ASYMMETRIC SYNTHESIS OF THIETANOSE ‡

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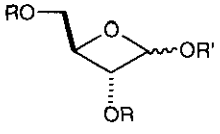
Abstract- Syntheses of optically active thietanose, (2*R*,3*R*,4*R*)-4-acetoxymethyl-3-(*tert*-butyldimethylsilyl)oxy-2-ethoxythietane (**6**) and (2*R*,3*R*,4*R*)-3-(*tert*-butyldimethylsilyl)oxy-4-[(*tert*-butyldimethylsilyl)oxy]methyl-2-ethoxythietane (**23**) are described. The key intermediate, (2*S*,3*S*)-4,4-bis(ethoxy)-3-(*tert*-butyldimethylsilyl)oxy-1,2-epithiobutane (**7**) has been derived from (*Z*)-2-butene-1,4-diol in 13 steps. Although direct transformation of **7** to thietanose (**6**) failed, regio and stereospecific ring opening of the episulfide ring in **7** and acid catalyzed cyclization of the resulting 3-mercaptobutanal diethyl acetal (**20**) was successful in forming of a thietane ring to give **6**. The structure of **6** and **23** was confirmed by spectroscopic analyses including NOE experiments.

Four membered saturated heterocycles, such as oxetane,[1] thietane,[2] and phosphetane,[3] are interesting not only because of their chemical properties but also their biological activities, in particular, when the hydroxyl group is attached at the α position of the ring heteroatom. For example, when the heteroatom is oxygen, as shown in structure (**1**), it is a four membered sugar, so called oxetanose. This type of moiety has been observed in oxetanocine,[4] and thromboxane A_2.[5] An elegant synthesis of erythrooxetanose was achieved by Nishiyama and Yamamura *et al.* in the total synthesis of oxetanocin,[6] and the chemical properties of oxetanose were studied by Kirby *et al.*[7] However, thietanose, in which the ring heteroatom is sulfur, shown in structure (**2**), has been received little attention so far. Only two syntheses of thietan-1-ol and its acetate have been reported,[8,9] and none for its optically active derivatives have appeared. This may be due to the difficulty of introducing a hydroxyl function at the 2-position on the thietane ring, and the preparation of a chiral thiol unit. In this paper, we report the first synthesis of optically pure thietanose derivatives (**6**) and (**23**).[10]



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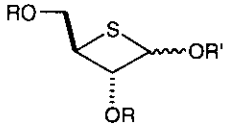

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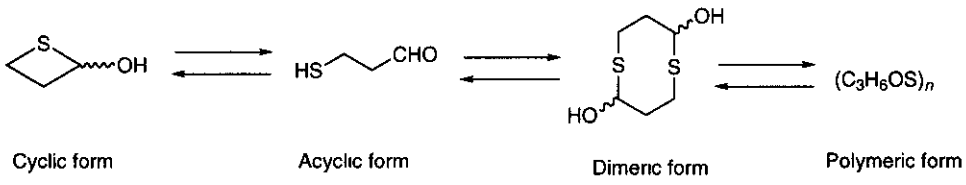
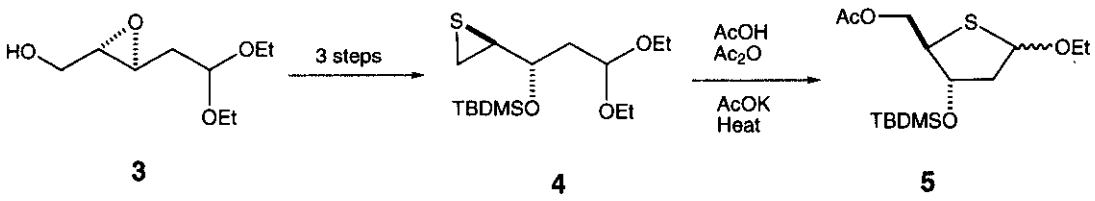
‡ This paper is dedicated to Dr. Koji Nakanishi on the occasion of his 75th birthday.

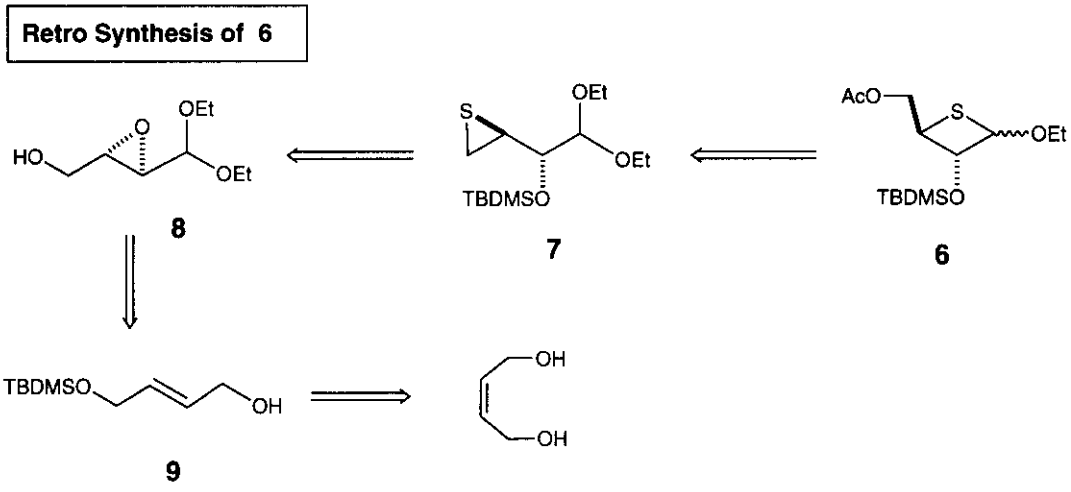


Scheme 1



Scheme 2

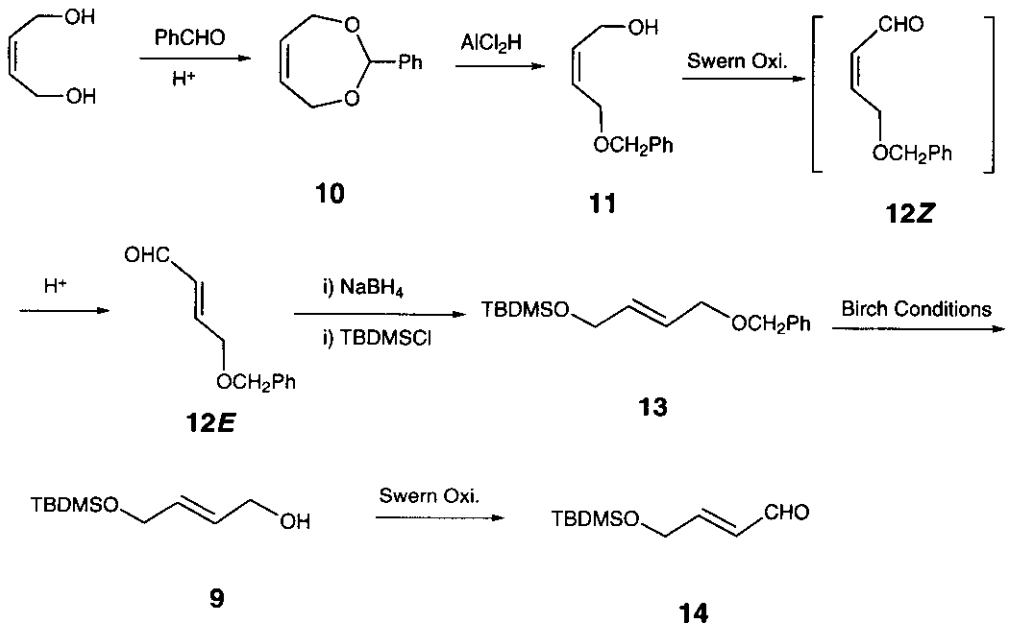
Thietan-1-ol is considered to exist in an equilibrium of 3-mercaptopropanal, its dimmer, and also oligomers (Scheme 1). Structural studies by Carlsen *et al.* have revealed that it exists in a cyclic form at least in the gas phase, and oligomerization takes place quite easily.[9] This suggests that formyl group should be protected by an appropriate protecting group until the final stage in the synthesis. Therefore, we chose diethyl acetal for its protection. Previously, we synthesized 4-thiofuranose (**5**), using stereospecific transformation of optically active 2,3-epoxy alcohol (**3**) and acid promoted ring formation to **5** *via* 3-silyloxy-1,2-episulfide (**4**),[11] shown in Scheme 2. Based on this method, our synthetic plan to **6** is illustrated in Scheme 3. Thus, compound (**7**) will be an appropriate precursor to **6**, which may be derived from epoxy alcohol (**8**). Chiral centers of **8** would be introduced by Sharpless asymmetric epoxidation of allylic alcohol (**9**), which can be obtained from commercially available 2-butene-1,4-diol.



Scheme 3

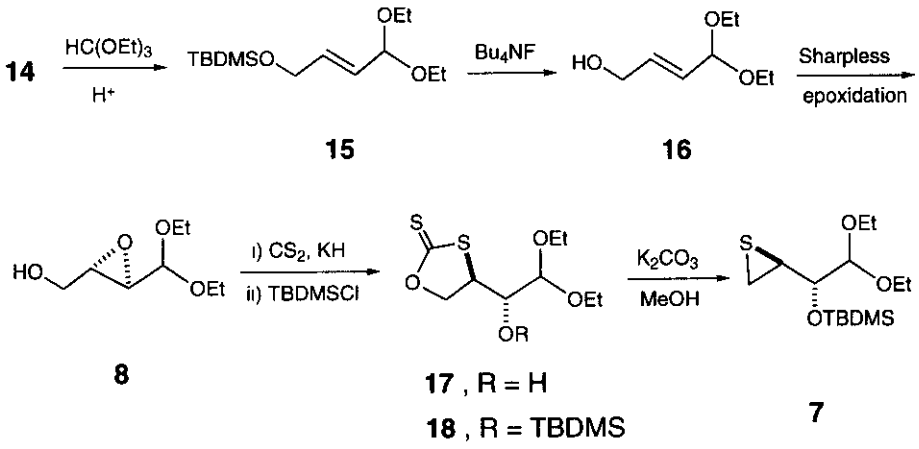
Preparation of Optically Pure Episulfide (7)

Allylic alcohol (**9**) was prepared from *cis*-2-butene-1,4-diol in 7 steps, including *cis-trans* isomerization of α,β-unsaturated aldehyde (**12**), as shown in Scheme 4. *cis*-2-Butene-1,4-diol was treated with benzaldehyde in the presence of *p*-toluenesulfonic acid to give cyclic acetal (**10**) in 75% yield. Hydrogenolysis of the acetal bond with $AlCl_2H$ afforded *cis*-2-butene-1,4-diol monobenzyl ether (**11**) in 91% yield. Although Swern oxidation of the alcohol gave the corresponding *cis*-aldehyde (**12*Z***) initially, partial isomerization occurred during the work up process. Acid treatment of the crude mixture completed the isomerization to furnish geometrically pure *trans*-4-benzyloxy-2-butenal (**12*E***) in 89% yield. Reduction of the aldehyde with $NaBH_4$ and silylation with *tert*-butyldimethylsilyl chloride afforded *trans*-2-butene-1,4-diol protected with silyl ether and benzyl ether (**13**), in 74% yield. Deprotection of the benzyl ether under Birch conditions afforded alcohol (**9**) in 85% yield, and Swern oxidation of **9** gave 4-(*tert*-butyldimethylsily)oxy-2-butenal (**14**) in 93% yield, which was identified with spectroscopic data reported in the literature.[12]



Scheme 4

Acid catalyzed acetalization of **14** with triethyl orthoformate in the presence of *dl*-camphorsulfonic acid, followed by desilylation of **15** with tetrabutylammonium fluoride, gave allylic alcohol (**16**) in 72% yield. Sharpless asymmetric epoxidation of **16** using diethyl D-tartrate as a chiral template induced an α-epoxide (**8**) in 87% yield with 95% enantiomeric excess, which was determined by Mosher analysis.[13] Introduction of a sulfur function to epoxy alcohol was achieved by the reaction with carbon disulfide reported previously.[14] Thus, potassium salt of **8** reacted with carbon disulfide to form potassium xanthate, which opened the epoxide ring intramolecularly to give hydoxyxanthate (**17**) in 75% yield, exclusively. Protection of the



Scheme 5

hydroxy group with *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of 2,6-lutidine afforded **18** in 96% yield. Methanolysis of cyclic xanthate[15] furnished episulfide (**7**) in 88% yield stereospecifically.

Ring Formation of Cyclic Sulfide from Episulfide Acetal.

We have reported the acetic acid catalyzed intramolecular carbon-sulfide bond formation of episulfide with diethyl acetal function, in which 3-(*tert*-butyldimethylsilyl)oxy-4,5-epithiopentanal diethyl acetal was cyclized to give 4-thiofuranose (**5**) in 87% yield along with 5-thiopyranose (**5'**) in 8% yield. This result was explained by the regioselective ring opening of episulfoinium intermediate,[11] shown in Figure 2.

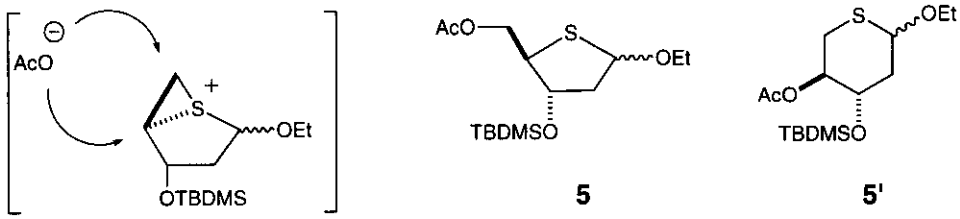
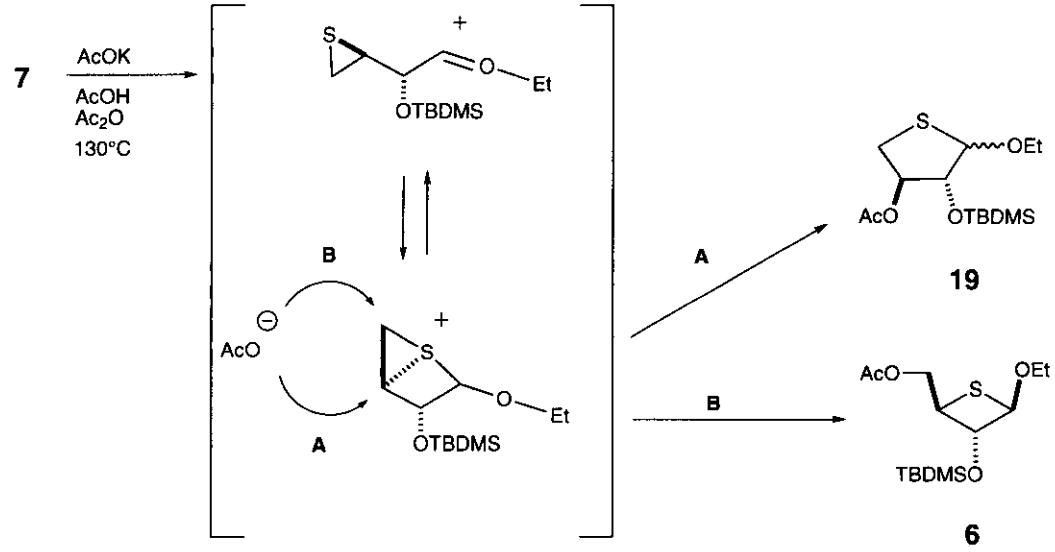


Figure 2

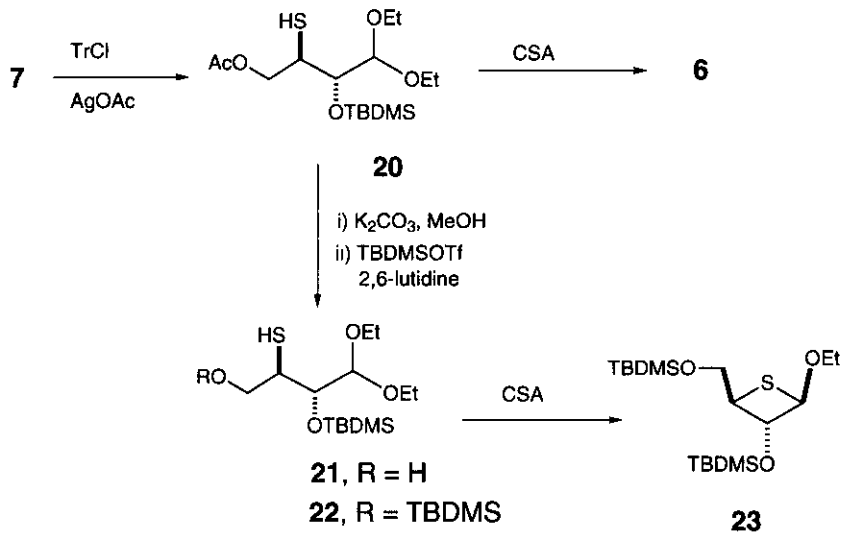
When the reaction of **7** was carried out under the same conditions for **5**, with potassium acetate in acetic acid and acetic anhydride at 130°C, 4-thiofuranose (**19**) was obtained in 17% yield along with 57% recovery of **7**. None of the desired thietane (**6**) was formed in the reaction. This reaction proceeds through the generation of an oxonium cation by activation of diethyl acetal, the formation of an episulfonium cation intermediate, and the regioselective attack of an acetate anion. In the final nucleophilic attack, two reaction paths, **A** and **B**, are available, which are described in Scheme 6. Acetoxy anion attacks *via* course **A** to provide **19**, or alternatively, *via* course **B** to provide **6**. It is noted that the less hindered side attack was favorable in the



Scheme 6

formation of **5**. On the other hand, in the case of **7**, hindered side path attack occurred predominantely. This result suggests that the reaction might give a more thermodynamically stable isomer. In fact, considering the reaction took place at 130°C, **19** would be produced much more favorable than **6**.

By this reasoning, we abandoned this method, and examined a stepwise route to reach **6**. Thus, the stepwise process involved a ring opening of episulfide by an acetate anion to form thiol first, and then cyclization of thiol with diethyl acetal to constract the thietane ring. Treatment of **7** with silver acetate in the presence of trityl chloride in refluxing toluene gave **20** in 92% yield. Cyclization of **20** to thietane (**6**) took place successfully in refluxing benzene for 2.5 h in the presence of *dl*-camphorsulfonic acid. Although the reaction was not clean, the desired **6** was obtained in 34% yield. This reaction proceeded stereoselectively, and only a single stereoisomer was detected. The stereochemistry was determined by NOE experiments and proton-proton coupling constants on the thietane ring. The coupling constants of $J_{H2\text{-}H3}$ and $J_{H3\text{-}H4}$ were 5.5 Hz, and 7.3 Hz, respectively. These values indicate typical relations between *trans* protons on the thietane ring.[16] Furthermore, no observation of NOE between H-2 and H-3, and H-3 and H-4, confirmed the relative structure of **6**. On the other hand, compound (**23**) was prepared from **20** in 3 steps. Replacement of the acetate in **20** to TBDMS ether was performed in two steps. Thus, potassium carbonate promoted methanolysis of **20** gave **21** in 94% yield, which was then silylated with TBDMSOTf in methylene chloride in the presence of 2,6-lutidine to provide **22** in 87% yield. Compound (**22**) was subjected to cyclization under the same reaction conditions described for **6**, and **23** was obtained in 48% yield. The ring protons of **23** appear at 5.01 ppm as a doublet (J=5.8 Hz) for H-2, at 4.30 ppm as a double doublets (J=7.0 and 5.8 Hz) for H-3, and at 3.25 ppm as a double double doublets (J=7.0, 6.6 and 4.7 Hz) for H-4. These results are satisfactory to confirm the structure of **23**.



Scheme 7

In conclusion, we have synthesized chiral 2-ethoxythietanes in an optically pure form. At this point, however, we have not succeeded in Lewis acid promoted replacement of the ethoxy group at the C-2 position to other nucleophiles such as a pyrimidyl group.

EXPERIMENTAL

General Melting points were uncorrected. ^1H and ^{13}C NMR were taken in $CDCl_3$ for ^1H (400 MHz or 300 MHz) and for ^{13}C (100 MHz or 75 MHz). The chemical shifts were shown as δ-value (ppm) using tetramethylsilane (0 ppm) for proton spectra and $CHCl_3$ (77.0 ppm) for carbon spectra as an internal standard. Infrared spectra (IR) were recorded as liquid films on NaCl plates or as tablets. Low and high resolution mass spectra (LRMS and HRMS) were obtained at 10 or 70 eV using the direct inlet method at the Analytical Center, in Okayama University of Science. Only significant peaks are described here for IR and MS. Analytical TLC was carried out on 0.25 mm precoated silica gel plates. Silica gel (70-300 mesh) was used for gravity column chromatography and silica gel (230-400 mesh) for flash column chromatography. All air sensitive reactions were conducted in flame dried glassware under Ar atmosphere. THF, ether and benzene, used as solvents for the reactions, were dried over sodium benzophenone ketyl, and methylene chloride was dried over phosphorus pentoxide. These solvents were freshly distilled just before use.

***(Z)*-2-Butene-1,4-diol benzylidene acetal (10)** : A mixture of (*Z*)-2-butene-1,4-diol (25 g, 0.283 mol) and benzaldehyde (42 g, 0.397 mol) in benzene (500 mL) was refluxed in the presence of *p*-toluenesulfonic acid (1.1 g, 5.7 mmol) and water which was produced, was removed by Dean Stark apparatus. After 3 h, the reaction mixture was cooled and washed with 5% $NaHCO_3$ (30 mL x2). The organic layer was dried over $MgSO_4$ and the solvent was removed. The residual liquid was distilled to give acetal (**10**) (37.3 g, bp 90-92°C/0.3 mmHg) in 75% yield and the recovery of benzaldehyde (8 g, bp 70-80°C/15 mmHg). **10**; Oil,

Rf=0.46 (10% EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ 7.54–7.52 (2H, m), 7.40-7.33 (3H, m), 5.86 (1H, s), 5.77 (2H, t, *J*=1.8 Hz), 4.39 (2H, dm, *J*=14.0), 4.28 (2H, dm, *J*=14.0); ^{13}C NMR ($CDCl_3$) δ 138.8, 129.8, 128.3, 128.1, 126.3, 102.0, 64.5.

(*Z*)-2-Butene-1,4-diol monobenzyl ether (11) : An ethereal solution of dichloroalane was prepared by the addition of ether (85 mL) suspension of $LiAlH_4$ (4.1 g, 0.1 mol) into $AlCl_3$ (58.1 g, 0.436 mol) in ether (440 mL) at 0°C. To this solution, was added **10** (37.3 g, 0.211 mol) in ether (345 mL) at 0°C. The mixture was stirred for 30 min and an excess of reagent was decomposed with 10% H_2SO_4 (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mLx3). The combined extracts were washed with water (30 mL), 5% $NaHCO_3$ (30 mL) and brine (30 mL), and dried over $MgSO_4$. The solvent was removed and the residual oil was distilled to give **11** (37.3 g) in 91% yield. **11**; Oil, bp 130-132/0.2 mmHg; Rf=0.32 (40% EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ 7.35–7.32 (5H, m), 5.82 (1H, m), 5.74 (1H, m), 4.53 (2H, s), 4.17 (2H, d, *J*=6.9 Hz), 4.09 (2H, dd, *J*=5.9 and 0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 137.7, 132.4, 128.4, 128.0, 127.8, 127.2, 72.4, 65.6, 58.5.

(*E*)-4-Benzyloxy-2-butenal (12*E*) : To a methylene chloride (310 mL) solution of oxalyl chloride (8.5 g, 67.0 mmol) at -78°C was dropped DMSO (7.4 g, 94.7 mmol) and it was stirred for 15 min. Then, a methylene chloride (50 mL) solution of **11** (10.0 g, 56.1 mmol) was added and the mixture was stirred for 20 min at the same temperature. Triethylamine (16.4 g, 163 mmol) was added and the reaction was continued for 30 min. The dryice cooled bath was changed to an ice bath. The mixture was stirred for an additional 30 min and diluted with a mixture of benzene and ether (1:1, 600 mL). It was washed with water (30 mLx3), and brine (30 mL). The organic extract was dried over $MgSO_4$. Evaporation of the solvent gave a crude aldehyde as a mixture of **12*E*** and **12*Z***. This was dissolved in methylene chloride (100 mL) containining *p*-toluenesulfonic acid (532 mg, 2.8 mmol) and the mixture was stirred for 1 hr at rt. Then, the mixture was diluted with EtOAc (800 mL), washed with sat. $NaHCO_3$ (60 mL), and brine (60 mL), and dried over $MgSO_4$. After removal of the solvent, the residual liquid was distilled to afford pure **12*E*** (8.8 g) in 89% yield. **12*E***; Oil, bp 113-116/0.2 mmHg; Rf=0.25 (20% EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ 9.58 (1H, d, *J*=8.1 Hz), 7.39–7.29 (5H, m), 6.85 (1H, dt, *J*=15.8 and 4.1 Hz), 6.41 (1H, ddt, *J*=15.8, 8.1 and 1.8 Hz), 4.60 (2H, s), 4.29 (2H, dd, *J*=4.0 and 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 153.0, 137.3, 131.6, 128.4, 127.8, 127.5, 72.9, 68.4.

(*E*)-4-Benzyloxy-2-butenyl *tert*-butyldimethylsilyl ether (13) : To a methanol (310 mL) solution of **12*Z*** (26.8 g, 0.152 mol) was added $NaBH_4$ (6.2 g, 0.167 mol) by several portions. After 15 min, the mixture was quenched with 5% HCl (200 mL) and extracted with EtOAc (400 mL). The organic layer was separated, washed with water (50 mL x2) and brine (50 mL), and dried over $MgSO_4$. After removal of the solvent, the crude alcohol was dissolved in DMF (130 mL), and imidazole (20.5 g, 0.309 mol) and *tert*-butyldimethylsilyl chloride (20.5 g, 0.136 mol) were added. The mixture was stirred for 30 min at rt and poured into ice water (200 mL). It was extracted with EtOAc and hexane (300 mL, 1:2) and the organic layer was washed with water (10 mL x5) and brine (10 mL), and dried over $MgSO_4$. The solvent was removed and the residual

liquid was distilled to give **13** (32.6 g) in 74% yield. **13** ; Oil, bp 128-131/0.3 mmHg; Rf=0.28 (5% EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ 7.37–7.29 (5H, m), 5.89-5.77 (2H, m), 4.70 (2H, s), 4.20-4.18 (2H, m), 4.16-4.14 (2H, m), 0.91 (9H, s), 0.08 (6H, s); ^{13}C NMR ($CDCl_3$) δ 138.3, 132.5, 128.3, 127.7, 127.5, 126.2, 72.0, 70.2, 63.1, 25.9, 18.4, -5.3.

(*E*)-4-*tert*-Butyldimethylsilyl)oxy-2-buten-1-ol (9) : An excess of freshly cut pieces of sodium metal (800 to 900 mg) was added to a solution of **13** (6.0 g, 20.4 mmol) in a mixture of liquid NH_3 (70 mL) and THF (40 mL) at -78°C, until the color of the solution turned to blue. Then, the reaction mixture was quenched with methanol (1 mL) and the bath was removed. Liquid ammonia was evaporated and the residual oil was diluted with ether (250 mL) and washed with water (10 mL x2) and brine (10 mL). The extract was dried over $MgSO_4$ and evaporated. The residue was distilled to give **9** (3.5 g) in 85% yield. **9** ; Oil, bp 114-116/6 mmHg; Rf=0.24 (10% EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ 5.86 (1H, ddt, *J*=15.4, 5.1 and 1.5 Hz), 5.80 (1H, dtt, *J* =15.4, 4.4 and 1.5 Hz), 4.18 (2H, dd, *J*=4.4 and 1.5 Hz), 4.16 (2H, dd, *J*=5.1 and 1.1 Hz), 0.91 (9H, s), 0.07 (6H, s); ^{13}C NMR ($CDCl_3$) δ 130.7, 129.0, 63.1, 62.9, 25.9, 18.3, -5.3.

(*E*)-4-(*tert*-Butyldimethylsilyl)oxy-2-butenal (14)[12]: To a methylene chloride (170 mL) solution of oxalyl chloride (5.8 g, 45.6 mmol) was dropped DMSO (5.1 g, 64.6 mmol) at -78°C and the mixture was stirred for 20 min at the same temperature. Then, a methylene chloride (40 mL) solution of alcohol **(9)** (7.7 g, 38.0 mmol) was added dropwise to the mixture. After being stirred for 20 min at the same temperature, the mixture was quenched with triethylamine (11.2 g, 110.3 mmol). It was stirred for an additional 20 min at -78°C and the bath was changed to an ice water bath. Sat. NH_4Cl (30 mL) was poured into the mixture, and the mixture was extracted with EtOAc (500 mL). The organic layer was washed with sat. NH_4Cl (30 mL), water (30 mL) and brine (30 mL), then dried over $MgSO_4$, and evaporated. The oily residue was purified by column chromatography on silica gel eluted with 50% EtOAc in hexane to give **14** (7.1 g) in 93% yield. **14** ; Oil, Rf=0.32 (10% EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ 9.60 (1H, d, *J*=8.1 Hz), 6.88 (1H, dt, *J*=15.4 and 3.3 Hz), 6.40 (1H, ddt, *J*=15.4, 8.1 and 2.2 Hz), 4.45 (2H, dd, *J*=3.3 and 2.2 Hz), 0.92 (9H, s), 0.09 (6H, s),; ^{13}C NMR ($CDCl_3$) δ 193.3, 156.5, 130.5, 62.2, 25.7, 18.2, -5.5; IR (film) 1690 cm^{-1}.

(*E*)-4-(*tert*-Butyldimethylsilyl)oxy-2-butenal diethyl acetal (15) : A mixture of aldehyde **(14)** (7.1 g, 35.4 mmol), triethyl orthoformate (23.5 mL, 21 g, 142 mmol) and *dl*-camphorsulfonic acid (0.7 g, 3 mmol) was stirred for 1 h at rt. Then triethylamine (1.67 mL, 1.21 g, 12 mmol) was added to the mixture at 0°C. The reaction mixture was diluted with ether (150 mL) and washed with 5% $NaHCO_3$ (15 mL x2), and water (15 mL). The organic layer was dried over $MgSO_4$ and condensed. Distillation of the residual oil afforded **15** (7.39 g) in 76% yield. **15**; Oil, bp 141~144°C/0.1 mmHg, Rf=0.30 (7.5% EtOAc in hexane).^{1}H NMR ($CDCl_3$) δ 5.91 (1H, dtd, *J*=15.4, 4.4, and 0.9 Hz), 5.72 (1H, ddt, *J*=15.8, 5.1, and 1.8 Hz), 4.92 (1H, dd, *J*=5.1 and 0.7 Hz), 4.20 (2H, ddd, *J*=4.4, 1.84 and 1.1 Hz), 3.68~3.58 (2H, m), 3.50 (2H, m), 1.21 (6H, t, *J*=7.1 Hz), 0.90 (9H, s), 0.06 (6H, s); ^{13}C NMR ($CDCl_3$) δ 133.4, 126.9, 101.1, 62.7, 60.8, 25.9, 18.3, 15.2, -5.3; MS (EI) *m/z* (rel. intensity) 274 (M^+, 3), 229 (36), 228 (56), 217 (34), 75 (base); MS (FAB) *m/z* 275 (M^++1). HRMS (FAB) Anal. Calcd for $C_{14}H_{31}O_3Si$: 275.2043. Found: 275.2048.

(*E*)-4,4-Bis(ethoxy)-2-buten-1-ol (16) : To a THF (110 mL) solution of **15** (7.39 g, 26.9 mmol) was added tetrabutylammonium fluoride (28 mL of 1M solution in THF, 28 mmol) and the mixture was stirred for 20 min at rt. After a removal of THF under reduced pressure, EtOAc (200 mL) and water (5 mL) were added to the residue, and the organic layer was washed with water (5 mL) and brine (5 mL). The extract was dried over $MgSO_4$ and purified by column chromatography on silica gel eluted with 40% EtOAc in hexane. Alcohol (**16**) (4.1 g) was obtained in 95% yield. **16**; Oil, Rf=0.38 (40% EtOAc in hexane). ^1H NMR ($CDCl_3$) δ 5.99 (1H, dtd, *J*=15.4, 5.1, and 0.7 Hz), 5.76 (1H, ddt, *J*=15.4, 5.1 and 1.5 Hz), 4.91 (1H, dd, *J*=5.1 and 0.7 Hz), 4.18 (2H, dd, *J*=5.1 and 1.5 Hz), 3.69~3.61 (2H, m), 3.54~3.46 (2H, m), 1.68 (1H, brs), 1.21 (6H, t, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 133.3, 127.5, 100.9, 61.9, 60.9, 14.9; IR (film) 3380 cm^{-1}; MS (EI) *m/z* (rel. intensity) 143 (M^+-18, 17), 129 (39), 115 (88), 103 (97), 87 (base); MS (FAB) *m/z* 161 (M^++1). HRMS (FAB) Anal. Calcd for $C_8H_{17}O_3$: 161.1178. Found: 161.1186.

(2*S*,3*R*-*trans*)-4,4-Bis(ethoxy)-2,3-epoxybutan-1-ol (8) : To a mixture of titanium tetraisopropoxide (15.1 g, 53.0 mmol) and diethyl D-tartrate (10.9 g, 53.0 mmol) in dry methylene chloride (160 mL) was added a methylene chloride (40 mL) solution of **16** (3.4 g, 21.2 mmol) at -20°C. The mixture was stirred for 20 min and *tert*-butyl hydroperoxide (46.4 mL, 1.6M in methylene chloride) was added to the mixture. The reaction mixture was kept in a refrigerator at -20°C for 22 h. Then, 10% tartric acid solution (20 mL) was added and it was stirred for 90 min at rt. The organic layer was separated, washed with water (10 mL x2), and concentrated. The residual oil was diluted with ether (400 mL) and vigorously shaken with 2N sodium hydroxide (69 mL) for 30 min. The ether layer was washed with brine (30 mL), and dried over MgSO4. The solvent was evaporated and the residual oil was purified by column chromatography on silica gel eluted with 50% EtOAc in hexane to give **8** (3.24 g) in 87% yield. The optical purity was determined to be 95% enantiomeric excess by Mosher analysis.[13] **8**; Oil, $[\alpha]_D^{24}$ -17.1° (*c* 1.0, $CHCl_3$), Rf = 0.36 (50% EtOAc in hexane). ^1H NMR ($CDCl_3$) δ 4.55 (1H, d, *J*=4.1 Hz), 3.97 (1H, dd, *J*=12.8 and 2.4 Hz), 3.78~3.55 (5H, m), 3.23 (1H, dt, *J*=4.4 and 2.2 Hz), 3.15 (1H, dd, *J*=4.1 and 2.2 Hz), 1.25 (3H, t, *J*=7.3 Hz), 1.22 (3H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 100.5, 62.7, 62.1, 60.9, 55.2, 54.9, 15.0, 14.9; IR (film) 3440 cm^{-1}; MS (EI) *m/z* (rel. intensity) 131 (M^+-45, 13), 129 (9), 103 (base), 75 (43); MS (FAB) *m/z* 177 (M^++1). HRMS (FAB) Anal. Calcd for $C_8H_{17}O_4$: 77.1127. Found: 77.1148.

[4*R*,(1'*S*)]-4-[2,2-Bis(ethoxy)-1-hydroxy-1-ethyl]-1,3-oxathiolane-2-thione (17) : To a dispersion of sodium hydride (816 mg, 60% in mineral oil) in a mixture of THF (25 mL) and carbon disulfide (40 mL) was added epoxy alcohol (**8**) (2.4 g, 13.62 mmol) in THF (25 mL) at -78°C during 5 min. After the addition, the reaction mixture was warmed up to -30°C slowly. The starting material (Rf=0.36) and the desired compound (Rf=0.40) were carefully monitored by TLC (50% EtOAc in hexane). The reaction was stopped when less polar material (Rf=0.9 in the same tlc solvent system) appeared. It usually required for 1-1.5 h. Powder ammonium chloride (900 mg) and sat. NH_4Cl solution (80 mL) were added. The mixture was extracted with ether (600 mL) and the extract was washed with water (20 mL) and brine (20 mL). The ether extract was dried over $MgSO_4$ and the solvent was evaporated. The crude material was purified by column chromatog-

raphy on silica gel eluted with 50% EtOAc in hexane to give cyclic xanthate (**17**) (2.57 g) in 75% yield. Some starting material (180 mg) was recovered. **17**; Oil, $[\alpha]_D^{24}$ -55.9° (*c* 1.0, $CHCl_3$), Rf = 0.44 (60% EtOAc in hexane). ^1H NMR ($CDCl_3$) δ 5.01 (1H dd, *J*=10.0 and 6.5 Hz), 4.94 (1H, dd, *J*=10.0 and 7.1 Hz), 4.45 (1H, d, *J*=4.5 Hz), 4.20 (1H, dt, *J*=7.1 and 6.5 Hz), 3.86~3.74 (3H, m), 3.64~3.53 (2H, m), 2.56 (1H, d, *J*=5.3 Hz), 1.25 (3H, t, *J*=7.0 Hz), 1.24 (3H, t, *J*=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 213.3, 102.4, 79.6, 72.3, 64.7, 64.3, 50.9, 15.1, 15.0; IR (film) 3440, 2320 cm^{-1}; MS (EI) *m/z* (rel. intensity) 252 (M^+, 52), 207 (4), 161 (4), 103 (base), 75 (51). HRMS (EI) Anal. Calcd for $C_9H_{16}O_4S_2$: 252.0490. Found: 252.0509.

[4*R*,(1'*S*)]-4-[2,2-Bis(ethoxy)-1-(*tert*-butyldimethylsilyl)oxy-1-ethyl]-1,3-oxathiolane-2-thione (18) : To a mixture of **17** (3.7 g, 14.7 mmol) and 2,6-lutidine (4.5 g, 42 mmol) in anhydrous methylene chloride (60 mL) was dropped *tert*-butyldimethylsilyl trifluoromethanesulfonate (6.6 g, 25.2 mmol) and the mixture was stirred for 1.5 h at rt. The mixture was diluted with EtOAc (500 mL) and washed with 5% $NaHCO_3$ (30 mL x2), water (30 mL), and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residual oil was purified by column chromatography on silica gel eluted with 10% EtOAc in hexane to give **18** (5.16 g) in 96% yield. **18**; Oil, $[\alpha]_D^{25}$ +2.2° (*c* 1.0, $CHCl_3$), Rf=0.32 (40% EtOAc in hexane). ^1H NMR ($CDCl_3$) δ 5.10 (1H, dd, *J*=9.9 and 6.3 Hz), 4.88 (1H, dd, *J*=9.9 and 7.8 Hz), 4.42 (1H, ddd, *J*=7.8, 6.2 and 3.5 Hz), 4.34 (1H, d, *J*=3.2 Hz), 3.82 (1H, dd, *J*=3.4 and 3.2 Hz), 3.74 (1H, dq, *J*=9.3 and 7.1 Hz), 3.71 (1H, dq, *J*=9.3 and 7.1 Hz), 3.60 (1H, dq, *J*=9.3 and 7.1 Hz), 3.48 (1H, dq, *J*=9.3 and 7.1 Hz), 1.23 (3H, t, *J* = 7.1 Hz), 1.21 (3H, t, *J* = 7.1Hz), 0.91 (9H, s), 0.14 (3H, s), 0.11 (3H, s); ^{13}C NMR ($CDCl_3$) δ 213.3, 104.3, 79.2, 74.0, 66.0, 64.1, 51.2, 25.7, 25.6, 15.3, 15.1, -4.3, -4.9; IR (film) 2320 cm^{-1}; MS (EI) *m/z* (rel. intensity) 309 (M^+-57, 37), 293 (11), 279 (4), 249 (7), 103 (base), 75 (39); HRMS (FAB) *m/z* 367 (M^++1). HRMS (FAB) Anal. Calcd for $C_{15}H_{31}O_4S_2Si$: 367.1433. Found: 367.1418.

(2*S*,3*S*)-4,4-Bis(ethoxy)-3-(*tert*-butyldimethylsilyl)oxy-1,2-epithiobutane (7) : A methanol (80 mL) solution of **18** (4.3 g, 11.73 mmol) was stirred for 2.5 h in the presence of anhydrous potassium carbonate (800 mg, 5.8 mmol). Then, the mixture was filtered and EtOAc (500 mL) and water (20 mL) were added. The organic layer was washed with brine (20 mL), dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel eluted with 3% EtOAc in hexane to give **7** (3.16 g) in 88% yield. **7** ; Oil, $[\alpha]_D^{24}$ +13.9° (*c* 1.0, $CHCl_3$), Rf=0.37 (5% EtOAc in hexane). ^1H NMR ($CDCl_3$) δ 4.38 (1H, d, *J*=4.4 Hz), 3.77 (1H, dq, *J*=9.3 and 7.1 Hz), 3.72 (1H, dq, *J*=9.3 and 7.1 Hz), 3.64~3.53 (3H, m), 3.11 (1H, dd, *J*=6.5 and 5.5 Hz), 2.37 (1H, d, *J*=6.5 Hz), 2.31 (1H, d, *J*=5.5 Hz), 1.23 (3H, t, *J*=7.1 Hz), 1.22 (3H, t, *J*=7.1 Hz), 0.87 (9H, s), 0.06 (3H, s), 0.04 (3H, s); ^{13}C NMR ($CDCl_3$) δ 104.8, 75.5, 64.1, 63.5, 34.2, 25.8, 21.1, 18.2, 15.4, 15.2, -4.2, -4.7; LRMS (EI) *m/z* (rel. intensity) 249 (m-57, 35), 229 (5), 218 (26), 204 (22), 103 (base); HRMS (FAB) *m/z* 307 (M^++1). HRMS (FAB) Anal. Calcd for $C_{14}H_{31}O_3SSi$: 307.1763. Found: 307.2758.

Ethyl 3-*O*-acetyl-2-*O*-(*tert*-butyldimethylsilyl)-4-thio-L-threose (19) : A mixture of **7** (50 mg, 0.16 mmol) and KOAc (81 mg, 0.83 mmol) in a mixture of AcOH (0.43 mL) and Ac_2O (0.54 mL), was heated at 120°C for 10 h. After cooling, the AcOH and Ac_2O were removed under reduced pressure, and the residue was

chromatographed on silica gel eluted with 30% EtOAc in hexane. Starting material was recovered in 57% yield along with **19** (9 mg) in 17% yield. **19** ; Oil, Rf=48(10 % EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ 5.05 (1H, ddd, *J*=7.2, 6.3 and 5.9 Hz), 4.89 (1H, d, *J*=3.6 Hz), 4.30 (1H, dd, *J*=6.3 and 3.6 Hz), 3.64 (1H, dq, *J*=9.2 and 7.0 Hz), 3.33 (1H, dq, *J*=9.2 and 7.0 Hz), 3.17 (1H, dd, *J*=11.0 and 5.9 Hz), 2.92 (1H, dd, *J*=11.0 and 7.2 Hz), 2.06 (3H, s), 1.21 (3H, t, *J*=7.0 Hz), 0.88 (9H, s), 0.11 (6H, s); ^{13}C NMR ($CDCl_3$) δ 170.5, 90.5, 81.8, 78.1, 65.7, 31.1, 25.6, 21.0, 18.0, 14.8, -4.7, -4.9; IR (film) 1770 cm^{-1}; MS (EI) *m/z* (rel. intensity) 263 (M^+-57, 23), 217 (25), 204 (18), 203 (base), 175 (16), 159 (10), 117 (69); HRMS (FAB) *m/z* 321 (M^++1). HRMS (FAB) Anal. Calcd for $C_{14}H_{29}O_4SSi$: 321.1556. Found: 321.1553.

(2*R*,3*S*)-Acetoxy-4,4-bis(ethoxy)-3-(*tert*-butyldimethylsilyl)oxybutane-2-thiol (20) : A mixture of silver acetate (1.3 g, 7.8 mmol) and trityl chloride (1.6 g, 5.8 mmol) was heated in refluxing toluene (40 mL) for 10 min. To this mixture, a toluene (10 mL) solution of **7** (1.2 g, 3.9 mmol) was dropped, and the whole mixture was refluxed for 2.5 h. After cooling, the mixture was diluted with benzene (300 mL) and washed with water (10 mL x3) and brine (10 mL). The insoluble materials were filtered through a celite pad under a reduced pressure, and the filtrate was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel eluted with 20% EtOAc in hexane to give **20** (1.3 g) in 92% yield. **20** ; Oil, $[\alpha]_D^{24}$ -9.1° (*c*, 1.0, $CHCl_3$), Rf = 0.37 (20% EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ 4.68 (1H, d, *J*=5.9 Hz), 4.49 (1H, dd, *J*=11.4 and 5.1 Hz), 4.03 (1H, dd, *J*=11.4 and 8.1 Hz), 3.86 (1H, dd, *J*=5.9 and 2.6 Hz), 3.74~3.67 (2H, m), 3.65~3.57 (3H, m), 2.11 (3H, s), 1.23 (3H, t, *J*=7.0 Hz), 1.22 (3H, t, *J*=7.0 Hz), 0.91 (9H, s), 0.16 (3H, s), 0.13 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.5, 103.7, 68.8, 64.6, 63.8, 45.4, 26.2, 26.0, 21.4, 18.4, 15.4, 15.4, -4.0, -4.3; IR (film) 1740 cm^{-1}; MS (EI) *m/z* (rel. intensity) 309 (M^+-57, 3), 279 (5), 252 (5), 217 (11), 103 (72), 56 (base); HRMS (FAB) *m/z* 367 (M^++1). HRMS (FAB) Anal. Calcd for $C_{16}H_{35}O_5SSi$: 367.1975. Found: 367.2005.

(2*R*,3*R*,4*R*)-2-Ethoxy-3-(*tert*-butyldimethylsilyl)oxy-4-acetoxymethylthietane (6) : A mixture of mercaptan (**20**) (104 mg, 0.28 mmol) and *dl*-camphorsulfonic acid (12 mg, 0.05 mmol) in anhydrous benzene (60 mL) was refluxed for 2.5 h. During this time, ethanol,which was formed, was removed as an azeotropic mixture with benzene, and the same volume of anhydrous benzene was added back to the reaction flask. After the mixture was cooled to rt, it was diluted with ether (100 mL) and washed with 5% $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography on silica gel eluted with 20% EtOAc in hexane to give **6** (30 mg) in 34% yield. **6** ; Oil, $[\alpha]_D^{24}$ -52.4° (*c* 1.0, $CHCl_3$), Rf=0.52 (15% EtOAc in hexane). ^{1}H NMR ($CDCl_3$) δ 5.04 (1H, d, *J*=5.8 Hz), 4.33 (1H, dd, *J*=11.9 and 5.5 Hz), 4.31 (1H, dd, *J*=7.3 and 5.5 Hz), 4.17 (1H, dd, *J*=11.9 and 6.2 Hz), 3.55 (1H, dq, *J*=9.5 and 6.8 Hz), 3.49 (1H, dq, *J*=9.5 and 6.8 Hz), 3.34 (1H, ddd, *J*=7.3, 6.2 and 5.5 Hz), 2.07 (3H, s), 1.21 (3H, t, *J*=6.8 Hz), 0.88 (9H, s), 0.08 (6H, s); ^{13}C NMR ($CDCl_3$) δ 170.3, 87.2, 76.4, 65.7, 65.5, 42.1, 25.3, 20.5, 17.5, 14.3, -5.0, -5.3; IR (film) 1740 cm^{-1}; MS (EI) *m/z* (rel. intensity) 263 (M^+-57, 2), 252 (9), 230 (11), 217 (6), 203 (25), 173 (19), 117 (base), 103 (32), 75 (24); HRMS (FAB) *m/z* 321 (M^++1). HRMS (FAB) Anal. Calcd for $C_{14}H_{29}O_4SSi$: 321.1556. Found: 321.1582.

(2*R*,3*S*)-4,4-Bis(ethoxy)-3-(*tert*-butyldimethylsilyl)oxy-1-hydroxybutane-2-thiol (21) : A methanol solution of **20** (236 mg, 0.64 mmol) was stirred for 2 h at rt in the presence of anhydrous K_2CO_3 (178 mg, 1.28 mmol). After a removal of methanol under reduced pressure, the residual oil was chromatographed on silica gel eluted with 30% EtOAc in hexane to give mercapto alcohol **21** (196 mg) in 94% yield. **21** ; Oil, $[\alpha]_D^{24}$ -32.8° (*c* 1.0, $CHCl_3$), Rf=0.31 (20 % EtOAc in hexane). ^1H NMR ($CDCl_3$) δ 4.68 (1H, d, *J*=4.4 Hz), 4.03 (1H, br s), 3.91~3.85 (2H, m), 3.75~3.57 (5H, m), 3.42 (1H, m), 1.92 (1H, br s), 1.22 (3H, t, *J*=7.0 Hz), 1.21 (3H, t, *J*=7.0 Hz), 0.91 (9H, s), 0.21 (3H, s), 0.12 (3H, s); ^{13}C NMR ($CDCl_3$) δ 103.3, 78.6, 66.7, 63.9, 63.5, 47.2, 26.5, 18.5, 15.5, 15.4, -3.7, -4.0; IR (film) 3340 cm^{-1}; MS (EI) *m/z* (rel. intensity) 293 (M^+-31, 31), 279 (14), 247 (7), 103 (base); HRMS (FAB) *m/z* 325 (M^++1). HRMS (FAB) Anal. Calcd for $C_{14}H_{33}O_4SSi$: 325.1869. Found: 325.1889.

(2*R*,3*S*)-4,4-Bis(ethoxy)-1,3-di(*tert*-butyldimethylsilyl)oxybutane-2-thiol (22) : To a methylene chloride (50 mL) solution of **21** (1.51 g, 4.65 mmol) and 2,6-lutidine (1.16 g, 10.8 mmol) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.37 g, 5.2 mmol) dropwise at -20°C. After the mixture was stirred for 15 min at the same temperature, an ice cooled 5% $NaHCO_3$ (10 mL) was added and the reaction mixture was stirred vigorously for 5 min. The reaction mixture was extracted with EtOAc (200 mL), and the extract was washed with water (15 mL X2), and brine (10 mL). The extract was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel eluted with 5% EtOAc in hexane to give **22** (1.78 g) in 87% yield. **20** ; Oil, $[\alpha]_D^{24}$ -18.1° (*c* 1.0, $CHCl_3$), Rf=0.30 (5 % EtOAc in hexane)· ^1H NMR ($CDCl_3$) δ 4.82 (1H, d, *J*=6.2 Hz), 4.02 (1H, dd, *J*=9.7 and 8.1 Hz), 3.93 (1H, dd, *J*=6.2 and 2.6 Hz), 3.74~3.54 (5H, m), 3.41 (1H, br), 1.21(6H, t, *J*=7.0 Hz), 0.91 (9H, s), 0.89 (9H, s), 0.15 (3H, s), 0.12 (3H, s), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR ($CDCl_3$) δ 103.9, 75.0, 68.3, 64.4, 63.3, 49.2, 26.3, 26.2, 18.5, 18.4, 15.6, 15.4, -3.8, -4.0, -4.7, -4.9; MS (EI) *m/z* (rel. intensity) 335 (M^+-103, 9), 303 (8), 279 (59), 167 (76), 149 (91), 103 (base); HRMS (FAB) *m/z* 439 (M^++1). HRMS (FAB) Anal. Calcd for $C_{20}H_{47}O_4SSi_2$: 439.2734. Found: 439.2750.

(2*R*,3*R*,4*R*)-2-Ethoxy-3-(*tert*-butyldimethylsilyl)oxy-4-(*tert*-butyldimethylsilyl)oxymethylthietane (23) : The reaction of mercaptan (**22**) (248 mg, 0.565 mmol) and *dl*-camphorsulfonic acid (30 mg) in anhydrous benzene (25 mL), was carried out in the same manner described for **6**. The reaction completed in 1 h. Purification was performed by silica gel column chromatography eluted with 10% EtOAc in hexane to give **22** (106 mg) in 48% yield. **23** ; Oil, $[\alpha]_D$ -47.7° (*c* 1.0, $CHCl_3$), Rf=0.48 (2.5 % EtOAc in hexane). ^1H NMR ($CDCl_3$) δ 5.01 (1H, d, *J*=5.8Hz), 4.30 (1H, dd, *J*=7.0 and 5.8 Hz), 3.88 (1H, dd, *J*=11.0 and 4.7 Hz), 3.73 (1H, dd, *J*=11.0 and 6.6 Hz), 3.56 (1H, dq, *J*=9.5 and 7.0 Hz), 3.47 (1H, dq, *J*=9.5 and 7.0 Hz), 3.25 (1H, ddd, *J*=7.0, 6.6 and 4.7 Hz), 1.21 (3H, t, *J*=7.0 Hz), 0.89 (9H, s), 0.88 (9H, S), 0.08 (3H, s), 0.07(3H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR ($CDCl_3$) δ 86.9, 76.7, 65.6, 65.5, 46.6, 25.9, 25.6, 18.3, 17.9, 14.7, -4.7, -4.9, -5.1, -5.3; MS (EI) *m/z* (rel. intensity) 335 (M^+-57, 25), 301 (40), 289 (8), 245 (base); HRMS (FAB) *m/z* 393 (M^++1). HRMS (FAB) Anal. Calcd for $C_{18}H_{41}O_3SSi_2$: 393.2315. Found: 393.2303

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