Stereocontrolled Synthesis of DTPA Analogues Branched in the Ethylene Unit

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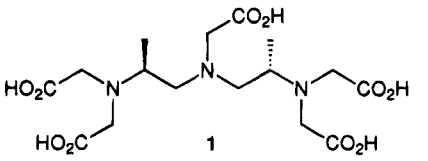
Stereochemically controlled synthesis of diethylenetriaminepentaacetic acid (DTPA) analogues substituted on the ethylene backbones with methyl groups, the chiral center α to the terminal nitrogen being derived from (*S*)- or (*R*)-alanine, has been achieved. The key intermediate (*S*)-propylenediaminetriacetic acid triester was synthesized via selective detosylation of the alkylation product derived from (*S*)-alanine and *tert*-butyl glycinate. Attaching the remaining modified alanine (or glycine) fragment through acyl coupling and then selective reduction of the amide followed by hydrolysis of the esters afforded the substituted DTPA analogues. Ester differentiation has been accomplished through alkylation rather than acylation of the (*S*)-propylenediaminetriacetic acid triester. A byproduct from this alkylation is the oxazoloisoindole formed by internal alkylation of the oxygen of the phthaloyl protecting group. Phthaloyl deprotection followed by dialkylation afforded the ester-differentiated (*S,S*)-dipropylenetriaminepentaacetic esters. The enantiomeric purity of the chiral intermediates (*S*)-alaninol and (*S*)-propylenediamines were determined by HPLC using epimeric standards.

Introduction

Complexes of an organic ligand bound to a radioactive metal have been valuable agents in magnetic resonance imaging (MRI) and as radiopharmaceuticals.[1] Since the first demonstration that polyaminocarboxylate-metal ion complexes are useful imaging agents,[2] modifications of these ligands have been developed in the search for better complexes. Initial studies centered around complexes with EDTA (ethylenediaminetetraacetic acid) and its analogues. Theoretical studies[3] led to the conclusion that the stability of the metal–ligand complex increases with substitution on the ethylene bridge and that the steric effect of these groups is of little consequence since methyl- and phenyl-substituted ligands have similar stability constants.

Many other polyaminocarboxylates have been investigated, in particular diethylenetriaminepentaacetic acid (DTPA), which can ligate through three amines and five carboxylates, leading to $[Gd(DTPA)(H_2O)]^{2-}$, an effective contrasting agent in the diagnosis of tumors in human.[4] Since the introduction of this imaging agent, efforts have been directed at improving this ligand by increasing the stability of the complex. Functionalization of one or two of the carboxylate groups,[5] substitution on the methylene α to the carboxylates,[6] or modification of the ethylene backbone[7] have been reported to enhance the stability of the metal–ligand ion complex; however, in no case was the effect of stereochemistry on the metal–ligand ion complex examined.

Recently, the enantiomerically and diastereomerically pure syntheses of some DTPA analogs have been reported,[8] in which substitution on the central acetic acid residue and conformationally constrained rings has been introduced. Also, these syntheses permitted ester differentiation and selective cleavage of the east and west ester pairs. We now present the stereocontrolled synthesis of DTPA analogues substituted on the ethylene backbone. The substitution pattern has been based on the introduction of methyl groups in the ethylene backbone by a methodology that can be extended to many other substituents. The target ligands are dipropylenetriaminepentaacetic acids (DPTPA) **1** and **2** and the mixed propylene–ethylene analogue **3** as the optically active isomer, the meso isomer, and the *S*-enantiomer, respectively.



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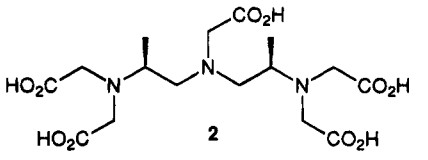

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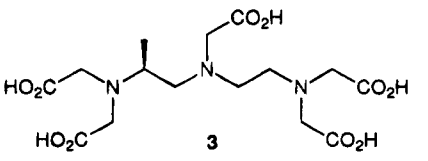

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Results and Discussion

Examination of the targets **1**, **2**, and **3** led to the initial projection that they could be constituted from suitably substituted alanines and glycines by acyl coupling of

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(2) Sundberg, M. W.; Meares, C. F.; Goodwin, D. A.; Diamante, C. I. *J. Med. Chem.* **1974**, *17*, 1304.
(3) Margerum, D. W.; Cayley, G. R., Weatherbaum, D. C., Pagenkoph, G. K. In *Cooridination Chemistry Monograph 174*; American Chemical Society: Washington, DC, 1978; Vol. 2, Chapter 1.
(4) Carr, D. H.; Brown, J.; Bydder, G. M. *Lancet* **1984**, *1*, 484.
(5) Sherry, A. D.; Cacheris, W. P.; Kaun, K. T. *Magn. Reson. Med.* **1988**, *8*, 180.
(6) (a) Westerberg, D. A.; Carney, P. L.; Rogers, P. E.; Kline, S. J.; Johnson, D. K. *J. Med. Chem.* **1989**, *32*, 236. (b) Keana, J. F. W.; Mann, J. S. *J. Org. Chem.* **1990**, *55*, 2868.

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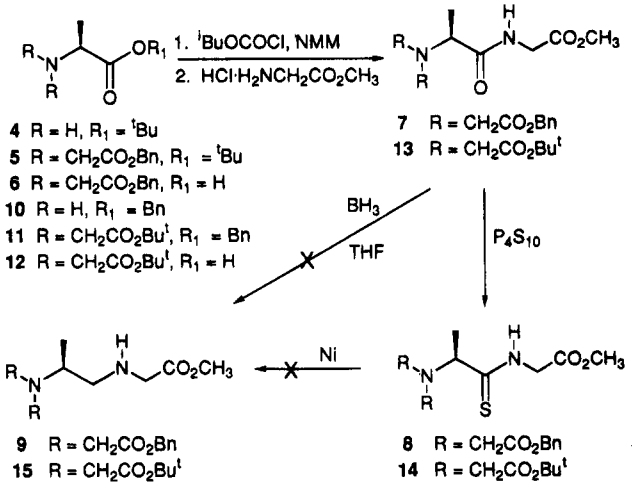
Scheme 1. Acylation/Reduction Approach



these fragments and then reduction of the amide to produce the appropriate ethylenediamine (Scheme 1). Thus, (*S*)-alanine *tert*-butyl ester (**4**) was alkylated with benzyl iodoacetate and yielded dialkylated product **5**. Hydrolysis of the *tert*-butyl ester produced *N*,*N*-dialkylated acid **6** which was coupled with glycine methyl ester to produce *N*-substituted amide **7** in 74% overall yield. Attempted selective reduction of amide **7** in the presence of the three esters using BH_3·THF[9] failed to produce the secondary amine; instead, reduction of the esters was observed. Alternatively, conversion to thioamide **8** and desulfurization using W-2 Raney Ni[10] also failed to produce secondary amine **9**; thioamide **8** was recovered unchanged. To minimize ester reduction, the corresponding di-*tert*-butyl analogue, amide **13**, was prepared; however, **13** behaved the same as **7**: BH_3·THF reduced the esters and W-2 Raney Ni failed to desulfurize the thioamide. Since this acylation/reduction approach failed to produce substituted propylenediamines **9** or **15**, we pursued the alternative of reduction first followed by alkylation.

The reduction/alkylation sequence required an *N*-substituted alaninol which would be used to alkylate the glycine fragment. The alaninol moiety, prepared from (*S*)-alanine by reduction with $LiAlH_4$, was isolated as (*S*)-*N*-CBZ-alaninol (**16**)[11-13] (Scheme 2). Proceeding with **16**, hydrogenolysis followed by dialkylation of the amine with benzyl bromoacetate produced alcohol **17**. Attempted purification of alcohol **17** by chromatography led to lactone **20** in a 79% yield, apparently as a result of silica-mediated cyclization. To avoid this lactone formation, crude alcohol **17** was converted into bromide **18** which was equally unstable. On standing at room temperature, aziridinium ion **19** formed rapidly, and on treatment with phosphate buffer (1.0 M, pH 7.0), a 4/1 mixture (as determined by ^1H NMR) of two lactones, **20** and **21**, was formed. Clearly, the intermediate aziridinium ion **19** was opening in both modes. This loss of regiochemical integrity forced us to abandon this approach.

To prevent this scrambling caused by participation of the nitrogen, the amine nucleophilicity was reduced by conversion to (*S*)-BOC-alaninol (**22**)[14] and the alcohol was converted into mesylate **23** and iodide **24**. Mesylate **23** failed to react with glycine *tert*-butyl ester, and iodide **24** in the presence or absence of glycine *tert*-butyl ester was converted to 4-methyl-2-oxazolidinone (**26**) in 73% yield via cyclization on the carbonyl oxygen of the carbamate.[15] Attempts to prepare triflate **25** from (*S*)-BOC-alaninol (**22**) led only to mixtures containing major amounts of cyclized product **26**.

Protection of the amine required the introduction of two acyl groups, and this was finally achieved as a phthaloyl group. (*S*)-*N*-Phthaloylalaninol (**27**) was prepared from (*S*)-alaninol using *N*-(ethoxycarbonyl)phthalimide[16] in a reaction that proceeds with no racemization.[17] This alcohol was converted into mesylate (*S*)-**28** and iodide (*S*)-**29** in 90% and 76% yields, respectively, from (*S*)-*N*-phthaloylalaninol (**27**). Reactions of mesylate **28** and iodide **29** with glycine *tert*-butyl ester afforded only small yields of the alkylation product, secondary amine (*S*)-**31**, even at elevated temperatures and in polar solvents. Greater reactivity was needed and was achieved with triflate (*S*)-**30**, prepared in a 90% isolated yield. When triflate (*S*)-**30** reacted with glycine *tert*-butyl ester in the presence of DIEA at 0 °C, secondary amine **31** was isolated in a 60% yield along with oxazoloisoindole **32** in a 26% yield. The structure and formation of oxazoloisoindoles will be discussed below. To establish the enantiomeric purity of (*S*)-**31**, we also prepared secondary amine (*R*)-**31**. Treatment of (*S*)-**31** and (*R*)-**31** with excess (*R*)-α-methylbenzyl isocyanate formed the ureas **33** and **34**, respectively, and analytical HPLC[18] showed that for both (*S*)-**31** and (*R*)-**31** the er's were in excess of 99/1.

To obtain selective alkylation at the C-2 nitrogen of the propylenediamine, it was necessary to protect the secondary amine of (*S*)-**31** before deprotecting the primary amine (Scheme 3). Since recent evidence indicated that an *N*-BOC could be selectively removed in the presence of a *tert*-butyl ester,[19] the secondary amine (*S*)-**31** was acylated with BOC_2O, producing carbamate **35** in 95% yield. Phthaloyl deprotection over 24 h at rt using methylamine gave primary amine **36** in low yields, and lactam **37** was isolated in 85% yield. A satisfactory yield

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(9) (a) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912. (b) Brown, H. C.; Heim, P., Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 1637.

(10) (a) Kornfeld, E. C. *J. Org. Chem.* **1951**, *16*, 131. (b) Pettit, G. R.; van Tamelen, E. E. *Org. React.* **1962**, *12*, 356.

(11) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083.

(12) Poindexter, G. S.; Meyers, A. I. *Tetrahedron Lett.* **1977**, *18*, 3527. To determine the enantiomeric purity of the (*S*)-alaninol, hydrogenolysis of its CBZ derivative **16** and treatment of the product and racemic alaninol with excess (*R*)-α-methylbenzyl isocyanate gave the corresponding ureas. Analysis by HPLC[13] established the enantiomeric ratio (er) of the (*S*)-alaninol to be >99/1.

(13) HPLC conditions: mobile phase 60% EtOAc/PE; column 4.6 × 250 mm, 5 mm silica; flow rate 0.5 mL/min; detector 254 nm. For *S*,*R* diastereomer, t_R = 30.5 min; for *R*,*R* diastereomer, t_R = 24.5 min. The detection limit for the presence of either diastereomer was <1%.

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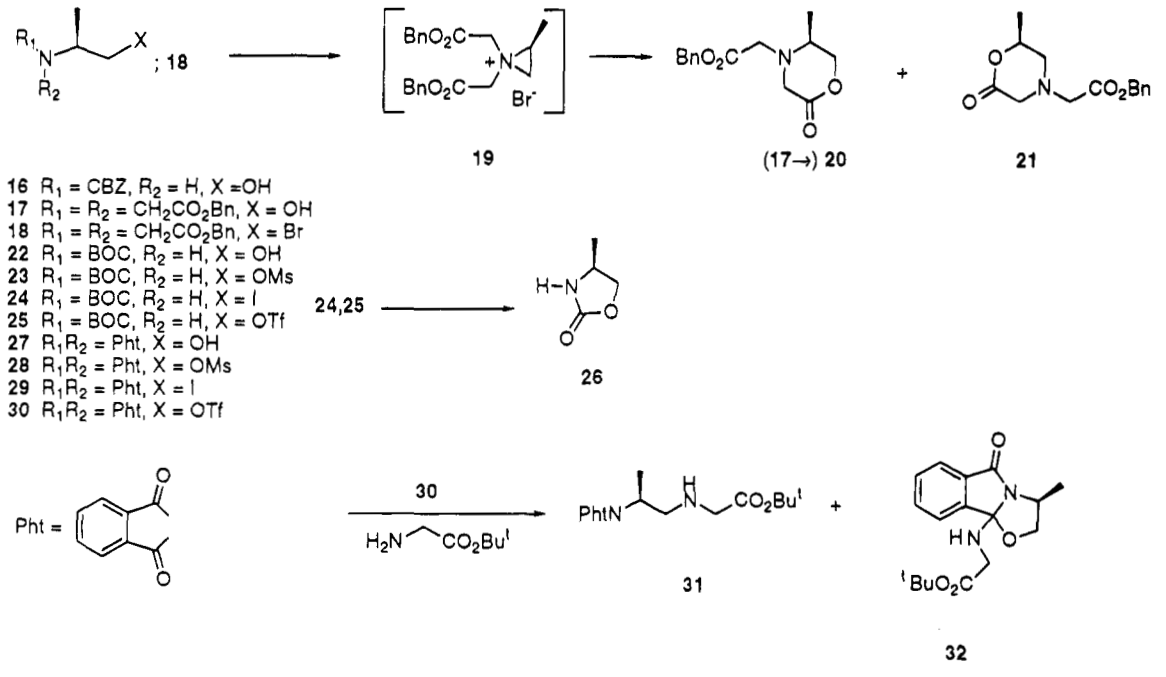
(17) McArthur, C. R.; Worster, P. M.; Okon, A. U. *Synth. Commun.* **1983**, *13*, 311.

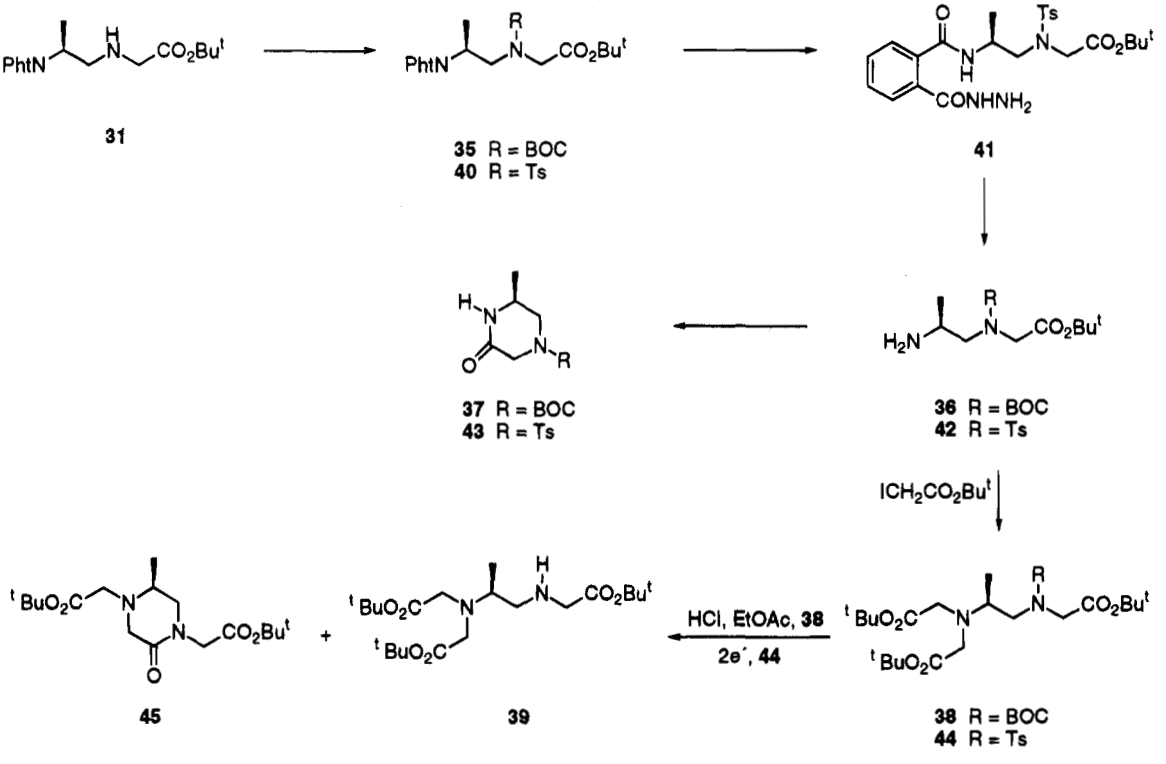
(18) HPLC conditions: mobile phase 17% EtOAc/hexanes; column 4.6 × 250 mm; 5 mm silica; flow rate 0.5 mL/min; detector 254 nm. For diastereomer **33**, t_R = 70.8 min; for diastereomer **34**, t_R = 64.8 min. The detection limit for the presence of either diastereomer was <1%.

(19) Gibson, F.; Bergmeier, S.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216.

Scheme 2. Reduction/Alkylation Approach



Scheme 3. Phthaloyl Removal and Alkylation of Terminal Nitrogen



of amine **36** (approximately 70% by ^{1}H NMR), however, was obtained by reducing the deprotection time to 6.5 h. Alkylation of crude primary amine **36** using *tert*-butyl iodoacetate afforded *N*-BOC tri-ester **38** in 50% overall yield. Selective removal of the *N*-BOC from **38** using 1.0 M HCl in EtOAc gave only an 18% yield of secondary amine **39** after 1 h. A procedure using *p*-TsOH in Et_2O[20] produced a similar result.

Since selective removal of the *N*-BOC was achieved only poorly, it was replaced with a *p*-toluenesulfonyl moiety. Tosyl chloride was added to secondary amine (*S*)-**31**, producing *N*-Ts derivative **40** in an 82% yield. Phthaloyl deprotection using conditions previously applied for *N*-BOC analogue **35** gave only low yields (20–30%) of primary amine **42**. Using hydrazine as the deprotection agent and examining concentration, water content, and reaction time, conditions were found which gave hydrazide **41**, primary amine **42**, and lactam **43** in 9%, 70%, and 10% yields, respectively. Characterization of hydrazide **41** was accomplished by conversion to the *N*-BOC hydrazide and the *N*-BOC amine derived from phthaloyl extrusion. Anticipating that a 4-nitrophthaloyl group would be removed more easily,[21] the 4-nitrophthaloyl analogue of **40** was prepared as described for **40**. A

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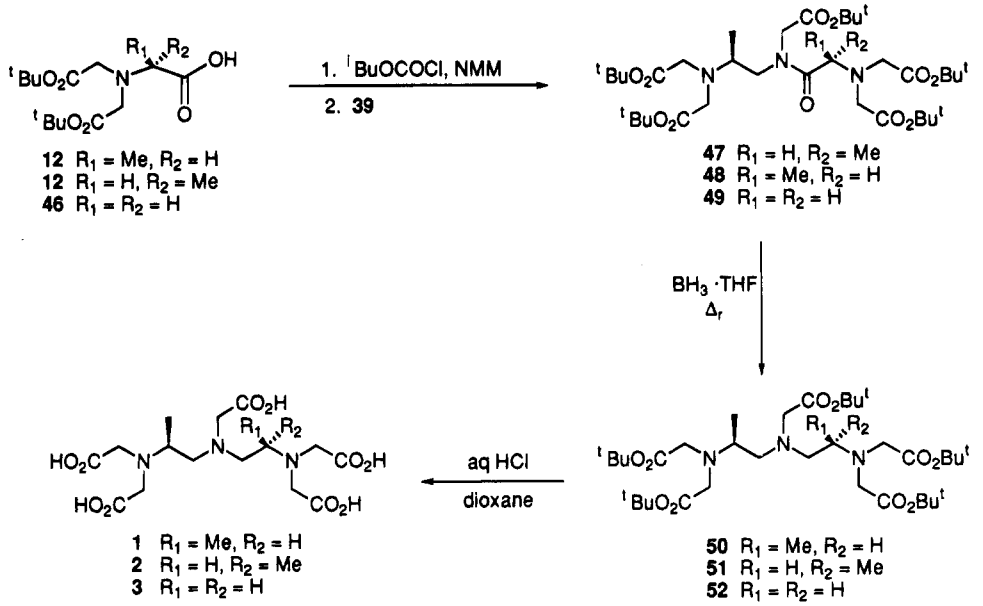
Scheme 4. Preparation of Propylenediamine Analogues 1, 2, and 3 through Acyl Coupling and Reduction



study of phthaloyl removal showed that the 4-nitrophthaloyl group indeed was removed faster (2×), but the yield of the primary amine **42** was not significantly increased.

Dialkylation of primary amine **42** using *tert*-butyl iodoacetate afforded a mixture of tertiary amine **44** (68% yield) and secondary amine (19% yield); recycling this secondary amine increased the yield of tertiary amine **44** to 85%. A number of procedures were applied for the removal of the *N*-Ts group in the presence of *tert*-butyl esters: sodium naphthalide,[22] dissolving metal reduction,[23] and buffered sodium amalgam;[24] all failed to be selective. Electrochemical reduction,[25] however, did occur specifically in the presence of the *tert*-butyl esters. The reduction potential for the *N*-Ts group of **44** was directly measured as $E°_{1/2} = -1.825$ V versus a silver wire reference electrode. Allowing the electrochemical reduction to proceed until all of **44** had disappeared (8 h/rt) gave lactam **45** in 80% yield and secondary amine **39** in 18% yield. Limiting the electrolysis time to 4.25 h afforded detosylated secondary amine **39** in 45% yield, lactam **45** in 5% yield, and recovered **44** in 46% yield. Two recycles of **44** increased the yield of secondary amine **39** to 76%.

Two methods were pursued for elaboration of the eastern ethylenediamine and propylenediamine units, namely coupling to secondary amine **39** through acylation or alkylation. Using the acylation process, formation of the *N,N*-disubstituted amide, reduction, and then ester hydrolysis would afford the target analogues (Scheme 4). Thus, secondary amine **39** was condensed with the mixed anhydride from carboxylic acid **12**, producing *N,N*-disubstituted amide (*S,S*)-**47** in 94% yield. Amide reduction using BH_3·THF gave penta-*tert*-butyl ester (*S,S*)-**50** in 57% yield. Acid hydrolysis yielded (*S,S*)-DPTPA (**1**) as its trihydrochloride salt in 98% yield. The (*S,R*)-**2** and (*S*)-**3** analogues were prepared under similar conditions and in similar yields.

In pursuit of an ester-differentiated pentaacetic acid analogue, the acylation protocol was applied, substituting two benzyl esters for two *tert*-butyl esters. The *N,N*-disubstituted amide (*S,S*)-**53** was prepared through mixed anhydride coupling of secondary amine **39** with carboxylic acid **6** in 95% yield (Scheme 5). On reduction (BH_3·THF) of amide **53**, the benzyl esters were reduced faster than the *N,N*-disubstituted amide. Since other attempts at direct and selective reduction failed, efforts were applied to prepare thioamide **54**, which then was to be desulfurized using Ni. Subjecting amide **53** to thiation (P_4S_{10} or Lawesson's reagent) in a variety of solvents (toluene, THF, dioxane, pyridine, HMPA) at varying temperatures (rt to reflux) failed to produce thioamide **54**. An attractive alternative for the preparation of thioamides appeared to be the use of a recently developed[26] thioacyl transfer reagent. This method was applied in an attempt to prepare thioamide **54**. *o*-Aminoanilide **55** was prepared through a mixed anhydride coupling of carboxylic acid **6** with 1,2-phenylenediamine. Thiation of *o*-aminoanilide **55** with P_4S_{10} afforded *o*-aminothioanilide **56**, and intramolecular cyclization with 1,1-carbonyldi(1,2,4-)triazole then gave benzimidazolone **57** in a 52% overall yield. When **57** was treated with secondary amine **39**, no thioamide **54** was isolated; rather lactam **45** was obtained in 85% yield. Since both acylation processes failed to lead to an ester-differentiated analogue, an alkylative coupling method was examined.

The alkylation method was to consist of alkylating secondary amine **39**, removing the phthaloyl group, and then dialkylating the liberated primary amine. Triflate (*S*)-**30** was reacted with secondary amine **39**, producing two products, oxazoloisoindole **59** and the desired *N*-Pht

(21) Tsubouchi, H; Tsuji, K.; Ishikawa, H. *Synlett* **1994**, 63.

(22) (a) Closson, W. D.; Ji, S.; Schulenberg, S. *J. Am. Chem. Soc.* **1970**, *92*, 650. (b) Closson, W. D.; Wriede, P.; Bank, S. *J. Am. Chem. Soc.* **1966**, *88*, 1581.

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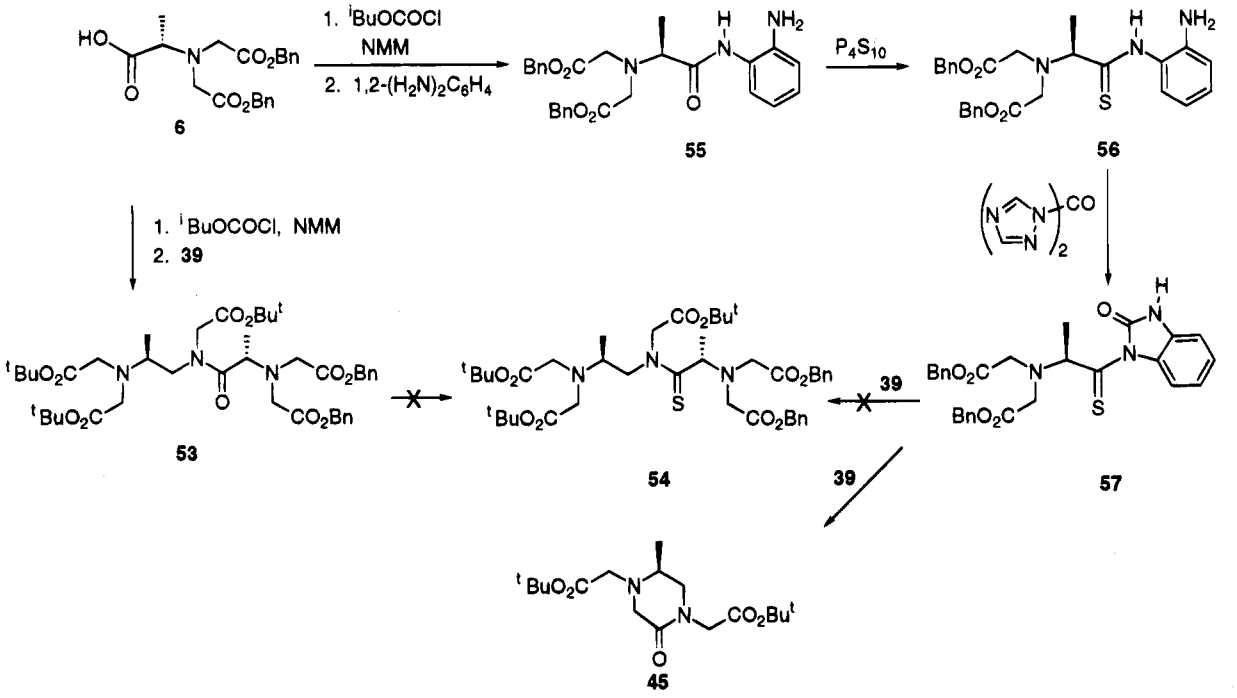
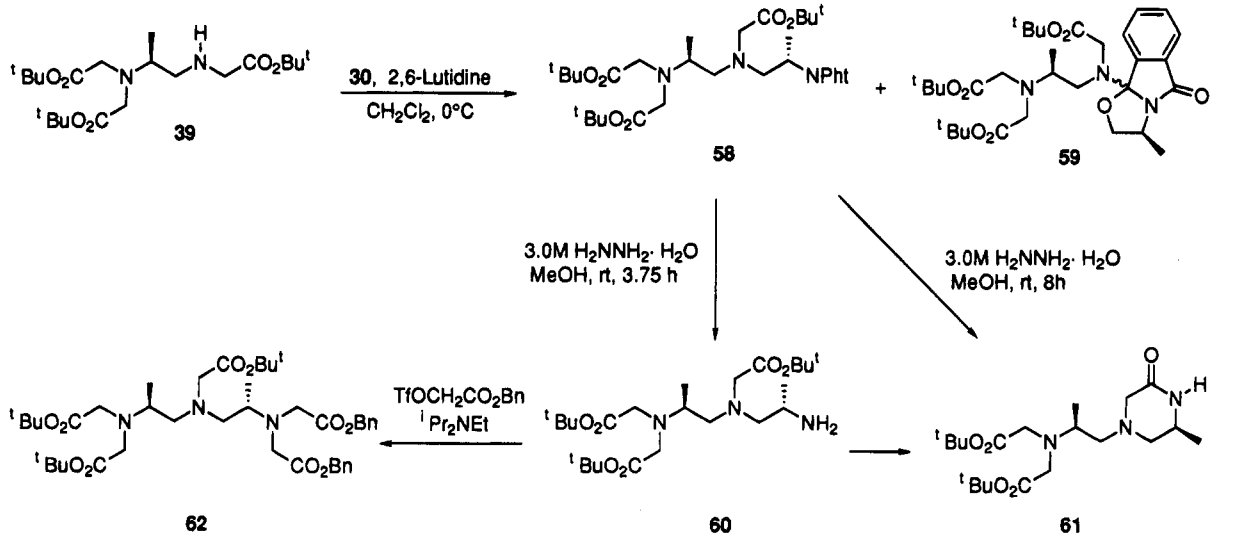
Scheme 5. Attempted Formation of Thioamide



Scheme 6. Preparation of Ester-Differentiated DTPA Analogue



58 (Scheme 6). After a study of reaction parameters (solvent, base, temperature, time), conditions were established under which the yield of *N*-alkylated material **58** was 69% and the ratio of **58** to oxazoloisoindole **59** was 2.3 to 1.0.

To remove the *N*-protecting group, the phthaloyl deprotection protocol for **40** was applied to the mixture of **58** and **59** and led to the isolation of primary amine **60** in 62% yield. Extending the deprotection reaction to 6 h afforded an 89% yield of lactam **61**. Completion of the sequence to the differentiated ester analogue by alkylation of primary amine **60** with the triflate of benzyl glycolate gave tertiary amine **62** in 87% yield. In consideration of the instability of primary amine **60**, the entire crude deprotection mixture was submitted to alkylation conditions. From this telescoped procedure, tertiary amine **62** was obtained in a 61% overall yield from the *N*-Pht **58**.

Since the unexpected oxazoloisoindoles **32** and **59** were encountered, further evidence for this heterocyclic structure was sought. Only one prior report[27] of oxazoloisoindole formation has appeared. This tricycle occurs by an intramolecular cyclization on the phthaloyl oxygen by the triflate (*S*)-**30**, producing intermediate iminium ion **63** (Scheme 7). Attempts at direct reduction of iminium ion **63** while preserving the oxazoloisoindole ring system using standard methods ($NaBH_4$, $NaBH_3CN$, 5% Pd/C and H_2, 5% Pt/C and H_2)[28] gave complex mixtures. A ring-intact oxazoloisoindole derivative was attained, however, through reaction of triflate (*S*)-**30** with an excess of benzyl mercaptan, producing equal amounts of diastereomers **65** and **66** in 86% yield and a 9% yield of the ring-opened product, *S*-**64**. Desulfurization of **65** and **66** using Raney Ni T_1[29] did not retain the ring system, rather the oxoisoindole **67** was obtained in 68% and 73%

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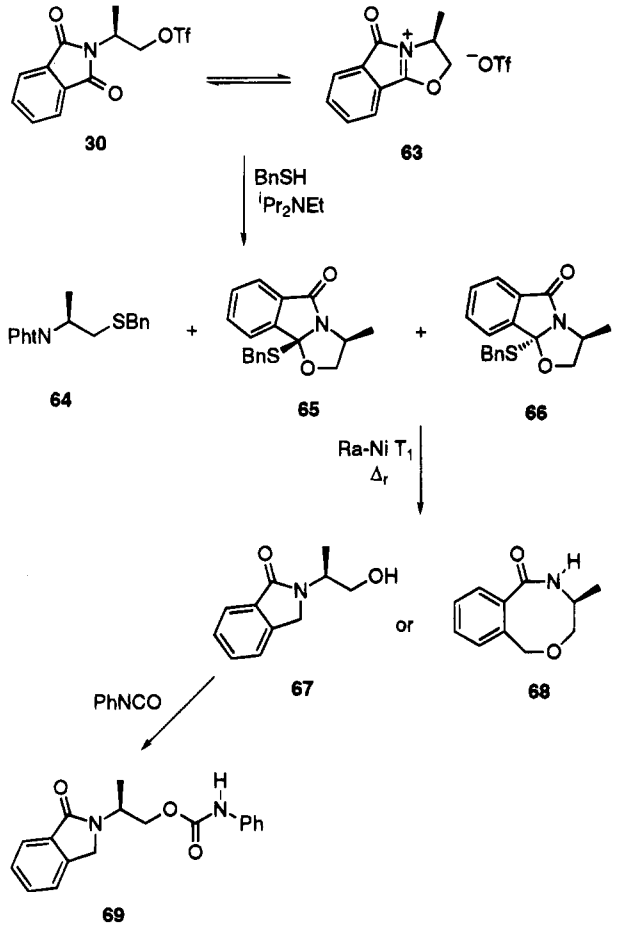
(28) Hudlicky, M. In *Reductions in Organic Chemistry*; John Wiley & Sons: New York, 1984.

(29) Compagnone, R. S.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1713.

Scheme 7. Characterization of Oxazoloisoindole



yields, respectively. A further consideration was isomeric structure **68**, instead of **67**, which could possibly result from the desulfurization reaction. Confirmation of structure **67** was obtained by reacting the product with phenyl isocyanate, forming phenyl carbamate **69** in 92% yield.

Conclusion

Preparation of the DTPA analogues, DPTPA's **1** and **2**, and the mixed ethylenediaminepropylenediamine **3** through an enantiomerically controlled synthesis has been described using a combination of alkylation followed by an acylation–reduction sequence. Ester differentiation at the eastern and western termini also has been achieved. Use of *N*-phthaloyl and *N*-tosyl protecting groups proved essential to overcome the marked tendency for lactam formation with this methyl-branched ethylenediamine. The phthaloyl group unexpectedly led to significant amounts of oxazoloisoindoles, intramolecular cyclization byproducts, when the β-hydroxy was converted to a good leaving group.

Experimental Section

General. ^{1}H NMR spectra were obtained in $CDCl_3$ and were referenced to an internal standard of tetramethylsilane; when D_2O was used, internal 3-(trimethylsilyl)propionate-d_4 was the reference. ^{13}C NMR spectra were obtained in $CDCl_3$ (reference δ 77.0 ppm) and D_2O (internal dioxane reference δ 69.3 ppm). J values are in hertz. All organic solutions from extractive isolation were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure (water aspirator) at 30–40 °C unless otherwise indicated. TLC analysis was performed on aluminum-backed silica gel 60 F_{254} (EM Separations) and visualized with UV light (254 nm), ethanolic phosphomolybdic acid, ethanolic ninhydrin, or ethanolic anisaldehyde followed by heating. Melting points are uncorrected. Chromatography was performed on silica gel 60 (70–230 mesh) using the described solvent system. HPLC (high-pressure liquid chromatography) was conducted on a 4.6 × 250 mm 5 mm Microsorb Si normal phase column, monitoring at 254 nm. Cyclic voltammetry was performed on a Bioanalytical Systems Model 100A electrochemical analyzer. Preparative electrochemistry was performed on a Princeton Applied Research Model 173 potentiostat/galvanostat maintaining the potential throughout the electrolysis. Relevant information concerning dimensions of electrochemical cell and equipment have been presented previously.[30] All reactions were performed under a nitrogen atmosphere unless otherwise indicated. Tetraethylammonium bromide (TEAB) was recrystallized three times from absolute ethanol and then dried under vacuum (100 °C, 0.1 Torr, 16 h). Phenol was distilled at 80 °C (20 Torr) prior to use. Anhydrous THF was distilled from sodium/benzophenone ketyl. Diisopropylethylamine, *N*-methylmorpholine, triethylamine, and 2,6-lutidine were distilled from CaH_2 and then stored over activated 3-Å molecular sieves under an argon atmosphere. Dichloromethane was distilled from CaH_2. Acetonitrile was first distilled from P_2O_5 and then from CaH_2 directly before use. Methanol was distilled from magnesium methoxide.

(*S*)-*N*,*N*-Bis[(*tert*-butoxycarbonyl)methyl]alanine Benzyl Ester (11). The preparation of **11** followed the same procedure as for the preparation of **5**[31] using (*S*)-alanine benzyl ester tosylate (**10**, 12.30 g, 35.0 mmol), *tert*-butyl iodoacetate (25.42 g, 105.0 mmol), 1.0 M pH 7.0 phosphate buffer (105 mL), and DMSO (250 mL) with a reaction time of 48 h. After extractive isolation, benzyl ester **11** (10.6 g, 26.1 mmol, 75% yield) was obtained via chromatography, eluting with 15% Et_2O/hexanes, as a colorless oil which solidified at 0 °C: R_f (20% Et_2O/hexanes) 0.34; mp 33 °C; $[\alpha]^{23}_D$ −18.1° (*c* 0.70, $CHCl_3$); ^{1}H NMR δ 7.4 (5H, m), 5.1 (2H, ABq, J = 3.7), 3.7 (1H, q, J = 7.1), 3.5 (4H, s), 1.43 (18H, s), 1.36 (3H, d, J = 7.1); ^{13}C NMR δ 173.0, 170.6, 136.1, 128.5, 128.1, 80.8, 66.1, 59.7, 53.4, 28.0, 16.3. Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.8; H, 8.2; N, 3.4. Found: C, 65.1; H, 8.1; N, 3.5.

(*R*)-Alanine benzyl ester tosylate ((*R*)-10) was prepared as directed for glycine benzyl ester tosylate.[32] From 16.0 g of (*R*)-alanine was obtained 60.0 g, 95% yield, of (*R*)-**10** tosylate: mp 105 °C (lit.[33] mp 113 °C); $[\alpha]^{22}_D$ +7.1° (*c* 1.54, $CHCl_3$); ^{1}H NMR δ 8.2 (2H, m), 7.7 (2H, d, J = 8.1), 7.3 (5H, m), 7.05 (2H, d, J = 8.0), 5.0 (2H, ABq, J = 12.3), 4.0 (1H, q, J = 7.3), 2.3 (3H, s), 1.4 (3H, d, J = 7.2); ^{13}C NMR δ 169.7, 141.4, 140.3, 134.8, 128.8, 128.5, 128.3, 128.1, 126.0, 67.7, 49.1, 21.2, 15.7. Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.1; H, 6.0; N, 4.0. Found: C, 57.8; H, 6.1; N, 3.9.

(*R*)-*N*,*N*-Bis[(2-*tert*-butoxycarbonyl)methyl]alanine benzyl ester ((*R*)-11) was prepared as directed for the *S*-isomer **11**. From 8.69 g of (*R*)-**10** tosylate was obtained 7.31 g, 73% yield, of (*R*)-**11**: mp 32 °C; $[\alpha]^{23}_D$ +17.0° (*c* 1.26, $CHCl_3$); ^{1}H and ^{13}C NMR identical to those of (*S*)-**11**. Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.8; H, 8.2; N, 3.4. Found: C, 65.1; H, 8.1; N, 3.4.

(*S*)-*N*,*N*-Bis[(*tert*-butoxycarbonyl)methyl]alanine (12). To a solution of benzyl ester **11** (7.94 g, 19.6 mmol) dissolved in MeOH (100 mL) was added 5% Pd/C (800 mg), and the reaction mixture was exposed to H_2 (balloon, 760 Torr) with stirring for 32 h. The mixture was filtered through a fritted funnel containing Celite, rinsing the filter with MeOH (50 mL), and the filtrate was evaporated. The residue was titurated with Et_2O and filtered, and the white solid was dried for 12 h under vacuum (40 °C, 0.1 Torr), producing **12** (6.18 g, 19.5 mmol, 99% yield): mp 83 °C; $[\alpha]^{23}_D$ +3.05° (*c* 1.08, $CHCl_3$); ^{1}H NMR δ 3.5 (1H, q, J = 7.5), 3.44 (2H, s), 3.41 (2H, s), 1.47

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(18H, s), 1.34 (3H, d, J = 7.2); ^{13}C NMR δ 174.9, 171.5, 82.5, 61.5, 53.9, 28.0, 13.2. Anal. Calcd for $C_{15}H_{27}NO_6$: C, 56.8; H, 8.6; N, 4.4. Found: C, 57.1; H, 8.4; N, 4.4.

(*R*)-*N*,*N*-Bis[(2-*tert*-butoxycarbonyl)methyl]alanine ((*R*)-12) was prepared as directed for the *S*-isomer **12**. From 5.75 g of (*R*)-**11** was obtained 4.50g, 99% yield, of (*R*)-**12**, identical in properties to (*S*)-**12** and with an equal and opposite sign of rotation. Anal. Calcd for $C_{15}H_{27}NO_6$: C, 56.8; H, 8.6; N, 4.4. Found: C, 57.1; H, 8.5; N, 4.4.

(*S*)-2-Phthalimido-1-propanol (27). To a suspension of $LiAlH_4$ (38.0 g, 1.0 mol) in THF (1.50 L) cooled to 0 °C was added (*S*)-alanine (44.5 g, 0.5 mol) in portions over 30 min. After the addition was complete, the reaction was stirred at rt for 12 h, refluxed for 18 h, and cooled to 0 °C, and 2.0 M NaOH (275 mL) was added dropwise over 30 min. The resulting mixture was stirred at rt for 6 h. The aluminum salts were removed by filtration and then rinsed with THF (0.3 L) and refluxed for 3 h with THF (0.5 L). This digestion was repeated two more times. The filtrates were combined (total volume of approximately 3.0 L), and to this solution of (*S*)-alaninol were added *N*-(ethoxycarbonyl)phthalimide[34] (110.0 g, 0.55 mol) and Na_2CO_3 (58.3 g, 0.55 mol). After stirring for 24 h at rt, isolation left an oil which was Kugelrohr distilled to remove the ethyl carbamate. The residue of (*S*)-2-phthalimido-1-propanol (**27**, 76.0 g, 0.37 mol, 74% yield) was isolated by crystallization from toluene (25 mL) and petroleum ether (10 mL). **27**: mp 79 °C (lit.[16] mp 79–81 °C).

(*R*)-2-Phthalimido-1-propanol ((*R*)-27) was prepared as described for the *S*-isomer **27**. From 17.1 g of (*R*)-alanine was obtained 25.0 g, 64% yield, of (*R*)-**27**: R_f (30% EtOAc/hexanes) 0.25; mp 80 °C; $[\alpha]^{23}_D$ −12.2° (*c* 1.13, $CHCl_3$); ^{1}H and ^{13}C NMR identical to those of (*S*)-**27**. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.4; H, 5.4; N, 7.0. Found: C, 64.5; H, 5.4; N, 7.0.

(*S*)-2-Phthalimido-1-propyl Trifluoromethanesulfonate (30). To a solution of **27** (220 mg, 1.07 mmol) in CH_2Cl_2 (10 mL), cooled to −25 °C, was added diisopropylethylamine (208 mg, 1.61 mmol). Freshly distilled triflic anhydride (332 mg, 1.18 mmol) was added dropwise over 10 min. This mixture was stirred for 45 min at −25 °C, warmed to rt, and then evaporated, maintaining the bath temperature below 20 °C. Triflate **30** (340 mg, 1.00 mmol, 94% yield) was obtained as a solid by chromatography (plug), eluting with 50% CH_2Cl_2/hexanes: R_f (70% CH_2Cl_2/hexanes) 0.50; mp 38 °C; ^{1}H NMR δ 7.87 (2H, dd, J = 5.5, 3.1), 7.76 (2H, dd, J = 5.4, 3.1), 5.10 (1H, t, J = 9.6), 4.80 (1H, m), 4.68 (1H, dd, J = 10.0, 5.0), 1.54 (3H, d, J = 7.0); ^{13}C NMR δ 167.6, 134.3, 131.4, 123.4, 118.3 ($J_{C\text{-}F}$ = 222.6), 74.9, 45.7, 14.5.

(*R*)-2-Phthalimido-1-propyl trifluoromethanesulfonate ((*R*)-30) was prepared as directed for the *S*-isomer **30**. From 1.12 g of (*R*)-**27** was obtained 1.69 g, 92% yield, of (*R*)-triflate **30**, having identical physical properties to those of (*S*)-**30**.

(*S*)-*N*-(2-Phthalimido-1-propyl)glycine *tert*-Butyl Ester (31) and (*S*)-3-Methyl-5-oxo-10-[[(*tert*-butoxycarbonyl)-methyl]amino]-2,3,5,10-tetrahydrooxazolo[2,3-*a*]isoindole (32). To a solution of *tert*-butyl glycinate[35] (39.3 g, 0.30 mol) and diisopropylethylamine (42.7 g, 0.33 mol) dissolved in DMF (600 mL) cooled to 0 °C was added (*S*)-triflate **30** (91.1 g, 0.27 mol) in CH_2Cl_2 (600 mL). The mixture was stirred at 0 °C for 36 h, then poured into CH_2Cl_2 (600 mL), and washed with water (5 × 200 mL) and brine (200 mL). After isolation, the (*S*)-secondary amine **31** (56.0 g, 0.18 mol, 60% yield, colorless oil) and oxazoloisoindole **32** (15.4 g, 0.08 mol, 26% yield, crystalline solid) were obtained by chromatography, eluting with 50% Et_2O/hexanes. **31**: R_f (60% Et_2O/hexanes) 0.45; $[\alpha]^{23}_D$ +24.1° (*c* 0.726, $CHCl_3$); ^{1}H NMR δ 7.81 (1H, dd, J = 5.4, 3.0), 7.69 (1H, dd, J = 5.5, 3.0), 4.44 (1H, m), 3.26 (2H, s), 3.24 (1H, dd, J = 12.3, 9.7), 2.92 (1H, dd, J = 12.4, 5.4), 1.50 (1H, br s, NH), 1.47 (3H, d, J = 7.0), 1.44 (9H, s); ^{13}C NMR δ 172.0, 168.8, 134.0, 132.3, 123.3, 81.4, 51.8, 51.5, 47.1, 28.4, 16.7. Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.1; H, 7.0; N, 8.8. Found: C, 64.3; H, 7.0; N, 8.7. **32**: R_f (60% Et_2O/hexanes) 0.22; mp 56–58 °C; $[\alpha]^{23}_D$ −7.0° (*c* 1.01, $CHCl_3$); ^{1}H NMR δ 7.80–7.77 (2H, m), 7.62–7.58 (2H, m), 5.38 (1H, br s, NH), 4.68 (1H, m), 4.59 (2H, m), 3.82 (2H, s), 1.43 (9H, s), 1.34 (3H, d, J = 7.1); ^{13}C NMR δ 169.0, 167.2, 154.0, 133.2, 132.6, 132.3, 129.4, 125.4, 123.9, 82.1, 64.8, 52.4, 49.4, 28.0, 14.3. Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.1; H, 7.0; N, 8.8. Found: C, 63.7; H, 6.9; N, 8.7.

(*R*)-*N*-(2-Phthalimido-1-propyl)glycine *tert*-butyl ester (31) was prepared as directed for (*S*)-**31** using the following quantities of reagents: *tert*-butyl glycinate[35] (400 mg, 3.05 mmol) and diisopropylethylamine (1.43 g, 11.08 mmol) in DMF (15 mL) and triflate (*R*)-**30** (935 mg, 2.77 mmol) in CH_2Cl_2 (15 mL). After isolation, (*R*)-secondary amine **31** (462 mg, 1.45 mmol, 52% yield) was obtained in a similar manner and identical in properties to (*S*)-**31** with an equal and opposite sign of rotation. Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.1; H, 7.0; N, 8.8. Found: C, 63.9; H, 6.9; N, 8.5.

***N*-(*S*)-(2-Phthalimido-1-propyl)-*N*-(*R*)-[[(α-methylbenzyl)amino]carbonyl]glycine *tert*-Butyl Ester (33).** To a solution of (*S*)-secondary amine **31** (190 mg, 0.59 mmol) in THF (5.0 mL) was added (*R*)-α-methylbenzyl isocyanate (140 mg, 0.71 mmol) dropwise, and the reaction was stirred at rt for 16 h. The solvent was evaporated, and the residue was dissolved in EtOAc (25 mL) and washed with water (3 × 25 mL) and brine (25 mL). An aliquot of the crude reaction mixture (10 mg) dissolved in CH_2Cl_2 (5 mL) was used for analytical HPLC.[18] After isolation, urea **33** (175 mg, 0.38 mmol, 64% yield) was obtained as a colorless oil by chromatography, eluting with 50% Et_2O/petroleum ether: R_f (80% Et_2O/petroleum ether) 0.39; $[\alpha]^{23}_D$ −63.3° (*c* 0.98, $CHCl_3$); ^{1}H NMR δ 7.81 (2H, dd, J = 5.4, 3.1), 7.72 (2H, dd, J = 5.4, 3.1), 7.29 (5H, s), 5.19 (1H, d, J = 7.1, NH), 4.85 (1H, app pent, J = 6.9), 4.61 (1H, m), 3.97 (2H, dd, J = 15.5, 10.4), 3.85 (2H, ABq, J = 17.5), 3.44 (2H, dd, J = 15.4, 5.4), 1.48 (3H, d, J = 7.0), 1.39 (9H, s), 1.30 (3H, d, J = 6.9); ^{13}C NMR δ 169.1, 168.8, 157.1, 144.3, 134.1, 131.7, 128.4, 126.8, 125.9, 123.2, 81.6, 50.6, 50.1, 49.1, 44.7, 27.9, 22.6, 15.8. Anal. Calcd for $C_{26}H_{31}N_3O_5$: C, 67.1; H, 6.7; N, 9.0. Found: C, 67.1; H, 6.9; N, 9.0.

***N*-(*R*)-(2-Phthalimido-1-propyl)-*N*-(*R*)-[[(α-methylbenzyl)amino]carbonyl]glycine *tert*-butyl ester (34)** was prepared as directed for urea **35** using the following quantities of reagents: (*R*)-secondary amine **31** (100 mg, 0.31 mmol), (*R*)-α-methylbenzyl isocyanate (91 mg, 0.62 mmol), dissolved in THF (10 mL). An aliquot of the crude reaction mixture (10 mg) dissolved in CH_2Cl_2 (5 mL) was used for analytical HPLC.[18] After isolation, urea **34** (124 mg, 0.26 mmol, 86% yield) was obtained by chromatography, eluting with 50% Et_2O/petroleum ether: R_f (80% Et_2O/petroleum ether) 0.39; mp 52 °C; $[\alpha]^{23}_D$ +50.0° (*c* 0.70, $CHCl_3$); ^{1}H NMR δ 7.73 (4H, m), 7.13 (5H, s), 5.25 (1H, d, J = 7.1), 4.82 (1H, app pentet, J = 6.9), 4.60 (1H, m), 4.01 (1H, dd, J = 15.4, 5.4), 3.82 (2H, ABq, J = 17.4), 3.44 (1H, dd, J = 15.4, 5.5), 1.49 (3H, d, J = 6.9), 1.42 (3H, d, J = 8.6), 1.40 (9H, s); ^{13}C NMR δ 169.2, 168.8, 157.2, 144.3, 134.0, 131.6, 128.2, 126.6, 125.8, 123.4, 81.6, 50.7, 50.3, 48.9, 44.7, 28.0, 22.8, 15.8. Anal. Calcd for $C_{26}H_{31}N_3O_5$; C, 67.1; H, 6.7; N, 9.0. Found: C, 66.7; H, 6.8; N, 8.9.

(*S*)-*N*-(2-Phthalimido-1-propyl)-*N*-(*tert*-butoxycarbonyl)glycine *tert*-Butyl Ester (35). To a solution of **31** (1.30 g, 4.08 mmol) in THF (25 mL) was added BOC_2O (1.78 g, 8.16 mmol), and the mixture was stirred at rt for 24 h. After solvent evaporation, the residue was dissolved in Et_2O (50 mL) and washed with 5% (w/w) $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). After isolation, *N*-BOC **35** (1.62 g, 3.87 mmol, 95% yield) was obtained as a colorless oil by chromatography, eluting with 25% Et_2O/petroleum ether: R_f (30% Et_2O/petroleum ether) 0.31; $[\alpha]^{22}_D$ +84.9° (*c* 1.63, $CHCl_3$); ^{1}H NMR δ 7.85 (2H, m), 7.70 (2H, m), 4.64 (1H, m), 3.79 (4H, m), 1.48 (3H, d, J = 7.1), 1.41 (9H, s), 1.36 (9H, s); ^{13}C NMR δ 168.7, 168.5, 155.3, 133.8, 131.8, 123.0, 81.4, 80.5, 50.9, 49.9, 45.3, 27.9, 27.7, 15.7. Anal. Calcd for $C_{22}H_{30}N_2O_6$: C, 63.1; H, 7.2; N, 6.7. Found: C, 63.3; H, 7.5; N, 6.7.

(*S*)-1-(*tert*-Butoxycarbonyl)-6-methyl-2-oxopiperazine (37). *N*-BOC **35** (900 mg, 2.15 mmol) was dissolved in 5.0 M $MeNH_2$ in absolute EtOH (15 mL, 97.5 mmol) and the mixture stirred at rt for 48 h. After solvent evaporation, the residue was dissolved in EtOAc (50 mL) and washed with water (2 × 10 mL) and brine (10 mL). Isolation, followed by

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chromatography, eluting with 5% MeOH/CH_2Cl_2, gave piperazine **37** (392 mg, 1.83 mmol, 85% yield): R_f (10% MeOH/CH_2Cl_2) 0.38; mp 106 °C; $[\alpha]^{23}_D$ +20.5° (*c* 0.95 $CHCl_3$); ^{1}H NMR δ 8.06 (1H, NH), 4.03 (2H, ABq, *J* = 18.5), 3.91 (1H, m), 3.62 (1H, m), 2.94 (1H, m), 1.47 (9H, s), 1.21 (3H, d, *J* = 4.7); ^{13}C NMR δ 168.5, 153.7, 80.5, 47.0, 46.3, 45.6, 28.1, 18.9. Anal. Calcd for $C_{10}H_{18}N_2O_3$: C, 56.1; H, 8.5; N, 13.1; Found: C, 55.9; H, 8.4; N, 12.9.

(*S*)-2-*N*,2*N*-Bis[(*tert*-butoxycarbonyl)methyl)-1-*N*′-(*tert*-butoxycarbonyl)-1*N*′-(*tert*-butoxycarbonyl)methyl]diaminopropane (38). *N*-BOC **35** (1.03 g, 2.46 mmol) was dissolved in 5.0 M $MeNH_2$ in absolute EtOH (20.0 mL, 130.0 mmol) and stirred at rt for 6.5 h. After evaporation, maintaining the bath temperature at 20 °C, the white gummy residue was dissolved in ^{i}PrOH (10.0 mL) and the solution evaporated. This procedure was repeated one more time. To the residue of crude primary amine **36** suspended in CH_3CN (20.0 mL) was added diisopropylethylamine (946 mg, 7.32 mmol) followed by *tert*-butyl iodoacetate (1.33 g, 5.5 mmol), and the mixture was stirred at rt for 24 h. After diluting with EtOAc (100 mL), the organic phase was washed with water (3 × 15 mL), 10% (w/w) $NaHCO_3$ (2 × 10 mL), and brine (20 mL). Isolation, followed by chromatography, eluting with 5% Et_2O/CH_2Cl_2 gave tertiary amine **38** (610 mg, 1.18 mmol, 50% yield) as a colorless oil: R_f (5% Et_2O/CH_2Cl_2) 0.38; $[\alpha]^{23}_D$ +18.6° (*c* 1.45, $CHCl_3$); ^{1}H NMR δ 3.93 (2H, ABq, *J* = 17.8), 3.38 (4H, m), 3.21 (1H, m), 3.07 (2H, m), 1.46 (9H, s), 1.45 (9H, s), 1.44 (18H, s), 1.05 (3H, d, *J* = 6.9); ^{13}C NMR δ 171.1, 169.5, 155.5, 80.9, 80.6, 79.6, 56.9, 53.1, 51.8, 51.0, 28.1, 28.0, 14.1. Anal. Calcd for $C_{26}H_{48}N_2O_8$: C, 60.4; H, 9.4; N, 5.4. Found: C, 60.6; H, 9.4; N, 5.5.

(*S*)-*N*-(2-Phthalimido-1-propyl)-*N*-(*p*-toluenesulfonyl)-glycine *tert*-Butyl Ester (40). To a solution of **31** (15.00g, 47.1 mmol) dissolved in CH_2Cl_2 (400 mL) and cooled to 0 °C was added pyridine (5.59 g, 70.7 mmol) followed by *p*-toluenesulfonyl chloride (11.22 g, 58.9 mmol) added in portions over 20 min. The reaction mixture was stirred for 30 min at 0 °C and 4.5 h at rt and then washed with water (2 × 50 mL), 2.0 M NaOH (3 × 25 mL), water (2 × 50 mL), 1.0 M H_3PO_4 (3 × 20 mL), water (2 × 50 mL), and brine (50 mL). After isolation, the residue was placed on a short column, eluting first with 15% EtOAc/petroleum ether then EtOAc (600 mL). To the EtOAc fraction was added petroleum ether, and after cooling at 0 °C overnight, the *N*-Ts **40** was isolated via filtration. Two additional crops of *N*-Ts **40** were isolated from the mother liquor. The combined *N*-Ts **40** (18.25g, 38.6 mmol, 82% yield) was dried overnight under vacuum (rt, 0.1 Torr): R_f (25% EtOAc/hexanes) 0.24; mp 160 °C; $[\alpha]^{23}_D$ +15.6° (*c* 1.35 $CHCl_3$); ^{1}H NMR δ 7.79 (2H, dd, *J* = 5.5, 2.2), 7.69 (2H, dd, *J* = 5.5, 2.3 Hz), 7.61 (2H, d, *J* = 8.2), 7.13 (2H, d, *J* = 8.2), 4.58 (1H, m), 4.06 (2H, ABq, *J* = 18.5), 4.04 (1H, dd, *J* = 14.9, 10.6), 3.41 (1H, dd, *J* = 14.7, 4.1), 2.32 (3H, s), 1.48 (3H, d, *J* = 7.1), 1.37 (9H, s); ^{13}C NMR δ 168.3, 167.7, 143.1, 136.6, 133.7, 131.9, 129.3, 127.4, 123.1, 82.1, 49.8, 48.2, 44.3, 27.9, 21.5, 15.8. Anal. Calcd for $C_{24}H_{28}N_2O_6S$: C, 61.0; H, 6.0; N, 5.9. Found: C, 61.3; H, 6.1; N, 6.0.

(*S*)-*N*-[2-*N*′-[2′-(Hydrazinocarbonyl)benzoyl]amino]-1-propyl]-*N*-(*p*-toluenesulfonyl)glycine *tert*-Butyl Ester (41), (*S*)-*N*-(2-Amino-1-propyl)-*N*-(*p*-toluenesulfonyl)glycine *tert*-Butyl Ester (42), and (*S*)-6-Methyl-4-(*p*-toluenesulfonyl)-2-oxopiperazine (43). To a solution of *N*-Ts **40** (14.2 g, 30.0 mmol) dissolved in MeOH (100 mL) was added hydrazine monohydrate (15.0 g, 0.30 mol), and the reaction was stirred at rt for 3 h. After evaporation, maintaining the bath temperature at 20 °C, the solid residue was stirred with 3.0 M NaOH (25 mL) for 5 min and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), combined, and washed with saturated brine (25 mL). After isolation, three compounds were obtained after chromatography, eluting with 3% MeOH/CH_2Cl_2: hydrazide **41** (1.3 g, 2.7 mmol, 9% yield), primary amine **42** (7.2 g, 21.0 mmol, 70% yield), and lactam **43** (1.3 g, 5.0 mmol, 10% yield). **41**: R_f (10% MeOH/CH_2Cl_2) 0.30; ^{1}H NMR δ 7.71 (2H, d, *J* = 8.2), 7.30 (2H, d, *J* = 8.2), 3.90 (2H, ABq, *J* = 18.0), 3.08 (3H, m), 2.42 (3H, s), 2.15 (2H, br s, NH_2), 1.41 (9H, s), 1.08 (3H, d, *J* = 5.5 Hz); ^{13}C NMR δ 168.2, 143.5, 136.1, 129.6, 127.3, 82.4, 57.7, 50.7, 45.7, 27.9, 21.5, 20.4. **42**: R_f (10% MeOH/CH_2Cl_2) 0.42; ^{1}H NMR δ 8.20 (1H, br s, NH), 7.63 (2H, d, *J* = 8.3), 7.60–7.38 (4H, m), 7.23 (2H, d, *J* = 8.1), 4.31 (1H, m), 4.03 (2H, ABq, *J* = 18.6), 3.47 (1H, dd, *J* = 14.7, 9.0), 3.28 (1H, dd, *J* = 14.6, 4.3), 2.36 (3H, s), 1.26 (9H, s), 1.15 (3H, d, *J* = 6.1); ^{13}C NMR δ 169.6, 168.7, 168.0, 143.6, 136.1, 134.9, 133.3, 130.4, 130.2, 129.6, 128.5, 127.9, 127.2, 82.2, 64.3, 52.5, 43.5, 27.8, 21.5, 18.1. **43**: R_f (10% MeOH/CH_2Cl_2) 0.51; mp 187 °C; $[\alpha]^{23}_D$ +1.1° (*c* 2.14 $CHCl_3$); ^{1}H NMR δ 7.65 (2H, d, *J* = 8.3), 7.52 (1H, br s, NH), 7.36 (2H, d, *J* = 8.2), 3.69 (1H, m), 3.62 (2H, ABq, *J* = 16.8), 3.56 (1H, dd, *J* = 12.0, 3.8), 2.53 (1H, dd, *J* = 12.0, 8.3), 2.44 (3H, s), 1.20 (3H, d, *J* = 6.4); ^{13}C NMR δ 166.5, 144.3, 131.7, 129.9, 127.6, 48.7, 47.9, 47.3, 21.5, 19.2. Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.7; H, 6.0; N, 10.4; Found: C, 53.6; H, 6.0; N, 10.5.

To further characterize hydrazide **41**, a sample (420 mg, 0.83 mmol) was dissolved in THF (10 mL). After BOC_2O (218 mg, 1.00 mmol) was added, the reaction was stirred at rt for 16 h. After evaporation, the residue was dissolved in EtOAc (50 mL) and washed with 1.0 M H_3PO_4 (2 × 20 mL), water (2 × 20 mL), and brine (20 mL). Isolation from the organic phase and chromatography, eluting with 50% EtOAc/hexanes, gave the *N*-BOC derivative of **41** (275 mg, 0.45 mmol, 55% yield) and **(*S*)-*N*-[[2-(*tert*-butoxycarbonyl)amino]-1-propyl]-*N*-(*p*-toluenesulfonyl)glycine *tert*-butyl ester** (90 mg, 0.21 mmol, 25% yield) as colorless oils which solidified. *N*-BOC of **41**: R_f (50% EtOAc/hexanes) 0.18; mp 85–87 °C; $[\alpha]^{23}_D$ +2.1° (*c* 1.13, $CHCl_3$); ^{1}H NMR δ 8.80 (1H, br s, NH), 7.70–7.10 (8H, m), 7.01 (1H, br s, NH), 4.34 (1H, m), 4.05 (2H, ABq, *J* = 18.6), 3.40 (2H, m), 2.40 (3H, s), 1.46 (9H, s), 1.30 (9H, s), 1.24 (3H, d, *J* = 7.1); ^{13}C NMR δ 168.7, 168.2, 168.1, 155.2, 143.5, 136.1, 135.1, 132.2, 132.1, 130.8, 130.1, 129.5, 129.0, 128.9, 128.2, 127.2, 82.1, 81.3, 52.6, 49.1, 43.8, 28.1, 27.7, 21.5, 17.9. Anal. Calcd for $C_{29}H_{40}N_4O_8S$: C, 57.6; H, 6.7; N, 9.3. Found: C, 57.8; H, 6.6; N, 9.1. **(*S*)-*N*-[[2-(*tert*-Butoxycarbonyl)amino]-1-propyl]-*N*-(*p*-toluenesulfonyl)glycine *tert*-butyl ester:** R_f (50% EtOAc/hexanes) 0.74; mp 83–85 °C; $[\alpha]^{23}_D$ −14.9° (*c* 0.63, $CHCl_3$); ^{1}H NMR δ 7.68 (2H, d, *J* = 8.0), 7.28 (2H, d, *J* = 7.8), 4.83 (1H, br s, NH), 3.96 (2H, ABq, *J* = 18.6), 3.80 (1H, m), 3.31 (1H, dd, *J* = 13.8, 7.5), 3.21 (1H, dd, *J* = 14.1, 6.5), 2.41 (3H, s), 1.43 (9H, s), 1.37 (9H, s), 1.19 (3H, d, *J* = 6.5); ^{13}C NMR δ 167.8, 155.4, 143.4, 136.5, 129.5, 127.3, 81.4, 79.3, 60.4, 52.7, 49.0, 44.4, 28.3, 27.9, 21.5, 18.5. Anal. Calcd for $C_{21}H_{34}N_2O_6S$: C, 57.0; H, 7.7; N, 6.3. Found: 57.2; H, 7.8; N, 6.3.

(*S*)-2-*N*,2-*N*-Bis[(*tert*-butoxycarbonyl)methyl]-1-*N*′-[(*tert*-butoxycarbonyl)methyl]-1*N*′-(*p*-toluenesulfonyl)diaminopropane (44). To a solution of primary amine **42** (7.2 g, 21.0 mmol) dissolved in DMSO (100 mL) was added *tert*-butyl iodoacetate (25.0 g, 105 mmol). After cooling the mixture to 0 °C, pH 7.0, 1.0 M phosphate buffer (250 mL) was added dropwise over 10 min; then the mixture was stirred at rt for 12 h. The mixture was diluted with EtOAc (1000 mL) and then washed with H_2O (5 × 250 mL) and brine (250 mL). After isolation and chromatography, eluting with 20% EtOAc/hexanes, the tertiary amine **44** (8.1 g, 14.2 mmol, 68% yield) was obtained along with secondary amine (*S*)-**1**. **2-*N*,2-*N*-Bis-[(*tert*-butoxycarbonyl)methyl]-1-*N*′-(*p*-toluenesulfonyl)-diaminopropane** (1.4 g, 4.0 mmol, 19% yield) [R_f (70% EtOAc/hexanes) 0.48; ^{1}H NMR δ 7.71 (2H, d, *J* = 8.2), 7.28 (2H, d, *J* = 8.1), 4.07 (2H, ABq, *J* = 18.4), 3.28 (2H, ABq, *J* = 15.3), 3.17 (2H, m), 2.91 (1H, m), 2.41 (3H, s), 1.47 (9H, s), 1.36 (9H, s), 1.04 (3H, d, *J* = 6.3)] was obtained as a colorless oil by elution with 50% EtOAc/hexanes. **44**: R_f (20% EtOAc/hexanes) 0.40; $[\alpha]^{23}_D$ +10.9° (*c* 0.98, $CHCl_3$); ^{1}H NMR δ 7.69 (2H, d, *J* = 8.2), 7.26 (2H, d, *J* = 8.2), 4.27 (2H, ABq, *J* = 18.5), 3.38 (4H, ABq, *J* = 17.0), 3.22 (2H, m), 3.16 (1H, m), 2.40 (3H, s), 1.44 (18H, s), 1.35 (9H, s), 1.08 (3H, d, *J* = 6.5 Hz); ^{13}C NMR δ 171.0, 168.3, 143.0, 136.8, 129.3, 127.3, 81.4, 80.0, 57.4, 53.2, 51.5, 49.6, 28.0, 27.8, 21.4, 14.5. Anal. Calcd for $C_{28}H_{46}N_2O_8S$: C, 58.9; H, 8.1; N, 4.9; Found: C, 58.9; H, 8.1; N, 4.8.

(*S*)-2-*N*,2-*N*,1-*N*′-Tris[(*tert*-butoxycarbonyl)methyl]-diaminopropane (39) and (*S*)-1,4-Bis[(*tert*-butoxycarbonyl)methyl]-5-methyl-2-oxopiperazine (45). A dried H-cell (two halves, length, 15.0 cm; inner diameter, 4.5 cm)[30] was assembled with a Fisher Porter Solv Seal (9 mm, Teflon sleeve,

neoprene O-ring seals) equipped with an extra-coarse porosity frit. A 1.5 cm Hg pool was placed in the cathode chamber, and 8 g of tetraethylammonium bromide (TEAB) was added to the anode chamber. Into each chamber was placed 100 mL of degassed 0.1 M TEAB in CH_3CN. The electrodes were positioned in each chamber: Pt foil, 10 cm × 3 cm × 0.002 mm, as the anode; Cu wire, 18 guage, sealed in 7 mm Pyrex tubing with the wire extending 2 cm beyond the seal, bent and submerged in the Hg pool, as the cathode. A nitrogen bubbler (9 mm Pyrex tube) was placed in the cathode chamber, and a flow of nitrogen was started in the chamber (approximately one bubble per second); the cathode chamber was thus degassed for 15 min. This apparatus was preelectrolyzed at −1.925 V until the current reached 1.0 mA. Phenol (1.50 g, 16.0 mmol) was added to the cathode chamber as a solution in 0.1 M TEAB/CH_3CN (5.0 mL), and after degassing for 15 min, it was preelectrolyzed at −1.925 V until the current reached 1.0 mA. To the cathode chamber was added *N*-T **44** (3.0 g, 5.3 mmol) as a solution in 0.1 M TEAB/CH_3CN (5 mL). This mixture was degassed and electrolyzed at −1.825 V for 4.25 h, and the content of each electrode chamber was poured into a separate Erlenmeyer flask. The anode solution was discarded, and the cathode solution was decanted away from the mercury. After evaporation at or below 20 °C, the residue was dissolved in EtOAc (150 mL) and washed with water (2 × 50 mL), 1.0 M NaOH (2 × 50 mL), water (50 mL), and brine (25 mL). After isolation, secondary amine **39** (910 mg, 2.37 mmol, 45% yield), recovered **44** (1.38 g, 2.42 mmol, 46% yield), and lactam **45** (90 mg, 0.26 mmol, 5% yield) were obtained as colorless oils after chromatography, eluting with 4% MeOH/CH_2Cl_2. **39**: R_f (7% MeOH/CH_2Cl_2) 0.46; $[\alpha]^{23}_D$ +9.35° (*c* 3.10, $CHCl_3$); ^{1}H NMR δ 3.42 (4H, ABq, *J* = 17.4), 3.31 (2H, ABq, *J* = 17.3), 3.02 (1H, m), 2.50 (2H, m), 1.46 (9H, s), 1.45 (18H, s), 1.01 (3H, d, *J* = 6.7); ^{13}C NMR δ 171.6, 171.4, 80.7, 80.6, 57.4, 53.0, 52.7, 51.5, 28.1, 14.8. Anal. Calcd for $C_{21}H_{40}N_2O_6$: C, 60.5; H, 9.7; N, 6.7. Found: C, 60.2; H, 9.5; N, 6.7. **45**: R_f (7% MeOH/CH_2Cl_2) 0.58; $[\alpha]^{23}_D$ +36.0° (*c* 0.96, $CHCl_3$); ^{1}H NMR δ 4.01 (2H, s), 3.53 (2H, ABq, *J* = 16.8), 3.28 (5H, m), 1.47 (18 H, s), 1.15 (3H, d, *J* = 6.2); ^{13}C NMR δ 169.5, 167.7, 167.4, 81.9, 81.4, 55.0, 54.2, 53.5, 51.2, 48.0, 28.1, 28.1, 28.0, 15.1. Anal. Calcd for $C_{17}H_{30}N_2O_5$: C, 59.6; H, 8.8; N, 8.2. Found: C, 59.3; H, 8.6; N, 8.0.

***N,N*-Bis[(*tert*-butoxycarbonyl)methyl]glycine (46)** was prepared as directed for **12** using the following quantities of reagents: benzyl ester of glycine tosylate[36] (3.17 g, 8.06 mmol), 5% Pd/C (320 mg), and MeOH (50 mL). After isolation, acid **46** (2.42 g, 2.44 mmol, 99% yield) was obtained as a white solid after drying for 12 h under vacuum (40 °C, 0.1 Torr): mp 88 °C; ^{1}H NMR δ 3.48 (2H, s), 3.47 (4H, s), 1.48 (18H, s); ^{13}C NMR δ 172.3, 170.8, 82.7, 58.2, 57.3, 28.1. Anal. Calcd for $C_{14}H_{25}NO_6$: C, 55.4; H, 8.3; N, 4.6; Found: C, 55.4; H, 8.1; N, 4.6.

(*S*)-*N*-[2-[*N',N'*-Bis[(*tert*-butoxycarbonyl)methyl]amino]-1-propyl]-(*S*)-*N*-[2-[*N',N'*-[bis*tert*-butoxycarbonyl)methyl]-amino]-1-oxo-1-propyl]glycine *tert*-Butyl Ester (47). To a solution of **12** (800 mg, 2.50 mmol) dissolved in THF (50.0 mL) and cooled to −30 °C were added *N*-methylmorpholine (300 mg, 3.00 mmol) and then isobutyl chloroformate (342 mg, 2.50 mmol) dropwise. This mixture was stirred for 10 min at −25 °C; then a cooled solution at −25 °C of the secondary amine **39** (770 mg, 2.00 mmol) and *N*-methylmorpholine (405 mg, 4.00 mmol) in THF (10.0 mL) was added by cannula. The reaction was stirred for 5 h at −30 to −25 °C after which it was evaporated at rt. After dissolving the residue in EtOAc (250 mL), the organic phase was washed with 5% (w/w) $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), 1.0 M H_3PO_4, (2 × 50 mL), water (2 × 50 mL), and brine (50 mL). Isolation after chromatography, eluting with 15% EtOAc/hexanes, gave the *N,N*-disubstituted amide **47** (1.33 g, 1.86 mmol, 94% yield) as a colorless oil (mixture of rotamers): R_f (20% EtOAc/hexanes) 0.20; $[\alpha]^{23}_D$ +16.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 5.16 (2H, m), 4.30−4.00 (1H, m), 4.00−3.60 (1H, m), 3.50−3.30 (8.2H, m), 3.10−2.90 (1.8H, m), 1.47, 1.45, 1.44, 1.43 (45H, m), 1.20 (1.1H, d, *J* = 6.8), 1.17 (1.9H, d, *J* = 6.7), 1.09 (1.1H, d, *J* = 6.7), 0.99 (1.9H, d, *J* = 6.7); ^{13}C NMR δ 173.0, 172.8, 171.2, 171.0, 170.6, 170.3, 169.7, 168.5, 81.4, 80.9, 80.7, 80.6, 80.5, 80.4, 57.8, 57.1, 56.4, 55.7, 53.2, 53.1, 53.0, 52.7, 52.1, 50.6, 50.2, 28.3, 28.0, 14.4, 13.8, 12.5, 11.6. Anal. Calcd for $C_{36}H_{65}N_3O_{11}$: C, 60.4; H, 9.1; N, 5.9; Found: C, 60.7; H, 8.9; N, 6.2.

(*S*)-*N*-[2-[*N',N'*-Bis[(*tert*-butoxycarbonyl)methyl]amino]-1-propyl]-(*R*)-*N*-[2-[*N',N'*-bis[(*tert*-butoxycarbonyl)methyl]-amino]-1-oxo-1-propyl]glycine *tert*-butyl ester (48) was prepared and isolated as described for amide **47.** Combining (*R*)-**12** (790 mg, 2.49 mmol) and secondary amine **39** (770 mg, 2.00 mmol) produced amide **48** (1.37 g, 1.92 mmol, 96% yield, mixture of two rotamers) as a colorless oil: R_f (20% EtOAc/hexanes) 0.19; $[\alpha]^{23}_D$ +8.8° (*c* 1.07, $CHCl_3$); ^{1}H NMR δ 5.37 (2H, m), 4.20−4.00 (2H, m), 3.99 (0.7H, q, *J* = 6.7), 3.78 (0.3H, dd, *J* = 6.8, 2.1), 3.50 (6.75H, m), 3.20−3.00 (2.25H, m), 1.46, 1.45, 1.44, 1.43 (45H, s), 1.23 (0.87H, d, *J* = 6.8), 1.18 (1.13H, d, *J* = 6.7), 1.08 (0.87H, d, *J* = 6.8), 1.03 (1.13H, d, *J* = 6.7); ^{13}C NMR δ 173.4, 172.8, 171.1, 170.8, 170.6, 170.2, 169.7, 168.6, 81.2, 80.7, 80.5, 80.4, 80.3, 80.2, 57.7, 57.1, 56.3, 56.2, 52.9, 52.8, 52.0, 51.8, 51.5, 49.3, 28.1, 27.9, 27.7, 14.7, 14.4, 12.9, 11.3. Anal. Calcd for $C_{36}H_{65}N_3O_{11}$: C, 60.4; H, 9.1; N, 5.9. Found: C, 60.4; H, 9.0; N, 6.2.

(*S*)-*N*-[2-[*N',N'*-[Bis(*tert*-butoxycarbonyl)methyl]amino]-1-propyl]-*N*-[2-[*N',N'*-bis[(*tert*-butoxycarbonyl)methyl]-amino]-1-oxo-1-ethyl]glycine *tert*-butyl ester (49) was prepared and isolated as described for amide **47.** Coupling of acid **46** (760 mg, 2.50 mmol) and secondary amine **39** (800 mg, 1.93 mmol) produced amide **49** (1.35 g, 1.92 mmol, 95% yield, mixture of rotamers) as a colorless oil: R_f (20% EtOAc/hexanes) 0.21; $[\alpha]^{23}_D$ +21.5° (*c* 0.90, $CHCl_3$); ^{1}H NMR δ 4.51 (1.2H, ABq, *J* = 18.6), 4.13 (0.8H, s), 3.80−3.30 (11.3H, m), 3.12 (1.7H, m), 1.46, 1.45 (45H, m), 1.08 (1.2H, d, *J* = 6.1), 1.01 (1.8H, d, *J* = 6.1); ^{13}C NMR δ 171.1, 171.0, 170.5, 170.4, 170.1, 170.0, 169.4, 168.7, 81.4, 81.1, 80.8, 80.6, 57.5, 56.4, 56.1, 55.7, 55.6, 55.4, 53.2, 53.0, 52.0, 51.0, 50.7, 49.2, 28.1, 28.0, 14.2, 14.0. Anal. Calcd for $C_{35}H_{63}N_3O_{11}$: C, 59.9; H, 9.0; N, 6.0. Found: C, 59.5; H, 9.1; N, 5.8.

(*S*)-*N*-[2-[*N',N'*-Bis[(*tert*-butoxycarbonyl)methyl]amino]-1-propyl]-(*S*)-*N*-[2-[*N',N'*-bis[(*tert*-butoxycarbonyl)methyl]-amino]-1-propyl]glycine *tert*-Butyl Ester (50). To BH_3·THF (1.0M, 5.32 mmol) cooled to 0 °C was added a solution of amide **47** (1.27 g, 1.77 mmol) dissolved in THF (5.3 mL) and cooled at 0 °C. After stirring at 0 °C for 5 min, the mixture was refluxed for 1 h and cooled to 0 °C, the reaction was quenched with 2.0 M NaOH (1.5 mL), then the solution was refluxed for 2.5 h. After cooling to rt and evaporating, the residue was extracted with 20% ^{i}PrOH/$CHCl_3$ (3 × 20 mL). Isolation from the combined extracts after washing with brine (30 mL) gave tertiary amine **50** (708 mg, 1.00 mmol, 57% yield) as a colorless oil after chromatography, eluting the column with 30% EtOAc/hexanes: R_f (50% EtOAc/hexanes) 0.46; $[\alpha]^{23}_D$ +24.0° (*c* 0.95, $CHCl_3$); ^{1}H NMR δ 3.43 (8H, s), 3.34 (2H, m), 2.92 (2H, m), 2.81 (2H, dd, *J* = 12.9, 8.8), 2.33 (2H, dd, *J* = 12.8, 8.9), 1.45 (45H, br s), 1.08 (6H, d, *J* = 6.4); ^{13}C NMR δ 171.5, 170.9, 80.6, 80.5, 59.5, 56.7, 55.8, 53.2, 28.2, 28.1, 15.8. Anal. Calcd for $C_{36}H_{65}N_3O_{11}$: C, 60.4; H, 9.1; N, 5.9. Found: C, 60.7; H, 8.9; N, 6.2.

(*S*)-*N*-[2-[*N',N'*-Bis[(*tert*-butoxycarbonyl)methyl]amino]-1-propyl]-*N*-(*R*)-[2-[*N',N'*-bis[(*tert*-butoxycarbonyl)methyl]-amino]-1-propyl]glycine *tert*-butyl ester (51) was prepared as described for amine **50.** Amide **48** (1.20 g, 1.68 mmol) gave amine **51** (640 mg, 0.91 mmol, 54% yield) as a colorless oil after isolation: R_f (50% EtOAc/hexanes) 0.47; $[\alpha]^{22}_D$ 0.0° (*c* 1.02, $CHCl_3$); ^{1}H NMR δ 3.45 (8H, s), 3.36 (2H, s), 3.00 (2H, s), 2.81 (2H, dd, *J* = 13.1, 5.3), 2.40 (2H, dd, *J* = 13.1, 7.7), 1.45 (45H, s), 1.07 (3H, d, *J* = 6.5); ^{13}C NMR δ 171.6, 171.2, 80.5, 80.4, 59.9, 56.7, 55.9, 53.5, 28.2, 28.1, 16.1. Anal. Calcd for $C_{36}H_{67}N_3O_{10}$: C, 61.1; H, 9.6; N, 6.0. Found: C, 61.5; H, 9.4; N, 6.0.

(*S*)-*N*-[2-[*N',N'*-Bis[(*tert*-butoxycarbonyl)methyl]amino]-

(36) The preparation of N,N-bis(*tert*-butoxycarbonylmethyl)glycine benzyl ester followed the procedure for **11**: glycine benzyl ester tosylate (12.80 g, 37.9 mmol) gave the *N,N*-substituted benzyl ester (7.90 g, 20.0 mmol, 53% yield) after chromatography (eluting with 17% Et_2O/hexanes) as a colorless oil: R_f (20% Et_2O/hexanes) 0.37; ^{1}H NMR δ 7.36 (5H, m), 5.15 (2H, s), 3.70 (2H, s), 3.55 (4H, s), 1.45 (18H, s); ^{13}C NMR δ 170.7, 169.9, 135.5, 128.4, 128.1, 128.0, 81.0, 66.2, 55.7, 54.8, 28.0. Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.1; H, 7.9; N, 3.6. Found: C, 63.8; H, 7.9; N, 3.6.

1-propyl]-*N*-[2-[*N'*,*N'*-bis[(*tert*-butoxycarbonyl)methyl]-amino]-1-ethyl]glycine *tert*-butyl ester (52) was prepared as described for amine **50.** Amide **49** (1.22 g, 1.73 mmol) gave amine **52** (640 mg, 0.93 mmol, 54% yield) after isolation as a colorless oil: R_f (50% EtOAc/hexanes) 0.48; $[\alpha]^{23}_D$ +21.7° (*c* 1.11, $CHCl_3$); ^1H NMR δ 3.4–3.55 (11H, m), 2.81 (6H, m), 1.45 (45H, br s), 1.06 (3H, d, J = 6.3 Hz); ^{13}C NMR δ 171.5, 171.1, 170.8, 80.8, 80.6, 80.5, 59.5, 56.1, 55.9, 55.7, 53.3, 53.1, 45.8, 28.1, 28.0, 16.8. Anal. Calcd for $C_{35}H_{65}N_3O_{10}$: C, 61.1; H, 9.5; N, 6.1. Found: C, 61.2; H, 9.5; N, 5.7.

(*S,S*)-2,6-Dipropylenetriaminepentaacetic Acid Trihydrochloride (1). To a solution of pentaester **50** (1.13 g, 1.61 mmol) dissolved in 1,4-dioxane (5.0 mL) cooled to 0 °C was added 12 M HCl (5.0 mL) dropwise, and the mixture was stirred for 1 h at rt, then evaporated (bath temperature, 40 °C) to dryness, and further dried under high vacuum (40 °C, 0.10 Torr). The crude hydrochloride **1** was decolorized by adding the solution of the hydrochloride in distilled water (5.0 mL) to activated charcoal[37] (2.0 g). After stirring for 30 min at rt, the charcoal was removed via filtration through a Millipore filter and the filtrate was evaporated to dryness. Further drying under vacuum (40 °C, 0.10 Torr, 24 h) gave the pentaacid trihydrochloride **1** (840 mg, 1.58 mmol, 98% yield) as an off-white solid: mp 207 °C; $[\alpha]^{23}_D$ −8.1° (*c* 1.48 H_2O); ^1H NMR δ 4.20 (8H, ABq, J = 17.3), 3.88 (2H, m), 3.73 (2H, m), 3.18 (2H, dd, J = 14.8, 9.0), 3.00 (2H, dd, J = 14.7, 4.5), 1.36 (6H, d, J = 6.5); ^{13}C NMR δ 176.9, 171.8, 63.9, 58.9, 56.5, 55.4, 55.3, 14.0. Anal. Calcd for $C_{16}H_{30}Cl_3N_3O_{10}$: C, 36.2; H, 5.7; N, 7.9. Found: C, 36.2; H, 5.9; N, 7.7.

(*S,R*)-2,6-Dipropylenetriaminepentaacetic acid trihydrochloride dihydrate (2) was prepared as described for pentaacid **1.** From pentaester **51** (600 mg, 0.85 mmol) after decolorizing and drying, pentaacid **2** (450 mg, 0.82 mmol, 96% yield) was obtained as an off-white solid: mp 208 °C; $[\alpha]^{23}_D$ 0.0° (*c* 1.02, H_2O); ^1H NMR δ 4.18 (8H, ABq, J = 17.2), 3.79 (2H, m), 3.66 (2H, m), 3.10 (4H, m), 1.38 (6H, d, J = 6.4); ^{13}C NMR δ 176.5, 171.7, 62.8, 58.0, 56.6, 55.1, 13.6. Anal. Calcd for $C_{16}H_{34}Cl_3N_3O_{12}$: C, 33.9; H, 6.0; N, 7.4. Found: C, 34.3; H, 5.9; N, 7.5.

(*S*)-2-Methyldiethylenetriaminepentaacetic acid trihydrochloride monohydrate (3) was prepared as described for pentaacid **1.** Pentaester **52** (1.36 g, 1.97 mmol) gave, after decolorizing and drying, pentaacid **3** (1.02 g, 1.90 mmol, 99% yield) as an off-white solid: mp 203 °C; $[\alpha]^{23}_D$ +13.7° (*c* 1.02, H_2O); ^1H NMR δ 4.29 (4H, ABq, J = 19.0), 4.14 (4H, ABq, J = 17.9), 3.81 (1H, m), 3.62 (2H, m), 3.30–2.90 (6H, m), 1.29 (3H, d, J = 4.3); ^{13}C NMR δ 176.5, 172.4, 171.1, 62.4, 58.4, 58.1, 56.6, 56.0, 54.9, 51.2, 12.8. Anal. Calcd for $C_{15}H_{30}Cl_3N_3O_{11}$: C, 33.7; H, 5.6; N, 7.9. Found: C, 33.7; H, 5.3; N, 7.7.

(*S*)-*N*-[2-[*N'*,*N'*-Bis[(*tert*-butoxycarbonyl)methyl]amino]-1-propyl]-(*S*)-*N*-[2-[*N'*,*N'*-bis[(benzyloxycarbonyl)methyl]-amino]-1-propyl]glycine *tert*-butyl ester (53) was prepared as described for amide **47.** Secondary amine **39** (280 mg, 0.67 mmol) and **6** (323 mg, 0.83 mmol) gave amide **53** (501 mg, 0.64 mmol, 95% yield) after isolation and chromatography, eluting with 20% EtOAc/hexanes, as a colorless oil and mixture of two rotamers: R_f (20% EtOAc/hexanes) 0.18; $[\alpha]^{23}_D$ +23.2° (*c* 1.42, $CHCl_3$); ^1H NMR δ 7.32 (10H, s), 5.11, 5.10 (4H, s), 4.78 (0.5H, d, J = 13.0), 4.25 (0.5H, s, J = 19.0), 4.10 (1H, m), 4.00–3.87 (1H, m), 3.67–3.51 (5.5H, m), 3.36–3.31 (4.5H, m), 3.21–2.98 (2H, m), 1.46, 1.44, 1.43, 1.42 (27H, s), 1.23 (1.1H, d, J = 6.7), 1.21 (1.9H, d, J = 6.7), 1.03 (1.1H, d, J = 6.6), 0.95 (1.9H, d, J = 6.5); ^{13}C NMR δ 173.1, 172.9, 171.0, 170.9, 170.8, 169.4, 168.4, 135.6, 135.5, 128.3, 128.0, 127.9, 81.5, 81.0, 80.7, 80.4, 66.0, 65.9, 57.2, 56.1, 53.1, 52.7, 52.6, 52.2, 50.4, 50.2, 27.9, 27.8, 13.9, 13.7, 13.1, 12.7. Anal. Calcd for $C_{42}H_{61}N_3O_{11}$: C, 64.3; H, 7.8; N; 5.4. Found: C, 64.1; H, 7.7; N, 5.3.

(*S*)-*o*-Amino-2-[*N'*,*N'*-bis[(benzyloxycarbonyl)methyl]-amino]propionanilide (55). To a solution of **6** (400 mg, 1.04 mmol) dissolved in THF (20 mL) and cooled to −20 °C was added *N*-methylmorpholine (157 mg, 1.55 mmol) followed by dropwise addition of isobutyl chloroformate (156 mg, 1.14 mmol). After stirring for 15 min at −20 °C, 1,2-phenylenediamine (224 mg, 2.07 mmol) was added and the reaction was warmed to 0 °C and stirred for 9 h. After solvent evaporation, the gummy residue was dissolved in EtOAc (100 mL) and then washed with 1.0 M citric acid (25 mL), 5% (w/w) $NaHCO_3$ (2 × 25 mL), water (25 mL), and brine (25 mL). Isolation followed by chromatography, eluting with 30% EtOAc/hexanes, gave *o*-aminoanilide **55** (465 mg, 0.98 mmol, 94% yield) as a colorless oil: R_f (30% EtOAc/hexanes) 0.18; $[\alpha]^{23}_D$ −6.35° (*c* 0.84, $CHCl_3$); ^1H NMR δ 9.73 (1H, br s, NH), 7.44 (1H, dd, J = 6.7, 1.3), 7.31 (10H, s), 6.98 (1H, td, J = 7.6, 1.4), 6.73 (2H, m), 5.13 (4H, s), 4.03 (2H, br s, NH_2), 3.58 (5H, m), 1.33 (3H, d, J = 7.1); ^{13}C NMR δ 171.7, 171.5, 139.3, 134.9, 128.5, 128.4, 128.3, 128.2, 125.8, 124.2, 123.4, 118.7, 117.1, 66.9, 62.2, 52.9, 12.9. Anal. Calcd for $C_{27}H_{29}N_3O_5$: C, 68.2; H, 6.1; N, 8.8. Found: C, 68.3; H, 6.2, N, 8.9.

(*S*)-*o*-Amino-2-[*N'*,*N'*-bis[(benzyloxycarbonyl)methyl]-amino]thiopropionanilide (56) was prepared as described for thioamide **8** using the following quantities of reagents: *o*-aminoanilide **55** (400 mg, 0.84 mmol) and P_4S_{10} (374 mg, 0.84 mmol) dissolved in THF (20 mL). After isolation, thioamide **56** (256 mg, 0.52 mmol, 62% yield) was obtained as a colorless oil after chromatography, eluting with 25% EtOAc/hexanes: R_f (30% EtOAc/hexanes) 0.33; $[\alpha]^{23}_D$ −1.2° (*c* 0.86, $CHCl_3$); ^1H NMR δ 7.32 (11H, m), 7.10 (1H, td, J = 13.9, 7.6), 6.78 (2H, m), 5.14 (4H, ABq, J = 12.1), 4.05 (1H, q, J = 7.0), 3.98 (2H, br s, NH_2), 3.62 (4H, ABq, J = 18.1), 1.52 (3H, d, J = 7.0); ^{13}C NMR δ 203.5, 171.5, 141.1, 134.8, 128.5, 128.4, 128.3, 128.2, 125.7, 124.8, 118.6, 117.4, 69.6, 67.0, 53.0, 17.6. Anal. Calcd for $C_{27}H_{29}N_3O_4S$: C, 66.0; H, 6.0; N, 8.5. Found: C, 66.3; H, 6.3, N, 8.1.

1-[(*S*)-2-[*N'*,*N'*-Bis[(benzyloxycarbonyl)methyl]amino]-1-thioxopropionyl]-2-benzimidazolone (57). To a solution of thioanilide **56** (170 mg, 0.35 mmol) dissolved in THF (2.5 mL) and then cooled to 0 °C was added 1,1-carbonyldi(1,2,4)-triazole[38] (115 mg, 0.70 mmol). The mixture was warmed to rt then stirred for a total of 1.5 h. After solvent evaporation, benzimidazolone **57** (163 mg, 0.31 mmol, 90% yield) was obtained as a yellow oil after chromatography, eluting with 50% Et_2O/hexanes: R_f (70% Et_2O/hexanes) 0.29; $[\alpha]^{22}_D$ −233° (*c* 1.48, $CHCl_3$); ^1H NMR δ 9.08 (1H, br s, NH), 8.28 (1H, d, J = 7.8), 7.28 (10H, m), 7.06 (2H, m), 6.91 (1H, dd, J = 7.4, 1.4), 5.86 (1H, q, J = 6.8), 4.98 (4H, ABq, J = 12.3), 3.83 (2H, s), 3.82 (2H, s), 1.48 (3H, d, J = 6.7); ^{13}C NMR δ 216.1, 171.8, 152.0, 135.6, 129.3, 128.7, 128.4, 128.2, 128.1, 124.9, 121.8, 115.3, 109.5, 66.3, 64.1, 52.4, 17.9. Anal. Calcd for $C_{28}H_{27}N_3O_5S$: C, 65.0; H, 5.3; N, 8.1. Found: C, 65.3; H, 5.3; N, 8.0.

(*S*)-*N*-[2-[*N'*,*N'*-Bis[(*tert*-butoxycarbonyl)methyl]amino]-1-propyl]-(*S*)-*N*-(2-phthalimido-1-propyl)glycine *tert*-Butyl Ester (58) and Oxazoloisoindole 59. To a solution of the secondary amine **39** (210 mg, 0.50 mmol) dissolved in dichloromethane (1.0 mL) and then cooled to 0 °C was added 2,6-lutidine (107 mg, 1.0 mmol) followed by triflate **30** (250 mg, 0.75 mmol). After stirring for 2 days at 0°C, the reaction was quenched with 5% (w/w) $NaHCO_3$ (5 mL); then the solution was extracted with CH_2Cl_2 (3 × 20 mL). Combining the organic extracts, washing with brine (10 mL), and isolation gave tertiary amine **58** (147 mg, 0.23 mmol, 50% yield) and oxazoloisoindole **59** (63 mg, 0.10 mmol, 21% yield) as colorless oils after chromatography, eluting with 15% EtOAc/hexanes. Flushing the column with 4% MeOH/CH_2Cl_2 yielded lactam **45** (30 mg, 0.09 mmol, 18% yield) as a colorless oil. **58**: R_f (20% EtOAc/hexanes) 0.38; $[\alpha]^{23}_D$ +9.5° (*c* 1.01, $CHCl_3$); ^1H NMR δ 7.80 (2H, dd, J = 5.5, 3.1), 7.68 (2H, dd, J = 5.5, 3.0), 4.43 (1H, m), 3.34 (4H, s), 2.94 (1H, dd, J = 12.5, 4.8), 2.87 (1H, m), 2.31 (1H, dd, J = 12.7, 8.2), 1.43 (27 H, s), 1.41 (3H, d, J = 6.3), 0.86 (3H, d, J = 6.4); ^{13}C NMR δ 171.4, 170.7, 168.5, 133.6, 132.1, 122.9, 80.7, 80.5, 59.3, 57.9, 56.0, 55.0, 53.1, 45.5, 28.1, 28.0, 16.3, 15.6. Anal. Calcd for $C_{32}H_{49}N_3O_8$: C, 63.7; H, 8.2; N, 7.0. Found: C, 63.7; H, 8.1; N, 7.3. **59**: R_f (20% EtOAc/hexanes) 0.33; $[\alpha]^{23}_D$ +4.5° (*c* 0.98, $CHCl_3$); ^1H NMR δ 7.74 (1H, dd, J = 6.6, 1.5), 7.58 (3H, m), 4.52 (1H, t, J = 7.8), 4.28 (1H, t, J = 7.8), 4.18 (1H, m), 3.50–2.90 (9H, m), 1.50 (3H, d, J = 6.4), 1.45 (18H, s), 1.37 (9H, s), 1.26 (3H, d,

(37) Charcoal was activated by refluxing in 1.0 M HCl for 1 h and then washing with two sucessive portions of water.

(38) Stabb, H. A. *Liebigs Ann. Chem.* **1957**, *609*, 75.

J = 6.3); ^{13}C NMR δ 172.7, 171.5, 170.7, 142.0, 133.0, 132.6, 130.2, 124.1, 122.8, 110.1, 80.7, 80.6, 77.3, 57.0, 55.7, 55.4, 53.2, 51.0, 28.1, 28.0, 27.9, 19.5, 15.5. Anal. Calcd for $C_{32}H_{49}N_3O_8$: C, 63.7; H, 8.2; N, 7.0; Found: C, 63.6; H, 8.0; N, 6.8.

(*S,S*)-2,6-Dimethyl-1,1,4-tris[(*tert*-butoxycarbonyl)-methyl]diethylenetriamine (60). To a solution of **58** and **59** (total 102 mg, 0.17 mmol; **58/59**, 2/1) in MeOH (373 mL) was added hydrazine monohydrate (56 mg, 1.12 mmol), and this solution was stirred at rt for 3.75 h. After solvent evaporation, maintaining the bath temperature at 20 °C, the white solid residue was dissolved in 3.0 M NaOH (2.5 mL) and extracted with 20% ^{i}PrOH/$CHCl_3$ (3 × 25 mL). The combined organic extracts were washed with brine (10 mL), and after isolation, primary amine **60** (32 mg, 0.067 mmol, 62% yield) was obtained as a colorless oil after chromatography, eluting with 0.1% NEt_3/4% MeOH/CH_2Cl_2. R_f (0.1% NEt_3/5% MeOH/CH_2Cl_2) 0.27; ^{1}H NMR δ 3.42 (9H, m), 3.07 (1H, m), 2.57 (2H, d, J = 7.0), 1.47 (9H, s), 1.02 (3H, d, J = 6.7).

(*S,S*)-4-[2-[*N,N*-Bis[(*tert*-butoxycarbonyl)methyl]amino-1-propyl]-6-methyl-2-oxopiperazine (61). To a solution of **58** and **59** (total 120 mg, 0.20 mmol; **58/59**, 2/1) dissolved in MeOH (670 mL) was added hydrazine monohydrate (100 mg, 2.00 mmol), and the reaction was stirred at rt for 8 h. After solvent removal, the white solid residue was dissolved in 3.0 M NaOH (5.0 mL) and the aqueous solution was extracted with 20% ^{i}PrOH/$CHCl_3$ (3 × 25 mL). Washing the combined extracts with brine (2 × 10 mL), isolation, and chromatography, eluting with 2% MeOH/CH_2Cl_2, gave lactam **61** (71 mg, 0.178 mmol, 89% yield) as a colorless oil: R_f (5% MeOH/CH_2Cl_2) 0.32; $[\alpha]^{23}_D$ +10.0 (*c* 0.51, $CHCl_3$); ^{1}H NMR δ 5.94 (1H br s, NH), 3.63 (1H, m), 3.45 (4H, s), 3.13 (2H, ABq, J = 15.6), 3.10 (1H, app hextet, J = 6.4), 2.55 (1H, dd, J = 12.7, 6.7), 2.15 (3H, m), 1.45 (18H, s), 1.15 (3H, d, J = 6.4), 1.07 (3H, d, J = 6.6); ^{13}C NMR δ 171.4, 169.5, 80.8, 61.9, 57.3, 56.6, 54.6, 53.5, 47.7, 28.1, 20.2, 16.1. Anal. Calcd for $C_{20}H_{37}N_3O_5$: C, 60.1; H, 9.3; N, 10.5. Found: C, 59.7; H, 9.7; N, 10.2.

(*S,S*)-2,6-Dimethyl-7,7-bis[(benzyloxycarbonyl)methyl]-1,1,4-tris[(*tert*-butoxycarbonyl)methyl]diethylene-triamine (62). A. From Purified 60. To a solution of primary amine **60** (25 mg, 0.052 mmol) dissolved in CH_3CN (1.0 mL), cooled to 0 °C, were added diisopropylethylamine (20 mg, 0.156 mmol) and then the triflate of benzyl glycolate[8b] (38 mg, 0.13 mmol). After stirring at 0 °C for 16 h, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (10 mL) and then washed with 5% $NaHCO_3$ (3 × 5 mL) and brine (1 × 5 mL). After isolation, the tertiary amine **62** (34 mg, 0.044 mmol, 87% yield) was obtained as a colorless oil after chromatography, eluting with 35% EtOAc/hexanes: R_f (50% EtOAc/hexanes) 0.46; $[\alpha]^{23}_D$ −25.9° (*c* 1.06, $CHCl_3$); ^{1}H NMR δ 7.34 (10H, s), 5.11 (4H, s), 3.60 (4H, s), 3.41 (4H, s), 3.28 (2H, ABq, J = 17.0), 2.93 (2H, m), 2.79 (2H, m), 2.34 (2H, m), 1.43 (27H, s), 1.05 (3H, d, J = 6.8), 1.04 (3H, d, J = 6.7); ^{13}C NMR δ 171.9, 171.5, 171.0, 135.0, 128.5, 128.3, 128.2, 80.7, 80.5, 66.2, 59.5, 59.3, 56.6, 56.1, 55.8, 53.2, 52.5, 28.2, 28.1, 15.8, 15.7. Anal. Calcd for $C_{42}H_{63}N_3O_{10}$: C, 65.5; H, 8.2; N, 5.5. Found: C, 65.7; H, 8.5; N, 5.1.

B. Directly from 58/59. To a solution of **58** and **59** (116 mg, 0.19 mmol; **58/59**, 2.3/1.0) dissolved in MeOH (385 mL) was added hydrazine monohydrate (58 mg, 1.16 mmol), and the mixture was stirred at rt for 3 h 45 min. After solvent evaporation, the white solid residue was dissolved in 3.0 M NaOH (3.0 mL). After extraction with 20% ^{i}PrOH/$CHCl_3$ (3 × 25 mL), combining extracts, and washing with brine (1 × 10 mL), crude primary amine **60** (125 mg) was isolated as a colorless oil. To the crude primary amine **60** dissolved in CH_3CN (2.0 mL), cooled to 0 °C, was added diisopropylethylamine (57 mg, 0.44 mmol, 62 mL) followed by the triflate of benzyl glycolate[8b] (98 mg, 0.33 mmol), and the mixture was stirred at 0 °C for 16 h. After solvent evaporation, the residue was dissolved in CH_2Cl_2 (25 mL) and washed with 5% $NaHCO_3$ (3 × 10 mL) and brine (10 mL). After isolation, tertiary amine **62** (52 mg, 0.067 mmol, 61% yield) and oxazoloisoindole **59** (42 mg, 0.07 mmol) were isolated as colorless oils after chromatography, eluting with 35% EtOAc/hexanes.

Iminium Triflate 63. Purified triflate **30** (330 mg, 0.98 mmol) was dissolved in CH_2Cl_2 (10 mL), and this solution was stirred at rt for 16 h. The solvent was removed under reduced pressure maintaining the bath temperature at 20 °C, and the residue was subjected to spectroscopic examination. Ratio of **63/30**, 70/24. For **63**: ^{1}H NMR δ 7.9−7.6 (4H, m), 4.69 (1H, m), 4.06 (2H, m), 1.47 (3H, d, J = 7.1); ^{13}C NMR δ 169.2, 167.8, 134.9, 134.4, 131.3, 130.9, 123.9, 123.5, 119.0 ($J_{C\text{-}F}$ = 318.5), 65.7, 47.4, 14.7.

***N*-[(*S*)-3-(Benzylthio)-2-propyl]phthalimide (64), (*S*)-3-Methyl-5-oxo-(*S**)-10-(benzylthio)-2,3,5,10-tetrahydrooxazolo[2,3-*a*]isoindole (65), and (*S*)-3-Methyl-5-oxo-(*R**)-10-(benzylthio)-2,3,5,10-tetrahydrooxazolo[2,3-*a*]-isoindole (66).** To (*S*)-triflate **30** (780 mg, 2.32 mmol) dissolved in CH_2Cl_2 (20 mL) were added diisopropylethylamine (600 mg, 4.64 mmol) and then benzyl mercaptan (317 mg, 2.55 mmol) dropwise over 5 min. After stirring for 16 h at rt, the solution was washed with saturated $NaHCO_3$ (3 × 25 mL), water (2 x25 mL), and brine (25 mL). After isolation, thioether **64** (70 mg, 0.22 mmol, 9% yield), oxazoloisoindole **65** (higher R_f diastereomer, 311 mg, 1.0 mmol, 43% yield), and oxazoloisoindole **66** (lower R_f diastereomer, 309 mg, 0.99 mmol, 43% yield) were obtained as oils from column chromatography, eluting with 20% Et_2O/hexanes. **64**: R_f (50% Et_2O/hexanes) 0.56; $[\alpha]^{23}_D$ +109° (*c* 0.85, $CHCl_3$); ^{1}H NMR δ 7.82 (2H, dd, J = 5.5, 3.0), 7.70 (2H, dd, J = 5.5, 3.0), 7.30 (5H, m), 4.52 (1H, m), 3.70 (2H, ABq, J = 13.4), 3.05 (1H, dd, J = 13.9, 10.1), 2.72 (1H, dd, J = 14.0, 6.5), 1.51 (3H, d, J = 7.0); ^{13}C NMR δ 168.3, 137.3, 133.8, 131.8, 128.9, 128.5, 127.0, 123.1, 45.7, 35.5, 34.2, 18.0. Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.4; H, 5.5, N, 4.5. Found: C, 69.3; H, 5.7; N, 4.4. **65**: R_f (50% Et_2O/hexanes) 0.52; $[\alpha]^{23}_D$ +86.4° (*c* 0.83, $CHCl_3$); ^{1}H NMR δ 7.71 (1H, dd, J = 6.7, 1.3), 7.53 (2H, m), 7.15 (5H, m), 7.05 (1H, m), 4.68 (1H, t, J = 7.5), 4.18 (1H, app sextet, J = 6.6), 3.93 (1H, dd, J = 7.9, 1.9), 3.41 (2H, ABq, J = 13.0), 1.64 (3H, d, J = 6.7); ^{13}C NMR δ 167.9, 143.8, 136.9, 133.1, 132.9, 130.3, 128.5, 126.8, 123.4, 123.0, 107.5, 79.4, 51.1, 35.2, 15.1. Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.4; H, 5.5, N, 4.5. Found: C, 69.0; H, 5.5; N, 4.4. **66**: R_f (50% Et_2O/hexanes) 0.44; $[\alpha]^{23}_D$ −51.5° (*c* 0.90, $CHCl_3$); ^{1}H NMR δ 7.71 (1H, dd, J = 1.2), 7.55 (2H, m), 7.15 (5H, m), 7.04 (1H, m), 4.64 (1H, m), 4.29 (2H, m), 3.50 (2H, ABq, J = 12.9), 1.52 (3H, d, J = 6.1); ^{13}C NMR δ 171.9, 144.6, 136.9, 133.5, 131.6, 130.6, 128.7, 128.3, 126.9, 123.8, 123.4, 106.7, 77.4, 50.9, 35.3, 20.0. Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.4; H, 5.5, N, 4.5. Found: C, 69.1; H, 5.6; N, 4.5.

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Supporting Information Available: Experimental procedures and characterization of compounds **5**, **6**, **7**, **8**, **13**, **14**, **18**, **20**, **21**, **23**, **24**, **26**, **28**, **29**, *N*-(ethoxycarbonyl)-4-nitrophthalimide, (*S*)-2-(4-nitrophthalimido)-1-propanol, **67**, and **69** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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