Synthesis and Oxidative Cleavage of 1- and 2-Alkyl Derivatives of (*exo*,*exo*)-5,6-Dihydroxy-4,5,6,7-tetrahydro-4,7-methanoindazoles

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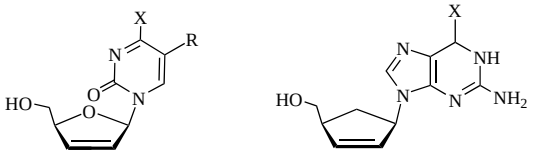
Abstract: Reaction of hydrazine with *exo*,*exo*-3-hydroxymethylene-5,6-isopropylidenedioxybicyclo[2.2.1]heptan-2-one led to norbornenepyrazole **7**, which was converted to its 1- and 2-alkyl derivatives. Deprotection of the vicinal hydroxyls, oxidative cleavage of the resulting glycol and reduction of the dialdehyde so obtained afforded 1- and 2-alkylcyclopenta[*c*]pyrazole-4,6-dimethanols, which are of interest as intermediates in the preparation of nucleoside analogues derived from 1*H*- and 2*H*-cyclopenta[*c*]pyrazole.

Key words: indazoles, pyrazoles, heterocycles, alkylations, cleavage, nucleosides

Among the many modifications that have been made to nucleosides with a view to increasing their therapeutic power and scope, one of the most successful has been the introduction of a double bond between positions 2′ and 3′ of the sugar ring, which gives 2′,3′-didehydro-2′,3′-dideoxyribonucleosides (d4Ns). It has been known since the original work of Balzarini et al.[1] that the d4Ns derived from cytosine (d4C) **1** and thymidine (d4T) **2** (Figure 1), both possess anti-HIV activity, and the latter is now marketed for clinical use under the name (Stavudine®).[2] It has been hypothesized that its antiviral activity is in great part due to the conformational restrictions imposed by the double bond in the pseudosugar moiety[3] and to its lipophilicity facilitating access to the central nervous system, which is a major HIV reservoir.[4] The carbocyclic nucleoside analogues carbovir (**3**) and abacavir (**4**), which have double bonds in the same position as d4Ns, also possess great anti-HIV activity.[5,6]



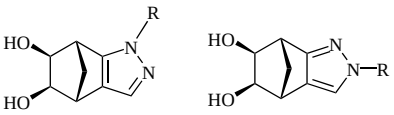
1: X = NH_2, R = H
2: X = OH, R = CH_3

3: X = OH
4: X = NH

Figure 1

We ourselves recently prepared analogous carbocyclic compounds,[7,8] in which a purine or pyrimidine base is linked to an indan system. Some of these show considerable cytostatic activity against human T lymphocytes (Molt4/C8 and CEM/0). We are currently[9] interested in replacing the benzene ring of these compounds with a variety of heterocyclic systems with a view to modifying both lipophilicity and the polar interactions of the pseudosugar moiety while retaining structural rigidity.

Here we report the synthesis of 1- and 2-alkyl derivatives of *exo*,*exo*-5,6-dihydroxy-4,5,6,7-tetrahydro-4,7-methanoindazole (**5** and **6**, respectively) (Figure 2), and of 1- and 2-alkylcyclopenta[*c*]pyrazole-4,6-dimethanols obtained these by oxidative cleavage of the glycol and reduction of the resulting dialdehyde. It is envisaged that the dimethanols will be easily convertible into carbocyclic analogues of nucleosides by well-known synthetic procedures.[10]



5a (R = Et)
5b (R = Me)

6a (R = Et)
6b (R = Me)

Figure 2

Compounds **5** and **6** were prepared by constructing the pyrazole ring on the bicyclic hydroxymethylene ketone **7**[11] (Scheme 1). In a first attempt, compound **7** was treated for 45 minutes with hydrazine dihydrochloride in refluxing anhydrous ethanol, and after removal of the solvent the product of this reaction was taken into methanol and passed through a basic ion exchange resin [Amberlite IRA-400 (OH)], affording *exo*,*exo*-5,6-dihydroxy-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (**8**). In order to prevent deprotection of the hydroxyl groups, the reaction was then carried out using hydrazine hydrate, after which the solvent was removed and the resulting residue was refluxed in toluene for 12 hours, giving compound **9**. In both cases the major product was the 2*H* tautomer (vide infra), which was attributed, following Elguero et al.[12] (who worked with the simpler compound, 1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole), to the strained ring favouring the Mills–Nixon tautomer (the one with the ring-fusing

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bond of lesser order). In our case the plausibility of this argument is increased by the methylene bridge making the rings of **8** and **9** more strained than in 1,4,5,6-tetrahydrocyclopenta[*c*]pyrazole, as in the camphor derivative 7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methanoindazole.[13] However, the predominance of the 2*H* tautomers is also in keeping with the well-known fact that for a 3,4-dialkyl-substituted pyrazole the most abundant tautomer is the less acidic (Gustafsson's paradox).[14]

Treatment of **9** with triethyloxonium tetrafluoroborate afforded, according to ^{1}H NMR spectroscopy, an approximately 9:1 mixture of the 1- and 2-ethyl derivatives **10** and **11**, which were converted almost quantitatively into the desired products **5a** and **6a**, respectively, by hydrolysis of their isopropylidene protecting groups.

To obtain the corresponding methyl derivatives **5b** and **6b**, we first attempted a convergent approach, reacting ketone **7** with *N*-methylhydrazine; but the only product of the reaction after 15 minutes in toluene was the alcohol **12**, the structure of which was confirmed by X-ray crystallographic analysis of a single crystal (Figure 3),[15] while reaction in ethanol gave only a 24% yield of **5b**.

We therefore proceeded as for the ethyl derivatives, obtaining the intermediates **13** and **14** by methylation of **9**. An attempt at methylation with diazomethane completely failed; only unreacted **9** could be isolated. Methylation with trimethyloxonium tetrafluoroborate afforded the 1-methyl derivative **13** in only 51% yield, whereas reaction

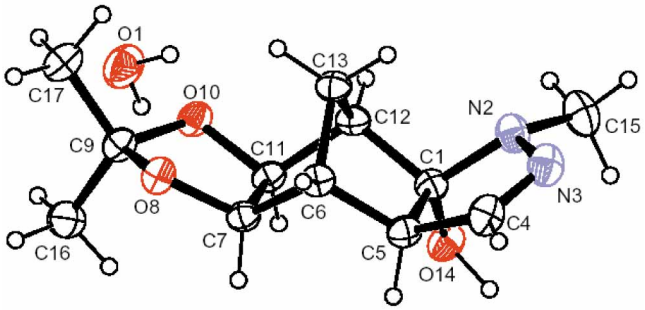
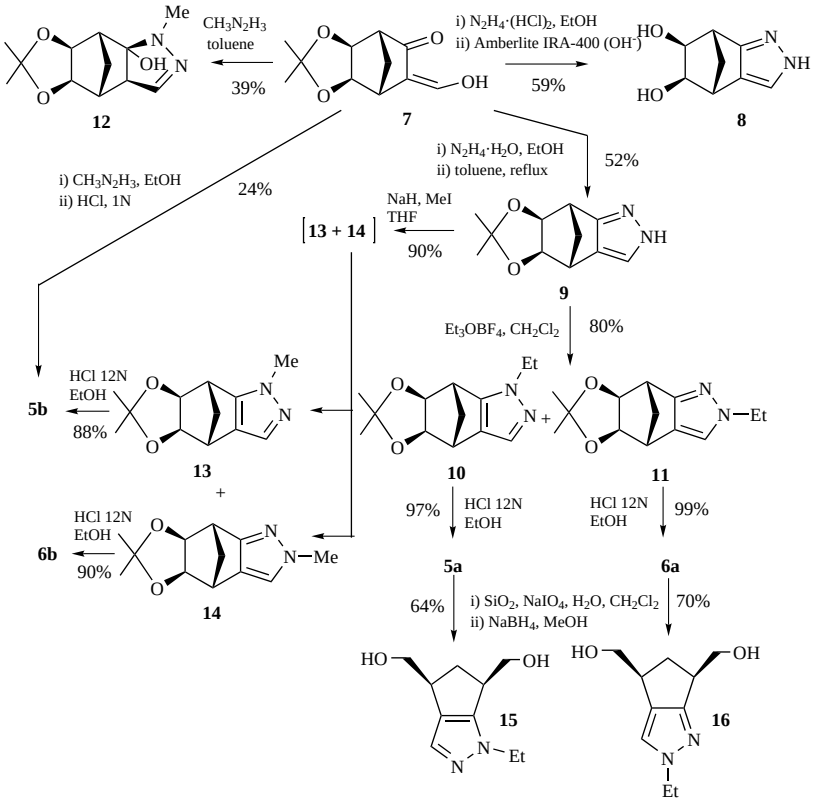


Figure 3

of **9** with methyl iodide in the presence of sodium hydride gave a mixture (1:2, ^{1}H NMR) of **13** and **14** in 90%. This mixture was cleanly separated in 79% yield by MPLC. Hydrolysis of **13** and **14** then afforded the desired products **5b** and **6b**, respectively, in high yield (88–90%).

The assignment of the hydrogens of **8** and **9**, and of the alkyls of **6a**, **6b**, **11** and **14**, to position 2, and of the alkyls of **5a**, **5b**, **10** and **13** to position 1, was based on the chemical shifts of C3 and C7a (Table 1).[13,16] The C3 signals in the spectra of **8** (δ =121.10), **9** (δ = 121.71) and **6a**, **6b**, **11** and **14** (δ = 122.17–123.60) were all very close and lay about 9 ppm upfield from those of **5a**, **5b**, **10** and **13** (δ = 131.00–132.46), while the C-7a signals of **8**, **9**, **6a**, **6b**, **11** and **14** lay in the interval δ = 161.08–162.27, about 10 ppm downfield from those of **5a**, **5b**, **10** and **13** (δ = 150.66–151.90).



Scheme 1

Table 1 ^{13}C NMR Chemical Shift (δ) Data of Bicyclopyrazoles **5**, **6**, **8**–**11**, **13** and **14**.

	C7a	C3a	C3	C4,C7	C5,C6	C8	NCH_3	NCH_2CH_3	NCH_2CH_3	$C(CH_3)_3$	$C(CH_3)_3$
5a	150.73	127.32	131.68	45.79, 45.12	72.06, 71.09	46.31, 46.08		46.08, 46.31	16.09		
5b	151.50	126.85	131.00	45.09, 44.89	71.44, 69.99	46.09	37.24				
10	150.66	127.55	132.25	43.15, 42.39	83.54, 81.82	46.81, 46.16		46.16, 46.81	16.01	114.55	26.42, 24.76
13	151.90	127.50	132.46	42.81, 42.75	83.44, 81.69	46.96	37.70			114.56	26.41, 24.73
8	162.15	126.71	121.10	45.08, 44.06	72.18, 71.15	45.20					
6a	161.78	125.31	122.17	46.22, 44.82	72.93, 71.27	47.00, 45.20		45.20, 47.00	16.17		
6b	161.08	124.75	123.47		72.09, 71.08	44.78	38.38	45.24, 44.26			
9	162.27	124.62	121.71	42.87, 41.71	83.29, 82.24	45.91				113.63	26.31, 24.68
11	161.64	124.62	122.09	43.09, 42.00	83.41, 82.42	47.04, 45.66		45.66, 47.04	16.18	113.56	26.33, 24.70
14	161.94	125.09	123.60	43.02, 41.96	83.39, 82.40	45.64	38.84			113.58	26.31, 24.66

Finally, oxidative cleavage of **5a** and **6a**, followed by reduction of the resulting dialdehydes, afforded the corresponding cyclopenta[*c*]pyrazole-4,6-dimethanol derivatives **15** and **16** in satisfactory yields (64 and 70%, respectively). Oxidative cleavage of **5a** and **6a** was performed using sodium periodate on silica gel,[17] subsequently followed by reduction of the the dialdehyde intermediate with $NaBH_4$ in MeOH; no attempt was made at isolation, because in the ^1H NMR spectrum of the crude oxidation products, the existence of two aldehyde groups was clearly shown by the presence of two distinct singlets in the δ = 9.65–9.70 region. Unequivocal determination of the structure of **15** by X-ray crystallography (Figure 4)[15] corroborated the position of the ethyl group of **5a** and showed that no epimerization had occurred during the tandem oxidation–reduction process (which was presumably also the case for **16**).

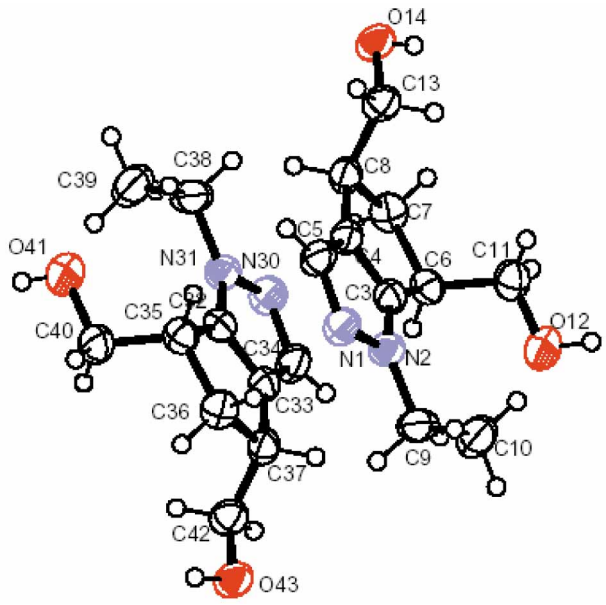


Figure 4

All chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. and used without further purification. Mps were measured in a Reichert Kofler Thermopan and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1640 FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in a Bruker AMX 300 spectrometer at 300 and 75.47 MHz, respectively, using TMS as internal standard (chemical shifts in δ values, *J* in Hz). Mass spectra were recorded on a Kratos MS-59 spectrometer. Microanalyses were performed in a Perkin–Elmer 240B Elemental Analyser at the University of Santiago Microanalysis Service. Analyses indicated by the symbols of elements were within ± 0.4% of the theoretical values. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TCL on pre-coated silica gel plates (Merck 60 F_{254}, 0.25 mm). MPLC separations were carried out using a Biotage Flash 4Di system with a Biotage column (Si-40B, silica gel). X-ray diffraction data were collected in an Enraf–Nonius CAD4 automatic diffractometer using the program CAD4-EXPRESS.

(±)-(*exo*,*exo*)-5,6-Dihydroxy-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (8)

Hydrazine dihydrochloride (0.15 g, 1.44 mmol) was added under argon to a solution of freshly prepared **7** (0.30 g, 1.44 mmol) in an-

hyd EtOH (10 mL) at 5–10 ºC, and the mixture was refluxed for 45 min and then concentrated to dryness. The residue was taken into MeOH (5 mL) and loaded on a column packed with Amberlite IRA-400 (OH^-) (14 mL), which was then eluted with MeOH (100 mL). The alkaline eluate was concentrated to dryness and the resulting solid residue (0.30 g) was washed with cold EtOH (15 mL) leaving **8**.

Yield: 0.14 g (59%); white solid (that was recrystallized from EtOH); mp 246–250 ºC.

IR (KBr): 3493, 3250, 2990, 2933, 2859, 2717, 1150, 1071, 1048, 962 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.81 (d, 1 H, *J* = 8.99 Hz, H*H*-8), 2.23 (d, 1 H, *J* = 8.99 Hz, *H*H-8), 2.95 (d, 2 H, *J* = 4.08 Hz, H-7, H-4), 3.46 (virtual s, 2 H, H-5, H-6), 4.94 (d, 1 H, D_2O exch., *J* = 4.30 Hz, OH), 4.99 (d, 1 H, D_2O exch., *J* = 4.30 Hz, OH), 7.24 (s, 1 H, H-3), 11.94 (br s, 1 H, D_2O exch., NH).

EIMS: *m*/*z* (%) = 166 (M, 6), 137 (21), 121 (14), 119 (15), 109 (11), 107 (22), 106 (100), 105 (35), 92 (12), 80 (17), 79 (30), 65 (12), 54 (12), 53 (12), 52 (26), 51 (13).

Anal. Calcd for $C_8H_{10}N_2O_2$ (166.17): C, 57.82; H, 6.07; N, 16.86. Found: C, 58.02; H, 5.99; N, 17.02.

(±)-(*exo,exo*)-5,6-(Isopropylidenedioxy)-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (9)

Hydrazine hydrate (0.61 mL, 19.72 mmol) was added under argon to a well-stirred solution of freshly prepared **7** (2.06 g, 9.86 mmol) in anhyd EtOH (50 mL), and the mixture was refluxed for 5 h and then concentrated to dryness. The residue was taken into toluene (50 mL), this solution was refluxed for a further 12 h and concentrated to dryness, and purification of the resulting residue (2.68 g) on a column (silica gel; hexane–EtOAc, 1:1), followed by concentration to dryness afforded **9**.

Yield: 1.06 g (52%); white solid (that was washed with pentane); mp 147–149 ºC.

IR (KBr): 3250, 2984, 2934, 1462, 1446, 1379, 1263, 1212, 1160, 1068, 1052, 1026, 866, 577 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.31 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 2.13 (ddd, 1 H, *J* = 9.55, 6.81, 2.75 Hz, H*H*-8), 2.49 (ddd, 1 H, *J* = 9.48, 6.78, 2.60 Hz, *H*H-8), 3.26 (virtual s, 1 H, H-4), 3.33 (virtual s, 1 H, H-7), 4.21 (d, 2 H, *J* = 5.21 Hz, H-6 or H-5), 4.28 (d, 1 H, *J* = 5.21 Hz, H-5 or H-6), 7.15 (s, 1 H H-3), 12.01 (br s, 1 H, D_2O exch., NH).

EIMS: *m*/*z* (%) = 207 (M + 1, 1.5), 206 (M, 9), 177 (9), 120 (12), 119 (100), 106 (14), 93 (7), 92 (16), 65 (8).

Anal. Calcd for $C_{11}H_{14}N_2O_2$ (206.24): C, 64.06; H, 6.84; N, 13.58. Found: C, 64.28; H, 6.99; N, 13.67.

(±)-(*exo,exo*)-1-Ethyl-5,6-isopropylidenedioxy-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (10) and (±)-(*exo,exo*)-2-Ethyl-5,6-isopropylidenedioxy-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (11)

A solution of **9** (1.50 g, 6.0 mmol) and $Et_3O{\cdot}BF_4$ (3.70 g, 19.47 mmol) in anhyd CH_2Cl_2 (45 mL) was stirred under argon at r.t. for 21 h, sat. aq $NaHCO_3$ (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was dried (Na_2SO_4) and concentrated to dryness, and the resulting yellowish oil (1.69 g) was chromatographed (silica gel; hexane–EtOAc, 2:1). Removal of the solvents from the early and late product-containing fractions afforded **11** (54 mg) and **10** (0.71 g), respectively, as colourless oils that were crystallized when stored in the refrigerator, while the intermediate fractions gave a mixture of **10** and **11** (0.60 g) that was partially resolved by MPLC (hexane–EtOAc, 2:1) [the early MPLC fractions contained a mixture of **10** and **11** (0.21 g), and the later fractions pure **10** (0.36 g)]; overall yield (**10** + **11**), 80%.

Compound 10

Mp 64–65 ºC.

IR (KBr): 2984, 1534, 1436, 1387, 1369, 1261, 1205, 1167, 1058, 1024, 1012, 986, 964, 907, 870, 787 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.31 (s, 3 H, CH_3), 1.45 (t, 3 H, *J* = 7.34 Hz, CH_2CH_3), 1.51 (s, 3 H, CH_3), 2.22 (dd, 1 H, *J* = 9.34, 1.43 Hz, H*H*-8), 2.49 (dd, 1 H, *J* = 9.33, 1.51 Hz, *H*H-8), 3.20 (virtual s, 1 H, H-7 or H-4), 3.29 (virtual s, 1 H, H-4 or H-7), 4.10 (q, 2 H, *J* = 7.33 Hz, CH_3CH_2), 4.16 (d, H, *J* = 5.24 Hz, H-6 or H-5), 4.22 (d, 1 H, *J* = 5.24 Hz, H-5 or H-6), 7.14 (s, 1 H, H-3).

EIMS: *m*/*z* (%) = 234 (M, 1), 147 (5), 134 (2), 119 (2), 92 (1), 58 (100).

Anal. Calcd for $C_{13}H_{18}N_2O_2$ (234.29): C, 66.64; H, 7.74; N, 11.96. Found: C, 66.86; H, 7.85; N, 12.07.

Compound 11

Mp 75–76 ºC.

IR (KBr): 2988, 2939, 1570, 1457, 1380, 1332, 1262, 1207, 1177, 1666, 1056, 1026, 981, 961, 867, 796, 775 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.30 (s, 3 H, CH_3), 1.42 (t, 3 H, *J* = 7.26 Hz, CH_2CH_3), 1.51 (s, 3 H, CH_3), 2.10 (dd, 1 H, *J* = 9.40, 1.29 Hz, H*H*-8), 2.45 (dd, 1 H, *J* = 9.40, 1.23 Hz, *H*H-8), 3.11 (virtual s, 1 H, H-7 or H-4), 3.28 (virtual s, 1 H, H-4 or H-7), 4.06 (dq, 2 H, *J* = 7.30, 5.72 Hz, CH_3CH_2), 4.19 (d, H, *J* = 5.24 Hz, H-6 or H-5), 4.27 (d, 1 H, *J* = 5.24 Hz, H-5 or H-6), 6.97 (s, 1 H, H-3).

EIMS: *m*/*z* (%) = 235 (M + 1, 1), 234 (M, 7), 205 (M – Et, 2), 148 (7), 147 (53), 134 (12), 119 (20), 92 (9), 65 (6), 59 (6), 58 (100).

Anal. Calcd for $C_{13}H_{18}N_2O_2$ (234.29): C, 66.64; H, 7.74; N, 11.96. Found: C, 66.81; H, 7.92; N, 11.89.

(±)-(3a*R,4*R**,5*R**,6*S**,7*R**,7a*R**)-7a-Hydroxy-5,6-isopropylidenedioxy-1-methyl-3a,4,5,6,7,7a-hexahydro-4,7-methano-1*H*-indazole (12)**

N-Methylhydrazine (0.20 g, 4.30 mmol) was added under argon to a well-stirred solution of freshly prepared **7** (0.48 g, 2.30 mmol) in anhyd toluene (25 mL) in an ice bath, and the mixture was stirred for 15 min at r.t., after which removal of the solvent under reduced pressure left a brownish oily residue (0.70 g) that upon purification by chromatography (silica gel; hexane–EtOAc, 15:1) afforded **12**.

Yield: 0.21 g (39%); lightly coloured solid that was crystallized from EtOAc–pentane; mp 144–145 ºC.

IR (KBr): 3512, 3187, 2996, 2954, 1646, 1571, 1466, 1447, 1380, 1338, 1303, 1268, 1238, 1220, 1208, 1182, 1161, 1021, 1071, 1043, 969, 812 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.20 (d, 1 H, *J* = 11.11 Hz, H*H*-8), 1.45 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.66 (dd 1 H, *J* = 11.12, 1.56 Hz, *H*H-8), 2.13 (virtual s, 1 H), 2.33 (virtual s, 1 H), 2.46 (virtual s, 1 H), 2.51 (virtual s, 1 H), 2.93 (s, 3 H, CH_3), 4.28 (d, 1 H, *J* = 5.37 Hz, H-6), 4.67 (d, 1 H, *J* = 5.37 Hz, H-5), 6.64 (s, 1 H, H-3).

EIMS: *m*/*z* (%) = 239 (M + 1, 11), 238 (M, 72), 223 (63), 220 (9), 164 (9), 163 (81), 162 (12), 133 (25), 124 (8), 111 (15), 99 (100), 98 (37), 97 (12), 83 (12), 82 (20), 81 (8), 66 (7), 58 (19).

Anal. Calcd for $C_{12}H_{18}N_2O_3$ (238.28): C, 60.49; H, 7.61; N, 11.76. Found: C, 60.65; H, 7.83; N, 11.91.

Single crystals suitable for X-ray diffractometry were obtained by dissolving crystals of **12** in the least possible quantity of cold Et_2O in an open vial that was then placed in a larger container with a little pentane in its bottom; the container was closed, and after a few days in a cool, dark place free from vibrations afforded the desired single crystals.

(±)-(*exo,exo*)-5,6-Isopropylidenedioxy-1-methyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (13) and (±)-(*exo,exo*)-5,6-Isopropylidenedioxy-2-methyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (14)

Method A

A suspension of NaH (60%, 38 mg, 1.6 mmol) and **9** (0.20 g, 0.97 mmol) in anhyd THF (5 mL) was stirred for 20 min at r.t., methyl iodide (514 mg, 3.6 mmol) was added, stirring was continued for a further 30 min, H_2O (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The pooled organic phases were washed with H_2O (50 mL), dried (Na_2SO_4) and concentrated to dryness, and the resulting residue (250 mg) was resolved by MPLC (hexane–EtOAc, 3:2). The first and last fractions afforded **14** (100 mg, 47%) and **13** (50 mg, 24%), respectively, as dense colourless oils, and the intermediate fractions a mixture of compound **13** and **14** (40 mg, 19%).

Compound 13

IR (film): 2925, 2855, 1732, 1458, 1379, 1271 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 2.21 (d, 1 H, *J* = 9.35 Hz, H*H*-8), 2.49 (d, 1 H, *J* = 9.35 Hz, *H*H-8), 3.25 (virtual s, 1 H), 3.20 (virtual s, 1 H), 3.80 (s, 3 H, CH_3), 4.16–4.21 (m, 2 H, H-5 + H-6), 7.13 (s, 1 H, H-3).

EIMS: *m*/*z* (%) = 220 (M, 22), 205 (9), 134 (11), 133 (100), 131 (6), 120 (16), 119 (23), 118 (20), 106 (10), 92 (12), 85 (9), 77 (8), 66 (5), 65 (6).

HRMS: *m*/*z* calcd for $C_{12}H_{16}N_2O_2$: 220.1212; found: 220.1231.

Compound 14

IR (film): 2986, 2946, 1570, 1424, 1392, 1372, 1255, 1206, 1169, 1064, 1022, 985, 870, 811, 518 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.29 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 2.08 (dt, 1 H, *J* = 9.42, 1.44 Hz, *H*H-8), 2.43 (dt, 1 H, *J* = 9.42, 1.44 Hz, H*H*-8), 3.20 (virtual s, 1 H), 3.26 (virtual s, 1 H), 3.77 (s, 3 H, CH_3), 4.17 (d, 1 H, *J* = 5.28 Hz, H-6 or H-5), 4.25 (d, 1 H, *J* = 5.28 Hz, H-5 or H-6), 6.92 (s, 1 H, H-3).

EIMS: *m*/*z* (%) = 220 (M, 1), 167 (28), 149 (100), 133 (15), 118 (41), 104 (3), 88 (4), 85 (3), 71 (8), 58 (92), 57 (18), 52 (6).

HRMS: *m*/*z* calcd for $C_{12}H_{16}N_2O_2$: 220.1212; found: 220.1226.

Method B

A solution of $Me_3O{\cdot}BF_4$ (1.0 g, 6.76 mmol) in anhyd CH_2Cl_2 (10 mL) was added under argon to a solution of **9** (0.2 g, 0.97 mmol) in CH_2Cl_2 (10 mL) at –10° C. This mixture was stirred for 24 h, and then sat. aq $NaHCO_3$ (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the organic phase was dried (Na_2SO_4) and concentrated to dryness, affording a yellowish oil (0.21 g) that was passed through a column (silica gel; hexane–EtOAc, 1:3). Removal of the solvent from the product-containing fractions yielded **13** with spectroscopic data identical to those of the compound obtained by Method A.

Yield: 0.11 g (51%); colourless oil.

(±)-(*exo,exo*)-5,6-Dihydroxy-1-methyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (5b)

N-Methylhydrazine (0.17 g, 3.74 mmol) was added under argon in one portion to a well-stirred solution of freshly prepared **7** (0.40 g, 1.91 mmol) in anhyd EtOH (25 mL) in an ice bath, and the mixture was stirred for 15 min at r.t., treated with aq HCl (1 M; 1 mL), refluxed for 30 min, and concentrated to dryness. The residue (0.60 g) was dissolved in MeOH (15 mL) and passed through a column packed with Amberlite IRA-400 (200 mL; OH^-) using MeOH (200 mL) as eluent. Evaporation of the solvent under reduced pressure left a solid residue (0.41 g) that upon purification by chromatography (silica gel; CH_2Cl_2–MeOH, 15:1) afforded **5b** from which a small sample was taken and washed with Et_2O for analysis.

Yield: 0.08 g (24%); white solid; mp 150–151 °C.

IR (KBr): 3358, 2977, 2932, 2876, 1444, 1176, 1078, 962 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.91 (ddd, 1 H, *J* = 9.08, 2.99, 1.49 Hz, H*H*-8), 2.23 (ddd, 1 H, *J* = 8.93, 3.00, 1.50 Hz, *H*H-8), 2.91 (virtual s, 1 H, H-7), 3.14 (virtual s, 1 H, H-4), 3.39–3.44 (m, 2 H, H-5, H-6), 3.72 (s, 3 H, CH_3), 4.88 (s, 1 H, D_2O exch., OH), 5.08 (s, 1 H, D_2O, exch., OH), 7.01 (s, 1 H, H-3).

EIMS: *m*/*z* (%) = 195 (M + 1, 1), 194 (M, 10), 147 (9), 134 (100), 133 (14), 119 (41), 107 (9), 106 (67), 105 (10), 92 (12), 79 (8), 77 (9).

Anal. Calcd for $C_9H_{12}N_2O_2$ (180.20): C, 59.99; H, 6.71; N, 15.55. Found: C, 60.18; H, 6.85; N, 15.71.

Hydrolysis of the Isopropylidene Group; General Procedure

Aq HCl (12 M; 1.5 mL) was added to a stirred solution of the pyrazole derivative **10**, **11**, **13** or **14** (3 mmol) in EtOH (25 mL) in an ice–H_2O bath. This mixture was allowed to return to r.t. and was then refluxed for 2 h. The solvents were removed, and the residue was dissolved in MeOH (15 mL) and passed through a column packed with Amberlite IRA-400 (OH^-) (40 mL) using MeOH (250 mL) as eluent. Evaporation of the solvent under reduced pressure then afforded pyrazoles **5** and **6**.

(±)-(*exo,exo*)-1-Ethyl-5,6-dihydroxy-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (5a)

Yield: 97%; white solid from which a small sample was taken and washed with Et_2O for analysis; mp 112–114 °C.

IR (KBr): 3394, 2980, 2934, 1416, 1335, 1179, 1162, 1076, 1015, 960 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.44 (t, 3 H, *J* = 7.32 Hz, CH_2CH_3), 2.14 (d, 1 H, *J* = 9.54 Hz, *H*H-8), 2.37 (d, 1 H, *J* = 9.54 Hz, H*H*-8), 3.12 (virtual s, 1 H, H-7), 3.23 (virtual s, 1 H, H-4), 3.64–3.65 (m, 1 H, the residual H_2O signal overlaps this signal, addition of D_2O simplifies both this signal and at δ = 3.70–3.75, H-5 and H-6), 3.70–3.72 (m, 1 H), 3.86–3.88 (m, 2 H, D_2O exch., 2 OH), 4.13 (q, 2 H, *J* = 7.32 Hz, CH_3CH_2), 7.10 (s, 1 H, H-3).

EIMS: *m*/*z* (%) = 194 (M, 10), 165 (1), 147 (9), 134 (100), 133 (14), 120 (5), 119 (41), 118 (4), 107 (9), 106 (67), 105 (10), 93 (4), 92 (12), 80 (5), 79 (7), 77 (9), 65 (5).

Anal. Calcd for $C_{10}H_{14}N_2O_2$ (194.23): C, 61.84; H, 7.27; N, 14.42. Found: C, 61.96; H, 7.41; N, 14.33.

(±)-(*exo,exo*)-2-Ethyl-5,6-dihydroxy-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (6a)

Yield: 99%; white solid, from which a small sample was taken and washed with Et_2O for analysis; mp 115–116 °C.

IR (KBr): 3497, 3189, 3003, 2983, 2942, 1570, 1458, 1428, 1395, 1358, 1333, 1277, 1174, 1154, 1140, 1069, 1017, 995, 969, 818, 759, 748 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.41 (t, 3 H, *J* = 7.27 Hz, CH_2CH_3), 2.04 (d, 1 H, *J* = 9.54 Hz, *H*H-8), 2.40 (d, 1 H, *J* = 9.54 Hz, H*H*-8), 3.19 (d, 2 H, *J* = 1.93 Hz, H-4, H-7), 3.70 (d, 1 H, *J* = 5.25 Hz, H-5, H-6), 3.81 (dd, 1 H, *J* = 5.70, 0.94 Hz), 4.04 (q, 2 H, *J* = 7.27 Hz, CH_3CH_2), 5.00 (br s, 2 H, D_2O exch., 2 OH), 6.97 (s, 1 H, H-3).

EIMS: *m*/*z* (%) = 194 (M, 30), 165 (30), 149 (17), 135 52, 134 (70), 133 (20), 119 (100), 105 (52), 92 (28), 80 (18), 77 (16), 65 (21), 58 (62).

Anal. Calcd for $C_{10}H_{14}N_2O_2$ (194.23): C, 61.84; H, 7.27; N, 14.42. Found: C, 61.65; H, 7.19; N, 14.28.

(±)-(*exo,exo*)-5,6-Dihydroxy-1-methyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (5b)
The spectroscopic data were identical to those of the compound **5b** obtained by condensation of **7** as described previously.

Yield: 88%; white solid.

(±)-(*exo,exo*)-5,6-Dihydroxy-2-methyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole (6b)
Yield: 90%; white solid, from which a small sample was recrystallized from EtOAc for analysis; mp 160–161 ºC.

IR (KBr): 3473, 3198, 2939, 1387, 1263, 1177, 1164, 1081, 1017, 971, 803, 785, 761, 602, 502 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.78 (d, 1 H, *J* = 9.08 Hz, H*H*-8), 2.20 (d, 1 H, *J* = 9.08 Hz, *H*H-8), 2.93 (d, 2 H, *J* = 10.17 Hz, H-4, H-7), 3.46 (virtual s, 2 H, H-5, H-6), 3.67 (s, 3 H, CH_3), 4.96–4.98 (m, 2 H, D_2O, exch., 2 × OH), 7.21 (s, 1 H, H-3).

EIMS: *m*/*z* (%) = 181 (M + 1, 5), 180 (M, 36), 151 (36), 149 (12), 135 (24), 133 (18), 123 (15), 120 (100), 119 (81), 105 (33), 93 (25) 92 (13), 77 (10), 58 (17).

Anal. Calcd for $C_9H_{12}N_2O_2$ (180.20): C, 59.99; H, 6.71; N, 15.55. Found: C, 60.34; H, 6.83; N, 15.67.

(±)-*cis*-1-Ethylcyclopenta[*c*]pyrazole-4,6-dimethanol (15)
An aq solution of $NaIO_4$ (0.65 M; 6.25 mL, 4.0 mmol) was added dropwise to a vigorously stirred suspension of chromatography grade silica gel (6.25 g) in CH_2Cl_2 (50 mL). After addition of compound **5a** (0.56 g, 2.88 mmol) in CH_2Cl_2 (5 mL) to the resulting flaky solution, stirring was continued for other 15 min and then passed through a filter pad onto a small quantity of Na_2SO_4; the retained silica gel was washed with CH_2Cl_2 (10 mL) and the washings were pooled with the filtrate. Removal of the solvent left the dialdehyde as an oily reddish residue, which was dissolved in MeOH (25 mL). $NaBH_4$ (0.7 g, 15.31 mmol) was added in a single portion and stirring was continued for 10 min. After cooling with an ice bath, H_2O (10 mL) was added. The MeOH was removed under reduced pressure. The aq solution was neutralized (pH 7) with aq HCl (2 M), and concentrated to dryness. The resulting solid residue was extracted with hot EtOAc (4 × 100 mL), and removal of the solvent from the pooled extracts under reduced pressure afforded **15** (0.36 g, 64%) as a dense oil that crystallized upon treatment with Et_2O. Single crystals suitable for X-ray diffractometry were obtained by dissolving a sample of **15** in the least possible quantity of cold EtOAc in an open vial that was then placed in a larger container with a little hexane in its bottom; the container was closed, and after a few days in a cool, dark place free from vibrations afforded the desired single crystals, one of which was analysed by X-ray diffractometry.

Mp 100–101 ºC.

IR (KBr): 3418, 1639, 1552, 1205, 742 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.43 (t, 3 H, *J* = 7.22, CH_3), 2.13 (t, 1 H, *J* = 3.91 Hz, H*H*-5), 2.17 (br s, 2 H, D_2O exch., 2´OH), 2.18 (t, 1 H, *J* = 3.91 Hz, *H*H-5), 2.97 (dt, 1 H, *J* = 13.85, 9.27 Hz), 3.18 (dd, 1 H, *J* = 13.93, 9.08 Hz), 3.29 (dd, 1 H, *J* = 14.55, 9.41 Hz), 3.66 and 3.87 (AB part of ABX system, 2 H, *J* = 10.58, 5.14, 4.90 Hz), 3.75–3.81 (m, 2 H), 4.12 (dq, 2 H, *J* = 7.29, 7.04 Hz, CH_3CH_2), 7.19 (s, 1 H, H-3).

^{13}C NMR ($CDCl_3$): δ = 149.74 (C3a), 133.07 (C3), 128.13 (C6a), 66.80 and 65.41 (2 CH_2OH), 45.67 (CH_3CH_2), 39.64 (C6), 38.62 (C5), 38.45 (C4), 15.96 (CH_3).

EIMS: *m*/*z* (%) = 197 (M + 1, 1), 196 (M, 11), 166 (11), 165 (100), 147 (13), 137 (26), 119 (24), 109 (21), 92 (12), 80 (10), 65 (10), 58 (24), 52 (11).

Anal. Calcd for $C_{10}H_{16}N_2O_2$ (196.24): C, 61,20; H, 8.22; N, 14.27. Found: C, 61.39; H, 8.34; N, 14.46.

(±)-*cis*-2-Ethylcyclopenta[*c*]pyrazole-4,6-dimethanol (16)
Obtained from **6a** in the same way as **15** from **5a**. A small quantity was washed with Et_2O for analysis.

Yield: 70%; white solid; mp 59–60 ºC.

IR (KBr): 3356, 2935, 1654, 1560, 1400, 1154, 1035 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.45 (t, 3 H, *J* = 7.33 Hz, CH_3), 1.88 (dt, 1 H, *J* = 13.52, 6.02 Hz, H*H*-5), 2.19 (br s, 2 H, D_2O exch., 2´OH), 2.71 (dt, 1 H, *J* = 13.52, 8.66 Hz, *H*H-5), 3.20–3.34 (m, 2 H), 3.60 (dd, 1 H, *J* = 10.31, 6.56 Hz), 3.64–3.76 (m 2 H), 3.84 (dd, 1 H, *J* = 10.59, 5.50 Hz), 4.10 (dq, 2 H, *J* = 7.35, 7.18 Hz, CH_3CH_2), 7.12 (s, 1 H, H-3).

^{13}C NMR ($CDCl_3$): δ = 161.54 (C3a), 125.94 (C6a), 123.45 (C3), 67.18 and 66.12 (2 CH_2OH), 47.58 (CH_3CH_2), 40.60 (C6), 39.40 (C5), 36.81 (C4), 16.23 (CH_3).

EIMS: *m*/*z* (%) = 197 (M + 1, 4), 196 (M, 15), 166 (31), 165 (100), 147 (59), 137 (22), 135 (15), 134 (11), 119 (43), 109 (14), 92 (10).

HRMS: *m*/*z* calcd for $C_{10}H_{16}N_2O_2$: 196.1212; found: 196.1236.

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References

(1) Balzarini, J.; Kang, G.-J.; Dala, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G. *Mol. Pharmacol.* **1987**, *32*, 162.
(2) Lea, A. P.; Faulds, D. *Drugs* **1996**, *51*, 846.
(3) Krayevsky, A. A.; Watanabe, K. A. *Modified Nucleosides as Anti-AIDS Drugs: Current Status and Perspectives*; Bioinform: Moscow, **1993**.
(4) Thomas, S.; McDowall, J. E.; Cheah, V.; Bye, A.; Segal, M. B. *The Entry of Abacavir into the Guinea-pig Brain: Comparison with Other Reverse Transcriptase Inhibitors*; Presented at the 12th World AIDS Conference: Geneva, **1998**.
(5) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192.
(6) (a) Daluge, S. M.; Good, S. S.; Faletto, M. B.; Miller, W. H.; Wayne, H.; St. Clair, M. H.; Boone, L. R.; Tisdale, M.; Parry, N. R.; Reardon, J. E.; Dornsife, R. E.; Averett, D. R.; Krenitsky, T. A. *Antimicrob. Agents Chemother.* **1997**, *41*, 1082. (b) Faletto, M. B.; Miller, W. H.; St. Clair, E. P.; Garvey, M. H.; Daluge, S. M.; Good, S. S. *Antimicrob. Agents Chemother.* **1997**, *41*, 1099. (c) Foster, R. H.; Faulds, D. *Drugs* **1998**, 729.
(7) Fernández, F.; García-Mera, X.; Morales, M.; Rodríguez-Borges, J. E. *Synthesis* **2001**, 239.
(8) Fernández, F.; García-Mera, X.; Morales, M.; Rodríguez-Borges, J. E.; De Clercq, E. *Synthesis* **2002**, 1084.
(9) López, C.; Caamaño, O.; Hergueta, A. R.; Fernández, F.; García, M. D. *Tetrahedron Lett.* **2002**, *43*, 5311.
(10) Agrafoglio, L.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611.
(11) Saksena, A. K.; McPhail, A. T.; Onan, K. D. *Tetrahedron Lett.* **1981**, *22*, 2067.

(12) (a) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic Press: New York, **1976**, 29. (b) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic Press: New York, **1976**, 266. (c) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic Press: New York, **1976**, 412.
(13) Watson, A. A.; House, D. A.; Steel, J. P. *Polyhedron* **1989**, *8*, 1345.
(14) Martínez, A.; Jimeno, M. L.; Elguero, J. *New J. Chem.* **1994**, *18*, 269.
(15) The crystallographic data of **12** and **15** have been deposited at the Cambridge Crystallographic Data Centre as Supplementary Publications, CCDC 189028 and CCDC 189029, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.
(16) Kotsuki, H.; Wakao, M.; Hayakawa, H.; Shimanouchi, T.; Shiro, M. *J. Org. Chem.* **1996**, *61*, 8915.
(17) Dumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Le Goffic, F. *Synthesis* **1989**, 664.