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Total Synthesis of 3′,5′-C-Branched Nucleosides

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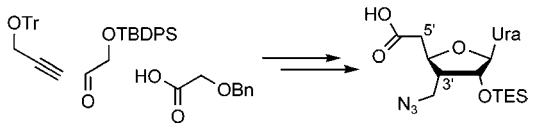
ABSTRACT



A novel total synthesis of 3′,5′-C-branched uridine azido acid has been accomplished using stereoselective aldehyde alkynylation, Ireland–Claisen rearrangement, and iodolactonization as the key reactions. Compared to traditional routes that start from carbohydrates, the present methodology is more efficient, flexible for future optimization, and provides access to both enantiomers of the products. Because the key chemistry does not involve the 3′- and 5′-C substituents, our route is a general approach to 3′,5′-C alkyl nucleoside analogues.

Biopolymer mimics possessing controllable folding into well-defined structures represent a broad and active research area.[1] Among biopolymers, RNA is unique because it exhibits the two functions most important for life: information storage and catalysis. RNA mimics with improved chemical stability, folding, and catalytic function will be extremely useful in biomedicine, materials science, and industrial applications. Our recent work suggests that replacement of the negatively charged phosphates by a neutral amide backbone will create RNA mimics with promising biophysical properties.[2] However, synthetic challenges, in particular, poor access to monomeric amino acid equivalents **1** (Figure 1), have so far hindered full exploration of amide-linked RNA.

Despite some progress[3] in synthesis and structural studies on amide linkages in DNA[4] and RNA,[5] azido acids **1** and the corresponding oligoamides have not been prepared. The 3′,5′-C-branched nucleosides are particularly difficult to make using the traditional carbohydrate chemistry. Synthesis from nucleosides requires formation of two new carbon−carbon bonds in a highly functionalized and sensitive molecule and would be an inherently complicated and inefficient task.[6] Recently, we proposed a new total synthesis approach to related 3′-C-branched azido acids.[7] In this communication, we report the total synthesis of uridine azido acid **1a** using a novel and general approach to 3′,5′-C-branched ribonucleosides.

Our retrosynthetic analysis of **1** (Figure 1) first disconnects the heterocyclic base and after functional group adjustment identifies lactone **2** as the first key intermediate. Opening of the five-membered tetrahydrofuran ring (iodolactonization) reveals the unsaturated carboxylic acid **3**. These disconnections reduce the complexity from two heterocycles and four

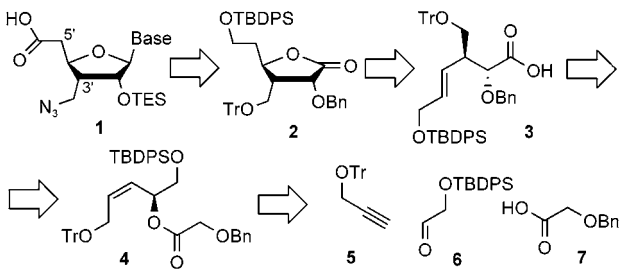


Figure 1. Retrosynthetic analysis of 3′,5′-C-branched nucleosides.

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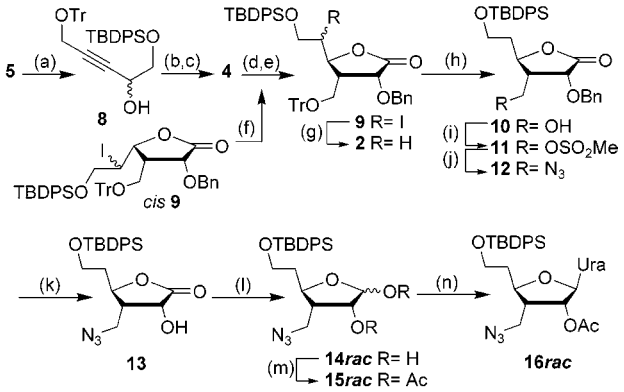
Scheme 1. Total Synthesis of Racemic 3′,5′-Branched Uridine[a]

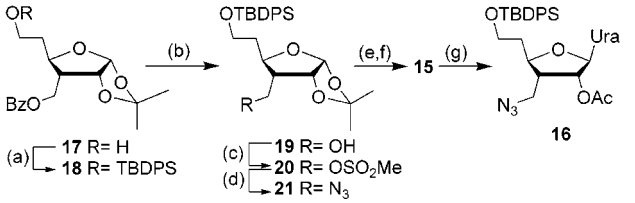


[a] Conditions: (a) *n*-BuLi, THF, −78 °C then **6**, THF, −78 °C, 4 h, 81%; (b) Lindlar catalyst, H_2, MeOH, rt, 2 h 15 min; (c) **7**, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 3 h, 92% (two steps); (d) LHMDS, TMSCl, THF, −78 °C to rt, 3.5 h; (e) I_2, $NaHCO_3$, THF/H_2O (5/12), 0 °C, 3 h, 66% (two steps and recycling); (f) Zn, NH_4Cl, H_2O/ethyl acetate, rt, 2.5 h; (g) Bu_3SnH, AIBN, toluene, 95 °C, 1 h 25 min, 96%; (h) TFA, Et_3SiH, CH_2Cl_2, 0 °C, 30 min, 81%; (i) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C to rt, overnight, 93%; (j) NaN_3, DMF, 60 °C, 4 h, 94%; (k) BCl_3, CH_2Cl_2/hexanes (10/1), −78 to −20 °C, 3 h, 91%; (l) DIBAL-H, THF, −85 °C, 3 h, 65% (recycling); (m) Ac_2O/pyridine (1/1), 24 h, rt, 94%; (n) 2,4-*O*,*O*′-bis(trimethylsilyl)uracil, TMSOTf, CH_2Cl_2, rt, 2 h, 86%.

stereogenic centers in **1** to only two stereogenic centers in the acyclic **3**. Acid **3** can be obtained from allylic ester **4** via Ireland−Claisen rearrangement. Further disconnection reveals simple organic compounds: alkyne **5**, aldehyde **6**, and carboxylic acid **7** as the starting materials.

The realization of this plan started with the synthesis of propargyl alcohol **8** (Scheme 1) that was further subjected to Lindlar reduction and acylation with **7** to give allylic ester **4**. Ireland−Claisen rearrangement of **4** and iodolactonization were performed in the same reaction mixture without isolation of the unsaturated carboxylic acid **3**.[8] Silica gel chromatography yielded pure *trans*-lactone **9** (42%) and some cis isomer (34%) as the major byproduct. The two-step one-pot procedure (**4** to **9**) was remarkably efficient in building structural complexity. The problem of the low

Scheme 2. Synthesis of 3′,5′-Branched Uridine from Glucose[a]



[a] Conditions: (a) TBDPSCl, imidazole, DMF, rt, 24 h; (b) NaOH, *iso*-PrOH, 70 °C, 30 min, 77% (two steps); (c) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C to rt, overnight; (d) NaN_3, DMF, 60 °C, 20 h, 76% (two steps); (e) BCl_3, CH_2Cl_2/hexanes (6/1), −78 °C, 20 min; (f) Ac_2O/pyridine (1/1), rt, 24 h, 61% (two steps); (g) 2,4-*O*,*O*′-bis(trimethylsilyl)uracil, TMSOTf, CH_2Cl_2, rt, 1.5 h, 86%.

stereoselectivity in the iodolactonization step could be alleviated by recycling of the cis isomer: treatment with Zn powder in aqueous NH_4Cl followed by iodolactonization increased the combined yield of **9** to 60 and 66% after one and two recyclings, respectively. Structural assignment of the trans and cis isomers of **9** was initially performed using NOESY experiments and later confirmed by independent synthesis of **16**.

Reductive removal of iodine, installation of the azido function, and removal of the benzyl protecting group gave the azido lactone **13**. Selective reduction of the lactone[9] in **13** was somewhat capricious, possibly because of the spatially close azide function. The best result was achieved when the reaction was stopped and the products were separated at approximately 30% conversion. Recycling of recovered starting material gave **14*rac*** in acceptable yield. Acylation of the free hydroxyl groups and standard nucleoside synthesis proceeded uneventfully to complete the total synthesis of 3′,5′-C-branched uridine **16*rac*** in 13 steps and 16% overall yield from **5** and **6**.

To confirm the structure of **16*rac*** and to gauge the efficiency of the total synthesis we also designed a traditional carbohydrate route to **16** (Scheme 2). We started from the advanced intermediate **17** prepared as reported by Huang et al. from diacetone-D-glucose in eight steps and 24% yield.[10] Protecting group manipulation followed by installation of the azide function gave **21**. The challenging selective cleavage of the acetonide protection in **21** was achieved using boron trichloride[11] and followed by acetylation and nucleoside synthesis to give **16** as a single enantiomer in 15 steps and 7% overall yield from diacetone-D-glucose. In accord with our initial structural assignments, the ^1H spectra of **16** and **16*rac*** were identical, whereas the spectrum of the putative cis isomer of **16rac** independently prepared from *cis*-**9** following the chemistry outlined in Scheme 1 was distinctly different (see Supporting Information).

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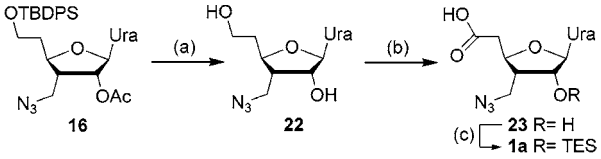
Scheme 3. Synthesis of Uridine Azido Acid[a]

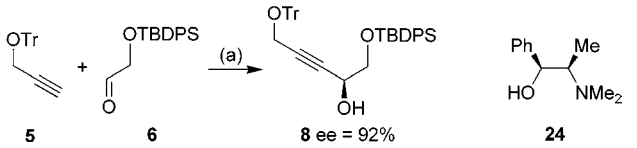


[a] Conditions: (a) HCl, methanol, rt, 5 days, 91%; (b) TEMPO, [bis(acetoxy)iodo]benzene, CH_3CN/H_2O (1:1), rt, 27 h; (c) TESCl, pyridine, rt, 24 h, 65% (two steps).

Final steps toward the azido acid **1a** starting from the enantiomerically pure material **16** are shown in Scheme 3. Deprotection of both silyl and acetyl groups under acidic conditions gave diol **22**. Selective oxidation of the primary alcohol[12] in diol **22** followed by protection of the secondary 2′-OH with triethylsilyl group gave the target azido acid **1a** as a highly crystalline material. Because the 2′-OH in **23** was clearly more hindered than in nonmodified nucleosides, we chose the 2′-*O*-triethylsilyl protection instead of the more traditional 2′-*O*-*tert*-butyldimethylsilyl group. The protecting groups in **1** will have to be later optimized during synthesis of amide-linked RNA.

Our racemic synthesis in Scheme 1 can be rendered asymmetric using any reaction that reliably controls the absolute stereochemistry of alcohol **8**, for example, the zinc acetylide chemistry developed by Carreira and co-workers.[13] In preliminary experiments, reaction of **5** and **6** in the presence of zinc triflate and *N*-methylephedrine **24** gave the nonracemic **8** in 50% yield and 92% ee (Scheme 4). The use of bulky trityl and TBDPS protecting groups was important; the reaction between MOM-protected propargyl alcohol and TBS-protected aldehyde gave the target product in low yield (>10%) and ca. 80% ee. The stereochemistry of **8** synthesized using (1*S*,2*R*)-*N*-methylephedrine **24** was assigned as (*S*)- on the basis of analogy with literature precedents.[13] Because both enantiomers of **24** are inexpensive and readily available, the total synthesis approach has the advantage that both enantiomers of **1** can be prepared by choosing the appropriate chiral catalyst, thereby providing access to both enantiomers of amide-linked RNA. This is important for development of enantioselective ribozyme catalysts. Seelig et al.[14] showed that artificially selected ribozymes built of D- and L-nucleosides catalyzed Diels–Alder reactions yielding enantiomeric products.

Scheme 4. Enantioselective Synthesis of Propargyl Alcohol **8**[a]



[a] Conditions: (a) **24**, $Zn(OSO_2CF_3)_2$, NEt_3, toluene, rt, 2 h, 50%.

In summary, we have developed a novel total synthesis approach to 3′,5′-C-branched nucleosides that culminates in preparation of the uridine azido acid **1a**. Although relatively small in size, these highly functionalized compounds are difficult to prepare using the traditional routes of carbohydrate chemistry. Currently, the total synthesis of **1a** is somewhat more efficient (overall 16 steps, 9% yield, Schemes 1 and 3) than the traditional carbohydrate approach (overall 18 steps, 4% yield, Schemes 2 and 3). However, the former is more flexible for further improvement. Because the total synthesis does not depend on a particular starting material, it can be readily optimized using most current developments in synthetic organic chemistry, e.g., improved variants of iodolactonization[15] and alternative syntheses of **3** and other key intermediates.

Another feature of our synthesis in Scheme 1 is the generality. Because the key substituents in the modified nucleoside, the 3′-C and the 5′-C alkyl branches, do not directly participate in the chemical transformations, our route can be used to prepare other analogues having different 3′ and 5′ substituents.

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Supporting Information Available: Experimental procedures, spectral data, and copies of ^1H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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