A Novel Approach toward the Synthesis of Chiral 2,3-Dideoxy Nucleosides and Their Carbocyclic Analogues[1]

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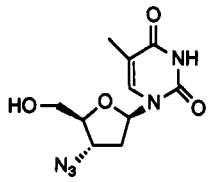
Photochemical ring-expansion of chiral 2(*S*),3(*R*)-bis[(benzoyloxy)methyl]cyclobutanone (**3**) in the presence of alcohols and acidic N–H functional groups gives anomeric mixtures of acetals and *N*-amino acetals, respectively, with retention of stereochemistry of the ring substituents. In the presence of purine and 6-chloropurine the corresponding protected nucleosides are obtained. The photoadduct with 6-chloropurine is converted to the known medicinally active deprotected adenine nucleoside with methanolic ammonia. One-carbon homologation of ketone **3** with diazomethane produces the corresponding optically pure cyclopentanone **8** with retention of stereochemistry. This ketone is converted to the optically pure cyclopentylamine **10** in two steps. Racemic amine **10** has been used as a key intermediate in the preparation of carbocyclic nucleosides.

Introduction

Modified nucleosides have occupied a central role in medicinal chemistry research with the recognition of their role in interfering with DNA replication processes. A number of 2′-deoxy- and 2′,3′-dideoxynucleosides have been shown to exhibit anticancer[2,8] and antiviral activity.[3] Of note is the activity of specific derivatives as inhibitors of human immunodeficiency virus (HIV) responsible for the etiology of acquired immune deficiency syndrome (AIDS).[4] For example, 3′-azido-3′-deoxythymidine (**1**, AZT) and 2′,3′-dideoxyinosine (**2**, ddI) have been approved by the US Food and Drug Administration for the treatment of AIDS.[5]



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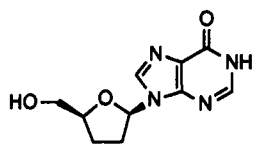

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Carbocyclic nucleoside analogues have been of interest in this area as well since it is known that replacing a furanose ring oxygen by carbon would increase the metabolic stability of these derivatives toward phosphorylase enzymes that cleave the glycosidic linkage of normal nucleosides. In recent years a number of synthetic methods have been described for the preparation of specific carbocyclic[6] and normal[7] 2′,3′-dideoxynucleosides as potential anti-HIV agents. Many of these syntheses are based on structural modifications of nucleosides[6] or sugar moieties not always conveniently accessible. Other synthetic methods involve the cyclization or annelation of chiral C-3[8] or C-4[9] open-chain fragments. A study of a ring-expansion of a four-membered chiral oxetane, oxetanocin, to produce a furanoside has been reported recently.[10] In view of the availability of cyclobutane derivatives[11] and their tendency to undergo ring-opening and ring-expansion reactions in a regio- and stereoselective manner,[12] we explored the possible use of cyclobutanones as starting materials in the synthesis of carbocyclic and ribosidic nucleosides. The impetus for this work is the increasing number of methods reported recently for the preparation of chiral cyclobutanones[11] and our observation of the photochemical insertion of transient cyclic oxacarbenes into N–H functions with formation of *N*-furanoside derivatives.[13] In this study we report the preparation of a series of 2′,3′-dideoxy-3(*S*)-*C*-hydroxymethyl nucleosides and their carbocyclic analogues using a photochemical ring-expansion for the former and a one-carbon ring expansion for the latter. The starting material for the divergent synthesis is the optically pure protected 2,3-bis(hydroxymethyl)cyclobutanone **3**[14] obtained by a modified literature procedure involving the stereospecific metal-catalyzed [2 + 2] cycloaddition of 1,1-dimenthyl fumarate with 1,1-dimethoxyethylene as the key step.[14] The use of two chiral auxiliary groups in the cycloaddition gives optically pure cycloadduct (>98% de). The photochemical ring-expansion and insertion of the cyclic oxacarbene into acidic N–H functions of nucleic acid bases would give 2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides, some of which have been shown to be very potent inhibitors

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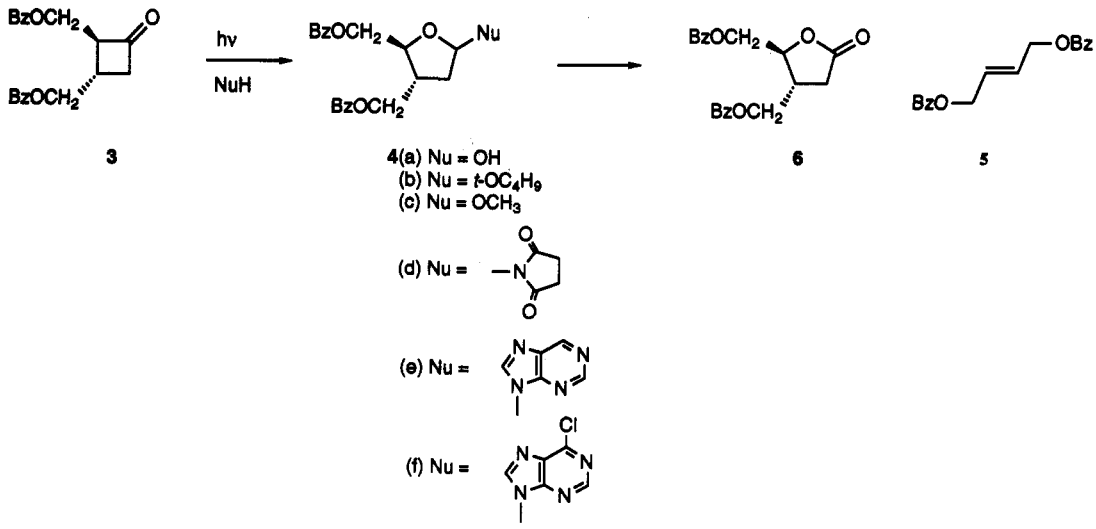

of HIV. Homologous ring-expansion of ketone **3** would give carbocyclic analogues of 2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides (Nucleoside numbering system is retained in the carbocyclic analogues). Herein we report the details of the photochemical ring-expansion as well as the regio- and stereochemistry of the one-carbon homologation of chiral ketone **3**.

Results and Discussion

Photochemical Ring-Expansion of 2(*S*),3(*R*)-Bis[(benzoyloxy)methyl]cyclobutanone (3). Ketone **3** was prepared according to the method of Ahmad.[14] UV irradiation of ketone **3** in THF/water gave an epimeric mixture of hemiacetals **4a** in 58% yield. The remaining components of the mixture consisted principally of the cycloelimination product **5**. The relative stereochemistry at the chiral centers C-3 and C-4 of **4a** was confirmed by its oxidation to lactone **6**. That a single stereoisomer was produced was evident from its ^{1}H-NMR spectrum. Homonuclear decoupling of the C–5 methylene protons in **6** resulted in the simplification to a doublet (J = 3.4 Hz) for the H-4 signal typical for *trans vicinal* coupled protons. Furthermore, NOED experiments carried out for **6** provided further evidence for the *trans* relationship between the two (benzoyloxy)methyl groups. Selective irradiation of the C-5 methylene protons (δ 4.59) resulted in signal enhancements for the H-4 (δ 4.80), H-3 (δ 2.95) and H-2β (δ 2.90) protons. Since photochemical conversion of **3** to **4** formally involves α-bond breaking and possible formation of a 1,4-diradical, any epimerization would be observed at the C-4 chiral center in both **4** and **6** which would result in a mixture of *cis* and *trans* stereoisomers of **6**. The fact that a single *trans* stereoisomer of **6** is produced is indicative that the initial photochemical ring-expansion of ketone **3** must have proceeded stereospecifically. In addition, since the absolute configuration for ketone **3** has been assigned by X-ray crystallography of one of its analogues,[15] the assignment of the 3(*S*),4(*R*) configurations for hemiacetal **4a** and lactone **6** is secure. Further confirmation of the structural assignment of acetals **4** was obtained by separating the β-anomer of **4c** which has identical spectral and physical properties as those reported in the literature.[16] The optical purities of **4a** and **4c** were shown to exceed 98% by ^{1}H NMR spectroscopy using Eu(tfc)$_3$ as the chiral shift agent and comparison with spectra of **4a** and **4c** obtained from racemic **3**. The stereospecificity of the photochemical ring-expansion of ketone **3** is consistent with other observations of cyclobutanone phototransformations and indicative of either a short-lived 1,4-diradical or a concerted isomerization to the transient cyclic oxacarbene.[12,17]

Similarly, irradiation of ketone **3** in THF containing *tert*-butyl alcohol, methanol, succinimide, purine, and 6-chloropurine in separate experiments produced the photoadducts **4**, in yields ranging from 9 to 60%. In all cases the ring-expansions were accompanied by cycloeliminations as was evident from the observation of (*E*)-1,4-bis(benzoyloxy)-2-butene (**5**)[24] in the reaction mixtures. The extent of photocycloelimination is often solvent dependent[12] and can be minimized by using excess quenching agent for the transient carbene which is formed reversibly. The use of excess quencher to maximize yields of photoadducts is sometimes impractical because of solubility limitations in the case of succinimide and purine derivatives. It is interesting to note that the use of the more soluble 6-chloropurine causes an increase in the yield of the photoadduct **4f** relative to purine. The low yield of the *tert*-butyl alcohol adduct **4b** is attributed to the bimolecular reaction with the bulky *tert*-butyl alcohol being not as favored relative to the unimolecular cycloelimination pathway. Most of the photoadducts **4** are formed as anomeric mixtures consisting of equal amounts of the α- and β-forms as was evident from their ^{1}H-NMR spectra and the doubling of the signals in the region δ 5–6 ppm associated with the anomeric protons. Some stereoselectivity was observed for the *tert*-butyl alcohol photoadduct **4b** (4:1 in favor of the α-epimer).

Since the methanol adduct **4c** has been coupled with cytosine[9] and a purine[16] by standard methods, the above described procedure for the preparation of **4c** constitutes a formal total synthesis of protected 2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides. Direct insertion of the ox-

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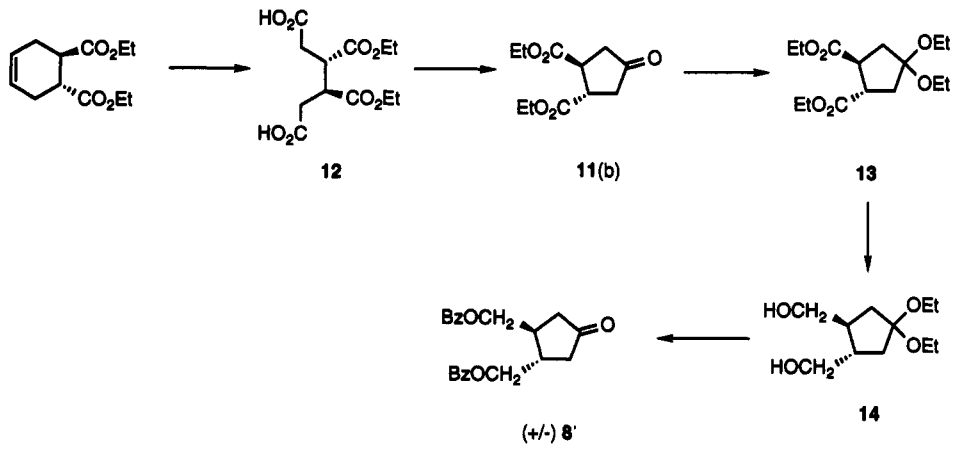
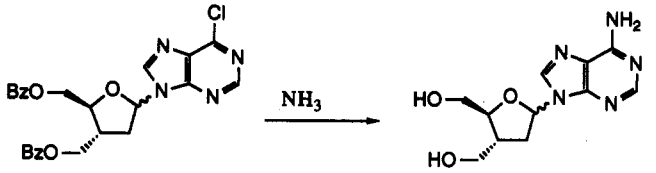
Scheme 1

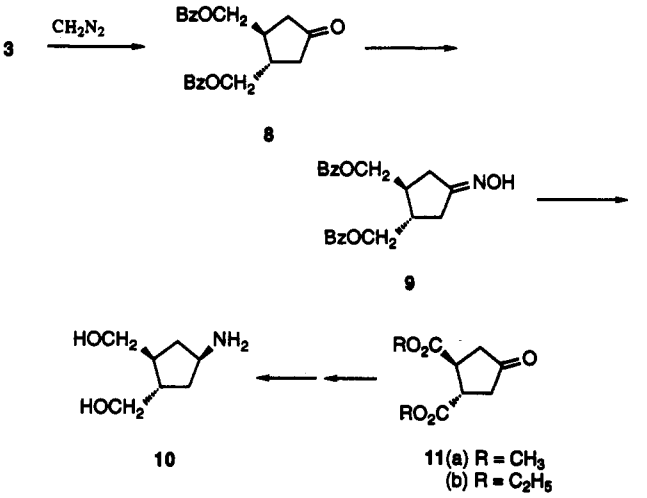


acarbene derived from 3 into the acidic N–H bond of



purines gives these nucleosides by a more direct route. The regiochemistry of the chloropurine photoadduct **4f** was shown by conversion to the known adenine nucleoside **7** with methanolic ammonia at 100 °C.[9] Since 6-chloropurine can be readily converted to 6-alkoxypurines and certain 2′,3′-dideoxy nucleosides have been shown to exhibit anti-HIV-1 activity,[18] the preparation of a series of 6-alkoxypurine 2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides is being carried out using this methodology.

Preparation of a Key Intermediate in the Synthesis of Carbocyclic Analogues of 2′,3′-dideoxy-3′-*C*-hydroxymethyl Nucleosides. Although a number of methods have been reported for the preparation of carbocyclic nucleosides,[6] one general method involves the elaboration of the amino group in cyclopentylamines to a pyrimidine or purine base. Recently the chirospecific synthesis of (1*S*,3*R*)-1-amino-3-(hydroxylmethyl)cyclopentane, a key intermediate for the preparation of carbocyclic analogues of 2′,3′-dideoxy nucleosides, was reported.[19] One-carbon homologation of cyclobutanones constitutes a very general approach to cyclopentane ring systems,[12] and occurs with some regioselectivity in unsymmetrical cyclobutanones depending on the nature of the α-substituent as well as the reagent used. With diazomethane, mixtures of regioisomers are obtained with some selectivity in favor of the product derived from migration of the more substituted carbon (other than halogen).[20] Stereoselectivity is also observed in these reactions.[20] Cyclopentylamine **10** has been prepared in racemic form and used as a key intermediate in the synthesis of carbocyclic analogues of 2′,3′-dideoxy-3′-hydroxymethyl nucleosides.[21] This intermediate was prepared in five steps from acyclic precursors.[21] In view of the availability of chiral ketone **3**, we were interested in the regio- and stereoselectivity for the one-carbon ring-expansion reaction using diazomethane. The reaction conditions used were similar to those reported by Greene.[20]



Treatment of **3** with diazomethane afforded cyclopentanone **8** in 36% yield. The remaining portion of the mixture consisted of unreacted starting material as well as overalkylated products which were not identified. Proof of the regiochemistry was established by conversion by cycylopentylamine **10** which exhibited identical spectral properties with those of racemic **10** prepared independently using Legraverend's route from the keto diester intermediate **11**.[21,22] Racemic keto diester **8** was also prepared independently by the route shown in Scheme 1 and compared with chiral **8** obtained from the ring-expansion of cyclobutanone **3**. The optical purity of ketone **8** was established by observing the ^{1}H-NMR spectrum of oxime **9** in the presence of Eu(tfc)$_3$ and comparison with the spectrum of racemic **9** under the same conditions. In the absence of shift reagent both chiral and racemic **9** showed identical spectra with the *ortho*-protons of the benzoyl group exhibiting two doublets (δ 8.05 ppm) slightly shifted as the result of the nonequivalence of the benzoyl substituents in the oxime. In the presence of chiral shift reagent, the two doublets of chiral **9** are better resolved and show four distinct peaks. On the other hand, the same spectrum for racemic **9** shows in addition to the four

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peaks a signal at δ 8.19 ppm consisting of a partially resolved set of four peaks with equal intensity. Similarly the number of signals associated with the methylene protons of the (benzoyloxy)methyl substituents is doubled in the case of racemic **9** with $Eu(tfc)_3$ present. Within the NMR detection limits, oxime **9** obtained from chiral **3** is optically pure. Hydride reduction of oxime **9** can only lead to a single stereoisomer of cyclopentylamine **10** which was obtained in 43% yield. Since the absolute stereochemistry of ketone **3** has been previously established,[15] the absolute stereochemistry of cyclopentylamine **10** corresponds to that of the natural nucleosides.

Conclusion

Appropriately substituted chiral cyclobutanones can be used as starting materials for the synthesis of nucleosides using a key photochemical ring-expansion reaction which occurs in a regio- and stereospecific manner. The alcohol photoadducts can be structurally elaborated to nucleoside derivatives by literature methods. Alternatively, the transient oxacarbene intermediates can insert into acidic N–H bonds of purine to give nucleoside derivatives in a more direct fashion. One-carbon ring-expansion of a chiral cyclobutanone with diazomethane occurs regio- and stereospecifically (albeit in modest yield) and the resultant ketone can be structurally elaborated to a chiral cyclopentylamine which is a key intermediate in the preparation of carbocyclic nucleosides. With the increasing availability chiral cyclobutanones, our method constitutes a novel alternative to nucleoside synthesis.

Experimental Section

General. Melting points (mp) were determined on a Reichert melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on Pye Unicam SP-1000 and SP3-200 spectrometers as thin films or KBr pellets. NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer in $CDCl_3$ solutions unless noted otherwise. Mass spectra were recorded on a VG Micromass 16F spectrometer. Elemental analyses were performed by Guelph Chemical Laboratories Ltd. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. 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. The samples were degassed with Ar for 1 h prior to irradiation. All solvents used in these reactions were dried and distilled. Preparative thin-layer chromatography was conducted on BDH silica gel 60F 254 precoated glass plates. (1*S-trans*)-3,3-Dimethoxy-1,2-cyclobutanedimethanol was synthesized according to the literature.[14]

(2*S-trans*)-2,3-Bis[(benzoyloxy)methyl]cyclobutanone (3). The title compound was prepared by a modified procedure.[14] To a solution of 4.79 g (26.6 mmol) of (1*S-trans*)-3,3-dimethoxy-1,2-cyclobutanedimethanol in 60 mL of dry pyridine at 5 °C under argon was added dropwise 4 mL of benzoyl chloride. The mixture was stirred at this temperature for 3 h and further stirred for another 12 h at room temperature. The reaction was quenched by the addition of 2 mL of water. After evaporation of the solvent, the residue was partitioned between ethyl acetate and water. The organic layer was washed with water (3 × 320 mL), saturated sodium bicarbonate (2 × 50 mL), and water (3 × 30 mL). After drying with Na_2SO_4 and evaporation of the solvent, the residue (8.7 g), containing mostly ketal, was added to a solution of 200 mL of acetonitrile containing 70 mL of 0.5 N H_2SO_4. The mixture was stirred at room temperature for 18 h and diluted with 200 mL of ethyl acetate, washed with water (2 × 200 mL), saturated sodium bicarbonate (200 mL), water (2 × 200 mL), and brine (200 mL). The organic phase was dried over Na_2SO_4 and concentrated to a solid by evaporation. Recrystallization from anhydrous ether gave 7.1 g of the title compound, mp 98–99.5 °C. The ^{1}H-NMR spectrum and mp of the product were in agreement with those previously reported.[14]

5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-α- and -β-D-*erythro*-pentofuranose (4a). A solution containing 338 mg (1 mmol) of ketone **3** in 200 mL of THF and 10 mL water was irradiated for 2 h. After evaporation of the solvent the residue was purified by column chromatography (3:1 hexane:ethyl acetate) giving 207 mg (58%) of a white solid $[\alpha]^{20}_D$ + 13.2° (*c*, 1.0, $CHCl_3$); mp 71–73 °C; ^{1}H NMR δ 8.16–7.94, 7.65–7.35 (m, 10H), 5.66, 5.60 (two dd, 1H), 4.66–4.28 (m, 5H), 3.06 (br s, 1H), 2.90, 2.55 (m, 1H), 2.39, 2.21 (m, 1H), 1.90 (m, 1H); MS *m/z* 339 (M^+ – OH), 105 ($C_6H_5CO^+$). Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.4; H, 5.7. Found: C, 67.4; H, 5.9.

(*E*)-Butene-1,4-diol Dibenzoate (5). In the above photomixture was isolated after thin-layer chromatography a nonpolar crystalline fraction (44 mg, 15%) identified as **5**: mp 99–100 °C (lit.[24] mp 100–100 °C); ^{1}H NMR δ 8.10–7.43 (m, 10H), 6.10 (t, 2H), 4.48 (d, 4H).

5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-*erythro*-furanololactone (6). Pyridinium chlorochromate (1.0 g, 4.7 mmol) was suspended in 15 mL of dichloromethane, and 55 mg (0.15 mmol) of hemiacetal **4a** in 5 mL of dichloromethane was added. After 4 h of stirring at room temperature the reaction mixture was diluted with 20 mL of diethyl ether. The solids were removed by filtration. Solvent evaporation followed by column chromatography (3:1 hexane:ethyl acetate) afforded 30 mg (55%) of the title lactone as an oil: $[\alpha]^{20}_D$ +12.2° (*c*, 0.5 $CHCl_3$); IR (neat) 1770, 1710 cm^{-1}; ^{1}H NMR δ 8.02, 7.60–7.42 (m, 10H), 4.80 (m, 1H), 4.63–4.37 (m, 4H), 3.01–2.87 (m, 2H), 2.60–2.53 (dd, 1H); ^{13}C NMR δ 174.8, 162.1, 133.5, 129.7, 129.6, 128.6, 79.7, 65.0, 64.9, 36.5, 31.5; CI-MS 372 (M + NH_4), 355 (M + H). HRMS Calcd for $C_{20}H_{18}O_6$ *m/z* 355.1176 (M^+ + 1), found 355.1166.

***tert*-Butyl 5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-α- and -β-D-*erythro*-pentofuranoside (4b).** A solution of 136 mg (0.4 mmol) of ketone **3** in 65 mL of tetrahydrofuran and 6.5 mL of *tert*-butyl alcohol was irradiated for 1 h. Evaporation of the solvent followed by column chromatography (8:1 hexane:ethyl acetate) gave 16 mg (9%) of the title compound as an oil: ^{1}H NMR δ 8.10–8.01, 7.70–7.31 (m, 10H), 5.56–5.49 (m, 1H), 4.57–4.28 (m, 5H), 2.97–2.83, 2.66–2.51 (m, 1H), 2.37–2.10 (m, 1H), 1.99–1.81 (m, 1H), 1.26, 1.23 (s, 9H). Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.9; H, 6.8. Found: C, 68.98; H, 6.50.

Methyl 5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-α- and -β-D-*erythro*-pentofuranoside (4c). A solution containing 102 mg (0.3 mmol) of ketone **3** and 6.5 mL of methanol in 65 mL of tetrahydrofuran was irradiated for 2 h. Evaporation of the solvent followed by column chromatography (8:1 hexane:ethyl acetate) gave 69 mg (62%) of **4c** as an amorphous solid. This mixture (33 mg) of anomers was subjected to preparative thin-layer chromatography (8:1 hexane:ethyl acetate) repeated 10 times to give 15 mg of the β-anomer identical in all respect with those reported in the literature,[16] however no specific rotation was reported. $[\alpha]^{20}_D$ of β-anomer −46.40° (*c*, 1.0, $CHCl_3$) α-anomer: $[\alpha]^{20}_D$ + 39.8° (*c*, 1.0, $CHCl_3$); ^{1}H NMR δ 8.04–8.02, 7.57–7.39 (m, 10H), 5.13 (d, 1H), 4.58–4.34 (m, 5H), 3.37 (s, 3H), 2.65–2.61 (m, 1H), 2.39–2.30 (m, 1H), 1.91–1.85 (m, 1H).

1-*N*-Succinimidyl 5-*O*-Benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-α- and -β-D-*erythro*-furanoside (4d). A solution containing 136 mg (0.4 mmol) of ketone **3** and 198 mg (2 mmol) of succinimide in 100 mL of tetrahydrofuran was irradiated for 2 h. Removal of the solvent followed by column chromatography (2:1 hexane:ethyl acetate) yielded 30 mg of **4d** as an amorphous solid: mp 72–74 °C; ^{1}H NMR δ 8.10–8.02, 7.63–7.37 (m, 10H), 6.08–5.98 (two d, 1H), 4.69–4.22 (m, 5H), 2.82–2.42 (m, 2H), 2.63, 2.61 (s, 4H), 2.35–2.25 (m, 1H). HRMS calcd for $C_{24}H_{23}NO_7$ *m/z* 438.1546 (M^+ + 1), found *m/z* 438.1551.

1-*N*-Purin-9-yl 5-*O*-benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-α- and -β-D-*erythro*-furanoside 4e. A solution containing 34 mg (0.1 mmol) of ketone **3** and 18 mg (0.15 mmol) of purine in 60 mL of acetonitrile was irradiated for 36 h. Removal

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of solvent by rotary evaporation followed by preparative thin-layer chromatography (95:5 CH_2Cl_2:methanol) gave 9 mg (19%) of a yellow semisolid: ^1H NMR (DMSO-d_6) δ 9.18, 9.16, (s, 1H), 8.94, 8.91 (s, 1H), 8.86, 8.82 (s, 1H), 8.08–7.98, 7.85–7.42 (m, 10H), 6.58–6.50 (m, 1H), 4.79–4.41 (m, 5H), 3.02–2.90 (m, 1H), 2.89–2.74 (m, 1H), 2.69–2.54 (m, 1H); HRMS calcd for $C_{25}H_{22}N_4O_5$ m/z 458.1585; found m/z 458.1587.

1-*N*-(6-Chloropurin-9-yl) 5-*O*-benzoyl-3-*C*-[(benzoyloxy)-methyl]-2,3-dideoxy-α- and -β-*erythro*-furanoside 4f. A solution consisting of 135 mg (0.4 mmol) of ketone **3** and 92 mg (0.6 mmol) of 6-chloropurine in 150 mL of acetonitrile was irradiated for 36 h. Evaporation of the solvent followed by preparative thin-layer chromatography (96:4 CH_2Cl_2:methanol) gave 85 mg (43%) of a pale yellow solid: mp 56–58 °C; ^1H NMR (DMSO-d_6) δ 8.97, 8.91 (s, 1H), 8.76, 8.72 (s, 1H), 8.07–7.95, 7.79–7.42 (m, 10H), 6.58–6.48 (m, 1H), 4.80–4.40 (m, 5H), 3.02–2.91 (m, 1H), 2.89–2.73 (m, 1H), 2.69–2.56 (m, 1H); MS m/z 492 (M^+, 3), 494 (M^+ + 2, 1) 339 ($M^+ - C_5H_2N_4Cl$, 10); HRMS calcd for $C_{25}H_{21}N_4O_5Cl$ m/z 492.1196, found m/z 492.1181.

Conversion of the 6-Chloropurine Adduct 4f to 9-[2′,3′-Dideoxy-3′-*C*-(hydroxymethyl)-α- and -β-D-*erythro*-pentofuranosyl]adenine (7). The identical procedure was used as described by Sammuelson.[9] A solution consisting of 250 mg of **4f** in 5 mL of saturated methanolic ammonia was placed in a sealed tube which was inserted in a pressure reactor heated to 100 °C for 20 h. Using the literature-described workup procedure, 105 mg of a mixture of α- and β-anomers of **7** was obtained. The ^1H NMR data (TSP internal reference) were identical to those reported for the individual anomers.

Racemates of 3, 4a, and 4c. Racemic ketone **3** was prepared using the identical procedure as for the preparation of chiral **3**[14] except that *d,l*-dimenthyl fumarate was used in place of *d*-dimenthyl fumarate in the Lewis acid-catalyzed cycloaddition to 1,1-dimethoxyethylene. The racemic photoadducts **4a** and **4c** were prepared in identical fashion as described above.

3(*S*)-*trans*-3,4-Bis[(benzoyloxy)methyl]cyclopentanone (8). A solution containing 169 mg (0.5 mmol) of ketone **3** in 20 mL of ether and 8 mL of methanol was added to 20 mL of an ether solution containing diazomethane (~14 mmol generated from Diazald) cooled in an ice-water bath. On addition, nitrogen gas evolution was immediately observed. After stirring for 2 h the excess diazomethane was quenched by dropwise addition of acetic acid. The solvent was evaporated and the residue chromatographed on a silica gel thin-layer plate (3:1 hexane:ethyl acetate). The product (64 mg, 36%) was obtained as a white crystalline solid: $[\alpha]^{20}_D$ + 37.8° (*c*, 1.0, $CHCl_3$); mp 74–75 °C; IR (KBr) 1740, 1715 cm^{-1}; ^1H NMR δ 8.05–7.92, 7.61–7.38 (m, 10H), 4.50 (d, 4H), 2.76–2.56 (m, 4H), 2.38–2.23 (m, 2H, H-3, H-4); MS 353 (M + 1); HRMS calcd for $C_{21}H_{20}O_5$ m/z 353.1383 (M + 1); found m/z 353.1372.

3(*S*)-*trans*-3,4-Bis[(benzoyloxy)methyl]cyclopentanone Oxime (9). A mixture containing 110 mg (0.3 mmol) of ketone **8** and 210 mg (3 mmol) of hydroxylamine hydrochloride in 5 mL of pyridine and 5 mL of ethanol was stirred for 30 min at room temperature. The mixture was partitioned between 15 mL of brine and 15 mL of ethyl acetate. The aqueous phase was extracted with 3 × 10 mL of ethyl acetate. The organic extracts were combined, dried over $MgSO_4$, and evaporated to dryness. The residue was separated by preparative thin-layer chromatography (1:1 hexane:ethyl acetate) giving 76 mg (70%) of oxime **9**: mp 104–105.5 °C; $[\alpha]^{20}_D$ + 29.8° (*c*, 0.5, $CHCl_3$); ^1H NMR δ 8.08–7.98, 7.62–7.42 (m, 10H), 7.20 (br.s, 1H) 4.57–4.47 (m, 4H), 3.08–3.00 (m, 1H), 2.90–2.76 (m, 1H), 2.54–2.43 (m, 4H).

(1β,3α,4β)-3,4-Bis(hydroxymethyl)-1-cyclopentylamine (10). A solution consisting of 85 mg (0.23 mmol) of oxime **9** in 15 mL of tetrahydrofuran was added dropwise to a well-stirred suspension of 100 mg (0.26 mmol) of lithium aluminum hydride in 20 mL of tetrahydrofuran while cooled in an ice–water bath. The mixture was stirred for 2 h at this temperature under an atmosphere of argon. Stirring was continued overnight at room temperature and then heated to reflux for 4 h. To the mixture was added 0.25 mL of a 15% solution of NaOH, it was diluted with 50 mL of tetrahydrofuran and filtered, and the filtrate was dried over $MgSO_4$. Evaporation of the solvent gave a syrup which was passed through a column of Dowex 50X 4-400 cation exchange resin (H^+ form) in methanol. The column was washed with methanol–water (9:1, 100 mL) and eluted with 2 N NH_4OH in methanol giving 15 mg (43%) of an oil: $[\alpha]^{20}_D$ + 8.0° (*c*, 0.23, CH_3OH); IR (neat) 3350 (br), 1050 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.56–3.20 (m, 9H), 2.10–1.39 (m, 5H), 1.15–1.05 (m, 1H); MS m/z 144 (M − 1), 114 (M − CH_2OH). This sample was identical in all respects (except for $[\alpha]^{20}_D$) with a racemic sample of **10** prepared independently from the keto diester **11a** or **11b** via their respective oximes as described according to the literature.[21]

Preparation of Racemic Ketone 8. *threo*-3,4-Bis(ethoxycarbonyl)hexanedioic Acid (12). To a mechanically stirred cooled (ice–water) solution of $KMnO_4$ (25 g, 0.158 mol) in water (400 mL) was slowly added diethyl *trans*-Δ^4-tetrahydrophthalate[23] (10.7 g, 0.05 mol). Stirring was continued at room temperature for 5 h after which 200 mL of water was added and the pH adjusted to 10 by addition of 10% aqueous NaOH. Subsequently 2 g of Na_2SO_3 was added. The solids were filtered over Celite and washed with water. The filtrate was acidified to pH 2 by the addition of concentrated HCl and then extracted with ether (3 × 300 mL). The combined ether extracts were dried over $MgSO_4$. After evaporation of the ether, a solid residue was obtained which was recrystallized from hexane/ethyl acetate to give 8.25 g (57%) of crystalline **12**: mp 159–160.5 °C; IR (KBr) 3350–2900 (br), 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$ plus DMSO-d_6) δ 4.20 (q, 4H), 3.32 (m, 2H), 2.96 (m, 2H), 2.64 (m, 2H), 1.28 (t, 6H).

(±)-*trans*-4-Oxo-1,2-cyclopentanedicarboxylic Acid, Diethyl Ester (11b). A well-stirred suspension of diacid **12** (2.9 g, 10 mmol) and anhydrous sodium acetate (708 mg, 8.63 mmol) in acetic anhydride (15 mL) was heated under reflux for 1.5 h. The reaction mixture was then cooled and stored overnight at 5 °C. The precipitate formed was filtered off and the acetic anhydride was removed in *vacuo*. The residue was purified by flash column chromatography (5:1 hexane:ethyl acetate) giving 1.5 g (65%) of **13**: IR (neat) 1750, 1735 cm^{-1}; ^1H NMR δ 4.20 (q, 4H), 3.42–3.32 (m, 2H), 2.73–2.61 (m, 2H), 2.58–2.46 (m, 2H) 1.28 (t, 6H).

(±)-*trans*-4,4-Diethoxy-1,2-cyclopentanedicarboxylic Acid, Diethyl Ester (13). A mixture consisting of 440 mg (3.08 mmol) of ethyl orthoformate, 460 mg of keto diester **11b** in 10 mL of absolute ethanol, and a drop of concentrated HCl was heated at 40–42 °C with stirring for 5 h. The reaction mixture was left at room temperature for 16 h at which time sodium ethoxide in ethanol was added to make the solution slightly alkaline. The solvent was evaporated in *vacuo* and the residue purified by preparative thin-layer chromatography (9:1 hexane:ethyl acetate) giving 388 mg (64%) of **13** as a colorless oil: ^1H NMR δ 4.13 (q, 4H), 3.43 (q, 4H), 3.29–3.20 (m, 2H), 2.29–2.05 (m, 4H), 1.24 (t, 6H), 1.13 (t, 6H).

(±)-*trans*-3,4-Bis[(benzoyloxy)methyl]cyclopentanone (8). A solution containing **13** (350 mg, 1.116 mmol) in 10 mL of tetrahydrofuran was added dropwise to a suspension of 200 mg of lithium aluminum hydride in 20 mL of tetrahydrofuran cooled to 0–5 °C over a period of 2 h. After addition, stirring was continued for another 2 h and then heated to reflux for 4 h. After cooling to 0–5 °C the following reagents are added sequentially: 0.1 mL of water, 0.1 mL of 15% aqueous sodium hydroxide, and 1 g of $MgSO_4$. The resulting suspension was stirred for 30 min at room temperature. The solids were removed by filtration and the filtrate concentrated to give 260 mg of crude ketal diol **14** used in the next step: IR (neat) 3350 cm^{-1}.

To a solution of 250 mg (1.15 mmol) of the ketal diol in 5 mL of dry pyridine cooled to 5 °C under argon was added dropwise 0.6 mL of benzoyl chloride. The mixture was stirred at this temperature for 3 h after which 0.2 mL of water was added. The solvent was evaporated in *vacuo*. The residue was partitioned with ethyl acetate and water. The organic layer was washed with water, saturated sodium bicarbonate, and brine. After drying with $MgSO_4$, the solution was concentrated and purification by preparative thin-layer chromatography was carried out giving 255 mg (63%) of ketone **8** identical in all respects (except for $[\alpha]^{20}_D$) with chiral ketone **8** described above.

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