

A facile and simple entry into isodideoxynucleosides

1
PERKIN

Angshuman Chattopadhyay* and Avinash Salaskar

Bio-organic Division, Bhabha Atomic Research Centre, Mumbai-400 085, India

Received (in Cambridge, UK) 25th October 2001, Accepted 25th January 2002

First published as an Advance Article on the web 18th February 2002

Sharpless asymmetric dihydroxylations of homoallylic alcohol derivative **3** with AD mix- α afforded α addition product **4a** predominantly. Compound **4a** was produced with very high selectivity when **3** was treated with AD mix- β . The inherent hydroxylic functionalities of **4a** were judiciously exploited to develop a simple and efficient synthesis of (3',5',5')-isodideoxynucleosides. **I** and **II** are two representative target molecules for our synthesis in this regard.

Introduction

During the last two decades, there has been ever-increasing attention paid to the synthesis of different analogs of natural nucleosides and to understanding their chemistry with regard to biological perspectives. This has been triggered by the finding that a number of 2',3'-dideoxynucleosides like ddI, ddC, AZT, *etc.* are effective therapeutic agents for the treatment of AIDS.¹ Subsequently, many modified nucleosides have become useful agents for the treatment of cancer and viral diseases due to their good antitumour and antiviral activity.² Unfortunately, the therapeutic use of these dideoxynucleosides and other deoxy-purine nucleosides is often restricted due to the rapid hydrolysis of their glycosidic linkage under acidic conditions, such as those in the gastric environment, and because of the action of enzymes.³ In view of this, the molecular design and synthesis of bioactive nucleosides that are stable towards acid and enzymatic deamination has drawn considerable attention in recent years. Besides this, the toxicities associated with certain nucleoside analogs, as well as the emergence of drug-resistant viral strains, warrant the search for additional novel and structurally diverse compounds with improved biological efficiency and minimal toxic effects.

Among different nucleoside analogs, isonucleosides represent a class in which the nucleobase is linked with 2'-deoxyribose at different positions other than the C-1' of the normal 2',3'-dideoxynucleosides (using normal nucleoside numbering, Chart 1). Consequently, several D- and L-isonucleosides are reported to

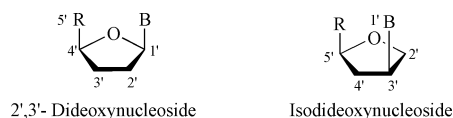
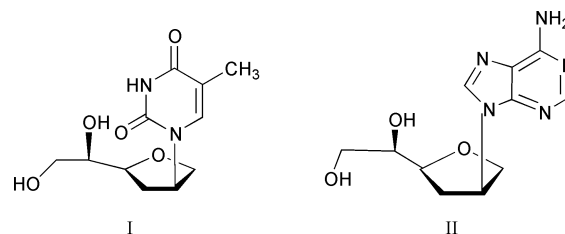


Chart 1

exhibit activity against a broad spectrum of viruses and some tumour cell lines,⁴ in addition to a number of branched-chain sugar isonucleosides that are found to possess interesting biological activities.⁵ Quite obviously, the absence of a glycosidic linkage in their structures makes isodideoxynucleosides considerably stable chemically. In view of their possible therapeutic potential, the preparation of isonucleosides with varied structural and/or stereochemical combinations has drawn enormous attention from synthetic chemists in recent years.⁶

In our ongoing programme on the synthesis of bioactive compounds, we have earlier exploited the easily available (*R*)-2,3-*O*-cyclohexylidene-glyceraldehyde (**1**) for the synthesis of 2',3'-dideoxynucleosides.^{7a-c} We herein report its utility in developing a short and very simple route for the synthesis of

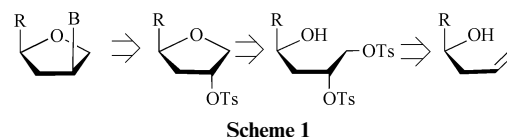
dideoxyisodideoxynucleosides as well. Here, in order to establish the viability of our strategy, we present the synthesis of a pyrimidine-isodideoxynucleoside (**I**) and a purine-isodideoxynucleoside (**II**), as representative target molecules, both with *S,S* absolute



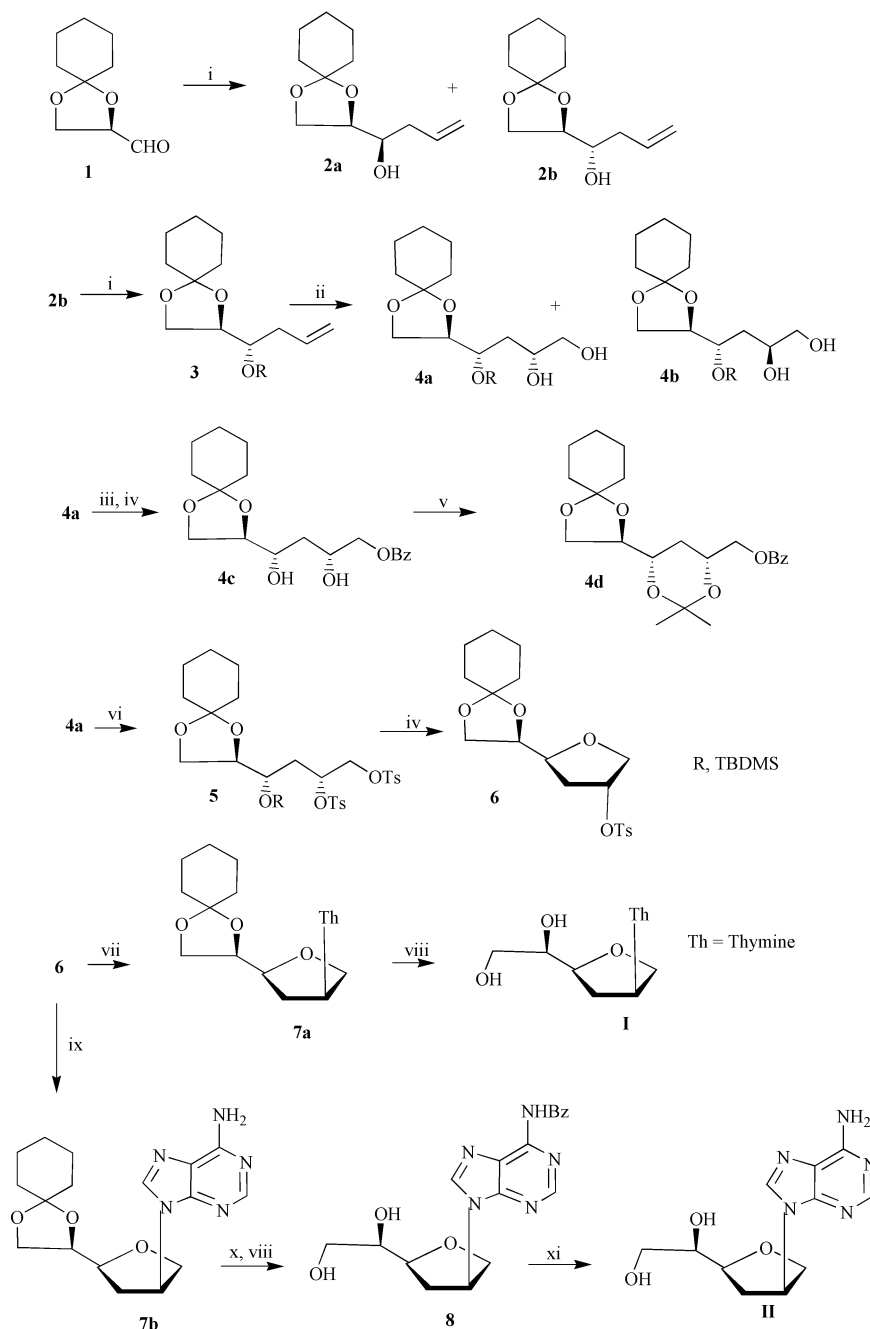
stereochemistry which is comparable with L-dideoxynucleosides. It is worth mentioning that a variety of L-enantiomers of known antiviral nucleosides have antiviral activity equal to or better than their D-enantiomers, besides having lower cytotoxicity.^{6e,f} It is believed that these L-isomers or their triphosphate derivatives interact with viral enzymes and inhibit viral DNA production without causing any significant change to normal human DNA. Thus, the synthesis of modified L-nucleosides assumes enormous significance in one's hopes of producing safer drugs. Both **I** and **II** comprise a pentofuranose skeleton with a base and a functionalized as well as chiral carbon substituent at the 3'- and 5'-position, respectively, maintaining a *cis* relationship with each other (in isonucleosides the numbering of the furan ring atoms is different from that of the normal nucleosides as shown in Chart 1). As will be evident later on, our route has an inherent flexibility regarding the achievement of various stereochemical and structural modifications of the resulting isodideoxynucleosides.

Results and discussion

Our retrosynthetic analysis is outlined in Scheme 1. We envis-



aged the synthesis of the target molecules *via* an asymmetric dihydroxylation of an olefin and a ring-closing reaction as the key steps. We started with silyl derivative **3^{7d}** (Scheme 2) of the homoallylic alcohol **2b** that is stereoselectively preparable^{7d} from **1** on a practical scale. The terminal olefin of **3** was subjected to asymmetric dihydroxylation using both types of Sharpless reagent,⁸ AD mix- α [$K_2OsO_2(OH)_4$, (DHQ)₂-PHAL (hydroquinine 1,4-phthalazinediyl diether), $K_3Fe(CN)_6$ and



Scheme 2 Reagents: i) ref. 7d; ii) AD mix- α or AD mix- β , *t*-BuOH–H₂O; iii) BzCN, TEA, CH₂Cl₂; iv) TBAF, THF; v) 2,2-dimethoxypropane, PTSA; vi) *p*-Tos-Cl, Py, DMAP; vii) thymine, K₂CO₃, 18-Crown-6, DMF; viii) CF₃COOH–H₂O, CH₂Cl₂; ix) adenine, K₂CO₃, 18-Crown-6, DMF; x) BzCl, TMSCl, Py; xi) NH₃, MeOH.

K₂CO₃] and AD mix- β [K₂O₂(OH)₄, (DHQD)₂-PHAL (hydroquinidine 1,4-phthalazinediyl diether), K₃Fe(CN)₆ and K₂CO₃] to produce diols **4a** and **4b** in good yield and in both the cases hydroxylation predominantly took place from the α -face. However, AD mix- α reaction yielded **4a** and **4b** as the major and minor products respectively (**4a** : **4b** 77.5 : 22.5), while use of AD mix- β produced **4a** with very high selectivity (**4a** : **4b** 95.5 : 4.5). The diastereomers **4a** and **4b** are conveniently separable from each other by normal column chromatography. The stereochemistry at the site (C-2 position) bearing the freshly generated secondary hydroxy group of diol **4a** was assigned to be similar to that of the major product in the case of a reported AD mix- α dihydroxylation of a homoallylic alcohol^{9a} that has good structural resemblance with **2b**. Furthermore, the pattern of the ¹H-NMR spectrum of diol **4a** showing four nicely separable multiplets at δ 3.41–3.50 (1H), 3.57–3.65 (1H), 3.76–3.84 (2H) and 4.01–4.10 (3H) is appreciably comparable (in that spectral region) to that of the major dihydroxylation product.^{9a} Finally, the C-2 stereochemistry of diol **4a** was determined from

the acetonide (**4d**) that was prepared in three steps, *viz* selective monobenzylation of the primary hydroxy group of **4a**, desilylation of its other hydroxy group, and acid-catalyzed reaction of the resulting 1,3-diol (**4c**) with 2,2-dimethoxypropane. In the ¹³C-NMR spectrum of compound **4d**, the signals at δ_c 19.7 and 31.0 (due to two methyls) and at δ_c 98.6 (due to ketal carbon) of the acetonide moiety of the six membered ring confirm the *syn* relationship¹⁰ of the corresponding 1,3-diol unit of diol **4c**. It is worth mentioning that the ¹H-NMR spectrum of the minor product (**4b**) shows three nearly overlapping multiplets at δ 3.42–3.47 (1H), 3.50–3.8 (3H) and 3.84–4.2 (3H). It is interesting to note that both AD mix- α and AD mix- β gave the same compound **4a** as the major product, in contrast with the usual observations that show a change in selectivity.^{8b} Moreover, for dihydroxylation of their homoallylic alcohol substrate Herdewijn *et al.* didn't observe appreciable variation of selectivity while using AD mix- α ^{9a} or AD mix- β .^{9b} However, in our case the selectivity of the formation of diol **4a** improved drastically in the case of AD mix- β .

Tosylation of diol **4a** using two equivalents of toluene-*p*-sulfonyl chloride yielded ditosyl derivative **5** in appreciable yield. Desilylation of **5** with tetrabutylammonium fluoride (TBAF) took place with concomitant intramolecular substitution of the primary OTs group to generate compound **6** only. In this case, the tetrahydrofuran moiety of **6** was produced with absolute regioselectivity as the other route, involving the formation of a highly strained oxetane *via* intramolecular substitution of the secondary OTs group of **5**, is thermodynamically unfavourable. Moreover, substitution of the more reactive and less hindered primary OTs group in **5** is kinetically favourable with respect to substitution of the secondary one. Now, compound **6** has been separately treated with thymine and adenine to produce isodideoxynucleosides **7a** and **7b**, respectively, following invertive S_N2 displacement of OTs at C-3' with the bases. After usual work-up, the crude residue containing compound **7a** was as such subjected to deketalization by treatment with aqueous trifluoroacetic acid to yield compound **I**. Benzoylation of the NH₂ group of **7b** and deketalization of the product afforded the diol **8**. Finally, debenzoylation of compound **8** has been effected smoothly to afford compound **II**.

Conclusions

In summary, a short and straightforward route for the synthesis of isodideoxynucleosides has been developed starting with easily available aldehyde **1**. This has been generalized through the preparation of both a pyrimidyl (**I**) and a purinyl (**II**) nucleoside. Both nucleoside analogs **I** and **II** have, at the C-5' position, rather than a hydroxymethyl functionality as observed normally, a functionalized chiral substituent comprising both a primary and a secondary hydroxy group that are amenable to versatile chemical and stereochemical elaboration independently of each other. The efficacy of this approach lies in the easy availability of *anti*-**2b** on a reasonably good scale^{7d} and the highly stereoselective dihydroxylation of olefin **3** under practically stereospecific conditions. Moreover, the reasonable stability of the cyclohexylidene ketal functionality proved to be considerably advantageous as this, by efficiently protecting two hydroxy groups, affords selective manipulation of the other (protected) hydroxy group of the intermediates without any difficulty. In hindsight, this route has the inherent advantage of attaining stereochemical flexibility through exploitation of the corresponding *syn*-alcohol **2a** that can be prepared stereoselectively.^{7c} Furthermore, starting from readily available aldehyde (*S*)-**(1)**¹¹ the present protocol is likely to produce another series of isomers of **I** and **II**.

Experimental

Chemicals used as starting materials are commercially available and were used without further purification. All solvents used for extraction and chromatography were distilled twice at atmospheric pressure prior to use. Tetrahydrofuran and ether were dried by heating over LiAlH₄. *N,N*-Dimethylformamide was dried by heating over calcium hydride and was then distilled under reduced pressure. IR spectra were recorded with a Perkin-Elmer spectrophotometer model 837. ¹H- and ¹³C-NMR spectra were scanned with a Bruker Ac-200 (200 MHz) instrument for solutions in CDCl₃. Optical rotations were measured with a JASCO DIP-360 polarimeter; [α]_D-values are given in units of 10⁻¹ deg cm⁻² g⁻¹. Organic extracts were desiccated over dry Na₂SO₄.

5,6-*O*-Cyclohexylidene-4-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-D-ribo-hexitol (**4a**) and 5,6-*O*-cyclohexylidene-4-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-D-arabino-hexitol (**4b**)

Using AD mix- α . A solution of olefin **3** (1.63 g, 0.005 mole) in a solvent mixture of *t*-BuOH–water (1 : 1; 25 mL) was added to a cooled (0 °C) and well stirred suspension of AD mix- α (8 g) in

the same solvent mixture (120 mL). The mixture was stirred at 0 °C for 6 h and then at room temperature overnight. It was then cooled to 0 °C and treated with solid Na₂SO₃ (7 g). The mixture was stirred for 1 h at room temperature and extracted with chloroform. The combined organic extract was washed successively with water and brine and then dried. Solvent removal and column chromatography of the residue (silica gel; 0–5% methanol in chloroform, v/v) afforded diols **4a** (1.17 g, 65%) and **4b** (340 mg, 18.9%). The R_f (5% methanol in chloroform)-values of **4a** and **4b** are 0.60 and 0.51, respectively.

Diol 4a. [α]_D²² +9.03 (*c* 0.30, CHCl₃); ν_{\max} /cm⁻¹ (film) 3419, 2857, 1364, 1252; ¹H-NMR (CDCl₃) δ 0.08 (s, 6H), 0.87 (s, 9H), 1.4–1.6 (m, 10H, overlapped with br s, D₂O-exchangeable, 2H), 1.7–1.8 (m, 2H), 3.41–3.50 (m, 1H), 3.57–3.65 (m, 1H), 3.76–3.84 (m, 2H), 4.01–4.10 (m, 3H).

Diol 4b. [α]_D²² +20.72 (*c* 0.40, CHCl₃); ν_{\max} /cm⁻¹ (film) 3419, 2857, 1364, 1252; ¹H-NMR (CDCl₃) δ 0.078 (s, 6H), 0.89 (s, 9H), 1.4–1.6 (m, 10H), 1.7–1.8 (m, 2H, overlapped with br s, D₂O exchangeable, 2H), 3.42–3.47 (m, 1H), 3.50–3.80 (m, 3H), 3.84–4.2 (m, 3H).

Using AD mix- β . Following an identical experimental procedure as above, olefin **3** (1.64 g, 0.005 mol) was treated with AD mix- β (14.5 g) in *t*-BuOH–water (1 : 1, v/v) to produce diols **4a** (1.47 g, 81.7%) and **4b** (70 mg, 3.9%).

1-*O*-Benzoyl-2,4-*O*-isopropylidene-5,6-*O*-cyclohexylidene-3-deoxy-D-ribo-hexitol (**4d**)

To a cooled (0 °C) solution of diol **4a** (108 mg, 0.3 mmol) in dichloromethane (20 mL) containing triethylamine (0.02 mL) was added a solution of benzoyl cyanide (40 mg, 0.31 mmol) in dichloromethane (10 mL) over a period of 40 min. The mixture was stirred at that temperature for 30 min more and quenched with water. The organic layer was washed successively with 5% aqueous HCl, water, and brine and then dried. Solvent was removed and the residue was filtered through a short pad of silica gel with elution with ethyl acetate in hexane (20%, v/v). The residue after solvent removal from the filtrate was dissolved in THF (15 mL) and treated with a solution of tetrabutylammonium fluoride in THF (2.5 mL; 1 M). The mixture was stirred for 1 h, then treated with water, and extracted with chloroform. After usual work-up and solvent removal from the organic layer, the residue was purified by passage through a short pad of silica gel and elution with MeOH in CHCl₃ (5%, v/v).

The resulting diol **4c** was mixed in 2,2-dimethoxypropane (4 mL) and a catalytic amount of toluene-*p*-sulfonic acid. The mixture was stirred for 1 h and treated with water. This mixture was then extracted with diethyl ether. Usual work-up and solvent removal from the organic extract gave a residue that was purified by column chromatography (silica gel; 0–10% ethyl acetate in petroleum ether (60–80 °C), v/v) to afford compound **4d** (70 mg, 59.8%); ¹H NMR (CDCl₃) δ 1.35 (s, 3H), 1.37 (s, 3H), 1.4–1.6 (m, 10H); 1.8–2.0 (m, 2H), 3.7–4.0 (m, 4H), 4.22–4.32 (m, 3H), 7.30–7.57 (m, 3H), 8.01 (m, 2H); ¹³C NMR (CDCl₃) δ_c 166.3 (CO), 132.8 (C, *para*), 129.9 (C–CO), 129.5 (2C, *meta*), 128.2 (2C, *ortho*), 109.9 (O–C–O, cyclohexylidene), 98.6 (O–C(CH₃)₂–O), 70.3, 67.9, 67.3, 66.8, 64.8 (C-1, C-2, C-4, C-5, C-6), 36.3 (cyclohexylidene), 34.7 (cyclohexylidene), 31.0 (CH₃), 29.7 (C-3), 24.6 (cyclohexylidene), 23.8 (cyclohexylidene), 23.6 (cyclohexylidene), 19.7 (CH₃).

5,6-*O*-Cyclohexylidene-4-*O*-(*tert*-butyldimethylsilyl)-1,2-di-*O*-tosyl-3-deoxy-D-ribo-hexitol (**5**)

To a solution of diol **4a** (3.6g, 0.01 mol) and 4-(dimethylamino)pyridine (DMAP) (100 mg) in pyridine (30 mL) at 0 °C was added *p*-tosyl chloride (4.2 g, 0.021 mol). The mixture was stirred at 0 °C for 4 h and then at room temperature overnight.

It was treated with cold water and extracted with ether. The combined organic extract was washed successively with water, and brine and then dried. Solvent removal and column chromatography of the residue (silica gel; 0–10% ethyl acetate in hexane, v/v) afforded compound **5** (5.9 g, 88.3%); $[\alpha]_D^{22} + 3.17$ (*c* 0.725, CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (film) 2857, 1597, 1371, 1176; ¹H-NMR (CDCl₃) δ 0.068 (s, 6H), 0.85 (s, 9H), 1.4–1.6 (m, 10H), 1.9–2.0 (m, 2H), 2.44 (s, 6H), 3.5–3.8 (m, 3H), 3.9–4.3 (m, 3H), 4.95 (m, 1H), 7.25–7.35 (m, 4H), 7.68–7.72 (m, 4H).

2*S*,4*R*)-4-(*p*-Tolylsulfonyloxy)-2-[(1*R*)-1,2-cyclohexylidenedioxyethyl]tetrahydrofuran (**6**)

A solution of tetrabutylammonium fluoride in THF (25 mL; 1 M) was added to a solution of **5** (3.34 g, 0.005 mol) in THF (50 mL). The resulting solution was stirred at room temperature overnight. The reaction was quenched by the addition of saturated aqueous NH₄Cl (10 mL). The mixture was diluted with ether, the phases were separated, and the aqueous phase was thoroughly extracted with ether. The combined organic extract was washed successively with water and brine. Solvent was removed under reduced pressure and the residue was chromatographed (silica gel; 0–15% ethyl acetate in hexane, v/v) to afford compound **6** (1.51 g, 79.5%) (Found: C, 59.42; H, 7.05. C₁₉H₂₆O₆S requires C, 59.66; H, 6.85%); $[\alpha]_D^{22} - 2.01$ (*c* 1.19, CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (film) 1375, 1180; ¹H-NMR (CDCl₃) δ 1.4–1.6 (m, 10H), 1.95–2.34 (m, 2H), 2.44 (s, 3H), 3.66–3.73 (m, 1H), 3.75–3.86 (m, 1H), 3.93–4.13 (m, 4H), 5.11 (m, 1H), 7.34 (d, *J* = 8 Hz, 2H), 7.78 (d, *J* = 8 Hz, 2H).

1-[(3*S*,5*S*)-5-[(1*R*)-1,2-Dihydroxyethyl]tetrahydrofuran-3-yl]thymine (**I**)

A mixture of thymine (200 mg, 1.6 mmol), potassium carbonate (276 mg, 2 mmol), 18-crown-6 (528 g, 2 mmol) and compound **6** (382 mg, 1 mol) in DMF (25 mL) was stirred at 75–80 °C for 15 h. It was cooled to room temperature and chloroform was added. The organic layer was thoroughly washed with water to remove DMF, then with brine, and was then dried. Solvent was removed under reduced pressure. The residue was partially purified by loading on a short silica gel column and was eluted successively with ethyl acetate in hexane (15%, v/v) and methanol in chloroform (5%, v/v) to isolate compound **7a** in the latter fraction which was concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (40 mL) and stirred with 80% aqueous trifluoroacetic acid (10 mL) at 0 °C for nearly 1 h until starting material **7a** had disappeared (TLC). The reaction mixture was concentrated under reduced pressure. The residue was loaded on a silica gel column and eluted successively with ethyl acetate, acetone, and methanol in chloroform (7%, v/v) to obtain pure compound **I** in the last fraction (108 mg, 42.2%) as a white solid (Found: C, 51.36; H, 6.50; N, 11.18. C₁₁H₁₆O₅N₂ requires C, 51.55; H, 6.29; N, 10.93%); $[\alpha]_D^{22} - 5.29$ (*c* 0.378, MeOH); ¹H-NMR (CD₃OD) δ 1.86 (s, 3H) 1.87–2.07 (m, 1H), 2.25–2.50 (m, 1H), 3.40–3.65 (m, 3H), 3.75–4.0 (m, 2H), 4.05–4.10 (m, 1H), 5.1–5.3 (m, 1H, H-3), 7.63 (s, 1H, thymine); ¹³C-NMR (CD₃OD) δ_c 164.3 (C-4), 151.1 (C-2), 137.6 (C-6), 111.1 (C-5), 79.7 (C-5'), 71.7 (C-2'), 70.5 (C-6'), 63.1 (C-7'), 54.6 (C-3'), 32.4 (C-4'), 11.6 (5-CH₃).

9-[(3*S*,5*S*)-5-[(1*R*)-1,2-Cyclohexylidenedioxyethyl]tetrahydrofuran-3-yl]adenine (**7b**)

Following a similar procedure of glycosylation as above, adenine (404 mg, 3 mmol) was treated with potassium carbonate (552 mg, 4 mmol), 18-crown-6 (1.056 g, 4 mmol) and compound **6** (764 mg, 2 mmol) in DMF (30 mL). After usual work-up, column chromatography of the residue (silica gel; 0–5% methanol in chloroform, v/v) afforded compound **7b** (432 mg, 62.6%) (Found: C, 59.33; H, 6.60; N, 20.50. C₁₇H₂₃O₃N₅ requires C, 59.12; H, 6.71; N, 20.28%); $[\alpha]_D^{22} - 14.10$

(*c* 1.09, CHCl₃); ¹H-NMR (CDCl₃) δ 1.3–1.6 (m, 10H), 2.0–2.2 (m, 1H), 2.6–2.8 (m, 1H), 3.65–3.83 (ddd, *J* = 11.7, 5.7, 4.8 Hz, 1H), 3.9–4.3 (m, 4H), 4.44 (dd, *J* = 9.8, 5.4 Hz, 1H), 5.33 (m, 1H, H-3), 5.70 (br s, 2H, NH₂), 8.23 (s, 1H, adenine), 8.35 (s, 1H, adenine).

9-[(3*S*,5*S*)-5-[(1*R*)-1,2-Dihydroxyethyl]tetrahydrofuran-3-yl]-N⁶-benzoyladenine (**8**)

Following a reported procedure,¹² compound **7b** (345 mg, 1 mmol) was treated with trimethylsilyl chloride (540 mg, 5 mmol) and benzoyl chloride (700 mg, 5 mmol) in pyridine (10 mL) to yield the benzoylated product. After usual work-up, and solvent removal under reduced pressure, the crude residue was obtained in almost quantitative yield.

This, without being purified further, was subjected to deket-alization by treating its solution in CH₂Cl₂ (40 mL) with 80% aqueous trifluoroacetic acid (10 mL) at 0 °C. The reaction mixture was concentrated under reduced pressure. The residue was loaded on a silica gel column and eluted successively with ethyl acetate, acetone, and methanol in chloroform (7%, v/v) to afford compound **8** (290 mg, 81.2%); $[\alpha]_D^{22} - 15.19$ (*c* 0.38, MeOH); ¹H-NMR (CD₃OD) δ 2.20–2.50 (m, 1H), 2.55–2.75 (m, 1H), 3.50–3.70 (m, 2H), 3.75–4.0 (m, 1H), 4.0–4.50 (m, 3H), 5.43 (m, 1H), 7.52–7.63 (m, 3H, aromatic), 8.0 (d, *J* = 5.5 Hz, 2H, aromatic), 8.28 (s, 1H, adenine), 8.73 (s, 1H, adenine).

9-[(3*S*,5*S*)-5-[(1*R*)-1,2-Dihydroxyethyl]tetrahydrofuran-3-yl]adenine (**II**)

A solution of compound **8** (200 mg, 0.54 mmol) in saturated methanolic ammonia (30 mL) was stirred for 18 h at room temperature. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel; 0–12% methanol in chloroform, v/v) to afford compound **II** (117 mg, 81.9%) as white solid (Found: C, 50.05; H, 5.88; N, 26.59. C₁₁H₁₅O₃N₅ requires C, 49.80; H, 5.69; N, 26.39%); $[\alpha]_D^{22} - 9.84$ (*c* 0.12, MeOH); ¹H-NMR (CD₃OD) δ 2.23 (m, 1H), 2.52 (m, 1H), 3.4–3.6 (m, 2H), 3.7–4.04 (m, 3H), 4.10–4.16 (m, 1H), 5.16 (m, 1H), 8.15 (s, 1H, adenine), 8.18 (s, 1H, adenine); ¹³C-NMR (CD₃OD) δ_c 156.3 (C-6), 153.1 (C-2), 146.1 (C-4), 137.4 (C-8), 119.1 (C-5), 82.4 (C-5'), 71.8 (C-2'), 69.5 (C-6'), 63.3 (C-7'), 57.1 (C-3'), 33.4 (C-4').

References

- (a) H. Mitsua and S. Broder, *Proc. Natl. Acad. Sci. U.S.A.*, 1986, **83**, 1911; (b) H. Mitsua, K. J. Weinhold, P. A. Furman, M. H. St. Clair, S. N. Lehrman, R. C. Gallo, D. Bolognesi, D. W. Barry and S. Broder, *Proc. Natl. Acad. Sci. U.S.A.*, 1985, **82**, 7096.
- (a) *Nucleosides and Nucleotides as Antitumour and Antiviral Agents*, eds. C. K. Chu and D. C. Baker, Plenum, New York, 1993; (b) E. De Clercq, in *Targets for the Design of Antiviral Agents*, eds. E. De Clercq and R. T. Walker, Plenum, New York, 1994, pp. 203–230; (c) D. M. Huryn and M. Okabe, *Chem. Rev.*, 1992, **92**, 1745; (d) C. Perigaud, G. Gosselin and J. L. Imbach, *Nucleosides, Nucleotides*, 1992, **11**, 903; (e) H. Mitsua, R. Yarchoan and S. Broder, *Science*, 1990, **249**, 1533; (f) E. De Clercq, *Nucleosides Nucleotides*, 1994, **13**, 1271.
- (a) J. L. York, *J. Org. Chem.*, 1981, **46**, 2171; (b) V. E. Marquez and M. I. Lim, *Med. Res. Rev.*, 1986, **6**, 1; (c) V. E. Marquez, C. K. Tseng, J. A. Kelly, H. Mitsua, S. Broder, J. Roth and J. Driscoll, *Biochem. Pharmacol.*, 1987, **36**, 2719; (d) T. Kawaguchi, S. Fukushima, M. Ohmura, M. Mishima and M. Nakano, *Chem. Pharm. Bull.*, 1989, **37**, 1944; (e) V. Nair and G. S. Buenger, *J. Org. Chem.*, 1990, **55**, 3695.
- (a) V. Nair and T. S. Jahnke, *Antimicrob. Agents Chemother.*, 1995, **39**, 1017; (b) V. Nair and Z. M. Nuesca, *J. Am. Chem. Soc.*, 1992, **114**, 7951; (c) K. F. Soike and V. J. Whiterock, *Antiviral Res.*, 1994, **23**, 219; (d) D. M. Huryn, B. C. Sluboski, S. Y. Tam, M. Weigle, I. Sim, B. D. Anderson, H. Mitsua and S. Broder, *J. Med. Chem.*, 1992, **35**, 2347; (e) M. F. Jones, S. E. Noble, C. A. Robertson, R. Storer, R. M. Highcock and R. B. Lamont, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1437.

- 5 (a) T. Kira, A. Lakefuda, S. Shuto, A. Matsuda, M. Baba and S. Shigeta, *Nucleosides, Nucleotides*, 1995, **14**, 571; (b) A. Kakefuda, S. Shuto, T. Nagahada, J. Seki, T. Sasaki and A. Matsuda, *Tetrahedron*, 1994, **50**, 10167; (c) J. A. Tino, J. M. Clark, A. K. Field, G. A. Jacobs, K. A. Lis, T. L. Michalik, B. McGreever-Rubin, W. A. Slarsuchyk, S. H. Spengel, J. E. Sundeen, A. V. Tuomari, E. R. Weaver, M. G. Young and R. J. Zahler, *J. Med. Chem.*, 1993, **36**, 1221.
- 6 (a) D. M. Huryn, B. C. Sluboski, S. Y. Tam, L. J. Todaro and M. Weigele, *Tetrahedron Lett.*, 1989, **30**, 6259; (b) P. J. Bolon, T. B. Sells, Z. M. Nuesca, D. F. Pardy and V. Nair, *Tetrahedron*, 1994, **50**, 7747; (c) See ref. 4a; (d) R. R. Talekar and R. H. Wightman, *Tetrahedron*, 1997, **53**, 3831; (e) Y. Diaz, F. Bravo and S. J. Castillon, *J. Org. Chem.*, 1999, **64**, 6508 and references cited therein; (f) M. E. Jung and C. J. Nichols, *J. Org. Chem.*, 1998, **63**, 347 and references cited therein.
- 7 (a) A. Chattopadhyay, *Tetrahedron Asymmetry*, 1997, **8**, 2727; (b) A. Chattopadhyay, S. Hassrajani and B. Dhotare, *J. Org. Chem.*, 1999, **64**, 6874; (c) B. Dhotare and A. Chattopadhyay, *Synthesis*, 2001, 1347; (d) A. Chattopadhyay, *J. Org. Chem.*, 1996, **61**, 6104.
- 8 (a) C. H. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483; (b) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. Jeong, H. Kwong, K. Morikawa, Z. Wang, D. Xu and X. Zhang, *J. Org. Chem.*, 1992, **57**, 2768.
- 9 (a) N. Hossain, J. Rozenski, E. D. Clercq and P. Herdewijn, *Tetrahedron*, 1996, **52**, 13655; (b) N. Hossain, Z. Rozenski, E. D. Clercq and P. Herdewijn, *J. Org. Chem.*, 1997, **62**, 2442.
- 10 (a) D. A. Evans, D. L. Riger and J. R. Gage, *Tetrahedron Lett.*, 1990, **31**, 7099; (b) S. D. Rychnovsky and D. J. Skalitzky, *Tetrahedron Lett.*, 1990, **31**, 945.
- 11 M. Grauert and U. Scholkopf, *Justus Leibigs Ann. Chem.*, 1985, 1817.
- 12 G. S. Ti, B. L. Gaffney and R. A. Jones, *J. Am. Chem. Soc.*, 1982, **104**, 1316.