A New Synthesis of 4-Thiofuranosides via Regioselective Opening of an Episulfide with Allylmagnesium Bromide

Jonas Brånalt, Ingemar Kvarnström, and Stefan C. T. Svensson

Department of Chemistry, Linköping University, S-581 83 Linköping, Sweden

Björn Classon and Bertil Samuelsson*,†

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden

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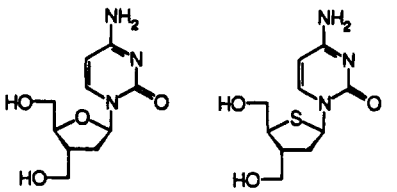
A new synthesis of 4-thiofuranosides which might be of general interest is described. (2*R*,3*S*)-3-[[(4-Bromobenzyl)oxy]methyl]oxirane-2-methanol (**1**) was converted to the corresponding epithio derivative **2** with inversion of configuration at both chiral centers. Regioselective opening of compound **2** with allylmagnesium bromide gave thiol **3a** which was benzoylated. Oxidative cleavage of the olefinic bond, followed by ring closure and protective group exchange, gave the desired 4-thiofuranoside derivative **9**.

Introduction

Nucleoside derivatives where the ring oxygen in the furanose part is replaced by sulfur were reported in the 1970's to have both antiviral and antitumor activities.[1] In recent years, 4′-thionucleosides have been synthesized and evaluated as potential inhibitors of human immunodeficiency virus, HIV.[2] The methods of synthesis for this class of compounds include nucleophilic substitution of a carbohydrate precursor by a sulfur-containing nucleophile, followed by ring closure or ring contraction,[1,3] acetolysis of an γ,γ-diethoxy epithio derivative,[4] or ring closure of dialkyl dithioacetals.[2b-g,5] Recently, we reported the synthesis of compound **II**,[6] which is the 4′-thio analogue of **I**, a potent inhibitor of HIV activity *in vitro*.[7]

In the present paper we describe a new and convenient route to the thiofuranoside moiety of **II**, which might be of general interest for the synthesis of this class of compounds. The synthetic strategy includes a high-yield conversion of chiral epoxide **1** to the corresponding epithio derivative **2** which has both centers of chirality inverted. A key step in the synthesis was the opening of epithio derivative **2** using allylmagnesium bromide which proceeded in good yield and with high regioselectivity. Regioselective opening of oxiranes with carbon-centered nucleophiles such as a lithium or magnesium organic species is a well-studied process,[8] whereas there are remarkably few examples of the corresponding reaction with epithio derivatives.[9] The general reaction of organometallic reagents with epithio derivatives is to form the corresponding olefin.[10,11] The liberated thiol group in **3a** was immediately benzoylated to avoid S–H addition to the allyl olefinic bond. The benzoyl group also serves to protect the thiol group from being oxidized in the following step. Oxidative cleavage of the olefinic bond in **6** followed by standard manipulations yielded the desired 4-thiofuranoside derivative **9**.



I II

Results and Discussion

Compound **1** was converted to the 2,3-epithio derivative **2** in 67% yield by reacting **1** with thiourea in methanol for 5 days[12] (Scheme 1). Gao and Sharpless[13] have previously reported that if titanium isopropoxide is used as catalyst in this reaction it proceeds faster and

† Additional address: Astra Hässle AB, S-431 83 Mölndal, Sweden.

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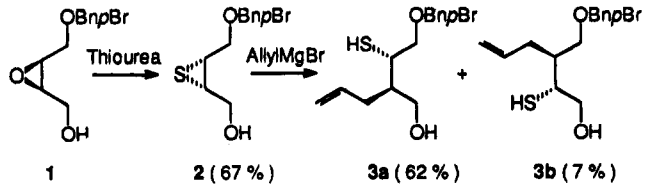
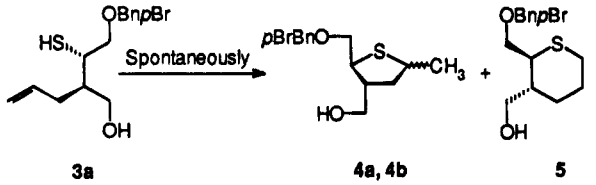
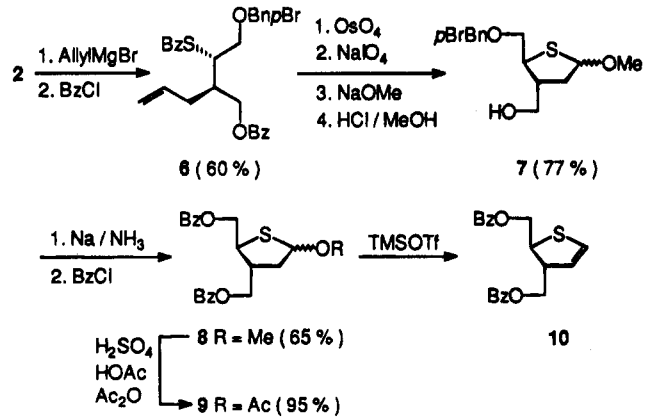
Scheme 1



Scheme 2



Scheme 3



with complete inversion of configuration at both stereogenic centers. We obtained the same product with identical optical purity for both reagent systems, but the yields were lower for the titanium isopropoxide-catalyzed reaction. The episulfide **2** was regioselectivity opened by allylmagnesium bromide in diethyl ether. The regioselectivity was 9:1 giving the desired **3a** in 62% and **3b** in 7% yield, as determined by ^{1}H NMR. The epoxide **1** has previously been opened with allylmagnesium bromide in diethyl ether giving a regioselectivity of 2.7:1 in 64% and 24% yield, respectively.[7] A remarkable difference in reaction rate was also observed between oxirane **1** and thiirane **2**. Compound **1** was opened at −50 °C in 30 min whereas compound **2** required room temperature for 24 h to ensure complete disappearance of starting material. Compounds **3a** and **3b** were very unstable even at refrigerator temperature and rapidly reacted further. The three main products formed, as an unseparable mixture, were tentatively identified as **4a**, **4b**, and **5**, formed via intramolecular 5-*exo-trig* and 6-*endo-trig* addition of the thiol group to the olefin[14] (Scheme 2). To avoid this reaction, the crude mixture of **3a** and **3b** was immediately benzoylated after workup to give the stable compound **6** in 60% yield from **2** (Scheme 3). The benzoylation of the thiol group is also crucial for the success of the following step where it serves to protect the thiol group from being oxidized. Reacting **6** with a catalytic amount of osmium tetraoxide using *N*-methylmorpholine *N*-oxide as reoxidant, followed by cleavage of the resulting diol with sodium periodate, debenzoylation with sodium methoxide in methanol, and acidification with hydrogen chloride, gave methyl thiofuranoside **7**, as an anomeric mixture, in 77% yield from **6**. Deblocking of **7** with sodium in liquid ammonia followed by benzoylation gave compound **8** in 65% yield. Compound **8** was treated with a catalytic amount of sulfuric acid in acetic acid−acetic anhydride to give the acetate **9** in 95% yield.[15] The *erythro* configuration and optical purity of compound **9** was established by conversion of compound **9** to compound **10** using trimethylsilyl triflate.[6] ^{1}H NMR, ^{13}C NMR, and optical rotation of compound **10** were in agreement with those previously reported.[6]

Experimental Section

General methods were the same as those previously described.[6]

(2*S*,3*R*)-2,3-Epithio-4-[(*p*-bromobenzyl)oxy]-1-butanol (2). To a solution of compound **1** (6.80 g, 24.9 mmol) in methanol (30 mL) was added thiourea (9.48 g, 0.125 mol). The suspension was stirred for 5 days at room temperature. After evaporation of the solvent, the residue was partitioned between dichloromethane and water. The organic phase was dried, filtered, concentrated, and purified by flash chromatography (toluene−ethyl acetate (3:1)) to give compound **2** (4.81 g, 67%) as a colorless syrup. **2**: $[\alpha]^{22}_D$ −27° (*c* 0.5, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.8 (1H, b), 3.0−3.6 (4H, m), 4.0 (2H, m), 4.5 (2H, s), 7.1−7.5 (4H, m). ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 34.7, 37.9, 62.5, 70.5, 72.7, 121.9, 129.2, 131.5, 135.6. Anal. Calcd for $C_{11}H_{13}O_2SBr$: C, 45.68; H, 4.53; S, 11.09. Found: C, 45.82; H, 4.46; S, 10.89.

(2*S*,3*R*)-2-*S*,4-*O*-Dibenzoyl-1-*O*-(*p*-bromobenzyl)-3-(2′-propenyl)-2-thio-1,4-butanediol (6). To an ice-cold suspension of **2** (516 mg, 1.78 mmol) in diethyl ether (15 mL) was added allylmagnesium bromide (15 mL) as a 1 M solution in diethyl ether. The mixture was allowed to attain room temperature and was stirred for 24 h. The reaction was quenched with water, the phases were separated, and the water phase was extracted with diethyl ether. The combined organic phase was dried, filtered, concentrated, and purified by column chromatography to give an unseparable mixture of **3a** and **3b** (405 mg, 69%) in a ratio of 9:1 as judged by ^{1}H NMR. **3a**, **3b**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.61 (1H, d), 1.8−2.3 (4H, m), 3.3−3.5 (1H, m), 3.5−3.7 (4H, m), 4.43 and 4.49 (2H, 2s), 4.8−5.1 (2H, m), 5.6−6.1 (1H, m), 7.1−7.5 (4H, m). These compounds were too unstable for further characterization. Instead, the crude mixture of **3a** and **3b** obtained from compound **2** (187 mg, 0.647 mmol), following the procedure described above, was immediately dissolved in pyridine (4 mL), and benzoyl chloride (0.22 mL, 1.94 mmol) was added. After 1 h at room temperature the reaction was quenched with water and the solvent was evaporated. The crude product was dissolved in dichloromethane, washed with 1 M hydrogen chloride and saturated aqueous sodium hydrogen carbonate, dried, filtered, concentrated, and purified by column chromatography (toluene−ethyl acetate 50:1) to give compound **6** (201 mg, 60%) as a colorless syrup. **6**: $[\alpha]^{22}_D$ −16° (*c* 0.6, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.0−2.8 (3H, m), 3.7 (2H, d), 4.2−4.7 (5H, m), 5.0−5.1 (2H, m), 5.6−6.1 (1H, m), 7.1−8.2 (14H, m); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 33.3, 38.5, 44.3, 64.7, 70.4, 71.9, 117.1, 121.1−135.4, 136.5, 165.8, 189.8. Anal. Calcd for $C_{28}H_{27}O_4SBr$: C, 62.34; H, 5.04; S, 5.94. Found: 62.11; H, 4.86; S, 5.79.

Methyl 5-*O*-(*p*-Bromobenzyl)3-*C*-(hydroxymethyl)-2,3-dideoxy-4-thio-α- and -β-D-*erythro*-pentofuranoside (7). To an ice-cold mixture of compound **6** (243 mg, 0.451 mmol) and *N*-methylmorpholine *N*-oxide (122 mg, 0.902 mmol) in tetrahydrofuran−water (3:1, 10 mL) was added osmium tetraoxide (1.13 mL, 0.022 mmol, 0.02 M in *tert*-butyl alcohol, stabilized with 1% *tert*-butyl hydroperoxide). After a few minutes the ice bath was removed and the reaction mixture was stirred overnight at room temperature. Sodium hydrogen

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sulfite (0.4 g) was added, and the reaction mixture was stirred for 15 min. The mixture was concentrated and the aqueous residue was partitioned between ethyl acetate and 1 M hydrogen chloride. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried, filtered, and concentrated. The crude compound was dissolved in tetrahydrofuran–water (3:1, 10 mL) and treated with sodium periodate (193 mg, 0.902 mmol) at room temperature. The diol was completely cleaved after 1 h. The mixture was concentrated, and the aqueous residue was partitioned between saturated aqueous sodium chloride and diethy ether. The organic phase was dried, filtered, and concentrated. The crude aldehyde was dissolved in methanol (15 mL), and sodium methoxide (1.0 M, 0.90 mL) was added. After 1 h at room temperature, the mixture was acidified to pH 2–3 by the addition of methanolic hydrogen chloride and was stirred for 1 additional h. The mixture was neutralized by addition of sodium hydrogen carbonate, the solvent was evaporated, and the crude compound was partitioned between ethyl acetate and water. The organic phase was dried, filtered, concentrated, and purified by column chromatography (toluene–ethyl acetate 2:1) to give an anomeric mixture of compound **7** (121 mg, 77%) as a colorless syrup. **7**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.8–2.8 (3H, m), 3.26, 3.30 (3H, 2s), 3.5–4.0 (5H, m), 4.49, 4.52 (2H, 2s), 4.9–5.0 (1H, m), 7.1–7.5 (4H, m). ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 40.6, 43.2, 47.5, 49.3, 50.5, 55.9, 56.5, 64.9, 72.2, 72.5, 73.3, 74.9, 89.7, 90.9, 121.5–136.4. Anal. Calcd for $C_{14}H_{19}O_3SBr$: C, 48.42; H, 5.51; S, 9.23. Found: C, 48.65; H, 5.53; S, 9.11.

Methyl 5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-4-thio-α- and -β-D-*erythro*-pentofuranoside (8). A solution of compound **7** (121 mg, 0.348 mmol) in diethyl ether (2 mL) was dissolved in liquid ammonia (30 mL) in a Dewar bottle. Sodium (100 mg) was added in small portions over 5 min. The solution was stirred for 30 min and then quenched by ammonium chloride. The ammonia was evaporated under a stream of nitrogen, and the solid residue was diluted with ethyl acetate. The solids were filtered off and washed several times with ethyl acetate. The filtrate was concentrated, and residual solvent was evaporated with added toluene. The crude residue was dissolved in pyridine (5 mL), benzoyl choride (0.12 mL, 1.05 mmol) was added, and the solution was stirred overnight at room temperature. Water (1 mL) was added, and the mixture was concentrated to dryness. The residue was dissolved in dichloromethane, washed with 1 M hydrogen chloride and saturated aqueous sodium hydrogen carbonate, dried, filtered, concentrated, and purified by column chromatography (toluene–ethyl acetate 9:1) to give an anomeric mixture of compound **8** (87 mg, 65%) as a colorless syrup. **8**: ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.0–2.7 (2H, m), 2.8–3.2 (1H, m), 3.3 (3H, s), 3.8–4.2 (1H, m), 4.5–4.9 (4H, m), 5.1–5.4 (1H, m), 7.5–8.5 (10H, m); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 42.7, 43.7, 48.3, 56.0, 56.6, 65.4, 67.9, 90.3, 91.3, 128.4–132.8, 165.8. Anal. Calcd for $C_{21}H_{22}O_5S$: C, 65.27; H, 5.74; S, 8.30. Found: C, 65.36; H, 5.65; S, 8.09.

Acetyl 5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-4-thio-α- and β-D-*erythro*-pentofuranoside (9). To an ice-cold solution of compound **8** (24 mg, 0.062 mmol) in acetic acid–acetic anhydride (1:1, 4 mL) was added sulfuric acid (0.25 mL, as a 0.5% solution in acetic acid). The mixture was stirred at room temperature for 1 h and then neutralized with sodium acetate. The resulting mixture was partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane, and the combined organic phases were dried, filtered, concentrated coevaporated with methanol, and purified by column chromatography (toluene–ethyl acetate 9:1) to give an anomeric mixture of **9** (24 mg, 95%) as a colorless syrup. ^{1}H NMR and ^{13}C NMR were in agreement with those previously reported.[6]

5-*O*-Benzoyl-3-*C*-[(Benzoyloxy)methyl]–1,2,3-trideoxy-4-thio-D-*erythro*-pent-1-enofuranose (10). Compound **9** was treated with trimethylsilyl triflate, following the previously reported procedure,[6] to give compound **10**. ^{1}H NMR, ^{13}C NMR, and $[\alpha]^{22}_D$ were in agreement with those previously reported.[6]

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