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Note

# Selective deprotection of 2′,6′-di-*O*-benzyl-2,3:5,6:3′,4′-tri-*O*-isopropylidenelactose dimethyl acetal☆

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**Abstract**

The reactivity order of O-deisopropylidenation of the three isopropylidene protecting groups of 2′,6′-di-*O*-benzyl-2,3:5,6:3′,4′-tri-*O*-isopropylidenelactose dimethyl acetal (**2**) with various reagents was established. The 5,6-acetal group was, although to a limited extent, more reactive as compared with the 3′,4′ group, while the 2,3-*O*-isopropylidene group was definitely less reactive. Conditions were determined for the direct preparation of the 5,6,3′,4′-tetraol **5** (60% aqueous acetic acid, room temperature, 48 h, 73% yield) and the 5,6-diol **4** (propylene glycol and *p*-toluenesulphonic acid in dichloromethane, 46% yield). The diacetonated derivative **3**, formally arising from a selective 3′,4′-O-deisopropylidenation, was obtained in high yield (90%) through a selective acetonation with 2-methoxypropene of the tetraol **5**. 

*Keywords:* 2′,6′-Di-*O*-benzyl-2,3:5,6:3′,4′-tri-*O*-isopropylidenelactose dimethyl acetal; Selective O-deisopropylidenation; 2-Methoxypropene; Selective isopropylidenation

## 1. Introduction

Lactose, an abundant side product from the dairy industry, is one of the cheapest natural sugars and can therefore be of great interest as the starting point for an approach to more complex saccharidic structures of high added value. Since this disaccharide is both a β-D-galactopyranoside and a 4-*O*-protected D-glucose, it can be used for selective operations on both its monosaccharidic moieties, and for elongations leading to biologically relevant tri- and oligosaccharides. A prerequisite for the success of these transformations is the availability of simple methods for the selective protection of the eight hydroxyl groups of lactose.

A well-established procedure for an extensive protection of disaccharides, such as lactose [2–4], maltose [5] and cellobiose [6], is their reaction with 2,2-dimethoxypropane under acidic catalysis, leading, in the case of lactose, in excellent yield to the tetraacetal **1**, ('triacetonlactose dimethyl acetal'), in which the OH groups 2,3:5,6 and 3′,4′ are protected by isopropylidene groups and the aldehydic group of the acyclic D-glucose moiety as a dimethyl acetal. This compound is useful for

☆ A preliminary account of this work has been presented; see Ref. [1].

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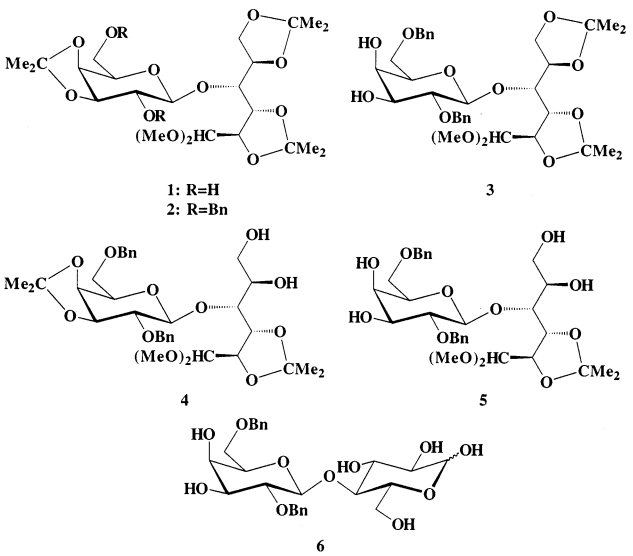
operations on the free 2′- and 6′-OH of the galactosyl moiety, such as the preparation of the fully protected di-*O*-benzyl derivative **2**, which can thus be obtained from lactose on a large scale and in high yield [4].

Compound **2** can be used as the starting material for further transformations if efficient methods for the selective removal of each of the three cyclic acetal functions are available. Rules for the prediction of the relative hydrolysis rates of isopropylidene groups located an structurally different diol functions have been formulated [7] and the purpose of the present work was to extend these rules to the specific case of **2**.

## 2. Results and discussion

The hydrolysis of **2** with aqueous acetic acid was studied first, the reagent previously reported for the complete O-deisopropylidenation of several derivatives of triacetonlactose dimethyl acetal substituted in positions 2′ [3,8] and 2′,6′ [3]. The deacetonation was performed in these cases by prolonged heating with 60–80% (v/v) aqueous acetic acid and led to the simultaneous liberation of the aldehyde function with the spontaneous hemiacetalization with re-pyranylization of the reducing unit.




A preliminary estimation of the evolution of the hydrolysis reaction with 60% (v/v) aqueous acetic acid at room temperature with tests at various times within 48 h revealed that mixtures of three product were always formed. Pure samples of the three O-deisopropylidenation products were easily obtained by flash chromatography of the above mixtures. The spectra of the two products having higher $R_f$ values than silica were both characterized by the presence of two isopropylidene acetal groups, whereas in the spectra of the third hydrolysis product only one dioxolane ring remained. The $^1$H NMR spectra of the peracetates of these products showed, in all cases, well separated and diagnostic signals for the protons geminal to the acetoxy groups (Section 3), which thus allowed their structures to be established, which were, in order of decreasing $R_f$, the 3′,4′-diol **3**, the 5,6-diol **4** and the 3′,4′,5,6-tetraol **5**.

This first phase of the hydrolysis reaction was characterized by a practically constant ratio between the two mono-deacetonated products **3** and **4**, ranging from 1:2 to 1:3.5, while the ratio **5**:**3** + **4** constantly increased with time. From a practical point of view, these hydrolytic conditions are useful for the preparation of tetraol **5**, obtained by simple crystallization of the crude product of a 48 h reaction in an acceptable 73% yield. In no case, however, was an acceptable yield of the major mono deacetonation product **4** obtained, the best result being lower than 15%.

The above results indicate that the 5,6-*O*-isopropylidene group of **2** involving a primary hydroxyl group, although to a limited extent, is more sensitive to acidic hydrolysis than the 3′,4′ one. Conversely, the third isopropylidene group of **2**, located on the secondary threo-disposed hydroxyl groups 2 and 3 of the acyclic portion, is much less reactive, in accordance with previous results on 2′-acetamido polyacetonated disaccharide analogues [9,10].

When the reaction time was further prolonged, a more polar product was formed, obtained practically pure under more forcing conditions, i.e., by treatment with 80% (v/v) aqueous acetic acid for 24 h at 50 °C. Flash chromatography of the crude product left an analytically pure sample of this compound (75% yield) that was characterized as the previously unreported 2′,6′-di-*O*-benzyllactose (**6**).

Some other O-deisopropylidenation methods were further tried in order to improve the selectivity of the mono-deacetonation of **2**. Hydrogen chloride in methanol failed to bring about selective hydrolysis of the tetra-acetal. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in $CD_3CN–H_2O$ [11] showed a similar selectivity to 60% aqueous acetic acid, yielding **5** in 72% yield.

Interestingly, the selectivity of mono-deacetonation sensibly increased when **2** was O-deisopropylidenated through the 'sacrificial glycol' method proposed by Andrews and Gould [12]. The treatment of **2** with 1,2-propanediol and *p*-toluenesulfonic acid in dichloromethane at room temperature for 1 h led to a mixture of compounds **3**–**5**, the major component of which was the 5,6-diol **4**, isolated after flash chromatography in 46% yield, together with **3** and **5** isolated in 10 and 25% yield, respectively.

Owing to the virtual impossibility of obtaining the diol **3** in an acceptable yield through direct hydrolysis of **2**, an alternative method for its preparation was devised, involving a selective acetonation of the 5,6-diol function of **5**. Treatment of **5** with 2-methoxypropene and pyridinium tosylate as catalyst led to the formation of **3** as the sole product, obtained after usual work-up in analytically pure form either by flash chromatographic purification (90% yield) or by crystallization from $Et_2O$–hexane (87% yield).

## 3. Experimental

*General methods.*—Compound **2** was prepared according to the published procedure [4]. The following standard procedure was used for acetylation: a solution of the compound in a 2:1 (v/v) mixture (15 mL/mmol) of pyridine and $Ac_2O$ was left at room temperature (rt) for 24 h, then repeatedly co-evaporated under diminished pressure with toluene and the residue was purified by chromatography on silica.

*4-O-(2,6-Di-O-benzyl-β-D-galactopyranosyl)-2,3-O-isopropylidene*-aldehydo-D-*glucose dimethyl acetal* (**5**)

*Method A (with 60% (v/v) aq AcOH).* A solution of **2** (5.70 g, 8.27 mmol) in AcOH (37 mL) was treated with water (25 mL) and stirred at rt. After 48 h, TLC analysis (3:7 hexane–EtOAc) revealed almost complete transformation of **2** ($R_f$ 0.71) with the prevalent formation of **5** ($R_f$ 0.12) and small amounts of products **4** ($R_f$ 0.31) and **3** ($R_f$ 0.42). The aq soln was extracted with toluene ($4 \times 50$ mL) in order to remove the more lipophilic compounds **3** and **4**. The aq phase was carefully neutralized at 0 °C by addition of aq 50% NaOH and extracted with $CH_2Cl_2$ ($5 \times 50$ mL). The combined organic extracts were washed with $H_2O$ (30 mL), dried, filtered, and concentrated. The residue (3.98 g) was crystallized from EtOAc to give pure **5** (3.68 g, 73% yield).

*Method B [with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)].* To a solution of **2** (2.00 g, 2.90 mmol) in 9:1 $CH_3CN–H_2O$ (30 mL) was added DDQ (70 mg, 0.30 mmol) and the dark-red reaction mixture was stirred at rt. After 24 h, TLC analysis (3:7 hexane–EtOAc) revealed the complete disappearance of **2**. The solution was decolourized by addition of charcoal (500 mg), followed by stirring at 80 °C for 2–3 min. The suspension was allowed to reach rt, filtered, and extensively washed with MeCN (30 mL) and hot MeOH (100 mL). The solution and washings were combined, evaporated in vacuo, and the residue (1.86 g) was subjected to crystallization from EtOAc (40 mL) to give pure **5** (1.28 g, 72%): $R_f$ 0.12 (3:7 hexane–EtOAc); mp 171–173 °C (EtOAc); $[\alpha]_D$ −11.4° (*c* 1.0, $CHCl_3$). $^1H$ NMR ($CD_3CN–D_2O$): $\delta$ 7.35–7.28 (m, 10 H, aromatic H), 4.77, and 4.64 (AB system, 2 H, $J_{A,B}$ 11.0 Hz, benzylic $CH_2$), 4.48 (s, 2 H, benzylic $CH_2$), 4.52–4.36 (m, 3 H, H-1, H-2, and H-1′), 4.29 (dd, 1 H, $J_{2,3}$ 6.0, $J_{3,4}$ 1.2 Hz, H-3), 3.77–3.51 (m, 9 H, H-4, H-5, H-6a, H-6b, H-3′, H-4′, H-5′, H-6′a, and H-6′b), 3.38 (dd, 1 H, $J_{1',2'}$ 7.5, $J_{2',3'}$ 9.8 Hz, H-2′), 3.26, and 3.25 (2 s, each 3 H, 2 × OMe), 1.40, and 1.34 (2 s, each 3 H, C*Me*$_2$). $^{13}C$ NMR ($CD_3CN–D_2O$): $\delta$ 139.00, and 138.67 (aromatic C), 129.38–128.78 (aromatic CH), 111.61 (*C*Me$_2$), 105.42 (C-1), 102.90 (C-1′), 80.57 (C-2′), 78.16 (C-3), 76.69 (C-2), 76.46 (C-4), 75.88 (benzylic $CH_2$), 74.10 (C-3′), 73.96 (benzylic $CH_2$), 73.57

(C-5′), 72.36 (C-5), 70.01 (C-6′), 69.96 (C-4′), 62.80 (C-6), 56.10, and 53.72 (2 × OMe), 27.91, and 27.28 (C*Me*$_2$). Anal. Calcd for $C_{31}H_{44}O_{12}$: C, 61.17; H, 7.29. Found: C, 61.31; H, 7.45.

The acetylation of **5** (500 mg, 0.82 mmol) gave, after flash chromatography on silica gel (EtOAc), its 3′,4′,5,6-tetra-*O*-acetyl derivative (595 mg, 93%) as a syrup; $R_f$ 0.71 (EtOAc); $[\alpha]_D$ +0.3° (*c* 1.2, $CHCl_3$). $^1$H NMR ($CD_3CN$): $\delta$ 7.38–7.29 (m, 10 H, aromatic H), 5.36 (dd, 1 H, $J_{4',5'}$ 1.0 Hz, H-4′), 5.27 (ddd, 1 H, $J_{4,5}$ 5.6 Hz, H-5), 5.04 (dd, 1 H, $J_{3',4'}$ 3.6 Hz, H-3′), 4.78 (d, 1 H, H-1′), 4.67 (dd, 1 H, $J_{5,6a}$ 2.5 Hz, H-6a), 4.87, and 4.63 (AB system, 2 H, $J_{A,B}$ 11.5 Hz, benzylic $CH_2$), 4.53, and 4.42 (AB system, 2 H, $J_{A,B}$ 11.9 Hz, benzylic $CH_2$), 4.41 (m, 2 H, H-1, and H-2), 4.33 (dd, 1 H, $J_{6a,6b}$ 12.3, $J_{5,6b}$ 7.0 Hz, H-6b), 4.13 (m, 1 H, H-3), 4.10 (m, 1 H, H-4), 3.96 (ddd, 1 H, H-5′), 3.61 (dd, 1 H, $J_{1',2'}$ 7.8, $J_{2',3'}$ 10.1 Hz, H-2′), 3.55 (dd, 1 H, $J_{5',6'a}$ 5.8 Hz, H-6′a), 3.45 (dd, 1 H, $J_{6'a,6'b}$ 9.6, $J_{5',6'b}$ 7.3 Hz, H-6′b), 3.35, and 3.34 (2 s, each 3 H, 2 × OMe), 2.03, 2.02, 2.00, and 1.91 (4 s, each 3 H, 4 × *Me*CO), 1.46, and 1.40 (2 s, each 3 H, C*Me*$_2$). $^{13}$C NMR ($CD_3CN$): $\delta$ 171.28, 171.04, 170.77, and 170.77 (4 × Me*CO*), 139.24, and 139.08 (aromatic C), 129.25–128.61 (aromatic CH), 110.94 (*C*Me$_2$), 106.19 (C-1), 103.07 (C-1′), 78.16 (C-2′), 78.04 (C-3), 76.52 (C-2), 75.80 (C-4), 75.72, and 73.85 (2 × benzylic $CH_2$), 73.52 (C-5), 73.36 (C-3′), 72.44 (C-5′), 68.70 (C-4′), 68.18 (C-6′), 61.91 (C-6), 56.27, and 54.00 (2 × OMe), 27.67, and 27.30 (C*Me*$_2$), 21.20, 20.96, 20.96 and 20.78 (4 × *Me*CO). Anal. Calcd for $C_{39}H_{52}O_{16}$: C, 60.30; H, 6.75. Found: C, 60.10; H, 6.83.

*4*-O-*(2,6-Di*-O-*benzyl-3,4*-O-*isopropylidene-β*-D-*galactopyranosyl)-2,3*-O-*isopropylidene*-aldehydo-D-*glucose dimethyl acetal* (**4**).—A solution of **2** (7.84 g, 11.4 mmol) in dry $CH_2Cl_2$ (200 mL) was treated with 1,2-propanediol (5.90 mL, 79.7 mmol), TsOH (400 mg, 2.30 mmol), and stirred at rt. After 1 h, TLC analysis (3:7 hexane–EtOAc) revealed four spots corresponding to the products **3**, **4**, **5** and unreacted **2**. The reaction mixture was quenched by addition of satd aq $NaHCO_3$ (10 mL), followed by stirring at rt for 10 min. The organic phase was washed with water (3 × 50 mL) to eliminate the excess propylene glycol, dried, filtered, evaporated under reduced pressure, and the crude products (7.25 g) subjected to flash chromatography on silica gel (9:1 $CH_2Cl_2$–$Me_2CO$). The following products were obtained in the order: unreacted **2** (1.10 g), **3** (776 mg, 10.5% yield), **4** (3.40 g, 46% yield), and **5** (1.73 g, 25% yield).

Compound **4** was a syrup; $R_f$ 0.31 (3:7 hexane–EtOAc); $[\alpha]_D$ −13.5° (*c* 1.0, $CHCl_3$). $^1$H NMR ($CD_3CN$–$D_2O$): $\delta$ 7.36–7.27 (m, 10 H, aromatic H), 4.77, and 4.69 (AB system, 2 H, $J_{A,B}$ 12.0 Hz, benzylic $CH_2$), 4.55, and 4.48 (AB system, 2 H, $J_{A,B}$ 12.2 Hz, benzylic $CH_2$), 4.53 (d, 1 H, H-1′), 4.44–4.33 (m, 2 H, H-1, and H-2), 4.26 (m, 1 H, H-3), 4.13–4.08 (m, 2 H, H-3′, and H-4′), 3.94 (m, 1 H, H-5′), 3.79–3.57 (m, 6 H, H-4, H-5, H-6a, H-6b, H-6′a, and H-6′b), 3.29, and 3.28 (2 s, each 3 H, 2 × OMe), 3.26 (m, 1 H, H-2′), 1.36 (s, 6 H, C*Me*$_2$), 1.25, and 1.24 (2 s, each 3 H, C*Me*$_2$). $^{13}$C NMR ($CD_3CN$–$D_2O$): $\delta$ 139.02 (aromatic C), 129.32–128.59 (aromatic CH), 110.87, and 110.44 (2 × *C*Me$_2$), 106.05 (C-1), 102.63 (C-1′), 80.83 (C-2′), 79.56 (C-3′), 77.92 (C-3), 77.14 (C-2), 76.52 (C-4), 74.83 (C-4′), 74.13 (benzylic $CH_2$), 73.83 (C-5), 72.79 (benzylic $CH_2$), 72.32 (C-5′), 69.63 (C-6′), 62.96 (C-6), 56.24, and 54.32 (2 × OMe), 28.09, 27.69, 27.29, and 26.49 (2 × C*Me*$_2$). Anal. Calcd for $C_{34}H_{48}O_{12}$: C, 62.95; H, 7.46. Found: C, 63.00; H, 7.71.

Acetylation of **4** (500 mg, 0.77 mmol) gave, after flash chromatography on silica gel (4:6 hexane–EtOAc), its 5,6-di-*O*-acetyl derivative (547 mg, 96%) as a syrup; $R_f$ 0.56 (4:6 hexane–EtOAc); $[\alpha]_D$ +6.7° (*c* 1.1, $CHCl_3$). $^1$H NMR ($CD_3CN$): $\delta$ 7.39–7.31 (m, 10 H, aromatic H), 5.25 (ddd, 1 H, $J_{4,5}$ 5.2 Hz, H-5), 4.84, and 4.75 (AB system, 2 H, $J_{A,B}$ 12.00 Hz, benzylic $CH_2$), 4.66 (dd, 1 H, $J_{5,6a}$ 2.5 Hz, H-6a), 4.61 (m, 1 H, H-1′), 4.59, and 4.52 (AB system, 2 H, $J_{A,B}$ 12.1 Hz, benzylic $CH_2$), 4.39 (m, 1 H, H-1), 4.38 (m, 1 H, H-2), 4.32 (dd, 1 H, $J_{6a,6b}$ 12.4, $J_{5,6b}$ 7.1 Hz, H-6b), 4.20 (m, 1 H, H-4′), 4.19 (m, 1 H, H-3′), 4.13 (m, 1 H, H-3), 4.07 (m, 1 H, H-4), 3.96 (m, 1 H, H-5′), 3.70 (dd, 1 H, $J_{5',6'a}$ 5.7 Hz, H-6′a), 3.64 (dd, 1 H, $J_{6'a,6'b}$ 10.0, $J_{5',6'b}$ 6.6 Hz, H-6′b), 3.34, and 3.33 (2 s, each 3 H, 2 × OMe), 3.29 (m, 1 H,

H-2′), 2.03, and 2.00 (2 s, each 3 H, 2 × *Me*CO), 1.38, 1.37, 1.34, and 1.31 (4 s, each 3 H, 2 × C*Me*$_2$). $^{13}$C NMR ($CD_3CN$): $\delta$ 171.26, and 170.75 (2 × Me*CO*), 139.45, and 139.36 (aromatic C), 129.51–128.37 (aromatic CH), 110.95, and 110.30 (2 × *C*Me$_2$), 106.25 (C-1), 102.52 (C-1′), 81.19 (C-2′), 79.85 (C-3′), 78.22 (C-3), 76.85 (C-2), 75.82 (C-4), 74.79 (C-4′), 74.01, and 73.79 (2 × benzylic $CH_2$), 73.68 (C-5), 72.82 (C-5′), 69.77 (C-6′), 63.00 (C-6), 56.31, and 54.37 (2 × OMe), 28.20, 27.66, 27.27, and 26.56 (2 × C*Me*$_2$), 21.19, and 20.96 (2 × *Me*CO). Anal. Calcd for $C_{38}H_{52}O_{14}$: C, 62.28; H, 7.15. Found: C, 62.40; H, 7.26.

*4*-O-*(2,6-Di*-O-*benzyl*-β-D-*galactopyranosyl)*-*5,6:2,3-di*-O-*isopropylidene*-aldehydo-D-*glucose dimethyl acetal* (**3**).—To a mixture of **5** (1.0 g, 1.60 mmol), pyridinium tosylate (40 mg, 0.16 mmol) and activated powdered 4 Å molecular sieves (340 mg) in dry $CH_2Cl_2$ (30 mL), was slowly added under Ar after 15 min stirring, a 1:9 solution of 2-methoxypropene in dry $CH_2Cl_2$ (2.0 mL, 2.0 mmol). The mixture was stirred at rt for 40 min until the starting material had disappeared (TLC analysis, 3:7 hexane–EtOAc). The suspension was neutralized by addition of satd aq $NaHCO_3$ (10 mL), stirred for 15 min at rt and extracted with $CH_2Cl_2$ (3 × 30 mL). The organic phase was dried, filtered and evaporated in vacuo to give a residue (991 mg) constituted exclusively by **3** (NMR). Flash chromatography on silica gel (2:3 hexane–EtOAc) yielded pure **3** (935 mg, 90%). Pure samples of **3** were also obtained in 87% yield by crystallization ($Et_2O$–hexane) of the crude product obtained as above: $R_f$ 0.42 (3:7 hexane–EtOAc); mp 72–75 °C (from $Et_2O$–hexane); $[\alpha]_D$ +13.5° (*c* 1.1, $CHCl_3$). $^1$H NMR ($CD_3CN$–$D_2O$): $\delta$ 7.37–7.21 (m, 10 H, aromatic H), 4.84, and 4.68 (AB system, 2 H, $J_{A,B}$ 11.3 Hz, benzylic $CH_2$), 4.57 (d, 1 H, H-1′), 4.50 (s, 2 H, benzylic $CH_2$), 4.43 (dd, 1 H, H-2), 4.33 (d, 1 H, $J_{1,2}$ 6.5 Hz, H-1), 4.20 (ddd, 1 H, H-5), 4.10 (dd, 1 H, $J_{2,3}$ 6.4 Hz, H-3), 4.01 (dd, 1 H, $J_{5,6a}$ 6.0 Hz, H-6a), 3.87 (dd, 1 H, $J_{5,6}$ 6.3, $J_{6a,6b}$ 8.6 Hz, H-6b), 3.83 (dd, 1 H, $J_{3,4}$ 1.5, $J_{4,5}$ 6.3 Hz, H-4), 3.76 (dd, 1 H, $J_{4',5'}$ 0.8 Hz, H-4′), 3.65–3.53 (m, 3 H, H-5′, H-6′a, and H-6′b), 3.51 (dd, 1 H, $J_{3',4'}$ 3.4 Hz, H-3′), 3.34 (dd, 1 H, $J_{1',2'}$ 7.6, $J_{2',3'}$ 9.6 Hz, H-2′), 3.30, and 3.28 (2 s, each 3 H, 2 × OMe), 1.41, 1.35, 1.33, and 1.26 (4 s, each 3 H, 2 × C*Me*$_2$). $^{13}$C NMR ($CD_3CN$–$D_2O$): $\delta$ 139.72, and 139.12 (aromatic C), 129.12–128.44 (aromatic CH), 111.30, and 109.35 (2 × *C*Me$_2$), 105.86 (C-1), 103.67 (C-1′), 80.89 (C-2′), 78.63 (C-3), 77.53 (C-2), 76.43 (C-4), 76.25 (C-5), 75.61 (benzylic $CH_2$), 74.22 (C-3′), 73.87 (benzylic $CH_2$), 73.81 (C-5′), 70.00 (C-6′), 69.96 (C-4′), 66.41 (C-6), 56.08, and 53.94 (2 × OMe), 27.85, 27.22, 26.92, and 25.52 (2 × C*Me*$_2$). Anal. Calcd for $C_{34}H_{48}O_{12}$: C, 62.95; H, 7.46. Found: C, 62.82; H, 7.45.

The acetylation of **3** (120 mg, 0.18 mmol) yielded, after chromatography of the crude product on silica gel (2:3 hexane–EtOAc), the pure 3′,4′-di-*O*-acetyl derivative (124 mg, 94%) as a syrup; $R_f$ 0.70 (2:3 hexane–EtOAc); $[\alpha]_D$ +2.7° (*c* 1.0, $CHCl_3$). $^1$H NMR ($CD_3CN$): $\delta$ 7.35–7.29 (m, 10 H, aromatic H), 5.29 (dd, 1 H, H-4′), 4.93 (dd, 1 H, $J_{3',4'}$ 3.6 Hz, H-3′), 4.80 (d, 1 H, H-1′), 4.83, and 4.56 (AB system, 2 H, $J_{A,B}$ 11.6 Hz, benzylic $CH_2$), 4.51, and 4.40 (AB system, 2 H, $J_{A,B}$ 11.4 Hz, benzylic $CH_2$), 4.37 (d, 1 H, H-1), 4.35 (ddd, 1 H, H-5), 4.25 (dd, 1 H, $J_{1,2}$ 6.5 Hz, H-2), 4.10 (dd, 1 H, $J_{4,5}$ 5.5 Hz, H-3), 4.09 (dd, 1 H, $J_{5,6a}$ 6.4 Hz, H-6a), 3.95 (dd, 1 H, $J_{6a,6b}$ 8.5, $J_{5,6b}$ 6.1 Hz, H-6b), 3.92 (dd, 1 H, $J_{2,3}$ 6.5, $J_{3,4}$ 1.4 Hz, H-4), 3.89 (ddd, 1 H, $J_{4',5'}$ 1.2 Hz, H-5′), 3.52 (dd, 1 H, $J_{1',2'}$ 7.8, $J_{2',3'}$ 10.1 Hz, H-2′), 3.51 (dd, 1 H, $J_{5',6'a}$ 5.7 Hz, H-6′a), 3.40 (dd, 1 H, $J_{6'a,6'b}$ 9.5, $J_{5',6'b}$ 7.4 Hz, H-6′b), 3.32, and 3.30 (2 s, each 3 H, 2 × OMe), 2.18, and 2.00 (2 s, each 3 H, 2 × *Me*CO), 1.41, 1.35, 1.34, and 1.27 (4 s, each 3 H, 2 × C*Me*$_2$). $^{13}$C NMR ($CD_3CN$): $\delta$ 171.14, and 170.88 (2 × Me*CO*), 139.52, and 139.16 (aromatic C), 129.29–128.29 (aromatic CH), 110.78, and 109.18 (2 × *C*Me$_2$), 106.21 (C-1), 103.79 (C-1′), 78.52 (C-3), 78.19 (C-2′), 77.85 (C-2), 76.39 (C-4), 76.16 (C-5), 75.58, and 73.56 (2 × benzylic $CH_2$), 73.35 (C-3′), 72.19 (C-5′), 68.72 (C-4′), 68.18 (C-6′), 66.36 (C-6), 56.06, and 53.83 (2 × OMe), 27.64, 27.25, 26.87, and 25.46 (2 × C*Me*$_2$), 20.89, and 20.76 (2 × *Me*CO). Anal. Calcd for $C_{38}H_{52}O_{14}$: C, 62.30; H, 7.15. Found: C, 62.39; H, 7.18.

*4*-O-*(2,6-Di*-O-*benzyl*-β-D-*galactopyranosyl)*-α,β-D-*glucopyranose* (**6**).—A solution of **2** (500 mg, 0.73 mmol) in aq 80% (v/v) AcOH (40 mL) was stirred at 50 °C. After 24 h, TLC analysis revealed the complete transformation

of **2** into **6**. The solution was allowed to reach rt and co-evaporated three times with toluene ($3 \times 50$ mL). Flash chromatography of the crude product (350 mg, quantitative) on silica gel (93:7 $CH_2Cl_2$–MeOH) yielded analytically pure **6** (276 mg, 75%) as a 1:1 mixture of the α- and β-pyranosidic forms measured on the relative intensities of the C-1 signals ($\delta$ ($D_2O$) 93.57 and 97.79, respectively). Compound **6** is a solid, $R_f$ 0.14 (93:7 $CHCl_3$–MeOH); $[\alpha]_D$ +27.2° (*c* 1.0, $CHCl_3$); mp 92–94 °C. $^{13}C$ NMR ($D_2O$): $\delta$ for β-**6** 139.77–139.28 (aromatic C), 129.30–128.50 (aromatic CH), 104.31 (C-1′), 97.79 (C-1), 80.85 (C-2′), 80.57 (C-4), 75.86 (C-5′), 74.92 (C-3), 74.54 (C-5), 76.19, and 74.33 ($2 \times$ benzylic $CH_2$), 73.47 (C-2), 72.98 (C-3′), 70.53 (C-4′), 70.25 (C-6′), 61.45 (C-6); for α-**6** 139.77–139.28 (aromatic C), 129.30–128.50 (aromatic CH), 104.31 (C-1′), 93.57 (C-1), 80.85 (C-2′), 80.23 (C-4), 76.38 (C-5), 75.86 (C-5′), 76.19, and 74.33 ($2 \times$ benzylic $CH_2$), 72.98 (C-3′), 71.33 (C-3), 70.53 (C-4′), 70.53 (C-2), 70.25 (C-6′), 61.45 (C-6). Anal. Calcd for $C_{26}H_{34}O_{10}$: C, 61.65; H, 6.77. Found: C, 61.53; H, 6.81.

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## References

[1] G. Catelani, F. D'Andrea, L. Puccioni, European Lactose Symposium, March 25–26 1999, The Hague (NL), Abs., p. 34.
[2] H.H. Baer, S.A. Abbas, *Carbohydr. Res.*, 84 (1980) 53–60.
[3] T. Yoshino, G. Reuter, S. Kelm, K. Schauer, *Glycoconjugate J.*, 3 (1986) 7–14.
[4] P.L. Barili, G. Catelani, F. D'Andrea, F. De Rensis, P. Falcini, *Carbohydr. Res.*, 298 (1997) 75–84.
[5] Y. Ueno, K. Hori, R. Yamauchi, M. Kiso, A. Hasegawa, K. Kato, *Carbohydr. Res.*, 89 (1981) 271–278.
[6] Y. Ueno, K. Hori, R. Yamauchi, M. Kiso, A. Hasegawa, K. Kato, *Carbohydr. Res.*, 96 (1981) 65–72.
[7] (a) S.A. Barker, E.J. Bourne, *Adv. Carbohydr. Chem.*, 7 (1952) 137–207. (b) A.N. De Belder, *Adv. Carbohydr. Chem. Biochem.*, 20 (1965) 220–302. (c) A.N. De Belder, *Adv. Carbohydr. Chem. Biochem.*, 34 (1977) 179–241. (d) A.H. Haines, *Adv. Carbohydr. Chem. Biochem.*, 39 (1981) 11–109.
[8] S.A. Abbas, J.J. Barlow, K.L. Matta, *Carbohydr. Res.*, 88 (1981) 51–60.
[9] P.L. Barili, G. Catelani, F. D'Andrea, L. Puccioni, *J. Carbohydr. Chem.*, in press.
[10] J.N. Glushka, A.S. Perlin, *Carbohydr. Res.*, 205 (1990) 305–321.
[11] (a) K. Tanemura, T. Suzuki, T. Horaguchi, *J. Chem. Soc., Chem. Commun.*, (1992) 979–980. (b) J.M. Garcia Fernandez, C. Ortiz Mellet, A.M. Marin, J. Fuentes, *Carbohydr. Res.*, 274 (1995) 263–268.
[12] M.A. Andrews, G.L. Gould, *Carbohydr. Res.*, 229 (1992) 141–147.