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Alternative synthetic routes to 2′,3′-didehydro-2′,3′-dideoxy-5-hydroxymethyluridine

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Abstract—Alternative syntheses for the nucleoside analogue 2′,3′-didehydro-2′,3′-dideoxy-5-hydroxymethyluridine starting from 5-methyluridine and uridine are described.

Several 2′,3′-dideoxynucleosides and 2′,3′-didehydro-2′,3′-dideoxynucleosides have been used for the treatment of patients with human immunodeficiency virus (HIV). These nucleosides, in their 5′-triphosphate form, inhibit the polymerization of proviral DNA facilitated by HIV reverse transcriptase. 2′,3′-Dideoxynucleosides that are FDA-approved for clinical use include 2′,3′-dideoxycytidine (ddC), 2′,3′-dideoxyinosine (ddI) and 3′-azido-3′-deoxythymidine (AZT). 2′,3′-Didehydro-2′,3′-dideoxythymidine (d4T) has also been FDA-approved for the treatment of HIV. However, resistance to these nucleoside RT inhibitors (NRTIs) has become a major obstacle in HIV therapy and the development of new NRTIs is paramount.

2′,3′-Didehydro-2′,3′-dideoxy-5-hydroxymethyluridine **(1)** is a compound similar in structure to d4T. In contrast to d4T, 2′,3′-didehydro-2′,3′-dideoxy-5-hydroxymethyluridine possesses a pendant hydroxyl moiety off of the 5-methyl substituent on the pyrimidine base. Gavriliu et al.[1] and Renoud-Grappin et al.[2] have synthesized 2′,3′-didehydro-2′,3′-dideoxy-5-hydroxymethyluridine and exploited the hydroxyl group as a handle for further chemical transformation in studies directed towards the synthesis of new d4T-derived anti-HIV compounds. Pugazhenthi et al.[3] have also solved the X-ray crystal structure of this compound.

It is apparent from previously published work[1,2] as well as ongoing work in our laboratory that 2′,3′-didehydro-2′,3′-dideoxy-5-hydroxymethyluridine **(1)** is an important intermediate towards potential inhibitors containing analogues of d4T. In our laboratory, alternative syntheses of 2′,3′-didehydro-2′,3′-dideoxy-5-hydroxymethyluridine **(1)** have been developed to provide straightforward synthesis of **1** without the need for special equipment or reagents and allows for a wider range of transformations that can be carried out on the 5-hydroxymethyl substituent.

The synthesis of hydroxymethyluridine **1** was initiated with commercially available uridine **(2)**. First, the 2′ and 3′ hydroxyls of uridine were protected as an acetonide by reaction with 2,2-dimethoxypropane in the presence of *p*-toluensulfonic acid using a modified literature procedure.[4] The resulting alcohol **3** was subjected to hydroxymethylation conditions (0.5 M KOH, paraformaldehyde, 60 °C) described by Gavriliu et al.[1] to give the bis alcohol product **4**. At this point, the purification of **4** proved to be a challenge due to the co-elution of a side product of similar polarity during flash column chromatography. As a result, compound **4** was only purified on a short silica gel column to remove most of the impurities present. Bis alcohol **4** was treated with 50% acetic acid solution to yield intermediate **5**, which was not purified. Instead, the primary hydroxyl groups of crude **5** were protected as *t*-butyldiphenylsilyl ethers, resulting in compound **6** in a moderate yield. The free vicinal diol was converted to the corresponding bisxanthate **(7)** by reaction with 5 N NaOH and carbon disulfide, followed by the addition of methyl iodide. The reaction of **7** under radical deoxygenation conditions (Bu_3SnH, AIBN, toluene, reflux) enabled the formation of 2′,3′-didehydro-2′,3′-dideoxynucleoside **8** in a 77% isolated yield.[5] Finally, cleavage of the silyl ethers with

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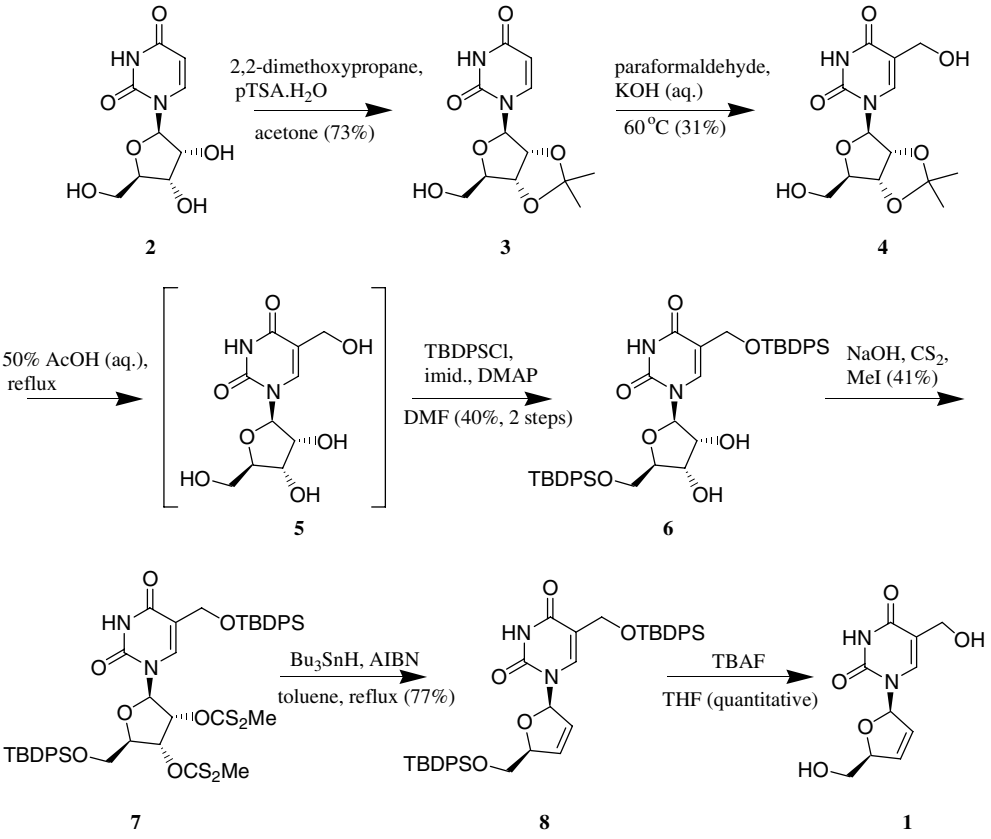
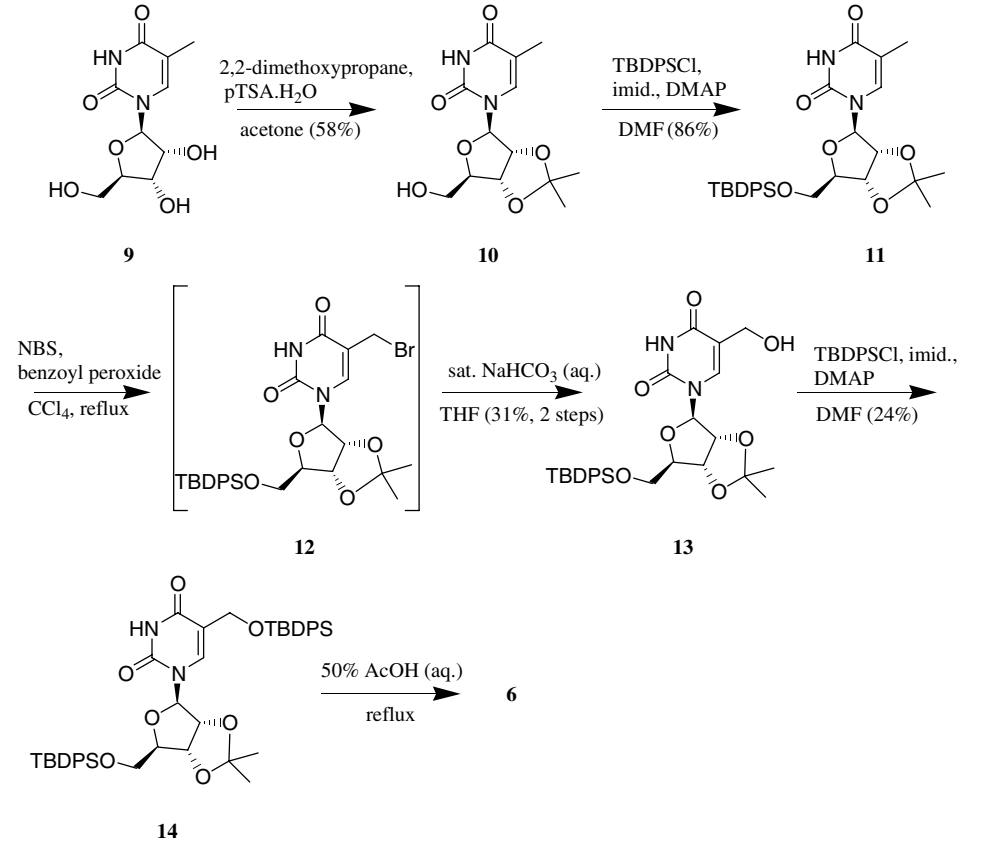


Scheme 1.



Scheme 2.

tetrabutylammonium fluoride (TBAF) resulted in the formation of 2′,3′-didehydro-2′,3′-dideoxy-5-hydroxymethyluridine **(1)** in a quantitative yield (Scheme 1). The structure of **1** was confirmed by comparing our X-ray crystallographic data to a published crystal structure.[3]

Alternatively, a synthesis of compound **1** starting with commercially available 5-methyluridine **(9)** was also developed. Starting with compound **9**, the 2′ and 3′ hydroxyls were protected as an acetonide to yield compound **10** in a moderate yield (58%). The 5′ hydroxyl of **10** was immediately protected as the *t*-butyldiphenylsilyl ether to give compound **11** in an 86% isolated yield. Following a published procedure,[6] the 5-methyl substituent was halogenated in the presence of *N*-bromosuccinimide and benzoyl peroxide in boiling CCl_4 to give an intermediate bromide **12**. Due to instability concerns, bromide **12** was not purified. Compound **12** was immediately subjected to reaction with saturated sodium bicarbonate in aqueous solution. THF was added to facilitate dissolution of compound **12**. The desired product **13** was then reacted with TBDPSCl to protect the free hydroxyl to give compound **14**. The reaction of the doubly protected **14** with 50% acetic acid cleaved the acetonide to give compound **6** without cleavage of the silyl ethers (Scheme 2). It is noteworthy to mention that it is advantageous to start with 5-methyluridine because it allows for the manipulation of the 5-hydroxymethyl substituent without reaction at the 5′ hydroxyl. Abdel-Rahman and El Ashri has been able to synthesize compound **13** directly from compound **3**. However, their method required the use of microwave irradiation to affect the hydroxymethylation step.[7]

In conclusion, we have developed alternate synthetic routes to 2′,3′-didehydro-2′,3′-dideoxy-5-hydroxymethyluridine **(1)**. The first route takes the advantage of *t*-butyldiphenylsilyl protecting groups to aid in chromatographic purification as well as utilizes standard organic transformations to facilitate ease of synthesis. In addition, the second route allows the manipulation of the hydroxyl at the 5 position of the base without reaction of the 5′ hydroxyl, opening the door to general alcohol transformations at that position. This compound presents an opportunity for the development of new NRTIs as its 5-hydroxymethyl functionality and allows chemists to perform chemical transformations to vary substituents and explore diversity at that location in the molecule. The utility of this molecule has already been demonstrated by other research groups[1,2] and these alternative routes present various possibilities for chemistry that may not have been possible in previous synthetic endeavors.

Supplementary data

Experimental procedures and spectral data for compounds **1**, **3**, **4**, **6**–**8**, **10**, **11**, **13** and **14** are available with this article. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.083.

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