# Aliphatic Amino Azides as Key Building Blocks for Efficient Polyamine Syntheses

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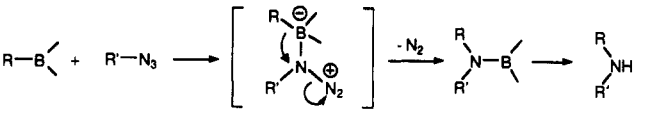
New routes to open-chain polyamines have been developed using aliphatic amino azides as common precursors for the construction of the carbon–nitrogen framework. These α,ω-diaminoalkane synthetic equivalents were combined with (ω-halogenoalkyl)dichloroboranes to extend the polyamine chain from the azido moiety. An extension from the free amino group can also be achieved *via* a Michael type addition with acrylonitrile or a reductive amination with a γ-azido ketone. Further transformations led to a large variety of regioselectively C- or (and) N-substituted polyamines.

Polyamines such as putrescine, spermidine, and spermine are ubiquitous biomolecules which play major roles in cellular differentiative and proliferative processes. For example, the elevation of polyamine levels in human subjects can be correlated with the rate of proliferation of cancer cells.[1] In addition to their presence in native form, they often occur conjugated with sugars,[2] steroids,[3] phospholipids,[4] aminoacids,[5] peptides[6] and are also substructural units of numerous alkaloids.[7] Many of these natural products have shown biological activity as antibiotic, antiproliferative, or immunosuppressive agents.[8]

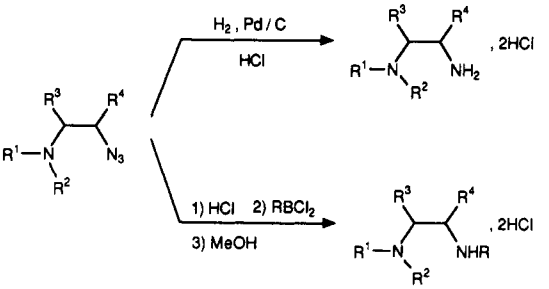
In view of this considerable medicinal interest, a great deal of effort has been devoted to the design of new convenient routes to polyamine analogues. Most syntheses required the creation of a new carbon–nitrogen bond that has been accomplished *via* various reactions: alkylation, acylation, reductive amination, Michael type addition.[9] But, to the best of our knowledge, the reductive alkylation of an azide by a borane, an efficient chemoselective secondary amine synthesis discovered by H. C. Brown *et al.* in 1971.[10] (Scheme I), was never employed.

We have recently demonstrated the utility of 1,2-disubstituted 1-amino-2-azidoethanes for preparing unsymmetrical vicinal diamines (Scheme II).[11]

**Scheme I**



**Scheme II**



As an extension of this work, we now report new approaches for the synthesis of selectively C- or (and) N-substituted acyclic polyamines where ω-aminoalkyl azides **1** are used as key building blocks.[12] The synthetic interest of such bifunctional compounds lies in the fact that each nitrogen site reacts independently. This enables the extension of the chain with complete regiocontrol by reductive alkylation with (ω-halogenoalkyl)dichloroboranes (path 1) or, when $R^1$ = H, by Michael addition to acrylonitrile or reductive amination of a γ-azido ketone (path 2). Furthermore, it circumvents the use of protective and deprotective steps usually employed when starting from the corresponding 1, ω-diamines (Scheme III).

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(6) Hettinger, T. P.; Kurylo-Borowska, Z.; Craig, L. C. *Ann. N.Y. Acad. Sci.* **1970**, *171*, 1002. Sakai, N.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 3183.

(7) Wasserman, H. H.; Wu, J. S. *Heterocycles* **1982**, *17*, 581. Guggisberg, A.; Hesse, M. In *The Alkaloids*; Brossi, A., Ed., Academic Press: New York, 1983, *22*, 85.

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(9) For a recent review, see: Bradshaw, J. S.; Krakowiak, K. E.; Yzatt, R. M. *Tetrahedron* **1992**, *48*, 4475. For additional recent references, see also: Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* **1991**, *74*, 654. Edwards, M. L.; Stemerick, D. M.; Bitonti, A. J.; Dumont, J. A.; Mc Cann, P. P.; Bey, P.; Sjoerdsma, A. *J. Med. Chem.* **1991**, *34*, 569. Cohen, G. M.; Cullis, P. M.; Hartley, J. A.; Mather, A.; Symons, M. C. R.; Wheelhouse, R. T. *J. Chem. Soc. Chem. Commun.* **1992**, 298. Araryo, M. J.; Ragnarsson, U.; Almeida, M. L. S.; Amaral Trigo, M. J. *J. Chem. Res. (S)* **1992**, 120. Okawara, T.; Uchiyama, K.; Okamoto, Y.; Yamasaki, T.; Furukawa, M. *J. Chem. Res. (S)* **1992**, 264. Lakanen, J. R.; Coward, J. K.; Pegg, A. E. *J. Med. Chem.* **1992**, *35*, 724.

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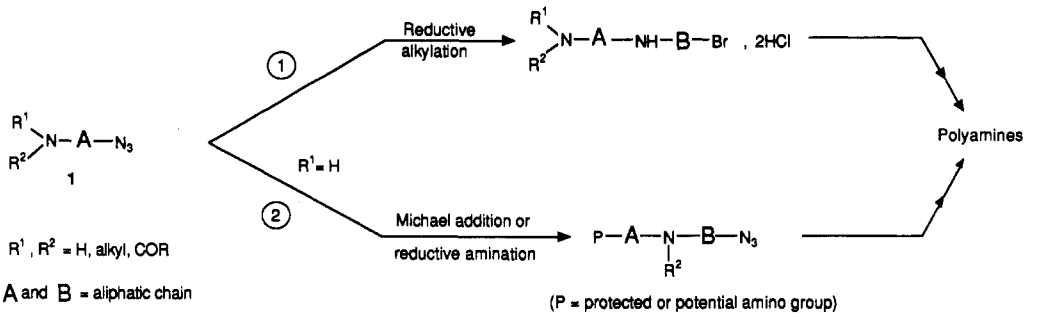
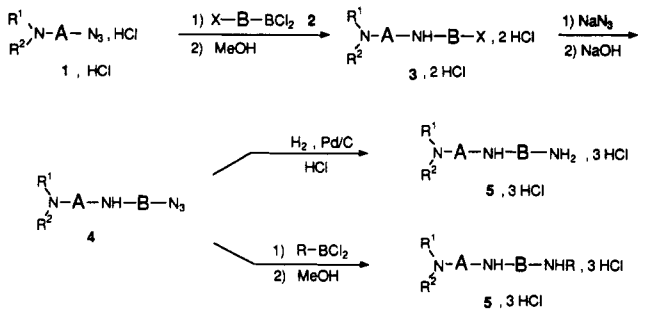
0022-3263/93/1958-3736$04.00/0 

**Scheme III**



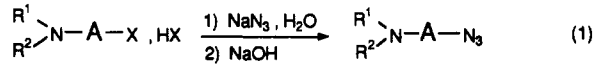

**Scheme IV**




## Results and Discussion

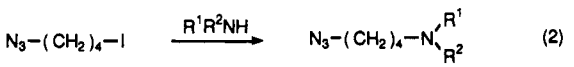
ω-Aminoalkyl azides **1** were prepared according to various procedures.

(1) Treatment of an ω-halogeno amine hydrohalide with $NaN_3$ in refluxing water (**1a-g**) (eq 1).



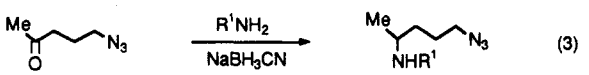

(1)

(2) Reaction of 4-iodo-1-azidobutane with excess of amine (**1h, 1i**) (eq 2).



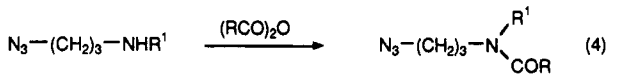

(2)

(3) Reductive amination of 5-azidopentan-2-one (**1j–1l**) (eq 3).




(3)

(4) Acylation of **1b** with acetic or trifluoroacetic anhydride (**1m, 1n**) (eq 4).




(4)

The first route to acyclic polyamines is outlined in Scheme IV.

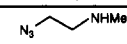
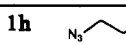
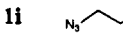
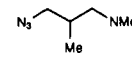
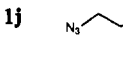
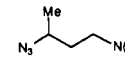
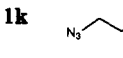
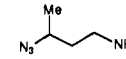
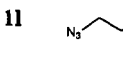
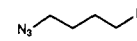
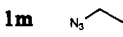
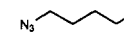
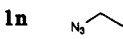
The appropriate dichloroboranes **2** were prepared as described earlier from the corresponding boronic esters.[13,14] 1, ω-Aminoalkyl azide hydrochlorides **1**·HCl were converted to diamine dihydrochlorides **3** with good yields by reaction with **2** followed by methanolysis (Table II).[10,11]

Reaction of **3**·2HCl with sodium azide in water followed by treatment with NaOH produced azide **4** with good yields (Table III), except for **4c** where a competitive intramolecular cyclization occurred leading to a 35/65 mixture of **4c**, 2HCl and **6**·2HCl (Scheme V).

Catalytic hydrogenation of **4** in the presence of aqueous HCl or reductive alkylation with a dichloroborane followed by methanolysis afforded the triamine trihydrochlorides **5**·3HCl (Table IV).

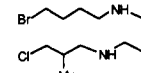
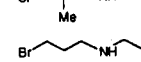
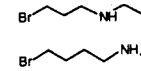
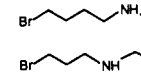
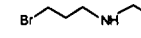
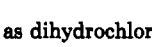
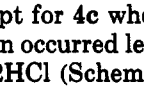
The above results clearly demonstrate the synthetic potential of this approach. Yields in the different steps are good and no sophisticated purification is necessary. For example, the diamines **3** are easily obtained as their dihydrochlorides by filtration after addition of diethyl ether to the crude mixture. Selected ω-aminoalkyl azides **1** and (ω-halogenoalkyl)dichloroboranes **2** have been used to test the viability of this sequence, but it can extended to a large variety of starting compounds and, therefore, to a large variety of substituted triamines. It should also be emphasized that the reductive alkylation with boranes is

**Table I. Synthesis of ω-Aminoalkyl Azides 1**

| | compound (% yield)[a] | % yield[a] | | compound | % yield[a] |
|---|---|---|---|---|---|
| **1a** |  | 73 | **1h** |  | 61 |
| **1b** |  | 80 | **1i** |  | 80 |
| **1c** |  | 45 | **1j** |  | 70 |
| **1d** |  | 78 | **1k** |  | 78 |
| **1e** |  | 80 | **1l** |  | 90 |
| **1f** |  | 50 | **1m** |  | 72 |
| **1g** |  | 68 | **1n** |  | 73 |

[a] Isolated yields. [b] Competitive intramolecular cyclization afforded a mixture of **1f** and pyrrolidine (70/30).

**Table II. Synthesis of Diamine Hydrochlorides 3·xHCl**

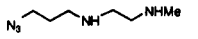
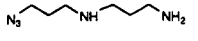
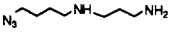
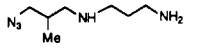
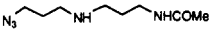
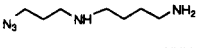
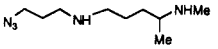
| azide | borane | diamine | | % yield[a] |
|---|---|---|---|---|
| **1a** | **2a** |  | **3a** | 87 |
| **1b** | **2a** |  | **3b** | 79 |
| **1b** | **2b** |  | **3c** | 80 |
| **1b** | **2c** |  | **3d** | 80 |
| **1m** | **2a** |  | **3e** | 76 |
| **1n** | **2b** |  | **3f** | 70 |
| **1f** | **2a** |  | **3g** | 65 |
| **1k** | **2a** |  | **3h** | 80 |

[a] Isolated yields as dihydrochlorides, except **3f**·HCl.

(13) Jego, J. J.; Carboni, B.; Vaultier, M.; Carrie, R. *Bull. Soc. Chem. Fr.* **1992**, 554.

(14) Abel, E. W.; Dandegaenker, S. H.; Gerrard, W.; Lappert, M. F. *J. Chem. Soc.*, **1956**, 4697. See also Cole, T. E.; Quintanilla, R.; Smith, B. M.; Hurst, D. *Tetrahedron Lett.* **1992**, *33*, 2761 and Brown, H. C.; Salunke, A. M.; Argade, A. *Organometallics* **1992**, *11*, 3094.

**Table III. Synthesis of Diamino Azides 4**

| diamine | diamino azide | | % yield[a] |
|---|---|---|---|
| **3a** |  | **4a** | 66 |
| **3b** |  | **4b** | 70 |
| **3c** |  | **4c** | 30[b] |
| **3d** |  | **4d** | 70 |
| **3e** |  | **4e** | 90[c] |
| **3g** |  | **4g** | 85 |
| **3h** |  | **4h** | 90 |

[a] Isolated yields. [b] Estimated yield after bulb-to-bulb distillation of the mixture **4c** + **6**. [c] Crude yield; **4e** was the only product detected in $^1H$ and $^{13}C$ NMR spectra.

**Scheme V**

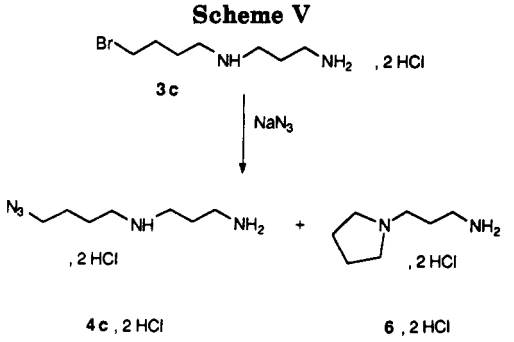
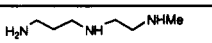
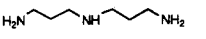
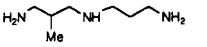
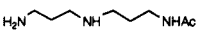
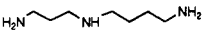
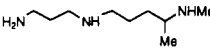
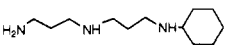


**Table IV. Synthesis of Triamine Hydrochlorides 5·xHCl**

| azide | triamine | | % yield[a] |
|---|---|---|---|
| **4a** |  | **5a** | 90 |
| **4b** |  | **5b** | 92 |
| **4d** |  | **5d** | 80 |
| **4e** |  | **5e** | 91 |
| **4g** or **4c** |  | **5g** | 91 |
| **4h** |  | **5h** | 83 |
| **4b** |  | **5i** | 75 |

[a] Isolated yields as trihydrochlorides except for **5e** and **5h** where the reduction was run without aqueous HCl.

compatible with the presence of an *N*-acetyl or *N*-trifluoroacetyl group (**1m** → **3e** and **1n** → **3f**) that allows, for example, the generation of the mono-$N^1$-acetylnorspermidine (**5e**).

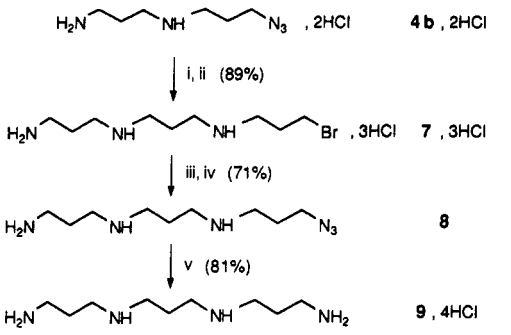
This triamine synthesis can be extended to the preparation of tetraamines, as demonstrated by the synthesis of thermine tetrahydrochloride (**9**·4HCl) from azide **4b** and dichloroborane **2a** (overall yield = 42%) (Scheme VI).

The synthetic utility of ω-aminoalkyl azides **1** is not restricted to the above methodology. The azido group is compatible with numerous reagents,[15] thus facilitating the construction of the carbon–nitrogen framework of polyamines from the free amino moiety leaving the azido group intact. Two routes have been evaluated starting from azides **1b** and **1k**, but these approaches could be extended to other ω-aminoalkyl azides.

Reductive amination of **1b** with 5-azido-pentan-2-one in the presence of sodium cyanoborohydride afforded the

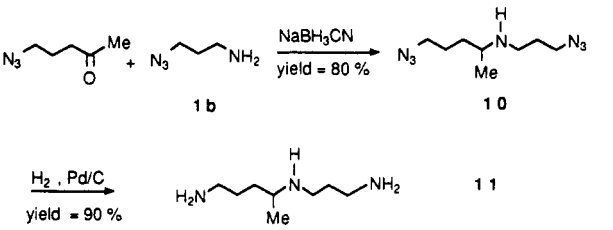
(15) Scriven, E. F. V.; Turnblum, K. *Chem. Rev.* **1988**, *88*, 297.

**Scheme VI**[a]

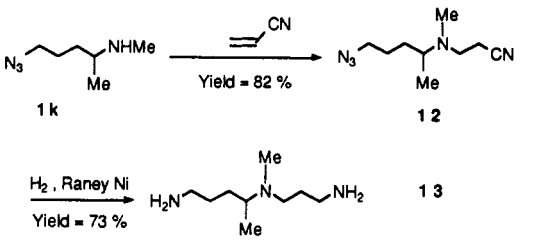


[a] (i) $Br(CH_2)_3BCl_2$; (ii) MeOH; (iii) $NaN_3$; (iv) NaOH; (v) $H_2$, Pd/C, HCl.

**Scheme VII**



**Scheme VIII**



bis-azide **10** which was easily hydrogenated over palladium on charcoal to give **11** in an overall yield of 72% (Scheme VII).

Michael type addition of **1k** to acrylonitrile produced the azide **12** which was reduced in the presence of Raney nickel to give **13** with a 60% overall yield (Scheme VIII).

In summary, we present a convenient and practical regiospecific synthesis of acyclic polyamines from ω-aminoalkyl azides. These key building blocks are easily accessible by various methods depending on the desired structure. Functional group manipulations of the azido or the amino moiety allow the extension of the chain with total regiocontrol. These approaches efficiently complement known methods and should be of special value to prepare selectively C- or (and) N-substituted polyamines.

## Experimental Section

$^1H$ and $^{13}C$ NMR spectra were recorded, respectively, at 300 and 75.5 MHz using $CDCl_3$ as solvent unless otherwise indicated. Chemical shifts are reported in δ (ppm) and coupling constants are given in hertz. Mass spectra were measured at 70 eV on a Varian MAT 311 spectrometer (Centre Régional de Mesures Physiques de l'Ouest). Elemental analyses were performed by the Laboratoire Central d'Analyses du C.N.R.S., Lyon. Melting points were determined with a Kofler apparatus and are uncorrected.

**Materials.** Reagent grade reactants and solvents were used as received from chemical suppliers (Aldrich). All the operations with borane reagents were carried out under a nitrogen atmosphere with oven-dried glassware. Methylene chloride was distilled over $P_2O_5$.

**CAUTION:** *Because of their potentially explosive properties, all reactions involving ω-aminoalkyl azides were carried out with the appropriate protection under a well ventilated hood.*

**Synthesis of ω-Aminoalkyl Azides. Preparation of ω-Aminoalkyl Azides 1 from an ω-Halogeno Amine Hydrohalide. General Procedure.** A solution of ω-halogeno amine hydrochloride or hydrobromine and sodium azide (3 equiv) in water (1 mL/mmol) was heated at 80 °C for 15 h. After removing most of the water by distillation under vacuum, the reaction mixture was cooled in an ice bath. Diethyl ether (50 mL) and then KOH pellets (4 g) were added keeping the temperature below 10 °C. After separation of the organic phase, the aqueous layer was further extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried over $K_2CO_3$ and concentrated to give an oil which was purified by bulb-to-bulb distillation.

**1-Azido-2-(*N*-methylamino)ethane (1a).** 1-Bromo-2-(*N*-methylamino)ethane hydrobromide[16] (10 g) gave 3.2 g of **1a** (70%): bp 70–75 °C (15 mmHg); $^1$H NMR (80 MHz) δ 1.55 (s, 1H), 2.42 (s, 3H), 2.67–2.85 (m, 2H), 3.43 (t, 2H, *J* = 5.7); IR (neat, cm$^{-1}$) 2100 ($N_3$). Anal. Calcd for $C_9H_{11}N_7O_7$ (picrate, mp 77–78 °C): C, 32.84; H, 3.34; N, 29.77. Found: C, 33.0; H, 3.4; N, 29.6.

**1-Azido-3-aminopropane (1b).** 1-Chloro-3-aminopropane hydrochloride (6.5 g) gave 4 g of **1b** (80%): bp 48–50 °C (15 mmHg); $^1$H NMR (80 MHz) δ 1.25 (s, 2H), 1.75 (quint, 2H, *J* = 6.8), 2.80 (t, 2H, *J* = 6.8), 3.37 (t, 2H, *J* = 6.7); IR (neat, cm$^{-1}$) 2100 ($N_3$). Anal. Calcd for $C_9H_{11}N_7O_7$ (picrate, mp 99–100 °C) C, 32.84; H, 3.34; N, 29.77. Found: C, 33.1; H, 3.3; N, 30.0.

**2-Azido-3-methyl-3-(*N*,*N*-dimethylamino)propane (1c).** 1-Chloro-2-methyl-3-(*N*,*N*-dimethylamino)propane hydrochloride (5 g) gave 1.8 g of **1c** (45%): bp 45–50 °C (8 mmHg); IR (neat, cm$^{-1}$) 2090 ($N_3$); $^1$H NMR (80 MHz) δ 0.95 (d, 3H, *J* = 6.2), 1.62–2.45 (m, 6H), 2.17 (s, 3H), 3.15 (dd, 1H, *J* = 11.8 and 5.6), 3.38 (dd, 1H, *J* = 11.8 and 4.7). Anal. Calcd for $C_{12}H_{17}N_7O_7$ (picrate, mp 68–70 °C): C, 38.81; H, 4.58; N, 26.41. Found: C, 38.8; H, 4.6; N, 26.2.

**2-Azido-4-(*N*-methyl-*N*-benzylamino)butane (1d).** 2-Chloro-4 (*N*-methyl-*N*-benzylamino)butane hydrochloride[17] (1.5 g) gave 1 g of **1d** (82%): bp 45–50 °C (0.01 mmHg); $^1$H NMR (80 MHz) δ 1.12 (d, 3H, *J* = 6.6), 1.40–1.72 (m, 2H), 2.08 (s, 3H), 2.37 (t, 2H, *J* = 7.0), 3.12–3.75 (m, 3H), 7.08–7.37 (m, 5H): IR (neat, cm$^{-1}$) 2095 ($N_3$). Anal. Calcd for $C_{18}H_{21}N_7O_7$ (picrate, mp 87–89 °C): C, 48.32; H, 4.73; N, 21.92. Found: C, 48.3; H, 4.7; N, 21.3.

**2-Azido-4-(*N*-methylamino)butane (1e).** 2-Chloro-4-(*N*-methylamino)butane hydrochloride[18] (0.47 g) gave 0.31 g of **1e** (80%): bp 80–85 °C (15 mmHg); IR (neat, cm$^{-1}$) 2100 ($N_3$); $^1$H NMR (80 MHz) δ 1.28 (d, 3H, *J* = 6.5), 1.50–1.83 (m, 3H), 2.45 (s, 3H), 2.70 (t, 2H, *J* = 7.1), 3.58 (sext, 1H, *J* = 6.5). Anal. Calcd for $C_{11}H_{15}N_7O_7$ (picrate, mp 62–64 °C): C, 36.97; H, 4.20; N, 27.45. Found: C, 36.9; H, 4.0; N, 27.2.

**1-Azido-4-aminobutane (1f).** 1-Chloro-4-aminobutane hydrochloride[19] (1.82 g) gave 0.72 g of **1f** (50%): bp 65–70 °C (15 mmHg); IR (neat, cm$^{-1}$) 2095 ($N_3$); $^1$H NMR (80 MHz) δ 1.55–1.87 (m, 4H), 1.67 (s, 2H), 2.80 (t, 2H, *J* = 6.5), 3.35 (t, 2H, *J* = 6.3). Anal. Calcd for $C_{10}H_{13}N_7O_7$ (picrate, mp 113–114 °C): C, 34.99; H, 3.81; N, 28.56. Found: C, 34.8; H. 4.0; N, 28.3.

**1-Azido-5-aminopentane (1g).** 1-Chloro-5-aminopentane hydrochloride[20] (0.38 g) gave 0.21 g of **1g** (68%): bp 70–75 °C (15 mmHg); IR (neat, cm$^{-1}$) 2095 ($N_3$); $^1$H NMR (80 MHz) δ 1.33 (s, 2H), 1.35–1.75 (m, 6H), 2.67–2.80 (m, 2H), 3.29 (t, 2H, *J* = 6.3). Anal. Calcd for $C_{11}H_{15}N_7O_7$ (picrate, mp 104–106 °C): C, 36.97; H, 4.20; N, 27.44. Found: C, 36.8; H, 3.8; N, 27.2.

**Preparation of ω-Aminoalkyl Azides 1 from 1-Azido-4-iodobutane. General Procedure.** 1-Azido-4-iodobutane[21] and the minumum amount of ethanol to obtain a homogeneous mixture was added to a 40% wt solution of amine in water (20 equiv). The resulting solution was kept for 20 h at room temperature and then extracted with pentane (5 × 20 mL). The organic layers were combined and dried over $K_2CO_3$. Concentration and bulb-to-bulb distillation gave the pure azide **1** as a colorless oil.

**1-Azido-4-(*N*-methylamino)butane (1h).** 1-Azido-4-iodobutane (1.13 g) and 8 mL of methylamine solution gave 0.39 g of azide **1h** (61%): bp 80–85 °C (15 mmHg); IR (neat, cm$^{-1}$) 2100 ($N_3$); $^1$H NMR (80 MHz) δ 1.30 (s, 1H), 1.40–1.87 (m, 4H), 2.40 (s, 3H), 2.50–2.70 (m, 2H), 3.30 (t, 2H, *J* = 6.4). Anal. Calcd for $C_{11}H_{15}N_7O_7$ (picrate, mp 87–88 °C): C, 36.97; H, 4.20; N, 27.44. Found: C, 37.1; H, 4.2; N, 27.5.

**1-Azido-4-(*N*,*N*-dimethylamino)butane (1i).** 1-Azido-4-iodobutane (3.80 g) and 38 mL of dimethylamine solution gave 2.00 g of **1i** (80%): bp 70–75 °C (8 mmHg); IR (neat, cm$^{-1}$) 2100 ($N_3$); $^1$H NMR (80 MHz) δ 1.35–1.85 (m, 4H), 2.15–2.37 (m, 2H), 2.20 (s, 6H), 3.30 (t, 2H, *J* = 6.4). Anal. Calcd for $C_{12}H_{17}N_7O_7$ (picrate, mp 108–110 °C): C, 38.81; H, 4.58; N, 26.41. Found: C, 38.8; H, 4.6; N, 26.5.

**Preparation of ω-Aminoalkyl Azides 1 from 5-Azidopentan-2-one General Procedure.**[22] 2 N HCl–methanol was added to a solution of 5-azidopentan-2-one[23] (1.27 g, 10 mmol), ammonium chloride (5.75 g, 100 mmol), and sodium cyanoborohydride (380 mg, 6 mmol) in 30 mL of absolute methanol until pH = 6. After stirring for 72 h at room temperature, concentrated HCl was added until pH < 2. The methanol was removed *in vacuo*. The residue was dissolved in water. The aqueous solution was brought to pH > 10 with solid KOH, saturated with NaCl, and then extracted with five 20-mL portions of ether. The combined extracts were dried ($K_2CO_3$) and evaporated in vacuo to give a crude oil which was purified by bulb-to-bulb distillation.

**1-Azido-4-aminopentane (1j).** 5-Azidopentan-2-one (1.27 g) and 7.7 g of ammonium acetate gave 0.9 g of **1j** (70%): bp = 60–65 °C (15 mmHg); IR (neat, cm$^{-1}$) 2090 ($N_3$); $^H$ NMR (80 MHz, $CDCl_3$) δ 1.03 (d, 3H, *J* = 6.3), 1.12–1.83 (m, 6H), 2.87 (sext, 1H, *J* = 6.3), 3.25 (t, 2H, *J* = 6.7). Anal. Calcd for $C_5H_{12}N_4{\cdot}C_6H_3N_3O_7$ (picrate, mp 125–127 °C): C, 36.97; H, 4.20; N, 27.45. Found: C, 37.0; H, 4.5; N, 27.7.

**1-Azido-4-(*N*-methylamino)pentane (1k).** 5-Azidopentan-2-one (1.27 g) and 6.76 g of methylamine hydrochloride gave 1.1 g of **1k** (78%): bp 95–100 °C (15 mmHg); IR (neat, cm$^{-1}$) 2100 ($N_3$); $^1$H NMR (80 MHz) δ 0.97 (d, 3H, *J* = 6.4), 1.17–1.85 (m, 5H), 2.30–2.72 (sext, 1H, *J* = 6.4), 2.33 (s, 3H), 3.25 (t, 2H, *J* = 6.8). Anal. Calcd for $C_{12}H_{17}N_7O_7$ (picrate, mp 74–76 °C): C, 38.81; H, 4.61; N, 26.40. Found: C, 38.7; H, 4.5; N, 26.1.

**1-Azido-4-(*N*-benzylamino)pentane (1l).** A solution of benzylamine (1.07 g, 10 mmol) and 5-azidopentan-2-one (1.27 g, 10 mmol) in 20 mL of diethyl ether was stirred for 18 h at room temperature with 1 g of 3-Å molecular sieves. After filtration and washing with 2 × 10 mL of diethyl ether, the combined organic layers were evaporated in vacuo to give 1.95 g of a colorless oil which can be purified by bulb-to-bulb distillation: bp 50–60 °C (0.004 mmHg). Sodium borohydride (0.4 g, 10.2 mmol) was added to a solution of this imine in 30 mL of absolute ethanol. After 15 h at reflux, the ethanol was removed *in vacuo*. The residue was dissolved in 10 mL of water and extracted with 3 × 20 mL of ether. The combined extracts were dried ($K_2CO_3$) and evaporated to give an oil which was purified by bulb-to-bulb distillation (1.67 g, 90%): bp = 70–75 °C (0.004 mmHg); IR (neat, cm$^{-1}$) 2100 ($N_3$); $^1$H NMR (80 MHz, $CDCl_3$) δ 1.05 (d, 3H, *J* = 6.3), 1.12–1.83 (m, 5H), 2.65 (sext, 1H, *J* = 6.2), 3.17 (t, 2H, *J* = 6.4), 3.79 (d, 1H, *J* = 13.3), 3.71 (d, 1H, *J* = 13.3), 7.08–7.37 (m, 5H). Anal. Calcd for $C_{12}H_{18}N_4{\cdot}HCl$ (mp 138–140 °C): C, 56.58; H, 7.46; N, 22.00. Found: C, 56.3; H, 7.7; N, 21.8.

**Preparation of ω-Aminoalkyl Azides 1 from 1-Azido-3-aminopropane. *N*-Acetyl-1-azido-3-aminopropane (1m).** Acetic anhydride (3.06 g, 2.8 mL, 30 mmol) in 5 mL of $CH_2Cl_2$ was slowly added to a solution of **1b** (3 g, 30 mmol) in 30 mL of $CH_2Cl_2$. The resulting mixture was stirred for 15 h at room temperature, washed with 1 M sodium bicarbonate (2 × 10 mL)

(16) Cortese, F. *Organic Syntheses*; J. Wiley: New York, 1946; Collect. Vol. 2, p 91.

(17) 2-Chloro-4-(*N*-methyl-*N*-benzylamino)butane hydrochloride was prepared according to the following sequence: Michael type addition of *N*-methylbenzylamine to 3-buten-2-one (92%), reduction with $NaBH_4$ (88%), reaction with $PCl_5$ (59%).

(18) 2-Chloro-4-(*N*-methylamino)butane hydrochloride was prepared as above, except that catalytic hydrogenation in the presence of 10% Pd/C (80%) was performed before treatment with $PCl_5$ (61%).

(19) 1-Chloro-4-aminobutane hydrochloride was prepared according to the following sequence: Reaction of 1-bromo-4-chlorobutane with $NaN_3$ (86%), hydrogenation over 10% Pd/C in the presence of HCl (88%).

(20) 1-Chloro-5-aminopentane hydrochloride was prepared according to the following sequence: Reaction of 1-bromo-5-chloropentane with $NaN_3$ (90%), hydrogenation over 10% Pd/C in the presence of HCl (75%).

(21) 1-Azido-4-iodobutane was prepared according to the following sequence: Reaction of 1-bromo-4-chlorobutane with $NaN_3$ (86%), treatment with NaI (75%).

(22) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(23) Vaultier, M.; Lambert, P. H.; Carrié, R. *Bull. Soc. Chem. Fr.* **1986**, 83.

and water (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil was purified by bulb-to-bulb distillation to give 3.1 g of **1m** (73%): bp 95–100 °C/0.1 mmHg); IR (neat, $cm^{-1}$) 2100 ($N_3$). $^1H$ NMR (80 MHz) $\delta$ 1.83 (quint, 2H, $J$ = 6.6); 1.97 (s, 3H); 3.33 (q., 2H, $J$ = 6.4), 3.40 (t, 2H, $J$ = 6.7), 7.17 (s, 1H). Anal. Calcd for $C_5H_{10}N_4O$: C, 42.25; H, 7.04; N, 39.43. Found: C, 42.1; H, 7.1; N, 39.5.

***N*-(Trifluoroacetyl)-1-azido-3-aminopropane (1n).** A solution of trifluoroacetic anhydride (4.7 g, 3.2 mL, 22.4 mmol) in 5 mL of $CH_2Cl_2$ was added dropwise to a solution of **1b** (2.15 g, 21.5 mmol) and triethylamine (2.17 g, 21.5 mmol) in 20 mL of $CH_2Cl_2$. The resulting mixture was stirred at room temperature for 15 h then worked up as was **1m** to give 3.27 g of **1n** (78%): bp 85–90 °C (0.01 mmHg); IR (neat, $cm^{-1}$) 2100 ($N_3$); $^1H$ NMR (80 MHz) $\delta$ 1.85 (quint, 2H, $J$ = 6.5), 3.42 (t, 2H, $J$ = 6.4), 3.47 (q., 2H, $J$ = 6.4), 7.12 (s, 1H). Anal. Calcd for $C_5H_7F_3N_4O$: C, 30.62; H, 3.59; N, 28.56. Found: C, 30.8; H, 3.7; N, 28.7.

**Reaction of ω-Aminoalkyl Azide Hydrochlorides 1·HCl with Dichloroboranes 2. General Procedure.** A volume of 10 mL of a 1 N HCl diethyl ether solution was added dropwise to a solution of ω-aminoalkyl azide **1** (4 mmol) in 10 mL of diethyl ether. After 5 min, the diethyl ether and excess HCl were evaporated under reduced pressure and methylene chloride (10 mL) was added. This was followed by a slow addition of a solution of the dichloroborane **2**[13,14] (6 mmol) in 5 mL of $CH_2Cl_2$ to the reaction mixture. Nitrogen evolution started after a few seconds. The reaction mixture was kept at room temperature for 15 h. Addition of 2 mL of anhydrous methanol followed 10 min later by 15 mL of diethyl ether provoked the precipitation of white crystals of **3**·HCl which were isolated by filtration.

***N*¹-(3-Bromopropyl)-*N*²-methyl-1,2-diaminoethane Dihydrochloride (3a·2HCl).** Azide **1a** (400 mg, 4.0 mmol) and 1.3 g (6.0 mmol) of (3-bromopropyl)dichloroborane (**2a**) gave 930 mg of **3a**·2HCl (87%): mp 195–196 °C; $^1H$ NMR ($D_2O$) $\delta$ 2.26 (quint, 2H, $J$ = 6,3), 2.78 (s, 3H), 3,28 (t, 2H, $J$ = 7.4), 3.42–3.47 (m, 4H), 3.52 (t, 2H, $J$ = 6.3); $^{13}C$ NMR ($D_2O$) $\delta$ 31.1, 32.2, 36.1, 45.8, 47.1, 49.7. Anal. Calcd for $C_6H_{17}BrCl_2N_2$: C, 26.87; H, 6.34; N, 10.45. Found: C, 27.0; H, 6.4; N, 10.6.

***N*-(3-Bromopropyl)-1,3-diaminopropane Dihydrochloride (3b·2HCl).** Azide **1b** (400 mg, 4.0 mmol) and 1.3 g (6.0 mmol) of (3-bromopropyl)dichloroborane (**2a**) gave 847 mg of **3b**·2HCl (79%): mp 242–244 °C; $^1H$ NMR ($D_2O$) $\delta$ 2.03–2.23 (m, 4H), 3.10 (t, 2H, $J$ = 7.9), 3.15–3.22 (m, 2H), 3.25 (t, 2H, $J$ = 7.5), 3.69 (t, 2H, $J$ = 6.1); $^{13}C$ NMR ($D_2O$) $\delta$ 26.5, 31.0, 39.4, 44.3, 47.4, 48.2. Anal. Calcd for $C_6H_{17}BrCl_2N_2$: C, 26.84; H, 6.34; N, 10.44. Found: C, 26.9; H, 6.3; N, 10.5.

***N*-(4-Bromobutyl)-1,3-diaminopropane Dihydrochloride (3c·2HCl).** Azide **1b** (300 mg, 3.0 mmol) and 980 mg (4.5 mmol) of (4-bromobutyl)dichloroborane (**2b**) gave 677 mg of **3c**·2HCl (80%): mp 222–223 °C; $^1H$ NMR ($D_2O$) $\delta$ 1.78–1.99 (m, 4H), 2.02–2.15 (m, 2H, $J$ = 7.8), 3.10 (t, 4H, $J$ = 8.0), 3.15 (t, 2H, $J$ = 7.9), 3.51 (t, 2H, $J$ = 6.3); $^{13}C$ NMR ($D_2O$) $\delta$ 26.7, 27.2, 31.8, 36.6, 39.8, 47.5, 50.0. Anal. Calcd for $C_7H_{19}BrCl_2N_2$: C, 28.78, H, 6.55, N, 9.59. Found: C, 28.8; H, 6.8; N, 9.5.

***N*-(3-Chloro-2-methylpropyl)-1,3-diaminopropane Dihydrochloride (3d·2HCl).** Azide **1b** (700 mg, 7.0 mmol) and 1.82 g (10.5 mmol) of (2-methyl-3-chloropropyl)dichloroborane (**2c**) gave 1.33 g of **3d**·2HCl (80%): mp 202–202 °C; $^1H$ NMR ($D_2O$) $\delta$ 1.06 (d, 3H, $J$ = 6.6), 2.01–2.14 (m, 2H), 2.31 (oct, 1H, $J$ = 6.5), 2.93–3.26 (m, 6H), 3.56 (dd, 1H, $J$ = 6.2 and 11.6), 3.64 (dd, 1H, $J$ = 4.9 and 11.6); $^{13}C$ NMR ($D_2O$) $\delta$ 17.6, 26.1, 35.2, 39.1, 47.7, 50.1, 53.4. Anal. Calcd for $C_7H_{19}Cl_3N_2$: C, 35.36, H, 8.00; N, 11.79. Found: C, 35.7; H, 8.1; N, 11.6.

***N*¹-Acetyl-*N*³-(3-bromopropyl)-1,3-diaminopropane Dihydrochloride (3e·2HCl).** Azide **1m** (1.2 g, 8.45 mmol) and 2.6 g (12.67 mmol) of (3-bromopropyl)dichloroborane (**2a**) gave 2.0 g of **3e**·2HCl (76%): mp 60–62 °C; $^1H$ NMR ($D_2O$) $\delta$ 1.85 (quint, 2H, $J$ = 6.8), 1.95 (s, 3H), 2.20 (quint, 2H, $J$ = 6.5), 3.03 (t, 2H, $J$ = 7.7), 3.16 (t, 2H, $J$ = 7.7), 3.23 (t, 2H, $J$ = 6.6), 3.49 (t, 2H, $J$ = 6.2); $^{13}C$ NMR ($D_2O$) $\delta$ 24.2, 27.8, 31.2, 32.2, 38.8, 47.5, 48.7, 177.1. Anal. Calcd for $C_5H_{19}BrCl_2N_2O$: C, 30.96; H, 6.13; N, 9.03. Found: C, 30.8; H, 6.1; N, 9.1.

***N*¹-(Trifluoroacetyl)-*N*³-(3-bromopropyl)-1,3-diaminopropane Hydrochloride (3f·HCl).** Azide **1m** (736 mg, 3.75 mmol) and 1.22 g (5.6 mmol) of (3-bromopropyl)dichloroborane (**2a**) gave 1.0 g of **3f**·HCl (70%): mp 134–136 °C; $^1H$ NMR ($D_2O$) $\delta$ 1.75–2.03 (m, 6H), 30.7 (t, 4H, $J$ = 7.7), 3.42 (t, 2H, $J$ = 6.8), 3.50 (t, 2H, $J$ = 6.3); $^{13}C$ NMR ($D_2O$) $\delta$ 28.9, 27.6, 31.4, 36.1, 39.5, 47.6, 49.5, 118.5, 161.8. Anal. Calcd for $C_9H_{17}BrClF_3N_2O$: C, 31.62; H, 4.98; N, 8.20. Found: C, 31.8; H, 5.0; N, 8.2.

***N*-(3-Bromopropyl)-1,4-diaminobutane Dihydrochloride (3g·2HCl).** Azide **1f** (342 mg, 3 mmol) and 918 mg (4.5 mmol) of (3-bromopropyl)dichloroborane (**2a**) gave 550 mg of **3g**·2HCl (65%): mp 234–235 °C; $^1H$ NMR ($D_2O$) $\delta$ 1.70–1.88 (m, 4H), 2.27 (quint, 2H, $J$ = 7.3), 3.00–3.19 (m, 4H), 3.24 (t, 2H, $J$ = 7.6), 3.56 (t, 2H, $J$ = 6.2); $^{13}C$ NMR ($D_2O$) $\delta$ 25.4, 26.6, 31.1, 32.3, 41.5, 49.0, 49.7. Anal. Calcd for $C_7H_{19}BrCl_2N_2$: C, 29.80; H, 6.74; N, 9.92. Found: C, 30.0; H, 6.8; N, 10.0.

***N*¹-Methyl-*N*³-(3-bromopropyl)-2-methyl-1,4-diaminobutane dihydrochloride (3h·2HCl).** Azide **1k** (1.60 g, 11.3 mmol) and 3.45 g (17.0 mmol) of (3-bromopropyl)dichloroborane (**2a**) gave 2.80 g of **3h**·2HCl (80%): mp 170–172 °C; $^1H$ NMR ($D_2O$) $\delta$ 1.29 (d, 3H, $J$ = 6.6), 1.58–1.89 (m, 4H), 2.24 (quint, 2H, $J$ = 6.7), 2.67 (s, 3H), 3.10 (t, 2H, $J$ = 7.3), 3.19–3.34 (m, 1H), 3.21 (t, 2H, $J$ = 7.6), 3.52 (t, 2H, $J$ = 6.3); $^{13}C$ NMR ($D_2O$) $\delta$ 17.5, 24.3, 31.0, 31.7, 32.2, 32.4, 48.8, 49.7, 57.3. Anal. Calcd for $C_9H_{23}BrCl_2N_2$: C, 34.83; H, 7.42; N, 9.03. Found: C, 34.9; H, 7.7; N, 9.0.

**Synthesis of the Diamino Azides 4. General Procedure.** A solution of the diamine dihydrochloride **3**·2HCl (5 mmol) and sodium azide (25 mmol) in 10 mL of water was heated at 80 °C for 15 h (except for **3d**, 30 h). Most of the water was evaporated (~5 mL) and 10 mL of diethyl ether was added. The aqueous layer was made strongly basic with 40% sodium hydroxide. The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 10 mL). The combined organic phase was dried over potassium carbonate. The solvent was evaporated and the residue purified by bulb-to-bulb distillation.

***N*¹-(3-Azidopropyl)-*N*²-methyl-1,2-diaminoethane (4a).** **3a**·2HCl (860 mg, 3.2 mmol) and 624 mg (9.6 mmol) of sodium azide gave 330 mg of **4a** (66%): bp 55–60 °C (0.1 mmHg); IR (neat, $cm^{-1}$) 2095 ($N_3$); $^1H$ NMR 1.12 (s, 2H), 1.56 (quint, 2H, $J$ = 6.9), 2.23 (s, 3H), 2.45–2.55 (m, 6H), 3.17 (t, 2H, $J$ = 6.7); $^{13}C$ NMR $\delta$ 29.5, 36.4, 46.9, 49.2, 49.6, 51.6. Anal. Calcd for $C_6H_{17}Cl_2N_5$ (dihydrochloride): C, 31.30; H, 7.39. Found: C, 31.2; H, 7.4.

***N*-(3-Azidopropyl)-1,3-diaminopropane (4b).** **3b**·2HCl (600 mg, 2.24 mmol) and 437 mg (6.72 mmol) of sodium azide gave 246 mg of **4b** (70%): bp 85–90 °C (0.1 mmHg); IR (neat, $cm^{-1}$) 2095 ($N_3$); $^1H$ NMR $\delta$ 1.10 (s, 3H), 1.42–1.92 (m, 4H), 2.25–2.85 (m, 6H), 3.36 (t, 2H, $J$ = 6.6). Anal. Calcd for $C_{18}H_{21}N_{11}O_{14}$ (dipicrate, mp 166–168 °C): C, 35.12; H, 3.41; N, 25.06. Found: C, 34.8; H, 3.3; N, 24.9.

***N*-(3-Azido-2-methylpropyl)-1,3-diaminopropane (4d).** **3d**·2HCl (2.00 g, 8.4 mmol) and 2.73 g (42.1 mmol) of sodium azide gave 1.0 g of **4d** (70%): bp 60–65 °C (0.1 mmHg); IR (neat, $cm^{-1}$) 2100 ($N_3$); $^1H$ NMR $\delta$ 0.81 (d, 3H, $J$ = 6.8), 1.15 (s, 3H), 1.46 (quint, 2H, $J$ = 6.8), 1.71 (oct, 1H, $J$ = 6.4), 2.33 (dd, 1H, $J$ = 6.2 and 11.9), 2.42 (dd, 1H, $J$ = 6.8 and 11.9), 2.50 (t, 2H, $J$ = 6.9), 2.60 (t, 2H, $J$ = 6.8), 3.08 (dd, 1H, $J$ = 6.4 et 12.0), 3.18 (dd, 1H, $J$ = 5.8 and 12.0); $^{13}C$ NMR $\delta$ 16.1, 33.6, 33.9, 40.4, 48.0, 53.4, 55.8. Anal. Calcd for $C_{19}H_{23}N_{11}O_{14}$ (dipicrate, mp 164–166 °C): C, 36.24; H, 3.65; N, 24.48. Found: C, 36.3; H, 3.8; N, 24.2.

***N*¹-Acetyl-*N*³-(3-azidopropyl)-1,3-diaminopropane (4e).** **3e**·2HCl (683 mg, 2.5 mmol) and 487 mg (7.5 mmol) of sodium azide gave 447 mg of **4e** (90%); IR (neat, $cm^{-1}$) 2100 ($N_3$); $^1H$ NMR $\delta$ 1.50 (s, 1H), 1.60 (quint, 2H, $J$ = 6.5), 1.70 (quint, 2H, $J$ = 6.7), 1.89 (s, 3H), 2.62 (t, 4H, $J$ = 6.6), 3.25 (q, 2H, $J$ = 6.0), 3.31 (t, 2H, $J$ = 6.6), 6.87 (s, 1H); $^{13}C$ NMR $\delta$ 23.3, 29.1, 29.3, 38.7, 47.0, 48.1, 49.6, 170.1. Anal. Calcd for $C_{14}H_{20}N_8O_8$ (picrate, mp 118–119 °C): C, 39.25; H, 4.67; N, 26.17. Found: C, 39.3; H, 4.7; N, 25.7.

***N*-(3-Azidopropyl)-1,4-diaminobutane (4g).** **3g**·2HCl (564 mg, 2.0 mmol) and 390 mg (6.0 mmol) of sodium azide gave 290 mg of **4g** (85%): bp 80–85 °C (0.01 mmHg); IR (neat, $cm^{-1}$) 2100 ($N_3$); $^1H$ NMR $\delta$ 1.15 (s, 3H), 1.21–1.38 (m, 4H), 1.56 (quint, 2H, $J$ = 6.8), 2.41 (t, 2H, $J$ = 6.9), 2.49 (t, 2H, $J$ = 7.0), 2.50 (t, 2H, $J$ = 6.5), 3.17 (t, 2H, $J$ = 6.7); $^{13}C$ NMR $\delta$ 27.4, 29.2, 31.4, 42.0, 46.8, 49.5, 49.7. Anal. Calcd for $C_{19}H_{23}N_{11}O_{14}$ (dipicrate, mp 161–163 °C) C, 36.25; H, 3.68; N, 24.48. Found: C, 36.3; H, 3.8; N, 24.4.

***N*¹-Methyl-*N*³-(3-azidopropyl)-2-methyl-1,4-diaminobutane (4h).** **3h**·2HCl (1.6 g, 5.16 mmol) and 1.0 g (15.5 mmol) of sodium azide gave 924 mg of **4h** (90%): bp 55–60 °C (0.01 mmHg);

IR (neat, $cm^{-1}$) 2100 ($N_3$); $^1H$ NMR $\delta$ 1.04 (d, 3H, $J$ = 6.2), 1.13 (s, 2H), 1.23–1.57 (m, 4H), 1.76 (quint, 2H, $J$ = 6.8), 2.40 (s, 3H), 2.46–2.59 (m, 1H), 2.60 (t, 2H, $J$ = 6.7), 2.69 (t, 2H, $J$ = 6.9), 3.36 (t, 2H, $J$ = 6.7); $^{13}C$ NMR 19.7, 26.5, 29.3, 33.8, 34.4, 46.9, 49.5, 50.1, 54.7. Anal. Calcd for $C_{21}H_{27}N_{11}O_{14}$ (dipicrate, mp 128–130 °C): C, 38.35; H, 4.10; N, 23.44. Found: C, 38.1; H, 4.3; N, 23.6.

**Synthesis of Triamines. General Procedure.** A solution of the amino azide 4 (3 mmol) in ethanol (10 mL) and HCl 12 N (1 mL) (except for **4e** and **4h**) was hydrogenated over 10% palladium on charcoal (50 mg) at 60 psi hydrogen in Parr hydrogenation apparatus for 18 h at room temperature. The catalyst was separated by filtration and the solvent was evaporated under reduced pressure. The residue was washed with diethyl ether (30 mL) and filtered to give a solid used for characterization without further purification.

***N*¹-(3-Aminopropyl)-*N*²-methyl-1,2-diaminoethane Trihydrochloride (5a·3HCl).** Azide **4a** (318 mg, 2.0 mmol) gave 436 mg of **5a**·3HCl (90%): mp 250–253 °C dec; $^1H$ NMR ($D_2O$) $\delta$ 2.11 (quint, 2H, $J$ = 6.6), 2.79 (s, 3H), 3.11 (t, 2H, $J$ = 7.3), 3.24 (t, 2H, $J$ = 7.4), 3.39–3.54 (m, 4H); $^{13}C$ NMR ($D_2O$) $\delta$ 26.3; 36.0, 39.1, 45.7, 46.9; 47.7. Anal. Calcd for $C_6H_{20}Cl_3N_3$: C, 29.93; H, 8.31; N, 17.46. Found: C, 30.0; H, 8.2; N, 17.2.

***N*-(3-Aminopropyl)-1,3-diaminopropane Trihydrochloride (5b·3HCl).** **4b** (250 mg, 1.6 mmol) gave 350 mg of **5b**·3HCl (92% yield): mp 230–232 °C dec; $^1H$ NMR ($D_2O$) $\delta$ 1.98–2.11 (t, 4H), 3.05 (t, 4H, $J$ = 7.8), 3.13 (t, 4H, $J$ = 7.8); $^{13}C$ NMR ($D_2O$) $\delta$ 26.4, 39.3, 47.4. Anal. Calcd for $C_6H_{20}Cl_3N_3$: C, 29.93; H, 8.31; N, 17.46. Found: C, 30.1; H, 8.0; N, 17.3.

***N*-(3-Amino-2-methylpropyl)-1,3-diaminopropane Trihydrochloride (5d·3HCl).** **4d** (280 mg, 1.63 mmol) gave 330 mg of **5d**·3HCl (80%): mp 200–204 °C; $^1H$ NMR ($D_2O$) $\delta$ 1.15 (d, 3H, $J$ = 6.8), 2.06–2.20 (m, 2H), 2.26–2.44 (m, 1H), 2.88–3.26 (m, 8H); $^{13}C$ NMR ($D_2O$) $\delta$ 16.9, 26.2, 32.0, 39.1, 44.9, 47.9, 53.3. Anal. Calcd for $C_7H_{22}Cl_3N_3$: C, 33.00; H, 8.64; N, 16.50. Found: C, 33.2; H, 8.8; N, 16.3.

***N*¹-Acetyl-*N*³-(3-aminopropyl)-1,3-diaminopropane (5e).** **4e** (260 mg, 1.3 mmol) gave 205 mg of **5e** (91%); $^1H$ NMR $\delta$ 1.63 (quint, 2H, $J$ = 6.9), 1.65 (quint, 2H, $J$ = 6.8), 1.72 (s, 3H), 1.95 (s, 3H), 2.65 (t, 2H, $J$ = 6.9), 2.69 (t, 2H, $J$ = 6.3), 2.77 (t, 2H, $J$ = 6.8), 3.31 (q, 2H, $J$ = 6.0), 6.90 (s, 1H); $^{13}C$ NMR $\delta$ 23.3, 28.8, 33.6, 38.7, 40.4, 47.7, 48.2, 170.2 Anal. Calcd for $C_{20}H_{25}N_9O_{15}$ (dipicrate, mp 177–178 °C) C, 38.03; H, 3.96; N, 19.96. Found: C, 38.2; H, 4.1; N, 19.6.

***N*-(3-Aminopropyl)-1,4-diaminobutane Trihydrochloride (5g·3HCl).** **4g** (340 mg, 2 mmol) gave 460 mg of **5g**·3HCl (91%): mp 250–254 °C (dec; $^1H$ NMR ($D_2O$) $\delta$ 1.63–1.80 (m, 4H), 1.63–1.80 (m, 4H), 1.98–2.10 (m, 2H), 2.98 (t, 2H, $J$ = 7.34), 3.02–3.17 (m, 6H); $^{13}C$ NMR ($D_2O$) $\delta$ 25.4, 26.4, 26.6, 39.4, 41.7, 47.3, 49.8.

***N*¹-Methyl-*N*³-(3-aminopropyl)-2-methyl-1,4-diaminobutane (5h).** **4h** (214 mg) gave 150 mg of **5h** (83%): bp 50–55 °C (0.001 mmHg); $^1H$ NMR $\delta$ 1.04 (d, 3H, $J$ = 6.2), 1.20–1.59 (m, 8H), 1.63 (quint, 2H, $J$ = 6.9), 2.40 (s, 3H), 2.47–2.59 (m, 1H), 2.61 (t, 2H, $J$ = 6.9), 2.67 (t, 2H, $J$ = 6.9), 2.75 (t, 2H, $J$ = 6.8); $^{13}C$ NMR $\delta$ 19.8, 26.5, 33.8 (2C), 34.4, 40.5, 47.8, 50.3, 54.7. Anal. Calcd for $C_{27}H_{32}N_{12}O_{14}$ (tripicrate, mp 203–205 °C) C, 37.67; H, 3.72; N, 19.53. Found: C, 37.3; H, 3.9, N, 19.6.

***N*¹-(3-Aminopropyl)-*N*³-cyclohexyl-1,3-diaminopropane Trihydrochloride (5i·3HCl).** Hydrogen chloride (6 mmol; 2 mL of a 3 N solution in diethyl ether) were slowly added to a solution of azide **4b** (471 mg, 3.0 mmol) in dry diethyl ether (10 mL) which induced the precipitation of the hydrochloride. After 10 min, the solvent was evaporated under reduced pressure and methylene chloride (4 mL) was added. A solution of the cyclohexyldichloroborane[24] (752 mg, 4.0 mmol) in $CH_2Cl_2$ was then added dropwise over 15 min. The nitrogen evolution started after a few seconds. The reaction mixture was kept at room temperature for 18 h. Addition of 2 mL of anhydrous methanol, followed by 10 mL of anhydrous diethyl ether induced the precipitation of 730 mg of white crystals which were collected by filtration (75%): mp 200–203 °C dec; $^1H$ NMR ($D_2O$) $\delta$ 0.79–0.90 (m, 3H), 1.24–1.39 (m, 6H), 1.65 (quint, 2H, $J$ = 7.4), 2.02–2.15 (m, 4H), 3.03 (t, 2H, $J$ = 7.8), 3.08 (t, 4H, $J$ = 8.2), 3.15 (t, 2H, $J$ = 7.9); $^{13}C$ NMR ($D_2O$) $\delta$ 16.0, 24.4, 25.5, 26.6, 28.0, 28.2, 33.2, 39.6, 47.2, 47.6 (2C), 50.6. Anal. Calcd for $C_{12}H_{32}Cl_3N_3$: C, 44.37; H, 9.86; N, 12.94. Found: C, 44.2; H, 9.8; N, 12.9.

**Synthesis of Thermine Tetrahydrochloride (9·4HCl).** The procedures used were similar to that described above.

***N*¹-(3-Bromopropyl)-*N*³-(3-aminopropyl)-1,3-diaminopropane Trihydrochloride (7·3HCl).** Azide **4b** (471 mg, 3.0 mmol) as its dihydrochloride and 918 mg of (3-bromopropyl)dichloroborane (**2a**) (4.5 mmol) gave 965 mg of white crystals (89%): mp 260–263 °C; $^1H$ NMR ($D_2O$) $\delta$ 2.05–2.24 (m, 6H), 3.11 (t, 2H, $J$ = 7.9), 3.19 (t, 6H, $J$ = 8.1), 3.25 (t, 2H, $J$ = 7.5), 3.70 (t, 2H, $J$ = 6.1); $^{13}C$ NMR ($D_2O$) $\delta$ 25.5, 26.7, 31.3, 32.6, 39.7, 47.5, 47.6, 47.7, 49.4. Anal. Calcd for $C_9H_{25}BrCl_3N_3$: C, 29.88; H, 6.91; N, 11.62. Found: C, 29.8; H, 6.8; N, 11.4.

***N*¹-(3-Azidopropyl)-*N*³-(3-aminopropyl)-1,3-diaminopropane (8).** 7·3HCl (723 mg, 2 mmol) and 390 mg (6.0 mmol) of sodium azide gave 300 mg of **8** (71%) which was used in the next step without further purification: $^1H$ NMR ($D_2O$) $\delta$ 1.50 (s, 4H), 1.58–1.72 (m, 4H), 1.76 (quint, 2H, $J$ = 6.8), 2.62–2.70 (m, 8H), 2.75 (t, 2H, $J$ = 6.8); 3.36 (t, 2H, 6.7). $^{13}C$ NMR ($D_2O$) $\delta$ 29.4, 30.3, 33.8, 40.5, 47.0, 47.9, 48.5, 48.6, 49.6. Anal. Calcd for $C_9H_{25}Cl_3N_6$ (trihydrochloride): C, 33.38; H, 7.72; N, 25.97. Found: C, 33.1; H, 7.5; N, 25.7.

***N*¹,*N*³-Bis(3-aminopropyl)-1,3-diaminopropane (Thermine) Tetrahydrochloride (9·4HCl).** **8** (220 mg) gave 280 mg of **9**·4HCl (81%): mp > 260 °C; $^1H$ NMR ($D_2O$) $\delta$ 1.87–2.37 (m, 6H), 3.03–3.35 (m, 2H); $^{13}C$ NMR ($D_2O$) $\delta$ 25.5, 26.6, 39.5, 47.4, 47.6. Anal. Calcd for $C_9H_{28}Cl_4N_4$: C, 32.33; H, 8.38; N, 16.76. Found: C, 32.3; H, 8.4; N, 17.0.

**Synthesis of Triamine 11 by Reductive Amination. 1-Azido-4-[*N*-(3-azidopropyl)amino]pentane (10).** This compound was prepared according the procedure described for the synthesis of **1k**. Azide **1b** (1.0 g, 10.0 mmol) and 318 mg of 5-azidopentan-2-one (2.5 mmol) gave 420 mg of **10** (80%): bp 70–75 °C (0.06 mmHg); IR (neat, $cm^{-1}$) 2110 ($N_3$); $^1H$ NMR $\delta$ 0.91 (s, 1H), 1.06 (d, 3H, $J$ = 6.2), 1.30–1.56 (m, 2H), 1.63 (quint, 2H, $J$ = 6.7), 1.74 (quint, 2H, $J$ = 6.8), 2.59–2.78 (m, 3H), 3.28 (t, 2H, $J$ = 6.8), 3.37 (t, 2H, $J$ = 6.6); $^{13}C$ NMR $\delta$ 18.0, 26.8, 27.9, 32.3, 45.0, 51.0, 53.4, 57.0. Anal. Calcd for $C_8H_{18}ClN_7$ (hydrochloride): C, 38.78; H, 7.27. Found: C, 38.7; H, 7.4.

***N*¹-(3-Aminopropyl)-2-methyl-1,4-diaminobutane (11).** Catalytic hydrogenation of 440 mg (2.0 mmol) of **10** according to the procedure used for **5e** gave 300 mg of **11** (90%): bp 65–70 °C (0.1 mmHg); $^1H$ NMR $\delta$ 1.04 (d, 3H, $J$ = 6.2), 1.29–1.50 (m, 9H), 1.62 (quint, 2H, $J$ = 6.9), 2.57–2.73 (m, 5H), 2.76 (t, 2H, $J$ = 6.8); $^{13}C$ NMR $\delta$ 20.3, 30.2, 34.1, 34.3, 40.6, 42.4, 45.2, 53.2. Anal. Calcd for $C_{26}H_{30}N_{12}O_{21}$ (tripicrate, mp 244–246 °C): C, 36.88; H, 3.54; N, 19.85. Found: C, 37.0; H, 3.6; N, 19.8.

**Synthesis of Triamine 13 by Pseudo-Michael Addition. 1-Azido-4-[*N*-methyl-*N*-(2-cyanoethyl]aminopentane (12).** Acrylonitrile (56 mg, 1.0 mmol) was added dropwise at 0 °C to a solution of the azide **1k** (150 mg, 1.0 mmol) in 1 mL of ethanol. After 30 h at room temperature, the solvent was removed under reduced pressure. Bulb-to-bulb distillation gave 170 mg of **12** (82%): bp 70–75 °C (0.01 mmHg); IR (neat) $\nu$ 2095 ($N_3$), 2260 (CN); $^1H$ NMR $\delta$ 0.86 (d, 3H, $J$ = 6.6), 1.10–1.53 (m, 6H), 2.14 (s, 3H), 2.38 (t, 2H, $J$ = 6.8), 2.50–2.70 (m, 5H); $^{13}C$ NMR $\delta$ 13.5, 17.3, 30.7, 30.9, 36.1, 42.0, 48.8, 58.2, 119.0. Anal. Calcd for $C_{15}H_{20}N_8O_7$ (picrate, mp 52–56 °C): C, 42.45; H, 4.71. Found: C, 42.5; H, 4.9.

***N*¹-(3-Aminopropyl)-*N*¹-methyl-1,4-diaminopentane (13).** Compound **12** (130 mg, 0.75 mmol) was dissolved in 10 mL of ethanol. The reaction mixture was saturated with $NH_3$. After addition of Raney nickel slurry (150 mg), the mixture was shaken under a hydrogen atmosphere (40 psi) for 15 h. Following the removal of the solvent, the residue was purified by bulb-to-bulb distillation to give 95 mg of **13** (72%): bp 55–60 °C (0.1 mmHg); $^1H$ NMR $\delta$ 0.92 (d, 3H, $J$ = 6.5), 7.20–1.32 (m, 1H), 1.35–1.65 (m, 9H), 2.16 (s, 3H), 2.32–2.51 (m, 2H), 2.57–2.69 (m, 1H), 2.68 (t, 2H, $J$ = 6.8), 2.74 (t, 2H, $J$ = 6.8); $^{13}C$ NMR 13.1, 30.9, 31.2, 31.7, 36.4, 40.6, 42.3, 51.1, 58.0. HRMS $m/z$ 173.1891 $M^{+\cdot}$; calcd for $C_9H_{23}N_3$ 173.1901. Anal. Calcd for $C_{27}H_{32}N_{12}O_{21}$ (tripicrate): C, 37.94; H, 3.79. Found: C, 37.7; H, 3.7.

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