Convenient Glycoside Synthesis of Amino Sugars: Michael-Type Addition to 2-Nitro-D-galactal

Jagattaran Das and Richard R. Schmidt*

Fakultät für Chemie, Universität Konstanz, Fach M 725,
D-78457 Konstanz, Germany
Fax: (internat.) + 49(0)7531/88-3135

Received March 2, 1998

Keywords: Glycals, nitro / Michael additions / Glycosylations / Glycosides, galactosamine / Reduction, nitro group

Formation of 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal (**3**) was readily accomplished starting from tri-*O*-benzyl-D-galactal (**1**) by acetyl nitrate addition to **2** and base-promoted acetic acid elimination. Addition of alcohols to **3** under conditions of base catalysis afforded 2-deoxy-2-nitrogalactopyranosides **4a–e** in high yields; high α-selectivity was obtained with strong bases, whereas weaker bases furnished mainly the corresponding β-galactopyranosides. Chemoselective nitro group reduction in these glycosides was successfully carried out in the case of disaccharide **4cα** using Raney nickel as catalyst, thereby affording after *N*-acetylation the corresponding 2-acetylamino-2-deoxy derivative **5cα**.

D-Galactosamine and D-glucosamine are important constituents of various glycoconjugates[1], which are most frequently found in *N*-acetylated form. *N*-Acetylglucosamine is mainly found in β-glycosidic linkages, whereas *N*-acetylgalactosamine occurs in α- and in β-glycosidic linkages. The generation of β-glycosides can be controlled through the anchimeric assistance of participating groups attached to the amino group[1][2][3][4][5][6]. Control of the α-glycosidic linkage generally relies on solvent and stereoelectronic effects exerted in amino sugar derivatives by non-participating latent amino groups, for instance the azido group[1][2][3]. Even the synthesis of these starting materials tends to be cumbersome and, therefore, particularly for the generation of α-glycosides of *N*-acetylgalactosamine, efficient methods are highly desirable. We report herein our results on Michael-type additions of alcohols to 2-nitrogalactal.

Some years ago, Lemieux et al.[7] transformed tri-*O*-acetylglucal into the corresponding 2-nitroglucal and, by Michael-type addition of methanol, obtained methyl 2-deoxy-2-nitro-D-glucopyranosides. Since then, only a few studies involving other *O*-protected 2-nitroglucals, methanol, and lithium and thallium salts of simple alcohols (EtOH, $C_6H_{11}OH$) have been conducted[8][9], which have led to varying results[7][8][9]. Clearly, application of this approach to 2-nitro-D-galactal derivatives could be particularly rewarding, inasmuch as alcohol addition can be selectively guided to α- and/or β-galactopyranoside formation. Subsequent nitro group reduction to the corresponding amine and *N*-acetylation would furnish the desired glycosides.

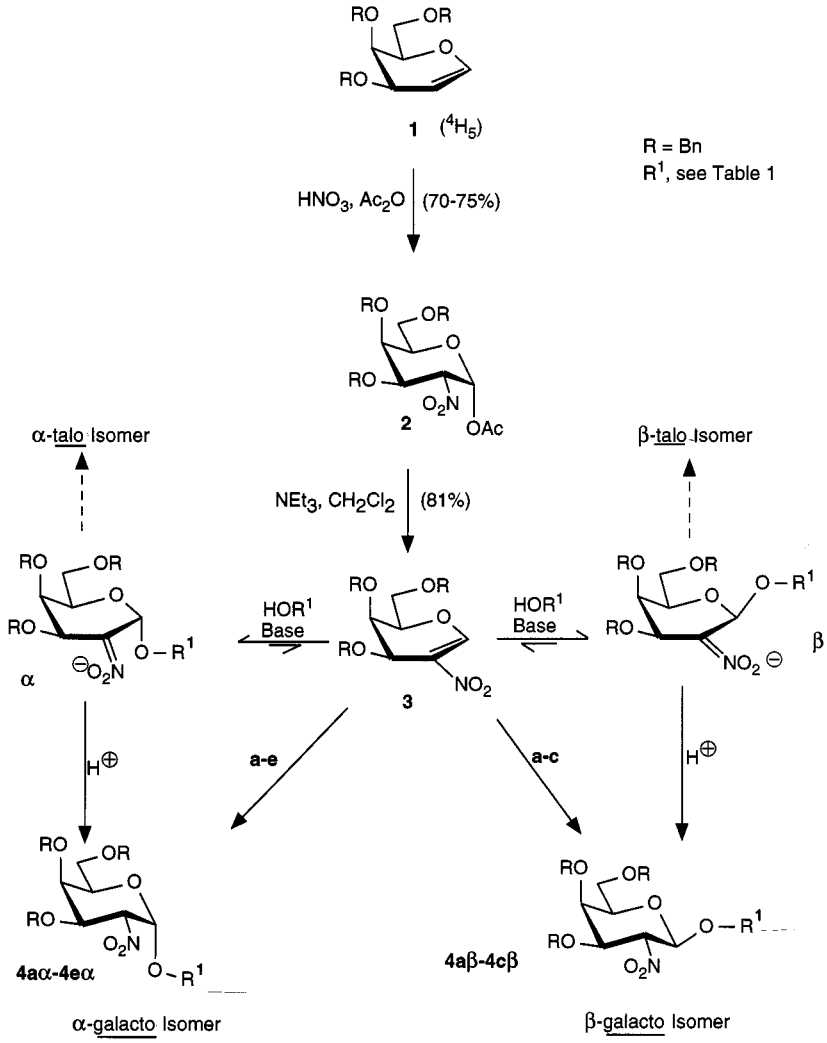
For the synthesis of the starting material, known tri-*O*-benzyl-D-galactal (**1**)[10] was transformed into the required 2-nitro derivative **3** according to a slight modification of a procedure for the synthesis of ethyl 2-nitrovinyl ether from ethyl vinyl ether (Scheme 1)[11]. To this end, **1** was treated with acetyl nitrate, which was generated in situ by the addition of nitric acid to acetic anhydride under strict temperature control[11][12]. In this way, 2-deoxy-2-nitrogalactopyranoside **2** was obtained in good yields (70−75%)[13]. Addition of triethylamine to a solution of **2** in dichloromethane furnished target molecule **3** in 81% yield.

For stereoelectronic reasons, addition of nucleophiles to **3** in the $^4H_5$ conformation should occur from the α side[14]. Therefore, as a test case, a 0.1 M solution of sodium methoxide in methanol was added to a solution of **3** in THF at room temperature (Table 1, entry 1). This led mainly to the expected α-glycoside **4aα** in high yield; only minor amounts of the β-galactopyranoside **4aβ** could be isolated (92%; **4aα**/**4aβ**, 8:1). However, when this reaction was carried out using excess methanol in the presence of triethylamine as base (entry 2), predominantly the β isomer **4aβ** was obtained (90%, α/β, 1:8). Under neither reaction conditions could any of the α- or β-glycosides of the corresponding *talo* isomer be detected. Our findings are at variance with the results of additions to 2-nitroglucal derivatives[7][8][9]. They imply that in the presence of an amine base addition from the β side of **3** is kinetically favoured, possibly due to hydrogen bond interactions of methanol with the 4-*O* and/or 6-*O* of the galactose moiety, or due to preferred reaction of the $^5H_4$ conformer of **3**. Then, for stereoelectronic and/or thermodynamic reasons, the β intermediate (Scheme 1) is transformed by protonation at the β side solely into the β-galactoside **4aβ**. With a strong base, having for instance sodium or potassium as counterion, the free alkoxide oxygen atom attacks for stereoelectronic reasons the $^4H_5$ conformer of **3** preferentially from the α side yielding **4aα**.[15]

This interpretation could be established in subsequent reactions. Addition of an excess of octanol (Table 1, **b**) to **3** in the presence of triethylamine as base (entry 4) afforded mainly the β isomer **4bβ** (66%; **4bα**/**4bβ**, 1:8). When methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**c**)[16] was used as the donor alcohol, with either triethylamine or 1,8-diaza-

  1434−193X/98/0808−1609 $ 17.50+.50/0

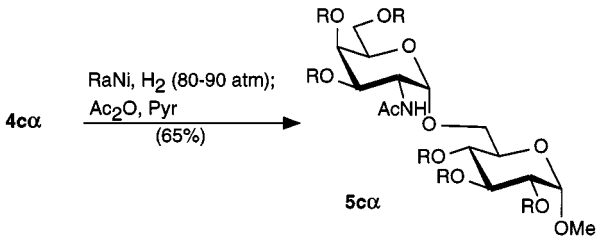
Scheme 1



bicyclo[5.4.0]undec-7-ene (DBU) as the base (entries 6 and 7), the yields of addition to **3** were high, although in this case predominant formation of the β isomer **4cβ** was not observed. This change in the α:β ratio compared with **4aβ** and **4bβ** formation is presumably due to steric factors, which result in guidance of the nucleophile to the α side both in the $^4H_5$ and $^5H_4$ conformers of **3**. However, in the presence of equimolar amounts of a strong base, octanol (**b**), methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**c**), methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**d**)[16], and 2,3:4,5-di-*O*-cyclohexylidene-1-*O*-(−)-menthyloxycarbonyl-D-*myo*-inositol (**e**)[17] (entries 3, 5, 8, and 9) all gave essentially exclusively the corresponding α-galactopyranosides **4bα**−**4eα** in high yields. Thus, at least for the synthesis of α-glycosides of galactosamine, the utility of this convenient glycosylation method is apparent.

In order to demonstrate the general usefulness of this method, investigations aimed at transforming the nitro group into the commonly found *N*-acetylamino group were undertaken. Amongst the various methods for nitro group reduction, Raney Ni catalyzed hydrogenation at elevated pressure (80−90 atm) and subsequent *N*-acetylation proceeded highly selectively. Thus, **4cα** was readily transformed into the corresponding *N*-acetylamino derivative **5cα** (Scheme 2). All compounds could be structurally assigned on the basis of their ^{1}H-NMR data.

Scheme 2



This work was supported by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie.* J. D. is grateful for an *Alexander von Humboldt Fellowship.*

Experimental Section

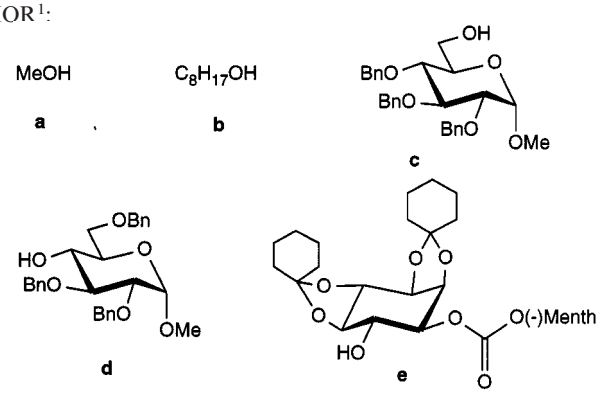
General: Solvents were purified by standard procedures; the boiling range of the petroleum ether used was 35−60°C. − Melting points are uncorrected. − Optical rotations: Perkin-Elmer polar-

Table 1. Results of Michael-type additions to 2-nitrogalactal **3** as acceptor

Entry	Michael donor	Base	Product	Yield [%][a]	α:β
1	**a**	NaOMe	**4a**	92	8:1
2	**a**	NEt_3	**4a**	90	1:8
3	**b**	*t*BuOK	**4b**	72	8:1
4	**b**	NEt_3	**4b**	66	1:8
5	**c**	$KN(SiMe_3)_2$	**4c**	89	1:0
6	**c**	$NEt_3 + K_2CO_3$	**4c**	86	1:1
7	**c**	DBU	**4c**	79	2:3
8	**d**	$KN(SiMe_3)_2$	**4d**	79	1:0
9	**e**	*t*BuOK	**4e**	80	8:1

[a] Yields calculated on the basis of starting alcohol consumed, unless mentioned otherwise.

HOR[1]:



imeter 241 MC; 1-dm cell, all values were measured at 22°C and are uncorrected. − Thin-layer chromatography (TLC): Plastic sheets, silica gel 60 F_{254} (Merck, layer thickness 0.2 mm); detection by UV light (254 nm) or by spraying with 5% $(NH_4)_2MoO_4$ and 0.1% $Ce(SO_4)_2$ in 10% H_2SO_4 and heating to 120°C. − Flash chromatography: Silica gel (J. T. Baker, particle size 40 mm). − ^1H NMR: Bruker AC 250 (250 MHz) Cryospec, Bruker DRX 600 (600 MHz). − ^{13}C NMR: Bruker AC 250 (62.9 MHz) Cryospec, Bruker DRX 600 (150 MHz), internal standard tetramethylsilane (TMS). − Elemental analyses: Heraeus CHN-O-Rapid.

3,4,6-Tri-O-benzyl-D-galactal (**1**): Prepared from 3,4,6-tri-*O*-acetyl-D-galactal according to the reported procedure[10].

1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-nitro-α-D-galactopyranose[12] (**2**): Conc. HNO_3 (5 ml, 79 mmol) was added dropwise to Ac_2O (50 ml) at 10°C under argon. The external temp. was further lowered to −10°C to keep the internal temperature in the range 20−25°C during the addition. Once the addition was complete, the solution was further cooled to −33°C. Then, a solution of compound **1** (8.6 g, 20.7 mmol) in Ac_2O (10 ml) was added over a period of 10−15 min and the mixture was stirred at this temp. for 0.5 h. The cooling bath was then removed, the temp. was allowed to rise to 0°C, and the mixture was poured into 150 ml of iced water. Brine (100 ml) was added and the aqueous layer was extracted with diethyl ether (3 × 150 ml). The combined organic extracts were dried with $MgSO_4$ and the solvent was removed. The pasty residue obtained was crystallized from MeOH (50 ml) to yield **2** (6.8 g, 63%). A second crystallization of the mother liquor proved difficult. However, a further 1−1.2 g of **3** (next step) could be obtained directly by treating the mother liquor (after removal of the solvent) with NEt_3, improving the total yield to 70−75%, m.p. 103°C. − TLC (toluene/ethyl acetate, 9:1): $R_f = 0.35$. − $[\alpha]_D = -15.5$ (c = 1, chloroform). − ^1H NMR (250 MHz, $CDCl_3$): δ = 2.05 (s, 3 H, OCH_3), 3.75 (m, 2 H, 6-H, 6′-H), 3.9 (t, J = 2.47 Hz, 1 H, 4-H), 4.20 (m, 1 H, 5-H), 4.3 (dd, $J_{1,2}$ = 2.25, $J_{2,3}$ = 4.4 Hz, 1 H, 2-H), 4.40−4.90 (m, 7 H, 3 OCH_2Ph, 3-H), 6.72 (d, 1 H, J = 4.1 Hz, 1-H), 7.20−7.30 (m, 15 H, arom.). − $C_{29}H_{31}O_8N$ (521.6): calcd. C 66.78, H 5.99, N 2.69; found C 67.05, H 5.90, N 2.88. − MS (MALDI): calcd. 521 + 23 (Na) = 544; found 544.

3,4,6-Tri-O-benzyl-2-nitro-D-galactal (**3**): NEt_3 (0.95 ml, 6.8 mmol) was slowly added to a stirred solution of **2** (3.0 g, 5.76 mmol) in CH_2Cl_2 (30 ml) at 0°C. Once the addition was complete, the cooling bath was removed and the mixture was stirred for 0.5 h at ambient temp. It was then diluted with further CH_2Cl_2 (30 ml), washed with water, 1 N HCl, satd. $NaHCO_3$ solution, and brine, and then dried with $MgSO_4$. Removal of the volatiles and purification of the residue by column chromatography (toluene/ethyl acetate, 98:2) furnished **3** (2.14 g, 81%). − TLC (toluene/ethyl acetate, 9:1): $R_f = 0.65$. − $[\alpha]_D = -10.2$ (c = 1, chloroform). − ^1H NMR (250 MHz, $CDCl_3$): δ = 3.92 (m, 3 H, 6-H, 6′-H, 4-H), 4.40−4.95 (m, 8 H, 3 OCH_2Ph, 3-H, 5-H), 7.30 (m, 15 H, arom.), 8.08 (s, 1 H, 1-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 67.43, 71.95, 72.94, 73.21, 74.73, 77.20, 77.89, 127.47−128.47 (m, arom.), 131.39−137.59 (t, arom.), 154.3 (C-2). − $C_{27}H_{27}O_6N$ (461.5): calcd. C 70.27, H 5.90, N 3.04; found C 70.09, H 5.88, N 2.94. − MS (MALDI): calcd. 461 + 23 (Na) = 484; found 484.

Methyl 3,4,6-Tri-O-benzyl-2-deoxy-2-nitro-D-galactopyranoside (**4aα,β**). − *Procedure A*: To a stirred solution of **3** (236 mg, 0.51 mmol) in dry THF (2 ml) was added NaOMe solution (0.1 M in methanol, 1.0 ml). After stirring at room temp. for 1 h, the reaction mixture was neutralized with Amberlite IRA-120 resin (H^+ form, 400 mg). Filtration of the reaction mixture, followed by concentration of the filtrate and purification of the residue by column chromatography (petroleum ether/ethyl acetate, 90:10) yielded **4aα** (206 mg, 82%), m.p. 77°C. − TLC (petroleum ether/ethyl acetate, 4:1): $R_f = 0.60$. − $[\alpha]_D = +83.1$ (c = 1, chloroform). − ^1H NMR (600 MHz, $CDCl_3$): δ = 3.35 (s, 3 H, OCH_3), 3.55 (q, 2 H, 6-H, 6′-H), 3.96 (t, 1 H, J = 6.50 Hz, 5-H), 3.99 (d, 1 H, J = 1.96 Hz, 4-H), 4.45 (m, 4 H, 2 OCH_2Ph), 4.72 (q, 2 H, OCH_2Ph), 4.83 (d, 1 H, J = 11.2 Hz, 3-H), 5.0 (dd, 1 H, $J_{1,2}$ = 4.13, $J_{2,3}$ = 10.65 Hz, 2-H), 5.2 (d, 1 H, J = 4.12 Hz, 1-H), 7.30 (m, 15 H, arom.). − ^{13}C NMR (150 MHz, $CDCl_3$): δ = 55.71, 68.38, 69.55, 73.09, 73.20, 73.57, 75.06, 75.14, 84.32, 97.30, 128 (m, arom.), 137.28−137.92 (t, arom.). − $C_{28}H_{31}O_7N$ (461.5): calcd. C 68.14, H 6.33, N 2.84; found C 67.92, H 6.47, N 2.78. − MS (MALDI): calcd. 493 + 23 (Na) = 516; found 517. − **4aβ**: Yield 26 mg, (10%), m.p. 130°C. − TLC (petroleum ether/ethyl acetate, 4:1): $R_f = 0.50$. − $[\alpha]_D = +16.5$ (c = 1, chloroform). − ^1H NMR (600 MHz, $CDCl_3$): δ = 3.45 (s, 3 H, OCH_3), 3.64 (m, 3 H, 6-H, 6′-H, 4-H), 3.98 (d, 1 H, J = 1.98 Hz, 5-H), 4.04 (dd, 1 H, $J_{2,3}$ = 10.70, $J_{3,4}$ = 2.6 Hz, 3-H), 4.55 (m, 6 H, 3 OCH_2Ph), 4.64 (d, 1 H, J = 8.0 Hz, 1-H), 4.83 (d, 1 H, J = 11.2 Hz, 2-H), 7.3 (m, 15 H, arom.). − ^{13}C NMR (150 MHz, $CDCl_3$): δ = 57.12, 67.96, 71.43, 72.36, 73.63, 73.85, 74.75, 79.48, 87.41, 101.09, 128 (m, arom.), 137 (t, arom.). − $C_{28}H_{31}O_7N$ (461.5): calcd. C 68.14, H 6.33, N 2.84; found C 68.14, H 6.48, N 2.83. − MS (EI): *m/z*: 493 [M^+], 402 [$M^+ - 91$] in a ratio of 8:1. Yield calculated on the basis of compound **3** consumed.

Procedure B: To a stirred mixture of 0.2 ml methanol (5 mmol) and 1 ml NEt_3, a solution of **3** (210 mg, 0.45 mmol) in dry THF (1 ml) was added dropwise under argon. After stirring the reaction mixture at room temp. for 5 h, the volatiles were removed in vacuo. The pasty residue thus obtained was purified by column chromatography as described above to yield **4aα** (22 mg, 10%) and **4aβ** (180 mg, 80%). Yields calculated on the basis of compound **3** consumed.

Octyl 3,4,6-Tri-O-benzyl-2-deoxy-2-nitro-D-galactopyranoside (**4bα,β**). − *Procedure A:* To a stirred solution of **3** (140 mg, 0.3 mmol) and 1-octanol (41 mg, 0.32 mmol) in THF (1 ml) was added a solution of potassium *tert*-butoxide (0.5 ml, 10 mg/ml) in THF. After stirring the reaction mixture at room temp. for 2 h, it was neutralized with Amberlite IRA resin (H^+ form). The resin was filtered off and the solvent was evaporated from the filtrate. Purification of the residue by column chromatography (petroleum ether/ethyl acetate, 95:5) yielded **4bα** (115 mg, 64%). − TLC (petroleum ether/ethyl acetate, 4:1): $R_f = 0.80$. − $[\alpha]_D = +77.7$ ($c = 1$, chloroform). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, $J = 6.5$ Hz, CH_3), 1.25 [br. s, 10 H, (CH_2)$_5$], 1.50 (dist. t, 2 H, CH_2), 3.35 (m, 1 H, 4-H), 3.55 (m, 2 H, 6-H, 6′-H), 3.65 (m, 1 H, 3-H), 4.00 (dist. t, 2 H, OCH_2), 4.45 (m, 4 H, 2 OCH_2Ph), 4.80 (m, 3 H, 5-H, OCH_2Ph), 4.98 (dd, 1 H, $J_{1,2} = 4.2$ Hz, $J_{2,3} = 10.6$ Hz, 2-H), 5.30 (d, 1 H, $J = 4.2$ Hz, 1-H), 7.30 (m, 15 H, arom.). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.03, 22.56, 25.74, 28.95, 29.09, 29.12, 31.70, 68.30, 68.68, 69.47, 72.93, 73.13, 73.43, 74.96, 75.15, 84.30, 96.16, 128 (m, arom.), 138 (t, arom.). − $C_{35}H_{45}O_7N$ (591.7): calcd. C 71.04, H 7.66, N 2.37; found C 71.03, H 7.78, N 2.20. − MS (MALDI): calcd. 591 + 23 = 614; found 615. − **4bβ**: Yield 14 mg (8%), m.p. 32−33°C. − TLC (petroleum ether/ethyl acetate, 4:1): $R_f = 0.75$. − $[\alpha]_D = +15.6$ ($c = 1$, chloroform). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (dist. t, 3 H, CH_3), 1.25 [br. s, 10 H, (CH_2)$_5$], 1.50 (dist. t, 2 H, CH_2), 3.41 (m, 1 H, 4-H), 3.62 (m, 4 H, 6-H, 6′-H, OCH_2), 3.82 (m, 1 H, 3-H), 4.05−4.58 (m, 6 H, 3 OCH_2Ph), 4.72 (d, 1 H, $J = 8.04$ Hz, 1-H), 4.81 (d, 1 H, $J = 4.33$ Hz, 5-H), 4.87 (dd, 1 H, $J_{1,2} = 8.04$, $J_{2,3} = 7.72$ Hz, 2-H), 7.30 (m, 15 H, arom.). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.03, 22.56, 25.57, 29.08, 29.11, 29.13, 29.22, 31.71, 67.99, 70.26, 71.47, 72.23, 73.54, 73.78, 74.69, 79.49, 87.48, 100.18, 128 (m, arom.), 137 (t, arom.). − $C_{35}H_{45}O_7N$ (591.7): calcd. C 71.04, H 7.66, N 2.37; found C 70.90, H 7.72, N 2.37. − MS (MALDI): calcd. 591 + 23 = 614; found 616. Yield calculated on the basis of compound **3** consumed.

Procedure B: To a stirred solution of 1-octanol (41 mg, 0.32 mmol) and NEt_3 (1 ml) was added a solution of **3** (110 mg, 0.24 mmol) in THF (1 ml). After stirring the reaction mixture at room temp. for 2 d, the volatiles were removed in vacuo. Chromatographic purification of the residue yielded **4bα** (11 mg, 8%) and **4bβ** (82 mg, 58%). The yields are calculated on the basis of compound **3** consumed.

Methyl 2,3,4-Tri-O-benzyl-6-O-(3,4,6-tri-O-benzyl-2-deoxy-2-nitro-D-galactopyranosyl)-α-D-glucopyranoside (**4cα,β**). − *Procedure A:* To a solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[16] (185 mg, 0.40 mmol) in dry THF (2 ml) at −50°C, a solution of potassium hexamethyldisilazide (KHMDS) in toluene (0.5 M, 0.9 ml, 0.45 mmol) was added dropwise under argon. The solution was then cooled further to −78°C, whereupon a solution of compound **3** (221 mg, 0.48 mmol) in THF (2 ml) was slowly added and stirring was continued at this temp. for 2 h. The cooling bath was then removed and the mixture was allowed to warm to 0°C. Saturated ammonium chloride solution was added and the mixture was extracted with diethyl ether (3 × 15 ml). The combined ethereal extracts were washed with satd. $NaHCO_3$ solution and brine, and then dried ($MgSO_4$). Evaporation of the solvent and chromatographic purification of the residue (petroleum ether/ethyl acetate, 80:20) yielded **4cα** (327 mg, 89%). − TLC (petroleum ether/ethyl acetate, 4:1): $R_f = 0.50$. − $[\alpha]_D = +78.7$ ($c = 1$, chloroform). − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.36 (s, 3 H, OCH_3), 3.41 (t, 1 H, $J = 9.2$ Hz, 4a-H), 3.55−3.61 (m, 3 H, 2a-H, 6b-H, 6′b-H), 3.66 (m, 1 H, 5a-H), 3.68−3.80 (m, 2 H, 6a-H, 6′a-H), 3.98−4.04 (m, 3 H, 3a-H, 4b-H, 5b-H), 4.42 (m, 1 H, 3b-H), 4.41−4.94 (m, 12 H, 3 OCH_2Ph), 4.56 (d, 1 H, $J = 3.40$ Hz, 1a-H), 5.01 (dd, 1 H, $J_{1,2} = 4.03$, $J_{2,3} = 10.9$ Hz, 2b-H), 5.48 (d, 1 H, $J = 4.02$ Hz, 1b-H), 7.3 (m, 30 H, arom.). − ^{13}C NMR (150 MHz, $CDCl_3$): δ = 54.98, 68.11, 69.47, 70.15, 72.82, 73.04, 73.35, 73.49, 74.88, 74.95, 75.49, 77.20, 80.03, 81.68, 84.23, 96.61, 97.84, 128 (m, arom.), 138 (sext, arom.). − $C_{55}H_{59}O_{12}N$ (926.1): calcd. C 71.33, H 6.42, N 1.51; found C 71.51, H 6.66, N 1.42. − MS (MALDI): calcd. 926 + 39 (K) = 965; found 967.

Procedure B: To a solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[16] (230 mg, 0.495 mmol) in NEt_3 (1 ml) was added a solution of **3** (270 mg, 0.585 mmol) in THF (1 ml). Stirring was continued at room temp. while 50-mg portions of solid K_2CO_3 were added at intervals of 12 h. After 24 h, the reaction mixture was diluted with diethyl ether (25 ml) and the ether layer was washed sequentially with water (3 × 15 ml) and with brine. Concentration of the organic phase and purification of the residue by column chromatography as described above yielded **4cα** (63 mg, 43%) and **4cβ** (63 mg, 43%). Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (150 mg, 65%) was recovered. **4cβ**: M.p. 122°C. − TLC (petroleum ether/ethyl acetate, 4:1): $R_f = 0.40$. − $[\alpha]_D = +18.4$ ($c = 1$, chloroform). − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.31 (s, 3 H, OCH_3), 3.35 (t, 1 H, $J = 9.6$ Hz, 4a-H), 3.48 (dd, 1 H, $J_{1,2} = 3.47$, $J_{2,3} = 9.63$ Hz, 2a-H), 3.55−3.65 (m, 3 H, 6b-H, 6a-H, 6′a-H), 3.61 (m, 1 H, 5b-H), 3.70 (dd, 1 H, $J_{1,2} = 3.51$, $J_{2,3} = 9.95$ Hz, 5a-H), 3.93 (t, 1 H, $J = 9.3$ Hz, 3a-H), 3.97 (d, 1 H, $J = 2.21$ Hz, 4b-H), 4.03 (d, 2 H, $J = 3.4$ Hz, 6′a-H, 3b-H), 4.38−4.94 (m, 12 H, 3 OCH_2Ph), 4.56 (d, 1 H, $J = 3.41$ Hz, 1a-H), 4.74 (d, 1 H, $J = 7.96$ Hz, 1b-H), 4.90 (dd, 1 H, $J_{1,2} = 8.13$, $J_{2,3} = 10.5$ Hz, 2b-H), 7.3 (m, 30 H, arom.). − ^{13}C NMR (150 MHz, $CDCl_3$): δ = 55.18, 67.78, 68.56, 69.45, 71.59, 72.38, 73.38, 73.57, 73.88, 74.77, 74.84, 75.73, 77.45, 79.56, 79.76, 82.06, 87.18, 97.99, 100.53, 128 (m, arom.), 138 (sext, arom.). − $C_{55}H_{59}O_{12}N$ (926.1): calcd. C 71.33, H 6.42, N 1.51; found C 71.12, H 6.61, N 1.48. − MS (MALDI): calcd. 926 + 23 (Na) = 949; found 951.

Procedure C: A solution of **3** (240 mg, 0.52 mmol) in THF (2 ml) was added to a stirred solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[16] (200 mg, 0.43 mmol) and DBU (2 drops) in dry THF (2 ml). A further 2 drops of DBU was added after 4 h, and the reaction mixture was allowed to stir at room temp. for a total period of 8 h. It was then diluted with diethyl ether (15 ml), the organic phase was washed with water and brine, dried ($MgSO_4$), and worked-up as described above to yield **4cα** (101 mg, 25%) and **4cβ** (151 mg, 38%). 40 mg of starting alcohol was recovered.

Methyl 2,3,6-Tri-O-benzyl-4-O-(3,4,6-tri-O-benzyl-2-deoxy-2-nitro-α-D-galactopyranosyl)-α-D-glucopyranoside (**4dα**). − *Procedure A:* The procedure adopted was analogous to that described for the preparation of **4cα** (Procedure A). **4dα** (197 mg, 79%) was obtained from 125 mg (0.27 mmol) of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside[16] and **3** (190 mg, 0.41 mmol). − TLC (toluene/ethyl acetate, 9:1): $R_f = 0.60$. − $[\alpha]_D = +85.7$ ($c = 1$, chloroform). − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.40 (s, 3 H, OCH_3), 3.43−3.54 (m, 2 H, 6a-H, 6′a-H), 3.59 (dd, 1 H, $J_{1,2} = 3.50$, $J_{2,3} = 9.50$ Hz, 2a-H), 3.67−3.70 (m, 2 H, 6b-H, 6′b-H), 3.80 (d, 1 H, $J = 8.3$ Hz, 5b-H), 3.91−4.01 (m, 4 H, 3a-H, 4a-H, 5a-H, 4b-H), 4.20−5.07 (m, 12 H, 3 OCH_2Ph), 4.31 (dd, 1 H, $J_{1,2} = 2.80$ Hz, $J_{2,3} = 10.80$ Hz, 3b-H), 4.60 (d, 1 H, $J = 3.79$ Hz, 1a-H), 5.02 (dd, 1 H, $J_{1,2} = 4.50$, $J_{2,3} = 10.80$ Hz, 2b-H), 6.21 (d, 1 H, $J = 4.50$ Hz, 1b-H), 7.3 (m, 30 H, arom.). − ^{13}C NMR (150 MHz, $CDCl_3$): δ = 55.26, 67.84, 69.05, 69.35, 69.85, 72.03, 72.71, 73.07, 73.15, 73.35, 74.24, 74.86, 74.99, 80.71, 81.12, 84.32, 95.12, 97.52, 128 (m, arom.), 138 (sext., arom.). − $C_{55}H_{59}O_{12}N$ (926.1): calcd. C 71.33,

H 6.42, N 1.51; found C 71.25, H 6.61, N 1.55. − MS (MALDI): calcd. 926 + 23 (Na) = 949; found 951.

2,3:4,5-Di-O-cyclohexylidene-1-O-(1R)-menthyloxycarbonyl-6-O-(3,4,6-tri-O-benzyl-2-deoxy-2-nitro-α-D-galactopyranosyl)-D-myo-inositol (**4eα**). − *Procedure A:* To a stirred solution of 2,3:4,5-di-*O*-cyclohexylidene-1-*O*-(1*R*)-menthyloxycarbonyl-D-*myo*-inositol[17] (120 mg, 0.23 mmol) and **3** (130 mg, 0.28 mmol) in dry THF (3 ml), was added a solution of potassium *tert*-butoxide (0.5 ml, 20 mg/5 ml of THF). A further 0.25 ml of potassium *tert*-butoxide solution was added after 6 h. The reaction mixture was stirred at room temp. for 12 h and was then neutralized with Amberlite IRA (H^+ form) resin. The resin was filtered off and the solvent was evaporated from the filtrate. The crude product was purified by column chromatography (toluene/ethyl acetate, 97:3) to yield **4eα** (161 mg, 71%) and **4eβ** (20 mg, 9%). **4eα**: M.p. 82−83°C. − TLC (toluene/ethyl acetate, 9:1): R_f = 0.65. − $[\alpha]_D$ = +30.5 (*c* = 1, chloroform). − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.74, 0.85, 0.90 (3 d, 9 H, 3 CH_3), 1.10 (m, 3 H, $H_{menth.}$), 1.3−1.75 (m, 24 H, 20 $H_{cycloh.}$, 4 $H_{menth.}$), 1.90 (m, 1 H, $H_{menth.}$), 2.12 (m, 1 H, $H_{menth.}$), 3.47 (dd, 1 H, J_1 = 8.90, J_2 = 10.6 Hz, 3-$H_{ino.}$), 3.56 (dd, 1 H, J_1 = 5.02, J_2 = 8.50 Hz, 6-$H_{gal.}$), 3.66 (t, 1 H, *J* = 8.7 Hz, 6′-$H_{gal.}$), 3.88 (dd, 1 H, J_1 = 7.80, J_2 = 10.7 Hz, 4-$H_{ino.}$), 4.03 (dd, 1 H, J_1 = 3.77, J_2 = 8.80 Hz, 2-$H_{ino.}$), 4.13 (d, 1 H, *J* = 2.8 Hz, 4-$H_{gal.}$), 4.27 (dd, 1 H, J_1 = 5.15, J_2 = 8.90 Hz, 5-$H_{gal.}$), 4.30 (t, 1 H, *J* = 7.2 Hz, 5-$H_{ino.}$), 4.46 (m, 4 H, 3-$H_{gal.}$, 6-$H_{ino.}$, OCH_2Ph), 4.48 (d, 1 H, *J* = 11.13 Hz, OCH_2Ph), 4.53 (dt, 1 H, J_d = 6.55, J_t = 10.95 Hz, $H_{menth.}$), 4.72 (t, 1 H, *J* = 4.0 Hz, 1-$H_{ino.}$), 4.73 (s, 2 H, OCH_2Ph), 4.82 (d, 1 H, *J* = 11.11 Hz, OCH_2Ph), 5.0 (dd, 1 H, J_1 = 4.20, J_2 = 10.6 Hz, 2-$H_{gal.}$), 5.66 (d, 1 H, *J* = 4.26 Hz, 1-H $_{gal.}$), 7.3 (m, 15 H, arom.). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.2, 20.73, 21.95, 23.25, 23.46, 23.57, 23.78, 23.85, 24.99, 26.04, 26.90, 31.41, 34.09, 34.58, 36.45, 36.53, 40.45, 47.03, 67.66, 69.26, 72.83, 73.09, 73.56, 75.05, 75.14, 75.94, 76.04, 76.31, 76.37, 77.45, 79.21, 84.10, 95.28, 111.93, 113.20, 128 (m, arom.), 138 (t, arom.), 153.86. − $C_{56}H_{73}O_{14}N$ (984.2): calcd. C 68.34, H 7.48, N 1.42; found C 68.59, H 7.66, N 1.34. − MS (MALDI): calcd. 984 + 23 (Na) = 1007; found 1010. No satisfactory spectrum was obtained for **4eβ**.

Methyl 2,3,4-Tri-O-benzyl-6-O-(3,4,6-tri-O-benzyl-2-deoxy-2-acetamido-α-D-galactopyranosyl)-α-D-glucopyranoside (**5cα**): A solution of **4cα** (120 mg, 0.13 mmol) in methanol (10 ml) was hydrogenated in an autoclave for 16 h at 80−90 atm hydrogen pressure in the presence of Raney Ni[18] (100 mg) as catalyst. The catalyst was then filtered off and the methanol was evaporated from the filtrate. The crude product was acetylated with pyridine/Ac_2O (2:1, 1.5 ml, overnight). Pieces of ice were then added and the mixture was extracted with diethyl ether (3 × 10 ml). The combined ethereal extracts were washed with water and brine. The solvent was then removed and the residue was purified by column chromatography (toluene/ethyl acetate, 3:2) to yield **5cα** (79 mg, 65%), m.p. 160°C. − TLC (toluene/ethyl acetate, 1:1): R_f = 0.28. − $[\alpha]_D$ = +73.8 (*c* = 1, chloroform). − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.82 (s, 3 H, OCH_3), 3.29 (s, 3 H, CH_3), 3.30 (dist. t, 1 H, 4a-H), 3.43 (dd, 1 H, $J_{1,2}$ = 3.50, $J_{2,3}$ = 9.60 Hz, 2a-H), 3.52 (d, 1 H, *J* = 3.10 Hz, 3b-H), 3.53−3.64 (m, 3 H, 6b-H, 6′b-H, 6a-H), 3.69 (br. d, 1 H, 5a-H), 3.83 (m, 1 H, 6′a-H), 3.91 (t, 1 H, *J* = 7.2 Hz, 4b-H), 4.00 (m, 2 H, 3a-H, 5b-H), 4.53 (d, 1 H, *J* = 3.50 Hz, 1a-H), 4.67 (m, 1 H, 2b-H), 4.83 (d, 1 H, *J* = 3.3 Hz, 1b-H), 4.40−5.00 (m, 12 H, 3 OCH_3Ph), 5.24 (d, 1 H, *J* = 9.20 Hz, NH), 7.3 (m, 30 H, arom.). − ^{13}C NMR (150 MHz, $CDCl_3$): δ = 48.97, 55.01, 66.78, 68.82, 69.70, 69.97, 70.98, 72.35, 73.22, 73.39, 74.43, 75.04, 75.73, 76.53, 77.74, 79.89, 81.85, 97.78, 98.58, 128 (m, arom.), 138 (q, arom.), 169.52 (C=O). − $C_{57}H_{63}O_{11}N$ (938.1): calcd. C 72.98, H 6.77, N 1.49; found C 72.79, H 6.92, N 1.43. − MS (MALDI): 938 + 23 (Na) = 961; found 961.

[1] R. R. Schmidt, W. Kinzy, *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123; H. G. Garg, K. von dem Bruch, H. Kunz, *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 277−310; and references therein.

[2] J. Banoub, P. Boullanger, D. Lafont, *Chem. Rev.* **1992**, *92*, 1167−1195; D. Lafont, P. Boullanger, *J. Carbohydr. Chem.* **1992**, *11*, 567−586.

[3] R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213−236; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212−235; H. Paulsen, *Angew. Chem.* **1982**, *94*, 184−201; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155−173; *Chem. Soc. Rev.* **1984**, 15−45.

[4] J. C. Castro-Palomino, R. R. Schmidt, *Tetrahedron Lett.* **1995**, *36*, 5343−5346; **1995**, *36*, 6871−6874.

[5] J. Debenham, R. Rodebaugh, B. Fraser-Reid, *Liebigs Ann.* **1997**, 791−802.

[6] E. Meinjohanns, M. Meldal, H. Paulsen, K. Bock, *J. Chem. Soc., Perkin Trans. 1* **1995**, 405−415.

[7] R. U. Lemieux, T. L. Nagabushan, I. K. O′Neill, *Tetrahedron Lett.* **1964**, *5*, 1909−1916; *Can. J. Chem.* **1968**, *46*, 413−418.

[8] T. Takamoto, R. Sudoh, T. Nakagawa, *Carbohydr. Res.* **1973**, *27*, 135−140; T. Sakakibara, Y. Tachimori, R. Sudoh, *Tetrahedron Lett.* **1982**, *23*, 5545−5548.

[9] C. W. Holzapfel, C. F. Marais, M. S. van Dyk, *Synth. Commun.* **1988**, *18*, 97−114.

[10] N. V. Bovin, S. E. Zurabyan, A. Y. Khorlin, *Carbohydr. Res.* **1981**, *98*, 25−35.

[11] T. P. Kogan, F. C. A. Gaeta, *Synthesis* **1988,** 706−707.

[12] Preparation of acetyl nitrate has to be undertaken with care; see ref. [7] of ref.[11].

[13] Transformation of 2-amino sugars into 2-nitro sugars can also be performed, as has been recently reported: J. M. Vega-Perez, J. I. Candela, F. Iglesias-Guerra, *J. Org. Chem.* **1997**, *62*, 6608−6611.

[14] P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, **1983**, pp. 29−40.

[15] Equilibration of **4aβ**, **4aα**, and **4dα** to **4aα** in the presence of additional acceptor (CH_3OH, CD_3OD) and strong basic conditions could be observed. Yet, due to concomitant decomposition reactions thermodynamically controlled α-galactoside formation under the reaction conditions is not clearly established.

[16] M. Oikawa, W.-C. Liu, Y. Nakai, S. Koshida, K. Fukase, S. Kusumoto, *Synlett* **1996**, 1179−1180; P. J. Garegg, H. Hultberg, S. Wallin, *Carbohydr. Res.* **1982**, *108*, 97−101; A. Liptak, I. Jodal, P. Namasi, *Carbohydr. Res.* **1975**, *44*, 1−11.

[17] T. G. Mayer, R. R. Schmidt, *Liebigs Ann.* **1997**, 859−863; R. R. Schmidt, T. G. Mayer, B. Kratzer, *Angew. Chem.* **1994**, *106*, 2289−2293; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2177−2181.

[18] For the preparation of Raney nickel, see *Org. Synth.* **1955**, *coll. vol. 3*, 181−183.

[98078]