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Synthesis of L-Deoxyribonucleosides from D-Ribose

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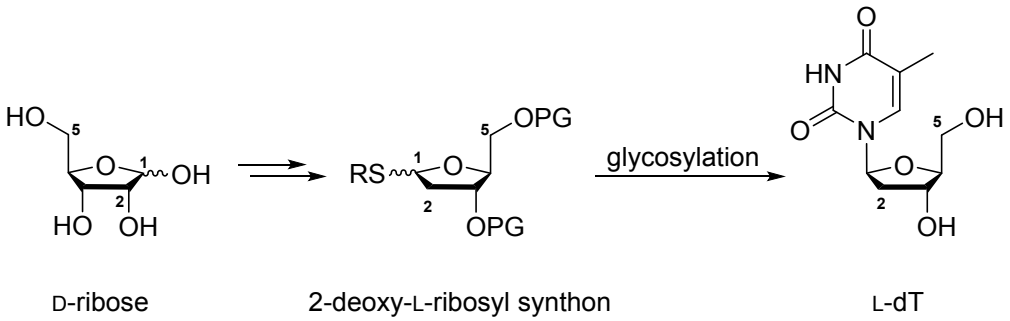
[TOC graphic]



Abstract:

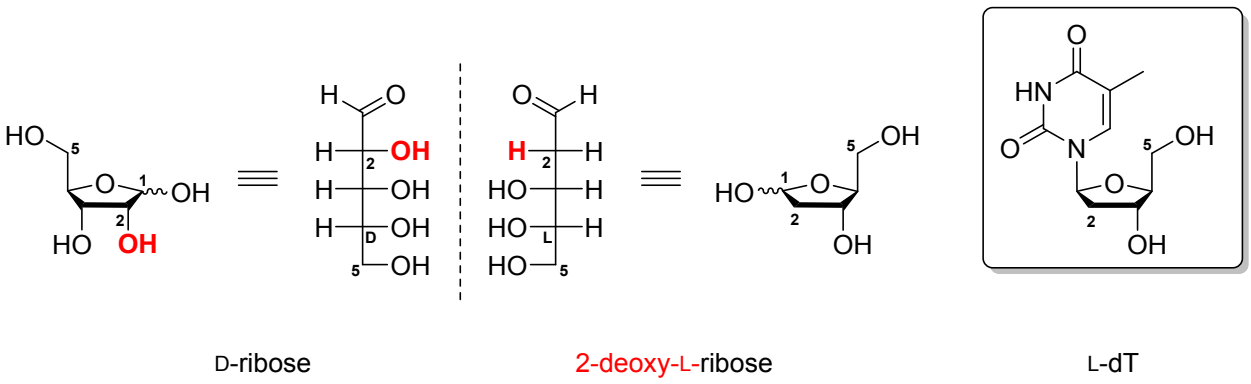
The preparation of 2-deoxy-L-ribose derivatives or mirror image deoxyribonucleosides (L-deoxyribonucleosides) from D-ribose is reported. Starting from inexpensive D-ribose, an acyclic D-form carbohydrate precursor was synthesized to study a unique carbonyl translocation process. In this novel radical reaction, not only was the configuration of the sugar transformed from the D-form to the L-form, but also deoxygenation at the C(2) position of the sugar was successfully achieved. This is one of the most practical methods for converting a D-sugar to a 2-deoxy-L-sugar in a one-step reaction.

To further identify the reaction product, radical reactions followed by treatment with 1,3-propanedithiol and then benzoylation were performed to afford a dithioacetal derivative. The stereochemistry and configuration of the 2-deoxy-L-ribose dithioacetal derivative were confirmed by its X-ray crystal structure. To further apply this methodology, a diethyl thioacetal derivative was formed, followed by selective benzoyl protection, and an NIS-initiated cyclization reaction to give the desired ethyl *S*-L-2-deoxyriboside, which can be used as a 2-deoxy-L-ribosyl synthon in the formal total synthesis of various L-deoxyribonucleosides, such as L-dT.

Introduction

L-Deoxysugars are less abundant in nature compared to their mirror image isomers, D-deoxysugars.[1] Among all of the L-deoxysugars, 2-deoxy-L-ribose is obviously an important carbohydrate, because it could be used as the starting material for the synthesis of many biological important molecules.[2] 2-Deoxy-L-ribose also serves as the sugar backbone for preparing unnatural L-DNA, which could be used in studies of nucleic acid recognition with natural D-DNA.[3] Moreover, modified L-deoxyribonucleosides, such as L-FMAU (Clevudine), L-dT (Telbivudine), and val-L-dC (Valtorcitabine), are promising antitumor or antiviral drugs.[4] These modified L-deoxyribonucleosides all contain 2-deoxy-L-ribose as their sugar components. It is noteworthy that, even 2-deoxy-L-ribose itself has been reported to inhibit the growth of tumor cells through its ability to regulate the action of thymidine phosphorylase (TP).[5] Because of such biological importance, a number of synthetic

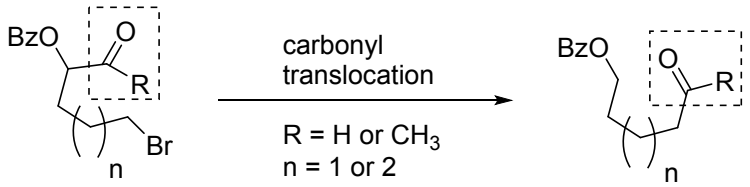
methods for preparing 2-deoxy-L-sugar derivatives and L-deoxyribonucleosides have been reported.[6-8] Although the synthesis of derivatives of 2-deoxy-L-sugar derivatives and L-deoxyribonucleosides from less abundant L-sugars has been reported,[6] the use of inexpensive D-sugars as starting materials in their synthesis would be a more practical approach.[7] However, preparing L-sugars from inexpensive D-sugars is complex and involves multiple steps, since all of the stereocenters in the molecule would need to be changed to the opposite configuration. To produce the L-form of a 2-deoxy sugar would then require the selective deoxygenation of the C-2 hydroxy group. Lastly, it would be necessary to convert the 2-deoxy-L-ribose into a suitable 2-deoxy-L-ribosyl sugar donor for glycosylation reactions with nucleobases, and to eventually produce the desired L-deoxyribonucleosides, as shown in Scheme 1.



Scheme 1 Stereochemical configurations of D-ribose, 2-deoxy-L-ribose, and L-dT.

A unique radical process involving carbonyl translocation was developed recently in this laboratory,[9] as shown in Scheme 2. This carbonyl translocation process was used to transform inexpensive D-sugars into rare L-deoxysugars.[10] However, an early attempt to prepare 2-deoxy-L-

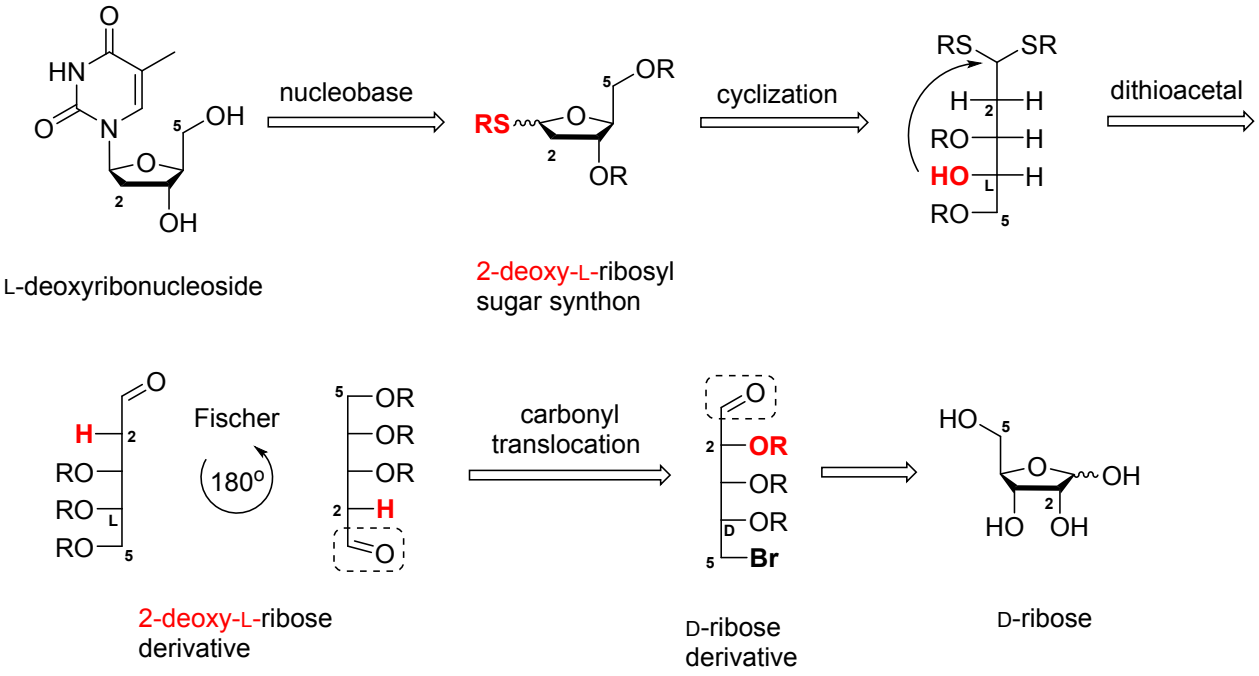
ribose from a D-hexitol met with only partial success.[10c] The inefficiency associated with this synthesis of the radical precursor and the fact that the corresponding alcohol (L-2-deoxyribitol) was produced, rather than 2-deoxy-L-ribose itself prompted us to develop a more practical methodology. A practical synthetic approach that starts from a simple D-sugar and ends with the formation of the mirror image deoxyribonucleosides, L-deoxyribonucleosides, would be highly attractive for organic chemists because of the potential biological properties of such compounds.



Scheme 2 Radical cyclization followed by fragmentation of a carbonyl compound.

Retrosynthetic plan

Herein, we report on an efficient synthetic methodology for converting a simple D-sugar to a deoxy-L-nucleoside. In our retrosynthetic plan, a 2-deoxy-L-ribosyl sugar synthon could be used to prepare various L-deoxyribonucleosides. This 2-deoxy-L-ribosyl sugar synthon was envisioned to arise from the selective cyclization reaction of a dithioacetal derivative, which can be directly generated using our previously developed carbonyl translocation process. Using this radical process, it is possible to transform a D-ribose derivative into a 2-deoxy-L-ribose derivative in a one-step reaction. The radical precursor could be prepared from the commercially available D-ribose, as shown in Scheme 3.

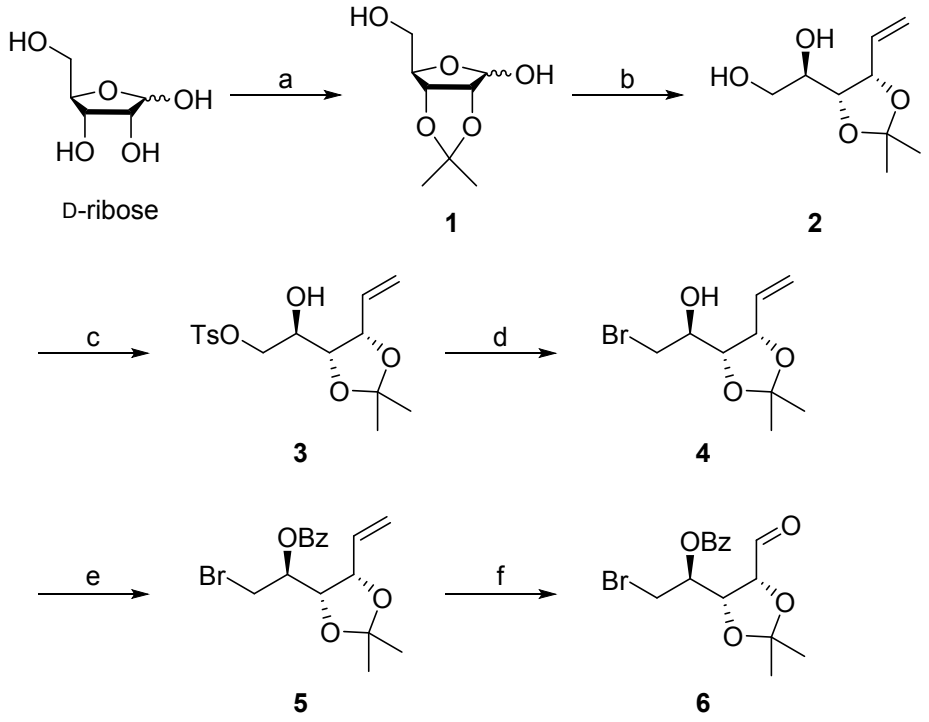


Scheme 3 Retrosynthetic plan.

Results and Discussion

The inexpensive D-ribose was used as the starting material, as shown in Scheme 4. To differentiate between all of the hydroxyl groups, the C2 and C3 hydroxyl groups (syn orientation) were protected by an isopropylidine group, thus leaving the primary (C5) hydroxyl group available for further manipulation. The conditions for this reaction involved reacting the starting material with acetone in the presence of conc. H_2SO_4 to give compound **1**.[11] Protecting carbonyl group using a Wittig phosphonium salt (Ph_3PMeBr) and potassium *tert*-butoxide (KO*t*-Bu) afforded the acyclic compound **2**.[11] Selective bromination of the primary hydroxyl group using *p*-toluenesulfonyl chloride (TsCl) and a catalytic amount of dibutyltin oxide (Bu_2SnO),[12] followed by treatment with tetrabutylammonium bromide (TBAB)[13] smoothly generated compound **4**. The remaining hydroxyl group was protected by

a benzoyl group (Bz) to give compound **5**. Ozonolysis then afforded the radical precursor **6** in only six steps, which is a far more efficient than a previous synthesis in which a D-hexoitol was used as the starting material.[10c] This radical precursor **6** was directly used, without further purification, in the following radical reactions.

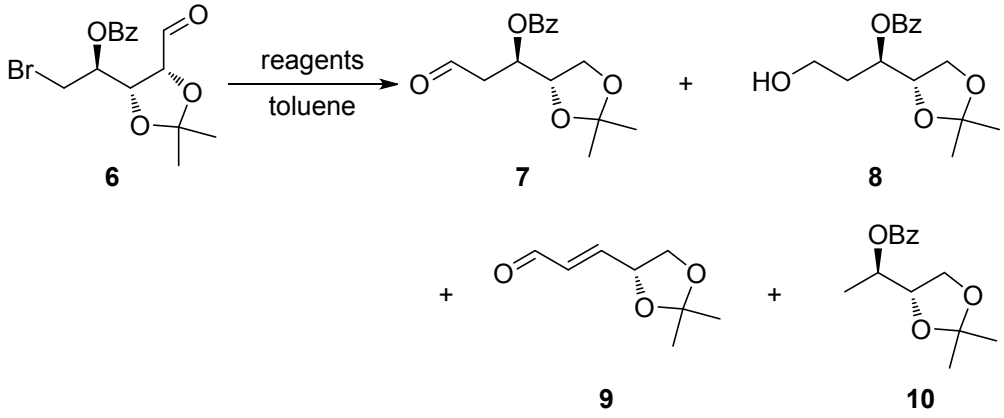


Scheme 4 *Reagents and Conditions*: (a) conc. H_2SO_4, acetone, rt, 2 h, 71%; (b) Ph_3PMeBr, KO*t*-Bu, THF, reflux, 1 h, 78%; (c) *p*-TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 0 °C~rt, 5.5 h, 95%; (d) $Bu_4N^+Br^-$, DMF, 70–80 °C, 1 h, 88%; (e) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C~rt, 7 h, 90%; (f) O_3, CH_2Cl_2, –78 °C, then Me_2S, –78 °C to rt, 4 h, 99%.

A series of radical reactions involving radical cyclization followed by the fragmentation of molecule **6** bearing an isopropylidine protecting group were studied. The product ratios as a function of slow

addition and reaction time are shown in Table 1. Standard radical reaction conditions using two different hydrogen sources, i.e., tributyltin hydride (entry 1–4) and tristrimethylsilylsilane (TTMSS, entry 5–8) were tested. The first attempt involved the use of previously developed conditions (entry 1; Bu_3SnH/AIBN = 1.5/0.2 equiv).[10c] The ^1H spectrum of the crude reaction mixtures indicated that the desired product **7** was formed along with the unexpected over-reduction product **8** and the elimination product **9** in a ratio of **7**:**8**:**9** =1:1.09:0.16. This result indicates that the isopropylidine protecting group covering the syn-diol groups on the molecules **6** may enhance the reaction efficiency of carbonyl translocation processes.[14] However, it was not possible to isolate the desired product **7** bearing a β-leaving group (OBz).[15] The side reaction product **8** was formed by the further reduction of compound **7** with an excess amount of Bu_3SnH reagent. The side reaction product **9** was generated by an elimination reaction of compound **7**. Other attempts (entry 2–3) to decrease the reagent equivalents provided the best results (entry 3 table 1) in the products ratios of (**7**:**8**:**9** =1:0.15:0.01). A further reduction in the reagent equivalents and a decrease in the reaction time (entry 4) failed to afford better product ratios. Oxidation of alcohol **8** back to the desired compound **7** is difficult due to the instability of these reaction products.

Table 1 Radical cyclization/fragmentation reactions of the precursor **6**.



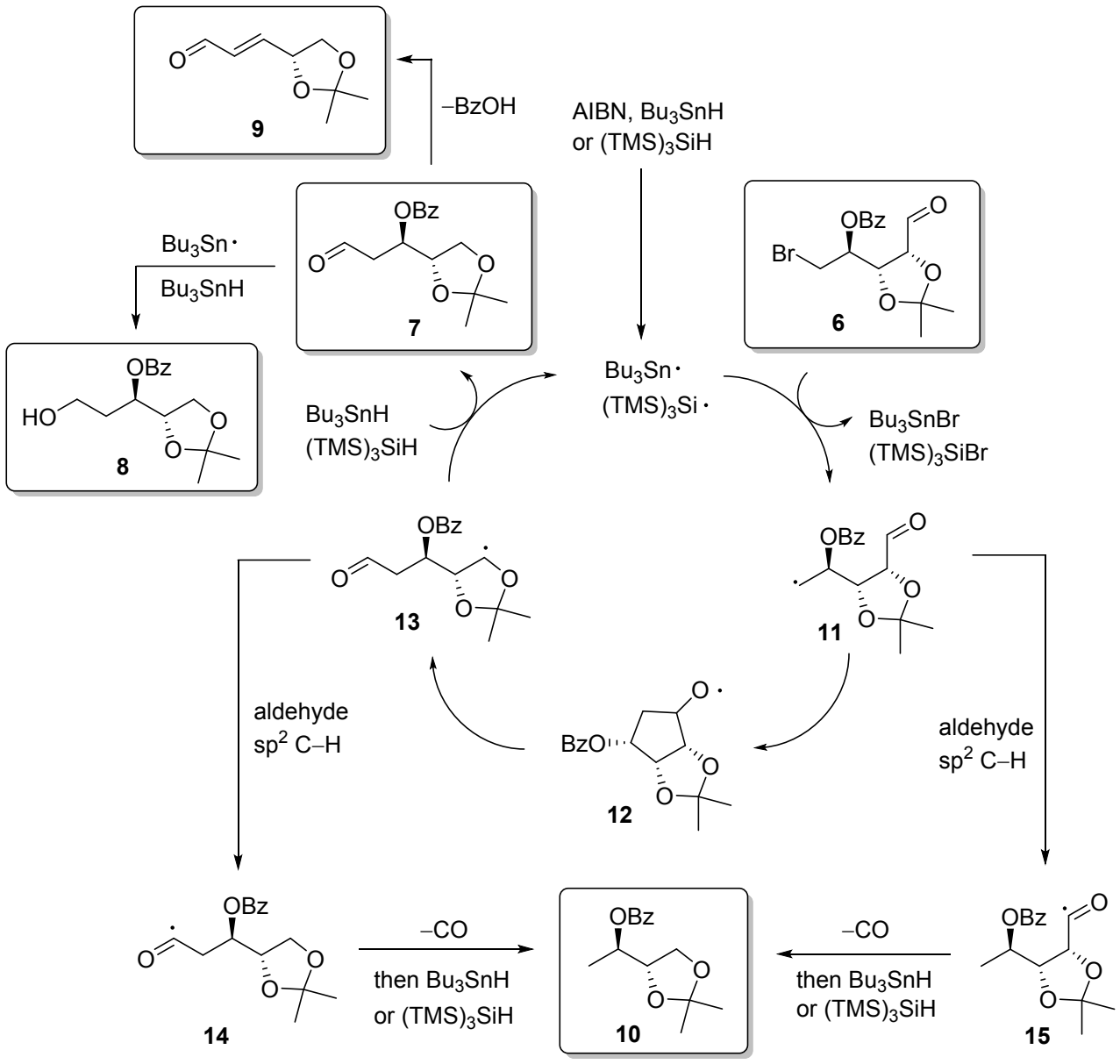
entry	AIBN/Bu_3SnH (equivalents)	concentration (M)	slow addition (mins)	reaction time (mins)	products ratio[a] (**7**:**8**:**9**)
1	(0.2/1.5)	0.03	0	10	1:1.09:0.16[b]
2	(0.2/1.2)	0.03	0	10	1:1.04:0.14
3	(0.1/1.05)	0.03	0	7	1:0.15:0.01[c]
4	(0.05/1.0)	0.03	0	5	1:0.23:0.06

entry	AIBN/TTMSS (equivalents)	concentration (M)	slow addition (mins)	reaction time (mins)	products ratio[a] (**7**:**10**)
5	(0.2/1.5)	0.03	120	120	1:1.64[d]
6	(0.2/1.5)	0.03	30	120	1:1.16
7	(0.2/1.5)	0.03	15	120	1:1.28
8	(0.2/1.5)	0.03	7	120	1:1.29

[a] Product ratios were determined by ^1H NMR integrations.
[b] Compound **7** was unable to isolated; compound **8** was isolated in 29%.
[c] The best result in this table
[d] Compound **10** was isolated in 25%.

Tristrimethylsilylsilane (TTMSS) is an alternative reagent[16] for decreasing the reduction products in the hydrogen abstraction step because the Si–H bond of TTMSS is relatively stronger than the Sn–H bond of Bu_3SnH.[17] Under standard slow addition conditions (entry 5, addition time of 2h), the desired product **7** along with a byproduct **10** were formed in a ratio of **7**:**10** =1:1.64. The byproduct **10** was

produced as a result of the intramolecular hydrogen abstraction from the aldehyde C–H bond, followed by the elimination of a molecule of carbon monoxide (CO). To reduce the amount of byproduct **10** that is formed in the reaction, the addition time was gradually decreased from 120 mins to 7 mins. However, no improvements in product ratios were detected from this technique (entry 6-8). The use of TTMSS as the hydrogen source resulted in a decrease in the amount of reduction product **8**, but the rate for the intermolecular hydrogen abstraction step was also lowered. Therefore, the fragmentation product **10** was produced when TTMSS was used as the hydrogen source (entry 5-8, Table 1).



Scheme 5 Proposed mechanism.

A proposed mechanism for this radical reaction is shown in Scheme 5. Tributyltin radical or tris(trimethylsilyl)silyl (TTMSS) radical were generated respectively by reaction with Bu_3SnH or TTMSS with AIBN. In the cases of tributyltin-mediated reactions (entry 1-4, Table 1), the tributyltin radical reacts with compound **6** to give an alkyl radical **11**. Radical cyclization affords the cyclic alkoxy radical **12**. In our systems, β-fragmentation occurs to generate the α-oxy radical **13** upon regeneration of a carbonyl π-bond, resulting in the carbonyl translocation process. The α-oxy radical

13 abstracts a hydrogen atom from Bu_3SnH to afford the desired product **7** with regeneration of the tributyltin radical, which could participate in radical chain reactions. When an excess amount (1.5 equiv) of Bu_3SnH was used (entry 1, table 1), the over-reduction product **8** was obtained from the reactions of the product **7** with an excess amount of tributyltin radical/tributyltin hydride (Bu_3SnH). The byproduct **9** is generated via elimination reactions of the product **7**, assisted by the Lewis acidity of tributyltin bromide (Bu_3SnBr).[18] The formation of compound **8** and **9** could be suppressed efficiently by reducing the amount of Bu_3SnH used in the reaction (entry3, table 1).

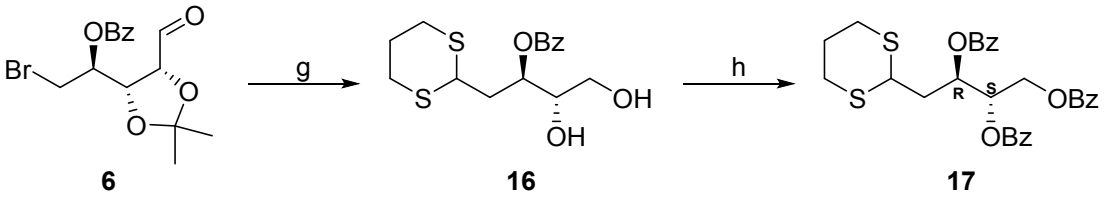
In the cases of tris(trimethylsilyl)silyl (TTMSS) radical-mediated reactions (entry 5-8, Table 1), the product **7** could be generated in a similar manner, through radical cyclization followed by a fragmentation process. However, the different results were observed. The byproduct **10** is formed through TTMSS-mediated reactions. Two mechanisms are possible for the formation of compound **10**. The first possibility is from the alkyl radical **11**. If the cyclization (**11**→ **12**) is not an efficient process, intramolecular hydrogen abstraction from the aldehyde C–H bond (**11**→ **15**) proceeds to give the acyl radical **15**.[19] Compound **10** is obtained upon the release of a CO molecule from the radical **15**. The second possibility is from the α-oxy radical **13**. Because the Si–H bond is relatively stronger than the Sn–H bond, hydrogen abstraction from TTMSS would be relatively slower than an abstraction from Bu_3SnH. The α-oxy radical **13** abstracts a hydrogen atom from TTMSS to give the product **7**, which is not an efficient process. Therefore, the intramolecular abstraction of hydrogen from its aldehyde C–H bond (**13**→ **14**) occurs, in part, to give the acyl radical **14**.[19] Followed by the elimination

of a CO molecule, the product **10** could also be produced through this process. However, the concentration effect (entries 6–8, Table 1) indicates that adjustments in a slow addition time (from 120 mins to 7 mins) had almost no influence on the product ratios. It can therefore be concluded that compound **10** may be formed from the alkyl radical **11** through the acyl radical **15** upon releasing a CO molecule.[19]

In general, the compound **6** bearing an isopropylidine protecting group on the syn-diol moieties showed an enhanced cyclization rate to give the desired product **7** through cyclization followed by a fragmentation process. However, an excess amount of Bu_3SnH reagent would result in the formation of the over-reduction product **8** and the elimination product **9**. But this could be suppressed by lowing the amount of Bu_3SnH reagent used in the reaction. In the TTMSS-mediated reactions, neither the cyclization reaction (**11** → **12**) nor hydrogen abstraction (**13** → **7**) are efficient processes. Hence, both radicals **11** and **13** are involved in partial elimination reactions to give the compound **10** upon releasing a molecule of CO.

Concerning the synthesis of the mirror image deoxyribonucleoside, the radical reaction product **7** needed to be isolated and its stereochemistry indirectly confirmed. The crude reaction mixture from the radical reaction (entry 3, Table 1) was directly treated with 1,3-propanedithiol in the presence of borontrifluoride-diethyletherate ($BF_3{\cdot}OEt_2$)[20] to give the dithiane **16** with partial deprotection of the isopropylidine group, as shown in Scheme 6. Therefore, direct quenching with aqueous hydrochloride

(0.1 N) furnished compound **16** in 51% (over four steps, **5** → **16**). At this stage, we confirmed that we developed a unique methodology for transforming D-ribose to a 2-deoxy-L-ribose derivative **16** in 7 steps.[21] The dithiane **16** is a convenient synthon for many syntheses in which dithioacetal 2-deoxy-L-ribose is used.[22] Direct protection of the two other hydroxyl groups of compound **16** produced compound **17** as a while solid. The stereochemistry and configuration of compound **17** was confirmed by an X-ray crystal structure analysis, which showed that it is indeed a derivative of 2-deoxy-L-ribose with a (3*R*,4*S*) configuration, as shown in Figure 1. Compared to previously reported methods,[21] this is one of the practical method for transforming D-ribose to 2-deoxy-L-ribose.



6 **16** **17**

Scheme 6 *Reagents and Conditions*: (g) 1) AIBN, Bu_3SnH, toluene, 88 °C, 7 min; 2) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −10 °C, 30 min; 3) 0.1 N HCl, 0 °C, 1 h, 51% (over four steps); (h) BzCl, Et_3N, CH_2Cl_2, 0 °C~rt, 10 h, 63%.

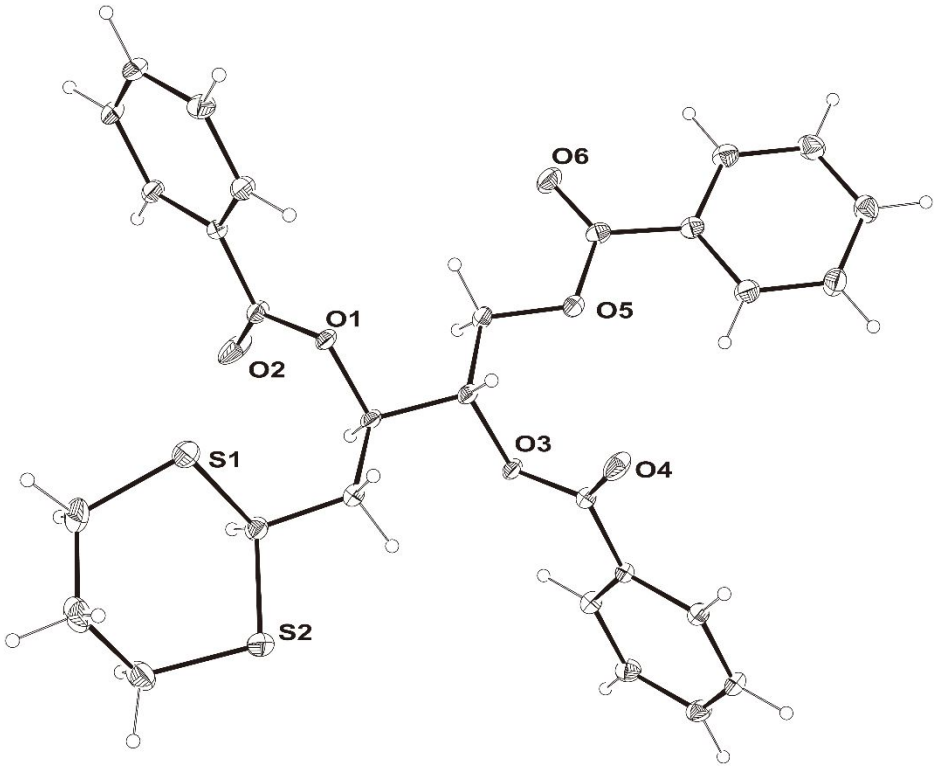
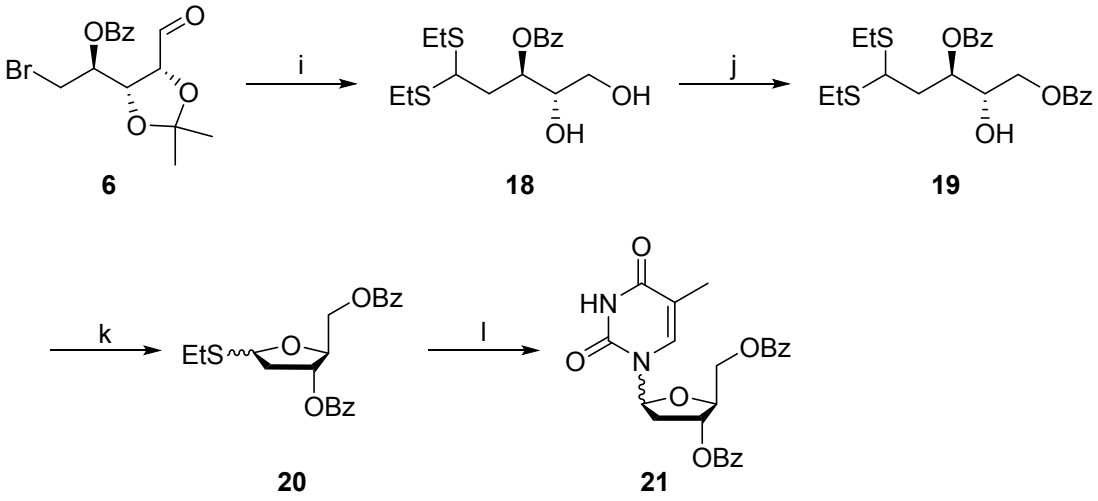


Figure 1. X-ray crystal structure of compound **17** with a (3*R*,4*S*) configuration.

To extend this synthetic methodology to the synthesis of the mirror image deoxyribonucleoside or L-DNA, an acyclic dithiane (diethylthio acetal) derivative was employed to prepare an alkyl *S*-2-deoxy-L-riboside, which is a 2-deoxy-L-ribosyl sugar synthon for glycosylation reactions with a nucleobase, as shown in Scheme 7. Direct treatment of the crude radical products with ethanethiol (EtSH) in the presence of $BF_3{\cdot}OEt_2$ and followed by quenching with an aqueous HCl solution completed the formation of the diethylthio acetal **18** with a 2-deoxy-L-ribose configuration.[23] Regioselective benzoylation in the presence of a catalytic amount of dimethyltin dichloride (Me_2SnCl_2) gave compound **19**.[24] A NIS-promoted cyclization reaction[25] furnished ethyl *S*-2-deoxy-L-riboside **20**, which can be used as a 2-deoxy-L-ribosyl sugar synthon for the synthesis of various L-deoxyribonucleosides. Compared to other syntheses,[21] We could use this synthetic methodology for

converting D-ribose to a 2-deoxy-L-ribosyl sugar synthon **20** in nine steps and to L-deoxyribonucleosides in ten steps. Formal total synthesis of L-dT could be completed by treating *S*-2-deoxy-L-riboside **20** with silylated Thymine, as reported in the literature.[26]



Scheme 7 *Reagents and Conditions*: (i) 1) AIBN, Bu_3SnH, toluene, 88 °C, 7 min; 2) EtSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −10 °C, 30 min; 3) 0.1 N HCl, 0 °C, 1 h, 43% (over four steps); (j) BzCl, Me_2SnCl_2, K_2CO_3, THF, 0 °C~rt, 1.5 h, 63%; (k) NIS, CH_2Cl_2, 0 °C, 15 min, 62%; (l) Silylated Thymine, NBS, DCM, rt. 10 h, 99 %, (α/β = 1/0.3).

Conclusions

A synthetic approach for preparing mirror image deoxyribonucleosides (L-deoxyribonucleoside) from D-ribose is reported. Starting from inexpensive D-ribose, an acyclic D-form carbohydrate precursor was synthesized and then used in a unique radical reaction involving a carbonyl translocation process. In this novel radical reaction, not only was the configuration of the sugar transformed from D to L, but

deoxygenation at the C(2) position of the sugar could be achieved. This is one of the most practical methods for converting a D-sugar to a 2-deoxy-L-sugar in a single organic reaction. To further identify the reaction product, radical reactions followed by treatment with 1,3-propanedithiol and further benzoylation afforded a dithioacetal derivative. The stereochemistry and configuration of the L-2-deoxyribose derivative were confirmed by an X-ray crystal structure. To further apply this methodology to the synthesis of L-deoxyribonucleosides, diethyl thioacetal formation, followed by selective benzoyl protection, and an NIS-initiated cyclization reaction gave the desired ethyl *S*-2-deoxy-L-riboside, which can be used as a 2-deoxy-L-ribosyl sugar synthon for the synthesis of various L-deoxyribonucleosides. This synthetic methodology represents another method for preparing mirror image deoxynucelosides, such as L-dT, starting from an inexpensive D-sugar. The overall conversion was completed within ten steps. Since some L-deoxyribonucleosides are antitumor or antiviral agents, the development of potential L-deoxyribonucleosides with chemotherapeutic activities using these methods are currently underway. Meanwhile, a combination of the methods here and phosphorylation methods[27] developed in our laboratory for the synthesis of various L-deoxynucleotides or L-DNA are also ongoing.

Experimental Section

General. ^{1}H NMR (300 MHz),^{13}C{^{1}H}-DEPT-NMR (75 MHz) for proton-decoupled carbon data, 2D spectra were recorded on a 300 MHz. The NMR spectra were recorded in $CDCl_3$ or CD_3OD.

Chloroform (δ = 7.26 ppm in ^{1}H NMR; δ = 77.0 ppm in ^{13}C NMR) and methanol (δ = 3.31 ppm in ^{1}H NMR; δ = 49.00 ppm in ^{13}C NMR) were used as internal standard, respectively. Splitting patterns were reported as following: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet. Coupling constant (J) was reported in Hz. IR were recorded on a FT-IR spectrometer and reported in cm^{-1}. High resolution mass spectrometry (HRMS) were recorded on a LCMS-IT-TOF spectrometer (ESI-MS) or a magnetic sector spectrometer (EI-MS). Optical rotations were measured on a Digital polarimeter. Crystallographic data were obtained from a Single Crystal XRD. Elementary analysis (EA) were recorded on a c u b e spectrometer. TLC (0.25 mm) precoated sheet was used. The reaction products were isolated by flash chromatography performed on (0.040–0.063 mm) silica gel. Yields of products refer to chromatographically purified products unless otherwise stated. THF were distilled by refluxing them over traces of sodium metal using benzophenone as indicator under N_2. Toluene were distilled by refluxing them over traces of sodium metal under N_2. Dichloromethane, pyridine, triethylamine, and dimethylformamide were dried over CaH_2 and then distilled. Methanol and ethanol was dried over magnesium/iodine and then distilled. Benzoyl chloride were distilled before use. The toluene used for radical cyclizations was deoxygenated by passing a gentle stream of argon through for 30 min before use. All reactions were performed under a blanket of N_2 or Ar.

2,3-*O*-Isopropylidene-β-D-ribofuranose (1)

To a solution of D-ribose (4.00 g, 26.64 mmol) in 40 mL of reagent grade acetone was slowly added con. H_2SO_4 (0.12 mL). The reaction mixture was stirred at rt for 1.5 h. The reaction mixture

was added solid $NaHCO_3$ to neutralize the solution until the pH value was 7 and then directly concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 60/40 to give the desired product **1** (3.56 g, 70%) as a colorless oil. $[\alpha]^{23}_D$ −39.05 (c = 1.68, acetone); IR (neat) 3373 (OH), 1265 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.39 (d, J = 6.0 Hz, 1H, H_1), 5.19 (br s,1H, OH), 4.81 (d, J = 6.0 Hz, 1H, H_3), 4.56 (d, J = 6.0 Hz, 1H, H_2), 4.38 (br s, 1H, H_4), 3.93 (br s, 1H, OH), 3.77–3.62 (m, 2H, H_5, H_5'),1.47 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.1 (C), 102.8 (CH), 87.7 (CH), 86.7 (CH), 81.6 (CH), 63.5 (CH_2), 26.3 (CH_3), 24.7 (CH_3); HRMS (ESI^-): m/z calcd. for $C_8H_{13}O_5$ $[M-H]^-$: 189.0762; found: 189.0759.

5,6-Dideoxy-3,4-*O*-isopropylidene-D-ribo-hex-5-enitol (2)

To a refluxing solution of methyltriphenylphosphonium bromide (2.94 g, 8,23 mmol) in 8 mL of tetrahydrofuran was added potassium *tert*-butoxide (0.74 g, 6.58 mmol). The mixture was refluxed for 30 mins, and then was added a solution of compound **1** (0.63 g, 3.29 mmol) in 8.5 mL of tetrahydrofuran. The mixture was refluxed for another 1 h. The reaction was quenched with water (30 mL) and then concentrated to dryness under vacuum. The residue was dissolved in EtOAc (150 mL), washed with saturated $NaHCO_{3(aq)}$ (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 7/3 to 1/5 to give the desired product **2** (0.48 g, 77%) as a colorless oil. $[\alpha]^{20}_D$ +5.86 (c = 2.71, $CHCl_3$); IR (neat) 3407 (OH) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (ddd,

J = 17.1, 10.2, 7.0 Hz, 1H, H_5), 5.46 (d, J = 17.1 Hz, 1H, H_6), 5.33 (d, J = 10.5 Hz, 1H, H_6'), 4.70 (t, J = 6.6 Hz, 1H, H_4), 4.10 (t, J = 7.1 Hz, 1H, H_3), 3.86–3.77 (m, 1H, H_1), 3.77–3.66 (m, 2H, H_1', H_2), 2.37 (br s,2H, OH), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.7 (C), 118.5 (CH_2), 109.0 (C), 78.5 (CH), 78.1 (CH), 69.8 (CH), 64.3 (CH_2), 27.7 (CH_3), 25.2 (CH_3); HRMS (ESI$^+$) : m/z calcd. for $C_9H_{17}O_4$ $[M+H]^+$: 189.1121; found: 189.1122.

5,6-Dideoxy-3,4-*O*-isopropylidene-1-*O*-toluenesulfonate-D-ribo-hex-5-enitol (3)

To a solution of compound **2** (3.71 g, 19.71 mmol) in 66 mL of dry CH_2Cl_2 was added dibutyltin oxide (0.10 g, 0.39 mmol). This solution was then cooled to 0 °C before triethylamine (4.10 mL, 29.57 mmol) was added. Then, the reaction solution was added *p*-toluenesulfonyl chloride (4.13 g, 21.68 mmol) under Ar. The resulting mixture was stirred at rt for 5.5 h. The reaction was then quenched with water (80 mL) and concentrated to dryness under vacuum. The residue was dissolved in EtOAc (240 mL), washed with saturated $NaHCO_{3(aq)}$ (80 mL), and brine (80 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 30/70 to give the desired product **3** (6.42 g, 95%) as a colorless oil. $[\alpha]^{24}_D$ +29.20 (c = 2.12, $CHCl_3$); IR (neat) 3579 (OH) cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 5.93 (ddd, J = 17.1, 10.5, 6.5 Hz, 1H, H_5), 5.42 (d, J = 17.1 Hz, 1H, H_6), 5.28 (d, J = 10.5 Hz, 1H, H_6'), 4.68 (t, J = 6.3 Hz, 1H, H_4), 4.31 (dd, J = 10.5, 2.3 Hz, 1H, H_1), 4.07 (dd, J = 10.5, 6.6 Hz, 1H, H_1'), 4.00 (dd, J = 9.0, 6.3 Hz, 1H, H_3), 3.84 (t, J = 6.8 Hz,

1H, H_2), 2.45 (s, 3H, PhC$\underline{H}_3$), 1.39 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1 (C), 133.1 (CH), 132.6 (C), 129.9 (CH), 128.1 (CH), 118.4 (CH_2), 109.1 (C), 78.2 (CH), 77.5 (CH), 72.2 (CH_2), 68.3 (CH), 27.6 (CH_3), 25.2 (CH_3), 21.7 (CH_3) ; HRMS (ESI$^+$) : m/z calcd. for $C_{16}H_{22}O_6SNa$ $[M+Na]^+$: 365.1029; found: 365.1031.

1-Bromo-5,6-dideoxy-3,4-*O*-isopropylidene-D-ribo-hex-5-enitol (4)

To a flask containing solid tetrabutylammonium bromide (7.50 g, 23.15 mmol) was dried under reduced pressure at 50–60 °C for 3 h, and then it was added a solution of compound **3** (3.17 g, 9.26 mmol) in 46 mL of dry dimethylformamide. The resulting mixture was stirred at 70–80 °C for 1 h. The reaction was concentrated to dryness under vacuum. The residue was dissolved in EtOAc (230 mL), washed with water (45 mL), saturated $NaHCO_{3(aq)}$ (45 mL), and brine (45 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 10/90 to 30/70 to give the desired product **4** (2.05 g, 88%) as a colorless oil. $[\alpha]^{25}_D$ +12.80 (c = 2.13, $CHCl_3$); IR (neat) 1217 (C-O) cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (ddd, J = 17.1, 10.5, 6.6 Hz, 1H, H_5), 5.46 (dt, J = 17.1, 1.5 Hz, 1H, H_6), 5.32 (dt, J = 10.5, 1.5 Hz, 1H, H_6'), 4.72 (t, J = 6.5 Hz, 1H, H_4), 4.06 (dd, J = 8.7, 6.3 Hz, 1H, H_3), 3.81–3.71 (m, 2H, H_1,H_2), 3.58 (dd, J = 10.5, 7.1 Hz, 1H, H_1'), 2.21 (d, J = 5.4 Hz, 1H, OH), 1.47 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4 (C), 118.3 (CH_2), 109.1 (C), 78.6 (CH), 78.3 (CH), 69.2 (CH), 38.5 (CH_2), 27.7 (CH_3), 25.3 (CH_3); *Note: this is a special case. Due to the molecular ion (M^+)*

is not stable in the ion channel, several attempts to obtain the molecular peak (M^+) were not successful. Eventually, we found a peak of (M^+–CH_3), which could be referred to the elimination of a [CH_3] *fragment from the isopropylidine group.* HRMS (EI^+): m/z calcd. for $C_8H_{12}O_3{}^{79}Br$ $[M–CH_3]^+$: 234.9969; found: 234.9967; m/z calcd. for $C_8H_{12}O_3{}^{81}Br$ $[M–CH_3]^+$: 236.9949; found: 236.9956.

2-Benzoyl-1-bromo-5,6-dideoxy-3,4-*O*-isopropylidene-D-ribo-hex-5-enitol (5)

To a solution of compound **4** (3.98 g, 15.85 mmol) in 53 mL of dry CH_2Cl_2 was added 4-dimethylaminopyridine (0.02 g, 0.16 mmol). This solution was then cooled to 0 °C before trimethylamine (3.30 mL, 23.77 mmol) and benzoyl chloride (2.20 mL, 19.02 mmol) were added. The resulting mixture was stirred at rt for 7 h. The reaction was quenched with water (10 mL) and then concentrated to dryness under vacuum. The residue was dissolved in EtOAc (240 mL), washed with saturated $NaHCO_{3(aq)}$ (80 mL), and brine (80 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 1/20 to give the desired product **5** (5.63 g, 90%) as a colorless oil. $[\alpha]^{25}_D$ –24.28 (c = 2.07, $CHCl_3$); IR (neat) 1723 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H), 7.59 (tt, J = 7.5, 1.5 Hz, 1H), 7.45 (t, J = 6.9 Hz, 2H), 5.77 (ddd, J = 17.1, 10.2, 6.8 Hz, 1H, H_5), 5.32 (dt, J = 17.1, 1.3 Hz, 1H, H_6), 5.13–5.04 (m, 2H, H_6', H_2), 4.76 (t, J = 6.5 Hz, 1H, H_4), 4.57 (dd, J = 8.4, 6.3 Hz, 1H, H_3), 3.83 (dd, J = 3.3, 1.1 Hz, 2H, H_1), 1.52 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 165.1 (C), 133.4 (CH), 132.0 (CH), 129.7 (CH×2), 129.5 (C), 128.4 (CH×2), 118.5 (CH_2), 109.3 (C), 78.1 (CH), 76.3 (CH), 69.8 (CH), 33.3 (CH_2), 27.7 (CH_3), 25.3 (CH_3) ； HRMS (ESI^+) : m/z calcd. for $C_{16}H_{20}O_4{}^{79}Br$ $[M+H]^+$: 355.0539; found: 355.0540; m/z calcd. for $C_{16}H_{20}O_4{}^{81}Br$ $[M+H]^+$: 357.0519; found: 357.0514.

2-Benzoyl-1-bromo-3,4-*O*-isopropylidene-D-ribose (6)

The compound **5** (0.62 g, 1.74 mmol) was dissolved in 17 mL of dry CH_2Cl_2 in a round-bottomed flask with the concentration of 0.1 M. The solution was cooled to −78 °C, and then a stream of ozone (O_3) was bubbled into the reaction solution through a pipet for about 20 min. Once the color of the solution turned blue, oxygen (O_2) was continuously bubbled into the reaction for another 5 min in order to disperse the ozone remained in the reaction solution. While the color of solution turned from blue to colorless, excess of Me_2S (3.5 mL) was added at −78 °C. The reaction temperature was allowed to warm up gradually to the room temperature and the reaction mixture was stirred at rt for 4 h. The resulting solution was directly concentrated to give the desired aldehyde product **6** (0.62 g, >99%) as a colorless viscous liquid. $[\alpha]^{23}_D$ −32.16 (c = 1.83, $CHCl_3$); IR (neat) 1728 (C=O) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 9.65 (d, J = 3.0 Hz, 1H, H_1), 8.00 (d, J = 7.2 Hz, 2H), 7.60 (tt, J = 7.4, 1.6 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 5.27 (dt, J = 7.8,3.9 Hz, 1H, H_4), 4.87 (t, J = 7.4 Hz, 1H, H_3), 4.59 (dd, J = 6.9, 2.9 Hz, 1H, H_2), 3.84 (dd, J = 11.4, 4.2 Hz, 1H, H_5), 3.76 (dd, J = 11.4, 3.6 Hz, 1H, H_5'), 1.58 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4 (CH), 164.9 (C), 133.7 (CH), 129.9 (CH×2),

128.9 (C), 128.6 (CH×2), 111.6 (C), 80.7 (CH), 76.8 (CH), 69.4 (CH), 31.8 (CH_2), 27.4 (CH_3), 25.3 (CH_3); HRMS (ESI^+): m/z calcd. for $C_{15}H_{18}O_5{}^{79}Br$ $[M+H]^+$: 357.0332; found: 357.0334; m/z calcd. for $C_{15}H_{18}O_5{}^{91}Br$ $[M+H]^+$: 359.0312; found: 359.0308.

(3*R*,4*S*)-3-Benzoyl-4,5-*O*-isopropylidene-1,3,4,5-pentanetetrol (8)

To a refluxed solution of the radical precursor **6** (85.90 mg, 0.24 mmol) in 4 mL of toluene at 88 °C was added a solution of AIBN (8.00 mg, 0.05 mmol) and tributyltin hydride (0.10 mL, 0.36 mmol) in 4 mL of toluene. The resulting solution was continuously stirred at the same temperature for 10 min. The solution was then cooled down and directly concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 40/60 to give the desired product **8** (19.2 mg, 29%) as a colorless oil. $[\alpha]^{26}_D$ –119.48 (c = 0.12, $CHCl_3$); IR (neat) 3437 (OH), 1718 (C=O) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d,*J* = 7.9 Hz, 2H), 7.59 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 5.32 (ddd, *J* = 9.3, 5.7, 3.6 Hz, 1H, H_3), 4.32 (q, *J* = 6 Hz, 1H, H_4), 4.13 (dd, *J* = 8.4, 6.6 Hz, 1H, H_5), 3.94 (dd, *J* = 8.4, 1.6 Hz, 1H, H_5'), 3.75 (ddd, *J* = 11.7, 5.6, 4.4 Hz, 1H, H_1), 3.63 (ddd, *J* = 11.7, 9.8, 3.8 Hz, 1H, H_1'), 2.15–2.02 (m, 1H, H_2), 1.88–1.76 (m, 1H, H_2'), 1.39 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 133.4 (CH), 129.8 (CH×2), 129.5 (C), 128.5 (CH×2), 109.9 (C), 77.0 (CH), 72.0 (CH), 66.2 (CH_2), 58.2 (CH_2), 34.2 (CH_2), 26.4 (CH_3), 25.1 (CH_3); HRMS (ESI^+): m/z calcd. for $C_{15}H_{21}O_5$ $[M+H]^+$: 281.1384; found: 281.1387.

(2*S*,3*R*)-2-Benzoyl-3,4-*O*-isopropylidenebutane (10)

To a refluxed solution of the radical precursor **6** (0.20 g, 0.57 mmol) in 9.5 mL of toluene at 88 °C was added a solution of AIBN (0.02 g, 0.11mmol) and TTMSS (0.26 mL, 0.86 mmol) in 9.5 mL of toluene over 1h via a syringe pump. The resulting solution was continuously stirred at the same temperature for another 2h. The solution was then cooled and directly concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 1/12 to give the desired product **10** (39.40 mg, 25%) as a colorless oil. $[\alpha]^{23}_{D}$ –34.16 (c = 0.57, $CHCl_3$); IR (neat) 1718 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 7.8Hz, 2H), 7.55 (tt, J = 7.2, 1.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 5.25–5.14 (m, 1H, H_2), 4.23 (q, J = 5.9 Hz, 1H, H_3), 4.11 (dd, J = 8.4, 6.8 Hz, 1H, H_4), 3.92 (dd, J = 8.4, 6 Hz, 1H, H_4'), 1.38 (d, J = 6.6 Hz, 3H, H_1, overlapping with two s at 1.40 and at 1.37, CH_3×2, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (C), 133.0 (CH), 130.2 (C), 129.6 (CH×2), 128.3 (CH×2), 109.7 (C), 77.7 (CH), 71.1 (CH), 66.1 (CH_2), 26.4 (CH_3), 25.2 (CH_3), 16.3 (CH_3); HRMS (ESI^+) : m/z calcd. for $C_{14}H_{19}O_4$ $[M+H]^+$: 251.1278; found: 251.1279.

(*3R*,4*S*)-1-(1,3-Dithian-2-yl)-4,5-dihydroxypentan-2-yl benzoate (16)

To a refluxed solution of the radical precursor **6** (0.44 g, 1.22 mmol) in 20.4 mL of toluene at 88 °C was added a solution of AIBN (0.02 g, 0.12 mmol) and tributyltin hydride (0.34 mL,1.28 mmol) in 20.3 mL of toluene. The resulting solution was continuously stirred at the same temperature for 7

min. The solution was then cooled and directly concentrated to give a crude residue, which was directly used for the next step without further purification.

To a solution of the previous crude residue (0.34 g, 1.22 mmol) in 2.4 mL of CH_2Cl_2 were added 1,3-propanedithiol (0.25 mL, 2.44 mmol) and $BF_3{\cdot}OEt_2$ (1.30 mL, 9.77 mmol) at −10 °C. The reaction mixture was stirred at the same temperature for 30 min then was added 0.1 N HCl (2.4 mL) at the same temperature. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was worked up by addition of saturated $NaHCO_{3(aq)}$ and then concentrated to dryness under vacuum. The residue was dissolved in EtOAc (100 mL) washed with saturated $NaHCO_{3(aq)}$ (20 mL× 2) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes =30/70 to 50/50 to give the desired product **16** (0.21 g, 51%, over four steps) as a coloress oil. $[\alpha]^{23}_D$ +47.19 (c = 1.04, $CHCl_3$); IR (neat) 3045 (OH), 1716 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.07 (d, *J* = 8.1 Hz, 2H), 7.60 (tt, *J* = 7.4, 1.6 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 5.32 (ddd, *J* = 9.3, 7.1, 2.6 Hz, 1H, H_3), 4.13 (dd, *J* = 9.0, 5.3 Hz, 1H, H_1), 3.76–3.55 (m, 3H, H_4,H_5, H_5'), 2.90–2.70 (m, 6H, SCH_2×2, OH×2), 2.49 (ddd, *J* = 15.0, 9.3, 2.7 Hz, 1H, H_2'), 2.29 (ddd, *J* = 15.0, 9.5, 5.6 Hz, 1H, H_2), 2.13–2.00 (m, 1H, $SCH_2C\underline{H}_2$), 1.94–1.80 (m, 1H, $SCH_2C\underline{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 133.6 (CH), 130.0 (CH×2), 129.3 (C), 128.5 (CH×2), 72.9 (CH), 71.9 (CH), 62.1 (CH_2), 43.6 (CH), 36.8 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 25.6 (CH_2) ; HRMS (ESI^+): m/z calcd. for $C_{15}H_{20}O_4S_2Na$ $[M+Na]^+$: 351.0695; found: 351.0698.

(3*R*,4*S*)-1-(1,3-Dithian-2-yl)pentane-3,4,5-triyl tribenzoate (17)

To a solution of compound **16** (0.02 g, 0.07 mmol) in 0.33 mL of dry CH_2Cl_2. This solution was then cooled to 0 °C before trimethylamine (0.03 mL, 0.23 mmol) and benzoyl chloride (0.02 mL, 0.16 mmol) was added. The resulting mixture was stirred at rt for 10 h. The reaction was quenched with water (6 mL). The residue was dissolved in CH_2Cl_2 (20 mL), washed with saturated $NaHCO_{3(aq)}$ (6 mL), and brine (6 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 15/85 to 25/75 to give the desired product **17** (0.02 g, 63%) as a white solid.mp 116–118 ℃; $[\alpha]^{25}_D$ +3.68 (c = 2.15, $CHCl_3$); IR (neat) 1722 (C=O) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08–7.96 (m, 6H), 7.62–7.50 (m, 3H), 7.48–7.36 (m, 6H), 5.89 (dt, J = 9.3, 3.8 Hz, 1H, H_3), 5.80 (dt, J = 6.6, 4.2 Hz, 1H, H_4), 4.74 (dd, J = 12.0, 4.2 Hz, 1H, H_5), 4.60 (dd, J = 12.0, 6.9 Hz, 1H, H_5'), 4.15 (dd, J = 9.0, 5.4 Hz, 1H, H_1), 2.92–2.72 (m, 4H, SCH_2×2), 2.51–2.29 (m, 2H, H_2,H_2'), 2.14–2.01 (m, 1H, $SCH_2C\underline{H}_2$), 1.94–1.77 (m, 1H, $SCH_2C\underline{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (C), 165.6 (C), 165.5 (C), 133.3 (CH_2×2), 133.1 (CH), 129.9 (CH), 129.8 (CH), 129.7 (CH), 129.6 (C), 129.4 (C×2), 128.5 (CH×2), 128.4 (CH), 72.2 (CH), 70.2 (CH), 62.6 (CH_2), 43.1 (CH), 36.3 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 25.6 (CH_2); HRMS (ESI^+): m/z calcd. for $C_{29}H_{29}O_6S_2$ $[M+H]^+$: 537.1400; found: 537.1412.

(3*R*,4*S*)-1,1-Bis(ethylthio)-4,5-dihydroxypentan-3-yl benzoate (18)

To a refluxed solution of the radical precursor **6** (0.11 g, 0.31 mmol) in 5.1 mL of toluene at 88 °C was added a solution of AIBN (5.10 mg, 0.03mmol) and tributyltin hydride (0.09 mL, 0.32 mmol) in 5.1 mL of toluene. The resulting solution was continuously stirred at the same temperature for 7 min. The solution was then cooled and directly concentrated to give a crude residue, which was directly used for the next step without further purification.

To a solution of the previous crude residue (0.09 g, 0.31 mmol) in 0.6 mL of CH_2Cl_2 were added ethanethiol (0.11 mL, 1.54 mmol) and $BF_3{\cdot}OEt_2$ (0.30 mL, 2.46 mmol) at −10 °C. The reaction mixture was stirred at the same temperature for 30 min and then was added 0.1 N HCl (0.6 mL). The reaction mixture was stirred at 0 °C for 1 h. The reaction was worked up by addition of saturated $NaHCO_{3(aq)}$ and then concentrated to dryness under vacuum. The residue was dissolved in EtOAc (60 mL) washed with saturated $NaHCO_{3(aq)}$ (10 mL), brine (10 mL), dried over$MgSO_4$, filtered, and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes =40/60 to 50/50 to give the desired product **18** (0.11 g, 43%, over four steps) as a colorless oil. $[\alpha]^{23}_D$ +50.80 (c = 0.62, $CHCl_3$); IR (neat) 3406 (OH), 1740 (C=O) cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) 8.04 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 5.39 (ddd, *J* = 10.8, 8.7, 3.6 Hz, 1H, H_3), 3.91 (dd, *J* = 9.6, 5.1 Hz, 1H, H_1), 3.78–3.56 (m, overlapping with one dd at 3.60, *J* = 12.3, 4.1 Hz, H_4,H_5, H_5'), 2.96 (br s, 1H, OH), 2.85 (br s, 1H, OH), 2.76–2.49 (m, 4H, $SC\underline{H}_2$×2), 2.49–2.28 (m, 2H, H_2,H_2'), 1.22 (t, *J* = 7.5 Hz, 3H, $SCH_2C\underline{H}_3$), 1.17 (t, *J* = 7.5 Hz, 3H, $SCH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 133.6 (CH), 129.8 (CH×2), 129.3 (C), 128.5 (CH×2), 72.9 (CH), 72.6 (CH), 62.2 (CH_2), 47.6 (CH), 37.5 (CH_2), 24.3 (CH_2), 23.6 (CH_2), 14.3 (CH_3×2); HRMS (ESI^+): m/z calcd.

for $C_{16}H_{24}O_4S_2Na$ $[M+Na]^+$: 367.1008; found: 367.1005.

2-Deoxy-3,5-Di-*O*-benzoyl-L-ribose diethyl dithioacetal (19)

To a solution of compound **18** (28.80 g, 0.08 mmol) in 0.42 mL of tetrahydrofuran. Then, was added dimethyltin dichloride (0.20 mg, 0.84 μmol) under nitrogen. This solution was then cooled to 0 °C and stirred at the same temperature for 15 min before potassium carbonate (23.20 mg, 0.17 mmol) and benzoyl chloride (12.00 μL, 0.01 mmol) was added. The resulting mixture was stirred at rt for 1.5 h. The reaction was quenched with water and then concentrated to dryness under vacuum. The residue was dissolved in EtOAc (30 mL), washed with saturated $NaHCO_{3(aq)}$ (4 mL), and brine (4 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 15/85 to 25/75 to give the desired product **19** (23.70 mg, 63%) as a colorless oil. $[\alpha]^{24}_D$ –6.94 (c = 0.47, $CHCl_3$); IR (neat) 3481 (OH), 1722 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.09–7.99 (m, 4H), 7.61–7.53 (m, 2H), 7.48–7.39 (m, 4H), 5.67–5.59 (m, 1H, H_3), 4.53 (dd, *J* = 11.7, 4.1 Hz, 1H, H_5), 4.42 (dd, *J* = 11.7, 6.6 Hz, 1H, H_5'), 4.27 (br s, 1H, H_4), 3.95 (dd, *J* = 9.6, 4.8 Hz, 1H, H_1), 2.97 (br s, 1H, OH), 2.76–2.53 (m, 4H, $SC\underline{H}_2\times2$), 2.53–2.39 (m, 1H, H_2), 2.27 (ddd, *J* = 14.4, 10.2, 3.8 Hz, 1H, H_2'), 1.22 (t, *J* = 7.5 Hz, 3H, $SCH_2\underline{H}_3$), 1.19 (t, *J* = 7.5 Hz, 3H, $SCH_2\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C), 166.3 (C), 133.4 (CH), 133.2 (CH), 129.7 (CH×4), 129.5 (C×2), 128.5 (CHx2), 128.4 (CH×2), 73.7 (CH), 71.5 (CH), 65.6 (CH_2), 47.5 (CH), 37.0 (CH_2), 24.3 (CH_2), 23.9 (CH_2),14.3 ($CH_3\times2$); HRMS (ESI^+): m/z calcd. for

$C_{23}H_{28}O_5S_2Na$ $[M+Na]^+$: 471.1270; found: 471.1265.

Ethyl 3,5-di-*O*-benzoyl-2-deoxy-1-thio-L-threo-pentofuranoside (20)

To a reaction mixture of compound **19** (0.017 g, 0.039 mmol) and solid $NaHCO_3$ (0.003 g, 0.039 mmol) in 0.2 mL of CH_2Cl_2, was cooled to 0 °C and *N*-iodosuccinimide (0.008 g, 0.035 mmol, 0.9 equiv) was added. The reaction mixture was stirred at the same temperature for 15 min. The reaction was then quenched with saturated sodium thiosulfate (0.6 mL) and the residue was dissolved in EtOAc (20 mL), washed with saturated $NaHCO_{3(aq)}$ (5 mL), brine (5 mL). The organic layer was dried over $MgSO_4$ and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 15/85 to 3/7 give the desired product **20** (9.3 mg, 62%, α:β= 1:0.8) as a colorless oil. IR (neat) 1718 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.13–7.98 (m, 4H), 7.63–7.51 (m,2H), 7.51–7.37(m, 4H), 5.64 (dd, J = 7.8, 2.1 Hz, 1H, H_1, major), 5.61–5.55 (m, 1H, H_1, minor), 5.55–5.39 (m, 1H, H_3), 4.72–4.55 (m, 3H, H_4, H_5, H_5'), 2.96–2.82(m, 1H, H_2, major), 2.82–2.62 (m, 2H, $SC\underline{H}_2CH_3$), 2.60–2.49 (m, 1H, H_2, minor), 2.49–2.35 (m, 1H, H_2', minor), 2.19 (d, J = 14.4 Hz,1H, H_2', major), 1.32 (q, J = 7.2 Hz, 3H, $SCH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (C), 165.9 (C), 133.3 (CH×2), 133.1 (CH), 129.8 (CH×2), 129.7 (CH), 128.4 (CH×2), 84.6 (CH), 83.8 (CH), 82.9 (CH), 80.6 (CH), 76.3 (CH), 74.8 (CH), 64.7 (CH_2), 64.1 (CH_2), 39.5 (CH_2), 39.0 (CH_2), 25.9 (CH_2), 25.3 (CH_2), 15.1 (CH_3); HRMS (ESI^+): m/z calcd. for $C_{21}H_{22}O_5SNa$ $[M+Na]^+$: 409.1080; found: 409.1076.

1-(3′,5′-Di-*O*-benzoyl-2′-deoxy-αβ-L-ribofuranosyl)-thymine (21)

To a round-bottomed flask containing *O*,*O*′-bis(trimethylsilyl)thymine (24.30 mg, 0.09 mmol) and molecular sieves 4Å (17.50 mg),was added a solution of compound **20** (17.50 g, 0.05 mmol) in 0.45 mL of CH_2Cl_2. The resulting mixture was stirred at rt for 20 min. Then *N*-bromosuccinimide (8.90 mg, 0.05 mmol) was added and the reaction was stirred at rt for another 20 min. The reaction was diluted in CH_2Cl_2 (20 mL), washed with saturated sodium thiosulfate (5 mL). The organic layer was dried over Na_2SO_4 and concentrated to give a crude product, which was purified by flash chromatography with the eluent of EtOAc/hexanes = 55/45 to give the desired product **21** (22.5 mg, ~99%, α:β= 1:0.3) as a colorless oil. IR (neat) 3459 (NH), 1738 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.54 (s, 1H, NH, major), 8.45 (s, 1H, NH, minor), 8.10–8.01 (m, 2.5H), 7.95–7.89 (m, 1.5H), 7.67–7.56 (m, 2H), 7.53–7.38 (m, 5H), 6.47 (dd, J = 9.0, 5.4 Hz,1H, $H_{1\beta}$), 6.39 (dd, J = 7.2, 1.7 Hz,1H, $H_{1\alpha}$), 5.70–5.60 (m, overlapped with one d at 5.63, J = 6.3Hz, 1H, H_3), 4.91 (t, J = 4.1 Hz,1H, $H_{4\alpha}$), 4.81 (dd, J = 12.0, 2.9 Hz,1H, $H_{5\beta}$), 4.68 (dd, J = 12.3, 3.3 Hz,1H, $H_5'_\beta$), 4.58 (dd, J = 12.0, 4.2 Hz,1H, $H_{5\alpha}$), 4.52 (dd, J = 12.0, 4.5 Hz,1H, $H_5'_\alpha$), 2.98 (dt, J = 15.9, 6.9 Hz,1H, $H_{2\alpha}$), 2.72 (dd, J = 14.7, 5.7 Hz, 1H, $H_{2\beta}$), 2.50 (d, J = 15.0 Hz,1H, $H_2'_\alpha$), 2.41–2.27 (m, 1H, $H_2'_\beta$), 1.86 (d, J = 0.9 Hz,3H, CH_3, H_α),1.61 (d, J = 1.2 Hz,3H, CH_3, H_β); HRMS (ESI^+): m/z calcd. for $C_{24}H_{23}O_7N_2$ $[M+H]^+$: 451.1500; found: 451.1495.

(3*R*,4*S*)-1-(1,3-Dithian-2-yl)pentane-3,4,5-triol (22)

To a solution of compound **16** (0.02 g, 0.04 mmol) in a co-solvent system (THF/MeOH = 1/4, 0.41 mL) was added NaOMe (0.01 g, 0.12 mmol). The resulting mixture was stirred at rt for 3.5 h. The reaction mixture was then added acetic acid to neutralize the solution until the pH value was 7 and then directly concentrated to give a crude product, which was purified by flash chromatography with the eluent of CH_2Cl_2/MeOH = 10/1 to give the desired product **22** (0.01 g, 95%) as a white solid. mp: 116–118 ℃; $[\alpha]^{23}_D$ +39.77 (c = 0.53, MeOH); IR (neat) 3484 (OH) cm^{-1} ; ^1H NMR (300 MHz, CD_3OD) δ 4.30 (dd, J = 10.8, 3.8 Hz, 1H, H_1), 3.84 (ddd, J = 9.9, 6.9, 2.6 Hz, 1H, H_3), 3.73 (dd, J = 11.1, 3.9 Hz, 1H, H_5), 3.57 (dd, J = 11.1, 6.5 Hz, 1H, H_5'), 3.44 (td, J = 6.6, 3.9 Hz, 1H, H_4), 3.03–2.80 (m, 4H, SCH_2×2), 2.19–2.07 (m, 2H, H_2,H_2'), 1.93–1.70 (m, 2H, $SCH_2C\underline{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.5 (CH), 69.9 (CH), 64.8 (CH_2), 44.9 (CH), 40.4 (CH_2), 31.3 (CH_2), 30.6 (CH_2), 27.5 (CH_2); MS (ESI$^+$): m/z calcd. for $C_{23}H_{38}O_9S_3$ $[M+H]^+$: 554.17; found: 554.17. Notes: we additionally made this compound for data comparison, which is not shown in the text and schemes. The enantiomer of compound **22**, prepared from 2-deoxy-D-ribose, were reported in literatures, please see reference 28.

(3*R*,4*S*)-1,1-Bis(ethylthio)pentane-3,4,5-triol (+)-23

To a solution of compound **18** (0.31 g, 0.89 mmol) in a co-solvent system (THF/MeOH = 1/4,

8.80 mL) was added NaOMe (0.05 g, 0.89 mmol). The resulting mixture was stirred at rt for 3 h. The reaction mixture was then added acetic acid to neutralize the solution until the pH value was 7 and then directly concentrated to give a crude product, which was purified by flash chromatography with the eluent of CH_2Cl_2/MeOH = 15/1 to 10/1 to give the desired product (+)-**23** (0.12 g, 84%) as a colorless oil. $[\alpha]^{26}_D$ +19.88(c = 1.28, CH_3OH); IR (neat) 3424 (OH) cm^{-1}; ^1H NMR (300 MHz, CD_3OD) 4.11 (dd, *J* = 11.1, 3.6 Hz, 1H, H_1), 3.89 (ddd, *J* = 9.9, 7.1, 2.6 Hz, 1H, H_3), 3.72 (dd, *J* = 11.1, 3.8 Hz, 1H, H_5), 3.56 (dd, *J* = 11.1, 6.5 Hz, 1H, H_5'), 3.49–3.39 (m, 1H, H_4), 2.79–2.52 (m, 4H, $SC\underline{H}_2\times2$), 2.08 (ddd, *J* = 14.1, 11.4, 2.6 Hz, 1H, H_2), 1.87 (ddd, *J* = 14.4, 10.2, 3.9 Hz, 1H, H_2'), 1.26 (t, *J* = 7.5 Hz, 3H, $SCH_2C\underline{H}_3$), 1.25 (t, *J* = 7.5 Hz, 3H, $SCH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, CD_3OD) δ 76.5 (CH), 70.9 (CH), 64.8 (CH_2), 47.7 (CH), 40.9 (CH_2), 25.3 (CH_2), 24.3 (CH_2), 15.1 (CH_3), 15.0 (CH_3); HRMS (ESI^+): m/z calcd. for $C_9H_{20}O_3S_2Na$ $[M+Na]^+$: 263.0746; found: 263.0743.

(3*S*,4*R*)-1,1-Bis(ethylthio)pentane-3,4,5-triol (–)-23

To a round-bottom flask containing 2-deoxy-D-ribose (0.50 g, 3.73 mmol) was cooled to 0 °C, then was added ethanethiol (0.70 mL,9.32 mmol) and con. HCl (2.30 mL). The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then added lead(II) carbonate to neutralize the solution until the pH value was 7 and then directly concentrated to give a crude product, which was purified by flash chromatography with the eluent of CH_2Cl_2/MeOH = 18/1 to 10/1 to give the desired product (–)-**23** (0.74 g, 83%) as a colorless oil. $[\alpha]^{26}_D$ –17.84 (c = 2.25, CH_3OH); IR (neat) 3405 (OH) cm^{-1};

^{1}H NMR (300 MHz, CD_3OD) 4.11 (dd, J = 11.1, 3.6 Hz, 1H, H_1), 3.93–3.84 (m, 1H, H_3), 3.72 (dd, J = 11.1, 3.8 Hz, 1H, H_5), 3.56 (dd, J = 11.4, 6.5 Hz, 1H, H_5'), 3.49–3.40 (m, 1H, H_4), 2.79–2.52 (m, 4H, SCH_2×2), 2.08 (t, J = 12.8 Hz, 1H, H_2), 1.87 (ddd, J = 14.4, 10.1, 3.8 Hz, 1H, H_2'), 1.25 (t, J = 7.5 Hz, 3H, SCH_2CH_3), 1.24 (t, J = 7.5 Hz, 3H, SCH_2CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 76.5 (CH), 70.9 (CH), 64.8 (CH_2), 47.7 (CH), 41.0 (CH_2), 25.3 (CH_2), 24.3 (CH_2), 15.1 (CH_3), 15.0 (CH_3); HRMS (ESI$^+$): m/z calcd. for $C_9H_{20}O_3S_2Na$ $[M+Na]^+$: 263.0746; found: 263.0743.

Supporting Information

Copies of ^{1}H, ^{13}C/DEPT, and COSY NMR spectra of compound **1**, **2**, **3**, **4**, **5**, **6**, **8**, **10**, **16**, **17**, **1**8, **19**, **20**, **21**, **22**, and **23**. Copies of X-ray data of **17** (deposition numbers CCDC 1858050)

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14. In our previous studies, radical reagents (Bu_3SnH/AIBN = 1.5/0.2 equiv) were required to completely convert the starting material to the carbonyl translocation product, please see 10c. But in this case, the reduction product **8** was obtained in 29% yield using the same equivalent of radical reagents.

15. The direct isolation of the carbonyl translocation product **7** was not feasible, because

compound **7** bearing a β-leaving group (OBz) was not stable in column chromatography.

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21. A representative example from D-ribose to 2-deox-L-ribose was reported in two separated documents. The first document required six steps to transform form D-ribose to L-ribose, please see reference 7(c). The second document also required another six steps to transform L-ribose to 2-deoxy-L-ribose, please see reference 7(d). Hence, a total of 12 synthetic steps were needed to complete the transformation from D-ribose to 2-deoxy-L-

ribose. In addition, several steps were needed to transform from 2-deoxy-L-ribose to a L-deoxyribonucleoside and then further to L-dT.

22. Compound **16** was treated with NaOMe/MeOH to afford (3*R*,4*S*)-1-(1,3-dithian-2-yl)pentane-3,4,5-triol, as compound **22**. For detailed procedures for the synthesis of compound **22**, please see the experimental section. For selected reviews on convenient synthons in dithioacetal sugar synthesis, please see: (a) Horton, D.; Norris, P. in *Preparative Carbohydrate Chemistry*, (Ed: Hanssian, S.), Marcel Dekker, New York, **1997**, p. 35–52. (b) Horton, D.; Wander, J. D. Dithioacetals of Sugars. *Adv. Carbohydr. Chem. Biochem.* **1976**, *32*, 15–123.

23. To confirm that compound **18** had a 2-deoxy-L-ribose configuration, compound **18** was treated with NaOMe/MeOH and afforded (3*R*,4*S*)-1,1-bis(ethylthio)pentane-3,4,5-triol as compound (+)-**23**. The specific rotation of (+)-**23** is $[\alpha]^{26}_{D}$ +19.88 (c = 1.28, CH_3OH). However, its enantiomer, compound (–)-**23** could be prepared by the reaction of 2-deoxy-D-ribose with ethanethiol (EtSH) in acidic condition. The specific rotation of (–)-**23** is $[\alpha]^{26}_{D}$ –17.84 (c = 2.25, CH_3OH). Please see the experimental section.

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