Synthesis of benzyl *O*-(2,3,3′-tri-*O*-acetyl-β-*D*-apiofuranosyl)-(1→3)-2,4-di-*O*-benzoyl-α-*D*-xylopyranoside and its X-ray structure

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The protected apiose-containing disaccharide, benzyl *O*-(2,3,3′-tri-*O*-acetyl-β-*D*-apiofuranosyl)-(1→3)-2,4-di-*O*-benzoyl-α-*D*-xylopyranoside, was synthesized and its X-ray structure provided.

Keywords Apiose, isomerization, synthesis, X-ray structure

Introduction

The branched-chain *D*-apiose has a very widespread occurrence in the plant kindom. It exits usually as a terminal residue in plant glycosides, such as saponins, flavonoids, phenol glycosides, and anthraquinone glycosides, *etc*. These *D*-apiose-containing glycosides play an integral role in the biochemistry of plants.[1] However, there are few reports about the chemical synthesis of glycosides that have an apiosyl residue.[2-4] Methyl 2,3,3′-tri-*O*-acetyl-1-thio-β-*D*-apiofuranoside,[2] 2, 3, 3′-tri-*O*-acetyl-*D*-apiofuranosyl acetate,[3] and 2-*O*-acetyl-3,3′-*O*-benzyl-*D*-apiofuranosyl bromide[4] have been used as glycosyl donors. Because of the neighboring participation of the 2-*O*-acetyl group in these donors, only β-apiosides were formed. Herein, we report the synthesis of a protected disaccharide, benzyl *O*-(2,3,3′-tri-*O*-acetyl-β-*D*-apiofuranosyl)-(1→3)-2,4-di-*O*-benzoyl-α-*D*-xylopyranoside (**5**), which is a fragment of the significant immunological adjuvant QS-21.[5]

Results and discussion

2,3-*O*-Isopropylidene-*D*-apiofuranose (**1**) was prepared from *D*-xylose in six steps and 20% overall yield.[6] Removal of the isopropylidene protection under Dowex-50 (H^+) resin followed by acetylation produced a mixture of the four compounds (**2a** and **2b**, α and β), which could not be separated by silica gel chromatography. As shown in Scheme 2, *D*-apiose can exist in two furanose forms, *i. e.* 3-*C*-(hydroxyl)-*D*-erythrofuranose and 3-*C*-(hydroxyl)-*L*-erythrofuranose, which resulted in the mixture of **2a** and **2b** after acetylation. Treatment of the mixture of **2a** and **2b** with EtSH and $BF_3 \cdot OEt_2$ afforded a mixture of the thioglycosides (**3a** and **3b**, α and β) in 63% yield. Again, these four thioglycosides could not be separated by silica gel column chromatography. Either the mixtures of the acetates (**2**) or the thioglycosides (**3**) gave a very complicated ^1H NMR spectrum, so that the ratio of each components contained in the resulting mixtures could not be determined. We directly applied the mixture of the thioglycosides (**3**) in the following glycosylation with benzyl 2,4-di-*O*-benzoyl-α-*D*-xylopyranoside (**4**), which was readily prepared from *D*-xylose in two steps (27% overall yield).[7] Due to neighbouring participation of the 2-*O*-acetyl group in the thioglycosides (**3**), two β-linked disaccharides (**5** and **6**) were produced. Two promotion conditions were used in the above glycosylation: NIS/AgOTf and $CuBr_2$/TBAB/AgOTf,[4] both led to the disaccharide products in good yields (~69%). Compound **5** (1.3 g, 45%) was crystallized from the mixture in petroleum ether-EtOAc, and then the mother solution was concentrated and applied to a silica gel chromtography to obtain a little amount of the pure compound **6** (5 mg).

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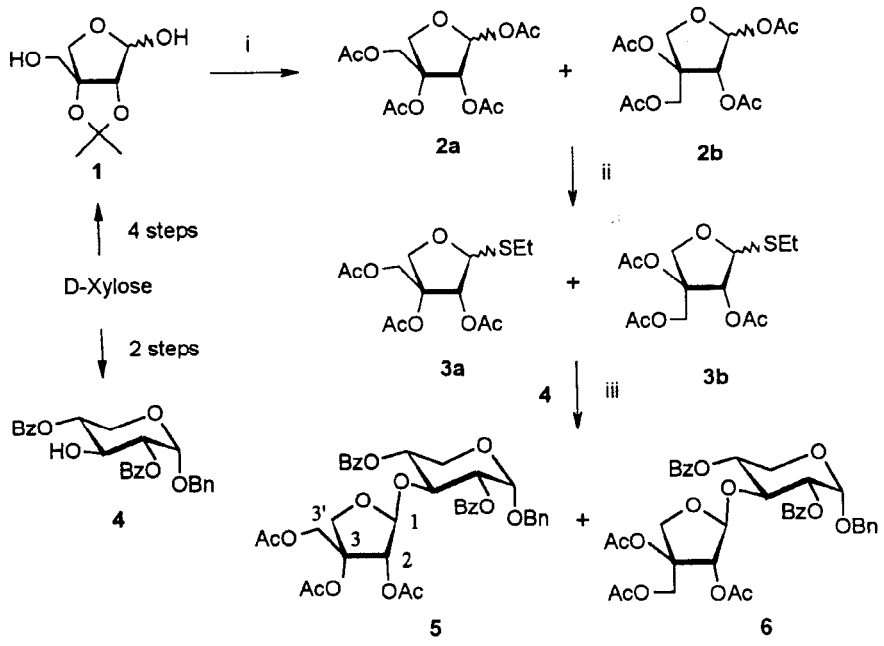
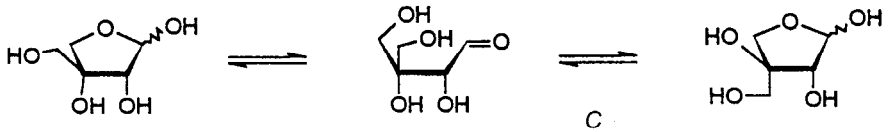
Scheme 1



Reagents and conditions: i) Dowex-50W (H^+), H_2O, 70℃, 5 h; then Ac_2O, pyridine, rt, 96.2% (two steps); ii) EtSH, $BF_3 \cdot OEt_2$, CH_2Cl_2, rt, 63.1%; iii) NIS, AgOTf, CH_2Cl_2, 4Å MS, −20℃, 69.2% (**5**:**6** = 3:1).

Scheme 2



3-*C*-(Hydroxymethyl)-*D*-erythrofuranose — *D*-Apiose — 3-*C*-(Hydroxymethyl)-*L*-threofuranose

The structure of **5** was determined by ^1H and ^{13}C NMR spectroscopy and was further confirmed by its X-ray crystallography (Fig. 1)[8] The ^1H NMR spectrum of **6** was found to be virtually the same as that of **5**. However, a NOE signal between the H-2 and one of the H-3′of the apiose residue in **5** was detected, but not in **6**. Compared the ^{13}C NMR spectra of **5** with **6**, the most signals were well overlapped except the signal for C-2, C-3, C-3′ of the apiose residue, among which the signal of C-2 was overlapped inthe solvent($CDCl_3$) signals(76.57—77.42) in **5** moved downfield to 80.94 in **6**. These informations were suggestive of the configuraion difference between the C-3 of the apiose residue of **5** and **6**.

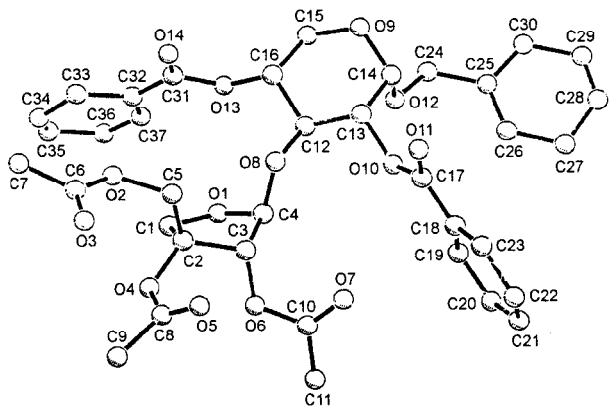


Fig. 1 X-Ray structure of compound **5**.

Experimental

Optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter. TLC was performed on precoated plates of Silica Gel HF_{254}(0.5 mm, Qingdao, China). Flash column chromatography was carried out on Silica

Gel H (400 mesh, Qingdao, China). ^1H NMR spectra were recorded on a Bruker AM-300 spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal reference. All chemical shifts (δ) were reported in parts per million and J values in hertz. Mass spectra were recorded on an HP5989A mass spectrometer. X-ray diffraction measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Mo-K_α radiation and a 12 kW rotating anode generator.

Synthesis of 1,2,3,3′-*tetra-O-acetyl-α/β-D-apiofuranose* (**2**)

A solution of **1** (1.46 g, 7.70 mmol) in water (25 mL) was treated with Dowex 50w(H^+) resin (2.30 g) at 70℃ for 5 h. The resin was removed, washed with MeOH, and the aqueous was evaporated under vacuum to give a syrup, which was then dissolved in Ac_2O (5 mL) and Py (25 mL), and stirred overnight at room temperature. After being quenched with MeOH, the mixture was diluted with EtOAc. The organic layer was washed with diluted HCl, saturated $NaHCO_3$, and brine, respectively, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude **2** (2.30 g, 96%), which was directly used in the next reaction without further purificatiuon.

*Synthesisofethyl*2,3,3′-*tri-O-acetyl*-1-*thio-α/β-D-apiofuranoside* (**3**)

Ethanethiol (0.80 mL, 10.83 mmol) was added to a solution of **2** (2.30 g, 7.23 mmol) in CH_2Cl_2(40 mL) under argon. Freshly distilled BF_3 etherate (0.73 mL, 5.76 mmol) was added and the mixture was stirred overnight. $NaHCO_3$(aq., sat., 9 mL) was added and the mixture was stirred for another 1 h, whereafter the organic phase was separated, dried ($MgSO_4$), and concentrated. Silica gel chromatography (6:1 petroleum ether-EtOAc) of the residue afforded thioglycoside **3** (1.46 g, 63.1%).

3 Colorless syrup, *m/z*(%): 319(M^+ - 1, 0.5), 305(M^+ - Me, 12.7), 291(M^+ - Et, 4.3), 259(M^+ - SEt, 17.1), 43(Ac, 100). Anal. $C_{13}H_{20}O_7S$. Calcd: C, 48.74; H, 6.29. Found: C, 48.26; H, 6.40.

Synthesis of benzyl O-(2,3,3′-*tri-O-acetyl-β-D-apiofuranosyl*)-(1→3)-(2,4-*di-O-benzoyl-α-D-xylopyranoside*(**5**)

Thioglycoside **3** (1.32 g, 4.12 mmol) was added to a solution of alcohol **4** (1.66 g, 3.70 mmol) in CH_2Cl_2 (55 mL) containing powdered 4Å molecular sieves. After being stirred for 30 min, the mixture was cooled at -20℃ and NIS (1.38 g, 6.13 mmol) and AgOTf (420 mg, 1.63 mmol) in toluene (0.4 mL) were added successively. The coupling was allowed to continue for 20 min, before being quenched with Et_3N and filtered through Celite. The filtrate was diluted with EtOAc and washed with aqueous $Na_2S_2O_3$, then with water, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (5 : 1 petroleum ether - EtOAc) to give a colorless syrup **5** and **6** (1.81 g, 69.2%), **5** was crystallized from EtOAc-petroleum ether.

5 Colorless crystal (1.30 g, 45%), mp 130—132℃, $[\alpha]_D$ + 14.5 (*c* 1.05, $CHCl_3$). ν_{max}: 3066, 1753, 1723, 1454, 1367, 1273, 1251, 1221, 1117, 1048, 934, 711 cm^{-1}. δ_H: 8.09—8.03 and 7.61—7.18(m, 15H), 5.26(s, 1H), 5.20(d, J = 3.6 Hz, 1H), 5.17(s, 1H), 5.32—5.21(m, 1H), 5.13 (dd, J = 3.6, 9.6 Hz, 1H), 4.76, 4.51(AB, J = 12.3 Hz, 2H), 4.52(t, J = 9.5 Hz, 1H), 4.49, 4.26 (AB, J = 12.4 Hz, 2H), 3.95(dd, J = 10.9, 6.0 Hz, 1H), 3.87(s, 2H), 3.81(t, J = 10.8 Hz, 1H), 1.87(s, 6H), 1.66(s, 3H). δ_C: 170.21, 169.44, 168.35, 165.44, 165.29, 136.96, 133.34, 133.22, 129.83, 129.57, 128.38, 127.89, 127.67, 106.82 (A-1), 95.38(X-1), 83.69(A-3), 75.38(A-4), 73.68(X-4), 72.22(X-2), 69.85(OCH_2Ph), 69.78 (X-3), 62.42(A-3′), 59.09(X-5), 20.96, 20.43, 19.93. *m/z*(%): 663(M^+ - Ac, 0.2), 615(M^+ - Bn, 10.2), 432(M^+ - apiose, 10.1), 105(Bz, 100). Anal. $C_{37}H_{38}O_{14}\cdot 0.5H_2O$. Calcd: C, 62.09; H, 5.49. Found: C, 61.96; H, 5.34.

6 5 mg, δ_H: 8.08—8.02 and 7.61—7.18 (m, 15H), 5.29(s, 1H), 5.31—5.21(m, 1H), 5.19 (s, 1H), 5.19—5.14(m, 2H), 4.76, 4.51(AB, J = 12.4Hz, 2H), 4.48(t, J = 12.1Hz, 1H), 4.47, 4.34(AB, J = 12.4Hz, 2H), 3.96(dd, J = 10.9, 6.0 Hz, 1H), 3.91—3.78(m, 3H), 1.92(s, 3H), 1.87(s, 3H), 1.51(s, 3H). δ_C: 170.18, 169.78, 168.19, 165.43, 165.09, 136.90, 133.38, 133.13, 129.75, 128.40, 128.34, 127.84, 127.61, 107.56 (A-1), 95.30(X-1), 85.60(A-3), 80.94(A-2), 74.62

(A-4), 73.78(X-4), 72.11(X-2), 69.84(OCH_2Ph), 69.71(X-3), 60.97(A-3′), 58.98(X-5), 21.03, 20.50, 19.71. *m/z*(%): 615(M^+ - Bn, 3.0), 431 (M^+ - 1 - apiose, 1.0), 259(M^+ - xylose - OBn, 10.8), 105(Bz, 100).

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8. Details of the crystal structure investigations may be obtained from the Cambridge Crystallographic Data Centre.

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