Synthesis of Carbocyclic Aminonucleosides

Susan Daluge* and Robert Vince*

Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455

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The syntheses of the racemic carbocyclic analogues of puromycin aminonucleoside (**33**), 3′-amino-3′deoxyadenosine (**26**), and 3′-amino-3′-deoxyarabinosyladenine (**21**) are described. Acidic hydrolysis of 2-azabicyclo[2.2.1]-hept-5-en-3-one (**1**), followed by esterification and acetylation, gave methyl *cis*-4-acetamidocyclopent-2-enecarboxylate (**2a**). Reduction of **2a** with calcium borohydride gave, after acetylation, *cis*-4-acetamidocyclopent-2-enemethyl acetate (**3b**). Epoxidation of **3b** gave only *cis*-epoxide **6b**, which was opened with sodium azide to give, after acetylation, 4α-acetamido-3α-acetoxy-2β-azido-1α-cyclopentanemethyl acetate (**7a**) as the major regioisomer. Catalytic hydrogenation of **7a**, followed by immediate acetylation, gave 3α-acetoxy-2β,4α-diacetamido-1α-cyclopentanemethyl acetate (**9a**). Selective hydrolysis of the 4-acetamido group of **9a** and formation of the purine moiety at this position, followed by hydrolysis of the remaining acetamido group, gave the arabino analogue **21**. Epimerization at C-2′ gave access to ribo analogues **33** and **26**. Preliminary in vitro screening data indicate that carbocyclic 3′-amino-3′-deoxyadenosine exhibits highly significant antiviral activity.

Carbocyclic analogues of purine and pyrimidine nucleosides, in which a methylene group replaces the O atom of the ribofuranose ring, have been the object of the synthetic efforts of a number of groups.[1a,2] Since carbocyclic nucleosides lack the labile glycosidic bond, they would be expected to be stable to cleavage by phosphorylases or hydrolases, while retaining the potential for therapeutically useful interaction with other enzymes involved in nucleoside metabolism. The antitumor activity of 6-dimethylamino-9-(3′-amino-3′-deoxy-β-D-ribofuranosyl)purine (puromycin aminonucleoside) and 3′-amino-3′-deoxyadenosine has generated considerable interest in the biological properties of aminonucleosides.[1b] Our particular goal has been the hybridization of these two types of nucleosides to provide a novel class of aminocarbocyclic nucleosides with potential chemotherapeutic properties. In addition, carbocyclic puromycin would be a valuable tool in our continuing study of the precise requirements for inhibition of protein synthesis at the ribosomal level. We have previously described the interesting activity of a variety of simplified carbocyclic puromycin analogues,[3] all lacking the 5′-hydroxymethyl group.

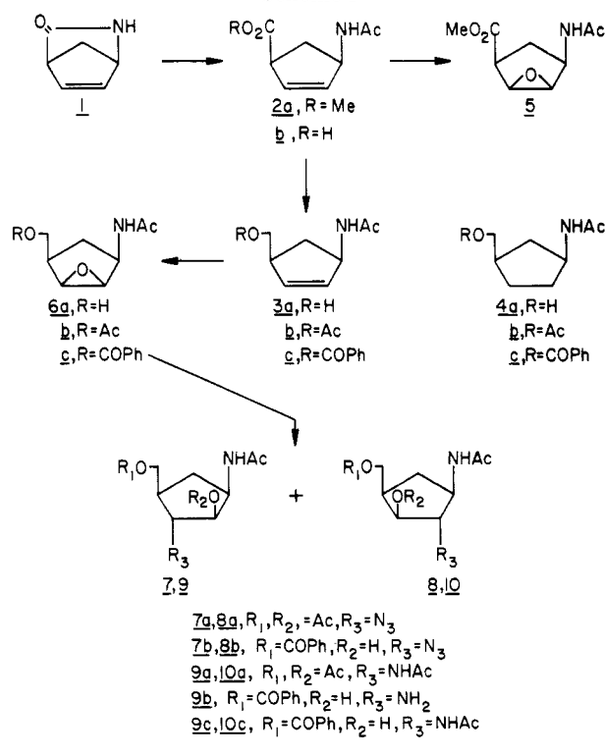
Elaboration of the lengthy, low-yield routes to carbocyclic adenosines which have been described[1a,2] seemed to us to be an extremely limited approach to the synthesis of new carbocyclic nucleosides, especially those requiring stereochemical modifications or substitutions in the cyclopentane ring. Many of the most interesting candidates for synthesis in this area, e.g., carbocyclic analogues of puromycin aminonucleoside, 3′-amino-3′-deoxyadenosine, *ara*-A, and *ara*-C, have been inaccessible. We were, therefore, impressed with the need for a simple, high-yield route to carbocyclic nucleosides using intermediates which would allow modifications to be made in a stereospecific manner in the cyclopentane ring.

The present report provides a detailed account of our preliminary communication[4] describing the development of a flexible route to 2′- and 3′-amino-(2′)3′-deoxycarbocyclic purine nucleosides. This route is also proving versatility in providing access to other carbocyclic nucleosides. For example, a preliminary account has been communicated describing the facile conversion of one of the intermediates described here (epoxide **6b**) to carbocyclic arabinosyladenine (C-*ara*-A), an adenosine deaminase resistant analogue of *ara*-A, which exhibits promising antiviral and antitumor activity.[5]

It has recently been reported that cyclopentadiene and tosyl cyanide react readily to give 3-tosyl-2-azabicyclo[2.2.1]-hepta-2,5-diene.[6a] This adduct, although quite unstable, is easily hydrolyzed to 2-azabicyclo[2.2.1]hept-5-en-3-one (**1**).[6b] The unsaturated lactam **1** offers unique possibilities as a starting material for the synthesis of a variety of carbocyclic nucleosides having the required cis orientation of the hydroxymethyl and heterocycle functions. Large-scale preparation of **1** by the literature procedure, with minor modifications, was carried out in 72% yield. The only difficulty encountered was in the synthesis of tosyl cyanide, which proved to be considerably less stable than indicated by the literature description.[7,8] A modification in the workup (see Experimental Section) avoided the violent decomposition which occasionally occurred during drying and gave a nearly quantitative yield of tosyl cyanide.

Lactam **1** was easily hydrolyzed in dilute acid. The resulting amino acid (not isolated) was esterified and then acetylated to give a high yield of methyl *cis*-4-acetamidocyclopent-2-enecarboxylate (**2a**), a stable crystalline compound (Scheme I). When the hydrolysis product from **1** was acetylated directly, the carboxylic acid **2b** was isolated. Esterification of **2b** also gave **2a**, but the overall yield was higher when esterification was carried out before acetylation.

Scheme I



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Reduction of the methyl ester function of **2a** presented an unexpected difficulty. Lithium borohydride was chosen as the reducing agent, since it is reported to reduce ester groups smoothly without attacking isolated double bonds and amides.[9] However, the samples of **3a** obtained from the reduction of **2a** with lithium borohydride under a variety of conditions (see Experimental Section) contained a significant amount of **4a,** in which the double bond had been reduced. The ratio of **3a/4a,** determined by integration of the NMR spectra, was frustratingly irreproducible. On a small scale or when older samples of lithium borohydride were used, samples of **3a** with almost perfect integration of the NMR were obtained. Larger scale reactions resulted in ratios of **3a/4a** of as high as 1:1. Possibly, deactivation of the lithium borohydride by traces of moisture was the most critical factor in lowering the extent of double bond reduction. We are unaware of previous reports of the reduction of an isolated double bond with lithium borohydride. In an attempt to facilitate separation, the mixture of **3a** and **4a** was acetylated. The resulting mixture of acetates **3b** and **4b** was an oil which could not be separated by distillation or chromatography. In the purest sample of **3b** obtained by this method (NMR integration and elemental analysis correct), the mass spectrum contained an (M + 2) ion of greater intensity than that of the molecular ion of **3b,** indicating contamination by **4b.** Benzoylation of the mixture of **3a** and **4a** was also carried out. The crystalline benzoate **3c** could be separated from contaminating **4c** (not isolated, detected by NMR) in 25–66% yield by crystallization. However, the variability of this reduction on a large scale made it desirable to find another method.

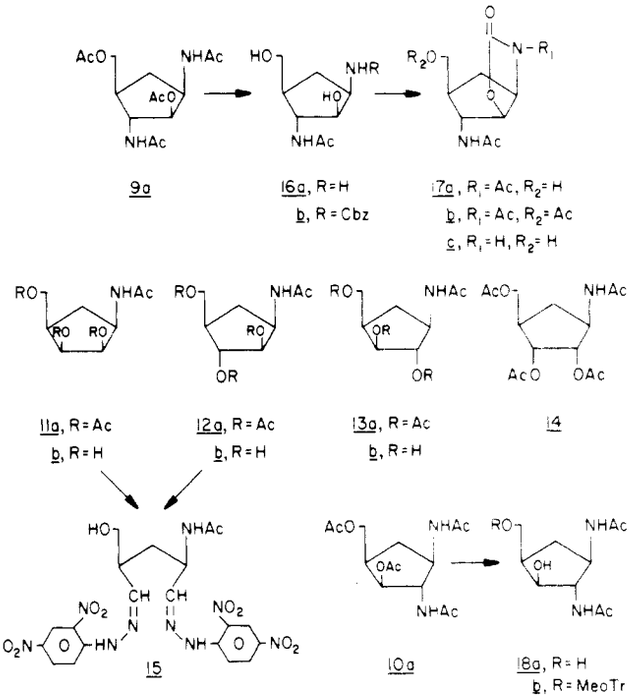
The method involving reduction of a mixed anhydride with sodium borohydride[10] was applied. Carboxylic acid **2b** was reacted with ethyl chloroformate to form a mixed anhydride (not isolated) which was then reduced to **3a** by addition to an aqueous solution of sodium borohydride. The **3a** isolated from this reaction showed no contamination by **4a.** However, the yield of **3a** was only 20–40%, with a great deal of **2b** being recovered, even after 18 h with an excess of reagents.

The reduction of **2a** with calcium borohydride was then investigated with excellent results. This reagent, easily generated in situ from sodium borohydride and calcium chloride,[11] gave reproducible high yields (94%) of **3b,** after acetylation, which showed no contamination by **4b** and solidified for the first time. Calcium borohydride has so many advantages over other reagents for the reduction of an ester, e.g., insensitivity to moisture, greater selectivity,[9,12] and ease and safety of use in large-scale reductions, that it is surprising that it is so rarely used.

Epoxidation of **3b** with *m*-chloroperbenzoic acid was highly stereoselective due to the syn-directing allylic amide group,[13] giving only the expected *cis*-epoxide **6b** (89%). The cis structure of epoxide **6b** was confirmed by later reactions. Epoxidation could also be carried out on the methyl ester **2a** or on benzoate **3c,** resulting in good yields of **5** or **6c,** respectively, presumed by analogy to be the *cis*-epoxides.

In order to generate the precursor of 3′-amino-3′-deoxycarbocyclic nucleosides, epoxide **6b** was opened with buffered sodium azide. Attack occurred predominantly at the position farthest from the acetamido group due to the inductive effect of the nitrogen,[14] giving (after acetylation) azido acetates **7a** and **8a** in a ratio of 4:1 (determined by NMR). Azide opening of epoxide **6c** resulted in azido alcohols **7b** and **8b,** also in a ratio of 4:1. This ratio was increased to 5.5:1 by hydrolysis of the ester of **6b** to alcohol **6a** prior to azide treatment. The relatively weak influence of this more distant group on the position of epoxide attack by azide is also explainable on inductive grounds.[15] When epoxide **5** was subjected to the same conditions, a complex mixture resulted, attack at both positions being approximately equally favored. The opening of **5** was also complicated by hydrolysis and lactone formation. Consideration of a route via **5** was thus abandoned due to the complexity of the epoxide opening.

Scheme II



The major azido acetate **7a** was easily separated from **8a** (not isolated) by crystallization. Catalytic hydrogenation of **7a** in ethanol with platinum catalyst, followed by acetylation, gave diacetamide **9a** in 70% yield. Hydrogenation followed by acetylation of a mixture of **7a** and **8a** gave diacetamides **9a** and **10a,** separable by chromatography. The amines formed by reduction of **7a** and **8a** cound not be characterized; their ethanolic solutions darkened rapidly in air. This was surprising, since the hydrogenation of 2α-acetamido-5β-azidocyclopentan-1α-ol under the same conditions gave an almost quantitative yield of the corresponding amine.[3d] The difference from this simpler series of compounds is that acetylation was carried out to facilitate recovery and separation of the isomeric azides **7a** and **8a.** Thus, the hydrogenation was carried out on the azido acetates, instead of the azido alcohols. Neighboring group interference by the secondary acetate being conceivable, we desired to study the hydrogenation of the corresponding azido alcohol. An attempt to convert **7a** to the corresponding azido diol by mild ammonia–methanol treatment gave an 80% yield of epoxide **6a.** The hydrogenation of azido alcohols **7b** and **8b** was therefore studied. Although in this case it was possible to characterize the free amine **9b** resulting from reduction of **7b,** solutions darkened rapidly and the yield was low (50%), unless acetylation to **9c** was carried out quickly. In the reduction of **8b,** the product turned dark red on contact with air and could be characterized only as acetamide **10c.** It was concluded that the apparent instability of the products resulting from hydrogenation of these azides is *not* associated with esterification of the adjacent hydroxyl group.

In an attempt to avoid decomposition and increase the yield of **9a,** the hydrogenation of **7a** was carried out with acetic anhydride as the solvent. Although no darkening of the product in air was noted, the yield of **9a** (64%) was not improved due to formation of a new product, **11a** (35%), a crystalline solid having the composition $C_{14}H_{21}NO_7$ (Scheme II). The opening of epoxide **6b** in dilute aqueous sulfuric acid followed by acetylation resulted in two products, **12a** and **13a,** having the same composition as **11a.**[5] Although the infrared

and high-resolution mass spectra of **11a, 12a,** and **13a** are almost identical, the NMR spectra show small differences in splitting patterns and chemical shifts. Another isomer, **14,** has been previously described as a syrup.[16] Ammonia–methanol treatment of **11a, 12a,** and **13a** gave the corresponding acetamido triols **11b, 12b, 13b.** Oxidation of these triols with 1 equiv of sodium metaperiodate resulted in the same dialdehyde, characterized as the di(2,4-dinitrophenylhydrazone) **15.** Thus **11a, 12a,** and **13a** differ only in configuration at the 2 and 3 positions, and **11a** may be assigned the lyxo stereochemistry shown in Scheme II. Corroboration of this assignment is given by acyl migration studies described below. Apparently, backside displacement of the azido group of **7a** by acetate is possible under the conditions of this hydrogenation. Prolonged (4–5 days) exposure of azide **7a** to acetic anhydride or of epoxide **6b** or diacetamide **9a** to the hydrogenation conditions in acetic anhydride gave no detectable **11a.** No **11a** was detected when reduction of the azide in ethanol was completed and then acetic anhydride added immediately before filtration of the platinum catalyst.

The best yield of **9a** was obtained by catalytic hydrogenation of **7a** in chloroform–ethanol.[17] The resulting amine hydrochloride was immediately acetylated by addition of sodium acetate and acetic anhydride, giving pure **9a** in 84% yield.

In an attempt to circumvent difficulties encountered in the catalytic reduction of **7a,** epoxide **6b** was treated with boron trifluoride etherate in acetonitrile.[18] Although this procedure gave a fair yield of **9a** on a small scale, on a preparative scale the yield was only 11% and a great deal of black tarry material resulted.

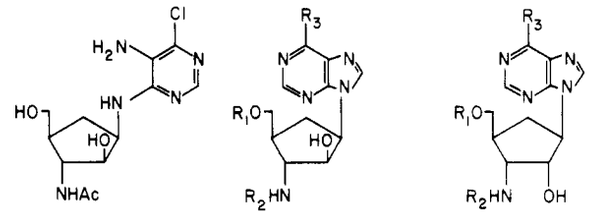
The assignment of the stereochemistry of epoxide **6a** and the structures of azides **7a** and **8a** derived from opening **6a** (or **6b**) is based, in part, on the behavior of diacetamides **9a** and **10a** in dilute hydrochloric acid. It is well known that the acid-catalyzed hydrolysis of an amide is remarkably facilitated by the presence of an adjacent *cis*-hydroxyl group, due to acyl migration.[19] As expected, mild acidic hydrolysis of **9a** resulted in monoacetamide **16a**[20] (Scheme II), one of the acetamido groups having undergone acyl migration followed by hydrolysis. The cis relationship of the amino and secondary hydroxyl groups of **16a** was further confirmed by cyclic carbamate formation: the benzyloxycarbonyl derivative **16b** cyclized to carbamate **17c,** characterized after acetylation to **17b.** The presence of the cis vicinal hydroxy and acetamido groups in **9a** also confirms the cis structure of epoxide **6a.** The *trans*-epoxide could not result in such a grouping when opened as described.

When **10a** was subjected to the same mild acidic hydrolysis conditions, neither of the acetamido groups was hydrolyzed. The resulting diacetamide **18a** was characterized as the 4-methoxytrityl derivative **18b.** When **11a, 12a,** and **13a** were subjected to this acidic treatment, the acetamido group of **11a** and **12a** was hydrolyzed, while that of **13a** was not, thus also confirming these assignments.

The selective hydrolysis of one acetamido group of **9a** is an integral part of this route to aminocarbocyclic nucleosides, making the use of different blocking groups for the two amines unnecessary. Amine **16a** was condensed with 5-amino-4,6-dichloropyrimidine and the resulting pyrimidine **19** (76%) closed with diethoxymethyl acetate (Scheme III) to the 6-chloropurine (not isolated). Reaction of the chloropurine with ammonia or dimethylamine gave **20** or **27,** respectively, isolated in good yield as crystalline solids after brief treatment with dilute acid to remove ethoxymethylidenes and acetates formed during the diethoxymethyl acetate reaction. Basic hydrolysis of **20** gave carbocyclic 3′-amino-3′-deoxyarabinosyladenine **21.**

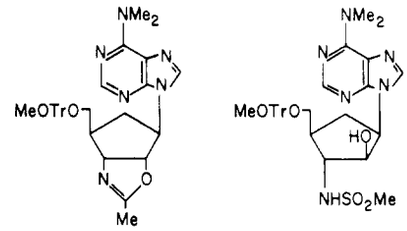
The 6-amino group of **20** was blocked by reaction with *N,N*-dimethylformamide dimethyl acetal, giving **22.** The 5′-hydroxyl group was then tritylated by reaction with chloro(*p*-methoxyphenyl)diphenylmethane, followed by removal of the 6-*N*-(dimethylamino)methylene group with ammonia, to give the 5′-*O*-mono-*p*-methoxytrityl derivative **23.** The 5′-*O*-*p*-methoxytrityl derivative **28** was prepared by tritylation of **27.** Epimerization at C-2 was carried out via a standard method in carbohydrate chemistry,[21] sulfonation of the 2′-hydroxyl of **23** or **28,** followed by inversion with sodium acetate in hot aqueous 2-methoxyethanol. We are aware of several examples of the use of this inversion method on amino sugar nucleosides,[22] none of them involving adenine or 6-dimethylaminopurine as the heterocycle component. In contrast to the literature examples, a mesylate could not be detected (by NMR) in the mixtures resulting from treatment of **23** or **28** with 1.5 equiv of methanesulfonyl chloride in pyridine. Instead, a mixture of oxazoline, epimerized product, and starting material resulted from which, after sodium acetate hydrolysis, **24** or **29** could be isolated in good yield. The 2′-mesylates of **23** and **28** would be expected to be more reactive than the 2′-mesylates of nucleosides and are apparently displaced by the 3′-acetamido group as formed or during workup, without the sodium acetate treatment normally used for this purpose. We continued to use the sodium acetate hydrolysis to convert any oxazoline present to *cis*-acetamido alcohol. An attempt was made to characterize the oxazolines, but they proved to be decomposing slowly to the acetamido alcohols on silica gel eluted with methanol–chloroform. A quite pure sample of **30** was obtained which NMR confirmed to be oxazoline. The use of 2–3 equiv of methanesulfonyl chloride resulted in more complex dark mixtures and lower yields. In the epimerization of **28,** these complex mixtures were chromatographed. In addition to lowered yields of **29** and **30,** an additional product, **31,** was isolated (11% with 2 equiv of methanesulfonyl chloride, 26% with 3 equiv). The singlet at δ 2.80 in the NMR spectrum of **31** indicates that the acetyl group has been replaced by a methanesulfonyl group, and the absence of acetamide bands in the IR spectrum along with the presence of characteristic sulfonamide bands at 1320 and 1140 cm^{-1} supports this as-

Scheme III



19 20–23,27,28 24–26,29,32–34

20,25, R_1 = H, R_2 = Ac, R_3 = NH_2
22, R_1 = H, R_2 = Ac, R_3 = N=CHNMe$_2$
23,24, R_1 = MeOTr, R_2 = Ac, R_3 = NH_2
21,26, R_1 = H, R_2 = H, R_3 = NH_2
27,32, R_1 = H, R_2 = Ac, R_3 = NMe_2
28,29, R_1 = MeOTr, R_2 = Ac, R_3 = NMe_2
33 R_1 = H, R_2 = H, R_3 = NMe_2
34 R_1 = H, R_2 = L-p-MeOPhe, R_3 = NMe_2



30 31

sumption. The mass spectrum of **31**, while not showing a molecular ion, does contain a peak at *m/e* 369 attributable to loss of the methoxytrityl group from the molecular ion, a prominent fragmentation for trityl derivatives such as **24** and **29**. Apparently, perhaps due to the proximity of the purine, the mesylation of the 2′-hydroxyl proceeds slowly enough that a competing mesylation of the acetamide nitrogen is possible.[23] The resulting *N*-acetylsulfonamide would be hydrolyzed during workup to sulfonamide **31**. The configuration of **31** is uncertain, but since inversion and oxazoline formation would protect the nitrogen and since an *N*-acetylsulfonamide would be a poor neighboring group, it seems likely that inversion at C-2 has not occurred. The only example we have found of the use of this inversion method with a purine nucleoside having geometry comparable to that of **23** and **28** is Baker and Schaub's report of the inversion of 2-methylmercapto-6-dimethylamino-9-(2-*O*-mesyl-3-acetamido-3-deoxy-5-*O*-trityl-β-D-arabinofuranosyl)purine.[24] Unfortunately, the intermediates were not characterized sufficiently in this work to allow comparisons to be made with the present study.

Detritylation of **24** and **29** with formic acid gave the 3′-acetamido-3′-deoxycarbocyclic nucleosides **25** and **32**. Basic hydrolysis of **25** gave the ribonucleoside analogue **26**, (±)-9-[3β-amino-2β-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine. Carbocyclic puromycin aminonucleoside **33** resulted on deacetylation of **32**. Carbocyclic puromycin (**34**) has been synthesized from **33**.[25]

Preliminary in vitro antiviral screening data indicate that the most active compound of this series, carbocyclic 3′-amino-3′-deoxyadenosine (**26**), exhibits highly significant activity. Virus ratings calculated as previously described[5] were 2.1 and 2.2 against Herpes simplex virus type 1 (strain HF) and vaccinia virus (strain Lederle Chorioallantoic), respectively. Further work is continuing in this laboratory and elsewhere to study the antiviral spectrum and therapeutic effects of these compounds in animals.

Experimental Section

Thin-layer chromatography (TLC) was done using 0.25-mm layers of Merck silica gel 60F-254 and column chromatography on Merck silica gel 60. Melting points were determined with a Mel-Temp apparatus and are uncorrected. UV spectra were taken with a Beckman 25 spectrophotometer, IR with a Perkin-Elmer 237B spectrophotometer, NMR with a Varian A-60D or a Varian T-60 spectrometer using an internal standard of tetramethylsilane, and mass spectra with an AEI Scientific Apparatus Limited MS-30 mass spectrometer. Low-resolution mass spectra were run on all compounds and the molecular ion and fragmentation patterns were reasonable. All evaporations were carried out at reduced pressure with a bath temperature of <50 °C. Samples were dried at 56 °C (0.1 mm) before analysis.

Tosyl Cyanide. The literature preparation of tosyl cyanide[8] gives very little detail. As difficulties were encountered when working with large quantities of the compound, as much detail as possible will be given here. A 1 M aqueous solution of sodium toluene-*p*-sulfinate or its hydrate (1 L) was prepared in a 2-L flask equipped with magnetic stirring, sintered glass gas inlet tube, thermometer, and exit tube to a trap containing 6 N sodium hydroxide. The contents of the flask was stirred vigorously and maintained at 20 °C while cyanogen chloride (Matheson) was bubbled vigorously into the solution for 30 min (solid started to form almost immediately). The gas inlet tube was disconnected and the flask was stoppered and cooled well for 30 min in an ice–salt bath. (Failure to chill well causes loss of product as an oil which passes through filter paper.) The white fluffy solid was filtered off and washed with ice water (100 mL). The damp[26] solid was immediately washed into a separatory funnel with carbon tetrachloride (500 mL). The carbon tetrachloride solution was shaken with saturated sodium chloride (100 mL), dried ($CaSO_4$) for 30 min, and evaporated to dryness (<40 °C) in the flask in which the next reaction was to be run. The white solid tosyl cyanide (consistently 98–99% yield), mp 45.5–47 °C [lit.[7] 46–48 °C], had ^1H NMR (CCl_4) and IR spectra identical with those reported.[7] The solid was used immediately for the next reaction.

2-Azabicyclo[2.2.1]hept-5-en-3-one (1). The literature procedure[6b] was modified to allow for large-scale preparation. A solution of freshly prepared tosyl cyanide (425 g, 2.35 mol) in freshly cracked cyclopentadiene (3 L) was stirred while coming to room temperature over a period of 40 min (the cyclopentadiene started out at freezer temperature, −20 °C). The resulting solution was evaporated to dryness without heating. The residue was cooled and swirled while *cold* glacial acetic acid (750 mL) was poured rapidly into the flask.[27] The resulting mixture was quickly poured into ice–water (3 L). Celite was added and the mixture filtered. The filter pad was washed with additional water (1 L). The filtrate–wash was then cooled (<20 °C) and stirred while cold 12 N sodium hydroxide was added to a pH of 8. This solution was saturated with sodium chloride and extracted with methylene chloride (3 × 3 L). A final extraction with additional methylene chloride (3 L) was carried out by allowing the layers to stir together vigorously overnight. All extracts were combined and dried ($CaSO_4$). Evaporation left a brown oil (200 g) which was purified by distillation to give 2-azabicyclo[2.2.1]hept-5-en-3-one as a pale yellow syrup which solidified on standing (184 g, 72%): bp 102–106 °C (0.25 mm); mp 50–52 °C (lit.[6b] 61%, mp 54–56 °C); IR and ^1H NMR identical with those reported.[6b]

Methyl *cis*-4-Acetamidocyclopent-2-enecarboxylate (2a). 2-Azabicyclo[2.2.1]hept-5-en-3-one (64.2 g, 0.588 mol) was dissolved in 5% hydrochloric acid (2.5 L) and the solution stirred at room temperature for 3.5 days. Sufficient 6 N sodium hydroxide was added (with cooling) to give pH 1.0. The pale yellow solution was evaporated to dryness (<50 °C). The residue was azeotroped with benzene–methanol, dried, and then refluxed in dry methanol (1 L) for 18 h. The sodium chloride was filtered off and washed with additional methanol. The filtrate–wash was evaporated to dryness and the residual yellow syrup dissolved in pyridine (500 mL). Acetic anhydride (300 mL) was added to the cooled (ice bath) solution. The solution was allowed to come to room temperature and after 1 h evaporated to dryness. The residue was dissolved in methylene chloride (500 mL), extracted with saturated sodium bicarbonate (3 × 200 mL) and saturated sodium chloride (50 mL), and dried ($CaSO_4$). Evaporation and azeotroping with toluene (3 × 200 mL) to remove pyridine left a yellow syrup (103.5 g) which solidified within a few minutes with the generation of considerable heat. The ^1H NMR spectrum of this off-white solid was identical with that of an analytical sample. Sublimation [70–80 °C (0.003 mm)] gave **2a** as white crystals (96.1 g, 89%): mp 66–67 °C; IR (KBr) 3300 (NH), 1725 (CO_2Me), 1622 br (C=C, amide 1), 1535 cm^{-1} (amide 2); ^1H NMR ($CDCl_3$) δ 6.25 (br, 1, NCH=O), 5.82 (s, $w_{1/2}$ = 2.5 Hz, 2, CH=CH), 4.97 (m, 1, CHN), 3.68 (s, 3, OCH_3), 3.6–3.4 (m, 1, $CHCO_2Me$), 1.91 (s) overlapped by 2.7–1.5 (m, 5, CH_3C=O and CH_2).

Anal. Calcd for $C_9H_{13}NO_3$ (183.21): C, 59.00; H, 7.15; N, 7.65. Found: C, 59.25; H, 7.04; N, 7.51.

This compound was also prepared by refluxing a solution of **2b** (11.85 g, 70.0 mmol) and *p*-toluenesulfonic acid (50 mg) in dry methanol (300 mL) for 18 h. The solution was evaporated to dryness and the residue dissolved in methylene choride (250 mL). This solution was extracted with half-saturated sodium bicarbonate (25 mL), dried ($CaSO_4$), and evaporated, leaving white solid (12.8 g). Crystallization from benzene–hexanes gave **2a** as white crystals (11.4 g, 89%): melting point, IR, and ^1H NMR identical with those of the analytical sample.

***cis*-4-Acetamidocyclopent-2-enecarboxylic Acid (2b).** A solution of **1** (10.1 g, 92.6 mmol) in 2 N hydrochloric acid (1 L) was stirred at room temperature for 3 days. The solution was concentrated to 150 mL and neutralized with 6 N sodium hydroxide while being cooled (ice bath). The temperature was kept at 10–15 °C with vigorous stirring while acetic anhydride (50 mL) and 6 N sodium hydroxide (sufficient to maintain basic pH) were added in alternating portions over 10 min. The solution was stirred an additional 5 min with cooling and then 5 min without cooling. The pH was adjusted to 1 with concentrated hydrochloric acid (with cooling) and the solution saturated with sodium chloride and extracted with methylene chloride (4 × 500 mL). The extracts were dried ($CaSO_4$) and evaporated, leaving white powder (14.72 g). Crystallization from acetonitrile gave **2b** as white needles (11.9 g, 76%): mp 146–147.5 °C; IR (KBr) 3300, 3069, 2950–2450 (OH, NH), 1700 sh, 1680 br (COOH), 1625, 1530 cm^{-1} (NHAc); ^1H NMR (Me_2SO-d_6) δ 12.0–11.7 (br, 1, exchanging in this solvent, COOH), 7.85 (d, *J* = 7.0 Hz, 1, NHC=O), 6.9–6.5 (m, 2, CH=CH), 5.0–4.0 (m, 1, CHN), 3.6–3.2 (m, 1, CHCOOH), 2.8–1.4 (m) with discernible singlet at 1.82 (5, CH_2, CH_3C=O).

Anal. Calcd for $C_8H_{11}NO_3$ (169.18): C, 56.79; H, 6.55; N, 8.28. Found: C, 56.98; H, 6.72; N, 8.29.

***cis*-4-Acetamidocyclopent-2-enemethyl Acetate (3b).** A mixture of calcium chloride (31.8 g, 0.286 mol) and sodium borohydride

(21.7 g, 0.572 mol) in tetrahydrofuran (600 mL) was stirred at room temperature for 1.0 h. A solution of **2a** (35.0 g, 0.191 mol) in tetrahydrofuran (500 mL) was added all at once. The resulting mixture was stirred at room temperature for 18 h. It was then cooled (ice bath) and ice water (700 mL) added dropwise (much effervescence at first). Cold 6 N hydrochloric acid (110 mL) was then added (to a pH of 1.5) and the resulting clear solution stirred at room temperature for 1.0 h. Evaporation and azeotroping with methanol (4 × 500 mL) and with pyridine (2 × 500 mL) gave a mixture of white solid and pale yellow syrup. Pyridine (250 mL) was added, and the insoluble inorganics were filtered off. Acetic anhydride (250 mL) was added to the pyridine filtrate and stirring was continued at room temperature for 18 h. After evaporation, methanol (250 mL) was added to the residual syrup and the resulting solution refluxed for 10 min. After evaporation of the methanol, the residue was stirred with methylene chloride (500 mL)–water (250 mL) while sufficient solid sodium bicarbonate was added to make the aqueous layer basic. The layers were separated and the aqueous layer was extracted with additional methylene chloride (2 × 250 mL). The combined organic layers were dried ($CaSO_4$) and evaporated. The residue was azeotroped with toluene (3 × 250 mL), leaving a yellow oil (39.1 g); ^1H NMR almost identical with that of an analytical sample. Distillation gave a colorless syrup (36.7 g, 98%, bp 132–134 °C (0.04 mm), which solidified to white crystals, mp 62–63 °C. Sublimation of such a sample [60 °C (0.1 mm)] gave an analytical sample of **3b** as white crystals: mp 62–63 °C; IR (neat, on syrup immediately after distillation) 3260 br (NH), 3050 (CH=CH), 1735 (OAc), 1638 (C=C, amide 1), 1530 cm^- (amide 2); ^1H NMR (CCl_4) δ 7.83 (d, J = 7.5 Hz, 1, NHC=O), 5.83 (s, $w_{1/2}$ = 2.5 Hz, 2, CH=CH), 4.93 (m, 1, CHN), 4.04 (d, J = 6.5 Hz, 2, CH_2O), 3.25–2.18 (m, 2, H-1 and H-5), 2.07 and 1.95 (both s, 6, CH_3CO_2 and CH_3CON), 1.50–1.00 (m, 1, H-5, probably the H cis to the acetamido group).

Anal. Calcd for $C_{10}H_{15}NO_3$ (197.24): C, 60.89; H, 7.67; N, 7.10. Found: C, 60.95; H, 7.97; N, 7.07.

An average yield of 94% was achieved for numerous runs of this size or larger.

Lithium Borohydride Reduction of 2a; Isolation of Mixtures of 3b and 4b or 3c and 4c. A solution of **2a** (3.40 g, 18.6 mmol) in dry tetrahydrofuran (100 mL) was added to a stirred solution of lithium borohydride (810 mg) and dry tetrahydrofuran (400 mL) under nitrogen at room temperature over a period of 1.0 h. Stirring was continued overnight. The resulting mixture (a large quantity of gummy white precipitate had formed) was cooled (ice bath) while ice water (300 mL) was added dropwise over 1.0 h. Amberlite IRA-120 (H^+) resin (5 g) was then added cautiously and the resulting mixture stirred for 2.0 h. The resin was filtered off and the filtrate evaporated to dryness. The residue was dissolved in portions of methanol (5 × 200 mL) and repeatedly evaporated to dryness. The residue was then dissolved in water (200 mL) and stirred with Amberlite IRA-400 (OH^-) resin (20 mL) for 30 min. Evaporation to dryness left colorless syrup (3.59 g) which appears from the ^1H NMR integration to be a mixture of **3a** and **4a:** IR (neat) CO_2Me absent; ^1H NMR ($CDCl_3$) δ 7.9–6.7 (m, 1, 2 partially overlapping NHC=O), 5.9–5.6 (t-like m, 1.7, CH=CH), 5.2–4.7 (m, 1, CHN), 3.9–3.3 (m, 3, CH_2O and OH, br s due to OH shifts upfield to 3.17 on heating to 60 °C), 3.1–1.0 (m) with discernible singlets at 1.98 (minor) and 1.95 (6.5, CH, all CH_2, CH_3CO). The integration of the olefinic peaks and the methylene envelope indicate, for this particular run, that the sample consists of 85% of **3a** and 15% of **4a.** The ratio of **3a/4a** was not reproducible (range from 1:1 to 6:1) and did not vary in any consistent way with changes in reaction conditions such as temperature, time, reversal of addition, rate of addition, or ratio of [H^-] to [**2a**].

Such mixtures of **3a** and **4a** were acetylated in acetic anhydride–pyridine (1:1) at room temperature overnight. After evaporation, the residue was dissolved in methylene chloride, extracted with half-saturated sodium bicarbonate, dried ($CaSO_4$), and evaporated, leaving a mixture of **3b** and **4b** as a colorless oil (78–86% from **2a**), chromatographically homogeneous on TLC (5% MeOH–$CHCl_3$). Two distillations of such a mixture gave a sample of **3b** as a colorless oil: bp 134–136 °C (0.1 mm); ^1H NMR integration and mass spectrum relative intensity ratio of $(M + 2)^+/M^+$ of 10:1 indicate contamination by **4b.**

Anal. Calcd for $C_{10}H_{15}NO_3$ (197.24): C, 60.89; H, 7.67; N, 7.10. Found: C, 6.093; H, 7.88; N, 7.35.

Benzoylation of the mixture of **3a** and **4a** gave a mixture of benzoates **3c** and **4c.** Fractional crystallization from benzene–hexanes gave **3c** as needles (25–66%): mp 84–85 °C; IR, NMR, and mass spectra as expected.

Anal. Calcd for $C_{15}H_{17}NO_3$ (259.31): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.60; H, 6.71; N, 5.20.

The mother liquors contained additional **3c** contaminated by **4c** (detected by ^1H NMR).

Methyl 4α-Acetamido-2α,3α-epoxycyclopentane-1α-carboxylate (5). A solution of **2a** (366 mg, 2.00 mmol) and *m*-chloroperbenzoic acid (487 mg, 85%, 2.4 mmol) in carbon tetrachloride (18 mL) was refluxed for 2 h. Potassium carbonate (415 mg, 3.00 mmol) was added and the slurry added to a silica gel column packed in chloroform. Elution with chloroform gave initial fractions containing *m*-chloroperbenzoic acid followed by fractions containing **5** (370 mg). Crystallization from ethyl acetate–hexanes gave **5** as a fluffy white solid (288 mg, 73%): mp 117.5–118.5 °C; IR (KBr) 3275 (NH), 1735 (CO_2Me), 1635, 1550 (NHAc), 863, 840 cm^{-1} (epoxide); ^1H NMR ($CDCl_3$) δ 6.68 (d, J = 8.0 Hz, 1, NHC=O), 4.44 (q-like m, 1, CHN), 3.72 (s) overlapped by 3.7–3.4 (m, 5, CO_2Me and c-CHOCH), 3.1–2.7 (m, 1, $CHCO_2Me$), 1.99 (s) overlapped by 2.6–1.1 (m, 5, CH_3C=O, CH_2).

Anal. Calcd for $C_9H_{13}NO_4$ (199.21): C, 54.26; H, 6.58; N, 7.03. Found: C, 54.11; H, 6.71; N, 6.79.

4α-Acetamido-2α,3α-epoxycyclopentane-1α-methyl Acetate (6b). A solution of **3b** (36.7 g, 0.186 mol) and *m*-chloroperbenzoic acid (37.8 g, 85%, 0.186 mol) in carbon tetrachloride (700 mL) was refluxed for 2.0 h. The solution was concentrated to 200 mL and methylene chloride (500 mL) added. This solution was extracted with saturated sodium bicarbonate (150 mL), dried ($CaSO_4$), and evaporated, leaving **6b** as a yellow oil (40.8 g) which solidified on standing: ^1H NMR almost identical with that of an analytical sample. Such material was sufficiently pure for use. An analytical sample was prepared by preparative TLC (10% MeOH–$CHCl_3$), giving **6b** as a colorless oil (89%) that slowly changed to a gummy amorphorus solid on drying at 0.1 mm: mp 68–72 °C; all attempts to crystallize were unsuccessful; attempts to distill or sublime **6b** caused decomposition; IR (KBr) 3300 (NH), 1735 (OAc), 1635 br, 1540 (NHAc), 865, 830 cm^{-1} (epoxide); ^1H NMR ($CDCl_3$) δ 6.98 (d, J = 7.5 Hz, 1, NHC=O), 4.42 (m) overlapping 4.03 (d, J = 7.0 Hz, 3, CHN and OCH_2), 3.45 (m, 2, c-CHOCH), 2.08 and 2.02 (both s) overlapped by 2.5–0.5 (m, 9, CH_3CO_2, CH_3CON, CH, CH_2).

Anal. Calcd for $C_{10}H_{15}NO_4$ (213.24): C, 56.33; H, 7.09; N, 6.57. Found: C, 56.16; H, 6.98; N, 6.60.

4α-Acetamido-2α,3α-epoxycyclopentane-1α-methyl Benzoate (6c). Epoxidation of **3c** exactly as in the preparation of **6b** gave **6c** as white needles (90% after crystallization from benzene–hexanes): mp 138–139 °C; IR, ^1H NMR, and mass spectra analogous to those of **6b.**

Anal. Calcd for $C_{15}H_{17}NO_4$ (275.31): C, 65.44; H, 6.22; N, 5.09. Found: C, 65.72; H, 6.29; N, 5.10.

4α-Acetamido-2α,3α-epoxycyclopentane-1α-methanol (6a). Ammonia was bubbled through a solution of **6b** (5.62 g, 26.4 mmol) in methanol (150 mL) for 2 min at room temperature. The flask was stoppered and allowed to stand overnight. Evaporation left a yellow oil which crystallized from ethyl acetate to give white crystals (1.60 g, 35%). An analytical sample of **6a** was prepared by two recrystallizations from absolute ethanol: mp 172–173 °C; IR (KBr) 3250 br, 3000–2700 (OH, NH), 1635 br, 1565 (NHAc), 875, 830 cm^{-1} (epoxide); ^1H NMR (Me_2SO-d_6) δ 7.97 (d, J = 8.0 Hz, 1, NHC=O), 4.64 (t, J = 5.0 Hz, 1, CH_2OH) partially overlapping 4.5–3.8 (m, 1, CHN), 3.45 (m, 4, c-CHOCH, CH_2OH), 1.82 (s) overlapped by 2.4–0.5 (m, 6, CH_3C=O, CH_2, CH).

Anal. Calcd for $C_8H_{13}NO_3$ (171.20): C, 56.13; H, 7.65; N, 8.18. Found: C, 56.19; H, 7.74; N, 8.00.

In practice, no attempt was made to crystallize **6a.** The ammonia–methanol was evaporated to dryness and the residue used immediately in the next reaction.

4α-Acetamido-3α-acetoxy-2β-azido-1α-cyclopentanemethyl Acetate (7a) and 4α-Acetamido-2α-acetoxy-3β-azido-1α-cyclopentanemethyl Acetate (8a). A sample of **6a** prepared from **3b** (23.9 g, 0.121 mol) by epoxidation and then ammonia–methanol treatment, as described above, was stirred with sodium azide (31.5 g, 0.484 mol), ammonium chloride (6.79 g, 0.127 mol), 2-methoxyethanol (330 mL), and water (50 mL) at 75 °C for 18 h. The reaction mixture was evaporated to dryness and the residue dried by azeotroping with pyridine (2 × 200 mL). The residue was stirred with pyridine (300 mL)–acetic anhydride (200 mL) overnight. The solid was filtered off and the filtrate evaporated to dryness. The residue was dissolved in methylene chloride and extracted with saturated sodium bicarbonate (2 × 50 mL), dried ($CaSO_4$), and evaporated to dryness. The residual tan solid (32.2 g, 89% as mixture of **7a** and **8a**) was crystallized from chloroform–carbon tetrachloride, giving white prisms of **7a** (18.0 g, 50% from **3b**): mp 103–106 °C; ^1H NMR identical with that of an analytical sample. An analytical sample of **7a** was prepared from such a sample by crystallization from carbon tetrachloride: white prisms; mp 103–104 °C; IR (KBr) 3255, 3090 (NH),

2110 (N_3), 1745 (OAc), 1645, 1555 cm^{-1} (NHAc); ^1H NMR ($CDCl_3$) δ 6.38 (br d, J = 8 Hz, 1, NHC=O), 5.00 (m, 1, CHO), 4.8–4.2 (m, 1, CHNHCO), 4.12 (d, J = 5.5 Hz, 2, OCH_2CH) partially overlapping 4.60 (m, 1, CHN_3), 2.14, 2.13, 2.00 (all s) overlapped by 2.8–1.3 (m, 12, $3CH_3C$=O, CH, CH_2).

Anal. Calcd for $C_{12}H_{18}N_4O_5$ (298.31): C, 48.32; H, 6.08; N, 18.78. Found: C, 48.27; H, 6.12; N, 18.65.

Evaporation of the mother liquors left a yellow glass (14.0 g) which ^1H NMR showed to be a mixture of **7a** and **8a** in a ratio of ~1.2:1 (as determined by integration of the NHC=O resonances, the minor isomer's NH being slightly downfield from that of the major). Attempts to separate this mixture by column chromatography (0.5–2.5% MeOH–$CHCl_3$) gave enrichment of the major isomer **7a** in the early fractions. A pure sample of **8a** could not be obtained. Such mixtures of **7a** and **8a** could be hydrogenated to **9a** and **10a**, which were easily separated (see later). Both ^1H NMR and relative yields of **9a** and **10a** indicated the ratio of **7a** to **8a** formed in the epoxide opening to be 5.5:1.

4α-Acetamido-2β-azido-3α-hydroxy-1α-cyclopentanemethyl Benzoate (7b) and 4α-Acetamido-3β-azido-2α-hydroxy-1α-cyclopentanemethyl Benzoate (8b). A solution of **6c** (3.00 g, 10.9 mmol), sodium azide (3.78 g, 58.1 mmol), and ammonium chloride (777 mg, 14.5 mmol) in water (15 mL) and 2-methoxyethanol (40 mL) was maintained at 70 °C for 18 h. After evaporation to dryness, the residue was partitioned between water (15 mL) and methylene chloride (2 × 75 mL). The combined organic layers were dried ($CaSO_4$) and evaporated, leaving a mixture of **7b** and **8b** (2.6 g) in a ratio of 4:1 (from integration of the NH resonances in the ^1H NMR). Crystallization from benzene–hexanes gave **7b** as white crystals (1.30 g, 37%): mp 111.5–112 °C; IR and ^1H NMR analogous to those of **7a**.

Anal. Calcd for $C_{15}H_{18}N_4O_4$ (318.34): C, 56.59; H, 5.70; N, 17.60. Found: C, 56.62; H, 5.85; N, 17.73.

A small sample of the minor isomer **8b** was obtained by column chromatography of the mother liquors (5% MeOH–$CHCl_3$). Initial fractions appeared (from ^1H NMR) to be free of **7b**. This sample of **8b** was a colorless glass which could not be solidified and retained solvents on drying. Hydrogenation (see below) gave **10c** which was not contaminated by **9c**.

3α-Acetoxy-2β,4α-diacetamido-1α-cyclopentanemethyl Acetate (9a) and 2α-Acetoxy-3β,4α-diacetamido-1α-cyclopentanemethyl Acetate (10a). A. Catalytic Hydrogenation of 7a and Mixtures of 7a and 8a. 1. In Ethanol. A solution of **7a** (500 mg, 1.68 mmol) in absolute ethanol (20 mL) was shaken with prereduced platinum oxide (100 mg) under hydrogen (50 psi) overnight. The catalyst was filtered off and the filtrate evaporated to dryness. The residual glass[28] was immediately dissolved in acetic anhydride (20 mL)[29] and warmed gently on the steam bath for 2 min. Evaporation and azeotroping with toluene left a yellow glass (575 mg). Crystallization from ethanol–ethyl acetate gave **9a** as white needles (165 mg, 31%): mp 168–169.5 °C; IR (KBr) 3300 (NH), 1737 (OAc), 1653, 1553 cm^{-1} (NHAc); ^1H NMR ($CDCl_3$) δ 7.18 (br d, J = 8.0 Hz, 1, NHC=O), 6.46 (br d, J = 8.0 Hz, 1, NHC=O), 5.3–3.9 (m, 5, CHO, 2CHN, OCH_2), 2.11, 2.08, and 2.01 (all s) overlapped by 2.8–1.7 (m, 15, 4 CH_3C=O, CH, CH_2).

Anal. Calcd for $C_{14}H_{22}N_2O_6$ (314.35): C, 53.49; H, 7.05; N, 8.91. Found: C, 53.31; H, 6.97; N, 8.70.

The ethanol–ethyl acetate mother liquor darkened rapidly and TLC (10% MeOH–$CHCl_3$) showed numerous spots. Addition of acetic anhydride (20% of ethanol) to the Parr shaker immediately on opening (before filtration of the catalyst) avoided much of this decomposition. After warming gently on the steam bath for 30 min, the catalyst was filtered off and the solution evaporated to dryness. The residual colorless glass crystallized to **9a** (70%).

When a mixture of azides **7a** and **8a** was subjected to the same hydrogenation conditions and acetylation, a mixture of **9a** and **10a** was obtained as a yellow syrup. The isomers could be separated by column chromatography (2% MeOH–$CHCl_3$). The minor isomer **10a** was eluted from the column first and crystallized from chloroform–hexanes to white granules (12% from **6b**): mp 163.5–164.5 °C; mmp with **9a**, 138–147 °C; IR (KBr) 3300, 3100 (NH), 1745, 1730 (OAc), 1650, 1635, 1550 (NHAc); ^1H NMR ($CDCl_3$) δ 7.5–7.1 (m, 2, 2NHC=O), 5.4–5.3 (m, 1, CHO), 4.6–3.7 (m, 4, 2CHN, OCH_2), 2.07, 2.03, 1.98 (all s) overlapped by 3.0–1.2 (m, 15, $4CH_3C$=O, CH, CH_2).

Anal. Calcd for $C_{14}H_{22}N_2O_6$ (314.35): C, 53.49; H, 7.05; N, 8.91. Found: C, 53.47; H, 7.05; N, 8.85.

Continued elution of the column gave isomer **9a** (65% from **6b**).

2. In Acetic Anhydride: Isolation of 4α-Acetamido-2α,3α-diacetoxy-1α-cyclopentanemethyl Acetate (11a). A solution of **7a** (8.59 g, 28.8 mmol) in acetic anhydride (100 mL) was shaken with prereduced platinum oxide (500 mg) under hydrogen (50 psi) overnight. Workup as above gave a yellow syrup which crystallized from chloroform–hexanes to **9a** (5.76 g, 64%). The mother liquors contained mostly a material of greater R_f than **9a** or **10a** which could not be solidified. Further purification by column chromtography (1% MeOH–$CHCl_3$) gave **11a** as a colorless syrup (3.18 g, 35%); ^1H NMR identical with that of an analytical sample. Crystallization of such a sample from EtOAc gave white granules of **11a**: mp 115–116 °C; IR (KBr) 3270, 3080 (NH), 1735 (OAc), 1645, 1560 cm^{-1} (NHAc); ^1H NMR ($CDCl_3$) δ 5.30 (br d, J = 8.5 Hz, 1, NHC=O), 5.6–5.1 (m, 2, 2CHO), 4.8–4.0 (m, 1, CHN), 4.04 (d, J = 8.0 Hz, 2, OCH_2), 1.43, 1.37, and 1.34 (all s) overlapped by 2.8–1.2 (m, 15, $4CH_3C$=O, CH_2, CH), addition of D_2O resulted in a slow disappearance of the NH resonance; mass spectrum (20 eV, 50 °C) almost identical with that of 4α-acetamido-2β,3α-diacetoxy-1α-cyclopentanemethyl acetate,[5] high resolution confirms composition of M^+.

Anal. Calcd for $C_{14}H_{21}NO_7$ (315.33): C, 53.33; H, 6.71; N, 4.44. Found: C, 53.59; H, 6.95; N, 4.68.

3. In Chloroform–Ethanol.[17] A solution of **7a** (5.02 g, 16.8 mmol) in 5% chloroform–absolute ethanol (250 mL) was shaken with prereduced platinum oxide (250 mg) under hydrogen (50 psi) overnight. The Parr flask was opened and sodium acetate (1.38 g, 16.8 mmol) and acetic anhydride (25 mL) were added immediately. The mixture (including catalyst) was warmed gently on a steam bath for 30 min. During this time a cloudy white precipitate of sodium chloride formed. The mixture was filtered through Celite and the filter pad washed with additional hot ethanol (100 mL). The residue left after evaporation of the ethanol was triturated with refluxing chloroform and the undissolved sodium chloride filtered off. Evaporation of the chloroform left a colorless syrup that crystallized from ethanol–ethyl acetate to give **9a** as white needles (4.44 g, 84%): mp 168.5–169.5 °C; IR and NMR identical with those of the analytical sample.

B. Acid-Catalyzed Opening of 6b in Acetonitrile.[18] To a solution of **6b** (426 mg, 2.00 mmol) in dry acetonitrile (8 mL) was added boron trifluoride etherate (1.25 mL, ~10.0 mmol). The clear pale yellow solution was stirred at room temperature for 24 h. Water (8 mL) was added and stirring continued for 30 min. In a modification of the literature procedure, this solution was passed through a column of Amberlite IRA-400 (OH^-) resin (50 mL). The basic eluent (120 mL) was evaporated and the residue azeotroped dry with absolute ethanol, leaving yellow glass (458 mg). Acetic anhydride (5 mL) and pyridine (10 mL) were added. After standing overnight, the solution was evaporated, treated with refluxing ethanol, and azeotroped with toluene to give yellow glass (550 mg); TLC (10% MeOH–$CHCl_3$) shows major spot of same R_f as **9a** plus several minor spots of greater R_f. Crystallization from chloroform–hexanes gave **9a** (328 mg, 52%): mp 168–169.5 °C; NMR same as that of analytical sample.

When this reaction was run on a larger scale starting with **6b** (32.1 g, 0.151 mol), the literature workup was used (neutralization with aqueous $NaHCO_3$) and the material isolated was black tar. After extensive chromatography and crystallization, about 11% of **9a** was isolated.

Oxidation of 11b and Characterization of the Product as a Di(2,4-dinitrophenylhydrazone) (15). A solution of **11a** (158 mg, 0.500 mmol) in methanol saturated with ammonia (10 mL) was allowed to stand at room temperature overnight in a stoppered flask. Evaporation left a colorless glass (95 mg) which was dissolved in absolute ethanol (5 mL) and added all at once to a solution of sodium metaperiodate (107 mg, 0.500 mequiv) in water (2.5 mL). A white precipitate started to form within 5 min. After 3.5 h, the mixture was diluted to 20 mL with absolute ethanol and cooled (ice bath) for 30 min. The white precipitate was filtered off and washed with additional ethanol. To the filtrate–wash was added a warm solution of 2,4-dinitrophenylhydrazine (250 mg, ~20% H_2O, ~1.0 mmol) in absolute ethanol (5 mL)–concentrated hydrochloric acid (0.5 mL). An orange precipitate was filtered off, washed with ethanol, and air dried to give **15** (208 mg, 76%), mp 206–209 °C dec. Resolidification from nitromethane gave fluffy yellow solid (140 mg, 51%): mp 219–222 °C dec; IR (KBr) 3400, 3280 (NH, OH), 1650 (amide 1), 1620 (C=C), 1587 (amide 2), 1513 and 1328 cm^{-1} (NO_2).

Anal. Calcd for $C_{20}H_{21}N_9O_{10}$ (547.46): C, 43.88; H, 3.87; N, 23.03. Found: C, 43.91; H, 3.95; N, 23.24.

The same conversion was also carried out on the xylo and arabino isomers (**12a** and **13a**)[5] and the resulting phenylhydrazones gave no depression of a mixture melting point with the sample of **15** derived from **11a**.

4α-Acetamido-2β-amino-3α-hydroxy-1α-cyclopentanemethyl Benzoate (9b): Acetylation to 9c. A solution of **7b** (2.45 g, 7.70 mmol) in absolute ethanol (20 mL) was shaken with prereduced platinum oxide (250 mg) under hydrogen (50 psi) for 18 h. Filtration

and evaporation left yellow gum (2.5 g) that crystallized from chloroform–hexanes to white granules of **9b** (1.17 g, 52%): mp 174–178 °C; IR (KBr) 3300 br, 3065 (OH, NH), 1712 (benzoate), 1640, 1535 (NHAc), 1595 cm^{-1} (C=C).

Anal. Calcd for $C_{15}H_{20}N_2O_4$ (292.34): C, 61.63; H, 6.90; N, 9.58. Found: C, 61.39; H, 7.04; N, 9.63.

Although crystalline **9b** was stable, mother liquors darkened rapidly. Acetylation of **9b** by refluxing in methanol–acetic anhydride (1:1) for 30 min gave **9c** as white needles (89% after crystallization from ethyl acetate): mp 200–202 °C; IR (KBr) 3330, 3260, 3075 (OH, NH), 1708 (benzoate), 1660, 1640, 1550 cm^{-1} (2NHAc); ^1H NMR (Me_2SO-d_6) δ 8.0–7.2 (m, 7, C_6H_5 and 2NHC=O), 5.00 (br s, 1, OH), 4.20 (d, J = 6.0 Hz) overlapped by 4.4–3.5 (m, 5, $CHCH_2O$, CHO, 2 CHN), 1.83 and 1.80 (both s) overlapped by 2.3–1.3 (m, 9, $2CH_3CO$, CH_2, CH).

Anal. Calcd for $C_{17}H_{22}N_2O_5$ (334.38): C, 61.06; H, 6.63; N, 8.38. Found: C, 61.27; H, 6.70; N, 8.37.

3β,4α-Diacetamido-2α-hydroxy-1α-cyclopentanemethyl Benzoate (10c). Hydrogenation of **8b** exactly as for **7b** gave a colorless glass that turned red on contact with air. Immediate acetylation (as for **9c**) gave **10c** as white granules (70% after crystallization from ethyl acetate): R_f on TLC (5% MeOH–$CHCl_3$) greater than that of **9c**; mp 190–191 °C; IR, NMR, and mass spectra similar to those of **10c.**

Anal. Calcd for $C_{17}H_{22}N_2O_5$ (334.38): C, 61.06; H, 6.63; N, 8.38. Found: C, 61.22; H, 6.88; N, 8.35.

2β-Acetamido-4α-amino-3α-hydroxy-1α-cyclopentanemethanol (16a). A solution of **9a** (5.75 g, 18.3 mmol) in 2 N hydrochloric acid (220 mL) was maintained at 70 °C for 1.0 h. After evaporation, the residue was dried by evaporation of portions of absolute ethanol and toluene, leaving the hydrochloride of **16a** as a hygroscopic white solid foam; ^1H NMR (CD_3OD) shows only once acetyl group. The solid foam was dissolved in methanol and passed through a column of Amberlite IRA-400 (OH^-) resin (100 mL). The basic methanol eluent (600 mL) was evaporated, leaving **16a** which was pure enough for use as an intermediate as a colorless glass (3.60 g, contains solvent). Attempts to solidify **16a** or to remove traces of solvent by drying were unsuccessful.

2β-Acetamido-4α-benzyloxycarbonylamino-3α-hydroxy-1α-cyclopentanemethanol (16b). A sample of crude hydrochloride of **16a** prepared by hydrolysis of **9a** (1.00 g, 3.18 mmol) as described above was dissolved in dry dimethylformamide (20 mL). The solution was cooled (ice bath) and triethylamine (1.2 mL, 8.4 mmol) and carbobenzoxy chloride (0.53 mL, 4.8 mmol) were added. The ice bath was removed and stirring continued for 1.0 h. Ice water (20 mL) was added and stirring continued for 20 min. The resulting mixture (some white solid formed) was evaporated to a glass. After trituration with ether (2 × 20 mL), a white solid remained (931 mg, 91%): mp 142–148 °C; IR identical with that of an analytical sample. Resolidification of such a sample from methylene chloride gave an analytical sample of **16b** as white powder: mp 152.5–153.5 °C; IR (KBr) 1688 (Cbz), 1640, 1537 cm^{-1} (NHAc); ^1H NMR (Me_2SO-d_6) δ 7.98 (br d, J = 7.5 Hz, 1, NHC=O), 7.37 (br s, 5, C_6H_5), 6.63 (br d, J = 7.5 Hz, 1, NHC=O), 5.07 (s) overlapped by 5.0–4.7 (m, 3, OCH_2Ph and OH), 4.3–3.0 (m, 6.4, CHO, 2CHN, OCH_2CH, OH, and contaminating H_2O in solvent), 1.68 (s) overlapped by 2.3–1.0 (m, 6, CH_3C=O, CH_2, CH).

Anal. Calcd for $C_{16}H_{22}N_2O_5$ (322.37): C, 59.61; H, 6.88; N, 8.69. Found: C, 59.37; H, 6.88; N, 8.65.

2β,4α-Diacetamido-3α-hydroxy-1α-cyclopentanemethyl Acetate 3,4-Carbamate (17b). To a solution of **16b** (200 mg, 0.653 mmol) in dry dimethylformamide (3 mL) was added a 1.5 N solution of sodium methoxide in dry methanol (0.1 mL). The solution was stirred at 100 °C for 1.5 h and evaporated, and the residual colorless glass was extracted with ether (3 × 20 mL) and dried. This crude **17c** was only partially acetylated in acetic anhydride–methanol, giving a mixture of **17a** and **17c** (~1:1 from TLC and NMR). Acetylation was completed in acetic anhydride (10 mL)–pyridine (10 mL) at room temperature overnight. Evaporation and trituration of the residue with carbon tetrachloride (20 mL) left chromatographically homogeneous white powder (160 mg, 82%): mp 172–178 °C; IR and R_f identical with an analytical sample of **17b.** Resolidification of such a sample from methylene chloride–carbon tetrachloride gave white powder: mp 168–174 °C effervesces; IR (KBr) 3250, 3080 (NH), 1770 (urethane C=O), 1735 (OAc), 1697 ($AcNCO_2$), 1635 and 1540 cm^{-1} (NHAc); ^1H NMR (Me_2SO-d_6) δ 8.10 (br d, J = 8.0 Hz, 1, NHC=O), 5.0–3.7 (m, 5, CHO, 2CHN, CH_2O), 2.40 (s, CH_3CONCO_2–), 2.02 and 1.88 (both s, CH_3CO_2 and CH_3CONH) overlapped by 2.4–1.0 (m, total 12, 3Ac, CH, CH_2).[30]

Anal. Calcd for $C_{13}H_{18}N_2O_6$ (298.30): C, 52.34; H, 6.08; N, 9.39. Found: C, 52.18; H, 6.10; N, 9.42.

Hydrolysis of 10a to 3β,4α-Diacetamido-2α-hydroxy-1α-cyclopentanemethanol (18a): Characterization of 18a as the 4-Methoxytrityl Derivative (18b). A solution of **10a** (200 mg, 0.636 mmol) in 2 N hydrochloric acid (10 mL) was maintained at 70 °C for 1.0 h. The solution was evaporated and the residual glass azeotroped dry by evaporation of portions of absolute ethanol and toluene, and dried. Since the resulting glass still contained HCl, it was dissolved in methanol and stirred with Amberlite IRA-400 (OH^-) resin (10 mL). Evaporation of the methanol left a colorless glass (147 mg, 100% as **18a**) which was hygroscopic and could not be solidified: ^1H NMR (CD_3OD) δ 4.62 (br s, 4, MeOH due to exchangeable protons, 2NHC=O and 2OH), 4.2–3.3 (m, 5, CH_2O, CHO, 2 CHN), 1.78 and 1.74 (both s) overlapped by 3.0–0.9 (m, 9, $2CH_3C$=O, CH_2, CH).

Such a sample of **18a** obtained from the hydrolysis of **10a** (200 mg, 0.636 mmol) as described above was dissolved in dry pyridine (5 mL) and stirred with 4-methoxytrityl chloride (236 mg, 0.763 mmol) for 2 days. The solution was poured into ice water (5 mL), neutralized with sodium bicarbonate, and extracted with methylene chloride (3 × 10 mL). The combined organic layers were dried ($CaSO_4$) and evaporated, leaving pale yellow solid foam (300 mg); TLC (5% MeOH-$CHCl_3$) shows one major band plus several minor greater R_f bands. The foam was chromatographed on two 20 × 20 cm silica gel F254 preparative plates (2 mm) developed in 10% MeOH–$CHCl_3$. Extraction of the major band gave **18b** as a colorless glass which solidified to a white powder on trituration with carbon tetrachloride (164 mg, 51%): mp 158–160 °C effervesces; IR (KBr) 3400 sh, 3260, 3060 (OH, NH), 1650 br, 1550 br cm^{-1} (NHAc); ^1H NMR ($CDCl_3$) δ 7.6–6.7 (m, 15, $2C_6H_5$, OC_6H_4, NHC=O), 6.40 (d, J = 6.0 Hz, 1, NHC=O), 4.43 (br s, 1, OH), 3.78 (s) overlapped by 4.2–3.5 (m, 6, OMe, CHO, 2CHN), 3.30 (d, J = 5.8 Hz, 2, OCH_2CH), 1.95, 1.87 (both s) overlapped by 2.7–1.2 (m, 9, $2CH_3CO$, CH, CH_2).

Anal. Calcd for $C_{30}H_{34}N_2O_5$ (502.62): C, 71.69; H, 6.82; N, 5.57. Found: C, 71.58; H, 6.62; N, 5.36.

5-Amino-4-*N*-[3β-acetamido-2α-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]amino-6-chloropyrimidine (19). A solution of **16a** from the hydrolysis of **9a** (5.77 g, 18.4 mmol) as described above, 5-amino-4,6-dichloropyrimidine (6.10 g, 37.2 mmol), and triethylamine (12.7 mL, 91 mmol) in 1-butanol (90 mL) was refluxed under nitrogen for 24 h. The solution was evaporated to dryness and the residue stirred vigorously with water (150 mL)–chloroform (75 mL). The aqueous layer was separated and extracted with additional chloroform (3 × 25 mL). The aqueous layer was stirred briefly with Amberlite IRA-400 (OH^-) resin (40 mL). Evaporation left **19** as cream-colored powder (5.21 g): TLC (20% MeOH–$CHCl_3$) shows one major spot plus a minor contaminant at slightly greater R_f.[31] One resolidification from absolute ethanol gave chromatographically homogeneous **19** as a cream-colored powder (4.45 g, 77%), mp 239–240 °C dec. An analytical sample was prepared by resolidification of such a sample from absolute ethanol–ether, giving **19** as an off-white powder: mp 254–256 °C dec (varies with rate of heating); IR (KBr) 3450–3050 (OH, NH), 1645 br (amide 1), 1585 br, 1570, 1560 (C=C, C=N), 1540 br cm^{-1} (amide 2); ^1H NMR (Me_2SO-d_6) δ 7.93 (d, J = 7.5 Hz, 1, NHC=O) 7.62 (s, 1, pyrimidine CH), 6.40 (d, J = 6.5 Hz, 1, OH), 5.4–3.0 (m, 10, NH_2, NH, OH, CH_2O, CHO, 2CHN, H_2O in solvent), 1.83 (s) overlapped by 2.4–1.2 (m, 6, CH_3C=O, CH, CH_2).

Anal. Calcd for $C_{12}H_{18}N_5O_3Cl$ (315.77): C, 45.64; H, 5.75; Cl, 11.23; N, 22.18. Found: C, 45.52; H, 5.95; Cl, 11.09; N, 22.07.

9-[3β-Acetamido-2α-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine (20). A mixture of **19** (1.76 g, 5.57 mmol) and diethoxymethyl acetate (20 mL) was stirred at room temperature overnight and then at 100 °C for 1.0 h. The solution was evaporated to a yellow foam which showed numerous spots on TLC (10% MeOH–$CHCl_3$). The foam was shaken with liquid ammonia (100 mL) in a stainless steel bomb at room temperature for 3 days. Evaporation left a yellow glass which was dissolved in 1 N hydrochloric acid (100 mL) and maintained at 60 °C for 45 min. The solution was evaporated to dryness and the residue was dissolved in methanol and passed through a column of Amberlite IRA-400 (OH^-) resin (50 mL). Evaporation of the basic methanol eluent (500 mL) left orange glass mixed with solid. Crystallization from absolute ethanol gave **20** as white granules (967 mg, 54%): mp 218–222 °C dec; UV max ($\epsilon \times 10^{-3}$) 258 nm (14.5) in 0.1 N HCl, 260 nm (14.6) in H_2O, 260 nm (14.8) in 0.1 N NaOH; IR (KBr) 3360, 3160 (OH, NH), 1670, 1607, 1570 (C=C, C=N), 1650, 1545 cm^{-1} (NHAc); ^1H NMR (Me_2SO-d_6) δ 8.08 (s) overlapping 8.1–7.9 (m, 3, purine H-2 and H-8, NHC=O), 7.07 (br s, 1.5, exchanges in this solvent, NH_2), 5.5–3.1 (m, 9, 2 OH, CHO, 2CHN, CH_2O, H_2O), 1.89 (s) overlapped by 2.5–1.3 (m, 6, CH_3C=O, CH, CH_2); mass spectrum essentially the same as that of stereoisomer **25.**

Anal. Calcd for $C_{13}H_{18}N_6O_3 \cdot H_2O$ (324.35): C, 48.14; H, 6.22; N, 25.91. Found: C, 48.07; H, 6.34; N, 25.68.

Column chromatography of the mother liquor contents (20–30% MeOH–$CHCl_3$) gave additional **20** (397 mg, 22% after crystallization from absolute ethanol): melting point and TLC same as those of the analytical sample.

9-[3β-Acetamido-2α-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-6-dimethylaminopurine (27). A sample of **19** (3.76 g, 11.9 mmol) was reacted with diethoxymethyl acetate as described above. The resulting crude chloropurine was refluxed with 40% aqueous dimethylamine (75 mL) for 3 h. After evaporation the residue was dissolved in 1 N hydrochloric acid (60 mL) and maintained at 65 °C for 45 min. After evaporation, the residue was dissolved in methanol (300 mL) and stirred with Amberlite IRA-400 (OH^-) resin (100 mL) for 10 min. Evaporation left white solid (3.73 g). Crystallization from absolute ethanol gave white granules of **27** (2.96 g, 74%): mp 257–258.5 °C; IR (KBr) 3450, 3280, 3085 (OH, NH), 1665, 1560 (NHAc), 1603 cm^{-1} (C=C, C=N); mass spectrum (70 eV, 200 °C) *m/e* 334 (5.3, M^+), 164 (81.0, BH_2^+), 163 (100, BH^+), almost identical with the spectrum of stereoisomer **32.**

Anal. Calcd for $C_{15}H_{22}N_6O_3$ (334.39): C, 53.88; H, 6.63; N, 25.13. Found: C, 53.71; H, 6.88; N, 25.01.

The mother liquors contained more **27** and a lower R_f contaminant. Additional **27** (~5%) could be isolated by column chromatography. No attempt was made to identify the lower R_f impurity.

5′-*O*-(4-Methoxytrityl) Derivative (23) of 20. A solution of **20** (1.89 g, 5.84 mmol) and dimethylformamide dimethyl acetal (3.5 g, 29 mmol) in dry dimethylformamide (25 mL) was stirred at room temperature overnight. After evaporation, the residue was triturated with absolute ethanol (15 mL) until white solid formed. The mixture was diluted with ether (100 mL) and analytical quality **22** was filtered off (2.0 g, 95%): mp 227–231 °C dec; IR (KBr) 3280, 3100, 3050 (OH, NH), 1680, 1595 br (C=C, C=N), 1635 and 1540 cm^{-1} (NHAc).

Anal. Calcd for $C_{16}H_{23}N_7O_3$ (361.42): C, 53.17; H, 6.41; N, 27.13. Found: C, 52.90; H, 6.44; N, 27.09.

A solution of **22** (1.99 g, 5.51 mmol) and chloro(*p*-methoxyphenyl)diphenylmethane (2.04 g, 6.60 mmol) in dry pyridine (50 mL) was stirred at room temperature in the dark for 24 h, at which time TLC (10% MeOH–$CHCl_3$) showed no **22** left. The solution was concentrated to a small volume and methylene chloride (50 mL), ice water (20 mL), and excess sodium bicarbonate were added. After vigorous stirring, the organic layer was separated and the aqueous layer extracted with additional methylene chloride (2 × 100 mL). The combined methylene chloride layers were dried ($CaSO_4$) and evaporated, leaving pale yellow solid foam (3.90 g). Such a sample (3.06 g) was stirred with concentrated ammonium hydroxide–water–pyridine (1:1:1, 150 mL) overnight. The white precipitate which formed was filtered off, washed with water (50 mL), and dried, leaving **23** as a white powder (2.10 g, 66% from **22**): collapses to a semiopaque glass at 150–154 °C, turns red at ~220 °C, becomes completely fluid at ~240 °C. Resolidification of such a sample from chloroform gave an analytical sample of **23** as a white powder: melting point, same as before resolidification; IR (KBr) 3410 br (OH, NH), 1635 very br, 1600 sh, 1560 sh cm^{-1} (NHAc, C=C, C=N); ^1H NMR (1:1 $CDCl_3$–CD_3OD) δ 8.08, 8.01 (both s, 2, purine H-2 and H-8), 7.4–6.5 (m, 14.4, $2C_6H_5$, OC_6H_4, partially exchanged NHC=O), 4.58 (br s), overlapped by 5.5–4.2 (m, 8, HDO from exchangeable protons, CHO, 2CHN, H_2O in solvent), 3.98 (br d, J = 4.5 Hz, 2, CH_2O), 3.75 (s, 3, OCH_3), 1.97 (s) overlapped by 2.6–1.8 (m, 6, CH_3C=O, CH_2, CH).

Anal. Calcd for $C_{33}H_{34}N_6O_4$ (578.68): C, 68.49; H, 5.92; N, 14.52. Found: C, 68.41; H, 5.99; N, 14.56.

Evaporation of the ammonium hydroxide–pyridine filtrate left a yellow glass (0.75 g), which solidified to a white powder on trituration with chloroform (680 mg, 21%); melting point and TLC (5% MeOH–$CHCl_3$) same as the analytical sample of **23.**

5′-*O*-(4-Methoxytrityl) Derivative (28) of 27. Methoxytritylation of **27** as described for the preparation of **23** gave crude **28** as a white solid on evaporation of the methylene chloride. Trituration with chloroform gave chromatographically homogeneous **28** (92–94%): melting point shrinks to glass at 118–130 °C, becoming fluid at ~160 °C; very difficult to handle when dry due to static; IR and NMR identical with those of an analytical sample.[32] Crystallization from methanol gave **28** as white granules: mp 195–196 °C; IR (KBr) 3400 (br), 3280, 3060 (OH, NH), 1640, 1555 (NHAc), 1600 br cm^{-1} (C=C, C=N); ^1H NMR (Me_2SO-d_6) δ 8.10, 7.72 (both s, 2, purine H-2 and H-8) 7.9–6.5 (m, 15, $2C_6H_5$, OC_6H_4, NHC=O), 5.4–4.8 (m, 2, OH, CHO), 4.2–3.8 (m, 2, 2CHN), 3.72 (s, 3, OCH_3), 3.44 (s, 5.8, $N(CH_3)_2$) partially overlapping 3.4–2.9 (m, 3.2, CH_2O, H_2O in solvent), 1.90 (s) overlapped by 2.4–1.4 (m, 6, CH_3C=O, CH_2, CH); mass spectrum (70 eV, 120 °C) *m/e* 606 (0.4, M^+), 333 (77.6, M^+ – MeOTr), 273 (MeOTr), 190 (14.8, $^+BHCH{=}CH_2$), 164 (38.1, BH_2^+), 163 (54.3, BH^+), 134 (17.7, $BH^+ - NCH_3$).

Anal. Calcd for $C_{35}H_{38}N_6O_4$ (606.74): C, 69.29; H, 6.31; N, 13.85. Found: C, 69.25; H, 6.25; N, 13.64.

Epimerization of 23 to 24. A stirred mixture of **23** (1.83 g, 3.17 mmol) and dry pyridine (25 mL) was cooled (ice bath) while methanesulfonyl chloride (0.37 mL, 4.8 mmol) was added. Stirring was continued for 3 days at room temperature. During this period, solid **23** slowly dissolved. TLC (10% MeOH–$CHCl_3$) showed two major spots at greater R_f than **23** and many minor spots. Ethanol (4 mL) was added and stirring was continued for several hours. The solution was evaporated to dryness and the residual brown glass dissolved in methylene chloride (100 mL). This solution was extracted with saturated sodium bicarbonate (15 mL), dried ($CaSO_4$), and evaporated to dryness, leaving tan solid foam (2.0 g). The foam was dissolved in 2-methoxyethanol (47.5 mL)–water (2.5 mL). Sodium acetate (1.30 g, 15.8 mmol) was added and the solution maintained at 60–65 °C overnight. At this point, TLC (10% MeOH–$CHCl_3$) showed one major spot at R_f slightly lower than that of **23.** The solution was evaporated to dryness and the residue dried by azeotroping with absolute ethanol, leaving yellow solid foam (3.30 g). Column chromatography (10% MeOH–$CHCl_3$) gave numerous impurities of greater R_f than **23** (0.29 g), followed by unreacted **23** (0.16 g, 9%), followed by **24** as white solid (1.22 g, 67%), sufficiently pure for use. Resolidification of such a sample from methanol gave **24** as white powder: softens at 160 °C, turns clear with effervescence at ~200 °C; IR (KBr) 3345, 3200, 3060 (OH, NH), 1660 very br, 1595, 1565 cm^{-1} (NHAc, C=C, C=N); ^1H NMR (1:1 $CDCl_3$–CD_3OD) δ 8.07, 8.00 (both s, 2, purine H-2 and H-8), 7.6–6.6 (m, 14, 2 C_6H_5, OC_6H_4), 4.67 (br s) overlapped by 5.5–4.0 (m, 10, HDO from exchangeable protons, CHO, 2CHN, CH_2O), 3.73 (s, 3, OCH_3), 1.97 (s) overlapped by 2.8–1.8 (m, 6, CH_3C=O, CH_2, CH).

Anal. Calcd for $C_{33}H_{34}N_6O_4$ (578.68): C, 68.49; H, 5.92; N, 14.52. Found: C, 68.56; H, 5.98; N, 14.53.

Epimerization of 28 to 29. A mixture of **28** (5.02 g, 8.27 mmol) and dry pyridine (65 mL) was stirred and cooled (ice bath) while methanesulfonyl chloride (0.97 mL, 12.4 mmol) was added. Stirring was continued for 3 days at room temperature. The same workup described for the epimerization of **23** gave red solid foam (5.22 g); TLC (10% MeOH–$CHCl_3$) shows at least five spots having R_f greater than **28** and one spot with the same R_f as **28**; ^1H NMR ($CDCl_3$) looks like complex mixture, no indication of mesylate. Treatment with sodium acetate as described above followed by column chromatography (1–2% MeOH–$CHCl_3$) gave **30** as a pale yellow solid foam (2.50 g, 51%): ^1H NMR ($CDCl_3$) δ 8.33 (s, 1, purine H-8), 7.74 (s, 1, purine H-2), 7.6–6.7 (m, 14, $2C_6H_5$, OC_6H_4), 5.38 (dd, $J_{2,1}$ = 6.5 Hz, $J_{2,3}$ = 10.0 Hz, 1, CHO), 5.9–4.1 (m, 2, 2CHN), 3.80 (s, 3, OCH_3), 3.57 (s) overlapped by 3.4–3.1 (m, 8, $N(CH_3)_2$, OCH_2), 2.7–2.1 (m, 3, CH, CH_2), 2.02 (s, 3, CH_3C=O). Several attempts to further purify this material by chromatography on silica gel preparative plates (5% MeOH–$CHCl_3$) gave slow conversion of the higher R_f **30** to a material having the same R_f as **28** or **29.**[33]

Continued elution of the column (2–4% MeOH–$CHCl_3$) gave **29** as a pale yellow solid foam (2.11 g, 40%); same R_f as **28** (10% MeOH–$CHCl_3$); NMR same as analytical sample. An analytical sample of **29** was obtained as a white solid foam by rechromatography on preparative plates (10% MeOH–$CHCl_3$): IR (KBr) 3280 br, 3050 (NH, OH), 1680 sh, 1650, 1560 (NHAc), 1600 br cm^{-1} (C=C, C=N); ^1H NMR ($CDCl_3$) δ 8.16 (s, 1, purine H-2), 7.71 (s, 1, purine H-8), 7.6–6.6 (m, 14, $2C_6H_5$, OC_6H_4), 6.63 (d, J = 7.0 Hz, 1, NHC=O), 5.39 (br s, 1, OH), 4.8–3.8 (m, 3, CHN, 2CHO), 3.77 (s, 3, OCH_3), 3.49 (s) overlapped by 3.7–2.9 (m, 8, $N(CH_3)_2$, OCH_2), 1.93 (s) overlapped by 2.7–1.2 (m, 6, CH_3C=O, CH_2, CH); mass spectrum almost identical with that of stereoisomer **28.**

Anal. Calcd for $C_{35}H_{38}N_6O_4 \cdot 2H_2O$ (642.77): C, 65.40; H, 6.59; N, 13.08. Found: C, 65.63; H, 6.56; N, 13.10.

Detritylation of such samples of **29** to **32** (see below) indicate contamination by a few percent of **28.** Attempts to effect complete epimerization by using 2 equiv of methanesulfonyl chloride resulted in formation of a new product **31** (11%); with 3 equiv of methanesulfonyl chloride, the yield of **31** rose to 26% and the **29** isolated was still contaminated by unreacted **28.** Use of more methanesulfonyl chloride also resulted in more decomposition; the reactions were darker and less of the starting material was accounted for, with the dark material staying on the silica gel columns. A sample of **31** was separated from **29** and **30** by chromatography on preparative plates (10% MeOH–$CHCl_3$). Extraction of the band having R_f between that of **29** and **30** gave **31** as a pale yellow solid foam: IR (KBr) 3260 br (OH, NH), 1595 br (C=C, C=N), 1320, 1140 cm^{-1} (-SO_2NH-); ^1H NMR ($CDCl_3$) δ 8.10 (s, 1, purine H-2), 7.55 (s) overlapped by 8.0–6.6 (m, 15, purine H-8, $2C_6H_5$, C_6H_4), 6.3 (m, 1, OH) partially overlapping 5.49 (d, J = 6.0 Hz, 1, $NHSO_2CH_3$), 3.73 (s, OCH_3) and 3.45 (s, $N(CH_3)_2$) over-

lapped by 4.8–3.2 (m, 14, CHO, 2CHN, CH_2O), 2.80 (s) overlapped by 3.0–1.4 (m, 6, $NHSO_2CH_3$, CH, CH_2); mass spectrum (70 eV, 100 °C) *m/e* (relative intensity) no M^+, 369 (4.0, $M^+ - MeOTr$), 273 (100, MeOTr), 164 (90.6, BH_2^+), 163 (28.3, BH^+), 134 (49.7, $BH^+ - NCH_3$).

Anal. Calcd for $C_{34}H_{38}N_6O_5S \cdot \frac{1}{2}H_2O$ (651.80): C, 62.65; H, 6.03; N, 12.89; S, 4.92. Found: C, 62.86; H, 6.17; N, 12.91; S, 4.68.

9-[3β-Acetamido-2β-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine (25). A solution of **24** (931 mg, 1.61 mmol) in 97% formic acid (25 mL) was stirred at room temperature for 4 h and then diluted with 1:1 toluene–1-butanol (50 mL). The solution was concentrated to a small volume, diluted with additional toluene–1-butanol (50 mL), and reconcentrated. This process was repeated again, and then the residue was evaporated to dryness, leaving a white powder. After extraction with hexane (100 mL) the powder was dissolved in methanol (400 mL) and stirred with Amberlite IRA-400 (OH^-) resin (20 mL). Evaporation left chromatographically homogeneous **25** as a glass (457 mg, 93%). Crystallization of such a sample from absolute ethanol gave **25** as white granules (85%): R_f (20% MeOH–$CHCl_3$) same as **20**; mp 153–154 °C effervesces; UV max ($\epsilon \times 10^{-3}$) 258 nm (14.2) in 0.1 N HCl, 260 nm (14.4) in H_2O, 260 nm (14.7) in 0.1 N NaOH; IR (KBr) 3500–3050 (NH, OH), 1673, 1607 (C=C, C=N), 1635, 1565 cm^{-1} (NHAc); ^1H NMR (Me_2SO-d_6) δ 8.13, 8.07 (both s, 2, purine H-2 and H-8), 7.67 (d, 1, NHC=O), 7.10 (br s, 2, NH_2), 6.5–3.0 (m, 7.5, 2OH, CHO, 2CHN, CH_2O, H_2O in solvent), 1.90 (s) overlapped by 2.5–1.1 (m, 6, CH_3C=O, CH, CH_2); mass spectrum (70 eV, 175 °C) *m/e* (relative intensity) 306 (M^+), 275 (1.8, $M^+ - CH_2OH$), 162 (33.3, $^+BHCH{=}CH_2$), 154 (30.9 $M^+ - B - H_2O$), 136 (100, BH_2^+), 135 (24.4, BH^+).

Anal. Calcd for $C_{13}H_{18}N_6O_3$ (306.34): C, 50.97; H, 5.92; N, 27.44. Found: C, 50.94; H, 6.18; N, 27.41.

9-[3β-Acetamido-2β-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-6-dimethylaminopurine (32). Detritylation of samples of **29** or mixtures of **29** and **30** and workup, as described for the preparation of **25**, gave **32** (often contaminated by a few percent of **27**) as a solid foam (89%). Two crystallizations from absolute ethanol–ethyl acetate were sufficient to remove any contaminating **27** (detectable at a lower R_f on TLC with 20% MeOH–$CHCl_3$), giving **32** as white granules (76%): mp 169–170 °C; UV max ($\epsilon \times 10^{-3}$) 268 nm (18.2) in 0.1 N HCl, 276 nm (18.4) in H_2O, 276 nm (18.5) in 0.1 N NaOH; IR (KBr) 3325, 3245, 3060 (OH, NH), 1650, 1550 (NHAc), 1595 cm^{-1} (C=C, C=N); mass spectrum (70 eV, 250 °C) *m/e* (relative intensity) 334 (3.4, M^+), 303 (1.9, $M^+ - CH_2OH$), 190 (22.6, $^+BHCH{=}CH_2$), 164 (100, BH_2^+), 163 (58.9, BH^+).

Anal. Calcd for $C_{15}H_{22}N_6O_3$ (334.39): C, 53.88; H, 6.63; N, 25.13. Found: C, 54.15; H, 6.56; N, 24.92.

9-[3β-Amino-2α-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine (21). A solution of **20** (250 mg, 0.771 mmol) in 0.5 N barium hydroxide (10 mL) was refluxed under nitrogen for 6 h. The solution was then neutralized with CO_2 and the precipitated $BaCO_3$ removed by filtration through Celite. The filtrate was evaporated to dryness, leaving a white solid foam (225 mg) which appears from IR to be the acetic acid salt of **21**. The foam was dissolved in MeOH and stirred with Amberlite IRA-400 (OH^-) resin (10 mL). Evaporation left white solid foam which solidified from absolute ethanol, giving **21** as white powder (134 mg, 66%):[34] R_f (20% MeOH–$CHCl_3$) lower than that of **20**; mp 199–201 °C; UV max ($\epsilon \times 10^{-3}$) 258 nm (14.3) in 0.1 N HCl, 260 nm (14.9) in H_2O, 260 nm (14.9) in 0.1 N NaOH; IR (KBr) 3480, 3320, 3180, 3120 (OH, NH_2), 1680, 1650, 1605, 1570 cm^{-1} (C=C, C=N, NH_2); mass spectrum (70 eV, 200 °C) *m/e* (relative intensity) 264 (0.3, M^+), 233 (0.7, $M^+ - CH_2OH$), 216 (1.6, $M^+ - CH_2OH - NH_3$), 215 (2.0, $M^+ - CH_2OH - H_2O$), 190 (6.2, B + 56), 178 (6.4, $^+BHCH{=}CHOH$), 162 (32.4, $^+BHCH{=}CH_2$), 136 (87.5, BH_2^+), 135 (16.6, BH^+), 112 (100, $M^+ - B - H_2O$).

Anal. Calcd for $C_{11}H_{16}N_6O_2$ (264.30): C, 49.99; H, 6.10; N, 31.80. Found: C, 49.92; H, 6.09; N, 31.81.

9-[3β-Amino-2β-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine (26). A solution of **25** (165 mg, 0.539 mmol) in 0.5 N barium hydroxide (10 mL) was refluxed under nitrogen for 2 h, at which time TLC (20% MeOH–$CHCl_3$) showed one spot at R_f lower than **25**. The solution was diluted with ethanol (5 mL) and neutralized with carbon dioxide. The barium carbonate was removed by filtration through Celite. Evaporation of the filtrate and drying by evaporation of several portions of absolute ethanol left a white solid foam (169 mg, 94%), the acetic acid salt hemihydrate of **26**:[35] UV max ($\epsilon \times 10^{-3}$) 258 nm (14.4) in 0.1 N HCl, 260 nm (14.5) in H_2O, 260 nm (14.8) in 0.1 N NaOH; IR (KBr) 3500–3050, 2800–2500 (OH, NH_2, NH_3^+), 1650 br, 1600 (C=C, C=N), 1575, 1520, 1410 br cm^{-1} ($-NH_3^+OAc^-$); mass spectrum (20 eV, 100 °C) *m/e* (relative intensity), 265 (1.4), 264 (0.3, M^+ of free base), 233 (0.8, $M^+ - CH_2OH$), 216 (4.9, $M^+ - CH_2OH - NH_2$), 162 (16.9, $^+BHCH{=}CH_2$), 136 (74.1, BH_2^+), 135 (13.2, BH^+), 112 (78.3, $M^+ - B - H_2O$), 60 (89.2), 45 (100), 43 (92.8).

Anal. Calcd for $C_{11}H_{16}N_6O_2 \cdot CH_3CO_2H \cdot \frac{1}{2}H_2O$: C, 46.84; H, 6.35; N, 25.21. Found: C, 47.07; H, 6.43; N, 24.96.

9-[3β-Amino-2β-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-6-dimethylaminopurine (33). Hydrolysis of **32** (632 mg, 1.89 mmol) exactly as described for the synthesis of **26** gave the acetic acid salt hemihydrate of **33** as a white solid foam (649 mg, 95%):[35] TLC (20% MeOH–$CHCl_3$) one spot at R_f lower than that of **32**; UV max ($\epsilon \times 10^{-3}$) 268 nm (19.3) in 0.1 N HCl, 276 nm (19.5) in H_2O, 276 nm (19.6) in 0.1 N NaOH; IR (KBr) 3500–3050, 2800–2400 (OH, NH_2, NH_3^+), 1600 br, 1560, 1410 cm^{-1} (C=C, C=N, $-NH_3^+OAc^-$); mass spectrum (70 eV, 150 °C) *m/e* (relative intensity) 293 (0.8), 292 (0.6, M^+ of free base), 244 (6.5, $M^+ - H_2O - HCHO$), 190 (16.0, $^+BHCH{=}CH_2$), 164 (51.8, BH_2^+), 163 (33.5, BH^+), 134 (28.9, $BH^+ - NCH_3$), 112 (40.2, $M^+ - B - H_2O$), 60 (61.6), 45 (100), 43 (93.4).

Anal. Calcd for $C_{13}H_{20}N_6O_2 \cdot CH_3CO_2H \cdot \frac{1}{2}H_2O$: C, 49.85; H, 6.97; N, 23.26. Found: C, 49.67; H, 7.05; N, 22.98.

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Registry No.—**1**, 61865-48-3; **2a**, 61865-49-4; **2b**, 65898-96-6; **3a**, 65942-42-9; **3b**, 61865-50-7; **3c**, 65969-56-4; **4a**, 65898-97-7; **4b**, 65898-98-8; **5**, 65898-99-9; **6a**, 61865-52-9; **6b**, 62357-71-5; **6c**, 65899-00-5; **7a**, 61865-53-0; **7b**, 65899-01-6; **8a**, 61865-65-4; **8b**, 65899-02-7; **9a**, 61865-54-1; **9b**, 65899-03-8; **9c**, 65899-04-9; **10a**, 61865-66-5; **10c**, 65899-05-0; **11a**, 65841-40-4; **11b**, 65941-41-5; **15**, 65942-43-0; **16a**, 61865-55-2; **16a** HCl, 65941-42-6; **16b**, 61865-63-2; **17a**, 65898-88-6; **17b**, 65898-89-7; **17c**, 65898-90-0; **18a**, 61865-67-6; **18b**, 61865-68-7; **19**, 61865-56-3; **20**, 61865-57-4; **21**, 61914-36-1; **22**, 61865-58-5; **23**, 61865-59-6; **24**, 61914-32-7; **25**, 61914-33-8; **26**, 61865-69-8; **27**, 61865-60-9; **28**, 61865-61-0; **29**, 61914-34-9; **30**, 65898-91-1; **31**, 65942-44-1; **32**, 61914-35-0; **33**, 61865-71-2; 2-(hydroxymethyl)-4-acetamidopentanedial, 65898-92-2; 4α-acetamido-3β-amino-2α-hydroxy-1α-cyclopentanemethyl benzoate, 65898-93-3; 5-amino-4,6-dichloropyrimidine, 5413-85-4; (±)*N*-acetyl-9-[β-(3α-amino-2α-hydroxy)cyclopentyl]-6-dimethylaminopurine, 65898-94-4; 3α-hydroxy-2β,4α-bis(3-chloro-4-aminopyrimidin-6-yl)-1α-cyclopentanemethanol, 65898-95-5.

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(26) Repeated attempts to dry this solid in a vacuum desiccator for a few hours or overnight resulted in loss of the product. The solid turned from a white fluffy material to a shrunken tan mass no longer soluble in CCl_4. Although it was occasionally possible to dry samples of tosyl cyanide, especially in smaller runs, the unpredictability of this decomposition led to changing the workup. Another person in this lab reported an explosion of sufficient force to blow the top off a large vacuum desiccator when drying a 100-g sample of tosyl cyanide.
(27) Failure to adequately cool in one run resulted in generation of considerable heat; **1** was separated with difficulty in low yield (~30%) from black tarry material by column chromatography.
(28) Attempts to characterize the free amine were unsuccessful as it appears to decompose on contact with air. Solutions darkened rapidly and attempts to solidify the material gave only colloidal yellow solid that turned to gum on contact with the air. Immediately after opening the Parr shaker, TLC (20% MeOH–$CHCl_3$) showed one major spot and one minor lower R_f spot. However, after a few hours, numerous new spots started to appear.
(29) An attempt to carry out the acetylation with acetic anhydride–pyridine gave tar. Apparently the free amine is base sensitive.
(30) In order to confirm spectral assignments, a sample of (±)-9-[β-(3α-amino-2α-hydroxy)cyclopentyl]-6-dimethylaminopurine 2′,3′-carbamate[3a] was acetylated in acetic anhydride–pyridine and the *N*-acetyl derivative characterized: 74% (from ethyl acetate–hexanes); mp 142–143 °C; IR (KBr) 1790 (urethane C=O, appears at 1779 before acetylation), 1705 cm^{-1} ($AcNCO_2$); ^1H NMR (Me_2SO-d_6) δ 2.40 (s, CH_3CONCO_2–). Anal. C, H, N.
(31) Preparative TLC (15% MeOH–$CHCl_3$) of such mother liquor contents gave a pure sample of the greater R_f impurity as a pale yellow solid foam (3%). Elemental analysis, mass spectrum, and NMR agree for $C_{14}H_{18}N_8O_2Cl_2 \cdot CH_3CO_2Et$ (ethyl acetate used to obtain foam). Apparently, hydrolysis of **9a** results in a small amount of diamine which reacts with two molecules of 5-amino-4,6-dichloropyrimidine.
(32) The chloroform mother liquors contained, in addition to more **28,** a higher R_f product. Purification of a portion of such material by chromatography on preparative plates developed in 15% MeOH–$CHCl_3$ gave a colorless glass (~5%) which NMR ($CDCl_3$) showed to be a di-4-methoxytrityl derivative.
(33) The oxazoline intermediate formed in the epimerization of **23** is hydrolyzed completely to **24** by sodium acetate, but the same hydrolysis conditions here leave a considerable amount of unhydrolyzed oxazoline. When the hydrolysis of the crude reaction products was carried out for longer periods (2–3 days) at 65 °C or at reflux temperature overnight, the reaction mixture turned dark brown and the combined yield of **29** and **30** was lower, but the ratio of **29/30** was greater. In practice such mixtures of **29** and **30** were not separated, but converted by formic acid treatment to **32** (see below).
(34) TLC (20% MeOH–$CHCl_3$) of the mother liquor showed a mixture of unhydrolyzed **20** and **21.**
(35) An attempt was made to characterize the free base by neutralization of the acetic acid salt with Amberlite IRA-400 (OH^-) resin as for the synthesis of isomer **21.** The gummy material isolated could not be solidified and appeared to decompose slowly in air. This behavior has been noted with other *cis*-aminocyclopentanols, in contrast to the stable, solid trans isomers.[3g]

Convenient Synthesis of Some Purine 8,5′-Imino Cyclonucleosides

Tadashi Sasaki,* Katsumaro Minamoto, and Hidemi Itoh

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

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Synthesis of some purine 8,5′-imino and aminimino cyclonucleosides was achieved starting from 2′,3′-*O*-isopropylidene-5′-*O*-tosyl-8-bromoadenosine (**1**) and anhydrous hydrazine. **1** with anhydrous hydrazine in ethanol gave 8,5′-aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**2a**), which was oxidatively converted to the corresponding 8,5′-imino cyclonucleoside (**2b**). The *N*-amino group in **2a** was quantitatively protected with hot acetic acid and phthalic anhydride to afford the 8,5′-acetamidimino (**2c**) and 8,5′-phthalimidimino analogues (**8**), respectively. Acidic treatment of **2a** and **2b** gave the parent cyclonucleosides **4a–b.** On the other hand, treatment of **2a, 2c,** and **8** with nitrous acid gave the corresponding inosine analogues **5, 7,** and **9.** Dephthaloylation of **9** with methanolic hydrazine gave 8,5′-aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**10**) as a 1:1 complex with the released phthalazine-1,4-dione. Treatment of **5** and **10** with 90% trifluoroacetic acid gave the corresponding parent hypoxanthine analogues **6** and **11,** while the treatment of a mixture of **10** and **11** with methanol–concentrated hydrochloric acid (3:1) gave the derivative of 2,5′-aminimino-bridged AICA riboside (**12**).

In recent years a large number of cyclonucleosides have been synthesized as basic models for gaining insight into the relationship between conformation and biological activity[1] or physicochemical properties.[2] Limiting the viewpoint to the synthesis in the purine series, the accumulated data have demonstrated the possibility of bonding the 8 position of the base with $C_{2'}$, $C_{3'}$, and $C_{5'}$ of the sugar through a heteroatom (O, S, or limitedly N)[3] or directly with $C_{5'}$.[4] Although the synthesis of oxygen- and sulfur-bridged nucleosides has been and continues to be elaborated for various purine nucleosides,[3c,5] the recorded synthesis of nitrogen isostere is quite limited. The hitherto known four compounds of this class are all 8,2′-imino cyclonucleosides obtainable by heating 8-amino-2′-*O*-triisopropylbenzenesulfonyladenosine with base[3b] or of preformed 8-aminopurinenucleosides with diphenyl carbonate.[3c]

8-Aminoadenosine is known to exhibit significant inhibition of sarcoma 180 ascites cells and is resistant toward adenosine deaminase.[6] 8-Aminopurinenucleosides also attracted much interest because of their structural similarity to a paralytic marine toxin, saxitoxin.[7] These findings gave an impetus to the extensive synthesis of a variety of 8-aminopurinenucleosides and their analogues.[8]

In view of these facts, synthesis of purine 8,5′-iminonucleosides and analogues which are restricted in anti conformation seemed to be of primary importance, and we herein describe a simple and effective synthesis of this class of compounds from 2′,3′-*O*-isopropylidene-5′-*O*-tosyl-8-bromoadenosine (**1**)[9] and hydrazine as the nitrogen source.

To circumvent the formidable N^3,$C_{5'}$ cyclization of **1** (this excludes a priori the application of the methods used for the synthesis of 8,2′-imino purinenucleosides), **1** was treated with

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