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Synthesis of a series of ω-dimethylaminoalkyl substituted ethylenediamine ligands for use in enantioselective catalysis

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ABSTRACT

The title compounds $H_2NCH((CH_2)_nNMe_2)CH_2NH_2$ **L1**–**L4** (n = 1–4) are efficiently synthesized in enantiopure form. The commercial starting materials, L-asparagine, (*S*)-5-hydroxymethyl-2-pyrrolidinone, and (*S*)-6-(((benzyloxy)carbonyl)-amino)-2-((*tert*-butoxycarbonyl)amino)hexanoic acid, are elaborated in 6–9 standard steps to give **L1** (18% overall), **L2** (13%), **L3** (36%) and **L4** (38%) or the corresponding tris(hydrochloric acid) salts $[H_3NCH((CH_2)_nNHMe_2)CH_2NH_3]^{3+}$ $3Cl^-$, which are preferable for long term storage. The sequences make use of isobutyl carbamate, Cbz, and Boc protecting groups and Hofmann type rearrangements; the dimethylamino groups are introduced at late stages, either via reductive dimethylations or nucleophilic displacements involving mesylates and $HNMe_2$. **L1**–**L4** chelate to $[Co(en)_2]^{3+}$ fragments to give octahedral complexes that catalyze numerous enantioselective reactions.

1. Introduction

Over the last fifteen years, a variety of small molecule hydrogen bond donor catalysts have been developed and found diverse applications in enantioselective syntheses.[1] Some of the most useful catalysts have been based upon urea and thiourea moieties.[2] These readily bind to a number of Lewis basic organic functional groups, as demonstrated by a series of crystal structures.[3] Importantly, some of the most effective urea and thiourea catalysts are bifunctional, incorporating an auxiliary tertiary amine group.[2b,4] This can serve as either a Lewis or Brønsted base during the catalytic cycle.

We have begun to study Werner complexes as possible NH hydrogen bond donor catalysts for enantioselective organic syntheses.[5,6] This includes the historically important chiral-at-metal tris(ethylenediamine)cobalt trication $[Co(en)_3]^{3+}$, which was among the first few inorganic species to be resolved into enantiomers,[7] as well as analogues with substituted diamines, such as 1,2-diphenylethylenediamine (dpen).[6] We have also developed cationic ruthenium complexes in which NH bonds remote from the metal effect the catalysis.[8,9] Dramatic improvements in the performance of this catalyst family were realized when dimethylamino substituents were incorporated into the NH containing ligand.[8b] Closely related themes have also received attention from Meggers et al.[10]

In our first communication, which focused on the additions of malonates to enones in organic media, we were only able to realize modest enantioselectivities using lipophilic salts of $[Co(en)_3]^{3+}$.[5] We speculated that the adducts of ethylenediamine ligands containing an ω-dimethylaminoalkyl substituent might give improved results. Hence, we sought to synthesize a series of ligands $H_2NCH((CH_2)_nNMe_2)CH_2NH_2$ in enantiopure form, so that they could be incorporated into cobalt complexes such as $\mathbf{I}^{3+}$ (Fig. 1) without increasing the numbers of diastereomers.

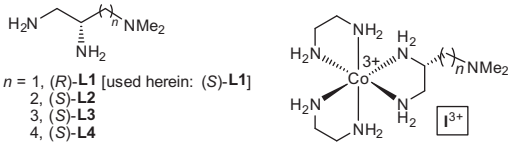

Figure 1. Target ligands and complexes.

Curiously, we could only locate one such triamine in the literature, that with n = 2.[11] The overall yield was modest, and only the ^{1}H NMR spectrum and specific rotation were reported. Hence, we set out to prepare ligands with n = 1–4, termed **L1**–**L4** (Fig. 1), and/or the functionally equivalent tris(hydrochloric acid) salts. Herein, we describe practical six to nine step syntheses for all of these species from inexpensive, commercially available enantiopure starting materials in 38–13% overall yields (average: 26%),

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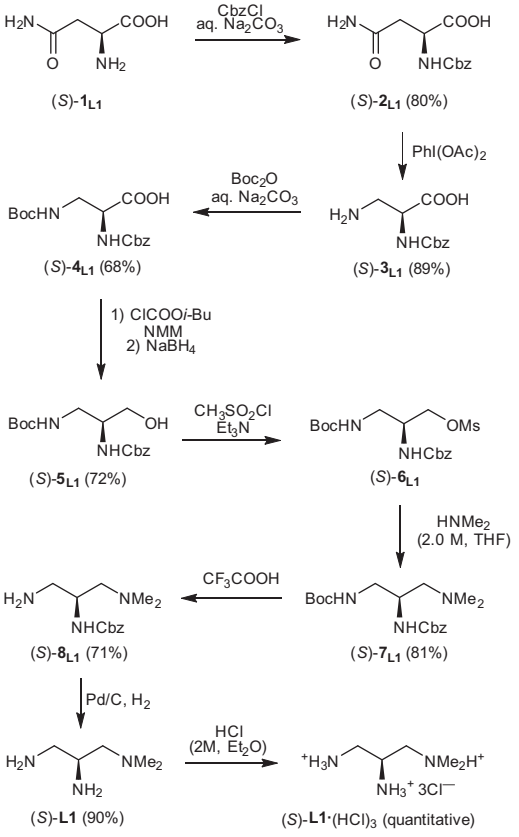
and their detailed characterization. The applications of these ligands will be described separately.[12]

2. Results

2.1. Synthesis of ligand L1

As shown in Scheme 1, commercial (*S*)-asparagine [L-asparagine or (*S*)-**1$_{L1}$**][13a] was elaborated in a series of five known steps.[14,15] The first step involved treatment with CbzCl to give the Cbz protected amine (*S*)-**2$_{L1}$** (our yield/lit: 80/84%).[14a] A Hofmann type rearrangement was then effected with PhI(OAc)$_2$ to give ß-amino acid (*S*)-**3$_{L1}$** (our yield/lit: 89/89%),[14b] which was protected with Boc to afford (*S*)-**4$_{L1}$** (our yield/lit: 68/91%).[14a,16] Following a patent procedure, the carboxylic acid was activated with isobutyl chloroformate, after which a reaction with $NaBH_4$ gave the primary alcohol (*S*)-**5$_{L1}$** (our yield/lit: 72/55%).[15,16] Mesylation was effected to give (*S*)-**6$_{L1}$**,[15] the last known compound in this sequence, which was employed in the following step assuming a quantitative yield.

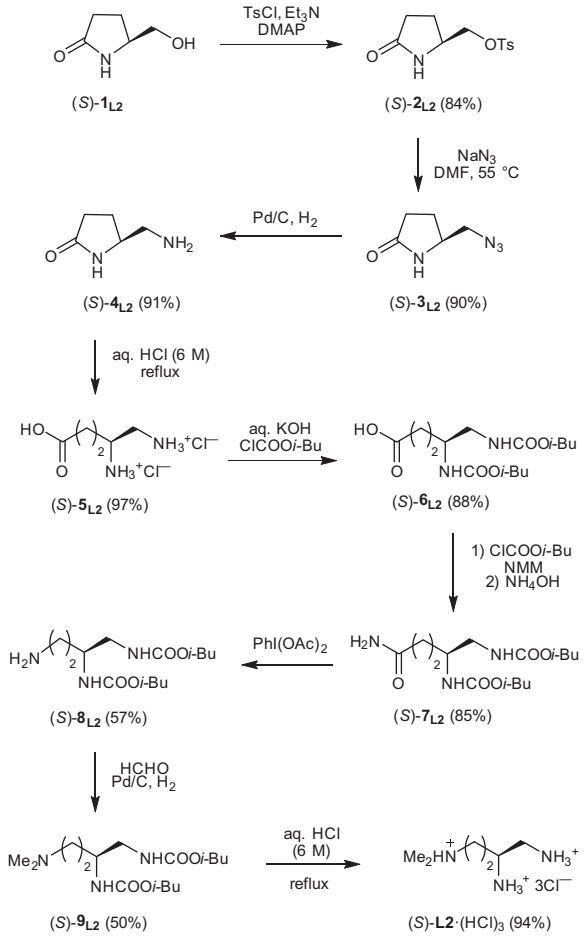
In order to introduce the dimethylamino group, (*S*)-**6$_{L1}$** and a THF solution of $HNMe_2$ were refluxed (Scheme 1). Work up gave the protected triamine (*S*)-**7$_{L1}$** (81%, two steps). The addition of CF_3CO_2H removed the Boc protecting group, to afford the diamine (*S*)-**8$_{L1}$** (71%). Hydrogenolysis then detached the Cbz group, to give the target triamine (*S*)-**L1** (90%) in 18% overall yield from (*S*)-**1$_{L1}$**. For long term storage, this was converted into the tris(hydrochloric acid) salt (*S*)-[$H_3NCH((CH_2)NHMe_2)CH_2NH_3]^{3+}$ $3Cl^-$ ((*S*)-**L1**·$(HCl)_3$) in 99% yield. This sequence has been repeated by several coworkers, sometimes with even higher yields than those indicated above and in the experimental section (maximum values for the first five yields in Scheme 1: 85%, 90%, 80%, 80%, 86%).



Scheme 1. Synthesis of the tris(hydrochloric acid) salt of (*S*)-**L1**.

2.2. Synthesis of ligand L2

As shown in Scheme 2, commercial (*S*)-5-hydroxymethyl-2-pyrrolidinone (*S*)-**1$_{L2}$**[13b] was elaborated in a series of five known steps.[17] The first involved treatment with tosyl chloride to give the tosylate (*S*)-**2$_{L2}$** (our yield/lit: 84/93%).[17a] Subsequent reaction with NaN_3 afforded (*S*)-**3$_{L2}$** (our yield/lit: 90/99%).[17a] The azide was reduced to the primary amine (*S*)-**4$_{L2}$** with Pd/C and H_2 (our yield/lit: 91/99%).[17a] Hydrolysis (6 M HCl) then provided (*S*)-**5$_{L2}$** (our yield/lit: 97/83%).[17b] Both primary amine groups were protected using isobutyl chloroformate to give (*S*)-**6$_{L2}$** (our yield/lit: 88/88%).[17b]



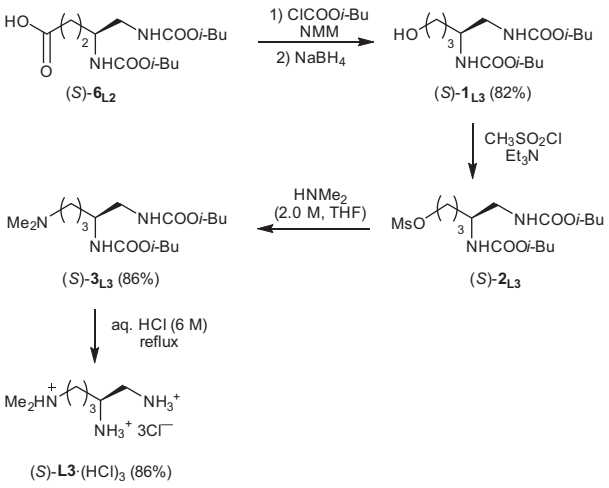
Scheme 2. Synthesis of the tris(hydrochloric acid) salt of (*S*)-**L2**.

We next sought to remove a methylene group from the carboxylic acid chain. Thus, (*S*)-**6$_{L2}$** was first converted into the corresponding amide (*S*)-**7$_{L2}$** (85%), a new compound. A modified Hofmann rearrangement was then carried out using PhI(OAc)$_2$. The resulting primary amine (*S*)-**8$_{L2}$** (57%) was a known compound.[17b] A reductive dimethylation (aqueous HCHO, Pd/C, H_2) yielded the new tertiary amine (*S*)-**9$_{L2}$** (50%). Refluxing aqueous HCl afforded the tris(hydrochloric acid) salt (*S*)-[$H_3NCH((CH_2)_2NHMe_2)CH_2NH_3]^{3+}$ $3Cl^-$ (*S*)-**L2**·$(HCl)_3$ as a colorless sticky compound in 13% overall yield from (*S*)-**1$_{L2}$**. As noted above, this compound has been previously synthesized, but in only 7% overall yield, although the sequence involved one fewer step.[11]

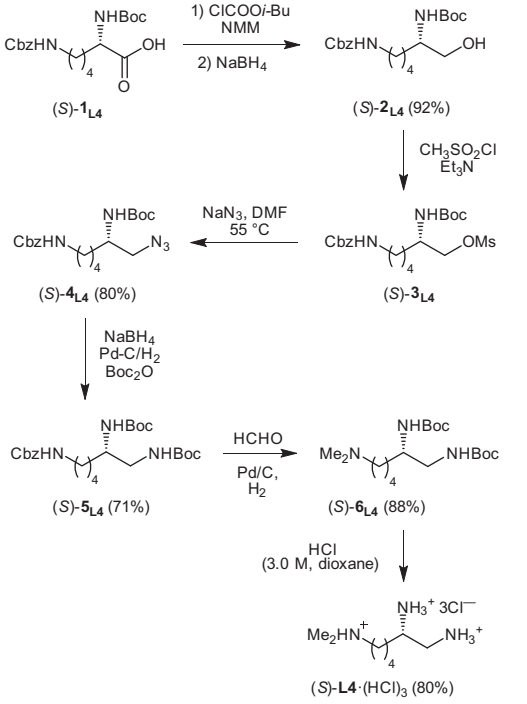
2.3. Synthesis of ligand L3

As shown in Scheme 3, **L3** can be accessed using (*S*)-**6$_{L2}$** from Scheme 2. The carboxylic acid was first activated with isobutyl

chloroformate, and $NaBH_4$ reduction gave the new primary alcohol (*S*)-**1**$_{L3}$ (82%). Mesylation was effected to give (*S*)-**2**$_{L3}$. The crude mesylate was refluxed in a THF solution of $HNMe_2$ to afford the corresponding dimethylamine (*S*)-**3**$_{L3}$ (86%, two steps). The protecting groups were removed in refluxing aqueous HCl to give the new tris(hydrochloric acid) salt (*S*)-$[H_3NCH((CH_2)_3NHMe_2)CH_2NH_3]^{3+}$ $3Cl^-$ (*S*)-**L3**·$(HCl)_3$ as a colorless sticky compound in 86% yield or 36% overall yield from the starting material in Scheme 2, (*S*)-**1**$_{L2}$.



Scheme 3. Synthesis of the tris(hydrochloric acid) salt of (*S*)-**L3**.



Scheme 4. Synthesis of the tris(hydrochloric acid) salt of (*S*)-**L4**.

2.4. Synthesis of ligand L4

As shown in Scheme 4, commercial (*S*)-6-(((benzyloxy)carbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)hexanoic acid (*S*)-**1**$_{L4}$[13a] was elaborated in a series of three known steps.[18] The carboxylic acid was first activated with isobutyl chloroformate, and $NaBH_4$ reduction yielded the primary alcohol (*S*)-**2**$_{L4}$ (our yield/lit: 92/94%).[18a] Mesylation was effected to give (*S*)-**3**$_{L4}$, which was treated with NaN_3 to give (*S*)-**4**$_{L4}$ (our yield/lit: 80/86%).[18b]

The azide was reduced to the primary amine using $NaBH_4$ in the presence of Pd/C. This was protected in situ with Boc to give (*S*)-**5**$_{L4}$ (71%). During the preparation of this manuscript, an independent synthesis of (*S*)-**5**$_{L4}$ was reported by Carell et al.[19] Their route, which involves a starting material of similar cost, is slightly more efficient (five steps, 55% overall yield vs. four steps, 52% overall yield).

Next, (*S*)-**5**$_{L4}$ was treated with aqueous HCHO in the presence of Pd/C and H_2. This removed the Cbz protecting group and gave the new tertiary amine (*S*)-**6**$_{L4}$ (88%). Finally, the Boc groups were removed using HCl in aqueous dioxane to give the new tris (hydrochloric acid) salt (*S*)-$[H_3NCH((CH_2)_4NHMe_2)CH_2NH_3]^{3+}$ $3Cl^-$ (*S*)-**L4**·$(HCl)_3$ as a colorless sticky compound in 80% yield or 38% overall yield from (*S*)-**1**$_{L4}$.

All of the new compounds described above gave correct microanalyses. They were furthermore characterized by ^1H and ^{13}C NMR spectroscopy, as summarized in the experimental section, and sometimes by additional methods.

3. Discussion

The syntheses in Schemes 1–4 represent highly optimized protocols leading to a novel family of enantiopure triamine ligands **L1**–**L4**. One common feature is that the dimethylamino groups are introduced at late stages, either via reductive dimethylations or nucleophilic displacements involving mesylates and $HNMe_2$. A Hofmann type rearrangement allows **L2** and **L3** to be accessed from the same precursor, and **L1** to be prepared from a less costly precursor [(*S*)-**1**$_{L1}$ vs (*S*)-**3**$_{L1}$].

To the best of our knowledge, only one of the ligands and two late stage intermediates, (*S*)-**L2**·$(HCl)_3$),[11] (*S*)-**8**$_{L2}$,[17b] and (*S*)-**5**$_{L4}$,[19] have been independently synthesized. Our route to (*S*)-**L2**·$(HCl)_3$) constitutes a distinct improvement. However, the literature preparation of (*S*)-**5**$_{L4}$, which was only reported in 2015, is competitive with our methodology. Importantly, the enantiomers of the three starting materials used in Schemes 1–4 are commercially available, but at prices that are 3–4 times greater per mole.

In the planned applications with cobalt(III) complexes (e.g., $\mathbf{I}^{3+}$), the two primary amino groups of **L1**–**L4** are intended to serve as chelates. The tertiary dimethylamino groups are designed, by analogy to their roles in thiourea and urea catalysts,[2b,4] to aid the activation of substrates. However, other coordination modes and roles can be envisioned, suggesting a class of compounds that may have a mechanistically diverse range of applications in enantioselective synthesis. Also, although **L4** has not previously been synthesized, it has served as a linking unit in a series of cisplatin-*N*-mustard conjugates.[19]

4. Conclusion

In conclusion, a series of four homologous ω-dimethylaminoalkyl substituted ethylenediamine ligands **L1**–**L4** are now readily available in enantiopure form. In future reports, cobalt(III) complexes that contain one to three such ligands will be described.[12] Some of these will be highly enantioselective hydrogen bond donor catalysts, superior to those detailed previously.[6]

5. Experimental

5.1. General

^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on standard 300–500 MHz spectrometers at ambient probe temperatures. Chemical

shifts (δ in ppm) were referenced to residual solvent signals (^{1}H: $CHCl_3$, 7.26; DMSO-d_5, 2.49, HOD, 4.79 ppm; ^{13}C: $CDCl_3$, 77.2; DMSO-d_6, 39.5),[20] except for $^{13}C\{^1H\}$ spectra recorded in D_2O, which were referenced to internal dioxane (67.2).[20] IR spectra were recorded on ASI React IR®-1000 or Shimadzu IRAffinity-1 spectrometers. Microanalyses were conducted by Atlantic Microlab or in house using a Carlo Erba EA 1110 CHN instrument. Optical rotations were measured with a Perkin–Elmer model 431 polarimeter as described previously.[21]

Reactions were conducted under air unless noted. Chemicals were treated as follows: DMSO-d_6 and $CDCl_3$ (Cambridge Isotopes), stored over molecular sieves; CH_2Cl_2 (EMD Chemicals, ACS grade), CH_3OH (EMD, anhydrous, 99.8%), hexanes (Macron, ACS grade), Et_2O (Macron, ACS grade), EtOAc (Macron, ACS grade), THF (Macron, ACS grade), DMF (Mallinckrodt, ACS grade), EtOH (BDH, ACS grade), dioxane (Macron, ACS grade), 1,2-dimethoxyethane (Acros, 99+%), acetone (BDH, ACS grade), L-asparagine (Aroz Technologies, LLC, 98%), (*S*)-5-hydroxymethyl-2-pyrrolidinone (AK Scientific, Inc, 98%), (*S*)-6-(((benzyloxy)carbonyl)amino)-2-((*tert*-butoxycarbonyl)amino)hexanoic acid (Aroz Technologies, LLC, 98%), citric acid (EMD, ACS grade), tosyl chloride (TsCl, Alfa Aesar, 98%), *N*-methyl morpholine (NMM, Acros, 99%), isobutyl chloroformate (ClCOO*i*-Bu, Alfa Aesar, 98%), iodosobenzenediacetate (PhI(OAc)$_2$, Alfa Aesar, 98+%), CbzCl (TCI, 30–35 wt % in toluene), Boc_2O (Chem-Impex International, Inc., 98%), Concd NH_4OH (30%, EMD, ACS grade), aqueous HCHO (EMD, ACS grade), $NaBH_4$ (Aldrich, 98%), methanesulfonyl chloride (CH_3SO_2Cl, Acros, 99.5%), $HNMe_2$ (2.0 M in THF, Alfa Aesar), Pd/C (10%, Aldrich), Pd/C (10%, 'nominally 50% water wet', Alfa Aesar), NaOH (Macron, ACS grade), Et_3N (Alfa Aesar, 98%), NaN_3 (Alfa Aesar, 99%), $NaHCO_3$ (Alfa Aesar, 98%), CF_3COOH (99%, Acros), HCl (2.0 M in Et_2O, Acros), $KHSO_4$ (Alfa Aesar, 98%), Celite 545 (Aldrich), and Na_2SO_4 (EMD), used as received.

5.1.1. (*S*)-N^2-Benzyloxycarbonyl-N^3-*tert*-butyloxycarbonyl-2,3-diaminopropan-1-ol or (*S*)-((*t*-BuOC(O))NHCH$_2$CH(CH$_2$OH)NH(C(O)OCH$_2$Ph) (*S*)-**5$_{L1}$**[15,16]

A round bottom flask was charged with (*S*)-**4$_{L1}$** (15.90 g, 47.0 mmol),[14a] and 1,2-dimethoxyethane (65 mL), and *N*-methyl morpholine (5.4 mL; 5.0 g, 49 mmol) were added with stirring. The solution was cooled to −25 °C, and isobutyl chloroformate (6.50 mL; 6.8 g, 50 mmol) was slowly added. The cold bath was then removed. After 30 min, the precipitate was collected by filtration and washed with 1,2-dimethoxyethane (2 × 30 mL). The combined filtrate and washings were sparged with nitrogen and cooled to 0 °C. A solution of $NaBH_4$ (2.52 g, 66.5 mmol) in EtOH (150 mL) was then added dropwise with stirring. After 1 h, H_2O (10 mL) was cautiously added, after which the cold bath was removed. After 12 h, the solvent was removed by rotary evaporation. The solid was dissolved in EtOAc (200 mL), and H_2O (200 mL) was added. The aqueous phase was extracted with EtOAc (2 × 50 mL) and the combined organic phases were dried ($MgSO_4$). The solvent was removed by rotary evaporation and the solid was chromatographed on a silica gel column (4 × 17 cm, 20:80 to 50:50 v/v EtOAc/hexane). The solvent was removed from the product containing fraction by rotary evaporation. The residue was dried by oil pump vacuum to give (*S*)-**5$_{L1}$** (11.0 g, 33.8 mmol, 72%) as a white solid. NMR (DMSO-d_6, δ in ppm): ^{1}H (400 MHz)[16] 7.37–7.28 (m, 5H, *Ph*), 6.86 (d, $^3J_{HH}$ = 8.4 Hz, 1H, CHN*H*), 6.72 (t, $^3J_{HH}$ = 5.2 Hz, 1H, CH$_2$N*H*), 4.99 (m, 2H, OC*H*$_2$Ph), 4.61 (t, $^3J_{HH}$ = 5.6 Hz, 1H, O*H*), 3.52–3.48 (m, 1H, C*H*NHCbz), ca. 3.4 (C*H*$_2$OH, signal obscured by solvent impurity), 3.10–3.03 (m, 1H, C*H*H′NHBoc), 2.98–2.93 (m, 1H, CH*H*′NHBoc), 1.35 (s, 9H, C(C*H*$_3$)$_3$); $^{13}C\{^1H\}$ ($CDCl_3$, 75.5 MHz) 157.6 and 156.3 (2× s, (*C*=O)O from Boc and Cbz); *Ph* at 136.1 (s, *i*), 128.4 (s, *m*),[22] 128.0 (s, *p*), 127.9 (s, *o*); 80.1 (s, *C*(CH$_3$)$_3$), 66.7 (s, OCH$_2$Ph), 61.3 (s, *C*H$_2$OH), 52.8 (s, *C*HNHCbz), 40.1 (s, *C*H$_2$NHBoc), 28.2 (s, C(*C*H$_3$)$_3$).

5.1.2. (*S*)-N^2-Benzyloxycarbonyl-N^3-*tert*-butyloxycarbonyl-2,3-diaminopropyl methanesulfonate or (*S*)-((*t*-BuOC(O))NHCH$_2$CH(CH$_2$OSO$_2$Me)NH(C(O)OCH$_2$Ph) (*S*)-**6$_{L1}$**[15]

A Schlenk flask was charged with (*S*)-**5$_{L1}$** (10.4 g, 32.1 mmol), CH_2Cl_2 (150 mL), and Et_3N (10.7 mL, 7.77 g, 76.9 mmol), and cooled to −78 °C. Methanesulfonyl chloride (4.7 mL, 7.0 g, 61 mmol) was added dropwise with stirring. The cold bath was allowed to warm to 0 °C over the course of 3 h. Aqueous citric acid (20% w/v, 200 mL) and CH_2Cl_2 (100 mL) were then added. The organic phase was separated, washed with saturated $NaHCO_3$ (200 mL) and brine (200 mL), and dried ($MgSO_4$). The solvent was removed by an oil pump vacuum to give (*S*)-**6$_{L1}$** as a white solid. This material was used without further purification. NMR (DMSO-d_6, δ in ppm): ^{1}H (500 MHz): 7.36–7.28 (m, 5H, *Ph*), 5.73 (br d, $^3J_{HH}$ = 5.2 Hz, 1H, CHN*H*), 5.07 (s, C*H*$_2$OPh), 4.94 (br t, $^3J_{HH}$ = 6 Hz, 1H, CH$_2$N*H*), 4.27–4.21 (m, 2H, C*H*$_2$OS), 3.98–3.93 (m, 1H, C*H*NHCbz), 3.36–3.30 (m, 2H, C*H*$_2$NHBoc), 2.98 (s, 3H, SC*H*$_3$), 1.40 (s, 9H, C(C*H*$_3$)$_3$).

5.1.3. (*S*)-N^1,N^1-Dimethyl-N^2-benzyloxycarbonyl-N^3-*tert*-butyloxycarbonyl-N^1,N^1-dimethylpropane-1,2,3-triamine or (*S*)-((*t*-BuOC(O))NHCH$_2$CH(CH$_2$NMe$_2$)NH(C(O)OCH$_2$Ph) (*S*)-**7$_{L1}$**

A round bottom flask was charged with the crude (*S*)-**6$_{L1}$** from the preceding synthesis and $HNMe_2$ (2.0 M in THF; 80 mL, 160 mmol), and fitted with a condenser cooled to −55 °C (using a cold fluid recirculating bath) to return the $HNMe_2$ to the flask. The flask was placed in a 80 °C oil bath. After 9 h, the bath was allowed to cool to rt and the solvent was removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 (200 mL), washed with saturated $NaHCO_3$ (200 mL) and brine (200 mL), and dried ($MgSO_4$). The solvent was removed by rotary evaporation and the oily yellow residue was chromatographed on a silica gel column (3 × 30 cm, 10:1 v/v CH_2Cl_2/CH_3OH). The solvent was removed from the product containing fractions by rotary evaporation to give (*S*)-**7$_{L1}$** as a white solid (9.08 g, 25.8 mmol, 81% for two steps), mp 88 °C (open capillary). Anal. Calcd for $C_{18}H_{29}N_3O_4$ (351.44): C, 61.52; H, 8.32; N, 11.96. Found: C, 61.50; H, 8.29; N, 11.74. $[\alpha]_{24}^{589} = -2.6 \pm 0.2$ (*c* 0.125, CH_3OH). NMR ($CDCl_3$, δ in ppm): ^{1}H (400 MHz) 7.34–7.28 (m, 5H, *Ph*), 5.43 (br s, 1H, CHN*H*Cbz), 5.16 (br s, 1H, CH$_2$N*H*Boc), 5.07 (m, 2H, OC*H*$_2$Ph), 3.68–3.66 (m, 1H, C*H*NHCbz), 3.41–3.35 (m, 1H, C*H*H′NHBoc), 3.22–3.17 (m, 1H, CH*H*′NHBoc), 2.35 (dd, $^2J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, C*H*H′N(CH$_3$)$_2$), 2.24 (dd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 7.0 Hz, 1H, CH*H*′N(CH$_3$)$_2$), 2.19 (s, 6H, N(C*H*$_3$)$_2$), 1.41 (s, 9H, C(C*H*$_3$)$_3$); $^{13}C\{^1H\}$ (100.6 MHz) 156.7 and 156.6 (2× s, (*C*=O)O from Boc and Cbz); *Ph* at 136.4 (s, *i*), 128.4 (s, *m*),[22] 128.03 (s, *p*), 127.97 (s, *o*); 79.4 (s, *C*(CH$_3$)$_3$), 66.7 (s, OCH$_2$Ph), 60.6 (s, *C*H$_2$N(CH$_3$)$_2$), 50.7 (s, *C*HNHCbz), 45.6 (s, N(*C*H$_3$)$_2$), 43.2 (s, *C*H$_2$NHBoc), 28.3 (s, C(*C*H$_3$)$_3$). IR (powder film, cm^{-1}): 3358 (m, ν_{NH}), 1677 (vs, $\nu_{C=O}$), 1522 (vs, δ_{NH}); MS:[23] 352 (100) [**21**+H]+, 296 (100) [**21**+2H−C(CH$_3$)$_3$]$^+$.

5.1.4. (*S*)-N^2-Benzyloxycarbonyl-N^1,N^1-dimethylpropane-1,2,3-triamine or (*S*)-NH$_2$CH$_2$CH(CH$_2$NMe$_2$)NH(C(O)OCH$_2$Ph) (*S*)-**8$_{L1}$**

A round bottom flask was charged with (*S*)-**7$_{L1}$** (9.08 g, 25.8 mmol) and CH_2Cl_2 (150 mL). Next, CF_3COOH (40.0 mL, 61.9 g, 540 mmol) was added in one portion with stirring. After 14 h, aqueous NaOH (10%, 200 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 150 mL) and the combined organic phases were dried (Na_2SO_4). The solvent was removed by rotary evaporation and the clear oil was chromatographed on a silica gel column (3 × 15 cm, 1:1 v/v CH_2Cl_2/CH_3OH). The solvent was removed from the product containing fractions (R_f = 0.09, TLC) by rotary evaporation to give (*S*)-**8$_{L1}$** as a waxy solid (5.08 g, 18.18 mmol, 71%).

Anal. Calcd for $C_{13}H_{21}N_3O_2{\cdot}0.33CH_2Cl_2$ (279.35): C, 57.31; H, 7.82; N, 15.04. Found: C, 57.00; H, 7.44; N, 14.97. $[\alpha]_{24}^{589} = -5.3 \pm 0.2$ (*c* 1.15, CH_3OH). NMR ($CDCl_3$, δ in ppm): ^1H (400 MHz): 7.32–7.25 (m, 5H, *Ph*), 5.34 (br s, 1H, N*H*), 5.06 (m, 2H, OCH_2Ph), 3.65–3.64 (m, 1H, *CH*NHCbz), 2.83 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 4.4 Hz, 1H, *CH*H′NH_2), 2.73 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 4.4 Hz, 1H, CH*H*′NH_2), 2.33 (dd, $^2J_{HH}$ = 11.8 Hz, $^3J_{HH}$ = 8.2 Hz, 1H, *CH*H′$N(CH_3)_2$), 2.22 (dd, $^2J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 6.6 Hz, 1H, CH*H*′$N(CH_3)_2$), 2.18 (s, 6H, $N(CH_3)_2$), 1.37 (br s, 2H, NH_2); $^{13}C\{^1H\}$ (100.6 MHz) 156.2 (s, (*C*=O)O), *Ph* at 136.2 (s, *i*), 128.0 (s, *m*),[22] 127.6 (s, *p*), 127.5 (s, *o*); 66.1 (s, OCH_2Ph), 60.3 (s, $CH_2N(CH_3)_2$), 53.1 (s, CH_2Cl_2), 50.8 (s, *C*HNHCbz), 45.3 (s, $N(CH_3)_2$), 43.8 (s, CH_2NH_2). IR ((powder film, cm^{-1}): 3358 (m, ν_{NH}), 2995, 2822, and 2771 (3 × m, ν_{CH}), 1693 (vs, $\nu_{C=O}$), 1531 (s, δ_{NH}), 1247 (vs, $\nu_{(C=O)OC}$); MS:[23] 252 (95) [**22**+H]$^+$, 180 (100) [**22**+H–$C_3H_8N_2$]$^+$.

5.1.5. (*S*)-N^1,N^1-Dimethylpropane-1,2,3-triamine or (*S*)-NH_2CH_2-$CH(CH_2NMe_2)NH_2$ (*S*)-L1

A Schlenk flask was charged with (*S*)-**8$_{L1}$** (5.08 g, 18.18 mmol), CH_3OH (60 mL), and Pd/C (10%, 0.795 g). The solution was sparged with H_2 and stirred under an H_2 atmosphere (balloon). After 14 h, the mixture was filtered through a plug of Celite and the solvent was removed under reduced pressure (17 mbar) at 0 °C to give (*S*)-**L1** as a colorless oil (1.90 g, 16.3 mmol, 90%). $[\alpha]_{24}^{589} = -9.3 \pm 0.1$ (*c* 0.108[1] CH_3OH). NMR ($CDCl_3$, δ in ppm): ^1H (400 MHz): 2.90–2.85 (m, 1H, *CH*NH_2), 2.72 (dd, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 4.0 Hz, 1H, *CH*H′NH_2), 2.52 (dd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 7.0 Hz, 1H, *CH*H′$N(CH_3)_2$), 2.21 (s, 6H, $N(CH_3)_2$, partly overlapped by CH*H*′$N(CH_3)_2$), 2.16 (m, 1H, CH*H*′$N(CH_3)_2$, partly overlapped by $N(CH_3)_2$), 2.10 (dd, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 4.4 Hz, 1H, CH*H*′NH_2); $^{13}C\{^1H\}$ (75.5 MHz) 64.1 (s, $CH_2N(CH_3)_2$), 50.1 (s, *C*HNH_2), 46.1 (s, CH_2NH_2), 45.5 (s, N$(CH_3)_2$). IR (powder film, cm^{-1}): 3280 (m, ν_{NH}), 2949 and 2831 (2× m, ν_{CH}), 1571 (s, δ_{NH}), 1461 (s, δ_{CH_2}); MS:[24] 118 (100) [**23**+H]$^+$.

5.1.6. Tris(hydrochloric acid) salt of (*S*)-N^1,N^1-dimethylpropane-1,2,3-triamine or (*S*)-$H_3NCH_2CH(CH_2NMe_2H)NH_3]^{3+}$ $3Cl^-$ (*S*)-L1·$(HCl)_3$

A Schlenk flask was charged with (*S*)-**L1** (1.90 g, 16.3 mmol) and CH_3OH (10 mL). A solution of HCl in Et_2O (2.0 M, 12 mL) was then added dropwise to form a precipitate. The supernatant was decanted and the precipitate was washed with Et_2O (2 × 10 mL) and dried by oil pump vacuum to give (*S*)-**L1**·$(HCl)_3{\cdot}H_2O$ as a white powder (3.95 g, 16.1 mmol, 99%), dec pt 213 °C (capillary). Anal. Calcd for $C_5H_{18}Cl_3N_3{\cdot}H_2O$ (244.59): C, 24.55; H, 8.24; N, 17.18. Found: C, 24.58; H, 8.00; N, 16.96. $[\alpha]_{24}^{589} = -8.7 \pm 0.4$ (*c* 0.116, H_2O). NMR (D_2O, δ in ppm): ^1H (400 MHz): 4.20–4.13 (m, 1H, *CH*NH_3), $CH_2N(CH_3)_2H$ and CH_2NH_3 at 3.68–3.57 (m, 2H) and 3.54–3.42 (m, 2H), 3.06 (s, 6H, $N(CH_3)_2H^+$); $^{13}C\{^1H\}$ (100.6 MHz) 59.4 (s, $CH_2N(CH_3)_2H$), 47.7 (s, $N(CH_3)_2H$), 46.6 (s, *C*HNH_3), 42.4 (s, CH_2NH_3). IR (powder film, cm^{-1}): 3479 and 3424 (2× m, ν_{OH}), 2902 and 2816 (2× s, ν_{CH}), 2708 and 2627 (2× s, $\nu_{NH_3^+}$), 1625 (w, δ_{NH}), 1481 (vs, δ_{CH_2}).

5.1.7. (*S*)-N^4,N^5-Di-*i*-butoxycarbonyl-4,5-diaminopentamide or (*S*)-(*i*-BuOC(O))NHCH($CH_2CH_2CONH_2$)CH_2NH(C(O)O*i*-Bu) (*S*)-7$_{L2}$

A round bottom flask was charged with (*S*)-**6$_{L2}$** (4.010 g, 12.078 mmol)[17b] and THF (130 mL). Next, *N*-methyl morpholine (1.70 mL, 1.565 g, 15.49 mmol) was added with stirring and the solution was cooled to −20 °C. Isobutyl chloroformate (2.0 mL, 2.091 g, 15.30 mmol) was slowly added. After 0.5 h, aqueous NH_4OH (30%, 8.8 mL) was added. The cold bath was allowed to warm to 0 °C over the course of 6 h. The solvent was removed by rotary evaporation and the residue was chromatographed on a silica gel column (3 × 14 cm, 93:7 v/v CH_2Cl_2/(85:15 v/v CH_3OH/30% aqueous NH_4OH)). The solvent was removed from the product containing fractions by rotary evaporation. The residue was dried by oil pump vacuum to give (*S*)-**7$_{L2}$** (3.42 g, 10.2 mmol, 85%) as a white solid, mp 126–129 °C (open capillary). Anal. Calcd for $C_{15}H_{29}N_3O_5$ (331.41): C, 54.36; H, 8.82, N, 12.68. Found: C, 54.33; H, 8.71; N, 12.54. NMR (DMSO-d_6, δ in ppm): ^1H (500 MHz) 7.21 (br s, 1H, CHN*H*), 7.04 (t, $^3J_{HH}$ = 5.5 Hz, 1H, CON*H*H′), 6.83 (m, 1H, CONH*H*′), 6.68 (br s, 1H, CH_2NH), 3.70 (d, $^3J_{HH}$ = 7.0 Hz, 4H, 2× $OCH_2CH(CH_3)_2$), 3.44 (br s, 1H, *CH*NH), 2.98 (t, $^3J_{HH}$ = 6.0 Hz, 2H, CH_2NH), 2.09–1.93 (m, 2H, CH_2CONH_2), 1.87–1.73 (m, 2H, 2× *CH*$(CH_3)_2$), 1.69–1.57 (m, 1H, CHC*H*H′CH_2), 1.50–1.37 (m, 1H, CHCH*H*′CH_2), 0.94–0.77 (m, 12H, 2× CH$(CH_3)_2$); $^{13}C\{^1H\}$ (125 MHz) 174.0 (s, *C*ONH_2), 157.6 and 156.2 (2× s, 2× (C=O)O), 69.7 and 69.6 (2× s, 2× $OCH_2CH(CH_3)_2$), 50.6 (s, *C*HNH), 44.2 (s, CH_2NH), 31.7 (s, CH_2CONH_2), 27.68 and 27.65 (2× s, 2× *C*H$(CH_3)_2$), 27.5 (s, CHC*H*H′CH_2), 19.0 and 18.9 (2× s, 2× CH$(CH_3)_2$). IR (powder film, cm^{-1}): 3414 (m, ν_{NH}), 3352 and 3312 (m, ν_{NH}), 2959 and 2876 (2× m, ν_{CH}), 1690, 1678, and 1663 (3× vs, 3× $\nu_{C=O}$), 1539 (s, δ_{NH}).

5.1.8. (*S*)-N^1,N^2-Di-*i*-butoxycarbonyl-1,2,4,-triaminobutane or (*S*)-(*i*-BuOC(O))NHCH($CH_2CH_2NH_2$)CH_2NH(C(O)O*i*-Bu) (*S*)-8$_{L2}$

A round bottom flask was charged with (*S*)-**7$_{L2}$** (3.0 g, 8.96 mmol), CH_3CN (25 mL), EtOAc (25 mL), H_2O (12 mL), and PhI$(OAc)_2$ (4.2 g, 13 mmol) with stirring. After 15 h, the solvents were removed by rotary evaporation. The residue was chromatographed on a silica gel column (3 × 8 cm, 100:0 to 80:20 v/v CH_2Cl_2/CH_3-OH). The solvent was removed from the product containing fractions to give (*S*)-**8$_{L2}$** (1.55 g, 5.05 mmol, 57%)[17b] as a colorless sticky liquid. NMR ($CDCl_3$, δ in ppm): ^1H (500 MHz) 5.57 (br s, 1H, CHN*H*), 5.43 (br s, 1H, CH_2NH), 3.89–3.70 (m, 5H, 2× $OCH_2CH(CH_3)_2$ and *CH*NH), 3.26 (br s, 2H, CH_2NH), 2.81 (t, $^3J_{HH}$ = 5 Hz, 2H, CH_2NH_2), 2.36 (br s, 2H, NH_2), 1.94–1.79 (m, 2H, 2× *CH*$(CH_3)_2$), 1.73–1.63 (m, 1H, CHC*H*H′CH_2), 1.60–1.47 (m, 1H, CHCH*H*′CH_2), 0.89 (d, $^3J_{HH}$ = 5 Hz, 12H, 2× CH$(CH_3)_2$); $^{13}C\{^1H\}$ (125 MHz) 157.6 and 157.4 (2× s, 2× (*C*=O)O), 71.1 and 71.0 (2× s, 2× $OCH_2CH(CH_3)_2$), 49.9 (s, *C*HNH), 45.1 (s, CH_2NH), 38.2 (s, CH_2NH_2), 35.1 (s, CHC*H*H′CH_2), 28.0 (s, 2× *C*H$(CH_3)_2$), 19.0 (s, 2× CH$(CH_3)_2$).

5.1.9. (*S*)-N^1,N^2-Di-*i*-butoxycarbonyl-N^4,N^4-dimethyl-1,2,4-triaminobutane or (*S*)-(*i*-BuOC(O))NHCH($CH_2CH_2NMe_2$)CH_2NH(C(O)O-*i*-Bu) (*S*)-9$_{L2}$

A Fischer Porter bottle was charged with (*S*)-**8$_{L2}$** (1.80 g, 5.863 mmol), CH_3OH (50 mL), distilled H_2O (15 mL), and 37% aqueous HCHO (1.6 mL). The mixture was stirred for 1 h, then 10% Pd/C (1.2 g, ′nominally 50% water wet′) was added, and 50 psi of H_2 were introduced. After 24 h, the mixture was filtered through a plug of Celite and washed with CH_3OH/distilled H_2O (1:1 v/v). The solvent was removed by rotary evaporation and the residue was chromatographed on a silica gel column (3 × 8 cm, 100:0 to 80:20 v/v CH_2Cl_2/CH_3OH). The solvent was removed from the product containing fractions by rotary evaporation and oil pump vacuum to give (*S*)-**9$_{L2}$** (1.02 g, 2.87 mmol, 50%) as a colorless oil that often solidified upon storage, mp 47–50 °C (open capillary). Anal. Calcd for $C_{16}H_{33}N_3O_4{\cdot}0.75CH_3OH$, (355.48): C 56.59, H 10.21, N 11.82; Calcd for $C_{16}H_{33}N_3O_4{\cdot}0.33CH_3OH$, (342.02, corresponding to ^1H NMR integration): C 57.35, H 10.11, N 12.29; found C 56.26, H 9.95, N 12.22. NMR ($CDCl_3$, δ in ppm): ^1H (500 MHz) 5.98 (br s, 1H, CHN*H*), 5.53 (br s, 1H, CH_2NH), 3.87–3.78 (m, 4H, 2× $OCH_2CH(CH_3)_2$), 3.77–3.70 (m, 1H, *CH*NH), 3.47 (s, 1H, *CH*$_3$OH), 3.37–3.30 (m, 1H, CH*H*′NH), 3.29–3.19 (m, 1H, *CH*H′NH), 2.57–2.39 (m, 2H, $CH_2N(CH_3)_2$), 2.30 (s, 6H, N$(CH_3)_2$), 1.96–1.82 (m, 2H, 2× *CH*$(CH_3)_2$), 1.82–1.72 (m, 1H, CHC*H*H′CH_2), 1.71–1.57 (m, 1H, CHCH*H*′CH_2), 1.02–0.83 (m, 12H, 2× CH$(CH_3)_2$); $^{13}C\{^1H\}$ (125 MHz) 157.5 and 157.2 (2× s, 2× (*C*=O)O), 71.1 and 71.0 (2× s, 2× $OCH_2CH(CH_3)_2$), 56.0 (s, CH_2N

(CH_3)$_2$), 51.0 (s, *C*HNH), 45.1 and 45.0 (2× s, *C*H_2NH and N(*C*H_3)$_2$), 29.2 (s, 2× CH*C*H*H*′CH_2), 28.0 (s, 2× *C*H(CH_3)$_2$), 19.0 (s, 2× CH(*C*H_3)$_2$). IR (powder film, cm^{-1}): 3325 (m, ν_{NH}), 2959, 2874, and 2762 (m and 2× w, ν_{CH}), 1684 (vs, $\nu_{C=O}$), 1533 (s, δ_{NH}).

5.1.10. Tris(hydrochloric acid) salt of (*S*)-*N*^{4},*N*^{4}-dimethylbutane-1,2,4-triamine or (*S*)-$H_3NCH(CH_2CH_2NMe_2H)CH_2NH_3]^{3+}$ 3Cl$^-$ (*S*)-**L2**·(HCl)$_3$

A round bottom flask was charged with (*S*)-**9$_{L2}$** (0.9 g, 2.7 mmol) and aqueous HCl (6.0 M, 50 mL) with stirring and fitted with a condenser. The solution was then refluxed. After 50 h, the solvent was removed by rotary evaporation (using a base trap to protect the pump). The residue was dissolved in H_2O and the solution was washed with CH_2Cl_2. The solvent was removed from the aqueous phase by rotary evaporation and the residue was dried by oil pump vacuum to give (*S*)-**L2**·(HCl)$_3$ (0.607 g, 2.53 mmol, 94%)[11] as a sticky solid. NMR (D_2O, δ in ppm): ^{1}H (500 MHz) 3.88–3.72 (m, 1H, C*H*NH$_3$), 3.51–3.32 (m, 4H, C*H*$_2$NH(CH$_3$)$_2$ and C*H*$_2$NH$_3$), 2.96 (s, 6H, NH(C*H*$_3$)$_2$), 2.40–2.19 (m, 2H, CHC*H*H′CH$_2$); ^{13}C{^{1}H} (125 MHz) 53.9 (s, *C*H$_2$NH(CH$_3$)$_2$), 47.9 (s, *C*HNH$_3$), 43.7 (s, NH(*C*H$_3$)$_2$), 41.3 (s, *C*H$_2$NH$_3$), 26.4 (s, CHCHH′*C*H$_2$).

5.1.11. (*S*)-N^4,N^5-Di-*i*-butoxycarbonyl-4,5-diaminopentane-1-ol or (*S*)-((*i*-BuOC(O))NHCH(CH$_2$CH$_2$CH$_2$OH)CH$_2$NH(C(O)O*i*-Bu) (*S*)-**1$_{L3}$**

A round bottom flask was charged with (*S*)-**6$_{L2}$** (14.220 g, 42.831 mmol)[17b] and 1,2-dimethoxyethane (70 mL), and *N*-methyl morpholine (5.24 mL; 4.821 g, 47.73 mmol) was added with stirring. The solution was cooled to −25 °C, and isobutyl chloroformate (6.80 mL; 7.11 g, 52.03 mmol) was slowly added. The cold bath was removed. After 30 min, the precipitate was collected by filtration and washed with 1,2-dimethoxyethane (2 × 30 mL). The combined filtrate/washings were sparged with nitrogen and cooled to 0 °C. A solution of $NaBH_4$ (2.43 g, 64.3 mmol) in EtOH (150 mL) was added dropwise with stirring. After 2 h, H_2O (10 mL) was cautiously added. The cold bath was removed. After 12 h, the solvent was removed by rotary evaporation. The solid was dissolved in EtOAc (300 mL), and H_2O (200 mL) was added. The aqueous phase was extracted with EtOAc (2 × 100 mL) and the combined extracts were dried (Na_2SO_4). The solvent was removed by rotary evaporation. The solid was chromatographed on a silica gel column (4 × 17 cm, 20:80 to 50:50 v/v EtOAc/hexane). The solvent was removed from the product containing fractions by rotary evaporation. The residue was dried by oil pump vacuum to give (*S*)-**1$_{L3}$** (11.137 g, 35.022 mmol, 82%) as a white solid, mp 87–90 °C (open capillary). Anal. Calcd for $C_{15}H_{30}N_2O_5$ (318.41): C 56.58, H 9.50, N 8.80; found: C, 56.30, H, 9.67, N, 8.73. NMR ($CDCl_3$, δ in ppm): ^{1}H (500 MHz) 5.17 (br s, 1H, CHN*H*), 5.08 (d, $^3J_{HH}$ = 10 Hz, 1H, CH$_2$N*H*), 3.90–3.76 (m, 4H, 2× OC*H*$_2$CH(CH$_3$)$_2$), 3.72 (br s, 1H, C*H*NH), 3.68–3.60 (m, 2H, C*H*$_2$OH), 3.26 (d, $^3J_{HH}$ = 5 Hz, 2H, C*H*$_2$NH), 1.97–1.81 (m, 2H, 2× C*H*(CH$_3$)$_2$), 1.69–1.56 (m, 3H, CHC*H*H′C*H*$_2$), 1.55–1.44 (m, 1H, CHCH*H*′CH$_2$), 0.97–0.86 (m, 12H, 2× CH(C*H*$_3$)$_2$); ^{13}C{^{1}H} (125 MHz) 157.6 and 157.3 (2× s, (*C*=O)O), 71.2 and 71.1 (2× OC*H*$_2$CH(CH$_3$)$_2$), 62.2 (s, *C*H$_2$OH), 51.7 (s, *C*HNH), 45.1 (s, *C*H$_2$NH), 29.2 and 28.6 (2× s, CHCHH′*C*H$_2$), 28.0 (s, 2× *C*H(CH$_3$)$_2$), 19.0 (s, 2× CH(*C*H$_3$)$_2$). IR (powder film, cm^{-1}): 3323 (m, ν_{OH}), 2957 and 2860 (2× w, ν_{CH}), 1684 (vs, $\nu_{C=O}$), 1541 (s, δ_{NH}).

5.1.12. (*S*)-N^4,N^5-Di-*i*-butoxycarbonyl-4,5-diaminopentyl methanesulfonate or (*S*)-(*i*-BuOC(O))NHCH(CH$_2$CH$_2$CH$_2$OSO$_2$CH$_3$)CH$_2$-NH(C(O)O*i*-Bu) (*S*)-**2$_{L3}$**

A round bottom flask was charged with (*S*)-**1$_{L3}$** (5.032 g, 15.82 mmol), CH_2Cl_2 (80 mL), and Et_3N (5.30 mL; 3.843 g, 38.04 mmol), and cooled to −78 °C. Methanesulfonyl chloride (2.30 mL; 3.404 g, 29.71 mmol) was added dropwise with stirring. The cold bath was allowed to warm to 0 °C over the course of 5 h. Aqueous citric acid (20% w/v, 140 mL) and CH_2Cl_2 (150 mL) were added and the phases were separated. The organic phase was washed with saturated aqueous $NaHCO_3$ and dried (Na_2SO_4). The solvent was removed by rotary evaporation. The residue was dried by oil pump vacuum to give crude (*S*)-**2$_{L3}$** (6.227 g, 15.72 mmol) as a yellowish white solid. This material was used without further purification. NMR ($CDCl_3$, δ in ppm): ^{1}H (500 MHz) 5.11 (br s, 1H, CHN*H*), 5.01 (br s, 1H, CH$_2$N*H*), 4.23 (t, $^3J_{HH}$ = 6 Hz, 2H, C*H*$_2$OS), 3.80 (br s, 4H, 2× OC*H*$_2$CH(CH$_3$)$_2$), 3.71 (br s, 1H, C*H*NH), 3.25 (br s, 2H, C*H*$_2$NH), 3.00 (s, 3H, SC*H*$_3$), 1.96–1.73 (m, 4H, 2× C*H*(CH$_3$)$_2$ and CHCHH′C*H*$_2$), 1.69–1.58 (m, 1H, CHCH*H*′CH$_2$), 1.55–1.43 (m, 1H, CHC*H*H′CH$_2$), 0.89 (d, $^3J_{HH}$ = 7 Hz, 12H, 2× CH(C*H*$_3$)$_2$); ^{13}C{^{1}H} (125 MHz) 157.4 and 157.0 (2× s, (*C*=O)O), 71.2 and 71.1 (2× OC*H*$_2$CH(CH$_3$)$_2$), 69.5 (s, *C*H$_2$OS), 51.3 (s, *C*HNH), 44.9 (s, *C*H$_2$NH), 37.3 (s, SC*H*$_3$) 28.7 and 25.6 (2× s, CHCHH′*C*H$_2$), 27.9 (s, 2× *C*H(CH$_3$)$_2$), 19.0 (s, 2× CH(*C*H$_3$)$_2$).

5.1.13. (*S*)-N^1,N^2-Di-*i*-butoxycarbonyl-*N*^{5},*N*^{5}-dimethyl-1,2,5-triaminopentane or (*S*)-(*i*-BuOC(O))NHCH(CH$_2$CH$_2$CH$_2$NMe$_2$)CH$_2$NH-(C(O)O*i*-Bu) (*S*)-**3$_{L3}$**

A sealable tube (180 mL, threaded cap) was charged with crude (*S*)-**2$_{L3}$** (6.227 g, 15.72 mmol) and $HNMe_2$ (2.0 M in THF; 80 mL, 160 mmol). The cap was tightened, and the bottom half of the tube was placed in an 80 °C oil bath. After 15 h, the bath was removed. After 2 h, the tube was vented and the solvent was removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 (200 mL), washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (100 mL), and dried (Na_2SO_4). The solvent was removed by rotary evaporation. The residue was chromatographed on a silica gel column (3 × 16 cm, 100:0 to 85:15 v/v CH_2Cl_2/CH_3OH). The solvent was removed from the product containing fractions to give (*S*)-**3$_{L3}$** (4.664 g, 13.52 mmol, 86% from (*S*)-**1$_{L3}$**) as a yellow oil which often solidified upon storage, mp 68–71 °C (open capillary). Anal. Calcd for $C_{17}H_{35}N_3O_4$ (345.48): C, 59.10; H, 10.21; N, 12.16. Found: C, 58.41; H, 10.09; N, 11.92. NMR ($CDCl_3$, δ in ppm): ^{1}H (500 MHz) 5.73 (d, $^3J_{HH}$ = 7 Hz, 1H, CHN*H*), 5.25 (br s, 1H, CH$_2$N*H*), 3.80 (d, $^3J_{HH}$ = 6 Hz, 4H, 2× OC*H*$_2$CH(CH$_3$)$_2$), 3.69–3.60 (m, 1H, C*H*NH), 3.39–3.14 (m, 2H, C*H*$_2$NH), 2.26 (br s, 2H, C*H*$_2$N(CH$_3$)$_2$), 2.20 (s, 6H, N(C*H*$_3$)$_2$), 1.98–1.78 (m, 2H, 2× C*H*(CH$_3$)$_2$), 1.62–1.36 (m, 4H, CHC*H*H′C*H*$_2$), 0.98–0.82 (m, 12H, 2× CH(C*H*$_3$)$_2$); ^{13}C{^{1}H} (125 MHz) 157.4 and 157.3 (2× s, (*C*=O)O), 71.1 and 70.9 (2× OC*H*$_2$CH(CH$_3$)$_2$), 59.1 (s, *C*H$_2$N(CH$_3$)$_2$), 51.5 (s, *C*HNH), 45.4 (s, *C*H$_2$NH), 45.1 (s, N(*C*H$_3$)$_2$), 30.4 and 23.6 (2× s, CHCHH′*C*H$_2$), 28.0 (s, 2× *C*H(CH$_3$)$_2$), 19.0 (s, 2× CH(*C*H$_3$)$_2$). IR (powder film, cm^{-1}): 3329 (m, ν_{NH}), 2961 and 2943 (2× m, ν_{CH}), 1697 and 1683 (s and vs, $\nu_{C=O}$), 1537 (s, δ_{NH}).

5.1.14. Tris(hydrochloric acid) salt of (*S*)-*N*^{5},*N*^{5}-dimethylpentane-1,2,5-triamine or (*S*)-$H_3NCH(CH_2CH_2CH_2NMe_2H)CH_2NH_3]^{3+}$ 3Cl$^-$ (*S*)-L3·(HCl)$_3$

A round bottom flask was charged with (*S*)-**3$_{L3}$** (4.212 g, 12.21 mmol) and aqueous HCl (6.0 M, 250 mL) and fitted with a condenser. The solution was refluxed. After 36 h, the solvent was removed by rotary evaporation (using a base trap to protect the pump). The residue was dissolved in H_2O and the solution was washed with CH_2Cl_2. The solvent was removed from the aqueous phase by rotary evaporation. The residue was washed with Et_2O and CH_3OH, and dried by oil pump vacuum. This gave the solvate (*S*)-**L3**·(HCl)$_3$·CH_3OH (2.994 g, 10.44 mmol, 86%) as a colorless sticky hygroscopic solid. Anal. Calcd for $C_7H_{22}Cl_3N_3$·CH_3OH (286.67):[25] C 33.52, H 9.14, N 14.66; Calcd for $C_7H_{22}Cl_3N_3$·0.33CH_3OH (265.2,

corresponding to ^{1}H NMR integration): C 33.20, H 8.86, N 15.84; found C 33.31, H 8.81, N 14.85. NMR (D_2O, δ in ppm): ^{1}H (500 MHz) 3.77–3.66 (m, 1H, C*H*NH_3), 3.42–3.37 (m, 2H, CH_2NH_3), 3.34 (s, 1H, CH_3OH), 3.26–3.18 (m, 2H, $CH_2NH(CH_3)_2$), 2.91 (s, 6H, $NH(CH_3)_2$), 2.01–1.74 (m, 4H, CHC*HH*′CH_2); ^{13}C{^{1}H} (125 MHz) 57.2 (s, CHNH_3), 49.6 (s, $CH_2N(CH_3)_2$), 43.4 (s, CH_2NH_3), 41.2 (s, $NH(CH_3)_2$), 27.7 and 20.7 (2× s, CHCH′CH_2).

5.1.15. (2*S*)-N^6-Benzyloxycarbonyl-N^1,N^2-di-*tert*-butoxycarbonyl-1,2,6-triaminohexane or (*S*)-(*t*-BuOC(O))NHCH($CH_2CH_2CH_2CH_2$NH-(C(O)OCH_2Ph))CH_2NH(C(O)O*t*-Bu) (*S*)-**5**$_{L4}$

A round bottom flask was charged with 10% Pd/C (0.16 g, 'nominally 50% water wet') and H_2O (8 mL) and flushed with N_2. After 10 min, a solution of $NaBH_4$ (0.284 g, 7.50 mmol) in H_2O (8 mL) was added with stirring, followed by solid Boc_2O (0.82 g, 3.75 mmol) and then a solution of (*S*)-**4**$_{L4}$ (0.98 g, 2.5 mmol)[18b] in CH_3OH (22 mL). After 1 h, the mixture was filtered through Celite. The filtrate was neutralized with $KHSO_4$, and the solvent was removed by rotary evaporation. Next, H_2O (50 mL) was added and the mixture was extracted with EtOAc (2 × 70 mL). The combined extracts were dried (Na_2SO_4). The solvent was removed by rotary evaporation and the solid was chromatographed on a silica gel column (3 × 8 cm, 20:80 to 50:50 v/v EtOAc/hexane). The solvent was removed from the product containing fractions by rotary evaporation. The residue was dried by oil pump vacuum to give (*S*)-**5**$_{L4}$ (0.823 g, 1.77 mmol, 71%)[19] as a white solid. NMR ($CDCl_3$, δ in ppm):[19] ^{1}H (500 MHz) 7.39–7.27 (m, 4H, *Ph*),[26] 5.07 (br s, 2H, OCH_2Ph), 4.96 (br s, 1H, N*H*(C=O)O), 4.85–4.61 (br m, 2H, 2× N*H* (C=O)O), 3.57 (br s, 1H, C*H*NH(Boc)), 3.22–3.03 (m, 4H, CH_2NH (Boc) and CH_2NH(Cbz)), 1.52–1.32 (m, 24H, 3 × CH_2, 2× OC$(CH_3)_3$); ^{13}C{^{1}H} (125 MHz) 156.6, 156.5, and 156.2 (3 × s, 3 × (C=O)O)); *Ph* at 136.6 (s, *i*), 128.4 (s, *o*), 128.0 (s, *p*), 127.9 (s, *m*);[22] 79.3 (s, 2× O$C(CH_3)_3$), 66.5 (s, OCH_2Ph), 51.1 (s, C*H*NH(Boc)), 44.5 (s, CH_2NH(Boc)), 40.4 (s, CH_2NH(Cbz)), 32.2 (s, CH_2), 29.5 (s, CH_2), 28.4 (s, 2× $C(CH_3)_3$), 22.7 (s, CH_2). IR (powder film, cm^{-1}): 3352 (m, ν_{NH}), 2982 and 2932 (2× w, ν_{CH}), 1682 (vs, $\nu_{C=O}$), 1530 (s, δ_{NH}).

5.1.16. (*S*)-N^1,N^2-Di-*tert*-butoxycarbonyl-N^6,N^6-dimethyl-1,2,6-triaminohexane or (*S*)-(*t*-BuOC(O))NHCH($CH_2CH_2CH_2CH_2$NMe_2)-CH_2NH(C(O)O*t*-Bu) (*S*)-**6**$_{L4}$

A Fisher Porter bottle was charged with (*S*)-**5**$_{L4}$ (5.72 g, 12.3 mmol), CH_3OH (100 mL), distilled H_2O (30 mL), and 37% aqueous HCHO (2.6 mL). The mixture was stirred for 1 h. Next, 10% Pd/C (3.0 g, 'nominally 50% water wet') was added, and H_2 was introduced (50 psi). After 24 h, the mixture was filtered through a plug of Celite and washed with CH_3OH/distilled H_2O (1:1 v/v). The solvent was removed by rotary evaporation. The residue was chromatographed on a silica gel column (3 × 14 cm, 100:0 to 85:15 v/v CH_2Cl_2/CH_3OH). The solvent was removed from the product containing fractions by rotary evaporation and oil pump vacuum to give (*S*)-**6**$_{L4}$ (4.07 g, 10.8 mmol, 88%) as a colorless sticky solid. Anal. Calcd for $C_{18}H_{37}N_3O_4{\cdot}H_2O$ (377.51): C, 57.27; H, 10.41; N, 11.13. Found: C, 57.22; H, 10.03; N, 10.58.[27] NMR ($CDCl_3$, δ in ppm): ^{1}H (500 MHz) 4.96 (br s, 1H, N*H*(C=O)O), 4.74 (br s, 1H, N*H*(C=O)O), 3.57 (br s, 1H, C*H*NH(Boc)), 3.22–3.03 (br s, 2H, CH_2NH(Boc)), 2.26 (t, $^3J_{HH}$ = 7.5 Hz, 2H, $CH_2N(CH_3)_2$), 2.21 (s, 6H, $N(CH_3)_2$), 1.52–1.31 (m, 26H, 3× CH_2, 2× C$(CH_3)_3$, and H_2O); ^{13}C{^{1}H} (125 MHz) 156.5, and 156.2 (2× s, 2× (*C*=O)O), 79.2 (s, 2× O$C(CH_3)_3$), 59.3 (s, $CH_2N(CH_3)_2$), 51.2 (s, C*H*NH(Boc)), 45.2 (s, $CH_2N(CH_3)_2$), 44.8 (s, CH_2NH(Boc)), 32.5 (s, CH_2), 28.3 (s, CH_2), 27.1 (s, 2× $C(CH_3)_3$), 23.5 (s, CH_2). IR (powder film, cm^{-1}): 3346 (m, ν_{NH}), 2976 and 2932 (2× m, ν_{CH}), 1682 (vs, $\nu_{C=O}$), 1526 (s, δ_{NH}).

5.1.17. Tris(hydrochloric acid) salt of (*S*)-N^6,N^6-dimethylhexane-1,2,6-triamine or (*S*)-$H_3NCH(CH_2CH_2CH_2CH_2NMe_2H)CH_2NH_3]^{3+}$ $3Cl^-$ (*S*)-**L4**·$(HCl)_3$

A round bottom flask was charged with (*S*)-**6**$_{L4}$ (3.61 g, 10.0 mmol) and 12.0 M HCl/dioxane (25:75 v/v; 150 mL) with stirring. After 12 h, the solvent was removed by rotary evaporation (using a base trap to protect the pump). The residue was dissolved in H_2O and the solution was washed with CH_2Cl_2. The solvent was removed from the aqueous phase by rotary evaporation. The residue was washed with Et_2O and CH_3OH, and dried by oil pump vacuum to give (*S*)-**L4**·$(HCl)_3{\cdot}CH_3OH$ (2.40 g, 7.98 mmol, 80%) as a colorless sticky hygroscopic solid. Anal. Calcd for $C_8H_{24}Cl_3N_3{\cdot}CH_3OH$ (300.67):[25] C, 35.95; H, 9.39; N, 13.97; Calcd for $C_8H_{24}Cl_3N_3{\cdot}0.33CH_3OH$ (279.23, corresponding to ^{1}H NMR integration): C, 35.83; H, 9.14; N, 15.05. Found: C, 35.97; H, 9.16; N, 13.81. NMR (D_2O, δ in ppm): ^{1}H (500 MHz) 3.75–3.69 (m, 1H, C*H*NH_3), 3.42–3.37 (m, 2H, CH_2NH_3), 3.36 (s, 1H, CH_3OH), 3.26–3.17 (m, 2H, $CH_2N(CH_3)_2$), 2.91 (s, 6H, $NH(CH_3)_2$), 1.94–1.78 (m, 4H, CHC*HH*′CH_2CH_2), 1.62–1.50 (m, 2H, CHCHH′CH_2CH_2); ^{13}C{^{1}H} (125 MHz) 57.8 (s, $CH_2N(CH_3)_2$), 49.9 (s, CHNH_3), 49.8 (s, CH_3OH), 43.4 (s, $NH(CH_3)_2$), 41.4 (s, CH_2NH_3), 30.2, 24.3, and 22.0 (3 × s, CHCHH′CH_2CH_2).

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26. This signal integrates to four protons rather than the expected five.
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