pentofuranose Diacetates (7d) and (8d). The following procedure was used to reduce the individual acetoxy lactones to furanose products. To a magnetically stirred solution of the acetoxy cis lactone **6b** (3.00 g, 11 mmol) in THF (70 mL) under nitrogen and chilled to −80 °C (dry ice/ether) was added DIBAL (1 M in THF, 32.5 mL, 32.5 mmol) slowly by syringe. The colorless solution was maintained at −78 °C for 1.5 h and then quenched with 75 mL of 4:1 methanol/water. The reaction mixture was warmed to room temperature, and saturated aqueous sodium potassium tartrate (30 mL) was added. The layers were separated, and the aqueous phase was extracted further with methylene chloride (2 × 25 mL). The combined organic solutions were dried over sodium sulfate, filtered, and evaporated at reduced pressure. The residue, a mixture of the acetoxy lactol **8a** and the deacetylated lactol **8b**, was dissolved in dry methanol, and ammonia was bubbled into the cold (0 °C) solution for 30 min. Evaporation of the methanol at reduced pressure gave 2.05 g (80%) of **8b** as a colorless oil: ^{1}H NMR (acetone-d_6) δ 7.67 (m, 5 H), 6.72 (br d, 1 H), 5.24 (m, 1 H), 4.91 (m, 1 H), 4.03 (m, 1 H), 3.56 (m, 2 H), 1.40 (m, 2 H); MS (FAB), m/e 238 (M + H), 106.

From the trans acetoxy lactone **5b** (3.00 g, 11 mmol) and DIBAL (1 M in THF, 32.5 mL, 32.5 mmol) there was obtained, after ammonolysis, 2.10 g (82%) of **7b** as a low-melting solid, mp < 50 °C: ^{1}H NMR (acetone-d_6) δ 7.68 (m, 5 H), 6.81 (br d, 1 H), 5.33 (m, 1 H), 4.98 (m, 1 H), 4.08 (m, 1 H), 3.63 (m, 2 H), 1.52 (m, 2 H); MS (FAB), m/e 238 (M + H), 106.

From the acetoxy lactone **5d** (2.50 g, 8.5 mmol) and DIBAL (1 M in THF, 25.6 mL, 25.59 mmol) there was obtained 1.95 g (78%) of **7d** as a colorless oil after acetylation with acetic anhydride and pyridine: ^{1}H NMR ($CDCl_3$) δ 7.58 (m, 5 H), 7.09 (br s, 1 H), 5.19 (q, J = 4.5 Hz, 1 H), 4.99 (dd, J = 4.4 Hz, J = 8.13 Hz, 1 H), 3.87 (m, 3 H), 2.65 (m, 2 H), 2.09 (s, 3 H), 1.65 (s, 3 H); MS (FAB), m/e 336 (M + H), 293, 250, 231.

From the acetoxy lactone **6d** (3.00 g, 10 mmol) and DIBAL (1 M in THF, 30.7 mL, 30.7 mmol) there was obtained 2.74 g (80%) of **8d** as a colorless oil after acetylation: ^{1}H NMR ($CDCl_3$) δ 7.63 (m, 5 H), 7.18 (br s, 1 H), 6.08 (m, 1 H), 5.54 (m, 1 H), 3.87 (m, 2 H), 2.33 (m, 2 H), 2.13 (s, 3 H), 2.11 (s, 3 H), 1.61 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 188.27, 185.89, 173.05, 131.72, 128.63, 126.68, 96.99, 85.29, 62.48, 60.26, 44.33, 23.11, 23.04, 21.14; MS (FAB), m/e 336 (M + H), 293, 231.

Acknowledgment. We acknowledge the generous support of the National Institutes of General Medical Sciences of the National Institutes of Health for support of this research (Grant GM 26574).

Registry No. **3a**, 7486-94-4; **3b**, 20012-94-6; **4a**, 110473-84-2; **4b**, 110473-85-3; **5a**, 110473-86-4; **5b**, 110473-91-1; **5c**, 110473-88-6; **5d**, 110473-93-3; **6a**, 110473-87-5; **6b**, 110473-90-0; **6c**, 110473-89-7; **6d**, 110473-92-2; **7b**, 110473-96-6; α-**7d**, 110485-89-7; β-**7d**, 110548-09-9; **8a**, 110473-94-4; **8b**, 110473-95-5; α-**8d**, 110548-10-2; β-**8d**, 110548-11-3.

Chemistry of Naturally Occurring Polyamines. 11. Unsaturated Spermidine and Spermine Derivatives[1]

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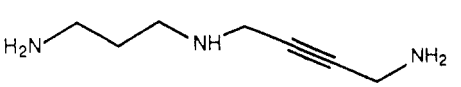
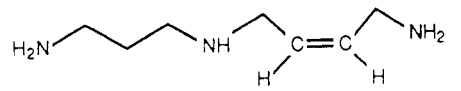
The ubiquitous polyamines putrescine, spermidine, and spermine are primary modulators of both normal and pathological cell growth. Catabolism of spermidine and spermine to lower amines is an important function of polyamine oxidase (PAO), a flavin-dependent enzyme that is widely distributed in plants, bacteria, fungi, and mammalian cells.[4] PAO catalyzes the same type of oxidations as mitochondrial monoamine oxidase, an enzyme that has been irreversibly inhibited using propargylic,[5] allylic,[6] and allenylamines.[7] Several *N*-2,3-butadienylputrescine derivatives were found to be potent irreversible inactivators of mammalian PAO, which oxidizes the aminopropyl residues of spermidine and spermine to 3-aminopropionaldehyde.[8] Recently Park and Folk have suggested that a different oxidative cleavage of spermidine to produce 4-aminobutyraldehyde and 1,3-propanediamine may be implicated in the biosynthesis of hypusine.[9] To investigate this possibility, we now report the synthesis of alkynyl and alkenyl analogues of spermidine (**1–3**) and spermine (**4–5**, Scheme I). Alkynylspermine **4** has previously been prepared by Fischer from the reaction of 1,4-dichloro-2-butyne with propane-1,3-diamine. Its hydrogenation led to regioselectively tritiated spermine possessing very high specific activity at inert, nonexchangeable sites.[10]

Scheme I



1



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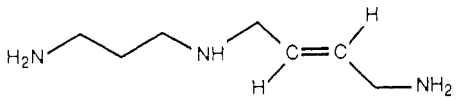

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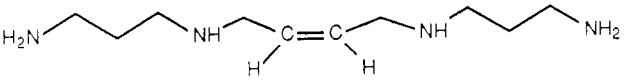
4



5

(1) For 10, see: Nagarajan, S.; Ganem, B. *J. Org. Chem.* **1986**, *51*, 4856.

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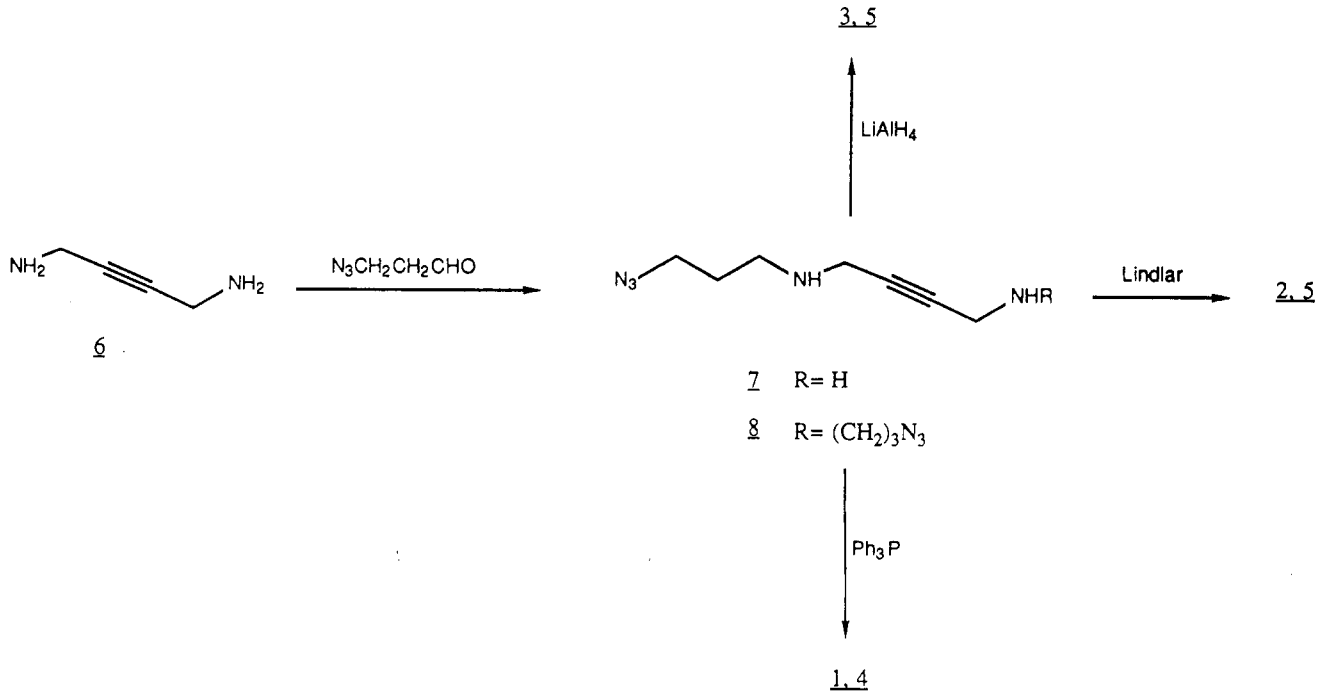
Scheme II



Syntheses of **1**–**5** were accomplished by starting with the known 1,4-diamino-2-butyne **6** (Scheme II).[11] Reductive amination with *N*-BOC-3-aminopropanal[12] gave complicated mixtures from which only low yields of 1:1 and 2:1 adducts could be obtained. However, slow addition of the known 3-azidopropanal[13] to excess **6** in the presence of $NaBH_3CN$ at pH 6 afforded **7** in 60% yield. Adding **6** slowly to 2 equiv of the azidoaldehyde followed by cyanoborohydride reduction (also at pH 6) gave the 2:1 adduct **8** (46%). Selective reduction of the azido groups in **7** and **8** without disturbing the alkyne functionality was achieved by using triphenylphosphine in aqueous THF[14] to afford acetylenic polyamines **1** (98%) and **4** (90%). Our overall yield of **4** (41%) is superior to that reported by Fischer (25%).[10] Both **7** and **8** reacted with H_2 and Lindlar catalyst (CH_3OH) to furnish the *cis*-alkenes **2** (25%) and **5** (57%). With $LiAlH_4$ in THF, triaminoalkyne **1** was reduced to trans-unsaturated spermidine analogue **3** (62%). However, the same reduction of tetraaminoalkyne **4** produced only the cis isomer **5** in modest yield. Similar results have been noted with other alkynes when toluene was used as solvent or when reaction times in THF were prolonged.[15] Compounds **1**–**5** and a related family of methylated polyamines[1] are presently being assayed as inhibitors of PAO and spermidine/spermine N^1-acetyltransferase as well as for their effect on SV-3T3 cell growth. Results will be reported elsewhere.

Experimental Section

Dichloromethane and Et_3N were distilled from CaH_2. All reactions were conducted under a N_2 or Ar atmosphere. IR spectra were determined on a Perkin-Elmer 681 infrared spectrophotometer. ^1H NMR spectra were recorded on a Bruker WM-300 spectrometer at 300 MHz. Chemical shifts were expressed relative to internal tetramethylsilane ($CDCl_3$) or to HOD at 4.8 ppm (D_2O). All new compounds were judged to be at least 95% pure on the basis of careful integration and peak analysis of ^1H NMR spectra. Mass spectra were obtained on a computerized AEI MS902 instrument using isobutane as reagent gas.

***N*-(3-Azidopropyl)-1,4-diamino-2-butyne (7).** A solution of 3-azidopropionaldehyde (0.548g, 5.54 mmol)[13] in methanol (4 mL) was slowly added to a solution of 1,4-diamino-2-butyne (1.86 g, 22.1 mmol)[11] in methanol (40mL) at room temperature. Then $NaBH_3CN$ (1.5 g) was added in small portions. The pH was adjusted to 6 by using methanolic HCl. After 18 h, excess reducing agent was destroyed by the addition of concentrated HCl and the reaction mixture was concentrated to dryness. The residue was dissolved in water (10 mL) and basified to pH 10 with solid NaOH pellets and the aqueous layer was extracted with $CHCl_3$ (4 × 25 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and purified by SiO_2 flash chromatography, eluting with 50:50:1 $CH_2Cl_2/CH_3OH/NH_4OH$ to afford **7** (0.554 g, 60%) as an oil: ^1H NMR ($CDCl_3$) 3.41, 3.42 (2 s,, 4 H), 3.41 (t, 2 H), 2.79 (t, 2 H), 1.79 (m, 2 H); IR (film) 3300, 2940, 2820, 2100 (N_3), 1260, 1030 cm^{-1}; CIMS, *m/e* (relative intensity) 168 (M + 1, 100), 97 (M − 70, 10).

***N*-(3-Aminopropyl)-1,4-diamino-2-butyne (1).** A mixture of **7** (0.340 g, 2.04 mmol) and triphenylphosphine (0.558 g, 2.24 mmol) in THF (10 mL) containing water (0.040 mL) was stirred at room temperature for 18 h and then concentrated in vacuo. The residue was chromatographed ($CH_2Cl_2/CH_3OH/NH_4OH$, lower layer used as eluant) to afford 0.282 g (98%) of **1** as an oil: ^1H NMR (D_2O) 3.40 (s, 4 H), 2.83 (t, 2 H), 2.72 (t, 2 H), 1.73 (m, 2 H); IR (film) 3300, 2900, 2500, 1570, 1470, 1340 cm^{-1}; HRMS (20 eV), calcd for $C_7H_{15}N_3$ 141.2176, found 141.2143.

***N*-(3-Aminopropyl)-1,4-diamino-*cis*-2-butene (2).** A mixture of **7** (0.176 g, 1.05 mmol) and Lindlar's catalyst (0.1 g) in CH_3OH (25 mL) was stirred under 1 atm of hydrogen for 6 h. The catalyst was removed by filtration and washed with CH_3OH. The combined filtrates were concentrated and flash chromatographed ($CH_2Cl_2/CH_3OH/NH_4OH$, 2:2:1) to afford 0.035 g (25%) of the desired alkene **2** as an oil: ^1H NMR (D_2O) 5.6–5.77 (m, 2 H), 3.31 (m, 4 H), 2.75 (t, 2 H), 2.66 (t, 2 H), 1.71 (m, 2 H); IR (film 3350, 2940, 1580, 1330, 1100 cm^{-1}; CIMS, *m/e* (relative intensity) 144 (M + 1, 100).

***N*-(3-Aminopropyl)-1,4-diamino-*trans*-2-butene (3).** A THF solution of $LiAlH_4$ (1 M, 1.9 mL, 1.9 mmol) was added slowly to a stirred solution of triamine **1** (0.050 g, 0.357 mmol) in THF

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(11) Marszak-Fleury, A. *Liebigs Ann. Chem.* **1958**, 656.
(12) Prepared from 3-aminopropanol by reaction with (a) BOC-ON and (b) PDC.
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(8 mL) at room temperature and the mixture brought to reflux for 6 h. The flask was then cooled to 0 °C and its contents were carefully treated with aqueous KOH (2 M, 0.9 mL, 1.8 mmol). After 5 min, more THF (15 mL) was added and the mixture again brought to reflux for 0.5 h, then cooled, and allowed to stand overnight. The supernatant was decanted, more THF (15 mL) added to the residue, and decanting repeated. The combined THF layers were concentrated and the residue was flash chromatographed ($CH_2Cl_2/CH_3OH/NH_4OH$, 2:2:1) to afford *trans*-alkene **3** (0.025 g, 62%) as an oil, along with recovered **1** (0.010 g). For **3**: ^1H NMR (D_2O) 5.79, 5.67 (dt, 2 H, J = 15.5, 6 Hz), 3.21 (t, 4 H), 2.67 (t, 2 H), 2.61 (t, 2 H), 1.64 (m, 2 H); IR (film) 3300, 2930, 2860, 1600, 1140, cm^{-1}; HRMS (20 eV) calcd for $C_7H_{17}N_3$ 143.2334, found 143.2238.

N^1,N^4-Bis(3-azidopropyl)-1,4-diamino-2-butyne (8). A solution of 1,4-diamino-2-butyne (0.326 g, 3.88 mmol) in CH_3OH (10 mL) was added to 3-azidopropionaldehyde (1.52 g, 15.35 mmol) in CH_3OH (15 mL) at room temperature. Sodium cyanoborohydride (1.75 g) was added in portions and the pH adjusted to 6 with methanolic HCl. After stirring 16 h, the product was isolated as above for **7** and purified by flash chromatography to afford **8** (0.24 g, 46%) as an oil: ^1H NMR ($CDCl_3$) 3.43 (s, 4 H), 3.39 (t, 4 H), 2.77 (t, 4 H), 1.77 (m, 4 H); IR (film) 3300, 2940, 2820, 2100 (N_3) 1450, 1260, 1030 cm^{-1}; CIMS, m/e (relative intensity) 251 (M + 1, 100), 168 (16).

N^1,N^4-Bis(3-aminopropyl)-1,4-diamino-2-butyne (4). A mixture of diazide **8** (0.035 g, 0.14 mmol) and triphenylphosphine (0.075 g, 0.28 mmol) in THF (4 mL) containing water (0.0075 g, 0.28 mmol) was stirred at room temperature for 16 h. The bulk of solvent was removed in vacuo and the residue was flash chromatographed ($CH_2Cl_2/CH_3OH/NH_4OH$, 2:2:1) to afford 0.025 g (90%) of **4** as an oil: ^1H NMR (D_2O) 3.40 (3, 4 H), 2.73 (t, 4 H), 2.70 (t, 4 H), 1.67 (m, 4 H); IR (film) 3300, 2940, 2860, 1320 cm^{-1}; HRMS (20 eV) calcd for $C_{10}H_{22}N_4$ 198.3136, found 198.3001.

N^1,N^4-Bis(3-aminopropyl)-1,4-diamino-*cis*-2-butene (5). A mixture of **8** (0.066 g, 0.262 mmol) and Lindar's catalyst (0.02 g) in CH_3OH (15 mL) was stirred under 1 atm of hydrogen for 8 h. The catalyst was removed by filtration and washed with CH_3OH. The combined filtrates were concentrated and chromatographed ($CH_2Cl_2/CH_3OH/NH_4OH$, (2:2:1) to afford 0.030 g (57%) of **5** as an oil: ^1H NMR (D_2O, 200 MHz) 5.65 (m, 2 H), 3.31 (s, 2 H), 3.28 (d, 2 H) 2.73 (t, 4 H), 2.65 (t, 4 H), 1.68 (m, 4 H); IR (film) 3310, 2950, 2860, 1455, 1310, 11 cm^{-1}; CIMS, m/e (relative intensity) 201 (M + 1, 100), 127 (63).

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Registry No. 1, 110319-63-6; 2, 110319-64-7; 3, 110319-65-8; 4, 110319-67-0; 5, 110319-68-1; 6, 53878-96-9; 7, 110319-62-5; 8, 110319-66-9; $N_3(CH_2)_2CHO$, 58503-60-9.

Polycyclic Heterocycles from Glutaraldehyde in One Reaction

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We have found that glutaraldehyde adducts (see Scheme I) readily react under anhydrous acidic conditions with the three possible positional isomers of piperidinecarboxamide, **5** (pipecotamide), **6** (nipecotamide), and **7** (isonipecotamide), to give the novel heterocycles **1–3**, respectively. The ready formation of these polycyclic, multifunctional molecules in a single reaction entails generation of three new bonds and a new stereogenic center.

Scheme I

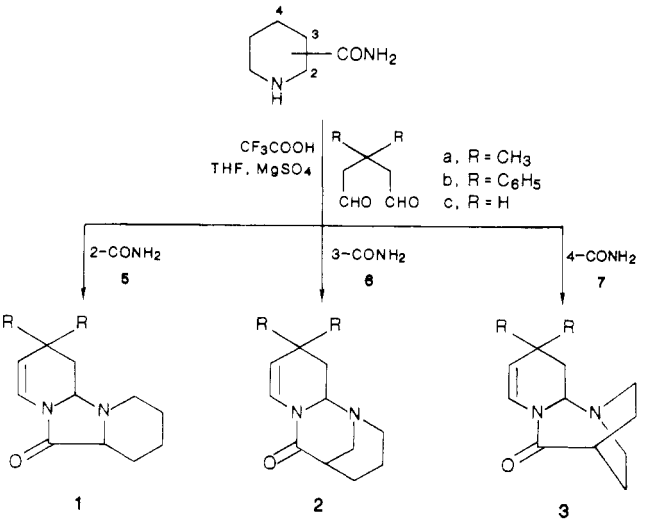
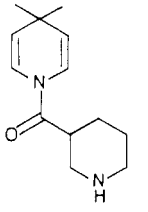


Table I. Product Characterization

compound	yield, %[a]	isomer ratio[b]	mp,[c] °C
1a	14 (88)	91:9	113–115
1b	16 (70)	95:5[d]	159.5–162
2a	48 (79)	83:17	93–94.5 97.5–99 (trans)
2b	31 (81)	86:14	252–254[e]
2c	7 (65)	75:25[f]	50.5–53
3a	4 (22)		93–95.5

[a] Yields are not maximized and represent analytically pure samples. Crude mass return is given in parentheses, and gas chromatography showed the isomeric products to account for 90–95% of the mixture. [b] Determined by gas chromatography from crude reaction mixtures and isomers verified by GC/MS. [c] For major isomer (cis) unless indicated. [d] This ratio determined from isolated masses after chromatography. [e] 2-Naphthalenesulfonic acid salt of 93:7 isomer mixture. [f] The minor isomer was never isolated.

A related reaction of glutaraldehyde with chiral aminoethanol derivatives and KCN at pH 3–4 has been reported to give a versatile chiral intermediate, **8**, which was further elaborated to several enantiomerically pure alkaloids.[1]



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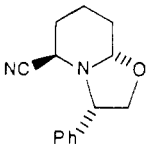

8

Using the reaction conditions outlined in Scheme I, we expected to obtain dihydropyridine **4** from 3,3-dimethylglutaraldehyde and nipecotamide, as precedented by Fraenkel's previous reports.[2] Instead, a product was obtained with an ^1H NMR spectrum inconsistent with such a symmetrical structure. Closer examination showed that a mixture of diastereomeric products had been formed in a ratio of 79:21 (see Table I). These were chromatographically separated and analyzed by 360-MHz ^1H NMR to determine that the structure of the isolated product was **2a**.[3] The relative stereochemistry of the bridgehead

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(3) Detailed analyses of the ^1H NMR spectra of these compounds will be submitted for publication in a separate article.

0022-3263/87/1952-5046$01.50/0