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Note

An efficient synthesis of methyl 2,3-anhydro-α-D-ribofuranoside

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Abstract

An efficient synthesis of methyl 2,3-anhydro-α-D-ribofuranoside is reported. Its preparation is achieved via a four-step sequence from methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside in 74% overall yield. © 2001 Elsevier Science Ltd. All rights reserved.

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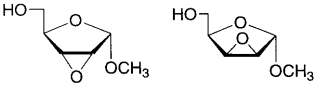
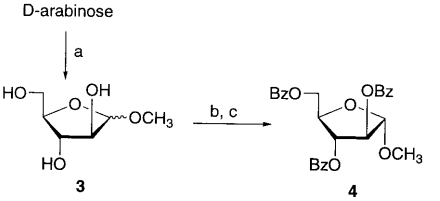
2,3-Anhydrofuranose derivatives **1** and **2** (Chart 1) have found widespread application in the synthesis of modified nucleoside analogs[1] and carbohydrate derivatives[2] due to the ease with which the epoxide moiety can be regioselectively opened by nucleophiles.[3] Although an expeditious synthesis of **2** has been reported,[4] a similarly efficient route for the preparation of **1** is not available. Anhydro sugar **1** was first synthesized by Baker and co-workers[5] in 1958. Using 1,2-*O*-isopropylidene-α-D-xylofuranose as the starting material, the product was obtained in approximately 25% overall yield in five steps. A modification of this procedure, which provides higher yields, has since been reported;[6] however, this route still involves five steps with purification of each intermediate. In this Note, we report an efficient synthesis of **1** from methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (**4**), a compound that can be easily prepared[7] in multigram quantities from D-arabinose (Scheme 1).



1 **2**

As illustrated in Scheme 2, our route to **1** began with Zemplén deacylation of **4**. Following the reaction, the solution was neutralized, concentrated to an oil, and the resulting residue was partitioned between water and dichloromethane. Evaporation of the aqueous layer, followed by coevaporation with toluene, provided the product **5**, which was sufficiently pure for the subsequent reaction. Treatment of this triol with 1,3-dibromo-1,1,3,3-



3 **4**

Scheme 1. As described in Ref. 7: (a) CH_3OH, HCl, rt; (b) BzCl, pyridine, 0 °C → rt; (c) crystallization.

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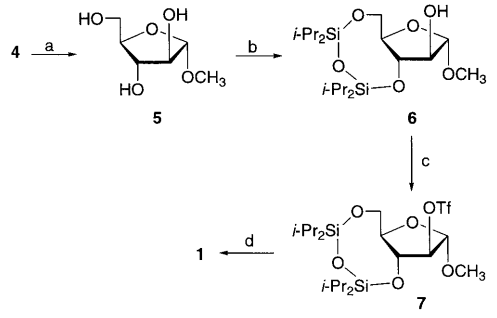
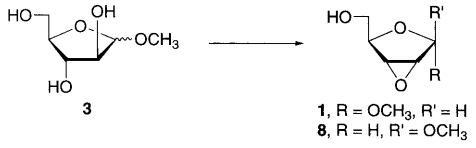


Scheme 2. (a) $NaOCH_3$, CH_3OH, rt, quantitative; (b) $(i\text{-}Pr_2SiBr)_2O$, pyridine, 0 °C → rt, 89%; (c) $(CF_3SO_2)O$, pyridine, 0 °C; (d) $n\text{-}Bu_4NF$, THF, 83%, two steps.



Scheme 3.

tetraisopropyldisiloxane[8] in pyridine provided the known alcohol **6**[9], which was easily purified by chromatography. The resulting oil was dissolved in pyridine, cooled to 0 °C, and then stirred with triflic anhydride for 5 min. Conventional workup provided crude triflate **7**, which was immediately treated with tetra-*n*-butyl ammonium fluoride at room temperature. After stirring for 1 h, TLC indicated a clean conversion of **7** to the target, **1**. Workup and chromatography afforded the product in 74% overall yield from **4**.

The conversion of **4** to **1** can easily be carried out in less than 3 days. Nevertheless, in an effort to further speed access to **1**, we investigated the possibility that triflate **7** could be synthesized in one pot from **5**, thus eliminating a chromatographic purification. We therefore treated triol **5** with 1,3-dibromo-1,1,3,3-tetraisopropyldisiloxane and pyridine and then, upon indication of its complete conversion to **6** (by TLC), added triflic anhydride. Unfortunately, this resulted in the formation of, in addition to **7**, a number of unidentifiable byproducts. When crude triflate **7** synthesized in this way was treated with tetra-*n*-butyl ammonium fluoride, epoxide **1** was isolated in only 50% yield from **4**. We also investigated if the crude reaction product **3**, which resulted from Fisher glycosylation of methanol with D-arabinose, could be used as the starting material. Indeed, we found (Scheme 3) that **3** could be converted to a mixture of epoxides, **1** and **8** using the route outlined in Scheme 2. The overall yield for this reaction sequence was comparable to that obtained for the transformation of **4** to **1**. However, it was not possible to separate **1** and **8** either by crystallization or by chromatography.[†] Furthermore, attempts to derivatize the mixture with benzoyl chloride, triphenylmethyl chloride, or *t*-butylchlorodiphenylsilane produced inseparable mixtures of glycoside products.[‡]

In summary, we report an efficient synthesis of methyl 2,3-anhydro-α-D-ribofuranoside (**1**) from readily available methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (**4**). The product is produced in 74% overall yield via a four-step sequence that can be carried out in less than 3 days. Only two chromatographic purifications are required. We have also demonstrated that subjecting methyl β-D-arabinofuranoside, present in an anomeric mixture of methyl D-arabinofuranosides, to this reaction sequence affords methyl 2,3-anhydro-β-D-ribofuranoside (**8**). Therefore, the method described here could also be used for the preparation of **8**, through either fractional distillation of the α/β epoxide mixture obtained from **3** or by starting with pure methyl β-D-arabinofuranoside.[§] It should also be mentioned that the route described here could be used to prepare the enantiomers of **1** and **8** from L-arabinose, which is considerably less expensive than the L-xylose required by the previously described method.[¶,6]

[†] It has been reported (Ref. 5) that **1** and **8** can be separated by fractional distillation.

[‡] The 5-*O*-*p*-toluenesulfonyl derivatives of **1** and **8** have been reported (Ref. 2a) to be separable both by chromatography and by crystallization.

[§] Pure methyl β-D-arabinofuranoside is conveniently obtained by chromatography of the mother liquor from the crystallization of **4** (Scheme 1), followed by Zemplén deacylation. C.S. Callam and T.L. Lowary, unpublished results.

[¶] 100 g of L-arabinose can be purchased (from Sigma Chemical Co.) for US$ 75.00; the same amount of L-xylose is US$ 380.

1. Experimental

General.—Solvents were distilled from the appropriate drying agents before use. Unless stated otherwise, all reactions were carried out at rt under a positive pressure of Ar and were monitored by TLC on Silica Gel 60 F_{254} (0.25 mm, E. Merck). Spots were detected under UV light or by charring with 10% H_2SO_4 in EtOH. Solvents were evaporated under reduced pressure and below 40 °C (water bath). Organic solutions of crude products were dried over anhyd Na_2SO_4. Column chromatography was performed on Silica Gel 60 (40–60 μm). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). ^{1}H NMR spectra were recorded in $CDCl_3$ at 500 MHz, and chemical shifts are referenced to TMS (0.0). ^{13}C NMR spectra were recorded in $CDCl_3$ at 125 MHz and ^{13}C chemical shifts are referenced to internal $CDCl_3$ (77.00). The assignment of resonances in the ^{1}H and ^{13}C NMR spectra of **1** were made by two-dimensional homonuclear and heteronuclear shift correlation experiments. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

Methyl α-D-arabinofuranoside (**5**).—To a solution of methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside (**4**) (5.00 g, 10.5 mmol) in 7:1 CH_3OH–CH_2Cl_2 (100 mL) was added a 1 M solution of NaOMe (2 mL, 2 mmol). The solution was stirred at rt until the reaction was complete by TLC and then neutralized by the addition of HOAc. The reaction mixture was concentrated, and the resulting residue was partitioned between CH_2Cl_2 and water. The aq layer was extracted twice with CH_2Cl_2 and then concentrated. Residual water was removed by co-evaporation (twice) with MePh, and the product was then dried under vacuum overnight to yield **5** as a colorless oil (1.72 g, quantitative). The ^{1}H and ^{13}C NMR spectra of this compound were identical to that previously reported for **5**.[10]

Methyl 3,5-O-(tetraisopropylsiloxane-1,3-diyl)-α-D-arabinofuranoside (**6**).—A solution of 1,1,3,3-tetraisopropylsiloxane (2.71 g, 11 mmol) in dry CCl_4 (50 mL) was cooled to 0 °C, and Br_2 (3.70 g, 23 mmol) was added dropwise over 30 min. The solution was brought to rt and allowed to stir for 4 h. The solvent was evaporated and the residue was co-evaporated with CCl_4 (2×20 mL). The flask was then cooled to 0 °C, and a solution of methyl-α-D-arabinofuranoside (**5**) (1.72 g, 10.5 mmol) in C_5H_5N (50 mL) was added dropwise. The reaction mixture was brought to rt and then stirred for 1.5 h, before water (100 mL) was added. Diethyl ether (100 mL) was added, the phases separated, and the organic layer was washed with satd aq sodium bicarbonate (25 mL) before being dried. The drying agent was then removed by filtration, and the solvent was evaporated to yield crude **6** (4.86 g). Purification of the product by chromatography (5:1 hexane–EtOAc) afforded **6** as a clear oil (3.8 g, 89%). The ^{1}H and ^{13}C NMR spectra of this compound were identical to that previously reported for **6**.[9]

Methyl 2,3-anhydro-α-D-ribofuranoside (**1**).—A solution of **6** (3.8 g, 9.4 mmol) in dry C_5H_5N (50 mL) was cooled to 0 °C in an ice bath. To this solution was added $(CF_3SO)_2O$ (3.96 g, 14.1 mmol), and the reaction mixture was stirred for 5 min before water (25 mL) and CH_2Cl_2 (25 mL) were added. The organic layer was washed with water (25 mL), dried, filtered, and concentrated to yield crude **7** as a light orange oil which was co-evaporated twice with MePh. The residue was dissolved in THF (50 mL) and then tetra-*n*-butyl ammonium fluoride trihydrate (8.86 g, 28.2 mmol) was added. The solution was stirred for 1 h and then concentrated. The resulting oil was purified by column chromatography (3:1 EtOAc–hexane) to yield **1** as a clear colorless oil (1.14 g, 83% over two steps). R_f 0.3 (3:1 EtOAc–hexane); $[\alpha]_D^{23}$ +19.2° (*c* 2.3, H_2O); lit.,[5] $[\alpha]_D^{29}$ +13.1° (*c* 2.3, H_2O) lit.,[6] $[\alpha]_D^{20}$ +21.6° (*c* 2.3, H_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 5.22 (d, 1 H, $J_{1,2}$ 0.4 Hz, H-1), 4.35 (dd, 1 H, $J_{4,5}$ 3.7, $J_{4,5'}$ 3.9 Hz, H-4), 3.82 (dd, 1 H, $J_{1,2}$ 0.4, $J_{2,3}$ 2.9, Hz, H-2), 3.76 (dd, 1 H, $J_{4,5}$ 3.7, $J_{5,5'}$ 11.8, H-5) 3.74 (d, 1 H, $J_{2,3}$ 2.9 Hz, H-3), 3.69 (dd, 1 H, $J_{4,5'}$ 3.9, $J_{5,5'}$ 11.8, H-5′), 3.53 (s, 3 H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 102.6 (C-1), 78.9 (C-4), 63.0 (C-5), 56.8 (C-3), 56.7 (OCH_3), 56.3 (C-2); Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.28; H, 6.93.

Acknowledgements

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