A Convenient Route to *O*-Glycosyl Lactates via Conjugate Addition to 2-Nitroglycals: Ring Closure to Novel Pyrano[2.3-*b*][1,4]-oxazines

Ahmed I. Khodair,[b] Kandasamy Pachamuthu,[a] Richard R. Schmidt*[a]

[a] Fachbereich Chemie, Universität Konstanz, Fach M 725, 78457 Konstanz, Germany
Fax +49(7531)883135; E-mail: Richard.Schmidt@uni-konstanz.de

[b] On leave from the Chemistry Department, Faculty of Education, Tanta University, Kafr El-Sheikh Branch, Kafr El-Sheikh, Egypt

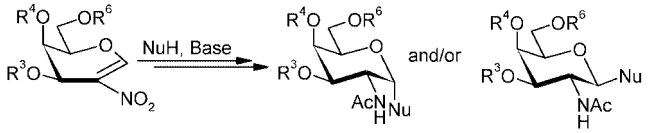
Received 26 June 2003; revised 9 October 2003

Dedicated to Professor Dr. Wolfgang Steglich on the occasion of his 70th birthday.

Abstract: Lactate esters D-**2a**, L-**2a**, and D-**2b** could be readily added to 3,4,6-tri-*O*-benzyl-2-nitro-galactal (**1**) and 3,4,6-tri-*O*-benzyl-2-nitro-glucal (**4**), affording exclusively α- and β-anomers with galacto- and gluco-configuration, respectively. Nitro group reduction to the amino group and ester cleavage led to compounds **6a**, **6b**, and **7**, which can be regarded as dipeptide mimetics. For these compounds the bicyclic pyrano[2.3-*b*][1,4]-oxazines **8**–**10** were prepared via ring closure.

Key words: glycal, nitroolefin, Michael additions, glycosides, peptide mimetic, bicyclic systems, azadioxadecalines

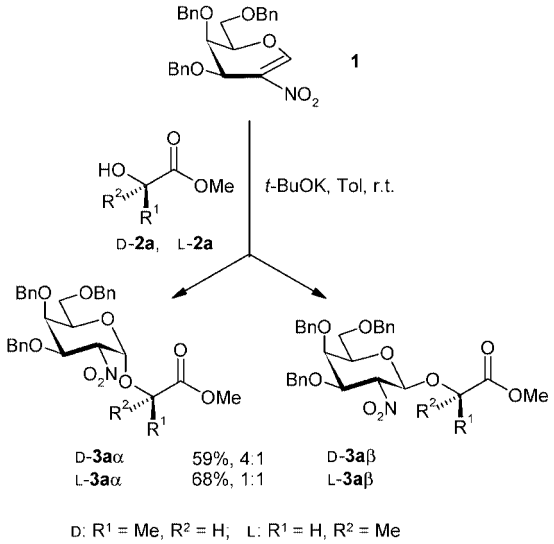
Glycosylation of α-hydroxycarboxylic acid with glycosyl donors derived from α-aminosugars should lead to a variety of interesting compounds, which can be regarded as a new type of dipeptide mimetics.[1] Possibly, due to the decreased nucleophilicity of the α-hydroxy group, these compounds have gained little attention thus far.[2] However, the successful direct base-catalysed addition of *O*-, *N*-, and *C*-nucleophiles to 2-nitroglycals (Scheme 1), as recently introduced by us,[3–5] made these type of compounds readily available. Hence, we performed an exploratory study with alkyl lactates as nucleophiles. The liberation of the underlying dipeptide mimetics and ring closure to a novel bicyclic system was also investigated.



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

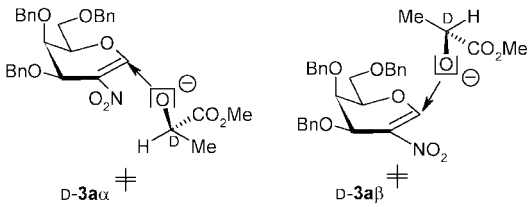
3,4,6-Tri-*O*-benzyl-2-nitro-D-galactal (**1**), which is readily available via nitration of the corresponding galactal derivative,[3a,6] furnished with methyl D-lactate (D-**2a**) in the presence of potassium *tert*-butoxide as base and toluene as solvent, D-**3aα** together with some β-anomer D-**3aβ** (α:β = 9:2) in good yield (Scheme 2).

The two compounds could be readily separated and structurally assigned by their NMR data (D-**3aα**): $J_{1,2}$ = 4.1 Hz,



Scheme 2 Synthesis of **3aα** and **3aβ**.

$J_{2,3}$ = 10.7 Hz; D-**3aβ**: $J_{1,2}$ = 8.1Hz; $J_{2,3}$ = 9.4 Hz]. The same reaction with the L-isomer L-**2a** led to a 1.2:1 ratio of L-**3aα** and L-**3aβ**, thus indicating that the α/β ratio depends not only on the chirality of the sugar moiety but also on the stereochemistry of lactate. Inspection of the plausible transition state of this reaction, as shown for D-**2a** in Scheme 3, exhibits that formation of D-**3aα** via transition state D-**3aα**$^{\neq}$ is sterically favoured over formation of D-**3aβ** via transition state D-**3aβ**$^{\neq}$ whereas the opposite is true for the formation of the L-isomers.



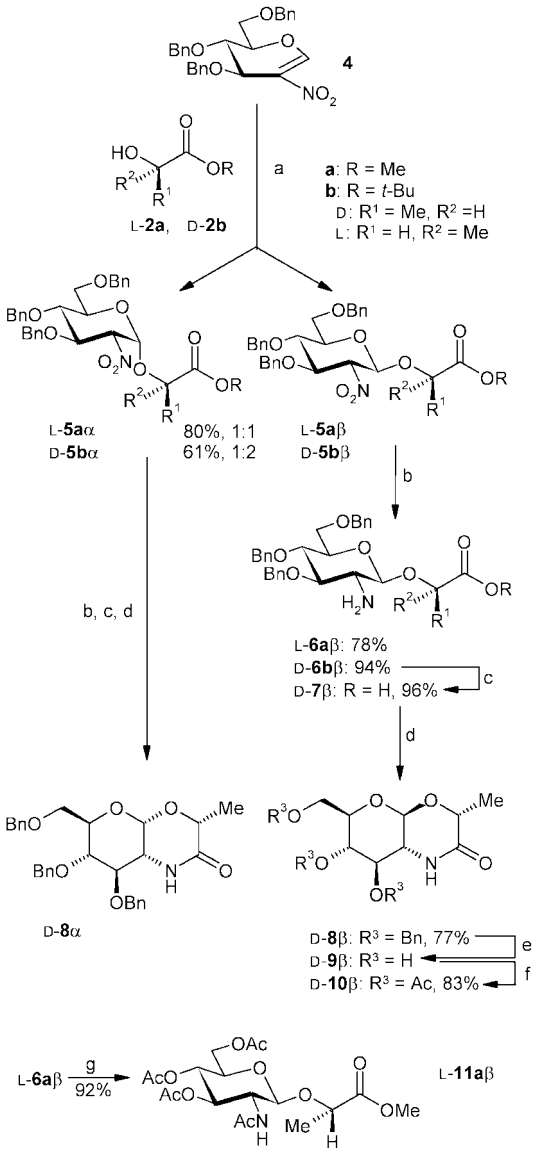
Scheme 3 Possible transition states.

Hence, together with the stereoelectronically favoured α-side attack, there should be, as is observed, a clear preference for D-**3aα** formation. This effect is also exhibited in the addition of L-threonine esters, in which the carbon connected to the hydroxy group, has D-configuration;

SYNTHESIS 2004, No. 1, pp 0053–0058
Advanced online publication: 19.11.2003
DOI: 10.1055/s-2003-42494; Art ID: T05803SS.pdf

therefore, mainly or exclusively the α-anomer was obtained.[3b–d]

Extension of this reaction to the corresponding 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal[7,8] (**4**, Scheme 4) furnished less stereocontrol than with the *galacto*-isomer **1**.



Scheme 4 Reagents and conditions: (a) *t*-BuOK, Tol, r.t. (b) Raney Ni (T4), H_2, EtOH, r.t. (c) TFA, CH_2Cl_2, r.t. (d) DPPA, NEt_3, DMF, r.t. (e) Pd/C, H_2, MeOH–HOAc, r.t. (f) Ac_2O, Pyr. (g) Pd/C, H_2, MeOH–HOAc; Ac_2O, Pyr. r.t.

Similar observations were previously made with simple alcohols,[7–9] and also an inspection of the corresponding transition states as shown for **1** in Scheme 3, supports these results. Thus, with L-**2a**, L-**5aα** and L-**5aβ** were obtained in an approximately 1:1 ratio (NMR: L-**5aα**, $J_{1,2}$ = 3.4 Hz, L-**5aβ**, $J_{1,2}$ = 8.0 Hz). For the D-isomer D-**2b** the β-isomer D-**5bβ** was even the major isomer (α:β ca. 1:2). The diastereomers could be readily separated and further reactions were investigated. Thus, reduction of the nitro group of L-**5aβ** and D-**5bβ** in the presence of platinized Raney-nickel[10] as catalyst afforded dipeptide mimetics L-**6aβ** and D-**6bβ**, respectively. Ensuing hydrogenolytic *O*-debenzylation, for instance, of L-**6aβ** with Pd/C as catalyst and then *N*- and *O*-acetylation furnished L-**11aβ**. Treatment of D-**6bβ** with trifluoroacetic acid (TFA) readily led to the removal of the *tert*-butyl group, thus furnishing D-**7β** with deprotection of the peptide mimetic part. Obviously, this type of compounds can be readily ring closed. For instance, treatment with diphenyl phosphoryl azide as condensing agent[11] in the presence of Et_3N as base, affords the novel bicyclic system D-**8β**. Hydrogenolytic *O*-debenzylation in the presence of Pd/C as catalyst (→ D-**9β**) and then *O*-acetylation with acetic anhydride in pyridine afforded *O*-acetyl protected D-**10β**. The reaction sequence from **5** to **8** could also be performed without isolation of intermediates **6** and **7** as shown for D-**5bα** which gave D-**8α** in 55% overall yield.

In conclusion, base catalysed α-hydroxycarboxylate addition to 2-nitroglycals readily provides the corresponding α- and β-glycosides with generation of two new stereogenic centres, of which one is highly stereoselectively formed. Transformation of these compounds gives access to dipeptide mimetics and to novel bicyclic pyrano[2.3-b][1.4]-oxazines.

Solvents were removed under reduced pressure while the water bath temperature was maintained below 40 °C. Solvents for chromatography were distilled prior to use. Petroleum ether (bp 35–80 °C) was used. Chromatography was performed on silica gel for flash chromatography (40 μm; J. T. Baker) at a pressure of 3 bar. For TLC, 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 spectra were measured on Bruker AC-250 Cryospec, Bruker DR-600 spectrometers. TMS or the solvent residual peaks were used as internal standard. $^3J_{C,H}$ couplings were observed in gradient-selected heteronuclear multi-bond correlations (HMBC). For MALDI-MS, Kratos Kompact Maldi 1 and 2,5-dihydroxybenzoic acid (as matrix) were used. FAB–MS was measured on Finnigan MAT 312/AMD-5000 instrument at 790 eV and 70 °C. Calculated yields are based on consumed starting material where its recovery is stated.

Methyl *O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranosyl)-L-lactate (L-3aα) and Methyl *O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-β-D-galactopyranosyl)-L-lactate (L-3aβ)

Methyl L-lactate L-**2a** (0.45 g, 4.34 mmol) and 2-nitrogalactal **1** (1.00 g, 2.17 mmol) were dried under high vacuum and dissolved in anhyd toluene (30 mL) under Ar. Freshly activated molecular sieves (3 Å, 1.50 g) were introduced and the mixture stirred for 1 h. Then 1 M *t*-BuOK solution in THF (0.20 mL, 0.20 mmol) was added and stirring was continued for 12 h at r.t. HOAc (0.20 mL) was used to acidify the reaction mixture, the molecular sieves were filtered off and the solvents removed under reduced pressure. The residue was purified by column chromatography (petroleum ether–EtOAc, 9:1) to furnish L-**3aα** (0.45 g, 37%) and L-**3aβ** (0.38 g, 31%) as colorless oils.

L-3aα

R_f 0.58 (petroleum ether–EOAc, 8:2); $[\alpha]_D$ +60.25 (*c* 0.79, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36 (d, $^3J_{\beta,\alpha}$ = 6.8 Hz, 3 H, β-CH_3), 3.46 (dd, $^3J_{6,5}$ = 5.7 Hz, $^2J_{6,6'}$ = 9.1 Hz, 1 H, 6-H), 3.60 (m, 1 H, 6′-H), 3.65 (s, 3 H, OMe), 4.11 (m, 2 H, 4-H, 5-H), 4.37 (q, $^3J_{\alpha,\beta}$ = 6.8 Hz, 1 H, α-CH), 4.49–4.58 (m, 4 H, 2 × OC*H*$_2$Ph), 4.78 (d, ^2J = 11.3 Hz, 2 H, OC*H*$_2$Ph), 4.88 (d, ^2J = 11.2 Hz, 1 H, OC*H*$_2$Ph), 5.06 (dd, $^3J_{2,1}$ = 4.3 Hz, $^3J_{2,3}$ = 10.7 Hz, 1 H, 2-H), 5.39 (d, $^3J_{1,2}$ = 4.3 Hz, 1 H, 1-H), 7.23–7.41 (m, 15 H, Ar-H).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 17.67 (β-CH_3), 51.88 (OCH_3), 67.77 (α-CH), 69.97 (C-6), 72.83 (C-5), 73.07 (C-4), 73.20 (O*C*H$_2$Ph), 74.56 (O*C*H$_2$Ph), 74.92 (C-3), 74.99 (O*C*H$_2$Ph), 84.18 (C-2), 97.13 (C-1), 127.54, 127.66, 127.90, 127.98, 128.03, 128.20, 128.27, 128.37, 128.40,.137.31, 137.77, 137.96 (C-Ar), 172.21 (COOMe).

EI–MS: *m*/*z* = 565 [M$^+$].

Anal. Calcd for $C_{31}H_{35}NO_9$ (565.6): C, 65.83; H, 6.24; N, 2.48. Found: C, 66.28; H, 6.02; N, 2.64.

L-3aβ

R_f 0.508 (petroleum ether–EtOAc, 8:2); $[\alpha]_D$ –7.32 (*c* 0.41, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40 (d, $^3J_{\beta,\alpha}$ = 6.9 Hz, 3 H, β-CH_3), 3.55–3.65 (m, 3 H, 6-H, 6′-H, 5-H), 3.68 (s, 3 H, OCH_3), 3.73 (d, $^3J_{4,3}$ = 5.8 Hz, 1 H, 4-H), 4.04 (m, 1 H, α-CH), 4.40–4.61 (m, 7 H, 5 OC*H*$_2$Ph, 3-H, 2-H), 4.82–4.88 (m, 2 H, OC*H*$_2$Ph, 1-H), 7.22–7.40 (m, 15 H, Ar-H).

EI–MS: *m*/*z* = 565 [M$^+$].

Anal. Calcd for $C_{31}H_{35}NO_9$ (565.6): C, 65.83; H, 6.24; N, 2.48. Found: C, 65.66; H, 6.15; N, 2.31.

Methyl *O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranosyl)-D-lactate (D-3aα) and Methyl *O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-β-D-galactopyranosyl)-D-lactate (D-3aβ)

D-**3aα** and D-**3aβ** were obtained as described for L-**3aα** and L-**3aβ**.

D-3aα

Yield: 587 mg (48%).

R_f 0.78 (petroleum ether–EtOAc, 8:2); $[\alpha]_D$ +112.0 (*c* 1, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.44 (d, $^3J_{\beta,\alpha}$ = 6.9 Hz, 3 H, β-CH_3), 3.55 (d, $^3J_{6,5}$ = 6.5 Hz, 2 H, 6-H, 6′-H), 3.71 (s, 3 H, OMe), 4.03–4.27 (m, 2 H, 4-H, 5-H), 4.32 (q, $^3J_{\alpha,\beta}$ = 6.9 Hz, 1 H, α-CH), 4.35–4.88 (m, 7 H, 3-H, 3 × OC*H*$_2$Ph), 5.03 (dd, $^3J_{2,1}$ = 4.1 Hz, $^3J_{2,3}$ = 10.7 Hz, 1 H, 2-H), 5.45 (d, $^3J_{1,2}$ = 4.1 Hz, 1 H, 1-H), 7.09–7.37 (m, 15 H, Ar-H).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 18.3 (β-CH_3), 52.1 (OCH_3), 68.3 (α-CH), 70.2 (C-6), 71.5 (C-5), 73.1 (C-4), 73.13 (O*C*H$_2$Ph), 73.5 (O*C*H$_2$Ph), 75.0 (C-3), 75.1 (O*C*H$_2$Ph), 83.9 (C-2), 95.5 (C-1), 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.5, 137.3, 137.6, 137.8 (C-Ar), 171.7 (COOMe).

MS (MALDI): *m*/*z* = 588 [MNa$^+$].

Anal. Calcd for $C_{31}H_{35}NO_9$ (565.6): C, 65.83; H, 6.24; N, 2.48. Found: C, 65.76; H, 6.27; N, 2.67.

D-3aβ

Yield: 136 mg (11%).

R_f 0.70 (petroleum ether–EtOAc, 8:2); $[\alpha]_D$ = +20.8 (*c* 1, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (d, $^3J_{\beta,\alpha}$ = 6.8 Hz, 3 H, β-CH_3), 3.52–3.67 (m, 3 H, 6-H, 6′-H, 5-H), 3.68 (s, 3 H, OMe), 3.99–4.19 (m, 2 H, 3-H, 4-H), 4.18 (q, $^3J_{\alpha,\beta}$ = 6.8 Hz, 1 H, α-CH), 4.43–4.63 (m, 5 H, 2 × OC*H*$_2$Ph, 1-H), 4.82–4.94 (m, 3 H, 2-H, OC*H*$_2$Ph), 7.23–7.36 (m, 15 H, Ar-H).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 17.6 (β-CH_3), 52.1 (OCH_3), 67.9 (α-CH), 71.4 (C-6), 72.3 (C-5), 73.6 (C-4), 74.0 (O*C*H$_2$Ph), 74.8 (O*C*H$_2$Ph), 75.2 (C-3), 79.4 (O*C*H$_2$Ph), 87.1 (C-2), 99.7 (C-1), 127.8, 127.9, 128.1, 128.2, 128.3, 128.5, 128.6, 136.5, 137.5, 137.8 (C-Ar), 171.9 (COOMe).

MS (MALDI): *m*/*z* = 588 [MNa$^+$].

Anal. Calcd for $C_{31}H_{35}NO_9$ (565.6): C, 65.83; H, 6.24; N, 2.48. Found: C, 65.99; H, 6.35; N, 2.23.

Methyl *O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-α-D-glucopyranosyl)-L-lactate (L-5aα) and Methyl *O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-β-D-glucopyranosyl)-L-lactate (L-5aβ)

L-**5aα** and L-**5aβ** were obtained as described for L-**3aα** and L-**3aβ**.

L-5aα

Yield: 0.53 g (43%); white foam.

R_f 0.50 (petroleum ether–EtOAc, 8:2); $[\alpha]_D$ +47.5 (*c* 0.32, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.38 (d, $^3J_{\beta,\alpha}$ = 6.8 Hz, 3 H, β-CH_3), 3.62 (dd, $^3J_{6,5}$ = 2.0 Hz, $^2J_{6,6'}$ = 10.9 Hz, 1 H, 6-H), 3.70 (s, 3 H, OCH_3), 3.81–3.87 (m, 2 H, 6′-H, 5-H), 4.15 (q, $^3J_{\alpha,\beta}$ = 6.8 Hz, 1 H, α-CH), 4.27 (d, $^3J_{4,3}$ = 10.3 Hz, 1 H, 4-H), 4.48–4.67 (m, 5 H, 2 × OC*H*$_2$Ph, 3-H), 4.85 (d, ^2J = 10.9 Hz, 1 H, OC*H*$_2$Ph), 4.95 (s, 2 H, OC*H*$_2$Ph, 2-H), 5.42 (dd, $^3J_{1,2}$ = 3.4 Hz, 1 H, 1-H), 7.21–7.40 (m, 15 H, Ar-H).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 17.16 (β-CH_3), 51.53 (OCH_3), 67.01 (α-CH), 70.74 (C-6), 72.92 (C-5), 74.46 (C-4, O*C*H$_2$Ph), 75.20 (O*C*H$_2$Ph), 76.47 (C-3, O*C*H$_2$Ph), 86.09 (C-2), 96.61 (C-1), 127.04, 127.26, 127.34, 127.83, 137.01, 137.20, 137.25 (C-Ar), 171.54 (COOMe).

EI–MS: *m*/*z* = 565 [M$^+$].

Anal. Calcd for $C_{31}H_{35}NO_9$ (565.6): C, 65.83; H, 6.24; N, 2.48. Found: C, 65.67; H, 6.10; N, 2.48.

L-5aβ

Yield: 0.45 g (37%): white foam.

R_f 0.48 (petroleum ether–EtOAc, 8:2); $[\alpha]_D$ –19.12 (*c* 0.34, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.45 (d, $^3J_{\beta,\alpha}$ = 7.0 Hz, 3 H, β-CH_3), 3.53 (m, 1 H, 6-H), 3.66–3.74 (m, 6 H, 6′-H, 5′-H, OCH_3, 4-H), 4.25 (dd, $^3J_{3,2}$ = 8.8 Hz, $^2J_{3,4}$ = 10.3 Hz, 1 H, 3-H), 4.42–4.62 (m, 7 H, α-CH, 3 × OC*H*$_2$Ph), 4.78 (dd, $^3J_{2,3}$ = 8.8 Hz, 1 H, 2-H), 4.92 (d, $^3J_{2,1}$ = 8.0 Hz, $^3J_{2,3}$ = 8.7 Hz, 1 H, 1-H), 7.14–7.33 (m, 15 H, Ar-H).

^{13}C NMR (62.8 Hz, $CDCl_3$): δ = 18.42 (β-CH_3), 52.06 (OCH_3), 67.77 (α-CH), 72.57 (C-6), 73.52 (C-5, O*C*H$_2$Ph), 75.09 (C-4), 75.30 (O*C*H$_2$Ph), 75.48 (C-3), 81.36 (O*C*H$_2$Ph), 89.66 (C-2), 98.35 (C-1), 127.81, 127.98, 128.04, 128.45, 136.98, 137.49, 137.71 (C-Ar), 171.92 (COOMe).

EI–MS: *m*/*z* = 565 [M$^+$].

Anal. Calcd for $C_{31}H_{35}NO_9$ (565.6): C, 65.83; H, 6.24; N, 2.48. Found: C, 65.56; H, 6.22; N, 2.51.

***tert*-Butyl *O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-α-D-glucopyranosyl)-D-lactate (D-5bα) and *tert*-Butyl *O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-nitro-β-D-glucopyranosyl)-D-lactate (D-5bβ)**

tert-Butyl-D-lactate D-**2b** (317 mg, 2.17 mmol) and 2-nitroglucal **4** (1.00 g, 2.17 mmol) were dried under high vacuum and dissolved in anhyd toluene (30 mL) under Ar. The reaction was carried out as described for the synthesis of L-**3a** to furnish D-**5bα** (0.30 g, 23%) and D-**5bβ** (0.50 g, 38%) as white foams.

D-5bα

R_f 0.56 (petroleum ether–EtOAc, 8:2); $[\alpha]_D$ +77.39 (*c* 0.23, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40 (d, $^3J_{\beta,\alpha}$ = 6.9 Hz, 3 H, β-CH_3), 1.47 (s, 9 H, C*Me*$_3$), 3.62–3.90 (m, 4 H, 6-H, 6′-H, 5-H, 4-H), 4.21 (q, $^3J_{\alpha,\beta}$ = 6.8 Hz, 1 H, α-CH), 4.49–4.66 (m, 5 H, 3-H,

OCH_2Ph, 2-H), 4.84 (d, ^2J = 10.7 Hz, 1 H, OCH_2Ph), 4.92 (s, 2 H, OCH_2Ph), 5.50 (d, $^3J_{1,2}$ = 3.0 Hz, 1 H, 1-H), 7.17–7.36 (m, 15 H, Ar-H).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 18.19 (β-CH_3), 27.82 (CMe_3), 67.76 (α-CH), 71.26 (C-6), 71.57 (C-5), 73.56 (C-4), 75.20 (OCH_2Ph), 75.81 (C-3), 77.16 (OCH_2Ph), 78.12 (OCH_2Ph), 82.17 (CMe$_3$), 86.47 (C-2), 95.01 (C-1), 127.76, 127.81, 127.94, 128.36, 128.40, 128.46, 137.53, 137.75 (C-Ar), 170.16 (C=O).

MS (MALDI): *m*/*z* = 630 [MNa^+], 646 [MK^+].

Anal. Calcd for $C_{34}H_{41}NO_9$ (607.7): C, 67.20; H, 6.80; N, 2.30. Found: C, 67.16; H, 6.79; N, 2.52.

D-5bβ

R_f 0.48 (petroleum ether–EtOAc, 8:2). $[\alpha]_D$ –12.80 (*c* 0.18, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30 (d, $^3J_{\beta,\alpha}$ = 6.9 Hz, 3 H, β-CH_3), 1.42 (s, 9 H, CMe_3), 3.66–3.74 (m, 4 H, 6-H, 6′-H, 5-H, 4-H), 4.03 (q, $^3J_{\alpha,\beta}$ = 6.8 Hz, 1 H, α-CH), 4.20 (dd, $^3J_{3,2}$ = 8.3 Hz, $^3J_{3,4}$ = 8.2 Hz, 1 H, 3-H), 4.42–4.58 (m, 5 H, OCH_2Ph), 4.70 (dd, $^3J_{2,1}$ = 8.0 Hz, $^3J_{2,3}$ = 8.2 Hz, 1 H, 2-H), 4.76 (d, ^2J = 10.5 Hz, 1 H, OCH_2Ph), 4.86 (d, $^3J_{1,2}$ = 8.0 Hz, 1 H, 1-H), 7.13–7.33 (m, 15 H, Ar-H).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 17.79 (β-CH_3), 27.88 (CMe_3), 53.38 (α-CH), 68.21 (C-6), 73.52 (C-5), 75.12 (C-4), 75.30 (OCH_2Ph), 75.61 (C-3), 75.84 (OCH_2Ph), 77.40 (OCH_2Ph), 81.42 (CMe$_3$), 89.52 (C-2), 99.53 (C-1), 127.69, 127.73, 127.84, 127.90, 127.96, 128.06, 128.08, 128.23, 128.37, 128.43, 128.46, 128.58, 136.95, 137.53, 137.83 (C-Ar), 170.62 (C=O).

MS (MALDI): *m*/*z* = 631 [MNa^+].

Anal. Calcd for $C_{34}H_{41}NO_9$ (607.7): C, 67.20; H, 6.80; N, 2.30. Found: C, 67.56; H, 7.27; N, 2.24.

Methyl *O*-(2-Amino-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-L-lactate (L-6aβ)

Nitroglycoside L-**5aβ** (0.13 g, 0.23 mmol) was dissolved in EtOH (5 mL), and transferred to a hydrogen vessel. Platinized Raney Ni T4 catalyst was freshly prepared as described in ref.[10] and the material obtained from 2 g of Raney Ni/Al alloy was suspended in EtOH (15 mL). From a homogeneous suspension of this catalyst 10 mL was added to the reaction vessel and the suspension shaken under H_2 for 48 h at ambient temperature and pressure. The catalyst was filtered off and the solvent evaporated. The residue was purified by column chromatography (CH_2Cl_2–MeOH, 98:2) to furnish L-**6aβ** (96 mg, 78%) as a colorless oil; R_f 0.52 (CH_2Cl_2–MeOH, 95:5); $[\alpha]_D$ 31.58 (*c* 0.28, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41 (d, $^3J_{\beta,\alpha}$ = 6.6 Hz, 3 H, β-CH_3), 2.53 (br s, 2 H, NH_2), 3.52–7.79 (m, 7 H, 6-H, 6′-H, OMe, 5-H, 4-H), 4.02 (m, 1 H, 3-H), 4.18 (q, $^3J_{\alpha,\beta}$ = 6.6 Hz, 1 H, α-CH), 4.45–4.99 (m, 8 H, 2-H, 3 × OCH_2Ph, 1-H), 7.18–7.33 (m, 15 H, Ar-H).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 17.92 (β-CH_3), 51.80 (OCH_3), 68.77 (C-6), 69.02 (α-CH), 71.45 (C-5), 73.31 (C-4), 73.64 (OCH_2Ph), 74.44 (OCH_2Ph), 75.01 (C-3), 75.42 (OCH_2Ph), 78.46 (C-2), 99.86 (C-1), 127.51, 127.56, 127.62, 127.77, 128.19, 128.35, 137.75, 138.05, 138.38 (C-Ar), 172.97 (COOMe).

MS (MALDI): *m*/*z* = 536 [MH^+], 558 [MNa^+], 574 [MK^+].

Anal. Calcd for $C_{31}H_{37}NO_7 \cdot 1.25\ H_2O$ (558.1): C, 66.65; H, 6.98; N, 2.51. Found: C, 66.52; H, 6.86; N, 2.50.

***tert*-Butyl *O*-(2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-D-lactate (D-6bβ)**

Nitroglycoside D-**5bβ** (0.35 g, 0.57 mmol) was dissolved in EtOH (10 mL), and transferred to a hydrogen vessel. The reaction was carried out as described for the synthesis of L-**6aβ** to furnish D-**6bβ** (310 mg, 94%) as a colorless oil which was immediately used in the next step; R_f 0.36 (CH_2Cl_2–MeOH, 95:5); $[\alpha]_D$ +43.33 (*c* 0.18, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (d, $^3J_{\beta,\alpha}$ = 7.0 Hz, 3 H, β-CH_3), 1.44 (s, 9 H, CMe_3), 3.49 (m, 1 H, 6-H), 3.63–3.75 (m, 5 H, 6′-H, 5-H, NH_2, 4-H), 4.96 (m, 1 H, 3-H), 4.25 (q, $^3J_{\alpha,\beta}$ = 7.0 Hz, 1 H, α-CH), 4.41–4.91 (m, 8 H, 2-H, OCH_2Ph, 1-H), 7.11–7.34 (m, 15 H, Ar-H).

MS (MALDI): *m*/*z* = 579 [MH^+], 601 [MNa^+].

Anal. Calcd for $C_{34}H_{43}NO_7$ (577.7): C, 70.69; H, 7.50; N, 2.42. Found: C, 70.94; H, 7.50; N, 2.45.

***O*-(2-Amino-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-D-lactic Acid (D-7β)**

Aminoglycoside D-**6bβ** (0.30 g, 0.52 mmol) was dissolved in a mixture of trifluoroacetic acid and CH_2Cl_2 (20 mL, 1:1) and the solution stirred at r.t. for 12 h. Then all the solvents were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 followed by addition of sat. aq $NaHCO_3$ with vigorous stirring. The layers were separated and the aq phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified by column chromatography (CH_2Cl_2–MeOH, 95:5) to furnish D-**7β** (0.26 g, 96%) as a white foam which, was immediately used in the next step; R_f 0.40 (CH_2Cl_2–MeOH, 95:5); $[\alpha]_D$ +49.09 (*c* 0.33, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32 (d, $^3J_{\beta,\alpha}$ = 7.0 Hz, 3 H, β-CH_3), 3.52 (d, $^3J_{6,6'}$ = 10.6 Hz, 1 H, 6-H), 3.66–3.80 (m, 5 H, 6′-H, 5-H, NH_2, 4-H), 4.01 (t, $^3J_{3,4}$ = $^3J_{3,2}$ = 9.7 Hz, 1 H, 3-H), 4.28 (q, $^3J_{\alpha,\beta}$ = 6.9 Hz, 1 H, α-CH), 4.31–4.91 (m, 8 H, 2-H, OCH_2Ph, 1-H), 5.17 (br s, 1 H, COOH), 7.04–7.38 (m, 15 H, Ar-H).

MS (MALDI): *m*/*z* = 523 [MH^+], 545 [MNa^+], 561 [MK^+].

Anal. Calcd for $C_{30}H_{35}NO_7$ (521.6): C, 69.08; H, 6.76; N, 2.69. Found: C, 69.78; H, 7.09; N, 2.26.

(3*R*,4a*S*,6*R*,7*S*,8*R*,8a*R*)-7,8-Bis-benzyloxy-6-benzyloxymethyl-3-methyl-hexahydro-pyrano[2,3-*b*][1,4]-oxazin-2-one (D-8β)

To a solution of the aminoglycoside D-**7β** (0.30 g, 0.57 mmol) in DMF (10 mL) was added Et_3N (0.25 mL, 1.80 mmol). After being stirred for 10 min, diphenyl phosphoryl azide (DPPA) (0.36 mL, 1.80 mmol) was added and the resulting reaction mixture was further stirred at r.t. for 1.5 h. The reaction mixture was quenched with sat. aq NaCl (20 mL) and extracted with Et_2O (3 × 10 mL). The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether–EtOAc, 8:2) to furnish D-**8β** (0.20 g, 77%) as a colorless oil; R_f 0.60 (petroleum ether–EtOAc, 6:4); $[\alpha]_D$ –5.20 (*c* 0.25, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.51 (d, $^3J_{Me,3}$ = 6.9 Hz, 3 H, CH_3), 3.72–3.81 (m, 5 H, 8a-H, 1′a-H, 1′b-H, 7-H, 8-H), 4.29 (m, 2 H, OCH_2Ph, 3-H), 4.27–4.50 (m, 4 H, OCH_2Ph, 6-H), 4.52 (d, ^2J = 12.0 Hz, 1 H, OCH_2Ph), 4.60 (d, ^2J = 12.0 Hz, 1 H, OCH_2Ph), 4.95 (d, $^3J_{4a,8a}$ = 7.7 Hz, 1 H, 4a-H), 6.12 (s, 1 H, NH), 7.15–7.35 (m, 15 H, Ar-H).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 17.71 (CH_3), 53.22 (C-8a), 67.67 (C-1′), 71.13 (C-8), 71.60 (OCH_2Ph), 72.74 (OCH_2Ph), 73.18 (OCH_2Ph), 73.34 (C-3), 75.09 (C-7), 76.17 (C-6), 91.41 (C-4a), 127.60, 127.71, 127.86, 127.95, 128.15, 128.36, 128.46, 128.54, 129.67, 137.04, 137.32, 137.86 (C-Ar), 172.01 (CO).

MS (MALDI): *m*/*z* = 505 [MH^+], 527 [MNa^+], 543 [MK^+].

Anal. Calcd for $C_{30}H_{33}NO_6$ (503.59): C, 71.55; H, 6.61; N, 2.78. Found: C, 71.36; H, 6.33; N, 2.67.

(3*S*,4a*S*,6*R*,7*S*,8*R*,8a*R*)-7,8-Diacetoxy-3-methyl-2-oxo-hexahydro-pyrano[2,3-*b*][1,4]-oxazin-6-ylmethyl acetate (D-10β)

Compound D-**8β** (50 mg, 0.10 mmol) was dissolved in MeOH–HOAc (1:1, 4 mL) and Pd/C (50 mg, 10% Pd) was suspended in the solution. This mixture was stirred for 24 h under H_2 at r.t. After complete disappearance of the starting material (TLC, CH_2Cl_2–MeOH, 9:1), the catalyst was filtered off and all the solvents were removed under reduced pressure. The residue of *O*-unprotected material D-**9β** {MS (MALDI): *m*/*z* calcd 233 + 23 [Na]: 256; found: 256 [M + Na]$^+$} was treated with pyridine–acetic anhydride (3:2, 6 mL) and stirred at r.t. for 12 h. All volatiles were evaporated and the residue was purified by flash column chromatography (CH_2Cl_2–MeOH, 98:2) to furnish D-**10β** (30 mg, 83%) as a white foam.

D-10β

R_f 0.42 (CH_2Cl_2–MeOH, 95:5); $[\alpha]_D$ +3.33 (*c* 0.12, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.53 (d, $^3J_{Me,3}$ = 6.9 Hz, 3 H, Me), 2.11, 2.13, 2.17 (3 × s, 9 H, 3 × Ac), 3.83 (dd, $^3J_{8a,8}$ = 2.9 Hz, $^3J_{8a,NH}$ = 7.8 Hz, 1 H, 8a-H), 4.23 (dd, $^3J_{1'a,6}$ = 5.5 Hz, $^3J_{1'a,1'b}$ = 11.7 Hz, 1 H, 1′a-H), 4.38 (dd, $^3J_{6,1'a}$ = 5.7 Hz, $^3J_{6,7}$ = 8.4 Hz, 1 H, 6-H), 4.42 (q, $^3J_{3,Me}$ = 6.9 Hz, 1 H, 3-H), 4.65 (dd, $^3J_{1'b,6}$ = 8.8 Hz, $^3J_{1'b,1'}$ = 11.8 Hz, 1 H, 1′b-H), 4.88 (d, $^3J_{7,8}$ = 2.2 Hz, 1 H, 7-H), 5.06 (d, $^3J_{4a,8a}$ = 7.8 Hz, 1 H, 4a-H), 5.28 (m, 1 H, 8-H), 5.99 (s, 1 H, NH).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 17.60 (Me), 20.75, 20.80 (3Ac), 52.95 (C-8a), 59.99 (C-1′), 66.86 (C-7), 67.61 (C-8), 73.80 (C-3), 75.93 (C-6), 90.62 (C-4a), 169.24, 170.10, 170.82 (3 × Ac), 170.60 (CO).

MS (MALDI): *m*/*z* = 360 [MH$^+$], 382 [MNa$^+$], 398 [MK$^+$].

Anal. Calcd for $C_{15}H_{21}NO_9$ (359.3): C, 50.14; H, 5.89; N, 3.90. Found: C, 50.15; H, 6.04; N, 3.97.

(3*S*,4a*R*,6*R*,7*S*,8*R*,8a*R*)-7,8-Bis-benzyloxy-6-benzyloxymethyl-3-methyl-decahydro-pyrano[2,3-*b*][1,4]oxazin-2-one (D-8α)

Nitroglycoside D-**5bα** (50 mg, 0.09 mmol) was dissolved in EtOH (3 mL), and transferred to a hydrogenation vessel. Platinized Raney Ni T4 catalyst was freshly prepared as described in ref.[10] and the material obtained from 1 g of Raney Ni/Al alloy was suspended in EtOH (5 mL). From a homogeneous suspension of this catalyst 3 mL was added to the reaction vessel and the suspension shaken under H_2 for 48 h at ambient temperature and pressure. The catalyst was filtered off and the solvent evaporated. The residue was immediately used in the next step. To a solution of the crude aminoglycoside in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (5 mL). After being stirred for 12 h at r.t., the solvents were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 followed by addition of sat. aq $NaHCO_3$ with vigorous stirring. The layers were separated and the aq phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, concentrated under reduced pressure. The residue was immediately used in the next step. To a solution of the crude free acid in DMF (3 mL) was added Et_3N (70 μL, 0.50 mmol). After being stirred for 10 min, diphenylphosphoryl azide (DPPA) (100 L, 0.50 mmol) was added and the resulting reaction mixture was further stirred at r.t. for 1.5 h. The reaction mixture was quenched with sat. aq NaCl (6 mL) and extracted with Et_2O (3 × 5 mL). The extract was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether–EtOAc, 8:2) to furnish D-**8α** (25 mg, 55%) as a colorless oil; R_f 0.50 (petroleum ether–EtOAc, 6:4); $[\alpha]_D$ +62.0 (*c* 0.25, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.42 (d, $^3J_{Me,3}$ = 6.8 Hz, 3 H, CH_3), 3.35 (m, 1 H, 8a-H), 3.66–3.81 (m, 4 H, 1′a-H, 1′b-H, 7-H, 8-H), 4.05 (m, 1 H, 6-H), 4.33 (q, $^3J_{3,Me}$ = 6.8 Hz, 1 H, 3-H), 4.49–4.69 (m, 4 H, OCH_2Ph), 4.80 (d, ^2J = 10.5 Hz, 1 H, OCH_2Ph), 4.96 (d, ^2J = 11.0 Hz, 1 H, OCH_2Ph), 5.20 (d, $^3J_{4a,8a}$ = 2.9 Hz, 1 H, 4a-H), 6.07 (br d, $^3J_{NH,8a}$ = 3.7 Hz, 1 H, NH), 7.18–7.35 (m, 15 H, Ar-H).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 17.52 (CH_3), 55.91 (C-8a), 67.80 (C-1′), 73.09 (C-6), 73.27 (C-3), 73.63 (OCH_2Ph), 74.91 (OCH_2Ph), 75.78 (OCH_2Ph), 77.40 (C-7), 83.06 (C-8), 93.15 (C-4a), 127.82, 127.85, 127.97, 128.16, 128.44, 128.50, 128.68, 137.64 (C-Ar), 169.75 (CO).

MS (MALDI): *m*/*z* = 505 [MH$^+$], 527 [MNa$^+$].

Anal. Calcd for $C_{30}H_{33}NO_6 \cdot 0.5\ H_2O$ (512.6): C, 70.23; H, 6.43; N, 2.73. Found: C, 70.60; H, 6.87; N, 2.76.

Methyl *O*-(2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-L-lactate (L-11aβ)

Aminoglycoside L-**6aβ** (53.5 mg, 0.1 mmol) was dissolved in MeOH–HOAc (2:1, 6 mL) and Pd/C (50 mg, 10% Pd) was suspended in the solution. This mixture was stirred for 24 h under H_2 at r.t. After complete disappearance of the starting material (TLC: CH_2Cl_2–MeOH, 9:1), the catalyst was filtered off and all the solvents were removed under reduced pressure. The residue was treated with pyridine–acetic anhydride (3:2, 6 mL) and stirred at r.t. for 12 h. All volatiles were evaporated and the residue was purified by flash column chromatography (petroleum ether–EtOAc, 6:4) to furnish L-**11aβ** (40 mg, 92%) as a colorless oil; R_f 0.56 (petroleum ether–EtOAc, 50:50); $[\alpha]_D$ +60.83 (*c* 0.24, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (d, $^3J_{\beta,\alpha}$ = 6.9 Hz, 3 H, β-CH_3), 1.92, 1.99, 2.00, 2.05 (4 × s, 12 H, 4 × Ac), 3.71 (s, 3 H, OMe), 3.98 (m, 1 H, 6-H), 4.06–4.34 (m, 3 H, 6′-H, 5-H, 4-H), 4.33 (dd, $^3J_{3,4}$ = 9.3 Hz, 1 H, 3-H), 4.90 (q, $^3J_{\alpha,\beta}$ = 6.9 Hz, 1 H, α-CH), 5.10 (dd, $^3J_{2,3}$ = 9.6 Hz, $^3J_{2,1}$ = 9.8 Hz, 1 H, 2-H), 5.20 (d, $^3J_{1,2}$ = 9.8 Hz, 1 H, 1-H), 5.86 (d, $^3J_{NH,2}$ = 9.2 Hz, 1 H, NH).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 17.60 (β-CH_3), 23.97, 26.38, 26.49 (4 × Ac), 51.92 (OCH_3), 52.92 (α-CH), 61.64 (C-6), 67.60 (C-5), 67.82 (C-4), 71.12 (C-3), 74.01 (C-2), 97.55 (C-1), 169.28 (COOMe), 169.97, 170.68, 171.37, 172.42 (4 Ac).

MS (MALDI): *m*/*z* = 434 [MH$^+$], 456 [MNa$^+$], 472 [MK$^+$].

Anal. Calcd for $C_{18}H_{27}NO_{11}$ (433.4): C, 49.88; H, 6.28; N, 3.23. Found: C, 49.64; H, 6.26; N, 2.87.

Acknowledgment

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. and K. P. are grateful for the Alexander von Humboldt-Fellowships. We are grateful to Ms. Anke Friemel for her help in the structural assignments by NMR experiments.

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