A Mild and General Solid-Phase Method for the Synthesis of Chiral Polyamines. Solution Studies on the Cleavage of Borane−Amine Intermediates from the Reduction of Secondary Amides

Sukhdev Manku, Carmen Laplante, Dan Kopac, Timothy Chan, and Dennis G. Hall*

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

dennis.hall@ualberta.ca

Received September 14, 2000

A mild oxidative workup protocol using iodine in an acetic acid−acetate buffer solution is described for the cleavage of borane−amine adducts arising from the borane-promoted reduction of polyamides supported onto practical trityl-based resins. Chiral polyamines with diverse side-chain functionalities can be generated as free bases without premature release from the solid support and with essentially no racemization using this method. A series of model oligomeric secondary diamides **6** containing various α-amino acid residues (Val, Phe, Tyr, Ser, Cys, Met, Gln, Trp) provided triamine products **8** in high yields and good to excellent purity. On the other hand, a substrate containing a tertiary amide (**15**) formed a rather unusual triaminoborane intermediate that required more stringent workup conditions to liberate the polyamine product **20**. The reduction of oligomeric tertiary amides such as **9** was found sluggish, but these compounds could nonetheless be obtained in high purity from in situ reductive amination of the corresponding secondary amines. Control studies, carried out in solution with model secondary amide **23**, confirmed the efficiency of the buffered iodine solution and highlighted several advantages (no heating necessary, no need for strong bases or acids) over existing methods for the cleavage of borane−amine adducts. A possible mechanism involving all buffer components (iodine, acetic acid, and acetate ion) is proposed in which borane−amine adducts are transformed first to the monoiodoborane−amine and then to the corresponding acetoxyborane−amine adduct of much weaker coordination affinity. The latter would dissociate readily and get trapped by the acetic acid to provide the desired secondary amine. This reduction/oxidative workup protocol is useful as a general method for the facile solid-phase synthesis of polyamines for eventual release in solution and use in various applications. It is also potentially very useful toward the synthesis and screening of bead-supported libraries of free oligoamines assembled through split-pool methods.

Introduction

Polyamines, exemplified in particular by spermine and spermidine, are ubiquitous biomolecules of prime importance in living systems.[1−3] In fact, polyamines constitute one of very few classes of small organic compounds capable of interacting with the three natural biopolymers: polypeptides and proteins, nucleic acids, and oligosaccharides.[1,4] Being mainly fully protonated in water at physiological pH, polyamines are cationic molecules. As such, they are involved in a variety of biological processes dependent upon the condensation and structural stabilization of DNA[5] and RNA[6] via electrostatic interactions with phosphate anions. Biogenic polyamines also have an essential role in cell growth and differentiation.[1,7] Various analogues have been evaluated as potential drugs against cancer,[8] other diseases,[3] and as gene delivery agents.[9] Several insects employ polyamine-based compounds as venom constituents for paralyzing preys or predators.[10] One such example is philanthotoxin-433, produced by the digger wasp *Philanthus triangulum*,[11] and known to inhibit signal transmission in the central nervous system of mammals.[12] In addition, acyclic and macrocyclic oligoamines such as cyclen are useful as

* To whom correspondence should be addressed. Tel.: (780) 492-3141. Fax: (780) 492-8231.

(1) Cohen, S. S. *A Guide to the Polyamines*; Oxford University Press: New York, 1998.

(2) Blagbrough, I. S.; Carrington, S.; Geall, A. J. *J. Pharm. Sci.* **1997**, *3*, 223.

(3) Karigiannis, G.; Papaioannou, D. *Eur. J. Chem.* **2000**, 1841−1863.

(4) For an example of polyamine-based receptor for sugar-containing molecules, see: Eliseev, A. V.; Schneider, H.-J. *J. Am. Chem. Soc.* **1994**, *116*, 6081−6088.

(5) For a recent example, see: Blagbrough, I. S.; Al-Hadithi, D.; Geall, A. J. *Tetrahedron* **2000**, *56*, 3439−3447.

(6) For recent examples, see: (a) Frydman, B.; Westler, W. M.; Samejima, K. *J. Org. Chem.* **1996**, *61*, 2588−2589. (b) Olive, J. E.; Collins, R. A. *Biochemistry* **1998**, *37*, 6476−6484. (c) Hamachi, I.; Yamada, Y.; Eboshi, R.; Hiroaka, T.; Shinkai, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1215−1218.

(7) Tabor, C. W.; Tabor, H. *Annu. Rev. Biochem.* **1984**, *53*, 749−790.

(8) Tumor cell growth is often accompanied by unusually high levels of biogenic polyamine concentrations. The development of polyamine-based inhibitors for the anabolic enzymes has been considered as a potential approach for anticancer therapy. For a review, see: Marton, L. J.; Pegg, A. E. *Annu. Rev. Pharmacol. Toxicol.* **1995**, *35*, 55−91.

(9) For a recent example, see: Garrett, S. W.; Davies, O. R.; Milroy, D. A.; Wood, P. J.; Pouton, C. W.; Threadgill, M. D. *Bioorg. Med. Chem.* **2000**, *8*, 1779−1797, and references therein.

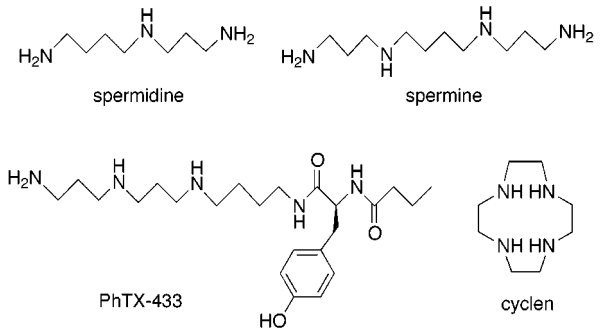
(10) Schulz, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 314−326.

(11) Eldefrawi, A. T.; Eldefrawi, M. E.; Konno, K.; Mansour, N. A.; Nakanishi, K.; Oltz, E.; Usherwood, P. N. R. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4910−4913.

(12) Bähring, R.; Mayer, M. L. *J. Physiol.* **1998**, *509*, 635−650.

10.1021/jo005647g CCC: $20.00
Published on Web 01/09/2001

artificial receptors[13] and as ligands for organometallic reagents and catalysts in organic synthesis.[14]



The importance of polyamines combined with their limited availability from natural or commercial sources have generated significant interest in the development of efficient methods to synthesize a wide variety of unnatural ones.[15] Our laboratory has initiated a program on the applications of libraries of polyamine derivatives in chemical biology and combinatorial catalysis. As part of these efforts we were prompted to develop an efficient and practical solid-phase synthetic methodology suitable for the production of large, bead-supported oligoamine libraries. Toward this end, the exhaustive reduction of polypeptide precursors appeared as a very attractive strategy.[16] First, solid-phase methods to access polypeptides are practiced routinely. Second, as opposed to a linear strategy in which masked diamine building blocks are added one by one through sequential manipulations of nitrogen-containing functionalities,[15,17] the reduction of polypeptide precursors constitutes an expedient, convergent strategy.[18] Moreover, this approach would allow the inclusion of chiral side chains derived from α-amino acids.

Mechanistically, the reduction of secondary amides by diborane is believed to proceed as shown in Figure 1.[19] Hydrogen evolution is first observed as a result of an acid−base reaction between the first equivalent of borane and three amidic hydrogens. Then, the resulting intermediate **I** requires the addition of two hydride equivalents per amide unit in order to effect complete reduction leading to the triaminoborane intermediate **II**.[20] In theory three hydride equivalents should be sufficient for the reduction of a secondary amide. It is known, however, that the formation of a stable borane−amine aminoborane adduct of type **III** occurs faster than the reduction of intermediate **I**. Under normal temperature conditions (<65 °C), species **III** are not sufficiently active to further reduce **I**. Consequently, excess borane is required to ensure complete reduction of **I** such that six hydride equivalents per amide are required in the overall process. A number of protocols were developed in order to avoid the unnecessary waste of an extra molar equivalent of borane. Brown and co-workers proposed the use of boron trifluoride,[21] a superior amine coordinating agent which is mutually compatible with borane, thus allowing the use of only one equivalent of the latter. Alternatively, it was found that the use of elevated temperatures such as refluxing toluene (110 °C) makes the use of only three hydride equivalents possible.[22] Presumably, the intermediate **III** initially formed is reductively active under these thermal conditions, thereby avoiding the addition of an extra equivalent of borane. The disproportionation of **III** to aminoborane **IV** and borane may occur, or perhaps a more plausible explanation is that the dissociation of **III** back to **II** and borane may become rapid enough to allow further reduction of leftover **I**. The above protocols with minimal borane, anyhow, do not constitute

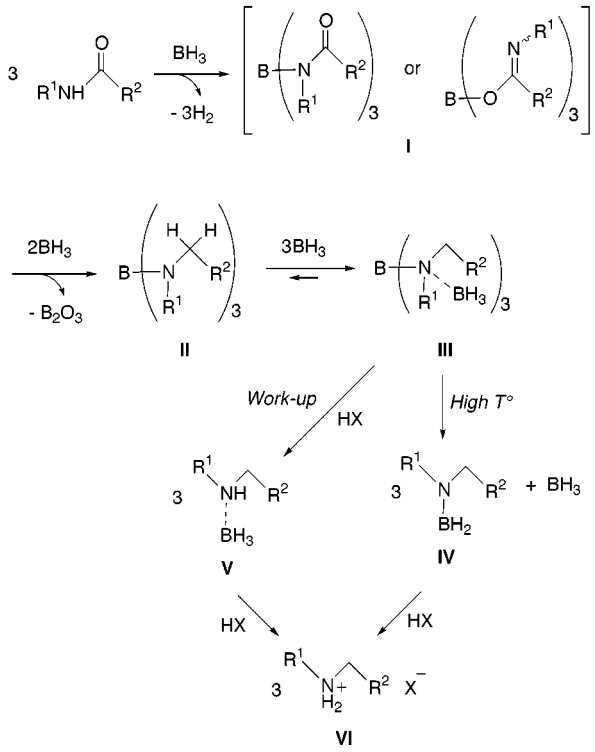


Figure 1. Mechanistic scheme showing probable intermediates in the reduction of secondary amides by borane.

(13) For a review, see: Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1995**, *95*, 2529−2586.

(14) For an example, see: Matsuo, J.-i.; Odashima, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 345−347.

(15) For recent reviews on the synthesis of polyamines, see ref 3, and: Kuksa, V.; Buchan, R.; Thoo Lin, P. K. *Synthesis* **2000**, 1189−1207.

(16) Selected examples of peptide reduction in solution-phase: (a) Roeske, R. W.; Weitl, F. L.; Prasad, K. U.; Thompson, R. M. *J. Org. Chem.* **1976**, *41*, 1260. (b) Northrop, R. C., Jr.; Russ, P. L. *J. Org. Chem.* **1977**, *42*, 4148. (c) Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *J. Org. Chem.* **1991**, *56*, 5196. (d) Cuervo, J. H.; Weitl, F.; Ostresh, J. M.; Hamashin, V. T.; Hannah, A. L.; Houghten, R. A. In *Peptides 1994, Proceedings of the 23rd European Peptide Symposium*; Maia, H. L. S., Ed.; ESCOM, Leiden, 1995; p 465.

(17) For examples of solid-phase hemisyntheses of polyamine derivatives elaborated from an advanced polyamine template, see: (a) Fauchet, V.; Bourel, L.; Tartar, A.; Sergheraert, C. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2559−2562. (b) Nash, I. A.; Bycroft, B. W.; Chan, W. C. *Tetrahedron Lett.* **1996**, *37*, 2625−2628. (c) Byk, G.; Frederic, M.; Scherman, D. *Tetrahedron Lett.* **1997**, *38*, 3219−3222. (d) Marsh, I. R.; Bradley, M. *Tetrahedron* **1997**, *53*, 17317−17334. (e) Page, P.; Burrage, S.; Baldock, L.; Bradley, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1751−1756. (f) Jefferson, E. A.; Sprankle, K. G.; Swayze, E. E. *J. Comb. Chem.* **2000**, *2*, 441−444.

(18) For examples of monoamide reduction on solid support, see: (a) Paikoff, S. J.; Wilson, T. E.; Cho, C. Y.; Schultz, P. G. *Tetrahedron Lett.* **1996**, *37*, 5653. (b) Brown, P. J.; Hurley, K. P.; Stuart, L. W.; Willson, T. M. *Synthesis* **1997**, 778.

(19) (a) Brown, H. C.; Choi, Y. M.; Narasimhan S. *J. Org. Chem.* **1982**, *47*, 3153−3163. (b) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.

(20) On the basis of possible structural restraints, the existence of intramolecular trimeric species such as **I** and **II** is not obvious in the reduction of hindered or rigid polyamides. Similarly, partial site isolation in solid-supported chemistry may alter the formation of such aggregates.

(21) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, 996−997.

(22) Bonnat, M.; Hercouet, A.; Le Corre, M. *Synth. Commun.* **1991**, *21*, 1579.

viable options in solid-phase chemistry where the use of excess reagents is necessary to favor reaction completion.

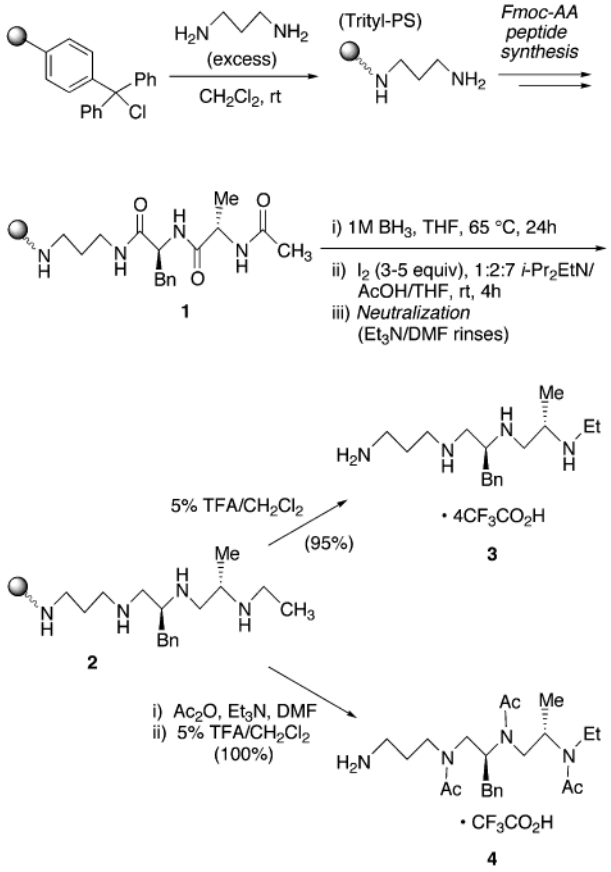
Several workup procedures have been reported for breaking up the robust borane−amine adducts **V** in solution-phase and provide the secondary amine product **VI** (Figure 1). Other reported conditions include basic hydrolysis with aqueous carbonate,[23] prolonged exposure to refluxing methanol,[24] and protolytic conditions such as the use of concentrated hydrochloric acid, aqueous saturated ammonium chloride (for tertiary amine−boranes)[25] or trifluoroacetic acid.[26] These conditions are incompatible with most types of useful acid- and base-sensitive supports and linkers for solid-phase synthesis. The use of strong acid conditions was described by Houghten and co-workers although the triamine products were cleaved from the Merrifield resin rather inconveniently with a special apparatus required to handle HF safely.[27] Another report describes the reduction of tritylpolystyryl-supported polyamides but in this case borane−amine cleavage is effected concomitantly with the release of polyamine products from the support using trifluoroacetic acid.[28] There remains a need for mild workup conditions to generate the free resin-bound polyamine without causing premature release from the support. The use of excess amines such as piperidine to effect borane exchange has been described on solid-phase.[29] Unfortunately, these methods require high temperatures and extended reaction times to allow sufficiently fast dissociation of borane−amine adducts.[30]

Recently, we have reported an alternative oxidative workup to cleave the borane−amine adducts with iodine in acetic acid−acetate buffered organic solvent.[31] These conditions were found very appropriate for the solid-phase synthesis of polyamines using the practical, mild acid-sensitive trityl resin. We have demonstrated the utility of this method in the preparation of PhTX-433 and analogues.[32] Herein, we disclose a thorough examination on the optimization and generality of this oxidative workup for the cleavage of borane−amine adducts from the reduction of solid-supported polyamides. A solution-phase study of mechanistic aspects and a comparison with other workup protocols are also discussed.

Results and Discussion

Optimization of a New Oxidative Workup for the Cleavage of Resin-Bound Borane−Amine Adducts. Preliminary investigations on the iodine-promoted workup were carried out using trityl-polystyrene bound $H_2N(CH_2)_3NH$-LPhe-LAla-Ac tripeptide **1** (Scheme 1).[33] The latter was easily assembled from 1,3-diaminopropyl

Scheme 1



tritylpolystyrene using standard methods for peptide synthesis with Fmoc-amino acids. For the reduction step, the use of a large excess of concentrated BH_3 (> 40 equiv) was found necessary to ensure complete reduction in a relatively short time. A reaction time of 24 h at 65 °C under nitrogen atmosphere was found sufficient for the reaction of model tripeptide substrate **1**, as evidenced by the absence of amide absorption by single bead Fourier transform infrared (FT-IR) microscopy, and by the absence of $[MH + n14]^+$ signals from underreduced residues in the electrospray mass spectrum (ES-MS) of cleaved tetraamine **3**. Longer reduction times, however, maybe necessary for longer polyamides and sterically hindered residues such as valine (vide infra). Efforts to increase the rate of polyamide reduction with the use of borane−DMS in refluxing toluene were in vain.[22] In addition, the combined use of equimolar amounts of borane, methylborate, and boric acid as described by Houghten and co-workers failed to give any reduction in our hands.[27]

Prior to the workup step, excess borane is rinsed away with dry THF. The resin is then suspended in the 7:2:1 THF/AcOH/DIPEA buffer system used for the actual workup. The use of buffered media, i.e., the presence of a trialkylamine, is required in order to trap the iodohydric acid released in the process, whereas the use of

(23) Schwartz, M. A.; Rose, B. F.; Vishnuvajjala, B. *J. Am. Chem. Soc.* **1973**, *95*, 612−613.
(24) Dubowchik, G. M.; Firestone, R. A. *Tetrahedron Lett.* **1996**, 37, 6465−6468.
(25) Ferey, V.; Vedrenne, P.; Toupet, L.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **1996**, *61*, 7244−7245.
(26) Choi, S.; Bruce, I.; Fairbanks, A. J.; Fleet, G. W. J.; Jones, A. H.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1991**, *32*, 5517−5520.
(27) Nefzi, A.; Ostresh, J. M.; Meyer, J.-P.; Houghten, R. A. *Tetrahedron Lett.* **1997**, *38*, 931.
(28) Karigiannis, G.; Mamos, P.; Balayiannis, G.; Katsoulis, I.; Papaioannou, D. *Tetrahedron Lett.* **1998**, *39*, 5117−5120.
(29) For recent examples of peptide reduction/piperidine exchange on methylbenzhydrylamine polystyrene resin followed by HF cleavage, see: (a) Nefzi, A.; Giulianetti, M. A.; Houghten, R. A. *Tetrahedron* **2000**, *56*, 3319−3326. (b) Nefzi, A.; Ong, N. A.; Houghten, R. A. *Tetrahedron Lett.* **2000**, *41*, 5441−5446. (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron* **1999**, *55*, 335−344, and references therein.
(30) (a) Reetz, T. *J. Am. Chem. Soc.* **1960**, *82*, 5039. (b) Baldwin, R. A.; Washburn, R. M. *J. Org. Chem.* **1961**, *26*, 3549. (c) Young, D. E.; McAchran, G. E.; Shore, S. G. *J. Am. Chem. Soc.* **1966**, *88*, 4390.
(31) Hall, D. G.; Laplante, C.; Manku, S.; Nagendran, J. *J. Org. Chem.* **1999**, *64*, 698−699.
(32) Wang. F.; Manku, S.; Hall, D. G. *Org. Lett.* **2000**, *2*, 1581−1583.
(33) Aliquots of all resin-bound peptide precursors were cleaved from the resin and provided satisfactory analytical data (ES-MS, ^1H NMR) (see Supporting Information).

excess acetic acid is required both as a protic/nucleophilic source and for maintaining a relatively mild pH (see mechanistic studies below). The aminotrityl linkage is fully tolerant of these conditions. A major proportion of THF is employed in order to allow sufficient swelling of the resin. Immersion of the resin is immediately followed by addition of excess iodine (typically 3−5 equiv per amide, added in a concentrated THF solution).[34] After a few hours, the resin is rinsed successively with THF, with a basic neutralizing solution (3:1 DMF/Et_3N) to form the free resin-bound tetraamine **2**, and then with methanol and dichloromethane. Whereas a bromophenol blue test performed prior to the oxidative workup is negative, the same test shows a positive outcome when performed at this final stage, thus hinting at the successful generation of a free polyamine. Supported product **2** was cleaved from the resin with dilute trifluoroacetic acid to give tetraamine **3** as a poly(trifluoroacetate)ammonium salt. Alternatively, it was fully acetylated to afford compound **4** after cleavage. Both reduced peptide derivatives **3** and **4** were obtained as crude material in high overall yield and were fully characterized. Analysis by RP-HPLC under both UV and ES-MS detection confirmed their high degree of purity (91% and 95%, respectively). At this stage, a comparison of the iodine-promoted workup with a borane-exchange protocol was carried out. To this end, model tripeptide **1** was reduced and then treated using either (a) the above conditions with iodine, (b) neat piperidine for 24 h at 65 °C,[29] or (c) direct addition of acetic anhydride to the resulting oligo(borane−amine) adducts (Ac_2O, Et_3N). Interestingly, acetic anhydride appeared to act as an electrophilic reagent of sufficient strength to breakdown the borane−amine adducts and subsequently acylate the resulting secondary amines to provide **4** in 78% crude yield, although with a lower purity (84%). The resin-bound products from the iodine-promoted workup and the piperidine-exchange were independently acetylated to afford **4** in quantitative yields. Both methods were found comparable as isolated crude materials from the borane-exchange workup provided purity of 89% and 94% for products **3** and **4**, respectively (see Supporting Information for chromatograms).

Although previous reports hint at the absence of epimerization in borane promoted reductions of peptide derivatives,[16] we wished to ascertain this by synthesizing all four diastereomers of supported tripeptide **1**.[33] After reduction/oxidative workup, the resulting diastereomeric tetraamines (Figure 2) were compared by NMR and optical rotation and analyzed by RP-HPLC to quantify the extent of epimerization at the side-chain centers. For instance, were LL-**3** to show partial epimerization at any one or both of its two stereogenic centers, the availability of all resulting diastereomers would allow detection and quantitation of racemization. Should it undergo complete racemization at all centers, two peaks of equal intensity corresponding to two racemic mixtures of diastereomeric tetramines would be detected. Optimal conditions for HPLC analysis were found where sets of tetraamine diastereomers are clearly separated. As shown in Figure 3, LD-**3** and DD-**3** gave effective separation when coinjected as an equimolar mixture. Yet, both give single peaks when injected independently. The DL-**3**/LL-**3** pair gave an identical outcome, indicating the absence of any appreciable racemization in this borane reduction/oxidative workup process. It remains unknown, however, whether all chiral amino acid residues behave similarly.

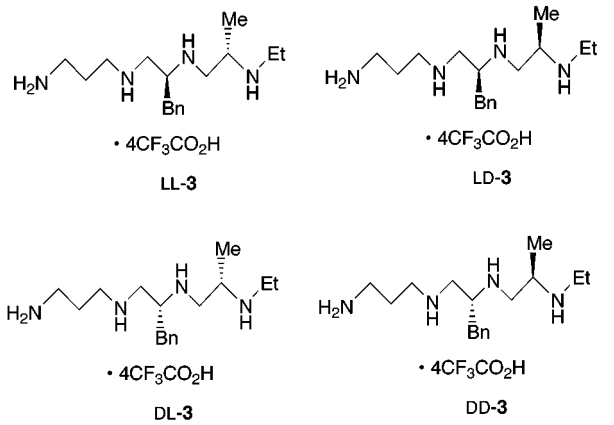


Figure 2. All four possible diastereomeric tetraamines **3** containing a reduced Phe-Ala dipeptide unit.

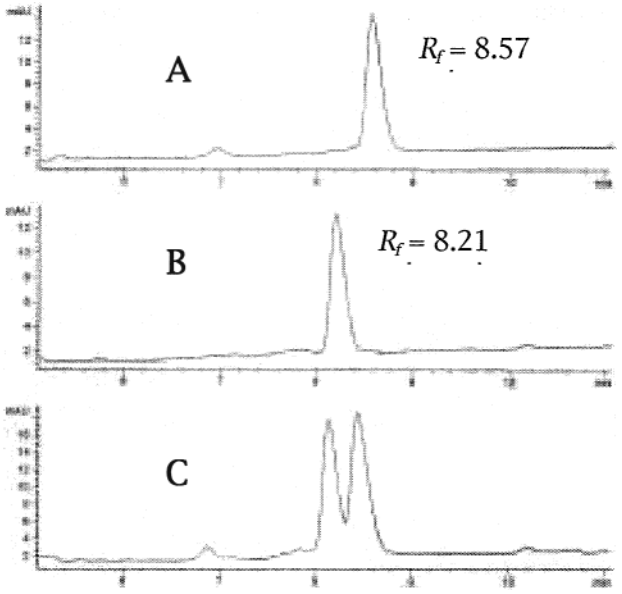


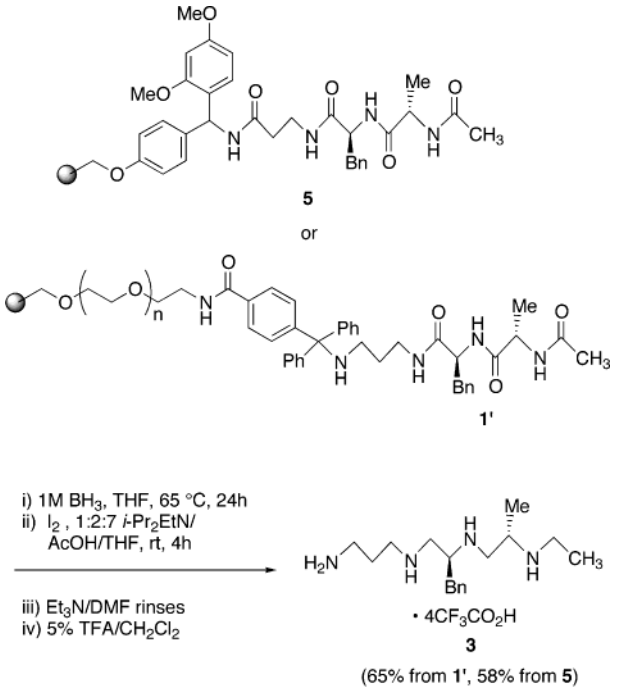
Figure 3. A: HPLC-ES-MS trace of **LD-3**. **B:** HPLC-ES-MS trace of **DD-3**. **C:** Co-injection of **LD-3** and **DD-3**. See Experimental Section for detailed conditions.

Scope of Compatible Linkers and Supports. Houghten and co-workers have previously reported similar peptide reductions on a methylbenzhydryl support that can withstand the strongly aqueous acid conditions employed to breakdown the resulting borane−amine adducts.[29] Unfortunately, this particular linker requires HF cleavage techniques to liberate the polyamine product. Although these can be performed safely with special apparatus, we have elected to develop conditions for working on trityl-based linkers for practical reasons. The loading of amines and other functionalities onto chlorotrityl resins is straightforward, and eventual cleavage of products can be carried out conveniently using dilute TFA.[35] We have also explored the use of Rink resin linker

(34) In some cases where lower amounts of iodine were used (e.g., 2 equiv/borane−amine adduct), a minor ($M^+ + 24$) peak corresponding to the molecular ion plus B_2H_2 was observed in the resulting ES-MS spectra of cleaved polyamine products. The use of larger amounts of iodine tends to suppress this peak.

(35) Nash, I. A.; Bycroft, B. W.; Chan, W. C. *Tetrahedron Lett.* **1996**, *37*, 2625−2628.

Scheme 2



(Scheme 2). Supported tetraamide **5**[33] was reduced and treated as described before but provided tetraamine **3**, after cleavage of the resin, with a noticeably lower purity and yield as compared to the trityl resin example described above. In addition, ester-based linkers such as the hydroxymethylphenoxy handle (Wang) were found unsuitable as the use of a large excess of borane under extreme conditions of temperature and time leads to significant levels of reductive cleavage. As expected, these stringent reaction conditions limit the possible choices of linker and support.

With the intent to plan on applications whereby water-soluble biomolecules could be screened against large libraries of bead-supported polyamines, we have also examined the suitability of polystyrene−poly(ethylene glycol) copolymers (e.g., Tentagel). Very few commercial PS-PEG resins are available with a trityl linker. To the best of our knowledge, all of these resins have the trityl linker attached either via a 4-carboxamide or a 4-phenoxy anchor. All our attempts with the latter type met with failure as none or little polyamine product was recovered following reduction, workup, and cleavage of the resin. Presumably, the phenoxymethylene group is reducible under these conditions, leading to premature release of the resin-bound material. On the other hand, as demonstrated with the synthesis of tetraamine **3** from supported tripeptide **1′**, the 4-carboxamide derivatized PS-PEG-trityl resin was found resistant to the reduction conditions although lower yield (65%) and purity (62%) were obtained as compared to the use of trityl-PS (Scheme 2). Moreover, it is likely that the linker's 4-carboxamide group also gets reduced to the corresponding secondary amine. This may be undesirable for on-bead screening applications and cases where the supported polyamine product must be further functionalized selectively. We are currently working on the development of a "borane-proof" trityl-based linker for PS-PEG copolymer supports.

Side-Chain Generality. The chemoselectivity of diborane has been well documented in the literature.[19] However, to assess the scope of compatible side-chain functionalities from α-amino acid components, we were interested in examining the combined effect of borane with the iodine-promoted workup. To this end, a series of model dipeptides **6** were synthesized and treated as described above (Scheme 3).[33] Some of the examples collected in Table 1 are particularly noteworthy. For instance, tyrosine-based dipeptide **6c** showed no sign of electrophilic ortho-iodination (entry 3). Similarly, *tert*-butyl-protected cysteine and methionine residues of **6e** and **6f** were found to be resistant under the oxidative workup and afforded respectively triamines **8e** and **8f** in excellent yields and purity (entries 5 and 6). Ester-containing dipeptides **6g** and **6h**, made respectively of

Scheme 3

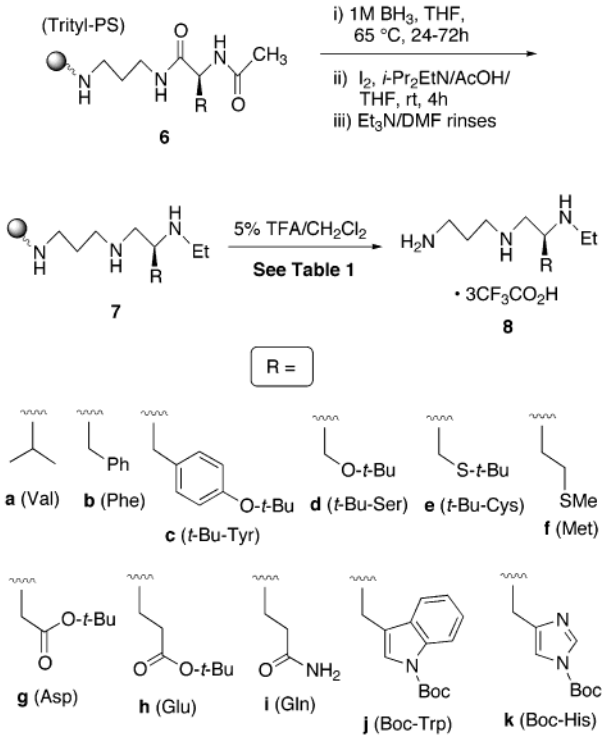


Table 1. Side-Chain Generality Study[a]

entry	peptide substrate	triamine product	yield[b] (%)	purity[c] (%)	ES-MS calcd	anal. obsd
1	**6a** (Val)	**8a**	79	>90	188.2	188.2
2	**6b** (Phe)	**8b**	75	95	236.2	236.2
3	**6c** (*t*-Bu-Tyr)	**8c**[d]	70	>90	252.2[d]	252.2
4	**6d** (*t*-Bu-Ser)	**8d**	61	90[e]	232.2	232.2[e]
5	**6e** (*t*-Bu-Cys)	**8e**	79	>95	248.2	248.2
6	**6f** (Met)	**8f**	90	90	220.2	220.2
7	**6g** (*t*-Bu-Asp)	**8g**[f]	81	–[f]	222.2	–[f]
8	**6h** (*t*-Bu-Glu)	**8h**[f]	79	–[f]	236.2	–[f]
9	**6i** (Gln)	**8i**[g]	95[h]	>80[h]	203.2[g]	203.2
10	**6j** (Boc-Trp)	**8j**	79	95	375.3	375.3
11	**6k** (Boc-His)	**8k**	–	–	326.3	–

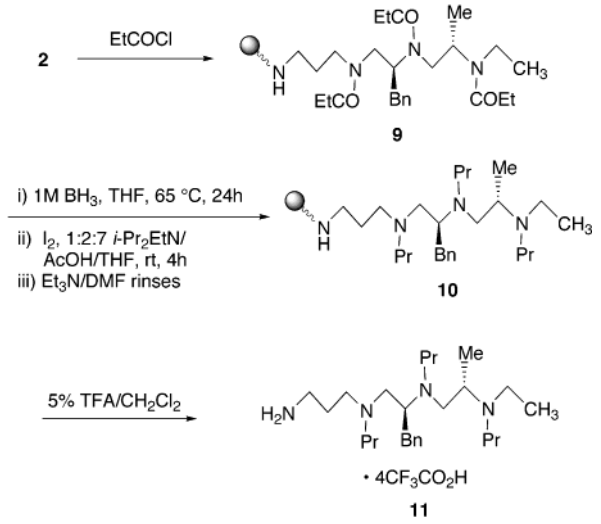
[a] General reaction conditions: typical scale 0.4 g resin **6**, 1 M BH_3, 65 °C, 1−5 d; workup: 2−3 equiv of I_2 in THF−AcOH−DIPEA 5:2:1. [b] Nonoptimized yields after cleavage from the resin (5% TFA/CH_2Cl_2, additives used when necessary) and one round of precipitation with ether. [c] Purity was estimated by ^{13}C NMR (peak height comparison between peaks from products **8** and unknown ones). [d] Significant loss of the *t*-Bu group was observed in the resin cleavage operation so it was characterized as a free phenol. [e] A 5−10% loss of the *t*-Bu group was observed. [f] The ester side chain undergoes modifications whereby a mixture of the corresponding *tert*-butyl ether and primary alcohol is obtained. [g] The glutamine side chain undergoes a modification to the corresponding primary amine. [h] Crude yield and purity (no ether precipitation).

protected Asp and Glu residues gave products **8g** and **8h** as mixtures containing variable proportions of the free alcohol side chain (from ester reduction) and the corresponding *tert*-butyl ether (entries 7, 8). None of the polyamine with intact *tert*-butyl ester group was observed. Indeed, it is known from the literature that the reduction of esters with proximal basic groups can lead to anomalous reduction products such as ethers.[36] As expected, the primary amide of glutamine-containing dipeptide **6i** was reduced to triamine **8i** with the corresponding side chain of ornithine (entry 9). Whereas tryptophan-containing substrate **6j** resisted our conditions and provided triamine **8j** cleanly (entry 10), histidine (i.e., **6k**) underwent degradation whether protected or not (entry 11). It is not clear at this point whether these problems originate from the reduction step or the iodine-promoted workup. Valine-containing polyamides such as dipeptide **6a** tend to undergo reduction at a slower rate (entry 1). For such hindered residues we have found it preferable to use longer reaction times (e.g., 72+ hours). Although crude materials were found of reasonable purity, all triamine tris(trifluoroacetatic acid) salt products described in Table 1 were further purified by ether precipitation and fully characterized. They were obtained in moderate to high yields and high purity by ^{13}C NMR analysis, although slight loss of the *tert*-butyl-based side-chain protective groups was occasionally observed as a consequence of the resin cleavage operation using 5% TFA/CH_2Cl_2.[37] In the case of tyrosine-containing triamine **8c**, significant loss of the *tert*-butyl group was found unavoidable; thus, it was characterized as its unprotected form.

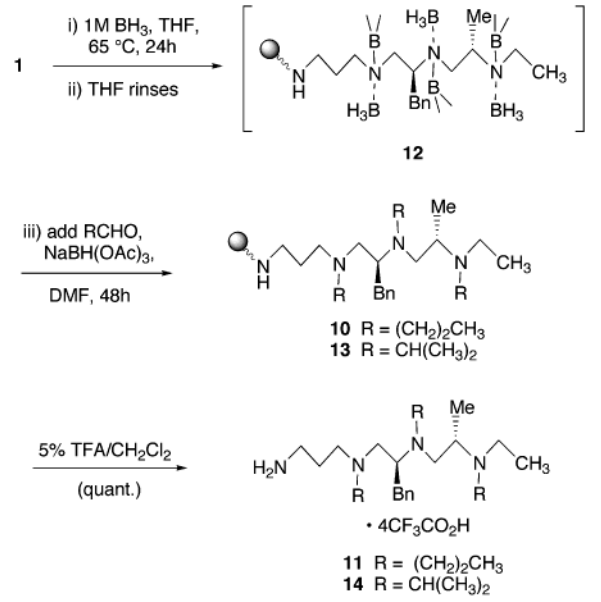
Reduction of Tertiary Amides. An Approach to Oligo(*tert*-amines). In principle, access to oligomeric tertiary amines could arise from the exhaustive reduction of a polypeptide made of tertiary amide residues. However, as a result of sluggish coupling rates between terminal secondary amines and activated amino acids, tertiary amides are difficult to synthesize using standard amide coupling methods. Therefore, we have examined the use of oligo(*sec*-amines) as precursors for oligo(*tert*-amines). Indeed, the former could be acylated to provide tertiary polyamide derivatives, and subsequent reduction would provide the oligo(*tert*-amines) with a constant lateral chain. We have tested this two-step approach to oligo(*tert*-amines) from model triamide **9** (Scheme 4). The latter was obtained from acylation of **2** with propionyl chloride.[33] The borane reduction of **9**, however, turned out to be very sluggish, giving a complex mixture of partial reduction products with little of the desired tetraamine **11** after 5 days at 65 °C. The reduction of a polybenzoylated analogue gave a similar outcome.

We were aware that borane−amine adducts can serve as hydride donors for the reductive amination of aldehydes.[38] Thus, we attempted the direct reaction of oligo(borane−amine) intermediate **12** (Scheme 5), the product from the reduction of **1** not subjected to any workup, with

Scheme 4



Scheme 5



excess propionaldehyde. Although some fully alkylated product **11** was obtained after cleavage of the resin, there were significant amounts of incomplete alkylation. Ultimately, this was solved by the in situ addition of sodium triacetoxyborohydride as external hydride source, providing tetraamine **11** in high yield and good purity. The use of a branched aldehyde, isobutyraldehyde, was also successful and afforded **14** cleanly. Interestingly, the same procedure performed with benzaldehyde resulted rather in large proportions of the putative, bridged *N*,*N*-acetals under all conditions examined. Apparently, this intramolecular side-reaction competes with hydride addition to the iminium intermediate in the case of aromatic aldehydes.

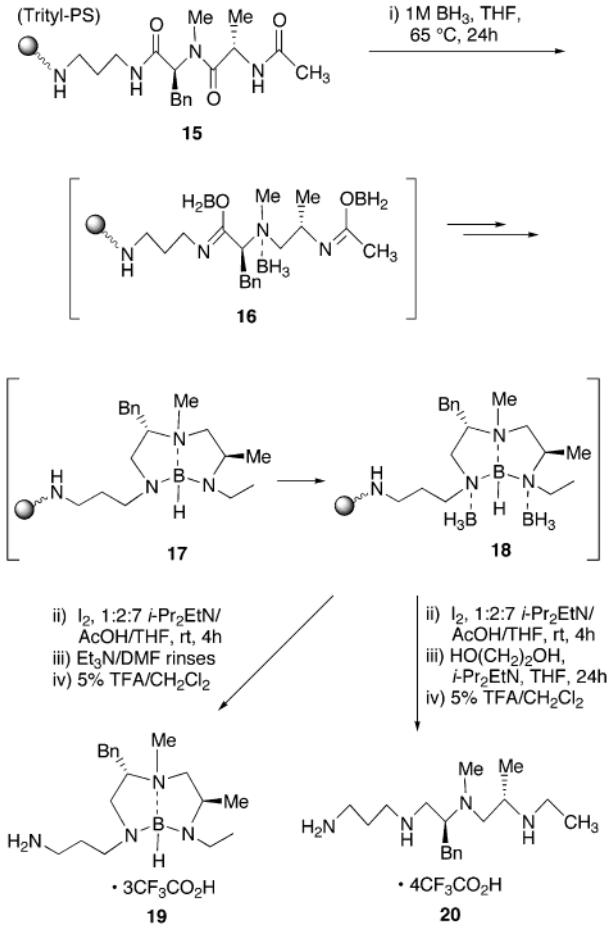
The reduction of model tripeptide **15** with a central tertiary amide was also investigated and resulted in a rather unexpected outcome (Scheme 6).[33] According to ^1H and ^{13}C NMR as well as ES-MS, the usual iodine-promoted workup and resin cleavage steps led to the isolation of triaminoborane **19** as major product. The ^{11}B NMR spectra confirmed the presence of boron with a chemical shift (18.3 ppm) consistent with a tetracoordinated species. An extra workup operation was required

(36) Kornet, M. J.; Thio, P. A.; Tan, S. I. *J. Org. Chem.* **1968**, *33*, 3637.

(37) The use of methanol has been found effective to rinse off products from the resin and provide increased yields. However, in the evaporation of filtrates containing dilute TFA in dichloromethane, methanol also tends to give increased cleavage of the *t*-Bu and Boc protecting groups.

(38) (a) Lane, C. F. *Aldrichimica Acta* **1973**, *6*, 51. (b) Hutchins, R. O.; Learn, K.; Nazer, B.; Pytlewski, D. *Org. Prep. Proc. Int.* **1984**, *16*, 335. (c) Carboni, B.; Monnier, L. *Tetrahedron* **1999**, *55*, 1197−1248.

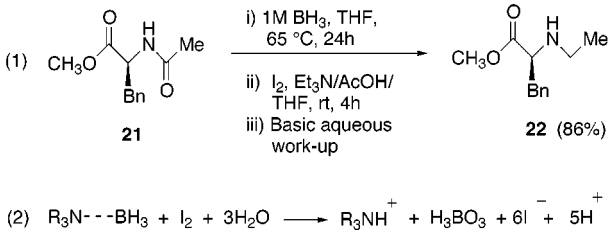
Scheme 6



in order to extrude boron by transesterification with ethylene glycol and isolate the desired tetraamine **20**. We tentatively attribute the anomalous behavior of triamide **15** to the faster reduction rate of tertiary amides with diborane. In the current case, we hypothesize that borane−amine adduct **16** is formed initially, allowing a facile double intramolecular hydride delivery to give intermediate **17**. The latter may also absorb excess borane to give **18** as end-product prior to the workup.

Mechanistic Studies and Comparison of Various Workup Protocols. The properties and reactivity of borane−amines have been extensively studied.[38] Yet, there are several mechanistic issues to be addressed in this new oxidative workup for borane−amine cleavage. First, evidence is required to explain the efficiency and exact role of the buffered iodine solution. In fact, the trifluoroacetic acid used to release the product from the support alone could cleave the multiple borane−amine adducts resulting from the solid-phase reduction of polyamides.[26] In other words, is the buffered iodine truly effective, or is it rather the TFA used in the product release operation that cleaves the borane−amine adducts? As stated in the Introduction, this is crucial toward applications requiring bead-supported free polyamines for screening purposes. By avoiding the TFA cleavage operation necessary in solid-phase reductions, the solution-phase reduction of amino esters unarguably addressed this first issue. For instance, we have treated *N*-acetyl amino acid ester **21** under the usual reduction conditions followed by the buffered iodine workup and obtained a high yield of crude *N*-alkylated product **22** with no traces of borane−amine adduct (Scheme 7, eq 1). In fact, there is precedent for the efficiency of iodine for the purpose of cleaving borane−amine adducts. A 1967 patent describes a method for the quantitative determination of borane−amines using iodine in a sodium acetate/acetic acid aqueous buffer.[39] In this method, the borane is titrated with 3 equiv of iodine in the presence of starch, giving a sharp and rapid end point. Boric acid, the amine, and six iodide ions are produced (Scheme 7, eq 2).

Scheme 7



Scheme 8

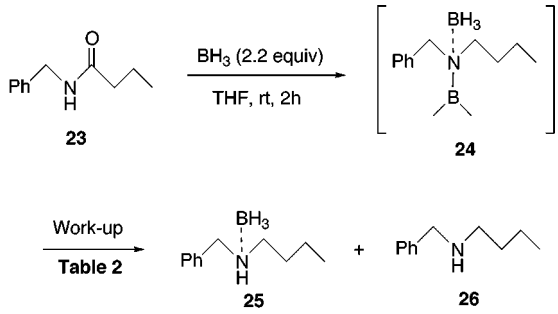


Table 2. Assays toward Mechanistic Studies

entry	conditions[a]	temp (°C)	time (h)	ratio **25:26** (%)[b]
1	acidic workup (aq 1 N HCl)	rt	2	0:100
2	no workup	rt	2	80:20
3	1:2:7 DIPEA/AcOH/THF	rt	2	60:40
4	same solvent, 0.5 equiv of I_2	rt	2	30:70
5	same solvent, 1.0 equiv of I_2	rt	2	0:100
6	MeOH/THF	rt	2	80:20
7	1:2:7 DIPEA/MeOH/THF	rt	2	80:20
8	same solvent, 1.0 equiv of I_2	rt	3	75:25
9	excess TFA, THF	rt	2	0:100
10	aq concentrated NaOH, THF	rt	20	75:25
11	1:9 DIPEA/THF	rt	2	85:15
12	morpholine (excess), THF	rt	2	0:100

[a] General conditions: model amide **23** was reduced with 2.2 equiv. BH_3, 65 °C, 3−4 h; then the indicated workup is applied, followed by addition of aqueous base and thiosulfate (if necessary), followed by extractions with diethyl ether. [b] Measured by comparison of integrals of representative signals from the ^{1}H NMR spectra of the crude reaction mixture (estimated error: 5%).

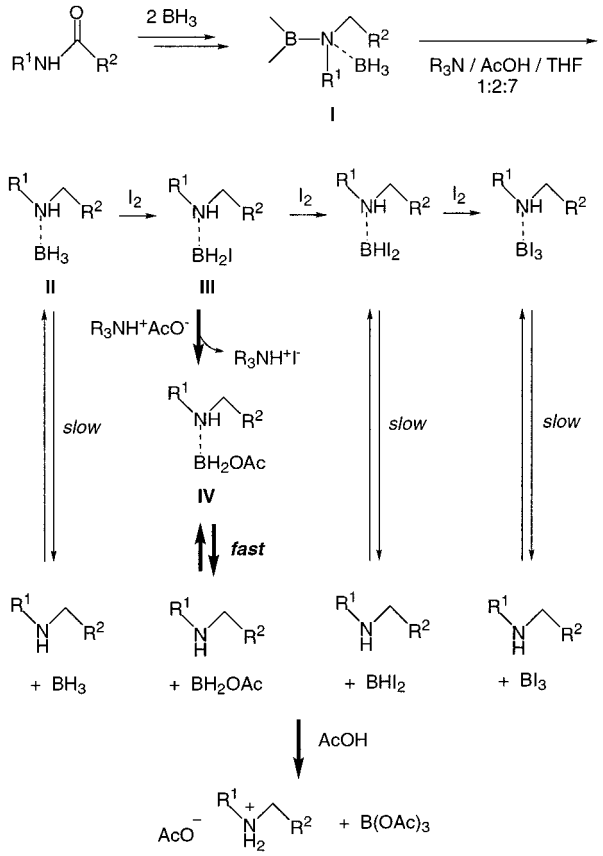
As indicated above, we have adapted our workup procedure in buffered organic solution in order to allow resin swelling, and we favored the use of excess iodine to ensure completion of borane−amine cleavage in a minimal time. We had previously observed that amounts of iodine beyond one equivalent lead to decolorization of the solution from purple to yellow and even clear. This is certainly understandable as three hydrides from the borane−amine adducts are potentially reducible. However, we wondered how many equivalents of iodine are truly necessary to ensure total cleavage of the borane−amine adducts. To this end, we have synthesized a simple

(39) Berzins, T. U.S. Patent 3,338,726 (Aug. 29, 1967).

model secondary amide (**23**) for solution-phase studies (Scheme 8). For comparison purposes, a sample of the amine product **26** was synthesized following a strong acid workup and basic extractions (Table 2, entry 1). In addition, the corresponding borane−amine adduct **25** was made independently from the reaction of amine **26** with one equivalent of borane. Next we planned a series of test reductions of **23** with a slight excess of borane (2.2 equiv) in THF and a workup with a variable amount of iodine in the usual buffered solution (excess 2:1 AcOH/DIPEA buffer added to the THF reaction mixture). Unless indicated otherwise, the reaction products were isolated following addition of aqueous base containing some thiosulfate (to neutralize any leftover iodine), and multiple extractions with diethyl ether. First, a control experiment in the absence of buffered iodine solution revealed that borane−amine adducts were cleaved to the extent of about 20% under the basic extraction conditions used to recover crude materials (entry 2). Also, a control workup with 1:2:5 DIPEA/AcOH/THF for 2 h in absence of iodine revealed substantial cleavage (40%) of the borane−amine adduct to give amine **26** (entry 3). Thus, by difference with the value obtained from entry 2, it appears that the acetic acid−acetate buffer alone can be accounted for approximately 20% cleavage of the borane−amine adduct **25**. The workup trial with 0.5 equiv of iodine gave 70% cleavage (entry 4). Finally, **25** was entirely transformed to **26** using only one equivalent of iodine (entry 5). Background cleavage makes it difficult to quantify the exact amount of borane−amine cleaved through the single action of iodine. However, these results confirm that iodine is required for achieving full cleavage within a reasonable time frame, and that a single equivalent seems sufficient to obtain the desired effect. The use of excess iodine, however, is advisable in order to accelerate solid-supported reactions.

The above observations led us to propose the preliminary mechanistic pathway shown in Scheme 9. First, the presence of any oxygen-based nucleophile such as acetate ion from the buffer is very likely to cleave the aminoborane unit of adduct **I** rapidly. Aminoborane compounds are known to be very labile whenever opportunity to form a new, thermodynamically favored B−O bond is present.[40,41] From the resulting borane−amine adduct **II**, increasing equivalents of iodine are expected to substitute each hydride successively to give the monoiodoborane (**III**), diodoborane, and ultimately the triiodoborane−amine adduct. The direct synthesis of monoiodo- and diiodoborane−amine adducts from the corresponding borane−amines and the required amount of iodine has been described long ago by Nöth.[42] There are very few relative kinetic measurements available for the acidic hydrolysis of these compounds.[43,44] However, the accepted general order of Lewis acidity for trihaloboranes is BF_3 < BH_3 < BCl_3 < BBr_3 < BI_3.[44,45] Consequently, substitution of hydrides in **II** for iodides is expected to strengthen the amine adducts and reduce their susceptibility to dissociate and undergo protolysis by the acid from the buffer. On the other hand, solvolysis by amines[46] and substitution of iodine in monoiodoborane amine adducts by charged nucleophiles have been shown possible.[47] It has been proposed that the mechanism is identical to an S_N2 reaction on a primary alkyl halide.[48] Herein, since a single equivalent of iodine is necessary for cleavage, we hypothesize that the monoiodide **III** is displaced by the acetate anion (present in large excess from the buffer) to give the acetoxyborane adduct **IV** (bold arrows in Scheme 9). However, due to the back-bonding of oxygen, the latter is a much weaker adduct than the monoiodoborane adduct and is thus expected to dissociate readily.[45,49] Under such circumstances, acetic acid would be strong enough a protic source to trap the free amine irreversibly and lead to solvolysis of the vulnerable, uncomplexed acetoxyborane. We have also tested the use of methanol in place of acetic acid but under all conditions tried, with or without iodine, no cleavage was observed over background (Table 2, entries 6−8) although decolorization of the solution lends to the suggestion that iodoborane−amine species are formed here as well. This points out

Scheme 9



(40) Steinberg, H.; Brotherton, R. J. *Organoboron Chemistry*; John Wiley and Sons: New York, 1966; Vol. 2.

(41) In fact the borane−amine adduct isolated after reduction of **23** without oxidative workup (entry 2) is identical to the authentic sample of **25** made directly by adding borane to amine **26**. This indicates that the aminoborane bond of **24** is hydrolyzed in the basic aqueous extractions performed to isolate crude materials.

(42) (a) Nöth, H.; Beyer, H. *Chem. Ber.* **1960**, *93*, 2251−2263. (b) Nöth, H.; Beyer, H.; Vetter, H.-J. *Chem. Ber.* **1964**, *97*, 110−118.

(43) Ryschkewitsch, G. E. *J. Am. Chem. Soc.* **1960**, *82*, 3290−3294.

(44) Nöth, H. In *Progress in Boron Chemistry*; Brotherton, R. J., Steinberg, H., Eds.; Pergamon Press: Oxford, 1970; Vol. 3, Chapter 4, pp 211−312.

(45) Young, D. E.; McAchran, G. E.; Shore, S. G. *J. Am. Chem. Soc.* **1966**, *88*, 4390−4396.

(46) (a) Douglass, J. E. *J. Am. Chem. Soc.* **1964**, *86*, 5431. (b) Ryschkewitsch, G. E. *J. Am. Chem. Soc.* **1967**, *89*, 3145.

(47) (a) Bratt, P. J.; Brown, M. P.; Seddon, K. R. *J. Chem. Soc, Dalton Trans.* **1974**, 2161−2163. (b) Mills, W.; Todd, L. J.; Huffman, J. C. *J. Chem. Soc., Chem. Commun.* **1989**, 900−901.

(48) Vedrenne, P.; Le Guen, V.; Toupet, L.; Le Gall, T.; Mioskowski, C. *J. Am. Chem. Soc.* **1999**, *121*, 1090−1091.

(49) Sana, M.; Leroy, G.; Wilante, C. *Organometallics* **1992**, *11*, 781.

for the need of a protic/nucleophilic source of sufficient strength in our workup procedure.

Other workup conditions reported in the literature were also evaluated (Table 2). The use of trifluoroacetic acid (entry 9),[26] albeit not applicable to the synthesis of trityl resin-bound polyamines, is extremely effective. On the other hand, basic aqueous conditions for borane exchange were found ineffective at room temperature (entry 10). Similarly, the use of a large excess of a tertiary amine like diisopropylethylamine (entry 11) to effect cleavage of **25** by borane exchange was unsuccessful under conditions comparable to the oxidative workup (rt, 2 h). Various attempts using phosphines and phosphites were also futile. On the other hand, much to our surprise, similar treatment with the secondary amine morpholine resulted in complete cleavage to **26** (entry 12). It remains uncertain if these particular conditions are equally efficient and practical on solid-phase at room temperature. We suspect that this is not the case as Houghten and co-workers describe the use of piperidine for their workup of solid-phase reductions at 65 °C for >12 h.[29]

Conclusions

In summary, we have described a mild workup protocol for the cleavage of borane−amine adducts arising from the reduction of polyamides supported onto practical trityl-based resin linkers. We have demonstrated that chiral polyamines with diverse side-chain functionalities can be generated as free bases without premature release from the solid support, and with essentially no racemization using this method. When subjected to this method, supported oligomeric secondary amides **6** provided triamine products **8** in high yields and good to excellent purity. On the other hand, substrates such as **15** containing a tertiary amide required more stringent workup conditions to liberate the polyamine product **20**. Model studies carried out in solution with model amide **23** confirmed the efficiency of the buffered iodine solution and highlighted several advantages (no heating necessary, no need for strong bases or acids) over existing methods for the cleavage of borane−amine adducts. Although the use of excess iodine is recommended in solid-phase applications, control solution-phase experiments revealed that only one equivalent of iodine is necessary to effect complete cleavage of borane−amine adducts. The acetic acid−acetate buffer also plays a crucial role since its replacement with methanol was found ineffective. Consequently, a possible mechanism involving all components (iodine, acetic acid, and acetate from the buffer system) is proposed in which borane−amine adducts are transformed first to the monoiodoborane−amine and then to the corresponding acetoxyborane−amine adducts of much weaker coordination affinity. The latter would dissociate readily and get trapped by excess acetic acid to provide the desired secondary amine in its protonated form.

Additional requirements encountered in solid-phase synthesis, such as the need to attach the substrate to a linker that resists subsequent transformations and can be cleaved selectively at the end, provide impetus on the development of increasingly more effective and milder reaction conditions. In turn, these methods can find use in solution-phase synthesis. In addition to showing that this new iodine-promoted workup is useful in the borane-promoted reduction of amides in solution, control experiments helped prove that the buffered iodine solution is truly effective for cleaving borane−amine adducts, as opposed to the trifluoroacetic acid employed in the resin cleavage operation. Therefore, this reduction/oxidative workup protocol is not limited as a general method for the synthesis of polyamines to be released and employed in solution. It is also potentially useful toward the screening of bead-supported libraries of oligoamine derivatives assembled through split-pool synthesis. Work in these directions is in progress and will be reported in due course.

Experimental Section

General. All Fmoc-amino acids and reagents employed are commercially available and were used without purification. All resins used were purchased from Rapp-Polymere (Tübingen, Germany) or NovaBiochem (San Diego, California). In most cases the loading value stated by the supplier was used. Solid-phase reactions that required heating were performed in glassware silanized by treatment with 20% TMSCl/toluene for >12 h. Those done at room temperature, including the iodine-promoted workups, were agitated inside polypropylene (PP) filter vessels. THF was dried by distillation over sodium/benzophenone ketyl. Anhydrous DMF was obtained commercially and stored at 4 °C to reduce decomposition to dimethylamine and carbon dioxide. ^{1}H NMR spectra were recorded at 300 MHz in CD_3OD while APT (Attached Proton Test) ^{13}C NMR spectra were recorded at 75.5 or 125 MHz in the same solvent (chemical shifts for both proton and carbon NMR are expressed in parts per million and were referenced against residual CHD_2OD). Signals arising from the trifluoroacetate counteranions were not listed. ^{11}B NMR were acquired at 64.2 MHz in CD_3OD. Low resolution electrospray mass spectra were acquired using atmospheric pressure ionization (API) with a quadrupole detector (positive mode). High resolution (HRMS) analyses was obtained on a time-of-flight instrument. Specific conditions for HPLC analysis whether using UV or ES-MS detection were described for each compound concerned.

General Procedure for the Synthesis of a Polyamide on 1,3-Diaminopropyl Trityl Resin. The 1,3-diaminopropyl tritylpolystyrene resin was weighed into a polypropylene filter vessel and rinsed three times with DMF. A 0.5 M solution of Fmoc-amino acid (2 equiv with respect to the commercial loading of the resin) in DMF was then added to the resin. The suspension was vortexed for 2 to 5 min before the addition of a 0.5 M DMF solution of either 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and *N*-hydroxybenzotriazole (HOBt·H_2O) (2 equiv for coupling onto primary amines) or 2-(1*H*-7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (2 equiv for secondary amines). After an additional 2 to 5 min of vortexing, DIPEA (4 equiv) was added. The suspension was then agitated on an orbital shaker for 1 to 2 h, drained, and rinsed five times with DMF. The Fmoc protecting group was removed by treating the resin with 20% piperidine in DMF two times—first for 5 min then for 30 min. The resin was then rinsed five times with DMF. Ninhydrin and bromophenol blue assay on the resin should be negative. Both the amino acid coupling and the Fmoc removal were repeated until the final amino acid was attached. To terminate the peptide sequence with an acetyl group the Fmoc group was first removed from the peptide. The resin was then swelled in DMF, and Et_3N (0.4 mL per gram of resin) was added. This suspension was vortexed for 2 to 5 min before the addition of acetic anhydride (1.0 mL per gram of resin). The suspension was agitated for 1 h after which time the resin was drained and rinsed with DMF (3×), methanol (3×), and dichloromethane (5×). It was then dried under high vacuum for 16 h.

General Procedure for the Borane Reduction/Iodine Workup of Resin-Bound Polyamides. To the resin-bound polyamide, weighed inside a silanized round-bottom flask, was

added the 1.0 M BH_3/THF solution (minimum of 10 equiv per amide) while under nitrogen atmosphere. The suspension was then refluxed gently (65 °C) under nitrogen atmosphere until the reaction was complete (typically 24−72 h). Upon being cooled to room temperature, the suspension was quickly transferred into a PP vessel via a silanized pipet using dry THF to rinse the flask. Dry THF, *i*-Pr_2NEt, and then glacial acetic acid were then added successively in a ratio of approximately 7:1:2 and for a total volume of ca. 10 mL/g resin. This was followed by the addition of iodine (3−5 equiv per borane−amine adduct) as a concentrated THF solution. The vessel was then agitated on an orbital shaker for 2−4 h at room temperature. Afterward the resin was filtered and rinsed with THF (3×), 1:3 Et_3N/DMF (3×), methanol (3×), and CH_2Cl_2 (5×) and dried under high vacuum for >12 h to give the resin-bound neutral polyamine.

Typical Cleavage of Polyamide/Polyamines from Solid Support (method A: for compounds with unfunctionalized side chains). To cleave the resin off the solid support, a portion was transferred into a round-bottom flask and stirred in a 5% TFA/CH_2Cl_2 solution (10−20 mL per gram of resin) for 1−2 h. The contents were then filtered through glass wool (or a fritted glass funnel), and the resin was rinsed thoroughly with 5% TFA/CH_2Cl_2 and methanol. The filtrate was evaporated and dried under high vacuum for >12 h to afford the crude polyamine as a poly(trifluoroacetate) ammonium salt.

Typical Cleavage of Polyamides/Polyamines from Solid Support (method B: for compounds functionalized or *t*-Bu/Boc-protected side chains). To a 0.5 g sample of the prepared resin bound, sulfur-containing polyamine in a round-bottom flask was charged dry CH_2Cl_2 (5.0 mL) (ca. 10 mL per gram of resin) followed by 50 μL of ethanedithiol (use 100 μL of triisopropylsilane instead if the peptide or triamine does not contain sulfur) and 0.25 mL of TFA. The resin was slurried for 0.5 h at room temperature and then filtered as above and rinsed into a round-bottom flask with CH_2Cl_2 (3×) and 10 mL of 1:1 CH_2Cl_2: dry MeOH. The filtrate was concentrated under reduced pressure in a bath that is below 20 °C. To the resulting residue was slowly added 20 mL of ether while vigorously swirling the flask. The ether was then decanted, and the remaining residue was placed under high vacuum for 12 h to provide the polyamine product as a poly(trifluoroacetate) ammonium salt.

12-Amino-(4*S*)-methyl-(7*S*)-benzyl-3,6,9-triazaundecane Tetrakis(trifluoroacetatic acid) Salt (LL-3). Resin-bound triamide **1** (0.351 g, 0.259 mmol, 0.74 mmol/g) was reduced as described in the general procedure to give the supported tetraamine **2**. A portion of the tetraamine (0.174 g, 0.134 mmol, 0.77 mmol/g) was cleaved to provide 95 mg (crude yield of 95%) of **LL-3** as a yellow oil. Purity by HPLC was 82% (a/a) (Depending on reaction scale and HPLC conditions a typical range of purity obtained for crude **3** was 80−95%). HPLC conditions; column: Zorbax XDB−C8 (4.6 × 50 mm, 3.5 μm); eluent: 10% acetonitrile (0.1% TFA) and 90% water (0.1% TFA) to 20% acetonitrile over 15 min at 0.70 mL/min; column temperature: 20 °C; detection: UV diode array at 250 nm; t_R = 8.109 min. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.38−7.18 (m, 5H), 3.24−2.84 (m, 12H), 2.79 (dd, J = 4.2, 13.5 Hz, 1H), 2.63 (dd,J = 7.8, 13.5 Hz, 1H), 2.20−2.00 (m, 2H), 1.31 (t, J = 7.3 Hz, 3H), 1.27 (d, J = 6.8 Hz, 3H). APT ^{13}C NMR (75.5 MHz, CD_3OD) δ: 138.5 (C), 130.3 (CH), 129.9 (CH), 127.9 (CH), 58.2 (CH), 54.9 (CH), 52.2 (CH_2), 49.2 (CH_2), 45.9 (CH_2), 41.3 (CH_2), 39.5 (CH_2), 37.8 (CH_2), 25.2 (CH_2), 14.8 (CH_3), 11.5 (CH_3). ESMS *m*/*z* 315.5 (M^+ + Na), 293.5 (M + H), 147.6 ((M^+ + 2H)/2). HRMS (ES) for $C_{17}H_{33}N_4$ (M^+ + H) calcd 293.270522, found 293.271472. IR (methanol cast) 3001 (N−H stretches), 1675, 1202, 1131, 799, 721. $[\alpha]_D$ = (+) 14.6° (*c* = 76.8 mg/mL in MeOH).

12-Amino-(4*R*)-methyl-(7*R*)-benzyl-3,6,9-triazaundecane Tetrakis(trifluoroacetatic acid) Salt, (DD-3). Crude yield: 92.5%. Purity by HPLC (same conditions as for **LL-3**): 86% (a/a); t_R = 8.234 min. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.40−7.20 (m, 5H), 3.22−2.84 (m, 12H), 2.80 (dd, J = 4.2, 13.5 Hz, 1H), 2.63 (dd, J = 7.8, 13.5 Hz, 1H), 2.18−2.00 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H), 1.28 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75.5 MHz, CD_3OD) δ: 138.5, 130.3, 130.0, 128.0, 58.2, 54.9, 52.0, 49.2, 45.9, 41.3, 39.3, 37.8, 25.2, 14.8, 11.5. ESMS *m*/*z* 315.5 (M^+ + Na), 293.5 (M^+ + H). HRMS (ES) for $C_{17}H_{33}N_4$ (M^+ + H) calcd 293.270522, found 293.270779. IR (methanol cast) 3006 (N−H stretches), 1673 cm^{-1}. $[\alpha]_D$ = (−) 14.7° (*c* = 24.3 mg/mL in MeOH).

12-Amino-(4*S*)-methyl-(7*R*)-benzyl-3,6,9-triazaundecane Tetrakis(trifluoroacetatic acid) Salt (LD-3). Crude yield: 99.5%. Purity by HPLC (same conditions as for **LL-3**): 78% (a/a); t_R = 9.261 min. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.40−7.20 (m, 5H), 3.24−2.82 (broad m, 12H), 2.65 (dd, J = 7.2, 7.2 Hz, 1H), 2.61 (dd,J = 7.8, 7.8 Hz, 1H), 2.14−2.00 (m, 2H), 1.30 (t, J = 7.5 Hz, 3H), 1.29 (d, J = 7.2 Hz, 3H). ^{13}C NMR (75.5 MHz, CD_3OD) δ: 138.5, 130.7, 130.0, 128.0, 58.4, 54.9, 52.0, 50.7, 45.9, 40.6, 39.2, 37.8, 25.2, 14.5, 11.6. ES-MS *m*/*z* 315.5 (M^+ + Na), 293.5 (M^+ + H). IR (methanol cast) 3006 (N−H stretches), 1675 cm^{-1}. HRMS (ES) for $C_{17}H_{33}N_4$ (M^+ + H) calcd 293.270522, found 293.270182. $[\alpha]_D$ = (+) 1.45° (*c* = 25.2 mg/mL in MeOH).

12-Amino-(4*R*)-methyl-(7*S*)-benzyl-3,6,9-triazaundecane Tetrakis(trifluoroacetatic acid) Salt (DL-3). Crude yield: 95%. Purity by HPLC (same conditions as for **LL-3**): 80% (a/a); t_R = 9.012 min. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.40−7.20 (m, 5H), 3.24−2.82 (broad m, 12H), 2.65 (dd, J = 8.4, 9.9 Hz, 1H), 2.60 (dd, J = 8.4, 8.4 Hz, 1H), 2.14−2.00 (m, 2H), 1.30 (t, J = 7.5 Hz, 3H), 1.29 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75.5 MHz, CD_3OD) δ: 138.5, 130.3, 130.0, 128.0, 58.4, 55.0, 52.0, 50.7, 46.0, 40.6, 39.3, 37.8, 25.2, 14.5, 11.8. ESMS *m*/*z* 315.5 (M^+ + Na), 293.5 (M^+ + H). HRMS (ES) for $C_{17}H_{33}N_4$ (M^+ + H) calcd 293.270522, found 293.270825. IR (methanol cast) 3006 (N−H stretches), 1674 cm^{-1}. $[\alpha]_D$ = (−) 1.17° (*c* = 28.3 mg/mL in MeOH).

***N*^{3,6,9}-Triacetyl-12-amino-(4*S*)-methyl-(7*S*)-benzyl-3,6,9-triazaundecane Trifluoroacetatic Acid Salt (4).** The supported tetraamine **2** (85.8 mg, 0.072 mmol, 0.84 mmol/g) was swelled in 1.0 mL of DMF. Et_3N (0.21 mL, 1.51 mmol) was then added and the resin vortexed for 1 min before the addition acetic anhydride (0.34 mL, 3.60 mmol). The suspension was agitated for 16 h, rinsed with DMF (3×), methanol (3×), and dichloromethane (5×), and then dried under high vacuum for >12 h to give the resin-bound triacetamide (0.130 g). A portion of the resin (26.4 mg, 0.020 mmol, 0.76 mmol/g) was cleaved from the support with 5% TFA/CH_2Cl_2 as described above to afford 10.6 mg (100% crude yield) of **4**. Purity by HPLC: 95% (a/a). HPLC conditions; column: Zorbax SB−C8 (4.6 × 50 mm, 3.5 μm); eluent: 10% acetonitrile (0.1% TFA) and 90% water (0.1% TFA) to 40% acetonitrile over 4 min and maintained for an additional 6 min at 0.90 mL/min; column temperature: 20 °C; detection: UV diode array at 210 nm; t_R = 5.649 min. ^{1}H NMR (300 MHz, CD_3OD) δ (complex mixture of 8 amide rotomers). IR (methanol cast) 2984.34 (N−H stretches), 1677, 1617. HRMS (ES) for $C_{23}H_{39}N_4O_3$ (M^+ + H) calcd 419.302217, found 419.301333.

(4*R*)-Isopropyl-9-amino-3,6-diazanonane Tris(trifluoroacetatic acid) Salt (8a). 1,3-Diaminopropane linked *N*-acetyl-L-valine trityl resin **7a** was constructed from **6a** as described above. Cleavage of the triamine product off of the resin (0.38 g, 0.37 mmol) was accomplished using method A mentioned above. After ether precipitation, an oily white solid corresponding to **8a** was obtained (0.16 g, 79% crude yield). ^{1}H NMR (CD_3OD) δ: 3.47 (m, 1 H), 3.41 (d, J = 3.5 Hz, 2H), 3.31−3.17 (m, 4H), 3.07 (t, J = 7.9, 7.5 Hz, 2H), 2.28 (m, 1H), 2.14 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H); ^{13}C NMR (CD_3OD) δ: 61.7, 47.0, 46.9, 43.1, 37.8, 28.7, 25.5, 18.3, 16.6, 11.4; HRMS (ES) for $C_{10}H_{26}N_3$ (M^+ + H) calcd 188.212673 found 188.212895. $[\alpha]^{25}_D$ = (+) 10.0° (*c* = 2.41, MeOH).

(4*S*)-Benzyl-9-amino-3,6-diazanonane Tris(trifluoroacetatic acid) Salt (8b). Phenylalanine-derivatized resin **7b** was constructed from **6b** as described above. Cleavage of the triamine product off of the resin (0.44 g, 0.41 mmol) was accomplished using method A. After ether precipitation, an off-white solid corresponding to **8b** was obtained (0.18 g, 75% crude yield). ^{1}H NMR (CD_3OD) δ: 7.5 (m, 5H), 3.93 (m, 1H), 3.51 (dd, J = 14.2, 7.7 Hz, 1H), 3.30−2.95 (m, 5H), 3.11 (t, J

= 7.6 Hz, 2H), 3.03 (t, J = 7.7 Hz, 2H), 2.08 (m, 2H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CD_3OD) δ: 135.9, 130.4, 130.3, 128.9, 57.9, 48.9, 46.8, 42.3, 37.7, 36.0, 25.4, 11.6; HRMS (ES) for $C_{14}H_{26}N_3$ (M^+ + H) calcd 236.212673 found 236.212665. $[\alpha]^{25}_D$ = (+) 8.52° (c = 6.19, MeOH).

(4*S*)-*p*-Hydroxybenzyl-9-amino-3,6-diazanonane Tris-(trifluoroacetatic acid) Salt (8c). Tyrosine-derivatized resin **7c** was constructed from **6c** as described above. Cleavage of the triamine product off of the resin (0.40 g, 0.39 mmol) was accomplished using method B. To characterize this compound in its unprotected form, the resulting concentrated crude residue (0.175 g) was then treated with a 95:5:5 TFA: triisopropylsilane:H_2O cleavage cocktail for 4 h at room temperature. The mixture was concentrated under reduced pressure, and 20 mL of Et_2O was added slowly to the residue. After precipation, the solvent was decanted off, and the residue was placed under high vacuum for 12 h to give off-white solid **8c** as a free phenol (0.15 g, 66% overall crude yield). ^{1}H NMR (CD_3OD) δ: 7.13 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 5.00 (br s), 3.84 (m, 1H), 3.47 (m, 1 H), 3.30−3.05 (m, 5H), 3.01 (t, J = 7.6 Hz, 3H), 2.85 (dd, J = 14.4 Hz, 8.7 Hz, 1H), 2.60 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CD_3OD) δ: 158.3, 131.5, 126.1, 117.1, 58.0, 48.9, 46.8, 42.3, 37.7, 35.2, 25.3, 11.6. HRMS (ES) for $C_{14}H_{20}N_3O$ (M^+ + H) calcd 252.207588 found 252.207932. $[\alpha]^{25}_D$ = (+) 6.63° (c = 6.42, MeOH).

(4*R*)-*tert*-Butoxymethyl-9-amino-3,6-diazanonane Tris-(trifluoroacetatic acid) Salt (8d). Serine-derivatized resin **7d** was constructed on solid support from **6d** as described above. Cleavage of the triamine product off of the resin (0.48 g, 0.39 mmol) was accomplished using method A mentioned above except there was no MeOH rinse forward, and the flask was evaporated in a cooled water bath to minimize clevage of the *tert*-butoxy group. A white oily solid corresponding to **8d** was obtained (0.14 g, 61% crude yield). The NMR data shows partial cleavage (5−10% of the *tert*-butyl protecting group). ^{1}H NMR (CD_3OD) δ: 3.80 (m, 3H), 3.49 (d, J = 4.7 Hz, 2H), 3.40 (m, 4H), 3.07 (t, J = 7.6 Hz, 2H), 2.15 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H), 1.23 (s, 9H); ^{13}C NMR (CD_3OD) δ: 75.96, 59.37, 55.7, 47.7, 46.9, 42.2, 37.7, 27.4, 25.3, 11.4; HRMS (ES) for $C_{12}H_{30}N_3O$ (M^+ + H) calcd 232.238888 found 232.238733. $[\alpha]^{25}_D$ = (−) 2.17° (c = 2.49, MeOH).

(4*R*)−(*tert*-Butyl)thiomethyl-9-amino-3,6-diazanonane Tris(trifluoroacetatic acid) Salt (8e). Cysteine-derivatized resin **7e** was constructed on solid support from **6e** as described above. Cleavage of the triamine product off of the resin (0.46 g, 0.45 mmol) was accomplished using method B mentioned above except there was no MeOH rinse forward. A pale yellow oil corresponding to **8e** was obtained (0.20 g, 79% crude yield). ^{1}H NMR (CD_3OD) δ: 5.05 (br s), 3.77 (m, 1H), 3.49 (d, J = 5.5 Hz, 2H), 3.34−2.93 (m, 7H), 2.97 (dd, J = 13.7, 7.1 Hz, 1H), 2.13 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H), 1.35 (s, 1.35, 9H); ^{13}C NMR (CD_3OD) δ: 56.4, 48.9, 46.9, 44.7, 42.1, 37.7, 31.0, 28.1, 25.2, 11.5. HRMS (ES) for $C_{12}H_{30}N_3S$ (M^+ + H) calcd 248.216045 found 248.215786. $[\alpha]^{25}_D$ = (+) 6.72° (c = 11.94, MeOH).

(4*S*)-(2′-Methylthio)ethyl-9-amino-3,6-diazanonane Tris-(trifluoroacetatic acid) Salt (8f). Methionine-derivatized resin **7f** was constructed on solid support from **6f** as described above. Cleavage of the triamine off of the resin (0.48 g, 0.46 mmol) was accomplished using method B, except there was no MeOH rinse forward. A pale yellow oil corresponding to **7f** was obtained (0.20 g, 78% crude yield). ^{1}H NMR (CD_3OD) δ: 4.90 (br s), 3.71 (m,1H), 3.43 (d, J = 5.3 Hz, 2H), 3.31−3.10 (m, 4H), 3.06 (t, J = 7.6 Hz, 2H), 2.65 (m, 2H), 2.12 (s, 3H), 2.16−1.98 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CD_3-OD) δ: 66.9, 55.8, 48.8, 46.9, 42.1, 37.8, 30.0, 29.3, 25.3, 15.1,-11.6; HRMS (ES) for $C_{10}H_{26}N_3S$ (M^+ + H) calcd 220.184745 found 220.185011. $[\alpha]^{25}_D$ = (+) 7.69° (c = 5.88, MeOH, turbid solution).

(4*S*)-(3′-Amino)propyl-9-amino-3,6-diazanonane Tetrakis(trifluoroacetatic acid) Salt (8i). Glutamine-derivatized resin **7i** was constructed on solid support from **6i** as described above. Cleavage of the triamine off of the resin (52 mg, 0.044 mmol) was accomplished using method A. A pale yellow oil corresponding to **7f** was obtained (30 mg, 95% crude yield). ^{1}H NMR (CD_3OD, 300 MHz) δ: 3.70−3.54 (m, 1H), 3.42 (d, J = 5.7 Hz, 2H), 3.28−3.12 (m, 4H), 3.10−3.02 (t, J = 7.6 Hz, 2H), 2.99 (t, J = 6.5 Hz, 2H), 2.22−2.00 (m, 2H), 1.96−1.76 (m, 4H), 1.30 (t, J = 6.9 Hz, 3H). ^{13}C NMR (CD_3OD, 125.3 MHz) δ: 56.2, 47.0, 42.1, 39.9, 37.8 (2), 26.8, 25.5, 24.2, 11.6. ES-MS: m/z (intensity) 203.1 (M^+ + H, 100), 231.1 (15), 245.1 (40). LC-ESMS: 0.1% MeCN (0.1% TFA): 99.9% H_2O (0.1% TFA), 0.50 mL/min for 10 min: peak corresponding to product at 1.383 min, mass of 203.2 m/z, purity based on LC-MS 80%. HRMS (ES) for $C_{10}H_{27}N_4$ (M^+ + H) calcd 203.223572 found 203.223771.

(4*R*)-((*N*-*tert*-butoxycarbonyl)-3-methylindolyl)-9-amino-3,6-diazanonane Tris(trifluoroacetatic acid) Salt (8j). Tryptophan-derivatized resin **7j** was constructed on solid support from **6j** as described above. Cleavage of the triamine product off of the resin (0.46 g, 0.32 mmol) was accomplished using method A, except there was no MeOH rinse forward. A light-brown solid corresponding to **8j** was obtained (0.18 g, 79% crude yield). ^{1}H NMR (CD_3OD) δ: 8.14 (d, J = 8.1 Hz, 1H), 7.71 (s, 1H), 7.64 (d, J = 7.3 Hz, 2H), 7.30 (m, 2H), 5.00 (br s), 4.00 (m, 1H), 3.50 (dd, J = 14.1, 7.7 Hz, 1H), 3.40 to 2.95 (m, 9H), 2.10 (m, 2H), 1.66 (s, 9H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CD_3OD) δ: 150.7, 137.0, 130.8, 126.5, 125.0, 124.1, 119.8, 46.4, 42.0, 37.8, 28.3, 25.9, 25.5, 11.6; HRMS (ES) for $C_{21}H_{35}N_4O_2$ (M^+ + H) calcd 375.276002 found 375.276561. $[\alpha]^{25}_D$ = (+) 1.62° (c = 6.56, MeOH).

***N*^{3,6,9}-Tripropyl-12-amino-(4*S*)-methyl-(7*S*)-benzyl-3,6,9-triazaundecane Tetrakis(trifluoroacetatic acid) Salt (11).** To the supported borane−amine adduct **12** (obtained after reduction of **1** not subjected to any workup, 0.250 g, 0.21 mmol, 0.84 mmol/g) swollen in DMF (4.0 mL) in a large PP vessel was added propionaldehyde (0.77 mL, 10.5 mmol) followed by vortexing for 10 min. At this time $NaBH(OAc)_3$ (2.44 g, 11.5 mmol) was added, and the suspension was agitated for 48 h. The suspension was then drained and washed with DMF (3×), methanol (3×), and dichloromethane (5×), and the resulting resin **10** was dried in vacuo. A small sample of the resin (22 mg) was then cleaved giving **11** (17 mg, 100% crude yield). HPLC-MS conditions; column: Zorbax XDB−C8 (2.1 × 50 mm, 5.0 μm); eluent: 15−85% MeCN (0.1% TFA) in water (0.1% TFA) over 2 min, and 85% for 4 min, 0.6 mL/min): single peak at 4.581 min corresponding to tetraamine product **11**. ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.45−7.20 (m, 5H), 3.6−2.52 (m, 20H), 2.18−1.86 (m, 3H), 1.82−1.42 (m, 4H), 1.44−1.16 (m, 9H), 1.1−0.9 (m, 7H). APT ^{13}C NMR (CD_3OD, 75.5 MHz) δ: 139.6 (C), 130.5 (CH), 130.0 (CH), 129.9 (CH), 127.9 (CH), 62.2 (CH), 58.4 (CH), 54.9 (CH_2), 52.0 (CH_2), 49.9 (CH_2), 46.1 (CH_2), 39.6 (CH_2), 37.8 (CH_2), 35.7 (CH_2), 27.6 (CH_2), 26.0 (CH_2), 25.2 (CH_2), 23.1 (CH_2), 19.7 (CH_2), 19.2 (CH_2), 12.1 (CH_3), 12.0 (CH_3), 11.2 (CH_3), 11.0 (CH_3), 10.6 (CH_3). IR (MeOH cast) in cm^{-1}: 3300−2600 (N−H stretch), 1674.36 (C═O, TFA salt), 1202.64 (C−N stretch), 1133.99 (C−N stretch) ESMS m/z (intensity): 515.5 (M^+ + TFA, 10), 419.5 (M^+ + H, 100), 317.4 (B−N compound, 20). HRMS (ES) for $C_{26}H_{51}N_4$ (M^+ + H) calcd 419.411373 found 419.410714.

***N*^{3,6,9}-Triisobutyryl-12-amino-(4*S*)-methyl-(7*S*)-benzyl-3,6,9-triazaundecane Tetrakis(trifluoroacetatic acid) Salt (14).** The supported borane-adduct **12** (0.84 mmol/g resin, 0.21 mmol) was treated with isobutyraldehyde (0.96 mL 10.5 mmol) and $NaBH(OAc)_3$ (2.44 g 11.5 mmol) as described above for **11**. A small sample of the resin (24 mg) was then cleaved with 5% TFA in CH_2Cl_2 giving **14** (20 mg, 100% crude yield). HPLC-MS conditions; column: Zorbax XDB−C8 (4.6 × 50 mm, 3.5 μm); eluent: 25−85% MeCN (0.1% TFA) in water (0.1% TFA) over 5 min, and 85% for 7 min, 0.7 mL/min): single peak at 6.258 min corresponding to product **14**. ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.40−7.18 (m, 5H), 3.6−2.70 (m, 13H), 2.55−2.45 (m, 1H), 2.40−2.25 (m, 1H), 2.20−1.85 (m, 4H), 1.8−1.6 (m, 1H), 1.5−0.78 (m, 29H). APT ^{13}C NMR (CD_3OD, 75.5 MHz) δ: 139.7 (C), 130.4 (2x CH), 129.9 (2x CH), 127.9 (CH), 63.1 (CH), 61.2 (CH), 60.5 (CH), 56.8 (CH_2), 53.3 (CH_2), 52.0 (CH_2), 46.4 (CH_2), 39.8 (CH_2), 37.9 (CH_2), 37.3 (CH_2), 28.0 (CH_3), 26.2 (CH_3), 25.8 (CH_3), 25.6 (CH_3), 25.2 (CH_2), 22.9 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 21.0 (CH_3), 20.9 (CH_3), 20.6 (CH_3), 11.7 (CH_3), 10.3

(CH_3). IR (MeOH cast) cm^{-1}: 3300−2600 (N−H stretch), 1674.38 (C═O, TFA salt), 1202.66 (C−N stretch), 1134.52 (C−N stretch). ES-MS *m/z* (intensity): 461.5 (M^+ + H, 100), 433.5 (8), 231.4 (M^+ + 2H, 15). HRMS (ES) for $C_{29}H_{57}N_4$ (M^+ + H) calcd 461.45823 obsd 461.457653.

***N*^{6}-Methyl-12-amino-(4*S*)-methyl-(7*S*)-benzyl-3,6,9-triazaundecane Tetrakis(trifluoroacetatic acid) Salt (20).** The resin bound triamide **15** (0.100 g, 0.104 mmol, 0.79 mmol/g) was subjected to borane reduction and subsequent iodine workup using the procedure described above. A small sample of the resin was cleaved with 5% TFA in CH_2Cl_2 giving a mixture of **19** and **20**. ^{11}B NMR analysis confirmed the presence of boron with a singlet at 18.31 ppm; HRMS (ES) for $C_{18}H_{34}BN_4$ (M^+ + H) calcd 317.287653 obsd 317.288218. To 50 mg of the resin, re-suspended in THF, was added DIPEA (0.100 mL, 2 mL/g resin), ethylene glycol (0.200 mL, 4 mL/g resin). The resulting suspension was agitated for 16 h at room temperature. The suspension was drained and washed with THF, methanol, and dichloromethane (3 times each). The resin was then dried in vacuo for >12 h. A small sample of the resin (15 mg) was cleaved with 5% TFA/CH_2Cl_2 giving tetramine **20** (yellow oil, 10 mg, 100% crude yield). HPLC-MS: using the same conditions as described for **11**: major peak at 5.252 min corresponding to tetraamine product **20** (purity >80%). ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.40−7.20 (m, 5H), 3.50 (m, 14H), 2.38 (s, 3H), 2.1 (m, 3H), 1.40−1.15 (m, 5H). APT ^{13}C NMR (CD_3OD, 125 MHz) δ: 139.4 (C), 130.2 (CH), 130.0 (CH), 127.8 (CH), 64.2 (CH_3), 58.4 (CH_2), 53.7 (CH), 46.2 (CH_2), 41.2 (CH_2), 38.0 (CH_2), 37.7 (CH), 32.4 (CH_2), 25.2 (CH_2), 14.4 (CH_3), 11.5 (CH_3). ES-MS *m/z* (intensity): 307.3 (M^+ + H, 100). HRMS (ES) for $C_{18}H_{35}N_4$ (M^+ + H) calcd 307.286172 obsd 307.286305.

***N*-Ethyl-L-phenylalanine Methyl Ester (22).** A solution of borane−tetrahydrofuran (1 M, 10.0 mL, 10.0 mmol) was added dropwise to a solution of amide **21** (1.0 g, 4.5 mmol) in dry tetrahydrofuran (10 mL) maintained at 0 °C. The resulting solution was warmed to room temperature, heated at 65 °C for 3 h, and then cooled back to room temperature. Triethylamine (2.0 mL), glacial acetic acid (3.0 mL), and iodine (1.25 g, 5.0 mmol, dissolved in 5 mL THF) were successively added. The mixture was stirred for 1 h, after which time a solution of aqueous sodium hydroxide (1 M, 100 mL) was slowly added, followed by aqueous saturated sodium thiosulfate (10 mL). The resulting mixture was extracted with diethyl ether (2 × 50 mL) and ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous magnesium sulfate, evaporated, and then dried under high vacuum. Crude amine **22** was obtained as an oil (0.85 g, 86%).^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40−7.15 (m, 5H), 3.63 (s, 3H), 3.55 (t, J = 7.0 Hz, 1H), 2.97 (AB m, 2H), 2.70−2.45 (AB m, 2H), 1.75 (br s, 1H), 1.07 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.9 (C), 137.1 (C), 128.9 (CH), 128.2 (CH), 126.5 (CH), 62.7 (CH_3), 51.3 (CH), 42.2 (CH_2), 39.5 (CH_2), 15.0 (CH_3). ES-MS *m/z* (intensity): 208.1 (M^+ + H, 100).

***N*-Benzyl Butyramide (23).** To a solution of benzylamine (6.0 mL, 0.055 mol) and triethylamine (15.2 mL, 0.110 mol) in anhydrous DMF (50 mL) was slowly added butyric anhydride (44.7 mL, 0.275 mol). The solution was stirred for 5 h at room temperature after which time it was reduced to half volume on a rotary evaporator. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with 10% aqueous acetic acid (3 × 30 mL), aqueous saturated sodium bicarbonate (3 × 30 mL), and brine (3 × 30 mL) and dried over anhydrous magnesium sulfate. The solution was evaporated, and the resulting light beige solid was dried under high vacuum for >12 h (7.16 g, 74%).^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40−7.25 (m, 5H), 5.70 (br s, 1H), 4.21 (d, J = 6 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.70 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H).

***N*′-Butyl-*N*-benzylamine (26).** A solution of borane−tetrahydrofuran (1 M, 2.50 mL, 2.50 mmol) was added dropwise to a solution of amide **23** (2.0 g, 11.3 mmol) in dry tetrahydrofuran (2.5 mL) at room temperature. The resulting solution was heated at 65 °C for 12 h and then cooled to room temperature. Methanol was added (1.0 mL) to neutralize excess borane. Then, a 4 M solution of HCl/dioxane (0.60 mL) was added slowly and stirred for 2.5 h. Aqueous sodium hydroxide (1 M, 15 mL) was added and the mixture was extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate, evaporated, and dried under high vacuum for no longer than 15 min in order to minimize evaporation of the amine product. Crude amine **26** was obtained as a clear oil in essentially pure form (1.5 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.4−7.2 (m, 5H), 3.80 (s, 2H), 2.60 (t, J = 7 Hz, 2H), 1.5 (m, 2H), 1.3 (m, 2H), 0.95 (t, J = 7 Hz, 3H). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.4−7.2 (m, 5H), 3.85 (s, 2H), 2.72 (m, 2H), 1.50 (m, 2H), 1.36 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H).

Borane−Amine Adduct 25. Under a nitrogen atmosphere, a solution of borane−tetrahydrofuran (1 M, 53 μL, 0.053 mmol) was added slowly to a solution of amine **26** (79 mg, 0.49 mmol) in tetrahydrofuran (1.0 mL) at room temperature. After 2 h, excess borane was neutralized by addition of a solution of methanol−tetrahydrofuran (1:1, 4 mL). The resulting solution was evaporated and dried under high vacuum to provide **25** as a white solid (85 mg). The chiral adduct shows several diastereotopically distinguished hydrogens by proton NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45−7.2 (m, 5H), 4.20 (dd, J = 14 Hz, 4 Hz, 1H), 3.66 (dd, J = 14 Hz, 9 Hz, 1H), 3.35 (br s, 1H), 2.68 (m, 2H), 1.68 (m, 1H), 1.58 (m, 1H), 1.19 (m, 2H), 2.0−1.3 (br s, 3H, $-BH_3$, merges as a sharp singlet (1.70 ppm) upon ^{1}H[^{11}B] decoupling)), 0.80 (t, J = 8 Hz, 3H). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.45−7.2 (m, 5H), 4.05 (d, J = 10 Hz, 1H), 3.55 (d, J = 10 Hz, 1H), 2.58 (m, 1H), 2.43 (m, 1H), 1.66 (m, 1H), 1.53 (m, 1H), 1.18 (m, 2H), 2.0−1.3 (br s, 3H, $-BH_3$), 0.83 (t, J = 7 Hz, 3H). ^{11}B [^{1}H] NMR (128.4 MHz, CD_3OD) δ: − 14.9 (q, J = 90 Hz). APT ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.5 (C), 129.3 (CH), 129.2 (CH), 128.9 (CH), 60.1 (CH_2), 53.2 (CH_2), 28.5 (CH_2), 19.9 (CH_2), 13.5 (CH_3).

Control Experiments for Iodine Equivalence. A sample of amide **23** (0.10 g, 0.57 mmol) was reduced with borane−tetrahydrofuran (1 M, 1.30 mL, 1.30 mmol) in tetrahydrofuran (1.3 mL) as described above for the preparation of **26**. The mixture was stirred at 65 °C for 12 h after which time it was cooled to room temperature. Diisopropylethylamine (0.75 mL) and glacial acetic acid (1.5 mL) were successively added, followed by the necessary amount of iodine indicated in Table 2 (as a concentrated THF solution). The solution was stirred for 3 h, and then aqueous saturated sodium thiosulfate (10 mL) and aqueous saturated sodium bicarbonate (15 mL) were added. The mixture was extracted with diethyl ether (3 × 15 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated and then dried under high vacuum for 15 min. The relative ratio of **25** and **26** was quantified by ^{1}H NMR analysis (integration and peak heights from representative signals).

Acknowledgment. This research was supported by the Natural Science and Engineering Research Council (NSERC) of Canada, the Alberta Heritage Foundation for Medical Research (AHFMR), a Research Innovation Award (to D.H.) from Research Corporation (Tucson, AZ), and the University of Alberta. AHFMR (to S.M.) and NSERC (to D.K.) are gratefully acknowledged for graduate scholarships.

Supporting Information Available: Characterization data (ESMS and ^{1}H NMR) for selected polyamide precursors cleaved from the support, and selected ^{13}C NMR and HPLC data for all polyamine products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005647G