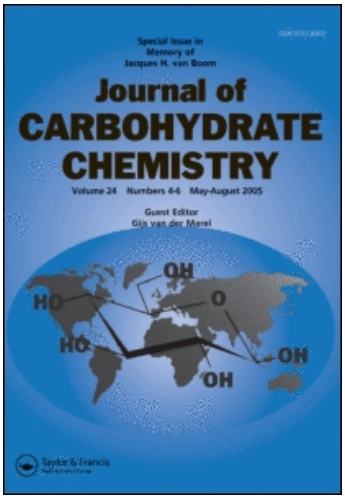

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SYNTHESIS AND CHEMICAL BEHAVIOUR OF 4,5-DIDEOXY-4,5--EPITHIO-2,3-DI-O-METHANESULFONYL-L-XYLOSE DIMETHYL ACETAL

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ABSTRACT

Selective substitution of the primary sulfonate group in 2,3,4,5-tetra-O-methanesulfonyl-D-arabinose dimethyl acetal (1) gives 5-S-acetyl-2,3,4-tri-O-methanesulfonyl--5-thio-D-arabinose dimethyl acetal (2) which is further converted into the title compound (3). Reductive desulfurization of 3 afforded deoxy dimethyl acetal derivatives 5 and 6 in a low yield. Unsaturated monosaccharide derivative 7 was obtained as the only reaction product from 3 with triphenylphosphine. Catalytic hydrogenation of 7 gave dideoxy-sugar 6 in a satisfactory yield. Finally, episulfide 3 with acetyl chloride afforded 4-chloro-4-deoxy derivative 4, which can be recycled into the starting 3.

INTRODUCTION

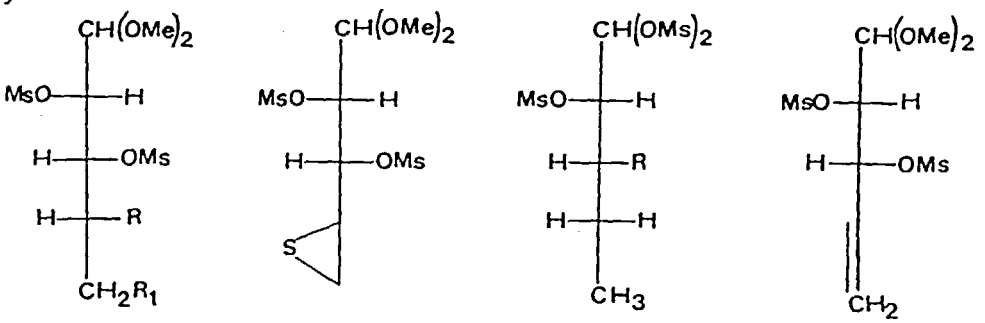
Episulfides have not frequently been used in synthetic carbohydrate chemistry. Such compounds show interesting and useful properties and could serve as convenient intermediates in the synthesis of thio-sugars,[1] unsaturated sugars,[2] and deoxysugars.[3] We have therefore carried out some preli-

minary investigations in order to produce a terminal episulfide function in acyclic multifunctionalized monosaccharide derivatives.

Preparative methods for carbohydrate episulfides have been known involving treating epoxides with thiourea[4] or thiocyanate,[5] or vicinal thioacetate-sulfonate (acetate) esters with sodium methoxide.[6] Such methods cannot be used in cases where other sensitive functional groups are present. No data could be found in the literature on the formation of carbohydrate episulfides under strongly acidic conditions, so we also studied the acid-catalyzed cyclization of the acyclic primary thioacetate derivative 2.

RESULTS AND DISCUSSION

2,3,4,5-Tetra-O-methanesulfonyl-D-arabinose dimethyl acetal (1, Scheme 1), readily available from D-arabinose diethyl dithioacetal in a two-step sequence,[7] has been used as a starting compound for the preparation of a new monosaccharide episulfide (3). A clean, regioselective substitution of the primary mesyloxy group in compound 1, using potassium thioacetate in boiling benzene in the presence of poly(dibenzo-18-crown-6-ether), gave the corresponding 5-mono-substituted derivative 2 in 68% yield.[8]



1: R=R1=OMs
2: R=OMs; R1=SAc
4: R=Cl; R1=SAc

3

5: R=H
6: R=OMs

7

Scheme 1

A ready intramolecular displacement of the 4-sulfonyloxy group in 5-S-acetyl-2,3,4-tri-O-methanesulfonyl-5-thio-D-arabinose dimethyl acetal (2) occurred in boiling methanolic hydrogen chloride to give episulfide 3 (in 83% yield). The structure of 3 is supported by characteristic signals in the ^{1}H NMR spectrum, two-proton doublet of doublets at 2.47 ppm (H-5a, $J_{4,5a}$=5 Hz, $J_{5a,5b}$=2 Hz) and 2.66 ppm (H-5b, $J_{4,5b}$=6.75 Hz). The higher field signal for methylene protons and the geminal coupling constant $J_{5a,5b}$ (2 Hz) of compound 3 indicate the terminal position of the episulfide ring. Other relevant ^{1}H NMR data are given in Experimental Section.

Reductive desulfurization of compound 3 with Raney nickel in dioxane gave (2S)-methanesulfonyloxypentanal dimethyl acetal (5) and (2S),(3R)-di-methanesulfonyloxypentanal dimethyl acetal (5) and (2S),(3R)-di-methanesulfonyloxypentanal dimethyl acetal (6) in very low yields.

However, treatment of episulfide 3 with triphenylphosphine in boiling benzene gave the terminal olefin (7) in 95% yield, which was further reduced catalytically (with Adams' platinum catalyst) in acetic acid to afford dideoxysugar 6 in 63% yield. There are two characteristic signals in the ^{1}H NMR spectrum of compound 6, a three-proton triplet at 1.05 ppm ($-CH_2-\underline{CH}_3$, $J_{4,5}$=6,5 Hz) and two-proton multiplet at 1.88 ppm ($-\underline{CH}_2-CH_3$). Other ^{1}H NMR data are also consistent with structure 6.

The so-called "abnormal" fission of the tiirane ring with acetyl chloride has been known.[9] This reaction has a preparative value, hence our interest to check whether such a transformation could be usefully applied to the synthesis of chlorodeoxysugars. The method was indeed successfully used here for the preparation of 5-S-acetyl-4-chloro-4-deoxy-2,3-di-O-methanesulfonyl-5-thio-D-arabinose dimethyl acetal (4) from episulfide 3. Thus, treatment of 3 with acetyl chloride at room temperature (for 24 hours) gave compound 4 in 76% yield. The structure of 4 was confirmed chemically and spectroscopically. When 4 was treated with methanolic

sodium hydrogen carbonate at room temperature, or with boiling methanolic hydrogen chloride, it was cleanly recycled into the starting episulfide 3.

EXPERIMENTAL

General Procedures. IR Spectra have been recorded with a Perkin-Elmer 457 spectrophotometer and band positions (ν_{max}) are given in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded with a Bruker WP 200 SY instrument in $CDCl_3$ solutions with tetramethylsilane as an internal standard. Mass spectra were recorded on A.E.I. MS9 spectrometer and MS-902 mass spectrometer (70 eV, 190 °C, first number denotes m/e value, while ion abundances are given in parentheses). Melting points were determined using a Büchi SMP-20 apparatus and were not corrected. Optical rotations were measured on Polamat A (Karl Zeiss-Jena) polarimeter in chloroform solutions at 25 °C. TLC was performed on "DC-Alufolien Kieselgel 60" (Merck). Column chromatography was performed on silica gel 60 (70-200 mesh).

5-S-Acetyl-2,3,4-tri-O-methanesulfonyl-5-thio-D-arabinose dimethyl acetal (2). 2,3,4,5-Tetra-O-methanesulfonyl--D-arabinose dimetyl acetal (1)[7] (1.07 g, 2.09 mmol), potassium thioacetate (0.31 g, 2.71 mmol), poly(dibenzo--18-crown-6-ether) (1.5 g) and dry benzene (50 mL) were stirred and refluxed for 12 h. After filtration and removal of solvent in vacuum, a brown oil remained. Upon fast chromatographic purification on a column of silica gel (60 g, benzene--acetone 98:2, 95:5), the pure compound 2 was obtained (0.7 g, 68.32%), as a yellow syrup, $[\alpha]_D$ +49.97° (c 2.315); IR (film) 1690 (C=O from SAc), 1350 (as S=O), 1180 (sym S=O); ^1H NMR δ 2.37 (s, 3H, CH_3 from SAc), 3.12, 3.20 and 3.22 (3s, 9H, $3CH_3SO_2$), 3.25 (dd, 1H, $J_{4,5a}$=8.5 Hz, $J_{5a,5b}$=14.5 Hz, H-5a), 3.36 (dd, 1H, $J_{4,5b}$=4.75 Hz, H-5b), 3.52 and 3.57 (2s, 6H, $2OCH_3$), 4.67 (d, 1H, $J_{1,2}$=3.75 Hz, H-1), 4.82 (dd, 1H, $J_{2,3}$=7 Hz, H-2), 5.07 (ddd, 1H, $J_{3,4}$=2,25 Hz, H-4), 5.25 (dd, 1H, H-3); ^{13}C NMR δ 28.51 (C-5), 30.30

($\underline{C}H_3COS$), 38.72, 39.06 and 39.37 (3 $\underline{C}H_3SO_2$), 56.14 and 57.34 ($2O\underline{C}H_3$), 76.90, 77.94 and 78.43 (C-2, C-3 and C-4), 103.49 (C-1), 128.25 ($CH_3\underline{C}OS$); FAB MS 488.2 (M^+; 22), 458.1 (M^++M-MeO; 14), 75.3 ($CH(OMe)_2$; 100).

Starting material was also recovered (0.225 g, 21%); mp 108 °C (from dichloromethane-hexane).

4,5-Dideoxy-4,5-epithio-2-3-di-O-methanesulfonyl-L-xylose dimethyl acetal (3). A solution of 2 (0.7 g, 1.432 mmol) in dry methanol (35 mL) and concd hydrochloric acid (2.8 mL) was refluxed for 2 h, cooled and poured into a saturated solution of $NaHCO_3$ (600 mL). The resulting suspension was extracted with chloroform (4 x 25 mL), the combined extracts were washed with water (to pH 6-7) and dried (Na_2SO_4). After removal of solvent, a yellow oil remained (0.65 g). The syrup was crytallized from diisopropyl ether affording a pure product 3 as colourless crystals, mp 79-80 °C (0.42 g, 83%). On recrystallization from diisopropyl ether an analytical sample of 3 was obtained in the form of needles; mp 96-98 °C: $[\alpha]_D$ +36.76° (c 4.35); ^{1}H NMR δ 2.475 (dd, 1H, $J_{4,5}$=5 Hz, $J_{5a,5b}$=2 Hz, H-5a), 2.66 (dd, 1H, $J_{4,5b}$=6.75 Hz, H-5b), 3.16 and 3.18 (2s, 6H, 2 CH_3SO_2), 3.3 (ddd, 1H, $J_{3,4}$=8.5 Hz, H-4), 3.50 and 3.52 (2S, 6H, $2OCH_3$), 4.55 (dd, 1H, $J_{2,3}$=3.75 Hz, H-3), 4.63 (d, 1H, $J_{1,2}$=5.75 Hz, H-1), 4.72 (dd, 1H, H-2); ^{13}C NMR δ 22.85 (C-5), 33.36 (C-4), 39.01 and 39.92 (2 $\underline{C}H_3SO_2$ 55.45 and 56.79 (2 $O\underline{C}H_3$), 80.54 (C-3), 83.39 (C-2), 102.59 (C-1); FAB MS 319 (M^+-OMe; 100).

Anal. Calcd for $C_9H_{18}O_8S_3$: C, 30.84; H, 4.90; S, 27.41. Found: C, 31.03; H, 5.14; S, 26.67.

Desulfurizatin of 3. The episulfide 3 (0.22 g, 0,63 mmol) and Raney nickel (ca 1.5 mL) were stirred in dioxane under a hydrogen atmosphere for 24 h. Filtration and evaporation gave a colourless oil (0.023 g). Chromatography on a column of silica gel (5 g, benzene-acetone 95:5) afforded 5 (0.002 g, 1.4%) and 6 (0.008 g, 4%), $[\alpha]_D$ +2.18 (c 0.78). Comparison of NMR spectra and $[\alpha]_D$ values proved the product to be identical to compound 6 which was described earlier.

5-S-Acetyl-4-chloro-4-deoxy-2,3-di-O-methanesulfonyl--5-thio-D-arabinose dimetyl acetal (4). A solution of 3 (0.205 g, 0.59 mmol) in acetyl chloride (2 mL) was left at room temperature for 24 h. After addition of ice (20 g), the reaction mixture was neutralized with a solution of $NaHCO_3$ to pH 7-8. The resulting suspension was extracted with methylene chloride (3 x 10 mL) and the combined extracts were washed with water (to pH 6-7), dried (Na_2SO_4) and concentrated, whereupon a crude product 4 remained as a syrup (0.31 g). After rapid chromatographic purification of the syrup on a column of silica gel (15 g) with benzene--acetone (98:2), 4 (0.19 g, 75.74%) was obtained as a colourless syrup: $[\alpha]_D$ -27.86 (c 2.26); IR (film) 1700 (C=O from SAc): ^{1}H NMR δ 2.43 (s, 3H, SAc), 3.20 and 3.23 (2s, 6H, $2CH_3SO_2$), 3.48 and 3.51 (2s, 6H, $2OCH_3$), 3.68 (dd, 1H, $J_{5a,5b}$=11.3 Hz, $J_{4,5a}$=5.1 Hz, H_{5a}), 3.84 (dd, 1H, $J_{4,5b}$=9.5 Hz, H-5b), 4.14 (ddd, 1H, $J_{4,3}$=2.2 Hz, H-4), 4.49 (d, 1H, $J_{1,2}$=3.65 Hz, H-1), 4.82 (dd, 1H, $J_{2,3}$=7,7 Hz, H-2), 5.46 (dd, 1H, H-3); ^{13}C NMR 30.60 (CH_3COS), 38.92 and 39.16 ($2CH_3SO_2$), 43.90 (C-5), 46.73 (C-4), 55.75 and 56.83 ($2OCH_3$), 75.67 and 78.37 (C-3 and C-2), 102.91 (C-1); MS m/e: 355 (indicated Cl; 1.4), 353 (M^+-SAc or $(CH_3O)_2CH$; 2.9), 318 (353-Cl; 4.8), 258 (353-MsO; 39), 165 (indicated Cl, 45), 163 (258-MsO; 92).

Methanolysis of 4. (a) A solution of 4 (0.1 g, 0.23 mmol) in dry methanol(3 mL) and concd hydrochloric acid (0.03 mL) was refluxed for 2 h. Using the same work-up procedure as described from compound 2, crude compound 3 was obtained as white crystals (0.05 g, 55%), mp 96 °C.

(b) A suspension of 4 (0.025 g, 0.05 mmol) and $NaHCO_3$ (0.05 g) in methanol (3 mL) was stirred at room temperature for 3 h. After filtration and concentration to dryness, the resulting syrup was extracted with hot diisopropyl ether.

Compound 5: ^{1}H NMR δ 0.967 (t, 3H, $C_{(5)}H_3$), 1.32-1.72 (m, 4H, $C_{(3)}H_2$ and $C_{(4)}H_2$), 3.07 (s, 3H, CH_3SO_2), 3.44 and 3.45 (2s, 6H, $2OCH_3$), 4.35 (d, 1H, $J_{1,2}$=5 Hz, H-1), 4.63 (m, 1H, H-2).

Compound 6: ^{1}H NMR δ 1.05 (t, 3H, $J_{4,5}$=6.5 Hz, $C_{(5)}H_3$), 1.887 (qd, 2H, $C_{(4)}H_2$), 3.1 and 3.15 (2s, 6H, $2CH_3SO_2$), 3.48 and 3.51 (2s, 6H, $2OCH_3$), 4.57 (d, 1H, $J_{1,2}$=6.25 Hz, H-1), 4.67 (dd, 1H, $J_{2,3}$=3 Hz, H-2), 4.93 (ddd, 1H, $J_{3,4a}=J_{3,4b}$=6.5 Hz, H-3); ^{13}C NMR δ 9.08 (C-5), 24,80 (C-4), 39.07 ($2CH_3SO_2$), 54.93 and 55.82 ($2O\underline{C}H_3$), 79.28 and 80.54 (C-2 and C-3), 102.43 (C-1); FAB MS 319 (M^+-H; 5), 289 (M^+-OMe; 31), 193 (M^+-MeO-MsOH; 100), 97 (M^+-MeO- 2MsOH; 65).

(2S),(3R)-Bis[methanesulfonyloxy]pent-4-enal dimethyl acetal (7). A solution of 3 (0.08 g, 0.23 mmol) and triphenylphosphine (0.089 g, 0.34 mmol) in dry benzene (2 mL) was stirred under reflux for 6.5 h. The product was purified by chromatography on a column of silica gel (5 g) first with benzene as the eluent followed by benzene-acetone (98:2; 95:5) to give 7 (0.069 g, 94.5%) as a syrup, $[\alpha]_D$ -5.7° (c, 2.98); ^{1}H NMR δ 3.00 and 3.15 (2s, 6H, $2CH_3SO_2$), 3.48 and 3.54 (2s, 6H, $2OCH_3$), 4.53 (d, 1H, $J_{1,2}$=6 Hz, H-1), 4.67 (dd, 1H, $J_{2,3}$=4 Hz, H-2), 5.33 (dd, 1H, $J_{3,4}$=7.5 Hz, H-3), 5,56 (dd, 1H, $J_{4,5a}$=10.25 Hz, $J_{5a,5b}$=3 Hz, H-5a), 5.62 (dd, 1H, $J_{4,5b}$=17.25 Hz, H-5b), 5.99 (ddd, 1H, H-4); ^{13}C-NMR δ 39.21 and 39.69 ($2\underline{C}H_3SO_2$), 55.04 and 56.50 ($2O\underline{C}H_3$), 80.32 and 80.56 (C-2 and C-3), 102.37 (C-1), 122.37 (C-5), 131.07 (C-4); FAB MS 317 (M^+-H; 3.6), 287 (M^+-OMe; 9.1), 191 (M^+-OMe-MsOH; 15).

Hydrogenation of Olefin 7. A mixture of 7 (0.152 g, 0.48 mmol) in acetic acid (1.5 mL) was hydrogenated in the presence of PtO_2 (0.017 g) at atmospheric pressure for 4 h. The catalyst was filtered off and washed with 1:1 chloroform-toluene. The filtrate and washings were combined and concentrated under reduced pressure(<30 °C) to dryness and purified on a silica gel column (15 g) with benzene-acetone (95:5) to give 6 (0.097 g, 63.41%) as a colourless syrup.

Compound 3 was obtained as white needles (0.005 g, 22%), mp 96 °C and its IR spectrum was the same as that obtained from authentic 3.

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