

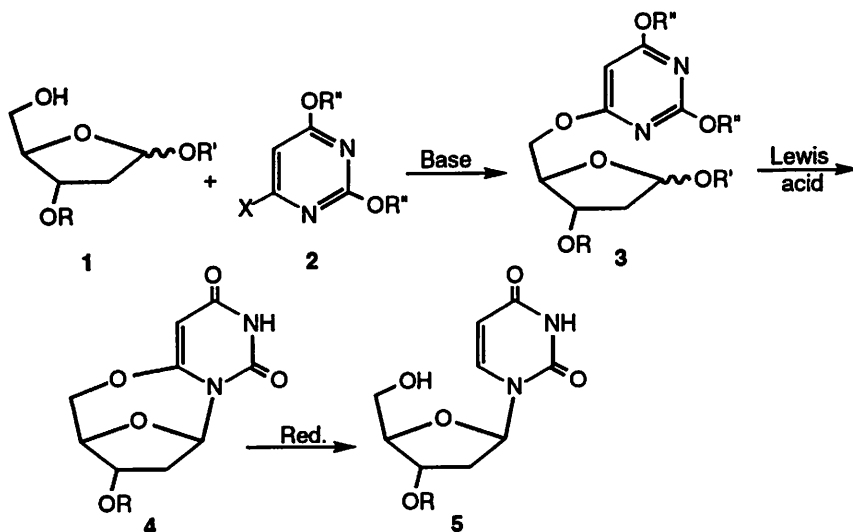
NOVEL LEWIS ACID-CATALYZED REARRANGEMENT OF A SUGAR-BASE HYBRID TO AFFORD AN ANHYDRONUCLEOSIDE

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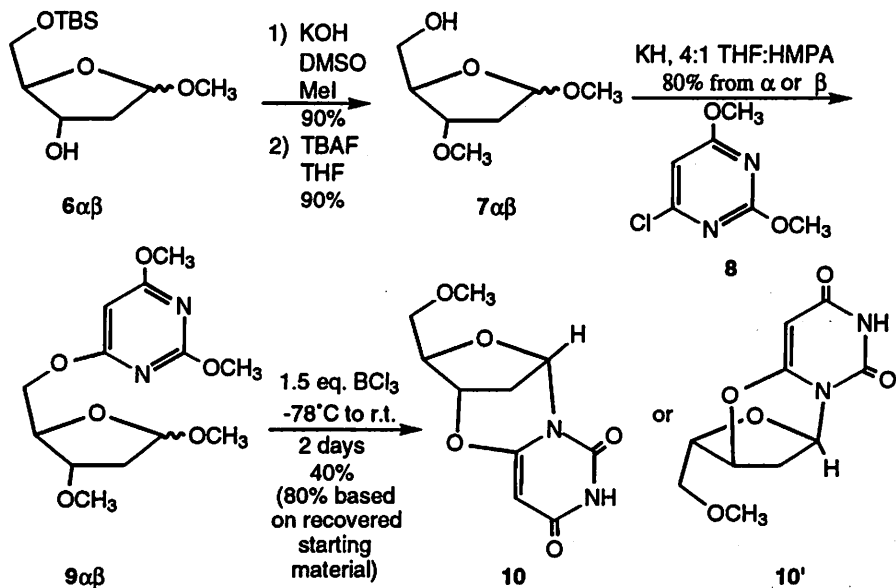
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ABSTRACT: Treatment of the sugar-base hybrid **9** with boron trichloride at low temperature for 40 h affords the 6,3'-anhydro-2'-deoxyuridine **10** in 40% yield (80% based on recovered **9**) via a novel structural rearrangement.

During the course of studies aimed at developing an intramolecular Vorbrüggen coupling of sugar-base hybrids joined at the 5-position of the sugar and the 2-position of the base to generate, after hydrolysis, only the desired β -anomers of 2'-deoxynucleosides,^{4,5} we examined the preparation and cyclization of the sugar-base hybrid **3** in which the deoxyribose component **1** was added to a 6-halo-2,4-dialkoxy pyrimidine **2**. We hoped that intramolecular coupling could be effected in the presence of a suitable Lewis acid catalyst to produce, after aqueous workup, the 6,5'-anhydro barbituric acid nucleoside **4**.



These are important modified nucleosides themselves as well as potential intermediates for the synthesis of normal pyrimidine nucleosides. Reduction (or hydrolysis-reduction) of the vinyl ether of 4 could give the desired 2'-deoxyuridine 5.⁶ We now report a novel Lewis acid-catalyzed rearrangement of a sugar-base hybrid such as 3 which produced an unexpected 6,3'-anhydronucleoside in fair yield.



The two *O*⁶,5'-bridged precursors 9 $\alpha\beta$ were prepared separately from the known⁷ methyl ribosides 6 $\alpha\beta$ as follows. Methylation (KOH, DMSO, MeI, 90%) afforded the methyl ether which was desilylated (TBAF, THF, 90%) to give each of the methyl ribosides 7 $\alpha\beta$.⁸ Formation of the anion with base and addition of the commercially available 6-chloro-2,4-dimethoxypyrimidine 8 gave the desired sugar-base hybrids 9 $\alpha\beta$. A variety of Lewis acids (TMSOTf, TBSOTf, SnCl₄, TiCl₄, Et₂AlCl) were ineffective at promoting

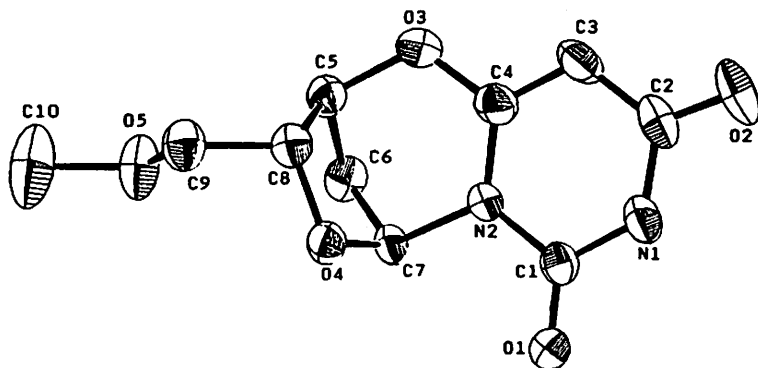
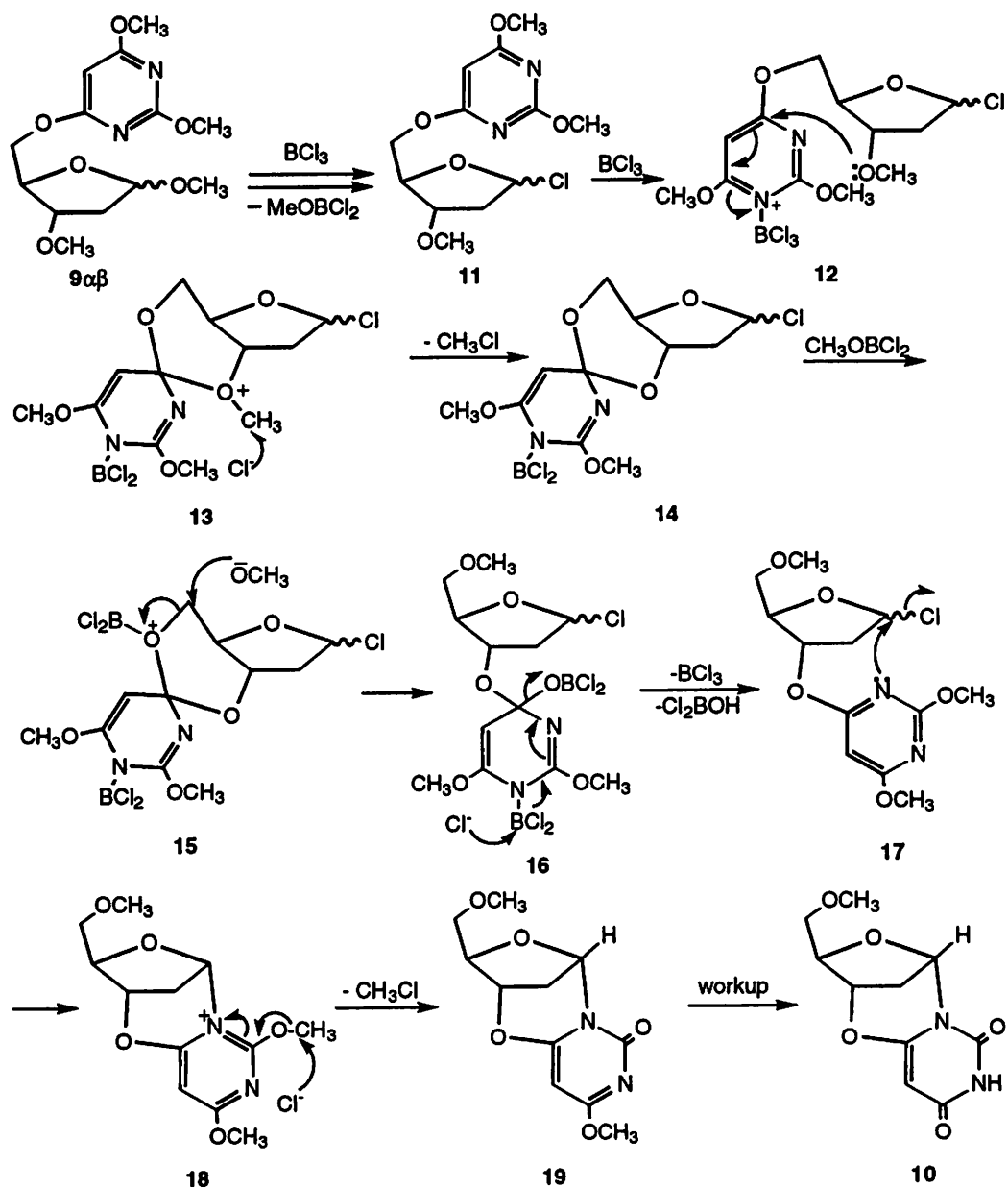


FIG. 1



Scheme

cyclization. Anomerization and/or hydrolysis of the methyl riboside were the only processes observed. However, when either anomer of $9\alpha\beta$ was treated with boron trichloride, the crystalline anhydro compound **10** was isolated in 40% yield along with 50% of recovered anomerized starting material and some minor unidentified adducts. The surprising structure of **10** was suggested by its ^1H NMR spectrum which showed the 3'-proton at low field [δ 5.05 (1H, d, $J = 0.8, 2.9$ Hz)] and the 5'-protons at much higher field [δ 3.57 (1H, dd, $J = 3.4, 10.9$ Hz) and δ 3.39 (1H, dd, $J = 4.6, 10.8$ Hz)], which implied that the substituent on the 3'-oxygen was electron withdrawing while that on the oxygen at 5' was not. The structure was proven conclusively by an x-ray crystal structure (Figure 1). Unfortunately, the poor quality of the crystal did not allow us to identify which enantiomeric form of **10** had been produced. However the compound isolated was optically active [α] $_{\text{D}}^{25} = +21.3$ (c 1.4, CHCl_3) and we believe that **10** is a more reasonable structure than **10'** because that structure would require inversions at both C-3 and C-4, which would be very difficult to explain.

The probable mechanism for the formation of **10** is shown in the Scheme, namely an intramolecular transfer of the base to the 3'-oxygen followed by cyclization. Conversion of the anomeric methoxyl group to chloride **11** presumably occurs first. Activation of the pyrimidine ring by boron trichloride **12** leads to attack by the 3' methoxy to afford the salt **13** which can lose methyl chloride to generate the spirocyclic orthoamide **14**. Activation of the bridging oxygen with methoxyboron dichloride would give an intermediate salt **15** which would react with methoxide to afford the 5'-methoxy compound **16**. Rearomatization of the pyrimidine would produce the sugar-base hybrid linked at the 3'-position of the sugar **17**. Final intramolecular glycosidation would give **18** which on loss of methyl chloride would furnish the methyl imidate of the product **19** or its regioisomer.⁹ Hydrolysis on workup would then produce the observed product **10**. There are other possible pathways, e.g., formation of the 5'-chloro compound which could afford the 5'-methoxy compound via an internal displacement of the type suggested by Horowitz.¹⁰ Obviously the reaction could also take place by an intermolecular process although that seems less likely.

In summary we have shown that a $O^6,5'$ -bridged sugar-base hybrid **8** is converted with boron trichloride into the 6,3'-anhydro-2'-deoxyuridine **9** in 40% yield (80% based on recovered starting material) via an unusual structural rearrangement. We will report soon the use of 3'-linked base-sugar hybrids for the stereospecific preparation of only the desired β -anomers of 2'-deoxynucleosides by an internal Vorbrüggen process.⁹

Acknowledgment: We thank the National Institutes of Health (GM 47228) for generous financial support.

REFERENCES AND NOTES

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- 6) Several methods exist for the hydrogenolysis of phenols to give the corresponding arenes. For an example, see: Musliner, W. J.; Gates, J. W., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 4271.
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- 8) The procedure for forming 7 $\alpha\beta$ involved addition of powdered KOH to a solution of the methyl ribosides 6 $\alpha\beta$ and MeI in DMSO and stirring at ambient temperature for 5h. Desilylation was effected by the normal technique (TBAF and the silyl ether were stirred together in THF for 1.5 h at ambient temperature). The proton NMR spectra of 7 $\alpha\beta$ corroborate their structures, e.g., the OH proton of 7 β is a dd ($J = 9, 3.3$ Hz) coupled to the two C5 protons, and therefore no shift of the TBS group from the oxygen at C3 to that at C5 occurred during the base-promoted methylation. We thank the referee for suggesting that possibility.
- 9) Such intramolecular Vorbrüggen reactions from the 3'-position to the anomeric center proceed in reasonable yields. a) Xia, X.; Wang, J.; Hager, M. W.; Sisti, N.; Liotta, D. C. *Tetrahedron Lett.* **1997**, *38*, 1111. b) Jung, M. E.; Castro, C.; Yang, E. unpublished results.
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Received 2/10/98

Accepted 6/26/98