Studies Related to the Total Synthesis of Pentostatin. Approaches to the Synthesis of (8*R*)-3,6,7,8-Tetrahydroimidazo-[4,5-*d*][1,3]diazepin-8-ol and *N*-3 Alkyl Congeners (1a)

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A number of synthetic approaches to the (8*R*)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol ring system (**3**) of pentostatin (**1**) are reported. These involve the synthesis of a number of 4-*C*-derivatives of *N*-alkyl-5-amino- and 5-nitro-1*H*-imidazoles derived from 4-methyl-5-nitro-1*H*-imidazole.

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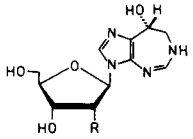
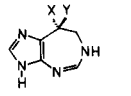
Introduction.

The literature abounds in recent entries of novel and potentially therapeutically significant inhibitors of adenosine deaminase (2) (adenosine aminohydrolase EC 3.5.4.4), including pentostatin (**1**) (3), a nucleoside of unusual structure initially derived from the fermentation beers of *Streptomyces antibioticus* NRRL 3238 (4), and its D-*ribo* analog, coformycin (**2**) (5). Pentostatin represents the most potent inhibitor known of this enzyme showing a $K_i = 2.5 \times 10^{-12}$ *M* against human erythrocytic adenosine deaminase (6). This agent holds considerable promise as a co-drug in combination with other therapeutically useful adenosine-type nucleosides for the treatment of both hematologic malignancies and various solid tumors based on human *in vitro* tissue culture and *in vivo* xenograph studies (7). The drug is currently under phase-I clinical trials in combination of 9-β-D-arabinofuranosyladenine (vidarabine) against acute myelogenous leukemia (8).

The structures of **1** and **2** incorporate a novel 5-7- membered fused aglyconic moiety, *i.e.*, (8*R*)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol (**3**) that (a) contains a chiral center and (b) renders these molecules maximally stable in the *p*H 6.5-10 range. Previous reports from these laboratories (9) have described synthetic efforts which have resulted in a practical synthesis to multigram quantities of pentostatin from readily available precursors. Pivotal to these efforts was the construction of the imidazole ketoaglycone **4**, structurally a vinylogous amide, which was stable enough for subsequent synthetic operations. Reported herein are approaches to the synthesis of **3**, structurally a vinylogous carbinolamine, which would possibly allow for the planned introduction of aglycone chirality preceding glycosylation.



1 R = H
2 R = OH

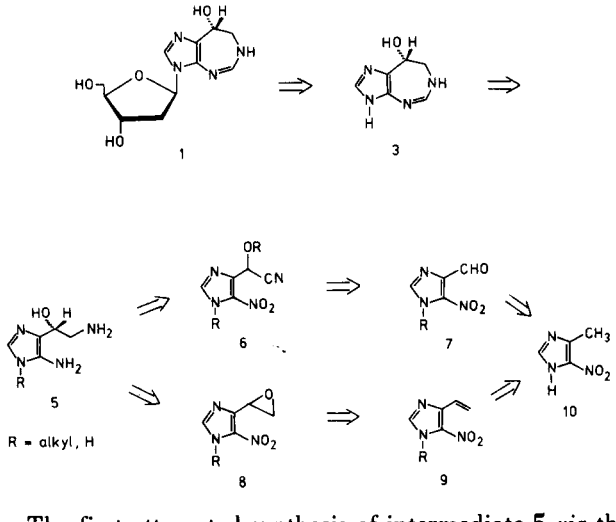


3 X = OH, Y = H
4 X,Y = O

Results and Discussion.

In accordance with the general strategy adumbrated in Scheme I, it was envisioned that the synthesis of aglycone **3** would proceed *via* ring closure of the key imidazole diamine **5**, which should be accessible from either the protected cyanohydrin **6** or epoxide **8**, both of which would be easily prepared from the aldehyde **7** and olefin **9**, respectively. These intermediates in turn should be readily derived from commercially available 4-methyl-5-nitro-1*H*-imidazole (**10**) (10).

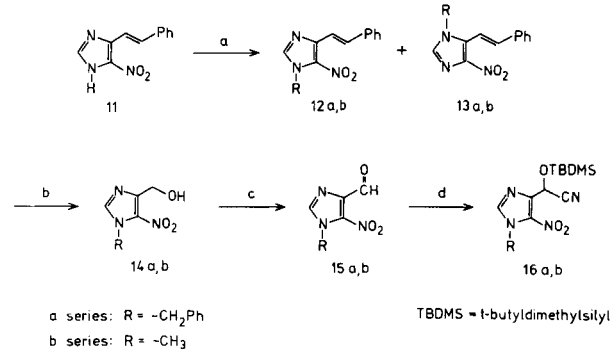
SCHEME I



The first attempted synthesis of intermediate **5** *via* the cyanohydrin route is depicted in Scheme II. Benzylation of 5-nitro-4-(2-phenylethenyl)-1*H*-imidazole (**11**) by the published procedure (9c) afforded in 96% yield a chromatographically separable mixture of the isomeric *N*-benzyl derivatives **12a** and **13a** in a 3:1 ratio, respectively. Ozonolysis of isomer **12a** at −78°, followed by reduction of the ozonide with sodium borohydride, gave pure 5-nitro-1-(phenylmethyl)-1*H*-imidazole-4-methanol (**14a**) in 93% yield. Subsequent conversion to the corresponding carboxaldehyde **15a** proceeded smoothly at 5° in 88% yield using classical Pfitzner-Moffatt conditions. Generation of

the masked cyanohydrin **16a** was effected in 66% yield by room temperature reaction of **15a** with *t*-butyldimethylcyanosilane (11,12) and zinc chloride. This variant of the original Evans procedure (13) which utilized trimethylcyanosilane, is especially useful for those cases in which chromatography of a stable cyanohydrin derivative is desirable (14). Furthermore, we hoped to retain the *t*-butyldimethylsilyl moiety as an alcohol protecting group during subsequent reductive operations. However, to our disappointment, attempted nitrile reduction of **16a** to the primary amine utilizing various procedures, including lithium aluminum hydride (15), diborane-dimethylsulfide complex, or Raney nickel hydrogenation resulted in either unconsumed starting material or gross reaction mixtures containing none of the desired product.

SCHEME II



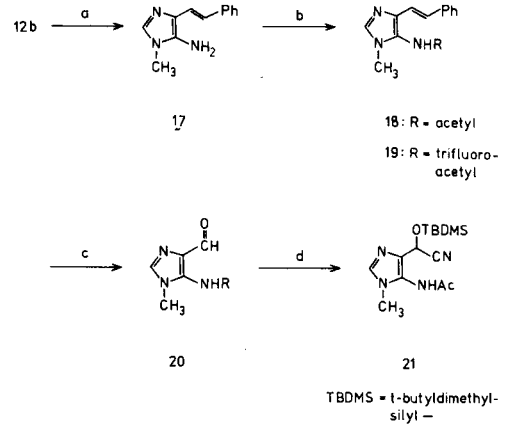
(a) For R = CH_2Ph, see reference 9c; for R = CH_3:TlOEt, DMF, 25°; CH_3I. (b) For **12a,b**: O_3, CH_2Cl_2-CH_3OH, −78°; $NaBH_4$, −40°. (c) DCC, DMSO, dichloroacetic acid, 25°. (d) *t*-Butyldimethylcyanosilane, anhydrous $ZnCl_2$, CH_2Cl_2, 25°.

In an attempt to synthesize structural relatives of **3** containing *N*-3 alkyl substituents, we repeated the above sequence for R = CH_3 (Scheme II). Alkylation of the thallium(I) salt of **11** with methyl iodide furnished in quantitative yield a chromatographically separable mixture of *N*-methyl isomers **12b** and **13b** in a 7:3 ratio, respectively (16), which represents a considerable improvement over the original procedures (17). Identification of each isomer was made by pmr in an analogous fashion as for **12a** and **13a** (9c). Further conversion of **12b** to masked cyanohydrin **16b** *via* intermediates **14a** and **15b** was carried out analogously as described for the *N*-3 benzyl sequence (*vide supra*) without yield optimization. Attempts to effect selective nitrile reduction on **16b** again failed (18).

Since it was suspected that substrate over-reduction due to the presence of the nitro and benzyl functionalities was possibly the culprit in our attempts to effect chemoselective nitrile reduction in **16a**, it was decided to synthesize model compound **21** for further studies (See Scheme III).

Reduction of 1-methyl-5-nitro-4-(2-phenylethenyl)-1*H*-imidazole **12b** with stannous chloride-concentrated hydrochloric acid furnished *(E)*-1-methyl-4-(2-phenylethenyl)-1*H*-imidazol-5-amine hydrochloride (**17**) in 84% yield. Acylation under standard conditions afforded the acetamide **18** or the trifluoroacetamide **19** in 98% and 76% yields, respectively. Ozonolysis of **18** at −78°, followed by reduction of the ozonide with methyl sulfide, provided aldehyde **20** as a glass in 51% yield. Subsequent conversion of **20** to its *t*-butyldimethylcyanosilane adduct **21** was effected in 56% yield (*vide supra*). Surprisingly attempted reduction of **21** by Raney nickel hydrogenation with a variety of hydride reagents resulted in no reaction. Under forcing conditions utilizing Raney cobalt at 130°/1500 psi, a small amount of substrate conversion to an unknown, non-amine product resulted. With these findings in hand, attempts to construct diamine **5** *via* cyanohydrin methodologies were summarily abandoned.

SCHEME III

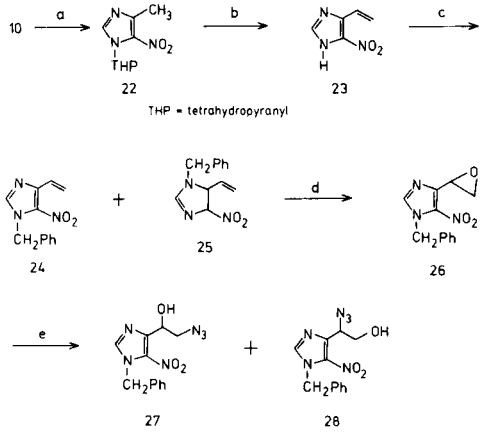


(a) $SnCl_2$·H_2O, concentrated HCl. (b) Ac_2O or trifluoroacetic anhydride, pyridine, 0°. (c) For R = Ac, O_3, CH_2Cl_2, −78°; $(CH_3)_2S$. (d) *t*-Butyldimethylcyanosilane, anhydrous $ZnCl_2$, CH_2Cl_2, 25°.

An alternate approach to diamine **5** *via* the epoxide intermediate **26** is depicted in Scheme IV. The nitroimidazole **10** was converted to its *N*-tetrahydropyranyl derivative **22** in quantitative yield. Without extensive purification, **22** was then subjected to standard Mannich conditions to provide 4-ethenyl-5-nitro-1*H*-imidazole (**23**) in 36% yield. Thallium(I) salt formation, followed by benzylation as previously described, then provided in 61% yield a chromatographically separable mixture of *N*-benzyl isomers **24** and **25** in a 7:3 ratio, respectively (pmr integration). Structural assignments were made in an analogous fashion as for **12a** and **13a** (9c). Epoxidation of vinyl imidazole **24** with *m*-chloroperbenzoic acid afforded in almost

quantitative yield epoxide **26** which was pure by pmr, but unstable to both alumina and silica gel chromatography. Also upon standing at room temperature, **26** slowly decomposed, thus precluding complete characterization. Disappointingly, room temperature reaction of **26** with lithium azide in *N,N*-dimethylformamide afforded, in both poor yield and regioselectivity, a mixture of desired azide **27** and undesired isomer **28** in a 1:3 ratio, respectively (19). At this juncture, synthetic efforts toward 1,3-diazepinone **4** had been completed in a high overall yield and augured well for an eventual synthesis of pentostatin (9). Hence the attempted synthesis of diamine **5** and thence 1,3-diazepenol **3** *via* the epoxide scheme was abandoned.

SCHEME IV



(a) Dihydropyran, *bis*-(*p*-nitrophenyl)phosphate, EtOAc-DMF. (b) 37% aqueous CH_2O, piperidine, H_2O-EtOH, reflux; CH_3I, 25°, triethylamine, reflux. (c) TlOEt, DMF, 25°, then $PhCH_2Br$. (d) For **24**, MCPBA, CH_2Cl_2, 25°. (e) One equivalent LiN_3, DMF, 25°.

Further studies directed toward the successful synthesis of various *N*-3 alkyl congeners of pentostatin with accompanying biological data will be reported shortly (20).

EXPERIMENTAL

Melting points (mp) were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Digilab FTS-14 or Beckman IR-9 prism grating dispersion instrument. Ultraviolet (uv) spectra were taken on a Cary Model 118C recording spectrophotometer. Proton magnetic resonance (pmr) spectra were recorded on a Varian EM-390 or Brüker WH-90 instrument. The Brüker WH-90 was modified with a Nicolet Technology Corporation B-NC12 data acquisition system. Chemical shifts are reported as δ units in parts per million downfield from internal tetramethylsilane. Mass spectra (ms) were obtained on a Finnigan 4120C instrument operating at 70 eV. Combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer.

Thin-layer chromatography (tlc) was performed on E. Merck 5 × 10 cm glass plates coated with silica gel 60F-254, 0.25 mm. Silica gel was E. Merck "Silica Gel 60", 70-230 mesh ASTM.

When necessary, solvents and reagents were dried prior to use. Charcoal refers to activated "Darco" G-60. *In vacuo* refers to 1.0-1.5 torr. All solvents were concentrated on a rotary evaporator at 30-40° (15-20 torr) unless noted otherwise.

(E)-1-Methyl-5-nitro-4-(2-phenylethenyl)-1*H*-imidazole (**12b**) and *(E)*-1-Methyl-4-nitro-5-(2-phenylethenyl)-1*H*-imidazole (**13b**).

To a solution of 25 g (116 mmoles) of 5-nitro-4-(2-phenylethenyl)-1*H*-imidazole, **11** (9c) in 460 ml of *N,N*-dimethylformamide was added at 25° 8.3 ml (117 mmoles) of thallium(I) ethoxide. The mixture was stirred for 1 hour, then treated dropwise during 3 hours with a solution of 15.5 ml (249 mmoles) of iodomethane in 240 ml of *N,N*-dimethylformamide. After the reaction was stirred overnight, the thallium(I) salts were filtered off, the residues were washed well with ether, and the filtrate was concentrated *in vacuo* to a yellow solid which was triturated with *ca.* 1 liter of dichloromethane. A solid (1.7 g) corresponding to starting material was filtered off. The filtrate, containing a *ca.* 7:3 mixture of **12b:13b**, respectively, by pmr (R_f **12b** = 0.63; **13b** = 0.34 in 1:1 ether-tetrahydrofuran), was concentrated slightly to leave a solid that was collected and dried to yield 11.4 g of pure **12b** as deep yellow needles, mp 211.5-213°; [lit (17a,17b) mp 213-214°, 214-215°, respectively]; uv (methanol): 376 (ϵ 17,055), 272 nm (24,415); ir (potassium bromide): 3120, 1628, 1505, 1332, 1322, 760 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 3.89 (s, 3H), 7.27-7.76 (m, overlapping s at δ 7.63, 7H), 8.01 (s, 1H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.54; H, 4.97; N, 18.12.

The filtrate described in the foregoing section was concentrated to dryness, and the resultant solid was purified by silica gel chromatography. Elution with ethyl acetate, then with methanol-ethyl acetate (5:95) gave 4.6 g of additional **12b**, 1.2 g of a mixture of **12b** and **13b**, and 7.3 g of **13b**, mp 133-136°. Crystallization from cyclohexane gave pure **13b** as a yellow solid, mp 145-147°, [lit (17a,17b), mp 143-144°, 150-151°, respectively]; uv (methanol): 358 (ϵ 12,100), 267 nm (21,825); ir (potassium bromide): 3160, 1640, 1550, 1510, 1490 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 3.87 (s, 3H), 7.35-7.80 (m, overlapping s at δ 7.46, 7H), 7.90 (s, 1H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 63.15; H, 5.01; N, 18.17.

Total yield of both isomers, 24.5 g (100% based on recovered starting material).

5-Nitro-1-(phenylmethyl)-1*H*-imidazole-4-methanol (**14a**).

Into a −78° solution of 10.0 g (33 mmoles) of 5-nitro-4-(2-phenylethenyl)-1-(phenylmethyl)-1*H*-imidazole, **12a**, (9c) in 1.2 liters of dichloromethane:methanol (7:5) was bubbled ozone until the initial yellow color dissipated and a blue color persisted (*ca.* 15 minutes). The solution was slowly warmed to −40° under a nitrogen purge to dispel the excess ozone. A solution of 1.27 g (33.6 mmoles) of sodium borohydride in 100 ml of 95% ethanol was added dropwise during 0.5 hour, and the mixture was stirred for 0.5 hour, then treated with 2 ml of acetic acid.

The solution was concentrated to a solid residue which was partitioned between chloroform and water. The chloroform layer was dried (magnesium sulfate), then concentrated to a solid which was dissolved in hot methanol. The solution was decolorized with charcoal, then concentrated to a solid which was recrystallized from cyclohexane-acetone to give 7.1 g (93%) of pure **14a** as a tan solid, mp 124-125°; uv (methanol): 302 (ϵ 7560), 231 nm (3730); ir (potassium bromide): 3270 (br), 1560, 1495, 1370, 730 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 4.61 (d, J = 5.5 Hz, collapses to s with deuterium oxide, 2H), 5.14 (t, J = 5.5 Hz, exchanges deuterium oxide, 1H), 5.53 (s, 1H), 7.04-7.49 (m, 5H), 8.21 (s, 1H).

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.53; H, 4.89; N, 17.90.

1-Methyl-5-nitro-1*H*-imidazole-4-methanol (**14b**).

Reaction of 13.5 g (59 mmoles) of *(E)*-1-methyl-5-nitro-4-(2-phenylethenyl)-1*H*-imidazole (**12b**) dissolved in 2.5 liters of dichloromethane:methanol (3:2) with ozone as previously described for **12a** was followed by ozonide reduction with 1.7 g (46 mmoles) of sodium borohydride in 130

ml of 95% ethanol. The solution was concentrated to a solid that was partitioned between hexane and water. The aqueous layer was then concentrated to a solid which was repeatedly triturated with acetone. The triturates were combined, diluted with 200 ml of cyclohexane, then concentrated to the cloud point on the steam bath. Upon cooling, crystallization afforded 7.1 g of **14b** as a pale yellow solid, mp 146-148°; uv (methanol): 304 (ε 7,890), 231 nm (3240); ir (potassium bromide): 3220 (br), 1555, 1485, 1360, 1025 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 3.89 (s, 3H), 4.61 (d, J = 6.0 Hz, collapses to s with deuterium oxide, 2H), 5.12 (t, J = 6.0 Hz, exchanges deuterium oxide, 1H), 7.96 (s, 1H).

Processing of the mother liquors afforded an additional 1.2 g of product. Total yield: 8.3 g (90%) of **14b** that was used directly without further purification.

5-Nitro-1-(phenylmethyl)-1*H*-imdiazole-4-carboxaldehyde (**15a**).

To a 5° solution of 5.0 g (21.4 mmoles) of the imidazole alcohol **14a**, 13.3 g (64.4 mmoles) of *N,N'*-dicyclohexylcarbodiimide and 50 ml of dimethyl sulfoxide was added carefully 0.9 ml (10.8 mmoles) of dichloroacetic acid. The mixture was warmed to room temperature where it was maintained for 3 hours, then treated with a methanolic solution of 3.2 g (25.2 mmoles) of oxalic acid. After the carbon dioxide evolution had subsided, the precipitated *N,N'*-dicyclohexylurea was filtered off and washed with a minimal quantity of tetrahydrofuran. The filtrate was concentrated to a dimethyl sulfoxide solution which was lyophilized to give a red-orange residue. Additional urea could be precipitated by trituration of the solid with minimal tetrahydrofuran at −78°. After concentration of the solution to an oily residue, the product was precipitated by trituration with ether (prolonged scratching required!) to leave 4.4 g (88%) of **15a** as a pale yellow solid, mp 109-111°; ir (potassium bromide): 3115, 1685, 1495, 840, 730 cm^{-1}; pmr (chloroform-d): δ 5.54 (s, 2H), 7.09-7.50 (m, 5H), 7.64 (s, 1H), 10.37 (s, 1H).

Compound **15a** was used directly without further purification.

1-Methyl-5-nitro-1*H*-imidazole-4-carboxaldehyde (**15b**).

Reaction of 6.6 g (42 mmoles) of the imidazole alcohol **14b**, 25.9 g (125 mmoles) of *N,N'*-dicyclohexylcarbodiimide, 1.72 ml (20.9 mmoles) of dichloroacetic acid, and 100 ml of dimethylsulfoxide, followed by workup as previously described for **15a**, gave 2.8 g of a solid residue whose purification on silica gel, eluting with chloroform:methanol (9:1), afforded 2.39 g (37%) of aldehyde **15b** as an orange-brown solid, mp 86-90°; ir (potassium bromide): 3100, 1690, 1500, 845 cm^{-1}; pmr (chloroform-d): δ 4.04 (s, 3H), 7.62 (s, 1H), 10.38 (s, 1H).

Compound **15b** was used directly without further purification.

α-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-nitro-1-(phenylmethyl)-1*H*-imidazole-4-acetonitrile (**16a**).

To a mixture of 1.0 g (7.1 mmoles) of *t*-butyldimethylcyanosilane (12) and 5 mg of anhydrous zinc chloride at room temperature was added slowly a solution of 1.5 g (6.5 mmoles) of aldehyde **15a** in 30 ml of dichloromethane. The mixture was stirred for 3.5 hours, then poured onto a silica gel column. Elution with 100 ml of hexane, then with ether, followed by evaporation of product fractions, left a solid whose trituration from hexane gave 1.3 g of **16a** as a white solid, mp 68-69°; uv (methanol): 300 nm (ε 6,585); ir (potassium bromide): 1560, 1495, 1370, 840 cm^{-1}; pmr (chloroform-d): δ 0.18 (s, 3H), 0.24 (s, 3H), 0.89 (s, 9H), 5.50 (s, 2H), 6.12 (s, 1H), 7.07-7.44 (m, 5H), 7.54 (s, 1H).

Anal. Calcd. for $C_{18}H_{24}N_4O_3Si$: C, 58.04; H, 6.49; N, 15.04. Found: C, 58.09; H, 6.78; N, 14.81.

Processing of the mother liquors afforded 0.3 g of additional product. Total yield, 1.6 g (66%) of **16a**.

α-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-methyl-5-nitro-1*H*-imidazole-4-acetonitrile (**16b**).

Reaction of a mixture of 150 mg (1.06 mmole) of *t*-butyldimethylcyanosilane (12), 155 mg (1.0 mmole) of aldehyde **15b**, 1 mg of anhydrous zinc chloride, and 5 ml of dichloromethane, followed by purification as previously described for **16a**, gave 173 mg (59%) of product. Crystallization from hexane:ether (1:1) afforded analytically pure **16b**, mp 73.5-74.5°; ir (potassium bromide): 1560, 1500, 1090, 845 cm^{-1}; pmr (chloroform-d): δ 0.19 (s, 3H), 0.26 (s, 3H), 0.89 (s, 9H), 4.01 (s, 3H), 6.13 (s, 1H), 7.54 (s, 1H).

Anal. Calcd. for $C_{12}H_{20}N_4O_3Si$: C, 48.62; H, 6.80; N, 18.90. Found: C, 48.61; H, 6.94; N, 18.58.

(E)-1-Methyl-4-(2-phenylethenyl)-1*H*-imidazol-5-amine Monohydrochloride (**17**).

A suspension of 5.0 g (22 mmoles) of the methyl imidazole derivative **12b**, 19.7 g (87 mmoles) of tin(II) chloride monohydrate, and 110 ml of concentrated hydrochloric acid was stirred for 17 hours at room temperature. The yellow solid was filtered, then suspended in a mixture of 700 ml of chloroform-water (5:2). The biphasic mixture was treated dropwise with 50% aqueous sodium hydroxide with vigorous stirring until all solids dissolved, then the layers were separated. The aqueous layer was extracted twice with chloroform, and the combined organic layers were washed with brine, dried, and concentrated to a solid which was dissolved in 400 ml of ethanol:ether (1:1). The solution was acidified to *p*H 2 with ethanolic hydrogen chloride to precipitate the product. Additional ether was added to complete the precipitation, and the solids were filtered and washed with acetone to give 4.0 g of **17** as a light gray solid, mp 204.5° (dec); uv (methanol): 327 (ε 23,930), 231 nm (10,910); ir (potassium bromide): 3300-3440 (br), 3170 (br), 1660, 960, 750 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 3.61 (s, 3H), 6.29 (br, s, 2H, exchanges with deuterium oxide), 7.03 (d, J = 16.0 Hz, 1H), 7.13-7.58 (m, 7H), 8.70 (s, 1H).

Anal. Calcd. for $C_{12}H_{14}ClN_3 \cdot 0.2H_2O$: C, 60.22; H, 6.06; Cl, 14.81; N, 17.56. Found: C, 59.97; H, 6.24; Cl, 15.19; N, 17.24.

Further processing of the filtrate afforded 0.4 g of additional product, total yield, 4.4 g (84%) of **17**.

(E)-*N*-[1-Methyl-4-(2-phenylethenyl)-1*H*-imidazol-5-yl]acetamide (**18**).

To an ice-cold suspension of 5.0 g (21 mmoles) of the amino imidazole **17** in 42 ml of pyridine was added dropwise 2.0 ml (21 mmoles) of acetic anhydride. After being stirred at 0° for 1 hour, ice was added to the blue solution, and mixture was partitioned between dichloromethane and water. The organic phase was washed with water, dried, and concentrated to give 5.0 g (98%) of pure product as a glass. Crystallization from tetrahydrofuran:hexane gave analytically pure **18** as a white solid, mp 159-160°; uv (methanol): 308 (ε 26,880), 300 (26,200), 233 (12,640), 226 nm (13,850); ir (potassium bromide): 3220 (br), 1690, 1495, 1250, 750 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 2.13 (s, 3H), 3.42 (s, 3H), 7.01 (d, J = 6.0 Hz, 1H), 7.18-7.70 (m, overlapping s at δ 7.60, 7H), 9.69 (br s, 1H, exchanges with deuterium oxide).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.57; H, 6.30; N, 17.30.

(E)-2,2,2-Trifluoro-*N*-[1-methyl-4-(2-phenylethenyl)-1*H*-imidazol-5-yl]-acetamide (**19**).

Reaction of the amino imidazole **17** with trifluoroacetic anhydride on the same scale as described for **18**, followed by purification by silica gel chromatography (eluting with ethyl acetate), gave 4.7 g (76%) of **19** as a white solid, mp 181-183°; uv (methanol): 306 (ε 25,300), 233 (11,540), 226 nm (13,020); ir (potassium bromide): 1735, 1210, 960, 750 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 3.48 (s, 3H), 7.04 (d, J = 6.0 Hz, 1H), 7.20-7.64 (m, 6H), 7.80 (s, 1H), 11.63 (br s, 1H, exchanges deuterium oxide).

Anal. Calcd. for $C_{14}H_{12}F_3N_3O$: C, 56.95; H, 4.10; N, 14.20. Found: C, 57.08; H, 4.13; N, 14.00.

N-(4-Formyl-1-methyl-1*H*-imidazol-5-yl)acetamide (**20**).

A solution of 1.4 g (5.8 mmoles) of imidazole acetamide **18** in 100 ml of dichloromethane and 0.25 ml methanol was ozonized at −78° as previously described for **14a**. Methyl sulfide (5 ml) was added, and the solution was allowed to warm to room temperature. A fine precipitate was separated by centrifugation. The soluble component was concentrated, then chromatographed on silica gel, eluting first with 200 ml of choroform, then with chloroform:methanol (9:1) to yield 490 mg (51%) of **20** as a yellow glass; uv (methanol): 269 nm (ε 6,750); ir (chloroform): 3380

(br), 1715, 1670, 1580, 1385 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 2.07 (s, 3H), 3.42 (s, 3H), 7.70 (s, 1H), 9.59 (s, 1H), 10.19 (br s, 1H, exchanges with deuterium oxide).

Aldehyde **20** was further characterized as its *N,N*-diphenyltetrahydroimidazole derivative (21), mp 188-190° after crystallization from methanol.

Anal. Calcd. for $C_{21}H_{23}N_5O \cdot 0.4CH_3OH$ (for the *N,N*-diphenyltetrahydroimidazole derivative): C, 68.68; H, 6.52; N, 18.71. Found: C, 68.44; H, 6.43; N, 19.03.

N-[4-[Cyano[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1-methyl-1*H*-imidazoyl-5-yl]acetamide (**21**).

A suspension of 1.1 g (6.5 mmoles) of aldehyde **20**, 2.0 g (14 mmoles) of *t*-butyldimethylcyanosilane (12), 50 mg of anhydrous zinc chloride and 50 ml of dichloromethane was stirred at room temperature for 85 hours. The solution was concentrated, and the residue was purified on silica gel, eluting first with 500 ml of chloroform, then with chloroform:methanol (9:1), to give 996 mg (56%) of **21** as a white glass; ir (chloroform): 3420, 1720, 1610, 1095, 840 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 0.09 (s, 3H), 0.13 (s, 3H), 0.87 (s, 9H), 2.09 (s, 3H), 3.40 (s, 3H), 5.64 (s, 1H), 7.60 (s, 1H), 9.67 (br s, 1H, exchanges deuterium oxide).

Anal. Calcd. for $C_{14}H_{24}N_4O_2Si \cdot 0.1H_2O$: C, 54.19; H, 7.86; N, 18.06. Found: C, 54.08; H, 7.78; N, 17.75.

4-Ethenyl-5-nitro-1*H*-imidazole (**23**).

To a mixture of 12.5 g (98 mmoles) of 4-methyl-5-nitro-1*H*-imidazole (**10**), 254 mg of *bis*-(*p*-nitrophenyl)phosphate, and 350 ml of ethyl acetate:*N,N*-dimethylformamide (6:1) was added 100 ml of dihydropyran. The solution was heated under reflux for 1 day, then concentrated to leave a dark brown syrup. Trituration of the residue with dichloromethane gave 2.9 g of recovered **10**. Purification of the triturate by silica gel chromatography, eluting first with 2 liters of chloroform, then 1 liter of chloroform:methanol (4:1) gave 20.7 g (100%) of crude **22** as a glass that was used directly in the following step; pmr (methyl sulfoxide-d_6): δ 1.22-2.22 (m, 6H), 2.60 (s, 3H), 3.33-4.13 (m, 2H), 5.24-5.44 (t, 1H), 7.93 (s, 1H).

A solution of 15.9 g (75 mmoles) of tetrahydropyranyl-1*H*-imidazole **22**, 7.5 ml (76 mmoles) of piperidine, 12.2 ml (152 mmoles) of 37.5% aqueous formaldehyde, 150 ml of ethanol, and 13 ml of water was heated at reflux overnight. The mixture was concentrated to a brown oil which was subsequently dissolved in 250 ml of methanol, then treated with 14.1 ml (226 mmoles) of iodomethane. The solution was stirred at room temperature for 3 hours, treated with 31.2 ml (224 mmoles) of triethylamine, heated at reflux for 1 day, then concentrated to a brown glass. Crystallization from chloroform-ether afforded 25 g of triethylmethylammonium iodide. The mother liquor was concentrated to a dark residue which was purified by silica gel chromatography with stepwise gradient elution using chloroform, followed sequentially by 97:3, 95:5, 90:10, and 80:20 chloroform-methanol to give a solid residue whose trituration from dichloromethane afforded 3.8 g (36%) of **23** as a yellow powder, mp 174-176°; uv (methanol): 322 (ε 9,130), 223 nm (16,070); ir (potassium bromide): 1560, 1490 (br), 1350 (br), 770, 650 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 5.57 (dd, J = 1 Hz, 11.5 Hz, 1H), 5.98 (dd, J = 1 Hz, 18 Hz, 1H), 7.10 (dd, J = 11.5 Hz, 18 Hz, 1H), 7.76 (s, 1H).

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 42.79; H, 3.59; N, 30.39.

4-Ethenyl-5-nitro-1-(phenylmethyl)-1*H*-imidazole (**24**) and Isomer (**25**).

Reaction of 2.1 g (15 mmoles) of vinyl imidazole **23** with 1.1 ml (16 mmoles) of thallium(I) ethoxide, 1.9 ml (16 mmoles) of benzyl bromide, and 45 ml of *N,N*-dimethylformamide as described previously for **13b**, followed by similar workup, gave a solid containing a 7:3 ratio of **24:25**, respectively, as determined by pmr. Silica gel chromatography gave 1.4 g (41%) of **24** as a tan solid, followed by 680 mg (20%) of impure **25**. Isomer **24** (crystallization from acetone-cyclohexane), mp 118-120°; ir (potassium bromide): 1510, 1485, 1365, 840, 700 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 5.55 (s, 2H), 5.62 (dd, J = 2 Hz, 10 Hz, 1H), 6.29 (dd, J = 2 Hz, 18 Hz, 1H), 7.00-7.45 (m, 6H), 8.23 (s, 1H).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.56; H, 4.81; N, 18.10.

Isomer **25**: pmr (methyl sulfoxide-d_6): δ 5.45 (s, 2H), 5.60-5.91 (dd overlapping dd, 2H), 6.73-7.50 (m, 6H), 8.00 (s, 1H).

5-Nitro-4-(2-oxiranyl)-1-(phenylmethyl)-1*H*-imidazole (**26**).

A solution of 1.15 g (5 mmoles) of the vinyl imidazole **24**, 1.3 g (6.4 mmoles) of 85% *m*-chloroperbenzoic acid, and 50 ml of dichloromethane was stirred at room temperature for 50 hours. The mixture was washed successively with 10% aqueous sodium hydroxide, water, and brine, then dried and concentrated to leave 1.2 g (97%) of pure **26** (by pmr) as a yellow syrup; ir (liquid film): 1560, 1490, 1360, 1325, 1240 cm^{-1}; pmr (methyl sulfoxide-d_6): δ 3.09-3.24 (m, 2H), 4.36 (t, J = 3 Hz, 1H), 5.53 (s, 2H), 7.02-7.47 (m, 5H), 8.21 (s, 1H); ms [m/z (relative intensity)] 245 (0.25), 199 (2.51), 154 (5.35), 149 (9.01), 91 (100).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.45; H, 4.68; N, 16.03.

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A mixture of 10.30 g (68.3 mmoles) of *t*-butyldimethylchlorosilane and 6.79 g (68.5 mmoles) of trimethylcyanosilane was slowly heated and distilled through a short, 15-cm Vigreux column. A forerun, bp 65-67°, consisting of trimethylchlorosilane, a center-cut fraction, bp 112-127°, consisting of *t*-butyldimethylchlorosilane and trimethylcyanosilane, was

followed by 7.39 g (77%) of the desired product: bp 166-167°; mp 82-84° [lit (11b) mp 76-78°]; pmr (chloroform-d, 60 MHz): δ 0.29 (6H), 1.00 (9H).

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(18) In order to synthesize a model compound with electronic properties similar to target diamine **5**, nitro alcohol **14b** was subjected to a plethora of nitro reduction methods. Under varying *p*H conditions and conditions in which an incipient amine might be acylated, either complex, nondescript product mixtures were obtained, or starting material was recovered, or both.

(19) Pmr (methyl sulfoxide-d_6): Isomer **27**; δ 3.47-3.62 (m, collapses to dd with deuterium oxide, 2H), 5.07-5.40 (m, collapses to dd with deuterium oxide, 1H), 5.56 (s, 2H), 5.80 (d, exchanges deuterium oxide, 1H), 7.00-7.51 (m, 5H), 8.24 (s, 1H). Isomer **28**; δ 3.80 (br t, J = 6.0 Hz, collapses to d, J = 6.0 Hz, with deuterium oxide, 2H), 4.96 (t, J = 6.0 Hz, 2H), 5.29 (br t, exchanges deuterium oxide, 1H), 5.53 (s, 2H), 7.00-7.44 (m, 5H), 8.24 (s, 1H).

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