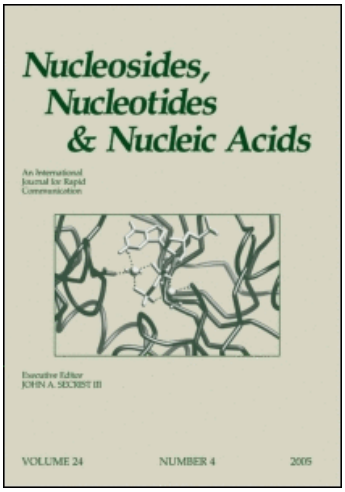

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Synthesis of (2'*S*)-1-(2-*C*-Azidomethyl-2-deoxy and 2-*C*-Cyanomethyl-2-deoxy-β-D-arabinofuranosyl)cytosines

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SYNTHESIS OF (2'*S*)-1-(2-*C*-AZIDOMETHYL-2-DEOXY AND 2-*C*-CYANOMETHYL-2-DEOXY-β-D-ARABINOFURANOSYL)CYTOSINES

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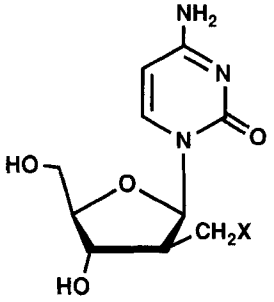
ABSTRACT: 2'-*C*-Cyanomethyl-2'-deoxy-arabinosylcytosine **3** and 2'-*C*-azidomethyl-2'-deoxy-arabinosylcytosine **4** were synthesized from uridine. The antineoplastic activities of these compounds were evaluated.

Developing new drugs effective for cancer chemotherapy is one of the target for synthetic nucleoside antimetabolites. Many efforts have been made to synthesize a number of nucleoside analogues and some 2'-*C*-substituted 2'-deoxycytidine derivatives show potent antineoplastic activities.



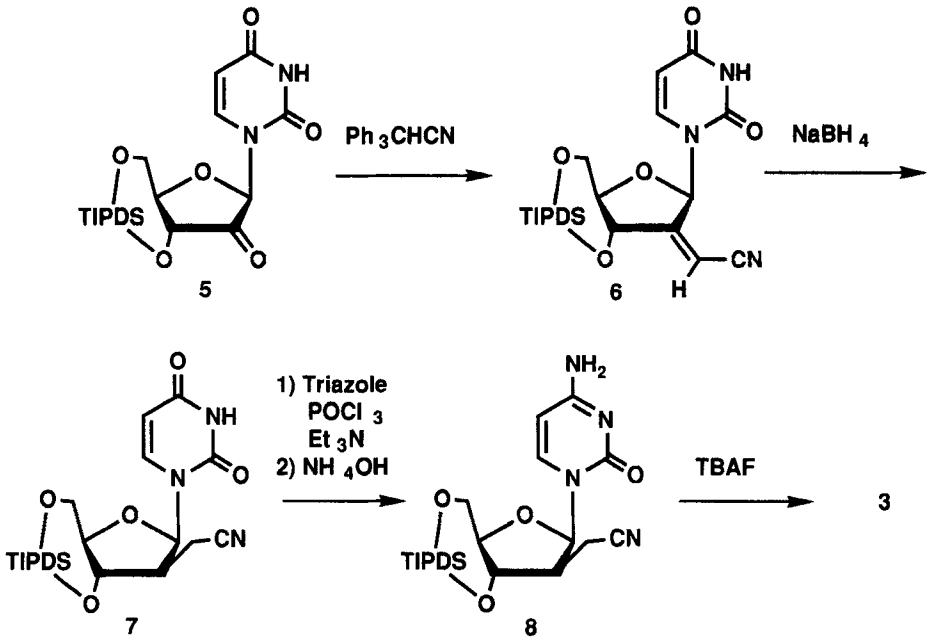
1: X = H (SMDC)
2: X = F (SFDC)
3: X = CN
4: X = N 3

Chart 1

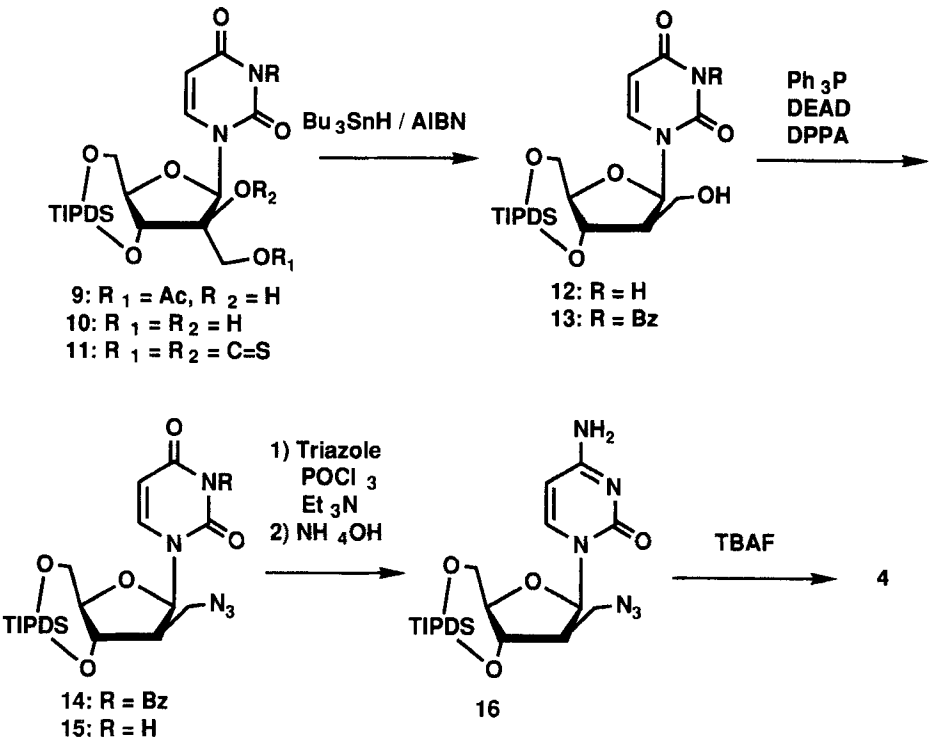
For example, (2'*S*)-1-(2-Deoxy-2-*C*-methylarabinofuranosyl)cytosine **1** (SMDC) and its fluoromethyl derivative **2** (SFDC) have antileukemic activities *in vitro*.[1,2] These results prompted us to synthesize SMDC derivatives bearing an electron-withdrawing substituent at the 2'-methyl group. In this report we describe the synthesis and the antineoplastic activity of cyano and azido substituted SMDC analogues (Chart 1).

2'-Ketouridine **5**[3], easily obtained from uridine, was treated with cyanomethylenetriphenylphosphorane to give cyanomethylene uridine **6** in good yield. Compound **6** was reduced by sodium borohydride to give β-cyanomethyl derivative **7** stereoselectively.[4] The bulky 1'-heterocyclic moiety blocked the hydride approaching from the β-side and this should cause stereoselective reduction. The cyanomethyluridine **7** was converted to the cytidine analogue **8**, using the triazole method[5] and, finally, the protecting group was removed by tetrabutylammonium fluoride (TBAF) treatment to furnish **3** (Scheme 1).

The branched nucleoside **9**[6] was selectively deacetylated by triethylamine-MeOH to afford *cis*-diol **10**. The *tert*-alcohol of **10** was removed by the radical deoxygenation of cyclic thiocarbonate **11**, which was obtained from **10** by treatment with 1, 1'-thiocarbonyldiimidazole, using tributyltin hydride in



Scheme 1



Scheme 2

the presence of AIBN. The radical deoxygenation occurred regio- and stereoselectively, as expected, to give the 2'-deoxy-2'-*C*-hydroxymethylarabinosyluracil **12** in 56% yield.

For the introduction of the azido group at 2'-branched chain, the N-3 position had to be protected by a benzoyl group to avoid the formation of an anhydronucleoside.[7] This was achieved by trimethylsilylation at the 2'-free hydroxyl group of **12**, followed by benzoylation at N-3 and acidic deprotection of TMS group. The Mitsunobu reaction of **13** using diphenyl phosphorylazide as the azide source[7] afforded **14** in 78 % yield. After debenzoylation, the compound **15** was converted to 2'-*C*-azidomethyl-2'-deoxy-arabinosylcytosine **4** by the method described above (Scheme 2).

The antineoplastic activities of **3** and **4** were evaluated. The azidomethyl derivative **4** showed weak activity toward human leukemic T-cells [CCRF-HSB-2 (IC_{50} = 8.50 μg/ml)], while the cyanomethyl derivative **3** was inactive (IC_{50} = 44.7 μg/ml). Both compounds were inactive against solid tumor cells [KB cells (IC_{50} = >10 μg/ml)].

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