Carbohydrate Research 382 (2013) 30–35

Contents lists available at ScienceDirect

Carbohydrate Research

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

Note

De novo synthesis of 1-deoxythiosugars

Thanikachalam Gunasundari, Srinivasan Chandrasekaran *

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

ARTICLE INFO

Article history:
Received 12 June 2013
Received in revised form 12 September 2013
Accepted 26 September 2013
Available online 3 October 2013

Keywords:
Tetrathiomolybdate
1-Deoxythiosugars
Aldonoditosylate
Thiosugar lactone
Borohydride exchange resin

ABSTRACT

A short and efficient chemical synthesis of biologically potent and novel 1-deoxythiosugars is accomplished. Introduction of sulfur mediated by benzyltriethylammonium tetrathiomolybdate, as a sulfur transfer reagent through nucleophilic double displacement of tosylate in α,ω-di-*O*-tosyl aldonolactones in an intramolecular fashion is the key feature. The subsequent reduction of thiosugar lactones with borohydride exchange resin (BER) offers a number of deoxythiosugars in good overall yield.

The uniqueness of thio-analogs of carbohydrates (thiosugars[1]) is preponderant as they play an important part in sulfur organics especially, as saccharide bioisoteres with 'biological relevance as potentially new therapeutics'.[2] In particular, the fundamental physico-chemical properties of sulfur in thiosugars enable them to serve as good mechanism based glycosidase inhibitors.[3,4] They provide mechanistic scope for probing enzyme mechanism by mimicking the conventional sugars through their conformational flexibility.[3,5,6] Furthermore, the glycosidase inhibitors also serve as potential agents against virus,[7] metastasis, and diabetes[8] etc. Similarly, deoxythiosugars, the deoxy analog of thiosugars, have become increasingly important molecules due to their enhanced hydrophobicity pivotal in many physiological processes effecting the rate of glycosidic hydrolysis.[9] However, despite the importance of sulfur-based glycomimetics,[10] their unambiguous chemical synthesis remains a major challenge owing to their intriguing complexity.

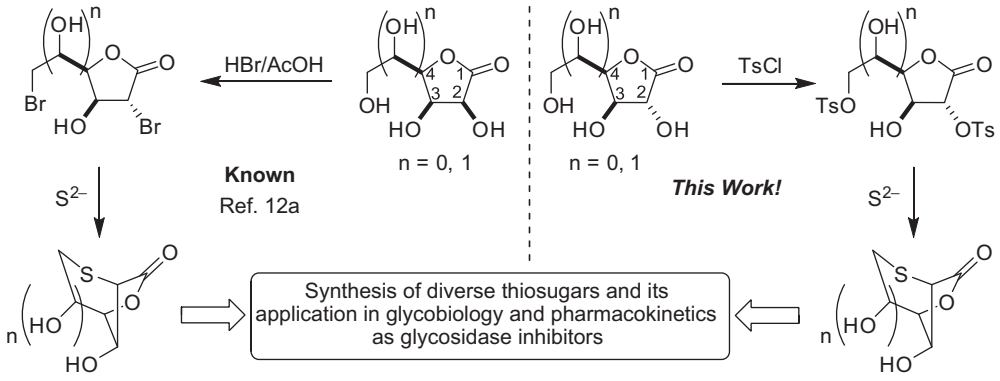
In this context, recently we employed benzyltriethylammonium tetrathiomolybdate[11] $[BnEt_3N]_2MoS_4$ **1** as an efficient sulfur transfer reagent for the synthesis of biologically relevant deoxythiosugars and derivatives[12] starting from aldonolactones.[13] Earlier strategy[12a] adopted by us had the prerequisite of having the C-2 and C-3 hydroxy groups *cis* in the aldonolactones for an efficient synthesis of dibromolactones. This precursor for the sulfur transfer reaction, should have C-2-bromide and C-4-side chain in *trans* orientation (Scheme 1, left hand side).[14a] This limits the synthesis of diverse deoxythiosugars from all the available carbohydrates. Hence, the design and development of a more general and complementing methodology is vital.

Consequently, we envisioned the synthesis of appropriate substrate/s for the sulfur transfer reaction with tetrathiomolybdate through selective ditosylation of aldonolactones. The present methodology will not require the presence of *cis*-hydroxy groups at C-2 and C-3 and will widen the scope of tetrathiomolybdate mediated synthesis of deoxythiosugars from most of the readily available carbohydrates. Not only will this complement our earlier report, (Scheme 1, right hand side)[14b] but, this strategy will also demonstrate the efficiency of tetrathiomolybdate mediated sulfur transfer reaction in the protection/deprotection-free synthesis of 1-deoxythiofuranoses and pyranoses from aldonolactones.

The thiosugar, 1,4-anhydro-4-thio-D-arabinitol **5**, the core structure present in many of the natural products such as salaprinol, salacinol, ponkoranol, kotalanol, and de-O-sulfonated kotalanol (highly potent α-glucosidase inhibitors[15]) known especially for the treatment of diabetes mellitus, was of contemporary interest in sulfur-based glycomimetics. Accordingly, the synthesis of xylonoditosylate **3** was investigated through selective tosylation employing the procedure reported by Lundt and Madsen.[16] Treatment of xylonolactone **2** with TsCl/ pyridine in acetone at 0 °C afforded xylonoditosylate **3** in 28% yield.[17] The reaction of xylonoditosylate **3** with benzyltriethylammonium tetrathiomolybdate **1** in DMSO at room temperature provided the expected bicyclic thiosugar lactone, 1-deoxy-4-thio-D-lyxono-2,5-lactone **4** in 53% yield (Scheme 2). Further reduction of lactone **4** with borohydride exchange resin (BER)[18] in methanol furnished the desired 1-deoxythiosugar, 1,4-dideoxy-1,4-epithio-D-arabinitol **5** in good yield.

* Corresponding author. Tel.: +91 80 2293 2404x2360 2423; fax: +91 80 2360 0529.
E-mail address: scn@orgchem.iisc.ernet.in (S. Chandrasekaran).

0008-6215/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.carres.2013.09.009



Scheme 1. Effect of bromide and tosylate as leaving groups on aldono-γ-lactone on the course of reaction with tetrathiomolybdate **1**.

This result demonstrates a short synthesis of 1,4-dideoxy-1,4-epithio-D-arabinitol **5** from D-xylose which otherwise requires nine[19a,b] or six[19c] linear steps from D-xylose and 12 linear steps[19d] from D-glucose.

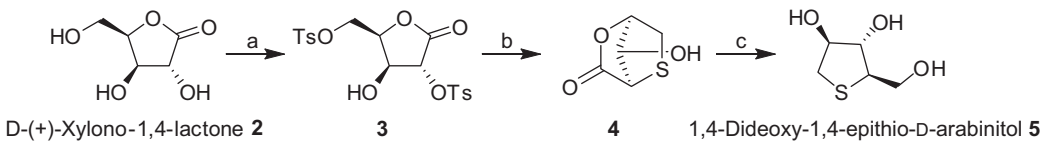
To further demonstrate the usefulness of this methodology, we decided to synthesize 1,4-anhydro-4-thio-D-lyxitol **9**, a pentose sugar, ubiquitous and fundamental in many biological processes. Tosylation of ribonolactone **6** with tosyl chloride/pyridine generated the ribono ditosylate **7**[16] in 63% yield. Treatment of ribono ditosylate **7**, with benzyltriethylammonium tetrathiomolybdate **1** furnished the 1-deoxy-4-thio-D-arabino-2,5-lactone **8** in good yield (68%) (Scheme 3). The structure of the bicyclic lactone **8** was further confirmed by X-ray analysis (Fig. 1). Reduction of 1-deoxy-4-thio-D-arabino-2,5-lactone **8** with borohydride exchange resin in methanol produced the thiosugar, 1,4-anhydro-4-thio-D-lyxitol **9** in 67% yield. Remarkably, the synthesis of **9** is achieved in three steps with an overall yield of 29%. This route is superior to the only known report[20] that utilizes eleven linear steps for the synthesis of 1,4-anhydro-4-thio-D-lyxitol **9** starting from D-lyxose.

A plausible mechanism is proposed to rationalize the formation of thiosugar lactone **8** from ditosylaldono lactone **7** (Scheme 4). The reaction of ditosylaldono lactone **7** with benzyltriethylammonium tetrathiomolybdate **1** involves S_N2 displacement of the tosyloxy group at carbon alpha (α-) to the carbonyl (the most reactive position of the available reactive sites) to form the intermediate **A**.[21] An internal redox process takes place in the intermediate **A** where the oxidation of the ligand and concomitant reduction of the metal center gives the disulfide **B**.[22] Based on our earlier work[11c–e] and that of Stiefel and co-workers,[23] disulfide **B** can then undergo reductive cleavage of the disulfide bond mediated by benzyltriethylammonium tetrathiomolybdate **1** to afford the thiolate intermediate **C**.[24] Finally the displacement of the primary tosylate by the resultant sulfide anion in intermediate **C** in an intramolecular fashion is hypothesized to result in the formation of the bicyclic thiosugar lactone **8** in a stereospecific manner.[11f]

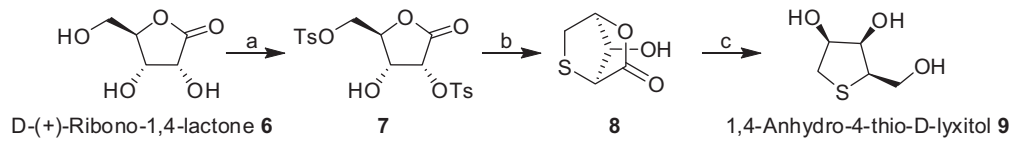
The generality of the approach was further demonstrated in the synthesis of thiopyrano sugar, 1-deoxythiotalonojirimycin **13** which was envisaged from the rare sugar derivative, D-allono-1,4-lactone **10**.[25] Thus, the tosylation of the resulting D-allono-1,4-lactone **10** was achieved using tosyl chloride/pyridine.[17] Reaction of 2,6-di-*O*-tosyl-allono lactone **11** with tetrathiomolybdate **1** smoothly furnished the expected 1-deoxy-5-thio-D-talopyrano-3,6-lactone **12** in 49% yield (Scheme 5, Fig. 2). Subsequently, BER reduction of 1-deoxy-5-thio-D-talopyrano-3,6-lactone **12** resulted in the formation of 1-deoxythiotalonojirimycin **13** in 58% yield.

Interestingly, the synthesis of 1-deoxythioidonojirimycin **17** was also achieved from gulono-1,4-lactone **14**. The ditosylate, 2,6-di-*O*-tosyl-gulono lactone **15** was obtained in 69% yield, by adding a neat solution of tosyl chloride in acetone to a solution of L-(+)-gulono-1,4-lactone **14** in pyridine at 0 °C for 3 h, as reported.[16] However, a slight change in the work-up procedure was essential to improve the isolated yield of aldonoditosylate **15** when compared to the literature report (reported yield 44%). Further, treatment of 2,6-di-*O*-tosyl-gulono lactone **15** with benzyltriethylammonium tetrathiomolybdate **1**, in DMSO at room temperature gave the bicyclic lactone ring system **16**, 1-deoxy-5-thio-D-glucopyrano-2,6-lactone in 56% yield as a white crystalline solid (Scheme 6). The structure of the bicylic lactone **16** was further confirmed by X-ray analysis (Fig. 3). The formation of the bicyclic lactone is anticipated through the rearrangement of 2,6-di-*O*-tosyl-gulono lactone **15** or its corresponding C-2-sulfide to the reactive δ-lactone **15a**, since the aldonoditosylate **15** cannot undergo double displacement due to the *syn*-orientation of C-2-tosyl and C-4-side chain. Lactone **15a** then undergoes subsequent reaction to provide the 1-deoxy-5-thio-D-glucopyrano-2,6-lactone **16**. The reduction of bicyclic lactone **16** with BER in methanol provided the 1-deoxythioidonojirimycin **17** in 67% yield.

In conclusion, synthesis of biologically relevant thiofuranoses, 1,4-dideoxy-1,4-epithio-D-arabinitol and 1,4-anhydro-4-thio-D-lyxitol and the synthesis of rare thiopyranoses such as 1-deoxythiotalonojirimycin and 1-deoxythioidonojirimycin were achieved. The present methodology involves the synthesis of ditosylates, sulfur transfer reaction with $[BnEt_3N]_2MoS_4$ **1** followed by BER reduction reactions. The examples developed through this approach demonstrate the generality of this methodology and wider applicability of the synthesis of 1-deoxythiosugars through a protection/deprotection-free sequence.



Scheme 2. Synthesis of 1,4-dideoxy-1,4-epithio-D-arabinitol **5**. Reagents and conditions: (a) TsCl/pyridine:acetone, 0 °C, 5 h, 28%; (b) $[BnEt_3N]_2MoS_4$ **1**, DMSO, rt, 16 h, 53%; (c) BER, MeOH, 0 °C–rt, 7.5 h, 65%.



Scheme 3. Synthesis of 1,4-anhydro-4-thio-D-lyxitol **9**. Reagents and conditions: (a) TsCl/pyridine:acetone, 0 °C, 5 h, 63%; (b) $[BnEt_3N]_2MoS_4$ **1**, DMSO, rt, 12 h, 68%; (c) BER, MeOH, 0 °C–rt, 10 h, 67%.

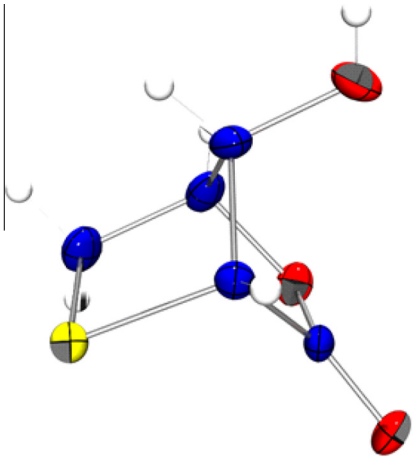
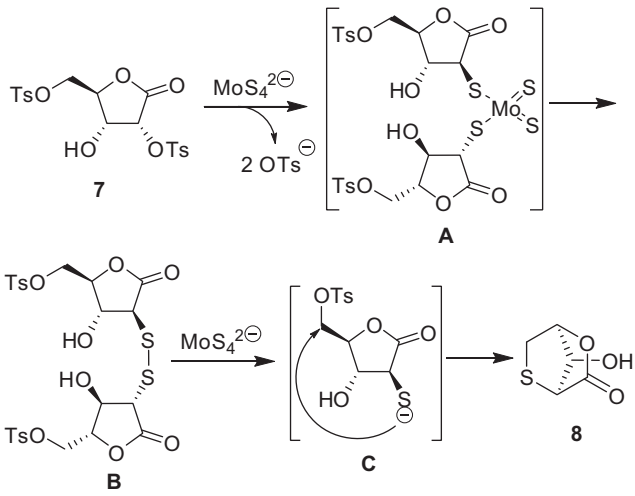


Figure 1. ORTEP diagram of 1-deoxy-4-thio-D-arabino-2,5-lactone **8**.



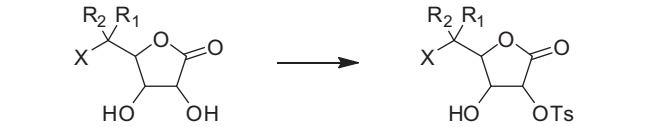
Scheme 4. Proposed mechanism for the nucleophilic double displacement of ditosylaldono lactone **7** in an intramolecular fashion mediated by $[BnEt_3N]_2MoS_4$ **1**.

1. Experimental

1.1. General methods

Melting points were recorded on a BUCHI B540 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a BRUKER-400 and 100 MHz spectrometer, respectively. Chemical shifts are reported in parts per million downfield from the internal reference, tetramethylsilane. Coupling constants are reported wherever necessary in Hertz (Hz). Column chromatography was performed on silica gel (230–400 mesh). IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. Mass spectra were recorded on a Q-TOF electrospray instrument. Micro analysis was recorded on Thermo Finnigan FLASH EA 1112 CHNS analyser. Optical rotation was recorded on polarimeter model P-1020 (A077860638). X-ray data collection was recorded on a BRUKER-SMART APEX CCD-single crystal diffractometer.

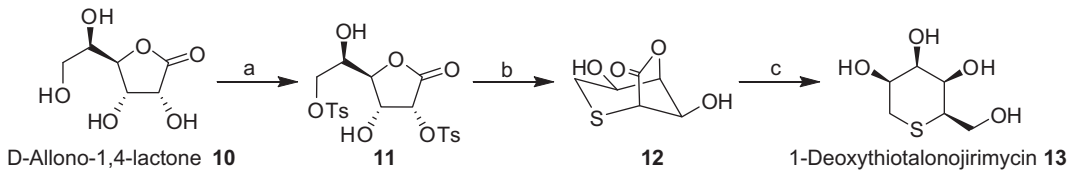
1.2. Typical procedure for the synthesis of 2,5-ditosyloxy-2,5-dideoxy- and 2,6-ditosyloxy-2,6-dideoxy-D-glycono-1,4-lactones[16]



To a solution of aldono-1,4-lactone (3.0 g, 0.02 mol) in dry pyridine (15 mL) at 0 °C was added TsCl (8.88 g, 0.047 mol) dissolved in acetone (15 mL) over a period of 10 min. The reaction mixture was then stirred at 0 °C for a given period of time after which it was neutralized with 6 M HCl until pH 1. The compound was extracted using EtOAc (3 × 15 mL), dried (Na_2SO_4), and concentrated and subjected to column chromatography (elution with EtOAc:hexanes) to give the pure ditosylaldono lactone.

1.2.1. 2,5-Di-*O*-tosyl-xylono-1,4-lactone (3)

IR (neat): 3430, 1777, 1420, 1211, 1180, 1070, 1027, 996 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 2.53 (s, 6H), 3.98–4.08 (m, 2H), 4.7 (t, J = 3.1 Hz, 1H), 5.22 (d, J = 4.9 Hz, 1H), 5.49 (t, J = 4.3 Hz, 1H), 7.56–7.58 (m, 4H), 7.83–7.89 (m, 4H) ppm; ^{13}C NMR



Scheme 5. Synthesis of 1-deoxythiotalonojirimycin **13**. Reagents and conditions: (a) TsCl/pyridine:acetone, 0 °C, 3 h, 29%; (b) $[BnEt_3N]_2MoS_4$ **1**, DMSO, rt, 48 h, 49%; (c) BER, MeOH, 0 °C–rt, 4 h, 58%.

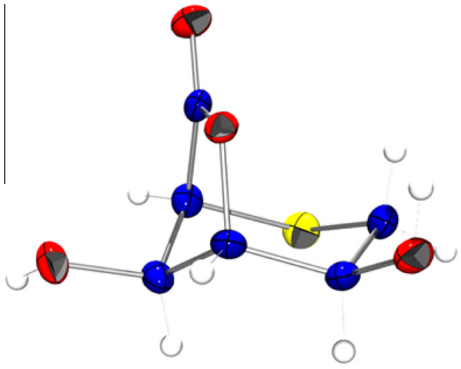


Figure 2. ORTEP structure of 1-deoxy-5-thio-D-talopyrano-3,6-lactone **12**.

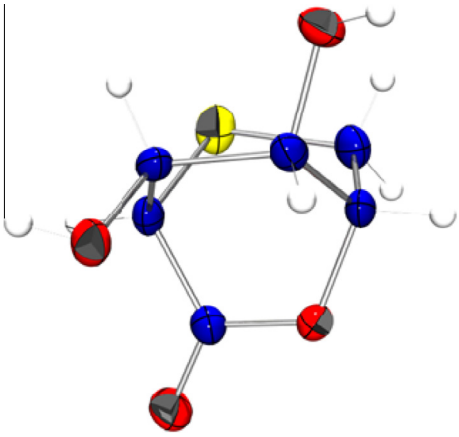


Figure 3. ORTEP diagram of 1-deoxy-5-thio-D-glucopyrano-2,6-lactone **16**.

(100 MHz, CD_3COCD_3) δ 20.5, 20.6, 70.0, 71.0, 75.2, 81.0, 128.0, 128.1, 129.9, 130.0, 130.2, 130.3, 137.0, 138.1, 165.6 ppm.

1.2.2. 2,5-Di-*O*-tosyl-ribono lactone (7)

IR (neat): 3438, 1777, 1424, 1219, 1181, 1073, 1028, 993 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 2.44 (s, 6H), 4.34–4.49 (m, 2H), 4.66 (t, J = 3.4 Hz, 1H), 5.23 (d, J = 5.2 Hz, 1H), 5.38 (t, J = 4.4 Hz, 1H), 7.48 (d, J = 7.9 Hz, 4H), 7.77 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3) δ 20.6, 20.7, 68.17, 68.3, 73.8, 82.7, 127.8, 128.1, 130.0, 130.2, 132.3, 132.7, 145.6, 145.7, 168.7 ppm; HRMS for $C_{19}H_{20}O_9S_2Na$ $[M+Na]^+$ calcd 479.0446; found 479.0443.

1.2.3. 2,6-Di-*O*-tosyl-allono lactone (11)

IR (neat): 3509, 1803, 1598, 1362, 1192, 1177, 1096, 814, 670 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 2.53 (s, 6H), 4.18 (dd, J = 7.2, 9.9 Hz, 2H), 4.31–4.24 (m, 3H), 4.48 (d, J = 1.8 Hz, 2H), 5.11 (t, J = 5.5 Hz, 2H), 5.28 (d, J = 4.5 Hz, 1H), 7.56 (d, J = 8.1 Hz, 4H), 7.90 (d, J = 8.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3) δ 20.6, 29.8, 68.1, 70.3, 72.7, 74.5, 79.2, 127.8, 130.0, 133.0, 145.1, 173.4 ppm; HRMS for $C_{20}H_{22}O_{10}S_2Na$ $[M+Na]^+$ calcd 509.0552; found 509.0553.

1.2.4. 2,6-Di-*O*-tosyl gulonolactone (15)

A slight change from the typical procedure was necessary in order to improve the yield of aldonoditosylate **15**. Thus, the work-up involved removal of the solvent under vacuum followed by short column chromatography to yield the ditosylgulono lactone **15** in 69% (6.36 g).

Elution with EtOAc:hexanes (2:3); IR (neat): 3438, 1777, 1424, 1219, 1181, 1073, 1028, 993 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 2.40 (s, 3H), 2.46 (s, 3H), 3.84 (d, J = 10.1 Hz, 2H), 3.98 (dd, J = 10.1, 3.9 Hz, 1H), 4.46 (d, J = 3.7 Hz, 1H), 4.71 (t, J = 4.3 Hz, 1H), 4.95 (d, J = 3.1 Hz, 1H), 5.53 (d, J = 4.8 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.885 (d, J = 8.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3) δ 21.3, 21.5, 74.6, 75.4, 76.0, 77.4, 86.3, 127.1, 128.7, 128.9, 129.0, 130.0, 130.9, 133.9, 140.2, 143.1, 146.5 169.9 ppm; HRMS for $C_{20}H_{22}O_{10}S_2Na$ $[M+Na]^+$ calcd 509.0552; found 509.0556.

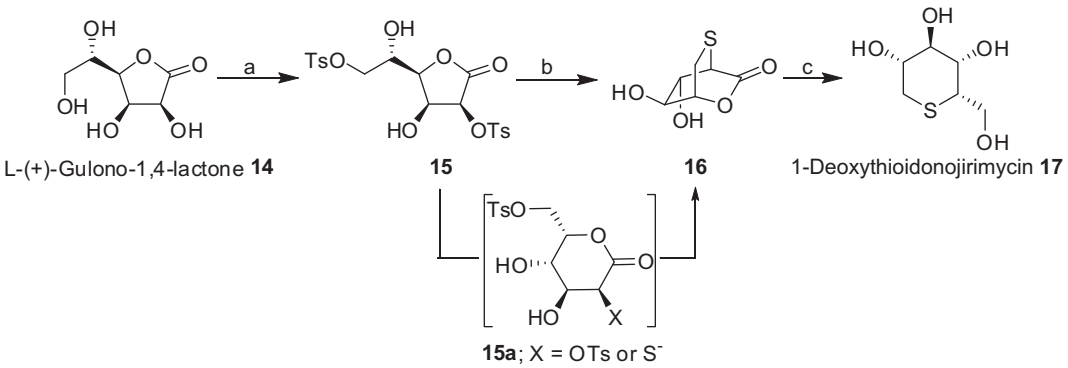
1.3. Typical procedure for the synthesis of thiosugar lactones

A solution of aldonoditosylate (1.0 mmol) in DMSO (2 mL) was added to a solution of $[BnEt_3N]_2MoS_4$ **1** (2.19 mmol) in DMSO (15 mL) over a period of 5 min. The reaction mixture was stirred at room temperature for the given period of time. The work-up procedure was performed by two different methods which are as follows:

Method A: DMSO from the reaction mixture was removed under reduced pressure and the residue was repeatedly extracted with THF (4 × 5 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 the thiosugar lactone.

Method B: The reaction mixture was diluted with H_2O (20 mL) and the compound was extracted using EtOAc (3 × 8 mL). The extracted organic layer was dried (Na_2SO_4), and concentrated to give the crude product which was subjected to column chromatography on silica gel (elution with hexanes:ethyl acetate 1:1) furnishing the thiosugar lactone.

Method A was adopted as work-up procedure in all cases unless otherwise mentioned.



Scheme 6. Synthesis of 1-deoxythioidonojirimycin **17**. Reagents and conditions: (a) TsCl/pyridine:acetone, 0 °C, 3 h, 69%; (b) $[BnEt_3N]_2MoS_4$ **1**, DMSO, rt, 2 h, 56%; (c) BER, MeOH, 0 °C–rt, 20 h, 67%.

1.3.1. Synthesis of 1-deoxy-4-thio-D-lyxono-2,5-lactone (4)

IR (neat): 3400, 1779, 1436, 1330, 1126, 1046 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 3.01 (d, J = 10.9 Hz, 1H), 3.25 (d, J = 10.9 Hz, 1H), 3.62 (s, 1H), 3.68 (d, J = 11.4 Hz, 1H), 4.48 (s, 1H), 4.88 (s, 1H) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3) δ 33.0, 48.2, 72.5, 80.8, 171.1 ppm; HRMS for $C_5H_6O_3SNa$ $[M+Na]^+$ calcd 168.9922; found 168.9933.

1.3.2. Synthesis of 1-deoxy-4-thio-D-arabino-1,4-lactone (8)

CCDC 870210; mp: 88–90 °C; IR (neat): 3402, 1781, 1436, 1332, 1131, 1018, 1054 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 2.96 (d, J = 11.0 Hz, 1H), 3.30 (d, J = 11.1 Hz, 1H), 4.41 (s, 1H), 4.87 (s, 1H), 5.33 (d, J = 2.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3) δ 31.8, 44.9, 78.7, 82.4, 173.2 ppm; HRMS for $C_5H_6O_3SNa$ $[M+Na]^+$ calcd 168.9935; found 168.9933; Anal. Calcd for: C, 41.09; H, 4.14; S, 21.94. Found: C, 41.1; H, 4.24; S, 21.51.

Crystal structure data: CCDC 870210: $C_5H_6O_3S_1$, Mwt = 146.14, crystal dimensions 0.28 × 0.24 × 0.15, T = 296(2) K, tetragonal, space group $P2(1)$, a = 6.0800(5), b = 8.4996(8), c = 6.0825(6) Å, $\alpha = \gamma = 90.00°$, β = 111.262(2)°, Z = 2, V = 292.93(5) cm^3, ρ_{calcd} = 1.657 g/cm^3, MoK$_\alpha$ radiation (λ° = 0.71073 Å), μ = 4.72 mm^{-1}, 2θ = 3.59–29.89°; of 1043 reflections collected, 681 were independent (R(int) = 0.0468); refinement method full matrix least squares on F_2, 83 refined parameters, absorption correction (SADABS, Bruker, 1996 software, T_{min} 0.8793 and T_{max} 0.9326), GooF = 1.008, R_1 = 0.0468, wR_2 = 0.0965 (σ >2σ(I)), absolute structure parameter 0.02(14), residual electron density 0.134/−0.185 eÅ^{-3}.

1.3.3. 1-Deoxy-5-thio-D-talopyrano-3,6-lactone (12)

CCDC 774512; mp: 145–146 °C; $[\alpha]_D$ +24.5 (c 1.0, MeOH); IR (neat): 3419, 3265, 1421, 1358, 1159, 1037 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 2.61 (dd, J = 13.0, 10.2 Hz, 1H), 2.86 (dd, J = 13.1, 5.8 Hz, 1H), 3.26 (s, 1H), 4.08 (td, J = 10.1, 5.9 Hz, 1H), 4.27 (d, J = 2.9 Hz, 1H), 4.59 (s, 1H), 4.78 (d, J = 6.1 Hz, 1H), 5.21 (d, J = 2.9, 1H) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3) δ 28.8, 44.7, 70.0, 77.1, 89.2, 173.7 ppm; HRMS for $C_6H_8O_4SNa$ $[M+Na]^+$ calcd 199.0041; found 199.3421; Anal. Calcd for: C, 40.85; H,5.27; S, 17.92. Found: C, 40.90; H, 4.58; S, 18.20.

1.3.4. 1-Deoxy-5-thio-D-glucopyrano-2,6-lactone (16)

CCDC 802220; mp: 178–179 °C; $[\alpha]_D$ −43.5 (c 1.0, MeOH); IR (neat): 3350, 3339, 1734, 1527, 1156, 1038, 672 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 2.99 (dd, J = 11.7, 3.8 Hz, 1H, –SCH_2–), 3.22 (m, J = 20.7, 11.7 Hz, 2H, –SCH_2– and –SCH–), 3.96 (br s, 1H), 4.15 (d, J = 2.1 Hz, 1H), 4.87 (t, J = 4.1 Hz, 1H), 5.03 (d, J = 4.5 Hz, 1H), 5.10 (d, J = 3.4 Hz, 1H, –CHOCO–) ppm; ^{13}C NMR (100 MHz, CD_3COCD_3) δ 23.2 (–SCH_2–), 40.6 (–SCH–), 73.9 [–CH(OH)–], 77.7 [–CH(OH)–], 78.0 (–*C*HOCO–), 169.3 [–OC(O)–] ppm; HRMS for $C_6H_8O_4SNa$ $[M+Na]^+$ calcd 199.0041; found 199.0039; Anal. Calcd for: C, 40.9; H, 4.58; S, 18.2. Found: C, 40.8; H, 4.6; S, 18.2.

1.4. Typical procedure for reduction of the thiosugar lactone using BER

To a stirred solution of thiosugar lactone (1.0 mmol) in dry methanol (12.5 mL) at 0 °C was added borohydride exchange resin (7.5 mmol, 2.5 g) and the solution was stirred for a given period of time. The reaction mixture was filtered and methanol (10 mL) was added to the resin and was sonicated (ultrasonic cleaning bath, 20 kHz) for 5 min at room temperature. The reaction mixture was then neutralized using glacial acetic acid. The reaction mixture was filtered and concentrated in vacuo to afford the crude product which was subjected to column chromatography on silica gel elution with methanol/chloroform 1.5:8.5 to furnish the 1-deoxythiosugar.

1.4.1. 1,4-Dideoxy-1,4-epithio-D-arabinitol (5)

^1H NMR (400 MHz, CD_3OD) δ 2.71 (dd, J = 6.2, 10.8 Hz, 1H, –SCH_2–), 2.99 (dd, J = 5.6, 10.8 Hz, 1H), 3.23 (dd, J = 5.5, 17.5 Hz, 1H), 3.60 (dd, J = 6.8, 11.0 Hz, 1H), 3.80 (d, J = 5.4 Hz, 1H), 3.85 (dd, J = 5.5, 11.0 Hz, 1H), 4.12 (dd, J = 5.8, 11.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 32.9 (–SCH_2–), 52.3 (–SCH–), 64.1 (–CH_2–OH–), 77.8 [–CH(OH)–], 79.2 [–CH(OH)–] ppm; HRMS for $C_5H_{10}O_3$–SNa $[M+Na]^+$ calcd 173.0248; found 173.0278.

1.4.2. Synthesis of 1,4-anhydro-4-thio-D-lyxitol (9)

^1H NMR (400 MHz, CD_3OD) δ 2.82 (d, J = 7.4 Hz, 2H, –SCH_2–), 3.45 (dd, J = 6.3, 11.0 Hz, 1H), 3.57 (dd, J = 6.4, 10.9 Hz, 1H), 3.86 (dd, J = 6.9, 10.9 Hz, 1H), 4.13–4.19 (m, 2H), 4.57 (t, J = 3.3 Hz, 1H), 4.83 (t, J = 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 31.7 (–SCH_2–), 48.9 (–SCH–), 61.5 (–CH_2OH–), 73.6 [–CH(OH)–], 75.9 [–CH(OH)–] ppm; HRMS for $C_5H_{10}O_3SNa$ $[M+Na]^+$ calcd 173.0248; found 173.0243.

1.4.3. 1-Deoxythiotalonojirimycin (13)

$[\alpha]_D$ +20.6 (c 1.0, MeOH), lit. $[\alpha]_D$ +28.0 (c 1.1, MeOH); IR (neat): 3369, 2916, 1420, 1073, 1018 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.57 (bd, J = 13.1 Hz, 1H, –SCH_2–), 2.78 (dd, J = 13.5, 7.6 Hz, 1H), 2.87 (td, J = 6.1, 3.5 Hz, 1H), 3.59 (s, 1H), 3.85–3.74 (m, 2H), 3.89 (dt, J = 7.6, 3.2 Hz, 1H), 4.00 (t, J = 3.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, D_2O) δ 30.1 (–SCH_2–), 47.5 (–SCH–), 61.3 (–CH_2OH–), 69.5 [–CH(OH)–], 70.9 [–CH(OH)–], 71.4 [–CH(OH)–] ppm; HRMS for $C_6H_{12}O_4SNa$ $[M+Na]^+$ calcd 203.0354; found 203.0356.

1.4.4. 1-Deoxythioidonojirimycin (17)

$[\alpha]_D$ −34.5 (c, 1.0, MeOH); IR (neat): 3448, 3444, 3410, 1699, 1526, 1253, 1169, 1033 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 2.45 (dd, J = 13.8, 4.4 Hz, 1H, –SCH_2–), 2.58 (t, J = 13.7 Hz, 1H, –SCH_2–), 2.89–2.84 (m, 1H, –SCH–), 3.23 (dd, J = 18.3, 9.1 Hz, 1H, –*CH*$_2$OH), 3.58–3.53 (m, 1H, –*CH*$_2$OH), 3.62 (t, J = 10.4 Hz, 1H, –*CH*(OH)–), 3.82–3.80 (m, 1H, –*CH*(OH)–), 3.87 (dd, J = 11.6, 4.0 Hz, 1H, –*CH*(OH)–) ppm; ^{13}C NMR (100 MHz, D_2O) δ 27.3 (–SCH_2–), 45.9 (–SCH–), 57.1 (–CH_2OH–), 72.9 [–CH(OH)–], 73.6 [–CH(OH)–], 73.7 [–CH(OH)–] ppm; HRMS for $C_6H_{12}O_4SNa$ $[M+Na]^+$ calcd 203.0354; found 203.0356.

The structures of compounds **8**, **12,** and **16** were solved and refined using the programs WinGXv1.64.05, Sir92, and SHELXL-97. 'Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC 870210 (compound **8**), CCDC 774512 (compound **12**), and CCDC 802220 (compound **16**). Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambrige, CB2 1EZ, UK. (fax: +44 1223 336033, email: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).'

Acknowledgments

The authors thank IISc, Bangalore for the award of senior research fellowship to T.G., and the Department of Science and Technology (DST), New Delhi for the CCD X-ray facility. We also thank DST for the award of J.C. Bose National Fellowship to S.C.N. Finally we thank Mr. Amol Dikundwar and Mr. Sajesh P. Thomas for help in single crystal analysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2013.09.009.

References

1. (a) Raymond, A. L. *J. Biol. Chem.* **1934**, *107*, 85–96; (b) Valderrama, A. A.; Dobado, J. A. *J. Carbohydr. Chem.* **2006**, *25*, 557–594. and quoted references.
2. (a) Witczak, Z. J. *Curr. Med. Chem.* **1999**, *6*, 165–178; (b) Witczak, Z. J.; Culhane, J. M. *Appl. Microbiol. Biotechnol.* **2005**, *69*, 237–244; (c) Bojarová, P.; Křen, V. *Trends Biotechnol.* **2009**, *27*, 199–209.
3. (a) Robina, I.; Vogel, P.; Witczak, Z. J. *Curr. Org. Chem.* **2001**, *5*, 1177–1214; (b) Stutz, A. E.; Wrodnigg, T. M.; Sprenger, F. K. F.; Spreitz, J.; Greimel, P. The Organic Chemistry of Sugars. In *Sugars with Endocyclic Heteroatoms Other than Oxygen*; Levy, D. E., Fügedi, P., Eds.; CRC Press, 2005; pp 383–412.
4. (a) Walsh, C. T.; Garneau-Tsodikova, S.; Gatto, G. J., Jr. *Angew. Chem., Int. Ed.* **2005**, *44*, 7342–7372; (b) Schmaltz, R. M.; Hanson, S. R.; Wong, C.-H. *Chem. Rev.* **2011**, *111*, 4259–4307.
5. Asano, N. *Cell. Mol. Life Sci.* **2009**, *66*, 1479–1492.
6. (a) Yuasa, H.; Izumi, M.; Hashimoto, H. *Curr. Top. Med. Chem.* **2009**, *9*, 76–86; (b) Xie, W.; Tanabe, G.; Matsuoka, K.; Amer, M. F. A.; Minematsu, T.; Wu, X.; Yoshikawa, M.; Muraoka, O. *Bioorg. Med. Chem.* **2011**, *19*, 2252–2262; (c) Buchotte, M.; Bello, C.; Vogel, P.; Floquet, N.; Muzard, M.; Royon, R. P. *Tetrahedron: Asymmetry* **2009**, *20*, 2038–2042. and quoted references; (d) Sørensen, J. F.; Kragh, K. M.; Sibbesen, O.; Delcour, J.; Goesaert, H.; Svensson, B.; Tahir, T. A.; Brufau, J.; Vendrell, A. M. P.; Bellincampi, D.; D'Ovidio, R.; Camardella, L.; Giovane, A.; Bonnin, E.; Juge, N. *Biochim. Biophys. Acta* **2004**, *1696*, 275–287. and quoted references.
7. Gunaga, P.; Moon, H. R.; Choi, W. J.; Shin, D. H.; Park, J. G.; Jeong, L. S. *Curr. Med. Chem.* **2004**, *11*, 2585–2637.
8. de Melo, E. B.; da Silveira Gomes, A.; Carvalho, I. *Tetrahedron* **2006**, *62*, 10277–10302.
9. Hanessian, S. Deoxy Sugars In *Advances in Carbohydrate Chemistry*; Melville, L. W., Tipson, R. S., Eds.; Academic Press, 1967; Vol. 21, pp 143–150.
10. Hadwiger, P.; Stutz, A.; Wrodnigg, T.; Hadwiger, P.; Stutz, A. E.; Wrodnigg, T. M. Sulfur Containing Glycomimetics. In *Glycoscience: Chemistry and Chemical Biology I–III*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin Heidelberg, 2001; pp 2663–2678.
11. (a) *Benzyltriethylammonium Tetrathiomolybdate: e-EROS Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons Ltd.: Chichester, UK, 2001.; (b) Ho, T.-L.; Fieser, M.; Fieser, L. *Benzyltriethylammonium Tetrathiomolybdate: Fieser and Fieser's Reagents for Organic Synthesis*; John Wiley and Sons, 2006; (c) Prabhu, K. R.; Devan, N.; Chandrasekaran, S. *Synlett* **2002**, 1762–1778; (d) Sureshkumar, D.; Srinivasa Murthy, K.; Chandrasekaran, S. *J. Am. Chem. Soc.* **2005**, *127*, 12760–12761; (e) Sureshkumar, D.; Gunasundari, T.; Ganesh, V.; Chandrasekaran, S. *J. Org. Chem.* **2007**, *72*, 2106–2117; (f) Ramu Sridhar, P.; Prabhu, K. R.; Chandrasekaran, S. *Eur. J. Org. Chem.* **2004**, 4809–4815.
12. (a) Gunasundari, T.; Chandrasekaran, S. *J. Org. Chem.* **2010**, *75*, 6685–6688; (b) Gunasundari, T.; Chandrasekaran, S. *Eur. J. Org. Chem.* **2012**, 6986–6995.
13. (a) Lundt, I. *Top. Curr. Chem.* **1997**, *187*, 117–156; (b) Xavier, N. M.; Rauter, A. P.; Queneau, Y. *Top. Curr. Chem.* **2010**, *295*, 19–62.
14. (a) For instance considering the prerequisite of the reactions out of eight hexose sugars, only two (mannose and gulose) will undergo bromination followed by tetrathiomolybdate reaction to give corresponding thiosugars.; (b) The present methodology will convert (tosylation followed by tetrathiomolybdate reaction) four hexose sugars (allose, glucose, idose, and talose) to corresponding thiosugars. However, we investigated only few substrates due to their limited availability.
15. (a) Jayakanthan, K.; Mohan, S.; Pinto, B. M. *J. Am. Chem. Soc.* **2009**, *131*, 5621–5626; (b) Muraoka, O.; Xie, W.; Osaki, S.; Kagawa, A.; Tanabe, G.; Amer, M. F. A.; Minematsu, T.; Morikawa, T.; Yoshikawa, M. *Tetrahedron* **2010**, *66*, 3717–3722; (c) Eskandari, R.; Jayakanthan, K.; Kuntz, D. A.; Rose, D. R.; Pinto, B. M. *Bioorg. Med. Chem.* **2010**, *18*, 2829–2835.
16. Lundt, I.; Madsen, R. *Synthesis* **1992**, 1129–1132.
17. Various attempts to increase the yield of the xylonoditosylate/allonoditosylate were unsuccessful. This is in agreement with similar report by Lundt and Madsen.[16]
18. (a) Bandgar, B. P.; Modhave, R. K.; Wadgaonkar, P. P.; Sande, A. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1993–1994; (b) Gibson, H. W.; Bailey, F. C. *J. Chem. Soc., Chem. Commun.* **1977**, 815a–816a.
19. (a) Yuasa, H.; Kajimoto, T.; Wong, C.-H. *Tetrahedron Lett.* **1994**, *35*, 8243–8246; (b) Muraoka, O.; Yoshikai, K.; Takahashi, H.; Minematsu, T.; Lu, G.; Tanabe, G.; Wang, T.; Matsuda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2006**, *14*, 500–509; (c) Satoh, H.; Yoshimura, Y.; Sakata, S.; Miura, S.; Machida, H.; Matsuda, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 989–992; (d) Yoshimura, Y.; Kitano, K.; Yamada, K.; Satoh, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 3140–3152.
20. Kumar, N. S.; Pinto, B. M. *Carbohydr. Res.* **2005**, *340*, 2612–2619.
21. Driguez, H.; Macauliffe, J. C.; Stick, R. V.; Tilbrook, D. M. G.; Williams, S. J. *Aust. J. Chem.* **1996**, *49*, 343–348.
22. For the isolation of disulfides derived from sugar derivatives see: (a) Bhar, D.; Chandrasekaran, S. *Carbohydr. Res.* **1997**, *301*, 221–224; (b) Sridhar, P. R.; Saravanan, V.; Chandrasekaran, S. *Pure Appl. Chem.* **2005**, *77*, 145–153.
23. (a) Pan, W.-H.; Harmer, M. A.; Halbert, T. R.; Stiefel, E. I. *J. Am. Chem. Soc.* **1984**, *106*, 459–460; (b) Coyle, C. L.; Harmer, M. A.; Gorge, G. N.; Daage, M.; Stiefel, E. I. *Inorg. Chem.* **1990**, *29*, 14–19. and quoted references.
24. Isolation of thiolate: (a) Kruhlak, N. L.; Wang, M.; Boorman, P. M.; Parvez, M.; McDonald, R. *Inorg. Chem.* **2001**, *40*, 3141–3148; (b) Boorman, P. M.; Wang, M.; Parvez, M. *J. Chem. Soc., Chem. Commun.* **1995**, 999–1000.
25. James, W. P.; Richtmeyer, N. K. *J. Am. Chem. Soc.* **1955**, *77*, 1906–1908.