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Enantioselective and Protecting Group-Free Synthesis of 1-Deoxythionojirimycin, 1-Deoxythiomannojirimycin, and 1-Deoxythiotalonojirimycin

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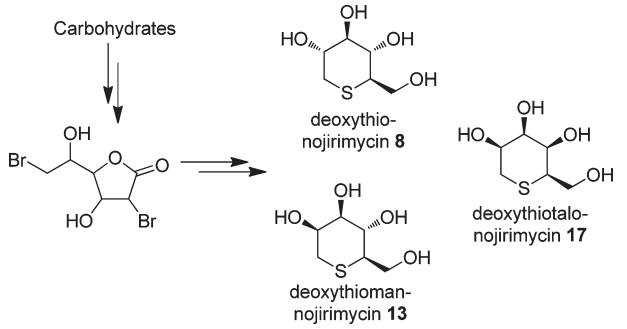

1-Deoxythioglyconojirimycins were synthesized by using a protecting group-free strategy, starting from readily available carbohydrates, in good overall yield. Use of benzyltriethylammonium tetrathiomolybdate, $[BnEt_3N]_2MoS_4$, as a sulfur transfer reagent and borohydride exchange resin (BER) reduction of a lactone enabled the efficient synthesis of the title compounds.

Glycosidases are essential biological enzymes found in all domains of life that catalyze the hydrolysis of glycosidic linkage. Hence, their function or dysfunction implicates different disease states like viral infections such as influenza and HIV, lysosomal storage disorders, cancer and diabetes, and mutational diseases (Gaucher and Fabry disease etc.),[1] and the activity of glycosidase can be controlled by glycosidase inhibitors. Many of the clinically used and the naturally occurring glycosidase inhibitors are aza-sugars. Acarbose, miglitol, deoxynojirimycin, and swainsonine are a few notable examples.[2] On the other hand, thio-sugars isolated from natural sources also possess promising inhibiting activity against glycosidase.[3] But, only limited examples such as 5-thio-mannose **1**, salacinol **2**, kotalanol **3**, and some side chain derivatives of salacinol are known (Figure 1). To understand the activity of thio-sugars as glycosidase inhibitors and to elucidate the structure−activity relationship (SAR), considerable efforts have been devoted to the synthesis of thio-sugars based on the natural templates.[4] In addition, replacement of nitrogen with sulfur in aza-sugars to obtain the thio-analogues of aza-sugars also gained much attention for comparing the bioactivities.[5]

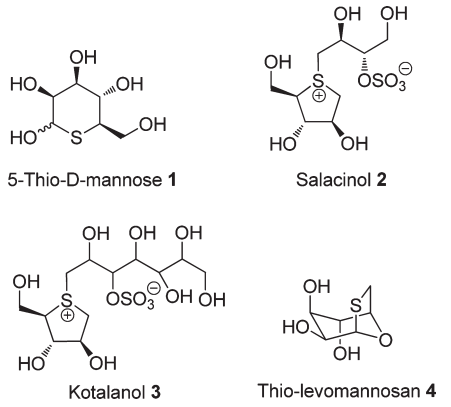

FIGURE 1. Representative examples of thio-sugars as potent glycosidase inhibitors.

The vital steps in the synthesis of thio-sugars or thio-sugar analogues are the introduction of sulfur and protection and deprotection of functional groups, and these steps always make the synthesis of thio-sugars or thio-sugar analogues difficult and more challenging. Traditional methods of introducing sulfur for the synthesis of thio-sugars include the nucleophilic displacement of the leaving group with Na_2S[6] or

(1) (a) Gloster, T. M.; Davies, D. J. *Org. Biomol. Chem.* **2010**, *8*, 305. (b) Rempel, B. P.; Withers, S. G. *Glycobiology* **2008**, *18*, 570. (c) Lieberman, R. I.; Wustman, B. A.; Huertas, P.; Powe, A. C.; Pine, C. J.; Khanna, R.; Schlossmacher, M. G.; Ringe, D.; Petsko, G. A. *Nat. Chem. Biol.* **2007**, *3*, 101. (d) Brumshtein, B.; Greenblatt, H. M.; Butters, T. D.; Shaaltiel, Y.; Aviezer, D.; Silman, I.; Futerman, A. H.; Sussman, J. L. *J. Biol. Chem.* **2007**, *282*, 29052.

(2) For books and reviews see: (a) *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Stutz, A. E., Ed.; Wiley-VCH: Weinheim, Germany, 1999. (b) *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, P., Martin, O. R., Eds.; John Wiley: Chichester, UK, 2007. (c) Asano, N. *Glycobiology* **2003**, *13*, 93R. (d) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515 and references cited therein. (e) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199.

(3) (a) Witczak, Z. J.; Culhane, J. M. *Appl. Microbiol. Biotechnol.* **2005**, *69*, 237. (b) Capon, R. J.; MacLeod, J. K. *J. Chem. Soc., Chem. Commun.* **1987**, 1200.

(4) For recent references see: (a) Jayakanthan, K.; Mohan, S.; Pinto, B. M. *J. Am. Chem. Soc.* **2009**, *131*, 5621. (b) Mohan, S.; Pinto, B. M. *Carbohydr. Res.* **2007**, *342*, 1551 and references cited therein. (c) Eskandari, R.; Jayakanthan, K.; Kuntz, D. A.; Rose, D. R.; Pinto, B. M. *Bioorg. Med. Chem.* **2010**, *18*, 2829. (d) Ghavami, A.; Johnston, B. D.; Pinto, B. M. *J. Org. Chem.* **2001**, *66*, 2313. (e) Kumar, N. S.; Pinto, B. M. *J. Org. Chem.* **2006**, *71*, 1262. (f) Kumar, N. S.; Pinto, B. M. *Carbohydr. Res.* **2006**, *341*, 1685. (g) Yuasa, H.; Izumi, M.; Hashimoto, H. *Curr. Top. Med. Chem.* **2009**, *9*, 76.

(5) (a) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159 and references cited therein. (b) Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036. (c) Malle, B. M.; Lundt, I.; Wrodnigg, T. M. *Org. Biomol. Chem.* **2008**, *6*, 1779. (d) Song, X.; Hollingsworth, R. I. *Tetrahedron Lett.* **2007**, *48*, 3115.

(6) (a) Halila, S.; Benazza, M.; Demailly, G. *Tetrahedron Lett.* **2001**, *42*, 3307. (b) Benazza, M.; Halila, S.; Viot, C.; Danquigny, A.; Pierru, C.; Demailly, G. *Tetrahedron* **2004**, *60*, 2889. (c) Merrer, Y. L.; Fuzier, M.; Dosbaa, I.; Foglietti, M. J.; Depezay, J. C. *Tetrahedron* **1997**, *53*, 16731 and references cited therein.

(7) (a) Cubero, I. I.; López-Espinosa, M. T. P.; Richardson, A. C.; Suarez Ortéga, M. D. *Carbohydr. Res.* **1993**, *242*, 109. (b) Chou, W. C.; Chen, L.; Fang, J. M.; Wong, C. H. *J. Am. Chem. Soc.* **1994**, *116*, 6191.

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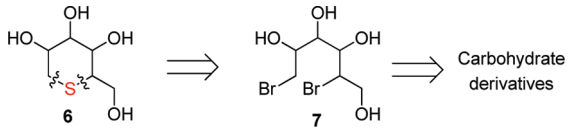
SCHEME 1. Retrosynthesis of Thio-Analogues of 1-Deoxyglyconojirimycin



KSAc,[7] NaSH,[8] $(NH_2)_2CS$,[9] and AcSH,[10] and they have been utilized earlier in the synthesis of targeted thio-sugars, deoxythionojirimycin (**8**),[6c] deoxythiomannojirimycin (**13**),[7a] and deoxythiotalonojirimycin (**17**).[10b]

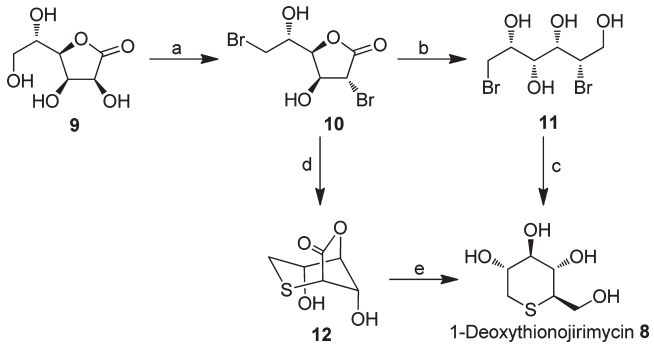
Our long-standing interest in the use of benzyltriethylammonium tetrathiomolybdate, $[BnEt_3N]_2MoS_4$ (**5**), as a sulfur transfer reagent[11] and our recent success in the synthesis of conformationally locked thio-levomannosan **4** as mannosidase inhibitor[12] prompted us to develop an efficient synthesis of various thio-sugars utilizing the same. Additionally, benzyltriethylammonium tetrathiomolybdate (**5**) was shown to be a mild reagent and more specific toward certain kinds of functional groups.[11] Herein, we disclose the protecting group-free synthesis of thio-analogues of deoxyglyconojirimycins using tetrathiomolybdate **5**.

We envisioned that the synthesis of thio-analogues of 1-deoxyglyconojirimycins **6** can be readily achieved starting from commercially available carbohydrates, one of the functionally richest building blocks (Scheme 1). Thus, conversion of carbohydrate into suitably positioned dibromide **7** followed by reaction with benzyltriethylammonium tetrathiomolybdate (**5**) was expected to yield the 1-deoxythioglyconojirimycins.

Initially, synthesis of 1-deoxythionojirimycin (**8**) was visualized from commercially available L-gulonic acid-γ-lactone (**9**). Thus, bromination of **9** with HBr in acetic acid yielded 2,6-dibromo-2,6-dideoxy-D-idono-1,4-lactone (**10**) in excellent yield.[13] Dibromolactone **10** on reduction with sodium borohydride in the presence of Amberlite 120 H^+ resin gave the required dibromide **11**,[14] the precursor for the synthesis of 1-deoxythionojirimycin (**8**), in 20% yield.[15] Subsequently, the reaction of **11** with tetrathiomolybdate **5** in acetonitrile/ethanol (1:1) mixture provided the expected 1-deoxythionojirimycin (**8**) in 38% yield.[15] Although the synthesis of **8** was achieved in three steps starting from readily available **9**, the overall yield was low (Scheme 2). To improve the overall yield, the synthetic strategy was modified slightly and we decided to use the dibromolactone **10** as the precursor for the sulfur transfer reaction.

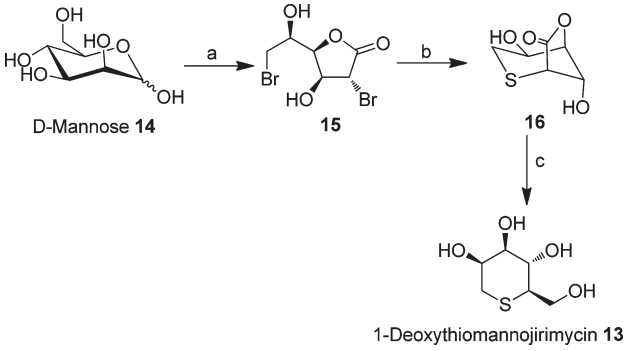
To our delight, 2,6-dibromo-2,6-dideoxy-D-idono-1,4-lactone (**10**) on reaction with benzyltriethylammonium tetrathiomolybdate (**5**) smoothly furnished the axially enriched

SCHEME 2. Synthesis of 1-Deoxythionojirimycin (8)[a]



[a]Reaction conditions: (a) HBr/AcOH, 30 °C, 4.5 h, 86%; (b) $NaBH_4$, MeOH, Amberlite 120 H^+, 20%; (c) $[BnEt_3N]_2MoS_4$, CH_3CN:EtOH (1:1), rt, 30 min, 38%; (d) $[BnEt_3N]_2MoS_4$, DMSO, rt, 30 min, 56%; (e) BER, MeOH, 0 °C−rt, 18 h, 62%.

SCHEME 3. Synthesis of 1-Deoxythiomannojirimycin (13)[a]



[a]Reaction conditions: (a) (i) $Br_2/BaCO_3$, 2 h, (ii) HBr/AcOH, 4 h, rt, 27% in two steps; (b) $[BnEt_3N]_2MoS_4$, DMSO, rt, 30 min, 59%; (c) BER, MeOH, 0 °C−rt, 4 h, 74%.

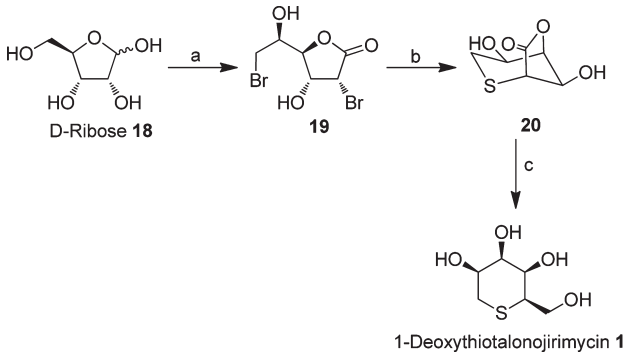
1-deoxy-5-thio-D-glucopyrano-3,6-lactone (**12**) in good yield (56%).[16] The structure and stereochemistry of **12** was unambiguously confirmed by X-ray analysis (see the Supporting Information). Reduction of bicyclic thialactone **12** with borohydride exchange resin (BER)[17] in methanol furnished the 1-deoxythionojirimcin (**8**) in good yield with excellent purity.

Similarly, synthesis of 1-deoxythiomannose (1-deoxythiomannojirimycin) (**13**) was started from D-mannose (**14**). D-Mannose (**14**) was converted to mannono-1,4-lactone, followed by reaction with HBr/acetic acid to yield the 2,6-dibromo-2,6-dideoxy-D-glucono-1,4-lactone (**15**).[18] Reaction of dibromo lactone **15** with benzyltriethylammonium tetrathiomolybdate (**5**) (DMSO, rt, 30 min) afforded the 1-deoxy-5-thio-D-mannopyrano-3,6-lactone (**16**) in 59% yield (Scheme 3). Subsequent reduction of bicyclic thialactone **16** with BER furnished the 1-deoxythiomannose (**13**) in good yield.

Next, the synthesis of 1-deoxythiotalonojirimycin (**17**) was accomplished starting from D-ribose **18**. Accordingly, one

(8) Robert, C. C.; Benazza, M.; Fréchou, C.; Demailly, G. *Carbohydr. Res.* **1997**, *303*, 359.
(9) Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1993**, *76*, 2687.
(10) (a) Hashimoto, H.; Kawanishi, M.; Yuasa, H. *Carbohydr. Res.* **1996**, *282*, 207. (b) Cubero, I. I.; López-Espinosa, M. T. P.; Asenjo, R. A.; Fernández, A. R. *Carbohydr. Lett.* **1999**, *3*, 323.
(11) (a) Prabhu, K. R.; Devan, N.; Chandrasekaran, S. *Synlett* **2002**, *11*, 1762. (b) Sureshkumar, D.; Koutha, S. M.; Chandrasekaran, S. *J. Am. Chem. Soc.* **2005**, *127*, 12760. (c) Sureshkumar, D.; Gunasundari, T.; Ganesh, V.; Chandrasekaran, S. *J. Org. Chem.* **2007**, *72*, 2106.
(12) (a) Sivapriya, K.; Chandrasekaran, S. *Carbohydr. Res.* **2006**, *341*, 2204. (b) Sivapriya, K.; Hariharaputran, S.; Suhas, V. L.; Chandra, N.; Chandrasekaran, S. *Bioorg. Med. Chem.* **2007**, *15*, 5659.
(13) (a) Vekemans, J. A. J. M.; Dapperens, C. W. M.; Claessen, R.; Koten, A. M. J.; Godefroi, E. F. *J. Org. Chem.* **1990**, *55*, 5336. (b) Bock, K.; Lundt, I.; Pedersen, C.; Refn, S. *Acta Chem. Scand.* **1986**, *B40*, 740.
(14) Lundt, I.; Madsen, R. *Synthesis* **1993**, 720.
(15) The low yield of products **8** and **11** is attributed to difficulties in isolation from the reaction medium.
(16) The reaction of dibromolactone **10** with Na_2S (DMSO, 30 min) gave a mixture of products from which bicyclic thialactone **12** could be isolated in 11% yield.
(17) (a) Bandgar, B. P.; Modhave, R. K.; Wadgaonkar, P. P.; Sande, A. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1993. (b) Gibson, H. W.; Bailey, F. C. *J. Chem. Soc., Chem. Commun.* **1977**, 815a.
(18) Lundt, I.; Pedersen, C. *Synthesis* **1991**, 669.

SCHEME 4. Synthesis of 1-Deoxythiotalonojirimycin (17)[a]



[a]Reaction conditions: (a) (i) Reference 19, (ii) HBr/AcOH, 2 h, rt, 49%; (b) $[BnEt_3N]_2MoS_4$, DMSO, rt, 30 min, 63%; (c) BER, MeOH, 0 °C−rt, 4 h, 58%.

carbon extension of D-ribose using NaCN under Kiliani−Fischer synthesis conditions produced altronolactone,[19] which on subsequent bromination with HBr in acetic acid afforded the 2,6-dibromo-2,6-dideoxy-D-allono-1,4-lactone (**19**). Double displacement of dibromide in **19** with benzyltriethylammonium tetrathiomolybdate **5** in DMSO smoothly furnished the bicyclic thialactone **20** in 63% yield. BER reduction of 1-deoxy-5-thio-D-talopyrano-3,6-lactone (**20**) in methanol yielded the required 1-deoxythiotalonojirimycin **17** in good yield (Scheme 4).

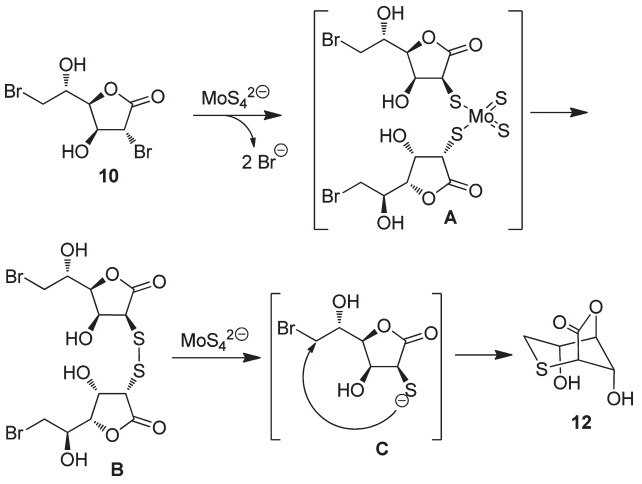
In our opinion the reaction of dibromo lactone **10** with benzyltriethylammonium tetrathiomolybdate **5** leads to the intermediate **A** via S_N2 displacement of the more reactive bromide with sulfide anion.[20] Intermediate **A** can then undergo an internal redox process[21a,b] with the oxidation of the ligand and concomitant reduction of the metal center to give the disulfide **B**. On the basis of our own earlier work[11] and that of Stiefel,[21c,d] **B** can undergo reductive cleavage of the disulfide bond with tetrathiomolybdate **5** to give thiolate intermediate **C**.[21c,d] Finally an intramolecular displacement of primary bromide with sulfide anion in **C** results in the formation of bicyclic thialactone **12** in a stereospecific manner (Scheme 5).

In conclusion, efficient synthesis of 1-deoxythioglycono-jirimycins is accomplished in good overall yield employing a protecting group-free strategy. Effective utilization of benzyltriethylammonium tetrathiomolybdate, $[BnEt_3N]_2MoS_4$ (**5**), as sulfur transfer reagent and borohydride exchange resin (BER) as reducing reagent are notable features of the methodology.

Experimental Section

Typical Procedure for the Synthesis of 1-Deoxy-5-thio-D-glucopyrano-3,6-lactone (12) from 2,6-Dibromo-2,6-dideoxy-D-idono-1,4-lactone (10). A solution of dibromolactone **10** (0.320 g, 1.05 mmol) in DMSO (2 mL) was added to a solution of benzyltriethylammonium

SCHEME 5. Proposed Mechanism for the Double Displacement of Dibromolactone 10 with $[BnEt_3N]_2MoS_4$ (5)



tetrathiomolybdate ($[BnEt_3N]_2MoS_4$ (**5**), 1.411 g, 2.3 mmol) in DMSO (15 mL) over a period of 15 min. After the reaction mixture was stirred for 30 min, DMSO was removed under reduced pressure and the residue was repeatedly extracted with THF (5 × 10 mL) and filtered over a Celite pad. The solvent was concentrated to give the crude product, which was subjected to column chromatography on silica gel (elution with hexanes:ethyl acetate 1:1) furnishing a white solid. It was then recrystallized from acetone to afford colorless crystals of the bicyclic thialactone **12** (0.104 g, 56%). Mp 156−157 °C; $[\alpha]_D$ +13.0 (*c* 1.0, MeOH); IR (neat) 3422, 1430, 1288, 1170, 1116, 1054 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 2.68 (d, J = 15 Hz, 1H), 3.20 (dd, J = 14.5, 3.3 Hz, 1H), 3.41 (d, J = 5.5 Hz, 1H), 4.36 (br s, 1H), 4.55 (t, J = 5.4 Hz, 1H), 4.60 (br s, 1H), 5.43 (d, J = 5.3 Hz, 1H), 5.63 (d, J = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 31.5, 44.6, 66.7, 69.0, 74.5, 171.8; HRMS for $C_6H_8O_4S$ + Na calcd 199.0041, found 199.0043. Anal. Calcd: C, 41.01; H, 5.08; S, 17.98. Found: C, 40.90; H, 4.58; S, 18.2. Crystal structure data CCDC 774511; C6 H8 O4 S1; mol wt = 176.18, crystal dimensions 0.26 × 0.21 × 0.18, T = 293(2) K, orthorhombic, space group P 21 21 21, a = 5.7460(18) Å, b = 11.149(4) Å, c = 11.329(4) Å, $\alpha = \beta = \gamma = 90.00°$, Z = 4, V = 725.8(4) cm^3, ρ_{calcd} = 1.61 g/cm^3, Mo Kα radiation (λ° = 0.71073 Å), μ = 4.06 mm^{-1}, 2θ = 2.60−28.0°; of 3594 reflections collected, 1623 were independent (R(int) = 0.0337); refinement method full matrix least-squares on F_2, 102 refined parameters, absorption correction (SADABS, Bruker, 1996 software, T_{min} 0.9019 and T_{max} 0.9306), GooF = 1.221, R_1 = 0.0620, wR_2 = 0.1907 ($\sigma > 2\sigma(I)$), absolute structure parameter 0.00(2), residual electron density 0.553/−0.739 e$Å^{-3}$. The structure was solved and refined with the programs WinGXv1.64.05, Sir92, and SHELXL-97.

Typical Procedure for the Synthesis of 1-Deoxythionojirimycin (8) from 1-Deoxy-5-thio-D-glucopyrano-3,6-lactone (12). To a stirred solution of bicyclic thialactone **12** (0.100 g, 0.587 mmol) in dry methanol (6 mL) at 0 °C was added borohydride exchange resin (0.782 g, 2.34 mmol) and the solution was stirred for 18 h. The reaction mixture was filtered and methanol (10 mL) was added to the resin and the mixture was sonicated (ultrasonic cleaning bath, 20 kHz) for 5 min at room temperature. To the sonicated resin glacial acetic acid was added to neutralize then the solution was filtered. The solution was then concentrated in vacuo to afford the crude product which was subjected to column chromatography on silica gel eluting with methanol/chloroform 1.5:8.5 to furnish 1-deoxythionojirimycin (**8**) as a gummy solid (0.063 g, 62%). $[\alpha]_D$ +78.6 (*c* 1.0, MeOH) [lit.[6c] $[\alpha]_D$ +50.0 (*c* 1.39, H_2O)]; IR (neat) 3368, 2925, 1430, 1103, 1043 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 4.27 (quint, J = 2.0 Hz,

(19) Pratt, J. W.; Richtmyer, N. K. *J. Am. Chem. Soc.* **1955**, *77*, 1906.
(20) Driguez, H.; Macauliffe, J. C.; Stick, R. V.; Tilbrook, D. M. G.; Williams, S. J. *Aust. J. Chem.* **1996**, *49*, 343.
(21) (a) Kruhlak, N. L.; Wang, M.; Boorman, P. M.; Parvez, M. *Inorg. Chem.* **2001**, *40*, 3141. (b) Boorman, P. M.; Wang, M.; Parvez, M. *J. Chem. Soc., Chem. Commun.* **1995**, 999. (c) Pan, W. H.; Harmer, M. A.; Halbert, T. R.; Stiefel, E. I. *J. Am. Chem. Soc.* **1984**, *106*, 459. (d) Coyle, C. L.; Harmer, M. A.; George, G. N.; Daage, M.; Stiefel, E. I. *Inorg. Chem.* **1990**, *29*, 14 and references cited therein.

1H), 4.01 (t, J = 3.2 Hz, 1H), 3.71−3.62 (m, 2H), 3.61−3.53 (m, 1H), 3.31 (quint, J = 1.6 Hz, 1H), 3.19 (dd, J = 11.3, 4.4 Hz, 1H), 2.67 (dd, J = 11.3, 1.2 Hz, 1H), 2.11−2.00 (m, 1H), 1.86−1.75 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 34.2, 36.7, 47.8, 62.2, 79.4, 80.0; HRMS for $C_6H_{12}O_4S + 1$ calcd 181.0535, found 181.0526.

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Supporting Information Available: Experimental procedures and spectroscopic data for the compounds and copies of ^{1}H NMR, ^{13}C NMR spectra, and CIF tables. This material is available free of charge via the Internet at http://pubs.acs.org.