Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 1870

www.rsc.org/obc

PAPER

Enantioselective synthesis of the carbocyclic nucleoside (−)-abacavir†

Grant A. Boyle,[a] Christopher D. Edlin,[a] Yongfeng Li,[b] Dennis C. Liotta,[b] Garreth L. Morgans*[a] and Chitalu C. Musonda[a]

Received 21st October 2011, Accepted 5th December 2011
DOI: 10.1039/c2ob06775g

An enantiopure β-lactam with a suitably disposed electron withdrawing group on nitrogen, participated in a π-allylpalladium mediated reaction with 2,6-dichloropurine tetrabutylammonium salt to afford an advanced *cis*-1,4-substituted cyclopentenoid with both high regio- and stereoselectivity. This advanced intermediate was successfully manipulated to the total synthesis of (−)-Abacavir.

Introduction

Acquired immune deficiency syndrome (AIDS) has rapidly become one of the major causes of death in the world.[1] It is estimated that over 60 million people have been infected with the human immunodeficiency virus (HIV), which is the causative agent of AIDS. Since the discovery of HIV in the 1980s, remarkable progress has been made in the development of novel antiviral drugs.[2] Entecavir **1**, Carbovir **2a**, and Abacavir **2b** are some well known examples of carbocyclic nucleosides that have arisen from this extraordinary effort (Fig. 1). Carbocyclic nucleosides have been the subject of extensive investigation into their potential uses as antiviral agents for example as therapeutic agents to address hepatitis and herpes virus and HIV.[3,4] The antiviral properties exhibited by these carbocyclic nucleosides are due, in part, to their metabolic and chemical stability towards phosphorylases and phosphotransferases.[5] These compounds are structural analogues of endogenous nucleosides in which the oxygen atom in the furanose ring has been replaced by an isoteric methylene or ethylene group (*vida infra*).

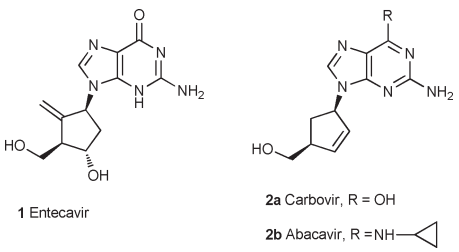


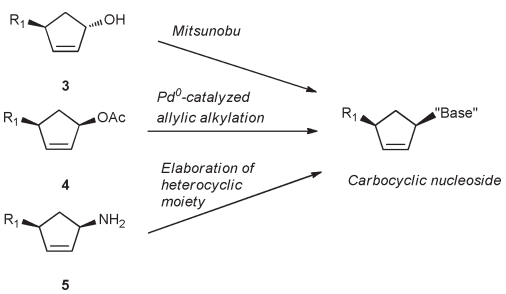
Fig. 1 Some examples of relevant carbocyclic nucleosides.

The construction of carbocyclic nucleosides, more specifically the putting together of a heterocyclic base with a 1,4-substituted carbocyclic sugar analogue is generally carried out in one of three ways. Firstly, by direct substitution of the hydroxyl group by a Mitsunobu coupling reaction on the general carbocyclic ring **3** with a heterocyclic base (Scheme 1).[6] These reactions result in a net inversion of hydroxyl stereochemistry.

A second approach is to use Trost palladium catalysed allylic alkylation chemistry of activated esters such as **4**. This protocol follows a double displacement/inversion and a resultant net retention of configuration. This is a particularly useful method for the convergent synthesis of carbocyclic nucleosides and can be achieved directly from a chiral sugar or from desymmetrization of a *meso* intermediate, amongst others.[7–11]

A final general approach to this class of molecules follows the synthesis of the carbocyclic nucleoside by linear construction of the heterocyclic fragment from an amino group of the cyclopentyl moiety **5**.[12–14] Also, Jung reported the use of an activated amine as a leaving group in a palladium catalysed substitution reaction.[15]

The utilization of functionalized cyclopentene as the source of the sugar fragment is a common approach to the synthesis of carbocyclic nucleosides, particularly in conjunction with



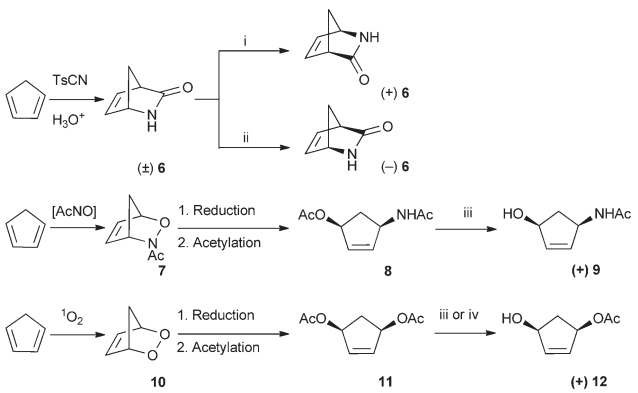
Scheme 1 General approaches to carbocyclic nucleosides.

[a]*iThemba Pharmaceuticals PTY (Ltd.), PO BOX 21Modderfontein, 1645 Gauteng, South Africa. E-mail: gmorgans@ithembapharma.com; Fax: +27 (0)11 372-4518; Tel: +27 (0)11 372-4500*
[b]*Emory University, Department of Chemistry, 1521 Dickey Dr Emerson 403, Atlanta, GA, USA, 30322. Tel: 404-727-8130*

†Electronic supplementary information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/c2ob06775g

asymmetric synthesis, chiral pool and enzymatic resolution approaches.[16,17]

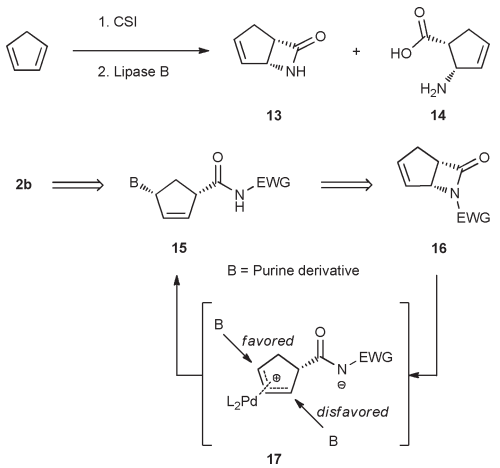
Among these, the enantioselective construction of the cyclopentenoids has involved two discreet stages, an initial [4 + 2] cycloaddition reaction of cyclopentadiene with either C═N, N═O and O_2 dienophiles, followed by enzymatic hydrolysis. An example of a C═N dienophile-enzymatic hydrolysis approach has made use of 2-azabicyclo[2.2.1]hept-5-en-3-one (±) **6**, which is readily prepared from the [4 + 2] cycloaddition between cyclopentadiene and tosylcyanide, followed by aqueous hydrolysis.[18] The resultant lactam can be enzymatically resolved to either enantiomer **6** (Scheme 2).[19] Similarly, an N═O dienophile-enzymatic hydrolysis approach has made use of 4-acetamidocyclopent-2-en-1-yl acetate **8** which is readily synthesized from the [4 + 2] cycloaddition of cyclopentadiene and nitrosocarbamate, generated *in situ*, to afford adduct **7**.[20] Compound **8** is conveniently resolved *via* an enzymatic hydrolysis that utilizes electric eel acetyl cholinesterase to afford enantiomerically pure **9**. Finally, di-acetate **11** can formally be regarded as the reduction and acetylation product of the [4 + 2] cycloaddition product **10** of cyclopentadiene and singlet oxygen.[21] The *bis*-acetate **11** can be resolved by enantioselective enzymatic hydrolysis with electric eel acetyl cholinesterase[22] or with porcine pancreas lipase to afford enantiomerically pure **12**.[23]



Resolving agent: (i) *Pseudomonas flourescens* (ENZ A22) (ii) *Aureobacterium* (ENZ A25) (iii) Electric eel acetyl cholinesterase (EEAC) (iv) Porcine pancreas lipase (PPL)

Scheme 2 Some relevant [4 + 2]–enzymatic hydrolysis approaches to chiral sugar building blocks.

We hypothesized that carbocyclic nucleosides could be prepared using a complementary approach involving a [2 + 2] cycloaddition of cyclopentadiene with chlorososulfonyl isocyanate (CSI), followed by enzymatic resolution and nucleobase addition by way of a π-allylpalladium intermediate. Specifically, racemic lactam **13**, readily prepared from cyclopentadiene and CSI after reductive workup, can be efficiently resolved by enzyme catalyzed hydrolysis (Scheme 3).[24] We envisioned that a suitably activated derivative **16** might be an attractive precursor of a π- allylpalladium intermediate **17** that could be captured directly by an intact nucleobase. Based on the chemistry developed by Trost, we thought it likely that the reaction of the nucleobase with a π-allylpalladium intermediate would be both regioselective and stereoselective (see Scheme 3). The formation



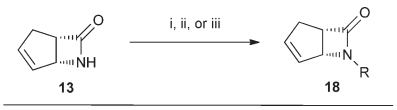
Scheme 3 Proposed use of π-allylpalladium chemistry for the synthesis of advanced intermediate **15** from lactam **16**.

of the π-allylpalladium complex would be facilitated by the relief of the four membered ring strain[25] and the formation of the requisite *cis*-1,4-substituted cyclopentenoid moiety would proceed with a net retention of configuration as a consequence of the well established double inversion that is operative in these reactions. Finally, further manipulation of intermediate **15** might then result in the formation of the carbocyclic nucleoside Abacavir **2b**.

While there have been many reported methods for the synthesis of various substituted carbocyclic nucleosides, particularly Abacavir,[26–35] overall yields of the reported synthetic routes are generally low and the synthetic schemes often require extensive manipulations of the [4 + 2] cycloadduct being utilized. Because Abacavir has proven to be an important component of many HIV combination regimens, particularly paediatrics, there is a need for improved methods for producing Abacavir that require fewer synthetic steps and higher overall yields.

Results and discussion

With this in mind, the starting material for the synthesis was the known β-lactam **13**, which was prepared in two steps and in high enantiomeric purity.[24] To facilitate the novel π-allylpalladium complex formation an anion stabilizing electron withdrawing group needed to be installed onto the nitrogen of lactam **13**, and cheap readily available sulfonyl chlorides, sulfonyl anhydrides and carbamates were initially screened (Scheme 4). An initial screen of alkyl and aromatic sulfonylchlorides (entries 1–3) proved disappointing as complex reaction mixtures were obtained. However after further optimization, treatment of the resolved lactam **13** with *n*-butyllithium, followed by quenching with *p*-toluenesulfonyl chloride gave the desired product **18d** in 60% yield (entry 4) after conventional workup. Initially, these compounds exhibited poor shelf stability. However, subsequent studies showed that the compounds were indefinitely stable as long as they were pure, dry and free of residual acid. Subsequently, a more reliable process was developed, *i.e.*, lactam **13** was allowed to react with 4-methylbenzenesulfonic anhydride in the presence of triethylamine and catalytic DMAP to afford **18d**



Entry	R	Yield %
1	**18a**, CH_3SO_2	0
2	**18b**, 4-$CNC_6H_4SO_2$	0
3	**18c**, 4-$ClC_6H_4SO_2$	Trace
4	**18d**, 4-$CH_3C_6H_4SO_2$	60
5*	**18d**, 4-$CH_3C_6H_4SO_2$	75-81
6	**18e**, Boc	71

* See text for discussion

Reagents and *conditions*: (i) For entries **1**–**4**: *n*-BuLi, THF, –78 °C, 1 h, then sulfonyl chloride, –78 °C to RT (ii) For entry **5**: DCM, Et_3N, DMAP (cat.), then 4-methylbenzenesulfonic anhydride, RT, 24 h (iii) For entry **6**: $(Boc)_2O$, THF, 0 °C to RT, 48 h

Scheme 4 Summary of attempts at installing an electron withdrawing group onto lactam **13**.

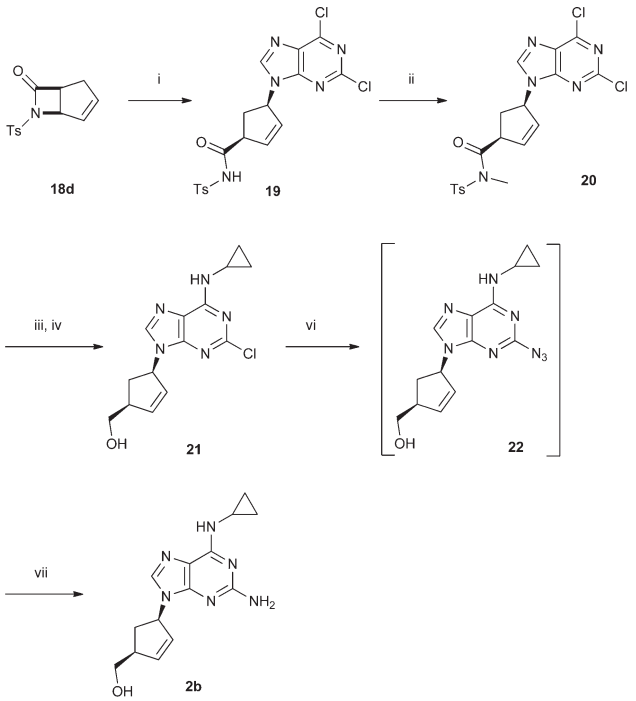
in reproducible yields of 75–81% (entry 6). Presumably, this increase in yield observed when sulfonyl anhydrides are used in place of the corresponding sulfonyl chlorides is a consequence of the relatively low reactivity of the conjugate base, *p*-toluenesulfonate, relative to chloride, as well as the absence of a Lewis acid. Finally, reaction with di-*tert*-butyl dicarbonate afforded the known compound **18e**[36] in 71% yield (entry 7).

With the *N*-sulfonylamido and Boc derivatives in hand, we were in a position to attempt the key reaction in our sequence, *i.e.*, the formation of a nucleoside intermediate through the direct introduction of 2,6-dichloropurine[37] tetrabutylammonium salt by way of a π-allylpalladium complex. Reaction of **18d** with 2,6-dichloropurine tetrabutylammonium salt using either $Pd(OAc)_2$ or $Pd_2(dba)_3$ in the presence of $P(i\text{-}OPr)_3$ as the phosphine ligand in tetrahydrofuran at ambient temperature afforded **19** in 75% yield (Scheme 5). Moreover, analysis of the crude reaction sample of **19** by ^1H NMR indicated *ca.* 7% of the *N*7 regioisomer, attesting to the high regioselectivity of the reaction protocol. Also, reaction of the 2,6-dichloropurine salt with **18e**, using identical conditions to those described above, failed to give the desired product, suggesting that the Boc group was not sufficiently electron-withdrawing to facilitate the ring-opening reaction.

Next, the transformation of **19** to **21** was carried out. That is, *N*-methylation of **19** which can be achieved using methyl iodide (74%), dimethylsulfate (70%) or under Mitsunobu conditions (94%) to afford **20** in good to excellent yields. Smooth reductive amido bond cleavage of **20** with sodium borohydride followed by heterocyclic amination with cyclopropylamine in refluxing ethanol finally afforded **21** in 63% over the two steps.

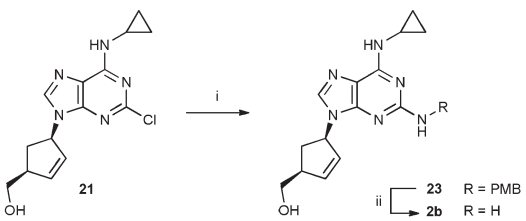
The synthesis of Abacavir **2b** was completed by reaction of **21** with hydrazine hydrate in warm methanol/water mixture followed by treatment with sodium nitrite to afford the putative intermediate **22**. The product was not characterized but immediately subjected to stannous chloride mediated reduction to afford Abacavir **2b** in 70% yield over the three steps.

Finally, a more direct approach to introduce the NH_2 functionality at the 6-position of the purine base was investigated using 4-methoxybenzylamine as an ammonia surrogate (Scheme 6). This route appeared attractive as it avoids the use of potentially explosive and toxic reagents as exhibited in the closing synthetic sequences in Scheme 5. Thus, reaction of **21** with an excess of



Reagents, *conditions and yields*: (i) 2,6-Dichloropurine tetrabutylammonium salt, $Pd_2(dba)_3$, $P(i\text{-}OPr)_3$, THF, RT, 90 min, 75% (ii) MeI, K_2CO_3, acetone, reflux, 4 h, 74%; ***or*** Dimethylsulfate, K_2CO_3, acetone, RT, 16 h, 70%; ***or*** MeOH, PPh_3, DIAD, THF, RT, 94% (iii) $NaBH_4$, iPrOH/THF, 0 °C, 1 h then RT, 2h, 86% (iv) Cyclopropylamine, EtOH, 50 °C, 5 h, 73% (v) NH_2NH_2, MeOH, 50 °C, 16 h, then (vi) $NaNO_2$, $AcOH/H_2O$ (9:1), 0 °C, 1 h, then (vii) $SnCl_2.2H_2O$, EtOH, reflux, 2 h, 70% over 3 steps.

Scheme 5 Synthesis of Abacavir **2b**.



Reagents, *conditions and yields*: (i) 4-Methoxybenzylamine (excess), DMSO, 150 °C, 16 h, 90% (ii) TFA, reflux, 72 h, 73%

Scheme 6 Use of 4-methoxybenzylamine as an ammonia surrogate.

4-methoxybenzylamine in hot DMSO afforded compound **23** in 90% isolated yield. This compound when warmed in DMSO in the presence of HCl resulted in full decomposition of starting material as assessed by TLC analysis. However, when **23** was exposed to neat TFA at 50 °C for 72 h, (−)-Abacavir **2b** was obtained in 73% yield.

In summary, an efficient enantioselective synthesis of the carbocyclic nucleoside, (−)-Abacavir **2b** has been accomplished by exploiting an enzymatic resolution sequence for the rapid asymmetric construction of the sugar fragment of the nucleoside. In addition, a direct palladium catalyzed coupling of the sugar fragment to the purine base allowed for the highly convergent assembly of the nucleoside analogue **19** which was seamlessly

converted to (−)-Abacavir **2b**. Lastly, introduction of the amine functional group at the 6-position of the purine base was approached in a more direct manner from **21** using 4-methoxybenzylamine as an ammonia surrogate. This allowed for one less step as well as avoiding potentially explosive intermediates (azide **22**) and toxic reagents ($SnCl_2$) *en route* to (−)-Abacavir **2b**.

Experimental

All the reactions dealing with air or moisture sensitive compounds were carried out in a dry reaction vessel under a positive pressure of nitrogen. Analytical thin-layer chromatography was performed on an aluminium backed plates coated with 0.25 mm 230–400 mesh silica gel containing a fluorescent indicator. Thin layer chromatography plates were visualized by exposure to ultraviolet light (254 nm) and/or by immersion in basic $KMnO_4$ followed by heating. Organic solutions were concentrated by rotary evaporation at *c.a.* 30 mmHg. Flash column chromatography was performed on Silica gel 60 (230–400 mesh, ASTM).

IR spectra were recorded as neat liquids or KBr pellets and absorptions are reported in cm^{-1}. NMR spectra were measured on a Bruker 400 MHz Avance instrument at 400 MHz for ^1H and 100 MHz for ^{13}C NMR, using tetramethylsilane as an internal reference and $CDCl_3$ or d_6-DMSO as a solvent. Chemical shift values for protons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual proton of $CDCl_3$ (δ 7.26) or residual protons of d_6-DMSO (δ 2.50). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz: chemical shifts for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of $CDCl_3$ (δ 77.0) or the carbon resonance of d_6-DMSO (δ 39.51). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet and/or multiplet resonances, br = broad), coupling constant in hertz (Hz), and signal area integration in natural numbers. High resolution mass spectra were measured using a Waters API Q-TOF Ultima instrument. Optical rotations were recorded on a Jasco DIP-370 Polarimeter at 20 °C or 25 °C.

All reagents were purchased from commercial sources unless otherwise noted.

(1*S*,5*R*)-6-Azabicyclo[3.2.0]hept-3-en-7-one 13

6-Azabicyclo[3.2.0]hept-3-en-7-one[38] (55.0 g, 504 mmol) was added to diisopropyl ether (1000 mL) and filtered through a porosity 3 glass sintered funnel to give a yellow homogeneous solution. Novozyme® 435 (53.0 g, 53 mg mL^{-1}) and distilled water (9.10 mL, 1.00 equiv.) was added. The reaction mixture was heated, without stirring, to 70 °C over 1 h and maintained at that temperature for 11 h. The reaction mixture was allowed to cool overnight and the enzyme filtered off. The enzyme was washed with diisopropyl ether (5 × 75 mL) and the combined organic fractions were evaporated to give an orange solid. The solid was recrystallized from diisopropyl ether (75 mL) to afford **13** (23.0 g, 42%) as a crystalline tan solid. $[\alpha]_D^{20}$ −42.0 (*c* 0.5 in $CHCl_3$), lit.,[36] $[\alpha]_D^{25}$ −35.0 (*c* 0.2 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$, Me_4Si) 2.40–2.50 (m, 1H), 2.65–2.75 (m, 1H), 3.75–3.85 (m, 1H), 4.5 (s, 1H), 5.90–5.95 (m, 1H), 6.00–6.05 (m, 1H), 6.4 (br s, 1H); δ_C (100 MHz, $CDCl_3$) 172.5, 136.7, 130.6, 59.1, 53.0, 30.6

(1*S*,5*R*)-6-Tosyl-6-azabicyclo[3.2.0]hept-3-en-7-one 18d

Method 1. Compound **13** (15.0 g, 137 mmol) was added to dichloromethane (160 mL) and cooled to 0 °C under nitrogen. DMAP (1.68 g, 13.8 mmol) and triethylamine (16.7 g, 165 mmol) were added and the mixture stirred for 2 min to completely dissolve the solids. 4-Methylbenzenesulfonic anhydride (55.0 g, 169 mmol) was added portion wise to the reaction mixture over 5 min. The reaction mixture went to a dark brown red colour and was allowed to warm to room temperature and stirred at ambient temperature for an additional 24 h. The reaction mixture was washed with brine (2 × 100 mL) and water (2 × 100 mL). The organic extract was dried over sodium sulfate, filtered and evaporated to afford a brown residue. The residue was dissolved into a minimum amount of dichloromethane and filtered through a silica gel pad with dichloromethane as the eluent. The washings were monitored by TLC to ensure all the product had eluted. The residue was recrystallized from ethyl acetate–hexane mixtures to afford **18d** (27.0 g, 75%) as a crystalline white solid. mp: 93–95 °C (ethyl acetate–hexane); $[\alpha]_D^{20}$ −125.3 (*c* 0.50 in $CHCl_3$); ν_{max}/cm^{-1} 3068, 2921, 1781, 1348, 119; δ_H (400 MHz, $CDCl_3$, Me_4Si) 7.86 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6.04–6.02 (m, 2H), 5.02–4.99 (m, 1H), 3.85–3.81 (m, 1H), 2.71–2.66 (m, 1H), 2.54–2.45 (m, 1H), 2.44 (s, 3H); δ_C (100 MHz, $CDCl_3$) 167.0, 145.0, 138.7, 136.4, 129.9, 128.3, 127.3, 66.0, 51.8, 31.0, 21.6; *m*/*z* 264.0651 (MH^+, $C_{13}H_{14}NO_3S$ requires 264.0694).

Method 2. A solution of **13** (2.00 g, 18.32 mmol) in dry THF (33 mL) was added drop wise to a stirred mixture of 1.6 M *n*-BuLi in hexane (19.5 mL, 31.21 mmol) in dry THF (33 mL) at −78 °C under Argon. The mixture was stirred at −78 °C for 1 h and *p*- toluenesulfonyl chloride (4.65 g, 24.40 mmol) was added. The reaction mixture was gradually warmed to ambient temperature. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography (SiO_2, hexane–ethyl acetate, 4 : 1) to give **18d** (2.90 g, 60%) as a white solid. Analytical data were identical to those reported above.

(1*S*,5*R*)-*tert*-Butyl-7-oxo-6-azabicyclo[3.2.0]hept-3-ene-6-carboxylate 18e

To a solution of **13** (1.00 g, 9.16 mmol), DMAP (0.22 g, 1.8 mmol) and Et_3N (3.80 mL, 27.3 mmol) in tetrahydrofuran (20 mL), Boc_2O (2.00 g, 9.16 mmol) was added in several portions at 0 °C. The mixture was stirred at ambient temperature over the weekend. The reaction mixture was diluted with ethyl acetate (60 mL) and washed with water (3 × 20 mL). The organic extract was dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (SiO_2, hexane–ethyl acetate, 4 : 1) to afford **18e** (1.44 g, 75%) as an orange oil. The spectral and analytical properties matched those reported in the literature.[36]

(1*S*,4*R*)-4-(2,6-Dichloro-9*H*-purin-9-yl)-*N*-tosylcyclopent-2-enecarboxamide 19

Small scale. To a stirred solution of tetrabutylammonium salt of 2,6-dichloropurine (0.67 g, 1.5 mmol) in anhydrous THF (20 mL) was added DMF (10 mL). $Pd(OAc)_2$ (34 mg, 0.15 mmol) and triisopropyl phosphite (0.21 mL, 0.91 mmol) were added and stirred under argon at ambient temperature for 1 h. A solution of **18d** (0.40 g, 1.5 mmol) in dry THF (5 mL) was added drop wise to the resultant mixture, which was then stirred for a further 2 h. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography (SiO_2, dichloromethane–methanol, 19 : 1) to give **19** (0.33 g, 49%) as a yellow solid. mp 214–215 °C (from MeOH); $[\alpha]_D^{25}$ −81.6 (*c* 0.50 in MeOH); ν_{max}/cm^{-1} 3256, 2966, 1686, 1683, 1609, 1503; δ_H (400 MHz, $CDCl_3$, Me_4Si) 12.35 (brs, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H) 6.22–6.18 (m, 1H), 6.12–6.07 (m, 1H), 5.7.–5.63 (m, 1H), 3.76–3.68 (m, 1H), 2.80–2.70 (m,1H), 2.38 (s, 3H), 2.00–2.05 (m, 1H); δ_C (100 MHz, $CDCl_3$) 171.1, 152.9, 150.8, 149.5, 146.1, 144.3, 136.2, 135.1, 130.9, 130.6, 129.5, 127.5, 59.6, 50.7, 32.8, 21.0; *m*/*z* 452.0342 (MH^+, $C_{18}H_{16}Cl_2N_5O_3S$ requires 452.0351).

Large scale preparation. 2,6-Dichloropurine (15.0 g, 79.0 mmol) was partially dissolved into tetrahydrofuran (50 mL). A freshly prepared solution of tetrabutylammonium hydroxide hydrate (Sigma-Aldrich, 63.5 g, 79.0 mmol) in deionised water (200 mL) was added to the reaction mixture. The mixture solubilised and after 2 h the solvents were evaporated. Toluene (50 mL) was added and evaporated to dryness again. This process was repeated twice more. The semi-solid residue was triturated with diethyl ether (300 mL) under rapid stirring for 3 h. The solids were filtered and dried under high vacuum to afford tetrabutylammonium 2,6-dichloropurin-9-ide (32.2 g, 94%) as a white free-flowing solid. The solid was stored in a well sealed desiccator and away from light when not in use. $Pd_2(dba)_3$ (1.74 g, 1.90 mmol) and triisopropylphosphite (2.00 mL, 7.70 mmol) were added to dry tetrahydrofuran (100 mL), degassed and purged with nitrogen 5 times, and allowed to stir for 30 min during which time the solution changed from purple to dark green. Tetrabutylammonium 2,6-dichloropurin-9-ide (16.4 g, 38.0 mmol) was added and allowed to stir until all the solids had dissolved. Finally, **18d** (10.0 g, 38.4 mmol) was added and the reaction mixture was degassed and purged with nitrogen 5 times. The reaction mixture was allowed to stir for 90 min. The reaction mixture was filtered through Celite and the Celite pad was washed with additional tetrahydrofuran (3 × 50 mL). The solvent was evaporated to give a red oil. Analysis by proton NMR suggested that the N7 *vs.* N9 substitution ratio as 7% and 93% respectively. The oil was taken up into ethyl acetate (500 mL) and washed with 10% HCl (4 × 50 mL) and brine (50 mL). The organic extract was dried over magnesium sulfate, filtered and evaporated to dryness to afford a red glass. The glass was rapidly stirred in hexane (50 mL) and acetone (75 mL) was added until solids started to crash out of solution. The heterogeneous solution was stirred at 0 °C for 30 min and filtered. The solids were washed with chilled acetone–hexane mixtures (1 : 1, 3 × 15 mL), and air-dried on the filter for 5 min. The solids were further dried under high vacuum to afford **19** (12.8 g, 75%) as a white solid. The solid was isolated as a tenacious acetone adduct which could not be removed after extended high vacuum drying at 60 °C. This adduct had no consequence in the next step though.

Routes to (1*S*,4*R*)-4-(2,6-dichloro-9*H*-purin-9-yl)-*N*-methyl-*N*-tosylcyclopent-2-enecarboxamide 20

Iodomethane as the electrophile. Compound **19** (5.00 g, 11.05 mmol) in acetone (50 mL) was reacted with methyl iodide (6.81 g, 48.0 mmol) in the presence of K_2CO_3 (4.58 g, 33.2 mmol) at reflux temperature for 4 h. The reaction mixture was filtered through Celite and the Celite pad was washed with additional acetone (50 mL). The solvent was evaporated and the residue was taken into ethyl acetate (50 mL), and washed with water (25 mL) and brine (25 mL). The organic extract was dried over sodium sulfate, filtered and evaporated. The residue was triturated with diethyl ether to afford **20** (3.80 g, 74%). $[\alpha]_D^{20}$ −73.3 (*c* 0.5 in MeOH); ν_{max}/cm^{-1} 3256, 2966, 1686, 1683, 1609, 1503; δ_H (400 MHz, $CDCl_3$, Me_4Si) 8.33 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.21–6.78 (m, 1H), 6.01–5.99 (m, 1H), 5.87–5.83 (m, 1H), 4.60–4.57 (m, 1H), 3.27 (s, 3H), 2.93–2.85 (m, 1H), 2.47 (s, 3H), 2.20–2.14 (m, 1H); δ_C (100 MHz, $CDCl_3$) 173.7, 152.7, 152.6, 151.5, 145.5, 145.3, 136.8, 135.8, 130.8, 130.5, 130.2, 127.2, 59.4, 50.9, 35.5, 33.4, 21.6; *m*/*z* 466.0524 (MH^+, $C_{19}H_{18}Cl_2N_5O_3S$ requires 466.0507).

Dimethylsulfate as the electrophile. Compound **19** (1.00 g, 2.21 mmol) in acetone (50 mL) was reacted with dimethylsulfate (0.73 g, 5.7 mmol) in the presence of K_2CO_3 (0.76 g, 5.53 mmol) at ambient temperature overnight. The reaction mixture was filtered through Celite and the Celite pad was washed with additional acetone (50 mL). The solvent was evaporated and the residue was taken into ethyl acetate (50 mL), and washed with water (25 mL) and brine (25 mL). The organic extract was dried over sodium sulfate, filtered and evaporated. The residue was triturated with diethyl ether to afford **20** (0.72 g, 70%). The analytical data matched those reported above.

Mitsunobu reaction. To a stirring solution of **19** (0.65 g, 1.44 mmol) in THF–CH_2Cl_2 (1 : 1, 20 mL) was added methanol (0.2 mL), PPh_3 (1.33 g, 5.76 mmol), and diisopropyl azodicarboxylate (0.98 mL, 5.74 mmol). After stirring for 30 min under argon, the solvent was evaporated *in vacuo* to give a residue, which was purified by flash chromatography (SiO_2 hexane–ethyl acetate, 1 : 2) to afford **20** (0.63 g, 1.35 mmol, 94%) as a solid. The analytical data matched those reported above.

((1*S*,4*R*)-4-(2-Chloro-6-(cyclopropylamino)-9*H*-purin-9-yl) cyclopent-2-en-1-yl)methanol 21

A solution of **20** (2.80 g, 6.00 mmol) in isopropyl alcohol (8 mL) and tetrahydrofuran (32 mL) was cooled to 0 °C. Sodium borohydride (0.227 g, 6.00 mmol) was added portion wise over 1 min, and stirring was continued until TLC analysis indicated a complete reaction. This took 60 min. The reaction was quenched with water (20 mL) at 0 °C and allowed to warm to ambient temperature for 2 h. The reaction mixture was taken into ethyl acetate (100 mL) and washed with water (50 mL) and brine

(2 × 50 mL). The aqueous layer was re-extracted with ethyl acetate (2 × 50 mL). The pooled organic extract was dried over magnesium sulfate, filtered and evaporated to give a brown residue. Flash chromatography (SiO_2, hexane–ethyl acetate, 1 : 2) afforded ((1*S*,4*R*)-4-(2,6-dichloro-9*H*-purin-9-yl)cyclopent-2-en-1-yl)methanol (1.48 g, 86%) as a viscous oil. δ_H (400 MHz, $CDCl_3$, Me_4Si) 8.52 (s, 1H), 6.25–6.23 (m, 1H), 5.88–5.85 (m, 1H), 5.80–5.77 (m, 1H), 3.90 (dd, J = 10.5, 3.7, 1H), 3.75 (dd, J = 10.5, 3.7, 1H), 3.50 (brs, 1H), 3.12–3.10 (m, 1H), 2.93–2.84 (m, 1H), 1.92–1.86 (m, 1H); δ_C (100 MHz, $CDCl_3$) 152.7, 152.6, 151.2, 145.7, 140.3, 130.6, 128.8, 64.0, 60.6, 47.5, 34.0. The data matched those in the literature.[35] Dry ethanol (10 mL) was added to the above oil (1.48 g, 5.19 mmol) and stirred until the oil dissolved completely. Cyclopropylamine (2.00 mL, 28. 4 mmol) was added and the reaction mixture was warmed to 50 °C and maintained at that temperature for 5 h. The solvent was evaporated and the residue taken up into acetone (25 mL) and stirred with sodium bicarbonate (500 mg) for 30 min. The organic layer was filtered and evaporated to give a residue that was purified by flash chromatography (SiO_2, ethyl acetate) to afford **21** (1.15 g, 3.76 mmol, 73%) as a white foam that collapsed into a gum over time. $[\alpha]_D^{20}$ = 23.3 (*c* 0.50 in $CHCl_3$) ν_{max}/cm^{-1} 3322, 3256, 1686, 1683, 1503; δ_H (400 MHz, $CDCl_3$, Me_4Si) 7.81 (s, 1H), 6.80 (brs, 1H), 6.14 (m, 1H), 5.81 (m, 1H), 5.62 (m, 1H), 3.77 (m, 1H), 3.66 (m, 1H), 2.97 (m, 3H), 2.81 (m, 1H), 1.81 (m, 1H), 0.87 (m, 2H), 0.6 (m, 2H); δ_C (100 MHz, $CDCl_3$) 156.2, 154.1, 138.9, 138.8, 129.6, 118.6, 64.5, 60.0, 47.5, 34.0, 7.2; *m*/*z* 306.1122 (MH^+, $C_{14}H_{17}ClN_5O$ requires 306.1122).

Routes to Abacavir 2b

Azide route. Compound **21** (0.20 g, 0.66 mmol) was dissolved in hydrazine monohydrate (10 mL) and methanol (5 mL) and heated at 50 °C overnight. The reaction mixture was concentrated to dryness and co-evaporated with 2-propanol (2 × 30 mL) until a white gum was obtained. The residue was dissolved in a 10% aqueous acetic acid solution (10 mL) and cooled in an ice bath. Sodium nitrite (75 mg, 1.10 mmol) was added, and the mixture was stirred for 1 h. After evaporating the solvent, the crude product was dissolved in ethanol (20 mL) and tin(II) chloride dihydrate (315 mg, 1.41 mmol) was added and the reaction mixture was refluxed for 2 h. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, dichloromethane–methanol, 19 : 1) to afford **2b** (0.13 g, 70% yield) as a solid. $[\alpha]_D^{25}$ −37.9 (*c* 0.29 in MeOH), lit.[35] $[\alpha]_D^{24}$ −37.5 (*c* 0.51 in MeOH), ν_{max}/cm^{-1} 3221, 3207, 1589, 1474; δ_H (400 MHz, $CDCl_3$, Me_4Si) 7.48 (s, 1H), 6.37 (brs, 1H), 6.09–6.08 (m, 1H), 5.76–5.74 (m, 1H), 5.42–5.40 (m, 1H), 5.12 (brs, 2H), 3.81–3.78 (m, 1H), 3.72–3.69 (m, 1H), 3.4 (brs, 1H), 3.05–2.92 (m, 2H), 2.76–2.70 (m, 2H), 2.00–1.94 (m, 1H), 0.82–0.77 (m, 2H), 0.58–0.54 (m, 2H); δ_C (100 MHz, $CDCl_3$) 159.4, 156.3, 149.9, 138.1, 136.6, 130.3, 115.1, 65.0, 61.1, 47.6, 32.6, 23.5, 7.3

Ammonia surrogate route. Compound **21** (0.17 g, 0.57 mmol) was added to DMSO (2.00 mL). 4-Methoxybenzylamine (0.40 mL, 3.1 mmol) was added and the reaction mixture was heated to 150 °C and maintained at that temperature overnight. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (3 × 25 mL) and brine (20 mL). The organic extract was dried over sodium sulfate, filtered and evaporated to give an oil that was chromatographed (SiO_2, ethyl acetate–methanol, 98 : 2) twice by way of preparative TLC to afford ((1*S*,4*R*)-4-(6-(cyclopropylamino)-2-((4-methoxybenzyl) amino)-9*H*-purin-9-yl)cyclopent-2-en-1-yl)methanol **23** (0.21 g, 90%) as an orange gum. $[\alpha]_D^{20}$ −2.7 (*c* 0.50 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$, Me_4Si) 7.41 (s, 1H), 7.30 (d, J = 8.7, 2H), 6.81 (d, J = 8.7, 2H), 6.09–6.03 (m, 1H), 5.90 (brs, 1H), 5.79–5.73 (m, 1H), 5.46–5.37 (m, 1H), 5.24–5.16 (m, 1H), 4.56 (brs, 1H), 4.54 (brs, 1H), 3.83–3.77 (m, 1H), 3.76 (s, 3H), 3.74–6.37 (m, 1H), 3.05 (brs, 1H), 2.94 (brs, 1H), 2.82–2.64 (m, 1H), 2.21 (brs, 1H), 2.08–1.97 (m, 1H), 0.83–0.72 (m, 2H), 0.62–0.49 (m, 2H); δ_C (100 MHz, $CDCl_3$) 159.0, 158.6, 156.0, 137.7, 136.2, 132.5, 130.6, 129.1, 114.9, 113.7, 65.2, 60.8, 55.2, 47.7, 45.4, 32.7, 23.6, 7.2; *m*/*z* 407.2208 (MH^+, $C_{22}H_{27}N_6O_2$ requires 407.2195).

Compound **23** (0.16 g, 0.38 mmol) was dissolved into chloroform (5 mL) and stirred under nitrogen. TFA (1.5 mL) was added and the reaction mixture was heated at 50 °C for 18 h. More TFA (2.5 mL) was added and stirring was continued an additional 18 h at 50 °C. Finally, an additional aliquot of TFA (2.5 mL) was added and stirring was continued for 18 h at 50 °C. The solvent was evaporated and the residue was neutralized with saturated sodium carbonate solution (20 mL) and extracted with chloroform (4 × 10 mL) and dried over magnesium sulfate. Preparative TLC (SiO_2, chloroform–methanol, 97 : 3) afforded **2b** (0.080 g, 73%) as a solid. The analytical data matched those given earlier for **2b** above.

References

1 UNAIDS, WHO (December 2009). "The Global Aids Epidemic".http://data.unaids.org/pub/FactSheet/2009/20091124_FS_global_en.pdf. Retrieved 18 December 2010.
2 E. De Clercq, "The design of drugs for HIV and HCV", *Nat. Rev. Drug Discovery*, 2007, **6**, 1001.
3 D. M. Huryn and M. Okabe, *Chem. Rev.*, 1992, **92**, 1745.
4 C. Simons, *Nucleoside Mimetics: Their Chemistry and Biological Properties*, Gordon and Breach Science Publishers, Amsterdam, 2001.
5 G. N. Jenkins and N. J. Turner, *Chem. Soc. Rev.*, 1995, **24**, 169.
6 For an example see M. Asami, J. Takahashi and S. Inoue, *Tetrahedron: Asymmetry*, 1994, **5**, 1649.
7 B. M. Trost, G.-H. Kuo and T. Benneche, *J. Am. Chem. Soc.*, 1988, **110**, 621.
8 B. M. Trost, L. Li and S. D. Guile, *J. Am. Chem. Soc.*, 1992, **114**, 8754.
9 B. M. Trost, R. Madsen, S. D. Guile and A. E. H. Elia, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1569.
10 B. M. Trost, R. Madsen, S. D. Guile and B. Brown, *J. Am. Chem. Soc.*, 2000, **122**, 5947.
11 B. M. Trost, M. Osipov, P. S. J. Kaib and M. T. Sorum, *Org. Lett.*, 2011, **13**, 3222.
12 J. R Huff, *Bioorg. Med. Chem.*, 1999, **7**, 2667.
13 M. Tanaka, Y. Norimine, T. Fujita, H. Suemune and K. Sukai, *J. Org. Chem.*, 1996, **61**, 6952.
14 M. Tanaka, M. Yoshioka and K. Sakai, *Tetrahedron: Asymmetry*, 1993, **4**, 981.
15 M. E. Jung and H. Rhee, *J. Org. Chem.*, 1994, **59**, 4719.
16 M. T. Crimmins, *Tetrahedron*, 1998, **54**, 9229.
17 C. A. M. Afonso and V. B. Kurteva, *Chem. Rev.*, 2000, **109**, 6809.
18 R. Vince, M. Hua, J. Brownell, S. M. Daluge, F. C. Lee, W. M. Shannon, G. C. Lavelle, J. Quails, O. S Weislow, R. Kiser, P. G. Canonico, R. H. Schultz, V. L. Narayanan, J. G. Mayo, R. H. Shoemaker and M. R. Boyd, *Biochem. Biophys. Res. Commun.*, 1988, **156**, 1046.

19 S. J. C. Taylor, R. McCague, R. Wisdom, C. Lee, K. Dickson, G. Ruecroft, F. O'Brien, J. Littlechild, J. Bevan, S. M Roberts and C. T. Evans, *Tetrahedron: Asymmetry*, 1993, **4**, 1117.
20 M. J. Mulvihill, J. A. Gage and M. J. Miller, *J. Org. Chem.*, 1998, **63**, 3357.
21 C. Kaneko, A. Sugimoto and S. Tanaka, *Synthesis*, 1974, 876.
22 D. R. Deardorff, C. Q. Windham and C. L. Craney1, *Org. Synth.*, 1996, **73**, 25.
23 K. Laumen and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1986, 1298.
24 E. Forró and F. Fülöp, *Tetrahedron: Asymmetry*, 2004, **15**, 573.
25 For an analogous reaction on 2-azabicyclo[2.2.1]hept-5-en-3-one, see: N. Katagiri, M. Takebayashi, H. Kokufuda, C. Kaneko, K. Kanehira and M. Torihara, *J. Org. Chem.*, 1997, **62**, 1580.
26 A. Vazquez-Romero, J. Rodriguez, A. Lledo, X. Verdaguer and A. Riera, *Org. Lett.*, 2008, **10**, 4509.
27 A. Kim and J. H. Hong, *Bull. Korean Chem. Soc.*, 2007, **28**, 1545.
28 M. Freiria, A. J. Whitehead and W. B. Motherwell, *Synthesis*, 2005, **18**, 3079.
29 G.-I. An and H. Rhee, *Nucleosides, Nucleotides Nucleic Acids*, 2002, **21**, 65.
30 M. T. Crimmins, B. W King, W. J. Zuercher and A. L. Choy, *J. Org. Chem.*, 2000, **65**, 8499.
31 S. M. Daluge, M. T. Martin, B. R. Sickles and D. A. Livingston, *Nucleosides, Nucleotides Nucleic Acids*, 2000, **19**, 297.
32 M. T. Crimmins and W. J. Zuercher, *Org. Lett.*, 2000, **2**, 1065.
33 H. F. Olivo and J. Yu, *J. Chem. Soc. Perkin Trans. 1*, 1998, **3**, 391.
34 S. M. Daluge, S. S. Good, M. B. Faletto, W. H. Miller, M. H St. Clair, L. R. Boone, M. Tisdale, N. R. Parry, J. E. Reardon, R. E. Dornsife, D. R. Averett and T. A Krenitsky, *Antimicrob. Agents and Chem.*, 1997, **41**, 1082.
35 M. T. Crimmins and B. W. King, *J. Org. Chem.*, 1996, **61**, 4192.
36 L. Kiss, E. Forró, R. Sillanpaa and F. Fülöp, *J. Org. Chem.*, 2007, **72**, 8786.
37 Utilizing 2,6-dichloro-9*H*-purine has two advantages over 2,6-diamino-9*H*-purine and 2-amino-6-chloro-9*H*-purine as the nucleophile: it has good solubility, and the resulting product does not require protection for subsequent alkylation chemistry. For example see ref. 25.
38 T. Durst and M. J. O'sullivan, *J. Org. Chem.*, 1970, **56**, 2043.

