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Synthesis and transformations of (1*R*,2*R*,3*S*,4*R*)-4-*O*-benzylhydroxylamino-2,3-*O*-isopropylidene-1,2,3-cyclopentanetriol: synthesis of (1*S*,2*R*,3*S*,4*R*)-4-amino-2,3-*O*-isopropylidene-1,2,3-cyclopentanetriol

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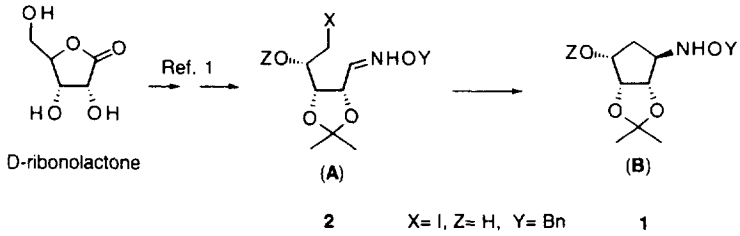
Abstract: The synthesis and some new transformations of (1*R*,2*R*,3*S*,4*R*)-4-*O*-benzylhydroxylamino-2,3-*O*-isopropylidene-1,2,3-cyclopentanetriol are described. Particularly relevant is the synthesis of (1*S*,2*R*,3*S*,4*R*)-4-amino-2,3-*O*-isopropylidene-1,2,3-cyclopentanetriol **7** from D-ribonolactone, *via* intermediate **1**, in eight steps and 12% overall yield. © 1997 Elsevier Science Ltd

Introduction

Previously, we have described new, simple and chiral approaches for the synthesis of aminocyclopentitol derivatives.[1,2] These compounds are valuable intermediates for the synthesis of pharmacologically important molecules such as carbocyclic nucleosides.[3]

Strategies for the preparation of enantiomerically pure aminocyclopentanetriols are scarce and limited to the resolution of racemates by physical[4] or enzymatic[5] methods and to the synthesis from carbohydrates by the nitromethane reaction.[6] A general and enantiospecific synthetic approach is still lacking. We have recently described a new strategy for solving this problem. Our method for the preparation of enantiomerically pure 4-amino-1,2,3-cyclopentanetriols is based on the tributyltin hydride mediated free radical cyclization of conveniently functionalized precursors (**A**: X=halogen; Y=CH_3, $CH_2C_6H_5$), derived from D-ribonolactone, leading to the key intermediates (**B**)[1] (Scheme 1).



Scheme 1.

The 5-exo-trig free radical cyclization of 5-bromo-5-deoxy-D-ribose derivatives, using α,β-unsaturated esters as radical traps, was first reported by Wilcox in 1985.[7a] Bartlett[7b] later described the use of carbohydrate-derived oxime ethers as efficient radical traps when compared to aldehydes[8] for similar ring closures. Both papers moved us to explore the synthesis and carbocyclization of 5-bromo-5-deoxy-2,3-*O*-isopropylidene-D-ribose-*O*-benzyl oxime ether derivatives.[1,9] This protocol should provide simple and ready chiral access to the 4-amino-1,2,3-cyclopentanetriols (**B**; Scheme 1). This structural motive is found in interesting, recently discovered antiviral agents.[10]

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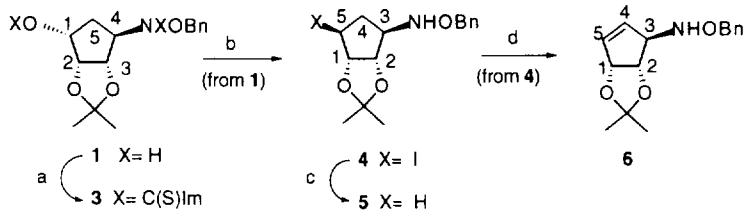
We report here in full some results concerning the free radical cyclization of precursor **2**[1a] and some new transformations of compound **1** (Scheme 1).

Results and discussion

Compound **2** has been prepared and cyclized as described, but we have recently improved the ring closure step. When radical precursor **2** was reacted with tributyltin hydride (2.4 equiv) and AIBN (0.1 equiv), we found that compound **1** was obtained as the sole isomer, in an increased chemical yield (75%) compared to the previously reported (26%).[1b] With this compound in hand, we attempted several selected transformations.

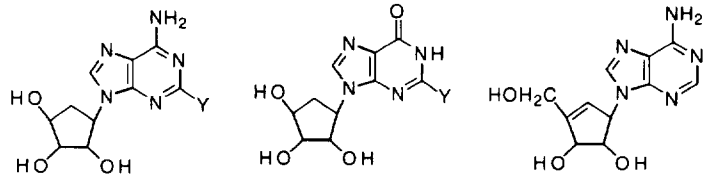
With the aim at obtaining the deoxygenated product at C-1, we synthesized the *N,O*-thiocarbonyldiimidazole **3** (Scheme 2) by standard methodology. This compound was very unstable and after spectroscopic analysis (^{1}H and ^{13}C NMR) was submitted to further reaction. The free radical reduction with tributyltin hydride gave a complex reaction mixture and we were unable to detect and isolate the desired reduced product. The C5 iodide **4** (Scheme 2) was, however, found to be a more suitable precursor. This compound was obtained in the usual iodination conditions (I_2, Ph_3P, imidazole), in moderate yield and with complete inversion of the configuration. This was evident after analysis of the ^{1}H NMR spectrum: a new signal appears at 4.92 ppm (d, $J_{2,3}$=6.1 Hz, 1 H) with $J_{5,1}$=0 Hz, corresponding to H1. These data suggest a *trans* arrangement between H5 and H1.[1b] In the ^{13}C NMR spectrum of compound **4** we analyzed C5 at 24.9 ppm; in agreement with this, an HMQC analysis showed that the signal at 3.62 ppm (m, 1H) corresponded to H1 and was correlated with the signal at 24.9 in the ^{13}C NMR spectrum. Tributyltin hydride reduction of compound **4** gave the deoxygenated product **5** (Scheme 2) in 46% yield. Using the iodide **4** as starting material, reaction with DBU in acetonitrile gave the unsaturated aminocyclitol **6** (Scheme 2) in good yield (91%). The ^{1}H NMR spectrum of this compound showed the new vinyl protons at 6.02 and 5.76 ppm; in the ^{13}C NMR spectrum we detected the corresponding carbons (C4 and C5) at 136.3 and 132.0 ppm.



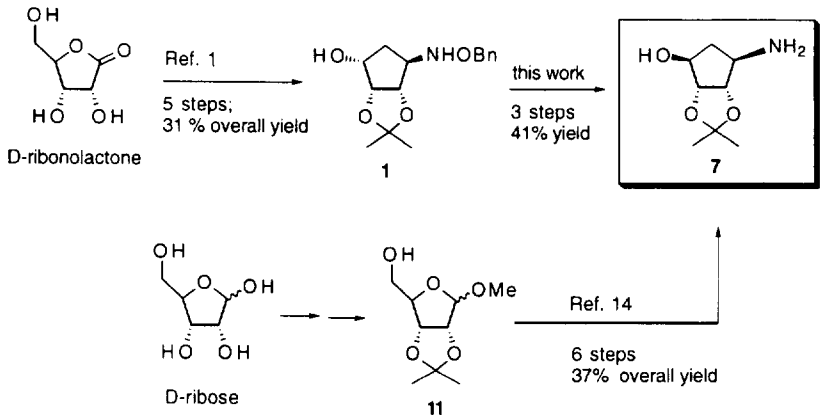
Scheme 2. Reagents: a. 1,1′-thiocarbonyldiimidazole, CH_2Cl_2 (42%); b. Ph_3P, I_2, imidazole, toluene (69%); c. $HSnBu_3$, AIBN, toluene (46%); d. DBU, acetonitrile (91%).

Continuing with the transformations of compound **1**, we directed our attention to (1*S*,2*R*,3*S*,4*R*)-4-amino-2,3-*O*-isopropylidene-1,2,3-cyclopentanetriol **7**[11] (Scheme 3). This compound is a key intermediate in the synthesis of the racemic 5′-noraristeromycin derivatives **8**,**9**[12] (in three steps) and neplanocin A (**10**)[12] (in ten steps; 11% overall yield). Although aminocyclitol **7** is known in the racemic form,[13] only very recently the first asymmetric synthesis of **7** has been reported in six steps and 37% overall yield from intermediate **11** derived from D-ribose (Scheme 3).[14]

The essential aspects of the conversion of (1*R*,2*R*,3*S*,4*R*)-4-*O*-benzylhydroxylamino-2,3-*O*-isopropylidene-1,2,3-cyclopentanetriol **1** into the aminocyclitol **7** are shown in Scheme 4. Mitsunobu inversion[15] of the free, secondary hydroxyl group, cleanly performed using *p*-nitrobenzoic acid under standard conditions, afforded compound **12**. The inversion at C1 was clearly shown in the ^{1}H NMR spectrum: the more deshielded H–CO-proton (H1) appeared at 5.31 ppm as a doublet showing a *trans* arrangement between the two vicinal protons H2 ($J_{1,2}$=0 Hz) and H5 ($J_{1,5}$=0 Hz), and a vicinal coupling constant ($J_{1,5'}$=5.5 Hz) with the only *cis* H5′ proton. Attempted total and simultaneous reduction of the ester moiety and cleavage of the N–O bond in compound **12**, using



8 (Y= H, NH_2) 9 (Y= H, NH_2) 10



Scheme 3

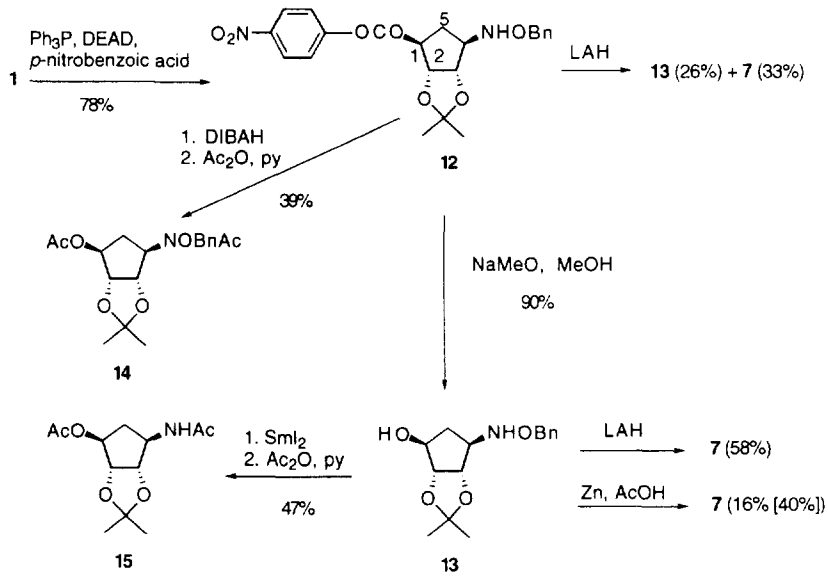
lithium aluminium hydride (LAH) in THF, at reflux, gave a mixture of *O*-benzyl-hydroxylamine **13** (26% yield) and compound **7** (33% yield). This compound showed analytical data according to this structure and analogous spectroscopic values to those recorded in literature.[13,14] Compound **13** could also be prepared in 90% yield by sodium methoxide/methanol catalyzed hydrolysis of ester **12**. Using DIBAH as reducing agent, product **12** also gave the desired alcohol **13**, which was difficult to separate from *p*-nitrobenzyl alcohol; the crude reaction mixture was fully acetylated to give compound **14** in 39% overall yield from compound **12**. We have also analyzed our recently described method for the cleavage of N–O bonds using samarium diiodide.[16] Under the established conditions the reaction proceeded as expected, but we found difficulties in the final purification of product **7**, probably due to the formation of complexes with samarium salts. However, when the crude reaction product was treated with acetic anhydride in pyridine at room temperature, the peracetylated material **15** was isolated in 47% overall yield from **13**. The reduction of compound **13** with LAH at reflux in THF gave compound **7** in 58% yield. Finally, we tested the zinc/acetic acid method[13] that has proven its efficiency in related processes.[14] Using diethyl ether as solvent, we obtained the desired aminoalcohol **7** in 16% yield (40% taking into account the recovered starting material).

In summary, we have described a new method for the preparation of (1*S*,2*R*,3*S*,4*R*)-4-amino-2,3-*O*-isopropylidene-1,2,3-cyclopentanetriol from D-ribonolactone in 8 steps and 12% overall yield (route: **12**→**13** (LAH)→**7**; Scheme 4). This synthetic alternative complements the methodology described by Gallos.[14]

Experimental

General methods

Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5554). Detection was done by UV (254 nm) followed by charring with



Scheme 4.

sulfuric–acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous $MgSO_4$ was used to dry organic solutions during workups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using Kieselgel 60 (230–400 mesh, Merck) and hexane–ethyl acetate mixtures as eluent. Optical rotations were determined with a Perkin–Elmer 257 instrument. ^1H and ^{13}C NMR spectra were recorded with a Varian VXR-300S spectrometer, using tetramethylsilane as internal standard.

(1R,2S,3S,4R)-4-O-Benzylhydroxyl(N-thiocarbonylimidazolyl)amino-2,3-O-isopropylidene-1-O-thiocarbonylimidazolyl-1,2,3-cyclopentanetriol **3**

To a a solution of compound **1** (219 mg, 0.79 mmol, 1.0 equiv) in dry THF (7 mL), at reflux, 1,1′-thiocarbonyldiimidazole (670 mg, 3.9 mmol, 5 equiv) was added. The mixture was further refluxed for 26 h. The reaction was cooled and the solvent was evaporated. The residue was submitted to chromatography (hexane/AcOEt 20%), giving compound **3** (166 mg, 42%) as an oil: ^1H NMR ($CDCl_3$) δ 8.31 (s, 1 H, Im), 8.08 (s, 1 H, Im), 7.60 (s, 1 H, Im), 7.43 (s, 1 H, Im), 7.39–7.23 (m, 5 H, aromat), 7.06 (s, 1 H, Im), 7.00 (s, 1 H, Im), 5.90 (dd, 1 H, *J*=5.4 Hz, 8.2 Hz, H1), 5.13 (m, 1 H, H4), 4.91 (t, 1 H, *J*=5.5 Hz, H2), 4.80 (d, 1 H, *J*=5.7 Hz, H3), 4.78 (d, 2 H, *J*=9.7 Hz, OCH_2Ph), 2.58 (m, 2 H, 2 H5), 1.40 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 183.8, 138.4, 137.4, 132.6, 131.4, 128.8, 111.9, 82.9, 78.7, 74.8, 63.4, 63.3, 32.3, 26.7, 24.9. This compound was very unstable and we were unable to obtain a good elemental analysis. The reaction with tributyltin hydride was performed with crude **3**, but a complex reaction resulted.

(1S,2S,3R,5S)-4-O-Benzylhydroxylamino-5-iodo-2,3-O-isopropylidene-1,2-cyclopentanediol **4**

To a solution of compound **1** (46 mg, 0.17 mmol) in toluene (8 mL), at reflux, triphenylphosphine (131 mg, 0.5 mmol), imidazole (34 mg, 0.5 mmol) and iodine (84 mg, 0.33 mmol) were added and heated for 24 h. The solution was cooled, diluted with ethyl acetate, washed with a 10% aqueous solution of sodium bicarbonate, a 10% aqueous solution of sodium thiosulfate and brine. After drying over sodium sulfate, the solvent was evaporated and the residue purified by chromatography (hexane:ethyl acetate, 85:15) to give product **4** (44 mg, 69% yield) as an oil: $[\alpha]_D^{25}$ +13.2 (*c* 4.1, $CHCl_3$); IR (film) υ 3260, 2990, 1500, 1460, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.28 (m, 5 H,

Ph), 5.65 (br s, 1 H, NH), 4.92 (d, 1 H, J=6.1 Hz, H1), 4.73 (s, 2 H, OCH_2Ph), 4.55 (d, 1 H, J=6.1 Hz, H2), 4.09 (d, 1 H, J=6.1 Hz, H3), 3.62 (br m, 1 H, H5), 2.77 (ddd, 1 H, J=6.1, 7.0, 14.9 Hz, H4), 2.14 (d, 1 H, J=14.9 Hz, H4′), 1.43 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.2, 129.2, 128.9, 128.4, 112.5, 90.4, 84.1, 76.9, 67.8, 40.0, 27.5, 25.2, 24.9; MS (70 eV) *m/z* 389 (1), 374 (1), 262 (1), 204 (15), 187 (1), 125 (1), 96 (3), 91 (100), 77 (7), 70 (4), 65 (6), 59 (5), 43 (9). Anal. Calcd for $C_{15}H_{20}INO_3$: C, 46.29; H, 5.18; N, 3.60. Found: C, 46.01; H, 5.11; N, 3.48.

*(1*R*,2*S*,3*R*)-3-*O*-Benzylhydroxylamino-1,2-*O*-isopropylidene-1,2-cyclopentanediol* **5**

Compound **4** (90 mg, 0.23 mmol, 1.0 equiv) was dissolved in dry toluene (5 mL) and the solution was deoxygenated for 30 min. Then, $HSnBu_3$ (9.4 μL, 0.35 mmol, 1.5 equiv) and AIBN (6.8 mg, 0.04 mmol, 0.2 equiv) were added at reflux. After 3 h the same quantities of $HSnBu_3$ and AIBN were added, and the mixture was heated at reflux for 30 min. The mixture was cooled and the solvent was removed. The residue was suspended in a mixture (1:1) of Et_2O and a 15% aqueous solution of KF; the mixture was stirred overnight. The organic phase was separated and dried ($MgSO_4$). The solvent was eliminated and the residue purified by chromatography (hexane/ethyl acetate, 20%) to give product **5** (28 mg, 46%) as a viscous oil: $[\alpha]_D^{25}$ −21.7 (*c* 2.3, $CHCl_3$); IR (KBr) υ 3260, 2990, 2940, 1460, 1385, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37–7.27 (m, 5 H, aromatic), 5.32 (br d, J=4.1 Hz, 1 H, NH), 4.68 (s, 2 H, OCH_2Ph), 4.64 (m, 1 H, H1), 4.35 (d, J=5.6 Hz, 1 H, H2), 3.51 (br t, J=4.1 Hz, 1 H, H3), 1.85 (m, 4 H, 2 H4 and 2 H5), 1.44 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 137.7, 128.6, 128.4, 127.9, 109.6, 83.2, 80.7, 76.7, 66.7, 31.0, 26.6, 26.3, 23.9; MS (70 eV) *m/z* 264 (1), 248 (3), 172 (1), 157 (2), 149 (1), 140 (1), 114 (3), 105 (1), 98 (5), 91 (100), 77 (6), 65 (5), 59 (5), 43 (8). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.22; H, 7.88; N, 5.04.

*(1*R*,2*S*,3*R*)-3-*O*-Benzylhydroxylamino-1,2-*O*-isopropylidene-cyclopent-4-en-1,2-diol* **6**

To a solution of compound **4** (79 mg, 0.20 mmol, 1.0 equiv) in acetonitrile (14 mL), DBU (38 μL, 0.25 mmol, 1.25 equiv) was added; after 7 h the mixture was heated at reflux, and the more DBU (7.5 μL, 0.05 mmol, 0.25 equiv) was added and the reaction was heated for a further 7 h. The reaction was cooled and the solvent was removed; the residue was purified by chromatography (hexane/AcOEt 10%) giving product **6** as an oil: $[\alpha]_D^{25}$ −130 (*c* 4.2, $CHCl_3$); IR (film) υ 3260, 3060, 3040, 2990, 1750, 1500, 1455, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37–7.34 (m, 5 H, Ph), 6.02 (dd, 1 H, J=5.8, 1.6 Hz, H5), 5.76 (dt, 1 H, J=5.8, 0.8 Hz, H4), 5.49 (br s, 1 H, NH), 5.20 (ddd, 1 H, J=5.8, 1.6, 0.8 Hz, H1), 4.70 (s, 2 H, OCH_2Ph), 4.61 (d, 1 H, J=5.8 Hz, H2), 4.16 (d, 1 H J=0.8 Hz, H3), 1.42 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.2, 136.3, 132.0, 129.0, 128.9, 128.4, 111.3, 85.1, 82.5, 77.2, 72.8, 27.8, 26.1; MS (70 eV) *m/z* 262 (1), 246 (3), 204 (3), 186 (9), 96 (5), 92 (13), 91 (100), 81 (19), 77 (5), 65 (5), 59 (2), 51 (2), 43 (9). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.77; H, 7.20; N, 5.11.

*Free radical cyclization of 5-deoxy-5-iodo-2,3-*O*-isopropylidene-D-ribose* O*-benzyl oxime ether* **2**

Compound **2** (340 mg, 0.84 mmol, 1.0 equiv) was dissolved in dry toluene (42 mL, 0.02 M) and the solution was deoxygenated for 30 min with argon. Then, a solution of $HSnBu_3$ (0.5 mL, 2.01 mmol, 2.4 equiv) and AIBN (14 mg, 0.08 mmol, 0.1 equiv) in dry toluene (0.5 mL) was slowly added by syringe pump in 3 h 30 min. After addition was complete, the mixture was refluxed for 30 min. The reaction was cooled, the solvent removed, the residue suspended in a mixture of Et_2O and a 15% aqueous solution of KF (1:1) and the mixture was stirred for 15 h at room temperature. The organic phase was separated and dried ($MgSO_4$). The solvent was removed and the residue submitted to chromatography (hexane/AcOEt 40%) giving compound **1** (176 mg, 75%) as an oil, showing identical spectroscopic data to those previously described.[1b]

(1S,2S,3S,4R)-4-O-Benzylhydroxylamino-2,3-O-isopropylidene-1-O-p-nitrobenzoyl-1,2,3-cyclopentanetriol ***12***

To a solution of compound **1** (295 mg, 1.06 mg, 1.0 equiv) in dry THF (10 mL) under argon, triphenylphosphine (553 mg, 2.11 mmol, 2 equiv) and *p*-nitrobenzoic acid (353 mg, 2.11 mmol, 2 equiv) were added. This suspension was warmed at reflux and DEAD (332 μL, 2.11 mmol, 2 equiv) was slowly added in 10 min; after 30 min the solution was cooled and washed with a saturated aqueous solution of sodium bicarbonate. The organic phase was separated and dried over Na_2SO_4. The solvent was removed and the residue was purified by chromatography (hexane/AcOEt 15%), giving **12** (352 mg,78%) as a white solid: mp 101–103°C; $[\alpha]_D^{25}$ +26.9 (*c* 0.2, $CHCl_3$); IR (KBr) υ 3500–3200, 2920, 1720, 1610, 1535, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17 and 8.04 (AB system, 4 H, *J*=9.0 Hz, aromat), 7.34 (m, 5 H, aromat), 5.46 (br s, 1 H, NH), 5.31 (d, 1 H, *J*=5.5 Hz, H1), 4.74 (s, 2 H, OCH_2Ph), 4.68 and 4.55 (system AB, 2 H, *J*=5.8 Hz, H2, H3), 3.73 (d, 1 H, *J*=6.1 Hz, H4), 2.51 (ddd, 1 H, *J*=15.3, 6.1, 5.5 Hz, H5′), 1.85 (br d, *J*=15.3 Hz, 1 H, H5), 1.48 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 164.1, 151.1, 138.2, 135.8, 131.2, 128.9, 128.8, 128.5, 124.1, 111.6, 84.9, 83.0, 81.0,77.0, 66.8, 33.0, 26.9, 24.6; MS (70 eV) *m/z* 429 (1), 413 (2), 370 (2), 150 (12), 120 (2), 104 (7), 92 (18.6), 91 (100), 77 (4), 76 (4), 65 (4), 43 (5). Anal. Calcd for $C_{22}H_{24}N_2O_7$: C, 61.68; H, 5.65; N, 6.54. Found: C, 61.55; H, 5.33; N, 6.32.

(1S,2R,3S,4R)-4-O-Benzylhydroxylamino-2,3-O-isopropylidene-1,2,3-cyclopentanetriol ***13***

To a solution of **12** (138 mg, 0.32 mmol, 1.0 equiv) in MeOH (10 mL) heated at reflux, a solution of sodium methoxide in MeOH (3.2 mL, 0.16 mmol, 0.5 equiv; 0.05 M) was added and stirred for 30 min; the solution was cooled and the solvent was removed. The residue was purified by chromatography (hexane/AcOEt 30%) giving product **13** (80.9 mg, 90%) as a white solid: mp 98–101°C; $[\alpha]_D^{25}$ +17.7 (*c* 0.6, $CHCl_3$); IR (film) υ 3600–3300, 3260, 2980, 1460, 1385, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.32 (m, 5 H, aromat), 5.52 (br s, 1 H, NH), 4.71 (s, 2 H, OCH_2Ph), 4.48 and 4.34 (AB system, 2 H, *J*=5.5 Hz, H2, H3), 4.04 (br s, 1 H, H1), 3.62 (d, 1 H, *J*=5.7 Hz, H4), 3.38 (br s, 1 H, OH), 2.18 (ddd, 1 H, *J*=14.6, 5.7, 4.7 Hz, H5′), 1.61 (d, 1 H, *J*=14.6 Hz, H5), 1.40 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 136.9, 128.7, 128.6, 128.2, 109.9, 86.3, 81.7, 76.8,76.7, 66.7, 34.3, 26.2, 23.7; MS (70 eV) *m/z* 279 (1), 264 (2), 221 (1), 188 (1), 178 (2), 149 (3), 105 (1), 92 (12), 91 (100), 77 (6), 65 (5), 59 (6), 43 (8). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.38; H, 7.44; N, 4.86.

LAH reduction of compound ***12***

To a solution of compound **12** (156 mg, 0.36 mmol) in dry THF, heated at reflux, LAH (935 mg, 2.18 mmol, 6.0 equiv) was slowly added; the suspension was stirred for 48 h. The mixture was cooled and water (80 μL), 15% aqueous solution of NaOH (80 μL) and water (240 μL) were added; the precipitated salts were filtered over Celite, washed several times with THF. The solvent was evaporated and purified by chromatography eluting with hexane/AcOEt 30% to give product **13** (26 mg, 26%) and eluting with CH_2Cl_2/MeOH 20% afforded compound **7** (20.4 mg, 33%): mp 126–7°C (lit.[13] mp 128°C); $[\alpha]_D^{25}$ +22 (*c* 0.3, $CHCl_3$) {lit.[14] $[\alpha]_D^{25}$ −51.5 (*c* 0.33, $CHCl_3$)}; IR (film) υ 3500–3100, 2930 1740, 1640, 1580, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.63 (d, 1 H, *J*=5.3 Hz, H3), 4.41 (d, 1 H, *J*=5.3 Hz, H2), 4.06 (d, 1 H, *J*=4.3 Hz, H1), 3.55 (d, 1 H, *J*=5.5 Hz, H4), 2.50 (br s, 3 H, NH_2, OH), 2.06 (ddd, 1 H, *J*=14.2, 5.5, 4.3 Hz, H5), 1.64 (d, 1 H, *J*=14.2 Hz, H5′); ^{13}C NMR ($CDCl_3$) δ 110.1, 86.4, 84.9, 77.2, 57.5, 36.2, 26.0, 23.8. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.22; H, 8.52; N, 7.85.

DIBAH reduction of compound ***12***

To a solution of compound **12** (152 mg, 0.25 mmol) in toluene, under argon and at −78°C, diisobutylaluminium hydride (DIBAH) (0.88 μL, 0.88 mmol, 2.5 equiv) was slowly added. The reaction was stirred 30 min at −78°C, and at room temperature 30 min. Then, MeOH (30 mL) was

added and the salts were removed after filtration over Celite, washing several times with MeOH. The solvent was eliminated in vacuo and the residue was purified by chromatography (hexane/AcOEt 30%) giving **13** (60.1 mg, 61%) and a mixture of compound **13** and *p*-nitrobenzylic alcohol in a 2:1 ratio (37 mg). This mixture was treated with pyridine–acetic anhydride (1:1) at room temperature. After 27 h, the solvent was evaporated in vacuo and the residue was purified by chromatography (hexane/AcOEt 10%) giving *p*-nitrobenzyl acetate (19 mg) and compound **14** (22 mg, 39% yield from compound **12**) as an oil: $[\alpha]_D^{25}$ +10.5 (*c* 1.4, $CHCl_3$); IR (film) υ 2990, 2940, 1740, 1680, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47–7.28 (m, 5 H, aromat), 4.98 (d, 1 H, *J*=5.9 Hz, H4), 4.91 (s, 2 H, OCH_2Ph), 4.88 (d, 1 H, *J*=7.3 Hz, H2), 4.61 (d, 1 H, *J*=7.3 Hz, H3), 4.38 (d, 1 H, *J*=7.2 Hz, H1), 2.6 (ddd, 1 H, *J*=14.4, 7.2, 5.9 Hz, H5), 2.3 (m, 1 H, H5′), 2.14 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.5, 170.8, 134.8, 129.5, 129.2, 113.6, 83.8, 80.9, 78.7, 77.8, 63.9, 33.6, 27.8, 25.6, 21.9, 21.4; MS (70 eV) *m/z* 279 (1), 264 (2), 221 (1), 188 (1), 178 (2), 149 (3), 105 (1), 92 (12), 91 (100), 77 (6), 65 (5), 59 (6), 43 (8). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.66; H, 6.77; N, 3.57.

*Samarium diiodide reduction of compound **13***

Compound **13** (66 mg, 0.234 mmol), was dissolved, under argon, in dry THF (0.05 M) and SmI_2 (9.4 mL, 4 equiv; 0.1 M THF solution) were added *via cannula* at room temperature. The reaction was stirred for 3 h; then, water (126 μL, 7.02 mmol, 30 equiv) was added. After 30 min, the mixture was filtered over Celite, and the solid was washed several times with MeOH. The solvent was eliminated in vacuo and the residue was treated with pyridine–acetic anhydride (1:1) and the reaction was stirred for 48 h at room temperature.The solvent was removed and the residue purified by chromatography (CH_2Cl_2/MeOH 20%) giving compound **15** (28 mg, 47%): mp 149–152°C; $[\alpha]_D^{25}$ +17 (*c* 0.4, $CHCl_3$); IR (KBr) υ 3380, 2980, 1750, 1675, 1650, 1450, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80 (br s, 1 H, *J*=7.2 Hz, NH), 5.15 (d, 1 H, *J*=5.2 Hz, H4), 4.52 (s, 3 H, OCH_3), 4.51 and 4.47 (AB system, 2 H, *J*=5.6 Hz, H2, H3), 4.41 (d, 1 H, *J*=6.6 Hz, H1), 2.42 (ddd, 1 H, *J*=15.1, 6.6, 5.2 Hz, H5′), 2.09 (s, 3 H, CH_3), 1.97 (s, 3 H, CH_3), 1.72 (br d, 1 H, *J*=15.1 Hz, H5), 1.42 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.1, 169.0, 110.9, 85.1, 84.0, 79.8, 55.4, 33.5, 26.2, 23.8, 23.4, 21.1; MS (70 eV) *m/z* 258 (3), 242 (10), 200 (5), 14.1 (6), 140 (42), 139 (24), 114 (5), 98 (15), 97 (19), 85 (24), 84 (11), 80 (15), 69 (11), 68 (12), 60 (11), 44 (10), 43 (100). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.89; H, 7.32; N, 5.23.

*LAH reduction of compound **13***

To a solution of compound **13** (21 mg, 0.08 mmol) in dry THF (5 mL), heated at reflux, LAH (35 mg, 0.91 mmol, 12.0 equiv) was slowly added; the mixture was stirred at reflux for 3 days. The reaction was cooled and water (350 μL), 15% aqueous solution of NaOH (350 μL) and water (1 mL) were added. The precipitated salts were filtered over Celite, washing several times with THF. The solvent was evaporated in vacuo and the residue was purified by chromatography (CH_2Cl_2/MeOH 20%) giving compound **7** (7.6 mg, 58%).

*Zn/AcOH reduction of compound **13***

To a solution of compound **13** (81 mg, 0.29 mmol) in dry ethyl ether (4.6 mL), acetic acid (0.53 mL) and dry activated Zn (196 mg, 3.5 mmol, 15.1 equiv) were added; the mixure was stirred at room temperature for 48 h. The reaction was treated with NaOH 2 M (5.3 mL), the precipitated was filtered over Celite and washed several times with CH_2Cl_2. The solvent was removed and the residue was extrated water/CH_2Cl_2; the organic phase was dried ($NaSO_4$) and the solvent was evaporated. The residue was purified by chromatography (hexane/AcOEt 30%), giving **13** (49.1 mg, 61%); eluting with (CH_2Cl_2/MeOH 20%) afforded compound **7** (7.8 mg, 40%).

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