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Tetrahedron Letters 45 (2004) 4365–4369
Tetrahedron Letters

Versatile use of bis-cyclic thionocarbonates of polyols as bis-electrophilic intermediates. Synthesis of polyhydroxylated thioanhydropentitols with D,L-*arabino*, L-*ribo* and L-*xylo*, and thioanhydroaldoses with D-*lyxo*, L-*ribo*, D-*xylo*, D-*allo*, D-*gulo* and D-*altro* configurations

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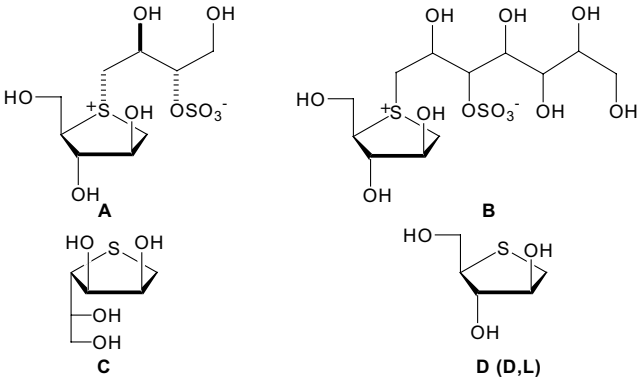
Received 20 October 2003; revised 25 March 2004; accepted 31 March 2004

Abstract—1-*O*-Benzylpentitols (with D-*arabino*, D-*lyxo*, D,L-*xylo* and D,L-*ribo* configurations) and aldose dibenzyldithioacetals (with L-*arabino*, D-*lyxo*, D-*xylo*, D-*ribo*, D-*galacto*, D-*gluco* and D-*manno* configurations) were directly and efficiently transformed into their cyclic bis-thionocarbonate derivatives (61–73%) by reaction with diimidazolyl thione (Im_2CS) in 1,4-dioxane. These bis-electrophilic adducts react regioselectively with $Na_2S{\cdot}9H_2O$ to lead to 1,4-, 2,5- or 3,6-thioanhydroalditol derivatives in good yields (47–65%). Thioanhydro configurations D,L-*arabino*, L-*ribo* and L-*xylo* from pentitols, and D-*lyxo*, L-*ribo*, D-*xylo*, D-*allo*, D-*gulo* and D-*altro* from aldoses were obtained.

In our ongoing program we were interested in the polyhydroxylated tetrahydrothiophenes, as possible bioisosteric analogues of some pyrrolidine competitive glycosidase inhibitors.[1] These five-membered ring analogues of anhydro sugars, where the oxygen atom has been replaced by a sulfur atom, are important building blocks of a large number of very interesting biological compounds. For instance, they can be incorporated into nucleoside analogues,[2] and constitute the backbone of compounds where the sulfur atom in the ring is in a trivalent state including zwitterionic systems such as the sulfimides,[3] salacinol (**A**) and kotalanol (**B**), which are potent α-glycosidase inhibitors used in the treatment of Type II noninsulin-dependent diabetes.[4]



One of the most important routes to polyhydroxylated thiaheterocycles is the *S*-heterocyclisation of bis-electrophilic alditols such as bis-epoxides,[5] bis-halogenated derivatives,[6] bis-sulfonates,[7] bis-cyclic sulfates[8] and more recently bis-cyclic thionocarbonates[9] in the presence of sodium sulfide nonahydrate. Some six- and seven-membered rings obtained following this approach could subsequently be converted to tetrahydrothiophenes by transannular processes by reaction with trimethylsilyl halides,[10] with PPh_3/CBr_4 and when undergoing the Mitsunobu reaction[11] or by intramolecular S_N2 substitution with appropriately mesylated thiepane.[12]

Keywords: Alditols; Aldoses dithioacetals; Pentoses; Hexoses; Thioanhydro; Bis-thionocarbonates; Thiaheterocyclisation.
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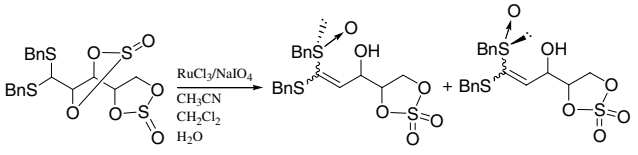
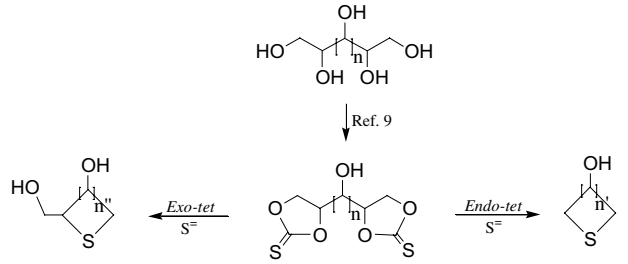
doi:10.1016/j.tetlet.2004.03.197

We recently reported a short synthesis of D-*talo*-tetrahydroxythiolane **C** and D,L-arabinotrihydroxythiolane **D** (a racemic mixture of the thioanhydroarabinitol subunit of salacinol) for the first time by the use of *S*-heterocyclisation of the bis-cyclic sulfate derivatives of 1,2-*O*-isopropylidene-D-mannitol and 1-*O*-benzyl-D,L-xylitol, respectively.[8] The use of this kind of intermediate obtained by oxidation of the corresponding cyclic sulfite with substrates like pentose dithioacetals met a serious limitation because of the oxidation induced α,β-unsaturated monosulfoxide formation (Scheme 1).[13] Owing to this undesirable dithioacetal oxidation, the use of cyclic-thionocarbonates as electrophilic intermediates appears to be an alternative because of their easy formation from diols and polyols. For instance, the 1,2:4,5- and 1,2:5,6-bis-thionocarbonates were formed from pentitol and hexitol stannyleneacetal complexes, respectively, and phenyloxychlorothionoformate (PhO-CSCl) under mild conditions (Scheme 2). We carried out, on this bis-electrophilic system, for the first time, thiaheterocyclisation using a $S^{=}$ bi-anion as a soft binucleophilic reagent. Unfortunately this original heterocyclisation often led to inseparable mixtures of *endo-tet* and *exo-tet* thiaheterocycles.[9]



Scheme 1.



Scheme 2. $n = 0$ (tetritols) or 1 (pentitols); $n' = 2$, 3 or 4; $n'' = 2$ or 3.

The heterocyclisation involving primary–secondary electrophilic sites in an *exo-tet* process is of interest and could be exploited in the synthesis of a wide range of thiolane rings. Herein, we describe a short and versatile synthesis of precursors of trihydroxythiolane derivatives from monobenzylpentitols with D-*arabino*, D-*lyxo*, D,L-*xylo* and D,L-*ribo* configurations,[14] and from the dibenzyldithioacetal of aldoses with L-*arabino*, D-*lyxo*, D-*xylo*, D-*ribo*, D-*galacto*, D-*gluco* and D-*manno* configurations. Both pentitols and aldose dibenzyldithioacetal substrates react smoothly with diimidazolyl thione (Im_2CS, 2.2 equiv) in dry 1,4-dioxane (0.5 g/mL) at room temperature overnight to give the corresponding bis-thionocarbonates in good yields (Table 1).

The first synthesis of the bis-thionocarbonate derivatives was carried out with a mixture of 1-*O*-benzyl-D-arabinitol (**1**) and 1-*O*-benzyl-D-lyxitol (**4**) (entry 1) obtained regioselectively from the D-arabinitol stannylether complex and BnBr in a 52% overall yield (in a 1:1 ratio).[14] This inseparable mixture was trans-

Table 1. Isolated yields of bis-thionocarbonates and thiaheterocycles* obtained from monobenzyl pentitols[14] and aldose dithioacetal derivatives** as substrates

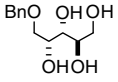
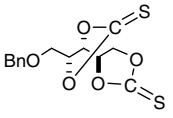
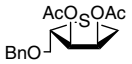
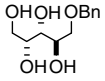
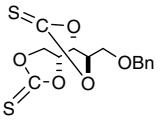
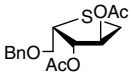
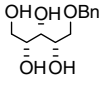
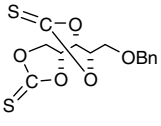
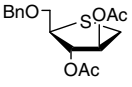
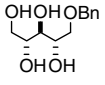
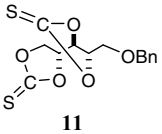
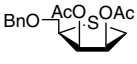
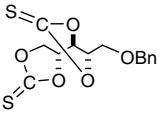
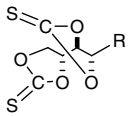
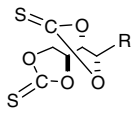
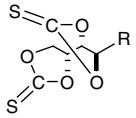
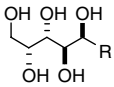
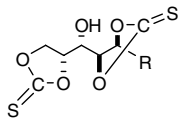
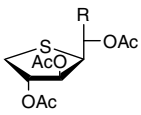
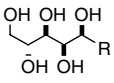
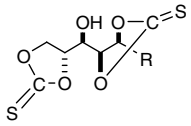
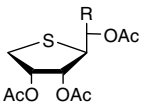
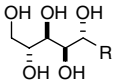
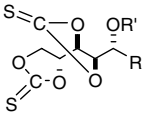
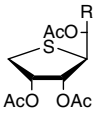
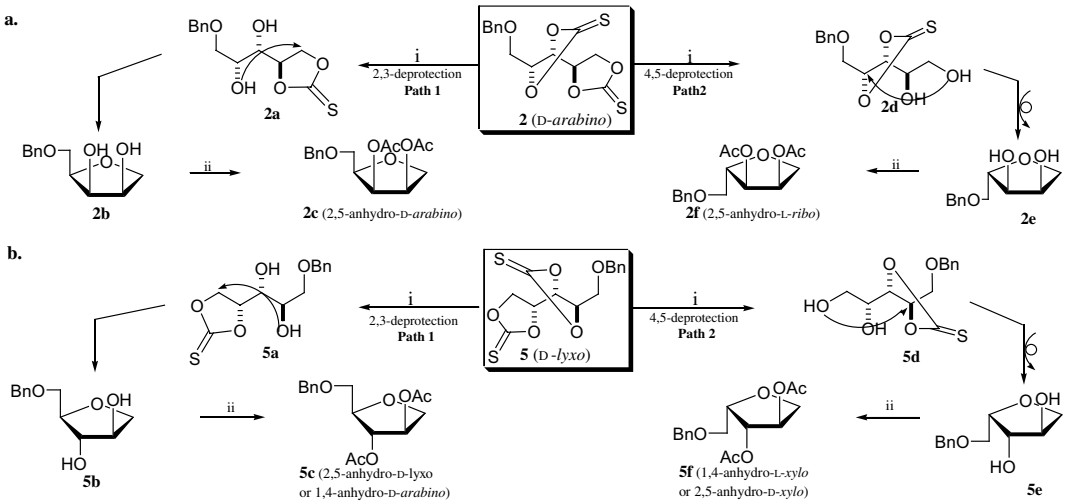
Entry	Substrate	Bis-thionocarbonate	Yield (%)	Isolated	Yield (%)
1	 **1** (1-*O*-Bn-D-*arabino*)	 **3**	32[a]	 **3** (2,5-Thioanhydro-D-*ribo* or 1,4-L-*ribo*)	47
	 **4** (5-*O*-Bn-D-*arabino* or **1**-*O*-Bn-D-*lyxo*)	 **5**	40[a]	 **6** (1,4-Thioanhydro-L-*xylo* or 2,5-D-*xylo*)	65
2	 **7** (D,L-*xylo*)	 **8**	61	 **9** (1,4-Thioanhydro-D,L-*arabino*)	55
3	 **10** (D,L-*xylo*)	 **11**	72	 **12** (2,5-Thioanhydro-D,L-*arabino*)	45

Table 1 (*continued*)

Entry	Substrate	Bis-thionocarbonate	Yield (%)	Isolated	Yield (%)
4	 **13** (D-*xylo*)	 **14**	73	 **15** (2,5-Thioanhydro-D-lyxose)	60
5	 **16** (D-*ribo*)	 **17**	76	 **17a** (2,5-D-*arabino*)	0
6	 **18** (L-*arabino*)	 **19**	68	 **20** (2,5-Thioanhydro-L-ribose)	50
7	 **21** (D-*lyxo*)	 **22**	73	 **23** (2,5-Thioanhydro-D-xylose)	60
8	 **24** (D-*galacto*)	 **25**	65	 **26** (3,6-Thioanhydro-D-gulose)	60
9	 **27** (D-*gluco*)	 **28**	60	 **29** (3,6-Thioanhydro-D-allose)	51
10	 **30** (D-*manno*)	 **31** R = H **32** R′ = CSIm	R′ = H 23 R′ = CSIm 34	 **33** (3,6-Thioanhydro-D-altrose)	36[b] 16[c]

[a] From starting mixture of **2** and **5**.
[b] From isolated **31**.
[c] From isolated **32** R = $CH(SBn)_2$.
[*] 1.5 equiv of $Na_2S{\cdot}9H_2O$, 80 °C, 2 h, DMSO.
[**] HCl (12 N), BnSH (2.2 equiv).

formed to the corresponding bis-cyclic thionocarbonate derivatives **2** (D-*arabino*) and **5** (D-*lyxo*) separated by chromatography on silica gel in 32% and 40% yields, respectively (yields evaluated from the starting mixture of **1** and **4**). The identification of these two regioisomers was achieved by NMR spectroscopy of their anhydro derivatives D-*arabino* **2c** (from 2,3-deprotection, path 1, Scheme 3a) or L-*ribo* **2f** (from 4,5-deprotection, path 2) and D-*lyxo* **5c** (from 2,3-deprotection, path 1, Scheme 3b) or L-*xylo* **5f** (from 4,5-deprotection, path 2) obtained in 31% and 47% yields, respectively, by reaction of **2** and **5** with a catalytic amount of MeONa in MeOH. Compounds **2c** (or **2f**) and **5c** (or **5f**) were characterised by $J_{3,4}$ coupling constants equal to 5.01 Hz for the *syn*-methine configuration of H-3,4 and ≈0 Hz for the *trans*-methine configuration of H-3,4, respectively. Consequently, by TLC performed on silica gel, the most polar is the bis-thionocarbonate derivative of D-lyxose **5** ($R_f = 0.08$, 7/3 hexane–EtOAc) and the less polar is the D-*arabino* derivative **2** ($R_f = 0.17$). The possible deprotection of cyclic thionocarbonates in compounds **2** and **5** had not been elucidated until now.



Scheme 3. Reagents and conditions: (i) MeONa in MeOH, rt, 16 h; (ii) Ac_2O, pyridine.

With the rest of the pentitol derivatives and pentoses the vicinal bis-cyclic thionocarbonates were formed similarly in good isolated yields (from pentitols: **8** (D,L-*xylo*) (61%), **11** (D,L-*ribo*) (72%) (entries 2 and 3)); from pentoses: **14** (D-*xylo*) (73%), **17** (D-*ribo*) (76%), **19** (L-*arabino*) (68%) and **22** (D-*lyxo*) (73%) (entries 4–7). With hexoses bearing five free hydroxyl groups, the configurations of the hexose studied appeared to control the regioselectivity of the bis-cyclic thionocarbonate formation. Thus the D-*galacto* and the D-*gluco* isomers **24** and **27** showed 2,3:5,6-bis-cyclic thionocarbonate formation with the hydroxyl in the 4-position left free (entries 8 and 9). In contrast, the *manno* configuration **30** led to the bis-cyclic thionocarbonate derivatives **31** with the free 2-OH in 23% yield and **32** with the imidazolyl thionocarbonate group in the 2-position in 34% yield.

The 2,3:5,6-positions in **25** (*galacto*) and **28** (*gluco*) and 3,4:5,6-position of the cyclic thionocarbonate groups in **31** (*manno*) were easily confirmed by ^{13}C NMR spectroscopy.[15] In fact, while **25** and **28** showed 2-C and 4-C chemical shifts at approximately 84.8 and 69.6 ppm, respectively, the *manno* compound **31** showed 2-C at 72.5 and 4-C at 82.6 ppm. The 2-C signals in **25** and **28** and 4-C signal in **31** were shifted upfield due to the cyclic thionocarbonate group. The unexpected formation of the *trans*-2,3:5,6-bis-thionocarbonate **28** is probably due to the bent conformation involved by the stereoelectronic 1,3-parallel interaction between 2-OH and 4-OH in zigzag form of the *gluco* configuration.

The first thiaheterocyclisation attempted with **2** by reaction with $Na_2S{\cdot}9H_2O$ in DMSO at room temperature led to a complex mixture with no formation of the expected thioanhydro derivative. When the temperature was increased to 80 °C for 1 h, 3,4-di-*O*-acetyl-2,5-thioanhydro-L-ribitol (**3**) was isolated after acetylation in 47% yield (entry 1). The same conditions when applied to **5** with the D-*lyxo* configuration, led to the L-*xylo* thioanhydro derivative **6** in a better yield (65%) (entry 1). This is probably due to the steric hindrance caused by the *cis*-configuration of the 3-OH/4-OH group in the transition state, which limits the thiaheterocyclisation of **2**. Steric hindrance could also be invoked in the cases of **12** (entry 3, 45%) and in a large part with **17a** (entry 5) for which the formation was excluded due to the interaction between 3-OH, 4-OH and the bulky dibenzyldithioacetal group in the *syn*-position.

A very interesting result was obtained with hexose dithioacetals where the 1,4-thiolane rings were formed regioselectively from both 2,3:5,6- and 3,4:5,6-bis-cyclic thionocarbonate derivatives. Thus the 2,4,5-tri-*O*-acetyl-3,6-thioanhydro-D-glucose (**26**), D-allose (**29**) and D-altrose (**33**) (entries 8–10) were obtained in 60%, 51% and 36% yields, respectively. With the D-*manno* configuration, the 2-imidazolylthionocarbonate **32** was also submitted to the thiaheterocyclisation reaction. Only a 16% yield was extracted from a complex mixture.

The 3,6-thiaheterocyclisation leading to **26**, **29** and **33** is justified by ^{13}C NMR spectroscopy, which shows 3-C signals at 50.6, 49.2 and 49.6 ppm, and 6-C signals at 36.1, 31.0 and 31.1 ppm, respectively.[16]

In conclusion, we report a general and versatile use of bis-cyclic thionocarbonates as intermediates for a wide range of polyhydroxylated 1,4-, 2,5- and 3,6-thiolanes from both pentitols and linear aldose substrates. It is of interest to point out that the eight thiaheterosugar analogues described herein are enantiopure.

Acknowledgements

The authors thank the Conseil régional de Picardie & le fonds social Européen for their financial support.

References and notes

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15. ^{13}C NMR in DMSO (Bruker 300 WB spectrometer) for **25**: δ 52.2 (C-1), 84.9 (C-2), 85.2 (C-3), 69.5 (C-4), 82.4 (C-5), 72.5 (C-6), 36, 36.3 (Ph*C*H_2–), 128.1–137.9 (Ph–), 137.8, 137.9 (C-*ipso*), 191.2, 192.6 (C=S); for **28**: δ 50 (C-1), 84.7 (C-2), 83.7 (C-3), 69.7 (C-4), 81.7 (C-5), 70.7 (C-6), 36.6, 36.7 (Ph*C*H_2–), 128.2–137.2 (Ph-), 137.1 (C-*ipso*), 190.3, 191.8 (C=S); for **31**:δ 53.5 (C-1), 72.8 (C-2), 82.6 (C-3, C-4), 75.6 (C-5), 65.5 (C-6), 35.6, 35.8 (Ph*C*H_2–), 127.9-138.6 (Ph–), 138.5–138.6 (C-*ipso*),191, 192.8 (C=S).
16. ^{13}C NMR in $CDCl_3$ for **26**: δ 53.6 (C-1), 72.2 (C-2), 50.6 (C-3), 76.3 (C-4), 78.0 (C-5), 36.1 (C-6), 36, 36.8 (Ph*C*H_2–), 127.6–130.5 (Ph–), 137.5, 137.8 (C-*ipso*), 21.1, 21.4, 21.5 (CH_3), 170.0, 170.1, 170.2 (CO); for **29**: δ 52.8 (C-1), 75.9, 76.0 (C-2,4), 49.2 (C-3), 74.0 (C-5), 31.0 (C-6), 35.5, 36.2 (Ph*C*H_2–), 127.5–129.7 (Ph–), 138.1, 138.2 (C-*ipso*), 20.3 (CH_3), 169.5, 169.8, 170.0 (CO); for **33**: δ 54.0 (C-1), 71.9, 73.5, 75.5 (C-2,4,5), 49.6 (C-3), 31.1 (C-6), 35.4, 35.7 (Ph*C*H_2–), 127.6–129.7 (Ph–), 137.6 (C-*ipso*), 21.2, 21.3 (CH_3), 170.5 (CO).