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Pyrrolidine Based Analogs of 3'-Deoxythymidine

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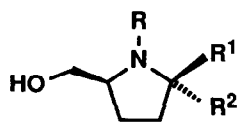
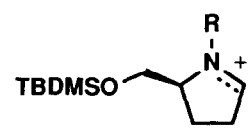
Abstract: *Pyrrolidine based analogs of 3'-deoxythymidine* ***1a,b*** *and* ***2a,b*** *have been prepared via N-acyliminium ion intermediates* ***3*** *and* ***4****.*

Over the last few years there has been an ever increasing interest in the synthesis and the pharmacological properties of 2',3'-dideoxynucleosides,[1,2] due to the ability of a number of these compounds to inhibit the growth of various types of viruses. Two of the most prominent examples are azidothymidine (AZT) and 2',3'-dideoxycytidine, which are both used in the treatment of AIDS.[2]

Among others, one of the approaches pursued to create more effective and especially more selective antiviral inhibitors has been the replacement of the tetrahydrofuran ring of 2',3'-dideoxynucleosides by a cyclopentane moiety, leading to carbocyclic nucleosides,[3] or by other five-membered heterocyclic rings. The latter class includes compounds that are derived from tetrahydrothiophene,[4] 1,3-dioxolane,[5a] 1,3-oxathiolane,[5b] isoxazole,[6] and pyrrolidine.[7,8] In all the *pyrrolidine* based analogs of 2',3'-dideoxynucleosides reported so far, the nitrogen replaces either C-1'[7] or C-3'[8] of a carbocyclic nucleoside; in contrast, no analogs are known in the literature where a nitrogen-atom is substituted for the oxygen-atom of the dideoxyribose moiety.[9]

This paper now describes the synthesis of pyrrolidine based analogs of α- and ß-3'-deoxythymidine **1a,b** and **2a,b** as the first examples of a potential new class of antiviral agents.





1: R = BnOCO (Z)
2: R = CH_3CO (Ac)

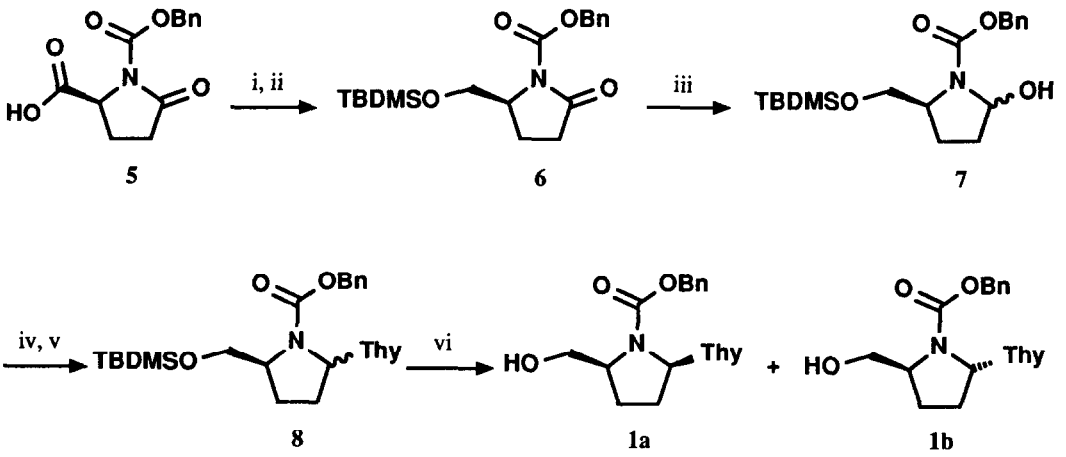
a: R^1 = thymine, R^2 = H
b: R^1 = H, R^2 = thymine

3: R = BnOCO
4: R = CH_3CO

The synthetic strategy applied is based on the Lewis acid catalyzed *in situ* generation of N-acyliminium ions[10] **3** and **4** from the corresponding acetates and subsequent reaction of these key reactive intermediates with silylated thymine as a nucleophile.

The synthesis of Z-protected compounds **1a** and **1b** (Scheme 1) started from Z-protected (*S*)-pyroglutamic acid **5**[11] which was converted to the TBDMS protected alcohol **6**.[12] Selective reduction of

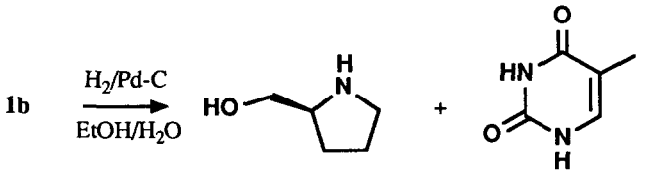
the lactam carbonyl group with $NaBH_4/MeOH$[13] then gave the N-acylated acetal **7** in 95% yield as a mixture of diastereomers. Acetylation of **7** and subsequent reaction of the crude acetate with the bis-TMS derivative of thymine (generated *in situ* from thymine and N,O-bis-trimethylsilyl acetamide (BSA)) in the presence of $SnCl_4$ furnished protected nucleoside analog **8** in 64% yield as an inseparable mixture of diastereomers.[14a] Desilylation of **8** with TBAF gave the target compounds **1a** and **1b** in 47% and 41% isolated yield, respectively.[14b]



Scheme 1

i: a. EtOC(O)Cl/N-methyl morpholine, THF, -5 °, 5 min; b. $NaBH_4$, 68 %; ii: TBDMS-Cl, imidazole, DMF, quant.; iii: $NaBH_4$ (10 equiv.), MeOH, -5 °, 30 min, 95 %; iv. Ac_2O, DMAP (0.1 equiv.), CH_2Cl_2/pyridine; v. $(TMS)_2$-thymine, $SnCl_4$, 3 h, - 15 °, 64 % (2 steps); vi. TBAF, THF, **1a**: 47 %, **1b**: 41 %.

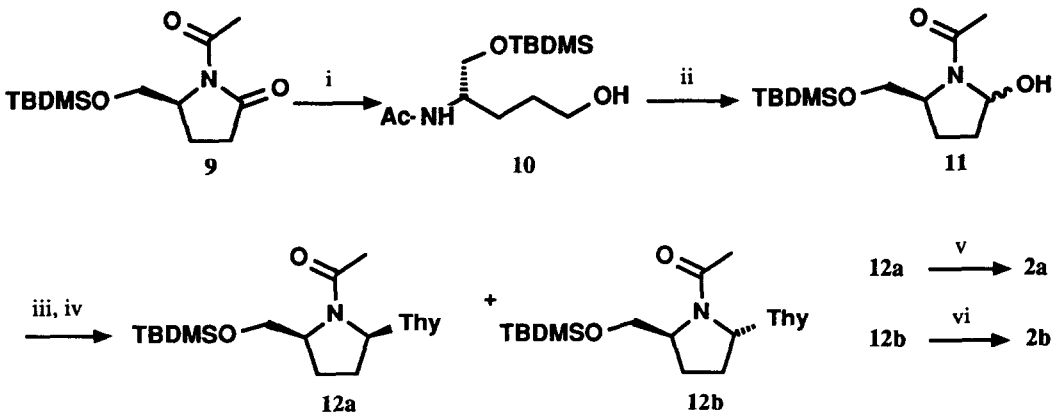
Catalytic hydrogenation of **1b** produced none of the deprotected dideoxynucleoside analog (with a free NH-group), but resulted in the formation of thymine and (*S*)-prolinol (Scheme 2).



Scheme 2

Presumably removal of the Z-protecting group from the pyrrolidine nitrogen is followed by rapid elimination of the base and the resulting imine is further hydrogenated to give (*S*)-prolinol.

The synthesis of dideoxynucleoside analogs **2a** and **2b** from acetylated lactam **9** (obtained from (*S*)-5-hydroxymethyl-2-pyrrolidinone (FLUKA) via silylation with TBDMS-Cl[15] and subsequent acetylation with Ac_2O/DMAP; 80%) proved to be less straightforward than the preparation of **1a** and **1b** from **6** (Scheme 3).



Scheme 3

i: $NaBH_4$, MeOH, - 5 °, 20 min, 48 %; ii: $[n\text{-}C_3H_7]_4N(RuO_4)$ (0.1 equiv.), N-methyl morpholine N-oxide x H_2O (1.1 equiv.), mol. sieves, CH_2Cl_2, r.t., 3 h, 46 %; iii: Ac_2O, DMAP (0.1 equiv.), CH_2Cl_2/pyridine; iv: $(TMS)_2$-thymine, $SnCl_4$, CH_3CN, - 15 °, 3 h, 55 % (**12a**: 21 %, **12b**: 31 %); v; vi: TBAF, THF, 64 %; 79 %.

In contrast to the N-Z-protected lactam **6** treatment of **9** with $NaBH_4$ under conditions that led to virtually quantitative conversion of **6** to **7** gave alcohol **10** as the major product in 48 % yield.[16] Oxidation of **10** with tetra-n-propylammonium perruthenate (TPAP)/N-methyl morpholine N-oxide[17] afforded the desired acetal **11** in 46 % yield, the moderate yield being due to rapid further oxidation of **11** to lactam **9**. If the oxidation is carried out with PCC[18] or PDC[19] the ratio **8/11** even increases and the reactions are generally less clean. Activation of **11** by acetylation and subsequent reaction of the crude acetate with (isolated) bis-TMS-thymine under $SnCl_4$ catalysis gave a 55 % yield of a *ca.* 2/3 mixture of diastereomers **12a** and **12b**, which could be separated by silica gel chromatography in AcOEt/MeOH to furnish **12a** and **12b** in 21 % and 31 % isolated yield, respectively. Interestingly, the stereochemical outcome of the reaction of bis-silylated thymine with N-acyliminium ion **4** does not conform to the pronounced "cis-effect" that is usually observed for related systems.[20]

Desilylation of **12a** and **12b** produced the target compounds **2a** and **2b** in 64% and 78% yield, respectively.[21]

In summary, the synthesis of four representative examples of a new class of dideoxynucleoside analogs has been accomplished. The synthetic strategy outlined in this report for the synthesis of **1a,b** and **2a,b** is equally applicable to compounds of type **1** and **2** incorporating nucleic acid bases other than thymine. Moreover, this strategy has also been applied to the synthesis of the corresponding N-acetylated *thymidine* analog which may be an interesting building block for antisense oligonucleotides.[22]

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12. N-Z-(*S*)-5-hydroxymethyl-2-pyrrolidinone derived from the reduction of N-Z-(*S*)-pyroglutamic acid was also converted to the free pyrrolidinone by catalytic hydrogenation. The $[\alpha]_D^{25}$ of this material was + 23.5 °; comparison with the $[\alpha]_D^{25}$ of commercially available material (FLUKA) (+ 34.2 °) indicates an ee of 69 % which should be identical with the ee of **6**.
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14. a. Due to the presence of rotamers, the ^{1}H-NMR spectrum of **8** at r.t. was completely uninformative with respect to the ratio of diastereomers. b. **1a**: ^{1}H-NMR (400 MHz, CD_3OD) δ 8.10 (s, br, 1H, H-6), 7.30 (m, br, 5H, H_{ar}), 6.15 (m, br, 1H, H-1'), 5.25 (m, br, 1H, CH_2(Z)), 4.90 (m, br, 1H, CH_2(Z)), 4.15 (m, br, 1H, H-5'), 3.95 (m, 1H, H-4'), 3.68 (d, J=3.0 Hz, 0.5H, H-5'), 3.66 (d, J=3.0 Hz, 0.5H, H-5'), 2.30 (m,1H, H-2'), 2.10 (m, br, 3H, H-2' + H-3'), 1.80 (s, br, 3H, CH_3(Thy)). **1b**: ^{1}H-NMR (400 MHz, CD_3OD) δ 7.40 - 7.15 (m, 5.33H, H_{ar} + H-6 (rotamer 1)), 7.00 (s, br, 0.67H, H-6 (rotamer 2)), 6.15 (d, J=8.0 Hz, 0.67 H, H-1'), 6.10 (d, J=6.5 Hz, 0.33H, H-1'), 5.35 (d, J=12.5 Hz, 0.67H, CH_2(Z)), 5.15 (s, br, 0.67H, CH_2(Z)), 4.80 (d, J=12.5 Hz, 0.67H, CH_2(Z)), 4.25 (m, 1H, H-4'), 3.82 (d, J=3.0 Hz, 0.33H, H-5'), 3.78 (d, J=3.0 Hz, 0.33H, H-5'), 3.65 (m, 1.34H, H-5'), 3.65 (m, 1H), 2.30 - 2.15 (m, 1H), 2.10 -2.00 (m, 1H), 1.95 - 1.85 (m, 1H), 1.85 (s, br, 1H, CH_3(Thy)), 1.70 (s, br, 2H, CH_3(Thy)).
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20. **2a**: ^{1}H-NMR (250 MHz, $(CD_3)_2SO$) δ 8.19 (s, br, 0.55H, H-6 (rotamer 1)), 7.55 (s, br, 0.45H (rotamer 2)), 6.20 (m, br, 0.55H, H-1'), 5.95 (m, br, 0.45H, H-1'), 4.10 - 3.50 (m, br, 3H, H-5' + H-4'), 2.25 (m, br, 1H), 2.10 (s, br, 1.5H, CH_3(Ac)), 2.05 - 1.80 (m, 4.5H, incl. s 1.85 (CH_3(Ac))), 1.75 (s, br, 3H, CH_3(Thy)). **2b**: (400 MHz, CD_3OD)) δ 7.27 (d, J<1 Hz, 0.46H, H-6 (rotamer 1)), 7.17 (d, J<1 Hz, 0.54H, H-6 (rotamer 2)), 6.29 (d, J=7.5 Hz, 0.54H, H-1'), 6.17 (d, J=7.5 Hz, 0.46H, H-1'), 4.45 - 4.35 (m, 1H, H-4'), 3.79 (dd, J=10.0 Hz, J=5.0 Hz, 0.54H, H-5'), 3.68 (dd, J=10.0 Hz, J=3.0 Hz, 0.54H, H-5'), 3.63 (m, 0.92H, H-5'), 2.66 - 2.48 (m, 1H), 2.39 -2.28 (m, 0.46H), 2.38 - 2.12 (m, 2.9H, incl. s 2.22 (CH_3(Ac))), 2.07 - 1.85 (m, 5.7H, incl. s 1.98 (CH_3(Ac)), s 1.90 (CH_3(Thy)), s 1.85 (CH_3(Thy))).
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