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Note

An improved preparation of 3,4-*O*-isopropylidene derivatives of α- and β-D-galactopyranosides

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The classic method of isopropylidenation of carbohydrates involves acid-catalysed reaction with acetone, which often gives single thermodynamic products that can be isolated easily in high yields[1–3]. However, for α- and β-D-galactopyranosides (**1**), the formation of the 3,4-*O*-isopropylidene derivative (**2**) is accompanied by significant amounts of the 4,6-isopropylidene acetal (**3**) and the preparative separation of these compounds can be tedious[4–8].

We now report a simple, two step, one-pot procedure for the preparation in high yields of almost pure 3,4-*O*-isopropylidene-α- and -β-D-galactopyranosides through mild selective hydrolysis of the acyclic acetal group of the mixed-acetal derivatives obtained[9] in the transacetalation of D-galactopyranosides with 2,2-dimethoxypropane. A similar route suggested by Lipták *et al.*[10,11] did not prove satisfactory in our hands.

When a 0.05M solution of benzyl β-D-galactopyranoside[9] (**1b**) in 2,2-dimethoxypropane containing toluene-*p*-sulfonic acid was kept for 48 h at room temperature, the product was mainly (>95%) the 6-*O*-(1-methoxy-1-methylethyl) derivative **4b**. The crude product, isolated after neutralisation with triethylamine and concentration, contained triethylammonium tosylate which functioned as a weak acid catalyst when a solution of the crude product in 10:1 methanol–water was boiled

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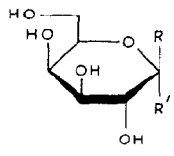

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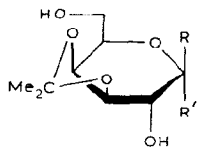

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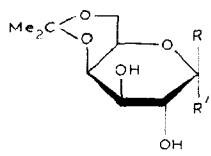

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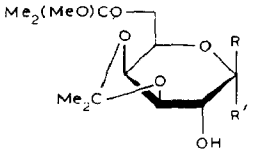

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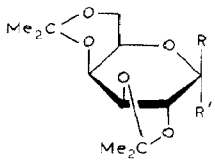

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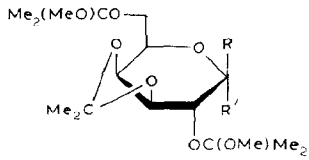
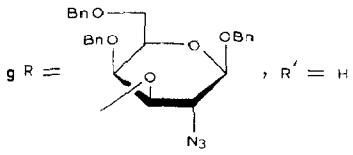


6

a R = OMe, R′ = H
b R = OBn, R′ = H
c R = OAllyl, R′ = H
d R = SPh, R′ = H
e R = H, R′ = OMe
f R = H, R′ = OAllyl



g R =

under reflux for 5 h. T.l.c then revealed the 3,4-*O*-isopropylidene derivative **2b** together with negligible amounts of the 2,3:4,6-diacetal[12] **5b** and the 4,6-acetal **3b**. This product, which can be used as such for further reactions, gave, on flash chromatography, 93% of pure **2b**.

For larger scale reactions, 0.1M solutions of **1b** in 2,2-dimethoxypropane were used with camphorsulfonic acid as the catalyst, and there was no appreciable change in the final yield of **2b**. Application of the procedure to methyl (**1a**) and allyl β-D-galactopyranoside (**1c**) and phenyl 1-thio-β-D-galactopyranoside (**1d**) gave 91–95% of the 3,4-*O*-isopropylidene derivatives.

In the α series, the mixture of products was more complex, since 3,4-*O*-isopropylidene-2,6-di-*O*-(1-methyoxy-1-methylethyl) derivatives **6** were formed also, but the two types of mixed-acetals (**4** and **6**) completely disappeared in the hydrolysis step and the yields of almost pure 3,4-isopropylidene acetal were, for example, 90 and 91% for **2e** and **2f**.

Application of the procedure to benzyl 2-azido-4,6-di-*O*-benzyl-2-deoxy-3-*O*-β-D-galactopyranosyl-β-D-galactopyranoside (**1g**) gave 85% of the 3,4-acetal **2g** (*cf.* 68% obtained by direct acetonation[7]). The isolated yield of **2g** did not exceed 85% because of the formation (8% isolated) of an uncharacterised product, probably the diacetal **5g**.

EXPERIMENTAL

General methods are those previously reported[12]. ^{13}C- and ^{1}H-n.m.r. spectra were obtained with a Bruker AM-400 spectrometer on solutions in $CDCl_3$ (internal Me_4Si). Flash chromatography was performed on Kieselgel 60 (Merck, 230–400 mesh) in the stated solvents which also contained 0.1% of triethylamine. The methyl D-galactopyranosides and phenyl 1-thio-β-D-galactopyranoside **1d** were commercial products, and the other D-galactopyranosides were obtained by the reported methods[4,7,8,13]. Pure reference samples of **3b**, **4b**, and **5b** were obtained as previously described[9,12].

Benzyl 3,4-O-isopropylidene-β-D-galactopyranoside (**2b**). — To a solution of **1b** (1.62 g, 6.0 mmol) in 2,2-dimethoxypropane (60 mL) was added dry camphorsulfonic acid (60 mg, 0.26 mmol). The mixture was stirred for 48 h at room temperature under argon, triethylamine (0.36 mL, 2.6 mmol) was then added, and the mixture was stirred for 15 min. T.l.c. (hexane–ethyl acetate, 6:4) showed that the product was almost pure **4b** (R_F 0.37). The mixture was concentrated to dryness and toluene (3 x 20 mL) was evaporated from the residue in order to remove traces of triethylamine. A solution of the crude product in 10:1 MeOH–H_2O (60 mL) was boiled under reflux until t.l.c. showed the complete disappearance of **4b** (5 h). The mixture was concentrated, and toluene (3 x 20 mL) was evaporated from the residue. T.l.c. (hexane–ethyl acetate, 4:6) showed that the residue contained **2b** (R_F 0.23) together with traces of **3b** (R_F 0.09) and **5b** (R_F 0.84). Flash chromatography (hexane–ethyl acetate, 4:6) then gave **2b** (1.73 g, 93%), m.p. 123–126° (from hexane–ethyl acetate), $[\alpha]_D$ −2.8° (*c* 1.6, chloroform); lit.[4] m.p. 123–124°, $[\alpha]_D^{25}$ −1.47° (*c* 1.12, chloroform). The structure of **2b** was verified by the n.m.r. data.

The following products were obtained by the above procedure. The structures of the known compounds were verified by the n.m.r. data.

Methyl 3,4-*O*-isopropylidene-β-D-galactopyranoside (**2a**, 93%), R_F 0.26 (acetone–hexane, 1:1), m.p. 134–135° (from acetone–hexane), $[\alpha]_D$ +18° (*c* 1.6, chloroform); lit.[4] m.p. 132–134°, $[\alpha]_D^{24}$ +21° (*c* 1.1, water).

Allyl 3,4-*O*-isopropylidene-β-D-galactopyranoside (**2c**, 95%), R_F 0.46 (ethyl acetate), m.p. 93–95° (from ethyl acetate–hexane), $[\alpha]_D$ +11° (*c* 1.1, chloroform); lit.[8] m.p. 91–92°, $[\alpha]_D^{22}$ +10° (*c* 2, chloroform).

Phenyl 3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside* (**2d**, 91%), R_F 0.37 (ether), syrup, $[\alpha]_D$ +4.8° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): ^{1}H (400 MHz), δ 7.54–7.50 and 7.32–7.25 (2 m, 5 H, Ph), 4.48 (d, 1 H, $J_{1,2}$ 10.2 Hz, H-1), 4.15 (dd, 1 H, $J_{3,4}$ 5.6, $J_{4,5}$ 2.0 Hz, H-4), 4.09 (dd, 1 H, $J_{2,3}$ 6.8 Hz, H-3), 3.96 (ddd, 1 H, $J_{5,6a}$ 6.8, $J_{6a,6b}$ 10.7, $J_{6a,OH}$ 3.5 Hz, H-6a), 3.85 (ddd, 1 H, $J_{5,6b}$ 3.6 Hz, H-5), 3.79 (ddd, 1 H, $J_{6b,OH}$ 9 Hz, H-6b), 3.56 (ddd, 1 H, $J_{2,OH}$ 3.0 Hz, H-2), 3.18 (d, 1 H, HO-2), 2.80 (dd, 1 H, HO-6), 1.40 and 1.32 (2 s, 6 H, Me_2C); ^{13}C, δ 132.09, 132.06, 128.94, and 127.82 (aromatic carbons), 110.29 (CMe_2), 87.39 (C-1), 79.19, 76.95,

*Previously prepared by S. Hourdin and P. Sinaÿ (Ecole Normale Supérieure, France).

73.67, and 71.28 (C-2,3,4,5), 62.29 (C-6), 27.86 and 26.22 (Me_2C).

Anal. Calc for $C_{15}H_{20}O_5S$: C, 57.7; H, 6.5. Found: C, 57.8; H, 6.6.

Benzyl 2-azido-4,6-di-*O*-benzyl-2-deoxy-3-*O*-(3,4-*O*-isopropylidene-β-D-galactopyranosyl)-β-D-galactopyranoside (**2g**, 85%), R_F 0.38 (ethyl acetate–hexane, 2:1), syrup, $[\alpha]_D$ −3.5° (*c* 1, chloroform), was identical with the authenthic compound[7]. A faster-moving uncharacterised compound (R_F 0.55) was also isolated (8%).

Methyl 3,4-*O*-isopropylidene-α-D-galactopyranoside (**2e**, 90%), R_F 0.45 (ethyl acetate–acetone, 5:1), m.p. 100.5–102.5° (from acetone–hexane), $[\alpha]_D$ +151° (*c* 1, chloroform); lit.[6a] m.p. 103–104°, $[\alpha]_D^{22}$ +161° (*c* 2.0, chloroform); lit.[6b] m.p. 97–98°, $[\alpha]_D^{27}$ +135° (*c* 1.61, chloroform).

Allyl 3,4-*O*-isopropylidene-α-D-galactopyranoside (**2f**, 91%), R_F 0.36 (ether), syrup, $[\alpha]_D$ +139.5° (*c* 1, chloroform); lit.[5] syrup, $[\alpha]_D^{25}$ +131° (*c* 1, chloroform).

ACKNOWLEDGMENTS

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REFERENCES

1 A. B. Foster, in W. Pigman and D. Horton (Eds.), *The Carbohydrates*, Vol IA, Academic Press, New York, 1972, pp. 391–402.
2 A. N. de Belder, *Adv. Carbohydr. Chem. Biochem.*, 34 (1977) 179–242.
3 D. M. Clode, *Chem. Rev.*, 79 (1979) 491–513.
4 A. Stoffyn and P. Stoffyn, *J. Org. Chem.*, 32 (1967) 4001–4006.
5 M. A. Nashed, M. S. Chowdhary, and L. Anderson, *Carbohydr. Res.*, 102 (1982) 99–110.
6 J. G. Buchanan and R. M. Saunders, *J. Chem. Soc.*, (1964) 1796–1803; M. L. Wolfrom, F. Shafizadeh, R. K. Armstrong, and T. M. Shen Han, *J. Am. Chem. Soc.*, 81 (1959) 3716–3719.
7 G. Catelani, A. Marra, F. Paquet, and P. Sinaÿ, *Carbohydr. Res.*, 155 (1986) 131–140.
8 A. Y. Chernyak, A. B. Levinsky, B. A. Dmitriev, and N. K. Kochetkov, *Carbohydr. Res.*, 128 (1984) 269–282.
9 P. L. Barili, G. Berti, G. Catelani, F. Colonna, and A. Marra, *Tetrahedron Lett.*, 27 (1986) 2307–2310.
10 A. Lipták, P. Fügedi, J. Kerékgyártó, and P. Nánási, *Carbohydr. Res.*, 113 (1983) 225–231.
11 A. Lipták, J. Imre, and P. Nánási, *Carbohydr. Res.*, 92 (1981) 154–156.
12 P. L. Barili, G. Catelani, F. Colonna, A. Marra, S. Cerrini, and D. Lamba, *Carbohydr. Res.*, 177 (1988) 29–41.
13 R. T. Lee and Y. C. Lee, *Carbohydr. Res.*, 37 (1974) 193–201.