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SYNTHESIS OF [3.3.0] BICYCLIC ISOXAZOLIDINYL NUCLEOSIDES

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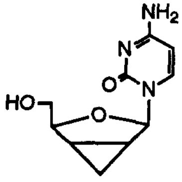
Abstract: The isoxazolidine derivative **6**, prepared from an intermolecular 1,3-dipolar cycloaddition of the (5*S*)-unsaturated lactone **5** and *N*-methylnitrone, was effectively used for the synthesis of [3.3.0] bicyclic isoxazolidinyl cytidine **4a** and thymidine **4b**. Copyright © 1996 Elsevier Science Ltd

The utility of modified nucleosides as enzyme inhibitors has attracted great attention of synthetic chemists, as well as biologists, for the discovery of agents with divergent biological properties, particularly with anti-HIV activity.[1] Towards this goal, several sugar-modified derivatives have been developed exhibiting excellent antiviral activity.[1-2] Of particular interest are the bicyclic nucleosides **1-3**, in which the furanosyl moiety is fused to a 3-, 5-, or 6-membered ring.[2-4] While the studies found **1**[2] and **3**[4] to be moderately anti-HIV active, these investigations did not include the steric effects of strained bicyclic systems on the activity. Therefore, we are interested in the design and synthesis of various bicyclic nucleosides such as **4** to provide diverse models for further search towards novel analogs.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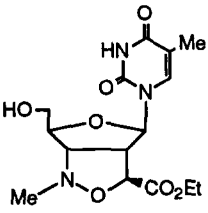
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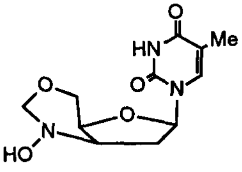
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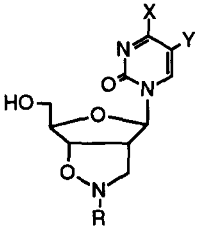
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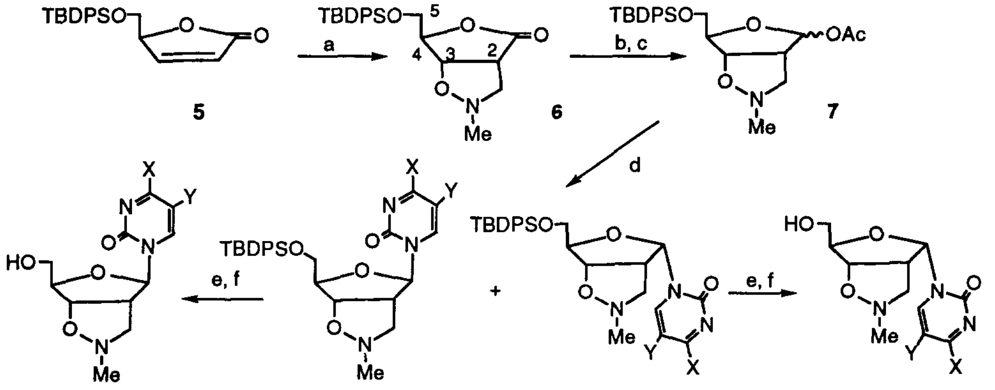
The bicyclic nucleosides **4**, containing N-O moieties, can be structurally manipulated for the desired electronic or steric properties. Recently,[5-6] we reported the syntheses of several classes of isoxazole-related nucleosides for antiviral studies and the 1,3-dipolar cycloaddition method afforded dihydroisoxazole nucleosides with moderate anti-HIV-1 activities.[5] Intramolecular variant of 1,3-dipolar cycloaddition has been used for the synthesis of bulky bicyclic 1,2-isoxazolidine-fused nucleosides

2.[3a] Herein, we report an intermolecular 1,3-dipolar cycloaddition for the efficient construction of 2',3'-dideoxy-2',3'-isoxazolidine-α-fused bicyclic nucleosides **4**. This method offers several advantages: (i) a versatile intermediate **7** can be efficiently constructed, and (ii) **7** can be readily condensed with several nucleoside bases leading to a class of fused bicyclic-isoxazolidine analogs.



4a: X = NH_2, Y = H
4b: X = OH, Y = Me

8a: X = NHBz, Y = H
8b: X = OH, Y = Me

9a: X = NHBz, Y = H
9b: X = OH, Y = Me

10a: X = NH_2, Y = H
10b: X = OH, Y = Me

Scheme 1. (a) Paraformaldehyde, MeNHOH.HCl, Et_3N, PhH, reflux, 12 h; (b) DIBAL, CH_2Cl_2, -78 °C, 1 h; (c) AcCl, Et_3N, CH_2Cl_2, rt, 3 h; (d) Silylated pyrimidine, CH_2Cl_2, TMSOTf, rt, 12 h; (e) TBAF, THF, rt, 30 min; (f) Saturated NH_3, MeOH, rt, 12 h.

The cycloaddition of nitrones to α,β-unsaturated γ-lactones[7-8] has been widely studied for the preparation of bicyclic isoxazolidine compounds in which the regiochemistry is controlled by the use of "bulky" nitrones. In our experiment, the "small" nitrone, derived from the condensation of *N*-methylhydroxylamine and paraformaldehyde,[9] reacted with (5*S*)-[(*tert*-butyldiphenylsilyl)oxymethyl]-5*H*-furan-2-one **5** under refluxing conditions to afford the cycloaddition compound **6** as a single isomer in 90% yield.[10] The configuration of **6** was confirmed from its ^1H NMR spectrum in which the H-3 (δ = 4.85 ppm) and H-2 (δ = 3.55-3.58 ppm) chemical shifts were consistent with the literature reports.[8c] Reduction of **6** by DIBAL, followed by acetylation provided **7** in 66% yield as a mixture of α and β isomers (α:β, 2:3). Condensation of **7** with silylated N^4-benzoylated cytosine in the presence of TMSOTf yielded the nucleosides **8a** and **9a**, which were separable by silica gel chromatography. Of the two reaction solvents, methylene chloride gave a slightly higher α:β ratio (**9a**:**8a**, 4:1, 75%) than acetonitrile (**9a**:**8a**, 5:3, 83%). Particularly noteworthy is the formation of the α isomer as the major product in the condensation. The desired nucleosides **4a** (94%) and **10a** (97%) were obtained after deprotection by TBAF, and followed by treatment with saturated methanolic ammonia.[11-12] The αstereochemistry of cytosine analog **10a** was deduced from the studies of its ^{1}H NMR NOE data. Saturation of H1' in the α-isomer **10a** gives NOE only at H2', whereas the saturation of H1' in the β-nucleosides gives NOE at both H2' and H4'.[3a]

The corresponding thymidine analogs were prepared in a similar procedure. The α:β ratio of the condensed products was again higher in CH_2Cl_2 (**9b**:**8b**, 3:1, 88%) than in CH_3CN (**9b**:**8b**, 3:2, 68%). While the two isomers could not be separated by silica gel chromatography, the α isomer **10b** was obtained by fractional crystallization from the α and β mixture in methanol and chloroform.[13] Preliminary biological studies of **4a**, **10a**, **10b**, and the mixture of **4b** and **10b** against HIV-1 revealed no significant activities or cytotoxicities up to 100 μM level in acutely infected lymphocytes.

The present method provides a simple approach to the synthesis of a new class of 2',3'-*cis*-α-fused-isoxazolidine nucleosides. Since a variety of nitrones are conveniently available from *N*-alkyl hydroxylamines and aldehydes, the *N*-Me and *N*-methylene groups of isoxazolidine **7** could be easily replaced with other alkyl groups. In addition, the reduction or oxidation of the N-O moiety of isoxazolidine **7** will lead to 2'-modified sugar intermediates for their subsequent conversion to the corresponding monocyclic nucleosides.

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10. Compound **6**: ^{1}H NMR (CDCl$_3$): δ 7.40-7.66 (m, 10H, Ph), 4.87 (d, *J* = 7.1 Hz, 1H, H-3), 4.57 (m, 1H, H-4), 3.75-3.96 (m, 2H, H-5), 3.55-3.58 (m, 2H, H-2 and CH$_2$N), 2.72 (m, 4H, NMe and CH$_2$N), 1.04 (s, 9H, Me). Anal. calcd for $C_{23}H_{29}NO_4Si$: C, 67.06; H, 7.10; N, 3.40. Found: C, 67.06; H, 7.14; N, 3.33.
11. Compound **4a**: $[\alpha]_D^{25}$ +29.4 ° [c 1.29, MeOH]. ^{1}H NMR (DMSO-*d*$_6$): δ 7.72 (d, *J* = 7.2 Hz, 1H, H-6), 7.18 (bs, 2H, NH$_2$), 5.83 (d, *J* = 5.1 Hz, 1H, H-1'), 5.74 (d, *J* = 7.2 Hz, 1H, H-5), 4.98 (t, *J* = 5.1 Hz, 5'-OH), 4.58 (m, 1H, H-3'), 3.91(m, 1H, H-4'), 3.60 (m, 2H, H-5'), 3.10 (m, 1H, H-2'), 2.65 (s, 3H, NMe), 2.43-2.53 (m, 2H, NCH$_2$). Anal. calcd for $C_{11}H_{16}N_4O_4 \cdot 1.0\ H_2O$: C, 46.15; H, 6.33; N, 19.57. Found: C, 46.16; H, 6.37; N, 19.57.
12. Compound **10a**: $[\alpha]_D^{25}$ -57.4 ° [c 1.68, MeOH]. ^{1}H NMR (DMSO-*d*$_6$): δ 7.63 (d, *J* = 7.2 Hz, 1H, H-6), 7.12-7.18 (m, 2H, NH$_2$), 6.04 (d, *J* = 7.0 Hz, 1H, H-1'), 5.74 (d, *J* = 7.2 Hz, 1H, H-5), 5.02 (t, *J* = 4.9 Hz, 5'-OH), 4.71 (m, 1H, H-3'), 4.24 (m, 1H, H-4'), 3.52-3.63 (m, 3H, H-2', H-5'), 2.50 (m, 5H, NMe, NCH$_2$). Anal. calcd for $C_{11}H_{16}N_4O_4 \cdot 0.25\ H_2O$: C, 48.44; H, 6.10; N, 20.54. Found: C, 48.43; H, 6.10; N, 20.44.
13. Compound **10b**: $[\alpha]_D^{25}$ -1.0 ° [c 0.81, MeOH]. ^{1}H NMR (DMSO-*d*$_6$): δ 7.51 (s, 1H, H-6), 6.09 (d, *J* = 7.1 Hz, 1H, H-1'), 5.02 (t, *J* = 4.2 Hz, 5'-OH), 4.74 (m, 1H, H-3'), 4.30 (m, 1H, H-4'), 3.52-3.56 (m, 3H, H-2', H-5'), 2.70 (m, 1H, NCH$_2$), 2,53 (m, 4H, NMe, NCH$_2$), 1.80 (s, 3H, Me). Anal. calcd for $C_{12}H_{17}N_3O_5$: C, 50.88; H, 6.05; N, 14.83. Found: C, 50.70; H, 6.03; N, 14.74.

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