A Convergent Approach to Cryptophycin 52 Analogues: Synthesis and Biological Evaluation of a Novel Series of Fragment A Epoxides and Chlorohydrins

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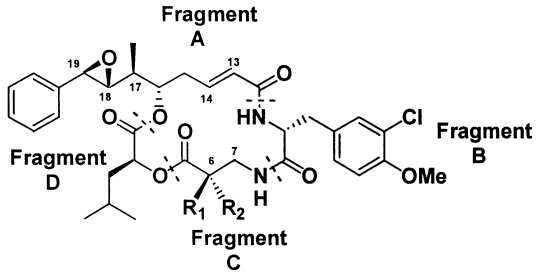
Cryptophycin 52 is a synthetic derivative of Cryptophycin 1, a potent antimicrotubule agent isolated from cyanobacteria. In an effort to increase the potency and water solubility of the molecule, a structure−activity relationship study (SAR) was initiated around the phenyl ring of fragment A. These Cryptophycin 52 analogues were accessed using a Wittig olefination reaction between various triphenylphosphonium salts and a key intermediate aldehyde prepared from Cryptophycin 53. Substitution on the phenyl ring of fragment A was well tolerated, and several of these analogues were equally or more potent than Cryptophycin 52 when evaluated in vitro in the CCRF-CEM leukemia cell line and in vivo against a murine pancreatic adenocarcinoma.

Introduction

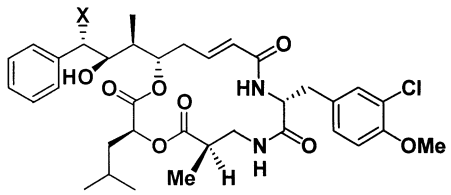
Blue-green algae or cyanobacteria have been a source of a wide range of novel and structurally complex cyclic peptides and depsipeptides.[1] The Cryptophycins are a family of naturally occurring potent antitumor agents originally isolated from terrestrial blue-green algae *Nostoc* sp. ATCC 53789 by Schwartz et al.[2] and later by Moore and co-workers[3] from *Nostoc* sp. GSV 224. The depsipeptide, Cryptophycin 1 (Figure 1), was the main component of the algal extract and accounted for most of its antiproliferative activity.[3] The structure of this 16-membered depsipeptide can be divided into four fragments A−D as shown in Figure 1. Through the convergent assembly of the different fragments, Moore et al. were able to accomplish the first total synthesis of Cryptophycin 1.[4] When first isolated in 1990, Cryptophycin 1 was classified as an antifungal agent with an unknown mechanism of action but was later found to be an antimitotic agent that disrupted the microtubule assembly in cultured cells.[5] Furthermore, this novel macrocycle showed excellent in vivo activity against both murine and human solid tumors.[6]

In addition to Cryptophycin 1, Moore isolated 24 minor natural Cryptophycins, with modifications in fragments A through D, but none were as active as the parent compound.[7] These included Cryptophycins lacking either the methyl group at C17 of fragment A or the double bond of the enone moiety. Several structure−activity relationship (SAR) observations can be made from his synthetic work around position C18 and C19 of this fragment.[1b] Two semisynthetic prodrug derivatives of Cryptophycin 1, the anti chloro and bromohydrins (Figure 2), were also evaluated in vivo. The chlorohydrin (or Cryptophycin 8) was markedly more efficacious than Cryptophycin 1 or vinblastine when evaluated against a panel of solid tumors. At doses 4−8-fold higher than those of the parent compound, Cryptophycin 8 was highly active and possessed a high therapeutic window whereas the bromohydrin was more toxic and less active than Cryptophycin 1.[1b,8] A compound containing a styrene, an α epoxide, or hydroxyls at C18 and C19 instead of the naturally occurring β



CRYPTOPHYCIN 1 (R_1 = Me, R_2 = H)
CRYPTOPHYCIN 52 (LY355703) (R_1 = R_2 = Me)
ARENASTATIN A (R_1 = R_2 = H, Deschloro in Fragment B)

Figure 1.



Chlorohydrin X = Cl
Bromohydrin X = Br

Figure 2.

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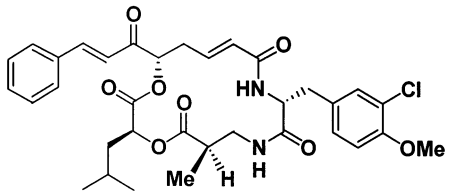


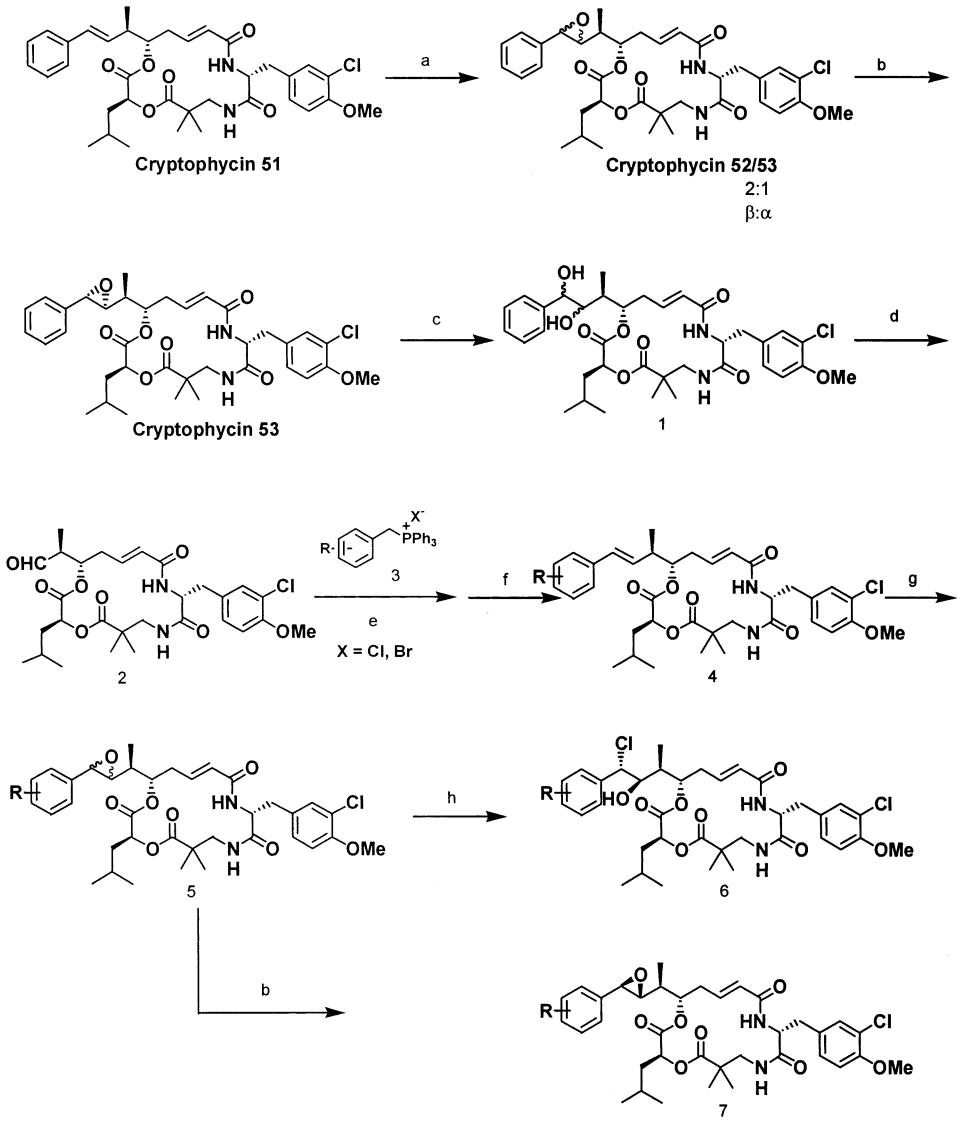
Figure 3.

epoxide functionality of fragment A had diminished activity both in vitro and in vivo.[1b]

Three of the compounds that Moore isolated with modifications in fragment B lacked either the methoxy or chloro group or possessed the demethylated chlorohydroxy functionality instead of the chloro-methoxy present in Cryptophycin 1. He also isolated compounds where the isobutyl group in fragment D was replaced with *n*-propyl, isopropyl, or *sec*-butyl group, and these were less active than the parent compound.[7a] Although a compound lacking the methyl group in fragment C was active in vitro, it was found to be completely ineffective in vivo.[1b,7b] This result is consistent with the related natural product Arenastatin A (Figure 1), a potent constituent of the Okinawan marine sponge *Dysidea arenaria*.[9] Arenastatin A differs from the Cryptophycins in that it lacks both the methyl group of the β-alanine unit of fragment C and the chloro group on the phenyl ring of the B fragment. Although Arenastatin exhibited potent in vitro cytotoxicity it had marginal in vivo activity. The methyl group in the β-alanine portion of the Cryptophycins prevents hydrolysis of the labile ester linkage between fragments C and D that is thought to be critical for the antitumor activity of the compounds.[10]

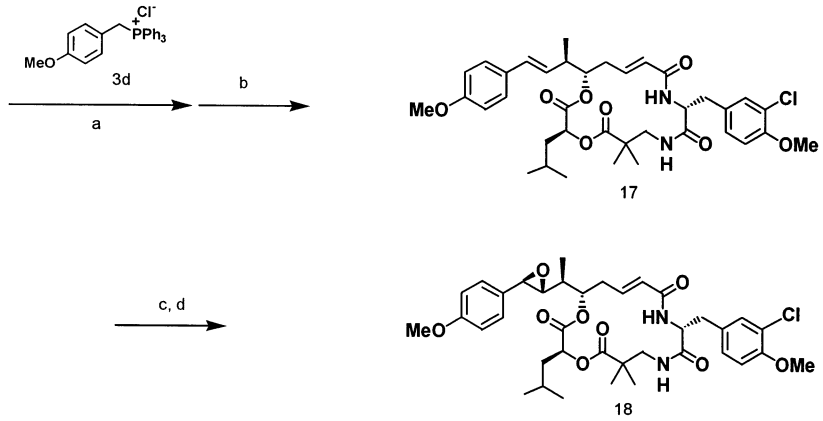
Cryptophycin 52 (LY355703), a synthetic derivative of the naturally occurring Cryptophycin 1, contains a *gem*-dimethyl group at C6 of fragment C (Figure 1). Like the natural product, Cryptophycin 52 inhibits the polymerization of microtubules by suppressing microtubule dynamics and hence arresting cells in the G_2/M phase of the cell cycle.[11] Unlike other antimitotic agents such as paclitaxel, vincristine, and vinblastine, Cryp-

Scheme 1[a]



[a] Reagents and conditions: (a) mCPBA, CH_2Cl_2, rt; (b) Reverse phase HPLC; (c) $HClO_4$, DME, H_2O, rt; (d) $NaIO_4$, THF, H_2O, rt; (e) *n*-BuLi, THF, −78 °C to room temperature; (f) VAZO, PhSH, benzene Δ; (g) mCPBA, CH_2Cl_2, rt or dioxirane; (h) TMSCl, $CHCl_3$ or HCl, −60 °C to room temperature.

Scheme 2[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C to room temperature; (b) VAZO, PhSH, benzene Δ, (36%); (c) Oxone, acetone, H_2O, $NaHCO_3$, CH_2Cl_2, 0 °C; (d) reverse phase HPLC, (39%).

tophycin 52 maintained its excellent antiproliferative activity against cancer cells that expressed multidrug resistance phenotypes (MDR1 and MRP),[12] which resulted in an excellent in vivo efficacy profile against a wide range of resistant human xenografts and murine solid tumors.

Due to their novelty and synthetically challenging structures, the Cryptophycins have attracted the attention of many synthetic groups.[13] Most of the synthetic efforts have centered around new approaches to fragment A, the most challenging fragment due to its four contiguous stereogenic centers. Several reports have appeared which focus on SARs around fragments A through D of the Cryptophycins: for example, Norman and co-workers[14] prepared isosteres of fragments C and D, whereas Patel and co-workers[15] reported their findings on fragment B analogues. The preparation of 15-membered macrocycles and fragment C analogues by Shih[10] and Varie[16] demonstrated that a smaller ring size and bulky substituents at C6 of the β alanine unit were not favorable. In addition, Lavalee and co-workers[17] suspected the poor correlation between in vitro (picomolar) to in vivo (∼30−40 mg/kg in mice) potencies of Cryptophycin 1 might be due to the formation of inactive metabolites of the epoxide. This hypothesis was tested with over 30 analogues that involved replacing the benzylic epoxide with enones (Figure 3) and ynones. These electrophilic functionalities proved to be detrimental to activity and confirmed the importance of the benzylic β epoxide and the C17 methyl group and their relative stereochemistry to the biological activity of this class of natural products.

Like Paclitaxel, the formulation of Cryptophycins 1 and 52 requires the excipient Cremophor EL for intravenous administration. An increase in the aqueous solubility and potency of the Cryptophycins could lead to a more practical clinical formulation for this class of compounds. Hence, we embarked on a SAR study around fragment A of Cryptophycin 52, where we hoped to improve several of the molecule's physical and biological properties through the modification of the phenyl ring.[18] We describe herein our synthetic approaches to fragment A analogues and report their in vitro and in vivo biological evaluation.

Chemistry

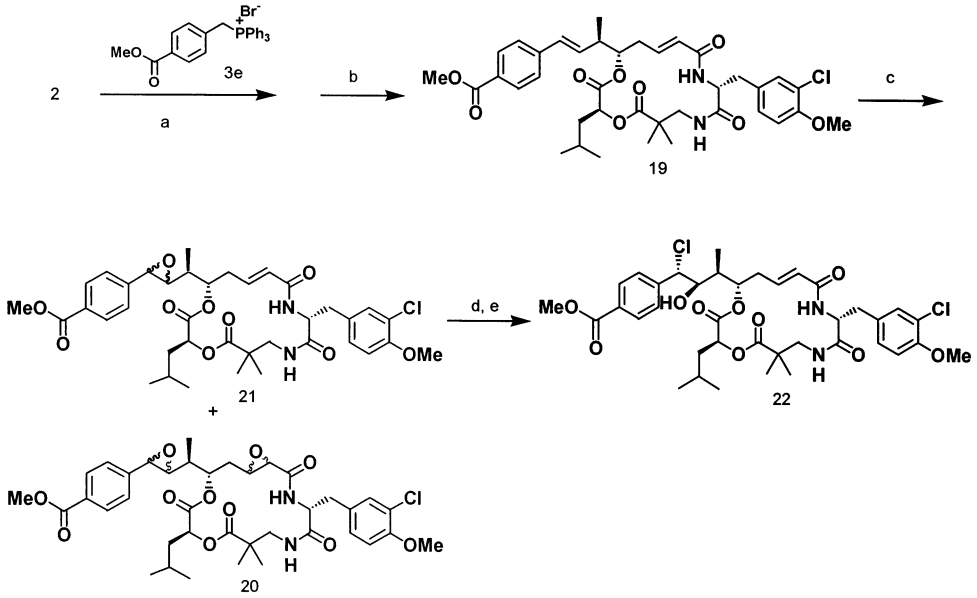
Our strategy involved the recycling of the undesired Cryptophycin 53[31] (α epoxide) that is formed in the process of preparing the more biologically relevant Cryptophycin 52 (β epoxide) (Scheme 1). We envisioned Wittig type couplings between various triphenylphosphonium salts and aldehyde **2**, prepared from Cryptophycin 53, as an efficient and concise entry to various analogues.[19]

Initial one-pot conversion of Cryptophycin 53 to the aldehyde **2** utilizing periodic acid proved to be problematic. The aldehyde generated in situ was unstable under the reaction conditions and decomposed prior to consumption of the starting material. Therefore, a two-step transformation beginning with an epoxide opening with aqueous perchloric acid was used to generate a mixture of alcohols **1** (Scheme 1). Oxidative cleavage of the resulting diols **1** by sodium periodate generated the key intermediate aldehyde **2** as a solid in quantitative yield. The labile aldehyde **2** could be stored at −23 °C for a reasonable period of time and was utilized without further purification.

As a general route to fragment A analogues (Scheme 1), the aldehyde **2** was coupled with an appropriate phosphonium salt to generate a variable ratio of *E* and *Z* alkene isomers. The isomerization of the styrene mixtures, to the thermodynamically more stable *E* isomer (**4**), was accomplished in benzene at reflux with 1,1′-azabis(cyclohexanecarbonitrile) (VAZO) as a radical initiator in the presence of thiophenol.[20] Subsequent epoxidation of the *E* styrene was achieved with mCPBA or dioxirane, depending on the substrate, to give a mixture of α and β epoxides (**5**) which were separable by preparative reverse phase high-pressure liquid chromatography (HPLC). The anti chlorohydrin **6** was obtained by treatment of the epoxide mixture **5** with chlorotrimethylsilane or hydrogen chloride solution followed by normal phase silica gel chromatographic separation of the diastereomeric chlorohydrins generated.

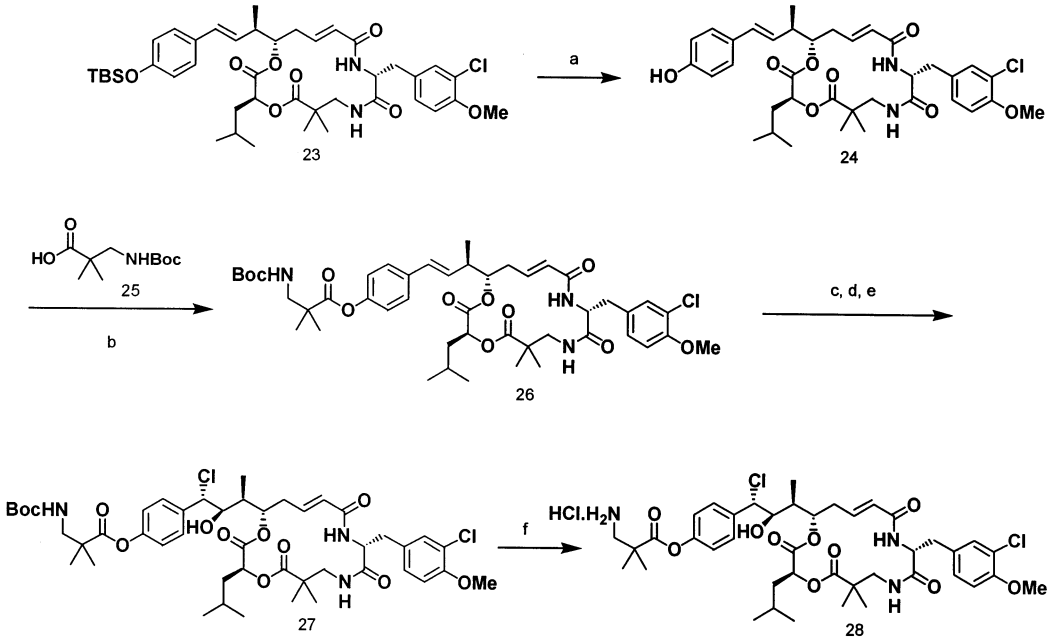
The methyl-substituted compounds **8**−**16** (shown in Table 2) were prepared following the same general sequence described in Scheme 1. Epoxidation of styrenes with a strong electron-donating or -withdrawing group on the phenyl ring such as a methoxy group (**17**, Scheme

Scheme 3[a]



[a] Reagents and conditions: (a) NaH, DMF; (b) VAZO, PhSH, benzene Δ, (23%); (c) Oxone, acetone, H_2O, CH_2Cl_2, $NaHCO_3$, rt, (33%); (d) reverse phase HPLC; (e) TMSCl, $CHCl_3$, −60 °C to room temperature, (30%).

Scheme 4[a]



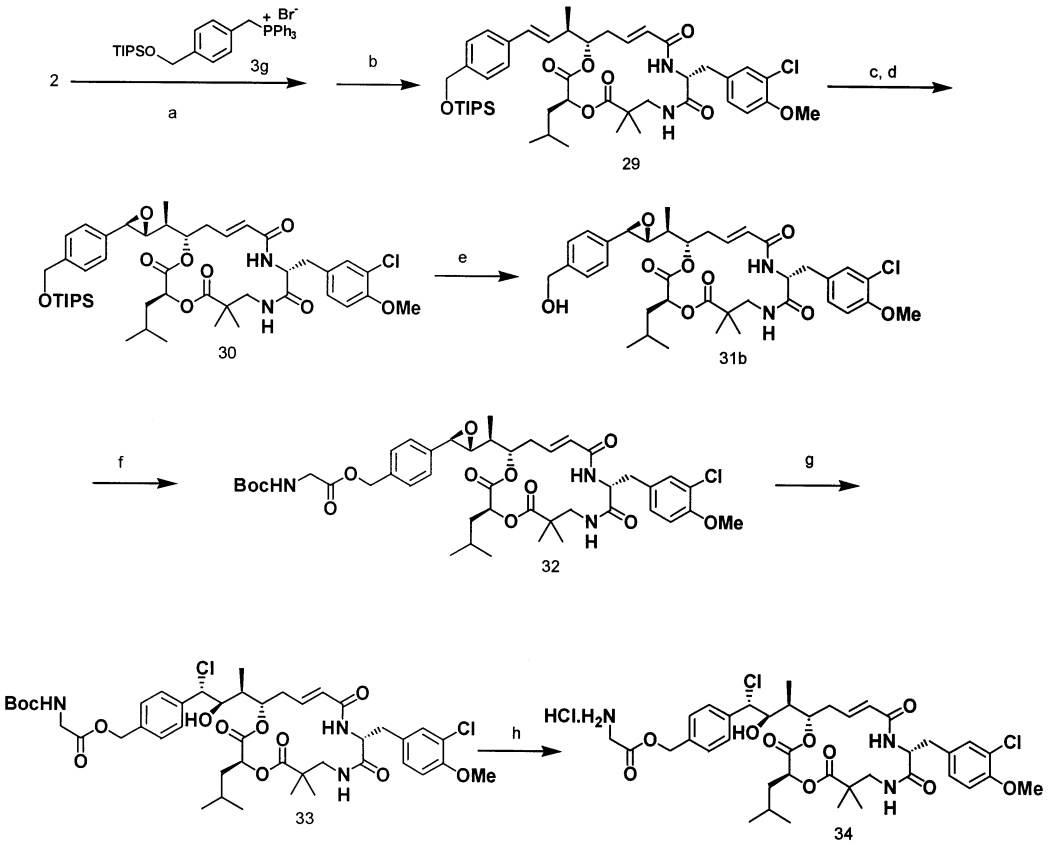
[a] Reagents and conditions: (a) TBAF, THF, −70 °C, (93%); (b) CDI, 45 °C to room temperature, (75%); (c) Oxone, acetone, H_2O, $NaHCO_3$, CH_2Cl_2, 0 °C; (d) TMSCl, $CHCl_3$ then HCl, −60 °C to room temperature; (e) reverse phase HPLC, (31%); (f) 4 M HCl, CH_2Cl_2, (95%).

2) or a methyl ester (**19**, Scheme 3) was problematic. Use of 3-chloroperoxybenzoic acid in the case of styrene **17** led to the protonation and subsequent opening of the epoxide mixture by the 3-chlorobenzoic acid, formed in situ as a byproduct of the epoxidation. Neutralization with sodium bicarbonate minimized this side reaction; however, use of dioxirane prepared in situ at 0 °C completely circumvented the problem (Scheme 2).

The methyl ester **19**, with its electron-withdrawing effect, led to a decrease in the reactivity of the styrene alkene in comparison to the enone (Scheme 3). Epoxidation of **19** required the use of the stronger oxidizing agent, dioxirane, at room temperature which resulted in the formation of bis-epoxide **20** along with the desired diastereomeric mono-epoxide **21**. These were separated by reverse phase HPLC, and the mixture of diastereomers **21** was treated with TMSCl to give, following chromatographic separation, the anti chlorohydrin **22**.

Condensation of 4-(*tert*-butyldimethylsiloxy)benzyltriphenylphosphonium chloride ylide **3f**[21] with aldehyde **2** followed by deprotection of the resulting silyl ether **23** with TBAF furnished phenol **24** (Scheme 4). The phenolic derivative **24** was coupled with Boc protected 3-amino-2-dimethyl propionic acid (fragment C′, **25**) in the presence of 1,1′-carbonyldiimidazole, at 45 °C, to generate ester **26** in 75% yield. The epoxidation was in turn accomplished with dioxirane, and the mixture of

Scheme 5[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C to room temperature; (b) VAZO, PhSH, benzene, D, (92%); (c) mCPBA, CH_2Cl_2; (d) reverse phase HPLC, (53%); (e) TBAF, THF, 0 °C to room temperature, (84%); (f) Boc-glycine, DCC, DMAP, CH_2Cl_2, rt, (72%); (g) TMSCl, $CHCl_3$, −60 °C to room temperature, (35%); (h) 4 M HCl/dioxane, CH_2Cl_2, (100%).

epoxides was treated with chlorotrimethylsilane followed by HCl to generate a mixture of diasteriomeric chlorohydrins. The desired anti chlorohydrin **27** was isolated in 31% yield for the two-step sequence.

With a few analogues possessing both electron-donating and electron-withdrawing functionalities in hand, we turned our attention to substituents that might increase the hydrophilicity of the Cryptophycins. Many of the analogues we envisioned evaluating were synthesized from benzyl alcohol **31b**, prepared in four steps as shown in Scheme 5, from aldehyde **2** and the ylide of 4-(triisopropylsiloxymethyl)benzyltriphenylphosphonium bromide **3g**.[22] Coupling of *N*-Boc-glycine and alcohol **31b** in the presence of DCC and DMAP furnished ester **32** in 72% yield. The hydrochloride salt **34** was obtained through opening of the epoxide with chlorotrimethylsilane and separation of the chlorohydrins, followed by removal of the Boc group.

Alternatively, quantitative deprotection of silyl ether **29** with tetrabutylammonium fluoride provided alcohol **35** which in turn was coupled with acid **25** in the presence of DCC and DMAP to furnish the hindered ester **36** (Scheme 6). Epoxidation of **36** with mCPBA, followed by subsequent treatment with chlorotrimethylsilane and hydrogen chloride, resulted in anti chlorohydrin **38**.

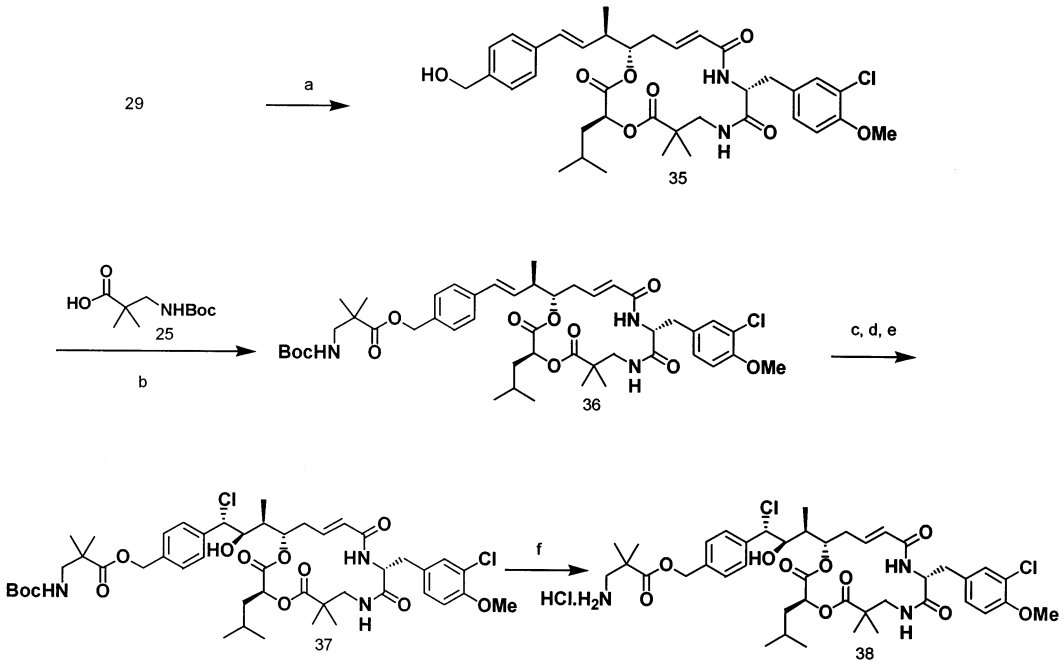
Three amine hydrochloride salts (**41a**−**c**, Scheme 7) were prepared to impart additional aqueous solubility to the molecule. These were accessed from benzyl chloride **39**, obtained from the treatment of alcohol **31** with *N*-chlorosuccinimide and triphenylphosphine in the presence of sodium bicarbonate (Scheme 7). Simple displacement of the benzylic chloride **39** with various alkylamines led to the *N*-alkylated products **40a**−**c**. Opening of the respective epoxides with chlorotrimethylsilane or a 4 M solution of HCl in dioxane, with concomitant removal of the Boc groups, yielded the corresponding hydrochloride salts **41a**−**c**.

In an attempt to prepare amide **44** (Scheme 8), the benzylic alcohol **35** was converted to its corresponding amine **43** via phthalimide **42** by a Mitsunobu protocol.[23] The primary amine **43** was coupled with Boc-protected sarcosine in the presence of 1-hydroxybenzotriazole hydrate (HOBT) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) in 71% yield. Epoxidation of the styrene **44**, preparation of the chlorohydrin **45**, and deprotection of the Boc group was accomplished in the usual manner already described to give the sarcosine amide **46**.

Preparation of an acetic acid derivative **51** (Scheme 9) required the oxidation of hydroxyethyl intermediate **49** that was obtained in the usual manner from phosphonium salt **3h**.[24] Acid **51** was produced in a stepwise fashion using two consecutive mild oxidations to ensure the stability of the epoxide under the reaction conditions. Initially, tetrapropylammonium perruthenate[25] was utilized, but it led to oxidation at the benzylic position. The best sequence involved treatment of alcohol **49** with the Dess−Martin[26] periodinate reagent and subsequent oxidation of the resulting aldehyde **50** with sodium chlorite[25] to yield the desired acid **51** (37%).

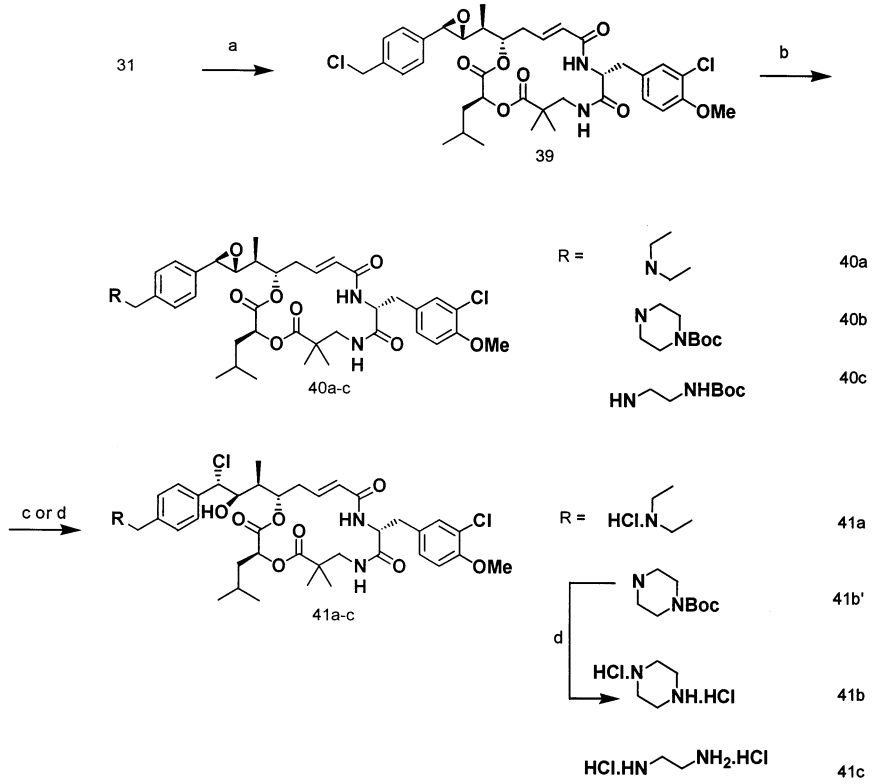
The thiazole group which is present in many biologi-

Scheme 6[a]



[a] Reagents and conditions: (a) TBAF, THF, −70 °C, (99%); (b) DCC, DMAP, CH_2Cl_2, D, (85%); (c) mCPBA, CH_2Cl_2; (d) TMSCl, $CHCl_3$ then HCl −60 °C to room temperature; (e) reverse phase HPLC, (22%); (f) 4 M HCl/dioxane, CH_2Cl_2, (100%).

Scheme 7[a]

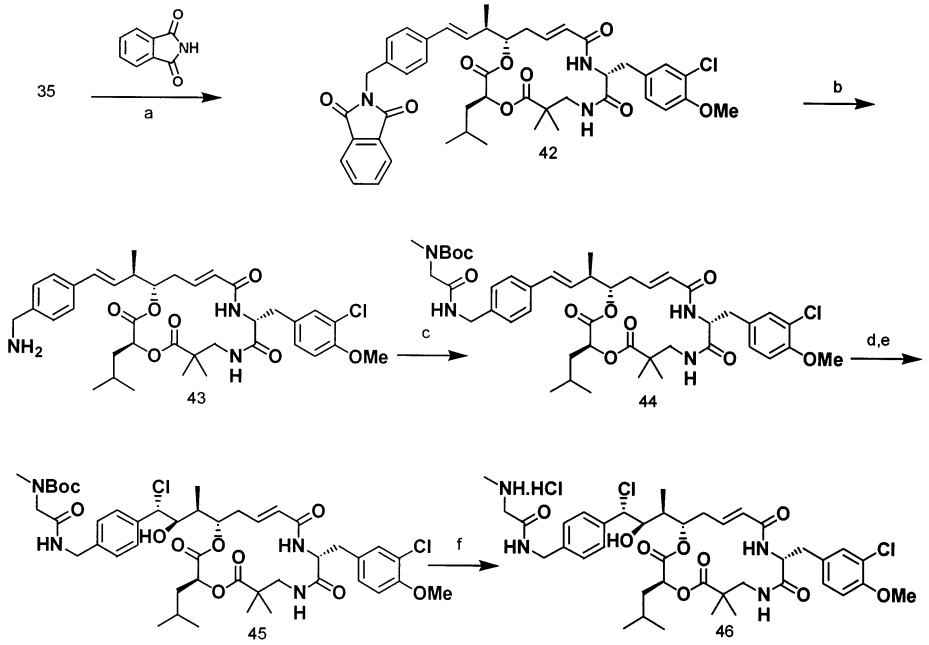


[a] Reagents and conditions: (a) *N*-chlorosuccinimide, PPh_3, $NaHCO_3$, CH_2Cl_2; (b) amine, THF, rt; (c) TMSCl; (d) 4 M HCl/dioxane, CH_2Cl_2.

cally active natural products was chosen to replace the phenyl ring of fragment A with a heterocyclic one.[27] This bioisostere was prepared as described in Scheme 10 from the aldehyde **2** and triphenylphosphonium salt **3i**[28] to give the trans olefin **52** in 34% yield. The desired β epoxide **53** was isolated in 35% yield by reverse phase HPLC, following the epoxidation of **52**.

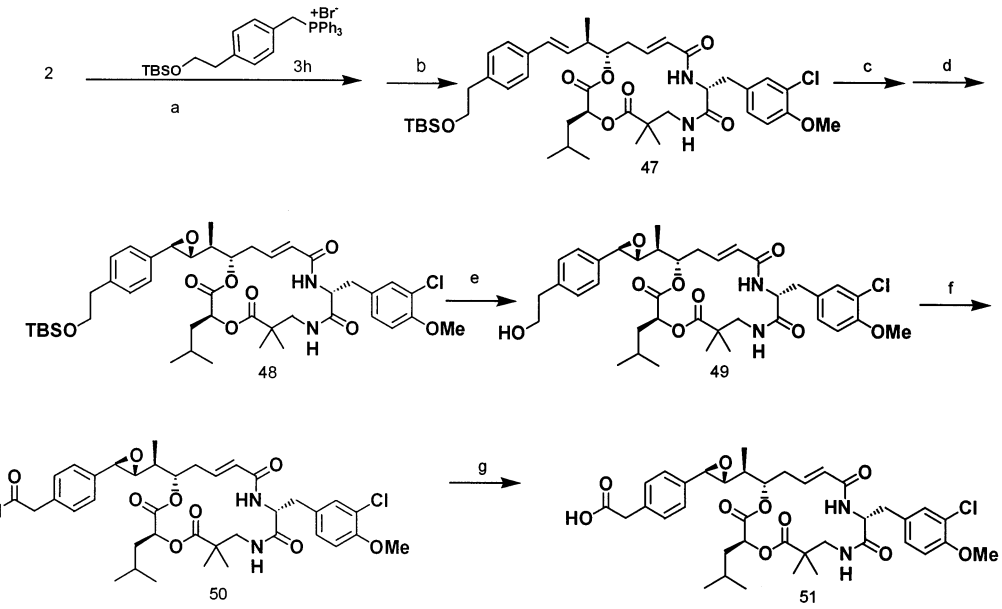
The stereoselective opening of the β epoxides was found to be substrate and reagent dependent. Using the pure β epoxide **9**, these observations were confirmed by a direct comparison of the two reagents, chlorotrimethylsilane and hydrogen chloride (Table 1). Three separate experiments were conducted and the syn to anti chlorohydrin ratio was determined from the crude reaction

Scheme 8[a]



[a] Reagents and conditions: (a) DEAD, PPh_3, THF, rt, (90%); (b) *n*-butylamine, EtOH, 75 °C, (57%); (c) Boc-sarcosine, EDCI, HOBT, DMF, rt, (71%); (d) mCPBA, CH_2Cl_2; (e) TMSCl, $CHCl_3$, −50 °C to room temperature, (48%); (f) 4 M HCl/dioxane, CH_2Cl_2, rt, (100%).

Scheme 9[a]

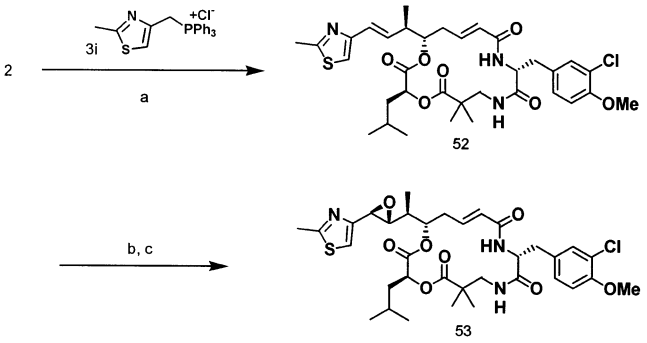


[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C to room temperature; (b) VAZO, PhSH, benzene Δ, (68%); (c) mCPBA, CH_2Cl_2; (d) reverse phase HPLC, (15%); (e) TBAF, THF, 0 °C to room temperature, (94%); (f) Dess−Martin, pyridine, CH_2Cl_2, (59%); (g) NaClO2, NaH_2PO_4, 2-methyl-2-butene, THF, H_2O, (37%).

mixtures by reverse phase HPLC. Initially, the substrate **9** in $CHCl_3$ was treated with 5 equiv of TMSCl at −60 °C. The reaction temperature was maintained between −60 °C and −40 °C for 1 h and was slowly allowed to rise to room temperature over 3 h (entry 1). The second attempt at epoxide opening used 4 M hydrogen chloride in dioxane under the same reaction conditions described above (entry 2). The third experiment also utilized hydrogen chloride, but the reaction temperature was maintained between −78 °C and −60 °C for 2 h prior to warming up to room temperature (entry 3). The results listed in Table 1 prove the effectiveness of HCl in providing more of the desired anti rather than syn chlorohydrin. Maintaining the reaction at lower temperatures over a longer period of time did not provide any significant advantage. It is noteworthy that the stereochemistry of Cryptophycin 52 epoxide opening was not reagent specific in that when treated with either HCl or TMSCl the undesirable syn chlorohydrin was not detected by HPLC. The methyl group on the phenyl ring of compound **9** must be inductively influencing the stereoselectivity of the epoxide opening.

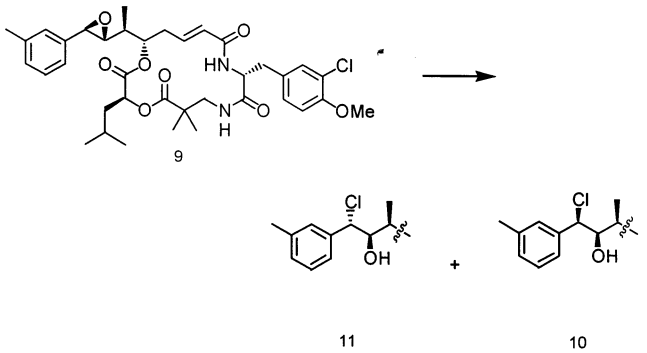
In Vitro Cell Growth Inhibition. The growth inhibitory effect of the Cryptophycin 52 fragment A analogues were evaluated in human CCRF-CEM leu-

Scheme 10[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C to room temperature, (34%); (b) Oxone, acetone, H_2O, $NaHCO_3$, CH_2Cl_2, 0 °C; (d) reverse phase HPLC, (35%).

Table 1. HCl vs TMSCl



entry	reagent	temperature	ratio anti: syn
1	TMSCl	−60 °C to room temperature	1.4:1.0
2	HCl	−60 °C to room temperature	3.2:1.0
3	HCl	−60 °C	3.8:1.0

kemia cells, following a 72 h exposure, as the IC_{50} concentrations (nM) (Table 2). Cryptophycins 52 and 55 were very potent growth inhibitors in this cell line with IC_{50} values of 0.022 and 0.05 nM, respectively. The IC_{50} values for the 3-methyl (**9**), the 2,5- (**16b**), and the 3,4-dimethyl (**13**) phenyl compounds indicated that a meta (**9**, IC_{50} = 0.15 nM) or meta, para (**13**, IC_{50} = 0.05 nM) substitution pattern on the phenyl ring was better tolerated than the ortho, meta substitution pattern (**16b**, IC_{50} = 2 nM).

Preliminary investigation of the effect of electron-donating and -withdrawing groups at the para position of the phenyl ring led to the preparation of the phenolic derivatives **18**, **28**, and the methyl ester **22**. The 4-methoxyphenyl β epoxide **18** (IC_{50} = 0.28 nM) was 13-fold less potent than Cryptophycin 52 (IC_{50} = 0.022 nM). Whereas the chlorohydrin **28** (IC_{50} = 0.79 nM) was 16-fold less active than Cryptophycin 55 (IC_{50} = 0.05 nM), the methyl ester **22** (IC_{50} = 0.037 nM) had comparable activity to Cryptophycin 55 (IC_{50} = 0.05 nM). The electronic effects of the phenyl ring substituents may influence the stability, and hence the growth inhibitory activity of the epoxide or chlorohydrin and might account for the lower potency of analogues **18** and **28**.

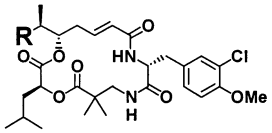
The key hydroxymethyl intermediate epoxide **31b** and its derivatives **32**, **34**, and **38** were all more potent than Cryptophycins 52 or 55. Epoxides **31b** (IC_{50} = 0.004 nM) and **32** (IC_{50} = 0.0055 nM) were, respectively, 5.5- and 4-fold more active than Cryptophycin 52 (IC_{50} = 0.022 nM). Chlorohydrins **34** (IC_{50} = 0.013 nM) and **38** (IC_{50} = 0.004 nM) were ∼ 4 and >12-fold more potent cell growth inhibitors than Cryptophycin 55 (IC_{50} = 0.05 nM). Evaluation of the unnatural α epoxide **31a** (IC_{50} = 0.29 nM) revealed a 73-fold loss in potency, in comparison to the corresponding β epoxide **31b** (IC_{50} = 0.004 nM). These results were consistent with the 50-fold difference in IC_{50} concentrations between the α and β epoxides **16a** (IC_{50} = 100 nM) and **16b** (IC_{50} = 2.0 nM).

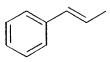
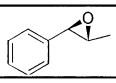
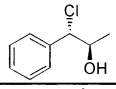
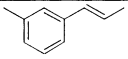
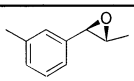
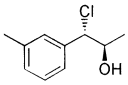
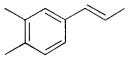
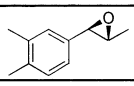
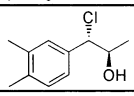
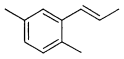
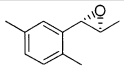
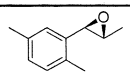
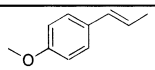
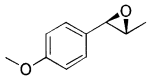
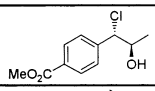
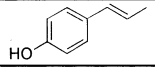
The IC_{50} concentrations for the more water soluble amine hydrochloride salts **41a**−**c** ranged between 0.005 and 0.092 nM and compared favorably with that of Cryptophycin 55 (IC_{50} = 0.05 nM). The sarcosine amide derivative **46** (IC_{50} = 0.04 nM) was equipotent to Cryptophycin 55 but about 3-fold less potent than the corresponding glycine ester **34** (IC_{50} = 0.013 nM). However, the amide **46** was expected to be metabolically more stable in vivo than the ester **34**. With a 36-fold lower potency than Cryptophycin 52, the acid **51** (IC_{50} = 0.79 nM) revealed the negative impact of an acidic functionality, whereas thiazole **53** (IC_{50} = 0.19 nM) confirmed the importance of the phenyl ring of fragment A to the antiproliferative activity of the Cryptophycins. If compared to Cryptophycin 51, the IC_{50} concentrations of all the olefins was predictive of the activity of their corresponding β epoxides or chlorohydrins with the exception of two (**17** and **24**). Although the phenolic styrenes **17** (IC_{50} = 12 nM) and **24** (IC_{50} = 4 nM) were equal to or more potent than Cryptophycin 51 (IC_{50} = 14 nM), their corresponding epoxide **18** and chlorohydrin **28** were significantly less active than Cryptophycins 52 and 55. Several of the fragment A analogues listed in Table 2 had sufficient antiproliferative activity warranting additional in vivo testing.

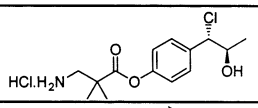
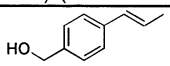
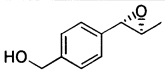
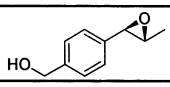
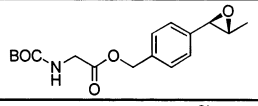
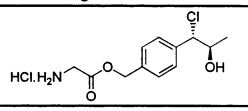
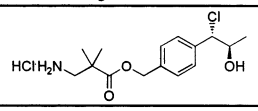
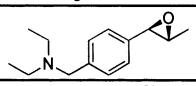
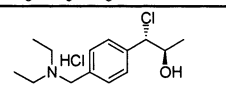
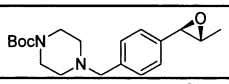
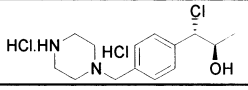
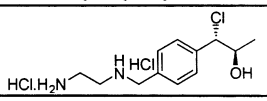
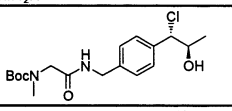
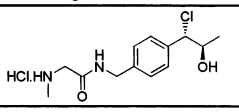
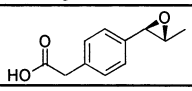
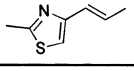
In Vivo Antitumor Activity. The in vivo evaluation of these analogues utilized the drug sensitive murine pancreatic adenocarcinoma (Panc-03). The effectiveness of the drugs was determined with two parameters; percent *T*/*C* and log kill values. A *T*/*C* equal to or less than 42% is considered significant antitumor activity, where *T* and *C* are the median tumor burden in the treatment group and control group, respectively, multiplied by 100. Tumor cell kill is determined from the difference in tumor growth delay in days, between the treated and control animals, to reach 1000 mg in tumor weight. Panc-03 (Table 3) was found to be more sensitive to Paclitaxel (log kill = 4.2) and Cryptophycin 55 (log kill > 4.5) than to Doxorubicin (log kill = 1.5) and Cryptophycin 52 (log kill = 1.9) administered at maximum tolerated doses. Cryptophycin 55 was the most efficacious compound tested, requiring 6- to 12-fold higher doses than Cryptophycin 52. It had a wider therapeutic window than Cryptophycin 52 in that the 200 and 400 mg/kg total doses of Cryptophycin 55 were equally effective and well tolerated.

Chlorohydrin **11** was inactive in vivo (*T*/*C* = 46) at 72 mg/kg total dose but showed marginal activity at 162 mg/kg total dose (log kill = 1.5). The animals did not experience weight loss and therefore, it is likely that higher doses of chlorohydrin **11** would have been tolerated. With maximum tolerated doses of 3.5 to 6 mg/kg, at least 5-fold lower than Cryptophycin 52, there is a clear correlation between the in vitro and in vivo

Table 2. In Vitro Growth Inhibitory Activity in the Human CCRF-CEM Leukemia Cell Line

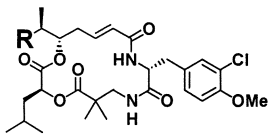


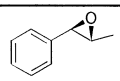
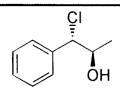
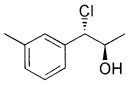
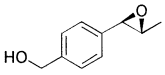
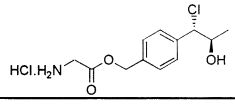
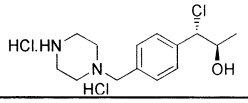
Compound #	R	IC_{50} nM
Crypto 51		14.0
Crypto 52		0.022
Crypto 55		0.05
8		25
9		0.15
11		0.3
12		70
13		0.05
14		0.6
15		440
16a		100
16b		2.0
17		12
18		0.28
22		0.037
24		4

Compound #	R	IC_{50} nM
28		0.79
35		0.79
31a		0.29
31b		0.004
32		0.0055
34		0.013
38		0.004
40a		0.003
41a		0.005
40b		0.001
41b		0.021
41c		0.092
45		0.02
46		0.04
51		0.79
52		460

potencies of epoxide **31b**. The glycinate ester salt **34** was quite efficacious in producing a *T*/*C* of zero across three dose levels and log kills of 3.6 and 3.7 at the nontoxic total doses of 9 and 18 mg/kg. Unlike the epoxide **31b**, the piperizinyl dihydrochloride salt **41b** was much more potent in vivo than would be predicted from its relative in vitro activity. At 1.6 mg/kg, the piperizinyl dihydrochloride salt **41b**, produced a 16% average weight loss in the animals and a 4.7 log kill value which was comparable to log kill values for Cryptophycin 55, but at 100 to 250-fold increased potency. Clearly, fragment A analogues (**31b**, **34**, and **41b**) are effective against the

Table 3. In Vivo Antitumor Activity of Cryptophycin Analogues against Murine Pancreatic Adenocarcinoma



Compound #	R	Schedule (days)[a]	Total Dose[b] (mg/K)	Death	Weight Loss %[c]	T/C %[d]	Log Kill[e]
Crypto 52		3-9 3-10	42 32	3/5 0/5	-9.6 +1.6	1 3	--- 1.9
Crypto 55		5-10 5-10 5-10	402 270 210	0/5 0/5 0/5	-6.0 -5.0 -5.0	0 0 0	>4.5 >4.5 >4.5
Paclitaxel		10-14	41	0/6	-5.0	0	4.2
Doxorubicin		3,8	16	0/5	-12	16	1.5
11		1-6 1-6	162 72	0/5 0/5	+7.0 +12	0 46	1.5 ---
31b		3,4,6 3,4,6 3,4,6,10	12 6 3.5	4/4 1/4 0/4	-18.4 -19.5 +10.5	--- 2 14	--- --- ---
34		3,5,7 3,5,7 3,5,7	36 18 9	3/4 0/4 0/4	-20 -4.0 -2.0	0 0 0	--- 3.7 3.6
41b		3 3,5 3,5	2 1.6 1	2/5 0/5 0/5	-26 -16 -3.0	8 0 33	4.7 4.7 0.8

[a] Days of treatment after tumor inplantation. [b] Dose administered close to the maximum tolerated dose. [c] Maximal animal weight loss. [d] The ratio of the median tumor weight in the treatment group (*T*) over the median tumor weight in the control group (*C*) multiplied by a 100. *T/C* is calculated when control median tumor weight is at 1 g. [e] Log cell kill of tumor bearing mice, a calculation based on tumor growth delay.

murine Panc-03 tumor at much lower total doses than are required for either Cryptophycin 52 or 55.

Conclusions

A Wittig approach involving the key intermediate aldehyde **2**, prepared from Cryptophycin 53, expedited a SAR study around the fragment A of Cryptophycin 52. Several transformations were effected, while maintaining the chemical integrity of the acid labile β epoxide, with use of the benzyl chloride **39** or the benzyl alcohol **31b** as precursors in the preparation of several analogues. When the phenyl ring is substituted, epoxide opening to the chlorohydrin was found to be substrate dependent, with hydrogen chloride providing the best anti to syn chlorohydrin ratio.

The substitution pattern on the phenyl ring affected the antiproliferative activity of analogues **9**, **13**, and **16b** with the less sterically demanding meta and para positions being better tolerated than the ortho. Several of these synthetic analogues (Table 2) compared favorably with Cryptophycin 52 and 55 whereas the β epoxides **31b**, **32**, **40a**, and **40b** were 4- to 20-fold more potent than Cryptophycin 52 as growth inhibitors in cell culture. This exciting antiproliferative activity translated to the in vivo setting in the case of the benzylic alcohol **31b** and its glycine ester derivative **34**. Replacement of the phenyl ring of fragment A with a thiazole caused an >8-fold drop in potency in vitro as compared to Cryptophycin 52. A similar decrease in antitumor activity was observed with the phenolic derivatives **18**, **28**, and acid **51**. The piperazine dihydrochloride salt **41b**, while improving the aqueous solubility of the molecule, was as active as Cryptophycin 55 in vitro against the CCRF-CEM cells and was over a 100-fold more potent and equally efficacious when tested in vivo against the Panc-03 tumor. In summary, preparation of novel Cryptophycin 52 fragment A analogues produced effective antitumor agents with potentially improved physical, chemical, and biological profiles.

Experimental Section

General Experimental Procedure. Anhydrous solvents were purchased from Aldrich Chemical Co. Proton NMR spectra were obtained on a Varian 300 or 500 MHz Brucker spectrometer. Carbon NMR spectra were obtained on a Brucker AC-250. Proton NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and

b (broad). IR Spectra were recorded on Nicolet 510 P FT-IR Spectrometer. High-resolution mass spectra were obtained on a VG-ZAB2SE spectrometer. Optical rotation was measured on an Autopol III automatic polarimeter. Combustion analyses (C, H, N) were performed on a 440 Elemental Analyzer. Separation of epoxide mixtures was achieved by reverse phase HPLC on a Beckman instrument using a preparative C18 column and acetonitrile and water as solvents.

In Vitro Growth Inhibition Assay. Concentration−response curves were generated to determine the concentration required for 50% inhibition of growth (IC_{50}). Test compounds were dissolved initially in DMSO at a concentration of 0.2 mg/mL. Serial 1:3 dilutions were made in DMSO using a Biomek Automated Workstation (Beckman, Fullerton, CA). Micropipet tips were changed with each dilution. We have previously shown that cryptophycins need to be serially diluted in DMSO to reduce drug adsorption onto plastic and glass surfaces.[29] Log-phase human CCRF-CEM leukemia cells were plated into 24-well plates (Costar, Cambridge, MA) at 4.8×10^4 cells/2 mL assay medium/well. Assay medium consisted of RPMI-1640 medium supplemented with 10% dialyzed fetal bovine serum and 25 mM HEPES buffer. The series of compound dilutions in DMSO were added to duplicate wells at 10 μL per well. Two wells on each individual plate received 10 μL of DMSO without compound as controls. The final concentration of DMSO per well was 0.5%. Plates were incubated for 72 h at 37 °C in a humidified 5% CO_2-in-air atmosphere. After incubation, the number of leukemia cells in each well was determined using a ZBI Coulter counter, and an IC_{50} was determined as described previously.[29]

In Vivo Antitumor Activity Experiment. 1. BDF male inbred mice (C57B1/6, C3H/He) were implanted bilaterally SC on day zero with 30 to 60 mg tumor fragments of Panc03.

2. Chemotherapy, delivered iv bolus, was started either within 3 days after implantation (early stage disease) or after the tumors had grown to a palpable size, 200−700 mg in size (upstaged disease).

3. Tumors were measured with caliper once or twice weekly until either the tumors exceeded 1600 mg or cure was assured. Tumor weights were estimated from two dimensional measurements:

tumor weight (mg) = $(a \times b^2)/2$ [a and b are tumor length and width (mm)]

End points used to assess antitumor activity were (1) tumor growth delay ($T - C$ value), (2) tumor cell kill, and (3) tumor growth inhibition (% T/C value)

Most Cryptophycin analogues were formulated in propylene glycol 2%, Cremophor EL 8%. Chlorohydrins were acidified with 0.05% citric acid. All injections were carried out within 20 min of aqueous preparation from stock solutions.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-5-hydroxy-6-methyl-7-oxo-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (2). To a solution of Cryptophycin 53[31] (2.0 g, 2.99 mmol) in DME (30 mL) was added a 2 M aqueous perchloric acid solution (15 mL, 30 mmol), and the resulting mixture was stirred for 6 h. Upon careful neutralization with saturated $NaHCO_3$ (50 mL), the mixture was extracted with CH_2Cl_2 (4 × 100 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography (silica gel, 5% MeOH/CH_2Cl_2) gave diols **1** (1.5 g) in 72% yield as a 3:1 anti/syn mixture.

To a solution of diols **1** (1.0 g, 1.46 mmol) in THF (20 mL) and water (15 mL) was added $NaIO_4$ (1.9 g, 8.9 mmol), and the mixture was stirred under nitrogen overnight. Upon removing the bulk of the THF under reduced pressure, the residue was diluted with water (100 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were washed with brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. Residual benzaldehyde was removed by dissolving the solid in toluene (100 mL) and subsequently removing the toluene at 40 °C on a rotary evaporator. Two additional evaporations from toluene gave the aldehyde as a yellow foam (0.828 g) in 98% yield. The resulting aldehyde **2** was used without further purification and was stored at −23 °C for stability reasons: $[\alpha]^{20}_D$ +23.0 (*c* 0.565, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64−9.63 (d, 1 H, J = 1.4 Hz), 7.28−7.26 (m, 1 H), 7.21−7.20 (d, 1 H, J = 1.9 Hz), 7.08−7.05 (dd, 1 H, J = 7.1, 1.7 Hz), 6.87−6.84 (d, 1 H, J = 8.5 Hz), 6.82−6.72 (m, 1 H), 5.80−5.75 (d, 1 H, J = 15.0 Hz), 5.54−5.51 (d, 1 H, J = 7.7 Hz), 5.40−5.33 (m, 1 H), 4.85−4.81 (dd, 1 H, J = 9.7, 3.2 Hz), 4.78−4.71 (m, 1 H), 3.88 (s, 3 H), 3.46−3.39 (dd, 1 H, J = 13.5, 8.6 Hz), 3.17−3.05 (m, 3 H), 2.68−2.35 (m, 3 H), 1.82−1.63 (m, 2 H), 1.45−1.37 (m, 1 H), 1.24 (s, 3 H), 1.19−1.16 (d, 3 H, J = 7.1 Hz), 1.18 (s, 3 H), 0.94−0.92 (d, 3 H, J = 6.5 Hz), 0.89−0.87(d, 3 H, J = 6.5 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 200.7, 177.8, 170.6, 170.1, 165.1, 153.9, 141.1, 130.7, 129.8, 128.1, 124.9, 122.3, 112.3, 73.4, 71.1, 56.0, 54.6, 49.9, 46.4, 42.7, 39.2, 36.1, 35.2, 24.7, 22.8, 22.7, 21.3, 10.7; IR ($CHCl_3$) 3422, 2964, 2936, 1755, 1730, 1718, 1678, 1529, 1504, 1487,1474, 1464, 1442, 1320, 1303, 1281, 1259, 1244, 1185, 1151, 1127, 1067 cm^{-1}. Anal. Calcd for ($C_{29}H_{39}ClN_2O_6$): C, 60.15; H, 6.79; N, 4.84. Found: C, 60.36; H, 6.94; N, 4.57.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-5-hydroxy-6-methyl-8-[4-[[[tris-(1-methylethyl)silyl]oxy]methyl]phenyl]-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (29). To 4-(triisopropylsiloxymethyl)benzyltriphenylphosphonium bromide (**3g**) (7.6 g, 12.2 mmol) in THF (100 mL) at −50 °C was added dropwise a 1.5 M solution of *n*-butyllithium (8.1 mL, 12.2 mmol). The mixture was warmed slowly to room temperature and stirred for an additional 30 min. To aldehyde **2** (2.95 g, 5.1 mmol) in THF (100 mL) at −78 °C was added dropwise the red ylide solution via a double-tipped needle. The resulting mixture was stirred at −78 °C for 3 h and at room temperature for 45 min. Saturated NH_4Cl (100 mL) was added along with ethyl acetate (100 mL), the layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with water (3 × 40 mL) and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow residue was purified by column chromatography (silica gel, 10−50% EtOAc/hexanes) to give 3.6 g (84%) of the desired styrene as a white solid and as a mixture of *E*:*Z* isomers.

The mixture of isomers (7.3 g, 8.7 mmol) was dissolved in benzene (240 mL) and heated to reflux in the presence of 1,1′-azobis(cyclohexanecarbonitrile) (VAZO) (0.32 g, 0.87 mmol) and thiophenol (3.7 mL, 4.0 mmol). Following 5 h at reflux, the solution was concentrated, and the residue was purified by column chromatography (silica gel, 5−50% EtOAc/hexanes) to give 6.7 g (92%) of the *E* isomer **29** as a white solid: $[\alpha]^{20}_D$ +31.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3−7.22 (m, 5 H), 7.20−7.19 (d, 1 H, J = 1.95 Hz), 7.07−7.04 (dd, 1 H, J = 8.4, 2.0 Hz), 6.85−6.82 (d, 1 H, J = 8.5 Hz), 6.8−6.7 (m, 1 H), 6.4−6.38 (d, 1 H, J = 15.8 Hz), 6.02−5.94 (dd, 1 H, J = 15.8, 8.8 Hz), 5.77−5.72 (d, 1 H, J = 14.9 Hz), 5.56−5.54 (d, 1 H, J = 7.9 Hz), 5.1−4.7 (m, 5 H), 3.9 (s, 3 H), 3.45−3.37 (dd, 1 H, J = 13.5, 8.5 Hz), 3.2−3.0 (m, 3 H), 2.6−2.3 (m, 3 H), 1.7−1.5 (m, 2 H), 1.4−1.25 (m, 1 H), 1.24−1.0 (m, 30 H), 0.75−0.71 (t, 6 H, J = 6.1 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.8, 170.5, 170.4, 165.2, 153.9, 142.1, 141.1, 135.2, 131.5, 130.8, 129.7, 129.6, 128.1, 125.9, 124.5, 122.4, 112.2, 77.0, 71.4, 64.7, 56.0, 54.4, 46.4, 42.7, 42.2, 39.4, 36.5, 35.3. 24.5, 22.8, 22.6, 22.5, 21.2, 17.9, 17.2, 11.9; IR ($CHCl_3$) 3423, 2962, 2945, 2867, 1746, 1712, 1681, 1652, 1528, 1503, 1485, 1473, 1464, 1303, 1259 cm^{-1}. Anal. Calcd for ($C_{46}H_{67}ClN_2O_8Si$): C, 65.81; H, 8.04; N, 3.33. Found: C, 65.64; H, 7.98; N, 3.29.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-5-hydroxy-6-[(2*S*,3*S*)-3-[4-[[[tris(1-methylethyl)silyl]oxy]methyl]phenyl]oxiranyl]-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (30a) and Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-5-hydroxy-6-[(2*R*,3*R*)-3-[4-[[[tris(1-methylethyl)silyl]oxy]methyl]phenyl]oxiranyl]-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (30b). 3-Chloroperoxybenzoic acid[30] (0.27 g, 1.59 mmol) was added to a 0 °C solution of styrene **29** (1.25 g, 1.49 mmol) in CH_2Cl_2 (20 mL). The solution

was stirred at 0 °C for 1 h and at room-temperature overnight. It was concentrated in vacuo, and the resulting epoxides were separated by reverse phase HPLC to yield 0.67 g of the β epoxide **30b** and 0.36 g of the α epoxide **30a** as white solids in 80% combined yield. α epoxide **30a**: $[\alpha]^{20}_D$ +16.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 6 H), 7.09−7.06 (d, 1 H, J = 8.4 Hz), 6.86−6.83 (d, 1 H, J = 8.3 Hz), 6.83−6.7 (m, 1 H), 5.9−5.6 (m, 2 H), 5.25−5.15 (m, 1 H), 4.95−4.85 (m, 1 H), 4.81 (s, 2 H), 4.8−4.7 (m, 1H), 3.9 (s, 3 H), 3.6 (s, 1 H), 3.47−3.4 (dd, 1 H, J = 13.0, 8.7 Hz), 3.2−3.0 (m, 3 H), 2.92−2.9 (d, 1 H, J = 7.6 Hz), 2.8−2.5 (m, 2 H), 1.8−1.4 (m, 4 H), 1.3−1.0 (m, 30 H), 0.9−0.85 (t, 6 H, J = 7.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.7, 170.6, 170.4, 165.3, 153.9, 141.9, 141.87, 135.4, 130.7, 129.9, 128.1, 125.8, 125.2, 124.6, 122.3, 112.2, 76.7, 71.3, 64.6, 63.1, 56.2, 56.0, 54.6, 46.4, 42.7, 40.8, 39.2, 36.7, 35.3, 24.7, 22.9, 22.8, 22.7, 21.3, 17.9, 13.4, 11.9; IR ($CHCl_3$) 3422, 2963, 2945, 2867, 1750, 1712, 1681, 1528, 1503, 1485, 1473, 1259, 1191, 1151 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{46}H_{67}ClN_2O_9Si$ (M^+ + H) 855.4383, found 855.4371.

β epoxide **30b**: $[\alpha]^{20}_D$ +20.9 (*c* 0.76, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.33 (d, 2 H, J = 7.8 Hz), 7.26−7.2 (m, 4 H), 7.05−7.02 (bd, 1 H, J = 8.2 Hz), 6.84−6.81 (d, 1 H, J = 8.4 Hz), 6.81−6.65 (m, 1 H), 5.8−5.65 (m, 2 H), 5.25−5.15 (m, 1 H), 4.9−4.7 (m, 4 H), 3.9 (s, 3 H), 3.7 (s, 1 H), 3.46−3.42 (dd, 1 H, J = 13.4, 8.8 Hz), 3.15−3.0 (m, 3 H), 2.93−2.9 (d, 1 H, J = 7.3 Hz), 2.6−2.4 (m, 2 H), 1.8−1.6 (m, 3 H), 1.4−1.0 (m, 31 H), 0.83−0.79 (t, 6 H, J = 5.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.7, 170.5, 170.4, 165.1, 153.9, 142.1, 141.6, 136.7, 135.1, 130.7, 129.8, 128.1, 125.9, 125.5, 124.6, 122.3, 112.2, 75.9, 71.0, 64.6, 63.0, 58.9, 56.0, 54.6, 46.3, 42.7, 40.5, 39.2, 36.8, 35.2. 24.2, 22.8, 22.7, 22.6, 18.0, 13.4, 11.9; IR ($CHCl_3$) 3424, 2962, 2945, 2867, 1751, 1712, 1682, 1528, 1503, 1485, 1473, 1464, cm^{-1}. Anal. Calcd for ($C_{46}H_{67}ClN_2O_9Si$): C, 64.58; H, 7.89; N, 3.27. Found: C, 64.3; H, 7.92; N, 3.28.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*)-5-hydroxy-6-[(2*R*,3*R*)-3-[4-(hydroxymethyl)phenyl]oxiranyl]-1-oxo-2-heptenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-β-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-lactone, (2*S*)- (31b). Tetrabutylammonium fluoride (0.14 mL, 0.14 mmol), as a 1.0 M solution in THF, was added dropwise to a 0 °C solution of the β epoxide **30b** (0.1 g, 0.117 mmol) in THF (3.5 mL). The solution was allowed to warm to room temperature, was stirred for another 20 min, and finally was quenched with water (10 mL) and ethyl acetate (20 mL). The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to yield the free alcohol. Purification by column chromatography (silica gel, 70−100% EtOAc/hexanes) yielded 0.068 g (84%) of the pure alcohol **31b** as a white solid: $[\alpha]^{20}_D$ +26.2 (*c* 0.435, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.36 (d, 2 H, J = 7.8 Hz), 7.26−7.23 (d, 3 H, J = 9.1 Hz), 7.18 (s, 1 H), 7.05−7.02 (d, 1 H, J = 8.5 Hz), 6.85−6.82 (d, 1 H, J = 8.2 Hz), 6.82−6.7 (m, 1 H), 5.72−5.67 (d, 1 H, J = 15.1 Hz), 5.55−5.52 (d, 1 H, J = 7.8 Hz), 5.22−5.17 (m, 1 H), 4.85−4.7 (m, 4 H), 3.9 (s, 3 H), 3.7 (s, 1 H), 3.45−3.38 (dd, 1 H, J = 13.4, 9.3 Hz), 3.2−3.0 (m, 3 H), 2.92−2.89 (d, 1 H, J = 7.6 Hz), 2.65−2.4 (m, 2 H), 1.8−1.6 (m, 4 H), 1.4−1.2 (m, 1 H), 1.22 (s, 3 H), 1.16 (s, 3 H), 1.16−1.13 (d, 3 H, J = 7.2 Hz), 0.86−0.82 (t, 6 H, J = 6.5 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.8, 171.0, 170.4, 165.5, 153.8, 141.5, 141.4, 135.7, 133.5, 130.6, 130.0, 128.0, 127.1, 125.6, 124.6, 122.2, 112.3, 77.2, 76.5, 76.0, 71.0, 64.2, 63.1, 58.8, 56.0, 54.7, 46.3, 42.7, 40.5, 39.3, 36.9, 35.1, 24.5, 22.7, 22.5, 22.1, 13.4; IR ($CHCl_3$) 3422, 2992, 2963, 2936, 2874, 1751, 1713, 1682, 1651, 1504, 1486, 1303, 1259, 1186, 1165, 1151, 1067 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{37}H_{47}ClN_2O_9$ (M^+ + H) 699.3048, found 699.3054. Anal. Calcd for ($C_{37}H_{47}ClN_2O_9$.0.5 H_2O): C, 62.75; H, 6.83; N, 3.96. Found: C, 62.97, H, 6.53; N, 3.78.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*)-5-hydroxy-6-[(2*S*,3*S*)-3-[4-(hydroxymethyl)phenyl]oxiranyl]-1-oxo-2-heptenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-β-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-lactone, (2*S*)- (31a). Similarly alcohol **31a** was obtained as a white solid: $[\alpha]^{20}_D$ +24.1 (*c* 2.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.35 (d, 2 H, J = 7.8 Hz), 7.28−7.2 (m, 5 H), 7.08−7.05 (dd, 1 H, J = 8.3, 1.95 Hz), 6.86−6.84 (d, 1 H, J = 8.3 Hz), 6.82−6.74 (m, 1 H), 5.81−5.77 (dd, 1 H, J = 15.1, 0.98 Hz), 5.54−5.52 (d, 1 H, J = 7.8 Hz), 5.22−5.15 (m, 1 H), 4.93−4.9 (dd, 1 H, J = 10.1, 3.2 Hz), 4.8−4.72 (m, 1 H), 4.7−4.69 (d, 1 H, J = 5.4 Hz), 3.88 (s, 3 H), 3.6−3.59 (d, 1 H, J = 1.95 Hz), 3.46−3.4 (dd, 1 H, J = 13.6, 8.8 Hz), 3.16−3.08 (m, 3 H), 2.91−2.88 (dd, 1 H, J = 7.8, 1.95 Hz), 2.74−2.54 (m, 2 H), 1.8−1.6 (m, 4 H), 1.5−1.4 (m, 1 H), 1.24 (s, 3 H), 1.18 (s, 3 H), 1.05−1.03 (d, 3 H, J = 7.3 Hz), 0.91−0.89 (d, 3 H, J = 6.35 Hz), 0.88−0.86 (d, 3 H, J = 6.8 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.9, 170.6, 170.5, 165.2, 154.1, 142.1, 141.3, 136.4, 130.9, 129.7, 128.3, 127.2, 125.7, 125.6, 124.7, 122.6, 112.4, 76.7, 71.4, 64.8, 63.3, 56.2, 54.5, 46.5, 42.8, 40.9, 39.3, 36.8, 35.3, 24.8, 23.0, 22.9, 22.7, 21.4, 13.4; IR ($CHCl_3$) 3424, 2965, 2936, 2874, 1751, 1712, 1681, 1527, 1503, 1442, 1304, 1259, 1151, 1066 cm^{-1}. Anal. Calcd for ($C_{37}H_{47}ClN_2O_9$): C, 63.56; H, 6.77; N, 4.01. Found: C, 63.34; H, 6.94; N, 3.99.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*)-5-hydroxy-6-[(2*R*,3*R*)-3-[4-(hydroxymethyl)phenyl]oxiranyl]-1-oxo-2-heptenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-β-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-lactone, 1^6-Ester with *N*-[(1,1-Dimethylethoxy)carbonyl]glycine, (2*S*)- (32). To a 0 °C solution of alcohol **31b** (0.08 g, 0.114 mmol), *N*-(*tert*-butoxycarbonyl)glycine (0.034 g, 0.194 mmol), and 4-(dimethylamino)-pyridine (DMAP) (0.004 g, 0.034 mmol) in CH_2Cl_2 (2.0 mL) was added 1,3-dicyclohexylcarbodiimide (DCC) (0.040 g, 0.194 mmol). The mixture was stirred at 0 °C for 10 min and at room temperature for 45 min, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography (silica gel, 70−80% EtOAc/hexanes) to give 0.07 g (72%) of ester **32** as a white solid: $[\alpha]^{20}_D$ +18.5 (*c* 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 6 H), 7.11−7.08 (dd, 1 H, J = 8.4, 1.8 Hz), 6.9−6.87 (d, 1 H, J = 8.4 Hz), 6.86−6.7 (m, 1 H), 5.78−5.73 (d, 1 H, J = 15.2 Hz), 5.64−5.62 (d, 1 H, J = 7.4 Hz), 5.3−5.22 (m, 1 H), 5.22 (s, 2 H), 5.1−5.0 (bs, 1 H), 4.9−4.7 (m, 2 H), 4.0−3.99 (d, 2 H, J = 5.4 Hz), 3.9 (s, 3 H), 3.73−3.72 (d, 1 H, J = 1.0 Hz), 3.5−3.43 (dd, 1 H, J = 13.4, 8.6 Hz), 3.2−3.0 (m, 3 H), 2.95−2.92 (d, 1 H, J = 6.4 Hz), 2.65−2.4 (m, 2 H), 1.8−1.6 (m, 3 H), 1.5 (s, 9 H), 1.45−1.3 (m, 1 H), 1.26 (s, 3 H), 1.2 (s, 3 H), 1.2−1.17 (d, 3 H, J = 8.7 Hz), 0.9−0.86 (t, 6 H, J = 6.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.7, 170.6, 170.3, 170.2, 165.1, 155.6, 153.8, 141.4, 137.1, 135.6, 130.6, 129.9, 128.6, 128.0, 125.7, 124.7, 122.2, 112.2, 79.9, 75.8, 70.9, 66.4, 63.1, 58.5, 56.0, 54.7, 48.9, 46.3, 42.7, 42.4, 40.5, 39.3, 36.8, 35.2, 28.2, 24.5, 22.8, 22.7, 22.6, 21.2, 13.5. Anal. Calcd for ($C_{44}H_{58}ClN_3O_{12}$): C, 61.71; H, 6.83; N, 4.91. Found: C, 61.43; H, 6.92; N, 5.11.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-chloro-5,7-dihydroxy-8-[4-(hydroxymethyl)phenyl]-6-methyl-1-oxo-2-octenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-β-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-lactone, 1^8-Ester with *N*-[(1,1-Dimethylethoxy)carbonyl]glycine, (2*S*)- (33). Chlorotrimethylsilane (0.09 mL, 0.75 mmol) was added to a −60 °C solution of β epoxide **32** (0.16 g, 0.187 mmol) in $CHCl_3$ (5.0 mL). Following 2 h of stirring between −60 °C to −40 °C, an additional 0.09 mL of TMSCl was added, and stirring was continued for 3 h. The solution was allowed to warm to room temperature and was concentrated in vacuo. The two resulting chlorohydrins were separated by reverse phase preparative HPLC with (55:45) CH_3CN:H_2O to give 0.058 g (35%) of the desired anti chlorohydrin **33** as a white solid: $[\alpha]^{20}_D$ +50.5 (*c* 1.075, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.2 (m, 6 H), 7.13−7.09 (dd, 1 H, J = 8.4, 1.8 Hz), 6.9−6.87 (d, 1 H, J = 8.4 Hz), 6.85−6.7 (m, 1 H), 5.9−5.8 (m, 2 H), 5.2 (s, 3 H), 5.15−5.05 (m, 1 H), 5.0−4.9 (m, 1 H), 4.8−4.72 (m, 1 H), 4.71−4.68 (d, 1 H, J = 9.7 Hz), 4.07−4.03 (d, 1 H, J = 9.3 Hz), 3.99−3.97 (d, 2 H, J = 5.5 Hz), 3.9 (s, 3 H), 3.44−3.37 (dd, 1 H, J = 13.6, 8.3 Hz), 3.23−3.14 (m, 2 H), 3.08−3.0 (dd, 1 H, J = 14.5, 8.0 Hz), 2.75−2.4 (m, 3 H), 2.0−1.7 (m, 3 H), 1.5 (s, 10 H), 1.26 (s, 3 H), 1.21 (s, 3 H), 1.08−1.06 (d, 3 H, J = 7.0 Hz), 0.98−0.94 (m, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 177.5, 170.5, 170.2, 170.1, 165.3, 153.9, 142.2, 139.0, 138.3, 136.1, 130.8, 129.9, 128.7, 128.2, 128.1, 124.5, 122.3, 112.2, 80.0, 76.1, 73.9, 71.1,

66.2, 61.7, 56.1, 54.6, 46.4, 42.7, 42.3, 39.6, 38.4, 36.3, 35.1, 28.2, 24.8, 23.0, 22.9, 22.7, 21.5, 8.6; IR ($CHCl_3$) 3428, 3009, 2966, 2935, 1750, 1714, 1683, 1504, 1486, 1369, 1259, 1193, 1162, 1127, 1067; HRMS (FAB, *m/z*) calcd for $C_{44}H_{59}Cl_2N_3O_{12}$ ($M^+ + H$) 892.3554, found 892.3565. Anal. Calcd for ($C_{44}H_{59}Cl_2N_3O_{12}\cdot 1.0\ H_2O$): C, 58.02; H, 6.75; N, 4.61. Found: C, 58.4; H, 6.65; N, 4.44.

Pentanoic acid, 3-chloro-*N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-chloro-5,7-dihydroxy-8-[4-(hydroxymethyl)phenyl]-6-methyl-1-oxo-2-octenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-lactone, 1^8-ester with glycine, monohydrochloride, (2*S*)- (34). A 4 M solution of hydrogen chloride in 1,4-dioxane (0.08 mL, 0.33 mmol) was added to a solution of ester **33** (0.058 g, 0.065 mmol) in CH_2Cl_2 (0.2 mL). The resulting mixture was stirred at room temperature for 3 h, concentrated in vacuo and maintained under vacuum for 3 days to remove the 1,4-dioxane thus giving the desired hydrochloride salt **34** in quantitative yield: $[\alpha]^{20}_D$ +26.2 (*c* 0.58, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 8.51−8.48 (d, 1 H, J = 7.6 Hz), 7.8−7.77 (d, 1 H, J = 8.4 Hz), 7.45−7.37 (m, 5 H), 7.26−7.25 (d, 1 H, J = 1.56 Hz), 7.17−7.13 (dd, 1 H, J = 8.5, 1.7 Hz), 6.96−6.94 (d, 1 H, J = 8.5 Hz), 6.74−6.64 (m, 1 H), 5.96−5.91 (d, 1 H, J = 15.3 Hz), 5.26 (s, 2 H), 5.16−5.0 (m, 2 H), 4.8−4.77 (d, 1 H, J = 9.6 Hz), 4.01−3.98 (d, 1 H, J = 9.6 Hz), 3.86 (s, 2 H), 3.81 (s, 3 H), 3.5−3.42 (dd, 1 H, J = 13.4, 10 Hz), 3.2−3.0 (m, 2 H), 2.8−2.65 (m, 2 H), 2.5−2.2 (m, 2 H), 1.85−1.45 (m, 3 H), 1.2 (s, 3 H), 1.16 (s, 3 H), 1.0−0.94 (m, 9 H); ^{13}C NMR (62.5 MHz, CD_3OD) δ 178.9, 173.8, 171.9, 168.3, 155.3, 144.2, 141.8, 136.7, 132.3, 131.5, 129.75, 129.7, 129.4, 125.2, 123.3, 113.5, 77.2, 74.7, 72.6, 68.5, 63.5, 57.6, 56.7, 47.6, 44.1, 41.1, 40.4, 37.9, 36.5, 26.3, 23.6, 23.5, 22.2, 9.0; IR (KBr) 3412, 2961, 2935, 1752, 1722, 1669, 1504, 1473, 1279, 1259, 1207, 1151, 1126, 1065 cm^{-1}; HRMS (FAB, *m/z*) calcd for $C_{39}H_{52}Cl_3N_3O_{10}$ (M^+- Cl) 792.3030, found 792.3020.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-5-hydroxy-6-methyl-8-(3-methylphenyl)-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (8). Styrene **8** (0.67 g) was prepared from aldehyde **2** (1.0 g, 1.73 mmol) and 3-methylbenzyl triphenylphosphonium chloride (**3a**) (0.886 g, 2.2 mmol) in 58% yield according to the procedure described for styrene **29**: $[\alpha]^{20}_D$ +33.1 (*c* 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−7.0 (m, 7 H), 6.85−6.82 (d, 1 H, J = 8.4 Hz), 6.82−6.7 (m, 1 H), 6.39−6.34 (d, 1 H, J = 15.8 Hz), 6.03−5.95 (dd, 1 H, J = 15.8, 8.7 Hz), 5.78−5.73 (d, 1 H, J = 15.2 Hz), 5.67−5.64 (d, 1 H, J = 7.8 Hz), 5.1−5.0 (m, 1 H), 4.87−4.83 (dd, 1 H, J = 10.2, 3.5 Hz), 4.8−4.7 (m, 1 H), 3.9 (s, 3 H), 3.45−3.38 (dd, 1 H, J = 13.4, 8.6 Hz), 3.2−3.0 (m, 3 H), 2.6−2.3 (m, 3 H), 2.32 (s, 3 H), 1.75−1.55 (m, 2 H), 1.4−1.25 (m, 1 H), 1.22 (s, 3 H), 1.15 (s, 3 H), 1.13−1.11 (d, 3 H, J = 6.8 Hz), 0.75−0.72 (t, 6 H, J = 5.7 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.9, 170.5, 170.3, 165.1, 154.0, 142.1, 138.0, 136.6, 131.8, 130.8, 129.9, 129.6, 128.4, 128.22, 128.17, 126.7, 124.5, 123.3, 122.5, 112.3, 71.4, 56.1, 54.3, 46.4, 42.7, 42.2, 39.4, 36.5, 35.3, 24.5, 22.8, 22.6, 22.56, 21.2, 21.1, 17.2; IR ($CHCl_3$) 3424, 3021, 3017, 2965, 1747, 1711, 1680, 1652, 1528, 1503, 1485, 1259, 1151, 1067 cm^{-1}. Anal. Calcd for ($C_{37}H_{47}ClN_2O_7$): C, 66.6; H, 7.1; N, 4.2. Found: C, 66.79; H, 7.03; N, 4.25.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-5-hydroxy-6-[(2*R*,3*R*)-3-(3-methylphenyl)oxiranyl]-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (9). 3-Chloroperoxybenzoic acid (0.19 g, 1.1 mmol) was added to styrene **8** (0.667 g, 1.0 mmol) in CH_2Cl_2 (5.0 mL). The resulting solution was stirred overnight, concentrated in vacuo to give the β and α epoxides in a 1.8:1 ratio, in favor of the β. Separation of the two epoxides by reverse phase HPLC with (70:30) CH_3CN:H_2O gave 0.20 g of the major β epoxide **9** as a white solid: $[\alpha]^{20}_D$ +21.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3−7.0 (m, 7 H), 6.9−6.87 (d, 1 H, J = 8.4 Hz), 6.87−6.75 (m, 1 H), 5.79−5.74 (d, 1 H, J = 14.8 Hz), 5.54−5.51 (d, 1 H, J = 7.8 Hz), 5.28−5.22 (m, 1 H), 4.89−4.85 (dd, 1 H, J = 10.4, 3.5 Hz), 4.82−4.75 (m, 1 H), 3.9 (s, 3 H), 3.69−3.68 (d, 1 H, J = 1.6 Hz), 3.51−3.44 (dd, 1 H, J = 13.4, 8.6 Hz), 3.2−3.1 (m, 3 H), 2.98−2.95 (dd, 1 H, J = 7.6, 1.6 Hz), 2.65−2.45 (m, 2 H), 2.32 (s, 3 H), 1.85−1.6 (m, 3 H), 1.4−1.25 (m, 1 H), 1.27 (s, 3 H), 1.21 (s, 3 H), 1.21−1.18 (d, 3 H, J = 7.5 Hz), 0.90−0.86 (t, 6 H, J = 6.13 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.8, 170.4, 165.0, 153.9, 141.7, 138.4, 136.6, 130.7, 129.6, 129.2, 128.5, 128.1, 126.0, 124.6, 122.8, 122.3, 112.2, 75.8, 71.0, 62.9, 59.0, 56.0, 54.4, 46.3, 42.7, 40.6, 39.2, 36.8, 35.2, 24.4, 22.8, 22.7, 22.6, 21.3, 21.1, 13.5; IR ($CHCl_3$) 3423, 2964, 2936, 2874, 1751, 1712, 1682, 1527, 1503, 1486, 1259, 1188, 1152 cm^{-1}. Anal. Calcd for ($C_{37}H_{47}ClN_2O_8\cdot 0.2\ H_2O$): C, 64.7; H, 6.96; N, 4.08. Found: C, 64.47; H, 6.76; N, 4.21.

***β* Epoxide opening of 9 with TMSCl or HCl: Pentanoic acid, 3-chloro-*N*-[(2*E*,5*S*,6*S*,7*R*,8*R*)-8-chloro-5,7-dihydroxy-6-methyl-8-(3-methylphenyl)-1-oxo-2-octenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-lactone, (2*S*)- (10). Pentanoic acid, 3-chloro-*N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-chloro-5,7-dihydroxy-6-methyl-8-(3-methylphenyl)-1-oxo-2-octenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3→1^5)-lactone, (2*S*)- (11).**

Entry 1: To a solution of the β epoxide **9** (0.1 g, 0.147 mmol) in CH_2Cl_2 (5.0 mL) at −60 °C was added chlorotrimethylsilane (0.093 mL, 0.74 mmol). The solution was allowed to warm to room temperature over 4 h before being concentrated under vacuum. The resulting residue, containing a 40:60 mixture of the syn and anti chlorohydrins, was purified by reverse phase HPLC with (45:55) CH_3CN:H_2O to yield 0.018 g of the syn isomer **10**: $[\alpha]^{20}_D$ -41.6 (*c* 1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.15 (m, 6 H), 7.13−7.1 (dd, 1 H, J = 10.3, 1.9 Hz), 6.89−6.87 (d, 1 H, J = 8.5 Hz), 6.88−6.73 (m, 1 H), 5.77−5.72 (d, 1 H, J = 15.3 Hz), 5.63−5.60 (d, 1 H, J = 7.7 Hz), 5.19−5.13 (t, 1 H, J = 9.6 Hz), 4.98−4.92 (m, 1 H), 4.90−4.87 (d, 1 H, J = 9.7 Hz), 4.8−4.72 (m, 1 H), 4.14−4.11 (dd, 1 H, J = 9.4, 1.0 Hz), 3.91 (s, 3 H), 3.49−3.42 (dd, 1 H, J = 13.5, 8.3 Hz), 3.25−3.0 (m, 3 H), 2.6−2.45 (m, 2 H), 2.4 (s, 3 H), 2.3−2.15 (m, 1 H), 1.9−1.4 (m, 4 H), 1.28 (s, 3 H), 1.22 (s, 3 H), 1.02−0.99 (d, 3 H, J = 6.7 Hz), 0.98−0.96 (d, 6 H, J = 6.7 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) 177.8, 170.3, 170.0, 165.0, 142.4, 138.8, 138.0, 137.5, 130.8, 129.9, 129.6, 128.9, 128.2, 128.0, 124.3, 112.2, 75.8, 74.3, 71.2, 68.7, 56.0, 54.3, 46.4, 42.7, 39.6, 38.3, 36.2, 35.2, 24.8, 22.9, 22.8, 22.7, 21.7, 21.3, 8.6; IR (KBr) 3419, 3305, 2960, 2932, 2872, 1754, 1721, 1675, 1535, 1504, 1473, 1258, 1194, 1150, 1066 cm^{-1}; HRMS (FAB, *m/z*) calcd for $C_{37}H_{49}Cl_2N_2O_8$ (M^+ +H) 719.2866, found 719.2876. Anal. Calcd for ($C_{37}H_{48}Cl_2N_2O_8\cdot 0.2\ H_2O$): C, 61.44; H, 6.74; N, 3.87. Found: C, 61.18, H, 6.47; N, 3.77 and 0.030 g of the desired anti isomer **11** in a 46% combined yield: $[\alpha]^{20}_D$ +63.8 (*c* 1.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.2 (m, 6 H), 7.13−7.1 (dd, 1 H, J = 8.3, 1.9 Hz), 6.91−6.88 (d, 1 H, J = 8.5 Hz), 6.88−6.78 (m, 1 H), 5.86−5.81 (d, 1 H, J = 15.0 Hz), 5.73−5.71 (d, 1 H, J = 7.8 Hz), 5.24−5.17 (t, 1 H, J = 9.4 Hz), 5.0−4.96 (dd, 1 H, J = 9.6, 2.9 Hz), 4.81−4.74 (m, 1 H), 4.67−4.64 (d, 1 H, J = 9.7 Hz), 4.06−4.03 (dd, 1 H, J = 9.6, 1.1 Hz), 3.92 (s, 3 H), 3.47−3.39 (dd, 1 H, J = 13.2, 8.3 Hz), 3.25−3.0 (m, 3 H), 2.8−2.7 (m, 1 H), 2.6−2.45 (m, 1 H), 2.4 (s, 3 H), 1.9−1.4 (m, 4 H), 1.28 (s, 3 H), 1.22 (s, 3 H), 1.09−1.07 (d, 3 H, J = 7.0 Hz), 0.98−0.96 (d, 6 H, J = 6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) 177.6, 170.4, 170.2, 165.2, 153.9, 142.4, 138.8, 138.2, 130.8, 129.8, 129.7, 128.8, 128.5, 128.1, 124.9, 124.4, 122.3, 112.2, 76.0, 73.8, 71.1, 62.0, 56.0, 54.4, 46.4, 42.7, 39.6, 38.3, 36.4, 35.2, 24.7, 23.0, 22.8, 22.7, 21.5, 21.3, 8.6; IR ($CDCl_3$) 3588, 3424, 2964, 2934, 1751, 1714, 1680, 1528, 1503, 1486, 1259, 1152 cm^{-1}. Anal. Calcd for ($C_{37}H_{48}Cl_2N_2O_8$): C, 61.75; H, 6.72; N, 3.89. Found: C, 61.99; H, 6.61; N, 3.88.

Entry 2: To a solution of the β epoxide **9** (0.05 g, 0.073 mmol) in CH_2Cl_2 (2.3 mL) at −60 °C, was added 4 M HCl in dioxane (0.093 mL, 0.37 mmol). The solution was allowed to warm to room temperature over 4 h before being concentrated under vacuum. The resulting residue was analyzed by reverse phase HPLC and was found to contain a 24:76 mixture of the syn/anti chlorohydrins.

Entry 3: To a solution of the β epoxide **9** (0.05 g, 0.073 mmol) in CH_2Cl_2 (2.3 mL) at −70 °C was added 4 M HCl in dioxane (0.093 mL, 0.37 mmol). The solution was maintained

between −70 °C and −60 °C for 2 h before being warmed to room temperature and concentrated under vacuum. The resulting residue was analyzed by reverse phase HPLC and was found to contain a 21:79 mixture of the syn and anti chlorohydrins.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-8-(3,4-dimethylphenyl)-5-hydroxy-6-methyl-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (12). Styrene **12** (0.095 g) was prepared from aldehyde **2** (0.2 g, 0.345 mmol) and 3,4-dimethylbenzyl triphenylphosphonium chloride (**3b**) (0.26 g, 0.62 mmol) in 63% yield according to the procedure described above for styrene **29**: $[\alpha]^{20}_D$ +27.8 (*c* 0.576, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.25−7.0 (m, 6 H), 6.87−6.81 (d, 1 H, *J* = 8.3 Hz), 6.80−6.71 (m, 1 H), 6.40−6.30 (d, 1 H, *J* = 15.8 Hz), 6.0−5.88 (dd, 1 H, *J* = 15.8, 8.8 Hz), 5.80−5.70 (d, 1 H, *J* = 15.1 Hz), 5.55−5.45 (d, 1 H, *J* = 7.7 Hz), 5.10−4.97 (m, 1 H), 4.90−4.80 (dd, 1 H, *J* = 9.4, 2.8 Hz), 4.80−4.70 (m, 1 H), 3.88 (s, 3 H), 3.45−3.37 (dd, 1 H, *J* = 13.3, 8.54 Hz), 3.20−3.0 (m, 3 H), 2.60−2.48 (m, 2 H), 2.45−2.30 (m, 1 H), 2.24 (s, 3 H), 2.23 (s, 3 H), 1.80−1.55 (m, 2 H), 1.40−1.30 (m, 1 H), 1.22 (s, 3 H), 1.16 (s, 3 H), 1.14−1.10 (d, 3 H, *J* = 6.8 Hz), 0.77−0.73 (t, 6 H, *J* = 5.57 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 177.9, 170.5, 170.3, 165.1, 154.0, 142.2, 136.5, 135.9, 134.3, 131.6, 130.8, 129.7, 129.5, 128.8, 128.1, 127.2, 124.4, 123.6, 122.4, 112.2, 71.4, 56.0, 54.2, 46.4, 42.6, 42.1, 39.4, 36.4, 35.2, 24.5, 22.7, 22.6, 22.5, 21.1, 19.6, 19.3, 17.2; IR ($CHCl_3$) 3424, 2965, 2935, 1746, 1711, 1681, 1652, 1527, 1503, 1485, 1259, 1187, 1164, 1151, 1067, 970, 727 cm^{-1}; Calcd for ($C_{38}H_{49}ClN_2O_7$): C, 66.99; H, 7.25; N, 4.11. Found: C, 66.78; H, 7.0; N, 4.12.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-6-[(2*R*,3*R*)-3-(3,4-dimethylphenyl)-oxiranyl]-5-hydroxy-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (13). The *β* epoxide **13** (0.06 g) was prepared from the styrene **12** (0.3 g, 0.44 mmol) and 3-chloroperoxybenzoic acid (0.081 g, 0.47 mmol) in 20% yield according to the procedure described for epoxide **30b**: $[\alpha]^{20}_D$ +20.0 (*c* 1.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.26−6.96 (m, 6 H), 6.84−6.82 (d, 1 H, *J* = 8.5 Hz), 6.79−6.65 (m, 1 H), 5.73−5.68 (d, 1 H, *J* = 14.9 Hz), 5.69−5.67 (d, 1 H, *J* = 7.4 Hz), 5.29−5.15 (m, 1 H), 4.83−4.76 (dd, 1 H, *J* = 9.7, 2.8 Hz), 4.75−4.68 (m, 1 H), 3.86 (s, 3 H), 3.61−3.60 (d, 1 H, *J* = 1.6 Hz), 3.46−3.38 (dd, 1 H, *J* = 13.4, 8.8 Hz), 3.14−2.97 (m, 3 H), 2.92−2.89 (dd, 1 H, *J* = 7.7, 1.6 Hz), 2.59−2.35 (m, 2 H), 2.25 (s, 6 H), 1.78−1.58 (m, 3 H), 1.21 (s, 4 H), 1.15 (s, 3 H), 1.15−1.12 (d, 3 H, *J* = 7.8 Hz), 0.81−0.79 (d, 3 H, *J* = 6.25 Hz), 0.8−0.78 (d, 3 H, *J* = 6.29 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 177.8, 170.4, 170.3, 164.9, 154.0, 141.7, 137.0, 136.9, 134.0, 130.8, 129.9, 129.5, 128.1, 126.7, 124.6, 123.2, 122.4, 122.3, 75.9, 71.04, 62.8, 59.1, 56.1, 54.3, 46.4, 42.7, 40.7, 39.2, 36.8, 35.2, 24.4, 22.8, 22.6, 21.0, 19.7, 19.4, 13.6; IR (KBr) 3419, 2962, 1752, 1721, 1681, 1654, 1534, 1504, 1473, 1442, 1302, 1282, 1259, 1192, 1126, 1066 cm^{-1}. Anal. Calcd for ($C_{38}H_{49}ClN_2O_8$): C, 65.46; H, 7.08; N, 4.02. Found: C, 65.29; H, 6.98; N, 4.03.

Pentanoic acid, 3-chloro-*N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-chloro-8-(3,4-dimethylphenyl)-5,7-dihydroxy-6-methyl-1-oxo-2-octenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-lactone, (2*S*)- (14). To a solution of styrene **12** (0.492 g, 0.72 mmol) in CH_2Cl_2 (2.4 mL) at 0 °C was added 3-chloroperoxybenzoic acid (0.137 g, 0.79 mmol) and toluene (1.2 mL), and stirring was continued at 0 °C for 30 min. The ice-bath was removed, and the reaction mixture was stirred at room temperature for 24 h. After diluting with CH_2Cl_2 (10 mL), the solution was washed with 10% Na_2SO_3 (1 × 10 mL), H_2O (1 × 10 mL), and 10% $NaHCO_3$ (1 × 10 mL) and dried over Na_2SO_4. Concentration provided a mixture of the *β*/α crude epoxides in a 2:1 ratio.

The crude epoxides (0.445 g, 0.638 mmol) were dissolved in dry $CHCl_3$ (10 mL), cooled to −60 °C, and treated with chlorotrimethylsilane (0.2 mL, 1.5 mmol). Stirring was continued for 90 min and the solution was concentrated in vacuo. The crude chlorohydrins were purified by reverse-phase HPLC (CH_3CN/H_2O) to give anti chlorohydrin **14** (0.115 g) in 21% yield as a white solid: $[\alpha]^{20}_D$ -45.9 (*c* 0.59, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.26−7.0 (m, 6 H), 6.85−6.82 (d, 1 H, *J* = 8.4 Hz), 6.80−6.71 (m, 1 H), 5.71−5.66 (d, 1 H, *J* = 15.1 Hz), 5.50−5.47 (d, 1 H, *J* = 7.6 Hz), 5.13−5.08 (t, 1 H, *J* = 8.8 Hz), 4.89−4.84 (m, 2 H), 4.81−4.71 (m, 1 H), 4.09−4.06 (d, 1 H, *J* = 9.4 Hz), 3.87 (s, 3 H), 3.44−3.37 (dd, 1 H, *J* = 13.4, 8.4 Hz), 3.16−3.06 (m, 3 H), 2.60−2.54 (m, 2 H), 2.26 (s, 6 H), 2.26−2.14 (m, 1 H), 1.89−1.81 (m, 1 H), 1.70−1.62 (m, 1 H), 1.58−1.46 (m, 2 H), 1.23 (s, 3 H), 1.17 (s, 3 H), 0.97−0.90 (m, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 177.7, 170.5, 170.1, 165.2, 153.9, 142.3, 137.7, 137.3, 135.1, 130.7, 130.2, 129.8, 128.5, 128.1, 124.6, 124.4, 122.3, 112.2, 75.9, 74.2, 71.2, 68.8, 56.0, 54.4, 46.4, 42.7, 39.6, 38.4, 36.2, 35.2, 24.8, 22.9, 22.8, 22.7, 21.7, 19.8, 19.5, 8.6; IR (KBr) 3421, 2960, 1756, 1721, 1675, 1504, 1258, 1195, 1151, 1126, 1066 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{38}H_{50}Cl_2N_2O_8$ ($M^+ + H$) 733.3022, found 733.3029. Anal. Calcd for ($C_{38}H_{50}Cl_2N_2O_8$): C, 62.21; H, 6.87; N, 3.82. Found: C, 61.97; H, 6.61; N, 3.74.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-8-(2,5-dimethylphenyl)-5-hydroxy-6-methyl-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (15). Styrene **15** (0.44 g) was prepared from aldehyde **2** (0.5 g, 0.87 mmol) and 2,5-dimethylbenzyl triphenylphosphonium chloride (**3c**) (0.5 g, 1.2 mmol) in 75% yield according to the procedure described above for styrene **29**: $[\alpha]^{20}_D$ +36.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.3−7.2 (m, 3 H), 7.09−7.07 (dd, 1 H, *J* = 8.4, 2.1 Hz), 7.05−7.04 (d, 1 H, *J* = 7.7 Hz), 6.99−6.97 (d, 1 H, *J* = 7.7 Hz), 6.88−6.86 (d, 1 H, *J* = 8.4 Hz), 6.84−6.78 (m, 1 H), 6.64−6.6 (d, 1 H, *J* = 15.7 Hz), 5.95−5.91 (dd, 1 H, *J* = 15.8, 8.8 Hz), 5.79−5.76 (dd, 1 H, *J* = 15.2, 1.1 Hz), 5.49−5.48 (d, 1 H, *J* = 7.9 Hz), 5.12−5.09 (ddd, 1 H, *J* = 11.2, 6.1, 1.7 Hz), 4.90−4.87 (dd, 1 H, *J* = 10.3, 3.6 Hz), 4.8−4.76 (m, 1 H), 3.91 (s, 3 H), 3.46−3.42 (dd, 1 H, *J* = 13.6, 8.6 Hz), 3.17−3.11 (m, 3 H), 2.65−2.55 (m, 2 H), 2.5−2.4 (m, 1 H), 2.33 (s, 3 H), 2.31 (s, 3 H), 1.8−1.62 (m, 2 H), 1.43−1.35 (m, 1 H), 1.26 (s, 3 H), 1.19 (s, 3 H), 1.17−1.16 (d, 3 H, *J* = 6.8 Hz), 0.8−0.78 (d, 6 H, *J* = 7.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 177.9, 170.5, 170.3, 165.0, 154.0, 142.2, 135.3, 131.8, 130.9, 130.8, 130.2, 129.5, 129.4, 128.2, 128.1, 125.8, 124.5, 122.4, 112.2, 71.4, 60.3, 56.0, 54.3, 46.4, 42.6, 42.3, 39.4, 36.5, 35.2, 24.5, 22.7, 22.6, 22.5, 21.1, 20.9, 19.2, 17.3, 14.1; IR ($CHCl_3$) 3424, 2965, 2934, 2873, 2841, 1746, 1712, 1680, 1651, 1606, 1528, 1503, 1485, 1464, 1441, 1320, 1281, 1259, 1151 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{38}H_{49}ClN_2O_7$ ($M^+ + H$) 697.3256, found 697.3249. Anal. Calcd for ($C_{38}H_{49}ClN_2O_7$): C, 67.0; H, 7.25; N, 4.11. Found: C, 66.96; H, 7.23; N, 3.95.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-6-[(2*R*,3*R*)-3-(2,5-dimethylphenyl)-oxiranyl]-5-hydroxy-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (16b). 3-Chloroperoxybenzoic acid (0.069 g, 0.4 mmol) was added to the styrene **15** (0.26 g, 0.38 mmol) in CH_2Cl_2 (2.5 mL). The resulting solution was stirred overnight and concentrated in vacuo to give the *β* and α epoxides in a 1.8:1 ratio, in favor of the *β*. Separation of the two epoxides by reverse phase HPLC with (70:30) $CH_3CN:H_2O$, gave 0.140 g of the major *β* epoxide and 0.08 g of the minor α epoxide (83% combined yield) as white solids. *β* epoxide **16b**: $[\alpha]^{20}_D$ +30.6 (*c* 0.53, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.25−7.22 (m, 2 H), 7.09−7.04 (m, 3 H), 6.95 (s, 1 H), 6.88−6.87 (d, 1 H, *J* = 8.4 Hz), 6.83−6.77 (m, 1 H), 5.76−5.73 (d, 1 H, *J* = 15.1 Hz), 5.48−5.46 (d, 1 H, *J* = 7.8 Hz), 5.26−5.24 (dd, 1 H, *J* = 9.2, 2.8 Hz), 4.88−4.85 (dd, 1 H, *J* = 9.9, 3.3 Hz), 4.8−4.76 (m, 1 H), 3.91 (s, 3 H), 3.89−3.88 (d, 1 H, *J* = 1.23 Hz), 3.48−3.43 (dd, 1 H, *J* = 13.5, 8.7 Hz), 3.14−3.11 (m, 3 H), 2.89−2.87 (dd, 1 H, *J* = 7.0, 1.5 Hz), 2.63−2.5 (m, 2 H), 2.4 (s, 3 H), 2.3 (s, 3 H), 1.93−1.65 (m, 3 H), 1.42−1.32 (m, 1H), 1.26 (s, 3 H), 1.19 (s, 3 H), 1.18−1.16 (d, 3 H, *J* = 6.9 Hz), 0.89−0.87 (d, 3 H, *J* = 6.6 Hz), 0.87−0.85 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 177.8, 170.3, 164.9, 154.0, 141.7, 135.8, 134.5, 132.5, 130.8, 130.0, 129.6, 128.6, 128.1, 124.5, 122.4, 112.3, 75.7, 71.2, 62.5, 56.2, 56.1, 54.4, 46.4, 42.7, 40.1, 39.3, 36.6, 35.2, 24.5, 22.8, 22.7, 22.6, 21.2, 20.9, 18.4, 13.1; IR ($CHCl_3$) 3423, 2965, 2936, 2874, 2841, 1752, 1712, 1682, 1528, 1504, 1485, 1464,

1303, 1259, 1189, 1151, 1067 cm^{-1}. Anal. Calcd for ($C_{38}H_{49}ClN_2O_8$): C, 65.46; H, 7.08; N, 4.02. Found: C, 65.29; H, 6.98; N, 4.06.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-5-hydroxy-8-(4-methoxyphenyl)-6-methyl-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (17). Styrene **17** (0.21 g) was prepared from aldehyde **2** (0.5 g, 0.87 mmol) and 4-methoxybenzyl triphenylphosphonium chloride (**3d**) (0.47 g, 1.12 mmol) in 36% yield according to the procedure described above for styrene **29**: $[\alpha]^{20}_D$ +31.6 (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.26−7.23 (d, 3 H, *J* = 8.4 Hz), 7.20−7.19 (d, 1 H, *J* = 1.8 Hz), 7.07−7.03 (dd, 1 H, *J* = 8.4, 1.9 Hz), 6.84−6.81 (d, 3 H, *J* = 8.5 Hz), 6.80−6.7 (m, 1 H), 6.36−6.31 (d, 1 H, *J* = 15.8 Hz), 5.89−5.81 (dd, 1 H, *J* = 15.8, 8.8 Hz), 5.78−5.73 (d, 1 H, *J* = 13.7 Hz), 5.68−5.66 (d, 1 H, *J* = 7.9 Hz), 5.05−4.99 (ddd, 1 H, *J* = 10.6, 6.6, 1.6 Hz), 4.87−4.82 (dd, 1 H, *J* = 9.7, 3.1 Hz), 4.78−4.7 (m, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.45−3.37 (dd, 1 H, *J* = 13.4, 8.6 Hz), 3.15−3.0 (m, 3 H), 2.6−2.25 (m, 3 H), 1.7−1.3 (m, 3 H), 1.22 (s, 3 H), 1.15 (s, 3 H), 1.12−1.1 (d, 3 H, *J* = 6.8 Hz), 0.76−0.73 (m, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 177.8, 170.5, 170.4, 165.1, 159.1, 153.9, 142.1, 135.8, 131.0, 130.8, 129.7, 129.5, 128.2, 127.9, 127.2, 124.5, 122.4, 113.9, 112.3, 77.1, 71.4, 56.0, 55.2, 54.4, 46.4, 42.7, 42.1, 39.4, 36.4, 35.3, 24.5, 22.8, 22.6, 21.2, 17.3; IR ($CHCl_3$) 3422, 3003, 2964, 2936, 2873, 2840, 1746, 1712, 1681, 1651, 1607, 1527, 1512, 1504, 1485, 1465, 1301, 1251 cm^{-1}. Anal. Calcd for ($C_{37}H_{47}ClN_2O_8$): C, 65.04; H, 6.93; N, 4.1. Found: C, 64.98; H, 7.05; N, 3.98.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-5-hydroxy-6-[(2*R*,3*R*)-3-(4-methoxyphenyl)oxiranyl]-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (18). To a 0 °C mixture of styrene **17** (0.3 g, 0.44 mmol) in acetone (19 mL), H_2O (9 mL) and CH_2Cl_2 (9 mL) were added solid $NaHCO_3$ (1.2 g, 14.5 mmol) and 2 mL of an Oxone solution [(1.08 g, 1.8 mmol) in 9 mL of H_2O]. Following 30 min of vigorous stirring at 0 °C, 2 mL of Oxone solution was added and again another 2.0 mL following another 30 min, for a total of 6 mL of Oxone solution. The reaction progress was monitored by reverse phase HPLC and was completed after 2.5 h of stirring. While still at 0 °C, the reaction was quenched with saturated aq $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL). The layers were separated, and the organic layer was washed with aq 10% Na_2SO_3 (50 mL), followed by saturated aq $NaHCO_3$ (50 mL) then brine, and finally was dried over Na_2SO_4, filtered and concentrated in vacuo. The mixture of *β* and α epoxides was separated by reverse phase HPLC with (45:55) CH_3CN:H_2O to provide 0.12 g of the *β* epoxide **18** as a white solid in 39% yield: $[\alpha]^{20}_D$ +25.8 (*c* 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.26−7.15 (m, 4 H), 7.05−7.03 (d, 1 H, *J* = 8.6 Hz), 6.9−6.87 (d, 2 H, *J* = 8.6 Hz), 6.85−6.82 (d, 1 H, *J* = 8.5 Hz), 6.82−6.7 (m, 1 H), 5.74−5.69 (d, 1 H, *J* = 15.1 Hz), 5.54−5.52 (d, 1 H, *J* = 7.8 Hz), 5.22−5.16 (m, 1 H), 4.84−4.7 (m, 2 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.63 (s, 1 H), 3.46−3.38 (dd, 1 H, *J* = 13.5, 8.8 Hz), 3.2−3.0 (m, 3 H), 2.91−2.89 (d, 1 H, *J* = 7.4 Hz), 2.6−2.38 (m, 2 H), 1.8−1.6 (m, 3 H), 1.4−1.23 (m, 1 H), 1.22 (s, 3 H), 1.15 (s, 3 H), 1.15−1.12 (d, 3 H, *J* = 8.9 Hz), 0.84−0.80 (t, 6 H, *J* = 6.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 177.7, 170.5, 170.4, 165.1, 159.8, 153.9, 141.6, 136.8, 130.7, 129.7, 128.6, 128.1, 126.9, 124.6, 122.3, 114.1, 112.2, 75.9, 71.0, 62.8, 58.9, 56.0, 55.2, 54.6, 46.3, 42.7, 40.6, 39.2, 36.8, 35.2, 24.4, 22.8, 22.7, 22.6, 21.1, 13.5; IR ($CHCl_3$) 3423, 3009, 2964, 2936, 2874, 2840, 1751, 1713, 1681, 1653, 1614, 1517, 1504, 1486, 1464, 1442, 1303, 1281, 1257, 1183, 1173, 1152 cm^{-1}. Anal. Calcd for ($C_{37}H_{47}ClN_2O_9$): C, 63.56; H, 6.78; N, 4.01. Found: C, 63.28; H, 6.72; N, 3.99.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-5-hydroxy-8-[4-(methoxycarbonyl)phenyl]-6-methyl-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (19). A suspension of sodium hydride (60% dispersion in mineral oil) (0.041 g, 1.0 mmol) and 4-carbomethoxybenzyltriphenylphosphonium bromide (**3e**) (0.5 g, 1.0 mmol) in THF (10 mL) was heated at 65 °C for 1 h and cooled back to room temperature. This orange mixture was added dropwise to a solution of aldehyde **2** (0.46 g, 0.79 mmol) in THF (10 mL) at −78 °C. The resulting mixture was warmed to room temperature, stirred for an additional 2 h, and quenched with saturated aq NH_4Cl (30 mL) and EtOAc (30 mL). The layers were separated, and the aqueous one was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude styrene was purified by column chromatography (silica gel, 50−65% EtOAc/hexanes) to give styrene **19** (0.129 g) in 23% yield: $[\alpha]^{20}_D$ +29.7 (*c* 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.03−8.0 (d, 2 H, *J* = 8.2 Hz), 7.44−7.41 (d, 2 H, *J* = 8.3 Hz), 7.3−7.25 (m, 1 H), 7.24−7.23 (d, 1 H, *J* = 1.6 Hz), 7.11−7.08 (dd, 1 H, *J* = 8.3, 1.9 Hz), 6.89−6.86 (d, 1 H, *J* = 8.5 Hz), 6.86−6.8 (m, 1 H), 6.52−6.46 (d, 1 H, *J* = 15.9 Hz), 6.23−6.15 (dd, 1 H, *J* = 15.8, 8.8 Hz), 5.83−5.8 (d, 1 H, *J* = 15.3 Hz), 5.64−5.61 (d, 1 H, *J* = 7.9 Hz), 5.14−5.09 (dd, 1 H, *J* = 9.4, 6.5 Hz), 4.91−4.87 (dd, 1 H, *J* = 10.2, 3.6 Hz), 4.85−4.75 (m, 1 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.5−3.4 (dd, 1 H, *J* = 13.5, 8.7 Hz), 3.2−3.1 (m, 3 H), 2.9−2.3 (m, 3 H), 1.8−1.6 (m, 2 H), 1.4−1.3 (m, 1 H), 1.26 (s, 3 H), 1.2 (s, 3 H), 1.2−1.18 (d, 3 H, *J* = 6.9 Hz), 0.8−0.76 (t, 6 H, *J* = 5.8 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 177.8, 170.4, 166.7, 165.1, 153.9, 141.8, 141.1, 133.1, 130.8, 129.9, 129.7, 128.9, 128.2, 125.9, 124.6, 122.4, 112.2, 76.8, 71.3, 56.0, 54.4, 52.0, 46.4, 42.7, 42.2, 39.5, 36.5, 35.2, 24.5, 22.8, 22.6, 21.2, 17.1; IR ($CHCl_3$) 3424, 2964, 2936, 2874, 2841, 1748, 1716, 1681, 1608, 1528, 1503, 1485, 1437, 1283, 1259 cm^{-1}. Anal. Calcd for ($C_{38}H_{47}ClN_2O_9$): C, 64.17; H, 6.66; N, 3.94. Found: C, 63.95; H, 6.77; N, 3.66.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-chloro-5,7-dihydroxy-8-[4-(methoxycarbonyl)phenyl]-6-methyl-1-oxo-2-octenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-Lactone, (2*S*)- (22). To styrene **19** (0.42 g, 0.59 mmol) were added acetone (30 mL), H_2O (15 mL), CH_2Cl_2 (15 mL), and solid $NaHCO_3$ (1.7 g, 20.2 mmol), and the mixture was cooled to 0 °C. A solution of Oxone (1.4 g, 2.3 mmol) in H_2O (12 mL) was prepared and added (2 mL) to the cold styrene mixture. Following 30 min of vigorous stirring at 0 °C, an additional 2 mL of Oxone solution was added, and the solution was warmed to room temperature. An additional 2 mL of Oxone solution was added every 30 min until a total of 12 mL of oxone was consumed. The reaction was stirred for a total of 5 h and was quenched with saturated aq $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL). The layers were separated, and the organic layer was washed with aq 10% Na_2SO_3 (50 mL), followed by saturated aq $NaHCO_3$ (50 mL) then brine, and finally was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was purified by reverse phase HPLC with (45:55) CH_3CN:H_2O to provide 0.14 g (33% yield) of the epoxides **21** and 0.14 g of the bisepoxides **20**.

The mixture of *β*/α epoxides **21** (0.14 g, 0.19 mmol) was dissolved in $CHCl_3$ (3.0 mL) and cooled to −60 °C. Chlorotrimethylsilane (0.1 mL, 0.77 mmol) was added to the −60 °C solution, and the mixture was stirred for 1.5 h. More TMSCl (0.1 mL, 0.77 mmol) was added, and the solution was allowed to warm to room temperature. Following 1 h of stirring at room temperature, the solution was concentrated and purified by radial PLC (1−2% MeOH/CH_2Cl_2) to give 0.044 g (30% yield) of the desired chlorohydrin **22** as a white solid: $[\alpha]^{20}_D$ +50.0 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.1−8.08 (d, 2 H, *J* = 8.1 Hz), 7.54−7.51 (d, 2 H, *J* = 8.2 Hz), 7.3−7.25 (m, 1 H), 7.25 (s, 1 H), 7.13−7.09 (dd, 1 H, *J* = 8.5, 1.5 Hz), 6.91−6.88 (d, 1 H, *J* = 8.3 Hz), 6.87−6.78 (m, 1 H), 5.86−5.8 (d, 1 H, *J* = 15.5 Hz), 5.7−5.6 (m, 1 H), 5.24−5.18 (t, 1 H, *J* = 9.2 Hz), 4.99−4.95 (dd, 1 H, *J* = 10.0, 3.6 Hz), 4.8−4.7 (m, 1 H), 4.76−4.73 (d, 1 H, *J* = 9.5 Hz), 4.09−4.06 (d, 1 H, *J* = 9.6 Hz), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.45−3.38 (dd, 1 H, *J* = 13.6, 8.6 Hz), 3.25−3.0 (m, 3 H), 2.75−2.62 (m, 1 H), 2.6−2.4 (m, 2 H), 1.9−1.6 (m, 3 H), 1.5−1.4 (m, 1 H), 1.27 (s, 3 H), 1.22 (s, 3 H), 1.1−1.07 (d, 3 H, *J* = 6.95 Hz), 0.98−0.95 (t, 6 H, *J* = 5.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 177.5, 170.6, 170.3, 166.3, 165.4, 153.9, 143.8, 142.2, 138.7, 130.7, 130.4, 129.9, 128.1, 128.0, 124.6, 122.3, 112.2, 76.1, 73.8, 71.1, 61.4, 56.0, 54.6, 52.2, 46.4, 42.7, 39.6, 38.4, 36.3, 35.1, 24.8, 23.0, 22.9, 22.7, 21.5, 8.7; IR

($CHCl_3$) 3425, 2962, 2935, 2873, 2842, 1750, 1720, 1680, 1528, 1504, 1484, 1438, 1284, 1259, 1194, 1152, 1114, 1067 cm^{-1}. Anal. Calcd for ($C_{38}H_{48}Cl_2N_2O_{10}$): C, 59.76; H, 6.34; N, 3.67. Found: C, 59.53; H, 6.61; N, 3.51.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-8-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-5-hydroxy-6-methyl-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (23). Styrene **23** (0.649 g) was prepared from aldehyde **2** (0.911 g, 1.57 mmol) and 4-(*tert*-butyldimethylsiloxy)benzyltriphenylphosphonium chloride (**3f**) (1.7 g, 3.27 mmol) in 53% yield according to the procedure described above for styrene **29**: $[\alpha]^{20}_D$ + 30.8 (*c* 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3−7.27 (m, 2 H), 7.26−7.22 (d, 2 H, *J* = 8.5 Hz), 7.12−7.06 (dd, 1 H, *J* = 8.3, 1.6 Hz), 6.92−6.86 (d, 1 H, *J* = 8.5 Hz), 6.85−6.76 (m, 3 H), 6.44−6.33 (d, 1 H, *J* = 15.9 Hz), 5.95−5.85 (dd, 1 H, *J* = 15.8, 8.8 Hz), 5.85−5.77 (d, 1 H, *J* = 15.5 Hz), 5.68−5.55 (d, 1 H, *J* = 7.9 Hz), 5.15−5.0 (m, 1 H), 4.95−4.80 (dd, 1 H, *J* = 10.0, 3.0 Hz), 4.85−4.75 (m, 1 H), 3.91 (s, 3 H), 3.53−3.43 (dd, 1 H, *J* = 13.4, 8.6 Hz), 3.23−3.08 (m, 3 H), 2.65−2.3 (m, 3 H), 1.78−1.6 (m, 2 H), 1.45−1.36 (m, 1 H), 1.27 (s, 3 H), 1.2 (s, 3 H), 1.16−1.13 (d, 3 H, *J* = 6.8 Hz), 1.01 (s, 9 H), 0.85−0.74 (m, 6 H), 0.22 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.8, 170.5, 170.4, 165.1, 155.2, 153.9, 142.1, 131.1, 130.8, 130.1, 129.7, 128.2, 128.1, 127.1, 124.5, 122.4, 120.2, 112.2, 77.1, 71.4, 56.0, 54.4, 46.4, 42.7, 42.2, 39.4, 36.5, 35.3, 25.6, 24.5, 22.8, 22.7, 21.2, 18.1, 17.3, −4.5; IR ($CHCl_3$) 3422, 3030, 3008, 2961, 2932, 2899, 2860, 1745, 1712, 1681, 1604, 1527, 1509, 1485, 1442, 1370, 1339, 1303, 1258, 1169, 1151, 1067, 1007, 970, 912, 841, 822, 792 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{42}H_{59}ClN_2O_8Si$ (M^+ + H) 783.3807, found 783.3798. Anal. Calcd for ($C_{42}H_{59}ClN_2O_8Si$): C, 64.39; H, 7.59; N, 3.58. Found: C, 64.69; H, 7.25; N, 3.28.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*R*,7*E*)-5-hydroxy-8-(4-hydroxyphenyl)-6-methyl-1-oxo-2,7-octadienyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-Lactone, (2*S*)- (24). To a −78 °C solution of the silyl protected phenol **23** (0.084 g, 0.107 mmol) in dry THF (4 mL) was added a 1.0 M THF solution of tetrabutylammonium fluoride (TBAF) (0.11 mL, 0.11 mmol). The light yellow solution was stirred at −78 °C for 30 min, then quenched with saturated aq NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by radial PLC (silica gel, 50−100% EtOAc/hexanes) gave the desired alcohol **24** (0.067 g) in 93% yield as a white solid: $[\alpha]^{20}_D$ +27.5 (*c* 0.47, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.2 (m, 4 H), 7.13−7.05 (dd, 1 H, *J* = 8.3, 1.6 Hz), 6.95−6.75 (m, 4 H), 6.57 (s, 1 H), 6.42−6.33 (d, 1 H, *J* = 15.9 Hz), 5.93−5.83 (dd, 1 H, *J* = 15.8, 8.8 Hz), 5.83−5.78 (d, 1 H, *J* = 15.5 Hz), 5.75−5.73(d, 1 H, *J* = 7.9 Hz), 5.15−5.0 (m, 1 H), 4.93−4.85 (dd, 1 H, *J* = 10.0, 3.0 Hz), 4.85−4.75 (m, 1 H), 3.90 (s, 3 H), 3.54−3.4 (dd, 1 H, *J* = 13.4, 8.6 Hz), 3.25−3.02 (m, 3 H), 2.65−2.35 (m, 3 H), 1.80−1.60 (m, 2 H), 1.45−1.36 (m, 1 H), 1.27 (s, 3 H), 1.20 (s, 3 H), 1.17−1.12 (d, 3 H, *J* = 6.8 Hz), 0.86−0.74 (d, 6 H, *J* = 5.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.9, 170.7, 170.6, 165.4, 156.0, 154.0, 142.6, 137.1, 131.3, 130.8, 129.5, 128.9, 128.1, 127.4, 124.3, 122.5, 115.6, 112.3, 77.2, 71.5, 56.1, 54.5, 46.5, 42.7, 42.1, 39.4, 36.5, 35.3, 24.6, 22.8, 22.7, 21.2, 17.3; IR ($CHCl_3$) 3597, 3421,3319. 2964, 2935, 2874, 2841, 1746, 1711, 1680, 1652, 1610, 1513, 1504, 1485, 1464, 1259, 1170, 1152, 1067 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{36}H_{45}ClN_2O_8$ (M^+ + H) 669.2943, found 669.2953. Anal. Calcd for ($C_{36}H_{45}ClN_2O_8$): C, 64.61; H, 6.78; N, 4.19. Found: C, 64.36; H, 6.51; N, 3.88.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-8-[4-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxopropoxy]phenyl]-5-hydroxy-6-methyl-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (26). A solution of the acid **25** (0.040 g, 0.184 mmol) and carbonyldiimidazole (CDI) (0.040 g, 0.25 mmol) in toluene (2 mL) was heated under nitrogen at 45 °C for 45 min. Following the addition of phenol **24** (0.10 g, 0.15 mmol) in toluene (1 mL), the reaction was again heated at 45 °C for 4 h. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc (50 mL) and washed with 0.1 N HCl (1 × 10 mL), water (1 × 10 mL), saturated aq $NaHCO_3$ (1 × 10 mL), and brine (1 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to provide the crude ester as a yellow foam. Purification by radial PLC (silica gel, 50% EtOAc/hexanes) provided the pure ester **26** (0.097 g) in 75% yield as a yellow solid: $[\alpha]^{20}_D$ +17.2 (*c* 0.58, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.34 (d, 2 H, *J* = 8.5 Hz), 7.29−7.22 (m, 2 H), 7.13−7.0 (m, 3 H), 6.92−6.86 (d, 1 H, *J* = 8.8 Hz), 6.86−6.76 (m, 1 H), 6.50−6.38 (d, 1 H, *J* = 15.9 Hz), 6.10−5.97 (dd, 1 H, *J* = 15.8, 8.8 Hz), 5.85−5.75 (d, 1 H, *J* = 15.1 Hz), 5.55−5.45 (d, 1 H, *J* = 7.9 Hz), 5.15−5.0 (m, 2 H), 4.95−4.72 (m, 2 H), 3.92 (s, 3 H), 3.53−3.35 (m, 3 H), 3.22−3.06 (m, 3 H), 2.65−2.50 (m, 2 H), 2.48−2.35 (m, 1 H), 1.8−1.65 (m, 2 H), 1.49 (s, 10 H), 1.40 (s, 6 H), 1.27 (s, 3 H), 1.21 (s, 3 H), 1.20−1.15 (d, 3 H, *J* = 6.9 Hz), 0.86−0.77 (d, 6 H, *J* = 6.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.8, 170.5, 170.4 165.1, 156.0, 153.9, 150.0, 142.0, 134.5, 130.8, 130.6, 130.4, 129.6, 128.2, 126.9, 124.6, 122.4, 121.5, 112.2, 79.2, 71.3, 56.0, 54.4, 48.2, 46.4, 44.0, 42.7, 42.1, 39.5, 36.5, 35.2, 28.3, 24.9, 24.5, 22.9, 22.8, 22.7, 21.3, 17.2; IR ($CHCl_3$) 3425, 2970, 2934, 2874, 1746, 1711, 1684, 1604, 1505, 1442, 1394, 1368, 1305, 1258, 1166, 1123, 1067, 1015, 971 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{41}H_{55}ClN_3O_9$ (M^+-Boc) 768.3627, found 768.3620. Anal. Calcd for ($C_{46}H_{62}ClN_3O_{11}$): C, 63.62; H, 7.2; N, 4.84. Found: C, 63.32; H, 6.94; N, 4.54.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-chloro-8-[4-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxopropoxy]phenyl]-5,7-dihydroxy-6-methyl-1-oxo-2-octenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3*β*1^5)-Lactone, (2*S*)- (27). Styrene **26** (0.276 g, 0.32 mmol) was epoxidized similarly to styrene **17** with a total of 6 mL of a solution of Oxone (0.78 g, 1.27 mmol) in H_2O to give 0.272 g of the crude epoxides as a yellow foam. To a solution of the epoxide mixture in 4 mL of CH_2Cl_2 at −60 °C was added chlorotrimethylsilane (0.2 mL, 1.54 mmol). After 3 h at −60 °C, 5 mL of 0.1 N HCl was added, and the mixture was warmed to room temperature. The layers were separated, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude chlorohydrins were purified twice by radial PLC (silica gel, 50−100% EtOAc/hexanes) and finally by reverse-phase HPLC (CH_3CN/H_2O) to give the product **27** (0.090 g, 31%) as a white solid: $[\alpha]^{20}_D$ +42.7 (*c* 3.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.44 (d, 1 H, *J* = 8.4 Hz), 7.31−7.26 (m, 3 H), 7.16−7.10 (m, 3 H), 6.92−6.89 (d, 1 H, *J* = 8.4 Hz), 6.87−6.81 (m, 1 H), 5.84−5.79 (d, 1 H, *J* = 15.1 Hz), 5.58−5.55 (d, 1 H, *J* = 7.8 Hz), 5.24−5.19 (t, 1 H, *J* = 8.9 Hz), 5.05−4.95 (m, 2 H), 4.79−4.75 (m, 1 H), 4.72−4.69 (d, 1 H, *J* = 9.5 Hz), 4.04−4.01 (dd, 1 H, *J* = 9.3, 1.3 Hz), 3.93 (s, 3 H), 3.47−3.40 (m, 3 H), 3.25−3.06 (m, 3 H), 2.75−2.7 (m, 1 H), 2.55−2.41 (m, 2 H), 1.90−1.6 (m, 4 H), 1.48 (s, 9 H), 1.39 (s, 6 H), 1.28 (s, 3 H), 1.22 (s, 3 H), 1.09−1.06 (d, 3 H, *J* = 6.9 Hz), 1.0−0.96 (t, 6 H, *J* = 5.9 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.6, 170.4, 170.2, 165.2, 153.9, 142.3, 136.1, 130.8, 129.7, 129.1, 128.2, 124.5, 122.4, 121.9, 112.2, 76.1, 74.0, 71.1, 61.5, 56.5, 54.4, 46.4, 44.1, 42.7, 39.6, 38.4, 36.3, 35.2, 28.3, 24.8, 22.9, 22.8, 22.7, 21.5, 8.6; IR ($CHCl_3$) 3417, 2974, 2934, 1755, 1720, 1677, 1505, 1473, 1368, 1320, 1258, 1205, 1167, 1153, 1123, 1066 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{46}H_{63}Cl_2N_3O_{12}$ (M^+-Boc) 820.3343, found 820.3354.

Pentanoic Acid, *N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-[4-(3-Amino-2,2-dimethyl-1-oxopropoxy)phe- nyl]-8-chloro-5,7-dihydroxy-6-methyl-1-oxo-2-octenyl]-3-chloro-*O*-methyl-D-tyrosyl −2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-Lactone, Monohydrochloride, (2*S*)- (28). To the BOC-protected amine **27** (0.070 g, 0.067 mmol) in CH_2Cl_2 (0.25 mL) was added a 4 M HCl solution (0.1 mL, 0.4 mmol) in 1,4-dioxane. Following 2 h of stirring at room temperature, the solvents were removed under vacuum, and the resulting residue was maintained under high vacuum for 2 days to give the product **28** as a white solid (0.062 g) in 95% yield: $[\alpha]^{20}_D$ +27.7 (*c* 2.52, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79−7.76 (d, 1 H, *J* = 7.9 Hz), 7.48−7.38 (m, 2 H), 7.27−7.26 (d, 1

H, J = 1.2 Hz), 7.17−7.08 (m, 4 H), 6.98−6.95 (d, 1 H, J = 8.5 Hz), 6.71−6.60 (m, 1 H), 5.95−5.90 (d, 1 H, J = 15.2 Hz), 5.14−5.01 (m, 2 H), 4.85−4.8 (m, 1 H), 4.50−4.46 (dd, 1 H, J = 11.0, 3.0 Hz), 3.99−3.96 (d, 1 H, J = 9.1 Hz), 3.82 (s, 3 H), 3.49−3.42 (m, 1 H), 3.19 (s, 2 H), 3.19−3.06 (m, 2 H), 2.77−2.68 (m, 2 H), 2.49−2.46 (t, 1 H, J = 6.8 Hz), 2.44−2.31 (m, 1 H), 1.85−1.5 (m, 4 H), 1.46 (s, 6 H), 1.20 (s, 3 H), 1.16 (s, 3 H), 1.08−0.94 (m, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.9, 175.6, 173.8, 171.9, 168.3, 155.3, 151.8, 144.2, 139.5, 132.2, 131.5, 130.7, 129.4, 125.2, 123.3, 122.6, 113.5, 77.2, 74.8, 72.6, 63.2, 57.6, 56.7, 47.5, 44.1, 42.7, 41.1, 40.4, 37.8, 36.5, 28.8, 26.2, 23.6, 23.4, 22.2, 9.0; IR (KBr) 3418, 2961, 2934, 1751, 1724, 1671, 1608, 1505, 1474, 1464, 1442, 1303, 1282, 1259, 1203, 1169, 1152, 1126, 1065, 1018; HRMS (FAB, *m*/*z*) calcd for $C_{41}H_{56}Cl_3N_3O_{10}$ (M^+-Cl) 820.3343, found 820.3354.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*R*,7*E*)-5-hydroxy-8-[4-(hydroxymethyl)phenyl]-6-methyl-1-oxo-2,7-octadienyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-Lactone, (2*S*)- (35). Tetrabutylammonium fluoride (TBAF) (4.0 mL, 4.1 mmol), as a 1.0 M solution in THF, was added dropwise to a −78 °C solution of the silyl ether **29** (3.1 g, 3.69 mmol) in THF (120 mL). The solution was stirred at −78 °C for 10 min, and the dry ice bath was removed, allowing it to warm to room temperature. Following 30 min at room temperature, the reaction was quenched with water (80 mL) and ethyl acetate (100 mL). The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to yield the free alcohol. Purification by column chromatography (silica gel, 50−100% EtOAc/hexanes) yielded 2.51 g (99%) of the pure alcohol **35** as a white solid: $[\alpha]^{20}_D$ +30.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 4 H), 7.26−7.21 (m, 1 H), 7.2−7.19 (d, 1 H, J = 1.8 Hz), 7.07−7.03 (dd, 1 H, J = 8.4, 1.7 Hz), 6.85−6.82 (d, 1 H, J = 8.4 Hz), 6.82−6.7 (m, 1 H), 6.43−6.37 (d, 1 H, J = 15.9 Hz), 6.05−5.97 (dd, 1 H, J = 15.9, 8.7 Hz), 5.77−5.72 (d, 1 H, J = 15.0 Hz), 5.58−5.55 (d, 1 H, J = 7.9 Hz), 5.08−5.02 (dd, 1 H, J = 9.4, 6.3 Hz), 4.87−4.83 (dd, 1 H, J = 10.2, 3.1 Hz), 4.8−4.67 (m, 1 H), 4.67 (s, 2 H), 3.87 (s, 3 H), 3.44−3.37 (dd, 1 H, J = 13.5, 8.5 Hz), 3.2−3.0 (m, 3H), 2.6−2.3 (m, 3 H), 1.8−1.6 (m, 3 H), 1.4−1.25 (m, 1 H), 1.22 (s, 3 H), 1.15 (s, 3 H), 1.14−1.12 (d, 3 H, J = 6.8 Hz), 0.76−0.73 (t, 6 H, J = 5.5 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.7, 170.7, 170.5, 165.4, 153.8, 142.0, 140.5, 135.9, 131.3, 130.7, 130.0, 129.9, 128.1, 127.1, 126.1, 124.5, 122.2, 112.2, 77.0, 71.3, 64.6, 56.0, 54.6, 46.4, 42.7, 42.1, 39.4, 36.4, 35.2, 24.5, 22.8, 22.6, 21.2, 17.2; IR ($CHCl_3$) 3423, 3011, 2965, 2935, 2874, 2841, 1747, 1712, 1681, 1652, 1528, 1503, 1485, 1442, 1371, 1303, 1259, 1151 cm^{-1}. Anal. Calcd for ($C_{37}H_{47}ClN_2O_8$): C, 65.04; H, 6.93; N, 4.1. Found: C, 65.25; H, 6.66; N, 3.87.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-8-[4-[[3-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxopropoxy]methyl]phenyl]-5-hydroxy-6-methyl-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (36). A mixture of acid **25** (0.22 g, 1.02 mmol), DMAP (0.032 g, 0.26 mmol), and DCC (0.21 g, 1.02 mmol) in CH_2Cl_2 (6.5 mL) was stirred at 0 °C for 30 min. Alcohol **35** (0.35 g, 0.51 mmol) in CH_2Cl_2 (6 mL) was added dropwise via a double-tipped needle. The mixture was stirred at 0 °C for 10 min and at room temperature for 24 h and finally was heated at reflux for 3 h and cooled back to room temperature. The reaction mixture was concentrated in vacuo and filtered through Celite with EtOAc. The resulting residue was purified by column chromatography (silica gel, 60−70% EtOAc/hexanes) to give 0.38 g (85%) of ester **36** as a white solid: $[\alpha]^{20}_D$ +23.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 6 H), 7.12−7.08 (dd, 1 H, J = 8.4, 2.0 Hz), 6.9−6.87 (d, 1 H, J = 8.5 Hz), 6.87−6.75 (m, 1 H), 6.47−6.42 (d, 1 H, J = 15.8 Hz), 6.11−6.03 (dd, 1 H, J = 15.8, 8.8 Hz), 5.82−5.77 (d, 1 H, J = 14.9 Hz), 5.61−5.58 (d, 1 H, J = 7.8 Hz), 5.12 (s, 2 H), 5.12−4.75 (m, 4 H), 3.9 (s, 3 H), 3.49−3.42 (dd, 1 H, J = 13.4, 8.7 Hz), 3.29−3.27 (d, 2 H, J = 6.5 Hz), 3.2−3.1 (m, 3 H), 2.65−2.3 (m, 3 H), 1.8−1.6 (m, 2 H), 1.47 (s, 9 H), 1.45−1.3 (m, 1 H), 1.3−1.15 (m, 15 H), 0.79−0.75 (t, 6 H, J = 6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.8, 170.4, 165.1, 153.9, 141.9, 136.7, 135.1, 131.1, 130.8, 129.7, 128.3, 128.2, 126.2, 124.6, 122.4, 112.2, 76.9, 71.3, 66.0, 56.0, 54.4, 48.2, 46.4, 43.7, 42.6, 42.2, 39.4, 36.4, 35.2, 28.3, 24.5, 22.8, 22.7, 22.6, 21.2, 17.2; IR ($CHCl_3$) 3426, 2968, 2935, 2874, 2841, 1746, 1713, 1684, 1652, 1504, 1486, 1474, 1368, 1318, 1304, 1259, 1244, 1165, 1151, 1067 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{42}H_{64}ClN_3O_{11}$ (M^+ + H − Boc) 782.3783, found 782.3788.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-chloro-8-[4-[[3-[[(1,1-dimethylethoxy)carbonyl]amino]-2,2-dimethyl-1-oxopropoxy]methyl]phenyl]-5,7-dihydroxy-6-methyl-1-oxo-2-octenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-Lactone, (2*S*)- (37). 3-Chloroperoxybenzoic acid (0.092 g, 0.54 mmol) was added to a 0 °C solution of alkene **36** (0.45 g, 0.51 mmol) in CH_2Cl_2 (9 mL). The solution was stirred at 0 °C for 1 h and at room-temperature overnight. It was concentrated in vacuo, and the resulting epoxides were dissolved in $CHCl_3$ (10 mL) and cooled to −60 °C.

Chlorotrimethylsilane (0.25 mL, 1.95 mmol) was added to the −60 °C solution, and the mixture was stirred for 1 h. More TMSCl (0.5 mL, 3.9 mmol) was added and the stirring continued between −60 °C to −40 °C for an additional 2 h. The solution was warmed to room temperature, and additional TMSCl (0.25 mL, 1.95 mmol) was added. Following 30 min of stirring at room temperature the solution was concentrated in vacuo and purified by preparative HPLC with (45:55) CH_3CN:H_2O to give 0.1 g (22%) of the desired chlorohydrin **37**: $[\alpha]^{20}_D$ +47.9 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5−7.2 (m, 6 H), 7.13−7.10 (dd, 1 H, J = 8.4, 1.9 Hz), 6.91−6.88 (d, 1 H, J = 8.5 Hz), 6.87−6.75 (m, 1 H), 5.85−5.8 (d, 1 H, J = 14.9 Hz), 5.75−5.6 (m, 1 H), 5.22−5.1 (m, 3 H), 5.0−4.9 (m, 2 H), 4.8−4.72 (m, 1 H), 4.71−4.68 (d, 1 H, J = 9.6 Hz), 4.07−4.03 (d, 1 H, J = 9.5 Hz), 3.9 (s, 3 H), 3.45−3.38 (dd, 1 H, J = 13.4, 8.5 Hz), 3.31−3.26 (d, 2 H, J = 6.4 Hz), 3.25−3.0 (m, 3 H), 2.8−2.65 (bd, 1 H), 2.6−2.35 (m, 2 H), 1.9−1.7 (m, 3 H), 1.47 (s, 10 H), 1.27−1.22 (m, 12 H), 1.09−1.07 (d, 3 H, J = 7.0 Hz), 0.98−0.96 (m, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.5, 170.5, 165.2, 153.9, 142.5, 137.0, 130.8, 129.8, 128.2, 124.5, 122.4, 112.2, 79.1, 76.1, 73.9, 71.1, 65.6, 61.7, 56.1, 54.5, 48.2, 46.4, 43.7, 42.7, 39.6, 38.4, 36.3, 35.2, 28.3, 24.8, 23.0, 22.9, 22.8, 22.7, 21.5, 8.6; IR ($CHCl_3$) 3426, 2967, 2934, 2873, 2841, 1715, 1684, 1605, 1504, 1485, 1474, 1442, 1368, 1305, 1258, 1151 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{47}H_{65}Cl_2N_3O_{12}$ (M^+ + H − Boc) 834.3499, found 834.3487. Anal. Calcd for ($C_{47}H_{65}Cl_2N_3O_{12}$·0.2$H_2O$): C, 60.38; H, 7.01; N, 4.49. Found: C, 60.15; H, 7.02; N, 4.48.

Pentanoic Acid, *N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-[4-[(3-Amino-2,2-dimethyl-1-oxopropoxy)methyl]phenyl]-8-chloro-5,7-dihydroxy-6-methyl-1-oxo-2-octenyl]-3-chloro-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-Lactone, Monohydrochloride, (2*S*)- (38). A 4 M solution of hydrogen chloride in 1,4-dioxane (0.11 mL, 0.43 mmol) was added to a solution of chlorohydrin **37** (0.08 g, 0.086 mmol) in CH_2Cl_2 (0.35 mL). The resulting mixture was stirred at room temperature for 3 h, concentrated in vacuo, and maintained under vacuum for 3 days to remove the 1,4-dioxane, thus giving the desired hydrochloride salt **38** (0.075 g) in quantitative yield: $[\alpha]^{20}_D$ +28.0 (*c* 0.5, CH_3OH); ^{1}H NMR (300 MHz, CD_3OH) δ 8.52−8.49 (d, 1 H, J = 7.5 Hz), 7.84−7.81 (d, 2 H, J = 9.6 Hz), 7.49−7.39 (q, 5 H, J_{AB} = 8.3 Hz), 7.32−7.31 (d, 1 H, J = 1.9 Hz), 7.22−7.19 (dd, 1 H, J = 8.4, 2.1 Hz), 7.02−7.0 (d, 1 H, J = 8.4 Hz), 6.8−6.7 (m, 1 H), 6.0−5.9 (dd, 1 H, J = 15.4, 1.0 Hz), 5.22 (s, 2 H), 5.2−5.0 (m, 2 H), 4.85−4.81 (d, 1 H, J = 9.6 Hz), 4.6−4.5 (m, 1 H), 4.06−4.03 (dd, 1 H, J = 9.6, 1.5 Hz), 3.9 (s, 3 H), 3.54−3.46 (dd, 1 H, J = 13.5, 9.7 Hz), 3.25−3.11 (m, 2 H), 3.11 (s, 2 H), 2.8−2.7 (m, 2 H), 2.6−2.3 (m, 2 H), 1.9−1.5 (m, 3 H), 1.3 (s, 6 H), 1.25 (s, 3 H), 1.2 (s, 3 H), 1.06−0.99 (m, 9 H); ^{13}C NMR (62.5 MHz, CD_3OH) δ 178.9, 176.5, 173.8, 171.8, 168.3, 155.3, 144.2, 141.6, 137.4, 132.3, 131.5, 129.8, 129.4, 129.3, 125.2, 123.3, 113.5, 77.2, 74.7, 72.6, 67.8, 63.5, 57.6, 56.7, 47.7, 47.6, 44.1, 42.3, 41.1, 40.4, 37.9, 36.5, 26.2, 23.7, 23.4, 22.2, 9.0; IR ($CHCl_3$) 3421, 2964, 2935, 2873, 2841, 1717, 1676, 1528, 1504, 1477,

1464, 1405, 1282, 1259, 1185, 1152, 1067 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{42}H_{58}Cl_3N_3O_{10}$ (M^+- Cl) 834.3499, found 834.3504. Anal. Calcd for ($C_{42}H_{58}Cl_3N_3O_{10}$· 1.0 H_2O): C, 56.73; H, 6.8; N, 4.72. Found: C, 56.52; H, 6.4; N, 4.5.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-6-[(2*R*,3*R*)-3-[4-(chloromethyl)phenyl]oxiranyl]-5-hydroxy-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (39). To a 0 °C solution of the alcohol **31** (0.32 g, 0.46 mmol) in CH_2Cl_2 (8.5 mL) was added solid $NaHCO_3$ (0.19 g, 2.29 mmol), triphenylphosphine (0.18 g, 0.69 mmol), and *N*-chlorosuccinimide (0.092 g, 0.69 mmol). The mixture was stirred at 0 °C for 20 min and quenched with saturated aq $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude yellow solid was purified by radial PLC (silica gel, 40−60% EtOAC/hexanes) to give 0.26 g of benzyl chloride **39** as a white solid, contaminated with triphenylphosphine oxide. An analytical sample of **39** (0.07 g), as a white solid, was obtained by reverse phase HPLC purification of 0.1 g of crude product with (50:50) CH_3CN:H_2O: $[\alpha]^{20}_D$ +25.6 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.4−7.38 (d, 2 H, J = 7.9 Hz), 7.26−7.23 (d, 3 H, J = 8.3 Hz), 7.19−7.18 (d, 1 H, J = 1.9 Hz), 7.06−7.03 (dd, 1 H, J = 8.3, 1.9 Hz), 6.85−6.82 (d, 1 H, J = 8.4 Hz), 6.8−6.7 (m, 1 H), 5.74−5.69 (d, 1 H, J = 15.4 Hz), 5.49−5.47 (d, 1 H, J = 7.8 Hz), 5.22−5.17 (m, 1 H), 4.85−4.8 (dd, 1 H, J = 9.7, 3.0 Hz), 4.78−4.7 (m, 1 H), 4.6 (s, 2 H), 3.9 (s, 3 H), 3.69−3.68 (d, 1 H, J = 1.3 Hz), 3.45−3.38 (dd, 1 H, J = 13.4, 8.6 Hz), 3.2−3.0 (m, 3 H), 2.92−2.89 (dd, 1 H, J = 7.6, 1.6 Hz), 2.6−2.4 (m, 2 H), 1.8−1.6 (m, 3 H), 1.4−1.3 (m, 1 H), 1.22 (s, 3 H), 1.16 (s, 3 H), 1.16−1.13 (d, 3 H, J = 8.6 Hz), 0.86−0.82 (t, 6 H, J = 6.8 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.8, 175.1, 170.4, 170.3, 164.9, 154.0, 141.6, 137.7, 137.1, 130.8, 129.5, 128.9, 128.1, 125.9, 124.6, 122.4, 112.3, 77.2, 75.8, 71.1, 63.1, 58.5, 56.1, 54.4, 46.4, 45.7, 42.7, 40.5, 39.3, 36.8, 35.2, 24.5, 22.8, 22.6, 21.2, 13.5; IR ($CHCl_3$) 3416, 3284, 2961, 2933, 2873, 2839, 1752, 1721, 1680, 1658, 1536, 1504, 1473, 1442, 1321, 1302, 1281, 1259, 1192, 1150, 1126, 1066 cm^{-1}. Anal. Calcd for ($C_{37}H_{46}Cl_2N_2O_8$): C, 61.92; H, 6.46; N, 3.9. Found: C, 61.62; H, 6.37; N, 3.61.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-6-[(2*R*,3*R*)-3-[4-[(diethylamino)methyl]phenyl]oxiranyl]-5-hydroxy-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (40a). Diethylamine (0.09 mL, 0.84 mmol) was added to benzyl chloride **39** (0.03 g, 0.042 mmol) in THF (0.3 mL). The mixture was stirred at room-temperature overnight and quenched with saturated aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude yellow solid was purified by radial PLC (silica gel, 50−80% EtOAc/hexanes) to give 0.026 g of amine **40a** in a 82% yield as a white solid: $[\alpha]^{20}_D$ +25.9 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.32 (d, 2 H, J = 7.9 Hz), 7.25−7.12 (m, 4 H), 7.06−7.02 (dd, 1 H, J = 8.4, 1.6 Hz), 6.84−6.82 (d, 1 H, J = 8.5 Hz), 6.82−6.7 (m, 1 H), 5.74−5.69 (d, 1 H, J = 15.2 Hz), 5.57−5.55 (d, 1 H, J = 7.8 Hz), 5.22−5.17 (m, 1 H), 4.85−4.7 (m, 2 H), 3.86 (s, 3 H), 3.66 (s, 1 H), 3.57 (s, 2 H), 3.46−3.38 (dd, 1 H, J = 13.4, 8.7 Hz), 3.2−3.0 (m, 3 H), 2.93−2.91 (d, 1 H, J = 7.4 Hz), 2.6−2.4 (m, 6 H), 1.8−1.6 (m, 3 H), 1.4−1.3 (m, 1 H), 1.22 (s, 3 H), 1.15 (s, 3 H), 1.15−1.12 (d, 3 H, J = 9.2 Hz), 1.07−1.03 (t, 6 H, J = 7.1 Hz), 0.86−0.82 (t, 6 H, J = 6.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.9, 170.4, 170.3, 164.9, 154.0, 141.7, 140.1, 135.2, 130.8, 129.6, 129.1, 128.1, 125.4, 124.6, 122.4, 112.3, 77.2, 75.8, 71.1, 62.9, 58.9, 57.1, 56.0, 54.4, 46.6, 46.4, 42.7, 40.6, 39.3, 36.8, 35.2, 24.5, 22.8, 22.6, 21.2, 13.5, 11.5; IR ($CHCl_3$) 3424, 2969, 2936, 2874, 1752, 1711, 1682, 1605, 1527, 1503, 1485, 1303, 1259, 1190, 1151, 1067 cm^{-1}. Anal. Calcd for ($C_{41}H_{56}ClN_3O_8$): C, 65.28; H, 7.48; N, 5.57. Found: C, 65.5; H, 7.5; N, 5.65.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-chloro-8-[4-[(diethylamino)methyl]phenyl]-5,7-dihydroxy-6-methyl-1-oxo-2-octenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1[5])-Lactone, Monohydrochloride, (2*S*)- (41a). To a −66 °C solution of epoxide **40a** (0.05 g, 0.066 mmol) in $CHCl_3$ (0.8 mL) was added dropwise a 4 M solution of HCl in 1,4-dioxane (0.04 mL, 0.166 mmol). The mixture was stirred at −66 °C for 10 min upon which time the dry ice bath was removed, allowing the solution to slowly warm to room temperature. The solvents were removed in vacuo, and the resulting salt was placed under high vacuum for 3 days to remove the residual dioxane, hence yielding 0.054 g of the desired chlorohydin **41a** in quantitative yield: $[\alpha]^{20}_D$ +29.3 (*c* 1.0, MeOH); ^1H NMR (300 MHz, MeOD) δ 8.5−8.47 (d, 1 H, J = 7.5 Hz), 7.79−7.76 (d, 1 H, J = 8.8 Hz), 7.53 (s, 4 H), 7.26−7.25 (d, 1 H, J = 1.6 Hz), 7.17−7.14 (dd, 1 H, J = 8.6, 1.6 Hz), 6.97−6.94 (d, 1 H, J = 8.4 Hz), 6.75−6.6 (m, 1 H), 5.96−5.90 (d, 1 H, J = 15.3 Hz), 5.2−5.0 (m, 2 H), 4.85−4.82 (m, 2 H), 4.5−4.4 (m, 1 H), 4.33 (s, 2 H), 4.02−3.98 (d, 1 H, J = 9.3 Hz), 3.8 (s, 3 H), 3.49−3.42 (dd, 1 H, J = 13.3, 9.9 Hz), 3.2−3.0 (m, 6 H), 2.8−2.6 (m, 2 H), 2.5−2.2 (m, 2 H), 1.8−1.5 (m, 3 H), 1.34−1.3 (m, 7 H), 1.2 (s, 3 H), 1.15 (s, 3 H), 1.01−0.94 (m, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.9, 173.8, 171.8, 168.3, 155.4, 144.1, 143.4, 132.3, 132.2, 131.5, 131.1, 130.4, 129.4, 125.2, 123.3, 113.5, 77.2, 74.8, 72.6, 63.2, 57.6, 56.7, 56.6, 48.0, 47.5, 44.1, 41.1, 40.4, 37.8, 36.5, 26.2, 23.6, 23.4, 22.2, 9.07, 9.0; IR (KBr) 3414, 2960, 2934, 1751, 1721, 1671, 1521, 1504, 1463, 1443, 1259, 1197, 1155, 1127, 1065 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{41}H_{58}Cl_3N_3O_8$ (M^+-Cl) 790.3601, found 790.3609.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-6-[(2*R*,3*R*)-3-[4-[[4-[(1,1-dimethylethoxy)carbonyl]-1-piperazinyl]methyl]phenyl]oxiranyl]-5-hydroxy-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (40b). Epoxide **40b** (0.147 g) was prepared in 81% yield from benzyl chloride **39** (0.15 g, 0.21 mmol) and *N*-(*tert*-butoxycarbonyl)-piperazine (0.195 g, 1.05 mmol) according to the procedure described for **40a**: $[\alpha]^{20}_D$ +25.4 (*c* 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.23 (m, 6 H), 7.11−7.08 (d, 1 H, J = 8.6 Hz), 6.9−6.87 (d, 1 H, J = 8.5 Hz), 6.86−6.72 (m, 1 H), 5.78−5.73 (d, 1 H, J = 15.2 Hz), 5.53−5.5 (d, 1 H, J = 7.7 Hz), 5.28−5.23 (m, 1 H), 4.88−4.70 (m, 2 H), 3.9 (s, 3 H), 3.7 (s, 1 H), 3.54 (s, 2 H), 3.5−3.4 (m, 5 H), 3.2−3.05 (m, 3 H), 3.0−2.95 (d, 1 H, J = 7.4 Hz), 2.65−2.4 (m, 6 H), 1.85−1.6 (m, 3 H), 1.5 (s, 9 H), 1.45−1.4 (m, 1 H), 1.27 (s, 3 H), 1.2 (s, 3 H), 1.2−1.18 (d, 3 H, J = 8.3 Hz), 0.91−0.87 (t, 6 H, J = 6.1 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.9, 170.3, 170.2, 164.9, 154.7, 154.0, 141.7, 138.4, 135.6, 130.8, 129.5, 129.3, 128.1, 125.5, 124.6, 122.4, 112.3, 79.5, 77.2, 75.8, 71.1, 62.9, 62.6, 58.8, 56.1, 54.4, 52.8, 46.3, 42.7, 40.6, 39.3, 36.7, 35.2, 28.3, 24.5, 22.8, 22.6, 21.2, 13.4; IR ($CHCl_3$) 3425, 3008, 2965, 2937, 2874, 2817, 1752, 1709, 1683, 1527, 1484, 1463, 1459, 1427, 1367, 1259, 1167, 1150 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{46}H_{63}ClN_4O_{10}$ (M^+ + H) 867.4311, found 867.4300.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-chloro-8-[4-[[4-[(1,1-dimethylethoxy)carbonyl]-1-piperazinyl]-methyl]phenyl]-5,7-dihydroxy-6-methyl-1-oxo-2-octenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1[5])-Lactone, (2*S*)- (41b′). To a −66 °C solution of the epoxide **40b** (0.135 g, 0.156 mmol) in $CHCl_3$ (3 mL) was added dropwise chlorotrimethylsilane (0.16 mL, 1.2 mmol). The mixture was stirred at −66 °C for 2 h, and additional TMSCl was added (0.16 mL, 1.2 mmol). Following another 1 h at −66 °C, the ice bath was removed to allow the solution to slowly warm to room temperature. The solvents were removed in vacuo, and the resulting solid was purified by radial PLC (silica gel, 2−5% MeOH/CH_2Cl_2) to give 0.13 g of the anti chlorohydrin **41b′** in 92% yield: $[\alpha]^{20}_D$ +50.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 4 H), 7.21−7.2 (d, 2 H, J = 1.4 Hz), 7.08−7.05 (dd, 1 H, J = 8.6, 1.6 Hz), 6.86−6.83 (d, 1 H, J = 8.4 Hz), 6.82−6.7 (m, 1 H), 5.8−5.75 (d, 1 H, J = 15.1 Hz), 5.65−5.62 (d, 1 H, J = 7.8 Hz), 5.2−5.1 (t, 1 H), 5.0−4.7 (m, 2 H), 4.66−4.63 (d, 1 H, J = 9.7 Hz), 4.02−4.0 (d, 1 H, J = 9.6 Hz), 3.88 (s, 3 H), 3.49−3.48 (d, 2 H, J = 4.2 Hz), 3.45−3.3 (m, 5 H), 3.2−3.0 (m, 3 H), 2.7−2.3 (m, 7 H), 1.8−1.6 (m, 3 H), 1.45 (s, 10 H), 1.23 (s, 3 H), 1.17 (s, 3 H), 1.04−1.02 (d, 3 H, J = 6.9 Hz), 0.93−0.91 (d, 6 H, J = 6.3 Hz); ^{13}C NMR

(62.5 MHz, $CDCl_3$) δ 177.5, 170.5, 170.2, 165.2, 154.6, 153.9, 142.3, 139.1, 137.3, 130.8, 129.8, 129.5, 128.1, 127.9, 124.5, 122.3, 112.2, 79.5, 76.0, 73.9, 71.1, 62.4, 61.9, 56.1, 54.5, 52.8, 46.4, 42.7, 39.6, 38.4, 36.4, 35.2, 28.3, 24.7, 23.0, 22.9, 22.7, 21.5, 8.6; IR ($CHCl_3$) 3424, 3007, 2966, 2936, 2872, 2820, 1751, 1712, 1682, 1528, 1504, 1483, 1426, 1367, 1259, 1168, 1150, 1127, 1067, 1006 cm^{-1}. Anal. Calcd for ($C_{46}H_{64}Cl_2N_4O_{10}$): C, 61.12; H, 7.14; N, 6.2. Found: C, 60.85; H, 7.09; N, 6.43.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-chloro-5,7-dihydroxy-6-methyl-1-oxo-8-[4-(1-piperazinylmethyl)-phenyl]-2-octenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-β-alanyl-2-hydroxy-4-methyl-,(3→1^5)-Lactone,Dihydrochloride, (2*S*)- (41b). The dihydrochloride salt **41b** (0.116 g) of the BOC-protected piperazine (0.122 g, 0.13 mmol) was prepared with 4 M HCl in 1,4-dioxane (0.32 mL, 1.3 mmol) in quantitative yield according to the procedure described for **28**: $[\alpha]^{20}_D$ +26.3 (*c* 0.7, MeOH); ^{1}H NMR (300 MHz, MeOD) δ 8.47−8.45 (d, 1 H, J = 7.5 Hz), 7.78−7.75 (d, 1 H, J = 9.2 Hz), 7.6−7.52 (q, 5 H, J = 16.9, 7.9 Hz), 7.27−7.26 (d, 1 H, J = 1.15 Hz), 7.18−7.14 (dd, 1 H, J = 8.6, 1.8 Hz), 6.98−6.95 (d, 1 H, J = 8.4 Hz), 6.75−6.6 (m, 1 H), 5.95−5.9 (d, 1 H, J = 15.4 Hz), 5.2−5.0 (m, 2 H), 4.85−4.82 (m, 2 H), 4.5−4.4 (m, 1 H), 4.4 (s, 2 H), 4.0−3.98 (d, 1 H, J = 9.3 Hz), 3.8 (s, 3 H), 3.6−3.4 (m, 9 H), 3.32−3.29 (d, 1 H, J = 11.3 Hz), 3.19−3.13 (dd, 1 H, J = 14.8, 3.5 Hz), 3.1−3.06 (d, 1 H, J = 13.7 Hz), 2.8−2.6 (m, 2 H), 2.5−2.3 (m, 2 H), 1.85−1.5 (m, 3 H), 1.3−1.2 (m, 1 H), 1.2 (s, 3 H), 1.15 (s, 3 H), 1.02−0.95 (m, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.8, 173.7, 171.9, 168.3, 155.4, 144.2, 143.7, 132.8, 132.2, 131.5, 130.4, 129.9, 129.4, 125.2, 123.3, 113.5, 77.2, 74.8, 72.6, 63.1, 61.2, 57.6, 56.7, 49.2, 47.5, 44.1, 42.1, 41.1, 40.3, 37.8, 36.5, 26.3, 23.7, 23.4, 22.2, 9.0; IR (KBr) 3415, 2960, 2933, 2455, 1749, 1721, 1671, 1504, 1475, 1442, 1304, 1258, 1197, 1152, 1126, 1065, 1012 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{41}H_{58}Cl_4N_4O_8$ (M^+- HCl_2) 803.3553, found 803.3563. Anal. Calcd for ($C_{41}H_{58}Cl_4N_4O_8 \cdot 0.5\ H_2O$): C, 55.6; H, 6.71; N, 6.33. Found: C, 55.52; H, 6.97; N, 6.22.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*)-6-[(2*R*,3*R*)-3-[4-[[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]amino]-methyl]phenyl]oxiranyl]-5-hydroxy-1-oxo-2-heptenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-β-alanyl-2-hydroxy-4-methyl-, (3 → 1)-Lactone, (2*S*)- (40c). Epoxide **40c** (0.15 g) was prepared in 78% yield from benzyl chloride **39** (0.16 g, 0.22 mmol) and *tert*-butyl-*N*-(2-aminoethyl)carbamate (0.35 g, 2.22 mmol) according to the procedure described for **40a**: $[\alpha]^{20}_D$ +22.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.38 (d, 2 H, J = 7.8 Hz), 7.31 (s, 1 H), 7.26−7.24 (d, 3 H, J = 8.0 Hz), 7.11−7.08 (dd, 1 H, J = 8.4, 1.7 Hz), 6.88−6.86 (d, 1 H, J = 8.4 Hz), 6.86−6.72 (m, 1 H), 5.88−5.8 (bd, 1 H), 5.78−5.73 (d, 1 H, J = 15.2 Hz), 5.28−5.22 (m, 1 H), 5.2−5.08 (bs, 1 H), 4.95−4.7 (m, 2 H), 3.91 (s, 3 H), 3.87 (s, 2 H), 3.7 (s, 1 H), 3.45−3.38 (dd, 1 H, J = 13.4, 8.4 Hz), 3.35−3.0 (m, 6 H), 2.96−2.93 (dd, 1 H, J = 7.5, 1.2 Hz), 2.89−2.78 (m, 2 H), 2.65−2.4 (m, 2 H), 1.85−1.65 (m, 3 H), 1.49 (s, 9 H), 1.48−1.3 (m, 1 H), 1.27 (s, 3 H), 1.2 (s, 3 H), 1.19−1.17 (d, 3 H, 7.1 Hz), 0.91−0.87 (t, 6 H, J = 6.8 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.7, 170.4, 165.0, 156.0, 153.9, 141.5, 139.9, 135.6, 130.7, 129.7, 128.5, 128.1, 125.6, 124.7, 122.3, 112.2, 77.2, 75.7, 71.0, 63.0, 58.8, 56.0, 54.5, 52.9, 48.5, 46.3, 42.7, 40.5, 39.3, 36.8, 35.2, 28.3, 24.5, 22.83, 22.8, 22.6, 21.2, 13.5; IR ($CHCl_3$) 3425, 3009, 2967, 2936, 2874, 2841, 1751, 1709, 1685, 1504, 1368, 1280, 1259, 1165, 1153, 1067 cm^{-1}; Anal. Calcd for ($C_{44}H_{61}ClN_4O_{10}$): C, 62.81; H, 7.31; N, 6.66. Found: C, 62.77; H, 7.34; N, 6.81.

Pentanoic Acid, *N*-[(2*E*,5*S*,6*S*,7*R*,8*S*)-8-[4-[[(2-Aminoethyl)amino]methyl]phenyl]-8-chloro-5,7-dihydroxy-6-methyl-1-oxo-2-octenyl]-3-chloro-*O*-methyl-D-tyrosyl-2,2-dimethyl-β-alanyl-2-hydroxy-4-methyl-, (3 → 1^5)-Lactone, Dihydrochloride, (2*S*)- (41c). To a −78 °C solution of the epoxide **40c** (0.065 g, 0.076 mmol) in CH_2Cl_2 (0.9 mL) was added dropwise 4 M HCl in 1,4-dioxane (0.09 mL, 0.38 mmol). The solution was stirred at −78 °C for 30 min and was allowed to slowly warm to room temperature. It was stirred at room temperature an additional 2 h and was concentrated in vacuo to yield the chlorohydrin **41c** (0.063 g) in quantitative yield: $[\alpha]^{20}_D$ +16.6 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54−8.52 (d, 1 H, J = 7.7 Hz), 7.84−7.81 (dd, 1 H, J = 8.8, 1.7 Hz), 7.63−7.53 (q, 4 H, J = 20.0, 8.2 Hz), 7.31−7.3 (d, 1 H, J = 2.0 Hz), 7.22−7.18 (dd, 1 H, J = 8.4, 2.0 Hz), 7.02−6.99 (d, 1 H, J = 8.5 Hz), 6.8−6.7 (m, 1 H), 6.0−5.92 (d, 1 H, J = 15.0 Hz), 5.2−5.0 (m, 2 H), 4.9−4.8 (m, 1 H), 4.6−4.4 (m, 1 H), 4.3 (s, 2 H), 4.07−4.03 (dd, 1 H, J = 9.5, 1.4 Hz), 3.86 (s, 3 H), 3.6−3.1 (m, 7 H), 2.82−2.7 (m, 2 H), 2.6−2.3 (m, 2 H), 1.9−1.6 (m, 3 H), 1.25 (s, 3 H), 1.2 (s, 3 H), 1.05−0.99 (m, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.8, 173.8, 171.9, 168.3, 155.3, 144.2, 143.1, 132.2, 131.5, 131.4, 130.3, 129.4, 125.2, 123.2, 113.5, 77.2, 74.7, 72.6, 63.2, 57.6, 56.7, 52.4, 47.5, 45.5, 44.1, 41.1, 40.3, 37.8, 36.9, 36.5, 26.3, 23.7, 23.5, 22.2, 9.0; IR (KBr) 3412, 2961, 2933, 1749, 1721, 1663, 1504, 1462, 1442, 1259, 1199, 1152, 1126, 1065 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{39}H_{56}Cl_4N_4O_8$ (M^+ − HCl_2) 777.3397, found 777.3391; Anal. Calcd for ($C_{39}H_{56}Cl_4N_4O_8 \cdot 0.8\ H_2O$): C, 54.15; H, 6.71; N, 6.48. Found: C, 54.02; H, 6.65; N, 6.29.

Cyclo[2,2-dimethyl-β-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-8-[4-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methyl]phenyl]-5-hydroxy-6-methyl-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (42). To a solution of alcohol **35** (0.13 g, 0.19 mmol) in THF (2 mL) was added triphenylphosphine (0.065 g, 0.25 mmol), phthalimide (0.037 g, 0.25 mmol), and diethyl azodicarboxylate (DEAD) (0.04 mL, 0.25 mmol) dropwise. The resulting yellow solution was stirred at room temperature for 2 h and quenched with H_2O (10 mL) and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by radial PLC (silica gel, 50−70% EtOAc/hexanes) to give phthalimide **42** (0.14 g) as a white solid in 90% yield: $[\alpha]^{20}_D$ +19.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.9−7.8 (m, 2 H), 7.72−7.69 (m, 2 H), 7.39−7.36 (d, 2 H, J = 8.0 Hz), 7.28−7.26 (d, 2 H, J = 5.3 Hz), 7.25−7.2 (m, 1 H), 7.19−7.18 (d, 1 H, J = 1.9 Hz), 7.06−7.03 (dd, 1 H, J = 8.5, 1.9 Hz), 6.85−6.82 (d, 1 H, J = 8.4 Hz), 6.81−6.7 (m, 1 H), 6.39−6.33 (d, 1 H, J = 15.9 Hz), 6.01−5.93 (dd, 1 H, J = 15.8, 8.8 Hz), 5.75−5.7 (d, 1 H, J = 15.4 Hz), 5.47−5.44 (d, 1 H, J = 7.9 Hz), 5.05−5.0 (dd, 1 H, J = 9.4, 6.3 Hz), 4.8 (s, 2 H), 4.83−4.7 (m, 2 H), 3.87 (s, 3 H), 3.4−3.36 (dd, 1 H, J = 13.4, 8.6 Hz), 3.18−3.02 (m, 3 H), 2.6−2.25 (m, 3 H), 1.65−1.5 (m, 2 H), 1.35−1.22 (m, 1 H), 1.21 (s, 3 H), 1.14 (s, 3 H), 1.12−1.09 (d, 3 H, J = 6.8 Hz), 0.71−0.69 (d, 3 H, J = 6.4 Hz), 0.65−0.63 (d, 3 H, J = 6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.8, 170.5, 170.4, 167.8, 165.2, 153.9, 142.0, 136.3, 135.6, 133.9, 131.9, 131.1, 130.7, 130.6, 129.8, 128.9, 128.6, 128.5, 128.1, 126.3, 124.6, 123.2, 122.3, 112.2, 76.9, 71.3, 56.0, 54.5, 46.4, 42.6, 42.1, 41.2, 39.4, 36.4, 35.2, 24.4, 22.8, 22.6, 22.5, 21.1, 17.2; IR ($CHCl_3$) 3421, 2967, 2935, 2873, 2840, 1747, 1716, 1682, 1527, 1503, 1485, 1433, 1395, 1259, 1151 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{45}H_{50}ClN_3O_9$ (M^+ + H) 812.3314, found 812.3307; Anal. Calcd for ($C_{45}H_{50}ClN_3O_9 \cdot 0.1\ H_2O$): C, 66.39; H, 6.22; N, 5.16. Found: C, 66.03; H, 5.9; N, 4.81.

Pentanoic Acid, *N*-[(2*E*,5*S*,6*R*,7*E*)-8-[4-(Aminomethyl)-phenyl]-5-hydroxy-6-methyl-1-oxo-2,7-octadienyl]-3-chloro-*O*-methyl-D-tyrosyl-2,2-dimethyl-β-alanyl-2-hydroxy-4-methyl-, (3 → 1)-Lactone, (2*S*)- (43). To the phthalimide **42** (0.1 g, 0.123 mmol) in EtOH (1.8 mL) was added *n*-butylamine (0.04 mL, 0.369 mmol). The solution was heated at 75 °C for 2 days, concentrated in vacuo, and purified by radial PLC (silica gel, 10−25% MeOH/CH_2Cl_2) to provide the free amine **43** (0.048 g) in 57% yield.

Pentanoic Acid, *N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-methylglycyl-(2*E*,5*S*,6*R*,7*E*)-8-[4-(aminomethyl)phenyl]-5-hydroxy-6-methyl-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl-2,2-dimethyl-β-alanyl-2-hydroxy-4-methyl-, (5 → 2)-lactone, (2*S*)- (44). To *N*-(*tert*-butoxycarbonyl)sarcosine (0.07 g, 0.37 mmol) in DMF (1.5 mL) were added 1-hydroxybenzotriazole hydrate (HOBT) (0.05 g, 0.37 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (0.071 g, 0.37 mmol). Following 45 min of stirring at room temperature, amine **43** (0.17 g, 0.25 mmol) in DMF (2.5 mL) was added dropwise via a double-tipped needle to the solution.

The resulting mixture was stirred for an additional 3 h, quenched with H_2O (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the resulting crude product by radial PLC (silica gel, 70−100% EtOAc/hexanes) gave the desired amide **44** (0.15 g) in 71% yield as a white solid: $[\alpha]^{20}_D$ +22.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.1 (m, 6 H), 7.04−7.0 (dd, 1 H, *J* = 8.5, 1.9 Hz), 6.82−6.79 (d, 1 H, *J* = 8.5 Hz), 6.79−6.65 (m, 1 H), 6.38−6.32 (d, 1 H, *J* = 15.9 Hz), 6.32−6.1 (m, 1 H), 6.01−5.93 (dd, 1 H, *J* = 15.9, 8.7 Hz), 5.75−5.70 (d, 1 H, *J* = 15.0 Hz), 5.65−5.6 (m, 1 H), 5.0−4.99 (dd, 1 H, *J* = 9.3, 6.1 Hz), 4.84−4.79 (dd, 1 H, *J* = 9.6, 3.6 Hz), 4.74−4.67 (m, 1 H), 4.42−4.4 (d, 2 H, *J* = 5.7 Hz), 3.87 (s, 2 H), 3.84 (s, 3 H), 3.42−3.34 (dd, 1 H, *J* = 13.5, 8.6 Hz), 3.15−3.0 (m, 3 H), 2.9 (s, 3 H), 2.6−2.25 (m, 3 H), 1.8−1.5 (m, 2 H), 1.4 (s, 9 H), 1.39−1.25 (m, 1 H), 1.19 (s, 3 H), 1.12 (s, 3 H), 1.1−1.08 (d, 3 H, *J* = 6.8 Hz), 0.73−0.69 (m, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.7, 170.5, 170.4, 169.2, 165.2, 153.9, 141.9, 137.3, 136.0, 131.1, 130.7, 130.3, 129.8, 128.6, 128.1, 127.7, 126.3, 124.6, 122.3, 112.2, 80.6, 76.9, 71.3, 56.0, 54.5, 53.1, 46.4, 42.8, 42.7, 42.0, 39.4, 36.4, 35.8, 35.2, 28.2, 24.5, 22.8, 22.6, 21.2, 17.1; IR ($CHCl_3$) 3427, 2967, 2935, 2874, 2841, 1747, 1680, 1526, 1504, 1484, 1464, 1442, 1393, 1369, 1302, 1281, 1259, 1151, 1067 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{45}H_{61}ClN_4O_{10}$ (M^+ − Boc + H) 753.3630, found 753.3621; Anal. Calcd for ($C_{45}H_{61}ClN_4O_{10}$): C, 63.33; H, 7.2; N, 6.56. Found: C, 63.38; H, 7.07; N, 6.84.

Pentanoic Acid, *N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-methylglycyl-(2*E*,5*S*,6*S*,7*R*,8*S*)-8-[4-(aminomethyl)phenyl]-8-chloro-5,7-dihydroxy-6-methyl-2-octenoyl-3-chloro-*O*-methyl-D-tyrosyl-2,2-dimethyl-β-alanyl-2-hydroxy-4-methyl-, (5 → 2^5)-Lactone, (2*S*)- (45). Amide **44** (0.34 g, 0.398 mmol) was epoxidized with mCPBA (0.072 g, 0.42 mmol) in CH_2Cl_2 (1.2 mL) according to the previously described procedure to give the β and α epoxides in a 2:1 ratio. The resulting crude mixture of epoxides (0.3 g, 0.345 mmol) was dissolved in $CHCl_3$ (6.0 mL) and cooled to −60 °C. TMSCl (0.22 mL, 1.73 mmol) was added, and the solution was stirred between −50 °C and −20 °C for 2 h. More TMSCl (0.44 mL, 0.173 mmol) was added, and the solution was allowed to warm to room temperature. The solution was concentrated in vacuo, and the resulting crude product was purified twice by column chromatography (70−80% EtOAc/hexanes) and twice by radial PLC (silica gel, 2−5% MeOH/CH_2Cl_2) to give the anti chlorohydrin **45** (0.1 g) in 48% yield as a white solid: $[\alpha]^{20}_D$ +46.9 (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.34 (d, 2 H, *J* = 7.9 Hz), 7.29−7.26 (d, 2 H, *J* = 8.3 Hz), 7.21 (s, 2 H), 7.08−7.05 (d, 1 H, *J* = 8.3 Hz), 6.86−6.83 (d, 1 H, *J* = 8.5 Hz), 6.8−6.7 (m, 1 H), 6.5−6.2 (bs, 1 H), 5.79−5.74 (d, 1 H, *J* = 15.2 Hz), 5.64−5.62 (d, 1 H, *J* = 7.7 Hz), 5.18−5.12 (t, 1 H, *J* = 9.1 Hz), 4.94−4.9 (dd, 1 H, *J* = 9.9, 3.5 Hz), 4.8−4.67 (m, 1 H), 4.66−4.63 (d, 1 H, *J* = 9.6 Hz), 4.47−4.45 (d, 2 H, *J* = 5.3 Hz), 4.02−3.98 (d, 1 H, *J* = 9.5 Hz), 3.89 (s, 2 H), 3.88 (s, 3 H), 3.41−3.34 (dd, 1 H, *J* = 13.6, 8.5 Hz), 3.2−3.0 (m, 3 H), 2.94 (s, 3 H), 2.69−2.68 (bdd, 1 H, *J* = 14.3, 2.1 Hz), 2.51−2.3 (m, 2 H), 1.8−1.6 (m, 3 H), 1.42 (s, 10 H), 1.22 (s, 3 H), 1.17 (s, 3 H), 1.03−1.01 (d, 3 H, *J* = 6.9 Hz), 0.94−0.9 (t, 6 H, *J* = 5.5 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.6, 170.4, 170.2, 165.2, 153.9, 142.4, 139.1, 130.8, 129.7, 128.3, 128.2, 127.9, 124.4, 122.4, 112.2, 80.7, 76.1, 73.9, 71.2, 61.8, 56.1, 54.4, 53.1, 46.4, 42.7, 39.6, 38.4, 36.3, 35.9, 35.2, 28.2, 24.8, 23.0, 22.9, 22.7, 21.5, 8.5; IR (KBr) 3419, 3317, 2964, 2932, 1755, 1670, 1538, 1504, 1473, 1392, 1368, 1301, 1258, 1151, 1066; HRMS (FAB, *m*/*z*) calcd for $C_{45}H_{62}Cl_2N_4O_{11}$ (M^+ + H) 905.3870, found 905.3876.

Pentanoic Acid, *N*-Methylglycyl-(2*E*,5*S*,6*S*,7*R*,8*S*)-8-[4-(aminomethyl)phenyl]-8-chloro-5,7-dihydroxy-6-methyl-2-octenoyl-3-chloro-*O*-methyl-D-tyrosyl-2,2-dimethyl-β-alanyl-2-hydroxy-4-methyl-, (5 → 2^5)-Lactone, Monohydrochloride, (2*S*)- (46). The hydrochloride salt **46** (0.041 g) of the BOC-protected amine **45** (0.045 g, 0.05 mmol) was prepared with 4 M HCl in 1,4-dioxane in quantitative yield according to the previously described procedure for the preparation of **28**: $[\alpha]^{20}_D$ +11.5 (*c* 0.47, MeOH); ^{1}H NMR (300 MHz, MeOD) δ 8.47−8.45 (d, 1 H, *J* = 7.7 Hz), 7.79−7.76 (d, 1 H, *J* = 8.9 Hz), 7.39−7.36 (d, 2 H, *J* = 8.1 Hz), 7.3−7.27 (d, 3 H, *J* = 9.0 Hz), 7.17−7.14 (d, 1 H, *J* = 8.5 Hz), 6.98−6.95 (d, 1 H, *J* = 8.5 Hz), 6.75−6.6 (m, 1 H), 5.94−5.89 (d, 1 H, *J* = 15.1 Hz), 5.2−5.0 (m, 2 H), 4.78−4.75 (d, 1 H, *J* = 9.4 Hz), 4.5−4.42 (m, 1 H), 4.41 (s, 2 H), 4.01−3.98 (d, 1 H, *J* = 9.5 Hz), 3.82 (s, 3 H), 3.8 (s, 2 H), 3.5−3.4 (m, 1 H), 3.19−3.13 (dd, 1 H, *J* = 14.4, 3.4 Hz), 3.11−3.06 (dd, 1 H, *J* = 13.2, 1.9 Hz), 2.8−2.6 (m, 2 H), 2.7 (s, 3 H), 2.5−2.2 (m, 2 H), 1.85−1.45 (m, 3 H), 1.3−1.2 (m, 1 H), 1.2 (s, 3 H), 1.15 (s, 3 H), 1.0−0.94 (q, 9 H, *J* = 11.3, 6.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.9, 173.7, 171.9, 168.3, 166.3, 155.4, 144.2, 140.5, 139.7, 132.2, 131.5, 129.7, 129.4, 128.8, 125.2, 123.3, 113.5, 77.2, 74.7, 72.6, 63.7, 57.6, 56.6, 50.7, 47.4, 44.1, 43.9, 41.1, 40.4, 37.8, 36.5, 33.7, 26.2, 23.6, 23.4, 22.1, 9.0; IR (KBr) 3410, 3058, 2961, 2933, 1752, 1721, 1675, 1539, 1504, 1463, 1440, 1282, 1259, 1196, 1154, 1127, 1066 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{40}H_{55}Cl_3N_4O_9$ (M^+ − Cl) 805.3346, found 805.3341; Anal. Calcd for ($C_{40}H_{55}Cl_3N_4O_9 \cdot 1.0\ H_2O$): C, 55.85; H, 6.68; N, 6.51. Found: C, 55.69; H, 6.91; N, 6.49.

Cyclo[2,2-dimethyl-β-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-8-[4-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]phenyl]-5-hydroxy-6-methyl-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (47). Styrene **47** (1.2 g) as a mixture of *E* and *Z* isomers was prepared from aldehyde **2** (1.0 g, 1.73 mmol) and 4-(ethyl-2-*tert*-butyldimethylsiloxy)-benzyl triphenylphosphonium bromide (**3h**) (1.23 g, 2.08 mmol) in 86% yield according to the procedure described above for styrene **29**.

The mixture of isomers was dissolved in toluene (50 mL) and heated to reflux in the presence of 1,1′-azobis(cyclohexanecarbonitrile) (VAZO) (0.040 g, 0.16 mmol) and thiophenol (0.061 mL, 0.59 mmol) for 3 h. After concentration the residue was purified by radial PLC (20−75% EtOAc/hexanes) to give the *E* isomer **47** (0.81 g, 68%) as a white foam: $[\alpha]^{20}_D$ +35.6 (*c* 0.56, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.12 (m, 6 H), 7.07−7.04 (d, 1 H, *J* = 8.5 Hz), 6.85−6.82 (d, 1 H, *J* = 8.4 Hz), 6.82−6.70 (m, 1 H), 6.40−6.35 (d, 1 H, *J* = 15.8 Hz), 6.0−5.92 (dd, 1 H, *J* = 15.4, 8.7 Hz), 5.77−5.72 (d, 1 H, *J* = 15.2 Hz), 5.46−5.43 (d, 1 H, *J* = 7.7 Hz), 5.07−5.02 (m, 1 H), 4.86−4.83 (m, 1 H), 4.82−4.74 (m, 1 H), 3.88 (s, 3 H), 3.78−3.74 (t, 2 H, *J* = 7.1 Hz), 3.44−3.37 (dd, 1 H, *J* = 12.5, 8.6 Hz), 3.15−3.08 (m, 3 H), 2.81−2.77 (t, 2 H, *J* = 7.1 Hz), 2.57−2.52 (m, 2 H), 2.43−2.35 (m, 1 H), 1.74−1.56 (m, 2 H), 1.38−1.23 (m, 1 H), 1.22 (s, 3 H), 1.16 (s, 3 H), 1.13−1.11 (d, 3 H, *J* = 6.8 Hz), 0.88 (s, 9 H), 0.76−0.72 (t, 6 H, *J* = 5.6 Hz), 0.0 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.9, 170.5, 170.3, 165.1, 154.0, 142.2, 138.6, 134.6, 131.5, 130.9, 129.6, 129.4, 129.3, 128.2, 126.0, 125.3, 124.5, 122.5, 112.3, 92.9, 77.0, 71.4, 64.4, 56.1, 54.3, 46.5, 42.7, 42.2, 39.4, 39.2, 36.5, 35.3, 25.9, 24.5, 22.8, 22.7, 22.6, 21.2, 17.2, −5.44; IR ($CHCl_3$) 3423, 2959, 2931, 2858, 1747, 1712, 1681, 1605, 1527, 1503, 1485, 1442, 1370, 1339, 1303, 1281, 1258, 1194, 1151, 1095, 1067, 1025, 1007, 838 cm^{-1}; Anal. Calcd for ($C_{44}H_{63}ClN_2O_8Si$): C, 65.12; H, 7.82; N, 3.45. Found: C, 65.34; H, 7.79; N, 3.5.

Cyclo[2,2-dimethyl-β-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-6-[(2*R*,3*R*)-3-[4-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]phenyl]oxiranyl]-5-hydroxy-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (48). Epoxide **48** was prepared from the styrene **47** (2.77 g, 3.41 mmol) and mCPBA (0.63 mL, 3.65 mmol) in CH_2Cl_2 (11 mL) as was previously described. Purification of 0.95 g of the crude mixture by reverse phase HPLC with (45:55) CH_3CN:H_2O gave 0.42 g of the β epoxide as a white solid: $[\alpha]^{20}_D$ +21.7 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 7.2−7.1 (m, 6 H), 7.06−7.03 (d, 1 H, *J* = 8.16 Hz), 6.85−6.82 (d, 1 H, *J* = 8.4 Hz), 6.82−6.7 (m, 1 H), 5.73−5.68 (d, 1 H, *J* = 15.0 Hz), 5.46−5.43 (d, 1 H, *J* = 7.8 Hz), 5.22−5.17 (m, 1 H), 4.85−4.7 (m, 2 H), 3.87 (s, 3 H), 3.82−3.77 (t, 2 H, *J* = 7.0 Hz), 3.65 (s, 1 H), 3.45−3.38 (dd, 1 H, *J* = 13.6, 8.54 Hz), 3.15−3.05 (m, 3 H), 2.91−2.89 (d, 1 H, *J* = 7.4 Hz), 2.85−2.80 (t, 2 H, *J* = 7.0 Hz), 2.6−2.35 (m, 2 H), 1.8−1.6 (m, 3 H), 1.4−1.25 (m, 1 H), 1.22 (s, 3 H), 1.15 (s, 3 H), 1.15−1.13 (d, 3 H, *J* = 8.6 Hz), 0.87 (s, 9 H), 0.85−0.81 (t, 6 H, *J* = 6.4 Hz), 0.0 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ

177.8, 170.4, 170.3, 164.9, 154.0, 141.7, 139.6, 137.2, 134.4, 130.8, 129.5, 129.4, 128.1, 125.4, 124.6, 122.4, 112.3, 75.9, 71.0, 64.2, 62.9, 58.9, 56.0, 54.4, 46.4, 42.7, 40.5, 39.3, 39.2, 36.8, 35.2, 25.8, 24.5, 22.8, 22.7, 22.6, 21.1, 18.2, 13.4, −5.4; IR ($CHCl_3$) 3425, 2959, 2931, 1751, 1712, 1683, 1527, 1503, 1485, 1463, 1258, 1189, 1151, 1067, 836 cm^{-1}. Anal. Calcd for ($C_{44}H_{63}ClN_2O_9Si$): C, 63.86; H, 7.67; N, 3.39. Found: C, 63.77; H, 7.48; N, 3.47.

Pentanoic Acid, 3-Chloro-*N*-[(2*E*,5*S*,6*S*)-5-hydroxy-6-[(2*R*,3*R*)-3-[4-(2-hydroxyethyl)phenyl]oxiranyl]-1-oxo-2-heptenyl]-*O*-methyl-D-tyrosyl-2,2-dimethyl-*β*-alanyl-2-hydroxy-4-methyl-, (3 → 1[5])-Lactone, (2*S*)- (49). Alcohol **49** was prepared from the silyl ether **48** (0.37 g, 0.45 mmol) and TBAF (0.45 mL, 0.45 mmol) in THF (2.5 mL) as was previously described. Purification by radial PLC (silica gel, 70−100% EtOAc/hexanes) provided the desired alcohol **49** (0.3 g), in 94% yield as a white solid: $[\alpha]^{20}_D$ +32.5 (*c* 0.58, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 7.26−7.18 (m, 6 H), 7.06−7.02 (dd, 1 H, *J* = 8.3, 1.9 Hz), 6.85−6.82 (d, 1 H, *J* = 8.4 Hz), 6.77−6.72 (m, 1 H), 5.72−5.67 (d, 1 H, *J* = 15.5 Hz), 5.54−5.52 (d, 1 H, *J* = 7.8 Hz), 5.22−5.17 (m, 1 H), 4.84−4.8 (dd, 1 H, *J* = 10.2, 3.5 Hz), 4.78−4.7 (m, 1 H), 3.91−3.84 (m, 5 H), 3.66−3.65 (d, 1 H, *J* = 1.6 Hz), 3.45−3.38 (dd, 1 H, *J* = 13.4, 8.7 Hz), 3.12−3.05 (m, 3 H), 2.92−2.86 (m, 3 H), 2.59−2.41 (m, 2 H), 1.8−1.63 (m, 3 H), 1.49−1.45 (t, 1 H, *J* = 5.8 Hz), 1.38−1.23 (m, 1 H), 1.22 (s, 3 H), 1.16 (s, 3 H), 1.16−1.13 (d, 3 H, *J* = 8.2 Hz), 0.86−0.82 (t, 6 H, *J* = 6.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 177.8, 170.4, 170.35, 165.0, 153.9, 141.5, 139.1, 137.4, 134.8, 130.7, 129.7, 129.3, 128.1, 125.7, 124.6, 122.3, 112.2, 75.9, 71.1, 63.3, 62.9, 58.9, 56.1, 54.4, 46.4, 42.7, 40.6, 39.3, 38.8, 36.9, 35.2, 24.5, 22.8, 22.6, 21.2, 13.6; IR ($CHCl_3$) 3425, 2964, 2936, 1751, 1712, 1683, 1527, 1503, 1485, 1442, 1303, 1281, 1259, 1151, 1076, 1025, 1006, 908 cm^{-1}; MS (FD, *m*/*z*) calcd for $C_{38}H_{49}ClN_2O_9$ (M^+ + H) 713, found 713.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-5-hydroxy-6-[(2*R*,3*R*)-3-[4-(2-oxoethyl)phenyl]oxiranyl]-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (50). Pyridine (0.06 mL, 0.76 mmol) and the Dess−Martin reagent (0.161 g, 0.379 mmol) were added to a 0 °C solution of the alcohol **49** (0.135 g, 0.189 mmol) in CH_2Cl_2 (4.5 mL). The mixture was stirred at 0 °C for 30 min, at room temperature for 20 min, then was filtered through Celite with EtOAc and was finally concentrated in vacuo. Quick purification of the crude product by radial PLC (silica gel, 80−100% EtOAc/CH_2Cl_2) provided the desired aldehyde **50** (0.08 g), in 59% yield as a white solid: ^1H NMR (300 MHz, $CDCl_3$) 9.77−9.76 (t, 1 H, *J* = 2.0 Hz), 7.3−7.2 (m, 6 H), 7.06−7.02 (dd, 1 H, *J* = 8.3, 2.0 Hz), 6.85−6.82 (d, 1 H, *J* = 8.4 Hz), 6.81−6.7 (m, 1 H), 5.74−5.68 (d, 1 H, *J* = 15.3 Hz), 5.51−5.48 (d, 1 H, *J* = 7.8 Hz), 5.22−5.17 (m, 1 H), 4.85−4.81 (dd, 1 H, *J* = 10.3, 3.6 Hz), 4.77−4.71 (m, 1 H), 3.87 (s, 3 H), 3.72−3.71 (d, 2 H, *J* = 2.0 Hz), 3.69−3.68 (d, 1 H, *J* = 1.5 Hz), 3.45−3.38 (dd, 1 H, *J* = 13.5, 8.7 Hz), 3.17−3.0 (m, 3 H), 2.92−2.89 (dd, 1 H, *J* = 7.6, 1.8 Hz), 2.6−2.4 (m, 2 H), 1.8−1.6 (m, 3 H), 1.4−1.3 (m, 1 H), 1.22 (s, 3 H), 1.16 (s, 3 H), 1.16−1.13 (d, 3 H, *J* = 8.3 Hz), 0.86−0.82 (t, 6 H, *J* = 6.3 Hz).

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-6-[(2*R*,3*R*)-3-[4-(carboxymethyl)phenyl]oxiranyl]-5-hydroxy-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (51). To a 0 °C solution of aldehyde **50** (0.08 g, 0.112 mmol) in THF (3.2 mL) and H_2O (3.2 mL) were added 2-methyl-2-butene (3.2 mL), $NaClO_2$ (0.081 g, 0.896 mmol), and $NaH_2PO_4 \cdot H_2O$ (0.139 g, 1.0 mmol). The mixture was allowed to warm to room temperature and was stirred vigorously for 5 h. The solution was diluted with CH_2Cl_2 (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified twice by radial PLC (silica gel, 5−25% MeOH/CH_2Cl_2) to give 0.03 g of the carboxylic acid **51** in 37% yield as a white solid: $[\alpha]^{20}_D$ +24.5 (*c* 0.33, MeOH); ^1H NMR (300 MHz, CD_3OD) *δ* 7.75−7.71 (dd, 1 H, *J* = 10.3, 1.9 Hz), 7.31−7.2 (m, 5 H), 7.16−7.13 (dd, 1 H, *J* = 8.4, 1.9 Hz), 6.97−6.95 (d, 1 H, *J* = 8.4 Hz), 6.8−6.6 (m, 1 H), 5.87−5.81 (d, 1 H, *J* = 15.3 Hz), 5.19−5.14 (dd, 1 H, *J* = 11.0, 5.0 Hz), 4.94−4.9 (dd, 1 H, *J* = 9.8, 3.2 Hz), 4.48−4.43 (dd, 1 H, *J* = 11.5, 3.5 Hz), 3.8 (s, 3 H), 3.77 (s, 1 H), 3.53 (s, 2 H), 3.5−3.4 (m, 1 H), 3.17−3.11 (dd, 1 H, *J* = 14.3, 3.5 Hz), 3.05−3.0 (d, 1 H, *J* = 13.6 Hz), 2.95−2.92 (dd, 1 H, *J* = 7.7, 1.7 Hz), 2.8−2.6 (m, 2 H), 2.5−2.3 (m, 1 H), 1.8−1.6 (m, 3 H), 1.4−1.2 (m, 1 H), 1.17 (s, 3 H), 1.13 (s, 3 H), 1.13−1.1 (d, 3 H, *J* = 9.2 Hz), 0.83−0.81 (d, 6 H, *J* = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 178.8, 173.7, 172.0, 168.2, 155.4, 143.4, 138.1, 136.7, 132.2, 131.4, 130.8, 129.3, 126.8, 125.4, 123.3, 113.5, 77.7, 72.4, 64.4, 60.0, 57.5, 56.6, 47.4, 44.1, 41.7, 40.7, 38.5, 36.4, 25.9, 23.4, 23.3, 21.6, 14.0; IR (KBr) 3417, 2961, 2934, 2874, 1750, 1721, 1674, 1561, 1504, 1464, 1441, 1300, 1259, 1194, 1151, 1066 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{38}H_{47}ClN_2O_{10}$ (M^+ + H) 727.2997, found 727.3005.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*R*,7*E*)-5-hydroxy-6-methyl-8-(2-methyl-5-thiazolyl)-2,7-octadienoyl-3-chloro-*O*-methyl-D-tyrosyl] (52). To a mixture of [(2-methyl-4-thiazolyl)methyl]-triphenylphosphonium chloride (**3i**) (0.496 g, 1.2 mmol) in THF (10 mL) at −78 °C was added dropwise a 1.6 M solution of *n*-butyllithium (0.8 mL, 1.2 mmol). The mixture was warmed slowly to room temperature and stirred for an additional 45 min. To aldehyde **2** (0.5 g, 0.865 mmol) in THF (15 mL) at −78 °C was added dropwise the orange ylide solution via a double-tipped needle. The resulting mixture was stirred at −78 °C for 2 h and at room temperature for 1.5 h. Saturated aq NH_4Cl (30 mL) was added along with ethyl acetate (30 mL), the layers were separated, and the aqueous one was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (2 × 20 mL) and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow residue was purified by column chromatography (silica gel, 50−70−80% EtOAc/hexanes) to give 0.4 g of the desired styrene contaminated by triphenylphosphine oxide. The triphenylphosphine oxide was easily removed by reverse phase HPLC with CH_3CN:H_2O (50:50) to give 0.2 g (34%) of pure styrene **52** as a white solid: $[\alpha]^{20}_D$ +16.7 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.3−7.2 (m, 1 H), 7.18−7.17 (d, 1 H, *J* = 1.7 Hz), 7.06−7.03 (dd, 1 H, *J* = 8.5, 1.8 Hz), 6.83 (s, 1 H), 6.83−6.8 (d, 1 H, *J* = 9.0 Hz), 6.8−6.67 (m, 1 H), 6.37−6.35 (m, 2 H), 5.85−5.82 (d, 1 H, *J* = 7.9 Hz), 5.76−5.71 (d, 1 H, *J* = 15.1 Hz), 5.05−5.0 (dd, 1 H, *J* = 9.0, 6.0 Hz), 4.86−4.82 (dd, 1 H, *J* = 10.2, 3.6 Hz), 4.77−4.68 (m, 1 H), 3.85 (s, 3 H), 3.44−3.37 (dd, 1 H, *J* = 13.4, 8.6 Hz), 3.2−3.0 (m, 3 H), 2.68 (s, 3 H), 2.6−2.3 (m, 3 H), 1.8−1.6 (m, 2 H), 1.43−1.3 (m, 1 H), 1.2 (s, 3 H), 1.14 (s, 3 H), 1.12−1.1 (d, 3 H, *J* = 6.9 Hz), 0.79−0.76 (m, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 177.8, 170.5, 166.0, 165.2, 153.9, 153.0, 142.1, 136.7, 132.7, 130.8, 129.8, 128.1, 124.6, 124.4, 122.3, 114.1, 112.2, 76.9, 71.4, 56.0, 54.4, 46.4, 42.7, 41.9, 39.3, 36.5, 35.3, 24.5, 22.8, 22.7, 22.6, 21.2, 19.2, 17.1; IR ($CHCl_3$) 3423, 3027, 3008, 2965, 2935, 2874, 1747, 1712, 1681, 1652, 1604, 1528, 1504, 1485, 1259, 1181, 1152, 1067 cm^{-1}. Anal. Calcd for ($C_{34}H_{44}ClN_3O_7S$): C, 60.57; H, 6.58; N, 6.23. Found: C, 60.4; H, 6.62; N, 6.17.

Cyclo[2,2-dimethyl-*β*-alanyl-(2*S*)-2-hydroxy-4-methylpentanoyl-(2*E*,5*S*,6*S*)-5-hydroxy-6-[(2*R*,3*R*)-3-(2-methyl-5-thiazolyl)oxiranyl]-2-heptenoyl-3-chloro-*O*-methyl-D-tyrosyl] (53). To the styrene **52** (0.25 g, 0.37 mmol) were added acetone (15 mL), H_2O (6 mL), CH_2Cl_2 (6 mL) and solid $NaHCO_3$ (1.0 g, 11.9 mmol), and the mixture was cooled to 0 °C. A solution of Oxone (0.92 g, 1.5 mmol) in H_2O (8 mL) was prepared and added (2 mL) to the cold styrene mixture. Following 30 min of vigorous stirring at 0 °C, an additional 2 mL of Oxone solution was added, followed by another 2.0 mL, with stirring for another 30 min, for a total of 6 mL of Oxone solution. The reaction progress was monitored by reverse phase HPLC and was found to be complete after 2.0 h of stirring. While still at 0 °C the reaction was quenched with saturated aqueous $NaHCO_3$ (40 mL) and CH_2Cl_2 (40 mL). The layers were separated, and the organic layer was washed with aq 10% Na_2SO_3 (40 mL), followed by saturated aq $NaHCO_3$ (40 mL), then brine, and finally was dried over Na_2SO_4, filtered, and concentrated in vacuo. The mixture of *β* and α

epoxides (54:46) was separated by reverse phase HPLC with (50:50) CH_3CN:H_2O to provide 0.09 g of β epoxide **53** as a white solid in 35% yield: $[\alpha]^{20}_D$ +26.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19−7.18 (d, 2 H, J = 1.8 Hz), 7.1 (s, 1 H), 7.06−7.03 (dd, 1 H, J = 8.5, 1.9 Hz), 6.85−6.82 (d, 1 H, J = 8.4 Hz), 6.82−6.7 (m, 1 H), 5.76−5.71 (d, 1 H, J = 15.2 Hz), 5.49−5.47 (d, 1 H, J = 7.8 Hz), 5.23−5.18 (m, 1 H), 4.88−4.84 (dd, 1 H, J = 10.3, 3.6 Hz), 4.8−4.7 (m, 1 H), 3.88 (s, 3 H), 3.79 (d, 1 H, J = 0.93 Hz), 3.45−3.38 (dd, 1 H, J = 13.4, 8.6 Hz), 3.35−3.32 (d, 1 H, J = 7.2 Hz), 3.2−3.0 (m, 3 H), 2.7 (s, 3 H), 2.6−2.4 (m, 2 H), 1.8−1.6 (m, 3 H), 1.4−1.3 (m, 1 H), 1.23 (s, 3 H), 1.16 (s, 3 H), 1.14−1.12 (d, 3 H, J = 6.8 Hz), 0.89−0.87 (d, 3 H, J = 6.5 Hz), 0.86−0.84 (d, 3 H, J = 6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.9, 170.33, 170.3, 166.9, 165.0, 154.0, 151.9, 141.8, 130.8, 129.5, 128.2, 124.5, 122.4, 116.4, 112.3, 75.8, 71.1, 61.3, 56.1, 55.2, 54.3, 46.4, 42.7, 40.3, 39.3, 36.6, 35.2, 24.5, 22.85, 22.8, 22.6, 21.2, 19.1, 13.3; IR ($CHCl_3$) 3425, 3007, 2964, 2936, 2874, 2841, 1751, 1711, 1682, 1604, 1528, 1503, 1485, 1464, 1303, 1259, 1185, 1152, 1067 cm^{-1}; HRMS (FAB, *m*/*z*) calcd for $C_{34}H_{45}ClN_3O_8S$ (M^+ + H) 690.2616, found 690.2621. Anal. Calcd for ($C_{34}H_{44}ClN_3O_8S$): C, 59.16; H, 6.42; N, 6.09. Found: C, 59.11; H, 6.34; N, 6.27.

Note Added after ASAP Posting

The version of this paper posted May 22, 2003, was missing an author name in the byline. This name is included in the new version posted June 3, 2003.

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