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Synthesis of Novel 2'-Deoxy Type Trans-3',4'-Bridged Nucleic Acid

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SYNTHESIS OF NOVEL 2'-DEOXY TYPE *TRANS*-3',4'-BRIDGED NUCLEIC ACID

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□ We newly designed and synthesized a 2'-deoxy type *trans*-3',4'-bridged nucleic acid (*trans*-3',4'-BNA) analogues bearing a 4,7-dioxabicyclo[4.3.0]nonane structure. The synthesis of the *trans*-3',4'-BNA was carried out successfully from thymidine over 21 steps. The structure of *trans*-3',4'-BNA was confirmed by x-ray crystallographic analysis, indicating that the furanose ring has a typical S-type conformation with C_{3'}-*exo* puckering.

Keywords *Trans*-3',4'-BNA; x-ray crystallographic analysis; conformation

INTRODUCTION

Recently, nucleoside analogues with a restricted S-type sugar conformation have been designed and synthesized actively.^[1] Some of them were introduced into oligonucleotides and the hybridizing properties were evaluated. However, in many cases, only moderate increase or considerable decrease of duplex stability was observed, probably due to improper restriction of the sugar conformation and unexpected steric repulsion in the B-type DNA duplex.

To overcome these problems, we designed novel nucleosides, *trans*-3',4'-Bridged Nucleic Acids (*trans*-3',4'-BNAs) with S-type sugar conformation (Figure 1). Preliminary molecular modeling experiments showed that an additional six- or seven-membered ring between the C3' and C4' atoms of *trans*-3',4'-BNAs to restrict sugar conformation was located outside

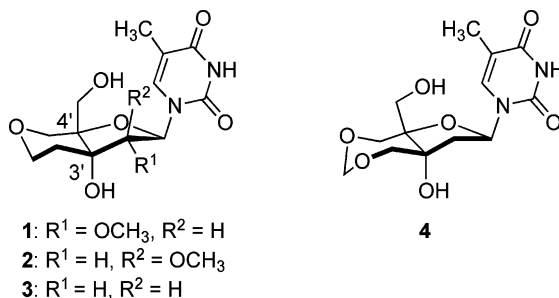
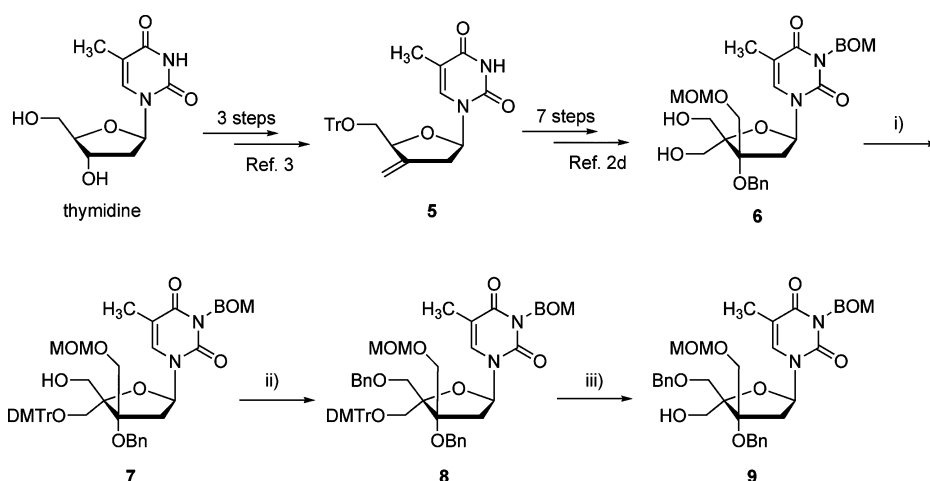


FIGURE 1 Structures of *trans*-3',4'-BNAs.

the B-type DNA duplex, indicating that the bridged structure has no adverse repulsion against neighboring residues. We successfully synthesized two *trans*-3',4'-BNAs (**1** and **2**) having the 4,7-dioxabicyclo[4.3.0]nonane skeleton from D-glucose.^[2a–2c] The thermodynamic stability of oligonucleotide duplexes containing **2** was evaluated. The results suggested that the C2'-substituent of the *trans*-3',4'-BNA affected duplex stability. Therefore, we newly designed and synthesized two 2'-deoxy type *trans*-3',4'-BNA analogues. One has a 4,7-dioxabicyclo[4.3.0]nonane structure and the other has a 3,5,8-trioxabicyclo[5.3.0]decane structure (**3** and **4**^[2d], respectively). In this article, we would like to report the synthesis of the novel 2'-deoxy type *trans*-3',4'-BNA **3**.

RESULTS AND DISCUSSION

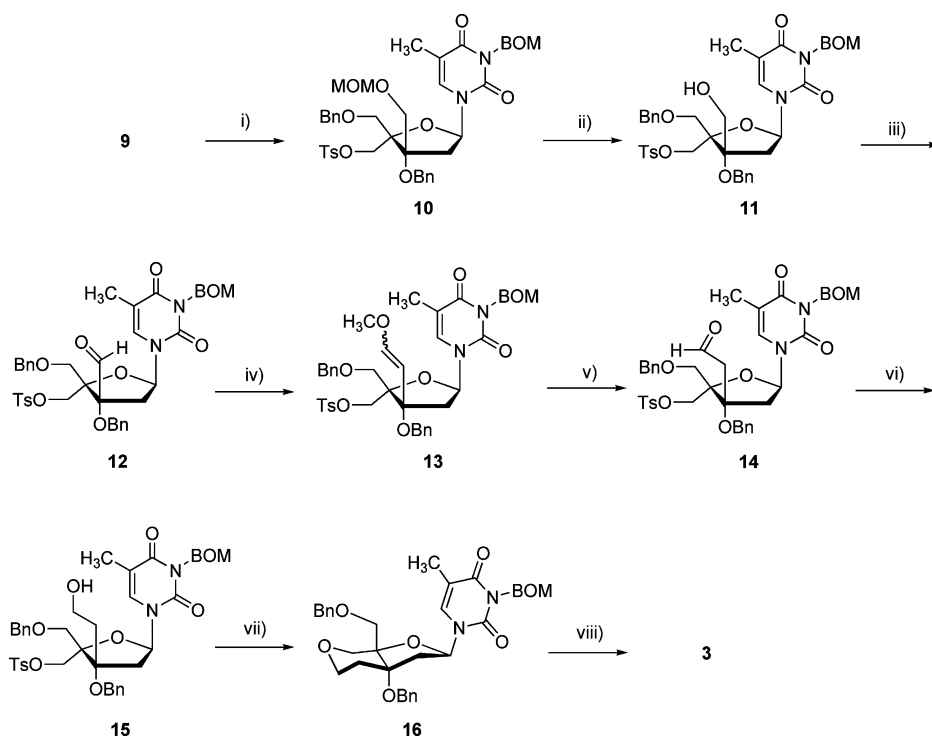
To prepare the nucleoside **3** having no substituent at the C2'-position, we chose thymidine as the starting material. The synthetic route for an



SCHEME 1 Reagents and conditions: i) DMTrCl, Et₃N, CH₂Cl₂, room temp.; ii) NaH, BnBr, *n*-Bu₄NI, DMF, room temp.; iii) (+)-10-camphorsulfonic acid, CH₂Cl₂–MeOH, room temp. (83% over 3 steps).

important intermediate **9** is shown in Scheme 1. Thymidine was transformed into known 3'-deoxy-3'-*C*-methylenethymidine derivative **5**.^[3] The diol **6** was prepared from **5** in a seven-step sequence according to our methodology.^[2d] After selective protection of the pro-*S* hydroxymethyl group in **6** by the dimethoxytrityl group, benzylation of another hydroxyl group in **7** provided **8**, followed by deprotection of the dimethoxytrityl group gave the intermediate **9** in good yield (83% over three steps).^[4] The nucleoside **9** was a common intermediate for the synthesis of not only *trans*-3',4'-BNA **3** but also *trans*-3',4'-BNA **4**.^[2d]

Next, we successfully synthesized **3** through the intermediate **9** as shown in Scheme 2. The tosyl group as leaving group was introduced into the hydroxyl group in **9** and the MOM group was removed by TMSBr to give alcohol **11**. The aldehyde **12** obtained by an oxidation of **11** was subjected to the Wittig reaction to give the enol ether **13** in 66% yield over 2 steps. Treatment of **13** with mercury acetate afforded the corresponding aldehyde **14**, which was reduced with NaBH₄ to afford the alcohol **15**. A base-mediated cyclization of **15** using NaHMDS^[2a] proceeded smoothly to give compound **16**.



SCHEME 2 Reagents and conditions: i) *p*-TsCl, Et₃N, DMAP, CH₂Cl₂, room temp. (quant); ii) TMSBr, CH₂Cl₂, -30°C (97%); iii) Dess–Martin periodinane, CH₂Cl₂, room temp.; iv) Ph₃PCH₂OMeCl, LiHMDS, THF, -78°C (66% over 2 steps); v) Hg(OAc)₂, TBAI, THF–H₂O, room temp.; vi) NaBH₄, THF–H₂O, 0°C (63% over 2 steps); vii) NaHMDS, THF, reflux (92%); viii) HCOONH₄, 20%Pd(OH)₂/C, EtOH containing a little amount of AcOH, reflux (50%).

Finally, full deprotection of **16** was accomplished by a catalytic hydrogenolysis over Pd(OH)₂-C with HCOONH₄ under subtle acidic conditions, affording the target molecule **3** in 50% yield. All spectral data were in agreement with the structure of **3** and it was confirmed by x-ray crystallographic analysis. The data showed that the sugar conformation of **3** was restricted to S-type puckering (C_{3'}-*exo*).

In conclusion, we have succeeded in preparation of a novel 2'-deoxy type *trans*-3',4'-BNA **3** having a 4,7-dioxabicyclo[4.3.0]nonane structure from thymidine. The oligonucleotides containing **3** are expected to form stable B-type DNA duplex. Further investigation on **3** and its oligonucleotide derivative is in progress.

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4. The direct benzylation of **6** under various conditions did not give **9** effectively.