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Asymmetric synthesis of thymine nucleoside analogues based on the isochroman core

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Abstract—Diastereoisomeric analogues of d4T having an isochroman core as the glycone moiety have been prepared in seven steps. Starting from phthalaldehyde, two chiral centres analogous to the α/β anomers of D/L sugars were created. The first was obtained enantiomerically pure via asymmetric dihydroxylation and the second via cyclisation of an aldehyde group with a primary hydroxyl group. Retention of chiral integrity at the C_4 site enabled enantiomerically pure nucleoside analogues to be obtained.

Over the past two decades, nucleoside chemistry has evolved to facilitate efficient routes to effective agents for the treatment of AIDS,[1] herpes[2] and viral hepatitis.[3] Consequently, a large number of modifications have been made to both the base and sugar moieties of natural nucleosides, accordingly, with the objective of increasing the therapeutic index of established antiviral agents. One of the most important discoveries in this area was the insertion of insaturation in the 2′,3′-position of the glycone moiety to give the 2′,3′-didehydro-2′,3′-dideoxy series of nucleosides (d4Ns). Various derivatives of the approved drug, Stavudine (2′,3′-didehydro-2′,3′-dideoxythymidine, d4T, **1**)[4] have been synthesised in which the 2′- and/or 3′-positions have been modified. Recent examples include the introduction of a fluoro atom,[5] cyano group,[6] alkyl chain[7] and a fused benzene ring system.[8] Replacement of the five-membered furanose ring with (i) an acyclic group such as acyclovir (**2**),[9] (ii) a cyclopentene core such as Abacavir (**3**)[10] and (iii) a six-membered ring such as D- and L-cyclohexenyl guanine (**4**)[11] have also been reported (Fig. 1).

In the search for new agents with a higher therapeutic index, conformationally restricted nucleosides have permitted a more intrusive investigation into the conformational aspects of enzyme–substrate interactions.[12] Recently, we synthesised the series of pyrimidine nucleoside analogues, **5**–**7**, which have a benzo[*c*]furan core and are analogues of d4Ns (Fig. 1). As a part of our continuing studies on the chemistry of d4Ns, we have synthesised the isochroman derivatives **8** and **9**.

Retrosynthetic analysis of the target compounds **8** and **9** suggested that *o*-phthalaldehyde **10** was the most promising starting point. Thus, phthalaldehyde **10** afforded the acetal derivative **11**, in 78% yield, by reaction with propan-1,3-diol in the presence of PTSA. The remaining aldehyde group of **11** was easily converted into the styrene analogue **12** via a classical Wittig homologation. Asymmetric dihydroxylation of the ethene derivative **12** with commercial AD-mix α gave the corresponding enantiomerically pure diol **13** (ee 98%). The absolute configuration *S* of this novel chiral centre was assigned by both the asymmetric dihydroxylation mnemonic rules and X-ray study.[13] The diol **13** was converted, using HCl in methanol, into a mixture of the corresponding 1-methoxy derivatives **14** and **15** having isochroman and isobenzofuran structures, respectively, in 75% yield. The mixture was difficult to separate by silica gel chromatography. Also, subsequent acetylation of the secondary hydroxyl group afforded the corresponding acetates **16** (51% yield, ratio 1:1) and **17** (34% yield, ratio 1:1), which were cleanly separated by column chromatography. Under such conditions the competitive cyclisation between the primary and secondary hydroxyl

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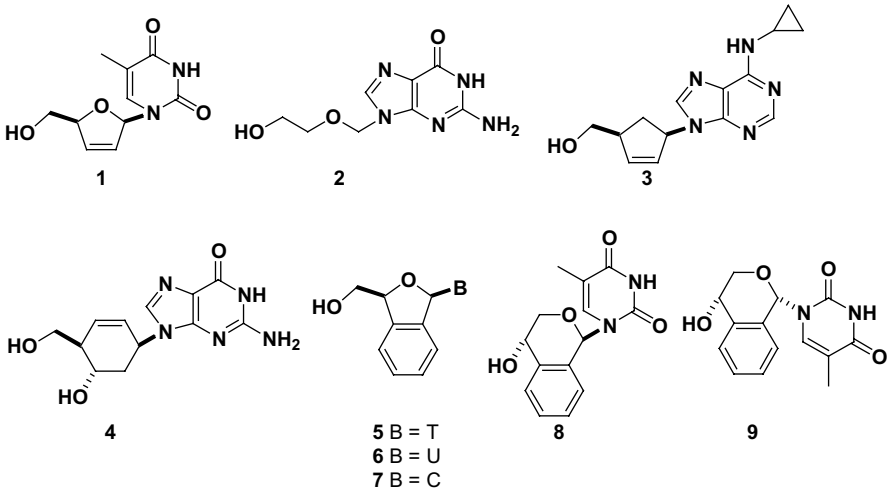


Figure 1. Nucleoside analogues **1**–**9**.

groups gave the more stable isochroman derivative **14**. Glycosylation of the methoxy derivatives **16** with bis(trimethylsilyl)thymine using the Vorbruggen methodology[14,15] afforded the two epimeric nucleoside analogues **18**[16] and **19**[17] in 35% and 33% yields, respectively. Classical deprotection of the secondary hydroxyl group on each of **18** and **19** afforded the target nucleosides **8**[18] and **9**[19] in quantitative yield (Scheme 1).

Assignment of the (*S*)-configuration at the $C_{4'}$ atom was made on the basis that the AD step occurred without any loss of chiral integrity during the successive cyclisation, glycosylation and deacetylation reactions. Anomeric configurations were established by NMR spectroscopy. The β-configuration of the thymine derivative **18** (i.e., $C_{1'}$ atom having *R* configuration) was established by NOE (Fig. 2): irradiation of the proton at $C_{1'}$ gave an enhanced signal for $H_{3'\alpha}$ and irradiation of the proton $H_{3'\beta}$ gave enhanced signals for $H_{4'}$ and H_6 and vice versa. These results showed that the thymine base was in the *anti* conformation in the nucleoside **18**. The α-configuration of **19** (i.e., $C_{1'}$ atom having *S* configuration) was also established by NOE (Fig. 2):

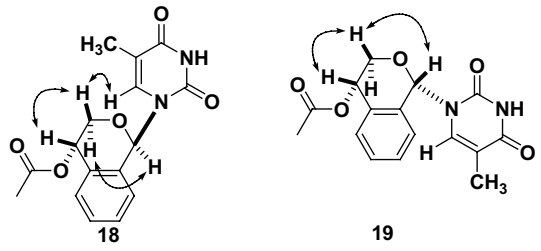
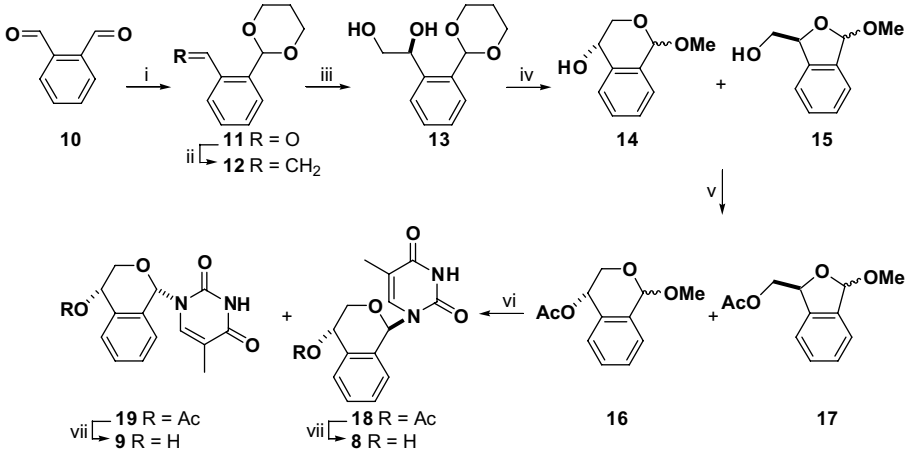


Figure 2. NOE experiments of nucleosides **18** and **19**.

irradiation of the proton at $C_{1'}$ gave an enhanced signal for $H_{3'\beta}$ and irradiation of the proton $H_{3'\beta}$ gave enhanced signals for $H_{4'}$ and $H_{1'\beta}$ and vice versa. It is notable that no NOE was detected for the protons $H_{3'\alpha}$ and H_6.

Comparison of the coupling constants between the $H_{3'}$ protons ($H_{3'\alpha}$ and $H_{3'\beta}$) and $H_{4'}$ proton for the two diastereoisomers **18** and **19** was also interesting (Fig. 3). In the case of the nucleoside **18**, correlation between the coupling constants ($J_{H3'\alpha,H4'} = 5.9$ Hz; $J_{H3'\beta,H4'} =$



Scheme 1. Reagents and conditions: (i) propan-1,3-diol, PTSA, toluene, reflux, 78%; (ii) $CH_3(C_6H_5)_3PBr$, BuLi, THF, 77%; (ii) AD-mix α, *t*-BuOH, H_2O, 85%; (iv) MeOH, HCl 1%, 75%; (v) Ac_2O, pyridine, 85%; (vi) silylated thymine, $SnCl_4$, $C_2H_4Cl_2$, 68%; (vii) NH_3, MeOH (quant.).

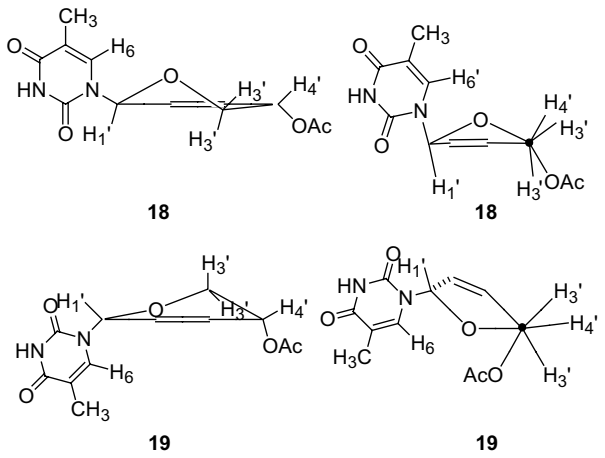


Figure 3. Nucleoside analogues **18** and **19**.

4.3 Hz) and the Karplus equation permitted prediction of the dihedral angles $H_{3'\alpha}C_{3'}C_{4'}H_{4'}$ (~−140°) and $H_{3'\beta}C_{3'}C_{4'}H_{4'}$ (~−22°), respectively, and consequently, the conformation of the target nucleoside **18** since both the dihedral angles $C_{1'}C_{9'}C_{10'}C_{4'}$ are planar and an NOE was obtained between the $H_{1'}$ and $H_{3'\alpha}$ protons indicating *syn* axial positions. Using a similar procedure for compound **19**, the weak *J* coupling of $H_{4'}$ proton between both $H_{3'\alpha}$ and $H_{3'\beta}$ protons ($J_{H3'\alpha,H4'}$ = 2.4 Hz; $J_{H3'\beta,H4'}$ = 1.7 Hz) enabled the dihedral angles $H_{3'\alpha}C_{3'}C_{4'}H_{4'}$ (~−70°) and $H_{3'\beta}C_{3'}C_{4'}H_{4'}$ (~+50°) to be predicted, and as a consequence, the conformation of the target nucleoside **19**.

In conclusion, a convenient route has been achieved to the highly enantiomerical pure bicyclic nucleosides involving AD using AD-mix α. The synthesis and biological evaluation of the corresponding cytosine, adenine and guanine derivatives, and their corresponding enantiomers are currently under investigation. Also, the secondary hydroxyl groups will be converted to phosphonates as prodrug analogues.

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15. A suspension of thymine (567 mg, 4.50 mmol) and a crystal of ammonium sulfate in 1,1,1,3,3,3-hexamethyldisilazane (10 mL) was refluxed with exclusion of moisture until a clear solution was obtained (3 h). Volatiles were

removed by repeated co-evaporation with toluene to leave the syrup. This syrup and the isochroman derivative **16** (500 mg, 2.25 mmol) were taken up in dry $C_2H_4Cl_2$ (12 mL) and $SnCl_4$ (528 μL, 4.50 mmol) added at −15 °C. After stirring overnight at room temperature, satd $NaHCO_3$ solution (20 mL) was added, the mixture stirred for 30 min and then extracted with CH_2Cl_2. This extract was worked up and the crude product chromatographed (hexane–EtOAc, 7:3, v/v) to give the diastereoisomer **18** (249 mg) in 35% yield as the first eluting compound and the diastereoisomer **19** (235 mg) in 33% yield as the second eluting compound.

16. Selected spectral data for compound **18**: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 1.81 (d, J = 1.0 Hz, 3H, CH_3–C_5), 2.17 (s, 3H, CH_3 acetyl), 3.98 (dd, J = 12.3 Hz, J = 5.9 Hz, 1H, $H_{3'\alpha}$), 4.27 (dd, J = 4.3 Hz, 1H, $H_{3'\beta}$), 6.06 (dd, 1H, $H_{4'}$), 6.64 (br s, 1H, H_5), 7.07 (d, J = 7.0 Hz, 1H, H arom), 7.19 (s, 1H, $H_{1'}$), 7.43–7.47 (m, 3H, H arom), 8.73 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 12.9 (CH_3–C_5), 21.5 (CH_3 acetyl), 65.4 ($C_{3'}$), 65.6 ($C_{4'}$), 80.3 ($C_{1'}$), 111.8 (C_5), 126.4, 128.6, 129.9, 130.0 (4C, C arom), 132.0, 134.5 (2C, $C_{9'}$, $C_{10'}$), 136.9 (C_6), 152.0 (C_2), 164.5 (C_4), 171.2 (COCH$_3$). MS (ES) 339.10 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{16}N_2O_5$ (316.11 g/mol): C, 60.75; H, 5.10; N, 8.86. Found: C, 60.77; H, 5.06; N, 8.91.
17. Selected spectral data for compound **19**: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 1.85 (d, J = 1.0 Hz, 3H, CH_3–C_5), 2.18 (s, 3H, CH_3 acetyl), 4.16 (dd, J = 13.3 Hz, J = 2.4 Hz, 1H, $H_{3'\alpha}$), 4.32 (dd, J = 1.7 Hz, 1H, $H_{3'\beta}$), 5.84 (dd, 1H, $H_{4'}$), 6.93 (q, 1H, H_5), 7.04 (s, 1H, $H_{1'}$), 7.08 (m, 1H, H arom), 7.42–7.50 (m, 3H, H arom), 8.73 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 13.0 (CH_3–C_5), 21.7 (CH_3 acetyl), 66.3 ($C_{4'}$), 68.2 ($C_{3'}$), 80.5 ($C_{1'}$), 112.4 (C_5), 126.1, 129.1, 130.6, 130.9 (4C, C arom), 133.2, 133.6 (2C, $C_{9'}$, $C_{10'}$), 136.9 (C_6), 151.7 (C_2), 164.1 (C_4), 170.1 (COCH$_3$). MS (ES) 339.10 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{16}N_2O_5$ (316.11 g/mol): C, 60.75; H, 5.10; N, 8.86. Found: C, 60.79; H, 5.07; N, 8.88.
18. Selected spectral data for compound **8**: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, ppm) δ: 1.66 (s, 3H, CH_3–C_5), 3.70 (dd, J = 11.2 Hz, J = 8.1 Hz, 1H, $H_{3'\alpha}$), 4.12 (dd, J = 5.0 Hz, 1H, $H_{3'\beta}$), 4.81 (dd, 1H, $H_{4'}$), 6.91 (s, 1H, H_6), 7.00 (m, 2H, $H_{1'}$, H arom), 7.30–7.61 (m, 3H, H arom), 11.5 (br s, 1H, NH). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, ppm) δ: 12.8 (CH_3–C_5), 63.4 ($C_{4'}$), 69.2 ($C_{4'}$), 80.6 ($C_{1'}$), 110.9 (C_5), 125.9, 128.1, 128.6, 129.4 (4C, C arom), 130.3, 132.5 (2C, $C_{9'}$, $C_{10'}$), 137.9 (C_6), 152.0 (C_2), 164.7 (C_4). MS (ES) 297.08 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{14}N_2O_4$ (274.10 g/mol): C, 61.31; H, 5.14; N, 10.21. Found: C, 61.35; H, 5.12; N, 10.25.
19. Selected spectral data for compound **9**: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, ppm) δ: 1.67 (s, 3H, CH_3–C_5), 3.96 (dd, J = 12.0 Hz, J = 2.8 Hz, 1H, $H_{3'\alpha}$), 4.05 (dd, J = 2.5 Hz, 1H, $H_{3'\beta}$), 4.49 (br s, 1H, $H_{4'}$), 6.83 (s, 1H, H_6), 7.00 (d, J = 7.5 Hz, 1H, H arom), 7.23 (s, 1H, $H_{1'}$), 7.30–7.50 (m, 3H, H arom), 11.5 (br s, 1H, NH). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, ppm) δ: 12.9 (CH_3–C_5), 63.9 ($C_{4'}$), 70.0 ($C_{4'}$), 80.3 ($C_{1'}$), 110.7 (C_5), 125.9, 129.3, 129.6, 130.3 (4C, C arom), 133.2, 139.0 (2C, $C_{9'}$, $C_{10'}$), 138.1 (C_6), 152.1 (C_2), 164.7 (C_4). MS (ES) 297.08 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{14}N_2O_4$ (274.10 g/mol): C, 61.31; H, 5.14; N, 10.21. Found: C, 61.35; H, 5.12; N, 10.25.