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A novel stereoselective synthesis of 1,2-*trans*-thioaldoses

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Abstract—A mild and one-pot protocol for the efficient and stereoselective synthesis of 1,2-*trans*-aldosyl mercaptans is presented.

Carbohydrates are known to play a significant role in many physiological processes such as cellular adhesion, signalling and recognition that initiate immune responses and induce cancer metastasis.[1,2] It has been reported that carbohydrates are also involved in the similar or the same modes of action with many drugs[3] so that they are recognized to have potential for the treatment of diabetes and cancer.[4,5] Carbohydrate mimetics are often used to investigate these processes. Thioalcohols are versatile synthetic intermediates and are of great importance in many biological processes because of their reducing properties and nucleophilicities.[6,7] Consequently an appropriate approach is to replace the oxygen atoms of the anomeric carbon with sulfur to result in glycosylmeraptans that may give analogues, which can serve as potential ligands binding carbohydrate-specific receptors or serve as derivative groups for glycoconjugation. Anomeric mercaptosugars are of particular interest as precursors in preparation of the widely used thioglycosides.[8] Some research has shown that thioaldoses are essential building blocks for various carbohydrate derivatives such as oligosaccharides,[9] carbohydrate clusters,[10] C-glycosides,[11] glycosyl sulfenamides,[12] glycosyl sulfonamides,[13] glycosyl disulfide,[14] thionolactones[15] and glycosylsulfenic acid.[16] On the other hand, thioaldoses and their resulting glycoconjugates have received considerable attention due to more effective resistance to both chemical and enzymatic degradation than O-glycosides.[17] Moreover, thioaldoses have been reported to act as glycosyltransferase inhibitors.[18,19]

The most frequently used method for the synthesis of thiosaccharides involves the treatment of glycosyl halides with a sulfur nucleophile such as thiourea, thioacetamide,[20] *N*,*N*-dimethylthioformamide[21] or KSAc,[22] followed by mild hydrolysis or alcoholysis. Recently, Davis reported[23] that Lawesson's reagent might be used to directly synthesize glycosyl thiols from their corresponding reducing sugars. Unfortunately, these synthetic strategies suffer from drawbacks such as long reaction time, use of expensive reagents, low yield and tedious work-up. Especially, the use of Lawesson's reagent is somewhat restricted without good stereoselectivity. Therefore, there is a need to develop a convenient and practical method for the synthesis of mercaptoaldoses. In this report we describe a stereoselective one-pot preparation of 1,2-*trans*-thiosugars using sodium thiophosphate in methanol.

Sodium thiophosphate is known to be an effective reagent for conversion from the halides to mercaptans.[24] In the current study sodium thiophosphate was used as the sulfur nucleophile to synthesize thioaldoses. Various glycosyl halides were chosen to test our method. It was observed that sodium thiophosphate (1.5 equiv per halide) in methanol (20 ml) at room temperature produced excellent yields of 1,2-*trans*-thiosugars within several hours. Interestingly, the reactions occurred with nearly complete inversion of anomeric configuration (Table 1). This reaction is presumably initiated by the formation of glycophosphorothioate intermediate, followed by nucleophilic attack of methanol to give products (Scheme 1). All products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. It is of pertinent note that the reaction conditions are mild and 1,2-*trans*-thiosaccharides are exclusively formed without

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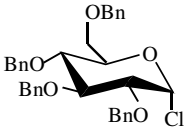
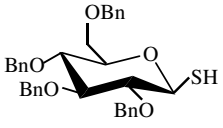
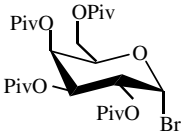
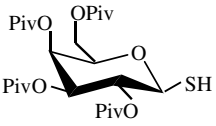
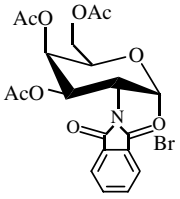
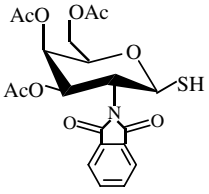
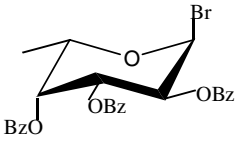
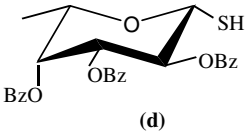
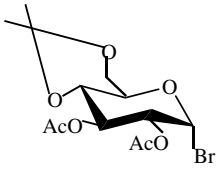
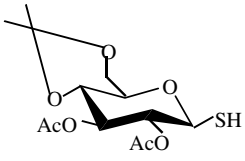
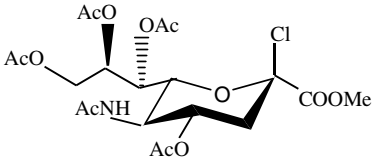
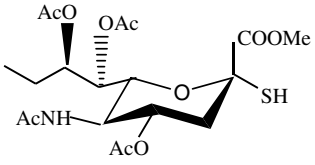
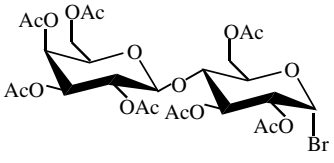
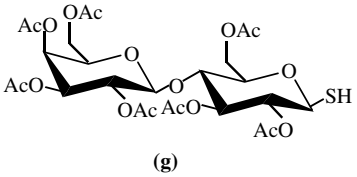
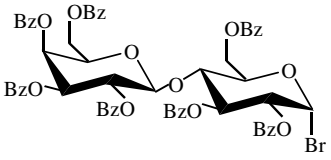
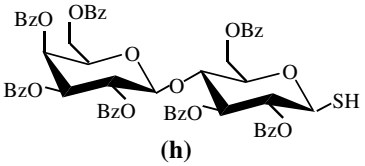
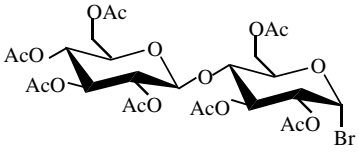
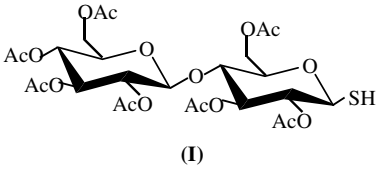
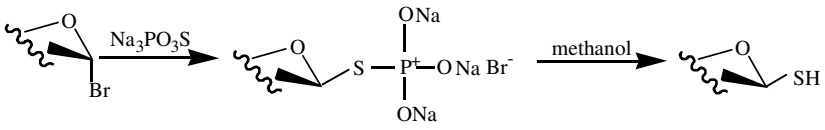
Table 1. Synthesis of 1,2-*trans*-adosyl mercaptans from glycosyl halides

Entry	Substrates	Products	Isolated yields (%)
1		 **(a)**	93.7
2		 **(b)**	96.8
3		 **(c)**	91.8
4		 **(d)**	94.0
5		 **(e)**	92.0
6		 **(f)**	83.4
7		 **(g)**	95.2
8		 **(h)**	88.2
9		 **(I)**	96.5



Scheme 1. Synthesis of aldosyl mercaptans.

the formation of 1,2-*cis*-α-glycosides or any undesired byproducts. For general pyranosides, assignment of the anomeric configuration is based on the $J_{H\text{-}1,H\text{-}2}$ coupling constants (α-isomers, ~2 Hz; β-isomers, 8–10.5 Hz). Although there is no anomeric proton in α-sialyl thiol, the anomeric configuration was inferred on the basis of the $J_{C\text{-}2,H\text{-}3ax}$ coupling constants (α-isomer, ~8 Hz).[25]

In conclusion, we have demonstrated that commercially available sodium thiophosphate is a novel reagent for stereoselective thiolation of aldosyl halides to produce 1,2-*trans*-1-thioaldoses while leaving protecting groups on sugar residues intact. Excellent yields, simple work-up and mild reaction conditions make this method an attractive addition to the present methodologies.

Typical experimental procedure: Sodium thiophosphate dodecahydrate (3 mmol) was added to a solution of D-aldosyl halides (2 mmol) in methanol (20 ml) under argon. The resulting mixture was stirred at room temperature for a period of 4–7 h until TLC indicated complete conversion of halides. The reaction mixture was poured into water and the products were extracted three times with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, rotary evaporated and the residue was recrystallized or purified by silica gel column chromatography. Spectral data for selected compounds: Compound **b** (2,3,4,6-tetra-*O*-pivaloyl-β-D-hiogalactopyranose): ^{1}H NMR 1.09 (s, 9H, CMe_3), 1.12 (s, 9H, CMe_3), 1.16 (s, 9H, CMe_3), 1.21 (s, 9H, CMe_3), 2.37 (d, 1H, $J_{1,SH} = 10.0$, SH), 4.63 (d, 1H, $J_{1,2} = 9.7$, H-1), 4.98 (dd, 1H, $J_{1,2} = 9.7$, $J_{2,3} = 2.3$, H-2), 5.27 (dd, 1H, $J_{3,4} = 9.4$, $J_{2,3} = 2.3$, H-3), 5.15 (dd, 1H, $J_{4,5} = 1.3$, $J_{3,4} = 9.4$, H-4), 3.72 (ddd, 1H, $J_{4,5} = 1.3$, $J_{5,6'} = 4.9$ and $J_{5,6} = 1.9$, H-5), 4.17 (dd, 1H, $J_{5,6} = 1.9$, $J_{6,6'} = 12.3$, H-6) and 4.08 (dd, 1H, $J_{5,6'} = 4.9$, $J_{6,6'} = 12.3$, H-6′). ^{13}C NMR 61.8(C-1), 67.5(C-2), 73.0(C-3), 73.5(C-4), 76.8(C-5), 79.0(C-6), 176.3, 176.8, 177.1 and 178.0 (C=O). HRESIMS (*m*/*z*): Calcd for $C_{26}H_{44}O_9SNa$ $[M+Na]^+$: 555.2741; found, 555.2750. Compound **e** (2,3-di-*O*-acetyl-4,6-isopropylidene-β-D-thioglucopyranose): ^{1}H NMR 2.30 (d, 1H, $J_{1,SH} = 9.9$ Hz, SH), 4.58 (d, $J_{1,2} = 8.1$, H-1), 4.72 (dd, $J_{2,3} = 9.4$, $J_{1,2} = 8.1$, H-2), 5.10 (dd, 1H, $J_{2,3} = 9.4$ Hz, $J_{3,4} = 9.7$ Hz, H-3), 3.42 (dd, $J_{3,4} = 9.7$, $J_{4,5} = 9.9$, H-4), 3.42 (ddd, 1H, $J_{4,5} = 10.0$ Hz, $J_{5,6} = 2.4$ Hz, $J_{5,6'} = 4.3$ Hz, H-5), 3.51 (dd, 1H, $J_{5,6} = 2.4$ Hz, $J_{6,6'} = 10.5$ Hz, H-6), 4.10 (dd, 1H, $J_{5,6'} = 4.3$, $J_{6,6'} = 10.5$ Hz, H-6′), 1.71(CH_3CO), 1.69(CH_3CO), 1.31(CCH_3), 1.14(CCH_3). ^{13}C NMR 79.6(C-1), 72.9(C-2), 69.6(C-3), 71.8(C-4), 77.7(C-5), 62.8(C-6), 19.8(CH_3CO), 20.5(CH_3CO), 28.2(Me_2C). HRESIMS (*m*/*z*): Calcd for $C_{13}H_{19}O_7SNa$ $[M+Na]^+$: 341.8354; found, 341.8343. Compound **h** (2,3,6,2′,3′,4′,6′-hepta-*O*-benzoyl-β-D-thiolactose): ^{1}H NMR 2.09 (d, 1H, $J_{1,SH} = 9.9$, SH), 4.69 (dd, 1H, $J_{1,2} = 10.1$, H-1), 5.48 (dd, 1H, $J_{1,2} = 10.1$ Hz, $J_{2,3} = 3.4$ Hz, H-2), 6.17 (t, 1H, $J = 9.6$ Hz, H-3), 5.55 (dd, 1H, $J_{3',4'} = 7.2$ Hz, $J_{2',3'} = 3.5$ Hz, H-3′), 4.25 (dd, 1H, $J_{3,4} = 9.6$ Hz, $J_{4,5} = 10.0$ Hz, H-4), 5.69–5.78 (m, 2H, H-2′, H-4′), 3.86–3.99 (m, 2H, H-5, H-5′), 4.44–4.58 (m, 2H, H-6), $\delta = 3.70$–3.77 (m, 2H, H-6′), 4.82 (d, 1H, $J_{1',2'} = 7.9$ Hz, H-1′), 7.07–8.04 (m, 35H, 7Ph). ^{13}C NMR 61.9(C-6), 61.4(C-6′), 76.9(C-5), 70.8(C-5′), 75.6(C-4), 66.9(C-4′), 73.3(C-3), 71.4(C-3′), 73.6(C-2), 69.5(C-2′), 80.1(C-1), 101.4(C-1′), 129.1–133.3 (7 × Ph), 163.4–166.8 (C=O). HRESIMS (*m*/*z*): Calcd for $C_{61}H_{50}O_{17}SNa$ $[M+Na]^+$: 1109.7984; found, 1109.7968.

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References and notes

1. Birk, R.; Ikan, A.; Bravdo, B.; Braun, S.; Shoseyov, O. *Appl. Biochem. Biotechnol.* **1997**, *66*, 25–38.
2. Sears, P.; Wong, C. H. *Cell. Mol. Life Sci.* **1998**, *54*, 223–252.
3. Varki, A. *Glycobiology* **1993**, *3*, 97–130.
4. Gabius, H. J. *Biochim. Biophys. Acta* **1991**, *1071*, 1–18.
5. Bertozzi1, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357–2364.
6. Wardell, J. L. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; Wiley: London, 1974; pp 1–479.
7. Pinehart, A.; Dallaire, C.; Bierbeek, A. V.; Gingras, M. *Tetrahedron Lett.* **1999**, *40*, 5479–5482.
8. Pachamuthu, K.; Schmidt, R. R. *Chem. Rev.* **2006**, *106*, 160–187.
9. Ponpipom, M. M.; Hagmann, W. K.; Grady, L. A.; Jackson, J. J.; Wood, D. D.; Zweerink, H. J. *J. Med. Chem.* **1990**, *33*, 861–867.
10. Herczegh, P.; Kovacs-Kulyassa, A.; Erdosi, G.; Kovacs, L.; Menyhart, T.; Szabo Pal, T.; Kornyei, J. *Carbohydr. Lett.* **1998**, *3*, 59–64.
11. Fugedi, P.; Garegg, J.; Lonn, H.; Norberg, T. *Glycoconjugate J.* **1987**, *4*, 97–108.
12. Taylor, R. J. K.; McAllister, G. D.; Franck, R. W. *Carbohydr. Res.* **2006**, *341*, 298–1311.
13. Knapp, S.; Darout, E.; Amorelli, B. *J. Org. Chem.* **2006**, *71*, 1380–1389.
14. Davis, B. G.; Ward, S. J.; Rendle, P. M. *Chem. Commun.* **2001**, 189–190.
15. Chayajarus, K.; Fairbanks, A. J. *Tetrahedron Lett.* **2006**, *47*, 3517–3520.

16. Aversa, M. C.; Barattucci, A.; Bilardo, M. C.; Bonaccorsi, P.; Giannetto, P.; Rollin, P.; Tatibouët, A. *J. Org. Chem.* **2005**, *70*, 7389–7396.
17. Crooke, S. T.; Snyder, M. R.; Butt, T. R.; Ecker, D. J.; Allaudeen, H. S.; Monia, B.; Mirabelli, C. K. *Biochem. Pharmacol.* **1986**, *35*, 3423–3431.
18. Steers, E.; Cijatrecasas, P.; Pollard, H. B. *J. Biol. Chem.* **1971**, *246*, 196–200.
19. Driguez, H. *Topics Curr. Chem.* **1997**, *187*, 85–116.
20. Fujihira, T.; Chida, M.; Kamijo, H.; Takido, T.; Seno, M. *J. Carbohydr. Chem.* **2002**, *21*, 287–292.
21. Fujihira, T.; Arakawa, G.; Kamijo, H. *J. Carbohydr. Chem.* **2003**, *22*, 73–78.
22. MacDougall, J. M.; Zhang, X. D.; Polgar, W. E.; Khroyan, T. V.; Toll, L.; Cashman, J. R. *J. Med. Chem.* **2004**, *47*, 5809–5815.
23. Bernardes, G. J. L.; Gamblin, D. P.; Davis, B. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 4007–4011.
24. Blenlarz, C.; Cornwell, M. J. *Tetrahedron Lett.* **1993**, *34*, 939–942.
25. Prytulla, S.; Lambert, J.; Lauterwein, J.; Klessinger, M.; Thiem, J. *Magn. Reson. Chem.* **1990**, *28*, 888–901.