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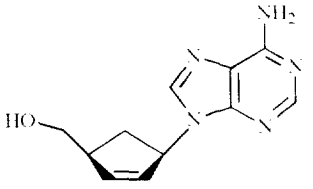
Synthesis of a Precursor of Cyclobutane Carbocyclic Nucleosides from α-Pinene

Franco Fernández*, Carmen López and Antonio R. Hergueta

Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Santiago, E-15706 - Santiago de Compostela, Spain

Abstract: (+)-(1*R*,*cis*)-3-(Aminomethyl)-2,2-dimethylcyclobutylmethanol (**4**), a useful precursor for synthesis of analogues of Cyclobut-G, was prepared from (-)-(1*S*)-α-pinene (**5**) in five steps.

Carbocyclic analogues of nucleosides (CANs) can present interesting antiviral[1] and antineoplastic[2] properties, and so much of the recent work on these compounds has been in connection with the search for effective anti-HIV agents (for example, Carbovir (**1**) and Cyclobut-G (**2**) have shown promise as treatments of AIDS).[3] Synthesis of CANs generally involves construction of the purine or pyrimidine base about an appropriate amino alcohol, which in the case of Cyclobut-G is compound **3**.[4]



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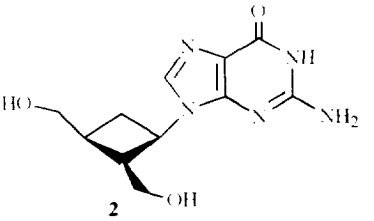

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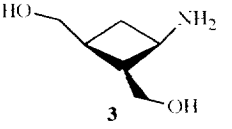

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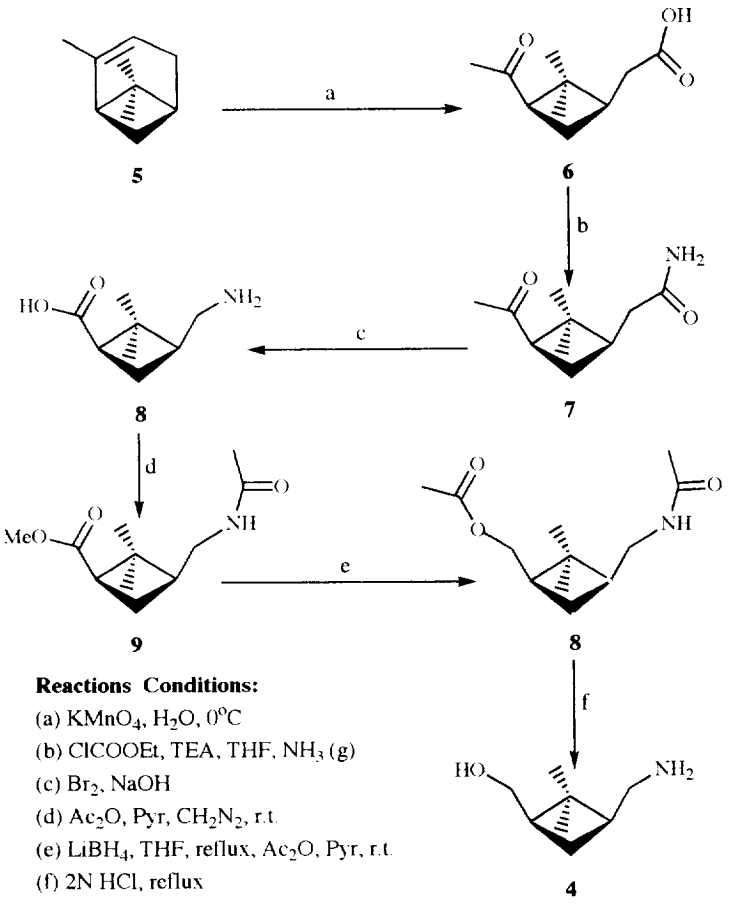
As part of a research programme examining how the structural and configurational features of the amino alcohol moiety influence the antiviral activity of CANs, we required amino alcohol **4**. Herein we describe a successful synthetic approach to (+)-**4** starting from readily available (−)-(1*S*)-α-pinene (**5**). This approach should be equally applicable to synthesis of (−)-*ent*-**4** from (+)-(1*R*)-α-pinene (also available commercially). Amino alcohols (+)-**4** and (−)-*ent*-**4** are also potentially useful as chiral ligands in transition metal complexes.

Oxidation of commercial α-pinene (optical purity 82%) with permanganate afforded (1*R*,*cis*)-pinonic acid **6** in good yield. Two independent methods were used to confirm that the optical purity of **6** ($[\alpha]_D^{25}$ −77.1) was unaltered by purification: in the first, the optical purity was calculated to be 81.1 ± 1.5% by



SCHEME

assuming that the highest absolute value of the specific rotation ($[\alpha]_D$ + 95)[5d,e] among those reported[5] for (+)- and (−)- *cis*-pinonic acids (*ent*-**6** and **6**, respectively) corresponded to 100% pure dextrorotatory enantiomer; in the second method, the ^{1}H NMR spectrum of a 1:5 mole ratio of lanthanide shift reagent Eu(hfc)$_3$[6] and **6** was obtained: the signals corresponding to the *gem*-dimethyl group were observed at δ 1.50 and 2.04 for the predominant, 1*R* enantiomer, and at δ 1.60 and 2.09 for the 1*S* enantiomer; the ratio of the areas of the peaks due to the more deshielded methyl group of the individual enantiomers indicated optical purity 83 ± 2% for **6**.

(−)-Pinonamide **7** ($[\alpha]_D^{25}$ −45.7) was obtained in good yield by reaction of the mixed anhydride of **6** and ethyl chloroformate with gaseous ammonia. The ^{1}H NMR spectrum of a 1:5 mole ratio of Eu(hfc)$_3$ and recrystallized **7** indicated that none of the enantiomeric (+)-pinonamide was present (clean peaks at δ 1.64 and 2.11 were observed for the (−)-1*R* enantiomer). Since we found no data for the $[\alpha]_D$ of **7** of known optical purity in the literature, we estimated the optical purity of our sample from the limits of detection of

the NMR method, which indicated 98 ± 2%. All products obtained thereafter from this purified **7** were considered to be optically pure.

Upon treatment with sodium hypobromite in aqueous dioxane, pinonamide **7** underwent a Hofmann rearrangement and haloform reaction in tandem, affording amino acid **8**, which was not isolated. Acylation and esterification (using CH_2N_2) of crude **8** gave the more easily purified amido ester **9** in an overall yield of 50% from **7**. It is noteworthy that the latter yield matches reported yields for analogous substrates undergoing *each* of the reactions carried out in tandem above.[7]

Reduction of the ester group of **9** was initially carried out with $NaBH_4/CaCl_2$,[10] but better yields were subsequently obtained using $LiBH_4$ in dry THF.[11] In order to facilitate purification, the crude material was converted to the diacyl derivative **10** before it was chromatographed. Finally, hydrolysis of **10** afforded the pure amino alcohol **4** in good yield.

EXPERIMENTAL PART

Silica gel (400 mesh) for flash chromatography (FC) and pre-coated chromatoplates for TLC were from Merck. Reagents and solvents were of commercial grade and were from Aldrich Chemical Co. Melting points are uncorrected and were determined in a Reichert Kofler Thermopan; microanalyses were performed by a Perkin-Elmer 240B Elemental Analyser (Microanalysis Service, University of Santiago) and were all within ± 0.3% of calculated values; sodium D line polarimetry was performed in a Perkin-Elmer 241 polarimeter; IR spectra of samples in KBr discs (for solids) or as films between NaCl plates (for oils) were recorded in a Perkin-Elmer 1600 FT spectrometer; ^1H and ^{13}C NMR spectra were recorded in a Bruker AMX300 spectrometer,at 300 and 75 MHz, respectively, using TMS as internal standard.

(1*R*,*cis*)-3-Acetyl-2,2-dimethylcyclobutaneacetic acid (6). (−)-(1*S*)-α-pinene (**5**) was oxidized to **6** as per Delépine.[5d] M.p. 68°C (lit.[5d] 68-69°C); $[\alpha]_D^{25}$ −77.1 (*c* 5.0, $CHCl_3$) (lit.[5d,e] $[\alpha]_D$ +95 (*c* 10, $CHCl_3$) for (1*S*,*cis*)-enantiomer). ^1H NMR ($CDCl_3$): δ 0.85 (3H, s, *t*-2-CH_3), 1.31 (3H, s, *c*-2-CH_3), 1.87-2.03 (2H, m, 4-H_2), 2.03 (3H, s, CH_3CO), 2.22-2.41 (3H, m, 1-H + 1-CH_2), 2.87 (1H, dd, J = 8.89, J = 7.79, 3-H), 11.60 (1H, broad s, CO_2H). ^{13}C NMR ($CDCl_3$): δ 17.55 (*t*-2-CH_3), 23.19 (C4), 30.42 ($\underline{C}H_3CO$ and *c*-2-CH_3), 35.11 ($\underline{C}H_2CO_2H$), 37.90 (C1), 43.45 (C2), 54.42 (C3), 179.35 (CO_2H), 208.08 (3-$\underline{C}OCH_3$).

(1*R*,*cis*)-3-Acetyl-2,2-dimethylcyclobutaneacetamide (7) To a stirred solution of ethyl chloroformate (15 mL, 157 mmol) in dry THF (90 mL) at -10 to 0°C was added, under an argon atmosphere, a solution of **6** (15 g, 81.5 mmol) and dry triethylamine (11 mL) in dry THF (90 mL). After 2h, cooling was ceased and dry ammonia gas was bubbled through the stirred suspension for 1h. The reaction mixture was poured into CH_2Cl_2 (400 mL), washed with 5% NaOH solution (2×50 mL), then water, and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* and purification of the oily residue (15.04 g) by FC (375 g of silica gel), using EtOAc as eluant and TLC to monitor the eluates, afforded spectroscopically pure (^1H NMR) **7** (11.4 g, 77% yield). A optically pure material (^1H NMR/Eu(hfc)$_3$) was obtained after three recrystallitations of chromatographed material from a toluene/hexane solvent pair: m.p. 118 - 119°C; $[\alpha]_D^{25}$ −45.7 (*c* 2.0, EtOH); IR (ν): 3380 (NH), 3194 (NH), 1700 (CO, ketone), 1663 (CO, amide I), 1627, 1430, 1411 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (3H, s, *t*-2-CH_3), 1.34 (3H, s, *c*-2-CH_3), 1.88-2.09

(2H, m, 4-H_2), 1.99 (3H, s, CH_3CO), 2.16 (1H, dd, J = 14.53, J = 8.67, 1-C<u>H</u>HCON), 2.24 (1H, dd, J = 14.53, J = 6.62 Hz, 1-CH<u>H</u>CON), 2.35-2.47 (1H, m, 1-H), 2.91 (1H, dd, J = 9.80, J = 7.78, 3-H), 5.94 and 6.07 (2H, 2 broad s, NH_2); ^{13}C NMR ($CDCl_3$): δ 17.66 (*t*-2-CH_3), 23.18 (C4), 30.39 (<u>C</u>H_3CO or *c*-2-CH_3), 30.49 (*c*-2-CH_3 or <u>C</u>H_3CO), 36.86 (1-CH_2), 38.55 (C1), 54.41 (C3), 43.58 (C2), 175.14 (CON), 208.23 (<u>C</u>OCH_3). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.33; H, 9.46; N, 7.54.

Methyl (1*R*,*cis*)-3-acetamidomethyl-2,2-dimethylcyclobutanecarboxylate (9). Sodium hypobromite was prepared by slowly adding bromine (13 mL, 252 mmol) to 1N NaOH (1100 mL) stirring at between -5 and -10°C. When all the bromine had dissolved, a solution of **7** (11 g, 60 mmol) in dioxane (120 mL) was added, and the mixture was stirred at 0°C for 1 h, at rt for 1 h, and at 60°C for 1 h. After cooling the reaction mixture to 0°C, it was vigorously stirred while a single portion of solid $Na_2S_2O_5$ (1.7 g, 9.5 mmol) was added, followed by slow addition of 12 N HCl (62 mL) and, subsequently, AcOH (62 mL). The volatile components were evaporated *in vacuo* to leave a solid residue, which was suspended in dry pyridine (150 mL), mixed with acetic anhydride (150 mL), and left stirring overnight at rt. The reaction mixture was then cooled to 0°C, stirred with saturated sodium chloride solution (300 mL) for 30 min, then extracted with EtOAc (4×200 mL). The organic extracts were washed with 2 N HCl (4×300 mL), then water, and dried (Na_2SO_4). The solvent was removed *in vacuo* to leave a syrup (10.4 g), which was dissolved in THF (100 mL) and mixed with 150 mL of 0.5 M ethereal diazomethane.[12] After 2 h, the solvent was removed *in vacuo* and the oily residue (10.4 g) was purified by FC (300 g of silica gel) with EtOAc as eluant. Compound **9** was isolated as a spectroscopically pure (^1H NMR), colourless oil (6.38 g, 50%). $[\alpha]_D^{25}$ − 80.5 (*c* 0.5, EtOH); IR (ν): 3300 (NH), 1734 (CO ester), 1654 (CO, amide I), 1560 (NH, amide II), 1437, 1369, 1232, 1195 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (3H, s, *t*-2-CH_3), 1.15 (3H, s, *c*-2-CH_3), 1.74-1.94 (2H, m, 4-H_2), 1.83 (3H, s, CH_3CO), 1.99-2.10 (1H, m, 3-H), 2.55 (1H, dd, J = 10.01, J = 7.84, 1-H), 2.99 (1H, ddd, J = 13.52, J = 6.97, J = 5.61, 3-C<u>H</u>HNH), 3.08 (1H, virtual dt, J(d) = 13.52 Hz , J(t) = 6.71 Hz , 3 -CH<u>H</u>NH), 3.48 (3H, s, CO_2CH_3), 6.98 (1H, virtual t, J = 5.20, NH); ^{13}C NMR ($CDCl_3$): δ 17.45 (*t*-2-CH_3), 22.82 (C4), 22.94 (<u>C</u>H_3CON), 30.37 (*c*-2-CH_3), 40.18 (3-CH_2), 41.18 (C3), 42.07 (C2), 45.67 (C1), 170.56 (CON or CO_2), 173.31 (CO_2 or CON).

(1*R*,*cis*)-[3-(acetamidomethyl)-2,2-dimethylcyclobutyl]methyl acetate (10) Lithium borohydride (1.03 g, 47.5 mmol) was refluxed in dry THF (55 mL) for 1.5 h, following which a solution of **9** (5.03 g, 23.45 mmol) in the same solvent (10 mL) was added and refluxed for a further 2.5 h. The reaction mixture was cooled to 0°C, 40 mL of water and an acidic ion-exchange resin (Amberlite IR-120(plus), 24 g) were added, and the suspension was left stirring at rt overnight. Then, the resin was filtered out and washed with methanol (100 mL), and basic ion-exchange resin (Amberlite IRA-420) was added to the combined filtrate and washings until their pH was neutral. The resin was filtered out and washed with methanol as before, and the combined filtrate and washings were evaporated *in vacuo* to leave an oily residue (3.8 g). This residue was dissolved in dry pyridine (100 mL), mixed with acetic anhydride (100 mL), and stirred overnight at rt. After cooling the reaction mixture to 0°C, water (200 mL) was added and the mixture was stirred for 1 h, and then extracted with EtOAc (4×200 mL). The combined organic extracts were washed

with 2 N HCl (4×200 mL), then water, and dried (Na_2SO_4). The solvent was evaporated *in vacuo*, and the oily residue (4.6 g) was purified by FC (150 g of silica gel) with 1:1 CH_2Cl_2/EtOAc as eluant. Compound **10** was isolated as a spectroscopically pure (^1H NMR), colourless oil (3.2 g, 64%). $[\alpha]_D^{25}$ +10.2 (*c* 1.0, EtOH); IR (*ν*): 3300 (NH), 1740 (CO, ester), 1654 (CO, amide I), 1557 (NH, amide II), 1456, 1367, 1242 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.94 (3H, s, *t*-2-CH_3), 1.07 (3H, s, *c*-2-CH_3), 1.18-1.26 (2H, m, 4-H_2), 1.90 (3H, s, CH_3CON), 1.93-2.02 (1H, m, 3-H), 1.97 (3H, s, CH_3CO_2), 2.06-2.17 (1H, m, 1-H), 3.10 (1H, virtual dt, J(d) = 13.48, J(t) = 5.83, 3-C<u>H</u>HNH), 3.19 (1H, virtual dt, J(d) = 13.48, J(t) = 6.89, 3-CH<u>H</u>NH), 3.90 (1H, dd, J = 11.14, J= 8.69, 1-C<u>H</u>HO), 3.98 (1H, dd, J = 11.14, J = 6.32, 1-CH<u>H</u>O), 5.71 (1H, broad s, NH); ^{13}C NMR ($CDCl_3$): δ 16.74 (*t*-2-CH_3), 21.19 (<u>C</u>H_3CON or <u>C</u>H_3CO_2), 23.47 (<u>C</u>H_3CO_2 or <u>C</u>H_3CON), 24.69 (C4), 31.02 (*c*-2-CH_3), 39.48 (C2), 40.53 (C3 or C1), 40.57 (3-CH_2), 41.75 (C1 or C3), 64.97 (1-CH_2), 170.22 (CON or CO_2), 171.28 (CO_2 or CON).

(1*R*, *cis*)-3-Aminomethyl-2,2-dimethylcyclobutylmethanol (4) A mixture of **10** (2.5 g, 11 mmol) and 2N HCl (145 mL) was refluxed for 5 h. The solvent was evaporated *in vacuo*, and the oily residue (2.0 g) was dissolved in methanol, and passed through a column of basic ion exchange resin (95 mL of Amberlite IRA-400(OH)). The methanol was evaporated *in vacuo* to leave a reddish syrup (2.0 g), which was purified by FC (50 g of silica gel) with 1:1 CH_2Cl_2/MeOH (500 mL) then MeOH (600 mL) as eluants, and monitoring the eluates by TLC. Compound **4** was isolated as a spectroscopically pure (^1H NMR), colourless oil (1.31 g, 84%). $[\alpha]_D^{25}$ +14.5 (*c* 0.5, EtOH); IR (*ν*): 3364, 2953, 1574, 1462, 1383, 1014 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.89 (3H, s, *t*-2-CH_3), 0.95-1.18 (2H, m, 4-H_2), 1.08 (3H, s, *c*-2-CH_3), 1.75-1.86 (1H, m, 3-H), 1.89-2.00 (1H, m, 1-H), 1.94 (1H, broad s, exchangeable with D_2O, OH), 2.37 (2H, broad s, exchangeable wit6h D_2O, NH_2), 2.44 (1H, dd, J = 12.41, J = 7.81, 3-C<u>H</u>HN), 2.62 (1H, dd, J = 12.41, J = 7.13, 3-CH<u>H</u>N), 3.39 (1H, dd, J = 10.84, J = 6.36, 1-C<u>H</u>HO), 3.48 (1H, dd, J = 10.84, J = 7.51, 1-CH<u>H</u>O); ^{13}C NMR ($CDCl_3$): δ 16.52 (*t*-2-CH_3), 24.90 (C4), 31.57 (*c*-2-CH_3), 39.16 (C2), 42.84 (3-CH_2), 43.98 (C3 or C1), 44.86 (C1 or C3), 62.81 (1-CH_2). Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.30; H, 11.75; N, 9.54.

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5. Reported values of $[\alpha]_D$ for the 1*S* enantiomer are +92.6 (*c* 2.5, $CHCl_3$),[a] +94 (*c* 5, $CHCl_3$),[b] +94.7 (*c* 5-10, $CHCl_3$),[c] +95 (*c* 4-10, $CHCl_3$)[d] and +95±1 (*c* 10, $CHCl_3$);[e] and for the 1*R* enantiomer, -92 (*c* 5, $CHCl_3$)[b] and -94.2 (*c* 5-10, $CHCl_3$)[c]: a) Briggs, C. H.; Taylor, W. I. *J. Org. Chem.*, **1947**, *12*, 551; b) Harispe, M.; Pernin, J. *Bull. Soc. Chim. France*, **1950**, 660; c) Thoi, L.-V. *Ann. Chim. (Paris)*, **1955**, *10*, 35; d) Delépine, M. *Bull. Soc. Chim. France*, **1936**, 1369; e) Harispe, M.; Méa, D. *Bull. Soc. Chim. France*, **1962**, 1340.

6. Europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato].

7. The haloform reaction of an analogous dimethylcyclobutyl derivative gave the corresponding acid in 45% yield;[8] the Hofmann rearrangement of an analogous amido acid afforded, after esterification and *N*-acylation, the corresponding acetamido methyl ester in 56% yield.[9]

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