($CDCl_3$) δ 2.20 (3 H, s, Ac), 2.25 (3 H, s, 5-Me), 3.22 (3 H, s, NMe), 3.41 (3 H, s, NMe), 6.82 (1 H, s, H-3′), 8.08 (1 H, s, H-6). Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.10; H, 5.07; N, 10.07. Found: C, 56.01; H, 5.11; N, 9.98.

1,3-Dimethyl-5-(5-methyl-4-oxo-4,5-dihydrofuran-2-yl)-uracil (13). To a solution of **12** (163 mg, 0.5 mmol) in EtOH (5 mL) was added concentrated NH_4OH (5 mL). The mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was crystallized from EtOH to give **13** (160 mg, 98%): mp 204.5–206 °C; UV (MeOH) λ_{max} 325.0 and 255.5 nm; ^1H NMR ($CDCl_3$) δ 1.36 (3 H, d, spacing 7.14 Hz), 3.22 (3 H, s, NMe), 3.46 (3 H, s, NMe), 4.69 (1 H, q, H-5′), 6.24 (1 H, s, H-3′), 8.54 (1 H, s, H-6). Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.23; H, 5.02; N, 11.92.

5-(2,3-Di-*O*-acetyl-5-deoxy-4-methoxy-β-D-ribofuranosyl)-1,3-dimethyluracil (14) and 5-(2,3-Di-*O*-acetyl-5-deoxy-4-methoxy-α-L-lyxofuranosyl)-1,3-dimethyluracil (15). To a solution of **6** (600 mg, 1.77 mmol) in anhydrous MeOH (5 mL) was added a drop of AcOH. The mixture was heated under reflux, excluding moisture, for 3 days. After removal of the solvent in vacuo, the residue was chromatographed on a column of silica gel (EtOAc).

Compound **15** was eluted from the column first (R_f 0.54 on TLC, AcOEt) (88.5 mg, 13.5%): mp 109–110 °C (after crystallization from Et_2O); UV (MeOH) λ_{max} 269.2 nm (ε 12000), 206.8 (ε 13600), λ_{min} 234.8 (ε 880); ^1H NMR ($CDCl_3$) δ 1.43 (3 H, s, 5′-Me), 2.03 (3 H, s, OAc), 2.13 (3 H, s, OAc), 3.30 (6 H, s, 2 NMe), 3.38 (3 H, s, OMe), 5.08 (1 H, d, H-1′, $J_{1',2'}$ = 7.0 Hz), 5.26 (1 H, d, H-3′, $J_{2',3'}$ = 5.0 Hz), 5.57 (1 H, dd, H-2′), 7.28 (1 H, s, H-6). Anal. Calcd for $C_{16}H_{22}N_2O_8$: C, 51.88; H, 5.99; N, 7.56. Found: 51.68; H, 5.99; N, 7.51.

Compound **14** was then eluted from the column (R_f 0.28 on TLC, EtOAc) (501.5 mg, 76.5%): mp 100–101 °C (crystallization from Et_2O); UV (MeOH) λ_{max} 270.8 nm (ε 8200), 210.0 (ε 8500), λ_{min} 234.8 (ε 220); ^1H NMR ($CDCl_3$) δ 1.50 (3 H, s, 5′-Me), 2.12 (6 H, s, 2 OAc), 3.32 (6 H, s, NMe and OMe), 3.40 (3 H, s, NMe), 4.65 (1 H, d, H-1′, $J_{1',2'}$ = 3.0 Hz), 5.12–5.43 (2 H, m, H-2′,3′), 7.17 (1 H, s, H-6). Anal. Calcd for $C_{16}H_{22}N_2O_8$: C, 51.88; H, 5.99; N, 7.56. Found: C, 51.62; H, 5.99; N, 7.40.

5-[2,3-Di-*O*-acetyl-5-deoxy-4-(1*H*-1,2,4-triazol-1-yl)-β-D-ribofuranosyl]-1,3-dimethyluracil (16) and 5-[2,3-Di-*O*-acetyl-5-deoxy-4-(1*H*-1,2,4-triazol-1-yl)-α-L-lyxofuranosyl]-1,3-dimethyluracil (17). To a mixture of **6** (200 mg, 0.6 mmol) and 1,2,4-triazole (100 mg, 1.45 mmol) in dry MeCN (3 mL) was added a drop of H_3PO_4. The mixture was heated under reflux overnight. After concentration in vacuo, the residue was chromatographed on a silica gel column (EtOAc).

Compound **17** eluted from the column (R_f 0.43 on TLC $CHCl_3$–MeOH, 15:1) (70.9 mg, 29%): mp 136–137 °C (after crystallization from CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.98 (3 H, s, 5′-Me), 2.13 (3 H, s, OAc), 2.17 (3 H, s, OAc), 3.38 (3 H, s, NMe), 3.43 (3 H, s, NMe), 5.18 (1 H, d, H-1′, $J_{1',2'}$ = 5.0 Hz), 5.78 (1 H, t, H-2′, $J_{1',2'} = J_{2',3'}$ = 5.0 Hz), 6.03 (1 H, d, H-3′), 7.47 (1 H, s, H-6), 8.05 (1 H, s, triazole), 8.47 (1 H, s, triazole). Anal. Calcd for $C_{17}H_{21}N_5O_7$: C, 50.12; H, 5.20; N, 17.19. Found: C, 50.13; H, 5.18; N, 17.33.

Compound **16** was then eluted from the column (R_f 0.32 on TLC $CHCl_3$–MeOH, 15:1 v/v) (151.5 mg, 62% after recrystallization from CH_2Cl_2): mp 150–151 °C; UV (MeOH) λ_{max} 266.8 nm (ε 11000), 204.4 (ε 15900), λ_{min} 231.6 (5300); ^1H NMR ($CDCl_3$) δ 1.93 (6 H, s, 2 OAc), 1.97 (3 H, s, 5′-Me), 3.33 (3 H, s, NMe), 3.42 (3 H, s, NMe), 5.06 (1 H, d, $J_{1',2'}$ = 4.0 Hz), 5.63 (1 H, dd, H-2′, $J_{1',2'}$ = 4.0, $J_{2',3'}$ = 6.0 Hz), 5.78 (1 H, d, H-3′), 7.27 (1 H, s, H-6), 7.87 (1 H, s, triazole), 8.30 (1 H, s, triazole). Anal. Calcd for $C_{17}H_{21}N_5O_7$: C, 50.12; H, 5.20; N, 17.19. Found: C, 49.87; H, 5.15; N, 17.04.

Anchimeric Assistance of a 5′-*O*-Carbonyl Function for Inversion of Configuration at the 3′-Carbon Atom of 2′-Deoxyadenosine. Synthesis of 3′-Azido-2′,3′-dideoxyadenosine and 3′-Azido-2′,3′-dideoxyinosine

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3′-Azido-2′,3′-dideoxyadenosine was synthesized in two steps from N^6,5′-*O*-dibenzoyl-2′-deoxyadenosine in 65% yield. The configuration at the 3′ position was inverted by reaction of N^6,5′-*O*-dibenzoyl-2′-deoxyadenosine with triflic anhydride–pyridine and water. The product distribution under different reaction conditions is described together with a benzoyl migration reaction. The azido group was introduced by a nucleophilic substitution reaction with lithium azide on the 3′-*O*-triflate of *N*-benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine. Enzymatic deamination of 3′-azido-2′,3′-dideoxyadenosine gave 3′-azido-2′,3′-dideoxyinosine.

Introduction

3′-Azido-2′,3′-dideoxyadenosine (**3**) is a nucleoside analogue with interesting antitumoral activity.[1] It has been tested against the multiplication of the human immunodeficiency virus (HIV)[2] in vitro, but its selectivity index is too low. With respect to the synthesis of larger amounts of **3** for further in vivo tests on its antitumoral characteristics, a new and more straightforward synthesis than those described[2-5] is needed. Apart from these considerations, the continual research on effective and less toxic nucleosides such as 3′-azido-2′,3′-dideoxythymidine against the replication of the AIDS virus prompted us to synthesize 3′-azido-2′,3′-dideoxyinosine (**4**). Because of the altered substrate specificity of the HIV reverse transcriptase, compared to DNA polymerases,[6] it was reasoned that compound **4**, as its triphosphate, could eventually block selectively the function of the first enzyme. On the other hand, inosine 5′-phosphate is a direct precursor of

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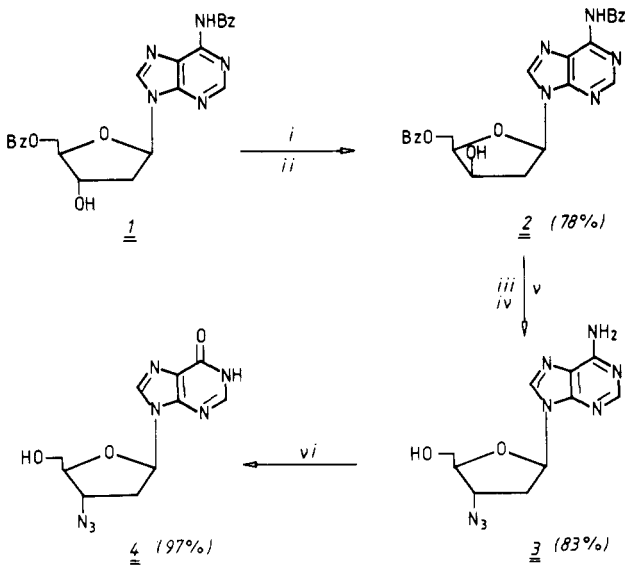
0022-3263/88/1953-5050$01.50/0

Scheme I[a]

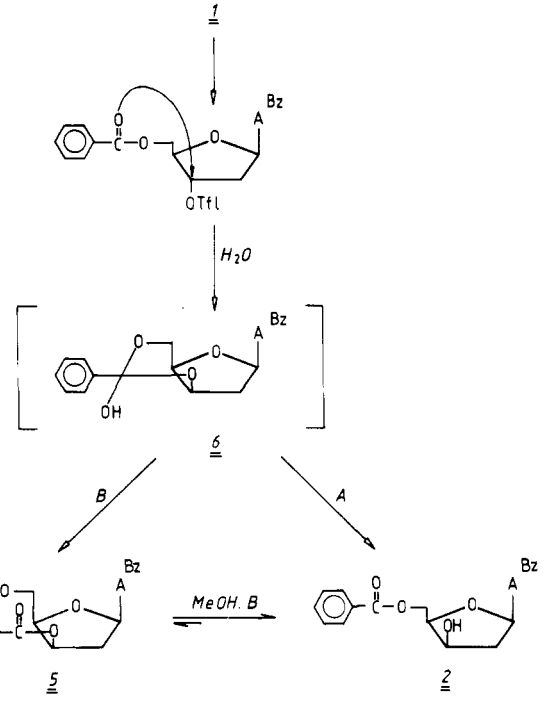


[a] (i) $(CF_3SO_2)_2O$, C_5H_5N, CH_2Cl_2, H_2O; (ii) MeOH, $NaHCO_3$; (iii) $(CF_3SO_2)_2O$, C_5H_5N, CH_2Cl_2; (iv) LiN_3, DMF; (v) MeOH, NH_3; (vi) adenosine deaminase, phosphate buffer pH 7.5.

adenosine 5′-phosphate (adenylosuccinate synthetase and adenylosuccinase) and of xanthosine 5′-phosphate (inosinate dehydrogenase) and further to guanosine 5′-phosphate (xanthylate aminase). This makes the study of the metabolism, in relationship to the activity, of sugar-modified inosine analogues a very interesting undertaking.

Reversal of the configuration at the 3′ position of 2′-deoxynucleosides is an easy reaction in the pyrimidine series because of the possibility of assistance of the base. The situation is somewhat more complex with purine nucleosides. In these cases, intramolecular reaction between the base and sugar moiety, without prior oxidation at the 8 position, is unwanted because it gives cyclonucleosides in which the heteroatom involved is part of the purine base itself. Stabilization occurs by attack of an external nucleophile, for example, a hydroxyl ion, on C-2[7] followed by opening of the pyrimidine ring. This side reaction occurs frequently when a leaving group is present on the 5′-O or 3′-O position of natural nucleosides. One way to prevent this reaction is to reduce the nucleophilicity of the heterocyclic base by acylation of the exocyclic amino group.[8] This method is, however, not absolute. A direct nucleophilic substitution reaction to invert the configuration at the 3′ position of 2′-deoxyadenosine seems therefore problematic. The elegant method, which has been used for the synthesis of, for example, *ara*A, of oxidation of the secondary alcohol followed by stereospecific reduction is not applicable on 2′-deoxyadenosine. This is because of the ease with which the 3′-keto intermediate undergoes β-elimination with loss of the base part.[9] Different syntheses of 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine have been described.[10-12] Hydride reduction of *lyxo* epoxides gives mostly the 3′-deoxy-*threo* product and only about 15% of the 2′-deoxy-*threo* isomer.[10] The method

Scheme II[a]



[a] Tfl = (trifluoromethyl)sulfonyl; A = adenosine; Bz = benzoyl.

described by Ikehara et al.[11] comprises many steps and starts with not easily accessible starting material. Although its use on large amounts is rather unpleasant and can give rise to burns, the only good method is that described by Hansske and Robins:[12] the regioselective 2′-*O*-tosylation[13] of adenosine followed by a hydride shift reaction with lithium triethylborohydride. This method is also applicable on 5′-*O*-tritylated adenosine.[4,12] We present here a one-step synthesis of N^6-benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**2**) from the easily accessible starting material N^6,5′-*O*-dibenzoyl-2′-deoxyadenosine[14] (**1**). This method has the advantage that the resulting nucleoside is protected at the appropriate positions, with a base-labile protecting group, for direct introduction of a 3′-down substituent. This is shown by the synthesis of 3′-azido-2′,3′-dideoxyadenosine (**3**) and 3′-azido-2′,3′-dideoxyinosine (**4**). These molecules are otherwise difficult to achieve.

Results and Discussion

When N^6,5′-*O*-dibenzoyl-2′-deoxyadenosine (1 mmol) (**1**) was treated with 1.5 equiv of trifluoromethanesulfonic anhydride in dichloromethane, containing an excess of pyridine (1 mL, 12 mmol), the 3′-*O*-trifluoromethanesulfonate was formed rapidly as judged by TLC ($CHCl_3$–MeOH 9:1). Addition of H_2O (1 mL), as a weak nucleophile, gave two compounds that were identified as N^6-benzoyl-9-(3-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**5**) (61% yield) and N^6-benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**2**) (27% yield). The ^1H NMR spectrum of **5** shows H-1′ as a triplet. Apart from ^1H NMR, UV, MS, and elemental analysis, the structure of both compounds was proven by conversion into the known 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine[10] by treatment with ammonia in meth-

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anol. The same reaction on N^6-benzoyl-5′-*O*-monomethoxytrityl-2′-deoxyadenosine gave no rearrangement products, excluding the possibility of a direct attack of H_2O on the 3′-position. The 3′-*O*-triflate of N^6-benzoyl-5′-*O*-monomethoxytrityl-2′-deoxyadenosine is relatively stable under the reaction conditions. When **1** was treated similarly but in the presence of less pyridine [0.24 mL (3 mmol) per mmol nucleoside] and 3 mmol of benzoic acid was added together or before the hydrolysis step, the selectivity was reversed and 59% of **2** was obtained together with 30% of **5**. The reaction was conducted at 0 °C in order to minimize the acid-catalyzed hydrolysis of the glycosidic bond. Thus, by changing the reaction conditions either mainly **5** or the isomeric **2** is obtained.

A possible explanation for the different 5:2 ratios under the different reaction conditions could be as follows: because a primary alcohol is a better leaving group than a secondary alcohol, formation of the 3′-benzoate (**5**) is normally preferred. When the reaction mixture is more acidic, more of the 5′-benzoate (**2**) could be expected because the secondary alcohol is preferably protonated.

When N^6-benzoyl-9-(3-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**5**) was dissolved in methanol containing a weak base like sodium bicarbonate, the expected transesterification of the benzoyl group occurred and a 78% yield of **2** was obtained: *O*-benzoyl migration occurs in the direction of the less sterically hindered 5′-hydroxyl group leading to an energetically more stable isomer. This isomerization does not go to completion, since, after 2 h 30 min, more polar compounds appear on TLC, showing debenzoylation as a side reaction. So the reaction was interrupted after about 2 h. When the triflate displacement, with an excess of pyridine, was followed by the base-catalyzed isomerization in two successive steps, without intermediary purification, a 78% yield of isolated **2** was obtained. A role of the purine base in the transesterification, by catalyzing the benzoyl transfer, cannot be excluded. This is supported by the observation that the reaction mixture of the transbenzoylation contains N^6-benzoyladenine. An explanation for the formation of this compound could be as follows. Attack of N-3 on the carbonyl group of the 3′-*O*-benzoyl function of **5** might afford a pyrimidinium intermediate which can be stabilized either by cleavage of the glycosidic bond or by migration of the benzoyl group from the N-3 to the 5′-*O* position.

Reaction of **2** with trifluoromethanesulfonic anhydride in dichloromethane–pyridine followed by addition of an excess of lithium azide gave only one compound on TLC. In the same reaction sequence, this compound was debenzoylated with ammonia in methanol and purified by column chromatography. 3′-Azido-2′,3′-dideoxyadenosine (**3**) was isolated in 83% yield from **2**.

The deamination of adenosine and 2′-deoxyadenosine to form inosine and 2′-deoxyinosine is catalyzed by adenosine deaminase. This enzyme shows a broad substrate specificity and only the presence of a 5′-hydroxyl group seems a prerequisite for its activity.[15] When 3′-azido-2′,3′-dideoxyadenosine was treated with adenosine deaminase at 30 °C in a 0.05 M phosphate buffer (pH 7.5), deamination occurred smoothly as judged by the hypsochromic shift of the UV maximum from 260 nm to 249 nm and 3′-azido-2′,3′-dideoxyinosine was isolated in quantitative yield.

Conclusion

Two types of intramolecular reactions are very common in the nucleoside field, i.e., the formation of an anhydro bond between the base and the sugar part of pyrimidine nucleosides and neighboring group transformations in the sugar moiety, which has been used most often in the purine series.[16] As an example of the last method, a neighboring trans benzoate group has been used to invert the configuration at the 2′-position of 9-(β-D-xylofuranosyl)adenine.[17] A 5′-*O*-benzoyl group, however, can replace the function of the pyrimidine base by purine nucleosides to invert the configuration at the 3′-position in a total yield of 90%. The position of the protecting groups can be influenced by altering the reaction circumstances of the triflate displacement. This method makes 3′-substituted 2′,3′-dideoxypurine nucleosides more easily available than before.

Experimental Section

Melting points were determined in capillary tubes with a Büchi-Tottoli apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 257 spectrophotometer on samples in potassium bromide disks at 1.5%. Ultraviolet spectra were recorded with a Philips PU 8740 spectrophotometer. Mass spectra were determined with an AEI MS-12 apparatus. The ^1H NMR and ^{13}C NMR spectra were determined with a JEOL FX 90Q spectrometer with tetramethylsilane as internal standard (s = singlet; d = doublet, t = triplet, q = quadruplet; br = broad signal; m = multiplet). Precoated Merck silica gel F254 plates were used for TLC, and the spots were examined with UV light and sulfuric acid–anisaldehyde spray. Column chromatography was performed on silica gel (Janssen Chimica, 0.060–0.200 mm). Dichloromethane was stored for 16 h on P_2O_5 and distilled; *N*,*N*-dimethylformamide was purified by distillation; pyridine was refluxed overnight over potassium hydroxide and distilled; and methanol was dried by distillation after it had been refluxed overnight with magnesium–iodine.

N^6-Benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (2) and N^6-Benzoyl-9-(3-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (5). A suspension of 920 mg (2 mmol) of N^6,5′-*O*-dibenzoyl-2′-deoxyadenosine[14] (**1**) (mp 173–175 °C) in 30 mL of anhydrous dichloromethane, containing 2 mL of pyridine, was cooled to −30 °C and 5.0 mL (3 mmol) of a solution of trifluoromethanesulfonic anhydride (10 vol %) in dichloromethane was added dropwise. The cooling bath was removed and the mixture was further stirred for 30 min. After 15 min, the reaction mixture cleared up. Then 1 mL of water was added and the reaction was further stirred for 2 h at room temperature. Water (5 mL) was added, the organic layer was separated, dried, evaporated, coevaporated, and purified by column chromatography ($CHCl_3$–MeOH, 97:3).

N^6-Benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (2): 250 mg (0.54 mmol, 27%); mp (acetone) 129–133 °C; MS (*m/e*) 459 (M^+); UV (MeOH) λ_{max} 281 nm (log ε 4.35); ^1H NMR ($CDCl_3$) δ 2.47–3.15 (m, H-2′, H-2″), 4.17–5.02 (m, H-3′, H-4′, H-5′, H-5″, $J_{5',5''}$ = 11.8 Hz, $J_{4',5'}$ = 6.6 Hz, $J_{4',5''}$ = 4.4 Hz), 6.26 (dd, *J* = 2.6 and 8.8 Hz, H-1′), 6.62 (br d, 3′-OH), 7.48 (m) and 8.02 (m) (2 × phenyl), 8.25 (s) and 8.76 (s) (H-8 and H-2), 9.22 (br s, NH). Anal. Calcd for $C_{24}H_{21}N_5O_5 \cdot H_2O$: C, 61.66; H, 4.96; N, 14.98. Found: C, 61.70; H, 4.82; N, 14.77.

N^6-Benzoyl-9-(3-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (5): 560 mg (1.22 mmol, 61%); MS (*m/e*) 459 (M^+); UV (MeOH) λ_{max} 281 nm (log ε 4.34); ^1H NMR ($CDCl_3$) δ 3.00 (t, H-2′, H-2″), 3.99 (d, H-5′, H-5″), 4.46 (q, H-4′), 5.78 (t, H-3′), 6.49 (t, H-1′), 7.35–8.07 (m, 2 × phenyl), 8.35 (s) and 8.68 (s) (H-8 and H-2), 9.28 (br s, NH). Anal. Calcd for $C_{24}H_{21}N_5O_5 \cdot H_2O$: C, 61.66; H, 4.96; N, 14.98. Found: C, 61.64; H, 4.90; N, 14.90.

Isomerization of 5 to 2. To a solution of 700 mg (1.52 mmol) of **5** in 50 mL of anhydrous methanol was added 100 mg of sodium bicarbonate, and the mixture was stirred for 1.5 h at room tem-

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perature. The reaction mixture was evaporated and purified by column chromatography ($CHCl_3$–MeOH, 97:3), yielding 550 mg (78%) of N^6-benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**2**).

Synthesis of N^6-Benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (2) from 1. Method A. A suspension of 920 mg (2 mmol) of **1** in anhydrous dichloromethane (50 mL) and pyridine (2 mL) was cooled to −30 °C and 5 mL of trifluoromethanesulfonic anhydride (10 vol % in dichloromethane) was added dropwise. After removal of the cooling bath, the reaction mixture was stirred for 30 min during which time it became complete clear. After addition of H_2O (1 mL), the emulsion was further stirred for 3 h at room temperature. Then 5 mL of H_2O was added, and the organic layer was separated, dried, evaporated, and coevaporated with toluene to remove pyridine. The residual oil was diluted with 50 mL of anhydrous methanol and 100 mg of sodium bicarbonate was added. The suspension was stirred for 2 h 15 min at room temperature, neutralized with acetic acid, evaporated, and purified by column chromatography ($CHCl_3$–MeOH, (97:3), yielding 720 mg (1.57 mmol, 78%) of N^6-benzoyl-9-(5-*O*-benzoyl-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**2**).

Method B. To a suspension of 460 mg (1 mmol) of **1** in 15 mL of anhydrous dichloromethane, containing 0.24 mL (3 mmol) of pyridine, was added dropwise 2.5 mL (1.5 mmol) of a solution of trifluoromethanesulfonic anhydride (10 vol %) in dichloromethane at −30 °C. The reaction mixture was warmed up to 0 °C over a period of 25 min. After 15 min, all the material was dissolved. Then 370 mg (3 mmol) of benzoic acid and 1 mL of H_2O were added successively and the emulsion was stirred for a further 6 h at 0 °C. The organic layer was isolated, dried, evaporated, and purified by column chromatography ($CHCl_3$–MeOH, 97:3), yielding 270 mg (0.59 mmol, 59%) of **2** and 140 mg (0.3 mmol, 30%) of **5**.

3′-Azido-2′,3′-dideoxyadenosine (3). A solution of 920 mg (2 mmol) of **2** in 20 mL of anhydrous dichloromethane, containing 2 mL of pyridine, was cooled to −30 °C. Then 5 mL (3 mmol) of a solution of trifluoromethanesulfonic anhydride in dichloromethane (10 vol %) was added dropwise. The cooling bath was removed and the reaction was stirred for a further 15 min. A solution of 980 mg (20 mmol) of lithium azide in 20 mL of dimethylformamide was added at once and the reaction was stirred, for 2 h at room temperature. H_2O (50 mL) and $CHCl_3$ (150 mL) were added, and the organic layer was separated, washed with H_2O (2 × 100 mL), dried, and evaporated. The oily residue was dissolved in methanol, saturated with ammonia, and kept overnight at room temperature. After evaporation and column chromatographic purification ($CHCl_3$–MeOH, 95:5), 460 mg (1.67 mmol, 83%) of crystalline **3** was obtained: mp 189–190 °C (lit.[3] mp 189–191 °C).

3′-Azido-2′,3′-dideoxyinosine (4). To a solution of 276 mg of 3′-azido-2′,3′-dideoxyadenosine in 200 mL of a 0.05 M phosphate buffer (pH 7.5), formed from KH_2PO_4 and Na_2HPO_4, was added 0.5 mL of a suspension of adenosine aminohydrolase (from bovine spleen type IV, 275 units/mg), and the mixture was stirred for 1 h at 30 °C. The reaction was monitored by UV analysis and the λ_{max} shifted from 260 nm to 249 nm. The reaction mixture was concentrated, applied on a XAD column, and eluted first with H_2O and then with methanol. The UV-absorbing fractions were pooled and evaporated, and the title compound was crystallized from MeOH: 270 mg (0.97 mmol, 97%); mp 191–192 °C; IR (KBr) 2100 cm^{-1} (N_3); UV (MeOH) λ_{max} 250 nm (log ε 4.10); ^1H NMR (DMSO-d_6) δ 2.40–2.68 (m, H-2′), 2.70–3.00 (m, H-2″), 3.59 (d, H-5′, H-5″), 3.93 (m, H-4′), 4.59 (m, H-3′), 6.29 (t, J = 6.2 Hz, H-1′), 8.07 (s) and 8.32 (s) (H-8 and H-2). Anal. Calcd for $C_{10}H_{11}N_7O_3$: C, 43.32; H, 4.00; N, 35.37. Found: C, 43.38; H, 4.27; N, 35.30.

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Intramolecular Carbene Chemistry. Evidence for Exclusive C–H Insertion in 8-Methylene-2-noradamantylidene

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8-Methylene-2-noradamantylidene (**5**) reacts by intramolecular γ-C,H insertion to produce 6-methylene-2,4-didehydronoradamantane (**4**) as the sole product (92%). Specifically labeled carbene 8-methylene-2-noradamantylidene-*4-d* (**5a**) produces **4** with the label located at only one position. This rules out the possible formation of the unstable olefin-cycloaddition product, 2,8-methano-2,8-didehydronoradamantane (**6**), followed by retro carbene ring opening to give **5**. The higher homologue of **5**, 4-methylene-2-adamantylidene (**2**), is known to react exclusively by intramolecular olefin cycloaddition to give 2,4-methano-2,4-didehydroadamantane, a [3.1.1]propellane, although the carbenic center and the olefinic bond in this carbene are less favorably arranged for cycloaddition than those in carbene **5**. This difference in behavior suggests a relatively late and high activation energy transition state between carbene **5** and the resultant intramolecular olefin-cycloaddition product **6**, a highly strained [2.1.1]propellane.

Intermolecular carbene cycloadditions to olefinic bonds as well as insertions into C–H bonds are generally unselective processes,[1] indicating that the respective activation energies are negligible or very small.[2] Yet, analogous *intramolecular carbene reactions may be highly selective.*[3-5]

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