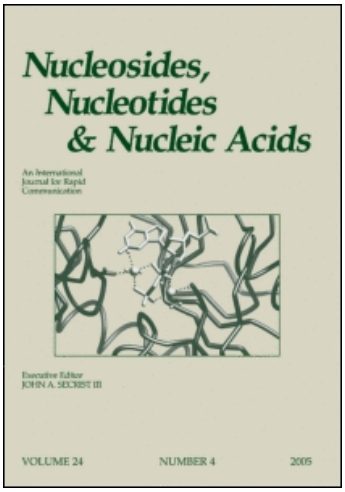

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PHOTOCHEMICAL SYNTHESIS OF NOVEL DIDEOXYNUCLEOSIDES

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PHOTOCHEMICAL SYNTHESIS OF NOVEL DIDEOXYNUCLEOSIDES

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ABSTRACT

A series of 2′,3′-dideoxynucleosides based on the apiose family was prepared from photochemical ring-expansion of a common cyclobutanone precursor. The starting ketone, (±) 3-[2′-(benzoyloxy)ethyl]-2,2-dimethylcyclobutanone (**12**) was prepared from commercially available (±)α-pinene. Since the optically pure antipodes of α-pinene are also commercially available, these nucleosides can be prepared optically pure using the identical procedure.

INTRODUCTION

The prominent role of nucleosides as antiviral and antitumor agents is well established (1). Modified nucleosides are known to interfere with DNA (or RNA) replication processes. The fact that many 2′,3′-dideoxynucleosides have been shown to act as inhibitors of the human immunodeficiency virus (HIV), responsible for acquired immune deficiency syndrome (AIDS), is of specific interest. Many of these phosphorylated derivatives act as DNA chain terminators due to the absence of the 3′-OH function (2). An interesting class of nucleoside analogues are those belonging to the apiose family. These nucleosides are related in structure to 9-(β-D-apio-D-furanosyl) adenine (**1**), a biologically active,[1] relatively non-toxic nucleoside in which the sugar moiety is based on D-apiose (3,4). This nucleoside analogue is

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[1]Nucleosides analogues related to natural D-apiose have been shown to inhibit lymphocyte proliferation and resist enzymatic deamination (3,4).

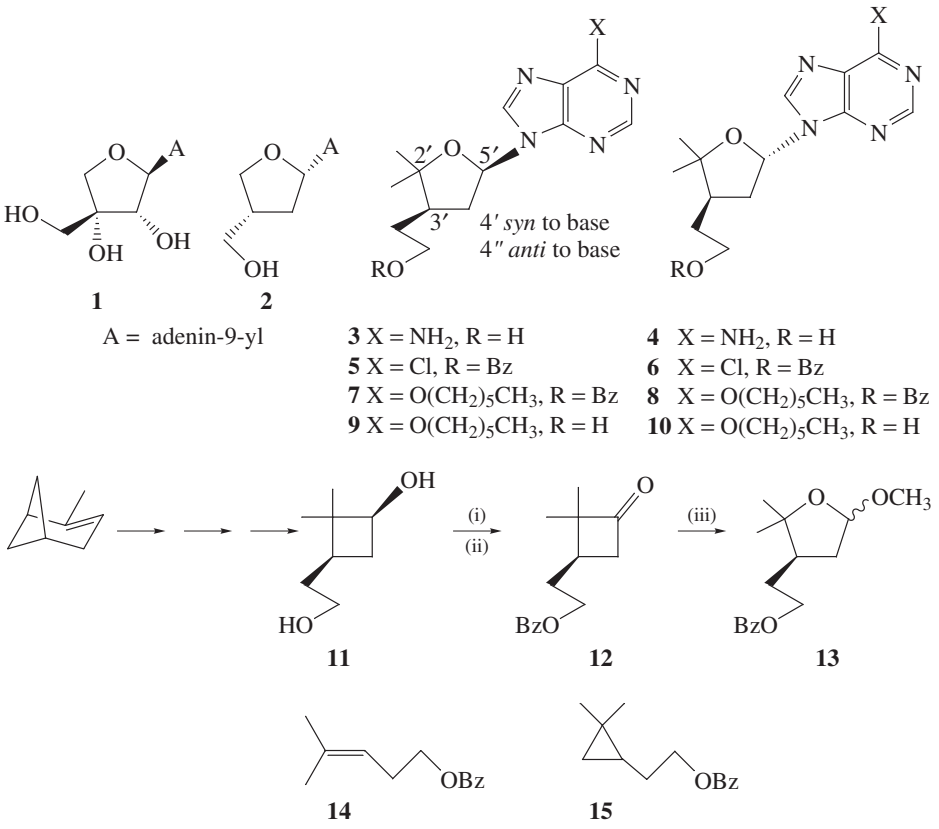
a regioisomer of adenosine via the transposition of the C-4′ hydroxymethyl to the C-3′ position.

Some of the dideoxygenated apio-adenosine analogues such as (1′(S), 3′(R))-(6-[2,3,4-trideoxy-3-hydroxymethyl]furanosyl) adenine (**2**) have been shown to possess potent anti-HIV activity in MT-4 cells with no apparent toxicity (5). Resistance to deamination by adenosine deaminase is exhibited by the isomeric nature of these compounds. Significant attention has also been directed towards the furanethanol derivatives (6). The presence of the primary alcohol function as part of an elongated chain can have interesting effects on cellular phosphorylation and anti-HIV activity (6). Furthermore, the addition of the methylene carbon adds a degree of hydrophobicity to the molecule, an important contributing factor in the delivery of potential prodrugs across cellular membranes. We describe the preparation of novel dideoxynucleosides based on the apiose family using a simple cyclobutanone photochemical ring-expansion sequence developed in our laboratory (7). The advantage of this method over more traditional ones is the availability of substituted cyclobutanones in both racemic and optically pure modifications (8). The photochemical ring-expansion of these ketones proceeds with stereochemical retention of the ring substitutents in the product ribosides and allows for the preparation of several modified nucleosides as potential antiviral and anticancer agents. The specific nucleosides described in this acticle are the *cis* and *trans* isomers of the apiose derivatives **3–10**. The additional two methyl substitutents should impart increased hydrophobicity rendering these nucleosides even more membrane permeable. Furthermore, the racemic modifications of **3–10** are desirable since both enantiomers can be screened for HIV inhibition. The employed synthetic procedure allows for the enantiospecific preparation of each antipode should any biological activity be observed for a racemic mixture.

RESULTS AND DISCUSSION

Cyclobutanones undergo photochemical ring expansion via an oxacarbene (7). Insertion of this carbene into OH and NH functional groups give 2-substituted tetrahydrofurans. The common precursors to nucleosides **3–10** is cyclobutanone **12** which was prepared in racemic form from racemic α-pinene via the known diol **11** (8) as shown in Scheme 1. Since both antipodes of α-pinene are commercially available, the optically pure enantiomer of cyclobutanone **12** could be prepared using the identical synthetic sequence as none of the steps involves epimerization at the stereogenic centers. Diol **11** was mono-benzoylated exclusively at the primary alcohol group. This mono-protected alcohol was subjected to Swern oxidation to give cyclobutanone **12** in 76% yield.

In order to assess the photochemical ring-enlargement reaction, ketone **12** was transformed to dihydrofuran **13** in 70% yield on irradiation in methylene chloride solutions containing methanol. A 1:1 anomeric mixture of the two acetals was obtained as evident from the acetal signals observed at δ 4.91–5.00 ppm in the ^{1}H-NMR spectrum of **13**. The cycloelimination (**14**) and decarbonylation (**15**)



i. BzCl/pyridine; ii. $(COCl)_2$, DMSO, CH_2Cl_2, $(C_2H_5)_3N$; iii. hυ/CH_3OH, CH_2Cl_2

products were also formed in 8.3 and 1.1% yields, respectively, and identified by comparison with authentic samples (9).

Irradiation of a 10^{-4} M solution of cyclobutanone **12** with 6-chloropurine (3 eq.) in acetonitrile solution resulted in the formation of the protected nucleosides **5** and **6** (64%) as the major photoproducts. The structures of the separated individual isomers were assigned based on the ^{1}H-NMR chemical shift values of the sugar ring and substituent protons (10). These protons are more deshielded in the *cis* stereochemistry relative to the purine base component. The more deshielded H-4′ proton assigned to the *syn* stereochemistry relative to the purine base is further deshielded in the *cis* isomer **5** relative to the *trans* isomer **6**. This is the result of the ring current effects associated with both contributions of the purine and the benzoate groups. The mass spectra of these photoproducts indicated the characteristic isotope signature pattern in the MH^+ and MH^- +2 mass fragments for chlorine (100:37). Deprotection and conversion of the 6-chloropurine unit to adenosine was accomplished in one step by reacting **5** or **6** in ammonia saturated methanol at 100°C in a sealed tube in yields of about 80%. The resultant nucleosides **3** and **4** were characterized individually by spectral and analytical data and in the case of the *cis* isomer **3** the X-ray crystal structure was determined

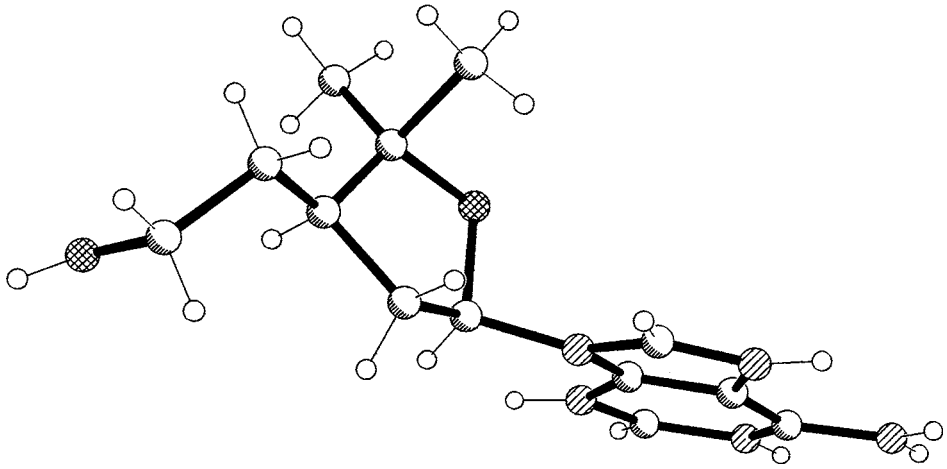


Figure 1. X-Ray crystal structure of nucleoside **3**.

(Figure 1) which confirmed the original stereochemical assignments of nucleosides **5** and **6**.

Nucleosides containing the 6-alkoxypurine as the base unit with the alkoxy substituent having a straight chain length of 6–7 carbon atoms exhibit significant anti-HIV activity (11). The 6-hexyloxypurine nucleosides **9** and **10** were prepared using a similar procedure. A solution of cyclobutanone **12** in dichloromethane containing 6-hexyloxypurine (11) was irradiated giving a mixture consisting of protected nucleosides **7** and **8** in 59% yield. Some stereoselectivity was observed with the *trans* isomer **8** predominating in a 3:2 ratio. The stereochemical assignments were based on relative chemical shifts of the tetrahydrofuran ring and the α-benzoyloxy methylene protons which are slightly more deshielded in the *cis* stereochemistry. The H-4′ (*syn* to the base) and H-4″ (*anti* to the base) were assigned by 2D-COSY (H, H) spectroscopy for both isomers (see Figure 2 for the *trans* isomer **8**). The more deshielded H-4′ proton signal absorbed at lower field (δ 2.87 ppm) for one of the isomers which was assigned the *cis* stereochemistry (vs δ 2.71 ppm for the H-4′ proton in the *trans* isomer). Further evidence for the stereochemical assignments came from NOE difference spectroscopy which showed a signal enhancement for the H-3′ proton (3%) upon irradiation of the H-4′ signal only in the case of isomer assigned the *trans* stereochemistry. This correlation is also seen in the NOESY spectrum for **8** (Figure 3) in which the proximity relationships are observed between the H-5′ (acetal,), H-4″ and the β-methylene protons of the hydroxyethyl substituents. Deprotection of **7** and **8** was accomplished by stirring each isomer in methanol saturated with ammonia with a yield of about 80%.

In summary, nucleosides **3**–**10** based on the apio-series were prepared from a common cyclobutanone precursor **12** by a photochemical ring-expansion. The nucleosides were prepared in racemic modification, however since the ketone **12** was ultimately prepared from α-pinene which is also commercially available in both

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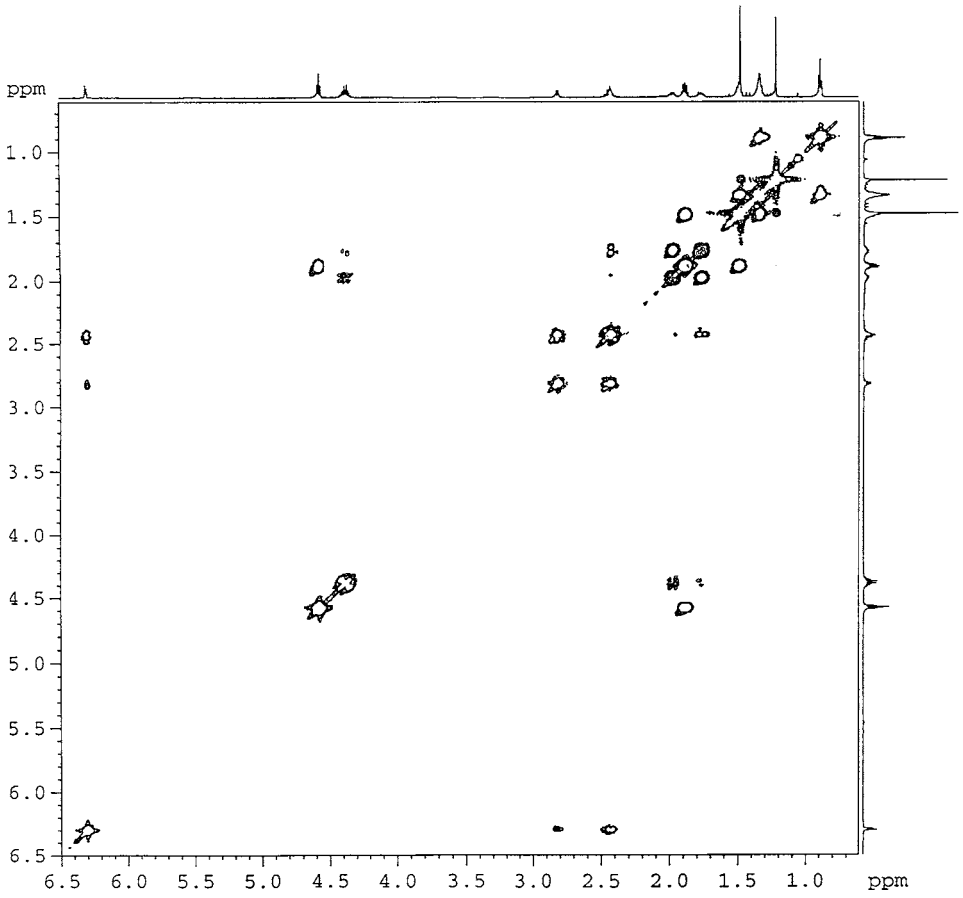

Figure 2. COSY (H,H) spectrum of nucleoside **8**.

enantiomerically pure forms, the identical synthetic sequence could be employed for the preparation of enantiomerically pure antipodes of nucleosides **3**–**10**. The racemic modification of nucleosides **3**, **4**, **9** and **10** are being screened for anti-HIV activity.

EXPERIMENTAL

Melting points (mp) were determined on a Reichert melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Pye Unicam SP3-200 spectrometer as thin films or KBr pellets, and NMR spectra were recorded on an ARX 400 MHZ superconducting Bruker NMR spectrometer in $CDCl_3$ solutions unless noted otherwise. The COSY (H, H) and NOESY 2D spectra were obtained using a Bruker 600 MHz Avance spectrometer. Mass spectra were obtained using a VG Micromass 16F spectrometer with ionization by electron impact or by liquid secondary ion MS (Isim) using 3-nitrobenzoic acid (3-NBA) as the matrix.

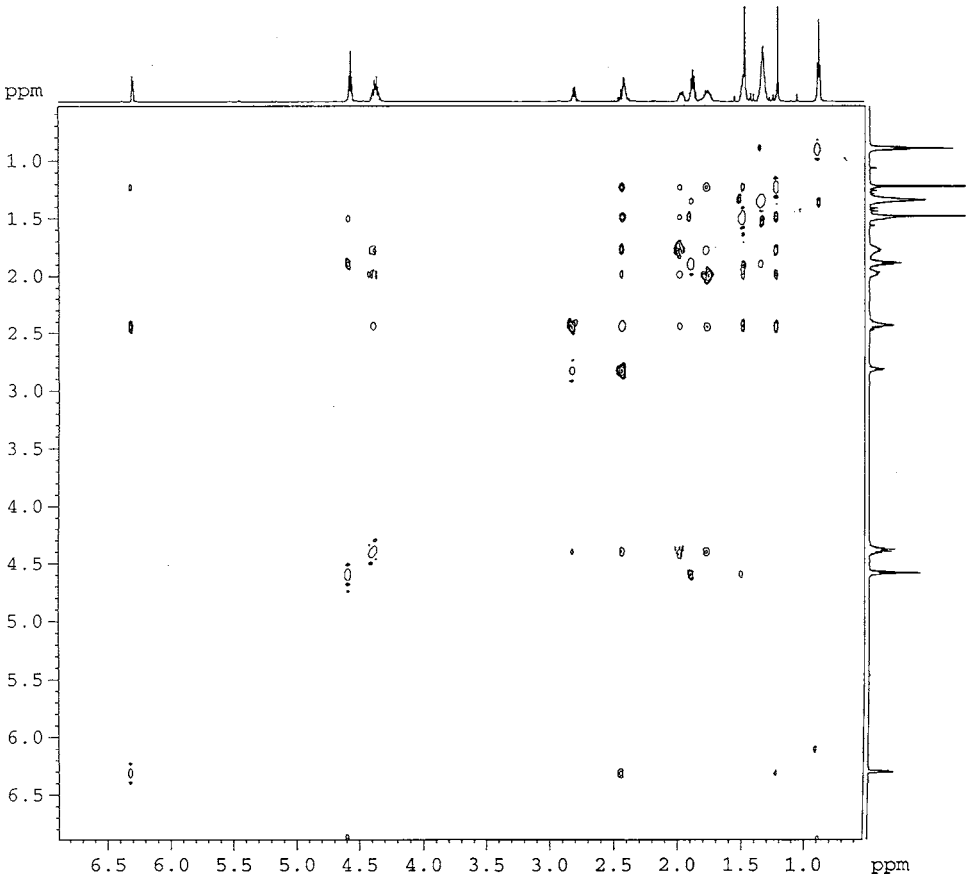

Figure 3. NOESY spectrum of nucleoside **8**.

Elemental analyses were performed by Guelph Chemical Laboratories Ltd. Preparative TLC was conducted using silica gel coated glass plate (750 μm thickness).

Photolyses were performed using a Hanovia 450-W medium pressure mercury arc lamp in a water-cooled quartz immersion well. Pyrex test tubes containing the samples were strapped around this well and the assembly immersed in an ice-water bath. These samples were degassed for 30 minutes with argon prior to irradiation, as well, argon balloons were used to maintain an inert atmosphere during the photolysis reactions.

All solvents used were dried and distilled according to standard procedures. Unless otherwise stated, precursor chemicals were obtained from Aldrich Chemical Company.

(±)-*cis*-3-[2-(Benzoyloxy)ethyl]-2,2-dimethylcyclobutan-1-ol

The racemic diol (±)-**11** (8), (9.4 g, 65.2 mmol), was added to a stirred solution of 118 mL dry pyridine, under argon. This stirred mixture was then cooled to 0°C

and 8.2 g (58.7 mmol, 0.9 equivalents) benzoyl chloride was added dropwise over a 30 min period. The reaction was mixed at ambient temperature for 24 h after which it was quenched by the addition of 10.0 mL H_2O followed by 30 min of additional stirring. The reaction mixture was concentrated by evaporation and then diluted with 300 mL CH_2Cl_2. The organic phase was then washed with successive portions of 3×50 mL H_2O, 3×50 mL $NaHCO_3$, 3×50 mL 1% HCl, and 2×50 mL H_2O. Evaporation of the solvent followed by flash column chromatography (6:1 hexane:ethyl acetate) gave 11.31 g, 45.7 mmol (70.0%) of the title compound as a clear oil. ^{1}H-NMR: δ 8.04-8.02 (d, 2H), 7.57-7.54 (t, 1H), 7.46-7.42 (t, 2H), 4.29-4.22 (m, 2H), 3.75 (dd, 1H), 2.39-2.14 (m, 1H), 1.88-1.50 (m, 5H), 1.09 (s, 3H), 0.99 (s, 3H). ^{13}C-NMR: δ 167, 133, 130, 131, 120, 128, 72, 64, 44, 35, 34, 29, 28, 15. IR (neat):3410 (OH), 2957, 2899, 2866, 1719 (CO benzoyl), 1275 cm^{-1}. MS *m/z* 249 (M + 1). Anal. Calculated for $C_{15}H_{20}O_{3.1/4}H_2O$: C, 71.26; H, 7.97. Found: C, 71.44; H, 8.45.

(±)-3-[2-(Benzoyloxy)ethyl]-2,2-dimethylcyclobutanone (12)

The title compound was prepared by a modified Swern oxidation (12). A solution of 1.25 mL (15 mmol) oxalyl chloride in 63.0 mL of dry CH_2Cl_2 was cooled using $CHCl_3$/dry ice, with constant stirring under argon. To this mixture, 2.0 g (25 mmol) DMSO in 12.5 mL dry CH_2Cl_2 was added over a 5 min period. After stirring the reaction for an additional 10 min, 2.5 g (10.1 mmol) of the mono-protected alcohol, prepared above, in 25.0 mL CH_2Cl_2, was promptly added over a 5 min period. After mixing for another 15 min, 7.0 mL TEA was added over a 5 min period, and the resulting mixture was allowed to warm to ambient temperature. The addition of 30 mL H_2O followed by 10 min of stirring allowed for the separation of the two phases. The organic phase was extracted with 2×50 mL portions of CH_2Cl_2. The CH_2Cl_2 extracts were combined and washed with successive portions of 2×50 mL 2% HCl, 1×50 mL H_2O, 1×50 mL sat. aq. $NaHCO_3$, and 1×50 mL sat. aq. NaCl. The organic phase was then dried over $MgSO_4$ and concentrated by evaporation. Purification by flash column chromatography (6.25:1 hexane:ethyl acetate) gave 1.9 g, 7.72 mmol (76.4%) of the title compound as a clear oil. ^{1}H-NMR: δ 8.05-8.03 (d, 2H), 7.58-7.55 (t, 1H), 7.47-7.43 (t, 2H), 4.40-4.35 (m, 2H), 3.24-3.18 (dd, 1H), 2.86-2.80 (dd, 1H), 2.23-2.10 (m, 2H), 1.91-1.85 (m, 1H), 1.22 (s, 3H), 1.15 (s, 3H). ^{13}C-NMR: δ 214, 167, 133, 130, 129.6, 128, 64, 61, 49, 33.6, 30, 23, 17. IR (neat): 2961, 2927, 2868, 1777 (CO), 1719 (CO benzoyl), 1275 cm^{-1}. MS *m/z* 246. Anal. Calculated for $C_{15}H_{18}O_3$:C, 73.14; H, 7.37. Found: C, 72.9; H, 7.8.

(±)-3-[2-(Benzoyloxy)ethyl]-2,2-dimethyl-5-methoxyoxolane, *cis* and *trans* isomers (13)

A solution consisting of (±)-cyclobutanone **12** (0.070 g, 0.285 mmol) and 6.0 mL methanol (freshly distilled from Na) in 65 mL dry CH_2Cl_2, was irradiated

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for 3 h. Evaporation of the solvent followed by preparative TLC (CH_2Cl_2:EtOAc, 24:1) gave 0.055 g, 0.198 mmol (69.5%) of the title compound as a ~1:1 anomeric mixture. ^{1}H-NMR: δ 8.05-8.03 (d, 2H), 7.57-7.55 (t, 1H), 7.47-7.43 (t, 2H), 5.00-4.91 (two m, 1H, acetal), 4.37-4.33 (m, 2H, BzOC**H$_2$**CH_2), 3.36-3.33 (two, s, 3H, methoxy), 2.56-2.28 (two m, 1H), 2.19-2.15, 1.90-1.87 (two m, 2H), 1.78-1.71 (m, 2H, BzOCH_2C**H$_2$**), 1.37, 1.29, 1.20, 1.08 (four s, 6H, methyl). IR (neat): 2972, 2935, 2898, 1720 (CO benzoyl), 1274, 1100, 1038 cm^{-1}. Anal. Calculated for $C_{16}H_{22}O_4$: C, 69.05; H, 7.97. Found: C, 69.3; H, 8.2.

(±)-3-[2-(Benzoyloxy)ethyl]-5-(6-chloropurin-9-yl)-2,2-dimethyloxolane (*cis*-5 & *trans*-6)

A solution of (±)-cyclobutanone **12** (0.070 g, 0.285 mmol) and 6-chloropurine (0.140 g, 0.906 mmol) in 65 mL dry CH_3CN was irradiated for 4 h. Evaporation of the solvent followed by flash column chromatography (15:1 CH_2Cl_2: EtOAc to elute non-polar photoproducts, followed by 15:2 CH_2Cl_2:EtOAc to elute protected nucleoside) gave 0.073 g, 0.181 mmol (63.5%) of the title compound as an anomeric mixture. 0.145 g of this mixture was further purified by preparative TLC (100:5 ether: EtOAc, 3 consecutive elutions) to give 0.074 g of the *trans* isomer (51%) and 0.071 g of the *cis* isomer (49%) as clear oils.

(±)-*cis*-isomer (5) ^{1}H-NMR: δ 8.72 (s, 1H), 8.34 (s, 1H), 8.05-8.03 (d, 2H), 7.60-7.57 (t, 1H), 7.47-7.44 (t, 2H), 6.29-6.26 (t, J = 6 Hz, 1H, H-5′ acetal), 4.45-4.39 (m, 2H, BzOC**H$_2$**CH_2), 3.03-2.98 (m, 1H, H-4′), 2.48-2.36 (m, 2H, H-4″ and H-3′), 2.03-1.99 (m, 1H, BzOCH_2C**H$_2$**), 1.84-1.78, (m, 1H, BzOCH_2C**H$_2$**), 1.45 (s, 3H), 1.32 (s, 3H). IR (neat): 2924, 2852, 1717, 1591, 1559, 1275 cm^{-1}). MS (Isim, 3-NBA) *m/z* 401 (MH^+), 403 ($MH^+ + 2$). Anal. Calculated for $C_{20}H_{21}N_4O_3Cl$: C, 59.93; H, 5.24; N, 13.98. Found: C, 59.5; H, 5.2; N, 14.2.

(±)-*trans*-isomer (6) ^{1}H-NMR: δ 8.65 (s, 1H), 8.29 (s, 1H), 7.99-7.98 (d, 2H), 7.60-7.56 (t, 1H), 7.46-7.42 (t, 2H), 6.31-6.29 (1H, H-5′ acetal), 4.45-4.33 (m, 2H, BzOC**H$_2$**CH_2), 2.89-2.86 (m, 1H, H-4′), 2.51-2.40 (m, 2H, H-4″ and H-3′), 2.00-1.97 (m, 1H, BzOCH_2C**H$_2$**), 1.81-1.76, (m, 1H, BzOCH_2C**H$_2$**), 1.48 (s, 3H), 1.23 (s, 3H). IR (neat): 2925, 2853, 1717, 1591, 1559, 1274 cm^{-1}). MS (sim, 3-NBA) *m/z* 401 (MH^+), 403 ($MH^+ + 2$), ratio 100:36.8 corresponding to ^{35}Cl: ^{37}Cl. Anal. Calculated for $C_{20}H_{21}N_4O_3Cl$: C, 59.93; H, 5.24; N, 13.98. Found: C, 59.8; H, 5.3; N, 14.1.

(±)-*cis*-9-[2,2-Dimethyl-3-(hydroxyethyl)-oxolan-5-yl]adenine (3)

A solution of (±)-*cis*-protected nucleoside **5** (0.039 g, 0.974 mmol) and 30.0 mL methanolic ammonia was placed in a thick walled glass tube. The reaction mixture was frozen with liquid N_2 and sealed in the tube under vacuum. The reaction vessel was then heated to 100°C for 24 h. After this period of time the tube

was cooled to −60.0°C ($CHCL_3$/dry ice) and cracked open. Solvent removal by evaporation followed by purification by TLC (1:9 CH_3OH:CH_2Cl_2) gave the target deprotected nucleoside 0.022 g, 0.0779 mmol (80.0%), as a white solid, mp 172-173°C. ^{1}H-NMR (DMSO) δ: 8.34 (s, 1H), 8.13 (s, 1H), 7.23 (s, 2H, amine), 6.14-6.12 (t, 1H, H-5′ acetal), 4.54-4.52 (t, 1H, OH), 3.52-3.40 (m, 2H, HOC**H$_2$**CH_2), 2.58-2.53 (m, 2H), 2.21-2.17 (m, 1H), 1.64-1.60 (m, 1H, $HOCH_2$C**H$_2$**), 1.50-1.44 (m, 1H, $HOCH_2$C**H$_2$**), 1.25 (s, 3H), 1.20 (s, 3H). IR (KBr): 3497, 3366, 3197 (OH), 2971, 2918, 2919 (NH_2), 1654, 1598, 1034 cm^{-1}. MS (Isim, 3-NBA) *m/z* 278 (MH^+). Anal. Calculated for $C_{13}H_{19}N_5O_2.^{2/3}H_2O$: C, 53.98; H, 7.04; N, 24.22. Found C, 53.9; H, 6.6; N, 23.9.

(±)-*trans*-9-[2,2-Dimethyl-3-(hydroxyethyl)-oxolan-5-yl]adenine (4)

The identical procedure was used as described for the preparation of the *cis*-nucleoside (±)-**6** giving 0.024 g, 0.0785 mmol (80.5%) of the target *trans*-nucleoside as a white solid, mp 145-146°C. ^{1}H-NMR (DMSO) δ: 8.18 (s, 1H), 8.12 (s, 1H), 7.23 (s, 2H, amine), 6.18-6.16 (d, J = 6.8 Hz, 1H, H-5′ acetal), 4.53-4.50 (t, 1H, OH), 3.49-3.43 (m, 2H, HOC**H$_2$**CH_2), 2.41-2.29 (m, 2H), 1.61-1.58 (m, 1H, $HOCH_2$C**H$_2$**), 1.30-1.32 (m, 1H, $HOCH_2$C**H$_2$**), 1.33 (s, 3H), 1.08 (s, 3H). IR (KBr): 3292, 3115, (OH) 2979, 2932, 2891 (NH_2), 1683, 1610, 1536, 1076 cm^{-1}. MS (Isim, 3-NBA) *m/z* 278 (MH^+). Anal. Calculated for $C_{13}N_5O_2$ $H_{19}.^{2/3}H_2O$: C, 53.98, H, 7.04; N, 24.22. Found C, 54.2; H, 7.2; N, 23.8.

6-Hexyloxypurine

In a 250 mL dry round bottom flask, 3.3 g (32 mmol) hexanol and 200 mL dry THF were cooled to 0°C under an inert atmosphere. To this stirred solution, 1.44 g (36 mmol) 60% mineral oil dispersion NaH was added. The resulting mixture was then heated to reflux for 2 h. After this period of time, the solution was cooled to 0°C and 1.0 g (6.47 mmol, 0.2 equivalents) 6-chloropurine was added. The reaction mixture was then heated to reflux for 24 h. After the reaction had completed, monitoring was accomplished using analytical TLC (2:1 ether: EtOAc), the solution was cooled to 0°C and quenched with 10 mL H_2O. The product was purified by adding 200 mL ether and washing the organic phase with successive portions of 1×100 mL 3% HCl, 2×100 mL H_2O and 1×100 mL sat. aq. NaCl. The organic phase was then dried over $MgSO_4$ and the solvent removed under reduced pressure. Further purification was afforded by recrystallization form CH_3CN, yielding 1.27 g, 5.76 mmol (90%) 6-hexyloxypurine as a white solid, mp 149-150 °C. The ^{1}H-NMR of this compound matched that of an authentic sample prepared by a literature procedure (11).

(±)-3-[2-(Benzoyloxy)ethyl]-5-(6-hexyloxypurin-9-yl)-2,2-dimethyloxolane (*cis*-7 & *trans*-8)

A solution of (±)-cyclobutanone **12** (0.070 g, 0.285 mmol) and 6-hexyloxypurine (0.126 g, 0.57 mmol) in 65 mL dry dichloromethane was placed in a Pyrex photolysis tube and irradiated for 4 h. Prior to the irradiation, this mixture was purged with argon for 0.5 h. After the photolysis, evaporation of the solvent followed by flash column chromatography (15:2 CH_2Cl_2: EtOAc) gave 0.078 g, 0.0165 mmol (58%) of the title compound as an anomeric mixture. A 0.154 g sample of this mixture was further purified by preparative TLC (100% diethyl ether) to give 0.098 g (64%) of the *trans* isomer and 0.055 g (36%) of the *cis* isomer as clear oils.

(±)-*cis*-isomer (7) ^{1}H-NMR ($CDCl_3$) δ:8.42 (s, 1H), 8.08 (s, 1H), 7.97-7.95 (d, 2H), 7.52-7.48 (t, 1H), 7.39-7.35 (t, 2H), 6.21-6.18 (t, 1H, H-5′, acetal), 4.53-4.49 (t, 2H,O**CH_2**$CH_2CH_2CH_2CH_2CH_3$), 4.34-4.21 (t, 2H, BzO**CH_2**-CH_2), 2.90-2.84 (m, 1H, H-4′), 2.35-2.29 (m, 2H, H-3′ and H-4″), 1.93-1.90 (m, 1H, BzOCH_2**CH_2**), 1.84-1.80 (m, 2H, OCH_2**CH_2**CH_2 $CH_2CH_2CH_3$) 1.76-1.73 (m, 1H, BzOCH_2**CH_2**), 1.44-1.40 (m, 2H, OCH_2CH_2**CH_2**$CH_2CH_2CH_3$), 1.36 (m, 3H, methyl), 1.29-1.25 (m, 4H, O$CH_2CH_2CH_2$**CH_2CH_2**CH_3), 1.24 (s, 3H, methyl) 0.83–0.80 (t, 3H, O$CH_2CH_2CH_2CH_2CH_2$**CH_3**); IR (neat): 1717 (CO) cm^{-1}. MS (lsim, 3-NBA) *m/z* 467 (MH^+). Anal. Calculated for $C_{26}H_{34}O_4N_4$: C, 66.93; H, 7.35; N, 12.02. Found C, 67.2; H; 7.5, N, 11.9.

(±)-*trans*-isomer (8) ^{1}H-NMR ($CDCL_3$) δ: 8.35 (s, 1H), 8.00 (s, 1H), 7.92-7.90 (d, 2H), 7.47-7.44 (t, 1H), 7.34-7.31 (t, 2H), 6.20-6.19 (d, 1H, H-5′, acetal), 4.49-4.46 (t, 2H, O**CH_2**$CH_2CH_2CH_2CH_2CH_3$), 4.30-4.25 (t, 2H, BzO**CH_2** CH_2), 2.72-2.71 (m, 1H, H-4′), 2.35-2.32 (m, 2H, H-3′and H-4″), 1.89-1.86 (m, 1H, BzOCH_2C**H_2**), 1.82-1.76 (m, 2H, OCH_2C**H_2**$CH_2CH_2CH_2CH_3$) 1.69-1.66 (m, 1H, BzOCH_2C**H_2**), 1.37 (m, 2H, OCH_2C**H_2**$CH_2CH_2CH_3$, and 3H, methyl), 1.25-1.22 (m, 4H, O$CH_2CH_2CH_2$C**H_2CH_2**CH_3), 1.11 (s, 3H, methyl), 0.8–0.77 (t, 3H,OCH_2 $CH_2CH_2CH_2CH_2$C**H_3**). IR (neat): 2959, 2933, 2871, 1718 (CO) 1599, 1456, 1274 cm^{-1}. MS (lsim, 3-NBA) *m/z* 467 (MH^+). Anal. Calculated for $C_{26}H_{34}O_4N_4$: C, 66.93; H, 7.35; N, 12.02. Found C, 67.3; H; 7.6, N, 11.7.

(±)-*cis*-9-[2,2-Dimethyl-3-(hydroxyethyl)-oxolan-5-yl]-6-hexyloxypurine (9)

A solution of the (±)-*cis*-protected nucleoside **7** (0.040 g, 0.086 mmol) and 30 mL methanolic ammonia was stirred at room temperature for 24 h. Solvent removal under reduced pressure followed by purification by TLC (1:15 CH_3OH: CH_2Cl_2) gave the target nucleoside, 0.023 g, 0.069 mmol (81%) as a clear oil. ^{1}H-NMR: δ: 8.49 (s, 1H), 8.12 (s, 1H), 6.25 (t, H-5,′ acetal), 4.58 (t, 2H, O**CH_2**CH_2CH_2 CH_2CH_3), 3.73 (m, 2H, OCH_2C**H_2**), 2.86 (m, 1H, H-4′), 2.32 (m, 2H, H-3′ and H-4″), 1.89 (m, 2H), 1.76–1.39 (m, 9H), 1.41 s, 3H), 1.28 (s 3H), 0.90 (t, 3H); IR (neat): 3450, 3310, (OH) cm^{-1}. MS (Isim, 3-NBA) *m/z* 363 (MH^+). Anal.

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Calculated for $C_{19}H_{30}O_3N_4 \cdot 1/2H_2O$: 61.46: H, 8.09; N, 15.09. Found C, 61.5; H, 8.5; N, 15.1.

(±)-*trans*-9-[2,2-Dimethyl-3-(hydroxyethyl)-oxolan-5-yl]-6-hexyloxypurine (10)

A solution of the (±)-*trans*-protected nucleoside **8** (0.060 g, 0.129 mmol) and 30 mL methanolic ammonia was stirred at room temperature for 24 h. Solvent removal under reduced pressure followed by purification by TLC (1:15 CH_3OH:CH_2Cl_2) gave the target nucleoside, 0.036 g, 0.103 mmol (80%) as a clear oil. ^{1}H-NMR: δ: 8.51 (s, 1H), 8.22 (s, 1H), 6.30 (t, H-5′, acetal), 4.58 (t, 2H), 3.75 (m, 2H), 2.80 (m, 1H, H-4′), 2.52 (br.s, 1H, OH) 2.37 (m, 2H), 1.90 (m, 2H), 1.45–1.30 (m, 8H), 1.50 (s, 3H), 1.27 (s, 3H), 0.90 (t, 3H); IR (neat): 3300 cm^{-1} (OH); MS (lsim, 3-NBA) *m/z* 363 (MH^+). Anal. Calculated for $C_{19}H_{30}O_3N_4 \cdot 1/2H_2O$: C, 61.46; H, 8.09; N, 15.09. Found C, 61.6; H, 8.6; N, 15.0.

X-ray Crystallography

Crystals of *cis*-(±)-9-[2,2-dimethyl-3-(hydroxyethyl)-oxolan-5-yl]adenine (**3**) were grown by evaporation from methanol under anhydrous conditions. X-ray diffraction data was collected on a Siemens R3/v diffractometer. The *cis* nucleoside (±) **3** was refined in triclinic Pi using 637 out of 1396 observed reflections. The structure was solved by Direct Methods followed by Fourier Synthesis. Final refinement was done using full-matrix least-squared procedures with isotropic thermal parameters on all non-hydrogen atoms. The hydrogen atoms were placed in idealized positions and refined isotropically using a riding model (C-H, 0.96 Å, $U_{11} = 0.08$ Å^2). This refinement gave a data/par ratio of 637/81 and an R value of 0.200.

The software used for the structural determination was the SHELX Plus (PC) Package (13). Prior to the application of Direct Methods, the default on TREF (i.e. in the initial instruction file) was changed to TREF 2000.

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