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Asymmetric Synthesis of D- and L-2-Deoxy-4-thioriboses

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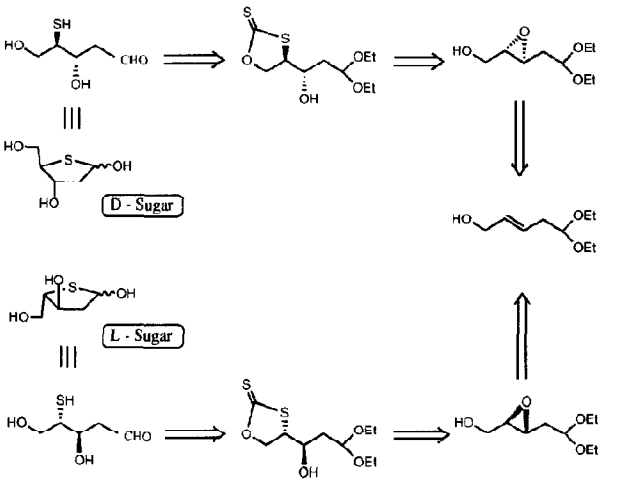
Abstracts: Both D- and L-enantiomers of 2-deoxy-4-thioribose derivatives **12** and **17** were prepared stereospecifically in 12 steps from 1,3-propanediol. The key intermediary 2,3-epoxy alcohols, **8** and **15** were obtained with high enantiomeric excess by the Sharpless asymmetric epoxidation using (+)-L-diethyl tartrate and (-)-D-diethyl tartrate.

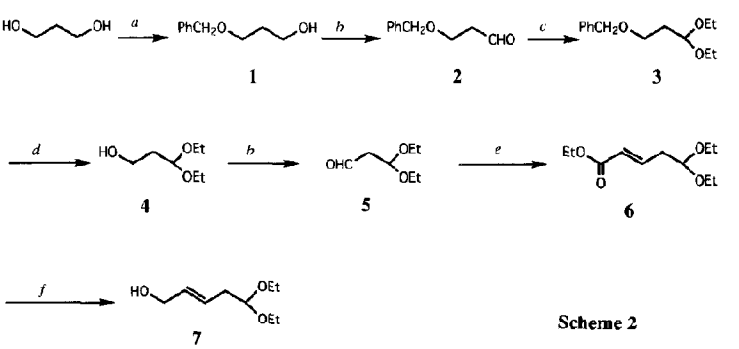
It has been believed that only D- 2-deoxyribonucleosides and ribonucleosides are recognized specifically by enzymes.[1] Chemists have not turned their efforts to synthesize the corresponding L-sugars. However recent findings of a novel class of anti-HIV reagents, such as (-)-BCH-189,[2] (-)-dioxolane-T and C[3] have revealed that those L-type of heteroatom nucleosides possess more potent activities against the virus than the D-isomers, and more importantly, they have lower toxicities. These biological results were rather surprising but were supported by Sparadi's recent experiments in which L-thymine was recognized in phosphorylation of the 5'-hydroxy group by thymine kinase.[4] These results suggest both enantiomers should be examined in *anti*-viral tests. Therefore, enantioselective syntheses of L- and D-sugars would become important. In order to synthesize heteroatom nucleosides,[5] preparations of heteroatom sugars have been developed, and for example, aza sugars,[6] phosphorous sugars[7] and sulfur sugars[8] have been reported. In particular sulfur sugars in which the ring oxygen atom of 2-deoxyribose is replaced by sulfur atom have been paid attentions by a few groups.[9] However these heteroatom sugars have been synthesized based on chemical transformations from natural sugars, and suffer therefore from a lack of synthetic flexibility and useless for the preparation of L-sugars. We have reported the stereospecific syntheses of D-4'-thio-2'-deoxyuridine[10] and D-4'-thiothymidine,[11] in which we achieved a novel preparation of the sulfur sugar part under acyclic stereocontrol. In this paper, we report the details of the stereospecific synthesis of D-2-deoxy-4-thioribose and the first asymmetric preparation of the L-enantiomer.

Our retrosynthetic route to 2-deoxy-4-thioribose is described in **Scheme 1**. 2-Deoxy-4-thioribose can be regarded as 4-formyl-2-mercapto-1,3-diol in acyclic form. We have recently reported the stereospecific preparation of 2-mercapto-1,3-diol units which are conveniently derived from chiral 2,3-epoxy alcohols.[12] Both enantiomers of 2-mercapto-1,3-diol would be obtained by this method from the optically active 2,3-epoxy alcohols, **8** and **15**. Enantioselective preparation of the epoxy alcohols would be performed from the corresponding allylic alcohol **7** by the Sharpless asymmetric epoxidation using (+)-L-tartrate or (-)-D-tartrate.[13] The starting allylic alcohol **7** was prepared from 1,3-propanediol by **7** steps, which is shown in **Scheme 2**.



Scheme 1

Propane-1,3-diol was benzylated with benzyl chloride and sodium hydride in DMF. Fractional distillation of the reaction products gave the mono-benzyl ether **1** in 51% yield, which was subjectd to the Swern oxidation to afford the corresponding aldehyde **2** in 84% yield. Zinc chloride mediated acetal formation of **2** with triethyl orthoformate gave diethyl acetal **3** in 90% yield. The benzyl group was removed under the Birch reduction conditions with sodium in liq. ammonia to form 3-hydroxypropanal diethyl acetal (**4**) in 95% yield. The hydroxy group was oxidized under the Swern conditions to afford aldehyde **5**, which was used for C-2 carbon extension with the Horner-Emmons reaction. The reaction of **5** with the sodium salt of triethyl phosphonoacetate gave mixtures of trans and cis unsaturated esters in 94% yield by two steps. The trans isomer **6** was obtained in 90% yield after chromatographic separation from the minor cis isomer which was

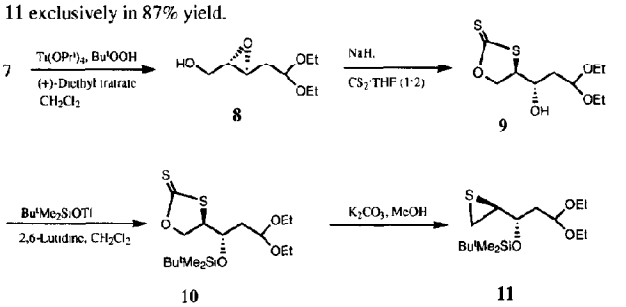


Scheme 2

Reagents and Conditions; a) NaH, $PhCH_2Cl$, DMF:THF(3:1), r.t., *b)* i) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, ii) Et_3N, *c)* $(EtO)_3CH$, $ZnCl_2$, r.t. ; *d)* Na, liq. NH_3, -78°C , *e)* $EtOOCCH_2PO(OEt)_2$, NaH, THF, r.t. ; *f)* DIBALH, CH_2Cl_2, -78°C.

isolated in 4% yield. Reduction of the ester **6** by DIBALH at -78°C in methylene chloride led allylic alcohol 7 in 95% yield.

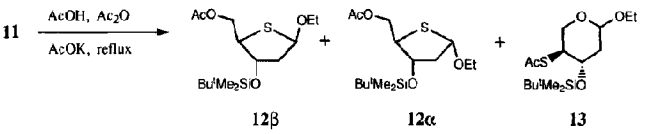
The allylic alcohol 7 was oxidized under the Sharpless conditions by treatment with $Ti(OPr^i)_4$ and Bu^tOOH at -20°C in the presence of (+)-L-diethyl tartrate to provide **8** in 95% yield. At this stage the enantiomeric excess was determined to be 95% e.e. by the Mosher's analysis.[14] Sulfur functionality was introduced to the carbon chain by treating of **8** with carbon disulfide and sodium hydride at -78°C. In this reaction, a xanthate anion was formed initially by the reaction of carbon disulfide and the sodium alkoxide, which then opened the epoxide ring in a 5-exo-tetragonal fashion stereospecifically to form the cyclic xanthate **9** in 86% yield. The hydroxy group in **9** was silylated with TBSOTf in the presence of 2,6-lutidine[15] to give silyl ether **10**. Methanolysis of the xanthate followed by cyclization to the episulfide in one pot by treating of **10** with K_2CO_3 in methanol gave 11 exclusively in 87% yield.



Scheme 3

Thiafuranose Formation

When episulfide **11** was heated in acetic acid and acetic anhydride in the presence of potassium acetate at 120°C for 2 hours, an anomeric mixtures of desired 2-deoxy-4-thioribose, **12α** and **12β** were obtained in 87% combined yield. A six membered thiopyranose derivative **13** was also isolated as a minor product in less than 8% yield. These were all separated by HPLC or flash column chromatography on silica gel. The structures of **12α** and **12β** were determined by the proton NMR spectra. The anomeric proton of **12α** appeared at δ=5.00 ppm as a double doublets whose coupling constants showed 5.1 and 2.6 Hz. This indicated a typical anomer proton of α-furanoside. On the other hand, those of **12β** were 5.6 and 5.1 Hz which were characterized to be an anomer proton of β-furanoside.



Scheme 4

The reaction conditions were examined and the results were shown in **Table**. In the higher temperature at 145°C (run 2), the reaction was complete in 15 min but the yield was slightly lower than that at 120°C. In toluene at reflux temperature, the reaction took a longer period of time (run 3). Without acetic anhydride in toluene, the reaction proceeded but slower (run 4). This cyclization process is mediated with acetic acid. In fact, in the absence of acetic acid (run 5), the reaction did not work at all. In run 6, even a large excess of acetate

anions associated with crown ether were present in refluxing toluene, the starting material was recovered quantitatively. These results suggest the reaction mechanism as following; i) the initial step is protonization of the acetal to generate the oxonium ion, ii) the episulfide closes to the cationic center to produce an episulfonium intermediate, iii) an acetate anion attacks to the terminal episulfide carbon, and finally gives the product.

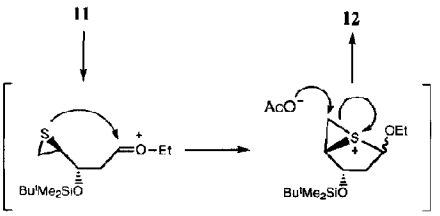
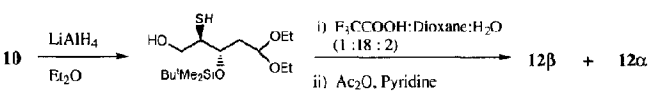


Table Ring Formation of **12** from **11**

Run	Reagent	Solvent	Temp (°C) [a]	Time (hr)	**12** Yield (%) [b]
1	AcOK, AcOH, Ac_2O	———	120	2.0	87
2	AcOK, AcOH, Ac_2O	———	145	0.25	75
3	AcOK, AcOH, Ac_2O	Toluene	120	5.0	87
4	AcOK, AcOH	Toluene	120	6.5	81
5	AcOK, Ac_2O	Toluene	120	8.0	No reaction
6	AcOK, 18-crown-O-6	Toluene	120	8.0	No reaction

a) Bath temperature, *b*) Isolated yields.

Alternatively, **12** was also prepared via mercapto alcohol **14** shown in **Sheme 5**. Reduction of the xanthate **10** by $LiAlH_4$ gave **14** in 56% yield. Ring closure of **14** was carried out under acidic conditions to form a thiafuranose ring, which was acetylated to give **12**β and **12**α (1:1) in 52% yield. The acid promoted ring formation reaction was rather sluggish. Undesired deprotections of the silyl ether and the ethyl glycoside took place and pyranose derivatives were also identified in the reaction mixtures. The yield of **12** could not be improved above than 52%, so that the former method via episulfide is better in practice.

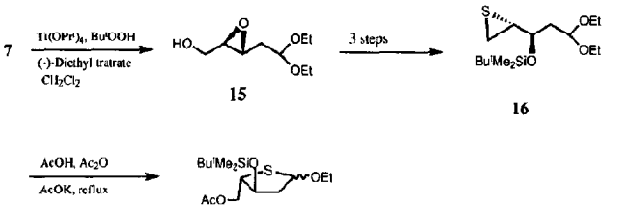


14

Scheme 5

Preparation of L-2-deoxy-4-thioribose

The chiral epoxy alcohol **8** was prepared by the Sharpless epoxidation using (+)-L-diethyl tartrate, while the enantiomer **15** was obtained under the same experimental conditions but using (-)-D-diethyl tartrate. After the introduction of the key stereogenic centers, the same three steps as before gave episulfide **16** in 65 to 72% yields from **15**. Acetic acid and potassium acetate mediated thiafuranose formation to give L-2-deoxy-4-thioriboses, **17**α and **17**β, in 85% combined yields. These enantiomers, **15**, **16**, **17**α and **17**β possessed about the same specific rotations but opposite signs.



Scheme 6

Conclusion

We have established flexible preparations of both D- and L-2-deoxy-4-thioriboses under acyclic stereocontrol. These methods should be useful not only for these thiafuranose syntheses but also for other novel thiaheterocyclic syntheses.

Experimental

General. Melting points were taken on a Yanako micro melting apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL GXS and Varian Gemini 300 for ^1H (400 MHz or 300 MHz) and for ^{13}C (100 MHz or 75 MHz). The chemical shifts were shown as δ-values using tetramethylsilane (0 ppm) for proton spectra and $CHCl_3$ (77.0 ppm) for carbon spectra as an internal standards. Infrared spectra (IR) were recorded by the use of JASCO IRA-1 spectrometer and were taken as liquid films on NaCl plates or as tablets. Low and high resolution mass spectra (LRMS and HRMS) were obtained on a JEOL JMS 303HF spectrometer at the Analytical Center of Okayama University of Science by the electron impact (EI) method at 70 eV unless otherwise stated. Only significant peaks are described here for IR and MS spectra. Silica gel (Merck 7734, 70-300 mesh) was used for gravity column chromatography and silica gel (Merck 9385, 230-400 mesh) for flash column chromatography. Precoated silica gel plates (Merck 5715, 60F254) were used for thin layer chromatography. All air sensitive reactions were conducted in flame dried glass ware under an Ar atmosphere. THF and ether used as solvents for reactions were dried over sodium benzophenone ketyl, and methylene chloride were dried over phosphorus pentoxide. These solvents were freshly distilled just before use.

3-Benzyloxy-1-propanol (1): To an ice cooled solution of propane-1,3-diol (10.0 g, 131.4 mmol) in DMF (100 ml) was added NaH (5.26 g, 60% in mineral oil) by several portions during 30 min. Then, the mixture was stirred further for 1 h at 0°C until hydrogen gas ceased. Benzyl chloride (16.1 g, 127.5 mmol) was added dropwise into the reaction mixture during 5 min. Then it was stirred for 10 h at room temperature. The mixture was quenched with water (10 ml) and extracted with ether (250 ml). The organic layer was washed with water (10 ml) and brine (10 ml). The extract was dried over $MgSO_4$ and concentrated. The residual oil was distilled to give mono benzyl ether **1** (10.7 g) in 51% yield, as an oil. **1**; bp 118~120°C/5 mmHg, Rf=0.15 (20% EtOAc in hexane); ^1H NMR ($CDCl_3$) δ= 7.37-7.26 (5H, m), 4.53 (2H, s), 3.79 (2H, t, J=5.7 Hz), 3.67 (2H, t, J =5.7 Hz), 1.87 (2H, quint, J=5.7 Hz) ; ^{13}C NMR ($CDCl_3$) δ= 137.9, 128.2, 127.5, 127.4, 73.0, 68.8, 61.1, 32.0 ; IR (film) 3370 cm^{-1} ; LRMS *m / z* (rel intensity, %) 166(90), 148(85), 147(base), 120(90); LRMS(FAB) *m / z* 167(M+1); HRMS Found: *m / z* 166.0995. Calcd for $C_{10}H_{14}O_2$:166.0993.

3-Benzyloxy-1-propanal (2): DMSO (4.32 g, 5.54 ml) in methylene chloride (5 ml) was added dropwise to a methylene chloride (100 ml) solution of oxalyl chloride (5.27 g, 41.5 mmol) at -78°C during 5 min. After stirring for 10 min, alcohol 1 (4.6 g, 27.7 mmol) was added to the mixture. It was stirred for 20 min at the same temprerature , and then triethylamine (9.8 g, 96.9 mmol) was added. The bath was replaced to an ice bath and it was stirred for 30 min. Water (10 ml), benzene (75 ml) and ether (75 ml) were added to the mixture. The organic layer was washed with 5% dil HCl (10 ml), water (10 ml) and brine (10 ml), and dried over $MgSO_4$. The solvent was evaporated and residual oil was distilled to give aldehyde **2** (3.8 g) in 84% yield, as an oil. **2**; bp 68~70°C / 3mmHg, Rf=0.37(20% EtOAc in hexane) ^{1}H NMR ($CDCl_3$) δ= 9.80 (1H, t, J=1.8 Hz), 7.37-7.26 (5H, m), 4.53 (2H, s), 3.81 (2H, t, J=6.0 Hz), 2.70 (2H, td, J=6.0 and 1.8 Hz) ; ^{13}C NMR ($CDCl_3$) δ=201.0, 137.7, 128.3, 127.6, 127.5, 73.0, 63.6, 43.6 ; IR (film) 1725 cm^{-1} ; LRMS *m / z* (rel intensity, %) 164(15), 120(base), 108(99), 125(70); LRMS (FAB) *m / z* 165(M+1); HRMS (FAB) Found: *m / z* 165.0946. Calcd for $C_{10}H_{13}O_2$: 165.0915.

3-Benzyloxy-1-propanal diethyl acetal (3): A mixture of the aldehyde **2** (5.5 g, 34.1 mmol) and $ZnCl_2$ (10.3 g, 68.2 mmol) in triethyl orthoformate (45 ml) was stirred for 1 hr at room temperature. Saturated aq. sodium bicarbonate (10 ml) was added, and the mixture was extracted with ether (100 ml). The extract was washed with water (10 ml X2) and brine (10 ml) and dried over $MgSO_4$. The solvent and triethyl orthoformate were removed under reduced pressure and the residual oil was distilled to give the diethyl acetal **3** (7.3 g) in 90% yield, as an oil. **3**; bp 122~126°C/2mmHg, Rf=0.48 (10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$) δ=7.36-7.26 (5H, m), 4.68 (1H, t, J=5.8 Hz), 4.50 (2H, s), 3.74-3.62 (2H, m), 3.56 (2H, t, J=6.2 Hz), 3.53-3.46 (2H, m), 1.93 (2H, td, J=6.2 and 5.8 Hz), 1.19 (6H, t, J=7.0 Hz) ; ^{13}C NMR ($CDCl_3$) δ= 138.3, 128.1, 127.4, 127.3, 100.5, 72.8, 66.2, 61.4, 34.1, 15.2 ; LRMS *m / z* (rel intensity, %) 193(92), 146(22), 117(65), 103(96), 92(base); LRMS (FAB) *m / z* 239(M+1); HRMS Found: *m / z* 238.1597. Calcd for $C_{11}H_{22}O_3$: 238.1591.

3-Hydroxypropanal diethyl acetal (4): To a mixture of the benzyl ether **3** (10.0 g, 42 mmol) in THF (80 ml) and liquid ammonia (150 ml) was added sodium pieces at -78°C until the solution became deep blue. The mixture was quenched carefully with methanol in order to destroy an excess of sodium metal. The dry ice bath was removed and ammonia was allowed to evaporate. The residue was diluted with ether (200 ml), and washed with water (10 mlX2), then brine (10 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by silica gel column chromatography eluted with 50% EtOAc in hexane to give alcohol **4** (5.9 g) in 95% yiled, as an oil. **4**; bp 101~105°C / 22 mmHg, Rf=0.27 (30% EtOAc in hexane) ; ^{1}H NMR ($CDCl_3$) δ=4.68 (1H, t, J=5.4 Hz), 3.80-3.40 (6H, m), 2.42 (1H, bs), 1.89 (2H, q, J=5.5 Hz), 1.22 (6H, t, J=7.0 Hz) ; ^{13}C NMR ($CDCl_3$) δ=101.5, 61.3, 59.1, 58.3, 35.7, 14.9, 14.5 ; IR (film) 3420 cm^{-1} ;LRMS *m / z* (rel intensity, %) 103(18), 97(10), 44(base); HRMS Found: *m / z* 103.077. Calcd for $C_5H_{11}O_2$ (M-45):103.0759.

(E)-Ethyl 5,5-bis(ethoxy)-2-pentenoate (6): Aldehyde **5** (Rf=0.60, 20% EtOAc in hexane) was obtained from **4** (4.9 g, 33 mmol) by the same Swern oxidation conditions described for **2**. The crude aldehyde was subjected to the next reaction. To a THF solution (100 ml) of sodium salt of triethyl phosphonoacetate, which was prepared from triethyl phosphonoacetate (8.1 ml, 40.4 mmol) and sodium hydride (1.5 g, 60% in oil dispersion), was added the crude aldehyde in THF (5 ml) at room temperature. The reaction was stirred for 30 min and quenched with aq. ammonium chloride (10 ml). It was extracted with ether (200 ml) and the ethereal extract was washed with water (10 ml) and brine (10 ml). Evaporation of the solvent and distillation of the residual oil gave **6** (6.5

g) in 94% yield, which contained 2~4% of the cis isomer. They are separable by silica gel column chromatography. **6**; bp 91~92°C/0.5 mmHg, Rf=0.63 (20% EtOAc in hexane) ; ^{1}H NMR ($CDCl_3$) δ=6.92 (1H, dt, J=15.8 and 7.0 Hz), 5.90 (1H, d, J=15.8 Hz), 4.58 (1H, d, J=5.9 Hz), 4.19 (2H, q, J=7.0 Hz), 3.66 (2H, dq, J=9.2 and 7.0 Hz), 3.51 (2H, dq, J=9.2 Hz and 7.0 Hz), 2.54 (2H, dtd, J=7.0, 5.9 and 1.1 Hz), 1.29 (3H, t, J=7.0 Hz), 1.21 (6H, t, J=7.0 Hz) ; ^{13}C NMR ($CDCl_3$) δ=166.2, 143.4, 123.6, 101.2, 61.3, 60.1, 36.8, 15.1, 14.1 ; IR (film) 1725 and 1655 cm^{-1} ; LRMS *m / z* (rel intensity, %) 171(base), 170(83), 143(72); LRMS (FAB) *m / z* 217(M+1); HRMS Found: *m / z* 171.1021. Calcd for $C_9H_{15}O_3$(M-45): 171.1021.

(E)-5,5-Bis(ethoxy)-2-penten-1-ol (7): To a stirred solution of **6** (2.8 g, 13.0 mmol) in methylene chloride (70 ml) was added DIBALH (30 ml, 0.95 M in hexane solution) at -78°C and it was stirred for 10 min. Aq. ammonium chloride (15 ml) and ether (150 ml) were added to the mixture and it was stirred for 1 h. The resulting precipitates were filtered through a celite pad and the organic layer of the filtrate was washed with aq. ammonium chloride (10 ml), water (10 ml), and brine (10 ml). The extract was dried over $MgSO_4$ and the solvent was removed. The residual oil was purified by column chromatography on silica gel eluted with 20% EtOAc in hexane to give oily allyl alcohol **7** (2.3 g) in 95% yield. **7**; Rf=0.63 (20% EtOAc in hexane) ; ^{1}H NMR ($CDCl_3$) δ= 5.78-5.64 (2H, m), 4.51 (1H, t, J=5.7 Hz), 4.11 (2H, d, J=4.4 Hz), 3.62 (2H, q, J=7.0 Hz), 3.54 (2H, q, J=7.0 Hz), 2.39 (2H, t, J=5.3 Hz), 1.20 (3H, t, J=7.0Hz), 1.20 (3H, t, J=7.0 Hz) ; ^{13}C NMR ($CDCl_3$) δ=131.9, 126.8, 102.1, 63.2, 61.0, 36.6, 15.1; IR (film) 3400 cm^{-1} ; LRMS *m / z* (rel intensity, %) 129(85), 104(26), 103(84), 83(base); LRMS (FAB) *m / z* 175(M+1); HRMS(FAB) Found: m / z 175.1364. Calcd for $C_9H_{19}O_3$: 175.1334.

(2S,3R-trans)-5,5-Bis(ethoxy)-2,3-epoxypentan-1-ol (8): To a mixture of titanium tetraisopropoxide (5.4 g, 18.9 mmol) and (+)-L-diethyl tartrate (3.9 g, 18.9 mmol) in dry methylene chloride (70 ml) was added a methylene chloride (16 ml) solution of **7** (1.47 g, 8.44 mmol) at -20°C. The mixture was stirred for 20 min and *tert*-butyl hydroperoxide (9.5 ml, 1.8M in toluene) was added to the mixture. The whole was kept in refrigerator at -20°C for 10 h. Then 10% aq. tartaric acid solution (20 ml) was added and stirred for 90 min at room temperature. The organic layer was separated, washed with water (10 ml X2), and concentrated. The residual oil was diluted with ether (140 ml), and vigorously shaked with 2N sodium hydroxide (29 ml) for 30 min. The ether layer was taken and washed with brine (10 ml), and dried over $MgSO_4$. The solvent was evaporated and the residual oil was purified by column chromatography on silica gel eluted with 80% EtOAc in hexane to give **8** (1.52 g) in 95% yield as an oil. The enantiomeric excess was determined to be 95% by the Mosher analysis. **8**; Rf=0.28 (60% EtOAc in hexane); $[\alpha]_D^{24}$ - 44.7 (*c* 1.0, chloroform) ; ^{1}H NMR ($CDCl_3$) δ=4.68 (1H, dd, J=7.0 and 4.8 Hz), 3.91 (1H, dd, J=12.5 and 2.6 Hz), 3.73-3.62(3H, m), 3.59-3.49 (2H, m), 3.06 (1H, ddd, J=7.0, 4.8 and 2.6 Hz), 2.97 (1H, dt, J=4.8 and 2.6 Hz), 1.96 (1H, ddd, J=11.7, 7.0 and 4.8 Hz), 1.82 (1H, ddd, J=11.7, 7.0 and 4.8 Hz), 1.23 (3H, t, J=7.0 Hz), 1.22 (3H, t, J=7.0 Hz) ; ^{13}C NMR ($CDCl_3$) δ=100.3, 61.8, 61.5, 61.1, 52.2, 36.1, 15.0 ; IR (film) 3460 cm^{-1} ; LRMS *m / z* (rel intensity, %) 146(60), 145(21), 129(15), 104(70), 71(base); HRMS Found: *m / z* 145.0835. Calcd for $C_7H_{13}O_3$ (M-45): 145.0865.

[4R,(1'S)]-4-[3,3-Bis(ethoxy)-1-hydroxy-1-propyl]-1,3-oxathiolane-2-thione (9): To a dispersion of sodium hydride (383 mg, 60% in mineral oil) in a mixture of THF (15 ml) and carbon disulfide (15 ml) was added the epoxy alcohol **8** (900 mg, 4.78 mmol) in THF (5 ml) during 5 min. With carefully monitoring of the desired compound (Rf=0.31) and the starting material (Rf=0.15) by tlc (40% EtOAc in hexane), the reaction mixture was warmed up slowly to -40°~ -30°C during 1h. The reaction was stopped when less polar material (Rf=0.9 in

the same tlc solvent system) appeared. Powdered ammonium chloride (100 mg) and sat. ammonium chloride solution (8 ml) were added. The mixture was extracted with ether (100 ml) and the extract was washed with water (4 ml) and brine (4 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. Crude compound was purified by column chromatography on silica gel eluted with 60% EtOAc in hexane to give cyclic xanthate **9** (1.09 g) in 86% yield as an oil. The starting material (75 mg) was recovered in the fraction eluted with 80% EtOAc in hexane. **9**; Rf=0.31 (60% EtOAc in hexane) ; $[\alpha]_D^{24}$ - 40.9 (*c* 1.0, chloroform) ; ^1H NMR ($CDCl_3$) δ=5.15 (1H, dd, J=9.9 and 2.6 Hz), 4.85 (1H, dd, J=9.9 and 6.2 Hz), 4.71 (1H, dd, J=5.7 and 3.5 Hz), 3.98-3.94 (2H, m), 3.77 (1H, dq, J=9.2 and 7.0 Hz), 3.66 (1H, dq, J=9.2 and 7.0 Hz), 3.58-3.49 (2H, m), 1.95-1.90 (1H, m), 1.87-1.80 (1H, m), 1.24 (3H, t, J=7.0 Hz), 1.23 (3H, t, J=7.0 Hz) ; ^{13}C NMR ($CDCl_3$) δ=211.9, 101.7, 79.1, 68.8, 63.0, 62.2, 55.5, 37.1, 15.0, 14.9 ; IR (film) 3405 and 1210 cm^{-1} ; LRMS *m / z* (rel intensity, %) 189(25), 177(37), 176(90), 143(74), 131(35), 85(base); LRMS (FAB) *m / z* 267(M+1); HRMS (FAB) Found:*m / z* 267.0698. Calcd for $C_{10}H_{19}O_4S_2$: 267.0725.

[4R,(1'S)]-4-[3,3-Bis(ethoxy)-1-(*tert*-butyldimethylsilyl)oxy-1-propyl]-1,3-oxathiolane-2-thione (10): To a mixture of **9** (1.4 g, 6 mmol) and 2,6-lutidine (1.28 g, 12 mmol) in dry methylene chloride (40 ml) was added tert-butyldimethylsilyl trifluoromethanesulfonate (2.06 ml, 2.38 g, 9 mmol) at room temperature. After 20 min, the reaction mixture was diluted with ether (200 ml) and washed with sat. sodium bicarbonate (10 ml X2), water (10 ml) and brine (10 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography on silica gel eluted with 10% EtOAc in hexane to give silyl ether **10** (1.86 g) in 93% yield as an oil. **10**; Rf=0.68 (30% EtOAc in hexane) ; $[\alpha]_D^{24}$ - 12.7 (*c* 1.0, chloroform) ; ^1H NMR ($CDCl_3$) δ=4.95 (1H, dd, J=10.3 and 3.3 Hz), 4.80 (1H, dd, J=10.3 and 7.3 Hz), 4.64 (1H, dd, J=5.9 and 4.4 Hz), 4.21 (1H, ddd, J=10.1, 7.3 and 3.3 Hz), 3.99 (1H, ddd, J=10.1, 5.9 and 4.4 Hz), 3.68-3.57 (2H, m), 3.50-3.43 (2H, m), 2.00 (1H, ddd, J=14.7, 5.9 and 4.4 Hz), 1.82 (1H, ddd, J=14.7, 5.9 and 4.4 Hz), 1.20 (6H, t, J=7.0 Hz), 0.90 (9H, s), 0.13 (3H, s), 0.10 (3H, s) ; ^{13}C NMR ($CDCl_3$) δ=212.7, 99.4, 78.5, 69.7, 61.7, 61.4, 55.6, 38.5, 25.6, 17.8, 15.3, 15.2, -4.5, -4.8 ; IR (film) 1200 cm^{-1} ; LRMS *m / z* (rel intensity, %) 335(29), 324(20), 323(23), 275(90), 249(40), 229(52), 216(base); LRMS (FAB) *m / z* 381(M+1); HRMS (FAB) Found: *m / z* 381.1584. Calcd for $C_{16}H_{33}O_4S_2Si$: 381.1589.

(3S,4S)-3-(*tert*-Butyldimethylsilyl)oxy-4,5-epithiopentanal diethyl acetal (11): A mixture of **10** (800 mg, 2.1 mmol) and anhydrous potassium carbonate (150 mg) in methanol (10 ml) was stirred for 2 h. Methanol was evaporated under reduced pressure and water (4 ml) was added. It was extracted with EtOAc (40 ml) and the extract was washed with water (4 ml) and brine (4 ml). It was dried over $MgSO_4$, and the solvent was evaporated. The residue was chromatographed on silica gel eluted with 2.5% EtOAc in hexane to give episulfide **11** (592 mg) in 87% yield as an oil. **11**; Rf=0.47 (5% EtOAc in hexane) ; $[\alpha]_D^{24}$ - 20.7 (*c* 1.0, chloroform) ; ^1H NMR ($CDCl_3$) δ=4.73 (1H, dd, J=7.3 and 4.4 Hz), 3.67-3.59 (2H, m), 3.51 (1H, dq, J=9.5 and 7.0 Hz), 3.45 (1H, dq, J=9.5 and 7.0 Hz), 3.36 (1H, ddd, J=7.7, 7.3 and 4.0 Hz), 2.96 (1H, ddd, J=7.3, 6.2 and 5.5 Hz), 2.47 (1H, dd, J=6.2 and 1.1 Hz), 2.25 (1H, dd, J=5.5 and 1.1 Hz), 2.02 (1H, ddd, J=13.9, 7.3 and 4.0 Hz), 1.94 (1H, ddd, J=13.9, 7.7 and 4.4 Hz), 1.20 (3H, t, J=7.0 Hz), 1.19 (3H, t, J=7.0 Hz), 0.89 (9H, s), 0.08 (3H, s), 0.06 (3H, s) ; ^{13}C NMR ($CDCl_3$) δ=99.7, 73.9, 61.0, 60.5, 41.4, 38.4, 25.8, 24.4, 15.3, -4.0, -4.8 ; LRMS *m / z*(rel intensity, %) 320(5), 275(54), 263(53), 204(74), 57(base); LRMS (FAB) *m / z* 321(M+1); HRMS (FAB) Found: *m / z* 321.1927. Calcd for $C_{15}H_{33}O_3SSi$: 321.1920.

4-Thiofuranose Formation by an Acetate Anion in Acetic acid : To a solution of **11** (850 mg, 2.6 mmol) in a mixture of acetic acid (3.1 ml) and acetic anhydride (3.5 ml) was added anhydrous potassium acetate (1.3 g, 13.5 mmol) and this was heated at 120°C for 2 h. After cooling, it was diluted with methylene chloride (100 ml), and potassium acetate was removed by filteration through celite pad. EtOAc (100 ml) was added to the filtrate and washed with water (15 ml X4), brine (10 ml X2). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography. Elution by 7.5% EtOAc gave 1:1 mixture of **12**α and **12**β (690 mg) in 87% combined yield, which were separated by HPLC (silica gel) eluted with 5% EtOAc in hexane. **Ethyl 5-O-acetyl-3-O-(*tert*-butyldimethylsilyl)-2-deoxy-4-thio-α-D-xylofuranoside (12α):** Oil, Rf=0.46 (10% EtOAc in hexane) ; $[\alpha]_D^{24}$ - 87.2 (*c* 1.0, chloroform) ; ^{1}H NMR ($CDCl_3$) δ=5.00 (1H, dd, J=5.1 and 2.6 Hz), 4.41 (1H, ddd, J=13.6, 8.1 and 5.3 Hz), 4.28 (1H, dd, J=11.2 and 6.2 Hz), 4.09 (1H, dd, J=11.2 and 6.6 Hz), 3.63 (1H, dq, J=9.2 and 70 Hz), 3.42 (1H, ddd, J=13.6, 7.0 and 6.2 Hz), 3.29 (1H, dq, J=9.2 and 7.0 Hz), 2.31 (1H, ddd, J=13.0, 5.1 and 2.6 Hz), 2.16 (1H, ddd, J=13.0, 8.1 and 5.1 Hz), 2.07 (3H, s), 1.18 (3H, t, J=7.0 Hz), 0.88 (9H, s), 0.09 (3H, s), 0.008 (3H, s) ; ^{13}C NMR ($CDCl_3$) δ=170.7, 86.2, 76.0, 66.5, 64.8, 52.7, 45.4, 25.7, 20.8, 17.9, 14.8, -4.6, -4.9: IR (film) 1740 cm^{-1} ; LRMS*m / z* (rel intensity, %) 334(2), 333(6), 289(10), 277(base), 233(66), 231(83);LRMS (FAB) *m / z* 335(M+1); HRMS (FAB) Found: *m / z* 335.1739. Calcd for $C_{15}H_{31}O_4SSi$: 335.1713. **Ethyl 5-O-acetyl-3-O-(*tert*-butyldimethylsilyl)-2-deoxy-4-thio-β-D-xylofuranoside (12β):** Oil, Rf=0.40 (10% EtOAc in hexane) ; $[\alpha]_D^{24}$ + 196.8 (*c* 1.0, chloroform) ; ^{1}H NMR ($CDCl_3$) δ=5.17 (1H, dd, J=5.6 and 5.1 Hz), 4.30 (1H, dd, J=11.4 and 4.9 Hz), 4.10-4.06 (1H, m), 4.04 (1H, dd, J=11.4 and 7.0 Hz), 3.31 (1H, dq, J=9.2 and 7.0 Hz), 3.56 (1H, td, J=7.0 and 4.9 Hz), 3.31 (1H, dq, J=9.2 and 7.0 Hz), 2.53 (1H, dt, J=12.8 and 6.6 Hz), 2.06 (3H, s), 2.06-2.03 (1H, m), 1.20 (3H, t, J=7.0 Hz), 0.88 (9H, s), 0.06 (3H, s), 0.05 (3H, s) ; ^{13}C NMR ($CDCl_3$) δ= 170.7, 85.0, 75.0, 65.1, 64.4, 52.1, 43.9, 25.6, 20.8, 17.9, 14.8, -4.7, -5.0 ; IR (film) 1740 cm^{-1} ; LRMS *m / z* (rel intensity, %) 333(2), 277(17), 233(12), 231(42), 41(base); LRMS (FAB) *m / z* 335(M+1); HRMS (FAB) Found: *m / z* 335.1725. Calcd for $C_{15}H_{31}O_4SSi$: 335.1713. Elution by 9% EtOAc in hexane gave 6-membered cyclic byproduct **13** (73 mg) in 8% yield. **Ethyl 4-acetylthio-3-(*tert*-butyldimethylsilyl)oxy-2,3-dideoxy-D-xylopyranoside (13):** Oil, Rf=0.51 (10% EtOAc in hexane) ;$[\alpha]_D^{24}$ + 129.7 (*c* 1.0, chloroform) ; ^{1}H NMR ($CDCl_3$) δ=4.83 (1H, ddd, J=13.2, 8.8 and 4.0 Hz), 4.55 (1H, br), 4.00 (1H, ddd, J=13.6, 8.8 and 4.5 Hz), 3.79 (1H, dq, J=9.5 and 7.0 Hz), 3.34 (1H, dq, J=9.5 and 7.0 Hz), 2.76(1H, dd, J=13.8 and 10.8 Hz), 2.58 (1H, ddd, J=12.8, 4.4 and 1.5 Hz), 2.39(1H, dt, J=13.6 and 4.0 Hz), 2.10-2.03 (1H, m), 2.06 (3H, s), 1.20 (3H, s), 0.86 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR ($CDCl_3$) δ=170.2, 79.4, 76.1, 68.2, 63.9, 44.0, 25.8, 25.6, 21.3, 17.9, 14.9, -4.6, -4.8; LRMS *m / z* (rel intensity, %) 277(63), 241(23), 229(43), 217(84), 205(base);LRMS (FAB) *m / z* 335(M+1); HRMS (FAB) Found: *m / z* 335.1686. Calcd for $C_{15}H_{31}O_4SSi$: 335.1713.

L-enantiomers: The enantiomers **15**, **16**, **17**α, and **17**β were prepared exactly according to the same experimental method used for the corresponding D-series. Only their optical rotations were as follows; **15** $[\alpha]_D^{24}$ +41.9 (*c* 1.0, chloroform), **16** $[\alpha]_D^{24}$ +19.6 (*c* 1.0, chloroform), **17**α $[\alpha]_D^{24}$ +86.2 (*c* 1.0, chloroform), **17**β $[\alpha]_D^{24}$ -190.3 (*c* 1.0, chloroform).

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