Preparation of methyl 6-*O*-β-D-galactopyranosyl-α- and -β-D-galactopyranosides

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By condensation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactose with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide in acetonitrile in the presence of $Hg(CN)_2$ 1,2:3,4-di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranose has been prepared. This derivative on deacetylation and removal of the protecting groups afforded 6-*O*-β-D-galactopyranosyl-D-galactopyranose. Glycosidation of per-*O*-acetyl-6-*O*-β-D-galactobiose in acetonitrile in the presence of $Hg(CN)_2$ gave a mixture of methyl 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β- and -α-D-galactopyranosides. When using Ag_2CO_3 and iodine in dichloromethane, only the β-anomer was formed. After deacetylation methyl 6-*O*-β-D-galactopyranosyl-β-D-galactopyranoside and methyl 6-*O*-β-D-galactopyranosyl-α-D-galactopyranoside were obtained.

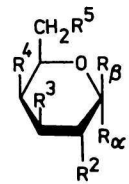
Посредством конденсации 1,2:3,4-ди-*O*-изопропилиден-α-D-галактозы с 2,3,4,6-тетра-*O*-ацетил-α-D-галактопиранозилбромидом в ацетонитриле в присутствии $Hg(CN)_2$ была получена 1,2:3,4-ди-*O*-изопропилиден-6-*O*-(2,3,4,6-тетра-*O*-ацетил-β-D-галактопиранозил)-α-D-галактопираноза. Из этого производного после деацетилирования и удаления защитных групп была получена 6-*O*-β-D-галактопиранозил-D-галактопираноза. Гликозидация пер-*O*-ацетил-6-*O*-β-D-галактобиозы в ацетонитриле в присутствии $Hg(CN)_2$ привела к образованию смеси метил-2,3,4-три-*O*-ацетил-6-*O*-(2,3,4,6-тетра-*O*-ацетил-β-D-галактопиранозил)-β- и -α-D-галактопиранозидов. При использовании Ag_2CO_3 и иода в хлористом метилене образовывался только β-аномер. После деацетилирования были получены метил-6-*O*-β-D-галактопиранозил-β-D-галактопиранозид и метил-6-*O*-β-D-галактопиранозил-α-D-галактопиранозид.

Thus far, only few authors [1—4] have dealt with chemical synthesis of methyl glycosides of 6-*O*-D-galactobiose. In some cases [1, 2] this synthesis represented only an intermediate step in syntheses of higher oligomers. *Srivastava* [1] by treatment of methyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-β-D-galactoside with 1-*O*-tosyl-2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-acetyl-α-D-galactopyranose and subsequent modifications obtained methyl 6-*O*-β-D-galactopyranosyl-β-D-galactopyranoside as an intermediate in the preparation of methyl glycoside

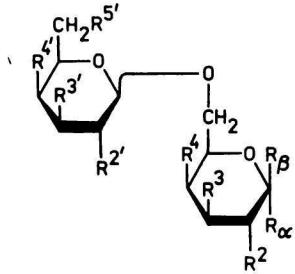
of 6-*O*-β-D-galactotriose. *Gorin* [3] used methyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide as the starting compounds to prepare methyl 6-*O*-β-D-galactopyranosyl-β-D-galactopyranoside. *Kováč* [4] in the preparation of methyl 6-*O*-α- and -β-D-galactopyranosyl-β-D-galactopyranosides made use of the condensation reaction of methyl 2,3,4-tri-*O*-acetyl-β-D-galactopyranoside with 2,3,4,6-tetra-*O*-acetyl-α-D--galactopyranosyl bromide in the presence of $Hg(CN)_2$ and $HgBr_2$.

Preparation of methyl 6-*O*-β-D-galactopyranosyl-D-galactopyranoside by using 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (*I*) as the nucleophile in the presence of $Hg(CN)_2$ has not been described yet. Though *Lee* [5] in preparation of the disaccharide used *I* in toluene—acetonitrile (φ_r(volume ratio) = 1 : 1) in the presence of $Hg(CN)_2$, the result was only a mixture of 1,2:3,4-di-*O*--isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranose (*III*) and the respective α-analogue in the mass ratio of 7 : 3. The individual anomers were not separated from the mixture.

In the framework of study of composition, structure, and biosynthesis of plant polymers, model compounds, methyl 6-*O*-β-D-galactopyranosyl-α- and -β-D-galactopyranosides have been prepared. The compound *I* was used as the nucleophile which by the reaction with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (*II*) in acetonitrile in the presence of $Hg(CN)_2$ gave the β-anomer (*III*), the structure of which was confirmed by ^{13}C NMR spectroscopy. After deacetylation and subsequent deisopropylidenation of *III* 6-*O*-β-D--galactopyranosyl-D-galactopyranose (*V*) was obtained. Its acetylation afforded per-*O*-acetyl 6-*O*-β-D-galactopyranosyl-D-galactopyranose (*VI*) which was converted to 2,3,4-tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)--α-D-galactopyranosyl bromide (*VII*). Glycosidation of *VII* in acetonitrile in the presence of $Hg(CN)_2$, followed by deacetylation, resulted in methyl 6-*O*-β-D--galactopyranosyl-β-D-galactopyranoside (*IX*) and methyl 6-*O*-β-D-galactopyranosyl-α-D-galactopyranoside (*XI*) in the mass ratio of 1.2:1. When Ag_2CO_3 with iodine was used as the catalyst, only the glycoside *IX* was obtained.

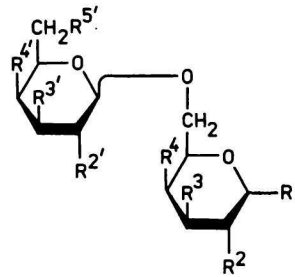


	R_β	R_α	R^2	R^3	R^4	R^5
I	H	O—iPr—O		O—iPr—O		OH
II	H	Br	OAc	OAc	OAc	OAc



	R_β	R_α	R^2	R^3	R^4	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$
III	H	O—iPr—O		O—iPr—O		OAc	OAc	OAc	OAc
IV	H	O—iPr—O		O—iPr—O		OH	OH	OH	OH
VII	H	Br	OAc	OAc	OAc	OAc	OAc	OAc	OAc
VIII	OMe	H	OAc	OAc	OAc	OAc	OAc	OAc	OAc
IX	OMe	H	OH	OH	OH	OH	OH	OH	OH
X	H	OMe	OAc	OAc	OAc	OAc	OAc	OAc	OAc
XI	H	OMe	OH	OH	OH	OH	OH	OH	OH

iPr = isopropylidene.



	R	R^2	R^3	R^4	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$
V	OH	OH	OH	OH	OH	OH	OH	OH
VI	OAc	OAc	OAc	OAc	OAc	OAc	OAc	OAc

Experimental

Melting points were determined on a Kofler stage. Optical rotation was measured with a Perkin—Elmer 141 apparatus at 20 °C and $\lambda = 585$ nm. Preparative column chromatography was performed on Silica gel L 100/250 (Lachema, Brno) and on a mixture of Celite—charcoal (mass ratio = 1 : 1). Thin-layer chromatography was carried out on Silufol sheets (Kavalier) by using the elution systems *A*: benzene—acetone ($\varphi_r = 5:1$), *B*: benzene—acetone ($\varphi_r = 2:1$), and *C*: ethyl methyl ketone—water ($\varphi_r = 90:8$). Paper chromatography was performed on Whatman No. 1 paper in the

system *D*: ethyl acetate—pyridine—water ($\varphi_r = 8:2:1$) with subsequent detection with anilinium hydrogen phthalate or the solution of potassium permanganate in potassium carbonate—potassium periodate ($\varphi_r = 1:4$). Thin-layer sheets were detected with 20 % aqueous solution of ammonium sulfate and heating until lasting intensity of the spots. Further, Dowex 50W x 8 (0.075—0.15 mm) ion exchanger in H^+ form was used. The compound *IV* was dried in the Abderhalden apparatus over P_2O_5 prior to optical rotation measurement. The compound *XI* was dried in a similar way.

^{13}C NMR spectra were measured with a Bruker AM 300 spectrometer in $CDCl_3$ (compounds *I*, *III*, *IV*, *VI*, *VIII*, and *X*; internal standard TMS) and in D_2O (compounds *V*, *IX*, and *XI*; internal standard methanol, δ(TMS) = 50.15 ppm).

1,2 : 3,4-Di-*O*-isopropylidene-α-D-galactopyranose (*I*) was prepared by the modified procedure reported in [6, 7] and purified by column chromatography: $[\alpha](\varrho = 10.0\ \mathrm{g\ dm^{-3}}$, pyridine) = −71.0°; ^{13}C NMR, δ/ppm: 96.3 (C-1), 70.8 (C-2), 70.6 (C-3), 68.2 (C-4), 71.6 (C-5), 62.2 (C-6), 109.5, 108.7 (C-quart.), 26.0, 25.9, 24.9, 24.3 (C-isoprop.).

The compound *VII* was prepared by treatment of *VI*, dissolved in dry dichloromethane, with HBr in glacial acetic acid for 15 min.

1,2:3,4-Di-O-isopropylidene-6-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-α-D-galactopyranose (III)

Into the mixture of *I* (2 g; 7.68 mmol) in acetonitrile (15 cm^3), $Hg(CN)_2$ (2 g), and Drierite (7 g), agitated for 2 h under exclusion of moisture, 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (*II*) (3.2 g; 7.78 mmol) in acetonitrile (15 cm^3) was added. After 2 h stirring the mixture was filtered and the filter cake was washed with chloroform. The chloroform solution was washed with 30 % aqueous solution of KI (2 × 100 cm^3), water (3 × 200 cm^3), saturated aqueous solution of sodium hydrogen carbonate (2 × 100 cm^3), water (3 × 200 cm^3), and dried with anhydrous sodium sulfate. Separation on silica gel column by using the system *A* and subsequent crystallization from ethanol with addition of water gave *III* ($R_f = 0.33$, system *A*). Yield = 3.5 g (77.3 %), m.p. = 54—55 °C, $[\alpha](\varrho = 4.6\ \mathrm{g\,dm^{-3}}$, carbon tetrachloride) = −43.5° · ^{13}C NMR, δ/ppm: 96.1 (C-1), 101.9 (C-1′), 70.8 (C-2), 69.6 (C-2′), 70.6 (C-3), 70.5 (C-3′), 68.6 (C-4), 67.8 (C-4′), 71.3 (C-5), 70.6 (C-5′), 67.0 (C-6), 61.2 (C-6′), 20.7, 20.6 (CH_3-isoprop.), 109.3, 108.6 (C-quart.), 26.0, 25.9, 24.3 (CH_3-acetyls).

For $C_{26}H_{38}O_{15}$ ($M_r = 590.57$) w_i(calc.): 52.88 % C, 6.49 % H; w_i(found): 52.80 % C, 6.51 % H. (Ref. [8] gives $[\alpha]$(585 nm, acetylene tetrachloride) = −44.7°, m.p. = 101—102 °C.)

1,2:3,4-Di-O-isopropylidene-6-O-(β-D-galactopyranosyl)-α-D-galactopyranose (IV)

The compound *III* (3.5 g; 5.88 mmol), dissolved in anhydrous methanol (50 cm^3), was deacetylated with freshly prepared 1 M methanolic solution of sodium methoxide (10 cm^3) for 24 h ($R_f = 0.25$, system *B*). After deionization with Dowex cation exchanger and separation on silica gel by using the system *C* the colourless sirupy compound *IV* was

obtained. Yield = 2.2 g (89.5 %), $[\alpha](\varrho = 15.6\,\mathrm{g\,dm^{-3}}$, chloroform) = − 53.9° · ^{13}C NMR, δ/ppm: 96.3 (C-1), 103.9 (C-1′), 71.1 (C-2), 71.3 (C-2′), 70.6 (C-3), 73.4 (C-3′), 68.9 (C-4), 69.1 (C-4′), 70.4 (C-5), 74.4 (C-5′), 67.8 (C-6), 61.6 (C-6′), 26.0, 24.4 (CH_3-isoprop.), 109.5, 108.9 (C-quart.).

For $C_{18}H_{29}O_{11}$ (M_r = 421.42) w_i(calc.): 51.30 % C, 6.94 % H; w_i(found): 51.25 % C, 6.86 % H.

6-O-β-D-Galactopyranosyl-D-galactopyranose (V)

Deisopropylidenation of *IV* (1.2 g) with Dowex in methanol (100 cm^3) at 45 °C and subsequent neutralization with sodium hydrogen carbonate resulted in 0.76 g (77.9 %) of the compound *V*, which on crystallization from methanol afforded white crystals with m.p. = 110—111 °C, $[\alpha](\varrho = 6.6\,\mathrm{g\,dm^{-3}}$, water) = + 32.4°. (Ref. [9] gives m.p. = = 110—148 °C, $[\alpha]$(585 nm, $\varrho = 22.0\,\mathrm{g\,dm^{-3}}$, water) = + 29°, Ref. [10] gives $[\alpha]$(585 nm, $\varrho = 10.0\,\mathrm{g\,dm^{-3}}$, water) = + 32°.) ^{13}C NMR, δ/ppm: 93.6 (C_α-1), 97.7 (C_β-1), 104.3 (C-1′), 70.5 (C_α-2), 73.1 (C_β-2), 72.0 (C-2′), 70.6 (C_α-3), 73.9 (C_β-3), 73.9 (C-3′), 69.6 (C_α-4), 70.1 (C_β-4), 69.9 (C-4′), 72.0 (C_α-5), 76.4 (C_β-5), 76.4 (C-5′), 70.6 (C_α-6), 70.3 (C_β-6), 62.2 (C-6′).

For $C_{12}H_{22}O_{11}$ (M_r = 342.29) w_i (calc.): 42.11 % C, 6.48 % H; w_i (found): 41.75 % C, 6.56 % H.

1,2,3,4-Tetra-O-acetyl-6-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)- -D-galactopyranose (VI)

The compound *V* (0.76 g) was acetylated with the mixture of pyridine—acetic anhydride (φ_r = 1 : 1) (50 cm^3) for 24 h. After usual treatment the sirupy compound *VI* (R_f = 0.23, system *A*) was obtained. The yield after crystallization from the solution of ethanol–water was 1.2 g (79.3 %), m.p. = 85—86 °C, $[\alpha](\varrho = 9.0\,\mathrm{g\,dm^{-3}}$, chloroform) = + 12.1°.^{13}C NMR, δ/ppm: 92.16 (C_α-1), 89.44 (C_β-1), 100.30 (C-1′), 67.01 (C_α-2), 67.47 (C_β-2), 67.80 (C-2′), 67.01 (C_α-3), 70.85 (C_β-3), 70.85 (C-3′), 65.55 (C_α-4), 66.44 (C_β-4), 67.01 (C-4′), 68.24 (C_α-5), 70.85 (C_β-5), 72.83 (C-5′), 67.01 ($C_{\alpha,\beta}$-6), 61.22 (C-6′).

For $C_{28}H_{38}O_{19}$ (M_r = 678.59) w_i(calc.): 49.56 % C, 5.65 % H; w_i(found): 49.48 % C, 5.60 % H.

Methyl 2,3,4-tri-O-acetyl-6-O-(2,3,4,6-tetra-O-acetyl-β-D- -galactopyranosyl)-β-D-galactopyranoside (VIII)

The mixture of Ag_2CO_3 (0.5 g), Drierite (1 g), and iodine (0.8 g) in anhydrous methanol (20 cm^3) was stirred for 2 h in the dark under exclusion of moisture. The compound *VII* (0.35 g; 0.5 mmol) in dry dichloromethane (5 cm^3) was added. After 19 h another portions of Ag_2CO_3 (0.5 g), Drierite (1 g), iodine (0.8 g), and the second portion of *VII* (0.37 g; 0.53 mmol) were added. After 24 h the mixture was filtered on Celite and the solid was washed with dichloromethane. The supernatant and the washings were combined

and concentrated. The chloroform solution of the reaction mixture was extracted with water (3 × 200 cm^3), solution of sodium thiosulfate (3 × 100 cm^3), water (3 × 200 cm^3), and dried with anhydrous sodium sulfate. Separation on the silica gel column by using the system *B* afforded 0.43 g (64.1 %) of the compound *VIII* which crystallized from the solution of ethanol—water and had m.p. = 81—82 °C, $[\alpha](\varrho = 10.4\ g\ dm^{-3}$, chloroform) = − 4.1°. (Ref. [4] gives $[\alpha](585\ nm, \varrho = 12.0\ g\ dm^{-3}$, chloroform) = − 13.7°.) ^{13}C NMR, δ/ppm: 100.74 (C-1), 102.08 (C-1′), 68.55 (C-2), 68.85 (C-2′), 70.75 (C-3), 70.86 (C-3′), 66.90 (C-4,4′), 71.01 (C-5), 72.25 (C-5′), 67.61 (C-6), 61.18 (C-6′), 57.05 (OMe).

For $C_{27}H_{38}O_{18}$ (M_r = 650.58) w_i(calc.): 49.85 % C, 5.89 % H; w_i(found): 49.91 % C, 5.79 % H.

Methyl 6-O-β-D-galactopyranosyl-β-D-galactopyranoside (IX)

Deacetylation of *VIII* (0.43 g) in anhydrous methanol (25 cm^3) with freshly prepared 1 M methanolic solution of sodium methoxide (5 cm^3), deionization with Dowex, purification on a short column of Celite—charcoal, and crystallization from methanol resulted in *IX*. Yield = 0.2 g (84.0 %), m.p. = 218—220 °C, $[\alpha](\varrho = 8.2\ g\ dm^{-3}$, water) = − 7.0°. (Ref. [4] gives m.p. = 218—219 °C, $[\alpha](585\ nm, \varrho = 12.5\ g\ dm^{-3}$, water) = − 9.5°.) ^{13}C NMR, δ/ppm: 104.97 (C-1), 104.44 (C-1′), 72.00 (C-2), 71.91 (C-2′), 73.98 (C-3,3′), 70.14 (C-4), 69.95 (C-4′), 74.98 (C-5), 76.35 (C-5′), 69.81 (C-6), 62.25 (C-6′), 58.53 (OMe).

For $C_{13}H_{24}O_{11}$ (M_r = 356.32) w_i(calc.): 43.82 % C, 6.79 % H; w_i(found): 43.73 % C, 6.73 % H.

Methyl 2,3,4-tri-O-acetyl-6-O-(2,3,4,6-tetra-O-acetyl-β-D--galactopyranosyl)-β-(VIII) and -α-D-galactopyranoside (X)

2,3,4-Tri-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranosyl bromide *VII* (0.31 g; 0.44 mmol) in acetonitrile (5 cm^3) was added into the reaction mixture (anhydrous methanol (20 cm^3), $Hg(CN)_2$ (2 g), and Drierite (1 g) stirred for 4 h under exclusion of moisture) which was agitated for 20 h at room temperature. The insoluble portion was filtered off and the supernatant was concentrated. The sirup obtained was washed with 30 % aqueous solution of KI (3 × 100 cm^3), water (3 × 200 cm^3), saturated solution of sodium hydrogen carbonate (3 × 100 cm^3), water (2 × 200 cm^3), and dried with anhydrous sodium sulfate. The sirup was separated on the silica gel column by using the system *A* to give the compounds *VIII* (0.13 g; 45.2 %) of R_f = 0.25 and *X* (0.11 g; 38.3 %) of R_f = 0.27, m.p. = 72—73 °C, $[\alpha](\varrho = 10.0\ g\ dm^{-3}$, chloroform) = + 87°. ^{13}C NMR, δ/ppm: 96.65 (C-1), 102.20 (C-1′), 67.82 (C-2,2′), 67.48 (C-3), 71.09 (C-3′), 65.71 (C-4), 66.45 (C-4′), 68.80 (C-5), 71.46 (C-5′), 66.45 (C-6), 61.53 (C-6′), 57.03 (OMe).

For $C_{27}H_{38}O_{18}$ (M_r = 650.58) w_i(calc.): 49.85 % C, 5.89 % H; w_i(found): 49.56 % C, 5.90 % H.

Methyl 6-O-β-D-galactopyranosyl-α-D-galactopyranoside (XI)

Deacetylation of *X* (0.11 g) in anhydrous methanol (25 cm^3) with 1 M methanolic solution of sodium methoxide (5 cm^3) and deionization with Dowex gave the compound *XI*. Yield = 0.05 g (84.8 %), $[\alpha](\varrho = 10.0\ g\ dm^{-3}$, water) = + 82.7°. ^{13}C NMR, δ/ppm: 99.44 (C-1), 104.94 (C-1′), 69.48 (C-2), 71.96 (C-2′), 70.70 (C-3), 74.02 (C-3′), 70.48 (C-4), 69.95 (C-4′), 72.18 (C-5), 74.15 (C-5′), 67.44 (C-6), 62.42 (C-6′), 58.32 (OMe).

For $C_{13}H_{24}O_{11}$ (M_r = 356.32) w_i(calc.): 43.82 % C, 6.79 % H; w_i(found): 43.71 % C, 6.83 % H.

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References

1. Srivastava, V. K., Sondheimer, S. J., and Schuerch, C., *Carbohydr. Res. 86*, 203 (1980).
2. Kováč, P., Yeh, H. J. C., and Glaudemans, C. P. J., *Carbohydr. Res. 140*, 277 (1985).
3. Gorin, P. A. J., *Carbohydr. Res. 101*, 13 (1982).
4. Kováč, P., Sokolski, E. A., and Glaudemans, C. P. J., *Carbohydr. Res. 128*, 101 (1984).
5. Lee, R. T. and Lee, Y. C., *Carbohydr. Res. 101*, 39 (1982).
6. Link, K. P., *Biochem. Prep. 3*, 74 (1953).
7. Morgenlie, S., *Acta Chem. Scand. 27*, 3609 (1973).
8. Freudenberg, K., Wolf, A., Knopf, E., and Zaheer, S. H., *Ber. 61*, 1743 (1928).
9. Smith, F. and Stephen, A. M., *J. Chem. Soc. 1961*, 4892.
10. Stephen, A. M., Kirkwood, S., and Smith, F., *Can. J. Chem. 40*, 151 (1962).

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