Pergamon

Tetrahedron Vol. 50, No. 7, pp. 2175-2182, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0157-B

Synthesis of (1*R*,*cis*)-3-Aminomethyl-1,2,2-trimethylcyclopentane-methanol: Two Approaches Using α-Camphidone

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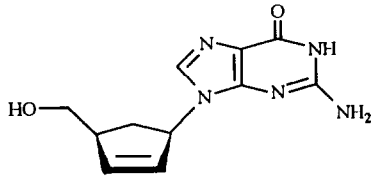
Abstract: *(1R)-α-camphidone has proved to be extremely resistant to alkaline and acid hydrolysis, but the latter can be accomplished under drastic conditions. The aminoacid so obtained was transformed into the aminoalcohol 3, a desirable intermediate in the synthesis of carbocyclic nucleoside analogues. Alternatively, the N-tosyl derivative of α-camphidone can be reductively cleaved under mild conditions and the resulting tosylaminoalcohol converted into 3 in good yield.*

The growing interest in carbocyclic nucleoside analogues (CNA) has been aroused by the significant antineoplastic and antiviral properties[1] of some of these compounds. Carbovir (**1**), for instance, is prominent place among potentially effective anti-AIDS drugs.[2] The synthesis of CNAs requires the building of a natural or modified purine or pyrimidine moiety on an appropriate aminoalcohol[3,4] such as the aminocyclopentenylmethanol **2**, which is the key intermediate in the synthesis of carbovir.[4]

We are currently engaged in assessing the dependence of the biological activity of CNAs on various structural parameters of the precursor aminoalcohols, such as their conformational mobility, relative and absolute stereochemistry, the N-O distance and the presence of lipophilic or hydrophilic groups. In this context the interesting features of aminoalcohol **3** are that its N and O atoms are separated by one C-C bond more than in "conventional" molecules, and that its three methyl groups increase its lipophilic character and restrict the conformational flexibility of the cyclopentane ring.



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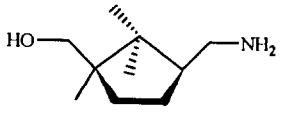


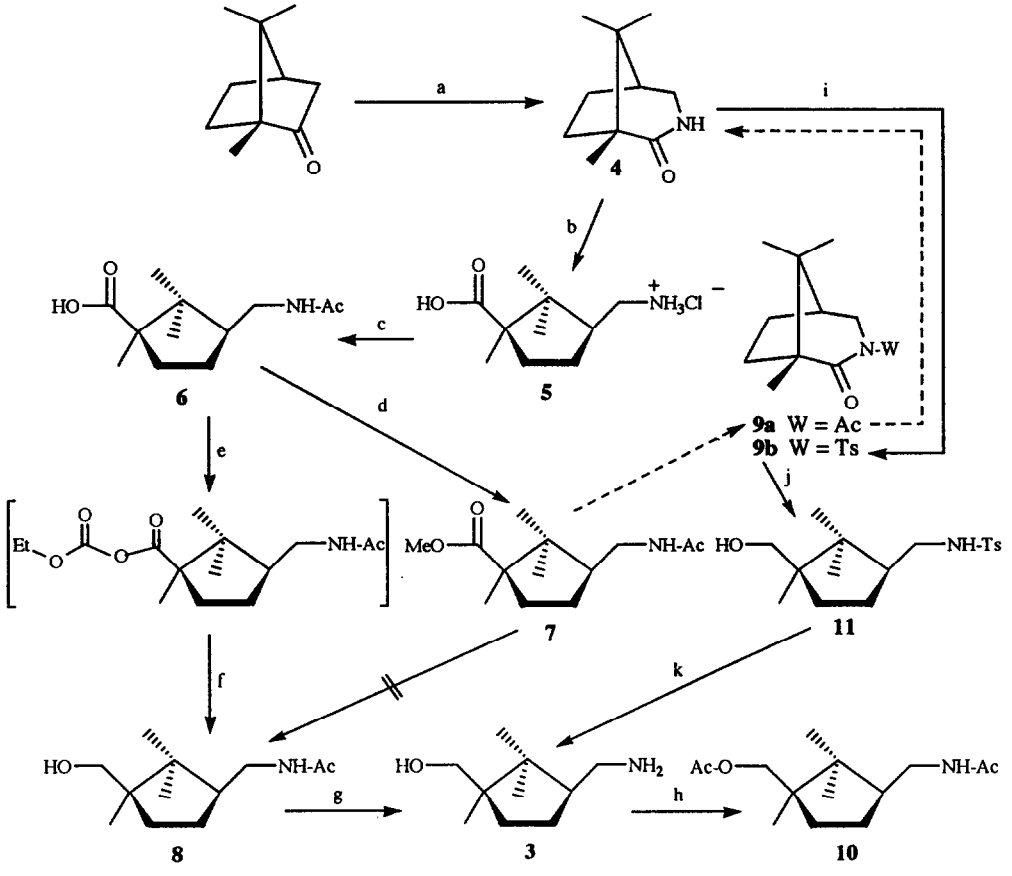
3

We found no specific references to **3** in the literature, though its racemic mixture, referred to as "*allo*-camphoramine alcohol", seems to have been prepared from (±)-camphoric anhydride in unspecified overall

yield.[5] As the evidence for its structure given there seems not conclusive, we chose to synthesize **3** from (1*R*)-1,8,8-trimethyl-3-azabicyclo-[3.2.1]octan-2-one (α-camphidone, **4**), following a sequence of hydrolysis and reduction that is standard for analogous lactams[6] (see Scheme 1).

RESULTS AND DISCUSIONS

When camphor oxime is subjected to Beckmann rearrangement conditions in the presence of various catalysts such as PCl_5, $SOCl_2$ and strong acids the products are variously rearranged cleavage compounds[7] derived from fragmentation at quaternary carbon 1 of the corresponding oxime. The best method for



Reaction Conditions: (a) H_2N-O-SO_3H, AcOH, reflux; (b) 12N HCl, reflux; (c) 6N NaOH, Ac_2O, 25°C; (d) CH_2N_2, Et_2O/MeOH, 0°C; (e) $ClCO_2Et$, Et_3N, THF, -7°C; (f) $NaBH_4$, THF, MeOH, 10°C; (g) 2N HCl, reflux; (h) Ac_2O, Py, 25°C; (i) NaH, TsCl, THF, 25°C; (j) $LiBH_4$, THF, reflux; (k) Na/liq. NH_3.

Scheme 1

preparation of **4** reported so far involves refluxing camphor with hydroxylamine-*O*-sulphonic acid (H_2N-O-SO_3H) in acetic acid for 8 h.[7,8]

We have been unable to find out whether α-camphidone has ever been obtained in an optically pure form. No previous reference to its synthesis reports the configuration of the starting camphor or the optical rotation of the α-camphidone obtained, which is arbitrarily represented as the (1*R*)[7] or (1*S*)[8] isomer. In the only paper claiming synthesis of a specific enantiomer [erroneously designated as (1*R*,5*R*)],[9] the authors failed to provide an optical rotation value. Our α-camphidone, obtained from optically pure (1*R*)-(+)-camphor, had an $[\alpha]_D$ -36.01 (*c* 2, CH_3OH) and, assuming the accepted mechanism of formation,[7] is the (1*R*,5*S*) isomer.

Application of various acidic[6,10] or basic[11,12] conditions for amide hydrolysis to **4** proved to be ineffective. Only refluxing with concentrated hydrochloric acid for 15 days eventually yielded the aminoacid hydrochloride **5**. The need for hydrolysis conditions that are much more severe than in reference syntheses may be ascribed to the strong steric hindrance existing around the carbonyl group of lactam **4**, which impedes the approach of nucleophilic reagents, whether in acidic or in basic media.

By means of a general method for acetylation of analogous aminoacids (Ac_2O, 6N NaOH),[6] compound **6** was prepared and subsequently esterified with CH_2N_2 to obtain the amidoester **7**. Compound **7** was then subjected to various ester reduction methods involving $LiBH_4$,[13,14] $NaBH_4$[15] or $LiAlH_4$[16] with a view to obtaining hydroxyamide **8**. The results are listed in Table 1.

Table 1. Conditions Tried for the Reduction of **7**

Test no.	Reagent	Reductant/7 mole ratio	Solvent	*t* (h)	*T* (°C)	Isolated product[a]
1	$NaBH_4$/MeOH	2.5	THF	49	66	**7**
2	$NaBH_4$/MeOH/AcOH	2.0	THF	48	66	**7**
3	$LiBH_4$	3.7	THF	2	66	**7**
4	$LiAlH_4$	0.5	Et_2O	3.5	35	**7**
5	$LiBH_4$	3.7	THF	22	66	**4**
6	$LiAlH_4$	0.5	THF	38	35	**4**

[a] In more than 85% yield and identified by ^1H NMR analysis.

Here, too, the extreme steric hindrance around the ester carbonyl group prevented reduction under the usual conditions, which only yielded the starting material. The sole change observed when the reaction time was prolonged (tests 5 and 6) was the re-formation of α-camphidone; this may plausibly be ascribed to intramolecular attack by imidate ion formed in the basic medium provided by the reductant, and to the product, the bicyclic *N*-acetyl lactam **9a**, subsequently being deacetylated under the hydrolytic conditions of the final work-up.

However, *in situ* formation of a mixed anhydride from **6** and ethyl chloroformate in THF[17,18] increased the reactivity of the carbonyl group enough for it to be selectively reduced to the desired

hydroxyamide **8** in a one-pot sequence. Acid hydrolysis of **8** yielded **3**, the structure of which was unequivocally established by analysing its ^{1}H NMR, ^{13}C NMR and mass spectra, and by synthesis and characterization of its diacetyl derivative, **10**.

Searching for a shorter, more expeditious pathway from lactam **4** to aminoalcohol **3**, we studied the reductive cleavage of suitable derivatives of **4** with an electron-withdrawing group, such as the tosyl group. The rationale was that the tosyl group in **9b** would not only activate the amide carbonyl group because of its electron-withdrawing character, but also facilitate the subsequent N-C cleavage of the ring to give an intermediate aldehyde[19] which would be further reduced to **11** under the prevailing reaction conditions (see Scheme 1).

The *N*-tosyl derivative **9b** was synthesized by the usual procedure involving treatment of **4** with tosyl chloride in an oily dispersion of NaH. The standard treatment[19] of **9b** with $NaBH_4$ in methanol in the presence of K_2CO_3 did not provide the expected results, the starting material being recovered unaltered. However, use of $LiBH_4$ as reductant afforded **11** in 82% yield. Compound **11** was finally *N*-detosylated by reductive cleavage of the arylsulphonyl group with Na in liquid NH_3,[20] which gave a product identical with aminoalcohol **3** obtained *via* the hydrolysis-reduction pathway.

EXPERIMENTAL

Silica gel (230 mesh) was purchased from Merck. All other chemicals used were of reagent grade and 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 25°C with a Perkin-Elmer 241 polarimeter. Microanalyses were performed on a Perkin-Elmer 240B element analyser by the Microanalysis Service of the University of Santiago; all measured values were within ± 0.3% of the calculated values. Infrared spectra were recorded on a Perkin-Elmer 681 spectrophotometer, while ^{1}H NMR and ^{13}C NMR spectra were obtained on a 250 MHz or a 300 MHz Bruker WM spectrometer. Mass spectra were recorded on a Kratos MS-59 spectrometer.

(1*R*)-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-one (4). Lactam **4** was synthesized by the method reported by Satyanarayana *et al.*[8]. An analytical sample was obtained by repeated recrystallization from 3:8 AcOEt/Hex. Mp 231-232°C (Lit.[8] 230-232°C). $[\alpha]_D^{25}$ - 36.01° (*c* 2, MeOH). ^{1}H and ^{13}C NMR as reported.[8,9]

(1*R,cis*)-1,2,2-trimethyl-3-aminomethylcyclopentanecarboxylic acid hydrochloride (5). A solution of **4** (5.2 g, 31.14 mmol) in 200 mL of 12 N HCl was refluxed for 15 days. Toluene was added to the solid residue (6.87 g) obtained by evaporation of the solvent, and the insoluble fraction (**5**) was filtered out (6.83 g, 99%). Mp 280-284°C (dec). IR (KBr): 3046, 2965, 1684, 1616, 1514-1219 cm^{-1}.

(1*R,cis*)-3-acetylaminomethyl-1,2,2-trimethylcyclopentanecarboxylic acid (6). To a cold solution (0-5°C) of **5** (3.40 g, 15.35 mmol) in 85 mL H_2O, Ac_2O (8.5 mL) and 6 N NaOH (sufficient to maintain basic pH) were added in small alternating portions over 10 min with vigorous stirring. The mixture was further stirred at room temperature for 16 h, and brought to acid pH with 12 N HCl, which gave rise to a brownish white precipitate (2.48 g, 71%). An analytical sample was purified by recrystallization from 7:3 AcOEt/Hex. Mp 172-174°C. $[\alpha]_D^{25}$ + 55.15° (*c* 2, MeOH). IR (KBr): 3648, 3376, 3285, 2967, 1707, 1670, 1654, 1543, 1373 cm^{-1}. ^{1}H NRM (250 MHz, $CDCl_3$) δ: 5.39 (s, 1H, N*H*), 3.39 (ddd, 1H, *J*=

13.04, 5.47, 4.56 Hz, NH-C*H*), 3.08 (ddd, 1H, *J*= 13.06, 9.51, 5.57 Hz, NH-C*H*), 2.49 (m, 1H), 1,98 (s, 3, COCH_3), 2.05-1.81 (m, 2H), 1.53-1.36 (m, 2H), 1.22 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 0.83 (s, 3H, CH_3). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 181.30, 170.28, 56.04, 50.82, 46.82, 41.34, 31.98, 25.69, 23.35, 22.18, 21.67, 19.58. MS *m/z*: 227 (8, M^+), 212 (4, M-CH_3), 184 (12, M-$COCH_3$), 141 (45), 126 (22), 123 (27), 107 (24), 98 (31), 95 (23), 82 (36), 73 (86), 72 (100). Calcd. for $C_{12}H_{21}NO_3$ (227.3): C, 63.41; H, 9.31; N, 6.16. Found: C, 63.51; H, 9.36; N, 6.26.

Methyl (1*R*,*cis*)-3-acetylaminomethyl-1,2,2-trimethylcyclopentanecarboxylate (7). To a solution of **6** (1.55 g, 6.83 mmol) in 35 mL of THF was added an ether solution of CH_2N_2 (1.15 g, 27.4 mmol)[21]. The mixture was allowed to stand at room temperature for 30 min, after which the solvents were evaporated *in vacuo* and the resulting liquid residue (1.61 g) was chromatographed on silica gel [1:2 Hex/AcOEt] to yield **7** (1.50 g, 91%) as a white solid of mp 56-57°C. $[\alpha]_D^{25}$ + 53.87 (*c* 2, MeOH). IR (KBr): 3295, 2965, 1728, 1654, 1558, 1458, 1373, 1251, 1123 cm^{-1}. ^{1}H NRM (250 MHz, $CDCl_3$) δ: 5.65 (s, 1H, N*H*), 3.64 (s, 3H, CO_2CH_3), 3.34 (ddd, 1H, *J*= 12.99, 5.47, 4.51 Hz, NH-C*H*), 3.03 (ddd, 1H, *J*= 13.03, 9.54, 5.58 Hz, NH-C*H*), 2.50 (m, 1H), 1.95 (s, 3H, COCH_3), 2.05-1.79 (m, 2H), 1.50-1.31 (m, 2H), 1.14 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 0.70 (s, 3H, CH_3). ^{13}C NMR (250 MHz, $CDCl_3$) δ: 176.76, 170.28, 56.22, 51.30, 46.71, 44.96, 41.16, 32.18, 25.72, 23.09, 22.18, 21.60, 19.51. MS *m/z*: 242 (2.7, MH^+), 241 (10.5, M^+), 226 (7, M-CH_3), 182 (M-CO_2CH_3), 170 (5), 168 (32), 141 (42), 126 (24), 123 (34), 112 (19), 109 (46), 107 (34), 101 (76), 98 (31), 95 (30), 82 (39), 73 (75), 60 (50), 59 (53). Calcd. for $C_{13}H_{23}NO_3$ (241.3): C, 64.70; H, 9.61; N, 5.80. Found: C, 64.83; H, 9.85; N, 5.76.

(1*R*,*cis*)-*N*-(3-hydroxymethyl-2,2,3-trimethylcyclopentylmethyl)acetamide (8). Ethyl chloroformate (0.75 mL, 7.88 mmol) was added over 15 min to a cold solution (-7°C) of **6** (1.79 g, 7.88 mmol) and Et_3N (1.1 mL, 7.88 mmol) in 15 mL of anhydrous THF. The mixture was stirred under the same conditions for 30 min, and the solid thus formed was filtered out under vacuum and washed with anhydrous THF (4 x 15 mL). To the filtrate, at 10°C, was added $NaBH_4$ (1.03 g, 47.35 mmol, in one portion) followed by MeOH (4.7 mL, dropwise, over 1 h). The reaction mixture was stirred at 10°C for 30 min, after which 6 N HCl (12 mL) was added and the mixture diluted with 60 mL of H_2O. The resulting solution was extracted with CH_2Cl_2 (3 x 75 mL). After the solvent was evaporated, the residue was chromatographed on silica gel (9:1 $HCCl_3/CH_3OH$) to obtain **8** (1.34 g, 80%) as a white solid. An analytical sample was recrystallized from AcOEt. Mp 89-90°C. $[\alpha]_D^{25}$ + 59.68° (*c* 2, MeOH). IR (KBr): 3296, 2964, 2873, 1652, 1563, 1453-1292, 1031. ^{1}H NMR (300MHz, $CDCl_3$) δ: 5.72 (s, 1H, N*H*), 3.54 and 3.42 (AB system, 2H, *J*= 10.69 Hz, HOCH_2), 3.29 (virtual dt, 1H, *J*= 12.95, 4.85 Hz, NH-C*H*), 3.03 (ddd, 1H, *J*= 12.95, 9.65, 5.59 Hz, NH-C*H*), 2.21 (br s, 1H, O*H*), 1.99-1.91 (m, 1H), 1.93 (s, 3H, COCH_3), 1.90-1.79 (m, 1H), 1.61-1.50 (m, 1H), 1.36-1.27 (m, 2H), 0.96 (s, 6H, 2 CH_3), 0.76 (s, 3H, CH_3). ^{13}C NMR (300MHz, $CDCl_3$) δ: 170.56, 69.29, 48.81, 48.06, 44.34, 41.65, 33.86, 26.64, 23.82, 23.56, 20.89, 18.56. MS *m/z*: 213 (8, M^+), 196 (19, M-OH), 154 (24), 123 (63), 121 (38), 109 (19), 98 (32), 95 (30), 84 (45), 82 (42), 81 (66), 73 (79), 72 (95, $[CH_2NHCOCH_3]^+$), 69 (59), 60 (100, $[CH_3CO_2H]^+$). Calcd. for $C_{12}N_{23}NO_2$ (213.3): C, 67.57; H, 10.87; N, 6.57. Found: C, 67.28; H, 10.92; N, 6.87.

(1*R*)-*N*-tosyl-1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-2-one (9b). To a mixture of NaH (60% suspension in oil; 0.96 g, 24.09 mmol) and anhydrous THF (30 mL) was added lactam **4** (3.3 g, 19.76 mmol) in 30 mL of anhydrous THF. The mixture was stirred at room temperature for 1 h, and tosyl chloride (4.59 g, 24.09 mmol) in 24 mL of anhydrous THF was added. The new mixture was then stirred at room

temperature overnight, after which it was added to wet ether. The combined organic phase was successively washed with an aqueous solution of 10% Na_2CO_3 (3 x 150 mL) and a saturated NaCl solution, and then was dried (Na_2SO_4). After removal of the solvent, an oily residue that crystallized spontaneously was obtained. On recrystallization from 3:1 Hex/AcOEt, it yielded **9b** (3.81 g, 60%). Mp 142-143°C. $[\alpha]_D^{25}$ -78.88° (*c* 2, MeOH); IR (KBr): 2890, 2350, 1658, 1613-1536, 1448, 1426, 1367, 1280-980 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 7.87 (d, 2H, *J*=8.30 Hz, $H_{2'}$+ $H_{6'}$), 7.30 (d, 2H, *J*= 8.30 Hz, $H_{3'}$+ $H_{5'}$), 3.85 (dd, 1H, *J*= 11.14, 1.56 Hz, H_4), 3.77 (dd, 1H, *J*= 11.14, 1.84, Hz, H_4), 2.42 (s, 3H, $C_6H_4CH_3$), 2.17-2.05 (m, 2H), 1.99-1.87 (m, 1H), 1.77-1.63 (m, 2H), 1.00 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.81 (s, 3H, CH_3). ^{13}C NMR (250 MHz, $CDCl_3$) δ: 176.23, 136.18, 129.39, 128.36, 54.37, 51.99, 44.09, 42.50, 36.18, 27.20, 22.91, 21.56, 18.94, 13.45. MS *mz*: 322 (0.79, MH^+), 257 (100, M-SO_2), 242 (48), 188 (14), 120 (40), 91 (45), 81 (19). Calcd. for $C_{17}H_{23}NO_3S$ (321.4): C, 63.52; H, 7.21; N, 4.36; S, 9.98. Found: C 63.36; H, 7.50; N, 4.42; S 10.13.

(1*R,cis*)-*N*-tosyl-3-aminomethyl-1,2,2-trimethylcyclopentylmethanol (11). A solution of $LiBH_4$ (1.44 g, 37.95 mmol) in anhydrous THF (37 mL) was refluxed with stirring for 1 h, and then **9b** (4.25 g, 13.24 mmol) in anhydrous THF (25 mL) was added dropwise. The mixture was refluxed with stirring for 18 h and, once cold, was added to ice water (50 mL). After removal of THF at vacuum, it was extracted with CH_2Cl_2 (3 x 150 mL). The pooled organic layers were dried over Na_2SO_4 and the solvent was evaporated to dryness. The residue thus obtained (4.23 g) was chromatographed on silica gel [6:4 Hex/AcOEt] to obtain **11** (3.54 g, 82%) as white crystals of mp 84-86°C; $[\alpha]_D^{25}$ + 37.08° (*c* 2, MeOH). IR (KBr): 3543, 3287, 2962, 2872, 1452-1319, 1158, 1040 cm^{-1}. ^1H NMR (250 MHz,$CDCl_3$) δ: 7.74 (d, 2H, *J*= 8.32 Hz, $H_{2'}$+ $H_{6'}$), 7.30 (d, 2H, *J*= 8.31 Hz, $H_{3'}$ + $H_{5'}$), 3.51 and 3.39 (AB system, 2H, *J* = 10.74 Hz, $HOCH_2$), 2.99 (ddd, 1H, *J*= 11.80, 6.57, 4.10 Hz, NH-C*H*), 2.68 (ddd, 1H, *J*= 11.74, 9.48, 5.71 Hz, NH-C*H*), 2.41 (s, 3H, $C_6H_4CH_3$), 1.91-1.80 (m, 2H), 1.56-1.44 (m, 2H), 1.33-1.16 (m, 2H), 0.89 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.67 (s, 3H, CH_3). ^{13}C-NMR (250 MHz, $CDCl_3$) δ: 143.36, 137.02, 129.74, 127.15, 68.99, 48.54, 47.60, 45.03, 44.01, 33.43, 26.22, 23.45, 21.42, 20.42, 18.13. MS *m/z*: 325 (0.11, M^+), 184 (72, $[CH_2NHSO_2C_6H_4CH_3]^+$), 170 (27, M-$SO_2C_6H_4CH_3$), 155 (100, $[SO_2C_6H_4CH_3]^+$), 141 (1, M-$CH_2NHSO_2C_6H_4CH_3$), 91 (60), 69 (11), 65 (12). Cald. for $C_{17}H_{27}NO_3S$ (325.5): C, 62.74; H, 8.36; N, 4.30; S, 9.85. Found : C, 62.58; H, 8.46; N, 4.43; S, 10.03.

(1*R,cis*)-3-aminomethyl-1,2,2-trimethylcyclopentylmethanol (3). *Method A*. A solution of **8** (1 g, 4.69 mmol) in 60 mL of 2 N HCl was refluxed for 5 h, after which the solvent was evaporated. The resulting residue was dried successive dissolution in and evaporation of absolute ethanol (25 mL) and toluene (2 x 25 mL) to obtain the hydrochloride of 3 as a white solid (0.88 g). Mp 258-260°C (reported for *rac*-3HCl,[5] mp 256°C). IR (KBr): 3903, 3853-3800, 2966-2344, 1602, 1558, 1521 cm^{-1}. The solid 3HCl was dissolved in 20 mL of CH_3OH and passed through a column packed with Amberlite IRA-400 resin in OH^- form (15 mL). The alkaline CH_3OH eluted (40 mL) was concentrated to dryness at low pressure to yield 3 (0.73 g, 91%) as a colourless oil that crystallized spontaneously. An analytical sample was purified by recrystallization from AcOEt. Mp = 100-102°C. $[\alpha]_D^{25}$ + 65.20° (*c* 2, MeOH). IR (KBr): 3355, 2961, 2870, 1594, 1458, 1368, 1144-1049 cm^{-1}. ^1H NMR (300MHz, DMSO-d_6) δ 3.68- 2.99 (br s, 3H, NH_2 + O*H*), 3.33 and 3.17 (AB system, 2H, *J*= 10.54 Hz, $HOCH_2$), 2.60 (dd, 1H, *J*= 11.68, 3.66 Hz, H_2N-C*H*), 2.26 (dd, 1H, *J*= 11.68, 9.43 Hz, H_2N-C*H*), 1.90-1.69 (m, 2H), 1.49-1.38 (m, 1H), 1.24-1.13 (m, 2H), 0.89 (s, 6H, $2CH_3$), 0.65 (s, 3H, CH_3). ^{13}C NMR (300MHz, DMSO-d_6) δ: 67.18, 51.12, 48.27,

43.39, 43.22, 33.62, 26.42, 23.74, 21.05, 18.03. MS *m/z*: 171 (16, M^+), 123 (36), 109 (40), 95 (31), 84 (27), 82 (31), 81 (100), 70 (26), 69 (99), 67 (37), 56 (25), 55 (34). Calcd. for $C_{10}H_{21}NO$ (171.3): C, 70.12; H 12.36; N, 8.18. Found: C, 70.43; H, 12.21; N, 7.85.

Method B. Sulphonamide **11** (1.27 g, 3.90 mmol) was placed in a flask furnished with a dry ice condenser and then anhydrous ammonia was introduced and condensed (50 mL). To the vigorously stirred solution, small pieces of Na were added until a blue colour persisted. After 10 min the reaction was quenched with solid NH_4Cl, the ammonia was allowed to evaporate, and the resulting solid residue was extracted with hot AcOEt (4 x 30 mL). The organic extract was dried (Na_2SO_4) and concentrated to obtain an oily residue (0.74 g) that was column chromatographed on silica gel [1:1 Hex/AcOEt] to yield **3** (0.4 g, 60%) as a colourless oil identical to that provided by method A.

(1*R*,*cis*)-3-(acetylaminomethyl)-1,2,2-trimethylcyclopentylmethanol acetate (10). A mixture of **3** (0.4 g, 2.34 mmol) in 2 mL of Ac_2O and 1.7 mL of pyridine was stirred at room temperature for 18 h. The solid obtained after concentration to dryness was dissolved in 30 mL of CH_2Cl_2, and the organic layer was washed with saturated $NaHCO_3$ and H_2O and dried (Na_2SO_4), after which it was concentrated to yield an oily residue (0.44 g) which was purified by column chromatography on silica gel [1:2 Hex/AcOEt] to obtain **10** (0.36 g, 60%) as a colourless oil that crystallized on cooling. Mp 56-57°C. $[\alpha]_D^{25}$ + 50.26° (*c* 2, MeOH). IR (KBr): 3298, 3089, 1740, 1653, 1558 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 5.70 (s, 1H, N*H*), 3.94 and 3.89 (AB system, 2H, *J*= 10.05 Hz, O-C*H*$_2$), 3.32 (m, 1H, NH-C*H*), 3.02 (ddd, 1H, *J*= 13.03, 9.42, 5.41 Hz, NH-C*H*), 2.02 (s, 3H, O_2CCH_3), 1.94 (s, 3H, $NHCOCH_3$), 1.89-1.84 (m, 2H), 1.61-1.53 (m, 1H), 1.40-1.30 (m, 2H), 0.96 (s, 3H, C*H*$_3$), 0.94 (s, 3H, C*H*$_3$), 0.75 (s, 3H, C*H*$_3$). ^{13}C NMR (250 MHz, $CDCl_3$) δ: 171.32, 170.11, 70.32, 47.70, 46.90, 44.30, 41.26, 33.70, 26.28, 23.26, 23.20, 21.05, 20.83, 18.35. MS *m/z*: 255 (2, M^+), 212 (2, M-$COCH_3$), 196 (58, M-O_2CCH_3), 137 (18), 121 (34), 80 (47), 73 (45, $[CH_2O_2CCH_3]^+$), 72 (100, $[CH_2NHCOCH_3]^+$), 60 (46, $[HO_2CCH_3]^+$), 43 (89, $[OCCH_3]^+$). Calcd. for $C_{14}H_{25}NO_3$ (255.4): C, 65.85; H, 9.87; N, 5.49. Found: C, 65.68; H, 10.08; N, 5.56.

Acknowledgements

Authors thank Spanish Ministry of Education and Science (MEC-DGICYT, PB89-0541) and Xunta de Galicia (XUGA 20304B91) for financially supporting this work.

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(*Received in UK* 27 *September* 1993; *revised* 15 *November* 1993; *accepted* 19 *November* 1993)