An Alternative Synthesis of Anomeric Methyl 2-Deoxy-4-thio-D-*erythro*-pentofuranosides

Yun-Lung Fu and Miroslav Bobek*

Department of Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Institute, Buffalo, New York 14263

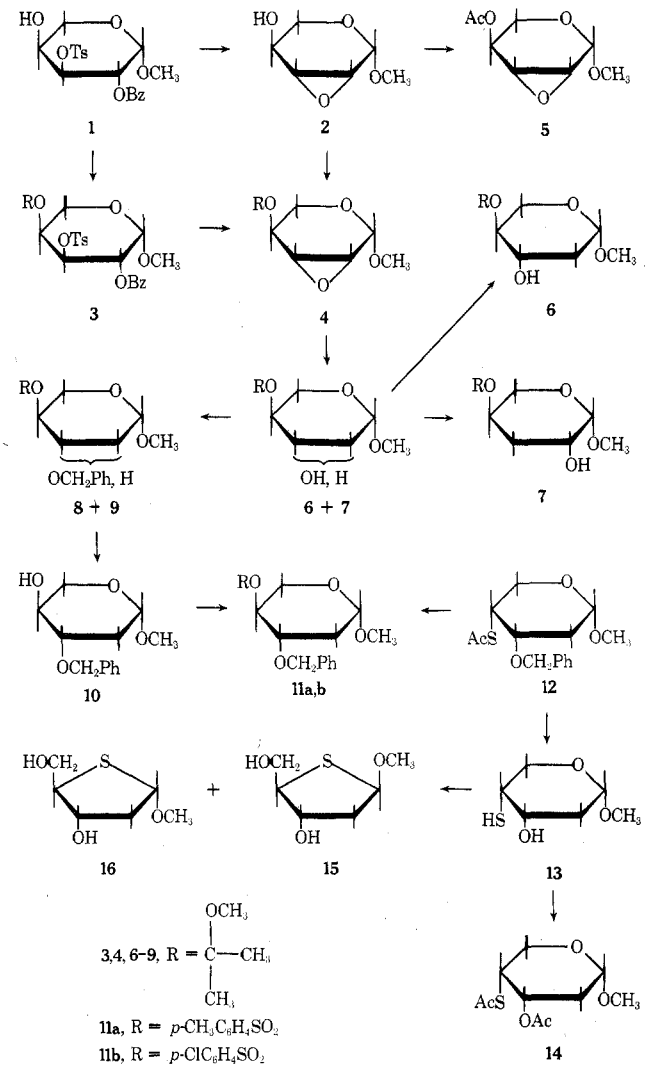
Received May 24, 1976

The anomeric methyl 2-deoxy-4-thio-D-*erythro*-pentofuranosides (**15, 16**), which are useful precursors for the synthesis of 2′-deoxy-4′-thionucleosides, were prepared from the readily available methyl 2-*O*-benzyl-3-*O*-tosyl-β-L-arabinopyranoside (**1**). Successive treatment of **1** with sodium methoxide and 2-methoxypropene–HCl gave methyl 2,3-anhydro-4-*O*-(2-methoxyisopropyl)-β-L-lyxopyranoside (**4**). Opening the anhydro ring in **4** with $LiAlH_4$ furnished, in high yield, a 12:1 mixture of the 2-deoxy (**6**) and 3-deoxy (**7**) acetals. Benzylation of **6** with benzyl bromide–sodium hydride and acetic acid hydrolysis gave methyl 3-*O*-benzyl-2-deoxy-β-L-*threo*-pentopyranoside (**10**). Tosylation or *p*-chlorobenzenesulfonylation of **10**, followed by nucleophili displacement of the tosyloxy or *p*-chlorobenzensulfonyloxy groups with potassium thioacetate, afforded methyl 3-*O*-benzyl-4-*S*-acetyl-4-thio-2-deoxy-α-D-*erythro*-pentopyranoside (**12**). Treatment of **12** with sodium–NH_3 gave methyl 4-thio-2-deoxy-α-D-*erythro*-pentopyranoside (**13**), which was converted to a mixture of α and β anomers (**15, 16**) of methyl 2-deoxy-4-thio-D-*erythro*-pentofuranoside by acid methanolysis.

The preparation of anomeric methyl 2-deoxy-4-thio-D-*erythro*-pentofuranosides (**15, 16**) has been described by Nayak and Whistler.[1,2] The synthesis, which starts from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and comprises 15 steps, does not readily lend itself to the preparation of the relatively large amounts of the sugar intermediate needed for the synthesis of nucleosides. We have, therefore, developed a shorter route to the synthesis of **15** and **16**.

The readily available starting material, methyl 2-*O*-benzoyl-3-*O*-*p*-toluenesulfonyl-β-L-arabinopyranoside (**1**), was prepared from methyl 2-*O*-benzoyl-β-L-arabinopyranoside by a slight modification of the procedure of Reist et al.[3] It has been reported that compound **1** when treated with 2 mol of sodium methoxide in methanol at room temperature for 18 h gives an 80% yield of semicrystalline methyl 2,3-anhydro-β-L-lyxopyranoside[3] (**2**). In addition, Buchanan and Fletcher[4] showed that treatment of the 4-*O*-acetyl derivative of **1** with 3 mol of sodium methoxide in methanol at room temperature for 6 h gave a 1:5.6 mixture of methyl 3,4-anhydro-β-L-arabinopyranoside and **2** in 61% yield; formation of the second epoxide derivative is thought to be due to migration of the epoxide. By modifying the reaction conditions, we were able to obtain a nearly quantitative yield of **2**. Acetylation of **2**, using acetic anhydride in pyridine, produced crystalline methyl 2,3-anhydro-4-*O*-acetyl-β-L-lyxopyranoside (**5**) in quantitative yield. Treatment of compound **2** in a chloroform–benzene solution with 2-methoxypropene,[5] in the presence of a catalytic amount of hydrogen chloride, gave methyl 2,3-anhydro-4-*O*-(2-methoxyisopropyl)-β-L-lyxopyranoside (**4**) in 94% yield. For large-scale preparations of **4**, it was more advantageous to introduce the acetal protecting group into **1**, and subsequent treatment with sodium methoxide produced compound **4** in almost a quantitative yield. The NMR spectrum of **4** showed a singlet corresponding to two *C*-methyl groups and two singlets for two *O*-methyl groups. The signal for the anomeric proton appeared in the spectrum as a doublet at δ 4.93.

Anhydro-ring opening of **4** with lithium aluminum hydride in ether gave a 94% yield of a 12:1 mixture of 2-deoxy and 3-deoxy acetals **6** and **7** which were separated by silica gel chromaography. The structures of **6** and **7** were established on the basis of their NMR spectra which gave signals for two *C*-methyl and two *O*-mthyl groups, and signals for the anomeric protons of **6** (d of d, $J_{1-2,2'}$ = 2.7 and 7.4 Hz) and **7** (d, $J_{1,2}$ = 3 Hz). It is interesting to note that compound **4** underwent $LiAlH_4$ reduction predominantly at C-2, possibly due to steric hindrance of the large vicinal trans acetal group. For large-scale preparation, separation of **6** and **7** can be omitted. Benzylation of the crude mixture of **6** and **7** with benzyl bromide–sodium hydride in dioxane, or benzyl bromide–sodium hydride in Me_2SO, followed by mild acetic acid hydrolysis of the protecting acetal group, gave a mixture of methyl 3-*O*-benzyl-2-deoxy-β-L-*threo*-pentopyranoside (**10**) and methyl 2-*O*-benzyl-3-deoxy-β-L-*threo*-pentopyranoside, from which **10** was separated by fractional crystallization in 63 and 72% overall yield, respectively. No attempt was made to increase the yield of **10** by separation of mother liquors because of the



close similarity of R_f of **10** and its 3-deoxy isomer. Treatment of **10** with *p*-toluenesulfonyl or *p*-chlorobenzenesulfonyl chloride in a chloroform–pyridine solution afforded methyl 2-deoxy-3-*O*-benzyl-4-*O*-(*p*-toluenesulfonyl)-β-L-*threo*-pentopyranoside (**11a**) or methyl 2-deoxy-3-*O*-benzyl-4-*O*-(*p*-chlorobenzenesulfonyl)-β-L-*threo*-pentopyranoside (**11b**), respectively, in almost quantitative yields.

Nucleophilic displacement of the secondary *p*-toluenesulfonyloxy group with thioacetate[1,2,6,7] has been widely used for the introduction of the thio groups into sugars. When polar and steric effects in the reacting systems are unfavorable, the reaction requires relatively high temperatures to proceed and may be accompanied by undesirable side reactions. Because the leaving capability of the arenesulfonyloxy group in nucleophilic displacement reactions increases with increasing electron-withdrawing power of the substituents on the phenyl ring,[8-10] the readily available *p*-chlorobenzenesulfonate should have a rate advantage over the corresponding tosylate. Displacement of *p*-bromobenzenesulfonate or *p*-nitrobenzenesulfonate, which are also better leaving groups than is the tosylate, with thioacetate may be complicated by aromatic ring substitution; these groups have been shown to undergo aromatic ring substitution in displacement reactions with sodium azide[10] and dimethylamine.[11] Comparison of **11a** to **11b** in the reaction with potassium thioacetate showed that while the tosyloxy group required 110–117 °C and 24 h for its displacement, the *p*-chlorobenzenesulfonyl group could be displaced at 75–80 °C in 16 h. The yield of methyl 3-*O*-benzyl-4-*S*-acetyl-4-thio-2-deoxy-α-D-*erythro*-pentofuranoside (**12**) from **11b** was 66% as compared with a 45% yield of **12** obtained from **11a** where the tosyl group was used. Deblocking of the benzyl protecting group with concurrent removal of the acetyl group in **12**, using sodium in liquid NH_3, gave a syrupy methyl 4-thio-2-deoxy-α-D-*erythro*-pentopyranoside (**13**). The ir spectrum of **13** showed no absorption bands corresponding to the benzyl and thio acetyl groups. The presence of the mercapto group was indicated by a positive nitroprusside reaction[12,13] and the absorption band at 2570 cm^{-1} in the ir spectrum of **13**. Proof that **13** was not a "dimer" was further substantiated by preparation of its di-*O*-acetyl derivative **14**. The NMR spectrum of **14** gave signals for the *O*-acetyl and *S*-acetyl groups. The presence of the *S*-acetyl group was also shown by a characteristic absorption band at 1695 cm^{-1} in the ir spectrum of **14**. Acid methanolysis of **13** at a reflux temperature afforded a mixture of α and β anomers of methyl 2-deoxy-4-thio-D-*erythro*-pentofuranosides (**15** and **16**) in 96% yield.

Experimental Section

Melting points were determined on a Thermolyne, No. MP-126000 melting point apparatus and are not corrected. The NMR spectra were recorded on a Varian A-60 or XL-100 spectrometer using Me_4Si as the internal standard. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer. Optical rotation data were determined on a Perkin-Elmer 141 polarimeter. Solvents were removed under reduced pressure on a Buchler rotary evaporator. Thin layer chromatography was performed on precoated plastic sheets (silica gel N-HR/UV_{254}, Brinkman Instruments, Inc.), in the following solvent systems: (A) benzene–acetone (9:1); and (B) chloroform–methanol (10:1). The spots were detected by uv absorbance or by spraying the sheets with 10% (v/v) sulfuric acid–ethanol and heating. Column chromatography was run on silica gel (J.T. Baker No. 3405). Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J.

Methyl 2-*O*-Benzoyl-3-*O*-(*p*-toluenesulfonyl)-β-L-arabinopyranoside (1). The following procedure was a modification of the method reported by Reist et al.[3] Methyl 2-*O*-benzoyl-β-L-arabinopyranoside (60 g, 0.224 mol) in pyridine (200 ml) was cooled below −10 °C. To this solution was added dropwise with stirring and continued cooling a solution of *p*-toluenesulfonyl chloride (45.2 g, 0.236 mol) in anhydrous pyridine (200 ml), precooled to 0 °C. The reaction mixture was stirred at 0 °C for 16 h and then at room temperature for 7 h. TLC (solvent A) showed four spots corresponding to starting material, 3,4-di-*O*-tosyl derivative, 3-*O*-tosyl derivative **1**, and presumably the 4-*O*-tosyl derivative of methyl 2-*O*-benzoyl-β-L-arabinopyranoside. The reaction was stopped by the dropwise addition of ice–water (800 ml) with stirring. The mixture was then stirred at room temperature for 16 h. The precipitate, which contained largely the ditosyl byproduct and some **1** was filtered and the filtrate was extracted with chloroform (4 × 200 ml). The chloroform extract was washed with dilute hydrochloric acid, water, saturated sodium bicarbonate solution, and water. After drying (Na_2SO_4), it was evaporated to a syrup. Crystallization twice from methanol gave 48 g of **1**, mp 112.5–112.7 °C (lit.[3] 111–113 °C).

Fractional crystallization of the precipitate portion from ethanol gave an additional 6 g of **1**, the total yield of **1** being 54 g (57.5%).

Methyl 2,3-Anhydro-β-L-lyxopyranoside (2). A chloroform (50 ml) solution of methyl 2-*O*-benzoyl-3-*O*-(*p*-toluenesulfonyl)-β-L-arabinopyranoside (**1**, 21 g, 49.8 mmol) was diluted with benzene (200 ml) and the solution was then cooled to 0 °C. To this solution was added with stirring a precooled (0 °C) solution of sodium methoxide in methanol (50 ml containing 1.2 g, 52 mmol of sodium). The reaction mixture was kept at room temperature and the progress of the reaction was followed by TLC (solvent A). After completion of the reaction (4 h), the white precipitate (sodium *p*-toluenesulfonate) was filtered and washed with benzene and ether. The combined filtrate and washings were concentrated to a syrup. Methyl benzoate was removed at 40 °C (10^{-2} mmHg). Methyl 2,3-anhydro-β-L-lyxopyranoside (**2**) crystallized readily from ethyl acetate–petroleum ether as long needles (7.15 g, 98%): mp 71–72 °C (lit. 65–66,[4] 70–70.5 °C[3]); NMR (acetone-d_6) δ 3.37 (s, 3 H, OCH_3), 4.85 (d, 1 H, $J_{1,2}$ = 3 Hz, H-1).

Methyl 4-*O*-Acetyl-2,3-anhydro-β-L-lyxopyranoside (5). Compound **2** (2.54 g) was acetylated overnight at room temperature using pyridine (50 ml) and acetic anhydride (10 ml). The excess acetic anhydride was decomposed by addition of methanol. The reaction mixture was poured into ice water and extracted with benzene (3 × 50 ml). The benzene solution was washed successively with cold dilute hydrochloric acid, water, sodium bicarbonate solution, and water. It was dried (Na_2SO_4) and concentrated to a syrup which crystallized slowly on storing in a desiccator over P_2O_5: mp 30–31 °C; $[\alpha]^{25}D$ +92.8° (*c* 1.0, $CHCl_3$) lit.[4] $[\alpha]D$ +81.7°); NMR ($CDCl_3$) δ 2.14 (s, 3 H, $CH_3C{=}O$), 3.46 (s, 3 H, OCH_3), 3.37–4.00 (4 H, H-2, H-3, and H-5), 4.95 (d, 1 H, $J_{1,2}$ = 3.0 Hz, H-1), 5.08 (br s, 1 H, H-4).

Methyl 2-*O*-Benzoyl-3-*O*-*p*-toluenesulfonyl-4-*O*-(2-methoxyisopropyl)-β-L-arabinopyranoside (3). Compound **1** (41 g) was dissolved in a mixture of alcohol-free chloroform (100 ml) and anhydrous benzene (100 ml) with stirring. To this solution was added 2-methoxypropene (50 g) followed by 5 drops of chloroform saturated with gaseous hydrogen chloride. After 1 h at room temperature, the reaction was completed as shown by TLC (solvent A). The reaction mixture was neutralized by the addition of triethylamine (1 ml) and concentrated to a syrup. On addition of absolute ethanol, **3** crystallized readily, mp 118–119 °C. The yield was quantitative: $[\alpha]^{25}D$ +198.3° (*c* 2.9, $CHCl_3$); NMR ($CDCl_3$) δ 1.41 (s, 6 H, 2 CCH_3), 2.29 (s, 3 H, tosyl CH_3), 3.30 and 3.33 (two s, 6 H, 2 OCH_3), 3.77 (m, 2 H, H-5), 4.35 (m, 1 H, H-4), 4.88–5.63 (m, 3 H, H-1, H-2, and H-3), 6.98–7.88 (m, 9 H, aromatic). Anal. Calcd for $C_{24}H_{30}O_9S$: C, 58.3; H, 6.11; S, 6.48. Found: C, 58.1; H, 6.1; S, 6.6.

Methyl 2,3-Anhydro-4-*O*-(2-methoxyisopropyl)-β-L-lyxopyranoside (4). A. From 3. Compound **3** (51 g, 0.103 mol) was dissolved in anhydrous benzene (500 ml) and the solution was cooled to 0 °C. To this solution was added with stirring a methanolic sodium methoxide solution (2.5 g, 0.109 mol of sodium in 125 ml of anhydrous methanol) which was precooled to 0 °C. The reaction mixture was kept at room temperature for 5 h. The precipitate (sodium tosylate) was filtered and washed with anhydrous benzene. The combined filtrate and washings were evaporated to a syrup, redissolved in benzene (1 l.), washed with a small amount of water (50 ml) saturated with sodium chloride, and evaporated to a syrup. Methyl benzoate was removed at 40 °C (10^{-2} mmHg). The product crystallized as white needles during the evaporation: mp 48.5–49 °C; yield 21.7 g (96.5%); $[\alpha]^{25}D$ +56.5° (*c* 3.3, $CHCl_3$); NMR ($CDCl_3$) δ 1.42 (s, 6 H, 2 CCH_3), 3.26 and 3.45 (two s, 6 H, 2 OCH_3), 4.93 (d, 1 H, $J_{1,2}$ = 2.2 Hz, H-1). Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.0; H, 8.31. Found: C, 54.8; H, 8.4.

B. From 2. Compound **2** (7.3 g, 0.05 mmol) was dissolved in alcohol-free chloroform (20 ml) and anhydrous benzene (10 ml). To this solution was added 2-methoxypropene (10 g) and a drop of chloroform saturated with hydrogen chloride gas. After 1 h at room temperature, triethylamine (1 ml) was added and the solution was evaporated to a syrup at a bath temperature below 25 °C. The syrup was dissolved in absolute alcohol and cooled to 0 °C to give **4** as long needles (10.3 g, 94%), mp 47–48 °C.

Methyl 2-Deoxy-4-*O*-(2-methoxyisopropyl)-β-L-*threo*-pentopyranoside (6) and Methyl 3-Deoxy-4-*O*-(2-methoxyisopropyl)-β-L-*threo*-pentopyranoside (7). Lithium aluminum hydride (9 g) was suspended in anhydrous ether (500 ml) in a 2-l. three-necked round-bottomed flask which was equipped with a stirrer, a dropping funnel, and a reflux condenser. To the stirred suspension was added dropwise a solution of **4** (21.8 g, 0.1 mol) in anhydrous ether (500 ml) in such a way as to produce gentle refluxing. After 3 h, TLC (solvent A) showed that the starting material disappeared. The excess hydride was decomposed by the dropwise addition of ethyl acetate followed by water. The white precipitate was filtered and washed thoroughly with ethyl ether. To the combined filtrates was added solid sodium chloride (20 g) and the mixture was extracted with benzene (4 × 100 ml). The benzene extract was evaporated to give a crude syrupy mixture of **6** and **7** (20.8 g, 94.4%). A portion (2 g) of this mixture was separated by chromatography on a dry silica gel column, eluted with a benzene–ethyl acetate–triethylamine (10:1:1) mixture to give syrupy products **6** (1.8 g) and **7** (0.15 g). For **6**: NMR (acetone-d_6) δ 1.35 (s, 6 H, 2 CCH_3), 3.21 and 3.35 (two s, 6 H, 2 OCH_3), 4.48 (d of d, 1 H, $J_{1-2,2'}$ = 2.7 and 7.4 Hz, H-1). Anal. Calcd for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 55.9; H, 9.1. For **7**: NMR (acetone-d_6) δ 1.30 (s, 6 H, 2 CCH_3), 3.2 and 3.35 (two s, 6 H, 2 OCH_3), 4.52 (d, 1 H, $J_{1,2}$ = 3 Hz, H-1). Anal. Calcd for $C_{10}H_{20}O_5 \cdot \frac{1}{4}C_6H_6$: C, 57.60; H, 9.03. Found: C, 57.7; H, 8.9.

Methyl 2-Deoxy-3-*O*-benzyl-β-L-*threo*-pentopyranoside (10). A. By Benzylation of 6 and 7 with Benzyl Bromide–Sodium Hydride in Dioxane. To a crude mixture of **6** and **7** (20.75 g), dissolved in freshly distilled dioxane (250 ml), was added sodium hydride (20 g of 50% oil dispersion, washed with anhydrous ethyl ether and dried under reduced pressure) and the reaction mixture was stirred at room temperature under nitrogen overnight. To this cooled (5 °C) reaction mixture was added dropwise benzyl bromide (10 ml) with stirring and cooling. The reaction mixture was kept at room temperature for 24 h and cooled to 5 °C, and more prewashed sodium hydride (10 g) followed by benzyl bromide (10 ml) was added. This procedure was repeated two more times at 24-h intervals. After 7 days, when the reaction was completed as shown by TLC (solvent A), triethylamine (30 ml) was added to the reaction mixture to convert the excess benzyl bromide into quaternary amine salt and the excess sodium hydride was decomposed by addition of water while the reaction mixture was kept cool by an ice–water bath. The mixture was saturated with solid sodium chloride and extracted with benzene (4 × 300 ml). The benzene solution was dried (Na_2SO_4) and concentrated at a bath temperature of 30 °C to a syrup. The syrup was dissolved in 80% acetic acid (50 ml) and stirred at room temperature for 10 min. The reaction mixture was evaporated to a syrup which was coevaporated with toluene to remove residual acetic acid. Fractional crystallization of the residue from benzene–cyclohexane gave 14.2 g (63.3%) of **10** as white needles, mp 73–73.5 °C, $[\alpha]^{25}D$ +95.9° (*c* 1.0, $CHCl_3$).

B. By Benzylation of 6 and 7 with Benzyl Bromide–Sodium Hydride in Me_2SO. Sodium hydride (12 g, obtained from 25 g of a 50% oil dispersion) was added in small portions to a solution of a crude mixture of **6** and **7** in freshly distilled Me_2SO (200 ml) under nitrogen with stirring and cooling in an ice bath. After 4 h, benzyl bromide (10 ml) was added dropwise to the cooled mixture which was then stirred at room temperature for 6–8 h. Sodium hydride (12 g) followed by benzyl bromide (15 ml) were added to the reaction mixture, cooled in an ice bath and the mixture then was stirred at room temperature for 6–8 h. This procedure was repeated two more times. Triethylamine (30 ml) and water were added to the reaction mixture followed by saturation with solid sodium chloride. Extractions of the mixture with chloroform (4 × 300 ml) and evaporation of the chloroform solution under reduced pressure (10^{-2} mmHg) and at a bath temperature of 70 °C gave a syrupy residue which was treated with 80% acetic acid (50 ml) at room temperature for 10 min. The reaction mixture was worked up as described under A benzylation to give 20.7 g (72%) of crystalline **10**: mp 73–74 °C; NMR ($CDCl_3$) δ 1.65 and 2.24 (two m, 2 H, H-2), 3.48 (s, 3 H, OCH_3), 4.39 (d of d, 1 H, $J_{1-2,2'}$ = 2.8 and 8.2 Hz, H-1), 4.62 (d of d, 2 H, *J* = 12 Hz, benzylic H), 7.34 (br s, 5 H, aromatic H). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61. Found: C, 65.8; H, 7.5.

Methyl 2-Deoxy-3-*O*-benzyl-4-*O*-(*p*-toluenesulfonyl)-β-L-*threo*-pentopyranoside (11a). To a solution of compound **10** (3.87 g, 16.2 mmol) in alcohol-free chloroform (3 ml) and dry pyridine (50 ml) was added a solution of *p*-toluenesulfonyl chloride (15 g, 78.6 mmol) in alcohol-free chloroform (10 ml) and dry pyridine (100 ml), and the reaction mixture was stirred for 24 h, when TLC (solvent A) showed that the reaction was completed. The reaction mixture was cooled and poured into 500 ml of ice and water and the mixture was stirred at room temperature for 16 h. The mixture was then extracted with chloroform (4 × 100 ml) and the combined chloroform extracts were washed with cold hydrochloric acid, water, dilute sodium bicarbonate solution, and finally with water until neutral. The solution was dried (Na_2SO_4) and evaporated to yield a syrup which crystallized from 95% ethanol: yield 6.26 g (98.5%) of **11a** as small needles; mp 75–76 °C; $[\alpha]^{25}D$ +48° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) δ 1.66 and 2.27 (two m, 2 H, H-2), 2.40 (s, 3 H, tosyl CH_3), 3.40 (s, 3 H, OCH_3), 3.61 (m, 1 H, H-3), 4.36–4.56 (3 H, benzylic and H-1, overlap), 7.20–7.80 (m, 9 H, aromatic H). Anal. Calcd for $C_{20}H_{24}O_6S$: C, 61.2; H, 6.16; S, 8.17. Found: C, 61.0; H, 6.2; S, 8.0.

Methyl 2-Deoxy-3-*O*-benzyl-4-*O*-(*p*-chlorobenzenesulfonyl)-β-L-*threo*-pentopyranoside (11b). **11b** was prepared from **10** (6 g, 0.025 mol) and *p*-chlorobenzenesulfonyl chloride (30 g, 0.142 mol) by the procedure used for the preparation of **11a**: yield 11.2 g (98%); mp 126–127 °C; $[\alpha]^{25}D$ +56.7° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) δ 1.68 and 2.22 (two m, 2 H, H-2), 3.44 (s, 3 H, OCH_3), 3.59 (m, 1 H, H-3), 4.34–4.62 (3 H, benzylic and H-1, overlap), 7.12–7.88 (m, 9 H, aromatic H). Anal. Calcd for $C_{19}H_{21}O_6SCl$: C, 55.3; H, 5.13; S, 7.77; Cl, 8.59. Found: C, 55.3; H, 5.2; S, 8.0; Cl, 8.8.

Methyl 2-Deoxy-3-*O*-benzyl-4-*S*-acetyl-4-thio-α-D-*erythro*-pentopyranoside (12). From 11a. Compound **11a** (2.5 g, 25.6 mmol) and freshly recrystallized potassium thioacetate (2.92 g, 25, 6 mmol) were stirred in freshly distilled DMF (50 ml) at an oil bath temperature of 117 °C under a current of dry nitrogen for 24 h. The reaction mixture was cooled to 0 °C and poured with stirring into dry xylene (150 ml). After 16 h at room temperature, the precipitated salts were filtered and washed with dry xylene. The combined filtrates were evaporated to a syrupy residue at a bath temperature of 40 °C. Extraction of the residue with *n*-heptane (4 × 50 ml) and evaporation of the heptane solution gave a syrup, which was dissolved in dry pyridine (20 ml) and cooled to 0 °C. Acetic anhydride (5 ml) was added to this solution, and the reaction mixture was stirred at room temperature for 16 h. The mixture was then poured with stirring into ice–water (50 ml) and stirring was continued at room temperature for 16 h. The mixture was extracted with chloroform and the extract was washed with water (2 × 10 ml), dried (Na_2SO_4), and evaporated to a syrup. Crystallization of this syrup from 95% ethanol gave compound **12** (0.85 g, 45%) as long needles: mp 69.5–79 °C; $[\alpha]^{25}D$ +13.4° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) δ 1.86 (m, 2 H, H-2), 2.38 (s, 3 H, thioacetyl H), 3.46 (s, 3 H, OCH_3), 4.42 (d of d, 1 H, $J_{1-2,2'}$ = 7.0 and 3.5 Hz, H-1), 4.58 (s, 2 H, benzylic H), 7.36 (br s, 5 H, aromatic H). Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.8; H, 6.80; S, 10.8. Found: C, 60.7; H, 6.9; S, 10.8.

B. From 11b. Compound **11b** (20 g, 48.4 mmol) was stirred with potassium thioacetate (20 g, 175 mmol) in dry DMF (200 ml) at 75–80 °C in an oil bath under a current of dry nitrogen for 16 h. The reaction mixture was worked up as described above. The yield of **12** was 9.5 g (66.2%), mp 69–70 °C.

Methyl 2-Deoxy-4-thio-α-D-*erythro*-pentopyranoside (13) and Methyl 2-Deoxy-3-*O*-acetyl-4-*S*-acetyl-4-thio-α-D-*erythro*-pentopyranoside (14). Ammonia (200 ml), distilled from sodium, was added to a solution of **12** (3.25 g, 11 mmol) in 1,2 dimethoxyethane (20 ml) under nitrogen with stirring at a temperature of −78 °C (acetone–dry ice bath). Freshly cut sodium was added in small pieces (70–150 mg) to the stirred solution until the blue color of the solution persisted for 30 min. The excess sodium was decomposed by the addition of solid ammonium chloride, and ammonia was allowed to evaporate in a current of dry nitrogen. The mixture was extracted with chloroform (4 × 50 ml) and filtered and the solid washed with chloroform (2 × 10 ml). The combined filtrates were evaporated to a syrup (1.3 g). The ir spectrum of **13** showed no benzyl and thioacetyl absorption bands, whil it gave mercapto and hydroxy group absorption bands at 2570 and 3500 cm^{-1}, respectively. Compound **13** gave also a positive nitroprusside reaction.

Syrupy **13** (1.3 g) was acetylated with acetic anhydride (5 ml) in pyridine (15 ml) at room temperature overnight. Workup of the reaction gave **14** as syrup in quantitative yield: ir (film) 1695 (–SAc), 1740 cm^{-1} (–OAc); $[\alpha]^{25}D$ +114.4° (*c* 1.03, $CHCl_3$); NMR (acetone-d_6) δ 1.93 (s, 3 H, acetyl), 2.33 (s, 3 H, thioacetyl), 3.37 (s, 3 H, OCH_3), 4.57 (d of d, 1 H, $J_{1-2,2'}$ = 5.6 and 3.4 Hz, H-1). Anal. Calcd for $C_{10}H_{16}O_5S$: C, 48.37; H, 6.50; S, 12.9. Found: C, 48.4; H, 6.7; S, 13.1.

Methyl 2-Deoxy-4-thio-β- and α-D-*erythro*-pentofuranosides (15 and 16). Methyl 2-deoxy-4-thio-α-D-*erythro*-pentopyranoside (**13**, 6.5 g) was dissolved in 0.1% methanolic HCl solution (500 ml) and the solution was refluxed under nitrogen for 90 min, when TLC (solvent B) showed that the reaction was completed. The solution was cooled to room temperature and neutralized with solid lead carbonate. The precipitate was filtered and washed thoroughly with methanol. Evaporation of combined filtrates gave a syrupy mixture of **15** and **16** which was separated by dry silica gel column chromatography using solvent B as the eluent to give methyl 2-deoxy-4-thio-α-D-*erythro*-

pentofuranoside (**16**, 2.39 g, 37%), $[\alpha]^{25}D$ +315.6° (*c* 1.08, $CHCl_3$) [lit.[2] $[\alpha]^{25}D$ +314° (*c* 1, $CHCl_3$)], and methyl 2-deoxy-4-thio-β-D-*erythro*-pentofuranoside (**15**, 3.86 g, 59.5%), $[\alpha]^{25}D$ −278° (*c* 1.02, $CHCl_3$) (lit.[2] $[\alpha]^{25}D$ −277.6°).

Acknowledgment. This investigation was supported in part by Grant 125 from the American Cancer Society, Grant CA-13038 from the National Cancer Institute, USPHS, and RPMI Core Grant P01-CA-16056.

Registry No.—**1**, 6254-69-9; **2**, 6207-00-7; **3**, 60295-22-9; **4**, 60295-23-0; **5**, 32589-06-3; **6**, 60295-24-1; **7**, 60295-25-2; **10**, 60295-26-3; **11a**, 60295-27-4; **11b**, 60295-28-5; **12**, 60295-29-6; **13**, 60295-30-9; **14**, 60295-31-0; **15**, 24707-95-7; **16**, 24707-94-6; 2-methoxypropene, 16519-32-7; benzyl bromide, 100-39-0; *p*-toluenesulfonyl chloride, 98-59-9; *p*-chlorobenzenesulfonyl chloride, 98-60-2; potassium thioacetate, 10387-40-3.

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Reduction of Ketones with Incorporation of Deuterium at the α Position. Anomalous Reduction of Keto Sugar Derivatives[1,2]

David C. Baker, Jacques Defaye, Andrée Gadelle, and Derek Horton*

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, and Centre de Recherches sur les Macromolécules Végétales, Centre National de la Recherche Scientifique, B.P. 53, 38041, Grenoble, France

Received January 20, 1976

Reduction of the 3-keto sugar methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (**1**) with sodium borohydride in moist methanol proceeded stereospecifically to the allose derivative (**2**) having the 3-hydroxyl group axially oriented. Use of sodium borodeuteride under similar conditions gave the corresponding labeled analogue (characterized as its diacetate **11**) deuterated completely and exclusively at C-3, indicating equatorial attack on **1** by the reductant. In contrast, when the reduction was performed in dry 2-propanol, there resulted a 1:1 mixture of the axial 3 alcohol (allo derivative **2**) nd the equatorial 3 alcohol (gluco derivative **3**). When the latter reduction was repeated with sodium borodeuteride in dry 2-propanol, the allo product was again found to be labeled completely and exclusively at C-3 (as shown by the NMR spectrum of its diacetate **11**), but the gluco product **3** (studied as its diacetate **12**) was found to be fully protiated at C-3 and fully deuterated at C-2. The labeling experiments thus show that the gluco product **3** arises not by axial attack of the reductant at the ketonic (C-3) position of the precursor (**1**), but by stereospecific attack at the α position (C-2) of a presumed enediolic intermediate derived from **1**. The ready generation of a 2,3-enediol from **1** is demonstrated by preparation of the enediol diacetate **4**. Lithium aluminum hydride in tetrahydrofuran and sodium borohydride in *N,N*-dimethylformamide both reduce **1** exclusively to the axial 3 alcohol **2**. Zinc borohydride in 1,2-dimethoxyethane reduced **1** without cleavage of the 2-*O*-acetyl group to give mainly the allo product (**8**), together with a small proportion of gluco derivative (**9**). These results indicate the need for caution in interpreting results of label incorporation through reduction as a means of locating carbonyl groups in sugar derivatives, at least when dry alcoholic media are used. The results also suggest useful possibilities for synthesis of specifically labeled sugars.

The reduction of sugar derivatives having one free ketonic group gives mixtures of two secondary alcohols, isomeric at the original carbonyl position, in relative proportions strongly controlled by steric factors. The sequence of oxidation–reduction is commonly used[3] to prepare alcohols of inverted stereochemistry from the precursor and for "marking" the site of oxidation with deuterium or tritium by use of appropriately labeled reductants.[4,5] The present report developed on the one hand from a program[6,7] designed to furnish specifically labeled sugars of use as biochemical probes and for interpretation of complex NMR and mass spectral patterns, and on the other from studies[8–10] concerning the mechanism whereby metal salts protect cellulose from oxidative degradation during bleaching.

This study describes the use of a model ketone, methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose[10,11] (**1**), and related derivatives for evaluation of the regio- and stereoselectivity of its reduction with deuterated hydride reductants. It is shown that, according to the nature of the solvent used, reduction may take place exclusively (as is usually supposed) at the carbonyl group, or alternatively by attack at the position α to the carbonyl group, to give concurrently the corresponding α-labeled derivative.

Results and Discussion

Reduction of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (**1**) with sodium borohydride in aqueous methanol gave methyl 4,6-*O*-benzylidene-α-D-allopyranoside (**2**), iolated in near-quantitative yield, as a chromatographically homogeneous dihydrate. The product was further characterized as the anhydrous compound by recrystallization from benzene. Conversion of **2** under essentially nonacidic conditions into methyl 4,6-*O*-benzylidene-2,3-*O*-isopropylidene-α-D-allopyranoside (**5**) served to establish the 2,3-cis geometry of the reduced product. Furthermore, hydrolysis of **2** led exclusively to D-allose, detected chromatographically on paper and clearly differentiated from either glucose, mannose, or galactose. The free sugar obtained by