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Note

Convenient synthetic approach towards C-3 modified methyl β-lactosides

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Selective modification of oligosaccharides (i.e., replacement of one of the OH groups by another group) provides important information for the study of structure–biological activity relationships. In the present study our interest was directed to the chemical syntheses of C-3 modified methyl β-lactoside (methyl 4-*O*-β-D-galactopyranosyl-β-D-glucopyranosides) [1]. The OH-3 group of lactose is related to certain biological and stereochemical properties. For example, the OH-3 position is glycosylated by fucosyl transferase [2]. X-Ray analysis [3] has shown that the OH-3 group is involved in intramolecular hydrogen bonding with O-5′ which may stabilize the three dimensional structure of lactose in aqueous solution. Sagrego et al. [4,5] have recently reported that C-3 deoxy and methoxy analogues showed different binding affinities with galactose binding lectins and studied the conformational properties of C-3 modified lactosides by NMR spectroscopy.

Syntheses of some C-3 modified (C-3 deoxy and methoxy) lactoses have already been reported [6]. Recently, Wong et al. [7] reported an enzymic approach towards C-3 modified lactose and *N*-acetyl lactosamine derivatives using galactosyltransferase (GaIT). In our experiments [1], a similar chemoenzymic approach was attempted using GaIT to prepare C-3 modified lactoses. However, C-3 modified glucoses (3-deoxy, -fluoro, -azido, -methoxy) were too poor substrates to be applied for practical purposes. Although 3-acetamido-3-deoxy-D-glucose (Glc3NAc) was an exceptionally good substrate, the product was not a lactose derivative but β-D-Gal-(1 → 1)-β-D-Glc3NAc of the β,β-trehalose type [8]. Consequently, a chemical approach is described for the preparations of C-3 modified methyl β-lactosides.

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1. Results and discussion

Our approach was initiated with the isopropylidenation of methyl β-lactoside (**1a**) [9]. Recently, improved methods have been reported for the 3′,4′-*O*-isopropylidenation of benzyl β-lactoside (**1b**) [10,11]. Application of the method by Yoshino et al. [10] gave a mixture of isopropylidene derivatives from which the desired 3′,4′-*O*-isopropylidene derivative (**2a**) could be separated in 60% yield by chromatography on silica gel. Here we wish to describe a more efficient and simple method using trimethylsilylchloride (TMSCl) and acetone [12]. A suspension of **1a** in a mixture of acetone and TMSCl was stirred at room temperature for 3 h and concentrated to afford **2a** quantitatively. In the same manner, benzyl 3′,4′-*O*-isopropylidene β-lactoside (**2b**) could be obtained quantitatively.

Selective protection of both primary hydroxy groups (OH-6 and OH-6′) of **2a** with *tert*-butyldimethylsilylchloride (TBDMSCl) [13] in pyridine gave **3** in 80% yield. Epoxidation of **3** was performed according to the Mitsunobu reaction [14] which was recently applied for the preparations of 2,3- and 3,4-anhydro derivatives from 6-*O*-protected methyl β-D-glucopyranoside [15]. Here, the desired epoxide **4** was selectively obtained in 70–80% yield from **3** after chromatographic purification on silica gel.

Nucleophilic opening of the epoxide by different nucleophiles was expected to take place mainly at the C-3 position [16–19] to give a variety of C-3 modified lactosides. As expected, hydride reduction of **4** with $LiAlH_4$ in refluxing tetrahydrofuran gave the 3-deoxy isomer exclusively. After deprotection (de-*O*-silylation and de-*O*-isopropylidenation) with aqueous trifluoroacetic acid, methyl 3-deoxy-β-lactoside **5** was obtained in 65% yield from **4**. The low yield may be ascribed mainly to losses during the isolation procedure since the product is highly hygroscopic [6d]. After hydrolysis, no degradation product other than **4** was observed by TLC.

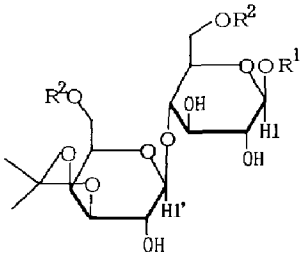
Epoxide opening of **4** with sodium azide (NaN_3) in dimethylformamide (130°C for 15 h) gave the 3-azido-3-deoxy derivative. Deprotection as described above gave methyl 3-azido-3-deoxy-β-lactoside **6** in 85% yield from **4**. When **4** was refluxed with anhydrous cation exchange resin (Amberlyst^{R}15, H^+ form) in anhydrous methanol, epoxide opening and deprotection subsequently occurred to give methyl 3-*O*-methyl-β-lactoside **7** in 50% yield after crystallization. The lower yield may be related to the formation of byproducts possibly involving the 2,3-altroside stereoisomer. When refluxing was continued for more than 4 h, methanolysis of the glycoside linkage took place to give a complex mixture of products.

In order to obtain the 3-fluoro-3-deoxy derivative, **4** was treated with potassium hydrogen fluoride (KHF_2) in ethyleneglycol at 180–190°C [18]. Complete desilylation and partial deisopropylidenation took place under these conditions to afford a complex mixture of products. Partial purification after treatment with 10% aqueous trifluoroacetic acid to complete the deisopropylidenation and ^1H NMR analysis indicated that the mixture contained methyl 3-deoxy-3-fluoro-β-lactoside **8** (ca. 30%), methyl 2-deoxy-2-fluoro-4-*O*-(β-D-galactopyranosyl)-β-D-altropyranoside (ca. 30%), methyl 3,6-anhydro-4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranoside (ca.

20%) and methyl 4-*O*-(β-D-galactopyranosyl)-3-*O*-(2-hydroxyethyl)-β-D-glucopyranosides (ca. 20%). In order to improve this approach, the intermediate **4** was converted into the 2′,6,6′-tri-*O*-benzyl derivative **9** by initial treatment with cesium fluoride (100–110°C) and then benzylbromide–sodium hydride (20°C) in dimethylformamide. The epoxide **9** was submitted to the same procedure for the fluorination of **4** and deisopropylidenation gave a mixture of 3-deoxy-3-fluoro-β-lactoside **10** (ca. 40%), its altroside isomer (ca. 30%), and 3-*O*-(2-hydroxyethyl) lactoside (ca. 30%). The main component **10** was separated by column chromatography on silica gel and hydrogenated with palladium hydroxide in methanol to afford **8**.

In conclusion, four different 3-modified methyl β-lactosides were prepared using **4** or **9** as key intermediates. The epoxide opening with $LiAlH_4$ and NaN_3 under basic conditions gave higher stereoselectivity compared with the procedure under acidic conditions (Amberlyst in MeOH or KHF_2). A similar tendency was observed for reactions of 2,3-anhydro-D-allopyranoside with nucleophiles [16–19].

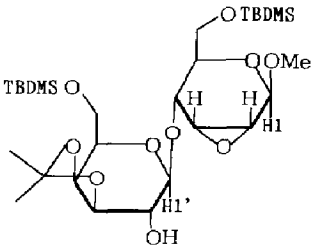
The present approach should be suitable to prepare other C-3 modified lactose analogues such as C-3 modified benzyl β-lactoside for further modifications at the



2a: R^1 = CH_3, R^2=H

2b: R^1 = benzyl (Bn), R^2=H

3 : R^1 = CH_3, R^2=TBDMS ($Si(Me)_2{}^tBu$)



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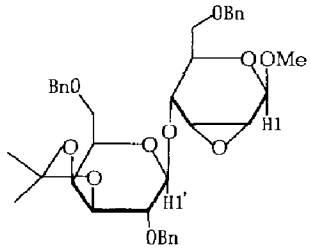

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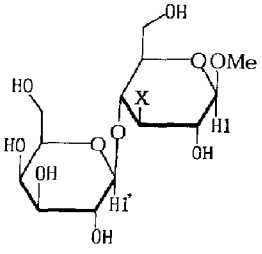
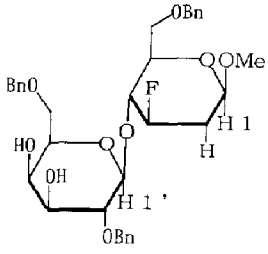


5: X=H

6: X=N_3

7: X=OMe

8: X=F



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C-1 position. Since many sialooligosaccharides are composed of lactose units, this approach can be applied to prepare sialooligosaccharides selectively modified in the lactose unit.

2. Experimental

General methods.—Melting points (mp) were uncorrected. ^{1}H NMR spectra were recorded at 400 MHz. Optical rotations were recorded on a Jasco J-20 spectrometer set at 589 nm. All solvents were purified by distillation before use.

Methyl 4-O-(3,4-O-isopropylidene-β-D-galactopyranosyl)-β-D-glucopyranoside (**2a**).—A mixture of methyl β-lactoside [9] (1 g, 2.9 mmol), acetone (10 mL) and trimethylsilyl chloride (4 mL) was stirred at room temperature under N_2. After 3 h, the mixture was suspended with *n*-hexane (10 mL) and evaporated in vacuo to give **2a** (1.11 g, 100%). The solid was pure based on its ^{1}H NMR spectrum and was used for the next reaction; mp 221–222°C; $[\alpha]_D^{22}$ +2.8° (*c* 0.3, CH_3OH). ^{1}H NMR (D_2O): 1.65 and 1.80 (3 H, s, CH_3 of isopropylidene), 3.80 (3 H, s, OMe), 4.66 (1 H, d, $J_{1,2}$ 7.8 Hz, H-1), 4.75 (1 H, d, $J_{1',2'}$ 8.5 Hz, H-1'). Anal. Calcd for $C_{16}H_{28}O_{11}$: C, 48.47; H, 7.13. Found: C, 48.22; H, 7.07.

*Methyl 4-O-(3,4-O-isopropylidene-6-O-*tert*-butyldimethylsilyl-β-D-galactopyranosyl)-6-O-*tert*-butyldimethylsilyl-β-D-glucopyranoside* (**3**).—A mixture of **2a** (200 mg, 0.51 mmol), *tert*-butyldimethylsilyl chloride (190 mg), 4-(*N*,*N*-dimethylamino)-pyridine (10 mg), and triethylamine (1 mL) in dichloromethane (10 mL) was stirred at room temperature for 12 h. The mixture was evaporated, and the residue purified by chromatography on silica gel (toluene–EtOAc). The fraction containing the main product was collected and concentrated to give **3** as a waxy solid (240 mg, 80%); mp 125–126°C; $[\alpha]_D^{22}$ +1.2°, $[\alpha]_{300}^{22}$ +3.8° (*c* 0.76, MeOH). Anal. Cacld for $C_{28}H_{56}O_{11}Si_2$:C, 53.80; H; 9.05. Found: C, 53.91; H; 9.09.

The structure of the 2,3,2'-tri-*O*-acetate was identified by ^{1}H NMR spectroscopy ($CDCl_3$) as follows: 0.07, 0.08, 0.09, and 0.10 (3 H, s, Si–CH_3), 0.90 and 0.91 (9 H, s, *tert*-Bu), 1.31 and 1.54 (3 H, s, isopropylidene–CH_3), 2.02, 2.02, and 2.09 (3 H, s, $OCOCH_3$), 3.44 (3 H, s, OCH_3), 4.35 (1 H, d, $J_{1,2}$ 7.7 Hz, H-1), 4.49 (1 H, d, $J_{1',2'}$ 7.8 Hz, H-1'), 4.85 (1 H, dd, $J_{1,2}$ 7.7, $J_{2,3}$ 9.3 Hz, H-2), 4.85 (1 H, dd, $J_{1',2'}$ 7.7, $J_{2',3'}$ 9.3 Hz, H-2'), 5.13 (1 H, t, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-3).

*Methyl 2,3-anhydro-4-O-(3,4-O-isopropylidene-6-O-*tert*-butyldimethylsilyl-β-D-galactopyranosyl)-6-O-*tert*-butyldimethylsilyl-β-D-allopyranoside* (**4**).—A mixture of **3** (200 mg, 0.34 mmol), triphenylphosphine (114 mg, 0.44 mmol), and diethylazodicarboxylate (76 mg, 0.44 mmol) in toluene (10 mL) was stirred under N_2 for 8 h at 80°C. The solution was diluted with EtOAc (20 mL) and washed with aq 0.5% HCl, satd NaCl, satd $NaHCO_3$, and water. The dried solution ($MgSO_4$) was concentrated, and the main product was purified by chromatography on silica gel (toluene–EtOAc) to give **4** as a syrup (115 mg, 80%); $[\alpha]_D^{22}$ + 3.7°, $[\alpha]_{400}^{22}$ +8.9° (*c* 0.76, MeOH). The structure of the 2'-*O*-acetate was identified by ^{1}H NMR spectroscopy ($CDCl_3$) as follows: 0.06, 0.07, 0.07, and 0.15 (3 H, s, Si–CH_3), 0.82

and 0.83 [9 H, s, $Si(CH_3)_3$], 1.33 and 1.50 (3 H, s, isopropylidene–CH_3), 2.04 (3 H, s, $OCOCH_3$), 3.19 (1 H, d, $J_{2,3}$ 4.5 Hz, H-2), 3.37 (1 H, ddd, $J_{5,6a}$ 1.5, $J_{5,6b}$ 3.5, $J_{4,5}$ 9.5 Hz, H-5). 3.42 (3 H, s, OCH_3), 3.52 (1 H, br d, $J_{2,3}$ 4.5 Hz, H-3), 4.01 (1 H, dd, $J_{3,4}$ 1.5, $J_{4,5}$ 9.5 Hz, H-4), 4.05 (1 H, dd, $J_{3',4'}$ 5.5, $J_{2',3'}$ 8.0 Hz, H-3'), 4.13 (1 H, dd, $J_{4',5'}$ 1.5, $J_{3',4'}$ 5.5 Hz, H-4'), 4.45 (1 H, d, $J_{1',2'}$ 8.5 Hz, H-1'), 4.66 (1 H, br s, H-1), 4.93 (1 H, dd, $J_{2',3'}$ 8.0, $J_{1',2'}$ 8.5 Hz, H-2').

Methyl 3-deoxy-β-lactoside (**5**).—A mixture of **4** (260 mg, 0.43 mmol) and $LiAlH_4$ (26 mg) in tetrahedrofuran (10 mL) was refluxed under N_2 for 5 h. To the mixture was added EtOAc (10 mL) and then satd aq NaCl. The organic layer was separated and dried over $MgSO_4$. After evaporation the crude syrup was diluted with EtOAc and filtered through silica gel in 1:1 EtOAc–toluene. After evaporation, the syrupy residue was diluted with aq 10% trifluoroacetic acid. The solution was stirred for 12 h at room temperature and concentrated with toluene. The syrupy residue was treated with MeOH–ethylether to give **5** as an amorphous powder (95 mg, 65%); mp 180–183°C; $[\alpha]_D^{22}$ −1.3°, $[\alpha]_{300}^{22}$ −10.6° (*c* 0.22, MeOH), [lit. [6d] mp 185–186 (hygroscopic solid) $[\alpha]_D^{25}$ +3.5° (H_2O)]. ^1H NMR (D_2O): 3.41 (1 H, dd, $J_{1,2}$ 7.8, $J_{2,3}$ 10.0 Hz, H-2), 3.50 (1 H, t, $J_{2,3} = J_{3,4} = 10.0$ Hz, H-3), 3.56 (1 H, dd, $J_{1',2'}$ 7.6, $J_{2',3'}$ 10.0 Hz, H-2'), 3.64 (3 H, s, OCH_3), 3.97 (1 H, br d, $J_{3',4'}$ 3.5 Hz, H-4'), 4.05 (1 H, dd, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.44 (1 H, d, $J_{1,2}$ 7.8 Hz, H-1), 4.50 (1 H, d, $J_{1',2'}$ 7.7 Hz, H-1'). Anal. Calcd for $C_{13}H_{24}O_{10} \cdot 0.8H_2O$: C, 44.50; H, 7.22. Found: C, 44.48; H, 6.95.

Methyl 3-azido-3-deoxy-β-lactoside (**6**).—A mixture of **4** (200 mg, 0.33 mmol) and sodium azide (200 mg) in *N*,*N*-dimethylformamide (DMF, 15 mL) was stirred at 130–135°C for 12 h under N_2. The mixture was concentrated in vacuo, diluted with EtOAc, washed with aq satd NaCl, dried over $MgSO_4$, and evaporated. The syrupy residue was passed through a short silica gel column (5 cm) with 1:1 EtOAc–toluene. After evaporation, the residue was treated with aq 10% trifluoroacetic acid and processed in the same manner as described for the preparation of **5**. Compound **6** was obtained as an amorphous solid from MeOH–ethyl ether (107 mg, 85%); mp 107–110°C (dec); $[\alpha]_D^{22}$ +2.8°, $[\alpha]_{300}^{22}$ +17.7° (*c* 0.32, MeOH). Anal Calcd for $C_{13}H_{23}N_3O_{10}$: C, 40.94; H, 6.09; N, 11.02. Found: C, 40.32; H, 6.66; N, 10.05.

Methyl 3-O-methyl-β-lactoside (**7**).—A mixture of **4** (200 mg, 0.33 mmol) and Amberlyst^{R}15 (200 mg) in anhyd MeOH (10 mL) was refluxed for 3 h. The solution was filtered and treated with triethylamine (0.1 mL), then concentrated, and the residue was dissolved in EtOH and precipitated from ethyl ether to give **7** (61 mg, 50%); mp 198–200°C; $[\alpha]_D^{22}$ −2.4°, $[\alpha]_{300}^{22}$ −18.4° (*c* 0.34, MeOH). ^1H NMR (D_2O): 3.41 (1 H, dd, $J_{1,2}$ 7.8, $J_{2,3}$ 10.0 Hz, H-2), 3.50 (1 H, t, $J_{2,3} = J_{3,4} = 10.0$ Hz, H-3), 3.56 (1 H, dd, $J_{1',2'}$ 7.6, $J_{2',3'}$ 10.0 Hz, H-2'), 3.61 and 3.64 (3 H, s, OCH_3), 3.97 (1 H, br d, $J_{3',4'}$ 3.5 Hz, H-4'), 4.05 (1 H, dd, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.44 (1 H, d, $J_{1,2}$ 7.8 Hz, H-1), 4.50 (1 H, d, $J_{1',2'}$ 7.7 Hz, H-1'). Anal. Calcd for $C_{14}H_{26}O_{11}$: C, 45.39; H, 7.09. Found: C, 44.82; H, 6.96.

*Methyl 2,3-anhydro-6-O-benzyl-4-O-(2,6-di-O-benzyl-3,4-O-isopropylidene-β-*D*-galactopyranosyl)-β-*D*-allopyranoside* (**9**).—To a solution of **4** (200 mg, 0.33 mmol) in DMF (20 mL) was added cesium fluoride (150 mg) at 110°C. The solution was

stirred for 30 min and then cooled to room temperature. To the mixture were added benzylbromide (1 mL) and then sodium hydride (100 mg, ca. 60% dispersion in mineral oil), and the temperature was kept at 0°C. After stirring at room temperature for 12 h, MeOH (1 mL) was added to decompose the excess NaH. The mixture was diluted in satd aq NaCl (20 mL), extracted with EtOAc (2 × 30 mL), dried over $MgSO_4$, and concentrated. The syrupy residue was purified on silica gel (20:1 toluene–EtOAc) to give **9** (175 mg, 82%); mp 95–97°C; $[\alpha]_D^{22}$ +7.4° (*c* 0.25, MeOH). ^{1}H NMR ($CDCl_3$): 1.32 and 1.38 (3 H, s, isopropylidene–CH_3), 3.29 (1 H, d, $J_{2,3}$ 4.5 Hz, H-2), 3.43 (1 H, dd, $J_{2',3'}$ 6.5, $J_{1',2'}$ 8 Hz, H-2′), 3.51 (3 H, s, OCH_3), 4.34 (1 H, d, $J_{1',2'}$ 8.0 Hz, H-1′), 4.75 (1 H, s, H-1), benzyl methylene protons appeared as a doublet at 4.40, 4.54, 4.59, 4.70, and 4.75 ppm. Anal. Calcd for $C_{37}H_{44}O_{10}$: C, 68.49; H, 6.85. Found: C, 68.30; H, 6.79.

Methyl 3-deoxy-3-fluoro-β-lactoside (**8**).—A mixture of **9** (100 mg, 0.15 mmol) and KHF_2 (300 mg) in ethylene glycol (2 mL) was heated at 180–190°C under N_2 for 5 h. The mixture was cooled to room temperature, diluted with satd NaCl, extracted with dichloromethane (2 × 10 mL), and washed with water (1 × 10 mL). The organic layer was concentrated. The residue was dissolved in 10% trifluoroacetic acid, stirred for 3 h, and concentrated with toluene. Thin layer chromatography (silica gel, toluene–EtOAc–EtOH) indicated three spots with R_f 0.5, 0.48, and 0.30. Partial chromatographic separation and ^{1}H NMR analysis of the mixture showed that the second spot was the desired C-3 fluorinated derivative **10** (ca. 40%), the first spot (R_f 0.5) was the C-2 fluorinated product (ca. 30%), and the third was methyl 3-*O*-(2-hydroxyethyl)-β-lactoside (ca. 30%). The C-3 fluorinated product **10** was separated by silica gel chromatography and treated with ethyl ether to give a crystalline solid (28 mg, 29%); mp 106–108°C; $[\alpha]_D^{22}$ −20.7° (*c* 1, MeOH). ^{1}H NMR ($CDCl_3$): 3.56 (3 H, s, OCH_3), 3.91 (1 H, br d, $J_{3',4'}$ 3.0 Hz, H-4′), 4.00 (1 H, ddd, $J_{3,4}$ 9.0, $J_{4,5}$ 10.2, $J_{4,F}$ 14.5 Hz, H-4), 4.18 (1 H, d, $J_{1',2'}$ 7.5, H-1′), 4.40 (1 H, br d, $J_{1,2}$ 7.3 Hz, H-1), 4.52 (1 H, ddd, $J_{2,3} = J_{3,4} = 9.0$. $J_{3,F}$ 52.0 Hz, H-3), benzyl methylene protons appeared as a doublet at 4.44, 4.54, 4.58, 4.58, 4.70, and 4.78 ppm. Anal. Calcd for $C_{34}H_{41}FO_{10}$: C, 64.94; H, 6.59. Found: C, 64.51; H, 6.43.

The solid (10 mg) was dissolved in MeOH containing palladium hydroxide (10 mg) and hydrogenated with H_2 at room temperature. After 8 h the mixture was filtered and concentrated to afford **8** as a syrup (5 mg). ^{1}H NMR (D_2O): 3.53 (1 H, dd, $J_{1',2'}$ 8.0, $J_{2',3'}$ 9.5 Hz, H-2′), 3.58 (3 H, s, OCH_3), 3.73 (1 H, dd, $J_{5',6a'}$ 4.5, $J_{6a',6b'}$ 11.2 Hz, H-6a′), 3.79 (1 H, dd, $J_{5',6b'}$ 8.0, $J_{6a',6b'}$ 11.2 Hz, H-6b′), 3.85 (1 H, dd, $J_{5,6b}$ 5.0, $J_{6a,6b}$ 12.5 Hz, H-6b), 3.92 (1 H, br d, $J_{3',4'}$ 2.7 Hz, H-4′), 3.98 (1 H, ddd, $J_{3,4} = J_{4,5} = 9.0$, $J_{4,F}$ 13.0 Hz, H-4), 4.02 (1 H, dd, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 12.5 Hz, H-6b), 4.44 (1 H, d, $J_{1,2}$ 8.0 Hz, H-1), 4.48 (1 H, d, $J_{1',2'}$ 8.0 Hz, H-1′), 4.59 (1 H, ddd, $J_{2,3} = J_{3,4}$ 9.0, $J_{3,F}$ 52.2 Hz, H-3). FABMS (MeOH–glycerol): 359 $(M + 1)^+$, 381 $(M + Na)^+$.

Benzyl 4-O-(3,4-O-isopropylidene-β-D-galactopyranosyl)-β-D-glucopyranoside (**2b**).—A mixture of benzyl β-lactoside [20] (1 g) and trimethylsilylchloride (4 mL), and acetone (10 mL) was stirred at room temperature for 3 h and concentrated with *n*-hexane (1 mL) to give a white solid (1.09 g, 100%); mp 194–196°C; $[\alpha]_D^{22}$ ±0° (*c* 0.2, MeOH); $[\alpha]_{300}^{22}$ −12.1° (*c* 0.2, MeOH); lit. [10] 196–197°C, $[\alpha]_D^{25}$ −1.0°

(*c* 0.73, pyridine). Anal. Calcd for $C_{22}H_{32}O_{11} \cdot 0.81H_2O$: C, 54.20; H, 6.90. Found: C, 54.20; H, 6.86.

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