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Carbohydrate Research 338 (2003) 1787–1792
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Note

Synthesis of a novel N–O-interglycosidic disaccharide

Miklós Hornyák, Ferenc Sztaricskai,* István F. Pelyvás, Gyula Batta

Research Group of Antibiotics of the Hungarian Academy of Sciences, and Department of Pharmaceutical Chemistry, University of Debrecen, P.O. Box 70, Debrecen H-4010, Hungary

Received 14 March 2003; accepted 20 May 2003

Abstract

The carbohydrate subunits carrying an N–O-interglycosidic bond play a very important role in the biological activity of the enediyne antibiotics. Condensation of *O*-(α- and β-D-glucopyranosyl)hydroxylamine (**5a** and **5b**) with the hex-3-ulopyranoside (**6**) furnished methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyloxy)imino-α- and β-D-*erythro*-hexopyranoside (**7a** and **7b**). Stereoselective reduction of the C=N bond of **7a** and **7b** with sodium cyanoborohydride resulted in the formation of the required protected N–O-interglycosidic disaccharides (**8a** and **8b**). Finally, catalytic hydrogenation of **8a** afforded methyl 2,3-dideoxy-3-(α-D-glucopyranosyloxy)amino-α-D-*ribo*-hexopyranoside (**9a**). Under similar conditions the β anomer **8b** underwent decomposition.

Keywords: N–O-interglycosidic disaccharide; Synthesis; ^{1}H and ^{13}C NMR

The enediyne antibiotics[1] calicheamycin (**1**) and esperamycin (**2**) (Fig. 1) exert their antibacterial and antitumor activity[2] via DNA splitting,[3–5] thus causing apoptosis of the cells. In some cases the biological activity of the enediyne antibiotics is 2–4000-fold higher[6] than that of adriamycin, a drug nowadays extensively used in clinical practice.

It was assumed[7] that the N–O-interglycosidic moiety and its conformation play an important role in the activity of these antibiotics. No such type of interglycosidic bond has been elucidated thus far in any other compounds of natural origin.

Recently, we reported the first definitive synthesis[8] of methyl α-L-kedarosaminide, a carbohydrate component of the enediyne antibiotic kedarcidin.[9] In this work our goal was to synthesize new N–O-interglycosidic disaccharides similar to those present in the molecules of antibiotics **1** and **2**.

There are two practical methods for the synthesis of the N–O-interglycosidic bond in disaccharides: (i) the target interglycosidic linkage is developed *via* *O*-glycosylation of *N*-hydroyaminosugar derivatives; (ii) glyculose derivatives of sugars are condensed with an *O*-glycosylhydroxylamine. Nevertheless, in the latter reaction, theoretically four isomers (*syn*- and *anti*- as well as α- and β-) are produced (Fig. 2).

During the stereoselective reduction of the C=N bond in $\mathbf{I_{a-d}}$ a mixture of only two components $\mathbf{II_{a-b}}$ can be formed. The situation is further simplified when the starting material is an *O*-glycosylhydroxylamine derivative having fixed and known anomeric configuration. The present paper reports the use of such a synthetic strategy.

The known[10] crystalline phthaloyl glycosides **4a** and **4b**, synthesized from 2,3,4,6-tetra-*O*-benzyl-D-glucose[11] (**3**) under Mitsunobu conditions were dephthaloylated with hydrazine hydrate, and the resulting crude *O*-(α- and β-D-glucopyranosyl)hydroxylamines (**5a** and **5b**) were used in the next step (Scheme 1). Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose[12] (**6**) was selected as the other building block of our target disaccharides. The freshly prepared **5a** and **5b** were allowed to react with a 1.5 molar excess of the

* Corresponding author. Fax: +36-52-512914.
E-mail address: antibiotics@tigris.klte.hu (F. Sztaricskai).

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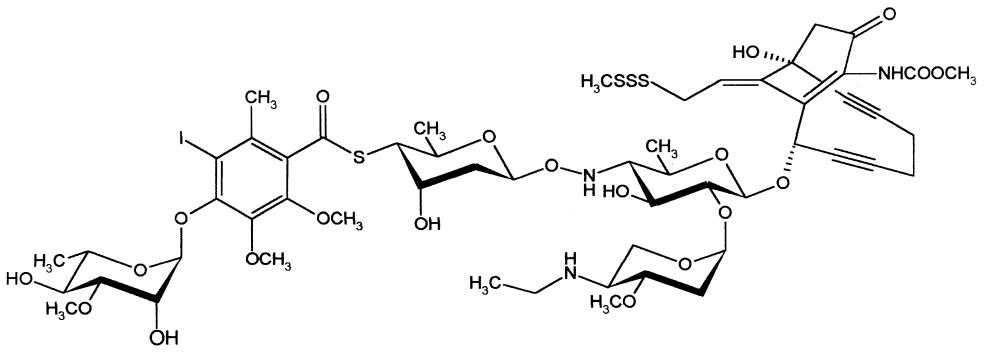
doi:10.1016/S0008-6215(03)00270-2



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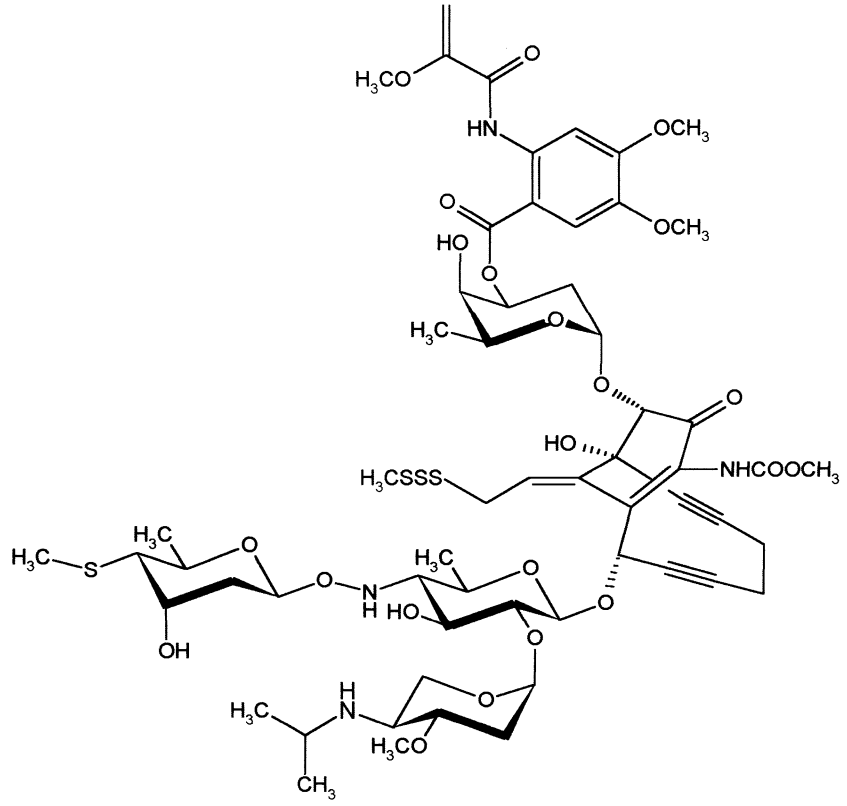

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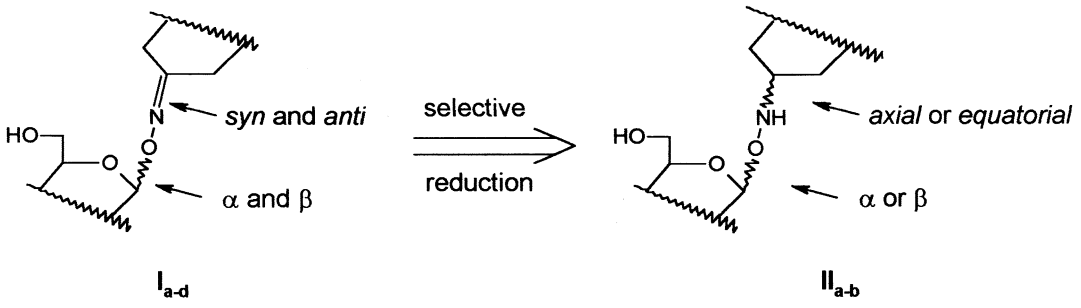
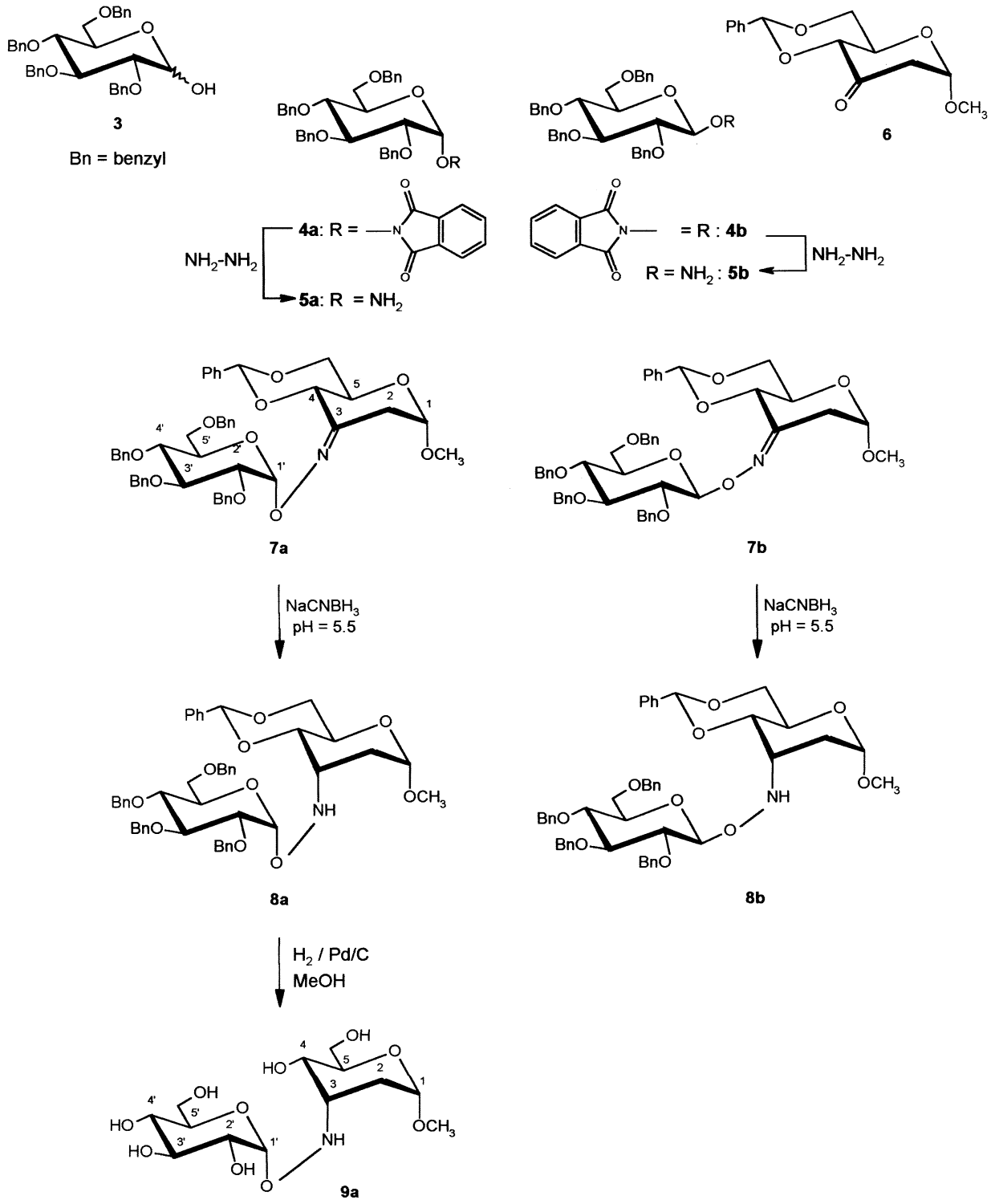
Fig. 1. Structures of calicheamycin γ_1^I (**1**) and esperamycin A_1 (**2**).



I_{a-d} II_{a-b}

Fig. 2. Reduction of an –O-N= interglycosidic linkage.



Scheme 1. Synthesis of the target N-O-glycosidic disaccharide **9a.**

glyculoside **6** in the presence of 4 Å molecular sieves and pyridine *p*-toluenesulfonate (PPTS) in dry benzene to afford methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-(2,3,4,6-tetra-*O*-benzyl-α- and β-D-glucopyranosyloxy)imino-α-D-*erythro*-hexopyranoside (**7a** and **7b**). Although the condensation of **5a** with **6** proceeded almost completely, in the case of **5b** the yield was only 40% because the product partly decomposed upon column-chromatographic purification.

In the ^{1}H NMR spectra of **7a** and **7b** no duplicate signals appear, implying that one of the possible stereoisomers was formed exclusively in both cases. In

the ^{13}C NMR spectrum of **7a** the chemical shift for C-3 (149.4 ppm) indicates the presence of the C=N double bond. The $^{3}J_{1',2'}$ value of 4.0 Hz implies the α anomeric configuration of the D-glucopyranosyl unit of the disaccharide. The $^{3}J_{1',2'}$ value of 8.3 Hz observed in the spectrum of **7b** supports that the glucopyranosyl moiety carries an *axial* (β anomeric) proton, and the ^{13}C NMR shift for C-3 (149.6 ppm) indicates a C=N double bond.

Reduction of **7a** and **7b** with sodium cyanoborohydride in methanol (pH ~5) resulted in the stereoselective formation of the target disaccharides **8a** and **8b** with the planned N–O-interglycosidic bond with good yields. The $^{3}J_{1,2ax}$ value 3.9 Hz for **8a** confirms the α anomeric configuration at C-1, and the change in the ^{13}C NMR shift to 56.18 ppm indicates a successful reduction of the double bond. The $^{3}J_{1',2'}$ coupling constant (3.9 Hz) implies that the α anomeric configuration of the non-reducing unit remained unchanged. In the disaccharide **8b** the $^{3}J_{1',2'}$ value 8.3 Hz denotes the *axial* orientation (and the β anomeric configuration) of H-1′ whereas the $^{3}J_{1,2ax}$ value 4.3 Hz indicates the α-glycosidic structure of the 2,3-dideoxy sugar unit. The structures of **7a** and **7b**, as well as **8a** and **8b** were convincingly proved by means of electron-spray (ES) mass spectral investigation.

Finally, removal of the protecting groups of **8a** by catalytic hydrogenation (Pd/C; MeOH) furnished methyl 2,3-dideoxy-3-(α-D-glucopyranosyloxy)amino-α-D-*ribo*-hexopyranoside (**9a**), which was purified with column chromatography. Unfortunately, under comparable conditions **8b** was unstable and decomposed. The small $^{3}J_{1,2ax}$ and $^{3}J_{1',2'}$ values (3.9 Hz) observed in the ^{1}H NMR spectrum of the disaccharide **9a** prove the α anomeric configuration of both sugar units. In addition, the ^{13}C NMR shift for C-1′ (102.78 ppm) indicates an α anomeric carbon, while the lower value observed for C-3 (59.05 ppm) is attributable to the vicinity of the nitrogen atom.

1. Experimental

1.1. General methods

Melting points were determined with a Kofler hot-stage apparatus, and the data are uncorrected. The specific optical rotation values were measured on a Perkin–Elmer 241 automatic polarimeter at room temperature. The ^{1}H and ^{13}C NMR spectra were recorded with Bruker 200, 360 and 500 MHz spectrometers with Me_4Si as the internal standard. The mass spectra were obtained with a VG Micromass 7035 spectrometer. Column chromatography was performed on Silicagel 60 (Merck, size 0.063–0.1 mm), and the thin-layer chromatographic (TLC) examinations were carried out on precoated Silica gel 60 F_{254} sheets (Merck). Evaporation of the solutions were carried out under diminished pressure (bath temperature max 40 °C).

1.2. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyloxy)imino-α-D-*erythro*-hexopyranoside (7a)

To a stirred solution of **4a**[10] (0.15 g, 0.22 mmol) in MeOH (6 mL) hydrazine hydrate (0.017 mL, 0.35 mmol) was added. After the disappearance of the starting material, the mixture was filtered through a pad of Celite, which was then washed with 2 × 15 mL of Et_2O. The solvent was removed in vacuo, and the residue was redissolved in Et_2O (15 mL) and filtered again through a Celite pad. To the crude, syrupy **5a** the C-3 keto sugar **6** (0.081 g, 0.32 mmol) was added, and 3 × 10 mL of dry C_6H_6 was distilled off from the mixture. The syrupy residue obtained was dissolved in dry C_6H_6 (10 mL), and the solution stirred in the presence of several crystals of PPTS and 4 Å molecular sieves for 48 h. After evaporation, the residue was purified by column chromatography (20:1 hexane–Et_2O) to afford 0.170 g (approx. 100%) of pure **7a**: mp 112–114 °C; $[\alpha]_D^{25}$ +110° (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.37 (dd, 1 H, $J_{2a,2e}$ 14.9 Hz, H-2a), 3.33 (s, 3 H, OCH_3), 3.64 (d, 1 H, H-2e), 3.78 (dd, 1 H, $J_{6'e,6'a}$ 11 Hz, $J_{6'e,5'}$ 2 Hz, H-6′e), 3.80 (dd, 1 H, $J_{2',3'}$ 9.5 Hz, H-2′), 3.81 (t, 1 H, $J_{3',4'} = J_{4',5'} = 9.5$ Hz, H-4′); 3.87 (dd, 1 H, $J_{6'a,5'}$ 3.1 Hz, H-6′a), 3.89 (t, 1 H, $J_{6a,6e} = J_{5,6a} = 10.4$ Hz, H-6a), 4.00 (ddd, 1 H, H-5′), 4.02 (t, 1 H, H-3′), 4.11 (m, 1 H, $J_{5,6e}$ 4.8 Hz, H-5), 4.32 (d, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 4.35 (1 H, H-6e), 4.56–5.06 (8 × d, 8 H, 4 × $C_6H_5CH_2$), 4.91 (d, 1 H, $J_{1,2a}$ 4.3 Hz, H-1), 5.63 (s, 1 H, C_6H_5CH), 5.87 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1′), 7.2–7.6 (m, 25 H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 32.76 (C-2), 55.10 (OCH_3), 65.64 (C-5), 68.81 (C-6′), 69.98 (C-6), 71.32 (C-5′), 73.42, 73.83, 75.71 (O$CH_2C_6H_5$), 78.3 (C-4′), 78.92 (C-4), 79.71 (C-2′), 82.87 (C-3′), 98.96 (C-1), 99.36 (C-1′), 102.99 (C_6H_5CH), 126.6, 128.2, 129.1, 137.2, 137.7 (C_6H_5), 149.4 (C-3); $MS_{electrospray}$ M+H$^+$ 802.9, M+Na$^+$ 824.9, M+K$^+$ 841. Anal. Calcd for $C_{48}H_{51}NO_{10}$: C, 71.89; H, 6.41; N, 1.75. Found: C, 71.79; H, 6.56; N, 1.70.

1.3. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyloxy)imino-α-D-*erythro*-hexopyranoside (7b)

To a stirred solution of **4b**[10] (0.685 g, 1.0 mmol) in MeOH (6 mL) hydrazine hydrate (0.072 mL, 1.5 mmol) was added. The reaction and purification were performed as described for **7a**, and 0.317 g (40%) of **7b** was isolated: mp 170–173 °C; $[\alpha]_D^{25}$ +62° (*c* 5.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.35 (dd, 1 H, $J_{2a,2e}$ 15.1 Hz, H-2a), 3.23 (s, 3 H, OCH_3), 3.61 (d, 1 H, H-2e), 3.54 (ddd, 1 H,

H-5′), 3.60 (t, 1 H, $J_{1',2'} = J_{2'3'} = 8.49$ Hz, H-2′), 3.61 (d, 1 H, H-2e), 3.71 (t, 1 H, H-3′), 3.73 (t, 1 H, $J_{3',4'} = J_{4',5'} = 8.56$ Hz, H-4′), 3.76 (d, 2 H, $J_{6'a,6'e}$ 11 Hz, H-6′ and H-6′e), 3.87 (t, 1 H, $J_{6a,6e}$ 10.3 Hz, H-6a), 4.09 (ddd, 1 H, $J_{5,6e}$ 4.64 Hz, H-5), 4.30 (d, 1 H, $J_{4,5}$ 9.4 Hz, H-4), 4.35 (1 H, ddd, H-6e), 4.48–4.99 (8 × d, 8 H, 4 × $C_6H_5CH_2$), 4.91 (d, 1 H, $J_{1,2a}$ 4.2 Hz, H-1), 5.29 (d, 1 H, $J_{1',2'}$ 8.29 Hz, H-1′), 5.67 (s, 1 H, C_6H_5CH), 7.2–7.6 (m, 25 H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 31.7 (C-2), 55.0 (OCH_3), 65.36 (C-5), 68.84 (C-6′), 70.0 (C-6), 75.0 (C-5′), 73.91, 73.73, 75.75 ($OCH_2C_6H_5$), 77.83 (C-4′), 78.65 (C-4), 81.44 (C-2′), 85.22 (C-3′), 98.9 (C-1), 102.8 (C_6H_5CH), 105.9 (C-1′), 126.6, 128.2, 129.1, 137.2, 137.7 (C_6H_5), 149.6 (C-3); $MS_{electrospray}$ $M+H^+$ 802.9, $M+Na^+$ 824.9, $M+K^+$ 841. Anal. Calcd for $C_{48}H_{51}NO_{10}$: C, 71.89; H, 6.41; N, 1.75. Found: C, 71.91; H, 6.52; N, 1.55.

1.4. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyloxy)-amino-α-D-*ribo*-hexopyranoside (8a)

To a solution of **7a** (0.1 g, 0.12 mmol) in a mixture of dry CH_2Cl_2 (2 mL) and dry MeOH (5 mL) sodium cyanoborohydride (0.032 g, 0.48 mmol) was added in small quantities. After adding each portion of the reducing agent the pH of the solution was adjusted to 5.5 with HCl in MeOH. After 3 h the solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (15 mL). The organic solution was washed with satd $NaHCO_3$ solution (15 mL) and water (5 mL), and then dried over $MgSO_4$, filtered, and concentrated. The resulting syrup was purified by column chromatography (50:1 toluene–Et_2O) to yield 0.082 g (82%) of pure syrupy **8a**: $[\alpha]_D^{25}$ +75.25° (*c* 5.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.87 (ddd, 1 H, $J_{2a,2e}$ 15, $J_{2a,3}$ 4.2 Hz, H-2a), 2.36 (d, 1 H, H-2e), 3.31 (s, 3 H, OCH_3), 3.56 (dd, 1 H, $J_{2'3'}$ 9.9 Hz, H-2′), 3.62 (t, 1 H, $J_{3',4'}$ 9.55 Hz, H-4′), 3.70 (dd, 1 H, $J_{6e,6a}$ 10.4, $J_{5,6e}$ 3.9 Hz, H-6e), 3.74 (dd, 1 H, $J_{4,5}$ 10.6, $J_{3,4}$ 3.9 Hz, H-4), 3.80 (t, 1 H, H-3), 3.87 (t, 1 H, H-3′), 4.02 (dd, 1 H, H-5′), 4.09 (m, 1 H, H-5), 4.29 (dd, 1 H, $J_{5,6a}$ 5.1 Hz, H-6a), 4.50–4.93 (8 × d, 8 H, 4 × $C_6H_5CH_2$), 4.70 (d, 1 H, $J_{1,2a}$ 3.9 Hz, H-1), 5.35 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1′), 5.59 (s, 1 H, C_6H_5CH), 7.2–7.6 (m, 25 H, C_6H_5); ^{13}C NMR ($CDCl_3$): 33.15 (C-2), 55.55 (OCH_3), 56.18 (C-3), 59.22 (C-5), 69.12 (C-6′), 70.05 (C-6), 70.99 (C-5′), 73.02, 73.85, 75.95 ($OCH_2C_6H_5$), 78.26 (C-4′), 79.15 (C-4), 80.05 (C-2′), 82.41 (C-3′), 98.8 (C-1), 100.7 (C-1′), 102.8 (C_6H_5CH), 126.6, 128.2, 129.1, 137.2, 137.7 (C_6H_5); $MS_{electrospray}$ $M+H^+$ 804.96, $M+Na^+$ 826.95, $M+K^+$ 843.0. Anal. Calcd for $C_{48}H_{53}NO_{10}$: C, 71.71; H, 6.64; N, 1.74. Found: C: 69.82; H, 6.82; N, 1.63.

1.5. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyloxy)amino-α-D-*ribo*-hexopyranoside (8b)

To a stirred solution of **7b** (0.1 g, 0.12 mmol) in the mixture of dry CH_2Cl_2 (2 mL) and dry MeOH (5 mL) sodium cyanoborohydride (0.032 g, 0.48 mmol) was added in small quantities. The reaction and purification was performed as described bove for **8a**, to afford 70 mg (70%) of pure, syrupy **8b**: $[\alpha]_D^{25}$ +45° (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.80 (ddd, 1 H, $J_{2a,2e}$ 14.9, $J_{2a,3}$ 4.1 Hz, H-2a), 2.50 (d, 1 H, H-2e), 3.35 (s, 3 H, OCH_3), 3.45 (t, 1 H, H-2), 3.51 (dd, 1 H, H-5′), 3.68 (dd, 1 H, $J_{6e,6a}$ 10.4, $J_{5,6e}$ 3.9 Hz, H-6e), 3.70 (t, 1 H, H-3′), 3.72 (m, 2 H, H-3 and H-4′), 3.79 (dd, 1 H, $J_{4,5}$ 10.2, $J_{3,4}$ 3.9 Hz, H-4), 4.23 (m, 1 H, H-5), 4.27 (dd, 1 H, $J_{5,6a}$ 5.1 Hz, H-6), 4.50–5.0 (4 × d, 8 H, 4 × $C_6H_5CH_2$), 4.67 (d, 1 H, $J_{1,2a}$ 4.3 Hz, H-1), 4.93 (d, 1 H, $J_{1',2'}$ 8.3 Hz, H-1′), 6.10 (s, 1 H, C_6H_5CH), 7.1–7.5 (m, 25 H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 30.0 (C-2), 55.2 (C-3), 55.8 (OCH_3), 58.9 (C-5), 68.8 (C-6′), 70.0 (C-6), 75.0 (C-5′), 73.8, 74.9, 75.7 ($OCH_2C_6H_5$), 78.2 (C-4′), 78.8 (C-4), 81.7 (C-2′), 85.4 (C-3′), 98.7 (C-1), 102.5 (C_6H_5CH), 106.4 (C-1′), 126.6, 128.2, 129.1, 137.2, 137.7 (C_6H_5); $MS_{electrospray}$ $M+H^+$ 804.96, $M+Na^+$ 826.95, $M+K^+$ 843.0. Anal. Calcd for $C_{48}H_{53}NO_{10}$: C, 71.71; H, 6.64; N, 1.74. Found: C, 71.62; H, 6.53; N, 1.76.

1.6. Methyl 2,3-dideoxy-3-(α-D-glucopyranosyloxy)amino-α-D-*ribo*-hexopyranoside (9a)

A solution of **8a** (0.1 g, 0.12 mmol) in dry MeOH (10 mL) was hydrogenated in the presence of Pd/C catalyst (0.1 g) at atmospheric pressure. After 12 h, the catalyst was filtered off and washed with MeOH (3 × 5 mL). The combined methanolic solution was evaporated to dryness, and the residual syrup was purified by means of column chromatography (9:1:0.1 CH_2Cl_2–MeOH–concd NH_4OH) to afford 0.037 g (84%) of syrupy **9a**: $[\alpha]_D^{25}$ +97.2° (*c* 2.0, $CHCl_3$); ^{1}H NMR (D_2O): δ 1.89 (ddd, 1 H, $J_{2a,2e}$ 14.9, $J_{2a,3}$ 4.1 Hz, H-2a), 2.46 (d, 1 H, H-2e), 3.43 (s, 3 H, OCH_3), 3.47 (dd, 1 H, H-5′), 3.56 (dd, 1 H, $J_{2',3'}$ 9.9 Hz, H-2′), 3.26 (t, 1 H, $J_{3',4'}$ 9.65 Hz, H-4′), 3.59 (t, 1 H, H-3), 3.62 (t, 1 H, H-3′), 3.89 (dd, 1 H, $J_{6e,6a}$ 10.4, $J_{5,6e}$ 3.9 Hz, H-6e), 3.71 (dd, 1 H, $J_{4,5}$ 10.6, $J_{3,4}$ 3.9 Hz, H-4), 3.92 (dd, 1 H, $J_{5,6a}$ 5.1 Hz, H-6a), 3.98 (m, 1 H, H-5), 4.82 (d, 1 H, $J_{1,2a}$ 3.9 Hz, H-1), 5.35 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1′); ^{13}C NMR (D_2O): δ 33.25 (C-2), 55.9 (OCH_3), 59.05 (C-3), 62.31 (C-6′), 62.65 (C-6), 68.65 (C-4), 69.32 (C-5), 71.31 (C-4′), 73.06 (C-5′), 73.15 (C-2′), 74.8 (C-3′), 100.8 (C-1), 102.78 (C-1′). Anal. Calcd for $C_{13}H_{25}NO_{10}$: C, 43.94; H, 7.09; N, 3.94. Found: C, 44.11; H, 7.14; N, 4.01.

Acknowledgements

This work was financially supported by the Hungarian Academy of Sciences, and by the National Scientific Research Found (Budapest, Hungary) with the Grants OTKA T 029075, T 029027 and T 042567. The authors thank Dr Zoltán Dinya for the mass spectral measurements. A part of this work is included in the Ph.D. Theses of M.H.

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