Pergamon

Tetrahedron 58 (2002) 967–974

TETRAHEDRON

# Synthetic approaches to (±)-*c*-4-amino-*r*-1,*c*-2,*t*-3-cyclopentanetrimethanol: a precursor of higher homologues of *xylo*-carbocyclic nucleosides

María José Figueira, Olga Caamaño,* Franco Fernández, Xerardo García-Mera and Marcos Daniel García

*Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Santiago de Compostela, E-15782 Santiago de Compostela, Spain*

Received 9 October 2001; revised 28 November 2001; accepted 30 November 2001

**Abstract**—Aminoalcohol **3**, a compound of interest for the synthesis of carbocyclic analogs of nucleosides, was prepared from (±)-(2*endo*,3*exo*)bicyclo[2.2.1]hept-5-ene-2,3-dimethanol. In the key step, oxidative degradation of a carboxamide was efficiently achieved by treatment of amidoester **10** with lead tetraacetate in *tert*-butanol. © 2002 Published by Elsevier Science Ltd.

## 1. Introduction

A number of nucleosides and nucleoside analogs are known to be potent selective inhibitors of the replication of HIV-1, HSV-2, HBV and/or HCMV in vitro and in vivo, and some now constitute the basis of clinically important therapies.[1] One major class of modified nucleosides comprises the carbocyclic nucleosides,[2] in which the furan ring is replaced by a carbocycle. Aristeromycin (**1**), a natural member of this family obtained from *Streptomyces citricolor*,[3] is highly toxic to cell cultures,[4] is active against vaccinia virus[5] and inhibits AdoHcy hydrolase with a $K_i$ of 5 nM.[6] Abacavir (**2**)[7] is a synthetic cyclopentenoid nucleoside with great anti-HIV activity that is used clinically to treat AIDS and AIDS-related complex.

Given the above precedents, a large number of carbocyclic nucleoside derivatives of pentane, with pseudosugar configurations matching those of all the pentofuranoses, have been prepared and subjected to more or less extensive evaluation of their biological activity.[8–12] Both antiviral and antitumoural activities have been found among those with *xylo* configuration.[13,14]

In view of the above, and of the fact that there are also biologically active nucleoside analogs that have a hydroxymethyl group directly bound to the carbocycle,[15] we have embarked on the development of versatile methods for the synthesis of series of higher homologues of carbocyclic nucleosides. Here we describe a convenient synthesis of the aminotriol **3**, a key intermediate in the preparation of higher homologues of *xylo*-carbocyclic nucleosides such as **4** (Fig. 1).

## 2. Discussion

Direct retrosynthetic analysis led to the choice of

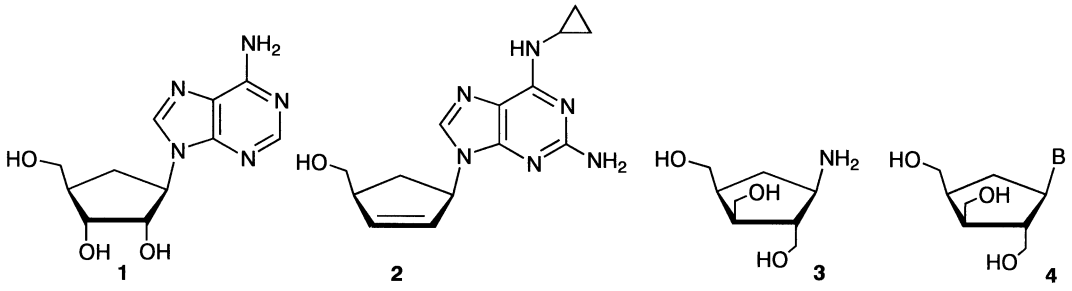
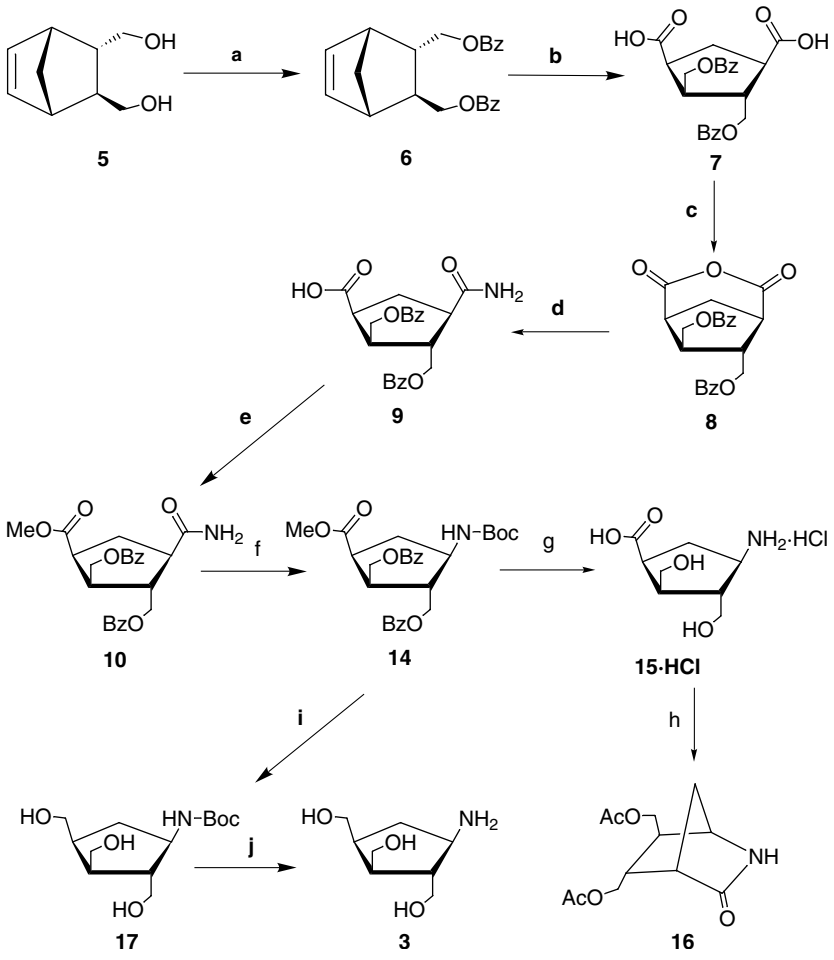



**Figure 1.**

*Keywords*: *xylo*-carbocyclic nucleosides; oxidative degradation; aminoalcohol.

0040–4020/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4020(01)01191-7




**Scheme 1.** (a) BzCl, pyridine, rt, 48 h; (b) $KMnO_4$, AcOH, Aliquat 336, benzene, rt, 5 h; (c) $Ac_2O$, reflux, 24 h; (d) $NH_3$ gas, THF, 0°C, 45 min; (e) MeOH, *p*-TsOH; (f) $Pb(OAc)_4$, *t*-BuOH, $Et_3N$, reflux, 2 h; (g) 12N HCl, AcOH, reflux, 12 h; (h) $LiAlH_4$, THF, reflux, 6.5 h; (i) 1.5 M DIBAL-H in toluene, −75°C, 2.5 h; (j) 2N HCl, MeOH, reflux, 4 h; then Amberlite IRA-400 (OH), MeOH.

(±)-(2*endo*,3*exo*)-bicyclo[2.2.1]hept-5-eno-2,3-dimethanol (**5**) as starting material. This compound is easily obtained by $LiAlH_4$ reduction of the product of the Diels–Alder reaction between diethyl fumarate and cyclopentadiene,[16] and oxidative cleavage of its double bond, followed by modification of the resulting carboxy groups, would lead to a final product with the desired configuration.

The route actually followed is shown in Scheme 1 (in which all compounds represent racemic mixtures). Diol **5** was protected as its bis-benzoate (**6**), which afforded the dicarboxylic acid **7** when subjected to oxidative ring-opening with potassium permanganate in $CH_2Cl_2$/AcOH in the presence of Aliquat 336. Heating **7** in refluxing acetic anhydride gave the cyclic anhydride **8** in excellent yield. Gaseous ammonia treatment of a solution of **8** in dry THF at 0–5°C then afforded the carbamoylcarboxylic acid **9** with a high selectivity that is attributed to the two carbonyl groups being associated with different degrees of steric hindrance to nucleophilic attack, the neighboring benzoyloxymethyl group being *cis* to the carbonyl in one case and *trans* in the other (the reactive carbonyl was assumed to be the one with the *trans* benzoyloxymethyl) (Fig. 2).

Oxidative degradation of the carbamoyl group of **9** under classical Hofmann conditions afforded an intractable mixture that NMR studies showed to include the products of partial deprotection of the hydroxymethyl groups. Treatment of the ester **10** with HTIB in acetonitrile,[17] followed by 4N NaOH, likewise led to a complex mixture, from which only a 12% yield of the aminoester **11** was isolated; while treatment of **10** with lead tetraacetate in refluxing acetic acid[18,19] gave an even smaller yield of the acetamide ester **12** (9%, although 35% of the starting material was

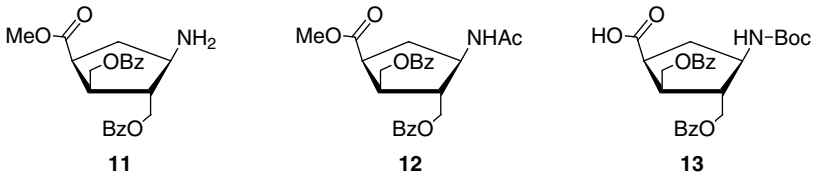



**Figure 2.**

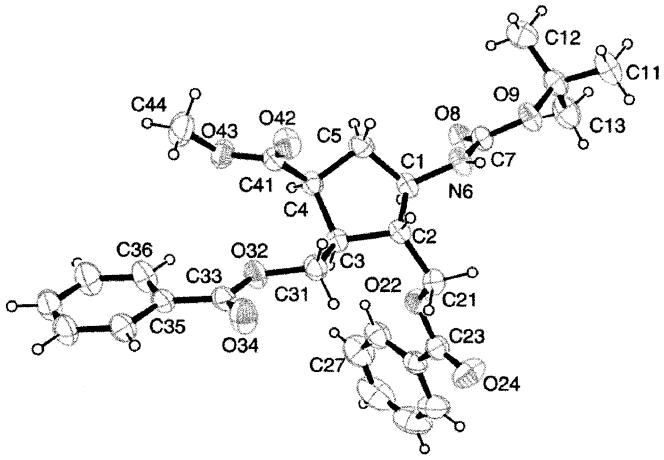



**Figure 3.** X-Ray crystallographic structure of **14**.

recovered). However, treatment of **9** with lead tetraacetate in *tert*-butyl alcohol, with triethylamine as catalyst, gave the *N*-Boc derivative **13** as the only product in 59% yield, and application of the same procedure to the ester **10** afforded a 93% yield of the corresponding ester **14**, the structure of which was confirmed by an X-ray diffractometric study of a single crystal (Fig. 3).[20] Though obtained from a racemic solution, this crystal was composed solely of molecules with 1S configuration. Their structure confirmed that in step **8→9** it was the carbonyl *trans* to its neighboring OBz that was reactive, and also that no epimerization processes occurred under the reaction conditions used to arrive at **14**.

Transformation of **14** into **3** requires both the reduction of the ester group and deprotection of the nitrogen. Deprotection by acid hydrolysis gave the hydrochloride form of an amino acid (**15**·HCl), which after reduction with excess $LiAlH_4$ in refluxing THF was treated with water (just sufficient to destroy the excess $LiAlH_4$), concentrated to dryness, and then treated with acetic anhydride and pyridine.[21] These post-reduction steps were carried out under the assumption that the reduction product was **3**, and were aimed at obtaining a peracetylated product that would be more easily isolatable than this aminopolyol, but in the event only the lactam **16** was isolated, in 82% yield. This is not the first time we have obtained bicyclic lactams upon $LiAlH_4$ treatment of *cis*-1,3-disubstituted cyclopentanes with a sterically hindered carbonyl.[19]

In view of the above, we decided to reduce the ester group before removal of Boc. Selective reduction of **14** with $LiBH_4$,[22] followed by conventional work-up, afforded just a 25% yield of the tris(hydroxymethyl)carbamate **17**, although the total yield of compounds readily convertible to **3** increased to 47% when the aqueous phase obtained during work-up was concentrated to dryness and the resulting solid was acetylated, chromatographic fractionation of the products affording the carbamate **18** and the formamide **19** in 4 and 18% yield, respectively. However, reduction of **14** with DIBAL–H[23] directly gave 59% yield of **17**. Finally, the Boc group was removed with refluxing HCl (2N in methanol), and the resulting solution of **3**·HCl was passed through a basic ion-exchange resin (Amberlite IRA-400 (OH)) to obtain the free aminoalcohol **3** (Fig. 4).

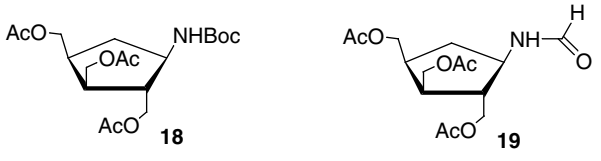



**Figure 4.**

## 3. Experimental

### 3.1. General

Silica gel (230 mesh) was purchased from Merck. All other chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. Melting points were measured in a Reichert Kofler Thermopan and are uncorrected. Infrared spectra were recorded in a Perkin–Elmer 1640 FTIR spectrophotometer. $^1$H NMR spectra (300 MHz) and $^{13}$C NMR spectra (75.47 MHz) were recorded in a Bruker AMX 300 spectrometer, using TMS as internal standard (chemical shifts in $\delta$ values, $J$ in Hz). Mass spectra were recorded on a Kratos MS-59 spectrometer. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TCL on pre-coated silica gel plates (Merck 60 F254, 0.25 mm). X-Ray diffraction data were collected in an Enraf Nonius CAD4 automatic diffractometer using the program CAD4-EXPRESS.

**3.1.1. (±)-(2*endo*,3*exo*)-Bicyclo[2.2.1]hept-5-en-2,3-dimethanol dibenzoate (6).** Benzoyl chloride (11.39 mL, 97.76 mmol) was added dropwise under argon, over 20 min, to a solution of diol **5** (6.16 g, 39.94 mmol) in dry pyridine (46 mL). The reaction mixture was stirred at room temperature for 48 h, cooled to 5–10°C, brought to strongly basic pH with aqueous 2N NaOH, and extracted with $Et_2O$ (2×150 mL). The pooled organic phases were washed with $H_2O$ and dried ($Na_2SO_4$) and the solvent was removed in vacuo, leaving **6** as a colorless oily residue (14.04 g, 97%). IR (film): 2967, 1718, 1450, 1314, 1271, 1111, 709 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 8.09–8.04 [m, 4H, 2×(2′-H+6′-H)]; 7.59–7.56 (m, 2H, 2×4′-H); 7.55–7.41 [m, 4H, 2′(3′-H+5′-H)]; 6.32 (dd, 1H, $J$=5.67, 3.13 Hz,

*H*C═CH); 6.15 (dd, 1H, *J*=5.67, 2.85 Hz, HC═C*H*); 4.50 (dd, 1H, *J*=10.93, 6.54 Hz, C*H*HOBz); 4.34 (dd, 1H, *J*=10.93, 8.59 Hz, CH*H*OBz); 4.19 (dd, 1H, *J*=10.79, 6.84 Hz, C*H*HOBz); 4.07 (dd, 1H, *J*=10.79, 8.94 Hz, CH*H*OBz); 3.01 (s, 1H, 1-H ó 4-H); 2.83 (s, 1H, 4-H ó 1-H); 2.30–2.22 (m, 1H, 2*exo*-H); 1.63–1.55 (m, 3H, 3*endo*-H+7-$H_2$). $^{13}$C NMR ($CDCl_3$) $\delta$: 167.00 and 166.89 (2′CO); 138.33 and 134.55 (C═C); 133.39 and 133.33 (2′C4′); 130.69 and 130.62 (2′C1′); 130.01 and 130.00 [2×(C2′+C6′)]; 128.82 and 128.80 [2×(C3′+C5′)]; 68.62 and 68.33 (2×*C*$H_2$OBz); 46.72 (C7); 44.93 and 44.61 (C1+C4); 43.46 and 42.97 (C2+C3). EIMS *m*/*z* (%): 362 (M, 4); 175 (34); 105 (100); 77 (60); 66 (37); 51 (14). Anal. calcd for $C_{23}H_{22}O_4$ (362.42): C, 76.22; H, 6.12. Found: C, 76.42; H, 6.35.

**3.1.2. (±)-*c*-4,*t*-5-Bis(benzoyloxymethyl)-*r*-1,*c*-3-cyclopentanedicarboxylic acid (7).** A solution of **6** (5.00 g, 13.80 mmol) in benzene (210 mL) was added dropwise to a vigorously stirred solution of $KMnO_4$ (6.65 g, 42.1 mmol), Aliquat 336 (1.00 g, 2.49 mmol) and AcOH (1.53 mL) in water (210 mL) at 0–5°C. The mixture was stirred at room temperature for 5 h, cooled to 5–10°C, treated dropwise with a solution of $Na_2S_2O_5$ (8.00 g, 42.03 mmol) in the least possible quantity of water, and acidified with 2N $H_2SO_4$ (30 mL). The aqueous phase was extracted with $Et_2O$, this extract was pooled with the organic phase, and this combined organic phase was washed with saturated $Na_2CO_3$ solution until the washings were basic. This basic extract was acidified with 2N $H_2SO_4$ and kept at 0°C for 12 h, and the resulting precipitate was filtered out. Crystallization from toluene afforded **7** as a white solid (4.64 g, 79%). Mp 134–135°C. IR (KBr): 2964, 1713, 1490, 1451, 1313, 1298, 1271, 1116, 711 $cm^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 9.99 (bs, 2H, $D_2O$ exch., 2×$CO_2$H); 7.99–7.95 [m, 4H, 2×(2′-H+6′-H)]; 7.56–7.47 (m, 2H, 2×4′-H); 7.43–7.34 [m, 4H, 2×(3′-H+5′-H)]; 4.54–4.41 (m, 4H, 2×$CH_2$OBz); 3.13–3.06 (m, 1H); 2.91–2.80 (m, 2H); 2.74–2.65 (m, 1H); 2.46–2.36 (m, 1H); 2.30–2.20 (m, 1H). $^{13}$C NMR ($CDCl_3$): 180.15 and 179.41 (2×$CO_2$H); 166.82 and 166.67 (2×*C*OPh); 133.62 and 133.53 (2×C4′); 130.07 and 129.99 [2×(C2′+C6′)]; 130.02 (2×C1′); 128.89 and 128.83 [2×(C3′+C5′)]; 65.86 and 64.51 (2×*C*$H_2$OBz); 46.04 and 45.67 (C1+C3); 44.35 and 44.09 (C4+C5); 32.19 (C2). Anal. calcd for $C_{23}H_{22}O_8$ (426.42): C, 64.78; H, 5.20. Found: C, 65.01; H, 5.44.

**3.1.3. (±)-*c*-4,*t*-5-Bis(benzoyloxymethyl)-*r*-1,*c*-3-cyclopentanedicarboxylium anhydride (8).** A solution of **7** (5.95 g, 13.95 mmol) in $Ac_2O$ (35 mL) was refluxed for 24 h. Removal of excess $Ac_2O$ by codistillation with dry toluene at reduced pressure afforded solid **8** (5.66 g, 99%). Mp 164–165°C. IR (KBr): 1814, 1765, 1712, 1277, 1122, 1000, 990, 708 $cm^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 8.05–8.02 [m, 4H, 2×(2′-H+6′-H)]; 7.63–7.55 (m, 2H, 2×4′-H); 7.50–7.44 [m, 4H, 2×(3′-H+5′-H)]; 4.58–4.51 (m, 2H, $CH_2$OBz); 4.50–4.38 (m, 2H, $CH_2$OBz); 3.47 (s, 1H); 3.31 (d, 1H, *J*=3.85 Hz); 2.74–2.66 (m, 2H); 2.38–2.32 (m, 1H); 2.22–2.10 (m, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$: 168.65 and 167.83 (OC–O–CO); 166.67 and 166.53 (2×Ph*C*O); 134.06 and 133.90 (2×C4′); 133.63 and 133.54 (2×C1′); 130.17, 130.07, 129.98 and 129.50 [2×(C2′+C6′)]; 129.10, 129.02, 128.89 and 128.83 [2×(C3′+C5′)]; 65.83 and 63.43 (2×*C*$H_2$OBz); 46.29 and 45.31 (C1+C3); 44.39 and 42.09 (C4+C5); 32.19 (C2). Anal. calcd for $C_{23}H_{20}O_7$ (408.40): C, 67.74; H, 4.94. Found: C, 67.89; H, 5.13.

**3.1.4. (±)-*c*-2,*t*-3-Bis(benzoyloxymethyl)-*c*-4-carbamoyl-*r*-1-cyclopentanecarboxylic acid (9).** A stream of gaseous $NH_3$ was passed for 45 min over a solution of **8** (5.68 g, 13.91 mmol) in dry THF (150 mL) in an ice bath. The resulting suspension was concentrated dryness, and the brownish solid residue (6.05 g) was taken up in water (150 mL), cooled to 0°C and acidified with 2N HCl (5 mL). Compound **9** was precipitated as a solid that was filtered out, dried to constant weight (5.74 g) and recrystallized from EtOH (4.72 g, 80%). Mp 168–170°C. IR (KBr): 3478, 3204, 2962, 1715, 1643, 1602, 1584, 1452, 1315, 1270, 1208, 1118, 1071, 1024, 709 $cm^{-1}$. $^1$H NMR (DMSO-$d_6$) $\delta$: 12.36 (bs 1H, $D_2O$ exch., $CO_2$H); 7.96–7.93 [m, 4H, 2×(2′-H+6′-H)]; 7.66–7.60 (m, 2H, 2×4′-H); 7.50–7.44 [m, 5H, 4H after $D_2O$ (2×(3′-H+5′-H)+NH*H*)]; 6.93 (bs, 1H, $D_2O$ exch., N*H*H); 4.33 (dd, 4H, *J*=12.00, 4.52 Hz, 2×$CH_2$OBz); 3.13–3.04 (m, 1H); 2.62–2.54 (m, 3H); 2.15–1.90 (m, 2H). $^{13}$C NMR (DMSO-$d_6$) $\delta$: 175.38 ($CO_2$H); 174.57 ($CONH_2$); 166.05 and 166.00 (2×PhCO); 133.63 (2×C4′); 130.03 and 129.96 (2×C1′); 129.61 and 129.57 [2×(C2′+C6′)]; 129.03 and 128.97 [2×(C3′+C5′)]; 66.57 and 65.06 (2×$CH_2$OBz); 45.91, 45.20 and 44.51 (C1+C2+C4); 42.31 (C3); 33.22 (C5). EIMS *m*/*z* (%): 198 (3); 182 (3); 181 (4); 138 (8); 123 (4); 122 (8); 106 (8); 105 (100); 93 (6); 91 (4); 84 (5); 79 (8); 78 (5); 77 (42); 66 (7); 51 (10). Anal. calcd for $C_{23}H_{23}NO_7$ (425.46): C, 64.93; H, 5.45; N, 3.29. Found: C, 65.20; O, 5.67; N, 3.45.

**3.1.5. Methyl (±)-*c*-2,*t*-3-bis(benzoyloxymethyl)-*c*-4-carbamoyl-*r*-1-cyclopentanecarboxylate (10).** A solution of **9** (1.86 g, 4.37 mmol) in dry MeOH (126 mL) was refluxed for 24 h in the presence of a catalytic amount of *p*-TsOH acid (0.05 g, 0.26 mmol). After removal of MeOH, the resulting brownish solid residue (2.04 g) was fractionated by column chromatography using 1:2 hexane/AcOEt as eluent, and the fractions containing the product were concentrated to dryness, affording **10** (1.70 g, 89%) as a colorless oil that crystallized upon cooling. Mp 81–83°C ($Et_2O$/AcOEt). IR (KBr): 3403, 3144, 2951, 1736, 1721, 1699, 1684, 1451, 1316, 1274, 1181, 1115, 708 $cm^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 8.01–7.97 [m, 4H, 2×(2′-H+6′-H)]; 7.58–7.52 (m, 2H, 2×4′-H); 7.44–7.38 [m, 4H, 4×(3′-H+5′-H)]; 6.50 (bs, 1H, $D_2O$ exch., N*H*H); 5.51 (bs, 1H, $D_2O$ exch., NH*H*); 4.59 (dd, 1H, *J*=11.55, 4.64 Hz, 2-C*H*HOBz); 4.48 (d, 2H, *J*=5.70 Hz, 3-$CH_2$OBz); 4.43 (dd, 1H, *J*=11.55, 4.84 Hz, 2-CH*H*OBz); 3.59 (s, 3H, $CH_3$); 3.14–3.11 (m, 1H); 2.82–2.65 (m, 3H); 2.43–2.41 (m, 1H); 2.31–2.26 (m, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$: 176.09 (*C*$O_2CH_3$); 174.83 ($CONH_2$); 167.19 and 166.62 (2×Ph*C*O); 133.69 and 133.54 (2×C4′); 130.04 [2×(C2′+C6′)]; 129.98 (2×C1′); 128.90 and 128.85 [2×(C3′+C5′)]; 65.59 and 64.38 (2×*C*$H_2$OBz); 52.41 ($OCH_3$); 48.01 (C1); 45.83 (C4); 45.77 (C2); 44.33 (C3); 32.69 (C5). EIMS *m*/*z* (%): 439 (1, $M^+$); 334 (3); 318 (1); 317 (2); 195 (7); 152 (17); 106 (7); 105 (100); 93 (6); 77 (36). Anal. calcd for $C_{24}H_{25}NO_7$ (439.46): C, 65.59; H, 5.73. Found: C, 65.74; H, 5.90.

**3.1.6. Methyl (±)-*c*-2,*t*-3-bis(benzoyloxymethyl)-*c*-4-amino-*r*-1-cyclopentanecarboxylate (11).** A solution of **10** (0.47 g, 1.07 mmol) in $CH_3CN$ (5.4 mL) was treated under argon with a suspension of HTIB (0.62 g, 1.07 mmol) in $CH_3CN$ (5.4 mL). The mixture was stirred at room temperature for 10 min, refluxed for 24 h, allowed to cool, filtered, and concentrated under reduced pressure. The resulting residue was treated with 0.4N NaOH (3×10 mL), and this solution was stirred and extracted with $CH_2Cl_2$ (3×25 mL). The pooled organic phases were dried over $Na_2SO_4$, and evaporation of the solvent under reduced pressure yielded 0.5 g of an oily product that was fractionated by column chromatography using 1:1, 1:1.5, 1:2 and 0:1 hexane/AcOEt mixtures as successive eluents. Removal of the solvent under reduced pressure from the fractions eluted with AcOEt gave 0.19 g of a yellowish oil that upon further chromatography with 30:1–1:1 $CH_2Cl_2$/MeOH mixtures as successive eluents afforded compound **11** (70 mg, 12%) in the last few fractions. IR (film): 2952, 1718, 1316, 1274, 1177, 1111, 1069, 710 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 8.01–7.97 [m, 4H, 2×(2′-H+6′-H)]; 7.57–7.52 (m, 2H, 2×4′-H); 7.44–7.38 [m, 4H, 2×(3′-H+5′-H)]; 4.60–4.40 (m, 4H, 2×$CH_2$OBz); 3.57 (s, 3H, $CH_3O$); 3.33 (q, 1H, $J$=7.97 Hz, 4-H); 3.16 (bs, 2H $D_2O$ exch., $NH_2$); 3.09 (q, 1H, $J$=7.86 Hz, 1-H); 2.68–2.62 (m, 1H); 2.36–2.17 (m, 2H); 2.04–1.99 (m, 1H). $^{13}C$ NMR ($CDCl_3$) $\delta$: 175.38 (*C*OOCH$_3$); 166.88 and 166.60 (2×Ph*C*O); 133.57 and 133.55 (2×C4′); 130.09 (2×C1′); 130.03 and 129.96 [2×(C2′+(C6′)]; 128.88 and 128.85 [2×(C3′+C5′)]; 64.70 and 64.51 (2×*C*H$_2$OBz); 54.59 (C4); 52.42 ($CH_3O$); 49.42 (C1); 44.14 and 43.51 (C2+C3); 37.51 (C5). EIMS *m*/*z* (%): 347 (3); 346 (14); 330 (6); 167 (9); 122 (5); 108 (12); 106 (9); 105 (100); 96 (5); 94 (5); 91 (5); 83 (5); 79 (5); 78 (5); 77 (51); 51 (7). Anal. calcd for $C_{23}H_{25}NO_6$ (411.45): C, 67.14; H, 6.12; N, 3.40. Found: C, 67.33; H, 6.31; N, 3.51.

**3.1.7. Methyl (±)-*c*-2,*t*-3-bis(benzoyloxymethyl)-*c*-4-acetamido-*r*-1-cyclopentanecarboxylate (12).** A suspension of **10** (1.00 g, 2.27 mmol) and $Pb(OAc)_4$ (1.24 g, 2.79 mmol) in AcOH (6 mL) was refluxed for 2 h. Removal of AcOH by distillation at reduced pressure left a dark brown residue that was dissolved in water (25 mL). After addition of $CH_2Cl_2$ (25 mL), neutralization of this solution with saturated $NaHCO_3$ precipitated a solid that was filtered out and washed with $CH_2Cl_2$. The organic phase was removed from the filtrate, the aqueous phase was extracted with $CH_2Cl_2$ (2×25 mL), and the pooled organic phases were dried over $Na_2SO_4$. Removal of the solvent left a residue (0.70 g) that was fractionated by column chromatography using 60:1 $CH_2Cl_2$/MeOH as eluent. The first fractions eluted afforded **12** (90 mg, 9%) as a colorless oil, and the following fractions unaltered **10** (0.35 g). Compound **12**: IR (film): 3383, 1717, 1654, 1451, 1272, 1176, 1113, 711 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 8.02–7.94 [m, 4H, 2×(2′-H+6′-H)]; 7.56–7.48 (m, 2H, 2×4′-H); 7.43–7.34 [m, 4H, 2×(3′-H+5′-H)]; 6.56 (d, 1H, $D_2O$ exch., $J$=8.84 Hz, NH); 4.57–4.36 [m, 5H, (2×$CH_2$OBz+4-H)]; 3.54 (s, 3H, $CH_3O$); 3.16–3.09 (m, 1H, 1-H); 2.65–2.55 (m, 1H); 2.41–2.31 (m, 2H); 1.95 (s, 3H, $CH_3CO$); 1.92–1.86 (m, 1H). $^{13}C$ NMR ($CDCl_3$) $\delta$: 176.10 (*C*O–O); 169.98 (*C*O–N); 166.76 and 166.53 (2×PhCO); 133.56 and 133.48 (2×C4′); 130.18 (2×C1′); 129.99 and 129.96 [2×(C2′+C6′)]; 128.85 and128.80 [2×(C3′+C5′)]; 65.33 and 64.29 (2×*C*H$_2$OBz); 52.45 (C4); 51.76 ($CH_3O$); 47.94 (C1); 45.07 and 44.59 (C2+C3); 35.95 (C5); 23.82 (*C*H$_3$CO). EIMS *m*/*z* (%): 453 (0.1, $M^+$); 288 (3); 210 (3); 209 (14); 167 (12); 166 (12); 150 (29); 106 (10); 105 (100); 77 (33). Anal. calcd for $C_{25}H_{27}NO_7$ (453.48): C, 66.21; H, 6.00; N, 3.09. Found: C, 66.33; H, 6.14; N, 3.19.

**3.1.8. (±)-*c*-2,*t*-3-Bis(benzoyloxymethyl)-*c*-4-*tert*-butoxycarbonylamino-*r*-1-cyclopentanecarboxylic acid (13).** Lead tetraacetate (0.55 g, 1.23 mmol) was added under argon to a suspension of carbamoyl acid **9** (0.42 g, 1.00 mmol) in dry *t*-BuOH (5 mL). The reaction mixture was heated to 70°C, dry $Et_3N$ (0.4 mL) was added dropwise, and this mixture was refluxed for 7 h. Removal of the solvents under vacuum left a solid residue (0.70 g) that was fractionated by column chromatography using 25:1 $CH_2Cl_2$/MeOH as eluent. Concentration of the fractions containing **13** to dryness left 0.29 g (59%) of a white solid. Mp 144–146°C, after grinding and washing with $CH_2Cl_2$. IR (KBr): 2974, 1761, 1711, 1685, 1514, 1394, 1367, 1282, 1166, 1118, 715 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$) $\delta$: 12.31 (bs, 1H, $D_2O$ exch., $CO_2H$); 7.94–7.92 [m, 4H, 2×(2′-H+6′-H)]; 7.66–7.60 (m, 2H, 2×4′-H); 7.50–7.43 [m, 4H, 2×(3′-H+5′-H)]; 7.09 (d, 1H, $D_2O$ exch., $J$=7.97 Hz, NH); 4.37–4.25 (m, 4H, 2×$CH_2$OBz); 3.82–3.76 (m, 1H, 4-H); 3.07–2.98 (m, 1H, 1-H); 2.61–2.58 (m, 1H); 2.20–2.18 (m, 1H); 2.08–2.04 (m, 1H); 1.95–1.87 (m, 1H); 1.33 [s, 9H, C($CH_3$)$_3$]. $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 174.50 ($CO_2H$); 165.71 and 165.68 (2×PhCO); 153.31 (N–CO–O); 133.29 (2×C4′); 129.73 and 129.61 (2×C1′); 129.34 and 129.22 [2×(C2′+C6′)]; 128.71 and 128.62 [2×(C3′+C5′)]; 77.70 [*C*($CH_3$)$_3$]; 65.26 and 64.67 (2×$CH_2$OBz); 52.17 (C4); 46.26 (C1); 42.18 (C3); 38.69 (C2); 34. 48 (C5); 28.21 [C(*C*H$_3$)$_3$]. EIMS *m*/*z* (%): 274 (10); 197 (15); 154 (21); 153 (37); 152 (70); 149 (23); 122 (10); 108 (12); 106 (11); 105 (100); 97 (11); 77 (35); 69 (12); 58 (18); 57 (42). Anal. calcd for $C_{27}H_{31}NO_8$ (497.54): C, 65.18; H, 6.28; N, 2.82. Found: C, 65.40; H, 6.37; N, 2.99.

**3.1.9. Methyl (±)-*c*-2,*t*-3-bis(benzoyloxymethyl)-*c*-4-*tert*-butoxycarbonylamino-*r*-1-cyclopentanecarboxylate (14).** Lead tetraacetate (1.46 g, 3.30 mmol) was added under argon to a solution of carbamoyl ester **10** (1.18 g, 2.69 mmol) in *t*-BuOH (7 mL). The mixture was heated to 70°C, $Et_3N$ (1.06 mL, 3.28 mmol) was added dropwise, and the resulting suspension was refluxed for 2 h, filtered while warm, and concentrated in vacuo, affording 1.82 g of a yellowish solid that was fractionated by column chromatography using 2:1 hexane/AcOEt (10×50 mL followed by 15×100 mL) as eluent. Concentration of fractions 7–25 to dryness yielded solid carbamate **14** (1.26 g, 92%). An analytical sample was obtained by recrystallization from AcOEt/$Et_2O$. Mp 149–150°C. IR (KBr): 3377, 2973, 1727, 1703, 1514, 1452, 1370, 1320, 1277, 1205, 1164, 1123, 712 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 8.00–7.96 [m, 4H, 2×(2′-H+6′-H)]; 7.58–7.51 (m, 2H, 2×4′-H); 7.45–7.37 [m, 4H, 2×(3′-H+5′-H)]; 5.25 (d, 1H, $D_2O$ exch., $J$=8.57 Hz, NH); 4.57 (dd, 1H, $J$=11.43, 4.44 Hz, C*H*HOBz); 4.52–4.41 (m, 2H, $CH_2$OBz); 4.41 (dd, 1H, $J$=11.43, 5.71 Hz, CH*H*OBz); 4.22–4.17 (m, 1H, 4-H); 3.57 (s, 3H, $CH_3O$); 3.11 (dt, 1H, $J$=7.72, 5.55 Hz, 1-H); 2.66–2.56 (m, 1H); 2.43–2.33 (m, 2H); 1.97–1.89 (m,

1H); 1.42 [s, 9H, $C(CH_3)_3$]. $^{13}C$ NMR ($CDCl_3$) $\delta$: 175.62 ($CO_2CH_3$); 166.79 and 166.56 (2×Ph*C*O); 155.88 (CONH); 133.53 and 133.43 (2×C4′); 130.26 (2×C1′); 130.02 [2×(C2′+C6′)]; 128.82 [2×(C3′+C5′)]; 79.83 [$C(CH_3)_3$]; 65.23 and 64.41 (2×$CH_2OBz$); 53.25 (C4); 52.37 ($CH_3O$); 47.95 (C1); 44.59 and 43.96 (C2+C3); 36.17 (C5); 28.78 [$C(CH_3)_3$]. EIMS *m/z* (%): 288 (6); 211 (9); 167 (14); 152 (9); 108 (23); 106 (10); 105 (100); 77 (30); 57 (25). Anal. calcd for $C_{28}H_{33}NO_8$ (511. 65): C, 65.74; H, 6.50; N, 2.74. Found: C, 65.91; H, 6.66; N, 2.81.

**3.1.10. (±)-*c*-4-Amino-*c*-2,*t*-3-bis(hydroxymethyl)-*r*-1-cyclopentanecarboxylic acid hydrochloride (15·HCl).** A solution of **14** (0.50 g, 0.98 mmol) in a mixture of AcOH (6.3 mL) and 12N HCl (4.2 mL) was refluxed for 12 h, and removal of the solvents in vacuo by successive coevaporations with toluene afforded 0.38 g of a solid residue that was recrystallized from EtOH/$Et_2O$ and identified as **15**·HCl (0.10 g; 49%). Mp 228–229°C. IR (KBr): 3236, 2951, 2920, 1741, 1174, 1024, 988 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$) $\delta$: 8.17 (bs, 3H, $D_2O$ exch., $NH_3^+$); 5.02 (bs, 1H, $D_2O$ exch., OH); 4.32 and 4.22 (part AB system ABX, 2H, $J$=9.25, 6.53, 1.12 Hz, 2-$CH_2$); 3.62 and 3.57 (part AB system ABX, 2H, $J$=11.30, 5.26, 4.86 Hz, 3-$CH_2$, reduces to a doublet upon treating the sample with $D_2O$, $J$=5.50 Hz); 3.32 (q, 1H, $J$=9.55 Hz, 4-H); 3.08 (dt, 1H, $J$=5.63, 10.02 Hz, 1-H); 2.77–2.69 (m, 1H, 3-H); 2.52–2.41 (m, 1H); 1.92–1.84 (m, 1H); 1.81–1.72 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 180.21 ($CO_2H$); 70.68 and 59.44 (2×$CH_2OH$); 52.98 (C4); 50.00 (C3); 41.54 and 40.93 (C1+C2); 32.31 (C5).

**3.1.11. (±)-(5*endo*,6*exo*)-5,6-Bis(acetoxymethyl)-2-aza-bicyclo-[2.2.1]-heptan-3-one (16).** **15**·HCl (60 mg, 0.29 mmol) was added under argon in one dose to a suspension of $LiAlH_4$ (20 mg, 0.53 mmol) in dry THF (4 mL) at 0°C, and the mixture was stirred at this temperature for 15 min, refluxed for 6.5 h, and cooled again to 0°C. Water was added, and removal of the solvents by successive coevaporations with toluene under reduced pressure left a white solid that was taken up in 10 mL of $Ac_2O$. After addition of pyridine (10 mL) and stirring under argon at room temperature for 24 h this mixture was concentrated to dryness, the residue was taken up in 25 mL of $NaHCO_3$, the resulting mixture was extracted with $CH_2Cl_2$ (3× 25 mL), and the pooled organic phases were dried over $Na_2SO_4$. Evaporation of the solvent in vacuo left a brown oil (70 mg) that was fractionated by column chromatography using, successively, 1:3 hexane/AcOEt, 1:4 hexane/AcOEt, AcOEt and MeOH as eluents. Lactam **16** was isolated as a white solid (60 mg, 82%) from the fractions eluted with MeOH, and was recrystallized from hexane/AcOEt. Mp 155.5–157°C. IR (KBr): 3340, 2949, 1766, 1729, 1648, 1541, 1252, 1175, 1046 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 5.64 (d, 1H, $D_2O$ exch., $J$=7.66 Hz, NH); 4.42 (dd, 1H, $J$=9.69, 6.52 Hz, C*H*HOAc); 4.30–4.24 (m, 3H, CH*H*OAc+$CH_2OAc$); 4.07 (dd, 1H, $J$=11.55, 6.79 Hz, 1-H); 3.04 (dt, 1H, $J$=5.00, 9.75 Hz, 4-H); 2.79–2.71 (m, 1H); 2.61 (ddd, 1H, $J$=13.89, 10.01, 8.36 Hz); 2.07 (s, 3H, $CH_3CO$); 2.02–1.92 (m, 1H); 1.97 (s, 3H, $CH_3CO$); 1.81 (ddd, 1H, $J$=13.91, 8.55, 5.10 Hz). $^{13}C$ NMR ($CDCl_3$) $\delta$: 179.95 (CONH); 170.75 and 170.09 (2×$CH_3CO$); 70.84 and 63.97 (2×$CH_2OAc$); 52.77 (C1); 49.40 (C4); 42.43 and 41.40 (C5+C6); 34.15 (C7); 23.27 and 20.81 (2×$CH_3CO$). EIMS *m/z* (%): 255 (4, $M^+$); 212 (M–$COCH_3$, 15); 196 (14); 177 (25); 170 (25); 154 (94); 153 (88); 152 (100); 150 (58); 140 (27); 136 (57); 126 (20); 123 (23); 108 (40); 100 (27); 94 (32); 92 (40); 91 (33); 82 (40); 79 (27); 69 (34); 60 (40); 58 (35). Anal. calcd for $C_{12}H_{17}NO_5$ (255.27): C, 56.46; H, 6.71; N, 5.49. Found: C, 56.59; H, 6.88; N, 5.56.

**3.1.12. Reduction of 14: preparation of *tert*-butyl (±)-*N*-[*t*-2,*c*-3,*c*-4-tris(hydroxymethyl)-*r*-1-cyclopentyl]carbamate (17), (±)-*c*-4-*tert*-butoxycarbonylamino-*r*-1,*t*-2,*c*-3-cyclopentyltrimethyl triacetate (18) and (±)-*c*-4-formylamino-*r*-1,*t*-2,*c*-3-cyclopentyltrimethyl triacetate (19).** *Method A*. $LiBH_4$ (0.67 g, 30.8 mmol) was suspended in dry THF (150 mL) and refluxed under argon for 1 h. A solution of **14** (1.50 g, 2.93 mmol) in dry THF (20 mL) was added dropwise, refluxing was continued for 4 h, MeOH (15 mL) and water (3 mL) were added, and refluxing was continued for another 30 min. The organic solvents were removed under reduced pressure and the resulting solid residue was dissolved in water (75 mL). This solution was extracted with AcOEt (4×74 mL), and the pooled organic extracts were dried over $Na_2SO_4$ and concentrated to dryness in vacuo, yielding 0.80 g of a solid that was fractionated by column chromatography using, successively, 1:1, 1:2 and 1:4 hexane/AcOEt, AcOEt and 3:1 AcOEt/MeOH as eluents. Removal of the solvent from the last fractions eluted left the trihydroxycarbamate **17** (0.20 g, 25%) as a colorless oil. IR (film): 3387, 2926, 2247, 1654, 1560, 1363, 914 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 5.07 (d, 1H, $D_2O$ exch., $J$=8.31 Hz, NH); 4.15 (bs, 3H, $D_2O$ exch., 3× OH); 3.79–3.59 (m, 7H, 3×C$H_2$OH+1-H); 2.28–2.22 (m, 1H); 2.17–2.02 (m, 2H); 1.64–1.53 (m, 1H); 1.43 [s, 9H, $C(CH_3)_3$]; 1.40–1.29 (m, 1H). $^{13}C$ NMR ($CDCl_3$) $\delta$: 156.73 (NCOO); 79.87 [$C(CH_3)_3$]; 62.63 (2×$CH_2OH$); 61.71 ($CH_2OH$); 52.62 (C1); 51.47 (C2); 43.90 (C3); 40.31 (C4); 34.55 (C5); 28.35 [$C(CH_3)_3$]. Anal. calcd for $C_{13}H_{25}NO_5$ (275.34): C, 56.71; H, 9.15; N, 5.09. Found: C, 56.88; H, 9.28; N, 5.19.

The aqueous phases obtained above during the extraction with AcOEt were pooled and concentrated to dryness, and the resulting solid residue was taken up in $Ac_2O$ (40 mL). After addition of pyridine (40 mL), this solution was stirred for 30 h, the solvents were removed under reduced pressure, and the brown residue so obtained was taken up in $NaHCO_3$ (50 mL). This solution was extracted with AcOEt (2× 50 mL), and the pooled organic phases were dried over $Na_2SO_4$ and concentrated, affording 0.20 g of an oil that was fractionated by column chromatography on silica gel using 1:5 hexane/AcOEt (3×10 mL) and AcOEt (10× 10 mL) as successive eluents. Carbamate **18** (0.05 g, 4%) was isolated from the fractions eluted with hexane/AcOEt, and formamide **19** (0.17 g, 18%) from those eluted with AcOEt.

*Compound* **18**: transparent oil. IR (film): 3628, 3362, 2972, 1684, 1506, 1456, 1243, 1034 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 4.58 (bs, 1H, $D_2O$ exch., NH); 4.21 (dd, 1H, $J$=11.14, 4.48 Hz, C*H*HOAc); 4.12–4.06 (m, 5H, CH*H*OAc+2× $CH_2OAc$); 3.85–3.76 (m, 1H, 1-H); 2.41–2.35 (m, 1H); 2.27–2.20 (m, 2H); 2.05 (s, 9H, 3×$CH_3CO$); 1.85–1.83 (m, 1H); 1.43 [s, 9H, $C(CH_3)_3$]; 1.40–1.32 (m, 1H). $^{13}C$

NMR ($CDCl_3$) $\delta$: 171.39, 171.29 and 171.21 (3×$CH_3CO$); 155.79 (NCOO); 80.38 [$C(CH_3)_3$]; 65.36, 64.86 and 64.63 (3×$CH_2OAc$); 53.50 (C1); 48.50 (C2); 40.96 (C3); 37.99 (C4); 36.33 (C5); 28.76 [$C(CH_3)_3$]; 21.32 (3×$CH_3CO$). EIMS *m/z* (%): 328 (3); 241 (15); 240 (100); 225 (23); 224 (14); 182 (13); 180 (36); 165 (55); 164 (28); 122 (26); 121 (25); 120 (29); 108 (22); 105 (17); 93 (13); 57 (63). Anal. calcd for $C_{19}H_{31}NO_8$ (401.45): C, 56.84; H, 7.78; N, 3.49. Found: C, 57.06; H, 7.92; N, 3.59.

*Compound* **19**: colorless oil. IR (film): 3648, 3362, 2959, 1734, 1654, 1541, 1458, 1388, 1242, 1034 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 8.14 (s, 1H, NCHO); 6.25 (bs, 1H, $D_2O$ exch., NH); 4.21 (dd, 1H, *J*=11.41, 4.92 Hz, C*H*HOAc); 4.18–4.05 (m, 6H, CH*H*OAc+2×$CH_2OAc$+4-H); 2.46–2.44 (m, 1H); 2.32–2.23 (m, 2H); 2.05 (s, 9H, 3×$CH_3CO$); 2.03–1.94 (m, 1H); 1.43–1.39 (m, 1H). $^{13}C$ NMR ($CDCl_3$) $\delta$: 171.41, 171.36 and 171.25 (3×$CH_3CO$); 161.30 (NCHO); 65.17, 64.63 and 64.37 (3×$CH_2OAc$); 50.75 (C4); 48.11 (C3); 41.25 (C2); 38.38 (C1); 35.82 (C5); 21.33, 21.28 and 21.23 (3×$CH_3CO$). EIMS *m/z* (%): 286 (0.1, M−$COCH_3$); 269 (2); 226 (7); 149 (63); 136 (37); 122 (28); 121 (31); 120 (20); 109 (22); 108 (23); 105 (31); 104 (100); 94 (18); 93 (36); 91 (40); 81 (25); 79 (36); 69 (28). Anal. calcd for $C_{15}H_{23}NO_7$ (329.35): C, 54.70; H, 7.04; N, 4.25. Found: C, 54.98; H, 7.21; N, 4.44.

*Method B*. A solution of **14** (0.94 g, 1.84 mmol) in dry toluene (25 mL) was slowly added under argon to a commercial 1.5 M solution of DIBAL-H in toluene (14 mL, 21 mmol) at −75°C. This mixture was stirred for 2.5 h at −75°C, 10:1 toluene/MeOH (11 mL), MeOH (2 mL) and water (10 mL) were successively added at the same temperature, and when the resulting mixture had reached room temperature the solid formed was filtered out and washed with AcOEt (150 mL). The pooled filtrates were dried over $Na_2SO_4$, and removal of the solvents under reduced pressure left an oily residue (0.63 g) that was fractionated by column chromatography using 1:2 hexane/AcOEt followed by AcOEt as eluents. Concentration in vacuo of the fractions containing product yielded **17** (0.30 g, 59%) as a colorless oil identical to that obtained by method A.

**3.1.13. (±)-*c*-4-Amino-*r*-1,*c*-2,*t*-3-cyclopentanetrimethanol (3).** A solution of **17** (150 mg, 0.54 mmol) in MeOH (4 mL) and 2N HCl (4 mL) was refluxed for 4 h. Removal of the solvents by successive coevaporations with toluene and EtOH then yielded **3**·HCl as a dense yellowish oil (0.15 g). $^1H$ NMR (DMSO-$d_6$), $\delta$: 7.93 (bs, 3H, $D_2O$ exch., $NH_3^+$); 4.89 (bs, 2H, $D_2O$ exch., 2×OH); 4.35 (t, 1H, $D_2O$ exch., *J*=5.05 Hz, OH); 3.67–3.38 (m, 6H, 3×$CH_2OH$); 3.26–3.19 (m, 1H, 4-H); 2.15–1.91 (m, 2H); 1.90–1.71 (m, 2H); 1.49–1.40 (m, 1H).

A solution of 0.14 g of this oil in MeOH (2.5 mL) was loaded on a column of Amberlite IRA-400 ($Cl^-$) (4.7 mL) in water (previously activated with 33 mL of 1N NaOH), and was eluted with MeOH (30 mL). Concentration in vacuo of the alkaline solution so obtained yielded amino-alcohol **3** as a dense ochre-colored oil (93 mg, 98%). IR (film): 3356, 1458, 1027 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$) $\delta$: 3.54–3.33 (m, 6H, 3×$CH_2OH$); 2.84–2.76 (m, 1H, 4-H); 2.07–2.00 (m, 1H); 1.85–1.76 (m, 2H); 1.33–1.24 (m, 1H); 1.10–1.00 (m, 1H). $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 64.04, 62.28 and 61.95 (3×$CH_2OH$); 54.98 (C4); 53.84 (C3); 45.59 (C2); 41.72 (C1); 39.39 (C5). Anal. calcd for $C_8H_{17}NO_3$ (175.23): C, 54.84; H, 9.78; N, 7.99. Found: C, 55.05; H, 9.96; N, 8.12.

## Acknowledgements

The authors thank the Spanish Ministry of Education and Science (MEC-DGICYT) and the Xunta de Galicia for financial support under project PB94-0617 and XUGA 20309B98, respectively.

## References

1. (a) De Clercq, E. *Clin. Microbiol. Rev.* **1995**, 200–239. (b) Kolb, M. V. *Prog. Drug Res.* **1997**, *48*, 195–232. (c) Colacino, J. M.; Staschke, K. A. *Prog. Drug Res.* **1998**, *50*, 259–322.
2. For recent reviews on CANs: (a) Zhu, X.-F. *Nucleosides, Nucleotides Nucleic Acids* **2000**, *19*, 651–690. (b) Marquez, V. E. *Adv. Antiviral Drugs Des.* **1996**, *2*, 89–146. (c) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611–10670. (d) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571–623.
3. (a) Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T. K. *J. Antibiot.* **1968**, *21*, 255–263. (b) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885–3887. (c) Boyer, S. J.; Leahy, J. W. *J. Org. Chem.* **1997**, *62*, 3976–3980.
4. Shealy, Y. F.; Clayton, J. D. *J. Pharm. Sci.* **1973**, *62*, 858–859.
5. Houston, D. M.; Dolence, E. K.; Keller, B. T.; Patel-Thombre, U.; Borchardt, R. T. *J. Med. Chem.* **1985**, *28*, 471–477.
6. Guranowski, A.; Montgomery, J. A.; Cantoni, G. L.; Chiang, P. K. *Biochemistry* **1981**, *20*, 110–115.
7. (a) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192–4193. (b) Daluge, S. M.; Good, S. S.; Faletto, M. B.; Miller, W. H.; Wayne, H.; St. Clair, M. H.; Boone, L. R.; Tisdale, M.; Parry, N. R.; Reardon, J. E.; Dornsife, R. E.; Averett, D. R. R.; Krenitsky, T. A. *Antimicrob. Agents Chemother.* **1997**, *41*, 1082–1093. (c) Faletto, M. B.; Miller, W. H.; Garvey, E. P.; St. Clair, M. H.; Daluge, S. M.; Good, S. S. *Antimicrob. Agents Chemother.* **1997**, *41*, 1099–1107. (d) Foster, R. H.; Faulds, D. *Drugs* **1998**, 729–736.
8. Shealy, Y. F.; Clayton, J. D. *J. Pharm. Sci.* **1973**, *62*, 1432–1434.
9. Vince, R.; Daluge, S. *J. Med. Chem.* **1977**, *20*, 612–613.
10. Shealy, Y. F.; O'Dell, C. A.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1983**, *26*, 156–161.
11. Shealy, Y. F.; Clayton, J.; Arnett, G.; Shannon, W. M. *J. Med. Chem.* **1984**, *27*, 670–674.
12. Peterson, M. L.; Vince, R. *J. Med. Chem.* **1990**, *33*, 1214–1219.
13. Vince, R.; Brownell, J.; Daluge, S. *J. Med. Chem.* **1984**, *27*, 1358–1360.
14. Vince, R.; Turakhia, R. H.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1987**, *30*, 2026–2030.

15. (a) Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ichikawa, Y.-I.; Takahashi, T. *J. Antibiot.* **1989**, *42*, 1854–1859. (b) Norbeck, D. W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erickson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. *J. Med. Chem.* **1990**, *33*, 1281–1285. (c) Smee, D. F.; Barnett, B. B.; Sidwell, R. W.; Reist, E. J.; Holy, A. *Antiviral Res.* **1995**, *26*, 1. (d) Yang, H. R.; Drain, R. L.; Franco, C. A.; Clark, J. M. *Antiviral Res.* **1996**, *29*, 233–241. (e) Tenney, D. J.; Yamanaka, G.; Voss, S. M.; Cianci, C. W.; Tuomari, A. V.; Sheaffer, A. K.; Alam, M.; Colonno, R. J. *Antimicrob. Agents Chemother.* **1997**, *41*, 2680–2685.
16. Naemura, K.; Nakazuki, M. *Bull. Chem. Soc. Jpn* **1973**, *46*, 888–892.
17. (a) Lazbin, I. M.; Koser, G. F. *J. Org. Chem.* **1987**, *52*, 476–477. (b) Vasudevan, A.; Koser, G. F. *J. Org. Chem.* **1988**, *53*, 5158–5160.
18. Handa, S.; Earlam, G. J.; Geary, P. J.; Hawes, J. E.; Phillips, G. T.; Pryce, R. J.; Ryback, G.; Shears, J. H. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1885–1886.
19. Nieto, M. I.; Blanco, J. M.; Caamaño, O.; Fernández, F.; Gómez, G. *Tetrahedron* **1998**, *54*, 7819–7830.
20. The crystallographic data of **14** have been deposited at Cambridge Crystallographic Data Centre as supplementary publication No. 14 CCDC 171793. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.
21. Figueira, M. J.; Blanco, J. M.; Caamaño, O.; Fernández, F.; García-Mera, X.; López, C. *Synthesis* **2000**, 1459–1463.
22. Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000–4005.
23. Csuk, R.; von Scholz, V. *Tetrahedron* **1994**, *50*, 10431–10442.