Pergamon

Tetrahedron Letters, Vol. 37, No. 28, pp. 4877-4880, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00999-9

ENANTIOSELECTIVE SYNTHESIS OF ISOXAZOLIDINYL THYMINE AND CYTOSINE NUCLEOSIDES

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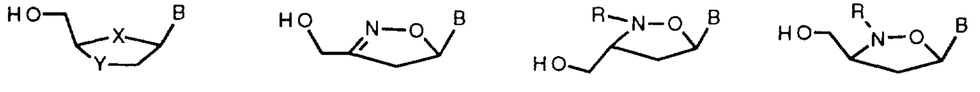
Summary: A diastereo- and enantioselective synthesis of isoxazolidinyl nucleosides (**4**) is described. The required isoxazolidine intermediate (**16**) was successfully prepared by the dioxolane-derived tautomerization of the corresponding lactol (**13**) which, in turn, was obtained from the reduction of the Michael adduct of N-methyl hydroxylamine and the unsaturated γ-lactone (**5**).

Modification of naturally occurring nucleosides has resulted in the development of important anti HIV agents such as AZT, ddI, ddC, d4T and 3TC.[1,2] 2',3'-Dideoxyucleoside analogs (**1**), lacking the 3'-hydroxyl group (Scheme 1), are expected to terminate viral DNA synthesis after their incorporation in the chains. Other strategies for the development of selective and potent antiviral agents include the insertion of a second heteroatom into the furanose ring of 2',3'-dideoxynucleoside analogs (**1**; X, Y = O or S). Recently, we reported the racemic synthesis of diheteroatom-containing compounds (**2-4**),[3,4] and found that the adenine and 6-chloropurine analogs of (**2**) exhibited moderate anti HIV-1 activities.[4] Since the original method employed a nitrile oxide cycloaddition reaction, nucleosides (**2**) were obtained as a racemic mixture. In this regard, we envision that the enantioselective synthesis of derivatives (**3**) or (**4**) will allow their potential transformation to optically active compounds (**2**). Furthermore, the parent analogs (**3-4**) can be used for the studies of the steric effect of N-alkyl group on the antiviral activity of isoxazolidinyl nucleosides. Herein, we report the first example of an *enantioselective* and *diastereoselective* synthesis of isoxazolidine-related products (**4**, R = Me).[5]

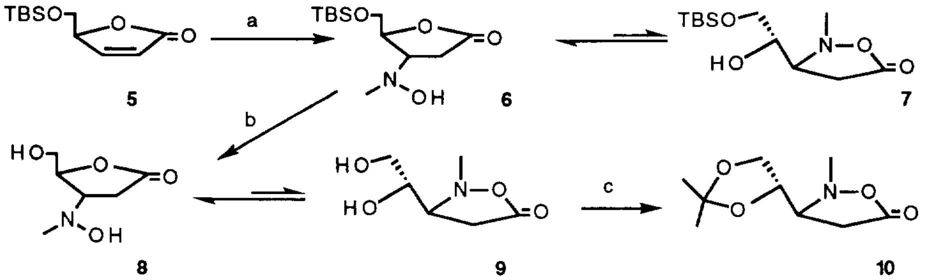
Scheme 1



1 **2** **3** **4**

The stereoselective Michael addition of nucleophiles to α, β-unsaturated δ-lactones is well recognized.[6] In our study (Scheme 2), we employed N-methyl hydroxylamine to react with the optically active lactones (**5**) via Michael addition. The major product was the lactone (**6**) (77%) which could not be rearranged to (**7**) even under mild basic conditions. This is in contrast to a similar hydroxylamine addition to the six-membered α, β-unsaturated lactones, which afforded the corresponding rearranged isoxazolidin-5-ones in good yields.[6a-b] Compound (**6**) was then deprotected by tetrabutylammonium fluoride to give (**8**), which presumably exists in equilibrium with (**9**). However, the use of 2,2-dimethoxypropane for the subsequent diol protection gave the isopropylidene-protected isoxazolidinone (**10**) in a low yield (6%).

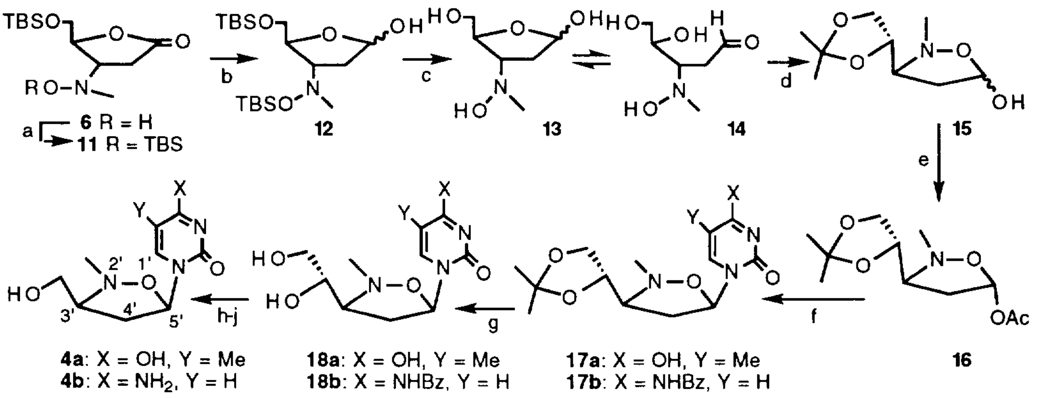
Scheme 2



(a) MeNHOH.HCl, Et_3N, THF, r t, 12 h; (b) TBAF, THF, r t, 1 h; (c) p-TsOH, $(MeO)_2CMe_2$, MeCOMe, pH =1, r t, 12 h.

Alternatively, the successful approach involves the conversion of lactol (**13**) to isoxazolidinyl lactol (**15**), probably via the aldehyde (**14**) as outlined in Scheme 3. The Michael adduct (**6**) was protected by TBS group to give (**11**) (82%) which was then reduced to lactol (**12**) by DIBAL in 78% yield. Desilylation of (**12**) produced a mixture which was converted the desired product (**15**) using 2,2-dimethoxypropane (52%). The preparation of acetate (**16**) from lactol (**15**) required a slightly acidic condition. Acetyl chloride (1.1 eq.) was premixed with pyridine (1.05 eq.) in methylene chloride and lactols (**15**) were then added to this solution to give acetate (**16**) in 66% yield.[7]

Scheme 3



(a) TBSCl, DMF, imidazole, r t, 2 h; (b) DIBAL, toluene, -78 °C, 1 h; (c) TBAF, THF, r t, 1h; (d) p-TsOH, 2,2-dimethoxypropane, acetone, pH =1, r t, 12 h; (e) AcCl, Py, CH_2Cl_2, r t, 12 h; (f) TMSOTf, silylated base, acetonitrile, r t, 3 h; (g) 60% AcOH, 70 °C, 30 min.; (h) $NaIO_4$, MeOH, H_2O, 0 °C, 1 h; (i) $NaBH_4$, 0 °C, 15 min.; j) NH_3, MeOH, r t, 12 h, for (**4b**).

Condensation of (**16**) with silylated thymine in acetonitrile in the presence of TMSOTf afforded a single isomer (**17a**) (53%). The exclusive formation of *cis* product was unexpected and, to our knowledge, such high selectivity in the process of non-metal-chelated glycosylation is unprecedented.[8] After deprotection of (**17a**) (67%), the resulting diol (**18a**) was oxidized to an aldehyde by sodium periodate at 0 °C. Direct reduction of the intermediate by sodium borohydride gave the desired compound (**4a**) in 60% overall yield. The *cis* stereochemistry of thymine analog (**4a**) was deduced from the comparison studies of its NMR NOESY data with that of the corresponding *trans* isomer.[9]

The scope of this synthetic scheme has also been tested by the preparation of cytidine analog which is generally believed to be a lead compound for the biological studies of a new class of nucleosides. Coupling of the silylated N^4-benzoylated cytosine with acetate (**16**) gave (**17b**) in 68% yield, which was then deprotected to diol nucleoside (**18b**) in 53% yield. Oxidation of (**17b**) followed by reduction and debenzoylation afforded the desired compound (**4b**) in 53% overall yield.[10]

The reported method provides an efficient procedure for the enantioselective synthesis of the biologically interesting isoxazolidine nucleosides (**4**) (R = Me). The scheme has been designed to allow the potential construction of other N-alkyl isoxazolidines. Special consideration has been made for the enantioselective synthesis of the N-(*p*-methoxybenzyl) derivative (**4**) (R = *p*-MeOBn) which will be converted to anti-HIV active dihydroisoxazoles (**2**) by oxidative removal of the *p*-methoxybenzyl group.[11] Meanwhile, the enantioselective syntheses and biological studies of other derivatives (**4**) containing different nucleoside bases are currently underway, and the results will be published in the due course.

Acknowledgments: We thank Professor Martin Semmelhack for his suggestions. K.Z. acknowledges financial support from the American Cancer Society (JFRA-517), the NSF Faculty Early Career Development Program (CHE-9502068), and the donors of the Petroleum Research Fund (28860-G1), administered by the American Chemical Society.

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5. For examples of the racemic synthesis of isoxazolidinyl nucleosides, see references 3, 4 and (a) Tronchet, J. M. J.; Iznaden, M.; Barbalat-Rey, F.; Dhimane, H.; Ricca, A.; Balzarini, J.; De Clercq, E. *Eur, J. Med. Chem.* **1992**, *27*, 555. (b) Tronchet, J. M. J.; Iznaden, M.; Barbalat-Rey, F.; Komaromi, I.; Dolatshahi, N.; Berbardinelli, G. *Nucleosides Nucleotides* **1995**, *14*, 1737.
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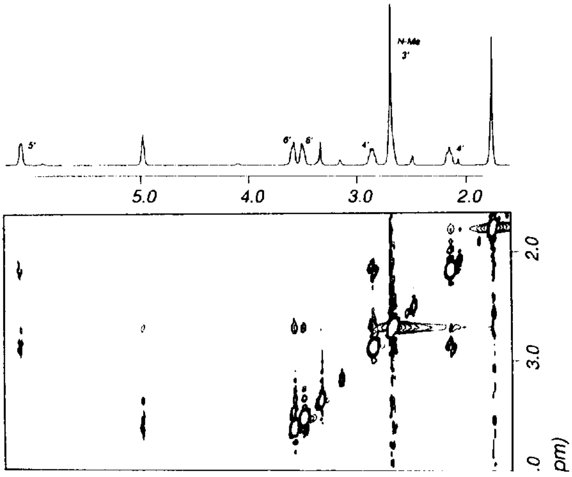
7. In the excess of pyridine, the hydroxylamine moiety was protected by acetate to produce a β-acetoxyamino aldehyde derivative. Compound (**16**): ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.32 (t, J = 3.6 Hz, 1H, H-5), 4.01 (m, 2H, H-6 and H-7), 3.73 (dd, J = 7.7, 5.0 Hz,1H, H-7), 3.13 (dd, J = 6.6, 13.5 Hz, 1H, H-3), 2.83 (s, 3H, N-Me), 2.54 (dd, J = 3.6, 6.8 Hz, 2H, H-4), 2.02 (s, 3H, Ac), 1.38 (s, 3H, Me), 1.29 (s, 3H, Me).
8. For the transition metal-chelated *cis* glycosylation of oxothiolanyl acetate and trimethylsilylated nucleoside bases, see: Wilson, L. J.; Choi, W.-B.; Spurling, T.; Liotta, D. C.; Schinazi, R. F.; Cannon, D.; Painter, G. R.; St. Clair, M.; Furman, P. A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 169.
9. A set of 2D TOCSY, DQF-COSY, and NOESY spectra was recorded for both (**4a**) and its *trans* analog (for the racemic preparation, see reference 3). In addition to the observed NOE peaks for both *cis* and *trans* compounds, only the *cis* isomer (**4a**) shows cross peaks between the $H_{5'}$-$H_{3'}$/N-CH_3 (Figure).



Figure

10. Compound (**4b**): ^{1}H NMR (200 MHz, CD_3OD) δ 8.03 (d, J = 7.5 Hz, 1H, H-6), 6.06 (dd, J = 3.7, 7.6 Hz, 1H, H-5'), 5.88 (d, J = 7.5 Hz,1H, H-5), 3.63 (ddd, J = 3.7, 13.5, 19.0 Hz, 2H, CH_2O), 3.02 (m, 1H, H-4'), 2.83 (bs, 4H, H-3' and N-Me), 2.15 (ddd, J = 3.9, 9.0, 12.8 Hz, 1H, H-4'). ^{13}C NMR (50 MHz, CD_3OD) δ 169.3; 143.1; 95.7; 85.4; 71.1; 62.6; 45.3; 42.9.
11. A method for the conversion of N-(*p*-methoxybenzyl)-isoxazolidines to dihydroisoxazoles by DDQ oxidation has been developed and a manuscript is in preparation.

(*Received in USA* 26 *March* 1996; *revised* 14 *May* 1996; *accepted* 15 *May* 1996)