Preparation of Functionalized, Conformationally Constrained DTPA Analogues from L- or D-Serine and *trans*-4-Hydroxy-L-proline. Hydroxymethyl Substituents on the Central Acetic Acid and on the Backbone

I. Fraser Pickersgill and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

Received January 19, 2000

The enantio- and diastereospecific syntheses of conformationally constrained diethylenetriaminepentaacetic acid (DTPA) analogues that are functionalized with a hydroxymethyl linker substituent on the central acetic acid or on the backbone are described. Key synthetic steps include (i) displacement of the 4-hydroxyl group of *N*-BOC-*trans*-4-hydroxy-L-proline benzyl ester, via activation as the triflate, with suitable amines derived from L- or D-serine, (ii) the low-temperature alkylation of diethylenetriamines with the triflate of benzyl glycolate, thereby minimizing competitive lactamization, to give DTPA pentabenzyl esters, and (iii) deprotection to afford the corresponding DTPA analogues under very mild hydrogenolysis conditions.

Introduction

Paramagnetic metals, in particular gadolinium, as chelated complexes with DTPA ligands have shown important applications as MRI contrast agents.[1] Also under investigation are Gd−DTPA and Yb−DTPA complexes for use as X-ray contrast agents.[2] In addition, DTPA ligands have attracted attention as ligands for radionuclides (e.g., ^{111}In, ^{90}Y, ^{117m}Sn, ^{153}Sm, ^{212}Bi, ^{64}Cu, ^{67}Cu, and ^{67}Ga) for use as diagnostic[3] or therapeutic[4] radiopharmaceuticals.

In all these applications site-specific delivery of the ligand−metal complex in vivo is highly desirable.[5] One method of achieving such a goal is to attach a receptor-targeting molecule to the DTPA ligand via a linker group. This "magic bullet" approach is well established, and there are several examples of functionalized DTPA ligands reported,[4b−h,6] bearing either an appended amino or carboxylic acid group to which a targeting group has been attached using an amide[6d] or thiourea[6e] linkage. The use of a hydroxymethyl linker also has been reported[7] and has been used successfully for the attachment of an albumin-targeting phosphate diester moiety to a Gd−DTPA complex.[8]

Due to the possibility of forming an ester or a more biologically stable ether linkage from a free alcohol residue, we have also selected a hydroxymethyl moiety as a functional attachment to our DTPA analogues. In addition, on the basis of work previously conducted in our laboratories,[9] we have introduced conformational constraint in the form of a pyrrolidine ring. This provides a more rigid DTPA ligand which in theory could provide more stable metal chelates,[10] a very important consideration given the toxicity of the metals employed. For example, upon metal complex dissociation, free ^{90}Y has been observed to accumulate in the cortex of the bone, potentially causing damage to the marrow.[4,e,f] The introduction of branching groups into the ethylenediamine backbone of DTPA ligands has been demonstrated to improve in vivo stability of ^{90}Y−DTPA complexes, with the greatest improvement in stability being observed using DTPA analogues having constraint introduced in the form of a cyclohexyl ring.[4b−h]

One important consequence of functionalization of the DTPA skeleton is the generation of stereocenters. Control of both the absolute and relative stereochemistry in the synthesis of the ligand is essential as the overall geometry and stability of the metal complex will conceivably be different for enantiomeric or diastereomeric ligands.[4g,h]

(1) (a) Caravan, P.; Ellison, J. J.; McMurry, T. J.; Lauffer, R. B. *Chem. Rev.* **1999**, *99*, 2293. (b) Lauffer, R. B. *Chem. Rev.* **1987**, *87*, 901.

(2) Yu, S.-B.; Watson, A. D. *Chem. Rev.* **1999**, *99*, 2353.

(3) (a) Anderson, C. J.; Welch, M. J. *Chem. Rev.* **1999**, *99*, 2219. (b) Brechbiel, M. W.; Gansow, O. A.; Atcher, R. W.; Schlom, J.; Esteban, J.; Simpson, D. E.; Colcher, D. *Inorg. Chem.* **1986**, *25*, 2772.

(4) (a) Volkert, W. A.; Hoffman, T. J. *Chem. Rev.* **1999**, *99*, 2269. (b) McMurry, T. J.; Pippin, C. G.; Wu, C.; Deal, K. A.; Brechbiel, M. W.; Mirzadeh, S.; Gansow, O. *J. Med. Chem.* **1998**, *41*, 3546. (c) Brechbiel, M. W.; Gansow, O. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1173. (d) Brechbiel, M. W.; Pippin, C. G.; McMurry, T. J.; Milenic, D.; Roselli, M.; Colcher, D.; Gansow, O. A. *J. Chem. Soc., Chem. Commun.* **1991**, 1169. (e) Brechbiel, M. W.; Gansow, O. A. *Bioconjugate Chem.* **1991**, *2*, 187. (f) Kozak, R. W.; Raubitschek, A.; Mirzadeh, S.; Brechbiel, M. W.; Junghaus, R.; Gansow, O. A.; Waldmann, T. A. *Cancer Res.* **1989**, *49*, 2639. (g) Wu, C.; Kobayashi, H.; Sun, B.; Yoo, T. M.; Paik, C. H.; Gansow, O. A.; Carrasquillo, J. A.; Pastan, I.; Brechbiel, M. W. *Bioorg. Med. Chem.* **1997**, *5*, 1925. (h) Kobayashi, H.; Wu, C.; Yoo, T. M.; Sun, B.; Drumm, D.; Pastan, I.; Paik, C. H.; Gansow, O. A.; Carrasquillo, J. A.; Brechbiel, M. W. *J. Nucl. Med.* **1998**, *39*, 829.

(5) A discussion of the principles involved in targeted radiopharmaceuticals is provided in Liu, S.; Edwards, D. S. *Chem. Rev.* **1999**, *99*, 2235.

(6) (a) Williams, M. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 1151. (b) Westerberg, D. A.; Carney, P. L.; Rogers, P. E.; Kline, S. J.; Johnson, D. K. *J. Med. Chem.* **1989**, *32*, 236. (c) Keana, J. F.; Mann, J. S. *J. Org. Chem.* **1990**, *55*, 2868. (d) Anelli, P. L.; Fedeli, F.; Gazzotti, O.; Lattuada, L.; Lux, G.; Rebasti, F. *Bioconjugate Chem.* **1999**, *10*, 137. (e) Lemieux, G. A.; Yarema, K. J.; Jacobs, C. L.; Bertozzi, C. R. *J. Am. Chem. Soc.* **1999**, *121*, 4278.

(7) (a) Amedio, J. C., Jr.; Bernard, P. J.; Fountain, M.; Van Wagenen, G., Jr. *Synth. Commun.* **1999**, *29*, 2377. (b) Sajiki, H.; Ong. K. Y.; Nadler, S. T.; Wages, H. E.; McMurry, T. J. *Synth. Commun.* **1996**, *26*, 2511.

(8) Lauffer, R. B.; Parmelee, D. J.; Dunham, S. U.; Ouellet, H. S.; Dolan, R. P.; Witte, S.; McMurry, T. J.; Walovitch, R. C. *Radiology* **1998**, *207*, 529.

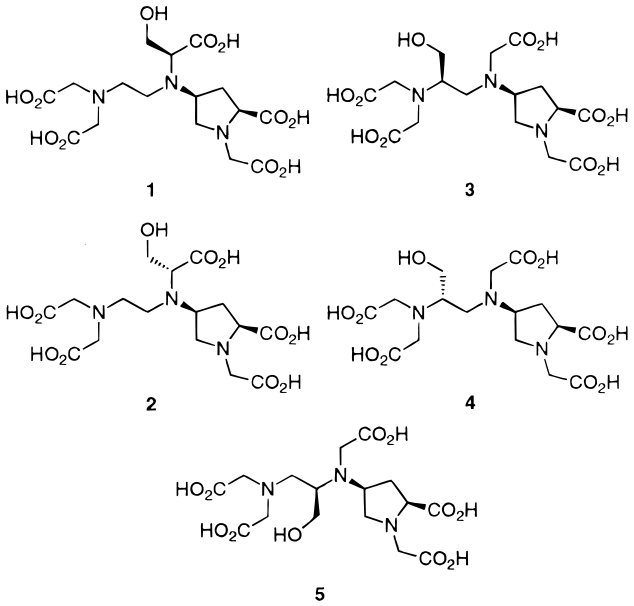
(9) Williams, M. A.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3616.

(10) Fossheim, R.; Dugstad, H.; Dahl, S. G. *J. Med. Chem.* **1991**, *34*, 819.

10.1021/jo000071g CCC: $19.00
Published on Web 05/25/2000

Also, the position of attachment of the hydroxymethyl linker to the DTPA analogue could be of importance in determining metal complex stability.

Another consideration is the isolation and purification of the highly polar DTPA analogues. The use of DTPA pentabenzyl esters as precursors to the corresponding DTPA analogues has previously been shown to be an effective methodology in DTPA synthesis.[6a,9] Thus, deprotection by catalytic hydrogenolysis is mild and allows for the direct isolation of the DTPA in high purity. With this precedent in mind we now present the syntheses of compounds **1**−**5**.



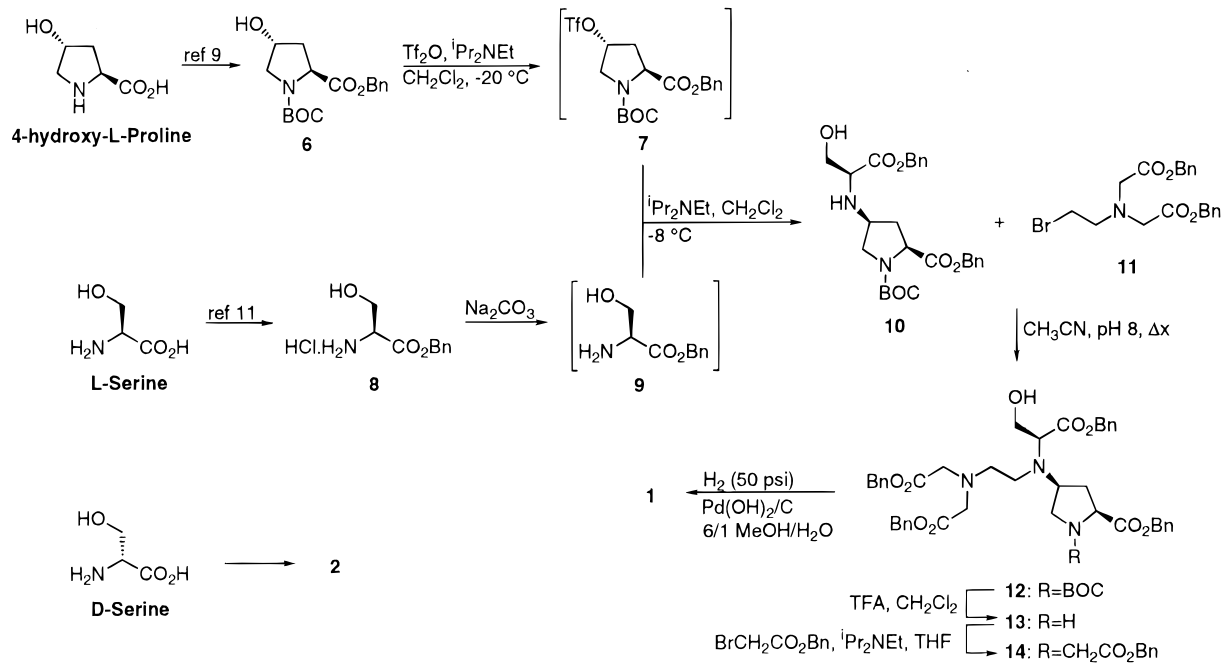
Results and Discussion

A. Hydroxymethyl Substituents on the Central Acetic Acid. Analogues **1** and **2** were prepared using the same convergent synthetic pathway from *trans*-4-hydroxy-L-proline and L- or D-serine, respectively. This route was used previously in the synthesis of similarly constrained, unfunctionalized DTPA analogues from *trans*-4-hydroxy-L-proline and glycine.[9]

The key synthetic step, as shown for the synthesis of **1** (Scheme 1), is the alkylation of the free amine of L-serine benzyl ester **9** with the triflate **7** of *N*-BOC-4-hydroxy-L-proline benzyl ester **6**. L-Serine benzyl ester hydrochloride **8** was prepared as reported,[11] and the free amine **9** was generated immediately prior to the alkylation reaction. Protected hydroxyproline **6** was prepared in high yield from *trans*-4-hydroxy-L-proline as reported[9] and was treated with triflic anhydride in the presence of diisopropylethylamine at −20 °C to generate triflate **7** in situ. The alkylation proceeds with inversion of stereochemistry on the proline ring. Previously,[9] several analogous alkylations also afforded ∼5% of the diastereomer corresponding to retention of configuration which proved inseparable by column chromatography. However, in the present case, any retention product was removed during purification and the *cis*-4-amino-L-proline analogue **10** was isolated in 64% yield as a single diastereomer as shown by ^{1}H NMR.

The remainder of the triamine backbone was then added by alkylation of **10** with known bromide **11**.[6a] For the serine-based analogues this alkylation proved to be more difficult than for the corresponding glycine-based analogue.[9] Previously, heating the amino proline derivative with bromide **11** at 50 °C in a biphasic mixture of acetonitrile and aqueous phosphate buffer for 22 h afforded the alkylated product in 78% yield. An attempt to alkylate **10** under these conditions gave essentially no alkylated product after 24 h. It was clear that the increased steric bulk imparted by the hydroxymethyl substituent in the serine-based analogues was hindering the alkylation, although refluxing conditions gave some alkylated product **12** as observed by TLC. Under these more drastic reaction conditions, however, bromide **11** was also being hydrolyzed to the alcohol, which subse-

Scheme 1. Conformationally Constrained Hydroxymethyl DTPAs Functionalized on the Central Acetate Arm



quently lactonized to give the corresponding 2-morpholinone and benzyl alcohol. Modification of the procedure to replenish both the phosphate buffer and **11** every 2 h for a total of 6 h followed by continued heating under reflux for 15 h afforded **12** in 25% yield with a 52% recovery of **10**. Attempts to perform the alkylation under anhydrous conditions at 50 °C using organic bases in DMSO and DMF as solvent gave complex mixtures, presumably due to epimerization at the amino acid chiral centers. Also, the use of more reactive alkylating agents analogous to **11** such as the mesylate or the triflate was not considered because past experience has demonstrated that these would prove of little benefit as the alkylation is believed to proceed via the corresponding aziridinium species.[12]

Removal of the *N*-BOC protecting group with TFA afforded secondary amine **13**, and alkylation of this material with benzyl bromoacetate gave the DTPA pentabenzyl ester **14** in 89% overall yield from **12**.

Deprotections of DTPA pentabenzyl esters by catalytic hydrogenolysis have typically been conducted in the presence of aqueous hydrochloric acid and the DTPA products isolated cleanly as their corresponding trihydrochloride salts.[6a,9] These conditions may be useful for unfunctionalized DTPA analogues; however, they are unsuitable for DTPA analogues bearing acid-sensitive functionality. Although **14** is not particularly sensitive to acid, DTPA analogues in which a moiety is attached via the hydroxymethyl linker may possess acid-sensitive groups, and therefore a deprotection in the absence of acid would be highly desirable.

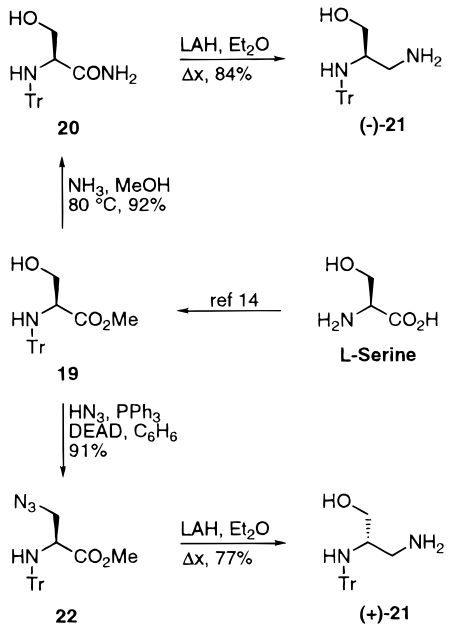
With this in mind, **14** was cleanly deprotected without the addition of aqueous hydrochloric acid to afford **1** in 95% yield. The solvent system used for the deprotection reaction was a 6/1 MeOH/H_2O mixture, the quantity of H_2O added being dictated by the necessity to keep the DTPA pentabenzyl ester starting material in solution. Deprotections in MeOH with 1 M HCl added have also been shown to furnish trace amounts of methyl ester byproducts as detected by mass spectrometry.[13] However, under the conditions described for the generation of **1** and **2** in the absence of added acid, no methyl ester impurities were observed.

The use of benzyl ester protection for DTPA analogues therefore provides a useful alternative to the more commonly employed *tert*-butyl ester protection, which requires the use of acid, typically TFA or HCl, for deprotection.

B. Hydroxymethyl Substituents on the Backbone. Diastereomeric DTPA precursors **26** and **30** were synthesized in good overall yield from L-serine and *trans*-4-hydroxy-L-proline (Schemes2 and 3). Again the synthetic strategy adopted hinged on alkylation using triflate **7**.

Monoprotected diamino alcohol (−)-**21** was accessible in two high-yielding steps from *N*-trityl-L-serine methyl ester **19** (Scheme 2). In the first step **19** was converted to primary amide **20** with a saturated solution of NH_3(g) in MeOH. Due to the steric bulk of the trityl group, the reaction required heating at 80 °C in a pressure vessel for 4−5 d to reach completion. Although these conditions appear harsh, the reaction proceeded cleanly to afford

Scheme 2. Enantiomeric Monoprotected Diamino Alcohols from L-Serine



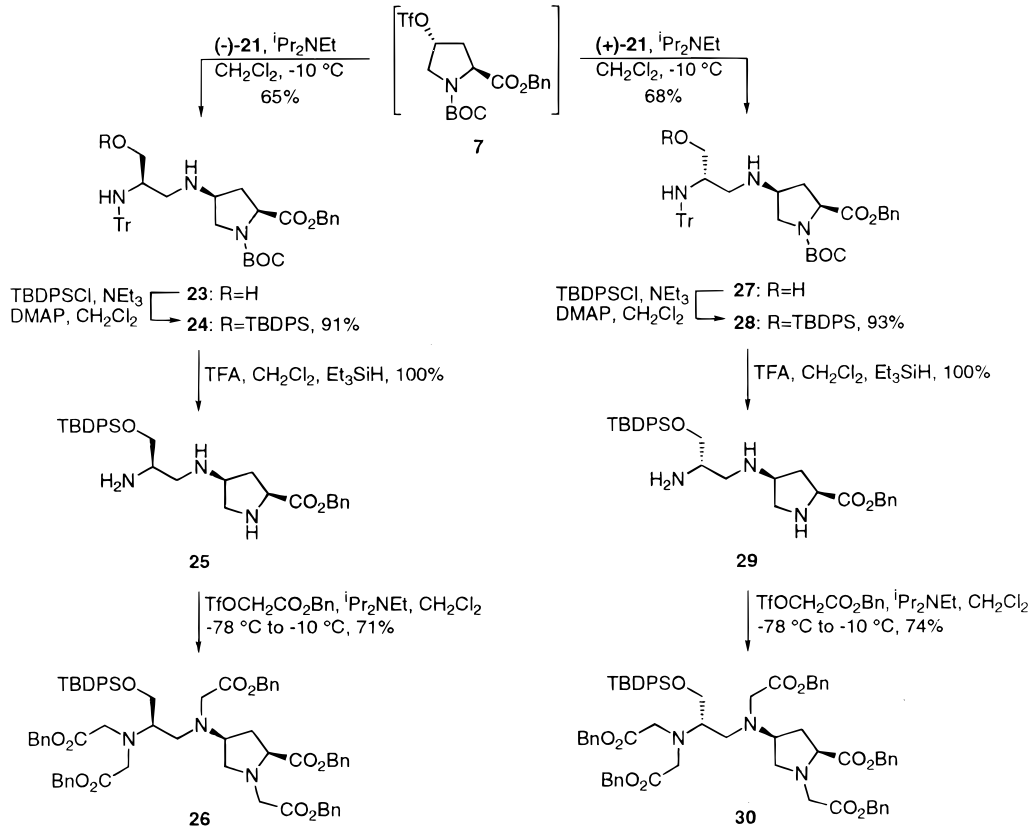
20 in 92% yield. The selection of the trityl group also proved beneficial in the next step as, upon reduction of amide **20** with lithium aluminum hydride (LAH) in Et_2O to give the highly polar (−)-**21**, purification was possible by precipitation from CH_2Cl_2/hexanes due to the crystallinity imparted by this protecting group. Reduction of amide **20** with BH_3·THF also was attempted; however, this resulted in the isolation of a boron chelate of **21** from which the boron could not be removed.

Although the trityl group, by virtue of its steric bulk, should serve to shield the relatively acidic amino acid ester α-proton from attack by base, both the amidation and reduction conditions are reasonably drastic, and therefore epimerization at the chiral center was considered to be a possibility. Chiral HPLC, however, established the enantiomeric purity of both **20** and (−)-**21** to be >99.5%,[15] demonstrating the protection against epimerization provided by the *N*-trityl group.

The enantiomeric diamino alcohol **(+)-21** was accessible, using the same chemistry, from D-serine; however, a more expedient synthesis was established from *N*-trityl-L-serine methyl ester **19** (Scheme 2). Conversion of the hydroxyl of **19** to the azide **22** via Mitsunobu reaction with hydrazoic acid proceeded in 91% yield. The azide and methyl ester functionalities were then simultaneously reduced using LAH to give **(+)-21**. This application of the Mitsunobu reaction is of particular interest in that it proceeds in high yield. Such high yields are uncommon when Mitsunobu chemistry is performed on serine alcohols as *β*-elimination is often a serious competing reaction.[16] Although hydrazoic acid has previously been demonstrated to be one of the better nucleophiles for serine-based Mitsunobu reactions,[17] the reported

(11) Folsch, G. *Acta Chem. Scand.* **1959**, *13*, 1407.
(12) Grote, C. W.; Kim, D. J.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 6987.
(13) Selchau, V.; Rapoport, H. Unpublished results.
(14) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309.
(15) The conditions used to establish the enantiomeric composition were: column, Chiracel OG; temperature, 40 °C; flow rate, 0.75 mL/min; detection, 230 nm; and eluent, 1/200/800 TFA/IPA/Hex.
(16) Mitsunobu, O. *Synthesis* **1981**, 1.
(17) (a) Golding, B. T.; Howes, C. *J. Chem. Res.* **1984**, 1. (b) Otsuka, M.; Kittaka, A.; Iimori, T.; Yamashita, H.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1985**, *33*, 509.

Scheme 3. Synthesis of Conformationally Constrained Hydroxymethyl DTPA Pentabenzyl Esters



yields are only around 70%, significantly lower than our observed 91%. This improvement may be attributable to the trityl protecting group once again shielding the acidic α-proton from attack by base. Indeed, this effect has recently been clearly demonstrated for a serine-based Mitsunobu reaction with *p*-nitrobenzoic acid.[18]

Monoalkylation of diamino alcohols (−)- and (+)-**21** with triflate **7** at −10 °C afforded **23** and **27** in 65% and 68% yields, respectively. These protected triamine backbones were then functionalized to give the corresponding diastereomeric DTPA pentabenzyl esters **26** and **30** using the methodology depicted in Scheme 3.

Before deprotection to give the triamine, the free alcohol of **23** was silylated with TBDPSCl to afford **24** in 91% yield. This silylation was done in anticipation of problems of lactonization associated with the DTPA pentabenzyl ester **38** to give 2-morpholinone **39** as a side product. Protecting the alcohol at this stage allows for isolation and storage of the DTPA pentabenzyl ester **26** without losses due to lactonization. As will be discussed later, the silyl group can then be removed and the free alcohol **38** isolated immediately prior to further manipulation. The choice of the relatively acid-stable TBDPS as the silyl group was dictated by the use of TFA in the succeeding step to simultaneously remove both trityl and BOC protection and afford triamine **25** in essentially quantitative yield.

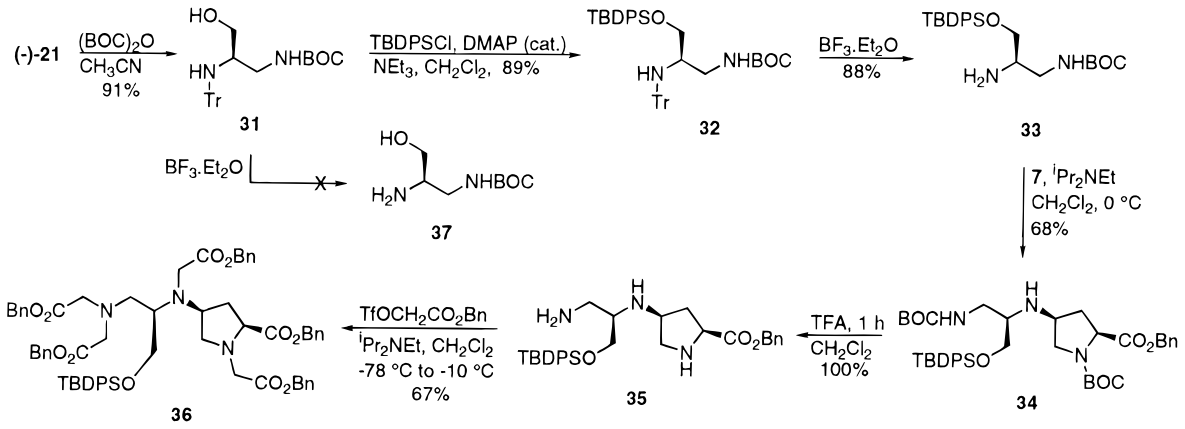
With triamine **25** in hand, all that was required was polyalkylation to generate the DTPA pentabenzyl ester **26**; however, this is not as trivial as it may first appear. Past experience[12] has demonstrated that the competitive formation of six-membered lactams is a significant problem in DTPA synthesis. Typically these problems have been addressed and to some extent controlled by the use of *tert*-butyl esters as protection for the acetic acid arms of the DTPA. Indeed, it is common practice to alkylate a diethylenetriamine backbone with *tert*-butyl bromoacetate to generate the DTPA penta-*tert*-butyl ester.[4c,7] The bulky *tert*-butyl esters decrease intramolecular cyclization of partially alkylated species to six-membered lactams during the course of the alkylation reaction. Benzyl esters do not provide the steric hindrance to prevent lactam formation. An analogy is the methyl ester, and the only reported attempt to alkylate a diethylenetriamine with methyl bromoacetate resulted in a complex mixture of lactam products with no DTPA pentamethyl ester being isolated.[4c]

Thus, it was clear that alkylation of triamine **25** with benzyl bromoacetate would provide little, if any, of the desired product **26**. Therefore, the much more reactive benzyl glycolate triflate was used in a low-temperature alkylation. An initial reaction temperature of −78 °C was maintained for 12 h before very gradual warming to −10 °C over 12 h. Holding the temperature at −10 °C for 4−5 h then ensured complete alkylation. Triethylamine was added to quench the excess alkylating agent, and tetraalkylated **26** was isolated in 71% yield. The reaction is clean, and no lactam products were observed.

Having established a synthetic route to **26** and **30**, we then synthesized a regioisomeric analogue **36** in which the hydroxymethyl unit is one carbon displaced along the backbone (Scheme 4). On the basis of the same methodology (cf., Scheme 3), it is apparent that **36** is accessible from a monoprotected diamine such as **37**, which in turn should be accessible from (−)-**21**, used previously in the synthesis of **26**, via a reversal in the nitrogen protection order.

(18) Cherney, R. J.; Wang, L. *J. Org. Chem.* **1996**, *61*, 2545.

Scheme 4. Regioisomeric Analogue



To this end the free amine of (−)-**21** was protected with a BOC group to afford **31**. An attempt to remove the trityl group selectively, however, by treatment of **31** with 105 mol % BF_3·Et_2O in 4/1 CH_2Cl_2/AcOH at 0 °C did not afford **37**, presumably due to difficulty in extracting the highly polar **37** from the aqueous phase. Therefore, **31** was initially silylated to afford **32**. As anticipated the early introduction of the silyl group proved beneficial, allowing for the isolation and purification of the more lipophilic **33** by chromatography after treatment with BF_3·Et_2O under the selective detritylation conditions.

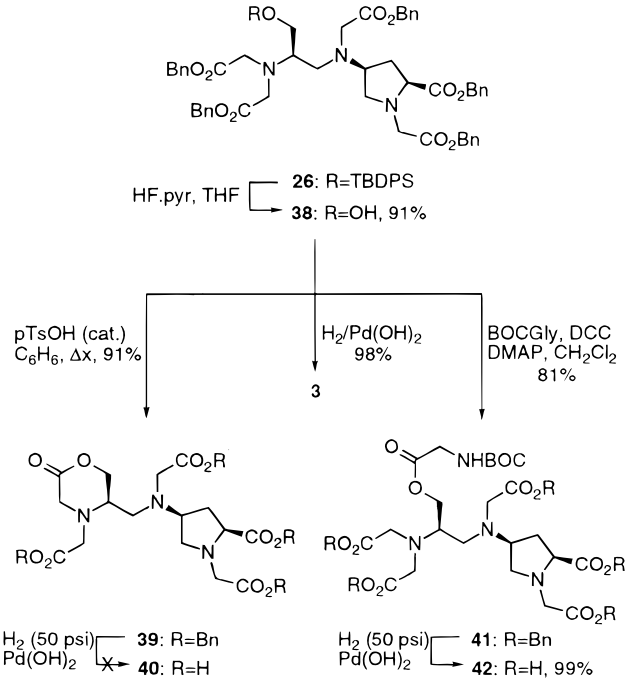
Alkylation of **33** with triflate **7** was very slow at −10 °C; however, at 0 °C the reaction progressed smoothly to afford the protected triamine backbone **34** in 68% yield. Subsequent removal of the *N*-BOC protection with TFA gave triamine **35** in quantitative yield, which was then alkylated with the triflate of benzyl glycolate at low temperature to afford **36** in 67% yield.

C. Deprotection To Afford DTPA Analogues. To demonstrate the potential of backbone-substituted DTPA pentabenzyl esters **26**, **30**, and **36** as precursors to functionalized DTPA analogues, a number of manipulations were performed on **26** (Scheme 5). Removal of the silyl group with pyridine·HF in THF proceeded cleanly at rt to afford alcohol **38**, as a 14/1 mixture with 2-morpholinone **39**, in 91% yield after rapid chromatography at 0 °C to minimize lactonization on the silica gel. While this material is of sufficient purity for further derivatization of the alcohol, for example, via esterification with *N*-BOC-glycine to afford **41**, it was not considered suitable for direct deprotection to afford DTPA **3**, primarily because of the absence of any subsequent purification of the deprotected product. For this purpose, **38** of greater purity could be obtained by a second column chromatography at 0 °C using a less polar eluent, to afford pure **38** in 55% yield. Hydrogenolysis of pure **38** in 7/1 MeOH/H_2O then gave **3** in 98% yield.

To test the objective of attaching and retaining an acid-sensitive moiety, *N*-BOC-glycine was selected as the attachment. A 14/1 mixture of **38/39**, isolated in >90% yield, was esterified with *N*-BOC-glycine using DCC as the coupling agent in the presence of catalytic DMAP, to afford **41** in 81% yield. Subsequent hydrogenolysis of **41** in 8/1 MeOH/H_2O then cleanly afforded **42** in 99% yield.

Although 2-morpholinone **39** was an undesirable side product, it provided an interesting example of a precursor to a diethylenetriaminetetraacetic acid ligand. Once again taking a 14/1 mixture of **38** and **39** and heating under reflux in benzene with a catalytic amount of *p*-TsOH allowed isolation of pure **39** in 91% yield. An attempt to generate the tetraacid **40** cleanly was not successful, with a mixture of **40**, **38**, and the monomethyl ester derivative of **38** being observed by ^1H and ^{13}C NMR and mass spectrometry. This result is consistent with reported methanolysis and hydrolysis of 2-morpholinones in MeOH and aqueous solutions, respectively.[19]

Scheme 5. Deprotection To Give Functionalized DTPA Derivatives



Conclusion

The synthesis of several hydroxymethyl-substituted, conformationally constrained DTPA analogues from *trans*-4-hydroxy-L-proline and L- or D-serine has been described. The polyalkylation of diethylenetriamine backbones with benzyl glycolate triflate to give DTPA pentabenzyl esters has been established at low temperature, minimizing competitive lactamization. In addition, attachment of an external acid-sensitive functionality in the form of an *N*-BOC-glycine ester linked via the hydroxymethyl substituent has been demonstrated to be stable under the

(19) Kashima, C.; Harada, K. *J. Org. Chem.* **1989**, *54*, 789.

mild hydrogenolysis conditions used for the deprotection of the DTPA pentabenzyl esters to the corresponding DTPA analogues. Presumably this protocol will be compatible with other acid-sensitive receptor targeting molecules similarly attached.

Experimental Section

General Procedures. All reactions were performed under an atmosphere of nitrogen or argon unless indicated otherwise. THF and Et_2O were distilled from Na−benzophenone ketyl; $^iPr_2NEt$, Et_3N, CH_3CN, and CH_2Cl_2 were distilled from CaH_2; MeOH was distilled from Mg, trifluoromethanesulfonic anhydride was prepared as reported[20] and distilled off P_2O_5 (10% w/v) prior to use. ^1H and ^{13}C NMR chemical shifts are reported in δ (ppm). ^1H NMR spectra were referenced as follows: $CDCl_3$ (internal tetramethylsilane, $\delta = 0.0$ ppm), CD_3OD (internal tetramethylsilane, $\delta = 0.0$ ppm), D_2O (HOD, $\delta = 4.80$ ppm). ^{13}C NMR spectra were referenced as follows: $CDCl_3$ ($\delta = 77.24$ ppm), CD_3OD ($\delta = 49.15$ ppm), D_2O (internal dioxane, $\delta = 67.19$ ppm). Melting points were determined in an open capillary and are uncorrected. All organic solutions from extractive isolation of products were dried over Na_2SO_4 and evaporated at 35−40 °C and aspirator pressure. Column chromatography was performed using silica gel 60, 230−400 mesh (EM Science). TLC analysis was performed on aluminum-backed silica gel 60 F_{254}, 0.2 mm plates (EM Science), visualized by UV light (254 nm) and/or ethanolic phosphomolybdic acid followed by heating. Elemental analyses and mass spectra were determined by the Micro-Mass Analytical Facility, University of California, Berkeley.

***N*-[(2*S*,4*S*)-4-[2-(Benzyloxycarbonyl)-1-(*tert*-butyloxycarbonyl)pyrrolidinyl]]-L-serine Benzyl Ester (10).** Amine **9** was prepared by partitioning hydrochloride salt **8** (3.00 g, 12.9 mmol) between $CHCl_3$ (10 mL) and 0.5 M Na_2CO_3 (30 mL). The organic phase was washed with a second portion of 0.5 M Na_2CO_3 (30 mL), and the combined aqueous phase was extracted with $CHCl_3$ (2 × 10 mL). The combined organic phase was washed with brine (30 mL), dried, filtered, and evaporated to afford **9** (2.18 g, 86%) as a pale yellow oil which, after drying under high vacuum for 30 min, was used directly in the following procedure: To a solution of **6** (1.48 g, 4.61 mmol) in CH_2Cl_2 (10 mL) cooled to −20 °C was added $^iPr_2NEt$ (DIEA; 1.69 mL, 9.70 mmol) followed by the dropwise addition of triflic anhydride (0.82 mL, 4.87 mmol). The resulting orange solution was stirred for 45 min at −20 °C before the dropwise addition of a solution of **9** (1.36 g, 6.93 mmol) in CH_2Cl_2 (5 mL). The reaction was allowed to warm to −8 °C over 1 h and held at this temperature overnight, then diluted with CH_2Cl_2 (45 mL), and washed with 0.5 M Na_2CO_3 (2 × 30 mL) and brine (30 mL). Drying, filtering, and evaporating left an oil which was chromatographed (1/1 hexanes/EtOAc + 1% NEt_3) to afford amino alcohol **10** (1.46 g, 64%) as a pale yellow oil: $[\alpha]^{22}_D$ −56.7 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) rotamers δ 1.33, 1.45 (2s, 9H), 1.85 (br s, 1H), 1.95 (m, 1H), 2.32 (m, 1H), 3.10 (br s, 1H), 3.22−3.56 (m, 5H), 3.70 (m, 1H), 4.27 (dd, $J = 8.7$, 4.4 Hz, 0.6H), 4.41 (dd, $J = 8.7$, 3.5 Hz, 0.4H), 5.00−5.30 (m, 4H), 7.32−7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) rotamers δ 28.2, 28.4, 36.9, 37.6, 51.4, 51.7, 54.7, 55.5, 57.9, 58.1, 60.8, 60.9, 63.1, 66.9, 67.0, 80.2, 128.2, 128.3, 128.4, 128.51, 128.56, 128.6, 128.7, 135.4, 135.6, 135.8, 153.8, 154. 3, 172.7, 172.8, 172.9. Anal. Calcd for $C_{27}H_{34}N_2O_7$: C, 65.0; H, 6.9; N, 5.6. Found: C, 64.9; H, 7.1; N, 5.5.

***N*-[2-Bis[(benzyloxycarbonyl)methyl]aminoethyl]-*N*-[(2*S*,4*S*)-4-[2-(benzyloxycarbonyl)-1-(*tert*-butyloxycarbonyl)pyrrolidinyl]]-L-serine Benzyl Ester (12).** To a solution of amino alcohol **10** (440 mg, 0.88 mmol) and bromide **11** (743 mg, 1.77 mmol) in CH_3CN (3 mL) was added pH 8 phosphate buffer solution (2.2 M, 3 mL). The vigorously stirred biphasic mixture was heated at reflux for 2 h and cooled to ambient temperature, and the phases were separated. Bromide **11** (743 mg, 1.77 mmol) in CH_3CN (1 mL) was added to the organic phase followed by a fresh aliquot of phosphate buffer (3 mL), and the reaction heated at reflux again. This procedure was repeated for two further additions of **11**, after which heating at reflux was continued for a further 15 h. Separation of the organic phase and evaporation of the solvent gave a residue which was purified by chromatography (2/1 hexanes/ EtOAc + 1% NEt_3 to 1/1 hexanes/EtOAc + 1% NEt_3) to afford recovered **10** (228 mg, 52%) and alkylated product **12** (187 mg, 25%) as a pale yellow oil: $[\alpha]^{22}_D$ −50.9 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) rotamers δ 1.33 and 1.43 (2s, 9H), 1.78−1.89 (m, 1H), 2.29 (m, 1H), 2.61 (m, 1H), 2.74 (m, 2H), 2.85 (m, 1H), 3.13 (m, 1H), 3.44−3.70 (m, 8H), 3.79 (m, 2H), 4.12 (m, 0.6H), 4.20 (m, 0.4H), 5.06−5.27 (m, 8H), 7.24−7.31 (m, 20H); ^{13}C NMR ($CDCl_3$) rotamers δ 28.2, 28.4, 34.2, 35.1, 46.6, 47.8, 48.1, 54.4, 55.2, 57.2, 57.5, 59.3, 59.8, 60.3, 63.6, 65.0, 66.5, 66.6, 66.8, 80.2, 126.9, 127.3, 128.1, 128.2, 128.3, 128.4, 128.6, 128.7, 135.5, 135.7, 153.5, 154.2, 170.6, 171.8, 171.9, 172.4, 172.6. Anal. Calcd for $C_{47}H_{55}N_3O_{11}$: C, 67.4; H, 6.6; N, 5.0. Found: C, 67.4; H, 6.4; N, 5.0.

***N*-[2-Bis[(benzyloxycarbonyl)methyl]aminoethyl]-*N*-[(2*S*,4*S*)-4-[2-(benzyloxycarbonyl)-1-[(benzyloxycarbonyl)methyl]pyrrolidinyl]]-L-serine Benzyl Ester (14).** To a solution of **12** (110 mg, 0.131 mmol) in CH_2Cl_2 (0.6 mL), cooled to 0 °C, was added dropwise TFA (0.6 mL). The reaction mixture was warmed to rt and stirred for 1 h. Evaporation gave a residue which was dissolved in CH_2Cl_2 (2 mL) and washed with cold (0 °C) 1 M NaOH (2 mL). The aqueous phase was extracted with CH_2Cl_2 (2 mL), and the combined organic phases were washed with brine (2 mL), dried, filtered, and evaporated to afford secondary amine **13** (96 mg, 99%) as a yellow oil which was used directly without further purification: ^1H NMR (CD_3OD) δ 1.71 (m, 1H), 2.17 (m, 1H), 2.55−2.95 (m, 6H), 3.41−3.81 (m, 9H), 5.00−5.17 (m, 8H), 7.15−7.36 (m, 20H). To a solution of **13** (96 mg, 0.130 mmol) in THF (1 mL) cooled to 0 °C were added DIEA (25 μL, 0.144 mmol) and benzyl 2-bromoacetate (22 μL, 0.139 mmol). The reaction was stirred for 2 h at 0 °C and then 15 h at rt. The precipitated salt was removed by filtration, the filtrate evaporated, and the residue chromatographed (2/1 hexanes/EtOAc + 1% NEt_3) to afford pentabenzyl ester **14** (103 mg, 89% from **12**) as a pale yellow oil: $[\alpha]^{22}_D$ −60.0 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.90 (m, 1H), 2.30 (m, 1H), 2.65−2.83 (m, 4H), 2.94−3.00 (m, 1H), 3.07 (dd, $J = 9.5$, 5.6 Hz, 1H), 3.41 (AB_q, $J = 17.5$ Hz, 2H), 3.53−3.64 (m, 8H), 3.73 (dd, $J = 11.3$, 5.0 Hz, 1H), 3.80 (dd, $J = 9.7$, 5.0 Hz, 1H), 5.03−5.15 (m, 10H), 7.28−7.33 (m, 25H); ^{13}C NMR ($CDCl_3$) δ 35.5, 45.7, 52.6, 53.9, 54.2, 55.1, 58.2, 60.1, 62.2, 63.0, 66.2, 66.34, 66.40, 66.5, 128.2, 128.30, 128.34, 128.4, 128.5, 128.60, 128.61, 128.63, 135.65, 135.71, 135.8, 170.4, 170.7, 172.4, 172.9. Anal. Calcd for $C_{51}H_{55}N_3O_{11}$: C, 69.1; H, 6.3; N, 4.7. Found: C, 68.9; H, 6.4; N, 4.7.

***N*-[2-Bis(carboxymethyl)aminoethyl]-*N*-[(2*S*,4*S*)-4-[2-carboxy-1-(carboxymethyl)-pyrrolidinyl]]-L-serine (1).** To a degassed solution of **14** (450 mg, 0.51 mmol) in MeOH (43 mL) and H_2O (7 mL) was added Pearlman's catalyst (45% moisture, 20% $Pd(OH)_2$ by dry weight, 450 mg), and the mixture was shaken on a Parr apparatus at 50 psi of H_2 for 10 h. The catalyst was removed by filtration through a bed of Celite and washed with H_2O (4 mL) and the filtrate partially evaporated at 35 °C to afford an aqueous solution. Water (20 mL) was then added and the solution evaporated to dryness at 50 °C to give a colorless gum which under high vacuum afforded **1** as a pale yellow solid (210 mg, 95%): mp 151−152 °C dec; $[\alpha]^{22}_D$ −39.2 (*c* 0.9, H_2O); ^1H NMR (D_2O + 3 drops of Tf_2O) δ 2.07 (m, 1H), 2.68 (m, 1H), 3.23 (m, 2H), 3.49 (m, 2H), 3.56 (dd, $J = 12.5$, 8.8 Hz, 1H), 3.76 (m, 2H), 3.91 (m, 2H), 4.11 (m, 1H), 4.22 (AB_q, $J = 17.0$ Hz, 2H), 4.23 (s, 4H), 4.41 (dd, $J = 11.2$, 6.6 Hz, 1H); ^{13}C NMR (D_2O) δ 32.6, 43.5, 54.8, 55.6, 56.6, 57.1, 57.9, 61.1, 62.3, 67.0, 169.7, 169.8, 171.7, 175.6; MS (FAB, G) *m*/z 436 $(M + H)^+$. Anal. Calcd for $C_{16}H_{25}N_3O_{11}\cdot{}^1/_2H_2O$: C, 43.2; H, 5.9; N, 9.5. Found: C, 43.5; H, 5.5; N, 9.4.

***N*-[(2*S*,4*S*)-4-[2-(Benzyloxycarbonyl)-1-(*tert*-butyloxycarbonyl)pyrrolidinyl]]-D-serine benzyl ester (15),** structure not shown, was prepared by the same procedure as for **10** using D-serine benzyl ester hydrochloride as starting

(20) Burdon, J.; Farazmand, I.; Stacey, M.; Tatlow, J. C. *J. Chem. Soc.* **1957**, 2574.

material: **15** (68%) isolated as a pale yellow oil; $[\alpha]^{22}_D$ −9.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) rotamers δ 1.33 and 1.45 (2s, 9H), 2.00 (m, 1H), 2.14−2.31 (m, 1H), 2.50 (br s, 1−2H), 3.22−3.40 (m, 3H), 3.52 (m, 1H), 3.58−3.71 (m, 2H), 4.27 (dd, J = 8.7, 4.4 Hz, 0.6H), 4.40 (dd, J = 8.7, 3.9 Hz, 0.4H), 5.05−5.22 (m, 4H), 7.27−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) rotamers δ 28.2, 28.4, 35.2, 36.2, 52.8, 53.4, 54.6, 55.5, 57.7, 58.0, 61.1, 62.98, 63.17, 66.9, 67.0, 80.1, 80.2, 128.1, 128.18, 128.21, 128.4, 128.5, 128.6, 128.7, 135.4, 135.5, 135.7, 153.8, 154.2, 172.6, 172.8, 172.9. Anal. Calcd for $C_{27}H_{34}N_2O_7$: C, 65.0; H, 6.9; N, 5.6. Found: C, 64.8; H, 6.8; N, 5.6.

***N*-[2-Bis[(benzyloxycarbonyl)methyl]aminoethyl]-*N*-[(2*S*,4*S*)-4-[2-(benzyloxycarbonyl)-1-(*tert*-butoxycarbonyl)pyrrolidinyl]]-D-serine Benzyl Ester (16),** structure not shown, was prepared by the same alkylation procedure as for **12**: recovered **15** (55%) and **16** (27%) isolated as a pale yellow oil; $[\alpha]_D$22−2.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) rotamers δ 1.33 and 1.43 (2s, 9H), 1.73 (m, 1H), 2.30 (m, 1H), 2.53−2.94 (m, 4H), 3.21 (t, J = 9.9 Hz, 1H), 3.41−3.82 (m, 9H), 4.09−4.22 (m, 2H), 5.03−5.23 (m, 8H), 7.23−7.38 (m, 20H); ^{13}C NMR ($CDCl_3$) rotamers δ 28.1, 28.3, 32.1, 33.8, 46.3, 46.9, 49.4, 49.7, 53.5, 54.2, 54.8, 55.1, 57.5, 57.7, 59.5, 59.6, 60.2, 63.1, 63.9, 66.4, 66.7, 80.1, 128.0, 128.2, 128.36, 128.41, 128.53, 128.55, 128.6, 135.35, 135.45, 135.5, 135.7, 153.4, 154.1, 170.5, 171.6, 171.8, 172.2, 172.3. Anal. Calcd for $C_{47}H_{55}N_3O_{11}$: C, 67.4; H, 6.6; N, 5.0. Found: C, 67.0; H, 6.7; N, 4.9.

***N*-[2-Bis[(benzyloxycarbonyl)methyl]aminoethyl]-*N*-[(2*S*,4*S*)-4-[2-(benzyloxycarbonyl)-1-[(benzyloxycarbonyl)methyl]pyrrolidinyl]]-D-serine benzyl ester (18),** structure not shown, was prepared by the same deprotection/alkylation procedure as for **14**: **18** (86%) isolated as a pale yellow oil; $[\alpha]^{22}_D$ +6.4 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.97 (m, 1H), 2.20 (m, 1H), 2.64−2.85 (m, 4H), 2.92 (m, 1H), 3.06 (dd, J = 9.5, 5.9 Hz, 1H), 3.47 (AB_q, J = 17.6 Hz, 2H), 3.58−3.68 (m, 8H), 3.74 (dd, J = 11.3, 4.9 Hz, 1H), 3.82 (dd, J = 9.6, 4.9 Hz, 1H), 5.03−5.09 (m, 10H), 7.29 (m, 25H); ^{13}C NMR ($CDCl_3$) δ 32.6, 45.8, 52.7, 53.6, 54.8, 56.6, 58.1, 60.1, 62.6, 62.8, 66.1, 66.25, 66.29, 128.1, 128.19, 128.22, 128.25, 128.28, 129.5, 135.5, 135.59, 135.61, 135.7, 170.4, 170.7, 172.2, 172.8. Anal. Calcd for $C_{51}H_{55}N_3O_{11}$: C, 69.1; H, 6.3; N, 4.7. Found: C, 69.0; H, 6.4; N, 4.7.

***N*-[2-Bis(carboxymethyl)aminoethyl]-*N*-[(2*S*,4*S*)-4-[2-carboxy-1-(carboxymethyl)-pyrrolidinyl]]-D-serine (2)** was prepared by the same procedure as for **1**. Pentaacid **2** was isolated as a pale pink solid (97%): mp 144−145 °C dec; $[\alpha]^{22}_D$ −8.6 (*c* 1.0, H_2O); ^1H NMR (D_2O + 3 drops of Tf_2O) δ 2.03 (m, 1H), 2.68 (m, 1H), 3.24 (m, 2H), 3.45 (m, 2H), 3.52 (dd, J = 12.6, 8.5 Hz, 1H), 3.72 (m, 2H), 3.84 (m, 2H), 4.07 (m, 1H), 4.20 (AB_q, J = 17.1 Hz, 2H), 4.21 (s, 4H), 4.37 (dd, J = 11.5, 6.6 Hz, 1H); ^{13}C NMR (D_2O) δ 31.4, 43.9, 54.9, 56.4, 56.7, 57.3, 58.6, 61.4, 62.3, 67.7, 169.8, 169.9, 171.8, 175.6; MS (FAB, G) *m/z* 436 $(M + H)^+$. Anal. Calcd for $C_{16}H_{25}N_3O_{11}\cdot{}^1/_2H_2O$: C, 43.2; H, 5.9; N, 9.5. Found: C, 43.3; H, 5.8; N, 9.2.

***N*-Triphenylmethyl-L-serinamide (20).** A stirred suspension of *N*-trityl-L-serine methyl ester[14] **19** (3.00 g, 8.30 mmol) in MeOH (30 mL) was cooled to 0 °C and saturated with NH_3. The resultant pale yellow solution was heated to 80 °C in a stainless steel pressure vessel for a total of 4 d, with resaturation of the reaction solution with NH_3 at 0 °C every 24 h. The volatiles were evaporated to leave a yellow solid which was chromatographed (14/1 CH_2Cl_2/MeOH) to afford **20** (2.64 g, 92%) as a colorless solid: mp 135−136 °C (CH_2Cl_2/hexanes); $[\alpha]^{22}_D$ −84.3 (*c* 0.9, $CHCl_3$); enantiomeric purity >99.5% by chiral HPLC;[15] ^1H NMR (CD_3OD) δ 2.75 (dd, J = 10.8, 5.2 Hz, 1H), 3.21 (dd, J = 5.2, 3.7 Hz, 1H), 3.52 (dd, J = 10.8, 3.7 Hz, 1H), 7.15−7.26 (m, 9H), 7.50 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 59.2, 63.0, 71.6, 126.9, 128.2, 128.8, 146.1, 177.9. Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.3; H, 6.4; N, 8.1. Found: C, 75.9; H, 6.6; N, 8.1.

(2*R*)-Triphenylmethylamino-3-aminopropanol ((−)-21). To a stirred suspension of LAH (1.95 g, 51.3 mmol) in Et_2O (70 mL) cooled to 0 °C was added **20** (2.54 g, 7.33 mmol) portionwise over 15 min, the resultant mixture was heated at reflux for 60 h and then cooled to 0 °C, and wet Et_2O (60 mL) was gradually added followed by dropwise addition of water until hydrogen evolution ceased. After the white suspension was stirred at rt for 1 h, 3/1 $CHCl_3$/IPA (150 mL) was added, and the solvent was decanted from the white residue which was subsequently extracted with further portions of 3/1 $CHCl_3$/IPA (3 × 150 mL). The combined organic phase was dried, filtered, and evaporated to afford a crude solid (2.36 g, 97%) which was precipitated from CH_2Cl_2/hexanes to give (−)-**21** (two crops, 2.05 g, 84%) as a colorless gelatinous material which solidifies on drying: mp 98−99 °C; $[\alpha]^{22}_D$ −21.1 (*c* 0.9, $CHCl_3$); enantiomeric purity >99.5% by chiral HPLC;[15] ^1H NMR (CD_3OD) δ 2.25 (dd, J = 13.1, 6.6 Hz, 1H), 2.44 (dd, J = 13.1, 3.3 Hz, 1H), 2.58 (m, 1H), 2.92 (dd, J = 11.0, 6.5 Hz, 1H), 3.22 (dd, J = 11.0, 3.8 Hz, 1H), 7.14−7.28 (m, 9H), 7.56 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 46.2, 52.9, 65.8, 71.2, 126.5, 127.9, 128.7, 146.9. Anal. Calcd for $C_{22}H_{24}N_2O$: C, 79.5; H, 7.3; N, 8.4. Found: C, 79.1; H, 7.6; N, 8.1.

***N*-Triphenylmethyl-*β*-azido-L-alanine Methyl Ester (22).** To *N*-trityl-L-serine methyl ester **19**[14] (1.00 g, 2.77 mmol) in benzene (30 mL) was added PPh_3 (0.80 g, 3.05 mmol), and the mixture was stirred at rt until a solution was obtained. Hydrazoic acid (1.64 M in benzene,[21] 1.86 mL, 3.05 mmol) was added followed by the dropwise addition of DEAD (0.48 mL, 3.05 mmol). The reaction was stirred at rt for 15 min and filtered, and the solvent evaporated. The crude residue was chromatographed (9/1 hexanes/EtOAc) to afford **22** (0.97 g, 91%) as a colorless solid: mp 96−97 °C; $[\alpha]^{22}_D$ −18.1 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.93 (d, J = 9.9 Hz, 1H), 3.22 (S, 3H), 3.35 (m, 2H), 3.57 (m, 1H), 7.13−7.25 (m, 9H), 7.50 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 52.3, 55.1, 56.7, 71.4, 126.8, 128.1, 128.8, 145.6, 173.0. Anal. Calcd for $C_{23}H_{22}N_4O_2$: C, 71.5; H, 5.7; N, 14.5. Found: C, 71.2; H, 5.9; N, 14.4.

(2*S*)-Triphenylmethylamino-3-aminopropanol ((+)-21). To a suspension of LAH (1.73 g, 45.5 mmol) in Et_2O (60 mL) cooled to 0 °C was added portionwise **22** (2.50 g, 6.47 mmol), the resultant suspension was heated at reflux for 2 h and cooled to 0 °C, and water was added dropwise until hydrogen evolution ceased. The solvent was decanted from the resultant white paste which was then extracted with 3/1 $CHCl_3$/IPA (4 × 150 mL). The combined organic phase was washed with brine (100 mL), dried, filtered, and evaporated to afford a crude solid (2.05 g, 95%) which was precipitated from CH_2Cl_2/*n*-pentane to give (+)-**21** (3 crops, 1.66 g, 77%) as a colorless solid after drying: mp 99−100 °C; $[\alpha]^{22}_D$ +20.8 (*c* 1.1, $CHCl_3$); ^1H NMR (CD_3OD) δ 2.26 (dd, J = 13.1, 6.6 Hz, 1H), 2.44 (dd, J = 13.1, 3.3 Hz, 1H), 2.58 (m, 1H), 2.92 (dd, J = 11.0, 6.5 Hz, 1H), 3.22 (dd, J = 11.0, 3.8 Hz, 1H), 7.15−7.28 (m, 9H), 7.56 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 46.5, 53.0, 66.2, 71.3, 126.5, 127.9, 128.7, 146.9.

***N*-[(2*S*,4*S*)-4-[2-(Benzyloxycarbonyl)-1-(*tert*-butyloxycarbonyl)pyrrolidinyl]]-(2*R*)-triphenylmethylamino-3-hydroxypropylamine (23).** To a solution of *N*-BOC-4-hydroxy-L-proline benzyl ester **6** (2.03 g, 6.32 mmol) in CH_2Cl_2 (40 mL) cooled to −30 °C was added DIEA (2.19 mL, 12.6 mmol) followed by triflic anhydride (1.06 mL, 6.32 mmol) dropwise. The resultant orange mixture was stirred at −30 °C for 60 min, and then (−)-**21** (2.00 g, 6.02 mmol) was added dropwise as a solution in CH_2Cl_2 (25 mL). The reaction was held at −10 °C for 76 h, diluted with CH_2Cl_2 (150 mL), and then washed with 0.5 M Na_2CO_3 (2 × 120 mL) and brine (120 mL). Drying, Filtering, and Evaporating gave a crude product which was chromatographed (1/1 hexanes/EtOAc + 1% NEt_3 to EtOAc + 1% NEt_3) to afford **23** (2.49 g, 65%) as a colorless solid: mp 89−91 °C; $[\alpha]^{22}_D$ −40.5 (*c* 0.7, $CHCl_3$); ^1H NMR (CD_3OD) rotamers δ 1.30 and 1.45 (2s, 9H), 1.71 (m, 1H), 1.96 (dd, J = 11.7, 6.4 Hz, 0.4H), 2.05 (dd, J = 11.6, 6.5 Hz, 0.6H), 2.21−2.33 (m, 2H), 2.61 (m, 1H), 2.93 (m, 1H), 3.00−3.12 (m, 2H), 3.34 (m, 1H), 3.46 (m, 1H), 4.22 (m, 1H), 5.01−5.21 (m, 2H), 7.13−7.35 (m, 14H), 7.55 (m, 6H); ^{13}C NMR ($CDCl_3$) rotamers δ 28.3, 28.6, 35.7, 36.8, 51.5, 51.6, 51.7, 52.4, 52.8, 53.0, 56.6, 57.4, 57.9, 58.1, 67.0, 67.1, 67.4, 67.6, 71.4, 80.28, 80.34, 126.6, 128.0, 128.2, 128.3, 128.60, 128.63, 128.70, 128.76, 128.80,

(21) Equi, A. M.; Brown, A. M.; Cooper, A.; Ner, S. K.; Watson, A. B.; Robins, D. J. *Tetrahedron* **1991**, *47*, 507.

135.6, 135.8, 146.7, 153.9, 154.4, 173.0, 173.3. Anal. Calcd for $C_{39}H_{45}N_3O_5$: C, 73.7; H, 7.1; N, 6.6. Found: C, 73.4; H, 7.5; N, 6.5.

***N*-[(2*S*,4*S*)-4-[2-(Benzyloxycarbonyl)-1-(*tert*-butyloxycarbonyl)pyrrolidinyl]]-(2*R*)-triphenylmethylamino-3-(*tert*-butyldiphenylsilyloxy)propylamine (24).** A solution of **23** (2.80 g, 4.40 mmol), NEt_3 (0.67 mL, 4.84 mmol), DMAP (107 mg, 0.88 mmol), and TBDPSCl (1.26 mL, 4.84 mmol) in CH_2Cl_2 (70 mL) was stirred at rt for 1 h, then diluted with CH_2Cl_2 (100 mL), and washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (100 mL). Drying, filtering, and evaporating gave a residual oil which was chromatographed (4/1 hexanes/EtOAc + 1% NEt_3) to give **24** (3.49 g, 91%) as a colorless solid: mp 84−85 °C; $[\alpha]^{22}_D$ −13.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_3OD) rotamers δ 0.99 (s, 9H), 1.29 and 1.44 (2s, 9H), 1.64 (m, 1H), 1.93−2.06 (m, 1H), 2.24 (m, 1H), 2.36 (m, 1H), 2.61 (m, 1H), 2.86 (m, 1H), 2.94 and 3.03 (2m, 1H), 3.19 (m, 1H), 3.42 (m, 1H), 3.52 (dd, J = 10.1, 4.0 Hz, 1H), 4.18 (m, 1H), 4.94−5.12 (m, 2H), 7.10−7.60 (m, 30H); ^{13}C NMR ($CDCl_3$) rotamers δ 19.1, 26.9, 28.1, 28.4, 36.0, 36.8, 47.8, 51.9, 52.3, 52.9, 53.0, 56.4, 57.2, 57.9, 58.1, 64.7, 66.4, 70.8, 79.65, 79.70, 126.1, 127.6, 127.69, 127.73, 127.8, 127.9, 128.2, 128.26, 128.30, 128.5, 128.6, 129.6, 133.4, 135.5, 135.6, 147.0, 153.5, 154.2, 172.4, 172.6. Anal. Calcd for $C_{55}H_{63}N_3O_5Si$: C, 75.6; H, 7.3; N, 4.8. Found: C, 75.4; H, 7.3; N, 4.9.

***N*-[(2*S*,4*S*)-4-[2-(Benzyloxycarbonyl)pyrrolidinyl]]-(2*R*)-amino-3-(*tert*-butyldiphenylsilyloxy)propylamine (25).** To a stirred solution of **24** (3.34 g, 3.82 mmol) and triethylsilane (640 μL, 4.01 mmol) in CH_2Cl_2 (16 mL) cooled to 0 °C was added dropwise TFA (16 mL). The resultant colorless solution was allowed to warm to rt, with stirring continued for 1 h. The solvents were evaporated, the residue was triturated with hexanes (5 × 50 mL), the hexane extracts were discarded, and the oily residue was partitioned between 3/1 $CHCl_3$/IPA (250 mL) and 1 M NaOH (precooled to 0 °C, 100 mL). The aqueous phase was extracted with further portions of 3/1 $CHCl_3$/IPA (2 × 200 mL), and the combined organic phase was dried, filtered, and evaporated to give **25** (2.04 g, 100% crude yield) as a pale yellow oil: ^{1}H NMR (CD_3OD) δ 1.06 (s, 9H), 1.70 (m, 1H), 2.29 (m, 1H), 2.43 (dd, J = 11.8, 7.3 Hz, 1H), 2.61 (dd, J = 11.9, 4.6 Hz, 1H), 2.80 (dd, J = 11.0, 4.3 Hz, 1H), 2.89 (m, 2H), 3.15 (m, 1H), 3.60 (m, 2H), 3.74 (m, 1H), 5.11 (AB_q, J = 12.3 Hz, 2H), 7.26−7.45 (m, 11H), 7.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 20.2, 27.6, 37.7, 51.8, 53.3, 53.6, 58.1, 60.0, 65.2, 67.9, 129.0, 129.5, 129.7, 130.6, 131.2, 134.5, 136.8, 137.3, 175.5.

***N*-[(Benzyloxycarbonyl)methyl]-*N*-[(2*S*,4*S*)-4-[2-(benzyloxycarbonyl)-*N*-[(benzyloxycarbonyl)methyl]pyrrolidinyl]]-(2*R*)-*N*,*N*-[bis[(benzyloxycarbonyl)methyl]amino]-3-(*tert*-butyldiphenylsilyloxy)propylamine (26).** To a stirred solution of **25** (1.80 g, 3.38 mmol) and DIEA (4.71 mL, 27.0 mmol) in CH_2Cl_2 (85 mL) cooled to −78 °C was added dropwise over 30 min a precooled solution (−50 °C) of the triflate of benzyl glycolate[22] (8.06 g, 27.0 mmol) in CH_2Cl_2 (55 mL). The resultant solution was held at −78 °C for 14 h and then allowed to warm to −10 °C over 10 h, at which it was maintained for a further 5 h before the addition of Et_3N (11 mL). After being warmed to rt over 1 h, the mixture was partitioned between CH_2Cl_2 (110 mL) and saturated aqueous $NaHCO_3$ (275 mL), and the organic phase was washed with brine (150 mL), dried, filtered, and evaporated. The residue was chromatographed (3/1 hexanes/EtOAc +1% NEt_3) to afford **26** (2.70 g, 71%) as a pale yellow oil: $[\alpha]^{22}_D$ −18.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 9H), 1.80 (m, 1H), 2.18 (m, 1H), 2.67 (m, 1H), 2.75−2.83 (m, 2H), 3.01 (m, 2H), 3.39 (1/2 AB_q, J = 17.6 Hz, 1H), 3.48 (AB_q, J = 17.6 Hz, 2H), 3.56−3.71 (m, 9H), 4.99−5.09 (m, 10H), 7.25−7.37 (m, 31H), 7.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.1, 27.0, 33.6, 51.9, 52.4, 52.9, 53.5, 56.0, 60.2, 62.2, 62.8, 64.1, 66.0, 66.1, 66.2, 66.4, 127.8, 128.14, 128.17, 128.24, 128.26, 128.29, 128.34, 128.5, 128.60, 128.63, 129.76, 129.78, 133.3, 135.7, 135.8, 135.9, 135.97, 136.04, 170.5, 171.8, 172.0, 172.9. Anal. Calcd for $C_{67}H_{73}N_3O_{11}$-Si: C, 71.6; H, 6.5; N, 3.7. Found: C, 71.2; H, 6.6; N, 3.7.

***N*-[(2*S*,4*S*)-4-[2-(Benzyloxycarbonyl)-1-(*tert*-butyloxycarbonyl)pyrrolidinyl]]-(2*S*)-triphenylmethylamino-3-hydroxypropylamine (27).** To a solution of *N*-BOC-4-hydroxy-L-proline benzyl ester **6** (2.76 g, 8.59 mmol) in CH_2Cl_2 (50 mL) cooled to −30 °C was added DIEA (3.00 mL, 17.2 mmol) followed by triflic anhydride (1.45 mL, 8.61 mmol) dropwise. The resultant orange mixture was stirred at −30 °C for 60 min, and then **(+)-21** (2.72 g, 8.18 mmol) added dropwise as a solution in CH_2Cl_2 (35 mL). The reaction was held at −10 °C for 76 h, diluted with CH_2Cl_2 (200 mL), and then washed with 0.5 M Na_2CO_3 (2 × 150 mL) and brine (150 mL). Drying, Filtering, and Evaporating gave a residue which was chromatographed (1/1 hexanes/EtOAc + 1% NEt_3 to EtOAc +1% NEt_3) to afford **27** (3.54 g, 68%) as a colorless solid: mp 90−92 °C; $[\alpha]^{22}_D$ +11.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_3OD) rotamers δ 1.30 and 1.44 (2s, 9H), 1.71 (m, 1H), 2.07−2.37 (m, 3H), 2.63 (m, 1H), 2.95−3.12 (m, 3H), 3.38 (m, 1H), 3.51 (m, 1H), 4.22 (m, 1H), 5.03−5.18 (m, 2H), 7.13−7.40 (m, 14H), 7.56 (m, 6H); ^{13}C NMR ($CDCl_3$) rotamers δ 28.3, 28.5, 35.0, 36.2, 51.6, 51.8, 51.9, 52.7, 52.9, 53.1, 56.7, 57.4, 57.9, 58.2, 67.0, 67.1, 67.2, 67.3, 71.4, 80.3, 126.60, 126.64, 128.0, 128.2, 128.3, 128.6, 128.7, 135.5, 135.7, 146.7, 153.7, 154.4, 173.1, 173.2. Anal. Calcd for $C_{39}H_{45}N_3O_5$: C, 73.7; H, 7.1; N, 6.6. Found: C, 73.8; H, 7.1; N, 6.7.

***N*-[(2*S*,4*S*)-4-[2-(Benzyloxycarbonyl)-1-(*tert*-butyloxycarbonyl)pyrrolidinyl]]-(2*S*)-triphenylmethylamino-3-(*tert*-butyldiphenylsilyloxy)propylamine (28).** A solution of **27** (3.00 g, 4.72 mmol), Et_3N (0.72 mL, 5.17 mmol), DMAP (115 mg, 0.94 mmol), and TBDPSCl (1.35 mL, 5.19 mmol) in CH_2Cl_2 (75 mL) was stirred at rt for 1 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (100 mL). Drying, filtering, and evaporating gave a crude oil which was chromatographed (4/1 hexanes/EtOAc + 1% NEt_3) to give **28** (3.84 g, 93%) as a colorless solid: mp 83−84 °C; $[\alpha]^{22}_D$ −19.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_3OD) rotamers δ 0.99 (s, 9H), 1.30 and 1.43 (2s, 9H), 1.58 (m, 1H), 1.91 (m, 1H), 2.21 (m, 1H), 2.33 (m, 1H), 2.58 (m, 1H), 2.81 (m, 1H), 2.98 (m, 1H), 3.24 (m, 1H), 3.43 (m, 1H), 3.53 (m, 1H), 4.18 (m, 1H), 4.96−5.13 (m, 2H), 7.12−7.58 (m, 30H); ^{13}C NMR ($CDCl_3$) rotamers δ 19.4, 27.1, 28.3, 28.6, 36.2, 37.1, 48.2, 48.3, 52.2, 52.7, 53.2, 56.6, 57.3, 58.0, 58.3, 64.7, 64.9, 66.8, 71.1, 80.0, 80.1, 126.4, 127.8, 127.9, 128.2, 128.5, 128.6, 128.7, 128.8, 129.8, 133.6, 133.7, 135.7, 135.8, 147.2, 153.7, 154.4, 172.7, 173.0. Anal. Calcd for $C_{55}H_{63}N_3O_5Si$: C, 75.6; H, 7.3; N, 4.8. Found: C, 75.3; H, 7.3; N, 4.9.

***N*-[(2*S*,4*S*)-4-[2-(Benzyloxycarbonyl)pyrrolidinyl]]-(2*S*)-amino-3-(*tert*-butyldiphenylsilyloxy)propylamine (29).** To a stirred solution of **28** (3.17 g, 3.63 mmol) and triethylsilane (609 μL, 3.81 mmol) in CH_2Cl_2 (15 mL) cooled to 0 °C was added dropwise TFA (15 mL), and the resultant colorless solution was allowed to warm to rt, with stirring continued for 1 h. The solvents were evaporated, the residue was triturated with hexanes (5 × 50 mL), the hexane extracts were discarded, and the oily residue was partioned between 3/1 $CHCl_3$/IPA (3 × 250 mL) and 1 M NaOH solution (precooled to 0 °C, 100 mL). The combined organic phase was dried, filtered, and evaporated to give **29** (1.93 g, 100% crude yield) as a pale yellow oil: ^{1}H NMR (CD_3OD) δ 1.05 (s, 9H), 1.71 (m, 1H), 2.30 (m, 1H), 2.38 (dd, J = 11.8, 7.8 Hz, 1H), 2.61 (dd, J = 11.8, 4.6 Hz, 1H), 2.79−2.90 (m, 3H), 3.16 (m, 1H), 3.55 (dd, J = 10.1, 6.0 Hz, 1H), 3.62 (dd, J = 10.1, 5.5 Hz, 1H), 3.74 (dd, J = 8.9, 6.1 Hz, 1H), 5.12 (AB_q, J = 12.2 Hz, 2H), 7.26−7.45 (m, 11H), 7.67 (m, 4H); ^{13}C NMR (CD_3OD) δ 20.2, 27.6, 37.9, 52.0, 53.1, 53.8, 59.9, 60.0, 68.0, 68.1, 129.0, 129.5, 129.7, 130.6, 131.1, 134.6, 136.8, 137.4, 175.6.

***N*-[(Benzyloxycarbonyl)methyl]-*N*-[(2*S*,4*S*)-4-[2-(benzyloxycarbonyl)-*N*-[(benzyloxycarbonyl)methyl]pyrrolidinyl]]-(2*S*)-*N*,*N*-[bis[(benzyloxycarbonyl)methyl]amino]-3-(*tert*-butyldiphenylsilyloxy)propylamine (30).** To a stirred solution of **29** (1.65 g, 3.10 mmol) and DIEA (4.32 mL, 24.8

(22) Generated from benzyl glycolate in CH_2Cl_2 with triflic anhydride (100 mol %) at 0 °C in the presence of 100 mol % 2,6-lutidine. Evaporation and subsequent trituration of the residue with hexanes cleanly extracted the desired triflate from the solid lutidine salts. The triflate was used directly without further purification.

mmol) in CH_2Cl_2 (80 mL) cooled to −78 °C was added dropwise over 30 min a precooled solution (−50 °C) of the triflate of benzyl glycolate (7.40 g, 24.8 mmol)[22] in CH_2Cl_2 (50 mL). The resultant solution was held at −78 °C for 12 h and then allowed to warm to −10 °C over 12 h. This temperature was maintained for a further 4 h before the addition of Et_3N (10 mL). After being warmed to rt over 1 h, the mixture was partitioned between CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ (250 mL), and the organic phase was washed with brine (150 mL), dried, filtered, and evaporated, leaving a residue which was chromatographed (4/1 hexanes/EtOAc +1% NEt_3) to afford **30** (2.58 g, 74%) as a pale yellow oil: $[\alpha]^{22}_D$ −22.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 9H), 1.82 (m, 1H), 2.22 (m, 1H), 2.76 (m, 3H), 3.02 (m, 2H), 3.42−3.63 (m, 6H), 3.66 (s, 4H), 3.71 (m, 2H), 5.01−5.09 (m, 10H), 7.22−7.38 (m, 31H), 7.61−7.63 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.3, 27.1, 34.0, 51.9, 52.5, 53.1, 53.6, 55.6, 60.4, 62.2, 62.9, 64.2, 66.1, 66.28, 66.32, 66.5, 127.9, 128.26, 128.27, 128.29, 128.37, 128.39, 128.5, 128.6, 128.70, 128.74, 129.8, 129.9, 133.4, 135.80, 135.83, 135.9, 136.0, 136.1, 170.7, 171.9, 172.1, 173.0. Anal. Calcd for $C_{67}H_{73}N_3O_{11}Si$: C, 71.6; H, 6.5; N, 3.7. Found: C, 71.2; H, 6.4; N, 3.6.

(2*R*)-Triphenylmethylamino-3-(*tert*-butyloxycarbonyl)aminopropanol (31). To a stirred suspension of **(−)-21** (3.46 g, 10.4 mmol) in CH_3CN (75 mL) cooled to 0 °C was added dropwise a solution of di-*tert*-butyl dicarbonate (2.52 g, 11.5 mmol) in CH_3CN (25 mL). The reaction was stirred at 0 °C for 30 min and then at rt for 1 h. The solvent was evaporated and the residue chromatographed (4/1 hexanes/EtOAc + 1% NEt_3 to 3/1 hexanes/EtOAc + 1% NEt_3) to give **31** (4.09 g, 91% yield) as a colorless solid: mp 70−71 °C; $[\alpha]^{22}_D$ −38.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.00 (br s, 1H), 2.53−2.68 (m, 3H), 3.05 (m, 1H), 3.16 (br d, 1H), 3.63 (br s, 1H), 4.58 (br t, 1H), 7.16−7.30 (m, 9H), 7.55 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 28.5, 41.2, 53.9, 61.7, 71.1, 80.2, 126.7, 128.2, 128.7, 147.0, 157.8. Anal. Calcd for $C_{27}H_{32}N_2O_3$: C, 75.0; H, 7.5; N, 6.5. Found: C, 74.9; H, 7.5; N, 6.6.

***O*-(*tert*-Butyldiphenylsilyl)-(2*R*)-(triphenylmethyl)amino-3-(*tert*-butyloxycarbonyl)aminopropanol (32).** To a solution of **31** (1.95 g, 4.51 mmol) in CH_2Cl_2 (50 mL) were added Et_3N (0.69 mL, 4.96 mmol), DMAP (110 mg, 0.90 mmol), and TBDPSCl (1.29 mL, 4.96 mmol), and the resulting solution was stirred at rt for 40 h. The mixture was partitioned between CH_2Cl_2 (80 mL) and 0.5 M Na_2CO_3 (80 mL), the organic phase was further washed with 0.5 M Na_2CO_3 (80 mL) and brine (80 mL), the combined organic phase was dried, filtered, and evaporated, and the residue was chromatographed (9/1 hexanes/Et_2O) to give **32** (2.69 g, 89%) as a colorless solid: mp 54−56 °C; $[\alpha]^{22}_D$ −10.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) rotamers δ 1.01 (s, 9H), 1.40 (br s, 9H), 2.44 (br s, 1H), 2.72 (m, 1H), 2.88 (m, 1H), 2.98 (m, 1H), 3.09 (m, 1H), 3.19 (m, 1H), 4.54 (m, 1H), 7.10−7.53 (m, 25H); ^{13}C NMR ($CDCl_3$) rotamers δ 19.3, 27.1, 28.6, 43.3, 53.2, 65.1, 71.1, 78.8, 126.5, 127.8, 127.9, 128.0, 128.8, 129.9, 133.3, 133.4, 135.76, 135.82, 146.9, 156.2. Anal. Calcd for $C_{43}H_{50}N_2O_3Si$: C, 77.0; H, 7.5; N, 4.2. Found: C, 76.8; H, 7.6; N, 4.1.

***O*-(*tert*-Butyldiphenylsilyl)-(2*R*)-amino-3-(*tert*-butyloxycarbonyl)aminopropanol (33).** To a solution of **32** (2.67 g, 3.98 mmol) in CH_2Cl_2 (27 mL) cooled to 0 °C were added glacial acetic acid (6.7 mL) and $BF_3{\cdot}Et_2O$ (529 μL, 4.17 mmol) dropwise, and the mixture was stirred at 0 °C for 2 h. Cold (0 °C) 1 M NaOH (160 mL) was added and the mixture partioned between 3/1 $CHCl_3$/IPA (320 mL) and cold (0 °C) 1 M NaOH (66 mL), followed by extraction with further portions of 3/1 $CHCl_3$/IPA (2 × 160 mL). The combined organic phase was dried, filtered, and evaporated to a residue which was chromatographed (19/1 CH_2Cl_2/MeOH to 9/1 CH_2Cl_2/MeOH) to give **33** (1.50 g, 88%) as a colorless oil: $[\alpha]^{22}_D$ +3.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H), 1.42 (s, 9H), 1.51 (br s, 2H), 2.97 (m, 1H), 3.05 (m, 1H), 3.23 (m, 1H), 3.53 (dd, *J* = 10.1, 5.4 Hz, 1H), 3.63 (dd, *J* = 10.1, 4.7 Hz, 1H), 5.21 (m, 1H), 7.35−7.43 (m, 6H), 7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.3, 26.9, 28.4, 44.2, 52.6, 67.3, 79.0, 127.8, 129.9, 133.2, 135.6, 156.3. Anal. Calcd for $C_{24}H_{36}N_2O_3Si$: C, 67.3; H, 8.5; N, 6.5. Found: C, 66.9; H, 8.3; N, 6.4.

***N*-[(2*S*,4*S*)-4-[2-(Benzyloxycarbonyl)-1-(*tert*-butyloxycarbonyl)pyrrolidinyl]]-(1*R*)-[(*tert*-butyldiphenylsilyloxy)methyl]-2-(*tert*-butyloxycarbonyl)aminoethylamine (34).** To a solution of *N*-BOC-4-hydroxy-L-proline benzyl ester **6** (1.00 g, 3.12 mmol) in CH_2Cl_2 (10 mL) cooled to −30 °C was added DIEA (1.19 mL, 6.86 mmol) followed by triflic anhydride (0.58 mL, 3.43 mmol) dropwise. The resultant orange mixture was stirred at −30 °C for 60 min and then **33** (0.89 g, 2.08 mmol) was added dropwise as a solution in CH_2Cl_2 (5 mL). The reaction was allowed to warm to 0 °C, stirred at 0 °C for 72 h, diluted with CH_2Cl_2 (50 mL), and then washed with 0.5 M Na_2CO_3 (2 × 50 mL) and brine (50 mL). Drying, filtering, and evaporating gave a residue which was chromatographed (4/1 hexanes/EtOAc + 1% NEt_3 to 3/1 hexanes/EtOAc + 1% NEt_3) to afford **34** (1.04 g, 68%) as a colorless solid: mp 42−43 °C; $[\alpha]^{22}_D$ −19.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) rotamers δ 1.05 and 1.06 (2s, 9H), 1.33 and 1.46 (2s, 9H), 1.41 (s, 9H), 1.62 (br s, 1H), 1.86 (m, 1H), 2.23 (m, 1H), 2.64 (m, 1H), 3.05−3.28 (m, 4H), 3.52−3.69 (m, 3H), 4.26 (dd, *J* = 8.6, 5.0 Hz, 0.6H), 4.36 (dd, *J* = 8.6, 4.8 Hz, 0.4H), 4.93 (br m, 1H), 5.09−5.29 (m, 2H), 7.28−7.45 (m, 11H), 7.63 (d, *J* = 7.3 Hz, 4H); ^{13}C NMR ($CDCl_3$) rotamers δ 18.85, 18.86, 26.7, 28.0, 28.2, 35.7, 36.6, 41.9, 52.7, 53.1, 54.2, 56.4, 56.5, 57.6, 57.9, 63.6, 63.8, 66.5, 78.6, 79.56, 79.61, 127.60, 127.61, 127.80, 127.82, 128.1, 128.2, 128.28, 128.31, 129.7, 132.7, 132.8, 135.3, 135.4, 135.6, 153.4, 153.9, 155.9, 172.4, 172.7. Anal. Calcd for $C_{41}H_{57}N_3O_7Si$: C, 67.3; H, 7.9; N, 5.7. Found: C, 67.0; H, 7.8; N, 5.7.

***N*-[(2*S*,4*S*)-4-[2-(Benzyloxycarbonyl)pyrrolidinyl]]-1*R*-[(*tert*-butyldiphenylsilyloxy)methyl]-2-aminoethylamine (35).** To a stirred solution of **34** (941 mg, 1.29 mmol) in CH_2Cl_2 (4.8 mL) cooled to 0 °C was added dropwise TFA (4.8 mL), and the mixture was stirred at 0 °C for 30 min and then at rt for 1 h. The solvents were evaporated, and the residue was partioned between 3/1 $CHCl_3$/IPA (3 × 60 mL) and cold (0 °C) 1 M NaOH (30 mL). The combined organic phase was dried and evaporated to give **35** (685 mg, 100%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.60 (br s, 4H), 1.76 (m, 1H), 2.16 (m, 1H), 2.47 (m, 1H), 2.61 (dd, *J* = 12.7, 6.9 Hz, 1H), 2.74 (m, 2H), 2.95 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.22 (m, 1H), 3.60 (m, 2H), 3.78 (dd, *J* = 9.0, 5.2 Hz, 1H), 5.15 (AB_q, *J* = 12.4 Hz, 2H), 7.26−7.44 (m, 11H), 7.63 (d, *J* = 6.7 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 19.3, 27.0, 37.1, 43.6, 54.3, 55.7, 59.1, 63.7, 66.8, 127.8, 128.3, 128.4, 128.6, 129.9, 133.4, 135.6, 135.8, 175.1.

***N*-[(Benzyloxycarbonyl)methyl]-*N*-[(2*S*,4*S*)-4-[2-(benzyloxycarbonyl)-*N*-[(benzyloxycarbonyl)methyl]pyrrolidinyl]]-(1*R*)-[(*tert*-butyldiphenylsilyloxy)methyl]-2-*N*,*N*-[bis[(benzyloxy-carbonyl)methyl]amino]ethylamine (36).** To a solution of **35** (300 mg, 0.56 mmol) in CH_2Cl_2 (15 mL) cooled to −78 °C was added DIEA (0.98 mL, 5.60 mmol) followed by the dropwise addition of a precooled solution (−78 °C) of the triflate of benzyl glycolate (1.67 g, 5.60 mmol)[22] in CH_2Cl_2 (10 mL) over 20 min. The temperature was held at −78 °C for 10 h, then allowed to warm to −10 °C over 17 h, and held at −10 °C for 6 h. A further quantity of DIEA (175 μL, 1.01 mmol) and benzyl glycolate triflate (300 mg, 1.01 mmol) was added and the reaction held at −10 °C for a further 4 h. Triethylamine (2 mL) was added and the reaction allowed to warm to rt, diluted with CH_2Cl_2 (20 mL), and washed with saturated $NaHCO_3$ (50 mL) and brine (30 mL). Drying, filtering, and evaporating gave a residue which was chromatographed (4/1 hexanes/EtOAc + 1% NEt_3) to afford **36** (421 mg, 67%) as a pale yellow oil: $[\alpha]_D^{22}$ −15.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9H), 1.87 (m, 1H), 2.15 (m, 1H), 2.76 (m, 2H), 2.96 (m, 3H), 3.45 (AB_q, *J* = 17.5 Hz, 2H), 3.54−3.74 (m, 10H), 5.03−5.10 (m, 10H), 7.26−7.39 (m, 31H), 7.60 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.1, 27.0, 34.6, 49.7, 52.7, 53.9, 55.3, 56.3, 57.7, 61.1, 62.7, 64.2, 66.1, 66.17, 66.20, 66.4, 127.8, 128.1, 128.18, 128.24, 128.26, 128.29, 128.4, 128.5, 128.59, 128.64, 129.76, 129.79, 133.25, 133.29, 135.69, 135.74, 135.8, 135.9, 136.1, 170.5, 171.2, 173.0, 173.1. Anal. Calcd for $C_{67}H_{73}N_3O_{11}Si$: C, 71.6; H, 6.5; N, 3.7. Found: C, 71.4; H, 6.4; N, 3.5.

***N*-[(Benzyloxycarbonyl)methyl]-*N*-[(2*S*,4*S*)-4-[2-(benzyloxycarbonyl)-*N*-[(benzyloxycarbonyl)methyl]pyrrol-

idinyl]]-(2*R*)-*N*,*N*-[bis[(benzyloxycarbonyl)methyl]amino]-3-hydroxy-propylamine (38). To a solution of **26** (1.00 g, 0.89 mmol) in THF (22 mL) was added dropwise pyridine·HF (1.44 mL), and the mixture was stirred at rt for 90 min. Saturated aqueous $NaHCO_3$ solution was added dropwise until CO_2 evolution ceased, and then the mixture was partitioned between saturated aqueous $NaHCO_3$ (40 mL) and CH_2Cl_2 (100 mL). The aqueous phase was extracted with further portions of CH_2Cl_2 (2 × 50 mL), and the combined organic phase was dried and evaporated to leave a crude oil which was chromatographed (1/1 hexanes/EtOAc) at 0 °C to afford **38** as a ∼14/1 mixture with lactone **39**, 717 mg, 91%. By further chromatography (3/2 hexanes/EtOAc) at 0 °C pure **38** (430 mg, 55%) was obtained as a colorless oil: $[\alpha]^{22}_D$ −37.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.87 (m, 1H), 2.29 (m, 1H), 2.51 (m, 1H), 2.74 (m, 2H), 2.96 (m, 1H), 3.08 (m, 1H), 3.37−3.49 (m, 4H), 3.50−3.67 (m, 8H), 4.07 (br s, 1H), 5.06 (m, 10H), 7.28 (m, 25H); ^{13}C NMR ($CDCl_3$) δ 33.4, 51.3, 52.66, 52.71, 52.77, 54.9, 59.8, 61.9, 62.0, 62.6, 66.0, 66.1, 66.3, 66.4, 127.97, 128.04, 128.1, 128.17, 128.20, 128.3, 128.40, 128.44, 128.5, 135.51, 135.53, 135.58, 135.60, 170.1, 171.5, 172.2, 172.5. Anal. Calcd for $C_{51}H_{55}N_3O_{11}$: C, 69.1; H, 6.3; N, 4.7. Found: C, 68.8; H, 6.3; N, 4.7.

***N*-[Carboxymethyl]-*N*-[(2*S*,4*S*)-4-[2-(carboxy)-*N*-[carboxymethyl]pyrrolidinyl]]-(2*R*)-*N*,*N*-[bis(carboxymethyl)amino]-3-hydroxypropylamine (3).** To a degassed solution of **38** (400 mg, 0.45 mmol) in MeOH (40 mL) and H_2O (6 mL) was added Pearlman's catalyst (45% moisture, 20% $Pd(OH)_2$ dry weight, 400 mg). The mixture was shaken on a Parr apparatus at 50 psi of H_2 for 13 h, the catalyst was removed by filtration through a bed of Celite and washed with H_2O (4 mL), and the filtrate was partially evaporated at 35 °C to afford an aqueous solution. Water (19 mL) was then added and the solution slowly evaporated to dryness at 40 °C to give a pink gum which upon further drying under high vacuum afforded **3** (192 mg, 98%) as a pale pink solid: mp 112−114 °C dec; $[\alpha]^{22}_D$ −2.1 (*c* 0.9, H_2O); ^{1}H NMR (D_2O + 3 drops of Tf_2O) δ 2.05 (m, 1H), 2.73 (m, 1H), 2.90 (m, 1H), 3.01 (m, 1H), 3.47−3.70 (m, 3H), 3.73−3.93 (m, 4H), 4.13 (m, 1H), 4.24 (AB_q, J = 17.0 Hz, 2H), 4.28 (s, 4H), 4.43 (dd, J = 11.8, 6.5 Hz, 1H); ^{13}C NMR (D_2O) δ 29.5, 49.7, 51.1, 54.5, 56.2, 57.2, 57.9, 59.1, 63.1, 68.0, 169.8, 170.9, 171.8, 174.5. MS (FAB, G) *m*/*z* 436 $(M + H)^+$. Anal. Calcd for $C_{16}H_{25}N_3O_{11}\cdot{}^1/_2H_2O$: C, 43.2; H, 5.9; N, 9.5. Found: C, 42.8; H, 5.5; N, 9.0.

4-[(Benzyloxycarbonyl)methyl]-(5*R*)-aminomethyl-[*N*-(benzyloxycarbonyl)methyl-*N*-[(2*S*,4*S*)-4-[2-(benzyloxycarbonyl)-*N*-[(benzyloxycarbonyl)methyl]pyrrolidinyl]]]-2-morpholinone (39). To a solution of **38** (14/1 mixture with lactone **39**, 570 mg, 0.64 mmol) in benzene (30 mL) was added *p*-TsOH·H_2O (6 mg, 0.032 mmol), and the mixture was heated at reflux for 2 h. The solvent was evaporated and the residue chromatographed (3/2 hexanes/EtOAc) to afford **39** (455 mg, 91%) as a pale yellow oil: $[\alpha]^{22}_D$ −49.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.01 (m, 1H), 2.40 (m, 1H), 2.64 (dd, J = 13.7, 8.5 Hz, 1H), 2.83−2.94 (m, 2H), 3.18 (m, 2H), 3.40−3.81 (m, 10H), 4.35 (dd, J = 11.5, 5.5 Hz, 1H), 4.45 (dd, J = 11.6, 3.9 Hz, 1H), 5.20 (m, 8H), 7.41 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 33.4, 51.3, 51.8, 52.7, 53.5, 54.0, 55.6, 60.6, 62.6, 66.1, 66.2, 66.31, 66.34, 68.6, 128.1, 128.17, 128.21, 128.24, 128.31, 128.35, 128.45, 128.47, 128.51, 135.3, 135.49, 135.54, 135.6, 169.5, 170.2, 170.3, 171.2, 172.5. Anal. Calcd for $C_{44}H_{47}N_3O_{10}$: C, 67.9; H, 6.1; N, 5.4. Found: C, 67.7; H, 5.9; N, 5.3.

***N*-[(Benzyloxycarbonyl)methyl]-*N*-[(2*S*,4*S*)-4-[2-(benzyloxycarbonyl)-*N*-[(benzyloxy-carbonyl)methyl]pyrrolidinyl]]-(2*R*)-*N*,*N*-[bis[(benzyloxycarbonyl)methyl]amino]-3-hydroxy-*O*-[[*N*-(*tert*-butyloxycarbonyl)]aminoacetyl]propylamine (41).** To a stirred mixture of *N*-BOC-glycine (149 mg, 0.85 mmol) and DMAP (11 mg, 0.09 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C was added DCC (175 mg, 0.85 mmol). After the mixture was stirred at 0 °C for 5 min, a solution of **38** (14/1 mixture with lactone **39**, 500 mg, 0.56 mmol) in CH_2Cl_2 (7 mL) was added dropwise. A reaction temperature of 0 °C was maintained for 30 min, and then the reaction was allowed to warm to rt. The solvents were evaporated, Et_2O (80 mL) was added, the white precipitate was removed by filtration, and the filtrate was washed with saturated $NaHCO_3$ (60 mL) and brine (60 mL). Drying, filtering, and evaporating left a residue which was chromatographed (2/1 Et_2O/hexanes) to afford **41** (477 mg, 81%) as a colorless oil: $[\alpha]^{22}_D$ −31.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.86 (m, 1H), 2.26 (m, 1H), 2.61 (m, 1H), 2.81 (m, 2H), 3.09 (m, 2H), 3.39−3.68 (m, 10H), 3.82 (br d, 2H), 4.24 (m, 2H), 5.06 (m, 10H), 5.25 (m, 1H), 7.30 (m, 25H); ^{13}C NMR ($CDCl_3$) δ 28.2, 33.8, 42.4, 51.3, 52.7, 52.8, 55.2, 59.2, 60.4, 62.6, 64.2, 66.0, 66.1, 66.2, 66.3, 79.5, 128.0, 128.15, 128.19, 128.21, 128.24, 128.4, 128.5, 135.55, 135.62, 135.7, 155.6, 170.1, 170.3, 171.5, 171.6, 172.6. Anal. Calcd for $C_{58}H_{66}N_4O_{14}$: C, 66.8; H, 6.4; N, 5.4. Found: C, 67.0; H, 6.6; N, 5.3.

***N*-[Carboxymethyl]-*N*-[(2*S*,4*S*)-4-[2-(carboxy)-*N*-[carboxymethyl]pyrrolidinyl]]-(2*R*)-*N*,*N*-[bis(carboxymethyl)amino]-3-hydroxy-*O*-[[*N*-(*tert*-butoxycarbonyl)]aminoacetyl]propylamine (42).** To a degassed solution of **41** (432 mg, 0.41 mmol) in MeOH (41 mL) and H_2O (5.1 mL) was added Pearlman's catalyst (45% moisture, 20% $Pd(OH)_2$ dry weight, 432 mg). The mixture was shaken on a Parr apparatus at 50 psi of H_2 for 10 h, the catalyst was removed by filtration through a bed of Celite and washed with H_2O (3 mL), and the filtrate was partially evaporated at 25 °C to afford an aqueous solution. Water (5 mL) was then added and the solution slowly evaporated to dryness at 40 °C to give a pale yellow gum which upon further drying under high vacuum afforded **42** (243 mg, 99%) as a pale yellow solid: mp 125−127 °C dec; $[\alpha]^{22}_D$ +4.1 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 1.41 (s, 9H), 2.10 (m, 1H), 2.76 (m, 1H), 3.22 (m, 2H), 3.61−3.98 (m, 12H), 4.15−4.51 (m, 5H); ^{13}C NMR (D_2O) δ 28.3, 29.8, 42.7, 51.1, 51.9, 54.2, 55.8, 56.9, 59.8, 61.9, 67.5, 82.3, 158.7, 170.1, 171.7, 172.1, 172.3, 173.1; MS (FAB, TG/G) *m*/*z* 615 (M + Na), 593 (M + H). Anal. Calcd for $C_{23}H_{36}N_4O_{14}\bullet H_2O$: C, 45.3; H, 6.3; N, 9.2. Found: C, 45.3; H, 6.4; N, 9.0.

Acknowledgment. We thank Al Mical of the DuPont Pharmaceuticals Co. for his most generous and expert assistance in determining enantiomeric purities by chiral HPLC.

JO000071G