Expeditious Synthesis of β-Linked Glycosyl Serine Methylene Isosteres (β-*C*-Gly Ser) via Ethynylation of Sugar Lactones

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Received 16 July 2001

Abstract: The addition of the lithium derivative of *N*-Boc 4-ethynyl-2,2-dimethyl-1,3-oxazolidine to tetra-*O*-benzyl-D-gluco- and galactonolactone and 2-azido-2-deoxy congeners afforded the corresponding ethynyl ketoses in fairly good yields (64–78%). Following the conversion of the ketoses into *O*-acetates and removal of the acetoxy group by silane reduction, the resulting β-linked ethynyl glycosides were transformed into *N*-Boc *C*-glycosyl α-aminobutyric acids by reduction of the triple bond using H_2/Pd(OH)$_2$ and oxidative cleavage of the oxazolidine ring using the Jones' reagent. After the removal of *O*-benzyl groups of the carbohydrate moieties by hydrogenation and the reduction of azido to amino group, all compounds were subjected to acetylation and isolated as *O*- and *N*-acetyl derivatives. The *C*-glycosyl α-amino acids prepared correspond to methylene isosteres of *O*-glycosyl serines.

Key words: alkynyl glycosides, glycopeptides, *C*-glycosides, *C*-glycosyl amino acids

Among the various types of glycosyl amino acids featuring an unnatural anomeric carbon linkage between the carbohydrate and the glycinyl moiety, CH(NH$_2$)CO$_2$H (*C*-glycosyl amino acids), the α- and β-linked *C*-glycosyl serines shown in the Figure (X = CH$_2$) are in the forefront of current synthetic work in this field of research.[1] These compounds as methylene isosteres of *O*-glycosyl serines (X = O), the main constituents of naturally occurring *O*-glycopeptides and proteins, are precious tools in studies of glycobiology directed toward a better understanding at molecular level of the primary role exerted by glycans in glycopeptide biological activity.[2] Moreover, given the expected higher resistance of the *C*-glycosidic bond with respect to the *O*-glycosidic linkage toward the chemical and enzymatic degradation, the *C*-glycosyl serines can be used for the preparation of glycosidase inhibitors and lead compounds for drug discovery.

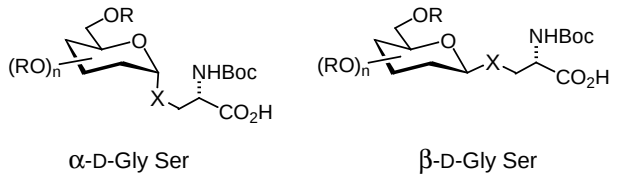


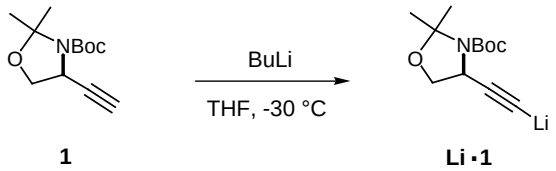
Figure Natural α-and β-linked *O*-glycosyl serines (X = O) and their unnatural methylene isosteres (X = CH$_2$). One or more OR groups represent mono- or oligosaccharide residues.

Synthesis 2001, No. 14, 26 10 2001. Article Identifier:
1437-210X,E;2001,0,14,2129,2137,ftx,en;E14701SS.pdf.

ISSN 0039-7881

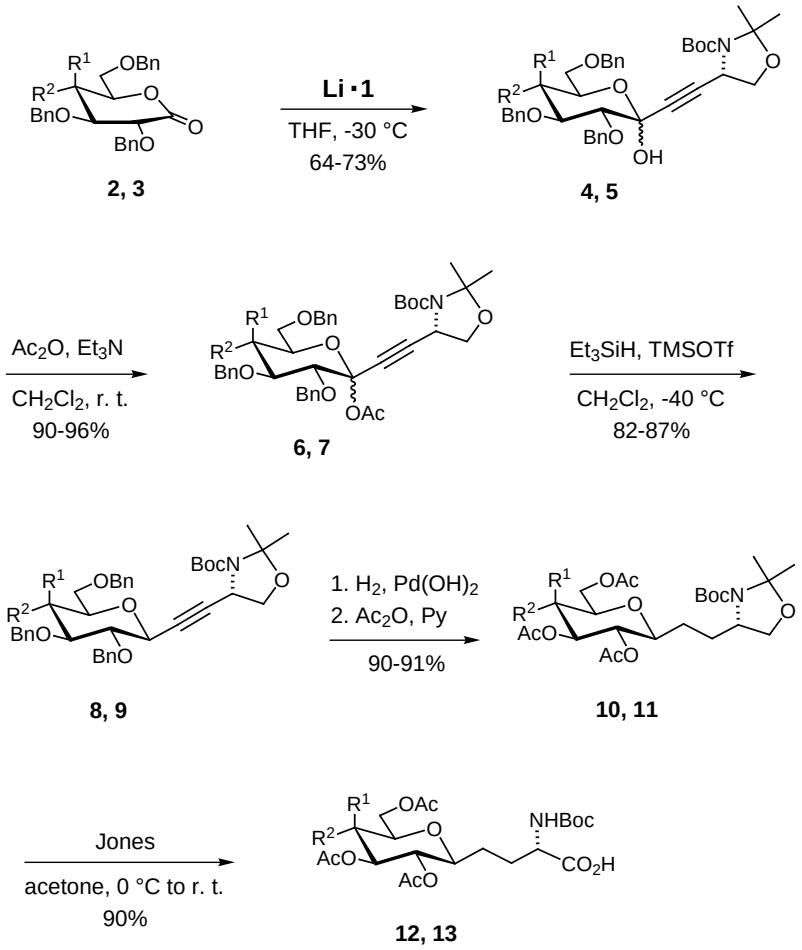
Since natural *O*-glycopeptides feature carbohydrate residues of various complexity in which the first carbohydrate moiety is either α-D-*O*-linked[3] or β-D-*O*-linked[4] to L-serine (or threonine), both α-and β-D-*C*-glycosyl serines incorporating mono-and oligosaccharide moieties are high value artificial amino acids. However, the stereoselective installation of an α-amino acid chain at the anomer carbon atom of sugars with a good control of the α/β selectivity is by far a not trivial problem. An additional concern is about the orthogonal protection of the hydroxy groups of the carbohydrate residue and amino and carboxylate groups of the glycinyl moiety, a prerequisite that permits the use of these amino acids in solution or solid phase peptide assembly. While these issues have been only partially addressed, various synthetic methods leading to α- or β-linked *C*-glycosyl serines based on both linear and convergent techniques have been reported from various laboratories including our own.[1,5] Worth mentioning here are the methods of Dorgan and Jackson,[6] Beau and Skrydstrup,[7] and our procedure[8] which were especially designed for the preparation of α-linked methylene isosteres of glycosyl serines via the coupling of homoalanine equivalent reagents with anomerically activated glycosyl acceptors. However, in all instances the key *C*-glycosidation reaction presented some limitations with respect to α/β selectivity and/or chemical yield. Hence there is still a pressing need for synthetic methods leading to these *C*-glycosyl amino acids endowed with generality, simplicity, and high efficiency. We report here on a new expeditious method for the synthesis of β-linked *C*-glycosyl serines employing the ethynyl oxazolidine **1** as a homoalanine equivalent and sugar lactones as glycosyl donors. While the latter compounds are classical reagents in carbohydrate chemistry and can be prepared in a multigram scale by oxidation of suitably protected glycopyranoses,[9] the alkyne **1** has recently become readily available in an enantiomerically pure form through the efficient procedure of Villalgordo and co-workers[10] involving the Horner–Wadsworth–Emmons-type ethynylation of D-serine derived aldehyde (Garner aldehyde),[11,12] using dimethyl 1-diazo-2-oxopropylphosphonate. It has been amply demonstrated that the chiral ethynyl oxazolidine **1** can be transformed into the corresponding lithium derivative Li·**1** under conditions which do not affect the configuration of the stereocenter of the oxazolidine ring (Scheme 1) and that the latter reacts readily with carbonyl compounds while maintaining the same stereochemical integrity. Also the use of the other partner, the sugar lactones, in this new

convergent approach to β-D-linked *C*-glycosyl serines relied on earlier reactions of these compounds with various organometallic reagents including metalated acetylides[13] to give ketoses which were deoxygenated selectively to β-*C*-glycosides.

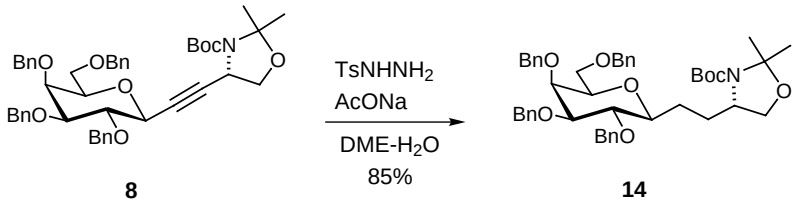


Scheme 1

A model reaction was generated by addition of a slight excess (1.3 equiv) of the lithium acetylide Li·**1** generated in situ as shown in Scheme 1 to the tetra-*O*-benzyl-D-galactonolactone **2** in THF at –30 °C. (Scheme 2). The reaction afforded a mixture of diastereomeric galactose oxazolidinylacetylenes **4** in 64% isolated yield. The use of the cerium derivative of **1** (2 equiv) as reported in other addition reactions of alkynes to sugar lactones,[13b] resulted in the formation of **4** in much lower yield (ca. 20%). Very likely this is due to the presence of the *N*-Boc group which binds to organometallic reagent due to the high affinity of cerium for oxygen and nitrogen atoms. Attempts to reduce the mixture of ketoses **4** under the standard anomeric deoxygenation conditions[13a] using Et_3SiH, $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at –10 °C induced mainly the cleavage of the acid-sensitive oxazolidine ring, the key moiety of the side chain which was devoted to serve as the glycinyl group equivalent. However, the almost quantitative conversion of **4** into the mixture of ketose acetates **6** and treatment at –40 °C with the Et_3SiH, TMSOTf (0.5 equiv) reducing system, which was successfully employed in an earlier work in our laboratory,[9,14] resulted in the formation of the β-linked *C*-galactosyl alkyne **8** in a rewarding 82% isolated yield. These milder reaction conditions were compatible with the integrity of the oxazolidine ring. Nevertheless the structure of this compound with particular regard to the configuration of the stereocenter of the oxazolidine ring was confirmed by transformation into the *C*-galactosyl alkane **14** via diimide reduction of the triple bond (Scheme 3) and comparison with the same product prepared by another route.[8] Next, the elaboration of the alkyne side-chain of **8** was carried out by two sequential high yield steps. First of all, the hydrogenation over $Pd(OH)_2$ reduced the triple bond and at the same time re-



Scheme 2 *Galacto* series: for **2**, **4**, **6**, **8** R^1 = OBn, R^2 = H; for **10** and **12** R^1 = OAc, R^2 = H. *Gluco* series: for **3**, **5**, **7**, **9** R^1 = H, R^2 = OBn; for **11** and **13** R^1 = H, R^2 = OAc



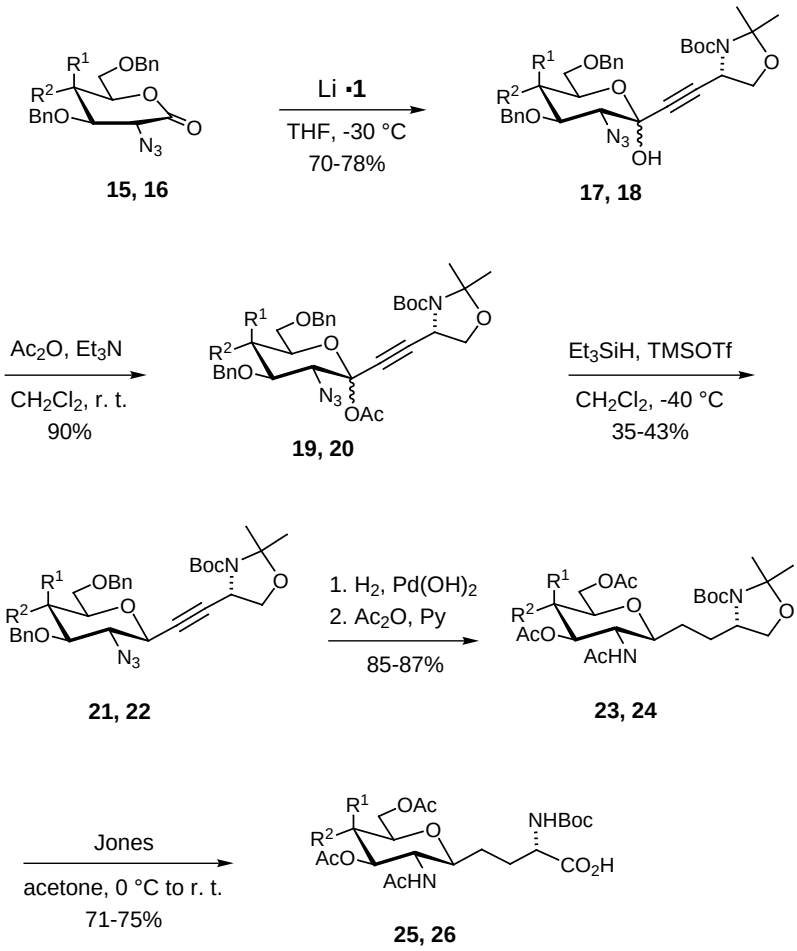
Scheme 3

moved the *O*-benzyl protective groups. The acetylation of the resulting crude *C*-alkyl glycoside afforded the tetra-*O*-acetyl derivative **10** (90% yield). Then this compound was subjected to the oxidative cleavage of the *N*-Boc oxazolidine ring using the Jones' reagent (CrO_3, H_2SO_4, H_2O) to give in a single step[8,15] the β-D-galactosyl α-aminobutyric acid **12**, the galactosyl serine methylene isostere (β-D-*C*-Gal Ser) according to the structures shown in Figure 1. The same reaction sequence was followed for the synthesis of the β-linked glucosyl serine methylene isostere (β-D-*C*-Glc Ser, **13**) by initial coupling of D-gluconolactone **3** with lithium ethynyloxazolidine Li·**1**. Yields of each steps and stereoselectivity in the crucial reductive step of the alkynyl ketose acetate **7** were comparable to those registered in the *galacto* series.

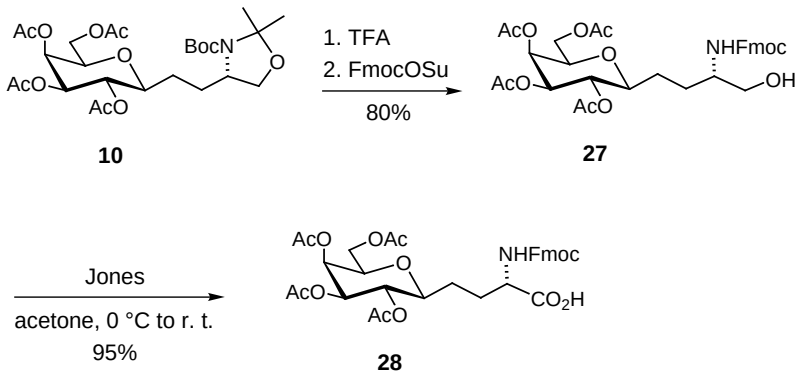
As an expanded scope of the methodology we considered the synthesis of the 2-acetamido-2-deoxy derivatives of the above *C*-glucosyl and *C*-galactosyl serines. Although in the high percentages of naturally occurring *O*-glucopeptides of cell surfaces, serine (or threonine) residues are α-D-*O*-linked to *N*-acetylgalactosamine (GalNAc) or *N*-acetylglucosamine (GlcNAc),[16] β-D-*O*-linkages between the same amino acid and sugar residues have been observed in nuclear and cytoplasmatic proteins.[17] Hence the synthesis of analogue glycosyl amino acids with β-*C*-linkages is undoubtedly of great interest.[18] The various steps leading to the 2-acetamido-2-deoxy galactosyl serine methylene isostere (β-D-*C*-GalNAc Ser, **25**) and the glucosyl derivative (β-D-*C*-GlcNAc Ser, **26**) starting from the corresponding 2-azido-2-deoxygalacto- and gluconolactones **15** and **16** are shown in Scheme 4. While the initial step involving the addition of Li·**1** to the lactones occurred smoothly to give the ketoses **17** and **18** in similar good yields to those registered in Scheme 2, the deoxygenation of the ketose acetates **19** and **20** to the *C*-alkynyl glycosides **21** and **22** presented some problems. For this reaction to proceed, an excess of Lewis acid promoter (TMSOTf) was required, however, under these conditions the oxazolidine ring could not longer survive. After some experimentation we found that the use of 2.5–3.0 equivalents of TMSOTf and 10 equivalents of Et_3SiH at –40 °C in CH_2Cl_2 reduced **19** and **20** to **21** and **22**, respectively, in 35–43% yield while ca. 30% of the unaltered ketose acetates were recovered. Finally, the hydrogenation of **21** and **22** was a quite productive operation since it reduced in one step the triple bond to single bond, the azido group to the amino group, and removed the *O*-benzyl protective groups. In both cases the acetylation of the resulting reaction mixtures afforded the peracetylated *C*-glycosides **23** and **24**, which upon treatment with the Jones' reagent were transformed into the final products **25** and **26**. On the basis of the above observations (see Scheme 3) and the literature precedents,[15] it was reasonably assumed that the integrity of the stereocenter bearing the nitrogen atom remained intact throughout the whole reaction sequence and therefore the original (*S*)-configuration of **1** was also assigned to the glycinyl moiety of the amino acids **25** and **26**. As a confirmation of this assumption, the methyl ester of **26** appeared to be identical based on the optical rotation value to the same product recently prepared by Fuchss and Schmidt by another route.[18]

In conclusion, a new synthetic route has been described leading to β-D-linked methylene isosteres of glycosyl serines starting from readily available sugar lactones. The methodology involves a sequence of simple and efficient reactions and appears to be of general application for the synthesis of compounds containing totally hydroxylated sugar residues or their 2-acetamido-2-deoxy derivatives. Owing to the orthogonal protection of their functional groups, the *C*-glycosil amino acids prepared are suitably tailored for their use as building blocks in glycopeptide assembly by both *N*-Boc and *N*-Fmoc techniques. To this aim, the preparation of the *N*-Fmoc protected derivatives **28** is illustrated in Scheme 5. This compound was synthesized by elaboration of the oxazolidine ring of **10**, the same intermediate leading to the *N*-Boc derivative **12** (see Scheme 2), by hydrolysis, *N*-protection and oxidation in 76% overall yield.

All moisture-sensitive reactions were performed under N_2 using oven-dried glassware. Anhyd solvents were dried over standard drying agents[19] and freshly distilled prior to use. Commercially available powdered 4Å molecular sieves (5 μm average particle size) were used without further activation. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with H_2SO_4 and/or ninhydrin. Flash column chromatography[20] was performed on silica gel 60 (230–400 mesh). Melting points were determined with a capillary apparatus. Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^1H NMR (300 MHz) spectra were recorded for $CDCl_3$ solutions at r.t. unless otherwise specified: Chemical shifts are in ppm (δ) from TMS as internal standard; assignments were aided by homo- and heteronuclear two dimensional experiments. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix.



Scheme 4 *Galacto* series: for **15**, **17**, **19**, **21** R^1 = OBn, R^2 = H; for **23** and **25** R^1 = OAc, R^2 = H. *Gluco* series: for **16**, **18**, **20**, **22** R^1 = H, R^2 = OBn; for **24** and **26** R^1 = H, R^2 = OAc



Scheme 5

6,7,8,10-Tetra-*O*-benzyl-2,3,4-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*glycero*-L-*gluco*-decopyran-3-yn-5-ulose (4); Typical Procedure

To a cooled (–30 °C) and stirred solution of **1** (0.60 g, 2.67 mmol) in anhyd THF (11 mL) was slowly added BuLi (1.6 mL, 2.6 mmol, of a 1.6 M solution in hexane) and the stirring was continued at –30 °C for an additional 30 min. To this mixture was added dropwise a solution of the lactone **2** (1.10 g, 2.04 mmol) in anhyd THF (5 mL). The mixture was stirred at –30 °C for 1.5 h, treated with 1 M phosphate buffer at pH 7 (5 mL) and allowed to reach r.t. The suspension was diluted with Et_2O (20 mL) and the phases were separated. The aqueous layer was extracted twice with Et_2O (20 mL), the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with cyclohexane–EtOAc (from 9:1 to 3:1) to afford first the unreacted **1** (0.25 g, 42%). The second fraction eluted was the syrupy **4** as a 1:1 mixture of anomers (1.00 g, 64%).

^{1}H NMR (DMSO-d_6 + D_2O, 100 °C): δ (selected data) = 7.40–7.18 (m, 20 H, 4 C_6H_5), 5.58 (d, 0.5 H, J = 10.0 Hz, PhCH_2), 5.44 (d, 0.5 H, J = 9.0 Hz, PhCH_2), 4.86–4.62 (m, 8 H), 4.52–4.32 (m, 3 H), 4.06 (ddd, 0.5 H, $J_{8,9}$ = 1.0, $J_{9,10a}$ = 6.0, $J_{9,10b}$ = 6.0 Hz, H-9α), 3.98 (dd, 0.5 H, $J_{7,8}$ = 3.0 Hz, H-8α), 3.94 (dd, 0.5 H, $J_{7,8}$ = 4.0, $J_{8,9}$ = 1.0 Hz, H-8β), 3.89 (d, 0.5 H, $J_{6,7}$ = 10.0 Hz, H-6β), 3.86 (dd, 0.5 H, H-7β), 3.80 (dd, 0.5 H, $J_{9,10a}$ = 3.0, $J_{9,10b}$ = 3.0 Hz, H-9β), 3.72 (d, 0.5 H, $J_{6,7}$ = 10.0 Hz, H-6α), 3.63–3.44 (m, 2 H, 2 H-10), 1.41 (br s, 15 H).

MALDI-TOF MS: m/z = 787.5 (M^+ + Na), 803.7 (M^+ + K).

Anal. Calcd for $C_{46}H_{53}NO_9$: C, 72.32; H, 6.99; N, 1.83. Found:C, 72.39; H, 7.05; N, 1.96.

6,7,8,10-Tetra-*O*-benzyl-2,3,4-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*glycero*-D-*ido*-decopyran-3-yn-5-ulose (5)

Treatment of **3** (538 mg, 1.00 mmol) with **1** (300 mg, 1.30 mmol) as described for the preparation of **4** gave, after column chromatography on silica gel (6:1 cyclohexane–EtOAc), the syrupy **5** (560 mg, 73%) as a 7:3 mixture of anomers.

^{1}H NMR (DMSO-d_6, 120 °C): δ (selected data) = 7.40–7.18 (m, 20 H, 4 C_6H_5), 5.65 (d, 0.7 H, J = 11.0 Hz, PhCH_2α), 4.86–4.62 (m, 8 H), 4.52–4.32 (m, 4 H), 3.72 (d, 0.7 H, $J_{6,7}$ = 9.5 Hz, H-6α), 3.61–3.44 (m, 2 H, 2 H-10).

MALDI-TOF MS: m/z = 786.9 (M^+ + Na), 802.7 (M^+ + K).

Anal. Calcd for $C_{46}H_{53}NO_9$: C, 72.32; H, 6.99; N, 1.83. Found: C, 72.35; H, 7.10; N, 1.83.

6-Azido-7,8,10-tri-*O*-benzyl-2,3,4,6-tetradeoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*glycero*-L-*gluco*-decopyran-3-yn-5-ulose (17)

Treatment of **15** (1.70 g, 3.60 mmol) with **1** (1.06 g, 4.70 mmol) as described for the preparation of **4** gave, after column chromatography on silica gel with 5:1 cyclohexane–EtOAc, the syrupy **17** (1.85 g, 78%) as a 1.5:1 mixture of anomers.

^{1}H NMR (DMSO-d_6 + D_2O, 120 °C): δ (selected data) = 7.41–7.22 (m, 15 H, 3 C_6H_5), 4.80–4.45 (m, 7 H), 4.10–4.02 (m, 3 H), 3.91 (dd, 0.6 H, $J_{7,8}$ = 3.0, $J_{8,9}$ = 1.0 Hz, H-8α), 3.89 (dd, 0.4 H, $J_{7,8}$ = 2.5, $J_{8,9}$ = 0.5 Hz, H-8β), 3.72–3.50 (m, 3 H), 1.58 and 1.47 (2 s, 3.6 H, 2 αCH_3), 1.55 and 1.44 (2 s, 2.4 H, 2 βCH_3), 1.46 (s, 5.4 H, αt-C_4H_9), 1.43 (s, 3.6 H, βt-C_4H_9).

MALDI-TOF MS: m/z = 721.8 (M^+ + Na), 737.6 (M^+ + K).

Anal. Calcd for $C_{39}H_{46}N_4O_8$: C, 67.03; H, 6.64; N, 8.02. Found: C, 66.98; H, 6.70; N, 8.09.

6-Azido-7,8,10-tri-*O*-benzyl-2,3,4,6-tetradeoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*glycero*-D-*ido*-decopyran-3-yn-5-ulose (18)

Treatment of **16** (1.00 g, 2.11 mmol) with **1** (0.61 g, 2.71 mmol) as described for the preparation of **4** gave, after column chromatography on silica gel (4:1 cyclohexane–EtOAc), the syrupy **18** (1.00 g, 70%) as a 1.5:1 mixture of anomers.

^{1}H NMR (DMSO-d_6, 120 °C): δ (selected data) = 7.35–7.21 (m, 15 H, 3 C_6H_5), 4.83 (dd, 0.6 H, $J_{1a,2}$ = 6.0, $J_{1b,2}$ = 2.5 Hz, H-2α), 4.79 and 4.52 (2 d, 1.2 H, J = 11.5 Hz, PhCH_2), 4.64 and 4.54 (2 d, 2 H, J = 11.4 Hz, PhCH_2), 4.74–4.45 (m, 5 H), 4.14 (dd, 0.6 H, $J_{1a,1b}$ = 10.0 Hz, H-1aα), 4.09 (dd, 0.6 H, H-1bα), 4.09–4.06 (m, 0.8 H), 4.02–3.90 (m, 3 H), 3.72–3.58 (m, 3 H), 1.62 and 1.54 (2 s, 3.6 H, 2 αCH_3), 1.60 and 1.53 (2 s, 2.4 H, 2 βCH_3), 1.45 (s, 5.4 H, αt-C_4H_9), 1.43 (s, 3.6 H, βt-C_4H_9).

MALDI-TOF MS: m/z = 721.3 (M^+ + Na), 737.6 (M^+ + K).

Anal. Calcd for $C_{39}H_{46}N_4O_8$: C, 67.03; H, 6.64; N, 8.02. Found: C, 67.10; H, 6.64; N, 7.95.

5-*O*-Acetyl-6,7,8,10-tetra-*O*-benzyl-2,3,4-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*glycero*-L-*gluco*-decopyran-3-yn-5-ulose (6); Typical Procedure

A solution of **4** (652 mg, 0.82 mmol), Et_3N (1.18 mL, 8.50 mmol), and Ac_2O (0.81 mL, 8.50 mmol) in anhyd CH_2Cl_2 (4 mL) was kept at r.t. for 12 h, and then concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane–EtOAc to afford the syrupy **6** (637 mg, 96%) as a 1:1 mixture of anomers.

^{1}H NMR (DMSO-d_6, 140 °C): δ (α-anomer) = 7.38–7.24 (m, 20 H, 4 C_6H_5), 4.85 and 4.79 (2 d, 2 H, J = 11.4 Hz, PhCH_2), 4.85 and 4.57 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.75 and 4.71 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.68 (dd, 1 H, $J_{1a,2}$ = 6.0, $J_{1b,2}$ = 2.0 Hz, H-2), 4.56 and 4.48 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.14 (ddd, 1 H, $J_{8,9}$ = 1.0, $J_{9,10a}$ = 6.0, $J_{9,10b}$ = 6.0 Hz, H-9), 4.09 (dd, 1 H, $J_{1a,1b}$ = 8.5 Hz, H-1a), 4.04 (dd, 1 H, $J_{7,8}$ = 3.0 Hz, H-8), 3.99 (d, 1 H, $J_{6,7}$ = 9.5 Hz, H-6), 3.90 (dd, 1 H, H-1b), 3.84 (dd, 1 H, H-7), 3.69 (dd, 1 H, $J_{10a,10b}$ = 10.0 Hz, H-10a), 3.56 (dd, 1 H, H-10b), 1.99 (s, 3 H, CH_3CO), 1.56 and 1.45 (2 s, 6 H, 2 CH_3), 1.42 (s, 9 H, t-C_4H_9).

^{1}H NMR (DMSO-d_6, 140 °C): δ (β-anomer) = 7.38–7.22 (m, 20 H, 4 C_6H_5), 4.97 and 4.85 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.81 and 4.58 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.77 and 4.70 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.61 (dd, 1 H, $J_{1a,2}$ = 6.0, $J_{1b,2}$ = 2.8 Hz, H-2), 4.54 and 4.46 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.11 (dd, 1 H, $J_{7,8}$ = 2.8, $J_{8,9}$ = 1.3 Hz, H-8), 4.04 (dd, 1 H, $J_{1a,1b}$ = 8.8 Hz, H-1a), 4.01 (d, 1 H, $J_{6,7}$ = 10.0 Hz, H-6), 3.94 (dd,1 H, H-7), 3.92 (ddd, 1 H, $J_{9,10a}$ = 6.0, $J_{9,10b}$ = 5.5 Hz, H-9), 3.86 (dd, 1 H, H-1b), 3.67 (dd, 1 H, $J_{10a,10b}$ = 10.2 Hz, H-10a), 3.54 (dd, 1 H, H-10b), 2.09 (s, 3 H, CH_3CO),1.52 and 1.43 (2 s, 6 H, 2 CH_3), 1.43 (s, 9 H, t-C_4H_9).

MALDI-TOFMS: m/z = 829.1 (M^+ + Na), 845.0 (M^+ + K).

Anal. Calcd for $C_{48}H_{55}NO_{10}$: C, 71.53; H, 6.88; N, 1.73. Found: C, 71.75; H, 6.83; N, 1.60.

5-*O*-Acetyl-6,7,8,10-tetra-*O*-benzyl-2,3,4-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*glycero*-D-*ido*-decopyran-3-yn-5-ulose (7)

Ketose **5** (547 mg, 0.72 mmol) was acetylated as described for the preparation of **6**. The crude product was eluted from a column of silica gel with 5:1 cyclohexane–EtOAc to afford the syrupy **7** (518 mg, 90%) as a 3:1 mixture of anomers.

^{1}H NMR (DMSO-d_6, 120 °C): δ (α anomer) = 7.40–7.21 (m, 20 H, 4 C_6H_5), 4.89 and 4.79 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.81 and 4.70 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.75 and 4.59 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.71 (dd, 1 H, $J_{1a,2}$ = 6.0, $J_{1b,2}$ = 2.0 Hz, H-2), 4.53 (s, 2 H, PhCH_2), 4.09 (dd, 1 H, $J_{1a,1b}$ = 8.5 Hz, H-1a), 3.98 (ddd, 1 H, $J_{8,9}$ = 10.0, $J_{9,10a}$ = 3.5, $J_{9,10b}$ = 7.0 Hz, H-9), 3.92 (dd, 1 H, H-1b), 3.84 (dd, 1 H, $J_{6,7}$ = 9.0, $J_{7,8}$ = 8.5 Hz, H-7), 3.72–3.63 (m, 3 H, H-6, 2 H-10), 3.60 (dd, 1 H, H-8), 2.00 (s, 3 H, CH_3CO), 1.58 and 1.48 (2 s, 6 H, 2 CH_3),1.42 (s, 9 H, t-C_4H_9).

^{1}H NMR (DMSO-d_6, 120 °C): δ (β anomer) = 7.40–7.22 (m, 20 H, 4 C_6H_5), 5.05 and 4.59 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.81 and 4.75 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.79 and 4.75 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.65 (dd, 1 H, $J_{1a,2}$ = 6.0, $J_{1b,2}$ = 2.5 Hz, H-2), 4.57 and 4.51 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.06 (dd, 1 H, $J_{1a,1b}$ = 9.0 Hz, H-1a), 3.88 (dd, 1 H, H-1b), 3.72–3.63 (m, 6 H), 2.15 (s, 3 H, CH_3CO), 1.52 and 1.22 (2 s, 6 H, 2 CH_3), 1.20 (s, 9 H, t-C_4H_9).

MALDI-TOF MS: m/z = 828.9 (M^+ + Na), 845.3 (M^+ + K).

Anal. Calcd for $C_{48}H_{55}NO_{10}$: C, 71.53; H, 6.88; N, 1.73. Found: C, 71.55; H, 6.80; N, 1.70.

5-*O*-Acetyl-6-azido-7,8,10-tri-*O*-benzyl-2,3,4,6-tetradeoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*glycero*-L-*gluco*-decopyran-3-yn-5-ulose (19); Typical Procedure

A solution of **17** (256 mg, 0.37 mmol) and 4-(dimethylamino)pyridine (10 mg) in Ac_2O (3 mL) and pyridine (3 mL) was kept at r.t.

for 30 min and then concentrated. The crude product was eluted from a column of silica gel with 5:1 cyclohexane–EtOAc to afford the syrupy **19** (244 mg, 90%) as a 7:3 mixture of anomers.

^{1}H NMR (DMSO-d_6, 100 °C): δ (α anomer) = 7.42–7.25 (m, 15 H, 3 C_6H_5), 4.82 and 4.67 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.80 and 4.56 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.69 (dd, 1 H, $J_{1a,2}$ = 6.0, $J_{1b,2}$ = 2.0 Hz, H-2), 4.55 and 4.47 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.14 (ddd, 1 H, $J_{8,9}$ = 0.5, $J_{9,10a}$ = 6.3, $J_{9,10b}$ = 6.0 Hz, H-9), 4.11 (dd, 1 H, $J_{7,8}$ = 2.8 Hz, H-8), 4.09 (dd, 1 H, $J_{1a,1b}$ = 8.5 Hz, H-1a), 3.97 (d, 1 H, $J_{6,7}$ = 10.5 Hz, H-6), 3.93 (dd, 1 H, H-1b), 3.79 (dd, 1 H, H-7), 3.68 (dd,1 H, $J_{10a,10b}$ = 10.0 Hz, H-10a), 3.56 (dd, 1 H, H-10b), 2.07 (s, 3 H, CH_3CO), 1.57 and 1.47 (2 s, 6 H, 2 CH_3), 1.46 (s, 9 H, t-C_4H_9).

MALDI-TOF MS: m/z = 763.6 (M^+ + Na), 779.9 (M^+ + K).

Anal. Calcd for $C_{41}H_{48}N_4O_9$: C, 66.47; H, 6.53; N, 7.56. Found: C, 66.40; H, 6.60; N, 7.51.

5-*O*-Acetyl-6-azido-7,8,10-tri-*O*-benzyl-2,3,4,6-tetradeoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*glycero*-D-*ido*-decopyran-3-yn-5-ulose (20)

Ketose **18** (174 mg, 0.25 mmol) was acetylated as described for the preparation of **19**. The crude product was eluted from a column of silica gel with 4:1 cyclohexane–EtOAc to afford syrupy **20** (166 mg, 90%) as a 3:1 mixture of anomers.

^{1}H NMR(DMSO-d_6, 120 °C): δ (α anomer) = 7.38–7.21 (m, 15 H, 3 C_6H_5), 4.79 (s, 2 H, PhCH_2), 4.75 and 4.61 (2 d, 2 H, J = 11.4 Hz, PhCH_2), 4.71 (dd, 1 H, $J_{1a,2}$ = 2.0, $J_{1b,2}$ = 6.0 Hz, H-2), 4.56 and 4.51 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.11 (dd, 1 H, $J_{1a,1b}$ = 8.8 Hz, H-1a), 3.94 (dd, 1 H, H-1b), 3.86 (d, 1 H, $J_{6,7}$ = 9.5 Hz, H-6), 3.78–3.66 (m, 5 H), 2.10 (s, 3 H, CH_3CO), 1.45 and 1.42 (2 s, 6 H, 2 CH_3), 1.41 (s, 9 H, t-C_4H_9).

MALDI-TOF MS: m/z = 763.7 (M^+ + Na), 779.7 (M^+ + K).

Anal. Calcd for $C_{41}H_{48}N_4O_9$: C, 66.47; H, 6.53; N, 7.56. Found: C, 66.50; H, 6.58; N, 7.50.

5,9-Anhydro-6,7,8,10-tetra-*O*-benzyl-2,3,4-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-dec-3-ynitol (8); Typical Procedure

A mixture of the acetate **6** (400 mg, 0.49 mmol), activated 4Å powdered molecular sieves (0.80 g), and anhyd CH_2Cl_2 (5 mL) was stirred at r.t. for 15 min, then cooled to –40 °C. To the mixture was added Et_3SiH (782 μL, 4.9 mmol) and then TMSOTf (44 μL, 0.25 mmol). Stirring was continued at –40 °C for an additional 2 h, then the mixture was diluted with Et_3N (70 μL, 0.5 mmol), filtered through Celite, and concentrated. The residue was eluted from a column of silica gel with 5:1 cyclohexane–EtOAc to afford **8** (300 mg, 82%) as a white solid; mp 111–113 °C (pentane); $[\alpha]_D$ +50.5 (c = 1.5, $CHCl_3$).

^{1}H NMR (DMSO-d_6, 120 °C): δ = 7.41–7.23 (m, 20 H, 4 C_6H_5), 4.90 and 4.78 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.83 and 4.55 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.76 and 4.63 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.63 (ddd, 1 H, $J_{1a,2}$ = 2.0, $J_{1b,2}$ = 3.0, $J_{2,5}$ = 1.5 Hz, H-2), 4.53 and 4.47 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.09 (dd, 1 H, $J_{5,6}$ = 9.0 Hz, H-5), 4.07 (dd, 1 H, $J_{1a,1b}$ = 8.5 Hz, H-1a), 4.01 (dd, 1 H, $J_{7,8}$ = 3.0, $J_{8,9}$ = 1.0 Hz, H-8), 3.88 (dd, 1 H, H-1b), 3.76 (dd, 1 H, $J_{6,7}$ = 9.5 Hz, H-6), 3.72 (dd, 1 H, $J_{9,10a}$ = 6.0, $J_{9,10b}$ = 6.0 Hz, H-9), 3.65 (dd, 1 H, H-7), 3.59 (dd, 1 H, $J_{10a,10b}$ = 10.0 Hz, H-10a), 3.57 (dd, 1 H, H-10b), 1.52 and 1.48 (2 s, 6 H, 2 CH_3), 1.43 (s, 9 H, t-C_4H_9).

MALDI-TOF MS: m/z = 771.2 (M^+ + Na), 787.2 (M^+ + K).

Anal. Calcd for $C_{46}H_{53}NO_8$: C, 73.87; H, 7.14; N, 1.87. Found: C, 73.65; H, 7.19; N, 1.68.

5,9-Anhydro-6,7,8,10-tetra-*O*-benzyl-2,3,4-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*galacto*-dec-3-ynitol (9)

Treatment of **7** (510 mg, 0.63 mmol) as described for the preparation of **8** gave, after column chromatography on silica gel (5:1 cyclohexane–EtOAc), **9** (410 mg, 87%) as a white solid; mp 95–96 °C (MeOH); $[\alpha]_D$ +63.0 (c = 1, $CHCl_3$).

^{1}H NMR (DMSO-d_6, 120 °C): δ = 7.38–7.19 (m, 20 H, 4 C_6H_5), 4.99 and 4.74 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.82 and 4.75 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.73 and 4.58 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.67 (ddd, 1 H, $J_{1a,2}$ = 6.5, $J_{1b,2}$ = 2.5, $J_{2,5}$ = 1.5 Hz, H-2), 4.56 and 4.51 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.18 (dd, 1 H, $J_{5,6}$ = 9.5 Hz, H-5), 4.07 (dd, 1 H, $J_{1a,1b}$ = 8.5 Hz, H-1a), 3.89 (dd, 1 H, H-1b), 3.74–3.61 (m, 2 H, 2 H-10), 3.68 (dd, 1 H, $J_{6,7}$ = 10.0 Hz, H-6), 3.57–3.53 (m, 1 H, H-9), 3.49 (dd, 1 H, $J_{7,8}$ = 9.0, $J_{8,9}$ = 8.0 Hz, H-8), 3.48 (dd, 1 H, H-7), 1.52 and 1.42 (2 s, 6 H, 2 CH_3), 1.42 (s, 9 H, t-C_4H_9).

MALDI-TOF MS: m/z = 770.9 (M^+ + Na), 787.0 (M^+ + K).

Anal. Calcd for $C_{46}H_{53}NO_8$: C, 73.87; H, 7.14; N, 1.87. Found: C, 73.91; H, 7.08; N, 1.97.

5,9-Anhydro-6-azido-7,8,10-tri-*O*-benzyl-2,3,4,6-tetradeoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-dec-3-ynitol (21)

Treatment of **19** (549 mg, 0.74 mmol) as described for the preparation of **8** gave, after column chromatography on silica gel (5:1 cyclohexane–EtOAc), first **21** (216 mg, 43%) as a syrup; $[\alpha]_D$ +66.7 (c = 0.5, $CHCl_3$).

^{1}H NMR (DMSO-d_6, 100 °C): δ = 7.42–7.23 (m, 15 H, 3 C_6H_5), 4.81 and 4.67 (2d, 2 H, J = 12.0 Hz, PhCH_2), 4.79 and 4.54 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.63 (ddd, 1 H, $J_{1a,2}$ = 6.3, $J_{1b,2}$ = 2.5, $J_{2,5}$ = 1.0 Hz, H-2), 4.51 and 4.46 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.05 (dd, 1 H, $J_{1a,1b}$ = 8.8 Hz, H-1a), 4.04 (dd, 1 H, $J_{7,8}$ = $J_{8,9}$ = 2.0 Hz, H-8), 4.03 (dd, 1 H, $J_{6,7}$ = 9.0 Hz, H-7), 3.91 (dd, 1 H, H-1b), 3.75 (ddd, 1 H, $J_{9,10a}$ = 5.5, $J_{9,10b}$ = 6.0 Hz, H-9), 3.66–3.62 (m, 2 H), 3.58 (dd, 1 H, $J_{10a,10b}$ = 10.0 Hz, H-10a), 3.54 (dd, 1 H, H-10b), 1.52 (s, 3 H, CH_3),1.43 (s, 12 H, CH_3, t-C_4H_9).

MALDI-TOF MS: m/z = 706.2 (M^+ + Na), 722.4 (M^+ + K).

Anal. Calcd for $C_{39}H_{46}N_4O_7$: C, 68.60; H, 6.79; N, 8.21. Found: C, 68.72; H, 6.70; N, 8.10.

Unreacted **19** was eluted out as the second fraction (164 mg, 30%).

5,9-Anhydro-6-azido-7,8,10-tri-*O*-benzyl-2,3,4,6-tetradeoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*galacto*-dec-3-ynitol (22)

Treatment of **20** (100 mg, 0.13 mmol) as described for the preparation of **8** gave, after column chromatography on silica gel (6:1 cyclohexane–EtOAc), first **22** (34 mg, 35%) as a syrup; $[\alpha]_D$ +42.2 (c = 0.8, $CHCl_3$).

^{1}H NMR (DMSO-d_6, 120 °C): δ = 7.40–7.20 (m, 15 H, 3 C_6H_5), 4.82 (s, 2 H, PhCH_2), 4.74 and 4.60 (2 d, 2 H, J = 11.3 Hz, PhCH_2), 4.66 (ddd, 1 H, $J_{1a,2}$ = 2.3, $J_{1b,2}$ = 2.5, $J_{2,5}$ = 1.8 Hz, H-2), 4.55 and 4.49 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.17 (dd, 1 H, $J_{5,6}$ = 9.8 Hz, H-5), 4.09 (dd, 1 H, $J_{1a,1b}$ = 8.8 Hz, H-1a), 3.93 (dd, 1 H, H-1b), 3.68 (dd, 1 H, $J_{6,7}$ = 9.0 Hz, H-6), 3.66–3.52 (m, 4 H, H-7, H-8, 2 H-10), 3.45 (dd, 1 H, $J_{7,8}$ = 9.3, $J_{8,9}$ = 9.0 Hz, H-8), 1.59 and 1.43 (2 s, 6 H, 2 CH_3), 1.43 (s, 9 H, t-C_4H_9).

MALDI-TOF MS: m/z = 706.0 (M^+ + Na), 722.2 (M^+ + K).

Anal. Calcd for $C_{39}H_{46}N_4O_7$: C, 68.60; H, 6.79; N, 8.21. Found: C, 68.70; H, 6.85; N, 8.29.

Unreacted **20** (29 mg, 29%) was eluted out as the second fraction.

6,7,8,10-Tetra-*O*-acetyl-5,9-anhydro-2,3,4-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-decitol (10); Typical Procedure

A vigorously stirred mixture of **8** (100 mg, 0.13 mmol), 20% $Pd(OH)_2$ on carbon (10 mg), and MeOH (3 mL) was degassed under vacuum and saturated with H_2 (by means of a H_2-filled balloon) three times. The suspension was stirred at r.t. for 12 h under a positive pressure of H_2 (8 bar), then filtered through a plug of cotton and concentrated. A solution of the crude product in Ac_2O (2 mL) and pyridine (2 mL) was kept at r.t. for 7 h, and then concentrated. The residue was eluted from a column of silica gel with 2:1 cyclohexane–EtOAc to afford **10** (68 mg, 91%) as a syrup; $[\alpha]_D$ +17.2 (*c* = 1, $CHCl_3$).

^{1}H NMR (DMSO-d_6, 120 °C): δ = 5.33 (dd, 1 H, $J_{7,8}$ = 3.5, $J_{8,9}$ = 0.5 Hz, H-8), 5.12 (dd, 1 H, $J_{6,7}$ = 10.0 Hz, H-7), 4.93 (dd, 1 H, $J_{5,6}$ = 9.0 Hz, H-6), 4.08–3.96 (m, 3 H), 3.92 (dd, 1 H, $J_{1a,2}$ = 6.0, $J_{1a,1b}$ = 8.5 Hz, H-1a), 3.83–3.82 (m, 1 H, H-2), 3.67 (dd, 1 H, H-1b), 3.55 (ddd, 1 H, $J_{4a,5}$ = 9.0, $J_{4b,5}$ = 3.0 Hz, H-5), 2.12–1.95 (4 s, 12 H, 4 CH_3CO), 1.70–1.52 (m, 4 H), 1.48 and 1.41 (2 s, 6 H, 2 CH_3), 1.40 (s, 9 H, *t*-C_4H_9).

MALDI-TOF MS: *m*/*z* = 583.0 (M^+ + Na), 599.0 (M^+ + K).

Anal. Calcd for $C_{26}H_{41}NO_{12}$: C, 55.80; H, 7.38; N, 2.50. Found: C, 55.71; H, 7.41; N, 2.60.

5,9-Anhydro-6,7,8,10-tetra-*O*-benzyl-2,3,4-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-decitol (14)

To a warmed (85 °C) and stirred solution of **8** (100 mg, 0.13 mmol) and freshly recrystallized *p*-toluenesulfonhydrazide (149 mg, 0.78 mmol) in dimethoxyethane (2 mL) was added 1 M aq NaOAc (0.78 mL) in six portions during 3 h. After an additional 2.5 h at 85 °C, the mixture was diluted with H_2O (1.5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with cyclohexane–EtOAc (from 5:1 to 4:1) to give **14** (83 mg, 85%) as a syrup. Compound **8** was identical in all respects to the product that we prepared by another route.[15a]

6,7,8,10-Tetra-*O*-acetyl-5,9-anhydro-2,3,4-trideoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*galacto*-decitol (11)

Compound **9** (285 mg, 0.38 mmol) was hydrogenated and acetylated as described for the preparation of **10**. The crude product was eluted from a column of silica gel with 5:2 cyclohexane–EtOAc to give **11** (192 mg, ~90%) as a syrup; $[\alpha]_D$ +8.3 (*c* = 1.5, $CHCl_3$).

^{1}H NMR (DMSO-d_6, 120 °C): δ = 5.18 (dd, 1 H, $J_{6,7}$ = 9.5, $J_{7,8}$ = 9.5 Hz, H-7), 4.88 (dd, 1 H, $J_{8,9}$ = 10.0 Hz, H-8), 4.72 (dd, 1 H, $J_{5,6}$ = 9.5 Hz, H-6), 4.14–4.06 (m, 2 H, 2 H-10), 3.91 (dd, 1 H, $J_{1a,1b}$ = 8.5, $J_{1a,2}$ = 3.0 Hz, H-1a), 3.86–3.30 (m, 2 H, H-2, H-9), 3.66 (dd, 1 H, $J_{1b,2}$ = 2.0 Hz, H-1b), 3.59 (ddd, 1 H, $J_{4a,5}$ = 9.2, $J_{4b,5}$ = 2.8 Hz, H-5), 2.00 and 1.94 (4 s, 12 H, 4 CH_3CO), 1.65–1.49 (m, 4 H), 1.47 and 1.43 (2 s, 6 H, 2 CH_3),1.41 (s, 9 H, *t*-C_4H_9).

MALDI-TOF MS: *m*/*z* = 582.7 (M^+ + Na), 599.1 (M^+ + K).

Anal. Calcd for $C_{26}H_{41}NO_{12}$: C, 55.80; H, 7.38; N, 2.50.Found: C, 55.91; H, 7.26; N, 2.61.

6-Acetamido-7,8,10-tri-*O*-acetyl-5,9-anhydro-2,3,4,6-tetradeoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-decitol (23); Typical Procedure

A vigorously stirred mixture of **21** (140 mg, 0.21 mmol), 20% $Pd(OH)_2$ on carbon (20 mg), EtOAc (1 mL), and MeOH (1 mL) was degassed under vacuum and saturated with H_2 (by means of a H_2-filled balloon) three times. The suspension was stirred at r.t. for 2 h under a slightly positive pressure of H_2 (balloon), then filtered through Celite and concentrated. A solution of the crude product in Ac_2O (1 mL) was kept at r.t. for 30 min and then concentrated. A vigorously stirred mixture of the crude acetamido derivative, 20% $Pd(OH)_2$ on carbon (20 mg), EtOAc (1 mL), and MeOH (1 mL) was degassed under vacuum and saturated with H_2 (by means of a H_2-filled balloon) three times. The suspension was stirred at r.t. for 12 h under a slightly positive pressure of H_2 (balloon), then filtered through a plug of cotton and concentrated. A solution of the crude product in Ac_2O (2 mL) and pyridine (2 mL) was kept at r.t. for 4 h, and then concentrated. The residue was eluted from a short column of silica gel (1 × 10 cm, d × h) with 3:1 CH_2Cl_2–acetone to give **23** (97 mg, 85%) as a syrup; $[\alpha]_D$ –14.6 (*c* = 0.4, $CHCl_3$).

^{1}H NMR (DMSO-d_6, 120 °C): δ = 6.08 (d, 1 H, $J_{2,NH}$ = 8.0 Hz, NH), 5.29 (dd, 1 H, $J_{7,8}$ = 3.0, $J_{8,9}$ = 0.5 Hz, H-8), 4.98 (d, 1 H, $J_{6,7}$ = 10.5 Hz, H-7), 4.02 (ddd, 1 H, $J_{5,6}$ = 9.0 Hz, H-6), 4.02–3.87 (m, 4 H), 3.91 (ddd, 1 H, $J_{9,10a}$ = 4.5, $J_{9,10b}$ = 2.5 Hz, H-9), 3.63–3.60 (m, 1 H, H-2), 3.42 (ddd, 1 H, $J_{4a,5}$ = 9.0, $J_{4b,5}$ = 2.0 Hz, H-5), 2.10–1.82 (4 s, 12 H, 4 CH_3CO), 1.65–1.45 (m, 4 H), 1.43 (s, 3 H, CH_3), 4.41 (s, 12 H, CH_3, *t*-C_4H_9).

MALDI-TOF MS: *m*/*z* = 581.9 (M^+ + Na), 597.9 (M^+ + K).

Anal. Calcd for $C_{26}H_{42}N_2O_{11}$: C, 55.90; H, 7.58; N, 5.01. Found:C, 55.95; H, 7.75; N, 5.17.

6-Acetamido-7,8,10-tri-*O*-acetyl-5,9-anhydro-2,3,4,6-tetradeoxy-1,2-*N*,*O*-isopropylidene-2-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*galacto*-decitol (24)

Compound **22** (50 mg, 0.07 mmol) was hydrogenated and acetylated as described for the preparation of **23**. The crude product was eluted from a short column of silica gel (1 × 10 cm, d × h) with 1:1:1 cyclohexane–EtOAc–CH_2Cl_2 to afford **24** (34 mg, 87%) as a white solid; mp 111–113 °C (Et_2O); $[\alpha]_D$ –8.3 (*c* = 0.4, $CHCl_3$).

^{1}H NMR (DMSO-d_6 –D_2O, 100 °C): δ = 5.04 (dd, 1 H, $J_{5,6}$ = 9.0, $J_{6,7}$ = 9.5 Hz, H-6), 4.80 (dd, 1 H, $J_{7,8}$ = 9.5 Hz, H-7), 4.12 (dd, 1 H, $J_{9,10a}$ = 5.5, $J_{10a,10b}$ = 12.0 Hz, H-10a), 4.04 (dd, 1 H, $J_{9,10b}$ = 3.0 Hz, H-10b), 3.89 (dd, 1 H, $J_{1a,2}$ = 2.5, $J_{1a,1b}$ = 8.8 Hz, H-1a), 3.81–3.78 (m, 1 H, H-2), 3.70 (dd, 1 H, $J_{8,9}$ = 9.5 Hz, H-8), 3.68 (ddd, 1 H, H-9), 3.63 (dd, 1 H, $J_{1b,2}$ = 1.8 Hz, H-1b), 3.44 (ddd, 1 H, $J_{4a,5}$ = 9.0, $J_{4b,5}$ = 3.0 Hz, H-5), 2.01–1.79 (4 s, 12 H, 4 CH_3CO), 1.80–1.60 (m, 4 H), 1.49 and 1.42 (2 s, 6 H, 2 CH_3), 1.44 (s, 9 H, *t*-C_4H_9).

MALDI-TOF MS: *m*/*z* = 581.6 (M^+ + Na), 597.8 (M^+ + K).

Anal. Calcd for $C_{26}H_{42}N_2O_{11}$: C, 55.90; H, 7.58; N, 5.01. Found: C, 55.75; H, 7.65; N, 5.12.

6,7,8,10-Tetra-*O*-acetyl-5,9-anhydro-2,3,4-trideoxy-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-deconic Acid (12); Typical Procedure

To a cooled (0 °C), stirred solution of **10** (150 mg, 0.27 mmol) in acetone (4 mL) was added freshly prepared Jones' reagent (1 M, 0.81 mL, 0.81 mmol). The mixture was allowed to warm to r.t. in 30 min, stirred at r.t. for an additional 3 h, and then diluted with propan-2-ol (0.35 mL). To the orange suspension was added dropwise propan-2-ol until a green color was observed, then the reaction mixture was diluted with CH_2Cl_2 (60 mL) and washed with brine (3 × 20 mL). The organic phase was dried (Na_2SO_4) and concentrated to afford **12** (129 mg, ~90%) as a syrup ~90% pure by ^{1}H NMR analysis.

^{1}H NMR: δ = 5.44 (dd, 1 H, $J_{7,8}$ = 3.0, $J_{8,9}$ = 0.5 Hz, H-8), 5.21–5.15 (m, 1 H, NH), 5.11 (dd, 1 H, $J_{5,6}$ = 9.3, $J_{6,7}$ = 10.0 Hz, H-6), 5.03 (dd, 1 H, H-7), 4.29–4.27 (m, 1 H, H-2), 4.12 (dd, 1 H, $J_{9,10a}$ = 6.0, $J_{10a,10b}$ = 11.0 Hz, H-10a), 4.10 (dd, 1 H, $J_{9,10b}$ = 6.0 Hz, H-10b), 3.89 (ddd, 1 H, H-9), 3.49 (ddd, 1 H, $J_{4a,5}$ = 9.3, $J_{4b,5}$ = 3.0 Hz, H-5), 2.18–2.00 (m, 4 H), 1.48 (s, 9 H, *t*-C_4H_9).

6,7,8,10-Tetra-*O*-acetyl-5,9-anhydro-2,3,4-trideoxy-2-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*galacto*-deconic Acid (13)
Oxidation of **11** (147 mg, 0.26 mmol) as described for the preparation of **12** gave **13** (120 mg, ~90%) as a syrup ~95% pure by ^{1}H NMR analysis.

^{1}H NMR: δ = 5.19 (dd, 1 H, $J_{6,7}$ = 9.5, $J_{7,8}$ = 9.5 Hz, H-7), 5.02 (dd, 1 H, $J_{8,9}$ = 10.0 Hz, H-8), 4.84 (dd, 1 H, $J_{5,6}$ = 9.0 Hz, H-6), 4.23–4.00 (m, 4 H), 3.64–3.52 (m, 2 H), 2.10–2.00 (4 s, 12 H, 4 CH_3CO), 1.43 (s, 9 H, *t*-C_4H_9).

6-Acetamido-7,8,10-tri-*O*-acetyl-5,9-anhydro-2,3,4,6-tetra-deoxy-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-deconic Acid (25)
Oxidation of **23** (97 mg, 0.17 mmol) as described for the preparation of **12** gave **25** (68 mg, ~75%) as an white foam ~90% pure by ^{1}H NMR analysis.

^{1}H NMR: δ (selected data): = 5.61–5.56 (m, 1 H, NH), 5.20–4.96 (m, 3 H), 4.32–3.88 (m, 2 H), 3.75–3.22 (m, 2 H), 3.10–3.07 (m, 1 H), 2.14–1.96 (4 s, 12 H, 4 CH_3CO), 1.65–1.47 (m, 4 H), 1.32 (s, 9 H, *t*-C_4H_9).

6-Acetamido-7,8,10-tri-*O*-acetyl-5,9-anhydro-2,3,4,6-tetra-deoxy-2-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*galacto*-deconic Acid (26)
Oxidation of **24** (80 mg, 0.14 mmol) as described for the preparation of **12** gave **26** (53 mg, ~71%) as a syrup ~90% pure by ^{1}H NMR analysis.

^{1}H NMR: δ (selected data) = 5.61–5.56 (m, 1 H, NH), 5.10–4.96 (m, 2 H), 4.23–3.98 (m, 3 H), 3.79–3.32 (m, 2 H, 2 H-10), 3.14–3.11 (m, 1 H, H-5), 2.14–1.96 (4 s,12 H, 4 CH_3CO), 1.65–1.47 (m, 4 H), 1.32 (s, 9 H, *t*-C_4H_9).

Methyl 6,7,8,10-Tetra-*O*-acetyl-5,9-anhydro-2,3,4-trideoxy-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-deconate (12 Me Ester)
Treatment of a solution of crude acid **12** in1:1 Et_2O–MeOH with ethereal diazomethane at 0 °C for 5 min gave, after column chromatography on silica gel with 1:1 cyclohexane–EtOAc, the methyl ester of **12** as a syrup; $[\alpha]_D$ +4.6 (*c* = 0.9, $CHCl_3$).

^{1}H NMR: δ = 5.43 (dd, 1 H, $J_{7,8}$ = 3.5, $J_{8,9}$ = 1.0 Hz, H-8), 5.09 (dd, 1 H, $J_{5,6}$ = 9.5, $J_{6,7}$ = 10.0 Hz, H-6), 5.02 (dd, 1 H, H-7), 4.33–4.24 (m, 1 H, H-2), 4.13 (dd, 1 H, $J_{9,10a}$ = 6.7, $J_{10a,10b}$ = 11.0 Hz, H-10a), 4.07 (dd, 1 H, $J_{9,10b}$ = 6.5 Hz, H-10b), 3.87 (ddd, 1 H, H-9), 3.76 (s, 3 H, OCH_3), 3.46 (ddd, 1 H, $J_{4a,5}$ = 9.0, $J_{4b,5}$ = 2.5 Hz, H-5), 2.19–2.00 (3 s, 12 H, 4 CH_3CO), 1.90–1.75 (m, 2 H), 1.69–1.55 (m, 2 H), 1.43 (s, 9 H, *t*-C_4H_9).

MALDI-TOF MS: *m*/*z* = 570.6 (M^+ + Na), 586.8 (M^+ + K).

Anal. Calcd for $C_{24}H_{37}NO_{13}$: C, 52.65; H, 6.81; N, 2.56. Found: C, 52.56; H, 6.90; N, 2.60.

Methyl 6,7,8,10-Tetra-*O*-acetyl-5,9-anhydro-2,3,4-trideoxy-2-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*galacto*-deconate (13 Me Ester)
Treatment of a solution of crude acid **13** in1:1 Et_2O–MeOH with ethereal diazomethane at 0 °C for 5 min gave, after column chromatography on silica gel (2:1 EtOAc–cyclohexane), the methyl ester of **13** as a white solid; mp 109–111 °C (cyclohexane–EtOAc); $[\alpha]_D$ –4.0 (*c* = 1, $CHCl_3$).

^{1}H NMR: δ = 5.19 (dd, 1 H, $J_{6,7}$ = 9.4, $J_{7,8}$ = 9.3 Hz, H-7), 5.06 (d, 1 H, $J_{2,NH}$ = 8.0 Hz, NH), 5.05 (dd, 1 H, $J_{8,9}$ = 10.0 Hz, H-8), 4.89 (dd, 1 H, $J_{5,6}$ = 9.9 Hz, H-6), 4.33–4.25 (m, 1 H, H-2), 4.24 (dd, 1 H, $J_{9,10a}$ = 5.1, $J_{10a,10b}$ = 12.3 Hz, H-10a), 4.11 (dd, 1 H, $J_{9,10b}$ = 2.2 Hz, H-10b), 3.76 (s, 3 H, OCH_3), 3.65 (ddd, 1 H, H-9), 3.48 (ddd, 1 H, $J_{4a,5}$ = 2.6, $J_{4b,5}$ = 8.0 Hz, H-5), 2.11, 2.06, 2.04 and 2.02 (4 s, 12 H, 4 CH_3CO), 2.01–1.44 (m, 4 H, 2 H-3, 2 H-4), 1.46 (s, 9 H, *t*-C_4H_9).

MALDI-TOF MS: *m*/*z* = 570.9 (M^+ + Na), 586.7 (M^+ + K).

Anal. Calcd for $C_{24}H_{37}NO_{13}$: C, 52.65; H, 6.81; N, 2.56. Found:C, 52.80; H, 6.79; N, 2.54.

Methyl 6-Acetamido-7,8,10-tri-*O*-acetyl-5,9-anhydro-2,3,4,6-tetradeoxy-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-deconate (25 Me Ester)
Treatment of a solution of crude acid **25** in 1:1 Et_2O–MeOH with ethereal diazomethane at 0 °C for 5 min gave, after chromatography on a short column of silica gel (1 × 10 cm, d × h; 2:1 CH_2Cl_2–acetone), the methyl ester of **25** as a syrup; $[\alpha]_D$ –7.5 (*c* = 0.5, $CHCl_3$).

^{1}H NMR: δ = 5.70 (d, 1 H, *J* = 8.5 Hz, NH), 5.37 (dd, 1 H, $J_{7,8}$ = 3.5, $J_{8,9}$ = 0.5 Hz, H-8), 4.97 (dd, 1 H, $J_{6,7}$ = 10.5 Hz, H-7), 4.68 (ddd, 1 H, $J_{5,6}$ = 9.0 Hz, H-6),4.12 (dd, 1 H, $J_{9,10a}$ = 6.5, $J_{10a,10b}$ = 11.0 Hz, H-10a), 4.10 (dd, 1 H, $J_{9,10b}$ = 9.0 Hz, H-10b), 4.05–4.03 (m, 1 H, H-2), 3.84 (ddd, 1 H, H-9), 3.77 (s, 3 H, OCH_3), 3.40 (ddd, 1 H, $J_{4a,5}$ = 9.2, $J_{4b,5}$ = 0.5 Hz, H-5), 2.14–2.00 (4 s,12 H, 4 CH_3CO), 1.75–1.56 (m, 4 H), 1.43 (s, 9 H, *t*-C_4H_9).

MALDI-TOF MS: *m*/*z* = 569.5 (M^+ + Na), 585.7 (M^+ + K).

Anal. Calcd for $C_{24}H_{38}N_2O_{12}$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.81; H, 7.09; N, 5.00.

Methyl 6-Acetamido-7,8,10-tri-*O*-acetyl-5,9-anhydro-2,3,4,6-tetradeoxy-2-(*tert*-butoxycarbonylamino)-D-*erythro*-L-*galacto*-deconate (26 Me Ester)
Treatment of a solution of crude acid **26** in 1:1 Et_2O–MeOH with ethereal diazomethane at 0 °C for 5 min gave, after column chromatography on silica gel (2:1 toluene–acetone), the methyl ester of **26** as a syrup; $[\alpha]_D$ –25.5 (*c* = 0.9, $CHCl_3$); $[\alpha]_D$ –26.2 (*c* = 0.8, CH_2Cl_2) {Lit.[18] $[\alpha]_D$ –27 (*c* = 1.0, CH_2Cl_2)}.

The ^{1}H NMR spectrum of the metyl ester of **26** was identical to that reported in Ref.[18]

6,7,8,10-Tetra-*O*-acetyl-5,9-anhydro-2,3,4-trideoxy-2-(9-fluorenylmethoxycarbonylamino)-D-*threo*-L-*galacto*-decitol (27)
To a cooled (0 °C), stirred solution of **10** (170 mg, 0.31 mmol) in CH_2Cl_2 (4 mL) was added dropwise trifluoroacetic acid (1.0 mL). The mixture was stirred at 0 °C for 30 min, and then allowed to warm up to r.t. After an additional 30 min at r.t., the solution was coevaporated with toluene (3 × 20 mL). To a solution of the residue in H_2O (2 mL) and MeCN (2 mL) was added at r.t. a solution of *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (125 mg, 0.37 mmol) in MeCN (1 mL) and then freshly distilled Et_3N (128 μL, 0.93 mmol) in order to maintain the pH of the reaction mixture at ca. 9. After 45 min the TLC analysis (2:1 EtOAc–cyclohexane) indicated the disappearance of the starting material. 0.1 M HCl was added until pH = 2. The mixture was diluted with CH_2Cl_2 (20 mL) and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was eluted from a column of silica gel with EtOAc–cyclohexane (from 1:1 to 2:1) to afford **27** (159 mg, 80%) as a white solid; mp 82–85 °C (EtOAc–cyclohexane); $[\alpha]_D$ –5.6 (*c* = 0.9, $CHCl_3$).

^{1}H NMR: δ = 7.82–7.78, 7.66–7.61, and 7.48–7.33 (3 m, 8 H_{arom}), 5.42 (dd, 1 H, $J_{7,8}$ = 3.0, $J_{8,9}$ = 1.0 Hz, H-8), 5.11 (dd, 1 H, $J_{5,6}$ = 9.0, $J_{6,7}$ = 10.0 Hz, H-6), 5.05 (br s, 1 H, NH), 5.02 (dd, 1 H, H-7), 4.54 (dd, 1 H, *J* = 6.5, 10.5 Hz, CH_2-Fmoc), 4.44 (dd, 1 H, *J* = 6.3, 10.5 Hz, CH_2-Fmoc), 4.24 (dd, 1 H, *J* = 6.3, 6.5 Hz, C*H*-Fmoc), 4.22–4.19 (m, 1 H, H-2), 4.13 (dd, 1 H, $J_{10a,10b}$ = 11.0, $J_{9,10a}$ = 7.0 Hz, H-10a), 4.04 (dd, 1 H, $J_{9,10b}$ = 6.0 Hz, H-10b), 3.77 (ddd, 1 H, H-9), 3.70–3.59 (m, 4 H), 3.43 (ddd, 1 H, $J_{4a,5}$ = 8.2, $J_{4b,5}$ = 3.3 Hz, H-5), 2.13, 2.03 and 2.00 (3 s, 12 H, 4 CH_3CO), 1.72–1.60 (m, 4 H).

Anal. Calcd for $C_{33}H_{39}NO_{12}$: C, 61.77; H, 6.13; N, 2.18. Found: C, 61.99; H, 6.00; N, 2.40.

6,7,8,10-Tetra-*O*-acetyl-5,9-anhydro-2,3,4-trideoxy-2-(9-fluorenylmethoxycarbonylamino)-D-*threo*-L-*galacto*-deconic Acid (28)

Treatment of **27** (98 mg, 0.15 mmol) as described for the preparation of **12** gave **28** (95 mg, ~95%) as a syrup ~95% pure by ^{1}H NMR analysis.

^{1}H NMR: δ = 7.83–7.76, 7.67–7.57, and 7.49–7.31 (3 m, 8 H_{arom}), 5.49 (d, 1 H, $J_{NH,2}$ = 7.8 Hz, NH), 5.43 (dd, 1 H, $J_{7,8}$ = 3.0, $J_{8,9}$ = 1.0 Hz, H-8), 5.11 (dd, 1 H, $J_{5,6}$ = 9.0, $J_{6,7}$ = 10.0 Hz, H-6), 5.03 (dd, 1 H, H-7), 4.52 (dd, 1 H, *J* = 7.0,10.5 Hz, CH_2-Fmoc), 4.44–4.34 (m, 2 H, CH_2-Fmoc, H-2), 4.25 (dd, 1 H, *J* = 6.5, 7.0 Hz, C*H*-Fmoc), 4.13 (dd, 1 H, $J_{9,10a}$ = 7.0, $J_{10a,10b}$ = 11.5 Hz, H-10a), 4.05 (dd, 1 H, $J_{9,10b}$ = 6.0 Hz, H-10b), 3.81 (ddd, 1 H, H-9), 3.48–3.43 (m, 1 H, H-5), 2.17, 2.05, 2.03 and 2.01 (4 s, 12 H, 4 CH_3CO),1.80–1.54 (m, 4 H).

Methyl 6,7,8,10-Tetra-*O*-acetyl-5,9-anhydro-2,3,4-trideoxy-2-(9-fluorenylmethoxycarbonylamino)-D-*threo*-L-*galacto*-deconate (28 Me Ester)

Treatment of a solution of crude acid **28** in 1:1 Et_2O–MeOH with ethereal diazomethane at 0 °C for 5 min gave, after column chromatography on silica gel (2:1 EtOAc–cyclohexane), the methyl ester **28** as a syrup; $[\alpha]_D$ +1.5 (*c* = 1.2, $CHCl_3$).

^{1}H NMR: δ = 7.83–7.75, 7.70–7.57, and 7.47–7.31 (3 m, 8 H_{arom}), 5.43 (dd, 1 H, $J_{7,8}$ = 3.0, $J_{8,9}$ = 1.0 Hz, H-8), 5.38 (d, 1 H, $J_{NH,2}$ = 7.5 Hz, NH), 5.11 (dd, 1 H, $J_{5,6}$ = 9.5, $J_{6,7}$ = 10.0 Hz, H-6), 5.03 (dd, 1 H, H-7), 4.49 (dd, 1 H, *J* = 6.5, 10.5 Hz, CH_2Fmoc), 4.39 (dd, 1 H, *J* = 7.0, 10.5 Hz, CH_2-Fmoc), 4.38–4.32 (m, 1 H, H-2), 4.25 (dd, 1 H, *J* = 6.5, 7.0 Hz, C*H*-Fmoc), 4.14 (dd, 1 H, $J_{9,10a}$ = 7.0, $J_{10a,10b}$ = 11.0 Hz, H-10a), 4.06 (dd, 1 H, $J_{9,10b}$ = 5.5 Hz, H-10b), 3.82 (ddd, 1 H, H-9), 3.79 (s, 3 H, OCH_3), 3.46 (ddd, 1 H, $J_{4a,5}$ = 9.0, $J_{4b,5}$ = 3.0 Hz, H-5), 2.18, 2.06, 2.04 and 2.00 (4 s, 12 H, 4 CH_3CO), 1.95–1.52 (m, 4 H).

Anal. Calcd for $C_{34}H_{39}NO_{13}$: C, 60.98; H, 5.87; N, 2.09. Found: C, 60.60; H, 6.00; N, 2.13.

Acknowledgement

We thank Mr. P. Formaglio (University of Ferrara, Italy) for NMR measurements. This research was financially supported by MURST, COFIN-2000 (Italy). We are grateful to Ajinomoto Co., Inc. (Tokyo, Japan) for an unrestricted grant.

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