Total Synthesis of Cryptophycins. Revision of the Structures of Cryptophycins A and C

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Abstract: The convergent total synthesis of cryptophycins C and D is described. It has been shown that in both natural products the absolute configuration of the α-amino acid corresponds to the D-series. The structural assignment for cryptophycin C has been corrected to reflect this fact. Since the structure of cryptophycin A has been correlated to cryptophycin C, the chloro-*O*-methyltyrosine unit in cryptophycin A has the D-configuration.

Cryptophycins are potent tumor-selective cytotoxins associated with the terrestrial blue-green algae *Nostoc* sp. GSV 224[1] and *Nostoc* sp. ATCC 53789.[2] The major cytotoxin in each alga, cryptophycin A, shows excellent activity against solid tumors implanted in mice, including a drug-resistant tumor. Over 20 related cytotoxins are present in the GSV 224 strain as minor constituents,[1,3] and some of these compounds, e.g., cryptophycins B and C, have been isolated in sufficient amounts for *in vivo* evaluation.[4] In order to acquire adequate quantities of selected naturally-occurring cryptophycins and synthetic analogs for structure–activity relationship (SAR) studies, preclinical evaluation, and human clinical trials, we have designed a general synthesis. Cryptophycins C and D, as described in the original paper, were chosen to be the initial targets as they represented examples from both of the alleged L- and D-tyrosine series. We report here the total syntheses of cryptophycins C and D which (1) revise the structures of cryptophycins A and C to reflect the D-configuration for the α-amino acid unit as depicted in the structural drawings in this paper and (2) confirm the structures of cryptophycins B and D.

Retrosynthetic analysis of the cryptophycins was straightforward: the structure is composed of four units (A–D, Figure 1); consequently several convergent approaches could be envisioned. The combination of two pairs of units (e.g., A–B and C–D) appeared to be optimally convergent. Since the success of the synthesis depended on the formation of a 16-membered depsipeptide from an acyclic precursor, a macrolactamization involving the amino group of unit C and the carboxylate of unit B appeared to be the best choice. The acyclic precursor to cryptophycin D would therefore be **1**. This, in turn, suggested a disconnection into two fragments, one represented by **2** and composed of (*S*)-(−)-2-hydroxy-4-methylvaleric (L-leucic) acid (D) and (*R*)-3-amino-2-methylpropanoic acid (C) units, and the other by **3** and composed of *O*-methyl-D-tyrosine (B) and (2*E*,7*E*,5*S*,6*R*)-5-hydroxy-6-methyl-8-phenyloctadienoic acid (A) units. In the direction of the synthesis, formation of an ester linkage between the carboxylate of unit D in **2** and the hydroxyl group of unit A in **3** would be followed

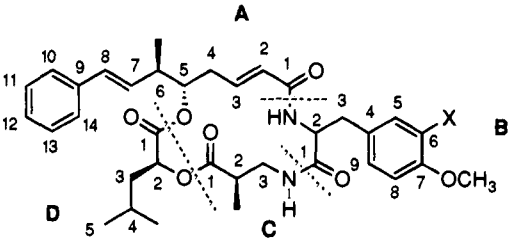
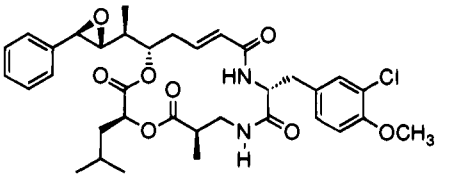
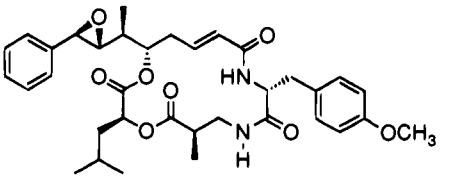


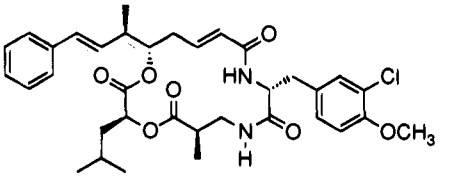
Figure 1. Numbering system for each of the units of cryptophycins C and D. This numbering system is used for the NMR data.



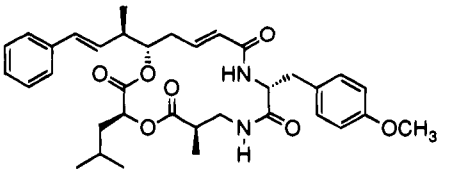
cryptophycin A



cryptophycin B



cryptophycin C



cryptophycin D

[⊗] Abstract published in *Advance ACS Abstracts*, February 15, 1995.

(1) Trimurtulu, G.; Ohtani, I.; Patterson, G. M. L.; Moore, R. E.; Corbett, T. H.; Valeriote, F. A.; Demchik, L. *J. Am. Chem. Soc.* **1994**, *116*, 4729–4737.

(2) Schwartz, R. E.; Hirsch, C. F.; Sesin, D. F.; Flor, J. E.; Chartrain, M.; Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch, J. M.; Yudin, K. *J. Ind. Microbiol.* **1990**, *5*, 113–24.

(3) Trimurtulu, G.; Ogino, J.; Heltzel, C. E.; Patterson, G. M. L.; Moore, R. E. Manuscript in preparation. An explanation of the structural misassignment for cryptophycins A and C is presented.

(4) Heltzel, C. E.; Ogino, J.; Trimurtulu, G.; Mooberry, S. L.; Patterson, G. M. L.; Moore, R. E.; Corbett, T. H.; Valeriote, F. A.; Demchik, L. Manuscript in preparation.

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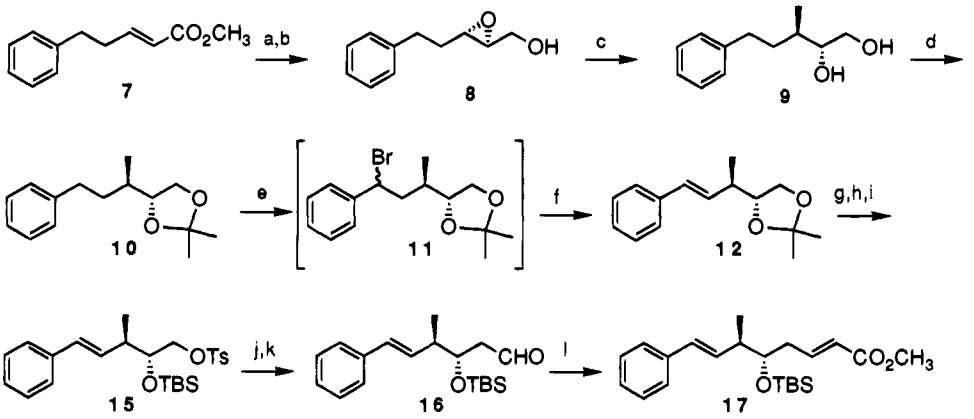
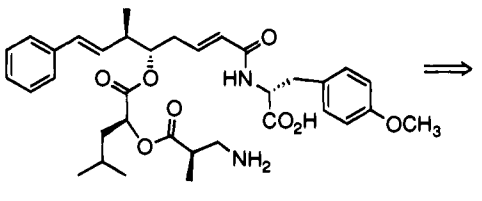
Scheme 1[a]

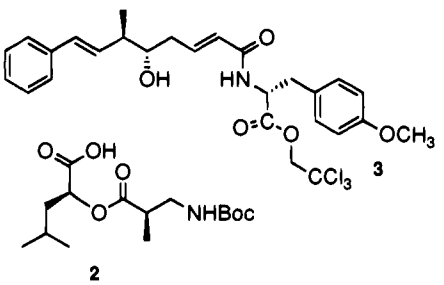


[a] (a) DIBAL, THF, −78 to 25 °C, 90%; (b) L-(+)-DET, Ti(O-iPr)$_4$, *t*-BuOOH, CH_2Cl_2, −20 °C, 94%; (c) $Al(CH_3)_3$, hexane/CH_2Cl_2, 0−25 °C, 95%; (d) $(CH_3O)_2C(CH_3)_2$, PPTS, CH_2Cl_2, 25 °C, 97%; (e) NBS, $(CH_3O)_2C(CH_3)_2$, CCl_4, *hv*, 25 °C; (f) DBU, 70 °C, 80% (two steps); (g) 1% aqueous HCl/CH_3OH, 25 °C, 93%; (h) $Bu_2Sn(OCH_3)_2$, $PhCH_3$, Dean−Stark; TsCl, Et_3N, 0−25 °C, 82%; (i) $TBSOSO_2CF_3$, Et_3N, CH_2Cl_2, 25 °C, 98%; (j) KCN, DMSO, 60 °C, 92%; (k) DIBAL, CH_2Cl_2, −78 to 25 °C, 95%; (l) $(CH_3O)_2POCH_2CO_2CH_3$, TMG, THF, −78 to 25 °C, 83%.

by deprotection and macrolactamization. Compound **2** would be used not only in the synthesis of cryptophycin D but in the synthesis of cryptophycin C as well.

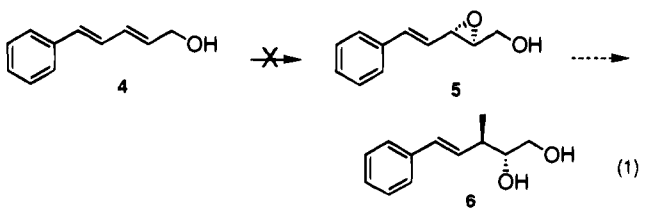


1



2

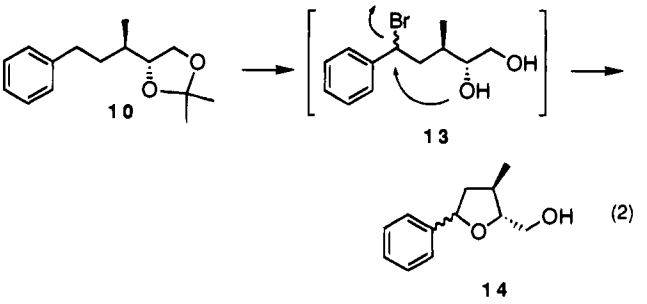
An early approach to the synthesis of the (2*E*,7*E*,5*S*,6*R*)-5-hydroxy-6-methyl-8-phenyloctadienoic acid (unit A) portion of cryptophycin C and D is summarized in eq 1. Attempted



(1)

Sharpless epoxidation of *trans,trans*-dienol **4**,[5] which was prepared from *trans*-cinnamaldehyde, failed to produce epoxy alcohol **5**, presumably due to the extreme lability of **5**.[6] Even if **5** had been successfully formed, the next step in the synthesis appeared to be problematic. When racemic **5**, which had been prepared by exposing **4** to *m*-chloroperoxybenzoic acid, was treated with trimethylaluminum, a mixture of products derived from the non-regiospecific addition of the methyl group was obtained.

This difficulty suggested that the styryl double bond should be deleted from the starting material and introduced at a later stage in the synthesis. Dihydrocinnamaldehyde was converted to enoate **7** (Scheme 1) in 86% yield by exposure to trimethyl phosphonoacetate and tetramethylguanidine (TMG) in tetrahydrofuran (THF). Ester reduction with diisobutylaluminum hydride (DIBAL; 90% yield),[7] followed by Sharpless epoxidation,[6,8] using L-(+)-diethyl tartrate as the catalyst, gave epoxy alcohol **8** (94% yield; >95% ee). The reaction of **8** with trimethylaluminum proceeded in the anticipated manner to produce 1,2-diol **9** in 95% yield.[9] The 1,3-diol which would arise from the alternative mode of attack on the epoxide ring was not detected in the reaction mixture. Introduction of the styryl double bond was accomplished in three steps, by converting **9** to an acetonide **10** (97% yield), benzylic bromination of **10** to **11**, and immediate dehydrobromination of **11** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to **12**.[10] In the process of scaling up the preparation of **12**, it was found that significant quantities of polar byproducts were formed which were shown to be diastereomers of tetrahydrofuran **14** (eq 2).



(2)

Acetonide cleavage by adventitious HBr had presumably led to an intermediate diol **13**, which had then undergone an intramolecular ring closure to **14**. This undesired process was effectively suppressed by the slow addition of 2,2-dimethoxypropane (1 equiv) during the photochemically catalyzed bromination reaction. The overall yield for the conversion of **10** to **12** was 80%. Hydrolysis of the acetonide group in **12** with aqueous acidic methanol proceeded in 93% yield. Selective monotosylation of the primary alcohol group in the resulting

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(6) Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regeneye, R. *Org. Synth.* **1985**, *63*, 66−78.

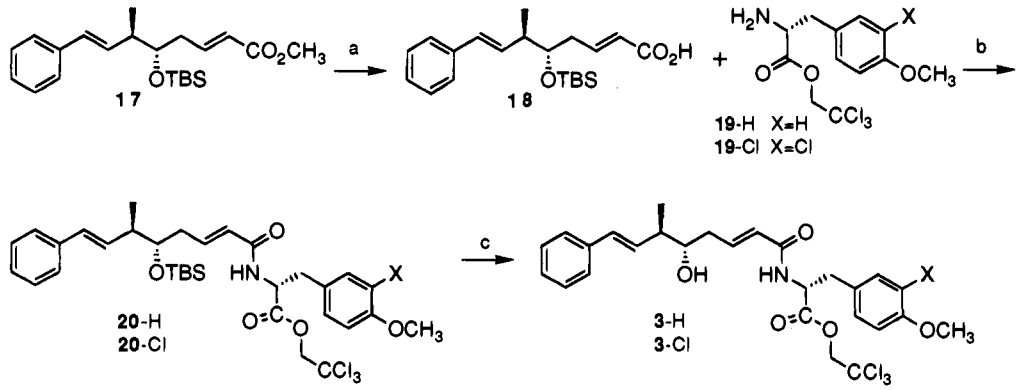
(7) Winterfeldt, E. *Synthesis* **1975**, 617−630.

(8) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *101*, 5974−5976.

(9) (a) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597−3600. (b) Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377−1380.

(10) Wolkoff, P. *J. Org. Chem.* **1982**, *47*, 1944−1948.

Scheme 2[a]



[a] (a)LiOH, acetone, 25 °C, 95%; (b) FDPP, DIEA, DMF, 25 °C, 80% **19**-H; 65% **19**-Cl; (c) CH_3CN, 50% aqueous HF (95/5), 25 °C, 98% **3**-H; 95% **3**-Cl.

(2*R*,3*R*)-3-methyl-5-phenylpent-(4*E*)-ene-1,2-diol was accomplished according to Ley's procedure, by converting the diol to a dibutylstannylene acetal and then exposing this intermediate to *p*-toluenesulfonyl chloride and triethylamine (82% yield).[11] Protection of the secondary alcohol group as the *tert*-butyldimethylsilyl (TBS) ether led to **15** in 98% yield.[12] Displacement of the primary tosylate with cyanide (92% yield) and reduction of the nitrile with DIBAL[7] (95% yield) gave aldehyde **16**, which was then converted to methyl ester **17** (the unit A precursor) in 83% yield by means of a Horner–Emmons reaction. Although the synthesis of **17** was long, the overall yield from dihydrocinnamaldehyde was relatively high at 29%.

The coupling of **17** with the *O*-methyl-D-tyrosine derivative is summarized in Scheme 2. Hydrolysis of the methyl ester group with lithium hydroxide in acetone produced carboxylic acid **18** in 95% yield. Coupling of **18** with trichloroethyl ester **19**-H to produce **20**-H was accomplished in 80% yield by treating a solution of **18** in *N*,*N*-dimethylformamide (DMF) with a small excess of pentafluorophenyl diphenylphosphinate (FDPP), an equimolar quantity of the trifluoroacetate salt of **19**-H, and 3 equiv of diisopropylethylamine (DIEA) at 25 °C.[13] Under these conditions the undesired trifluoroacetamide of **19**-H was not observed as a byproduct.[14] Fluorodesilylation of **20**-H led to **3**-H in 98% yield. Compound **3**-H appeared as a single diastereoisomer in the 300 MHz proton and the 75 MHz carbon NMR spectra, and therefore, the optical purity of **3**-H could be estimated to be >95%.

Protected amino acid **19**-H was prepared using a known general procedure. BOC-D-tyrosine was obtained in 95% yield by treating a suspension of the amino acid in 50% aqueous dioxane with 1.2 equiv of di-*tert*-butyl dicarbonate in the presence of 1.2 equiv of triethylamine. The resulting product was dimethylated with dimethyl sulfate in the presence of powdered potassium carbonate in refluxing acetone in 85% yield. The methyl ester was cleaved by careful saponification with sodium hydroxide in aqueous dioxane to yield BOC-*O*-methyl-D-tyrosine. The physical data for this compound, except for the sign of the optical rotation, corresponded to those of the known enantiomer.[15] Exposure of the BOC-*O*-methyl-D-tyrosine to trichloroethanol, pyridine, and DCC in dichloromethane led to trichloroethyl ester **19**-H in 37% overall yield from D-tyrosine. Dissolving this material in neat trifluoroacetic acid at 0 °C, followed by warming to 25 °C and evaporation of the solvent, produced the trifluoroacetate salt of **19**-H in quantitative yield as an amorphous solid. The optical purity was assessed by forming the (*S*)-Mosher amides of **19**-H and the corresponding racemic compound and comparing their 300 MHz ^{1}H NMR spectra. The optical purity of **19**-H was estimated to be >95%.

Having accomplished the coupling of units A and B, attention was focused on the synthesis of the remaining portion of the molecule. A chiral pool approach was chosen for the synthesis of the β-amino acid[16] unit C rather than one of the *de novo* methods.[17] The starting point for the unit C portion of **2** was commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropanoate (**21**) (Scheme 3). Ammonolysis of **21** with ammonia in methanol at 50 °C in a sealed tube for 1 week afforded (*S*)-3-hydroxy-2-methylpropanamide in 66% yield, along with unreacted methyl ester, which was recovered and recycled. The ammonolysis was faster in the presence of 10% sodium cyanide;[18] however, removal of the cyanide catalyst from the water-soluble hydroxamide by continuous extraction was tedious. Amide reduction with borane–THF complex gave the amino alcohol **22** in 77% yield after distillation. Protection of the amine by treatment with di-*tert*-butyl dicarbonate in the presence of triethylamine (100% yield) followed by oxidation of the primary alcohol with ruthenium tetraoxide (74% yield) gave carboxylic acid **23**.[19] L-leucic acid was converted to allyl ester **24** in 93% yield under phase-transfer conditions, by exposing it to a mixture of allyl bromide in dichloromethane and aqueous sodium bicarbonate containing tetra-*n*-butylammonium chloride.[20] The coupling reaction of **23** with **24** was

(11) Boons, G.-J.; Castle, G. H.; Clase, J. A.; Grice, P.; Ley, S. V.; Pinel, C. *Synlett*, **1993**, 913–914.

(12) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. *Tetrahedron Lett.* **1981**, *22*, 3455–3458.

(13) Chen, S.; Xu, J. *Tetrahedron Lett.* **1991**, *32*, 6711–6714.

(14) Couplings with DCC/hydroxybenzotriazole or *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (BOP-Cl) [Cabré, J.; Palomo, A. L. *Synthesis* **1984**, 413–417; not to be confused with BOP, (benzotriazolyloxy)tris(dimethylamino)phosphonium hexafluorophosphate, also known as Castro's reagent: Nguyen, D. L.; Seyer, R.; Heitz, A.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1025–1031] as condensing agents did not lead to improved yields of **20**-H. Furthermore, products were contaminated with the trifluoroacetamide to varying degrees. Exchange of the counterion of **19**-H to tosylate alleviated the latter problem, but led to significantly longer reaction times.

(15) Dourtoglou, V.; Gross, B.; Lambropoulou, V.; Zioudrou, C. *Synthesis* **1984**, 572–574.

(16) In contrast to the number of general methods available for the enantioselective synthesis of α-amino acids, there are fewer methods in the literature for the preparation of β-amino acids. (a) Gmeiner, P. *Tetrahedron Lett.* **1990**, *31*, 5717–5720. (b) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553–2557. (c) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3–11.

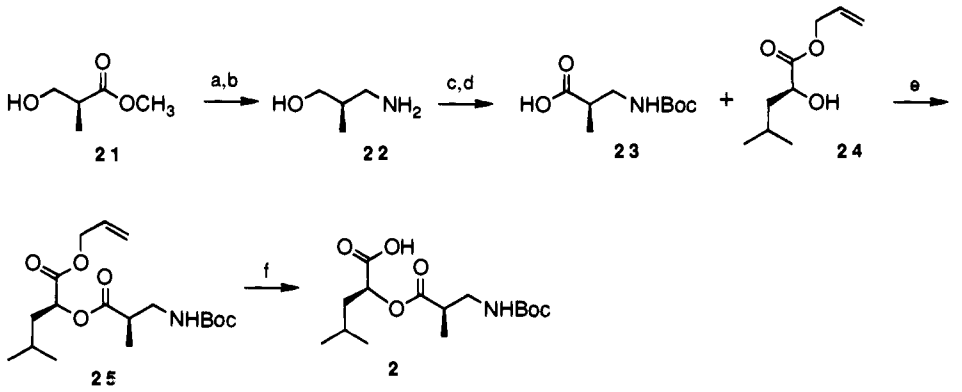
(17) (a) Furukawa, M.; Okawara, T.; Terawaki, Y. *Chem. Pharm. Bull.* **1977**, *25*, 1319–1325. (b) Gani, D.; Hitchcock, P. B.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1363–1372.

(18) Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033–2036.

(19) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

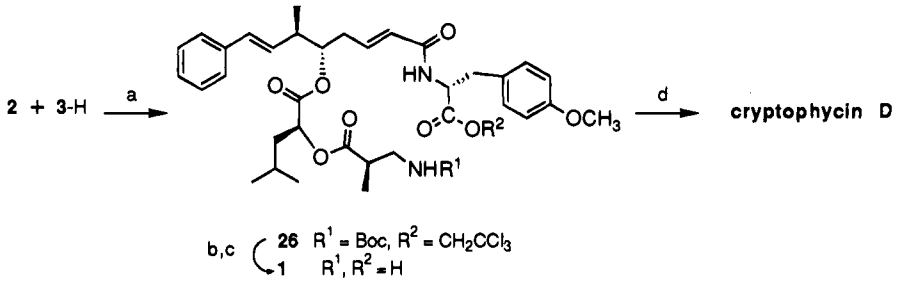
(20) Friedrich-Bochnitschek, S.; Waldmann, H.; Hunz, H. *J. Org. Chem.* **1989**, *54*, 751–756.

Scheme 3[a]



[a] (a) NH_3, CH_3OH, 50 °C, sealed tube, 7 days, 66%; (b) BH_3–THF, THF, 0 °C to reflux, 77%; (c) $(BOC)_2O$, Et_3N, CH_3OH, 25 °C, 100%; (d) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, 25 °C, 74%; (e) DMAP, DCC, CH_2Cl_2, 0–25 °C, 92%; (f) THF, morpholine, $Pd(PPh_3)_4$, 25 °C, 100%.

Scheme 4[a]



[a] (a) DCC, DMAP, CH_2Cl_2, 0–25 °C, 88%; (b) Zn, THF, CH_3CO_2H, sonicate, 25 °C; (c) CF_3CO_2H neat, 25 °C, 65% (two steps); (d) FDPP, DIEA, DMF, 25 °C, 62%.

carried out with 4-(dimethylamino)pyridine (DMAP) and dicyclohexylcarbodiimide (DCC) in dry dichloromethane to produce **25** in 92% yield. Allyl ester cleavage was carried out in THF containing dry morpholine and catalytic tetrakis(triphenylphosphine)palladium (100% yield).[21] The ^1H and ^{13}C NMR spectra of **25** and **2** indicated that these two compounds were not contaminated with other diastereoisomers; consequently, their optical purities had to be >95%.

Coupling of **2** and **3**-H was accomplished with DCC/DMAP in dichloromethane (Scheme 4). The fully protected product **26** was isolated in 88% yield as an amorphous solid. Proton and carbon NMR analyses indicated that **26** was diastereomerically pure to the limits of detection (>95%). Reductive cleavage of the trichloroethyl ester group in **26** was achieved using activated zinc dust in acetic acid. The reaction mixture was placed in an ultrasonic cleaner bath for 45 min, then removed, and stirred for 90 min. Filtration and solvent evaporation produced a residue, which was dissolved in neat trifluoroacetic acid to give **1** as the trifluoroacetate salt in 65% overall yield from **26**. Macrolactamization of **26** with FDPP produced cryptophycin D in 62% yield.[22] Synthetic cryptophycin D proved to be identical with an authentic sample of the natural product by spectroscopic comparison, optical rotation, and HPLC retention time.

For the synthesis of the cryptophycin C having a chloro-*O*-methyl-L-tyrosine unit, **27** was required and was obtained from commercial L-3-chlorotyrosine using the method outlined for **19**-Cl. Trichloroethyl ester **27** (Scheme 5) was coupled with **18** as before, in anhydrous DMF using FDPP and DIEA. The yield for **28** was 73%. Removal of the silyl protecting group with aqueous HF in acetonitrile led cleanly to alcohol **29** (90% yield). Coupling **29** with C,D-compound **2** provided **30** in 76% yield. Reductive cleavage of the trichloroethyl ester with zinc, followed by removal of the BOC group, led to *seco* amino acid **31** in 81% yield. Macrolactamization of **31** with FDPP led to a 62% yield of **32**. The 500 MHz ^1H NMR spectra of **32** and natural cryptophycin C were distinctly different (see supplementary material), as were the fingerprint regions in the infrared spectra and the optical rotations. There was no doubt that the two compounds were different, and that the structure of cryptophycin C had been misassigned.[1]

The data suggested that **32** was a diastereoisomer of cryptophycin C. Attention was therefore focused on the chloro-*O*-methyltyrosine unit, the point of difference between cryptophycins C and D. Accordingly, D-tyrosine was chlorinated with sulfuryl chloride in glacial acetic acid[23] and the product of this reaction was converted to chloro-*O*-methyl-D-tyrosine **19**-Cl using the procedure described for **19**-H. Optical purity was checked at the stage of the dimethyl derivative by removal of the nitrogen protecting group with neat TFA and formation of the Mosher amide. ^1H NMR analysis indicated optical purity to the limits of detection (>95% ee). Coupling of **19**-Cl with **18** produced **20**-Cl in 65% yield (Scheme 2), which was deprotected to give **3**-Cl in 95% yield. Coupling **3**-Cl with **2** (Scheme 6) gave protected amino acid **33** in 94% yield. Removal of the two protecting groups (89% yield) led to **34**, which was cyclized to cryptophycin C in 64% yield. Synthetic cryptophycin C was identical with an authentic sample of the natural product by comparison of the ^1H and ^{13}C NMR spectra and the optical rotations. This meant that cryptophycin C has the structure shown in this paper. Since cryptophycin A has been converted to cryptophycin C by reductive deoxygenation[24] of the epoxide group,[4] the chloro-*O*-methyltyrosine unit in cryptophycin A has to have the D-configuration. Cryptophycin A therefore has the structure shown in this paper. Synthetic

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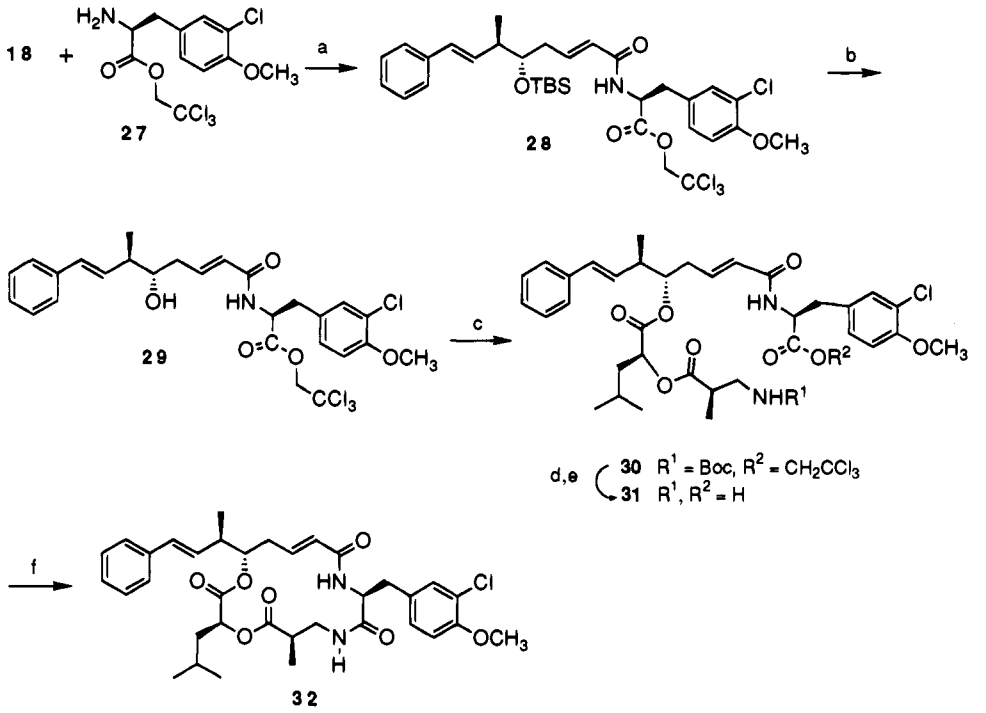
(22) Dudash, J., Jr.; Jiang, J.; Mayer, S. C.; Joullié, M. M. *Synth. Commun.* **1993**, *23*, 349–356.

(23) Zeynek, R. *Hoppe-Seyler's Z. Physiol. Chem.* **1926**, *144*, 247–254.

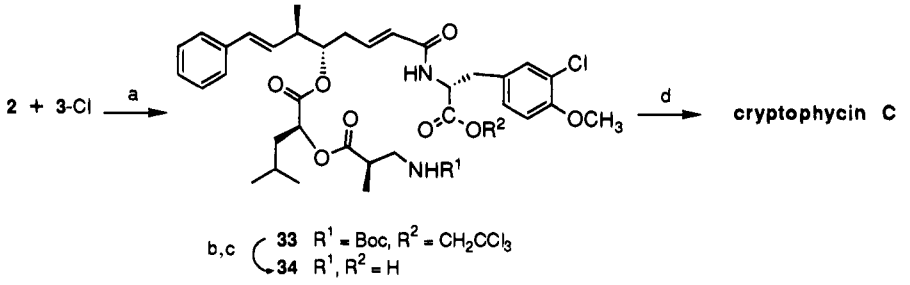
(24) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–997.

Scheme 5[a]



[a] (a) FDPP, DIEA, DMF, 25 °C, 73%; (b) CH_3CN, 50% aqueous HF (95/5), 25 °C, 90%; (c) **2**, DCC, DMAP, CH_2Cl_2, 0−25 °C, 76%; (d) Zn, THF, CH_3CO_2H, sonicate, 25 °C; (e) CF_3CO_2H neat, 25 °C, 81% (two steps); (f) FDPP, DIEA, DMF, 25 °C, 62%.

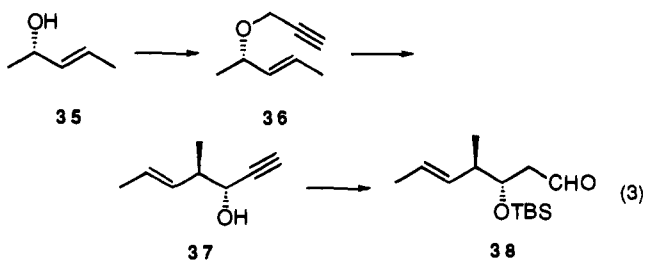
Scheme 6[a]



[a] (a) DCC, DMAP, CH_2Cl_2, 0−25 °C, 94%; (b) Zn, THF, CH_3CO_2H, sonicate, 25 °C; (c) CF_3CO_2H neat, 25 °C, 89% (two steps); (d) FDPP, DIEA, DMF, 25 °C, 64%.

cryptophycins C and D showed the same cytotoxicities against KB and LoVo as the natural compounds. Compound **32**, however, was 100 times less cytotoxic than cryptophycin C, indicating that the α-amino acid unit must have the D-configuration for optimum activity.

A potentially better synthesis of intermediate **17** is being developed. In this new route, allylic alcohol **35** is the starting



material and the key step is a stereoselective [2,3] Wittig rearrangement of propargyl ether **36** to **37**.[25] The desired *anti* compound **37** is the only product that can be detected by proton NMR analysis. After the hydroxyl group of **37** is protected as the *tert*-butyldimethylsilyl ether, hydroboration of the triple bond leads to an aldehyde **38**, which should lead to **17**.

Another task is concerned with the stereospecific introduction of the epoxide group which is present in the most cytotoxic cryptophycins A and B and is apparently needed for optimum activity. Treatment of cryptophycin C with mCPBA leads to a mixture of cryptophycin A and the corresponding (*S,S*)-*trans*-epoxide.[4] Although cryptophycin A can be separated from this mixture by HPLC, the yield is unsatisfactory. These points are being addressed and will be discussed further in a future publication.

Experimental Section

Spectral Analysis. NMR spectra were determined in $CDCl_3$ on a 7.05 T instrument operating at 300 MHz for ^1H and 75 MHz for ^{13}C, unless noted otherwise. $^1H/^{13}C$ chemical shifts are reported in δ units and are referenced to the solvent, i.e., 7.26/77.00 for $CDCl_3$, 7.15/128.0 for benzene-d_6, 2.04/29.8 for acetone-d_6, and 3.30/49.0 for CD_3OD. ^1H and ^{13}C chemical shift assignments are based on detailed analysis of two-dimensional NMR spectra (COSY, HMQC, and HMBC) when necessary. UV spectra were recorded on a diode array spectrophotometer in MeOH; IR spectra were recorded neat; EI and FAB mass spectra and high-resolution mass measurements were performed on a VG-70SE mass spectrometer.

General Procedures. Thin layer chromatography (TLC) was performed on Whatman precoated K6F analytical plates (0.25 mm).

(25) (a) Tsai, D. J.-S.; Midland, M. M. *J. Org. Chem.* **1984**, *49*, 1842–1843. (b) Mikami, K.; Azumi, K.; Nakai, T. *Tetrahedron* **1984**, *25*, 2303–2308.

Flash chromatography was performed on either Fisher silica gel (200–425 mesh) or Merck silica gel (230–400 mesh). Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl; *N,N*-dimethylformamide (DMF) was azeotropically distilled with benzene and then redistilled from CaH_2; triethylamine (Et_3N) was distilled from KOH pellets and stored over them; dichloromethane (CH_2Cl_2) was distilled fom CaH_2; toluene and hexane were distilled from sodium metal; *tert*-butyl hydroperoxide was dried according to the procedure of Gao et al.[26] Other reagents were obtained commercially and used as received unless otherwise specified. Where necessary, reactions were performed under a static nitrogen or argon atmosphere in flame-dried glassware.

Methyl 5-Phenylpent-2(*E*)-enoate (7). To a solution of dihydrocinnamaldehyde (15.0 g, 112 mmol) and trimethyl phosphonoacetate (21.8 g, 19.4 mL, 120 mmol) in anhydrous THF (200 mL) was added tetramethylguanidine (14.3 g, 15.5 mL, 124 mmol) under an argon atmosphere at −78 °C with stirring. The mixture was stirred at reduced temperature for 30 min, then allowed to warm to 25 °C, and stirred for an additional 2 h. Water (150 mL) was added, and the reaction mixture was extracted into Et_2O (2 × 100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil. Chromatographic filtration through a pad of silica (25% EtOAc in hexane) and concentration of the eluent *in vacuo* yielded **7** as a stable, colorless, mobile oil (18.3 g, 86% yield). ^{1}H NMR analysis showed that the product was a single geometrical isomer: EIMS *m/z* (relative intensity; assignment) 190 (13; M^+), 159 (41), 158 (39), 131 (30), 130 (62), 117 (22), 104 (12), 92 (57), 91 (100), 77 (21), 65 (59); HREIMS *m/z* 190.0998 ($C_{12}H_{14}O_2$, Δ −0.4 mmu); UV λ_{max} (ε) 210 (8400), 260 (230) nm; IR ν_{max} 3027, 2949, 1723, 1658, 1454, 1319, 1203, 978, 700 cm^{-1}; ^{1}H NMR δ (assignment; multiplicity, *J* in hertz) 7.15–7.3 (Ph-H_5; bm), 7.00 (3-H; dt, 15.6/6.6), 5.84 (2-H; dt, 15.6/1.2), 3.70 (OMe; s), 2.76 (5-H_2; t, 7.2), 2.51 (4-H_2; bdt, 6.6/7.2); ^{13}C NMR δ (carbon position) 166.9 (1), 148.3 (3), 140.6 (Ph 1′), 128.4/128.2 (Ph 2′/3′/5′/6′), 126.1 (Ph 4′), 121.4 (2), 51.3 (OMe), 34.2/33.8 (4/5).

(2*S*,3*S*)-2,3-Epoxy-5-phenyl-1-pentanol (8). To a solution of enoate **7** (17.0 g, 89 mmol) in dry THF (200 mL) was added a solution of DIBAL in toluene (1 M, 224 mmol, 224 mL) with stirring at −78 °C under an argon atmosphere. The reaction mixture was stirred at −78 °C for 30 min, then allowed to slowly warm to 25 °C, and stirred for 30 min more. Water (50 mL) was slowly added, and the mixture was transferred to a separatory funnel, diluted with Et_2O (400 mL), and washed successively with 200 mL amounts of 10% sodium tartrate solution, water, and brine. The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure to yield 5-phenylpent-2(*E*)-en-1-ol (13.0 g, 90% yield) as the sole product and a stable, mobile, colorless oil: bp 108–111 °C (0.7 mmHg); EIMS *m/z* 162 (1; M^+), 144 (16), 129 (7), 117 (9), 108 (6), 92 (17), 91 (100), 75 (5), 65 (12); HREIMS *m/z* 162.1049 ($C_{11}H_{14}O$, Δ −0.4 mmu); UV λ_{max} (ε) 206 (9900), 260 (360) nm; IR ν_{max} 3356, 2924, 1603, 1496, 1454, 970, 746, 700 cm^{-1}; ^{1}H NMR δ 7.15–7.3 (Ph-H_5; m), 5.70 (3-H; dt, 15.6/6.0), 5.61 (2-H; dt, 15.6/4.8), 4.02 (1-H_2; d, 4.8), 2.68 (5-H_2; t, 7.2), 2.40 (OH; bs), 2.36 (4-H_2; dt, 6.0/7.2); ^{13}C NMR δ 141.6 (Ph 1′), 131.8 (3), 129.5 (2), 128.3/128.2 (Ph 2′/3′/5′/6′), 125.7 (Ph 4′), 63.3 (1), 35.4/33.8 (4/5).

To a dry flask charged with dry CH_2Cl_2 (400 mL) and cooled to −20 °C under argon were added, in the following order, L-(+)-diethyl tartrate (14.5 g, 12.0 mL, 70.4 mmol), titanium tetraisopropoxide (19.3 g, 20.2 mL, 68.0 mmol), and *tert*-butyl hydroperoxide (5.1 M in CH_2Cl_2, 140.3 mmol, 27.5 mL). The mixture was stirred at −20 °C for 30 min before addition of the allylic alcohol, 5-phenylpent-2(*E*)-en-1-ol (12.5 g, 77.0 mmol), as a solution in dry CH_2Cl_2 (40 mL) via syringe over 10 min. The reaction mixture was stirred at reduced temperature for an additional 5 h, then allowed to warm to 0 °C, and poured into a chilled (0 °C) solution of ferrous sulfate heptahydrate (33 g) and tartaric acid (10 g) in 100 mL of water. The two-phase mixture was stirred for 15 min, and then the phases were separated. The aqueous phase was extracted with 2 × 200 mL Et_2O, and the combined organic phase was treated with a precooled solution (0 °C) of NaOH in brine (100 mL, 25% w/v). The heterogeneous reaction mixture was stirred for 1 h at 0 °C and then extracted with 2 × 200 mL Et_2O. Drying ($MgSO_4$) followed by solvent evaporation produced the desired epoxy alcohol **8** (12.9 g, 94% yield) as the only appreciable product and a stable, colorless, mobile oil. The enantiomeric excess, as determined by Mosher analysis, was >95%: $[\alpha]_D$ −32.0° (*c* 1.4, $CHCl_3$); bp 120–123 °C (0.7 mmHg); EIMS *m/z* 178 (<1; M^+), 160 (7), 147 (14), 144 (12), 129 (50), 118 (73), 117 (81), 115 (26), 107 (23), 105 (40), 104 (71), 92 (64), 91 (100), 78 (33), 77 (38), 65 (60), 51 (33); HREIMS *m/z* 178.1002 ($C_{11}H_{14}O_2$, Δ −0.8 mmu), 160.0880 ($C_{11}H_{12}O$, Δ 0.8 mmu); UV λ_{max} (ε) 208 (8100), 260 (100) nm; IR ν_{max} 3418, 2928, 1603, 1496, 1455, 1090, 1029, 880, 700 cm^{-1}; ^{1}H NMR δ 7.1–7.3 (Ph-H_5; m), 3.80 (1-H; dd, −12.6/2.7), 3.49 (1-H′; dd, −12.6/4.8), 2.95 (3-H; ddd, 5.7/5.7/2.4), 2.83 (2-H; ddd, 4.8/2.7/2.4), 2.77 (5-H; ddd, −13.8/8.1/8.1), 2.70 (5-H′; ddd −13.8/8.1/8.1), 1.87 (4-H_2; m); ^{1}H NMR (C_6D_6) δ 7.0–7.2 (Ph-H_5; m), 3.61 (1-H; dd, −12.6/2.7), 3.34 (1-H′; dd, −12.6/4.8), 3.01 (OH; bs, $W_{1/2} \approx 20$), 2.74 (3-H; ddd, 5.7/5.4/2.4), 2.61 (2-H; ddd, 4.8/2.7/2.4), 2.56 (5-H; ddd, −13.8/8.1/8.1), 2.49 (5-H′; ddd, −13.8/8.1/8.1), 1.61 (4-H_2; m); ^{13}C NMR δ 140.9 (Ph 1′), 128.3/128.2 (Ph 2′/3′/5′/6′), 126.0 (Ph 4′), 61.6 (1), 58.7 (2), 55.3 (3), 33.2 (5), 32.0 (4); ^{13}C NMR (C_6D_6) δ 141.5 (Ph 1′), 128.6 (Ph 2′/3′/5′/6′), 126.2 (Ph 4′), 62.1 (1), 59.1 (2), 55.3 (3), 33.7 (5), 32.4 (4).

(*R*)-Mosher Ester of 8. The Mosher ester was prepared according to the general procedure[27] to yield the required compound as a stable colorless oil: $[\alpha]_D$ 12.4° (*c* 0.4, $CHCl_3$); ^{1}H NMR δ 7.15–7.45 (two Ph-H_5), 4.49 (1-H; dd −12.3/3.0), 4.17 (1-H′; dd, −12.3/6.3), 3.56 (OMe; s), 2.95 (2-H; ddd, 6.3/3.0/2.4), 2.87 (3-H; ddd, 6.0/6.0/2.4), 2.80 (5-H; ddd, −13.8/6.9/6.9), 2.69 (5-H′; ddd, −13.8/7.5/7.5), 1.86 (4-H_2; m $W_{1/2} \approx 15$).

(*R*)-Mosher Ester of (2*R*,3*R*)-2,3-Epoxy-5-phenyl-1-pentanol. The epoxide of the opposite stereochemistry, *viz.*, 2*R*,3*R*, was prepared in an analogous manner to that for (2*S*,3*S*)-epoxide **8** using the procedure above, with the exception that D-(−)-DET was employed instead of L-(+)-DET. Spectroscopic data was identical to that of **8**, except for optical rotation, $[\alpha]_D$ 31.7° (*c* 1.8, $CHCl_3$).

The Mosher ester was prepared as a stable colorless oil: $[\alpha]_D$ 54.5° (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 7.15–7.55 (two Ph-H_5), 4.49 (1-H; dd −12.3/3.0), 4.15 (1-H′; dd, −12.3/5.7), 3.56 (MTPA OMe; d, $^5J_{H-F} \approx$ 1.5), 2.97 (2-H; ddd, 5.7/3.0/2.1), 2.88 (3-H; ddd, 5.7/5.7/2.1), 2.80 (5-H; ddd, −13.8/7.8/7.8), 2.69 (5-H′; ddd, −13.8/7.8/7.8), 1.86 (4-H_2; m).

(2*R*,3*R*)-3-Methyl-5-phenylpentane-1,2-diol (9). A flame-dried flask equipped with a magnetic stirbar under argon was charged with 100 mL of dry hexane and then chilled to 0 °C before addition of a solution of trimethylaluminum (1.8 M in hexane, 85 mL, 153 mmol, ≈2.5 equiv). The mixture was stirred for 10 min at reduced temperature, and then epoxy alcohol **8** (10.4 g, 58 mmol) was added via syringe as a solution in hexane/dichloromethane (5:1, 30 mL) over 30 min. The reaction mixture was allowed to warm to 25 °C and stirred for 4 h more. After this time the solution was again cooled to 0 °C and diluted with 100 mL of Et_2O. Dilute aqueous HCl solution (10% w/w) was added carefully with vigorous stirring, until the solid that had precipitated had redissolved. The organic phase was washed successively with 100 mL portions of water and brine, then dried ($MgSO_4$), and evaporated to give a viscous oil that was predominantly one compound. Column chromatography (silica, 230–400 mesh, Et_2O) produced **9** (10.7 g, 95% yield) as a stable, colorless, oil. Enantiomeric excess was assessed as >90% by analysis of the Mosher diester. Data for **9**: $[\alpha]_D$ 17.0° (*c* 2.5, $CHCl_3$); EIMS *m/z*; 194 (M^+, 3), 176 (4), 158 (7), 145 (32), 132 (12), 117 (33), 104 (49), 91 (100); HREIMS *m/z* 194.1304 ($C_{12}H_{18}O_2$, Δ 0.3 mmu), 176.1206 ($C_{12}H_{16}O$, Δ −0.5 mmu); UV (MeOH) λ_{max} (ε) 210 (7200), 260 (300) nm; IR ν_{max} 3360, 2924, 1603, 1496, 1454, 1070, 747, 699 cm^{-1}; ^{1}H NMR δ 7.15–7.3 (Ph-H_5; m), 3.66 (1-H; m, $W_{1/2} \approx 25$), 3.47 (1-H′/2-H; m), 2.97 (2 × OH; bs, $W_{1/2} \approx 36$), 2.73 (5-H; ddd, −13.7/10.2/4.9), 2.52 (5-H′; ddd, −13.7/9.9/6.6), 1.87 (4-H; dddd, −13.5/10.2/6.6/3.3), 1.59 (3-H; m, $W_{1/2} \approx$ 20), 1.44 (4-H′; dddd, −13.5/9.9/9.6/4.9), 0.94 (3-Me; d, 6.6); ^{13}C NMR δ 142.4 (Ph 1′), 128.3 (Ph 2′/3′/5′/6′), 125.7 (Ph 4′), 76.1 (2), 64.5 (1), 35.7 (3), 34.3 (5), 33.2 (4), 15.2 (3-Me).

(*R,R*)-Mosher Diester of 9. The MTPA diester of the diol **9** was prepared according to the standard procedure[27] as a colorless mobile oil in almost quantitative yield: $[\alpha]_D$ 38.4° (*c* 0.9, $CHCl_3$); ^{1}H NMR δ 7.15–7.55 (3 Ph-H_5; m), 5.23 (2-H; ddd, 8.3/7.2/2.1), 4.66 (1-H′; dd, −12.3/2.1), 4.33 (1-H; dd, −12.3/7.2 Hz), 3.46 (MTPA OMe; d, $^5J_{H-F}$

(26) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

(27) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

≈ 1.5 Hz), 3.37 (MTPA OMe; d, $^5J_{H-F}$ ≈ 1.5 Hz), 2.65 (5-H′; ddd, −13.8/10.5/5.4), 2.46 (5-H; ddd, −13.8/10.0/6.5), 1.85 (3-H; dddq, 9.6/8.3/4.2/6.9), 1.65 (4-H′; dddd, −13.8/10.5/6.5/4.2), 1.37 (4-H; dddd, −13.8/10.0/9.6/5.4), 0.89 (3-Me; d, 6.9).

(4*R*,1′*R*)-2,2-Dimethyl-4-[1′−methyl-3′-phenylpropyl]-1,3-dioxolane (10). To a solution of **9** (10.0 g, 51.5 mmol) and 2,2-dimethoxypropane (7.4 mL, ≈60 mmol) in 200 mL of dry CH_2Cl_2 was added PPTS (pyridinium *p*-toluenesulfonate, 500 mg, 2.0 mmol, ≈4 mol %) with stirring at 25 °C. After 2 h, powdered K_2CO_3 (1 g) was added to the reaction mixture, and the suspension was stirred for a further 30 min. Filtration and solvent evaporation produced a mobile oil, which was purified by distillation to give **10** (11.7 g, 97% yield) as a stable, colorless oil: $[\alpha]_D$ 3.0° (*c* 4.1, $CHCl_3$); bp 118−120 °C (2 mmHg); EIMS *m/z*; 234 (4; M^+), 219 (20), 176 (47), 158 (42), 143 (44), 117 (49), 104 (28), 101 (49), 91 (100), 72 (53); HREIMS *m/z* 234.1608 ($C_{15}H_{22}O_2$, Δ 1.2 mmu), 219.1416 ($C_{14}H_{19}O_2$, Δ −3.1 mmu); UV λ_{max} (ε) 208 (7300), 266 (350) nm; IR ν_{max} 2984, 1745, 1603, 1456, 1379, 1215, 1069, 860, 699 cm^{-1}; ^1H NMR δ 7.15−7.3 (Ph-H_5; m), 3.97 (5-H_{trans}; dd, 7.5/6.3), 3.87 (4-H; ddd 7.3/7.2/6.3), 3.58 (5-H_{cis}; dd 7.5/7.3), 2.75 (3′-H; ddd, −13.8/10.6/5.1), 2.56 (3′-H′; ddd, −13.8/10.2/6.6), 1.92 (4′-H; dddd, −13.8/10.6/6.6/3.9), 1.67 (1′-H; bm, $W_{1/2}$ ≈ 18), 1.42 (2′-H′; m), 1.38 (2-Me; s), 1.34 (2-Me; s), 0.91 (1′-Me; d, 6.9); ^{13}C NMR δ 142.4 (Ph 1″), 128.3/128.2 (Ph 2″/3″/5″/6″), 125.6 (Ph 4″), 108.6 (1), 80.2 (4), 67.4 (5), 35.9 (1′), 34.9 (3′), 33.0 (2′), 26.6 (2-Me), 25.5 (2-Me), 14.8 (1′-Me).

(4*R*,1′*R*)-2,2-Dimethyl-4-[1′-methyl-3′-phenylprop-2(*E*)-enyl]-1,3-dioxolane (12). To a solution of acetonide **10** (5.8 g, 24.8 mmol), dissolved in 200 mL of CCl_4 under argon, was added *N*-bromosuccinimide (4.7 g, 26.4 mmol). The reaction mixture was illuminated with a 500 W tungsten filament light source placed ≈2 cm away and stirred for 4 h, while 2,2-dimethoxypropane (3.1 g, 3.7 mL, 29.8 mmol) was added dropwise over this period. The mixture was then diluted with 100 mL of CCl_4, and the precipitated succinimide was removed by filtration through a plug of silica. The organic phase was evaporated to give crude benzylic bromide **11** as a mixture of epimers. This material was used immediately, without purification, in the next step.

To a neat sample of crude benzylic bromide **11** was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 5.7 mL, ≈37.2 mmol). The mixture was warmed to ≈70 °C with a heat gun (considerable darkening occurs) and stirred for 15−20 min, then cooled to 25 °C, and diluted with 100 mL of Et_2O. The ether layer was washed successively with 100 mL portions of water and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a mobile oil, which was subjected to flash chromatography on silica gel (200−430 mesh, 4% EtOAc in hexane) to give 4.6 g of **12** (80% overall yield from **10**): $[\alpha]_D$ 17.5° (*c* 2.7, $CHCl_3$); EIMS *m/z* 232 (1, M^+), 217 (5), 157 (7), 129 (11), 115 (7), 101 (96), 86 (65), 84 (100); HREIMS *m/z* 232.1490 ($C_{15}H_{20}O_2$, Δ −2.7 mmu), 217.1235 ($C_{14}H_{17}O_2$, Δ −0.7 mmu); UV λ_{max} (ε) 210 (12 400), 258 (15 200) nm; IR ν_{max} 2982, 2873, 1599, 1494, 1455, 1369, 1213, 1066, 860, 748, 694 cm^{-1}; ^1H NMR δ 7.20−7.35 (Ph-H_5; m), 6.43 (3′-H; d, 15.9), 6.23 (2′-H; dd, 15.9/7.2), 3.99−4.07 (5-H_{trans}/4-H; m), 3.68 (5-H_{cis}; dd, 6.9,6.9), 2.50 (1′-H; dqd, 7.2/6.9/6.3), 1.43 (2-Me; s), 1.36 (2-Me; s), 1.11 (1′-Me; d, 6.9); ^{13}C NMR δ 137.4 (Ph 1″), 131.6 (3′), 130.2 (2′), 128.4 (Ph 3″/5″), 127.1 (Ph 4″), 126.1 (Ph 2″/6″), 109.0 (1), 79.5 (4), 67.3 (5), 40.0 (1′), 26.5 (2-Me), 25.5 (2-Me), 16.0 (1′-Me). Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.48. Found: C, 76.37; H, 9.66.

(2*R*,3*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-5-phenylpent-4(*E*)-en-1-yl Tosylate (15). A solution of **12** (4.4 g, 19.0 mmol) in 100 mL of 1% aqueous HCl in MeOH was stirred for 2 h at 25 °C whereupon TLC analysis indicated that total conversion of starting material to a single, more polar product had occurred. The mixture was diluted with 200 mL of Et_2O, and the solution was washed with 2 × 100 mL of water, dried ($MgSO_4$), and concentrated under reduced pressure to give (2*R*,3*R*)-3-methyl-5-phenylpent-4(*E*)-ene-1,2-diol (3.4 g, 93% yield): $[\alpha]_D$ 46.9° (*c* 1.4, $CHCl_3$); EIMS *m/z* 192 (3; M^+), 177 (6), 174 (6), 161 (9), 143 (12), 132 (79), 131 (100), 117 (61), 115 (26), 104 (13), 91 (98), 77 (21), 61 (11); HREIMS *m/z* 192.1144 ($C_{12}H_{16}O_2$, Δ 0.6 mmu), 174.1051 ($C_{12}H_{14}O$, Δ −0.7 mmu); UV λ_{max} (ε) 208 (15 000), 258 (13 700), 284 (1100) nm; IR ν_{max} 3410, 2927, 1651, 1454, 1050, 698 cm^{-1}; ^1H NMR δ 7.15−7.35 (Ph-H_5; m), 6.42 (5-H; d, 15.9), 6.14 (4-H; dd, 15.9/8.7), 3.69 (1-H; m), 3.54 (1-H′/2-H; m), 2.99 (2 × OH; bs, $W_{1/2}$ ≈ 25), 2.42 (3-H; ddq, 8.7/7.5/6.9), 1.09 (3-Me; d, 6.9); ^{13}C NMR δ 137.0 (1′), 131.5 (5), 131.2 (4), 128.5 (2C, 3′), 127.3 (4′), 126.1 (2C, 2′), 75.4 (2), 64.6 (1), 40.4 (3), 16.7 (3-Me).

To a solution of the unsaturated diol (3.37 g, 17.6 mmol) in 300 mL of dry toluene was added dibutyltin dimethoxide (4.43 mL, 5.7 g, 19.3 mmol, ≈1.1 equiv), and the mixture was heated to reflux under a Dean−Stark apparatus for 2 h, during which time 50 mL of toluene was removed. The reaction mixture, containing the stannylene acetal, was placed under an argon atmosphere and cooled to 0 °C. Triethylamine (123 μL, 90 mg, ≈5 mol %) was added, followed by tosyl chloride (3.7 g, 19.5 mmol, ≈1.1 equiv) in 10 mL of dry toluene. The reaction mixture was stirred at reduced temperature for 4 h, then allowed to warm to 25 °C, and stirred for an additional 12 h. The reaction was quenched with 50 mL of water and extracted with 200 mL of Et_2O. The ether extract was washed with brine (2 × 100 mL) and water (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residual yellow oil by silica chromatography (CH_2Cl_2) gave (2*R*,3*R*)-2-hydroxy-3-methyl-5-phenyl-pent-4(*E*)-en-1-yl tosylate as a colorless oil (5.0 g, 82% yield): $[\alpha]_D$ 22.5° (*c* 2.2, $CHCl_3$); EIMS *m/z*, 346 (<1%; M^+), 328 (3), 215 (7), 172 (8), 155 (34), 131 (100), 117 (14), 104, (13), 91 (79); HREIMS *m/z* 346.1225 ($C_{19}H_{22}O_4S$, Δ 1.3 mmu), 328.1141 ($C_{19}H_{20}O_3S$, Δ −0.9 mmu); UV λ_{max} (ε) 216 (32 700), 228 (23 800), 252 (24 800), 282 (2000) nm; IR ν_{max} 3444, 2965, 1647, 1598, 1357, 1175, 967, 666 cm^{-1}; ^1H NMR δ 7.80 (Ts 2″/6″; d, 8.1), 7.32 (Ts 3″/5″; d, 8.1), 7.15−7.35 (Ph-H_5; m), 6.40 (5-H; d, 15.9), 6.09 (4-H; dd, 15.9/8.7), 4.10 (1-H; dd, −10.2/3.6), 4.01 (1-H′; dd, −10.2/6.3), 3.78 (2-H; ddd, 9.6/6.3/3.6), 2.51 (3-H; ddq, 9.6/8.7/6.9), 2.43 (Ts-Me; s), 1.13 (3-Me; d, 6.9); ^{13}C NMR δ 145.0 (Ts 1″), 136.8 (Ph 1′), 132.7 (Ts 4″), 131.9 (5), 129.9 (Ts 3″/5″ and 4), 128.5 (Ph 3′/5′), 127.9 (Ts 2″/6″), 127.5 (Ph 4′), 126.2 (Ph 2′/6′), 72.8 (2), 72.2 (1), 40.0 (3), 21.6 (Ts-Me), 16.8 (3-Me).

To a solution of the tosylate (4.16 g, 12.0 mmol) in 100 mL of dry CH_2Cl_2 under argon was added Et_3N (3.3 mL, 24 mmol, ≈2 equiv) followed by *tert*-butyldimethylsilyl triflate (TBSTf, 4.1 mL, 18 mmol, ≈1.5 equiv). The reaction mixture was stirred at 25 °C for 30 min whereupon 200 mL of Et_2O was added. The organic phase was separated and washed with 200 mL portions of water and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give a colorless oil, which was passed through a plug of silica (200−430 mesh) with 15% Et_2O/hexane. Evaporation of the solvent left **15** as a mobile colorless oil (5.42 g, 98% yield): $[\alpha]_D$ 15.5° (*c* 1.9, $CHCl_3$); EIMS *m/z*; 460 (not observed), 403 (3; M^+ − ^{t}Bu), 329 (34; M^+ − OTBS), 288 (12), 229 (100), 157 (56), 131 (87), 91 (82), 73 (97); HREIMS *m/z* 403.1432 ($C_{21}H_{27}O_4SiS$, Δ −3.3 mmu), 329.1254 ($C_{19}H_{21}O_3S$, Δ −4.5 mmu); UV (MeOH) λ_{max} (ε) 208 (21 200), 228 (14 900), 252 (16 100), 284 (1400) nm; IR ν_{max} 2956, 2857, 1598, 1462, 1366, 1255, 1177, 1098, 971, 832, 665 cm^{-1}; ^1H NMR δ 7.76 (Ts 2″-H; d, 8.1), 7.2−7.35 (Ts 3″-H/5″-H and Ph-H_5; m), 6.25 (5-H; d, 15.9), 6.04 (4-H; dd, 15.9/8.4), 3.8−3.9 (1-H_2/2-H; m), 2.49 (3-H; dqd, 8.4/6.9/2.4), 2.40 (Ts-Me; s), 1.08 (3-Me; d, 6.9), 0.86 ($SiCMe_3$; s), 0.06 (SiMe; s), 0.04 (SiMe; s); ^{13}C NMR δ 144.8 (Ts 1″), 137.3 (Ph 1′), 132.8 (Ts 4″), 131.0 (5), 130.3 (4), 129.8 (Ts 3″/5″), 128.4 (Ph 3′/5′), 127.9 (Ts 2″/6″), 127.1 (Ph 4′), 126.1 (Ph 2′/6′), 73.5 (2), 71.6 (1), 40.6 (3), 25.8 ($SiCMe_3$), 21.6 (Ts-Me), 18.0 (Si-CMe_3), 17.0 (3-Me), −4.4 (Si-Me), −4.9 (Si-Me).

(3*S*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-6-phenylhex-5(*E*)-enal (16). To a solution of the monotosylate **15** (5.3 g, 11.5 mmol) in 160 mL of wet DMSO was added KCN (1.55 g, 23.8 mmol, ≈2 equiv), and the mixture was stirred at ≈60 °C for 12 h. After this time the reaction mixture was poured into 100 mL of ice/water and extracted into 400 mL of Et_2O. The ethereal layer was washed with 2 × 200 mL of brine and 200 mL of water, dried ($MgSO_4$), and evaporated to give a colorless oil that was subjected to chromatographic filtration (silica, CH_2Cl_2), resulting in (3*S*,4*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-6-phenylhex-5(*E*)-enonitrile as the sole product (3.3 g, 92% yield): $[\alpha]_D$ 62.6° (*c* 1.4, $CHCl_3$); bp 138−140 °C (2.5 mmHg); EIMS *m/z* 315 (<1%; M^+), 300 (5), 258 (67), 205 (26), 184 (36), 143 (41), 131 (37), 129 (17), 128 (17), 98 (19), 91 (34), 75 (81), 73 (100); HREIMS *m/z* 315.2048 ($C_{19}H_{29}NOSi$, Δ −3.0 mmu); UV λ_{max} (ε) 206 (21 100), 258 (18 400), 284 (1700) nm; IR ν_{max} 2955, 2929, 2857, 2250, 1600, 1463, 1363, 1257, 1108, 1037, 837, 778, 694 cm^{-1}; ^1H NMR δ 7.2−7.4 (Ph-H_5; m), 6.47 (6-H; d, 15.9), 6.10 (5-H; dd, 15.9/8.4), 3.97 (3-H; ddd, 6.1/5.9/3.6), 2.61 (4-H; dqd, 8.4/6.9/3.6), 2.50 (2-H; dd,

−16.5/6.1), 2.43 (2-H′; dd, −16.5/5.9), 1.14 (4-Me; d, 6.9), 0.93 (SiCMe$_3$; s), 0.14 (SiMe; s), 0.11 (Si-Me; s); ^{13}C NMR δ 137.3 (Ph 1′), 131.7 (6), 129.8 (5), 128.6 (Ph 3′/5′), 127.4 (Ph 4′), 126.2 (Ph 2′/6′), 118.0 (1), 72.1 (3), 42.8 (4), 25.7 (SiC*Me*$_3$), 23.7 (2), 18.0 (Si*C*Me$_3$), 16.2 (4-Me), −4.5 (SiMe), −4.7 (SiMe). Calcd for $C_{19}H_{29}NOSi$: C, 72.31; H, 9.28; N, 4.43. Found: C, 72.08; H, 9.30; N, 4.22.

To a solution of the nitrile (1.0 g, 3.17 mmol) in 50 mL of dry CH_2Cl_2, was added a solution of DIBAL (1M, 3.8 mL, 3.8 mmol, 1.2 equiv) in toluene at −78 °C under argon. The mixture was stirred and warmed gradually to 25 °C over 1 h, at which time TLC analysis indicated complete consumption of starting material. Ether (30 mL) and silica (200−430 mesh, 2 g) were added, and the solution was stirred for 3 h at 25 °C. The reaction mixture was filtered through a pad of Celite, the filtrate diluted with 100 mL of Et_2O, and the ether extract washed successively with dilute HCl (0.2 M, 50 mL), water (100 mL), brine (100 mL), and water (100 mL), dried ($MgSO_4$), and evaporated to give **16** as a pale yellow oil (957 mg, 95% yield). This material could be used without further purification in the next step. Data for **16**: $[\alpha]_D$ 35.2° (*c* 0.9, $CHCl_3$); EIMS *m/z* 318 (not observed; M^+), 303 (1; $M^+ - CH_3$), 274 (1; $M^+ - C_2H_4O$), 261 (7; M^+-^{t}Bu), 187 (26), 169 (15), 143 (29), 131 (26), 115 (35), 101 (29), 91 (21), 75 (89), 73 (100); HREIMS *m/z* 303.1780 ($C_{18}H_{27}O_2Si$, Δ 0.1 mmu), 274.1749 ($C_{17}H_{26}OSi$, Δ 0.4 mmu), 261.1298 ($C_{15}H_{21}O_2Si$, Δ 1.3 mmu); UV λ_{max} (ε) 210 (13 600), 252 (15 900), 284 (2300) nm; IR ν_{max} 2954, 2855, 1725, 1687, 1461, 1375, 1254, 1096, 1030, 969, 836, 776, 693 cm^{-1}; ^{1}H NMR δ 9.79 (1-H; dd, 2.1/2.1), 7.15−7.35 (Ph-H$_5$; m), 6.38 (6-H; d, 16.2), 6.12 (5-H; dd, 16.2/8.1), 4.25 (3-H; ddd, 10.2/5.7/4.2), 2.55 (2-H$_2$/4-H; br m), 1.12 (4-Me; d, 6.9), 0.90 (SiCMe$_3$; s), 0.10 (SiMe; s), 0.06 (SiMe; s); ^{13}C NMR δ 202.0 (1), 137.3 (Ph 1′), 131.3 (6), 130.9 (5), 128.5 (Ph 3′/5′), 127.2 (4′), 126.1 (2′/6′), 71.4 (3), 48.2 (2), 43.3 (4), 25.8 (SiC*Me*$_3$), 18.0 (Si*C*Me$_3$), 15.3 (3-Me), −4.5 (SiMe), −4.6 (SiMe).

Methyl (5*S*,6*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-8-phenylocta-2(*E*),7(*E*)-dienoate (17). To a solution of aldehyde **16** (1.1 g, 3.46 mmol) and trimethyl phosphonoacetate (700 mg, 625 μL, 3.85 mmol, ≈1.1 equiv) in 50 mL of anhydrous THF was added tetramethylguanidine (430 mg, 470 μL, 3.75 mmol, ≈1.1 equiv) with stirring at −78 °C under argon. Stirring was continued at reduced temperature for 30 min, and then the mixture was allowed to warm to 25 °C and stirred for a further 2 h. After this time 50 mL of water was added, and the mixture was extracted with 50 mL of Et_2O. The ether extract was then washed with 50 mL portions of water and brine, dried ($MgSO_4$), and evaporated to give a pale yellow oil. Chromatographic purification (silica, 5% EtOAc in hexane) gave **17** as a stable, colorless, mobile oil (1.07 g, 83% yield). Analysis by 300 MHz ^{1}H NMR spectroscopy showed that the newly created double bond existed as a single geometrical isomer. Data for **17**: $[\alpha]_D$ 68.2° (*c* 1.5, $CHCl_3$); EIMS *m/z* 374 (<1%; M^+), 359 (1; $M^+ - CH_3$), 317 (10; $M^+ - {}^t$Bu), 275 (10), 243, (73), 143 (20), 115 (10), 97 (64), 89 (31), 73 (100); HREIMS *m/z* 374.2232 ($C_{22}H_{34}O_3Si$, Δ 4.5 mmu), 359.2031 ($C_{21}H_{31}O_3Si$, Δ 1.1 mmu), 317.1579 ($C_{18}H_{25}O_3Si$, Δ −0.6 mmu); UV (MeOH) λ_{max} (ε) 206 (33 500), 252 (20 100) nm; IR ν_{max} 2952, 2855, 1725, 1657, 1435, 1257, 1168, 1097, 970, 836, 775 cm^{-1}; ^{1}H NMR δ 7.2−7.4 (Ph-H$_5$; m), 6.96 (3-H; ddd, 15.6/7.8/7.5), 6.37 (8-H; d, 15.9), 6.16 (7-H; dd, 15.9/8.1), 5.84 (2-H; d, 15.6), 3.75 (5-H; ddd, 10.2/6.0/4.2), 3.72 (OMe; s), 2.44 (6-H; m), 2.36 (4-H$_2$; m), 1.10 (6-Me; d, 6.9), 0.91 (SiCMe$_3$; s), 0.06 (SiMe; s), 0.05 (SiMe; s); ^{13}C NMR δ 166.8 (1), 146.4 (3), 137.6 (Ph 1′), 131.9 (8), 130.4 (7), 128.5 (Ph 3′/5′), 127.0 (Ph 4′), 126.0 (Ph 2′/6′), 122.9 (2), 75.0 (5), 51.4 (OMe), 42.8 (6), 37.6 (4), 25.9 (SiC*Me*$_3$), 18.1 (Si*C*Me$_3$), 16.2 (6-Me), −4.4 (SiMe), −4.5 (SiMe). Calcd for $C_{22}H_{34}O_3Si$: C, 70.52; H, 9.17. Found: C, 70.72; H, 9.42.

(5*S*,6*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-8-phenylocta-2(*E*),7(*E*)-dienoic Acid (18). To a solution of ester **17** (159 mg, 0.43 mmol) in 7 mL of acetone was added 5 mL of 1 N aqueous LiOH. The mixture was stirred at 25 °C for 3 h, diluted with 20 mL of Et_2O, and acidified to pH ≈ 4 with 1 N HCl. The organic layer was separated and washed with 20 mL portions of brine and water, dried ($MgSO_4$), and evaporated. Chromatography of the residual oil on silica gel with 40% EtOAc in hexane containing 0.5% AcOH resulted in pure acid **18** as a pale yellow mobile oil (145 mg, 95% yield): $[\alpha]_D$ 87.0° (*c* 1.4, $CHCl_3$); EIMS *m/z*; 343 (1; $M^+ - OH$), 303 (5), 275 (9), 257 (4), 229 (62), 213 (16), 171 (22), 143 (37), 131 (16), 115 (23), 97 (100), 91 (44); HREIMS *m/z* 343.2107 ($C_{21}H_{31}O_2Si$, Δ −1.3 mmu), 229.1220 ($C_{15}H_{17}O_2$, Δ 0.9 mmu); UV λ_{max} (ε) 206 (24 500), 252 (15 600) nm; IR ν_{max} 3300−2800 (br), 2956, 2856, 1697, 1651, 1419, 1256, 1097, 836, 693 cm^{-1}; ^{1}H NMR δ 10.4 (CO_2H; bs, $W_{1/2}$ ≈ 100), 7.2−7.4 (Ph-H$_5$; m), 7.09 (3-H; ddd, 15.6/7.6/7.6), 6.39 (8-H; d, 15.9), 6.16 (7-H; dd, 15.9/8.1), 5.85 (2-H; d, 15.6), 3.78 (5-H; ddd, 6.0/6.0/4.2), 2.46 (6-H; m), 2.40 (4-H$_2$; m), 1.12 (6-Me; d, 6.9), 0.92 (SiCMe$_3$; s), 0.07 (SiMe$_2$; s); ^{13}C NMR δ 171.6 (1), 149.1 (3), 137.5 (Ph 1′), 131.8 (8), 130.5 (7), 128.5 (Ph 3′/5′), 127.1 (Ph 4′), 126.1 (Ph 2′/6′), 122.7 (2), 74.9 (5), 42.9 (6), 37.6 (4), 25.8 (SiC*Me*$_3$), 18.1 (Si*C*Me$_3$), 16.1 (6-Me), −4.4 (SiMe), −4.5 (SiMe).

2,2,2-Trichloroethyl Ester of *O*-Methyl-D-tyrosine (19-H). To a solution of BOC-protected *O*-methyl-D-tyrosine derived from 362 mg (2 mmol) of D-tyrosine[15] in 3.2 mL of CH_2Cl_2 at 0 °C were added sequentially 288 μL (3 mmol) of 2,2,2-trichloroethanol, 320 μL of pyridine, and 1.6 mL of a CH_2Cl_2 solution of DCC (400 mg, 2 mmol). The mixture was kept at 0 °C for 30 min and then at 25 °C for 3 h. The solvent was removed, and Et_2O was added. The ether solution was washed with water, saturated copper sulfate solution, and water again. The solvent and excess trichloroethanol were removed *in vacuo*. The residual solid was purified first by flash chromatography and then by recrystallization from EtOAc/hexane to give 460 mg of the 2,2,2-trichloroethyl ester of *N*-(*tert*-butoxycarbonyl)-*O*-methyl-D-tyrosine (54% yield), mp 115−116 °C: $[\alpha]_D$ −5.7° (*c* 12.0, $CHCl_3$); EIMS *m/z* (relative intensity) 427 (0.3), 425 (0.6), 371 (2.1), 369 (1.9), 352 (3.9), 310 (11.4), 308 (10.5), 121 (100); HREIMS *m/z* 425.0549 ($C_{17}H_{22}Cl_3NO_5$, Δ 1.5 mmu); IR ν_{max} 3359, 2932, 1760, 1716, 1515, 1250, 1163, 723 cm^{-1}; ^{1}H NMR δ 7.09 (5-H/9-H; d, 8.2), 6.83 (6-H/8-H; d, 8.2), 4.91 (NH; br d, 7.7), 4.80/4.72 (CH_2CCl_3; AB q, −11.7), 4.68 (2-H; m), 3.79 (OMe; s), 3.15 (3-H; dd, −12.8/5.5), 3.06 (3-H′; dd, −12.8/7.0), 1.38 (CMe$_3$; s); ^{13}C NMR δ 170.6 (1), 158.8 (7), 155.1 (BOC *C*O), 130.3 (5/9), 127.4 (4), 114.1 (6/8), 94.4 (CCl_3), 80.1 (*C*Me$_3$), 74.6 (*C*H$_2$CCl$_3$), 55.2 (OMe), 54.5 (2), 37.0 (3), 28.3 (C*Me*$_3$). The material from the preceding reaction (425 mg, 1 mmol) was dissolved in 2 mL of trifluoroacetic acid at 0 °C, and the solution was allowed to stand at 25 °C for 1 h and evaporated *in vacuo*, leaving behind 435 mg of **19**-H (trifluoroacetate salt) as an amorphous solid: $[\alpha]_D$ −1.6 (*c* 7.3, MeOH); IR ν_{max} 2958, 1754, 1678, 1613, 1515, 1252, 1203, 1138, 799, 723 cm^{-1}; ^{1}H NMR δ 7.17 (5-H/9-H; d, 8.2), 6.89 (6-H/9-H; d, 8.2), 4.89/4.72 (CH_2CCl_3; AB q, −11.8), 4.42 (2-H; dd, 7.4/5.3), 3.79 (OMe; s), 3.41 (3; dd, −14.7/4.5), 3.21 (3; dd, −14.7/7.9); ^{13}C NMR δ 169.0 (1), 160.7 (7), 131.5 (5/9), 126.6 (4), 115.5 (6/8), 95.2 (CCl_3), 75.9 (*C*H$_2$CCl$_3$), 55.7 (OMe), 55.1 (2), 36.5 (3).

2,2,2-Trichloroethyl Ester of 3-(3-Chloro-4-methoxyphenyl)-D-alanine (27). To a suspension of D-3-chlorotyrosine (1.08 g, 5 mmol) in 7.5 mL of water was added 0.84 mL (6 mmol, 1.2 equiv) of triethylamine followed by 7.5 mL of dioxane. The mixture was cooled in an ice bath, and 1.32 g (6 mmol, 1.2 equiv) of di-*tert*-butyl dicarbonate was added. The mixture was then stirred at 0 °C for 30 min, allowed to warm to room temperature and stirred for an additional 4 h, and concentrated *in vacuo*. Water (10 mL) was added, and the aqueous phase was washed with EtOAc (2 × 15 mL) and then cooled to 0 °C. Fresh EtOAc (25 mL) was added, and the mixture was carefully acidified with ice-cold 5% aqueous $KHSO_4$ solution (Congo Red end point). The phases were separated, and the aqueous phase was extracted with additional EtOAc (3 × 20 mL). The combined EtOAc extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo* to produce a foam (1.50 g, 94% yield). This material was dissolved in acetone, and 3.5 g (25 mmol, 5 equiv) of powdered anhydrous K_2CO_3 was added, followed by 0.657 mL of dimethyl sulfate. The mixture was heated to reflux and vigorously stirred for 4 h, cooled to room temperature, and filtered through a coarse sintered funnel, and the filtrate was evaporated *in vacuo*. The yellow residue was passed through a small silica column with 15% EtOAc in hexanes to give 1.42 g (84% yield) of the methyl ester of *N*-(*tert*-butoxycarbonyl)-3-(3-chloro-4-methoxyphenyl)-D-alanine as a colorless oil: $[\alpha]_D$ −45° (*c* 2.06, $CHCl_3$); IR ν_{max} 3368, 2977, 2840, 1745, 1715, 1607, 1504, 1441, 1366, 1282, 1258, 1214, 1167, 1066, 1023 cm^{-1}; ^{1}H NMR δ 7.1 (Ph 2; d, 1.8), 6.97 (Ph 6; dd, 7.8/1.2), 6.83 (Ph 5; d, 7.8), 5.0 (NH; d, 7.2), 4.51 (H-2; ddd, 7.2/5.8/5.3), 3.86 (4-OMe; s), 3.7 (COOMe, s), 3.05(H-3; dd, −11.2/5.3), 2.95 (H-3′; dd, −11.2, 5.8), 1.4 (C*Me*$_3$, br s); ^{13}C NMR δ 172.1 (1), 155.0 (BOC *C*O), 154.0 (Ph 4), 135.6 (Ph 3), 131.0 (Ph 2), 128.6 (Ph 1), 128.5 (Ph 6), 112.1 (Ph

5), 80.0 (CMe_3), 56.1 (Ph 4-OCH_3), 54.4 (2), 52.3 ($COOCH_3$), 37.5 (3), 28.3 (CMe_3). The methyl ester methyl ether (1.35 g, 4 mmol) was dissolved in 5 mL of dioxane and cooled to 4 °C with stirring, and 5 mL of 1 N aqueous NaOH was added. The mixture was allowed to warm to room temperature while the progress of the reaction was monitored by TLC. When all the starting material had been consumed, the pH was adjusted to 7 with cold 1 N HCl and the mixture was concentrated *in vacuo*. Water was added (5 mL), and the mixture was washed with diethyl ether (2 × 15 mL). The aqueous layer was cooled to 0 °C, EtOAc (25 mL) was added, and the mixture was acidified to the end point of Congo Red with cold 5% aqueous $KHSO_4$ solution. The phases were separated, the aqueous phase was extracted with additional EtOAc (3 × 20 mL), and the combined organic extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered, and evaporated to produce 1.1 g (86% yield) of *N*-(*tert*-butoxycarbonyl)-3-(3-chloro-4-methoxyphenyl)-D-alanine as a foam: $[\alpha]_D$ −59° (*c* 0.67, MeOH); IR ν_{max} 3331, 2978, 1713, 1661, 1602, 1502, 1448, 1395, 1366, 1259, 1164, 1063, 1022, 873, 755 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.28 (Ph 2; s), 7.19 (Ph 6; d, 8.3), 7.01(Ph 5; d, 8.3), 6.03 (NH; d, 7.3), 4.35 (2-H; br m,), 3.85 (OCH_3; s), 3.13 (3-H; dd, −13.8/4.6), 2.91(3-H′; dd, −13.8/8.9), 1.34 (CMe_3; br s); ^{13}C NMR (acetone-d_6) δ 173.5 (1), 154.2 (BOC *C*O), 153.6 (Ph 4), 131.5 (Ph 2), 128.5 (Ph 6), 127.8 (Ph 1), 122.3 (Ph 3), 112.5 (Ph 5), 79.5 (CMe_3), 55.8 (OCH_3), 54.7 (2), 38.8 (3), 28.4 (CMe_3).

To a solution of *N*-BOC-protected amino acid (3 mmol), 2,2,2-trichloroethanol (6 mmol, 3 equiv), and pyridine (2 mmol) in 5 mL of dry CH_2Cl_2 at 0 °C was added DCC (2.5 mmol) in 2 mL of dry CH_2Cl_2 dropwise with stirring under N_2. After 30 min, the mixture was warmed to room temperature and stirred overnight. EtOAc (30 mL) and water (15 mL) were added, and the phases were separated. The organic phase was washed with water (15 mL) and saturated aqueous $CuSO_4$ (2 × 10 mL), and the aqueous phases were reextracted with EtOAc (25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. After filtration through a plug of silica (15% EtOAc in hexanes) the product crystallized upon concentration *in vacuo*. Recrystallization from hexanes produced 600 mg (65% yield) of **27** as colorless crystals: mp 101−102 °C; $[\alpha]_D$ −11° (*c* 1.58, $CHCl_3$); IR ν_{max} 3391, 2978, 1760, 1714, 1607, 1504, 1442, 1368, 1258, 1162, 1066, 1025, 811, 786, 720 cm^{-1}; ^1H NMR δ 7.17 (Ph 2; d, 1.8), 7.02 (Ph 6; dd, 8.4/1.8), 6.83 (Ph 4; d, 8.4), 5.02 (N*H*; d, 8), 4.79/4.67 (CH_2CCl_3; AB q, −11.9), 4.63 (2-H; br m,), 3.83 (OCH_3, s), 3.12 (3-H; dd, −13.0/5.4), 2.98 (3-H; dd, −13.0, 6.8), 1.39 (CMe_3; s); ^{13}C NMR δ 170.5 (1), 155.1 (BOC *C*O), 154.3 (Ph 4), 131.1 (Ph 2), 128.8 (Ph 1), 128.6 (Ph 6), 122.5 (Ph 3), 112.3 (Ph 5), 94.5 (CCl_3), 80.4 (CMe_3), 74.7 (CH_2CCl_3), 56.2 (OCH_3), 54.5 (2), 36.9 (3), 28.3 (CMe_3).

2,2,2-Trichloroethyl Ester of 3-(3-Chloro-4-methoxyphenyl)-D-alanine (19-Cl). A sample of the D-chlorotyrosine BOC derivative (160 mg, 0.35 mmol) was dissolved in 3 mL of neat trifluoroacetic acid and allowed to stand at room temperature for 1 h. Removal of the excess reagent under reduced pressure returned the desired amine as the trifluoroacetate salt (165 mg, 100% yield): $[\alpha]_D$ 1.7° (*c* 5.2, $CHCl_3$); IR ν_{max} 3400−2500 (br), 1760, 1680, 1500, 1200, 1130, 1070, 805, 710 cm^{-1}; ^1H NMR δ 8.07 (NH_2; br m, $W_{1/2} \approx 45$), 7.27 (5-H; s), 7.12 (9-H; d, 8.1), 6.88 (8-H; d, 8.1), 4.86/4.67 (CH_2CCl_3; AB q, −12.0), 4.41 (2-H; bs, $W_{1/2} \approx 20$), 3.86 (OMe; s), 3.33 (3-H; dd, −14.4/3.6), 3.22 (3-H′; dd, −14.4/6.6); ^{13}C NMR δ 167.6 (1), 155.0 (7), 130.9 (5), 128.8 (9), 125.4 (4), 123.1 (6), 112.7 (8), 93.4 (CCl_3), 75.3 (CH_2CCl_3), 56.1 (OMe), 54.2 (2), 34.9 (3).

Pentafluorophenyl Diphenylphosphinate (FDPP). To a stirred solution of diphenylphosphinic chloride (1.03 g, 830 μL, 4.4 mmol) and pentafluorophenol (800 mg, 4.4 mmol) in 10 mL of dry CH_2Cl_2 at 25 °C under argon was added dropwise a solution of imidazole (300 mg, 4.4 mmol) in 5 mL of dry CH_2Cl_2. The reaction mixture was stirred for 3 h, and then the precipitated imidazole hydrochloride was filtered off by passing the mixture through a pad of silica with CH_2Cl_2. Evaporation of the CH_2Cl_2 in the filtrate left a colorless oil, which solidified in the freezer (1.62 g, 97%).

Protected Amide 20-H. To a stirred solution of **18** (25 mg, 0.07 mmol) in 3 mL of anhydrous DMF under argon were added successively FDPP (32 mg, 0.08 mmol), trifluoroacetate salt **19**-H (35 mg, 0.07 mmol), and diisopropylethylamine (DIEA, 27 mg, ≈36 μL, 0.21 mmol, ≈3 equiv). Stirring was continued at 25 °C for 1 h, and then the reaction mixture was extracted with 20 mL of Et_2O. The ether extract was washed with 10 mL of 1 N HCl, followed by 10 mL of saturated $NaHCO_3$, 20 mL of brine and 20 mL of water, dried ($MgSO_4$), and evaporated. The residual pale yellow oil was subjected to chromatography on silica gel (15% EtOAc in hexane) to give **20**-H as a colorless oil (37 mg, 80% yield): $[\alpha]_D$ 18.2° (*c* 2.0, $CHCl_3$); EIMS *m/z* 667/669/671/673 (<1; M^+), 610/612/614/616 (<1; $M^+ - {}^t$Bu), 536/538/540/542 (7/8/2/<1; M^+ − OTBS), 386/388 (15/9), 360 (41), 275 (37), 254 (31), 211 (34), 184 (100), 136 (80), 121 (84), 117 (46); HREIMS *m/z* 610.1374 ($C_{29}H_{35}Cl_3NO_5Si$, Δ −2.4 mmu), 536.1188 ($C_{27}H_{29}Cl_3NO_4$, Δ −2.6 mmu); UV λ_{max} (ϵ) 206 (29 800), 228 (19 300), 250 (16 200), 282 (2400) nm; IR ν_{max} 3281, 2954, 2928, 2855, 1762, 1668, 1636, 1513, 1250, 1034, 836, 776 cm^{-1}; ^1H NMR *unit A* δ 7.18−7.36 (Ph-H_5; m), 6.84 (3-H; m), 6.35 (8-H; d, 15.9), 6.16 (7-H; dd, 15.9/8.1), 5.78 (2-H; d, 15.3), 3.72 (5-H; m), 2.43 (6-H; m), 2.34 (4-H_2; m), 1.09 (6-Me; d, 6.9), 0.90 ($SiCMe_3$; s), 0.05 (SiMe; s), 0.04 (SiMe; s); *unit B* δ 7.02 (5-H/9-H; d, 8.4), 6.82 (6-H/8-H; d, 8.4), 5.77 (NH; d, 7.8), 5.07 (2-H; ddd, 7.8/6.0/5.7), 4.78/4.73 (CH_2CCl_3; AB q, −12.0), 3.77 (OMe; s), 3.22 (3-H; dd, −14.1/5.7), 3.13 (3-H′; dd, −14.1/6.0); ^{13}C NMR *unit A* δ 165.1 (1), 142.7 (3), 137.6 (9), 131.9 (8), 130.4 (7), 128.5 (11/13), 127.0 (12), 126.0 (10/14), 124.8 (2), 75.0 (5), 42.6 (6), 37.6 (4), 25.9 ($SiCMe_3$), 18.1 ($SiCMe_3$), 16.5 (6-Me), −4.3 (SiMe), −4.6 (SiMe); *unit B* δ 170.2 (1), 158.9 (7), 130.3 (5/9), 127.2 (4), 114.2 (6/8), 94.3 (CCl_3), 74.7 (CH_2CCl_3), 55.2 (OMe), 53.0 (2), 36.7 (3).

Protected Amide 20-Cl. This compound was prepared from **18** (90 mg, 0.25 mmol) and **19**-Cl (120 mg, 0.25 mmol) according to the same procedure, as a colorless oil (114.5 mg, 65% yield): $[\alpha]_D$ 11.8° (*c* 1.2, $CHCl_3$); EIMS *m/z* 644/646/648/650 (7/8/6/3; $M^+ - {}^t$Bu), 570/572/574 (46/100/21), 536/538 (18/15), 394/396 (67/29), 275 (20), 155/157 (29/9); HREIMS *m/z* 644.0981 ($C_{29}H_{34}Cl_4NO_5Si$, Δ −2.1 mmu); UV λ_{max} (ϵ) 204 (54 900), 230 (23 200), 248 (19 200), 284 (3500) nm; IR ν_{max} 3290, 2980, 2850, 1760, 1680, 1640, 1505, 1380, 1270, 1169, 990, 720 cm^{-1}; ^1H NMR *unit A* δ 7.2−7.4 (Ph-H_5; m), 6.87 (3-H; ddd, 15.0/7.8/7.5), 6.37 (8-H; d, 16.2), 6.18 (7-H; dd, 16.2/8.1), 5.82 (2-H; d, 15.0), 3.75 (5-H; ddd, 9.9/6.0/4.8), 2.46 (6-H; m), 2.36 (4-H_2; m), 1.11 (6-Me; d, 6.9), 0.91 ($SiCMe_3$; s), 0.07 (SiMe; s), 0.06 (SiMe; s); *unit B* δ 7.19 (5-H; d, 2.1), 7.04 (9-H; dd, 8.4/2.1), 6.85 (8-H; d, 8.4), 5.85 (NH; d, 7.8), 5.08 (2-H; ddd, 7.8/6.0/5.7), 4.81/4.74 (CH_2CCl_3; AB q, −11.7), 3.87 (OMe; s), 3.22 (3-H; dd, −14.1/5.7), 3.12 (3-H′; dd, −14.1/6.0); ^{13}C NMR *unit A* δ 165.1 (1), 143.0 (3), 137.6 (9), 132.0 (8), 130.4 (7), 128.5 (11/13), 127.0 (12), 126.0 (10/14), 124.7 (2), 75.0 (5), 42.6 (6), 37.6 (4), 25.9 ($SiCMe_3$), 18.1 ($SiCMe_3$), 16.5 (6-Me), −4.3 (SiMe), −4.6 (SiMe); *unit B* δ 170.1 (1), 154.3 (7), 131.1 (5), 128.5 (4/9), 122.6 (6), 112.2 (8), 94.2 (CCl_3), 74.8 (CH_2CCl_3), 56.1 (OMe), 53.0 (2), 36.5 (3).

Protected Amide 28. This compound was prepared from **18** (39 mg, 0.11 mmol) and **27** (58 mg, 0.11 mmol) according to the same procedure, to give pure **28** as a colorless oil (55 mg, 73% yield): $[\alpha]_D$ 53.3° (*c* 3.1, $CHCl_3$); EIMS *m/z* 644/646/648/650 (1/2/2/1; $M^+ - {}^t$Bu), 570/572/574 (5/7/4), 394/396 (15/7), 310 (19), 275 (10), 155/157 (42/15), 91 (46); HREIMS *m/z* 644.0962 ($C_{29}H_{34}Cl_4NO_5Si$, Δ −0.2 mmu); UV λ_{max} (ϵ) 206 (50 300), 230 (23 500), 248 (19 400), 282 (4000) nm; IR ν_{max} 3268, 2954, 2855, 1761, 1668, 1635, 1505, 1441, 1376, 1258, 1169, 1067, 836, 776 cm^{-1}; ^1H NMR *unit A* δ 7.2−7.4 (Ph-H_5; m), 6.87 (3-H; m), 6.39 (8-H; d, 15.9), 6.19 (7-H; dd, 15.9/8.0), 5.83 (2-H; d, 15.3), 3.77 (5-H; ddd, 6.0/6.0/3.9), 2.46 (6-H; m), 2.37 (4-H_2; m), 1.11 (6-Me; d, 6.9), 0.92 ($SiCMe_3$; s), 0.08 (SiMe; s), 0.06 (SiMe; s); *unit B* δ 7.19 (5-H; d, 1.8), 7.05 (9-H; dd, 8.4/1.8), 6.86 (8-H; d, 8.4), 5.88 (NH; d, 7.8), 5.09 (2-H; ddd, 7.8/6.0/5.7), 4.82/4.75 (CH_2CCl_3; AB q, −12.0), 3.89 (OMe; s), 3.21 (3-H; dd, −14.3/5.7), 3.13 (3-H′; dd, −14.1/6.0); ^{13}C NMR *unit A* δ 165.3 (1), 143.4 (3), 137.6 (9), 131.9 (8), 130.5 (7), 128.5 (11/13), 127.0 (12), 126.0 (10/14), 124.6 (2), 75.0 (5), 42.7 (6), 37.6 (4), 25.9 ($SiCMe_3$), 18.1 ($SiCMe_3$), 16.3 (6-Me), −4.3 (SiMe), −4.6 (SiMe); *unit B* δ 170.0 (1), 154.3 (7), 131.0 (5), 128.5 (4), 128.4 (9), 122.6 (6), 112.2 (8), 94.2 (CCl_3), 74.8 (CH_2CCl_3), 56.1 (OMe), 53.0 (2), 36.5 (3). Calcd for $C_{33}H_{43}Cl_4NO_5Si$: C, 56.31; H, 6.17; N, 1.99. Found: C, 55.90; H, 6.28; N, 1.96.

Compound 3-H. To a solution of **20**-H (24 mg, 0.035 mmol) in 2 mL of MeCN was added 200 μL of 49% aqueous HF, and the mixture was stirred for 1 h at 25 °C. Extraction into 15 mL of Et_2O, followed by washing the ether extract with 15 mL portions of saturated $NaHCO_3$,

brine, and water, drying ($MgSO_4$), and evaporation, gave alcohol **3**-H as a colorless oil (20 mg, 98% yield): $[\alpha]_D$ −1.5° (c 1.7, $CHCl_3$); EIMS *m/z* 553/555/557/559 (M^+, 0.5/1/1/<0.5), 462 (6), 424 (32), 422 (17), 403 (13), 377 (26), 312 (27), 310 (58), 308 (41), 276 (50), 274 (100), 246 (53), 217 (23); HREIMS *m/z* 555.1185 ($C_{27}H_{30}{}^{35}Cl_2{}^{37}ClNO_5$, Δ −2.5 mmu), 553.1124 ($C_{27}H_{30}{}^{35}Cl_3NO_5$, Δ 6.6 mmu); UV λ_{max} (ε) 206 (30 100), 230 (18 600), 250 (15 500), 282 (2700) nm; IR ν_{max} 3350, 3394, 2959, 1759, 1668, 1633, 1520, 1249, 1180, 1035, 972, 752 cm^{-1}; ^1H NMR *unit A* δ 7.12−7.32 (Ph-H_5; m), 6.84 (3-H; ddd, 15.3/7.5/7.5), 6.39 (8-H; d, 15.9), 6.06 (7-H; dd, 15.9/8.7), 5.81 (2-H; d, 15.3), 3.58 (5-H; ddd, 8.1/5.6/4.0), 2.2−2.4 (4-H_2/6-H; bm), 1.82 (OH; bs), 1.07 (6-Me; d, 6.9); *unit B* δ 7.00 (5-H/9-H; d, 8.5), 6.76 (6-H/8-H; d, 8.5), 5.82 (NH; d, 7.7), 4.99 (2-H; ddd, 7.7/6.0/5.7), 4.70/4.66 (CH_2CCl_3; AB q, −12.0), 3.70 (OMe; s), 3.14 (3-H; dd, −14.1/5.7), 3.06 (3-H′; dd, −14.1/6.0); ^{13}C NMR *unit A* δ 165.2 (1), 142.3 (3), 137.0 (9), 131.9 (8), 131.0 (7), 128.6 (11/13), 127.4 (12), 126.2 (10/14), 125.2 (2), 73.8 (5), 43.2 (6), 37.2 (4), 16.9 (6-Me); *unit B* δ 170.3 (1), 158.9 (7), 130.3 (5/9), 127.2 (4), 114.2 (6/8), 94.3 (CCl_3), 74.7 (CH_2CCl_3), 55.2 (OMe), 53.1 (2), 36.7 (3). Calcd for $C_{27}H_{30}Cl_3NO_5$: C, 58.41; H, 5.46; N, 2.52. Found: C, 58.95; H, 5.26; N, 2.42.

Amide 3-Cl. This compound was prepared from 50 mg (0.07 mmol) of **20**-Cl, according to the same procedure, as a colorless foam (40 mg, 95% yield): $[\alpha]_D$ −6.1° (c 1.3, $CHCl_3$); EIMS *m/z* (relative intensity) 587/589/591/593 (M^+, <1%), 552/554/556 (1/2/0.5), 456/458/460/462 (1/2/1/0.2), 342/344/346 (7/8/4), 212/214 (15/5), 195/197 (6/2), 155/157 (99/34), 131 (100), 91 (77); HREIMS *m/z* 587.0721 ($C_{27}H_{29}{}^{35}Cl_4NO_5$, Δ 7.9 mmu); UV λ_{max} (ε) 204 (56 500), 230 (22 100), 248 (18 100), 284 (3600) nm; IR ν_{max} 3400, 3300, 2980, 1780, 1680, 1640, 1505, 1270, 1180, 1090, 1000, 770 cm^{-1}; ^1H NMR *unit A* δ 7.2−7.4 (Ph-H_5; m), 6.92 (3-H; ddd, 15.3/7.8/7.5), 6.46 (8-H; d, 15.9), 6.14 (7-H; dd, 15.9/8.4), 5.90 (2-H; d, 15.3), 3.65 (5-H; ddd 7.8/5.6/4.0), 2.39 (6-H/4-H_2; bm), 1.78 (OH; bs, $W_{1/2} \approx 40$ Hz), 1.14 (6-Me; d, 6.9); *unit B* δ 7.18 (5-H; d, 1.8), 7.03 (9-H; dd, 8.4/1.8), 6.84 (8-H; d, 8.4), 5.97 (NH; d, 7.8), 5.06 (2-H; ddd, 7.8/6.0/5.7), 4.79/4.72 (CH_2CCl_3; AB q, −12.0), 3.86 (OMe; s), 3.20 (3-H; dd, −14.1/5.7), 3.10 (3-H′; dd, −14.1/6.0); ^{13}C NMR *unit A* δ 165.3 (1), 142.6 (3), 137.0 (9), 131.7 (8), 131.0 (7), 128.5 (11/13), 127.3 (12), 126.1 (10/14), 125.0 (2), 73.8 (5), 43.2 (6), 37.2 (4), 16.8 (6-Me); *unit B* δ 170.2 (1), 154.2 (7), 131.0 (5), 128.4 (9), 128.3 (4), 122.5 (6), 112.2 (8), 94.2 (CCl_3), 74.7 (CH_2CCl_3), 56.1 (OMe), 53.0 (2), 36.5 (3).

Amide 29. This compound was prepared from **28** (33 mg, 0.06 mmol), according to the same procedure, as a colorless oil (25 mg, 90% yield): $[\alpha]_D$ 51.1° (c 1.1, $CHCl_3$); EIMS *m/z* 587/589/591/593 (<1; M^+), 552/554/556 (1/2/0.5), 342/344/346 (25/32/19), 212/214 (24/10), 183/185 (33/12), 155/157 (95/70), 131 (100), 91 (93); HREIMS *m/z* 587.0721 ($C_{27}H_{29}Cl_4NO_5$, Δ 7.9 mmu); UV λ_{max} (ε) 204 (47 600), 230 (20 100), 248 (17 200), 282 (3600) nm; IR ν_{max} 3400, 3300, 2980, 1770, 1680, 1640, 1505, 1280, 1145, 1075, 980, 800, 745 cm^{-1}; ^1H NMR *unit A* δ 7.2−7.4 (Ph-H_5; m), 6.92 (3-H; ddd, 15.3/7.5/7.5), 6.46 (8-H; d, 15.9), 6.14 (7-H; dd, 15.9/8.7), 5.90 (2-H; d, 15.3), 3.65 (5-H; br m), 2.40 (4-H_2/6-H; m), 1.93 (OH; s), 1.14 (6-Me; d, 6.6); *unit B* δ 7.18 (5-H; d, 2.1), 7.03 (9-H; dd, 8.4/2.1), 6.85 (8-H; d, 8.4), 5.97 (NH; d, 7.8), 5.06 (2-H; ddd, 7.8/6.0/5.7), 4.79/4.73 (CH_2CCl_3; AB q, −11.7), 3.87 (OMe; s), 3.19 (3-H; dd, −14.3/5.7), 3.10 (3-H′; dd, −14.1/6.0); ^{13}C NMR *unit A* δ 165.2 (1), 142.5 (3), 137.0 (9), 131.9 (8), 130.9 (7), 128.6 (11/13), 127.4 (12), 126.2 (10/14), 125.1 (2), 73.8 (5), 43.3 (6), 37.2 (4), 16.8 (6-Me); *unit B* δ 170.1 (1), 154.3 (7), 131.0 (5), 128.5 (4), 128.4 (9), 122.6 (6), 112.3 (8), 94.2 (CCl_3), 74.8 (CH_2CCl_3), 56.1 (OMe), 53.0 (2), 36.5 (3).

(*R*)-3-Amino-2-methylpropan-1-ol (22). A solution of methyl (*S*)-(+)-3-hydroxy-2-methylpropanoate (**21**) (10 g, 85 mmol) in 300 mL of ca. 9 M ammonia in methanol was heated to 50 °C in a sealed glass flask for 168 h, flushed with nitrogen to remove excess ammonia, and then evaporated to dryness *in vacuo*. The residue was triturated with ether, leaving behind (*S*)-3-hydroxy-2-methylpropanamide (5.7 g, 66% yield) as a white solid, mp 85.5−87.5 °C: $[\alpha]_D$ 28.7° (c 3.5, MeOH); EIMS *m/z* (relative intensity) 88 (19, M − Me), 85 (35), 73 (69); HREIMS *m/z* 88.0397 ($C_3H_6NO_2$, Δ 0.2 mmu); IR ν_{max} 3384, 2960, 1671, 1473 cm^{-1}; ^1H NMR δ 5.83 (NH; br s), 5.42 (NH; br s), 3.73 (3-H_2; m), 2.55 (2-H; m), 1.19 (2-Me; d, 7.2); ^{13}C NMR δ 180.7 (1), 65.4 (3), 44.0 (2), 14.5 (2-Me). Anal. Found: C, 46.45; H, 8.83. Calcd for $C_4H_9NO_2$: C, 46.59; H, 8.79.

A suspension of (*S*)-3-hydroxy-2-methylpropanamide (2.1 g, 20 mmol) in anhydrous THF (20 mL) was added slowly to 1 M borane−THF complex (61 mmol, 61 mL) cooled to 0 °C. The mixture was refluxed for 6 h, cooled to 0 °C, carefully decomposed with concentrated HCl (10 mL), and concentrated *in vacuo*. The concentrate was saturated with NaOH (20 g) and extracted with $CHCl_3$ (15 mL × 4), and the combined extracts were dried ($MgSO_4$). After filtration and removal of solvent, distillation *in vacuo* yielded 1.4 g (77% yield) of **22** as a colorless oil, bp 110−112 °C (40 mmHg): $[\alpha]_D$ 8.9° (c 22.6, MeOH); IR ν_{max} 3358, 1873, 1598, 1466 cm^{-1}; ^1H NMR δ 5.18 (NH_2; br s), 3.8 (1-H_2; m), 2.95 (3-H; m), 2.68 (3-H; m), 1.81 (2-H; m), 0.82 (2-Me; d, 7.2); ^{13}C NMR δ 66.9 (1), 46.4 (3), 37.1 (2), 14.4 (2-Me).

(*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-methylpropanoic Acid (23). To a solution of amino alcohol **22** (2.0 g, 22 mmol) in 39 mL of a 10% solution of triethylamine in MeOH was added di-*tert*-butyl dicarbonate (5.4 g, 25 mmol), and the mixture was stirred at 25 °C for 30 min. After removal of solvent, the residue was dissolved in CH_2Cl_2 and the solution was washed twice with 1 M $KHSO_4$ (pH 2) and once with saturated NaCl solution and dried ($MgSO_4$). Removal of solvent *in vacuo* afforded 4.3 g (100% yield) of (*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-methylpropan-1-ol as a viscous oil, which was directly used for the next step without further purification (>95% pure by NMR analysis): IR ν_{max} 3356, 1976, 1686, 1523, 1456 cm^{-1}; ^1H NMR δ 4.82 (NH; br s), 3.54 (1-H; dd, −11.4/4.2), 3.31 (1-H/3−H; m), 3.25 (3-H; dd, −14.1/6.6), 1.77 (2-H; m), 1.44 (CMe_3; s), 0.87 (2-Me; d, 6.9).

To a solution of alcohol (*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-methylpropan-1-ol (2.2 g, 12 mmol) and sodium periodate (7.5 g, 35 mmol) in carbon tetrachloride (25 mL), acetonitrile (25 mL), and water (38 mL) was added ruthenium trichloride hydrate (51 mg, 0.25 mmol), and the mixture was stirred at 25 °C for 1 h. The mixture was diluted with CH_2Cl_2 (100 mL) and then filtered through Celite. The filtrate was basified (pH 9) with 2 M K_2CO_3 solution, and the water layer was washed with ether. The aqueous layer was acidified with 1 M $KHSO_4$ to pH 2 at 0 °C and extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were washed with saturated NaCl solution and dried ($MgSO_4$). Removal of solvent *in vacuo* yielded 2.0 g (85% yield) of **23** as a sticky solid. Pure **23** (1.75 g, 74% yield) crystallized from ether, mp 69.5−70.5 °C: $[\alpha]_D$ −18.4° (c 2, MeOH); EIMS *m/z* (relative intensity) 147 (60; $M^+ - Me_2C{=}CH_2$), 130 (12), 74 (29), 57 (100); HREIMS *m/z* 147.0517 ($C_5H_9NO_4$, Δ 1.4 mmu); IR ν_{max} 3322−2400, 2797, 1711, 1654, 1413 cm^{-1}; ^1H NMR of major conformer δ 5.00 (NH; br s), 3.32 (3-H; m), 3.24 (3-H′; m), 2.71 (2-H; m), 1.44 (CMe_3; s), 1.20 (2-Me; d); ^{13}C NMR of major/minor (2:1 ratio) conformers δ 180.7/179.5 (1), 156.0/157.7 (BOC *C*O), 79.5/81.0 (*C*Me_3), 42.7/44.0 (3), 39.9/40.2 (2), 28.3/28.3 (*CMe*$_3$), 14.6/14.6 (2-Me). Anal. Found: C, 53.04; H, 8.62. Calcd for $C_9H_{17}NO_4$: C, 53.18; H, 8.43.

Allyl (2*S*)-2-Hydroxy-4-methylpentanoate (24). To a solution of 2.66 g of L-leucic acid (20 mmol) and 1.74 g of sodium bicarbonate (20 mmol) in 30 mL water at 0 °C was added 30 mL of a CH_2Cl_2 solution of 6.44 g of tetrabutylammonium chloride (20 mmol) and 1.74 mL of allyl bromide (20 mmol). After the mixture was stirred vigorously for 24 h, the CH_2Cl_2 was evaporated. About 50 mL of water was added, and the aqueous layer was extracted four times with Et_2O. The ether solution was dried over anhydrous sodium sulfate and then evaporated. The residue was passed through a short Si column to give 3.21 g of **24** (93% yield) as a colorless oil: $[\alpha]_D$ −8.4° (c 1.1, $CHCl_3$); IR ν_{max} 3464, 2957, 1732, 1203, 1140, 1087 cm^{-1}; ^1H NMR δ 5.92 (allyl 2-H; m), 5.34 (allyl 3-H_Z; dd, 17.4/1.1), 5.28 (allyl 3-H_E; dd, 10.5/1.1), 4.67 (allyl 1-H_2; d, 5.7), 4.23 (2-H; br s), 2.64 (OH; br s), 1.89 (4-H; m), 1.57 (3-H_2; m), 0.96 (5-H_3; d, 6.5), 0.95 (4-Me; d, 6.7); ^{13}C NMR δ 175.3 (1), 131.4 (allyl C-2), 118.6 (3), 68.9 (2), 65.7 (allyl C-1), 43.2 (3), 24.1 (4), 23.0 (5), 21.3 (4-Me).

Allyl (2*S*,2′*R*)-2-[[3′-[(*tert*-Butoxycarbonyl)amino]-2′-methylpropanoyl]oxy]-4-methylpentanoate (25). To a solution of 1.74 g of **21** (8.55 mmol), 1.34 g of **24** (8.0 mmol), and 64 mg DMAP in 12 mL of dry CH_2Cl_2 at 0 °C was added dropwise 8 mL of a solution of DCC (2.47 g, 12 mmol) in CH_2Cl_2. The clear solution was stirred at 0 °C for 30 min and then at 23 °C for 3 h. The white precipitate was filtered off, the solvent was evaporated, and the residue was redissolved in Et_2O. The ether solution was washed successively with cold 0.5 N HCl, sodium bicarbonate, and brine. The dried (Na_2SO_4) ether layer was evaporated, and the product was purified by flash column chromatography (silica gel) to give 2.62 g (92% yield) of pure **25** as

a colorless oil: $[\alpha]_D$ −51.3° (*c* 3.41, $CHCl_3$); EIMS *m/z* (relative intensity) 301 (5.2), 284 (4.0), 258 (1.5), 228 (43.5), 170 (41.8), 130 (74.5), 112 (100); HREIMS *m/z* 301.1532 ($C_{14}H_{23}NO_6$, Δ −0.7 mmu, M − $Me_2C{=}CH_2$), 284.1496 ($C_{14}H_{22}NO_5$, Δ 0.2 mmu); IR ν_{max} 3395, 2962, 1747, 1715, 1515, 1251, 1175, 1083 cm^{-1}; ^1H NMR *unit C* δ 5.17 (NH; br s), 3.42 (3-H; m), 3.22(3-H′; m), 2.78 (2-H, m), 1.43 (CMe_3; br s), 1.21 (2-Me; d, 7.1); *unit D* δ 5.90 (allyl 2-H; m), 5.33 (allyl 3-H_Z; d, 16.3), 5.27 (allyl 3-H_E; d, 10.3), 5.09 (2-H; dd, 9.7/3.7), 4.63 (allyl 1-H_2; m), 1.80 (3-H_2; m), 1.64 (4-H; m), 0.96 (5-H_3; d, 6.5), 0.94 (4-Me; d, 7.3); ^{13}C NMR *unit C* δ 174.7 (1), 156.0 (BOC *C*O), 79.2 (*C*Me_3), 43.1 (3), 40.3 (2), 28.3 (C*Me*$_3$), 14.5 (2-Me); *unit D* δ 170.4 (1), 131.4 (allyl C-2), 119.0 (allyl C-3), 70.9 (2), 65.9 (allyl C-1), 39.6 (3), 24.7 (4), 23.0 (5), 21.5 (4-Me).

(2*S*,2′*R*)-2-[[3′-[(*tert*-Butoxycarbonyl)amino]-2′-methylpropanoyl]-oxy]-4-methylpentanoic Acid (2). To 10 mL of a solution of 282 mg (0.8 mmol) of **25** and 91 mg (0.08 mmol) of tetrakis(triphenylphosphine)palladium in dry THF was slowly added 688 μL (8 mmol) of dry morpholine. After stirring for 40 min, the solvent was evaporated and 100 mL of CH_2Cl_2 was added. The solution was washed successively with 2 N HCl and water. The organic layer was filtered, and the filtrate was extracted twice with saturated sodium bicarbonate. After back-washing with CH_2Cl_2, the aqueous layer was first acidified to pH 3 with cold $KHSO_4$ at 0 °C and then extracted three times with ether. The dried ether extract was evaporated to give 250 mg of **2** (100% yield) as a wax-like solid: $[\alpha]_D$ −47.9° (*c* 4.7, $CHCl_3$); EIMS *m/z* (relative intensity) 261 (12), 244 (18), 217 (28), 198 (17), 188 (100), 160 (61); HREIMS *m/z* 261.1221 ($C_{11}H_{19}NO_6$, Δ −0.8 mmu, M − $Me_2C{=}CH_2$), 244.1221 ($C_{11}H_{18}NO_5$, Δ −3.6 mmu); IR ν_{max} 3376, 2960, 1738, 1518, 1174, 786 cm^{-1}. ^1H NMR ($CDCl_3$ + D_2O) *unit C* δ 3.49 (H-3; dd, −13.8/3.5), 3.12(3-H; dd, −13.8/8.7), 2.68 (2-H; m), 1.43 (C*Me*$_3$; br s), 1.21 (2-Me; d, 7.1); *unit D* δ 5.12 (2-H; dd, 9.6/3.5), 1.90−1.68 (3-H_2/4-H; m), 0.97 (5-H_3; d, 6.1), 0.94 (4-Me; d, 6.0); ^{13}C NMR *unit C* δ 174.6 or 174.8 (1), 156.1 (BOC *C*O), 79.5 (*C*Me_3), 43.0 (3), 40.4 (2), 28.3 (C*Me*$_3$), 14.5 (2-Me); *unit D* δ 174.6 or 174.8 (1), 70.5 (2), 39.5 (3), 24.7 (4), 23.0 (5), 21.4 (4-Me).

Compound 26. To a solution of 33.8 mg of **3**-H (0.061 mmol), 29.1 mg of **2** (0.092 mmol), and 1.8 mg of DMAP in 306 μL of CH_2Cl_2 at 0 °C was added 306 μL of a solution of DCC (19 mg, 0.092 mmol) in CH_2Cl_2. The reaction mixture was kept at 0 °C for 10 min and then at room temperature overnight. Diethyl ether, ice, and 0.5 N HCl were added. The ether layer was washed successively with sodium bicarbonate solution and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue gave 46 mg of **26** (88% yield) as an amorphous solid: $[\alpha]_D$ −10.5° (*c* 0.56, $CHCl_3$); IR ν_{max} 3363, 2960, 1732, 1504, 1367, 1257, 1173, 1067, 750, 720, 695 cm^{-1}; ^1H NMR (500 MHz) *unit A* δ 7.2−7.35 (Ph-H_5; m), 6.77 (3-H; dt, 15.6/6.8), 6.40 (8-H; d, 15.9), 6.01 (7-H; dd, 15.9/8.7), 5.88 (2-H; d, 15.6), 5.03 (5-H; m), 2.60 (6-H; m), 2.53 (4-H_2; m), 1.11 (6-Me; d, 7.0); *unit B* δ 7.08 (5-H/9-H; d, 8.6), 6.81 (6-H/8-H; d, 8.6), 6.36 (NH; d, 7.9), 5.05 (2-H; dt), 3.77 (OMe; s), 4.76/4.72 (CH_2CCl_3; AB q, −11.8), 3.20 (3-H; dd, −14.2/5.9), 3.07 (3-H′; dd, −14.2/6.3); *unit C* δ 5.14 (NH; br t), 3.34/3.20 (3-H_2; m), 2.74 (2-H; m), 1.42 (C*Me*$_3$; s), 1.19 (2-Me; d, 7.2); *unit D* δ 4.92 (2-H; dd, 10.0/3.7), 1.71 (4-H; m), 1.5−1.7 (3-H_2; m), 0.86 (5-H_3; d, 6.6), 0.82 (4-Me; d, 6.6); ^{13}C NMR (125 MHz) *unit A* δ 165.2 (1), 139.1 (3), 136.8 (9), 131.7 (8), 130.1 (7), 128.5 (11/13), 127.4 (12), 126.1 (10/14), 125.7 (2), 76.5 (5), 41.0 (6), 33.6 (4), 16.7 (6-Me); *unit B* δ 170.4 (1), 158.7 (7), 130.3 (5/9), 128.9 (4), 114.0 (6/8), 94.3 (CCl_3), 74.6 (*C*H_2CCl_3), 55.2 (OMe), 53.3 (2), 36.8 (3); *unit C* δ 175.1 (1), 156.0 (BOC *C*O), 79.2 (*C*Me_3), 43.0 (3), 40.3 (2), 28.3 (C*Me*$_3$), 14.5 (2-Me); *unit D* δ 170.3 (1), 71.2 (2), 39.4 (3), 24.6 (4), 22.9 (5), 21.3 (4-Me).

Compound 30 was prepared from 25 mg of **29** and 20 mg of **2** in 76% yield using the procedure described above: $[\alpha]_D$ 8.8° (*c* 0.19, $CHCl_3$); IR ν_{max} 3368, 2962, 1732, 1504, 1367, 1259, 1172, 1067 cm^{-1}; ^1H NMR (500 MHz) *unit A* δ 7.33−7.21 (Ph-H_5; m), 6.77 (3-H; dt, 15.6/6.5), 6.40 (8-H; d, 15.9), 6.01 (7-H; dd, 15.9/8.7), 5.91 (2-H; d, 15.6), 5.06 (5-H; m), 2.61 (6-H; m), 2.54 (4-H; m), 1.12 (6−Me; d, 6.8); *unit B* δ 7.20 (5-H; d, 2.2), 7.05 (9-H; dd, 8.4 and 2.2), 6.84 (8-H; d, 8.4), 6.62 (NH; br d, 7.5), 5.06 (2-H; m), 4.76/4.71 (CH_2CCl_3; AB q, −11.9), 3.87 (OCH_3; s), 3.17 (3-H; dd, −14.2/6.0), 3.09 (3-H′; dd, −14.2/6.4); *unit C* δ 5.23 (NH; br t, 5.4), 3.32 (3-H; ddd, −13.3/7.3/5.4), 3.04 (3-H′; ddd, −13.3/8.6/5.4), 2.76 (2-H; m), 1.42 (CMe_3; br s), 1.17 (2-Me; d, 7.2); *unit D* δ 4.90 (2-H; dd, 10.2/3.8), 1.69 (4-H; m), 1.65 (3-H; ddd, −14.1/10.2/4.8), 1.52 (3-H′; ddd, −14.1/5.2/3.8), 0.84 (5-H_3; d, 6.5), 0.80 (4-Me, d, 6.4); ^{13}C NMR (125 MHz) *unit A* δ 165.6 (1), 125.4 (2), 139.2 (3), 33.3 (4), 76.3 (5), 41.2 (6), 130.1 (7), 131.7 (8), 136.8 (9), 126.1 (10 and 14), 128.6 (11 and 13), 127.5 (12), 16.6 (6-Me); *unit B* δ 170.5 (1), 154.2 (7), 131.0 (5), 128.7 (4), 122.4 (6), 128.6 (9), 112.2 (8), 94.2 (CCl_3), 74.7 (*C*H_2CCl_3), 56.1 (OMe), 53.2 (2), 36.7 (3); *unit C* δ 175.3 (1), 156.0 (BOC *C*O), 79.3 (*C*Me_3), 43.1 (3), 40.3 (2), 28.3 (C*Me*$_3$), 14.5 (2-Me); *unit D* δ 170.3 (1), 71.4 (2), 39.4 (3), 24.6 (4), 22.9 (5), 21.4 (4-Me).

Compound 33. This compound was prepared from **2** (28 mg, 0.09 mmol) and **3**-Cl (35 mg, 0.06 mmol) according to the procedure described above (50 mg, 94% yield): $[\alpha]_D$ −10.7° (*c* 2.2, $CHCl_3$); EIMS *m/z* 786/788/790/792 (<1; M^+ − BOC), 342/344/346 (8/10/5), 227 (24), 212/214 (6/3), 195/197 (13/6), 155/157 (100/31), 91 (81); HREIMS *m/z* 786.2024 ($C_{37}H_{46}Cl_4N_2O_8$, Δ −1.6 mmu); UV λ_{max} (ε) 204 (51 800), 230 (17 800), 248 (13 800), 282 (2900) nm; IR ν_{max} 3368, 2962, 1738, 1678, 1505, 1367, 1258, 1172, 971, 752 cm^{-1}; ^1H NMR *unit A* δ 7.2−7.4 (Ph-H_5; m), 6.77 (3-H; ddd, 15.6/6.6/6.3), 6.41 (8-H; d, 15.9), 6.02 (7-H; dd, 15.9/8.7), 5.89 (2-H; d, 15.6), 5.05 (5-H; m), 2.61 (6-H; m), 2.54 (4-H_2; m), 1.12 (6-Me; d, 6.6); *unit B* δ 7.19 (5-H; d, 2.1), 7.05 (9-H; dd, 8.4/2.1), 6.83 (8-H; d, 8.4), 6.56 (NH; d, 7.8), 5.05 (2-H; m), 3.86 (OMe; s), 4.79/4.71 (CH_2CCl_3; AB q, −12.0), 3.20 (3-H; dd, −14.1/6.0), 3.08 (3-H′; dd, −14.1/6.6); *unit C* δ 5.14 (NH; dd, 6.6/6.0), 3.33 (3-H; ddd, −12.9/6.0/5.7), 3.19 (3-H′; m), 2.75 (2-H; m), 1.42 (CO_2CMe_3; s), 1.19 (2-Me; d, 7.2); *unit D* δ 4.93 (2-H; dd, 9.9/3.6), 1.5−1.7 (3-H_2/4-H; m), 0.86 (5-H_3; d, 6.3), 0.81 (4-Me; d, 6.6); ^{13}C NMR *unit A* δ 165.4 (1), 139.2 (3), 136.9 (9), 131.7 (8), 130.1 (7), 128.6 (11/13), 127.5 (12), 126.2 (10/14), 125.5 (2), 76.4 (5), 41.2 (6), 33.5 (4), 16.7 (6-Me); *unit B* δ 170.5 (1), 154.1 (7), 131.2 (5), 128.9 (4), 128.5 (9), 122.3 (6), 112.1 (8), 94.3 (CCl_3), 74.6 (*C*H_2-CCl_3), 56.1 (OMe), 53.2 (2), 36.6 (3); *unit C* δ 175.2 (1), 156.0 (BOC *C*O), 79.3 (*C*Me_3), 43.1 (3), 40.4 (2), 28.4 (C*Me*$_3$), 14.4 (2-Me); *unit D* δ 170.1 (1), 71.4 (2), 39.5 (3), 24.7 (4), 22.9 (5), 21.4 (4-Me).

Compound 1. A sample of protected amino acid **26** (32 mg, 0.036 mmol) was placed in a thick-walled glass vial, and then activated Zn dust (125 mg, excess) and acetic acid (400 μL) were added. The heterogeneous mixture was placed in an ultrasonic cleaning bath for 45 min and then stirred for 90 min at room temperature. The Zn was removed by filtration through Celite with CH_2Cl_2. Solvent evaporation produced a colorless amorphous solid, which was immediately dissolved in TFA (2 mL) and allowed to stand at room temperature for 1 h. Evaporation of the TFA followed by chromatographic purification (Sep-Pak, silica, first CH_2Cl_2, then 10% MeOH/CH_2Cl_2) produced the trifluoroacetate ammonium salt of the desired compound. Addition of water followed by freezing and lyophilization led to free amino acid **1** as an amorphous solid: $[\alpha]_D$ −62.9° (*c* 0.28, $CHCl_3$); EIMS *m/z* (relative intensity) 605 (3.5; M^+ − OH), 559 (10), 468 (15), 405 (30), 387 (93), 359 (100); HREIMS *m/z* 605.3202 ($C_{35}H_{45}N_2O_7$, Δ 2.5 mmu); IR ν_{max} 3382, 2957, 1742, 1733, 1615, 1514, 1393, 1248, 1180, 1036 cm^{-1}; ^1H NMR (500 MHz) *unit A* δ 7.35−7.21 (Ph-H_5; m), 6.52 (3-H; dt, 15.8/7.0), 6.41 (8-H; d, 15.8), 5.98 (7-H; dd, 15.8/8.8), 5.89 (2-H; d, 15.8), 5.05 (5-H; ddd, 10.2/7.9/1), 2.56 (6-H; m), 2.50/2.40 (4-H_2; m), 1.12 (6-Me; d, 7.0); *unit B* δ 7.13 (5-H/9-H; d, 8.6), 6.74 (6-H/8-H; d, 8.6), 6.60 (NH; d, 7.7), 4.64 (2-H; m), 3.73 (OMe; s), 3.13 (3-H; dd, −13.7/4.6), 3.07 (3-H′; dd, −13.7/5.6); *unit C:* 2.95 (3-H; dd, −12.8/11.8), 2.88 (3-H′; dd, −12.8/4.5), 2.56 (2-H; m), 1.14 (2-Me; d, 7.2); *unit D* δ 4.89 (2-H; dd, 10.7/3.3), 1.71 (4-H; m), 1.61 (3-H; ddd, −14.3/10.7/4.9), 1.47 (3-H′; ddd, −14.3/9.3/3.3), 0.84 (5-H_3; d, 6.5), 0.76 (4-Me; d, 6.8); ^{13}C NMR (125 MHz) *unit A* δ 165.7 (1), 136.7 (9), 136.6 (3), 132.0 (8), 129.8 (7), 128.6 (11/13), 127.8 (2), 127.6 (12), 126.2 (10/14), 78.3 (5), 42.4 (6), 34.8 (4), 17.2 (6-Me); *unit B* δ 177.0 (1), 158.0 (7), 130.9 (5/9), 130.3 (4), 113.3 (6/8), 55.5 (OMe), 55.1 (2), 37.4 (3); *unit C* δ 173.7 (1), 42.5 (3), 38.1 (2), 14.8 (2−Me); *unit D* δ 172.1 (1), 72.0 (2), 39.2 (3), 24.7 (4), 22.8 (5), 21.2 (4-Me).

Amino acid 31 was prepared from **30** (20 mg, 0.023 mmol) with ≈82 mg of activated Zn dust in 200 μL of HOAc, according to the same procedure, as an amorphous solid (14 mg, 81% yield): $[\alpha]_D$ 18.5° (*c* 0.2, $CHCl_3$); FABMS *m/z* (glycerol) 657/659 (M + H); (glycerol + K) 657/659 (M + H), 695/697 (M + K); (thioglycerol) 657/659 (M + H), 765/767 (M + thioglycerol); IR ν_{max} 2961, 1733, 1680, 1506, 1280, 1259, 1066, 730 cm^{-1}; ^1H NMR (500 MHz) *unit A* δ 7.33−7.28 (Ph-H_5; m), 6.65 (3-H; br dt, 15.9/6.8), 6.45 (8-H; d, 15.8), 5.99 (7-H; dd, 15.8/8.6), 5.85 (2-H; 15.9), 5.06 (5-H; m), 2.57 (6-H; m), 2.55 (4-H;

m), 2.40 (4-H′; m), 1.12 (6-Me; d, 6.7); *unit B* δ 7.19 (5-H; br s), 7.05 (9-H; br d, 8.3), 6.84 (8-H; d, 8.3), 6.75 (NH; br d, 5.7), 4.59 (2-H; m), 3.84 (OMe; s), 3.10 (3-H; m); *unit C* δ 2.82 (3-H; m), 2.50 (2-H; m), 1.26 (2-Me; d, 5.7); *unit D* δ 4.82 (2-H; dd, 9.3 and 2.9), 1.67 (4-H; m), 1.60 (3-H; m), 1.47 (3-H′; m), 0.81 (5-H; d, 6.4), 0.76 (4-Me; d, 6.4); ^{13}C NMR (125 MHz) *unit A* δ 165.6 (1), 137.9 (3), 136.7 (9), 131.8 (8), 130.0 (7), 128.6 (11/13), 127.6 (12), 126.2 (10/14), 126.0 (2), 42.0 (6), 33.3 (4), 16.5 (6-Me); *unit B* δ 176.7 (1), 153.6 (7), 131.3 (5), 129.7 (4), 129.1 (9), 121.7 (6), 112.0 (8), 56.1 (2), 55.2 (OMe), 36.7 (3); *unit C* δ 173.8 (1), 41.0 (3), 37.4 (2), 15.1 (2-Me); *unit D* δ 170.8 (1), 71.9 (2), 39.3 (3), 24.7 (4), 22.9 (5), 21.4 (4-Me).

Amino acid 34 was prepared from **33** (32 mg, 0.036 mmol), according to the same procedure, as a colorless amorphous solid (21 mg, 89% yield): $[\alpha]_D$ −47.0° (*c* 1.2, $CHCl_3$) for the trifluoroacetate salt; FABMS *m/z* (glycerol) 657/659 (M + H); (glycerol + K) 657/659 (M + H), 695/697 (M + K); (thioglycerol) 657/659 (M + H), 765/767 (M + thioglycerol); UV λ_{max} (ε) 204 (52 100), 230 (16 100), 250 (16 500), 282 (2500) nm; IR ν_{max} 3400, 3290, 2960, 1732, 1668, 1614, 1504, 1392, 1258, 1194, 1066, 971, 751 cm^{-1}; ^{1}H NMR (500 MHz) *unit A* δ 7.4−7.2 (Ph-H$_5$; m), 6.43 (3-H; ddd, 16.0/6.8/6.5), 6.41 (8-H; d, 15.5), 5.96 (7-H; dd, 15.5/9.0), 5.92 (2-H; d, 16.0), 5.06 (5-H; ddd, 10.5/6.8/1.3), 2.54 (6-H; m), 2.50/2.42 (4-H$_2$; m), 1.12 (6-Me; d, 7.0); *unit B* δ 7.24 (5-H, d, 2), 7.05 (9-H; dd, 8.5/2.0), 6.78 (8-H; d, 8.5), 6.66 (NH; d, 7.8), 4.64 (2-H; ddd, 7.8/5.0/5.0), 3.81 (OMe; s), 3.12 (3-H; dd, −14.0/5.0), 3.08 (3-H′; dd, −14.0/5.0); *unit C* δ 3.02 (3-H; dd, −12.8/12.0), 2.85 (3-H′; dd, −12.8/4.5), 2.36 (2-H; m), 1.11 (2-Me; d, 7.5); *unit D* δ 4.88 (2-H; dd 10.8/3.3), 1.69 (4-H; m), 1.60 (3-H; ddd, −14.5/11.0/4.5), 1.47 (3-H′; ddd, −14.5/9.5/3.5), 0.84 (5-H$_3$; d, 6.5), 0.76 (4-Me; d, 6.5). ^{13}C NMR (125 MHz) *unit A* δ 165.8 (1), 136.0 (3), 136.6 (9), 132.0 (8), 129.7 (7), 128.6 (11/13), 127.6 (12), 126.2 (10/14), 128.2 (2), 78.5 (5), 42.4 (6), 34.9 (4), 17.3 (6-Me); *unit B* δ 176.3 (1), 153.2 (7), 131.3 (5), 131.6 (4), 129.7 (9), 121.1 (6), 111.6 (8), 55.9 (OMe), 55.2 (2), 37.0 (3); *unit C* δ 173.3 (1), 42.7 (3), 38.5 (2), 14.7 (2-Me); *unit D* δ 172.6 (1), 72.0 (2), 39.0 (3), 24.7 (4), 22.7 (5), 21.1 (4-Me) ppm. Cytotoxicity data: KB (IC_{50} 290 ng/mL); LoVo (IC_{50} 380 ng/mL).

Cryptophycin D. To a solution of amino acid **1** (4 mg, 0.0064 mmol) in 1 mL of anhydrous DMF were added FDPP (3.2 mg, 0.0082 mmol, ≈1.3 equiv) and DIEA (2.5 mg, 3.4 mL, 0.0194 mmol, ≈3 equiv). The reaction mixture was stirred under argon at 25 °C for 2.5 h, diluted with 10 mL of Et_2O, and washed successively with 10 mL portions of 1 M HCl, saturated $NaHCO_3$, brine, and water. The ethereal extract was dried ($MgSO_4$) and concentrated under reduced pressure to give a waxy solid, which was purified by passage through a silica Sep-Pak column, using ether as the eluant, to give the desired compound as a colorless amorphous solid (2.4 mg, 62% yield): $[\alpha]_D$ 22.8° (*c* 0.2, $CHCl_3$); UV λ_{max} (ε) 204 (34 500), 228 (16 600), 250 (14 700), 282 (2000) nm; ^{1}H NMR (500 MHz) *unit A* δ 7.35−7.20 (Ph-H$_5$; m), 6.71 (3-H; ddd, 15.3/10.3/5.0), 6.41 (8-H; d, 15.8), 6.01 (7-H; dd, 15.8/8.9), 5.74 (2-H; dd, 15.3/1.2), 5.02 (5-H; ddd, 11.0/6.3/1.8), 2.54 (6-H/4-H′; m), 2.36 (4-H; ddd, −14.5/11.0/10.3), 1.13 (6-Me; d, 6.5); *unit B* δ 7.12 (5-H/9-H; d, 8.8), 6.81 (6-H/8-H; d, 8.8), 5.62 (NH; d, 8.3), 4.80 (2-H; ddd, 8.3/7.0/5.5), 3.78 (OMe; s), 3.14 (3-H; dd, −14.4/5.5), 3.08 (3-H′; dd, −14.4/7.0); *unit C* δ 7.02 (NH; dd, 5.8/4.3), 3.41 (3-H; ddd, −13.5/4.3/4.3), 3.36 (3-H′; ddd, −13.5/7.5/5.8), 2.69 (2-H; m), 1.22 (2-Me; d, 7.5); *unit D* δ 4.84 (2-H; dd, 9.9/3.6), 1.65 (3-H/4-H; m), 1.35 (3-H′; m), 0.76 (5-H$_3$; d, 6.5), 0.72 (4-Me; d, 6.5); ^{13}C NMR (125 MHz) *unit A* δ 165.3 (1), 141.5 (3), 136.7 (9), 131.8 (8), 130.1 (7), 128.6 (11/13), 127.6 (12), 126.2 (10/14), 125.1 (2), 77.1 (5), 42.3 (6), 36.5 (4), 17.3 (6-Me); *unit B* δ 171.2 (1), 158.6 (7), 130.2 (5/9), 128.5 (4), 114.1 (6/8), 55.2 (OMe), 53.8 (2), 35.3 (3); *unit C* δ 175.9 (1), 40.8 (3), 38.1 (2), 14.2 (2-Me); *unit D* δ 170.8 (1), 71.6 (2), 39.5 (3), 24.5 (4), 22.7 (5), 21.2 (4-Me). Cytotoxicity data: KB (IC_{50} 22 ng/mL); LoVo (IC_{50} 16 ng/mL).

Cryptophycin C. This compound was prepared from amino acid **34** (14 mg, 0.021 mmol), according to the procedure described above, as a colorless amorphous solid (8.7 mg, 64% yield): $[\alpha]_D$ 28.8° (*c* 0.65, $CHCl_3$); EIMS *m/z* 640/638 (7/2; M$^+$), 414 (22), 412 (76), 282 (3), 280 (14), 227 (100), 195 (45), 91 (69); HREIMS *m/z* 638.2761 ($C_{35}H_{43}ClN_2O_7$, Δ −0.2 mmu); UV λ_{max} (ε) 204 (35 700), 230 (11 800), 250 (10 900), 282 (2000) nm; IR ν_{max} 3420, 3300, 2980, 1745, 1680, 1500, 1270, 1195, 1080, 750 cm^{-1}; ^{1}H NMR (500 MHz) δ *unit A* 7.4−7.2 (Ph-H$_5$; m), 6.68 (3-H; ddd 15.5/10.0/5.5), 6.41 (8-H; d, 15.8), 6.01 (7-H; dd, 15.8/9.0), 5.77 (2−H; d, 15.5), 5.00 (5-H; ddd, 10.5/6.5/1.5), 2.54 (4-H/6-H; m), 2.37 (4-H′; ddd, −14.2/10.5/10.0), 1.13 (6-Me; d, 6.5); *unit B* 7.21 (5-H; d, 2.0), 7.07 (9-H; dd, 8.5/2.0), 6.83 (8-H; d, 8.5), 5.73 (NH; d, 8.5), 4.81 (2-H; m), 3.86 (OMe; s), 3.13 (3-H; dd, −14.5/5.5), 3.03 (3-H′; dd −14.5/7.5); *unit C* 6.95 (NH; bdd, 6.5/4.5), 3.50 (3-H; ddd, −13.5/4.5/4.0), 3.27 (3-H′; ddd, −13.5/7.0/6.5), 2.71 (2-H; m), 1.21 (2-Me; d, 7.5); *unit D* 4.84 (2-H; dd, 10.0/3.0), 1.65 (3-H/4-H; m), 1.36 (3-H′; m), 0.77 (5-H$_3$; d, 6.5), 0.72 (4-Me; d, 6.5); ^{13}C NMR (125 MHz) δ *unit A* 165.5 (1), 141.4 (3), 136.7 (9), 131.8 (8), 130.0 (7), 128.6 (11/13), 127.6 (12), 126.1 (10/14), 125.2 (2), 77.4 (5), 42.2 (6), 36.4 (4), 17.3 (6-Me); *unit B* 171.0 (1), 153.9 (7), 131.0 (5), 129.8 (4), 128.4 (9), 122.4 (6), 112.2 (8), 56.1 (OMe), 53.6 (2), 35.0 (3); *unit C* 175.6 (1), 41.1 (3), 38.2 (2), 14.0 (2-Me); *unit D* 170.9 (1), 71.5 (2), 39.5 (3), 24.4 (4), 22.7 (5), 21.2 (4-Me). Cytotoxicity data: KB (IC_{50} 2.9 ng/mL); LoVo (IC_{50} 3.7 ng/mL).

Cyclic Depsipeptide 32. This compound was prepared from amino acid **31** (10 mg, 0.015 mmol), according to the procedure described above, as a colorless amorphous solid (6.0 mg, 62% yield): $[\alpha]_D$ −101.4° (c 0.2, $CHCl_3$); EIMS *m/z* 638/640 (1.3/0.5; M$^+$), 620 (3), 618 (5), 414 (11), 412 (25), 282 (5), 280 (17), 227 (32), 197 (13), 195 (39), 169 (17), 167 (31), 157 (33), 155 (100), 91 (92); HREIMS *m/z* 638.2761 ($C_{35}H_{43}{}^{35}ClN_2O_7$, Δ −0.2 mmu), 155.0248 ($C_8H_8{}^{35}ClO$, Δ 1.6 mmu); UV λ_{max} (ε) 206 (44 000), 230 (16 400), 248 (13 700), 282 (2600) nm; IR ν_{max} 3445, 3300, 2980, 1740, 1680, 1500, 1255, 1200, 1070, 750 cm^{-1}; ^{1}H NMR (500 MHz) *unit A* δ 7.35−7.2 (Ph-H$_5$; m), 6.45 (3-H; ddd, 15.9/7.8/6.6), 6.42 (8-H; d, 15.7), 6.00 (7-H; dd, 15.7/8.7), 5.88 (2-H; d, 15.9), 4.97 (5-H; ddd, 11.3/6.6/2.2), 2.57 (6-H; m), 2.51 (4-H; dddd, −14.4/6.6/2.2/1.7), 2.40 (4-H′; ddd, −14.4/11.3/7.8), 1.15 (6-Me; d, 6.9); *unit B* δ 7.22 (5-H; d, 2.2), 7.09 (9-H; dd, 8.6/2.2), 6.85 (8-H; d, 8.6), 5.67 (NH; d, 9.3), 4.82 (2-H; ddd, 9.3/7.3/5.4), 3.87 (OMe; s), 3.15 (3-H; dd, −14.4/5.4), 3.10 (3-H′; dd, −14.4/7.3); *unit C* δ 6.83 (NH; br m), 3.46 (3-H$_2$; m), 2.68 (2-H; m), 1.17 (2-Me; d, 7.3); *unit D* δ 4.91 (2-H; dd, 9.9/3.3), 1.63 (3-H/4-H; br m), 1.40 (3-H′; m), 0.79 (5-H$_3$; d, 6.4), 0.72 (4-Me; d, 6.6); ^{13}C NMR (125 MHz) *unit A* δ 166.3 (1), 139.0 (3), 136.6, (9), 132.0 (8), 129.9 (7), 128.6 (11), 127.6 (12), 126.8 (2), 126.1 (10), 78.3 (5), 42.3 (6), 35.2 (4), 17.3 (6-Me); *unit B* δ 170.6 (1), 153.9 (7), 131.1 (5), 130.0 (4), 128.5 (9), 122.3 (6), 112.3 (8), 56.1 (OMe), 53.5 (2), 35.0 (3); *unit C* δ 174.6 (1), 40.9 (3), 39.6 (2), 14.3 (2-Me); *unit D* δ 171.9 (1), 71.5 (2), 39.5 (3), 24.6 (4), 21.2 (5), 22.8 (4-Me). Calcd for $C_{35}H_{43}ClN_2O_7$: C, 65.75; H, 6.79; N, 4.38. Found: C, 65.87; H, 6.50; N, 4.10. Cytotoxicity data: KB (IC_{50} 310 ng/mL); LoVo (IC_{50} 380 ng/mL).

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Supplementary Material Available: ^{1}H and ^{13}C NMR and mass spectra of synthetic cryptophycins C and D and **32** and correlation of cryptophycins A and C (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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