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Divergent synthesis of two precursors of 3′-homo-2′-deoxy- and 2′-homo-3′-deoxy-carbocyclic nucleosides

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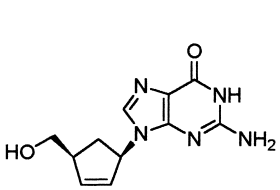
Abstract—Aminocyclopentanedimethanols **4** and **5**, which are of interest for the synthesis of higher homologues of 2′-deoxy- and 3′-deoxycarbonucleosides, respectively, were efficiently prepared by divergent routes starting from (±)-*exo*-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde. In the key step, ammonolysis of the common intermediate (±)-(1β,3β,4α)-4-benzoyloxymethyl-1,3-cyclopentanedicarboxylic anhydride and subsequent esterification afford near-equimolar amounts of two easily separable isomeric carbamoyl esters.

1. Introduction

Carbocyclic nucleosides (CNs) are compounds in which the furan ring of nucleosides has been replaced by a carbocyclic system. This modification increases resistance to hydrolases and phosphorylases, but in certain cases does not greatly reduce reactivity with other enzymes involved in nucleotide metabolism,[1] which can make the CNs active against viruses and/or neoplasias.[2,3] For example, carbovir (**1**)[4] and abacavir (**2**)[5–7] are good inhibitors of HIV replication, and the latter has recently been approved as an antiviral for treatment of HIV-infected adults (Ziagen®).



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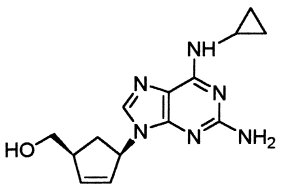

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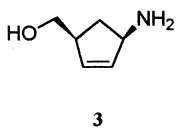

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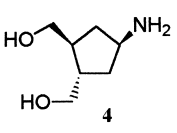

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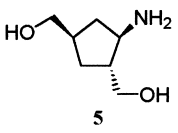

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In many cases, CNs are synthesized by construction of a purine or pyrimidine base on an appropriate amino alcohol precursor. For example, both carbovir[4] and abacavir[8] can be prepared in this way from aminocyclopentenylmethanol **3**. This approach allows ample and easy variation of the heterocyclic base, which multiplies the potential utility of efficient synthesis of suitable amino alcohol starting compounds.

For some years our group has been investigating the relationship between the biological properties of purine- and pyrimidine-based CNs[9–11] and the structures of their specifically synthesized carbocyclic fragments.[12–14] In view of reports that a 9-[3,4-bis(hydroxymethyl)cyclopentyl]adenine is highly active against HSV-1, with an $IC_{50}<0.0001$ μg/mL,[15] we are currently exploring CNs derived from bis- and tris(hydroxy-methyl)cyclopentanes.[16] Here we describe a divergent, highly efficient synthetic route to amino alcohols **4** and **5**.

The synthesis of **4**, **5** or of their simple derivatives have been dealt with in a very few cases. Marquez et al. report the preparation of a *O*-benzoil-*O*′-bencil derivative of (±)-**4** from a conveniently substituted cyclopentenone precursor in 11 synthetic steps and a 7% overall yield.[17] More efficiently, Legraverend et al. obtain (±)-**4** from commercially available materials in five steps and a 16% overall yield.[18] Enantiomerically pure (+)-**4** has been prepared by Lee-Ruff et al. from (1*S*-*trans*)-3,3-dimethoxy-1,2-cyclobutanedimethanol in four steps and a 8% overall yield,[19] although the yield in obtaining that chiral cyclobutane precursor from commercial materials (less than a 73%) is not precisely documented.[20] With regard to **5**, only a chirospecific synthesis of its bis(*O*-acetyl)-*N*-Boc derivative has been described in 10 synthetic steps and a 16% overall yield from (1*R*,2*R*)-*trans*-dimethyl 4-oxocyclopentane-1,2-dicarboxylate,[21a] which in turn can be obtained from

Keywords: amino cyclopentanemethanols; homonucleosides; deoxycarbocyclic nucleosides; divergent synthesis.

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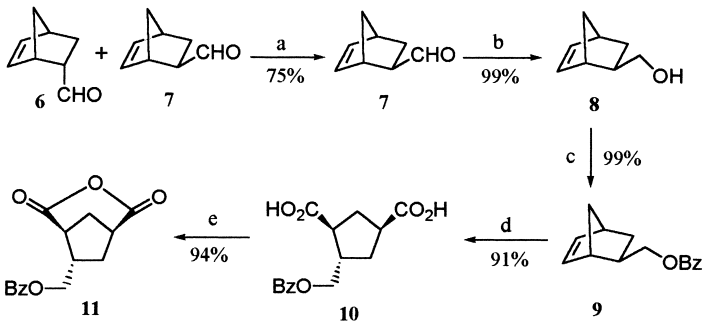


Scheme 1. (a) LiOH, THF, reflux; (b) $NaBH_4$, MeOH, 0°C; (c) BzCl, Et_3N, rt; (d) $KMnO_4$, AcOH, H_2O, C_6H_6, Aliquat 336, rt; (e) Ac_2O, reflux.

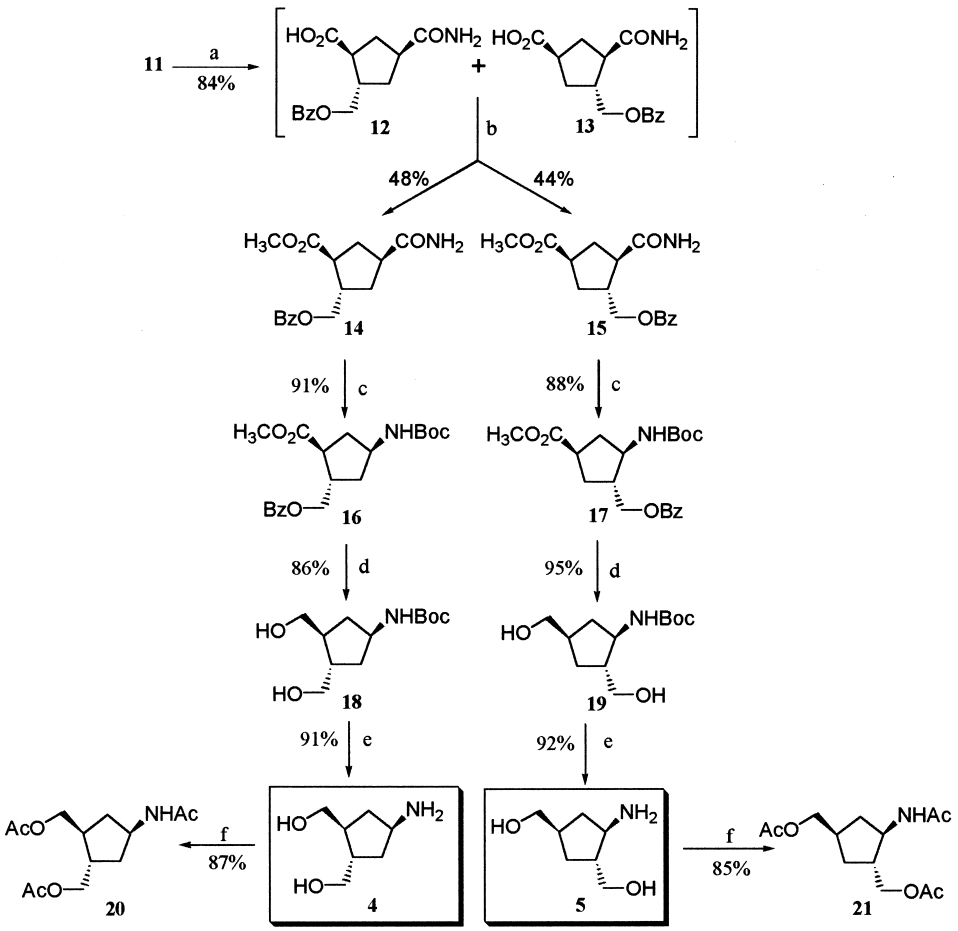
commercially available materials is four steps (one of them an enzymatic resolution) in a 26% overall yield (74% for the racemic version).[21b]

2. Results and discussion

Our synthetic strategy was to obtain both target amino alcohols **4** and **5** in racemic form from a common, readily available, synthetic intermediate, leaving to a later development the separation of the desired enantiomers if warranted by the biological activity of the CNs derived from them. To this end, the synthesis of anhydride **11** as the common synthetic precursor for both amino alcohols **4** and **5** was envisaged.

A 71:29 mixture of *endo*/*exo* aldehydes **6** and **7** was easily obtained by Diels–Alder reaction of acrolein and cyclopentadiene. Epimerization in LiOH/H_2O/THF and subsequent chromatographic separation (Scheme 1) afforded the *exo* isomer **7** in 75% yield and >99% purity (a considerable improvement on the previously published method).[22] Reduction of **7** with $NaBH_4$ in MeOH at 0°C gave alcohol **8**, which was benzoylated to **9**, and oxidative cleavage of the latter with $KMnO_4$ in benzene/water with Aliquat 336 as phase transfer catalyst[23] led to the dicarboxylic acid **10**, which was easily transformed into its anhydride **11** by reflux in Ac_2O. The overall yield of **11**, starting from **7**, was 84%.

Following ammonolysis of anhydride **11** (NH_3(g), THF,



Scheme 2. (a) NH_3 (g), THF, 0°C; (b) (1) MeOH, TsOH, reflux; (2) flash chromatography; (c) $Pb(AcO)_4$, *t*-BuOH, Et_3N, reflux; (d) 1.5 M DIBAL-H, toluene, −78°C; (e) (1) 2 M HCl, MeOH, reflux; (2) Amberlite IRA-400 (OH); (f) Ac_2O, Et_3N, rt.

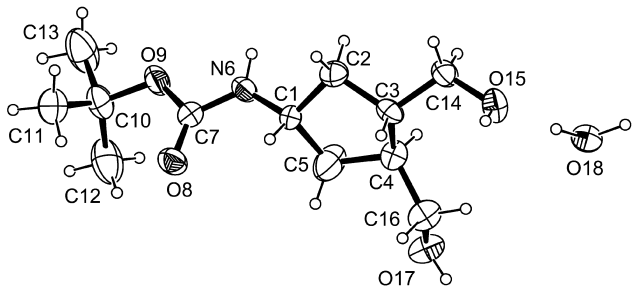


Figure 1. ORTEP plot of the crystal structure of (±)-**18**.

0°C) and esterification of the resulting isomeric carbamoylcarboxylic acids **12** and **13**, the routes to **4** and **5** diverged upon flash chromatographic separation of the methyl esters **14** and **15**, which were isolated in, respectively, 40 and 37% yield from **11** (Scheme 2). Oxidative degradation of the carbamoyl group with lead tetraacetate in dry *tert*-butyl alcohol[24,25] was used to convert **14** into the Boc-protected amino ester **16**, the ester groups of which were selectively reduced at low temperature with 1.5 M DIBAL-H in toluene.[26] Finally, removal of the Boc group of the resulting bis(hydroxymethyl)carbamate **18** by heating in a 1:1 (v/v) mixture of 2 M HCl and MeOH left a hydrochloride that was purified by ion exchange chromatography on a basic resin, affording racemic amino alcohol **4** in an overall yield of 71% from **14**. A parallel reaction sequence via the Boc-protected amino ester **17** and the bis(hydroxymethyl)-carbamate **19** afforded racemic amino alcohol **5** in an overall yield of 77% from carbamoyl ester **15**.

Compounds **4** and **5**, their triacetyl derivatives **20** and **21** (prepared for identification purposes), and all intermediates had IR, MS and ^{1}H and ^{13}C NMR spectra in accordance with the proposed structures. The unequivocal confirmation of the structures of **14**, **16**, **18** and **4** by X-ray crystallographic analysis of a single crystal of **18** (Fig. 1)[27] shows that under the working conditions used all these compounds (and **12**) conserve the relative configuration of the bicyclic precursor **11**, and indirectly also supports the proposed structures of **15**, **17**, **19** and **5**.

An attempt to strengthen the support of the structure of **19** by way of H–H NMR 2D correlation and NOE experiments was not entirely conclusive. In a COSY experiment, signals of the protons of the CH_2OH groups (those at δ 3.78–3.68 and 3.47–3.38 ppm) exclusively showed correlation with protons at δ 2.05 and 1.91 ppm, neither of which showed correlation with the proton at δ 3.96 ppm (this unequivocally being CH(N), as the only one to correlate with NH). A plausible explanation could be that in the most preferred conformation of **19**, as its Dreiding model seems to suggest, the dihedral angle between the vicinal CH(N) and CH(CH_2O) bonds is near 90°, thus leading to a virtually negligible coupling between those protons. A NOESY experiment, however, allowed to measure a 3.4% NOE between the signal of the CH(N) and the protons of a CH_2O group (those at δ 3.78–3.68 ppm), thus confirming a *cis* relationship between them, as the structure of **19** requires.

3. Experimental

3.1. General

Melting points are uncorrected and were determined in a Reichert Kofler Thermopan or in capillary tubes in a Büchi 510 apparatus. Infrared spectra were recorded in a Perkin–Elmer 1640 FTIR spectrophotometer. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded in a Bruker AMX 300 spectrometer using TMS as internal reference (chemical shifts in δ values, J in Hz). Mass spectra were recorded on a Kratos MS-59 spectrometer. Microanalyses were performed in a Perkin–Elmer 240B element analyzer by the Microanalysis Service of the University of Santiago. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TLC on precoated silica gel plates (Merck 60 F254, 0.25 mm). Crystallographic data were obtained with a MACH3 Enraf Nonius diffractometer.

3.1.1. (±)-*exo*-Bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (7). Cyclopentadiene (76 mL, 928 mmol) was added dropwise to a solution of acrolein (40 g, 714 mmol) in dry benzene (70 mL) and the mixture was heated under argon for 18 h at 65°C. Removal of benzene under reduced pressure left a liquid mixture of the *endo* and *exo* adducts **6** and **7** (86.2 g, *endo*/*exo* ratio 2.5:1 as estimated by ^{1}H NMR). A solution of this mixture (10 g, 82 mmol) in dry THF (180 mL) was refluxed, a solution of LiOH (0.53 g, 22 mmol) in the minimum possible amount of water (9 mL) was added in one dose, and after refluxing for a further 34 h the mixture was cooled in an ice bath and brought to pH 7.5 with 5% H_2SO_4 (20 mL). Removal of the solvents under reduced pressure in an ice–water bath left a liquid residue (7.81 g) that upon chromatography on silica gel (160 g) with 45:1 pentane/ether as eluent afforded the *exo* compound (±)-**7** as a transparent oil (7.51 g, 75% yield, >99% *exo*). IR (film) ν_{max}: 2969, 2871, 2813, 2712, 1718, 1458, 1447, 1332 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 9.76 (d, 1H, J=2.3 Hz, CHO), 6.16 (dd, 1H, J=5.6, 2.9 Hz, C*H*=CH), 6.1 (dd, 1H, J=5.5, 3.1 Hz, CH=C*H*), 3.09 (s, 1H, 1-H), 2.94 (s, 1H, 4-H), 2.25 (ddd, 1H, J=6.5, 4.3, 2.2 Hz, 2-H$_{endo}$), 1.93 (dt, 1H, J=11.9, 3.9 Hz, 3-H), 1.36–1.33 (m, 1H), 1.32–1.20 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 204.40 (CO), 138.96 and 135.67 (C=C), 52.12 (C2), 46.23 (C7), 44.65 and 42.20 (C4+C1), 27.49 (C3). EIMS, *m*/*z* (%): 122 (7, M$^+$); 91 (17); 77 (16); 66 (100). Anal. calcd for $C_8H_{10}O$ (122.16): C, 78.65; H, 8.25. Found: C, 78.77; H, 8.19.

3.1.2. (±)-*exo*-Bicyclo[2.2.1]hept-5-en-2-ylmethanol (8). A solution of (±)-**7** (11.67 g, 95.66 mmol) in MeOH (58 mL) was added dropwise over 1 h to a suspension of $NaBH_4$ (1.74 g, 46.03 mmol) in 2N NaOH (20 mL) at 0°C. After stirring at room temperature for a further hour, the pH was brought to 6 at 0°C with 30% H_2SO_4 (30 mL), the methanol was evaporated, and the resulting residue was extracted with Et_2O (3×70 mL). The pooled organic layers were washed with saturated $NaHCO_3$ (3×100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, affording (±)-**8** as a white liquid (11.74 g, 99%). IR (film) ν_{max}: 3327, 3058, 2961, 1569, 1460, 1445, 1332 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 6.12–6.05 (m, 2H, CH=CH), 3.70 and 3.53 (the AB part of an ABX system,

2H, J_{AB}=10.5 Hz, J_{AX}=8.9 Hz, J_{BX}=6.5 Hz, OCH_2), 2.81 and 2.74 (2s, 2H, 1-H+4-H), 1.69–1.56 (m, 1H), 1.51 (s, 1H, D_2O exch., OH), 1.36–1.20 (m, 3H), 1.14–1.07 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 137.12 and 136.86 (C=C), 67.61 (CH_2O), 45.29 (C7), 43.64, 42.10 and 41.88 (C2+C1+C4), 29.92 (C3). EIMS *m/z* (%): 124 (5, M^+), 91 (17), 77 (13), 67 (10), 66 (100), 65 (13). Anal. calcd for $C_8H_{12}O$ (124.18): C, 77.38; H, 9.74. Found: C, 77.59; H, 9.64.

3.1.3. (±)-*exo*-Bicyclo[2.2.1]hept-5-en-2-ylmethyl benzoate (9). A solution of (±)-**8** (9.02 g, 72.7 mmol) in dry Et_3N (246 mL) was added dropwise under argon to BzCl (16.7 mL, 119 mmol) at 0°C. After stirring at room temperature for 72 h, the mixture was cooled, basified with 2N NaOH (600 mL), stirred at room temperature for a further 2 h, and extracted with $CHCl_3$ (3×200 mL). The pooled organic layers were washed successively with saturated Na_2CO_3 (3×100 mL), saturated NaCl (3×100 mL) and water (5×200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to a yellow liquid (19.34 g) that upon chromatography on silica gel (340 g) with 15:1 hexane/EtOAc as eluent (17×125 mL) afforded (±)-**9** as a viscous white liquid (8.92 g, 99%). IR (film) ν_{max}: 3061, 2965, 2869, 1718, 1450, 1326, 1273 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.07 (d, 2H, *J*=7.1 Hz, (2-H+6-H)$_{arom}$), 7.57 (dt, 1H, *J*=7.4, 2.5 Hz, 4-H$_{arom}$), 7.45 (t, 2H, *J*=7.5 Hz, (3-H+5-H)$_{arom}$), 6.15–6.09 (m, 2H, CH=CH), 4.42 and 4.22 (the AB part of an ABX system, 2H, J_{AB}=10.9 Hz, J_{AX}=9.2 Hz, J_{BX}=6.5 Hz, OCH_2), 2.88 and 2.82 (2s, 2H, 1-H+4-H), 1.93–1.84 (m, 1H), 1.39 (s, 2H), 1.29–1.23 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 166.95 (C=O), 137.37 and 136.65 (C=C), 133.23 (C4$_{arom}$), 130.90 (C1$_{arom}$), 129.98 and 128.73 ((C2+C6+C3+C5)$_{arom}$), 69.37 (CH_2O), 45.43 (C7), 44.16, 42.06 and 38.54 (C1+C4+C2), 30.02 (C3). EIMS *m/z* (%): 229 (0.03, $(M+1)^+$), 228 (0.7, M^+), 169 (17), 105 (46), 77 (45), 66 (100). Anal. calcd for $C_{15}H_{16}O_2$ (228.29): C, 78.92; H, 7.06. Found: C, 79.11; H, 6.81.

3.1.4. (±)-(1β,3β,4α)-4-Benzoyloxymethyl-1,3-cyclopentanedicarboxylic acid (10). A solution of (±)-**9** (4.00 g, 17.54 mmol) and Aliquat 336 (1.11 g, 2.76 mmol) in benzene (100 mL) was added dropwise to a vigorously stirred solution of $KMnO_4$ (8.97 g, 56.79 mmol) and AcOH (4.8 mL) in water (200 mL) at 0–5°C. After stirring at room temperature for 23 h, the mixture was cooled, a solution of $Na_2S_2O_5$ (20 g, 105 mmol) in water (80 mL) was slowly added, and the resulting suspension was acidified with 2N H_2SO_4 (250 mL). The benzene phase was separated, the aqueous phase was washed with Et_2O (3×60 mL), and the pooled organic phases were extracted with saturated Na_2CO_3 until basic (3×120 mL). The combined basic extracts were then acidified with 2N H_2SO_4, left standing for 12 h at 0°C, and the resulting precipitate was filtered out. Its recrystallization from toluene afforded (±)-**10** as a white solid (4.64 g, 91%); mp 121.5–123°C. IR (KBr) ν_{max}: 3060, 2947, 1715, 1602, 1452, 1417, 1316, 1273 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 7.95 (d, 2H, *J*=7.1 Hz, (2-H+6-H)$_{arom}$), 7.65 (t, 1H, *J*=7.4 Hz, 4-H$_{arom}$), 7.52 (t, 2H, *J*=7.6 Hz, (3-H+5-H)$_{arom}$), 4.28 and 4.21 (the AB part of an ABX system, 2H, J_{AB}=10.9 Hz, J_{AX}=6.2 Hz, J_{BX}=5.7 Hz, OCH_2), 2.89–2.81 (m, 1H), 2.66–2.55 (m, 2H), 2.27–2.18 (m, 1H), 2.09–1.89 (m, 2H), 1.78–1.68 (m, 1H). ^{13}C NMR (DMSO-d_6) δ: 175.98 and 175.52 (2×CO_2H), 166.5 (CO_{benz}), 133.67 (C4$_{arom}$), 130.12 (C1$_{arom}$), 129.53 and 129.11 ((C2+C6+C3+C5)$_{arom}$), 67.23 (CH_2O), 47.30, 42.28 and 41.58 (C1+C3+C4), 34.01 and 32.20 (C2+C5). EIMS *m/z* (%). 217 (0.01, $(M+1)^+-C_6H_4$), 170 (9), 152 (13), 124 (29), 123 (21), 105 (100), 77 (46), 51 (18). Anal. calcd for $C_{15}H_{16}O_6$ (292.28): C, 61.64; H, 5.52. Found: C, 61.51; H, 5.62.

3.1.5. (±)-(1β,3β,4α)-4-Benzoyloxymethyl-1,3-cyclopentanedicarboxylic anhydride (11). A solution of the diacid (±)-**10** (3.94 g, 13.5 mmol) in Ac_2O (55 mL) was refluxed for 25 h. Removal of excess Ac_2O by azeotropic codistillation with dry toluene (2×40 mL) left a blackish solid that upon recrystallization from EtOAc afforded pure (±)-**11** (3.48 g, 94%). Mp 123–125°C. IR (KBr) ν_{max}: 2979, 1812, 1774, 1716, 1448, 1316, 1270 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.02 (d, 2H, *J*=7.3 Hz, (2-H+6-H)$_{arom}$), 7.61 (t, 1H, *J*=7.4 Hz, 4-H$_{arom}$), 7.47 (t, 2H, *J*=7.6 Hz, (3-H+5-H)$_{arom}$), 4.35 and 4.25 (the AB part of an ABX system, 2H, J_{AB}=11.3 Hz, J_{AX}=8.1 Hz, J_{BX}=5.8 Hz, OCH_2), 3.36–3.33 (m, 1H), 3.29–3.27 (m, 1H), 2.88–2.79 (m, 1H, 4-H), 2.40–2.25 (m, 2H), 2.02–1.87 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 169.59 and 168.90 (2×CO_{anh}), 166.64 (CO_{benz}), 133.93 (C4$_{arom}$), 130.04 and 129.02 ((C2+C6+C3+C5)$_{arom}$), 129.71 (C1$_{arom}$), 66.05 (CH_2O), 44.99, 42.72 and 39.45 (C1+C3+C4), 31.02 and 29.48 (C2+C5). EIMS *m/z* (%): 246 (0.44, (M^+-CO)), 202 (5), 122 (2), 105 (100), 80 (19), 79 (18), 77 (37), 67 (9), 55 (11), 51 (16). Anal. calcd for $C_{15}H_{14}O_5$ (274.27): C, 65.69; H, 5.15. Found: C, 65.93; H, 4.98.

3.1.6. (±)-(1β,2α,4β)-Methyl-2-benzoyloxymethyl-4-carbamoyl-1-cyclopentanecarboxylate (14) and (±)-(1β,3α,4β)-methyl-3-benzoyloxymethyl-4-carbamoyl-1-cyclopentanecarboxylate (15). A stream of gaseous ammonia was passed for 2 h through a solution of (±)-**11** (4.20 g, 15.33 mmol) in dry THF (130 mL) at 5°C. Concentration of the resulting suspension to dryness left a brown solid that was taken into water (150 mL). This solution was cooled to 0°C, acidified with 3N HCl (25 mL) and extracted with EtOAc (3×75 mL). The pooled organic phases were washed with water (3×75 mL) and dried over anhydrous Na_2SO_4, and concentration to dryness left a white foam (4.92 g) that was recrystallized from Et_2O to afford a mixture of **12** and **13** (3.75 g, 84%). A solution of this mixture (3.50 g, 11.46 mmol) in dry MeOH (70 mL) containing *p*-TsOH (80 mg, 0.46 mmol) was refluxed for 2 h under argon. Concentration to dryness left a white solid (3.74 g) that upon chromatographic separation on silica gel (112 g) with EtOAc/hexane/EtOH 44:30:1 as eluent, afforded successively pure (±)-**14** (1.76 g, 48%) and pure (±)-**15** (1.61 g, 44%).

(±)-**14**: mp 105–107°C (recrystallized from EtOAc/hexane 1:1). IR (KBr) ν_{max}: 3389, 3193, 2951, 1732, 1715, 1652, 1452, 1433, 1378, 1316, 1273 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 8.03 (dd, 2H, *J*=8.6, 1.4 Hz, (2-H+6-H)$_{arom}$), 7.58 (t, 1H, *J*=7.4 Hz, 4-H$_{arom}$), 7.46 (t, 2H, *J*=7.5 Hz, (3-H+5-H)$_{arom}$), 6.11 (bs, 1H, D_2O exch., N*H*H), 5.36 (bs, 1H, D_2O exch., NH*H*), 4.48 and 4.29 (the AB part of an ABX system, 2H, J_{AB}=11.3 Hz, J_{AX}=6.0 Hz, J_{BX}=5.2 Hz, OCH_2), 3.70 (s, 3H, OCH_3), 2.97–2.92 (m, 1H), 2.81–2.76 (m, 1H),

2.58–2.49 (m, 1H), 2.34–2.24 (m, 3H), 1.94–1.84 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 176.50 and 176.12 (2×CO), 167.21 (Ph–CO), 136.61 ($C4_{arom}$), 130.24 ($C1_{arom}$), 130.01 and 128.89 ($(C2+C6+C3+C5)_{arom}$), 66.95 (CH_2O), 52.41 (CH_3), 49.04, 43.14 and 42.97 (C4+C1+C2), 34.54 and 32.87 (C5+C3). EIMS *m/z* (%): 306 (0.13, $(M+1)^+$), 305 (2, M^+), 274 (4), 260 (0.23), 246 (5), 183 (15), 166 (10), 140 (18), 122 (3), 105 (100), 81 (28), 80 (22), 79 (23), 77 (50). Anal. calcd for $C_{16}H_{19}NO_5$ (305.33): C, 62.94; H, 6.27; N, 4.59. Found: C,63.16; H, 6.16; N, 4.73.

(±)-**15**: mp 100–102°C (recrystallized from EtOAc/hexane 13:10). IR (KBr) ν_{max}: 3393, 3198, 2951, 1727, 1656, 1450, 1431, 1378, 1317, 1266 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.99 (d, 2H, J=7.2 Hz, $(2\text{-H}+6\text{-H})_{arom}$), 7.55 (t, 1H, J=7.2 Hz, 4-H_{arom}), 7.43 (t, 2H, J=7.7 Hz, $(3\text{-H}+5\text{-H})_{arom}$), 5.92 (bs, 2H, D_2O exch., NH_2), 4.30 (d, 2H, J=6.3 Hz, CH_2O), 3.62 (s, 3H, OCH_3), 2.90–2.77 (m, 2H), 2.75–2.66 (m, 1H), 2.35–2.14 (m, 3H), 1.96–1.79 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 176.79 and 175.03 (2×CO), 166.42 (Ph–CO), 133.08 ($C4_{arom}$), 129.95 ($C1_{arom}$), 129.54 and 128.39 ($(C2+C6+C3+C5)_{arom}$), 66.71 (CH_2O), 51.97 (CH_3), 47.36, 43.97 and 42.00 (C4+C1+C3), 34.13 and 32.97 (C5+C2). EIMS *m/z* (%): 306 (0.03, $(M+1)^+$), 305 (0.07, M^+), 274 (2), 246 (0.11), 183 (15), 151 (8), 138 (27), 105 (100), 80 (17), 79 (20), 77 (42). Anal. calcd for $C_{16}H_{19}NO_5$ (305.33): C, 62.94; H, 6.27; N, 4.59. Found: C, 63.17; H, 6.43; N, 4.38.

3.1.7. (±)-(1β,2α,4β)-Methyl-2-benzoyloxymethyl-4-*tert*-butoxycarbonylamino-1-cyclopentanecarboxylate (16). Lead tetraacetate (3.55 g, 8.00 mmol) was added under argon to a solution of carbamoyl ester (±)-**14** (1.97 g, 6.46 mmol) in *t*-BuOH (40 mL), the mixture was heated to 70°C, Et_3N (2.74 mL, 8.48 mmol) was added dropwise, and the mixture was refluxed for 8 h. Concentration under reduced pressure by azeotropic codistillation with toluene afforded a yellow solid that upon chromatographic fractionation on silica gel (114 g) with hexane/EtOAc 10:3 as eluent gave (±)-**16** (2.21 g, 91%), as a solid. Mp 100.5–101.5°C. IR (KBr) ν_{max}: 3367, 2972, 1727, 1716, 1681, 1525, 1452, 1429, 1365, 1316, 1284 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.02 (d, 2H, J=7.4 Hz, $(2\text{-H}+6\text{-H})_{arom}$), 7.55 (t, 1H, J=7.4 Hz, 4-H_{arom}), 7.43 (t, 2H, J=7.6 Hz, $(3\text{H}+5\text{H})_{arom}$), 4.91 (bs, 1H, D_2O exch., NH), 4.40 and 4.27 (the AB part of an ABX system, 2H, J_{AB}=11.1 Hz, J_{AX}=6.6 Hz, J_{BX}=5.4 Hz, OCH_2), 4.01–3.91 (m, 1H, 4-H), 3.68 (s, 3H, OCH_3), 2.93–2.89 (m, 1H), 2.42–2.32 (m, 2H), 2.30–2.18 (m, 1H), 1.84–1.76 (m, 2H), 1.41 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ: 177.51 (1-CO), 166.88 (Ph–CO), 155.79 (N–CO–O), 133.38 ($C4_{arom}$), 130.50 ($C1_{arom}$), 130.01 and 128.77 ($(C2+C6+C3+C5)_{arom}$), 79.91 [$C(CH_3)_3$], 66.54 (CH_2O), 54.59 (C4), 52.42 (OCH_3), 45.32 and 40.91 (C1+C2), 36.88 and 31.80 (C5+C3), 28.76 [$C(CH_3)_3$]. EIMS *m/z* (%): 321 (0.37, $((M+1)^+-C(CH_3)_3)$), 304 (0.81, $(M^+-OC(CH_3)_3)$), 276 (0.09, M^+–Boc), 246 (1.37), 198 (7), 154 (49), 140 (12), 105 (60), 96 (40), 77 (35), 57 (100). Anal. calcd for $C_{20}H_{27}NO_6$ (377.43): C, 63.64; H, 7.21; N, 3.71. Found: C, 63.82; H, 7.42; N, 3.49.

3.1.8. (±)-(1β,3α,4β)-Methyl-3-benzoyloxymethyl-4-*tert*-butyloxycarbonylamino-1-cyclopentanecarboxylate (17). Crude (±)-**17** was obtained as a thick liquid from carbamoyl ester (±)-**15** (1.15 g, 3.77 mmol), lead tetraacetate (2.07 g, 4.66 mmol), *t*-BuOH (23 mL) and Et_3N (1.6 mL, 4.95 mmol) by a parallel procedure to that above described for (±)-**16**. Once similarly purified by column chromatography, (±)-**17** (1.25 g, 88%) crystallized spontaneously. Mp 50–52°C. IR (film) ν_{max}: 3378, 2974, 1720, 1601, 1584, 1452, 1366, 1274 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.01 (d, 2H, J=7.9 Hz, $(2\text{-H}+6\text{-H})_{arom}$), 7.55 (t, 1H, J=7.3 Hz, 4-H_{arom}), 7.44 (t, 2H, J=7.6 Hz, $(3\text{-H}+5\text{-H})_{arom}$), 5.05 (bs, 1H, D_2O exch., NH), 4.37–4.25 (m, 2H, CH_2O), 4.12–4.01 (m, 1H), 3.63 (s, 3H, OCH_3), 2.83–2.70 (m, 2H), 2.35–2.31 (m, 1H), 1.93–1.89 (m, 1H), 1.86–1.77 (m, 2H), 1.44 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ: 177.62 (1-CO), 166.67 (Ph–CO), 155.68 (N–CO–O), 133.46 ($C4_{arom}$), 130.39 ($C1_{arom}$), 129.97 and 128.78 ($(C2+C6+C3+C5)_{arom}$), 79.97 [$C(CH_3)_3$], 67.40 (CH_2O), 52.46 (OCH_3), 51.92 (C4), 46.01 and 41.71 (C1+C3), 37.14 (C2+C5), 28.81 [$C(CH_3)_3$]. EIMS *m/z* (%): 321 (4, $((M+1)^+-C(CH_3)_3)$), 304 (2, $M^+-(OC(CH_3)_3)$), 276 (15, (M^+-Boc)), 246 (2), 216 (2), 154 (28), 138 (8), 105 (90), 96 (21), 79 (11), 77 (36), 59 (16), 57 (100). Anal. calcd for $C_{20}H_{27}NO_6$ (377.43): C, 63.64; H, 7.21; N, 3.71. Found: C, 63.45; H, 7.43; N, 3.54.

3.1.9. (±)-(1β,3α,4β)-*tert*-Butyl *N*-[3,4-bis(hydroxymethyl)cyclopent-1-yl]carbamate (18). A solution of (±)-**16** (0.48 g, 1.30 mmol) in dry toluene (5 mL) was added dropwise under argon to a commercial 1.5 M solution of DIBAL-H in the same solvent (6.24 mL, 9.36 mmol) at −78°C, the mixture was stirred at this temperature for 3 h, and the reaction was quenched by cautious and successive addition of toluene/MeOH (9:1; 2 mL), MeOH (1 mL) and water (4 mL), then leaving the mixture to reach room temperature. The solid precipitate was filtered out and washed with EtOAc (4×40 mL). The combined liquid filtrate and washings were dried over anhydrous Na_2SO_4, the solvents were evaporated at low pressure, and the residue left was chromatographed on silica gel (15 g) with EtOAc as eluent to afford (±)-**18** (0.27 g, 86%), as a white solid. Mp 129–130.5°C (recrystallized from EtOAc/hexane 2:1). IR (KBr) ν_{max}: 3649, 3303, 2977, 2940, 1702, 1681, 1543, 1457, 1363, 1291 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 6.73 (d, 1H, J=7.8 Hz, D_2O exch., NH), 4.44 (t, 1H, J=5.2 Hz, D_2O exch., OH), 4.36 (t, 1H, J=5.1 Hz, D_2O exch., OH), 3.45–3.37 (m, 2H), 3.31–3.15 (m, 3H), 1.95–1.88 (m, 2H), 1.78–1.75 (m, 1H), 1.48–1.43 (m, 2H), 1.36 (s, 9H, $C(CH_3)_3$), 1.09–1.05 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 156.01 (CO), 80.77 [$C(CH_3)_3$], 67.15 and 64.23 (2×CH_2O), 54.65 (C1), 49.01 and 38.36 (C3+C4), 36.11 and 30.22 (C2+C5), 28.75 [$C(CH_3)_3$]. EIMS *m/z* (%): 189 (2, $(M+1)^+-(C(CH_3)_3)$), 172 (1, $(M^+-OC(CH_3)_3)$), 144 (7, (M^+-Boc)), 126 (4), 114 (21), 93 (8), 80 (17), 79 (11), 59 (13), 58 (11), 57 (100). Anal. calcd for $C_{12}H_{23}NO_4$ (245.32): C, 58.75; H, 9.45; N, 5.71. Found: C, 58.98; H, 9.32; N, 5.91.

3.1.10. (±)-(1β,2α,4β)-*tert*-Butyl *N*-[2,4-bis(hydroxymethyl)cyclopent-1-yl]carbamate (19). From carbamate (±)-**17** (0.34 g, 0.90 mmol) in dry toluene (4 mL) and commercial 1.5 M DIBAL-H in the same solvent (4.5 mL, 6.75 mmol), crude (±)-**19** was obtained as a viscous liquid by a parallel procedure to that above described for (±)-**18**. Once similarly purified by column chromatography, (±)-**19** (0.21 g, 95%) was isolated as a white solid. Mp 59.5–62°C.

IR (KBr) ν_{max}: 3343, 2978, 2945, 2866, 1683, 1531, 1457, 1365, 1302, 1276 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.61 (bs, 1H, D_2O exch., NH), 4.02–3.91 (m, 1H, 1-H), 3.78–3.68 (m, 2H, CH_2O), 3.47–3.38 (m, 2H, CH_2O), 3.15 (bs, 2H, D_2O exch., 2×OH), 2.23–2.17 (m, 1H), 2.08–2.02 (m, 1H), 1.96–1.87 (m, 1H), 1.70–1.65 (m, 2H), 1.43 (s, 9H, $C(CH_3)_3$), 1.22–1.15 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 155.95 (CO), 79.83 [$C(CH_3)_3$], 66.71 and 66.55 (2×CH_2O), 50.66 (C1), 46.43 and 45.41 (C2+C4), 37.51 and 36.92 (C5+C3), 28.83 [$C(CH_3)_3$]. EIMS *m/z* (%) 189 (4, $(M+1)^+-C(CH_3)_3$), 188 (12, $(M^+-C(CH_3)_3)$), 172 (3, $(M^+-OC(CH_3)_3)$), 144 (7, (M^+-Boc)), 126 (6), 114 (15), 93 (11), 80 (8), 79 (9), 69 (8), 67 (12), 59 (14), 58 (8), 57 (100). Anal. calcd for $C_{12}H_{23}NO_4$ (245.32): C, 58.75; H, 9.45; N, 5.71. Found: C, 58.61; H, 9.61; N, 5.92.

3.1.11. (±)-(1β,2α,4β)-4-Amino-1,2-cyclopentanedimethanol (4). A solution of (±)-**18** (0.18 g, 0.73 mmol) in a mixture of MeOH (3 mL) and 2N HCl (3 mL) was refluxed for 4 h, and after evaporation of the solvents remaining water was removed by azeotropic codistillation with EtOH (2×20 mL). The transparent residual paste was dissolved in MeOH (4 mL), loaded on a column of Amberlite IRA-400 (OH) (7 mL), and eluted with MeOH (100 mL). Concentration of the eluate under reduced pressure afforded (±)-**4** as a faintly yellow oil (0.10 g, 91%). IR (film) ν_{max}: 3342, 3298, 2926, 1594, 1456, 1376 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 4.57 (bs, 1H, D_2O exch., OH), 4.19 (bs, 1H, D_2O exch., OH), 3.40–3.27 (m, 4H, 2×CH_2O), 3.24 (d, 2H, D_2O exch., J=6.1 Hz, NH_2), 2.82–2.74 (m, 1H, 4-H), 1.98–1.83 (m, 2H), 1.56–1.40 (m, 2H), 1.37–1.27 (m, 1H), 0.99–0.90 (m, 1H). ^{13}C NMR (DMSO-d_6) δ: 66.08 and 64.47 (2×CH_2O), 56.37 (CHN), 49.44 and 38.68 (C1+C2), 40.07 and 30.56 (C3+C5). EIMS *m/z* (%): 146 (1, $(M+1)^+$), 145 (1, M^+), 128 (4, (M^+-OH)), 114 (87, $(M^+-(CH_2OH))$), 86 (44), 83 (13, $(M^+-(C_2H_6O_2))$), 81 (15), 79 (22), 70 (17), 69 (29), 67 (19), 58 (27), 57 (19), 56 (100). Anal. calcd for ($C_7H_{15}NO_2$) (145.20): C, 57.90; H, 10.41; N, 9.65. Found: C, 57.66; H, 10.64; N, 9.76.

For identification purposes, the triacetyl derivative (±)-**20** was prepared by treating **4** (60 mg, 0.41 mmol) with Ac_2O (2 mL) and dry Et_3N (2 mL) for 24 h at room temperature under argon. The mixture was concentrated to dryness and the solid residue was dissolved in $CHCl_3$ (15 mL). This solution was washed successively with saturated $NaHCO_3$ solution (3×20 mL) and water (3×40 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, affording a pasty residue that upon chromatography on silica gel (6 g) with 60:1 EtOAc/MeOH as eluent afforded (±)-**20** as a colorless viscous liquid (97 mg, 87%). IR (film) ν_{max}: 3283, 3074, 2950, 1738, 1651, 1551, 1446, 1368, 1240 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 5.73 (d, 1H, D_2O exch., J=7.8 Hz, NH), 4.17–4.11 (m, 1H, 4-H), 4.09–3.91 (m, 4H, 2×CH_2O), 2.35–2.24 (m, 2H), 2.10–2.05 (m, 1H), 2.04 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 1.66–1.59 (m, 2H), 1.18–1.09 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 171.60, 171.47 and 170.29 (3×CO), 68.14 and 66.35 (2×CH_2O), 53.26 (C4), 44.41 and 35.33 (C1+C2), 36.89 and 30.80 (C3+C5), 23.73 and 21.31 (3×CH_3). EIMS *m/z* (%): 271 (0.84, M^+), 228 (11, (M^+-Ac)), 198 (8), 186 (4, $(M^+-2×Ac)$), 168 (90), 151 (67), 150 (26), 138 (36), 126 (20), 110 (48), 109 (79), 108 (41), 96 (66), 94 (35), 93 (40), 92 (100), 81 (36), 79 (49), 69 (48), 68 (36), 60 (80), 56 (62). Anal. calcd for $C_{13}H_{21}NO_5$ (271.31): C, 57.55; H, 7.80; N, 5.16. Found: C, 57.72; H, 7.91; N, 4.94.

3.1.12. (±)-(1β,3α,4β)-4-Amino-1,3-cyclopentanedimethanol (5). A solution of (±)-**19** (1.10 g, 4.49 mmol) in a mixture of MeOH (20 mL) and 2N HCl (20 mL) was refluxed for 3 h, and further operations were performed as for the preparation of (±)-**4**. (±)-**5** was isolated as a viscous clear liquid (0.59 g, 92%). IR (film) ν_{max}: 3340, 3300, 2920, 1599, 1443, 1372 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 4.51 (bs, 2H, D_2O exch., 2×OH), 3.33 (d, 2H, J=5.5 Hz, CH_2O), 3.27 (d, 2H, J=6.6 Hz, CH_2O), 3.22–3.18 (m, 3H, two of them exch. D_2O, NH_2+4-H), 1.95–1.81 (m, 2H), 1.76–1.65 (m, 1H), 1.51–1.33 (m, 2H), 1.08–0.98 (m, 1H). ^{13}C NMR (DMSO-d_6) δ: 65.47 and 65.33 (2×CH_2O), 51.63 (CHN), 44.23 and 43.07 (C1+C3), 40.36 and 39.53 (C2+C5). EIMS *m/z* (%): 146 (0.85, $(M+1)^+$), 145 (0.50, M^+), 128 (5, (M^+-OH)), 114 (49, (M^+-CH_2OH)), 86 (43), 83 (7, $(M^+-(C_2H_6O_2))$), 81 (8), 79 (11), 70 (15), 69 (41), 68 (14), 67 (16), 57 (11), 56 (100). Anal. calcd for $C_7H_{15}NO_2$ (145.20): C, 57.90; H, 10.41; N, 9.65. Found: C, 57.72; H, 10.19; N, 9.89.

For identification purposes, the triacetyl derivative (±)-**21** was prepared by treating **5** (45 mg, 0.31 mmol) with Ac_2O (1 mL) and dry Et_3N (1 mL) under the same conditions, and followed by the same work-up, as for (±)-**20**, which afforded (±)-**21** as a faintly yellow viscous liquid (71 mg, 85%). IR (film) ν_{max}: 3287, 3078, 2953, 1734, 1652, 1557, 1436, 1368, 1244 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 5.73 (d, 1H, D_2O exch., J=6.2 Hz, NH), 4.28–4.21 (m, 1H, 4-H), 4.08–3.94 (m, 4H, 2×CH_2O), 2.31–2.22 (m, 1H), 2.15–2.08 (m, 1H), 2.05 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 1.89–1.80 (m, 2H), 1.73–1.63 (m, 1H), 1.29–1.20 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 171.43, 171.42 and 170.15 (3×CO), 67.39 and 67.32 (2×CH_2O), 49.88 (C4), 40.44 and 39.58 (C1+C3), 37.15 and 36.50 (C2+C5), 23.69 and 21.30 (3×CH_3). EIMS *m/z* (%): 271 (58, M^+), 228 (90, (M^+-Ac)), 198 (39), 186 (20), 168 (57), 152 (81), 151 (70), 150 (21), 138 (53), 136 (29), 128 (25), 126 (37), 110 (85), 109 (82), 108 (44), 96 (85), 94 (50), 93 (72), 92 (100), 91 (55), 81 (38), 79 (75), 69 (54), 68 (44), 60 (95), 56 (29). Anal. calcd for $C_{13}H_{21}NO_5$ (271.31): C, 57.55; H, 7.80; N, 5.16. Found: C, 57.71; H, 7.86; N, 4.93.

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References

1. Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Gudej, R. *Tetrahedron* **1994**, *50*, 10611–10670.
2. De Clercq, E. *Curr. Med. Chem.* **2001**, *8*, 1543–1572.

3. Zhu, X.-F. *Nucleosides Nucleotides Nucleic Acids* **2000**, *19*, 651–690.
4. Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17–21.
5. Daluge, S. M.; Good, S. S.; Faletto, M. B.; Miller, W. H.; St Clair, M. H.; Boone, L. R.; Tisdale, M.; Parry, N. R.; Reardon, J. E.; Dornsife, R. E.; Averett, D. R. *Antimicrob. Agents Chemother.* **1997**, *41*, 1082–1093.
6. Daluge, S. M.; Martin, M. T.; Sickles, B. R.; Livingston, D. A. *Nucleosides Nucleotides Nucleic Acids* **2000**, *19*, 297–327.
7. Hervey, P. S.; Perry, C. M. *Drugs* **2000**, *60*, 447–479.
8. Daluge, S. M. (The Wellcome Foundation Ltd). EP 434450, 1991; *Chem. Abstr. 115*, 208462.
9. Blanco, J. M.; Caamaño, O.; Fernández, F.; Gómez, G.; Nieto, M. I.; Balzarini, J.; Padalko, E.; De Clercq, E. *Nucleosides Nucleotides* **1997**, *16*, 159–171.
10. Nieto, M. I.; Blanco, J. M.; Caamaño, O.; Fernández, F.; García-Mera, X.; Balzarini, J.; Padalko, E.; Neyts, J.; De Clercq, E. *Nucleosides Nucleotides* **1998**, *17*, 1255–1266.
11. Nieto, M. I.; Blanco, J. M.; Caamaño, O.; Fernández, F.; García-Mera, X.; López, C.; Balzarini, J.; De Clercq, E. *Nucleosides Nucleotides* **1999**, *18*, 2253–2263.
12. Caamaño, O.; Fernández, F.; Gómez, G.; Nieto, M. I. *Tetrahedron* **1994**, *50*, 2175–2182.
13. Blanco, J. M.; Caamaño, O.; Fernández, F.; García-Mera, X.; Rodríguez, J. E. *Org. Prep. Proc. Int.* **1998**, *30*, 71–78.
14. Nieto, M. I.; Blanco, J. M.; Caamaño, O.; Fernández, F.; Gómez, G. *Tetrahedron* **1998**, *54*, 7819–7830.
15. Ichicawa, Y.; Sugawara, Y. Jpn. Kokai Tokkyo Koho JP03223264, 1991; *Chem. Abstr. 117*, 47983x.
16. Figueira, M. J.; Caamaño, O.; Fernández, F.; García-Mera, X.; García, M. D. *Tetrahedron* **2002**, *58*, 967–974.
17. Buenger, G. S.; Marquez, V. E. *Tetrahedron Lett.* **1992**, *33*, 3707–3710.
18. Boumchita, H.; Legraverend, M.; Bisagni, E. *Heterocycles* **1991**, *32*, 1785–1792.
19. Lee-Ruff, E.; Wan, W.-Q.; Jiang, J.-L. *J. Org. Chem.* **1994**, *59*, 2114–2118.
20. In the paper describing the preparation of (1*S-trans*)-3,3-dimethoxy-1,2-cyclobutanedimethanol it is said it could be efficiently separated from the chiral auxiliary, (−)-menthol, but no numerical yield for that separation is given: Ahmad, S. *Tetrahedron Lett.* **1991**, *32*, 6997–7000.
21. (a) Rosenquist, Å.; Kvarnström, I.; Svensson, S. C. T.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1994**, *59*, 1779–1782. (b) Rosenquist, Å.; Kvarnström, I.; Svensson, S. C. T.; Classon, B.; Samuelsson, B. *Acta Chem. Scand.* **1992**, *46*, 1127–1129.
22. Jenny, T. F. *Helv. Chim. Acta* **1993**, *76*, 248–258.
23. Krapcho, A. P.; Carson, J. R.; Eldridge, J. M. *J. Org. Chem.* **1977**, *42*, 3749–3753.
24. Acott, B.; Beckwith, A. L. J.; Hassanali, A.; Redmond, J. *Tetrahedron Lett.* **1965**, *45*, 4039–4045.
25. Baumgarten, H. E.; Smith, H. L.; Staklis, A. *J. Org. Chem.* **1975**, *40*, 3554–3561.
26. Csuk, R.; von Sholz, Y. *Tetrahedron* **1994**, *50*, 10431–10442.
27. The crystallographic data of **18** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 179869. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.