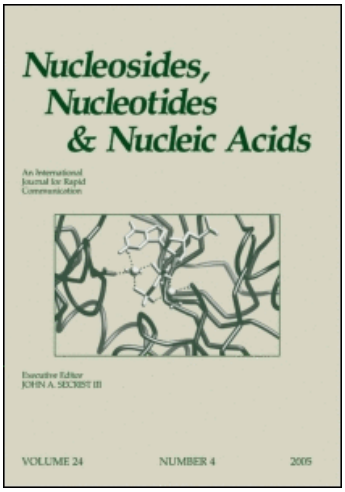

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Anne F. Cichy[a]; Purushotham Vemishetti[a]; Elie Abushanab[a]
[a] Department of Medicinal Chemistry, University of Rhode Island, Kingston, RI

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AN UNUSUAL DEPHOSPHORYLATION REACTION

Anne F. Cichy, Purushotham Vemishetti, and Elie Abushanab*
Department of Medicinal Chemistry
University of Rhode Island
Kingston, RI 02881

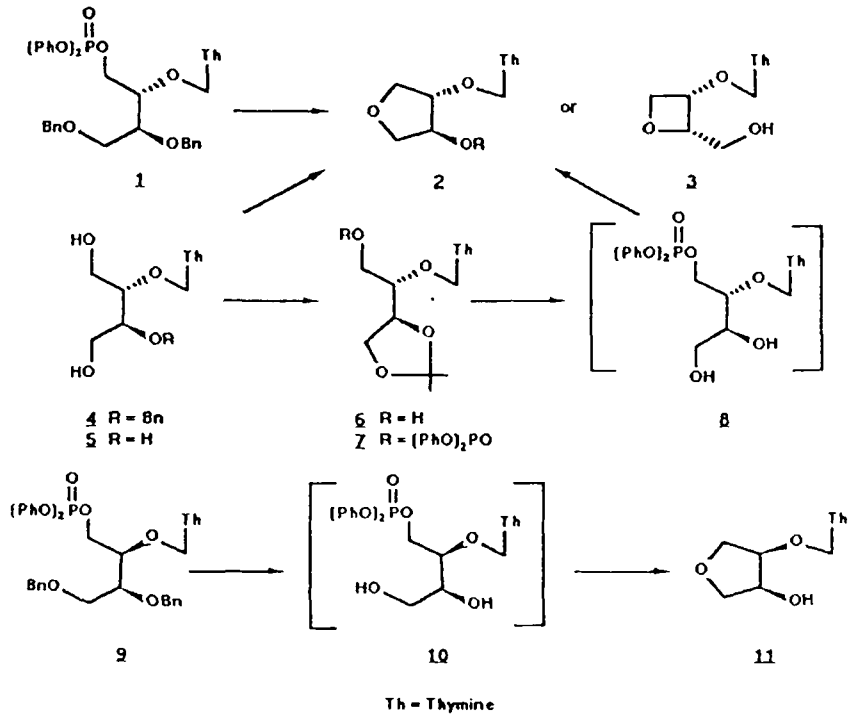
In the course of our work to prepare 1',2'-seco-nucleotides, an unusual dephosphorylation reaction took place. When compound 1 was subjected to transfer hydrogenation conditions, the expected product was not obtained. Instead, a crystalline solid that proved not to have phosphorus was isolated in 78% yield. ^{1}H and ^{13}C nmr analyses confirmed the hydrogenolysis of the benzyl groups as well as the loss of the phenyl esters. This information coupled with elemental analytical data suggested that the structure of the compound could be either the 2',5'-anhydro (2, R=H) or 3',5'-anhydro derivative 3. Structural similarities between 2 and 3 precluded the use of spectroscopic analyses to prove the structure. However, based on our experience with related compounds, structure 2 was favored, and we set out to prove it by another synthetic route.

An independent synthesis of the 2',5'-anhydro compound 2 (R=H) is depicted in the scheme. The partially protected nucleoside 4 was subjected to dehydrative cyclization conditions of the Mitsunobu reaction[1] to give the cyclized product 2 (R=Bn).

Subsequent debenzylation gave a compound that was identical in all respects to the dephosphorylation product described earlier. This provided conclusive evidence for its structural assignment.

Having found no literature precedents for this reaction, our attention was turned toward understanding the mechanism of the reaction. A question to be answered was whether the reaction proceeded by a radical or ionic mechanism. This necessitated the isolation of the 2',3'-dihydroxy 5'-phosphate ester 8 to study its behavior under identical and different reaction conditions.

An alternate route to 8 is shown in the scheme. Starting with the totally deblocked nucleoside 5 the 2',3'-isopropylidene (6) was prepared by the acetone/tosic acid method. Structure proof for 6 was derived from ^{13}C nmr analysis. It is reported that the chemical shifts of the methyl groups differ by approximately 1.0 ppm in a five membered isopropylidene ring. However, that value is about 10 ppm in a six membered ring.[2,3] The ^{13}C nmr



spectrum of the reaction product showed it to be 6, which was treated with diphenyl chlorophosphate to give 7. Acid hydrolysis of 7 at room temperature while following the reaction by TLC analysis (EtOAc:MeOH, 3:1) showed the disappearance of the starting material after 2 hours and the appearance of a more polar compound which was believed to be the desired product 8. However, ^{31}P nmr analysis showed it to be a mixture of two phosphorus containing compounds one of which proved to be diphenylphosphate. The presence of the latter compound prompted us to look for compound 2 (R=H) in the reaction mixture. Indeed, careful TLC analysis revealed the presence of two compounds only one of which contained phosphorus. When an aqueous solution of this mixture was gently warmed up in a water bath at 50°C, it resulted in the conversion of one product to the other. This latter compound proved to be the 2',5'-anhydro derivative 2 (R=H). This established 8 as an intermediate and ruled out the radical mechanism in this conversion.

The ease with which dephosphorylation took place prompted us to reexamine the debenzylation reaction of compound 1. Careful TLC monitoring of this reaction did reveal that deblocking took place at a faster rate than that reported in the literature[4], the reaction was complete in one hour, with partial simultaneous conversion to the 2',5'-anhydro compound 2 (R=H).

In an attempt to study the effect of chirality on the course of this reaction the diastereomeric compound 9, was subjected to the same reaction conditions for debenzylation mentioned earlier. Deblocking was complete in one hour resulting in the formation of a mixture of 10 and 11. Heating this mixture resulted in complete conversion of 10 to 11 which was isolated in 86% yield. Our current efforts are aimed at determining the scope and limitations of this reaction.

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