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Conformationally locked nucleosides. Synthesis of 3(*R*,*S*)-(adenin-9-yl)-1- and 3(*R*,*S*)-(cytosin-1-yl)-1-hydroxymethylbicyclo[2,1,1]hexanes

Guangyi Wang*

Chemistry Laboratory, ICN Pharmaceuticals, Inc., 3300 Hyland Avenue, Costa Mesa, California 92626, USA

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Abstract

3,3-Di(isopropoxycarbonyl)-1,1-dimethoxycyclobutane (**1**) was converted, in multi-steps, to 3-(1,3-dithiacyclohex-2-yl)-1,1-di(*p*-tosyloxymethyl)cyclobutane (**7**), which was subjected to a butyllithium-mediated cyclization to give the bicyclo[2,1,1]hexane ring system **8**. Further transformations afforded 1-(*t*-butyldimethylsilyloxymethyl)-3(*R*,*S*)-hydroxybicyclo[2,1,1]hexanes (**11**), which were condensed with 6-chloropurine and 4-acetylcytosine via Mitsunobu reactions to give, after further treatment, 3(*R*,*S*)-(adenin-9-yl)- and 3(*R*,*S*)-(cytosin-1-yl)-1-hydroxymethylbicyclo[2,1,1]hexanes (**14** and **17**), respectively. © 2000 Elsevier Science Ltd. All rights reserved.

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Conformationally restricted nucleosides have recently received medicinal chemists' attention as these nucleosides adopt certain desired, restricted geometrical shapes and are potentially useful as small molecule inhibitors or as building blocks of modified oligonucleotides. Partially rigid 2′,3′-didehydro-2′,3′-dideoxyribonucleoside analogues such as carbovir (**a**) and d4T (**b**), which have shown potent antiviral activities against HIV,[1,2] may be considered as the earlier examples in this class. Conformationally restricted nucleosides (**c**) containing the Northern bicyclo[3,1,0]hexane[3] as the sugar moiety were found potent against HSV-1, HSV-2, HCMV, and EBV.[4,5] The triphosphate of the conformationally restricted AZT analogue (**d**) having the bicyclo[3,1,0]hexane ring as the sugar moiety is an equipotent inhibitor of HIV reverse transcriptase.[6] However, the Southern isomers (not shown) did not show much activity against these viruses. Apparently, the restricted, Northern conformation is crucial to the activities of these nucleosides. A few other nucleosides having rigid sugar moieties were also reported, but their biological activity was either weak or not reported.[7–10] Recently, nucleosides containing small, rigid methylenecyclopropanes or spiropentanes were also synthesized and found active against certain DNA viruses.[11,12] If

* Corresponding author.

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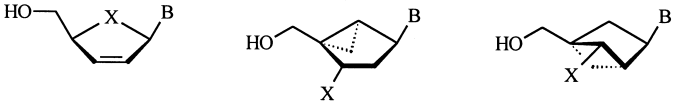
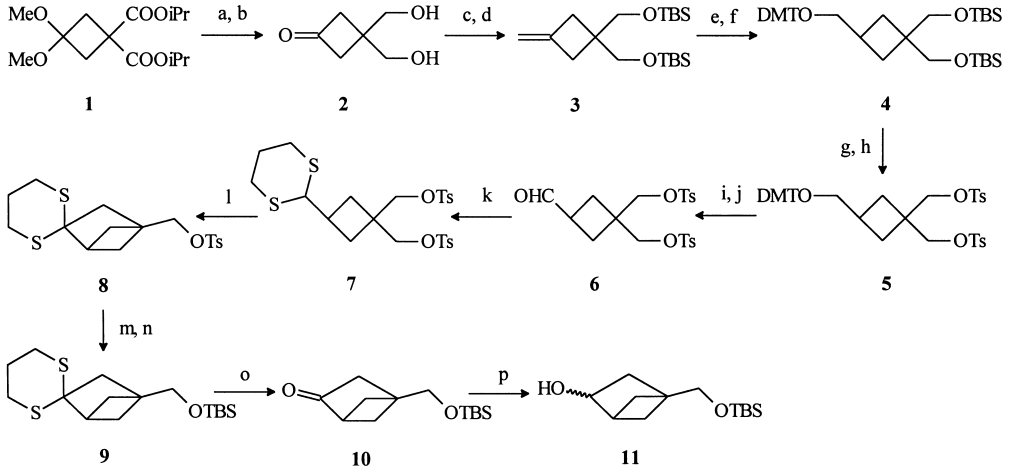
nucleosides containing unnatural 'sugar moieties', like acyclovir, can be selectively phosphorylated by viral nucleoside kinases, they may have a favorable toxicity profile. In fact, carbovir inhibits HIV infection in T cells at concentrations 200–400 times below its cytotoxic levels.[1] Similarly, the nucleosides (**c**) containing the Northern bicyclo[3,1,0]hexane ring also showed favorable selectivity profile.[4,5] It seems that conformationally rigid nucleosides deserve further exploration. It was also reported that 2′,4′-bridged nucleosides dramatically increased hybridization of the modified oligonucleotides to complementary RNA and DNA,[13–15] which was attributed to their favorable, conformationally locked, C3′-*endo* sugar pucker. Whether these 2′,4′-bridged nucleosides possess antiviral activity has not been reported so far. It seems that the known 2′,4′-bridged nucleosides[14,16] might be slightly larger than a favorable size to be a good substrate of nucleoside kinases. Can the 2′,4′-bridge be shortened? It means that highly strained, 2′,4′-one-atom-bridged nucleosides such as **e** and **f** need to be synthesized. In continuation of our efforts on conformationally locked nucleosides, we recently explored the synthetic feasibility of 2′,4′-one-atom-bridged nucleosides. In this communication, synthesis of 3(*R*,*S*)-(adenin-9-yl)- and 3(*R*,*S*)-(cytosin-1-yl)-1-hydroxymethylbicyclo[2,1,1]hexanes (**14** and **17**) is described.

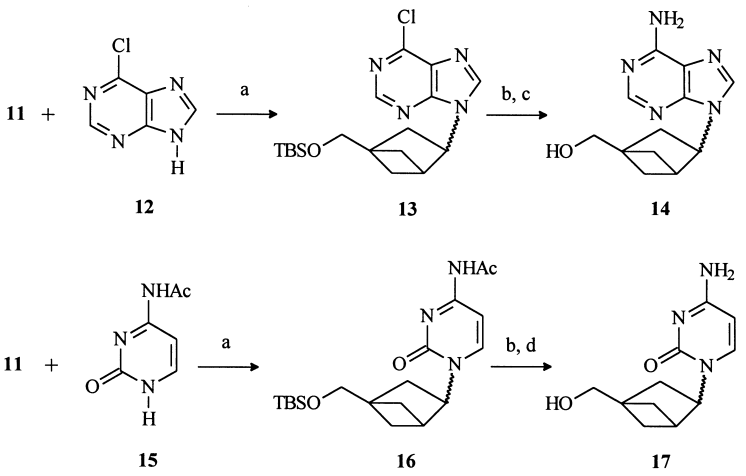


a B = G, X = CH_2
b B = T, X = O
c X = OH
d X = N_3
e X = H
f X = OH

The carbocyclic nucleosides **e** containing a bicyclo[2,1,1]hexane ring as the sugar moiety were prepared from condensation of the nucleoside bases and 1-(*t*-butyldimethylsilyloxymethyl)-3(*R*,*S*)-hydroxybicyclo[2,1,1]hexanes **11** as shown in Schemes 1 and 2. The synthesis of **11** started with 3,3-di(isopropoxycarbonyl)-1,1-dimethoxycyclobutane **1**, which was prepared from



Scheme 1. (a) LAH, THF, rt, 1.5 h, 66%; (b) TFA/$CHCl_3$, rt, 1 h; (c) TBS-Cl, pyridine, 45°C, 1 h, 53% (two steps); (d) $Ph_3P{=}CH_2$, ether, 0°C, 1 h, 100%; (e) (1) $BH_3{\cdot}SMe_2$, THF, rt, 1 h; (2) $NaBO_3$, dioxane/water, 60°C, 2 h, 77%; (f) DMT-Cl, pyridine, 40°C, 2 h; (g) TBAF, THF, 40°C, 1 h; (h) TsCl, pyridine, 50°C, 0.5 h; (i) 80% AcOH, 50°C, 0.5 h, 79% (four steps); (j) DMSO, DCC, TFA, pyridine, rt, 15 h, 91%; (k) 1,3-propanedithiol, $SOCl_2$/silica, CH_2Cl_2, rt, 2 h, 93%; (l) BuLi, THF, rt, 1 h, 42%; (m) NaOH, dioxane/water, 90°C, 3 days, 74%; (n) TBDMS-Cl, pyridine, rt, 1 h; (o) $Hg(ClO_4)_2$, $Ca(CO_3)_2$, THF, rt, 1 h, 83% (two steps); (p) LAH, THF, 0°C, 0.5 h, 84%



Scheme 2. (a) DEAD, Ph_3P, THF, rt, 2–3 days, 69% for **13**, 70% for **16**; (b) TBAF, THF, rt, 1 h; (c) NH_3/MeOH, 80°C, 15 h, 60% for **14** (two steps); (d) same as (c), 55°C, 24 h, 73% for **17** (two steps)

condensation of 1,3-dibromo-2,2-dimethoxypropane[17] and diisopropyl malonate according to a published procedure.[18] Compound **1** was reduced with lithium aluminum hydride (LAH) to give a 3,3-di(hydroxymethyl) derivative, which was treated with trifluoroacetic acid (TFA) to give the keto derivative **2** in good yield. An attempt to convert 3,3-di(*p*-tosyloxymethyl)cyclobutanone (prepared from **2**, not shown) to the corresponding 1-methylene derivative via Wittig reaction failed due to the instability of the tosyl group. After protection of the hydroxyls of **2** with *t*-butyldimethylsilyl (TBS) group, a Wittig reaction[16] converted the keto intermediate to the methylenecyclobutane derivative **3.** The hydroboration of **3** gave a hydroxymethyl intermediate, which was protected with dimethoxytrityl (DMT) group to give **4**. The TBS groups of **4** were removed and then replaced with two *p*-tosyl groups to give **5**. After removal of DMT from **5**, the resulting hydroxyl was oxidized to give the aldehyde **6**. Treatment of **6** with 1,3-propanedithiol and $SOCl_2$/silica[19] afforded the dithiane **7**, which was subjected to a cyclization in the presence of butyllithium.[20] This was the key step to the synthesis of the bicyclo[2,1,1]hexane ring system. With excess butyllithium (3 equivalents) at ambient temperature for 1 h, a moderate yield (~40%) of **8** was obtained. The side reactions included the removal of one or two tosyl groups and the formation of a spiro ring system from the monotosyl by-product. In an attempt to optimize the cyclization, the tosyl groups of **8** were replaced by mesyl. In this case, no desired product was formed and the side reactions predominated. Compound **8** was subjected to a vigorous hydrolysis with aqueous sodium hydroxide at 90°C, and fortunately, the bicyclo[2,1,1]ring system well survived the hydrolytic condition. The hydrolytic product was protected with TBS to give **9** in good yield. Removal of 1,3-dithiane was achieved by treatment with mercury(II) perchlorate[21] in THF in the presence of calcium carbonate to give the keto product **10**. Reduction of **10** with LAH afforded the desired **11** in good yield. Theoretically, the reduction of the symmetrical keto compound **10** should give a mixture of equal amounts of the 3(*R*)- and 3(*S*)-isomers, which formed an enantiomeric mixture and could not be distinguished by NMR. It was our interest to make both isomers and therefore a separation was not attempted.

Compound **11** was successfully condensed with 6-chloropurine **12** and 4-acetylcytosine **15**, respectively, via Mitsunobu reaction.[22,23] A typical procedure was as follow: DEAD (1.0 mmol) was added to a stirred mixture of nucleoside base (1.0 mmol) and triphenylphosphine (1.0 mmol)

in anhydrous THF (5 mL). The mixture was stirred at room temperature for 10 min, and a solution of **11** (0.5 mmol) in THF (1 mL) was added. The reaction mixture was stirred under argon for 2–3 days, evaporated, and subjected to a flash chromatography. Compound **13** was obtained in good yield and further converted to the adenosine analogue by treatment with ammonia-saturated methanol in a steel bomb. The condensation of **11** with 4-acetylcytosine afforded a good yield of **16**, which was subjected to removal of the TBS and acetyl to give the cytidine analogue **17**. Other purine and pyrimidine nucleosides containing 1-hydroxymethyl-3(*R*,*S*)hydroxybicyclo[2,1,1]hexanes are being synthesized in this laboratory.

The sugar moiety of the bicyclonucleosides **14** and **17** consists of a pair of the enantiomers as mentioned above, and therefore the nucleosides prepared from this 'sugar' are also a mixture of two enantiomers since the nucleoside bases do not have any chiral center. These compounds may be analogously named D- and L-nucleosides. In this case, the 3′-(*R*)-isomer is a β-D-nucleoside and the 3′(*S*)-isomer is a β-L-nucleoside as shown below.

3'(*S*)-enantiomer 3'(*R*)-enantiomer

In summary, this letter, has reported, for the first time the synthesis of nucleosides having 1-hydroxymethyl-3(*R*,*S*)-bicyclo[2,1,1]hexanes as the sugar moiety. The successful synthesis of 1-hydroxymethyl-3(*R*,*S*)-hydroxybicyclo[2,1,1]hexanes would encourage the exploration of nucleosides containing compact bicyclic ring systems. In this laboratory, the optimization of the synthetic route to the bicyclo[2,1,1]hexane ring system and synthesis of the 2′,4′-methylene nucleosides are under way.

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