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Novel synthesis of 5-thio-hexopyranoside: preparation of 5-thio-D- and L-glucose and 1,6-anhydro-5-thio-L- and D-altrose

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This paper is dedicated to Professor K. C. Nicolaou in honor of his receipt of the 2003 Tetrahedron Prize

Abstract—Asymmetric synthesis of both D- and L-isomers of 5-thioglucose and 1,6-anhydro-5-thioaltrose are described. The key intermediates, L- and D-threose diethylacetal derivatives, were derived by chemical transformation from D-xylose or D-arabinose and by Sharpless asymmetric dihydroxylation from γ-hydroxycrotylaldehyde diethylacetal. They transformed to γ-thiiranyl diethylacetal via *trans*-2,3-epoxy alcohol in seven steps. Acetic acid-promoted cyclization of γ-thiiranyl diethylacetal gave 5-thiopyranoside. Removal of the protected groups under the acidic conditions afforded 5-thio-D- and L-glucose and 1,6-anhydro-5-thio-L- and D-altrose, respectively.

1. Introduction

Thiosugar in which the ring oxygen atom is replaced with a sulfur atom in hexopyranose, was first prepared by Adley and Owen in 1961.[1] Since then, it has been developed by Whistler,[2] Hughes,[3] Hashimoto,[4] and others.[5] The biological interest in thiosugars has expanded to studies on diabetes, enzyme inhibitor, anti-viral and anti-tumor activities.[6] No thiosugars have been found in nature except for 5-thio-D-mannose, which was isolated from a marine sponge,[7] and 5-thio-hexopyranoses have so far been obtained by transformation of natural sugars. For the synthesis of 5-thio-D-hexopyranose, sulfur functionality located on the (*R*)-chiral center at the 5-position was introduced by a stereospecific substitution of the 5-hydroxy group in natural sugar. Namely, the hydroxy group was substituted by a sulfur group with net retention of the configuration by double inversion of the original (*R*)-hydroxycarbon center. The other chiral hydroxycarbon centers were used from those present in the original sugar. For example, 5-thio-D-glucose was derived from D-glucose.[8] Therefore, the synthesis of 5-thiopyranose is depended on the availability and the stereochemistry of natural sugar sources. Due to a lack of a general and flexible approach for the synthesis of 5-thio-D-hexopyranose and its L-isomer, we have started study on their syntheses from an acyclic precursor, and are planning to construct a library of optically pure 5-thio-D- and L-hexopyranoses. In this paper,

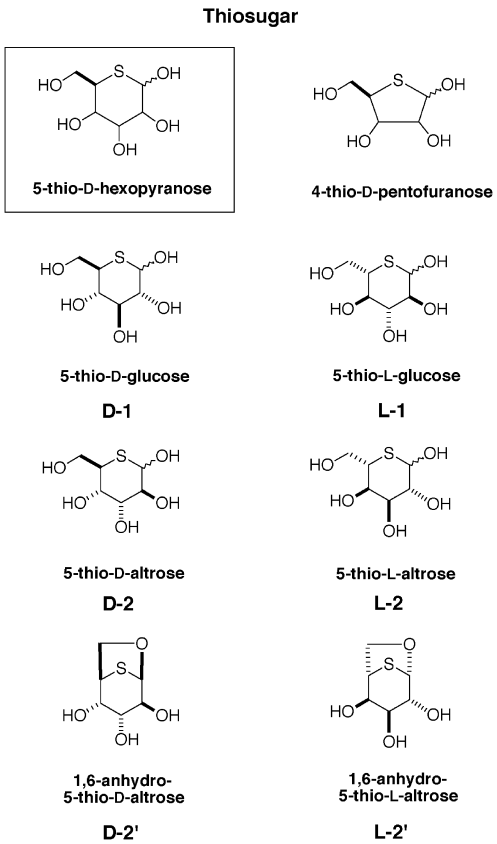

Figure 1.

Keywords: stereoselective synthesis; thiosugar; D- and L-5-thio-hexopyranoside; asymmetric dihydroxylation.

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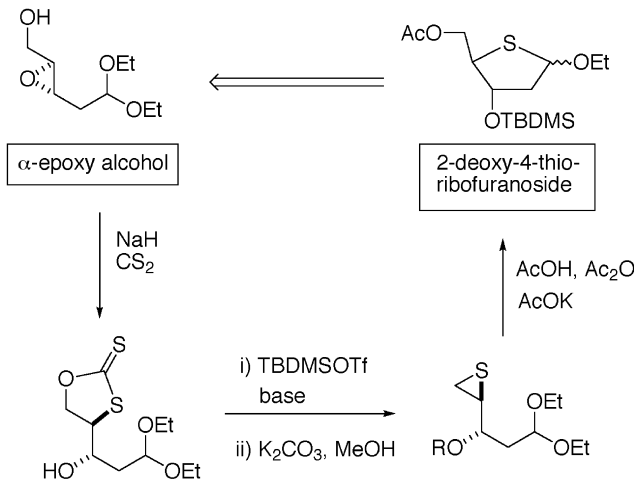
we report the asymmetric syntheses of D- and L-isomers of 5-thioglucose, **D-1** and **L-1**, and 1,6-anhydro-5-thioaltrose, **D-2′** and **L-2′**, in Figure 1.

2. Results and discussion

2.1. Synthetic plan

Our previous asymmetric synthesis of 2-deoxy-4-thio-D-ribofuranoside is shown in Scheme 1, in which stereospecific conversion of the optically active *trans*-α-2,3-epoxy alcohol to 2-deoxy-4-thio-D-ribose was accomplished in four steps.[9] In this synthesis, it should be noted that *trans*-α-2,3-epoxy alcohol gave 4-thio-D- while *trans*-β-2,3-epoxy alcohol gave 4-thio-L-furanoside.[10] Based on these results, we have planned for the syntheses of all the stereoisomers for 5-thio-glucose (**1**) and altrose (**2**), the strategy of which is outlined in Schemes 2 and 3.



Scheme 1.

Enantiomeric *trans* allyl alcohols have been chosen as potential precursors for the synthesis. It is expected that both 5-thio-D-glucose (**D-1**) and 5-thio-L-altrose (**L-2**) will be derived from the *trans* allyl alcohol via the α- and β-2,3-epoxy alcohols, and that 5-thio-L-glucose (**L-1**) and 5-thio-D-altrose (**D-2**) will be derived from the enantiomeric isomer of the *trans* allyl alcohol. As shown in Scheme 3, these allyl alcohols will be prepared by a two-carbon extension of L- and D-threose derivatives. The dihydroxy chiral carbon centers of these threoses may either be brought from those present in D-xylose and D-arabinose or be introduced by Sharpless asymmetric dihydroxylation of *trans*-alkene.

2.2. An approach from a chiral pool

As shown in Scheme 4, the chiral pool approach was started from D-xylose. Methyl 5-deoxy-5-iodo-D-xylofuranoside (**5**)[11] can be obtained in 55% yield from D-xylose in the following three steps; (i) methyl glycosidation in acidic methanol, (ii) tosylation with TsCl, and (iii) replacement of the tosylate with NaI. Silylation of **5** with TBDMSOTf in the presence of pyridine gave **6** in 86% yield. Treatment of **6** with activated zinc powder in a mixture of hot acetic acid and ethanol gave 4-pentenal (**7**) in 92% yield. Acetalization of **7** was performed by treating with triethyl orthoformate in the presence of BF_3 etherate to give **8** in quantitative yield. Ozonolysis of **8** and successive Horner–Emmons reaction with sodium triethyl phosphonoacetate gave α,β-unsaturated ester (**9**) in 61% yield in two steps. Reduction of α,β-unsaturated ester with DIBAL-H afforded *trans* allyl alcohol (**10**) quantitatively.

The preparation of the corresponding enantiomer **10′** started from D-arabinose. The same four steps from D-arabinose as those described for the synthesis of **6** afforded **14** in 46% yield. Reductive opening of the furanose ring for **14** with zinc powder and acetic acid gave **7′** in 92% yield. Exactly the same reaction sequence from **7′** as that described for **10** gave **10′** in a similar yield in four steps.

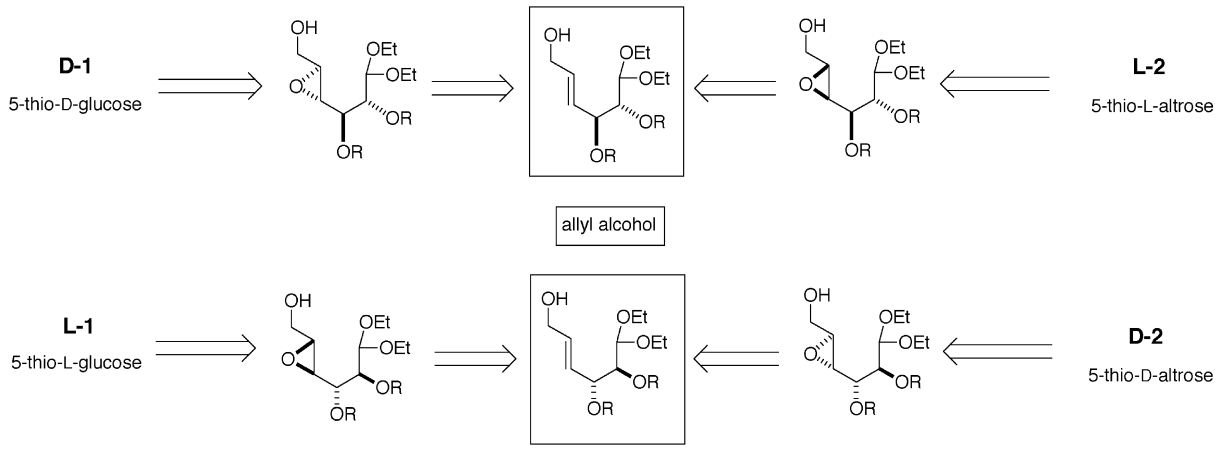
2.3. An approach by asymmetric reaction

This approach is outlined in Scheme 5. Protection of γ-hydroxycrotylaldehyde diethylacetal (**15**)[12] with benzoyl chloride gave benzoate (**16**) in 91% yield. Dihydroxylation of **16** using ADmix-α[13] proceeded stereospecifically over 95% e.e. to give β-dihydroxy isomer (**17**) in 59% yield. Protection of diol as a *tert*-butyldimethylsilyl ether and deprotection of the benzoate ester provided **19** in 87% yield in two steps. Tetrapropylammonium perruthenate (TPAP) oxidation gave aldehyde in 94% yield, and the aldehyde was then subjected to Horner–Emmons reaction to give **9** in 81% yield. Reduction of α,β-unsaturated ester with DIBAL-H gave **10** as the same reaction described above in Section 2.2.

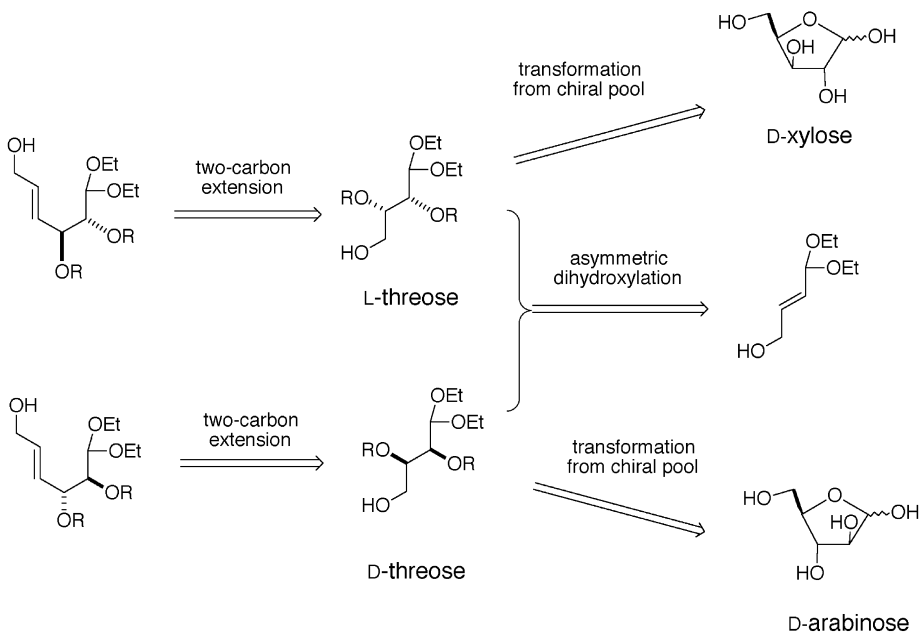
2.4. Epoxidation and cyclic xanthate formation

The stereochemical course in epoxidation of this allyl alcohol is a key for dividing a route to D- or L-sugar. As shown in Scheme 2, a *trans*-α-2,3-epoxy alcohol will give 5-thio-D-pyranose, while a *trans*-β-2,3-epoxy alcohol will give 5-thio-L-pyranose. We have examined a number of epoxidation conditions for **10**.[14] Oxidation with *m*CPBA gave a 1:1 ratio of inseparable diastereomeric epoxides, **20**α and **20**β, in 85–95% yield. Unfortunately, Sharpless asymmetric epoxidation gave disappointing results due to a poor reactivity and a formation of unknown products. $VO(acac)_2$-catalyzed oxidation[15] with *t*-BuOOH gave a single diastereomer in 70% yield, which was later identified to be **20**β. However, none of the oxidation conditions gave a satisfactory result in terms of favorable formation of α-2,3-epoxy alcohol (**20**α). Pure **20**α and **20**β were isolated by the following steps. Namely, after a mixture of **20**α and **20**β led to benzyloxycarbonates, they became separable. Hydrogenolysis of each carbonate afforded pure **20**α and **20**β in two steps in 18 and 26% yields, respectively.

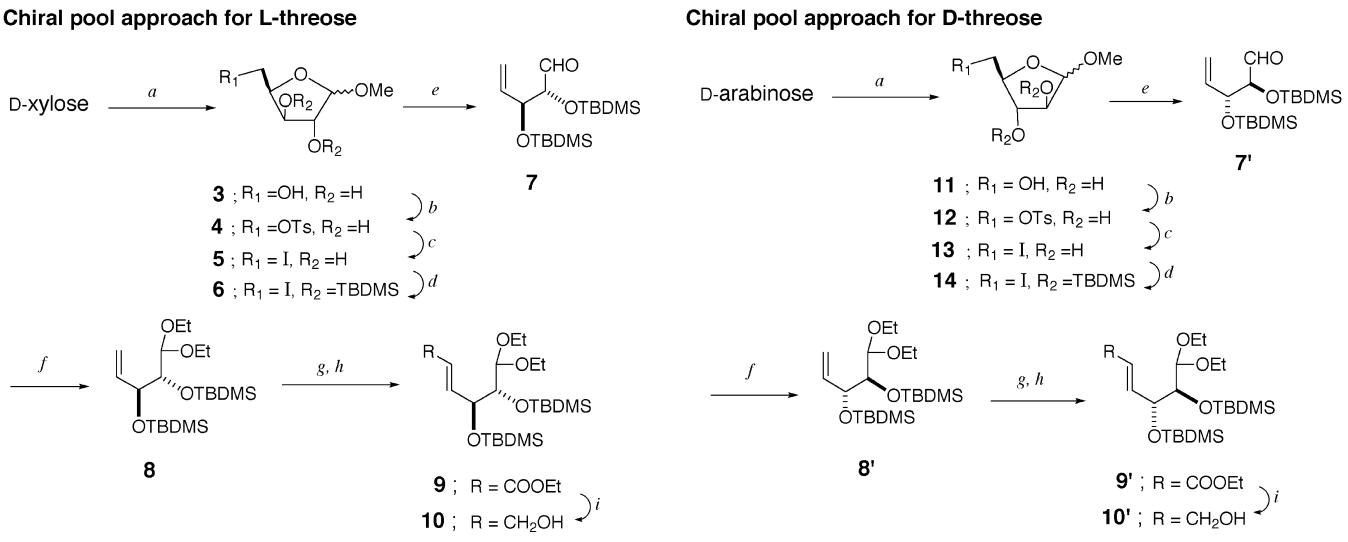
A 1:1 mixture of **20**α and **20**β obtained by the *m*CPBA oxidation, was treated with carbon disulfide in the presence of NaH resulting in a ring formation of hydroxy cyclic xanthate[16] to give **21** in 82% yield. After acetylation of the hydroxy group, diastereomers **22** and **23** became separable by silica gel column chromatography. A less-polar isomer,



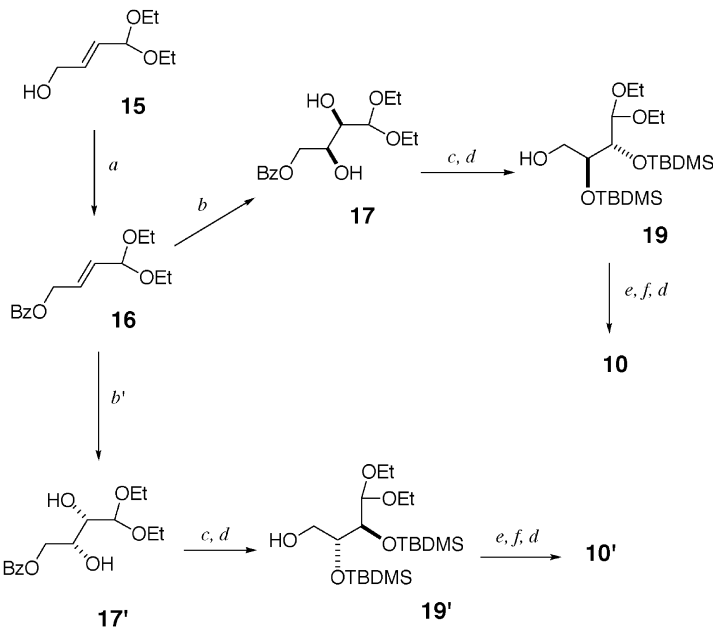
Scheme 2. Retro-synthetic plan for 5-thio-D- and L-glucose and altrose.



Scheme 3. Precursors in the retro-synthesis for 5-thio-D- and L-glucose and altrose.



Scheme 4. *Reagents and conditions*; *a*, HCl (gas), MeOH, rt; *b*, TsCl, pyrdine, rt; *c*, NaI, DMF, 110°C; *d*, TBDMSOTf, pyridine, CH_2Cl_2, rt; *e*, Zn, AcOH, EtOH, reflux; *f*, $CH(OEt)_3$, BF_3 etherate, reflux; *g*, Ozone, CH_2Cl_2 then Me_2S; *h*, NaH, $EtOOCCH_2PO(OEt)_2$, THF, rt; *i*, DIBAL-H, CH_2Cl_2, −78°C.



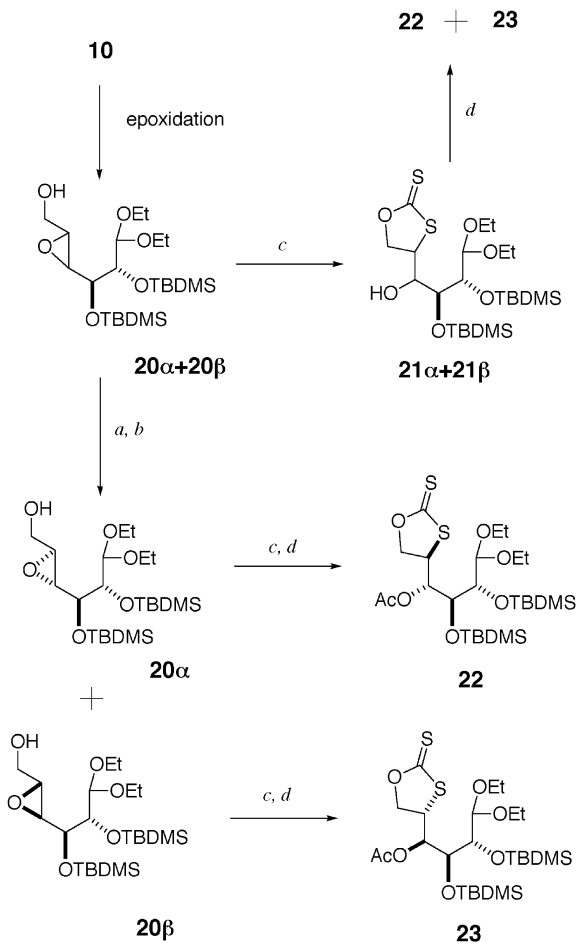
Scheme 5. *Reagents and conditions*; *a*, BzCl, pyridine, CH_2Cl_2, rt; *b*, ADmix-α, *t*-BuOH:H_2O (1:1), 0°C; *b'*, ADmix-β, *t*-BuOH:H_2O (1:1), 0°C; *c*, TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt; *d*, DIBAL-H, CH_2Cl_2, −78°C; *e*, TPAP, NMO, MS 4A, CH_2Cl_2, rt; *f*, NaH, $EtOOCCH_2PO(OEt)_2$, THF, rt.

which was obtained in 46% yield, was found later to be **22** affording ethyl 5-thio-D-glucopyranoside. Another polar isomer, obtained in 39% yield, was **23** affording ethyl 5-thio-L-altropyranoside. Independently, cyclic xanthate formation of **20**α and the following acetylation gave **22** in 74% yield in two steps. By the same two steps, **20**β gave **23** in 72% yield (Scheme 6).

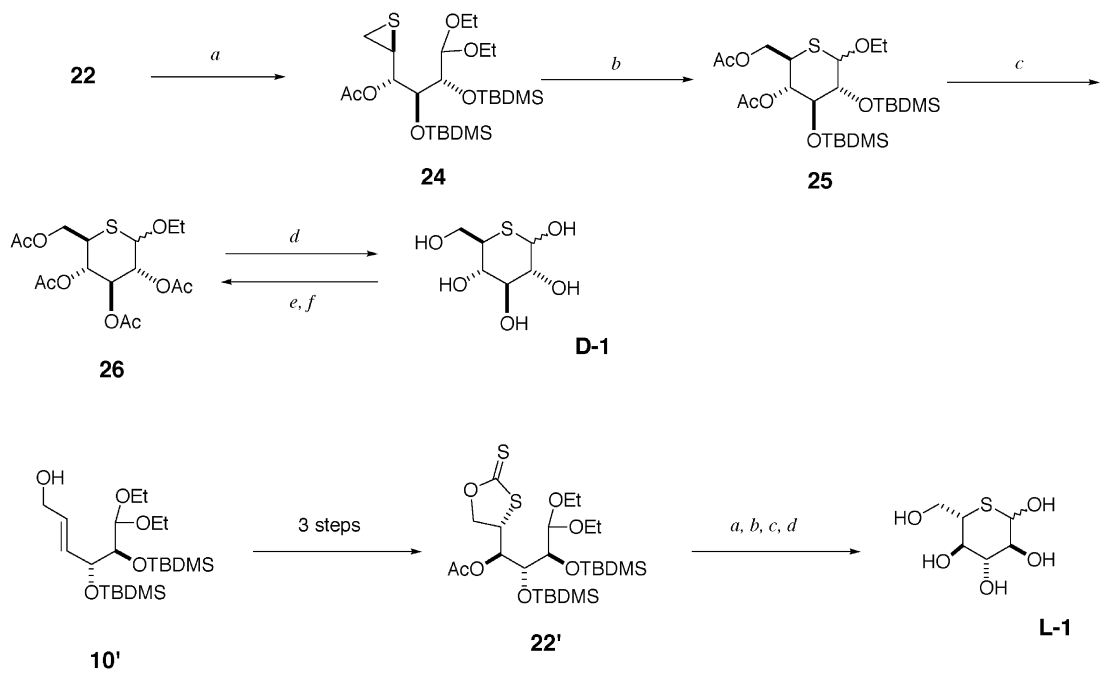
2.5. Synthesis of 5-thioglucose

Thiirane (**24**) was formed in 94% yield by potassium carbonate promoted methanolysis of **22**. The ring contraction reaction[17] was completed within 3 min at room temperature chemoselectively without a methanolysis of the acetate. Acid-promoted ring formation of ethyl 5-thioglucopyranoside was carried out by heating of the γ-thiiranyl diethylacetal (**24**) with a mixture of acetic anhydride and potassium acetate in acetic acid at 110°C. Compound **25** was obtained in 54% as a 1:1 ratio of an anomeric mixture. Deprotection of the two TBDMS groups with TBAF followed by acetylation with acetic anhydride gave tetraacetate (**26**) in 69% yield in two steps. Compound **26** was identified in comparison of its spectroscopic data with those derived from (+)-5-thio-D-glucose.[18] Thus, treatment of commercial **D-1** in ethanol saturated with HCl gas, gave ethyl glycoside, which was acetylated with acetic anhydride in pyridine to give **26** in 53% yield in two steps. Both materials were clearly identical.

All of the protecting groups of **26**, including acetate and ethyl glycoside, were hydrolyzed by heating in hot aq. HCl solution. After the acid was removed by the treatment of basic resin, evaporation of solvents in vacuo furnished the synthesis of pure 5-thio-D-glucose (**D-1**) in quantitative yield. All the spectroscopic and physical data, including mp, proton NMR, and specific rotation, were identical to those of the authentic 5-thio-D-glucose.[19]



Scheme 6. *Reagents and conditions*; *a*, $ClCOOCH_2Ph$, iPr_2NEt, CH_2Cl_2, rt, then chromatographic separation; *b*, cat. Pd–C (10%), H_2, EtOH, rt; *c*, NaH, cat. MeOH, CS_2, THF, −30°C; *d*, Ac_2O, pyridine, rt.

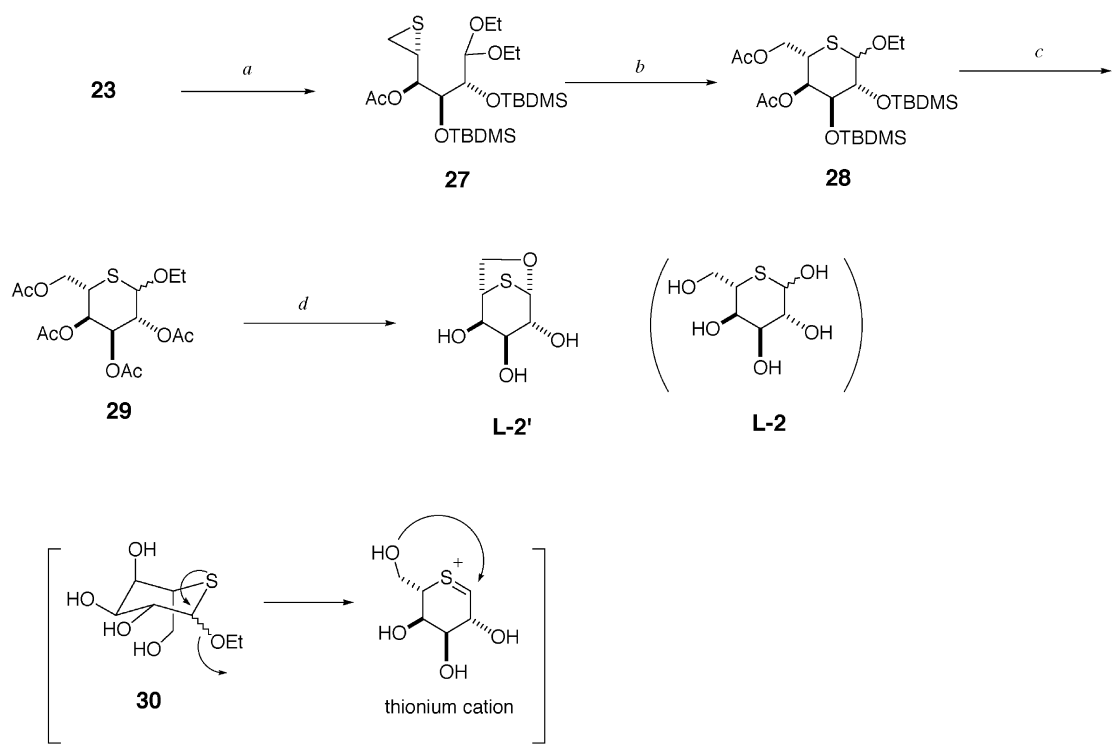


Scheme 7. *Reagents and conditions*; *a*, K_2CO_3, MeOH, rt, 3 min; *b*, AcOK, Ac_2O, AcOH, 110°C, 4 h; *c*, (i) TBAF, THF rt, (ii) Ac_2O, pyridine, rt; *d*, aq. HCl (3.4 M): THF (1:1), reflux; *e*, HCl gas, EtOH, rt; *f*, Ac_2O, pyridine, rt.

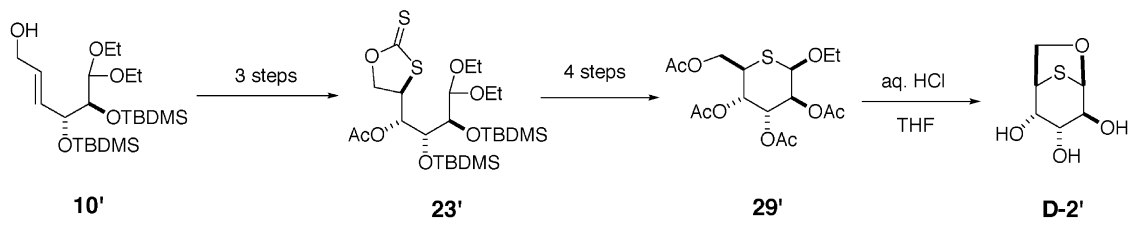
In the same manner, 5-thio-L-glucose (**L-1**) was obtained from **10′** in eight steps via cyclic xanthate **22′**. All the intermediates were in accordance with those for the synthesis of D-series except a sign of the specific rotations (Scheme 7).

2.6. Synthesis of 5-thioaltrose

On the other hand, compounds **23** and **23′** were attempted to lead to 5-thio-L-altrose (**L-2**) and D-altrose (**D-2**)[20] as shown in Schemes 8 and 9. The reactions are quite similar to those



Scheme 8. *Reagents and conditions*; *a*, K_2CO_3, MeOH, rt, 3 min; *b*, AcOK, Ac_2O, AcOH, 110°C, 4 h; *c*, (i) TBAF, THF, rt, (ii) Ac_2O, pyridine, rt; *d*, aq. HCl (3.4 M): THF (1:1), reflux.



Scheme 9.

for the synthesis for **D-1**. The thiirane formation of **23** proceeded well to give **27** in 91% yield. Cyclization of **27** to 5-thiopyranoside was carried out in a hot acetic acid in the presence of potassium acetate and acetic anhydride, to give **28** in 64% yield. Changing the *O*-silyl protecting group to acetate furnished the synthesis of ethyl 2,3,4,6-*O*-tetra-acetyl-5-thio-L-altropyranoside (**29**)[21] in 78% yield. However, removal of all the protecting groups under the acidic conditions gave 1,6-dehydrated 5-thio-L-altrose (**L-2′**) in 73% yield, and unexpectedly, **L-2** was not obtained at all.[22] Since Hughes reported that 6-hydroxymethyl group locates at the axial position in methyl 5-thio-β-D-altropyranoside,[21] the dehydration between 1,6-dihydroxy groups would take place quite easily under the acidic conditions. Thus, thionium cation could be produced from an intermediary ethyl glycoside (**30**), and a subsequent attack of 6-hydroxy group to the thionium cation from an axial direction resulted the 1,6-anhydro-5-thio-altrose (**L-2′**). In the same reaction sequences, 1,6-anhydro-5-thio-D-altrose (**D-2′**) was also obtained from **10′** via **23′**.

3. Conclusion

The asymmetric syntheses of 5-thio-D- and L-glucose, and 1,6-anhydro-5-thio-D- and L-altrose were accomplished in enantiomerically pure forms. Both the chiral pool approach from D-xylose or D-arabinose and the asymmetric approach using Sharpless asymmetric dihydroxylation worked effectively. The use of this methodology will enable the synthesis of other kinds of 5-thio-hexopyranosides, and that will bring a great contribution to pseudo sugar chemistry in carbohydrate research as well as to molecular recognition study in cell surface science.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 or 400 MHz and at 75 or 100 MHz, respectively. Melting points were obtained on a melting point apparatus and were uncorrected. Mass spectra were recorded using electron impact (EI) ionization at 70 eV. Fast atom bombardment (FAB) mass spectra were obtained using a glycerol as a matrix. Silica gel (70–230 mesh) was used for flash chromatography. Analytical thin-layer chromatography (TLC) was performed on glass pre-coated with silica gel (0.25 mm thickness). High performance liquid chromatography (HPLC) was carried out on a UV spectrophotomeric detector (254 nm) to which a 20×250 mm size column packed with silica gel was attached. All experiments were carried out under an argon atmosphere. THF and ether were dried over sodium/benzophenone ketyl, and CH_2Cl_2 was dried over P_2O_5, and they were distilled prior to use. The solvent extracts were dried over $MgSO_4$, and the solutions were evaporated under reduced pressure.

4.2. Preparation of 9 and 9′ from D-xylose and D-arabinose

4.2.1. Methyl 2,3-bis-*O-tert*-butyldimethylsilyl-5-deoxy-5-iodo-D-xylofuranoside (6). To a CH_2Cl_2 solution (40 mL) of methyl 5-deoxy-5-iodo-D-xylofuranoside (**5**)[11] (3.92 g, 14 mmol) and pyridine (9 mL) was dropped TBDMSOTf (9.46 g, 8 mL, 36 mmol) at 0°C and the mixture was stirred for 1 h at room temperature. Water was added and the mixture was extracted with EtOAc. The crude product was purified by silica gel flash chromatography eluted with 5% EtOAc in hexane to give **6** (6.16 g) in 86% yield as a 2:3 ratio of anomers. Colorless oil. R_f=0.45 (5% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (2/5H, d, *J*=3.9 Hz), 4.64 (3/5H, s), 4.34–4.22 (1H, m), 4.11 (2/5H, t, *J*=4.9 Hz), 4.00–3.84 (8/5H, m), 3.36 (6/5H, s), 3.29 (9/5H, s), 3.34–3.18 (2H, m), 0.82 (27/5H, s), 0.81 (27/5H, s), 0.80 (18/5H, s), 0.78 (18/5H, s), 0.03 (6/5H, s), 0.02 (12/5H, s), 0.01 (3H, s X2), 0.00 (18/5H, s), −0.07 (9/5H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.8, 103.6, 83.5, 82.7, 79.1, 78.8, 78.3, 77.6, 56.4, 55.9, 26.3, 26.2, 26.1, 26.1, 18.7, 18.4, 18.3, 18.3, 5.3, 4.8, −2.5, −3.9, −4.0, −4.1(×2), −4.2, −4.3, −4.4. MS (FAB) *m/z*: 525 $(M+Na)^+$. HR-MS (FAB) *m/z*: 525.1324 (Calcd for $C_{18}H_{39}IO_4Si_2Na$: 525.1328).

4.2.2. Methyl 2,3-bis-*O-tert*-butyldimethylsilyl-5-deoxy-5-iodo-D-arbinofuranoside (14). To a CH_2Cl_2 solution (50 mL) of methyl 5-deoxy-5-iodo-D-arabinofuranoside (**13**)[11] (5.6 g, 20.4 mmol) and pyridine (13.2 mL) was dropped TBDMSOTf (13.5 g, 11.7 mL, 51.1 mmol) at 0°C and the mixture was stirred for 1 h at room temperature. Water was added and the mixture was extracted with EtOAc. The crude product was purified by silica gel flash chromatography eluted with 5% EtOAc in hexane to give **14** (7.5 g) in 73% yield as a 1:4 ratio of anomers. Colorless oil. R_f=0.45 (5% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (4/5H, d, *J*=1.5 Hz), 4.72 (1/5H, d, *J*=3.7 Hz), 4.06 (1/5H, m), 4.04 (4/5H, dd, *J*=3.5, 1.5 Hz), 3.85 (1/5H, m), 3.85 (4/5H, dd, *J*=6.1, 3.5 Hz), 3.80–3.71 (1H, m), 3.45 (1/5H, m), 3.44 (3/5H, s), 3.43 (4/5H, dd, *J*=10.6, 4.8 Hz), 3.36 (12/5H, s), 3.25 (4/5H, dd, *J*=10.6, 5.5 Hz), 3.23 (1/5H, m), 0.90 (9H, s), 0.88 (36/5H, s), 0.84 (9/5H, s), 0.12 (3H, s), 0.11 (3H, s), 0.09 (3H, s), 0.08 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.6, 103.4,

84.1, 82.7, 82.5, 81.8, 80.0, 79.6, 55.6, 55.1, 25.8, 25.8, 25.7, 25.6, 18.2 (×2), 17.8, 17.8, 8.8, 7.1, −4.0, −4.1, −4.2, −4.3, −4.3, −4.4, −4.6, −4.9. MS (FAB) *m/z*: 525 $(M+Na)^+$. HR-MS (FAB) *m/z*: 525.1334 (Calcd for $C_{18}H_{39}IO_4Si_2Na$: 525.1329).

4.2.3. (2*R*,3*S*)-2,3-Bis(*tert*-butyldimethylsilyloxy)-4-pentenal (7) and its enantiomer (7′). A suspension of activated zinc powder (2.0 g, 30.1 mmol) and **6** (5.05 g, 10 mmol) in ethanol (25 mL) and acetic acid (5.1 mL, 85.4 mmol) was heated at 110°C for 30 min with stirring. After cooling, solid was removed by filtration and extracted with ether and washed with sodium bicarbonate. The extract was washed with water and brine. The crude product was purified by flash chromatography on silica gel eluted with 50% CH_2Cl_2 in hexane. Compound **7** (3.2 g) was obtained in 92% yield. Colorless oil. R_f=0.45 (5% EtOAc in hexane). $[\alpha]_{23}^{D}$=−47 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (1H, s), 6.0 (1H, ddd, *J*=17.3, 10.4, 5.0 Hz), 5.29 (1H, dt, *J*=17.3, 1.7 Hz), 5.05 (1H, dt, *J*=10.4, 1.7 Hz), 4.37 (1H, tt, *J*=5.0, 1.5 Hz), 3.99 (1H, dd, *J*=5.0, 1.2 Hz), 0.91 (9H, s), 0.90 (9H, s), 0.07 (6H, s), 0.05 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 136.4, 116.2, 80.2, 74.9, 25.7 (×2), 18.4, 18.1, −4.5, −4.6, −5.0, −5.1. IR (film) cm^{-1}: 1739. MS (CI) *m/z*: 345 (M+1, 18). HR-MS (CI) *m/z*: 345.2286 (Calcd for $C_{17}H_{37}O_3Si_2$: 345.2281).

The enantiomer **7′** was obtained in 92% yield from arabinoside **14** (6.0 g) by the same experimental operation described for **7**. The physical and spectroscopic data are exactly the same except a positive sign in specific rotation.

4.2.4. (2*R*,3*S*)-2,3-Bis(*tert*-butyldimethylsilyloxy)-4-pentenal diethylacetal (8) and its enantiomer (8′). To a mixture of **7** (3.2 g, 9.3 mmol) and triethyl orthoformate (46 mL) was added dropwise borontrifluoride etherate (1.32 g, 9.3 mmol) on an ice bath. The mixture was refluxed for 30 min. Saturated $NaHCO_3$ solution was added to the mixture and extracted with EtOAc. The residual oil of the extract was purified by flash chromatography on silica gel eluted with 50% CH_2Cl_2 in hexane to give **8** (3.8 g) in quantitative yield. Colorless oil. R_f=0.65 (CH_2Cl_2). $[\alpha]_{22}^{D}$=−17 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.9 (1H, ddd, *J*=17.2, 10.5, 6.6 Hz), 5.14 (1H, dt, *J*=17.2, 1.5 Hz), 5.05 (1H, dt, *J*=10.5, 1.5 Hz), 4.38 (1H, d, *J*=6.2 Hz), 4.21 (1H, dt, *J*=6.6, 1.3 Hz), 3.70–3.40 (5H, m), 1.17 (3H, t, *J*=7.0 Hz), 1.16 (3H, t, *J*=7.0 Hz), 0.86 (18H, s), 0.04 (3H, s), 0.01 (3H, s), 0.00 (3H, s), −0.01 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 114.8, 102.5, 76.8, 75.0, 63.4, 62.5, 25.9, 25.8, 18.3 (×2), 15.4, 15.2, −3.9, −4.4 (×2), −4.8. MS (FAB) *m/z*: 441 $(M+Na)^+$. HR-MS (FAB) *m/z*: 441.2828 (Calcd for $C_{21}H_{46}O_4Si_2Na$: 441.2824). Compound **8′** was also prepared in 80% yield from **7′** (3.8 g) by the same method described for **8**. The physical and spectroscopic data are exactly the same except a positive sign in specific rotation.

4.2.5. Ethyl (*E*,4*S*,5*R*)-4,5-bis(*tert*-butyldimethylsilyloxy)-6,6-diethoxy-2-hexenoate (9). Ozone was bubbled into a solution of **8** (2.5 g, 6 mmol) in CH_2Cl_2 (17 mL) at −78°C. After the reaction was completed, which was monitored by TLC, dimethyl sulfide (0.5 mL) was added and the mixture was allowed to warm up to room temperature. Then the mixture was diluted with EtOAc and washed with water, brine. The residual oil was purified by chromatography on silica gel eluted by 20% EtOAc in hexane to give crude aldehyde, which was used directly for the next reaction. To a solution of sodium salt of triethyl phosphonoacetate prepared by NaH (60% in mineral oil, 551 mg, 13.8 mmol) and triethyl phosphonoacetate (3.3 mL, 16.5 mmol) at 0°C in THF, was added the aldehyde in THF (6 mL) and the mixture was stirred for 15 min at room temperature. Sat. ammonium chloride was added and extracted with EtOAc. The residue of the extract was purified by flash chromatography on silica gel to give **9** (1.8 g) in 61% yield. Colorless oil. R_f=0.53 (10% EtOAc in hexane). $[\alpha]_{22}^{D}$=−12 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (1H, dd, *J*=15.7, 5.0 Hz), 5.93 (1H, dd, *J*=15.7, 1.7 Hz), 4.38–4.35 (2H, m), 4.15 (2H, ddd, *J*=14.3, 7.1, 2.4 Hz), 3.69–3.38 (5H, m), 1.25 (3H, t, *J*=7.0 Hz), 1.16 (3H, t, *J*=7.0 Hz), 1.13 (3H, t, *J*=7.0 Hz), 0.88 (9H, s), 0.86 (9H, s), 0.05 (3H, s), 0.02 (3H, s), 0.00 (3H, s), −0.01 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 149.7, 120.8, 102.3, 76.7, 73.6, 64.1, 63.0, 60.6, 26.3, 26.2, 18.6, 18.5, 15.7, 15.5, 14.7, −3.7, −3.8, −4.3, −4.5. IR ($CHCl_3$) cm^{-1}: 1724. MS (FAB) *m/z*: 513 $(M+Na)^+$. HR-MS (FAB) *m/z*: 513.3048 (Calcd for $C_{24}H_{50}O_6Si_2Na$: 513.3044). Compound **9′** was also prepared from **8′** by the same method described for **9**.

4.2.6. (*E*,4*S*,5*R*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-6,6-diethoxy-2-hexenol (10). To a stirred solution of **9** (1.7 g, 3.5 mmol) in CH_2Cl_2 was dropped DIBAL-H (7.4 mL in 0.93 M hexane solution, 7.0 mmol) at −78°C and the reaction was continued for 30 min at the same temperature. Sat. NH_4Cl was added and the mixture was vigorously stirred for 10 min. Solid was filtered through celite pad and the filtrate was extracted with ether. The crude product was purified by silica gel flash chromatography eluted with 20% EtOAc in hexane to give **10** (1.54 g) in quantitative yield. Colorless oil. R_f=0.45 (20% EtOAc in hexane). $[\alpha]_{21}^{D}$=−9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (1H, dd, *J*=15.8, 5.8 Hz), 5.75 (1H, dt, *J*=15.8, 4.6 Hz), 4.40 (1H, d, *J*=6.1 Hz), 4.30 (1H, m), 4.12 (2H, d, *J*=4.6 Hz), 3.72–3.40 (5H, m), 1.18 (3H, t, *J*=7.0 Hz), 1.17 (3H, t, *J*=7.0 Hz), 0.87 (18H, s), 0.06 (3H, s), 0.02 (3H, s), 0.00 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0, 129.2, 102.3, 76.7, 73.7, 63.5, 63.3, 62.5, 25.9, 25.8, 18.2, 18.0, 15.3, 15.2, −3.8, −4.0, −4.5, −4.8. IR (film) cm^{-1}: 3413. MS (FAB) *m/z*: 471 $(M+Na)^+$. HR-MS (FAB) *m/z*: 471.2933 (Calcd for $C_{22}H_{48}O_5Si_2Na$: 471.2928). Compound **10′** was also prepared from **9′** by the same method described for **10**.

4.3. Preparation of 9 by asymmetric dihydroxylation approach

4.3.1. (*E*)-4-Benzoyloxy-2-butenal diethylacetal (16). To a CH_2Cl_2 solution (40 mL) of **15** (2.0 g, 12.5 mmol) and pyridine (2 g, 25 mmol) was added benzoyl chloride at 0°C. The mixture was stirred for 30 min at room temperature, poured into water, and extracted with EtOAc. The extract was washed with water, brine. The residue was purified by flash chromatography on silica gel eluted with 20% EtOAc in hexane to give **16** (3.0 g) in 91% yield. Colorless oil. R_f=0.56 (20% EtOAc in hexane). ^{1}H NMR (300 MHz, C_6D_6) δ 8.20–8.14 (2H, m), 7.22–7.05 (3H, m), 6.03 (1H,

dt, J=15.6, 5.5 Hz), 5.90 (1H, dd, J=15.6, 4.2 Hz), 4.91 (1H, d, J=4.2 Hz), 4.70 (2H, d, J=5.5 Hz), 3.60 (2H, dq, J=9.5, 7.1 Hz), 3.40 (2H, dq, J=9.5, 7.1 Hz), 1.16 (6H, t, J=7.1 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 165.8, 132.8, 131.8, 130.7, 129.9, 128.5, 127.9, 100.3, 64.3, 60.6 (×2), 15.4 (×2). IR (film) cm^{-1}: 1720. MS (FAB) *m/z*: 287 (M+Na)$^+$. HR-MS (FAB) *m/z*: 287.1265 (Calcd for $C_{15}H_{20}O_4Na$: 287.1260).

4.3.2. 4-*O*-Benzoyl-L-threose diethylacetal (17). ADmix-α (3.16 g) was added to a solution of *t*-BuOH (8 mL) and water (8 mL) and the mixture was stirred for 5 min at room temperature and for additional 10 min at 0°C. Then, a solution of **16** (600 mg, 226 mmol) in a mixed solvent of *t*-BuOH (4 mL), water (4 mL) and THF (6 mL) was added into the former mixture, and the whole mixture was stirred for 12 h at 0°C. Then, powdered Na_2SO_3 was added and the mixture was extracted with EtOAc for 3 times. The crude product was purified by flash chromatography on silica gel eluted with 50% EtOAc in hexane to give **17** (402 mg) in 59% yield. Colorless oil. R_f=0.45 (40% EtOAc in hexane). $[\alpha]_{24}^{D}$=5 (*c* 1.25, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6) δ 8.16–8.12 (2H, m), 7.16–6.90 (3H, m), 4.64 (1H, dd, J=12.0, 7.0 Hz), 4.50 (1H, d, J=5.9 Hz), 4.54 (1H, dd, J=12.0, 5.5 Hz), 4.35 (1H, m), 3.67 (1H, d, J=5.9 Hz), 3.55–3.45 (2H, m), 3.48–3.15 (2H, m), 2.74 (1H, brs), 2.54 (1H, brs), 0.98 (6H, s, J=7.0 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 166.4, 132.8, 131.5, 130.0, 128.4, 103.5, 71.3, 68.8, 66.5, 64.5, 63.2, 15.4 (×2). IR (film) cm^{-1}: 3458, 1720. MS (FAB) *m/z*: 321 (M+Na)$^+$. HR-MS (FAB) *m/z*: 321.1310 (Calcd for $C_{15}H_{22}O_6Na$: 321.0306).

4.3.3. 4-*O*-Benzoyl-2,3-bis-*O*-(*tert*-butyldimethylsilyl)-L-threose diethylacetal (18). To a stirred solution of **17** (228 mg, 0.76 mmol) and 2,6-lutidine (0.72 mL, 6.1 mmol) in CH_2Cl_2 (7.6 mL) was added TBDMSOTf (0.61 g, 2.3 mmol) at room temperature. The mixture was stirred for 30 min and quenched with water. The mixture was extracted with EtOAc and washed with water and brine. The crude product was purified by silica gel flash chromatography eluted with 10% EtOAc in hexane to give **18** (384 mg) in 95% yield. Colorless oil. R_f=0.50 (10% EtOAc in hexane). $[\alpha]_{22}^{D}$=−21 (*c* 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6) δ 8.21–8.16 (2H, m), 7.15–7.00 (3H, m), 4.72 (1H, dd, J=11.0, 7.0 Hz), 4.70 (1H, d, J=5.7 Hz), 4.64 (1H, dd, J=11.0, 5.3 Hz), 4.43 (1H, ddd, J=7.0, 5.3, 2.6 Hz), 4.00 (1H, dd, J=5.7, 2.6 Hz), 3.64 (1H, dq, J=9.4, 7.0 Hz), 3.68–3.60 (3H, m), 1.14 (3H, t, J=7.0 Hz), 1.10 (3H, t, J=7.0 Hz), 1.06 (9H, s), 0.99 (9H, s), 0.25 (3H, s), 0.20 (3H, s), 0.18 (3H, s), 0.17 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 166.2, 132.8, 130.9, 129.8, 128.5, 101.8, 74.0, 71.7, 66.5, 63.4, 61.2, 26.2, 26.0, 18.6, 18.3, 15.6, 15.3, −3.6, −4.1, −4.6, −4.7. IR (film) cm^{-1}: 1716. MS (FAB) *m/z*: 549 (M+Na)$^+$. HR-MS (FAB) *m/z*: 549.3038 (Calcd for $C_{27}H_{50}O_6Si_2Na$: 549.3032).

4.3.4. 2,3-Bis-*O*-(*tert*-butyldimethylsilyl)-L-threose diethylacetal (19). DIBAL-H (0.93 M in hexane solution, 1.88 mL) was dropped to **18** (384 mg, 0.73 mmol) in CH_2Cl_2 (7.4 mL) at −78°C and the mixture was stirred for 30 min at the same temperature. Sat. NH_4Cl was added and the mixture was vigorously agitated. The precipitate was filtered through celite pad and the filtrate was extracted with ether. The crude product was purified by flash chromatography on silica gel eluted with 10% EtOAc in hexane to give **19** (282 mg) in 92% yield. Colorless oil. R_f=0.45 (10% EtOAc in hexane). $[\alpha]_{21}^{D}$=−11 (*c* 1.23, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6) δ 4.67 (1H, d, J=4.9 Hz), 3.99 (1H, td, J=5.5, 3.1 Hz), 3.93 (1H, dd, J=4.9, 3.1 Hz), 3.77 (2H, t, J=5.5 Hz), 3.64 (1H, dq, J=9.1, 7.0 Hz), 3.53–3.40 (3H, m), 1.75 (1H, m), 1.12 (3H, t, J=7.0 Hz), 1.11 (3H, t, J=7.0 Hz), 1.04 (9H, s), 1.00 (9H, s), 0.24 (3H, s), 0.19 (3H, s), 0.15 (3H, s), 0.14 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 102.0, 74.7, 74.0, 63.9, 63.1, 61.8, 26.2, 26.1, 18.6, 18.4, 15.5, 15.3, −3.8, −4.1, −4.5, −4.6. IR (film) cm^{-1}: 3465. MS (FAB) *m/z*: 445 (M+Na)$^+$. HR-MS (FAB) *m/z*: 445.2778 (Calcd for $C_{20}H_{46}O_5Si_2Na$: 445.2775).

4.3.5. Preparation of 9 from 19. A mixture of **19** (300 mg, 0.71 mmol), *N*-methylmorpholine *N*-oxide (124 mg, 1.1 mmol) and molecular sieves 4A (50 mg) was stirred in CH_2Cl_2 (7 mL) for 10 min. To this suspension TPAP (12 mg) was added and the mixture was stirred for 1 h at room temperature. The mixture was directly charged on silica gel eluted with CH_2Cl_2 to give aldehyde (280 mg) in 94% yield. Colorless oil. R_f=0.6 (10% EtOAc in hexane). $[\alpha]_{22}^{D}$=−17 (*c* 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (1H, s), 4.39 (1H, t, J=7.1 Hz), 3.99 (1H, d, J=3.8 Hz), 3.88 (1H, d, J=3.8 Hz), 3.65–3.36 (4H, m), 1.10 (3H, t, J=7.0 Hz), 1.06 (3H, t, J=7.1 Hz), 0.82 (9H, s), 0.77 (9H, s), −0.05 (6H, s), −0.04 (3H, s), 0.00 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 101.3, 78.6, 75.2, 63.7, 62.9, 25.8, 25.7, 18.2 (×2), 15.3, 15.0, −4.2, −4.4, −5.0, −5.2. IR (film) cm^{-1}: 1736. MS (FAB) *m/z*: 443 (M+Na)$^+$. HR-MS (FAB) *m/z*: 443.2628 (Calcd for $C_{20}H_{44}O_5Si_2Na$: 443.2625). This aldehyde was treated with sodium salt of triethyl phosphonoacetate as described for the synthesis of **9** from **8**. Yield of **9** from **19** was 76% in two steps.

4.3.6. Epoxidation of 10. *With mCPBA*. To a solution of **10** (0.66 g, 1.5 mmol) in CH_2Cl_2 (5 mL) was added *m*CPBA (507 mg, 3 mmol) at room temperature by several portions. After it was stirred for 1 h, the mixture was diluted with EtOAc, washed with $Na_2S_2O_3$, $NaHCO_3$, water, and brine. The residual oil was purified by flash chromatography on silica gel eluted with 15% EtOAc in hexane to give a mixture of **20**α and **20**β (650 mg) in 95% yield.

With $VO(acac)_2$. To a mixture of **10** (230 mg, 0.51 mmol) and $VO(acac)_2$ (6.8 mg, 26 μmol) in CH_2Cl_2 (2.5 mL) was added TBHP (2.91 M solution in CH_2Cl_2 0.53 mL, 1.55 mmol) at room temperature and stirred for 1 h at room temperature. An excess of dimethyl sulfide (0.2 mL) was added and solvent was removed. The crude product was purified by flash chromatography on silica gel eluted with 15% EtOAc in hexane to give **20**β (166 mg) as a single diastereomer in 70% yield.

Isolation of pure 20α and 20β. A mixture of **20**α and **20**β (300 mg, 0.6 mmol) and diisopropylethylamine (166 mg, 1.3 mmol) in CH_2Cl_2 (3 mL) was added benzyl chlorocarbonate (132 mg, 1.3 mmol) at 0°C. The mixture was stirred for 24 h at room temperature. Sat. $NaHCO_3$ was added and the mixture was extracted with EtOAc. The extract was washed with water and brine. The crude product was

purified by flash chromatography on silica gel eluted with 5% EtOAc in hexane to give a mixture of diastereomer (298 mg) and some recovery of the starting material. The mixture was separated by HPLC; column 20 × 500 mm, silica gel, eluent; 7% EtOAc in hexane, 15 mL/min. The carbonate derived from **20**α appeared at 9.9 min was isolated in 28% yield, and that from **20**β appeared at 8.5 min in 37% yield. Hydrogenolysis of the each benzyl carbonate (0.4 mmol) was conducted in EtOH (4 mL) in the presence of 10% Pd on charcoal (13 mg) under hydrogen gave **20**α in 64% yield and **20**β in 71% yield, respectively. **20**α Colorless oil. R_f=0.45 (20% EtOAc in hexane). $[\alpha]_{22}^{D}$=−14 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6) δ 4.65 (1H, d, *J*=4.9 Hz), 3.78 (1H, dd, *J*=3.3, 2.9 Hz), 3.65–3.28 (8H, m), 2.90 (1H, m), 1.50 (1H, m), 1.15–1.05 (6H, m), 1.08 (9H, s), 1.02 (9H, s), 0.40 (3H, s), 0.24 (3H, s), 0.22 (3H, s), 0.10 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 102.3, 77.0, 75.9, 63.5, 62.9, 61.8, 58.1, 56.6, 26.2, 26.1, 18.5, 18.4, 15.5, 15.3, −3.7, −3.8, −4.7, −5.0. IR (film) cm^{-1}: 3466. MS (FAB) *m/z*: 487 $(M+Na)^+$. HR-MS (FAB) *m/z*: 487.2892 (Calcd for $C_{22}H_{48}O_6Si_2Na$: 482.2888). **20**β Colorless oil. R_f=0.45 (20% EtOAc in hexane). $[\alpha]_{20}^{D}$=−9 (*c* 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6) δ 4.70 (1H, d, *J*=5.3 Hz), 4.04 (1H, dd, *J*=5.3, 2.6 Hz), 3.92 (1H, dd, *J*=4.8, 2.6 Hz), 3.72–3.31 (7H, m), 3.10 (1H, m), 1.55 (1H, m), 1.13 (3H, t, *J*=7.1 Hz), 1.08 (3H, t, *J*=7.1 Hz), 1.06 (9H, s), 0.99 (9H, s), 0.26 (3H, s), 0.24 (3H, s), 0.13 (6H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 101.2, 75.0, 72.6, 62.4, 61.9, 61.2, 57.6, 55.9, 26.1, 25.9, 18.5, 18.4, 15.4, 15.3, −3.8, −4.0, −4.7, −5.0. IR (film) cm^{-1}: 3465. MS (FAB) *m/z*: 487 $(M+Na)^+$. HR-MS (FAB) *m/z*: 487.2892 (Calcd for $C_{22}H_{48}O_6Si_2Na$: 482.2888).

4.4. Synthesis of 5-thio-hexopyranoside

4.4.1. Transformation of *trans*-2,3-epoxy alcohol to cyclic xanthate 21. To a stirred suspension of NaH (103 mg, 60% in mineral oil, 2.6 mmol) in CS_2 (4 mL) and THF (3 mL) was added a THF (2 mL) solution of **20**α and **20**β (600 mg, 1.3 mmol) at −30°C. A small amount of methanol (0.03 mL) was then dropped, and the reaction mixture was warmed up to 0°C during 15 min. Then, the mixture was re-cooled down to −30°C, and powder of silica gel (ca. 2 g) was added by several portions. The reaction mixture was stirred for 5 min at the same temperature and diluted with ether (30 mL). The whole was passed through silica gel column and silica gel was washed with ether. The ethereal filtrates were combined and condensed. The residual oil was purified by flash chromatography on silica gel eluted with 5% EtOAc in hexane to give **21** (572 mg) in 82% yield. Independently, the same reaction of **20**α gave **21**α and that of **20**β gave **21**β, respectively. These physical and spectroscopic data are following: **21**α Colorless oil. R_f=0.65 (20% EtOAc in hexane). $[\alpha]_{21}^{D}$=2 (*c* 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6) δ 4.97 (1H, dd, *J*=9.9, 5.0 Hz), 4.65 (1H, d, *J*=4.0 Hz), 4.24 (1H, d, *J*=4.0 Hz), 4.16–4.07 (2H, m), 3.84–3.71 (3H, m), 3.60 (1H, dq, *J*=9.0, 7.1 Hz), 3.53–3.42 (2H, m), 3.28 (1H, dq, *J*=9.0, 7.1 Hz), 1.04 (3H, t, *J*=7.1 Hz), 1.01 (3H, t, *J*=7.1 Hz), 0.99 (9H, s), 0.89 (9H, s), 0.15 (3H, s), 0.14 (3H, s), 0.04 (3H, s), −0.02 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 79.8, 75.4, 74.1, 69.6, 63.2, 63.1, 53.3 (×2), 26.0, 25.9, 18.2, 18.1, 15.3 (×2), −3.7, −4.4, −4.6 (×2). IR (film) cm^{-1}: 3376. MS (FAB) *m/z*: 563 $(M+Na)^+$. HR-MS (FAB) *m/z*: 563.2322 (Calcd for $C_{23}H_{48}O_6Si_2S_2Na$: 563.2328). **21**β Colorless oil. R_f=0.65 (20% EtOAc in hexane). $[\alpha]_{21}^{D}$=−2 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6) δ 4.80 (1H, dd, *J*=9.9, 5.8 Hz), 4.53 (1H, d, *J*=3.0 Hz), 4.34 (1H, dd, *J*=9.9, 6.8 Hz), 4.06 (1H, d, *J*=0.9 Hz), 4.06 (1H, m), 3.90 (1H, m), 3.87 (1H, dd, *J*=3.7, 3.0 Hz), 3.71 (1H, dd, *J*=5.8, 3.7 Hz), 3.54 (1H, dq, *J*=9.0, 7.0 Hz), 3.37 (1H, dq, *J*=9.0, 7.0 Hz), 3.34 (1H, dq, *J*=9.0, 7.0 Hz), 3.22 (1H, dq, *J*=9.0, 7.0 Hz), 1.04 (3H, t, *J*=7.0 Hz), 1.03 (3H, t, *J*=7.0 Hz), 0.98 (9H, s), 0.90 (9H, s), 0.18 (3H, s), 0.13 (3H, s), 0.03 (3H, s), 0.01 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 101.4, 79.4, 76.5, 75.3, 74.8, 63.9, 63.4, 53.1, 26.0 (×2), 18.4, 18.1, 15.4, 15.2, −4.2, −4.4, −4.5, −4.7. IR (film) cm^{-1}: 3466. MS (FAB) *m/z*: 563 $(M+Na)^+$. HR-MS (FAB) *m/z*: 563.2333 (Calcd for $C_{23}H_{48}O_6Si_2S_2Na$: 563.2328).

4.4.2. Acetylation of a mixture of 21α and 21β. To a mixture of **21**α and **21**β (130 mg, 0.24 mmol) in pyridine (1 mL) was added acetic anhydride (0.07 mL, 0.72 mmol) at 0°C. The mixture was stirred for 1 h and poured in water. The mixture was extracted with EtOAc and washed with water and brine. The crude product was purified by flash chromatography on silica gel eluted with 5% EtOAc in hexane to give a mixture of **22** and **23** as a 1:1 ratio. They were partially separable by flash column chromatography and completely separable by HPLC. HPLC separation was performed by the use of silica gel column; 20 mm×250 mm, eluent; 5% EtOAc in hexane. Less polar isomer appeared at 8.9 min was found to be **22** derived from **20**α, and polar isomer to be **23** appeared at 15.7 min derived from **20**β. The yields were 46% for **22** and 39% for **23**.

Compound **22**. Colorless oil. R_f=0.45 (10% EtOAc in hexane). $[\alpha]_{21}^{D}$=−35 (*c* 2.95, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (1H, d, *J*=9.4 Hz), 5.16 (1H, dm, *J*=7.2 Hz), 4.80 (1H, dd, *J*=9.9, 2.5 Hz), 4.51 (1H, s), 4.50 (1H, dd, *J*=9.9, 7.2 Hz), 3.80 (1H, d, *J*=3.8 Hz), 3.67 (1H, dd, *J*=9.4, 3.8 Hz), 3.49 (1H, dq, *J*=9.0, 7.0 Hz), 3.30 (2H, q, *J*=7.0 Hz), 3.07 (1H, dq, *J*=9.0, 7.0 Hz), 1.96 (3H, s), 1.00 (3H, t, *J*=7.0 Hz), 0.98 (3H, t, *J*=7.0 Hz), 0.89 (9H, s), 0.88 (9H, s), 0.14 (3H, s), 0.01 (6H, s), −0.01 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 169.6, 100.9, 78.3, 76.4, 74.5, 73.7, 65.1, 63.9, 51.2, 26.0, 25.7, 20.9, 18.4, 17.9, 15.4, 15.3, −4.4, −4.6, −4.7, −4.9. IR (film) cm^{-1}: 1747. MS (FAB) *m/z*: 605 $(M+Na)^+$. HR-MS (FAB) *m/z*: 605.2430 (Calcd for $C_{25}H_{50}O_7Si_2S_2Na$: 605.2435).

Compound **23**. Colorless crystals, mp 95–97°C. R_f=0.42 (10% EtOAc in hexane). $[\alpha]_{24}^{D}$=−1 (*c* 0.55, $CDCl_3$). ^{1}H NMR (300 MHz, C_6D_6) δ 5.76 (1H, dd, *J*=3.2, 2.4 Hz), 4.92 (1H, dd, *J*=9.9, 4.2 Hz), 4.62 (1H, ddd, *J*=7.3, 4.2, 3.2 Hz), 4.44 (1H, d, *J*=2.8 Hz), 4.34 (1H, dd, *J*=9.9, 7.3 Hz), 4.01 (1H, dd, *J*=4.6, 2.4 Hz), 3.74 (1H, dd, *J*=4.6 and 2.8 Hz), 3.59 (1H, dq, *J*=9.0, 7.0 Hz), 3.75 (1H, dq, *J*=9.0, 7.0 Hz), 3.74 (1H, dq, *J*=9.0, 7.0 Hz), 3.25 (1H, dq, *J*=9.0, 7.0 Hz), 1.72 (3H, s), 1.05 (3H, t, *J*=7.0 Hz), 1.04 (3H, t, *J*=7.0 Hz), 1.01 (9H, s), 0.88 (9H, s), 0.16 (3H, s), 0.15 (3H, s), 0.04 (3H, s), 0.02 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 211.4, 169.0, 101.7, 78.8, 76.1, 75.5, 73.3, 63.7, 62.8, 51.4, 26.1, 26.0, 20.4, 18.5, 18.2, 15.5, 15.4, −4.2, −4.3, −4.5, −4.6. IR (KBr) cm^{-1}: 1749. MS (FAB) *m/z*: 605 $(M+Na)^+$. HR-MS (FAB) *m/z*: 605.2438 (Calcd for $C_{25}H_{50}O_7Si_2S_2Na$:

605.2435). *Anal. Calcd* for $C_{25}H_{50}O_7Si_2S_2$: C, 51.51; H, 8.64. Found: C, 51.19; H, 8.83.

4.4.3. (2*R*,3*R*,4*S*,5*S*)-4-Acetoxy-2,3-bis-(*tert*-butyldimethylsilyloxy)-5,6-epithiohexanal diethylacetal (24). A methanol (0.5 mL) solution of **22** (52 mg, 0.089 mmol) was stirred in the presence of anhydrous K_2CO_3 (50 mg) for 3 min. The mixture was diluted with ether and washed with water and brine. The crude product was purified by flash chromatography on silica gel eluted with 5% EtOAc in hexane to give **24** (44 mg) in 94% yield. **24**. Colorless oil. R_f=0.5 (10% EtOAc in hexane). $[\alpha]_{21}^{D}=-17$ (*c* 0.55, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (1H, dd, *J*=6.3, 4.6 Hz), 4.73 (1H, d, *J*=2.8 Hz), 4.00 (1H, s), 3.99 (1H, dt, *J*=10.0, 3.7 Hz), 3.75–3.62 (2H, m), 3.55–3.35 (3H, m), 3.42 (1H, d, *J*=5.4 Hz), 2.19 (1H, d, *J*=6.3 Hz), 1.83 (3H, s), 1.17 (3H, t, *J*=7.0 Hz), 1.10 (3H, t, *J*=7.0 Hz), 1.00 (9H, s), 0.99 (9H, s), 0.23 (3H, s), 0.19 (3H, s), 0.16 (3H, s), 0.12 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 101.3, 75.9, 75.7, 73.7, 63.2, 63.1, 33.6, 26.1, 26.0, 21.3, 20.9, 18.5, 18.3, 15.5, 15.4, −4.0, −4.2, −4.4, −4.5. IR (film) cm^{-1}: 1744. MS (FAB) *m/z*: 545 $(M+Na)^+$. HR-MS (FAB) *m/z*: 545.2770 (Calcd for $C_{24}H_{50}O_6Si_2SNa$: 545.2764).

4.4.4. Ethyl 4,6-di-*O*-acetyl-2,3-bis-*O*-(*tert*-butyldimethylsilyl)-5-thio-D-glucopyranoside (25). A mixture of **24** (21.6 mg, 0.041 mmol), potassium acetate (224 mg, 2.2 mmol) and acetic anhydride (0.02 mL, 0.1 mmol) in acetic acid (1 mL) was heated in oil bath at 110°C for 4 h. After cooling, water was added and the mixture was extracted with ether. Ethereal extract was washed with water and brine. The crude product was purified by flash chromatography on silica gel eluted with 5% EtOAc in hexane to give **25** (12 mg) in 54% yield as a 1:1 ratio of anomers. Colorless oil. R_f=0.40 (10% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (1/2H, dd, *J*=10.2, 8.7 Hz), 5.48 (1/2H, t, *J*=5.1 Hz), 4.62 (1/2H, d, *J*=7.7 Hz), 4.49 (1/2H, dd, *J*=11.9, 4.6 Hz), 4.40 (1/2H, dd, *J*=13.8, 2.4 Hz), 4.19 (1/2H, t, *J*=8.8 Hz), 4.10 (1/2H, t, *J*=3.3 Hz), 4.08–3.50 (5/2H, m), 3.90 (1/2H, dq, *J*=9.0, 7.0 Hz), 3.74 (1/2H, dq, *J*=9.0, 7.0 Hz), 3.34 (1/2H, dt, *J*=10.6, 4.4 Hz), 3.26 (1/2H, m), 3.10 (1/2H, dq, *J*=9.0, 7.0 Hz), 3.04 (1/2H, dq, *J*=9.0, 7.0 Hz), 1.85 (3/2H, s), 1.78 (3/2H, s), 1.76 (3/2H, s), 1.73 (3/2H, s), 1.10–1.00 (3H, m), 1.01 (9/2H, s), 1.00 (9/2H, s), 0.97 (9H, s), 0.20 (3/2H, s), 0.19 (3H, s), 0.10 (3H, s), 0.08 (3/2H, s), 0.04 (3/2H, s), −0.04 (3/2H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.8, 169.6, 169.3, 85.0, 83.4, 78.6, 75.0, 73.9, 73.2, 72.9, 70.4, 66.0, 64.8, 64.3, 62.3, 40.8, 39.8, 26.3, 26.2, 25.9, 25.8, 21.2, 20.9, 20.4, 20.3, 18.4, 18.2, 18.1, 18.0, 15.0, 14.8, −2.2, −2.9, −4.1. −4.2, −4.4, −4.5, −4.6, −4.8. IR (film) cm^{-1}: 1748. MS (FAB) *m/z*: 559 $(M+Na)^+$. HR-MS (FAB) *m/z*: 559.2552 (Calcd for $C_{24}H_{48}O_7Si_2SNa$: 559.2557).

4.4.5. Ethyl 2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucopyranoside (26). *Preparation form **25***. A mixture of **25** (19 mg, 0.04 mmol) in THF (0.4 mL) and tetrabutylammonium fluoride (1 M THF solution, 0.14 mL, 0.14 mmol) was stirred for 1 h at room temperature. Then, solvent was removed. The crude product was dissolved in pyridine (0.4 mL) and acetic anhydride (16 μL, 0.16 mmol) was added at 0°C. The mixture was stirred for 2 h at room temperature, diluted with EtOAc, washed with water, and brine. The residue was purified by flash chromatography on silica gel eluted with 30% EtOAc in hexane. Compound **26** (9.6 mg) was obtained in 69% yield as a 1:1 ratio of α- and β-anomers.

*Preparation from **D-1***. A solution (+)-5-thio-D-glucose (**D-1**) (20 mg, 0.1 mmol) in ethanol (0.1 mL) was added 0.5 mL of ethanol saturated with HCl gas, and the mixture was stirred for 7 h at room temperature. An excess of silver carbonate was added and it was further stirred for 2 h. Precipitates were filtered and the filtrate was condensed. The crude product was dissolved in pyridine (0.4 mL), and acetic anhydride (0.15 mL, 1.6 mmol) was added. The mixture was stirred for 12 h and water and EtOAc were added. The organic layer was washed with water and brine. The residue was purified by flash chromatography on silica gel. Elution with 30% EtOAc gave **26** (21 mg) in 53% yield as a 10:1 ratio of α- and β anomers. The α-anomer (**26**α) was partially isolated by the column chromatography.

Compound **26**α. Colorless oil. R_f=0.55 (40% EtOAc in hexane). $[\alpha]_{22}^{D}=279$ (*c* 0.12, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (1H, t, *J*=9.5 Hz), 5.22 (1H, dd, *J*=10.1, 9.5 Hz), 5.06 (1H, dd, *J*=10.1, 2.9 Hz), 4.7 (1H, d, *J*=2.9 Hz), 4.32 (1H, dd, *J*=12.0, 4.5 Hz), 3.98 (1H, dd, *J*=12.0, 3.2 Hz), 3.79 (1H, dq, *J*=9.5, 7.0 Hz), 3.42–3.30 (2H, m), 2.00 (3H, s), 1.98 (3H, s), 1.95 (3H, s), 1.93 (3H, s), 1.16 (3H, t, *J*=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.2, 169.8, 169.6, 79.0, 74.8, 72.2, 70.9, 64.6, 61.3, 38.3, 20.8, 20.7, 20.6, 20.5, 14.6. IR (film) cm^{-1}: 1747. MS (FAB) *m/z*: 415 $(M+Na)^+$. HR-MS (FAB) *m/z*: 415.1046 (Calcd for $C_{16}H_{24}O_9SNa$: 415.1039). **26**β. Colorless oil. R_f=0.55 (40% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (1H, dd, *J*=10.0, 9.5 Hz), 5.00 (1H, dd, *J*=9.5, 9.2 Hz), 4.52 (1H, d, *J*=8.8 Hz), 4.20 (1H, dd, *J*=11.5, 5.5 Hz), 4.07 (1H, dd, *J*=11.5, 4.0 Hz), 3.78 (1H, m), 3.47 (1H, dq, *J*=9.5, 7.0 Hz), 3.42–3.30 (1H, m), 3.08 (1H, ddd, *J*=10.0, 5.5, 4.4 Hz), 2.00 (3H, s), 1.97 (3H, s), 1.95 (3H, s), 1.93 (3H, s), 1.12 (3H, t, *J*=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 169.8, 169.5, 169.4, 81.3, 74.7, 73.0, 71.7, 66.6, 62.1, 40.1, 20.7, 20.6, 20.6, 20.5, 14.9. IR (film) cm^{-1}: 1747. MS (FAB) *m/z*: 415 $(M+Na)^+$. HR-MS (FAB) *m/z*: 415.1046 (Calcd for $C_{16}H_{24}O_9SNa$: 415.1039).

4.4.6. Preparation of 5-thio-D-glucose (D-1). A solution of **26** (10 mg, 25 mmol) in 3.4 M HCl (0.5 mL) and THF (0.6 mL) was heated at refluxing temperature for 3 h. Then, the mixture was passed through IRA-400 eluted with 50% aqueous methanol. The eluents were combined and evaporated to give D-1 (5 mg) as a white solid. Mp 135–138 °C. R_f=0.35 (30% MeOH in $CHCl_3$). $[\alpha]_{21}^{D}=188$ (*c* 1.0, H_2O).

4.4.7. (2*R*,3*R*,4*R*,5*R*)-4-Acetoxy-2,3-bis-(*tert*-butyldimethylsilyloxy)-5,6-epithiohexanal diethylacetal (27). The ring contraction of **23** (86 mg, 0.15 mmol) was performed by the same reaction manner described for the synthesis of **24**. Compound **27** was obtained in 91% yield. Colorless oil. R_f=0.47 (10% EtOAc in hexane). $[\alpha]_{21}^{D}=-21$ (*c* 1.07, $CHCl_3$). ^{1}H NMR (300 MHz, C_6D_6) δ 5.40 (1H, dd, *J*=5.9, 3.7 Hz), 4.61 (1H, d, *J*=4.4 Hz), 4.00 (1H, dd, *J*=4.0, 3.7 Hz), 4.05 (1H, dd, *J*=4.4, 4.0 Hz), 3.63 (1H, dq, *J*=9.0, 7.0 Hz), 3.68–3.28 (4H, m), 2.39 (1H, d, *J*=5.5 Hz), 2.13 (1H, d, *J*=6.6 Hz), 1.73 (3H, s), 1.14 (3H, t, *J*=7.0 Hz), 1.12 (3H, t, *J*=7.0 Hz), 1.09 (9H, s), 1.01 (9H, s), 0.27 (6H,

s), 0.20 (3H, s), 0.15 (3H, s). ^{13}C NMR (75 MHz, C_6D_6) δ 169.1, 102.6, 76.8, 74.7, 74.2, 63.4, 62.0, 32.2, 26.4, 26.2, 22.0, 20.6, 18.7, 18.5, 15.6, 15.3, −3.9, −4.1, −4.2, −4.3. IR (neat) cm^{-1}: 1742. MS (FAB) *m/z*: 545 $(M+Na)^+$. HR-MS (FAB) *m/z*: 545.2772 (Calcd for $C_{24}H_{50}O_6Si_2SNa$: 545.2764).

4.4.8. Ethyl 4,6-di-*O*-acetyl-2,3-bis-*O*-(*tert*-butyldimethylsilyl)-5-thio-L-altropyranoside (28). The synthesis of **28** was performed from **27** (70 mg, 0.13 mmol) by the same reaction manner described for the synthesis of **25**. Compound **28** was obtained in 64% yield as a 10:1 ratio of α- and β-anomers. Colorless oil. R_f=0.37 (10% EtOAc in hexane). $[\alpha]_{22}^{D}$=7 (*c* 2.23, $CHCl_3$). Only a spectrum of α-anomer was indicated in ^{1}H NMR and ^{13}C NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (1H, dd, *J*=9.9, 1.8 Hz), 4.96 (1H, brs), 4.27 (1H, dd, *J*=11.5, 6.0 Hz), 4.10 (1H, dd, *J*=11.5, 4.2 Hz), 3.98 (2H, brs), 3.79 (1H, dq, *J*=9.0, 7.0 Hz), 3.55–3.42 (2H, m), 2.06 (3H, s), 2.05 (3H, s), 1.19 (3H, t, *J*=7.0 Hz), 0.94 (9H, s), 0.90 (9H, s), 0.09 (3H, s), 0.08 (3H, s), 0.05 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 169.9, 89.4, 74.3, 71.7, 66.2, 65.6, 63.4, 32.8, 25.7 (×2), 21.3, 20.7, 18.2, 18.0, 15.0, −4.3, −4.9 (×3). IR (neat) cm^{-1}: 1748. MS (FAB) *m/z*: 559 $(M+Na)^+$. HR-MS (FAB) *m/z*: 559.2563 (Calcd for $C_{24}H_{48}O_7Si_2SNa$: 559.2557).

4.4.9. Ethyl 2,3,4,6-tetra-*O*-acetyl-5-thio-L-altropyranoside (29). The synthesis of **29** was performed from **28** (44.6 mg, 0.083 mmol) by the same reaction manner described for the synthesis of **26**. Compound **29** was obtained in 78% yield as a 10:1 anomeric ratio. Colorless oil. R_f=0.50 (40% EtOAc in hexane). $[\alpha]_{22}^{D}$=171 (*c* 0.54, $CHCl_3$). Only a spectrum of α-anomer was indicated in ^{1}H NMR and ^{13}C NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (1H, t, *J*=3.1 Hz), 5.55 (1H, dd, *J*=10.8, 3.0 Hz), 5.45 (1H, dd, *J*=10.8, 3.1 Hz), 4.76 (1H, dd, *J*=3.0, 1.5 Hz), 4.43 (2H, m), 3.88 (1H, dq, *J*=9.0, 7.0 Hz), 3.38 (1H, dq, *J*=9.0, 7.0 Hz), 3.11 (1H, dddd, *J*=8.8, 7.1, 3.1, 1.5 Hz), 2.15 (3H, s), 2.09 (3H, s), 2.07 (3H, s), 2.01 (3H, s), 1.21 (3H, t, *J*=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.4, 170.2, 169.7, 80.7, 70.9, 69.8, 65.2, 64.7, 64.5, 42.8, 21.0, 20.9, 20.8, 20.7, 14.4. IR (film) cm^{-1}: 1742. MS (FAB) *m/z*: 415 $(M+Na)^+$. HR-MS (FAB) *m/z*: 415.1046 (Calcd for $C_{16}H_{24}O_9SNa$: 415.1039).

4.4.10. Removal of the protective groups for 29. Deproection of acetates and ethyl glycoside of **29** (21.6 mg) was carried out by the same reaction manner described for the synthesis of **D-1**. After purification by silica gel column chromatography eluted with 20% methanol in $CHCl_3$, **L-2′** (7.2 mg) was obtained in 73% yield as a white solid. Colorless crystals, mp 138–143°C. R_f=0.47 (20% MeOH in $CHCl_3$). $[\alpha]_{24}^{D}$=95 (*c* 0.25, MeOH). ^{1}H NMR (300 MHz, D_2O) δ 5.35 (1H, s), 4.23 (1H, t, *J*=4.8 Hz), 4.14 (1H, d, *J*=9.5 Hz), 3.99 (1H, t, *J*=4.5 Hz), 3.91 (1H, dd, *J*=9.5, 4.5 Hz), 3.64 (1H, m), 3.55 (1H, dd, *J*=8.6, 4.8 Hz). ^{13}C NMR (75 MHz, D_2O) δ 86.6, 77.0, 73.0, 72.6, 70.8, 52.5.

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