

## The Synthesis of a Novel 2',3'-Cyclic Phosphate Derived From 2'-Homouridine

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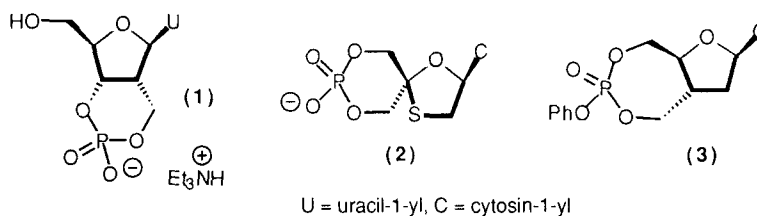
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Received 4 September 1998; accepted 14 September 1998

**Abstract:** The novel 2',3'-cyclic phosphate (1) derived from 2'-homouridine has been prepared by phosphorylation with 2-cyanoethyl *N,N,N',N'*-tetraisopropylphosphorodiamidite. © 1998 Published by Elsevier Science Ltd. All rights reserved.

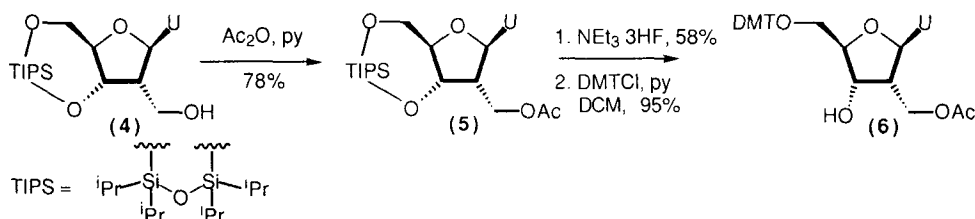
Cyclic phosphates play a key role in metabolic processes. For example, cyclic ADP ribose has been shown to play an important role as a secondary messenger involved in calcium signalling<sup>1</sup>. The importance of cyclic phosphates as precursors to phosphates has recently led to the synthesis of several synthetic cyclic phosphates as potential antiviral agents. For example, two groups have prepared the cyclic monophosphate of 4'-hydroxymethyl-2',3'-dideoxy-3'-thianucleoside (2)<sup>2</sup> and recently, Mann<sup>3</sup> has reported the 3',5'-linked cyclic phosphate analogue (3) (Figure 1).

Figure 1



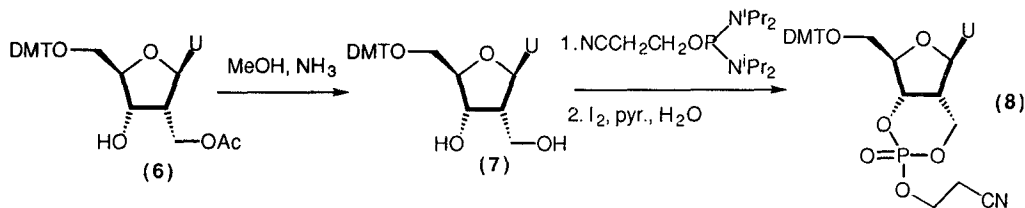
In this letter we report the first example of a 2',3' cyclic phosphate bearing a 2'-C substituent (1). This work was stimulated by our general interest in 2'-modified nucleosides and nucleotides<sup>4</sup> and in particular by our recent studies on oligomers containing 2'-homouridine.<sup>5</sup> Indeed, the hydrolysis of oligonucleotides containing 2'-homouridine might be expected to proceed *via* a cyclic phosphate such as (1). We have previously reported a concise route to the TIPS protected 2'-hydroxymethyl compound (4).<sup>5</sup> Starting from this material, acetylation of the free hydroxyl group proceeded smoothly to give (5). Removal of the TIPS protecting group followed by selective protection of the 5'-hydroxyl gave the DMT protected alcohol (6) in good yield. The compound now possessed two differentially protected primary hydroxyl groups (Scheme 1).

Scheme 1.



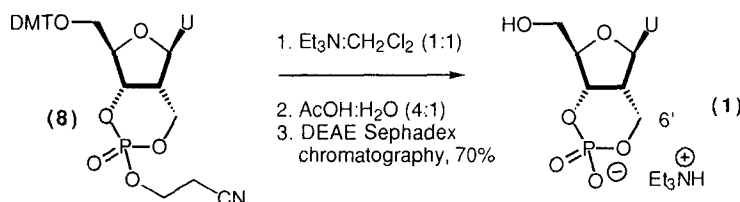
Selective removal of the acetyl group with methanolic ammonia yielded the diol (7). After thorough drying, diol was treated with 1.4 equivalents of 2-cyanoethyl *N,N,N',N'*-tetraisopropylphosphorodiamidite<sup>6</sup> in acetonitrile in the presence of 4 equivalents of tetrazole, to yield the phosphite intermediate which was observed in the <sup>31</sup>P spectrum as a pair of diastereoisomers at 128.95 and 126.06 ppm (Scheme 2).

Scheme 2.



*In situ* oxidation with aqueous iodine gave the fully protected cyclic phosphate (8) in 67% yield. The <sup>31</sup>P NMR spectrum of the product now consisted of a pair of peaks at -4.51 and -8.17 ppm, corresponding to a pair of diastereoisomeric phosphates. Formation of the product was also confirmed by FAB mass spectrometry which indicated the presence of the parent ion at 676 units. Full deprotection of phosphate (8) was achieved by sequential treatment with a solution of NEt<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (1:1) and 80% aqueous acetic acid (Scheme 3). The product was purified by sephadex ion exchange chromatography. <sup>1</sup>H NMR spectroscopy showed the expected down-field shift of the signals for the H-3' (4.60 in (7) to 4.81 ppm in (1)) and H6' (4.02 and 4.01 in (7) to 4.36 and 4.03 in (1)). Proton decoupled <sup>31</sup>P NMR (101MHz) showed a single peak at -4.70 ppm and FAB mass spectroscopy also showed a pseudomolecular ion with a mass value of 319.

Scheme 3.



In summary, we have prepared the first example of a cyclic phosphate derived from 2'-homouridine which will be useful in studying the hydrolytic behaviour of oligonucleotides containing 2'-homouridine. The work also demonstrates the utility of 2-cyanoethyl *N,N,N',N'*-tetraisopropylphosphorodiamidite as a bifunctional reagent for the synthesis of cyclic phosphates.

**Acknowledgements:** We would like to thank the EPSRC for a studentship to JBJP.

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