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Resolution of racemic carbonucleosides and assignment of the absolute configuration by NMR

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Abstract—Resolution of racemic *cis*-6-chloro-9-[2-(hydroxymethyl)cyclopentyl]-9*H*-purine **1** was performed using HPLC with a semipreparative column of β-cyclodextrin using 85:15 water/acetonitrile as eluent. The absolute configurations of the enantiomers were determined by NMR studies of their (*R*)- and (*S*)-methoxyphenylacetates.

Of the many classes of nucleoside analogues that have been synthesized with a view to clinical applications, one of the most interesting has been the carbonucleosides, compounds in which the oxygen of the nucleoside pentose ring is replaced by a methylene unit.[1] For some years we have explored the effects of changing the relative positions of the heterocyclic base and hydroxymethyl group on the carbocycle from 1,3 to 1,2.[2] Hitherto, however, we have worked exclusively with racemic mixtures. As a model procedure, here we describe the resolution of such mixtures by HPLC using a chiral column, and the identification of the absolute configurations of the enantiomers by analysis of the ^{1}H NMR spectra of appropriate derivatives (Mosher's method).[3] Specifically, we describe the case of (±)-*cis*-6-chloro-9-[2-(hydroxymethyl)cyclopentyl]-9*H*-purine **1**, the preparation and anticancer activity of the racemic mixture of which have been reported previously.[2]

The enantiomers of **1** (Scheme 1) were separated by HPLC using a semipreparative column of β-cyclodextrin derivatized with (*RS*)-hydroxypropylether (Cyclobond I 2000 RSP) and a 2 mL/min flow of 85:15 water/acetonitrile as eluent.[4] Compounds **2**–**5** were then obtained in almost quantitative yields by reaction of the separated enantiomers with (*R*)- and (*S*)-methoxyphenylacetic acid (MPA),[5] as follows. A mixture of (+)- or (−)-**1** (1 mol), (*R*)- or (*S*)-MPA (1 mol) and DCC (1.5 mol) in dry CH_2Cl_2 (150 mL) containing a catalytic amount of DMPA was stirred for 12 h at room temperature, filtered, and washed with hexane. The pooled organic layers were washed with 1 M HCl, $NaHCO_3$ and water and dried ($NaSO_4$), and the solvent was evaporated under reduced pressure. The crude product was purified by HPLC on a Partisil 10 column using a 2 mL/min flow of 8:2 hexane/isopropanol as eluent.[6]

^{1}H and ^{13}C NMR spectra were run in a Bruker AMX 500 apparatus, and the signals of all protons and carbons were identified by means of COSY experiments. Unequivocal identification of the absolute configurations of **2**–**5** at C1′ and C2′ was achieved by comparison of the (*R*)- and (*S*)-MPA esters as regards the chemical shifts of the protons on either side of the stereogenic center nearest the substituted hydroxymethyl group,[7] i.e. the proton on the carbon bearing the nitrogenated base (H1′) and those of the methylene contiguous to the carbon bearing the hydroxymethyl group (H3′) (see Fig. 1). In the case of the derivatives of (+)-**1** ($[\alpha]_D$ = +38.5 (*c* 0.002, MeOH)), the spectrum of the (*R*)-MPA ester **2** showed a downfield shift of 0.01 ppm for the H1′ signal and upfield shifts of −0.02 and −0.08 ppm for the H3′ signals relative to their positions in the spectrum of the (*S*)-MPA ester **3**; the absolute configuration of C2′ was accordingly identified as *S*, making (+)-**1** (1′*R*,2′*S*). Although this implied that (−)-**1** {($[\alpha]_D$ = −46.0 (*c* 0.002, MeOH)} is (1′*S*,2′*R*), this conclusion was confirmed by comparison of the ^{1}H NMR spectra of **4** and **5**, in the former of which the H1′ signal appeared 0.01 ppm upfield and the H3′ signals 0.01 and 0.09 ppm downfield of their positions in the latter.

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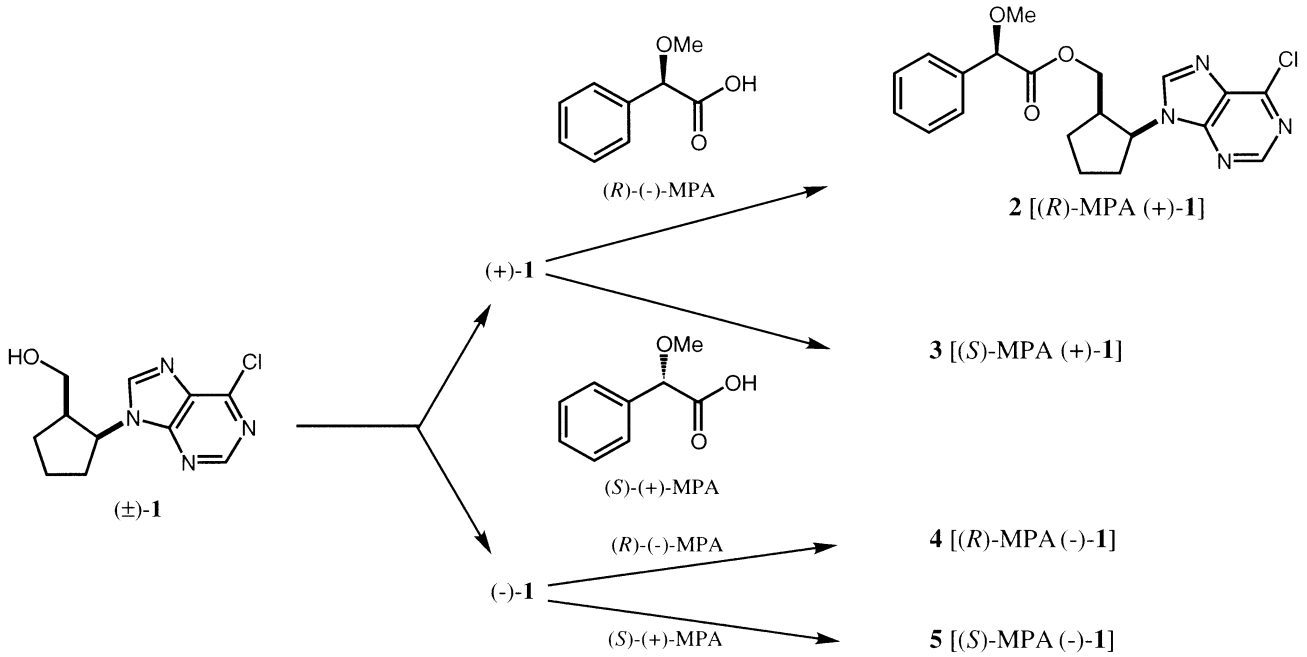

Scheme 1.

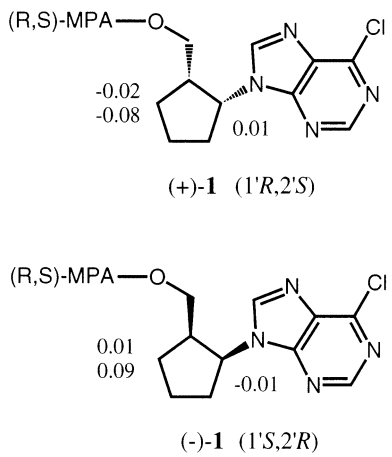

Figure 1. Absolute configurations of compounds (−)-**1** and (+)-**1**, with differences between the chemical shifts of protons H1′ and H3′ in the (*R*)- and (*S*)-MPA derivatives.

Acknowledgements

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References

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2. Estrada, E.; Uriarte, E.; Montero, A.; Teijeira, M.; Santana, L.; De Clercq, E. *J. Med. Chem.* **2000**, *43*, 1975–1985.
3. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
4. Compound **1**: mp 129–121°C; ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 1.42 and 1.94 (2m, 1+1H, H-3′), 2.03 and 2.13 (2m, 1+1H, H-4′), 2.34 and 2.45 (2m, 1+1H, H-5′), 2.55 (m, 1H, H-2′), 2.85 and 3.46 (2m, 1+1H, H-6′), 3.46 (bs, 1H, OH), 5.19 (m, 1H, H-1′), 8.11 (s, 1H, H-8), 8.76 (s, 1H, H-2); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 22.3 (4′), 24.6 (3′), 31.0 (5′), 47.9 (2′), 58.0 (1′), 61.1 (6′), 131.6 (5), 144.5 (8), 151.6 (4), 151.7 (2), 152.3 (6); IR (KBr): 3283, 2954, 1592, 1567, 1394, 1335, 1229, 632 cm^{-1}; MS *m*/*z* (%): 254 ([M+2]$^+$, 6), 252 (M$^+$, 18), 181 (31), 157 (35), 155 (100). Anal. calcd for $C_{11}H_{13}ClN_4O$: C, 52.28; H, 5.19; N, 22.17. Found: C, 52.40; H, 4.90; N, 21.87.
Compound (−)-**1**. HPLC: t_R = 57.67 min; $[\alpha]_D$ = −46.0 (*c* 0.002, MeOH).
Compound (+)-**1**. HPLC: t_R = 60.63 min; $[\alpha]_D$ = +38.5 (*c* 0.002, MeOH).
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6. (+)-*cis*-6-Chloro-9-[2-(hydroxymethyl)cyclopentyl]-9*H*-purine (*R*)-MPA ester **2**
HPLC: t_R = 41.20 min; $[\alpha]_D$ = −8.8 (*c* 0.0072, MeOH); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 1.25 (m, 1H, 1H-5′), 1.37 (m, 1H, 1H-3′), 1.48 (m, 2H, 1H-4′+1H-5′), 1.68 (m, 1H, H-4′), 1.78 (m, 1H, 1H-3′), 2.42 (m, 1H, H-2′), 2.47 (m, 1H, H-1′), 3.42 (s, 3H, OCH_3), 4.18 (m, 2H, H-6′), 4.80 (s, 1H, >CH-Ph), 7.26, 7.30 and 7.46 (3m, 1+2+2H, aromatics), 7.54 (s, 1H, H-8), 8.35 (s, 1H, H-2); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 22.5 (C-4′), 27.9 (C-3′), 29.0 (C-5′), 40.0 (C-2′), 42.1 (C-1′), 57.4 (MeO), 65.3 (C-6′), 82.6 (C-OMe), 127.3 (2Ph), 128.8 (2Ph), 128.9 (1Ph), 136.2 (C-5), 140.5 (C-8), 150.2 (C-6), 152.9 (C-2), 155.4 (C-4), 170.6 (CO); FABMS (positive ion) *m*/*z* (%): 403 ([M+3]$^+$, 14), 401 ([M+1]$^+$, 37), 231 (69), 154 (100).
(+)-*cis*-6-Chloro-9-[2-(hydroxymethyl)cyclopentyl]-9*H*-purine (*S*)-MPA ester **3**

HPLC: $t_R = 43.20$ min; $[\alpha]_D = +7.9$ (c 0.0065, MeOH); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 1.26 (m, 1H, 1H-5′), 1.46 (m, 1H, 1H-3′), 1.49 (m, 2H, 1H-4′+1H-5′), 1.72 (m, 1H, 1H-4′), 1.80 (m, 1H, 1H-3′), 2.37 (m, 1H, H-2′), 2.46 (m, 1H, H-1′), 3.42 (s, 3H, OCH_3), 4.14 (dd, 1H, 1H-6′, $J = 7.70$, 11.42), 4.25 (dd, 1H, 1H-6′, $J = 5.60$, 11.42), 4.78 (s, 1H, >CH-Ph), 7.35 and 7.47 (2m, 3+2H, aromatics), 7.55 (s, 1H, H-8), 8.35 (s, 1H, H-2); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 22.6 (C-4′), 27.9 (C-3′), 29.1 (C-5′), 40.0 (C-2′), 42.0 (C-1′), 57.4 (MeO), 65.3 (C-6′), 82.6 (C-OMe), 127.3 (2Ph), 128.7 (2Ph), 128.9 (1Ph), 136.2 (C-5), 140.5 (C-8), 150.2 (C-6), 152.9 (C-2), 155.4 (C-4), 170.6 (CO); FABMS (positive ion) m/z (%): 403 ([M+3]$^+$, 36), 401 ([M+1]$^+$, 100), 253 (33), 231 (44), 154 (90).

(−)-*cis*-6-Chloro-9-[2-(hydroxymethyl)cyclopentyl]-9*H*-purine (*R*)-MPA ester **4**

HPLC: $t_R = 39.6$ min; $[\alpha]_D = -11.0$ (c 0.0080, MeOH); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 1.25 (m, 1H, 1H-5′), 1.46 (m, 1H, 1H-3′), 1.49 (m, 2H, 1H-4′+1H-5′), 1.72 (m, 1H, 1H-4′), 1.78 (m, 1H, 1H-3′), 2.37 (m, 1H, H-2′), 2.46 (m, 1H, H-1′), 3.42 (s, 3H, OCH_3), 4.14 (dd, 1H, 1H-6′, $J = 7.70$, 11.40), 4.25 (dd, 1H, 1H-6′, $J = 5.55$, 11.40), 4.78 (s, 1H, >CH-Ph), 7.34 and 7.47 (2m, 3+2H, aromatics), 7.55 (s, 1H, H-8), 8.35 (s, 1H, H-2); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 22.6 (C-4′), 27.9 (C-3′), 29.2 (C-5′), 39.9 (C-2′), 41.9 (C-1′), 57.4 (MeO), 65.2 (C-6′), 82.5 (C-OMe), 127.3 (2Ph), 128.7 (2Ph), 128.9 (1Ph), 136.2 (C-5), 140.5 (C-8), 150.1 (C-6), 152.9 (C-2), 155.4 (C-4), 170.5 (CO); FABMS (positive ion) m/z (%): 403 ([M+3]$^+$, 19), 401 ([M+1]$^+$, 51), 231 (56), 154 (100).

(−)-*cis*-6-Chloro-9-[2-(hydroxymethyl)cyclopentyl]-9*H*-purine (*S*)-MPA ester **5**

HPLC: $t_R = 38.0$ min; $[\alpha]_D = +10.2$ (c 0.0077, MeOH); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 1.24 (m, 1H, 1H-5′), 1.37 (m, 1H, 1H-3′), 1.48 (m, 2H, 1H-4′+1H-5′), 1.68 (m, 1H, 1H-4′), 1.77 (m, 1H, 1H-3′), 2.40 (m, 1H, H-2′), 2.47 (m, 1H, H-1′), 3.42 (s, 3H, OCH_3), 4.18 (m, 2H, H-6′), 4.80 (s, 1H, >CH-Ph), 7.25, 7.31 and 7.46 (3m, 1+2+2H, aromatics), 7.55 (s, 1H, H-8), 8.34 (s, 1H, H-2); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 22.6 (C-4′), 27.9 (C-3′), 29.1 (C-5′), 39.9 (C-2′), 42.0 (C-1′), 57.4 (MeO), 65.2 (C-6′), 82.5 (C-OMe), 127.3 (2Ph), 128.7 (2Ph), 128.9 (1Ph), 136.2 (C-5), 140.5 (C-8), 150.1 (C-6), 152.9 (C-2), 155.4 (C-4), 170.5 (CO); FABMS (positive ion) m/z (%): 403 ([M+3]$^+$, 34), 401 ([M+1]$^+$, 100), 253 (39), 231 (30), 154 (82).

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