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SYNTHESIS OF NOVEL 3'-ISOMERIC DIDEOXYNUCLEOSIDES

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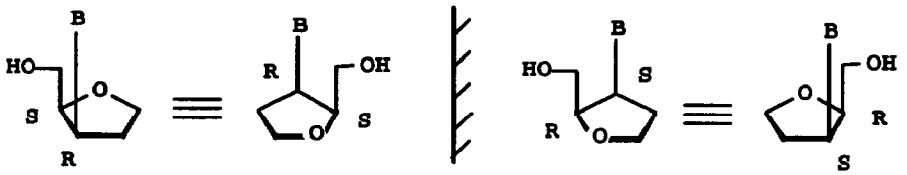
Summary: Approaches to representative examples of 3'-isomeric dideoxynucleosides with 2'(S),3'(R) and 2'(R),3'(S) absolute stereochemistry have been developed. These are among the first cases of isomeric dideoxynucleosides with the base moiety at the 3'-position. The chemistry developed has generality and can be applied to the synthesis of other related isomeric nucleosides.

Considerable attention has been focused recently on the synthesis of novel dideoxynucleosides with the realization that compounds of this family are potential inhibitors, as their triphosphates, of HIV RT.[1-4] Although numerous dideoxynucleosides have been prepared and investigated for their antiviral activity, the search still continues for new structures that have the potential for anti-HIV activity and that are related to the natural deoxynucleosides. Recent studies in our laboratory and elsewhere have focused attention on the synthesis of novel isomeric dideoxynucleosides, including anti-HIV active isodideoxyadenosines, where there is transposition of the base or the $-CH_2OH$ from the normal to a different position in the carbohydrate component.[5-13] Such dideoxynucleosides may also be looked upon as isomeric with respect to transposition of the endocyclic oxygen atom. One class of isomeric dideoxynucleosides, not previously studied, involves the arrangement of the base moiety, not at the normal anomeric position, but at the 3'-carbon (Scheme 1) and this communication is concerned with the development of approaches to enantiomers of this family of compounds.



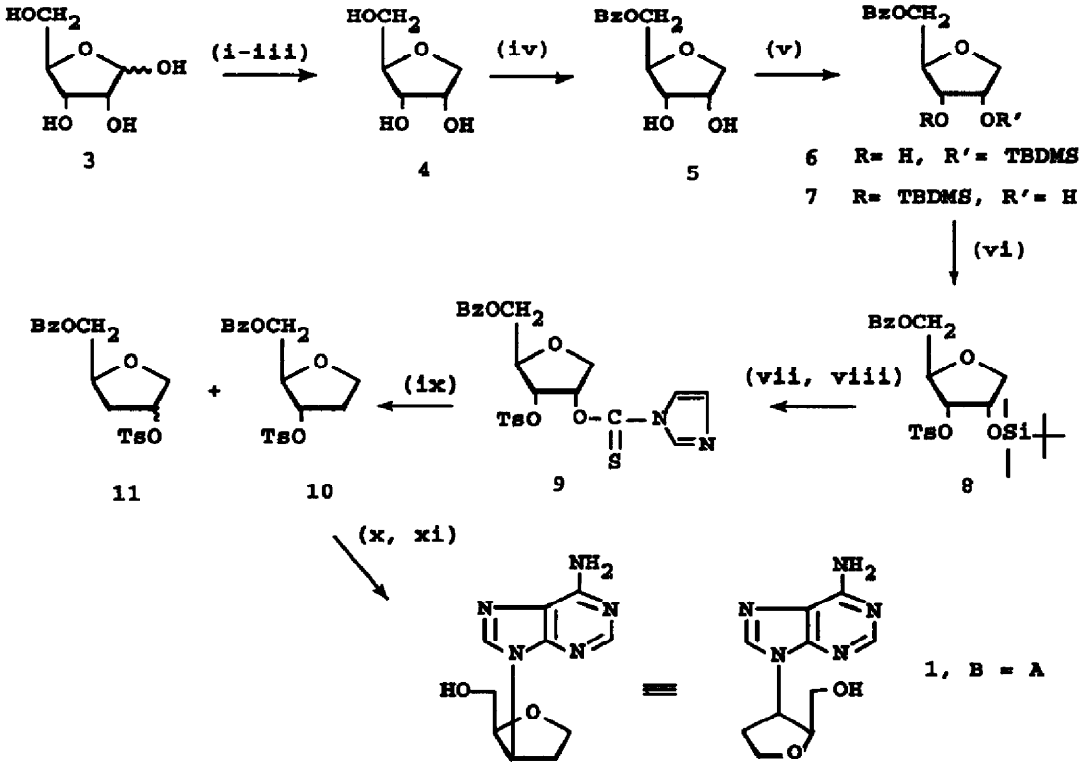
1 2

B = DNA Bases

Scheme 1

Synthesis of the 3(R)-(6-amino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol **1** (B = adenine) involved glycosylation of the appropriately tailored carbohydrate **10** with adenine. Compound **10** was synthesized in nine steps from D-ribose (Scheme 2). This synthesis commenced with the quantitative preparation of the methyl glycosides of D-ribose and their subsequent conversion in 71% yield to 1-deoxyribose (1,4-anhydroribitol) **4** *via* modification of a procedure by Bennek and Gray.[14] Selective benzoylation of the primary hydroxyl group of **4** by treatment with less than one equivalent of benzoyl chloride in pyridine provided the 5-O-benzoylated

compound **5** in 60% yield. The next step involved the monosilylation of the 2-hydroxyl group of compound **5** using TBDMSCl (1 equiv) in the presence of DMAP (0.5 equiv) and a slight molar excess of triethylamine to give a 2:1 separable mixture of **6** and **7**, respectively, in 55% yield. While intermediate **6** is the precursor of the 3'-isomeric series of this paper, compound **7** may provide entry into 2'-isomeric deoxynucleosides. Intermediates **6** and **7** were differentiated by ^{13}C and ^{1}H NMR data. However, the desired monosilyl compound **6** could be obtained in about 80% yield, and almost exclusively, when the reaction conditions were changed to TBDMSCl (1 equiv) in pyridine. Treatment of **6** with tosyl chloride and pyridine afforded **8** in 89% yield. None of the regioisomer, which could arise from the migration of the silyl group during the reaction, was discerned in the ^{1}H and ^{13}C NMR spectra of **8**. Compound **8** was desilylated with fluoride ions (80 % yield) and then converted quantitatively to its thiocarbonyl-imidazolide ester **9** which was deoxygenated with Bu_3SnH and AIBN[15] in refluxing toluene to give **10** in 55% yield. Interestingly, under the conditions of the reaction, small amounts (< 10%) of the cis and trans isomers of the 2-tosyl compounds **11** were also

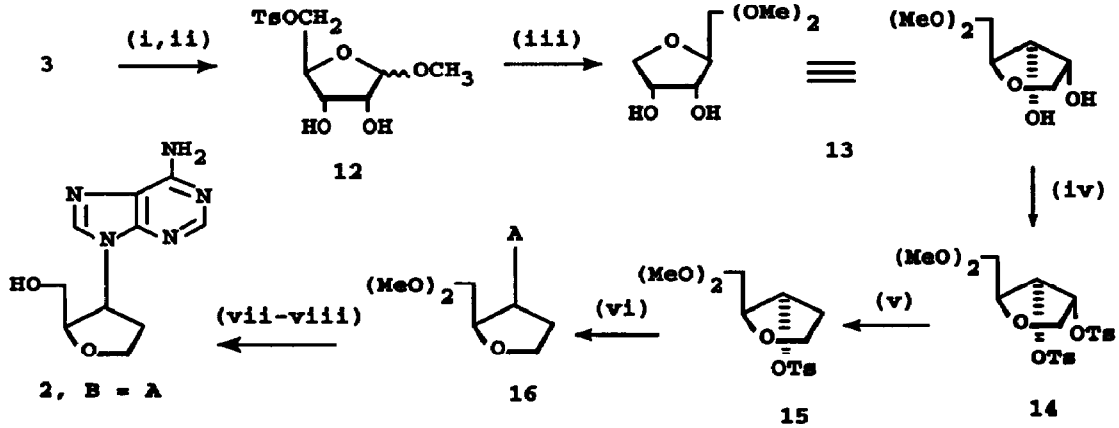


(i) HCl (0.1 eq), MeOH, 12 h; (ii) HMDS (14 eq), TMSCl (0.5 eq), 125 °C, 12 h; (iii) Et_3SiH (2.5 eq), TMSTf (1.3 eq), CH_3CN, 24 h; (iv) BzCl (0.8 eq), pyr, 1 h; (v) TBDMSCl (1 eq), DMAP (0.5 eq), Et_3N (1.3 eq), DMF-CH_2Cl_2 (4:1), 6 h; (vi) TsCl (1.5 eq), pyr, 0 °C, 15 h; (vii) Et_4NF (1.5 eq), CH_3CN, 1 h; (viii) Im_2CS (1.5 eq), $(CHCl)_2$, 85 °C, 3 h; (ix) n-Bu_3SnH (2.0 eq), AIBN (0.8 eq), toluene, 120 °C, 4 h; (x) adenine (1.5 eq), K_2CO_3 (2.0 eq), 18-crown-6 (1.0 eq), DMF, 90 °C, 9 h; (xi) NaOMe (0.2 eq), MeOH, 5 h.

Scheme 2

produced, presumably through a radical pathway involving migration of the tosyl group. Coupling of adenine with **10** was carried out in the presence of 18-crown-6 and K_2CO_3 in DMF to give, after deprotection (NaOMe/ MeOH), purification by reversed-phase HPLC (PRP-1) and crystallization (ethanol), 3'-isoddA (**1**, B = A). The structure of optically active **1** was confirmed by its UV spectrum, extensive ^1H and ^{13}C NMR data, mass spectral molecular ion and elemental analysis.[16]

The approach developed for the synthesis of 3(S)-(6-amino-9H-purin-9-yl)tetrahydro-2(R)-furanmethanol (**2**, B = A) utilized carbohydrate precursor **15** in the final coupling reaction with adenine (Scheme 3). Compound **15** was prepared in 5 steps from D-ribose. The key step in this preparation was the acid-catalyzed rearrangement of **12** to **13** (60% yield, 70% conversion), which apparently arises from the acid-catalyzed ring-opening by attack of methanol on C-1 followed by recyclization *via* nucleophilic displacement of the tosyl fragment by the 2-hydroxyl group.[10] The proton NMR spectrum of **13** showed two sharp singlets at 3.45 and 3.47 ppm corresponding to the two methyl groups of the acetal and a doublet of doublets at 3.79 and 4.03 ppm which were assigned to the ring methylene protons. Compound **13** was transformed to the bis-tosylate derivative **14** (82% conversion) by treatment with tosyl chloride and pyridine at room temperature for 12 h. Reductive detosylation of **14** with excess $LiEt_3BH$ in THF provided **15** (70%) which was coupled to adenine as described previously for the synthesis of **1**. The acetal group of the resulting nucleoside **16** was then removed by heating with 1M aqueous oxalic acid at 75 °C for 10 h and the aldehyde produced was reduced with excess sodium borohydride (50% overall yield). Pure target isonucleoside **2** (B = A) was obtained after purification by reversed-phase chromatography and crystallization from ethanol. It was characterized by UV, ^1H and ^{13}C NMR data, optical rotation, mass spectral data and elemental analysis.[17]



(i) HCl (g) (0.1 eq), MeOH, 12 h; (ii) TsCl (0.9 eq), pyr, 0 °C, 19 h; (iii) 1% TFA-MeOH, 75 °C, 40 h; (iv) TsCl (2.2 eq), pyr, 25 °C, 12 h; (v) 1M $LiEt_3BH$-THF (3.4 eq), THF, 24 h; (vi) adenine (1.5 eq), K_2CO_3 (2.0 eq), 18-crown-6 (1.0 eq), DMF, 80 °C, 19 h; (vii) 1 M aq. oxalic acid, 75 °C, 10 h; (viii) $NaBH_4$ (4 eq), 1 h.

Scheme 3

In summary, synthetic approaches to new, structurally isomeric dideoxygenated nucleosides related to known anti-HIV active compounds are described. The syntheses involved the condensation of appropriately tailored carbohydrate moieties with purine base in the presence of K_2CO_3 and 18-crown-6. The requisite sugar

precursors for these glycosylations were made *via* strategic modifications of a natural D-sugar. An interesting hydrolysis-rearrangement reaction was employed as a key step in the preparation of one of the sugar precursors. The chemistry developed has generality and can be adapted for the synthesis of many other isomeric dideoxynucleosides.

ACKNOWLEDGMENTS

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16. Data for 3(R)-(6-amino-9H-purin-9-yl)tetrahydro-2(S)-furanmethanol (**1**, B = A): mp 184-186 °C; $[\alpha]_D$ = + 48.1° (c = 0.24, CH_3OH); ^1H NMR (Me_2SO-d_6) δ 2.33 (m, 1H), 2.61 (m, 1H), 2.92 (m, 1H), 3.04 (m, 1H), 3.83 (ddd, 1H), 3.91 (ddd, 1H), 4.31 (ddd, 1H), 4.60 (t, 1H), 5.21 (m, 1H), 7.24 (s, 2H), 8.01 (s, 1H), 8.14 (s, 1H); ^{13}C NMR (Me_2SO-d_6) δ 31.8, 54.3, 59.6, 65.6, 81.8, 118.2, 139.4, 149.7, 152.4, 156.0; UV (H_2O) λ_{max} = 260 nm (ε 12,505); Mass spectrum, m/z 235 (M^+); Anal. Calcd. for $C_{10}H_{13}N_5O_2$: C 51.06; H 5.57; N 29.77. Found: C 51.38; H 5.65; N 29. 82.
17. Data for 3(S)-(6-amino-9H-purin-9-yl)tetrahydro-2(R)-furanmethanol (**2**, B = A): mp 172-174 °C; $[\alpha]_D$ = - 43.3° (c 0.24, CH_3OH); ^1H NMR (Me_2SO-d_6) δ 2.35 (m, 1H), 2.59 (m, 1H), 2.94 (m, 1H), 3.03 (m, 1H), 3.83 (ddd, 1H), 3.91 (ddd, 1H), 4.30 (ddd, 1H), 4.58 (t, 1H), 5.21 (m, 1H), 7.21 (s, 2H), 8.00 (s, 1H), 8.13 (s, 1H); ^{13}C NMR (Me_2SO-d_6) δ 31.7, 54.3, 59.5, 65.6, 81,8, 118.1, 139.4, 149.7, 152.4, 155.9; UV (H_2O) λ_{max} = 260 nm (ε 12, 550); Mass spectrum, m/z 235 (M^+); Anal. Calcd. for $C_{10}H_{13}N_5O_2$: C 51.06; H 5.57; N 29.77. Found: C 51.30; H 5.53; N 29.58.

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