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Synthesis of two enantiomerically pure precursors of cyclobutane carbocyclic nucleosides

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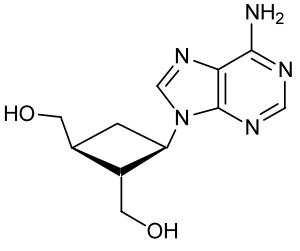
Abstract—Several bi-functionallized derivatives of cyclobutane have been synthesized by functional-group manipulation starting from (−)-*cis*-pinonic acid as a common precursor, the configuration of the pre-existing and newly formed stereogenic centers being determined by the configuration of the starting material, commercially available (−)-1*S*-α-pinene. Final products, (+)-(1*S*,1′*R*)-*cis*-1-[3′-(aminomethyl)-2′,2′-dimethylcyclobutyl]ethanol **5** and (+)-(1*S*,1′*R*)-*cis*-1-[3′-(2″-aminoethyl)-2′,2′-dimethylcyclobutyl]ethanol **6** are useful as precursors to cyclobutane carbocyclic nucleosides.

1. Introduction

In recent years there has been an increasing interest in carbocyclic analogues of nucleosides (CANs), many of which are potent antiviral or antineoplastic agents.[1,2] Typical examples are COXT-A **1** and COXT-G **2**,[3] in which a methylene replaces the oxygen of the oxetane ring possessed by the oxetanocin family of natural antibiotics.

Compounds **1** and **2** are active against a broad spectrum of herpes viruses and, at least in vitro, against hepatitis B virus.[4] The presence of the hydroxymethyl group that mimics the terminal carbon of the sugar in true nucleosides is not an essential feature for interesting biological activity, as it has been reported that a 6′-*C*-methylneplanocin A **3a** is more potent and/or selective than neplanocin A **3b** against a wide variety of viruses.[5]



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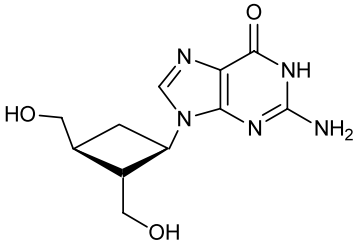

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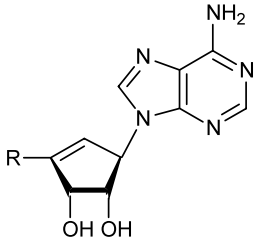
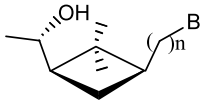
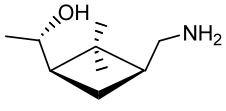


3a R = $CHOHCH_3$
3b R = CH_2OH



4 (n = 1,2; B: adenin-9-yl, hypoxanthin-9-yl, 8-azaadenin-9-yl)



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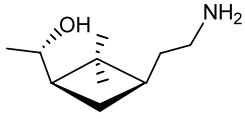

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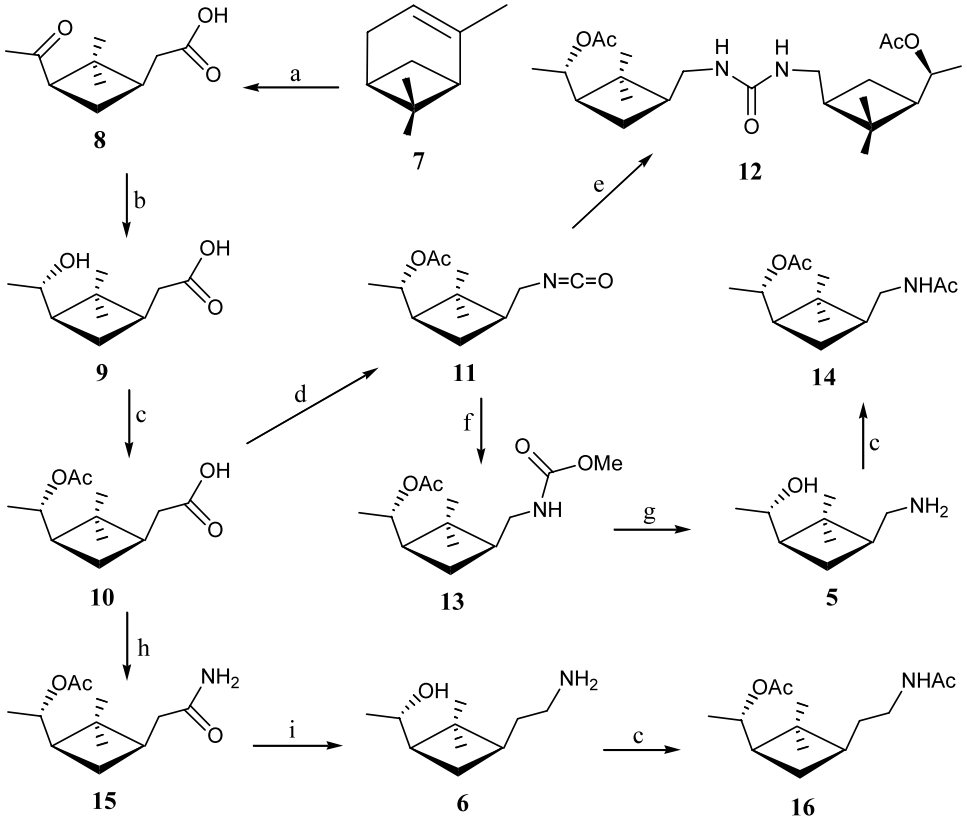
We have been occupied for some years in the synthesis and evaluation of the biological activities of CANs featuring structural and/or configurational alterations of the carbocyclic moiety.[6] Recently, we found that some adenine, hypoxanthine and 8-azadenine derivatives of type **4** show interesting activity in tests against respiratory syncytial virus and vaccinia virus, and/or moderate activity against murine and human tumoral cell lines.[7] These preliminary results stimulated the search for biological activities to other structurally related analogues.

Compounds of type **4**, as well as a variety of other purine and pyrimidine derivatives are best constructed from secondary cyclobutane amino alcohols **5** or **6**. As full details of the preparation of **5** and **6** have not yet been published, we disclose herein our studies on an efficient synthesis of enantiomerically pure amino alcohols **5** and **6**, which are prepared as shown in Scheme 1 from (−)-1*S*-α-pinene **7**. The preparation of other precursors to cyclobutane carbocyclic nucleosides from (−)-*S*-verbenone has been recently reported.[8]

Oxidative cleavage of **7** to (1*R*)-*cis*-(3-acetyl-2,2-dimethylcyclobutyl)acetic acid [(−)-*cis*-pinonic acid] **8** was achieved by a well documented procedure.[9] Keto acid **8** was reduced by $NaBH_4$ in ethanol to afford an almost quantitative yield of a mixture of diastereomers of pinolic acid with ^1H NMR signals for CHOH at δ 3.72 ($J=9.8$, 6.2 Hz; major isomer) and 3.66 ($J=9.6$, 6.1 Hz; minor isomer) in the crude product. Application of the Felkin–Anh model[10] to the reduction of **8** predicts the preferred formation of (1*R*,1′*S*)-*cis*-pinolic acid. Actually, after isolation by double recrystallization from water, the major isomer **9** obtained in this reaction had a specific rotation $[\alpha]_D^{25}$ of +26.5, almost equal in magnitude but of opposite sign to the published value (−27) for its enantiomer (1*S*,1′*R*)-*cis*-pinolic acid.[11]

Experiments carried out to optimize the stereoselectivity of the reduction of **8** identified L-Selectride and $NaBH_4$ as the reducing agents affording, respectively, greatest and least selectivity for the (1*R*,1′*S*)-*cis*-isomer and, respectively, least and greatest total yield of the mixture of diastereomers (Table 1). Borane–dimethyl sulphide complex reduced both the carbonyl and carboxyl groups of **8** (Scheme 2), affording a diol **9a**, to which the structure of (1*S*,1′*R*)-*cis*-1-[3′-(2-hydroxyethyl)-2′,2′-dimethylcyclobutyl]ethanol was assigned by assuming the absolute configuration at the secondary alcohol carbon as being the same as in the analogous carbon of the major isomer of hydroxy acid **9**.

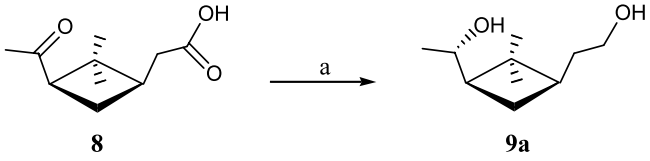


Scheme 1. *Reagents and conditions*: (a) $NaIO_4$, $RuCl_3$, CCl_4–MeCN–H_2O, rt, 24 h; (b) $NaBH_4$, $NaHCO_3/H_2O$, EtOH, reflux, 6.5 h; (c) Ac_2O, pyridine, rt, 18 h; (d) (1) EtOCOCl, acetone, Et_3N, −10 to 0°C, 30 min; (2) NaN_3/H_2O, 0°C, 30 min; (3) toluene, reflux, 1 h; (e) (1) 8N HCl/H_2O, reflux, 45 min; (2) Ac_2O, Et_3N, rt, 14 h; (f) MeOH/toluene, reflux, 18 h; (g) (1) KOH/MeOH, reflux, 18 h; then 2N H_2SO_4; (2) Amberlite IRA-400 (OH); (h) (1) EtOCOCl, THF, Et_3N, −10 to 0°C, 2 h; (2) NH_3 (g), rt, 30 min; (i) $LiAlH_4$, THF, reflux, 18 h.

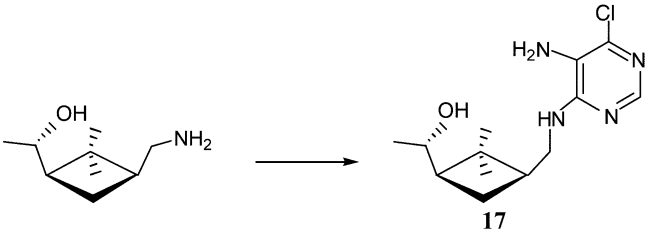
Table 1. Results obtained in the reduction of (−)-(1*R*)-*cis*-pinonic acid under different conditions

Reducing reagent	Solvent	Temp. (°C)	Time (h)	Global yield (%)	Major product	*S*/*R* ratio[a]
$NaBH_4$	EtOH	78	3	95	**9**	76/24
$LiBH_4$	THF	65	20	81	**9**	87/13
Super-hydride[b]	THF	25	8	85	**9**	85/15
L-Selectride[c]	THF	−78 (→25)	3 (→1)	63	**9**	>99
$Me_2S{\cdot}BH_3$	THF	65	5	85	**9a**	>95

[a] At the new stereogenic center, by ^1H NMR.
[b] $LiB(C_2H_5)_3H$.
[c] $LiB[CH(CH_3)CH_2CH_3]_3H$.



Scheme 2. *Reagents and conditions*: (a) $Me_2S{\cdot}BH_3$, THF, reflux, 5 h.



Scheme 3. *Reagents and conditions*: (a) 5-amino-4,6-dichloropyrimidine, Et_3N, BuOH, reflux, 72 h.

The hydroxyl group of **9** was protected in the form of its acetate **10** with acetic anhydride and anhydrous pyridine. Compound **10** was treated with ethyl chloroformate in the presence of triethylamine and subsequently with NaN_3 to obtain the corresponding azide, which underwent a Curtius rearrangement to isocyanate **11** when heated in refluxing anhydrous toluene. However, regardless of pH used to perform the hydrolysis of **11**, the major and only isolable product of this reaction was not amino alcohol **5** but the urea **12**. To circumvent this undesired result, the toluene solution of **11** was refluxed after addition of methanol to obtain the carbamate **13** (in 61% yield from acid **10**), and hydrolysis of **13** in basic medium, followed by passage of the reaction mixture through an ion exchange resin, afforded amino alcohol **5** in 85% yield.

Compound **5** was fully characterized by spectroscopic methods and by the preparation of its diacetyl derivative, **14**. An indirect though definitive confirmation of the structure of **5**, and hence of the (*S*)-configuration assigned to the 1-hydroxyethyl or 1-acetoxyethyl moiety of compounds **9**–**14**, was made by X-ray crystallographic analysis of a single crystal of compound **17** (Fig. 1),[12] a synthetic intermediate obtained by reaction of **5** with 5-amino-4,6-dichloropyrimidine (Scheme 3).[7]

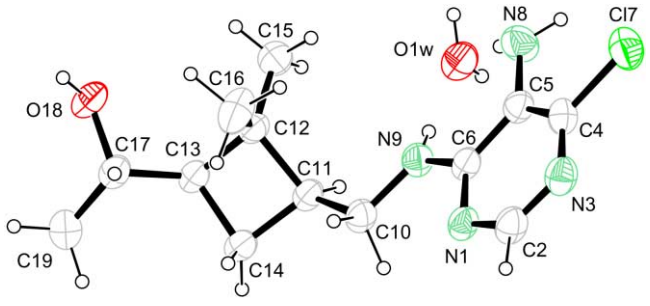


Figure 1. ORTEP plot of the molecular structure of **17** in the solid state.

To obtain amino alcohol **6**, the mixed anhydride derived from compound **10** and ethyl chloroformate in the presence of triethylamine was treated with gaseous ammonia to convert it to the amide **15**, which was reduced with $LiAlH_4$ to give **6** as an oily product in a fair yield. Though this product was initially colourless, gave proper spectra and could be satisfactorily used for subsequent synthetic steps within a few minutes of its preparation, it rapidly altered turning reddish. When not for immediate use, it is best kept in the form of its diacetyl derivative **16**, from which it can be recovered by the same procedure of saponification and isolation as described in the preparation of **5** from **13**.

2. Experimental

Melting points are uncorrected and were determined in a Reichert Kofler Thermopan or in capillary tubes in a Büchi 510 apparatus. Observed rotations at the NaD line were determined at 25°C in a Perkin–Elmer 241 polarimeter. IR spectra of samples as KBr disks (for solids) or films between NaCl plates (for oils) were recorded in a Perkin–Elmer FTIR 1640 spectrometer. ^1H NMR spectra (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in a Bruker WM spectrometer, using TMS as internal standard (chemical shits in δ values, *J* in Hz). EIMS and HRMS spectra were deter-

mined on a HP 5988A apparatus and on a Micromass Autospec apparatus, respectively. Microanalyses were performed in a Fisons EA-1108 by the Microanalysis Service of the University of Santiago. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh). Progress of the reactions and separations by flash chromatography were followed by analytical TLC, that was performed on pre-coated silica gel plates (Merck 60 F254, 0.25 mm).

2.1. (1*R*,1′*S*)-*cis*-[3-(1′-Hydroxyethyl)-2,2-dimethylcyclobutyl]acetic acid [(1*R*,1′*S*)-*cis*-pinolic acid] 9

A mixture of **8**[9] (5.00 g, 27.1 mmol), 0.5N $NaHCO_3$ (55 mL), $NaBH_4$ (1.00 g, 26.5 mmol) and EtOH (10 mL) was refluxed for 6.5 h, cooled to 0°C, and brought to pH 1 by addition of 2N HCl (20 mL). The organic phase obtained upon extraction with EtOAc was washed with saturated NaCl solution and dried with Na_2SO_4, and removal of the solvent at low pressure afforded a mixture of **7** and its (1*R*,1′*R*)-*cis* epimer as a white solid (4.80 g, 95%; 1′*S*/1′*R* ratio 76:24, according to ^{1}H NMR spectrometry). Double recrystallization from water removed the ^{1}H NMR signal corresponding to the 1′*R* epimer. Mp 120–121°C; $[\alpha]_D^{25}=+26.5$ (*c* 3.84, EtOH) [lit.[11] −27 (*c* 3.84, EtOH), for the (1*S*,1′*R*)-*cis* isomer]. IR (*v*): 3303, 1684, 1296, 1276, 1256, 1200, 1081, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.02 (3H, s, *t*-2-CH_3), 1.05 (3H, d, $J=6.2$, C<u>H</u>$_3$CH<), 1.14 (3H, s, *c*-2-CH_3), 1.18 (1H, q, $J=10.2$, 4-H<u>H</u>), 1.76 (1H, dt, $J=10.1$, 8.0, 4-H<u>H</u>), 1.96–2.05 (1H, m, 1-H), 2.17 (1H, dd, $J=10.1$, 8.1, C<u>H</u>HCO), 2.27 (1H, dd, $J=10.1$, 7.9, CH<u>H</u>CO), 2.37 (1H, dt, $J=10.0$, 7.9, 3-H), 2.84 (1H, broad s, D_2O exchang., OH), 3.72 (1H, dq, $J=9.8$, 6.2, 1′-H), 11.24 (1H, broad s, D_2O exchang., CO_2H). ^{13}C NMR ($CDCl_3$) δ: 17.02, 21.44, 26.73, 31.14, 35.15, 37.89, 40.10, 50.50, 69.53, 170.10. Anal. calcd for: $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.54; H, 10.02.

The product obtained upon reduction of **8** with borane–dimethyl sulphide complex was spectroscopically identified as (1*S*,1′*R*)-*cis*-1-[3′-(2-hydroxyethyl)-2′,2′-dimethylcyclobutyl]ethanol **9a**. IR (*v*): 3344, 2957, 1463, 1365, 1293, 1166, 1052, 986 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.98 (3H, s, *t*-2′-CH_3), 1.01 (3H, d, $J=6.3$, C<u>H</u>$_3$CH<), 1.09 (3H, s, *c*-2′-CH_3), 1.06–1.16 (1H, m, 4′-H<u>H</u>), 1.40 (1H, ddd, $J=13.5$, 8.5, 6.6, 4′-H<u>H</u>), 1.54–1.61 (1H, m, C<u>H</u>HCH_2O), 1.67 (1H, dt, $J=10.1$, 7.9, CH<u>H</u>CH_2O), 1.77–1.83 (1H, m, 3′-H), 1.88 (1H, dt, $J=9.8$, 7.9, 1′-H), 2.50–2.68 (2H, broad s, D_2O exchang., 2×OH), 3.52 (2H, t, $J=6.9$, C<u>H</u>$_2$OH), 3.68 (1H, dq, $J=9.9$, 6.2, 1-H). ^{13}C NMR ($CDCl_3$) δ: 17.04, 21.48, 26.84, 31.64, 33.64, 38.75, 39.93, 50.52, 61.62, 69.53. HRMS *m*/*z* calcd for [$C_{12}H_{20}O_3$] 172.1463, found: 172.1467.

2.2. (1*R*,1′*S*)-*cis*-[3-(1′-Acetoxyethyl)-2,2-dimethylcyclobutyl]acetic acid 10

A mixture of **9** (4.03 g, 21.6 mmol), anhydrous pyridine (50 mL) and acetic anhydride (50 mL) was successively stirred at room temperature for 18 h, cooled to 0°C and, after addition of water, stirred for a further 1 h. The organic phase obtained upon extraction with EtOAc was washed with 2N HCl, then with brine, and dried (Na_2SO_4). Removal of the solvent at low pressure afforded **10** as a colourless oil in quantitative yield (4.92 g). $[\alpha]_D^{25}=-52.0$ (*c* 2, EtOH). IR (*v*): 2960, 1730, 1705, 1371, 1248, 1034 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.76 (3H, s, *t*-2-CH_3), 0.94 (3H, d, $J=6.1$, C<u>H</u>$_3$CH<), 0.98 (3H, s, *c*-2-CH_3), 1.13 (1H, q, $J=9.8$, 4-H<u>H</u>), 1.88 (3H, s, CH_3CO), 1.86–2.00 (2H, m, 1-H+4-H<u>H</u>), 2.10 (1H, dd, $J=10.3$, 7.8, C<u>H</u>HCO), 2.17 (1H, dd, $J=10.3$, 7.0, CH<u>H</u>CO), 2.22–2.37 (1H, m, 3-H), 4.65 (1H, dq, $J=10.2$, 6.1 Hz, 1′-H), 10.58 (1H, broad s, D_2O exchang., CO_2H). ^{13}C NMR ($CDCl_3$) δ: 17.09, 17.97, 21.78, 26.75, 30.71, 35.28, 38.17, 40.25, 47.44, 72.20, 171.01, 179.63. HRMS *m*/*z* calcd for [$C_{12}H_{20}O_4$] 228.1362, found: 228.1365.

2.3. (1*S*,1′*S*)-*cis*-3-(1′-Acetoxyethyl)-2,2-dimethylcyclobutylmethyl isocyanate 11

Ethyl chloroformate (1.70 mL, 17 mmol) was slowly added to a cold (−10° to 0°C) solution of **10** (3.50 g, 15.3 mmol) and dry triethylamine (2.30 mL) in anhydrous acetone (11 mL), and after 15 minutes stirring was treated with a solution of NaN_3 (1.95 g, 30 mmol) in H_2O (6 mL). After a further 30 min stirring at 0°C the reaction mixture was poured on to ice and the resulting basic solution was extracted with toluene. The organic phase was dried (Na_2SO_4), filtered, and refluxed for 1 h, after which the toluene was removed at low pressure to obtain **11** as a yellowish oil (2.65 g, 77%). IR (*v*): 2959, 2259, 1734, 1458, 1374, 1248 cm^{-1}.

2.4. Hydrolysis of 11

A solution of **11** (0.73 g, 3.24 mmol) in THF (2 mL) was treated with 8N HCl (6.5 mL), and the mixture was refluxed for 45 min, basified with 5N NaOH (15 mL) and extracted with EtOAc. The organic phase was dried (Na_2SO_4), and removal of the solvent at low pressure left a reddish oily liquid (0.32 g) that was dissolved in dry triethylamine (5 mL) and added to acetic anhydride (5 mL). This mixture was stirred overnight at room temperature, and after cooling to 0°C and addition of water, stirring was continued for 1 h. The organic phase obtained upon extraction with Et_2O was washed with 2N HCl, saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated under reduced pressure to an oily residue (0.21 g). Flash chromatography (1:2 CH_2Cl_2/EtOAc) yielded as a colourless oil, *N*,*N*′-bis[(1*S*,1′*S*)-*cis*-3-(1′-acetoxyethyl)-2,2-dimethylcyclobutylmethyl]-urea **12**. Compound **12** was likewise obtained when **11** was hydrolysed with 10N NaOH in refluxing THF or with neutral water. $[\alpha]_D^{25}=-6.8$ (*c* 0.25, $CHCl_3$). IR (*v*): 3292, 1731, 1633, 1568, 1463, 1369, 1245, 1039 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.92 [6H, s, 2×(*t*-2-CH_3)], 1.08 [6H, d, $J=6.3$, 2×(C<u>H</u>$_3$CH<)], 1.11 [6H, s, 2×(*c*-2-CH_3)], 1.20 [2H, dt, $J=13.2$, 10.1, 2×(4-H<u>H</u>)], 1.66–2.17 [6H, m, 2×(1-H+3-H+4-H<u>H</u>)], 2.01 [6H, s, 2×(CH_3CO)], 3.08 [2H, dd, $J=6.6$, 5.4, 2×(C<u>H</u>HN)], 3.11 [2H, dd, $J=7.5$, 5.4, 2×(CH<u>H</u>N)], 4.13 [2H, broad s, D_2O exchang.,

2×(NH)], 4.79 [2H, dq, $J=10.2$, 6.0, $J(t)=2\times(1'\text{-H})$]. ^{13}C NMR ($CDCl_3$) δ: 16.77, 17.83, 21.54, 21.68, 24.61, 31.32, 39.47, 41.70, 46.73, 72.06, 158.93, 170.81. EIMS, m/z (%): 425 (M+1, 0.9); 424 (M^+, 0.4); 365 (15); 337 (11); 123 (13); 100 (11); 95 (13); 85 (17); 84 (18); 83 (11); 82 (31); 81 (15); 79 (13), 69 (17); 67 (30); 58 (11); 57 (13); 56 (19); 55 (28), 43 (100). HRMS m/z calcd for $[C_{23}H_{40}N_2O_5]$ 424.2937, found: 424.2944.

2.5. Methyl *N*-[(1*S*,1′*S*)-*cis*-3-(1′-acetoxyethyl)-2,2-dimethylcyclobutylmethyl]carbamate 13

To a solution of **11** in toluene, obtained from **10** (10.80 g; 47.3 mmol) as described above and kept at room temperature, anhydrous MeOH (75 mL) was slowly added and the resulting mixture was refluxed for 18 h. Removal of the solvents at low pressure left a yellowish oily liquid (9.76 g) that upon flash chromatography (9:1 CH_2Cl_2/EtOAc) afforded a colourless oil that ^1H NMR spectroscopy showed to be virtually pure **13** (7.43 g; 61% from **10**). $[\alpha]_D^{25}=-0.8$ (c 1, EtOH). IR (ν): 3370, 1732, 1529, 1465, 1370, 1247, 1194, 1145, 1075 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.90 (3H, s, t-2-CH_3), 1.05 (3H, d, $J=6.1$, C<u>H</u>$_3$CH<), 1.08 (3H, s, c-2-CH_3), 1.20 (1H, dt, $J=13.1$, 10.0, 4-H<u>H</u>), 1.88–1.94 (1H, m, 4-H<u>H</u>), 1.98 (3H, s, CH_3CO), 1.99 (1H, quint, $J=8.6$, 1-H), 2.18 (1H, dt, $J=11.7$, 10.0, 3-H), 3.08 (1H, t, $J=6.6$, C<u>H</u>HN), 3.12 (1H, t, $J=6.6$, CH<u>H</u>N), 3.62 (3H, s, CH_3O), 4.55 (1H, broad s, D_2O exchang., NH), 4.74 (1H, dq, $J=10.0$, 6.1, 1′-H). ^{13}C NMR ($CDCl_3$) δ: 16.80, 17.80, 21.67, 24.50, 31.25, 39.48, 41.54, 41.94, 46.68, 52.27, 71.96, 157.17, 170.71. HRMS m/z calcd for $[C_{13}H_{23}NO_4]$ 257.1627, found: 257.1630.

2.6. (1*S*,1′*R*)-*cis*-1-[3′-(Aminomethyl)-2′,2′-dimethylcyclobutyl]ethanol 5

A mixture of **13** (3.60 g, 14.0 mmol) and 5N KOH (25 mL) in MeOH (50 mL) was refluxed for 18 h and brought to pH 3 with 2N H_2SO_4. Removal of the solvents at low pressure afforded a white solid (10 g) that was extracted with MeOH, the extract was passed through basic ion exchange resin (Amberlite IRA-400(OH), 100 mL), and the eluate was concentrated under reduced pressure to a brown oil (2.81 g) that upon flash chromatography (1:1 EtOAc/MeOH) afforded a colourless oil that ^1H NMR spectroscopy showed to be virtually pure **5** (1.87 g, 85%). $[\alpha]_D^{25}=+22.6$ (c 0.52, MeOH). IR (ν): 3287, 2956, 1652, 1599, 1455, 1366, 1165, 1102, 991 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.03 (3H, s, t-2′-CH_3), 1.04 (3H, d, $J=6.2$, C<u>H</u>$_3$CH<), 1.07 (1H, q, $J=10.2$, 4′-H<u>H</u>), 1.17 (3H, s, c-2′-CH_3), 1.23–1.41 (3H, broad s, D_2O exchang., NH_2+OH), 1.69 (1H, dt, $J=10.1$, 7.9, 4′-H<u>H</u>), 1.81 (1H, dq, $J=10.0$, 7.5, 3′-H), 1.92 (1H, dt, $J=9.9$, 7.8, 1′-H), 2.52 (1H, dd, $J=12.4$, 7.5, C<u>H</u>HN), 2.70 (1H, dd, $J=12.4$, 7.3, CH<u>H</u>N), 3.69 (1H, dq, $J=9.9$, 6.2, 1-H). ^{13}C NMR ($CDCl_3$) δ: 16.93, 21.61, 24.97, 32.39, 39.63, 43.43, 45.13, 50.09, 69.69. HRMS m/z calcd for $[C_9H_{19}NO]$ 157.1467, found: 157.1472.

2.7. (1*S*,1′*R*)-*cis*-1-[3′-(Acetamidomethyl)-2′,2′-dimethylcyclobutyl]ethyl acetate 14

A mixture of **5** (0.50 g, 3.18 mmol), anhydrous pyridine (20 mL) and acetic anhydride (20 mL) was stirred at room temperature for 18 h, and after cooling to 0°C and addition of water, stirring was continued for a further 1 h. The organic phase obtained upon extraction with EtOAc was successively washed with 2N HCl, saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and condensed under reduced pressure to a brown oil (0.90 g) that upon flash chromatography (EtOAc) afforded a quantitative yield of **14** as a white solid (0.76 g). A analytical sample was obtained by recrystallization from cyclohexane. Mp 75–76°C. $[\alpha]_D^{25}=-4.7$ (c 1.06, MeOH). IR (ν): 3303, 2863, 1730, 1646, 1558, 1457, 1368, 1245, 1039 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.90 (3H, s, t-2′-CH_3), 1.04 (3H, d, $J=6.1$, C<u>H</u>$_3$CH<), 1.07 (3H, s, c-2′-CH_3), 1.18 (1H, q, $J=10.4$, 4′-H<u>H</u>), 1.88–2.12 (3H, m, 4′-H<u>H</u>+1′-H+3′-H), 1.91 (3H, s, CH_3CO), 1.97 (3H, s, CH_3CO), 3.13 (1H, dd, $J=13.6$, 7.1, C<u>H</u>HN), 3.17 (1H, dd, $J=13.6$, 7.2, CH<u>H</u>N), 4.74 (1H, dq, $J=10.1$, 6.1, 1-H), 5.53 (1H, broad s, D_2O exchang., NH). ^{13}C NMR ($CDCl_3$) δ: 17.03, 17.96, 21.82, 23.67, 24.85, 31.41, 39.71, 40.66, 41.42, 46.90, 72.09, 170.39, 170.86. Anal. calcd for: $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.54; H, 9.83; N, 5.71.

2.8. (1*S*,1′*R*)-*cis*-1-[3′-(Carbamoylmethyl)-2′,2′-dimethylcyclobutyl]ethyl acetate 15

A solution of **10** (9.00 g, 39.4 mmol) and dry triethylamine (11 mL) in anhydrous THF (45 mL) was added to a cold (–10° to 0°C) solution of ethyl chloroformate (7.50 mL, 78.5 mmol) in anhydrous THF (45 mL), and the mixture was stirred for 2 h at 0°C and then allowed to come to room temperature before dry gaseous NH_3 was bubbled through it for 30 min, after which it was poured into CH_2Cl_2. The solid was filtered out and the mother liquor was washed with 5% $NaHCO_3$ solution and brine, dried (Na_2SO_4) and evaporated under reduced pressure to leave **15** as a yellowish solid (7.54 g, 84%). The analytical data that follow are those of the white solid obtained upon recrystallization from hexane/toluene. Mp 122–124°C. $[\alpha]_D^{25}=+10.8$ (c 0.49, MeOH). IR (ν): 3374, 3198, 2957, 1732, 1664, 1627, 1348, 1245, 1030 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.88 (3H, s, t-2′-CH_3), 1.06 (3H, d, $J=6.1$, C<u>H</u>$_3$CH<), 1.09 (3H, s, c-2′-CH_3), 1.24 (1H, q, $J=8.8$, 4′-H<u>H</u>), 1.96–2.04 (1H, m, 4′-H<u>H</u>), 1.99 (3H, s, CH_3CO), 2.03–2.09 (1H, m, 3′-H), 2.10 (1H, dd, $J=10.5$, 5.4, C<u>H</u>HCO), 2.20 (1H, dd, $J=10.5$, 5.6, CH<u>H</u>CO), 2.23 (1H, dt, $J=10.2$, 5.6, 1′-H), 4.77 (1H, dq, $J=10.2$, 6.1, 1-H), 5.45 (1H, broad s, D_2O exchang., NH), 5.63 (1H, broad s, D_2O exchang., NH). ^{13}C NMR ($CDCl_3$) δ: 17.22, 18.01, 21.82, 26.97, 30.75, 37.06, 38.82, 40.31, 47.44, 72.17, 170.92, 175.07. Anal. calcd for: $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.64; H, 9.18; N, 5.91.

2.9. (1*S*,1′*R*)-*cis*-1-[3′-(2″-Aminoethyl)-2′,2′-dimethylcyclobutyl]ethanol 6

A solution of **15** (2.16 g, 9.50 mmol) in anhydrous THF (50 mL) was added to a suspension of $LiAlH_4$ (2.70 g, 71.05 mmol) in 50 mL of the same solvent, the mixture was refluxed for 18 h, and the solvent was then evaporated at low pressure. The solid residue left was extracted with EtOAc and removal of the solvent from the extract under reduced pressure yielded an oil that upon flash chromatography (7:3 EtOAc/MeOH) afforded a colourless oil that ^{1}H NMR spectroscopy showed to be virtually pure **6** (1.04 g, 64%). $[\alpha]_D^{25}=+24.6$ (*c* 0.78, MeOH). IR (*v*): 3360, 2956, 1651, 1462, 1365, 1243, 1097, 1042, 876 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.00 (3H, s, *t*-2′-CH_3), 1.03 (3H, d, $J=6.1$, C$\underline{H}_3$CH<), 1.08 (1H, q, $J=10.2$, 4′-$\underline{H}$H), 1.11 (3H, s, *c*-2′-CH_3), 1.23–1.37 (3H, broad s, D_2O exchang., NH_2+OH), 1.35 (1H, q, $J=8.1$, 4′-H$\underline{H}$), 1.49–1.58 (1H, m, C$\underline{H}$HCH_2N), 1.68 (1H, dt, $J=10.1$, 8.0, CH$\underline{H}$CH_2N), 1.71–1.80 (1H, m, 3′-H), 1.89 (1H, dt, $J=10.1$, 7.7, 1′-H), 2.47 (2H, t, $J=7.6$, CH_2N), 3.70 (1H, dq, $J=10.1$, 6.1, 1-H). ^{13}C NMR ($CDCl_3$) δ: 16.91, 21.59, 26.89, 31.27, 32.10, 38.37, 39.92, 42.81, 50.50, 69.81. HRMS *m*/*z* calcd for [$C_{10}H_{21}NO$] 171.1623, found: 171.1629.

2.10. (1*S*,1′*R*)-*cis*-1-[3′-(2″-Acetamidoethyl)-2′,2′-dimethylcyclobutyl]ethyl acetate 16

Obtained from **6** in the same way as **14** from **5**. White foam. $[\alpha]_D^{25}=+10.7$ (*c* 0.50, MeOH). IR (*v*): 3288, 3090, 1731, 1651, 1557, 1454, 1371, 1244, 1041 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.86 (3H, s, *t*-2′-CH_3), 1.06 (3H, d, $J=6.1$, C$\underline{H}_3$CH<), 1.06 (3H, s, *c*-2′-CH_3), 1.15 (1H, q, $J=10.1$, 4′-$\underline{H}$H), 1.37 (1H, q, $J=7.9$, 4′-H$\underline{H}$), 1.52 (2H, dt, $J=7.4$, 6.1, C$\underline{H}_2$CH_2N), 1.76 (1H, ddt, $J=10.4$, 7.6, 4.3, 3′-H), 1.95 (1H, dt, $J=10.2$, 7.9, 1′-H), 1.96 (3H, s, CH_3CO), 2.00 (3H, s, CH_3CO), 3, 14 (2H, dt, $J=7.4$, 6.1, CH_2N), 4.76 (1H, dq, $J=10.2$, 6.1, 1-H), 5.37 (1H, broad s, D_2O exchang., NH). ^{13}C NMR ($CDCl_3$) δ: 16.99, 18.03, 21.84, 23.73, 26.74, 30.56, 31.13, 38.47, 40.01, 40.08, 47.32, 72.28, 170.38, 170.94. HRMS *m*/*z* calcd for [$C_{14}H_{25}NO_3$] 255.1834, found: 255.1838.

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12. The crystallographic data of **17** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 216007. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.