Carbohydrate Research 415 (2015) 39–47

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

S-Ribosylhomocysteine analogs containing a [4-thio]ribose ring

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ARTICLE INFO

Article history:
Received 8 May 2015
Received in revised form 4 July 2015
Accepted 7 July 2015
Available online 23 July 2015

Keywords:
Homocysteine
LuxS
S-Ribosylhomocysteine
Thioacetals
Thiosugars

ABSTRACT

The [4-thio]-*S*-ribosylhomocysteine (SRH) analogs containing substitution of a sulfur atom for the endocyclic oxygen were synthesized by coupling of the 4-thioribose substrates with a thiolate generated from the protected homocysteine. Coupling of the protected 1-deoxy-5-*O*-mesyl-*S*-oxo-4-thio-D-ribofuranose with homocysteinate salt gave the C4 epimers of [4-thio]-SRH at the sulfoxide oxidation level lacking a hydroxyl group at anomeric carbon. Treatment of these sulfoxides with $BF_3{\cdot}Et_2O$/NaI affected simultaneous reduction to sulfide and global deprotection affording 1-deoxy-4-thio-SRH analog. Treatment of the protected 1-deoxy-*S*-oxo-4-thio-D-ribofuranose sulfoxide with DAST/$SbCl_3$ resulted in the fluoro-Pummerer rearrangement to give 4-thio-β-D-ribofuranosyl fluoride. Mesylation of the latter at 5-hydroxyl position followed by coupling with homocysteinate salt and subsequent global deprotection with trifluoroacetic acid afforded [4-thio]-SRH thiohemiacetal.

1. Introduction

Quorum sensing (QS) is a type of bacterial cell-to-cell communication mediated through the production, release and detection of the small signaling molecules called autoinducers (AIs).[1] Such communication allows bacterial control of crucial functions in united communities for enhancement of symbiosis, virulence, antibiotic production, biofilm formation, and many other processes.[2,3] There have been great interests in the synthesis of both small[4–8] and macro[9] molecules and that can modulate and/or inhibit QS pathways.

S-Ribosylhomocysteinase (LuxS; EC 4.4.1.21) is a key enzyme in the biosynthetic pathway of type II autoinducer, which mediates the interspecies QS among both Gram-positive and Gram-negative bacteria.[10] The biosynthesis of AI-2 starts with depurination of *S*-adenosyl-L-homo-cysteine (SAH) to *S*-ribosyl-L-homocysteine (SRH, Fig. 1). SRH is subsequently converted to L-homocysteine and 4,5-dihydroxy-2,3-pentadione (DPD) by the LuxS enzyme. DPD undergoes cyclization to **2** and complexation with borate to form a furanosyl borate diester, which acts as the AI-2 in some bacteria.[10,12] Chemical synthesis of the unstable DPD,[13,14] and its analogs,[6,15] allowed to study the complexation of DPD with borate[16] and its isomerization processes.[17]

LuxS is a small metalloenzyme (157 amino acids in the *Bacillus subtilis* enzyme) containing Fe^{2+} ion. The native enzyme is unstable under aerobic conditions, but substitution of Co^{2+} for Fe^{2+} gives a highly stable variant with essentially wild-type catalytic activity.[18,19] In the proposed catalytic mechanism, LuxS catalyzes consecutive aldose–ketose (**1a** → **1b**) and ketose–ketose (**1b** → **1c**) isomerization steps and then *β*-elimination of Hcy from a 3-keto intermediate (**1c** → **1d**) to form DPD.[11,12]

Various SRH analogs have been recently designed and synthesized as a mechanistic probes and/or inhibitors of LuxS enzyme.[5,6,20] Among them, SRH analogs that blocked initial (such as thioether **3**, Fig. 2) and final mechanistic steps of LuxS catalytic cycle,[21] stable analogs of the putative enediolate intermediate,[23] and substrates lacking enolizable hydroxyl group at C3[24] including mechanistically significant C3 halogenated [3-Br or F]-SRH analogs.[25] Recently, we reported [4-aza]-SRH analogs containing substitution of a nitrogen atom for the endocyclic oxygen.[22] The analog **4** that contains azahemiacetal (*N,O*-acetal) moiety exhibited time-dependent inhibition, consistent with LuxS-catalyzed ring opening and generation of 2- and/or 3-ketone intermediates, which presumably bind to the enzyme active site with higher affinity than the ribose natural substrate.[22] The cyclic azahemiacetals and their ancestor lactams were found to modulate *Pseudomonas aeruginosa* QS.[26]

Here, we report synthesis of [4-thio]-SRH mimics in which the furanose ring oxygen has been replaced by a sulfur atom. The resulting thiohemiacetals (*O,S*-acetals) should have different stabilities relative to the *O,O*-acetals present in SRH and as a result different rates of metabolic alteration. Although replacement of the sugar ring oxygen by sulfur provides close mimics of natural sugars, it is noteworthy that the sulfur atom is larger and more polarizable than oxygen and the carbon–sulfur bond is longer (C—S, 0.182 nm *vs.* C—O, 0.143 nm), weaker and less polar than a carbon–oxygen bond (electronegativities on the Sanders scale: O, 3.65; S, 2.96; C, 2.75).[27] Such differences are responsible for significant alterations in the anomeric

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http://dx.doi.org/10.1016/j.carres.2015.07.005
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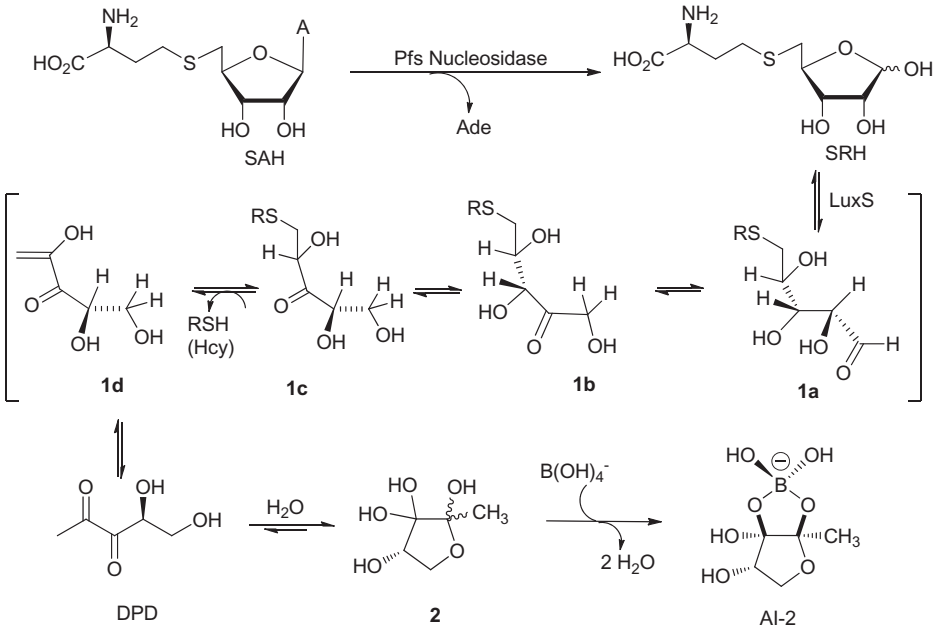


Fig. 1. Biosynthetic pathway to AI-2. Enzymatic conversion of SRH to DPD by LuxS.[11]

effect, conformational behavior, chemical reactivity, molecular recognition by proteins, biological activity,[28] and metabolic stability of thiosugars analogs in comparison with their oxygen counterparts. For example, mutarotation of such thiosugars is reported to be base- but not acid-catalyzed resulting from the lower basicity of sulfur compared to oxygen in natural sugars.[29] Also, an adjacent sulfur atom stabilizes a carbenium ion to a greater extent than an adjacent oxygen.[30] Moreover the *N*-4-thioriboyl linkage in thionucleosides is more stable against both chemical and enzymatic hydrolysis than the glycosylic bond in natural nucleosides.[31,32] Thus, increased stability of the cyclic thioacetal bonds (e.g. in **21**) should result in decreased rates of metabolic degradation and effect productions of the open chain aldehyde form necessary for the first LuxS-catalyzed isomerization to occur. Furthermore, the [4-thio]SRH analogs can be converted to a thio analog of DPD which could interfere QS because of different capabilities of sulfur atom to form covalent bonds to borate to generate a potential thio analogs of AI-2 signaling molecule.

2. Results and discussion

2.1. Synthesis of 1-deoxy-[4-thio]-S-ribosylhomocysteines

Our first target was [4-thio]-RSH analog **12a** lacking the hydroxyl group at C1 (Scheme 1). Compound **12a** cannot undergo ring opening which should preclude the initial step of LuxS-catalyzed reactions[21] and therefore act as competitive inhibitor of LuxS. Synthesis of **12a** started from 1-deoxy thiosugar precursor **5**, which can be prepared from D-ribose or D-gulonolactone following Matsuda[33] or Jeong[34,35] procedures. However, attempted

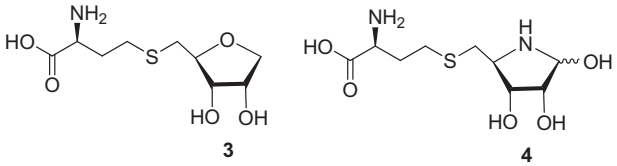
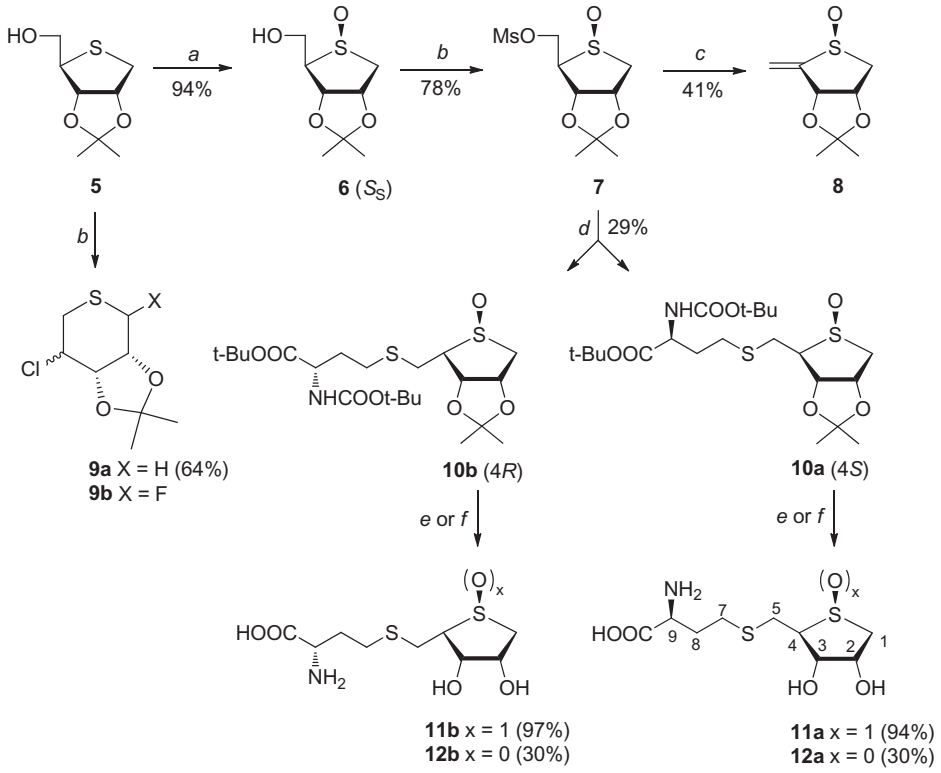


Fig. 2. 1-Deoxy and 4-aza analogs of *S*-ribosylhomocysteine.[21,22]

activation of the 5-hydroxyl group in **5** with mesyl chloride, instead of providing the corresponding 5-*O*-mesyl precursor for the coupling with homocysteine, resulted in the formation of thiopyranose **9a** as a mixture of two diastereoisomers (~3:1). Presumably the mesylated thiosugar underwent a rearrangement reaction into the thiopyranoses through an episulfonium ion intermediates.[36] To avoid such ring enlargement, thioether **5** was first oxidized to sulfoxide **6** with 3-chloroperbenzoic acid (*m*-CPBA). Interestingly, sulfoxide **6** was obtained in 94% yield as a single diastereoisomer,[37] whose stereochemistry was tentatively assigned as *S* at sulfur atom. The stereoselective oxidation likely is the result of the known complexation of alcohols (5-OH group) with *m*-CPBA which followed by *cis* delivery of oxygen to sulfur.[38] It also worth mentioning that oxidation of the analogous 5-*O*-protected 4-thiopentofuranoses with *m*-CPBA, which are depleting of such complexation, provided the corresponding sulfoxides as a mixture of diastereomers[33] (*vide infra* oxidation of **13** to **14**; Scheme 2). Mesylation of **6** provided stable 5-*O*-mesyl sufloxide **7** as a single isomer. From different approaches available for the coupling of ribose and Hcy derivatives,[11,21,24,39,40] we found that displacement of the mesylate group from **7** with a thiolate, generated from the suitably protected L-homocystine[24] and LDA in DMF yielded 5-thioethers **10a** and **10b** as a separable mixture of epimers at C4 [**10a** (4*S*, D-ribo)/**10b** (4*R*, L-lyxo), 45:55].

The structures for **10a** and **10b** were established based on the spectroscopic and experimental evidences as well as literature precedents. Thus, NOESY experiments of **10a** showed correlation between protons H3 and H5,5′ (*cis* to each other) and lack of cross peaks between protons H4 and H2 (*trans* to each other). On the other hand, NOESY experiment of **10b** showed cross peaks between protons H4 and H2 (*cis* to each other) and lack of space interactions between protons H3 and H5,5′ (*trans* to each other) confirming L-lyxose configuration. Apparently LDA base used for the condensation between thiofuranose **7** and Hcy caused epimerization at C4 position of the sugar. MacCulloch and Walker reported that treatment of the individual 4′-thionucleoside *R* and *S* sulfoxides with NaOD/D_2O resulted in the epimerization at C4′ without racemization of the chiral sulfoxides.[41] We also showed that treatment of **7** with LDA in DMF without Hcy presence resulted in the formation of exomethylene



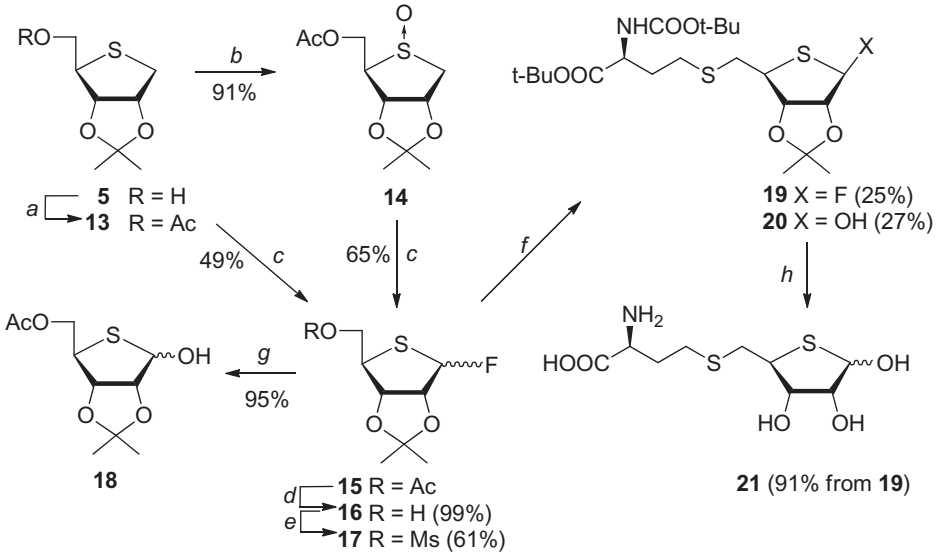
Scheme 1. Reagents and conditions: (*a*) MCPBA/CH_2Cl_2/–78 °C; (*b*) MsCl/Et_3N/CH_2Cl_2; (*c*) LDA/DMF; (*d*) BocNHCH(CHCHSH)CO_2*t*-Bu/LDA/DMF; (e) TFA/H_2O; (*f*) BF_3/Et_2O/NaI/CH_3CN.

thiosugar **8**, confirming the possibility of H4 abstraction under conditions required for the condensation.

Treatment of sulfoxides **10a** and **10b** with aqueous TFA affected removal of the *N*-Boc, acetonide and *t*-butyl ester protection groups in a single step yielding SRH analogs **11a** and **11b** lacking hydroxyl group at C1 and with the oxidized endocyclic sulfur atom (throughout the paper numbering of the atoms in the SRH analogs follow the nomenclature of S-ribosylhomocysteine). Treatment of the sulfoxides **10a** and **10b** with $BF_3{\cdot}Et_2O$/NaI/CH_3CN affected simultaneous reduction of the sulfoxides to sulfide and removal of all protection groups yielding two distinctive 1-deoxy-4-thio-SRH analogs **12a** and **12b**, respectively.

2.2. Synthesis of [4-thio]-S-ribosylhomocysteine

The next target was [4-thio]SRH thiohemiacetal **21**. Since only the open aldehyde form of SRH is catalytically active, we are interested in the effect of sulfur substitution on the ring opening. We initially attempted synthesis of thiohemiacetal **21** via the Pummerer rearrangement of **10a** since the analogous transformation for



Scheme 2. Reagents and conditions: (*a*) Ac_2O/DMAP; (*b*) MCPBA/CH_2Cl_2/–78 °C; (*c*) DAST/$SbCl_3$/CH_2Cl_2/55 °C; (*d*) NH_3/MeOH; (*e*) MsCl/Et_3N/CH_2Cl_2; (*f*) BocNHCH(CHCHSH)CO_2*t*-Bu/LDA/DMF; (*g*) H_2O/H^+; (*h*) TFA/H_2O (9:1).

thioribose sulfoxides are known.[32–34] However, treatment of **10a** with Ac_2O at elevated temperature (100 °C, 6 h) resulted in complex reaction mixture. In our efforts to synthesize thiohemiacetal **21**, we then explored possibility of employing thioribosyl fluorides as precursors to *O*,*S*-acetals (Scheme 2). Thus, acetylation of **5** gave **13** and subsequent oxidation afforded sulfoxides **14** as a 4:1 mixture of diastereoisomers at sulfur. Interestingly, analogous treatment of sulfoxides **6** with Ac_2O/DMAP failed to provide **14** probably due to H-bonding interaction between 5-hydroxy group and sulfoxide oxygen.

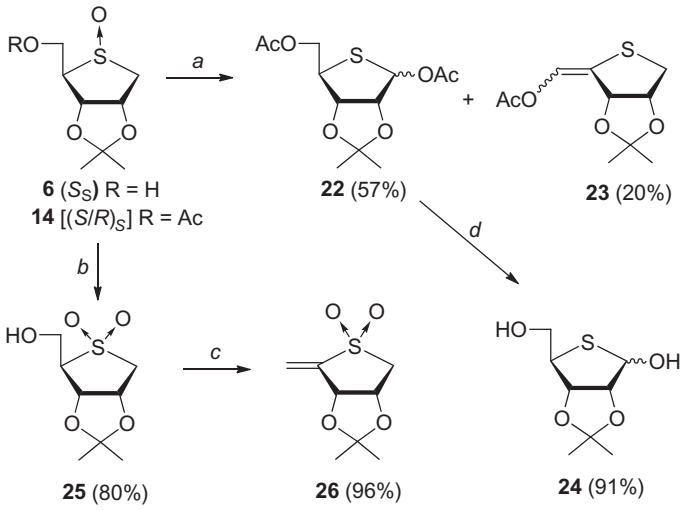
Treatment of sulfoxide **14** with DAST/$SbCl_3$ combination[42] resulted in fluoro-Pummerer rearrangement to give α-fluoro thioether **15** (α/β, ~1:20). Reaction of sulfide **13** with DAST/$SbCl_3$[43] also produced thioribosyl fluorides **15**. It is noteworthy that treatment of **14** or **13** with DAST alone provided **19** in much lower yields. Since α-fluoro thioethers are at the carbonyl oxidation level, these thioacetals are sensitive to acidic conditions.[42] We found that under slightly acidic conditions, such as even silica gel, a spontaneous hydrolysis of the α-fluoro thioethers **15** occurred to give thiohemiacetals **18**. Since α-fluoro thioethers are relatively stable to basic conditions in parallel with acetals, treatment of **15** (β-anomer) with methanolic ammonia affected deacetylation providing **16** as a single β-anomer. The fluoride **16** was then mesylated at the primary hydroxyl to give reasonable stable **17**. Rearrangement of mesylate **17** to the thiopyranose isomers of type **9b** (in analogy to the formation of **9a** upon attempted mesylation of **5** as depicted in Scheme 1) was also observed. We were fortunate to find that coupling of **17** with protected Hcy[24] indeed afforded relatively stable 4-thio-SRH fluoride **19**. Attempted purification of the crude **19** on silica gel column yielded separable mixture of **19** (25%) and protected 4-thio-SRH derivative **20** (27%) as a single β anomer. Treatment of **19** with aqueous TFA affected hydrolysis of fluoride as well as removal of the *N*-Boc, acetonide, and *t*-butyl ester protection groups in a single step to give 4-thio-SRH derivative **21** (91%). Acid catalyzed deprotection of **20** also produced **21**.

2.3. Pummerer rearrangement of [4-thio]-ribofuranose sulfoxides

To get insights of the unsuccessful Pummerer rearrangement of sulfoxide **10a** (*vide supra*), we investigated properties of the model thiosugar sulfoxides **14** toward the Pummerer rearrangement. Thus, heating of the **14** with Ac_2O (100 °C/6 h) gave desired 1-*O*-acetyl-4-thioribose **22** (α/β = 1:4, 57%). Careful chromatographic purification yielded also the (acetoxy)vinyl ether byproduct **23** (20%) as single isomer (Scheme 3). Analogous treatment of the single sulfoxide **6** with Ac_2O also produced a similar mixture of **22** (α/β = 1:5, 41%) and **23** (12%).[44] The enol acetate **23** is presumably formed by elimination of AcOH molecule from a regioisomeric Pummerer-rearranged 4-acetoxy intermediate. The chemical shifts and coupling constants for **23** are similar to those of the analogous vinyl derivatives in nucleoside series[45,46] but NOESY ^{1}H NMR experiments were inconclusive to assign *E* or *Z* stereochemistry in the absence of both geometric isomers. Deacetylation of **22** with NH_3/MeOH afforded thioribofuranose **24** (α/β = 1:9). Oxidation of **6** produced sulfone **25**. However, attempted 5-*O*-mesylation of **25** led to the elimination of MsOH molecule providing exomethylene sulfone **26**.

3. Conclusion

We have synthesized [4-thio]-*S*-ribosylhomocysteine analog and its 1-deoxy derivative in which the furanose ring oxygen has been substituted by a sulfur atom. Coupling of the protected 1-deoxy-5-*O*-methanesulfonyl-*S*-oxo-4-thio-D-ribofuranose with homocysteinate and subsequent deprotection with TFA gave C4 epimers of [4-thio]-SRH at sulfoxide oxidation level lacking hydroxyl



Scheme 3. Reagents and conditions: (*a*) Ac_2O/100 °C/6 h; (*b*) MCPBA/CH_2Cl_2/−78 °C; (*c*) MsCl/Et_3N/CH_2Cl_2; (*d*) NH_3/MeOH.

at C1 anomeric carbon. Employing (α-fluoro)thioethers *masked* chemistry at anomeric position the [4-thio]SRH thiohemiacetal analog was prepared. Pummerer-treatment of 1-deoxy-*S*-oxo-4-thio-D-ribofuranose derivatives with Ac_2O provided desired 1-*O*-acetyl-4-thioribose in addition to 5-(acetoxy)vinyl byproduct. The biological evaluation of the [4-thio]-SRH analogs will be published elsewhere.

4. Experimental part

The ^{1}H (400 or 600 MHz), ^{13}C (100 MHz), and ^{19}F (376 MHz) NMR spectra were determined with solutions in $CDCl_3$ unless otherwise noted. Mass spectra (MS) were obtained with atmospheric pressure chemical ionization (APCI) technique and HRMS in AP-ESI or TOF-ESI mode. TLC was performed with Merck kieselgel 60-F_{254} sheets. Products were detected with 254 nm light or by visualization with $Ce(SO_4)_2$/$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$/$H_2SO_4$/$H_2O$ reagent. Merck kieselgel 60 (230–400 mesh) was used for column chromatography. HPLC purifications were performed using XTerra preparative RP_{18} OBD column (5 μm 19 × 150 mm) with gradient program using CH_3CN/H_2O as a mobile phase. Reagent grade chemicals were used, and solvents were dried by reflux over and distillation from CaH_2 (except for THF/potassium) under argon.

4.1. 1-Deoxy-2,3-O-isopropylidene-S-oxo-4-thio-D-ribofuranose [6(S_S)]

A solution of MCPBA (281 mg, 1.14 mmol, ~70% reagent) in CH_2Cl_2 (4 mL) was added dropwise to a solution of **5**[33] (216 mg, 1.14 mmol) in CH_2Cl_2 (2 mL) at −78 °C, under Ar atmosphere. The resulting suspension was stirred for 30 min or until disappearance of **5** on TLC. The reaction mixture was treated with saturated NH_3/MeOH (20 mL), and was allowed to warm to ambient temperature, and was evaporated. The residual white solid (~485 mg) was column chromatographed (20% MeOH/EtOAc) to give **6**[32] (220 mg, 94%) as a colorless solidifying oil of a single diastereoisomer: ^{1}H NMR δ 1.34 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.00–3.80 (br s, 1H, OH), 3.33 (dd, *J* = 6.1, 14.1 Hz, 1H, H1), 3.43–3.48 (m, 2H, H1′,4), 4.12 (dd, *J* = 6.1, 12.4 Hz, 1H, H5), 4.35 (dd, *J* = 2.9, 12.4 Hz, 1H, H5′), 5.09 (dd, *J* = 3.6, 5.9 Hz, 1H, H3), 5.21 ("dt", *J* = 3.6, 6.0 Hz, 1H, H2); ^{13}C NMR δ 24.66 (CMe_2), 27.17 (CMe_2), 57.05 (C1), 58.15 (C5), 65.63 (C4), 79.80 (C2), 82.26 (C3), 112.17(CMe_2); MS (APCI) *m*/*z* 207 (MH^+). HRMS (AP-ESI) *m*/*z* calculated for $C_8H_{15}O_4S$ $[M+H]^+$ 207.0686; found 207.0691.

4.2. 1-Deoxy-2,3-O-isopropylidene-5-O-methanesulfonyl-S-oxo-4-thio-D-ribofuranose[7(S_S)]

Et_3N (0.464 mL, 337 mg, 3.34 mmol) and MsCl (0.129 mL, 191 mg, 1.67 mmol) were added dropwise to a stirred solution of **6** (160 mg, 0.78 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C. After 4 h, the reaction mixture was quenched with saturated $NaHCO_3/H_2O$, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was column chromatographed (EtOAc → 5% MeOH/EtOAc) to give **7** (173 mg, 78%) as a colorless oil: ^{1}H NMR δ 1.33 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.11 (s, 3H, Ms), 3.27 (dd, *J* = 6.2, 14.3 Hz, 1H, H1), 3.40 (dd, *J* = 3.4, 14.3 Hz, 1H, H1′) 3.52 ("dt", *J* = 4.5, 8.1 Hz, 1H, H4), 4.63 (dd, *J* = 7.9, 11.0 Hz, 1H, H5), 4.71 (dd, *J* = 4.1, 11.0 Hz, 1H, H5′), 4.97 (dd, *J* = 5.1, 6.0 Hz, 1H, H3), 5.19 (dt, *J* = 3.4, 6.2 Hz, H1, H2); ^{13}C NMR δ 24.56 (C*Me*$_2$), 27.11 (C*Me*$_2$), 37.54 (Ms), 56.66 (C1), 63.28 (C5), 63.46 (C4), 79.51 (C2), 81.85 (C3), 113.09(C*Me*$_2$); MS (APCI) *m*/*z* 285 (MH^+); MS (ESI) *m*/*z* 285 (20, $[MH]^+$); HRMS (AP-ESI) *m*/*z* calculated for $C_9H_{17}O_6S_2$ $[M+H]^+$ 285.0461; found 285.0465.

4.3. 4, 5-Didehydro-1,5-dideoxy-2,3-O-isopropylidene-S-oxo-4-thio-D-ribofuranose [8(S_S)]

LDA (2.0 M//THF/heptane/PhEt, 0.13 mL, 0.26 mmol) was added to a stirred solution of **7** (35 mg, 0.12 mmol) in dry DMF (2.0 mL) under Ar atmosphere at ambient temperature. After 3 days, reaction was quenched by addition of saturated $NaHCO_3/H_2O$ and was extracted with EtOAc. The combined organic layer was washed (brine), dried (Na_2SO_4) and evaporated to give crude product which was column chromatographed (5% MeOH/EtOAc) to give **8** (9.5 mg, 41%) as a colorless oil: ^{1}H NMR δ 1.36 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.79 (dd, *J* = 5.2, 13.2 Hz, 1H, H1), 3.73 ("br d", *J* = 13.2 Hz, 1H, H1′), 5.04 (ddd, *J* = 1.6, 5.2, 6.1 Hz, 1H, H2), 5.26 (d, *J* = 6.1 Hz, 1H, H3), 6.07 (t, *J* = 1.3 Hz, 1H, H5), 6.11 (br s, 1H, H5′); ^{13}C NMR δ 24.3 (C*Me*$_2$), 26.5 (C*Me*$_2$), 56.8 (C1), 76.3 (C2), 78.2 (C3), 111.9 (C*Me*$_2$), 122.0 (C5), 155.6 (C4). HRMS (AP-ESI) *m*/*z* calculated for $C_8H_{13}O_3S$ $[M+H]^+$ 189.0580; found 189.0588.

4.4. 4-Chloro-1,4-dideoxy-2,3-O-isopropylidene-5-thio-D-ribopyranose and 4-chloro-1,4-dideoxy-2,3-O-isopropylidene-5-thio-L-lyxopyranose (9a)

Compound **5** (57.5 mg, 0.3 mmol) was treated with MsCl (0.11 mL, 156 mg, 1.37 mmol) in the presence of Et_3N (0.38 mL, 276 mg, 2.73 mmol) as described in Section 4.2 (3 h). The crude product was column chromatographed (10% EtOAc/hexane) to give **9a** (40.5 mg, 64%) as mixture of streoisomers (3:1). Major isomer had: ^{1}H NMR (600 MHz) δ 1.35 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.98 (dd, *J* = 1.3, 13.0 Hz, 1H, H1), 3.15 (dd, *J* = 4.7, 13.1 Hz, 1H, H1′), 3.45 (dd, *J* = 10.3, 11.0 Hz, 1H, H5), 3.53 (ddd, *J* = 1.0, 4.6, 10.2 Hz, 1H, H4), 3.73 (dd, *J* = 4.6, 11.1 Hz, 1H, H5′), 4.89 (dd, *J* = 0.9, 5.6 Hz, 1H, H3), 4.97 ("dt", *J* = 1.3, 5.2 Hz, 1H, H2); ^{13}C NMR δ 24.67 (C*Me*$_2$), 26.48 (C*Me*$_2$), 37.83 (C1), 45.65 (C5), 55.27 (C4), 83.54 (C2), 86.17 (C3), 111.33 (C*Me*$_2$). Minor isomer had: ^{1}H NMR (600 MHz) δ 1.41 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.74 (dd, *J* = 10.5, 13.5 Hz, 1H, H5), 2.91 (ddd, *J* = 1.4, 5.4, 14.5 Hz, 1H, H1), 2.97 (ddd, *J* = 1.5, 3.9, 13.4 Hz, 1H, H1′), 2.97–2.30 (m, 1H, H5′), 4.11 (dd, *J* = 5.4, 7.4 Hz, 1H, H3), 4.24 (ddd, *J* = 3.7, 7.5, 10.5 Hz, 1H, H4), 4.45 (dt, *J* = 4.0, 5.3 Hz, 1H, H2); ^{13}C NMR δ 26.05 (C*Me*$_2$), 28.05 (C*Me*$_2$), 28.67 (C1), 32.44 (C5), 59.16 (C4), 73.36 (C2), 79.71 (C3), 109.30 (C*Me*$_2$); MS (ESI) *m*/*z* 173 (100, $[M\text{-}Cl]^+$). HRMS (AP-ESI) *m*/*z* calculated for $C_8H_{14}{}^{35}ClO_2S$ $[M+H]^+$ 209.0397; found 209.0391; calculated for $C_8H_{14}{}^{37}ClO_2S$ $[M+H]^+$ 211.0368, found 211.0359.

4.5. S-(1,5-Dideoxy-2,3-O-isopropylidene-S-oxo-4-thio-D-ribofuranos-5-yl)-N-tert-butoxycarbonyl-L-homocysteine tert-butyl ester [10a(S_S)] and S-(1,5-dideoxy-2,3-O-isopropylidene-S-oxo-4-thio-L-lyxofuranos-5-yl)-N-tert-butoxycarbonyl-L-homocysteine tert-butyl ester [10b(S_S)]

Step *a*. H_2O (0.24 mL) and tris(2-carboxyethyl)phosphine hydrochloride (88 mg, 0.31 mmol) were added to a stirred solution of *N,N′*-di(*tert*-butoxycarbonyl)-L-homocystine di(*tert*-butyl) ester[11] (160 mg, 0.28 mmol) in anhydrous DMF (2.4 mL) at ambient temperature under Ar atmosphere. After 20 h, the reaction mixture [TLC (EtOAc/hexane, 2:8) showed conversion of disulfide (R_f 0.55) into thiol (R_f 0.65)] was partitioned between EtOAc, and saturated $NaHCO_3/H_2O$. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give *N*-*tert*-butoxycarbonyl-L-homocysteine *tert*-butyl ester (159 mg, 99%) as colorless oil of sufficient purity to be directly used in next step. Step *b*. A freshly prepared (step *a*) homocysteine derivative (266 mg, 0.914 mmol) was dissolved in anhydrous DMF (2.0 mL), and was stirred under a vigorous stream of argon for 10 min at 0 °C (ice-bath). Next, a solution of LDA (0.46 mL, 2.0 M/THF and heptane, 0.914 mmol) was added dropwise and after an additional 10 min thiosugar **7** (245 mg, 0.863 mmol) in anhydrous DMF (2.5 mL) was added via syringe. After 15 min, ice-bath was removed and the reaction mixture was stirred for 48 h at ambient temperature (TLC showed consumption of **7**). Ice-cold saturated NH_4Cl/H_2O was added and the resulting suspension was diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4) and was evaporated to give 534 mg of yellow oil. The crude product was column chromatographed (80 → 90% EtOAc/hexane) to give a colorless oil (120 mg, 29%) of partially separable mixture of epimers **10a** and **10b** (45:55). Minor (less polar) epimer **10a** had: ^{1}H NMR δ 1.32 (s, 3H, CH_3), 1.43 (s, 9H, *t*-Bu), 1.46 (s, 9H, *t*-Bu), 1.48 (s, 3H, CH_3), 1.86–2.00 (m, 1H, H8), 2.08–2.18 (m, 1H, H8′), 2.64 (t, *J* = 8.0 Hz, 2H, H7,7′), 2.88 (dd, *J* = 7.1, 13.6 Hz, 1H, H5), 3.06 (dd, *J* = 8.7, 13.6 Hz, 1H, H5′), 3.17 (dd, *J* = 4.5, 14.7 Hz, 1H, H1), 3.22 ("q", *J* = 7.5 Hz, 1H, H4), 3.31 (dd, *J* = 6.4, 14.5 Hz, 1H, H1′), 4.23–4.29 (m, 1H, H9), 4.91 (t, *J* = 6.0 Hz, 1H, H3), 5.14 (br. d, *J* = 7.4 Hz, 1H, NH), 5.22 (dt, *J* = 4.6, 6.3 Hz, 1H, H2); ^{13}C NMR δ 24.91 (C*Me*$_2$), 26.91 (C5), 27.46 (C*Me*$_2$), 28.14 (*t*-Bu), 28.46 (*t*-Bu), 28.76 (C7), 33.07 (C8), 53.47 (C9), 55.49 (C1), 66.17 (C4), 79.96 (*t*-Bu), 80.23 (C2), 82.37 (*t*-Bu), 84.80 (C3), 113.52 (C*Me*$_2$), 155.52 (CO), 171.30 (C10); MS (ESI) *m*/*z* 480 (100, $[MH]^+$). Major (more polar) epimer **10b** had: ^{1}H NMR δ 1.17 (s, 3H, CH_3), 1.33 (s, 9H, *t*-Bu), 1.35 (s, 9H, *t*-Bu), 1.36 (s, 3H, CH_3), 1.74–1.97 (m, 1H, H8), 1.98–2.05 (m, 1H, H8′), 2.55 (t, *J* = 7.7 Hz, 2H, H7,7′), 2.68 (dd, *J* = 5.3, 13.2 Hz, 1H, H5), 2.80–2.83 (m, 1H, H1), 3.03 (d, *J* = 2.8 Hz, 1H, H1′), 3.05 (s, 1H, H4), 3.62 (d, *J* = 13.2 Hz, 1H, H5′), 4.13–4.15 (m, 1H, H9), 4.84 (s, 1H, H3) 4.85 (d, *J* = 2.3 Hz, 1H, H2), 5.00 (br d, *J* = 7.4 Hz, 1H, NH); ^{13}C NMR δ 23.73 (C*Me*$_2$), 26.01 (C*Me*$_2$), 27.41 (C4), 28.14 (*t*-Bu), 28.45 (*t*-Bu), 29.18 (C7), 33.14 (C8), 53.50 (C9), 58.12 (C5), 71.64 (C1), 76.08 (C2), 77.10 (C3), 79.95 (*t*-Bu), 82.34 (*t*-Bu), 110.68 (C*Me*$_2$), 155.48 (CO), 171.35 (C10); MS (ESI) *m*/*z* 480 (100, $[MH]^+$). HRMS (AP-ESI) *m*/*z* calculated for $C_{21}H_{37}NNaO_7S_2$ $[M+Na]^+$ 502.1904; found 502.1933.

4.6. S-(1,5-Dideoxy-S-oxo-4-thio-D-ribofuranos-5-yl)-L-homocysteine [11a(S_S)]

Compound **10a** (18 mg, 0.037 mmol) was dissolved in TFA/H_2O (9:1, 1.5 mL), and the resulting mixture was stirred at ambient temperature for 2 h. Volatiles were evaporated and coevaporated with toluene to give **11a** (10 mg, 94%) as a colorless oil: ^{1}H NMR (D_2O) δ 2.17–2.27 (m, 1H, H8), 2.30–2.40 (m, 1H, H8′), 2.86 (dt, *J* = 2.4, 7.4 Hz, 2H, H7,7′), 2.89 (dd, *J* = 11.5, 14.1 Hz, 1H, H5), 3.03 (dd, *J* = 5.2, 15.1 Hz, 1H, H1), 3.17 (dd, *J* = 4.2, 14.1 Hz, 1H, H5′), 3.38 (dt, *J* = 4.2,

10.8 Hz, 1H, H4), 3.72 (dd, J = 2.3, 15.1 Hz, 1H, H1′), 4.21 (t, J = 6.4 Hz, 1H, H9), 4.35(dd, J = 3.9, 10.1 Hz, 1H, H3), 4.67 (ddd, J = 2.4, 4.0, 5.3 Hz, 1H, H2); ^{13}C NMR (D_2O) δ 25.61 (C5), 27.35 (C7), 29.57 (C8), 51.89 (C9), 57.37 (C1), 61.72 (C4), 71.66 (C2), 75.87(C3), 171.90 (C10); MS (ESI) m/z 284 (100, $[MH]^+$). HRMS (AP-ESI) m/z calculated for $C_9H_{17}NNaO_5S_2$ $[M + Na]^+$ 306.0440; found 306.0449.

4.7. S-(1,5-Dideoxy-S-oxo-4-thio-L-lyxofuranos-5-yl)-L-homocysteine [11b(S_S)]

Compound **10b** (19 mg, 0.04 mmol) was treated with TFA/H_2O as described in Section 4.6. Volatiles were evaporated and coevaporated twice with toluene to give **11b** (10.9 mg, 97%) as colorless oil: ^{1}H NMR (D_2O) δ 2.07–2.15 (m, 1H, H8), 2.18–2.25 (m, 1H, H8′), 2.70 (dt, J = 3.0, 7.4 Hz, 2H, H7,7′), 2.92 (dd, J = 10.6, 14.2 Hz, 1H, H5), 3.03 (dd, J = 6.9, 14.1 Hz, 1H, H1), 3.13 (dd, J = 6.4, 14.2 Hz, 1H, H5′), 3.18 (dd, J = 10.6, 14.2 Hz, 1H, H1′), 3.27 (ddd, J = 3.9, 6.3, 10.3 Hz, 1H, H4), 4.09 (t, J = 6.4 Hz, 1H, H9), 4.42 (t, J = 3.4 Hz, 1H, H3), 4.82 (ddd, J = 3.1, 6.9, 10.3 Hz, 1H, H2); ^{13}C NMR (D_2O) δ 26.57 (C7), 27.01 (C5), 29.43 (C8), 51.93 (C9), 52.50 (C1), 73.12 (C2), 73.43 (C4), 74.10 (C3), 172.01 (C10); MS (ESI) m/z 284 (100, $[MH]^+$). HRMS (AP-ESI) m/z calculated for $C_9H_{17}NNaO_5S_2$ $[M + Na]^+$ 306.0440; found 306.0452.

4.8. S-(1,5-Dideoxy-4-thio-D-ribofuranos-5-yl)-L-homocysteine (12a)

NaI (45 mg, 0.3 mmol) followed by $BF_3{\cdot}Et_2O$ (29 μL, 32 mg, 0.224 mmol) were added to a stirred solution of **10a** (12 mg, 0.025 mmol) in dried CH_3CN (1.0 mL) under Ar atmosphere. The resulting mixture was stirred at ambient temperature for 2 h and then water (10 mL) was added. The volatiles were evaporated and the remaining aqueous solution (~8 mL) was washed with $CHCl_3$. The water layer was evaporated to give crude **12a** as a yellow solid. Crude product was purified by HPLC (CH_3CN/H_2O, 5:95; t_R = 17.0 min) to give **12a** (2 mg; 30%) as colorless oil: ^{1}H NMR (D_2O) δ 2.19–2.29 (m, 1H, H8), 2.31–2.40 (m, 1H, H8′), 2.77 (dd, J = 8.9, 13.4 Hz, 1H, H5), 2.82 (t, J = 7.5 Hz, 2H, H7,7′), 2.84 (dd, J = 1.8, 10.0 Hz, 1H, H1), 3.11 (t, J = 4.8 Hz, 1H, H1′), 3.13 (dd, J = 5.2, 6.7 Hz, 1H, H5′), 3.53 (ddd, J = 5.1, 7.0, 8.8 Hz, 1H, H4), 4.04 (dd, J = 3.4, 7.0 Hz, 1H, H3), 4.23 (t, J = 6.4 Hz, 1H, H9), 4.42 (q, J = 4.0 Hz, 1H, H2); ^{13}C NMR (D_2O) δ 27.17 (C7), 29.80 (C8), 32.53 (C1), 35.59 (C5), 48.65 (C4), 52.00 (C9), 74.27 (C2), 78.62 (C3), 171.81 (C10); MS (ESI) m/z 268 (100, $[MH]^+$). HRMS (AP-ESI) m/z calculated for $C_9H_{16}NO_4S_2$ $[M–H]^-$ 266.0526; found 266.0521.

4.9. S-(1,5-Dideoxy-4-thio-L-lyxofuranos-5-yl)-L-homocysteine (12b)

Compound **10b** (12 mg, 0.022 mmol) was treated with NaI (44 mg, 0.29 mmol) and $BF_3{\cdot}Et_2O$ (28 μL, 31 mg, 0.22 mmol), as described in Section 4.8, to give crude **12b** as a yellow solid. HPLC (CH_3CN/H_2O, 5:95; t_R = 17.1 min) purification gave **12b** (2 mg, 30%) as colorless oil: ^{1}H NMR (D_2O) δ 2.18–2.28 (m, 1H, H8), 2.29–2.38 (m, 1H, H8′), 2.75 (dd, J = 8.7, 13.3 Hz, 1H, H5), 2.81 (t, J = 7.4 Hz, 2H, H7,7′), 2.88 (t, J = 10.0 Hz, 1H, H1), 3.04 (dd, J = 7.1, 10.1 Hz, 1H, H1′), 3.10 (dd, J = 7.0, 13.3 Hz, 1H, H5′), 3.77 (ddd, J = 3.6, 7.1, 8.6 Hz, 1H, H4), 4.24 (t, J = 6.4 Hz, 1H, H9), 4.29 ("t", J = 3.1 Hz, 1H, H3), 4.38 ("ddd", J = 3.1, 7.2, 10.0 Hz, 1H, H2); ^{13}C NMR (D_2O) δ 26.87 (C7), 29.78 (C8), 31.73 (C1), 32.10 (C5), 47.47 (C4), 52.04 (C9), 73.95 (C3), 75.57 (C2), 171.92 (C10); MS (ESI) m/z 268 (100, $[MH]^+$). HRMS (AP-ESI) m/z calculated for $C_9H_{16}NO_4S_2$ $[M–H]^-$ 266.0526; found 266.0518.

4.10. 5-O-Acetyl-1-deoxy-2,3-O-isopropylidene-4-thio-D-ribofuranose (13)

DMAP (7 mg, 0.057 mmol) was added to a stirred solution of **5**[33] (117 mg, 0.62 mmol) in Ac_2O (6 mL) at ambient temperature. After 2.5 h, MeOH (15 mL) was added and resulting mixture was stirred for additional 1 h at 0 °C. The volatiles were evaporated to give the crude **13** (136 mg, 95%), of sufficient purity to be directly used in next step: ^{1}H NMR δ 1.34 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.10 (s, 3H, Ac), 2.94 (dd, J = 1.2, 13.0 Hz, 1H, H1), 3.12 (dd, J = 4.7, 13.0 Hz, 1H, H1′), 3.49 (ddd, J = 1.0, 5.9, 7.6 Hz, 1H, H4), 4.05 (dd, J = 8.4, 11.4 Hz, 1H, H5), 4.18 (dd, J = 5.8, 11.4 Hz, 1H, H5′), 4.70 (dd, J = 1.2, 5.6 Hz, 1H, H3), 4.94 ("dt", J = 1.3, 5.2 Hz, 1H, H2); ^{13}C NMR δ 20.92 (Ac), 24.66 (CMe_2), 26.46 (CMe_2), 37.70 (C1), 52.33 (C4), 64.82 (C5), 83.55 (C2), 85.72 (C3), 111.26 (CMe_2), 170.70 (Ac). HRMS (AP-ESI) m/z calculated for $C_{10}H_{17}O_4S$ $[MH]^+$ 233.0842; found 233.0858.

4.11. 5-O-Acetyl-1-deoxy-2,3-O-isopropylidene-S-oxo-4-thio-D-ribofuranose [14(R/S)$_S$]

Compound **13** (136 mg, 0.59 mmol) was treated with MCPBA (138 mg, 0.56 mmol, 70%) as described in Section 4.1 (14 h, –78 °C → RT). The reaction mixture was quenched with saturated $NaHCO_3$/H_2O, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was column chromatographed (50% EtOAc/hexane) to give unchanged **13** (7 mg, 5%) followed by (EtOAc → 10% MeOH/EtOAc) **14** (133 mg, 91%) as a separable mixture (4:1) of two diastereoisomers. Major isomer had: ^{1}H NMR δ 1.33 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.10 (s, 3H, Ac), 3.23 (dd, J = 4.1, 14.4 Hz, 1H, H1), 3.34 (dd, J = 6.4, 14.4 Hz, 1H, H1′), 3.36 ("dt", J = 5.6, 8.9 Hz, 1H, H4), 4.49 (dd, J = 8.8, 12.0 Hz, 1H, H5), 4.61 (dd, J = 4.9, 12.0 Hz, 1H, H5′), 4.94 (t, J = 6.1 Hz, 1H, H3), 5.22 (dt, J = 4.2, 6.3 Hz, 1H, H2); ^{13}C NMR δ 20.80 (Ac), 24.75 (CMe_2), 27.29 (CMe_2), 56.13 (C1), 58.19 (C5), 63.93 (C4), 79.86 (C2), 82.75 (C3), 113.47 (CMe_2), 170.29 (Ac). Minor isomer had: ^{1}H NMR δ 1.37 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 2.09 (s, 3H, Ac), 3.22 (dd, J = 6.0, 14.8 Hz, 1H, H1), 3.42 (td, J = 1.8, 14.8 Hz, 1H, H1′), 3.75–3.79 (m, 1H, H4), 4.35 (dd, J = 5.3, 12.2 Hz, 1H, H5), 4.39 (dd, J = 4.5, 12.2 Hz, 1H, H5′), 4.86 (dd, J = 2.7, 5.9 Hz, 1H, H3), 5.14 (dt, J = 2.2, 6.0 Hz, 1H, H2); ^{13}C NMR δ 20.69 (Ac), 24.48 (CMe_2), 26.82 (CMe_2), 57.25 (C1), 60.93 (C5), 71.40 (C4), 82.87 (C2), 84.45 (C3), 112.91 (CMe_2), 170.00 (Ac); MS (ESI) m/z 249 (100, $[MH]^+$).

4.12. 5-O-Acetyl-1-deoxy-1-fluoro-2,3-O-isopropylidene-4-thio-α/β-D-ribofuranose (15), and 5-O-acetyl-2,3-O-isopropylidene-4-thio-β-D-ribofuranose (18)

4.12.1. Method A

Deoxo-fluor (125 mg, 0.25 mL of 50% solution in THF, 0.57 mmol) was added to a stirred solution of sulfoxide **14** (15.5 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL) containing $SbCl_3$ (30 mg, 0.13 mmol) under Ar atmosphere at ambient temperature. Reaction mixture was heated at 55 °C for 3 h, and was quenched with saturated $NaHCO_3/H_2O$. The resulting mixture was extracted with CH_2Cl_2 and the combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was column chromatographed (20 → 25% EtOAc/hexane) to give **15** (9 mg, 58%) as colorless oil of major β anomer. ^{1}H NMR δ 1.33 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.10 (s, 3H, Ac), 3.67 (ddd, J = 2.5, 5.3, 10.1 Hz, 1H, H4), 4.06 ("t", J = 10.8 Hz, 1H, H5), 4.27 (dd, J = 5.3, 11.6 Hz, 1H, H5′), 4.94 (d, J = 5.4 Hz, 1H, H3), 5.03 (dd, J = 5.4, 9.5 Hz, 1H, H2), 5.97 (d, J = 54.0 Hz, 1H, H1); ^{13}C NMR δ 20.81 (Ac), 24.57 (CMe_2), 26.33 (CMe_2), 54.86 (d, J = 1.8 Hz, C4), 65.82 (C5), 84.81 (C3), 89.15 (d, J = 38.6 Hz, C2), 106.60 (d, J = 218.3 Hz, C1), 111.33 (CMe_2), 170.47 (Ac); ^{19}F NMR δ –140.85 (ddd, J = 2.3, 9.5, 54.0 Hz); MS (ESI) m/z 134 (100), 250 (7, M^+). A further elution (25% EtOAc/hexane) afforded an analytical sample of the minor α anomer

of **15** (1.1 mg, 7%): ^{1}H NMR δ 1.38 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.10 (s, 3H, Ac), 3.98–4.03 (m, 1H, H4), 4.19 (dd, *J* = 6.3, 11.6 Hz, 1H, H5), 4.34 (dd, *J* = 6.2, 11.5 Hz, 1H, H5′), 4.67 (dd, *J* = 3.5, 6.7 Hz, 1H, H3), 4.83 (ddd, *J* = 4.4, 6.7, 15.2 Hz, 1H, H2), 5.81 (dd, *J* = 4.4, 56.7 Hz, 1H, H1); ^{13}C NMR δ 20.72 (Ac), 25.82 (d, *J* = 1.4 Hz, C*Me*$_2$), 25.94 (d, *J* = 2.3 Hz, C*Me*$_2$), 48.96 (C4), 64.42 (d, *J* = 2.1 Hz, C5), 83.21 (C3), 85.06 (d, *J* = 19.8 Hz, C2), 98.02 (d, *J* = 231.5 Hz, C1), 115.27 (*C*Me$_2$), 170.49 (Ac); ^{19}F NMR δ –157.24 (dd, *J* = 15.2, 56.7 Hz); HRMS (AP-ESI) *m*/*z* calculated for $C_{10}H_{15}FNaO_4S$ $[M + Na]^+$ 273.0567; found 273.0558. Additional elution (40% EtOAc/hexane) gave the hydrolyzed product **18** (β-anomer; 2.6 mg, 17%). ^{1}H NMR δ 1.34 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.13 (s, 3H, Ac), 2.50 (br. s, OH), 3.63–3.68 (m, 1H, H4), 4.17 (dd, *J* = 8.9, 11.4 Hz, 1H, H5), 4.41 (dd, *J* = 5.8, 11.4 Hz, 1H, H5′), 4.87 (d, *J* = 5.4 Hz, 1H, H3), 4.92 (d, *J* = 5.4 Hz, 1H, H2), 5.37 (br. s, 1H, H1); ^{13}C NMR δ 20.90 (Ac), 24.56 (C*Me*$_2$), 26.44 (C*Me*$_2$), 54.83 (C4), 66.53 (C5), 85.78 (C3), 86.98 (C1), 90.47 (C2), 110.82 (*C*Me$_2$), 170.57 (Ac). HRMS (AP-ESI) *m*/*z* calculated for $C_{10}H_{16}NaO_5S$ $[M + Na]^+$ 271.0611; found 271.0619.

4.12.2. Note

Stirring of **15** (5 mg 0.2 mmol) in THF (1 mL) in the presence of 0.1 N HCl (0.1 mL) at ambient temperature for 1 h gave **18** (4.7 mg, 95%) with data as reported above.

4.12.3. Method B

Sulfide **13** (27.5 mg, 0.12 mmol) was treated with deoxo-fluor (127 mg, 0.26 mL, 50% soln in THF, 0.59 mmol) and $SbCl_3$ (30 mg, 0.13 mmol) as described above (*method A*, 4 h). The crude product was column chromatographed (20 → 25% EtOAc/hexane) to give major β anomer of **15** (14.5 mg, 49%) as colorless oil with data as reported above.

4.13. 1-Deoxy-1-fluoro-2,3-O-isopropylidene-4-thio-β-D-ribofuranose (**16**)

Compound **15** (β-anomer; 45 mg, 0.18 mmol) was dissolved in saturated methanolic ammonia solution (4 mL) and the resulting mixture was stirred for 15 h at ambient temperature. The volatiles were evaporated to give crude product **16** (37 mg, 99%) as a light yellow oil of sufficient purity to be used for next step. ^{1}H NMR δ 1.32 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.02 (s, 1H, OH), 3.64–3.79 (m, 3H, H4,H5,5′), 4.96 (d, *J* = 5.4 Hz, 1H, H3), 5.01 (dd, *J* = 5.4, 10.2 Hz, 1H, H2), 5.99 (d, *J* = 55.7 Hz, 1H, H1); ^{13}C NMR δ 24.43 (C*Me*$_2$), 26.37 (C*Me*$_2$), 59.38 (d, *J* = 1.9 Hz, C4), 64.97 (d, *J* = 1.4 Hz, C5), 85.22 (C3), 89.64 (d, *J* = 36.9 Hz, C2), 107.16 (d, *J* = 216.8 Hz, C1), 110.99 (*C*Me$_2$); ^{19}F NMR δ –137.16 (dd, *J* = 10.3, 55.8 Hz). MS (ESI) *m*/*z* 209 (100, $[MH]^+$).

4.14. 1-Deoxy-1-fluoro-2,3-O-isopropylidene-5-O-methanesulfonyl-4-thio-β-D-ribofuranose (**17**)

Compound **16** (37 mg, 0.18 mmol) was treated with MsCl (0.16 mL, 237 mg, 3.31 mmol) in the presence of Et_3N (0.6 mL, 437 mg, 4.33 mmol) as described in Section 4.2 (18 h, 0 °C → RT). The crude material (104 mg) was column chromatographed (20% EtOAc/hexane) to give rearranged byproduct **9b** (2 mg, 5%). Further elution (30 → 40% EtOAc/hexane) yielded **17** (31 mg, 61%): ^{1}H NMR δ 1.33 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.07 (s, 3H, Ms), 3.76 (ddd, *J* = 2.2, 5.3, 10.2 Hz, 1H, H4), 4.17 ("t", *J* = 10.5 Hz, 1H, H5), 4.34 (dd, *J* = 5.3, 10.7 Hz, 1H, H5′), 5.01–5.03 (m, 1H, H3), 5.03–5.07 (m, 1H, H2), 5.99 (d, *J* = 53.6 Hz, 1H, H1); ^{13}C NMR δ 24.49 (C*Me*$_2$), 26.24 (C*Me*$_2$), 37.73 (Ms), 54.80 (C4), 69.85 (C5), 84.16 (C3), 88.84 (d, *J* = 38.6 Hz, C2), 106.58 (d, *J* = 218.0 Hz, C1), 111.58 (*C*Me$_2$); ^{19}F NMR δ –140.85 (ddd, *J* = 1.9, 8.7, 53.6 Hz). HRMS (AP-ESI) *m*/*z* calculated for $C_9H_{16}NaO_6S_2$ $[M + Na]^+$ 307.0280; found 307.0268.

The byproduct **9b** was isolated as mixture of two diastereoisomers (8:1): Major isomer had: ^{1}H NMR δ 1.34 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.51 (d, *J* = 11.6 Hz, 1H, H5), 3.62–3.69 (m, 1H, H4), 3.74 (dd, *J* = 4.5, 11.0 Hz, 1H, H5′), 5.04 (dd, *J* = 5.4, 9.1 Hz, 1H, H3), 5.12 (d, *J* = 5.4 Hz, 1H, H2), 5.99 (d, *J* = 53.4 Hz, 1H, H1); ^{19}F NMR δ –140.31 (ddd, *J* = 2.2, 9.0, 53.4 Hz). MS (ESI) *m*/*z* 243 (100, $[M+17]^+$).

4.15. S-(1,5-Dideoxy-1-fluoro-2,3-O-isopropylidene-4-thio-β-D-ribofuranos-5-yl)-N-(tert-butoxycarbonyl)-L-homocysteine tert-butyl ester (**19**), and S-(5-deoxy-2,3-O-isopropylidene-4-thio-β-D-ribofuranos-5-yl)-N-(tert-butoxycarbonyl)-L-homocysteine tert-butyl ester (**20**)

Compound **17** (31 mg, 0.11 mmol) was treated with lithium homocysteinate (91 mg, 0.31 mmol) as described in Section 4.5 (3 h). The crude product was column chromatographed (15 → 20% EtOAc/hexane) to give **19** (13 mg, 25%) as a colorless oil: ^{1}H NMR δ 1.34 (s, 3H), 1.47 (s, 9H), 1.49 (s, 12H), 1.85–1.95 (m, 1H, H8), 2.04–2.16 (m, 1H, H8′), 2.60–2.66 (m, 2H, H7,7′), 2.71 (dd, *J* = 11.1, 13.9 Hz, 1H, H5), 2.87 (dd, *J* = 5.7, 13.9 Hz, 1H, H5′), 3.55 (ddd, *J* = 2.3, 5.4, 10.9 Hz, 1H, H4), 4.26–4.34 (m, 1H, H9), 5.04 (d, *J* = 0.8 Hz, 1H, H3), 5.06 (d, 1, *J* = 2.9 Hz, 1H, H2), 5.11 ("br. d", *J* = 6.9 Hz, 1H, NH), 6.00 (d, *J* = 53.7 Hz, 1H, H1); ^{13}C NMR δ 24.59 (C*Me*$_2$), 26.31 (C*Me*$_2$), 28.02 (t-Bu), 28.33 (C7, t-Bu), 33.11 (C8), 38.14 (C5), 53.32 (C9), 56.43 (d, *J* = 1.8 Hz, C4), 79.87 (t-Bu), 82.31 (t-Bu), 85.98 (C3), 88.86 (d, *J* = 39.2 Hz, C2), 107.09 (d, *J* = 216.9 Hz, C1), 111.21 (*C*Me$_2$), 155.35 (CO), 171.20 (C10); ^{19}F NMR δ –140.87 (dd, *J* = 3.8, 53.8 Hz); MS (ESI) *m*/*z* 462 (100, $[M-19]^+$). HRMS (AP-ESI) *m*/*z* calculated for $C_{21}H_{36}FNNaO_6S_2$ $[M + Na]^+$ 504.1860; found 504.1847.

Further elution (25 → 30% EtOAc/hexane) afforded **20** (14 mg, 27%) as a colorless oil of a single β anomer: ^{1}H NMR δ 1.33 (s, 3H), 1.47 (s, 9H), 1.49 (s, 9H), 1.51 (s, 3H), 1.89–2.00 (m, 1H, H8), 2.07 (tdd, *J* = 5.8, 9.6, 13.7 Hz, 1H, H8′), 2.59–2.67 (m, 1H, H7), 2.68–2.77 (m, 1H, H7′), 2.85–2.94 (br. s, 1H, OH), 2.89 (dd, *J* = 8.7, 13.5 Hz, 1H, H5), 2.97 (dd, *J* = 6.8, 13.6 Hz, 1H, H5′), 3.56 (t, *J* = 7.9 Hz, 1H, H4), 4.27–4.35 (m, 1H, H9), 4.87 (d, *J* = 5.4 Hz, 1H, H2), 4.95 (d, 1H, *J* = 5.4 Hz, 1H, H3), 5.18 ("br. d", *J* = 6.9 Hz, 1H, NH), 5.41 (s, 1H, H1); ^{13}C NMR δ 24.61 (C*Me*$_2$), 26.48 (C*Me*$_2$), 28.03 (t-Bu), 28.26 (C7), 28.34 (t-Bu) 33.05 (C8), 38.34 (C5), 53.31 (C9), 56.92 (C4), 80.01 (t-Bu), 82.39 (t-Bu), 87.37 (C1), 87.65 (C3), 90.22 (C2), 110.67 (*C*Me$_2$), 155.39 (CO), 171.21 (C10); MS (ESI) *m*/*z* 462 (100, $[M-17]^+$) 480 (30, $[MH]^+$); HRMS (ESI) *m*/*z* calculated for $C_{21}H_{37}NNaO_7S_2$ $[M + Na]^+$ 502.1909; found 502.1884.

4.16. S-(5-Deoxy-4-thio-D-ribofuranos-5-yl)-L-homocysteine (**21**)

4.16.1. Method A

Compound **19** (13 mg, 0.027 mmol) was treated with aqueous TFA, as described in Section 4.6 (4 h), to give colorless oil of **21** (7 mg, 91%) as a mixture of anomers whose ratio changed when stored in D_2O solution (1:1 → 1:4, α:β). Major β-isomer had: ^{1}H NMR (D_2O) δ 2.25–2.45 (m, 2H, H8,8′), 2.78 (dd, *J* = 8.7, 13.4 Hz, 1H, H5), 2.87 (t, *J* = 7.3 Hz, 2H, H7,7′), 3.20 (dd, *J* = 4.6, 13.4 Hz, 1H, H5′), 3.54 (ddd, *J* = 4.6, 7.8, 9.0 Hz, 1H, H4), 4.16–4.21 (m, 3H, H2,3,9), 5.14 (d, *J* = 1.6 Hz, 1H, H1); ^{13}C NMR (D_2O) δ 29.20 (C8), 32.32 (C7), 35.68 (C5), 48.81 (C4), 51.69 (C9), 76.75, 79.63 (C2, C3), 81.07 (C1), 171.79 (C10). Minor α-isomer had: ^{1}H NMR (D_2O) δ 2.25–2.45 (m, 2H, H8,8′), 2.67 (dd, *J* = 8.7, 13.5 Hz, 1H, H5), 2.87 (t, *J* = 7.3 Hz, 2H, H7,7′), 3.03 (dd, *J* = 5.5, 13.4 Hz, 1H, H5′), 3.77 (dt, *J* = 5.6, 8.7, Hz, 1H, H4), 4.10 (dd, *J* = 3.7, 5.7 Hz, 1H, H3), 4.16–4.21 (m, 1H, H9), 4.24 (t, *J* = 4.0 Hz, 1H, H2), 5.45 (d, *J* = 4.3 Hz, 1H, H1); MS (ESI) *m*/*z* 284 (100, $[MH]^+$). HRMS (AP-ESI) *m*/*z* calculated for $C_9H_{16}NO_5S_2$ $[M–H]^-$ 282.0475; found 282.0484.

4.16.2. Method B

Compound **20** (6 mg, 0.012 mmol) was treated with aqueous TFA, as described in Section 4.6 (4 h), to give **21** (3 mg, 85%) as a

colorless oil with spectral data identical to the sample of **21** from *method A*.

4.17. 1,5-O-Diacetyl-2,3-O-isopropylidene-4-thio-α/β-D-ribofuranose (**22**), and 5-O-acetyl-4,5-didehydro-1-deoxy-2,3-O-isopropylidene-4-thio-D-ribofuranose (**23**)

4.17.1. Method A

A solution of compound **14** (59 mg, 0.24 mmol) in Ac_2O (5 mL) was heated at 100 °C for 6 h. The reaction mixture was evaporated, coevaporated with toluene, and the residue was column chromatographed (25 → 30% EtOAc/hexane) to give **22**[32] (40 mg, 57%; α/β = 1:4) as separable mixture of anomers and less polar somewhat unstable **23** (12 mg, 20%). Compound **22** (α-anomer) had: ^{1}H NMR δ 1.38 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.12 (s, 3H, Ac), 2.17 (s, 3H, Ac), 3.92 (dt, *J* = 4.3, 6.1 Hz, 1H, H4), 4.21 (dd, *J* = 6.3, 11.5 Hz, 1H, H5), 4.37 (dd, *J* = 6.1, 11.5 Hz, 1H, H5′), 4.69 (dd, *J* = 4.2, 6.9 Hz, 1H, H3), 4.92 (dd, *J* = 5.3, 6.9 Hz, 1H, H2), 6.11 (d, *J* = 5.3 Hz, 1H, H1); ^{13}C NMR δ 20.81 (Ac), 21.18 (Ac), 25.58 (C*Me*$_2$), 26.29 (C*Me*$_2$), 49.09 (C4), 64.66 (C5), 78.63 (C1), 83.73 (C2), 84.03 (C3), 115.15 (*C*Me$_2$), 169.82 (Ac), 170.57 (Ac). MS (ESI) *m*/*z* 291 (9, [MH]$^+$), 308 (100, [M + 18]$^+$). Compound **22** (β-anomer) had: ^{1}H NMR δ 1.33 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.09 (s, 3H, Ac), 2.12 (s, 3H, Ac), 3.63 (dd, *J* = 5.8, 10.2 Hz, 1H, H4), 4.07 (dd, *J* = 10.3, 11.4 Hz, 1H, H5), 4.25 (dd, *J* = 5.8, 11.4 Hz, 1H, H5′), 4.90 (d, *J* = 5.5 Hz, 1H, H2), 4.92 (d, *J* = 5.5 Hz, 1H, H3), 6.06 (s, 1H, H1); ^{13}C NMR δ 20.90 (Ac), 21.26 (Ac), 24.67 (C*Me*$_2$), 26.44 (C*Me*$_2$), 53.92 (C4), 65.79 (C5), 85.21 (C3), 87.24 (C1), 88.62 (C2), 111.39 (*C*Me$_2$), 169.23 (Ac), 170.56 (Ac); HRMS (AP-ESI) *m*/*z* calculated for $C_{12}H_{18}NaO_6S$ [M + Na]$^+$ 313.0716; found 313.0711.

Compound **23** had: ^{1}H NMR δ 1.39 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.20 (s, 3H, Ac), 3.18 (dd, *J* = 2.4, 12.3 Hz, 1H, H1), 3.24 (dd, *J* = 4.9, 12.3 Hz, 1H, H1′), 4.91 ("dt", *J* = 2.4, 5.1 Hz, 1H, H2), 5.18 (dd, *J* = 5.3, 0.7 Hz, 1H, H3), 7.57 (d, *J* = 0.7 Hz, 1H, H5); ^{13}C NMR δ 20.60 (Ac), 25.66 (C*Me*$_2$), 27.37 (C*Me*$_2$) 36.86 (C1) 81.11 (C2), 83.57 (C3), 112.20 (*C*Me$_2$), 123.67 (C4), 131.37 (C5), 167.21 (Ac). MS (ESI) *m*/*z* 231 (10, [MH]$^+$). HRMS (AP-ESI) *m*/*z* calculated for $C_{10}H_{14}NaO_4S$ [M + Na]$^+$ 253.0505; found 253.05134.

4.17.2. Method B

Sulfoxide **6** (16 mg, 0.078 mmol) was heated with Ac_2O (1.0 mL) as described above (*method A*, 110 °C, 3.5 h). The crude reaction residue was column chromatographed (25 → 35% EtOAc/hexane) to give **22** (8.0 mg, 41%; α/β = 1:5) as separable mixture of anomers and less polar **23** (2.0 mg, 12%).

4.18. 2,3-O-Isopropylidene-4-thio-α/β-D-ribofuranose (**24**)

Compound **22** (4 mg, 0.016 mmol; α/β = 1:5) was dissolved in saturated NH_3/MeOH solution (3 mL) and the solution was stirred at ambient temperature for 15 h. The volatiles were evaporated to give **24** (3 mg, 91%, α/β = 1:9) as a colorless oil. Major β anomer had: ^{1}H NMR δ 1.32 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.04 (s, 2H, OH), 3.68 (t, *J* = 2.8 Hz, 1H, H4), 3.77 (dd, *J* = 2.6, 10.5 Hz, 1H, H5), 4.08 (dd, *J* = 3.1, 10.5 Hz, 1H, H5′), 4.77 (d, *J* = 5.4 Hz, 1H, H3), 4.91 (d, *J* = 5.4 Hz, 1H, H2), 5.32 (s, 1H, H1); ^{13}C NMR δ 24.40 (C*Me*$_2$), 26.49 (C*Me*$_2$), 57.73 (C4), 65.08 (C5), 86.91 (C3), 87.33 (C1), 92.13 (C2), 110.29 (*C*Me$_2$); MS (ESI) *m*/*z* 229 (100, [M + Na]$^+$).

4.19. 2,3-O-Isopropylidene-S,S-dioxo-1-deoxy-4-thio-D-ribofuranose (**25**)

Oxidation of **6** (31 mg, 0.15 mmol) with MCPBA (69 mg, 0.30 mmol, 75%), as described in Section 4.1 (30 min at −78 °C, followed by 2 h at RT; work up: $NaHCO_3/H_2O//CH_2Cl_2$; column: 80% EtOAc/hexane → 20% MeOH/EtOAc), gave **25** (27 mg, 80%) as white solid: ^{1}H NMR δ 1.38 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.33–3.40 (m, 2H, H1,4), 3.41–3.48 (m, 1H, H1′) 4.03 (dd, *J* = 4.6, 12.0 Hz, 1H, H5), 4.31 (dd, *J* = 2.7, 12.0 Hz, 1H, H5′), 4.91–4.93 (m, 2H, H2,3); ^{13}C NMR δ 24.56 (C*Me*$_2$), 26.55 (C*Me*$_2$), 56.82 (C1), 58.95 (C5), 66.58 (C4), 73.55, 77.87 (C2,3), 111.55(*C*Me$_2$); MS (APCI) *m*/*z* 287 (100, [M + 2MeOH + H]$^+$), 240 (60, [M + 18]$^+$).

Treatment of **5** (34 mg, 0.18 mmol) with MCPBA (104 mg, 0.45 mmol, 75%), as described in Section 4.1 (30 min at −78 °C followed by 2 h at RT; work up: $NaHCO_3/H_2O//CH_2Cl_2$; column: 80% EtOAc/hexane → 20% MeOH/EtOAc) gave **25** (34 mg, 85%) as white solid.

4.20. 4,5-Didehydro-1,5-dideoxy-2,3-O-isopropylidene-S,S-dioxo-4-thio-D-ribofuranose (**26**)

Compound **25** (15 mg, 0.068 mmol) was treated with MsCl (0.032 mL, 47 mg, 0.41 mmol) in the presence of Et_3N (0.113 mL, 83 mg, 0.82 mmol) as described in Section 4.2 (1 h). The crude product was column chromatographed (50 → 60% EtOAc/hexane) to give **26** (13 mg, 96%) as a colorless oil: ^{1}H NMR δ 1.42 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 3.34 (dd, *J* = 3.2, 14.3 Hz, 1H, H1), 3.45 (dd, *J* = 6.6, 14.3 Hz, 1H, H1′), 4.94 ("dt", *J* = 3.2, 6.6 Hz, 1H, H2), 5.14 ("td", *J* = 1.6, 7.0 Hz, 1H, H3), 6.07 ("t", *J* = 1.6 Hz, 1H, H5), 6.30 ("t", *J* = 1.6 Hz, 1H, H5′); ^{13}C NMR δ 25.22 (C*Me*$_2$), 26.88 (C*Me*$_2$), 54.53 (C1), 72.19 (C2), 74.43 (C3), 112.73 (*C*Me$_2$), 122.20 (C5), 147.86 (C4); MS (APCI) *m*/*z* 269 (M + 2MeOH + H$^+$); HRMS (APESI) *m*/*z* calculated for $C_8H_{13}O_4S$ [MH]$^+$ 205.0529; found 205.0514.

Acknowledgments

We thank NIH (1SC1CA138176) for financial support.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.carres.2015.07.005.

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