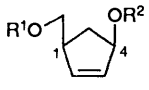
Enzymatic Resolution of *cis*- and *trans*-4-Hydroxycyclopent-2-enylmethanol Derivatives and a Novel Preparation of Carbocyclic 2',3'-Dideoxydidehydronucleosides and Aristeromycin

Stanley M. Roberts and Karoline A. Shoberu
Department of Chemistry, Exeter University, Exeter, Devon EX4 4QD, UK

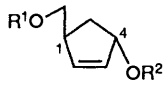
The (1*R*,4*S*)-acetate **3** and the (1*S*,4*S*)-alcohol **5** have been obtained optically pure by lipase catalysed esterification: compounds **3** and **5** have been converted into carbocyclic dideoxydidehydronucleosides and aristeromycin **9**.

There is intense current interest in the preparation of carbocyclic nucleosides,[1,2] particularly of the ribo-,[3] arabino-,[4] 2'-deoxyribo-,[5] 2',3'-dideoxy-[6] and 2',3'-dideoxydidehydro-type.[7] Herein, we describe a new method for the preparation of chiral synthons for the production of various carbocyclic nucleosides.

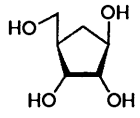
The 4-hydroxycyclopent-2-enylmethanol derivatives **1**, **2** and **5** are obtained, in racemic form, by a Prins reaction on cyclopentadiene followed by preferential protection of the primary hydroxy group.[1,8] The *cis*-1,4 derivative **2** was converted into the acetate **4** using acetic anhydride in pyridine (94%).



1 $R^1 = CPh_3$, $R^2 = H$
2 $R^1 = SiMe_2Bu^t$, $R^2 = H$
3 $R^1 = CPh_3$, $R^2 = Ac$
4 $R^1 = SiMe_2Bu^t$, $R^2 = Ac$



5 $R^1 = CPh_3$, $R^2 = H$
6 $R^1 = CPh_3$, $R^2 = Ac$



7

Hydrolysis of the acetate **4** over 20 h in pH 7 phosphate buffer using *Pseudomonas fluorescens* lipase (pfl) as catalyst gave the (1*R*,4*S*)-alcohol (+)-**2** (43% yield > 95% e.e.) and recovered (1*S*,4*R*)-acetate (−)-**4** (42% yield > 95% e.e.). The absolute configuration of the alcohol and the ester were determined by correlation with the tetraol **7**[9] and the enantiomeric excess (e.e.'s) were assessed using NMR spectroscopy and a chiral shift reagent.

Reaction of the trityloxymethylcyclopentenol **1** with vinyl acetate over 75 h using pfl as catalyst gave a 98% yield of equal amounts of the readily separated (1*S*,4*R*)-alcohol (−)-**1** and the (1*R*,4*S*)-acetate (+)-**3**. Both compounds showed excellent optical purities (>95% e.e.) as assessed by chiral shift NMR studies.

Similarly, the alcohol **5** was acetylated using pfl and vinyl acetate. After 48 h at room temp. roughly equal quantities of the (1*R*,4*R*)-alcohol (+)-**5** and the (1*S*,4*S*)-acetate (−)-**6** (combined yield 100%, e.e. 74% for both compounds) were obtained. Extending the reaction period to 72.5 h gave, as expected,[10] a decreased amount of the alcohol (+)-**5** of higher optical purity (37% yield; >95% e.e.).

The compounds **3**–**5** are extremely useful building blocks for the preparation of racemic or optically active carbocyclic nucleosides. Thus, the acetate (±)-**4** reacted with adenine in the presence of sodium hydride and tetrakis(triphenylphosphine)-palladium(0) to give the dideoxydidehydronucleoside (±)-**8** (Scheme 1). The latter compound was converted into an inseparable mixture of aristeromycin (±)-**9** and the isomer (±)-**10**.[11]

The ester (+)-**3** reacted with 6-chloropurine in the presence of sodium hydride and $Pd(Ph_3P)_4$ to give the cyclopentene derivative (+)-**11**. The same cyclopentene derivative was obtained by coupling the alcohol (+)-**5** and 6-chloropurine under Mitsunobu conditions. The purine (+)-**11** was bis-hydroxylated to give equal quantities of the readily separated diols (+)-**12** and (−)-**13**. The chloropurine (+)-**12** is readily transformed in high yield into (+)-aristeromycin **9** $[\alpha]_D^{27}$ +50* (*c* 0.44, dimethylformamide).[12]

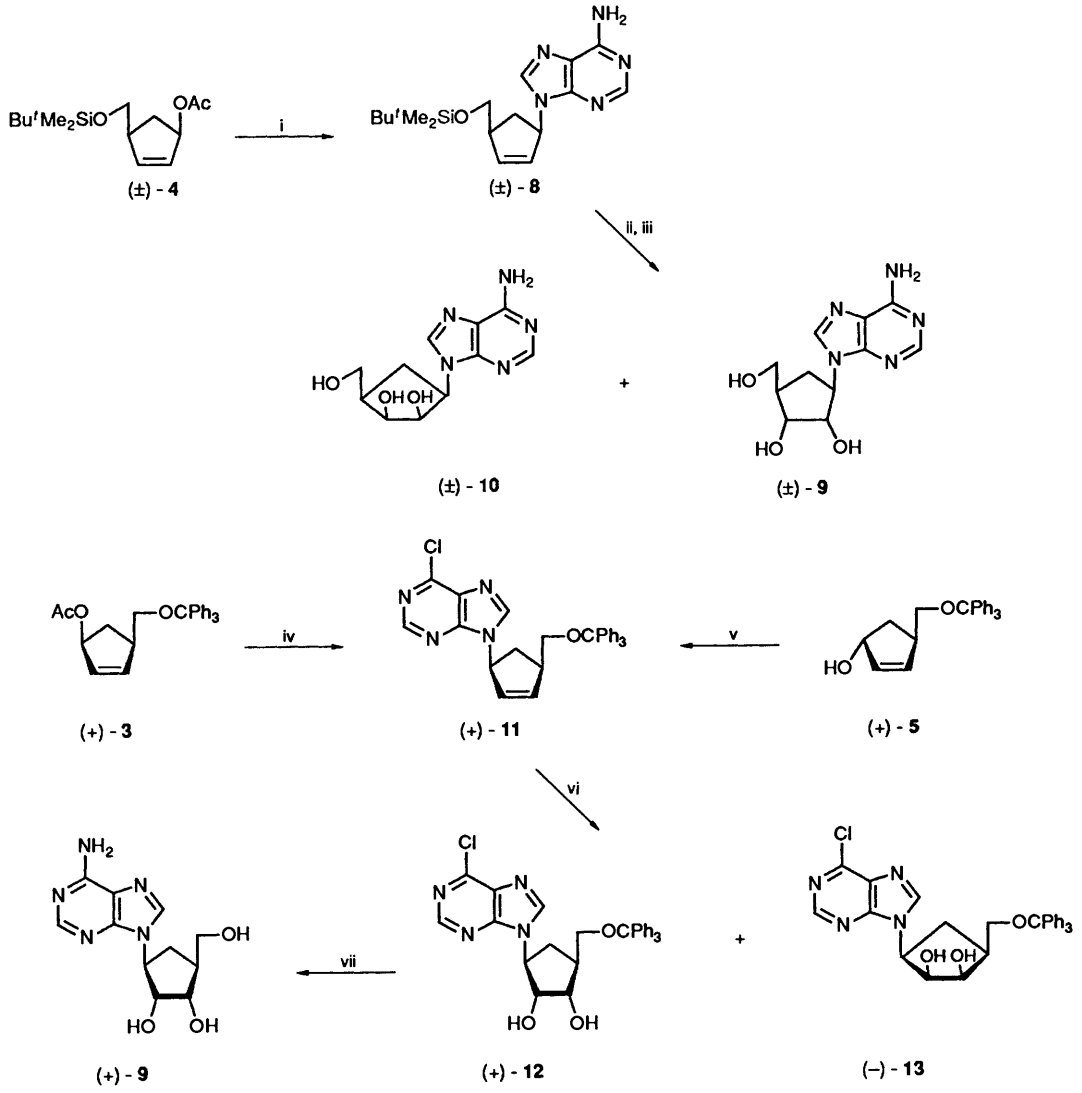
Similarly, the ester (+)-**3** was converted into the 2',3'-dideoxydihydronucleoside (+)-**14** using 2-amino-6-chloropurine, sodium hydride and tetrakis(triphenylphosphine)-palladium. Compound (+)-**14** was transformed into (+)-carbovir **15** {$[\alpha]_D^{20}$ +59.5 (*c* 0.4, methanol)} in the prescribed manner.[7,13]

Experimental

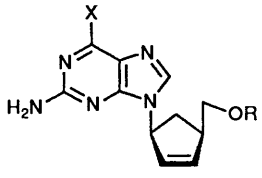
General Procedure of PFL-Catalysed Acetylation.—A suspension of (±)-(1β,4β)-1-(triphenylmethoxymethyl)cyclopent-2-en-4-ol **1** (529.2 mg, 1.49 mmol) and *Pseudomonas fluorescens* lipase (325.8 mg) in vinyl acetate (30 ml) was stirred for 75 h at room temperature. The enzyme was filtered off and the filtrate concentrated under reduced pressure. The residue (655.7 mg) was purified by flash chromatography on silica gel (4:1 petroleum–EtOAc) to give (1*R*,4*S*)-(+)-4-acetoxy-1-(triphenylmethyloxymethyl)cyclopent-2-ene **3** (295.8 mg, 50%, R_f 0.42) as an oil on evaporation of the solvent; $[\alpha]_D^{21}$ +16.2 (*c* 1.5 in $CHCl_3$) (82% e.e.); ν_{max}(neat)/cm^{-1} 3062, 3030, 2916, 2868s (CH), 1732s (CO) and 1597w (C=C); δ(250 MHz, $CDCl_3$) 1.54–1.67 (centred 1.60, 1 H, m, 5-H), 2.00 (3 H, s, AcO), 2.51 (1 H, ddd, *J* 14.5, 8 and 8, 5-H), 2.90–3.03 (centred 2.96, 1 H, m, 1-H), 3.05–3.19 (centred 3.12, 2 H, m, CH_2OTr), 5.64–5.73 (centred 5.67, 1 H, m, 4-H), 5.89 (1 H, ddd, *J* 5.5, 2 and 2, 2-H), 6.13 (1 H, ddd, *J* 5.5, 1 and 2, 3-H) and 7.21–7.58 (15 H, m, Tr); later fractions contained recovered starting **1** (253.8 mg, 48%, R_f 0.16) as a white solid on evaporation of the solvent; m.p. 113–114 °C; $[\alpha]_D^{21}$ −72.1 (*c* 1.2 in $CHCl_3$) (>95% e.e.); ν_{max}(KBr)/cm^{-1} 3382br (OH), 3059, 2938s (CH) and 1593s (C=C); δ(250 MHz, $CDCl_3$) 1.42 (1 H, ddd, *J* 14, 3.5 and 3.5, 5-H), 2.13 (1 H, br d, *J* 6.5, OH), 2.37 (1 H, ddd, *J* 14, 7.5 and 8.5, 5-H), 2.79–2.92 (centred 2.84, 1 H, m, 1-H), 3.08 (1 H, dd, *J* 5.5 and 9, CH_2OTr), 3.29 (1 H, dd, *J* 5 and 9, CH_2OTr), 4.71 (1 H, br s, 4-H), 5.97 (2 H, s, 2-H and 3-H), 7.29 (9 H, m, Ph) and 7.45 (6 H, m, Ph).

(+)-(1'R,4'S)-cis-6-*Chloro*-9-[4'-(*triphenylmethyloxymethyl*)*cyclopent*-2'-*enyl*-*purine* **11**.—A solution of 6-chloropurine (196.3 mg, 1.3 mmol) in dimethylformamide (1.2 ml) was stirred with sodium hydride (60% dispersion in oil; 48.9 mg, 1.2 mmol) for 2.5 h under nitrogen. This was added dropwise to a suspension of (+)-**3** (271 mg, 0.69 mmol), $[Pd(PPh_3)_4]$ (395.9 mg, 0.3 mmol, 0.5 equiv.) and PPh_3 (25.1 mg, 0.1 mmol, 15

* $[\alpha]_D$ Values recorded in 10^{-1} deg cm^2 g^{-1} throughout.



Scheme 1 *Reagents and conditions:* i, adenine, NaH, $Pd(PPh_3)_4$ (5 mol%) DMF–THF (1:1), 50 °C, 42%; ii, Bu_4NF, THF, 55%; iii, OsO_4 (0.01 equiv.), *N*-methylmorpholine *N*-oxide (NMO) (1.12 equiv.), acetone/H_2O (10:1), 89%; iv, 6-chloropurine, NaH, $Pd(PPh_3)_4$ (0.5 equiv.), PPh_3 (15 mol%), DMF–THF (1:1), 60 °C, 30%; v, 6-chloropurine, diethyl azodicarboxylate, PPh_3, room temp., 18 h, THF, 47%; vi, OsO_4 (0.01 equiv.), NMO, acetone/H_2O (10:1), 59%; vii, NH_3 then 80% aqueous acetic acid



14 X = Cl, R = CPh_3
15 X = OH, R = H

mol%) in THF (1.6 ml) under argon, and washed through with an extra aliquot of THF (0.5 ml). The reaction mixture was immersed in a pre-heated oil bath (60 °C) and stirred for 4 h. The mixture was cooled, diluted with water (4 ml) and extracted with ethyl acetate (10 ml × 4). The combined extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue (997.9 mg) was purified by flash chromatography over silica (3:1 hexane–EtOAc) and fractions corresponding to R_f 0.35 (1:1 hexane–EtOAc) were collected to give the title compound **11** as a white foam on evaporation of the solvent (100 mg, 30%); m.p. 58 °C; $[\alpha]_D^{25}$ +17.2 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3062, 2923, 2871s (CH), 1589 and 1558 (C=C and C=N); λ_{max}(MeOH)/nm 266.4; δ(250 MHz, $CDCl_3$) 1.66 (1 H, ddd, *J* 14, 5.5 and 5.5, 6′-H), 2.77–2.94 (centred 2.85, 1 H, m, 6′-H), 3.10–3.29 (centred 3.20, 3 H, m, CH_2OTr and 4′-H), 5.73–5.84 (centred 5.79, 1 H, m, 1′-H), 5.89 (1 H, d, *J* 5.5, 2′-H), 6.32 (1 H, d, *J* 5.5, 3′-H), 7.26 (9 H, m, Ar), 7.42 (6 H, m, Ar), 8.01 (1 H, s, 2-H) and 8.71 (1 H, s, 8-H); $\delta_C(CDCl_3)$ 35.40 (CH_2), 45.86 (CH), 60.24 (CH), 65.96 (CH_2), 86.68 (C), 127.15 (CH, Ar), 127.85 (CH, Ar), 128.64 (CH, Ar), 131.96 (C), 140.08, 143.37 (CH), 143.88 (C, Ar and CH), 150.90 (C), 151.58 (C) and 151.74 (CH) (Found: 493.1795, $C_{30}H_{25}ClN_4O$, $[M + H]^+$; Calc. for $C_{30}H_{25}ClN_4O$, $[M + H]^+$: 493.1795).

Acknowledgement

We thank the SERC and DTI for a research assistantship (to K. A. S.) under the IUBC Biotransformations LINK Scheme.

References

1 E. A. Saville-Stones, S. D. Lindell, N. S. Jennings, J. C. Head and M. J. Ford, preceding communication; we thank Dr. Stephen Lindell for a preprint of the Schering work, prior to publication.
2 V. E. Marquez and M. I. Lim, *Med. Res. Rev.*, 1986, **6**, 1; S. M. Roberts, *Chem. in Brit.*, 1991, 518.
3 M. F. Jones and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2927; M. S. Wolfe, B. L. Anderson, D. R. Borcherd and R. T. Borcherd, *J. Org. Chem.*, 1990, **55**, 4712.

4 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. V. Coates, *J. Med. Chem.*, 1990, **33**, 179.
5 R. M. Highcock, H. Hilpert, P. L. Myers, S. M. Roberts and R. Storer, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1127.
6 D. M. Coe, H. Hilpert, M. R. Peel, S. A. Noble, S. M. Roberts and R. Storer, *J. Chem. Soc., Chem. Commun.*, 1991, 312.
7 S. J. C. Taylor, A. G. Sutherland, C. Lee, R. Wisdom, S. Thomas, S. M. Roberts and C. Evans, *J. Chem. Soc., Chem. Commun.*, 1990, 1120; see also C. Evans, R. McCague, S. M. Roberts and A. G. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1991, 656.
8 J. J. S. Bajorek, R. Battaglia, G. Pratt and J. K. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1243; H. Pawson and U. Maaß, *Chem. Ber.*, 1981, **114**, 346.
9 Kin-Ichi Tadano, K. Hakuba, H. Kimura and S. Ogawa, *J. Org. Chem.*, 1989, **54**, 276.
10 C.-S. Chen and C. J. Sih, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 695.
11 B. M. Trost, Gee-Hong Kuo and T. Benneche, *J. Am. Chem. Soc.*, 1988, **110**, 621.
12 Naturally occurring (−)-aristeromycin has $[\alpha]_D$ −52.5 (*c*, 1 DMF); T. Kusaka, H. Yamamoto, M. Shibata, M. Muroi, T. Kishi and K. Hizuno, *J. Antibiot.*, 1968, **21**, 255.
13 (1*R*,4*S*)-(4-Hydroxymethyl)cyclopent-2-enylguanine has $[\alpha]_D$ −64 (*c*, 0.4 methanol); C. Williamson, A. M. Exall, M. F. Jones, C. L. Mo, P. L. Myers, I. L. Paternoster and R. Storer, poster presentation at SCI Medicinal Chemistry Symposium, Cambridge. 1989.

Paper 1/03280A
Received 2 *July* 1991
Accepted 16*th July* 1991