Radical-Induced Cyclization of the *S*-Methyl Dithiocarbonate of 1,2-*O*-Isopropylidene-α-xylose.

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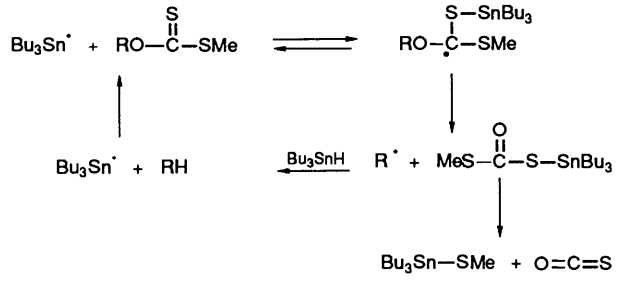
Reaction of the 3,5-bis-(*S*-methyl dithiocarbonate) of 1,2-*O*-isopropylidene-α-D-xylose with tributyltin hydride gives not the expected 3-deoxygenated *xylo*-furanose but instead the 3-thio-α-D-*xylo*-furanose derivative **4** resulting from radical cyclization. The structure of compound **4** was confirmed by X-ray crystallography. The absolute configuration has been established.

Homolytic cleavage of a carbon–oxygen bond followed by quenching of the resulting carbon radical by hydrogen transfer is the most widely used method for the deoxygenation of secondary alcohols.[1] This reaction is also very suitable for large-scale synthesis. Therefore the secondary alcohol could be converted into an *S*-methyl dithiocarbonate which is then treated with tributyltin hydride in the presence of azoisobutyronitrile (AIBN) as radical initiator in refluxing toluene. The mechanism of deoxygenation has been studied by Barton[2] and is depicted in Scheme 1. It consists of a fast and reversible addition of the stannyl radical, initially generated by means of AIBN, to the thiocarbonyl function, followed by a rate-determining slow fragmentation. The resulting carbon radical is then quenched by tributyltin hydride. This article describes the cyclization reaction which occurs during the deoxygenation of the bisxanthates of 1,2-*O*-isopropylidene-α-D-xylose.

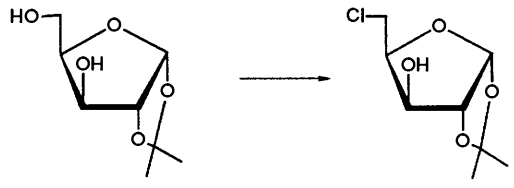


Scheme 1

Results and Discussion

Application of Barton-type deoxygenation to cyclic thiono carbonates of two secondary alcohols gives a mixture of two regioisomers. Primary alcohols are more difficult to deoxygenate than are secondary alcohols. Therefore, deoxygenation of a cyclic thiono carbonate formed between a primary and a secondary alcohol gives deoxygenation only at the secondary position.[3] This method looks very attractive for the synthesis of 1,2-*O*-isopropylidene-3-deoxy-α-D-*erythro*-pentofuranose starting from D-xylose. The synthesis of the 3,5-cyclic thiocarbonate of 1,2-*O*-isopropylidene-α-D-*xylo*-furanose, however, with thiophosgene and dimethylaminopyridine in 1,2-dichloroethane didn't proceed so smoothly and instead gave compound **2** as the major compound.

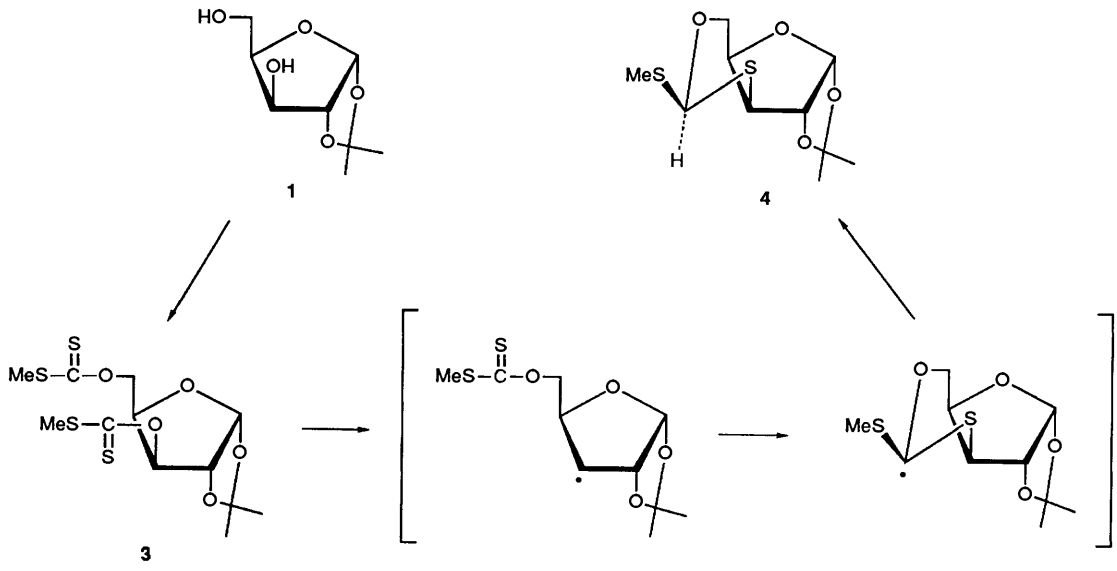
Therefore we decided to prepare the xanthates as intermediates. Since xanthates of primary alcohols require higher



1 **2**

temperatures for deoxygenation,[4] this method can also be applied to the selective removal of a secondary hydroxy group in the presence of a similarly modified primary hydroxy group by controlling the temperature of the reduction reaction, as suggested by Barton *et al.*[3,4] This method was used for the 3′-deoxygenation of thymidine, leading to 3′-deoxythymidine,[5] by using a stoicheiometric amount of Bu_3SnH. Therefore, 1,2-*O*-isopropylene-α-D-*xylo*-furanose was converted into the bis-(*S*-methyl dithiocarbonate) by reaction with carbon disulphide, NaOH, and methyl iodide. Reaction with 1.7 mol equiv. of tributyltin hydride in benzene at reflux temperature in the presence of AIBN for 2 h led to the complete disappearance of the starting material. One major compound was formed together with many minor impurities. The major compound was isolated by column chromatography in 52% yield, crystallized from MeOH, and identified as the MeS-substituted thioxane **4**. The initially formed carbon radical was cyclized by reaction with the thiocarbonyl function on the primary hydroxy group and the radical was quenched by tributyltin hydride. Only one isomer was obtained, resulting from attack at the least hindered site (Scheme 2). The structure of compound **4** was assigned by NMR and mass spectroscopy and confirmed by X-ray analysis.

This reaction demonstrates that, by making use of the difference in reactivity of a primary and a secondary hydroxy group, it is possible to synthesize the protected 1,2-*O*-isopropylidene-3-thio-α-D-*xylo*-furanose **4** from 1,2-*O*-isopropylidene-α-D-*xylo*-furanose **1** so that a hydroxy group can be replaced by a thiol group with retention of configuration. An analogous rearrangement was described by Barton and McCombie.[1] Normally, 1,2-dixanthate esters of aliphatic α-glycols yield olefins by radical elimination.[6] The reaction with bis(thiobenzoates), however, does not proceed so smoothly. A side-reaction, which was observed during the deoxygenation process of 4,6-*O*-benzylidine-2,3-bis-*O*-thiobenzoyl-α-D-*gluco*-pyranoside with an excess of tributyltin hydride in toluene at reflux, is



Scheme 3

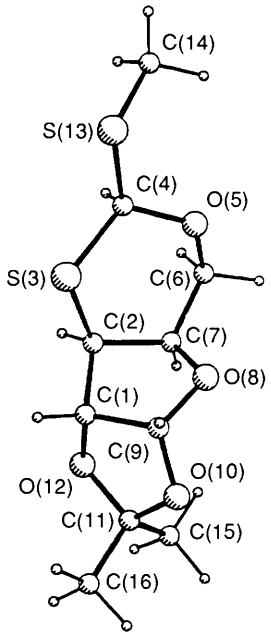


Figure 1 X-Ray molecular structure of compound **4**

Table 1 Atomic co-ordinates ($\times 10^4$) for compound **4**

	x	*y*	*z*
C(1)	457(4)	3 757(2)	5 086(2)
C(2)	1 118(3)	5 194(3)	4 933(2)
S(3)	406(1)	5 722(1)	3 917(1)
C(4)	334(4)	7 581(3)	4 089(2)
O(5)	−609(2)	7 932(2)	4 776(1)
C(6)	180(4)	7 537(3)	5 521(2)
C(7)	331(3)	5 992(2)	5 626(2)
O(8)	−1 270(3)	5 392(2)	5 707(1)
C(9)	−1 207(4)	4 001(3)	5 465(2)
O(10)	−1 294(4)	3 095(3)	6 128(2)
C(11)	262(5)	2 509(3)	6 295(2)
O(12)	1 368(3)	3 121(2)	5 725(1)
S(13)	−569(1)	8 303(1)	3 181(1)
C(14)	−43(5)	10 080(3)	3 331(2)
C(15)	785(11)	2 856(6)	7 143(3)
C(16)	139(6)	979(3)	6 149(3)

Table 2 Bond distances (Å) for compound **4**

C(2)–C(1)	1.513(3)	C(9)–C(1)	1.511(4)
O(12)–C(1)	1.421(3)	S(3)–C(2)	1.827(3)
C(7)–C(2)	1.512(3)	C(4)–S(3)	1.823(3)
O(5)–C(4)	1.400(3)	S(13)–C(4)	1.795(3)
C(6)–O(5)	1.426(3)	C(7)–C(6)	1.510(3)
O(8)–C(7)	1.437(3)	C(9)–O(8)	1.405(4)
O(10)–C(9)	1.393(4)	C(11)–O(10)	1.419(5)
O(12)–C(11)	1.425(4)	C(15)–C(11)	1.484(6)
C(16)–C(11)	1.504(4)	C(14)–S(13)	1.790(3)

Table 3 Bond angles (°) for compound **4**

C(9)–C(1)–C(2)	104.2(2)	O(12)–C(1)–C(2)	109.4(2)
O(12)–C(1)–C(9)	103.9(2)	S(3)–C(2)–C(1)	107.0(2)
C(7)–C(2)–C(1)	101.3(2)	C(7)–C(2)–S(3)	113.5(2)
C(4)–S(3)–C(2)	98.5(1)	O(5)–C(4)–S(3)	112.4(2)
S(13)–C(4)–S(3)	105.8(1)	S(13)–C(4)–O(5)	109.7(2)
C(6)–O(5)–C(4)	111.5(2)	C(7)–C(6)–O(5)	113.5(2)
C(6)–C(7)–C(2)	117.1(2)	O(8)–C(7)–C(2)	104.4(2)
O(8)–C(7)–C(6)	109.7(2)	C(9)–O(8)–C(7)	109.2(2)
O(8)–C(9)–C(1)	107.3(2)	O(10)–C(9)–C(1)	105.3(3)
O(10)–C(9)–O(8)	112.6(3)	C(11)–O(10)–C(9)	110.8(2)
O(12)–C(11)–O(10)	106.1(2)	C(15)–C(11)–O(10)	110.3(4)
C(15)–C(11)–O(12)	109.2(3)	C(16)–C(11)–O(10)	107.7(3)
C(16)–C(11)–O(12)	110.5(3)	C(16)–C(11)–C(15)	112.9(3)
C(11)–O(12)–C(1)	109.0(2)	C(14)–S(13)–C(4)	99.4(2)

the formation of a 2-phenyl thioxolane. The formation of this ring structure was also explained through reaction of the intermediate carbon radical on the thiocarbonyl function of the thiobenzoyl substituent on the adjacent secondary hydroxy group. During this reaction, a mixture of two isomers was obtained in 39% yield.

The atomic parameters of compound **4** are given in Table 1. Fig. 1 shows a view of the molecule, with the atom-numbering scheme.[7] Bond distances and angles are given in Tables 2 and 3, and torsion angles in Table 4.

Experimental

The m.p. was determined with a Büchi-Tottoli apparatus and is uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined with a JEOL FX 90A spectrometer with $SiMe_4$ as internal standard and *J*-values in Hz. Precoated Merck silica gel F254

Table 4 Torsion angles (°) (σ 1°) for compound **4**

C(9)-C(1)-C(2)-S(3)	−88
C(9)-C(1)-C(2)-C(7)	31
O(12)-C(1)-C(2)-S(3)	161
O(12)-C(1)-C(2)-C(7)	−79
C(2)-C(1)-C(9)-O(8)	−15
C(2)-C(1)-C(9)-O(10)	−135
O(12)-C(1)-C(9)-O(8)	100
O(12)-C(1)-C(9)-O(10)	−20
C(2)-C(1)-O(12)-C(11)	133
C(9)-C(1)-O(12)-C(11)	22
C(1)-C(2)-S(3)-C(4)	151
C(7)-C(2)-S(3)-C(4)	40
C(1)-C(2)-C(7)-C(6)	−158
C(1)-C(2)-C(7)-O(8)	−37
S(3)-C(2)-C(7)-C(6)	−44
S(3)-C(2)-C(7)-O(8)	77
C(2)-S(3)-C(4)-O(5)	−54
C(2)-S(3)-C(4)-S(13)	−174
S(3)-C(4)-O(5)-C(6)	70
S(13)-C(4)-O(5)-C(6)	−172
S(3)-C(4)-S(13)-C(14)	−165
O(5)-C(4)-S(13)-C(14)	73
C(4)-O(5)-C(6)-C(7)	−66
O(5)-C(6)-C(7)-C(2)	53
O(5)-C(6)-C(7)-O(8)	−65
C(2)-C(7)-O(8)-C(9)	29
C(6)-C(7)-O(8)-C(9)	156
C(7)-O(8)-C(9)-C(1)	−9
C(7)-O(8)-C(9)-O(10)	106
C(1)-C(9)-O(10)-C(11)	11
O(8)-C(9)-O(10)-C(11)	−105
C(9)-O(10)-C(11)-O(12)	2
C(9)-O(10)-C(11)-C(15)	120
C(9)-O(10)-C(11)-C(16)	−116
O(10)-C(11)-O(12)-C(1)	−16
C(15)-C(11)-O(12)-C(1)	−135
C(16)-C(11)-O(12)-C(1)	101

plates were used for TLC. Column chromatography was performed on Merck silica gel (0.063–0.200 mm).

The 3,5-*Bis*-(S-*methyl Dithiocarbonate*) *of* 1,2-O-*Isopropylidene*-α-D-*xylose compound* **3**.—To a solution of compound **1** (570 mg, 3 mmol) in dimethyl sulphoxide (10 cm^3) was added dropwise 5 mol dm^{-3} NaOH (2.7 cm^3). The brown mixture was stirred at room temperature for 20 min, and MeI (1.88 g, 13.2 mmol) was added. The reaction mixture was stirred at room temperature for another hour, dissolved in Et_2O, washed with water, dried Na_2SO_4, and evaporated. The residue was purified on a silica gel (50 g) column and eluted with Et_2O to give the title compound (820 mg, 92%), $\delta_H(CDCl_3)$ 1.34 and 1.55 (2 × 3 H, 2 × Me), 2.56 and 2.58 (6 H, 2 s, 2 × Me), 4.72–4.78 (4 H, m, 2- and 4-H, and 5-H_2) and 6.0 (2 H, m, 1- and 3-H); $\delta_C(CDCl_3)$ 18.9 and 19.1 (2 × Me), 25.9 and 26.4 (2 × Me), 69.4 (C-5), 76.2 (C-2), 82.6 (C-4), 83.7 (C-3), 104.7 (C-1) and 112.2 (CMe_2).

1,2-O-*Isopropylidene*-3-S,5-O-(*methylthiomethylene*)-3-*thio*-α-D-*xylose* **4**.—A solution of compound **3** (596 mg, 2 mmol) was refluxed with Bu_3SnH (0.9 cm^3, 3.3 mmol) and AIBN (70 mg, 0.4 mmol) in benzene (60 cm^3). After 1 h the reaction was not complete [TLC; Et_2O–hexane (1:1)] and further aliquots of Bu_3SnH (0.5 cm^3, 1.83 mmol) and AIBN (40 mg) were added. After 1 h of reflux, all starting material had disappeared. After evaporation, the crude product was purified on silica gel (60 g), and eluted with hexane followed by Et_2O–hexane (2:8). The title compound (275 mg, 52%) was obtained. The product was crystallized from MeOH, m.p. 143–144 °C; *m/z* 265 ($M^+ + 1$), 264 (M^+), 217 (M − 47, 100%) and 206 (M − 58); δ_H-($CDCl_3$) 1.32 and 1.51 (2 × 3 H, 2 × Me), 2.29 (3 H, s, Me), 3.85 (m, 3- and 5-H), 4.15 (1 H, m, 4-H), 4.39 (1 H, m, 2-H), 5.59 (1 H, s, CH) and 6.04 (1 H, d, $J_{1,2}$ 3.5, 1-H); $\delta_C(CDCl_3)$ 12.5 (Me), 26.1 and 26.4 (2 × Me), 46.6 (C-3), 68.6 (C-5), 69.5 (C-2), 82.9 (CH), 84.6 (C-4), 105.2 (C-1) and 111.7 (CMe_2).

X-*Ray Crystallography*.—D_m was not measured. A parallelepiped crystal with dimensions 0.5 × 0.2 × 0.08 mm was used. Lattice parameters were refined using 22 reflections in the range $12° \leqslant 2\theta \leqslant 49°$ on a Huber four-circle diffractometer and a Rigaku rotating anode, with graphite-monochromated Cu-Kα radiation. 2137 Independent reflections with $\sin\theta/\lambda \leqslant 0.69$ $Å^{-1}$; $-9 \leqslant h \leqslant 9$, $0 \leqslant k \leqslant 11$, $0 \leqslant l \leqslant 19$ and 2134 had $I \geqslant 2.5\sigma(I)$. A standard reflection (3,0,1) was checked every 50 reflections, no significant deviation being observed. The structure was solved by direct methods using SHELXS86.[8] H-Atoms were placed in computed positions. Anisotropic least-squares refinement[9] used *F*; H-atoms were treated as isotropic with a common refined temperature factor (*U* 0.094 $Å^2$). $w = 1/(\sigma^2 + 0.009\,53F^2)$, $R = 0.047$, $R_w = 0.052$, $S = 0.68$ for 2134 observed reflections. Final maximum shift to error was 0.01. Maximum and minimum heights in the final difference Fourier synthesis were 0.68 and −0.51 e $Å^{-3}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography.[10] At the end of the refinement, the 881 Friedel pairs of reflections present in the data set were sorted according to $w^{\frac{1}{2}}||F_c(h,k,l)| - |F_c(-h,-k,-l)||$, by decreasing magnitude. Among the first 200 pairs of reflections, the signs of 187 observed differences were consistent with the signs of the corresponding calculated differences, establishing that the molecule is described with the correct absolute configuration.*

Crystal data. $C_{10}H_{16}O_4S_2$, $M_r = 264.36$, orthorhombic, $P2_12_12_1$, $a = 8.172(1)$, $b = 9.683(1)$, $c = 16.284(2)$ Å, $V = 1288.5(3)$ $Å^3$, $Z = 4$, $D_x = 1.36$ g cm^{-3}, Cu-Kα, $\lambda = 1.541\,78$ Å, $\mu = 36.14$ cm^{-1}, $F(000) = 560$, $T = 291$ K, $R = 0.047$ for 2134 observed reflections.

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* *Supplementary data* (see section 5.6.3 of Instructions for Authors, in the January issue). Thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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