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A Claisen Approach to 4′-Ed4T

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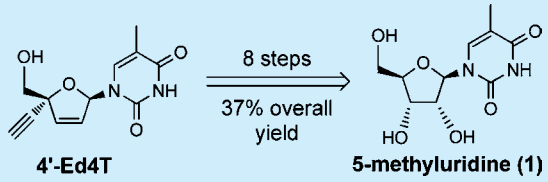
Supporting Information

ABSTRACT: An efficient, stereoselective synthesis of 4′-Ed4T is demonstrated. The synthesis is highlighted by a regioselective TMSOTf-mediated acetal opening, a Claisen rearrangement to set the key 4′-stereocenter as well as the olefin, and a one-pot nonaflation/elimination to deliver the alkyne moiety. The synthesis proceeds in eight steps from 5-methyluridine and occurs in 37% overall yield.



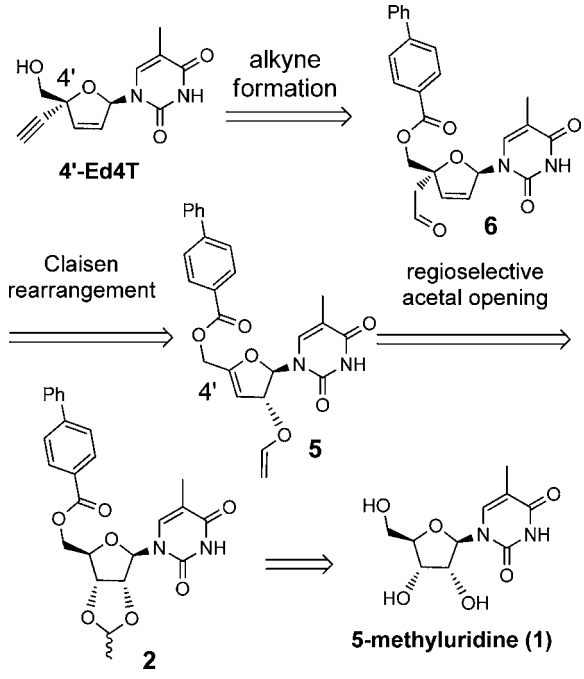
Nucleosides[1] are part of a key group of antiviral and antitumor agents. Due to the reported anti-HIV activity, their 4′-carbon-substituted analogues have attracted much interest. Existing synthetic methods[2] for the introduction of the 4′ethynyl group are limited by a lack of stereoselectivity and long synthetic sequences.[3] Preparative methods for 4′-carbon substituted nucleosides have mostly been centered on manipulations of 4′-hydroxymethyl derivatives of nucleosides or sugars. These derivatives are obtained by the familiar aldol–Cannizzaro reaction[4] of the corresponding aldehyde. Haraguchi[5] was able to introduce a leaving group to the 4′-position and executed a nucleophilic ethynylation. Other reported methods include intramolecular radical cyclization of a 3′-*O*-silicon-tethered nucleoside C4′-radical[6] and electrophilic substitution[7] of nucleoside 5′-esters. Herein, we describe our synthetic route toward 4′-Ed4T.[8]

The retrosynthetic analysis of 4′-Ed4T is shown in Scheme 1. The alkyne moiety would be derived from the corresponding aldehyde **6**. A Claisen rearrangement would occur with allylvinyl ether **5** to set the 4′ stereochemistry as well as the olefin geometry. The allylvinyl ether **5** would arise from a regioselective methyl acetal opening. The methyl acetal **2** would be easily accessed from 5-methyluridine[9] **1** and acetaldehyde.

The synthesis commenced with the acid-catalyzed acetal formation (Scheme 2). A screening of acids[10] revealed that H_2SO_4 (6 mol %) with acetaldehyde provided the acetal cleanly. Although the methyl acetal **2** could be isolated, it was found to be advantageous to telescope directly into the acylation. Once the acetalation was complete, it was quenched wth 10 N NaOH (12 mol %). The crude primary alcohol was azeotroped[11] with ACN until the Karl Fischer (KF) was <0.10 wt %. [1,1′-Biphenyl]-4-carbonyl chloride (1.1 equiv) was added followed by pyridine (1.3 equiv). After the mixture was heated at 50 °C for 2 h, it was cooled to 20 °C and was isolated by filtration to afford biphenylacetate[12] **2** in 90% yield over two steps.

Vinyl ethers are typically installed utilizing Hg-mediated[13] transvinylations. These traditional methods did not provide the desired vinyl ether. Brown[14] has shown that mixed acetals undergo a selective elimination of primary alcohols upon treatment with TMSOTf/Et_3N, affording reasonable yields of

Scheme 1. Retrosynthetic Analysis



the vinyl ethers. Hoye[15] has demonstrated that alkenyl-substituted ketals derived from 1,2-diols readily form vinyl ethers upon treatment with TESOTf/DIPEA. We reasoned that a methyl acetal, upon treatment with TMSOTf/Et_3N, could potentially lead to the desired vinyl ether. We were pleased to find that treating methyl acetal **2** with TMSOTf/Et_3N provided the desired vinyl ether[16] **3** with a high degree of regioselectivity. The use of the 4-(biphenyl)benzoyl protecting group proved to be pivotal, as it achieved the highest regioselectivity (Scheme 3). We postulate that the selectivity could be dependent on an internal delivery of a silyl cation. Mechanistic studies are underway to elucidate the origin of the regioselectivity and will

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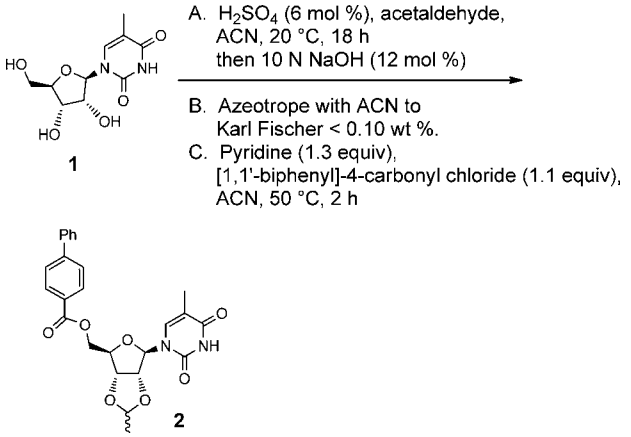
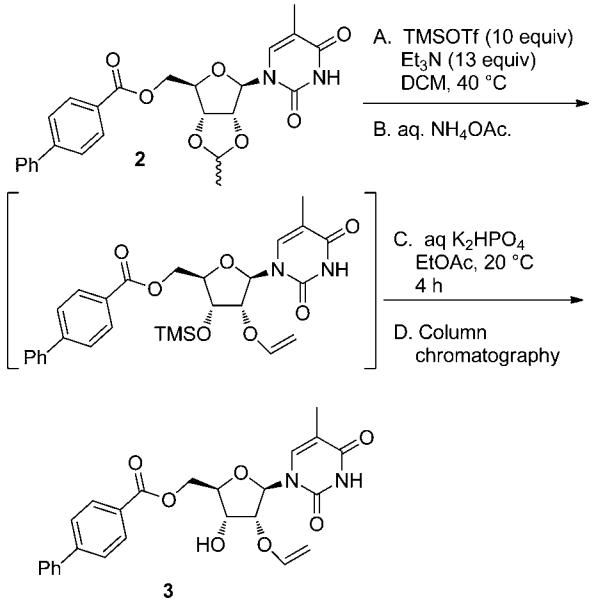
Scheme 2. Acetal Formation and Acylation



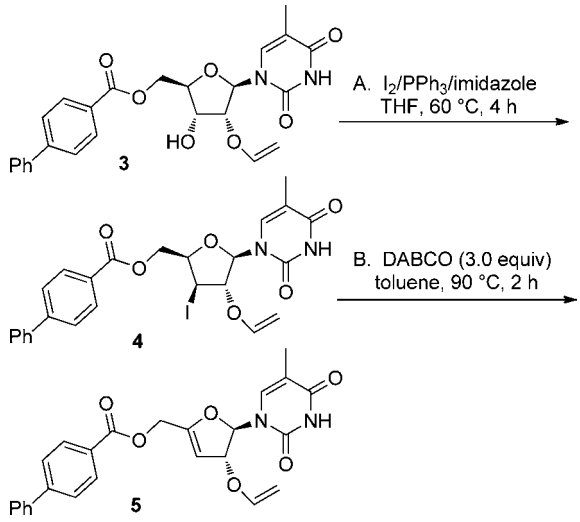
Scheme 3. Regioselective Acetal Opening



be reported in due course. Treatment of the methyl acetal **2** with Et_3N (13 equiv) and TMSOTf (10 equiv) at 40 °C in DCM for 18 h afforded the desired 2-vinyloxy **3** regioisomer in 85% yield (>24:1 by HPLC). The reaction needed to be quenched by slowly adding the reaction mixture to a solution of satd NH_4OAc. The TMS ether could be cleaved in situ by stirring a biphasic mixture of EtOAc and satd aq K_2HPO_4 for 4 h at 20 °C. The desired 2-vinyloxy **3**[17] was isolated by column chromatography.

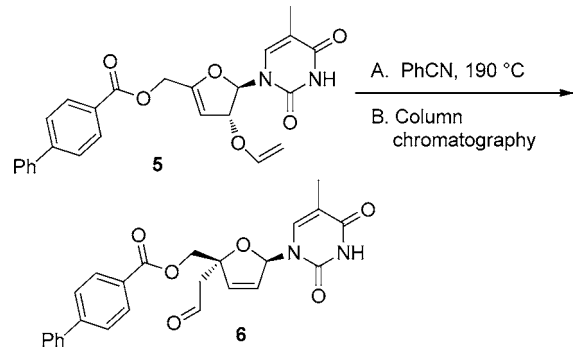
Haraguchi[18] has demonstrated use of I_2/PPh_3/imidazole as a highly stereoselective method to efficiently install 3′,4′-unsaturated nucleosides. Thus, treatment of the 2-vinyloxy-3-OH **3** with PPh_3, imidazole, and then I_2[19] in THF at 60 °C afforded the corresponding iodide **4** with inversion in 80% yield (Scheme 4). Other methods[20] to install the iodide were attempted, but all other methods led to decomposition of the reaction mixture. Elimination of the iodide occurred in the presence of DABCO in toluene at 90 °C for 2 h to afford the desired allylvinyl ether **5**[21] in 90% yield. With the allylvinyl ether **5** in hand, our attention was focused on the Claisen rearrangement.

Scheme 4. Iodidination/Elimination



Ireland[22] and Fraiser-Reid[23] have demonstrated that α-D-C-glycopyranosides can be prepared in excellent yields via a [3,3]-sigmatropic rearrangement displaying high degrees of stereocontrol. Our system demonstrates a Claisen rearrangement to set a tertiary stereocenter on a pyranoside. Our first attempts at the Clasien rearrangement[24] showed it was completed after 2 h using benzonitrile as the solvent (190 °C) affording aldehyde **6** in 85% yield (Scheme 5). The stereochemistry of the 4′-stereocenter was confirmed by NOE experiments. With the desired stereocenter and olefin, we could focus on the installation of the alkyne moiety.

Scheme 5. Clasien Rearrangement



Initially, the alkyne construction consisted of vinyl triflate formation[25] followed by base-induced elimination. This led to very low yields of the desired alkyne **7** (~15% yield). Lyapkalo[26] has shown that the use of nonafluorobutanesulfonyl fluoride (NfF) and phosphazane bases allows for a one-pot nonaflation/elimination to occur with aliphatic aldehydes. Using their conditions, we found that once again a low yield of the desired alkyne **7** was obtained. The remainder was decomposed material. We reasoned that competitve triflation/nonaflation at both the aldehyde and the NH moiety was complicating the reaction. If we could block the NH moiety in situ, we could potentially perform the nonaflation exclusively at the aldehyde. Treatment of the aldehyde **6** with TMSCl/Et_3N, followed by NfF and P_1-base[27] at −20 °C and then warming to 20 °C, allowed for the conversion to the desired alkyne **7** in 85% yield (Scheme 6).

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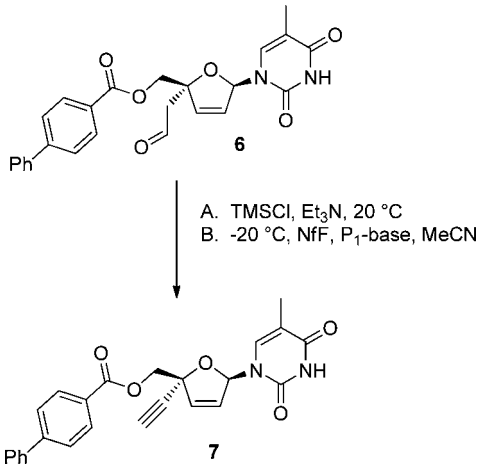
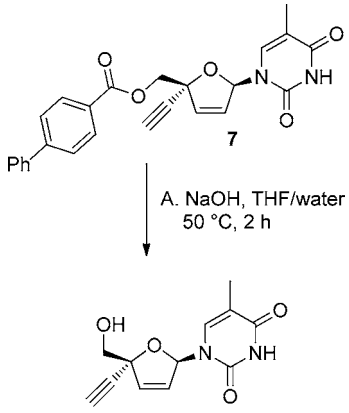
Scheme 6. Alkyne Formation



To complete the synthesis of 4′-Ed4T, **7** was treated with NaOH in THF/water to afford 4′-E-d4T in 95% yield. This material was compared to an authentic sample by HPLC, ^{1}H, ^{13}C, and HRMS.

In summary, an efficient stereoselective total synthesis of 4′-Ed4T has been achieved with the use of a unique TMSOTf-mediated regioselective acetal opening to install the vinyl ether. A highly stereoselective Claisen rearrangement set the 4′ stereocenter, and a one-pot nonaflation/elimination delivered the alkyne **7**. Our synthesis was eight steps from 5-methyluridine, and the overall yield was 37% (Scheme 7).

Scheme 7. End Game: Deprotection



■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) 5-Methyluridine (CAS no. 1463-10-1) is readily available from Sigma-Aldrich.

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(11) The azeotrope with acetonitrile allowed any residual inorganics to precipitate which could then be easily filtered off so as to not interfere with the subsequent acylation step.

(12) This was isolated as 1:1 ACN solvate as determined by ^{1}H NMR analysis.

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(16) Further studies are in progress to elucidate the mechanism of this process.

(17) The regioselectivity was confirmed by removing the acetate to provide the 3,5-diol-2-vinyloxy **A**. See the Supporting Information for experimental details.

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(19) With the presence of the vinyl ether **3**, it was critical that the I_2 be added last. If the I_2 was added first, the vinyl ether would react and regenerate the methyl-acetal **2**.

(20) Conversion to the corresponding mesylate/tosylate, followed by treatment with NaI, failed to provide the iodide; instead, decomposition of the reaction mixture resulted.

(21) Interestingly, prolonged holding (3 days) at 90 °C did not produce any of the desired Claisen product.

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(27) **P_1-base** = (*tert*-Butylimino)tripyrrolidinophosphorane (CAS no. 161118-67-8).

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