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Note

Synthesis of 2,3:4,6-di-*O*-isopropylidene-D-allopyranose from D-glucose

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Abstract—2,3:4,6-Di-*O*-isopropylidene-D-allopyranose can be conveniently prepared from D-glucose via a synthetic sequence, which includes Mitsunobu inversion at *O*-3, di-*O*-isopropylidenation of phenyl-1-thio-D-alloside and anomeric deprotection on treatment with NBS/$CaCO_3$.

Keywords: 2,3:4,6-Di-*O*-isopropylidene-D-allopyranose; Phenyl 1-thio-glycosides; NBS; Carbohydrate acetals

As part of a synthetic program intended for the preparation of carbasugars,[1–3] we have recently shown the usefulness of 2,3:4,6-di-*O*-isopropylidene acetals **1**–**3** of D-mannose,[2] D-glucose,[3] and D-galactose[3] as starting materials (Scheme 1). In this context, we published some time ago a method for the efficient preparation of **2** and **3**.[4] More recently, as a continuation of our research program, we required gram amounts of D-allose 2,3:4,6-di-*O*-isopropylidene acetal (**4**). In this Note, we disclose a practical method for the preparation of **4** from D-glucose.

D-Allose (**5**) is a commercially available monosaccharide, however its high price[5] has activated the development of several methods for its preparation from inexpensive D-glucose.[6] On the other hand, whereas the kinetic acetonation of D-mannose, according to Gelas and Horton,[7,8] is the method of choice for the preparation of **1**, similar acetonation of D-allose (**5**) led essentially exclusively (81%) to 4,6-*O*-isopropylidene-D-allopyranose (**6**) with only a minor amount (9%) of diacetonide **4**.[8,9] A survey of the literature did not show any additional procedure for the preparation of **4**.

Our strategy for the preparation of **4** (Scheme 2a) involved the synthesis of phenyl-1-thio-β-D-allopyranoside **8**, by Mitsunobu reaction of phenyl-1-thio-β-D-glucopyranoside **10**, followed by deacetylation, 2,3:4,6-di-*O*-isopropylidene acetal formation and anomeric deprotection (**8**→**9**→**4**, Scheme 2a). Phenyl-1-thio-β-D-glucopyranose (**10**) was readily prepared, according to Ferrier and Furneaux,[10] by treatment of β-D-glucopyranose pentaacetate[11] with boron trifluoride etherate and thiophenol. Mitsunobu reaction of methyl β-D-glucopyranoside with benzoic acid has been described by Weinges et al. to yield the corresponding 3,6-di-*O*-benzoyl-D-allopyranose derivative in 87% yield.[6] In the case of the glucose derivative **10**, this procedure gave poor yields of the corresponding allose dibenzoate. Alternatively, we have found that the use of acetic acid, rather than benzoic acid, triphenyl phosphine and diethyl azodicarboxylate yielded phenyl-3,6-di-*O*-acetyl-1-thio-β-D-allopyranoside **7** in 82–84% yield (Scheme 2a). The crude acetyl ester was saponified by the method of Zemplen[12a] to yield phenyl-1-thio-β-D-allopyranoside (**8**), which upon acetonation yielded thioglycoside **9**. Deprotection of the anomeric thiophenyl protecting group on compound **9** was carried out by treatment with NBS in the presence of $CaCO_3$ to yield the desired compound **4** ($J_{1,2}$ = 4.5 Hz, $CDCl_3$) in 88% yield. This compound has

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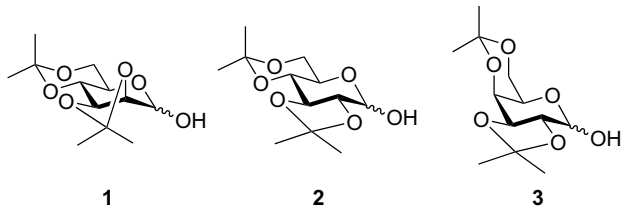
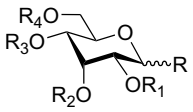
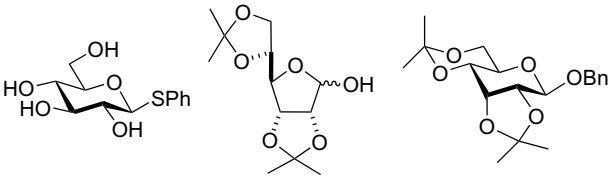
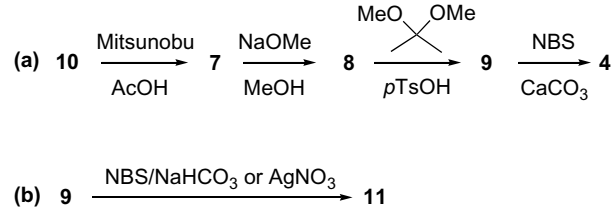




	R	R_1	R_2	R_3	R_4
4	β-OH	$-CMe_2-$		$-CMe_2-$	
5	OH	H	H	H	H
6	OH	H	H	$-CMe_2-$	
7	β-SPh	H	Ac	H	Ac
8	β-SPh	H	H	H	H
9	β-SPh	$-CMe_2-$		$-CMe_2-$	



Scheme 1.



Scheme 2.

previously been assigned as the β-anomer by Gelas and Horton,[9] which claimed a 'considerable flattening of the pyranose ring in the region of C-1, C-2 and C-3, with consequent distortion of the H-1-H-2 dihedral angle' as responsible for the relatively low observed value for $J_{1,2}$ (4.8 Hz in $CDCl_3$, 5.8 Hz in dimethyl sulfoxide-d_6). However, based on the observed large coupling constant H-1–H-2 ($J_{1,2}$ = 8.8 Hz, $CDCl_3$) in the β-allose diacetonide **9**, we believed that the anomeric stereochemistry in **4** needed to be established unequivocally. In this context, heating of **4** in C_6D_6 (40 °C) did not result in any observable mutarotation, which might have permitted assignment of the anomeric configuration. However, the observation of a NOE effect (400 MHz, $CDCl_3$) between H-1 and H-5 in **4**, allowed us to unambiguously assign a β-anomeric configuration for this compound.

Deprotection of the anomeric thiophenyl protecting group on compound **9** had proved to be troublesome. Treatment of **9** with either NBS in THF/saturated sodium bicarbonate solution or with $AgNO_3$ in acetone/water yielded rearranged furanose diacetonide **11** in 35% and 37% yield, respectively (Scheme 2b). In the course of this study, we have also considered benzyl allopyranoside **12** (Scheme 1) as a precursor for hemiacetal **4** by hydrogenolytic cleavage, and accordingly compound **12** was prepared through a similar synthetic sequence. However, attempted hydrogenation of **12** under a variety of conditions left, in our hands, its anomeric benzyl group unchanged.

In summary, a synthesis of 2,3:4,6-di-*O*-isopropylidene D-allopyranose (**4**) has been developed. This procedure represents the first high yield synthesis of the title compound and uses inexpensive D-glucose as the starting material.

1. Experimental

1.1. General methods

Melting points were determined in capillary tubes and are uncorrected. Optical rotations were determined at the sodium D line. ^{1}H NMR spectra were recorded at 200, 300 or 500 MHz; chemical shifts (δ) are relative to residual non-deuterated solvent as internal reference. TLC was conducted in precoated Kieselgel 60 F254. Detection was first by UV (254 nm), then charring with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g) and cerium(IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Column chromatography was carried out on Kieselgel (230–400 mesh) and, unless otherwise noted, mixtures of hexane–EtOAc were used as eluant. All reactions were conducted under atmosphere of argon. Anhydrous $MgSO_4$ or Na_2SO_4 was used to dry the organic solutions during work-ups and the removal of the solvents was done under vacuum with a rotavapor. Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Solvents were dried and purified using standard methods. Penta-*O*-acetylglucopyranose was prepared according to Wolfrom and Thompson,[11] by treatment of D-glucose with sodium acetate and Ac_2O. Phenyl-1-thio-β-D-glucopyranoside, **10**, was prepared according to a published procedure.[10]

1.2. Phenyl 3,6-di-*O*-acetyl-1-thio-β-D-allopyranoside (7)

To a suspension of phenyl 1-thio-D-glucoside **10** (10 g, 40 mmol) in dry THF (200 mL), acetic acid (6.4 mL, 120 mmol) and triphenylphosphine (29 g, 120 mmol) were added and the resulting solution heated at 60 °C.

To this mixture, diisopropyl azodicarboxylic acid (22 mL, 120 mmol) was added dropwise for 20 min and the solution refluxed for 3 h, after which the solution was cooled to room temperature and diethyl ether (500 mL) added. The resulting mixture was then washed with satd aq $NaHCO_3$ and brine, and the organic layer concentrated. Flash chromatography (hexane/ethyl acetate 3:7) yielded compound **7** as a syrup (10.5 g, 82%). $[\alpha]_D$ −28.5 (*c* 1.7, $CHCl_3$); *m/z* 379.1 ($M+Na^+$), ^1H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H, OAc), 2.17 (s, 3H, OAc), 3.6 (m, 2H, H-2, H-4), 3.85 (ddd, 1H, H-5, $J_{5,6}$ = 2.4 Hz, $J_{5,6'}$ = 4.9 Hz, $J_{4,5}$ = 10.0 Hz) 4.32 (dd, 1H, H-6, $J_{5,6'}$ = 4.9 Hz, $J_{6,6'}$ = 12.2 Hz) 4.42 (dd, 1H, H-6′, $J_{5,6}$ = 2.4 Hz, $J_{6,6'}$ = 12.2 Hz) 4.9 (d, 1H, H-1, $J_{1,2}$ 9.6 Hz), 5.6 (t, 1H, H-3, $J_{2,3} = J_{3,4}$ = 4.5 Hz), 7.5 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8 (Ac), 21.0 (Ac), 63.7 (C-6), 66.4, 68.0, 72.5, 74.7 (C-2, C-3, C-4, C-5), 85.0 (anomeric carbon), 128.1, 128.8 (×2), 131.6, 132.7 (×2), (6C, Ph), 171.3, 171.5 (C═O). Anal. Calcd for C_{16} $H_{20}O_7S$: C, 53.92; H, 5.66. Found: C, 54.04; H, 5.63.

1.3. Phenyl 2,3:4,6-di-*O*-isopropylidene-1-thio-β-D-allopyranoside (9)

Diacetate **7** (5 g, 14 mmol) was dissolved in MeOH (100 mL) and NaOMe (0.1 equiv) was added. After the disappearance of the starting material (3–4 h), the solution was neutralized with Amberlite (weakly acidic), filtered and concentrated. The crude product was dissolved in water and was subjected to continuous liquid–liquid extraction with hot ethyl acetate (24 h). Evaporation of the organic phase gave 2.8 g (75%) of tetraol **8** as a yellowish syrup. *m/z* 295.0 ($M+Na^+$), ^1H NMR (300 MHz, DMSO-d_6): δ 3.2–3.7 (m, 4H, H-2, H-4, H-5, H-6), 4.5 (t, 1H, H-3, $J_{2,3} = J_{3,4}$ = 4.5 Hz), 4.9 (d, 1H, H-1, $J_{1,2}$ 9.6 Hz), 7.5 (m, 5H, Ph). ^{13}C NMR (75 MHz, DMSO-d_6): δ 61.6 (C-6), 67.5, 69.9, 71.8, 77.2 (C-2, C-3, C-4, C-5), 84.7 (anomeric carbon), 126.5, 129.2 (×2), 129.9 (×2), 135.8 (6C, Ph).

Phenyl 1-thio-D-alloside, **8**, (2 g, 7.35 mmol) was dissolved in dry DMF (40 mL), then Sikkon-blue (4 g), dimethoxypropane (4.7 mL, 45 mmol) and *p*-toluenesulfonic acid (160 mg, 0.7 mmol) were added and the resulting solution was stirred overnight. A mixture of ether and toluene (8:2, 200 mL) was then added, and the organic phase was washed with satd $NaHCO_3$ solution (2 × 50 mL) and with water several times. Column chromatography of the crude product (hexane/EtOAc 8:2) furnished 1.9 g (73%) of diacetonide **9**, which was recrystallized from hot hexane to obtain white crystals. Mp = 122–124 °C, $[\alpha]_D$ −68.4 (*c* 1.05), *m/z* 375.1 ($M+Na^+$), ^1H NMR: δ 1.43, 1.49, 1.53, 1.58 (4s, 4 × 3H, 4 × CH_3), 3.79 (m, 2H, H-6, H-6′), 3.95 (m, 2H, H-4, H-5), 4.07 (dd, 1H, H-2, $J_{1,2}$ = 8.8 Hz, $J_{2,3}$ = 4.9 Hz), 4.49 (dd, 1H, H-3, $J_{3,4}$ = 3.6 Hz, $J_{2,3}$ = 4.9 Hz), 4.72 (d, 1H, H-1, $J_{1,2}$ 8.8 Hz,), 7.40 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 26.5, 28.7, 29.5 (4 × CH_3), 62.8 (C-6), 67.6, 69.6, 74.1, 76.4 (C-2, C-3, C-4, C-5), 87.1 (anomeric carbon), 100.5, 112.3, (2C quaternary), 128.2, 129.4 (×2), 132.5 (×2), 133.5 (6C, Ph). Anal. Calcd for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86. Found: C, 61.22; H, 6.83.

1.4. 2,3:4,6-di-*O*-isopropylidene-α-D-allopyranose (4)

To a vigorously stirred suspension of phenyl thioglycoside **9** (180 mg, 0.52 mmol) and calcium carbonate (500 mg, 2.5 mmol) in acetone/water (9:1, 10 mL) was added *N*-bromosuccinimide (190 mg, 1 mmol). After the disappearance of the starting material (24 h), the suspension was filtered and treated with satd aq $NaHCO_3$ and washed with ethyl acetate. The organic phase was separated, dried, filtered and evaporated. The product was filtered through a small silica gel column to give 118 mg (89%) of β–**4** as white crystals. Mp = 140–142 °C, Ref. 9 141–143 °C, $[\alpha]_D$ −19.5 (*c* 0.8), Ref. 9 −24.6 (*c* 0.1, $CHCl_3$) *m/z* 260.1 ($M+Na^+$), ^1H NMR: δ 1.37, 1.45, 1.49, 1.55 (4s, 4 × 3H, 4 × CH_3), 3.69 (m, 1H, H-6), 3.80 (m, 1H, H-5), 3.92 (dd, 1H, H-6′, $J_{5,6}$ = 5.1 Hz, $J_{6,6'}$ = 10.0 Hz), 4.07 (m, 3H, H-2, H-4, OH) 4.45 (dd, 1H, $J_{2,3}$ = 5.8 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.95 (t, 1H, H-1, $J_{1,2} = J_{1,OH}$ 4.5 Hz). ^{13}C NMR: δ 18.8, 25.3, 27.2, 29.0, 62.8 (C-6), 63.3, 68.6, 72.6, 77.7 (C-2, C-3, C-4, C-5), 95.0 (anomeric carbon), 100.0, 111.3. Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.33; H, 7.76.

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