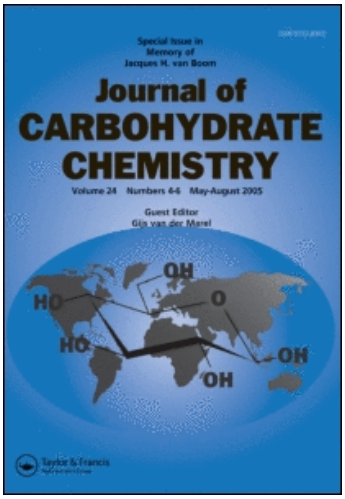

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Synthesis of Protected EPI-2-Deoxystreptamine and Analogs[†]

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ABSTRACT

A protected C-3 epi-2-deoxystreptamine was synthesized starting with the intermediate 2-L-1,3/2,4,5-1-acetamido-2,3,4-tri-*O*-benzyl-2,3,4,5-cyclohexanetetrol **8**, derived from D-glucose.

Key Words: Streptamine; Aminocyclitols; Aminoglycoside; Antibiotic.

INTRODUCTION

Aminocyclitols and diaminocyclitols are subunits of the aminoglycoside antibiotics, which are among the longest used and best known antibiotics. They have activities against a variety of aerobic bacteria[1] and are clinically important due to their effectiveness against certain bacterial infections, such as pneumonia and septicemia.[2]

[†]This paper is dedicated to Professor Gérard Descotes on the occasion of his 70th birthday.

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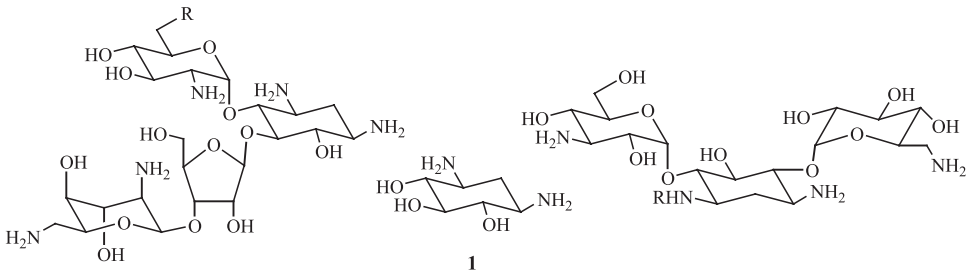

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Neomycin B R = NH_2
Paromomycin R = OH

Kanamycin R = H
Amikacin R = $COCH(OH)(CH_2)_2NH_2$

Figure 1.

Aminoglycoside antibiotics interact with RNA molecules, and those containing a 2-deoxystreptamine unit bind specifically to HIV RRE, which block binding of the HIV Rev protein to this RNA, and inhibit HIV replication in tissue culture cells.[3–5]

2-Deoxystreptamine is an aminocyclitol contained in many antibiotics such as neomycin B, paranomycin, kanamycin and amikacin (Figure 1).[6] The emergence of multiple resistant bacteria has created the need for new antibiotics. The structural stability and abundant functionality of 2-deoxystreptamine make it an attractive scaffold for the combinatorial generation of small molecules, and a large panel of compounds, derivatized with various substituents on the hydroxyl and amino groups of 2-deoxystreptamine have been synthesized for biological screening.[6–10]

In this paper, we wish to report the synthesis of the protected C-3 analogue of 2-deoxystreptamine, 2-L-1,3/2,4,5 1,5-diacetamido-2,3,4-tri-*O*-benzyl-2,3,4-cyclohexanetriol (**18**). This compound can be useful for synthesizing new aminoglycoside antibiotics.

RESULTS AND DISCUSSION

The oxime **2** was prepared from D-glucose *via* carbohydrate-inososе Ferrier rearrangement as previously described.[11,12] As reduction of **2** with $LiAlH_4$ does not proceed,[12] compound **2** was first converted to its benzyloxime **3** derivative (Scheme 1).[13] Reduction of **3** with $LiAlH_4$ gave a mixture of amine **4** (8%) and its epimer **5** (74%), along with the benzylhydroxylamine **6** (8%). These three compounds were purified by column chromatography. Compound **6** was quantitatively reduced to **5** using sodium borohydride and nickel chloride in methanol.

The *N*-acylated amines **7** and **8** were both obtained in 90% yield, by reaction of **4** and **5**, respectively, with acetic anhydride in methanol. Substitution of the hydroxyl groups of **7** was performed using DAST in methylene chloride. The expected fluorinated compound **9** was obtained in 70% yield. In a similar way compound **10** was prepared from **8** in the same yield.

Compound **8** was converted to the mesylate **11** in 88% yield (Scheme 2)[13] by treatment with methanesulfonyl choride in pyridine. Treatment of **11** with sodium azide

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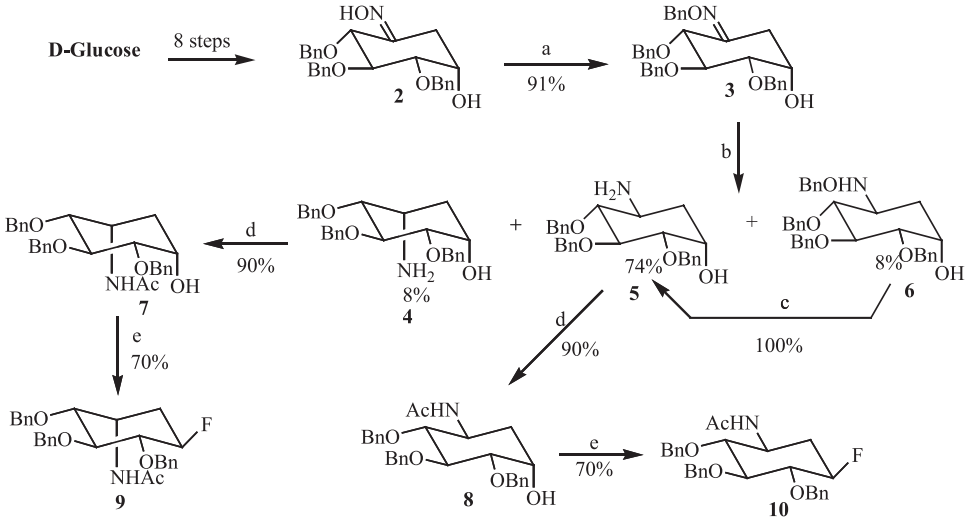
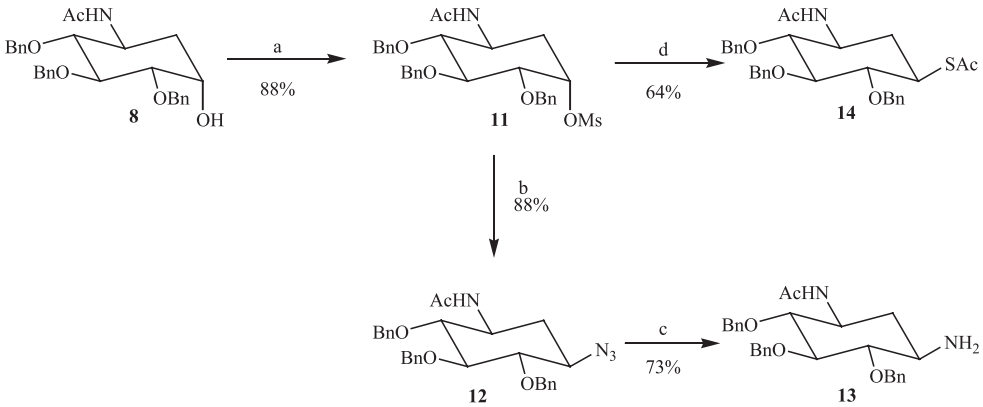


Scheme 1. a) $PhCH_2Cl$, NaH, DMF, 0°C, 24 h; b) $LiAlH_4$, THF, reflux, 12 h; c) $NaBH_4$, $NiCl_2.6H_2O$, MeOH, −10°C → rt, 8 h; d) Ac_2O, MeOH, rt, 4 h; e) DAST, CH_2Cl_2, 0°C → rt, 6 h.

in DMSO gave the compound **12** in 88% yield. The latter was reduced by triphenylphosphine in THF/H_2O giving the target compound **13** in 73% yield. Reaction of the mesylate **11** with potassium thioacetate in DMF afforded the desired compound **14** in 64% yield.

Oxidation of alcohol **8**[13] with PCC in dichloromethane furnished the cyclohexanone **15** in 86% yield (Scheme 3). Treatment of **15** with *O*-benzylhydroxylamine hydrochloride in pyridine afforded the *syn* benzyloxime **16** in quantitative yield, as a single isomer. The epi-deoxystreptamine **17**[14] was obtained in 60% yield by reduction of **16** with $LiAlH_4$ in



Scheme 2. a) MsCl, Py, 0°C → rt, 12 h; b) NaN_3, DMSO, 120°C, 48 h; c) PPh_3, THF, 0°C → rt, 24 h; d) KSAc, DMF, 100°C, 48 h.

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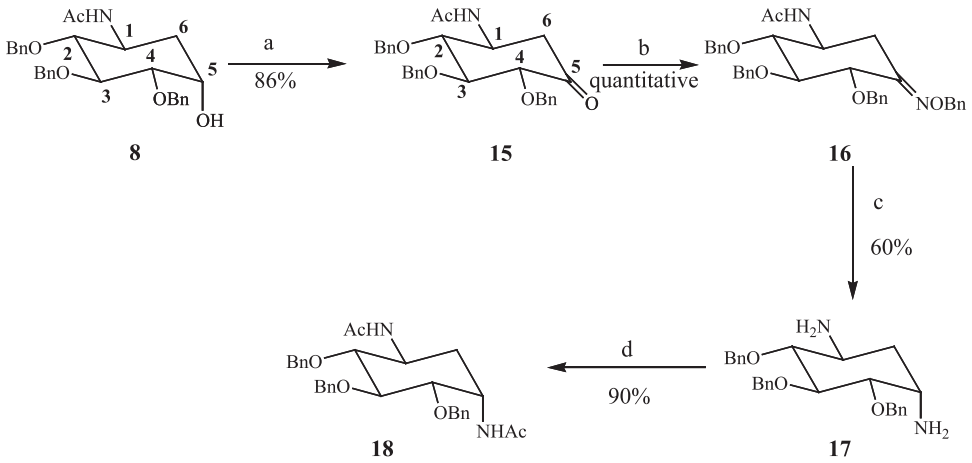

Scheme 3. a) PCC, CH_2Cl_2, rt, 48 h; b) $HCl.H_2NOBn$, Py, rt, 2 h; c) $LiAlH_4$, THF, reflux, 24 h; d) Ac_2O, Py, 0°C → rt, 8 h.

THF. Next, acetylation of **17** by treatment with acetic anhydride in pyridine produced the target compound **18**[14] in 90% yield.

The structures of all new compounds were unequivocally established by ^1H, COSY (^1H x ^1H) and ^{13}C NMR analyses. For practical purposes, atom number of all compounds, in their nomenclature and NMR analyses, is the same as that adopted for compounds **8** and **15** (Scheme 3).

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. ^1H NMR (200 and 400 MHz) and ^{13}C NMR (50.3 and 100.6 MHz) spectra were determined in deuterated chloroform or deuterated acetone containing *ca.* 1% tetramethylsilane as an internal standard on a Brucker DRX 200 and DRX 400 spectrometers. Coupling constants (J) are given in Hertz (Hz). The $[\alpha]_D$ were recorded on Perkin-Elmer 241-MC sodium absorption at 20°C. Infrared spectra were obtained on a Bomem FT IR MB-102 spectrometer in KBr pellets. Mass spectra (*m/z*) were recorded on atlas CH_4 or AEI MS9 spectrometers. Elemental analyses were carried at ''Laboratoire Central de Microanalyse du CNRS, ICSN, Gif sur Yvette, France.''

The progress of all reactions was monitored by thin-layer chromatography, which was performed on 2.0 cm X 6.0 cm aluminum sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under an ultraviolet light. For column chromatography, Merck silica gel (70–230 mesh) was used. Solvents used in the reactions were generally redistilled prior to use.

2-L-2,4,5/3 1-Benzyloximino-2,3,4-tri-*O*-benzyl-2,3,4,5-cyclohexanetetrol (3). To a mixture of **2** (1 g, 2.3 mmol) in DMF (10 mL) was added at 0°C a dispersion of NaH (0.11 g, 2.6 mmol) in mineral oil (60%), and then benzyl chloride (0.3 g, 2.4 mmol). The reaction mixture was stirred at 90°C for 3 h. Water was added (20 mL), and the resulting mixture was extracted with dichloromethane (3 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to furnish a crude residue. Purification by flash chromatography (hexane/ethyl acetate) yielded 1.1 g (91%) of benzyloxime **3** as a crystalline material, mp 82–84°C (hexane/ethyl acetate); $[\alpha]_D^{20}$ −16 (*c* 1.0; $CHCl_3$). ^{1}H NMR (200 MHz; $CDCl_3$) δ 2.70 (dd, 1H, H-6a, J_{6a-6e} = 15.0, J_{6a-5} = 5.0 Hz), 3.00 (dd, 1H, H-6e, J_{6e-5} = 7.0 Hz), 3.70 (s, 1H, H-4), 4.00 (m, 3H, H-2, H-3, H-5), 4.20–4.80 (m, 6H, 3C*H*$_2$Ph), 5.20 (s, 2H, NOC*H*$_2$Ph), 7.30 (m, 20H, Ph); ^{13}C NMR (50.3 MHz; $CDCl_3$) δ 27.7 (C-6), 66.6 (C-5), 71.5, 72.3, 73.7, 75.9 (*C*H$_2$Ph), 78.1, 79.0, 80.2 (C-2, C-3, C-4), 127.7, 127.9, 128.0, 128.3, 137.9, 138.1 (Ph), 153.6 (C1).

Anal. Calcd for $C_{34}H_{35}NO_5$: C, 75.95; H, 6.56; N, 2.60; Found: C, 75.76; H, 6.53; N, 2.50.

2-L-1,2,4,5/3 1-Amino-2,3,4-tri-*O*-benzyl-2,3,4,5-cyclohexanetetrol (4); 2-L-1, 3/2,4,5 1-amino-2,3,4-tri-*O*-benzyl-2,3,4,5-cyclohexanetetrol (5) and 2-L-1,3/2,4,5 1-benzylhydroxylamino-2,3,4-tri-*O*-benzyl-2,3,4,5-cyclohexanetetrol (6). To a solution of benzyloxime **3** (5.37 g, 10 mmol) in 30 mL of anhydrous THF was added $LiAlH_4$ (0.8 g, 21 mmol). The reaction mixture was stirred 12 h at reflux under an atmosphere of N_2. Methanol was added and the mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure. The crude residue was purified by chromatography yielding epimeric amines **4** (8%) and **5** (74%) (characterized as acetamide **7** and **8**) along with the benzylhydroxylamine **6** (8%). Compound **6** was characterized as its hydrochloride salt, dec.172–174°C (hexane/diethyl ether); $[\alpha]_D^{20}$ + 33 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.80 (m, 1H, H-6a), 2.60 (m, 1H, H-6e, J_{6a-6e} = 12.7 Hz), 3.35 (s, 1H, H-4), 3.80 (s, 3H, H-1, H-2, H-3), 4.05 (s, 1H, H-5), 4.50–4.90 (m, 6H, C*H*$_2$Ph), 5.20 (m, 2H, NOC*H*$_2$Ph), 7.00–7.40 (m, 20H, Ph); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ 28.0 (C-6), 58.1 (C-1), 65.4 (C-4), 77.7 (C-3), 82.5, 82.7 (C-2, C-5). MS (E. I): *m/z* 540 $[M + H]^+$.

Anal. Calcd for $C_{34}H_{37}NO_5$.HCl: C, 70.88; H, 6.47; N, 2.43; Found: C, 70.56; H, 6.51; N, 2.53.

2-L-1,2,4,5/3 1-Acetamido-2,3,4-tri-*O*-benzyl-2,3,4,5-cyclohexanetetrol (7). The amine **4** (866 mg, 2 mmol) was treated with acetic anhydride (408 mg, 4 mmol) in methanol (15 mL) for 4 h at rt. Then 15 mL of water was added and the mixture was extracted with dichloromethane (3 × 20 mL). The organic layer was concentrated furnishing a crude residue. Purification by column chromatography (hexane/ethyl acetate) gave 855 mg (90%) of compound **7** as an oil. $[\alpha]_D^{20}$ − 5 (*c* 2.7; CH_2Cl_2).

Anal. Calcd for $C_{29}H_{33}NO_5.H_2O$: C, 70.56; H, 7.15; N, 2.84; Found: C, 70.48; H, 6.91; N, 2.91.

2-L-1,3/2,4,5 1-Acetamido-2,3,4-tri-*O*-benzyl-2,3,4,5-cyclohexanetetrol (8). The amine **5** (866 mg, 2 mmol) was treated with acetic anhydride (408 mg, 4 mmol) in methanol (15 mL) for 4 h at rt. Then 15 mL of water was added and the mixture was

extracted with dichloromethane (3 × 20 mL). The organic layer was concentrated furnishing a crude residue. Purification by column chromatography (hexane/ethyl acetate) gave 855 mg (90%) of the compounds **8** as a solid, mp 194–196°C (hexane/ethyl acetate); $[\alpha]_D^{20}$ + 36 (*c* 1.1; $CHCl_3$). ^1H NMR (200 MHz; DMSO d_6) δ 1.20–1.60 (m, 1H, H-6a), 1.80–2.20 (m, 1H, H-6e), 3.40–3.50 (m, 2H, H-2, H-4), 3.50–3.80 (m, 1H, H-3), 4.10 (m, 2H, H-1, H-5), 4.40–5.00 (m, 6H, 3CH_2Ph), 7.00–7.60 (m, 15H, Ph), 8.43 (m, 2H, NH_2); ^{13}C NMR (50.3 MHz; DMSO d_6) δ 32.8 (C-6), 48.4 (C-5), 63.7 (C-1), 71.0, 74.3, 74.7 (*C*H_2Ph), 81.7, 82.8 (C-2, C-3, C-4), 127.8, 128.4, 138.9 (Ph).

Anal. Calcd for $C_{29}H_{33}NO_5$: C, 73.26; H, 6.95; N, 2.95; Found: C, 72.96; H, 6.99; N, 2.90.

Conversion of 6 in 5. To a solution of compound **6** (827 mg, 1.43 mmol) in methanol (30 mL) was added slowly 1.36 g (5.7 mmol) of $NiCl_2.6H_2O$ and then 1.63 g (42.8 mmol) of $NaBH_4$ at −10°C. The resulting mixture was stirred at this temperature for 8 h. The solvent was removed at reduced pressure and the residue was purified by flash chromatography to furnish 662 mg of the compound **5** (quantitative yield), characterized as acetamide **8**.

2-L-1,2,4/3,5 1-Acetamido-5-fluoro-2,3,4-tri-*O*-benzyl-2,3,4-cyclohexanetriol (9). A mixture of compound **7** (475 mg, 1 mmol) and DAST (0.4 mL, 3 mmol) in dichloromethane (20 mL) was stirred at 0°C for 4 h and at rt for further 2 h. Then, was added 5 mL of water and this mixture was extracted with dichloromethane (3 × 20 mL). The organic layer was submitted to the usual work-up furnishing a crude residue. Purification by column chromatography (hexane/ethyl acetate) yielded the compound **9** (70% yield). mp 73–75°C (hexane/ethyl acetate); $[\alpha]_D^{20}$ − 6 (*c* 1.3; CH_2Cl_2). ^1H NMR (400 MHz; C_6D_6) δ 0.67 (m, 1H, H-6a), 0.95 (s, 3H, CH_3), 1.85 (m, 1H, H-6e), 2.62 (dd, 1H, H-2, J_{2-1} = 4.7, J_{2-3} = 9.0 Hz), 2.77 (m, 1H, H-4), 2.98 (t, 1H, H-3, J_{3-4} = 8.5 Hz), 3.90 (m, 1H, H-1), 4.08 (m, 1H, H-5, J_{5-F} = 49, J_{5-4} = 8.5, J_{5-6e} = 3.5, J_{5-6a} = 9.8 Hz), 3.63–4.26 (m, 6H, CH_2Ph), 5.20 (d,1H, NH, J_{NH-1}= 6.9 Hz), 6.44–6.73 (m, 15H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23,3 (CH_3), 30.5, 30.7 (C-6), 44.2, 44.4 (C-1), 79.3 (C-2), 80.0, 80.1 (C-3), 82.8, 83.0 (C-4), 90.3, 92.1 (C-5,J_{5-F} = 177), 170.7 (C═O).

Anal. Calcd for $C_{29}H_{32}NO_4F$: C, 72.93; H, 6.75; N, 2.93; Found: C, 72.56; H, 6.77; N, 2.78.

2-L-1,3,5/2,4 1-Acetamido-5-fluoro-2,3,4-tri-*O*-benzyl-2,3,4-cyclohexanetriol (10). Compound **10** was prepared from **8** as described for the preparation of fluoride **9** from **7**. Yield: 70%. mp 169–171°C (hexane/ethyl acetate); $[\alpha]_D^{20}$ + 20 (*c* 0.4; $CHCl_3$). ^1H NMR (400 MHz; $CDCl_3$) δ 1.44 (m, 1H, H-6a, J_{6a-6e} = 12 Hz), 2.49 (m, 1H, H-6e), 3.35 (dd, 1H, H-2, J_{2-3} = 8.6, J_{2-1} = 10 Hz), 3.55 (t, 1H, H-3, J_{3-4} = 8.6 Hz), 3.60 (m, 1H, H-4, J_{4-5} = 8.5 Hz), 3.74 (m, 1H, H1), 4.60 (m, 1H, H-5, J_{5-F} = 49, J_{5-6a} = 9.3 Hz), 4.60–4.92 (m, 7H, CH_2Ph, NH), 7.25–7.40 (m, 15H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.3 (CH_3), 33.0, 33.2 (C-6), 47.1, 47.2 (C-1), 80.9 (C-2), 82.8, 82.9 (C-3), 83.7, 83.9 (C-4), 90.5, 92.3 (C5, J_{5-F} = 179 Hz), 169.9 (C═O).

Anal. Calcd for $C_{29}H_{32}NO_4F.1/2\ H_2O$: C, 71.58; H, 6.83; N, 2.83; Found: C, 71.87; H, 6.81; N, 2.86.

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2-L-1,3/2,4,5 1-Acetamido-2,3,4-tri-*O*-benzyl-5-*O*-methanesulfonyl-2,3,4,5-cyclohexanetetrol (11). To a solution of **8** (237 mg, 0.5 mmol) in pyridine (10 mL) was added 0.1 mL (1.4 mmol) of methanesulfonyl chloride. The mixture was stirred at 0°C for 12 h. Then 15 mL of water was added and this mixture was extracted with dichloromethane (3 × 20 mL). The organic layer was concentrated and the residue purified by flash cromatography to furnish 241 mg of **11** (88% yield). mp 175–177°C (hexane/ethyl acetate); $[\alpha]_D^{20}$ + 75 (*c* 0.7; $CHCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.72 (dt, 1H, H-6a), 1.75 (s, 1H, C*H*$_3$CONH), 2.42 (dt, 1H, H-6e, J_{6e-6a} = 14.6, $J_{6e-1} = J_{6e-5}$ = 4.3 Hz), 3.07 (s, 3H, C*H*$_3$SO$_3$R), 3.53 (dd, 1H, H-4, J_{4-3} = 9.2, J_{4-5} = 2.9 Hz), 3.57 (dd, 1H, H-2, J_{2-1} = 10, J_{2-3} = 9.0 Hz), 3.85 (t, 1H, H-3), 3.88 (m, 1H, H1), 4.60–4.93 (m, 6H, C*H*$_2$Ph), 5.13 (m, 1H, H-5), 5.20 (d, 1H, NH), 7.27–7.38 (m, 15H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.5 (*C*H$_3$CO), 31.6 (C-6), 39.3 (*C*H$_3$SO$_3$R), 48.4 (C-1), 76.7, 80.2, 80.7, 81.8 (C-2, C-3, C-4, C-5), 170.3 (C═O).

Anal. Calcd for $C_{30}H_{34}NO_7S$: C, 65.20; H, 6.20; N, 2.53; Found: C, 65.03; H, 6.47; N, 2.41.

2-L-1,3,5/2,4 1-Acetamido-5-azido-2,3,4-tri-*O*-benzyl-2,3,4-cyclohexanetriol (12). A solution of compound **11** (240 mg, 0.43 mmol) in DMSO (5 mL) was treated with sodium azide (113 mg, 1.74 mmol) at 120°C for 48 h. After addition of water (5 mL), the precipitate was collected and washed with water. This solid was recrystallized from a mixture of diethyl ether/hexane to gave 189 mg of **12** (88% yield). mp 211–213°C; $[\alpha]_D^{20}$ + 63 (*c* 0.9; $CHCl_3$). ^{1}H NMR (400 MHz; C_6D_6) δ 0.58 (q, 1H, H-6a, J_{6a-6e} = 13 Hz), 1.68 (dt, 1H, H-6e, $J_{6e-5} = J_{6e-1}$ = 4.5 Hz), 1.86 (s, 3H, CH_3), 2.53 (m, 1H, H-5, J_{5-4} = 9.8 Hz), 2.73 (dd, 1H, H-2, J_{2-1}= 10.2, J_{2-3} = 9.3 Hz), 2.88 (t, 1H, H-4, J_{4-3} = 9.8 Hz), 3.01 (t, 1H, H-3), 3.46 (m, 1H, H-1), 3.98 (d, 1H, NH, J_{NH-1} = 7.2 Hz), 4.17–4.57 (m, 6H, C*H*$_2$Ph), 6.70–7.10 (m, 15H, Ph); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ 23.3 (CH_3), 33.1 (C-6), 48.8 (C-1), 60.8 (C-5), 81.2 (C-2), 84.6, 84.9 (C-3, C-4), 169.9 (C═O).

Anal. Calcd for $C_{29}H_{31}N_4O_4$: C, 69.72; H, 6.26; N, 11.21; Found: C, 69.61; H, 6.46; N, 11.04.

2-L-1,3,5/2,4 1-Acetamido-5-amino-2,3,4-tri-*O*-benzyl-2,3,4-cyclohexanetriol (13). To a solution of **12** (300 mg, 0.6 mmol) in anhydrous THF (5 mL) was added PPh_3 (312 mg, 1.2 mmol). The mixture was stirred for 1 h at rt and water (1 mL) was added. After 12 h solvents were removed and the crude residue was purified by column chromatography (hexane/ethyl acetate) yielding 207 mg (73%) of **13**. Dec. 220–227°C (hexane/ethyl acetate); $[\alpha]_D^{20}$ + 22 (*c* 2.3; CH_2Cl_2).

Anal. Calcd for $C_{29}H_{34}N_2O_4$.HCl.H_2O: C, 65.83; H, 7.05; N, 5.29; Found: C, 65.75; H, 6.91; N, 5.25.

2-L-1,3,5/2,4 1-Acetamido-5-thioacetyl-2,3,4-tri-*O*-benzyl-2,3,4-cyclohexanetriol (14). A mixture of 180 mg (0.33 mmol) of **11** and 75 mg (0.65 mmol) of potassium thioacetate in 25 mL of DMF was stirred at 100°C for 48 h. Water (30 mL) was added, and the mixture was extracted with diethyl ether (4 × 30 mL). The organic layer was submitted to the usual work-up furnishing a crude residue. Purification by column chromatography (hexane/ethyl acetate) gave 110 mg (64%) of compound **14**. Dec. 204–206°C

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(hexane/ethyl acetate); $[\alpha]_D^{20}$ + 30 (*c* 1.4; $CHCl_3$). ^1H NMR (400 MHz; $CDCl_3$) δ 1.50 (q, 1H, H-6a), 1.71 (s, 3H, CH_3CON), 2.24 (s, 3H, CH_3COS), 2.35 (dt, 1H, H-6e, J_{6e-6a} = 13.0 Hz), 3.40 (dd, 1H, H-2, J_{2-1} = 10, J_{2-3} = 9.1 Hz), 3.50 (m, 2H, H-4, H-5, J_{4-3} = J_{4-5} = 9.0 Hz), 3.64 (t, 1H, H-3), 3.75 (m, 1H, H-1), 4.60–4.93 (m, 6H, CH_2Ph), 4.95 (d, 1H, NH, J_{NH-1} = 7.0), 7.25–7.37 (m, 15H, Ph); ^{13}C NMR(100.6 MHz; $CDCl_3$) δ 23.4 (*C*H_3CONH), 30.7 (*C*H_3COS), 33.9 (C-6), 43.4 (C-5), 50.8 (C-1), 81.3, 82.3, 86.4 (C-2, C-3, C-4), 169.8 (HNC═O), 194.4 (SC═O).

Anal. Calcd for $C_{31}H_{35}NO_5S$: C, 69.77; H, 6.61; N, 2.63; Found: C, 69.85; H, 6.91; N, 2.66.

2-L-1,3/2,4 1-Acetamido-5-oxo-2,3,4-tri-*O*-benzyl-2,3,4-cyclohexanetriol (15). To a solution of acetamide **8** (475 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added PCC (1.08 g, 5 mmol). The reaction mixture was stirred at rt for 48 h, water was added (20 mL) and the mixture was extracted with diethyl ether (3 × 10 mL). The organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to furnish the crude residue, that was purified by flash chromatography (ethyl acetate), yielding 407 mg (86%) of crystalline **15**. mp 200–202°C (hexane/ethyl acetate); $[\alpha]_D^{20}$ + 29 (*c* 1.5; $CHCl_3$); ^1H NMR (200 MHz; $CDCl_3$) δ 2.57 (dd,1H, H-6a, J_{6a-6e} = 14.0, J_{6a-5} = 10.0 Hz), 3.00 (dd,1H, H-6e, J_{6e-6a} = 14.0, J_{6a-5} = 5.0 Hz), 3.83 (m, 2H, H-2, H-4), 4.00 (m, 1H, H-3), 4.10 (m, 1H, H-5), 4.40–5.00 (m, 6H, 3CH_2Ph), 5.60 (d, 1H, NH, J_{NH-5} = 7.0 Hz), 7.30 (m, 15H, Ph); ^{13}C NMR (50.3 MHz; $CDCl_3$) δ 23.4 (*C*H_3CONH), 41.8 (C-6), 49.3 (C-1), 73.3–75.1 (3 *C*H_2Ph), 78.9 (C-3), 82.9 (C-2), 84.8 (C-4), 128.0–138.0 (Ph), 170.1 (HNC═O), 204.1 (C═O). MS (E.I): *m/z* 368 $[M + H]^+$.

Anal. Calcd for $C_{29}H_{31}NO_5$: C, 73.55; H, 6.59; N, 2.96; Found: C, 73.25; H, 6.59; N, 3.02.

2-L-1,3/2,4 1-Acetamido-5-benzyloximino-2,3,4-tri-*O*-benzyl-2,3,4-cyclohexanetriol (16). To a solution of **15** (473 mg, 1 mmol) in methanol (5 mL) and pyridine (1 mL) was added *O*-benzylhydroxylamine hydrochloride (240 mg, 1.5 mmol). The reaction mixture was stirred during 2 h at rt. The solvent was removed under reduced pressure, and water was added to the residue. After extraction with dichloromethane the organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to furnish **16** (570 mg, quantitative yield). The product was purified by recrystallization (hexane/diethyl ether), mp 176–178°C; $[\alpha]_D^{20}$ − 4 (*c* 0.5; $CHCl_3$); ^1H NMR (400 MHz; $CDCl_3$) δ 1.60 (s, 3H, CH_3), 2.80 (dd, 1H, H-6a, J_{6a-6a} = 14, J_{6a-1} = 4.0 Hz), 2.70 (dd, 1H, H6e, J_{6e-1} = 5.2 Hz), 3.60 (t, 1H, H-2, J_{2-3} = 2.8 Hz), 4.00 (t, 1H, H-3), 4.10 (d, 1H, H-4, J_{4-3} = 2.8 Hz), 4.41–4.45 (m, 1H, H-1), 6.02 (d, 1H, NH, J_{1-NH} = 8.0 Hz), 7.21–7.31 (m, 20H, Ph); ^{13}C NMR (50.3 MHz; $CDCl_3$) δ 23.9 (*C*H_3CONH), 25.2 (C-6), 48.7 (C-1), 71.1–73.2 (3 *C*H_2Ph), 76.6 (C═NO*C*H_2Ph), 77.1 (C-2), 77.2 (C-3), 80.1 (C-4), 128.2–138.8 (Ph), 154.6 (C-5), 170.1 (CO).

Anal. Calcd for $C_{36}H_{38}N_2O_5.1/2\ H_2O$: C, 73.57; H, 6.69; N, 4.77; Found: C, 73.56; H, 6.71; N, 4.65.

2-L-1,3/2,4,5 1,5-Diamino-2,3,4-tri-*O*-benzyl-2,3,4-cyclohexanetriol (17). To a solution of oxime **16** (290 mg, 0.5 mmol) in anhydrous THF (20 mL) was added $LiAlH_4$ (152 mg; 4 mmol). The reaction mixture was stirred during 24 h at reflux.

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The reaction mixture was cooled to 0°C and water was added slowly. After filtration over a pad of Celite the solvent was evaporated and the residue was purified by flash chromatography (CH_2Cl_2/MeOH) to afford 130 mg of the desired amine (60% yield) as an oil; ^{1}H NMR (400 MHz; Acetone-d_6) δ 1.39 (ddd, 1H, H-6a, J_{6a-6e} = 13.6, J_{6a-1} = 11.0, J_{6a-5} = 3.0 Hz), 1.76 (dt, 1H, H-6e, J_{6e-1} = J_{6e-5} = 3.6 Hz), 2.81 (s, 4H, NH_2), 3.20 (ddd, 1H, H-1, J_{1-2} = 9.2 Hz), 3.39 (t, 1H, H-3, J_{3-2} = J_{3-4} = 9.2 Hz), 3.61 (dd, 1H, H-4, J_{4-5} = 3.6 Hz), 4.07 (m, 1H, H-5), 4.19 (t, 1H, H-2), 4.60–5.00 (m, 6H, CH_2Ph), 7.20–7.35 (m, 15H, Ph); ^{13}C NMR (100.6 MHz; Acetone-d_6) δ 34.3 (C-6), 56.0, 56.7 (C-1,C-5), 72.8, .75.5, 75.6 (3 *C*H_2Ph), 83.9, 85.2, 86.7, (C-2, C-3, C-4), 127.8–140.7 (Ph).

Anal. Calcd for $C_{27}H_{32}N_2O_3$: C, 74.97; H, 7.46; N, 6.47; Found: C, 74.67; H, 7.66; N, 10.87.

2-L-1,3/2,4,5 1,5-Diacetamido-2,3,4-tri-*O*-benzyl-2,3,4-cyclohexanetriol (18). The amine **17** (216 mg, 0.5 mmol) was treated with acetic anhydride (204 mg, 2.0 mmol) in pyridine (10 mL) for 4 h at rt. Then, 15 mL of water were added and the mixture was extracted with dichloromethane (3 × 20 mL). The organic layer was concentrated furnishing a crude residue. Purification by column chromatography (ethyl acetate/methanol) gave 230 mg of the compound **18** (90%) as an oil. ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.57 (dt, 1H, H-6a, J_{6a-6e} = 14, J_{6a-1} = 10.4 Hz), 2.53 (dt, 1H, H-6e, J_{6e-1} = J_{6e-5} = 3.6 Hz), 3.44 (dd, 1H, H-3, J_{3-2} = 8.0, J_{3-4} = 10.0 Hz), 3.63 (m, 2H, H-2, H-4), 3.81 (ddd, 1H, H-1, J_{1-2} = 9.6 Hz), 4.35 (m, 1H, H-5), 4.50–5.00 (m, 6H, CH_2Ph), 7.15–7.35 (m, 15H, Ph); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ 22.4, 23.6 (CH_3), 30.1 (C-6), 46.3 (C-5), 55.5 (C-1), 71.9, 75.7, 75.9 (*C*H_2Ph), 80.0, 80.2, 83.2 (C-2, C-3, C-4), 127.6-138.8 (Ph), 170.9, 171.1 (C═O).

Anal. Calcd for $C_{31}H_{36}N_2O_5$: C, 72.09; H, 6.98; N, 5.43; Found: C, 72.01; H, 6.92; N, 5.64.

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