Pergamon

Tetrahedron Letters, Vol. 38, No. 7, pp. 1111-1114, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02520-8

Stereocontrolled Synthesis of β-2'-deoxypyrimidine Nucleosides via Intramolecular Glycosylations

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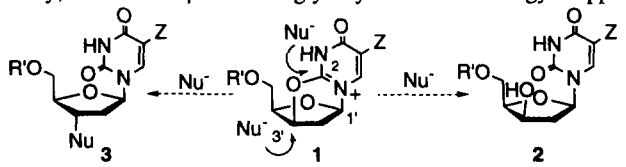
Abstract: A pyrimidine moiety was tethered at the 3'-β-position of D-*threo*-furanosides. By carefully controlling the reaction conditions, pyrimidine bases can be delivered to the anomeric center to give of β-pyrimidine nucleosides in good yield and with complete stereocontrol.

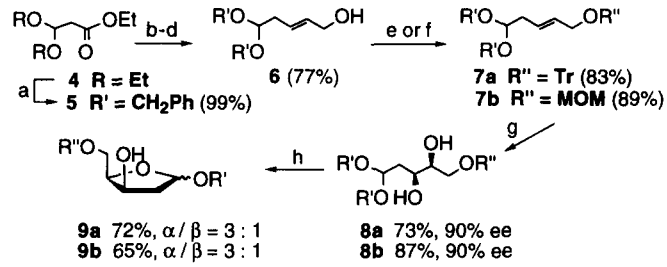
Since the discovery of antiviral activity of 3'-azido-3'-deoxythymidine (AZT) against human immunodeficiency virus (HIV), nucleoside analogues have received renewed attention as potential therapeutic agents for the treatment of HIV, as well as other viral infections such as hepatitis B. With this heightened interest came the requirement for efficient and versatile methods for preparing these analogues. In particular, although the coupling of a carbohydrate with a pyrimidine or purine base offers a simple and effective method for generating a variety of these nucleoside analogues,[1] the low diastereoselectivity usually observed in these glycosylation reactions often limits the utility of these approaches. Moreover, since only the β- isomers of nucleosides typically exhibit any biological activity, the need for β-selective glycosylation methodology is apparent.[2]



Scheme 1

As part of our continuing efforts to develop general methods for the exclusive formation of β-nucleosides, we have devised an intramolecular glycosylation strategy for pyrimidine nucleosides, the key step of which involves the delivery of a pyrimidine moiety, tethered at the 3'-β-position, to the 1'-β-position of a furanoside,[3,4] This process goes through an anhydro intermediate **1**, which could then be elaborated to different nucleoside derivatives. In principle, soft nucleophiles should preferentially attack **1** at either C-3', while hard nucleophiles should attack at C-2 (**Scheme 1**).[5] In this communication we demonstrate the viability of this approach.

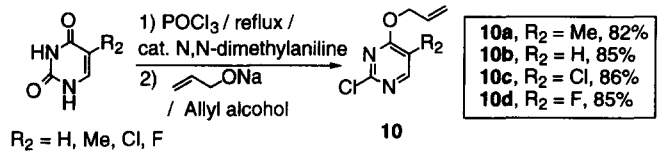
As depicted in **Scheme 2**, a variety of differentially-protected 2-deoxy-*threo*-pentofuranosides are readily accessible starting from achiral and acyclic precursors. Our starting material, 1,1-dibenzyloxy-5-hydroxyl-3,4-pentene **4**, was efficiently prepared from commercially-available ethyl vinyl ether and trichloroacetyl chloride. For convenience in subsequent work-up procedures, the hydrophilic diethoxypropanoate was converted to the dibenzyloxy derivative **5** in quantitative yield. Ethyl 3,3-dibenzyloxypropanoate **5** was reduced to the corresponding aldehyde, which was then exposed to Horner-Emmons conditions to yield an α,β-unsaturated



(a) $PhCH_2OH$, TsOH, hexane, 80°C; (b) DIBAL-H, Et_2O, -78°C; (c) $(iPrO)_2P(O)CH_2CO_2Et$, NaH, THF; (d) 2 equiv. DIBAL-H, Et_2O, -78°C; (e) TrCl, DMF, Et_3N, DMAP; (f) MOMCl, diisopropylethylamine; (g) $K_2OsO_4{\cdot}2H_2O$,$K_3Fe(CN)_6$, K_2CO_3, DHQD-PHN, H_2O, *t*-BuOH; (h) H_2SO_4, THF, 0°C.

Scheme 2

ester with a greater than 98:2 selectivity for the *E*-isomer.[6b] Upon treatment with 2.2 equivalents of DIBAL-H, the α,β-unsaturated ester was reduced to the prochiral allylic alcohol **6**. Protection of the primary alcohol as either its trityl or MOM ether, followed by dihydroxylation using the Sharpless asymmetric osmylation technique, provided the diol **8**.[7,8] with enantiomeric excess greater than 90%. Acid-catalyzed cyclization then yielded the desired protected pentofuranoside **9** and H^1 NMR analysis of the derived Mosher's ester showed the the enantiomeric excess of the D-xylofuranoside remained 90%. The appropriate choice of cinchona alkaloid catalyst (dihydrohydroquinidine 9-phenanthryl ether (DHQD-PHN) or its hydroquinine counterpart) made both **D**- and **L**-enantiomers readily accessible.

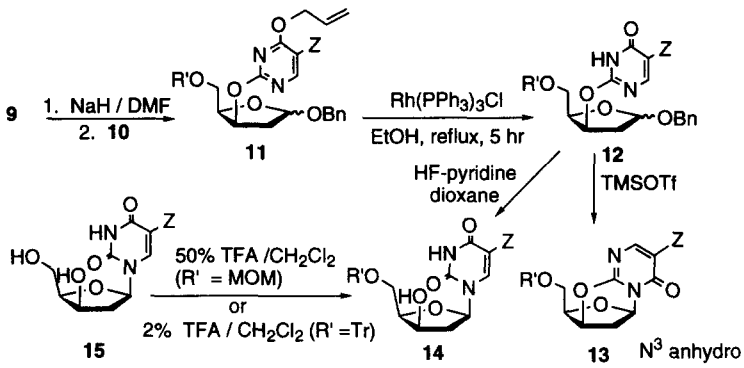


Scheme 3

Various 5-substituted uracils were converted to the corresponding 2,4-dichloropyrimidines in nearly quantitative yield by heating under reflux in phosphorous oxychloride (**Scheme 3**).[9] Interestingly, treatment of dichloropyrimidine with one equivalent of sodium allyloxide selectively afforded 4-allyloxy-2-chloro-pyrimidine when Na was used to generate sodium allyloxide **10** (the ratio of 4-substituted vs. 2,4-disubstituted pyrimidine greater than 10:1). If NaH was used in the reaction to replace Na, the selectivity dropped especially that of 2,4-dichloropyrimidine with 3:1 4-substituted/2,4-disubstituted selectivity observed. The allyloxypyrimidines **10** was readily coupled to pentofuranoside **9** using sodium hydride in DMF. Even though the coupling conditions yield a mixture of animal distereomers, the final selectivity of the cyclization should not be affected since both distereomers presumably cylized via iminium ion intermediate. It only remained for us to establish the appropriate acidic condition to promote the delivery of the pyrimidine from C-3' to C-1' of pentofuranoside for this stereocontrolled glycosylation to be successful.

In contrast to intermolecular Vorbrüggen-type glycosylations,[1] we were surprised to observe N^3-anhydronucleoside as the major product under typical intermolecular glycosylation conditions of **11**.[10] Apparently the N-3 nitrogen, despite its more hindered steric environment, preferentially attacked the oxonium ion

of the intermediate instead of N-1. To further confirm the sturcture of **13**, **13** was converted to a 3'-substituted nucleoside. Under the similar conditions as Horwitz's method of AZT formation, **13** (R' = Tr, Z = Me) was heated under reflux with sodium azide and DMF.[11] The single product isolated from the reaction gave data (complete charactization) that was similar to that of AZT. However, the H^1 NMR ($CDCl_3$) revealed that the anomeric proton (δ 6.70) was shifted downfield relative to that of AZT (δ 6.04). Shown by Vorbrüggen and co-workers, this downfield shift of the H-1' signal is characteristic of the N-3 regioisomer of nucleosides.[12] We reasoned that this impediment could be circumvented by modulating the relative nucleophilicity of the two



Entry	11	12	14	15
R' = Tr, Z = Me	70%	63%	60%	93%
R' = Tr, Z = H	70%	79%	61%	95%
R' = Tr, Z = Cl	67%	75%	55%	92%
R' = MOM, Z = Me	88%	87%	70%	90%
R' = MOM, Z = F	80%	84%	28%	86%

Scheme 4

nitrogens. Towards this end the allyl group was removed by treatment with 5% tris-(triphenylphosphine)rhodium chloride (Wilkinson's catalyst) in aqueous ethanol to give the corresponding pyrimidones **12** (**Scheme 4**). Since the pyrimidone N-1 nitrogen should now be more nucleophilic than the amide N-3 nitrogen, we expected the regioselectivity problem to vanish. However, the treatment of pyrimidone with trimethylsilyl triflate produced results similar to those described above. Alternatively, the use of other Lewis acids, such as tin(IV) chloride and titanium(IV) chloride, resulted only in decomposition of starting material.

The problem was ultimately solved by careful choice of the catalyst and the reaction conditions. Realizing that N-1 was by far the most basic site in **12**, we moved away from the more exotic oxaphilic catalysts to the most fundamental azaphilic catalyst, a proton. As long as there was less than one equivalent of proton source present, the inherent nucleophilicity of N-1 should dominate and the desired regiochemistry should result. However, simple acid catalysts, like *p*-toluenesulfonic acid, resulted in recovered **12**, *but only as its α-anomer*. This suggested that although intermediate **1** was forming, the reverse reaction was more favorable. Thus, in order to drive the reaction forward, a combination of a proton source and hard nucleophile was required. In a formal sense we chose the combination of H^+ and F^-. Indeed, slow addition of less than one equivalent of HF-pyridine to **12** in dioxane produced the desired β-glycosylation products, presumably due to fluoride attack at C-2, followed by

hydrolysis during work-up.[13] When more than one equivalent of HF-pyridine was added, N-3 glycosylated products were observed undoubtedly because N-1 was completely protonated. The protecting group on C-5' was easily removed by treatment with CF_3COOH in dichloromethane at room temperature to give the free nucleosides **15** which is a mixture of 95:5 D- and L- enantiomers as determined by H^1 NMR analysis of the derived Mosher's ester derivatives. Proof of the absolute stereochemistry was established by preparing the chiral derived Mosher's ester derivative of the D-enantiomer (major isomer) of compound **15** (Z = Me), and comparing the H^1 NMR shift with the Mosher's ester derivative of the authentic sample 5'-O-trityl-2'-deoxy-β-D-lyxofuranosylthymine from Aldrich after cleaving trityl group.

In conclusion, D-*threo*-furanosides can be readily converted to β-pyrimidine nucleosides via a novel intramolecular nitrogen glycosylation reaction. By carefully controlling the reaction conditions, pyrimidine bases can be delivered to the anomeric center in good yield and with complete stereocontrol.

Acknowledgments: We thank the National Institutes of Health (AI-28731) for generous financial support. We also thank Dr. Robert Young of GlaxoWellcome (formerly, the Wellcome Research Foundation) for informing us of his observation of the superiority of sodium over sodium hydride for preparing sodium allyloxide.

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13. The structure was confirmed by X-ray analysis of **14b.**

(*Received in USA* 11 *November* 1996; *revised* 18 *December* 1996; *accepted* 19 *December* 1996)