matograph. 1-Octene, $Hg(OAc)_2$, butanol, hexanol, octanol, and decanol were all used as received from Aldrich. Absolute ethanol was purchased from Aaper Alcohol and Chemical Co. THF was freshly distilled under nitrogen from sodium metal. Sodium dodecyl sulfate was purchased from Bio-Rad Laboratories and was recrystallized once from 95% ethanol. A plot of surface tension versus concentration for its solutions in water showed no hysteresis. Water was doubly distilled.

Alkoxymercuration in SDS. For experiments 1–5, 7, 12, and 13 (Table I), the following procedure was used. In a 50-mL round-bottom flask equipped with a magnetic stirrer were placed SDS (212 mg) and 25 mL of H_2O. 1-Octene (8.4 mg, 0.075 mmol) was added, and the solution was stirred to achieve homogeneity. Primary alcohol (0.75 mmol) was added, and this solution was again stirred to dissolve the alcohol. Some cloudiness persisted with the longer chain alcohols, but no phase separation was observed. $Hg(OAc)_2$ (23.9 mg, 0.075 mmol) in 1 mL of H_2O was added. Aliquots (5–10 mL) were removed from these reactions at the indicated times and were quenched with 2 mL of a 3.0 N NaOH solution followed by 2 mL of 0.5 N $NaBH_4$ in 3.0 N NaOH. The black suspension so obtained was stirred for an additional 30 min to allow the Hg^0 to coagulate. This solution was poured into a 50-mL screw-capped centrifuge tube that contained approximately 2 g of NaCl and 0.25 g of $BaCl_2$. The tube was capped and shaken; a light gray flocculent formed. Diethyl ether was added, and three extractions were done. Each extraction required that the tube be centrifuged for 3 min to cleanly separate the three phases: ether extract on top, compressed gray solid, and H_2O layer on bottom. The ether fraction was removed, and the procedure was repeated. The ether extracts were dried with $MgSO_4$ and concentrated. A similar procedure was used for experiments 6, 8, 9, and 14 with the indicated increases in olefin and Hg^{2+} concentrations. Experiments 10 and 11 were also similar, but the alcohol concentration was changed. GLC analysis (10% OV-17, 15 ft × $^1/_8$ in. on 100/120 Chrom W) at 60–230 °C gave cleanly resolved peaks for unreacted 1-octene, 2-octanol, and the alkyl ether. Relative FID response factors for 2-octanol and the alkyl ether products were determined for authentic mixtures. Assigning an arbitrary value of 1 to the 2-octanol, the relative response was 1.2 for the C_2 and C_4 ethers and 1.8 for the C_6, C_8, and C_{10} ethers. Each aliquot was analyzed three times and integrated by cutting and weighing three copies of each chromatogram.

Alkoxymercuration in THF. Experiment 16: A dry round-bottom flask equipped with a magnetic stirring bar, was charged with 25 mL of dry THF, 1-octene (84 mg), water (135 mg), and 1-octanol (1.185 g). To this solution was added solid $Hg(OAc)_2$ (239 mg). The flask was stoppered, and the resulting clear yellow solution was allowed to stir at room temperature for 40 h. The yellow color persisted throughout. Workup with 3 N NaOH and $NaBH_4$ solutions was followed by ether extraction. The combined ether extracts were dried with $MgSO_4$ and concentrated. Analyses by GC (OV-17 as above) showed >95% unreacted 1-octene. The ratio of 2-octanol to *n*-octyl 2-octyl ether for the small amount that did react was determined. Experiment 15 was identical with the SDS-mediated mercuration (experiment 7), except that the aqueous SDS solution was replaced with a 50/50 mixture (by volume) of water and THF.

***n*-Alkyl 2-Octyl Ethers.** Authentic samples of the ethers were prepared by the method of Brown,[3] where the alcohol is used as the reaction solvent. They were purified by preparative gas chromatography on an OV-17 column (9 ft × $^1/_8$ in., 60/80 mesh Chrom W) at temperatures between 150 and 230 °C with a flow rate of 25 mL/min. While the C_2 ether was a known compound,[6] the other four ethers are new materials. Their ^1H NMR ($CDCl_3$) and mass spectra (exact mass at 15–20 eV) are reported below.

2-Oxyethyl octane: ^1H NMR δ 3.45 (3 H, m), 1.25 (10 H, m), 1.16 (3 H, t, J = 7.0 Hz), 1.10 (3 H, d, J = 6.2 Hz), 0.86 (3 H, t, J = 6.1 Hz). 2-Oxybutyl octane: exact mass calcd 186.1985, found 186.1984; ^1H NMR δ 3.42 (3 H, m), 1.41 (14 H, m), 1.15 (3 H, d, J = 6.2 Hz), 0.92 (6 H, t, J = 6.1 Hz). 2-Oxyhexyl octane: exact mass calcd 214.2298, found 214.2301; ^1H NMR δ 3.33 (3 H, m), 1.40 (18 H, m), 1.08 (3 H, d, J = 6.2 Hz), 0.85 (6 H, t, J = 6.1 Hz). 2-Oxyoctyl octane: exact mass calcd 242.2611, found 242.2634; ^1H NMR δ 3.44 (3 H, m), 1.51 (22 H, m), 1.08 (3 H, d, J = 6.0 Hz), 0.85 (6 H, t, J = 6.4 Hz). 2-Oxydecyl octane: exact mass calcd 270.2923, found 270.2944; ^1H NMR δ 3.41 (3 H, m), 1.56 (26 H, m), 1.09 (3 H, d, J = 6.0 Hz), 0.86 (6 H, t, J = 5.9 Hz).

Acknowledgment. The financial support of the NIH (Grant GM-27355) and the award of an NIH Research Career Development Award (1983–1988) to C.N.S. are gratefully acknowledged.

Registry No. SDS, 151-21-3; $Hg(OAc)_2$, 1600-27-7; $C_6H_{13}CH(OC_2H_5)CH_3$, 63028-01-3; $C_6H_{13}CH(OC_4H_9)CH_3$, 110458-41-8; $C_6H_{13}CH(OC_6H_{13})CH_3$, 51182-98-0; $C_6H_{13}CH(OC_8H_{17})CH_3$, 20012-47-9; $C_6H_{13}CH(OC_{10}H_{21})CH_3$, 51183-01-8; 1-octene, 111-66-0; 2-octyl alcohol, 123-96-6.

(6) (a) Streitwieser, A.; Waiss, A. C. *J. Org. Chem.* **1962**, *27*, 290. (b) Moss, R. A.; Grover, E. R. *J. Org. Chem.* **1976**, *41*, 1128.

An Azetidinone Route to 2,3-Dideoxy-3-aminopentoses and 2,3-Dideoxy-3-*C*-methyl-3-aminopentoses

Frank M. Hauser,*[1] Suzanne R. Ellenberger, and Richard P. Rhee

Department of Chemical, Biological and Environmental Sciences, Oregon Graduate Center, Beaverton, Oregon 97006

Received April 1, 1987

We have shown previously that the azetidinone **1**, formed through regiospecific cycloaddition of chlorosulfonyl isocyanate and (*E*)-1,3-pentadiene, can be used as an intermediate for efficient, diastereoselective total syntheses of both racemic and optically active daunosamine (**2**)[2] (Figure 1). It was recognized, as indicated in Scheme I, that a parallel reaction sequence from the azetidinone adducts **3a** and **3b** would provide a brief route for preparation of the aminopentoses **7b** and **8b** and the *C*-methylaminopentoses **7d** and **8d**, respectively. However, the value of this approach as a preparative method was somewhat mitigated by the modest yields of azetidinones **3a** and **3b** that were attainable from the cycloaddition of butadiene or isoprene with chlorosulfonyl isocyanate.[3]

Recently, we discovered a procedure for high-yield (>90%) preparation of the needed azetidinones **3a** and **3b**[4] and now have established the generality of the preparative sequence to daunosamine (**2**) as a route to the aminopentoses **7** and **8**. An ancillary finding of this investigation is that the diastereoselectivity of the osmium tetraoxide hydroxylation of amides of allylamines is enhanced by an increase in alkyl substitution α to the amide nitrogen.

The azetidinone starting materials **3a** and **3b** were prepared in 95% yield through respective cycloaddition of butadiene and isoprene with chlorosulfonyl isocyanate.[4] Methanolysis (MeOH/HCl) of **3a** and **3b** followed by benzoylation furnished the corresponding methyl *N*-benzoyl-4-pentenoates **4a** and **4b** in 95% overall yield.

Osmium tetraoxide catalyzed cis hydroxylation of the pentenoate **4a**, with trimethylamino *N*-oxide (TMNO) to regenerate the tetraoxide, gave a 56:44 ratio of trans and cis lactones **5a** and **6a** in 96% yield. The isomers were separated initially by chromatography and then further purified by recrystallization. Subsequently, it was found that the more polar isomer **5a** could be isolated directly

(1) Present address: Department of Chemistry, State University of New York at Albany, Albany, NY 12222.
(2) Hauser, F. M.; Rhee, R. P.; Ellenberger, S. R. *J. Org. Chem.* **1984**, *49*, 2236.
(3) Moriconi, E. J.; Meyer, W. C. *J. Org. Chem.* **1971**, *36*, 2841. Goebel, P.; Clauss, K. *Liebigs Ann. Chem.* **1969**, 122.
(4) Hauser, F. M.; Ellenberger, S. R. *Synthesis*, in press.
(5) Hauser, F. M.; Ellenberger, S. R. *J. Org. Chem.* **1986**, *51*, 50.

0022-3263/87/1952-5041$01.50/0

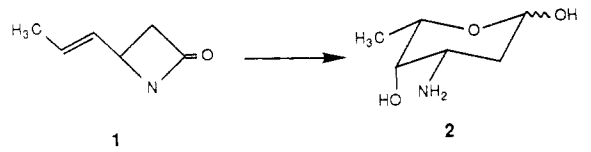
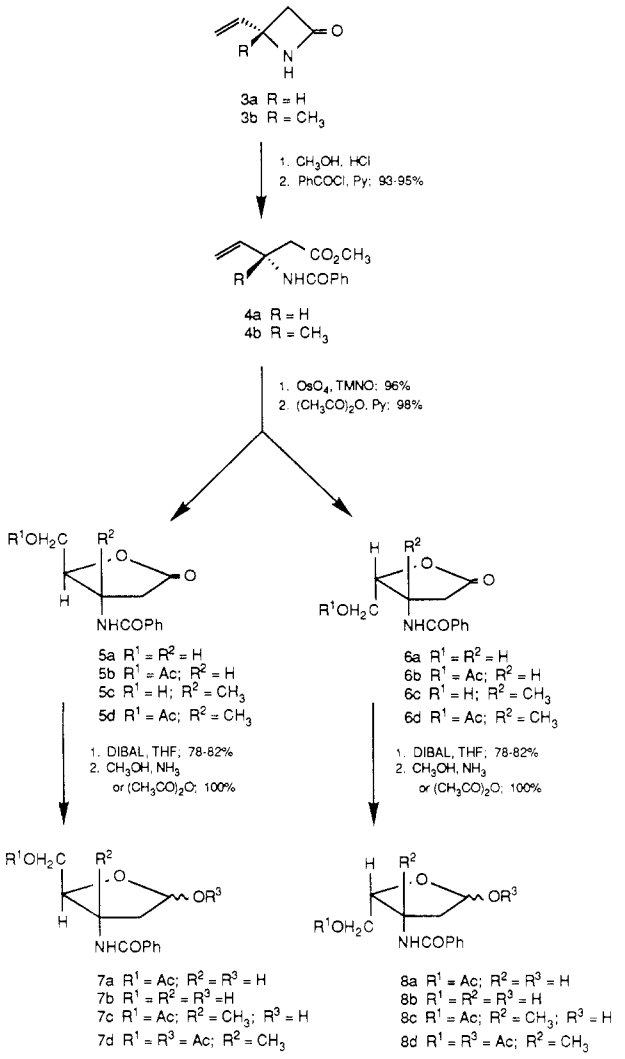


Figure 1.

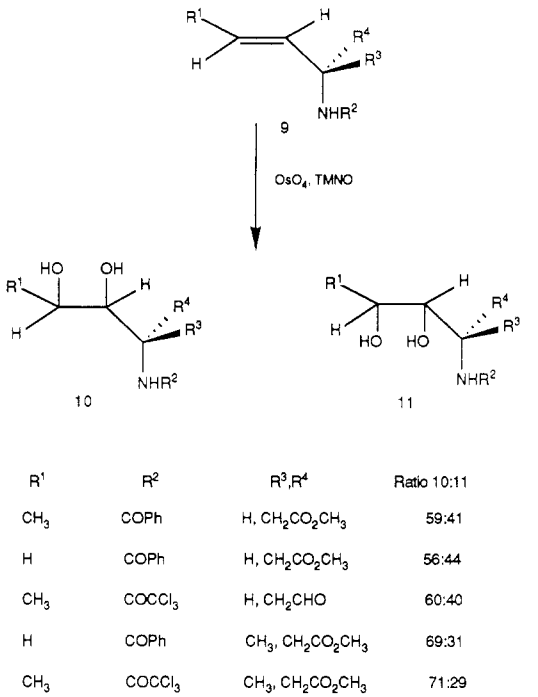
Scheme I



through crystallization of the initial mixture. The residue remaining after partial removal of the trans isomer **5a** was then chromatographed to obtain the pure cis isomer **6a**.

The chemical shifts of the various protons in the ^1H NMR spectra of the individual lactones **5a** and **6a** were well separated, which facilitated assignment of stereochemistry to the isomers. Irradiation of the C-5 protons at 3.87 ppm in **5a** led to collapse of the multiplet at 4.62 ppm (C-4 proton) to a doublet with J = 3.73 Hz, and irradiation of the C-5 protons at 3.84 ppm in **6a** led to collapse of the multiplet at 4.85 ppm (C-4 proton) to a doublet with J = 14.06 Hz. Since the dihedral angle between the C-3 and C-4 protons in trans-substituted five-membered lactones approaches 90°, the coupling constant is small; thus, **5a** was assigned the trans stereochemistry and **6a** the cis stereochemistry. Similar decoupling of the ^1H NMR spectra of the acetate derivatives **5b** and **6b** confirmed the stereochemical assignments.

DIBAL reduction (THF, −80 °C, 4 h) of the individual acetate derivatives **5b** and **6b** gave the acetylated lactols **7a** and **8a** in 85% yield along with 10% of the deacetylated products **7b** and **8b**. Respective ammonolysis (NH_3/MeOH, 0 °C, 1 h) of the initially received mixtures of **7a** and **8a** quantitatively furnished the aminopentoses **7b** and **8b**. The overall yield of the aminopentose **7b** with the erythro configuration was 40% and that of the aminopentose **8b** with the threo configuration was 31%. The combined overall yield of aminopentoses from **4a** was 71%.



R^1	R^2	R^3,R^4	Ratio 10:11
CH_3	COPh	H, $CH_2CO_2CH_3$	59:41
H	COPh	H, $CH_2CO_2CH_3$	56:44
CH_3	$COCCl_3$	H, CH_2CHO	60:40
H	COPh	CH_3, $CH_2CO_2CH_3$	69:31
CH_3	$COCCl_3$	CH_3, $CH_2CO_2CH_3$	71:29

Figure 2. Relative ratios of diols from cis hydroxylation of allyl amides with osmium tetraoxide.

Corresponding hydroxylation (OsO_4, TMNO) of the pentenoate **4b**, originating from the methyl-substituted azetidinone **3b**, gave the 3-*C*-methyl-substituted lactones **5c** and **6c** in a 69:31 ratio, respectively. The nuclear Overhauser effect (NOE) was employed to assign stereochemistry to the individual lactones. Irradiation of the C-4 proton at 4.56 ppm in the acetate derivative **6d** resulted in a 30% decrease in intensity of the methyl absorption at 1.53 ppm and thereby demonstrated the cis relationship of the C-4 proton and the methyl group. Corresponding irradiation of the C-4 proton in **5d** resulted in no change in the intensity of the methyl absorption.

Individual reductions of the acetate derivatives **5d** and **6d** with DIBAL furnished the lactols **7c** and **8c**, respectively, along with 10% of the deacetylated products. Acetylation of the individual lactol mixtures quantitatively furnished the 3-*C*-methylaminopentose diacetate derivatives **7d** and **8d** with the *erythro* and *threo* configurations, respectively.

The accomplished pentose preparations demonstrate that the sequence originally used for synthesis of daunosamine can be generally applied to the preparation of 2,3-dideoxy-3-amino sugars. Furthermore, the results obtained in this study and from our earlier[1,4] work on the osmium tetraoxide hydroxylation of amides of allylamines provides additional information on the factors governing the stereochemical course of this reaction. As indicated in Figure 2, substitution of the γ *E*-vinyl proton and/or the proton α to the amide nitrogen, by an alkyl group, increases the amount of anti hydroxylation product.[6,7]

(6) For the osmium tetraoxide hydroxylation of heterosubstituted allyl systems other than amides, see: Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943 and 3947. Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951. Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094.

Experimental Section

General Methods. Melting points were taken on a Kofler hot-stage microscope and are uncorrected. IR spectra were measured on a Perkin-Elmer 1800 Fourier transform spectrophotomer and are expressed in wave numbers. Proton and ^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer. Chemical shifts are reported as δ values in ppm relative to TMS. Mass spectra were obtained on a VG 7070E spectrometer. Analytical TLC was conducted on 5 × 10 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.25 mm) manufactured by E. Merck and Co. Silica gel for chromatography was from E. Merck (60, 70–230-mesh ASTM). A stock solution of osmium tetraoxide (1 g, dissolved in 200 mL of 3:1 *tert*-butyl alcohol/carbon tetrachloride) was used for hydroxylations.

Methanolysis and Benzoylation of Azetidinones: Methyl 3-Benzamido-4-pentenoate (4a) and Methyl 3-Benzamido-3-methyl-4-pentenoate (4b). Dry hydrogen chloride was bubbled for 30 min into a chilled (ice/salt bath) solution of the azetidinone **3a**[4] (18.00 g, 186 mmol) in anhydrous methanol (200 mL). The majority of the methanol was removed at reduced pressure in a cool water bath, and residual traces were removed with a vacuum pump. To a magnetically stirred, cold (0 °C) suspension of the crude amine hydrochloride salt in ether (200 mL) and pyridine (45 mL) was added dropwise benzoyl chloride (26.71 g, 190 mmol). Once the addition of benzoyl chloride was completed, the mixture was allowed to come to room temperature and stirred for 5 h. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (50 mL) and then solid sodium bicarbonate until foaming ceased. The layers were separated, and the organic phase was washed with 10% hydrochloric acid (3 × 50 mL), dried over magnesium sulfate, and filtered. Evaporation of the solvent at reduced pressure gave 41.07 g (95%) of **4a** as a colorless, low-melting (mp < 60 °C) solid, which usually was not purified further: ^1H NMR ($CDCl_3$) δ 7.79 (m, 2 H), 7.28 (m, 4 H), 5.93 (m, 1 H), 5.23 (m, 3 H), 3.68 (s, 3 H), 2.74 (d, J = 5.12 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 184.70, 176.25, 136.54, 131.50, 128.52, 126.95, 115.95, 51.70, 48.02, 38.16; IR (CH_2Cl_2) 3428, 3324 (N–H), 1662 (C=O amide), 1734 (C=O ester), 1517, 1265 (N–H), 1204, 1181 (C–O–C), 990, 928 (C–H olefin) cm^{-1}. An analytical sample was obtained through column chromatography (silica gel, 1:1 ethyl acetate/hexanes). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.71; H, 6.47; N, 6.06.

Methanolysis of the azetidinone **3b** (15.00 g, 135 mmol), followed by amidation with benzoyl chloride (19.68 g, 140 mmol) and pyridine (40 mL) gave 31.04 g (93%) of **4b** as colorless needles with mp 86–87 °C after crystallization from methylene chloride/hexanes: ^1H NMR ($CDCl_3$) δ 7.82 (m, 2 H), 7.55 (m, 3 H), 7.19 (br s, 1 H), 6.12 (dd, J = 10.32 Hz, J = 17.35 Hz, 1 H), 5.24 (d, J = 5.50 Hz, 1 H), 5.09 (d, J = 1.76 Hz, 1 H), 3.68 (s, 3 H), 2.84 (d, J = 1.76 Hz, 2 H), 1.68 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.86, 166.71, 141.58, 135.34, 131.28, 128.52, 126.79, 113.08, 55.71, 43.68, 25.16, 24.94. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.12; H, 6.95; N, 5.56.

***trans*- and *cis*-4-Benzamido-3,4-dihydro-5-(hydroxymethyl)-2(5*H*)-furanones (5a and 6a).** Osmium tetraoxide (1 mL of a stock solution) was added to a solution of **4a** (16.00 g, 69 mmol) and trimethylamine *N*-oxide monohydrate (16.78 g, 151 mmol) in acetone (100 mL) and water (20 mL). The yellow reaction mixture was stirred for 16 h, at which time analysis of a TLC indicated that the starting material had been consumed. Methylene chloride (50 mL) was added, and then saturated sodium bisulfite solution (25 mL) was added to reduce the osmium tetraoxide to the dioxide, which formed a black precipitate. The layers were separated, and the aqueous phase was further extracted with additional methylene chloride (2 × 30 mL). The combined organic solutions were dried over sodium sulfate, filtered, and evaporated at reduced pressure to give a yellow solid composed of the more polar, trans lactone **5a** and the less polar, cis lactone **6a** in a 56:44 ratio and in 96% yield. The trans isomer was crystallized from the mixture with methanol/methylene chloride and then recrystallized from methanol/ether to give 8.67 g of **5a** as colorless needles with mp 164–165 °C: ^1H NMR (MeOH-d_4) δ 7.67 (m, 6 H), 4.76 (m, 1 H), 4.62 (q, J = 3.30 Hz, 1 H), 3.87 (dd, J = 1.10 Hz, J = 2.85 Hz, 2 H), 2.91 (ddd, J = 4.84 Hz, J = 8.79 Hz, J = 22.63 Hz, 2 H); ^{13}C NMR (MeOH-d_4) δ 177.01, 169.38, 133.99, 132.05, 128.64, 127.44, 86.98, 73.54, 62.27, 35.35; IR ($CDCl_3$) 3751 (O–H), 3382 (N–H), 1752 (C=O lactone), 1640 (C=O amide), 1605 (N–H) cm^{-1}.

The cis lactone **6a** was isolated from the filtrate by column chromatography (200 g silica gel, 5% methanol/methylene chloride) and recrystallized from methanol/ether to give 6.82 g of **6a** as colorless plates with mp 139–141 °C: ^1H NMR (MeOH-d_4) δ 7.70 (m, 5 H), 4.91 (m, 1 H), 4.85 (m, 1 H), 3.84 (ddd, J = 3.51 Hz, J = 18.14 Hz, J = 3.63 Hz, 1 H), 2.91 (ddd, J = 8.13 Hz, J = 5.93 Hz, J = 17.58 Hz, 2 H); ^{13}C NMR (MeOH-d_4) δ 173.66, 170.46, 133.02, 132.75, 129.56, 128.31, 83.62, 73.92, 64.49, 37.08; IR ($CDCl_3$) 3373 (N–H), 3629 (O–H), 1600 (N–H), 1654 (C=O amide), 1760 (C=O lactone) cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 60.79; H, 5.69; N, 5.80.

4-Benzamido-3,4-dihydro-5-(hydroxymethyl)-4-methyl-2-(5*H*)-furanones (5c and 6c). The procedure employed for the hydroxylation of **4a** was used. From **4b** (12.00 g, 49 mmol), trimethylamine *N*-oxide (11.87 g, 107 mmol), and a catalytic amount of osmium tetraoxide in acetone/water there was obtained a 69:31 mixture of the lactones **5c** and **6c** in 95% yield. Column chromatography of the mixture (150 g silica gel, 5–7% methanol/methylene chloride) provided 3.56 g of the less polar lactone **6c** as colorless plates with mp 151–152 °C after recrystallization from methanol/hexanes: ^1H NMR (MeOH-d_4) δ 7.67 (m, 5 H), 4.57 (t, J = 3.74 Hz, 1 H), 3.92 (d, J = 3.74 Hz, 2 H), 3.32 (m, 1 H), 3.29 (d, J = 17 Hz, 1 H), 2.72 (d, J = 17 Hz, 1 H), 1.70 (s, 3 H); IR ($CDCl_3$) 3629 (O–H), 3219 (N–H), 1762 (C=O lactone), 1684 (C=O amide), 1647 (N–H) cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.27; H, 6.04; N, 5.48.

Continued elution provided 7.93 g of the lactone **5c** as colorless needles with mp 105–107 °C after recrystallization from methanol/methylene chloride: ^1H NMR (MeOH-d_4) δ 7.56 (m, 5 H), 4.98 (t, J = 3.30 Hz, 1 H), 3.92 (d, J = 3.30 Hz, 2 H), 3.32 (m, 1 H), 3.22 (d, J = 17 Hz, 1 H), 2.82 (d, J = 17 Hz, 1 H), 1.70 (s, 3 H); IR ($CDCl_3$) 3649 (O–H), 3434 (N–H), 1640 (N–H), 1654 (C=O amide), 1744 (C=O lactone) cm^{-1}.

Acetylation of (Hydroxymethyl)furanones: *trans*- and *cis*-5-(Acetoxymethyl)-4-benzamido-3,4-dihydro-2(5*H*)-furanones (5b and 6b) and *trans*- and *cis*-5-(Acetoxymethyl)-4-benzamido-3,4-dihydro-4-methyl-2(5*H*)-furanones (5d and 6d). The individual lactones **5a**, **6a**, **5c**, and **6c** were acetylated with acetic anhydride and pyridine at room temperature. From 5.00 g (21 mmol) of the cis lactone **6a** there was obtained 5.72 g (97%) of the acetate **6b** as colorless needles with mp 106–107 °C after recrystallization from ethyl acetate/hexanes: ^1H NMR ($CDCl_3$) δ 7.60 (m, 5 H), 6.86 (br d, 1 H), 5.31 (m, 1 H), 4.83 (m, 1 H), 4.14 (m, 2 H), 2.64 (m, 2 H), 2.05 (s, 3 H).

From 4.00 g (17 mmol) of the trans lactone **5a** there was obtained 4.53 g (96%) of the acetate **5b** as colorless crystals with mp 103–104 °C after recrystallization from acetone/hexanes: ^1H NMR ($CDCl_3$) δ 7.58 (m, 6 H), 5.17 (m, 1 H), 4.87 (m, 1 H), 4.34 (m, 2 H), 3.03 (dd, J = 18 Hz, J = 8 Hz, 1 H), 2.58 (dd, J = 18 Hz, J = 4 Hz, 1 H), 2.00 (s, 3 H).

From 3.00 g (12 mmol) of the hydroxy lactone **6c** there was obtained 3.44 g (98%) of **6d** as colorless chunks with mp 123–124 °C: ^1H NMR ($CDCl_3$) δ 7.42 (m, 5 H), 6.86 (br s, 1 H), 4.56 (dd, J = 3.51 Hz, J = 5.49 Hz, 1 H), 4.12 (m, 2 H), 2.96 (d, J = 17.14 Hz, 1 H), 2.46 (d, J = 17.35 Hz, 1 H), 1.87 (s, 3 H), 1.53 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.08, 170.18, 168.12, 131.84, 128.36, 127.00, 84.26, 62.37, 57.55, 41.84, 25.43, 20.55.

From 4.00 g (16 mmol) of the hydroxy lactone **5c** there was obtained 4.56 g (97%) of **5d** as colorless needles with mp 121–123 °C: ^1H NMR ($CDCl_3$) δ 7.60 (m, 5 H), 6.33 (br s, 1 H), 5.10 (dd, J = 3.30 Hz, J = 5.50 Hz, 1 H), 4.35 (ddd, J = 3.52 Hz, J = 3.1 Hz, J = 12.31 Hz, 2 H), 3.31 (d, J = 17.36 Hz, 1 H), 2.73 (d, J = 17.36 Hz, 1 H), 2.08 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.76, 170.40, 167.58, 132.09, 128.68, 126.89, 81.71, 62.43, 58.54, 41.79, 20.66, 20.33.

DIBAL Reduction of Lactones to *erythro*- and *threo*-Pentofuranoses: 2,3-Dideoxy-3-benzamidopentofuranoses (7b) and (8b) and 2,3-Dideoxy-3-benzamido-4-*C*-methyl-

(7) For the stereospecific osmium tetraoxide hydroxylation of allyl systems guided by remote sulfur species, see: Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458. Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459.

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]

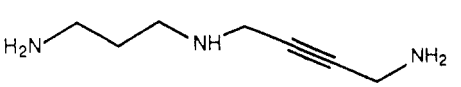
Srinivasan Nagarajan and Bruce Ganem*

Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853

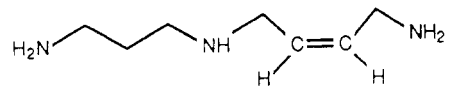
Received April 14, 1987

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]

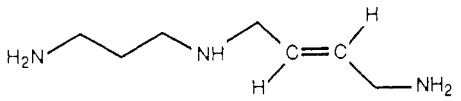
Scheme I



1

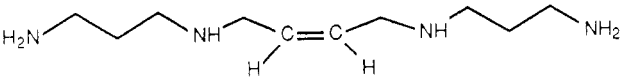


2



3

4



5

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

(2) Morris, D. R.; Marton, L. J., Eds. *Polyamines in Biology and Medicine*; Marcel Dekker Inc.: New York, 1981.

(3) Bachrach, U.; Kaye, A.; Chayen, R., Eds. *Advances in Polyamine Research*; Raven Press, New York, 1983, Vol. 4, and previous volumes in this series.

(4) (a) Bachrach, U. *Function of Naturally Occurring Polyamines*; Academic Press: New York, 1973; p 96. (b) Tabor, H.; Tabor, C. W., Eds. *Methods in Enzymology*; Academic Press: New York, 1983; Vol. 94, p 299.

(5) Fowler, C. J.; Mantle, T. J.; Tipton, K. F. *Biochem. Pharamcol.* **1982**, *31*, 3555.

(6) Rando, R.; Eigner, A. *Mol. Pharmacol.* **1977**, *13*, 1005.

(7) Krantz, A.; Kokel, B.; Sachdeva, Y. P.; Salach, J.; Claesson, A.; Sahlberg, C. In *Drug Action and Design: Mechanism-Based Enzyme Inhibitors*; Kalman, T. I., Ed.; Elsevier/North Holland: Amsterdam, 1979; p 145.

(8) Bey, P.; Bolkenius, F. N.; Seiler, N.; Casara, P. *J. Med. Chem.* **1985**, *28*, 1.

(9) Park, M. H.; Folk, J. E. *J. Biol. Chem.* **1986**, *261*, 14108.

0022-3263/87/1952-5044$01.50/0