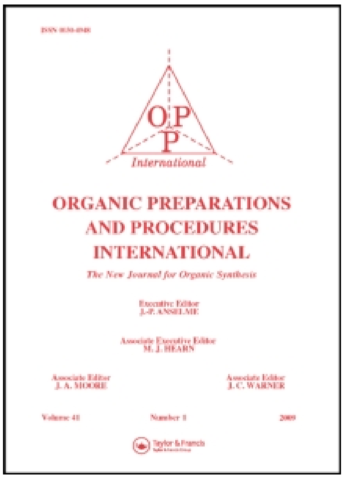

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SYNTHESIS OF (1*R*,3*S*)-3-AMINO-1,2,2-TRIMETHYLCYCLOPENTYLMETHANOL

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SYNTHESIS OF (1*R*,3*S*)-3-AMINO-1,2,2-TRIMETHYLCYCLOPENTYLMETHANOL

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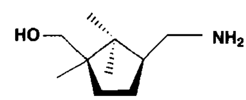
Carbocyclic analogues of nucleosides (CANs) possess a variety of biological activities and are of interest as potential antiviral and antitumour agents.[1] In most cases, CANs are prepared by constructing the purine or pyrimidine base from the appropriate amino alcohol precursor.[1,2] Starting from a single alicyclic precursor, this linear strategy allows preparation of large numbers of congeneric CANs that can then be screened for biological activity. Recently, as part of an ongoing research project examining the relationship between the biological activity of CANs and the structure of their amino alcohol moiety, we reported preparation of amino alcohol **1**[3] and now we describe the preparation of its lower homologue **2**, in which the hydroxy and amino groups have a spatial relation analogous to that in the unsaturated amino alcohol **3**, a synthetic precursor of the promising antiviral agent Carbovir **4**.[4,5]



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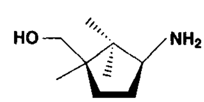

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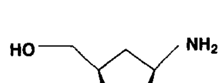

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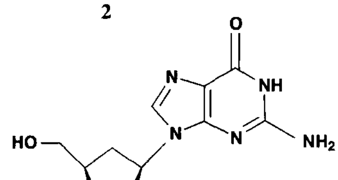

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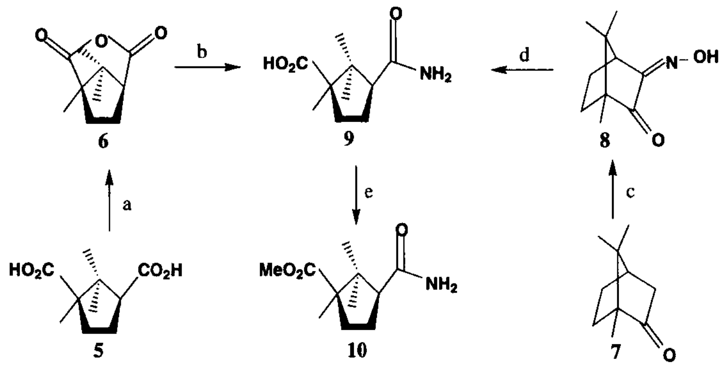
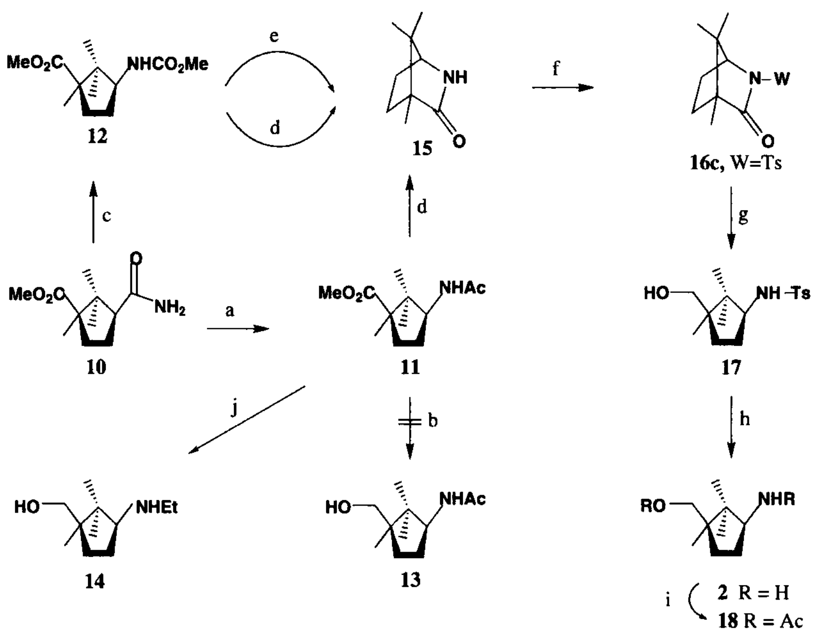
Starting from either (1*R*,3*S*)-(+)-camphoric acid (**5**) or *R*-(+)-camphor (**7**), **2** was efficiently prepared by the synthetic routes outlined in Schemes 1 and 2. First, camphoramic acid (**9**) was obtained in good yield by two routes: from camphoric acid (**5**) by dehydration to camphoric anhydride (**6**) followed by treatment with ammonia; or from camphor (**7**) using the procedure described by Boeckman,[6] in which **7** is first converted to camphorquinone-3-oxime (**8**) by treatment with isoamyl nitrite/potassium hexamethyldisilazane, and then cleaved to **9** in concentrated HCl. Using diazomethane, acid **9** was then esterified to methyl (1*R*,3*S*)-3-carbamoyl-1,2,2-trimethylcyclopentane-carboxylate (**10**) in almost quantitative yield.



a) Ac_2O, reflux; b) NH_3, THF; c) KHMDS, isoamyl nitrite, -78°; d) conc. HCl, r.t.; e) CH_2N_2, Et_2O.

Scheme 1

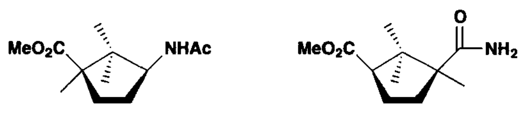
The most direct route to amino alcohol **2** was *via* Hofmann rearrangement of carbamoyl ester **10** to acetamido ester **11**, followed by reduction of the ester group of **11**. While the Hofmann rearrangement of **10** with lead tetraacetate went in reasonably high yield, reduction of **11** using typical reagents for reduction of an ester in the presence of an amide $NaBH_4$,[7] $NaBH_4/CaCl_2$[8] and $LiBH_4$,[9] consistently failed to give acetamido alcohol **13** (Table 1).



a) $Pb(AcO)_4$, AcOH glacial; b) $NaBH_4$, $LiBH_4$ or $Ca(BH_4)_2$, THF, reflux; c) Na, MeOH, Br_2. 10% HCl; d) $NaBH_4$ / $LiBH_4$, THF, reflux; e) NaH, THF, 0°, 10% HCl; f) NaH, TsCl, THF, r.t.; g) $LiBH_4$, THF, reflux; h) Na/NH_3 liq.; i) Ac_2O, Py, r.t.; j) $LiAlH_4$, THF, reflux.

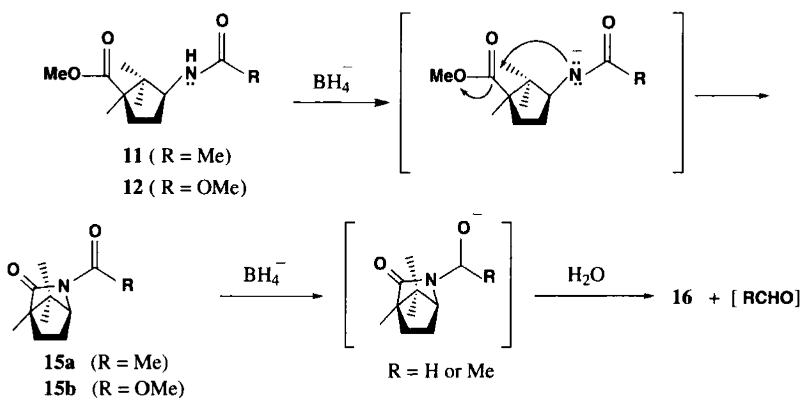
Scheme 2

These results are in keeping with those obtained for its higher homologue **19**,[3] and are attributable to the extreme steric hindrance at the ester carbonyl group that impedes the approach of the reductant. Reduction of the somewhat less hindered ester group at the otherwise similar molecule **20** to the corresponding hydroxymethyl amide by $LiBH_4$, has been reported to proceed in only an 8% yield.[12] Therefore, attempts to reduce **11** gave instead of the target alcohol **13**, either unchanged starting material or lactam **15**. Similar results were also obtained when reduction of carbamate **12** (prepared from carbamoyl ester **10** by the method of Boeckman *et al.*[6]) was attempted using lithium or



19 **20**

sodium borohydride. The formation of **15** may be explained by the reaction sequence in Scheme 3, in which the amidate ion generated in the basic medium from amide **11** or carbamate **12**, intramolecularly attacks the ester group to give *N*-acetyl lactam **16a** or *N*-methoxycarbonyl lactam **16b**, respectively. These lactams are then reductively cleaved by single or double hydride attack at the less sterically hindered carbonyl group to afford the final products **15** and methanal or ethanal, after standard aqueous work up. Lactam **15** is also formed when carbamate **12** is treated with a nonreducing hydride, NaH, after aqueous acid work up of reaction mixture.



Scheme 3

Only by employing the more potent reducing agent $LiAlH_4$[10] was it possible to reduce the ester group of **11**. As expected, however, this reagent also reduced the acetamide, and amino alcohol **14** was isolated in moderate yield (Table 1).

Finally, we set about preparation of amino alcohol **2** from lactam **15**. Firstly, to facilitate reduction of the carbonyl group, it was activated by introducing the tosyl group at the nitrogen as an electron-withdrawing group that was not susceptible to reduction by metal hydrides. As expected, the *N*-tosyl derivative **16c**, which was prepared in a fair yield from **15**, underwent reductive ring-opening upon treatment with $LiBH_4$ to afford *N*-tosylamino alcohol **17** in good yield. Treatment of **17** with Na in liquid ammonia to remove the tosyl group,[11] followed by column chromatography, gave amino alcohol **2** in 80% yield. The structure of **2** was unequivocally established from its physical and spectroscopic data and those of its diacetyl derivative **18**.

TABLE 1. Conditions Attempted for the Reduction of **11** and **12**.

Assay nº	Compound	Reagent	Mole Ratio (R/C)	Time (hrs)	Isolated Product	Yield (%)
1	11	$NaBH_4/CaCl_2$	3	18	**11**	–
2	11	$NaBH_4$	3.5	6	**16**	69
3	11	$LiBH_4$	3.5	6	**16**	78
4	11	$LiAlH_4$	3.4	8	**14**	60
5	12	$LiBH_4$	3.5	6	**16**	51
6	12	$NaBH_4$	3.5	6	**16**	54

EXPERIMENTAL SECTION

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 on a Kofler Thermopan Reichert instrument and are reported uncorrected. Observed rotations at the Na-D line were determined at 23° in a Perkin-Elmer 241 polarimeter. Microanalyses were performed in a Perkin-Elmer 240B element analyser by the Microanalysis Service of the University of Santiago. Infrared spectra were recorded in a Perkin-Elmer 681 spectrophotometer and ^{1}H NMR and ^{13}C NMR spectra were obtained on a 300 MHz Bruker WM spectrometer. Mass spectra were recorded on a Kratos MS-59 spectrometer.

(1*R*,3*S*)-3-Carbamoyl-1,2,2-trimethylcyclopentanecarboxylic Acid (9).- The starting camphoric anhydride **6** was prepared by dehydration of camphoric acid **5** with acetic anhydride.[12] A solution of **6** (5 g, 27.47 mmol) in THF (85 mL) was treated with ammonia gas for 40 min, and then left overnight at 4°. The solids were collected and dissolved in H_2O (45 mL), and this solution was adjusted to pH 2 with 12*N* HCl and extracted with diethyl ether (3 x 50 mL). The combined ethereal extracts were dried (anhydrous Na_2SO_4), and the solvent was evaporated. Recrystallization of the solid residue from H_2O gave **9** (4.33 g, 80%) as a white solid, mp. 174-176°, lit.[6] 176-177°. $[\alpha]_D^{23}$ = +20.51° (*c* 1, MeOH). IR (KBr): 3467, 3357, 2985, 1702, 1654, 1627, 1458, 1300, 1118 cm^{-1}. ^{1}H NMR (CD_3OD): δ 7.07 (s, 1H, NH), 6.80 (s, 1H, NH), 2.60 (t, 1H, *J* = 9.41 Hz, 3-H), 2.36 (td, 1H, J_t = 12.58 Hz, J_d = 6.78 Hz, 5-H), 1.97-1.89 (m, 1H, 5-H), 1.64-1.54 (m, 1H, 4-H), 1.32 (ddd, 1H, *J* = 13.29, 9.59, 4.12 Hz, 4-H), 1.12 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 0.71 (s, 3H, CH_3). ^{13}C NMR (CD_3OD): δ 179.54, 178.51, 57.30, 54.36, 47.10, 33.69, 23.80, 23.27, 22.32, 21.74. MS *m/z*: 199 (2, M^+), 182 (3, M-OH), 154 (40, M-CO_2H), 136 (44), 110 (25), 109 (98), 95 (48), 69 (43), 55 (60).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.27; H, 8.60; N, 7.02. Found.: C, 60.21; H, 8.81; N, 7.29

Carbamoyl acid **9** was also prepared from **7** following the procedure described by Boeckman.[6]

Methyl (1*R*,3*S*)-3-Carbamoyl-1,2,2-trimethylcyclopentanecarboxylate (10).- An ethereal solution of CH_2N_2[13] (2.12 g, 50 mmol) was added to a solution of **9** (4.84 g, 24.29 mmol) in $CHCl_3$ (100 mL),

and the mixture was stirred for 30 min at room temperature. The solvents were evaporated *in vacuo*, and the yellow solid obtained was washed copiously with water and then dried under vacuum to afford **10** (5.1 g, 97%) as a yellow solid, mp. 149-151° lit.[6] 151-153°. $[\alpha]_D^{23}$ = +21.67° (*c* 1, MeOH). IR (KBr): 3251, 2962, 1716, 1685, 1654, 1463, 1320, 1119 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.96 (broad s, 1H, NH), 5.44 (broad s, 1H, NH), 3.65 (s, 3H, CO_2CH_3), 2.79 (t, 1H, *J* = 9.40 Hz, 3-H), 2.61 (td, 1H, J_t = 12.61 Hz, J_d = 7.03 Hz, 5-H), 2.20-2.10 (m, 1H, 5-H), 1.85-1.76 (m, 1H, 4-H), 1.49 (ddd, 1H, *J* = 13.54, 9.49, 4.21 Hz, 4-H), 1.25 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 0.81 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 176.68, 175.61, 56.76, 54.37, 51.92, 46.75, 32.90 23.62, 23.46, 22.17, 21.34. MS *m/z*: 213 (8, M^+), 182 (16, M-OCH_3), 168 (74), 154 (48, M-CO_2CH_3), 153 (74), 110 (23), 109 (100), 95 (46), 69 (41), 55 (47).
Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.97; N, 6.56. Found.: C, 62.17; H, 9.21; N, 6.48

Methyl (1*R*,3*S*)-3-(Acetylamino)-1,2,2-trimethylcyclopentanecarboxylate (11).- A solution of **10** (2 g, 9.4 mmol) and $Pb(AcO)_4$ (6.26 g, 14.1 mmol) in glacial AcOH (40 mL) was refluxed for 90 min. The solvent was evaporated *in vacuo*, and the solid residue was washed with water (20 mL) and then dissolved in CH_2Cl_2 (20 mL). This solution was carefully neutralized with solid $NaHCO_3$, the solid precipitate was filtered off, and the CH_2Cl_2 layer of the filtrate was decanted, dried (anhydrous Na_2SO_4) and concentrated to dryness. Recrystallization of the solid residue from diethyl ether gave **11** (1.72 g, 80%) as a white solid, mp. 97-99°. $[\alpha]_D^{23}$ = - 63.18° (*c* 1, MeOH). IR (KBr): 3299, 2968, 1734, 1722, 1653, 1457 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.72-5.69 (m, 1H, NH), 4.34 (dd, 1H, 3-H), 3.67 (s, 3H, CO_2CH_3), 2.48-2.41 (m, 1H, 5-H), 2.14-2.03 (m, 1H, 5-H), 1.97 (s, 3H, $NHCOCH_3$), 1.45-1.34 (m, 2H, 4-H), 1.20 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.76 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 178.37, 169.89, 57.75, 54.79, 52.03, 47.02, 32.98 28.79, 23.98, 23.21, 21.64, 19.48. MS *m/z*: 227 (24, M^+), 212 (5, M-CH_3), 184 (19, M-$COCH_3$), 165 (13), 154 (30), 127 (65), 98 (100), 85 (20), 56 (63).
Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.40; H, 9.31; N, 6.15. Found.: C, 63.19; H, 9.53; N, 6.12

Methyl (1*R*,3*S*)-3-(Methoxycarbonylamino)-1,2,2-trimetihycyclopentanecarboxylate (12).- Following the method of Boeckman *et al.*,[6] carbamoyl ester **10** was converted into carbamate **12,** which was isolated as an oil. $[\alpha]_D^{23}$ = -35.71° (*c* 1, MeOH). IR and ^{1}H NMR as described.[6] ^{13}C NMR ($CDCl_3$): δ 177.65, 157.25, 59.55, 54.42, 52.33, 51.93, 46.49, 32.01 28.34, 22.42, 22.02, 19.17. MS *m/z*: 243 (14, M^+), 212 (4, M-OCH_3), 184 (14, M-$COCH_3$), 168 (12), 143 (33), 114 (100), 83 (10), 59 (14).
Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.23; H, 8.70; N, 5.75. Found.: C, 58.96; H, 8.98; N, 5.84

(1*S*,4*R*)-4,7,7-Trimethyl-2-azabicyclo[2.2.1]heptan-3-one (15).- A solution of $LiBH_4$ (0.27 g, 12.44 mmol) in dry THF (45 mL) was stirred under reflux for 1 h. A solution of acetamido ester **11** (0.81 g, 3.55 mmol) in dry THF (30 mL) was added dropwise, and the mixture was refluxed for an additional 6 h then cooled to room temperature and poured into wet ether (30 mL). The organic solvents were evaporated *in vacuo*, the inorganic solids were filtered out, and the aqueous filtrate was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated to a solid (0.49 g). Column chromatography of this solid on silica gel, using 1:1 CH_2Cl_2/EtOAc as eluant, gave **15** (0.43 g, 78%) as a white solid, mp. 204-206°, lit.[6] 204-205°. $[\alpha]_D^{23}$ = -35.71° (*c* 1, MeOH). IR (KBr): 3283, 2961, 1703, 1549, 1455, 1373, 1024 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ

5.70 (broad s, 1H, NH), 3.30 (s, 1H, 1-H), 2.02-1.93 (m, 1H, 5-H), 1.75-1.64 (m, 1H, 5-H), 1.54-1.43 (m, 2H, 6-H_2), 1.05 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.88 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 182.72, 62.40, 54.23, 51.34, 30.30, 29.30, 19.02, 18.75, 9.46. MS *m/z*: 153 (52, M^+), 138 (8, M-NH), 125 (18, M-CO), 110 (100), 95 (30), 83 (33), 67 (15), 55 (14).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.86; N, 9.13. Found.: C, 70.29; H, 10.13; N, 8.88

(1*S*,4*R*)-*N*-Tosyl-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptan-3-one (16c).- A solution of lactam **15** (6 g, 38.94 mmol) in dry THF (105 mL) was added to a suspension of NaH (60% suspension in oil; 1.89 g, 47.47 mmol) in 105 mL of the same solvent. After stirring the mixture for 1 h at room temperature, tosyl chloride (9.05 g, 49.80 mmol) in dry THF (80 mL) was added, and the mixture was left stirring overnight. The resulting mixture was cautiously poured into a stirred mixture of Et_2O (250 mL) and ice (300 g), then the ether and THF phases were separated, combined and washed with an aqueous solution of 10% Na_2CO_3 (3 x 150 mL) then saturated NaCl solution (125 mL), and dried (anhydrous Na_2SO_4). Evaporation of the solvent *in vacuo* gave a colorless oil that spontaneously crystallized. The resulting solid was recrystallized from hexane to give **16c** (6.18 g, 51%) as a white solid, mp. 102-104°. $[\alpha]_D^{23}$ = +21.92° (*c* 1, MeOH). IR (KBr): 2970, 2876, 1741, 1595, 1452, 1356, 1105 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.91 (d, 2H, *J* = 8.33 Hz, 2'H + 6'H), 7.31 (d, 2H, *J* = 8.11 Hz, 3'H + 5'H), 4.17 (d, 1H, *J* = 2 Hz, 1-H), 2.42 (s, 3H, $C_6H_4CH_3$), 2.03-1.93 (m, 1H, 5-H), 1.80-1.68 (m, 2H, 5-H + 6-H), 1.53-1.44 (m, 1H, 6-H), 0.96 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.79 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 176.77, 145.12, 136.66, 130.00, 128.08, 69.26, 56.63, 49.72, 29.87, 28.03, 22.06, 18.71, 18.08, 9.71. MS *m/z*: 307 (0.05, M^+), 243 (100, M-SO_2), 216 (4, M-$C_6H_4CH_3$), 215 (28), 200 (16), 155 (26, $SO_2C_6H_4CH_3^+$), 152 (6, M-$SO_2C_6H_4CH_3$), 138 (3, M-$NSO_2C_6H_4CH_3$), 110 (20), 109 (45), 91 (99, $C_7H_7^+$), 65 (43), 55 (37).

Anal. Calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.88; N, 4.55. Found: C, 62.25; H, 7.08; N, 4.50

(1*R*,3*S*)-3-(Tosylamino)-1,2,2-trimethylcyclopentylmethanol (17).- A solution of $LiBH_4$ (0.75 g, 34.57 mmol) in dry THF (150 mL) was stirred under reflux for 1 h; then a solution of *N*-tosyl lactam **16c** (5.18 g, 16.85 mmol) in dry THF (30 mL) was added dropwise, and the mixture was refluxed for a further 18 h then cooled to room temperature and poured into wet ether (200 mL). The organic solvents were evaporated *in vacuo*, the inorganic solids were filtered off, and the aqueous filtrate was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated to a colourless oil that spontaneously crystallized to a white solid identified as **17** (3.90 g, 74%), mp. 152-154°. $[\alpha]_D^{23}$ = -28.48° (*c* 1, MeOH). IR (KBr): 3563, 3237, 2962, 2876, 1452-1366, 1156, 1077 cm^{-1}. ^{1}H NMR (D_2O): δ 7.75 (d, 2H, *J* = 8.26 Hz, 2'H + 6'H), 7.28 (d, 2H, *J* = 8.11 Hz, 3'H + 5'H), 4.82 (broad s, 1H, 1-H), 3.45 and 3.41 (AB system, 2H, *J* = 10.66 Hz, OCH_2), 2.41 (s, 3H, $C_6H_4CH_3$), 1.84-1.70 (m, 1H, 5-H), 1.59-1.49 (m, 1H, 5-H), 1.31-1.13 (m, 2H, 4-H), 0.88 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.80 (s, 3H, CH_3). ^{13}C NMR (D_2O): δ 143.48, 138.83, 130.00, 127.38, 69.98, 62.80, 46.38, 45.52, 32.86, 29.26, 23.66, 21.93, 21.36, 18.15. MS *m/z*: 311 (0.04, M^+), 210 (100), 156 (63, M-$SO_2C_6H_4CH_3$), 155 (61, $SO_2C_6H_4CH_3^+$), 110 (6), 109 (71), 91 (76, $C_7H_7^+$), 65 (21), 55 (16).

Anal. Calcd for $C_{16}H_{25}NO_3S$: C, 61.70; H, 8.09; N, 4.49. Found.: C, 61.96; H, 8.29; N, 4.62

(1*R*,3*S*)-3-Amino-1,2,2-trimethylcyclopentylmethanol (2).- Sulfonamide **17** (3.00 g, 9.60 mmol) was placed in a flask fitted with a cold-finger condenser containing acetone/solid CO_2. Anhydrous ammonia (130 mL) was condensed in the flask, and solid sodium was added in small pieces to the stirred mixture until the solution was persistently dark blue. After 10 min, the reaction was quenched by addition of solid NH_4Cl, then stirred until the ammonia had evaporated. The remaining solid was extracted with hot EtOAc (3 x 100 mL), the extracts were combined and dried (anhydrous Na_2SO_4), and the solvent was removed *in vacuo*. Column chromatography of the resulting yellow oil (1.42 g) on silica gel, using 1:8 EtOAc/MeOH as eluant, gave **2** (1.20 g, 80%) as a pale yellow oil that spontaneously crystallized, mp. 82-84°. $[\alpha]_D^{23}$ = +22.72° (*c* 1, MeOH). IR (KBr): 3370, 2960, 2864, 1654, 1458, 1375 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.69-3.53 (broad s, 3H, OH + NH_2), 3.48 and 3.16 (AB system, 2H, *J* = 11.12 Hz, OCH_2), 3.11-3.08 (m, 1H, 3-H), 2.15-1.92 (m, 2H, 5-H_2), 1.69-1.51 (m, 1H, 4-H), 1.48-1.34 (m, 1H, 4-H), 0.94 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.82 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 70.44, 61.95, 48.55, 47.24, 34.16, 31.29, 27.14, 21.32, 18.12. MS *m/z*: 157 (1, M^+), 110 (7), 95 (22), 83 (24), 70 (10), 67 (7), 57 (19), 56 (100), 55 (15).

Anal. Calcd for $C_9H_{19}NO$: C, 68.73; H, 12.17; N, 8.90. Found.: C, 68.47; H, 12.31 N, 9.15

(1*R*,3*S*)-3-(Acetamido)-1,2,2-trimethylcyclopentylmethanol Acetate (18).- A mixture of **2** (0.57 g, 3.60 mmol) and Ac_2O (2.8 mL) in pyridine (2.5 mL) was stirred at room temperature for 18 h. The reaction mixture was concentrated to dryness, and the solid residue was dissolved in CH_2Cl_2 (30 mL) and washed with saturated $NaHCO_3$ solution and H_2O. The organic layer was dried (anhydrous Na_2SO_4) then concentrated *in vacuo* to a pale yellow oil (0.54 g). Vacuum distillation of this oil in a bulb-to-bulb distillation apparatus gave **18** (0.46 g, 53%) as a pale yellow oil that crystallized on cooling, mp. 85-87° (Hexane/AcOEt 10:1). $[\alpha]_D^{23}$ = -35.27° (*c* 1, MeOH). IR (KBr): 3301, 3089, 1740, 1651, 1548 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.40-5.37 (broad s, 1H, NH), 4.40-4.31 (m, 1H, 3-H) 3.94 and 3.89 (AB system, 2H, *J* = 11.04 Hz, OCH_2), 2.10-2.04 (m, 1H, 5-H), 2.04 (s, 3H, $OCOCH_3$), 1.98 (s, 3H, $NCOCH_3$), 1.65-1.57 (m, 1H, 5-H), 1.42-1.24 (m, 2H, 4-H_2), 1.03 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.78 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 171.65, 170.18, 71.03, 57.28, 45.59, 45.23, 32.56, 28.09, 23.99, 22.65, 22.00, 21.31, 18.10. MS *m/z*: 241 (62, M^+), 198 (12, M-$COCH_3$), 183 (4, M-$NHCOCH_3$), 182 (35, M-CO_2CH_3), 168 (6, M-CH_2OCOCH_3), 166 (11), 138 (44), 122 (18), 98 (100), 83 (54), 67 (19), 57 (36), 56 (74), 55 (30).

Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.60; N, 5.80. Found.: C, 64.48; H, 9.89; N, 5.78

(1*R*,3*S*)-3-(Ethylamino)-1,2,2-trimethylcyclopentylmethanol (14).- A solution of $LiAlH_4$ (0.28 g, 7.37 mmol) in dry THF (15 mL) was stirred under reflux for 1 h; then a solution of acetamido ester **11** (0.50 g, 2.19 mmol) in dry THF (15 mL) was added dropwise, and the mixture was refluxed for a further 8 h then cooled to room temperature and poured into aqueous ether (40 mL). The organic solvents were evaporated *in vacuo*, the inorganic solids were filtered off, and the aqueous filtrate was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated to a colourless oil that was identified as **14** (0.25 g, 60%). $[\alpha]_D^{23}$ = +46.64° (*c* 1.02, MeOH). IR (NaCl): 3283, 2962, 2872, 1458, 1373, 1057 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.25 (broad s, 2H,

OH + NH), 3.44 and 3.05 (AB system, 2H, J = 11.24 Hz, OCH_2), 2.74-2.69 (m, 1H, 3-H), 2.62-2.42 (m, 2H, CH_2CH_3), 1.92-1.81 (m, 2H, 5-H), 1.59-1.55 (m, 2H, 4-H), 1.03 (t, 3H, J = 7.15 Hz, CH_3), 0.89 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.73 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 70.59, 68.99, 48.35, 47.19, 41.78, 34.39, 27.91, 27.67, 20.80, 18.23. 15.34. MS m/z: 185 (16, M^+), 154 (7, M-CH_2OH), 123 (7), 110 (10, M-CH_2OH-$NHCH_2CH_3$), 95 (20), 84 (100), 70 (24), 56 (15), 55 (15).
Anal. Calcd for $C_{11}H_{23}NO$: C, 71.29; H, 12.51; N, 7.55. Found.: C, 71.06; H, 12.79; N, 7.81

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