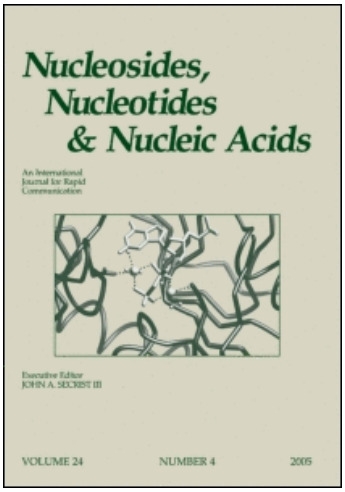

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

The Synthesis of 1-[7,8-Anhydr0-2,5,6-trideoxy-β-D-allo (and α-L-Talo)-Octofuranosyl]-Thymine as a Potential Enzyme Inhibitor

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To cite this Article Thomas, H. Jeanette , Riordan, James M. , Elliott, Robert D. and Montgomery, John A.(1989) 'The Synthesis of 1-[7,8-Anhydr0-2,5,6-trideoxy-β-D-allo (and α-L-Talo)-Octofuranosyl]-Thymine as a Potential Enzyme Inhibitor', Nucleosides, Nucleotides and Nucleic Acids, 8: 5, 947 — 950
To link to this Article: DOI: 10.1080/07328318908054251
URL: http://dx.doi.org/10.1080/07328318908054251

NUCLEOSIDES & NUCLEOTIDES, 8(5&6), 947-950 (1989)

THE SYNTHESIS OF 1-[7,8-ANHYDRO-2,5,6-TRIDEOXY-β-D-ALLO (AND α-L-TALO)-OCTOFURANOSYL]-THYMINE AS A POTENTIAL ENZYME INHIBITOR

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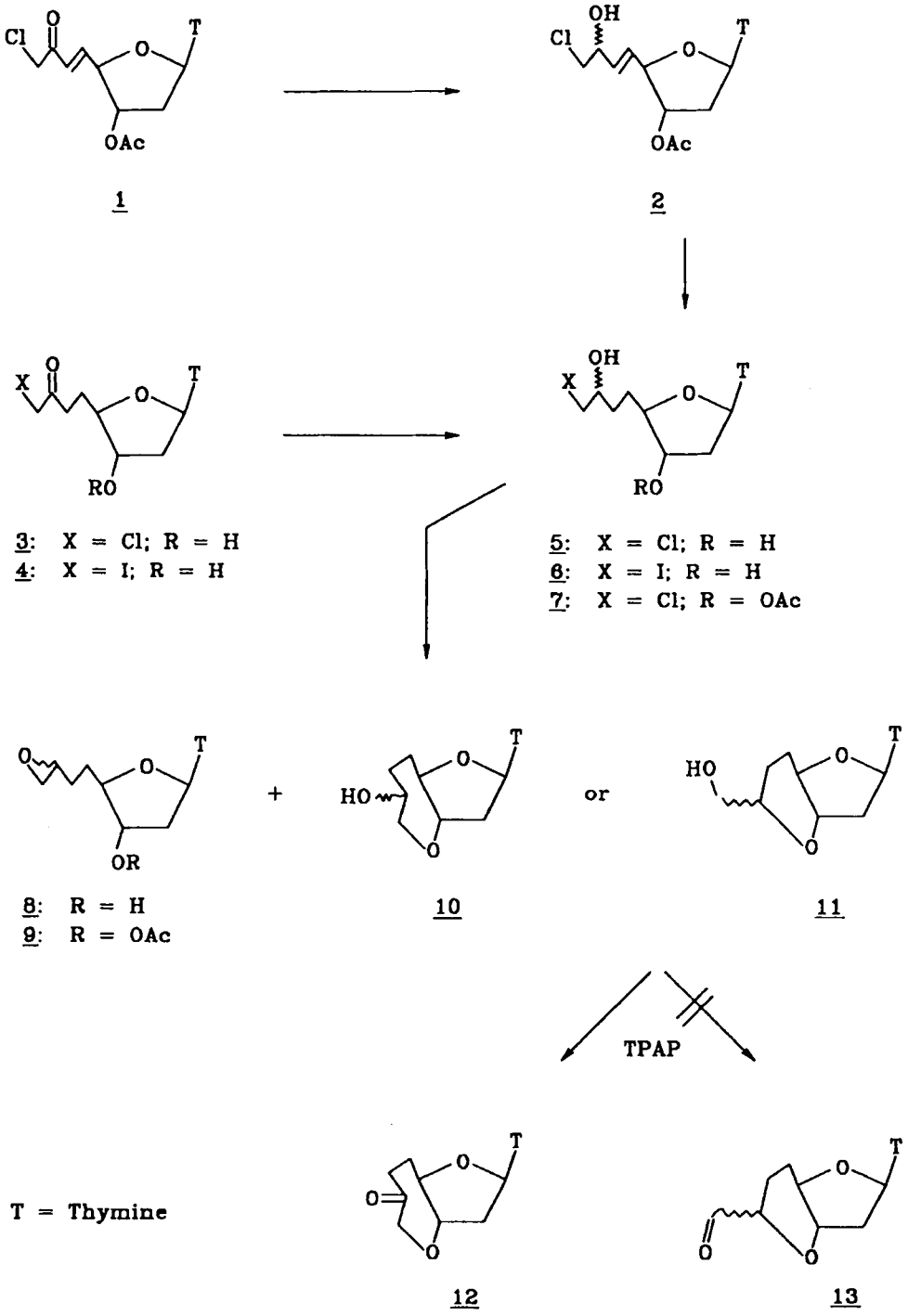
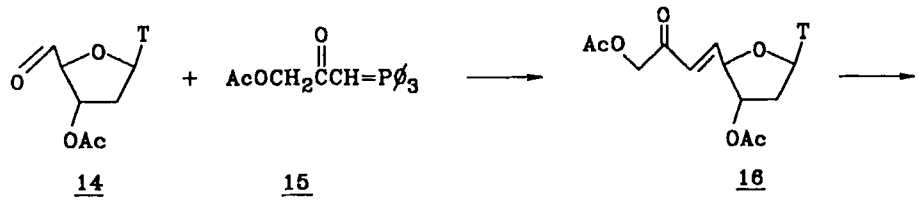
SUMMARY: The synthesis of an epoxide of thymidine resulted in an interesting by-product which was isolated and identified. An improved synthesis, giving only the epoxide was also carried out.

In our efforts to design and synthesize potential irreversible inhibitors of enzymes involved in the biosynthetic pathway to nucleic acids, we have prepared a number of nucleosides containing a chemically reactive function attached through a spacer to the 5'- position of the sugar moiety in the hope that such a function properly positioned could react with the binding sites for the phosphate moieties of nucleoside mono, di, and triphosphates.[1-8] It has been determined that a reactive carbon one and three atoms removed from the 5'- carbon should be in the proper position to react with the monophosphate binding sites.[1] For a nucleoside diphosphate, it should be ideally one, three or five carbons removed. Choice of the reactive function for reaction under *in vivo* conditions with the various possible binding sites is also critical. Certain groups require enzymatic activation *in vivo*, others such as the nitrosoureido group decompose to chemically reactive functions, while a third group is reactive as administered. The epoxide **8**, the synthesis of which is described here is of the third group.

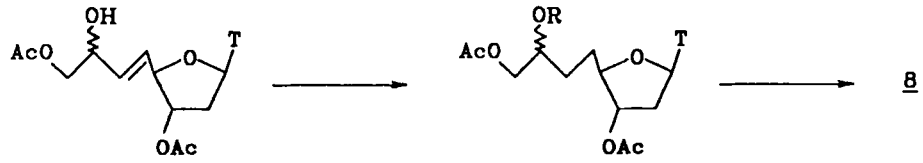
The synthesis of **8** was initiated by reacting either the chloro or iodohydrins **5** and **6** (prepared by sodium borohydride reduction of the respective haloketones[3] **3** and **4**) with sodium hydride in DMF. In both cases the epoxide **8** was contaminated with a by-product postulated to be either **10** or **11**. If the leaving group at the 8'-position were displaced with the 3'-oxygen anion, the 7-membered ring **10** would have formed as the sole product. Since the epoxide **8** is also obtained, it could have been opened by the 3'-oxygen anion to give either the 7-membered ring compound **10** or the 6-membered ring compound **11** depending upon the point of attack.

The mixture could not be resolved by chromatography, however treatment with 1N HCl resulted in conversion of the epoxide to the chlorohydrin **5** leaving the 3'-ether intact. The 3'-ether could be separated from the chlorohydrin **5** by preparative tlc. Oxidation of this product using tetra-n-propylammonium per-ruthenate[9] gave only the ketone **12**; none of the aldehyde **13**, which would have resulted from oxidation of **11** could be detected. NMR spectral data supported the structure of **12**, thus proving unequivocally that the structure of the unknown was an epimeric mixture of the 7-membered ring **10**.





14 15 16



17

18: R = H
19: R = Tosyl

In an attempt to prevent formation of **10**, **1**[3] was reduced with sodium borohydride to the unsaturated alcohol **2** which was further hydrogenated in the presence of palladium on charcoal to give the acetylated chlorohydrin **7**. Treatment of **7** with sodium hydride in DMF gave a low yield of **9** contaminated with **10**.

An improved approach to the epoxide was carried out by reacting 3'-O-acetylthymidine-5'-aldehyde **14** with [(acetoxymethyl)carbonyl]methylenetriphenylphosphorane[10] **15** to give **16**. Borohydride reduction of the carbonyl group gave **17**, followed by catalytic hydrogenolysis to give **18**. Tosylation of **18** gave **19**. Reaction of **19** with sodium methoxide-$CHCl_3$ gave as the sole product, the epoxide **8** as a mixture of epimers.

Treatment of the epoxide **8** with sodium hydride-DMF gave a mixture of about 3:1 **8** and **10**. Reaction of the chlorohydrin **5** with sodium methoxide-$CHCl_3$ again gave a mixture of the epoxide **8** and the 7-membered ring compound **10**. It appears that in order to obtain pure epoxide, it is necessary to have the leaving group on the 7-carbon rather than the primary or 8-carbon. The reaction is best carried out using sodium methoxide-$CHCl_3$.

The epoxide **8** was marginally cytotoxic to L1210 cells in culture[11] (I_{50} = 25 μM) and exhibited little cytotoxicity to H.Ep.-2 cells[12] (I_{50} = 80 μM). The 7-membered ring ether **10** showed no significant cytotoxicity.

Acknowledgment: This work was supported by the National Cancer Institute Contract #P01CA 34200.

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