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A Convenient Synthesis of Pyrano[2,3-*b*][1,5]oxazepines by Ring Closure of *O*-Glycosyl Amino Acids

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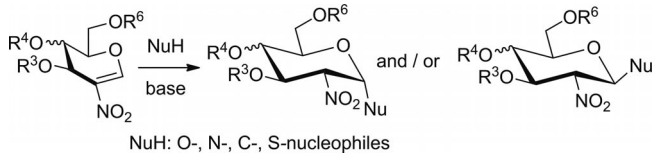
N-Boc-protected serine and threonine esters could be readily added to 2-nitroglycals, affording exclusively α- and β-anomers with *galacto*- and *gluco*-configuration, respectively. Nitro group reduction to the amino group and also ester cleavage led to compounds **2**, **6**, and **11**, which can be regarded as dipeptide mimetics. From these compounds, bicyclic pyrano[2.3-*b*][1,5]oxazepines **7**–**14** were prepared by ring closure.

Introduction

Glycans are polyalcohol compounds that exhibit broad diversity with respect to the presence of regioisomers and stereoisomers at the anomeric position. In the field of glycoscience, many glycochemists have made great efforts to efficiently construct the *O*-glycosidic linkage in highly regio/stereoselective ways.[1–4] 1,4(1,5)-Oxa(thia)zepine derivatives exhibit strong biological activity and have been extensively studied.[5] In particular, Sintamil is known as an efficient antidepressant.[6] Substituted 5,11-dihydrobenzo[*b*,*e*][1,4]oxazepines, which exhibit lower anticholinergic activity,[7–9] were also tested as a new generation of calcium antagonists. Piperazinyldibenzo[*b*,*f*][1,4]oxa(thia)zepine derivatives belong to a class of novel so-called atypical antipsychotic drugs that are effective in the treatment of psychoneurological disorders such as psychosis, depression, and schizophrenia.[10] 2,3,4,5-Tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide showed high inhibitory activity toward γ-secretase in the treatment of Alzheimer disease.[11] *O*-Glycosylation of β-hydroxycarboxylates and, particularly, of serine and threonine, having α-amino groups, with glycosyl donors derived from 2-amino-2-deoxy sugars leads to versatile building blocks for glycopeptide synthesis and for the generation of glycopeptide mimetics, and for various functional group manipulations.[12] The versatile direct base-catalyzed addition of O-, N-, C-, and S-nucleophiles to 2-nitroglycals (Scheme 1), as recently investigated by us,[13–22] have made these building blocks readily available.



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

In this paper, we demonstrate that bicyclic lactams are readily accessible through this route. Compounds of this type have been previously obtained essentially as by-products of *O*-glycosyl-serine or threonine liberation from protected precursors.[23–26]

Results and Discussion

Addition of *N*-protected serine ester to 2-nitro-galactal leads, depending on the type of *O*-protection and reaction conditions, to either mainly α-galactoside or to an α/β-anomeric mixture.[13–15] In this way, galactoside **1aα** and **1bα** can be readily obtained from 3,4,6-tri-*O*-benzyl-2-nitro-galactal[13] and *N*-Boc-protected serine *tert*-butyl and methyl ester, respectively[16] (Scheme 2).

Reduction of the nitro group in the presence of platinized Raney-nickel[27] as catalyst afforded the amino derivative **2aα**,[16] which, on treatment with fluorenylmethyloxycarbonyl chloride (FmocCl) in the presence of triethylamine, afforded *N*,*O*-protected intermediate **3aα**. Acid-catalyzed cleavage of the Boc group and of the *tert*-butyl ester led to formation of the versatile intermediate **4α**; attachment of a Boc group to the amino group furnished the orthogonally protected *O*-glycosyl serine derivative **5α**. No undesired ring closure to the lactam was observed in any of the reactions. To this end, **5α** was treated with morpholine to give, after Fmoc cleavage, *N*-deprotected **6α**, which, on reaction with diphenylphophoryl azide (DPPA)[28] in the presence of tri-

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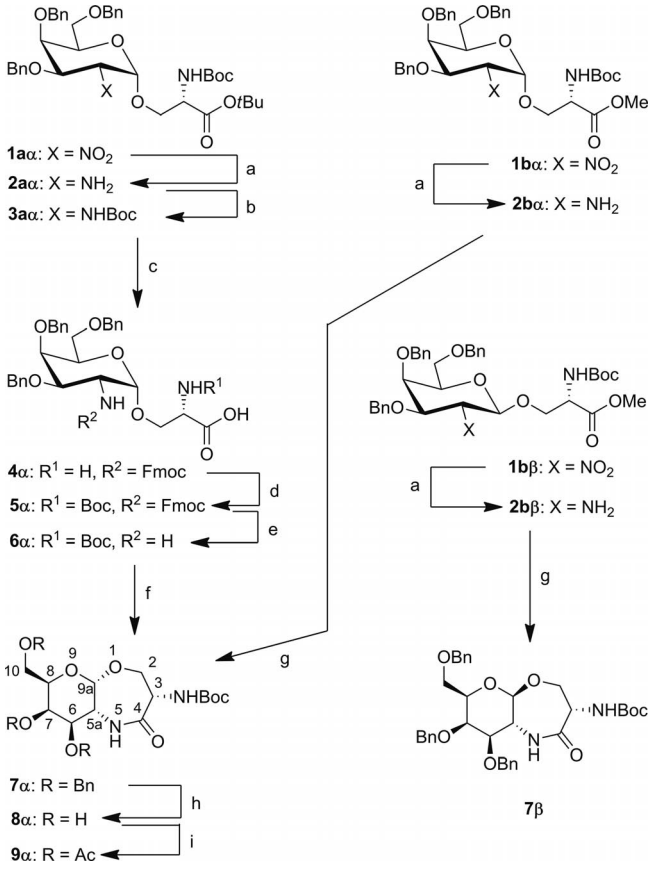
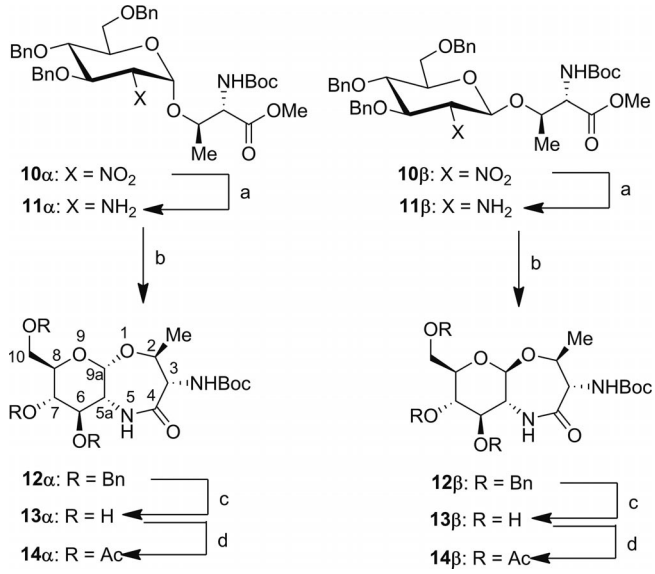


Scheme 2. Reagents and conditions: (a) Ra-Ni (T_4), H_2, EtOH, r.t.; (b) FmocCl, NEt_3, CH_2Cl_2; (c) TFA, CH_2Cl_2; (d) BocON, NEt_3, dioxane; (e) morpholine, CH_2Cl_2; (f) NEt_3, DPPA, DMF; (g) LiOH, H_2O; NEt_3, DPPA, DMF; (h) Pd/C, H_2, HOAc, MeOH; (i) Ac_2O, Pyr.



Scheme 3. Reagents and conditions: (a) Ra-Ni (T_4), H_2, EtOH, r.t.; (b) LiOH, H_2O; NEt_3, DPPA, DMF; (c) Pd/C, H_2, HOAc, MeOH; (d) Ac_2O, Pyr.

ethylamine as base, furnished bicyclic lactam **7α** in high yield. Clearly, this compound can be more readily obtained with the more reactive methyl ester **1bα**, which, as well as its β-anomer **1bβ**, is also obtained by *N*-Boc-protected serine methyl ester addition to 2-nitrogalactal (^{1}H NMR: **1bα**: $^3J_{1,2}$ = 4.0 Hz, **1bβ**: $^3J_{1,2}$ = 8.0 Hz). Reduction of the nitro group in **1bα** as described above (→ **2bα**), followed by hydrolysis of the methyl ester with lithium hydroxide, and ensuing lactam formation with DPPA/triethylamine, afforded **7α** directly in very good overall yield. Similarly, the diastereoisomer **7β** was obtained from **1bβ** via **2bβ**. Hydrogenolytic *O*-debenzylation of **7α** in the presence of palladium on carbon as catalyst afforded *O*-unprotected **8α**, which, for further characterization was transformed with acetic anhydride in pyridine into the per-*O*-acetylated derivative **9α**. The structural assignment of bicyclic lactams **7α** and **7β** were confirmed by ^{1}H NMR spectroscopic analysis. Addition of *N*-Boc-protected L-threonine methyl ester to 3,4,6-tri-*O*-benzyl-2-nitroglucal[18,29–32] afforded a 2:1 mixture of α- and β-anomers **10α** (^{1}H NMR: $^3J_{1,2}$ = 3.5 Hz) and **10β** (^{1}H NMR: $^3J_{1,2}$ = 8.1 Hz), which could be readily separated (Scheme 3).

Reduction of the nitro group in **10α** and **10β** as described above led to the amino derivatives **11α** and **11β** as intermediates, which, on treatment with diphenylphosphoryl azide (DPPA) and triethylamine, again afforded the bicyclic lactams **12α** and **12β**, respectively, in high overall yields. Hydrogenolytic *O*-debenzylation (→ **13α** and **13β**) and then *O*-acetylation furnished *O*-acetyl protected bicyclic lactams **14α** and **14β**, again in a very straightforward manner. The structural assignment of these compounds was fully supported by the physical data.

Conclusions

In conclusion, base-catalyzed *N*-Boc-protected serine and threonine ester addition to 2-nitroglycals readily provides the corresponding α- and β-glycosides together with the generation of two new stereogenic centers, of which one is formed highly stereoselectively. Transformation of these compounds allows access to dipeptide mimetics and to novel bicyclic pyrano[2,3-*b*][1,5]oxazepines.

Experimental Section

General Remarks: Solvents were removed under reduced pressure with the water bath temperature 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 rotation values were measured at 25 °C with a Perkin–Elmer 241/MS polarimeter at the sodium D line. NMR spectra were recorded with a Bruker AC-250 Cryospec or Bruker DR-600; TMS or the solvent residual peak were used as internal standard. $^3J_{C,H}$ couplings were

observed in gradient-selected heteronuclear multi-bond correlations (HMBC). MALDI-MS were measured with a Kratos Kompact Maldi 1; 2,5-dihydroxybenzoic acid was used as matrix. FAB-MS were measured with a Finnigan MAT 312/AMD-5000, 790 eV, 70 °C. Calculated yields are based on consumed starting material where its recovery is stated.

***O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranosyl)-*N*-(*tert*-butyloxycarbonyl)-L-serine Methyl Ester (1bα) and *O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-β-D-galactopyranosyl)-*N*-(*tert*-butyloxycarbonyl)-L-serine Methyl Ester (1bβ):** *N*-(*tert*-Butyloxycarbonyl)-L-serine methyl ester (1.10 g, 5 mmol) and 3,4,6-tri-*O*-benzyl-2-nitrogalactal (2.10 g, 5 mmol) were dried under high vacuum and dissolved in dry toluene (60 mL) under argon. Freshly activated molecular sieves (3 Å, 3 g) were introduced and the mixture was stirred for 1 h at room temperature. Potassium *tert*-butoxide (1 M in THF, 0.50 mL, 0.25 mmol) was added and stirring was continued for 120 min. Acetic acid (0.50 mL) was added to acidify the reaction mixture, the molecular sieves were filtered off and all the solvents were removed. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 90:10) to furnish **1bα** (2.04 g, 60%) as a white foam and the corresponding β-glycoside **1bβ** (1.02 g, 30%) as a white foam. Data for **1bα**: TLC (petroleum ether/ethyl acetate, 80:20): R_f = 0.66. $[a]_D$ = = +75.50 (*c* = 1.5; $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 1.49 [s, 9 H, $C(CH_3)_3$], 3.60 (m, 2 H, 6-H, 6′-H), 3.80 (s, 3 H, OCH_3), 3.90 (dd, $^3J_{\beta,\alpha}$ = 2.8 Hz, $^2J_{\beta,\beta'}$ = 9.0 Hz, 1 H, β-CH), 3.97 (d, $^2J_{\beta',\beta}$ = 9.1 Hz, 1 H, β′-CH), 4.03 (dd, $^3J_{5,6}$ = 6.6 Hz, $^3J_{5,6'}$ = 6.7 Hz, 1 H, 5-H), 4.08 (m, 1 H, 4-H), 4.43 (dd, $^3J_{3,4}$ = 2.8 Hz, $^3J_{3,2}$ = 10.7 Hz, 1 H, 3-H), 4.44–4.55 (m, 4 H, OCH_2Ph, α-CH), 4.76 (d, ^2J = 3.5 Hz, 2 H, OCH_2Ph), 4.86 (d, ^2J = 11.1 Hz, 1 H, OCH_2Ph), 5.00 (dd, $^3J_{2,1}$ = 4.1 Hz, $^3J_{2,3}$ = 10.6 Hz, 1 H, 2-H), 5.30 (d, $^3J_{1,2}$ = 4.0 Hz, 1 H, 1-H), 5.48 (d, $^3J_{NH,\alpha}$ = 8.0 Hz, 1 H, NH), 7.25–7.39 (m, 15 H, Ar-H) ppm. ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 28.27 [$C(CH_3)_3$], 52.71 (OCH_3), 53.72 (α-C), 68.00 (C-6), 69.90 (C-5, β-C), 72.84 (OCH_2Ph), 72.98 (C-4), 73.55 (OCH_2Ph), 74.93 (C-3), 75.10 (OCH_2Ph), 80.19 [$C(CH_3)_3$], 84.06 (C-2), 97.01 (C-1), 127.84, 127.89, 128.05, 128.11, 128.13, 128.33, 128.47, 137.21, 137.56, 137.82 (C-Ar), 155.30 ($COOCH_3$), 170.07 (NHBoc) ppm. MS (MALDI): *m*/*z* = 703 $[M + Na]^+$. $C_{36}H_{44}N_2O_{11}$ (680.74): calcd. C 63.52, H 6.51, N 4.12; found C 63.52, H 6.55, N 3.78. Data for **1bβ**: TLC (petroleum ether/ethyl acetate, 80:20): R_f = 0.42. $[a]_D$ = +26.13 (*c* = 1.5; $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 3.60–3.66 (m, 3 H, 6-H, 6′-H, 5-H), 3.74 (s, 3 H, OCH_3), 3.82 (dd, $^3J_{\beta,\alpha}$ = 3.4 Hz, $^2J_{\beta,\beta'}$ = 10.1 Hz, 1 H, β-CH), 4.04 (m, 1 H, 4-H), 4.07 (dd, $^3J_{3,4}$ = 2.6 Hz, $^3J_{3,2}$ = 10.6 Hz, 1 H, 3-H), 4.24 (br. d, $^2J_{\beta',\beta}$ = 10.0 Hz, 1 H, β′-CH), 4.42 (dd, $^3J_{\alpha,\beta}$ = 3.6 Hz, $^3J_{\alpha,NH}$ = 7.8 Hz, 1 H, α-CH), 4.47–4.51 (m, 3 H, OCH_2Ph), 4.58 (d, ^2J = 11.3 Hz, 1 H, OCH_2Ph), 4.64 (d, ^2J = 11.5 Hz, 1 H, OCH_2Ph), 4.77 (d, $^3J_{1,2}$ = 8.0 Hz, 1 H, 1-H), 4.85–4.90 (m, 2 H, OCH_2Ph, 2-H), 5.27 (d, $^3J_{NH,\alpha}$ = 7.8 Hz, 1 H, NH), 7.28–7.40 (m, 15 H, Ar-H) ppm. ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 28.23 [$C(CH_3)_3$], 52.56 (OCH_3), 53.64 (α-C), 67.64 (C-6), 69.47 (β-C), 71.38 (C-4), 72.32 (OCH_2Ph), 73.57 (OCH_2Ph), 73.92 (C-5), 74.85 (OCH_2Ph), 79.26 (C-3), 80.05 [$C(CH_3)_3$], 86.81 (C-2), 100.29 (C-1), 127.78, 127.89, 127.97, 128.16, 128.20, 128.33, 128.32, 128.49, 128.53, 136.45, 137.70 (C-Ar), 155.26 ($COOCH_3$), 170.15 (NHBoc) ppm. MS (MALDI): *m*/*z* = 703 $[M + Na]^+$. $C_{36}H_{44}N_2O_{11}$ (680.74): calcd. C 63.52, H 6.51, N 4.12; found C 63.29, H 6.60, N 3.88.

***O*-[(2-Fluorenyl-9-methyloxycarbonylamino)-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl]-*N*-(*tert*-butyloxycarbonyl)-L-serine *tert*-Butyl Ester (3aα):** Compound **2aα**[16] (1.38 g, 2 mmol) was suspended in dry CH_2Cl_2 (100 mL) and cooled to 0 °C. Triethylamine (0.84 mL) and FmocCl (0.49 mL, 2 mmol) were dropped into the reaction mixture simultaneously. Stirring was continued for 24 h at room temperature, then the reaction mixture was diluted with CH_2Cl_2 (50 mL) washed with 0.5 M HCl (3 × 10 mL) and H_2O, dried ($MgSO_4$), and filtered. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 90:10) to furnish **3aα** (1.24 g, 68%) as a colorless oil. TLC (petroleum ether/ethyl acetate, 80:20): R_f = 0.35. $[a]_D$ = +33.18 (*c* = 0.22; $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.41, 1.43 [2 s, 18 H, 2 $C(CH_3)_3$], 3.54–3.58 (m, 3 H, 6-H, 6′-H, 5-H), 3.81–4.15 (m, 4 H, β-CH_2, 4-H, Fmoc-CH), 4.29–4.72 (m, 11 H, Fmoc-CH_2, 3-H, α-CH, OCH_2Ph, 2-H), 4.82 (d, $^3J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 4.95 (d, $^3J_{NH,\alpha}$ = 11.6 Hz, 1 H, NHBoc), 5.40 (br. d, 1 H, NHFmoc), 7.18–7.76 (m, 23 H, Ar-H) ppm. MS (MALDI): *m*/*z* = 938 $[M + Na]^+$, 954 $[M + K]^+$. $C_{54}H_{62}N_2O_{11}\cdot 1H_2O$ (933.09): calcd. C 69.51, H 6.70, N 3.00; found C 69.28, H 6.99, N 2.85.

***O*-[(2-Fluorenyl-9-methyloxycarbonylamino)-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl]-*N*-(*tert*-butyloxycarbonyl)-L-serine (4α):** Compound **3aα** (0.90 g, 0.98 mmol) was dissolved in a mixture of trifluoroacetic acid and CH_2Cl_2 (50 mL, 1:1) and the solution was stirred at room temperature for 12 h. All the solvents were evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 followed by addition of saturated aqueous $NaHCO_3$ with vigorous stirring. The layers were separated and the aqueous 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 (petroleum ether/ethyl acetate, 80:20) to furnish **4α** (0.72 g, 97%) as a white foam, which was immediately used in the next step. TLC (CH_2Cl_2/MeOH, 95:5): R_f = 0.30. $[a]_D$ = = +31.2 (*c* = 0.17; $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.48 (m, 3 H, 6-H, 6′-H), 3.67 (m, 1 H, 5-H), 3.70–4.80 (m, 4 H, β-CH_2, 4-H, Fmoc-CH), 3.91–4.53 (m, 11 H, Fmoc-CH_2, 3-H, α-CH, OCH_2Ph, 2-H), 4.90 (m, 3 H, 1-H, NH_2), 5.40 (br. d, 1 H, NHFmoc), 7.10–7.64 (m, 23 H, Ar-H), 8.42 (br. S, COOH) ppm. MS (MALDI): *m*/*z* = 760 $[M + H]^+$, 782 $[M + Na]^+$. $C_{45}H_{46}N_2O_9$ (758.85): calcd. C 71.22, H 6.11, N 3.69; found C 71.32, H 5.86, N 3.29.

***O*-[(2-Fluorenyl-9-methyloxycarbonylamino)-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl]-*N*-(*tert*-butyloxycarbonyl)-L-serine (5α):** To a solution of **4α** (0.70 g, 0.09 mmol) in dioxane (10 mL) were successively added Et_3N (0.28 mL, 2 mmol) and 2-(*tert*-butoxyimino)-2-phenylacetonitrile (0.50 g, 2 mmol). The reaction mixture was stirred at room temperature for 24 h, then quenched with saturated aqueous NaCl and extracted with AcOEt. The extract was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 98:2) to furnish **5α** (0.56 g, 72%) as a white foam. TLC (CH_2Cl_2/MeOH, 95:5): R_f = 0.40. $[a]_D$ = +44.70 (*c* = 0.34, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 3.53–3.75 (m, 3 H, 6-H, 6′-H, 5-H), 3.94–4.12 (m, 5 H, β-CH_2, 4-H, Fmoc-CH, 3-H), 4.35–4.60 (m, 10 H, Fmoc-CH_2, α-CH, OCH_2Ph, 2-H), 4.95 (m, 2 H, 1-H, NHBoc), 6.05 (br. d, 1 H, NHFmoc), 7.03–7.73 (m, 23 H, Ar-H), 8.06 (br. s, 1 H, COOH) ppm. MS (MALDI): *m*/*z* = 882 $[M + Na]^+$, 898 $[M + K]^+$. $C_{50}H_{54}N_2O_{11}$ (858.97): calcd. C 69.91, H 6.34, N 3.26; found C 69.68, H 5.96, N 3.15.

(3*S*,5a*R*,6*R*,7*R*,8*R*,9a*S*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-6,7-bisbenzyloxy-8-benzyloxymethyloctahydropyrano[2,3-*b*]-1,5-oxazepin-4-one (7α)

Method A: To a solution of **5α** (215 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was added morpholine (1 mL). The reaction mixture was stirred at room temperature for 24 h, then the mixture was quenched with 0.5 M HCl and extracted with CH_2Cl_2. The ex-

tracted was dried with $MgSO_4$ and concentrated under reduced pressure to give *O*-(2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-*N*-(*tert*-butyloxycarbonyl)-L-serine (**6α**; 150 mg, 94%) as a white foam, which was immediately used in the next step. To a solution of **6α** (140 mg, 0.22 mmol) in dimethylformamide (5 mL) was added triethylamine (0.09 mL, 0.66 mmol). After stirring for 10 min, diphenylphosphoryl azide (DPPA; 0.14 mL, 0.66 mmol) was added and the resulting reaction mixture was further stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NaCl and extracted with Et_2O. The extract was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 99:1) to furnish **7α** (0.12 g, 78%) as a white foam. TLC (CH_2Cl_2/MeOH, 95:5): R_f = 0.60. $[\alpha]_D$ = +123.33 (c = 0.03; $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.43 [s, 9 H, C(CH_3)$_3$], 3.58 (d, $^2J_{10a,10b}$ = 6.6 Hz, 2 H, 10a-H, 10b-H), 3.64 (dd, $^3J_{2a,3}$ = 6.6 Hz, $^2J_{2a,2b}$ = 10.8 Hz, 1 H, 2a-H), 3.72 (d, $^3J_{6,5a}$ = 10.3 Hz, 1 H, 6-H), 3.90 (m, 1 H, 5a-H), 4.02 (br. s, 1 H, 7-H), 4.11 (dd, $^3J_{8,10a}$ = 6.9 Hz, $^3J_{8,10b}$ = 6.6 Hz, 1 H, 8-H), 4.22 (dd, $^2J_{2b,2a}$ = 10.8 Hz, $^3J_{2b,3}$ = 6.6 Hz, 1 H, 2b-H), 4.42–4.57 (m, 4 H, OCH_2Ph), 4.70 (m, 1 H, 3-H), 4.72 (d, ^2J = 9.1 Hz, 1 H, OCH_2Ph), 4.80 (d, ^2J = 11.4 Hz, 1 H, OCH_2Ph), 5.42 (br. d, $^3J_{NH,3}$ = 5.5 Hz, 1 H, NHBoc), 5.54 (br. s, 1 H, 9a-H), 6.12 (br. s, 1 H, NH), 7.26–7.36 (m, 15 H, Ar-H) ppm. ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 28.27 [C(CH_3)$_3$], 52.60 (C-3), 53.77 (C-5a), 67.88 (C-2), 68.10 (C-10), 71.17 (C-7), 71.41 (C-8), 71.78 (OCH_2Ph), 73.55 (OCH_2Ph), 74.52 (OCH_2Ph), 77.00 [C-9, C(CH_3)$_3$], 94.18 (C-9a), 127.81, 127.90, 127.98, 128.03, 128.38, 128.46, 128.76, 136.90, 137.97 (C-Ar), 156.20 (C-4), 170.24 (Boc-CO) ppm. MS (MALDI): m/z = 642 [M + Na]$^+$, 658 [M + K]$^+$. $C_{35}H_{42}N_2O_8$·0.5H_2O (627.73): calcd. C 66.97, H 6.74, N 4.46; found C 66.78, H 6.84, N 4.27.

Method B: α-Nitroglycoside **1bα** (1.02 g, 1.50 mmol) was dissolved in ethanol (15 mL) and transferred to a hydrogen vessel. Platinized Raney nickel T4 catalyst was freshly prepared as described[11] and the material obtained from 2 g of Raney nickel/aluminum 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 temperature 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 *O*-(2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-*N*-(*tert*-butoxycarbonyl)-L-serine methyl ester (**2bα**; 0.82 g, 84%) as a colorless oil, which was immediately used in the next step. TLC (CH_2Cl_2/MeOH, 90:10): R_f = 0.32. $[\alpha]_D$ = +70.67 (c = 0.30; $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, C(CH_3)$_3$], 3.30 (dd, $^3J_{6,5}$ = 3.5 Hz, $^3J_{6,6''}$ = 10.5 Hz, 1 H, 6-H), 3.44 (dd, $^3J_{6',5}$ = 2.4 Hz, $^3J_{6',6'}$ = 10.5 Hz, 1 H, 6′-H), 3.57–3.67 (m, 3 H, 5-H, 4-H, β-CH), 3.72 (s, 3 H, OCH_3), 3.74 (m, 1 H, β′-CH), 3.90 (m, 3 H, 3-H, NH_2), 4.01 (m, 1 H, α-CH), 4.41–4.57 (m, 5 H, OCH_2Ph), 4.75 (d, ^2J = 11.5 Hz, 1 H, OCH_2Ph), 4.84 (m, 2 H, 2-H, 1-H), 5.54 (d, $^3J_{NH,\alpha}$ = 9.0 Hz, 1 H, NHBoc), 7.25–7.37 (m, 15 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 28.29 [C(CH_3)$_3$], 51.08 (OCH_3), 52.46 (α-C), 54.05 (C-2), 68.81 (C-6), 70.24 (C-5, β-C), 71.80 (C-4), 72.41 (C-3), 73.54 (OCH_2Ph), 74.53 (OCH_2Ph), 80.00 [C(CH_3)$_3$], 80.91 (OCH_2Ph), 101.24 (C-1), 127.57, 127.71, 127.74, 127.85, 128.01, 128.23, 128.40, 128.50, 137.91, 137.96, 138.51 (C-Ar), 156.25 (COOCH$_3$), 170.96 (Boc-CO) ppm. MS (MALDI): m/z = 651 [M + H]$^+$, 673 [M + Na]$^+$. $C_{36}H_{46}N_2O_9$ (650.76): calcd. C 66.44, H 7.12, N 4.30; found C 66.28, H 7.42, N 4.13. To a solution of 2-aminoglycoside **2bα** (0.30 g, 0.46 mmol) in water (3 mL) was added lithium hydroxide (17 mg, 0.70 mmol). The reaction mixture was stirred at room temperature for 24 h, and then concentrated under reduced pressure to give the crude amino acid **6α**. To a solution of the crude material in DMF (10 mL) was added triethylamine (0.19 mL, 1.39 mmol). After stirring for 10 min, diphenylphosphoryl azide (DPPA; 0.30 mL, 1.39 mmol) was added and the resulting reaction mixture was further stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NaCl and extracted with Et_2O. The extract was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 99:1) to furnish **7α** in 86% overall yield as a white foam.

(3*S*,5a*R*,6*R*,7*R*,8*R*,9a*R*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-6,7-bisbenzyloxy-8-benzyloxymethyloctahydropyrano[2,3-*b*]-1,5-oxazepin-4-one (7β): β-Nitroglycoside **1bβ** (0.51 g, 0.75 mmol) was dissolved in ethanol (7.5 mL) and transferred to a hydrogen vessel. Platinized Raney nickel T4 catalyst was freshly prepared as described[11] and the material obtained from 1 g of Raney nickel/aluminum alloy was suspended in ethanol (7.5 mL). From a homogeneous suspension of this catalyst, 7.5 mL was added to the reaction vessel and the suspension was 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, 95:5) to furnish *O*-(2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranosyl)-*N*-(*tert*-butoxycarbonyl)-L-serine methyl ester (**2bβ**; 0.40 g, 82%) as a colorless oil, which was immediately used in the next step {TLC (CH_2Cl_2/MeOH, 90:10): R_f = 0.30}. To a solution of 2-aminoglycoside **2bβ** (0.30 g, 0.46 mmol) in water (3 mL) was added lithium hydroxide (17 mg, 0.70 mmol). The reaction mixture was stirred at room temperature for 24 h, and then concentrated under reduced pressure to give the crude amino acid. To a solution of the crude material in dimethylformamide (10 mL) was added triethylamine (0.19 mL, 1.39 mmol). After stirring for 10 min, diphenylphosphoryl azide (DPPA; 0.30 mL, 1.39 mmol) was added and the resulting reaction mixture was further stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NaCl and extracted with Et_2O. The extract was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 99:1) to furnish **7β** in 83% overall yield as a white foam. TLC (CH_2Cl_2/MeOH, 95:5): R_f = 0.48. $[\alpha]_D$ = +57.33 (c = 0.15; $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.43 [s, 9 H, C(CH_3)$_3$], 3.32 (dd, $^2J_{2a,2b}$ = 11.4 Hz, $^3J_{2a,3}$ = 11.0 Hz, 1 H, 2a-H), 3.52–3.85 (m, 3 H, 10a-H, 10b-H, 3-H), 3.73 (ddd, $^3J_{5a,6}$ = 2.4 Hz, $^3J_{5a,NH}$ = 8.2 Hz, $^3J_{5a,9a}$ = 10.6 Hz, 1 H, 5a-H), 4.03–4.08 (m, 3 H, 2b-H, 7-H, 6-H), 4.26 (dd, $^3J_{8,10a}$ = 6.7 Hz, $^3J_{8,10b}$ = 6.8 Hz, 1 H, 8-H), 4.43 (d, ^2J = 12.1 Hz, 1 H, OCH_2Ph), 4.44 (d, ^2J = 12.0 Hz, 1 H, OCH_2Ph), 4.52 (d, ^2J = 12.1 Hz, 1 H, OCH_2Ph), 4.60 (d, ^2J = 11.2 Hz, 1 H, OCH_2Ph), 4.75 (d, ^2J = 12.1 Hz, 1 H, OCH_2Ph), 4.87 (s, 1 H, OCH_2Ph), 4.88 (d, $^3J_{9a,5a}$ = 9.2 Hz, 1 H, 9a-H), 5.54 (d, $^3J_{NH,3}$ = 2.6 Hz, 1 H, NHBoc), 6.07 (d, $^3J_{NH,5a}$ = 8.0 Hz, 1 H, NH), 7.25–7.38 (m, 15 H, Ar-H) ppm. ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 28.32 [C(CH_3)$_3$], 53.96 (C-5a), 55.37 (C-3), 67.01 (C-2), 68.23 (C-10), 71.03 (OCH_2Ph), 71.51 (C-8), 73.04 (C-7), 73.42 (C-6), 74.99 (2 OCH_2Ph), 79.82 [C(CH_3)$_3$], 98.95 (C-9a), 127.82, 127.89, 127.98, 128.03, 128.11, 128.22, 128.36, 128.43, 128.53, 128.76, 136.97, 137.79, 138.11 (C-Ar), 154.85 (C-4), 173.84 (Boc-CO) ppm. MS (MALDI): m/z = 642 [M + Na]$^+$, 658 [M + K]$^+$. $C_{35}H_{42}N_2O_8$·2H_2O (654.76): calcd. C 64.20, H 6.46, N 4.28; found C 63.93, H 6.46, N 4.14.

(3*S*,5a*R*,6*R*,7*R*,8*R*,9a*S*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-6,7-dihydroxy-8-hydroxymethyloctahydropyrano[2,3-*b*]-1,5-oxazepin-4-one (8α): Compound **7α** (0.10 g, 0.16 mmol) was dissolved in methanol/acetic acid (9:1, 10 mL) and Pd/C (0.05 g, 10% Pd) was suspended in the solution. This mixture was stirred for 24 h under H_2 at room

temperature. After complete disappearance of the starting material (TLC: CH_2Cl_2/MeOH, 90:10), the catalyst was filtered off and all the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 95:5) to furnish **8α** (0.05 g, 90%) as a white solid. M.p. 136–138 °C. TLC (CH_2Cl_2/MeOH, 90:10): R_f = 0.20. $[\alpha]_D$ = +105.00 (c = 0.06; MeOH). ^{1}H NMR (250 MHz, CD_3OD): δ = 1.51 [s, 9 H, $C(CH_3)_3$], 3.62–4.60 (m, 9 H, 10a-H, 10b-H, 5a-H, 6-H, 7-H, 8-H, 2a-H, 2b-H, 3-H), 5.54 (br. s, 1 H, 9a-H) ppm. ^{13}C NMR (68.8 MHz, CD_3OD): δ = 28.64 [$C(CH_3)_3$], 56.13 (C-3), 56.80 (C-5a), 62.44 (C-2), 67.62 (C-10), 69.87 (C-7), 71.16 (C-8), 74.80 (C-6), 81.13 [$C(CH_3)_3$], 98.04 (C-9a), 157.55 (C-4), 174.20 (Boc-CO) ppm. MS (MALDI): m/z = 371 [M + Na]$^+$, 387 [M + K]$^+$. $C_{14}H_{23}N_2O_8 \cdot 1H_2O$ (366.37): calcd. C 45.89, H 6.60, N 7.64; found C 45.46, H 6.95, N 7.84.

(3*S*,5a*R*,6*R*,7*R*,8*R*,9a*S*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-6,7-bisacetoxy-8-acetoxymethyloctahydropyrano[2,3-*b*]-1,5-oxazepin-4-one (9α): Compound **8α** was treated with pyridine/acetic anhydride (3:2, 6 mL) and stirred at room temperature for 12 h. All volatiles were evaporated and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 99:1) to furnish **9α** (57 mg, 86%) as a white foam. TLC (CH_2Cl_2/MeOH, 95:5): R_f = 0.50. $[\alpha]_D$ = +59.74 (c = 0.39; $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 2.05, 2.14 (2 s, 9 H, 3 Ac), 3.70 (dd, $^3J_{5a,9a}$ = 3.1 Hz, $^3J_{5a,6}$ = 7.2 Hz, 1 H, 5a-H), 3.94 (m, 1 H, 2a-H), 4.04 (m, 1 H, 2b-H), 4.07 (dd, $^3J_{10a,8}$ = 7.0 Hz, $^2J_{10a,10b}$ = 11.4 Hz, 1 H, 10a-H), 4.12 (dd, $^3J_{10b,7}$ = 6.2 Hz, $^2J_{10b,10a}$ = 11.4 Hz, 1 H, 10b-H), 4.48 (dd, $^3J_{8,10a}$ = 6.3 Hz, $^3J_{8,10b}$ = 6.4 Hz, 1 H, 8-H), 4.58 (br. s, 1 H, 3-H), 5.33 (d, $^3J_{6,7}$ = 9.5 Hz, 1 H, 6-H), 5.42 (m, 2 H, 9a-H, 7-H), 5.84 (br. s, 1 H, NHBoc), 6.56 (br. s, 1 H, NH) ppm. ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 20.63, 20.66, 20.68 (3 Ac), 28.25 [$C(CH_3)_3$], 52.71 (C-5a), 55.39 (C-3), 61.58 (C-10), 67.05 (C-7), 67.31 (C-2), 68.70 (C-8), 70.01 (C-6), 80.34 [$C(CH_3)_3$], 96.45 (C-9a), 155.32 (C-4), 169.91, 170.45, 170.50, 171.58 (3 Ac, Boc-CO) ppm. MS (MALDI): m/z = 497 [M + Na]$^+$. $C_{20}H_{30}N_2O_{11}$ (474.46): calcd. C 50.63, H 6.37, N 5.90; found C 50.33, H 6.58, N 5.51.

***O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-α-D-glucopyranosyl)-*N*-(*tert*-butyloxycarbonyl)-L-threonine Methyl Ester (10α) and *O*-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-β-D-glucopyranosyl)-*N*-(*tert*-butyloxycarbonyl)-L-threonine Methyl Ester (10β):** *N*-(*tert*-Butyloxycarbonyl)-L-threonine methyl ester (1.17 g, 5 mmol) and 3,4,6-tri-*O*-benzyl-2-nitroglucal (2.10 g, 5 mmol) were dried under high vacuum and dissolved in dry toluene (60 mL) under argon. Freshly activated molecular sieve (3 Å, 3 g) was introduced and the mixture stirred for 1 h at room temperature. Potassium *tert*-butoxide (1 M in THF, 0.50 mL, 0.25 mmol) was added and stirring was continued for 120 min. Acetic acid (0.50 mL) was added to acidify the reaction mixture, the molecular sieve was filtered off and all the solvents were removed. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 90:10) to furnish **10α** (1.8 g, 52%) as a colorless oil and the corresponding β-glycoside **10β** (0.83 g, 24%) as a colorless oil.

Compound 10α: TLC (petroleum ether/ethyl acetate, 80:20): R_f = 0.30. $[\alpha]_D$ = +52.82 (c = 0.39; $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31 (d, $^3J_{\gamma,\beta}$ = 6.3 Hz, 3 H, γ-CH_3), 1.47 [s, 9 H, $C(CH_3)_3$], 3.65 (dd, $^3J_{6,5}$ = 1.6 Hz, $^2J_{6,6'}$ = 10.7 Hz, 1 H, 6-H), 3.70–3.80 (m, 6 H, 6′-H, OCH_3, 5-H, 4-H), 3.90 (dd, $^3J_{\alpha,\beta}$ = 6.5 Hz, $^3J_{\alpha,NH}$ = 9.8 Hz, 1 H, α-CH), 4.27–4.35 (m, 2 H, 3-H, β-CH), 4.46–4.55 (m, 3 H, OCH_2Ph, 2-H), 4.63 (d, ^2J = 12.0 Hz, 1 H, OCH_2Ph), 4.80 (d, ^2J = 10.6 Hz, 1 H, OCH_2Ph), 4.87 (s, 2 H, OCH_2Ph), 5.04 (d, $^3J_{NH,\alpha}$ = 9.8 Hz, 1 H, NHBoc), 5.36 (d, $^3J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 7.14–7.34 (m, 15 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 18.70 (γ-CH_3), 28.20 [$C(CH_3)_3$], 52.68 (OCH_3), 57.92 (α-C), 67.67 (C-6), 71.11 (C-5), 73.56 (β-C), 75.27 (C-4), 75.77 (C-3), 77.07 (OCH_2Ph), 78.05 (OCH_2Ph), 78.12 (OCH_2Ph), 80.13 [$C(CH_3)_3$], 86.66 (C-2), 97.48 (C-1), 127.77, 127.99, 128.36, 128.48, 137.36, 137.48, 137.64 (C-Ar), 155.96 ($COOCH_3$), 170.29 (NHBoc) ppm. MS (MALDI): m/z = 717 [M + Na]$^+$, 733 [M + K]$^+$. $C_{37}H_{46}O_{11} \cdot 1H_2O$ (712.79): calcd. C 62.34, H 6.50, N 3.93; found C 62.02, H 6.51, N 3.74.

Compound 10β: TLC (petroleum ether/ethyl acetate, 80:20): R_f = 0.24. $[\alpha]_D$ = +4.00 (c = 0.25; $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.13 (d, $^3J_{\gamma,\beta}$ = 6.4 Hz, 3 H, γ-CH_3), 1.43 [s, 9 H, $C(CH_3)_3$], 3.46 (d, $^2J_{6,6'}$ = 9.7 Hz, 1 H, 6-H), 3.62 (s, 3 H, OCH_3), 3.64–3.75 (m, 3 H, 6′-H, 5-H, 4-H), 4.17 (dd, $^3J_{3,4}$ = 9.9 Hz, $^3J_{3,2}$ = 10.3 Hz, 1 H, 3-H), 4.30 (dd, $^3J_{\alpha,\beta}$ = 2.2 Hz, $^2J_{\alpha,NH}$ = 9.5 Hz, 1 H, α-CH), 4.36–4.58 (m, 7 H, β-CH, OCH_2Ph), 4.69 (m, 3 H, 2-H, OCH_2Ph), 4.76 (d, $^3J_{1,2}$ = 8.12 Hz, 1 H, 1-H), 5.20 (d, $^3J_{NH,\alpha}$ = 9.5 Hz, 1 H, NHBoc), 7.14–7.34 (m, 15 H, Ar-H) ppm. ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 18.62 (γ-CH_3), 28.26 [$C(CH_3)_3$], 52.26 (OCH_3), 57.91 (α-C), 68.01 (C-6), 73.62 (C-5, OCH_2Ph), 75.14 (β-C), 75.23 (C-4), 75.26 (C-3), 77.22 (OCH_2Ph), 80.07 [$C(CH_3)_3$], 81.18 (OCH_2Ph), 89.53 (C-2), 97.98 (C-1), 127.75, 127.83, 128.03, 128.12, 128.44, 128.48, 136.88, 137.46, 137.65 (C-Ar), 156.07 ($COOCH_3$), 170.72 (NHBoc) ppm. MS (MALDI): m/z = 717 [M + Na]$^+$, 733 [M + K]$^+$. $C_{37}H_{46}O_{11} \cdot 0.25H_2O$ (699.27): calcd. C 63.55, H 6.63, N 4.01; found C 63.16, H 6.58, N 4.04.

(3*R*,2*S*,5a*R*,6*R*,7*S*,8*R*,9a*S*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-6,7-bisbenzyloxy-8-benzyloxymethyl-4-methyloctahydropyrano[2,3-*b*]-1,5-oxazepin-4-one (12α): Compound **10α** (0.69 g, 1.00 mmol) was dissolved in ethanol (10 mL) and transferred to a hydrogen vessel. Platinized Raney nickel T4 catalyst was freshly prepared as described[11] and the material obtained from 2 g of Raney nickel/aluminum alloy was suspended in ethanol (10 mL). From a homogeneous suspension of this catalyst, 10 mL was added to the reaction vessel and the suspension was 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, 95:5) to furnish *O*-(2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-*N*-(*tert*-butoxycarbonyl)-L-threonine methyl ester (**11α**; 0.60 g, 90%) as a colorless oil, which was immediately used in the next step. TLC (CH_2Cl_2/MeOH, 90:10): R_f = 0.30. $[\alpha]_D$ = +34.33 (c = 0.30; $CHCl_3$). MS (MALDI): m/z = 665 [M + H]$^+$, 687 [M + Na]$^+$, 703 [M + K]$^+$. To a solution of 2-aminoglycoside **11α** (0.50 g, 0.75 mmol) in water (3 mL) was added lithium hydroxide (28 mg, 1.16 mmol). The reaction mixture was stirred at room temperature for 24 h, and then concentrated under reduced pressure to give the crude amino acid. To a solution of the crude material in dimethylformamide (15 mL) was added triethylamine (0.32 mL, 2.31 mmol). After stirring for 10 min, diphenylphosphoryl azide (DPPA; 0.50 mL, 2.31 mmol) was added and the resulting reaction mixture was further stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NaCl and extracted with Et_2O. The extract was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 99:1) to furnish **12α** in 82% overall yield as a white foam. TLC (CH_2Cl_2/MeOH, 95:5): R_f = 0.62. $[\alpha]_D$ = +45.26 (c = 0.38; $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.16 (d, $^3J_{Me,2}$ = 5.6 Hz, 3 H, CH_3), 1.44 [s, 9 H, $C(CH_3)_3$], 3.60 (m, 1 H, 5a-H), 3.66 (m, 2 H, 10a-H, 10b-H), 3.70 (m, 1 H, 7-H), 3.76 (m, 1 H, 6-H), 3.99 (m, 1 H, 8-H), 4.34 (dd, $^3J_{3,NH}$ = 5.7 Hz, $^3J_{3,2}$ = 5.6 Hz, 1 H, 3-H), 4.48 (d, ^2J = 11.1 Hz, 1 H, OCH_2Ph), 4.52 (d, ^2J = 12.1 Hz, 1 H, OCH_2Ph), 4.60 (d, ^2J = 12.1 Hz, 1 H, OCH_2Ph), 4.64 (d, ^2J = 11.6 Hz, 2 H,

OCH_2Ph), 4.74 (dd, $^3J_{2,Me}$ = 5.6 Hz, $^3J_{2,3}$ = 5.6 Hz, 1 H, 2-H), 4.83 (d, ^2J = 11.5 Hz, 1 H, OCH_2Ph), 5.51 (d, $^3J_{9a,5a}$ = 3.3 Hz, 1 H, 9a-H), 5.55 (d, $^3J_{NH,3}$ = 5.7 Hz, 1 H, NHBoc), 6.02 (d, $^3J_{NH,5a}$ = 2.9 Hz, 1 H, NH), 7.13–7.38 (m, 15 H, Ar-H) ppm. ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 16.17 (CH_3), 28.28 [C(CH_3)$_3$], 55.17 (C-2), 56.02 (C-5a), 68.45 (C-10), 72.03 (C-3), 72.32 (C-8), 73.49 (OCH_2Ph), 73.91 (OCH_2Ph), 74.33 (OCH_2Ph), 76.26 (C-7), 79.40 (C-6), 80.13 [C(CH_3)$_3$], 93.38 (C-9a), 127.75, 127.93, 127.98, 128.04, 128.17, 128.23, 128.40, 128.52, 128.88, 137.29, 137.77 (C-Ar), 155.18 (C-4), 169.41 (Boc-CO) ppm. MS (MALDI): *m*/*z* = 655 [M + Na]$^+$. $C_{36}H_{44}N_2O_8$ (632.74): calcd. C 68.34, H 7.01, N 4.43; found C 67.98, H 7.27, N 4.27.

(3*R*,2*S*,5a*R*,6*R*,7*S*,8*R*,9a*R*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-6,7-bisbenzyloxy-8-benzyloxymethyl-2-methyloctahydropyrano[2,3-*b*]-1,5-oxazepin-4-one (12β): β-Nitroglycoside **10β** (0.69 g, 1.00 mmol) was dissolved in ethanol (10 mL) and transferred to a hydrogen vessel. Platinized Raney nickel T4 catalyst was freshly prepared as described[11] and the material obtained from 2 g of Raney nickel/aluminum alloy was suspended in ethanol (10 mL). From a homogeneous suspension of this catalyst, 10 mL was added to the reaction vessel and the suspension was 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, 95:5) to furnish *O*-(2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-*N*-(*tert*-butoxycarbonyl)-L-threonine methyl ester (**11β**; 0.58 g, 87%) as a colorless oil, which was immediately used in the next step {TLC (CH_2Cl_2/MeOH, 90:10): R_f = 0.36}. To a solution of **11β** (0.50 g, 0.75 mmol) in water (3 mL) was added lithium hydroxide (28 mg, 1.16 mmol). The reaction mixture was stirred at room temperature for 24 h, and then concentrated under reduced pressure to give the crude amino acid. To a solution of the crude material in dimethylformamide (15 mL) was added triethylamine (0.32 mL, 2.31 mmol). After stirring for 10 min, diphenylphosphoryl azide (DPPA; 0.50 mL, 2.31 mmol) was added and the resulting reaction mixture was further stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated aqueous NaCl and extracted with Et_2O. The extract was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 99:1) to furnish **12β** in 78% overall yield as a white foam. TLC (CH_2Cl_2/MeOH, 95:5): R_f = 0.65. $[\alpha]_D$ = +30.91 (*c* = 0.44; $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.15 (d, $^3J_{Me,2}$ = 5.8 Hz, 3 H, CH_3), 1.45 [s, 9 H, C(CH_3)$_3$], 3.63–3.83 (m, 5 H, 10a-H, 10b-H, 7-H, 6-H, 5a-H), 4.12 (m, 1 H, 8-H), 4.32 (m, 1 H, 3-H), 4.47–4.60 (m, 6 H, OCH_2Ph), 4.73 (dd, $^3J_{2,Me}$ = 5.6 Hz, $^3J_{2,3}$ = 5.6 Hz, 1 H, 2-H), 4.78 (d, $^3J_{9a,5a}$ = 7.0 Hz, 1 H, 9a-H), 5.30 (d, $^3J_{NH,3}$ = 5.9 Hz, 1 H, NHBoc), 5.89 (br. s, 1 H, NH), 7.22–7.34 (m, 15 H, Ar-H) ppm. ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 19.40 (CH_3), 28.47 [C(CH_3)$_3$], 56.02 (C-2), 61.98 (C-5a), 68.69 (C-10), 71.25 (C-3), 71.70 (C-8), 71.82 (OCH_2Ph), 72.01 (OCH_2Ph), 73.54 (OCH_2Ph), 74.13 (C-7), 76.35 (C-6), 80.64 [C(CH_3)$_3$], 99.51 (C-9a), 127.80, 128.00, 128.36, 128.44, 128.57, 128.80, 128.94, 137.07, 137.24, 138.07 (C-Ar), 155.32 (C-4), 173.46 (Boc-CO) ppm. MS (MALDI): *m*/*z* = 655 [M + Na]$^+$. $C_{36}H_{44}N_2O_8$ (632.74): calcd. C 68.34, H 7.01, N 4.43; found C 68.18, H 7.24, N 4.13.

(3*R*,2*S*,5a*R*,6*R*,7*S*,8*R*,9a*S*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-6,7-bishydroxy-8-hydroxymethyl-2-methyloctahydropyrano[2,3-*b*]-1,5-oxazepin-4-one (13α): Compound **12α** (0.10 g, 0.16 mmol) was dissolved in methanol/acetic acid (9:1, 10 mL) and Pd/C (0.05 g, 10% Pd) was suspended in the solution. This mixture was stirred for 24 h under H_2 at room temperature. After complete disappearance of the starting material (TLC: CH_2Cl_2/MeOH, 90:10), the catalyst was filtered off and all the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 95:5) to furnish **13α** (50 mg, 87%) as a white foam. TLC (CH_2Cl_2/MeOH, 90:10): R_f = 0.15. $[\alpha]_D$ = +67.27 (*c* = 0.11; MeOH). ^{1}H NMR (600 MHz, [D$_6$]-DMSO): δ = 1.05 (d, $^3J_{Me,2}$ = 6.0 Hz, 3 H, CH_3), 1.40 [s, 9 H, C(CH_3)$_3$], 3.01 (dd, $^3J_{3,2}$ = 3.9 Hz, $^3J_{3,NH}$ = 5.7 Hz, 1 H, 3-H), 3.11 (m, 1 H, 7-H), 3.45 (m, 1 H, 10a-H), 3.54 (m, 1 H, 5a-H), 3.58 (m, 1 H, 10b-H), 3.72 (m 1 H, 6-H), 3.94 (m, 1 H, 2-H), 4.11 (dd, $^3J_{8,10a}$ = 4.0 Hz, $^3J_{8,10b}$ = 6.0 Hz, 1 H, 8-H), 4.53 (m, 2 H, 10-OH, 7-OH), 5.05 (br. s, 1 H, 6-OH), 5.32 (br. s, 1 H, 9a-H), 5.36 (br. s, 1 H, NHBoc), 7.14 (s, 1 H, NH) ppm. ^{13}C NMR (150.8 MHz, [D$_6$]-DMSO): δ = 17.34 (Me), 28.08 [C(CH_3)$_3$], 57.91 (C-3), 60.74 (C-5a), 61.48 (C-2), 69.42 (C-10), 71.75 (C-7), 73.01 (C-8), 74.88 (C-6), 78.76 [C(CH_3)$_3$], 95.34 (C-9a), 155.36 (C-4), 169.92 (Boc-CO) ppm. MS (MALDI): *m*/*z* = 385 [M + Na]$^+$, 401 [M + K]$^+$. $C_{15}H_{26}N_2O_8$ (362.38): calcd. C 49.72, H 7.23, N 7.73; found C 49.40, H 7.61, N 7.52.

(3*R*,2*S*,5a*R*,6*R*,7*S*,8*R*,9a*R*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-6,7-bishydroxy-8-hydroxymethyl-2-methyloctahydropyrano[2,3-*b*]-1,5-oxazepin-4-one (13β): Compound **12β** (0.10 g, 0.16 mmol) was dissolved in methanol/acetic acid (9:1, 10 mL) and Pd/C (0.05 g, 10% Pd) was suspended in the solution. This mixture was stirred for 24 h under H_2 at room temperature. After complete disappearance of the starting material (TLC: CH_2Cl_2/MeOH, 90:10), the catalyst was filtered off and all the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 95:5) to furnish **13β** (53 mg, 92%) as a white foam. TLC (CH_2Cl_2/MeOH, 90:10): R_f = 0.20. $[\alpha]_D$ = +47.50 (*c* = 0.08; MeOH). ^{1}H NMR (250 MHz, [D$_6$]-DMSO): δ = 1.06 (d, $^3J_{Me,2}$ = 6.1 Hz, 3 H, CH_3), 1.41 [s, 9 H, C(CH_3)$_3$], 2.99–3.11 (m, 2 H, 10a-H, 10b-H), 3.33–3.69 (m, 4 H, 5a-H, 3-H, 7-H, 6-H), 3.94–4.14 (m, 2 H, 2-H, 8-H), 4.53 (m, 2 H, 10-OH), 5.04 (br. s, 1 H, 7-OH), 5.32–5.37 (m, 2 H, 6-OH, 9a-H), 6.22 (d, $^3J_{NH,3}$ = 8.7 Hz, 1 H, NHBoc), 7.16 (d, $^3J_{NH,5a}$ = 4.2 Hz, 1 H, NH) ppm. MS (MALDI): *m*/*z* = 385 [M + Na]$^+$, 401 [M + K]$^+$. $C_{15}H_{26}N_2O_8$ (362.38): calcd. C 49.72, H 7.23, N 7.73; found C 49.40, H 7.08, N 7.55.

(3*R*,2*S*,5a*R*,6*R*,7*S*,8*R*,9a*S*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-6,7-bisacetoxy-8-acetoxymethyl-2-methyloctahydropyrano[2,3-*b*]-1,5-oxazepin-4-one (14α): Compound **13α** (40 mg, 0.11 mmol) was treated with pyridine/acetic anhydride (3:2, 6 mL) and stirred at room temperature for 12 h. All volatiles were evaporated and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 99:1) to furnish **14α** (44 mg, 82%) as a white foam. TLC (CH_2Cl_2/MeOH, 95:5): R_f = 0.45. $[\alpha]_D$ = +72.77 (*c* = 0.22; $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.25 (d, $^3J_{Me,2}$ = 5.5 Hz, CH_3), 1.46 [s, 9 H, C(CH_3)$_3$], 2.05, 2.08, 2.11 (3 s, 9 H, 3 Ac), 3.54 (m, 1 H, 5a-H), 4.12 (m, 1 H, 10a-H), 4.27 (m, 3 H, 10b-H, 8-H, 2-H), 4.64 (m, 1 H, 3-H), 5.03 (dd, $^3J_{7,8}$ = 8.9 Hz, $^3J_{7,6}$ = 8.9 Hz, 1 H, 7-H), 5.34 (dd, $^3J_{6,5a}$ = 9.5 Hz, $^3J_{9,8}$ = 9.2 Hz, 1 H, 6-H), 5.43 (br. s, 1 H, 9a-H), 5.75 (d, $^3J_{NH,3}$ = 7.2 Hz, 1 H, NHBoc), 7.05 (br. s, 1 H, NH) ppm. ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 17.10 (CH_3), 20.60, 20.64, 20.69 (3 Ac), 28.24 [C(CH_3)$_3$], 56.22 (C-5a), 58.35 (C-3), 61.77 (C-10), 67.72 (C-7), 69.48 (C-8), 72.42 (C-6), 73.40 (C-3), 80.19 [C(CH_3)$_3$], 95.35 (C-9a), 155.58 (C-4), 169.45, 170.63, 170.76 (3Ac), 171.29 (Boc-CO) ppm. MS (MALDI): *m*/*z* = 511 [M + Na]$^+$. $C_{21}H_{32}N_2O_{11}$ (488.49): calcd. C 51.63, H 6.60, N 5.73; found C 51.34, H 6.70, N 5.68.

(3*R*,4*R*,5a*R*,7*R*,8*S*,9*R*,9a*R*)-3-[*N*-(*tert*-Butyloxycarbonyl)amino]-6,7-bisacetoxy-8-acetoxymethyl-2-methyloctahydropyrano[2,3-*b*]-1,5-oxazepin-4-one (14β): Compound **13β** (40 mg, 0.11 mmol) was treated with pyridine/acetic anhydride (3:2, 6 mL) and stirred at

room temperature for 12 h. All volatiles were evaporated and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 99:1) to furnish **14β** (50 mg, 93%) as a white foam. TLC (CH_2Cl_2/MeOH, 95:5): R_f = 0.50. $[\alpha]_D$ = +36.07 (c = 0.28; $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.24 (d, $^3J_{Me,2}$ = 6.2 Hz, CH_3), 1.44 [s, 9 H, $C(CH_3)_3$], 2.10, 2.14, 2.17 (3 s, 9 H, 3 Ac), 3.90–4.33 (m, 6 H, 5a-H, 10a-H, 10b-H, 3-H, 2-H, 8-H), 4.90 (m, 2 H, 7-H, 9a-H), 5.15 (m, 1 H, 6-H), 5.68 (d, $^3J_{NH,3}$ = 7.5 Hz, 1 H, NHBoc), 6.35 (br. s, 1 H, NH) ppm. ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 19.08 (CH_3), 20.74, 20.81, 20.85 (3 Ac), 28.24 [$C(CH_3)_3$], 52.02 (C-5a), 56.19 (C-3), 61.80 (C-10), 67.77 (C-7), 69.21 (C-8), 72.52 (C-6), 73.33 (C-2), 80.20 [$C(CH_3)_3$], 98.24 (C-9a), 155.02 (C-4), 169.14, 169.5, 170.606 (3 Ac), 172.60 (Boc-CO) ppm. MS (MALDI): m/z = 511 $[M + Na]^+$, 527 $[M + K]^+$. $C_{21}H_{32}N_2O_{11}$ (488.49): calcd. C 51.63, H 6.60, N 5.73; found C 51.50, H 6.11, N 5.82.

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[1] K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503–1531.
[2] X. Zhu, R. R. Schmidt, *Angew. Chem.* **2009**, *121*, 1932–1967; *Angew. Chem. Int. Ed.* **2009**, *48*, 1900–1934.
[3] J. P. Kamerling, G.-J. Boons, Y. C. Lee, A. Suzuki, N. Taniguchi, A. G. J. Voragen (Eds.), *Comprehensive Glycoscience*, Elsevier, Oxford, **2007**, vol. 1.
[4] A. I. H. Ando, H. Ishida, M. Kiso, *Curr. Org. Chem.* **2008**, *12*, 675–689.
[5] Z. N. Bang, V. N. Komissarov, Y. A. Sayapin, V. V. Tkachev, G. V. Shilov, S. M. Aldoshin, V. I. Minkin, *Russ. J. Org. Chem.* **2009**, *45*, 442–448.
[6] A. V. Samet, K. A. Kislyi, V. N. Marshalkin, V. V. Semenov, *Izv. Ross. Akad. Nauk* **2006**, 529.
[7] K. Sakata, T. Tsuji, N. Sasaki, K. Takahashi, US Patent no. 6 562 808, **2003**.
[8] K. Sakata, T. Tsuji, N. Sasaki, K. Takahashi, EU Patent no. 1 471 060, **2004**.
[9] T. Yuji, M. Keiji, K. Yoshinari, M. Masahiko, Kazuyoshi, O. Hiroki, K. Toshiaki, I. Kimihiro, S. Makoto, US Patent no. 6 436 922, **2002**.
[10] S. Kapur, R. McClelland, US Patent no. 6 890 919, **2005**.
[11] G. Galley, R. Goodnow, A. Goodnow, J. Peters, U. Peters, EU Patent no. 1 631 296, **2006**.
[12] For a review on glycosyl amino acids and carbohydrate-based peptide mimetics, see: F. Schweizer, *Angew. Chem.* **2002**, *114*, 240–264; *Angew. Chem. Int. Ed.* **2002**, *41*, 230–253 and references cited therein.
[13] J. Das, R. R. Schmidt, *Eur. J. Org. Chem.* **1998**, 169–1613.
[14] G. A. Winterfeld, Y. Ito, T. Ogawa, R. R. Schmidt, *Eur. J. Org. Chem.* **1999**, 1167–1171.
[15] G. A. Winterfeld, R. R. Schmidt, *Angew. Chem.* **2001**, *113*, 2718–2721; *Angew. Chem. Int. Ed.* **2001**, *40*, 2654–2657.
[16] G. A. Winterfeld, A. I. Khodair, R. R. Schmidt, *Eur. J. Org. Chem.* **2003**, 1009–1021.
[17] A. I. Khodair, G. A. Winterfeld, R. R. Schmidt, *Eur. J. Org. Chem.* **2003**, 1847–1852.
[18] A. I. Khodair, K. Pachamuthu, R. R. Schmidt, *Synthesis* **2004**, 53–58.
[19] B. G. Reddy, Y. D. Vankar, *Tetrahedron Lett.* **2003**, *44*, 4765–4767.
[20] G. A. Winterfeld, J. Das, R. R. Schmidt, *Eur. J. Org. Chem.* **2000**, 3047–3050.
[21] K. Pachamuthu, A. Gupta, J. Das, R. R. Schmidt, Y. D. Vankar, *Eur. J. Org. Chem.* **2002**, 1479–1483.
[22] G. A. Winterfeld, Ph.D. Thesis, University of Konstanz, **2000**.
[23] L. A. Salvador, M. Elofsson, J. Kihlberg, *Tetrahedron* **1995**, *51*, 5643–5656.
[24] K. J. Jensen, P. R. Hansen, D. Venugopal, G. Barany, *J. Am. Chem. Soc.* **1996**, *118*, 3148–3155.
[25] E. Meinjohanns, M. Meldal, T. Jensen, O. Werdelin, L. Galli-Stampino, S. Mouritsen, K. Bock, *J. Chem. Soc. Perkin Trans. 1* **1997**, 871–884.
[26] S. Bay, O. Berthier-Vergues, V. Biberovic, D. Cantacuzène, *Carbohydr. Res.* **1997**, *303*, 25–31.
[27] S. Nishimura, *Bull. Chem. Soc. Jpn.* **1959**, *32*, 61–64.
[28] This compound is commercially available.
[29] R. U. Lemieux, T. L. Nagabushan, S. W. Gunner, *Can. J. Chem.* **1968**, *46*, 405–411.
[30] C. W. Holzapfel, C. F. Marais, M. S. van Dyk, *Synth. Commun.* **1988**, *18*, 97–114.
[31] T. Takamoto, R. Sudoh, T. Nakagawa, *Carbohydr. Res.* **1973**, *27*, 135–140.
[32] T. Sakakibara, Y. Tachimori, R. Sudoh, *Tetrahedron Lett.* **1982**, *23*, 5545–5548.

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