Pergamon

Tetrahedron Letters, Vol. 35, No. 12, pp. 1843-1846, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0191-Y

Synthesis of 5-Thioaldopentopyranoside via Dithioacetal Rearrangement and Glycosidation to give Pseudodisaccharides

Carole Lépine, Caroline Roy[1] and Daniel Delorme*

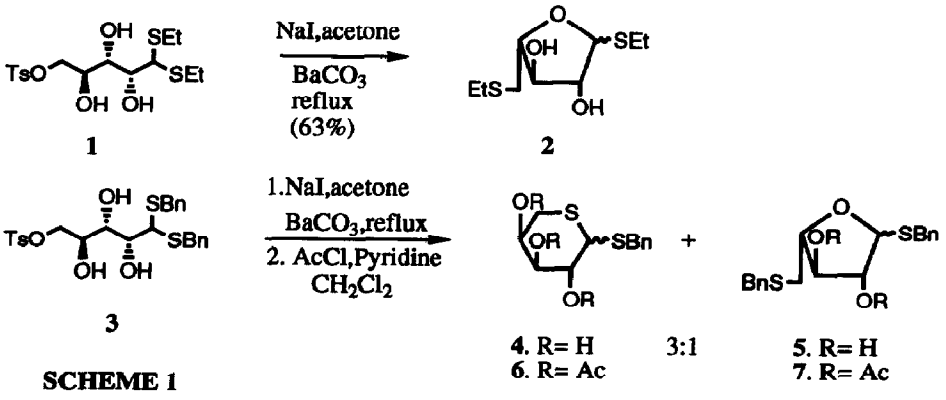
Merck Frosst Centre for Therapeutic Research
P.O. Box 1005, Pointe Claire-Dorval, Quebec, Canada H9R 4P8

Abstract: Rearrangement of acetylated 5-O-*p*-toluenesulfonyl-L-arabinose dibenzyl dithioacetal **10** gave benzyl 1,5-dithio-L-arabinopyranoside **6** which upon anomeric bromination followed by glycosidation led to pseudodisaccharide **20** containing a sulfur atom in the ring of the non-reducing unit. Similarly, benzyl 1,5-dithio-D-lyxopyranoside **17** was obtained from 5-O-*p*-toluenesulfonyl-D-lyxose dibenzyl dithioacetal **16**.

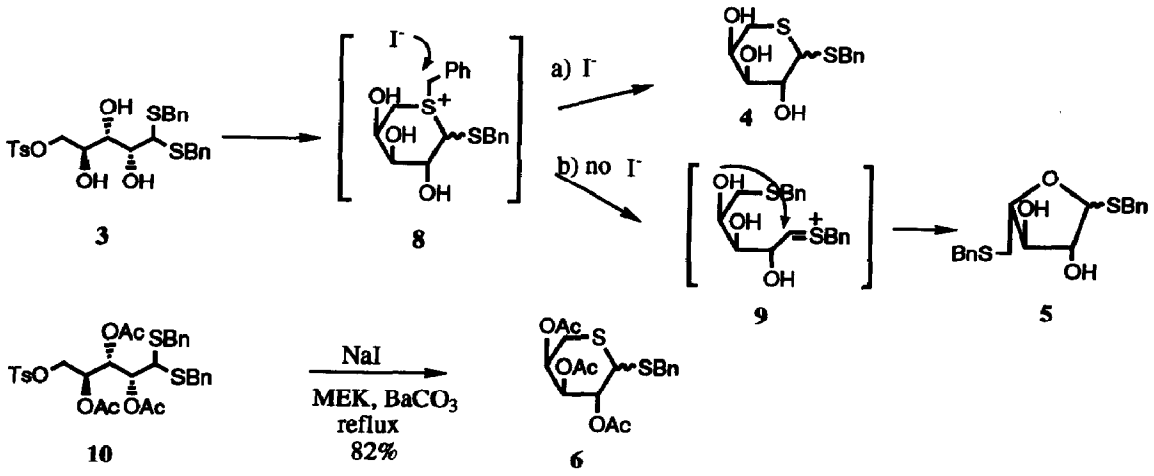
5-Thioaldohexopyranoses have been found to show remarkable biological activity. For example, 5-thio-D-glucose was found to inhibit the release of insulin[2] and 5-thio-L-fucose is a specific inhibitor of bovine α-L-fucosidase.[3] Also, 5-thio-D-mannose has been recently isolated from a natural source (marine sponge: *Clathia pyramida*) and is the first natural 5-thioaldose.[4] A variety of syntheses of 5-thioaldoses have been published and very often the strategy implies the introduction of the thiol function either via opening of a 5,6-epithiofuranose or a 5-O-*p*-toluenesulfonate displacement of a furanoside with thiolacetic acid salt followed by ring closure.[5] Recently, Hashimoto[6] published a new approach toward the formation of 5-thioaldoses using base induced ring closure of mesylated acyclic monothioacetals derived from pyranosides. Disaccharides having a sulfur atom in the ring of the reducing[7] or the non-reducing[8] monosaccharide unit are an interesting class of compounds since they can be valuable tools to study glycosidase reaction mechanism and are potential inhibitors of glycoside hydrolysis.

Inspired by the need for 5-thioaldopyranosides[9] and for their pseudodisaccharides,[10] we wish to report our results about the formation of these compounds using a dithioacetal rearrangement. The first dithioacetal rearrangement was observed by Hughes[11] in 1966 on 5-O-*p*-toluenesulfonyl-L-arabinose diethyl dithioacetal (**1**) (Scheme 1) to form ethyl 5-S-ethyl-1,5-dithio-L-arabinofuranoside (**2**). Later the same author described the formation of benzyl 1,5-dithio-L-arabinopyranoside (**4**) and benzyl 5-S-benzyl-1,5-dithio-L-arabinofuranoside (**5**) from 5-O-*p*-toluenesulfonyl-L-arabinose dibenzyl dithioacetal (**3**)[12] although no yield or ratio of **4** and **5** were reported. Thus, we have examined the product ratio from the rearrangement of dithioacetal **3** and extended the method to other pentoses. Glycosidation of the resulting products gave pseudodisaccharides having sulfur in the ring of the non-reducing unit.

Thus, treatment of dithioacetal (3)[13] with one equivalent of sodium iodide and 1.2 equivalent of barium carbonate in refluxing acetone gave after acetylation 41% yield of the acetylated benzyl 1,5-dithio-L-arabinopyranoside **6** and benzyl-5-S-benzyl-1,5-dithio-L-arabinofuranoside **7** in a 3:1 ratio[14] (Scheme 1). The same reaction performed without $BaCO_3$ gave a mixture of cyclic and acyclic acetonides[5] in 52% yield. The acetonides formation is probably due to the generation of a small amount of iodine in the reaction mixture.[15] The formation of both **4** and furanoside **5** have been mechanistically explained by Hughes[11] and involved two different pathways as shown in Scheme 2. The cyclic sulfonium ion **8** can be either trapped by iodide cleavage of the benzyl group (pathway a) or alternatively by ring opening leading to acyclic sulfonium ion **9**, followed by ring closure with the 4-OH to form the furanoside **5** (pathway b).



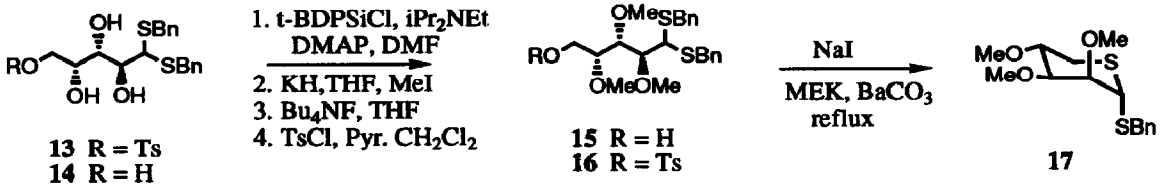
SCHEME 1



SCHEME 2

However, to prevent the ring closure of the intermediate **9**, a simple protection of the hydroxyl groups of triol **3** provides triacetate **10** and under the ring closure reaction condition permits the exclusive formation of **6** in 82% yield as a mixture of ß:α=2:1 (Scheme 2).

Application of this strategy to other aldoses was more problematic. In the case of 5-O-*p*-toluenesulfonyl-D-lyxose dibenzyl dithioacetal (**13**), it is known that the hydroxyl group at C-2 displaces the primary tosylate to give 2,5-anhydro-D-lyxose dibenzyl dithioacetal.[16] To prevent this undesired cyclization, protection of the remaining three hydroxyl groups was necessary (Scheme 3). Thus primary hydroxyl protection of D-lyxose dibenzyl dithioacetal (**14**) followed by methylation and desilylation gave **15**. Tosylation of compound **15**, afforded the expected primary tosylate **16** along with methylated benzyl 1,5-dithio-D-lyxopyranoside **17**. Treatment of **16** with sodium iodide in refluxing methyl ethyl ketone gave the 5-thiopyranoside **17** in 67% yield as the α anomer only.[17]



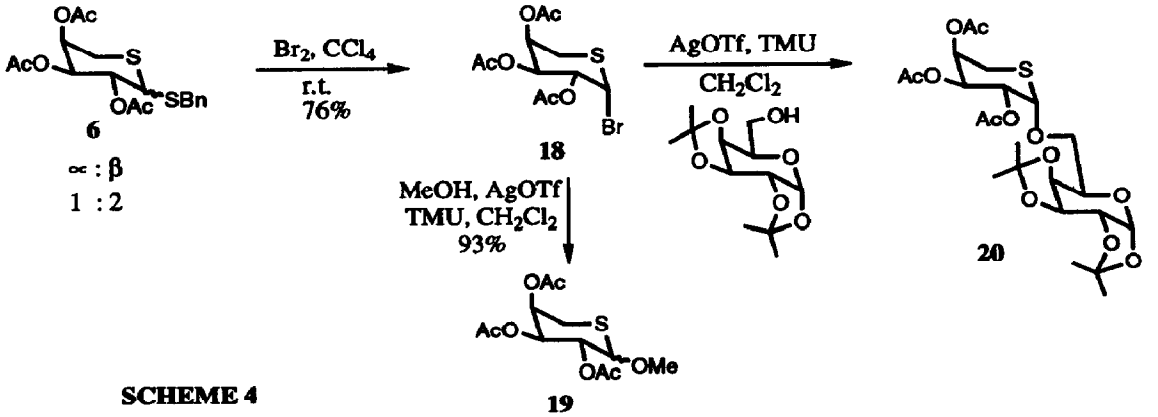
13 R = Ts
14 R = H

15 R = H
16 R = Ts

17

SCHEME 3

An interesting aspect and advantage of the cyclic dithioacetal **6** is that regioselective sulfur activation with respect to glycosidation can be effected. Thus bromination of **6** in carbon tetrachloride at room temperature gave exclusively the α bromide **18** in 76% yield (Scheme 4).[18] The anomeric bromide can be used in situ for glycosidation as exemplified by treatment of **6** with bromine followed by addition of methanol, silver trifluoromethanesulfonate and tetramethylurea[19] in dichloromethane to afford methyl 5-thioglycoside **19** in 93% yield as a mixture of α:ß=3:2.[20] Glycosidation under the same conditions with 1,2,3,4-di-O-isopropylidene-D-galactopyranose gave the pseudodisaccharide **20** in 30% yield as the α anomer.[21] This regioselective sulfur activation might rise questions regarding the relative basicity of heteroatoms in pyranoside acetals and subsequent acetal bond cleavage.



6

∝ : β
1 : 2

18

19

20

SCHEME 4

In conclusion, by the simple protection of the hydroxyl groups on the 5-O-*p*-toluenesulfonyl dithioacetals of L-arabinose and D-lyxose, the exclusive formation of 5-thiopyranoses can be obtained in excellent yield. Subsequent activation by anomeric bromination followed by glycosidation leads to the formation of pseudodisaccharides having a sulfur atom in the ring of the non-reducing unit.

Acknowledgements: We thank Dr. M. Bernstein for NMR spectra and Ms. C. Li for mass spectra.

References and Notes

1. Co-op student, University of Sherbrooke, Sherbrooke, Québec, Canada.
2. Hellman, B.; Lernmark, A.; Sehlin, J.; Taljedal, J.B.; and Whistler, R.L. *Biochem. Pharmacol.* **1973**, *22*, 29.
3. Hashimoto, H.; Fujimori, T.; Yuasa, H. *J. Carbohydr. Chem.* **1990**, *9*, 683.
4. Capon, R.J.; MacLeod, J.K. *J. Chem. Soc., Chem. Comm.* **1987**, 1200.
5. Nayak, U.G.; Whistler, R.L. *J. Org. Chem.* **1969**, *34*, 97; Anisuzzama, A.K.M.; Whistler, R.L. *Carbohydr. Res.* **1977**, *55*, 205.
6. Hashimoto, H.; Kawanishi, M.; Yuasa, H. *Tetrahedron Lett.* **1991**, *32*, 7087.
7. Wong, C.H.; Krach, T.; Gautheron-Le Narvor, C.; Ichikawa, Y.; Look, G.C.; Gaeta, F.; Thompson, D; Nicolaou, K.C. *Tetrahedron Lett.* **1991**, *32*, 4867.
8. Mehta, S.; Pinto, B.M. *Tetrahedron Lett.* **1992**, *33*, 7675; Yuasa, H.; Hindsgaul, O.; Palcic, M.M. *J. Am. Chem. Soc.* **1992**, 114, 5891.
9. Hughes, N.A.; Munkombwe, N.M. *Carbohydr. Res.* **1985**, *136*, 397.
10. Hashimoto, H.; Izumi, M. *Tetrahedron Lett.* **1993**, *34*, 4949.
11. Hughes, N.A.; Robson, R. *J. Chem. Soc. (C)*, **1966**, 2366.
12. Hughes, N.A.; Harness, J. *J. Chem. Soc., Chem. Comm.* **1971**, 811.
13. Baker, S.B. *J. Am. Chem. Soc.* **1952**, 74, 827; The selective tosylation is effected in CH_2Cl_2: Pyridine 1:1 with 1.2 equivalents of TsCl to give the primary tosylate in 75% yield.
14. Compound **6** (mixture ß:α=2:1); ^{1}H NMR ($CDCl_3$, 300MHz); δ 2.8 (dd, J=15.0, 6.4Hz, H-5eq., α); 2.85 (dd, J=14.3, 2.0Hz, H-5ax., ß); 2.97 (dd, J=14.3, 6.6Hz, H-5eq., ß); 3.23 (d, H-5ax., α); 3.73 (d, J=8.2Hz, H-1ax., ß); 3.91 (q., SCH_2); 4.19 (d, J=3.8Hz, H-1eq., ß); 4.91 (dd, J=8.2; 3.0Hz, H-3, ß); 5.21 (dd, J=9.4, 3.1Hz, H-3, α); 5.4 (m, H-2, H-4), 7.32 (m, Ph). M.S. (TSP); 416 $(M+NH_4)^+$, 279 $(MH^+$-2AcOH).
15. Kratha, K.P.R. *Tetrahedron Lett.* **1986**, *27*, 3415.
16. Wander, J.D.; Horton, D. *Adv. Carbohydr. Chem. Biochem.* **1976**, *32*, 15-123.
17. Compound **17**; ^{1}H NMR (Aced$_6$, 500 MHz); δ 3.28 (s, 3H, OCH_3); 3.33 (s, 3H, OCH_3); 3.34 (s, 3H, OCH_3); 3.36 (dd, 1H, J=9.5, 8.3Hz, H-5ax.); 3.45 (m, 1H, H-4); 3.67 (dd, 1H, J=9.5, 4.6Hz, H-5 eq.); 3.83 (dd, 1H, J=7.3, 3.3Hz, H-3); 3.88 (bt, 1H, J=3.4Hz, H-2); 4.2 (d, 1H, J=3.3Hz, H-1); 7.3 (m, 5H, Ph). M.S. (DCI, CH_4); 314 (M^+), 283 $(MH-CH_3OH)^+$, 191 $(M-CH_3OH-PhCH_2-)^+$; 159 $(M-2CH_3OH-PhCH_2-)$.
18. Compound **18**; ^{1}H NMR ($CDCl_3$, 400MHz); δ 2.00, 2.05, 2.12 (3s, 3x3H, $3COCH_3$); 2.85 (ddd, 1H, J=14.9, 4.4, 2.0Hz, H-5eq.); 3.35 (d,1H,J=14.9Hz, H-5ax.); 5.15 (dd, 1H, J=10.2, 3.5Hz, H-2); 5.37 (dd, 1H, J=10.3, 3.1Hz, H-3); 5.48 (m, 1H, H-4); 5.55 (t, 1H, J=3.4Hz, H-1). M.S. (DCI); 374 (Br81)/372(Br79) $M+NH_4)^+$.
19. Hanessian, S.; Banoub, *J. Carbohydr. Res.* **1977**, *53*, C13-C16.
20. Compound **19**α; ^{1}H NMR ($CDCl_3$, 400MHz); 1.95, 2.05, 2.15 (3s, 3x3H, $3COCH_3$), 2.57 (dd, 1H, J=14.6, 4.2Hz, H-5eq.); 3.09 (d, 1H, J=14.6Hz, H-5ax.); 3.40 (s, 3H, OCH_3); 4.61 (d, 1H, J=2.8Hz, H-1); 5.34 (dd, 1H, J=10.7, 3.0Hz, H-3); 5.45 (m, 2H, H-2, H-4).
21. Compound **20**; $_1$H NMR (Aced$_6$, 300 MHz); 1.32 (s, 6H, $2CH_3$); 1.38 (s,3H, CH_3); 1.49 (s, 3H, CH_3); 2.10, 2.05, 1.95 (3s, 3OAc); 2.63 (ddd, 1H, J=14.7, 4.2, 1.6 Hz, H-5^{1}e); 3.28 (dd, 1H, J=14.7, 1.5 Hz, H-5^{1}a); 3.64 (dd, 1H, J=10.3, 6.2 Hz, H-6); 3.85 (dd, 1H, J=10.3, 6.8 Hz, H-6); 4.02 (dt, 1H, J=6.5, 1.8 Hz, H-5); 4.30 (dd, 1H, J=7.9, 1.9 Hz, H-4); 4.35 (dd, 1H, J=5.1, 2.4 Hz, H-2); 4.64 (dd, 1H, J=7.9, 2.4 Hz, H-3); 4.89 ("t", 1H, J=2.1 Hz, H-1^1); 5.31 (dd, 1H, J=10.7, 3.1 Hz, H-3^1); 5.36 (dd, 1H, J=10.7, 2.7 Hz, H-2^1); 5.45 and 5.46 (2s, H-1, H-4^1).

(Received in USA 8 *December* 1993; *revised* 11 *January* 1994; *accepted* 18 *January* 1994)