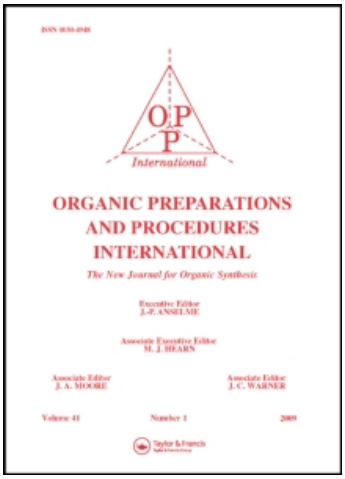

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CHEMOSELECTIVE SYNTHESIS OF PROTECTED POLYAMINES AND FACILE SYNTHESIS OF POLYAMINE DERIVATIVES USING *O*-ALKYL-*O'*-(*N*-SUCCINIMIDYL) CARBONATES

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CHEMOSELECTIVE SYNTHESIS OF PROTECTED POLYAMINES AND FACILE SYNTHESIS OF POLYAMINE DERIVATIVES USING *O*-ALKYL-*O'*-(*N*-SUCCINIMIDYL) CARBONATES

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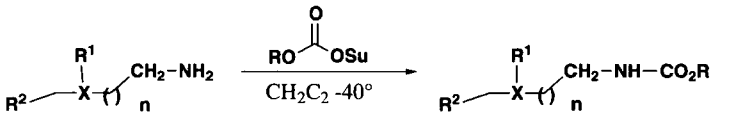
Recent interest in polyamines, which can serve as scaffolds for combinatorial libraries, peptidyl polyamines, chelates with gadolinium and other metals, has led to renewed efforts for their synthesis.[1-6] Previous syntheses of such compounds generally require cumbersome, stepwise synthesis from protected small amine building blocks.[7-9] Although there are literature examples describing synthesis of selectively protected polyamines, these methods employ reagents which initially afford mixtures that require extensive purification to afford the protected polyamine.[10] Krapcho described the protection of symmetrical alkanediamines which requires a large excess (5-10 equivalents) of amine to obtain the desired mono-protected carbamate;[11] however, in our hands this method produced mixtures which required purification when applied to other classes of polyamines. There exists no chemoselective method for the synthesis of polyamine carbamates which is practical, efficient, inexpensive and does not require purification. Herein we report the chemoselective protection of amino groups on primary carbons in various linear polyamines using *O*-alkyl-*O'*-(*N*-succinimidyl) carbonates and application of this method for the facile synthesis of polyamine derivatives.

Our initial efforts were directed to the products formed from of a variety of diamines with *O*-alkyl-*O'*-(*N*-succinimidyl) carbonates.[12] Typically, a succinimidyl carbonate (0.97 equivalents per



R = Benzy ort-Buty, Su = Succinmidyl

Diamines

A X= C-NH_2; R^1 = H or alkyl; R^2 = alkyl

B X= N ; R^1 = H; R^2 = alkyl, alkyl-OH

Triamines

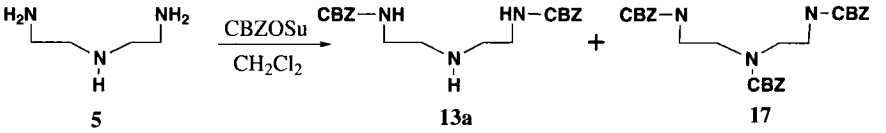
C X= N; R^1 = H; R^2 = alkyl-NH_2

D X= N; R^1 = H; R^2 = alkyl-NHBOC

Scheme 1

primary amine) in methylene chloride was added to a solution of polyamine in methylene chloride at -40° under nitrogen. After the reaction was complete, the product was isolated by aqueous workup to give the desired carbamate in good to high yield without any additional purification. Formation of the mono-protected diamine from unsymmetrical diamines was highly chemoselective (and economical using only 1.03 equivalents of diamine). This selectivity was observed for a primary amine on a primary carbon vs. case 1) a primary amine on a secondary carbon [**A** in Scheme 1 (R^2 = H); entries 1,2 in Table 1] or tertiary carbon [**A** in Scheme 1 (R^2 = alkyl); entries 3,4 in Table 1]; case 2, a secondary amine [**B** in Scheme 1; entries 5,6 in Table 1]. Additionally, a terminal alcohol group is unaffected during the selective protection of a primary amine in a polyamino alcohol [**B** in Scheme 1; entries 7,8 in Table 1].

The terminal bis-protection of a tri- or tetramine was accomplished using this method while previous syntheses of these compounds required a multi-step reaction sequence.[9] Selective protection of two primary amines in triamines and tetraamines was observed in the presence of a secondary amine(s) [**C** in Scheme 1, entries 9-12] to afford the desired product in good to high yields via a one step transformation. Our method was very amenable to scale- up of this transformation, e. g. reaction of **5** carried out on a larger scale (60-80 mmol) afforded **13a** and **13b** in 84% and 72% yield, respectively. The effect of reaction temperature was investigated in the formation of **13a** from the triamine **5**, see Scheme 2. Higher reaction temperatures afforded the primary carbamate product albeit in



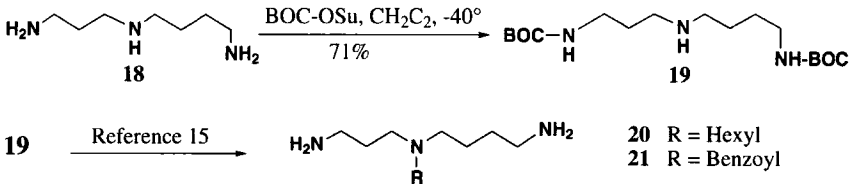
5 **13a** **17**

Temp	Yield (%)	Yield (%)
20°	37	35
0°	61	22
-40°	84	12
-78°	85	9

Scheme 2

significantly lower yield. For the differentiation of two primary amines in the presence of one or more secondary amines, it was essential to use lower temperatures to afford product (**13a**) in high yield.

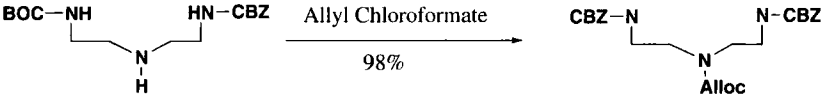
The practical utility of our method of selective protection of primary amines with *O*-alkyl-*O'*-(*N*-succinimidyl) carbonates is illustrated in the three following syntheses (Schemes 3-5). The first



Scheme 3

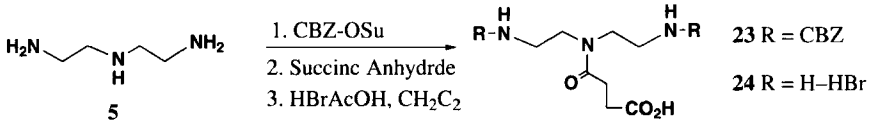
example is the facile synthesis of an intermediate (**19**) used in the preparation of N^4-spermidine derivatives, N^4-(hexyl)spermidine (**20**) and N^4-(benzoyl)spermidine (**21**), which have been found to be anticancer agents especially for leukemia[13,14] (Scheme 3). Previous syntheses of **19** required three to five steps and chromatographic purification to give **19** in 32-56% overall yield[15] while our method afforded **19** in 71% yield in one step from spermidine (**18**).

The orthogonal protection of polyamines is extremely useful in the synthesis of polyamine derivatives. A series of mono-protected polyamines,[11] were subjected to our procedure to afford differentially protected primary amines in high yield as shown in Scheme 1 [**D** in Scheme 1 and entries 13, 14 in Table 1]. A subsequent transformation allows for the synthesis of polyamine derivatives with different functionality (orthogonal protection) on each of the amines in a triamino or tetraamino polyamine, illustrated for the formation of orthogonally protected N^1-BOC, N^3-Alloc, N^5-CBZ triamine **22** in Scheme 4 (3 steps, 93% overall yield from diethylene triamine **5**), with no chromatographic purification necessary.



15 **Scheme 4** 22

Molecular scaffolds are of increasing value in synthesis, especially for the preparation of combinatorial libraries and dendrimers. The facile synthesis of a molecular scaffold using the chemoselective synthesis of primary amine carbamates is shown in Scheme 5. Diethylene triamine was transformed in three steps (73% overall yield) to afford the desired scaffold **24**, which has two amines and a carboxylic acid available for further synthetic transformations.



5

Scheme 5

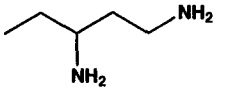
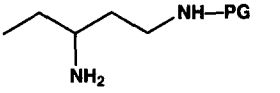
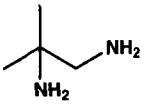
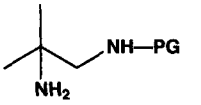
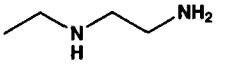
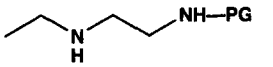
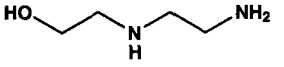
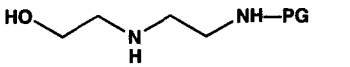
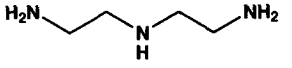
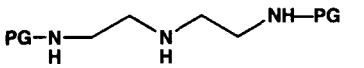
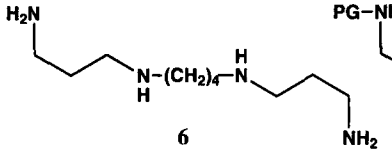
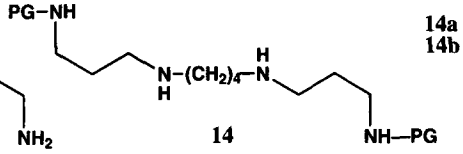
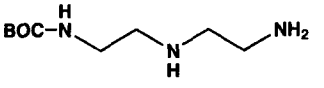
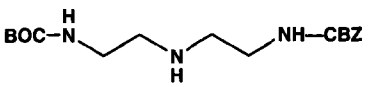
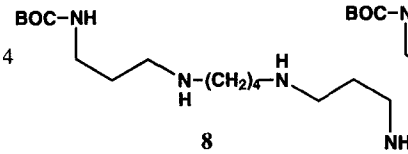
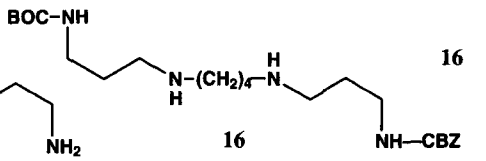
In summary, we have achieved a practical, efficient, and convenient synthesis of selectively protected polyamines using *O*-alkyl-*O'*-(*N*-succinimidyl) carbonates. The chemoselective transformation of the primary amine in a polyamine to a carbamate proceeds in good to high yield with no chromatographic purification necessary. This practical transformation has been shown to give differentially protected polyamines which are attractive building blocks for synthesis.

EXPERIMENTAL SECTION

All reagents were obtained from Aldrich, Milwaukee, WI except for *O*-*tert*-butyl-*O'*-(*N*-succinimidyl) carbonate[12] which was purchased from Fluka, Ronkonkoma, NY and were used without further purification, except where noted. CH_2Cl_2 was freshly distilled from CaH_2 under nitrogen. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were obtained as $CDCl_3$ solutions and recorded on a Varian Gemini 300 spectrometer. Low resolution mass spectra were determined on a Perkin-Elmer Sciex API III

electrospray ionization mass spectrometer. Melting points are uncorrected. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. All solvents employed were of HPLC grade, purchased from EM Science, Gibbstown, NJ and were used as received.

Table 1. Selective Protection of Polyamine Primary Amines with CBZ-OSu or BOC-OSu

Entry	Amine	Protected Amine[a]			Yield[b] (%)
1 2	 1	 9	**9a** **9b**	PG = CBZ PG = BOC	79 73
3 4	 2	 10	**10a** **10b**	PG = CBZ PG = BOC	97 80
5 6	 3	 11	**11a** **11b**	PG = CBZ PG = BOC	93 67
7 8	 4	 12	**12a** **12b**	PG = CBZ PG = BOC	94 63
10	 5	 13	**13a** **13b**	PG = CBZ PG = BOC	84 72
11 12	 6	 14	**14a** **14b**	PG = CBZ PG = BOC	77 63
13	 7	 15	**15**		96
14	 8	 16	**16**		69

a) PG = Protecting Group: CBZ = $PhCH_2OCO$-, BOC = *tert*-BuOCO- b) Yields were not optimized and all entries used 1 mmol polyamine with *O*-alkyl-*O'*-(*N*-succinimidyl) carbonate (0.97 mmol per primary amine on primary carbon). Yields calculated based on the limiting reagent, *O*-alkyl-*O'*-(*N*-succinimidyl)carbonate.

General Procedure for Selective Protection of Primary Amines on Primary Carbons.- A -40° solution of *O*-alkyl-*O'*-(*N*-succinimidyl) carbonate (0.97 mmol per primary amine) in CH_2Cl_2 (5 mL) was transferred by a double-tipped needle to a -40° solution of polyamine (1.00 mmol) in CH_2Cl_2 (5 mL) in a 25 mL round bottom flask under nitrogen. Reaction mixture was stirred at -40° for 3 hrs and allowed to gradually warm to room temperature overnight. Workup consisted of carefully pouring mixture into 50 mL Et_2O/75 mL pH 3, 100 mM phosphate buffer; separating and washing ether layer 1 x 10 mL pH 3 buffer; adjusting combined aqueous layers to pH 11 with 1 M aqueous NaOH; extracting 3 x 50 mL ethyl acetate and drying the combined ethyl acetate extracts over K_2CO_3. Solvents were removed *in vacuo* to afford desired product. Yields were calculated using amount of the limiting reagent, *O*- alkyl-*O'*-(*N*-succinimidyl) carbonate. All desired carbamate products were characterized by ^1H, ^{13}C NMR, and MS. Literature references are noted for the previously prepared compounds (**10a**, **11a**, **11b**, **14b**, **19**)[16] while the previously unknown carbamates are further characterized by high resolution mass spectra or elemental analysis.

***N*^{1}-(Carbobenzyloxy)-1,3-diaminopentane (9a)**.- A -40° solution of benzyl-succinimidyl carbonate (CBZ-OSu) (241 mg, 0.97 mmol) in CH_2Cl_2 (5 mL) was added to a -40° solution of 1,3-diaminopentane (**1**, 102 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) and ran as described above to afford 181 mg (79%) of **9a** as an oil. MS $[M+H]^+$ 237.1.

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 65.82; H, 8.50; N, 11.60

***N*^{1}-(Carbo-*tert*-butyloxy)-1,3-diaminopentane (9b)**.- A -40° solution of *tert*-butylsuccinimidyl carbonate (BOC-OSu) (209 mg, 0.97 mmol) in CH_2Cl_2 (5 mL) was added to a -40° solution of 1,3-diaminopentane (**1**, 102 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) and ran as described above to afford 143 mg (73%) of **9b** as an oil. MS $[M+H]^+$ 203.1.

Anal. Calcd for $C_{10}H_{22}N_2O_2$: C, 59.37; H, 10.96; N, 13.85. Found: C, 59.05; H, 10.79; N, 13.67

***N*^{1}-(Carbobenzyloxy)-1,2-diamino-2-methylpropane (10a)**.[16]- CBZ-OSu in CH_2Cl_2 (5 mL) was combined with a solution of 1,2-diamino-2-methylpropane (**2**, 88 mg, 1.00 mmol) as described in the general procedure to give 209 mg (97%) **10a** as an oil. MS $[M+H]^+$ 223.2.

***N*^{1}-(Carbo-*tert*-butyloxy)-1,2-diamino-2-methylpropane (10b)**.- BOC-OSu in CH_2Cl_2 (5 mL) was combined with a solution of 1,2-diamino-2-methylpropane (**2**, 88 mg, 1.00 mmol) as described in the general procedure to give 146 mg (80%) **10b** as a solid. MS $[M+H]^+$ 189.3; mp. 68-70°.

Anal. Calcd for $C_9H_{20}N_2O_2$: C, 57.42; H, 10.71; N, 14.88. Found: C, 57.33; H, 10.48; N, 14.77

***N*^{1}-(Carbobenzyloxy)-1-amino-3-azapentane (11a)**.[16]- CBZ-OSu in CH_2Cl_2 (5 mL) was added to a -40° solution of 1-amino-3-azapentane (**3**, 88 mg, 1.00 mmol) as described in the general procedure to give 200 mg (93%) **11a** as an oil after workup and removal of solvents *in vacuo*. MS: $[M+H]^+$ 223.1.

***N*^{1}-(Carbo-*tert*-butyloxy)-1-amino-3-azapentane (11b)**.[16]- BOC-OSu in CH_2Cl_2 (5 mL) was added to a -40° solution of 1-amino-3-azapentane (**3**, 88 mg, 1.00 mmol) as described in the general procedure to give 122 mg (67%) **11b** as an oil after workup and removal of solvents *in vacuo*. MS $[M+H]^+$ 189.3.

***N*^{1}-(Carbobenzyloxy)-1-amino-3-aza-5-hydroxypentane (12a)**.- A -40° solution of CBZ-OSu in CH_2Cl_2 (5 mL) was added to a solution of 1-amino-3-aza-5-hydroxypentane (**4**, 104 mg, 1.00 mmol)

in CH_2Cl_2 (5 mL) and ran as described above. Workup and removal of solvents *in vacuo* afforded 217 mg (94%) of **12a** as an oil. MS $[M+H]^+$ 239.1.

Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.48; H, 7.61; N, 11.76. Found: C, 60.25; H, 7.50; N, 11.53

***N*^{1}-(Carbo-*tert*-butyloxy)-1-amino-3-aza-5-hydroxypentane (12b)**.- A -40° solution of BOC-OSu in CH_2Cl_2 (5 mL) was added to a -40° solution of 1-amino-3-aza-5-hydroxypentane (**4**, 104 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) and ran as described in the general procedure. Workup and removal of solvents *in vacuo* afforded 124 mg (63%) of **12b** as an oil. MS $[M+H]^+$ 205.1. HRMS Calcd for $C_9H_{21}N_2O_3$ 205.1552; found 205.1557.

***N*^{1,5}-(Carbobenzyloxy)-1,5-diamino-3-azapentane (13a)**.- CBZ-OSu (482 mg, 1.94 mmol, 0.97 mmol per primary amine) in CH_2Cl_2 (5 mL) was combined with a solution of 1,5-diamino-3-azapentane (**5**, 103 mg, 1.00 mmol) as described in the general procedure to give 302 mg (84%) **13a** as an oil. MS $[M+H]^+$ 372.2.

Anal. Calcd for $C_{20}H_{25}N_3O_4$: C, 64.67; H, 6.78; N, 11.31. Found: C, 64.41; H, 6.75; N, 11.48

Scale-up of 13a.- A -40° solution of CBZ-OSu (32.7 g, 131.3 mmol) in CH_2Cl_2 (200 mL) was added to a -40° solution of diethylenetriamine (7.3 mL, 67.3 mmol) in CH_2Cl_2 (200 mL) and stirred overnight. Solvents were removed *in vacuo*, to the residue was added buffer (2000 mL, 0.05M phosphate)/ether (200 mL), adjusted to pH=3 and extracted with ether (2 x 900 mL). The aqueous layer was adjusted to pH 12 with 10 N NaOH, extracted with EtOAc (4 x 500 mL), washed organic layer with brine (1 x 500 mL) and dried over Na_2SO_4. Filtered mixture and removed solvents *in vacuo* to afford 21.7 g (87%) **13a**.

***N*^{1,5}-(Carbo-*tert*-butyloxy)-1,5-diamino-3-azapentane (13b)**.- BOC-OSu (418 mg, 1.94 mmol, 0.97 mmol per primary amine) in CH_2Cl_2 (5 mL) was combined with a solution of 1,5-diamino-3-azapentane (**5**, 103 mg, 1.00 mmol) as described in the general procedure to give 211 mg (72%) **13b** as an oil. MS $[M+H]^+$ 304.2.

Anal. Calcd for $C_{14}H_{29}N_3O_4$: C, 55.42; H, 9.63; N, 13.85. Found: C, 55.51; H, 9.47; N, 13.82

Scale-up of (**13b**)- A -40° solution of BOC-OSu (34.6 g, 160.7 mmol) in CH_2Cl_2 (200 mL) was added to a-40° solution of diethylenetriamine (8.9 mL, 82.4 mmol) in CH_2Cl_2 (200 mL) and stirred overnight. Solvents were removed *in vacuo*, to the residue was added buffer (1500 mL, 0.05M phosphate)/ether (200 mL), adjusted to pH=3 and extracted with ether (1 x 600 mL, 1 x 1000 mL). The aqueous layer was adjusted to pH=12 with 10 N NaOH, extracted with EtOAc (4 x 500 mL), washed organic layer with brine (1 x 500 mL) and dried over Na_2SO_4. Filtered, then solvents were removed *in vacuo* to afford 15.7 g (63%) **13b**.

***N*^{1,12}-(Carbobenzyloxy)-1,12-diamino-4,9-diazadodecane (14a)**.- A -40° solution of CBZ-OSu (482 mg, 1.94 mmol,) in CH_2Cl_2 (5 mL) was added to a -40° solution of spermine (**6**, 202 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) and ran as described above to afford 351 mg (77%) of the bis protected tetra amine **14a** as an oil. MS $[M+H]^+$ 471.3.

Anal. Calcd for $C_{26}H_{38}N_4O_4$: C, 66.35; H, 8.14; N, 11.391. Found: C, 66.20; H, 7.98; N, 11.73

TABLE 2. NMR Data for Carbamates **9a-19**

Cmpd	^{1}H NMR (δ: ppm, J: Hz)	^{13}C NMR (δ: ppm)
9a	7.35 (s, 5H), 5.70 (br s, 1H), 5.09 (s, 2H), 3.41-3.31(m, 1H), 3.30-3.18 (m, 1H), 2.72-.63 (m, 1H), 1.71-1.60 (m, 1H), 1.49-1.22 (m, 3H), 1.28 (br s, 2H), 0.90 (t, 2H, J = 7.91 Hz)	156.62, 136.78, 128.49(2C), 128.08, 128.03(2C), 66.39, 51.25, 38.82, 36.39, 31.26, 10.07
9b	5.20 (s, 1H), 3.40 (p, 1H, J = 6.61 Hz), 3.21-3.10 (m, 1H), 2.68-2.62 (m, 1H), 1.68-1.57 (m, 1H), 1.47-1.22 (m, 3H), 1.43 (s, 9H), 1.31 (br s, 2H), 0.91 (t, 2H, J = 7.42 Hz)	156.22, 78.87, 50.98, 38.1, 36.72, 31.01, 28.25(3C), 10.09
10a	7.36 (s, 5H), 5.19 (br s, 1H), 5.11 (s, 2H), 3.07 (d, 2H, J = 6.32 Hz), 1.29 (s, 2H), 1.09 (s, 6H)	157.04, 136.62, 128.53(3C), 128.12 (2C), 66.61, 52.41, 49.98, 28.08(2C)
10b	4.95-4.85 (br s, 1H), 2.99 (d, 2H, J = 6.32 Hz), 1.44 (s, 9H), 1.26 (s, 2H), 1.08 (s, 6H)	156.48, 78.85, 51.94, 49.98, 28.16(3C), 27.97(2C)
11a	7.36 (s, 5H), 5.23 (br s, 1H), 5.11 (s, 2H), 3.26 (q, 2H, J = 5.9 Hz), 2.73 (t, 2H, J = 5.9 Hz), 2.64 (q, 2H, J = 7.1 Hz), 1.24 (s, 1H), 1.10 (t, 2H, J = 7.1 Hz)	151.71, 74.45, 44.28, 39.06, 35.61, 23.71, 10.48
11b	5.00-4.90 (br s, 1H), 3.21 (q, 2H, J = 5.84 Hz), 2.73 (t, 2H, J = 5.91 Hz), 2.64 (q, 2H, J = 7.14 Hz), 1.44 (s, 9H), 1.10 (t, 2H, J = 7.14 Hz)	156.20, 78.94, 48.77, 43.55, 40.10, 28.20(3C), 14.97
12a	7.34 (s, 5H), 5.55 (br s, 1H), 5.08 (s, 2H), 3.62 (t, 2H, J = 5.08 Hz), 3.28 (app q, 2H, J = 5.62 Hz), 2.75-2.67 (m, 4H), 2.53 (br s, 2H)	156.83, 136.56, 128.53, 128.14, 66.61, 60.86, 50.82, 48.73, 40.64
12b	5.13 (br s, 1H), 3.64 (t, 2H, J = 5.15 Hz), 3.23 (app q, 2H, J = 5.81 Hz), 2.80-2.71 (m, 2H), 2.03 (br s, 2H), 1.43 (s, 9H)	156.41, 79.31, 60.85, 50.79, 48.85, 40.17, 28.28(3C)
13a	7.33 (s, 10 H), 5.18 (br s, 2H), 5.08 (s, 4H), 3.26 (app q, 4H, J = 5.63 Hz), 2.74 (t, 4H, J = 5.63 Hz), 1.31 (s, 1H)	156.73(2C), 136.57, 128.52(3C), 128.12(2C), 66.60(2C), 48.47(2C), 40.58(2C)
13b	4.91 (s, 2H), 3.22 (app q, 4H, J = 5.68 Hz), 2.72 (t, 4H, J = 5.68 Hz), 1.44 (s, 9H), 1.33 (s, 1H)	156.30(2C), 79.21(2C), 48.74(2C), 40.24(2C), 28.30(6C)
14a	7.34 (s, 10H), 5.68 (br s, 2H), 5.08 (s, 2H), 3.27 (app q,4H, J = 6.04 Hz), 2.65 (t, 4H, J = 6.52 Hz), 2.61-2.52(m, 4H), 1.64 (p, 4H, J = 6.32 Hz), 1.54-1.46 (m, 4H), 1.21 (br s , 2H)	156.56(2C), 136.84(2C), 128.48(6C), 128.00(4C), 66.33(2C), 49.57(2C), 47.80(2C), 39.97(2C), 29.37(2C), 27.64(2C)
14b	5.20 - 5.10 (broad s, 1H), 3.24 - 3.14 (m, 4H), 2.70 - 2.54 (m, 8H), 1.70 - 1.47 (m, 8H), 1.44 (s, 9H)	156.12(2C), 78.67(2C), 49.48 (2C), 47.39(2C), 38.88(2C), 29.60(2C), 28.17(6C), 27.51(2C)
15	7.18 - 7.10 (m, 5H), 5.19 (broad s, 1H), 5.10 (s, 2H), 4.86 (broad s, 1H), 3.29 (q, 2H, J = 5.63 Hz), 3.24 - 3.15 (m, 2H), 2.78 - 2.67 (m, 4H), 1.44 (s, 9H)	156.62, 156.16, 136.46, 128.28 (3C), 127.92, 127.85, 78.80, 66.26, 48.44, 48.30, 40.35, 39.88, 28.06(3C)
16	7.38-7.29 (m, 5H); 5.09 (s, 2H); 3.34-3.12 (m, 4H); 2.72-2.52 (m, 8H); 1.72-1.47 (m, 8H); 1.43 (s, 9H)	156.47, 156.06, 136.72, 128.28(3C), 127.80 (2), 78.56, 66.09, 49.38(2C), 47.48, 47.33, 39.62, 38.84, 29.50, 29.21, 28.11(3C), 27.45(2C)
19	5.55 (s, 1H), 5.23 (s, 1H), 3.25 (app q, 2H, J = 6.08 Hz), 3.17 (app q, 2H, J = 6.10 Hz), 2.73 (t, 2H, J = 7.01 Hz), 2.65 (t, 2H, J = 6.45 Hz), 1.68-1.60 (m, 2H), 1.59-1.43 (m, 4H), 1.44 (s, 18H), 1.30 (br s, 1H)	156.58(2C), 79.25, 79.19, 49.22, 47.64, 40.78, 39.77, 29.40, 28.34(6C), 27.62, 27.17

***N*^{1,12}-(Carbo-*tert*-butyloxy)-1,12-diamino-4,9-diazadodecane (14b).**[16]- A -40° solution of BOC-OSu (418 mg, 1.94 mmol, 0.97 mmol per primary amine) in CH_2Cl_2 (5 mL) was added to a -40° solution of spermine (**6**, 202 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) and ran as described above to afford 245 mg (63%) of the *bis* protected tetra amine **14b** as an oil. MS $[M+H]^+$ 403.6; HRMS Calcd for $C_{20}H_{43}N_4O_4$+ H^+: 403.3279. Found: 403.3279.

***N*^{1}-(Carbobenzyloxy)-*N*^{5}-(carbo-*tert*-butyloxy)-3-azapentane (15).**- CBZ-OSu (241 mg, 0.97 mmol) in CH_2Cl_2 (5 mL) was added to a -40° solution of *N*^{1}-(carbo-*tert*-butyloxy)-3-azapentane (**7**, 203 mg, 1.00 mmol) as described above to give 314 mg (96%) **15** as an oil after workup and removal of solvents *in vacuo*. MS $[M+H]^+$ 338.4; mp. 61 - 64°.

Anal. Calcd for $C_{17}H_{27}N_3O_4$: C, 60.51; H, 8.07; N, 12.45. Found: C, 60.41; H, 8.04; N, 12.64

***N*^{1}-(Carbobenzyloxy)-*N*^{12}-(carbo-*tert*-butyloxy)-1,12-diamino-4,9-diazadodecane (16).**- A -40° solution of CBZ-OSu (241 mg, 0.97 mmol) in CH_2Cl_2 (5 mL) was added to a -40° solution of *N*^{1}-(Carbo-*tert*-butyloxy)-1,12-diamino-4,9-diazadodecane (**8**, 302 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) and ran as described in the general procedure to afford 292 mg (69%) of **16** as an oil after workup and removal of solvents *in vacuo*. MS $[M+H]^+$ 437.6. HRMS Calcd for $C_{23}H_{41}N_4O_4$ + H^+: 437.3122; found: 437.3122.

***N*^{1,8}-(Carbo-*tert*-butyloxy)-1,8-diamino-4-azaoctane (19).**[16]- A -40° solution of BOC-OSu (418 mg, 1.94 mmol) in CH_2Cl_2 (5 mL) was added to a -40° solution of spermidine (**18**, 145 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) and ran as described above to afford 284 mg (71%) of the bis carbamate protected triamine **19** as an oil. MS $[M+H]^+$ 414.3.

***N*^{4}-(Carboallyloxy)-*N*^{1}-(carbobenzyloxy)-*N*^{5}-(carbo-*tert*-butyloxy)-3-azapentane (22).**- Allyl chloroformate (15.4 mL, 0.15 mmol, 0.98 eq) was added a dropwise to a solution of *N*^{1}-(carbobenzyloxy)-*N*^{5}-(carbo-*tert*-butyloxy)-3-azapentane (**15**) (50 mg, 0.15 mmol) and diisopropylethylamine (77 mL, 0.44 mmol) in THF stirring in an ice bath under N_2. The mixture was stirred for 4 hours at 0-5° then 1 hr at room temperature followed by removal of solvents *in vacuo*. Resulting residue was dissolved in aqueous buffer [0.05 M phosphate (pH=3), 30 mL)/Et_2O (20 mL) and extracted with Et_2O (3 x 20 mL), the combined organic extracts were washed with brine (1 x 20 mL) and dried over Na_2SO_4. Filtration and removal of solvents *in vacuo* afforded 60 mg (98%) of *N*^{1}-BOC-*N*^{3}-Alloc-*N*^{5}-CBZ-diethylenetriamine (**22**) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.35 (br s, 5H); 5.90 (br s, 1H); 5.34-5.15 (m, 2H); 5.09 (s, 2H); 4.56 (br s, 2H); 3.48-3.18 (m, 8H); 1.42 (s, 9H); ^{13}C NMR: δ 156.83 (3C), 136.60, 132.69, 128.52 (2C), 128.11 (3C), 117.88, 79.45, 66.57, 66.27, 47.61 (2C), 39.89, 39.30, 28.22 (3C); MS $[M+H]^+$ 422.3.

Anal. Calcd for $C_{21}H_{31}N_3O_6$: C, 59.84; H, 7.41; N, 9.97. Found: C, 59.80; H, 7.58; N, 9.75

1-Amino-5-aminoethyl-4-oxo-5-azaheptanoic acid (24).- Triethylamine (1.11 mL, 8.0 mmol) was added to a solution of bis CBZ amine **13a** (942 mg, 2.0 mmol), succinic anhydride (600 mg, 6.0 mmol) in dimethylformamide (DMF, 10 mL); reaction mixture was stirred at room temperature under N_2 for 14 hours and removed solvents *in vacuo*. Purification by flash chromatography (methanol:methylene chloride:acetic acid, 5:95:0.05 by volume) afforded the desired *bis* CBZ

protected amino acid **23** as an oil (1038 mg, 91%). ^{1}H NMR ($CDCl_3$): δ 7.30 (s, 10 H), 5.74 (br s, 1H), 5.61 (br s, 1H), 5.07 (s, 2H), 5.04 (s, 2H), 3.45-3.17 (m, 8H), 2.52 (br s, 4H); ^{13}C NMR: δ 176.32, 173.51, 157.09, 156.85, 136.59, 136.43, 128.59 (2C), 128.54 (2C), 128.22 (2C), 128.16 (4C), 66.80, 66.62, 48.01, 46.10, 39.30 (2C), 29.18, 27.55; MS $[M+H]^+$ 472.3.

Hydrogen bromide (30% in acetic acid, ~5.0 M, 4.0 mL, 20 mmol) was added to a solution of **23** (571 mg, 1.00 mmol) in 25 mL CH_2Cl_2 and stirred for 4 hours at room temperature under N_2. The resulting precipitate was filtered, washed with CH_2Cl_2 and dried to afford **24** (349 mg, 96%) as an off-white gum. ^{1}H NMR (D_2O:CD_3OD, 9:1): δ 3.62 (t, J = 7.3 Hz, 2H), 3.53 (t, J = 6.1 Hz, 2H), 3.13 (t, J = 7.3 Hz, 2H), 3.03 (t, J = 6.1 Hz, 2H), 2.62-2.50 (m, 4H); ^{13}C NMR: δ 178.5, 176.9, 45.7, 44.4, 38.8, 37.7, 29.8, 28.6; MS $[M+H]^+$ 204.2.

Anal. Calcd for $C_8H_{19}N_3O_3Br_2$: C, 26.32; H, 5.25; N, 11.51; Br, 43.78
Found: C, 26.03; H, 5.17; N, 11.41; Br, 43.75

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