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Studies directed toward anti-HIV compounds

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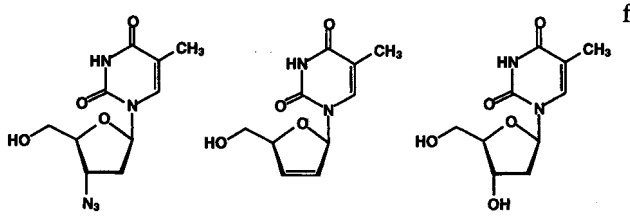
Abstract: Reaction of β-D-xylofuranosylthymine with diphenylcarbonate/ $NaHCO_3$/ DMF provided 2,2'-anhydro-β-D-arabinofuranosylthymine with concomitant isomerisation at C-3'. This novel rearrangement has been employed in the synthesis of β-thymidine, a precursor for anti-AIDS drugs - AZT and d_4T. The synthetic studies toward the anti-HIV marine guanidine alkaloid batzelladine A has also been described. The left hand bicyclic guanidine segment is obtained from ethylacetoacetate by involving tethered Biginelli condensation. Simultaneously the right hand tricyclic guanidine segment was synthesised stereospecifically from [3*R*(1'*R*,4*R*)]-(+)-4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone.

Scientifically and socially, AIDS (Aquired Immuno Deficiency Syndrome) has attracted much attention because of direct implications on human life. Advances (ref.1) made in AIDS research are indeed impressive but the fight is not yet over because no drug has thus far been discovered which can cure AIDS disease completely. The situation of AIDS in third world countries is more serious because anti-AIDS drugs are not easily accessible and highly priced. In principle propagation of HIV virus (etiological agent of AIDS) can be arrested at different levels of its life cycle. However, three major possible interventions for HIV replication have been accepted which have produced notable results in terms of drug development. These are (i) inhibition of binding of HIV virus to target cells (ii) inhibition of the viral enzyme reverse transcriptase (iii) inhibition of HIV proteases (ref.2).

The reverse transcriptase inhibitor - AZT (3'-azido-3'-deoxythymidine) (**1**) was the first drug to receive FDA approval and today by far the most useful therapeutic agent (ref.3). Other dideoxynucleosides such as ddI and ddC are also important for AZT-resistant cases (ref.4). Recently d_4T (**2**), related to thymidine family,



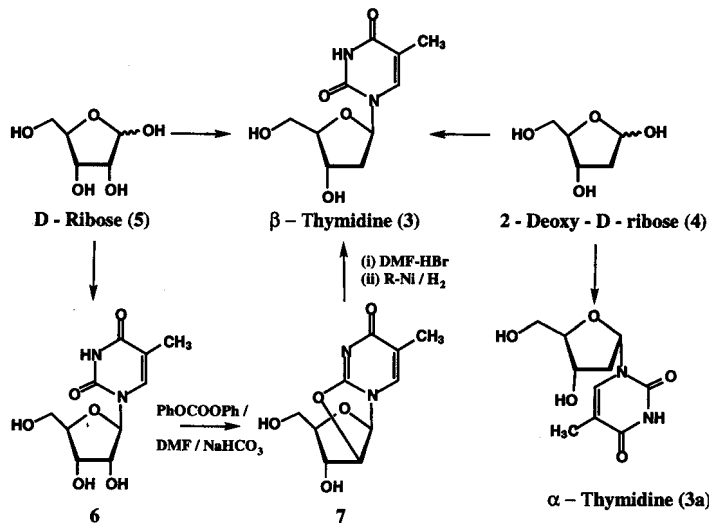
AZT (1) **D_4T (2)** **β – Thymidine (3)**

was approved (ref.5). We realised that although both AZT and d_4T are derived from β-thymidine (**3**), no effecient and cost effective process for the latter is reported. In other words, improving the route for β-thymidine synthesis should have profound influence on AZT or d_4T manufacturing.

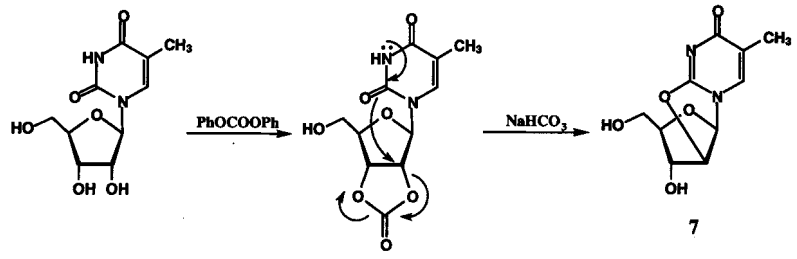
Although several methods for β-thymidine (**3**) synthesis have been reported, the two approaches (ref.6) starting from 2-deoxy-D-ribose (**4**) and D-ribose (**5**) are most convincing. However, 2-deoxyribose is not only an expensive sugar but its coupling with thymine provides a mixture of α- and β-thymidines (**3a** and **3**). This problem of anomers was circumvented with D-ribose (**5**) which was transformed *via* its corresponding 2,2'-anhydro derivative (**7**) into β-thymidine (**3**) (scheme **1**). It is pertinent to mention that in comparison with some naturally occurring D-pentoses such as D-xylose, the cost of D-ribose is apparantly too high. We believe that D-xylose should in fact be an ideal precursor for β-thymidine preparation.

If one visualises the rearrangement (scheme **2**) of conversion of ribofuranosylthymine (**6**) into 2,2'-anhydro derivative (**7**) using diphenylcarbonate/$NaHCO_3$/DMF it could be envisaged that a similar rearrangement of xylosyl intermediate (**8**) into **7** with similar reagents should also be possible with inversion of configuration at C-3' (scheme **3**). With this contention, the synthesis of **8** (ref.7) was first undertaken (scheme **4**). Indeed, subsequent treatment of **8** with diphenylcarbonate/DMF/$NaHCO_3$ at 150° for 4h gave

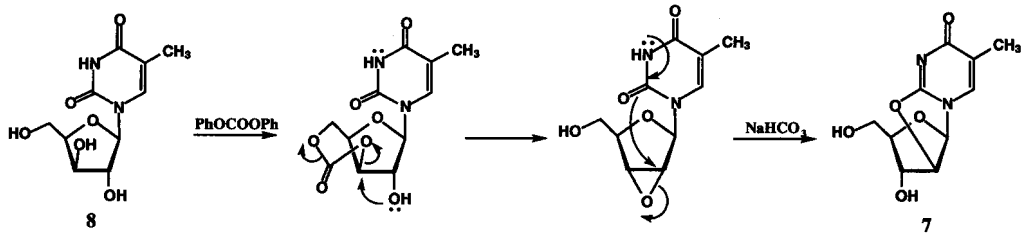
Scheme 1



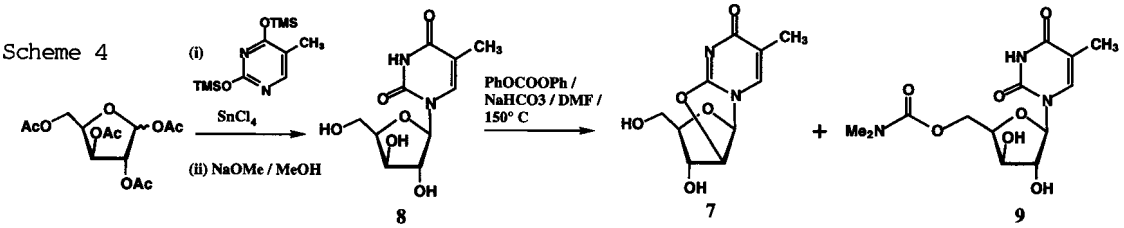
Scheme 2



Scheme 3

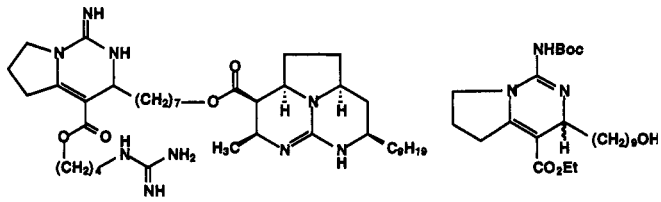


Scheme 4



7 (55%) along with 9 (25% yield) (ref.8).The ^{1}H-NMR, $[\alpha]_D$ and m.p. of 7 was identical with the product prepared by known procedure from D-ribose. Subsequent convertion of 7 into ß-thymidine was performed in two steps. Thus we have demonstrated a novel route to ß-thymidine from cheap sugar - D-xylose by involving a new rearrangement observed for the first time in nucleoside chemistry.

The Smith-Kline Beecham group reported (ref.9) the isolation of novel polycyclic guanidine alkaloids batzelladines A - E from the methanol extract of a bright red Caribbean sponge of genus *batzella*. These natural products not only possess unusual cyclic guanidine skeletons but show potent anti-HIV activity by virtue of their ability to antagonise CD4-gp120 interaction. Because of the absence of any prior data on the absolute stereochemistry of batzelladines and the lack of any appropriate methodology to construct cyclic guanidine segments, we made a decision to embark on the development of a general strategy for the synthesis of these molecules.To initiate the synthesis of batzelladine A (**10**), we first investigated a synthetic protocol for the



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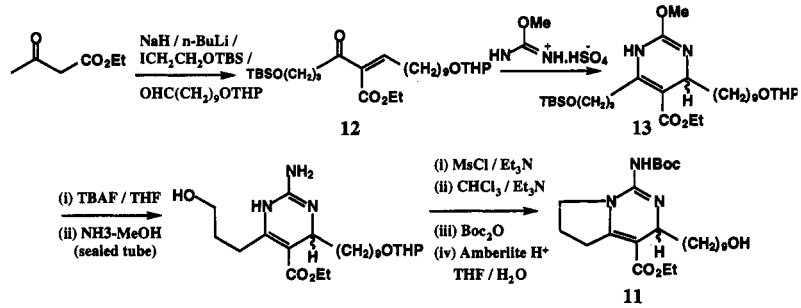
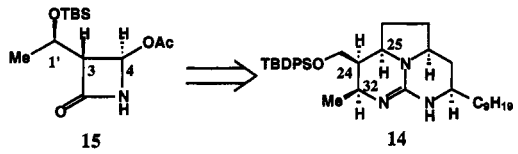
left hand bicyclic guanidine segment (**11**) starting from ethylacetoacetate (scheme **5**). It was first converted into the α-alkylidene-β-keto ester derivative (**12**) and then subjected to conjugate addition with concomitant cyclisation using O-methylisourea to give **13**. Subsequently **13** was transformed into the guanidine derivative **11** (ref.10).

Scheme 5



We next diverted our efforts to develop (ref.11) a synthetic methodology for the right hand tricyclic guanidine segment of batzelladine A (**14**). The commercially available azetidinone derivative **15** was selected as the starting material, primarily because of the inherent stereochemical correlation between the three contiguous centers at C-3, C-4 and C-1' of **15** with C-24, C-25 and C-32 of **14**. The stereospecific carbon-



15 14

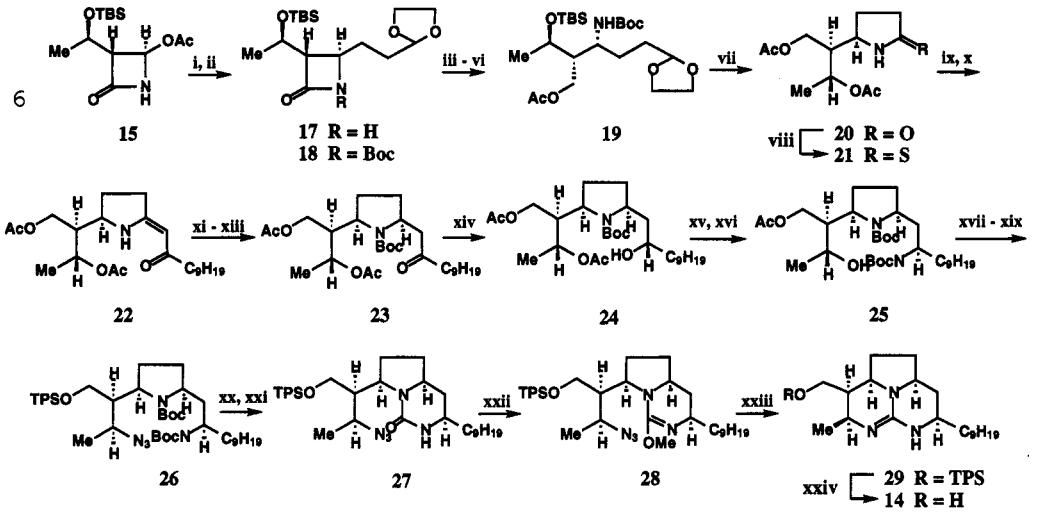
Stereochemical correlation

C-3 ⟶ C-24
C-4 ⟶ C-25
C-1' ⟶ C-32

carbon bond extension at C-4 position of the β-lactam ring was accomplished by the reaction between **15** and the Grignard reagent (**16**) to give **17**, whose free NH was protected as its N-Boc derivative (**18**). The *trans* stereochemistry of β-lactam ring was apparently proved by the characteristic coupling constant ($J_{2,3}$ = 3.0 Hz). The azetidinone ring was hydrolysed with 1 molar solution of LiOH in methanol followed by desilylation, reduction and acetylation to give **19**. Jones oxidation of **19** effected three transformations *vis* deacetalation, oxidation of intermediary hemiaminal derivative and deprotection of the N-Boc group leading to the formation of the 2-pyrrolidone derivative **20**. Eschenmoser's sulfide contraction of the corresponding thiolactam **21** with $BrCH_2COC_9H_{19}$ provided the α-β unsaturated ketone **22** whose reduction over PtO_2 in acetic acid followed by N-Boc protection and Jones oxidation gave **23** as the sole product (scheme **6**).

Among several reducing agents attempted for the stereoselective reduction of the 1,3-acylamino ketone **23**, we concluded that K-selectride at -78°C provided the best results in which *anti / syn* 1,3-acylamino alcohols (*anti* - **24**) were obtained in a 4:1 ratio. Introduction of azido group under Mitsonobu conditions followed by hydrogenation in presence of Pd-C and $(Boc)_2O$ gave the *bis*--N-Boc derivative **25**. Subsequently **25** was converted into the azido derivative **26**, in a sequence of three steps, which was deprotected with trifluoroacetic acid and then tethered with 1,1'-carbonyldiimidazole to give the cyclic urea **27**. Conversion of **27** into its methyl lactim ether **28** using dimethylsulfate, immediately followed by hydrogenation gave the guanidine derivative **29**. The structure of **29** was confirmed by ^{1}H-NMR and MS, the latter indicating the highest mass peak at *m/z* 578 (M+). Silyl deprotection gave the guanidine segment **14**, whose structure was assigned by the ^{1}H-NMR spectral analysis, including COSY, NOESY and proton decoupling experiments.

Scheme 6



Reagents and Conditions: i,$[O(CH_2)_2O]CH(CH_2)_2MgBr$ (**16**), THF, 0°C;ii,$(Boc)_2O$, DMAP,THF; iii, 1 mol dm^{-3} LiOH,MeOH,THF; iv, TBAF, THF; v, DIBAL-H, DCM, -20°C; vi, Ac_2O,DMAP, DCM; vii, Jones' reagent, MeCOMe, 56°C; viii, Lawesson's reagent, C_6H_6, heat; ix, $C_9H_{19}COCH_2Br$, DCM, $KHCO_3$; x, TPP,KOBu^t, Bu^{t}OH, C_6H_6, heat; xi, H_2, PtO_2, AcOH,45psi; xii, $(Boc)_2O$, $KHCO_3$,H_2O-EtOAc; xiii, Jones' reagent, MeCOMe, 0°C; xiv, K-Selectride, THF, -78°C; xv, DEAD, HN_3, TPP,THF; xvi, H_2, Pd-C, EtOAc,$(Boc)_2O$; xvii, 1 mol dm^{-3} LiOH,MeOH; xviii, TBDPSCl, DCM, Imd.; ix, DEAD, HN_3, TPP,THF; xx, TFA, DCM, 0°C; xxi, 1,1'-carbonyldiimidazole, THF, 0°C; xxii, Me_2SO_4, C_6H_6, heat; xxiii, Pd-$BaSO_4$, MeOH; xxiv, 1 mol dm^{-3}, HCl, MeOH, 50°C.

In conclusion we have demonstrated an enantiospecific synthesis of tricyclic guanidine segment of batzelladine A. However, a recent report by Snider et al (ref.12) indicated stereochemical revision for the structure of batzelladine A and D, wherein an *anti* relationship between the two six membered rings was reported. It is pertinent to mention that the above strategy developed for tricyclic guanidine (**14**) could be modified to synthesise the revised structure. This work is under progress.

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