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Synthesis of 2',3'-Dideoxycyclo-2'-pentenyl-3'-C-hydroxymethyl Carbocyclic Nucleoside Analogues as Potential Anti-viral Agents

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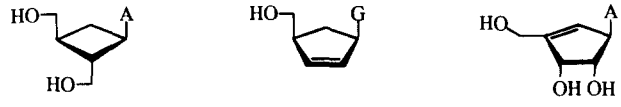
Abstract: The synthesis of optically pure unsaturated carbocyclic nucleoside analogues is described. (3,4*S*)-Bis(*t*-butyldiphenylsilyloxymethyl)-2-cyclopenten-1*R* and 1*S*-ol were coupled with 6-chloropurine and 2-amino-6-chloropurine respectively, using a modified Mitsunobu reaction. The products were reacted further using standard procedures to give compounds **12**, **14**, **16** and **18** which were tested for anti-HIV activity.

INTRODUCTION

Carbocyclic nucleosides have emerged as a promising group of compounds for drug discovery in the anti-viral field.[1-4] Compounds such as cyclobut A (**1**) and carbovir (**2**) are active against human immunodeficiency virus (HIV)[5,6] and (-) neoplanocin A (**3**) is active against certain RNA viruses (fig. 1).[7] A special feature of these compounds is the absence of a glycosidic linkage which increases the metabolic stability against nucleoside phosphorylases and hydrolases, thereby prolonging the half-life *in vivo*.[8,9] The comparatively higher lipophilicity of carbocyclic nucleosides is potentially beneficial for increasing oral availability and cell wall penetration.

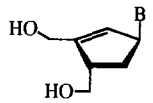
Fig. 1



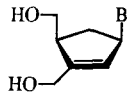
1 **2** **3**

Lately the synthesis of several different types of hydroxymethyl branched nucleoside analogues have been reported.[10-25] In order to further evaluate the anti-viral effect of hydroxymethyl substituted nucleosides, we have synthezised the 3'-hydroxymethyl substituted cyclopentenyl nucleoside analogues **12**, **14**, **16** and **18** (fig. 2). These derivatives can be viewed as structurally related to cyclobut A (**1**), carbovir (**2**) or (-)-neplanocin A (**3**).

Fig. 2



12: B=Adenin-9-yl
14: B=Guanin-9-yl

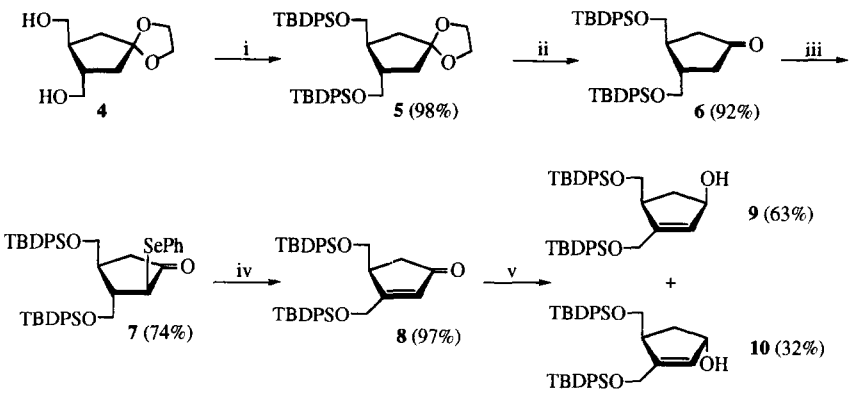


16: B=Adenin-9-yl
18: B=Guanin-9-yl

RESULTS AND DISCUSSION

Chemistry. As starting material the enantiomerically pure *(3R,4R)*-bis(hydroxymethyl)cyclo-pentanone ethylene glycol ketal (**4**)[26] was used (scheme 1). This compound was reacted with *t*-butyldiphenylsilyl chloride in dimethylformamide in the presense of imidazole to give **5** in 98% yield.[27] The ketal was hydrolyzed using a catalytic amount of *p*-toluenesulfonic acid in dioxane-water giving the ketone **6** in 92% yield. To introduce an olefinic bond between C-2 and C-3, compound **6** was reacted with lithium diisopropylamide and subsequently treated with phenylselenyl bromide to give the selenide **7** which was filtered through a pad of silica gel, concentrated and immediately reacted with hydrogen peroxide in dichloromethane to give the 2,3-unsaturated ketone **8** in 72% yield from **6**.[28,29] Selective reduction of the ketone function in **8** was accomplished in 95% yield using sodium borohydride-cerium trichloride in methanol-dichloromethane.[30] Separation of the two diastereomers by column chromatography yielded the allylic alcohols **9** and **10** in 63% and 32% yield, respectively. The stereoselectivity in the reduction can be rationalized from steric repulsion of the C-4 substituent which has a pseudo-equatorial orientation making the α-side sterically more accessible.

Scheme 1

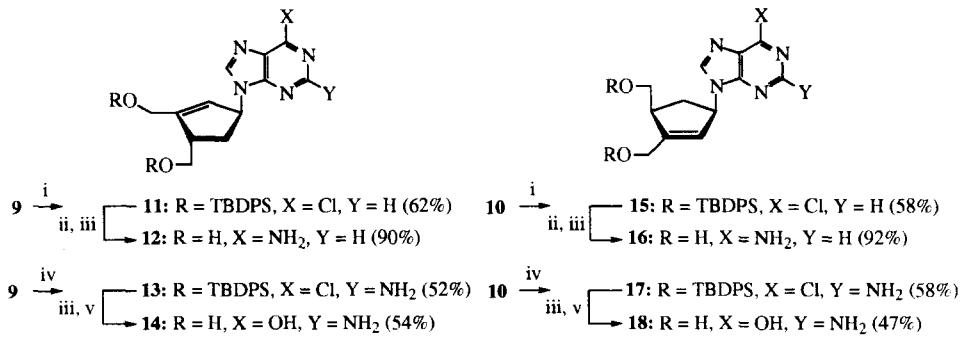


i: *t*-Butyldiphenylsilyl chloride, imidazole, DMF; **ii:** *p*TsOH, dioxane, H_2O, 50 °C; **iii:** LDA, phenylselenyl bromide, THF, -78 °C; **iv:** H_2O_2, CH_2Cl_2, 0 °C; **v:** $NaBH_4$, $CeCl_3$ x 7 H_2O, MeOH, CH_2Cl_2

Coupling of **9** and **10** with 6-chloropurine and with 2-amino-6-chloropurine, according to the Mitsunobu procedure,[31] gave diastereomeric mixtures, which could not be separated. Therefore a modified Mitsunobu reaction was developed in which the triphenylphosphine-diisopropyl azodicarboxylate (PPh_3-DIAD) complex in tetrahydrofuran was allowed to form at 0 °C. The mixture was cooled, and the alcohol and the purine were added at -78 °C. The temperature was raised and the reaction was left at 0 °C overnight giving **11**, **13**, **15** and **17** in 57-62% yield (scheme 2). No N-7 isomers were detected (NMR).

Compounds **12** and **16** were obtained in 90% and 92% yield, respectively, by ammonolysis of **11** and **15** in a sealed steel-vessel at 80 °C followed by desilylation using tetrabutylammonium fluoride in tetrahydrofuran.[32] Desilylation of **13** and **17** with tetrabutylammonium fluoride in tetrahydrofuran followed by treatment with 80% formic acid at 80 °C and by 25% ammonium hydroxide in methanol gave **14** and **18** in 54% and 47% yield respectively (scheme 2).[33]

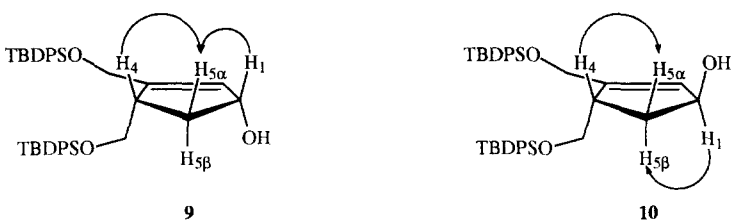
Scheme 2



i: 6-Chloropurine, Ph_3P-DIAD, THF, 0 °C; **ii:** NH_3, MeOH, dioxane, 80 °C; **iii:** $N(Bu)_4F$, THF; **iv:** 2-amino-6-chloropurine, Ph_3P-DIAD, THF, 0 °C; **v:** 80% HCO_2H, 80 °C then 25% NH_4OH, MeOH

Structure Assignments. Assignment of the configurations at C-1 in **9** and **10** were based on nOe (nuclear Overhauser effect) difference spectroscopy (fig 3). In both compounds the chemical shifts for H-5α and H-5β were well resolved. In compound **9** significant nOe's were found between H-1 and H-5α and between H-4 and H-5α and in compound **10** significant nOe's were found between H-1 and H-5β and between H-4 and H-5α.

Fig. 3



Biological Results. Compounds **12**, **14**, **16** and **18** were tested in an *in vitro* assay for HIV-1 RT inhibition[34] and in a XTT assay for anti HIV-1 and cytopathic effects.[35] Despite the structural similarities of these compounds to cyclobut A and carbovir, no anti-HIV activity of these compounds were found. These compounds will be further screened for biological activity.

EXPERIMENTAL SECTION

General procedures. All solvents were destilled prior to use. Thin layer chromatography was performed using silica gel 60 f-254 (Merck) plates with detection by UV and/or charring with 8% sulphuric acid. Column chromatography was performed on silica gel (Matrix Silica Si 60A, 35-70 m, Amicon). Organic phases were dried over anhydrous sodium sulphate. Concentrations were performed under reduced pressure. Optical rotations were recorded on a Perkin Elmer 241 polarimeter. NMR spectra were recorded on a JEOL GSX-270 instrument, shifts are given in ppm downfield from tetramethylsilane in $CDCl_3$ and CD_3OD, and from acetone (δ_H: 2.23, δ_C: 31.04) in D_2O.

(3*R*,4*R*)-Bis(*t*-butyldiphenylsilyloxymethyl)cyclopentanone ethylen glycol ketal (5). To an ice-cold solution of imidazole (2.60 g, 38.2 mmol) and (3*R*,4*R*)-bis(hydroxymethyl)cyclopentanone ethylen glycol ketal (**4**) (2.15 g, 11.4 mmol) in DMF (15 ml), *t*-butyldiphenylsilyl chloride (6.5 ml, 25.1 mmol) was added dropwise. The reaction mixture was stirred for 2 h at room temperature. Saturated aqueous $NaHCO_3$ (10 ml) was added and the mixture was extracted with toluene (2 x 25 ml). The organic layer was dried and concentrated and the residue purified by column chromatography ($CHCl_3$) to give **5** as a syrup (7.45 g, 98%), $[\alpha]_D$ +6.4° (c 1.04, $CHCl_3$); (Found: C, 73.79; H, 7.82. Calc. for $C_{41}H_{52}O_4Si_2$: C, 74.05; H, 7.88%); δ_H (270 MHz; $CDCl_3$) 1.00 (18 H, s, 6 CH_3), 1.78 (2 H, dd, CH_2), 1.96-2.14 (4 H, m, CH_2, 2 CH), 3.53 (2 H, d, CH_2OSi), 3.67 (2 H, dd, CH_2OSi), 3.86 (4 H, s, 2 OCH_2), 7.26-7.73 (20 H, m, 4 Ph); δ_C (67 MHz; $CDCl_3$) 19.2 (2 C-Si), 26.8 (6 CH_3), 39.1 (2 CH_2), 41.7 (2 CH), 64.2 (2 OCH_2), 66.7 (2 CH_2OSi), 116.7 (O-C-O), 127.6, 129.5, 133.8 and 135.6 (4 Ph).

(3*R*,4*R*)-Bis(*t*-butyldiphenylsilyloxymethyl)cyclopentanone (6). To a solution of compound **5** (7.45 g, 11.2 mmol) in dioxane (40 ml) and water (3 ml), *p*-toluene sulfonic acid (0.2 g) was added. The mixture was stirred for 2 h at 50 °C, then neutralized with saturated aqueous $NaHCO_3$ (5 ml). Water (30 ml) was added and the mixture extracted with $CHCl_3$ (2 x 40 ml). The organic layer was dried and concentrated. The product was purified by flash chromatography ($CHCl_3$) to give **6** as a colourless syrup (6.39 g, 92%), $[\alpha]_D$ +17.8° (c 1.52, $CHCl_3$); (Found: C, 75.3; H, 7.5. Calc. for $C_{39}H_{47}O_3Si_2$: C, 75.5; H, 7.6%); δ_H (270 MHz; $CDCl_3$) 1.00 (18 H, s, 6 CH_3), 2.19-2.48 (6 H, m, 2 CH_2, 2 CH), 3.57 (2 H, dd, CH_2OSi), 3.68 (2 H, dd, CH_2OSi), 7.29-7.77 (20 H, m, 4 Ph); δ_C (67 MHz; $CDCl_3$) 19.3 (2 C-Si), 26.9 (6 CH_3), 40.3 (2 CH_2), 41.6 (2 CH), 65.2 (2 CH_2OSi), 127.7, 129.7, 133.3 and 135.6 (4 Ph), 218.5 (C=O).

(3*R*,4*R*)-Bis(*t*-butyldiphenylsilyloxymethyl)-2-(phenylselenyl) cyclopentanone (7). To a solution of diisopropylamine (480 µl, 3.41 mmol) in THF (20 ml) under nitrogen at -78 °C was added dropwise *n*-butyllithium in hexane (1.7 ml, 1.6 M). The mixture was allowed to reach -20 °C before it was chilled to -78

°C again. Ketone **6** (1.51 g, 2.44 mmol) in THF (30 ml) was added dropwise during 1 h and the enolate was allowed to form while the reaction mixture reached -30 °C. Rechilled to -78 °C, phenylselenyl bromide (689 mg, 2.92 mmol) in THF (15 ml) was slowly added. After 5 min saturated aqueous NH_4Cl (5 ml) was added, and the mixture was allowed to warm to room temperature. Water (50 ml) was added and the mixture was extracted with Et_2O (2 x 50 ml). The organic layer was dried, evaporated and purified by column chromatography (toluene) to give **7** as a yellow syrup (1.40 g, 74%), which decomposed upon storage. δ_H (270 MHz; $CDCl_3$) 0.85 (9 H, s, 3 CH_3), 1.01 (9 H, s, 3 CH_3), 2.06-2.49 (4 H, m, CH_2, 2 CH), 3.41 and 3.60 (2 H, 2 dd, CH_2OSi, J=10.63, 3.66, 3.30 Hz), 3.53 and 3.83 (2 H, 2 dd, CH_2OSi, J=10.99, 2.75, 3.11 Hz), 3.84 (1 H, d, CH-Se, J=10.62 Hz), 7.12-7.64 (25 H, m, 5 Ph); δ_C (67 MHz; $CDCl_3$) 19.2 (C-Si), 19.3 (C-Si), 26.9 (6 CH_3), 38.0 (CH_2), 40.6 (CH), 45.5 (CH), 49.5 (CH-Se), 60.3 (CH_2OSi), 62.6 (CH_2OSi), 127.5, 127.6, 128.2, 128.3, 129.0, 129.7, 133.0, 133.1, 135.5 and 135.6 (5 Ph), 214.1 (C=O).

(3,4*R*)-Bis(*t*-butyldiphenylsilyloxymethyl)-2-cyclopentenone (8). To an ice-cold solution of 30% hydrogen peroxide (3.0 ml), selenyl **7** (1.40 g, 1.81 mmol) in CH_2Cl_2 (30 ml) was slowly added. The mixture was vigorously stirred for 15 min, washed with water (2 x 5 ml), dried and concentrated. The product was purified by column chromatography (hexane-EtOAc 10:1) to give compound **8** as a bright yellow syrup (1.08 g, 97%), $[\alpha]_D$ -26.6° (c 0.62, $CHCl_3$); (Found: C, 75.5; H, 7.6. Calc. for $C_{39}H_{46}O_3Si_2$ C, 75.6; H, 7.5%); δ_H (270 MHz; $CDCl_3$; TMS) 0.91 (9 H, s, 3 CH_3), 1.05 (9 H, s, 3 CH_3), 2.17 and 2.49 (2 H, 2 dd, H-5), 2.92 (1 H, m, H-4), 3.58 (2 H, ddd, CH_2OSi), 4.40 and 4.72 (2 H, 2 d, CH_2OSi), 6.43 (1 H, s, H-2), 7.13-7.70 (20 H, m, 4 Ph); δ_C (67 MHz; $CDCl_3$; TMS) 19.0 (C-Si), 19.2 (C-Si), 26.7 (6 CH_3), 38.9 (CH_2), 43.3 (CH), 63.4 (CH_2OSi), 64.8 (CH_2OSi), 127.7, 127.8, 129.8, 129.9, 132.8 and 135.5 (Ph), 129.6 (CH=), 181.8 (C=); 207.7 (C=O).

(3,4*S*)-Bis(*t*-butyldiphenylsilyloxymethyl)-2-cyclopenten-1*R*-ol (9) and (3,4*S*)-Bis(*t*-butyldiphenylsilyloxymethyl)-2-cyclopenten-1*S*-ol (10). To a mixture of the 2,3-unsaturated ketone **8** (1.08g, 1.75 mmol) in MeOH (2 ml) and CH_2Cl_2 (2 ml), $CeCl_3$ x 7 H_2O (651 mg, 1.75 mmol) was added. When dissolved, $NaBH_4$ (66.2 mg, 1.75 mmol) was added in portions during 2 min. After 5 min the mixture was neutralized with 0.5 M HCl (3 drp), washed with water (2 x 5 ml), dried, concentrated and purified by column chromatography (toluene-EtOAc 10:1) to give the diastereomers separated as colourless syrups **9** (694 mg, 63%) and **10** (346 mg, 32%). **9**; $[\alpha]_D$ -10.6° (c 0.825, $CHCl_3$); (Found: C, 75.5; H, 7.9. Calc. for $C_{39}H_{48}O_3Si_2$: C, 75.4; H, 7.8%); δ_H (270 MHz; $CDCl_3$) 0.95 (9 H, s, 3 CH_3), 1.05 (9 H, s, 3 CH_3), 1.63 (1 H, d, OH), 2.42 (1 H, ddd, H-5$_\alpha$, J=12.1, 8.7 and 7.0 Hz), 2.48 (1 H, d, H-5$_\beta$, J=12.1 Hz), 2.68 (1 H, m, H-4), 3.52 (2 H, dd, CH_2OSi), 4.14 and 4.33 (2 H, 2 d, CH_2OSi), 4.64 (1 H, m, H-1), 6.02 (1 H, s, H-2), 7.25-7.76 (20 H, m, 4 Ph); δ_C (67 MHz; $CDCl_3$) 19.2 (C-Si), 19.3 (C-Si), 26.8 (3 CH_3), 26.9 (3 CH_3), 38.2 (C-5), 45.9 (C-4), 61.9 (CH_2OSi), 64.7 (CH_2OSi), 75.0 (C-1), 127.7, 127.8, 129.7, 129.8, 132.9, 133.5, 135.5 and 135.6 (4 Ph), 129.4 (C-2), 147.8 (C-3). **10**; $[\alpha]_D$ -22.8° (c 0.65, $CHCl_3$); (Found: C, 75.5; H, 7.9. Calc. for $C_{39}H_{48}O_3Si_2$: C, 75.4; H, 7.8%); δ_H (270 MHz; $CDCl_3$) 0.91 (9 H, s, 3 CH_3), 1.05 (9 H, s, 3 CH_3), 1.46 (1 H, br, OH), 1.82 (1 H, ddd, H-5$_\alpha$, J=13.9, 8.2 and 3.6 Hz), 2.06 (1 H, ddd, H-5$_\beta$, J=13.9, 7.1 and 4.5 Hz), 2.93 (1 H, m, H-4), 3.5 (2 H, d, CH_2OSi), 4.22 and 4.41 (2 H, 2 d, CH_2OSi), 4.75 (1 H, m, H-1), 5.88 (1 H, s, H-2), 7.20-7.74 (20 H, m, 4 Ph); δ_C (67 MHz; $CDCl_3$) 19.1 (C-Si), 19.2 (C-Si), 26.7 (3 CH_3), 26.8 (3 CH_3),

38.5 (C-5), 46.6 (C-4), 62.4 (CH_2OSi), 66.3 (CH_2OSi), 76.1 (C-1), 127.6, 127.7, 129.6, 133.6, and 135.5 (4 Ph), 128.3 (C-2), 150.0 (C-3).

6-Chloro-9-[3',4'*S*-bis(*t*-butyldiphenylsilyloxymethyl)-2'-cyclopenten-1'*S*-yl]-9*H*-purine (11). To a solution of triphenylphosphine (260 mg, 0.99mmol) in THF (6 ml) under argon at 0 °C was added diisopropyl azodicarboxylate (DIAD, 195 ml, 0.99 mmol) over a period of 30 min. The solution was stirred for 40 min to yield a white precipitate of triphenylphosphine-DIAD complex. The mixture was cooled to -78 °C, and a suspension of 6-chloropurine (153 mg, 0.99 mmol) and alcohol **9** (409 mg, 0.66 mmol) in THF (3 ml) was added and allowed to stirr at 0 °C for 20 h. The mixture was concentrated and the product purified by column chromatography (toluene-EtOAc 3:1) to give **11** (312 mg, 62%); δ_H (270 MHz; $CDCl_3$) 0.96 (9 H, s, 3 CH_3), 1.07 (9 H, s, 3 CH_3), 2.07 (1 H, ddd, H-5'$_\alpha$, J=13.9, 8.4 and 4.2 Hz), 2.52 (1 H, ddd, H-5'$_\beta$, J=13.9, 8.1 and 5.4 Hz), 3.08 (1 H, m, H-4'), 3.62 (2 H, d, CH_2OSi), 4.34 and 4.52 (2 H, 2 d, CH_2OSi), 5.81 (1 H, m, H-1'), 5.95 (1 H, s, H-2'), 7.25-7.69 (20 H, m, 4 Ph), 7.97 (1 H, s, H-8), 8.72 (1 H, s, H-2); δ_C (67 MHz; $CDCl_3$) 19.1 (C-Si), 19.2 (C-Si), 26.8 (6 CH_3), 36.5 (C-5'), 47.0 (C-4'), 59.3 (C-1'), 62.2 (CH_2OSi), 65.3 (CH_2OSi), 122.4 (C-2'), 127.7, 127.8, 129.8, 129.9, 133.2, 135.4 and 135.5 (4 Ph), 132.0 (C-5), 143.4 (C-3'), 150,8 (C-4), 151.5 (C-6), 151.7 (C-8), 154.1 (C-2).

6-Amino-9-[3',4'*S*-bis(hydroxymethyl)-2'-cyclopenten-1'*S*-yl]-9*H*-purine (12). Compound **11** (312 mg, 0.41mmol) was dissolved in dioxane (3 ml) and treated with saturated methanolic ammonia (18 ml) in a sealed steel-vessel at 80 °C. After 18 h the mixture was concentrated and purified by column chromatography ($CHCl_3$-MeOH 20:1) to give 6-amino-9-[3',4'*S*-bis(*t*-butyldiphenylsilyloxymethyl)-2'-cyclopenten-1'*S*-yl]-9*H*-purine in 95% yield; δ_H (270 MHz; $CDCl_3$) 6.43 (2 H, s, NH_2). This compound (287 mg, 0.39 mmol) was dissolved in THF (3 ml) and a 1.1 M solution of QF in THF (0.74 ml) was added. After stirring for 2 h at room temperature the mixture was concentrated and the desilylated product was first purified by column chromatography ($CHCl_3$-MeOH 3:1), then it was passed through a pad of Dowex 50 WX 8 (Na^+) and finally purified on a Sephadex G-10 column to give **12** as a white solid (96 mg, 90%), $[\alpha]_D$ -30.9° (c 0.66, H_2O); (Found: C, 54.91; H, 5.79; N, 26.46. Calc. for $C_{12}H_{15}O_2N_5$: C, 55.16; H, 5.79; N, 26.80%); δ_H (270 MHz; D_2O) 2.13 (1 H, ddd, H-5'$_\alpha$, J=13.9, 8.5 and 4.4 Hz), 2.48 (1 H, ddd, H-5'$_\beta$, J=13.9, 8.3 and 5.1 Hz), 3.16 (1 H, m, H-4'), 3.71 (2 H, dd, CH_2OH), 4.33 (2 H, d, CH_2OH), 5.54 (1 H, m, H-1'), 5.92 (1 H, s, H-2'), 8.02 (1 H, s, H-8), 8.11 (1 H, s, H-2); δ_C (67 MHz; D_2O) 36.4 (C-5'), 47.1 (C-4'), 59.8 (C-1'), 61.0 (CH_2OH), 63.3 (CH_2OH), 119.1 (C-5), 124.5 (C-2'), 140.6 (C-3'), 148.6 (C-4), 152.1 (C-8), 152.6 (C-2), 155.6 (C-6).

2-Amino-6-chloro-9-[3',4'*S*-bis(*t*-butyldiphenylsilyloxymethyl)-2'-cyclopenten-1'*S*-yl]-9*H*-purine (13). To a solution of triphenylphosphine (173 mg, 0.66 mmol) in THF (5 ml) under argon at 0 °C was added diisopropyl azodicarboxylate (DIAD, 130 ml, 0.66 mmol) over a period of 30 min. The solution was stirred for 40 min to yield a white precipitate of triphenylphosphine-DIAD complex. The mixture was cooled to -78 °C, and a suspension of 2-amino-6-chloropurine (112 mg, 0.66 mmol) and alcohol **9** (273 mg, 0.44 mmol) in THF (2 ml) was added and allowed to stirr at 0 °C for 20 h. The mixture was concentrated and the product purified by column chromatography (toluene-EtOAc 2:1) to give **13** (194 mg, 57%); δ_H (270 MHz; MeOD) 0.95 (9 H, s, 3 CH_3), 1.05 (9 H, s, 3 CH_3), 2.03 (1 H, ddd, H-5'$_\alpha$, J=13.9, 8.4 and 4.2 Hz), 2.43 (1 H, ddd, H-

5'β, J=13.9, 8.3 and 5.3 Hz), 3.04 (1 H, m, H-4'), 3.60 (2 H, d, CH_2OSi), 4.31 and 4.49 (2 H, 2 d, CH_2OSi), 5.23 (2 H, s, NH_2), 5.59 (1 H, m, H-1'), 5.91 (1 H, s, H-2'), 7.18-7.69 (20 H, m, 4 Ph), 7.75 (1 H, s, H-8), δ_C (67 MHz; MeOD) 19.1 (C-Si), 19.2 (C-Si), 26.8 (6 CH_3), 36.4 (C-5'), 47.0 (C-4'), 58.5 (C-1'), 62.2 (CH_2OSi), 65.5 (CH_2OSi), 122.9 (C-2'), 125.6 (C-5) 127.7, 127.8, 129.8, 129.9, 133.1, 133.2, 135.4 and 135.5 (4 Ph), 140.6 (C-3'), 151.0 (C-6), 153.4 (C-4), 153.5 (C-2), 158.9 (C-8).

2-Amino-9-[3',4'*S*-bis(hydroxymethyl)-2'-cyclopenten-1'*S*-yl]-9*H*-purine-6(1*H*)-one (14). Compound **13** (194 mg, 0.25 mmol) was dissolved in THF (2 ml) and a 1.1 M solution of QF in THF (0.45 ml) was added. After stirring for 2 h at room temperature the mixture was concentrated and purified by column chromatography ($CHCl_3$-MeOH 10:1) to give 2-amino-6-chloro-9-[3',4'*S*-bis(hydroxymethyl)-2'-cyclopenten-1'*S*-yl]-9*H*-purine in 94% yield (checked by ^{1}H-NMR). This compound (69 mg, 0.23 mmol) was dissolved in 80% HCO_2H (3 ml) and stirred at 80 °C for 2 h. The mixture was concentrated and dissolved in MeOH (3 ml) and 25% NH_4OH (0.5 ml). After stirring for 2 h the mixture was concentrated and the residue was first purified by column chromatrography ($CHCl_3$-MeOH 3:1), then passed through a pad of Dowex 50 WX 8 (Na^+) and finally purified on a Sephadex G-10 column to give **14** as a white solid (37 mg, 54%), $[\alpha]_D$ -20.1° (c 0.40, H_2O); (Found: C, 51.67; H, 5.32; N, 24.99. Calc. for $C_{12}H_{15}O_3N_5$: C, 51.98; H, 5.45; N, 25.26%); δ_H (270 MHz; D_2O) 2.15 (1 H, ddd, H-5'α, J=13.9, 8.4 and 4.0 Hz), 2.46 (1 H, ddd, H-5'β, J=13.9, 8.4 and 5.5 Hz), 3.19 (1 H, m, H-4'), 3.70 (2 H, dd, CH_2OH), 4.32 (2 H, d, CH_2OH), 5.46 (1 H, m, H-1'), 5.87 (1 H, s, H-2'), 7.76 (1 H, s, H-8), δ_C (67 MHz; D_2O) 36.5 (C-5'), 47.2 (C-4'), 59.5 (C-1'), 60.0 (CH_2OH), 63.3 (CH_2OH), 116.9 (C-5), 125.1 (C-2'), 138.6 (C-3'), 152.1 (C-4), 152.2 (C-8), 154.1 (C-2), 159.9 (C-6).

6-Chloro-9-[3',4'*S*-bis(*t*-butyldiphenylsilyloxymethyl)-2'-cyclopenten-1'*R*-yl]-9*H*-purine (15). To a solution of triphenylphosphine (176 mg, 0.47 mmol) in THF (5 ml) under argon at 0 °C was added diisopropyl azodicarboxylate (DIAD, 132 ml, 0.67 mmol) over a period of 30 min. The solution was stirred for 40 min to yield a white precipitate of triphenylphosphine-DIAD complex. The mixture was cooled to -78 °C, and a suspension of 6-chloropurine (104 mg, 0.67 mmol) and alcohol **10** (279 mg, 0.45 mmol) in THF (2 ml) was added and allowed to stirr at 0 °C for 20 h. The mixture was concentrated and the product purified by column chromatography (toluene-EtOAc 3:1) to give **15** (197 mg, 58%); δ_H (270 MHz; $CDCl_3$) 0.95 (9 H, s, 3 CH_3), 1.07 (9 H, s, 3 CH_3), 1.71 (1 H, dt, H-5'β, J=13.2, and 6.2 Hz), 2.83 (1 H, dt, H-5'α, J=13.2, and 8.4 Hz), 2.91 (1 H, m, H-4'), 3.54 (2 H, dd, CH_2OSi), 4.34 and 4.57 (2 H, 2 d, CH_2OSi), 5.72 (1 H, m, H-1'), 5.91 (1 H, s, H-2'), 7.23-7.71 (20 H, m, 4 Ph), 8.08 (1 H, s, H-8), 8.72 (1 H, s, H-2); δ_C (67 MHz; $CDCl_3$) 19.1 (C-Si), 19.2 (C-Si), 26.8 (6 CH_3), 35.7 (C-5'), 47.3 (C-4'), 58.7 (C-1'), 62.3 (CH_2OSi), 65.3 (CH_2OSi), 122.3 (C-2'), 127.7, 127.8, 129.8, 129.9, 133.1, 133.2, 135.4 and 135.5 (4 Ph), 132.0 (C-5), 143.4 (C-3'), 150,8 (C-4), 151.5 (C-6), 151.7 (C-8), 153.5 (C-2).

6-Amino-9-[3',4'*S*-bis(hydroxymethyl)-2'-cyclopenten-1'*R*-yl]-9*H*-purine (16). Compound **15** (197 mg, 0.26 mmol) was dissolved in dioxane (2 ml) and treated with saturated methanolic ammonia (15 ml) in a sealed steel-vessel at 80 °C. After 18 h the mixture was concentrated and purified by column chromatography ($CHCl_2$-MeOH 20:1) to give 6-amino-9-[3',4'*S*-bis(*t*-butyldiphenylsilyloxymethyl)-2'-cyclopenten-1'*R*-yl]-9*H*-purine in 96% yield; δ_H (270 MHz; $CDCl_3$) 6.03 (2 H, s, NH_2). This compound (184 mg, 0.25 mmol) was

dissolved in THF (2 ml) and a 1.1 M solution of QF in THF (0.45 ml) was added. After stirring for 2 h at room temperature the mixture was concentrated and the desilylated product was first purified by column chromatography ($CHCl_3$-MeOH 3:1), then passed through a pad of Dowex 50 WX 8 (Na^+) and finally purified on a Sephadex G-10 column to give **16** as a white solid (66 mg, 92%), $[\alpha]_D$ -25.8° (c 0.66, H_2O); (Found: C, 55.09; H, 5.75; N,26.39. Calc. for $C_{12}H_{15}O_2N_5$: C, 55.16; H, 5.79; N, 26.80%); δ_H (270 MHz; D_2O) 1.72 (1 H, dt, H-5'β, J=13.9 and 5.1 Hz), 2.83 (1 H, dt, H-5'α, J=13.9 and 8.8 Hz), 3.01 (1 H, m, H-4'), 3.64 (2 H, d, CH_2OH), 4.29 and 4.40 (2 H, 2 d, CH_2OH), 5.40 (1 H, m, H-1'), 5.88 (1 H, s, H-2'), 7.99 (1 H, s, H-8), 8.00 (1 H, s, H-2); δ_C (67 MHz; D_2O) 35.7 (C-5'), 47.3 (C-4'), 59.6 (C-1'), 60.0 (CH_2OH), 63.1 (CH_2OH), 119.1 (C-5), 124.3 (C-2'), 140.9 (C-3'), 148.7 (C-4), 152.2 (C-8), 152.6 (C-2), 155.7 (C-6).

2-Amino-6-chloro-9-[3',4'*S*-bis(*t*-butyldiphenylsilyloxymethyl)-2'-cyclopenten-1'*R*-yl]-9*H*-purine (17). To a solution of triphenylphosphine (149 mg, 0.57 mmol) in THF (5 ml) under argon at 0 °C was added diisopropyl azodicarboxylate (DIAD, 112 ml, 0.57 mmol) over a period of 30 min. The solution was stirred for 40 min to yield a white precipitate of triphenylphosphine-DIAD complex. The mixture was cooled to -78 °C, and a suspension of 2-amino-6-chloropurine (97 mg, 0.57 mmol) and alcohol **10** (236 mg, 0.38 mmol) in THF (2 ml) was added and allowed to stirr at 0 °C for 20 h. The mixture was concentrated and the product purified by column chromatography (toluene-EtOAc 2:1) to give **17** (155 mg, 58%); δ_H (270 MHz; MeOD) 0.87 (9 H, s, 3 CH_3), 1.05 (9 H, s, 3 CH_3), 1.64 (1 H, dt, H-5'β, J=13.3, 6.6 Hz), 2.73 (1 H, dt, H-5'α, J=13.3 and 8.4 Hz), 2.87 (1 H, m, H-4'), 3.55 (2 H, dd, CH_2OSi), 4.31 and 4.55 (2 H, 2 d, CH_2OSi), 5.36 (2 H, s, NH_2), 5.51 (1 H, m, H-1'), 5.86 (1 H, s, H-2'), 7.23-7.74 (20 H, m, 4 Ph), 7.76 (1 H, s, H-8), δ_C (67 MHz; MeOD) 19.1 (C-Si), 19.2 (C-Si), 26.8 (6 CH_3), 35.7 (C-5'), 47.3 (C-4'), 58.0 (C-1'), 62.4 (CH_2OSi), 65.5 (CH_2OSi), 122.7 (C-2'), 125.9 (C-5) 127.7, 127.8, 129.8, 129.9, 133.1, 133.2 and 135.4 (4 Ph), 140.5 (C-3'), 152.7 (C-6) , 152.8 (C-4), 153.4 (C-2), 159.0 (C-8).

2-Amino-9-[3',4'*S*-bis(hydroxymethyl)-2'-cyclopenten-1'*R*-yl]-9*H*-purine-6(1*H*)-one (18). Compound **17** (155 mg, 0.22 mmol) was dissolved in THF (2 ml) and a 1.1 M solution of QF in THF (0.4 ml) was added. After stirring for 2 h at room temperature the mixture was concentrated and purified by column chromatography ($CHCl_3$-MeOH 10:1) to give 2-amino-6-chloro-9-[3',4'*S*-bis(hydroxymethyl)-2'-cyclopenten-1'*R*-yl]-9*H*-purine in 91% yield (checked by ^{1}H-NMR). This compound (56 mg, 0.20 mmol) was dissolved in 80% HCO_2H (3 ml) and stirred at 80 °C for 2 h. The mixture was concentrated and dissolved in MeOH (3 ml) and 25% NH_4OH (0.5 ml). After stirring for 2 h the mixture was concentrated and the residue was first purified by column chromatrography ($CHCl_3$-MeOH 3:1), then passed through a pad of Dowex 50 WX 8 (Na^+) and finally purified on a Sephadex G-10 column to give **18** as a white solid (29 mg, 47%), $[\alpha]_D$ -12.8° (c 0.25, H_2O); (Found: C, 51.75; H, 5.35; N,25.08. Calc. for $C_{12}H_{15}O_3N_5$: C, 51.98; H, 5.45; N, 25.26%); δ_H (270 MHz; D_2O) 1.78 (1 H, dt, H-5'β, J=13.9 and 5.1 Hz), 2.85 (1 H, dt, H-5'α, J=13.9 and 8.8 Hz), 3.01 (1 H, m, H-4'), 3.67 (2 H, dd, CH_2OH), 4.27 and 4.37 (2 H, 2 d, CH_2OH), 5.41 (1 H, m, H-1'), 5.86 (1 H, s, H-2'), 7.82 (1 H, s, H-8), δ_C (67 MHz; D_2O) 35.7 (C-5'), 47.3 (C-4'), 59.2 (C-1'), 60.0 (CH_2OH), 63.2 (CH_2OH), 117.5 (C-5), 124.9 (C-2'), 140.3 (C-3'), 150.3 (C-4), 151.6 (C-8), 154.6 (C-2), 159.7 (C-6).

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