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Synthesis of (±)-branched-chain azaisonucleosides via Michael addition of 5-nitro-2,2-pentamethylene-1,3-dioxane to methyl 2-bromoacrylate

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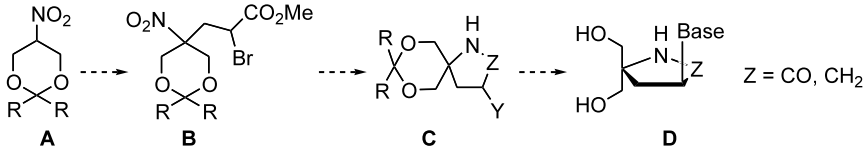
Abstract—Michael reaction of 2,2-pentamethylene-5-nitro-1,3-dioxane **1** with methyl 2-bromoacrylate, generated in situ from methyl 2,3-dibromopropanoate and triethylamine, afforded α-bromo-γ-nitroester **3**, which was readily converted into various 5,5-bis(hydroxymethyl)pyrrolidine analogues of nucleosides.

Many nucleoside analogues are potent antiviral and anticancer therapeutics, so synthesis of new nucleosides modified at the sugar, base and both moieties is a subject of great current interest. In sugar-modified derivatives native furanose is replaced by various cyclic moieties[1–5] and in the most extreme cases a cyclic mimic is replaced by an acyclic substituent.[6] Although numerous nucleosides have been obtained, only a few azaisonucleosides (pyrrolidin-3-yl mimics the sugar part)[7–10] have been synthesized thus far, most of them in recent years as building blocks for synthesis of peptide nucleic acids (PNA).[10] Usually *trans*-4-hydroxy-L-proline and L-pyroglutamic acid have been used for the synthesis of these nucleoside analogues.[7–10]

Based on our experience of nitroalkane chemistry we envisaged that 5-nitro-1,3-dioxane derivatives might be useful starting materials for a synthesis of novel branched-chain azaisonucleosides **D**. In our approach, outlined in Scheme 1, the analogues **D**, 5′,5′-bis(hydroxymethyl)pyrrolidin-2′-on-3′-yl and 5′,5′-bis(hydroxymethyl)pyrrolidin-3′-yl derivatives of native and synthetic bases, are prepared from the acyclic precursor **B**, available from a Michael addition of 5-nitro-1,3-dioxane **A** to methyl α-bromoacrylate, via the intermediate pyrrolidine **C**.

The Michael addition of various CH-acids to 2-bromoacrylates is well known,[11] but nitroalkanes have never been used for this reaction. To our pleasure, the addition of 2,2-pentamethylene-5-nitro-1,3-dioxane to methyl 2-bromoacrylate, generated in situ from methyl 2,3-dibromopropanoate and triethylamine (TEA),[12] proceeded smoothly in boiling methanol to afford crystalline α-bromo-γ-nitroester **3** in 72% yield (Scheme 2).[13,14]

Since in many nucleoside analogues various five-membered heterocycles imitate the native bases we set up as the first synthetic target compound **7** with a 4,5-bis(carboxamido)-1,2,3-triazole residue (Scheme 2).[15] The key heterocyclic intermediate **5** was obtained in two steps; the reaction of **3** with sodium azide under phase transfer catalysis conditions[16] giving the azide ester **4** in



Scheme 1.

Keywords: nitro compounds; α-bromoacrylate; Michael reaction; pyrrolidin-2-ones.

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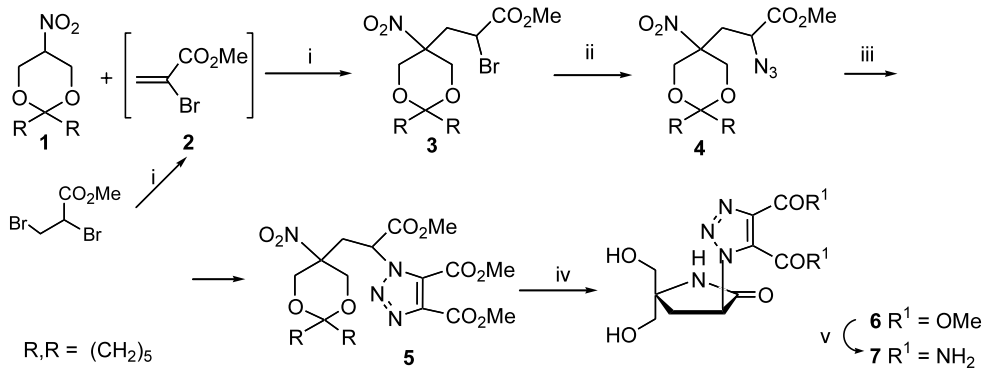
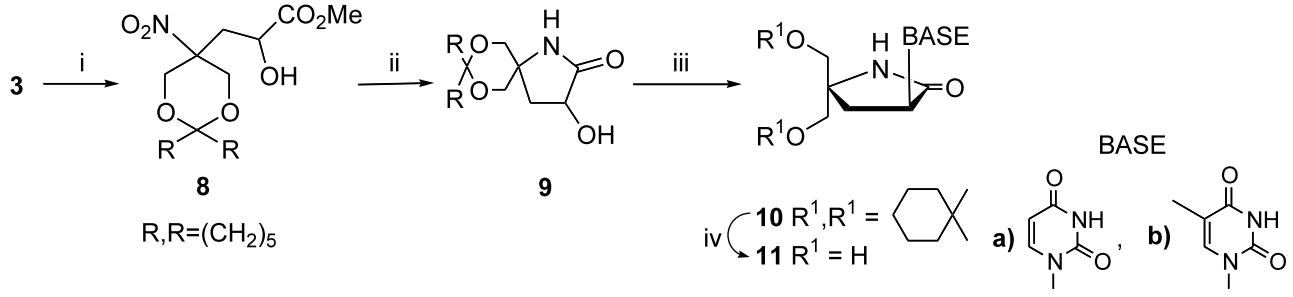


Scheme 2. *Reagents and conditions*: (i) TEA (1.1 equiv.), MeOH, reflux 4 h, 72%; (ii) NaN_3, cat. $Bu_4N^+Br^-$, MeCN, reflux 5 h, 40–61%; (iii) $MeO_2CC{\equiv}CCO_2Me$, benzene, reflux, 3 h, quantitative; (iv) H_2 (8 bar), 10% Pd/C, MeOH, 100°C, 20 h, quantitative; (v) NH_3/MeOH, rt, 4 h, 92%.

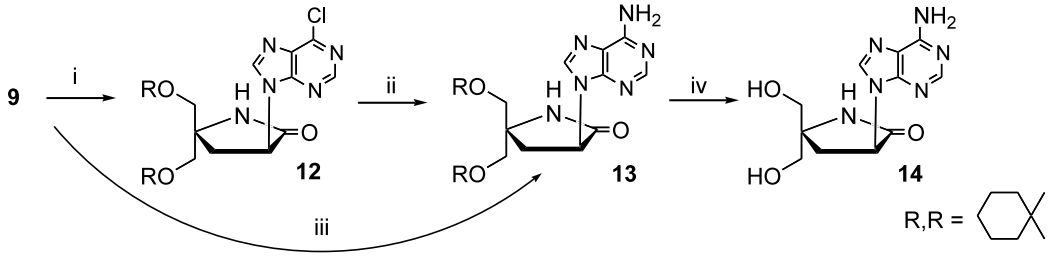
45–61% yield was followed by a 1,3-dipolar cycloaddition to dimethyl 2-butynedioate[15] to furnish the nearly pure acyclic derivative of triazole **5**. Palladium catalyzed hydrogenation of crude **5** proceeded under rather harsh conditions to afford, unexpectedly, the deprotected triazole diester **6**[17] in quantitative yield. The synthesis of the diamide **7** was completed by reaction of **6** with methanolic ammonia.[17]

The Mitsunobu reaction was employed for synthesis of azaisonucleosides **D**, derivatives of the natural bases.[9,10a,b,g–i,18] Necessary for this reaction, 3-hydroxypyrrolidin-2-one **9** was obtained in two steps (Scheme 3). The bromo derivative **3** was treated with potassium trifluoroacetate in boiling acetonitrile to afford the trifluoroacetate of **8**, which hydrolyzed during aqueous work-up to furnish hydroxy ester **8** in 45–68% yield.[19]

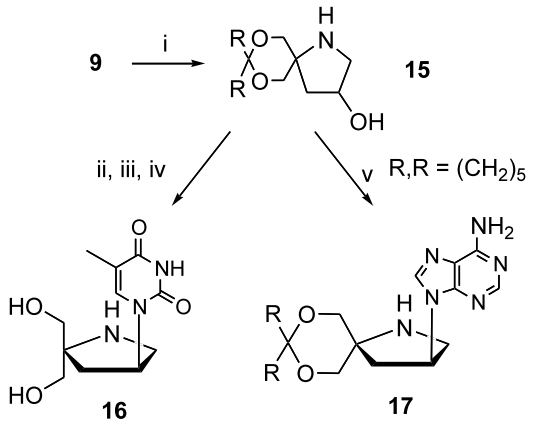
The palladium catalyzed hydrogenation of **8** gave crystalline 3-hydroxypyrrolidin-2-one **9** in 67–75% yield. The alcohol **9** reacted with N^3-benzoyluracil[20] in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine in THF to give, after chromatography, the 3-benzoyl derivative of **10a** (N^3-Bz-**10a**, 66% yield), which when treated with methanolic methylamine furnished **10a** in 51% overall yield.[10a,b,g,21,22] Since the isolation of N^3-Bz-**10a** was incomplete due to difficulties with separation of the product from triphenylphosphine oxide, in the next experiment the Mitsunobu reaction was followed by debenzoylation, without isolation of N^3-Bz-**10a**, to give **10a** in 70% yield. The thymine analogue **10b** was synthesized in a similar way in 68% yield. The syntheses of **11a** (60%) and **11b** (68%) were completed by treatment of **10a** and **10b** with 90% trifluoroacetic acid.



Scheme 3. *Reagents and conditions*: (i) CF_3CO_2K, MeCN, reflux, water work-up, 45–68%; (ii) H_2 (8 bar), 10% Pd/C, MeOH, 50°C, 6 h, 67–75%; (iii) (1) N^3-benzoyluracil or N^3-benzoylthymine, DEAD, PPh_3, THF, 0°C, 20 h, (2) 35% $MeNH_2$/MeOH, reflux, 3.5 h, 70% (**10a**), 68% (**10b**); (iv) 90% CF_3CO_2H, rt, 0.5–1 h, 60% (**11a**), 68% (**11b**).



Scheme 4. *Reagents and conditions*: (i) 6-chloropurine, DEAD, PPh_3, THF, 0°C→rt, 20 h, 86%; (ii) satd NH_3/MeOH, 50°C, 5 h, 53%; (iii) adenine, DEAD, PPh_3, dioxane, rt, 53%; (iv) HCl conc, MeOH/H_2O (2/1) rt, 77%.



Scheme 5. *Reagents and conditions*: (i) $BH_3{\cdot}SMe_2$ (10 equiv.), THF, rt, 24 h, then 10% Pd/C–MeOH, 60–70%; (ii) N^3-benzoylthymine, DEAD, PPh_3, THF, 0°C, 20 h, 49%; (iii) 35% $MeNH_2$/MeOH, reflux, 3.5 h, 70%; (iv) HCl conc, MeOH/H_2O (2/1) rt, 66%; (v) adenine, DEAD, PPh_3, dioxane, rt, 30%.

The adenosine analogue **14** was obtained in two ways (Scheme 4). First Mitsunobu coupling of **9** with 6-chloropurine was followed by heating with saturated methanolic ammonia to give **13** in 46% yield.[9,10i] The reaction of **9** with adenine[10h] provided **13** in 53% yield. Acidic hydrolysis of **13** completed the synthesis of **14**.

A reduction of 3-hydroxypyrrolidin-2-one **9** with borane–dimethylsulfide complex[23] followed by palladium catalyzed decomposition of the borane–**15** complex[24] furnished the somewhat unstable pyrrolidinol (oil) **15**[25] in 62–70% yield (Scheme 5). Despite the fact that for synthesis of azaisonucleosides only *N*-protected 3-hydroxypyrrolidines have been used,[9,10c,h] we decided to employ the *N*-unprotected alcohol **15** for the Mitsunobu reaction. This coupling gave a complex mixture from which the corresponding nucleosides were isolated after laborious chromatography in lower yield than when 3-hydroxypyrrolidin-2-one **9** was used.[26] Thus the reaction of **15** with N^3-benzoylthymine[19] afforded the *O*,*O*-cyclohexylidene derivative of N^3-Bz-**16** in 49% yield. Debenzoylation (70%) followed by acidic hydrolysis (66%) furnished thymine azaisonucleoside **16** in 23% overall yield. Synthesis of adenine derivative **17** (30%) was accomplished by coupling of adenine with **15**. This was left in the protected form.

In conclusion, we have accomplished the synthesis of novel (±)-5′,5′-bis(hydroxymethyl) derivatives of azaisonucleosides from acyclic α-bromo-γ-nitroester **3** readily available from the Michael addition of 5-nitro-1,3-dioxane to methyl 2-bromoacrylate. Studies on the extension of this reaction for the synthesis of various pyrrolidine derivatives are in progress.

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failed; **10a** was obtained in 5% yield and **13** was not isolated at all.
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26. Recently, Brandi and co-workers have reported that both unprotected thymine and uracil reacted with *N*-benzyl-3-hydroxypyrrolidine under Mitsunobu conditions in boiling dioxane to furnish the corresponding nucleoside analogues in 65–68% yield, while the use of N^3-benzoyl derivatives of the pyrimidine bases give the same nucleosides in only 30% yield. See: Richichi, B.; Cicchi, S.; Chiacchio, U.; Romeo, G.; Brandi, A. *Tetrahedron Lett*. **2002**, *43*, 4013–4015.