated with di-*tert*-butylsilyl bis(trifluoromethanesulfonate) at −20 °C to give 4,6-*O*-silylene D-glucal **11** in 84% yield. Oxidative ring cleavage with excess $NaIO_4$ in the presence of a catalytic amount of OsO_4 and reduction of the resulting aldehyde with $NaBH_4$ gave 1,3-*O*-di-*tert*-butylsilylene-L-erythritol **6** [(4*S*,5*R*)-2-di-*tert*-butyl-5-hydroxy-1,3-dioxa-2-silacyclohexane-4-methanol] in 84% yield. The enantiomeric isomer of **8** could be readily obtained from **6** by benzylidene acetal formation followed by desilylation.

We next turned our attention to the synthesis of tetrahydropyran **2** utilizing a chiral four-carbon building block **6** (Scheme 4). Regioselective activation and protection of two hydroxyl groups were carried out in a one-pot process.[2b] Treatment of a solution of **6** and 2,6-lutidine in CH_2Cl_2 with trifluoromethanesulfonic anhydride followed by triethylsilyl trifluoromethanesulfonate gave **12** in 95% yield. The corresponding TES-protected triflate prepared from **8** was found to be labile and decomposed during purification. Reaction of the triflate **12** with the oxiranyllithium generated from the racemic *trans*-epoxy sulfone **13**[13,14] in THF in the presence of HMPA at −100 °C gave the coupled product **14** in 91% yield.

As **14** is a diastereoisomeric mixture of α- and β-epoxides, cyclization of **14** was carried out according to the method we developed.[13] Thus, detriethylsilylation with *p*-toluenesulfonic acid in methanol followed by exposure to $MgBr_2 \cdot OEt_2$ in CH_2Cl_2 gave a mixture of hydroxy bromoketones, which was treated with DBU to afford an equilibrium mixture of cyclized products, from which the desired cyclic ketone **15** was isolated in 79% overall yield along with a 9% yield of its epimer. Finally, reduction of the ketone to alcohol **16** with sodium borohydride and debenzylation by hydrogenolysis gave the optically active tetrahydropyran diol **17** in 95% yield, which serves as useful starting material for marine polycyclic ether synthesis.

In conclusion, an efficient and enantioselective method to synthesize 1,3-*O*-silylene-protected D- and L-erythritols from D-glucose derivatives has been established. Each enantiomer would be useful as a four-carbon chiral building block, and the utilization of the chiral building blocks is very effective for the synthesis of dissymmetrically protected tetrahydropyrans.

Experimental Section

General. IR spectra were recorded in $CHCl_3$ solution on a JASCO FTIR-420 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL A-400 or A-600 spectrometer in $CDCl_3$ solution using TMS and $CDCl_3$ (77.00 ppm) as internal standards, respectively. Mass spectra were obtained on a JEOL JMS-700 mass spectrometer. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Air- and moisture-sensitive reactions were carried out under an argon atmosphere under anhydrous conditions. Flash chromatography was carried out with E. Merck silica gel 60 (230−400 mesh). The term "dried" refers to the drying of an organic solution over $MgSO_4$ followed by filtration.

(1*R*,6*S*,8*R*)-3,3-Di-*tert*-butyl-8-phenyl-2,4,7,9-tetraoxa-3-silabicyclo[4.4.0]decane (9). To a solution of 1,3-*O*-benzylidene-L-erythritol (**8**: (2*R*,4*S*,5*R*)-2-phenyl-5-hydroxy-1,3-dioxane-4-methanol)[7] (4.50 g, 21.43 mmol) and 2,6-lutidine (7.5 mL, 64.29 mmol) in DMF (30 mL) was added *tert*-$Bu_2Si(OTf)_2$ at 0 °C under argon, and the reaction mixture was stirred for 4 h. The mixture was extracted with Et_2O, and the combined extracts were washed with water and brine, dried, and evaporated. Purification of the residue by flash chromatography (20% Et_2O/hexane) gave **9** (7.09 g, 95%) as a crystalline solid: mp 124−125 °C; $[\alpha]^{24}_D$ +9.0 (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) 1473, 1103 cm^{-1}; ^1H NMR (400 MHz) δ 1.02 (s, 9H), 1.07 (s, 9H), 3.65 (t, *J* = 10.2 Hz, 1H), 3.83 (ddd, *J* = 10.2, 10.2, 5.1 Hz, 1H), 4.01(t, *J* = 9.5 Hz, 1H), 4.08 (ddd, *J* = 10.2, 9.5, 4.4 Hz, 1H), 4.22 (dd, *J* = 9.5, 5.1 Hz, 1H), 4.35 (dd, *J* = 10.2, 4.4 Hz, 1H), 7.33−7.47 (m, 5H); ^{13}C NMR (100 MHz) δ 20.10, 22.70, 27.05, 27.41, 66.50, 68.92, 71.39, 77.71, 101.63, 126.12, 128.34, 129.13; EIMS *m*/*z* 350 (M^+). Anal. Calcd for $C_{19}H_{30}O_4Si$: C, 65.11; H, 8.63. Found: C, 65.34; H, 8.58.

(4*R*,5*S*)-2,2-Di-*tert*-butyl-5-hydroxy-1,3-dioxa-2-silacyclohexane-4-methanol (5). A mixture of **9** (6.00 g, 17.14 mmol) and 20% $Pd(OH)_2$/C (600 mg) in EtOAc (86 mL) and AcOH (8.6 mL) was stirred for 15 h at room temperature under H_2 atmosphere. The reaction mixture was passed through a short column of Celite and eluted with EtOAc. The filtrate was washed with dilute NH_4OH and brine, dried, and evaporated. Purification by flash chromatography (50→60% EtOAc/hexane) gave **5** (4.4 g, 98%) as a crystalline solid: mp 106−107 °C; $[\alpha]^{20}_D$ +26.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3587, 3419 cm^{-1}; ^1H NMR (400 MHz) δ 0.99 (s, 9H), 1.05 (s, 9H), 2.21 (br t, *J* = 6.3 Hz, OH), 2.36 (br d, *J* = 4.9 Hz, OH), 3.77−3.85 (m, 4H), 3.90 (m, 1H), 4.11 (m,

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1H); ^{13}C NMR (100 MHz) δ 20.05, 22.69, 27.08, 27.46, 64.87, 66.28, 77.61; EIMS *m*/*z* 262 (M^+). Anal. Calcd for $C_{12}H_{26}O_4Si$: C, 54.93; H, 9.99. Found: C, 54.65; H, 10.27.

(1*S*,6*R*,10*R*)-3,3-Di-*tert*-butyl-10-hydroxy-2,4,7-trioxa-3-silabicyclo[4.4.0]dec-8-ene (11). To a solution of tri-*O*-acetyl-D-glucal (**10**: 15.5 g, 57.0 mmol) in MeOH (57 mL) was added K_2CO_3 (79 mg, 0.57 mmol), and the mixture was stirred at room temperature for 3 h. After the solvent was evaporated, the resulting D-glucal was suspended in $CHCl_3$ (50 mL) and then concentrated under reduced pressure to remove the residual MeOH. This operation was repeated three times. The D-glucal obtained was dissolved in DMF (40 mL) and 2,6-lutidine (15.9 mL, 142.5 mmol), and to this solution was added *tert*-$Bu_2Si(OTf)_2$ (20.8 mL, 57.0 mmol) at −20 °C under argon. After stirring at −20 °C for 30 min, the reaction mixture was warmed to 0 °C over a period of 30 min and extracted with Et_2O. The combined extracts were washed with water and brine, dried, and evaporated. The residue was purified by flash chromatography (15% EtOAc/hexane) to give **11** (13.7 g, 84%) as an oil: $[\alpha]^{24}_D$ −17.4 (*c* 0.58, $CHCl_3$); IR ($CHCl_3$) 3595, 1465, 1473 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.00 (s, 9H), 1.07 (s, 9H), 2.44 (br s, OH), 3.84 (ddd, *J* = 10.3, 10.3, 4.9 Hz, 1H), 3.92 (dd, *J* = 10.3, 7.3 Hz, 1H), 3.97 (t, *J* = 10.3 Hz, 1H), 4.18 (dd, *J* = 10.3, 4.9 Hz, 1H), 4.30 (br d, *J* = 6.8 Hz, 1H), 4.76 (dd, *J* = 5.9, 2.0 Hz, 1H), 6.27 (dd, *J* = 6.4, 2.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 19.84, 22.72, 26.90, 27.42, 65.71, 70.19, 72.26, 102.97, 143.62; HREIMS calcd for $C_{14}H_{26}O_4Si$ 286.1599, found 286.1571.

(4*S*,5*R*)-2,2-Di-*tert*-butyl-5-hydroxy-1,3-dioxa-2-silacyclohexane-4-methanol (6). To a stirred solution of **11** (12.9 g, 45.2 mmol) in MeOH (200 mL) were added a solution of $NaIO_4$ (38.7 g, 180.9 mmol) in water (300 mL), $NaHCO_3$ (7.60 g, 90.5 mmol), and a catalytic amount of OsO_4 (20 mg). The resulting suspension was stirred at room temperature for 24 h and then filtered through a short pad of Celite with MeOH. The MeOH was evaporated, and the residue was extracted with EtOAc. The combined extracts were washed with water and brine, dried, and evaporated to give a mixture of aldehyde and its dimeric hemiacetal. The crude product was dissolved in MeOH (60 mL), and $NaBH_4$ (1.55 g, 40.9 mmol) was added at 0 °C. The solution was stirred for 1 h, and then water (20 mL) was added. After evaporation of the solvent, the residue was extracted with EtOAc. The combined extracts were washed with water and brine, dried, and evaporated to give a solid. Purification by flash chromatography (35% EtOAc/hexane) gave **6** (9.92 g, 84%) as a solid: mp 105−107 °C; $[\alpha]^{25}_D$ −26.0 (*c* 0.47, $CHCl_3$). The ^{1}H NMR and ^{13}C NMR spectra were identical with those of compound **5**.

(4*S*,5*R*)-2,2-Di-*tert*-butyl-5-triethylsiloxy-1,3-dioxa-2-silacyclohexane-4-methyl Trifluoromethanesulfonate (12). To a stirred solution of diol **6** (1.40 g, 5.34 mmol) in dry CH_2Cl_2 (14 mL) at −78 °C under argon were added 2,6-lutidine (1.85 mL, 16.03 mmol) and triflic anhydride (0.94 mL, 5.61 mmol). After the mixture was stirred at −78 °C for 30 min, TESOTf (1.42 mL, 6.41 mmol) was added and stirring was continued for another 30 min. The reaction mixture was poured into water and extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$, water, and brine, dried, and evaporated. Purification by flash chromatography (3% EtOAc/hexane) gave **12** (2.59 g, 95%) as a pale yellow oil: $[\alpha]^{25}_D$ −38.5 (*c* 0.22, $CHCl_3$); IR ($CHCl_3$) δ 1473, 1413, 1225, 1207 cm^{-1}; ^{1}H NMR (600 MHz) δ 0.61 (q, *J* = 8.1 Hz, 6H), 0.95 (t, *J* = 8.1 Hz, 9H), 1.00 (s, 9H), 1.04 (s, 9H), 3.79 (m, 2H), 4.06 (m, 2H), 4.61 (dd, *J* = 10.3, 4.4 Hz, 1H), 4.68 (dd, *J* = 10.3, 2.2 Hz, 1H).

(1*S*,6*R*,8*S*)-8-(Benzyloxy)methyl-3,3-di-*tert*-butyl-2,4,7-trioxa-3-silabicyclo[4.4.0]deca-9-one (15). (i) Alkylation reaction: A solution of triflate **12** (2.59 g, 5.09 mmol) and the racemic *trans*-epoxy sulfone **13** (2.43 g 7.65 mmol) in HMPA (2.66 mL, 15.29 mmol) and dry THF (34 mL) under argon was cooled to −100 °C and treated with *n*-BuLi (4.78 mL of 1.6 M solution in hexane, 7.65 mmol). After the mixture was stirred at −100 °C for 40 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was warmed to 0 °C and extracted with EtOAc. The combined extracts were washed with water and brine, dried, and evaporated. Purification by flash chromatography (6% EtOAc/hexane) gave **14** (3.15 g, 91%) as a 1:1 mixture of two diastereoisomers.

(ii) Detriethylsilylation: Product **14** (3.15 g 4.65 mmol) obtained above was dissolved in MeOH (31 mL), and $TsOH\cdot H_2O$ (18 mg, 0.093 mmol) was added. After the mixture was stirred at room temperature for 2 h, the reaction was quenched with Et_3N (0.1 mL) and the solvent was evaporated. The residue was purified by flash chromatography (30% EtOAc/hexane) to give a 1:1 mixture of hydroxy epoxy sulfones (2.55 g, 98%).

(iii) Bromoketone formation: To a stirred solution of the hydroxy epoxy sulfones (2.55 g, 4.54 mmol) in CH_2Cl_2 (45 mL) was added $MgBr_2\cdot OEt_2$ (1.41 g, 5.44 mmol) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was poured into water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. Purification by flash chromatography (25% EtOAc/hexane) gave a 1:1 mixture of bromoketones (2.14 g, 97%).

(iv) Cyclization: To a stirred solution of the bromoketones (2.14 g, 4.39 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added DBU (0.69 mL, 4.61 mmol). After the mixture was stirred at 0 °C for 1 h, the reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with water, dried, and evaporated. Purification by flash chromatography (3→15% EtOAc/hexane) gave **15** (1.49 g, 83%) as a solid and its C(8)-epimer (162 mg, 9%) as an oil. **15**: mp 101−102 °C; $[\alpha]^{25}_D$ −12.08 (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) 1725, 1473, 1114 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.00 (s, 9H), 1.05 (s, 9H), 2.44 (dd, *J* = 16.1, 10.7 Hz, 1H), 3.04 (dd, *J* = 16.1, 5.9 Hz, 1H), 3.63 (ddd, *J* = 10.3, 10.3, 4.9 Hz, 1H), 3.66 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.87 (dd, *J* = 10.7, 2.9 Hz, 1H), 3.95 (t, *J* = 10.3 Hz, 1H), 4.06 (dd, *J* = 6.3, 2.9 Hz, 1H), 4.18 (ddd, *J* = 10.7, 10.3, 5.9 Hz, 1H), 4.31 (dd, *J* = 10.3, 4.9 Hz, 1H), 4.53 and 4.57 (each d, *J* = 12.1 Hz, 1H), 7.27−7.36 (m, 5H); ^{13}C NMR (100 MHz) δ 19.90, 22.59, 26.98, 27.37, 48.22, 66.54, 68.33, 72.49, 73.71, 76.05, 82.61, 127.73, 127.76, 128.39, 137.83, 203.93; EIMS *m*/*z* 406 (M^+). Anal. Calcd for $C_{22}H_{34}O_5Si$: C, 64.99; H, 8.43. Found: C, 64.62; H, 8.69.

(1*S*,6*R*,8*S*,9*R*)-8-(Benzyloxy)methyl-3,3-di-*tert*-butyl-2,4,7-trioxa-3-silabicyclo[4.4.0]decan-9-ol (16). To a stirred solution of **15** (1.49 g, 3.67 mmol) in CH_2Cl_2 (15 mL) and MeOH (15 mL) at −78 °C was added $NaBH_4$ (300 mg, 7.93 mmol), and the reaction mixture was stirred at −78 °C for 30 min. The reaction mixture was poured into water and extracted with EtOAc. The combined extracts were washed with water and brine, dried, and evaporated. Purification by flash chromatography (20% EtOAc/hexane) gave **16** (1.42 g, 95%) as a crystalline solid: mp 77−79 °C; $[\alpha]^{25}_D$ −6.16 (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) 3496, 1473, 1220, 1108 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.98 (s, 9H), 1.03 (s, 9H), 1.50 (q, *J* = 12.2 Hz, 1H), 2.47 (ddd, *J* = 12.2, 4.4, 4.4 Hz, 1H), 2.71 (br s, OH), 3.30 (ddd, *J* = 10.2, 9.3, 4.9 Hz, 1H), 3.36 (ddd, *J* = 9.3, 5.9, 4.9 Hz, 1H), 3.60 (dd, *J* = 11.2, 5.9 Hz, 1H), 3.69 (ddd, *J* = 11.2, 9.3, 4.4 Hz, 1H), 3.71 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.77 (ddd, *J* = 11.2, 9.3, 4.4 Hz, 1H), 3.78 (t, *J* = 10.2 Hz, 1H), 4.12 (dd, *J* = 10.2, 4.9 Hz, 1H), 4.53 and 4.58 (each d, *J* = 11.7 Hz, 1H), 7.27−7.37 (m, 5H); ^{13}C NMR (100 MHz) δ 19.93, 22.60, 27.04, 27.42, 40.96, 66.75, 68.38, 71.19, 72.01, 73.76, 77.05, 79.22, 127.84, 127.99, 128.55, 137.45; EIMS *m*/*z* 408 (M^+). Anal. Calcd for $C_{22}H_{36}O_5Si$: C, 64.67; H, 8.89. Found: C, 64.39; H, 8.96.

(1*S*,6*R*,8*S*,9*R*)-8-(Benzyloxy)methyl-3,3-di-*tert*-butyl-9-hydroxy-2,4,7-trioxa-3-silabicyclo[4.4.0]decane-8-methanol (17). A mixture of **16** (800 mg, 1.96 mmol) and 20% $Pd(OH)_2$/C (160 mg) in EtOAc (14 mL) was stirred for 40 min at room temperature under H_2 atmosphere. The reaction mixture was passed through a short column of Celite and eluted with EtOAc. The filtrate was evaporated to give **17** (622 mg, 100%) as a crystalline solid: mp 211−212 °C; $[\alpha]^{25}_D$ −37.4 (*c* 0.50, $CHCl_3$); IR (KBr) 3587, 3420 cm^{-1}; ^{1}H NMR (600 MHz, acetone-d_6) δ 0.98 (s, 9H), 1.02 (s, 9H), 1.51 (q, *J* = 11.7 Hz, 1H), 2.40 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 3.20 (ddd, *J* = 8.8, 5.9, 2.9 Hz, 1H), 3.31 (ddd, *J* = 9.5, 9.5, 5.1 Hz, 1H), 3.53 (t, *J* = 6.4 Hz, OH), 3.55−3.62 (m, 2H), 3.74 (t, *J* = 10.3 Hz, 1H), 3.77 (m, 2H), 4.07 (dd, *J* = 10.3, 5.1 Hz, 1H), 4.10 (d, *J* = 5.1 Hz, OH); ^{13}C NMR (150 MHz, acetone-d_6) δ 20.43, 23.11, 27.47, 27.79, 42.74, 63.13, 66.58, 67.66, 73.43, 77.66, 83.68; EIMS *m*/*z* 318 (M^+). Anal. Calcd for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.50. Found: C, 56.43; H, 9.76.

Acknowledgment. This work was generously supported by a grant of the High-Tech Research Center Project from Japanese Ministry of Education, Culture, Sports, Science and Technology.

JO0107103