Synthesis of Cyclopenta[d]pyridazinediol Precursors of Carbanucleosides

Isabel Pérez-Castro, a Olga Caamaño,* a Marcos D. García, a Generosa Gómez,* b Franco Fernández, a Joana Ferreira, a Carmen López a Departamento de Química Orgánica, Facultade de Farmacia, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain Fax +34(981)584912; E-mail: qoolga@usc.es

b Departamento de Química Orgánica, Facultade de Química, Lagoas-Marcosende, Universidade de Vigo, 36200 Vigo, Spain Fax +34(986)813663; E-mail: ggomez@uvigo.es

Received 20 March 2007; revised 30 April 2007

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 pyridazine7 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,c and murine leukaemia cells, as well as antiviral activity against the varicella zoster virus and cytomegalovirus,5b,e 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.

Here we describe the synthesis of diols 7 and 8 (Figure 2), which can be used to prepare the lower homologues of 67 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...
(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 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, cis-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\(^2\) from bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarbaldehyde\(^3\)). 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-butylimethylsilyl group was less efficient for 14 than it was for the diol precursor of 9,\(^7\) diol 14 was reacted with tert-butylidiphenylsilyl 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.

**Figure 3** ORTEP projection of the molecular structure of compound cis-7, showing the atomic numbering scheme.
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 reported as the average of at least three separate measurements. Elemental analyses were performed in a FISONS EA 1108 Elemental Analyser at the University of Santiago Microanalysis Service; all results are within ±0.4% of the theoretical values. X-ray diffraction data were collected on an Enraf-Nonius CAD4 automatic diffractometer using the program CAD–EXPRESS. All IR-sensitve 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 F254, 0.25 mm).

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

Method A: A solution of 10 (0.3 g, 0.70 mmol) in CH₂Cl₂–MeOH (1:1, 50 mL) was cooled to –78 °C in a bath of acetone and liquid N₂. Then, O₃ was bubbled through the mixture until, after 35 min, blue coloration showed the presence of excess O₃, which was removed by bubbling N₂ through the mixture. After bubbling, the mixture was stirred at r.t. for 16 h. The resulting residue (1.6 g) was chromatographed on a column (silica gel, 230–240 mesh) and eluted with the first solvent mixture (CH₂Cl₂–MeOH–H₂O 7:4:1, v/v). The eluted fractions were collected on an Enraf-Nonius CAD4 automatic diffractometer using the program CAD–EXPRESS. All IR-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 F254, 0.25 mm).

Yield: 0.86 g (91%).

O₃ was bubbled through the mixture until, after 25 min, blue coloration showed the presence of excess O₃, which was removed by bubbling N₂ through. The mixture was then treated with Me₂S (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.

1H NMR (300 MHz, CDCl₃): δ = 7.92–7.89 (m, 2 H), 7.86–7.82 (m, 2 H), 7.58–7.52 (m, 6 H), 6.61 (m, 1 H, 7-H), 3.62 (dd, J = 9.7, 2.8 Hz, 1 H, OCH₂), 3.36 (dd, J = 9.7, 3.8 Hz, 1 H, OCH₂), 2.89 (dd, J = 18.7, 7.6 Hz, 1 H, 6-H₂), 2.73 (dd, J = 18.7, 2.0 Hz, 1 H, 6-H₂), 0.60 [s, 9 H, C(CH₃)₃], –0.22 [s, 3 H, Si(CH₃)₂], –0.35 [s, 3 H, Si(CH₃)₂].

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

Anal. Calcd for C₂₆H₃₀N₂O₂Si: 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-5H-cyclopenta[d]pyridazin-5-ol (cis-7) and (±)-trans-7-[(tert-Butyldimethylsiloxy)methyl]-1,4-diphenyl-6,7-dihydro-5H-cyclopenta[d]pyridazin-5-ol (trans-7)

Method A: A solution of 10 (0.3 g, 0.70 mmol) in CH₂Cl₂–MeOH (1:1, 50 mL) was cooled to –78 °C in a bath of acetone and liquid N₂. Then, O₃ was bubbled through the mixture until, after 35 min, blue coloration showed the presence of excess O₃, which was removed by bubbling N₂ through. The mixture was then treated with NaBH₄ (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 chromatographed on a column (silica gel, hexane–EtOAc, 5:1 and then 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-7 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.

1H NMR (300 MHz, CDCl₃): 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, D₂O exchange, OH), 3.95 (d, J = 8.9 Hz, 1 H, 7-H), 3.68 (dd, J = 10.0, 2.3 Hz, 1 H, OCH₂), 3.54 (dd, J = 10.0, 2.3 Hz, 1 H, OCH₂), 2.66 (dd, J = 14.3, 9.0, 6.8 Hz, 1 H, 6-H₂), 2.08 (d, J = 14.3 Hz, 1 H, 6-H₂), 0.67 [s, 9 H, C(CH₃)₃], –0.15 [s, 3 H, Si(CH₃)₂], –0.26 [s, 3 H, Si(CH₃)₂].

13C NMR (75 MHz, CDCl₃): δ = 152.0 (C), 150.9 (C), 134.0 (C), 132.1 (C), 130.2 (CH), 129.9 (CH), 129.0 (CH), 128.5 (CH), 128.0 (CH), 62.3 (CH₂), 40.5 (CH₂), 39.2 (CH), 25.4 (C(CH₃)₃), 17.8 (C), –5.8 (CH₃), –6.0 (CH₃).

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

cis-8

A single crystal of cis-7 that was suitable for X-ray diffractionmetry 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): 2931, 2885, 2858, 1717, 1449, 1384, 1270, 1007, 841, 703 cm⁻¹.

**cis-6,7-Dihydro-SH-cyclopentadi[di]pyridazin-5,7-dimethanol (14)**

Ozone was bubbled for 10 min through a vigorously stirred solution of phthalazine 13(1.29 g, 8.99 mmol) in MeOH–CHCl₃ (1:1, 150 mL) at −78 °C. Then, NaBH₄ (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 rt. 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 give 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.

**cis-6,7-Dihydro-SH-cyclopenta[di]pyridazin-5,7-benzate (12)**

Under an inert atmosphere, a solution of DEAD (0.17 g, 0.96 mmol) in THF (0.6 mL) at 0 °C, and 60% NaH (0.032 g, 1.11 mmol) in MeOH–CHCl₃ (1:1, 150 mL) was stirred for 4.5 h at r.t. Then, 1 M NaHSO₄ (1.5 mL) was added to the mixture was stirred for 15 h with TLC monitoring (CH₂Cl₂–MeOH, 20:1) of the reaction. The resulting residue was extracted with CH₂Cl₂ (3 × 40 mL) and EtOAc (40 mL). The combined organic phase was dried (Na₂SO₄) and concentrated under reduced pressure to give 12 as a yellow solid. Yield: 0.032 g (12%).

Mp 120–122 °C.

**PAPER**

I. Pérez-Castro et al.

exchange, OH), 1.59 (dt, J = 13.4, 7.4 Hz, 1 H, 6-HH)], 1.02 [s, 9 H, C(CH3)3].

13C NMR (75 MHz, CDCl3): δ = 149.40 (CH), 149.07 (CH), 145.46 (C), 145.05 (CH), 135.58 (CH), 135.50 (CH), 132.99 (C), 132.93 (C), 129.90 (CH), 129.82 (CH), 128.91 (CH), 127.77 (CH), 65.91(CH3), 64.97 (CH3), 45.45 (CH), 45.23 (CH), 29.78 (CH3), 26.81 [C(CH3)3], 19.16 (C).

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

Anal. Calcd for C25H30N2O2Si: C, 71.73; H, 7.22; N, 6.69. Found: C, 71.98; H, 7.38; N, 6.91.

IR (KBr): 3067, 2930, 2856, 2099, 1581, 1466, 1427, 1383, 1260, 1110, 956, 704 cm–1.

13C NMR (75 MHz, CDCl3): δ = 150.55 (CH), 145.81 (CH), 145.25 (C), 144.80 (CH), 139.99 (C), 135.54 (CH), 135.50 (C), 132.96 (C), 129.92 (CH), 129.86 (CH), 127.84 (CH), 110.33 (CH3), 65.99 (CH3), 43.99 (CH), 33.58 (CH3), 26.75 [C(CH3)3], 19.17 (C).

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

Anal. Calcd for C28H36N4O2Si: C, 74.96; H, 7.05; N, 6.99. Found: C, 75.24; H, 6.97; N, 7.15.

(cis)-cis-7-[(tert-Butylidimethylsiloxy)methyl]-6,7-dihydro-5H-cyclopentada[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, 956, 704 cm–1.

1H NMR (300 MHz, CDCl3): δ = 9.31 (s, 1 H, Hpyrazine), 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 (dd, J = 10.1, 7.3, 3.0 Hz, 1 H, 5-H), 3.86–3.84 (m, 2 H, OCH3), 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 (dd, J = 14.3, 8.8, 7.3 Hz, 1 H, 6-HH), 1.95 (dt, J = 14.3, 3.5 Hz, 1 H, 6-HH), 0.92 [s, 9 H, C(CH3)3].

13C NMR (75 MHz, CDCl3): δ = 149.5 (CH), 148.7 (CH), 145.5 (C), 143.9 (C), 135.4 (CH), 132.4 (C), 130.1 (CH), 129.9 (CH), 127.9 (CH), 73.5 (CH), 65.8 (CH2), 44.0 (CH), 38.0 (CH2), 26.7 (CH3), 19.0 (C).

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

Anal. Calcd for C32H38N4O2Si: C, 71.25; H, 6.98; N, 6.92. Found: C, 71.56; H, 7.09; N, 7.08.

Acknowledgment

The authors thank the Xunta de Galicia for financial support of this work under project PIDT02BTF20305PR.

References


(10) The crystallographic data of cis-7 have been deposited with the Cambridge Crystallographic Data Centre (CCDC) with number 630734. Empirical formula: \(C_{26}H_{32}N_2O_2Si\); formula weight: 432.63; crystal system: monoclinic; lattice type: plate; lattice parameters: \(a = 6.309 (5) \text{ Å}, b = 12.889 (5) \text{ Å}, c = 15.172 (5) \text{ Å}, \alpha = 90 (5)^\circ, \beta = 96.818 (5)^\circ, \gamma = 90 (5)^\circ\), \(V = 1225 0(12) \text{ Å}^3\); space group: \(P2_1\); Z = 2; \(D_{calc} = 1.173 \text{ Mg/m}^3\); \(F(000) = 464; R1 = 0.0702, wR2 = 0.1624\). Diffractometer: Smart-1000 BRUKER. These data can be obtained free of charge from the CCDC via www.ccdc.ac.uk/data_request/cif.

