Table II. Localized MNDO Geometry

atom pair[a]	dist, Å	bond order	two-center energy, eV
1, 12	1.4743	1.0477	-16.698
4, 12	1.3722	1.8111	-22.867
1, 11	1.5231	0.9631	-14.717
4, 5	1.5143	0.9697	-15.200
1, 2	1.5345	0.9430	-13.012
3, 4	1.5447	0.9515	-14.114
2, 3	1.5402	0.9737	-14.641
10, 11	1.5653	0.9744	-13.875
5, 6	1.5806	0.9587	-13.841
1, 9	1.6969	0.8128	-8.143
4, 7	2.1814	0.0458	+0.254

[a] For atom numbering, see Table I.

cule,[11] SCF theory is not capable of giving an accurate description of the delocalized form and at least a simple 2 × 2 configuration interaction (CI) involving the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals is necessary.

Results

Initial MNDO–SCF calculations on compounds **3** indicated that only the localized structures are minima on the potential energy surface. The delocalized structure **3b** was only optimized by imposing the necessary symmetry constraints. This structure is a transition structure between the two localized forms and is 3.22 kcal/mol higher in energy. The MNDO-based 2 × 2 CI results also give the localized forms as minima but now the symmetric form is also a minimum. The calculated ΔH_f was 108.245 kcal/mol for the localized form and 98.877 kcal/mol for the symmetric form. More importantly, the symmetric form is 10.37 kcal/mol *lower* in energy than the localized forms. The geometries of the CI-optimized structures are given in Tables I and II.

Like the MNDO calculations the AM1–CI results indicated the symmetric form as the minimum-energy form. However, neither the AM1–SCF method nor the AM1 2 × 2–CI method was able to find a stable localized structure. The geometry of the AM1 results is given in Table I and the calculated ΔH_f is 117.049 kcal/mol. As a test of the AM1 procedure and for comparison with experimental results, calculations were done on semibullvalene itself. These results indicate the localized forms (ΔH_f(AM1) = 83.303 kcal/mol) are the minimum-energy forms with the symmetric geometry (ΔH_f(AM1) = 87.470 kcal/mol) being a transition structure. The AM1 barrier of 4.17 kcal agrees well with the previous MNDO calculation of 5.7 kcal and the experimental results of 4.8 kcal.[11]

The question that remains is whether or not the predicted symmetric double-annelated semibullvalene is homoaromatic. It is true that the ring strain and anti-Bredt character of the localized geometries will cause them to be of high energy. However, there must be some interaction causing the molecule to adopt a symmetric geometry and this may be homoaromatic stabilization. The degree of stabilization (or destabilization) associated with a particular interaction can be indicated by using the energy partitioning from the MOPAC program into one-center (atomic) and two-center (bond) terms.[18] As can be seen (Tables I and II) typical stabilizations associated with the semibullvalene type single bonds (e.g., 2–3) are approximtely −14 eV. Although the 1–9 and 4–7 interactions are much weaker it is apparent that in the symmetric (homoaromatic) system **3b** they are a stabilizing effect. For the localized form found in the MNDO calculations the 1–9 interaction is very stabilizing (corresponding to a single bond) and the 4–7 interaction is now destabilizing. It should be pointed out that the computed bond orders also indicate a favorable 1–9 and 4–7 interaction in the symmetric molecule. We, therefore, conclude that not only does the bisannelated semibullvalene **3** display appreciable homoconjugation but also that this homoconjugation is energy lowering and, therefore, **3** joins the elite ranks as a rare example of a neutral homoaromatic (ground state) hydrocarbon.

The disagreement between the MNDO and AM1 methods on the existence of a stable localized structure for the double-annelated semibullvalene **3a** is of some concern. To answer this question properly would require a more complete search of the potential energy surface in order to locate transition structures and other possible minima. Currently, this is not feasible with our version of the MOPAC program. We are, however, interested in exploring the differences between AM1 and MNDO and continuing our studies in this area by encorporating new searching routines in the MOPAC program.

Further studies are also under way using ab initio methods. It has been shown previously that to get qualitative information on other homoaromatic systems via ab inito methods, it may be necessary to use very good basis sets (including polarization function) and also to include electron correlation.[19,20] The inclusion of correlation at the second-order Moller–Plessett (MP2) level has been shown to have a dramatic effect on systems of this type.

Acknowledgment. We acknowledge computer support for this work provided by the Center for Earthquake Research and Information at Memphis State University.

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A Stereospecific Synthesis of 3-Aminodeoxystatine[1]

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Pepstatin (**1**), first isolated by Umezawa and co-workers in 1970,[2] is a pentapeptide that exhibits extremely potent inhibitory activity with a majority of the enzymatic family of aspartyl proteinases (for example, a K_i of 4.6×10^{-11} M vs pepsin[3]). Mechanistically, **1** derives its activity from

Iva-Val-Val-Sta-Ala-Sta-OH
1

the unusual amino acid statine (**2**), (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid, which functions either as a "transition state"[4] or "collected substrate"[5] insert

(1) Presented, in part, at the 20th National Medicinal Chemistry Symposium, Chapel Hill, NC, June 18, 1986, Abstract #34.

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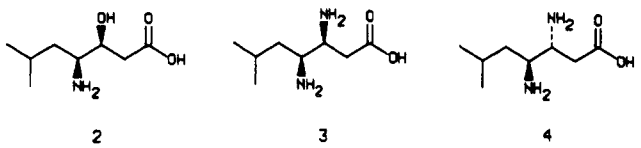
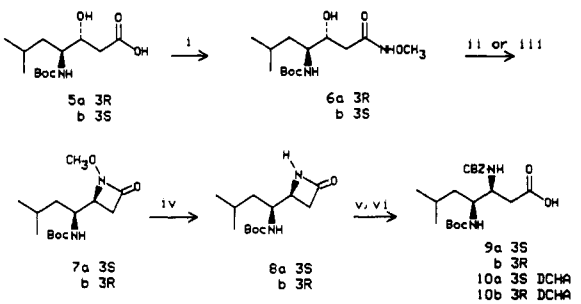


2 3 4

Figure 1. Statine (2) and isosteric analogues 3 and 4.

Scheme I (only a series stereochemistry shown)[a]



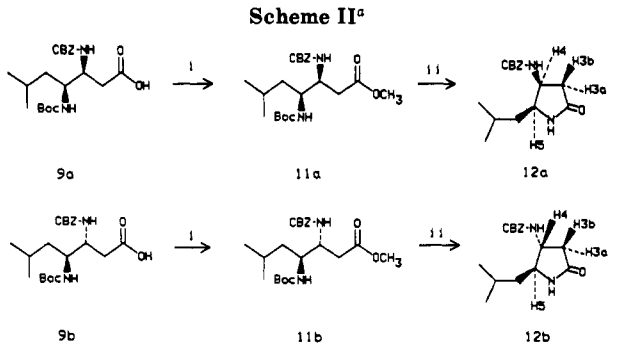
[a] Reaction conditions: (i) NH_2OCH_3·HCl, Et_3N, CH_2Cl_2; (ii) triphenylphosphine, DEAD, THF; (iii) MsCl, Pyr, then K_2CO_3, acetone; (iv) Na, NH_3, THF; (v) KOH, MeOH, H_2O; (vi) 1 M K_2CO_3, CBZCl.

based on its structural analogy to the metastable intermediate proposed in the amide bond hydrolysis mechanism of aspartyl proteinases. Of particular interest within this class has been the enzyme renin, a member of the renin-angiotensin cascade, whose inhibition may offer a useful treatment for human hypertension.[6]

This concept of transition-state analogy[7] has prompted a great deal of research in an effort to determine which electronic and structural parameters are important in designing effective statine analogues.[8] Our intent was the design and stereospecific synthesis of isosterically modified statine residues that may shed light on the importance of hydrogen-bonding and electrostatic interactions in this series of enzymatic inhibitors.[9] This note reports the stereospecific synthesis of two such analogues, (3*S*,4*S*)- and (3*R*,4*S*)-3-aminodeoxystatine (**3** and **4**), respectively[10] (Figure 1).

While literature procedures exist for the synthesis of β-amino acids,[11] we desired a stereochemically defined synthesis from starting materials of known absolute configuration which would eliminate the need for diastereomeric separations. This approach relied on the inversion of the β-hydroxyl of **5a** and **5b**, readily available through literature procedures,[12,13] with a nitrogen nucleophile that could easily be converted to a suitably protected form, as in **9a**. We chose to utilize the stereospecific intramolecular Mitsunobu[14] approach developed by Miller et al.[15] to provide the desired stereochemistry at the β position as shown in Scheme I. In this variant of the Mitsunobu reaction a β-hydroxy-*O*-alkyl hydroxamate is cyclized wherein the *O*-alkyl hydroxamate moiety functions as the internal nucleophile and the resulting product is a functionalized β-lactam as shown in Scheme I. This reaction succeeds because the pK_a of the *O*-alkyl hydroxamate group (pK_a = 9–10) is below that of the conjugate base of dicarbethoxyhydrazide (threshold $pK_a \leq 13$).[15]

Scheme II[a]



[a] Reaction conditions: (i) DBU, CH_3I, CH_3CN; (ii) TBSOTf, CH_2Cl_2, then saturated $NaHCO_3$.

Condensation of **5a** with *O*-methylhydroxylamine hydrochloride gave the crystalline *O*-methyl hydroxamate **6a** in 58% yield. Intramolecular Mitsunobu cyclization of **6a** was conducted by utilizing the standard reagents[16] to deliver the *N*-methoxy-β-lactam **7a** in 70% yield after chromatography on silica gel. Reductive removal of the amide methoxy[17] gave **8a**, which was subjected to aqueous potassium hydroxide to cleave the β-lactam ring and neutralized and the free amino moiety was protected as the benzyloxycarbonyl (CBZ) urethane. The crude acid **9a** was most conveniently purified by the formation of the crystalline dicyclohexylamine (DCHA) salt **10a**. This series of reactions thus resulted in the synthesis of **3** in a suitably protected form that allowed further synthetic manipulation.

With the 3*S* diastereomer **9a** in hand, the sequence was repeated to prepare the 3*R* isomer **9b**. Boc-statine (**5b**) was straightforwardly converted to the *O*-methyl hydroxamate **6b**; however, the cyclization conditions of DEAD/triphenylphosphine were replaced with the two-step procedure developed by Floyd et al.[17] The chromatographic removal of the byproducts of the Mitsunobu reaction, triphenylphosphine and dicarboethoxyhydrazide, had become exceedingly difficult on a large scale; thus the procedure of β-mesylation followed by cyclization mediated by potassium carbonate was utilized to prepare the *N*-

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methoxylactam **7b**. This intermediate was subjected to the same reduction/hydrolysis/protection protocol to provide the desired **10b** as a white crystalline product. We had, to this point, relied on literature precedent in the assignment of the absolute stereochemistry of **9a** and **9b**. Carbon-13 NMR spectra on both **6a** and **7a** had shown that a single diastereomer (**7a**) had been prepared from a diastereomerically pure starting material (**6a**). Miller's[15] studies had reported that these intramolecular reactions proceeded with inversion of configuration at the reaction center. The acids **9a** and **9b** were converted to the lactams **12a** and **12b**, respectively, as shown in Scheme II, to verify that inversion had occurred and the structural assignments presented in Scheme I were correct.

The free acids were converted into their methyl esters[18] and cyclized to the lactams by utilizing *tert*-butyldimethylsilyl trifluoromethanesulfonate followed by an aqueous bicarbonate workup. The cyclization most likely proceeded via an *N*-silyl intermediate that closed intramolecularly under the catalysis of the excess triflate. High field (500 MHz) NOE studies were then carried out to determine the relationship between the protons at carbons 4 and 5 in **12a** and **12b**. Irradiation of proton H4 in **12a** resulted in NOE's of 7.1% to H5 and 8.6% to H3a, while irradiation of H5 resulted in NOE's of 11.4% to H4 and 1.9% to H3a. Irradiation of H4 in **12b** gave only a 1.3% NOE to H5 and irradiation of H5 gave a 1.8% NOE to H4. This evidence verified the cis relationship of protons H5 and H4 in **12a** (trans in **12b**), the integrity of the inversion during intramolecular cyclization, and the absolute stereochemistry of the structures assigned to the products **9a** (3*S*,4*S*) and **9b** (3*R*,4*S*).

The initial goal of this effort was the development of a stereospecific synthesis of the statine isosteres **3** and **4**, which were suitably protected for further synthetic elaboration. We have accomplished this objective with the synthesis of the 3-aminodeoxystatine derivatives **9a** and **9b**. Further research directed toward the utilization of these intermediates in inhibition studies of the biologically important aspartyl proteinases has been published elsewhere.[1,19]

Experimental Section

Mass spectra, infrared spectra, optical rotations, combustion analyses, and high field ^{1}H NMR spectra at 200 MHz and 500 MHz were obtained by the Physical and Analytical Chemistry Department of The Upjohn Company. Other ^{1}H NMR spectra were determined on a Varian CFT-20 spectrophotometer at 80 MHz and chemical shifts are reported as δ units relative to tetrmethylsilane. Melting points are uncorrected.

Thin-layer chromatography was conducted with Analtech 0.25-mm glass plates precoated with silica gel GF. For column chromatography, E. Merck silica gel 60, 230–400 mesh, or E. Merck prepacked Lobar columns were used. All solvents for chromatography were Burdick and Jackson reagent grade distilled in glass.

Tetrahydrofuran was distilled under argon from sodium metal in the presence of benzophenone. Dichloromethane was distilled from calcium hydride. Diethyl phosphorocyanidate[20] was freshly distilled before use.

(3*R*,4*S*)-3-Hydroxy-4-[[(1,1-dimethylethoxy)carbonyl]-amino]-6-methylheptanoic acid (**5a**) and its 3*S*,4*S* isomer **5b** were prepared by the method of Rich et al.[13]

(1*S*,2*R*)-[2-Hydroxy-4-(methoxyamino)-1-(2-methylpropyl)-4-oxobutyl]carbamic Acid 1,1-Dimethylethyl Ester (6a). A solution of **5a** (5.0 g, 18.2 mmol), *O*-methylhydroxylamine hydrochloride (1.67 g, 20.0 mmol), and diethyl phosphorocyanidate (3.26 g, 20.0 mmol) in dichloromethane (100 mL) was stirred at 0 °C under argon and triethylamine (5.31 mL, 38.2 mmol) added via syringe over a period of 5 min. The reaction mixture was stirred at 0 °C for 1 h, poured into water, washed with brine, dried (anhydrous sodium sulfate), and concentrated to give a crude, crystalline product. Recrystallization of the residue from diethyl ether gave 3.2 g (58%) of **6a** as a fluffy white solid, mp 134–5 °C (from ether): $[\alpha]^{25}_D$ −13.5° (*c* 0.892, MeOH); IR (cm^{-1}, mull) 3334, 3270, 3040, 1680, 1668, 1535, 1389, 1174; ^{1}H NMR (80 MHz, $CDCl_3$) δ 9.42 (br s, 1 H), 4.57 (d, J = 8 Hz, 1 H), 3.78–3.48 (m, 1 H), 3.77 (s, 3 H), 3.48–2.93 (m, 2 H), 2.30 (dd, J = 1.4, 3.5 Hz, 2 H), 1.60–0.91 (m, 3 H), 1.44 (s, 9 H), 0.92 (d, J = 6.0 Hz, 3 H), 0.90 (d, J = 6.0 Hz, 3 H); MS (CI, isobutane), *m/z* (relative intensity) 305 $[M + H]^+$ (100), 249 (60), 609 (32), 306 (18), 189 (13). Anal. Calcd for $C_{14}H_{28}N_2O_5$: C, 55.14; H, 9.20; N, 9.20. Found: C, 54.94; H, 9.33; N, 9.14.

(1*S*,2*S*)-[2-Hydroxy-4-(methoxyamino)-1-(2-methylpropyl)-4-oxobutyl]carbamic Acid 1,1-Dimethylethyl Ester (6b). The synthesis of **6b** was carried out as described above for **6a** starting with **5b** (2.50 g, 9.1 mmol). Recrystallization from ethyl acetate/hexane provided **6b** (1.85 g, 67%), mp 92.5–94.5 °C: IR (mull, cm^{-1}) 3280, 3203, 1685, 1664, 1443, 1399, 1341, 1171; ^{1}H NMR (80 MHz, $CDCl_3$) δ 8.20 (br s, 1 H), 4.78 (d, J = 10 Hz, 1 H), 4.16–3.79 (m, 1 H), 3.75 (s, 3 H), 3.75–3.35 (m, 1 H), 2.27 (d, J = 6.3 Hz, 2 H), 1.88–1.09 (m, 3 H), 1.44 (s, 9 H), 0.90 (d, J = 5.8 Hz, 6 H); MS (EI), *m/z* (relative intensity) 86 (100), 130 (87), 57 (85), 118 (51), 140 (30). Anal. Calcd for $C_{14}H_{28}N_2O_5$: C, 55.14; H, 9.20; N, 9.20. Found: C, 55.37; H, 9.37; N, 9.24.

(1*S*,2*S*)-[1-(1-Methoxy-4-oxo-2-azetidinyl)-3-methylbutyl]carbamic Acid 1,1-Dimethylethyl Ester (7a). A solution of **6a** (304 mg, 1.0 mmol) and triphenylphosphine (524 mg, 2.0 mmol) in dry THF (5 mL) was stirred at room temperature under argon and diethyl azodicarboxylate (0.32 mL, 4.0 mmol) added via syringe. The reaction mixture was stirred for 30 min, concentrated in vacuo, and chromatographed on silica gel (elution with ethyl acetate/hexane 1:2) to deliver 200 mg (70%) of **7a** as a white crystalline solid, mp 96.5–97.5 °C (hexane/diethyl ether): $[\alpha]^{25}_D$ −76.2° (*c* 0.795, MeOH); IR (mull, cm^{-1}) 3348, 2951, 1797, 1792, 1682, 1537, 1250, 1176; ^{1}H NMR (80 MHz, $CDCl_3$) δ 4.55–4.17 (m, 1 H), 4.17–3.60 (m, 2 H), 3.78 (s, 3 H), 2.60 (dd, J = 12.6, 4.7 Hz, 1 H), 2.56 (dd, J = 12.6, 2.8 Hz, 1 H), 1.88–1.09 (m, 3 H), 1.43 (s, 9 H), 0.94 (d, J = 6.2 Hz, 6 H); MS (CI, NH_3), *m/z* (relative intensity) 248 (100), 304 $[M + NH_4]^+$ (95), 204 (29), 266 (21), 305 (16). Anal. Calcd for $C_{14}H_{26}N_2O_4$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.85; H, 9.29; H, 9.80.

(1*S*,2*R*)-[1-(1-Methoxy-4-oxo-2-azetidinyl)-3-methylbutyl]carbamic Acid 1,1-Dimethylethyl Ester (7b). A cold (0 °C) solution of **6b** (1.20 g, 3.95 mmol) in dry pyridine (10 mL) was stirred under argon and methanesulfonyl chloride (0.62 mL, 8.0 mmol) added via syringe. The reaction mixture was stirred at 0 °C for 2 h, poured into brine, and extracted with ethyl acetate. The extracts were combined, dried with anhydrous sodium sulfate, and concentrated. The red residue so obtained was dissolved in acetone (20 mL), anhydrous potassium carbonate (1.0 g, 7.2 mmol) was added, and the slurry was refluxed for 72 h. The solution was cooled, diluted with ethyl acetate, filtered through a medium porosity scintered glass funnel, and concentrated. Chromatography of the residue on silica gel (Merck Lobar B, elution with ethyl acetate/hexane 1:3) gave 680 mg (60%) of **7b** as a slightly yellow oil: IR (film, cm^{-1}) 3342, 2958, 1777, 1708, 1691, 1526, 1366, 1250, 1170; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.46 (d, J = 10 Hz, 1 H), 4.14–3.95 (m, 1 H), 3.90–3.82 (m, 1 H), 3.83 (s, 3 H), 2.77 (dd, J = 14.3, 5.4 Hz, 1 H), 2.52 (dd, J = 14.3, 3.0 Hz, 1 H), 1.73 (sep, J = 7.2 Hz, 1 H), 1.45 (s, 9 H), 1.35–1.20 (m, 2 H), 0.96 (d, J = 6.6 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H); MS (FAB), *m/z* (relative intensity) 187 (100), 57 (44), 231 (38), 154 (18), 140 (13), 128 (12); exact mass calcd for $C_{14}H_{26}N_2O_4$ 287.1971, obsd 287.1964.

(1*S*,2*S*)-[1-(4-Oxo-2-azetidinyl)-3-methylbutyl]carbamic Acid 1,1-Dimethylethyl Ester (8a). Sodium (75 mg, 3.1 mmol) was added to a cold (−78 °C) solution of dry ammonia (20 mL), and the mixture was stirred for 15 min until all the metal had dissolved. A solution of **7a** (200 mg, 0.7 mmol) in dry THF (5 mL) was slowly added, and the reaction mixture was allowed to warm to reflux (−33 °C). After 30 min, solid ammonium chloride (200 mg, 3.7 mmol) was added, and the resulting solution was

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allowed to warm to room temperature over a period of 2 h. The residue was diluted with ethyl acetate (50 mL), washed with water, dried (anhydrous sodium sulfate), and concentrated to deliver 180 mg (100%) of **8a** as a clear colorless oil: $[\alpha]^{25}_D$ −26.6° (*c* 1.09, MeOH); IR (film, cm^{-1}) 3317, 2956, 1761, 1707, 1685, 1535, 1367, 1252; ^1H NMR (80 MHz, $CdCl_3$) δ 6.15 (br s, 1 H), 4.53 (d, *J* = 9.3 Hz, 1 H), 4.03–3.53 (m, 2 H), 2.89 (dd, *J* = 2.3, 4.6 Hz, 1 H), 2.77 (d, *J* = 1.7 Hz, 1 H), 1.90–1.58 (m, 1 H), 1.44–1.11 (m, 2 H), 1.44 (s, 9 H), 0.93 (d, *J* = 6.3 Hz, 6 H); MS (CI, NH_3), *m/z* (relative intensity) 274 $[M + NH_4]^+$ (100), 69 (43), 124 (16), 218 (13), 94 (6); exact mass calcd for $C_{13}H_{24}N_2O_3$ 256.1787, obsd 256.1794.

(1*S*,2*R*)-[1-(4-Oxo-2-azetidinyl)-3-methylbutyl]carbamic Acid 1,1-Dimethylethyl Ester (8b). The synthesis of **8b** was carried out as described above for **8a**, starting with **7b** (4.70 g, 16.4 mmol). Chromatography on silica gel (elution with ethyl acetate/hexane 2:1) provided **8b** (3.76 g, 90%) as a white crystalline solid, mp 135.5–137 °C (from ethyl acetate/hexane): $[\alpha]^{24}_D$ −38.3° (*c* 1.00, MeOH); IR (mull, cm^{-1}) 3381, 3198, 1748, 1718, 1680, 1512, 1252, 1162; ^1H NMR (200 MHz, $CDCl_3$) δ 5.96 (br s, 1 H), 4.40 (d, *J* = 9.0 Hz, 1 H), 3.94 (m, 1 H), 3.63 (dt, *J* = 2.6, 4.6 Hz, 1 H), 2.92 (dd, *J* = 4.7, 15.4 Hz, 1 H), 2.70 (m, 1 H), 1.84–1.62 (m, 1 H), 1.46 (s, 9 H), 1.30–1.18 (m, 2 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 0.95 (d, *J* = 6.2 Hz, 3 H); MS (EI), *m/z* (relative intensity) 57 (100), 86 (89), 130 (57), 186 (32), 71 (14). Anal. Calcd for $C_{13}H_{24}N_2O_3$: C, 60.91; N, 9.44; N, 10.93. Found: C, 60.71; H, 9.30, N, 10.81.

(3*S*,4*S*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-6-methyl-3-[[(phenylmethoxy)carbonyl]amino]heptanoic Acid (9a). A solution of **8a** (466 mg, 1.8 mmol) and potassium hydroxide (10 mL of 1 N solution, 10 mmol) in methanol (10 mL) was stirred at room temperature for 3 h, cooled to 0 °C, neutralized with 6 N HCl, and concentrated. The residue was dissolved in DMF (5 mL), potassium carbonate added (10 mL of 1 M solution, 10 mmol), and the solution cooled to 0 °C. CBZCl (0.64 mL, 4.5 mmol) was added, the ice bath removed after 4 h, and the solution stirred at room temperature for 48 h. The reaction mixture was washed with diethyl ether, acidified to pH 2 with 6 N HCl, and extracted with dichloromethane. The extracts were combined, dried with anhydrous magnesium sulfate, and concentrated to give 750 mg (100%) of **9a** as a slightly yellow oil (crystalline analytical sample obtained upon acidification of the DCHA salt, mp 133–4.5 °C (lit.[10] mp 128–130 °C): $[\alpha]^{25}_D$ −43.5° (*c* 0.575, MeOH) (lit.[10] $[\alpha]^{25}_D$ −46.1° (*c* 0.5, MeOH)); IR (film cm^{-1}) 3310, 2940, 1690, 1500, 1230, 1150; ^1H NMR (80 MHz, $CDCl_3$) δ 9.24 (br s, 1 H), 7.30 (s, 5 H), 6.86–5.36 (m, 1 H), 5.07 (s, 2 H), 5.08–4.50 (m, 1 H), 4.22–3.47 (m, 2 H), 2.64–2.37 (m, 2 H), 1.70–0.79 (m, 3 H), 1.39 (s, 9 H), 0.87 (d, *J* = 6.0 Hz, 6 H); MS (EI), *m/z* (relative intensity) 91 (100), 86 (57), 54 (43), 186 (21), 136 (14), 408 (M^+, 4). Anal. Calcd for $C_{21}H_{32}N_2O_6$: C, 61.75; H, 7.90; N, 6.86. Found: C, 61.76; H, 8.06, N, 6.87.

(3*R*,4*S*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-6-methyl-3-[[(phenylmethoxy)carbonyl]amino]heptanoic Acid (9b). The synthesis of **9b** was carried out as described above for **9a** starting with **8b** (2.16 g, 8.4 mmol) to provide **9b** (3.40 g, 100%) as an off-white powder (crystalline analytical sample obtained upon acidification of the DCHA salt, mp 198–200 °C (lit.[10] mp 203–5 °C: $[\alpha]^{25}_D$ −3.3° (*c* 1.0, MeOH) (lit.[10] $[\alpha]^{25}_D$ −3.6° (*c* 0.5, MeOH)); ^1H NMR (80 MHz, $CDCl_3/CD_3OD$ 1:1) δ 7.32 (s, 5 H), 5.94 (m, 1 H), 5.09 (s, 2 H), 5.19–4.82 (m, 1 H), 3.79 (m, 2 H), 2.51 (m, 2 H), 1.42 (s, 9 H), 1.61–1.10 (m, 3 H), 0.92 (d, *J* = 6.1 Hz, 3 H), 0.88 (d, *J* = 6.2 Hz, 3 H); MS (EI), *m/z* (relative intensity) 57 (100), 86 (66), 91 (66), 130 (42), 139 (17), 186 (17).

(3*S*,4*S*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-6-methyl-3-[[(phenylmethoxy)carbonyl]amino]heptanoic Acid with *N*-Cyclohexylcyclohexanamine (10a). A solution of **9a** (1.44 g, 3.52 mmol) was stirred at room temperature in diethyl ether (20 mL) under argon and freshly distilled dicyclohexylamine (905 mg, 5.0 mmol) added via syringe. The resulting solution was stirred at room temperature overnight and the product filtered and dried to deliver 927 mg (45%) of **10a** as a white crystalline solid, mp 150–152 °C (ethyl acetate): $[\alpha]^{25}_D$ −28.5° (*c* 0.789, MeOH); IR (mull, cm^{-1}) 3324, 1923, 1723, 1713, 1538, 1451, 1255; MS (CI, NH_3), *m/z* (relative intensity) 426 $[M + NH_4]^+$ (100), 275 (54), 182 (25), 427 (24), 308 (13). Anal. Calcd for $C_{33}H_{55}N_3O_6$: C, 67.20; H, 9.40; N, 7.13. Found: C, 66.93; H, 9.59; N, 6.94.

(3*S*,4*R*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-6-methyl-3-[[(phenylmethoxy)carbonyl]amino]heptanoic Acid with *N*-Cyclohexylcyclohexanamine (10b). The synthesis of **10b** was carried out in ethyl acetate as described above for **10a** starting with **9b** (95 mg, 0.23 mmol) to give **10b** (96 mg, 71%) as an analytically pure solid, mp 166–167.5 °C (ethyl acetate): IR (mull, cm^{-1}) 3427, 3316, 1710, 1681, 1639, 1550, 1515, 1238; MS (CI, NH_3), *m/z* (relative intensity) 275 (100), 426 $[M + NH_4]^+$ (68), 382 (25), 308 (19), 427 (18). Anal. Calcd for $C_{33}H_{55}N_3O_6$: C, 67.20; H, 9.40; N, 7.13. Found: C, 67.19; H, 9.44; N, 7.04.

Methyl (3*S*,4*S*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-6-methyl-3-[[(phenylmethoxy)carbonyl]amino]heptanoate (11a). A solution of **9a** (17 mg, 0.042 mmol), methyl iodide (8.2 mg, 0.058 mmol), and DBU (9.5 mg, 0.067 mmol) in acetonitrile (1 mL) was stirred at room temperature under argon for 72 h. The reaction mixture was concentrated, passed through a Waters Sep-Pak (silica, elution with 9:1 hexane/ethyl acetate), and evaporated to give 12 mg (68%) of **11a** as a clear colorless oil: $[\alpha]^{25}_D$ −39.5° (*c* 0.597, MeOH); IR (mull, cm^{-1}) 3357, 1741, 1697, 1518, 1249, 1173; ^1H NMR (80 MHz, $CDCl_3$) δ 7.32 (s, 5 H), 5.42 (m, 1 H), 5.08 (s, 2 H), 4.48 (m, 1 H), 4.23–3.53 (m, 2 H), 3.64 (s, 3 H), 2.56 (m, 2 H), 1.83–1.07 (m, 3 H), 1.40 (s, 9 H), 0.90 (d, *J* = 6.2 Hz, 3 H), 0.88 (d, *J* = 6.2 Hz, 3 H); MS (FAB), *m/z* (relative intensity) 423 $[M + H]^+$; exact mass calcd for $C_{22}H_{34}N_2O_6$ 423.2495, obsd 423.2508.

Methyl (3*R*,4*S*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-6-methyl-3-[[(phenylmethoxy)carbonyl]amino]heptanoate (11b). The synthesis of **11b** was carried out as described above for **11a** starting with **9b** (20 mg, 0.049 mmol) to provide **11b** (19 mg, 82%) as a white crystalline solid: ^1H NMR (80 MHz, $CDCl_3$) δ 7.33 (s, 5 H), 5.61 (m, 1 H), 5.10 (s, 2 H), 4.38 (m, 1 H), 4.16–3.50 (m, 2 H), 3.64 (s, 3 H), 2.54 (d, *J* = 5.2 Hz, 2 H), 1.80–1.23 (m, 3 H), 1.42 (s, 9 H), 0.90 (d, *J* = 6.1 Hz, 3 H), 0.88 (d, *J* = 6.0 Hz, 3 H); MS (FAB), *m/z* (relative intensity) 423 $[M + H]^+$; exact mass calcd for $C_{22}H_{34}N_2O_6$ 423.2495, obsd 423.2528.

(4*S*,5*S*)-4-[[(Phenylmethoxy)carbonyl]amino]-5-(2′-methylpropyl)-2-oxopyrrolidine (12a). A solution of **11a** (12 mg, 0.028 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.2 mL, 0.87 mmol) in dichloromethane (1 mL) was stirred at room temperature under argon for 4 h. The reaction mixture was quenched with saturated sodium carbonate solution, extracted with dichloromethane, dried with anhydrous sodium sulfate, and concentrated. Chromatography of the residue on silica gel (Merck Lobar A, elution with 2.5% MeOH/dichloromethane) gave 5.2 mg (63%) of **12a** as a clear colorless oil which crystallized on standing: ^1H NMR (500 MHz, $CDCl_3/CD_3OD$) δ 7.38 (m, 5 H), 5.06 (AB q, *J* = 11.9 Hz, 2 H), 4.44 (m, 1 H), 3.80 (m, 1 H), 2.98 (m, 1 H), 2.61 (dd, *J* = 17.3, 7.9 Hz, 1 H), 2.18 (dd, *J* = 17.3, 4.8 Hz, 1 H), 1.57 (m, 1 H), 1.31–1.20 (m, 2 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 0.85 (d, *J* = 6.5 Hz, 3 H), other exchangeable protons not observed; MS (FAB), *m/z* (relative intensity) 291 $[M + H]^+$, exact mass calcd for $C_{16}H_{22}N_2O_3$ 291.1709, obsd 291.1718.

(4*R*,5*S*)-4-[[(Phenylmethoxy)carbonyl]amino]-5-(2′-methylpropyl)-2-oxopyrrolidine (12b). The synthesis of **12b** was carried out as described above for **12a** starting with **11b** (11 mg, 0.026 mmol) to provide **12b** (6.5 mg, 86%) as a clear colorless oil which crystallized on standing: ^1H NMR (500 MHz, $CDCl_3/CD_3OD$) δ 7.34 (m, 5 H), 6.35 (s, 1 H), 5.40 (s, 1 H), 5.10 (AB q, *J* = 13.0 Hz, 2 H), 4.05 (m, 1 H), 3.95 (m, 1 H), 3.48 (m, 1 H), 2.75 (dd, *J* = 17.6, 8.4 Hz, 1 H), 2.19 (dd, *J* = 17.6, 5.2 Hz, 1 H), 1.67 (m, 1 H), 1.58 (m, 1 H), 1.49 (m, 1 H), 0.94 (d, *J* = 6.5 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H); MS (FAB), *m/z* (relative intensity) 291 $[M + H]^+$, exact mass calcd for $C_{16}H_{22}N_2O_3$ 291.1709, obsd 291.1724.

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