Pergamon

Tetrahedron 54 (1998) 2827–2832

TETRAHEDRON

Stereoselective Synthesis of the *C*-Linked Analogue of β-D-Galactopyranosyl-L-serine

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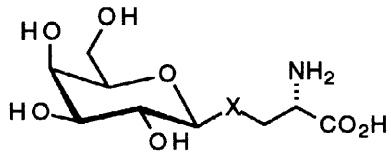
Received 5 December 1997; accepted 8 January 1998

Abstract: The coupling of the D-serinal derivative **7** with the D-galactopyranosylmethylene phosphorane generated from the phosphonium salt **6** and reduction of the resulting alkene led to the *C*-glycosylated amino alcohol **9** that in turn was oxidized to the title amino acid in 44% overall yield.

The synthesis of the so called *C*-glycosyl amino acids possessing an anomeric C-C bond instead of the C-N or C-O bond between the sugar and the amino acid moieties is an issue that is currently addressed in various laboratories.[1] These synthetic amino acids can be used for the modification of bioactive glycopeptides by the attachment of carbohydrates through chemical and enzymatic resistant carbon-carbon bond.[2] Among the few genuine isosteres so far reported wherein the glycosidic oxygen atom has been replaced by a methylene group,[1b,d,h,k,n] the *C*-analogue **2** of β-D-galactopyranosyl-L-serine (**1**) has been prepared[1d] and incorporated into a 17-amino acid α-helical peptide for both biological and conformational studies.[3] The amino acid **2** was also employed[1e] for the synthesis of water-soluble carbon-linked galactosphingolipid analogues that proved to bind specifically to HIV-1 gp120 and therefore represented potential inhibitors of the first step in the infection process causing the AIDS. In both cases tetra-*O*-benzylated *N*-Fmoc and *N*-Boc derivatives of **2** were prepared by Wittig condensation of the *C*-glycosyl aldehyde **3** (see Scheme 1) with a suitable phosphorane serving as a β-alaninol anion equivalent. Therefore the β-D-linkage at the anomeric centre of the sugar and the *S*-configuration at the carbon bearing the amino group were already in place in the reagents employed. We would like to describe the application of the same concept in a reversed manner and report below an improved synthesis of **2** by condensation of a β-linked D-galactose phosphorous ylide with a D-serine derived aldehyde as the key coupling step. We considered an alternative synthetic approach to the amino acid **2** because the Wittig olefination of the high value sugar aldehyde **3** was reported[1d] to occur in low yield (34%) whilst we needed substantial amounts of **2** for the synthesis of glycopeptide and sphingosine mimetics.



1 X = O
2 X = CH_2

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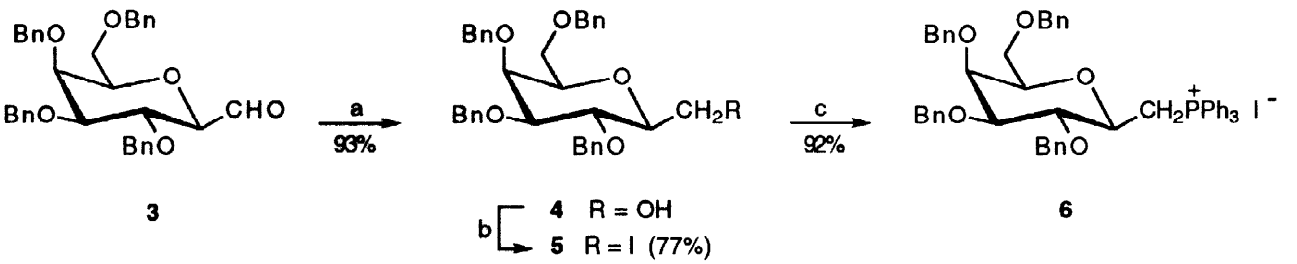
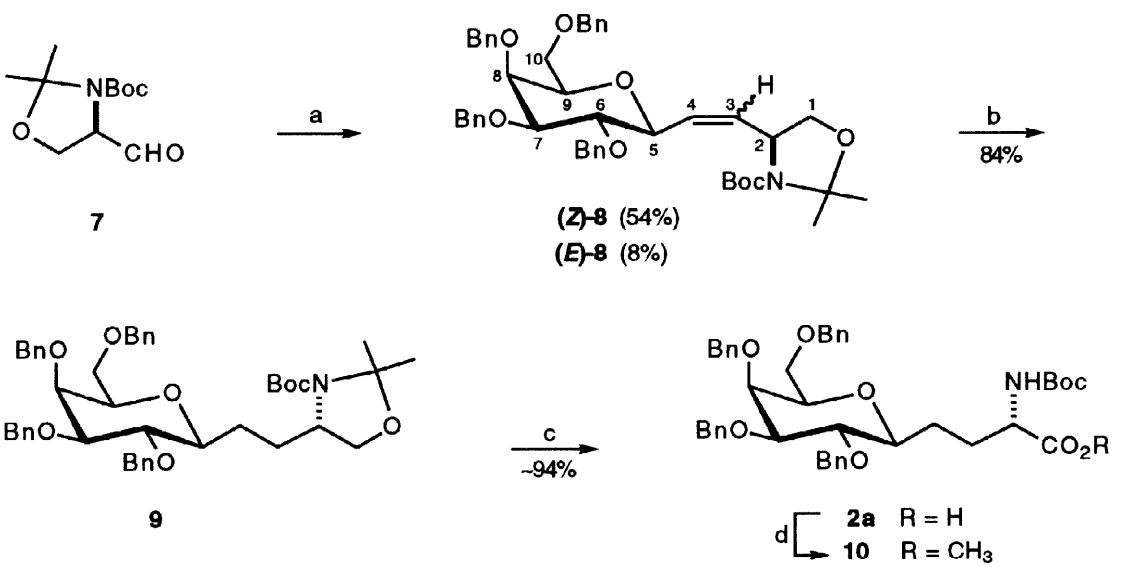
PII: S0040-4020(98)00032-5

The formyl *C*-glycoside **3** was prepared in gram quantities (1-5 g) by our thiazole-based method starting from tetra-*O*-benzyl-D-galactonolactone.[4] The crude product obtained by the improved thiazole-to-formyl unmasking protocol[5] was reduced ($NaBH_4$) to the alcohol **4** in almost quantitative yield (Scheme 1). Pure compound **4** was readily transformed into the iodomethyl derivative **5** under standard iodination conditions[6] and the latter was efficiently converted into the corresponding phosphonium iodide **6** by coupling with neat triphenylphosphine at 120 °C. When the same reaction was carried out in the presence of various solvents, the salt **6** was obtained in much lower yield. Compound **6** proved to be a non-hygroscopic material, storable for long period without appreciable decomposition.



Scheme 1. Reagents and conditions: a) $NaBH_4$, Et_2O-MeOH, 0 °C, 10 min; b) I_2, Ph_3P, Imidazole,toluene, reflux, 2 h; c) Ph_3P, 120 °C, 2 h.

With an efficient entry to the sugar phosphonium salt **6** at hand, suitable conditions were searched for an efficient coupling with the readily accessible[7] *N*-Boc-*N,O*-isopropylidene-D-serinal **7** (Scheme 2). The sugar phosphorane, generated from **6** by treatment with *n*BuLi (1 equiv) in THF-HMPA at -40 °C, was reacted with a solution of the aldehyde **7** (1 equiv) in THF and the mixture allowed to warm up to -10 °C. Suitable workup and flash chromatography on silica gel afforded pure (*Z*)-**8** (54%, $J_{3,4}$ = 11.3 Hz) and (*E*)-**8** (8%, $J_{3,4}$ = 16.0 Hz) slightly contaminated by uncharacterized byproducts.



Scheme 2. Reagents and conditions: a) **6**, *n*BuLi, 4:1 THF-HMPA, 4 Å MS, -40 to -10 °C, 2 h; b) $TsNHNH_2$, AcONa , 4:1 DME-H_2O, reflux, 5 h; c) Jones reagent, acetone, 0 °C to r.t., 3 h; d) CH_2N_2, Et_2O-MeOH, 0 °C, 5 min.

In order to preserve the *O*-benzyl protective groups of the sugar moiety, the double bond of the *Z*- and *E*-alkene **8** was reduced by the use of diimide[8] generated in situ from *p*-toluenesulfonhydrazide and sodium acetate.[1e] In this way each individual olefin afforded the same *C*-alkyl galactoside **9** in comparable yields (82-84%). That the original β-D-linkage at the anomeric carbon of **3** was maintained in **9** was demonstrated by the coupling constant value of 9.0 Hz between the trans-diaxial protons at C-5 and C-6. To complete the synthesis, deacetonation and oxidation of **9** with the Jones reagent afforded in a single step the crude tetra-*O*-benzyl-galactosyl-*N*-Boc-α-amino-acid **2a** in 94% yield, contaminated (~5%) by the corresponding α-amino-alcohol derivative[9] **11**. Moreover, the amino acid **2a** was fully characterized as the methyl ester **10**. The overall yield of isolated **2a** from the sugar phosphonium salt **6** was 44%.

In conclusion, a practical alternative procedure has been developed for the preparation of the *O*-benzyl *N*-Boc protected sugar amino acid **2a**. This kind of protection and the free carboxylic group provide the arrangement required for the incorporation of **2a** into a peptide chain. Both the sugar and the amino acid building blocks **6** and **7** can be easily prepared in gram quantities. In respect to the earlier synthesis,[1d] this procedure involves a higher yield (almost double) Wittig condensation and a simpler elaboration of the resulting alkene. The synthesis of **2a** illustrates a new approach that may be extended to other *C*-linked glycosyl serines starting from suitable sugar phosphoranes.

Acknowledgement. Financial support from the Ministero dell' Università e della Ricerca Scientifica e Tecnologica (Italy) is gratefully acknowledged. We thank Mr. P. Formaglio (University of Ferrara, Italy) for NMR measurements.

EXPERIMENTAL

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. All solvents were dried over standard drying agents[10] and freshly distilled prior to use. Commercially available powdered 4-Å molecular sieves (50 μm average particle size) were used without further activation. Flash column chromatography[11] was performed on silica gel 60 (230-400 mesh). Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid. Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20 ± 2 °C in the stated solvent. ^1H (300 MHz) and ^{13}C (75 MHz) NMR were recorded at r. t. for $CDCl_3$ solutions, unless otherwise specified. Assignments were aided by decoupling and/or homo- and heteronuclear two-dimensional experiments. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-D-*glycero*-L-*manno*-heptitol (4). To a stirred, cooled (0 °C) solution of aldehyde **3** (2.76 g, 5.0 mmol; >95% pure by ^1H NMR analysis at 140 °C in DMSO-d_6) in Et_2O (10 mL) and MeOH (10 mL) was added sodium borohydride (189 mg, 5.0 mmol). The mixture was stirred at 0 °C for 10 min, then diluted with acetone (2 mL) and concentrated. The residue was eluted from a short column of silica gel with 3:1 cyclohexane-AcOEt to give **4** (2.58 g, 93%) as a syrup; $[\alpha]_D$ = +2.2 (*c* 1, $CHCl_3$). ^1H NMR: δ 7.41-7.23 (m, 20 H, 4 Ph), 4.97 and 4.61 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.94 and 4.66 (2 d, 2 H, J = 10.7 Hz, PhCH_2), 4.78 and 4.71 (2 d, 2 H, J = 11.7 Hz, PhCH_2), 4.49 and 4.43 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 3.95 (dd, 1 H, $J_{4,5}$ = 2.8, $J_{5,6}$ = ~0.5 Hz, H-5), 3.95 (dd, 1 H, $J_{2,3}$ = 9.5, $J_{3,4}$ = 9.6 Hz, H-3), 3.87 (ddd, 1 H, $J_{1a,1b}$ = 11.5, $J_{1a,2}$ = 2.8, $J_{1a,OH}$ = 5.5 Hz, H-1a), 3.72 (ddd, 1 H, $J_{1b,2}$ = 5.2, $J_{1b,OH}$ = 7.5 Hz, H-1b),

3.65 (dd, 1 H, H-4), 3.62-3.50 (m, 3 H), 3.36 (ddd, 1 H, H-2), 2.03 (dd, 1 H, OH). Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found: C, 76.10; H, 7.03.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-iodo-D-*glycero*-L-*manno*-heptitol (5). A mixture of alcohol **4** (2.22 g, 4.0 mmol), triphenylphosphine (3.15 g, 12.0 mmol), imidazole (0.82 g, 12.0 mmol), iodine (2.03 g, 8.0 mmol), and anhydrous toluene (40 mL) was refluxed for 2 h, then cooled to r. t., diluted with Et_2O (50 mL), washed with 5% aqueous $Na_2S_2O_3$ (2 x 20 mL), and concentrated. The brown solid was triturated with Et_2O (50 mL) and filtered through a pad of Celite to remove most of crystalline triphenylphosphine oxide. The solution was concentrated and the residue was eluted from a column of silica gel with 7:1 cyclohexane-AcOEt to give **5** (2.05 g, 77%) as a syrup; $[\alpha]_D$ = -14.2 (*c* 1, $CHCl_3$). ^1H NMR: δ 7.41-7.23 (m, 20 H, 4 Ph), 4.99 and 4.71 (2 d, 2 H, *J* = 11.0 Hz, PhCH_2), 4.97 and 4.67 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.77 and 4.63 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.54 and 4.45 (2 d, 2 H, *J* = 11.7 Hz, PhCH_2), 4.01 (dd, 1 H, $J_{4,5}$ = 2.5, $J_{5,6}$ = ~0.5 Hz, H-5), 3.80 (dd, 1 H, $J_{2,3}$ = 9.2, $J_{3,4}$ = 9.4 Hz, H-3), 3.66-3.58 (m, 4 H), 3.54 (dd, 1 H, $J_{1a,1b}$ = 10.5, $J_{1a,2}$ = 2.3 Hz, H-1a), 3.30 (dd, 1 H, $J_{1b,2}$ = 7.0 Hz, H-1b), 3.19 (ddd, 1 H, H-2). Anal. Calcd for $C_{35}H_{37}IO_5$: C, 63.26; H, 5.61. Found: C, 63.55; H, 5.46.

(2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*glycero*-L-*manno*-heptitol-1-yl)triphenylphosphonium iodide (6). A mixture of iodide **5** (1.99 g, 3.0 mmol) and triphenylphosphine (3.93 g, 15.0 mmol) was heated with stirring at 120 °C under a nitrogen atmosphere for 2 h, then cooled to r. t., triturated with toluene (3 x 10 mL) and Et_2O (2 x 10 mL), and dried to give **6** (2.56 g, 92%) as a white amorphous solid ; $[\alpha]_D$ = -37.7 (*c* 1, $CHCl_3$). ^1H NMR: δ 7.75-7.50, 7.41-7.28, 7.14-7.10 (3 m, 35 H, 7 Ph), 5.03 and 4.95 (2 d, 2 H, *J* = 11.4 Hz, PhCH_2), 4.92 and 4.55 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 4.75 and 4.69 (2 d, 2 H, *J* = 11.6 Hz, PhCH_2), 4.18 and 4.10 (2 d, 2 H, *J* = 11.5 Hz, PhCH_2), 3.85 (dd, 1 H, $J_{4,5}$ = 2.8, $J_{5,6}$ = 0.8 Hz, H-5), 3.70-3.57 (m, 1 H), 3.54 (dd, 1 H, $J_{3,4}$ = 9.3 Hz, H-4), 3.45-3.28 (m, 3 H), 3.25 (ddd, 1 H, $J_{6,7a}$ = 4.8, $J_{6,7b}$ = 6.8 Hz, H-6), 3.12 (dd, 1 H, $J_{7a,7b}$ = 9.7 Hz, H-7a), 3.05 (dd, 1 H, H-7b). Anal. Calcd for $C_{35}H_{37}IO_5P$: C, 68.68; H, 5.65. Found: C, 68.96; H, 5.67. The use of refluxing toluene, DMF at 120 °C or sulfolane at 200 °C as the solvent led to very low yield of phosphonium salt **6**.

(*Z/E*)-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-enitol (8). To a stirred, cooled (-40 °C) mixture of phosphonium salt **6** (923 mg, 1.00 mmol), powdered 4-Å molecular sieves (1.00 g), anhydrous hexamethylphosphoramide (2 mL), and anhydrous THF (6 mL) was slowly added *n*butyllithium (400 μL, 1.00 mmol, of a 2.5 solution in hexanes). After 5 min, to the resulting red-coloured suspension was slowly added a solution of the aldehyde **7** (228 mg, 1.00 mmol) in anhydrous THF (2 mL). The mixture was allowed to warm up to -10 °C in 2 h, then diluted with E_2O (100 mL) and filtered through a pad of Celite. The solution was washed with 1 M phosphate buffer at pH = 7 (30 mL), dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel with 6:1 cyclohexane-AcOEt to afford first **(*Z*)-8** (405 mg, 54%) as a syrup; $[\alpha]_D$ = -22.3 (*c* 1, $CHCl_3$). ^1H NMR ($C_2D_2Cl_4$, 120 °C) selected data: δ 5.73 (dd, 1 H, *J* = 8.2, 11.3 Hz, CH=), 5.63 (dd, 1 H, *J* = 5.2, 11.3 Hz, CH=). MALDI-TOF MS: 773.4 (M^++Na), 789.4 (M^++K). Anal. Calcd for $C_{46}H_{55}O_8N$: C, 73.67; H, 7.39; N, 1.87. Found: C, 74.01; H, 7.48; N, 1.68. Eluted second was syrupy **(*E*)-8** (60 mg, ~8%) contaminated by small amounts of uncharacterised byproducts. ^1H NMR (DMSO-d_6, 160 °C) selected data: δ 5.77 (dd, 1 H, *J* = 6.0, 16.0 Hz, CH=), 5.70 (dd, 1 H, *J* = 5.1, 16.0 Hz, CH=), 4.84 and 4.58

(2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.77 and 4.68 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.74 and 4.63 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.53 and 4.48 (2 d, 2 H, J = 12.2 Hz, PhCH_2). MALDI-TOF MS: 773.2 (M^++Na), 789.2 (M^++K).

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 (9). To a stirred, warmed (85 °C) solution of alkene **(*Z*)-8** (375 mg, 0.50 mmol) and freshly recrystallized *p*-toluenesulfonhydrazide (186 mg, 1.00 mmol) in dimethoxyethane (5 mL) was added a 1 M aqueous solution of sodium acetate (1.00 mL) in four portions during 2 h. After an additional 3 h at 85 °C the reaction mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was eluted from a column of silica gel with 6:1 cyclohexane-AcOEt to give **9** (316 mg, 84%) as a syrup; $[\alpha]_D$ = +4.8 (*c* 1, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 160 °C): δ 7.40-7.20 (m, 20 H, 4 Ph), 4.84 and 4.63 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.84 and 4.57 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 4.78 and 4.67 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.53 and 4.48 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.04 (dd, 1 H, $J_{7,8}$ = 2.7, $J_{8,9}$ = ~0.5 Hz, H-8), 3.88 (dd, 1 H, $J_{1a,2}$ = 6.0, $J_{1a,1b}$ = 8.5 Hz, H-1a), 3.84-3.77 (m, 1 H, H-2), 3.70 (dd, 1 H, $J_{6,7}$ = 9.5 Hz, H-7), 3.66-3.54 (m, 5 H), 3.22 (ddd, 1 H, $J_{4a,5}$ = $J_{5,6}$ = 9.0, $J_{4b,5}$ = 2.8 Hz, H-5), 1.88-1.67 and 1.62-1.42 (2 m, 2 H-3, 2 H-4), 1.43 and 1.39 (2 s, 6 H, 2 Me), 1.40 (s, 9 H, *t*Bu). Anal. Calcd for $C_{46}H_{57}O_8N$: C, 73.47; H, 7.64; N, 1.86. Found: C, 73.62; H, 7.74; N, 1.73. When the same reaction was performed using **(*E*)-8** instead of **(*Z*)-8** as the starting material, similar results were obtained.

5,9-Anhydro-6,7,8,10-tetra-*O*-benzyl-2,3,4-trideoxy-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-deconic acid (2a). To a stirred, cooled (0 °C) solution of **9** (301 mg, 0.40 mmol) in acetone (8 mL) was added freshly prepared 1 M Jones reagent (1.20 mL, 1.20 mmol). The mixture was allowed to warm to r. t. in 30 min, stirred at r. t. for an additional 2.5 h and then diluted with isopropanol (~0.5 mL). The suspension was neutralized with saturated aqueous $NaHCO_3$, diluted with Et_2O (100 mL) and washed with brine (2 x 20 mL). The organic phase was dried ($MgSO_4$) and concentrated to afford **2a** (273 mg, ~94%) contaminated by the amino alcohol **11** and other minor byproducts. Compound **2a** showed ^{1}H and ^{13}C NMR spectra consistent with those reported.[1e] Prolonged reaction time or larger excess of Jones reagent led to lower yields of **2a** due to acidic cleavage of the benzyl groups.

Methyl 5,9-Anhydro-6,7,8,10-tetra-*O*-benzyl-2,3,4-trideoxy-2-(*tert*-butoxycarbonylamino)-D-*threo*-L-*galacto*-deconate (10). Treatment of a solution of crude acid **2a** in 1:1 Et_2O-MeOH with ethereal diazomethane at 0 °C for 5 min gave, after column chromatography on silica gel (4:1 cyclohexane-AcOEt), the ester **10** as a syrup, $[\alpha]_D$ = -4.3 (*c* 1, $CHCl_3$). ^{1}H NMR: δ 7.40-7.25 (m, 20 H, 4 Ph), 5.04 (d, 1 H, J = 8.0 Hz, NH), 4.93 and 4.63 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.93 and 4.62 (2 d, 2 H, J = 10.8 Hz, PhCH_2), 4.75 and 4.67 (2 d, 2 H, J = 11.7 Hz, PhCH_2), 4.47 and 4.41 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.27-4.20 (m, 1 H, H-2), 3.98 (dd, 1 H, $J_{7,8}$ = 2.6, $J_{8,9}$ = ~0.5 Hz, H-8), 3.68 (s, 3 H, OMe), 3.66-3.47 (m, 5 H), 3.18 (ddd, 1 H, $J_{4a,5}$ = $J_{5,6}$ = 9.0, $J_{4b,5}$ = 2.3 Hz, H-5), 1.95-1.75 (m, 3 H), 1.58-1.48 (m, 1 H), 1.41 (s, 9 H, *t*Bu). Anal. Calcd for $C_{44}H_{53}O_9N$: C, 71.42; H, 7.22; N, 1.89. Found: C, 71.20; H, 7.33; N, 1.78.

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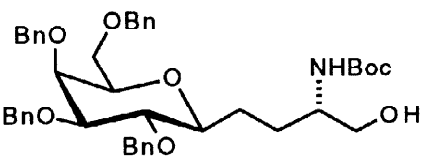
9. We prepared a pure sample of this alcohol by acid hydrolysis of **9** (4:1 AcOH-H_2O, 80 °C, 15 min) in 70% yield after column chromatography (3:1 Et_2O-cyclohexane); mp 87-89 °C (from hexane), lit.[1e] mp 80-81 °C; $[\alpha]_D$ = -11.6 (*c* 0.8, $CHCl_3$), previously[1e] unreported. Anal. Calcd for $C_{43}H_{53}O_8N$: C, 72.55; H, 7.50; N, 1.97. Found: C, 72.40; H, 7.62; N, 1.90. The alcohol **11** proved to be identical by NMR analysis with compound **7** described in ref. 1e.



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