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A GENERAL METHOD FOR CONTROLLING GLYCOSYLATION STEREOCHEMISTRY IN THE SYNTHESIS OF 2'-DEOXYRIBOSE NUCLEOSIDES

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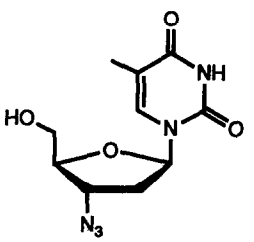
Summary: Glycosylation reactions of 2-arylsulfinyl-O-acetylribosides 6 with silylated thymine 11 produce 2'-deoxyribose nucleosides with high β-selectivity. An application of this directing effect in the synthesis of the antiretroviral agent D4T, 2, is described.

The use 2',3'-dideoxynucleoside derivatives, such as 3'-azido-3'-deoxythymidine (AZT, 1) and 3'-deoxy-2',3'-dehydrothymidine (D4T, 2), as antiviral agents against human immunodeficiency virus type 1 (HIV-1) has spurred the development of a variety of synthetic approaches to nucleosides.[1,2] The commonly-used chemical approaches for synthesizing these materials can be classified into two broad categories: (a) those which modify intact nucleosides by altering the carbohydrate, the base or both and (b) those which modify carbohydrates and incorporate the base (or its synthetic precursor) at a suitable stage in the synthesis. Since only the β-isomers generally exhibit useful biological activity, the most important factor in the latter strategy involves delivering the base from the β-face of the carbohydrate ring in the glycosylation reaction.



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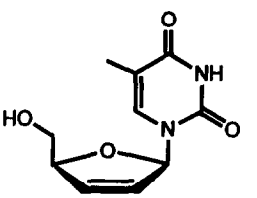

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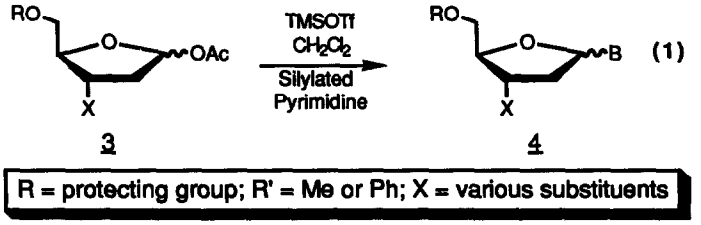
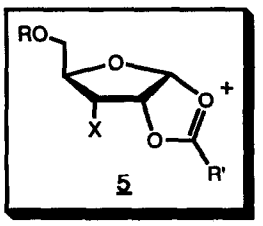
Because of the inconvenience and expense associated with the classical approaches, we have attempted to develop new synthetic protocols for preparing nucleosides (and nucleoside analogues) starting from inexpensive, non-carbohydrate precursors, which provide us with the option of introducing functionality as needed. While attractive in many respects, approaches of this type do possess one significant drawback. The absence of a 2-substituent precludes using the most popular method for effecting stereoselective introduction of bases to the anomeric centers of carbohydrates,[3] i.e., capitalizing on the neighboring group participation of a 2-acyloxy group as shown in 5. (e.g., see Eq.1, X = N_3 (β:α = 1:1),[4] CN (β:α = 4:5),[5] and SPh (β:α = 1:2).[6,7] We reasoned that the use of other substituents at C-2 which are both directing and disposable could provide the dual advantages

of selective β-glycosylation as well as offering the potential for performing a variety of synthetic transformations. In this letter we report on the ability of 2-aryl sulfide substituents for directing glycosylation reactions via episulfenium ion 8 (Eq. 2) and showcase the synthetic utility of these processes in a synthesis of D4T , 2.





When 2-arylsulfenyl-1-acetyl ribosides 6 are exposed to a Lewis acid and silylated thymine (11) (Eq.2), coupling occurs to provide the β-nucleoside as the major product in each case (Table 1).[8] As seen from the data, better selectivity is observed when the base and the Lewis acid are "precomplexed", prior to addition of the acetate (entries 2 and 3 versus 1 and 4). For example, glycosylation of an 8 : 1 mixture of acetates results in a 30 : 1 mixture of the corresponding nucleosides. Vorbruggen et al. have previously demonstrated that the equilibrium for mixtures of stannic chloride and various silylated bases lies heavily towards the complexed form, whereas trimethylsilyl triflate / silylated base combinations remain largely uncomplexed.[9] While the role that precomplexation plays in determining glycosylation selectivity remains unclear, the importance of this empirical observation can not be denied.

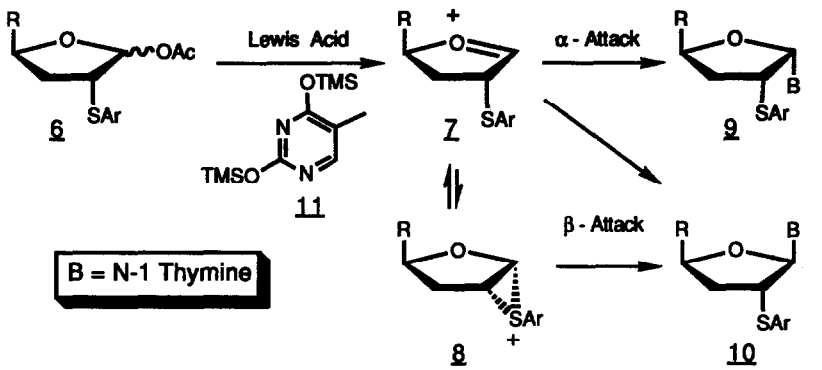
Table 1: Reaction Conditions of Various O-Acetyl Derivatives 6 with Silylated Thymine.

Entry [a]	Acetate 6		Isomeric ratio[d,e]	Lewis Acid	Ratio[d]	Temp. (°C)
	R	Ar	(trans : cis)		10 : 9	
1[c]	H	Ph	8 : 1	$SnCl_4$	17 : 1	-78→25
2[b]	H	Ph	8 : 1	$SnCl_4$	30 : 1	-78→25
3[b]	H	Ph	8 : 1	$SnCl_4$	30 : 1	25
4[c]	H	Ph	8 : 1	TMSOTf	4 : 1	25
5[b]	CH_2OR'	Ph	4 : 1	$SnCl_4$	14 : 1	-78→25
6[b]	H	2-NO_2Ph	8 : 1	$SnCl_4$	16 : 1	-78→25
7[b]	CH_2OR'	2-NO_2Ph	3 : 1	$SnCl_4$	9 : 1	-78→25

[a] All reactions were done in CH_2Cl_2. [b] The $SnCl_4$ and silylated base were precomplexed at 25°C for one hour and the acetate was added at the initially-indicated temperature. [c] Lewis Acid was added to base and acetate. [d] Ratios were determined by ^1H NMR integration of the glycosidic hydrogens. [e] Stereochemical assignments of acetates 6 are tentative. R' = t-butyldiphenylsilyl.

The intermediacy of episulfenium ion 8 can be argued from the fact that glycosylations with the smaller phenylsulfenyl substituent proceeded with higher selectivity than its larger, but less nucleophilic, 2-nitro counterpart (entries 6 and 7). Certainly, little selectivity would be expected if oxonium ion 7 were present in any significant quantities. There is also a significant decrease in selectivity which is observed when a protected C-5 hydroxy methyl group is resident in the riboside (entries 5 and 7). This is likely to be the result of a simple steric

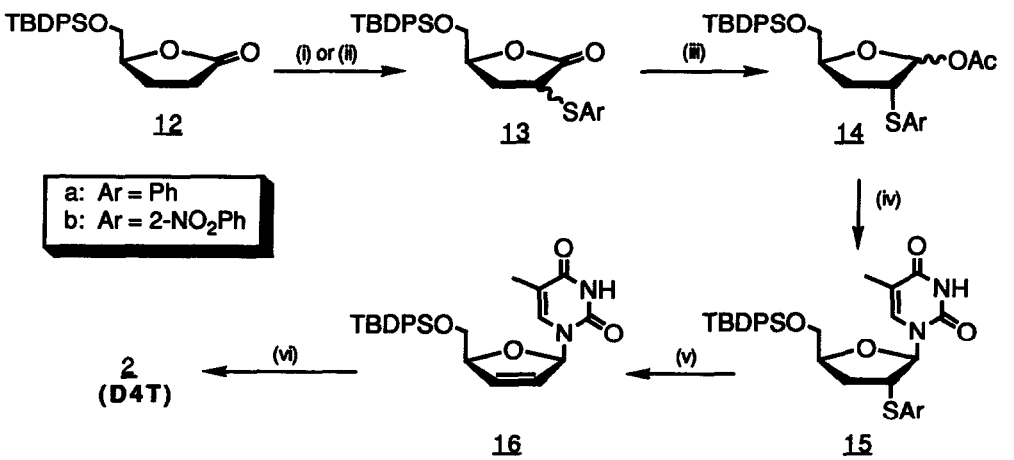
effect, i.e., increased hindrance on the top face of the system leads to lower selectivity.



(2)

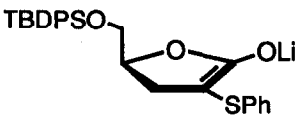
A use of this methodology for the synthesis of the antiviral compound D4T (2) is shown in **Scheme1**. Our approach to D4T focused on the incorporation of an aryl sulfenyl group in the 2 position of lactone 12, which is available in three steps in optically active form starting from the inexpensive (L)-glutamic acid.[11] Sulfenylation of 12 with diphenyldisulfide gave a 4 : 3 (trans : cis) mixture of lactone 13a in 85%. The relatively poor diastereofacial selectivity observed in this reaction presumably occurs because the kinetically formed product undergoes a rapid intermolecular proton transfer leading to enolate 17.[12] Protonation of 17 is not expected to occur with a high degree of facial selectivity.

Scheme I



Reagents : (i) LDA (2.5 equiv.) , THF , PhSSPh , HMPA , - 78° C → 25° C ; (ii) (a) LiHMDS , THF , - 78° C , 1h , then TMSCl , - 78° C → 25° C , 3h (b) 2-(NO_2)-PhSCl , CH_2Cl_2 , - 78° C → 25° C ; (iii) DIBAL- H , $PhCH_3$, - 78° C ; Ac_2O , pyridine , THF , 25° C ; (iv) $(TMS)_2$Thymine (1.5 equiv.) , $SnCl_4$ (1.5 equiv.) , CH_2Cl_2 , - 78° C → 0° C → 25° C , 5h ; (v) $NaIO_4$, THF / H_2O (5:1) , 25° C , then $PhCH_3$, pyridine , reflux ; (vi) $(Bu)_4NF$, THF, 25° C

Alternatively, formation of the silyl ketene acetal 18,[13] followed by reaction with 2-nitrophenylsulfenyl chloride leads to a 2 : 1 (trans : cis) mixture of 13b in 72% yield. Reductions of trans-13a and 13b with diisobutyl aluminum hydride, followed by reaction with acetic anhydride gave compounds 14a (4:1) and 14b (3:1), respectively. Coupling of these materials with precomplexed silylated thymine and stannous chloride gave compounds 15a in 51% and 15b in 52% overall yields from the lactones 13.[14] Oxidation and subsequent elimination of these materials resulted in the formation of compound 16 (65% from 15b; 80% from 15a).[12,15] Deprotection of 16 gave 2 in 90% yield, which was identical in both its physical and spectral characteristics with an authentic sample of D4T.[16,17]



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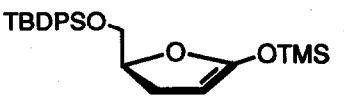

18

Applications of this methodology to the synthesis of other antiviral nucleosides will be the subject of future reports.

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15. The 2-nitrophenyl sulfoxide eliminated faster than the phenyl sulfoxide (4 versus 24 hours).
16. The structure and stereochemistry of all new compounds have been established by elemental analysis, IR, 1H NMR and 13C NMR spectral data.
17. An authentic sample of D4T, 2, was obtained from Dr. Raymond Schinazi, Emory University.

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