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Short and efficient synthesis of polyhydroxylated tetrahydrothiophene, tetrahydrothiopyrane and thiepane from bielectrophilic *erythro*, *threo*, *xylo*, *ribo*, *arabino*, *manno* and *gluco* α,ω-dibromoalditol derivatives

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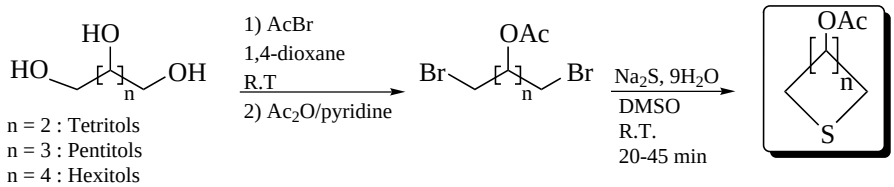
Abstract—Polyhydroxylated tetrahydrothiophene, tetrahydrothiopyrane and thiepane rings have been readily obtained in excellent yields (78–95%) from thioheterocyclisation of the bielectrophilic peracetylated α,ω-dibrominated derivatives of tetritols (erythritol (**1**) and D,L-threitol (**4**)), pentitols (xylitol (**7**), ribitol (**10**) and D-arabinitol (**14**)) and hexitols (D-mannitol (**17**) and D-glucitol (**20**)), respectively. With 2,3,4,5-tetra-*O*-acetyl-1,6-dibromo-1,6-dideoxy-D-glucitol (**21**) as substrate, the unexpected 2,6-anhydro derivative **25** was obtained. This could be attributed to previous $S^{=}$ regioselective nucleophilic attack at C-1 position followed by 1,2-transesterification and 2,6-*O*-heterocyclisation. The preferential attack at C-1 of the D-glucitol derivative **21** subsequently allowed a facile direct synthesis in good yields of 2,3,4,5,6-penta-*O*-acetyl-1-bromo-1-deoxy-D-glucitol (**26**), 2,3,4,5-tetra-*O*-acetyl-6-bromo-6-deoxy-1-thiobutyl-1-deoxy-D-glucitol (**28**) and 2,3,4,5-tetra-*O*-acetyl-6-bromo-6-deoxy-1-thiooctyl-1-deoxy-D-glucitol (**28**).

Tetrahydrothiophene is an important building block of a large number of compounds that are very interesting from the point of view of biological activity. In particular it enters into the structures of nucleoside analogues[1] and certain compounds where the sulfur atom in the ring is in a trivalent state (spirobicyclic-like), such as the sulfimides,[2] salicinol[3a] and kotalanol,[3b] which are excellent glycosidase inhibitors. Although analogues with more than six- or seven-membered rings (tetrahydrothiopyrane and thiepane) generally show weak glycosidase[4] inhibition activity, they are nevertheless excellent precursors for the thiacyclopentane ring through contraction of the ring[4,5] or for conduritol derivatives (from thiepane)[6] which are glycosidase inhibitors and much used as intermediates in the synthesis of inositol[7] and aminocyclitol derivatives.[8]

The use of alditols as bielectrophilic substrates in thioheterocyclisations has been reported in the literature. It has been shown that the thiepane ring is obtained mainly from bis-epoxyhexitol such as D-mannitol always protected in the 3,4-positions.[5b] However, this approach has limitations when applied to other alditols.[9] In our laboratory we have recently used alditol bis-cyclic-sulfates as bielectrophilic intermediates. Polyhydroxylated tetrahydrothiophene, tetrahydropyrane and thiepane derivatives have been isolated in good



Scheme 1.

Keywords: alditol; thioheterocyclisation; thiosugar; thiepane; thiophene; thiopyrane.

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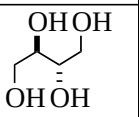
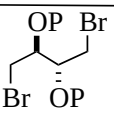
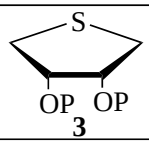
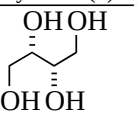
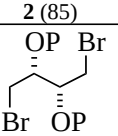
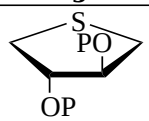
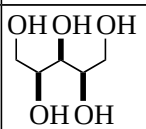
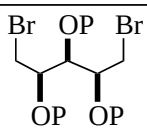
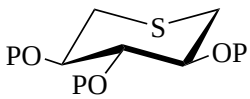
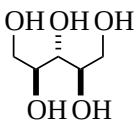
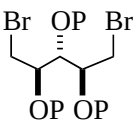
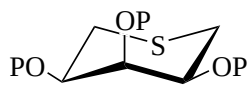
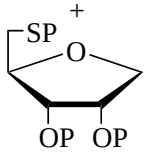
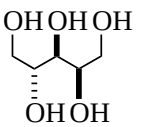
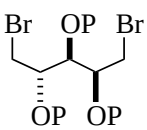
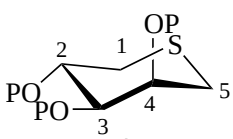
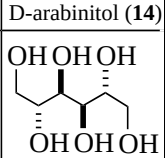
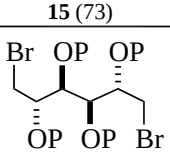
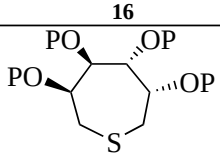
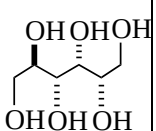
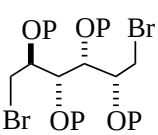
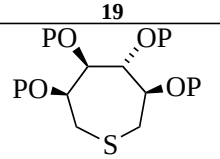
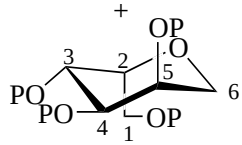
yields.[10] However, we have shown that this approach is only applicable to free tetritols and other partially protected alditols carrying only four free hydroxyl groups.

Table 1. Regioselective thioheterocyclisation of α,ω-dibromoalditols derivatives (1 mmol) using sodium sulfide nonahydrate as binucleophilic reagent. Solvent effect on the isolated yields

Entry	Substrates	α,ω-dibromoalditols derivatives (Yield (%))* P = Ac	Isolated thioheterocyclic products P = Ac	Isolated yields (%) with acetone-H_2O as solvent[a] Yield (%)**	Isolated yields (%) with DMSO as solvent[b] Yield (%)	Time
1	 Erythritol (**1**)	 **2** (85)	 **3**	93	92	20 min
2	 D,L-Threitol (**4**)	 (±)-**5** (86)	 (±)-**6**	95	95	"
3	 xylitol (**7**)	 **8** (70)	 **9**	90	87	30 min
4	 Ribitol (**10**)	 **11** (68)	 **12** +  (±)-**13**	70 20	78 0	"
5	 D-arabinitol (**14**)	 **15** (73)	 **16**	86	83	"
6	 D-mannitol (**17**)	 **18** (60)	 **19**	82	88	45 min
7	 D-glucitol (**20**)	 **21** (50)	 **23** +  **25** (2,6-anhydro)	75 10	85 0	"

*Isolated yields from the corresponding alditols; **Isolated yields from α,ω-dibromoalditols derivatives and after acetylation of crude product;

[a] 5 mmol of $Na_2S, 9H_2O$, 18 h; [b] 1.5 mmol of $Na_2S, 9H_2O$

Herein, we report a general, short and efficient synthesis affording polyhydroxylated tetrahydrothiophene, tetrahydrothiopyrane and thiepane rings from peracetylated α,ω-dibromoalditols with the *erythro*, *threo*, *xylo*, *ribo*, *arabino*, *manno* and *gluco* configurations (Scheme 1). The latter are obtained directly by bromination of the corresponding alditols.[11]

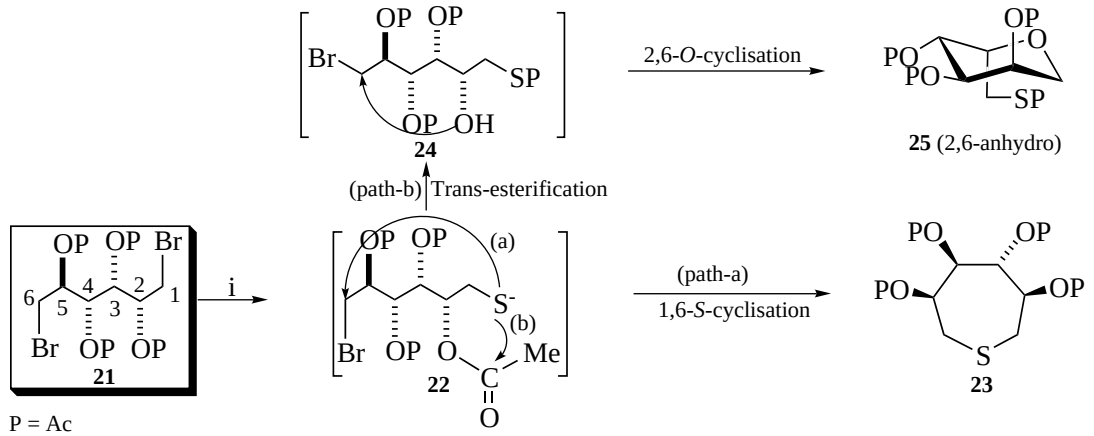
In the synthesis of thioheterocycles from bielectrophilic alditols derivatives, solvents such as EtOH,[4] MeOH[12] or a mixture of acetone–H_2O were used.[10] In the latter case, under mild conditions (rt, 15 min), cyclic tetritol bis-sulfates reacting with Na_2S, $9H_2O$ lead to the corresponding thiacyclopentane derivatives in good yields. Initially, applying these conditions 2,3,4-tri-*O*-acetyl-1,5-dibromo-1,5-dideoxyxylitol (**8**) (Table 1) led, after flash chromatography, to the xylotetrahydrothiopyrane derivative **9** in only 37% yield. When this reaction is followed by acetylation of the reaction mixture, the yield of compound **9** reaches 90% (entry 3). This is explained by the concomitant deacetylation of the heterocyclisation product.

Under the same conditions, thiocyclisation of α,ω-dibromoalditol derivatives **2**, **5**, **11**, **15**, **18** and **21** followed by acetylation leads to the tetrahydrothiophenes **3** and **6** (entries 1 and 2), tetrahydrothiopyranes **12** and **16** (entries 4 and 5) and thiepanes **19** and **23** (entries 6 and 7) in yields from 70 to 95% for a reaction time of 18 h for complete disappearance of substrate.

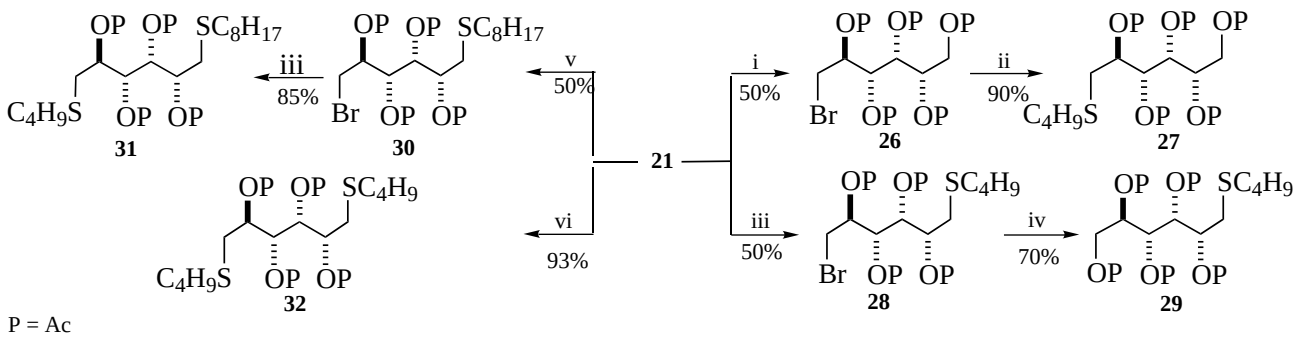
It is interesting to emphasise that with brominated ribitol **11** and D-glucitol **21** (entries 4 and 7) non-negligible amounts of anhydro compounds were isolated. In both cases the formation of these *O*-heterocyclic compounds could be explained by an initial attack at one of the primary sites by $S^=$, followed by transesterification and *O*-heterocyclisation leading to anhydro derivatives **13** and **25** after acetylation.

For compound **13**, ^{13}C NMR shows both an intracyclic secondary carbon atom at 70.82 ppm and another extra-cyclic at 30.90 ppm, plus a signal at 190 ppm shift for the thioacetate group. In ^1H NMR, the coupling constant $J_{2,3}=5.4$ Hz is in agreement with a 1,4-anhydroribitol structure.[13]

In the case of the derivative of anhydro-D-glucitol **25**, the sequence of coupling constants $J_{2,3}=3.48$ Hz, $J_{3,4}=10.96$ Hz and $J_{4,5}=0$ Hz favours a 2,6-anhydro-D-glucitol structure. Mechanistically, this requires an initial regioselective attack on the primary C-1 site of the disymmetric dibrominated D-glucitol derivative **21** (Scheme 2) followed by competition between *S*-cyclisation (path-a) leading to thiepane **23** and a 1,2-*trans*-esterification (path-b) leading to 2-hydroxy compound **24**. A subsequent *O*-heterocyclisation at 2,6 leads to



Scheme 2. (i) Na_2S, $9H_2O$, acetone–H_2O (15:1), rt, 18 h.



Scheme 3. (i) AcONa (3 equiv.), 60°C, 5 h, DMSO; (ii) C_4H_9SH (1.2 equiv.), NaH (1.1 equiv.), DMSO, rt, 15 min; (iii) C_4H_9SH (1.2 equiv.), NaH (1.1 equiv.), DMSO–THF (1:1), rt, 15 min; (iv) AcONa (3 equiv.), 60°C, 24 h, DMSO; (v) $C_8H_{17}SH$ (1.2 equiv.), NaH (1.1 equiv.), DMSO, T.A., 15 min; (vi) C_4H_9SH (2.2 equiv.), NaH (2.4 equiv.), DMSO–THF (1:1), rt, 15 min.

2,6-anhydro-D-glucitol derivatives **25**. To corroborate this higher reactivity of C-1 compared with C-6 in the derivative 1,6-dibromo-D-glucitol **21**, we attempted regioselective nucleophilic substitution using mononucleophiles such as the acetate ion (AcO^-) and the alkylthiolate anions (n-$C_4H_9S^-$ and n-$C_8H_{17}S^-$) (Scheme 3). In both cases we confirmed the high reactivity of C-1 leading, respectively, to 1,2,3,4,5-penta-*O*-acetyl-6-bromo-6-deoxy-D-glucitol (**26**), 2,3,4,5-tetra-*O*-acetyl-6-bromo-6-deoxy-1-thiobutyl-1-deoxy-D-glucitol (**28**) and 2,3,4,5-tetra-*O*-acetyl-6-bromo-6-deoxy-1-thiooctyl-1-deoxy-D-glucitol (**30**) in reasonable yields (50%). Derivatives **26**, **28** and **30** were, respectively, transformed into the derivatives 6-thiobutyl, 1-thiobutyl and 6-thiobutyl-1-thiooctyl-D-glucitols **27**, **29** and **31** in excellent yields. This regioselective functional transformation then enabled us to synthesise the 1,6-dithioalkyl derivative **31** with two alkyl chains of differing lengths. Note that with an excess of thiolate in the DMSO–THF mixture, the thioalkylation takes place indiscriminately at the two sites C-1 and C-6 to give the disubstituted compound **32**.[11]

Finally, while investigating the solvent effect on thioheterocyclisation, we were able, using DMSO as solvent, to isolate thioheterocyclic compounds in very good yields without subsequent acetylation and in particularly mild conditions (20–45 min, only 1.5 mmol of Na_2S–$9H_2O$ instead of 5 mmol in acetone–H_2O). Furthermore, in the case of ribitol (entry 4) and D-glucitol (entry 7) any amounts of anhydro derivatives **13** and **25** were observed.

In conclusion, this work has led to the short and efficient synthesis in excellent yields of polyhydroxylated tetrahydrothiophene, tetrahydrothiopyrane and thiepane derivatives in various configurations via dibrominated alditol derivatives that are readily prepared from the corresponding alditols. In addition we have shown a higher reaction rate at the primary C-1 compared with the C-6 site of the 1,6-dibromo-D-glucitol derivative **21**. This opens the way to numerous derivatives of D-glucitol with various functional groups, as well as to a rare sugar, gulose.[14]

Acknowledgements

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References

1. (a) Selwood, D. V.; Carter, K.; Young, R. J.; Jandu, K. S. *Bioorg. Med. Chem. Lett.* **1996**, *8*, 991–994; (b) Tber, B.; Fahmi, N. D.; Ronco, G.; Villa, P.; Ewing, D. F.; Mackenzie, G. *Carbohydr. Res.* **1995**, *267*, 2203–2216.
2. Yuasa, H.; Kajimoto, T.; Wong, C. H. *Tetrahedron Lett.* **1994**, *35*, 8243–8246.
3. (a) Yoshikawa, M.; Murakami, T.; Shimada, H.; Matsuda, H.; Yamahara, J.; Tanabe, G.; Muraoka, O. *Tetrahedron Lett.* **1997**, *38*, 8367–8370; (b) Yoshikawa, M.; Murakami, T.; Yashiro, K.; Matsuda, H. *Chem. Pharm. Bull.* **1998**, *46*, 1339.
4. Le Merrer, Y.; Fuzier, M.; Dosbaa, I.; Foglietti, M. J.; Depezay, J. C. *Tetrahedron* **1997**, *53*, 16731–16746.
5. (a) Cerè, V.; Peri, F.; Pollicino, S. *J. Org. Chem.* **1997**, *62*, 8572–8574; (b) Fuzier, M.; Le Merrer, Y.; Depezay, J. C. *Tetrahedron Lett.* **1995**, *36*, 6443–6446.
6. (a) Cerè, V.; Peri, F.; Pollicino, S.; Ricci, A. *Synlett* **1998**, 1197–1198; (b) Cerè, V.; Peri, F.; Pollicino, S. *Tetrahedron Lett.* **1997**, *38*, 7797–7800.
7. (a) Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439–9440; (b) Ley, S. V.; Sternfeld, F. *Tetrahedron Lett.* **1988**, *29*, 5305–5308.
8. Legler, G. W. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319.
9. Altenbach, H. J.; Merhof, G. F. *Tetrahedron: Asymmetry* **1996**, *7*, 3087–3090.
10. Glaçon, V.; Benazza, M.; Beaupère, D.; Demailly, G. *Tetrahedron Lett.* **2000**, *41*, 5053–5056.
11. Robert, C. C.; Benazza, M.; Fréchou, C.; Demailly, G. *Carbohydr. Res.* **1997**, *303*, 359–365.
12. Calvo-Flores, F. G.; Garcia-Mendoza, P.; Hernandez-Mateo, F.; Isac-Garcia, J.; Santoyo-Gonzalez, F. *J. Org. Chem.* **1997**, *62*, 3944–3961.
13. Benazza, M.; Masoui, M.; Uzan, R.; Demailly, G. *Carbohydr. Res.* **1995**, *275*, 421–431.
14. González, F. S.; Baer, H. *Carbohydr. Res.* **1990**, *202*, 33–47.