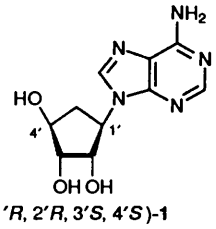
Synthesis of Optically Active 5'-Noraristeromycin: Enzyme-catalysed Kinetic Resolution of 9-(4-Hydroxycyclopent-2-enyl)purines

Valeria Merlo,[a] Fiona J. Reece,[a] Stanley M. Roberts,[a] Mike Gregson[b] and Richard Storer[b]
[a] *Department of Chemistry, Exeter University, Exeter, Devon EX4 4QD, UK*
[b] *Department of Medicinal Chemistry, Glaxo Group Research, Greenford, Middlesex UB6 0HE, UK*

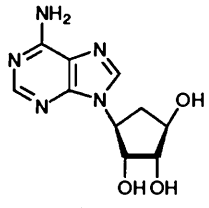
A facile chemo-enzymatic route to optically active 5'-noraristeromycin from the epoxide **2** employs an enantioselective *Pseudomonas cepacia* lipase-catalysed acetylation

Racemic 5'-noraristeromycin (±)-**1** has recently been synthesised from cyclopentadiene in nine steps and has been shown to be a potent inhibitor of *S*-adenosyl-L-homocysteine hydrolase. Moreover, the compound has noteworthy activity against a series of viruses, including human cytomegalovirus.[1]

As part of our programme of research into the synthesis and biological activity of carbocyclic nucleosides[2] we report a comparatively simple route to compounds of type **1** which, it should be emphasized, allows access to both enantiomeric forms of these nucleoside mimics.

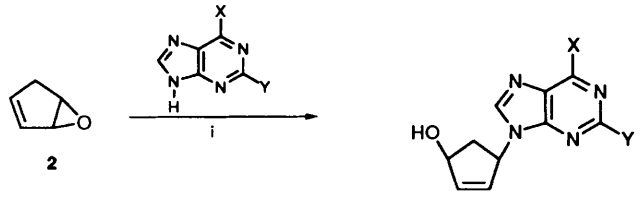


(1'*R*, 2'*R*, 3'*S*, 4'*S*)-**1**



(1'*S*, 2'*S*, 3'*R*, 4'*R*)-**1**

Cyclopentadiene was readily converted into the monoepoxide **2**. Reaction with selected deprotonated purines in the presence of a Pd^0 catalyst led to the formation of the corresponding cyclopentenols **3**–**5** (yields 40–90%)[3] (Scheme 1).



2

3 X = Cl, Y = H (80%)
4 X = Cl, Y = NH_2 (90%)
5 X = NH_2, Y = H (40%)

Scheme 1 *Reagents and conditions:* i, $Pd[P(Ph)_3]_4$, DMSO–THF, 0 °C to room temperature

Compounds of the type **3**–**5** can be resolved using *Pseudomonas cepacia* lipase (PCL) working in the esterification mode. For example the racemic alcohol **3** is acetylated enantiospecifically using PCL in vinyl acetate to yield the ester **6** (40%) and recovered alcohol (−)-**3** (44%) (Scheme 2) which were readily separated by column chromatography. The ester and alcohol were judged to be of high enantiomeric purity (>95% e.e.) by NMR spectroscopy using a chiral shift reagent [Eu(hfc)$_3$].

The absolute configuration of (−)-**3** was determined by comparison with a sample prepared (less efficiently) by treatment of (1*S*,4*R*)-4-acetoxycyclopent-1-enol with 6-chloropurine, pretreated with sodium hydride, under Pd^0 catalysis.[4]

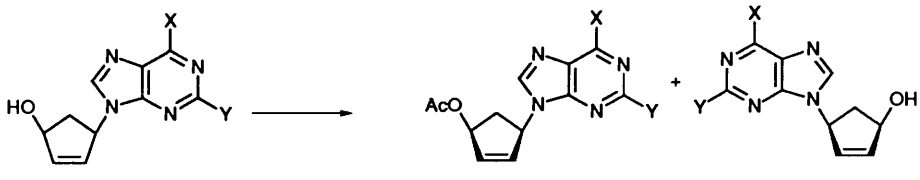
Treatment of the ester **6** with osmium tetraoxide (catalytic) and potassium ferricyanide furnished the chloropurine derivative (+)-**9** (90%) which can be transformed into (1'*R*,2'*R*,3'*S*,4'*S*)-**1** using ammonia. Similarly, the alcohol (−)-**3** furnished the chloropurine derivative (−)-**9** and thence (1'*S*,2'*S*,3'*R*,4'*R*)-**1**.

In addition, the chloropurine (+)-**9** has been protected as the acetonide derivative, treated with base and then the tosylate **10** to afford (after ammonolysis and deprotection) the AMP-mimic **11** (55% overall yield).

Resolution of the purine derivative **4** was effected using PCL-catalysed acetylation to give the ester **7** (38%; >95% e.e.) and the alcohol (−)-**4** (45%; 80% e.e.). The absolute configuration of (−)-**4** was determined by comparison with data reported in the literature.[5] This resolution is a key step in our projected synthesis of the two enantiomers of 'reversed carbovir triphosphate'.[6] Similarly, the adenine derivative **5** can be resolved using PCL in vinyl acetate to give the ester **8** (30%; >95% e.e.) and recovered alcohol (−)-**5** (30%; 63% e.e.).

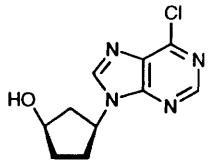
Experimental

9-[(1'β,4'β)-4'-Acetoxycyclopent-2'-enyl]-6-chloropurine **6**.—The alcohol **3** (1.08 g, 4.59 mmol) was dissolved in vinyl acetate (100 cm^3) and PCL (1.08 g, 14 605 units) was added to the solution. After the mixture had been stirred at room

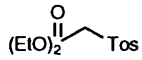


3...	X = Cl, Y = H	...**6**	(−)-**3**
4...	X = Cl, Y = NH_2	...**7**	(−)-**4**
5...	X = NH_2, Y = H	...**8**	(−)-**5**

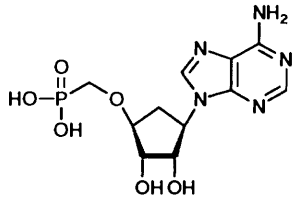
Scheme 2 *Reagents and conditions:* i, PCL, CH_2=CHOAc, 20–30 °C, 4–72 h



(+)-9



10



11

temperature for 4 h, the enzyme was filtered off and the filtrate evaporated. Purification of the resultant solid by flash column chromatography eluting with ethyl acetate gave the title compound (564 mg, 40%), m.p. 138 °C (decomp); $[\alpha]_D^{27}$ +51.3* (*c* 0.41 MeOH); λ_{max}(MeOH)/nm 207.1 and 265.9; ν_{max}(KBr)/cm^{-1} 1730 (C=O), 1590 and 1558, (C=C, C=N); δ_H(250 MHz, $CDCl_3$) 1.99 (1 H, m, 5'-Hβ), 2.06 (3 H, s, CH_3), 3.13 (1 H, m, 5'-Hα), 5.84 (2 H, m, 2'-H, 3'-H), 6.18 (1 H, m, 1'-H), 6.47 (1 H, m, 4'-H), 8.55 (1 H, s, 8-H) and 8.79 (1 H, s, 2-H); δ_C(62.9 MHz, $CDCl_3$) 20.72 (CH_3), 30.566 (C-5'), 57.871 (C-1'), 76.782 (C-4'), 133.01 (C-2'), 134.673 (C-3'), 145.469 (C-8), 151.409 (C-2) and 169.956 (C=O) [Found: (EI) M^+, 278.057 95. $C_{12}H_{11}ClN_4O_2$ requires *M*, 278.057 05] and the starting alcohol (−)-**3** 9-[(1'β,4'β)-4'-hydroxycyclopent-2'-enyl]-6-chloropurine (510 mg, 44%), m.p. 162–164 °C (decomp.) (from MeOH); $[\alpha]_D^{27}$ −60.9 (*c* 0.9, MeOH); λ_{max}(pH 6 phosphate buffer)/nm 203.1 and 265.7; ν_{max}(KBr)/cm^{-1} 3200–2800 (OH), 1592 and 1561 (C=C, C=N); δ_H(250 MHz, [$^2H_6$] DMSO) 1.78 (1 H, m, 5'-Hβ), 2.94 (1 H, m, 5'-Hα), 4.75 (1 H, m, 1'-H), 5.56 (1 H, br, OH), 5.59 (1 H, m, 4'-H), 6.06 (1 H, m, 2'-H), 6.24 (1 H, m, 3'-H), 8.56 (1 H, s, 8-H) and 8.72 (1 H, s, 2-H); δ_C(62.9 MHz, [$^2H_6$]-DMSO) 41.034 (C-5'), 57.875 (C-1'), 73.552 (C-4'), 129.993 (C-2'), 130.990 (C-5), 140.055 (C-3'), 145.68 (C-8), 148.941 (C-4), 151.265 (C-2) and 151.368 (C-6) [Found: (EI) M^+, 236.045 11. $C_{10}H_9ClN_4O$ requires *M*, 236.046 49].

*[α] Values in units of 10^{-1} deg. cm^2 g^{-1}.

Acknowledgements

We thank the SERC and Glaxo (CASE award to F. J. R.) as well as MURST (60% funds) for financial support to V. M.

References

1 S. D. Patil, S. W. Schneller, M. Hosoya, R. Snoeck, G. Andrei, J. Balzarini and E. De Clercq, *J. Med. Chem.*, 1992, **35**, 3372; see also S. M. Siddiqi, F. P. Oertel, X. Chen and S. W. Schneller, *J. Chem. Soc., Chem. Commun.*, 1993, 708.

2 C. F. Palmer, K. P. Parry and S. M. Roberts, *Tetrahedron Lett*, 1990, **31**, 279; A. D. Borthwick, D. N. Evans, B. E. Kirk, K. Biggadike, A. M. Exall, P. Youds, S. M. Roberts, D. J. Knight and J. A. C. Coates, *J. Med. Chem.*, 1990, **33**, 179; A. D. Borthwick, B. E. Kirk, K. Biggadike, A. M. Exall, S. Butt, S. M. Roberts, D. J. Knight, J. A. V. Coates and D. M. Ryan, *J. Med. Chem.*, 1991, **34**, 907; R. M. Highcock, H. Hilpert, P. L. Myers, S. M. Roberts and R. Storer, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1127; D. M. Coe, D. M. Parry, S. M. Roberts and R. Storer, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2373; S. M. Roberts and K. Shoberu, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2605; D. M. Le Grand and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1751; E. J. Hutchinson, S. M. Roberts and A. J. Thorpe, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2245; I. C. Cotterill and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2585; A. N. Payne and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2633; R. A. MacKeith, R. McCague, H. F. Olivo, C. F. Palmer and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1993, 313.

3 D. M. Coe, D. C. Orr, S. M. Roberts and R. Storer, *J. Chem. Soc., Perkin Trans. 1*, 1991, 3378; D. M. Coe, H. Hilpert, S. A. Noble, M. R. Peel, S. M. Roberts and R. Storer, *J. Chem. Soc., Chem. Commun.*, 1991, 312.

4 D. R. Deardorff, R. G. Linde, A. M. Martin and M. J. Shulman, *J. Org. Chem.*, 1989, **54**, 2759.

5 M. R. Peel, D. D. Sternbach and M. R. Johnson, *J. Org. Chem.*, 1991, **56**, 4990.

6 For the synthesis of racemic material see D. M. Coe, S. M. Roberts and R. Storer, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2695.

Paper 3/02887I
Received 20th *May* 1993
Accepted 27th *May* 1993