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TETRAHEDRON: *ASYMMETRY*

Diastereoselective and enantioselective synthesis of 4′-aza analogues of 2′,3′-dideoxynucleosides

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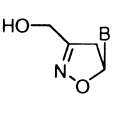
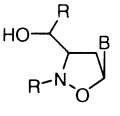
Abstract

A diastereo- and enantioselective synthesis of 4′-aza analogues of 2′,3′-dideoxynucleosides has been designed by the strategy of the 1,3-dipolar cycloaddition reaction of a Vasella-type nitrone. The reaction leads to (1′*R*)- and (1′*S*)-4′-aza analogues of 2′,3′-dideoxythimidine and fluorouridine, in enantiomerically pure forms.

Modification of naturally occurring nucleosides has led to the discovery of important HIV agents as AZT, D4T and 3TC.[1] In this context nucleosides **1** and **2** containing an isoxazoline or isoxazolidine moiety are of current interest as potential antiviral agents.[2,3]



1



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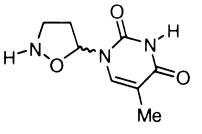
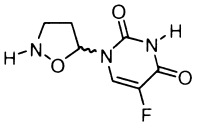


3



4

The synthesis of isoxazolidinyl nucleoside **3**, unsubstituted at the nitrogen atom and in racemic form, has been recently reported.[4] In particular, ADT **3** shows important antiviral and anti AIDS activity. Moreover, ADT inhibits HIV replication in C 8166, with an activity inversely related to the multiplicity of infection used;[4b] however, it is well known that both enantiomeric purity and absolute configuration are key factors in determining the physiological activity of drugs.[5]

Herein, we report the first example of an enantioselective and diastereoselective synthesis of (1′*R*)- and (1′*S*)-4′-aza analogues of 2′,3′-dideoxythimidine and fluorouridine **3** and **4**. The key step of our approach consists in the 1,3-dipolar cycloaddition of a chiral nitrone, containing a

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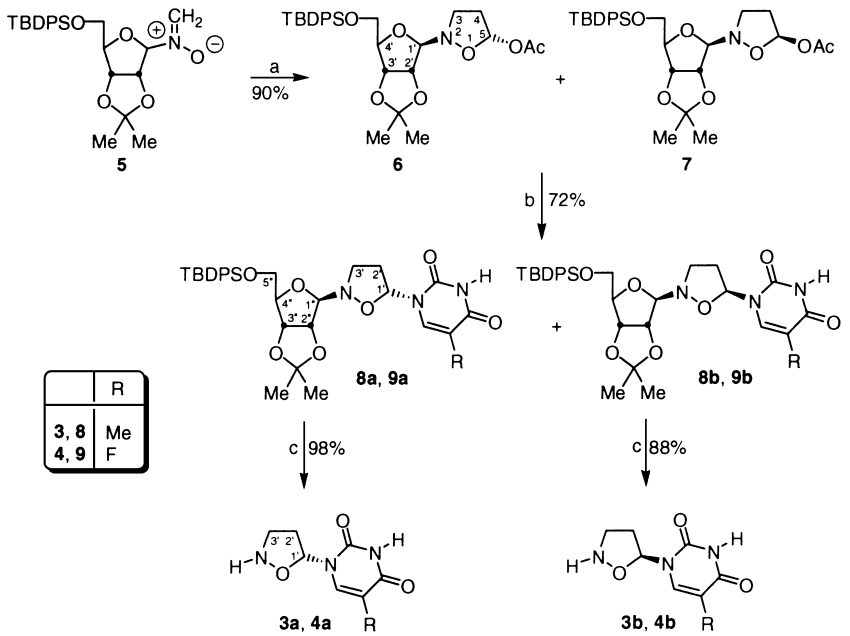
stereogenic centre at the nitrogen atom,[6] to vinyl acetate in order to construct the isoxazolidine ring. Thus, the Vasella-type nitrone **5**, prepared according to the previously reported methodology,[7] has been reacted with vinyl acetate in the absence of solvent, using a 1:10 relative ratio of dipole/dipolarophile, for 36 h to give a mixture of two homochiral isoxazolidines **6** and **7** (90% global yield), epimeric at C_5 of the isoxazolidine ring,[6,7] in a ratio 1.4:1 (Scheme 1).



Scheme 1. (a) Vinyl acetate, 70°C; (b) silylated base, TMSOTf or $SnCl_4$; (c) 1.5% HCl in EtOH

The epimeric isoxazolidines **6** and **7** were then coupled with silylated thymine in acetonitrile in the presence of TMSOTf or with 5-fluorouracil, in CH_2Cl_2 at 0°C, in the presence of one equivalent of $SnCl_4$, to afford, with a moderate stereoselectivity and in good yields, the expected isoxazolidinyl nucleosides **8a**,**b** and **9a**,**b**, respectively (**8a**/**8b** ratio 1.4:1, **9a**/**9b** ratio 1.8:1), which have been separated by HPLC chromatography.[8] The assigned stereochemistry of the obtained adducts is supported by NMR analyses. In fact, NOE measurements, performed on **8a**,**b** and **9a**,**b** show a positive NOE effect for protons 4″ when irradiating 1″ thus indicating a *cis* relationship between these protons.

Mixtures of diastereomeric invertomers could be observed for compounds **8** and **9**; however, the NMR data show, at room temperature, only one set of resonances thus suggesting the existence of only one isomer or a nitrogen inversion sufficiently fast to impart time-averaged properties to the observed compounds. Variable temperature NMR measurements were conducted: only one invertomer could be observed. In fact, when lowering the temperature to –80°C, it was impossible to reveal the presence of two invertomers.

PM3[9] and AM1[10] quantomechanical calculations allow for a clear rationalization of the obtained results. Structural analyses regarding the stabilities of the isomers formed indicate that the $N_{4'}$–$C_{1'}$ *trans* isomers are more stable than the *cis*. An energy difference of 4.3 kcal/mol for compound **8a** was calculated in favour of the *trans* isomer: this barrier sufficiently explains the fact that experimentally only one invertomer was formed. The calculated energy barrier for the nitrogen

inversion is 13.91 kcal/mol: a value of 16.2 is reported for similar systems.[11] The marked preference for the *trans* form makes these compounds analogues of α-nucleosides. Thus, for obtained α and β anomers, the difference of configuration of their $C_{1'}$ atoms is compensated by the nitrogen inversion and both anomers possess the same *trans* disposition of their $N_{4'}$ and $C_{1'}$ substituents.

On this basis and according with the quantomechanical calculations, the relative configuration at $N_{4'}$ and $C_{1'}$ for nucleosides **8** and **9** has been assigned as reported in Scheme 1. The major stereoisomers **8a** and **9a** can be assigned the configuration (1′*R*) which is more stable than the configuration (1′*S*) of about 0.8 kcal: this value is in agreement with the observed a/b ratio.

Finally, the synthetic scheme devoted towards the synthesis of homochiral 4′-aza-2′,3′-dideoxy-nucleosides has been completed by the selective cleavage of the sugar moiety, performed by treatment with 1.5% aqueous HCl: in this way two separate enantiomers **3a**,**b** and **4a**,**b** have been obtained.[12]

In conclusion, both anomers of 4′-aza-2′,3′-dideoxynucleosides have been synthesized in an enantiomerically pure form.[13] According to the reported biological activity,[4b] shown in vitro by this class of compounds, the designed methodology appears versatile and potentially extendable to the synthesis of other aza-nucleosides containing different purine and pyrimidine bases.

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8. HPLC separation for **8a** and **8b**: linear gradient of 2-propanol (6–10%, 0–15 min, flow 3.5 mL/min) in hexane. Compound **8a**: t_R 13.2 min; 42% yield; white solid; mp 61–63°C; $[\alpha]_D^{25} = -34.1$ ($c = 0.36$; $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.07 (s, 9H), 1.35 (s, 3H), 1.54 (s, 3H), 1.87 (d, 3H, $J = 1.1$ Hz), 2.23 (ddt, 1H, $J = 3.1$, 7.1 and 13.3 Hz,

$H_{2'a}$), 2.73 (dq, 1H, $J=7.1$ and 13.3 Hz, $H_{2'b}$), 3.18 (t, 2H, $J=7.1$ Hz, $H_{3'}$), 3.72 (dd, 1H, $J=6.3$ and 10.7 Hz, $H_{5''a}$), 3.74 (dd, 1H, $J=6.0$ and 10.7 Hz, $H_{5''b}$), 4.25 (ddd, 1H, $J=2.9$, 6.0 and 6.3 Hz, $H_{4''}$), 4.58 (dd, 1H, $J=2.9$ and 6.3 Hz, $H_{3''}$), 4.72 (dd, 1H, $J=2.5$ and 6.3 Hz, $H_{2''}$), 4.82 (d, 1H, $J=2.5$ Hz, $H_{1''}$), 5.99 (dd, 1H, $J=3.1$ and 7.1 Hz, $H_{1'}$), 7.40 (q, 1H, $J=1.1$ Hz, H_6), 7.36–7.68 (m, 10H), 8.59 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.64, 19.23, 25.40, 26.78, 27.18, 36.76, 48.26, 64.19, 81.19, 82.77, 84.16, 85.99, 90.04, 110.73, 113.31, 127.74, 129.80, 129.86, 133.18, 135.55, 150.00, 163.70. Anal. calcd for $C_{32}H_{41}N_3O_7Si$: C, 63.24; H, 6.80; N, 6.91%. Found: C, 63.22; H, 6.81; N, 6.90%. Compound **8b**: t_R 14.7 min; 30% yield; white solid; mp 57–58°C; $[\alpha]_D^{25}=+24.5$ ($c=0.29$; $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.06 (s, 9H), 1.35 (s, 3H), 1.53 (s, 3H), 1.83 (d, 3H, $J=1.2$ Hz), 2.18 (dddd, 1H, $J=3.2$, 6.5, 7.0 and 14.0 Hz, $H_{2'a}$), 2.76 (dddd, 1H, $J=7.0$, 7.2, 8.0 and 14.0 Hz, $H_{2'b}$), 3.12 (ddd, 1H, $J=6.5$, 8.0 and 10.5 Hz, $H_{3'a}$), 3.17 (dt, 1H, $J=7.0$ and 10.5 Hz, $H_{3'b}$), 3.72 (dd, 1H, $J=5.6$ and 10.7 Hz, $H_{5''a}$), 3.75 (dd, 1H, $J=6.1$ and 10.7 Hz, $H_{5''b}$), 4.29 (ddd, 1H, $J=1.5$, 5.6 and 6.1 Hz, $H_{4''}$), 4.63 (d, 1H, $J=1.4$ Hz, $H_{1''}$), 4.71 (dd, 1H, $J=1.5$ and 9.5 Hz, $H_{3''}$), 4.72 (dd, 1H, $J=1.4$ and 9.5 Hz, $H_{2''}$), 6.25 (dd, 1H, $J=3.2$ and 7.2 Hz, $H_{1'}$), 7.29 (q, 1H, $J=1.2$ Hz, H_6), 7.36–7.67 (m, 10H), 8.51 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.66, 19.22, 25.15, 26.79, 36.01, 48.46, 64.24, 81.45, 83.01, 84.15, 86.35, 99.75, 113.28, 127.75, 127.77, 129.88, 133.07, 135.40, 135.46, 135.51, 150.01, 163.72. Anal. calcd for $C_{32}H_{41}N_3O_7Si$: C, 63.24; H, 6.80; N, 6.91%. Found: C, 63.30; H, 6.79; N, 6.92%. HPLC separation for **9a** and **9b**: linear gradient of 2-propanol (5–7.5%, 0–13 min, flow 3.5 mL/min) in hexane. Compound **9b**: t_R 15.2 min; 26% yield; white solid; mp 69–71°C; $[\alpha]_D^{25}=-39.1$ ($c=0.32$; $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.07 (s, 9H), 1.30 (s, 3H), 1.54 (s, 3H), 2.23 (ddt, 1H, $J=2.8$, 7.5 and 13.5 Hz, $H_{2'a}$), 2.76 (ddt, 1H, $J=6.9$, 7.5 and 13.5 Hz, $H_{2'b}$), 3.16 (t, 2H, $J=7.5$ Hz, $H_{3'}$), 3.72 (dd, 1H, $J=5.9$ and 10.8 Hz, $H_{5''a}$), 3.73 (dd, 1H, $J=5.9$ and 10.8 Hz, $H_{5''b}$), 4.27 (dt, 1H, $J=2.9$ and 5.9 Hz, $H_{4''}$), 4.57 (dd, 1H, $J=2.8$ and 6.2 Hz, $H_{3''}$), 4.71 (dd, 1H, $J=2.5$ and 6.2 Hz, $H_{2''}$), 4.84 (d, 1H, $J=2.5$ Hz, $H_{1''}$), 5.92 (dd, 1H, $J=2.8$ and 6.9 Hz, $H_{1'}$), 7.36–7.68 (m, 10H), 7.73 (d, 1H, $J=6.0$ Hz, H_6), 9.49 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.08, 19.24, 25.38, 26.79, 27.18, 36.98, 47.88, 64.15, 81.15, 82.77, 84.50, 86.05, 98.70, 113.42, 124.34 (d, $J=34.1$ Hz), 127.70, 127.74, 129.81, 129.87, 133.16, 133.19, 135.55, 135.56, 148.67, 157.32. Anal. calcd for $C_{31}H_{38}FN_3O_7Si$: C, 60.87; H, 6.26; N, 6.87%. Found: C, 60.89; H, 6.25; N, 6.87%. Compound **9a**: t_R 16.0 min; 46% yield; white solid; mp 52–54°C; $[\alpha]_D^{25}=+15.2$ ($c=0.49$; $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.07 (s, 9H), 1.35 (s, 3H), 1.52 (s, 3H), 2.19 (dddd, 1H, $J=2.0$, 3.0, 7.0 and 13.5 Hz, $H_{2'a}$), 2.78 (dddd, 1H, $J=2.0$, 7.5, 8.0 and 13.5 Hz, $H_{2'b}$), 3.05 (ddd, 1H, $J=2.0$, 8.0 and 10.5 Hz, $H_{3'a}$), 3.16 (ddd, 1H, $J=2.0$, 7.0 and 10.5 Hz, $H_{3'b}$), 3.70 (dd, 1H, $J=6.0$ and 11.0 Hz, $H_{5''a}$), 3.74 (dd, 1H, $J=6.0$ and 11.0 Hz, $H_{5''b}$), 4.30 (dt, 1H, $J=1.5$ and 6.0 Hz, $H_{4''}$), 4.62 (d, 1H, $J=1.5$ Hz, $H_{1''}$), 4.70 (dd, 1H, $J=1.5$ and 7.5 Hz, $H_{3''}$), 4.71 (dd, 1H, $J=1.5$ and 7.5 Hz, $H_{2''}$), 6.20 (dd, 1H, $J=3.0$ and 7.5 Hz, $H_{1'}$), 7.37–7.66 (m, 10H), 7.58 (d, 1H, $J=6.0$ Hz, H_6), 9.19 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.10, 19.22, 25.10, 26.80, 26.84, 36.35, 48.56, 64.19, 81.41, 82.98, 84.60, 86.36, 99.98, 113.37, 124.10 (d, $J=33.6$ Hz), 127.76, 127.79, 129.91, 129.99, 132.95, 133.01, 135.44, 135.49, 148.58, 156.88. Anal. calcd for $C_{31}H_{38}FN_3O_7Si$: C, 60.87; H, 6.26; N, 6.87%. Found: C, 60.88; H, 6.27; N, 6.86%.

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12. Compound **3a**: 97.5% yield; white solid; mp 202–204°C; $[\alpha]_D^{25}=-93.7$ ($c=0.16$; CH_3OH); ^{1}H NMR ($DMSO_{d6}$, 500 MHz): δ 1.75 (d, 3H, $J=1.1$ Hz), 2.55 (dddd, 1H, $J=3.1$, 8.0, 9.0 and 14.0 Hz, $H_{2'a}$), 2.62 (dddd, 1H, $J=6.0$, 7.1, 9.0 and 14.0 Hz, $H_{2'b}$), 3.67 (ddd, 1H, $J=6.0$, 8.0 and 10.5 Hz, $H_{3'a}$), 3.97 (ddd, 1H, $J=7.1$, 9.0 and 10.5 Hz, $H_{3'b}$), 6.21 (dd, 1H, $J=3.1$ and 7.9 Hz, $H_{1'}$), 7.37 (q, 1H, $J=1.1$ Hz, H_6), 11.18 (bs, 1H, NH). ^{13}C NMR ($DMSO_{d6}$, 125 MHz): δ 14.51, 30.96, 47.14, 85.52, 110.18, 136.87, 151.06, 164.22. Anal. calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31%. Found: C, 48.71; H, 5.61; N, 21.33%. Compound **3b**: 98% yield; white solid; mp 202–204°C; $[\alpha]_D^{25}=+87.5$ ($c=0.09$; CH_3OH). Anal. calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31%. Found: C, 48.72; H, 5.62; N, 21.32%. Compound **4a**: 87% yield; white solid; mp 153–155°C; $[\alpha]_D^{25}=+78.6$ ($c=0.07$; CH_3OH); ^{1}H NMR (D_2O, 500 MHz): δ 2.36 (ddt, 1H, $J=3.0$, 6.2 and 14.1 Hz, $H_{2'a}$), 2.55 (ddt, 1H, $J=6.2$, 7.4 and 14.1 Hz, $H_{2'b}$), 3.13 (t, 2H, $J=6.2$ Hz, $H_{3'}$), 5.95 (dd, 1H, $J=3.0$ and 7.4 Hz, $H_{1'}$), 7.71 (d, 1H, $J=7.3$ Hz, H_6). ^{13}C NMR (D_2O, 125 MHz): δ 38.24, 49.34, 90.88, 129.00 (d, $J=34.4$ Hz), 140.91, 145.54, 151.92. Anal. calcd for $C_7H_8FN_3O_3$: C, 41.80; H, 4.01; N, 20.89%. Found: C, 41.79; H, 4.00; N, 20.90%. Compound **4b**: 88% yield; white solid; mp 152–155°C; $[\alpha]_D^{25}=-75.3$ ($c=0.05$; CH_3OH). Anal. calcd for $C_7H_8FN_3O_3$: C, 41.80; H, 4.01; N, 20.89%. Found: C, 41.77; H, 4.02; N, 20.91%.
13. The purity of all homochiral compounds has been tested with a 25 cm chiral Daicell OJ column with mixtures of *n*-hexane/2-propanol as eluent.