Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 11, pp. 3087-3090, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00404-1

Synthesis of 1-Deoxy-4-thio-L-ribose starting from D-Arabitol

Hans-Josef Altenbach* and Gerd F. Merhof

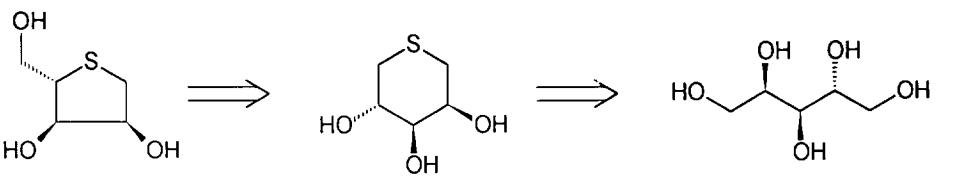
Bergische Universität-Gesamthochschule Wuppertal, Fachbereich Chemie, Gaußstr.20, D-42097 Wuppertal, Germany

Abstract: The synthesis of 1-deoxy-4-thio-L-ribose starting from D-arabitol is described. The keystep is the episulfonium rearrangenment of a protected 3,4,5-trihydroxy-tetrahydrothiopyran.

Copyright © 1996 Elsevier Science Ltd

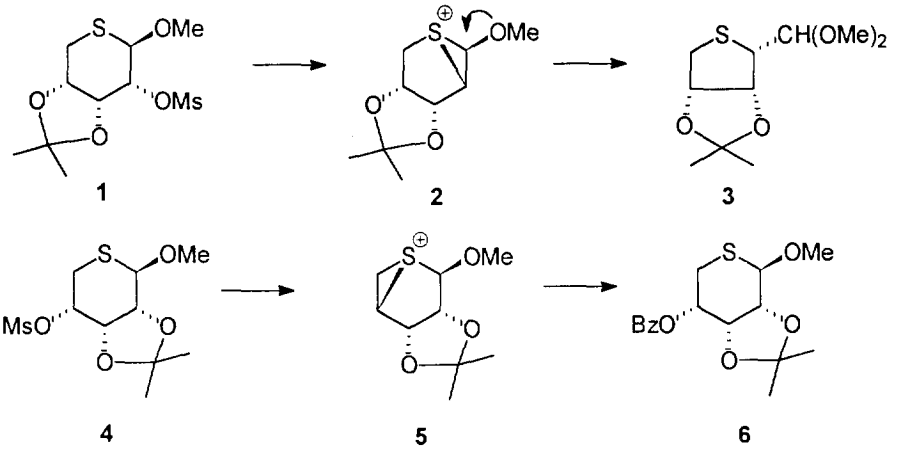
Thiasugars - sugar analogues where the ring oxygen of a pyranose or furanose is replaced by sulfur[1] - have interesting biological properties in most cases due to their resemblance to the corresponding sugars. Whereas 5-thiopyranose systems are well known and a lot of different approaches have been developed[2], 4-thiofuranose systems[3] have been the subject of much interest only recently especially with regard to their use in nucleoside analogues[4].

Looking for an easy method for the synthesis of 4-thiofuranoses we found that the 3,4,5-trihydroxy-tetrahydrothiopyran system might be a valuable key intermediate since ring contraction via an episulfonium rearrangement should lead to the desired target molecules. Such ring contractions have been successfully used in the preparation of 5-thiopyranoses from polyhydroxylated thiepane systems by Depezay et al[5] and in one case he has also observed a further ring contraction to a five membered ring system.



Scheme 1

To our surprise until now simple 3,4,5-trihydroxy-tetrahydrothiopyran systems, which should be easily obtained from arabitol after transformation of the primary hydroxyl functions into leaving groups and reaction with sulfide ion as a bisnucleophile, have not been utilized for the synthesis of 1-deoxy-4-thiofuranoses, although related systems like the thioarabinopyranoside **1** have been described by Hughes et al. to undero ring contraction into **3** via an episulfonium intermediate **2**[6]. On the other hand the isomeric compound **4** gave only the substituted benzoate **6** with retention of configuration by a regioselective attack of the more highly substituted position of the intermediate episulfonium ion **5** (Scheme 2).

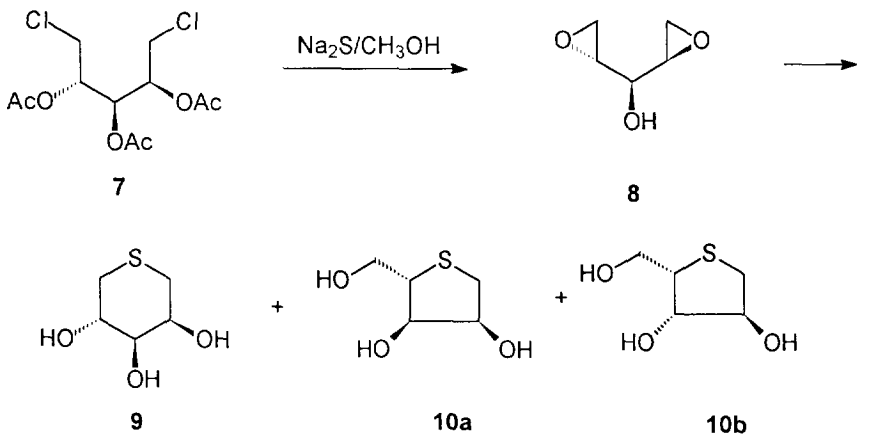


1 2 3

4 5 6

Scheme 2

In order to evaluate whether the help of an alkoxy group is necessary for a clean diastereoselective ring contraction we prepared the 3,4,5-trihydroxy-tetrahydrothiopyran **9** starting from the known 2,3,4-tri-*O*-acetyl-1,5-dichloro-1,5-dideoxy-D-arabitol **7**, prepared from D-arabitol according to literature[7] (Scheme 3).



7 **8**

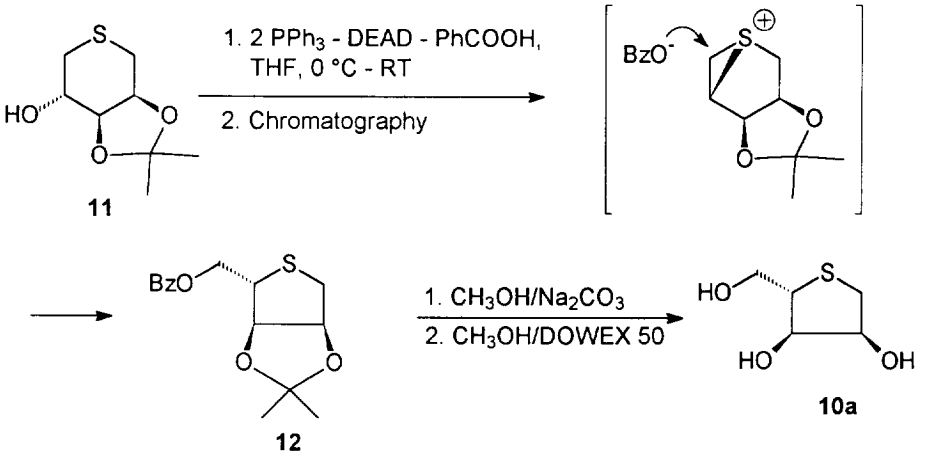
9 **10a** **10b**

Scheme 3

As expected the reaction of **7** with sodium sulfide in methanol led mainly to the tetrahydrothiopyran system **9**. The fact that besides **9** around 10 % of a mixture of two thiofuranoses, presumably **10a** and **10b**, are formed is suggestive of the in situ formation of 1,2;4,5-dianhydro-D-arabitol[8] (Scheme 3). This is further confirmed by the observation that the same composition of products was obtained starting from the preformed diepoxide **8**, whereas the direct cyclisation of **7** with sodium sulfide using DMF or DMSO was not successful. The (3*S*,5*S*)-

3,4,5-trihydroxy-tetrahydrothiopyran **9** could be obtained after chromatography on silica gel with CH_3OH/CH_2Cl_2 in 35 % yield as a colorless solid[9], under these conditions the thiofuranoses **10a** and **10b** could not be separated from each other. For the diastereoselctive ring contraction two hydroxygroups must be protected selectively, which could be done using dimethoxypropane under acid catalysis to form the isopropylidene compound **11**[10] as a colorless oil in 84 % yield.

A clean ring contraction of **11** could be achieved using Mitsunobu conditions[5,11]. With 2 equivalents of DEAD, triphenylphosphine and benzoic acid in THF the protected 4-thio-L-ribose derivative **12**[12] was isolated after chromatography in 80 % yield as an colorless oil (Scheme 4).



Scheme 4

After deprotection with CH_3OH/Na_2CO_3, followed by treatment with CH_3OH/DOWEX 50, 1-desoxy-4-thio-L-ribose **10a**[13] was obtained in 80 % yield as an oil.

Starting from L-arabitol, also commercially available but more expensive than the D-isomer, the (+)-enantiomer of **10a** is likewise accessible.

Acknowledgment: A scholarship (Land NRW) for G.F.M. is gratefully acknowledged.

References and Notes

1 Paulsen, H.; Todt, K. *Adv. Carbohydr. Chem.* **1968**, 23, 115.

2 Rowell, R.M.; Whistler, R.L. *J. Org. Chem.*. **1966**, 31, 1514.

Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1993**, 76, 2687; and references cited therein.

3 Uenishi, J.; Motoyama, M.; Takahashi, K. *Tetrahedron: Asymmetry* **1994**, 5, 101.
Yuasa, H.; Kajimoto, T.; Wong, C.-H. *Tetrahedron Lett.* **1994**, 35, 8243; and references cited therein.

4 Selwood, D.L.; Carter, K.; Young, R.J.; Jandu, K.S. *Bioorg. Med. Chem. Lett.* **1996**, 6, 991; and references cited therein.
Yoshimura, Y.; Kitano, K.; Sato, H.; Watanabe, M.; Miura, S.; Sakata, S.; Sasaki, T.; Matsuda, A. *J. Org. Chem.* **1996**, 61, 822; and references cited therein.

5 Fuzier, M.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1995**, 36, 6443.

6 Hughes, N.A..; Wood, C.J. *J. Chem. Soc., Perkin I.* **1986**, 695.

7 Benazza, M.; Massoui, M.; Uzan, R.; Demailly, G. *J. Carbohydr. Chem.* **1994**, 13, 967.

8 Nakatsuka, M.; Ragan, J.A.; Sammakia, T.; Smith, D.B.; Uehling, D.E.; Schreiber, S.L. *J. Am. Chem. Soc.* **1990**, 112, 5583.

9 (-)-**9**: ^{1}H NMR (400 MHz, D_2O): δ = 2.51-2.83 (m, 4H, CH_2S), 3.50 (m_c, 1H,CH-CH-CH), 3.94-4.24 (m, 2H, CH-CH_2); ^{13}C NMR (100 MHz, D_2O): δ = 31.5, 32.0, 69.0, 69.2, 74.2; $\alpha]_D^{20}$ = -33.6 (c = 1 H_2O); mp.: 127-128 °C.

10 (-)-**11**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39, 1.53 (s, 6H, CH_3), 2.52-2.97 (m, 4H, CH_2-S), 4.05 (t, 1H, ^{3}J=5.4Hz, CH-CH-CH), 4.15-4.39 (m, 2H, S-CH_2-CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 28.3, 29.0, 31.2, 67.7, 72.4, 76.9, 109.0; $\alpha]_D^{20}$ = -67.6 (c = 0.5 $CHCl_3$).

11 Mitsunobu, O. *Synthesis* **1981**, 1.

12 (-)-**12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.99-3.24 (m, 2H, CH_2S), 3.67-3.70 (m, 1H, CHS), 4.37 (ABX, 1H, ^{2}J=11.4Hz, ^{3}J=8.2Hz, CH_2O), 4.41 (ABX, 1H, ^{2}J=11.4Hz, ^{3}J=7.0Hz, CH_2O), 4.82-4.84 (m, 1H, CHCHCHS), 5.00-5.03 (m, 1H, CHCHCHS), 7.47-8.12 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9, 26.7, 37.9, 52.7, 65.4, 83.8, 86.0, 111.6, 128.6, 129.8, 129.9, 133.4, 166.4; $\alpha]_D^{20}$ = -68.2 (c = 1 $CHCl_3$).

13 (-)-**10a**: ^{1}H NMR (400 MHz, D_2O): δ = 2.76 (ABX, 1H, ^{2}J=11.7Hz ^{3}J=3.9Hz, CH_2S), 3.05 (ABX, 1H, ^{2}J=11.7Hz ^{3}J=4.7Hz, CH_2S), 3.36-3.40 (m, 1H, CHS), 3.64 (ABX, 1H, ^{2}J=11.2Hz ^{3}J=6.5Hz, CH_2O), 3.82 (ABX, 1H, ^{2}J=11.2Hz ^{3}J=3.8Hz, CH_2O), 4.02-4.04 (m, 1H, CHCHCHS), 4.34-4.37 (m, 1H, CHCHCHS); ^{13}C NMR (100 MHz, D_2O): δ = 32.2, 50.4, 63.4, 74.4, 76.2; $\alpha]_D^{20}$ = -73.2 (c 0.25 H_2O).

(*Received in UK* 2 *September* 1996)