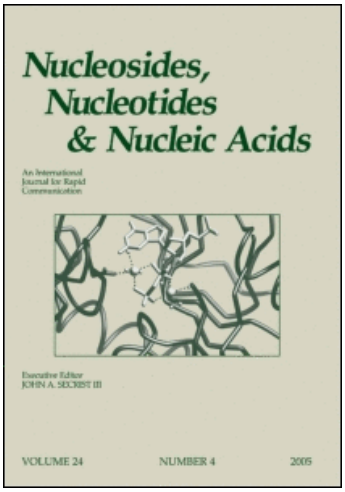

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Stereoselective Synthesis of Novel 4′-Branched and Bicyclo[3.1.0]hexane-Templated Nucleoside

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ABSTRACT

The racemic and stereoselective synthesis of a novel nucleoside 4′-branched and bicyclo[3.1.0]hexane templated nucleoside **15** was accomplished using a [3,3]-sigmatropic rearrangement, an intramolecular carbene cycloaddition reaction and a Curtius rearrangement as the key reactions.

Key Words: Nucleoside; Bicyclo[3.1.0]hexane; [3,3]-Sigmatropic rearrangement; Intramolecular carbene cycloaddition.

INTRODUCTION

The discovery of novel nucleosides for use as antiviral and anticancer agents has been a major goal of nucleoside research over the past few decades. In particular, since the emergence of the HIV pandemic, extensive studies have focused on various modifications in the sugar moiety of nucleosides, resulting in FDA approved anti-HIV agents such as AZT,[1] ddC,[2] ddI,[3] d4T,[4] 3TC,[5] abacavir[6] and bis(POC)PMPA.[7] In addition to these efforts, a number of 4′-branched nucleosides have been synthesized, which have exhibited significant antitumor or antiviral activities. Among them, 4′α-*C*-fluoromethyl-2′-deoxycytidine,[8] and 4′α-*C*-hydroxymethyl thymidine[9–11]

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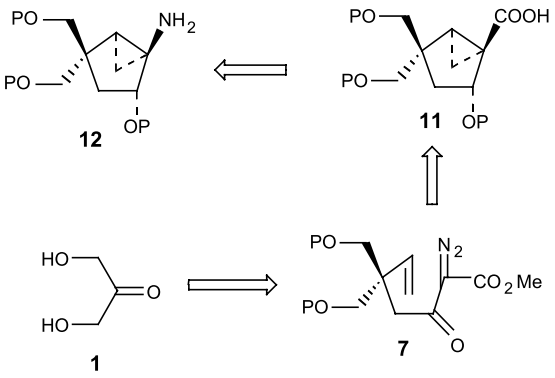


Scheme 1. Retrosynthesis of Key Intermediate **12**.

demonstrated quite potent biological activities. However, their high toxicity renders them useless as drugs.

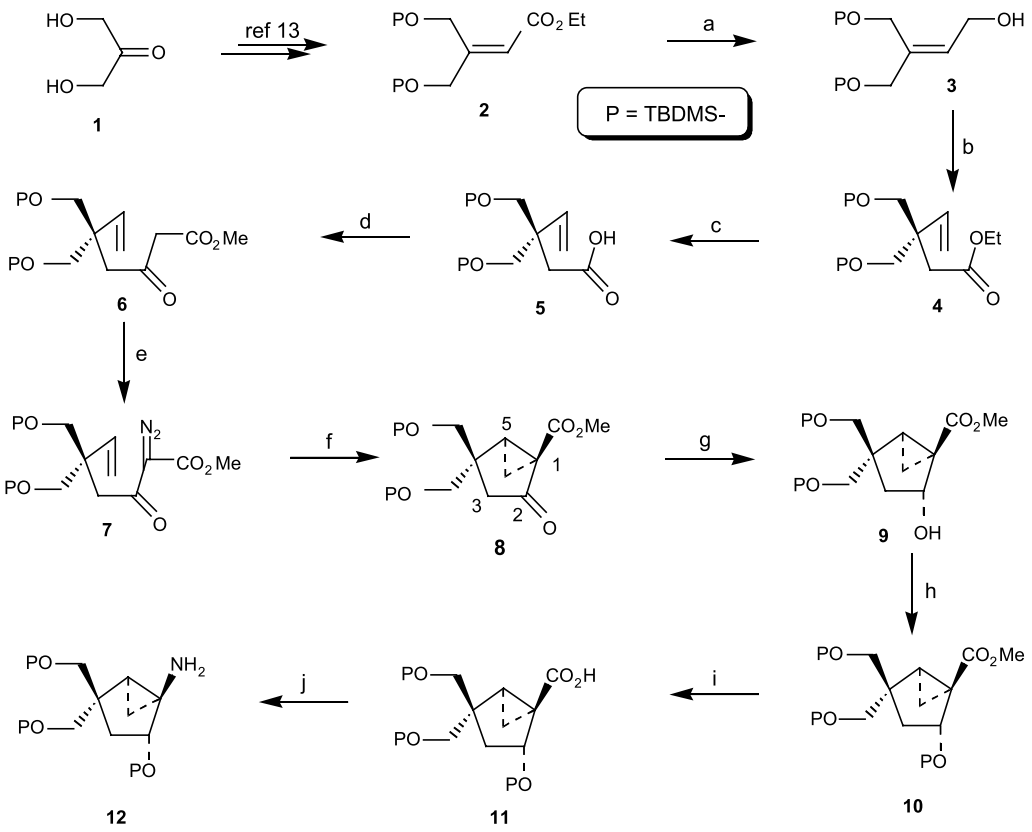
Recently, a number of purine and pyrimidine carbocyclic nucleosides built on a rigid bicyclo[3.1.0]hexane template, (selected references: Refs. [12–17]) which is a system that mimics either the northern-type conformation ($_2$E) or the southern-type conformation ($_3$E) as defined in the pseudorotational cycle[18] have been synthesized and evaluated for their potential as potent antitumor or antiviral agents. In view of the fact that the bicyclo[3.1.0]hexane template mimics the active, receptor-bound conformation of the nucleoside or nucleotide, it can provide an accurate identification of the favored sugar conformation that results in the optimal recognition by the target enzyme.

These findings, together with the promising activity of the 4′-branched nucleosides, prompted us to synthesize novel classes of nucleosides, which are hybrids of a 4′-branched nucleoside and a bicyclo[3.1.0]hexane templated nucleoside.

RESULTS AND DISCUSSIONS

The key strategy for synthesizing the target compound was based on a [3,3]-sigmatropic rearrangement in order to install two useful functionalities such as alkene and ester functional groups. As shown in the retrosynthesis (Scheme 1), it was envisaged that the bicyclo[3.1.0]hexane system might be stereoselectively constructed by an intramolecular olefin keto-carbene cycloaddition reaction of **7**. In addition, it was postulated that the amine **12** could be prepared from the acid **11** via a modified Curtius rearrangement. Furthermore, Shin et al. reported an excellent synthetic procedure of [3.1.0]hexane locked nucleosides with use of [3,3]-sigmatropic rearrangement.[19]

As shown in Scheme 2, commercially available 1,3-dihydroxy acetone **1** was used as a starting material. 1,3-Dihydroxyacetone was converted to an α,β-unsaturated ethyl ester **2** according to a well-known procedure.[20,21] The α,β-unsaturated ethyl ester **2** was reduced by DIBALH at -20°C in CH_2Cl_2 to give the allylic alcohol **3** in a 97% yield, which was subjected to a [3,3]-sigmatropic rearrangement[22–25] to produce a



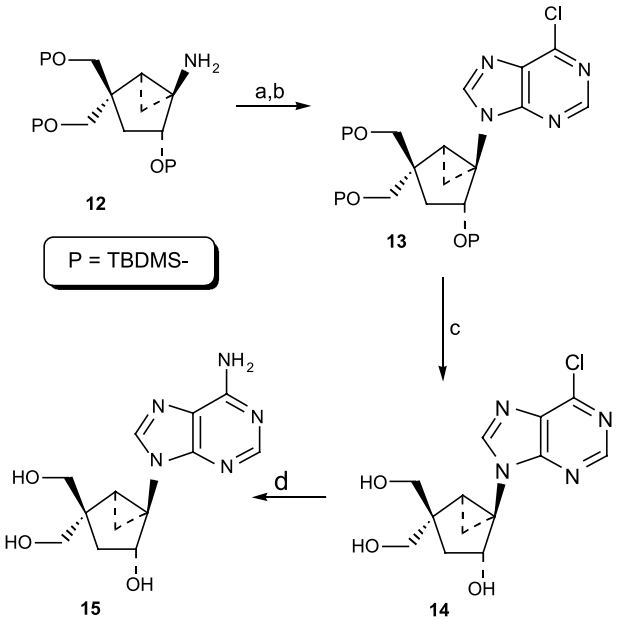
Scheme 2. Reagents: a) DIBALH, CH_2Cl_2, −20 °C, 2 h, 97%; b) $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$, overnight, 130 °C, 86%; c) 1 M KOH, EtOH, 50 °C, overnight, 87%; d) (i) carbonyldiimidazole, THF, −78 °C; (ii) $CH_3CO_2CH_3$, LDA, THF, −78 °C, 89%; e) TsN_3, TEA, CH_3CN, rt, overnight, 94%; f) Cupric acetylacetonate, cyclohexane, reflux, overnight, 72%; g) $NaBH_4$, $MeOH/CH_2Cl_2$, 0 °C, 88%; h) TBDMSCI, imidazole, CH_2Cl_2, rt, 3 h, 98%; i) 1 M KOH, EtOH, 50 °C, overnight, 90%; j) (i) $(PhO)_2PON_3$, TEA, benzene; (ii) NaOH, THF, 71%.

γ,δ-unsaturated ester **4**, which was followed by basic hydrolysis to give the acid derivative **5** in a 75% two step yield. With the desired olefinic acid **5** available, the second stage of the synthesis of the bicyclo[3.1.0]hexane system was begun by employing an intramolecular carbene cycloaddition reaction. Activation of the acid **5** with carbonyldiimidazole followed by a Dieckmann condensation using methyl 2-lithioacetate produced the β-keto ester **6**.

This was followed a diazo transfer with tosyl azide in the presence of triethylamine to give the diazo compound **7** in an 84% yield for the two steps. Thermolysis of **7** was examined using a couple of soluble catalysts. Copper (II) acetylacetonate gave the best results, forming the corresponding bicyclo[3.1.0]hexane template **8** in a 72% yield. $NaBH_4$ was used to reduce the keto group of **8** in a methanol solvent to **9** as a single isomer in an 88% yield. This stereochemical outcome could readily be explained in

terms of the convex nucleophilic addition of the diastereofacial bias of the bicyclo[3.1.0]hexane system.[19] The hydrolysis of ester **10** was followed by a modified Curtius rearrangement of the resulting acid **11** with diphenylphosphoryl azide in refluxing benzene to give an unstable isocyanate intermediate, which required further hydrolysis with sodium hydroxide to generate the corresponding amine **12** in a 64% two step yield. The amine derivative **12** was subjected to purine base build-up conditions using 4,6-dichloro-5-formamidopyrimidine[26] in the presence of formic acid-acetic anhydride followed by a closure of the imidazole intermediate by a reaction with diethoxymethyl acetate to give the 6-chloropurine nucleoside **13** in a 53% two step yield. Deblocking of **13** using tetrabutylammonium fluoride and ammonolysis of **14** was done to give the final nucleoside **15** in a 63% two step yield. The antiviral activity of compound **15** was evaluated against various viruses such as HIV-1, HSV-1, HSV and HCMV. However, no significant antiviral activity was observed up to 100 μM. A possible reason for the lack of activity could be originated from the presence of 2′-hydroxy functional group (Scheme 3).

In summary, this paper describes the novel synthesis of 4′-branched and bicyclo[3.1.0]hexane templated nucleoside using a [3,3]-sigmatropic rearrangement, an intramolecular carbene cycloaddition reaction and a Curtius rearrangement as the key reactions. The procedure can be widely used for the de novo stereoselective synthesis of novel nucleosides with dual properties of the branches and rigid bicyclic ring systems.



Scheme 3. Reagents: a) 4,6-dichloro-5-formamidopyrimidine, TEA, dioxane, reflux, overnight; b) $CH_3CO_2CH(OEt)_2$, 110 °C, overnight, 53%; c) TBAF, CH_3CN, rt, 5 h, 70%; d) NH_3/MeOH, 12 h, 76%.

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EXPERIMENTAL SECTION

All chemicals were of reagent grade and used as purchased. All moisture-sensitive reactions were performed in an inert atmosphere of either N_2 or Ar using distilled dry solvents. The elemental analyses were performed using an Elemental Analyzer System (Profile HV-3). The NMR spectra were obtained on a bruker 300 Fourier transform spectrometer and are reported in δ(ppm) downfield from tetramethylsilane (TMS).

4-(*tert*-Butyldimethylsilanyloxy)-3-(*tert*-butyldimethylsilanyyloxymethyl)-but-2-en-1-ol (3). To a solution of **2** (10 g, 25.7 mmol) in CH_2Cl_2 (300 mL), DIBALH (54.0 mL, 1.0 M solution in hexane) was added slowly at − 20 °C, and stirred for 2 h at the same temperature. Methanol (54 mL) was added to the resulting mixture. The mixture was stirred at room temperature for 3 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:4) to give allylic alcohol **3** (8.64 g, 97%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.82 (t, J = 8.4 Hz, 1H), 4.23 (s, 4H), 4.16 (s, 2H), 0.93 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 141.19, 125.38, 64.85, 59.40, 58.70, 25.92, 18.39, −5.35; Anal calc for $C_{17}H_{38}O_3Si_2$: C, 58.90; H, 11.05. Found: C, 58.69; H, 10.85.

3,3-Bis-(*tert*-butyldimethylsilanyloxymethyl)-pent-4-enoic acid ethyl ester (4). A solution of the allylic alcohol **3** (15 g, 43.3 mmol) in triethyl orthoacetate (300 mL) and 1.0 mL of propionic acid was heated at 130 °C overnight with constant stirring to allow for the removal of ethanol. The excess triethyl orthoacetate was removed by distillation and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **4** (15.5 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (dd, J = 18.0, 11.4 Hz, 1H), 5.09 (d, J = 11.1, Hz, 1H), 5.05 (d, J = 18.0 Hz, 1H), 4.05 (q, J = 7.5 Hz, 2H), 3.61 (dd, J = 15.6, 9.0 Hz, 4H), 2.40 (s, 2H), 1.24 (t, J = 7.5 Hz, 3H), 0.90 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 171.92, 139.76, 114. 48, 64.67, 59.88, 45. 98, 36. 84, 25.85, 18.25, 14.25, − 5.56; Anal calc for $C_{21}H_{44}O_4Si_2$: C, 60.52; H, 10.64. Found: C, 60.22; H, 10.51.

3,3-Bis-(*tert*-butyldimethylsilanyloxymethyl)-pent-4-enoic acid (5). To a solution of **4** (5.0 g, 12.0 mmol) in ethanol (100 mL), a KOH solution (24 mL 1.0 M solution in ethanol) was added and stirred overnight at 50 °C. After cooling to room temperature, the reaction solution was concentrated under reduced pressure. Water (200 mL) was poured into the residue, acidified to pH 4 with c-HCl at 0 °C and extracted twice with CH_2Cl_2. The combined organic extract was dried under anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give the acid derivative **5** (4.06 g, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.80 (dd, J = 18.0, 11.4 Hz, 1H), 5.12 (d, J = 10.2 Hz, 1H), 5.08 (d, J = 18.0 Hz, 1H), 3.60 (dd, J = 13.2, 9.3 Hz, 4H), 2.48 (s, 2H), 0.86 (s, 18H), − 0.00 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 177.09, 139.20, 115.12, 65.39, 45.87, 37.82, 25.81, 18.21, −5.62; Anal calc for $C_{19}H_{40}O_4Si_2$: C, 58.71; H, 10.37. Found: C, 58.34; H, 10.45.

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5,5-Bis-(*tert*-butyldimethylsilanyloxymethyl)-3-oxo-hept-6-enoic acid methyl ester (6). To a solution of acid **5** (2.0 g, 5.15 mmol) in dry THF (20 mL), carbonyldiimidazole (917 mg) was added at 0 °C. The temperature was maintained at 0 °C for 1 h and allowed to room temperature. After 2 h, a solution of $LiCH_2COOCH_3$ (prepared from $CH_3CO_2CH_3$, LDA) was added to the reaction mixture at −78 °C. After the addition, the reaction was stirred for a further 2 h at −78 °C, quenched with a 1 N HCl solution, allowed to reach room temperature, and acidified to pH 5 with additional HCl. The mixture was extracted using EtOAc (2 x 200 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:8) to give **6** (2.03 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.83 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.10 (d, *J* = 17.7, 11.1 Hz, 1H), 3.68 (s, 3H), 3.58 (dd, *J* = 12.3, 9.6 Hz, 4H), 3.43 (s, 2H), 2.63 (s. 2H), 0.85 (s, 18H), 0.00 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 201.45, 167.58, 139.93, 114.53, 64.77, 64.63, 52.08, 50.65, 46.73, 44.47, 25.82,18.20, −5.61; Anal calc for $C_{22}H_{44}O_5Si_2$: C, 59.41; H, 9.97. Found: C, 59.30; H, 9.78.

5,5-Bis-(*tert*-butyldimethylsilanyloxymethyl)-2-diazo-3-oxo-hept-6-enoic acid methyl ester (7). To a solution of **6** (1.0 g, 2.25 mmol) in dry CH_3CN (15 mL), triethylamine (0.63 mL) and *p*-toluenesulfonyl azide (444 mg, 2.25 mmol) was added slowly at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred overnight. The reaction mixture was poured into ether and a 2 N NaOH solution and stirred for an additional 30 min. The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under vacuum, and the residue was purified using silica gel column chromatography (EtOAc/hexane, 1:18) to give the diazo compound **7** (995 mg, 94%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.91 (dd, *J* = 18.0, 11.4 Hz, 1H), 5.09 (d, *J* = 10.2 Hz, 1H), 5.05 (d, *J* = 18.0 Hz, 1H), 3.81 (s, 3H), 3.67 (dd, *J* = 10.8, 9.0 Hz, 4H), 3.01 (s, 2H), 0.87 (s, 18H), −0.02 (s, 12H): ^{13}C NMR ($CDCl_3$) δ 191.21, 161.88, 140.20, 114.17, 64.81, 52.04, 47.25, 41.03, 25.84, 18.24, −5.56; Anal calc for $C_{22}H_{42}N_2O_5Si_2$: C, 56.13; H, 8.99. Found: C, 56.29; H, 9.10.

(*rel*)-(1*R*,5*S*)-4,4-Bis-(*tert*-butyldimethylsilanyloxymethyl)-2-oxo-bicyclo[3.1.0]-hexane-1-carboxylic acid methyl ester (8). To a solution of **7** (4.0 g, 8.5 mmol) in anhydrous cyclohexane (20 mL), acetylacetonate (2.3 g, 8.5 mmol) was added at room temperature. The reaction mixture was refluxed overnight, filtered through Celite and the solid cake was washed with EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give **8** (2.71 g, 72%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.72 (s, 3H), 3.57 (s, 2H), 3.53 (d, *J* = 2.4 Hz, 2H), 2.41 (dd, *J* = 8.4, 5.7 Hz), 2.00 (s, 2H), 1.91 (dd, *J* = 8.4, 4.8 Hz, 1H), 1.47 (t, *J* = 5.1 Hz, 1H), 0.85 (s, 18H), −0.02, −0.03 (s,s, 12H): ^{13}C NMR ($CDCl_3$) δ 204.73, 168.96, 67.04, 64.65, 52.26, 44.33, 40.12, 37.51, 37.08, 25.77, 19.91, 18.21, −5.61; Anal calc for $C_{22}H_{42}O_5Si_2$: C, 59.68; H, 9.56. Found: C, 59.44; H, 9.50.

(*rel*)-(1*R*,2*R*,5*S*)-4,4-Bis-(*tert*-butyldimethylsilanyloxymethyl)-2-hydroxy-bicyclo[3.1.0] hexane-1-carboxylic acid methyl ester (9). A stirred solution of bicyclic keto ester **8** (4.5 g, 10.2 mmol) in a 2:1 mixture of MeOH/CH_2Cl_2 was cooled to

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−20 °C and $NaBH_4$ (434 mg, 11.47 mmol then added. The mixture was stirred for 1 h at 0 °C and quenched by adding glacial acetic acid (0.2 mL). The resulting solution was extracted using EtOAc, washed with brine, dried over $MgSO_4$ and then filtered. The filtrate was concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give **9** (4.0 g, 88%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.66 (s, 3H), 3.50–3.36 (m, 4H), 2.19 (d, *J* = 3.9 Hz, 1H), 1.89–1.78 (m, 2H), 1.7 (d, *J* = 6.0 Hz, 2H), 0.90 (s, 18H), 0.00 (s, 12H): ^{13}C NMR ($CDCl_3$) δ 174.25, 71.37, 66.53, 65.18, 51.70, 48.46, 35.56, 34.65, 33.38, 25.81, 18.19, 13.29, − 5.67; Anal calc for $C_{22}H_{44}O_5Si_2$: C, 59.41; H, 9.97. Found: C, 59.45; H, 9.72.

(*rel*)-(1*R*,2*R*,5*S*)-(*tert*-Butyldimethylsilanyloxy)-4,4-bis-(*tert*-butyldimethylsilanyloxymethyl)-bicyclo[3.1.0]hexane-1-carboxylic acid methyl ester (10). To a stirred solution of **9** (698 mg, 1.57 mmol) and imidazole (212 mg, 3.12 mmol) in CH_2Cl_2 (10 mL), *t*-butyldimethylsilyl chloride (236 mg, 1.57 mmol) at 0 °C was added. The mixture was stirred at room temperature for 3 h, and quenched by adding a $NaHCO_3$ solution (2 mL). The mixture was extracted using CH_2Cl_2 (50 mL), dried over $MgSO_4$, filtered and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to give **10** (857 mg, 98%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.93 (t, *J* = 7.8 Hz, 1H), 3.63 (s, 3H), 3.49–3.34 (m, 4H), 1.77 (dd, *J* = 14.1, 8.4 Hz, 1H), 1.66 (dd, *J* = 8.4, 5.4 Hz, 1H), 1.32 (dd, *J* = 8.4, 4.8 Hz, 1H), 1.21 (t, *J* = 5.7 Hz, 1H), 0.83 (m, 27H), 0.00 (s, 18H): ^{13}C NMR ($CDCl_3$) δ 173.84, 71.74, 66.76, 65.37, 51.27, 48.60, 37.17, 35.90, 34.05, 25.81, 18.20, 12.78, −4.90, −5.65; Anal calc for $C_{28}H_{58}O_5Si_3$: C, 60.16; H, 10.46. Found: C, 60.38; H, 10.41.

(*rel*)-(1*R*,2*R*,5*S*)-(*tert*-Butyldimethylsilanyloxy)-4,4-bis-(*tert*-butyldimethylsilanyloxymethyl)-bicyclo[3.1.0]hexane-1-carboxylic acid (11). Compound **11** was prepared using a similar procedure as described for **5**. Yield: 90%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.90 (t, *J* = 8.1 Hz, 1H), 3.49–3.32 (m, 4H), 1.81–1.709 (m, 2H), 1.39 (dd, *J* = 8.1, 4.8 Hz, 1H), 1.26 (t, *J* = 5.4 Hz, 1H), 0.85 (m, 27H), 0.00 (s, 18H): ^{13}C NMR ($CDCl_3$) δ 179.87, 136.36, 71.39, 66.56, 65.24, 48.73, 36.98, 35.71, 35.03, 25.79, 18.01, 13. 40. −4.92, −5.61; Anal calc for $C_{27}H_{56}O_5Si_3$: C, 59.50; H, 10.36. Found: C, 59.88; H, 10.35.

(*rel*)-(1*R*,2*R*,5*S*)-(*tert*-Butyldimethylsilanyloxy)-4,4-bis-(*tert*-butyldimethylsilanyloxymethyl)-bicyclo[3.1.0]hex-1-ylamine (12). To a stirred solution of **11** (1.5 g, 2.75 mmol) in anhydrous benzene (20 mL), Et_3N (1.15 mL, 8.25 mmol) and diphenylphosphoryl azide (1.76 mL, 8.25 mmol) at 0 °C was added. The mixture was refluxed overnight with constant stirring, cooled to room temperature and then concentrated under reduced pressure. The crude isocyanate was treated with THF (30 mL) and 2 N NaOH (20 mL), and then stirred for a further 20 min at room temperature. The resulting solution was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to give **12** (1.0 g, 71%) as a colorless syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.26 (t, *J* = 8.1 Hz, 1H), 3.48 (d, *J* = 9.6 Hz, 1H), 3.42 (d, *J* = 9.6, 1H), 3.27 (dd, *J* = 14.7, 9.6 Hz, 2H), 1.66 (dd, *J* = 13.8, 8.1 Hz, 1H), 1.61 (Br

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s, 2H), 1.04 (dd, J = 8.7, 4.2 Hz, 1H), 0.86 (m, 27H), (m, 27H), 0.81–0.63 (m, 2H), 0.50 (dd, J = 7.5, 5.1 Hz, 1H), 0.00 (m, 18H): ^{13}C NMR ($CDCl_3$) δ 79.26, 67.18, 65.42, 47.63, 46.50, 36.89, 28.86, 25.89, 18.20, 11.79, −4.55, −5.89; Anal calc for $C_{26}H_{57}NO_3Si_3$: C, 60.52; H, 11.13. Found: C, 60.69; H, 11.27.

(*rel*)-(1′*R*,2′*R*,5′*S*)-9-[2-(*tert*-Butyldimethylsilanyloxy)-4,4-bis-(*tert*-butyldimethylsilanyloxymethyl)-bicyclo[3.1.0]hex-1-yl]-6-chloropurine (13). To a stirred solution of **12** (1.5 g, 2.91 mmol) in anhydrous 1,4-dioxane (20 mL), Et_3N (1.15 mL, 8.25 mmol) and 4,6-dichloro-5-formamidopyrimidine (560 mg, 2.91 mmol) was added. The mixture was refluxed overnight with constant stirring, cooled down to room temperature and the resulting solid was then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:2) to give then acyclic imidazole intermediate as a yellow solid. This compound was immediately treated with diethoxymethyl acetate (30 mL) and heated overnight at 110 °C. After cooling, the mixture was concentrated under reduced pressure, and the residue was purified by column chromatography to give **13** (1.0 g, 53%) as a yellowish solid: mp 169–172 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1H), 8.67 (s, 1H), 4.26 (t, J = 8.0 Hz, 1H), 3.49 (d, J = 9.4 Hz, 1H), 3.44 (d, J = 9.4, 1H), 3.25 (dd, J = 14.5, 9.4 Hz, 2H), 1.65 (dd, J = 13.4, 8.0 Hz, 1H), 1.48 (dd, J = 8.5, 4.0 Hz, 1H), 1.38–1.30 (m, 2H),), 0.86 (m, 27H), (m, 27H), 0.77 (dd, J = 7.2, 5.2 Hz, 1H), 0.00 (m, 18H): ^{13}C NMR ($CDCl_3$) δ 155.14, 152.39, 148.88, 147.02, 130.11, 90.84, 78.89, 67.21, 65.40, 47.68, 46.55, 36.91, 28.86, 26.01, 18.22, 11.81, −4.50, −5.81; Anal calc for $C_{31}H_{57}ClN_4O_3Si_3$: C, 56.97; H, 8.79; N, 8.57. Found: C, 57.22; H, 8.57; N, 8.34.

(*rel*)-(1′*R*,2′*R*,5′*S*)-9-[2-(Hydroxy)-4,4-bis-(hydroxymethyl)-bicyclo[3.1.0]hex-1-yl]6-chloropurine (14). A solution of **13** (520 mg, 0.795 mmol) in CH_3CN (15 mL) was treated with TBAF (1 M solution in THF (4 mL) and stirred at rt for 5 h. After concentrating the mixture, the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH = 7:1) to give **14** (173 mg, 70%) as a white solid: mp 184–186 °C; ^{1}H NMR (DMSO-d_6 + D_2O, 300 MHz) δ 8.72 (s, 1H), 8.61 (s, 1H), 4.25 (t, J = 8.1 Hz, 1H), 3.52 (d, J = 10.5 Hz, 1H), 3.42 (d, J = 10.5, 1H), 3.21 (s, 2H), 1.58 (dd, J = 14.1, 8.4 Hz, 1H), 1.46 (dd, J = 14.7, 8.1 Hz, 1H), 1.32 (dd, J = 6.6, 3.9 Hz, 1H), 0.99 (dd, J = 8.1, 3.6 Hz, 1H), 0.86 (dd, J = 7.5, 4.2Hz, 1H): ^{13}C NMR (DMSO-d_6+ D_2O) δ 155.12, 152.32, 150.58, 139.21, 117.98, 90.79, 78.89, 67.35, 65.56, 48.04, 45.05, 27.56, 12.81; Anal calc for $C_{13}H_{15}ClN_4O_3$: C, 50.25; H, 4.87; N, 18.03. Found: C, 50.47; H, 4.69; N, 17.79.

(*rel*)-(1′*R*,2′*R*,5′*S*)-9-[2-(Hydroxy)-4,4-bis-(hydroxymethyl)-bicyclo[3.1.0]hex-1-yl]adenine (15). Compound **14** (100 mg, 0.322 mmol) was dissolved in saturated methanolic ammonia (10 mL) and the resulting solution was stirred for 12 h at 90 °C in a steel bomb. After removing the reaction solvent, the yellowish residue was purified by column chromatography ($CHCl_3$:MeOH = 5:1) to give **15** as a solid (71 mg, 76%): mp 190–192 °C; UV (H_2O) λ_{max} 260.5 nm; ^{1}H NMR (DMSO-d_6+ D_2O, 300 MHz) δ 8.35 (s, 1H), 7.98 (s, 1H), 4.27 (t, J = 8.0 Hz, 1H), 3.53 (d, J = 9.8 Hz, 1H), 3.40 (d, J = 9.8, 1H), 3.22 (s, 2H), 1.58 (dd, J = 15.2, 8.2 Hz, 1H), 1.45 (dd, J = 13.5, 8.2 Hz, 1H), 1.24 (dd, J = 6.8, 3.8 Hz, 1H), 1.09 (dd, J = 8.2, 3.6 Hz, 1H), 0.92 (dd, J = 7.6,

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4.2Hz, 1H): ^{13}C NMR (DMSO-d_6+ D_2O) δ 156.34, 153.38, 151.68, 140.25, 119.02, 92.79, 80.09, 67.51, 65.48, 47.88, 45.15, 26.46, 13.22; Anal calc for $C_{13}H_{17}N_5O_3$: C, 53.60; H, 5.88; N, 24.04. Found: C, 53.81; H, 5.78; N, 23.97.

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