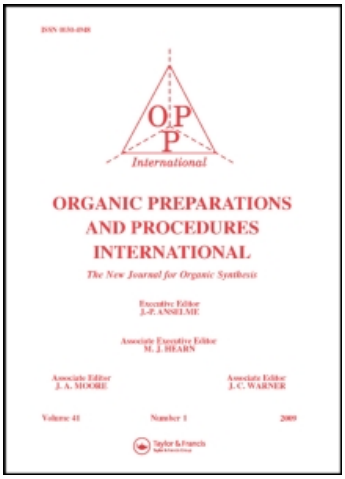

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Carmen Balo[a]; Belen Dominguez[a]; Franco Fernandez[a]; Evangelina Lens[a]; Carmen Lopez[a]
[a] Departamento de Quimica Orgdnica, Facultade de Farmacia, Santiago de Compostela, SPAIN

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OPPI BRIEFS

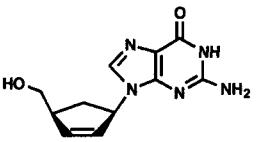
SYNTHESIS OF *cis*-[4-(AMINOMETHYL)-2-CYCLOPENTENYL]METHANOL FROM NORBORNADIENE

Submitted by (07/20/95)

Carmen Balo, Belén Domínguez, Franco Fernández, Evangelina Lens and Carmen López*

Departamento de Química Orgánica, Facultade de Farmacia
15706-Santiago de Compostela, SPAIN

In recent years there has been increasing interest in carbocyclic analogues of nucleosides (CANs) due to their frequent potent antiviral and antineoplastic activities.[1] For example, the powerful antiviral compound carbovir (**1**)[2] is active against HIV, the causative agent of AIDS. Synthesis of CANs generally involves construction of the purine or pyrimidine base about an appropriate intermediate,[3] which in the case of carbovir is amino alcohol **2**.[4] Herein we describe the synthesis of the homologue of **2**, the aminomethyl alcohol **3**, which is a synthetic precursor of potentially-active analogues of **1** (and its congeners) possessing a methylene between the guanine base and the cyclopentene ring.



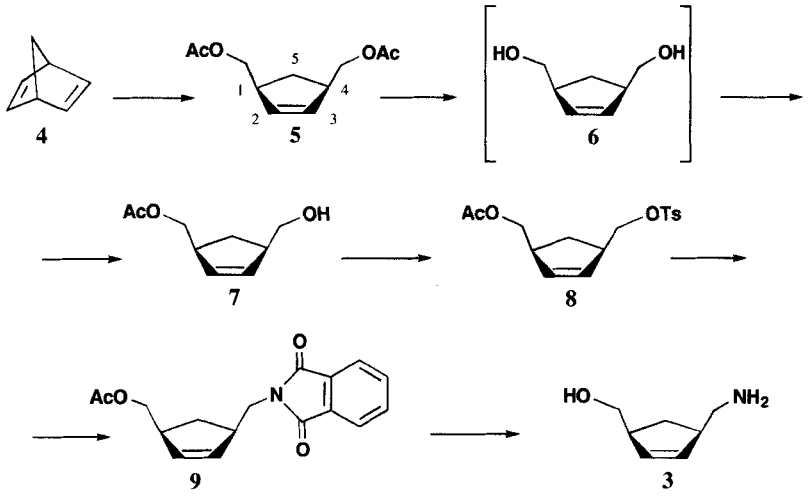
1

2

3

In order to obviate the complicated isolation of the highly water-soluble diol **6**, norbornadiene (**4**) was converted directly to diacetate **5** (54%) in a one-pot procedure involving ozonolysis of **4**, reduction of the resulting mono-ozonide with $NaBH_4$, and *in situ* acetylation of diol **6**. Saponification of diacetate **5**, however, in methanolic NaOH (1 equiv.) gave diol **6** instead of the desired monoacetate **7**, probably due to base-catalysed methanolysis of the latter. Monoacetate **7** was therefore prepared by treating the crude diol **6** (obtained by total saponification of **5**) with a stoichiometric amount of acetic anhydride under standard conditions. The monoacetate (major product) was easily separated from the minor amounts of diacetate and unreacted diol by column chromatography. Monoacetate **7** was used to prepare aminomethyl alcohol **3** by a modified Gabriel synthesis. Firstly, monoacetate **7** was converted to tosylate **8** by treatment with tosyl chloride in pyridine. Then, the required phthalimide **9** was prepared by reaction of tosylate **8** with potassium phthalimide in DMF at 150° for 9 hrs (the mild conditions previously described for bromides[5] proved ineffectual). Finally, rather than use acid hydrolysis under the drastic conditions described by Sheehan and Bolhoffer,[5] the

phthalate group of **9** was removed with hydrazine in methanol thereby avoiding the possibility of alteration of the remaining double bond. The acetate protecting group was conveniently removed in the same step. Work-up and ion-exchange chromatography afforded the desired aminomethyl alcohol **3** in 85% yield from **9**.



EXPERIMENTAL SECTION

Melting points are uncorrected and were determined on a Kofler Thermopan Reichert. IR spectra were obtained using a Perkin Elmer FTIR 1640 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were registered in $CDCl_3$, using a Bruker AMX-300 apparatus, with TMS as internal standard. EI-MS spectra were performed on a KRATOS MS-50 apparatus. Elemental analyses were determined on a Perkin Elmer 240 analyzer. Silica gel 60 Merck (70-230 mesh) was used for column chromatography. An ozone generator (Fischer-503) with an O_2 flow rate of 50 L/hr was used for O_3 oxidation.

***cis*-2-Cyclopentene-1,4-dimethanol Diacetate (5).-** Diacetate **5**, prepared by oxidation of norbornadiene (**4**) using the procedure of Tanaka *et al.*[6], was isolated in 54% yield as a colorless oil and had spectral data identical with those reported.[6] IR (film): 2950, 1739, 1385, 1365, 1245, 1036 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.73 (s, 2H, 2,3-$\underline{H}_2$); 4.03 [2H, A part of a ABM system, J_{AB} = 10.75 Hz, J_{AM} = 6.64 Hz, 1,4-(C$\underline{H}$H)$_2$]; 3.99 [2H, B part of a ABM system, J_{BA} = 10.75 Hz, J_{BM} = 6.27 Hz, 1,4-(CH$\underline{H}$)$_2$]; 3.06-3.01 (m, 2H, 1,4-$\underline{H}_2$); 2.25 (dt, 1H, J_{gem} = 13.41 Hz, J_{vic} = 8.76 Hz, 5-$\underline{H}$H,); 2.07 (s, 6H, 2*C$\underline{H}_3$); 1.27 (dt, 1H, J_{gem} = 13.41 Hz, J_{vic} = 6.54 Hz, 5-H$\underline{H}$,). ^{13}C NMR ($CDCl_3$): δ 171.6, 133.3, 68.2, 45.4, 30.4, 21.3.

***cis*-[4-(Hydroxymethyl)-2-cyclopentenyl]methyl Acetate (7).-** A solution of diacetate **5** (9.0 g, 42.5 mmol) in methanol (65 mL) was treated with 5N NaOH (17 mL) then refluxed for 4 hr. The reaction mixture was concentrated to a white solid residue, and dry pyridine (40 mL) and acetic anhydride (4 mL, 42 mmol) were added and the mixture was stirred overnight at room temperature. The solvent was evaporated to leave a brown oily residue, which was chromatographed on silica gel (200 g) using 4:1 toluene-ethyl acetate as eluant. Diacetate **5** (1.78 g, 26%) eluted first, then monoacetate **7** (3.88 g,

56%), which was isolated as a virtually spectroscopically pure (^{1}H NMR) colorless oil. Subsequently, elution with 1:1 toluene-ethyl acetate afforded a small amount of diol **6** (1.10 g, 18%), which was also isolated as a colorless oil.

Acetate **7**: IR (film): 3783, 3726, 3426, 2945, 2870, 1738, 1443, 1247, 1038 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.75 (virtual s, 2H, 2,3-$\underline{H}_2$); 4.05 (1H, A part of a ABM system, J_{AB} = 10.69 Hz, J_{AM} = 6.73 Hz, 1-C$\underline{H}$H,); 4.00 (1H, B part of a ABM system, J_{BA} = 10.69 Hz, J_{BM} = 6.43 Hz, 1-CH$\underline{H}$), 3.61-3.55 (m, 2H, 4-C$\underline{H}_2$); 3.06-3.00 (m, 1H, 1-$\underline{H}$); 2.99-2.93 (m, 1H, 4-$\underline{H}$); 2.23 (dt, 1H, J_{gem} = 13.36 Hz, J_{vic} = 8.88 Hz, 5-$\underline{H}$H,); 2.06 (s, 3H, C$\underline{H}_3$); 1.33 (dt, 1H, J_{gem} = 13.36 Hz, J_{vic} = 6.38 Hz, 5-H$\underline{H}$). ^{13}C NMR ($CDCl_3$): δ 171.7, 133.8, 133.5, 68.5, 66.8, 48.8, 45.4, 29.8, 21.4.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.78; H, 8.17

Diol **6**: IR (film): 3354, 2868, 1098, 1044 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.70 (s, 2H, 2,3-$\underline{H}_2$); 3.62 (2H, A part of a ABM system, J_{AB} = 10.55 Hz, J_{BM} = 4.74 Hz, 1,4-(C$\underline{H}$H)$_2$, 3.59(2H, B part of a ABM system, J_{BA} = 10.55 Hz, J_{BM} = 4.32 Hz, 1,4-(CH$\underline{H}$)$_2$; 3.01 (broad s, 2H, 1,4-(CH$_2$O$\underline{H}$)$_2$, D_2O exch.); 2.96-2.87 (m, 2H, 1,4-$\underline{H}_2$); 2.21 (dt, 1H, J_{gem} = 13.64 Hz, J_{vic} = 9.53 Hz, 5-$\underline{H}$H,); 1.44 (dt, 1H, J_{gem} = 13.64 Hz, J_{vic} = 5.37 Hz, 5-H$\underline{H}$). ^{13}C NMR ($CDCl_3$): δ 134.0, 66.4, 48.1, 29.0.

***cis*-[4-(Tosyloxymethyl-2-cyclopentenyl]methyl Acetate (8)**.- To a cooled (0°), stirred solution of acetate **7** (3 g, 17.6 mmol) in dry pyridine (10 mL) under argon, *p*-toluenesulfonyl chloride (4.77 g, 25 mmol) was added, and the mixture was further stirred at room temperature for 24 hr. The reaction mixture was carefully poured into 2N HCl (60 mL) and then extracted with diethyl ether (3 * 60 mL). The ethereal layers were combined, washed with 5% $NaHCO_3$ solution and then water, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude oily residue (4.2 g) was chromatographed on silica gel (110 g) with 9:1 toluene-ethyl acetate as eluant. Tosylate **8** (3.46 g, 63%) was isolated as a spectroscopically (^{1}H NMR) pure colorless oil. IR (film): 2952, 1739, 1598, 1449, 1359, 1243, 1176, 1097, 1038 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.78 (virtual d, 2H, J = 8.32 Hz, 2',6'-$\underline{H}_2$); 7.34 (d, 2H, J = 8.01 Hz, 3',5'-$\underline{H}_2$); 5.72-5.69 (m, 1H, 2-$\underline{H}$); 5.63-5.60 (m, 1H, 3-$\underline{H}$); 4.00-3.86 (m, 4H, 1,4-(C$\underline{H}_2$)$_2$); 3.06-2.96 (m, 2H, 1,4-$\underline{H}_2$); 2.45 (s, 3H, 4'-C$\underline{H}_3$); 2.20 (dt, 1H, J_{gem} = 13.57 Hz, J_{vic} = 8.81 Hz, 5-$\underline{H}$H); 2.01 (s, 3H, COC$\underline{H}_3$); 1.18 (dt, 1H, J_{gem} = 13.57 Hz, J_{vic} = 6.40 Hz, 5-H$\underline{H}$). ^{13}C NMR ($CDCl_3$): δ 171.5 (CO), 145.3 (C-1'), 134.3, 133.4 (C-4'), 132.0, 130.3, 128.3, 73.8, 67.8, 45.5, 45.3, 30.0 (C-5), 22.1, 21.3.

Anal. Calcd. for $C_{16}H_{20}O_5S$: C, 59.21; H, 6.21; S, 9.88. Found: C, 59.40; H, 5.96; S, 9.99

***cis*-[4-(Phthalimidomethyl)-2-cyclopentenyl]methyl Acetate (9)**.- Dry potassium phthalimide (1.68 g, 9 mmol) was added to a solution of acetate **8** (3 g, 9 mmol) in anhydrous DMF (20 mL) and refluxed for 9 hr. The cooled reaction mixture was lightly shaken with chloroform (12 mL) and water (45 mL), and the organic layer was separated and put aside. The aqueous layer was further extracted with chloroform (3 * 25 mL), and these extracts and the previous ones were combined, washed with 1N NaOH and then brine, and dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* afforded a paste, which was chromatographed on silica gel (50 g) with 9:1 toluene-ethyl acetate as eluant. Phthalimide **9** (1.3 g, 48%) was isolated as a white solid, which was recrystallized from

methanol, mp. 76-77°. IR (KBr): 2942, 1771, 1714, 1467, 1434, 1396, 1245, 1189, 1037 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.87-7.84 (m, 2H, 3',6'-$\underline{H}_2$); 7.73-7.70 (m, 2H, 4',5'-$\underline{H}_2$); 5.78-5.70 (m, 2H, 2,3-$\underline{H}_2$); 4.05 (1H, A part of a ABM system, J_{AB} = 10.80 Hz, J_{AM} = 6.27 Hz, 1-C$\underline{H}$H,); 3.98 (1H, B part of a ABM system, J_{BA} = 10.80 Hz, J_{BM} = 6.27 Hz, 1-CH$\underline{H}$); 3.72-3.70 (m, 2H, 4-C$\underline{H}_2$); 3.19-3.16 (m, 1H, 1-$\underline{H}$); 3.02-2.99 (m, 1H, 4-$\underline{H}$); 2.22 (dt, 1H, J_{gem} = 13.27 Hz, J_{vic} = 8.59 Hz, 5-$\underline{H}$H); 2.05 (s, 3H, COC$\underline{H}_3$); 1.34 (dt, 1H, J_{gem} = 13.27 Hz, J_{vic} = 7.02 Hz, 5-H$\underline{H}$). ^{13}C NMR ($CDCl_3$): δ 171.2 (CO), 168.6 (1',2'-$(CO)_2$), 134.0 (C-4'+C-5'), 133.6, 132.8, 132.0 (C-1'+C-2'), 123.3 (C-3'+C-6'), 67.6, 45.4, 45.0, 42.6, 31.0 (C-5), 20.9 (CH_3).

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.08; H, 5.82; N, 4.90

***cis*-[4-(Aminomethyl)-2-cyclopentenyl]methanol (3)**.- Hydrazine hydrate (98%; 1.2 mL, 34 mmol) was added to a solution of **9** (1 g, 3.34 mmol) in methanol (24 mL) and refluxed for 2 hr. The solvent was evaporated to leave a gum (0.94 g), which was broken up in 6N HCl (36 mL). The resulting suspension was filtered through Celite, and the filtrate was evaporated to dryness, redissolved in methanol and passed through a column of Amberlite IRA-420 (OH) ion-exchange resin (12 mL, equivalent to 16 meq. OH). Evaporation of the solvent afforded aminomethyl alcohol **3** (0.35 g, 85%) as a colorless oil. IR (film): 3285, 2921, 1734, 1649, 1557, 1334, 1042 cm^{-1}. ^1H NMR: δ 5.72 (dt, 1H, J_{cis} = 5.69 Hz, J = 1.95 Hz, 2-$\underline{H}$); 5.63 (dt, 1H, J_{cis} = 5.69, J = 1.96 Hz, 3-$\underline{H}$); 3.70 (1H, A part of a ABM system, J_{AB} = 10.68 Hz, J_{AM} = 4.10 Hz, 1-C$\underline{H}$H,); 3.68 (1H, B part of a ABM system, J_{BA} = 10.68 Hz, J_{BM} = 4.10 Hz, 1-CH$\underline{H}$); 2.91-2.77 (m, 3H, 1-$\underline{H}$ + 4-C$\underline{H}_2$); 3.08 (br s, 3H, O$\underline{H}$ + N$\underline{H}_2$, D_2O exch.); 2.71-2.66 (m, 1H, 4-$\underline{H}$); 2.22 (dt, 1H, J_{gem} = 13.60 Hz, J_{vic} = 9.37 Hz, 5-C$\underline{H}$H); 1.38 (dt, 1H, J_{gem} = 13.60 Hz, J_{vic} = 5.14 Hz, 5-CH$\underline{H}$,). ^{13}C NMR: δ 134.6, 133.8, 66.4, 48.6, 47.7, 46.3, 30.2. MS: *m/z* (%) 127 (M^+, 0.92), 79 (100), 77 (53), 67 (52), 66 (58), 65 (45).

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.85; H, 10.18; N, 10.92

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