SYNTHETIC APPROACHES TO NEW REGIOISOMERS OF AZT AND AZU

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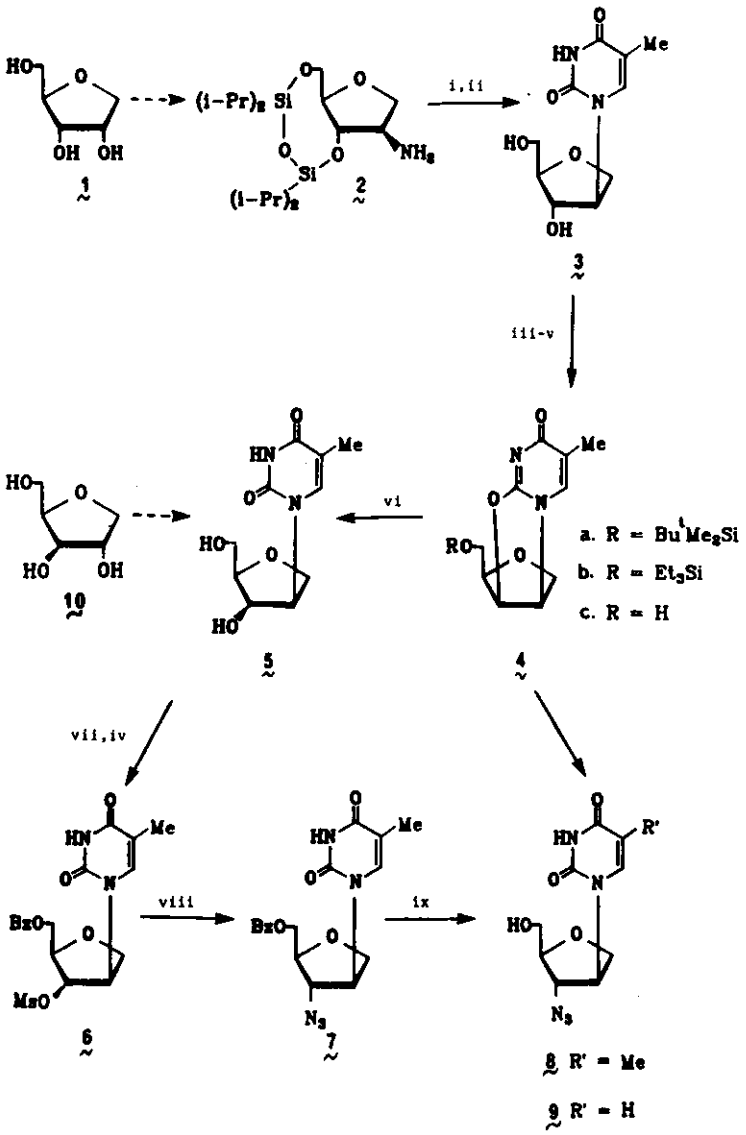
Abstract- Approaches to 1,4-anhydro-3-α-azido-2,3-dideoxy-2-β-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-D-arabinitol and 1,4-anhydro-3-α-azido-2,3-dideoxy-2-β-[3,4-dihydro-2,4-dioxo-1(2*H*)-pyrimidinyl]-D-arabinitol, conceptually new hydrolytically stable, optically active analogs of 3'-α-azido-3'-deoxythymidine (AZT) have been developed. These are among the first examples of regioisomeric analogs of AZT. The key synthetic steps and key intermediates are described. The generality aspects of the approaches are addressed.

Since the discovery of the human immunodeficiency virus (HIV) as the etiological agent of acquired immunodeficiency syndrome (AIDS),[1,2] 3'-α-azido-3'-deoxythymidine (AZT) has emerged as the first compound to be approved for clinical use in the United States for patients with AIDS and AIDS related complex (ARC).[3,4] Within the past several years, an extensive amount of research has been focused on the development of both purine and pyrimidine nucleoside analogs related to AZT such as 3'-azido-2',3'-dideoxy-uridine,[5] -guanosine,[6] and -adenosine.[7] Recently, the synthesis of 2'-β-azido-3'-deoxythymidine[8] and 2'-α-azido-3'-deoxythymidine has been reported.[9,10] However, there are no examples in the literature of regioisomeric analogs of AZT involving the glycosidic bond. This communication reports on the development of synthetic approaches to conceptually new, optically active, isomeric analogs of AZT and AZU.

The starting compound for the synthesis of the AZT analog (**8**) was the protected 2-amino-1,4-anhydro-2-deoxy-D-arabinitol (**2**), prepared from 1,4-anhydro-D-ribitol (**1**)[11] in four steps via the 2-azide.[12] Treatment of **2** with 3-methoxy-2-methylacryloyl isocyanate, prepared in situ from the corresponding acid chloride and silver isocyanate[13] followed by acid-catalyzed ring closure of the intermediate acryloylurea, afforded the deprotected arabinitol derivative (**3**) (88% for 2 steps). Selective protection of the primary hydroxyl group of **3** with *tert*-butyldimethylsilyl chloride, in the presence of triethylamine and DMAP in DMF,[14] was sluggish even at 55 °C, giving yields of less than 50%. Slightly higher yields (50%) were obtained when chlorotriethylsilane, a



Scheme 1. Reagents and conditions: i, 3-methoxy-2-methylacryloyl isocyanate, toluene, DMF, 0 °C to room temperature; ii, dioxane, 2N H_2SO_4, 100 °C; iii, Bu^{t}Me$_2$SiCl, DMAP, TEA, DMF, 55 °C; iv, MsCl, pyridine, 0 °C to room temperature; v, DBU, THF, 65 °C; vi, 1N NaOH, EtOH, 25 °C; vii, BzCl, pyridine, 0 °C; viii, LiN_3, DMF, 100 °C; ix, NH_3, MeOH, 0 °C.

more reactive silylating agent, was employed in the protection step. Subsequent transformation of the protected arabinitol into the new anhydro lyxitol (**4**) was accomplished by mesylation of the secondary hydroxyl followed by intramolecular cyclization in the presence of DBU in refluxing THF (90% yield for 2 steps). In the case where the protecting group was Et_3Si-, partial deprotection of the triethylsilyl ether occurred under the conditions for cyclization.

Attempted ring opening of protected anhydro nucleoside (**4a**) with azide ions under a variety of conditions (e.g. with HMPA or DMF in the presence of trifluoroacetic acid[9,15]) was difficult (cf. references 16,17) and only low yields of the azide (**8**) were isolated after deprotection. Unlike the 6-membered ring O^2,3'-anhydro nucleosides, the relatively strain free tricyclic nucleoside (**4**) containing a five-membered O^2,3'-anhydro ring displays unexpectedly remarkable stability toward nucleophilic ring opening of this anhydro linkage. This stability is comparable to anhydro C-nucleosides which are also resistant to nucleophilic ring opening with azide ions.[18] However, opening of the anhydro analog was possible by treatment of **4a** with sodium hydroxide in ethanol to afford the new deprotected lyxo derivative (**5**) (93%) with retention of the stereochemistry at C-3' which was confirmed by high-field nmr data.[19] Selective 5'-monobenzoylation of **5**, followed by mesylation (3'-OH) gave the protected mesylate (**6**) which was smoothly converted to the azido derivative (**7**) upon treatment with lithium azide in anhydrous DMF (86%). Deprotection of **7** with methanolic ammonia followed by purification by reversed-phase hplc (Delta Pak C_{18}, 20% EtOH/ H_2O) afforded the novel AZT analog (**8**) (63%). The structure of **8** including its stereochemistry was established by uv, FTir, mass spectrometry, and high-field ^1H nmr data.[20] The spectral data for **8** obtained in low yields by the nucleophilic ring opening with inversion (involving azide ions) of **4b** was identical to the data obtained for compound (**8**) derived from the lyxo nucleoside mesylate (**6**).

These studies were extended to the synthesis of the novel AZU analog (**9**). In addition, synthesis of the target molecules is also possible <u>via</u> **5** with the use of 1,4-anhydro-D-xylitol (**10**) instead of 1,4-anhydro-D-ribitol (**1**) as the starting compound. Further extension of these synthetic studies to other stereochemically defined regioisomeric analogs of AZT and AZU are in progress.

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19. Comparison of representative ^{1}H nmr data of compounds (**3**) and (**5**) upon D_2O exchange in Me_2SO-d_6 (300 MHz) δ (**3**): 3.82 (dd, 1H, J = 4.2, 9.9 Hz, 1'-H), 3.98 (dd, 1H, J = 7.3, 9.9 Hz, 1'-H), 4.11 (t, 1H, J = 5.0 Hz, 3'-H), 4.78 (ddd, 1H, J = 4.2, 5.0, 7.3 Hz, 2'-H); (**5**): 3.85 (dd, 1H, J = <1, 8.5 Hz, 1'-H), 3.96 (dd, 1H, J = 6.7, 8.5 Hz, 1'-H), 4.21 (dd, 1H, J = 4.0, 5.3 Hz, 3'-H), 5.04 (ddd, 1H, J = <1, 5.3, 6.7 Hz, 2'-H).

20. Data for 1,4-anhydro-3-azido-2,3-dideoxy-2-[3,4-dihydro-2,4-dioxo-5-methyl-1(2*H*)-pyrimidinyl]-D-arabinitol: mp 135-138 °C (H_2O); $[\alpha]_D$ = +30° (c = 0.28, MeOH); ^{1}H nmr (Me_2SO-d_6) δ 1.78 (s, 3H), 3.60 (m, 3H), 3.95 (dd, 1H, J = 7.0, 10.5 Hz), 4.05 (dd, 1H, J = 3.7, 10.5 Hz), 4.24 (dd, 1H, J = 4.2, 7.2 Hz), 4.92 (m, 1H), 5.05 (t, 1H, J = 5.3 Hz, exchangeable), 7.47 (s, 1H), 11.36 (br s, 1H, exchangeable); uv (MeOH) 269 nm (ε 9400); FTir (KBr) 2108 cm^{-1}; mass spectrum *m/z* 267 (M^+); Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.93; H, 4.91; N, 26.21. Found: C, 44.90; H, 4.90; N, 26.10.

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