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Synthesis of New Pyrrolidine *C*-Nucleosides *via* Staudinger-aza-Wittig Cyclization of γ-Azido Ketone

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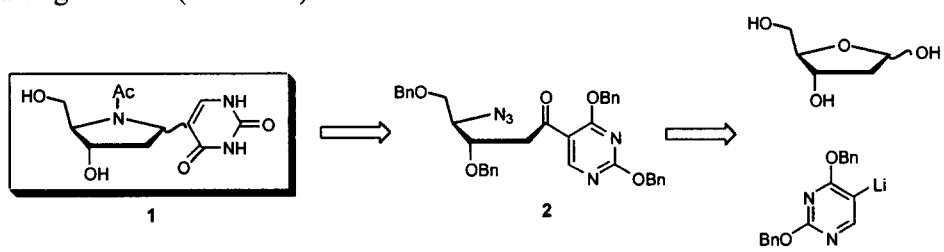
Abstract: Novel *N*-acetyl *C*-aza-2-deoxy-D-ribonucleosides were synthesized from 2-deoxy-D-ribose *via* a consecutive procedure of the addition of ortho-lithiated pyrimidine salt, Staudinger-aza-Wittig ring cyclization, and reduction of cyclic imine.

Keywords: Pyrrolidine *C*-nucleosides; Staudinger-aza-Wittig cyclization; γ-Azido ketone

During last decade structurally modified nucleosides have drawn a great deal of attention due to their potential as cancer and viral chemotherapy, and antisense oligonucleotides[1]. Especially, the nucleosides with modified sugar, in which the furanose ring is replaced by a different 5-membered heterocycle containing sulfur or nitrogen atom, have proved to be potent antiviral agents.[2]

Our interest is the development of novel bioactive and structurally modified *C*-aza-furanose nucleoside analogs, in which the pyrrolidinyl moiety is linked to pyrimidine base with a carbon-carbon glycosidic bond. We now wish to describe our results on the efficient synthesis of both α- and β-anomers of new class of *C*-azafuranose nucleosides **1** using Staudinger-aza-Wittig cyclization of γ-azido ketone **2** which is derived from 2-deoxy-D-ribose as a starting material (Scheme 1).



Scheme 1. Retrosynthesis of Pyrrolidine C-Nucleoside

Although several methods for the synthesis of *N*-azanucleosides[3-7] have been studied, only

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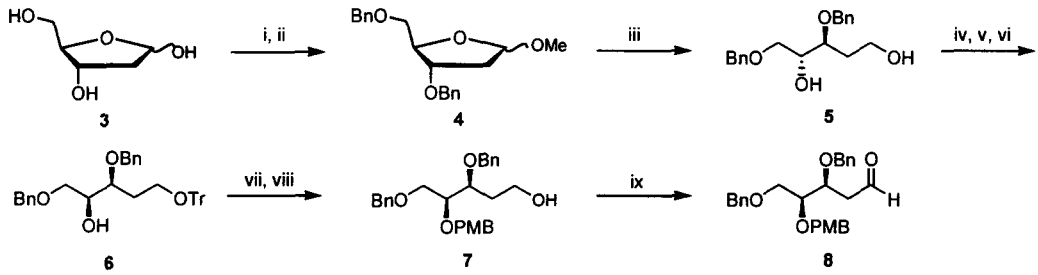
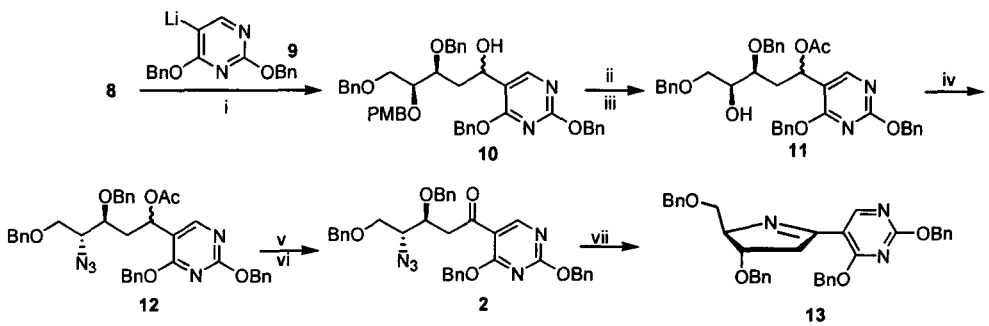
a few examples for *C*-azanucleosides[8-12] have been known. Recently, Yokoyama and coworkers reported the preparation of 4′-epimers of *C*-azanucleosides with various hetero-aromatic compounds using reductive aminocyclization of 1,4-diketones.[13]

Azido group has very useful functionality for the synthesis of various types of nitrogen-bearing heterocycles. The ready preparation of iminophosphoranes from azides by Staudinger reaction,[14] and their utilities for the formation of cyclic imines *via* intramolecular aza-Wittig type ring cyclization reactions were well known.[15] Based on these facts, Staudinger-aza-Wittig method was applied for the synthesis of *C*-azanucleosides in this work. The azide group with (*R*)-configuration at C-4 in **2** was introduced by a stepwise double inversion from 2-deoxy-D-ribose (**3**) using Mitsunobu method. And cyclic imine **13**, retaining configuration of the furanose ring at C-3 and C-4, was obtained by intramolecular ring cyclization under mild and neutral reaction conditions in excellent yield.



Scheme 2. *Reagents and reaction conditions:* (i) MeOH, HCl, Ag_2CO_3, 0°C (92%); (ii) BnBr, THF, NaH, TBAI, rt (87%); (iii) a. AcOH, H_2O, 100°C, b. $NaBH_4$, EtOH, 0°C (65%); (iv) TrCl, DMAP, DCM, Et_3N, rt (98%); (v) Ph_3P, DEAD, 4-nitro-benzoic acid, benzene, 0°C, 5h (93%); (vi) K_2CO_3, MeOH, rt, 3h (95%); (vii) 4-methoxybenzyl chloride, NaH, DMF, 0°C (92%); (viii) 4-$CH_3C_6H_4SO_3H$, DCM, MeOH, rt (98%); (ix) $(COCl)_2$, DMSO, Et_3N, DCM, -78°C (98%)

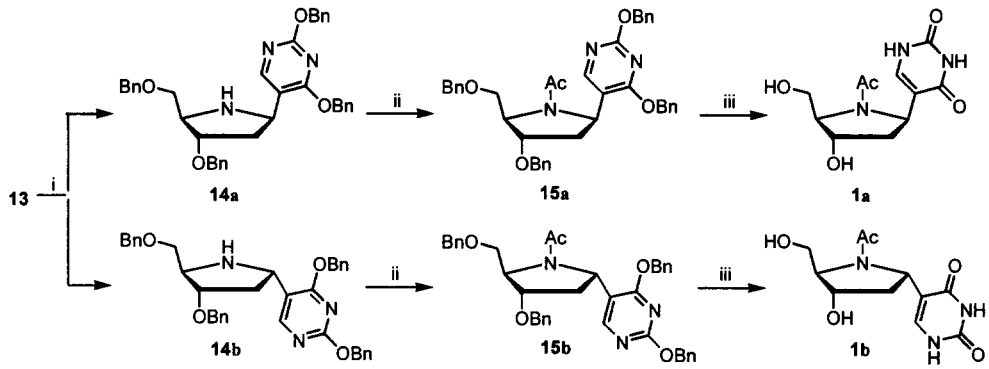
Etherification of the anomeric hydroxyl group of 2-deoxy-D-ribose (**3**) followed by treatment with benzyl bromide gave methyl 3,5-di-*O*-benzyl-2-deoxy-D-ribofuranoside (**4**) as depicted in Scheme 2. After hydrolysis with 80% aqueous acetic acid, the resulting aldehyde was reduced by $NaBH_4$ to afford the diol **5**. The (*R*)-configuration of secondary hydroxyl group at C-4 was inverted to (*S*)-configuration by Mitsunobu method to give **6**. The C-4 hydroxyl group of **6** was protected with 4-methoxybenzyl chloride. The selective deprotection of the trityl group afforded the primary alcohol **7**, which was then converted into the aldehyde **8** by



Scheme 3. *Reagents and reaction conditions:* (i) THF, -78°C (48%); (ii) Ac_2O, pyridine, DMAP, rt (93%); (iii) DDQ, DCM, H_2O, rt (84%); (iv) Ph_3P, DEAD, DPPA, THF, rt (91%); (v) K_2CO_3, MeOH, rt (98%); (vi) MnO_2, THF, 24h (81%); (vii) Ph_3P,THF,rt (91%)

Swern oxidation. Overall yield of **8** from **3** was about 40%.

The aldehyde **8** was served as a precursor for the synthesis of key intermediate, γ-azido ketone **2** as shown in Scheme 3. Condensation of the aldehyde **8** with ortho-lithiated 2,4-di-*O*-benzylpyrimidine **9**[16], which was prepared from lithium 2,2,6,6-tetramethylpiperidine and 2,4-di-*O*-benzylpyrimidine in THF at –78 °C, provided a 3:1 diastereomeric mixture of **10** in 48% yield. Protection of hydroxyl group at C-1 by acetic anhydride with the stereoisomeric mixture, and subsequent oxidative removal of 4′-methoxybenzyl group at C-4 by 2,3-dichloro-5,6-dicyanobenzoquinone[17] produced the secondary alcohol **11**. **11** was then treated with diphenylphosphoryl azide[18] by Mitsunobu method to give azide **12** with inversion of configuration at C-4. Base-catalyzed hydrolysis of **12** and subsequent oxidation of the resulting secondary alcohol by manganese(IV) oxide afforded γ-azido ketone[†] **2**. The cyclized imine **13** was prepared from **2** using triphenylphosphine in THF at room temperature for 18 hours *via* Staudinger-aza-Wittig ring cyclization in 91% yield.



Scheme 4. *Reagents and reaction conditions:* (i) $NaBH_3CN$, MeOH, *cat.* AcOH (**14a**:41%,**14b**:38%); (ii) Ac_2O, pyridine, *cat.* DMAP (**15a**:92%,**15b**:91%); (iii) 10% Pd/C, H_2, MeOH (**1a**:89%,**1b**:85%)

Reduction of the imine group in **13** was successfully accomplished with sodium cyanoborohydride in methanol at room temperature to afford a *ca.* 1:1 mixture of β– and α–anomers[‡] **14a** and **14b**, which could be separated by preparative TLC using $CHCl_3$/MeOH (98:2) in 41% and 38% isolated yields, respectively. The anomeric configurations of the two epimers were confirmed by NOE experiments.[ǁ] Acetylation of **14a** and **14b** followed by

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[†] Data for selected products are as follows. **2:** ^{1}H-NMR (300MHz, $CDCl_3$) δ 8.83 (s, 1H, pyrimidine H-6), 7.51-7.16 (m, 20H, 4Ar), 5.52-5.43 (m, 4H, 2CH_2Ar), 4.59-4.39 (m, 4H, 2CH_2Ar), 4.26 (ddd, 1H, J_1=8.0Hz, J_2=3.7Hz, J_3=4.4Hz, H-3′), 3.71-3.69 (m, 1H, H-4′), 3.58-3.45 (m, 2H, H-5′), 3.31 (dd, 1H, J_1=17.8Hz, J_2=8.0Hz, H-2′$_a$), 3.07 (dd, 1H, J_1=17.8Hz, J_2=3.7Hz, H-2′$_b$).

[‡] **14a:** ^{1}H-NMR (300MHz, $CDCl_3$) δ 8.34 (s, 1H, pyrimidine H-6), 7.49-7.21 (m, 20H, 4Ar), 5.41 (s, 2H, CH_2Ar), 5.39 (s, 2H, CH_2Ar), 4.55-4.45 (m, 5H, H-1′, 2CH_2Ar), 3.97-3.92 (m, 1H, H-3′), 3.52-3.41 (m, 3H, H-4′, H-5′), 2.30 (ddd, 1H, J_1=13.1Hz, J_2=6.2Hz, J_3=1.4Hz, H-2′$_\alpha$), 2.06-1.96 (bs, 1H, NH), 1,76 (ddd, 1H, J_1=13.1Hz, J_2=10.3Hz, J_3=6.3Hz, H-2′$_\beta$); **14b:** ^{1}H-NMR (300MHz, $CDCl_3$) δ 8.42 (s, 1H, pyrimidine H-6), 7.49-7.21 (m, 20H, 4Ar), 5.41 (d, 2H, *J*=2.4Hz, CH_2Ar), 5.40 (s, 2H, CH_2Ar), 4.52-4.45 (m, 4H, 2CH_2Ar), 4.42 (dd, 1H, J_1=7.6Hz, J_2=7.2Hz, H-1′), 4.02-3.94 (m, 1H, H-3′), 3.60-3.45 (m, 3H, H-4′, H-5′), 2.50 (ddd, 1H, J_1=13.0Hz, J_2=7.2Hz, J_3=6.7Hz, H-2′$_\beta$), 2.39-2.21 (bs, 1H, NH), 1.88 (ddd, 1H, J_1=13.0Hz, J_2=7.6Hz, J_3=6.3Hz, H-2′$_\alpha$).

[ǁ] The C-1 configurations of **14a** and **14b** were assigned by NOE experiments. At first, the irradiation of H_3 at C-3 in **14a** and **14b** led to a 1.4% and 1.7% increase in the intensity of signal for $H_{2\beta}$ at C-2, respectively. Secondly, in the case of **14a** the irradiation of $H_{2\alpha}$ at C-2 led to a 3.5% increase in the intensity of signal for H_1 and that of $H_{2\beta}$ at C-2 led to a 2.2% increase for H_3. However, in **14b**,

hydrogenolysis over 10% Pd-C provided the corresponding *N*-acetyl-5(*R*)-hydroxymethyl-4(*S*)-hydroxy-2(*R*)- and 2(*S*)-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyrrolidine[¶], **1a** and **1b** (Scheme 4).

In conclusion, an efficient method for the synthesis of new pyrrolidine *C*-nucleoside *via* Staudinger-aza-Wittig cyclization of γ-azido ketone has been developed. This research provides the possibility for the synthesis of other aza *C*-nucleosides using several sugars and lithium salts of heteroaromatic compounds. The biological evaluations and preparation for oligonucleotides using **1** are in progress.

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only when $H_{2\beta}$ at C-2 was irradiated, increases (5.4% and 2.4%) in the intensity of signals for H_1 and H_3 were observed. Accordingly, it is concluded that the configuration at C-1 of **14a** is β-anomer and that of **14b** is α-anomer.

[¶] **1a**: ^{1}H-NMR (300MHz, D_2O) δ 7.43 (s, 0.38H, pyrimidine H-6, rotamer), 7.15 (s, 0.62H, pyrimidine H-6, rotamer), 4.94-4.74 (m, 1H, H-1′), 4.31-4.21 (m, 1H, H-3′), 4.03-3.90 (m, 1H, H-4′), 3.70-3.50 (m, 2H, H-5′), 2.42-2.25 (m, 1H, H-2′$_\alpha$), 2.16-1.91 (m, 2.82H, H-2′$_\beta$, CH_3CO, rotamer), 1.87 (s, 1.18H, CH_3CO, rotamer); HRMS (FAB, NBA) [Found (M+H), 270.1089. Cal. for $C_{11}H_{16}N_3O_5$: $(M+H)^+$ *m/z*, 270.1090]; **1b**: ^{1}H-NMR (300MHz, CD_3OD) δ 7.18 (s, 0.64H, pyrimidine H-6, rotamer), 7.09 (s, 0.36H, pyrimidine H-6, rotamer), 4.94-4.79 (m, 1H, H-1′), 4.29-4.24 (m, 1H, H-3′), 4.09-4.03 (m, 0.60H, H-4′, rotamer), 3.97-3.90 (m, 0.60H, H-4′, rotamer), 3.68-3.38 (m, 2H, H-5′), 2.58-2.44 (m, 1H, H-2′$_\beta$), 2.08 (s, 1.24H, CH_3CO, rotamer), 1.88-1.70 (m, 2.76H, H-2′$_\alpha$, CH_3CO, rotamer); HRMS (FAB, NBA) [Found (M + H), 270.1091. Cal. for $C_{11}H_{16}N_3O_5$: $(M+H)^+$ *m/z*, 270.1090].