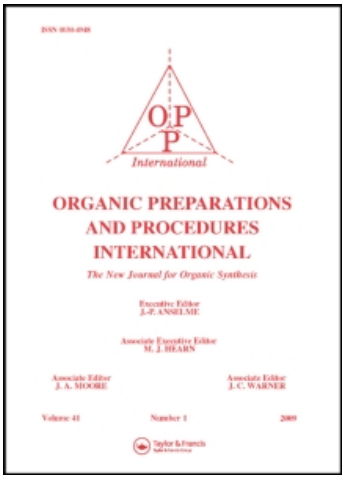

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SYNTHESIS OF (1*R,cis*)-2-(3-AMINO-2,2-DIMETHYLCYCLOBUTYL)ETHANOL, A PRECURSOR OF CYCLOBUTANE CARBOCYCLIC NUCLEOSIDES

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SYNTHESIS OF (*1R,cis*)-2-(3-AMINO-2,2-DIMETHYLCYCLOBUTYL)ETHANOL, A PRECURSOR OF CYCLOBUTANE CARBOCYCLIC NUCLEOSIDES

Submitted by (09/23/96)

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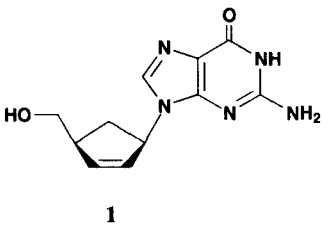
Carbocyclic analogues of nucleosides (CANs) can exhibit interesting antiviral[1] and antineoplastic[2] properties, and much of the recent work on these compounds has been in connection with the search for effective anti-HIV agents (for example, Carbovir (**1**) and Cyclobut-G (**2**) have shown promise 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] As part of a research program to examine the effect of the structural and configurational features of the amino alcohol moiety on the antiviral activity of CANs, we required amino alcohol **9**. Herein we



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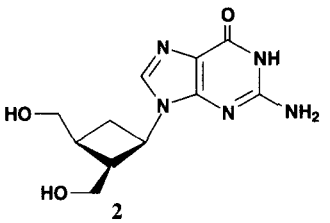

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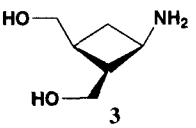

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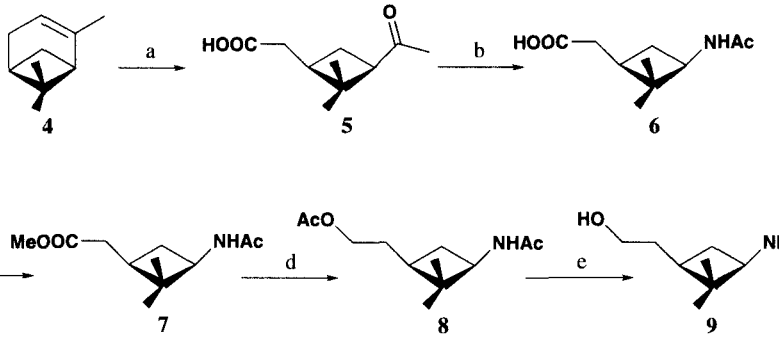
describe a successful synthetic approach to (+)-**9** starting from readily available (-)-(1*S*)-α-pinene (**4**) (Scheme 1). This approach should be equally applicable to synthesis of (-)-*ent*-**9** from (+)-(1*R*)-α-pinene (also available commercially). Amino alcohols (+)-**9** and (-)-*ent*-**9** are also potentially useful as chiral ligands in transition metal complexes.



a) $KMnO_4$; b) H_2NOSO_3H; c) CH_2N_2; d) $NaBH_4/CaCl_2$, then Ac_2O/Pyr; e) HCl

Oxidation of commercial α-pinene (optical purity 82%) with potassium permanganate afforded (-)-(1*R,cis*)-pinonic acid (**5**) in 60% yield. Two independent methods were used to confirm that the optical purity of **5** ($[\alpha]_D^{25}$ -77.1) was unaltered by purification. In the first, the optical purity was calculated to be 81 ± 2% by assuming that the highest absolute value of the specific rotation ($[\alpha]_D$ + 95)[5,6] among those reported for (+)- and (-)-*cis*-pinonic acids (*ent*-**5** and **5**, respectively) corresponded to 100% pure dextrorotatory enantiomer. The reported values of $[\alpha]_D$ for the 1*S* enantiomer are +92.6 (*c* 2.5, $CHCl_3$),[7] +94 (*c* 5, $CHCl_3$),[8] +94.7 (*c* 5-10, $CHCl_3$),[9] +95 (*c* 4-10, $CHCl_3$),[5] and +95±1 (*c* 10, $CHCl_3$);[6] and for the 1*R* enantiomer, -92 (*c* 5, $CHCl_3$)[8] and -94.2 (*c* 5-10, $CHCl_3$).[9] In the second method, the ^1H NMR spectrum of a 1:5 mole ratio of lanthanide shift reagent Eu(hfc)$_3$ {europium(III) *tris*[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]} and **5** was obtained and the ratio of the areas of the peaks due to the individual enantiomers (these were most clearly seen in the signal due to the more deshielded *gem*-methyl group) indicated optical purity 83 ± 2% for **5**.

Hydroxylamine-*O*-sulfonic acid was then employed for the Beckmann rearrangement[10] of **5** to previously unreported amido acid **6**. In order to achieve the specific reduction of its carboxy group, **6** was first converted into its methyl ester **7** with diazomethane. Similarly to **5**, acid **6** showed no definite tendency towards enantiomeric enrichment through recrystallization. However, the ^1H NMR spectrum of twice recrystallized **7** ($[\alpha]_D^{25}$ +110) in the presence of Eu(hfc)$_3$ (in 1:5 mole ratio) indi-

cated that none of (-)-*ent*-**7** was present. When the limits of detection of the NMR method are taken into account, the optical purity of this (+)-**7** was estimated to be 98 ± 2%. This estimate was further checked by preparation of a sample of (+)-**7** from (-)-(1*S*)-α–pinene of 97% ee by the same procedure, and it gave a value of ($[\alpha]_D^{25}$ +109. Therefore, all products obtained subsequently from this (+)-**7** were considered to be enantiomerically pure.

Reduction of the ester group of (+)-**7** was successfully carried out using $LiBH_4$ in dry THF,[11] or $NaBH_4$-$CaCl_2$,[12] although yields were better using the latter reagent. To facilitate chromatographic purification, the crude and partially hydrolyzed amido alcohol was reacetylated to the diacetyl derivative **8**. Acid hydrolysis of chromatographed **8** gave **9** in quantitative yield. Amino alcohol **9** slowly darkens and its rotation ($[\alpha]_D^{25}$) changes after periods of time, even if kept under Ar at -18°. The value reported here corresponds to the measurement made after isolation of the sample by ion exchange chromatography from the hydrolysate of **8**.

EXPERIMENTAL SECTION

Melting points are uncorrected and were determined in a Reichert Kofler Thermopan. IR Spectra were obtained using a Perkin-Elmer FTIR 1640 spectrometer. ^1H NMR-and ^{13}C NMR spectra were recorded on a Bruker AMX 300, with TMS as internal standard. EI-MS spectra were performed on a KRATOS MS-50 apparatus. Microanalyses were done at the Microanalysis Service, University of Santiago, using a Perkin-Elmer 240B Elemental Analyzer. Sodium D line polarimetry was performed in a Perkin-Elmer 241 polarimeter. Silica gel (400 mesh) for flash chromatography (FC) and precoated chromatoplates for TLC were from Merck.

(1*R*,*cis*)-(3-Acetyl-2,2-dimethylcyclobutyl)acetic Acid (5).- (–)-(1*S*)-α-Pinene (**4**) was oxidized to **5** according to Delépine's procedure,[5] mp. 68-69°, lit.[5] 68-69°. $[\alpha]_D^{25}$ -77.1 (*c* 5.0, $CHCl_3$), lit.[9] -94.2 (*c* 5-10, $CHCl_3$). IR (KBr): 3228, 2950, 1733, 1683, 1457, 1400, 1372, 1202, 1156, 814, 652 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.60 (1H, br. s, CO_2H); 2.87 (1H, dd, *J* = 8.89 Hz, *J* = 7.79 Hz, 3-H); 2.22-2.41 (3H, m, 1-H and 1-CH_2); 2.03 (3H, s, $COCH_3$); 1.87-2.03 (2H, m, 4-H_2); 1.31 (3H, s, *c*-2-CH_3); 0.85 (3H, s, *t*-2-CH_3). ^{13}C NMR ($CDCl_3$): δ 208.08 (3-$\underline{C}OCH_3$); 179.35 (CO_2H); 54.42 (C3); 43.45 (C2); 37.90 (C1); 35.11 ($HO_2C\underline{C}H_2$); 30.42 ($\underline{C}H_3CO$ and *c*-2-CH_3); 23.19 (C4); 17.55 (*t*-2-CH_3).

(1*R*,*cis*)-(3-Acetamido-2,2-dimethylcyclobutyl)acetic Acid (6).- A solution of **5** (25.0 g, 136 mmol) and hydroxylamine-*O*-sulfonic acid (23.1 g, 200 mmol) in glacial AcOH (525 mL) was refluxed for 17 hrs. The solvent was removed *in vacuo* and the residue obtained was dissolved in 2N HCl (100 mL) and extracted with ethyl acetate (4 x 100 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo* to afford **6** as a white solid (21.50 g, 79% yield). An analytical sample was obtained by recrystallization of the crude material from EtOAc/toluene, mp. 132-133°. $[\alpha]_D^{25}$ +111.3 (*c* 1, EtOH). IR (KBr): 3334, 2974, 2523, 1697, 1622, 1559, 1436, 1303, 1275 cm^{-1}. ^1H NMR ($CDCl_3$): δ 12.23 (1H, br. s, D_2O exch., CO_2H); 5.41 (1H, br d, *J* = 7.72 Hz, D_2O exch., NH); 4.06 (1H, dt, J_d = 9.82 Hz, J_t = 8.14 Hz, 3-H); 2.43 (1H, virtual dt, J_d = 11.03 Hz, J_t = 7.68 Hz, 1-H); 2.39 (1H, dd, *J* = 15.47 Hz, *J* = 7.39 Hz, 1-C$H\underline{H}$); 2.29

(1H, dd, J = 15.47 Hz, J = 7.89 Hz, 1-CHH); 2.17 (1H, dt, J_d = 10.14 Hz, J_t = 7.62 Hz, *c*-4-H); 1.98 (3H, s, CH_3CO); 1.42 (1H, virtual q, J = 10.34 Hz, *t*-4-H); 1.17 (3H, s, *c*-2-CH_3); 0.91 (3H, s, *t*-2-CH_3). ^{13}C NMR ($CDCl_3$): δ 177.82 (CO_2), 170.41 (CON), 50.72 (C3), 44.06 (C2), 35.67 (C1), 35.21 (1-CH_2), 31.92 (C4), 28.85 (*c*-2-CH_3), 23.56 (CH_3CON). 16.61 (*t*-2-CH_3). MS: *m/z* (%) 199 (M^+, 0.3), 154 (2), 140 (3), 113 (30), 96 (10), 86 (82), 85 (100), 71 (61), 70 (12), 69 (25), 56 (30).

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.12; H, 8.42; N, 7.13

(1*R*,*cis*)-Methyl (3-Acetamido-2,2-dimethylcyclobutyl) Acetate (7).- Diazomethane (300 mL of a 0.5M solution in ether)[13] was added to a solution of **6** (21.50 g, 108 mmol) in THF (100 mL) and left to stand at room temperature for 30 min. The solvent was evaporated *in vacuo* and the resulting white solid (21.90 g) was chromatographed on silica gel with AcOEt as eluent. Spectroscopically pure (^1H NMR) **7** was isolated as a white solid (20.25 g, 90% yield). Two recrystallizations of the chromatographed material from an ether/cyclohexane solvent pair afforded an enantiomerically pure product, mp. 76-77°. $[\alpha]_D^{25}$ +110 (*c*-1, EtOH). IR (KBr): 3297, 2862, 1741, 1638, 1559, 1377, 1166 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 5.64 (1H, br. d, J = 6.70 Hz, D_2O exch., NH); 4.01 (1H, dt, J_d = 9.88 Hz, J_t = 8.09 Hz, 3-H); 3.63 (3H, s, CO_2CH_3); 2.36 (1H, virtual dt, J_d = 10.92 Hz, J_t = 7.75 Hz, 1-H); 2.33 (1H, dd, J = 15.15 Hz, J = 7.72 Hz, 1-CHH); 2.23 (1H, dd, J = 15.15 Hz, J = 7.82 Hz, 1-CHH); 2.12 (1H, dt, J_d = 10.14 Hz, J_t = 7.59 Hz, *c*-4-H); 1.94 (3H, s, CH_3CO); 1.40 (1H, virtual q, J = 10.32 Hz, *t*-4-H); 1.12 (3H, s, *c*-2-CH_3), 0.87 (3H, s, *t*-2-CH_3). ^{13}C NMR ($CDCl_3$): δ 173.41 (CO_2), 170.05 (CON), 51.79 (CO_2CH_3 or C3), 50.46 (C3 or CO_2CH_3), 43.90 (C2), 35.64 (C1), 35.17 (1-CH_2), 31.59 (C4), 28.70 (*c*-2-CH_3), 23.41 (CH_3CON), 16.43 (*t*-2-CH_3). MS: *m/z* (%) = 213 (M^+, 1), 154 (8), 140 (59), 128 (77), 113 (52), 96 (38), 86 (100), 85 (83), 83 (22), 71 (68), 69 (53), 68 (22), 56 (23).

Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.56. Found: C, 62.16; H, 9.15; N, 6.69

(1*R*,*cis*)-2-(3-Acetamido-2,2-dimethylcyclobutyl)ethyl Acetate (8).- A mixture of $NaBH_4$ (5.30 g, 140 mmol) and $CaCl_2$ (7.80 g, 70 mmol) in dry THF (150 mL) was stirred for 1.5-hrs at room temperature, following which a solution of **7** (10.0 g, 46 mmol) in 80 mL of the same solvent was added and stirring was continued for a further 18 hrs. The reaction mixture was cooled to 0°, glacial AcOH (5 mL) was added and the solid precipitate which formed was filtered out and washed with EtOAc (200 mL). The filtrate and washings were combined, and the solvent was removed *in vacuo* to afford a syrup (14 g). This was dissolved in dry pyridine (100 mL), mixed with acetic anhydride (100 mL), and stirred overnight at room temperature. Then the cooled (0°) mixture was treated with water and stirred for a further 1 hr, whereupon it was extracted with EtOAc (4 x 100 mL). The combined organic extracts were successively washed with 2N HCl, saturated $NaHCO_3$ and brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the oily residue obtained (9.80 g) was purified by FC (250 g of silica gel) using (1:1) CH_2Cl_2/EtOAc as eluent. Compound **8** was isolated as a colorless oil (7.60 g, 71%). $[\alpha]_D^{25}$ +71.4 (*c* 1, EtOH). IR (film): 3288 , 3072, 1740, 1654, 1548, 1462, 1367, 1245 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.10 (1H, br. d, J = 7.83 Hz, NH); 3.91 (1H, dt, J_d = 9.52 Hz, J_t = 8.22 Hz, 3-H); 3.89 (2H, t, J = 6.70 Hz, OCH_2); 2.22 (1H, dt, J_d = 10.68 Hz, J_t = 7.55 Hz, 1-H); 1.95 (3H, s, $COCH_3$); 1.87 (3H, s, $COCH_3$); 1.56-1.69 (2H, m, 1-CH_2); 1.42-1.52 (1H, m, *c*-4-H); 1.32

(1H, virtual q, J = 10.22 Hz, *t*-4-H); 1.04 (3H, s, *c*-2-CH_3); 0.82 (3H, s, *t*-2-CH_3). ^{13}C NMR ($CDCl_3$): δ 171.32 (CO_2 or CON), 170.20 (CON or CO_2), 63.45 (AcO$\underline{C}H_2$), 50.40 (C3), 43.76 (C2), 36.48 (C1), 31.17 (C4 or 1-CH_2), 29.30 (1-CH_2 or C4), 29.04 (*c*-2-CH_3), 23.22 ($\underline{C}H_3CON$ or $\underline{C}H_3CO_2$), 21.19 ($\underline{C}H_3CO_2$ or $\underline{C}H_3CON$), 16.36 (*t*-2-CH_3). MS: *m/z* (%) 227 (M^+, 0.3), 167 (2), 154 (5), 113 (39), 86 (69), 85 (37), 83 (20), 82 (100), 81 (11), 71 (48), 69 (12), 67 (28), 56 (14).

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.22; H, 9.03; N, 5.89

(1*R*,*cis*)-2-(3-Amino-2,2-dimethylcyclobutyl)ethanol (9).- A mixture of **8** (7.50 g, 33 mmol) and 2N HCl (200 mL) was refluxed for 18 hrs, whereupon the solvent was evaporated *in vacuo* to afford a solid residue (5.90 g). This was dissolved in methanol and passed through a column of basic ion exchange resin (200 mL) of Amberlite IRA-400(OH). The methanolic column effluent was concentrated *in vacuo* to afford compound **9** as a spectroscopically pure (^1H NMR), colorless oil (4.70 g, 100%). $[\alpha]_D^{25}$ +26 (*c* 1, EtOH). IR (film): 3228, 2950, 1654, 1596, 1462, 1365, 1055 cm^{-1}. ^1H NMR($CDCl_3$): δ 3.46 (2H, t, J = 6.52 Hz, OCH_2); 2.81 (1H, dd, J = 9.65 Hz, J = 7.57 Hz, 3-H); 2.22 (1H, dt, J_d = 10.68 Hz, J_t = 7.30 Hz, 1-H); 1.99 (3H, br. s, D_2O exch., NH_2 and OH); 1.52-1.64 (2H, m, 1-CH_2); 1.35-1.45 (1H, m, *c*-4-H); 1.16 (1H, virtual q, J = 10.11 Hz, *t*-4-H); 0.97 (3H, s, *c*-2-CH_3); 0.82 (3H, s, *t*-2-CH_3). ^{13}C NMR ($CDCl_3$): δ 61.39 (CH_2OH), 54.42 (C3), 43.21 (C2), 36.17 (C1), 34.81 (1-CH_2 or C4), 33.68 (C4 or 1-CH_2), 28.79 (*c*-2-CH_3), 15.59 (*t*-2-CH_3). MS: *m/z* (%) 143 (M^+, 3), 128 (4), 125 (4), 113 (17), 86 (27), 85 (16), 83 (17), 82 (55), 81 (15), 71 (100), 70 (26), 69 (46), 67 (28), 57 (12), 56 (78), 55 (20), 53 (14).

Anal. Calcd. for $C_8H_{17}NO$: C, 67.17; H, 11.80; N, 9.80. Found: C, 67.22; H, 11.53; N, 9.98

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AN IMPROVED PROCEDURE FOR THE SYNTHESIS OF ANHYDROECGONINE METHYL ESTER

Submitted by (10/02/96)

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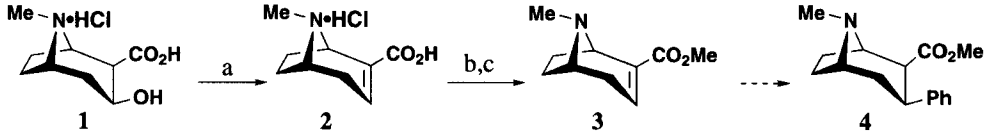
3β-phenyl-2β-carbomethoxytropane (**4**) and its analogs are widely used as probes for the cocaine receptor sites[1] and radiolabeled analogs are being evaluated as medical imaging agents.[2] (-)-Anhydroecgonine methyl ester (**3**), the key intermediate in the synthesis of compound **4**, has typically been prepared by phosphorus oxychloride dehydration of ecgonine hydrochloride (**1**) followed by methanolysis.[3] However, this method is not consistently reliable and uses phosphorus oxychloride as the solvent, posing handling and disposal problems with larger scale preparations. Analytical amounts of **3** have also been prepared *via* the synthesis and esterification of anhydroecgonine hydrochloride (**2**);[4] however, this approach has not found widespread use.



1 2 3 4

(a) 12 M HCl, 110°, 14–15 hrs; (b) acetyl chloride, MeOH, 0–65°; (c) sat. NH_4OH, 0°

As part of our ongoing studies of the structure-activity relationship between analogs of **4** and