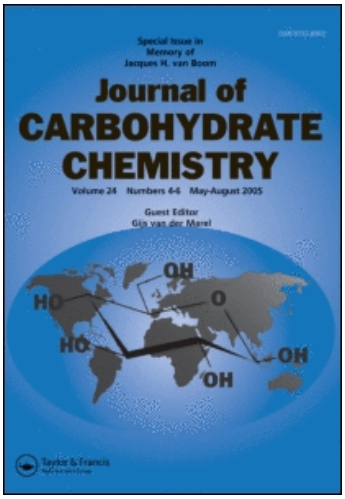

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FURANOSIDE *C*-GLYCOSIDES FROM AN *O*-METHYL PYRANOSIDE

An Unexpected ß-Hydroxy-1,3-Dithiane Rearrangement

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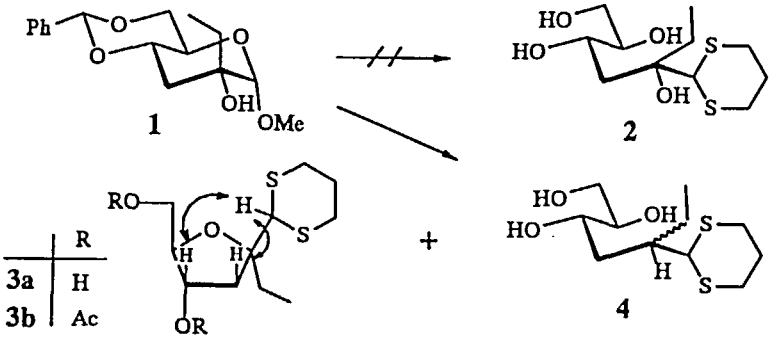
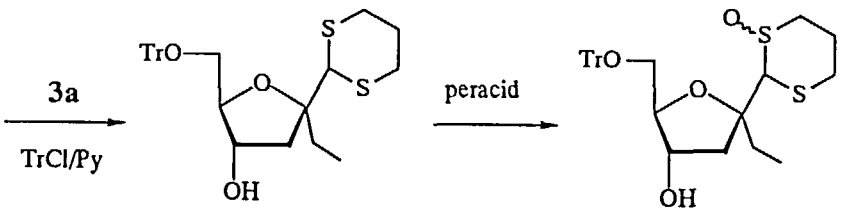
In the course of our investigations on the synthesis of enantiomerically pure anthracycline antibiotics by incorporation of chiral building blocks we prepared the *O*-methyl 3-deoxy-2-*C*-ethylribopyranoside **1**.[1] The further synthetic plan required the conversion of **1** to the dithioacetal **2** followed by glycol cleavage to a partially protected 1,4-dialdehyde for coupling experiments to leucoquinizarine in a Marschalk reaction. However, the reaction sequence failed[1] and optically active rhodomycinone had to be synthezised in a different way.[2] A reinvestigation of the synthesis revealed that the thioacetalization of **1** using the acidic conditions recommended by Corey et al.[3] did not yield the usual open chain dithioacetal **2** but rather three new unexpected products. The less polar fraction was identified by ^{1}H and ^{13}C NMR as tetrahydrofuran derivative **3a** with the dithiane ring in a ß-orientation. The solid polar fraction (12 %) consisted of a nonseparable 1:2.2 mixture of the epimeric deoxygenation products **4/5**.



The structure of the new products were elucidated by chemical transformations and from spectroscopic evidence. Acetylation of the major product **3a** to the diacetate **3b** showed the presence of only two hydroxy groups instead of the three reactive primary or secondary hydroxy groups expected for **2**. Nuclear Overhauser experiments conducted with **3a** confirmed the configuration of the less-polar product. The strong interaction of the dithiane proton at C-1 with the protons at C-3 and C-4 as depicted in formula **3a** proved the ß-orientation of the dithiane ring. Further structural evidence came from the conversion of **3a** to the monotrityl compound **6**. Subsequent oxidation of **6** with *meta*-chloroperbenzoic acid gave the corresponding monosulfoxides **7/8**. A new chiral center was created in the oxygenation step but the stereoselectivity was only 1:2.2 as deduced from the ^{1}H NMR spectrum.



6 **7/8**

All attempts to separate the epimeric mixture of the minor product failed. The complex coupling pattern was finally resolved in the 600 MHz NMR spectra. Additional 2 D COSY and Hetero-COSY experiments together with the molecular weight of M = 266 determined in the FAB mass spectra and the elemental analysis proved the deoxygenated branched arrangement of **4/5**.

The facile elimination of hydroxy groups in ß-position to dithioacetals is known, and the corresponding olefins can be isolated (see for example[4]). However, acid-catalysed addition normally occurs to the dithiane-carbon at C-1 of the dithioacetal to form spiro dithioacetals.[5] This reaction has been efficiently exploited to synthezise lactones from aldodithianes. The acid-catalysed addition to the ß-carbon to yield branched *C*-glycosides of type **3a** is unprecedented and occurs in good yield with remarkable stereoselectivity. The reaction may have synthetic importance for the construction of branched deoxy C-glycosides. The protected aldehyde functionality offers further possibilities for chain elongation and selective transformations. The pathway for the minor deoxygenation product is not yet clear. One possibility is the thiol-reduction of an intermediate cation.

In summary, acid-catalysed thioacetalysation of α-branched sugars proceeds abnormally giving rise to the formation of cyclized and reduced products. The cyclization can be exploited for the formation of branched furanoside *C*-glycosides from α-branched hexopyranosides of type **3a**.

EXPERIMENTAL

For general remarks and instrumentation see ref 1. In the ^{13}H NMR spectra the primary and tertiary carbon atoms are designed by (+), the secondary by (-), and the quarternary by (o).

2,5-Anhydro-3-deoxy-2-*C*-ethyl-D-ribo-hexose cyclic 1,3-propanediyl mercaptal (3a). 6 N HCl (36 mL) was added to a solution of **1** (4.32 g, 14.7 mmol) and propane-1,3-dithiol (7.95 g, 73.5 mmol) in chloroform in (6 mL). The mixture was stirred for 8 h at 0 °C and 12 h at 20 °C, diluted with water (100 mL) and neutralized with lead carbonate. The precipitate was filtered off and the clear solution was extraced with ethyl acetate (100 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was separated by layer chromatography (silica gel, 5 % methanol/ CH_2Cl_2) to afford from the less polar fraction oily **3a** (3.10 g, 80 %) and from the polar fraction **4/5** (469 mg, 12 %, ratio of minor to major isomer 1:2.2), mp 85 °C.

Data for 3a: $[a]^{20}D$ = + 10 ° (*c* = 0.6 in methanol); ^1H-NMR (300 MHz) δ 0.98 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.75 - 1.91 (m, 4 H, CH_2CH_3, $-CH_2-$ 3α-H), 2.12 (dt, *J* = 3.4, J_{gem} = 14.2 Hz, 1 H, $-CH_2-$), 2.64 (dd, J_{gem} = 13, $J_{3,4}$ = 8.5 Hz, 1 H, 3ß-H), 2.88 (m, 4 H, 2 CH_2S), 3.4 (broad, 2 H, OH), 3.71 (dd, J_{gem} = 11.9, $J_{5,6}$ = 3.0 Hz, 1 H, 6-H), 3.78 (dt, $J_{5,6}$ = 3.0 , $J_{4,5}$ = 7.2 Hz, 1 H, 5-H), 3.88 (dd, J_{gem} = 11.9, $J_{5,6}$ = 3.0 Hz, 1 H, 6-H), 4.32 (s, 1 H, 1-H), 4.49 (dt, $J_{3,4}$ = 8.5, $J_{4,5}$ = 7.2 Hz, 1 H, 4-H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 7.85 (+, CH_3CH_2), 25.96 (-, CH_2CH_3), 30.44 (-), 30.64 (-), 30.82 (-), 41.85 (-), 56.71 (+, 5-C), 61.80 (-, 6-C), 71.38 (+, 4-C), 84.85 (+, 1-C), 86. 28 (o, 2-C); IR ν 3450 cm^{-1} (OH), 2962, 2930, 2870, 910; UV λ_{max} (lg ε) 208 (3.18), 228 (2.91), 245 (2.96); MS (CI/ NH_3, pos) *m/z* (%) = 282 (100) $[M + NH_4]^+$, 265 (11) $[M]^+$, 192 (2), 176 (6), 159 (7), 145 (20).

Anal. Calcd for $C_{11}H_{20}O_3S_2$: Ber. C, 49.97; H, 7.63; S, 24.25. Found: C, 49.45; H, 7.58; S, 23.40.

2,3-Dideoxy-2-*C*-ethyl-arabino- and D-ribo-hexose cyclic 1,3-propanediyl mercaptal: MS (FAB, glycerine, neg: *m/z* (%) = 531 (20), $[2M - H]^-$, 357 (14) [M - H + glycerine]$^-$, 265 (100) $[M - H]^-$. (FAB, glycerine, pos): *m/z* (%) = 267 (83) $[M + H]^+$.

Anal. Calcd for $C_{11}H_{22}O_3S_2$: C. 49.59; H, 8.32; S, 24.07. Found: C, 49,45; H, 7.89; S, 23.70.

Data for major isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.78 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.26 (m, J = 7.4 Hz, 1 H, CH_2CH_3), 1.33 (ddd, J = 4.4, J = 10.1, J = 14.4 Hz, 1 H, 3-H), 1.55 (m, J = 7.4 Hz, 1 H, CH_2CH_3), 1.62 (m, 1 H, 3-H), 1.63 (m, 1 H, -CH_2-), 1.73 (m, 1 H, 2-H), 1.95 (dq, J_{gem} = 14.1 Hz, J = 2.4 Hz, 1 H, -CH_2-), 2.6 - 2.8 (m, 4 H, CH_2S), 3.38 (dt, J = 4.5, J = 4.8 Hz, 1 H, 5-H), 3.54 (m, 2 H, 6-H), 3.63 (ddd, J = 3.0, J = 4.8, J = 10.1 Hz, 1 H, 4-H), 4.16 (d, J = 3.4 Hz, 1 H, 1-H); ^{13}H NMR ($CDCl_3$, 150 MHz) δ 11.75 (+, CH_3), 24.88 (-, CH_2CH_3), 26.25 (-, -CH_2-), 30.89 (-, CH_2S), 30.96 (-CH_2S), 33.60 (-, 3-C), 41.79 (-, 2-C), 53.16 (+, 1-C), 63.00 (-, 6-C), 70.86 (+, 4-C), 74.64 (+, 5-C).

Data for minor isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.79 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.26 (m, J = 7.4 Hz, 1 H, CH_2CH_3), 1.41 (ddd, J = 2.4, J = 9.3, J = 14.3 Hz, 1 H, 3-H), 1.55 (m, J = 7.4 Hz, 1 H, CH_2CH_3), 1.61 (m, 1 H, 3-H), 1.63 (m, 1 H, -CH_2-), 1.77 (m, 1 H, 2-H), 1.95 (dq, J_{gem} = 14.1 Hz, J = 2.4 Hz, 1 H, -CH_2-), 2.6 - 2.8 (m, 4 H, CH_2S), 3.33 (dt, J = 3.9, J = 7.3 Hz, 1 H, 5-H),3.49 (m, 1 H, 4-H), 3.54 (m, 2 H, 6-H), 4.17 (d, J = 3.9 Hz, 1 H, 1-H); ^{13}H NMR ($CDCl_3$, 150 MHz) δ 11.41 (+, CH_3), 23.40 (-, CH_2CH_3), 26.15 (-, -CH_2-), 30.72 (-, CH_2S), 30.89 (-CH_2S), 34.52 (-, 3-C), 41.54 (-, 2-C), 53.45 (+, 1-C), 63.11 (-, 6-C), 70.86 (+, 4-C), 74.71 (+, 5-C).

4,6-Di-*O*-acetyl-2,5-anhydro-3-deoxy-2-*C*-ethyl-D-ribo-hexose cyclic 1,3-propanediyl mercaptal (3b). A solution of **3a** (100 mg, 0.38 mmol) in acetic anhydride (1 mL) and pyridine (2 mL) was treated with 4,4-dimethylaminopyridine (DMAP, 5 mg) at 20 °C and the mixture was stirred for 16 h. Usual workup afforded **3b** (91 mg, 70 %) as oil. ^{1}H-NMR (400 MHz) δ 0.92 (t, J = 7.3 Hz, 3 H, CH_3), 1.75 (dd, J_{gem} = 14.1, J = 3.9 Hz, 1 H, 3α-H), 1.83 (m, J = 7.3 Hz, 3 H, CH_2CH_3, -CH_2-), 2.02 (s, 3 H, CH_3CO), 2.03 (s, 3 H, CH_3CO), 2.2 (m, 1 H, -CH_2-), 2.74 (dd, $J_{3,4}$ = 8.4 Hz, 1 H, 3ß-H), 2.81 (m, 4 H, 2 CH_2S), 4.05 (dd, J = 4.7, J = 9.1 Hz, 1 H, 5-H), 4.12 (dd, J = 5.1 Hz, J_{gem} = 11.6 Hz, 1 H, 6-H), 4.28 (dd, J_{gem} = 11.6 Hz, 1 H, 6-H), 4.31 (s, 1 H, 1-H), 5.07 (m, 1 H, 4-H); ^{13}C-NMR ($CDCl_3$, 300 MHz) δ 7.86 (+, CH_3CH_2), 20.96 (+, CH_3CO_2), 25.83 (-, CH_2CH_3), 29.61 (-), 30.24 (-), 30.66 (-), 39.16 (-), 54.44 (+, 5-C), 63.95 (-, 6-C), 75.15 (+, 4-C), 81.19 (+, 1-C), 88.04 (o, 2-C) 170.24 (o, C=O), 170.80 (o, C=O); IR ν 2960 cm^{-1}, 2940, 2890, 1745, 1430, 1368, 1230, 1143, 705; MS (CI/ NH_3, pos) m/z (%) = 366 (100) [M + NH_4]$^+$, 349 (16) [M + 1]$^+$.

Anal. Calcd for $C_{15}H_{24}O_5S_2$: C, 51.70; H, 6.94; S 18.40. Found: C, 52.01; H, 6.81; S 16.79

2,5-Anhydro-3-deoxy-2-*C*-ethyl-6-*O*-(triphenylmethyl)-D-ribo-hexose cyclic 1,3-propanediyl mercaptal (6). A solution of **3a** (1.15 g, 4.4 mmol) in dry pyridine (10 mL) was treated with triphenylmethyl chloride (1.32 g, 4.7 mmol) and the mixture was stirred for 4 h at 90 °C (TLC control). The solution was poured into ice-water and extracted with dichloromethane. The organic phase was washed with a solution of ammonium chloride (10 mL) and dried (Na_2SO_4). Chromatographic separation on silica gel afforded **6** (2.34 g, 97 %) as an oil. ^{1}H-NMR (400 MHz) δ 0.95 (t, J = 7.3 Hz, 3 H, CH_3), 1.70 - 1.90 (m, 4 H, C*H*$_2$CH$_3$, -CH_2-, 3α-H), 2.04 (m, 1 H, -CH_2-), 2.65 (dd, J = 8.4, J_{gem} = 13.3 Hz, 1 H, 3ß-H), 2.79 (m, 4-H, 2 CH_2S), 3.26 (dd, $J_{5,6}$ = 6.8 Hz, J_{gem} = 9.3 Hz, 1 H, 6-H), 3.48 (dd, $J_{5,6}$ = 4.6 Hz, J_{gem} = 9.3 Hz, 1 H, 6-H), 3.82 (m, 1 H, 5-H), 4.22 (s, 1 H, 1-H), 4.29 (m, 1 H, 4-H), 7.18 - 7.47 (m, 15 H, Tr).

Anal. Calcd for $C_{30}H_{34}O_3S_2$: C, 70.93; H, 7.14; S, 12.62. Found: C, 70.58; H, 7.28; S, 11.03.

2,5-Anhydro-3-deoxy-2-*C*-ethyl-6-*O*-(triphenylmethyl)-D-ribo-hexose cyclic 1,3-propanediyl mercaptal *S*-oxide (7/8). A solution of **6** (150 mg, 0.3 mmol) in 7 mL of dry CH_2Cl_2 was treated at - 78 °C with a solution of MCPBA (1 equivalent, 55 mg) in 5 mL of CH_2Cl_2. After ca. 10 min. diethyl ether (10 mL) and an aqueous solution of sodium hydrogen carbonate (10 mL, 10 %) was added. The solution was dried (Na_2SO_4), evaporated at reduced pressure to afford **7/8** (147 mg, 96 %) as an oil. IR (KBr) ν 3460 cm^{-1} (OH), 3061, 2920, 2878, 1490, 1330, 1160, 1090, 1030, 1010, 890, 760, 700; ^{1}H-NMR (400 MHz) δ 0.98 (t, J = 7.4 Hz, CH_3), 1.04 (t, J = 7.4 Hz, CH_3), 1.66 (br, OH), 1.9 - 2.0 (m, 4 H, C*H*$_2$CH$_3$), 2.0 - 2.43 (m, -CH_2-, 3α-H), 2.4.7 - 2.73 (m, SCH_2), 2.94 (dd, J = 8.4, J = 13.3 Hz, 3ß-H), 3.26 - 3.32 (m, J = 5.7, J = 9.6 Hz, 6-H), 3.33 - 3.40 (m, CH_2SO), 3.42 - 3.48 (m, J = 4.9, J = 9.6 Hz, 6-H), 3.82 (s, 1-H), 3.83 (s, 1-H), 3.86 (dt, 5-H) 4.43 (m, 4-H), 4.54 (m, 4-H), 7.20 - 7.34 (m, Tr), 7.40 - 7.50 (m, Tr-H).

Anal. Calcd for: $C_{30}H_{34}O_4S_2$: C, 68.93; H, 6.56. Found: C, 68.98; H, 6.45.

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