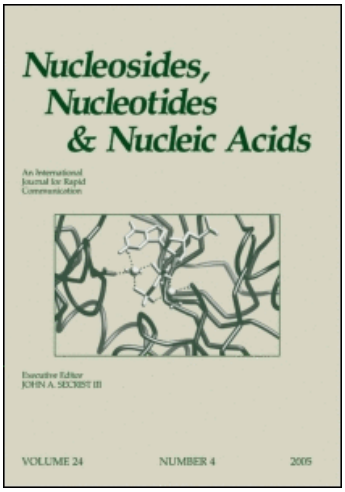

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SYNTHESIS OF 6-FORMYLURIDINE 5'-MONOPHOSPHATE: 6-FORMYL-UMP

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SYNTHESIS OF 6-FORMYLURIDINE 5′-MONOPHOSPHATE: 6-FORMYL-UMP

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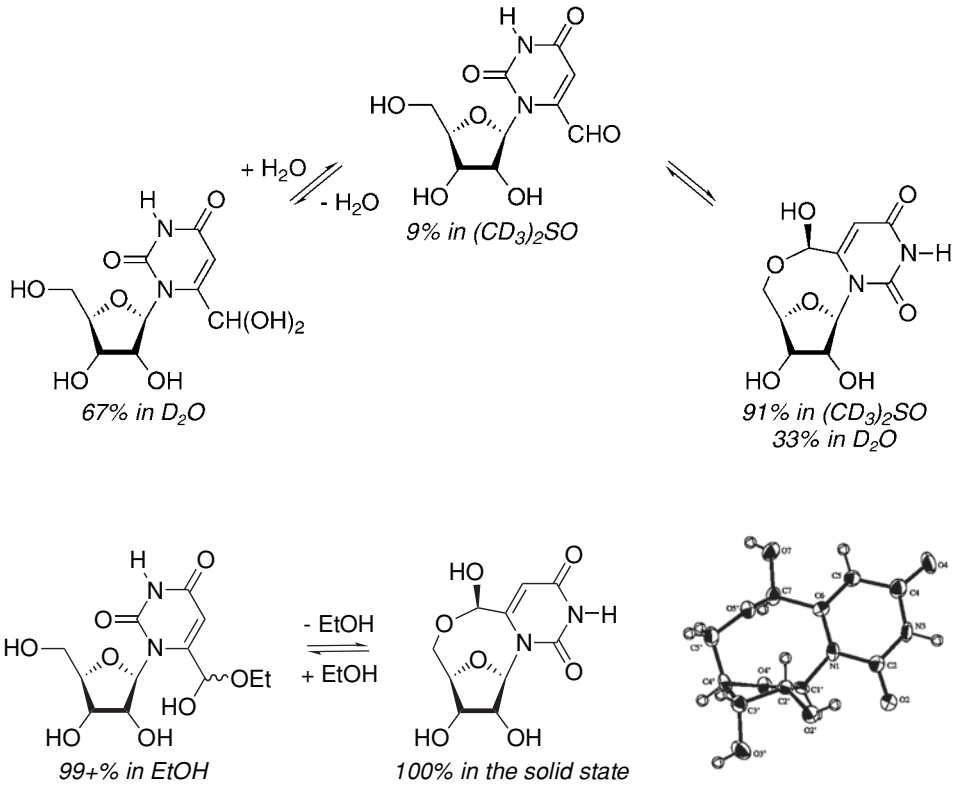
ABSTRACT

A synthesis of 6-formyluridine 5′-monophosphate (6-formylUMP) in 6 steps starting from uridine is described. This approach should be applicable to the preparation of other O5′-phosphorylated 6-formylUrds such as 6-formylUDP and 6-formylUTP.

Previous investigations in my laboratory have demonstrated that the nucleosides 6-formyluridine (6-formylUrd), 6-formyl-2-deoxyuridine, and 6-formyl-1-(β-D-arabinofuranosyl)uracil all possess the unusual carbohydrate-like property of existing to some degree in transglycosidic cyclic hemiacetal form, even in aqueous solution (1–6). This is a consequence of both the proximity of the formyl group to certain carbohydrate hydroxyl groups and to the strong electron-withdrawing force that the 1-alkyluracil-6-yl moiety exerts on the carboxaldehyde functionality. For example, 6-formylUrd exists in water as a 2:1 mixture of the aldehyde hydrate and the (*7R*)-O5′,7-intramolecular cyclic hemiacetal. In Me_2SO, it exists as a 1:10 mixture of the aldehyde and the same hemiacetal diastereomer. Finally, it exists as a 1:1 mixture of diastereomeric ethyl hemiacetals in EtOH, but 6-formylUrd crystallizes out of this solvent exclusively as the (*7R*)-O5′,7-cyclic hemiacetal.

The task of preparing a 5′-nucleotide derivative of 6-formylUrd such as 6-formylUMP presents a unique obstacle to overcome: Any attempt to directly O5′-phosphorylate an O5′-unprotected version of 6-formylUrd would surely fail because of the overwhelming predominance of the transglycosidic hemiacetal form that exists in anhydrous aprotic solvents. Thus, a less straightforward route—one involving a masked aldehyde—is required for accessing 6-formylUMP or indeed



any other O5′-phosphosphoryl derivatives that might be desired for investigations with nucleotide-utilizing enzymes.

RESULTS AND DISCUSSION

A 6-formylUrd derivative in which the 2′-OH, 3′-OH, and 6-CHO groups are all protected with acid-labile protecting groups might well be very useful in an efficient and successful synthetic approach to 6-formylUMP. Using such a derivative, a direct phosphorylation with, for instance, $POCl_3$ would be assuredly regiospecific for the 5′-OH group. Furthermore, the phosphorylation could be followed directly by an *in situ* removal of all of the protecting groups in the last step of the synthesis, taking advantage of the HCl that would be generated during an aqueous workup procedure.

With these points in mind, an efficient 6-step synthesis of 6-formylUMP starting from uridine was developed (Scheme 1). For its greater ease of removal compared to that of an isopropylidene group, one of Reese's 2′,3′-O-alkoxymethylidene groups (7) was employed for the simultaneous protection of the 2′- and 3′-OH groups in uridine. Its 5′-OH group was then protected with a TBDMS group, giving nucleoside **1**. A Miyasaka dianion (a uridine-3,6-diyldilithium species)

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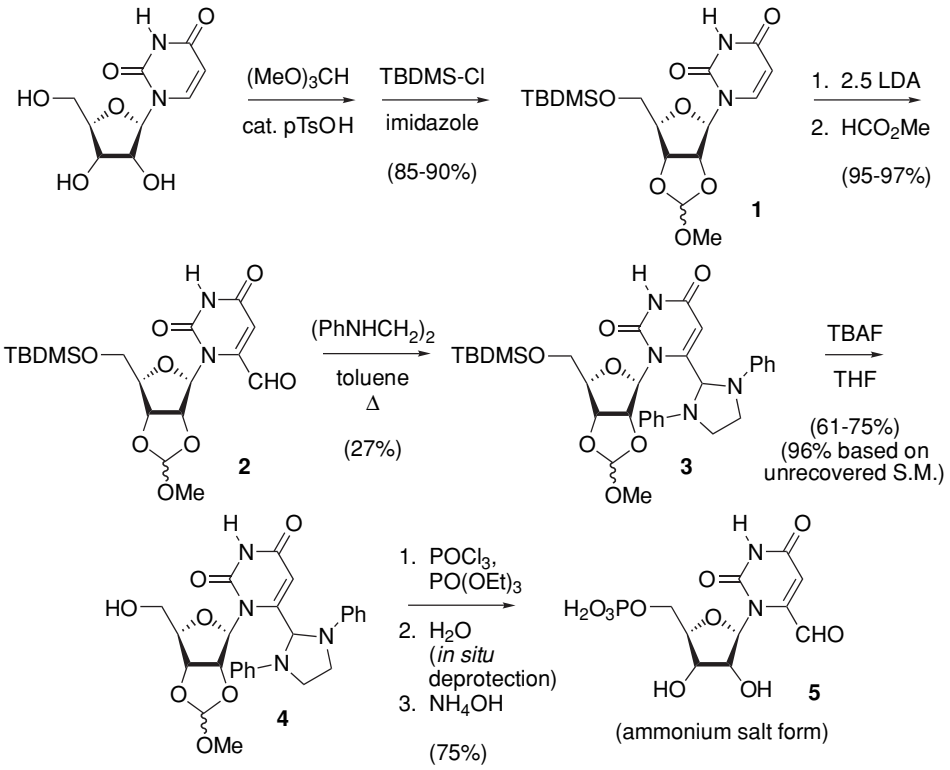

Scheme 1.

(8) was then generated from **1**, and this was quenched with HCO_2Me to give the carbohydrate-protected 6-formylUrd **2** in an excellent yield. In our earliest work with the 6-formylUrds, we found that their formyl group would undergo acetalation only under forcing conditions, (1) and so for the present synthesis of 6-formylUMP it instead was masked as a 1,3-diphenylimidazolidin-2-yl (DPI) moiety as was found advantageous in our most recently completed investigation (6).

This conversion of the 6-formyl group of **2** to the DPI one of **3** was the only problematic step encountered. It was conducted without the aid of an acid catalyst to avoid labilizing the acid-sensitive methoxymethylidene group. Perhaps due to a steric hindrance provided by the carbohydrate fragment or a competing intramolecular 5′-O-desilylation via silyl transfer to the hemiaminal intermediate, this conversion (not optimized) proceeded in only a 27% yield. The 5′-O-TBDMS group in **3** was removed by exposure to TBAF, and the subsequent O5′-phosphorylation of **4** with $POCl_3$ proceeded smoothly, as did the anticipated *in situ* removal of all the protecting groups effected simply by the introduction of water after the phosphorylation was complete. The aqueous solution of 6-formylUMP (**5**) that this procedure generated was promptly treated with NH_4OH to convert **5** to its ammonium salt

form. Extraction with Et_2O to remove the $(PhNHCH_2)_2$ and excess $PO(OEt)_3$ was followed by lyophilization, giving the target 6-formylUMP **5** as an anhydrous powder ready for desalting (9).

CONCLUSIONS

With a careful consideration for the unusual carbohydrate-like properties of 6-formylUrd, a general route to its O5′-phosphorylated derivatives like 6-formylUMP has now been developed. It should prove to be useful for the preparation of 6-formylUDP, 6-formylUTP, and other similar 5′-phosphorylated 6-formylUrd derivatives.

ACKNOWLEDGMENTS

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9. Preliminary characterization data obtained on un-desalted **5**: ^{1}H NMR (D_2O) δ 6.07 (s, 1, H5), 5.97 (s, 1, $CH(OD)_2$), 5.92 (d, J = 4Hz, 1, H1′), 4.40 (m, 1, H3′), 4.01 (m, 1, H4′), 3.87 (m, 2, 5′-CH_2). ^{13}C NMR (D_2O) δ 166 (C4), 156 and 152 (C2/C6), 101 (C5), 92 (C1′), 86 ($CH(OD)_2$), 82 (C4′), 72 (C2′), 69 (C3′), 64 (C5′). Low resolution DCI (direct current ionization) mass spectrum, *m/e*: 213 (phosphoribosyl-H+H^+).

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