Conjugate Addition of Phenols to 2-Nitrogalactal − Synthesis of *O*-(2-Acetamido-2-deoxygalactosyl)tyrosine

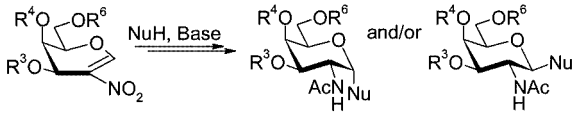
Ahmed I. Khodair,[a][‡] Gottfried A. Winterfeld,[a] and Richard R. Schmidt*[a]

Keywords: Carbohydrates / Galactosamine / Glycals / Glycosidation / Glycosides / Glycosylamino acid / Michael additions / Phenol

2-Nitrogalactal derivative **1** afforded 2-deoxy-2-nitrogalactopyranosides on treatment with phenol and substituted derivatives under base catalysis. Transformation of the nitro group into the amino and the acetamido groups and *O*-deprotection could readily be performed, thus providing aryl 2-acetamido-2-deoxygalactopyranosides **5** and **6** in high yields and with good stereoselectivities. The same reaction sequence could also be successfully applied to *N*-Boc-protected tyrosine methyl ester, to afford the *O*-galactopyranonsyl tyrosine derivative **10**.
(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2003)

Introduction

The low nucleophilicity of phenols has often been the cause of low yields in acid-promoted glycosidation reactions.[1] Because of the occurrence of quite a variety of aryl glycosides in nature,[2] the base-catalysed addition of phenols (i.e., the addition of more nucleophilic phenolates[3]) to 2-nitrogalactal was now investigated. This fundamentally new approach to glycoside bond formation, as outlined in Scheme 1, was shown to be a convenient method for the highly stereoselective syntheses of α- and β-*O*-glycosides with alcohols and also sugars as *O*-nucleophiles,[4] of β-nucleosides with heterocyclic bases as nucleophiles,[5] and of β-*C*-glycosides with CH-acidic compounds as nucleophiles.[6]



Scheme 1. Base-catalysed addition of nucleophiles to 2-nitroglycals

This method was also successfully extended to the synthesis of important GalNAcα(1-O)-Ser and GalNAcα(1-O)-Thr building blocks required for mucin *O*-glycopeptide synthesis.[7−9] If phenolates would also act as nucleophiles, aryl glycosides would then become readily available. Because of the frequent occurrence of *O*-glycosyl tyrosine constituents in nature [particularly Glcα(1-O)Tyr and Galβ(1-O)Tyr],[10−13] it was also of interest to investigate tyrosine addition.

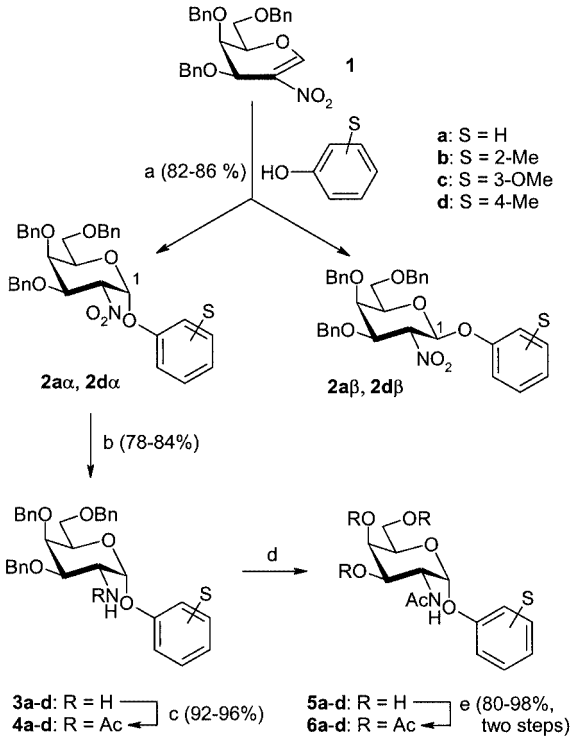
Results and Discussion

3,4,6-Tri-*O*-benzyl-2-nitro-D-galactal (Scheme 2, **1**), readily available through nitration of the corresponding galactal,[4] was treated with phenol in toluene as solvent in the presence of a catalytic amount of potassium *tert*-butoxide, thus affording a 13:1 ratio of α-anomer **2aα** and β-anomer **2bβ** in 92% yield.

The two compounds could be separated and structurally assigned by their NMR data (**2aα**: $^3J_{1,2}$ = 4.1, $^2J_{2,3}$ = 10.7 Hz; **2bβ**: $^3J_{1,2}$ = 8.1, $^3J_{2,3}$ = 10.6 Hz). The kinetically and thermodynamically preferred α-attack of phenolate and the thermodynamically preferred protonation from the β-side prevailed in this reaction, and so two new stereogenic centres were generated with high stereocontrol. Under the same conditions, *o*-cresol and resorcin monomethyl ether afforded α-anomers **2bα** and **2cα**, respectively; the corresponding β-anomers were not detected. With *p*-cresol, α-anomer **2dα** (84%) was also preferentially found, with only 8% of the β-anomer **2dβ** being isolated. Thus, as expected from previous investigations on *O*-nucleophiles,[4,7−9] addition of phenolates gave mainly α-anomers in high yields. Reduction of the 2-nitro group in **2aα**−**2dα** with hydrogen in the presence of platinised Raney nickel T4[14] as catalyst afforded amino derivatives **3a**−**d** in high yields, and these, on acetylation with acetic anhydride in pyridine, furnished aryl glycosides of *N*-acetylgalactosamine **4a**−**d**. Finally, hydrogenolytic *O*-debenzylation (→ **5a-d**) and then *O*-acetylation under standard conditions provided the desired target molecules **6a**−**d** in high yields.

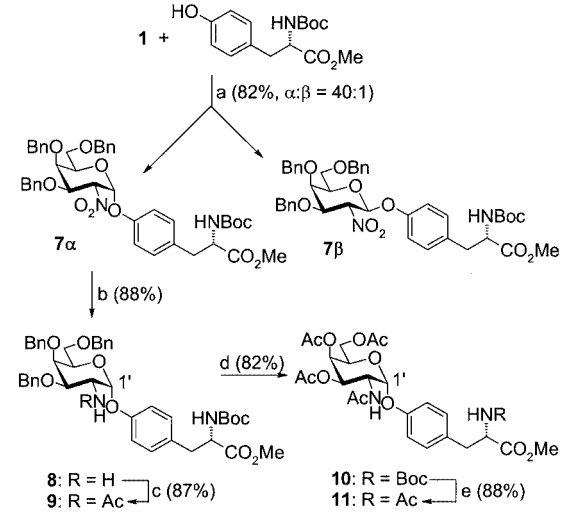
The excellent reactivity of phenols with 2-nitrogalactal **1** was reason also to investigate tyrosine addition. To this end,

[a] Fachbereich Chemie, Universität Konstanz,
Fach M725, 78457 Konstanz, Germany
Fax: (internat.) + 49-7531/883135
E-mail: richard.schmidt@uni-konstanz.de
[‡] On leave from the Chemistry Department, Faculty of Education, Tanta University, Kafr El-Sheikh Branch, Kafr El-Sheikh, Egypt



Scheme 2. Synthesis of phenyl 2-acetylamino-2-deoxy-D-galactopyranosides: (a) toluene, *t*BuOK; (b) Ra-Ni T4-Pt, H_2, EtOH; (c) Ac_2O, Pyr; (d) Pd/C, H_2, MeOH, HOAc; (e) Ac_2O, Pyr

commercially available *N*-Boc-protected tyrosine methyl ester was selected (Scheme 3).



Scheme 3. Synthesis of *O*-(2-acetylamino-2-deoxy-α-D-galactopyranosyl)tyrosine derivatives: (a) toluene, *t*BuOK; (b) Ra-Ni, T4-Pt, EtOH; (c) Ac_2O, Pyr; (d) Pd/C, H_2, MeOH, HOAc, Ac_2O, Pyr; (e) TFA, CH_2Cl_2, Ac_2O, Pyr

Treatment under the conditions described above afforded practically only the α-anomers **7α** (80% yield), with only 2% of the corresponding β-anomer **7β** being found. The two compounds could be separated and structurally assigned (^{1}H NMR: **7α**: δ = 5.84, $^3J_{1,2}$ = 4.1 Hz; **7β**: δ = 5.27, $^3J_{1,2}$ = 8.0 Hz). In addition, no racemisation of the tyrosine moiety was observed. Selective reduction of the nitro group in **7α** with platinised Raney nickel[14] afforded 2-amino derivative **8**, which on acetylation gave acetylamino derivative **9**. Hydrogenolytic *O*-debenzylation and then *O*-acetylation gave the desired *O*-acetyl-*N*-Boc-protected *O*-(α-D-galactosyl)tyrosine **10**. Acid-catalysed removal of the Boc protecting group with trifluoroacetic acid (TFA) in dichloromethane did not affect the glycosidic bond; ensuing *N*-acetylation furnished *N*,*O*-diacetyl derivative **11** in high yield.

In conclusion, base-catalysed addition of phenol and phenol derivatives to 2-nitrogalactal derivative **1** afforded mainly α-adducts with *galacto* configurations, two stereogenic centres thus being generated with high stereocontrol. Transformation of the adducts into the corresponding galactosamine target molecules could be readily performed with high yields.

Experimental Section

General Remarks: Solvents were removed under reduced pressure while the water bath temperature was maintained below 40 °C. Chromatography was performed on silica gel for flash chromatography (40 μm; J. T. Baker) at 3 bar pressure. For thin layer chromatography, TLC plastic sheets (60 F_{254} silica gel) were used and the compounds were viewed by illumination under UV light at 253 nm and by treatment with 5% $(NH_4)_2MoO_4$, 0.1% $Ce(SO_4)_2$ in 10% H_2SO_4 and heating to 160 °C. Optical rotations were measured at 25 °C with a Perkin−Elmer 241/MS polarimeter at the sodium D line. NMR: Bruker AC-250 Cryospec, Bruker DR-600; TMS or the solvent residual peak were used as internal standard. $^3J_{C,4}$ couplings were observed in gradient-selected heteronuclear multi-bond correlations (HMBC). MALDI-MS: Kratos Kompact Maldi 1; 2,5-dihydroxybenzoic acid was used as matrix. FAB-MS: Finnigan MAT 312/AMD-5000, 790 eV, 70 °C. Calculated yields are based on consumed starting material where its recovery is stated.

Phenyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranoside (2aα) and Its β-Anomer 2aβ: *t*BuOK (200 μL of a 1 M solution in THF) was added to a solution of nitrogalactal **1** (1.00 g, 2.16 mmol) and phenol (0.41 g, 4.33 mmol) in toluene (30 mL), and the solution was stirred at room temp. for 30 min. The reaction mixture was quenched with acetic acid (200 μL) and concentrated. The crude product was purified by flash chromatography on silica gel, eluting with toluene/ethyl acetate (98:2), to give **2aα** (1.03 g, 86%) as a white foam and **2aβ** (72 mg, 6%) as a colourless oil.

Compound 2aα: TLC (toluene/ethyl acetate, 95:5) R_f = 0.50. $[\alpha]_D$ = +90.5 (*c* = 0.18, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.54−3.69 (m, 2 H, 6-H, 6′-H), 4.12 (d, $^3J_{4,3}$ = 2.9 Hz, 1 H, 4-H), 4.23 (dd, $^3J_{5,6}$ = 6.7, $^3J_{5,6'}$ = 6.6 Hz, 1 H, 5-H), 4.35 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.42 (d, ^2J = 11.7 Hz, 1 H, C*H*HPh), 4.48 (d, ^2J = 11.1 Hz, 1 H, C*H*HPh), 4.67 (dd, $^3J_{3,4}$ = 3.0, $^3J_{3,2}$ = 10.6 Hz, 1 H, 3-H), 4.77 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 4.80 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 4.90 (d, ^2J = 11.2 Hz, 1 H, C*H*HPh), 5.18 (dd, $^3J_{2,1}$ = 4.2, $^3J_{2,3}$ = 10.7 Hz, 1 H, 2-H), 5.93 (d, $^3J_{1,2}$ = 4.1 Hz, 1 H, 1-H), 6.99−7.41 (m, 20 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 68.2 (C-6), 70.4 (C-5), 73.7 (C-4, C*H*HPh), 73.5 (C*H*HPh), 75.1 (C*H*HPh), 75.2 (C-3), 84.1 (C-2), 96.0 (C-1), 115.3, 117.4, 123.5, 127.8, 127.9, 128.1, 128.38, 128.42,

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

128.5, 129.6, 137.3, 137.7, 137.9, 156.2 (C-Ar) ppm. MS (MALDI): calcd. 555 + 23 [Na] = 578; found 578 $[M + Na]^+$. $C_{33}H_{33}NO_7$ (555.6): calcd. C 71.34, H 5.99, N 2.52; found C 71.59, H 6.15, N 2.47.

Compound 2aβ: TLC (toluene/ethyl acetate, 95:5) $R_f = 0.45$. $[\alpha]_D = +10.5$ ($c = 0.58$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.61 (m, 2 H, 6-H, 6′-H), 3.74 (dd, $^3J_{5,6} = 6.4$, $^3J_{5,6'} = 6.5$ Hz, 1 H, 5-H), 4.00 (d, $^3J_{4,3} = 2.5$ Hz, 1 H, 4-H), 4.12 (dd, $^3J_{3,4} = 2.5$, $^3J_{3,2} = 10.6$ Hz, 1 H, 3-H), 4.36−4.47 (m, 3 H, 3 C*H*HPh), 4.54 (d, $^2J = 11.4$ Hz, 1 H, C*H*HPh), 4.62 (d, $^2J = 11.6$ Hz, 1 H, C*H*HPh), 4.86 (d, $^2J = 11.4$ Hz, 1 H, C*H*HPh), 5.10 (dd, $^3J_{2,1} = 8.2$, $^3J_{2,3} = 10.6$ Hz, 1 H, 2-H), 5.27 (d, $^3J_{1,2} = 8.1$ Hz, 1 H, 1-H), 6.93−7.35 (m, 20 H, Ar-H) ppm. MS (MALDI): calcd. 555 + 23 [Na] = 578; found 578 $[M + Na]^+$. $C_{33}H_{33}NO_7$ (555.6): calcd. C 71.34, H 5.99, N 2.52; found C 71.25, H 5.99, N 2.52.

2-Methylphenyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranoside (2bα): This compound was prepared from *o*-cresol (468 μL, 4.33 mmol) in the manner described for **2aα**; the product was chromatographed on silica gel (toluene/ethyl acetate, 98:2) to give 1.01 g (82%) of **2bα** as a colourless oil. TLC (toluene/ethyl acetate, 95:5) $R_f = 0.48$. $[\alpha]_D = +98.4$ ($c = 0.25$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, CH_3), 3.52−3.67 (m, 2 H, 6-H, 6′-H), 4.11 (d, $^3J_{4,3} = 2.7$ Hz, 1 H, 4-H), 4.17 (dd, $^3J_{5,6} = 6.8$, $^3J_{5,6'} = 6.6$ Hz, 1 H, 5-H), 4.39 (d, $^2J = 11.6$ Hz, 1 H, C*H*HPh), 4.43 (d, $^2J = 11.7$ Hz, 1 H, C*H*HPh), 4.52 (d, $^2J = 11.1$ Hz, 1 H, C*H*HPh), 4.68 (dd, $^3J_{3,4} = 3.0$, $^3J_{3,2} = 10.7$ Hz, 1 H, 3-H), 4.79 (d, $^2J = 11.6$ Hz, 1 H, C*H*HPh), 4.80 (d, $^2J = 11.5$ Hz, 1 H, C*H*HPh), 4.90 (d, $^2J = 11.1$ Hz, 1 H, C*H*HPh), 5.16 (dd, $^3J_{2,1} = 4.1$, $^3J_{2,3} = 10.7$ Hz, 1 H, 2-H), 5.92 (d, $^3J_{1,2} = 4.1$ Hz, 1 H, 1-H), 6.92−7.37 (m, 19 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 15.4 (CH_3), 67.6 (C-6), 69.8 (C-5), 72.6 (C-4, C*H*HPh), 72.7 (C*H*HPh), 73.0 (C*H*HPh), 74.7 (C-3), 83.7 (C-2), 95.1 (C-1), 114.3, 122.5, 126.5, 127.1, 127.27, 127.34, 127.4, 127.56, 127.62, 127.7, 127.87, 127.90, 128.0, 130.5, 136.7, 137.1, 137.4, 153.7 (C-Ar) ppm. MS (MALDI): calcd. 569 + 23 [Na] = 592; found 592 $[M + Na]^+$. $C_{34}H_{35}NO_7$ (569.6): calcd. C 71.69, H 6.19, N 2.46; found C 71.08, H 6.51, N 2.27.

3-Methoxyphenyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranoside (2cα): This compound was prepared from 3-methoxyphenol (468 μL, 4.33 mmol) in the manner described for **2aα**; the product was chromatographed on silica gel (toluene/ethyl acetate, 98:2) to give 1.16 g of **2cα** as a colourless oil. TLC (toluene/ethyl acetate, 95:5) $R_f = 0.52$. $[\alpha]_D = +60.7$ ($c = 0.15$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.51−3.65 (m, 2 H, 6-H, 6′-H), 3.71 (s, 3 H, OCH_3), 4.10 (d, $^3J_{4,3} = 2.3$ Hz, 1 H, 4-H), 4.19 (dd, $^3J_{5,6} = 6.7$, $^3J_{5,6'} = 6.5$ Hz, 1 H, 5-H), 4.37 (d, $^2J = 11.7$ Hz, 1 H, C*H*HPh), 4.45 (d, $^2J = 11.7$ Hz, 1 H, C*H*HPh), 4.50 (d, $^2J = 11.2$ Hz, 1 H, C*H*HPh), 4.65 (dd, $^3J_{3,4} = 2.9$, $^3J_{3,2} = 10.7$ Hz, 1 H, 3-H), 4.79 (d, $^2J = 10.7$ Hz, 1 H, C*H*HPh), 4.83 (d, $^2J = 11.3$ Hz, 1 H, C*H*HPh), 4.89 (d, $^2J = 11.2$ Hz, 1 H, C*H*HPh), 5.14 (dd, $^3J_{2,1} = 4.1$, $^3J_{2,3} = 10.6$ Hz, 1 H, 2-H), 5.90 (d, $^3J_{1,2} = 4.1$ Hz, 1 H, 1-H), 6.56−7.36 (m, 19 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 68.2 (C-6), 70.4 (C-5), 73.2 (C-4, C*H*HPh), 73.5 (C*H*HPh), 75.1 (C*H*HPh), 75.2 (C-3), 84.1 (C-2), 95.9 (C-1), 103.5, 109.3, 109.4, 127.8, 127.9, 128.1, 128.2, 128.40, 128.42, 128.5, 130.0, 137.3, 137.6, 137.9, 157.3 (C-Ar) ppm. MS (MALDI): calcd. 585 + 23 [Na] = 608; found 608 $[M + Na]^+$. $C_{34}H_{35}NO_8$ (585.6): calcd. C 69.73, H 6.02, N 2.39; found C 69.73, H 5.87, N 2.52.

4-Methylphenyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranoside (2dα) and Its β-Anomer 2dβ: This compound was prepared from *o*-cresol (468 μL, 4.33 mmol) in the manner described for **2aα**; the product was chromatographed on silica gel (toluene/ethyl acetate, 98:2) to give 1.03 g (84%) of **2dα** as a white foam and 0.10 g (8%) of **2dβ** as a white foam.

Compound 2dα: TLC (toluene/ethyl acetate, 95:5) $R_f = 0.60$. $[\alpha]_D = +94.5$ ($c = 0.11$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 3.55−3.67 (m, 2 H, 6-H, 6′-H), 4.11 (d, $^3J_{4,3} = 2.7$ Hz, 1 H, 4-H), 4.23 (dd, $^3J_{5,6} = 6.7$, $^3J_{5,6'} = 6.6$ Hz, 1 H, 5-H), 4.40 (d, $^2J = 11.7$ Hz, 1 H, C*H*HPh), 4.45 (d, $^2J = 11.7$ Hz, 1 H, C*H*HPh), 4.52 (d, $^2J = 11.1$ Hz, 1 H, C*H*HPh), 4.65 (dd, $^3J_{3,4} = 3.0$, $^3J_{3,2} = 10.7$ Hz, 1 H, 3-H), 4.80 (d, $^2J = 11.8$ Hz, 1 H, C*H*HPh), 4.85 (d, $^2J = 11.8$ Hz, 1 H, C*H*HPh), 4.90 (d, $^2J = 11.2$ Hz, 1 H, C*H*HPh), 5.15 (dd, $^3J_{2,1} = 4.1$, $^3J_{2,3} = 10.6$ Hz, 1 H, 2-H), 5.86 (d, $^3J_{1,2} = 4.1$ Hz, 1 H, 1-H), 6.89−7.34 (m, 19 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 20.1 (CH_3), 67.7 (C-6), 69.9 (C-5), 72.7 (C-4), 72.8 (C*H*HPh), 73.0 (C*H*HPh), 74.68 (C*H*HPh), 74.71 (C-3), 83.7 (C-2), 95.8 (C-1), 116.9, 127.3, 127.4, 127.6, 127.7, 127.88, 127.92, 128.0, 129.6, 132.5, 136.8, 137.2, 137.5, 153.6 (C-Ar) ppm. MS (MALDI): calcd. 569 + 23 [Na] = 592; found 592 $[M + Na]^+$. $C_{34}H_{35}NO_7$ (569.6): calcd. C 71.69, H 6.19, N 2.46; found C 71.43, H 5.96, N 2.59.

Compound 2dβ: TLC (toluene/ethyl acetate, 95:5) $R_f = 0.55$. $[\alpha]_D = +8.9$ ($c = 0.18$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, CH_3), 3.58 (m, 2 H, 6-H, 6′-H), 3.65 (dd, $^3J_{5,6} = 5.7$, $^3J_{5,6'} = 5.8$ Hz, 1 H, 5-H), 3.96 (d, $^3J_{4,3} = 2.7$ Hz, 1 H, 4-H), 4.07 (dd, $^3J_{3,4} = 2.7$, $^3J_{3,2} = 10.5$ Hz, 1 H, 3-H), 4.37 (m, 3 H, C*H*HPh), 4.50 (d, $^2J = 11.4$ Hz, 1 H, C*H*HPh), 4.56 (d, $^2J = 11.6$ Hz, 1 H, C*H*HPh), 4.84 (d, $^2J = 11.4$ Hz, 1 H, C*H*HPh), 5.04 (dd, $^3J_{2,1} = 7.9$, $^3J_{2,3} = 10.4$ Hz, 1 H, 2-H), 5.20 (d, $^3J_{1,2} = 7.8$ Hz, 1 H, 1-H), 6.78−7.31 (m, 19 H, Ar-H) ppm. MS (MALDI): calcd. 569 + 23 [Na] = 592; found 592 $[M + Na]^+$. $C_{34}H_{35}NO_7$ (569.6): calcd. C 71.69, H 6.19, N 2.46; found C 71.37, H 6.00, N 2.48.

Phenyl 2-Amino-3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranoside (3a): Compound **2aα** (0.50 g, 0.90 mmol) was dissolved in ethanol (15 mL) and transferred to a hydrogenation vessel. Platinised Raney nickel T4 catalyst was freshly prepared as described in ref.[14], and the material obtained from 2.70 g of Raney nickel/aluminium alloy was suspended in ethanol (15 mL). From a homogeneous suspension of this catalyst, 15 mL was added to the reaction vessel and the suspension was shaken under H_2 for 48 h at ambient temp. and pressure. The catalyst was filtered off and the solvent was evaporated. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 95:5) to furnish **3a** (0.37 g, 78%) as a colourless oil. TLC (CH_2Cl_2/MeOH, 95:5) $R_f = 0.30$. $[\alpha]_D = +91.7$ ($c = 0.30$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.45−3.56 (m, 3 H, 6-H, 6′-H, 2-H), 3.65−3.74 (m, 2 H, 4-H, 5-H), 4.08 (m, 3 H, NH_2, 3-H), 4.37 (d, $^2J = 11.5$ Hz, 1 H, C*H*HPh), 4.44 (d, $^2J = 11.7$ Hz, 1 H, C*H*HPh), 4.56 (d, $^2J = 11.6$ Hz, 1 H, C*H*HPh), 4.60 (d, $^2J = 11.4$ Hz, 1 H, C*H*HPh), 4.80 (d, $^2J = 11.6$ Hz, 1 H, C*H*HPh), 4.90 (d, $^2J = 11.4$ Hz, 1 H, C*H*HPh), 5.57 (d, $^3J_{1,2} = 3.6$ Hz, 1 H, 1-H), 6.97−7.42 (m, 20 H, Ar-H) ppm. MS (MALDI): calcd. 525 + 23 [Na] = 548; found 548 $[M + Na]^+$. $C_{33}H_{35}NO_5$ (525.6): calcd. C 75.40, H 6.71, N 2.66; found C 74.91, H 6.80, N 2.62.

2-Methylphenyl 2-Amino-3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranoside (3b): This compound was prepared from **2bα** (512 mg, 0.90 mmol) in the manner described for **3a**; the product was chromatographed on silica gel (CH_2Cl_2/MeOH, 95:5) to give 442 mg (82%) of **3b** as a pale yellow oil. TLC (CH_2Cl_2/MeOH, 95:5) $R_f = 0.38$. $[\alpha]_D = +117.3$ ($c = 0.33$, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 3.46−3.57 (m, 3 H, 6-

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

H, 6′-H, 2-H), 3.67−3.74 (m, 2 H, 4-H, 5-H), 4.05−4.12 (m, 3 H, NH_2, 3-H), 4.40 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.45 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.55 (d, ^2J = 11.7 Hz, 1 H, C*H*HPh), 4.64 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 4.83 (d, ^2J = 11.7 Hz, 1 H, C*H*HPh), 4.93 (d, ^2J = 11.4 Hz, 1 H, C*H*HPh), 5.60 (d, $^3J_{1,2}$ = 3.4 Hz, 1 H, 1-H), 6.90−7.43 (m, 19 H, Ar-H) ppm. MS (MALDI): calcd. 539 + 23 [Na] = 562; found 562 [M + Na]$^+$. $C_{34}H_{37}NO_5$ (539.7): calcd. C 75.67, H 6.91, N 2.60; found C 75.28, H 7.05, N 2.60.

3-Methylphenyl 2-Amino-3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranoside (3c): This compound was prepared from **2cα** (526 mg, 0.90 mmol) in the manner described for **3a**; the product was chromatographed on silica gel (CH_2Cl_2/MeOH, 95:5) to give 400 mg (80%) of **3c** as a pale yellow foam. TLC (CH_2Cl_2/MeOH, 95:5) R_f = 0.40. $[\alpha]_D$ = +121.3 (c = 0.15, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.44−3.55 (m, 3 H, 6-H, 6′-H, 2-H), 3.64−3.70 (m, 2 H, 4-H, 5-H), 3.72 (s, 3 H, OCH_3), 4.07 (m, 3 H, NH_2, 3-H), 4.38 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.45 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.53 (d, ^2J = 11.7 Hz, 1 H, C*H*HPh), 4.59 (d, ^2J = 11.4 Hz, 1 H, C*H*HPh), 4.80 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.90 (d, ^2J = 11.4 Hz, 1 H, C*H*HPh), 5.55 (d, $^3J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 6.57−7.38 (m, 19 H, Ar-H) ppm. MS (MALDI): calcd. 555 + 23 [Na] = 578; found 578 [M + Na]$^+$. $C_{34}H_{37}NO_6$ (555.7): calcd. C 73.49, H 6.71, N 2.52; found C 73.19, H 6.73, N 2.42.

4-Methylphenyl 2-Amino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranoside (3d): This compound was prepared from **2dα** (512 mg, 0.90 mmol) in the manner described for **3a**; the product was chromatographed on silica gel (CH_2Cl_2/MeOH, 95:5) to give 407 mg (84%) of **3d** as a white foam. TLC (CH_2Cl_2/MeOH, 95:5) R_f = 0.30. $[\alpha]_D$ = +138.5 (c = 0.13, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.27 (s, 3 H, CH_3), 3.43−3.56 (m, 3 H, 6-H, 6′-H, 2-H), 3.67−3.73 (m, 2 H, 4-H, 5-H), 4.08 (m, 3 H, NH_2, 3-H), 4.37 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.44 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.55 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.60 (d, ^2J = 11.4 Hz, 1 H, C*H*HPh), 4.80 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.90 (d, ^2J = 11.4 Hz, 1 H, C*H*HPh), 5.51 (d, $^3J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 6.93−7.40 (m, 19 H, Ar-H) ppm. MS (MALDI): calcd. 539 + 23 [Na] = 562; found 562 [M + Na]$^+$. $C_{34}H_{37}NO_5$ (539.7): calcd. C 75.67, H 6.91, N 2.60; found C 75.81, H 6.83, N 2.36.

Phenyl 2-Acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranoside (4a): Compound **3a** (252 mg, 0.48 mmol) was treated with pyridine/acetic anhydride (6:4, 10 mL) and the mixture was stirred at room temp. for 12 h. All volatiles were evaporated under reduced pressure and the product was purified by flash chromatography (CH_2Cl_2/MeOH, 98:2) to give **4a** (262 mg, 96%) as a colourless oil. TLC (CH_2Cl_2/MeOH, 95:5) R_f = 0.60. $[\alpha]_D$ = +127.7 (c = 0.13, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.91 (s, 3 H, Ac), 3.52 (dd, $^3J_{6,5}$ = 5.5, $^3J_{6,6'}$ = 9.2 Hz, 1 H, 6-H), 3.67 (dd, $^3J_{6',5}$ = 7.6, $^3J_{6',6}$ = 9.1 Hz, 1 H, 6′-H), 3.84 (dd, $^3J_{3,4}$ = 2.4, $^3J_{3,2}$ = 11.1 Hz, 1 H, 3-H), 4.05 (dd, $^3J_{5,6}$ = 6.7, $^3J_{5,6'}$ = 6.8 Hz, 1 H, 5-H), 4.10 (m, 1 H, 4-H), 4.37 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.42 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 4.50 (d, ^2J = 12.3 Hz, 1 H, C*H*HPh), 4.62 (d, ^2J = 12.5 Hz, 1 H, C*H*HPh), 4.80 (d, ^2J = 12.3 Hz, 1 H, C*H*HPh), 4.85 (m, 1 H, 2-H), 5.00 (d, ^2J = 11.4 Hz, 1 H, C*H*HPh), 5.35 (d, $^3J_{NH,2}$ = 8.8 Hz, 1 H, NH), 5.60 (d, $^3J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 6.96−7.39 (m, 20 H, Ar-H) ppm. MS (MALDI): calcd. 567 + 23 [Na] = 590; found 590 [M + Na]$^+$. $C_{35}H_{37}NO_6$ (567.7): calcd. C 74.05, H 6.57, N 2.47; found C 73.67, H 6.64, N 2.55.

2-Methylphenyl 2-Acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranoside (4b): This compound was prepared from **3b** (259 mg, 0.48 mmol) in the manner described for **4a**; the product was chromatographed on silica gel (CH_2Cl_2/MeOH, 98:2) to give 256 mg (92%) of **4b** as a white solid; m.p. 153−155 °C. TLC (CH_2Cl_2/MeOH, 95:5) R_f = 0.58. $[\alpha]_D$ = +94.3 (c = 0.28, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.86 (s, 3 H, Ac), 2.06 (s, 3 H, CH_3), 3.53 (dd, $^3J_{6,5}$ = 5.5, $^3J_{6,6'}$ = 9.1 Hz, 1 H, 6-H), 3.66−3.74 (m, 1 H, 6′-H), 3.86 (dd, $^3J_{3,4}$ = 2.4, $^3J_{3,2}$ = 11.2 Hz, 1 H, 3-H), 4.00 (m, 1 H, 5-H), 4.13 (br. s, 1 H, 4-H), 4.35−4.53 (m, 3 H, C*H*HPh), 4.67 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.81 (d, ^2J = 12.2 Hz, 1 H, C*H*HPh), 4.93 (m, 1 H, 2-H), 5.00 (d, ^2J = 11.4 Hz, 1 H, C*H*HPh), 5.10 (d, $^3J_{NH,2}$ = 8.4 Hz, 1 H, NH), 5.61 (d, $^3J_{1,2}$ = 3.4 Hz, 1 H, 1-H), 6.88−7.40 (m, 19 H, Ar-H) ppm. MS (MALDI): calcd. 581 + 23 [Na] = 604; found 604 [M + Na]$^+$. $C_{36}H_{39}NO_6$ (581.7): calcd. C 74.33, H 6.76, N 2.41; found C 73.89, H 7.01, N 2.44.

3-Methoxyphenyl 2-Acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranoside (4c): This compound was prepared from **3c** (266 mg, 0.48 mmol) in the manner described for **4a**; the product was chromatographed on silica gel (petroleum ether/ethyl acetate, 80:20) to give 269 mg (94%) of **4c** as a white foam. TLC (petroleum ether/ethyl acetate, 50:50) R_f = 0.50. $[\alpha]_D$ = +92.9 (c = 0.14, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.92 (s, 3 H, Ac), 3.51−3.72 (m, 2 H, 6-H, 6′-H), 3.74 (s, 3 H, OCH_3), 3.86 (dd, $^3J_{3,4}$ = 2.5, $^3J_{3,2}$ = 11.0 Hz, 1 H, 3-H), 4.04−4.13 (m, 2 H, 5-H, 4-H), 4.37 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 4.45 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 4.50 (d, ^2J = 12.3 Hz, 1 H, C*H*HPh), 4.62 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.80 (d, ^2J = 12.1 Hz, 1 H, C*H*HPh), 4.86 (m, 1 H, 2-H), 5.01 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 5.41 (d, $^3J_{NH,2}$ = 8.7 Hz, 1 H, NH), 5.62 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 6.56−7.40 (m, 19 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 23.3 (Ac), 49.0 (C-2), 55.2 (OCH_3), 68.7 (C-6), 70.5 (C-5), 71.4 (C-4), 72.5 (C*H*HPh), 73.4 (C*H*HPh), 74.6 (C*H*HPh), 77.0 (C-3), 96.9 (C-1), 103.1, 108.1, 109.0, 127.6, 127.66, 127.73, 127.8, 128.0, 128.16, 128.23, 128.3, 128.5, 129.9, 137.8, 138.0, 138.4, 160.7 (C-Ar), 169.8 (Ac) ppm. MS (MALDI): calcd. 597 + 23 [Na] = 620; found 620 [M + Na]$^+$. $C_{36}H_{39}NO_7$ (597.7): calcd. C 72.34, H 6.58, N 2.34; found C 72.08, H 6.70, N 2.49.

4-Methylphenyl 2-Acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranoside (4d): This compound was prepared from **3d** (259 mg, 0.48 mmol) in the manner described for **4a**; the product was chromatographed on silica gel (petroleum ether/ethyl acetate, 80:20) to give 260 mg (93%) of **4d** as a white foam. TLC (petroleum ether/ethyl acetate, 50:50) R_f = 0.48. $[\alpha]_D$ = +117.5 (c = 0.16, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.93 (s, 3 H, Ac), 2.31 (s, 3 H, CH_3), 3.52 (dd, $^3J_{6,5}$ = 5.5, $^3J_{6,6'}$ = 9.2 Hz, 1 H, 6-H), 3.68 (dd, $^3J_{6',5}$ = 7.1, $^3J_{6',6}$ = 9.2 Hz, 1 H, 6′-H), 3.83 (dd, $^3J_{3,4}$ = 2.4, $^3J_{3,2}$ = 11.2 Hz, 1 H, 3-H), 4.10 (m, 2 H, 5-H, 4-H),), 4.40 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.42 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.52 (d, ^2J = 12.2 Hz, 1 H, C*H*HPh), 4.62 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.78 (d, ^2J = 12.1 Hz, 1 H, C*H*HPh), 4.92 (m, 1 H, 2-H), 5.00 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 5.38 (d, $^3J_{NH,2}$ = 8.6 Hz, 1 H, NH), 5.58 (d, $^3J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 6.90−7.40 (m, 19 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 20.5 (CH_3), 23.4 (Ac), 49.0 (C-2), 68.7 (C-6), 70.4 (C-5), 71.4 (C-4), 72.6 (C*H*HPh), 73.4 (2 × C*H*HPh), 74.6 (C-3), 97.1 (C-1), 116.8, 127.5, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.5, 130.0, 132.0, 137.9, 138.1, 138.5, 154.5 (C-Ar), 169.8 (Ac) ppm. MS (MALDI): calcd. 581 + 23 [Na] = 604; found 604 [M + Na]$^+$. $C_{36}H_{39}NO_6$ (581.7): calcd. C 74.33, H 6.76, N 2.41; found C 74.53, H 6.55, N 2.54.

Phenyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranoside (6a): Compound **4a** (0.20 g, 0.35 mmol) was dissolved in methanol/acetic acid (9:1; 10 mL), and Pd/C (0.126 g, 10% Pd) was sus-

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

pended in the solution. This mixture was stirred under H_2 for 3 h. After complete disappearance of the starting material (TLC: CH_2Cl_2/MeOH, 90:10), the catalyst was filtered off and all solvents were removed to afford phenyl 2-acetamido-2-deoxy-α-D-galactopyranoside (**5a**) as a white solid, which was used in the next step without purification. Compound **5a** was treated with pyridine/acetic acid (2:1, 10 mL) and the mixture was stirred at room temp. for 12 h. All volatiles were evaporated and the product was purified by column chromatography on silica gel with CH_2Cl_2/MeOH (98:2) to give **6a** (127 mg, 86%) as a white foam. TLC (CH_2Cl_2/MeOH, 95:5) R_f = 0.25. $[\alpha]_D$ = +139.2 (c = 0.50, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.87, 1.94, 1.99, 2.13 (4s, 12 H, 4 × Ac), 3.97 (dd, $^3J_{6,5}$ = 7.3, $^3J_{6,6'}$ = 11.3 Hz, 1 H, 6-H), 4.06 (dd, $^3J_{6',5}$ = 5.8, $^3J_{6',6}$ = 11.2 Hz, 1 H, 6′-H), 4.25 (dd, $^3J_{5,6}$ = 6.4, $^3J_{5,6'}$ = 6.7 Hz, 1 H, 5-H), 4.72 (ddd, $^3J_{2,1}$ = 3.5, $^3J_{2,NH}$ = 9.5, $^3J_{2,3}$ = 13.1 Hz, 1 H, 2-H), 5.33−5.40 (m, 2 H, 3-H, 4-H,), 5.56 (d, $^3J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 6.00 (d, $^3J_{NH,2}$ = 9.4 Hz, 1 H, NH), 7.00−7.05 (m, 3 H, Ar-H), 7.24−7.30 (m, 2 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 20.4, 20.5, 20.6, 23.1 (4 × Ac), 47.8 (C-2), 60.2 (C-6), 61.6 (C-5), 67.1 (C-4), 67.4 (C-3), 96.4 (C-1), 116.7, 123.0, 129.6, 156.0 (C-Ar), 170.1, 170.8 (4 × Ac) ppm. MS (MALDI): calcd. 423 + 23 [Na] = 446; found 446 [M + Na]$^+$. $C_{20}H_{25}NO_9$ (423.4): calcd. C 56.73, H 5.95, N 3.31; found C 56.64, H 5.45, N 3.25.

2-Methylphenyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranoside (6b): This compound was prepared from **4b** (203 mg, 0.35 mmol) in the manner described for **6a**; the product was chromatographed on silica gel (CH_2Cl_2/MeOH, 98:2) to give 142 mg (93%) of **6b** as a colourless oil. TLC (CH_2Cl_2/MeOH, 95:5) R_f = 0.40. $[\alpha]_D$ = +68.4 (c = 0.50, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.92, 1.95, 2.03, 2.17 (4s, 12 H, 4 × Ac), 2.26 (s, 3 H, CH_3), 4.03 (dd, $^3J_{6,5}$ = 7.2, $^3J_{6,6'}$ = 11.2 Hz, 1 H, 6-H), 4.12 (dd, $^3J_{6',5}$ = 5.9, $^3J_{6',6}$ = 11.3 Hz, 1 H, 6′-H), 4.26 (dd, $^3J_{5,6}$ = 6.2, $^3J_{5,6'}$ = 5.8 Hz, 1 H, 5-H), 4.74 (ddd, $^3J_{2,1}$ = 3.5, $^3J_{2,NH}$ = 9.5, $^3J_{2,3}$ = 13.1 Hz, 1 H, 2-H), 5.39 (dd, $^3J_{3,4}$ = 3.3, $^3J_{3,2}$ = 11.3 Hz, 1 H, 3-H), 5.45 (dd, $^3J_{4,5}$ < 1.1, $^3J_{4,3}$ = 3.2 Hz, 1 H, 4-H), 5.59 (d, $^3J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 5.70 (d, $^3J_{NH,2}$ = 9.4 Hz, 1 H, NH), 6.93−7.24 (m, 4 H, Ar-H) ppm. MS (MALDI): calcd. 437 + 23 [Na] = 460; found 460 [M + Na]$^+$. $C_{21}H_{27}NO_9$ (437.4): calcd. C 57.66, H 6.22, N 3.20; found C 57.69, H 5.58, N 2.94.

2-Methoxyphenyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranoside (6c): This compound was prepared from **4c** (209 mg, 0.35 mmol) in the manner described for **6a**; the product was chromatographed on silica gel (CH_2Cl_2/MeOH, 98:2) to give 140 mg (88%) of **6c** as a colourless oil. TLC (CH_2Cl_2/MeOH, 95:5) R_f = 0.43. $[\alpha]_D$ = +127.5 (c = 0.32, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.89, 1.94, 1.99, 2.14 (4s, 12 H, 4 × Ac), 3.75 (s, 3 H, OCH_3), 3.98−4.07 (m, 2 H, 6-H, 6′-H), 4.24 (dd, $^3J_{5,6}$ = 6.4, $^3J_{5,6'}$ = 6.5 Hz, 1 H, 5-H), 4.72 (ddd, $^3J_{2,1}$ = 3.5, $^3J_{2,NH}$ = 9.5, $^3J_{2,3}$ = 13.1 Hz, 1 H, 2-H), 5.31−5.39 (m, 2 H, 3-H, 4-H), 5.53 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 5.90 (d, $^3J_{NH,2}$ = 9.5 Hz, 1 H, NH), 6.56−7.24 (m, 4 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 20.4, 20.6, 20.7, 23.2 (4 × Ac), 47.8 (C-2), 55.3 (OCH_3), 61.7 (C-6), 67.2 (C-5), 67.5 (C-4), 68.2 (C-3), 96.5 (C-1), 103.3, 108.5, 108.8, 130.1, 157.2, 160.8 (C-Ar), 170.1, 170.21, 170.21, 170.1 (4 × Ac) ppm. MS (MALDI): calcd. 453 + 23 [Na] = 476; found 476 [M + Na]$^+$. $C_{21}H_{27}NO_{10}$ (453.4): calcd. C 55.62, H 6.00, N 3.09; found C 55.14, H 6.39, N 2.76.

4-Methylphenyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranoside (6d): This compound was prepared from **4d** (203 mg, 0.35 mmol) in the manner described for **6a**; the product was chromatographed on silica gel (CH_2Cl_2/MeOH, 98:2) to give 150 mg (98%) of **6d** as a yellow oil. TLC (CH_2Cl_2/MeOH, 95:5) R_f = 0.38. $[\alpha]_D$ = +125.7 (c = 0.35, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.91, 1.95, 2.01, 2.16 (4s, 12 H, 4 × Ac), 2.28 (s, 3 H, CH_3), 4.00 (dd, $^3J_{6,5}$ = 7.2, $^3J_{6,6'}$ = 11.3 Hz, 1 H, 6-H), 4.10 (dd, $^3J_{6',5}$ = 6.0, $^3J_{6',6}$ = 11.2 Hz, 1 H, 6′-H), 4.27 (dd, $^3J_{5,6}$ = 6.4, $^3J_{5,6'}$ = 6.7 Hz, 1 H, 5-H), 4.72 (ddd, $^3J_{2,1}$ = 3.6, $^3J_{2,NH}$ = 9.6, $^3J_{2,3}$ = 11.3 Hz, 1 H, 2-H), 5.37 (dd, $^3J_{3,4}$ = 3.3, $^3J_{3,2}$ = 11.2 Hz, 1 H, 3-H), 5.42 (d, $^3J_{4,3}$ = 3.4 Hz, 1 H, 4-H), 5.52 (d, $^3J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 5.73 (d, $^3J_{NH,2}$ = 9.6 Hz, 1 H, NH), 6.93, 7.24 (2d, J = 8.7 Hz, 4 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 20.5, 20.67, 20.73 (4 × Ac), 23.3 (CH_3), 48.0 (C-2), 61.7 (C-6), 67.3 (C-5), 67.5 (C-4), 68.3 (C-3), 96.7 (C-1), 116.6, 130.1, 132.6, 153.9 (C-Ar), 170.1, 170.3, 171.0 (4 × Ac) ppm. MS (MALDI): calcd. 437 + 23 [Na] = 460; found 460 [M + Na]$^+$. $C_{21}H_{27}NO_9$ (437.4): calcd. C 57.66, H 6.22, N 3.20; found C 57.69, H 6.06, N 3.05.

Methyl (2*S*)-2-*tert*-Butoxycarbonylamino-3-[4-(3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranosyloxy)phenyl]propionate (7α) and Its β-Anomer 7β: This compound was prepared from *N*-*tert*-butoxycarbonyl-L-tyrosine methyl ester (590 mg, 2 mmol) in the manner described for **2aα**; the product was chromatographed on silica gel (toluene/ethyl acetate, 90:10) to give 1.21 g (80%) of **7α** as a colourless oil and 0.03 g (2%) of **7β** as a white foam.

Compound 7α: TLC (toluene/ethyl acetate, 80:20) R_f = 0.60. $[\alpha]_D$ = +50.0 (c = 0.10, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, CMe_3), 3.00 (m, 2 H, 2m, 3a-H, 3b-H), 3.51−3.64 (m, 2 H, 6′-H, 6′′-H), 3.67 (s, 3 H, OMe), 4.09 (d, $^3J_{4',3'}$ = 2.5 Hz, 1 H, 4′-H), 4.17 (dd, $^3J_{5',6'}$ = 6.7, $^3J_{5',6''}$ = 6.5 Hz, 1 H, 5′-H), 4.35 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.45 (d, ^2J = 12.2 Hz, 1 H, C*H*HPh), 4.48 (d, ^2J = 11.3 Hz, 1 H, C*H*HPh), 4.53 (m, 1 H, 2-H), 4.63 (dd, $^3J_{3',4'}$ = 2.8, $^3J_{3',2'}$ = 10.6 Hz, 1 H, 3′-H), 4.78 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 4.80 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 4.86 (d, ^2J = 11.2 Hz, 1 H, C*H*HPh), 4.92 (d, $^3J_{NH,2}$ = 8.2 Hz, 1 H, NHBoc), 5.10 (dd, $^3J_{2',1'}$ = 4.2, $^3J_{2',3'}$ = 10.7 Hz, 1 H, 2′-H), 5.84 (d, $^3J_{1',2'}$ = 4.1 Hz, 1 H, 1′-H), 6.89−7.36 (m, 19 H, Ar-H) ppm. ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 28.3 (C*Me*$_3$), 37.5 (C-3), 52.2 (OMe), 54.4 (C-2), 68.0 (C-6′), 70.3 (C-5′), 73.0 (C-4′), 73.1 (C*H*HPh), 73.5 (C*H*HPh), 75.0 (C*H*HPh), 75.2 (C-3′), 80.1 (*C*Me$_3$), 84.0 (C-2′), 96.0 (C-1′), 117.4, 127.8, 127.9, 128.15, 128.22, 128.38, 128.44, 128.5, 130.5, 131.1, 137.2, 137.6, 137.9, 155.0 (C-Ar), 155.2 (CO-OMe), 172.2 (NHBoc) ppm. MS (MALDI): calcd. 756 + 23 [Na] = 779; found 779 [M + Na]$^+$. $C_{42}H_{48}N_2O_{11}$ (756.8): calcd. C 66.65, H 6.39, N 3.70; found C 66.86, H 6.60, N 3.38.

Compound 7β: TLC (toluene/ethyl acetate, 80:20) R_f = 0.52. $[\alpha]_D$ = −4.0 (c = 0.30, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, CMe_3), 3.00 (m, 2 H, 3a-H, 3b-H), 3.67 (m, 5 H, 6′-H, 6′′-H, OMe), 3.78 (dd, $^3J_{5',6'}$ = 6.7, $^3J_{5',6''}$ = 6.5 Hz, 1 H, 5′-H), 4.04 (d, $^3J_{4',3'}$ = 2.7 Hz, 1 H, 4′-H), 4.12 (dd, $^3J_{3',4'}$ = 2.8, $^3J_{3',2'}$ = 10.5 Hz, 1 H, 3′-H), 4.44−4.60 (m, 6 H, C*H*HPh, 2-H), 4.88 (d, ^2J = 11.4 Hz, 1 H, C*H*HPh), 4.92 (d, $^3J_{NH,2}$ = 8.2 Hz, 1 H, NHBoc), 5.12 (dd, $^3J_{2',1'}$ = 8.0, $^3J_{2',3'}$ = 10.5 Hz, 1 H, 2′-H), 5.27 (d, $^3J_{1',2'}$ = 8.0 Hz, 1 H, 1′-H), 6.87−7.32 (m, 19 H, Ar-H) ppm. MS (MALDI): calcd. 756 + 23 [Na] = 779; found 779 [M + Na]$^+$. $C_{42}H_{48}N_2O_{11}$ (756.8): calcd. C 66.65, H 6.39, N 3.70; found C 66.92, H 6.60, N 3.23.

Methyl (2*S*)-3-[4-(2-Amino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyloxy)phenyl]-2-*(tert*-butoxycarbonylamino)propionate (8): This compound was prepared from **7α** (680 mg, 0.90 mmol) in the manner described for **3a**; the product was chromatographed on silica gel (CH_2Cl_2/MeOH, 95:5) to give 575 mg (88%) of **8** as a white foam. TLC (CH_2Cl_2/MeOH, 95:5) R_f = 0.32. $[\alpha]_D$ = +7.1 (c = 0.17, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (s, 9 H,

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

CMe_3), 2.98 (br. s, 2 H, 3a-H, 3b-H), 3.43−3.71 (m, 8 H, 6′-H, 6′′-H, 2′-H, 4′-H, 5′-H, OMe), 4.07 (s, 3 H, NH_2, 3′-H), 4.38 (d, ^2J = 11.4 Hz, 1 H, C*H*HPh), 4.53 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 4.58 (d, ^2J = 11.5 Hz, 1 H, C*H*HPh), 4.75 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.85 (d, ^2J = 11.4 Hz, 1 H, C*H*HPh), 4.90 (d, ^2J = 11.2 Hz, 1 H, C*H*HPh), 4.92 (m, 1 H, 2-H), 5.50 (d, $^3J_{1',2'}$ = 3.4 Hz, 1 H, 1′-H), 6.70 (d, $^3J_{NH,2}$ = 8.4 Hz, 1 H, NHBoc), 6.91−7.37 (m, 19 H, Ar-H) ppm. MS (MALDI): calcd. 726 + 23 [Na] = 749; found 749 [M + Na]$^+$. $C_{42}H_{50}N_2O_9$ (726.8): calcd. C 69.40, H 6.93, N 3.85; found C 69.31, H 6.87, N 3.52.

Methyl *O*-(2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-*N*-*tert*-butoxycarbonyl)-L-tyrosinate (9): This compound was prepared from **8** (348 mg, 0.48 mmol) in the manner described for **4a**; the product was chromatographed on silica gel (petroleum ether/ethyl acetate, 80:20) to give 320 mg (87%) of **9** as a white foam. TLC (petroleum ether/ethyl acetate, 60:40) R_f = 0.25. $[\alpha]_D$ = +59.6 (c = 0.25, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, CMe_3), 1.90 (s, 3 H, Ac), 2.98 (m, 2 H, 3a-H, 3b-H), 3.49 (dd, $^3J_{6',5'}$ = 5.6, $^3J_{6',6''}$ = 9.1 Hz, 6′-H), 3.62 (m, 1 H, 6′′-H), 3.68 (s, 3 H, OMe), 3.80 (dd, $^3J_{3',4'}$ = 2.5, $^3J_{3',2'}$ = 11.1 Hz, 1 H, 3′-H), 3.98−4.09 (m, 2 H, 5′-H, 4′-H), 4.36 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.38 (d, ^2J = 1106 Hz, 1 H, C*H*HPh), 4.54 (d, ^2J = 12.2 Hz, 1 H, C*H*HPh), 4.57 (d, ^2J = 11.6 Hz, 1 H, C*H*HPh), 4.63 (m, 1 H, 2-H), 4.76 (d, ^2J = 12.2 Hz, 1 H, C*H*HPh), 4.85 (m, 2 H, 2′-H, NHBoc), 4.95 (d, ^2J = 11.4 Hz, 1 H, C*H*HPh), 5.26 (d, $^3J_{NH,2'}$ = 8.7 Hz, 1 H, NHAc), 5.55 (d, $^3J_{1',2'}$ = 3.6 Hz, 1 H, 1′-H), 6.85−7.38 (m, 19 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 23.3 (Ac), 28.2 (C*Me*$_3$), 37.4 (C-3), 49.0 (C-2′), 52.1 (OMe), 54.4 (C-2), 68.5 (C-6′), 70.4 (C-5′), 71.3 (C-4′), 72.4 (C*H*HPh), 73.4 (C*H*HPh), 74.5 (C*H*HPh), 76.7 (C-3′), 79.8 (*C*Me$_3$), 96.9 (C-1′), 116.9, 127.5, 127.7, 127.9, 128.0, 128.2, 128.3, 128.5, 130.1, 130.3, 137.8, 138.0, 138.4, 155.0 (C-Ar), 155.7 (CO-OMe), 169.8 (Ac), 172.2 (NHBoc) ppm. MS (MALDI): calcd. 769 + 23 [Na] = 792; found 792 [M + Na]$^+$. $C_{44}H_{52}N_2O_{10}$ (768.9): calcd. C 68.73, H 6.82, N 3.64; found C 68.79, H 6.85, N 3.40.

Methyl *O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranosyl)-*N*-*tert*-butoxycarbonyl)-L-tyrosinate (10): This compound was prepared from **9** (269 mg, 0.35 mmol) in the manner described for **6a**; the product was chromatographed on silica gel (CH_2Cl_2/MeOH, 98:2) to give 179 mg (82%) of **10** as a colourless oil. TLC (CH_2Cl_2/MeOH, 95:5) R_f = 0.30. $[\alpha]_D$ = +56.2 (c = 0.16, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, CMe_3), 1.91, 1.94, 2.00, 2.15 (4s, 3 H, 4 × Ac), 3.01 (m, 2 H, 3a-H, 3b-H), 3.69 (s, 3 H, OMe), 3.99 (dd, $^3J_{6',5'}$ = 6.8, $^3J_{6',6''}$ = 11.2 Hz, 1 H, 6′-H), 4.08 (dd, $^3J_{6'',5'}$ = 6.1, $^3J_{6'',6'}$ = 11.3 Hz, 1 H, 6′′-H), 4.24 (dd, $^3J_{5',6'}$ = 6.8, $^3J_{5',6''}$ = 6.8 Hz, 1 H, 5′-H), 4.51 (dd, $^3J_{2,3}$ = 6.0, $^3J_{2,NH}$ = 8.2 Hz, 1 H, 2-H), 4.72 (ddd, $^3J_{2',1'}$ = 3.6, $^3J_{2',NH}$ = 9.6, $^3J_{2',3'}$ = 11.1 Hz, 1 H, 2′-H), 4.96 (d, $^3J_{NH,2}$ = 8.2 Hz, 1 H, NHBoc), 5.36 (dd, $^3J_{3',4'}$ = 3.3, $^3J_{3',2'}$ = 11.2 Hz, 1 H, 3′-H), 5.40 (dd, $^3J_{4',5'}$ < 1.0, $^3J_{4',3'}$ = 3.3 Hz, 1 H, 4′-H), 5.53 (d, $^3J_{1',2'}$ = 3.5 Hz, 1 H, 1′-H), 5.78 (d, $^3J_{NH,2'}$ = 9.5 Hz, 1 H, NHAc), 6.94, 7.00 (2d, J = 8.7 Hz, 4 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 20.5, 20.7, 23.2 (4 × Ac), 28.2 (C*Me*$_3$), 37.4 (C-3), 47.9 (C-2′), 52.2 (OMe), 54.4 (C-2), 61.6 (C-6′), 67.1 (C-5′), 67.5 (C-4′), 68.1 (C-3′), 80.0 (*C*Me$_3$), 96.5 (C-1′), 116.6, 130.5, 130.7, 155.1 (C-Ar), 170.1, 170.2, 171.0, 172.2, 172.7 (5 × CO) ppm. MS (MALDI): calcd. 624 + 23 [Na] = 647; found 647 [M + Na]$^+$. $C_{29}H_{40}N_2O_{13}$ (624.6): calcd. C 55.76, H 6.45, N 4.48; found C 55.49, H 6.72, N 4.89.

Methyl *O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranosyl)-*N*-acetyl-L-tyrosinate (11): Compound **10** (12.50 mg, 0.02 mmol) was dissolved in trifluoroacetic acid/CH_2Cl_2 (1:1, 2 mL) and the solution was stirred at room temp. for 12 h. All solvents were then evaporated, and the residue was treated with pyridine/acetic anhydride (2:1, 3 mL) and stirred at room temp. for 12 h. All volatiles were evaporated and the product was purified by column chromatography (CH_2Cl_2/MeOH, 98:2) to give 10 mg (88%) of **11** as a pale yellow foam. TLC (CH_2Cl_2/MeOH, 95:5) R_f = 0.20. $[\alpha]_D$ = +50.0 (c = 0.10, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.92, 1.96, 1.98, 2.01, 2.16 (5s, 3 H, 5 × Ac), 3.06 (m, 2 H, 3a-H, 3b-H), 3.72 (s, 3 H, OMe), 4.01 (dd, $^3J_{6',5'}$ = 7.0, $^3J_{6',6''}$ = 11.3 Hz, 1 H, 6′-H), 4.08 (dd, $^3J_{6'',5'}$ = 6.0, $^3J_{6'',6'}$ = 11.2 Hz, 1 H, 6′′-H), 4.23 (dd, $^3J_{5',6'}$ = 7.0, $^3J_{5',6''}$ = 6.0 Hz, 1 H, 5′-H), 4.72 (ddd, $^3J_{2',1'}$ = 3.6, $^3J_{2',NH}$ = 9.4, $^3J_{2',3'}$ = 13.2 Hz, 1 H, 2′-H), 4.84 (dd, $^3J_{2,3}$ = 5.1, $^3J_{2,NH}$ = 8.5 Hz, 1 H, 2-H), 5.33−5.41 (m, 2 H, 3′-H, 4′-H), 5.54 (d, $^3J_{1',2'}$ = 3.6 Hz, 1 H, 1′-H), 5.80 (d, $^3J_{NH,2'}$ = 9.4 Hz, 1 H, NHAc), 5.98 (d, $^3J_{NH,2}$ = 8.6 Hz, 1 H, NHAc), 6.96, 6.98 (2d, J = 8.9 Hz, 4 H, Ar-H) ppm. MS (MALDI): calcd. 566 + 23 [Na] = 587; found 589 [M + Na]$^+$. $C_{26}H_{34}N_2O_{12}$ (566.6): calcd. C 55.12, H 6.05, N 4.94; found C 55.10, H 5.75, N 4.71.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft, the European Community (Grant No. HRPN-CT-2000-00001/GLYCOTRAIN) and the Fonds der Chemischen Industrie. A. I. K. is grateful for an Alexander von Humboldt Fellowship. We are grateful to Ms. Anke Friemel for her help in the structural assignments by NMR experiments.

[1] R. R. Schmidt, W. Kinzy, *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123; and references therein.
[2] J. B. Harborne, T. J. Mabry, *The Flavanoids, Advances in Research*, Chapman and Hall, London, **1982**.
[3] For work on direct anomeric *O*-arylation, see: U. Huchel, C. Schmidt, R. R. Schmidt, *Tetrahedron Lett.* **1995**, *36*, 9457−9460.
[4] J. Das, R. R. Schmidt, *Eur. J. Org. Chem.* **1998**, 1609−1613.
[5] G. A. Winterfeld, J. Das, R. R. Schmidt, *Eur. J. Org. Chem.* **2000**, 3047−3050.
[6] K. Pachamuthu, A. Gupta, J. Das, R. R. Schmidt, Y. D. Vankar, *Eur. J. Org. Chem.* **2002**, 1479−1483.
[7] G. A. Winterfeld, Y. Ito, T. Ogawa, R. R. Schmidt, *Eur. J. Org. Chem.* **1999**, 1167−1171.
[8] G. A. Winterfeld, Y. Ito, T. Ogawa, R. R. Schmidt, *Angew. Chem.* **2001**, *113*, 2718−2721; *Angew. Chem. Int. Ed.* **2001**, *40*, 2654−2657.
[9] G. A. Winterfeld, A. I. Khodair, R. R. Schmidt, *Eur. J. Org. Chem.*, submitted.
[10] M. D. Alonso, J. Lomako, W. M. Lomako, W. J. Whelan, *FASEB J.* **1995**, *9*, 1126.
[11] K. Bock, J. Schuster-Kolbe, E. Altman, G. Allmaier, B. Stahl, R. Christian, U. B. Sleytr, P. Messner, *J. Biol. Chem.* **1994**, *269*, 7137−.
[12] P. Messner, R. Christian, C. Neuninger, G. Schulz, *J. Bacteriol.* **1995**, *177*, 2188.
[13] V. Wittmann in *Glycoscience: Chemistry and Chemical Biology* (Eds.: B. Fraser-Reid, K. Tatsuta, J. Thiem), Springer Verlag, Heidelberg, **2001**, vol. III, chapter 8.1, p. 2.34.
[14] S. Nishimura, *Bull. Chem. Soc. Jpn.* **1959**, *32*, 61−64.

Received December 20, 2002

 © 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim