Enantioselective Preparation of 2′,3′-Dideoxynucleosides and Their Analogues from Ring-Expansion of Cyclobutanones. 2. Synthesis of 2′,3′-Dideoxyribosides and (1*S*,3*R*)-1-Amino-3-(hydroxymethyl)cyclopentane[1]

Edward Lee-Ruff,* Feng-de Xi, and Jiang Hua Qie

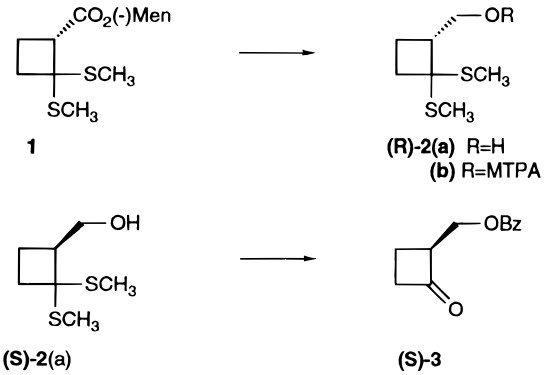
Department of Chemistry, York University, Toronto, Ontario M3J 1P3

Received September 19, 1995

Synthetic nucleosides have occupied a central role in medicinal chemistry with the observation of their activity as anticancer and antiviral agents.[2−4] Specifically, a number of 2′,3′-dideoxynucleosides have been shown to be effective as inhibitors of human immunodeficiency virus (HIV) responsible for the etiology of acquired immune deficiency syndrome (AIDS), and a few of these derivatives (AZT, ddI, d4T, and ddC) have been approved by the US Food and Drug Administration for the treatment of AIDS.[5]

Carbocyclic nucleoside analogues have also been of interest in this area since it is known that these are more stable than their oxygen heterocycles.[6] In recent years, a number of synthetic methods have been reported for the preparation of carbocyclic[6b] and normal[7] 2′,3′-dideoxynucleosides as potential anti-HIV agents. Many of these methods are based on structural modifications of heterocycles or sugar moieties not always readily accessible.[6b] Other methods for preparation of furanosides involve the cyclization or annulation of chiral C-3 or C-4 open-chain fragments.[3,8] In view of the availability of cyclobutane derivatives[9] and their tendency to undergo ring-expansion reactions in a regio- and stereoselective manner,[10] we explored the possible use of cyclobutanones as starting materials in the synthesis of carbocyclic and normal nucleosides. We have recently reported a novel approach to the synthesis of a series of 2′,3′-dideoxy-3′-*C*-(hydroxymethyl)nucleosides and a key intermediate in the synthesis of their carbocyclic analogues by ring-expansion reactions of a chiral cyclobutanone.[1] The key step involved the photochemical isomerization of a cyclobutanone to a transient oxacarbene and the insertion into the NH group of a purine.[11] This reaction proceeded with complete regio- and stereospecificity. The one-carbon ring homologation of cyclobutanones giving cyclopentanones has also been shown to occur in a regio- and stereospecific manner.[1] The chiral cyclopentanone can be structurally elaborated to cyclopentylamines which were key intermediates in the preparation of carbocyclic nucleosides.[12] In the present study we report on the photochemical ring-expansion of chiral 2(*S*)-[(benzoyloxy)methyl]cyclobutanone (**3**) as a route to the 2′,3′-dideoxynucleoside series. We also report the diazomethane ring-expansion of ketone **3** to give the known (1*S*,3*R*)-1-amino-3-(hydroxymethyl)cyclopentane[13] which is an important intermediate in the preparation of carbocyclic nucleosides of the 2′,3′-dideoxy series.

Scheme 1

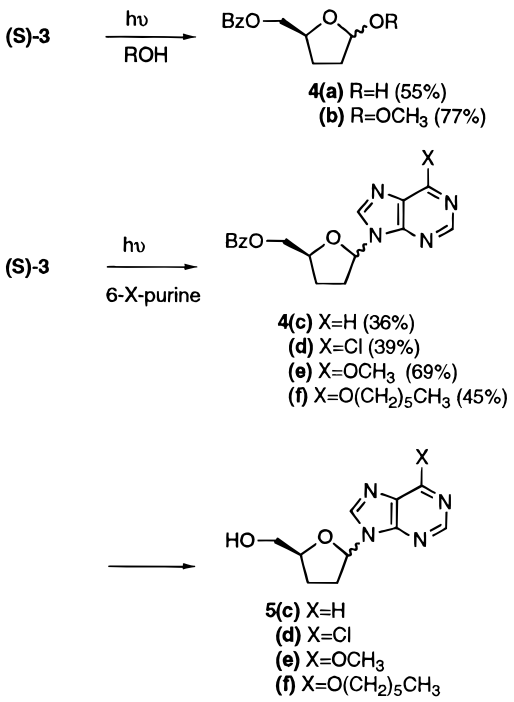


Several different methods have been attempted to prepare ketone **3**. Cycloaddition of (−)-menthyl acrylate to 1,1-dimethoxyethylene with Lewis acid catalysts did not result in [2 + 2] cycloaddition but led principally to mixtures of acyclic condensation products. Cycloaddition of (−)-menthyl acrylate with 1,1-bis(methylthio)ethylene gave the [2 + 2] cycloadduct **1** in 79% yield. However, the diastereomeric enrichment was found to be only 25% as determined by ^{1}H NMR analysis of its alcohol derivative **2b** obtained from hydride reduction of **1** followed by esterification with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA). Furthermore, the enantiomeric enrichment in **2** was in favor of the undesired (*R*)-(+)-**2a** isomer.[15] The racemate shows two sets of two singlet signals at 1.89, 1.92 and 1.92, 1.95 ppm associated with the methylthio substituents.[15] The optically pure (*S*)-derivative exhibits two singlet peaks at 1.92 and 1.95 ppm.[15] Our sample showed peaks at 1.89, 1.92, and 1.95 with the former two being more intense. From integration the optical purity was found to be 25% in favor of the (*R*)-derivative. The optical purity of our sample determined from specific rotations was found to be 27%. A recent report on the preparation of enantiomerically pure (*S*)-(−)-**2a**[15] prompted us to use this cyclobutane derivative as the precursor to ketone **3**. The enantioselective synthesis of (*S*)-(−)-**2a** is based on the cycloaddition of 3-acryloyl-1,3-oxazolidin-2-one and 1,1-bis(meth-

(1) For part 1 see: Lee-Ruff, E.; Wan, W.-Q.; Jiang, J.-L. *J. Org. Chem.* **1994**, *59*, 2114.
(2) Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. *J. Org Chem.* **1988**, *53*, 2406.
(3) Chou, T. S.; Heath, P. C.; Patterson, L. E.; Poteet, L. M.; Lakin, R. E.; Hunt, A. H. *Synthesis* **1992**, 565.
(4) Robins, R. K.; Revankar, G. R. in *Antiviral Drug Development*; De Clercq, E., Walker, R. T., Eds.; Plenum Press: New York, 1988; p 11.
(5) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533 and references cited therein.
(6) (a) Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* **1986**, 611. (b) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (c) Niitsuma, S.; Ichikawa, Y.-I.; Takita, T. *Studies in Natural Products Chemistry*; Elsevier Science Publishers: Amsterdam, 1992; p 585.
(7) (a) Manchand, P. S.; Belica, P. S.; Holman, M. J.; Huang, T.-N.; Maehr, H. Tam, S. Y.-K; Yang, R. T. *J. Org. Chem.* **1992**, *57*, 3473. (b) Beach, J. W.; Kim, H. O.; Jeong, L. S.; Nampalli, S.; Islam, Q.; Ahn, S. K.; Babu, J. R.; Chu, C. K. *Ibid.* **1992**, *57*, 3887.
(8) Svannson, L.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1991**, *56*, 2993.
(9) Lee-Ruff, E. In *Methods in Organic Chemistry;* De Meijere, A., Ed.; Houben-Weyl; G. Thieme Verlag: Stuttgart, Chapter 1.3, Vol. E17 (in press).
(10) Lee-Ruff, E. In *Advances in Strain in Organic Chemistry;* Halton, B., Ed.; G. Thieme Verlag: Stuttgart, 1991; Vol. 1, p 167.
(11) Hayes, I. E. E.; Jandrisits, L.; Lee-Ruff, E. *Can. J. Chem.* **1989**, *67*, 2057.
(12) (a) Boumchita, H.; Legraverend, M.; Bisagni, E. *Heterocycles* **1991**, *32*, 1785. (b) Rosenquist, A.; Kvarnström, I.; Svensson, S. C. T.; Classon, B.; Sammuelsson, B. *J. Org. Chem.* **1994**, *59*, 1779. (c) Park, K. H.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 394.
(13) (a) Bergmeier, S. C.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 5019. (b) Bergmeier, S. C.; Cobas, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369.
(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(15) Narasaka, K.; Kusama, H.; Hayashi, Y. *Bull Chem. Soc. Jpn.* **1991**, *64*, 1471.

0022-3263/96/1961-1547$12.00/0

Scheme 2



ylthio)ethylene using a chiral titanium catalyst.[15] Cyclobutanone **3** was obtained in 85% yield by benzoylation and dethioketalization of (−)-**2a**.

Irradiation of ketone **3** in either THF or acetonitrile solutions (10^{-2} to 10^{-3} M) with water, methanol, purine, 6-chloro-, 6-methoxy-, and 6-(hexyloxy)purine using a medium pressure mercury lamp gave in separate experiments the ring-expanded derivatives **4** as principal products (36−80% yields). In all cases a mixture of approximately equal amounts of both anomers were obtained as evident from the ^{1}H-NMR signals of equal intensities associated with the anomeric protons and the doubling of the methoxy signals in **4b** and **4e**.

Debenzoylation of **4c**−**f** was accomplished by treatment with methanolic ammonia. The resultant deprotected nucleosides **5c**−**f** could be separated by preparative thin-layer chromatography. The β-anomers of **5c,d** exhibited similar spectral data as reported in the literature.[16,17] Debenzoylation of the chloro derivative **4d** gave in addition to **5d** some of the methoxy nucleoside **5e** arising from nucleophilic displacement by methanol.

In order to explore the regio- and stereoselectivity of the one-carbon homologation of ketone **3** for the preparation of the corresponding (1*S*,3*R*)-1-amino-3-(hydroxymethyl)cyclopentane (**8**), ketone **3** was treated with diazomethane. This reaction led to a 49% conversion to the corresponding cyclopentanone **6**. The regiochemistry of the cyclopentanone was established by conversion to the cyclopentylamine **8** via oxime **7**. A racemic modification of cyclopentylamine **8** was prepared independently according to the literature starting from bicyclo[2.2.1]-hept-2-ene[18] and showed identical spectral properties (NMR and IR spectra) with the amine prepared from optically pure ketone (−)-**3**. The *cis* stereochemistry was expected for **8** since hydride reduction of oxime **7** would preferentially occur from the side opposite to the (benzoyloxy)methyl substituent in the cyclopentane ring of **7**.

In summary, 2′,3′-dideoxypurinyl nucleosides can be readily prepared from the photochemical ring-expansion of chiral (*S*)-2-(benzoyloxy)cyclobutanone in the presence of purines yielding both anomers in about equal proportions. Debenzoylation of the photoproducts with saturated ammonia methanol gave the known 6-substituted purine nucleosides, a number of which have been shown to be inhibitors of the cytopathic effect of HIV.[16,17]

A key intermediate, (1*S*,3*R*)-1-amino-3-(hydroxymethyl)cyclopentane (**8**), which can be used in the preparation of carbocyclic nucleosides, has been synthesized from chiral (*S*)-2-[(benzoyloxy)methyl]cyclobutanone ((−)-**3**) by one-carbon homologation with diazomethane and structural elaboration of the corresponding cyclopentanone. The ring-expansion occurs in a regio- and stereoselective manner.

The photochemical and one-carbon ring-expansion of chiral ketone **3** constitutes a simple enantioselective route to 2′,3′-dideoxy-nucleosides and carbocyclic analogues. The photochemical route is, however, limited by the formation of both anomers. The advantage of this method, apart from its simplicity, is the potential for preparing the enantiomeric forms of these nucleosides by using the optical antipode of the chiral titanium catalyst (derived from (+)-tartaric acid) in the preparation of cyclobutane **2a**. Recently, a number of investigators have looked at the anti-HIV activity of the enantiomeric forms of these nucleosides with promising results.[19−22]

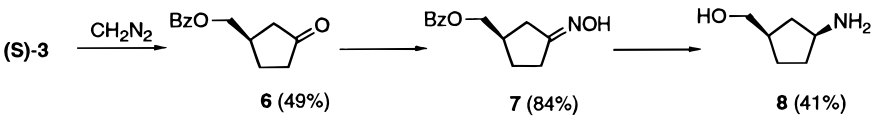
Experimental Section

General. Melting points (mp) were uncorrected. Infrared (IR) spectra were recorded as thin films or KBr pellets. NMR spectra were recorded on a Bruker ARX-400 (400 MHz) spectrometer in $CDCl_3$ solutions with TMS as internal reference (unless otherwise specified). Mass spectra were recorded on a VG Micromass 16F spectrometer. High resolution mass spectra were obtained on a VG Analytical-SE spectrometer at the University of Toronto Carbohydrate Research Center. Elemental analyses were performed by Guelph Chemical Laboratories Ltd. Photolyses were carried out using a Hanovia 450-W medium pressure mercury arc lamp in a water-cooled Pyrex immersion well. Pyrex tubes containing the samples were strapped around this well, and the assembly was immersed in an ice−water bath. The samples were degassed for 30 min prior to irradiation. All solvents used were dried and distilled. Preparative thin-layer chromatography was conducted on BDH silica gel 60F 254 precoated glass plates. Ketene dimethylthioacetal was prepared according to the literature.[23]

(−)-Menthyl Acrylate. To a cooled solution (0 °C) containing (−)- menthol (1.56 g, 10 mmol) and pyridine (0.95 mL) in 10 mL of heptane was added acryloyl chloride (1.09 g, 12 mmol) over a period of 20 min. Stirring was continued for a further 30 min at 0 °C and 3 h at room temperature. The reaction mixture was washed with aqueous sodium bicarbonate (5%, 2 × 8 mL) and water (2 × 8 mL) and dried over sodium sulfate. After evaporation of the solvent at reduced pressure, the residue was purified by column chromatography with silica gel (hexane:ethyl acetate, 9:1), giving a colorless oil (1.52 g, 72%): $[\alpha]^{25}_D$ −85.4° (*c*, 0.97, CH_2Cl_2); IR (neat) 1708, 1182 cm^{-1}; ^{1}H NMR δ 6.3 (d, J = 21 Hz, 1H), 6.0 (dd, J = 22, 11 Hz, 1H), 5.7 (d, J = 11 Hz 1H), 4.7

(16) Burns, C. L.; St. Clair, M. H.; Frick, L. W.; Spector, T.; Averett, D. R.; English, M. L.; Holmes, T. J.; Krenitsky, T. A.; Koszalka, G. W. *J. Org. Chem.* **1993**, *36*, 378.
(17) Chu, C. K.; Ullas, G. V.; Jeong, L. S.; Ahn, S. K.; Doboszewski, B.; Lin, Z. X.; Beach, J. W.; Schinazi, R. F.; *J. Med. Chem.* **1990**, *33*, 1553.
(18) Hronowshi, L. J. J.; Szarek, W. A. *Can. J. Chem.* **1988**, *66*, 61.
(19) Schinazi, R. F. et al. *Antimicrob. Agents Chemother.* **1994**, *38*, 2172.
(20) Lin, T. S. et. al. *Biochem. Pharmacol.* **1994**, *47*, 171.
(21) Gosselin G. et al. *Antimicrob. Agents Chemother.* **1994**, *38*, 1292.
(22) Lin, T. S.; Luo, M.-Z.; Liu, M. C. *Tetrahedron Lett.* **1994**, *35*, 3477.
(23) Kaya, R.; Beller, N. R. *J. Org. Chem.* **1981**, *46*, 196.

Scheme 3



6 (49%) **7** (84%) **8** (41%)

(m, 1H), 1.95 (m, 1H), 1.80 (m, 1H), 1.60 (m, 3H), 1.4 (m, 2H), 0.95 (m, 2H), 0.80 (dd, 6H), 0.70 (d, 3H). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.28; H, 10.48. Found: C, 74.13; H, 10.45.

(−)-Menthyl 2,2-Bis(methylthio)-1-cyclobutanecarboxylate (1). To a CH_2Cl_2 solution (5 mL) of 1,1-bis(methylthio)-ethylene[23] (0.24 g, 2.0 mmol) and menthyl acrylate (0.22 g, 1.2 mmol) was added dropwise diethylaluminum chloride (1.2 mmol, 1.0 M hexane solution) at 0 °C. The mixture was stirred for 1 h after which the reaction was quenched with ten drops of triethylamine and with 10% aqueous sodium bicarbonate (1 mL). The inorganic materials were removed by filtration. The organic materials were extracted with 30 mL of CH_2Cl_2 and dried over sodium sulfate. After removal of the solvent, the residue was purified on a silical gel column (hexane:ethyl acetate, 10:1) to give an oil (0.313 g, 79%); $[\alpha]^{25}_D$ −29.36° (*c*, 4.7, CH_2Cl_2); IR (neat) 1730, 1240, 1170 cm^{-1}; ^1H NMR δ 4.73 (m, 1H), 3.43 (dd, J = 12, 10 Hz, 1H), 2.55 (m, 1H), 2.1−2.4 (m, 4H), 2.15 (s, 3H), 2.04 (s, 3H), 1.95 (m, 1H), 1.05−1.75 (m, 7H), 0.95 (dd, J = 7, 3 Hz, 6H), 0.78 (d, J = 6 Hz, 3H). Anal. Calcd for $C_{17}H_{30}O_2S_2$: C, 61.77; H, 9.15. Found: C, 62.17; H, 9.20.

***(R)*-(+)-[2,2-Bis(methylthio)-1-cyclobutyl]methanol (2a).** To a THF suspension (40 mL) of lithium aluminum hydride (1.0 g, 26 mmol) was added a THF solution (25 mL) of 2,2-bis-(methylthio)-1-cyclobutanecarboxylic acid (−)-menthyl ester (**1**) (4.29 g, 13 mmol) at 0 °C. The mixture was stirred for 30 min. Then saturated aqueous sodium sulfate was added until hydrogen evolution ceased. The precipitate was filtered off and washed with THF. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography using silica gel (hexane:ethyl acetate, 9:1) to give a colorless oil: $[\alpha]^{25}_D$ +9.36° (*c*, 1.00, CH_2Cl_2). Our sample showed similar IR and ^1H NMR spectral data to that reported in the literature for the optically pure (*S*)-derivative.[15]

***(S)*-2-[(Benzoyloxy)methyl]cyclobutanone Bis(methylthio)ketal.** To a pyridine solution (6 mL) containing (*S*)-[2,2-bis-(methylthio)-1-cyclobutyl]methanol ((−)-**2a**) (0.482 g, 2.48 mmol)[15] was added dropwise benzoyl chloride (0.524 g, 3.73 mmol) at 5 °C. The solution was stirred for 30 min and then treated successively with saturated aqueous sodium bicarbonate and brine. The reaction mixture was extracted with ethyl acetate (2 × 50 mL), and the combined organic extracts were washed with brine and dried over sodium sulfate. After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, hexane:ethyl acetate, 10:1) to give a colorless oil (0.617 g, 88%); $[\alpha]^{28}_D$ +5.59° (*c*, 1.02, CH_2Cl_2); IR (neat) 1710, 1260 cm^{-1}; ^1H NMR δ 8.05 (d, J = 7 Hz, 2H), 7.55 (t, J = 7 Hz, 1H), 7.45 (t, J = 7 Hz, 2H), 4.50 (m, 2H), 3.0 (m, 1 H), 2.48 (m, 1H); 2.45 (m, 3H), 2.13 (s, 3H), 2.07 (s, 3H), MS (EI) m/z 282 (M^+). Anal. Calcd for $C_{14}H_{18}O_2S_2$: C, 59.54; H, 6.42; S, 22.71. Found: C, 59.89; H, 6.25; S, 22.75.

***(S)*-2-[(Benzoyloxy)methyl]cyclobutanone [(−)-3].** To a well stirred solution of *N*-chlorosuccinimide (2.01 g, 15 mmol) and silver nitrate (2.89 g, 17.0 mmol) in aqueous 90% acetonitrile was added a solution of (*S*)-2-[(benzoyloxy)methyl]cyclobutanone bis(thiomethyl)ketal (1.41 g, 5.0 mmol) at 0 °C. The mixture was stirred for 10 min and treated successively with saturated aqueous sodium sulfite, sodium bicarbonate and brine. The inorganic materials were removed by filtration. The filtrate was extracted with 100 mL of ethyl acetate, washed with brine, and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (silica gel, hexane:ethyl acetate 10:1) to give a colorless oil; $[\alpha]^{28}_D$ −13.8° (*c*, 1.06, CH_2Cl_2); IR (neat) 1780, 1715, 1270 cm^{-1}; ^1H NMR δ 8.0 (d, J = 7 Hz, 2H), 7.07 (t, J = 7 Hz, 1H), 7.50 (t, J = 7 Hz, 2H), 4.54 (d, J = 5 Hz, 2H), 3.76 (m, 1H), 3.10 (m, 2H), 2.30 (m, 1H), 2.10 (m, 1H); MS (EI) m/z 205 (M + 1). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.06; H, 5.92. Found: C, 69.80, H, 6.00.

Photolysis of Ketone (−)-3. General Procedure. A solution of ketone **3** in THF or acetonitrile containing the carbene scavenger was degassed with argon for 30 min. The solution was irradiated for the length of time indicated below. After evaporation of the solvent, the residue was purified by preparative thin-layer chromatography using silica gel.

5-*O*-Benzoyl-2,3-dideoxy-α- and *β*-D-*erythro*-pentofuranose (4a). From 0.204 g (1 mmol) of ketone **3** in 35 mL of THF containing 3 mL of water after irradiation for 30 min gave, after purification (TLC, hexane:ethyl acetate, 6:4), 0.127 g (55%) of a colorless oil; $[\alpha]^{28}_D$ +6.67° (*c*, 0.99, CH_2Cl_2); IR (neat) 3400, 1705, 1260 cm^{-1}; ^1H NMR δ 8.06, 8.03 (two d, 2H), 7.54 (t, 1H), 7.40, (t, 2H), 5.63, 5.50 (two d, 1H), 4.45 (m, 2H), 3.80 (m, 1H), 2.4−1.8 (m, 4H); MS (EI) m/z 205 (M − OH); HRMS calcd for $C_{12}H_{13}O_3^+$ (M^+ − OH) m/z 205.0865; found m/z 205.0849.

Methyl 5-*O*-Benzoyl-2,3-dideoxy-α- and -*β*-D-*erythro*-pentofuranoside (4). From 0.200 g (1 mmol) of ketone **3** in 36 mL of THF containing 3.5 mL of methanol after irradiation for 30 min gave, after purification by TLC (hexane:ethyl acetate, 8:2), 0.181 g (77%) of a colorless oil: $[\alpha]^{28}_D$ +4.92° (*c*, 1.28, CH_2Cl_2); IR (thin film) 1720, 1270, 1300 cm^{-1}, ^1H NMR δ 8.12, 8.05 (two d, 2H), 7.58 (t, 1H), 7.45 (t, 2H), 5.12, 5.03 (two d, 1H), 4.40 (m, 2H), 3.47, 3.34 (two s, 3H), 2.0 (m, 4H); MS (EI) m/z 235 (M^+ − H), 205 (M − OCH_3). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.10; H, 6.78. Found: C, 65.82, H, 6.80.

1-*C*-(Purin-*N*^{9}-yl)-5-*O*-benzoyl-1,2,3-dideoxy-α- and -*β*-D-*erythro*-furanose (4c). From a solution containing 0.020 g (0.1 mmol) of ketone **3** and 0.018 g (0.15 mmol) of purine in 60 mL of acetonitrile after 36 h of radiation gave upon purification by TLC (CH_2Cl_2:CH_3OH, 95.5) 0.012 g (36%) of a yellow oil: ^1H NMR δ 9.17, 9.14 (two s, 1H), 8.97, 8.93 (two s, 1H), 8.36, 8.24 (two s, 1H), 8.10, 8.02 (two d, 2H), 7.60 (m, 1H), 7.45 (m, 2H), 6.50, 6.48 (two d, 1H), 4.43−4.66 (m, 3H), 2.12−2.82 (m, 4H).

1-*C*-(6-Chloropurin-*N*^{9}-yl)-5-*O*-benzoyl-1,2,3-dideoxy-α- and -*β*-D-*erythro*-furanose (4d). From a solution containing 0.02 g (0.1 mmol) of ketone **3** and 0.023 g (0.15 mmol) of 6-chloropurine in 50 mL of acetonitrile after 36 h radiation was obtained upon purification by TLC (CH_2Cl_2:CH_3OH 96:4) 0.014 g of (39%) of a yellow oil: $[\alpha]^{22}_D$ −3.46° (*c*, 0.2, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 244 nm (ϵ = 3264); ^1H NMR δ 8.77, 8.73 (two s, 1H), 8.38, 8.26 (two s, 1H), 8.11, 8.01 (two d, 2H), 7.60 (m, 1H), 7.45 (m, 2H), 6.50, 6.42 (two m, 1H), 4.85 (m, 1H), 4.50 (m, 2H), 2.14−2.77 (m, 4H); MS (LSIM) m/z 359 (M + H).

1-*C*-(6-Methoxypurin-*N*^{9}-yl)-5-*O*-benzoyl-1,2,3-dideoxy-α- and *β*-D-*erythro*-furanose (4e). From a solution containing 0.200 g (1.0 mmol) of ketone **3** and 0.225 g (1.5 mmol) of 6-methoxypurine in 100 mL of acetonitrile after 38 h radiation was obtained upon purification by TLC (CH_2Cl_2:CH_3OH 95:5) 0.244 g of (69%) of a light yellow oil: $[\alpha]^{22}_D$ −5.17° (*c*, 0.6, CH_2Cl_2); UV (CH_2Cl_2); λ_{max} 240 nm (ϵ = 8875); IR (neat) 1705, 1580, 1260 cm^{-1}; ^1H NMR δ 8.56, 8.52 (two s, 1H), 8.55 (m, 1H), 8.50 (m, 2H); 8.18, 8.08 (two s, 1H), 8.05, 8.00 (two d, 2H), 6.45, 6.35 (two m, 1H), 4.90 (m, 1H), 4.40−4.62 (m, 2H), 4.22, 4.20 (two s, 3H), 2.05−2.79 (m, 4H); MS (LSIM) m/z 355 (M + H); HRMS (FAB) calcd for $C_{18}H_{19}O_4N_4$, (M + H) m/z 355.1406; found m/z 355.1425.

1-*C*-[6-(Hexyloxy)purin-*N*^{9}-yl]-5-*O*-benzoyl-1,2,3-dideoxy-α- and -*β*-D-*erythro*-furanose (4f). From a solution containing 0.02 g (0.1 mmol) of ketone **3** and 0.066 g (0.3 mmol) of 6-(hexyloxy)purine in 160 mL of acetonitrile after 36 h radiation was obtained upon purification by TLC (CH_2Cl_2:CH_3OH 95:5) 0.019 g of (45%) of a colorless oil: $[\alpha]^{22}_D$ −2.4° (*c*, 0.125, CH_2Cl_2); UV (CH_2Cl_2) λ_{max} 246 nm (ϵ = 2792); IR (neat) 1714, 1574, 1176, cm^{-1}; ^1H NMR δ 8.53, 8.51, (two s, 1H), 8.38, 8.23 (two s, 1H), 8.26, 8.05 (two d, 1H), 7.60 (m, 1H), 7.50 (m, 2H), 6.44, 6.33 (two d, 1H), 4.84 (m, 1H), 4.44−4.62 (m, 6H), 2.04−2.69 (m, 4H), 1.91 (m, 2H), 1.51, (m, 2H), 1.36 (m, 4H), 0.92 (t, 3H); MS (LSIM) m/z 425 (M + 1).

Debenzoylation of Nucleosides 4c−f. General Procedure. A solution consisting of 1 mmol of protected nucleoside in 60 mL of methanol saturated with ammonia was stirred for 24 h at room temperature. The solvent was removed and the residue was dissolved in water and washed with CH_2Cl_2 (3 × 6

mL). After evaporation of the water in the aqueous layer by rotoevaporation at a temperature <40 °C, the residue was purified by preparative thin-layer chromatography (CH_2Cl_2:CH_3OH, solvent ratio specified below).

1-*C*-(Purin-*N*⁹-yl)-1,2,3-dideoxy-α- and -*β*-D-*erythro*-furanose (5c). Total yield 69% (35% *β*- and 34% α-anomer). Solvent for TLC separation was CH_2Cl_2:CH_3OH, 100:10.

α-Anomer: mp 119−120 °C (lit.[17] mp 116−118 °C); $[\alpha]^{22}_D$ +6.0° (*c*, 2.82, CH_3OH); λ_{max} (CH_3OH) 264 (ϵ = 13062), IR (KBr) 3609, 1595, 1152 cm^{-1}; ^1H NMR δ 9.15 (s, 1H), 8.98 (s, 1H), 8.22 (s, 1H), 6.43 (dd, *J* = 6, 4 Hz, 1H), 4.59 (m, 1H), 3.65−3.86 (m, 2H), 2.05−2.72 (m, 4H), 1.80 (s, 1H); ^{13}C NMR δ 152.6, 150.8, 149.0, 143.5, 134.8, 86.2, 81.6, 64.5, 32.1, 26.1.

***β*-Anomer:** mp 141−142 °C (lit.[17] mp 149−150 °C); $[\alpha]^{22}_D$ −3.58° (*c*, 2.01 CH_3OH); λ_{max} (CH_3OH) 264 nm (ϵ = 7675); ^1H NMR δ 9.17 (s, 1H), 8.98 (s, 1H), 8.28 (s, 1H), 6.26 (t, 1H), 4.39 (m, 1H), 3.70 (m, 2H), 2.80 (m, 1H), 2.48 (m, 2H), 2.25 (m, 1H), 1.62 (s, 1H); ^{13}C NMR δ 152.2, 150.4, 149.3, 144.3, 135.4, 87.3, 81.9, 64.5, 32.5, 25.9; MS (LSIM) *m*/*z* 221 (M + 1).

1-*C*-(6-Chloropurin-*N*⁹-yl)-1,2,3-dideoxy-α- and -*β*-D-*erythro*-furanose (5d). After debenzoylation 22% of the anomeric mixture of **5d** was obtained in addition to 14% of 6-methoxy derivative **5e** as an anomeric mixture. Solvent for TLC separation was CH_2Cl_2:CH_3OH, 100:6.

α-Anomer: $[\alpha]^{22}_D$ +10.17 (*c*, 0.59, CH_3OH); UV (CH_3OH) λ_{max} 260 nm (ϵ = 9283); IR (KBr) 3351, 1649, 1259 cm^{-1}; ^1H NMR δ 8.36 (s, 1H), 7.92 (s, 1H), 6.35 (t, 1H), 5.53 (s, 1H, OH), 4.57, (m, 1H), 3.69 (m, 2H), 2.02−2.72 (m, 4H); ^{13}C NMR δ 155.4, 153.1, 149.0, 142.3, 138.6, 85.9, 81.3, 64.5, 32.1, 26.0.

***β*-Anomer:** mp 101−102 °C (lit.[17] mp 97−99 °C); $[\alpha]^{22}_D$ +8.89° (*c*, 0.63, CH_3OH); UV (CH_3OH) λ_{max} 260 nm (ϵ =8041); IR (KBr) 3369, 1652, 1244 cm^{-1}; ^1H NMR δ 8.34 (s, 1H), 7.87 (s, 1H), 6.12 (t, 1H), 5.57 (s, 1H, OH), 4.39 (m, 1H), 3.90 (m, 1H), 2.19−2.88 (m, 4H); ^{13}C NMR δ 155.2, 152.6, 148.9, 142.4, 139.9, 88.1, 81.7, 65.1, 32.3, 26.1; MS (LSIM) *m*/*z* 255 (M + 1).

1-*C*-(6-Methoxypurin-*N*⁹-yl)-1,2,3-dideoxy-α- and -*β*-D-*erythro*-furanose (5e). Total yield 43% consisting of 25% of the α-anomer and 18% of the *β*-anomer. Eluent for TLC separation was CH_2Cl_2:CH_3OH, 96:6.

α-Anomer: $[\alpha]^{22}_D$ −4.59° (*c*, 1.35, CH_3OH); UV (CH_3OH) λ_{max} 250 nm (ϵ = 7880); IR (thin film) 3640, 1605, 1165 cm^{-1}; ^1H NMR (D_2O referenced to H_2O) δ 8.52 (s, 1H), 8.47(s, 1H), 6.50 (t, 1H), 4.69 (m, 1H), 4.24, (s, 3H), 3.77 (m, 2H), 2.60 (m, 2H), 2.40 (m, 1H), 2.05 (m, 1H); ^{13}C NMR (D_2O referenced to TSP) δ 157.6, 148.5, 147.3, 138.4, 117.7, 82.5, 78.1, 60.0, 51.6, 27.9, 22.0.

***β*-Anomer:** mp 123−124 °C (lit.[16] mp 122−123 °C); $[\alpha]^{22}_D$ −13.27° (*c*, 4.46, CH_3OH); UV (CH_3OH) λ_{max} 250 nm (ϵ = 10417); IR (KBr) 3630, 1611, 1156 cm^{-1}; ^1H NMR (D_2O referenced to H_2O) δ 8.57 (s, 1H), 8.55 (s, 1H), 6.48 (m, 1H), 4.45 (m, 1H), 4.25 (s, 3H), 3.91 (m, 1H), 3.73 (m, 1H), 2.67 (m, 2H), 2.31 (m, 1H), 2.15 (m, 1H); ^{13}C NMR (D_2O referenced to TSP) δ 157.3, 148.4, 147.0, 138.3, 117.4, 82.5, 78.2, 60.1, 51.6, 28.0, 22.0; MS (LSIM) *m*/*z* 251 (M + 1).

1-*C*-(6-Hexyloxypurin-*N*⁹-yl)-1,2,3-dideoxy-α- and -*β*-D-*erythro*-furanose (5f). Total yield 80% consisting of 40% of the α-anomer and 40% of the *β*-anomer. Eluent for TLC separation was CH_2Cl_2:CH_3OH, 100:6.

α-Anomer: $[\alpha]^{22}_D$ = +12.12° (*c*, 2.64, CH_3OH); UV (CH_3OH) λ_{max} 250 nm (ϵ = 5,881); IR (thin film) 3356, 1600, 1180 cm^{-1}; ^1H NMR (D_2O referenced to H_2O) δ 8.52 (s, 1H), 8.47 (s, 1H), 6.52 (t, 1H), 4.70 (m, 1H), 3.80 (m, 1H), 3.69 (m, 1H), 2.66 (m, 2H), 2.36 (m, 1H), 2.08 (m, 1H), 1.93 (m, 2H), 1.54 (m, 2H), 1.38 (m, 4H), 0.92 (t, 3H).

***β*-Anomer:** $[\alpha]^{22}_D$ −4.50° (*c*, 2.71, CH3OH); UV (CH_3OH) λ_{max} 250 nm (ϵ = 8016); IR 3371, 1599, 1180 cm^{-1}; ^1H NMR (D_2O referenced to H_2O) δ 8.57 (s, 1H), 8.55 (s, 1H), 6.48 (m, 1H), 4.45 (m, 1H), 3.88 (m, 1H), 3.73 (m, 1H), 2.67 (m, 2H), 2.43 (m, 1H), 2.15 (m, 1H), 1.95 (m, 2H), 1.57 (m, 2H), 1.39 (m, 4H), 0.92 (t, 3H); MS (LSIM) *m*/*z* 321 (M + 1).

(*R*)-(+)-3-[(Benzoyloxy)methyl]cyclopentanone (6). To an ethereal solution (80 mL) of diazomethane (0.42 g, 10 mmol) was added ketone (−)-**3** (0.200 g, 1 mmol) in methanol (15 mL). The solution was stirred for 20 h at room temperature. The reaction was quenched by adding a few drops of acetic acid until the yellow color disappeared. The solvent was removed under reduced pressure and the product purified by column chromatography (silica gel, hexane:ethyl acetate 9:1) to give a colorless solid (0.107 g, 49%): mp 46−48 °C; $[\alpha]^{28}_D$ +26.45° (*c*, 1.07, CH_2Cl_2); IR (KBr) 1730, 1700, 1255 cm^{-1}; ^1H NMR δ 7.95 (d, 2H), 7.52 (t, 1H), 7.41 (t, 2H), 4.42 (d, 2H), 3.79 (m, 1H), 2.05−2.5 (m, 5H), 1.77 (m, 1H), MS (EI) *m*/*z* 218 (M^+) 106, 105, 96. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.56; H, 6.42. Found: C, 71.39; H, 6.40.

(*R*)-3-[(Benzoyloxy)methyl]cyclopentanone Oxime (7). To a solution of cyclopentanone **6** (0.114 g, 0.5 mmol) and pyridine (0.316 g, 4 mmol) in ethanol (10 mL) was added hydroxylamine hydrochloride (0.278 g, 4 mmol). The mixture was stirred for 30 min at room temperature. This mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by preparative TLC (silica gel, CH_2Cl_2:CH_3OH 9:1) to give a colorless solid (0.98 g, 84%): mp 102−104 °C; $[\alpha]^{28}_D$ +8.08 (*c*, 1.04, CH_2Cl_2); IR (KBr) 3220, 1703, 1260 cm^{-1}; ^1H NMR δ 7.95 (d, 2H), 7.50 (t, 1H), 7.38 (t, 2H), 4.28 (m, 2H), 2.2−2.9 (m, 6H), 2.00 (m, 1H), 1.60 (m, 1H); Anal Calcd for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.44. Found: C, 67.05; H, 6.35.

(1*S*,3*R*)-1-Amino-3-(hydroxymethyl)cyclopentane (8). To a suspension of $LiAlH_4$ (0.038 g, 1 mmol) in dry THF (5 mL) was added a solution of oxime **7** (0.0233 g, 0.1 mmol) in dry THF (5 mL) with stirring at −5 °C. The reaction mixture was stirred for a further 5 h at 0 °C. The reaction was quenched with 0.5 mL of water and filtered. The filtrate was extracted with ether (4 × 5 mL), dried over sodium sulfate, and evaporated under reduced pressure to give a colorless oil (0.0047 g, 41%). The hydrochloride salt was prepared by dissolving the oil in 0.1 mL of concd HCl and evaporation to dryness. $[\alpha]^{23}_D$ −4.8° (*c*, 0.28, 1 M HCl) (lit.[13b] $[\alpha]^{20}_D$ −7.4°); ^1H NMR (D_2O) 3.55 (m, 2H), δ 3.53 (m, 1H), 2.26 (m, 2H), 2.07 (m, 1H), 1.85 (m, 1H), 1.69 (m, 1H), 1.50 (m, 1H), 1.29 (m, 1H). The ^1H NMR data was identical with those of a sample of racemic **8** prepared according to the method of Hronowski and Szarek.[18]

Acknowledgment. We thank the Natural Sciences and Engineering Research Council for financial support of this work. Feng-de Xi also thanks Scientech (Hong Kong) for fellowship support.

JO9517151