($M^{\cdot+}$, <10%), 476 (<5%), 408 (<5%), 245 (30%), 227 (35%), 181 (55%), 153 (100%); accurate mass for $C_{31}H_{42}O_5$ ($M^{\cdot+}$), calcd 494.3033, found 494.3049.

Acknowledgment. We thank Pfizer Central Research, the Science and Engineering Council (U.K.), the Wolfson Foundation, and Northwestern University for generous support of our programs. Additionally we thank the National Institutes of Health for the purchase of a 400-MHz NMR spectrometer (Grant RR02314) and the Midwest Center for Mass Spectrometry, an NSF Regional Instrument Facility (NSF Grant CHE-8211164), for determining several mass spectra. We also thank Professors Amos B. Smith III and David R. Williams for the provision of spectroscopic and experimental data and for helpful discussion; Dr. Hiroshi Mishima at Sankyo Co. Ltd. for discussing data on milbemycin X **3b** prior to publication; Carolyn P. Brock for determining the X-ray crystallographic structure for **45f**; N. S. Mani for preparing additional quantities of **24** and **9**; Todd Miller, Nigel K. Capps, and Gregory G. Graboski for checking spectroscopic data on **3a**; Tony Raynham for assistance in preparation of the paper; and Xenia Kovacs at G. D. Searle and Co. for recording and checking many $[\alpha]_D$ values.

Registry No. **3a**, 56198-39-1; **4**, 10281-55-7; **5**, 16088-62-3; **6**, 102740-25-0; **7**, 104705-92-2; **9**, 82190-18-9; **10**, 104705-88-6; (±)-**11**, 82045-40-7; **11**, 82467-25-2; **12**, 72476-03-0; **13**, 56279-34-6; **14a**, 102740-19-2; **14b**, 102740-24-9; **15**, 79091-60-4; **16a**, 20521-96-4; **16b**, 20521-97-5; **17a**, 104996-17-0; **17b**, 104996-17-0; (±)-**18**, 104996-18-1; (±)-**19**, 104996-19-2; **21**, 78257-87-1; **24**, 104996-21-6; **26**, 105087-12-5; **27**, 105087-13-6; **28**, 105087-14-7; **29**, 104996-20-5; **31**, 105087-15-8; **33**, 104996-22-7; **34a**, 104996-23-8; **34b**, 104996-25-0; **35a**, 104996-24-9; **35b**, 104996-26-1; **36**, 104996-27-2; (±)-**37a**, 104996-28-3; (±)-**37b**, 105087-16-9; (±)-**37b** (diol), 104996-29-4; **38a**, 104996-30-7; **38b**, 104996-31-8; **39a**, 105087-17-0; **39b**, 105087-18-1; **40a**, 93904-58-6; **40b**, 69274-86-8; **41**, 105087-19-2; **44a**, 18370-95-1; **44b**, 104996-32-9; **44c**, 104996-33-0; **45a**, 104996-37-4; **45b**, 104705-89-7; **45c**, 105087-20-5; **45d**, 104996-35-2; **45e**, 104996-36-3; **45f**, 105087-22-7; **46**, 104996-34-1; **48**, 105087-21-6; **48b**, 102140-79-4; **48c**, 105087-27-2; **49a**, 105087-24-9; **49b**, 105087-25-0; **49c**, 105087-23-8; **49d**, 82415-18-7; **49e**, 104996-38-5; **49f**, 104996-39-6; **49g**, 104705-91-1; **50**, 105087-26-1; **51**, 104996-40-9; (*E*)-**52a**, 104705-94-4; (*Z*)-**52a**, 105087-28-3; (*E*)-**52b**, 105087-29-4; (*Z*)-**52b**, 105087-30-7; (*E*)-**52c**, 104759-57-1; (*Z*)-**52c**, 104759-58-2; **54**, 104705-97-7; **55**, 104759-59-3; **56**, 104705-98-8; **57**, 101977-94-0; $MeCH_2C{\equiv}CCO_2Et$, 55314-57-3; MeCOCHO, 78-98-8; $Ph_3P{=}CHCO_2Et$, 1099-45-2; $PhCH(OMe)CO_2H$, 26164-26-1; $H_2N(CH_2)_2NH_2{\cdot}LiC{\equiv}CH$, 6867-30-7; (2*R*,3*S*)-MeCH(OH)CH(Me)Et, 73176-98-4; MeO_2CCO_2Me, 553-90-2; $Ph_3P^+MeBr^-$, 1779-49-3.

Chemistry of Naturally Occurring Polyamines. 10.[1] Nonmetabolizable Derivatives of Spermine and Spermidine

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Received June 13, 1986

Polyamine oxidases (PAO's) play an important role in the oxidative metabolism of spermidine, spermine, and their derivatives. Since the actual oxidation step involves deprotonation at the α-carbon(s) of the amine, *gem*-dimethyl substitution at those sites should retard catabolism. Moreover, synthetic methylated analogues of known biologically active polyamine conjugates may be expected to display enhanced activity and/or longer duration of action. This paper describes the synthesis of stable hydrochloride salts of five *gem*-dimethylspermidines **8**–**12** and two spermine analogues **13** and **14** that were designed to act as PAO inhibitors and to serve as useful probes of complex polyamine biosynthesis.

Naturally occurring polyamines are primary modulators of both normal and pathological cell growth, a fact that has recently stimulated much research into their biosynthesis and metabolism.[2,3] Polyamine oxidases (PAO's) play an important role in the latter process and are widely distributed in plants, bacteria, and fungi as well as in mammalian cells.[4,5] Enzymic oxidation of spermidine (**1**) and spermine (**2**) (and their acetylated derivatives) produces complex, highly labile mixtures of imines, aldehydes, imino aldehydes, and resultant lower amines, depending on the source and type of PAO used.[4,6] Besides helping to regulate intracellular levels of spermidine and spermine, the oxidation of polyamines generates products (including H_2O_2) that are toxic to a variety of cell types and may be involved in the immune response to certain microbial and parasitic pathogens.[7,8]

Most PAO's are flavin-containing enzymes, some of which are Cu^{2+}-dependent.[5,9,10] Although mechanistic details are incompletely understood, it would appear that the amine and flavin combine to form an imine **3** that isomerizes to **4** and hydrolyzes, furnishing aldehyde **5**, amine **6**, and reduced cofactor **7** (see Scheme I).[9] Since the actual oxidation step in this scheme involves proton removal at the carbon α to nitrogen in **3**, we reasoned that *gem*-dimethyl groups at that position would block deprotonation and retard catabolism. Such achiral *gem*-dimethyl polyamines might act as PAO inhibitors and/or serve as useful probes of complex polyamine biosynthesis. Moreover, the corresponding analogues of pharmacologically active polyamine conjugates (e.g., with amino acids, sugars, steroids, phospholipids, and peptides[11]) might ex-

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(6) Croker, S. J.; Loeffler, R. S. T.; Smith, T. A.; Sessions, R. B. *Tetrahedron Lett.* **1983**, *24*, 1559.
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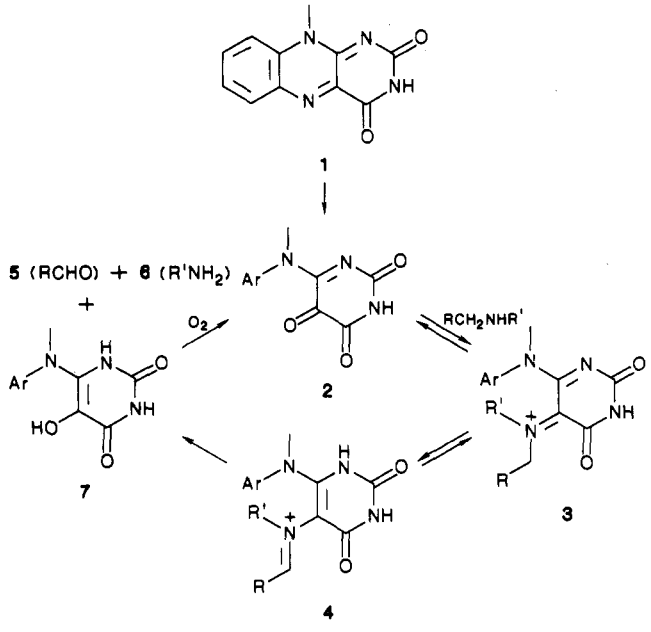
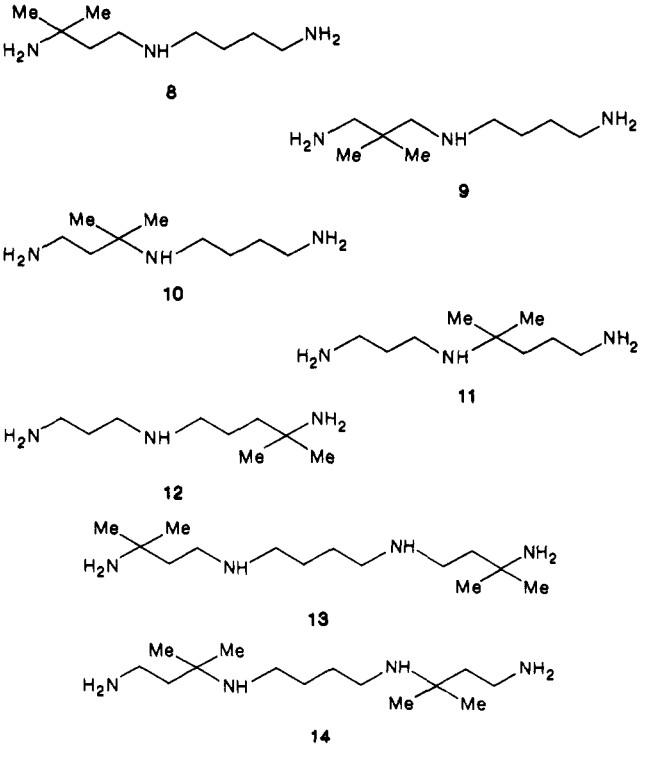
Scheme I



hibit higher in vivo activity by resisting oxidative metabolism. Geminal methyl substitution should block PAO's specific for either *pro-R* or *pro-S* hydrogens, while little affecting the solubility or transport properties of most polyamines.

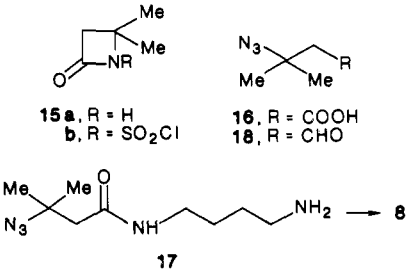
Here we describe the synthesis of stable hydrochloride salts of five *gem*-dimethylspermidines **8**–**12** and two spermine analogues **13** and **14**. While spermidine **9** may still undergo undergo oxidation at N^1, its *gem*-dimethyl groups at C2 should prevent the normal β-elimination to produce acrolein.



Results and Discussion

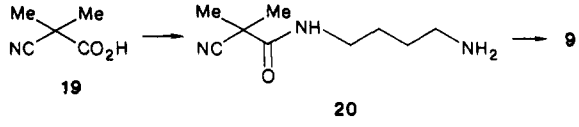
One route to triamine **8** was based on the coupling of a 3-amino-3-methylbutyric acid equivalent with butane-1,4-diamine (putrescine). Azetidinone (**15a**) represented one such equivalent, but it failed to condense with putrescine or γ-aminobutyronitrile even at elevated temperature. β-Lactam **15b** did react with γ-aminobutyronitrile in CH_3OH; however, the product could not be desulfonylated. Another approach, involving conjugate addition of benzylamine to β,β-dimethylacrylic esters, encountered problems in N-debenzylation.

Eventually we discovered that sodium azide underwent smooth addition to dimethylacrylic acid in aqueous acetic acid to afford the previously unknown 3-azido-3-methylbutyric acid (**16**) in 75% yield.[12] Coupling of **16** with

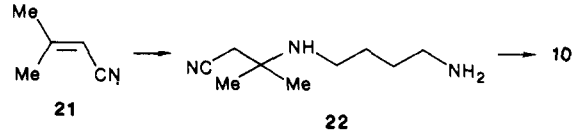


excess 1,4-diaminobutane using the mixed-anhydride method ($ClCO_2Et$, Et_3N, THF) furnished azido amide **17** (72%). However, reduction of the amide group in this substance proved troublesome and gave at best 30–35% of spermidine **8**. To solve this problem, **16** was first reduced with B_2H_6 and then oxidized with pyridinium dichromate (PDC) to azido aldehyde **18**, which smoothly condensed[12] with 1,4-diaminobutane (PtO_2–H_2, EtOH) to form **8** in 64% yield. As expected, **8**, like spermidine, reacted with aqueous formaldehyde to afford the corresponding hexahydropyrimidine which should be useful in the synthesis of conjugates.[11]

To construct triamine **9**, 2-cyano-2-methylpropionic acid (**19**) was prepared from ethyl cyanoacetate and condensed with putrescine (9 equiv) by the mixed-anhydride method ($ClCO_2Et$, Et_3N, THF) to afford amide **20** in 59% yield. This amide was best reduced using diborane (THF, reflux, 2 h) to afford the target polyamine **9** (49%).



For spermidine **10**, conjugate addition of putrescine to β,β-dimethylacrylonitrile (**21**, 1.5 equiv) afforded **22** in 52% yield, along with 10% of a 2:1 adduct (vide infra) that was



easily removed by chromatography. Reduction of **22** to triamine **10** could be achieved using $LiAlH_4$ (22%) or $NaBH_4$–Co_2B (27%);[13] however, product isolation problems were encountered during workup. The best yield of **10** (40%) was obtained with diborane (reflux, 1.5 h, THF).

The synthesis of polyamine **11** began with nitro nitrile **23**, readily prepared by the base-catalyzed addition of 2-nitropropane to acrylonitrile (KOH, EtOH, reflux) in

(11) For a review, see: Ganem, B. *Acc. Chem. Res.* **1982**, *15*, 290.

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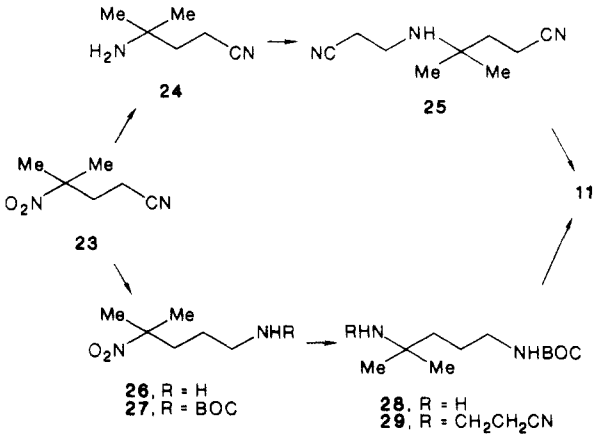
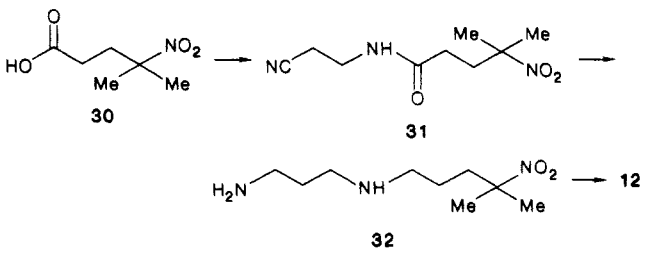
78% yield. In our first route to **11**, the nitro group in **23** was selectively reduced by transfer hydrogenation (10% Pd/C, HCO_2NH_4, CH_3OH) to furnish amino nitrile **24**.[14] Since **24** was unstable and underwent exceptionally facile cyclization during attempts to isolate it, acrylonitrile was added directly to the hydrogenation reaction mixture, giving **25** in 43% overall yield. Dinitrile **25** was also problematic and easily cyclized to the corresponding five-membered amidine. Therefore, it was immediately reduced ($LiAlH_4$, THF, reflux, 5 h, 18%) to spermidine **11**. While this synthetic route was relatively expedient, the resolution of impurities in **11** proved quite difficult and prompted the development of an alternative scheme.

Selective reduction of the nitrile group in **23** (BN_3–THF, 97%) afforded amine **26**, which could be protected as its BOC derivative **27** (BOC–ON, Et_3N, 94%). The nitro



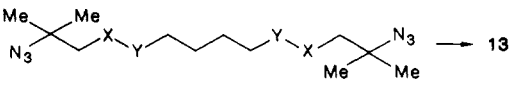
group in **27** was smoothly reduced by $NaBH_4$–Ni_2B according to a new procedure recently developed in our laboratory[15] to furnish differentially protected putrescine analogue **28**. Conjugate addition of **28** to acrylonitrile gave **29** in 81% yield. Hydrolysis of the BOC group and reduction of the nitrile furnished pure samples of **11** (40%). This spermidine derivative will be used to probe the detailed biosynthesis of hypusine, an unusual hydroxylated amino acid derived from lysine and an aminobutyl fragment of spermidine.[16]

The final spermidine analogue, **12**, was synthesized from 4-methyl-4-nitrovaleric acid (**30**), itself prepared by the



condensation of 2-nitropropane with methyl acrylate (Triton B, dioxane, 100 °C, 86%) and subsequent ester saponification. Dicyclohexylcarbodiimide coupling of nitro acid **30** with the fumarate salt of β-aminopropiononitrile afforded **31** in 97% yield. Reduction of both amide and nitrile functions in **31** by BH_3–THF (reflux, 2 h) led to nitro diamine **32** (92%). Although the final reduction of this highly branched nitro compound to triamine **12** could be achieved with Pd/C–HCO_2NH_4 (21% yield), our new $NaBH_4$–Ni_2B method was more than 3 times as efficient, giving **12** in 70% yield.[14]

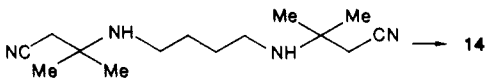
To assemble the carbon framework of spermine **13**, putrescine was coupled with 2 equiv of azido acid **16** ($ClCO_2Et$ method, 95% yield) to give diamide **33**. Unfortunately, azido aldehyde **18** did not cleanly form a 2:1 adduct with putrescine in several attempts at reductive amination. Therefore, diamide **33** was transformed to the



33, X—Y = CONH
34, X—Y = C(OMe)=N
35, X—Y = CH_2NH

sensitive bis(imino ether) **34** (Meerwein's salt, CH_2Cl_2) and then reduced by $NaBH_4$–CH_3OH to diazido diamine **35** (31% for two steps). Some **33** was also recovered from this process, along with the corresponding (partially reduced) monoamide. Finally, **35** was hydrogenated (PtO_2) to **13** (90%; 27% overall yield from 16).

The synthesis of spermine **14** was accomplished by condensing **22** with β,β-dimethylacrylonitrile to afford dinitrile **36** in 67% yield. Reduction of **36** to **14** worked best (53%) with $NaBH_4$–Co_2B in CH_3OH.[13]



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Experimental Section

General Section. Dichloromethane and triethylamine were distilled from CaH_2 prior to use. All reactions were conducted under a nitrogen or argon 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 are expressed relative to internal tetramethylsilane, $CDCl_3$, or HOD at 4.8 ppm (D_2O). Mass spectra were obtained on a computerized AEI MS902 instrument using isobutane as reagent gas. Thin-layer chromatography was carried out on Merck precoated silica gel 60F-254 plates. Flash chromatography refers to the technique of Still et al.[17] Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Synthesis of 3-Azido-3-methylbutyric Acid (16). A solution of sodium azide (Alfa-Ventron, 52 g, 0.8 mol) in water (100 mL) was added to a solution of β,β-dimethylacrylic acid (20 g, 0.2 mol) in glacial acetic acid (50 mL) and the mixture stirred 1 h at room temperature and then heated at 95 °C for 2 days. After cooling, more water (50 mL) was added and the aqueous solution extracted with ether (5 × 200 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to an oily residue that was fractionally distilled (0.017 torr). The fraction distilling at 92–95 °C was collected to afford 21.4 g (75%) of **16** as an oil: ^1H NMR δ 2.56 (s, 2 H), 1.43 (s, 6 H); IR (film) 3090, 2960, 2920, 2080, 1710, 1240 cm^{-1}; CIMS (isobutane) m/e 144 (M + 1, 44%), 116 (M + 1 − 43, 100%).

***N*-(4-Aminobutyl)-3-azido-3-methylbutyramide (17).** To an ice-cold solution of **17** (1.31 g, 9.14 mmol) in THF (40 mL) was added Et_3N (0.93 g, 9.21 mmol) and $ClCO_2Et$ (0.99 g, 9.11 mmol). After 2 h, Et_3N–HCl was filtered under nitrogen and the filtrate added dropwise to a solution of 1,4-diaminobutane (12.5 g, 0.142 mol) in THF (40 mL) at 0 °C. The mixture was stirred 12 h at room temperature, the THF removed in vacuo, and the residue taken up in CH_2Cl_2 (200 mL) and washed with water (50 mL). The aqueous layer was further extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated to an oil. Chromatography (SiO_2, 6:3:1 CH_2Cl_2–CH_3OH–NH_4OH) afforded **17** [1.40 g (72%)] as an oil: ^1H NMR ($CDCl_3$) δ 3.26 (t, 2 H, J = 6.7 Hz), 2.71 (t, 2 H, J = 6.7 Hz), 2.32 (s, 2 H), 1.49–1.58

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(m, 4 H), 1.41 (s, 6 H); IR (film) 3280, 2900, 2840, 2070, 1640, 1540, 1250 cm^{-1}; CIMS (isobutane) m/e 214 (M + 1, 17%), 57 (100%).

Reduction of 17 to *N*-(3-Amino-3-methylbutyl)-1,4-diaminobutane (8). A solution of 17 (0.75 g, 3.54 mmol) in THF (10 mL) was added to a stirred solution of BH_3–THF (1 M, 36 mL, 0.36 mmol) at room temperature under argon and the resulting solution heated to reflux for 1.5 h. The product mixture was cooled and hydrolyzed by careful addition of 6 N HCl (25 mL). When hydrogen evolution had subsided, the contents of the flask were heated to distill the bulk of THF, and the resulting aqueous mixture was refluxed for 3 h. After cooling, the reaction mixture was basified with solid NaOH and extracted with $CHCl_3$ (4 × 75 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Chromatography of the residue (SiO_2, 2:2:1 CH_2Cl_2–CH_3OH–NH_4OH) afforded 8 [0.20 g (33%)] as an oily free base: bp 130 °C (0.01 torr); ^1H NMR ($CDCl_3$) δ 2.61–2.71 (m, 6 H), 1.48–1.58 (m, 6 H), 1.11 (s, 6 H); IR (film) 3300, 2980, 2940, 2860, 1600, 1480 cm^{-1}; CIMS (isobutane) m/e 174 (M + 1, 100%).

A solution of 8 (0.129 g) in H_2O (20 mL) was treated with concentrated HCl (0.5 mL) and the solution concentrated to dryness. The remaining solid was recrystallized from ethanol–H_2O to afford the corresponding trihydrochloride salt: 0.211 g; mp 270 °C dec; ^1H NMR (D_2O) δ 3.08–3.27 (m, 6 H), 2.11 (m, 2 H), 1.80–1.83 (m, 4 H), 1.44 (s, 6 H).

The corresponding hexahydropyrimidine was prepared by dissolving 8 (0.1 g of the free base) in deionized water (4 mL) and adding aqueous 37% formalin solution (50 μL, 1 equiv) at room temperature. After stirring 2 h, the reaction mixture was extracted with $CHCl_3$ (4 × 10 mL), and then the combined organic extracts were dried and concentrated. The residue was chromatographed (SiO_2, 6:3:1 CH_2Cl_2–CH_3OH–NH_4OH) to afford pure hexahydropyrimidine: 91%; ^1H NMR ($CDCl_3$) δ 3.36 (s, 2 H), 2.54 (br m, 2 H), 2.41 (t, 2 H), 2.27 (br m, 2 H), 1.47–1.55 (m, 6 H), 1.10 (s, 6 H); CIMS (isobutane) m/e 186 (M + 1, 100%).

3-Azido-3-methylbutanal (18). Borane in THF (1 M, 30 mL, 30 mmol) was added over 20 min to 16 (4.29 g, 30 mmol) in THF (10 mL) at 0 °C and then the reaction mixture slowly warmed to room temperature and stirred for 2 h. After it was poured into 5% HCl, the reaction mixture was extracted with ether (4 × 200 mL), and the combined organic extracts were washed with $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated to afford 3.51 g (91%) of 3-azido-3-methyl-1-butanol: ^1H NMR ($CDCl_3$) δ 3.77 (t, 2 H, J = 6.4 Hz), 1.76 (t, 2 H, J = 6.4 Hz), 1.34 (s, 6 H); IR (film) 3350, 3480, 3440, 3380, 2100, 1370, 1250 cm^{-1}; CIMS (isobutane) m/e 130 (M + 1, 5%), 87 (100%).

A solution of this alcohol (0.1 g, 0.775 mmol) and PDC (0.50 g, 1.33 mmol) in dry CH_2Cl_2 (1.5 mL) was stirred at room temperature for 16 h. The mixture was diluted with ether (20 mL) and the supernatant passed through a short column of silica gel. The resulting colorless filtrate was concentrated to afford aldehyde 18 [0.09 g (91%)] which, though slightly impure, was used immediately in the synthesis of 8. A small portion was purified by chromatography (SiO_2, CH_2Cl_2): ^1H NMR ($CDCl_3$) δ 9.80 (t, 1 H, J = 2.5 Hz), 2.52 (d, 2 H, J = 2.5 Hz), 1.43 (s, 6 H); IR (film) 2980, 2940, 2110, 1730, 1330 cm^{-1}; CIMS (isobutane) m/e 128 (M + 1, 2%), 84 (100%).

Synthesis of 8 by Reductive Amination of 18. A mixture of 18 (0.85 g, 6.69 mmol), 1,4-diaminobutane (0.30 g, 3.4 mmol), and platinum oxide (0.20 g) in ethanol (50 mL) was hydrogenated for 22 h at 1 atm. The catalyst was filtered and the supernatant concentrated to an oil that was chromatographed (SiO_2, 2:2:1 CH_2Cl_2–CH_3OH–NH_4OH) to afford 0.25 g of 8 whose spectra were identical with material prepared by reduction of 17. Further elution afforded 0.10 g of recovered putrescine, so that the adjusted yield of 8 is 64%.

***N*-(4-Aminobutyl)-2-cyano-2-methylpropionamide (20).** To a 0 °C solution of 2-cyano-2-methylpropionic acid[18] (1.67 g, 14.78 mmol) in THF (50 mL) were added triethylamine (1.50 g, 14.85 mmol) and then $ClCO_2Et$ (1.59 g, 14.64 mmol), and the resulting mixture was stirred 2 h at room temperature. After the precipitated Et_3N–HCl salt was filtered, the filtrate was slowly added to a 0 °C solution of 1,4-diaminobutane (12.0 g, 0.14 mol) in THF (30 mL). The mixture was stirred 12 h at room temperature, the bulk of THF removed in vacuo, and the residue partitioned between CH_2Cl_2 and H_2O (50 mL each). The aqueous layer was further extracted with CH_2Cl_2 (3 × 60 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography of the residue (SiO_2, 6:3:1 CH_2Cl_2–CH_3OH–NH_4OH) gave 20 as an oil: 1.60 g (59%); ^1H NMR ($CDCl_3$) δ 3.30 (t, 2 H, J = 6.5 Hz), 2.74 (t, 2 H, J = 6.5 Hz), 1.49–1.65 (m, 4 H), 1.58 (s, 6 H); IR (film) 3360, 2990, 2940, 2860, 2240, 1680, 1540 cm^{-1}; CIMS (isobutane) m/e 184 (M^+, 100%).

***N*-(3-Amino-2,2-dimethylpropyl)-1,4-diaminobutane (9).** A solution of amide 20 (0.72 g, 3.94 mmol) in THF (10 mL) was added slowly to BH_3–THF (1 M, 27.6 mL, 27.6 mmol) at room temperature. The reaction mixture was heated at reflux for 2 h and then cooled and carefully hydrolyzed with 6 N HCl (25 mL). The bulk of THF was distilled away and the resulting aqueous mixture heated at reflux for 2 h. The mixture was cooled, basified (solid NaOH), and then extracted with $CHCl_3$ (4 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to a residue that was chromatographed (SiO_2, 2:2:1 CH_2Cl_2–CH_3OH–NH_4OH) to give 9 [0.34 g (49%)] as an oil: bp 142 °C (0.07 torr); ^1H NMR ($CDCl_3$) δ 2.69 (t, 2 H, J = 6.6 Hz), 2.59 (t, 2 H, J = 6.1 Hz), 2.51 (s, 2 H), 2.40 (s, 2 H), 1.46–1.51 (m, 4 H), .87 (s, 6 H); IR (film) 3300, 2940, 2880, 1600, 1480 cm^{-1}; CIMS (isobutane) m/e 174 (M^+, 100%).

A solution of 9 (0.05 g) in H_2O (25 mL) was treated with concentrated HCl (0.4 mL) to prepare the corresponding trihydrochloride salt: 0.075 g (93%); mp 265 °C dec; ^1H NMR (D_2O) δ 3.14–3.19 (m, 4 H), 3.11 (s, 2 H), 3.05 (s, 2 H), 1.81 (m, 4 H), 1.19 (s, 6 H).

Hexahydropyrimidine of 9: 52% yield; ^1H NMR (D_2O) δ 3.54 (br s, 2 H), 2.99 (t, 2 H), 2.52 (s, 2 H), 2.4 (s, 2 H), 2.37 (t, 2 H), 1.59–1.71 (m, 4 H), .96 (s, 6 H); CIMS (isobutane) m/e 186 (M + 1, 100%).

***N*-(2-Cyano-1,1-dimethylethyl)-1,4-diaminobutane (22).** A mixture of β,β-dimethylacrylonitrile[19] (10 g, 0.12 mol) and 1,4-diaminobutane (7 g, 0.07 mol) was heated with stirring at 100 °C for 8 days. Methanol (20 mL) wad added, the polymeric precipitate filtered, and the filtrate concentrated in vacuo. The residue was chromatographed (SiO_2, 2:2:1 CH_2Cl_2–CH_3OH–NH_4OH) to afford three fractions. The least polar fraction (R_f 0.88) corresponded to the 2:1 adduct 36 (vide infra). The middle fraction (R_f 0.69) was purified again (SiO_2, 6:3:1 CH_2Cl_2–CH_3OH–NH_4OH) to give 22: 5.5 g (52% based on 1.5 g of recovered butane-1,4-diamine); R_f 0.05; ^1H NMR δ 2.70 (t, 2 H), 2.54 (t, 2 H), 2.46 (s, 2 H), 1.51 (m, 4 H), 1.26 (s, 6 H); IR (film) 3300, 2960, 2920, 2850, 2240 cm^{-1}; EIMS (70 eV) m/e 169 (M^+, 4%), 57 (100%).

***N*-(3-Amino-1,1-dimethylpropyl)-1,4-diaminobutane (10).** A solution of 22 (0.96 g, 5.66 mmol) in THF (10 mL) was added to BH_3–THF (1 M, 22.4 mL, 22.4 mmol) under argon and heated at reflux for 1.5 h. The reaction mixture was cooled, aqueous HCl added (6 N, 8 mL), and the bulk of THF distilled away. The aqueous residue was basified (NaOH pellets) and extracted with $CHCl_3$ (4 × 75 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed (SiO_2, 2:2:1 CH_2Cl_2–CH_3OH–NH_4OH) to afford triamine 10 as an oil: 0.39 g (40%); bp 140 °C (0.03 torr); ^1H NMR ($CDCl_3$) δ 2.66–2.74 (m, 4 H), 2.52 (t, 2 H, J = 6.4 Hz), 1.54 (t, 2 H, J = 7.9 Hz), 1.47 (m, 4 H), 1.06 (s, 6 H); IR (film) 3280, 2960, 2920, 2850, 1650, 1600, 1450, 1380, 1360 cm^{-1}; CIMS (isobutane) m/e 174 (M + 1, 100%).

A solution of 10 (0.10 g) in H_2O (60 mL) was treated with concentrated HCl (1 mL) to afford the corresponding trihydrochloride: 0.16 g (100%); mp 280 °C dec; ^1H NMR (D_2O) δ 3.11–3.22 (m, 6 H), 2.10–2.15 (m, 2 H), 1.81–1.84 (m, 4 H), 1.43 (s, 6 H).

Hexahydropyrimidine of 10: 95% yield; ^1H NMR ($CDCl_3$) δ 3.42 (s, 2 H), 2.84 (m, 2 H), 2.68 (m, 2 H), 2.27 (br m, 2 H), 1.41–1.45 (m, 6 H), 1.04 (s, 6 H); CIMS (isobutane) m/e 186 (M + 1, 100%).

4-Methyl-4-nitro-*n*-pentylamine (26). A solution of 4-methyl-4-nitrovaleronitrile[20] (23; 8.0 g, 0.056 mol) in THF (30 mL)

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was slowly added to BH_3–THF (1 M, 112 mL, 0.112 mol) and the mixture heated at reflux for 2 h. The solution was cooled and hydrolyzed with HCl (6 N, 80 mL) and the bulk of THF removed in vacuo. The aqueous residue was basified (NaOH pellets) and extracted with $CHCl_3$ (3 × 200 mL). The combined extracts were dried ($MgSO_4$) and concentrated to furnish **26** as a pale yellow oil: 7.95 g (97%); ^1H NMR ($CDCl_3$) δ 2.69 (t, 2 H), 1.91–1.96 (m, 2 H), 1.59 (s, 6 H), 1.36–1.46 (m, 2 H); IR (film) 3380, 3000, 2940, 2880, 1540, 1400, 1370, 1350 cm^{-1}; CIMS (isobutane) *m/e* 147 (M + 1, 100%).

***N*-(*tert*-Butoxycarbonyl)-4-methyl-4-nitro-*n*-pentylamine (27).** A mixture of **26** (5.68 g, 0.039 mol), Et_3N (6.04 g, 0.060 mol), and BOC–ON (10.54 g, 0.043 mol) in THF (150 mL) was stirred at room temperature for 12 h. The bulk of THF was then removed in vacuo and the residue taken up in EtOAc (500 mL). The organic layer was washed with 5% NaOH (4 × 50 mL) and water (4 × 50 mL), dried ($MgSO_4$), and concentrated. Chromatography (SiO_2, 1:4 EtOAc–hexanes) of the oily residue afforded **27**: 8.90 g (94%); ^1H NMR ($CDCl_3$) δ 3.12 (q, 2 H), 1.89–1.94 (m, 2 H), 1.58 (s, 6 H), 1.41–1.49 (m, 2 H), 1.44 (s, 9 H); IR (film) 3440, 2980, 2940, 2880, 1700, 1540, 1370, 1350, 1280, 1250, 1170 cm^{-1}; CIMS (isobutane) *m/e* 183 (M + 1, 2%), 57 (100%).

4-[(β-Cyanoethyl)amino]-4-methyl-1-[(*tert*-butoxycarbonyl)amino]pentane (29). Sodium borohydride (0.5 g, 13.16 mmol) was added to a sonicated solution of $NiCl_2 \cdot 6H_2O$ (1.02 g, 4.29 mmol) in CH_3OH (100 mL) and sonication continued for 30 min. To the black suspension of Ni_2B was added a solution of nitro compound **27** (2.11 g, 8.58 mmol) in CH_3OH (10 mL). More $NaBH_4$ (2.11 g, 0.055 mol) was slowly added over 2 h to the sonicated reaction mixture. The black precipitate was then filtered through Celite and washed with CH_3OH. The combined filtrates were concentrated and the residue triturated with $CHCl_3$ (200 mL). Evaporation of the $CHCl_3$ solution afforded 1.58 g of **28** as an oil which, without further purification, was taken up in CH_3OH (30 mL) and treated with acrylonitrile (5 mL). The resulting solution was stirred 18 h at room temperature and concentrated. Chromatography (SiO_2, 5:95 CH_3OH–CH_2Cl_2) furnished the desired product **29**: 1.79 g (81% overall); ^1H NMR ($CDCl_3$ δ 3.11 q, 2 H), 2.82 (t, 2 H), 2.49 (t, 2 H), 1.34–1.53 (m, 4 H), 1.45 (s, 9 H), 1.07 (s, 6 H); IR (film) 3350, 2980, 2940, 2860, 2240, 1700, 1520, 1370, 1180 cm^{-1}; CIMS (isobutane) *m/e* 270 (M + 1, 44%), 214 (100%).

***N*-(4-Amino-1,1-dimethylbutyl)-1,3-diaminopropane (11).** BOC–amine **29** (1.79 g, 6.65 mmol) was stirred with HCl (3 N, 50 mL) for 0.5 h at room temperature. The reaction mixture was cooled in ice and basified with NaOH pellets. The basic layer was extracted with $CHCl_3$ (3 × 150 mL), and the combined extracts were dried ($MgSO_4$) and concentrated to afford 1.02 g (91%) of 4-[(β-cyanoethyl)amino]-4-methyl-1-aminopentane (not shown in text): ^1H NMR ($CDCl_3$) δ 2.82 (t, 2 H), 2.68 (t, 2 H), 2.47 (t, 2 H), 1.36–1.44 (m, 4 H), 1.07 (s, 6 H); IR (film) 3300, 2960, 2940, 2860, 2240, 1480 cm^{-1}; CIMS (isobutane) *m/e* 170 (M + 1, 41%), 57 (100%).

This sample was dissolved in THF (20 mL), added slowly to BH_3–THF (1 M, 30 mL, 30 mmol) at room temperature, and then heated at reflux for 2 h. The cooled reaction mixture was hydrolyzed by careful addition of HCl (6 N, 25 mL) and the bulk of the THF distilled away. The aqueous residue was basified with NaOH pellets and then extracted with $CHCl_3$ (4 × 50 mL). Drying ($MgSO_4$) and concentration afforded an oily residue that was chromatographed (SiO_2, 2:2:1 CH_2Cl_2–CH_3OH–NH_4OH) to afford pure **11**: 0.45 g (44%); bp 147 °C (0.1 torr); 40% from **29**; ^1H NMR ($CDCl_3$) δ 2.75 (t, 2 H), 2.67 (t, 2 H), 2.56 (t, 2 H), 1.57 (m, 2 H), 1.35–1.43 (m, 4 H), 1.05 (s, 6 H); IR (film) 3380, 3300, 2940, 2880, 1600, 1470 cm^{-1}; CIMS (isobutane) *m/e* 174 (M + 1, 10%), 57 (100%).

A solution of **11** (0.45 g) in H_2O (125 mL) was treated with concentrated HCl (3 mL) to afford the corresponding trihydrochloride: 0.74 g (100%); mp 260 °C dec; ^1H NMR (D_2O) δ 3.05–3.22 (m, 6 H), 2.06–2.17 (m, 2 H), 1.79 (m, 4 H), 1.41 (s, 6 H).

Hexahydropyrimidine of **11**: 84% yield; ^1H NMR ($CDCl_3$) δ 3.53 (s, 1 H), 3.39 (d, 1 H), 2.59–2.79 (m, 6 H), 1.37–1.63 (m, 6 H), 1.01 (s, 6 H); CIMS (isobutane) *m/e* 186 (M + 1, 100%).

***N*-(β-Cyanoethyl)-4-methyl-4-nitrovaleramide (31).** Dicyclohexylcarbodiimide (1.68 g, 8.17 mmol) was added to a 0 °C solution of 4-methyl-4-nitrovaleric acid[21] (1.19 g, 7.43 mmol) in CH_2Cl_2 (25 mL) and the resulting solution stirred 2 h. Precipitated dicyclohexylurea was filtered and washed with CH_2Cl_2, and the combined filtrates were cooled to 0 °C during the addition of β-aminopropionitrile fumarate salt (1.14 g, 8.91 mmol). The cooling bath was removed after 2 h and the reaction mixture stirred an additional 10 h at room temperature. The solvent was removed in vacuo and the residue taken up in EtOAc (150 mL) and then washed successively with aqueous citric acid (1 N, 3 × 30 mL), $NaHCO_3$ (3 × 30 mL), and brine (100 mL). Drying ($MgSO_4$) and concentration afforded an oil that was chromatographed (SiO_2, 4:96 CH_3OH–CH_2Cl_2). The desired amide **31** was obtained as an oil: 0.78 g (97%); ^1H NMR ($CDCl_3$) δ 3.48 (q, 2 H, *J* = 6.6 Hz), 2.6 (t, 2 H, *J* = 6.6 Hz), 2.22 (m, 4 H), 1.59 (s, 6 H); IR (film) 3300, 2940, 2240, 1650, 1540, 1350 cm^{-1}; CIMS (isobutane) *m/e* 214 (M + 1, 45%), 57 (100%).

***N*-(4-Methyl-4-nitropentyl)-1,3-diaminopropane (32).** A solution of amide **31** (1.21 g, 5.68 mmol) in THF (10 mL) was added slowly to BH_3–THF (1 M, 41 mL, 41 mmol) at room temperature and the resulting solution brought to reflux for 2 h. After cooling, the reaction mixture was carefully hydrolyzed with HCl (6 N, 25 mL) and the bulk of THF subsequently distilled. The aqueous residue was cooled, basified (NaOH pellets), and then extracted with $CHCl_3$ (3 × 75 mL). The combined extracts were dried ($MgSO_4$) and concentrated. Chromatography of the residue (6:3:1 CH_2Cl_2–CH_3OH–NH_4OH) afforded **32** [1.10 g (95%)] as an oil: ^1H NMR ($CDCl_3$) δ 2.74 (t, 2 H, *J* = 6.8 Hz), 2.64 (t, 2 H, *J* = 6.9 Hz), 2.60 (t, 2 H, *J* = 7.1 Hz), 1.91–1.96 (m, 2 H), 1.58–1.64 (m, 2 H), 1.58 (s, 6 H), 1.40–1.50 (m, 2 H); IR (film) 3300, 2940, 2860, 1540, 1350 cm^{-1}; CIMS (isobutane) *m/e* 204 (M + 1, 100%).

***N*-(4-Amino-4-methylpentyl)-1,3-diaminopropane (12).** To a sonicated solution of $NiCl_2 \cdot 6H_2O$ (0.25 g, 1.06 mmol) in CH_3OH (22 mL) was added $NaBH_4$ (0.12 g, 3.29 mmol). Sonication was continued for 30 min, and then a solution of **32** (0.43 g, 2.12 mmol) in CH_3OH was added to the black suspension of Ni_2B, followed by more $NaBH_4$ (0.46 g, 12.10 mmol) in portions over 2 h. The mixture was filtered through Celite and the collected solid washed with CH_3OH and NH_4OH. The combined methanol filtrates and NH_4OH wash were concentrated separately. Each residue was triturated with hot $CHCl_3$ (200 mL), and the combined $CHCl_3$ fractions were concentrated. Chromatography of the residue (SiO_2, 2:2:1 CH_2Cl_2–CH_3OH–NH_4OH) afforded 0.25 g (70%) of pure **12** as an oil: bp 145 °C (0.01 torr); ^1H NMR ($CDCl_3$) δ 2.75 (t, 2 H, *J* = 6.9 Hz), 2.66 (t, 2 H, *J* = 7.1 Hz), 2.59 (t, 2 H, *J* = 6.9 Hz), 1.64 (m, 2 H), 1.48–1.54 (m, 2 H), 1.33–1.39 (m, 2 H), 1.09 (s, 6 H); IR (film) 3300, 2960, 2940, 2880, 1600, 1470 cm^{-1}; CIMS (isobutane) *m/e* 174 (M + 1, 100%).

A solution of **12** (.25 g) in H_2O (30 mL) was treated with concentrated HCl (0.5 mL) to afford the corresponding trihydrochloride salt: 0.42 g; mp 260 °C dec; ^1H NMR (D_2O) δ 3.16, 3.22 (2 t, 6 H), 2.17 (m, 2 H), 1.78–1.82 (m, 4 H), 1.41 (s, 6 H).

Hexahydropyrimidine of **12**: 94% yield; ^1H NMR (D_2O) δ 3.39 (s, 2 H), 2.74 (t, 2 H), 2.63 (m, 2 H), 2.33 (m, 2 H), 1.62 (m, 2 H), 1.44–1.54 (m, 2 H), 1.31–1.36 (m, 2 H), 1.08 (s, 6 H); CIMS (isobutane) *m/e* 186 (M + 1, 100%).

***N,N'*-Bis(3-azido-3-methylbutyryl)-1,4-diaminobutane (33).** To a cooled (0–5 °C) solution of **17** (2.0 g, 14 mmol) in THF (60 mL) under N_2 was added triethylamine (1.42 g, 14.05 mmol) follwed by $ClCO_2Et$ (1.52 g, 14.03 mmol) and the resulting solution stirred for 2 h. Triethylamine hydrochloride was removed by filtration and the filtrate cooled in an ice bath while a solution of 1,4-diaminobutane (0.62 g, 7.05 mmol) in THF (15 mL) was added. After the mixture was stirred 16 h at room temperature, the bulk of solvent was removed in vacuo and the residue dissolved in CH_2Cl_2 (200 mL). The organic solution was washed with citric acid (1 M, 100 mL), dried ($MgSO_4$), and concentrated to afford nearly pure product. Chromatography (SiO_2, 92:8 CH_2Cl_2–CH_3OH) afforded pure **33**: 2.24 g (95%); mp 62–64 °C; ^1H NMR

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($CDCl_3$) δ 3.29 (m, 4 H), 2.33 (s, 4 H), 1.54–1.56 (m, 4 H), 1.41 (s, 12 H); IR (film) 3290, 2950, 2920, 2080, 1640, 1540, 1240 cm^{-1}; CIMS (isobutane) m/e 339 (M + 1, 31%), 98 (100%).

***N,N'*-Bis(3-azido-3-methylbutyl)-1,4-diaminobutane (35).** A mixture of bisamide **33** (0.757 g, 2.24 mmol) and trimethyloxonium fluoroborate (2.32 g, 15.68 mmol) in dry CH_2Cl_2 (15 mL) was stirred at room temperature for 20 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with cold dilute aqueous Na_2CO_3 (50 mL). The organic phase was dried and concentrated to afford the oily bis(imino ether) **34**: NMR ($CDCl_3$) δ 3.69, 3.62 (2 s, each 3 H). Compound **34** was immediately dissolved in anhydrous CH_3OH (20 mL) and cooled in ice water. Sodium borohydride was added in five or six portions over 1 h and the reduction allowed to proceed for 20 h. The solvent was evaporated and the resulting colorless solid triturated with hot $CHCl_3$ (4 × 50 mL). The combined $CHCl_3$ fractions were concentrated to a colorless oil. Flash chromatography (SiO_2, 50:50:1.5 CH_2Cl_2–CH_3OH–NH_4OH) afforded (in order of elution) diamide **33** (0.15 g), the corresponding (partially reduced) diazido monoamide [0.20 g (28%)] and diamine **35** [0.17 g (31% based on recovered **33**)]. Diazido monoamide (structure not shown): ^1H NMR ($CDCl_3$) δ 3.26 (t, 2 H, J = 6.6 Hz), 2.61–2.71 (m, 4 H), 2.31 (s, 2 H), 1.65–1.71 (m, 2 H), 1.53–1.57 (m, 4 H), 1.41 (s, 6 H), 1.29 (s, 6 H); IR (film) 3300, 2980, 2940, 2360, 2100, 1650, 1550, 1370, 1250 cm^{-1}; CIMS (isobutane) m/e 325 (M + 1, 100%). Diamine **35**: ^1H NMR ($CDCl_3$) δ 2.59–2.70 (m, 8 H), 1.50–1.71 (m, 8 H), 1.29 (s, 12 H); IR (film) 3300, 2980, 2940, 2860, 2100, 1470, 1370, 1250 cm^{-1}; CIMS (isobutane) m/e 311 (M + 1, 87%), 84 (100%).

***N,N'*-Bis(3-amino-3-methylbutyl)-1,4-diaminobutane (13).** A mixture of **35** (0.14 g, 0.45 mmol) and PtO_2 (0.10 g) in ethanol (20 mL) was stirred under an atmosphere of H_2 for 20 h. After the catalyst was filtered and rinsed with ethanol, the combined filtrates were concentrated to afford pure **13**: 0.11 g (90%); ^1H NMR ($CDCl_3$) δ 2.61–2.69 (m, 8 H), 1.52–1.58 (m, 8 H), 1.11 (s, 12 H); IR (film) 3300, 2980, 2940, 1470 cm^{-1}; CIMS (isobutane) m/e 259 (M + 1, 100%).

A solution of **13** (0.060 g) in H_2O (2 mL) was treated with concentrated HCl (0.3 mL) and concentrated. The residue was dried in vacuo to afford 0.093 g (99%) of the tetrahydrochloride: mp 195–210 °C dec; ^1H NMR (D_2O) δ 3.18–3.27 (m, 8 H), 2.08–2.14 (m, 4 H), 1.84 (m, 4 H), 1.44 (s, 12 H).

***N,N'*-Bis(2-cyano-1,1-dimethylethyl)-1,4-diaminobutane (35).** A mixture of **22** (1.23 g, 7.25 mmol) and β,β-dimethylacrylonitrile (1.5 g, 18.5 mmol) was heated at 100 °C for 4 days. Methanol (2–3 mL) was added and the supernatant filtered and then chromatographed (SiO_2, 6:3:1 CH_2Cl_2–CH_3OH–NH_4OH) to afford unreacted **22**, 0.89 g. A less polar fraction containing **35** was rechromatographed (3:97 CH_3OH–CH_2Cl_2) to afford pure **35** [0.33 g (67% based on recovered **22**)] as a yellow oil: ^1H NMR ($CDCl_3$) δ 2.55 (t, 4 H, J = 6.2 Hz), 2.45 (s, 4 H), 1.55–1.52 (m, 4 H), 1.24 (s, 12 H); IR (film) 3340, 2980, 2940, 2860, 2240, 1680, 1470, 1390 cm^{-1}; CIMS (isobutane) m/e 251 (M + 1, 51%), 210 (100%).

***N,N'*-Bis(3-amino-1,1-dimethylpropyl)-1,4-diaminobutane (14).** To a solution of dinitrile **36** (0.097 g, 0.391 mmol) and $CoCl_2 \cdot 6H_2O$ (0.372 g, 1.56 mmol) in CH_3OH (5 mL) was added excess $NaBH_4$ in small portions (1-g total) over 3 h. A black precipitate (Co_2B) appeared, and hydrogen was evolved. Concentrated HCl (6 mL) was added to decompose the boride, the reaction mixture was concentrated, and the residue was partitioned between $CHCl_3$ and concentrated NH_4OH. The aqueous layer was further dried ($MgSO_4$) and concentrated. Chromatography of the oily residue (SiO_2, 2:2:1 CH_2Cl_2–CH_3OH–NH_4OH) afforded pure **14**: 0.053 g (53%); ^1H NMR (D_2O) δ 2.80–2.69 (m, 8 H), 1.55–1.72 (m, 8 H), 1.23 (s, 3 H), 1.17 (s, 9 H); (CD_3OD) δ 2.99 (t, 4 H, J = 7.4 Hz), 2.75 (m, 4 H), 1.34 (s, 3 H), 1.25 (s, 9 H); IR (film) 3400, 2980, 2940, 2860, 1580, 1220 cm^{-1}; CIMS (isobutane) m/e 259 (M + 1, 100%).

A solution of **14** (0.116 g, .45 mmol) in H_2O (5 mL) was treated with concentrated HCl (0.5 mL) and the solution concentrated to dryness, affording the corresponding tetrahydrochloride salt: 0.18 g; mp >270 °C; ^1H NMR (D_2O) δ 3.15–3.21 (m, 8 H), 2.09–2.14 (m, 4 H), 1.81–1.85 (m, 4 H), 1.44 (s, 12 H).

Acknowledgment. We are grateful to the National Institutes of Health (Grant AM 26754) for generous support of this program. The Cornell Nuclear Magnetic Resonance Facility is supported by grants from the NSF (CHE 7904825, PCM 8018643) and NIH (RR02002).

Registry No. **8**, 105090-74-2; **8**·3HCl, 105091-03-0; **9**, 105090-79-7; **9**·3HCl, 105090-95-7; **10**, 105103-53-5; **10**·3HCl, 105090-97-9; **11**, 105090-85-5; **11**·3HCl, 105090-99-1; **12**, 102834-09-3; **12**·3HCl, 105102-23-6; **13**, 105090-92-4; **13**·4HCl, 105090-91-3; **14**, 105090-94-6; **14**·4HCl, 105091-02-9; **16**, 105090-72-0; **16** (R = CH_2OH), 105090-76-4; **17**, 105090-73-1; **18**, 105090-77-5; **19**, 22426-30-8; **20**, 105090-78-6; **21**, 4786-24-7; **22**, 105090-80-0; **23**, 16507-00-9; **26**, 5201-61-6; **27**, 105090-81-1; **28**, 105090-82-2; **29**, 105090-83-3; **30**, 32827-16-0; **31**, 105090-86-6; **32**, 102834-07-1; **33**, 105090-87-7; **34**, 105090-88-8; **35**, 105090-89-9; **35**(monoamide), 105090-90-2; **36**, 105090-93-5; β,β-dimethylacrylic acid, 541-47-9; 1,4-diaminobutane, 110-60-1; 1-(1-aminobut-4-yl)-4,4-dimethylhexahydropyrimidine, 105090-75-3; 4-[(β-cyanoethyl)amino]-4-methyl-1-aminopentane, 105090-84-4; β-aminopropionitrile·fumarate salt, 352-96-5; 1-(1-aminobut-4-yl)5,5-dimethylhexahydropyrimidine, 105090-96-8; 1-(1-aminobut-4-yl)6,6-dimethylhexahydropyrimidine, 105090-98-0; 1-(1-amino4-methylpent-4-yl)hexahydropyrimidine, 105091-00-7; 1-(2-amino-2-methylpent-5-yl)hexahydropyrimidine, 105091-01-8; spermine, 71-44-3; spermidine, 124-20-9.