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Synthesis of (±)-*c*-4-amino-*r*-1,*t*-2,*c*-3-cyclopentanetrimethanol and higher homologues of 8-azapurine arabino-carbocyclic nucleosides

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Abstract—(±)-*c*-4-Amino-*r*-1,*t*-2,*c*-3-cyclopentanetrimethanol (**4**) was synthesized from previously reported (±)-*c*-4,*t*-5-bis(benzoyloxymethyl)-*r*-1,*c*-3-cyclopentanedicarboxylic anhydride by methanolysis (which selectively esterified the less hindered carboxyl), oxidative degradation of the other to an amino group, and DIBAL-H reduction. Amino alcohol **4** was then converted into (±)-*c*-4-[(5-amino-6-chloropyrimidin-4-yl)amino]-*r*-1,*t*-2,*c*-3-cyclopentanetrimethanol, which was used for synthesis of 8-azapurine arabino-carbocyclic nucleoside analogues. Two *N*,*N*′-dicyclopentanylurea derivatives obtained as side products of the synthesis of **4** are also described.

1. Introduction

Research on modified nucleosides, notably carbocyclic analogues of nucleosides (CANs), has been spurred by the finding that certain members of this class are effective against viral diseases.[1] Ara-A (**1a**, 9-β-D-arabinofuranosyladenine) is active against a broad spectrum of DNA viruses,[2] but its clinical utility is limited by its being rapidly deaminated by adenosine deaminase to Ara-H (**1b**), which is considerably less active.[3] This problem is not shared by compounds such as the arabino-carbocyclic adenosine analogue cyclaradine (**2**)[4] or certain 8-aza CANs such as **3** (Fig. 1).[5] In view of this, and of the fact that there are also biologically active CANs in which one of the hydroxyls bound to the usual carbocycle have been replaced by hydroxymethyl[6] we have embarked on the development of versatile methods for the synthesis of series of such CANs.[7] Here we describe a convenient synthesis of the aminotriol **4**, which is a key intermediate in the preparation of higher homologues of arabino-carbocyclic nucleosides.

2. Results and discussion

The route developed is shown in Scheme 1, in which all compounds are racemic mixtures. Anhydride **5** can be easily obtained from (±)-(2*endo*,3*exo*)-bicyclo[2.2.1]hepten-5-eno-2,3-dimethanol,[8] following protection of its hydroxymethyl groups by benzoylation, oxidative cleavage of their double bond and dehydration.[7] Methanolysis of **5** selectively afforded the hemiester **6** through attack on the less-hindered carbonyl. Two paths were then taken to the protected amine **9**, and reduction of its methoxycarbonyl

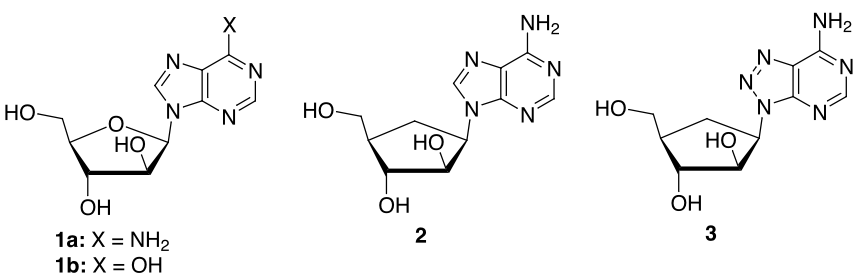

Figure 1.

Keywords: amino alcohol; homologues of arabino-carbocyclic nucleoside; 8-azapurine; acylazide; carboxamide; oxidative degradation; DIBAL-H ester reduction.

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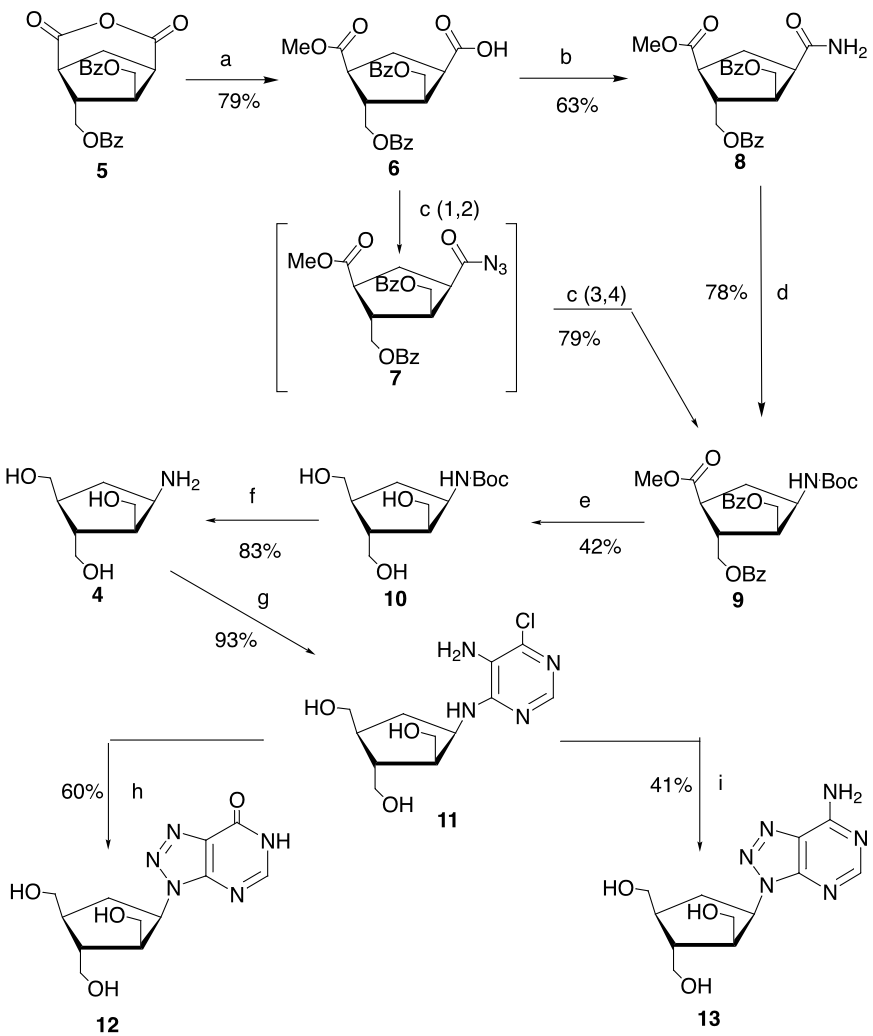

Scheme 1. (a) MeOH, reflux, 12 h; (b) $SOCl_2$, reflux, 6 h; then NH_4OH, CH_2Cl_2, rt, 18 h; (c) (1) ClCOOEt, acetone, Et_3N, −10 to 0°C, 2 h; (2) NaN_3/H_2O, −10 to 0°C, 1.5 h; (3) toluene, 80°C, 1 h; (4) *t*-BuOH, reflux, 17 h; (d) $Pb(AcO)_4$, *t*-BuOH, Et_3N, reflux, 5 h; (e) 1.5 M DIBAL-H, toluene, −75°C, 4 h; (f) 2N HCl, MeOH, reflux, 4 h; then Amberlite IRA-400 (OH); (g) 5-amino-4,6-dichloropyrimidine, Et_3N, *n*-butanol, reflux, 84 h; (h) $NaNO_2$, AcOH, H_2O, rt, 18 h; (i) $NaNO_2$, 1N HCl, H_2O, 0°C, 0.5 h; then 14 M NH_4OH, reflux, 2 h.

followed by removal of protecting groups afforded amino alcohol **4**, on which 8-azapurines were then constructed.

The first path from **6** to **9** consisted in treatment of **6** with ethyl chloroformate to obtain the corresponding mixed anhydride, conversion of the latter to acylazide **7** (not isolated) by reaction with sodium azide,[9] Curtius rearrangement of the azidocarbonyl group, and reaction with *t*-BuOH. The yield of **9** was found to be very sensitive to reaction conditions, temperature and reagent proportions and/or concentrations in both the first and second steps. Solvent used for extraction of the acylazide from the crude reaction mixture prior to its rearrangement, which influence the water content of the reaction mixture in the second step, seems also to be an important factor. In particular, the conditions affording the best yield (79% from **6**) differed from those used in less efficient procedures in that the temperature at which the first and second steps were carried out was lowered from 3–4°C to between −10 and 0°C, the sodium azide for step 2 was dissolved in the minimum possible amount of water, and the acylazide was extracted into CH_2Cl_2 instead of Et_2O.

In one of the experiments carried out to optimize the above path, work-up of a crude product in which the yield of **9** was only 20% also afforded the diastereomeric *N*,*N*′-disubstituted ureas **14** and **15** (Fig. 2), the structures of which were unequivocally determined by X-ray crystallographic

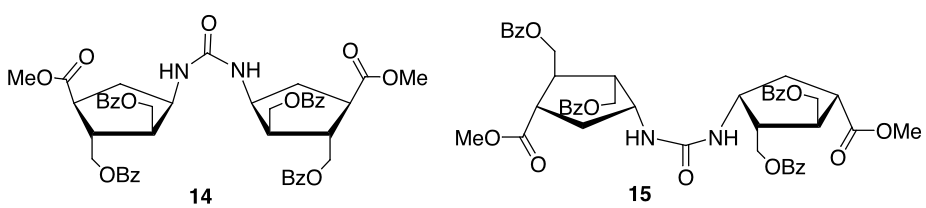

Figure 2.

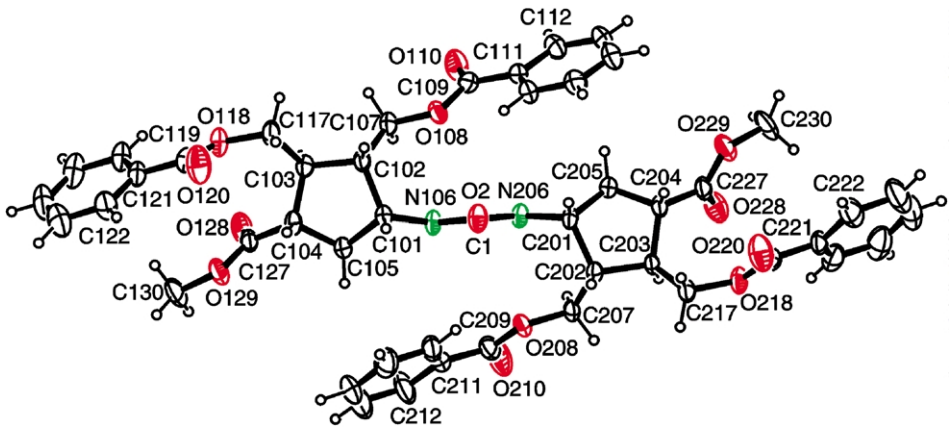

Figure 3. ORTEP projection of the molecular structure of compound **15**, showing the atomic numbering scheme.

Table 1. Formation of **8** from **6**

Entry	Reagent/solvent	Temperature	Time (h)	Result
1	(a) PCl_5/hexane	(a) rt	(a) 18	**8** (22%)+**16** (14%)+**6** (12%)
	(b) 14N NH_4OH	(b) 0°C	(b) 3	
2	(a) $SOCl_2$	(a) 79°C	(a) 6	**8** (53%)+**16** (19%)
	(b) NH_3liq/CH_2Cl_2	(b) −45°C to rt	(b) 18	
3	(a) $SOCl_2$	(a) 79°C	(a) 6	**8** (63%)+**16** (19%)
	(b) 14N NH_4OH /CH_2Cl_2	(b) 0°C to rt	(b) 18	

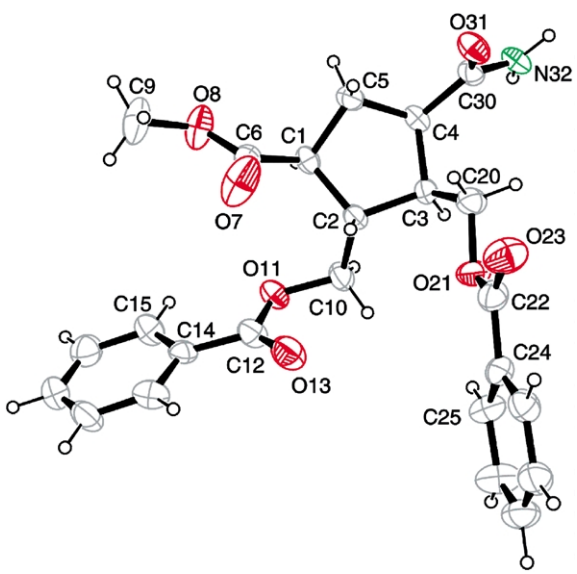

Figure 4. ORTEP projection of the molecular structure of compound **8**, showing the atomic numbering scheme.

analysis of a single crystal of the product of higher melting point, **15** (Fig. 3).[10]

In developing the second path from **6** to **9**, we initially proceeded by analogy with Boeckman et al.[11] preparing **8** by transformation of **6** into the corresponding acyl chloride by reaction with PCl_5 in hexane, followed by treatment with saturated aqueous NH_4OH (Table 1, entry 1). Subsequently, much a higher yield of **8**, 63%, was achieved by treating **6** with refluxing $SOCl_2$ and performing ammonolysis in CH_2Cl_2 (Table 1, entry 3). With both methods, **8** was accompanied by an approximately 15–20% yield of its isomer **16**; the structures of both were unequivocally established by X-ray crystallographic analysis of single crystals (Figs. 4 and 5), which in the case of **8** proved to be composed of enantiomerically pure (1*S*)-**8** in spite of the racemic nature of the uncrystallized product.[10] Oxidative degradation of **8** with lead tetraacetate in *t*-BuOH, with Et_3N as catalyst,[12] afforded **9** as the sole product in 78% yield (49% from **6**).

Removal of the Boc protecting group from **9** by reaction

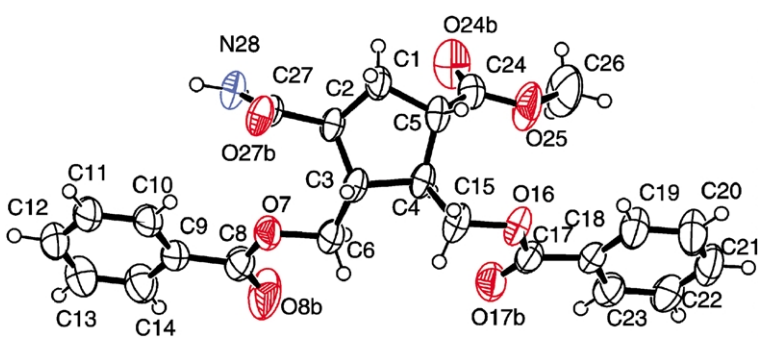

Figure 5. ORTEP projection of the molecular structure of compound **16**, showing the atomic numbering scheme.

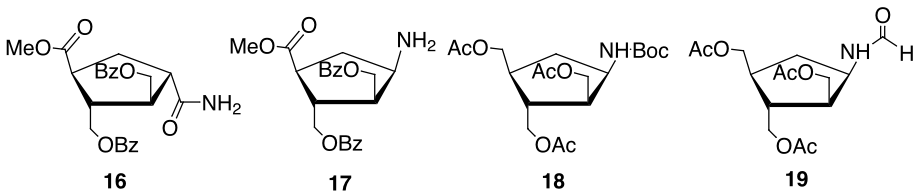

Figure 6.

with CF_3COOH in CH_2Cl_2,[13] afforded only a 28% yield of the deprotected amine **17**. We therefore proceeded to reduce the methoxycarbonyl group first. Reduction with $LiBH_4$ gave only a 22% yield of the tris(hydroxymethyl)carbamate **10**. The total yield of compounds readily convertible to **4** 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 afforded the triacetyl derivative **18** and the triacetylformamide **19** (produced, as in the case of related compounds,[7] by partial reduction of the Boc group), resulting in a total 47% yield of products that were readily convertible to **4** (Fig. 6). Reduction with DIBAL-H, a selective reducer of ester groups,[14] directly afforded a 42% yield of **10**. Finally, removal of the Boc group with refluxing HCl (2N in methanol), followed by passage of the resulting solution of **4**·HCl through a basic ion-exchange resin (Amberlite IRA-400(OH)), afforded the free amino alcohol **4** in 83% yield (22% from **5** via **7**).

Reaction of amino alcohol **4** with 5-amino-4,6-dichloropyrimidine under the usual conditions[15] gave a 93% yield of the substituted pyrimidine **11**. The structure was confirmed by X-ray crystallography (Fig. 7)[10] which also showed that no epimerization had taken place during the conversion of **9** into **4**. Compound **11** failed to afford the corresponding 6-chloropurine when reacted with $CH(OEt)_3$ under any of reaction conditions tried, this may be attributed to severe steric hindrance between the C4 amino group and the C2′ hydroxymethyl (Fig. 7). However, diazotation of **11** under the usual conditions and with the usual subsequent procedures[16] gave the 8-azapurine derivatives **12** and **13** (Scheme 1).

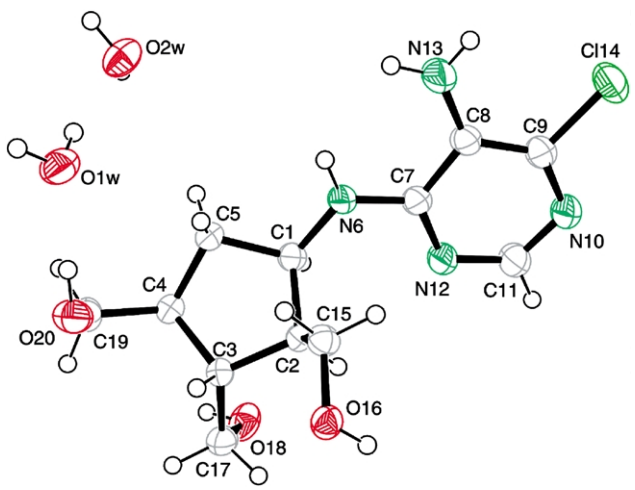

Figure 7. ORTEP projection of the molecular structure of compound **11**, showing the atomic numbering scheme.

3. Experimental

3.1. General

All chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. and used without further purifications. Melting points were measured in a Reichert Kofler Thermopan and are uncorrected. Infrared spectra were recorded in a Perkin–Elmer 1640 FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in a Bruker AMX 300 spectrometer at 300 and 75.47 MHz, respectively, using TMS as internal standard (chemical shifts in δ 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 F_{254}, 0.25 mm). X-Ray diffraction data were collected in an Enraf–Nonius CAD4 automatic diffractometer using the program CAD4-EXPRESS.

3.1.1. (±)-*c*-2,*t*-3-Bis(benzoyloxymethyl)-*c*-4-methoxycarbonyl-*r*-1-cyclopentanecarboxylic acid (6). A solution of **5**[7] (1.00 g, 2.50 mmol) in dry MeOH (30 mL) was refluxed under argon, with stirring, for 12 h. Removal of the solvent left a brown oil (1.05 g) that upon chromatography on silica gel with 1:1.5 hexane/AcOEt as eluent afforded **6** as a white solid (0.85 g, 79%). Mp 134.5–136°C (toluene). IR (KBr) ν (cm^{-1}): 2950, 1735, 1716, 1453, 1436, 1312, 1272, 1234, 1128, 1094, 1071, 724, 711. ^1H NMR ($CDCl_3$) δ (ppm): 8.00–7.97 (m, 4H, 2×(2′-H+6′-H)); 7.59–7.49 (m, 2H, 2×4′-H); 7.45–7.36 (m, 4H, 2×(3′-H+5′-H)); 4.48–4.44 (m, 4H, 2×CH_2OBz); 3.66 (s, 3H, OCH_3); 3.06 (q, 1H, J=8.33 Hz); 2.83–2.78 (m, 2H); 2.75–2.68 (m, 1H); 2.42–2.31 (m, 1H); 2.28–2.19 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 177.40 (COOH); 174.06 ($COOCH_3$); 166.34 and 166.18 (2×PhCO); 133.18 and 133.04 (2×C4′); 129.73 and 129.68 (2×C1′); 129.65 and 129.56 (2×(C2′+C6′)); 128.45 and 128.39 (2×(C3′+C5′)); 65.62 and 64.19 (2×CH_2OBz); 52.10 (CH_3O); 45.85 and 44.91 (C1+C4); 44.31 and 43.22 (C2+C3); 32.06 (C5). FABMS, m/z (%): 441.9 (MH^+, 28%). Anal. Calcd for $C_{24}H_{24}O_8$ (440.44): C, 65.45; H, 5.49. Found: C, 65.74; H, 5.56

3.1.2. Methyl (±)-*t*-2,*c*-3-bis(benzoyloxymethyl)-*c*-4-carbamoyl-*r*-1-cyclopentanecarboxylate (8) and methyl (±)-*t*-2,*c*-3-bis(benzoyloxymethyl)-*t*-4-carbamoyl-*r*-1-cyclopentanecarboxylate (16). *Method A*. PCl_5 (0.32 g, 1.53 mmol) was added in small portions, with stirring, to a suspension of hemiester **6** (0.65 g, 1.48 mmol) in dry hexane (7 mL) under argon, and stirring was continued overnight. The reaction mixture was then cooled to 0°C, 14N NH_4OH (2 mL) was added dropwise, and stirring was continued at

0°C for 3 h. Removal of solvents by coevaporation with toluene and EtOH under reduced pressure left an oily residue that was taken into water (30 mL), and the organic layers obtained by extracting this mixture with CH_2Cl_2 (3×30 mL) were pooled and dried over Na_2SO_4. Removal of solvent under reduced pressure now left an oily residue (0.33 g) that upon chromatography on silica gel with 1:1.5 hexane/AcOEt as eluent afforded first compound **6** (80 mg, 12%), then compound **16** (90 mg, 14%), and finally compound **8**, which was isolated as a white solid (150 mg, 23%).

Compound **8**: white needles. Mp 127–130°C (hexane/AcOEt). Single crystals suitable for X-ray diffractometry were obtained by placing an open vial containing a solution of **8** in AcOEt in a jar containing a small quantity of pentane, and then leaving the stoppered jar in a cool, dark, vibration-free place. IR (KBr) ν (cm^{-1}): 3436, 3202, 1729, 1654, 1629, 1450, 1263, 714. ^1H NMR ($CDCl_3$) δ (ppm): 8.01–7.96 (m, 4H, 2×(2′-H+6′-H)); 7.58–7.51 (m, 2H, 2×4′-H); 7.43–7.38 (m, 4H, 2×(3′-H+5′-H)); 5.89 (bs, 1H, D_2O exch, N*H*H); 5.50 (bs, 1H, D_2O exch, NH*H*); 4.57 (dd, 1H, *J*=11.41, 6.67 Hz, C*H*HOBz); 4.53–4.42 (m, 3H, CH*H*OBz+CH_2OBz); 3.67 (s, 3H, CH_3O); 3.04–2.81 (m, 3H); 2.71–2.63 (m, 1H); 2.47–2.37 (m, 1H); 2.33–2.23 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 175.27 and 174.74 (*C*OOCH$_3$+CONH$_2$); 166.77 and 166.70 (2×PhCO); 133.54 and 133.49 (2×C4′); 130.25 and 130.19 (2×C1′); 129.98 and 129.96 (2×(C2′+C′)); 128.84 and 128.83 (2×(C3′+C5′)); 66.16 and 65.17 (2×*C*H$_2$OBz); 52.57 (CH_3O); 46.97 and 46.44 (C1+C4); 45.25 and 44.18 (C2+C3); 32.52 (C5). EIMS *m/z* (%): 334 (M−Bz, 1); 317 (2); 212 (8); 195 (9); 152 (24); 106 (8); 105 (100); 93 (8); 92 (6); 79 (5); 77 (29); 51 (4). Anal. Calcd for $C_{24}H_{25}NO_7$ (439.46): C, 65.59; H, 5.73; N, 3.19. Found: C, 65.82; H, 5.91; N, 3.31.

Compound **16**: white solid. Mp 100–101°C (hexane/AcOEt). IR (KBr) ν (cm^{-1}): 3407, 1728, 1654, 1450, 1272, 1110, 713. ^1H NMR ($CDCl_3$) δ (ppm): 8.05–8.02 (m, 4H, 2×(2′-H+6′-H)); 7.60–7.54 (m, 2H, 2×4′-H); 7.48–7.42 (m, 4H, 2×(3′-H+5′-H)); 5.93 (bs, 1H, D_2O exch, N*H*H); 5.43 (bs, 1H, D_2O exch, NH*H*); 4.67 (dd, 1H, *J*=11.58, 3.90 Hz, C*H*HOBz); 4.55–4.44 (m, 2H, CH_2OBz); 4.40 (dd, 1H, *J*=11.58, 5.17 Hz, CH*H*OBz); 3.62 (s, 3H, CH_3O); 3.06–3.00 (m, 1H); 2.82–2.60 (m, 3H); 2.41–2.31 (m, 1H); 2.27–2.18 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 175.54 and 175.27 (*C*OOCH$_3$+CONH$_2$); 166.93 and 166.40 (2×PhCO); 133.36 and 133.16 (2×C4′); 129.81 (2×C1′); 129.69 and 129.65 (2×(C2′+C6′)); 128.55 and 128.47 (2×(C3′+C5′)); 65.62 and 64.86 (2×*C*H$_2$OBz); 52.04 (CH_3O); 47.11 (C1); 46.17 and 46.02 (C4+C2); 45.03 (C3); 32.92 (C5). EIMS *m/z* (%): 334 (M−Bz, 1); 317 (2); 304 (1); 212 (5); 195 (9); 163 (11); 152 (10); 106 (8); 105 (100); 93 (5); 79 (5); 77 (28). Anal. Calcd for $C_{24}H_{25}NO_7$ (439.46): C, 65.59; H, 5.73; N, 3.19. Found: C, 65.77; H, 5.85; N, 3.22.

Method B. A solution of hemiester **6** (0.63 g, 1.43 mmol) in $SOCl_2$ (6 mL) was refluxed under argon for 6.5 h, after which excess $SOCl_2$ was removed under reduced pressure and the resulting brown oily residue was dissolved in dry CH_2Cl_2 (7.15 mL), cooled to −45°C and treated with liquid NH_3 (2.5 mL). This mixture was stirred overnight while slowly returning to room temperature, and removal of solvents under reduced pressure left an oil (0.75 g) that upon chromatography on silica gel using 1:1.5 hexane/AcOEt as eluent afforded compounds **8** (0.33 g, 53%) and **16** (0.12 g, 19%).

Method C. A solution of hemiester **6** (3.05 g, 6.92 mmol) in $SOCl_2$ (28 mL) was refluxed under argon for 6 h, after which excess $SOCl_2$ was removed under reduced pressure and the resulting brown oily residue was dissolved in dry CH_2Cl_2 (12 mL) and added dropwise over 15 min to a 14N solution of NH_4OH in an ice bath. This mixture was stirred overnight, the organic and aqueous phases were separated, the latter was extracted with CH_2Cl_2 (3×20 mL), the organic phases were pooled and dried over Na_2SO_4, and removal of solvents under reduced pressure left an oil (2.85 g) that upon chromatography on silica gel using 1:1.5 hexane/AcOEt as eluent afforded compounds **8** (1.90 g, 63%) and **16** (0.58 g, 19%).

3.1.3. Methyl (±)-*t*-2,*c*-3-bis(benzoyloxymethyl)-*c*-4-*t*-butoxycarbonylamino-*r*-1-cyclopentanecarboxylate (9). *Method A*. Ethyl chloroformate (1.32 mL, 13.8 mmol) was added dropwise under argon, with stirring, to a solution of **6** (4.40 g, 10 mmol) and dry Et_3N (2 mL) in dry acetone (160 mL) in an ice bath. The mixture was stirred for 1.5 h at this temperature, a solution of NaN_3 (0.65 g, 10.0 mmol) in water (23 mL) was added, and stirring was continued for a further 1.5 h at the same temperature. Cold water (50 mL) was added, the resulting mixture was extracted with Et_2O (2×100 mL), and the pooled organic phases were dried over Na_2SO_4. Removal of the solvent under reduced pressure left a dark oil that was dissolved in dry toluene (45 mL) and heated for 1 h at 80°C, after which the toluene was removed under reduced pressure, and the resulting brown oily residue was dissolved in dry *t*-BuOH (120 mL) and refluxed under an inert atmosphere for 17 h. Removal of excess *t*-BuOH left a brown oil (3.62 g) that was fractionated on silica gel using 10:3 and 2:1 hexane/AcOEt as eluents. The fractions eluted with 10:3 hexane/AcOEt afforded **9** (1.03 g, 20%) as a colourless viscous oil that was crystallized by dissolution in Et_2O and addition of hexane. The first fractions eluted with 2:1 hexane/AcOEt afforded urea **15** as a white solid (0.84 g, 20%), and the later fractions urea **14** as a glassy solid (0.97 g, 23%).

Compound **9**: white solid. Mp 91–93°C (Et_2O/hexane). IR (KBr) ν (cm^{-1}): 3363, 2956, 1726, 1679, 1531, 1275, 1173, 1115, 712. ^1H NMR ($CDCl_3$) δ (ppm): 8.06–7.98 (m, 4H, 2×(2′-H+6′-H)); 7.59–7.53 (m, 2H, 2×4′-H); 7.46–7.41 (m, 4H, 2×(3′-H+5′-H)); 5.21 (d, 1H, D_2O exch, *J*=8.90 Hz, NH); 4.57–4.38 (m, 5H, 2×CH_2OBz+4-H); 3.64 (s, 3H, CH_3O); 2.90–2.82 (m, 1H); 2.79–2.72 (m, 1H); 2.52–2.47 (m, 1H); 2.40–2.30 (m, 1H); 1.99–1.90 (m, 1H); 1.39 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$) δ (ppm): 176.33 (*C*OOCH$_3$); 166.44 and 166.28 (2×PhCO); 155.36 (NCOO); 133.13 and 133.03 (2×C4′); 129.90 and 129.77 (2×C1′); 129.66 and 129.56 (2×(C2′+C6′)); 128.41 (2×(C3′+C5′)); 79.55 (*C*(CH_3)$_3$); 66.11 and 64.06 (2×*C*H$_2$OBz); 52.95 (C4); 52.21 (CH_3O); 44.87, 44.49 and 44.42 (C1+C2+C3); 36.12 (C5); 28.28 (C(*C*H$_3$)$_3$). EIMS *m/z* (%): 438 (M^+−OC(CH_3)$_3$, 1); 306 (4); 301 (3); 289 (4);

288 (20); 211 (19); 210 (9), 167 (19); 166 (23); 52 (11); 108 (17); 105 (100); 77 (26); 57 (25). Anal. Calcd for $C_{27}H_{31}NO_8$ (497.54): C, 65.18; H, 6.28; N, 2.82. Found: C, 65.37; H, 6.40; N, 2.88.

Compound **15**: white solid. Mp 144–145°C (AcOEt/cyclohexane). Single crystals for X-ray diffractometry were obtained by placing an open vial containing a solution of **15** in AcOEt in a jar containing a small quantity of pentane, and leaving the stoppered jar in a cool, dark, vibration-free place. IR (KBr) ν (cm^{-1}): 3676, 3268, 2949, 1717, 1648, 1316, 1277, 1174, 1116, 1070, 710. ^1H NMR ($CDCl_3$) δ (ppm): 8.02–7.97 (m, 8H, 4×(2′-H+6′-H)); 7.57–7.49 (m, 4H, 4×(4′-H)); 7.44–7.37 (m, 8H, 4×(3′-H+5′-H)); 5.15 (d, 2H, D_2O exch, J=8.48 Hz, 2×NH); 4.53–4.33 (m, 10H, (4×*C*H_2OBz)+(2×1-H)); 3.60 (s, 6H, 2×CH_3O); 2.84–2.75 (m, 2H); 2.73–2.69 (m, 2H), 2.52–2.47 (m, 2H); 2.24–2.15 (m, 2H); 1.84–1.75 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 176.94 (2×$COOCH_3$); 166.98 and 166.73 (4×PhCO); 157.20 (NCON); 133.54 and 133.46 (4×C4′); 130.34 and 130.07 (4×(C2′+C6′)); 130.23 (4×C1′); 129.99 and 128.84 (4×(C3′+C5′)); 66.77 and 64.89 (4×*C*H_2OBz); 52.98 (2×C1); 52.62 (2×CH_3O); 45.31, 45.19 and 44.64 (2×(C2+C3+C4)); 36.65 (2×C5). FABMS, *m*/*z* (%): 849.4 (MH^+, 100). Anal. Calcd for $C_{47}H_{48}N_2O_{13}$ (848.89): C, 66.50; H, 5.70; N, 3.30. Found: C, 66.87; H, 5.85; N, 3.22.

Compound **14**: glassy solid. Mp 52–53°C. IR (KBr) ν (cm^{-1}): 3380, 2951, 1718, 1602, 1544, 1451, 1274, 1176, 1111, 1069, 1025, 709. ^1H NMR ($CDCl_3$) δ (ppm): 8.02–7.98 (m, 8H, 2×(2′-H+6′-H)); 7.58–7.49 (m, 4H, 2×4′-H); 7.47–7.34 (m, 8H, 2×(3′-H+5′-H)); 5.21 (d, 2H, D_2O exch, J=8.46 Hz, 2×NH); 4.55–4.33 (m, 10H, (4×*C*H_2OBz)+(2×1-H)); 3.60 (s, 6H, 2×CH_3O); 2.83–2.78 (m, 2H); 2.71–2.67 (m, 2H); 2.47–2.42 (m, 2H); 2.33–2.24 (m, 2H); 1.91–1.82 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 176.88 (2×$COOCH_3$); 166.87 and 166.72 (4×PhCO); 157.23 (NCON); 133.52 and 133.40 (4×C4′); 130.31 and 130.23 (4×C1′); 130.06 and 129.97 (4×(C2′+C6′)); 128.83 and 128.80 (4×(C3′+C5′)); 66.85 and 64.73 (4×*C*H_2OBz); 52.85 (2×C1); 52.58 (4×CH_3O); 45.25, 45.03 and 44.67 (2×(C2+C3+C4)); 36.79 (2×C5). HRMS *m*/*z* calcd for [$C_{47}H_{49}N_2O_{13}$] (MH^+) 849.3235, found 849.3242.

Method B. Ethyl chloroformiate (0.36 mL, 4.10 mmol) was added dropwise under argon, with stirring, to a solution of **6** (1.50 g, 3.41 mmol) and dry Et_3N (0.53 mL) in dry acetone (22 mL) at between −10 and 0°C. The mixture was stirred at the same temperature for 2 h, a solution of NaN_3 (0.25 g, 3.85 mmol) in the least possible quantity of water (1.50 mL) was added, and stirring was continued at the same temperature for a further 1.5 h. The reaction mixture was then poured over 50 mL of cold saturated NaCl solution, which after stirring for 15 min was extracted with CH_2Cl_2 (3×40 mL). The pooled organic layers were dried over Na_2SO_4, and removal of the solvent under reduced pressure left a brown residue that was taken into dry toluene (30 mL) and heated at 80°C for 1 h under argon. Removal of the toluene at low pressure left a yellowish oil that was dissolved in dry *t*-BuOH (50 mL) and refluxed under argon for 17 h. Evaporation of excess *t*-BuOH now afforded **9** (1.37 g, 79%) as a slightly yellowish dense oil identical to that obtained by Method A.

Method C. A well-stirred suspension of **8** (0.35 g, 0.80 mmol) and $Pb(OAc)_4$ (0.50 g, 1.13 mmol) in dry *t*-BuOH (8 mL) was heated to 70°C under argon. Dry Et_3N (0.60 mL) was added, dropwise at first and more rapidly as soon as the colour of the mixture turned from brownish orange to beige, and the reaction mixture was then refluxed for 5 h and filtered while hot. The solid filtered out was washed with toluene, and evaporation of solvents from the pooled filtrates under reduced pressure left a brown solid (0.72 g) that upon purification on silica gel using 4:1 hexane/AcOEt as eluent afforded **9** (0.32 g, 78%) as a colourless dense oil.

3.1.4. Methyl (±)-*t*-2,*c*-3-bis(benzoyloxymethyl)-*c*-4-amino-*r*-1-cyclopentanecarboxylate (17). CF_3COOH (1.54 mL, 20.0 mmol) was added dropwise to a stirred solution of compound **9** (1.0 g, 1.95 mmol) in CH_2Cl_2 (12 mL) at 0°C, and the mixture was stirred at this temperature for 8.5 h. Removal of the solvents by coevaporation with toluene under reduced pressure left a residue that was taken into 2N NaOH (25 mL). This mixture was extracted with AcOEt (2×25 mL), the pooled organic phases were dried over Na_2SO_4, and removal of the solvent under reduced pressure left an oil (0.62 g) that upon chromatography on silica gel with 1:0.75 hexane/AcOEt as eluent afforded **17** as a colourless oil (0.22 g, 28%). IR (film) ν (cm^{-1}): 3360, 2959, 1716, 1650, 1540, 1262, 1098. ^1H NMR (DMSO-d_6) δ (ppm): 8.28 (d, 1H, D_2O exch, J=7.57 Hz, N*H*H); 7.96–7.93 (m, 2H, (2′-H+6′-H)); 7.82–7.79 (m, 2H, (2′-H+6′-H)); 7.69–7.64 (m, 1H, 4′-H); 7.56–7.44 (m, 5H, 4′-H+2×(3′-H+5′-H)); 4.74 (t, 1H, D_2O exch, J=4.83 Hz, NH*H*); 4.53–4.42 (m, 2H, CH_2OBz); 4.27 (dd, 1H, J=10.82, 7.19 Hz C*H*HOBz); 3.53 (s, 3H, CH_3O); 3.53–3.46 (m, 2H, CH*H*OBz+4-H); 2.79–2.71 (m, 2H); 2.24–2.17 (m, 2H), 2.04–2.00 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 180.13 (*C*$OOCH_3$); 168.79 and 166.68 (2×PhCO); 133.65 and 132.37 (2×C4′); 133.46 and 130.14 (2×C1′); 129.98 and 129.10 (2×(C2′+C6′)); 128.85 and 127.63 (2×(C3′+C5′)); 66.36 and 61.27 (2×*C*H_2OBz); 54.00 (CH_3O); 53.15 and 52.61 (C4+C1), 46.20 and 44.89 (C2+C3), 34.70 (C5). HRMS *m*/*z* calcd for [$C_{23}H_{26}NO_6$] 412.1760, found 412.1764.

3.1.5. *t*-Butyl (±)-*N*-[*c*-2,*t*-3,*c*-4-tris(hydroxy)-*r*-1-cyclopentylcarbamate (10). *Method A*. A suspension of $LiBH_4$ (0.45 g, 22.04 mmol) in dry THF (105 mL) was refluxed under argon, with vigorous stirring, for 1 h, after which a solution of **9** (0.94 g, 1.84 mmol) in dry THF (15 mL) was added dropwise and refluxing was continued for a further 5.25 h. Excess $LiBH_4$ was destroyed by addition of water (15 mL), the solvents were removed under reduced pressure, and a solution of the resulting white residue in water (50 mL) was extracted with CH_2Cl_2 (2×50 mL) and AcOEt (2×50 mL). The pooled organic phases were dried over Na_2SO_4, and removal of the solvents under low pressure afforded an oil (0.46 g) that was chromatographed on silica gel using 1:1 hexane/AcOEt, AcOEt and MeOH as successive eluents. Removal of the solvent from the methanolic fraction left tris(hydroxymethyl)carbamate **10** as a colourless oil (0.11 g, 22%). IR (film) ν (cm^{-1}): 3360, 2934, 1682, 1538, 1367, 1770. ^1H NMR ($CDCl_3$) δ (ppm): 5.71 (d, 1H, D_2O exch, J=7.92 Hz, NH); 4.12–4.08 (m, 1H, 1-H); 3.76–3.42 (m, 6H, 3×CH_2OH); 2.74 (bs, 3H, D_2O

exch, 3×OH); 2.26–2.16 (m, 1H); 2.07–1.99 (m, 2H); 1.81–1.73 (m, 1H); 1.44 (s, 9H, $C(CH_3)_3$); 1.28–1.23 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.42 (NCOO); 80.16 ($C(CH_3)_3$); 65.28, 65.07 and 62.14 (3×CH_2OH); 52.82 (C1); 50.95 (C2); 45.22 (C3); 43.63 (C4); 35.04 (C5); 28.80 ($C(CH_3)_3$). EIMS *m/z* (%): 219 (4); 202 (3); 174 (5); 170 (7); 156 (13); 126 (10); 95 (10); 93 (10); 81 (10); 79 (15); 69 (11); 67 (10); 59 (19); 57 (100; 56 (14); 55 (12). HRMS *m/z* calcd for [$C_{13}H_{25}NO_5$] 275.3413, found 275.3417.

The aqueous phase obtained in the extraction with CH_2Cl_2 and AcOEt was concentrated to dryness, Ac_2O (15 mL) and dry pyridine (15 mL) were added, and the mixture was stirred at room temperature for 18 h, after which the solvent and excess reagent were removed under reduced pressure and the resulting brown residue was taken into saturated $NaHCO_3$ solution (50 mL). This solution was extracted successively with Et_2O (3×50 mL) and AcOEt (2×50 mL), and the pooled organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography of the oily residue (0.20 g) on silica gel with hexane/AcOEt and AcOEt as successive eluents afforded **18** (50 mg, 7%) with the former and **19** (110 mg, 18%) with the latter.

Compound **18**: transparent oil. IR (film) ν (cm^{-1}): 3374, 2969, 1734, 1508, 1368, 1242, 1165, 1035. ^1H NMR ($CDCl_3$) δ (ppm): 4.83 (bs, 1H, D_2O exch, NH); 4.21–4.12 (m, 2H, CH_2OAc); 4.08–3.96 (m, 5H, 2×CH_2OAc+1-H); 2.28–2.04 (m, 3H); 2.04 (s, 3H, CH_3CO); 2.03 (s, 6H, 2×CH_3CO); 1.93–1.82 (m, 2H); 1.40 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.35 and 171.22 (3×CH_3CO); 155.64 (NCOO); 79.89 ($C(CH_3)_3$); 66.98, 66.43 and 64.20 (3×CH_2OAc); 52.27 (C1); 44.22 (C2); 42.68 (C3); 39.10 (C4); 36.18 (C5); 28.73 ($C(CH_3)_3$); 21.43 and 21.29 (3×CH_3CO). HRMS *m/z* calcd for [$C_{19}H_{32}NO_8$] 402.2128, found 402.2131.

Compound **19**: colourless oil. IR (film) ν (cm^{-1}): 3318, 2958, 1726, 1660, 1530, 1367, 1239, 1035, 975. ^1H NMR ($CDCl_3$) δ (ppm): 8.14 (s, 1H, NCHO); 6.05 (d, 1H, D_2O exch, J=8.24 Hz, NH); 4.60–4.50 (m, 1H, 4-H); 4.21–4.01 (m, 6H, 3×CH_2OAc); 2.39–2.28 (m, 1H); 2.27–2.12 (m, 2H); 2.05 (s, 9H, 3×CH_3CO); 1.99–1.89 (m, 1H); 1.46–1.36 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.30 and 171.25 (3×CH_3CO); 161.26 (NCHO); 66.87, 66.26 and 66.14 (3×CH_2OAc); 49.50 (C4); 43.42 and 43.08 (C3+C2); 39.04 (C1); 36.19 (C5); 21.40 and 21.27 (3×CH_3CO). FABMS, *m/z* (%): 330.1 (MH^+, 98.5%). HRMS *m/z* calcd for [$C_{15}H_{24}NO_7$] 330.1553, found 330.1555.

Method B. A solution of **9** (2.20 g, 4.30 mmol) in dry toluene (10 mL) was slowly added under argon to a commercial 1.5 M solution of DIBAL-H in toluene (30.78 mL, 46.18 mmol) at −75°C, and stirring was continued at this temperature for 3.75 h. After successive addition of 10:1 toluene/MeOH (10 mL), MeOH (1 mL) and water (15 mL), stirring was continued while the mixture regained room temperature. The solid formed was filtered out and washed repeatedly with AcOEt (total volume 400 mL), and the pooled filtrates were dried over Na_2SO_4. Removal of the solvents under reduced pressure left an oil (1.20 g) that was chromatographed on silica gel using 1:2 hexane/AcOEt, AcOEt and 1:0.1 AcOEt/MeOH as successive eluents. Evaporation of the solvent from the final fractions afforded tris(hydroxymethyl)carbamate **10** (0.5 g, 42%).

3.1.6. (±)-*c*-4-Amino-*r*-1,*t*-2,*c*-3-cyclopentanetrimethanol (4). A solution of **10** (0.93 g, 3.4 mmol) in MeOH (15 mL) and 2N HCl (15 mL) was refluxed for 4 h, and successive coevaporation of the solvents with toluene and EtOH then afforded **4**·HCl as a colourless dense oil (0.74 g). IR (film) ν (cm^{-1}): 3429, 3354, 1652, 1596, 1559, 1356, 1114. ^1H NMR (DMSO-d_6) δ (ppm): 7.81 (bs, 3H, D_2O exch, $^+NH_3$); 3.93 (bs, 3H, D_2O exch, 3×OH); 3.67–3.31 (m, 7H, 3×CH_2OH+4-H); 2.08–1.96 (m, 2H); 1.88–1.82 (m, 1H); 1.68–1.61 (m, 1H); 1.53–1.08 (m, 1H). ^{13}C NMR (DMSO-d_6) δ (ppm): 62.97, 59.84 and 56.37 (3×CH_2OH); 52.68 (C4); 45.69 (C3); 44.58 (C2); 41.99 (C1); 34.00 (C5).

A solution of **4**·HCl (0.73 g) in MeOH (10 mL) was loaded on a column of Amberlite IRA-400(Cl) (17 mL) that had previously been activated with 1N NaOH (112 mL), and elution with MeOH gave an eluate (210 mL) that upon concentration under reduced pressure afforded **4** (0.49 g, 83% from **10**) as a pale yellow oil. IR (film) ν (cm^{-1}): 3406, 1652, 1615, 1558, 1506, 1456, 1048. ^1H NMR (DMSO-d_6) δ (ppm):4.60 (bs, 5H, D_2O exch, 3×OH+NH_2); 3.50–3.21 (m, 7H, 2×CH_2OH+4-H); 1.89–1.72 (m, 2H); 1.70–1.56 (m, 2H); 1.19–1.12 (m, 1H). ^{13}C NMR (DMSO-d_6) δ (ppm): 65.09, 64.66 and 61.41 (3×CH_2OH); 52.88 (C4); 49.58 (C3); 46.08 (C2); 44.04 (C1); 38.66 (C5). HRMS *m/z* calcd for [$C_8H_{17}NO_3$] 175.1218, found 175.1221.

3.1.7. (±)-*c*-4-[(5-Amino-6-chloropyrimidin-4-yl)amino-(-*r*-1,*t*-2,*c*-3-cyclopentanetrimethanol (11). A mixture of freshly prepared amino alcohol **4** (0.35 g, 2.00 mmol) and 5-amino-4,6-dichloropyrimidine (0.49 g, 3.53 mmol) in Et_3N (2 mL) and *n*-BuOH (8.5 mL) was refluxed under argon for 84 h, the solvents were removed under reduced pressure, and the resulting brown oil (1.0 g) was chromatographed on silica gel using 10:1 CH_2Cl_2/MeOH as eluent. Addition of MeOH/Et_2O to the yellowish oil isolated from the eluate precipitated **11** (0.57 g, 93%) as a white solid. Mp 173–174°C (MeOH/Et_2O). A single crystal suitable for X-ray diffractometry was obtained by dissolving a sample in only as much water as was necessary for total dissolution at room temperature, and leaving this solution in a stoppered vial in a cool, dark, vibration-free place. IR (KBr) ν (cm^{-1}): 3365, 2881, 1647, 1593, 1475, 1420, 1056, 1009. ^1H NMR (DMSO-d_6) δ (ppm): 7.71 (s, 1H, 2-$H_{pyrimidine}$); 6.53 (d, 1H, D_2O exch, J=7.21 Hz, NH); 4.99 (s, 2H, D_2O exch, NH_2); 4.77 (t, 1H, D_2O exch, J=4.77 Hz, OH); 4.76 (t, 1H, D_2O exch, J=4.84 Hz, OH); 4.46 (t, 1H, D_2O exch, J=4.97 Hz, OH); 4.43–4.37 (m, 1H, 4-H); 3.47–3.33 (m, 4H, 2×CH_2OH); 3.29–2.22 (m, 2H, CH_2OH); 2.11–2.06 (m, 1H); 2.03–1.95 (m, 1H); 1.83–1.76 (m, 2H); 1.57–1.50 (m, 1H). ^{13}C NMR (DMSO-d_6) δ (ppm): 152.25 ($C6_{pyrimidine}$); 146.14 ($C2_{pyrimidine}$); 137.17 ($C4_{pyrimidine}$); 123.64 ($C5_{pyrimidine}$); 64.86, 64.61 and 61.35 (3×CH_2OH); 53.19 (C4); 46.85 and 46.32 (C2+C3); 42.78 (C1); 35.71 (C5). EIMS *m/z* (%): 302 (M, 6); 286 (M−NH_2, 11); 171 (7); 146 (32); 145 (31); 144 (100); 117 (9); 101 (7); 81 (11); 79 (13); 67 (10); 55 (8). Calcd for $C_{12}H_{19}ClN_4O_3$ (302.76): C, 47.61; H, 6.33; N, 18.51. Found: C, 47.15; H, 6.55; N, 18.11.

3.1.8. (±)-6,7-Dihydro-3-[*c*-2,*t*-3,*c*-4-tris(hydroxymethyl)-*r*-1-cyclopentyl(-3*H*-1,2,3-triazolo[4,5-*d*(pyrimidin-7-one (12). A solution of $NaNO_2$ (37 mg, 0.54 mmol) in water (1 mL) was added dropwise to a mixture of **11** (0.12 g, 0.40 mmol), water (1.32 mL) and AcOH (1.25 mL) at approx. −5°C, the mixture was stirred at room temperature for 18 h, and removal of the solvents left a solid (0.25 g) that upon chromatography on silica gel with 7:1 CH_2Cl_2/MeOH as eluent afforded **12** as a white solid (70 mg, 60%). Mp 190–192°C (MeOH). IR (KBr) ν (cm^{-1}): 3385, 1718, 1593, 1547, 1384, 1276, 1095, 1024, 1007. ^1H NMR (DMSO-d_6) δ (ppm): 12.50 (bs, 1H, D_2O exch, NH); 8.21 (s, 1H, $5H_{triazolopyrimidine}$); 5.25 (q, 1H, J=7.84 Hz, 1-H); 4.82 (t, 1H, D_2O exch, J=4.92 Hz, OH); 4.73 (t, 1H, D_2O exch, J=5.05 Hz, OH); 4.15 (t, 1H, J=4.52 Hz, D_2O exch, OH); 3.61–3.54 (m, 1H, C*H*HOH); 3.51–3.45 (m, 3H, CH*H*OH+CH_2OH); 3.22–3.15 (m, 1H, C*H*HOH); 2.97–2.89 (m, 1H, CH*H*OH); 2.39–2.23 (m, 3H); 2.03–2.00 (m, 1H); 1.87–1.84 (m, 1H). ^{13}C NMR (DMSO-d_6) δ (ppm): 155.90 (CO); 149.39 ($C5_{triazolopyrimidine}$+$C3a_{triazolopyrimidine}$); 129.63 ($C7a_{triazolopyrimidine}$); 64.34, 63.45 and 60.66 (3×CH_2OH); 58.86 (C1); 48.15 (C2); 46.98 (C3); 42.86 (C4); 34.04 (C5). FABMS, *m*/*z* (%): 296.1 (MH^+, 4.72%). Anal. Calcd for $C_{12}H_{17}N_5O_4$ (295.29): C, 48.81; H, 5.80; N, 23.67. Found: C, 49.04; H, 6.10; N, 24.85.

3.1.9. (±)-*c*-4-(7-Amino-3*H*-1,2,3-triazolo[4,5-*d*(pyrimidin-3-yl)-*r*-1,*t*-2,*c*-3-cyclopentanetrimethanol (13). To a solution of **11** (0.15 g, 0.49 mmol) in 1N HCl (6 mL) in a salted ice bath (approx. −5°C), a solution of $NaNO_2$ (45 mg, 0.65 mmol) in water (5 mL) was added slowly enough to prevent the temperature from rising above 0°C. The mixture was stirred in the salted ice bath for 30 min, treated with 14N NH_4OH (3 mL), and refluxed for 2 h. After removal of water by azeotropic distillation with toluene and EtOH, the resulting solid residue (0.45 g) was purified by chromatography on silica gel using 8:1 and 7:1 CH_2Cl_2/MeOH as successive eluents. Removal of the solvents from the latter eluate under reduced pressure left a solid residue (0.18 g) that upon recrystallization from MeOH afforded **13** (60 mg, 41%) as a white solid. Mp 227–228°C. IR (KBr) ν (cm^{-1}): 3356, 1681, 1614, 1575, 1385, 1325, 1057, 668. ^1H NMR (DMSO-d_6) δ (ppm): 8.30 (bs, 1H, D_2O exch, N*H*H); 8.26 (s, 1H, $5\text{-}H_{triazolopyrimidine}$); 8.00 (s an, 1H, D_2O exch, NH*H*); 5.28 (c, 1H, J=7.90 Hz, 4-H); 4.83 (t, 1H, D_2O exch, J=4.96 Hz, OH); 4.72 (t, 1H, D_2O exch, J=5.09 Hz, OH); 4.20–4.17 (m, 1H, D_2O exch, OH); 3.62–3.57 (m, 1H, C*H*HOH); 3.55–3.47 (m, 3H, CH*H*OH+CH_2OH); 3.14 (ddd, 1H, J=10.69, 6.41, 4.32 Hz, C*H*HOH); 2.96–2.88 (m, 1H, CH*H*OH); 2.42–2.30 (m, 3H); 2.06–1.99 (m, 1H); 1.94–1.89 (m, 1H). ^{13}C NMR (DMSO-d_6) δ (ppm): 156.65 ($C5_{triazolopyrimidine}$); 156.55 ($C7_{triazolopyrimidine}$); 149.60 ($C3a_{triazolopyrimidine}$); 124.06 ($C7a_{triazolopyrimidine}$); 64.44, 63.69 and 60.81 (3×CH_2OH); 58.54 (C4); 48.18 (C3); 47.26 (C2); 42.97 (C1); 33.99 (C5). FABMS, *m*/*z* (%): 295.1 (MH^+, 29.5%). Anal. Calcd for $C_{12}H_{18}N_6O_3$ (294.31): C, 48.97; H, 6.16; N, 28.56. Found: C, 49.32; H, 6.23; N, 28.77.

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