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Nucleic Acid Related Compounds. 30. Transformations of Adenosine to the First 2',3'-Aziridine-Fused Nucleosides, 9-(2,3-Epimino-2,3-dideoxy-β-D-ribofuranosyl)adenine and 9-(2,3-Epimino-2,3-dideoxy-β-D-lyxofuranosyl)adenine[1,2]

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Treatment of the diastereomeric epoxides derived from adenosine, 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine (1) and 9-(2,3-anhydro-β-D-ribofuranosyl)adenine (8), with azide gave the resulting 3'-azido diastereomers, 9-(3-azido-3-deoxy-β-D-arabinofuranosyl)adenine (2) and 9-(3-azido-3-deoxy-β-D-xylofuranosyl)adenine (9), in good yields plus minor quantities of the 2'-azido substitution products. Selective protection of the 5'-hydroxyl function, mesylation or tosylation of the 2'-hydroxyl group, and reduction of the resulting *trans*-3'-azido-2'-sulfonate ester with intramolecular displacement–cyclization provided the respective fused-ring aziridine products, 9-(2,3-epimino-2,3-dideoxy-β-D-ribofuranosyl)adenine (7) and 9-(2,3-epimino-2,3-dideoxy-β-D-lyxofuranosyl)adenine (12). Unusual ultraviolet circular dichroism and ^{1}H NMR spectral properties of these bicyclo[3.1.0] sugar–nucleoside systems are discussed.

The 2',3'-anhydro (oxirane) function has been known and utilized synthetically in nucleoside chemistry for a number of years.[5] However, no examples of nucleosides functionalized as the corresponding 2',3'-dideoxy-2',3'-epimino (aziridine) system have been reported, although such goals have been alluded to.[6,7h] Only very recently has a *p*-chlorobenzoyloxy-substituted nucleoside–aziridine been proposed as the reaction product of a postulated azirene intermediate in the uridine series.[6b]

The unambiguous synthesis of a number of pyranosyl and furanosyl fused aziridines have been reported in the carbohydrate field.[7] These compounds have been investigated as potential chemotherapeutic agents as well as useful synthetic intermediates. Amino–sugar chemistry has not been explored extensively or systematically in the nucleoside area, despite the number and variety of nucleoside antibiotics that have an amino–sugar moiety.[8] Prior studies in this area have concentrated primarily on total syntheses of the natural products per se and closely related analogues.[8a,9]

We have been interested in the investigation of general methods for the modification of intact nucleosides and nucleoside antibiotics[10] that are not dependent upon specific structural features such as participation of the base. We now wish to report the synthesis of the two diastereomeric 2',3'-dideoxy-2',3'-epimino compounds from adenosine and some unusual spectral effects of these bicyclo[3.1.0] fused aziridine–furanosyl nucleosides. These provide the first examples of the parent nucleoside–aziridine system (which are of intrinsic interest by analogy with natural products such as the antitumor antibiotic[11] mitomycin C, whose biological activity is thought to be related to reactions of the activated fused-aziridine moiety[12]) and also serve as useful synthetic intermediates for conversion to a variety of new mono-, di-, and triamino sugar nucleosides.

Treatment of 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine[9b,13] (1) with lithium azide in hot DMF[9c] gave 9-(3-azido-3-deoxy-β-D-arabinofuranosyl)adenine (2) (see Scheme I) in ~80% yield plus a minor amount (~8%) of the 2'-azido-

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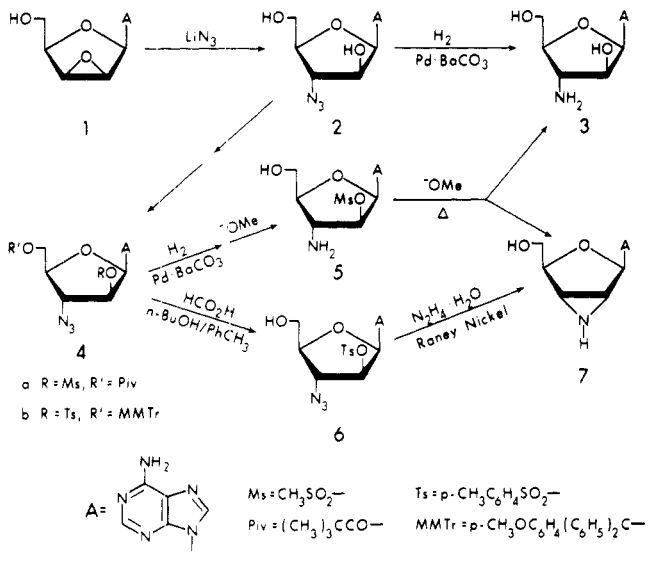
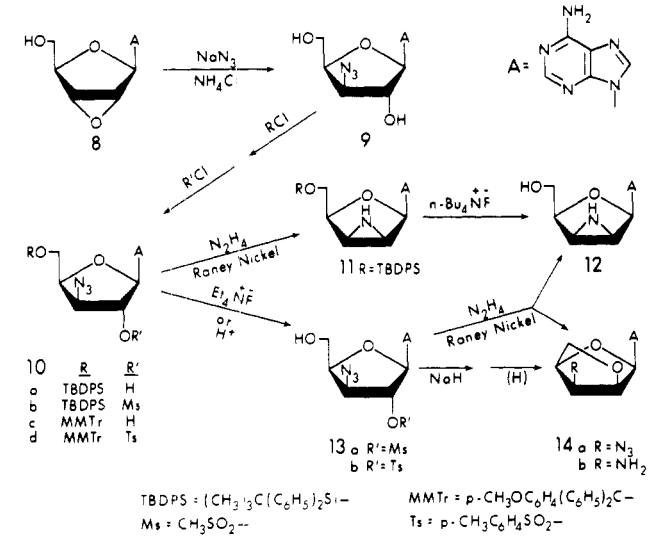
Scheme I



Scheme II



2′-deoxyxylo diastereomer essentially as described.[9a,c] The primary alcohol group was blocked selectively using pivalyl chloride or mono-*p*-methoxytrityl chloride in pyridine. The resulting base- or acid-labile protected derivatives were subjected to mesylation or tosylation in the usual manner to give 5′-*O*-pivalyl-2′-*O*-mesyl (**4a**) or 5′-*O*-(mono-*p*-methoxytrityl)-2′-*O*-tosyl (**4b**) intermediates. Catalytic hydrogenolysis of **4a** and deprotection of the resulting product in base gave 9-(3-amino-3-deoxy-2-*O*-mesyl-β-D-arabinofuranosyl)adenine (**5**). The *trans*-amino mesylate proved to be unexpectedly resistant toward cyclization. Extended heating of **5** in methanolic sodium methoxide solution resulted in closure to the desired aziridine **7**, but also caused accompanying demesylation at O-2′ (methoxide attack at sulfonyl sulfur) to give 9-(3-amino-3-deoxy-β-D-arabinofuranosyl)-adenine[9a] (**3**). The physical properties of **3** obtained from this reaction were compatible with reported data,[9a] and the structure was confirmed by direct comparison with a sample of **3** prepared by hydrogenolysis of **2**.

Deprotection of **4b** under acidic conditions gave 9-(3-azido-3-deoxy-2-*O*-tosyl-β-D-arabinofuranosyl)adenine (**6**). Treatment of **6** with hydrazine hydrate and Raney nickel[7b] resulted in conversion to 9-(2,3-epimino-2,3-dideoxy-β-D-ribofuranosyl)adenine (**7**). Microanalytical and mass spectral data were in accord with structure **7**. The ^{1}H NMR spectrum of **7** has a singlet resonance for the anomeric proton (H-1′) analogous to that of the corresponding oxirane compound

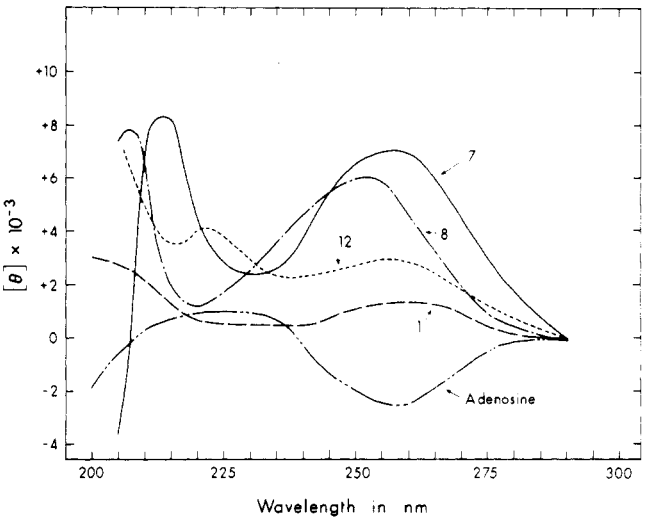


Figure 1. Ultraviolet circular dichroism (CD) spectra of adenosine (– · · –), the lyxo epoxide **1** (– – –), the ribo epoxide **8** (– · –), the lyxo aziridine **12** (· · ·), and the ribo aziridine **7** (–) in neutral aqueous solution.

8.[9b,14] The H-2′ and H-3′ resonance peaks are shifted upfield in harmony with spectra of other aziridine compounds.[7e] However, the ultraviolet circular dichroism (CD) spectrum of **7** has a long wavelength envelope (B_{2u} and B_{1u} transitions) centered near 257 nm that is of opposite sign and enhanced amplitude relative to that of adenosine. A parallel CD effect was also observed with the corresponding oxirane compound **8** (vide infra and Figure 1). In contrast with the epoxide, the ribo aziridine moiety is quite stable toward nucleophilic attack. Only trace decomposition of aziridine **7** was observed (TLC) upon heating an aqueous solution for over 12 h at reflux. The corresponding oxirane **8** is completely converted to pyrimidine ring-opened products via N-3 → C-3′ attack within 2 h under these conditions.[9b]

Direct treatment of the ribo epoxide (**8**) with sodium azide and ammonium chloride[9a] in hot DMF gave the 3′-azido-3′-deoxyxylo compound (**9**) as the major product (see Scheme II). Interfering degradation of **8** via N-3 → C-3′ intramolecular cyclization (cyclonucleoside formation) can be avoided by prior acylation of the adenine base.[9b] However, the direct treatment of **8** with azide allows deletion of the blocking and deblocking stages and gives **9** in yields approaching 80%. In larger scale experiments, the 2′-azido-2′-deoxyarabino diastereomer has been isolated in yields of ~1%. This again emphasizes the essentially exclusive regioselectivity for nucleophilic attack at C-3′ with oxirane **8**.[5b,c,9b,15] The primary alcohol function of **9** was selectively protected using *tert*-butyldiphenylsilyl chloride[16] or mono-*p*-methoxytrityl chloride in pyridine. Mesylation of the silyl ether **10a** and tosylation of the trityl derivative **10c** occurred smoothly at O-2′ to give **10b** and **10d**, respectively. Deprotection of O-5′ using tetraalkylammonium fluoride[17] or acidic conditions, respectively, gave 9-(3-azido-3-deoxy-2-*O*-mesyl-β-D-xylofuranosyl)adenine (**13a**) or the corresponding 2′-*O*-tosyl derivative (**13b**).

Treatment of **13a** or **13b** with hydrazine hydrate/Raney nickel gave 9-(2,3-epimino-2,3-dideoxy-β-D-lyxofuranosyl)-adenine (**12**) in ~70% yields. A small quantity of the presumed 2′,5′-anhydro compound **14b** was observed during preparative TLC purification of **12**. The TLC mobility of **14b** is only very slightly greater than that of **12**, and the presence of **14b** is difficult to assess on analytical TLC plates. Treatment of **13a** with sodium hydride in DMF gave the 2′,5′-anhydroazido derivative **14a** in 56% yield. Catalytic hydrogenolysis of **14a** gave the 3′-amino-2′,5′-anhydro compound (**14b**). The usual M − 30 (CH_2O-5′) mass spectral fragmentation was absent,

and the mass spectral base peak for **14a** and **14b** was at *m/e* 164 (100%, B + 30), which is unusual for adenine nucleosides.[18] The ^{1}H NMR spectrum of the strained dioxabicyclo[2.2.1] sugar system of **14a** exhibited singlet resonance peaks for H-1′ and H-4′ and a narrow overlapped resonance for H-2′ and H-3′. A Dreiding molecular model of **14a** suggests that endocyclic bond angle strain effects could cause expansion of the H–C–H angle at C-5′ and other exocyclic C–H angle and bonding effects that presumably result in the unexpected singlet resonances for the sugar ring protons.[19] Analogous 2′,5′-anhydro sugar–nucleoside structures have been reported previously,[20] arising from nucleophilic attack of O-2′ (in the arabino configuration) at C-5′. Similar NMR parameters were noted by Goodman for the 3′ epimer of **14a**.[20c]

Reductive cyclization (hydrazine/Raney nickel) of the 5′-*O*-*tert*-butyldiphenylsilyl protected derivative (**10b**) followed by deprotection using tetraalkylammonium fluoride provided **12** free of contamination with **14b**. The lyxo aziridine **12** has a less clearly defined melting behavior than that of **7**. The microanalytical and mass spectral data for **12** are in harmony with the proposed structure, and the ^{1}H NMR spectrum of **12** is similar to that of **7**. However, a small but definite splitting ($J_{1'-2'} \sim 1.6$ Hz) of the anomeric proton (H-1′) of **12** is observed. This is in contrast with the absence of observed coupling between H-1′ and H-2′ of the corresponding lyxo oxirane (**1**) as well as for the ribo oxirane (**8**), ribo aziridine (**7**), and related compounds[9b,14,21] (vide supra).

As seen in Figure 1, the CD spectrum of **12** has two positive spectral envelopes centered near 221 and 256 nm. These bands are similar to those of the ribo aziridine (**7**), although of lower intensity. The CD spectra of the ribo (**8**) and lyxo (**1**) oxirane compounds as well as of adenosine are included in Figure 1 for comparison. It is interesting to note that all four of these bicyclo[3.1.0] fused furanosyl nucleosides give rise to positive long (as well as short) wavelength Cotton effects. Most purine β-D-furanosyl nucleosides exhibit relatively weak negative long wavelength (B_{2u}) transitions (see that of adenosine in Figure 1) as originally noted in Ulbricht's rules.[22] This has been interpreted theoretically as resulting from n- and π-electron transitions in the symmetrical planar base interacting primarily with the chiral anomeric center attached at N-9 of the base.[23] Relationships which correlate the torsion angle (of rotation of the base relative to the sugar) and the sign and magnitude of the "B_{2u} transition" have been calculated.[24] "Normal nucleosides" are thought to have the "anti-range" preferentially populated, which corresponds to a negative B_{2u} transition for adenosine.

Fusion of the three-membered oxirane or aziridine ring with the five-membered furan ring would be expected to cause flattening of the furanosyl moiety with accompanying reorientation (partial rehybridization) of the 2′ C–H and 3′ C–H bonds. Such effects are apparent in the markedly reduced H-1′ to H-2′ and H-3′ to H-4′ coupling observed in ^{1}H NMR spectra of these compounds[9b,14,21] (vide supra). The same effects could reduce steric repulsions normally encountered by the base when over the sugar ring and give rise to preferential population of the syn conformation range. This would be expected[23b,24] to produce positive B_{2u} CD effects as observed. Detailed NMR studies are in progress, and single-crystal X-ray analyses are planned to further clarify these observations.

The present study defines generally accessible routes to the two diastereomeric 2′,3′-aziridine-fused furanosyl nucleoside systems. Their transformation to 2′-amino-2′-deoxyarabino,[27] 2′,3′-diamino-2′,3′-dideoxy, and other mono-, di-, and triamino nucleoside structures of putative biochemical and biological significance[28] will be reported separately.

Experimental Section

General Procedures. Melting points were obtained on Leitz or Reichert microscope blocks and are uncorrected. NMR spectra were determined on Jeol or Varian 100-MHz spectrometers in Me_2SO-d_6 (unless specified) with Me_4Si as an internal reference. UV spectra were recorded on Cary 15 spectrophotometers. CD spectra were measured on a Cary 60 instrument at the Universität Konstanz. Optical rotations were determined on a Perkin-Elmer MC141 polarimeter. Mass spectra (EI at 70 eV) were determined on AEI MS-12 and MS-50 (CI on MS-12) spectrometers using direct probe introduction at 150–230 °C. Elemental analyses were determined by the microanalytical laboratories of the University of Stuttgart or The University of Alberta. TLC was performed using Eastman Chromatogram Sheet (silica gel 13181 with 6060 indicator) or Schleicher and Schüll F 1500 CS 254 silica sheets with chloroform/methanol (5:1 to 10:1) as solvent. Preparative TLC used Merck silica gel 60 PF 254 or 60 F 254. Woelm 0.063–0.1 mm or J. T. Baker 3405 silica gel was used for column chromatography. Pyridine was purified and dried by distilling first from tosyl chloride and then from calcium hydride and was stored over 4 Å molecular sieves (predried by heating at 300 °C). Other chemicals and solvents were of reagent quality and/or were purified and/or distilled as appropriate. Yields and analyses are for samples dried for 24 h at 25–80 °C (0.01 mmHg) over P_4O_{10} unless specified otherwise. Evaporations were performed in vacuo (water aspirator at ~15 mmHg or mechanical oil pump at ~0.1 mmHg) using Büchler or Büchi rotary evaporators at <40 °C.

9-[3-Azido-3-deoxy-2-*O*-(*p*-toluenesulfonyl)-β-D-arabinofuranosyl]adenine (6). A mixture of 0.39 g (1.3 mmol) of **2** and 1.23 g (4 mmol) of mono-*p*-methoxytrityl chloride in 16 mL of dry pyridine was stirred for 2 days at room temperature. The resulting clear solution was treated with 2 mL of MeOH and then was added dropwise to 400 mL of ice water with vigorous stirring. The resulting precipitate was collected on a sintered glass funnel, washed with 4 × 20 mL of H_2O, pressed on a porous plate, and dried over $CaCl_2$ (12 mmHg) followed by further drying over P_4O_{10} (12 h, 0.01 mmHg) to give ~1 g (homogeneous by TLC) of crude 9-[3-azido-3-deoxy-5-*O*-(mono-*p*-methoxytrityl)-β-D-arabinofuranosyl]adenine: NMR δ 3.68 (br s, 5, CH_3O, H-5′, H-5″), 3.92 (br, 1, H-4′), 4.48 (m, 2, H-2′, H-3′), 6.13 (br s, 1, 2′-OH, exchanged with D_2O), 6.30 (br d, 1, H-1′), 6.78–7.56 (m, 16, aromatic, 6-NH_2), 7.81 and 8.20 (1 and 1, s and s, H-2 and H-8).

A solution of this crude product in 15 mL of dry pyridine was cooled in ice, and 2.32 g (12.2 mmol) of tosyl chloride was added. The solution was stirred for 4 days at 4 °C and then added dropwise with vigorous stirring to 400 mL of ice-cold saturated $NaHCO_3/H_2O$ solution. The precipitate was collected on a sintered glass funnel, washed with ice water repeatedly, pressed on a porous plate, and dried over $CaCl_2$ (12 mmHg) followed by drying over P_4O_{10} (20 h at 0.01 mmHg at 22 °C) to give 1.25 g (homogeneous by TLC) of crude 9-[3-azido-3-deoxy-5-*O*-(mono-*p*-methoxytrityl)-2-*O*-tosyl-β-D-arabinofuranosyl]adenine (**4b**).

A solution of crude **4b** in 10 mL of toluene/*n*-butyl alcohol/formic acid[25] (2:2:1) was stirred for 6 h at room temperature and then evaporated. The resulting syrup was partitioned between 20 mL of H_2O and 20 mL of EtOAc. The aqueous phase was extracted with 3 × 20 mL of EtOAc, and the combined organic phase was washed with saturated $NaHCO_3/H_2O$ and H_2O, dried (Na_2SO_4), and evaporated. The residue was heated with 10 mL of MeOH, cooled, and filtered. The precipitate was washed with MeOH and dried over P_4O_{10} (18 h, 0.01 mmHg, 50 °C) to give 0.3 g of **6** as a white powder. Preparative TLC of the combined MeOH washes gave an additional 53 mg of homogeneous **6** for a combined yield of 0.35 g (60% from **2**) of crude product. Recrystallization of the 53-mg sample from 4 mL of dry MeOH gave 32 mg of colorless fine needles of **6**: mp 192–193 °C; UV (MeOH) max 258, 227 nm (ε 14 300, 14 700), min 241 nm (ε 8500). Anal. Calcd for $C_{17}H_{18}N_8O_5S$: C, 45.74; H, 4.06; N, 25.10. Found: C, 45.68; H, 4.08; N, 25.17.

9-(2,3-Epimino-2,3-dideoxy-β-D-ribofuranosyl)adenine (7). Method A. To a solution of 475 mg (1.06 mmol) of **6** in 25 mL of MeOH at reflux was added a small quantity of Raney nickel catalyst followed by 2 mL of 100% hydrazine hydrate. Evolution of gas was observed, and two further portions of 0.5 mL of $N_2H_4 \cdot H_2O$ were added during a 48-h period. TLC indicated complete disappearance of **6** with formation of **7** and an intermediate in major proportion. (This intermediate was indistinguishable chromatographically from a reference sample of the 3′-amino-3′-deoxy-2′-*O*-tosylarabino compound prepared by hydrogenolysis of **6** over 5% Pd/C.) The Raney nickel was filtered and washed with 3 × 3 mL of hot MeOH. The combined methanolic solution was heated for an additional 4 days at reflux to complete ring closure. The solution was concentrated to ~3 mL, warmed to dissolve precipitated solid, filtered, and cooled at 4 °C. Analytically pure crystals (115 mg, 44%) which separated were collected and dried to give **7**: mp 220–221 °C (some resolidification and remelting at 224 °C); UV (MeOH) max 259 nm (ε 13 700), min 227 nm

Table I. ^{1}H NMR Chemical Shift Data [a]

compd	H-8,[b] H-2[b]	6-NH_2[b]	H-1′[c]	H-2′	H-3′	H-4′	H-5′,5″	other
4a[d]	8.38, 8.32	*d*	6.55	5.56 (t)	4.97 (t)	4.16 (m)	4.50 (d)	1.22 (s, 9, Piv), 3.02 (s, 3, Ms)
5	8.26, 8.13	7.24	6.43	5.10 (m)	3.70 (m)	3.50 (m)	3.70 (m)	3.13 (s, 3, Ms), 3.20 (br s, 2, 3′-NH_2)
6	8.15, 8.04	7.24	6.31	5.49 (t)	4.84 (t)	3.87 (m)	3.68 (m)	2.34 (s, 3, $ArCH_3$), 7.30 (m, 4, Ar)
10a	8.15, 8.13	7.28	5.91	4.83 (m)	4.48 (m)	4.48 (m)	3.98 (m)	1.03 (s, 9, CMe_3), 7.42 (m, 8, Ar, 6-NH_2), 7.65 (m, 4, Ar)
10b	8.18, 8.14	*e*	6.26	5.87 (t)	4.97 (q)	4.57 (m)	4.00 (m)	1.02 (s, 9, CMe_3), 3.29 (s, 3, Ms), 7.38 (m, 8, Ar, 6-NH_2), 7.67 (m, 4, Ar)
10c	8.16, 8.06	*e*	5.88	4.84 (m)	4.44 (m)	4.44 (m)	3.70 (m)	3.70 (s, 3, OMe), 6.76–7.50 (m, 16, Ar, 6-NH_2)
10d	8.03, 7.92	*e*	6.06	5.88 (q)	4.91 (q)	4.58 (m)	3.65 (m)	2.22 (s, 3, $ArCH_3$), ~3.65 (s, 3, OMe), 6.8–7.5 (m, 20, Ar, 6-NH_2)
11	8.32, 8.17	*e*	6.23	3.10 (br)	3.10 (br)	4.25 (t)	3.89 (m)	1.03 (s, 9, CMe_3), 1.89 (br 1, NH), 7.40 (m, 8, Ar, 6-NH_2), 7.68 (m, 4, Ar)
13a	8.32, 8.18	7.38	6.22	5.80 (t)	4.88 (t)	4.40 (m)	3.72 (m)	3.24 (s, 3, Ms)
13b	8.16, 8.01	7.23	6.04	5.72 (t)	4.88 (q)	4.34 (m)	3.64 (m)	2.26 (s, 3, $ArCH_3$), 7.23 (m, 4, Ar)
14a	8.36, 8.16	7.32	6.42[f]	4.82 (s)	4.82 (s)	4.74 (s)	4.29 (d)[g] 3.99 (d)[g]	
14b	8.31, 8.12	7.26	6.30	4.21 (br s)	3.78 (d)	4.36 (d)	4.08 (s)	1.98 (br s, 2, 3′-NH_2)

[a] Values are in δ (ppm) from internal Me_4Si in Me_2SO-d_6. Letters in parentheses indicate appearance of peak. [b] Singlet peaks. [c] Doublet peaks. [d] Spectrum determined in CD_3OD. [e] Peak obscured by aromatic region. [f] Singlet, irradiation of H-2′,3′ caused narrowing by ~0.8 Hz. [g] $J_{5'-5''} = -9$ Hz.

Table II. Approximate "Apparent" First-Order Coupling Constants [a]

compd	$J_{1'-2'}$	$J_{2'-3'}$	$J_{3'-4'}$	$J_{4'-5',5''}$
4a	6	6		5
5	6			
6	6.8	7		
10a	4.5	4		
10b	4.2	3.6	5.6	
10c	~6			
10d	6	5	7	
11	1.6			5.4
13a	4.8	4.7	6.4	4.4
13b	6.5	6.5	7	
14b	~1		2.5	

[a] In hertz.

(ε 2700); NMR δ 2.08 ("t", $J_{NH-2',3'} \sim 8$ Hz, 1, NH), 3.09 (m, $J_{3'-2'} \sim 4.3$ Hz, 1, H-3′), 3.34 (m, $J_{2'-3'} \sim 4.3$ Hz, 1, H-2′), 3.47 (m, 2, H-5′, H-5″), 4.03 ("t", $J \sim 5.5$ Hz, 1, H-4′), 4.92 (t, $J_{OH-5',5''} = 5.2$ Hz, 1, 5′-OH), 6.07 (s, 1, H-1′), 7.24 (br s, 2, 6-NH_2), 8.18 (s, 1, H-2), 8.37 (s, 1, H-8); $[\alpha]^{25}_D$ −28.9° (*c* 0.3, MeOH); CD (H_2O, pH 7) 213 (φ + 8400), 230 (φ +2500), 257 nm (φ +7100). Anal. Calcd for $C_{10}H_{12}N_6O_2$: C, 48.38; H, 4.87; N, 33.85. Found: C, 48.53; H, 4.97; N, 33.98.

9-(3-Azido-3-deoxy-2-*O*-mesyl-5-*O*-pivalyl-β-D-arabinofuranosyl)adenine (4a). A stirred solution of 0.53 g (1.8 mmol) of **2** in 25 mL of dry pyridine was cooled to 0 °C, treated with 0.33 g (2.7 mmol) of pivalic acid chloride, and stored at 5 °C for 2.5 days. Ice chips were added, and the mixture was stirred for 1 h at 5 °C and evaporated. The residual gum was dissolved in 30 mL of $CHCl_3$, washed with saturated $NaHCO_3/H_2O$ and H_2O, dried (Na_2SO_4), and evaporated. The resulting solid foam was dried over P_4O_{10} (15 h, 2 mmHg) to give 0.67 g (99%) of crude 9-(3-azido-3-deoxy-5-*O*-pivalyl-β-D-arabinofuranosyl)adenine: NMR ($CDCl_3$) δ 1.21 (s, 9, Piv), 4.09 (m, 1, H-4′), 4.30 (m, 1, H-3′), 4.38 (m, 2, H-5′, H-5″), 4.66 ("t", 1, H-2′), 6.20 (d, $J_{1'-2'} \sim 5.5$ Hz, 1, H-1′), 6.30 (br s, 2, 6-NH_2), 8.00 and 8.09 (s and s, 1 and 1, H-2 and H-8).

A stirred solution of 160 mg (0.425 mmol) of this crude product in 10 mL of dry pyridine was cooled to 0 °C, treated with 146 mg (1.28 mmol) of mesyl chloride, and stored at 5 °C overnight. Ice chips were added, and the mixture was stirred for 1 h and evaporated. A solution of this residue in 30 mL of $CHCl_3$ was washed with saturated $NaHCO_3/H_2O$ and H_2O, dried (Na_2SO_4), and evaporated. The crystalline residue (199 mg, quantitative) was recrystallized from 95% EtOH to give 130 mg (67%) of **4a**: mp 94–96 °C with solidification and remelting at 152–153 °C; UV (MeOH) max 259 nm (ε 15 700), min 227 nm (ε 3800); mass spectrum, *m/e* 454.1382 (3.5%; calcd for M^+, 454.1385). Anal. Calcd for $C_{16}H_{22}N_8O_6S \cdot 1.5H_2O$: C, 39.91; H, 5.23; N, 23.27. Found: C, 40.13; H, 4.72; N, 23.27.

9-(3-Amino-3-deoxy-2-*O*-mesyl-β-D-arabinofuranosyl)adenine (5). A solution of 136 mg (0.3 mmol) of **4a** in 20 mL of MeOH was hydrogenated at atmospheric pressure over 40 mg of 5% $Pd/BaCO_3$ for 24 h at room temperature. The mixture was filtered using a Celite pad, and the filtrate was evaporated. The resulting colorless glass was dissolved in 10 mL of MeOH and stirred with 49 mg (0.9 mmol) of NaOMe for 20 h at room temperature, during which time white crystals separated. These were filtered and washed well with MeOH to give 66 mg of **5**. The filtrate was neutralized with HOAc and concentrated, and the residue was purified by preparative TLC (developed using the upper phase of EtOAc/*n*-PrOH/H_2O, 4:1:2). Recrystallization of this material from MeOH/95% EtOH gave an additional 18 mg for a total yield of 84 mg (80%) of **5**: mp 175–176 °C; UV (H_2O) max 260 nm (ε 15 000), min 225 nm (ε 3000). Anal. Calcd for $C_{11}H_{16}N_6O_5S \cdot 0.5H_2O$: C, 37.39; H, 4.85; N, 23.78. Found: C, 37.49; H, 4.62; N, 23.30.

9-(2,3-Epimino-2,3-dideoxy-β-D-ribofuranosyl)adenine (7), Method B, and 9-(3-Amino-3-deoxy-β-D-arabinofuranosyl)-adenine (3). A mixture of 67 mg (0.19 mmol) of **5** and 16 mg (0.30 mmol) of NaOMe in 5 mL of absolute MeOH was stirred at reflux for 24 h. A clear solution resulted, but TLC indicated the presence of unreacted **5**. An additional 5.5 mg (0.1 mmol) of NaOMe was added, and heating was continued for 58 h. The solution was cooled, neutralized with Dowex 50 × 8 (H^+) resin, filtered, and concentrated to a small volume. This residue was applied to a 20 × 10 cm × 2 mm preparative TLC plate and developed several times in 15% MeOH/$CHCl_3$. The more rapidly migrating major band was eluted, evaporated, and recrystallized from MeOH to give 22 mg (47%) of **7**: mp 228–229 °C; mass spectrum, *m/e* 248.1035 (1.6%; calcd for M^+, 248.1024); other spectral properties agree with **7** prepared by method A. Anal. Calcd for $C_{10}H_{12}N_6O_2$: C, 48.38; H, 4.87; N, 33.85. Found: C, 48.08; H, 4.87; N, 33.77.

Elution of the more slowly migrating band, evaporation of the eluate, and crystallization of the residue from MeOH gave 17 mg (34%) of **3**, mp 239–241 °C [lit.[9a] mp 243.5–244.5 °C (corr)]. This product was identical with a sample of **3** prepared by atmospheric hydrogenolysis of **2** over $Pd/BaCO_3$ by mixture melting point, TLC, and spectroscopy.

A minor amount of adenine was also detected by elution from the preparative TLC plate.

9-(3-Azido-3-deoxy-β-D-xylofuranosyl)adenine (9). A mixture of 0.5 g (2 mmol) of **8**, 0.65 g (10 mmol) of NaN_3, and 0.54 g (10 mmol) of NH_4Cl[9a] in 50 mL of dry DMF was stirred for 30 h at 100 °C with exclusion of moisture. Solvent was evaporated, and the residual solid was dissolved in 16 mL of H_2O. Upon cooling, 0.44 g of light tan crystals separated. Concentration of the filtrate to ~3 mL and cooling afforded an additional 24 mg of **9**. The combined product (0.464 g, 79%) had mp 171–178 °C, UV (MeOH) max 260 nm (ε 14 800), was homogeneous by TLC, and cochromatographed with authentic **9** [lit.[9b] mp 177–178 °C, UV (H_2O) max 260 nm (ε 15 100)].

9-[3-Azido-3-deoxy-5-*O*-(*tert*-butyldiphenylsilyl)-β-D-xylofuranosyl]adenine (10a). A solution of 0.438 g (1.5 mmol) of crude **9** and 0.495 g (1.8 mmol) of *tert*-butyldiphenylsilyl chloride in 15 mL

of dry pyridine was stirred for 20 h at room temperature and was then evaporated. The solid was dried by coevaporation using 2 × 20 mL of toluene/95% EtOH (2:1) and was then crystallized from $CHCl_3$/isopropyl ether (3:1) to give 0.6 g of product. The filtrate was stored in a sealed desiccator[26] containing Et_2O, and an additional 0.18 g of crystals separated. Recrystallization of the combined crops (0.78 g, 98%) from 95% EtOH/H_2O (11:5) gave 0.63 g (79%) of analytically pure **10a:** mp 201–202 °C; UV (MeOH) max 260 nm (ε 16 700), min 233 nm (ε 4560); EI mass spectrum, *m/e* 473.1496 (calcd for M − 57, 473.1506); chemical ionization mass spectrum (NH_3), *m/e* 531 (M + 1, 18% relative to *m/e* 136, B + 2, 100%). Anal. Calcd for $C_{26}H_{30}N_8O_3Si$: C, 58.85; H, 5.70; N, 21.12. Found: C, 58.60; H, 5.72; N, 21.13.

9-[3-Azido-3-deoxy-5-*O*-(*tert*-butyldiphenylsilyl)-2-*O*-(methanesulfonyl)-β-D-xylofuranosyl]adenine (10b). Method A. A solution of 0.49 g (0.92 mmol) of **10a** in 3 mL of dry pyridine was cooled to 6 °C and treated with 0.21 g (1.8 mmol) of precooled mesyl chloride. After standing at 6 °C for 18 h, 1 mL of MeOH was added and the solution was stirred for 1 h at 6 °C. This solution was evaporated, and the residue was coevaporated using toluene/95% EtOH (1:2). The crude product was purified on a silica gel column (~15 g, packed in $CHCl_3$) by washing with $CHCl_3$ followed by elution with MeOH/$CHCl_3$ (8:92). Evaporation of appropriate fractions and crystallization of the product from 50 mL of $CHCl_3$/isopropyl ether (3:2) gave 0.51 g of product with mp 216–219 °C. Evaporation of the filtrate and crystallization of the residue from $CHCl_3$ by diffusion of Et_2O[26] gave an additional 33 mg of **10b** for a total yield of 0.543 g (97%). Recrystallization of a 100-mg sample from 18 mL of 95% EtOH gave 78 mg of analytically pure **10b:** mp 215–218 °C; UV (MeOH) max 259 nm (ε 18 200), min 233 nm (ε 4730); EI mass spectrum, *m/e* 551.1293 (calcd for M − 57, 551.1281); chemical ionization mass spectrum (NH_3), *m/e* 609 (M + 1, 24% relative to *m/e* 136, B + 2, 100%). Anal. Calcd for $C_{27}H_{32}N_8O_5SSi$: C, 53.27; H, 5.30; N, 18.41; S, 5.27. Found: C, 53.06; H, 5.41; N, 18.26; S, 5.06.

Method B. A solution of 1.08 g (3.7 mmol) of **9** and 1.52 g (5.53 mmol) of *tert*-butyldiphenylsilyl chloride in 10 mL of dry pyridine was stirred for 20 h at room temperature. This solution was cooled to 4 °C, and 0.85 g (7.4 mmol) of precooled mesyl chloride was added. After being stored for 18 h at 4 °C, 2 mL of H_2O was added and the solution was stirred for 1 h at 4 °C. The solution was evaporated, and the gummy solid was coevaporated repeatedly with 95% EtOH/toluene (7:3). Crystallization of the resulting solid from 71.5 mL of acetone/H_2O/95% EtOH (62:2.5:7) gave 2.05 g (91%) of **10b,** mp 217–220 °C, identical with the product from method A.

9-[3-Azido-3-deoxy-2-*O*-(methanesulfonyl)-β-D-xylofuranosyl]adenine (13a). A mixture of 1.72 g (2.83 mmol) of **10b** in 10 mL of THF and 0.84 g (5.63 mmol) of tetraethylammonium fluoride in 2.8 mL of MeOH was stirred for 21 h at room temperature. The resulting solution was treated with 3 g of silica, and the mixture was evaporated to dryness. The powder was added to a column (~30 g of silica packed in $CHCl_3$) and eluted with $CHCl_3$ (300 mL) followed by MeOH/$CHCl_3$ (1:9). Evaporation of appropriate fractions gave 0.94 g of white powder which was crystallized from 24 mL of 98% EtOH to give 0.91 g (87%) of **13a:** mp 191–195 °C; UV (MeOH) max 259 nm (ε 14 800), min 226 nm (ε 2540); mass spectrum, *m/e* 370.0808 (calcd for M^+, 370.0808). Anal. Calcd for $C_{11}H_{14}N_8O_5S$: C, 35.68; H, 3.81; N, 30.26; S, 8.66. Found: C, 35.34; H, 3.73; N, 30.44; S, 8.70.

9-[3-Azido-3-deoxy-2-*O*-(*p*-toluenesulfonyl)-β-D-xylofuranosyl]adenine (13b). A solution of 5.92 g (0.0203 mol) of **9** in 175 mL of dry pyridine was treated with 10.63 g (0.03446 mol) of mono-*p*-methoxytrityl chloride for 5 days at room temperature and was then further reacted as described for the conversion of **2** → **4** → **6.** The total yield of pure (TLC) **13b** was 4.51 g (50%). A sample of this material was recrystallized from acetone to give colorless crystals of **13b:** mp 208–209 °C dec; UV (MeOH) max 260 and 228 nm (ε 14 300 and 13 800), min 242 nm (ε 8300). Anal. Calcd for $C_{17}H_{18}N_8O_5S$: C, 45.74; H, 4.06; N, 25.10. Found: C, 45.66; H, 4.13; N, 24.84.

9-(2,3-Epimino-2,3-dideoxy-β-D-lyxofuranosyl)adenine (12). Method A. A solution of 0.8 g (1.8 mmol) of **13b** and 3 mL of 100% hydrazine hydrate in 50 mL of MeOH was heated at gentle reflux for 24 h with a small amount of Raney nickel. Moderate evolution of gas was observed, and three additional portions of 0.5 mL of $N_2H_4 \cdot H_2O$ were added during this time period. TLC indicated the disappearance of **13b** and formation of **12** (with the presence of an intermediate, presumably the amino tosyl derivative, detected only during initial stages of the reaction). The Raney nickel was filtered and extracted with 3 × 5 mL of MeOH at reflux. The combined MeOH filtrates were evaporated, and the residue was applied to two 20 × 40 cm × 2 mm preparative TLC plates. The plates were developed twice in $CHCl_3$/MeOH (4:1), and the major band was eluted. Evaporation of the eluate and drying gave 320 mg (72%) of **12** as a white powder. Crystallization of this material from 10 mL of absolute EtOH gave 270 mg (61%) of colorless microcrystals of **12:** mp 190–194 °C; UV (MeOH) max 259 nm (ε 14 400), min 227 nm (ε 2500); NMR δ 2.29 (br, 1, NH), 2.95 (m, $J_{3'-2'}$ = 4.6 Hz, $J_{3'-4'}$ = 1.6 Hz, 1, H-3'), 3.06 (m, $J_{2'-3'}$ = 4.6 Hz, $J_{2'-1'}$ = 1.6 Hz, 1, H-2'), 3.60 (m, 2, H-5', H-5''), 4.04 (sext, $J_{4'-5',5''} \sim$ 5.8 Hz, $J_{4'-3'}$ = 1.6 Hz, 1, H-4'), 4.80 (br, 1, 5'-OH), 6.16 (d, $J_{1'-2'} \sim$ 1.6 Hz, 1, H-1'), 7.22 (br s, 2, 6-NH_2), 8.15 (s, 1, H-2), 8.34 (s, 1, H-8); $[\alpha]^{25}_D$ +2.7° (*c* 0.3, MeOH); CD (H_2O, pH 7) 215 (φ +3500), 221 (φ +4200), 256 nm (φ +3800). Anal. Calcd for $C_{10}H_{12}N_6O_2$: C, 48.38; H, 4.87; N, 33.85. Found: C, 48.45; H, 4.85; N, 33.89.

9-(3-Azido-3-deoxy-2,5-anhydro-β-D-lyxofuranosyl)adenine (14a). A suspension of 160 mg (0.43 mmol) of **13a** and 18 mg (0.75 mmol) of NaH in 2 mL of DMF under N_2 was stirred for 2 h at room temperature. The mixture was neutralized with HOAc, evaporated, and chromatographed on a silica gel (10 g) column. Elution with $CHCl_3$ (60 mL, discarded) followed by $CHCl_3$/MeOH (95:5, 300 mL) and evaporation of the pooled latter fractions gave a white powder. This material was crystallized from 95% EtOH to give 66 mg (56%) of **14a** in two crops: mp 218–221 °C (prior softening at ~208–210 °C); UV max (MeOH or 0.1 N NaOH) 259, (0.1 N HCl) 258 nm; mass spectrum, *m/e* 274.0927 (4.4%; calcd for M^+ ($C_{10}H_{10}N_8O_2$), 274.0927), 164 (100%, B + 30), 136 (21%, B + 2H), 135 (23%, B + H).

9-(3-Amino-3-deoxy-2,5-anhydro-β-D-lyxofuranosyl)adenine (14b). A mixture of ~10 mg of **14a** and ~20 mg of Raney nickel in 2.5 mL of 1,4-dioxane/95% EtOH (1:1) under N_2 was stirred with 0.1 mL of 85% hydrazine hydrate for 1 h at room temperature. An additional 0.1 mL of $N_2H_4 \cdot H_2O$ was added, and stirring was continued for 1 h. The mixture was filtered using a Celite pad, and the filtrate was evaporated to give ~4 mg of **14b** as a TLC homogeneous colorless solid foam: mass spectrum, *m/e* 248.1024 (8%; calcd for M^+ ($C_{10}H_{12}N_6O_2$), 248.1022), 164 (100%, B + 30), 136 (66%, B + 2H), 135 (38%, B + H), 114 (8%, sugar ion). This product (**14b**) had identical TLC migration with that of the minor contaminant of treatment of **13a** with hydrazine hydrate and Raney nickel.

9-[5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-epimino-2,3-dideoxy-β-D-lyxofuranosyl]adenine (11). To a stirred solution of 1.1 g (1.8 mmol) of **10b** in 40 mL of THF/95% EtOH (3:1) under N_2 was added ~500 mg of Raney nickel and 1 mL of 85% hydrazine hydrate. The mixture was stirred at 80 °C (oil bath), and 1 mL of $N_2H_4 \cdot H_2O$ solution was added every 45 min for 6 h (9 mL total). After an additional hour at 80 °C, the suspension was filtered using a Celite pad and the filtrate was evaporated. The residue was partitioned between 30 mL of CH_2Cl_2 and 30 mL of H_2O. The organic phase was dried (Na_2SO_4) and evaporated to give 0.87 g (99%) of a TLC homogeneous colorless solid foam. Crystallization of this material from 8 mL of $CHCl_3$/Skellysolve B (3:2) gave 0.73 g (83%) of **11** as a white powder: mp ~170–179 °C; UV (MeOH) max 260 nm (ε 16 100), min 232 nm (ε 4690); EI mass spectrum, *m/e* 429.1490 (calcd for M − 57, 429.1495); chemical ionization mass spectrum (NH_3), *m/e* 487 (M + 1, 48% relative to *m/e* 136, B + 2, 100%). Anal. Calcd for $C_{26}H_{30}N_6O_2Si$: C, 64.17; H, 6.21; N, 17.27. Found: C, 63.82; H, 6.33; N, 16.98.

9-(2,3-Epimino-2,3-dideoxy-β-D-lyxofuranosyl)adenine (12). Method B. A mixture of 122 mg (0.25 mmol) of **11** in 2 mL of THF and 0.25 mL of a 2 M solution of tetra-*n*-butylammonium fluoride in THF was stirred for 24 h at room temperature and diluted with MeOH, and 0.5 g of silica was added. The suspension was evaporated to dryness, and the impregnated powder was applied to a column (~3 g of silica, packed in $CHCl_3$). The column was washed with 30-mL portions of $CHCl_3$, 5% MeOH/$CHCl_3$, and 10% MeOH/$CHCl_3$. The product was eluted with 60 mL of 15% MeOH/$CHCl_3$, which was evaporated to give 68 mg of colorless solid foam. Crystallization of this material from 1 mL of absolute EtOH gave 40 mg (64%) of **12,** mp ~208–219 °C. Recrystallization of this product gave **12:** mp 197–203 °C with resolidification and remelting at ~211–218 °C; mass spectrum, *m/e* 248.1027 (calcd for M^+, 248.1022). This product had identical mixture melting point, TLC, and spectral properties with a sample of purified **12** prepared by method A. Anal. Calcd for $C_{10}H_{12}N_6O_2$: C, 48.38; H, 4.87; N, 33.85. Found: C, 48.18; H, 5.08; N, 33.75.

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68965-88-8; mono-*p*-methoxytrityl chloride, 14470-28-1; *tert*-butyldiphenylsilyl chloride, 58479-61-1.

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(2) Taken in part from the Ph.D. Dissertation of J.-M. Seifert, Universität Konstanz, 1978.
(3) (a) The University of Alberta. (b) Postdoctoral Fellow 1975–present. (c) Postdoctoral Fellow 1975–1977, on leave from Kojihn Co. Ltd.
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Structure of Evillosin, a Novel Labdane Diterpenoid Lactone from *Eupatorium villosum* Sw.[1]

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A novel labdane diterpenoid, evillosin (1), has been isolated from *Eupatorium villosum* (Compositae), and its stereostructure determined from spectral and X-ray crystallographic analyses. Evillosin possesses a normal labdane skeleton, but incorporates an unusual structural feature of a lactone between C-12 and C-15. The absolute stereochemistry of 1 was deduced from the positive Cotton effect displayed by ketone 3.

Various species of the widespread genus *Eupatorium* (Compositae) show significant antitumor and cytotoxic activities, which are often due to the presence of certain sesquiterpenoids that possess the α-methylene-γ-butyrolactone moiety.[2] Intrigued by the observation that *E. villosum* Sw. ("bitter bush" in Jamaican folklore)[3] is toxic to cattle and to goats, we undertook isolation studies aimed at identifying the toxic principles of this plant, and report in the present article the isolation and structural elucidation of a novel diterpenoid, evillosin (1). Evillosin was, however, inactive against sarcoma-180 in rats and was not toxic.[4]

Evillosin (1), $C_{22}H_{34}O_5$, mp 160–161 °C, was isolated from a methylene chloride extract of the leaves of *E. villosum* and showed strong IR absorptions typical of hydroxyl (3500 cm^{-1}) and carbonyl (1756, 1740 cm^{-1}) groups. The presence of a broad one-proton singlet at δ 3.44 in the ^{1}H-NMR spectrum of 1 suggested that the alcohol group was secondary. This was confirmed by conversion of 1 into the crystalline acetate 2, in which the absorption at δ 3.44 was shifted to δ 3.65 (triplet, J = 2 Hz), and by Jones oxidation,[5] which gave ketone 3.

Although evillosin had strong absorptions in its IR (1640 cm^{-1}) and Raman (1665 cm^{-1}) spectra characteristic of an olefinic double bond conjugated to a carbonyl group, the presence of an α,β-unsaturated carbonyl group was not immediately apparent from the UV spectrum (λ max 209, ϵ 15 210)[6] but was inferred from NMR spectral studies. Evil-

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