Chemoenzymatic synthesis of carbocyclic nucleoside analogues with bicyclo[3.1.0]hexyl residues

Fritz Theil,*[a] Sibylle Ballschuh,[a] Martin von Janta-Lipinski[b] and Roger A. Johnson[c]

[a] *Institut für Angewandte Chemie Berlin-Adlershof, Rudower Chaussee 5, D-12484 Berlin, Germany*

[b] *Max-Delbrück-Centre of Molecular Medicine, Robert-Rössle-Straße 10, D-13125 Berlin, Germany*

[c] *Department of Physiology and Biophysics, Health Sciences Center, State University of New York at Stony Brook, Stony Brook, NY 11794-8661, USA*

The carbocyclic nucleoside analogues 8 and *ent*-8 have been prepared based on the enantiomerically pure bicyclo[3.1.0]hexane monoacetates 5 and *ent*-5 which were obtained by a lipase-catalysed asymmetrization of the *meso*-bicyclo[3.1.0]hexane derivatives 4 and 6, respectively. By an enantiodivergent approach both nucleoside analogues 8 and *ent*-8 have been synthesized starting from the common enantiomer 5. Furthermore, the adenine derivative *ent*-8 has been obtained from the monoacetate *ent*-5.

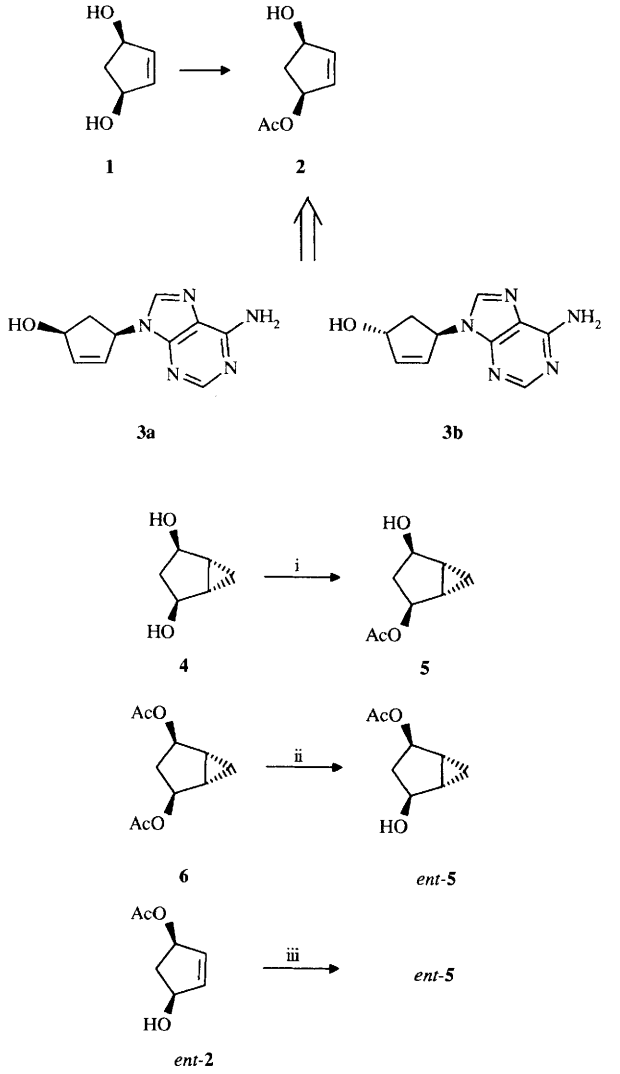
Carbocyclic nucleoside analogues, particularly in their optically active form, are of increasing interest in organic synthesis due to their biological properties,[1,2] particularly as potential antiviral or antineoplastic agents and inhibitors of several enzymes. Carbocyclic nucleosides are hydrolytically and enzymatically more stable than their natural parent compounds.

The use of biotransformations for the synthesis of enantiomerically pure compounds has been established as an important tool in organic synthesis during the last decade.[3] Among the biocatalysts used in organic synthesis, lipases have been employed most frequently because they are easy to handle, available from many sources and accept a broad range of substrates.[4] Enantiomerically pure intermediates for the synthesis of optically active carbocyclic nucleoside analogues have been prepared using different approaches to asymmetric synthesis including biocatalytic processes. Particularly, the application of lipase-catalysed kinetic resolutions or asymmetrizations of suitable building blocks has received increasing attention at present.[5] We very recently reported on the stereocontrolled synthesis of enantiomerically pure carbocyclic 2′,3′-dideoxy-2′,3′-didehydro-5′-noradenosines such as **3a** and **3b** as well as their corresponding enantiomers *via* the monoacetate **2** based on the lipase-catalysed asymmetrization of the *meso*-diol **1**. In our enantiodivergent approach we could demonstrate the synthesis of the four possible enantio- and diastereo-isomers starting from one common enantiomerically pure building block.[6]

In 1994 five papers reported on or envisaged the synthesis of carbocyclic nucleosides in which the sugar moiety of nucleosides was replaced by the bicyclo[3.1.0]hexyl residue.[7] In continuation of our recent work we now wish to report on the synthesis of enantiomerically pure bicyclo[3.1.0]hexyl adenines based on the lipase-catalysed asymmetrization of the bicyclic *meso*-diol **4** and the corresponding diacetate **6** (Scheme 1).

Results and discussion

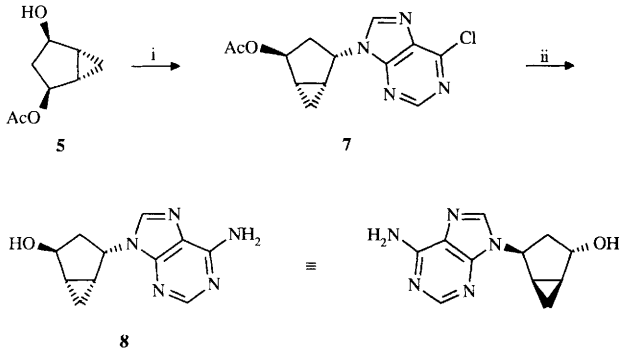
The target compounds **8** and *ent*-**8**, carbocyclic nucleoside analogues with *trans*-configuration of the adenine residue and the hydroxy group, were of interest as substrates to investigate the structure and properties of an allosteric inhibitory site of adenylyl cyclase.[8] The lipase-catalysed enantioselective trans-



Scheme 1 *Reagents and conditions:* i, vinyl acetate, pancreatin, THF, NEt_3, room temp., 32 h (94%, ee >99%) (lit.)[6]; ii, lipase SP 525, phosphate buffer pH 7, 35 °C, 20 h (70%, ee >99%); iii, CH_2N_2, $PdCl_2(PhCN)_2$, THF, CH_2Cl_2, 0 °C (80%)

esterification of the diol **4** with vinyl acetate in THF–triethylamine in the presence of pancreatin or lipase PS yielded the (*S*)-monoacetate **5**[9] in high chemical yield and in almost enantiomerically pure form. Although the corresponding enantiomer *ent*-**5** had not been available previously, the enantioselective hydrolysis of the *meso*-diacetate **6**[9] should give access to *ent*-**5** because lipases show the same stereopreference under conditions of transesterification and hydrolysis.[3,4] Testing several lipases we found that lipase SP 525 from Novo was the enzyme of choice. The diacetate **6** was hydrolysed at pH 7 to furnish the chiral monoacetate *ent*-**5** in 70% yield with >99% enantiomeric excess (ee). Surprisingly, pancreatin or lipase PS, which were the enzymes of choice in the transesterification of the diol **4** with vinyl acetate, were not able to catalyse the hydrolysis of the diacetate **6** to any great extent. Alternatively, *ent*-**5** was prepared by cyclopropanation of the enantiomerically pure monoacetate *ent*-**2** with diazomethane in the presence of $PdCl_2(PhCN)_2$ (Scheme 1).[9]

Reaction of the enantiomerically pure monoacetate **5** with the preformed Mitsunobu[10] reagent prepared by addition of diethyl azodicarboxylate (DEAD) to a suspension of 6-chloropurine and triphenylphosphine (PPh_3) in THF gave the *trans*-configurated chloropurine derivative **7** (46%) with inversion of configuration at the reacting (*R*)-hydroxy group of **5**. Subsequent ammonolysis of the purine derivative **7** on treatment with a solution of ammonia in MeOH at 100 °C in a sealed bomb yielded the enantiomerically pure adenine derivative **8** (93%) (Scheme 2). By an enantiodivergent approach, the monoacetate

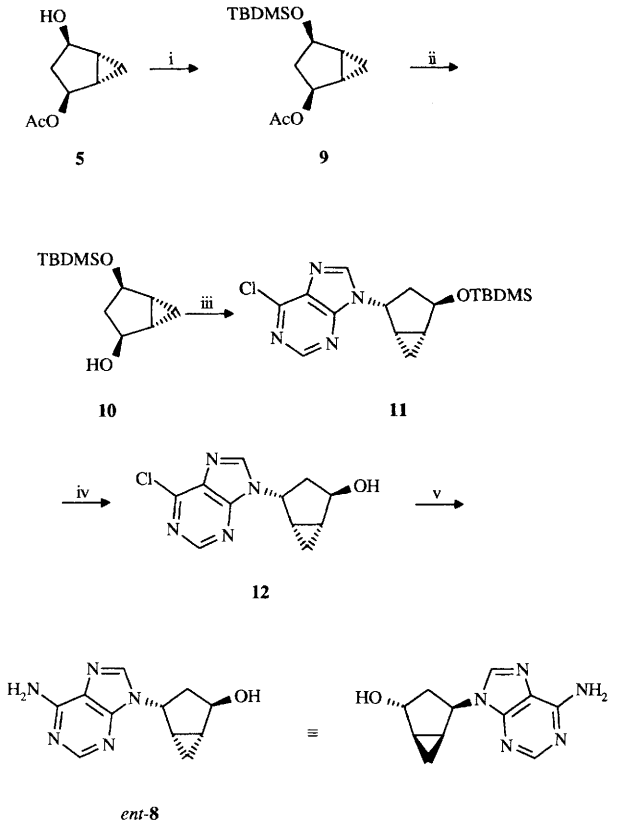


Scheme 2 *Reagents and conditions:* i, 6-Chloropurine, DEAD, PPh_3, THF, room temp., 20 h (46%); ii, NH_3, MeOH, 100 °C, 3 h (sealed bomb), (93%)

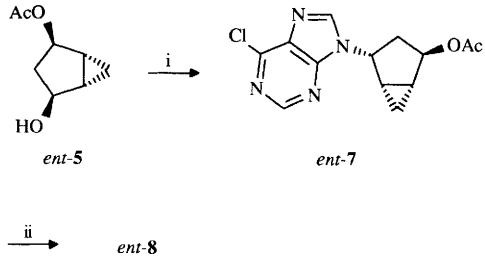
5 was also utilised to prepare the corresponding enantiomeric nucleoside analogue *ent*-**8**. Thus, the (*R*)-hydroxy group of **5** was protected by silylation with *tert*-butyldimethylsilyl chloride to give the silyl ether **9** and then the (*S*)-hydroxy group of compound **9** was deprotected by reaction with MeOH in the presence of the strong basic ion-exchange resin Wofatit SBW to yield the silyloxy alcohol **10**. Reaction of the silyloxy alcohol **10** with 6-chloropurine under Mitsunobu conditions afforded the chloropurine derivative **11** which could not be separated from diethyl hydrazodicarboxylate, the reaction product of DEAD, by chromatography. Therefore, crude **11** was desilylated with tetrabutylammonium fluoride (TBAF) to give the alcohol **12** in 25% yield (from **10**). Ammonolysis of the alcohol **12** with ammonia in methanol in a sealed bomb finally yielded the adenine derivative *ent*-**8** (Scheme 3).

In order to shorten the synthetic scheme and to improve the overall chemical yield of the adenine derivative *ent*-**8**, another synthetic pathway was performed. Starting from the enantiomerically pure monoacetate *ent*-**5**, the adenine derivative *ent*-**8** was prepared in two steps in 40% overall yield (Scheme 4) using the Mitsunobu reaction with 6-chloropurine and subsequent ammonolysis as described for its corresponding enantiomer **8**.

The analytical data of both enantiomeric nucleoside analogues **8** and *ent*-**8**, except for their specific rotation values, were identical.



Scheme 3 *Reagents and conditions:* i, Bu^tMe_2SiCl, imidazole, DMF, room temp., 20 h, (99%); ii, ion-exchange resin Wofatit SBW (OH^-), MeOH, room temp., 35 h, (88%); iii, 6-chloropurine, DEAD, PPh_3, THF, room temp., 2 h; iv, TBAF, THF, room temp., 2 h, (25% from **10**); v, NH_3, MeOH, 100 °C, 3 h (sealed bomb), (93%)



Scheme 4 *Reagents and conditions:* i, 6-Chloropurine, DEAD, PPh_3, THF, room temp., 20 h, (42%); ii, NH_3, MeOH, 100 °C, 3 h (sealed bomb), (95%)

Experimental

All reactions were monitored by TLC on glass plates coated with a 0.25 mm layer of silica gel. Compounds were visualized with a 3.5% solution of molybdatophosphoric acid in ethanol and/or by UV light. Flash chromatography was performed with silica gel 60 (0.040–0.063 mm). ^1H NMR spectra were recorded in $CDCl_3$ at 300 MHz on a Varian Gemini 300 spectrometer. ^{13}C NMR spectra were obtained at 75 MHz on the same spectrometer. *J* Values are given in Hz. EI mass spectra were measured at 70 eV on the GC/MS-Datensystem HP 5985 B. FAB mass spectra were recorded on the Autospec VG. UV spectra were recorded on a Shimadzu UV-2102 PC spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}.

(1*R*,2*R*,4*S*,5*S*)-(+)-4-Hydroxybicyclo[3.1.0]hexan-2-yl acetate *ent*-5 from 6

A solution of the diacetate **6**[9] (1.50 g, 7.5 mmol) in acetonitrile (5 cm^3) was added to Sörensen phosphate buffer pH 7 in water

(20 cm^3). This solution was treated with lipase SP 525 (0.20 g) and stirred at 35 °C for 20 h, during which time aq. NaOH (1 mol dm^{-3}; 8 cm^3, 8.0 mmol) was added to maintain the pH at 7. The solution was filtered through Celite and the filtrate was extracted three times with ethyl acetate (3 × 50 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to afford a residue, which was purified by flash chromatography on silica gel (100 g) with hexane–ethyl acetate (1:1) as eluent to give ***ent*-5** (0.815 g, 70%) as a colourless oil; $[\alpha]_D^{20}$ +17.1 (*c* 1.0 in $CHCl_3$) [lit.,[9] −16.0 (*c* 1.0 in $CHCl_3$ for the corresponding enantiomer)]; δ_H(300 MHz, $CDCl_3$) −0.10 (1 H, ddd, *J* 10, 6, 4), 0.54 (1 H, ddd, *J* 15, 8.5, 6), 1.62 (2 H, dd, *J* 8.5, 4), 1.69 (2 H, m), 1.93 (1 H, d, *J* 9), 2.01 (3 H, s), 4.13 (1 H, d, *J* 9) and 5.12 (1 H, m). The other analytical data were identical with those reported for the corresponding enantiomer.[9] The ee was determined by HPLC on Chiralpak AD (25 cm) with hexane–Pr^{i}OH (8:2) as eluent and found to be >99%.

Preparation of *ent*-5 from *ent*-2

A solution of enantiomerically pure monoacetate *ent*-**2** (1.10 g, 7 mmol) in tetrahydrofuran–dichloromethane (1:1, 16 cm^3) was treated with $PdCl_2(PhCN)_2$ (0.050 g) and an ethanol-free solution of diazomethane in diethyl ether at 0 °C. (Diazomethane was prepared from Diazald® in water–diethylene glycol monoethyl ether–diethyl ether.) The excess of diazomethane was destroyed by dropwise addition of glacial acetic acid to the reaction mixture, which was then filtered through a pad of Celite. The filter cake was washed with diethyl ether (3 × 20 cm^3) and the combined filtrates were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (100 g) with hexane–ethyl acetate (1:1) and subsequently distilled (Kugelrohr, 125 °C/1 Pa) to furnish the title compound (0.873 g, 80%); $[\alpha]_D^{20}$ +17.6 (*c* 1.0 in $CHCl_3$).

(1*S*,2*S*,4*S*,5*R*)-(−)-4-(6-Chloropurin-9-yl)bicyclo[3.1.0]hexan-2-yl acetate 7

A suspension of PPh_3 (2.85 g, 10.9 mmol) and 6-chloropurine (1.68 g, 10.9 mmol) in THF (50 cm^3) was treated at room temp. with DEAD (1.90 g, 10.9 mmol) and stirred for 1 h. A solution of the monoacetate **5**[9] (1.00 g, 6.4 mmol) in THF (5 cm^3) was added and the mixture was stirred at room temp. overnight. After evaporation of the mixture under reduced pressure, purification by flash chromatography on silica gel (150 g) with hexane–ethyl acetate (2:3) gave the title compound (0.860 g, 46%), mp 148–150 °C (from *tert*-butyl methyl ether–hexane) (Found: C, 53.3; H, 4.5; N, 19.15. $C_{13}H_{13}ClN_4O_2$ requires C, 53.35; H, 4.5; N, 19.15%); $[\alpha]_D^{20}$ −73.4 (*c* 1.0 in $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 0.84 (1 H, ddd, *J* 10, 6, 4), 0.99 (1 H, dd, *J* 14.5, 8), 1.76–1.89 (2 H, m), 2.05 (1 H, m), 2.14 (3 H, s), 2.59 (1 H, dd, *J* 15, 8), 5.34 (1 H, d, *J* 5.5), 5.45 (1 H, ddd, *J* 10, 8, 4.5), 8.37 (1 H, s) and 8.75 (1 H, s); δ_C(75 MHz, $CDCl_3$) 6.42, 18.98, 21.29, 21.81, 33.35, 56.09, 75.52, 132.13, 143.30, 151.08, 151.73, 152.07 and 170.49; *m*/*z* 292 (M^+), 233 (100%), 155, 119 and 79.

(1*S*,2*S*,4*S*,5*R*)-(−)-4-(6-Aminopurin-9-yl)bicyclo[3.1.0]hexan-2-ol 8

A solution of **7** (0.526 g, 2.1 mmol) in methanol saturated with NH_3 (40 cm^3) was heated at 100 °C for 3 h in a sealed steel bomb. After the mixture was evaporated under reduced pressure, the residue was purified by flash chromatography on silica gel with ethyl acetate–MeOH (5:2) to afford **8** (0.450 g, 93%), mp 231–232 °C (MeOH) (Found: C, 56.85; H, 5.6; N, 30.4. $C_{11}H_{13}PN_5O$ requires C, 57.15; H, 5.65; N, 30.3%); $[\alpha]_D^{20}$ −100.2 (*c* 1.0 in MeOH); λ_{max}(EtOH)/nm 210 (ε/dm^3 mol^{-1} dm^{-1} 15 500) and 261 (13 200); δ_H[300 MHz, $(CD_3)_2SO$] 0.57 (1 H, ddd, *J* 8, 6.5, 6.5), 0.81 (1 H, ddd, *J* 8, 4, 4), 1.50 (1 H, m), 1.76–1.87 (2 H, superimposed), 2.03 (1 H, dd, *J* 14, 8), 4.18 (1 H, dd, *J* 4, 4, after addition of D_2O d), 4.95 (1 H, d, *J* 4, exchangeable with D_2O), 5.27 (1 H, ddd, *J* 18.5, 9, 4.5), 7.18 (2 H, s), 8.12 (1 H, s) and 8.25 (1 H, s); δ_C[75 MHz, $(CD_3)_2SO$] 5.36, 19.26, 23.99, 35.10, 54.47, 70.98, 119.02, 138.83, 149.72, 152.15 and 155.84; *m*/*z* 231 (M^+), 214 (100%), 136 (100%), 135 (100%) and 108.

(1*S*,2*S*,4*R*,5*R*)-(+)-4-*tert*-Butyldimethylsilyloxybicyclo[3.1.0]-hexan-2-yl acetate 9

A solution of the monoacetate **5** (2.00 g, 12.8 mmol) in DMF (13 cm^3) was treated with imidazole (3.54 g, 52 mmol) and *tert*-butyldimethylsilyl chloride (3.95 g, 26 mmol) and stirred for 3 h at room temp. The mixture was diluted with hexane–diethyl ether (1:1) and washed with water (3 ×). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give a residue, which was distilled to yield **9** (3.410 g, 99%), bp 125 °C/1 Pa (Kugelrohr) (Found: C, 62.05; H, 10.05. $C_{14}H_{26}O_3Si$ requires C, 62.15; H, 9.7%); $[\alpha]_D^{20}$ +15.4 (*c* 1.0 in $CHCl_3$); δ_H(300 MHz, $CHCl_3$) −0.17 (1 H, ddd, *J* 6, 4, 4), 0.04 (3 H, s), 0.07 (3 H, s), 0.54 (1 H, ddd, *J* 6, 4, 2.5), 0.89 (9 H, s), 1.56–1.69 (4 H, superimposed), 2.03 (3 H, s), 4.22 (1 H, dd, *J* 2.5, 2.5) and 5.06 (1 H, dd, *J* 3, 3); δ_C(75 MHz, $CDCl_3$) −4.69, −4.61, 5.94, 18.05, 21.40, 21.59, 25.28, 25.82, 39.22, 73.51, 77.42 and 171.03; *m*/*z* 213 (M^+ − Bu^t), 159, 151, 135, 117 (100%) and 75.

(1*S*,2*S*,4*R*,5*R*)-(+)-4-*tert*-Butyldimethylsilyloxybicyclo[3.1.0]-hexan-2-ol 10

A solution of the silyloxy acetate **9** (3.30 g, 12.2 mmol) in MeOH (50 cm^3) was treated with basic ion-exchange resin Wofatit SBW (OH^-) (5 g) and stirred for 35 h at room temp. The ion-exchange resin was filtered off and the filtrate was evaporated under reduced pressure. The residue was distilled to give the title compound **10** (2.450 g, 88%), bp 130 °C/1 Pa (Kugelrohr) (Found: C, 62.8; H, 10.7. $C_{12}H_{24}O_2Si$ requires C, 63.1; H, 10.6%); $[\alpha]_D^{20}$ +5.2 (*c* 1.2 in $CHCl_3$); δ_H(300 MHz, $CDCl_3$) −0.22 (1 H, ddd, *J* 6, 4, 4), 0.01 (3 H, s), 0.03 (3 H, s), 0.37 (1 H, ddd, *J* 6, 4, 3), 0.81 (9 H, s), 1.35–1.61 (4 H, superimposed), 2.47 (1 H, d, *J* 11.5, exchangeable with D_2O), 4.01 (1 H, d, *J* 11.5) and 4.18 (1 H, d, *J* 4); δ_C −4.96, −4.81, 6.90, 17.88, 23.68, 23.98, 25.74, 39.92, 74.08 and 74.46; *m*/*z* (FAB) 229 (MH^+), 211 (100%) and 171.

(1*R*,2*R*,4*R*,5*S*)-(+)-4-(6-Chloropurin-9-yl)bicyclo[3.1.0]hexan-2-ol 12

A suspension of PPh_3 (1.96 g, 7.5 mmol) and 6-chloropurine (1.16 g, 7.5 mmol) in THF (50 cm^3) was treated at room temp. with DEAD (1.30 g, 7.5 mmol) and stirred for 1 h. To the resulting solution a solution of the silyloxy alcohol **10** (1.00 g, 4.4 mmol) in THF (10 cm^3) was added and the mixture was stirred at room temp. for 2 h. After evaporation of the mixture under reduced pressure, the residue was purified by flash chromatography on silica gel (100 g) with *tert*-butyl methyl ether–hexane (1:1) to give crude **11** (0.82 g). A solution of the crude silyl ether **11** in THF (20 cm^3) was treated with TBAF (1.90 g, 6 mmol) and stirred at room temp. for 2 h. The mixture was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (50 g) with ethyl acetate to yield **12** (0.272 g, 25%), mp 120–122 °C (from acetone–hexane) (Found: C, 52.6; H, 4.4; N, 22.5. $C_{11}H_{11}ClN_4O$ requires C, 52.7; H, 4.4; N, 22.35%); $[\alpha]_D^{20}$ +70.7 (*c* 1.0 in $CHCl_3$); δ_H[300 MHz, $(CD_3)_2SO$] 0.76 (1 H, ddd, *J* 8, 4, 4), 0.91 (1 H, dd, *J* 14, 8), 1.66–1.81 (2 H, superimposed), 1.90–2.07 (2 H, superimposed), 2.50 (1 H, ddd, *J* 14, 5, 7), 4.52 (1 H, d, *J* 4), 5.50 (1 H, ddd, *J* 10, 8, 4), 8.37 (1 H, s) and 8.73 (1 H, s); δ_C[75 MHz, $(CD_3)_2SO$] 6.63, 18.71, 24.60, 36.27, 56.27, 72.79, 132.10, 143.53, 150.93, 151.71 and 152.15; *m*/*z* 250 (M^+), 235, 233 (100%), 181, 157, 155, 154 and 119.

Preparation of (1*R*,2*R*,4*R*,5*S*)-(+)-4-(6-aminopurin-9-yl)-bicyclo[3.1.0]hexan-2-ol *ent*-8 from 12

Compound 12 (0.263 g, 1.05 mmol), on treatment as described above for **8**, yielded the adenine derivative *ent*-**8** (0.226 g, 93%),

mp 230–231 °C (from MeOH); $[\alpha]_D^{20}$ +100.2 (*c* 1.0 in MeOH); λ_{max}(EtOH)/nm 210 (ε/dm^3 mol^{-1} dm^{-1} 16 200) and 261 (13 500). The NMR data were identical with those of **8**.

(1*R*,2*R*,4*R*,5*S*)-(+)-4-(6-Chloropurin-9-yl)bicyclo[3.1.0]hexan-2-yl acetate *ent*-7

Compound *ent*-**5** (0.852 g, 5.45 mmol), on treatment as described above for **7** yielded *ent*-**7** (0.538 g, 42%), mp 145–148 °C (from *tert*-butyl methyl ether–hexane); $[\alpha]_D^{20}$ +84.7 (*c* 1.0 in $CHCl_3$). The other analytical data were identical with those for **7**.

Preparation of (1*R*,2*R*,4*R*,5*S*)-(+)-4-(6-aminopurin-9-yl)-bicyclo[3.1.0]hexan-2-ol *ent*-8 from *ent*-7

Compound *ent*-**7** (0.420 g, 1.4 mmol), on treatment as described for **8**, gave *ent*-**8** (0.307 g, 95%); $[\alpha]_D^{20}$ +100.6 (*c* 1.0 in MeOH). The other analytical data were identical with those for *ent*-**8** prepared from **12**.

Acknowledgements

This work was supported by the Deutsche Akademie der Naturforscher Leopoldina, Halle and the Fonds der Chemischen Industrie. We are grateful to Novo Nordisk A/S for a generous gift of lipase SP 525 and to Dr Annamarie Kunath for the determination of the ee of *ent*-**5**.

References

1 A. D. Borthwick and K. Biggadike, *Tetrahedron*, 1992, **48**, 571.
2 L. Agrofolio, E. Suhas, A. Farese, R. Condom, S. R. Challand, R. A. Earl and R. Guedj, *Tetrahedron*, 1994, **50**, 10 611.
3 E. Santaniello, P. Ferraboschi, P. Grisenti and A. Manzocchi, *Chem. Rev.*, 1992, **92**, 1071; L. Poppe and L. Novák, *Selective Biocatalysis*, VCH, Weinheim, 1992; S. M. Roberts, K. Wiggins and G. Casy (eds.), *Preparative Biotransformations*, Wiley, Chichester, 1992; K. Faber, *Biotransformations in Organic Chemistry*, 2nd edn., Springer-Verlag, Heidelberg, *1995*; eds. K. Drauz and H. Waldmann *Enzyme Catalysis in Organic Synthesis*, VCH, Weinheim, 1995.
4 W. Boland, C. Fröβl and M. Lorenz, *Synthesis*, 1991, 1049; K. Faber and S. Riva, *Synthesis*, 1992, 895; E. Santaniello, P. Ferraboschi and P. Grisenti, *Enzyme Microb. Technol.*, 1993, **15**, 367; F. Theil, *Catalysis Today*, 1994, **22**, 517; F. Theil, *Chem. Rev.*, 1995, **95**, 2203.
5 I. C. Cotterill, P. B. Fox, A. F. Drake, D. M. Le Grand, E. J. Hutchinson, R. Latouche, R. B. Pettman, R. J. Pryce, S. M. Roberts, G. Ryback, V. Sik and J. O. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1991, 3071; D. M. Le Grand and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1751; M. Tanaka, M. Yoshioka and K. Sakai, *J. Chem. Soc., Chem. Commun.*, 1992, 1454; S. M. Siddiqi, X. Chen, S. W. Schneller, S. Ikeda, R. Snoeck, G. Andrei, J. Balzarini and E. J. De Clercq, *J. Med. Chem.*, 1994, **37**, 551; H. Baumgartner, M. Bodenteich and H. Griengl, *Tetrahedron Lett.*, 1988, **29**, 5745; V. Merlo, S. M. Roberts, R. Storer and R. C. Bethell, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1477.
6 N. Dyatkina, B. Costisella, F. Theil and M. von Janta-Lipinski, *Tetrahedron Lett.*, 1994, **35**, 1961; N. B. Dyatkina, F. Theil and M. von Janta-Lipinski, *Tetrahedron*, 1995, **51**, 761.
7 H. Gooding, S. M. Roberts and R. Storer, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1891; K.-H. Altmann, R. Kesselring, E. Francotte and G. Rihs, *Tetrahedron Lett.*, 1994, **35**, 2331; K.-H. Altmann, R. Imwinkelried, R. Kesselring and G. Rihs, *Tetrahedron Lett.*, 1994, **35**, 7625; H. S. Chang, S. C. Bergmeier, J. A. Frick, A. Bathe, H. Rapoport, *J. Org. Chem.*, 1994, **59**, 5336; J. B. Rodriguez, V. E. Marquez, M. C. Nicklaus, H. Mitsuya and J. J. Barchi, Jr., *J. Med. Chem.*, 1994, **37**, 3389.
8 R. A. Johnson, S.-M. H. Yeung, M. Bushfield, D. Stübner and I. Shoshani, in *The Role of Adenosine and Adenine Nucleotides in the Biological Systems*, eds. S. Imai and M. Nakazawa, Elsevier, Amsterdam, 1990, p. 43.
9 F. Theil, H. Schick, G. Winter and G. Reck, *Tetrahedron*, 1991, **47**, 7569.
10 D. L. Hughes, *Organic Reactions*, Wiley, New York, 1992, vol. 42, p. 335.

Paper 5/05160F
Received 2*nd August* 1995
Accepted 15*th September* 1995