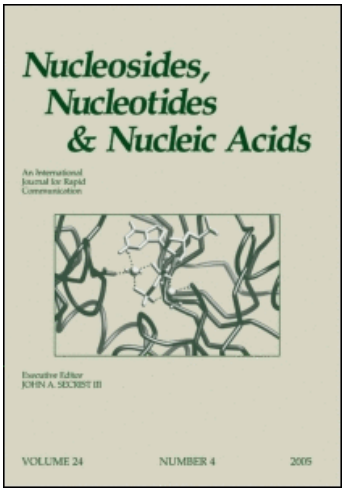


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Stereoselective Synthesis of Some 3-Nitroglucopyranosyladenine Analogues via a Nitroolefin: Intermediate as Potential Therapeutic Agents

Kazunari TSUBOIKE[a]; Katsumaro MINAMOTO[a]; Gen MIZUNO[a]; Kazufumi YANAGIHARA[b]
[a] Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Nagoya, Japan [b] Synthesis Research Dept., Central Research Institute, Chiba, Japan

To cite this Article TSUBOIKE, Kazunari , MINAMOTO, Katsumaro , MIZUNO, Gen and YANAGIHARA, Kazufumi(1998) 'Stereoselective Synthesis of Some 3-Nitroglucopyranosyladenine Analogues via a Nitroolefin: Intermediate as Potential Therapeutic Agents', Nucleosides, Nucleotides and Nucleic Acids, 17: 4, 745 — 758
To link to this Article: DOI: 10.1080/07328319808004672
URL: http://dx.doi.org/10.1080/07328319808004672

NUCLEOSIDES & NUCLEOTIDES, 17(4), 745-758 (1998)

STEREOSELECTIVE SYNTHESIS OF SOME 3-NITROGLUCOPYRANOSYLADENINE ANALOGUES VIA A NITROOLEFIN INTERMEDIATE AS POTENTIAL THERAPEUTIC AGENTS ¶

Kazunari TSUBOIKE, Katsumaro MINAMOTO*, Gen MIZUNO and Kazufumi YANAGIHARA †

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464, Japan; † Synthesis Research Dept., Central Research Institute, Nissan Chemical Industries, Ltd., 722-1, Tsuboi-cho, Funabashi-shi, Chiba 274, Japan

ABSTRACT: Three isomers of 9-(4,6-*O*-benzylidene-3-deoxy-β-D-hexopyranosyl) adenines (**2-4**) were isolated. The manno isomer **2** could be isomerized to the gluco isomer **3**. The manno (**2**) and galacto isomer (**4**) were deprotected to **5** and **7**, respectively. Michael addition of some organic amines and thiolates to the nitroolefin intermediate (**8**) gave the corresponding 2-(substituted)-3-nitro-glucopyranosides (**9a-h**). Compounds **9a,c,h** were deprotected to **10a,c,h**. Sodium azide with **8** gave the triazolo nucleoside **11**, which was deprotected to **12**. 2-Deoxy-3-nitro analogue **14** was also obtained.

Although the synthesis and biological studies of numerous aminosugar nucleosides have been documented,[1] the corresponding studies on nitrosugar nucleosides are notably lacking. A number of nitro or nitroso group-containing compounds are known to possess hazardous biological activities involving carcinogenicity,[2] while some nitro group-containing antibiotics of natural origin such as Chloramphenicol or Aureothin are known.[2]

In view of the recorded, various biological redox processes involving nitrite or nitrate compounds,[2] biological survey of a variety of nitro-, nitroso- or

¶ This paper is dedicated to the memory of the late Professor Tsujiaki Hata.

Tel, Fax: (052)789-3196. e-mail: minamoto@apchem.nagoya-u.ac.jp

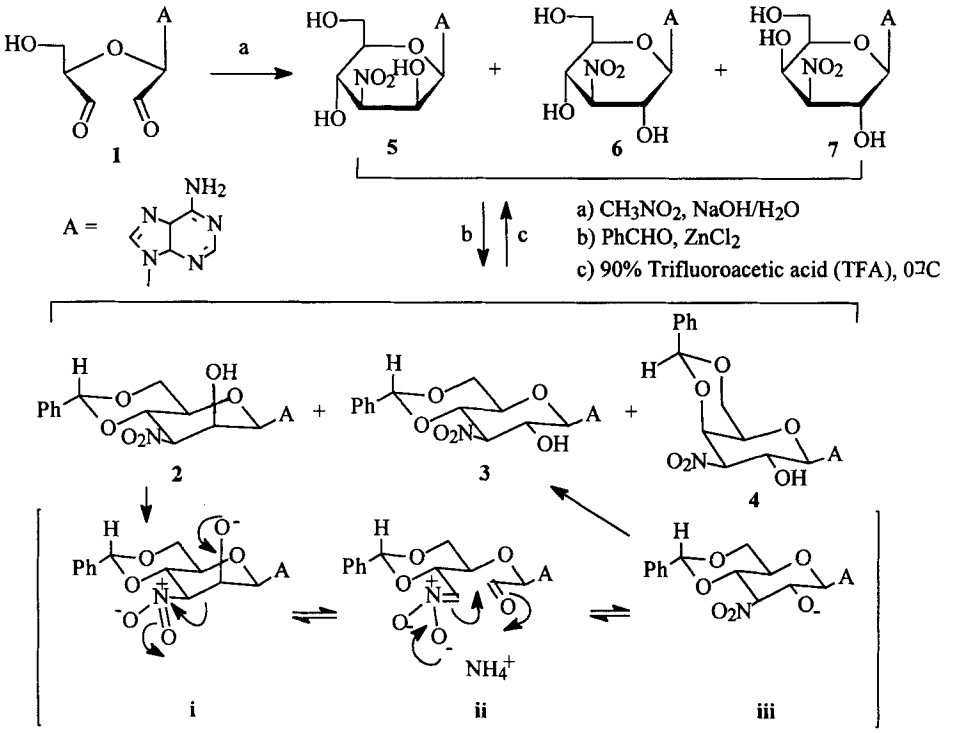
hydroxylaminosugar nucleosides would be both interesting and important. On the basis of these considerations, we recently reported the synthesis of some 2-(substituted)-2,3-dideoxy-3-nitroglucopyranosyl uracils *via* a nitroolefin intermediate.[3] As an extension, we herein describe the results of a rather tedious synthetic work aiming at similar analogues of adenine series.[4]

An inseparable diastereomeric mixture of 9-(3-deoxy-3-nitro-β-D-hexopyranosyl)adenines[6] obtainable from adenosine dialdehyde **1** and nitromethane was benzylidenated (SCHEME 1). The sparing solubility of the obtained mixture of the protected products in solvents suitable to column chromatography have hampered the large scale synthesis of these compounds. The selected, standardized experiment described here gave a 33% yield of 9-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranosyl)adenine (**3**) together with mannopyranosyl (**2**) (10%) and galactopyranosyl analogues (**4**) (20%). The structures of these compounds were established on the basis of the $J_{1,2}$, $J_{2,3}$ and $J_{3,4}$ values in their ^{1}H NMR spectra (see experimental section). The structure of the gluco isomer as starting material in this work was confirmed by the generally large J values. All these compounds proved to have an unusually strong propensity for solvation. Interestingly, the manno isomer **2** proved to be convertible into the thermodynamically more stable gluco isomer **3** by treatment with strong bases (7 N NH_3/MeOH, 100 ℃; or t-BuOK/DMF, room temperature). This observation is unprecedented in the area of nucleoside chemistry and explicable in terms of Retro-Henry reaction involving the intermediates **i**, **ii** and **iii**. This reaction usually gives an equilibrium mixture of **2** and **3**, overwhelmingly in favor of the latter. Repeated attempts at quantitative conversion of **2** into **3** for the sake of easier separation of **3** have failed.

Compounds **2** and **4** were deblocked with the use of 90% trifluoroacetic acid (TFA) and the parent compound, 9-(3-deoxy-3-nitro-β-D-mannopyranosyl)adenine (**5**) as well as its galacto isomer **7** was obtained as a crystalline monohydrate and hydrochloride salt, respectively, while the deprotected form of **3** has resisted crystallization.[7]

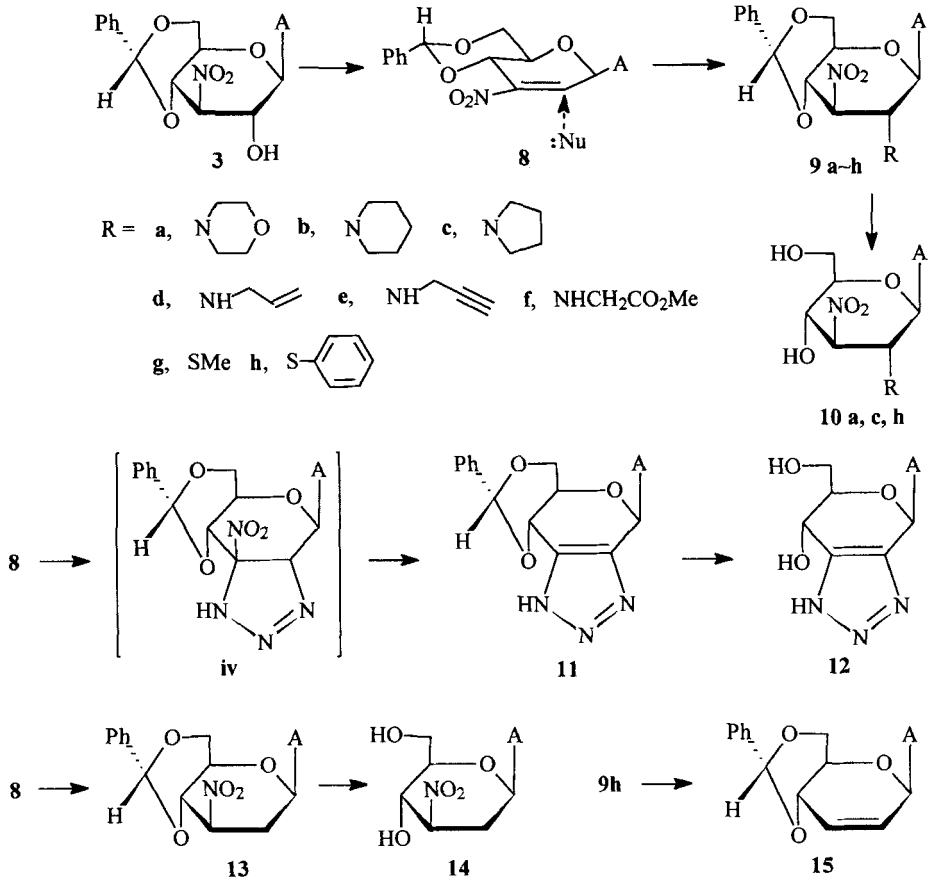
Treatment of compound **3** with acetic anhydride or methanesulfonic acid gave 9-(4,6-*O*-benzylidene-2,3-didehydro-2,3-dideoxy-3-nitro-β-D-hexopyranosyl)adenine (**8**) as nearly pure crystals, which could be stored in a refrigerator at least for a few weeks without notable decomposition for the next use, although satisfactory elemental analysis values for this compound have not yet been attained. Thus, this ready-made intermediate **8** was used sometimes as Michael acceptor together with the *in situ*-generated **8** in this piece of work (SCHEME 2).

Michael addition reactions of morpholine, piperidine, pyrrolidine, allylamine, propargylamine, methyl glycinate, methanethiolate and phenylthiolate with **8** were



SCHEME 1

conducted under a variety of conditions to give the corresponding 9-[4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-2-(substituted-amino or substituted-thio)-β-D-glucopyranosyl]-adenines (**9a-h**) (see experimental section). The yields were generally good to excellent except the cases of **9f,g**. On the other hand, treatment of **8** with sodium azide gave 9-[4,6-*O*-benzylidene-2,3-didehydro-2,3-dideoxy-2,3-(1,2,3-triazolo)-β-D-hexopyranosyl]-adenine (**11**), whose structure coincided with the general spectral data: striking paramagnetic shifts of the ^{1}H NMR signals of H-1 and H-4 are observed. This compound might have formed through the 1,3-dipolar addition reaction of the azide followed by elimination of nitrous acid. However, another possibility that an initially formed Michael addition product having a 2-azido group changed to the intermediate **iv** can not be ruled out (unusual azide insertion into the acidic H-3 bond as in the case of the well known tetrazole formations by the insertion of an azide group into an adjacent NH group on a heterocyclic ring[8]).[10] Anyway, the formation of **11** is in contrast with the facile isolation of a similar Michael adduct with a 2-azido group in the uracil series.[9,10] Deprotection of compound **9a**, **9c** as well as **9h** with 90% TFA gave 9-(2,3-dideoxy-2-*N*-morpholino-3-



SCHEME 2

nitro-β-D-glucopyranosyl)adenine (**10a**), its 2-pyrrolidino (**10c**) and 2-phenylthio analogue (**10h**), respectively, as a crystalline substance, whereas complete isolation of the deprotected forms of **9b** and **9d-g** has been unsuccessful: the deprotected forms of the Michael adducts from the primary amines were especially unstable and vulnerable to complex decomposition even on silica gel chromatography as in the case of uracil series.[3] Acidic deprotection of **11** was also difficult but the isolation of 9-[2,3-didehydro-2,3-dideoxy-2,3-(1,2,3-triazolo)-β-D-hexopyranosyl]adenine (**12**) was barely achieved under controlled conditions. Thus, as in the cases of uracil series,[3] the Michael additions of nucleophiles to the nitroolefin **8** proceeded in stereoselective way. This observation may also be explicable by the mechanism shown previously[3]: probably owing to the steric hindrance by the base, the nucleophiles might have attacked the 2-position of the

nitroolefin **8** from α-side (axial attack) to yield transiently a boat-like *aci*-nitro intermediate, which may flip to the more stable chair form with the 2-substituent in the equatorial configuration.

By analogy with the 2,3-dideoxy or 2,3-didehydro-2,3-dideoxy pentofuranosyl nucleosides as anti-AIDS substances,[11] the intermediate **8** was reduced to 9-(4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*arabino*-hexopyranosyl)adenine (**13**), which was deprotected to 9-(2,3-dideoxy-3-nitro-β-D-*arabino*-hexopyranosyl)adenine (**14**), while compound **9h** with tributyltin hydride-AIBN afforded a low yield of 9-(4,6-*O*-benzylidene-2,3-didehydro-2,3-dideoxy-β-D-hexopyranosyl)adenine (**15**). The formations of **13** and **15** suggest further important chemical modifications in the area of 2,3-dideoxy- and 2,3-didehydro-2,3-dideoxy-hexopyranosyl adenine nucleosides.

Experimental Section

Mps were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. UV spectra were measured on a JASCO Ubest V-560DS spectrophotometer. The 200 MHz ^{1}H NMR spectra were recorded on a GEMINI-200 FT NMR spectrometer. Elemental analyses were conducted using a Perkin-Elmer 240B elemental analyser. For preparative scale thick-layer chromatography, glass plates coated with 2-mm thickness of Wakogel B-5F silica gel were used after activation at 100 ℃ for 10-12 h. For column chromatography, Wakogel C-300 silica gel was used. All evaporations were carried out under reduced pressure at or below 40 ℃.

9-(4,6-*O*-Benzylidene-3-deoxy-3-nitro-β-D-hexopyranosyl)adenines (2-4). A mixture of 9-(3-deoxy-3-nitro-β-D-hexopyranosyl)adenines obtained through the dialdehyde (**1**) starting from adenosine (1.07 g, 3.99 mmol), benzaldehyde (7.0 ml, 69 mmol) and zinc chloride (1.98 g, 14.5 mmol) was stirred for 6 h at room temperature. After evaporation of the reaction mixture to dryness, the residue was partitioned between ethyl acetate (150 ml) and 1N sodium hydrogen carbonate (30 ml). The separated aqueous layer was again extracted with ethyl acetate (2 × 30 ml). The combined organic layer was dried over sodium sulfate and evaporated. The residue was thoroughly digested with diethyl ether (2 × 20 ml) and the ether washings decanted off. The residue was then fractionated on a silica gel column (3.5 × 35 cm; 10% MeOH/$CHCl_3$) to give from the first fraction 175.8 mg (10%) of 9-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-mannopyranosyl)adenine (**2**), mp 268 ℃ (MeOH): λmax (MeOH) 259 nm (ε 16300) ; ^{1}H NMR (Me_2SO-d_6) δ 3.31(2.5-3 H, br s, MeOH, H_2O), 3.95 (2H, m, H-5, H-6b), 4.33 (1H, m, H-6a), 4.52 (1H, m, H-2), 4.69 (1H, dd, $J_{4,5}$ = 10.0, H-4), 5.65 (1H, dd, $J_{3,2}$ = 2.8, $J_{3,4}$ = 10.2, H-3), 5.87 (1H, s, PhC**H**), 6.31 (1H, s, H-1), 6.62 (1H, d, $J_{OH,2}$ = 6.8, OH), 7.35(2H, br s, NH_2), 7.41 (5H, br s, aryl), 8.14 (1H, s, H2), 8.20 (1H, s, H8). *Anal.*

Calcd. for $C_{18}H_{18}N_6O_6 \cdot {}^1/_2CH_3OH \cdot {}^1/_2H_2O$: C, 50.57; H, 4.82; N, 19.13. Found: C, 50.61; H, 4.82;N, 19.10. The second fraction gave 562.7 mg (33 %) of hydrate of 9-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranosyl)adenine (**3**) after recrystallization from methanol, mp 268-269 ℃ (dec): λmax (MeOH) 25800 nm (ε 33100); ^{1}H NMR (Me_2SO-d_6) δ 3.34 (ca. 2H, br s, H_2O), 3.82 (1H, dd, $J_{6b,5}$ = 10.0, H-6b), 4.02 (1H, m, H-5), 4.30 (1H, dd, J_{gem} = 9.9, $J_{6a,5}$ = 4.9, H-6a), 4.36 (1H, dd, $J_{4,5}$ = 9.4, H-4), 5.03 (1H, m, H-2), 5.29 (1H, dd, $J_{3,2}$ = 9.7, $J_{3,4}$ = 9.8, H-3), 5.78 (1H, s, PhC**H**), 5.87 (1H, d, $J_{1,2}$ = 8.8, H-1), 6.47 (1H, d, $J_{OH,2}$ = 6.6, OH), 7.35 (2H, br s, NH_2), 7.40 (5H, br s, aryl), 8.20 (1H, s, H2), 8.45 (1H, s, H8). *Anal.* Calcd. for $C_{18}H_{18}N_6O_6 \cdot {}^2/_3H_2O$: C, 50.70; H, 4.57; N, 19.71. Found: C, 50.68; H, 4.54; N, 19.76. The third fraction gave 348 mg (20%) of 9-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-galactopyranosyl)adenine (**4**) as a methanolate-hydrate after recrystallization from methanol, mp 196-197 ℃ (sint): λmax (MeOH) 258 nm (ε 23200); ^{1}H NMR (Me_2SO-d_6) δ 3.31 (ca. 2H, br s, MeOH, H_2O), 4.10 (3H, m, H-5, H-6a, H-6b), 4.89 (1H, d, H-4), 5.16 (1H, m, H-2), 5.38 (1H, dd, $J_{3,2}$ = 10.2, $J_{3,4}$ = 3.5, H-3), 5.70 (1H, s, PhC**H**), 5.74 (1H, d, $J_{1,2}$ = 9.4, H-1), 6.14 (1H, d, $J_{OH,2}$ = 6.0, OH), 7.33 (2H, br s, NH_2), 7.45 (5H, m, aryl), 8.21 (1H, s, H2), 8.42 (1H, s, H8). *Anal.* Calcd. for $C_{18}H_{18}N_6O_6 \cdot {}^1/_2CH_3OH \cdot {}^1/_4H_2O$: C, 51.09; H, 4.75; N, 19.32. Found: C, 51.15, H, 4.76; N, 19.41.

Conversion of 9-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-mannopyranosyl)-adenine (2) into 9-(4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranosyl)adenine (3). A mixture of compound **2** (102 mg, 0.23 mmol) and 7 N ammonia in methanol (3 ml) was heated in a pressure tube at 100 ℃ for 140 min. After cooling, the mixture was evaporated and the residue partitioned between ethyl acetate (30 ml) and water (7 ml). The separated organic layer was washed with water (5 ml), dried over sodium sulfate, treated with Norit and thoroughly evaporated to a foam, ^{1}H NMR spectrometric estimation of which on the basis of signal intensities of 8-protons showed that the product was a 94:6 mixture of **3** and **2**. Treating the foam with a small volume of methanol gave 82 mg (80%) of **3** as crystals.

9-(3-Deoxy-3-nitro-β-D-mannopyranosyl)adenine (5). A mixture of compound **2** (201 mg, 0.46 mmol) and 80% acetic acid (12 ml) was heated at 70-75 ℃ for 6.5 h and evaporated. The residue was repeatedly co-evaporated with a 1:1 mixture of methanol and ethanol and then fractionated on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 8:2, developed 3 times). The major band was eluted with methanol to give a glass, which gave very gradually 55 mg (35%) of wooly crystals (**5**) from a small volume of water. This substance sintered at 190 ℃ (mp above 290 ℃): λmax (MeOH) 258 nm (ε 26400). *Anal.* Calcd for $C_{11}H_{14}N_6O_6 \cdot H_2O$: C, 38.37; H, 4.68; N, 24.41. Found: C, 38.55; H, 4.51; N, 24.40.

9-(3-Deoxy-3-nitro-β-D-galactopyranosyl)adenine (7). A mixture of compound **4** (200 mg, 0.46 mmol) and 90% trifluoroacetic acid (TFA) was left at 0 ℃ for 43 min and evaporated. The residue was repeatedly co-evaporated with 50% ethanol (6 × 4 ml) and then with EtOH/MeOH (2:1) to dryness. The residue in MeOH (7 ml) was neutralized with solid $NaHCO_3$ and the solid filtered off. The filtrate was evaporated and the residue fractionated on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 8:2, developed 3 times). Elution of the major fraction with methanol gave a nearly TLC-homogeneous glass, which resisted crystallization. The product in MeOH was acidified with 1N HCl and the solution evaporated. The residue was repeatedly co-evaporated with a mixture of MeOH and EtOH and left at room temperature with a few drops of MeOH to give crystals after 2 days. Recrystallization from a small volume of MeOH gave 80 mg (46%) of **7** as monohydrated hydrochloride, which sintered at 195 ℃ but did not melt below 290 ℃: λmax 259 nm (ε 17200). *Anal.* Calcd for $C_{11}H_{14}N_6O_6 \cdot HCl \cdot H_2O$: C, 34.70; H, 4.50; N, 22.07. Found: C, 34.79; H, 4.41; N, 22.07.

Preparation of 9-(4,6-*O*-benzylidene-2,3-didehydro-2,3-dideoxy-3-nitro-β-D-hexopyranosyl)adenine (8) as a crude intermediate. To an ice-cold solution of **3** (250 mg, 0.59 mmol) in a mixture of dichloromethane (4.5 ml) and pyridine (1.1 ml) was added acetic anhydride (0.083 ml, 0.88 mmol) and the mixture stirred at 0 ℃ for 2 h. The mixture was treated with methanol (1 ml) at room temperature for 15 min, evaporated and the residue fractionated on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 9:1). Elution of the major fraction with ethyl acetate gave 227 mg (ca. 98%) of **8** as a nearly TLC-pure foam, which crystallized from a small volume of methanol, mp 259 ℃ (sint): ^{1}H NMR (Me_2SO-d_6) δ 4.24 (1H, br d, $J_{6a,5}$ = 9.7, H-6a), 4.57 (1H, dd, J_{gem} = 10.2, $J_{6b,5}$ = 4.4, H-6b), 4.85 (1H, m, H-5), 4.92 (1H, d, $J_{4,5}$ = 12.2, H-4, partially overlapped the signal of H-5), 5.82 (1H, s, PhC**H**), 6.67 (1H, s, H-1), 7.44 (6H, br s, aryl and H-2), 7.66 (2H, br s, NH_2), 8.31 (1H, s, H2), 8.59 (1H, s, H8).

9-(4,6-*O*-Benzylidene-2,3-dideoxy-2-*N*-morpholino-3-nitro-β-D-gluco-pyranosyl)adenine (9a). To a mixture of nearly pure **8** (261 mg, 0.71 mmol) (see the above experiment) and potassium fluoride (34 mg, 0.59 mmol) in tetrahydrofuran (THF) (3.3 ml) was added morpholine (0.10 ml, 1.17 mmol) and the mixture heated to reflux for 2 h. After the solvent was evaporated off, the residue was partitioned between ethyl acetate (35 ml) and water (35 ml). The separated aqueous phase was extracted with ethyl acetate (2 × 10 ml). The combined organic layer was dried over sodium sulfate, evaporated and the obtained paste fractionated on a silica plate (20 × 20 cm; developed once with $CHCl_3$/MeOH, 9:1, then with $CHCl_3$/MeOH, 8:2, once) to give from the major fraction 232 mg (70%) of **9a** after crystallization from MeOH, mp 245 ℃ (dec): λmax (MeOH) 260 nm (ε 16300); ^{1}H NMR (Me_2SO-d_6) δ 2.35 -2.67 (4H, m, morpholino-H),

3.35 (4H, m,morpholino-H), 3.76 (1H, m, H-5), 3.38 (1H, br d, $J_{6a,5}$ = 9.9, H-6a), 4.02 (1H, dd, H-2), 4.39 (1H, dd, $J_{4,5}$ = 9.8, H-4), 4.40 (1H, dd, J_{gem} = 10.1, $J_{6b,5}$ = 3.4, H-6b), 5.11 (1H, dd, $J_{3,2}$ = 10.2, $J_{3,4}$ = 10.0, H-3), 5.61 (1H, s, PhC**H**), 5.93 (1H, d, $J_{1,2}$ = 10.2, H-1), 7.27 (2H, s, NH_2), 7.40 (5H, m, aryl), 8.02 (1H, s, H2), 8.42 (1H, s, H8). *Anal.* Calcd for $C_{22}H_{25}N_7O_6 \cdot {}^2/_3CH_3OH$: C, 53.93; H, 5.52; N, 19.42. Found: C, 53.84; H, 5.50; N, 19.38.

9-(4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-2-*N*-piperidino-β-D-gluco-pyranosyl)adenine (9b). Compound **8** (261 mg, 0.71 mmol) was reacted with piperidine (0.11 ml, 1.14 mmol) using the same procedure with that for compound **9a** to give , after preparative TLC (20 × 20 cm; 20% MeOH in $CHCl_3$) and crystallization from MeOH, 226 mg (71%) of **9b**, mp 249-250 ℃: λmax (MeOH) 260 nm (ε 15700); ^{1}H NMR (Me_2SO-d_6) δ 1.09 (6H, br m, piperidino-H), 2.39 (4H, m, piperidino-H), 3.81 (1H, dd, J_{gem} = 10.0, $J_{6a,5}$ = 10.0, H-6a), 4.02 (1H, m, H-5), 4.33 (3H, m, H-2, H-4 and H-6b), 5.59 (1H, dd, $J_{3,2}$ = 10.5, $J_{3,4}$ = 10.5, H-3), 5.77 (1H, s, PhC**H**), 6.10 (1H, d, $J_{1,2}$ = 9.4, H-1), 7.40 (7H, br s, aryl, NH_2), 8.22 (1H, s, H2), 8.60 (1H, s, H8). *Anal.* Calcd for $C_{23}H_{27}N_7O_5$: C, 57.37; H, 5.65; N, 20.36. Found: C, 57.41; H, 5.64; N, 20.31.

9-(4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-2-*N*-pyrrolidino-β-D-gluco-pyranosyl)adenine (9c). To a mixture of **3** (200 mg, 0.47 mmol) and 4-dimethylaminopyridine (4-DAP) (27 mg, 0.22 mmol) in EtOAc (12 ml) was added acetic anhydride (0.065 ml, 0.69 mmol). After 50 min, pyrrolidine (0.1 ml, 1.2 mmol) was added and the mixture stirred at room temperature for 20 min. At this stage, complete consumption of the starting material as well as intermediates and formation of a single product were confirmed by TLC (silica, $CHCl_3$/MeOH, 9:1). The mixture was diluted with EtOAc (20 ml) and washed with water (2 × 20 ml). The organic layer was dried over sodium sulfate and evaporated to give a crystalline solid, which was recrystallized from MeOH to yield 184 mg (82.9%) of **9c**, mp 212-213 ℃: λmax (MeOH) 259 nm (ε 26500); ^{1}H NMR (Me_2SO-d_6) δ 1.31 (4H, br s, pyrrolidino-H), 2.38 (2H, br m, pyrrolidino-H), 2.63 (2H, br m, pyrrolidino-H), 3.83 (1H, dd, J_{gem} = 9.8, $J_{6a,5}$ = 9.7, H-6a), 4.05 (1H, ddd, $J_{5,6a}$ = 9.7, $J_{5,6b}$ = 4.6, $J_{5,4}$ = 9.6, H-5), 4.32 (1H, dd, $J_{6b,5}$ = 4.6, H-6b), 4.38 (1H, dd, $J_{4,5}$ = 9.6, $J_{4,3}$ = 10.3, H-4), 4.67 (1H, br t, H-2), 5.63 (1H, dd, $J_{3,2}$ = 10.4, $J_{3,4}$ = 10.3, H-3), 5.78 (1H, s, PhC**H**), 6.20 (1H, d, $J_{1,2}$ = 9.3, H-1), 7.39 (2H, s, NH_2), 7.41 (5H, s, aryl), 8.21 (1H, s, H2), 8.51 (1H, s, H8). *Anal.* Calcd for $C_{22}H_{25}N_7O_5$: C, 56.52; H, 5.39; N, 20.98. Found: C, 56.61; H, 5.35; N, 20.93.

9-(2-*N*-Allyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranosyl)-adenine (9d). The intermediate **8** (261 mg, 0.71 mmol) was reacted with allylamine (0.09 ml, 1.23 mmol) using the same procedure with that for compound **9a** to give, after preparative TLC (20 × 20 cm; 20% MeOH in $CHCl_3$, twice developed) and

crystallization from MeOH, 255 mg (85%) of **9d**, mp 178 °C (dec): λmax (MeOH) 260 nm (ε 14900); ^{1}H NMR (Me_2SO-d_6) δ 2.43 (1H, m, -N**H**-CH_2-CH=CH_2), 2.72 (2H, m, -NH-C**H**$_2$-CH=CH_2), 3.30 (ca. 2H, s, MeOH), 3.86 (2H, m, H-5 and H-6a), 4.28 (1H, ill-resolved dd, H-2), 4.28 (1H, m, H-6b, overlapped the signals of H-4 and H-2), 4.36 (1H, br d, $J_{4,5}$ = 10.3, H-4), 4.75 (2H, m, -NH-CH_2-CH=C**H**$_2$), 5.28 (1H, dd, $J_{3,2}$ = 10.2, $J_{3,4}$ = 10.4, H-3), 5.34 (1H, m, -NH-CH_2-C**H**=CH_2), 5.77 (1H, s, PhC**H**), 5.94 (1H, d, $J_{1,2}$ = 9.6, H-1), 7.35 (2H, s, NH_2), 7.40 (5H, s, aryl), 8.20 (1H, s, H2), 8.43 (1H, s, H8). *Anal.* Calcd for $C_{21}H_{23}N_7O_5 \cdot {}^1/_2CH_3OH$: C, 55.00; H, 5.37; N, 20.88. Found: C, 54.99; H, 5.34; N, 20.92.

9-(4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-2-*N*-propargyl-β-D-glucopyranosyl)-adenine (9e). The reaction of the nitroolefin **8** (261 mg, 0.71 mmol) with propargylamine (0.08 ml, 1.14 mmol) under the same reaction conditions with those for **9a** afforded, after preparative TLC (20 × 20 cm; 10% MeOH in $CHCl_3$, twice developed) and recrystallization from MeOH, 222 mg (75%) of **9e**, mp 206-207 °C (dec): λmax (MeOH) 260 nm (ε 13000); ^{1}H NMR (Me_2SO-d_6) δ 2.75-3.19 (4H, m -N**H**-C**H**$_2$-C≡C**H**), 3.77-3.95 (2H, m, H-5, H-6a), 4.25-4.47 (3H, m, H-2, H-4, H-6b), 5.33 (1H, dd, $J_{3,2}$ = 10.4, $J_{3,4}$ = 10.4, H-3), 5.78 (1H, s, PhC**H**), 5.96 (1H, d, $J_{1,2}$ = 9.4, H-1), 7.37 (2H, s, NH_2), 7.40 (5H, s, aryl), 8.21 (1H, s, H2), 8.43 (1H, s, H8).

9-(4,6-*O*-Benzylidene-2,3-dideoxy-2-methoxycarbonylmethyleneamino-3-nitro-β-D-glucopyranosyl)adenine (9f). To a mixture of **8** (261 mg, 0.71 mmol) and potassium fluoride (102 mg, 1.76 mmol) in THF (3.3 ml) was added glycine methyl ester hydrochloride (144 mg, 1.15 mmol) and the mixture heated to reflux for 4.5 h. No noticeable reaction was observed. Hence, water (0.3 ml) was added and the mixture heated to reflux for additional 4.5 h. After evaporation, the residue was partitioned between ethyl acetate (35 ml) and water (35 ml). The separated aqueous layer was extracted with ethyl acetate (10 ml). The combined organic layer was dried over sodium sulfate, evaporated and the residue fractionated on 2 sheets of silica plates (20 × 20 cm; 10% MeOH in CH_2Cl_2, twice developed) to give 142 mg (44%) of a TLC-pure foam (**9f**), which crystallized from MeOH, mp 205-206 °C (dec): λmax (MeOH) 260 nm (ε 19400); ^{1}H NMR (Me_2SO-d_6) δ 3.03 (1H, d, C**H**$_a$H$_b$$CO_2$Me), 3.14 (1H, d, J_{gem} = 14.0, CH_a**H**$_b$$CO_2$Me), 3.36 (3H, s, CO_2Me), 3.84 (2H, m, H-5, H-6a), 4.25-4.55 (3H, m, H-2, H-4, H-6b), 5.37 (1H, dd, $J_{3,2}$ = 10.3, $J_{3,4}$ = 10.3, H-3), 5.77 (1H, s, PhC**H**), 5.95 (1H, d, $J_{1,2}$ = 9.4, H-1), 7.40 (7H, br s, aryl, NH_2), 8.20 (1H, s, H2), 8.43 (1H, s, H8). *Anal.* Calcd for $C_{21}H_{23}N_7O_7$: C, 51.96; H, 4.78; N, 20.20. Found: C, 51.91; H, 4.78; N, 20.20.

9-(4,6-*O*-Benzylidene-2,3-dideoxy-2-methylthio-3-nitro-β-D-glucopyranosyl)-adenine (9g). To a stirred ice-cooled solution of **3** (200 mg, 0.47 mmol) in pyridine (3 ml) was added acetic anhydride (0.07 ml, 0.7 mmol). After stirring at 0 °C for 1 h, the

mixture was treated with MeOH (1 ml) for 10 min and evaporated. A mixture of the residue, potassium fluoride (27 mg, 0.46 mmol) and sodium methanethiolate (ca. 15% aqueous solution) (0.44 ml, ca. 0.94 mmol) in THF (4.0 ml) was heated to reflux for 140 min and evaporated. The residue was partitioned between ethyl acetate (50 ml) and water (20 ml). The separated organic layer was dried over sodium sulfate, evaporated and the residue fractionated on a silica plate (20 × 20 cm; 15% MeOH in $CHCl_3$) to give 52 mg (24%) of **9g** as crystals of mp 245 ℃ (dec) after elution with MeOH and recrystallization from the same solvent: λmax (MeOH) 260 nm (ε 11000); ^{1}H NMR (Me_2SO-d_6) δ 1.94 (3H, s, SMe), 3.17 (3H, d, J = 5.4, MeOH), 3.85 (1H, dd, $J_{6a,5}$ = 10.2, H-6a), 4.09 (1H, m, H-5), 4.31 (1H, dd, J_{gem} = 10.2, $J_{6b,5}$ = 4.7, H-6b), 4.42 (1H, dd, $J_{4,5}$ = 9.6, H-4), 4.42 (1H, dd, $J_{2,4}$ = 9.6, H-2, overlapped the signal of H-4), 5.63 (1H, dd, $J_{3,2}$ = 10.0, $J_{3,4}$ = 10.4, H-3), 5.82 (1H, s, PhC**H**), 6.14 (1H, d, $J_{1,2}$ = 9.6, H-1), 7.38 (2H, s, NH_2), 7.41 (5H, s, aryl), 8.20 (1H, s, H2), 8.57 (1H, s, H8). *Anal.* Calcd for $C_{19}H_{20}N_6O_5S \cdot CH_3OH$: C, 50.41; H, 5.08; N, 17.64. Found: C, 50.32; H, 5.13; N, 17.68.

9-(4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-2-phenylthio-β-D-glucopyranosyl)-adenine (9h). A mixture of **8** (737 mg, 2.0 mmol), potassium fluoride (85 mg, 1.46 mmol) and thiophenol (0.38 ml, 2.92 mmol) in THF (10 ml) was heated to reflux for 3 h. The mixture was evaporated and the residue partitioned between ethyl acetate (200 ml) and water (25 ml). The separated organic layer was dried over sodium sulfate and evaporated to give a crystalline solid, which was recrystallized from MeOH to give 745 mg (71%) of **9h**, mp 247 ℃ (dec): λmax (MeOH) 259 nm (ε 17200); ^{1}H NMR (Me_2SO-d_6) δ 3.82 (1H, ill-resolved dd, $J_{6a,5}$ =10.0, H-6a), 4.05 (1H, m, H-5), 4.29 (1H, dd, J_{gem} = 10.0, $J_{6b,5}$ = 4.5, H-6b), 4.46 (1H, dd, $J_{4,5}$ = 9.7, H-4), 5.57 (1H, dd, $J_{3,2}$ = 10.6, $J_{3,4}$ = 10.2, H-3), 5.83 (1H, s, PhC**H**), 6.09 (1H, m, H-2), 6.84 (1H, d, $J_{1,2}$ = 7.0, H-1), 7.07 (5H, br s, aryl), 7.24 (2H, br s, NH_2), 7.40 (5H, s, aryl), 8.02 (1H, s, H2), 8.33 (1H, s, H8). *Anal.* Calcd for $C_{24}H_{22}N_6O_5S$: C, 56.91; H, 4.38; N, 16.59. Found: C, 56.99; H, 4.41; N, 16.29.

9-(2,3-Dideoxy-2-*N*-morpholino-3-nitro-β-D-glucopyranosyl)adenine (10a). Compound **9a** (190 mg, 0.38 mmol) in 90% TFA (5 ml) was left at room temperature for 2 h and evaporated. The residue was repeatedly co-evaporated with 50% EtOH (5 × 5 ml), then with MeOH/EtOH (1:1) (5 × 5 ml) and fractionated on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 8:2). The major fraction was eluted with MeOH and concentration of the combined eluants gave crystals, which was collected by suction (58 mg). The filtrate was again fractionated on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 85:15, twice developed) to give another crop. The total was recrystallized from a small volume of MeOH to afford 90 mg (58%) of **10a**, mp170-173 ℃: ^{1}H NMR (Me_2SO-d_6) δ 2.37 (4H, m, morpholino-H), 3.17 (3-4H, s, overlapped the morpholino-H, MeOH, H_2O), 3.20 (4H, m, morpholino-H), 3.4-3.8 (3H, m, H-6a, H-6b, H-5), 4.05 (2H, m, H-4, H-2), 4.75

(1H, 6-OH), 5.25 (1H, dd, $J_{3,4}$ = 10.0, $J_{3,2}$ = 10.6, H-3), 5.99 (1H, d, $J_{1,2}$ = 9.8, H-1), 6.07 (1H, d, $J_{OH,4}$ = 6.4, 4-OH), 7.38 (2H, s, NH_2), 8.21 (1H, s, H2), 8.59 (1H, s, H8). *Anal.* Calcd for $C_{15}H_{21}N_7O_6 \cdot CH_3OH \cdot {}^1/_2H_2O$: C,44.03; H, 6.01; N, 22.46. Found: C, 44.14; H, 5.72; N, 22.54.

9-(2,3-Dideoxy-2-*N*-pyrrolidino-3-nitro-β-D-glucopyranosyl)adenine (10c). A solution of compound **9c** (236 mg, 0.50 mmol) in 90% TFA (4 ml) was stirred at 0 °C for 30 min and evaporated. The residue was repeatedly co-evaporated with 60% EtOH (5 × 5 ml) and then with EtOH (5 × 5 ml) (partial decomposition of the product was shown by TLC at this evaporation step). The residue in EtOH (10 ml) was neutralized with solid $NaHCO_3$ and filtered. The filtrate was evaporated and the residue fractionated on a silica gel column (2.5 × 15 cm; 10% EtOH in $CHCl_3$). The major fraction was recrystallized from MeOH to give 107 mg (55%) of **10c**, mp 176-177 °C: λmax (MeOH) 259 nm (ε 27200); ^{1}H NMR (Me_2SO-d_6) δ 1.28 (4H, br s, pyrrolidino-H), 2.34 (2H, br m, pyrrolidino-H), 2.59 (2H, br m, pyrrolidino-H), 3.50 (1H, m, H-5), 3.68 (2H, m, H-6), 4.03 (1H, ddd, $J_{4,5}$ = 9.5, $J_{4,3}$ = 10.4, $J_{4,OH}$ = 6.2, H-4), 4.35 (1H, dd, $J_{2,1}$ = 10.1, $J_{2,3}$ = 10.4, H-2), 4.76 (1H, t, $J_{OH,6}$ = 5.4, 6-OH), 5.20 (1H, dd, $J_{3,2}$ = $J_{3,4}$ = 10.4, H-3), 6.00 (1H, d, $J_{OH,4}$ = 6.2, 4-OH), 6.01 (1H, d, $J_{1,2}$ = 9.6, H-1), 7.33 (2H, s, NH_2), 8.18 (1H, s, H2), 8.54 (1H, s, H8). *Anal.* Calcd for $C_{15}H_{21}N_7O_5 \cdot {}^1/_2H_2O$: C, 46.38; H, 5.71; N, 25.25. Found: C, 46.54; H, 5.66; N, 25.13.

9-(2,3-Dideoxy-2-phenylthio-3-nitro-β-D-glucopyranosyl)adenine (10h). A solution of **9h** (92 mg, 0.18 mmol) in 90% TFA (1.5 ml) was stirred at 0 °C for 25 min and evaporated. The residue was co-evaporated with 60% EtOH (4 × 3 ml) and then with EtOH (4 × 3 ml). The residue was digested with ether (2 ml) and the collected solid dried under high vacuum. The solid was dissolved in DMF (10 ml), neutralized with solid $NaHCO_3$ and the solid filtered off. The filtrate was evaporated and the residual solid recrystallized from a large volume of MeOH to give 50 mg (66%) of **10h**, which sintered above 210 °C and melted at 230-232 °C: λmax (MeOH) 258 nm (ε 13400); ^{1}H NMR (Me_2SO-d_6) δ 3.45 (1H, m, H-5), 3.66 (2H, m, H-6a and H-6b), 4.04 (1H, m, H-4), 4.78 (1H, t, $J_{OH,6}$ = 5.6, 6-OH), 5.04 (1H, dd, $J_{3,4}$ = $J_{3,2}$ = 10.4, H-3), 5.88 (1H, d, $J_{1,2}$ = 8.8, H-1), 6.22 (1H, d, $J_{OH,4}$ = 7.0, 4-OH), 6.92 (2H, s, NH_2), 6.9-7.3 (5H, m, phenyl), 8.07 (1H, br s, H2), 8.32 (1H, s, H8). *Anal.* Calcd for $C_{17}H_{18}N_6O_5S$: C, 48.89; H, 4.34; N, 20.09. Found: C, 48.90; H, 4.41; N, 19.92.

9-[4,6-*O*-Benzylidene-2,3-didehydro-2,3-dideoxy-2,3-(1,2,3-triazolo)-β-D-hexopyranosyl]adenine (11). Compound **3** (200 mg, 0.48 mmol) in pyridine (1.5 ml) was treated with acetic anhydride (0.057 ml, 0.61 mmol) at room temperature for 50 min. The mixture was treated with MeOH for 10 min, evaporated and the residue co-evaporated with EtOH (3 × 2 ml) below 38 °C to a paste, which was partitioned between ethyl

acetate (30 ml) and water (10 ml). The separated organic layer was again washed with water (3 × 10 ml), dried and thoroughly evaporated to a foam (finally under high vacuum), which was then taken in DMF (1.5 ml). After addition of sodium azide (111 mg, 1.71 mmol), the mixture was stirred for 2 days and evaporated. The residue in MeOH (20 ml) was neutralized with 2N AcOH/EtOH, evaporated and the residue partitioned between ethyl acetate (150 ml) and water (30 ml). The organic layer was dried over sodium sulfate and evaporated. The residue was dissolved in hot MeOH (50 ml) and cooled to room temperature to give a small amount of precipitate (a mixture of **11** and less polar impurities), which was filtered off. The filtrate gave very gradually congregated fine needles, recrystallization of which from MeOH gave 83 mg (43%) of **11**, mp 268-270 ℃: IR (KBr) no azide absorption; λmax (MeOH) 258 nm (ε 19900); ^{1}H NMR (Me_2SO-d_6) δ 3.32 (1H, br s, NH), 4.01 (1H, dd, $J_{6a,5}$ = 10.0, H-6a), 4.19 (1H, m, H-5), 4.35 (1H, dd, J_{gem} = 9.6, $J_{6b,5}$ = 4.1, H-6b), 5.23 (1H, br d, $J_{4,5}$ = 7.4, H-4), 5.98 (1H, s, PhC**H**), 7.50 (8H, m, phenyl, NH_2, H-1), 8.14 (1H, s, H2 or H8), 8.16 (1H, s, H8 or H2). *Anal.* Calcd for $C_{18}H_{16}N_8O_3$: C, 55.10; H, 4.11; N, 28.56. Found: C, 55.10; H, 4.02; N, 28.51.

9-[2,3-Didehydro-2,3-dideoxy-2,3-(1,2,3-triazolo)-β-D-hexopyranosyl]adenine (12). A solution of **11** (60 mg, 0.153 mmol) in 80% AcOH was stirred at 40-45 ℃ for 7.5 h. TLC-Monitoring at this stage indicated the presence of slight amounts of starting material and adenine.The mixture was evaporated, repeatedly co-evaporated with 60% EtOH, then with EtOH and the residue stirred with ether (6 ml). The sparingly soluble solid was collected by suction and again treated with ether (6 ml) overnight to give a nearly pure solid. The ether extracts were combined and fractionated on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 8:2, developed 3 times) to give a small amount of further crop. The combined solid was recrystallized from MeOH to give 15 mg (32.2%) of **12**, mp 219-221 ℃: λmax 258 nm (ε 23300); *Anal.* Calcd for $C_{11}H_{12}N_8O_3$: C, 43.42; H, 3.98; N, 36.83. Found: C, 43.55; H, 3.97; N, 36.70.

9-(4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-β-D-*arabino*-hexopyranosyl)adenine (13). Compound **3** (600 mg, 1.44 mmol) was dissolved in pyridine (10 ml) and evaporated. This procedure followed 3 times to remove the crystal-water. The obtained pasty residue in pyridine (4.5 ml) was treated with acetic anhydride (0.17 ml, 1.83 mmol) at room temperature for 40 min under stirring. The mixture was treated with MeOH (3 ml) for 10 min, evaporated and again co-evaporated with EtOH (6 ml) below 38 ℃. The residue was partitioned between ethyl acetate (80 ml) and water (20 ml). The organic layer was washed with water (3 × 15 ml), dried and thoroughly evaporated to dryness. The obtained foam in DMF (6 ml) was then treated with $NaBH_4$ (57 mg, 1.51 mmol)

under ice-cooling for 20 min and then at room temperature for 2 h. The mixture was neutralized with 1N AcOH/EtOH, evaporated and the residue partitioned between EtOAc (110 ml) and water (30 ml). The organic layer was again washed with water (2 × 20 ml). TLC of the organic layer showed the formation of a major product together with a small amount of a far less polar sideproduct, which proved to disappear on refluxing in MeOH in a trial experiment using an aliquot of the solution. Thus, the mixture recovered from the organic layer in MeOH (30 ml) was heated to reflux for 1 h and evaporated. Recrystallization of the residue from MeOH afforded 344 mg (60%) of **13**, which sintered above 280 °C and did not melt up to 300 °C: λmax (MeOH) 258 nm (ε 17100); ^{1}H NMR (Me_2SO-d_6) δ 2.84 (1H, m, H-2a), 3.29 (1H, m, H-2b), 3.85 (1H, dd, J_{gem} = 9.2, $J_{6a,5}$ = 10.2, H-6a), 3.94 (1H, ddd, $J_{5,6a}$ = 10.2, $J_{5,6b}$ = 3.7, $J_{5,4}$ = 9.6, H-5), 4.26 (1H, dd, J_{gem} = 9.2, $J_{6b,5}$ = 3.7, H-6b), 4.36 (1H, dd, $J_{4,3}$ = 10.0, $J_{4,5}$ = 9.6, H-4), 5.51 (1H, ddd, $J_{3,2b}$ = 4.8, $J_{3,2a}$ = $J_{3,4}$ = 10.0, H-3), 5.81 (1H, s, PhC**H**), 6.20 (1H, dd, $J_{1,2a}$ = 10.6, $J_{1,2b}$ = 1.4, H-1), 7.36 (2H, s, NH_2), 7.40 (5H, s, aryl), 8.19 (1H, s, H2), 8.49 (1H, s, H8). *Anal.* Calcd for $C_{18}H_{18}N_6O_5$: C, 54.27; H, 4.55; N, 21.10. Found: C, 54.17; H, 4.66; N, 21.09.

9-(2,3-Dideoxy-3-nitro-β-D-*arabino*-hexopyranosyl)adenine (14). A mixture of **13** (105 mg, 0.26 mmol) and 80% AcOH (10 ml) was stirred at 70-75 °C for 7 h and 25 min. After cooling, the mixture was evaporated and the residue repeatedly co-evaporated with 60% EtOH (4 × 5 ml) and then with MeOH/EtOH (1:1) (4 × 5 ml). The residue was digested with ether (3 ml) and the collected sparingly soluble solid recrystallized from a small volume of MeOH to give 30 mg (35%) of **14** as fine needles, which softened at 153 °C and melted at 162-164 °C (dec): λmax (MeOH) 259 nm (ε 13400). *Anal.* Calcd for $C_{11}H_{14}N_6O_5 \cdot H_2O$: C, 40.24; H, 4.91; N, 25.60. Found: C, 40.42; H, 4.80; N, 25,46.

9-(4,6-*O*-Benzylidene-2,3-didehydro-2,3-dideoxy-β-D-hexopyranosyl)adenine (15). A mixture of **9h** (100 mg, 0.17 mmol), 2,2'-azobisisobutyronitrile (30 mg, 0.17 mmol) and tributyltin hydride (0.14 ml, 0.51 mmol) in toluene (5 ml) was heated at 100 °C for 70 min and the solvent evaporated off. The residue was fractionated on a silica plate (20 × 20 cm; 10% MeOH in $CHCl_3$) and the major fraction recrystallized from MeOH to give 17 mg (25%) of **15**, mp 217-219 °C: λmax (MeOH) 259 nm (ε 22100); ^{1}H NMR (Me_2SO-d_6) δ 3.32 (ca. 2H, s, MeOH), 3.81 (1H, dd, $J_{6a,5}$ = 9.8, J_{gem} = 9.8, H-6a), 3.95 (1H, ddd, $J_{5,4}$ = 8.2, $J_{5,6a}$ = 9.8, H-5), 4.21 (1H, dd, J_{gem} = 9.8, $J_{6b,5}$ = 4.3, H-6b), 4.60 (1H, br d, H-4), 5.77 (1H, s, PhC**H**), 5.98 (1H, br d, H-3), 6.38 (1H, d, $J_{2,3}$ = 10.0, H-2), 6.67 (1H, br d, H-1), 7.33 (2H, s, NH_2), 7.40 (5H, m, aryl), 8.18 (1H, s, H2 or H8), 8.19 (1H, s, H8 or H2). *Anal.* Calcd for $C_{18}H_{17}N_5O_3 \cdot {}^2/_3CH_3OH$: C, 60.15; H, 5.32; N, 18.79. Found: C, 60.20; H, 5.31; N, 18.83.

REFERENCES AND NOTES

1. Fox, J. J.; Watanabe, K. A.; Bloch, A. "*Progress in Nucleic Acid Research and Molecular Biology*", Vol.5, ed. by Davidson, J. N. and Cohn, W. E., Academic Press, **1966**, p.251.
2. Venulet, J.; VanEtten, L. "*The chemistry of the nitro and nitroso group*", Part 2, ed. by Feuer, H., Interscience Publishers, **1970**, p.201.
3. Ohta, N.; Minamoto, K.; Yamamoto, T.; Koide, N.; Sakoda, S. *Nucleosides Nucleotides*, **1996**, *15*, 833-855.
4. In this context, the first synthesis of 3'-deoxy-3'-nitrothymidine and its 2',3'-didehydro analogue as potential anti-AIDS substances has been recorded recently by Hossain et al.[5]
5. (a) Hossain, N; Papchikhin, A.; Garg, N.; Fedorov, I.; Chattopadhyaya, J. *Nucleosides Nucleotides*, **1993**, *12*, 499-528. (b) Hossain, N.; Garg, N.; Chattopadhyaya, J. *Tetrahedron*, **1993**, *49*, 10061-10068.
6. Beranek, J.; Friedman, H.; Watanabe, K. A.; Fox, J. J. *J. Heterocycl. Chem.*, **1965**, *2*, 188-191.
7. An attempt to isolate compound **6** as a hydrochloride salt has also failed.
8. Biffin, M. E. C.; Miller, J.; Paul, D. B. "*The chemistry of azido group*", ed. by Patai, S., Interscience Publishers, **1971**, p. 57.
9. Yamamoto, T.; Tsuboike, K.; Minamoto, K. *Nucleic Acids Symp. Series*, **1996**, *35*, 35-36.
10. Similar azide reactions in THF or acetone revealed the formations of compound **11** and a similar amount of a far less polar product (silica gel TLC; $CHCl_3$/EtOH, 9:1). The latter compound was isolated by column chromatography, recrystallized from MeOH at room temperature (mp 178-180 ℃) and shown to absorb at 2140 cm^{-1} (N_3). However, repeated elemental analyses gave no satisfactory analysis values for this compound probably owing to thermal change to **11**. In fact, its partial conversion into **11** was observed by TLC after being heated in MeOH for 30 min. Probably, the more electronegative adenine base would make H-3 more labile, thus rendering the azide insertion of the initially formed Michael adduct more facile. Polarity or basisity of the reaction medium may also influence the insertion. Elimination of nitrous acid from **iv** would occur rapidly to effect resonance stabilization.
11. Huryn, D. M.; Okabe, M. *Chem. Rev.*, **1992**, *92*, 1745-1768.