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Norbornane as the novel pseudoglycone moiety in nucleosides

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ABSTRACT

Novel nucleoside analogues based on bicyclo[2.2.1]heptene/heptane were prepared by linear synthesis starting from commercially available 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene **1**. The crucial step of the synthesis was insertion of the amino group to the position 7 of the substituted bicyclo[2.2.1]heptene with *anti*-configuration by a Ritter reaction (H_2SO_4, AcOH, CH_3CN). All nucleobases were constructed at this amino function. The prepared family of the target nucleosides was tested for cytostatic and antiviral activity.

1. Introduction

Nucleosides and nucleotides are of fundamental importance for all living systems. Therefore, nucleoside analogues play an important role, mainly as antiviral and antitumor drugs. A disadvantage of analogues of natural nucleosides is cleavage of the *N*-glycosidic bond by phosphorylases. A modification, which increases resistance against enzymatic degradation, is substitution of the furanose ring of the sugar moiety by a hydrocarbon ring. Many of such modified analogues – carbocyclic nucleosides[1] – exhibit interesting antiviral activity. Analogues containing conformationally locked tricyclic systems were also synthesised. Well known are carbocyclic nucleosides with a fused cyclopropane moiety[2] (bicyclo[3.1.0]hexane). Recently, novel conformationally locked carbocyclic nucleosides based on 2-oxabicyclo[2.2.1]heptane ring system were described[3] (as precursors for carbocyclic locked nucleic acids). Bisphosphate of the 2-iodo-(6-methylamino)-purine analogue of this ring system displayed a potent binding affinity to the human $P2Y_1$ receptor. Recently, a series of carbocyclic analogues containing bicycloalkanes,[4] bicycloheteroalkanes[5] or tricycloheteroalkanes[6] with activity against Coxsackie viruses was prepared in our laboratory. Also, we have reported a synthesis of analogues[4b] with a bicyclo[2.2.1]heptene or heptane ring system substituted with nucleobase at position 7 with *syn*-configuration. This study concerns the synthesis of novel racemic conformationally locked nucleosides with bicyclo[2.2.1]hept-2-ene or heptane ring system substituted with nucleobase at position 7 with the *anti*-configuration (Fig. 1). These bicyclo systems (norbornene or norbornane), like the oxabicyclo[2.2.1]heptane, represent conformationally locked carbapentofuranose ring systems. Simple tricyclic derivatives of the original compounds were also prepared.

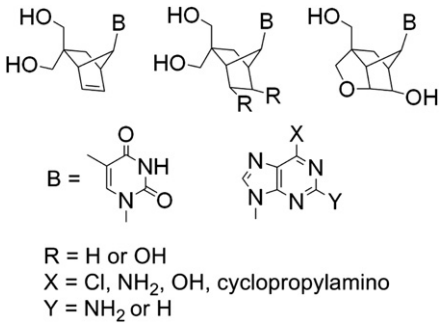

Figure 1.

2. Chemistry

The crucial compound for the synthesis of all the prepared nucleosides was amine **7** (Scheme 1), because our synthetic strategy was based on construction of the nucleobases at the amino group.[4a,7,8]

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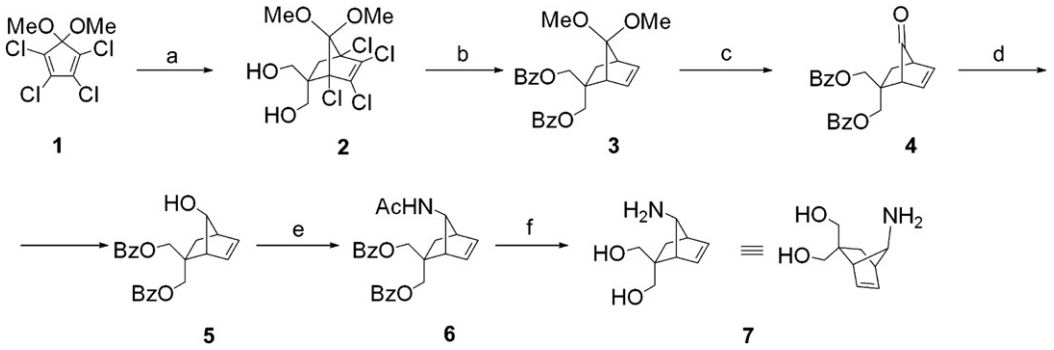
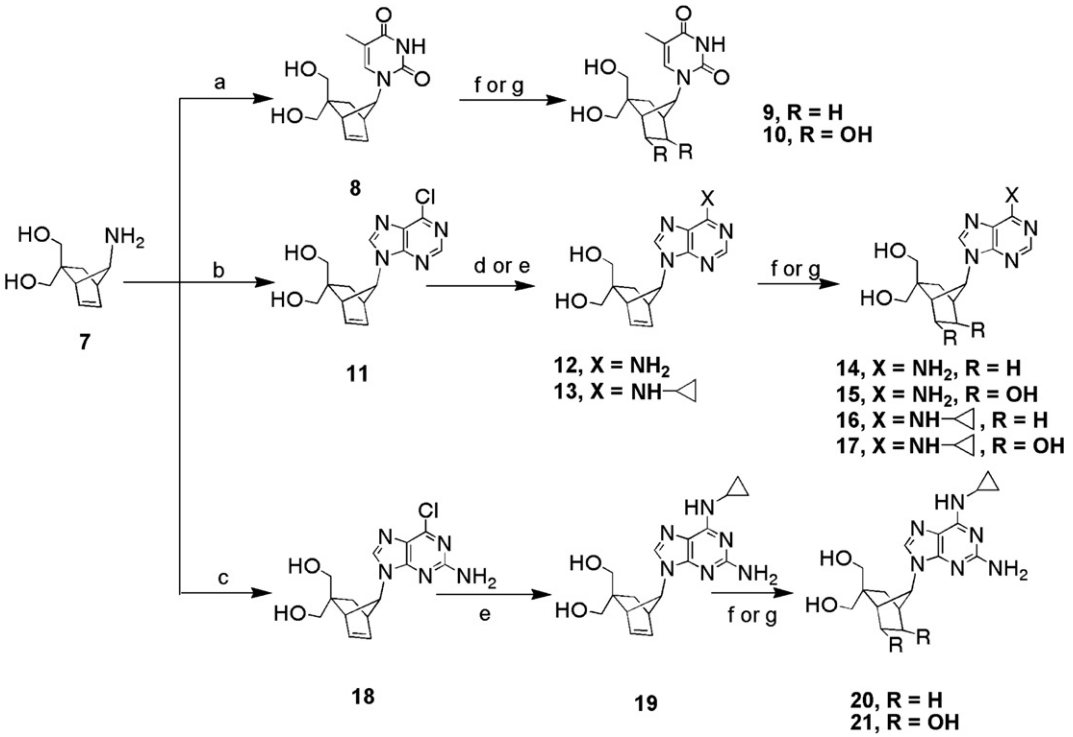


Scheme 1. Reagents and conditions: a) 1. acrolein, 55 °C, 8 h 2. aq HCHO, 55 °C, 4 h, 3. $NaBH_4$, MeOH, overnight, 82%; b) 1. Na, liq NH_3, THF–EtOH, −45 °C, 2 h, 2. BzCl, pyridine, overnight, 78%; c) Dowex 50 (H^+ form), dioxane–water, reflux, 10 h, 75%; d) $NaBH_4$, THF–H_2O, 0 °C, 30 min, 88%; e) CH_3CN, H_2SO_4–AcOH, rt 1 h, 84%; f) KOH, EtOH–H_2O, 100 °C, 9 h, 90%.

Amine **7** was prepared in six steps, starting from commercially available 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene **1**. The cyclopentadiene **1** was treated with acrolein[9] and the Diels–Alder intermediate – formyl derivative – was reacted with formaldehyde under basic conditions (NaOH) to yield, after reduction, the dihydroxymethyl derivative **2** (82%, overall yield from **1**). The chlorine atoms were removed with sodium in liquid ammonia,[10] and the free hydroxy groups were immediately protected by benzoylation (78%). Ketone **4** was then prepared by deketalization (Dowex 50, H^+ cycle) in refluxing mixture of dioxane–water. For satisfactory yield (75%), it was necessary to continuously remove methanol from the reaction mixture. Reduction of the keto group was achieved by reaction with sodium borohydride in mixture of tetrahydrofuran and water. Due to the steric hindrance (hydroxymethyl group against double bond) only one isomer (*anti*) was obtained in very good yield (88%). The configuration of the alcohol **5** was confirmed by 2DROESY spectrum where cross-peaks between hydrogen H-7 and hydrogens of the double bond (H-5 and H-6) and between OH and H-3*exo* were observed. The s*yn*-isomer was not observed in reaction mixture. Finally, the protected amino group was inserted by a Ritter reaction (84%, acetonitrile/acetic acid/sulfuric acid) with retention of the configuration.[11] The free amine **7** was finally released by basic deprotection (90%, KOH, ethanol–water). Many attempts to prepare the amino derivative directly from the protected ketone **4** were not successful. For example, we used reductive amination[12] (benzylamine/$NaBH_3CN$), oximation (NH_2OH) and reduction of the oxime ($LiAlH_4$),[13] insertion of the amino group by selective monoalkylation of ammonia method[14] (NH_4Cl/$Ti(OiPr)_4$). None of these methods gave any or satisfactory yield.

Amine **7** was then used for construction of the nucleosides (Scheme 2). The amine **7** was coupled with ethyl[(2E)-3-ethoxy-2-methylprop-2-enoyl]carbamate[4a,8] in dioxane and acyclic intermediate was closed under acidic conditions (Dowex 50, H^+ cycle) in dioxane giving thymine nucleoside **8** (Scheme 2). Purine nucleosides **11** and **18** were prepared by coupling with 4,6-dichloropyrimidin-5-amine[4a,15] and with 4,6-dichloropyrimidin-2,5-diamine,[7] respectively and the purine ring was then obtained by ring closure (triethyl orthoformate, HCl). Position 6 at the purine ring was further



Scheme 2. Reagents and conditions: a) 1. ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl]carbamate, dioxane, 100 °C, 3 h, 2. Dowex 50 (H^+ form), dioxane, 100 °C, 2.5 h, 55%; b) 1. 4,6-dichloropyrimidin-5-amine, Et_3N, EtOH, 100 °C, 144 h, 2. $CH(OEt)_3$, HCl, 48 h, 3. HCl, THF–H_2O, 3 h, 63%; c) 1. 4,6-dichloropyrimidine-2,5-diamine, Et_3N, EtOH, 100 °C, 6 d, 2. $CH(OEt)_3$, HCl, 120 h, 3. HCl, THF–H_2O, 4 h, 67%; d) NH_3 (l), 75 °C, 48 h, 91%; e) cyclopropylamine, MeOH, for **13**: 10 h, 92%, for **18**: 10 h, 80%; f) H_2, $Pd(OH)_2$/C, MeOH–H_2O; g) OsO_4, NMMO, acetone–water.