Synthesis of Cyclopenta[*d*]pyridazinediol Precursors of Carbanucleosides

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Abstract: The hemiprotected diols **7** and **8**, which are prospective precursors of carbanucleosides of this family, were prepared from the mesylates of the corresponding higher homologues by elimination of the mesyloxy group using 1,8-diazabicyclo[5.4.0]undec-7-ene followed by ozonolysis and reduction of the ozonide with sodium borohydride.

Key words: cyclopenta[*d*]pyridazines, silyl ethers, diols, ozonolysis, Mitsunobu reaction

Owing to their biological and chemotherapeutic properties,[1] nucleoside mimetics constitute an important target of chemical synthesis.[2] Natural and synthetic carbocyclic nucleosides can possess significant antitumour and/or antiviral activity; in particular, carbovir (**1**)[3] and abacavir (**2**)[4] have potent anti-HIV activity (Figure 1). On the basis of these interesting biological results, a significant amount of synthetic effort has been directed toward finding more selective analogues. As part of these efforts in previous work, our research group synthesised several 1′(*N*)-homocarbanucleosides in which the double bond of the cyclopentene ring of carbovir and abacavir analogues was replaced with a fused benzene,[5] pyrazole,[6] or pyridazine[7] ring (e.g., **3**–**6**, Figure 1). The fact that a number of these 1′(*N*)-homocarbanucleosides exhibited interesting cytostatic activity against human T lymphocytes,[5a,6c] and murine leukaemia cells, as well as antiviral activity against the varicella zoster virus and cytomegalovirus,[6a] encouraged us to synthesise the lower homologues of compounds **3**–**6** in which the purine or pyrimidine rings are directly linked to the cyclopentene-like moiety, with a view to correlating activity and structure.

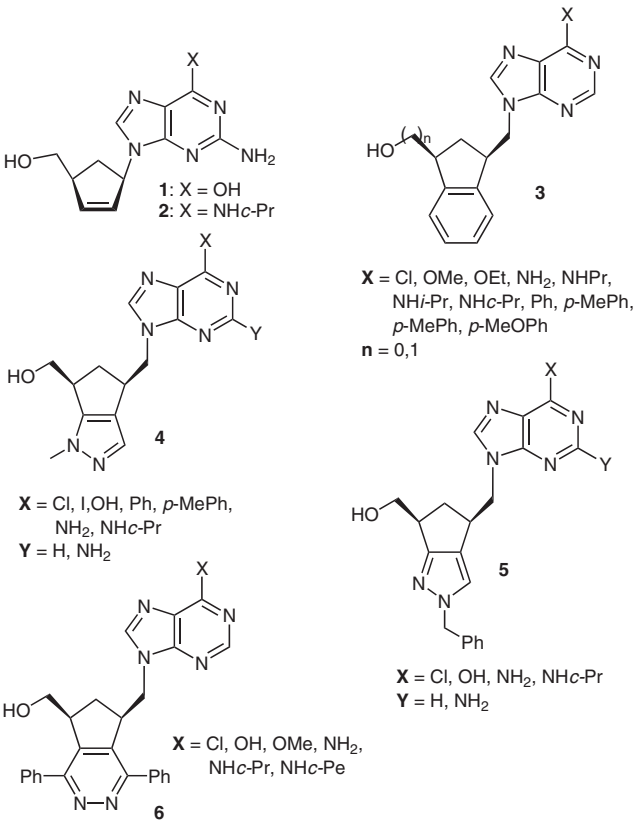

Figure 1

Here we describe the synthesis of diols **7** and **8** (Figure 2), which can be used to prepare the lower homologues of **6**[7] and their nonphenylated counterparts, respectively. It was envisaged that these diols could be converted into carbocyclic nucleosides by Mitsunobu reactions with the appropriate purine or pyrimidine derivatives.[5a,8]

Heating mesylate **9** for 24 hours at 55 °C with 6-chloropurine, sodium hydride, and 18-crown-6 in *N*,*N*-dimethylformamide afforded a significant proportion of the unsaturated alcohol together with the corresponding compound of substitution.[7] Preparation of methylidene derivative **10** was achieved in high yield from mesylate **9** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene

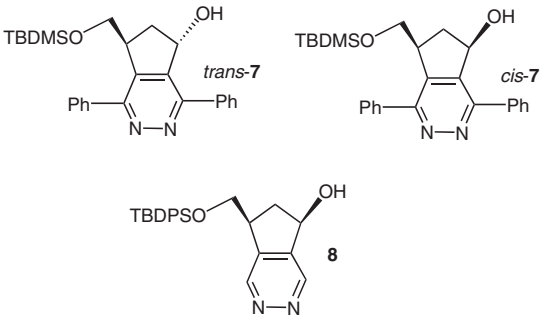

Figure 2

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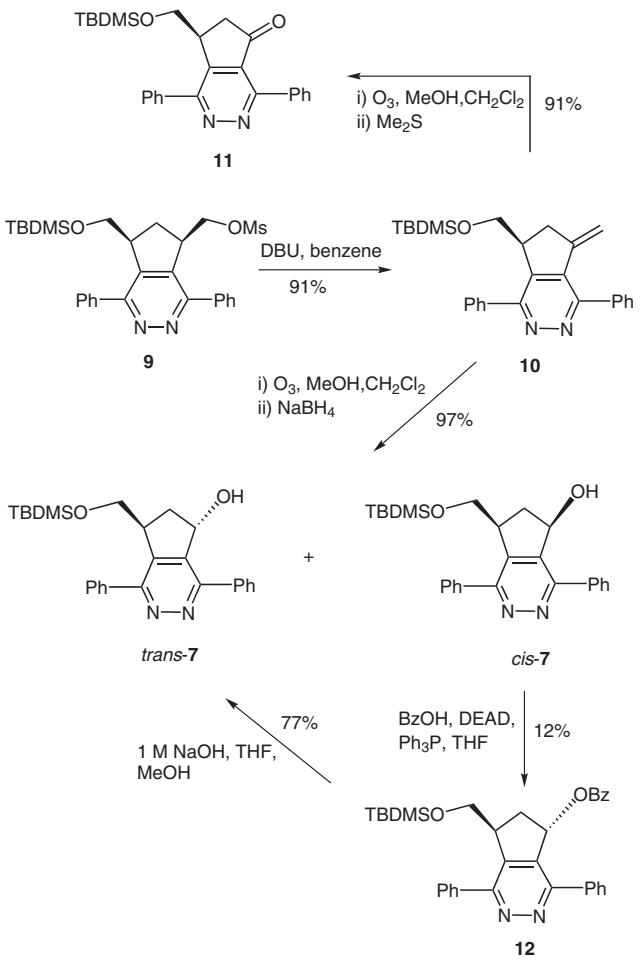
(DBU) in dry benzene[9] (Scheme 1). The exocyclic double bond of **10** then underwent ozonolysis, and the resulting ozonide was treated either with dimethyl sulfide to afford ketone **11**, or with sodium borohydride ($NaBH_4$) to directly afford a mixture of the desired alcohols *cis*- and *trans*-**7** in 97% yield from **10**.



Scheme 1

The ^{1}H NMR spectroscopic analysis of this mixture showed the *cis*/*trans* ratio to be approximately 21:1. The two isomers were efficiently separated by chromatography on silica gel with 7:1 and 3:1 mixtures of hexane–ethyl acetate as successive eluents. The product *cis*-**7** (84% from **10**) eluted in the early fractions of the 7:1 mixture, a mixture of *cis*- and *trans*-**7** (9%) was obtained in the later fractions, and *trans*-**7** (4%) was eluted using the 3:1 solvent mixture.

The *cis* configuration of the major alcohol was unequivocally determined by single-crystal X-ray crystallography; Figure 3 shows one of the enantiomers present in the racemic crystal.[10] This structural information was also used to determine the *trans* configuration of the other isomer.

The synthesis of carbanucleosides from alcohols such as **7** is conveniently performed by means of a Mitsunobu coupling[11] or by nucleophilic substitution of a suitable derivative. In both cases, the stereochemistry of the carbon

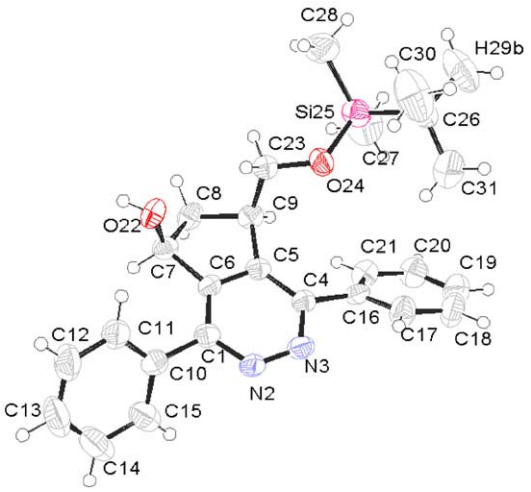
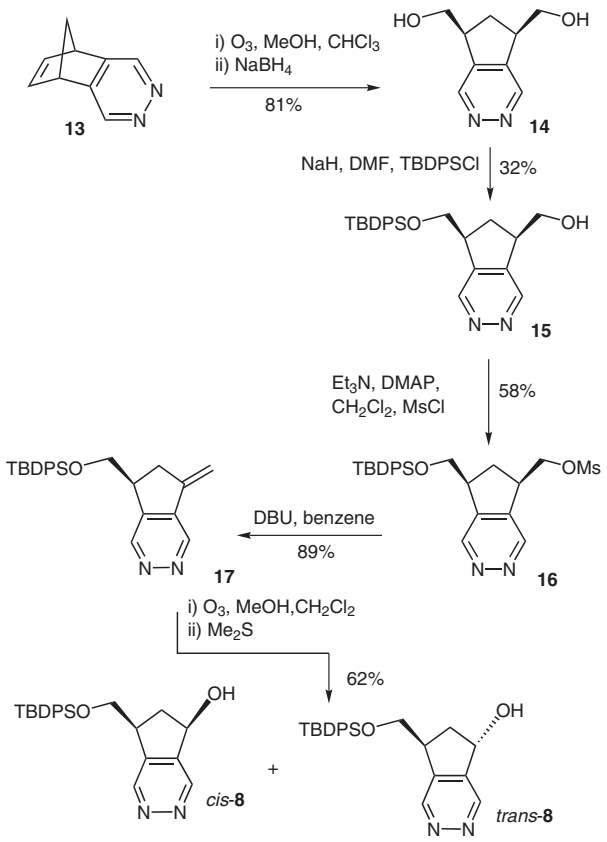


Figure 3 ORTEP projection of the molecular structure of compound *cis*-**7**, showing the atomic numbering scheme

bearing the hydroxy group is inverted. Because the substituents on the cyclopentene rings of the biologically active carbanucleosides carbovir (**1**) and abacavir (**2**) are *cis* to each other, *trans*-**7** is of greater interest than *cis*-**7**. To increase the overall yield of the former, *cis*-**7** was first transformed into the *trans*-benzoate **12** in 12% yield by reaction with benzoic acid for 15 hours under Mitsunobu conditions.[11] Longer reaction times resulted in the loss of *cis*-**7** without increasing the yield of **12**; with a 15-hour reaction, most untransformed *cis*-**7** was recovered. Benzoate **12** was then saponified with 1 M sodium hydroxide in methanol–tetrahydrofuran, affording *trans*-**7** in 77% yield.

Alcohol *cis*-**8**, the nonphenylated analogue of *cis*-**7**, was obtained in a similar manner from **17**. Methylidene-substituted compound **17** was prepared via mesylate **16** from 5,8-dihydro-5,8-methanophthalazine (**13**) (itself obtained[12] from bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarbaldehyde[13]). Compound **13** was cleanly transformed into diol **14** in one pot and in 81% yield by ozonolysis followed by reductive cleavage of the resulting ozonide with $NaBH_4$ (Scheme 2).[7] Because protection with a *tert*-butyldimethylsilyl group was less efficient for **14** than it was for the diol precursor of **9**,[7] diol **14** was reacted with *tert*-butyldiphenylsilyl chloride, giving silyl-protected **15** in 32% yield and with 50–60% recovery of substrate **14**. Mesylation, too, was less efficient for **15** than it was for the corresponding precursor of **9**.[7] However, reaction of mesylate **16** with DBU afforded an 89% yield of alkene **17**, which upon ozonolysis and subsequent reduction of the ozonide with $NaBH_4$ gave a 62% yield of *cis*- and *trans*-**8** in a 15:1 ratio. The major product was identified as *cis* from the ^{1}H NMR spectrum of the mixture, in which the CH_2 at C-6 signals (1.95 and 2.62 ppm) lay upfield and downfield, respectively, of those of the minor product (2.15 and 2.35 ppm). All these chemical shifts were very similar to those of the corresponding protons of *cis*- and *trans*-**7**.



Scheme 2

All chemicals used were of reagent grade and were obtained from Aldrich Chemical Co. and used without further purification. Melting points were measured in a Reichert Kofler Thermopan and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1640 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 spectrometer at 300 and 75 MHz, respectively, using TMS as an internal standard. Mass spectra were recorded on Hewlett-Packard HP5988A or Micromass Autospec spectrometers. Microanalyses were performed in a FISONS EA 1108 Elemental Analyser at the University of Santiago Microanalysis Service; all results shown are within ±0.4% of the theoretical values. X-ray diffraction data were collected on an Enraf-Nonius CAD4 automatic diffractometer using the program CAD4-EXPRESS. All air-sensitive reactions were carried out under argon. Flash chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TLC on precoated silica gel plates (Merck 60 F_{254}, 0.25 mm).

(±)-5-[(*tert*-Butyldimethylsiloxy)methyl]-7-methylidene-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine (10)

To a solution of compound **9** (1.3 g, 2.47 mmol) in dry benzene (25 mL) was added DBU (325 μL, 2.48 mmol) dropwise, and this mixture was stirred at r.t. for 16 h. The mixture was then heated at 50 °C for a further 2 h and concentrated to dryness under reduced pressure. The resulting residue (1.6 g) was chromatographed (silica gel, hexane–EtOAc, 5:1), and concentration of the nonvoid fractions to dryness afforded **10** as a yellowish white solid with physical and spectroscopic characteristics identical to those reported previously.[7]

Yield: 0.86 g (91%).

(±)-7-[(*tert*-Butyldimethylsiloxy)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-one (11)

A solution of **10** (0.86 g, 2.0 mmol) in CH_2Cl_2–MeOH (1:1, 142 mL) was cooled to –78 °C in a bath of acetone and liquid N_2. Then, O_3 was bubbled through the mixture until, after 25 min, blue coloration showed the presence of excess O_3, which was removed by bubbling N_2 through. The mixture was then treated with Me_2S (1 mL, 13.6 mmol) under an inert atmosphere and was left stirring until it reached r.t. The solvents were removed under reduced pressure, and the resulting green paste (1 g) was purified by chromatography (silica gel, hexane–EtOAc, 5:1 and then 3:1 mixtures as successive eluents). Concentration of the nonvoid fractions to dryness afforded **11** as a greenish oil that slowly solidified.

Yield: 0.79 g (91%).

Mp 91–93 °C.

IR (KBr): 2928, 2875, 2855, 2341, 1736, 1595, 1506, 1450, 1385, 1106, 836 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.89 (m, 2 H), 7.86–7.82 (m, 2 H), 7.58–7.52 (m, 6 H), 4.05–4.03 (m, 1 H, 7-H), 3.62 (dd, *J* = 9.7, 2.8 Hz, 1 H, OCH*H*), 3.36 (dd, *J* = 9.7, 3.8 Hz, 1 H, OC*H*H), 2.89 (dd, *J* = 18.7, 7.6 Hz, 1 H, 6-H*H*), 2.73 (dd, *J* = 18.7, 2.0 Hz, 1H, 6-*H*H), 0.60 [s, 9 H, C(CH_3)$_3$], –0.22 [s, 3 H, Si(CH_3)$_2$], –0.35 [s, 3 H, Si(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.8 (C), 160.2 (C), 155.5 (C), 152.0 (C), 135.9 (C), 134.0 (C), 132.1 (C), 130.2 (CH), 129.9 (CH), 129.0 (CH), 128.5 (CH), 128.0 (CH), 62.3 (CH_2), 40.5 (CH_2), 39.2 (CH), 25.4 [C(*C*H$_3$)$_3$], 17.8 (C), –5.8 (CH_3), –6.0 (CH_3).

MS (FAB): *m*/*z* (%) = 431.3 (100) [M + 1].

Anal. Calcd for $C_{26}H_{30}N_2O_2Si$: C, 72.52; H, 7.02; N, 6.51. Found: C, 72.65; H, 7.10; N, 6.59.

(±)-*cis*-7-[(*tert*-Butyldimethylsiloxy)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-ol (*cis*-7) and (±)-*trans*-7-[(*tert*-Butyldimethylsiloxy)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-ol (*trans*-7)

Method A: A solution of **10** (0.3 g, 0.70 mmol) in CH_2Cl_2–MeOH (1:1, 50 mL) was cooled to –78 °C in a bath of acetone and liquid N_2. Then, O_3 was bubbled through the mixture until, after 35 min, blue coloration showed the presence of excess O_3, which was removed by bubbling N_2 through. The mixture was then treated with $NaBH_4$ (0.11 g, 2.8 mmol) under an inert atmosphere and was left stirring until it reached r.t. The solvents were removed under reduced pressure, and the resulting residue (0.8 g) was purified by chromatography (silica gel, hexane–EtOAc, 7:1 and 3:1 mixtures as successive eluents). Upon concentration to dryness, the combined early nonvoid fractions eluted with the first solvent mixture afforded *cis*-**7** as a white solid, the later fractions gave a mixture of *cis*- and *trans*-**7** (0.026 g, 9%), and the fractions eluted with the second eluent produced *trans*-**7** as a white solid.

***cis*-7**

Yield: 0.25 g (84%).

Mp 178–179 °C.

IR (KBr): 3159, 2990, 2929, 1441, 1382, 1252, 1081, 843, 770, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31–8.28 (m, 2 H), 7.80–7.77 (m, 2 H), 7.58–7.47 (m, 6 H), 5.18 (dd, *J* = 11.6, 6.6 Hz, 1 H, 5-H), 4.52 (d, *J* = 11.6 Hz, 1 H, D_2O exchange, OH), 3.95 (d, *J* = 8.9 Hz, 1 H, 7-H), 3.68 (dd, *J* = 10.0, 2.3 Hz, 1 H, OCH*H*), 3.54 (dd, *J* = 10.0, 2.3 Hz, 1 H, OC*H*H), 2.66 (ddd, *J* = 14.3, 9.0, 6.8 Hz, 1 H, 6-H*H*), 2.08 (d, *J* = 14.3 Hz, 1 H, 6-*H*H), 0.67 [s, 9 H, C(CH_3)$_3$], –0.15 [s, 3 H, Si(CH_3)$_2$], –0.26 [s, 3 H, Si(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6 (C), 157.1 (C), 143.6 (C), 141.4 (C), 136.9 (C), 136.7 (C), 129.6 (CH), 129.4 (CH), 129.3 (CH), 128.8 (CH), 128.6 (CH), 72.8 (CH), 63.01 (CH_2), 44.8 (CH), 38.7 (CH_2), 25.6 [C(*C*H$_3$)$_3$], 18.2 (C), –5.8 (CH_3), –5.9 (CH_3).

MS (FAB): *m*/*z* (%) = 433.26 (100) [M + 1].

Anal. Calcd for $C_{26}H_{32}N_2O_2Si$: C, 72.18; H, 7.46; N, 6.48. Found: C, 72.55; H, 7.60; N, 6.69.

A single crystal of *cis*-**7** that was suitable for X-ray diffractometry was obtained by dissolving the chromatographically purified product in the smallest possible quantity of cold EtOAc in a vial. The vial was then surrounded by hexane in a container with a perforated lid and left in a cool, dark, vibration-free place for 15 d.

***trans*-7**

Yield: 0.013 g (4%).

Mp 157–160 °C.

IR (KBr): 3263, 3091, 3011, 2926, 2874, 2854, 1452, 1388, 1257, 1114, 1044, 992, 834, 774 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.93 (m, 2 H), 7.76–7.72 (m, 2 H), 7.56–7.48 (m, 6 H), 5.78–5.73 (m, 1 H, 5-H), 4.01–3.95 (m, 1 H, 7-H), 3.57 (dd, *J* = 9.9, 2.9 Hz, 1 H, OCH*H*), 3.31 (dd, *J* = 9.9, 4.4 Hz, 1 H, OC*H*H), 2.53 (ddd, *J* = 13.6, 7.3, 3.3 Hz, 1 H, 6-H*H*), 2.37 (d, *J* = 4.8 Hz, 1 H, D_2O exchange, OH), 2.25 (ddd, *J* = 13.6, 8.5, 5.1 Hz, 1 H, 6-*H*H), 0.68 [s, 9 H, $C(CH_3)_3$], –0.19 [s, 3 H, $Si(CH_3)_2$], –0.3 [s, 3 H, $Si(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5 (C), 157.2 (C), 144.0 (C), 142.8 (C), 137.3 (C), 136.9 (C), 129.9 (CH), 129.6 (CH), 129.4 (CH), 129.1 (CH), 129.0 (CH), 74.8 (CH), 63.9 (CH_2), 45.1 (CH), 39.0 (CH_2), 26.1 [$C(CH_3)_3$], 18.4 (C), –5.3 (CH_3), –5.4 (CH_3).

MS (EI, 70 eV): *m*/*z* (%) = 377 (8), 376 (28), 375 (100) [M – *t*-Bu], 300 (16), 299 (54), 271 (17), 241 (10), 239 (12), 228 (10), 202 (16), 180 (15), 128 (17), 127 (18), 77 (39), 75 (90), 73 (68), 59 (27), 58 (22), 57 (70), 56 (19).

Anal. Calcd for $C_{26}H_{32}N_2O_2Si$: C, 72.18; H, 7.46; N, 6.48. Found: C, 72.43; H, 7.64; N, 6.72.

Method B: 1 M NaOH (0.6 mL) was added to a solution of **12** (0.032 g, 0.06 mmol) in MeOH (0.6 mL) and THF (0.6 mL) at 0 °C, and the mixture was stirred for 4.5 h at r.t. Then, 1 M $NaHSO_4$ (1.5 mL) was added, and the mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give *trans*-**7** as a white solid. Yield: 0.02 g (77%).

(±)-*trans*-7-[(*tert*-Butyldimethylsiloxy)methyl]-1,4-diphenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl Benzoate (12)

Under an inert atmosphere, a solution of DEAD (0.17 g, 0.96 mmol) in dry THF (4 mL) was added dropwise over 20 min to a solution of *cis*-**7** (0.21 g, 0.48 mmol), Ph_3P (0.25 g, 0.96 mmol), and BzOH (0.12 g, 0.96 mmol) in THF (11 mL). This mixture was stirred for 15 h with TLC monitoring (CH_2Cl_2–MeOH, 20:1) of the reaction. The solvent was then removed under reduced pressure, and the resulting residue was dissolved in sat. $NaHCO_3$ soln (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL) and EtOAc (40 mL). The combined organic phase was dried (Na_2SO_4), and removal of the solvents under reduced pressure afforded a yellow oil (0.77 g) that was chromatographed (silica gel, hexane–EtOAc, 10:1, 8:1, 5:1, 4:1, and 3:1 mixtures as successive eluents). The fractions eluted with the 5:1 solvent mixture contained compound **12** together with other products; the following fractions contained unreacted *cis*-**7** (0.18 g). The fractions containing **12** were rerun twice using hexane–EtOAc (15:1) in the first run and hexane–EtOAc (10:1) in the second. The resulting fractions, upon removal of the solvent, gave **12** as a yellowish solid.

Yield: 0.032 g (12%).

Mp 120–122 °C.

IR (KBr): 2931, 2885, 2858, 1717, 1449, 1384, 1270, 1007, 841, 703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.70 (m, 5 H), 7.56–7.41 (m, 6 H), 7.35–7.21 (m, 4 H), 6.88 (dd, *J* = 7.0, 6.4 Hz, 1 H, 5-H), 4.03–4.00 (m, 1 H, 7-H), 3.65 and 3.41 (part AB of ABX system, *J* = 13.0, 10.0, 9.7 Hz, 2 H, OCH_2), 2.86 (ddd, *J* = 13.8, 10, 7.6 Hz, 1 H, 6-H*H*), 2.35–2.25 (m, 1 H, 6-*H*H), 0.73 [s, 9 H, $C(CH_3)_3$], –0.12 [s, 3 H, $Si(CH_3)_2$], –0.25 [s, 3 H, $Si(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0 (C), 157.9 (C), 157.1 (C), 142.9 (C), 140.4 (C), 136.8 (C), 136.2 (C), 133.0 (CH), 129.4 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 77.1 (CH), 63.6 (CH_2), 45.2 (CH), 37.2 (CH_2), 25.7 [$C(CH_3)_3$], 18.0 (C), –5.7 (CH_3), –5.8 (CH_3).

MS (FAB): *m*/*z* (%) = 537.27 (100) [M + 1].

Anal. Calcd for $C_{33}H_{36}N_2O_3Si$: C, 73.85; H, 6.76; N, 5.22. Found: C, 74.07; H, 6.97; N, 5.49.

***cis*-6,7-Dihydro-5*H*-cyclopenta[*d*]pyridazine-5,7-dimethanol (14)**

Ozone was bubbled for 10 min through a vigorously stirred solution of phthalazine **13**[11] (1.29 g, 8.99 mmol) in MeOH–$CHCl_3$ (1:1, 150 mL) at –78 °C. Then, $NaBH_4$ (1.47 g, 38.8 mmol) was added in small portions over 1 h at the same temperature and, after a further 15 min at –78 °C, the mixture was allowed to reach r.t. The solvents were removed under reduced pressure and the resulting residue was extracted with hot EtOAc (4 × 50 mL). Concentration of the combined organic phase to dryness gave **14** as a white solid.

Yield: 1.32 g (81%).

Mp 137–139 °C.

IR (KBr): 3405, 3199, 2965, 2922, 2846, 2229, 1663, 1574, 1340, 1277, 1043, 786, 682, 592 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 9.19 (s, 1 H, $H_{pyridazine}$), 9.17 (s, 1 H, $H_{pyridazine}$), 4.92–4.95 (m, 2 H, D_2O exchange, 2 OH), 3.66 (dd, *J* = 10.4, 4.8 Hz, 2 H, C*H*HOH), 3.56 (dd, *J* = 10.4, 4.8 Hz, 2 H, CH*H*OH), 3.40–3.29 (m, 2 H, 5-H, 7-H), 2.28 (dt, *J* = 13.2, 8.8 Hz, 1 H, 6-*H*H), 1.54 (dt, *J* = 13.2, 7.5 Hz, 1 H, 6-H*H*).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 149.12 (CH), 149.00 (CH), 145.58 (C), 145.56 (C), 63.42 (CH_2), 63.34 (CH_2), 45.06 (CH), 44.88 (CH), 30.06 (CH_2).

MS (EI, 70 eV): *m*/*z* (%) = 181 (8), 180 (70) [M], 150 (79), 149 (9), 133 (25), 132 (40), 131 (17), 120 (14), 119 (100), 118 (10), 104 (15), 103 (23), 92 (11), 91 (10), 89 (11), 78 (10), 77 (15).

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.33; H, 6.97; N, 15.67.

(±)-*cis*-{7-[(*tert*-Butyldiphenylsiloxy)methyl]-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl}methanol (15)

A suspension of diol **14** (0.20 g, 1.11 mmol) and 60% NaH (0.032 g, 1.33 mmol) in dry DMF (4 mL) was stirred under Ar at r.t. for 45 min, after which a solution of TBDPSCl (0.37 g, 1.33 mmol) was added. Stirring was continued for a further 4.5 h and the DMF was removed under reduced pressure. The resulting residue was fractionated on a silica gel column (hexane–acetone, 2:1 and CH_2Cl_2–MeOH, 20:1 and 10:1 mixtures as successive eluents). Compound **15** was isolated as a yellow oil from the fractions eluted with hexane–acetone, and unreacted **14** (0.11 g) was recovered from those eluted with CH_2Cl_2–MeOH.

Yield: 0.15 g, (32%).

IR (film): 3414, 2932, 1636, 1428, 1109, 702 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.23 (s, 1 H, 1-H), 9.20 (s, 1 H, 4-H), 7.63–7.58 (m, 4 H), 7.57–7.35 (m, 6 H), 3.86 (dd, *J* = 10.3, 5.7 Hz, 2 H, CH_2), 3.80–3.69 (m, 2 H, CH_2), 3.48–3.42 (m, 2 H, 5-H, 7-H), 2.37 (dt, *J* = 13.3, 8.8 Hz, 1 H, 6-*H*H), 1.95–2.03 (m, 1 H, D_2O

exchange, OH), 1.59 (dt, *J* = 13.4, 7.4 Hz, 1 H, 6-H*H*), 1.02 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.40 (CH), 149.07 (CH), 145.46 (C), 145.05 (C), 135.58 (CH), 135.50 (CH), 132.99 (C), 132.93 (C), 129.90 (CH), 129.82 (CH), 127.81 (CH), 127.77 (CH), 65.91(CH_2), 64.97 (CH_2), 45.45 (CH), 45.23 (CH), 29.78 (CH_2), 26.81 [C(*C*H_3)$_3$], 19.16 (C).

MS (ESI-TOF): *m*/*z* (%) = 419.21 (100) [M + 1].

Anal. Calcd for $C_{25}H_{30}N_2O_2Si$: C, 71.73; H, 7.22; N, 6.69. Found: C, 71.98; H, 7.38; N, 6.91.

(±)-*cis*-{7-[(*tert*-Butyldiphenylsiloxy)methyl]-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-yl}methyl Mesylate (16)

Mesyl chloride (0.29 g, 2.49 mmol) was added to a solution of **15** (0.35 g, 0.83 mmol), Et_3N (0.35 mL), and a catalytic amount of DMAP in dry CH_2Cl_2 (60 mL) stirred under Ar at –10 °C. After stirring for 1 h at r.t., the mixture was diluted with CH_2Cl_2 (60 mL) and washed successively with H_2O (2 × 40 mL), 2 M NaOH (2 × 60 mL), and brine (60 mL). The organic phase was then dried (Na_2SO_4) and concentrated under reduced pressure, leaving a residue that was column chromatographed (silica gel, hexane–EtOAc, 1:1.5). The resulting fractions gave, upon removal of the solvent, **16** as thick oil.

Yield: 0.24 g (58%).

IR (film): 2933, 1467, 1358, 1175, 1110, 956, 704 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.27 (s, 1 H, $H_{pyrazine}$), 9.24 (s, 1 H, $H_{pyrazine}$), 7.61–7.59 (m, 4 H), 7.57–7.26 (m, 6 H), 4.44 (dd, *J* = 10.0, 6.0 Hz, 1 H, O_2SOC*H*H), 4.28 (dd, *J* = 10.0, 7.3 Hz, 1 H, O_2SOCH*H*), 3.91 (dd, *J* = 10.2, 5.3 Hz, 1 H, SiOC*H*H), 3.81 (dd, *J* = 10.2, 6.7 Hz, 1 H, SiOCH*H*), 3.72–3.68 (m, 1 H, 5-H), 3.54–3.49 (m,1 H, 7-H), 2.96 (s, 3 H, CH_3), 2.49 (dt, *J* = 13.5, 8.8 Hz, 1 H, 6-*H*H), 1.69 (dt, *J* = 13.7, 7.6 Hz, 1 H, 6-H*H*), 1.03 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.36 (CH), 148.19 (CH), 146.19 (CH), 146.86 (C), 144.10 (C), 135.53 (CH), 132.61 (C), 130.08 (CH), 130.00 (CH), 127.94 (CH), 127.89 (CH), 69.56 (CH_2), 65.29 (CH_2), 45.51 (CH), 42.59 (CH), 37.58 (CH_3), 29.86 (CH_2), 26.75 [C(*C*H_3)$_3$], 19.18 (C).

MS (FAB): *m*/*z* (%) = 497.23 (100) [M + 1].

Anal. Calcd for $C_{26}H_{32}N_2O_4SSi$: C, 62.87; H, 6.49; N, 5.64. Found: C, 63.14; H, 6.61; N, 5.93.

(±)-5-[(*tert*-Butyldiphenylsiloxy)methyl]-7-methylidene-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazine (17)

Over 10 min, DBU (81 μL, 0.53 mmol) was added dropwise to a solution of compound **16** (0.24 g, 0.48 mmol) in dry benzene (10 mL), and this mixture was stirred at r.t. for 8 h. The solvent was removed under reduced pressure, and the resulting residue (0.32 g) was chromatographed (silica gel, pure CH_2Cl_2 and CH_2Cl_2–MeOH, 30:1, as successive eluents). Concentration of the nonvoid fractions to dryness afforded **17** as a white solid.

Yield: 0.17g (89%).

Mp 95–98 °C.

IR (KBr): 3067, 2930, 2856, 2099, 1581, 1466, 1427, 1383, 1260, 1108, 872, 819, 741, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.28 (s, 2 H, 1-H, 4-H), 7.59–7.56 (m, 4 H), 7.47–7.33 (m, 6 H), 5.80–5.78 (m, 1 H, =C*H*H), 5.38–5.37 (m, 1 H, =CH*H*), 3.81 (dd, *J* = 9.9, 5.5 Hz, 1 H, OC*H*H), 3.70 (dd, *J* = 9.9, 7.0 Hz, 1 H, OCH*H*), 3.55–3.47 (m, 1 H, 5-H), 2.92 (ddt, *J* = 17.2, 8.8, 2.6 Hz, 1 H, 6-*H*H), 2.62–2.55 (m, 1 H, 6-H*H*) 1.00 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.55 (CH), 145.81 (C), 145.25 (C), 144.80 (CH), 139.99 (C), 135.54 (CH), 135.50 (C), 132.96 (C), 129.92 (CH), 129.86 (C), 127.84 (CH), 110.33 (CH_2), 65.99 (CH_2), 43.99 (CH), 33.58 (CH_2), 26.75 [C(*C*H_3)$_3$], 19.17 (C).

MS (FAB): *m*/*z* (%) = 401.22 (100) [M + 1].

Anal. Calcd for $C_{25}H_{28}N_2OSi$: C, 74.96; H, 7.05; N, 6.99. Found: C, 75.24; H, 6.97; N, 7.15.

(±)-*cis*-7-[(*tert*-Butyldimethylsiloxy)methyl]-6,7-dihydro-5*H*-cyclopenta[*d*]pyridazin-5-ol (*cis*-8)

Compound *cis*-**8** was obtained from **17** (0.17 g, 0.43 mmol) as a white solid in the same way as *cis*-**7** and *trans*-**7** were obtained from **10**. Workup afforded a small quantity of pure *cis*-**8** and a larger quantity of *cis*-**8** containing a small portion of what may be the isomer *trans*-**8**; yield: 0.18 g (62%).

***cis*-8**

Mp 166–168 °C.

IR (KBr): 3187, 2929, 2881, 2857, 1583, 1466, 1387, 1331, 1110, 1092, 1072, 801, 706, 505 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.31 (s, 1 H, 1-H), 9.15 (s, 1 H, 4-H), 7.54 (t, *J* = 1.4 Hz, 2 H), 7.43–7.32 (m, 8 H), 5.23 (ddd, *J* = 10.1, 7.3, 3.0 Hz, 1 H, 5-H), 3.86–3.84 (m, 2 H, OCH_2), 3.37 (dd, *J* = 8.5, 4.0 Hz, 1 H, 7-H), 3.22 (d, *J* = 10.0 Hz, 1 H, OH), 2.62 (ddd, *J* = 14.3, 8.8, 7.3 Hz, 1 H, 6-H*H*), 1.95 (dt, *J* = 14.3, 3.5 Hz, 1 H, 6-*H*H), 0.92 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.5 (CH), 148.7 (CH), 145.5 (C), 143.9 (C),135.5 (CH), 135.4 (CH), 132.4 (C), 132.2 (C), 130.1 (CH), 129.9 (CH), 127.8 (CH), 73.5 (CH), 73.0 (CH), 65.8 (CH_2), 44.0 (CH), 38.0 (CH_2), 26.7 [C(*C*H_3)$_3$], 19.0 (C).

MS (FAB): *m*/*z* (%) = 405.18 (100) [M + 1].

Anal. Calcd for $C_{24}H_{28}N_2O_2Si$: C, 71.25; H, 6.98; N, 6.92. Found: C, 71.56; H, 7.09; N, 7.08.

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