Synthesis, Conformational Analysis, and Evaluation of the Multidrug Resistance-Reversing Activity of the Triamide and Proline Analogs of Hapalosin

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Received May 9, 1997[⊗]

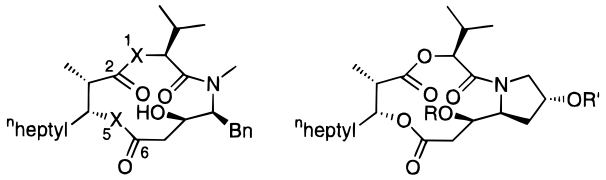
Four analogs were synthesized which have *trans*-4-hydroxyl-L−proline replacing the *N*-Me-L-phenylalanine moiety in hapalosin. The triamide analog of hapalosin containing two secondary amide bonds in lieu of the two ester bonds in hapalosin was also synthesized. Conformations of hapalosin, the triamide analog, and two of the four proline analogs in chloroform were calculated utilizing distance constraints between NOESY-correlated protons. The lowest-energy, distance-constrained conformation of hapalosin is similar to that of the triamide analog and does not differ substantially from that of the two proline analogs. All conformations have an *s-cis* tertiary amide bond. The analogs' ability to reverse **P**-glycoprotein-mediated multidrug resistance was evaluated in cytotoxicity and drug accumulation assays using MCF-7/ADR cells which overexpress P-glycoprotein. Two of the proline analogs are more potent than hapalosin (which has a similar activity as verapamil) whereas the other two proline analogs and the triamide analog are less active than hapalosin.

Introduction

The efficacy of cancer chemotherapy is often limited by multidrug resistance (MDR). This phenomenon is characterized by the resistance of tumor cells to a wide range of seemingly unrelated drugs. One of the principal mechanisms of MDR is the expulsion of structurally diverse drugs by the transmembrane ATPase P-glycoprotein (P-gp).[2] Hapalosin (**1**) is a novel cyclic depsipeptide which reverses MDR putatively via inhibition of P-gp.[3] Extant anti-MDR agents have not exhibited satisfactory clinical activity.[4] Hapalosin[5] represents a new class of potential MDR reversal agents.

We have been interested in the structure−activity relationship of hapalosin analogs. With the aid of ^{1}H,^{1}H-NOESY data, computation revealed that the major *s-cis* rotamer of hapalosin and the single *s-trans* rotamer of the non-*N*-Me hapalosin analog (having a secondary N−H amide bond instead of the tertiary N−Me amide bond in hapalosin) have very different conformations. By contrast, the minor *s-trans* rotamer of hapalosin and the non-*N*-Me analog have very similar conformations.[5d] The non-*N*-Me analog was found to possess substantially weaker MDR-reversing property than hapalosin.[5f,6]

trans-4-Hydroxy-L-proline (**7**) was selected as a component in a series of analogs (**3**−**6**) for several reasons. First, we wanted to see how the significant structural change from the *N*-Me-phenylalanine moiety in hapalosin to proline affects the conformations and anti-MDR activity. Computation suggested that utilization of L-proline will also favor the *s-cis* rotamer. Second, cycloamidation (forming **19**) was expected to be higher-yielding with a cyclic secondary amine than with an acyclic secondary amine. Third, the hydroxyl group on the proline ring can be functionalized.



1 X = O, Hapalosin
2 X = NH, triamide

3 R = PMB, R' = H
4 R = PMB, R' = C(O)NHBn
5 R = H, R' = H
6 R = H, R' = C(O)NHBn

The triamide analog of hapalosin, **2**, also seemed intriguing from several standpoints. First, the two additional amide bonds of the triamide analog are less likely to be cleaved *in vivo* than the two ester bonds of hapalosin. Second, the triamide analog should be more water-soluble than hapalosin. Third, the conformation-(s) of the triamide analog may differ from those of hapalosin because of potential intramolecular hydrogen bonding involving the two secondary amide bonds. In this paper, we present the synthesis, conformational analysis, and evaluation of the anti-MDR activity of the triamide and proline analogs of hapalosin.[7]

⊗ Abstract published in *Advance ACS Abstracts,* September 15, 1997.

(1) (a) University of California, Los Angeles. (b) Fox Chase Cancer Center.

(2) For reviews on multidrug resistance, including the involvement of P-glycoprotein, see: (a) Simon, S. M.; Schindler, M. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3497. (b) Gottesman, M. M.; Pastan, I. *Annu. Rev. Biochem.* **1993**, *62*, 385. (c) Ford, J. M.; Hait, W. N. *Pharmacol. Rev.* **1990**, *42*, 155. (d) Endicott, J. A.; Ling, V. *Annu. Rev. Biochem.* **1989**, *58*, 137.

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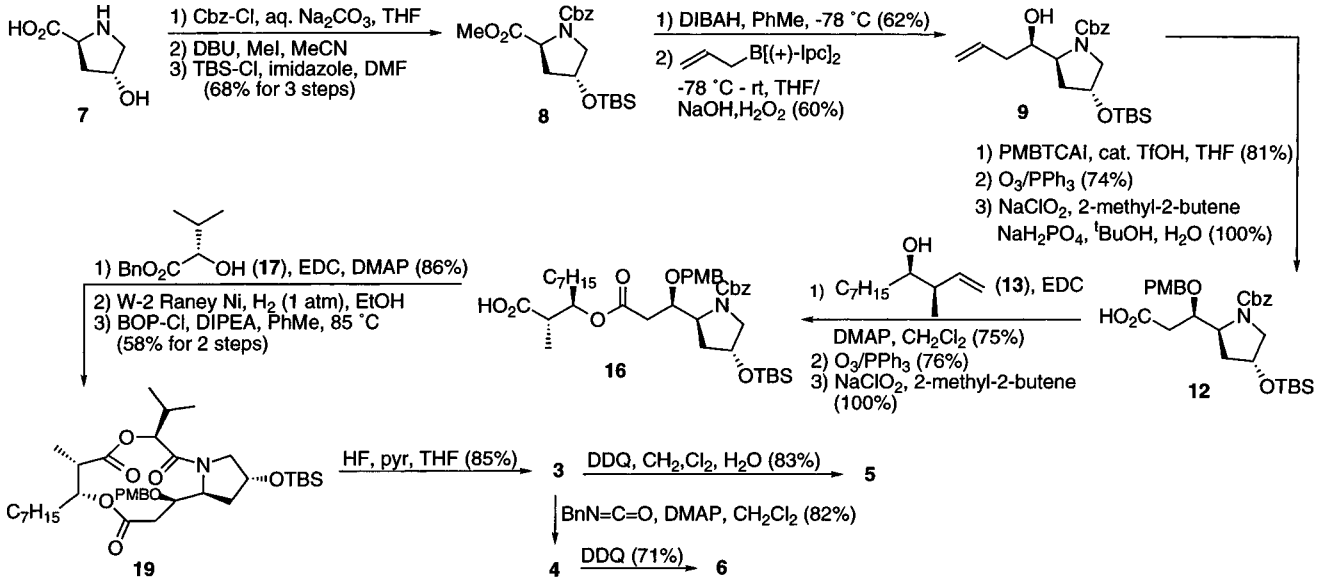
(5) For the synthesis of hapalosin, see: (a) Dinh, T. Q.; Armstrong, R. W. *J. Org. Chem.* **1995**, *60*, 8118. (b) Ghosh, A. K.; Liu, W.; Xu, Y.; Chen, Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 74. (c) Ohmori, K.; Okuno, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1996**, *37*, 3467. (d) Dinh, T. Q.; Du, X.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6606. (e) Wagner, B.; Beugelmans, R.; Zhu, J. *Tetrahedron Lett.* **1996**, *37*, 6557. (f) Okuno, T.; Ohmori, K.; Nishiyama, S.; Yamamura, S.; Nakamura, K.; Houk, K. N.; Okamoto, K. *Tetrahedron* **1996**, *52*, 14723.

(6) Dinh, T. Q.; Smith, C. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 790.

(7) The synthesis and MDR-reversing property of the proline analogs were first described in a communication in this journal (ref 6).

S0022-3263(97)00839-6 CCC: $14.00

Scheme 1



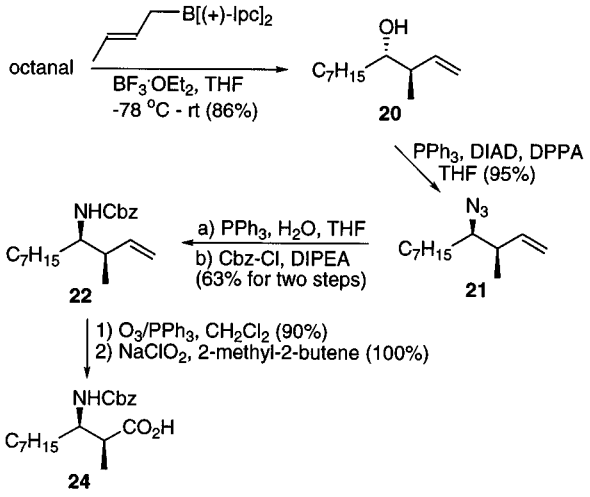
Results and Discussion

Synthesis. The synthesis of the four proline analogs of hapalosin, **3**−**6**, is illustrated in Scheme 1. *trans*-4-Hydroxy-L-proline (**7**) was tris-protected as ester **8**. The ester was converted to an aldehyde which underwent Brown allylboration[8] to produce homoallylic alcohol **9** in >90% de. The alcohol was protected with *p*-methoxybenzyl 2,2,2-trichloroacetimidate (PMBTCAI),[9] and the olefin was transformed to acid **12**. The acid was coupled to alkenol **13**[5d] using 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide (EDC), and the resulting olefin was oxidized to acid **16**. After the acid was coupled to alcohol **17**,[5d] the Cbz carbamate and benzyl ester were selectively deprotected in the presence of the PMB ether by hydrogenation over W-2 Raney nickel.[10] Cycloamidation of the amino acid with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) and $^{i}Pr_2NEt$ (DIPEA) in toluene at 85 °C[11] provided **19** in a good yield of 58% over the two steps.

The four proline analogs **3**−**6** were easily generated from macrolactam **19**. Desilation of **19** produced analog **3** whose PMB ether was deprotected to form analog **5**. Reaction of analog **3** with benzyl isocyanate yielded analog **4** whose benzyl group accounts for the benzyl group in hapalosin. Deblocking of the PMB ether of analog **4** resulted in analog **6**. The benzyl ether and the phenol ether (with the stereocenter inverted) of analog **3** could not be synthesized because the hydroxyl group of analog **3** was unreactive with benzyl 2,2,2-trichloroacetimidate/TfOH[12] and with DIAD/phenol/PPh_3.[13] The synthesis of the analogs was designed to be linear so that an alcohol different than **13** or **17** can be introduced at the particular position.

Synthesis of the triamide analog of hapalosin, **2**, used L-valine and *β*-amino acid **24** to form the two secondary amide bonds. In the synthesis of acid **24** (Scheme 2),

Scheme 2



octanal underwent Brown crotylboration[14] with *trans*-2-butene and (+)-*B*-methoxydiisopinocampheylborane to form *anti* homoallylic alcohol **20**[15] in >95% de and ee.[16] Mitsunobu reaction of *anti* alcohol **20** with diphenylphosphoryl azide (DPPA) as the azide source produced *syn* azide **21**.[17] The azide was reduced to an amine with PPh_3/H_2O,[18] and the amine was protected with benzyl chloroformate. Olefin **22** was then coverted to acid **24**.

The rest of the synthesis of the triamide analog is depicted in Scheme 3. Amino alcohol **25**[5d] was coupled to *N*-Boc-L-valine with (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate [BOP reagent (rgt)].[19] Carbamate **26** was deblocked and coupled with acid **24** to provide alcohol **27**.[20] The alcohol was silated,[21] and the olefin was oxidized to acid **30**. After

(8) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.
(9) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.
(10) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
(11) Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, *58*, 471.
(12) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.
(13) Hughes, D. L. *Org. React.* **1992**, *42*, 335.
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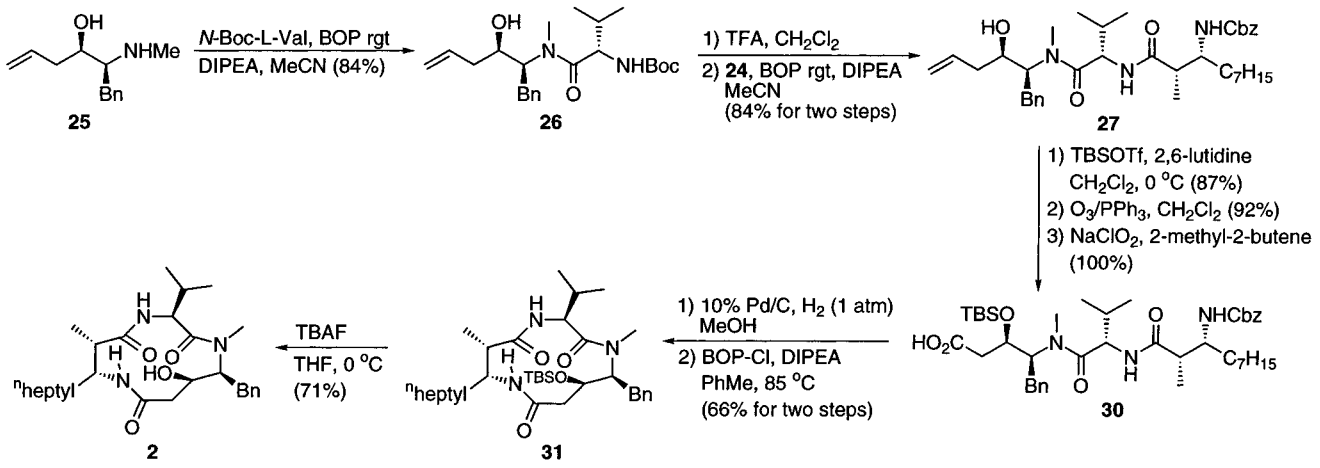
(15) Mitsunobu reaction of syn alcohol **13** with benzoic acid, PPh_3, and DIAD in THF was very slow and did not consume much of **13**.
(16) Although the specific rotation of alcohol **20** in $CHCl_3$ is zero, its ee is >95% since coupling of acid **24** and L-Val-OMe with BOP reagent quantitatively resulted in only one isomer of the amide product.
(17) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977−80.
(18) Nagarajan, S.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5044.
(19) Castro, B.; Dormoy, J.-R.; Dourtoglou, B.; Evin, G.; Selve, C.; Ziegler, J.-C. *Synthesis* **1976**, 751.

Scheme 3



the carbamate was deprotected, the amino acid was cyclized with BOP-Cl and DIPEA in toluene at 85 °C to afford the TBS ether of the triamide analog, **31**, in 66% yield over the two steps. Desilation resulted in the triamide analog of hapalosin, **2**.

Conformational Analysis. The conformational ratios of the modulators in $CDCl_3$ or MeOD at 25 °C are interesting. The conformations of all the compounds are due to the configurations of their tertiary amide bond. In $CDCl_3$, the three proline analogs with a β-PMB ether—**3**, **4**, and **19**—have a conformational ratio from 1.1:1 to 1.5:1 while the ratio is about 6:1 for the two analogs with a free β-hydroxyl group—**5** and **6**. On the other hand, the conformational ratio increases from 2.3:1 for hapalosin to 3.2:1 for the PMB ether of hapalosin in $CDCl_3$. With respect to the triamide analog **2** and its TBS ether **31**, both exist only as one conformer in $CDCl_3$. In MeOD, the conformational ratios are 4.3:1 for hapalosin, 1.9:1 for analog **3** (vs 1.1:1 for **3** in $CDCl_3$), and 2.5:1 for analog **6**. The triamide analog **2** also exists only as a single conformer in MeOD.

Nuclear magnetic resonance experiments were conducted to determine the effects of D_2O and KOAc on the conformations of analog **6** in MeOD at 25 °C. Analog **6** dissolved in a maximum of 30% D_2O/MeOD at a concentration of 12 mM. (The triamide analog **2** was not significantly more water-soluble than analog **6**.) The ^1H NMR spectrum of analog **6** in 30% D_2O/MeOD differed only a little from that of **6** in 100% MeOD as the chemical shifts of a few protons changed slightly. The conformational ratio of analog **6** remained the same (2.5:1) regardless of the amount of D_2O added. One-dimensional NOE difference spectroscopy demonstrated that the same amide bond rotamer was favored at all concentrations of D_2O in MeOD. To test whether a biologically ubiquitous cation could chelate to the Lewis basic heteroatoms of analog **6** and affect its conformations, a solution of KOAc in 25% D_2O/MeOD was added to a solution of analog **6** in 25% D_2O/MeOD. Varying amounts of KOAc up to 5 equiv were added, but the ^1H NMR spectra of analog **6** did not change.

For hapalosin (**1**) and analogs **2**, **5**, and **6**, molecular modeling studies were performed with Macromodel (v.4.5)[22] using AMBER* force field and GB/SA chloroform solvation.[23] Conformational searches were conducted employing Still's internal coordinate Monte Carlo protocol.[24] The search was done on blocks of 1000 Monte Carlo steps until no additional conformation was found to be of lower energy than the current global minimum. To simplify the number of conformations found and save computational time, the *n*-heptyl chain was replaced by a methyl group in hapalosin and the three analogs. ^1H,^1H-NOESY at 500 MHz was conducted on the modulators in $CDCl_3$ at 25 °C over three different mixing times—1.10, 1.80, and 2.50 s. The compounds engendered positive NOE's. In the computation, distance constraints for protons of the major conformers which exhibited NOESY crosspeaks of at least medium strength were set between 1.5 and 5.0 Å.[25]

With no distance constraint applied, hapalosin and analogs **2**, **5**, and **6** have *s-cis* and *s-trans* rotamers with the lowest-energy conformation of all four compounds bearing an *s-cis* tertiary amide bond.[26] The *s-cis* populations within a 5 kcal/mol energy difference from the lowest-energy conformation are 69% for hapalosin, 76% for analogs **5** and **6**, and 78% for the triamide analog **2**. In the *s-trans* rotamers of analogs **5** and **6**, the steric repulsion between the isopropyl group and the proline ring is very obvious while in the *s-trans* amide conformations of hapalosin the steric repulsion between the isopropyl group and the benzyl group is not as strong. This may explain why the two proline analogs have a more biased conformational ratio than hapalosin in chloroform (about 6:1 vs 2.3:1).

Application of distance constraints to pairs of NOESY-correlated protons confirmed that the triamide analog **2** and the major conformers of hapalosin and analogs **5** and **6** all possess an *s-cis* tertiary amide bond in chloroform (Figure 1). Only *s-cis* amide conformations were found for hapalosin and analogs **2** and **6**. For analog **5**, 81% of the distance-constrained conformations, including the lowest-energy one, have the *s-cis* configuration.[27] Figure

(20) After the ester generated by the coupling of acid **24** with L-Val-OMe was hydrolyzed, the resulting acid could not be coupled with amino alcohol **25** via various methods, including BOP reagent and HATU, to make alcohol **27**.

(21) Cycloamidation in the presence of a free β-hydroxyl group was initially attempted with BOP-Cl at 85 °C, but the ^1H NMR of the crude product was inauspicious.

(22) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(23) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127.

(24) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(25) Molecular modeling of the modulators in methanol was also desired. For Macromodel programs, the GB/SA solvation model is the best solvation model, but it is equipped with parameters only for chloroform or water.

(26) With or without distance constraints, the two secondary amide bonds of the triamide analog **2** are *s-trans*.

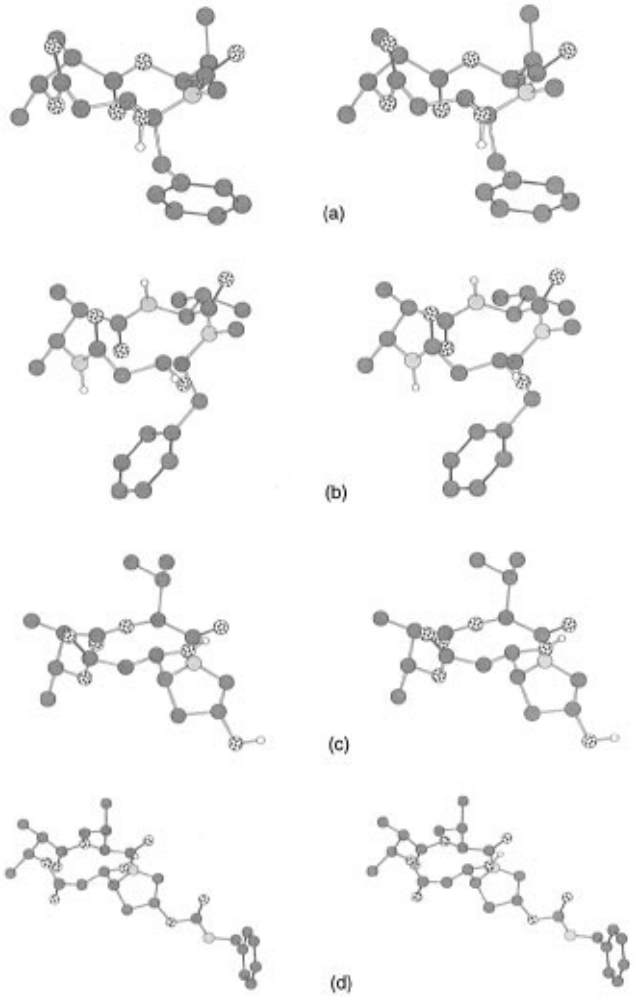


Figure 1. Stereoviews of the lowest-energy conformations found for hapalosin **1** (a) and analogs **2** (b), **5** (c), and **6** (d) in conformational searches with distance constraints. The computation was conducted with a methyl group replacing the *n*-heptyl group. All conformations have an *s-cis* tertiary amide bond. Protons on carbon atoms are removed for clarity. Dark circles, C; spotted circles, O; grey circles, N; white circles, H.

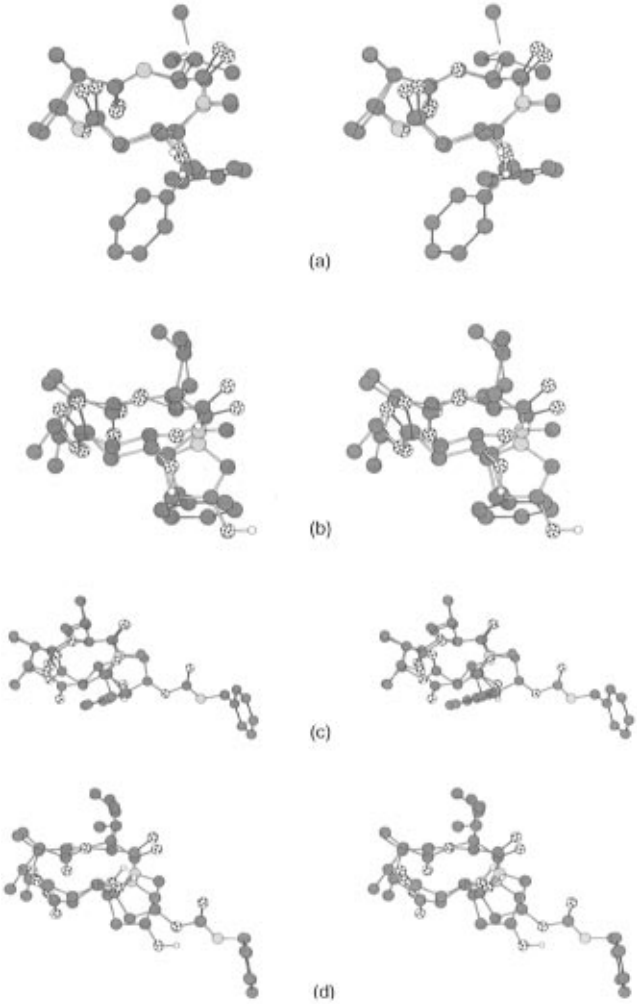


Figure 2. Stereoviews of the superimposed lowest-energy, distance-constrained conformations of (a) hapalosin **1** and triamide **2**, (b) **1** and analog **5**, (c) **1** and analog **6**, and (d) **5** and **6**. The *n*-heptyl group is replaced with a methyl group. Protons on carbon atoms are removed for clarity. Dark circles, C.; spotted circles, O.; grey circles, N.; white circles, H.

1 depicts the lowest-energy, distance-constrained conformations of the triamide analog **2** (b) and of the major conformers of hapalosin (a) and analogs **5** (c) and **6** (d). All four conformations surprisingly do not exhibit intramolecular hydrogen bonding of the β-hydroxyl group. The conformation of the triamide analog **2**, however, contains a transannular hydrogen bond between the amide N-H_1 proton and the C_6 carbonyl oxygen.[28] This agrees with the results of a deuterium exchange experiment in which D_2O was added to a solution of **2** in $CDCl_3$. The amide N-H_5 proton completely disappeared when less than 20 equiv of D_2O was added whereas the integration of the N-H_1 proton did not diminish at all regardless of the amount of D_2O added.

To compare the lowest-energy, distance-constrained conformations of the four modulators, the conformations are superimposed in Figure 2. Hapalosin and the triamide analog **2** (Figure 2a) differ in the orientation of the phenyl, isopropyl methyl, and β-hydroxyl groups. Nevertheless, they have very similar ring conformations as indicated by an rms (root mean squared) of 0.138 Å for the superimposition of the 12 ring atoms. The hydrogen bond between the amide N-H_1 proton and the C_6 carbonyl oxygen of analog **2** (Figure 1b) has little impact on its conformation. Contrasting hapalosin and analog **5** (Figure 2b), the β-hydroxyl, isopropyl methyl, and C_2 carbonyl groups point in different directions. The overlay of the ring conformations (rms of 0.412 Å) is quite good. With respect to hapalosin and analog **6** (Figure 2c), the structural change from phenylalanine to proline again does not substantially perturb the ring conformation (the superimposition rms is 0.474 Å). Noticeable features are the different orientations of the β-hydroxyl group and the opposite directions of the C_6 carbony group. Comparing to the proline analogs **5** and **6** (Figure 2d), the isopropyl methyl and C_6 carbonyl groups are oriented differently and the ring overlap is surprisingly not as good (the superimposition rms is 0.601 Å) as the overlay between hapalosin and analog **5** or **6**. The principal discrepancy between the two proline analogs, however, is that analog **6** bears a benzyl carbamate group instead of a hydroxyl group in analog **5**.

(27) In ref 6, it was reported that computation employing distance constraints resulted in seven conformations for analog **5**, all containing an *s-cis* amide bond. This is an error which stemmed from an incorrect proton being inputted in the distance constraints.

(28) The distance between the amide N-H_5 proton and the C_2 carbonyl oxygen (3.28 Å) nearly equals that between the amide N-H_1 proton and the C_6 carbonyl oxygen (3.25 Å). The O−H_5−N angle is 79° while the O−H_1−N angle is 104°. Since the former angle is <90°, it does not meet the requirement of a hydrogen bond.

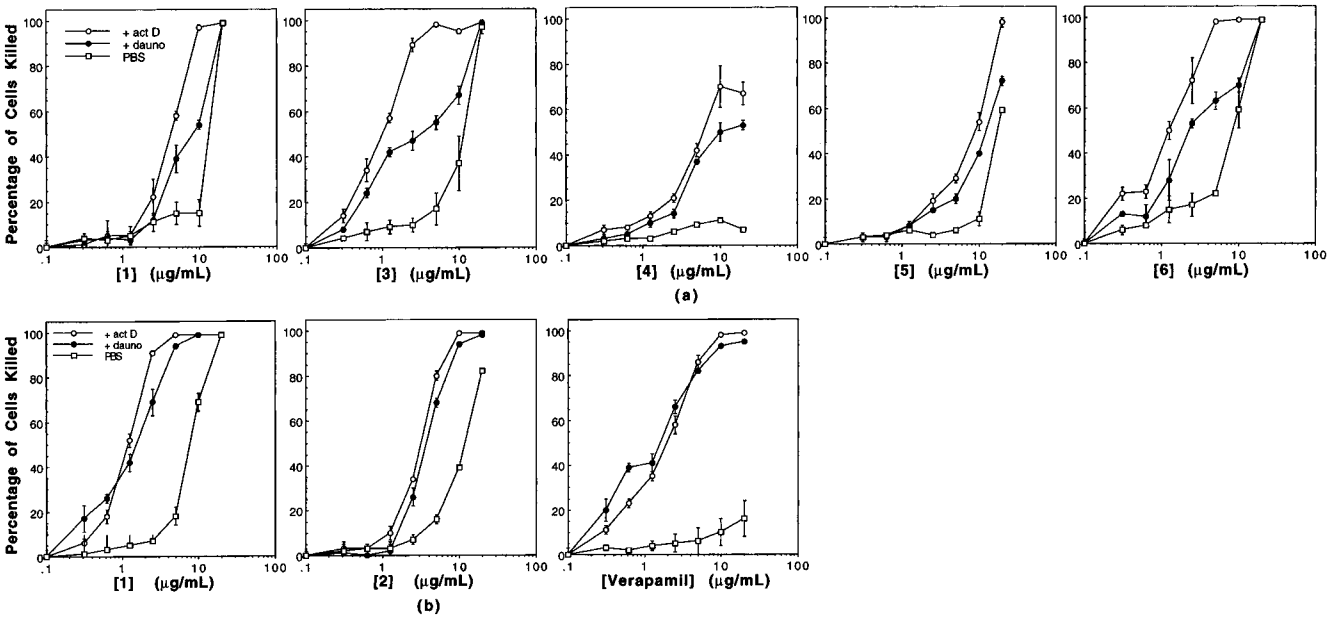


Figure 3. Reversal of MDR by hapalosin analogs. MCF-7/ADR cells were incubated with the indicated concentrations of modulators in the presence of phosphate-buffered saline (as a control) (□), 25 nM actinomycin D (○), or 2 μM daunomycin (●). Modulators **1** and **3**−**6** in (a) were tested at a different time than modulators **1**, **2**, and verapamil in (b). Cell survival after 48 h was determined as indicated in the Experimental Section. Values represent the mean ± SD of triplicate samples.

Multidrug Resistance-Reversing Activity. The anti-MDR activities of synthetic hapalosin and its analogs (modulators) were determined by cytotoxicity and drug accumulation assays using MCF-7/ADR cells which overexpress P-gp.[29] Verapamil was also tested as a positive control. In the cytotoxicity assay (Figure 3), cells were exposed to one of eight doses of a modulator alone (the PBS curves) or in the presence of 25 nM actinomycin D, 2 μM daunomycin, or 2 μM cisplatin. Cisplatin was included as a non-P-gp substrate to demonstrate selective enhancement of killing by actinomycin D and daunomycin, which are transported by P-gp. Moreover, the effects of the modulators on the killing of drug-sensitive MCF-7 cells, which do not overexpress P-gp, were tested. In the drug accumulation assay (Figure 4), MCF-7/ADR cells were treated with one of eight doses of a modulator and then incubated with [^{3}H]vinblastine, which is also transported by P-gp. Reversal of MDR is demonstrated if minimally cytotoxic doses of a modulator selectively increase cell killing by actinomycin D and daunomycin and increase the intracellular concentration of [^{3}H]-vinblastine.

The results of the cytotoxicity and drug accumulation assays are depicted in Figure 3a,b and Figure 4a,b, respectively. All the modulators in Figures 3a and 4a were tested at one time, and the same was true for the modulators in Figures 3b and 4b. The modulators in Figures 3a and 4a, however, were tested 5 months prior to the assays of the modulators in Figures 3b and 4b. Therefore, the results for the two different times are displayed separately. Nevertheless, synthetic hapalosin was evaluated on both occasions and serves as a reference by which the modulators in Figures 3a and 4a can be compared to those in Figures 3b and 4b. Data for cisplatin and MCF-7 cells are omitted since none of the modulators altered the sensitivity of MCF-7/ADR cells to cisplatin or the sensitivity of MCF-7 cells to any of the drugs, indicating that the modulators act on P-gp.

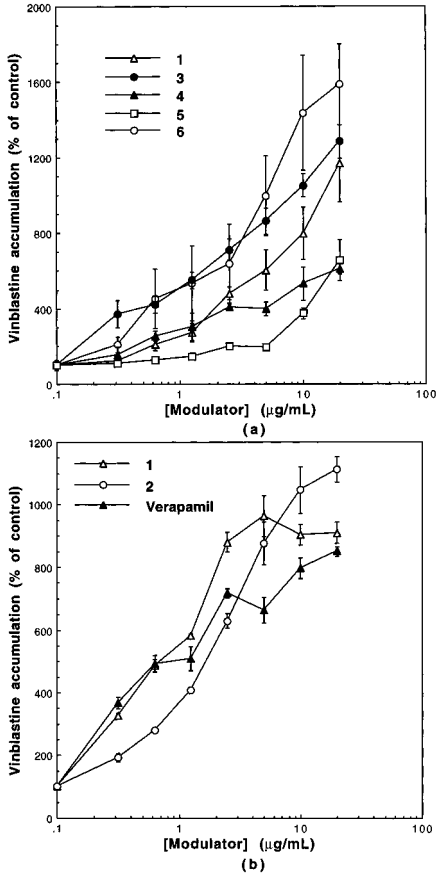


Figure 4. Effects of hapalosin analogs on [^{3}H]vinblastine accumulation by MDR cells. MCF-7/ADR cells were incubated with the indicated concentrations of modulators **1** (△), **3** (●), **4** (▲), **5** (□), or **6** (○) in (a) and **1** (△), **2** (○), or verapamil (▲) in (b). The modulators in (a) were tested at a different time than those in (b). The intracellular accumulation of [^{3}H]vinblastine was then determined as indicated in the Experimental Section. Values represent the mean ± SD of triplicate samples.

(29) These cytotoxicity and drug accumulation assays have been employed to test the MDR-reversing activity of hapalosin (ref 3) and dendroamide A and welwitindolinone analogs, respectively: (a) Ogino, J.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Nat. Prod.* **1996**, *59*, 581. (b) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharm.* **1995**, *47*, 241.

Comparing the ability of the proline analogs to potentiate the cytotoxicity of actinomycin D and daunomycin to that of hapalosin (**1**) (Figure 3a), analogs **3**[30] and **6** are better while analogs **4** and **5** are worse. However, analog **4** is much less intrinsically cytotoxic (the PBS curve) than the other four modulators. Hapalosin and verapamil are equally effective in causing cell death whereas the triamide analog **2** is worse, but verapamil is inherently the least cytotoxic (Figure 3b). With regard to enhancement of the intracellular concentration of [^{3}H]vinblastine (Figure 4a), analogs **3** and **6** are better than hapalosin, analog **4** is slightly worse, and analog **5** is substantially worse. Hapalosin and verapamil promote vinblastine accumulation similarly well while the triamide analog **2** is slightly worse (Figure 4b). In summary of the modulators' MDR-reversing property, analogs **3** and **6** are the most active, hapalosin and verapamil have similar activity, analogs **2** and **4** are less active than hapalosin, and analog **5** is substantially weaker than hapalosin. Analog **4** and verapamil (and the non-*N*-Me analog of hapalosin[6]), however are much less intrinsically cytotoxic than the other modulators. The reasons for the difference in the cytotoxicity of the modulators are not known.

Conclusion

The lowest-energy, distance-constrained conformations of hapalosin (**1**) and analogs **2**, **5**, and **6** in chloroform all possess an *s-cis* tertiary amide bond. The conformation of hapalosin is similar to that of the triamide analog **2** and is not substantially different than that of analogs **5** and **6**. In regard to reversal of P-gp-mediated MDR, analogs **3** and **6** are more effective than hapalosin while analogs **2**, **4**, and **5** are weaker. Considering that the conformations of hapalosin and analogs **5** and **6** are not that dissimilar, the weak activity of analog **5** suggests that an aromatic group may be important for MDR reversal.

It was originally conjectured that a simpler scaffold which mimics the core structure of hapalosin and presents the appropriate peripheral functionalities in the proper orientations may be bioactive.[31] Although the triamide analog **2** and hapalosin are structurally and conformationally similar, the triamide analog has a significantly weaker anti-MDR activity. This fact suggests that important contacts with P-gp may be lost in the ester-to-amide backbone permutation or that the more rigid triamide backbone may be less effective at presenting substituent groups in the appropriate fashion.

Experimental Section

Cell Culture and Cytotoxicity Assay. MCF-7 breast carcinoma cells and MCF-7/ADR cells, an MDR subline,[32] were obtained from the Division of Cancer Treatment of the National Cancer Institute and were grown in RPMI 1640 containing 10% fetal bovine serum and 50 μg/mL gentamycin sulfate.

To test the effects of drugs on growth, cells were seeded in 96-well tissue culture dishes at approximately 15% confluency and were allowed to attach and recover for at least 24 h. Varying concentrations of drugs alone or combined with a modulator were then added to each well, and the plates were incubated for an additional 48 h. The number of surviving cells was then determined by staining with sulforhodamine B as previously described.[33] The percentage of cells killed was calculated as the percentage decrease in sulforhodamine B binding compared with control cultures. Control cultures included equivalent amounts of ethanol, which does not modulate the growth or drug-sensitivity of these cells at does utilized in these studies. Reversal of MDR is defined as the ability of a compound to potentiate the cytotoxicity of P-glycoprotein-transported drugs.

[^{3}H]Drug Accumulation Assay. MCF-7/ADR cells were plated into 24-well tissue culture dishes and allowed to grow to 90% confluency. The cells were washed with phosphate-buffered saline (PBS) and then incubated in 0.5 mL RPMI 1640 medium containing a modulator and 10−20 nM [^{3}H]vinblastine sulfate (Amersham Corporation) for 60 min at 37 °C. The cultures were rapidly washed three times with ice-cold PBS. Intracellular [^{3}H]drug was solubilized with 0.3 mL of 1% sodium dodecyl sulfate in water and quantified by liquid scintillation counting.

General Procedures. All water-sensitive reactions were conducted in oven- or flame-dried glassware under a nitrogen atmosphere. The starting materials were azeotroped two or three times with benzene before the reactions. Solvents were distilled immediately prior to use: CH_2Cl_2 from P_2O_5, PhMe from CaH_2, MeOH from magnesium metal, and THF from sodium metal/benzophenone ketyl. Anhydrous DMF and MeCN were purchased from the Aldrich Chemical Co. and utilized without further purification. Most commercially available reagents were distilled before use. Thin-layer chromatography (TLC) was performed on silica gel-coated plates (Merck, Kieselgel 60 F_{254}, 0.25 mm thickness for analytical and 0.5 mm for preparative TLC) and visualized by UV light and/or *p*-anisaldehyde, ninhydrin, or bromocresol green (for carboxylic acids) staining. After all aqueous extractions of crude reaction products, the combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* before further treatment.

(4*R*)-*N*-(Benzyloxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-L-proline Methyl Ester (8). *trans*-4-Hydroxy-L-proline (**7**) (8.033 g, 61.26 mmol, Aldrich) was dissolved in 10% aqueous Na_2CO_3 (80 mL), and THF (50 mL) was added. Cbz-Cl (8.33 mL, 58.3 mmol) was added slowly at 25 °C. Much white precipitate soon formed in the slightly warming mixture. The mixture was stirred fast at 25 °C for 15 h, diluted with water (50 mL), cooled to 0 °C, carefully acidified to pH 1 with concentrated HCl (about 7 mL), and extracted in EtOAc (2 × 30 mL) with 0.1 N $NaHSO_4$ (50 mL).

To a solution of the above crude hydroxy acid in MeCN (70 mL) was slowly added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 7.49 mL, 50.0 mmol) at 25 °C. After the slightly warmed-up solution cooled to about 25 °C in approximately 7 min, MeI (3.12 mL, 50.0 mmol) was added and the flask was sealed. The solution was stirred at 25 °C for 15 h and extracted in EtOAc (2 × 300 mL) with 0.1 N $NaHSO_4$ (250 mL).

To a solution of the above crude alcohol in DMF (35 mL) were added imidazole (6.40 g, 94.0 mmol) followed by a solution of ^{t}BuMe$_2$SiCl (TBS-Cl, 11.33 g, 75.19 mmol) in DMF (20 mL). (In order for TBS-Cl to dissolve in DMF, the mixture had to be heated with a heatgun.) The solution was stirred at 25 °C for 15 h and extracted in EtOAc (2 × 300 mL) with 0.1 N $NaHSO_4$ (300 mL). Flash chromatography with silica gel (gradient to 60% EtOAc/hexanes) afforded TBS ether **8** (15.546 g, 68% yield for three steps) as a colorless oil: $[\alpha]^{22}_D$ −43° (*c* 0.039, $CHCl_3$); IR (neat) 1117, 1416, 1713, 1752, 2953 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), both rotamers unless stated otherwise, δ 0.04−0.06 (4 singlets, 6 H), 0.85 (s, 9 H, 1 rotamer), 0.86 (s, 9 H, 1 rotamer), 2.04 (m, 1 H), 2.20 (m, 1 H), 3.42 (m, 1 H, 1 rotamer), 3.51 (m, 1 H, 1 rotamer), 3.54 (s,

(30) The PMB ether of hapalosin has only marginal anti-MDR activity (ref 6).

(31) Hirschmann *et al* elegantly created nonpeptidal mimetics of the cyclic hexapeptide L-363,301 which utilize β-D-glucose as the scaffold and are agonists of the somatostatin receptor. See: Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, A. B., III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. R.; Strader, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 12550.

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3 H, 1 rotamer), 3.66 (m, 1 H), 3.76 (s, 3 H, 1 rotamer), 4.43 (m, 1 H), 4.48 (m, 1 H), 5.04 (d, J = 12.4 Hz, 1 H, 1 rotamer), 5.10 (d, J = 12.4 Hz, 1 H, 1 rotamer), 5.20 (d, J = 12.4 Hz, 1 H), 7.26−7.37 (m, 5 H); ^{13}C NMR (101 MHz, $CDCl_3$), both rotamers, δ −5.0, −4.93, −4.91, −4.88, 17.86, 17.92, 25.60, 25.64, 38.9, 39.8, 52.0, 52.3, 54.7, 55.2, 57.8, 58.0, 67.1, 69.7, 70.3, 127.7, 127.8, 127.88, 127.92, 128.3, 128.4, 136.4, 136.6, 154.3, 155.0, 173.1, 173.3; HRCI calcd for $C_{20}H_{32}O_5NSi$ [(M + H)$^+$] 394.2050, found 394.2048.

(2*S*,2(1*R*),4*R*)-*N*-(Benzyloxycarbonyl)-2-(1-hydroxybut-3-enyl)-4-[(*tert*-butyldimethylsilyl)oxy]pyrrolidine (9). A solution of ester **8** (14.32 g, 36.38 mmol) in PhMe (100 mL) was cooled to −78 °C, and DIBAH (72.8 mL in hexanes, 72.8 mol) was added over a 5 min period. After being stirred for 2.5 h at −78 °C, the solution was carefully quenched with −78 °C MeOH (35 mL) and stirring continued for an additional 5 min at −78 °C. The reaction solution was poured with swirling into a separatory funnel containing ice-cold 1.2 M HCl (250 mL). Extraction with EtOAc (2 × 250 mL) and flash chromatography with silica gel (gradient from 10% EtOAc/hexanes to 100% EtOAc) provided the aldehyde (8.20 g, 62% yield) as a colorless oil. The aldehyde underwent allylboration within 1 day.

To a solution of (+)-*B*-methoxydiisopinocampheylborane (9.28 g, 29.3 mmol) in THF (70 mL) at −78 °C was slowly added allylmagnesium bromide (27.1 mL in Et_2O, 27.1 mmol). The mixture was stirred for 15 min at −78 °C and for 1 h without the −78 °C bath. The resulting solution was recooled to −78 °C, and a solution of the above aldehyde (8.20 g, 22.6 mmol) in THF (40 mL) was added slowly. The solution was stirred for 3 h at −78 °C and for 2 h without the −78 °C bath. After being cooled to 0 °C, the solution was carefully quenched with 3 M aqueous NaOH (24.5 mL) and 30% aqueous H_2O_2 (10.5 mL). The ice bath was allowed to warm up to 25 °C, and stirring transpired for 12 h. Much THF was removed *in vacuo* from the supernatant of the reaction mixture, and extraction was performed in EtOAc (2 × 300 mL) with brine (250 mL) followed by water (200 mL). Most isopinocampheyl alcohol was removed under high vacuum at 90 °C using a Kugelrohr apparatus. Flash chromatography with silica gel (gradient to 70% EtOAc/hexanes) furnished alcohol **9** (5.50 g, 60% yield) as a colorless oil in >90% de: $[\alpha]^{22}_D$ −39° (*c* 0.039, $CHCl_3$); IR (neat) 835, 1111, 1420, 1686, 2930, 2953, 3441 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 2.7:1 rotamers), the major rotamer, δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.85 (s, 9 H), 1.88 (m, 1 H), 1.94 (m, 1 H), 2.12 (m, 2 H), 3.21 (broad s, 1 H), 3.38 (dd, J = 11.4, 4.1 Hz, 1 H), 3.56 (d, J = 11.4 Hz, 1 H), 4.07 (broad m, 1 H), 4.15 (m, 1 H), 4.36 (broad m, 1 H), 5.06−5.20 (m, 4 H), 5.88 (m, 1 H), 7.27−7.38 (m, 5 H); ^{13}C NMR (101 MHz, $CDCl_3$), the major rotamer, δ −4.9, −4.8, 17.9, 25.7, 35.5, 37.3, 56.2, 61.8, 67.0, 70.2, 70.9, 117.1, 127.7, 127.9, 128.5, 135.2, 136.6, 156.5; HREI calcd for $C_{22}H_{36}O_4NSi$ [(M + H)$^+$] 406.2413, found 406.2415.

(2*S*,2(1*R*),4*R*)-*N*-(Benzyloxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-[1H[(*p*-methoxybenzyl)oxy]but-3-enyl]-pyrrolidine (10). To a solution of alcohol **9** (5.00 g, 12.3 mmol) in THF (60 mL) was added PMBTCAI (5.11 mL, 24.6 mmol). A solution of TfOH (6.5 μL, 0.074 mmol) in THF (2 mL) was then added slowly. The solution was stirred at 25 °C for 2 h, and TfOH was quenched with triethylamine (20 μL). Flash chromatography with silica gel (gradient to 15% EtOAc/hexanes) produced the PMB ether **10** (5.22 g, 81% yield) as a colorless oil: $[\alpha]^{22}_D$ −51° (*c* 0.041, $CHCl_3$); IR (neat) 1107, 1250, 1414, 1514, 1705, 2930, 2953 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, reference is $CHCl_3$), both rotamers (1.7:1) unless stated otherwise, δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.84 (s, 9 H), 1.78 (m, 1 H), 2.03 (m, 1 H, 1 rotamer), 2.13 (m, 1 H, 1 rotamer), 2.18 (m, 1 H), 2.29 (m, 1 H), 3.35−3.54 (m, 2 H), 3.77 (s, 3 H, major rotamer), 3.79 (s, 3 H, minor rotamer), 3.89 (m, 1 H, 1 rotamer), 4.03 (m, 1 H), 4.17 (m, 1 H, 1 rotamer), 4.27−4.52 (m, 3 H), 4.97−5.18 (m, 4 H), 5.68 (m, 1 H, minor rotamer), 5.85 (m, 1 H, major rotamer), 6.83 (d, J = 8.6 Hz, 2 H, major rotamer), 6.84 (d, J = 8.6 Hz, 2 H, minor rotamer), 7.14 (d, J = 8.6 Hz, 2 H, 1 rotamer), 7.16 (d, J = 8.6 Hz, 2 H, 1 rotamer), 7.27−7.38 (m, 5 H); ^{13}C NMR (101 MHz, $CDCl_3$), both rotamers, δ −4.93, −4.90, −4.86, −4.8, 17.9, 25.7, 33.9, 34.6, 36.9, 37.2, 55.1, 55.19, 55.23, 55.5, 59.4, 60.2, 66.5, 66.8, 70.2, 70.6, 72.7, 73.1, 77.5, 78.3, 113.6, 113.7, 116.99, 117.02, 127.6, 127.8, 127.9, 128.38, 128.41, 129.20, 129.22, 130.7, 131.0, 134.6, 134.8, 136.7, 137.1, 154.9, 155.0, 159.0, 159.1; HREI calcd for $C_{30}H_{43}O_5NSi$ (M$^+$) 525.2910, found 525.2915.

(2*S*,2(1*R*),4*R*)-*N*-(Benzyloxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-[2-formyl-1-[(*p*-methoxybenzyl)oxy]-ethyl]pyrrolidine (11). Ozone was bubbled into a solution of olefin **10** (3.40 g, 6.47 mmol) in CH_2Cl_2 (150 mL) at −78 °C with stirring for 10 min when TLC showed no more olefin. Argon was bubbled into the colorless solution for 15 s, and PPh_3 (2.38 g, 9.06 mmol) was added. After the solution was stirred at −78 °C for 15 min, stirring continued for 15 h at 25 °C. Flash chromatography with silica gel (gradient to 40% EtOAc/hexanes) resulted in aldehyde **11** (2.513 g, 74% yield) as a colorless oil: $[\alpha]^{22}_D$ −59° (*c* 0.041, $CHCl_3$); IR (neat) 1109, 1250, 1414, 1701, 1725, 2930, 2953 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, reference is $CHCl_3$), both rotamers (2.0:1) unless stated otherwise, δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.84 (s, 9 H), 1.80 (m, 1 H), 2.15 (m, 1 H), 2.33−2.58 (m, 2 H), 3.34−3.59 (m, 2 H), 3.77 (s, 3 H), 3.92−4.03 (m, 1 H), 4.28−4.53 (m, 3 H), 4.69 (m, 1 H), 5.06−5.21 (m, 2 H), 6.83 (d, J = 8.5 Hz, 2 H), 7.10 (d, J = 8.5 Hz, 2 H, 1 rotamer), 7.12 (d, J = 8.5 Hz, 2 H, 1 rotamer), 7.27−7.39 (m, 5 H), 9.60 (broad m, 1 H, minor rotamer), 9.68 (broad m, 1 H, major rotamer); ^{13}C NMR (101 MHz, $CDCl_3$), both rotamers, δ −5.0, −4.8, 17.9, 25.7, 34.3, 35.0, 46.9, 47.0, 55.2, 55.6, 60.1, 60.8, 66.7, 67.0, 70.0, 70.4, 72.7, 73.3, 73.37, 73.43, 113.7, 127.7, 127.9, 128.1, 128.4, 128.5, 129.4, 129.5, 130.0, 130.2, 136.6, 136.8, 155.0, 155.4, 159.2, 200.0, 200.4; HRFAB calcd for $C_{29}H_{42}O_6NSi$ [(M + H)$^+$] 528.2781, found 528.2790.

(2*S*,2(1*R*),4*R*)-*N*-(Benzyloxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-[2-carboxy-1-[(*p*-methoxybenzyl)oxy]-ethyl]pyrrolidine (12). To a solution of aldehyde **11** (2.483 g, 4.705 mmol) and 2-methyl-2-butene (4.70 mL in THF, 9.41 mmol) in ^{t}BuOH (24 mL) was slowly added a solution of sodium chlorite (80% purity, 691 mg, 6.12 mmol) and NaH_2PO_4 (677 mg, 5.65 mmol) in water (6 mL). The flask was sealed and the mixture was vigorously stirred at 25 °C for 15 h. Extraction in CH_2Cl_2 (2 × 150 mL) with 0.1 N $NaHSO_4$ (100 mL) followed by water (75 mL) gave clean acid **12** (2.558 g, 100% yield) as a colorless oil: $[\alpha]^{22}_D$ −59° (*c* 0.039, $CHCl_3$); IR (neat) 1109, 1250, 1418, 1705, 1734, 2930, 2955, 3166 (shoulder) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, reference is $CHCl_3$), both rotamers unless stated otherwise, δ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.83 (s, 9 H), 1.81 (m, 1 H), 2.15 (m, 1 H), 2.34−2.51 (m, 2 H), 3.33 (dd, J = 11.1, 4.7 Hz, 1 H, 1 rotamer), 3.41 (m, 1 H), 3.54 (broad m, 1 H, 1 rotamer), 3.75 (s, 3 H), 3.97−4.07 (m, 1 H), 4.29−4.44 (m, 3 H), 4.53−4.62 (m, 1 H), 5.10−5.21 (m, 2 H), 6.81 (d, J = 8.5 Hz, 2 H), 7.11 (d, J = 8.5 Hz, 2 H, minor rotamer), 7.15 (d, J = 8.5 Hz, 2 H, major rotamer), 7.26−7.39 (m, 5 H); ^{13}C NMR (101 MHz, $CDCl_3$), both rotamers, δ −5.0, −4.9, −4.8, 17.9, 25.7, 34.4, 34.9, 37.9, 55.1, 55.2, 55.5, 59.9, 60.4, 66.8, 67.0, 70.0, 70.4, 73.5, 73.6, 74.6, 75.2, 113.6, 113.7, 127.8, 127.9, 128.1, 128.4, 129.4, 129.5, 130.2, 130.5, 136.6, 136.8, 155.1, 155.4, 159.1, 159.2, 176.0, 176.6; HRFAB calcd for $C_{29}H_{42}O_7NSi$ [(M + H)$^+$] 544.2731, found 544.2729.

(1*R*,2*R*)-1-Heptyl-2-methylbut-3-enyl (3*R*,3(2*S*,4*R*))-3-[*N*-(Benzyloxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-pyrrolidinyl]-3-[(*p*-methoxybenzyl)oxy]propanoate (14). To a solution of acid **12** (2.211 g, 4.067 mmol) and alcohol **13** (825 mg, 4.47 mmol) in CH_2Cl_2 (30 mL) was added DMAP (497 mg, 4.07 mmol) followed by EDC (1.09 g, 5.69 mmol). The solution was stirred at 25 °C for 15 h and extracted in CH_2Cl_2 (2 × 100 mL) with 0.1 N $NaHSO_4$ (100 mL). Flash chromatography with silica gel (gradient to 20% EtOAc/hexanes) provided ester **14** (2.168 g, 75% yield) as a colorless oil: $[\alpha]^{22}_D$ −37° (*c* 0.040, $CHCl_3$); IR (neat) 1107, 1250, 1414, 1705, 1734, 2928 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, reference is $CHCl_3$), both rotamers unless stated otherwise, δ −0.01 (s, 3 H), 0.00 (s, 3 H), 0.82 (s, 9 H), 0.87 (t, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H, minor rotamer), 1.00 (d, J = 6.8 Hz, 3 H major rotamer), 1.15−1.35 (broad m, 10 H), 1.51 (broad m, 2 H), 1.78 (m, 1 H), 2.15 (m, 1 H), 2.30−2.51 (m, 3 H), 3.31 (dd, J = 11.1, 4.7 Hz, 1 H, major rotamer), 3.37 (dd, J = 11.3, 4.6 Hz, 1 H, minor rotamer), 3.42 (broad d, 1 H, 1 rotamer), 3.55 (broad d, 1 H, 1 rotamer), 3.76 (s, 3 H, major rotamer), 3.78 (s, 3 H,

minor rotamer), 4.01 (m, 1 H), 4.27−4.48 (m, 3 H), 4.60 (d, J = 10.9 Hz, 1 H, 1 rotamer), 4.64 (broad m, 1 H, 1 rotamer), 4.86 (broad m, 1 H), 4.99−5.20 (m, 4 H), 5.73 (m, 1 H), 6.80 (d, J = 8.6 Hz, 2 H), 7.11 (d, J = 8.6 Hz, 2 H, 1 rotamer), 7.14 (d, J = 8.6 Hz, 2 H, 1 rotamer), 7.27−7.40 (m, 5 H); ^{13}C NMR (101 MHz, $CDCl_3$), both rotamers, δ −4.93, −4.89, −4.85, 14.1, 15.1, 15.2, 17.9, 22.6, 25.5, 25.7, 29.1, 29.5, 31.3, 31.8, 34.3, 35.0, 38.2, 38.3, 41.1, 41.2, 55.2, 55.6, 59.8, 60.6, 66.6, 66.8, 70.0, 70.5, 73.4, 73.8, 74.8, 75.6, 113.5, 113.6, 115.1, 127.7, 127.8, 128.0, 128.4, 129.2, 130.5, 131.0, 136.8, 137.0, 139.9, 140.0, 155.08, 155.13, 158.97, 159.05, 170.9; HRFAB calcd for $C_{41}H_{64}O_7NSi$ [(M + H)$^+$] 710.4452, found 710.4452.

(2*S*,3*R*)-2-Formyl-3-decyl (3*R*,3(2*S*,4*R*))-3-[*N*-(Benzyloxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-pyrrolidinyl]-3-[(*p*-methoxybenzyl)oxy]propanoate (15). Ozone was bubbled into a solution of olefin **14** (2.146 g, 3.022 mmol) in CH_2Cl_2 (70 mL) at −78 °C with stirring until the solution turned moderately blue (the color quickly faded). Argon was bubbled into the solution for 15 s, and PPh_3 (1.03 g, 3.93 mmol) was added. After the solution was stirred at −78 °C for 15 min, stirring continued for 15 h at 25 °C. Flash chromatography with silica gel (gradient to 25% EtOAc/hexanes) furnished aldehyde **15** (1.629 g, 76% yield) as a colorless oil: $[\alpha]^{22}_D$ −38° (*c* 0.012, $CHCl_3$); IR (neat) 1107, 1250, 1414, 1705, 1734, 2930 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, reference is $CHCl_3$), both rotamers (1.4:1) unless stated otherwise, δ −0.01−0.00 (4 singlets, 6 H), 0.82 (s, 9 H), 0.87 (t, J = 6.8 Hz, 3 H), 1.06 (d, J = 7.1 Hz, 3 H, minor rotamer), 1.10 (d, J = 7.0 Hz, 3 H, major rotamer), 1.17−1.38 (broad m, 10 H), 1.55 (broad m, 1 H), 1.63 (broad m, 1 H), 1.79 (broad m, 1 H), 2.12 (m, 1 H), 2.33 (m, 1 H), 2.43 (m, 1 H), 2.54 (m, 1 H), 3.28−3.56 (m, 2 H), 3.76 (s, 3 H, major rotamer), 3.78 (s, 3 H, minor rotamer), 4.00 (m, 1 H), 4.27−4.44 (m, 3 H), 4.54−4.62 (m, 1 H), 5.08−5.18 (m, 2 H), 5.30 (m, 1 H), 6.79−6.82 (2 overlapping doublets, 2 H), 7.09−7.17 (2 overlapping doublets, 2 H), 7.27−7.40 (m, 5 H), 9.65 (s, 1 H, minor rotamer), 9.70 (s, 1 H, major rotamer); ^{13}C NMR (101 MHz, $CDCl_3$ both rotamers, δ −4.93, 4.91, −4.88, −4.8, 7.9, 8.1, 14.1, 17.9, 22.6, 25.6, 25.7, 29.1, 29.3, 31.7, 31.8, 34.3, 35.0, 38.0, 38.2, 49.7, 49.8, 55.2, 55.6, 59.9, 60.5, 66.6, 66.9, 70.0, 70.5, 72.9, 73.1, 73.6, 73.8, 74.7, 74.8, 75.5, 113.6, 113.7, 127.76, 127.84, 127.9, 128.0, 128.4, 128.5, 129.2, 129.6, 130.5, 130.8, 136.8, 137.0, 155.1, 155.2, 159.0, 159.2, 170.7, 202.2, 202.5; HRFAB calcd for $C_{40}H_{62}O_8NSi$ [(M + H)$^+$] 712.4245, found 712.4219.

(2*S*,3*R*)-2-Carboxy-3-decyl [3*R*,3(2*S*,4*R*)]-3-[*N*-(Benzyloxycarbonyl)-4-[(*tert*-butyldimethylsilyl)oxy]-2-pyrrolidinyl]-3-[(*p*-methoxybenzyl)oxy]propanoate (16). The procedure for sodium chlorite oxidation of aldehyde **15** to acid **16** was based on that for making acid **12**. The crude product contained clean acid **16** (1.640 g, 100% yield) as a colorless oil: $[\alpha]^{22}_D$ −39° (*c* 0.033, $CHCl_3$); IR (neat) 1109, 1250, 1707, 1740, 2930, 3178 (shoulder) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, reference is $CHCl_3$), both rotamers unless stated otherwise, δ −0.01−0.01 (4 singlets, 6 H), 0.82 (s, 9 H), 0.87 (t, J = 6.9 Hz, 3 H), 1.14 (d, J = 7.1 Hz, 3 H, minor rotamer), 1.17 (d, J = 7.1 Hz, 3 H, major rotamer), 1.55 (broad m, 1 H), 1.62 (broad m, 1 H), 1.80 (broad m, 1 H), 2.13 (m, 1 H), 2.31−2.52 (m, 2 H), 2.68 (m, 1 H), 3.31−3.55 (m, 2 H), 3.76 (s, 3 H, major rotamer), 3.77 (2, 3 H, minor rotamer), 4.01 (m, 1 H), 4.27 (d, J = 10.8 Hz, 1 H, minor rotamer), 4.33 (d, J = 10.9 Hz, 1 H, major rotamer), 4.41 (broad m, 2 H), 4.44 (d, J = 10.8 Hz, 1 H, minor rotamer), 4.58 (d, J = 10.9 Hz, 1 H, major rotamer), 5.07−5.17 (m, 2 H), 5.25 (m, 1 H), 6.80 (d, J = 8.6 Hz, 2 H), 7.11 (d, J = 8.6 Hz, 2 H, minor rotamer), 7.14 (d, J = 8.6 Hz, 2 H, major rotamer), 7.26−7.41 (m, 5 H); ^{13}C NMR (101 MHz, $CDCl_3$), both rotamers, δ −5.0, −4.9, −4.8, 11.4, 11.7, 14.1, 17.9, 22.6, 25.5, 25.7, 29.1, 29.3, 31.5, 31.7, 31.8, 34.2, 35.0, 38.0, 38.2, 42.5, 55.1, 55.2, 55.6, 59.8, 60.5, 66.8, 66.9, 70.1, 70.5, 73.4, 73.5, 74.3, 74.5, 75.1, 75.6, 113.58, 113.64, 127.8, 127.9, 128.0, 128.4, 129.2, 129.3, 130.5, 130.8, 136.76, 136.81, 155.2, 159.0, 159.1, 170.6, 170.7, 177.8, 178.4; HRFAB calcd for $C_{40}H_{62}O_9NSi$ [(M + H)$^+$] 728.4194, found 728.4200.

Triester 18. To a solution of acid **16** (919 mg, 1.26 mmol) and alcohol **17** (289 mg, 1.39 mmol) in CH_2Cl_2 (14 mL) were added successively DMAP (154 mg, 1.26 mmol) and EDC (338 mg, 1.76 mmol). The solution was stirred at 25 °C for 15 h and extracted in CH_2Cl_2 (2 × 70 mL) with 0.1 N $NaHSO_4$ (70 mL). Flash chromatography with silica gel (gradient to 20% EtOAc/hexanes) generated triester **18** (997 mg, 86% yield) as a colorless oil: $[\alpha]^{22}_D$ −43° (*c* 0.034, $CHCl_3$); IR (neat) 1109, 1250, 1705, 1742, 2930 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, reference is $CHCl_3$), both rotamers unless stated otherwise, δ −0.01 (s, 3 H), 0.00 (s, 3 H), 0.82 (s, 9 H), 0.87 (t, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 1.17 (d, J = 7.2 Hz, 3 H, 1 rotamer), 1.20 (d, J = 7.2 Hz, 3 H, 1 rotamer), 1.12−1.37 (broad m, 10 H), 1.58 (broad m, 2 H), 1.78 (broad m, 1 H), 2.13 (m, 1 H), 2.24 (m, 1 H), 2.32−2.50 (m, 2 H), 2.75 (m, 1 H), 3.31 (dd, J = 11.1, 4.8 Hz, 1 H, 1 rotamer), 3.37 (dd, J = 11.1, 4.6 Hz, 1 H, 1 rotamer), 3.41 (broad dd, 1 H, 1 rotamer), 3.54 (broad dd, 1 H, 1 rotamer), 3.76 (s, 3 H, major rotamer), 3.77 (s, 3 H, minor rotamer), 3.99 (broad m, 1 H), 4.28 (d, J = 10.8 Hz, 1 H, 1 rotamer), 4.35 (d, J = 10.8 Hz, 1 H, 1 rotamer), 4.38 (broad m, 1 H), 4.46 (d, J = 10.8 Hz, 1 H, 1 rotamer), 4.48 (broad m, 1 H, 1 rotamer), 4.60 (d, J = 10.8 Hz, 1 H, 1 rotamer), 4.64 (broad m, 1 H, 1 rotamer), 4.85 (d, J = 4.3 Hz, 1 H), 5.08−5.19 (m, 4 H), 5.24 (broad m, 1 H), 6.80 (d, J = 8.6 Hz, 2 H), 7.11 (d, J = 8.6 Hz, 2 H, 1 rotamer), 7.14 (d, J = 8.6 Hz, 2 H, 1 rotamer), 7.24−7.41 (m, 10 H); ^{13}C NMR (101 MHz, $CDCl_3$), both rotamers, δ −4.94, −4.89, −4.8, 12.2, 12.3, 14.1, 17.1, 17.9, 18.8, 22.6, 25.4, 25.7, 29.1, 29.4, 30.0, 31.8, 31.9, 34.3, 35.1, 38.0, 38.1, 42.8, 42.9, 55.2, 55.6, 59.9, 60.5, 66.6, 66.8, 70.0, 70.5, 73.6, 73.9, 74.3, 74.8, 75.5, 76.8, 113.5, 113.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.26, 128.32, 128.4, 128.5, 129.2, 129.3, 130.6, 131.0, 135.3, 135.4, 136.8, 137.0, 155.1, 158.97, 159.04, 169.1, 170.7, 173.3, 173.4; HRFAB calcd for $C_{52}H_{76}O_{11}NSi$ [(M + H)$^+$] 918.5188, found 918.5179.

Macrolactam 19. A 50 mL round-bottom flask containing a solution of triester **18** (335 mg, 0.365 mmol) in EtOH (14 mL) was equipped with a 3.2-cm-long egg-shape stir bar. A bottle of Raney nickel (equivalent to W-2, 50% slurry water, Aldrich) was shaken well, and 55 drops of the Raney Ni from a Pasteur pipet were added. The flask was purged with N_2, and H_2 was bubbled into the mixture for 6 min. After the solution was stirred for 18 h at 25 °C under a balloon full of H_2, H_2 was again bubbled into the mixture for 6 min and stirring continued for 20 h more. After the flask was purged with N_2, the mixture was filtered through a small column of Celite and the Raney Ni clinging to the stir bar and the column were washed well with EtOH. ^{1}H NMR of the crude product (232 mg colorless film, 92% crude yield) showed that the Cbz and benzyl ester protecting groups were completely removed and the PMB ether was intact.

To a solution of the above crude amino acid (232 mg, 0.334 mmol) in PhMe (250 mL) were successively added DIPEA (582 μL, 3.34 mmol) and BOP-Cl (595 mg, 2.34 mmol). The mixture was stirred for 16 h at 85 °C and extracted with 0.1 N $NaHSO_4$ (60 mL). The aqueous layer was back-extracted with EtOAc (60 mL). The toluene layer from the previous extraction was again extracted with 0.1 N $NaHSO_4$ (60 mL), and the aqueous layer was back-extracted with the EtOAc layer from the previous back-extraction. Flash chromatography with silica gel (gradient to 20% EtOAc/hexanes) furnished macrolactam **19** (144 mg, 58% for two steps) as a white solid: $[\alpha]^{22}_D$ −33° (*c* 0.030, $CHCl_3$); IR (neat) 1171, 1250, 1651, 1732, 1748, 2930 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, reference is $CHCl_3$), both conformers (about 1.5:1) unless stated otherwise, δ −0.03 (s, 3 H, 1 conformer), −0.02 (s, 3 H, 1 conformer), −0.002 (s, 3 H, 1 conformer), 0.001 (s, 3 H, 1 conformer), 0.79−0.85 (a masked pair of doublets, 3 H), 0.82 (s, 9 H, 1 conformer), 0.84 (s, 9 H, 1 conformer), 0.88 (t, J = 7.0 Hz, 3 H), 0.95 (d, J = 6.5 Hz, 3 H, 1 conformer), 0.99 (d, J = 6.7 Hz, 3 H, 1 conformer), 1.15 (d, J = 7.2 Hz, 3 H, 1 conformer), 1.21 (d, J = 7.2 Hz, 3 H, 1 conformer), 1.22−1.32 (broad m, 10 H), 1.54 (m, 1 H), 1.63 (m, 1 H), 1.78 (m, 1 H), 1.88 (m, 1 H), 2.10 (m, 1 H, major conformer), 2.31 (m, 1 H, minor conformer), 2.42 (m, 1 H), 2.64 (m, 1 H), 3.08 (m, 1 H, minor conformer), 3.24 (m, 1 H, major conformer), 3.41 (dd, J = 11.9, 5.5 Hz, 1 H, 1 conformer), 3.48 (dd, J = 11.9, 3.0 Hz, 1 H, 1 conformer), 3.60 (dd, J = 12.4, 6.7 Hz, 1 H, 1 conformer), 3.68 (dd, J = 12.4, 4.9 Hz, 1 H, 1 conformer), 3.75 (m, 1 H, major conformer), 3.87 (m, 1 H, minor conformer), 4.27 (d, J = 10.9 Hz, 1 H, 1 conformer), 4.31 (d, J = 11.6 Hz, 1 H, 1 conformer), 4.34 (m, 1 H, 1 conformer), 4.53 (m, 1 H, 1 conformer), 4.58 (d, J = 11.6 Hz, 1 H, 1 conformer),

4.57 (a masked doublet, 1 H, 1 conformer), 4.65 (m, 1 H, major conformer), 4.74 (m, 1 H), 4.95 (m, 1 H, minor conformer), 5.15 (d, J = 10.9 Hz, 1 H, major conformer), 5.46 (d, J = 4.8 Hz, 1 H, minor conformer), 6.85 (d, J = 8.7 Hz, 2 H, minor conformer), 6.89 (d, J = 8.7 Hz, 2 H, major conformer), 7.17 (d, J = 8.7 Hz, 2 H, minor conformer), 7.27 (d, J = 8.7 Hz, 2 H, major conformer); ^{13}C NMR (101 MHz, $CDCl_3$), both conformers, δ −5.02, −5.00, −4.9, −4.8, 12.3, 12.9, 14.1, 17.7, 17.9, 18.0, 18.4, 19.0, 19.7, 22.6, 25.7, 25.8, 27.4, 28.6, 29.1, 29.2, 29.8, 31.72, 31.74, 32.3, 35.1, 35.6, 37.4, 39.1, 41.0, 41.8, 54.6, 55.20, 55.24, 56.7, 58.0, 58.8, 68.7, 70.6, 71.4, 71.6, 75.6, 76.5, 78.9, 79.92, 79.94, 82.3, 113.8, 113.9, 129.3, 129.71, 129.74, 159.3, 159.4, 167.4, 169.8, 170.0, 171.4, 172.6, 173.2; HRFAB calcd for $C_{37}H_{62}O_8NSi$ [(M + H)$^+$] 676.4245, found 676.4250.

Analog 3. A stock solution in a polyethylene bottle was prepared of 70% HF/pyridine (1.0 mL, purchased from Aldrich), pyridine (2.0 mL), and THF (8.0 mL). Most of this stock solution (9.5 mL) was added to a solution of TBS ether **19** (124 mg, 0.183 mmol) in THF (5.5 mL) in another polyethylene bottle. After being stirred for 15 h at 25 °C, the solution was extracted in CH_2Cl_2 (2 × 60 mL) with 0.1 N $NaHSO_4$ (3 × 40 mL). Preparative TLC (55% EtOAc/hexanes) produced analog **3** (R_f = 0.53, 88 mg, 85% yield) as a colorless film: $[\alpha]^{22}_D$ −37° (c 0.059, $CHCl_3$); IR (neat) 1171, 1250, 1514, 1626, 1730, 1748, 2928, 3428 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$), both conformers (about 1.1:1) unless stated otherwise, δ 0.81 (d, J = 6.6 Hz, 3 H, 1 conformer), 0.84 (d, J = 6.4 Hz, 3 H, 1 conformer), 0.88 (t, J = 6.9 Hz, 3 H), 0.95 (d, J = 6.1 Hz, 3 H, 1 conformer), 1.00 (d, J = 6.4 Hz, 3 H, 1 conformer), 1.15 (d, J = 6.9 Hz, 3 H, 1 conformer), 1.22 (d, J = 7.0 Hz, 3 H, 1 conformer), 1.23−1.41 (broad m, 10 H), 1.55 (broad m, 1 H, 1 conformer), 1.65 (broad m, 1 H), 1.84 (broad m, 1 H), 1.96 (broad m, 1 H), 2.14 (broad m, 1 H, 1 conformer), 2.32−2.51 (broad m, 2 H), 2.63 (m, 1 H), 3.06 (broad m, 1 H, 1 conformer), 3.25 (m, 1 H, 1 conformer), 3.43 (m, 1 H, 1 conformer), 3.59 (broad m, 1 H), 3.80 (s, 3 H), 3.82 (masked m, 1 H, 1 conformer), 3.90 (broad m, 1 H), 4.32 (m, 1 H), 4.45 (broad m, 1 H, 1 conformer), 4.54 (broad m, 1 H, 1 conformer), 4.57 (d, J = 11.3 Hz, 1 H), 4.67 (broad m, 1 H, 1 conformer), 4.76 (broad m, 1 H), 4.98 (broad m, 1 H, 1 conformer), 5.17 (d, J = 10.9 Hz, 1 H, 1 conformer), 5.46 (broad d, 1 H, 1 conformer), 6.87 (broad pair of doublets, 2 H), 7.17 (d, J = 8.0 Hz, 2 H, 1 conformer), 7.26 (d, J = 8.0 Hz, 2 H, 1 conformer); ^{13}C NMR (126 MHz, $CDCl_3$), both conformers, δ 12.2, 12.8, 14.0, 17.5, 18.1, 18.9, 19.7, 22.5, 25.7, 27.4, 28.5, 29.1, 29.8, 31.7, 32.3, 34.8, 35.1, 37.2, 38.9, 40.9, 41.8, 54.1, 55.2, 56.7, 57.8, 58.6, 68.4, 70.67, 70.71, 71.3, 75.6, 76.5, 79.3, 79.5, 79.8, 82.2, 113.7, 113.9, 129.1, 129.4, 129.5, 129.7, 159.2, 159.4, 167.7, 169.9, 170.2, 171.4, 172.6, 173.3; HRFAB calcd for $C_{31}H_{48}O_8N$ [(M + H)$^+$] 562.3380, found 562.3380.

Analog 4. To a solution of analog **3** (59 mg, 0.10 mmol) in CH_2Cl_2 (1.1 mL) were successively added DMAP (19 mg, 0.16 mmol) and benzyl isocyanate (45 μL, 0.37 mmol). The flask was sealed, and the solution was stirred for 15 h at 25 °C. After extraction in CH_2Cl_2 (2 × 20 mL) with 0.1 N $NaHSO_4$ (20 mL), preparative TLC (33% EtOAc/hexanes) provided analog **4** (R_f = 0.45, 60 mg, 82% yield) as a colorless film: $[\alpha]^{22}_D$ −17° (c 0.058, $CHCl_3$); IR (neat) 1248, 1514, 1725, 2928, 3335 cm^{-1}; ^{1}H NMR (500 mHz, $CDCl_3$), both conformers (about 1.4:1) unless stated otherwise, δ 0.80 (d, J = 6.6 Hz, 3 H, major conformer), 0.86−0.91 (1 triplet, 3 H; 1 pair of doublets, 3 H; 1 doublet, 3 H, minor conformer), 1.14 (d, J = 7.1 Hz, 3 H, major conformer), 1.20 (d, J = 7.2 Hz, 3 H, minor conformer), 1.22−1.40 (broad m, 10 H), 1.55 (m, 1 H, 1 conformer), 1.65 (m, 1 H), 1.81 (m, 1 H, 1 conformer), 1.90 (m, 1 H, 1 conformer), 2.02 (m, 1 H; m, 1 H, 1 conformer), 2.38 (m, 1 H), 2.49−2.64 (m, 2 H), 3.06 (m, 1 H, minor conformer), 3.27 (m, 1 H, major conformer), 3.42 (dd, J = 13.7, 4.5 Hz, 1 H, major conformer), 3.66 (m, 1 H, 1 conformer), 3.78 (s, 3 H, minor conformer), 3.80 (s, 3 H, major conformer), 3.83 (m, 1 H, 1 conformer), 3.87 (m, 1 H), 4.05 (dd, J = 13.3, 3.1 Hz, 1 H, minor conformer), 4.25−4.42 (m, 3 H), 4.56−4.59 (2 doublets, 1 H), 4.69 (m, 1 H, 1 conformer), 4.74 (m, 1 H), 4.97 (m, 1 H, 1 conformer), 507 (m, 1 H, 1 conformer), 5.13 (d, J = 11.0 Hz, 1 H), 5.16 (m, 1 H, 1 conformer), 5.29 (m, 1 H, minor conformer), 5.43 (d, J = 4.5 Hz, 1 H, minor conformer), 6.86 (d, J = 8.5 Hz, 2 H, minor conformer), 6.88 (d, J = 8.5 Hz, 2 H, major conformer), 7.18 (d, J = 8.5 Hz, 2 H, minor conformer), 7.23−7.34 (m, 5 H; masked doublet, 2 H, major conformer); ^{13}C NMR (126 MHz, $CDCl_3$), both conformers, δ 12.4, 12.9, 14.0, 17.4, 18.0, 18.9, 19.8, 22.5, 25.7, 27.2, 28.5, 29.0, 29.12, 29.13, 30.2, 31.66, 31.69, 32.2, 32.6, 35.2, 35.9, 37.0, 40.9, 41.8, 44.9, 45.0, 52.5, 53.9, 55.1, 55.2, 57.3, 58.4, 70.8, 71.0, 72.0, 74.7, 75.6, 79.2, 79.3, 79.8, 81.8, 113.8, 114.0, 127.37, 127.42, 127.5, 127.6, 128.57, 128.58, 128.7, 129.5, 129.6, 138.1, 138.3, 155.6, 155.9, 159.3, 159.4, 167.2, 169.8, 169.9, 171.2, 172.6, 173.4; HRFAB calcd for $C_{39}H_{55}O_9N_2$ [(M + H)$^+$] 695.3908, found 695.3911.

Analog 5. To a mixture of analog **3** (29 mg, 0.052 mmol) in CH_2Cl_2 (1.0 mL) and water (0.06 mL) was added DDQ (29 mg, 0.13 mmol). The flask was sealed, and the mixture was stirred vigorously for 2.5 h at 25 °C. After extraction in EtOAc (2 × 15 mL) with saturated $NaHCO_3$ (2 × 15 mL), preparative TLC (90% EtOAc/hexanes) produced analog **5** (R_f = 0.51, 19 mg, 83% yield) as a white solid: $[\alpha]^{22}_D$ −41° (c 0.019, $CHCl_3$); IR (neat) 1167, 1626, 1732, 1748, 2928, 3401 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, about 6.5:1 conformers), the major conformer, δ 0.88 (t, J = 6.9 Hz, 3 H), 0.92−1.05 (2 coincidental pairs of doublets, 6 H), 1.18 (d, J = 7.0 Hz, 3 H), 1.22−1.41 (broad m, 10 H), 1.54 (broad m, 1 H), 1.85 (broad m, 1 H), 2.09 (broad m, 1 H), 2.18 (broad m, 1 H), 2.27 (broad m, 1 H), 2.48 (broad d, 1 H, the hydroxyl group on the proline ring), 2.56 (m, 2 H), 3.13 (m, 1 H), 3.49 (broad m, 2 H, including the β-hydroxyl group), 3.67 (broad m, 1 H), 4.07 (broad m, 1 H), 4.48 (broad m, 1 H), 4.55 (broad m, 1 H), 4.83 (broad m, 1 H), 5.27 (d, J = 10.4 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$), the major conformer, δ 11.2, 14.1, 17.9, 19.8, 22.6, 25.4, 28.6, 29.1, 29.3, 29.5, 31.7, 38.8, 39.5, 41.0, 54.7, 62.1, 70.5, 72.9, 76.2, 82.0, 170.9, 171.3, 172.6; HRFAB calcd for $C_{23}H_{40}O_7N$ [(M + H)$^+$] 442.2805, found 442.2808.

Analog 6. The procedure for the synthesis of analog **5** was used. Preparative TLC (60% EtOAc/hexanes) afforded analog **6** (R_f = 0.55, 17.5 mg, 71% yield) as a colorless film: $[\alpha]^{22}_D$ −27° (c 0.017, $CHCl_3$); IR (neat) 1167, 1258, 1636, 1727, 2928, 3341 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, about 6.0:1 conformers), the major conformer, δ 0.86 (d, J = 5.2 Hz, 3 H), 0.88 (t, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.3 Hz, 3 H), 1.17 (d, J = 7.1 Hz, 3 H), 1.22−1.39 (broad m, 10 H), 1.52 (m, 1 H), 1.84 (m, 1 H), 2.00 (m, 1 H), 2.30 (m, 2 H), 2.48 (dd, J = 16.7, 10.2 Hz, 1 H), 2.68 (dd, J = 16.7, 4.3 Hz, 1 H), 3.12 (m, 2 H, including the hydroxyl group), 3.52 (dd, J = 13.0, 3.7 Hz, 1 H), 3.96 (d, J = 13.0 Hz, 1 H), 4.10 (m, 1 H), 4.29 (dd, J = 14.9, 5.8 Hz, 1 H), 4.38 (dd, J = 14.9, 6.3 Hz, 1 H), 4.43 (m, 1 H), 4.81 (m, 1 H), 5.12 (t, J = 6.0 Hz, 1 H (the N-H)), 5.20 (broad m, 1 H), 5.26 (d, J = 10.8 Hz, 1 H), 7.23−7.35 (m, 5 H); ^{13}C NMR (101 MHz, $CDCl_3$), the major conformer, δ 11.1, 14.1, 17.8, 19.9, 22.6, 25.4, 28.7, 29.1, 29.3, 29.7, 31.7, 35.6, 39.6, 41.0, 45.0, 53.1, 62.5, 72.5, 74.4, 76.3, 81.6, 127.6, 127.7, 128.7, 138.1, 155.6, 170.9, 171.1, 172.5; HRFAB calcd for $C_{31}H_{47}O_8N_2$ [(M + H)$^+$] 575.3332, found 575.3330.

(3*R*,4*S*)-3-Methylundec-1-en-4-ol (20). To a mixture of sublimed ^{t}BuOK (2.733 g, 24.35 mmol) in THF (30 mL) at −78 °C were added *trans*-2-butene (about 6 mL) and then ^{n}BuLi (13.4 mL, 22.14 mmol, 1.65 M in pentane). The bright yellow mixture was stirred at −78 °C for 30 min, and a solution of (+)-*B*-methoxydiisopinocampheylborane (8.40 g, 26.57 mmol) in THF (25 mL) was added, resulting in the disappearance of much of the yellow color. The solution was stirred at −78 °C for 30 min, and then BF_3·OEt_2 (3.65 mL, 28.78 mmol) was added, giving a white mixture. A solution of octanal (3.46 mL, 22.14 mmol) in THF (25 mL) was immediately added, and the thickened mixture was stirred for 2.5 h at −78 °C and 1.5 h without the −78 °C bath. The mixture was cooled to 0 °C, and 30% aqueous H_2O_2 (8 mL) and 3 M NaOH (16 mL) were added slowly. After the mixture was stirred overnight at 25 °C, most THF was removed *in vacuo* and extraction in EtOAc (2 × 150 mL) was done successively with brine (200 mL) and water (150 mL). Flash chromatography with silica gel (gradient to 8% EtOAc/hexanes) and concentration *in vacuo* at 30 °C provided alcohol **20** (3.50 g, 86% yield) as a colorless liquid in >95% de and >95% ee. (Though the specific rotation is zero, the ee of alcohol **20** is >95% since coupling of acid **24** and L-Val-OMe with BOP reagent quantitatively resulted in only one isomer of the amide product.) **20**: $[\alpha]^{22}_D$ 0° (c 0.029, $CHCl_3$);

IR (neat) 912, 999, 1460, 3368 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3 H), 1.03 (d, J = 6.9 Hz, 3 H), 1.22−1.40 (broad m, 10 H), 1.48 (broad m, 2 H), 2.21 (m, 1 H), 3.39 (m, 1 H), 5.08−5.12 (m, 2 H), 5.76 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1, 16.3, 22.6, 25.7, 29.3, 29.7, 31.8, 34.2, 44.1, 74.7, 116.1, 140.4; HREI calcd for $C_{12}H_{24}O$ (M^+) 184.1827, found 184.1822.

(3*R*,4*R*)-4-Azido-3-methyl-1-undecene (21). To a solution of alcohol **20** (512 mg, 2.78 mmol) and triphenylphosphine (1.24 g, 4.72 mmol) in THF (17 mL) at 0 °C were successively added diisopropyl azodicarboxylate (DIAD, 929 μL, 4.72 mmol) dropwise and diphenylphosphoryl azide (DPPA, 1.02 mL, 4.72 mmol). The milky beige mixture was stirred at 0 °C for 5 min and at 25 °C for 15 h. Addition of $CHCl_3$ (3 mL) dissolved the mixture and concentration *in vacuo* resulted in a thick oil. Flash chromatography with silica gel (eluent was 100% hexanes) and concentration *in vacuo* at 30 °C furnished azide **21** (550 mg, 95% yield) as a colorless liquid: $[\alpha]^{22}_D$ +32° (*c* 0.032, $CHCl_3$); IR (neat) 918, 1252, 1274, 1456, 2099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3 H), 1.07 (d, J = 6.7 Hz, 3 H), 1.22−1.38 (broad m, 10 H), 1.47 (m, 1 H), 1.55 (m, 1 H), 2.33 (m, 1 H), 3.15 (m, 1 H), 5.04−5.10 (m, 2 H), 5.75 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1, 15.9, 22.6, 26.4, 29.2, 29.4, 31.8, 31.9, 42.4, 67.6, 115.4, 140.4; HREI calcd for $C_{12}H_{24}N$ [$(M - N_2 + H)^+$] 182.1909, found 182.1903.

(3*R*,4*R*)-4-[*N*-(Benzyloxycarbonyl)amino]-3-methyl-1-undecene (22). Water (142 μL, 7.89 mmol) was added to a solution of azide **21** (550 mg, 2.63 mmol) and triphenylphosphine (896 mg, 3.42 mmol) in THF (10 mL). After the solution was stirred at 25 °C for 30 h, DIPEA (916 μL, 5.26 mmol) and benzyl chloroformate (488 μL, 3.42 mmol) were added. Stirring at 25 °C for 6 h, concentration *in vacuo*, and flash chromatography with silica gel (gradient to 10% EtOAc/hexanes) furnished carbamate **22** (527 mg, 63% yield for two steps) as flat, colorless crystals: $[\alpha]^{22}_D$ +25° (*c* 0.028, $CHCl_3$); IR (neat) 696, 916, 1243, 1542, 1687, 3319 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J = 7.0 Hz, 3 H), 1.01 (d, J = 6.9 Hz, 3 H), 1.13−1.33 (broad m, 10 H), 1.35 (broad m, 1 H), 1.54 (broad m, 1 H), 2.30 (m, 1 H), 3.58 (m, 1 H), 4.55 (d, J = 9.7 Hz, 1 H), 5.00−5.14 (m, 4 H), 5.71 (m, 1 H), 7.29−7.36 (m, 5 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1, 16.0, 22.6, 26.1, 29.2, 29.5, 31.76, 31.79, 42.6, 55.1, 66.5, 115.3, 127.97, 128.00, 128.5, 136.8, 140.5, 156.2; HREI calcd for $C_{20}H_{32}O_2N$ [$(M + H)^+$] 318.2433, found 318.2430.

(2*S*,3*R*)-3-[*N*-(Benzyloxycarbonyl)amino]-2-methyl-1-decanal (23). Ozone was bubbled into a solution of olefin **22** (468 mg, 1.47 mmol) in CH_2Cl_2 (20 mL) at −78 °C for 4 min. Triphenylphosphine (503 mg, 1.92 mmol) was added, the −78 °C bath was removed, and the solution was stirred at 25 °C for 12 h. Concentration *in vacuo* and flash chromatography with silica gel (gradient to 20% EtOAc/hexanes) produced aldehyde **23** (421 mg, 90% yield) as colorless crystals: $[\alpha]^{22}_D$ +47° (*c* 0.022, $CHCl_3$); IR (neat) 1254, 1536, 1692, 1720, 3316 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3 H), 1.08 (d, J = 7.2 Hz, 3 H), 1.20−1.35 (broad m, 10 H), 1.47 (broad m, 2 H), 2.55 (m, 1 H), 4.11 (m, 1 H), 4.76 (d, J = 9.3 Hz, carbamate N-H), 5.05 (d, J = 12.2 Hz, 1 H), 5.10 (d, J = 12.2 Hz, 1 H), 7.29−7.39 (m, 5 H), 9.72 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 8.5, 14.0, 22.6, 26.3, 29.1, 29.2, 31.7, 32.6, 50.6, 51.2, 66.8, 128.0, 128.2, 128.5, 136.3, 156.0, 203.5; HRFAB calcd for $C_{19}H_{30}O_3N$ [$(M + H)^+$] 320.2226, found 320.2233.

(2*S*,3*R*)-3-[*N*-(Benzyloxycarbonyl)amino]-2-methyl-1-decanoic Acid (24). To a solution of aldehyde **23** (350 mg, 1.10 mmol) in ^{t}BuOH (3.0 mL) were added 2-methyl-2-butene (1.10 mL, 2.19 mmol, 2.0 M in THF) and then a solution of 80% sodium chlorite (149 mg, 1.31 mmol) and NaH_2PO_4 (131 mg, 1.10 mmol) in water (1.0 mL). The round-bottom flask was sealed, and the mixture was stirred vigorously at 25 °C for 15 h. Extraction in EtOAc (3 × 40 mL) with 0.1 M $NaHSO_4$ (30 mL) followed by water (30 mL) gave clean acid **24** (367 mg, 100% yield) as a white solid: $[\alpha]^{22}_D$ +29° (*c* 0.018, $CHCl_3$); IR (neat) 1258, 1541, 1692, 3318 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 3 H), 1.18 (d, J = 7.1 Hz, 3 H), 1.20−1.33 (broad m, 10 H), 1.36 (broad m, 1 H), 1.52 (broad m, 1 H), 2.70 (m, 1 H), 3.87 (m, 1 H), 5.03 (d, J = 9.9 Hz, 1 H), 5.07 (d, J = 12.2 Hz, 1 H), 5.12 (d, J = 12.2 Hz, 1 H), 7.29−7.36 (m, 5 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.2, 14.1, 22.6, 26.3, 29.1, 29.3, 31.5, 31.7, 43.8, 53.2, 66.8, 128.0, 128.1, 128.5, 136.5, 156.2, 179.8; HRFAB calcd for $C_{19}H_{30}O_4N$ [$(M + H)^+$] 336.2175, found 336.2180.

(2*S*,3*R*)-2-[*N*-(*N*-(*tert*-Butyloxycarbonyl)-L-valyl)-*N*-methylamino]-1-phenylhex-5-en-3-ol (26). To a solution of amino alcohol **25** (225 mg, 1.10 mmol) and *N*-Boc-L-valine (262 mg, 1.21 mmol) in MeCN (9 mL) were successively added DIPEA (344 μL, 1.97 mmol) and BOP reagent (628 mg, 1.42 mmol). After the solution was stirred at 25 °C for 15 h, brine (2 mL) and AcOH (44 μL, 0.77 mmol, to quench excess DIPEA) were added to the brown solution and stirring was continued for 10 min. Much MeCN was removed *in vacuo* until bumping became a problem. Extraction in EtOAc (3 × 40 mL) with brine (40 mL) followed by 0.1 M $NaHSO_4$ (40 mL) and flash chromatography with silica gel (gradient to 25% acetone/hexanes) resulted in amide **26** (372 mg, 84% yield) as a colorless oil: $[\alpha]^{22}_D$ −36° (*c* 0.026, $CHCl_3$); IR (neat) 1173, 1368, 1497, 1630, 1705, 3416 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, about 4.5:1 rotamers), the major rotamer, δ 0.89 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 1.43 (s, 9 H), 1.80 (m, 1 H), 2.26−2.36 (m, 3 H), 2.76 (s, 3 H), 3.08 (broad m, 2 H), 3.93 (broad m, 1 H), 4.26 (dd, J = 9.4, 5.2 Hz, 1 H), 5.11 (d, J = 8.8 Hz, carbamate N-H), 5.15−5.17 (m, 2 H), 5.84 (m, 1 H), 7.14−7.29 (m, 5 H); ^{13}C NMR (126 MHz, $CDCl_3$), both rotamers, δ 16.7, 16.9, 19.0, 19.9, 22.6, 25.2, 28.3, 29.0, 30.6, 30.7, 31.5, 32.2, 34.2, 34.6, 38.7, 39.5, 54.5, 55.6, 72.3, 72.8, 79.4, 118.5, 119.0, 126.4, 126.7, 128.4, 128.7, 128.9, 129.2, 134.3, 134.5, 138.4, 138.8, 155.8, 173.2, 173.5; HRFAB calcd for $C_{23}H_{37}O_4N_2$ [$(M + H)^+$] 405.2753, found 405.2748.

Alcohol 27. Trifluoroacetic acid (585 μL, 7.59 mmol) was added to a solution of Boc carbamate **26** (307 mg, 0.759 mmol) in CH_2Cl_2 (5 mL). After the solution was stirred at 25 °C for 2 h, TFA and CH_2Cl_2 were removed *in vacuo*. Extraction in EtOAc (2 × 40 mL and 2 × 30 mL) with 1 M NaOH (40 mL) and then water (30 mL) gave the desired amino alcohol (227, mg, 98% crude yield) as a colorless oil.

To a solution of the above crude amino alcohol (205 mg, 0.673 mmol) and acid **24** (249 mg, 0.741 mmol) in MeCN (8 mL) were added DIPEA (211 μL, 1.21 mmol) and BOP reagent (387 mg, 0.875 mmol). After the solution was stirred at 25 °C for 15 h, brine (1.3 mL) and AcOH (27 μL) were added to the brown solution and stirring was continued for 10 min. After removing much MeCN *in vacuo*, extraction in EtOAc (3 × 40 mL) with brine (30 mL) followed by 0.1 M $NaHSO_4$ (30 mL) and flash chromatography with silica gel (gradient to 50% EtOAc/hexanes) provided alcohol **27** (350 mg, 84% yield for two steps) as a colorless oil: $[\alpha]^{22}_D$ −1.1° (*c* 0.038, $CHCl_3$); IR (neat) 699, 1255, 1455, 1534, 1624, 1636, 1696, 3304 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 4:1 rotamers), the major rotamer, δ 0.84−0.89 (overlapping d and t, 6 H), 0.90 (d, J = 6.9 Hz, 3 H), 1.14 (d, J = 7.0 Hz, 3 H), 1.16−1.32 (broad m, 10 H), 1.38 (broad m, 1 H), 1.48 (broad m, 1 H), 1.83 (broad m, 1 H), 2.27 (broad m, 3 H), 2.52 (broad m, 1 H), 2.76 (s, 3 H), 3.07 (broad m, 2 H), 3.70 (broad m, 1 H), 3.91 (broad m, 1 H), 4.57 (dd, J = 8.6, 4.6 Hz, 1 H), 5.09−5.18 (m, 4 H), 5.65 (d, J = 9.1 Hz, 1 H), 5.83 (m, 1 H), 6.07 (d, J = 8.1 Hz, 1 H), 7.13−7.39 (m, 10 H); ^{13}C NMR (126 MHz, $CDCl_3$), both rotamers, δ 14.1, 14.2, 16.3, 16.8, 19.5, 20.1, 22.59, 22.61, 26.36, 26.44, 29.1, 29.2, 29.30, 29.32, 29.6, 29.7, 29.9, 30.6, 31.7, 31.8, 32.2, 34.0, 38.7, 39.5, 45.2, 54.2, 54.4, 66.4, 72.7, 118.6, 118.8, 126.4, 126.7, 127.80, 127.84, 127.88, 127.90, 128.38, 128.40, 128.7, 128.9, 129.0, 129.1, 134.36, 134.43, 136.7, 136.8, 138.4, 138.7, 156.2, 156.3, 173.2, 173.3, 174.0, 174.1; HRFAB calcd for $C_{37}H_{56}O_5N_3$ [$(M + H)^+$] 622.4220, found 622.4212.

TBS Ether 28. To a solution of alcohol **27** (213 mg, 0.342 mmol) in CH_2Cl_2 (5 mL) at 0 °C were successively added 2,6-lutidine (80 μL, 0.685 mmol) and TBSOTf (118 μL, 0.514 mmol). After the solution was stirred at 0 °C for 1 h, extraction in EtOAc (3 × 30 mL) with aqueous $NaHCO_3$ (20 mL) followed by 0.1 M $NaHSO_4$ (30 mL) and flash chromatography with silica gel (gradient to 30% EtOAc/hexanes) afforded TBS ether **28** (219 mg, 87% yield) as a colorless oil: $[\alpha]^{22}_D$ −11° (*c* 0.042, $CHCl_3$); IR (neat) 696, 776, 836, 1063, 1257, 1535, 1641, 1694, 3296 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 4:1 rotamers), the major rotamer, δ 0.11 (s, 6 H), 0.82−0.88 (overlapping d and t, 6 H), 0.89 (d, J = 6.9 Hz, 3 H), 0.94 (s, 9 H), 1.14 (d, J = 7.1 Hz, 3 H), 1.16−1.32 (broad m, 10 H), 1.37 (broad m, 1 H), 1.46 (broad

m, 1 H), 1.82 (broad m, 1 H), 2.18−2.35 (m, 3 H), 2.47 (broad m, 1 H), 2.75 (broad m, 1 H), 2.86 (dd, J = 14.3, 10.7 Hz, 1 H), 2.99 (s, 3 H), 3.16 (dd, J = 14.3, 3.5 Hz, 1 H), 3.68 (broad m, 1 H), 4.51 (broad m, 1 H), 5.03−5.18 (m, 4 H), 5.91 (m, 1 H), 5.97 (d, J = 8.8 Hz, an N-H), 6.04 (d, J = 9.1 Hz, an N-H), 7.05−7.41 (m, 10 H); ^{13}C NMR (126 MHz, $CDCl_3$), both rotamers, δ −4.7, −4.6, −3.8, −3.6, 14.1, 14.2, 14.4, 15.6, 16.7, 18.02, 18.04, 19.9, 20.2, 22.59, 22.62, 25.89, 25.93, 26.5, 29.1, 29.2, 29.26, 29.34, 30.0, 30.2, 30.5, 31.8, 32.2, 40.4, 45.2, 45.3, 54.2, 54.4, 62.3, 66.3, 66.4, 75.1, 117.8, 118.5, 126.2, 126.6, 127.8, 127.9, 128.2, 128.29, 128.34, 128.4, 128.6, 128.9, 129.1, 133.8, 134.0, 136.9, 137.0, 138.8, 156.2, 172.0, 172.8, 173.87, 173.91; HREI calcd for $C_{43}H_{69}O_5N_3Si$ (M^+) 735.5006, found 735.5000.

Aldehyde 29. Ozone was bubbled into a solution of olefin **28** (199 mg, 0.270 mmol) in CH_2Cl_2 (8 mL) at −78 °C for 3 min. Triphenylphosphine (99 mg, 0.38 mmol) was added, the −78 °C bath was removed, and stirring transpired at 25 °C for 12 h. Flash chromatography with silica gel (gradient to 40% EtOAc/hexanes) gave aldehyde **29** (183 mg, 92% yield) as a colorless oil: $[\alpha]^{22}_D$ −17° (*c* 0.036, $CHCl_3$); IR (neat) 697, 777, 837, 1085, 1255, 1456, 1534, 1640, 1694, 1725, 3295 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 4:1 rotamers), the major rotamer, δ 0.09 (s, 3 H), 0.14 (s, 3 H), 0.80 (d, J = 6.4 Hz, 3 H), 0.85−0.89 (overlapping d and t, 6 H), 0.92 (s, 9 H), 1.10 (d, J = 6.0 Hz, 3 H), 1.15−1.33 (broad m, 10 H), 1.38 (broad m, 1 H), 1.46 (broad m, 1 H), 1.77 (broad m, 1 H), 2.50 (m, 1 H), 2.54 (m, 1 H), 2.63 (dd, J = 5.6, 2.3 Hz, 1 H), 2.67 (dd, J = 5.7, 2.4 Hz, 1 H), 2.73 (broad m, 1 H), 2.77 (m, 1 H), 2.85 (s, 3 H), 3.22 (broad m, 1 H), 3.67 (broad m, 1 H), 4.45 (broad m, 1 H), 5.13 (m, 2 H), 5.89 (d, J = 8.1 Hz, 1 H), 7.09−7.41 (m, 10 H), 9.78 (t, J = 2.1 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$), both rotamers, δ −4.8, −4.7, −4.3, −4.2, 14.1, 14.2, 15.6, 16.5, 17.9, 18.0, 20.0, 20.3, 22.6, 25.7, 25.9, 26.4, 26.5, 29.1, 29.2, 29.26, 29.30, 29.34, 29.6, 29.8, 30.2, 31.7, 31.8, 34.0, 34.4, 45.1, 48.8, 49.1, 54.2, 54.4, 65.0, 66.3, 66.4, 68.6, 68.7, 126.4, 126.8, 127.8, 127.9, 128.3, 128.35, 128.40, 128.5, 128.6, 128.8, 129.1, 136.8, 136.9, 138.4, 156.2, 156.3, 172.6, 173.3, 174.1, 174.2, 200.1, 200.9; HRFAB calcd for $C_{42}H_{68}O_6N_3Si$ [(M + H)$^+$] 738.4877, found 738.4882.

Acid 30. To a solution of aldehyde **29** (162 mg, 0.219 mmol) in ^{t}BuOH (2.0 mL) were added successively 2-methyl-2-butene (274 μL, 0.548 mmol, 2.0 M in THF) and a solution of 80% sodium chlorite (32 mg, 0.28 mmol) and NaH_2PO_4 (26 mg, 0.22 mmol) in water (0.6 mL). The flask was sealed and the mixture was stirred vigorously at 25 °C for 15 h. Extraction in EtOAc (3 × 25 mL) with 0.1 M $NaHSO_4$ (15 mL) and then water (10 mL) furnished acid **30** (165 mg, 100% crude yield) as a colorless oil: $[\alpha]^{22}_D$ −16° (*c* 0.021, $CHCl_3$); IR (neat) 698, 836, 1082, 1253, 1454, 1535, 1618, 1709, 3300 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), both rotamers, δ 0.13−0.17 (singlets, 6 H), 0.80−0.90 (m, 9 H), 0.93 (s, 9 H), 1.13 (overlapping doublets, 3 H), 1.16−1.50 (broad m, 12 H), 1.65 (broad m, 1 H), 2.29−2.95 (broad m, 7 H), 3.04−3.27 (broad m, 2 H), 3.51−3.81 (broad m, 1 H), 4.25−4.56 (broad m, 1 H), 4.71−4.97 (broad m, 1 H), 5.10 (m, 2 H), 5.28 (d, J = 11.4 Hz, 1 H, major rotamer), 5.96 (d, J = 9.7 Hz, 1 H, minor rotamer), 6.22−6.58 (broad d, 1 H), 7.07−7.39 (m, 10 H); ^{13}C NMR (101 MHz, $CDCl_3$), both rotamers, δ −5.0, −4.8, −4.3, −4.1, 14.1, 15.7, 17.8, 17.89, 17.94, 19.9, 21.0, 22.6, 25.8, 26.5, 26.8, 29.18, 29.24, 29.3, 29.4, 30.0, 30.7, 31.8, 34.2, 45.1, 46.5, 53.8, 54.0, 55.3, 66.5, 67.4, 71.3, 71.8, 126.5, 126.8, 127.7, 127.9, 128.37, 128.43, 128.5, 128.9, 129.0, 129.1, 136.1, 136.7, 138.4, 156.4, 158.2, 172.6, 175.1; HRFAB calcd for $C_{42}H_{68}O_7N_3Si$ [(M + H)$^+$] 754.4827, found 754.4822.

TBS Ether of the Triamide Analog of Hapalosin (31). To a solution of acid **30** (138 mg, 0.183 mmol) in MeOH (4 mL) was added 10% Pd on activated carbon (35 mg). The round-bottom flask was purged with N_2, H_2 was bubbled into the mixture for 3 min, and stirring occurred at 25 °C for 3 h with an H_2-filled balloon attached. Filtration through a short plug of Celite and thorough washing with MeOH and EtOAc resulted in the desired amino acid (112 mg, 99% crude yield) as white crystals.

To a solution of the above crude amino acid (110 mg, 0.177 mmol) in toluene (180 mL) were added DIPEA (308 μL, 1.77 mmol) and BOP-Cl (315 mg, 1.24 mmol). The mixture was stirred at 85 °C for 15 h and then the solution was extracted with 0.1 M $NaHSO_4$ (40 mL). The aqueous layer was back-extracted with EtOAc (3 × 30 mL), and the four organic layers were separately extracted with 0.1 M $NaHSO_4$ (30 mL). Flash chromatography with silica gel (gradient to 3.0% MeOH/CH_2Cl_2) afforded the TBS ether of the triamide analog of hapalosin, **31** (71 mg, 66% yield for two steps), as a colorless film: $[\alpha]^{22}_D$ −15° (*c* 0.017, $CHCl_3$); IR (neat) 830, 1063, 1530, 1654, 3281, 3380 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, only one conformer) δ 0.06 (d, J = 6.6 Hz, 3 H), 0.21 (s, 3 H), 0.22 (s, 3 H), 0.58 (d, J = 6.7 Hz, 3 H), 0.89 (t, J = 6.9 Hz, 3 H), 1.00 (s, 9 H), 1.11 (d, J = 7.1 Hz, 3 H), 1.18−1.35 (broad m, 10 H), 1.46 (broad m, 1 H), 1.66 (m, 1 H), 1.82 (m, 1 H), 2.39 (dd, J = 17.5, 1.8 Hz, 1 H), 2.51 (dd, J = 13.4, 11.0 Hz, 1 H), 2.66 (dd, J = 17.5, 5.0 Hz, 1 H), 2.85 (s, 3 H), 3.28−3.33 (m, 2 H), 3.67 (dd, J = 10.4, 8.5 Hz, 1 H), 3.75 (m, 1 H), 4.01 (m, 1 H), 4.08 (dt, J = 10.2, 2.6 Hz, 1 H), 6.12 (d, J = 10.5 Hz, an N-H), 6.94 (d, J = 6.1 Hz, an N-H), 7.22−7.34 (m, 5 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.9, −3.5, 13.1, 14.1, 17.6, 18.1, 19.0, 22.6, 26.0, 27.8, 28.3, 28.4, 29.26, 29.32, 30.0, 31.9, 36.5, 38.5, 41.2, 52.9, 53.4, 59.6, 71.8, 127.1, 128.9, 129.9, 137.2, 170.4, 171.7, 173.7; HRFAB calcd for $C_{34}H_{60}O_4N_3Si$ [(M + H)$^+$] 602.4353, found 602.4359.

Triamide Analog of Hapalosin (2). TBAF (70 μL, 0.070 mmol, 1.0 M in THF) was added to a solution of the TBS ether of the triamide analog, **31** (21 mg, 0.035 mmol), in THF (1.0 mL) and the solution was stirred at 0 °C for 1 h. Concentration *in vacuo* without warming the water bath and preparative TLC (45% acetone/$CHCl_3$) resulted in a band (R_f = 0.50, brown in ninhydrin staining) containing the triamide analog of hapalosin, **2** (12 mg, 71% yield), as a colorless, glassy film: $[\alpha]^{22}_D$ −24° (*c* 0.0080, CH_2Cl_2); IR (neat) 700, 1051, 1225, 1406, 1455, 1545, 1635, 1651, 1748, 3262 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, only one conformer) δ 0.17 (d, J = 6.7 Hz, 3 H), 0.62 (d, J = 6.8 Hz, 3 H), 0.89 (t, J = 6.9 Hz, 3 H), 1.11 (d, J = 7.1 Hz, 3 H), 1.22−1.43 (broad m, 10 H), 1.72 (m, 1 H), 1.77 (m, 1 H), 1.85 (m, 1 H), 2.26 (dd, J = 16.6, 1.2 Hz, 1 H), 2.64 (dd, J = 16.6, 5.6 Hz, 1 H), 2.70 (dd, J = 13.7, 9.9 Hz, 1 H), 2.88 (s, 3 H), 3.31−3.36 (m, 2 H), 3.69 (m, 1 H), 3.78 (t, J = 9.4 Hz, 1 H), 4.03 (dt, J = 8.1, 3.3 Hz, 1 H), 4.05 (broad m, 1 H), 6.60 (d, J = 10.3 Hz, an N-H), 7.10 (d, J = 5.8 Hz, an N-H), 7.24 (t, J = 7.0 Hz, 1 H), 7.30 (d, J = 7.0 Hz, 2 H), 7.33 (t, J = 7.0 Hz, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.0, 14.1, 17.8, 19.2, 22.6, 26.9, 27.8, 28.8, 29.2, 29.3, 30.2, 31.8, 35.7, 39.8, 41.1, 52.7, 53.9, 59.3, 70.9, 127.0, 128.8, 129.9, 137.3, 170.5, 171.6, 174.0; HREI calcd for $C_{28}H_{45}O_4N_3$ (M^+) 487.3410, found 487.3410.

Acknowledgment. T. D., X. D., and R. A. thank the NIH (Grant GM51095) and UCLA for financial support. Computational resources from Professors Y. Rubin and K. Houk's groups and the Office of Academic Computing at UCLA are greatly appreciated. Studies on the biological activities of the compounds were supported by NIH Grant CA64983 (C.S.).

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds in the three schemes (52 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9708396