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Synthetic Studies on Stevastelins. 1. Total Synthesis of Stevastelins B and B3

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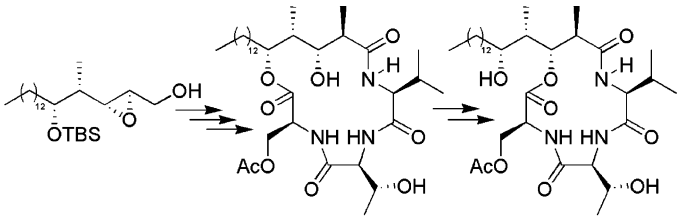

The synthesis of stevastelin B3 (**2**) and B (**5**) are described. In a first approach, epoxy cyclodepsipeptide **8** was considered as a promising candidate for the synthesis of the [15]-membered ring members of the stevastelins; however, the oxirane ring opening, required for the completion of the natural stevastelin synthesis, failed. Thus, we synthesized stevastelin B (**5**), carrying out the oxirane ring opening earlier in the synthesis and following a synthetic scheme capable of delivering analogues. On the other hand, a translactonization reaction of the [15]-membered ring derivative **59** led to the total synthesis of the natural [13]-membered ring component of the stevastelins family, stevastelin B3 (**2**).

Introduction

The isolation of the stevastelins (**1**−**5**) from culture broths of *Penicillium* sp. NK374186,[1] their structural elucidation,[2] and recognition as a new class of immunosuppressant agents[3] with intriguing biological properties prompted us to engage in a research program directed toward the total synthesis of these naturally occurring cyclic depsipeptides.[4] Biological investigations have revealed[5] that the action displayed by the stevastelins against OKT3-stimulated human T-cell proliferation is due to their inhibition of IL-2 and IL-6 gene expressions in a way similar to that of cyclosporin A,[6] FK506,[7] and sanglifehrin A.[8] The disclosure that the stevastelins do not inhibit the phosphatase activity of calcineurin suggests a novel mechanism of action for these cyclic depsipeptides, different from the above-mentioned immunosuppressants. These interesting biological findings demand further investigations to gain insights into the biology of these natural cyclic depsipeptides. To this aim, it was deemed of importance to develop strategies not only for the total synthesis of these natural substances but also of designed stevastelins for structure−activity

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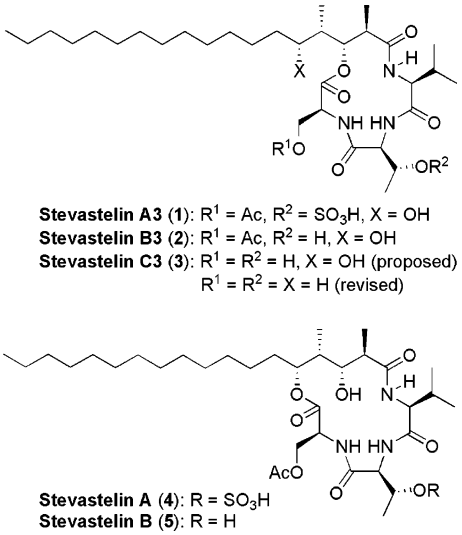
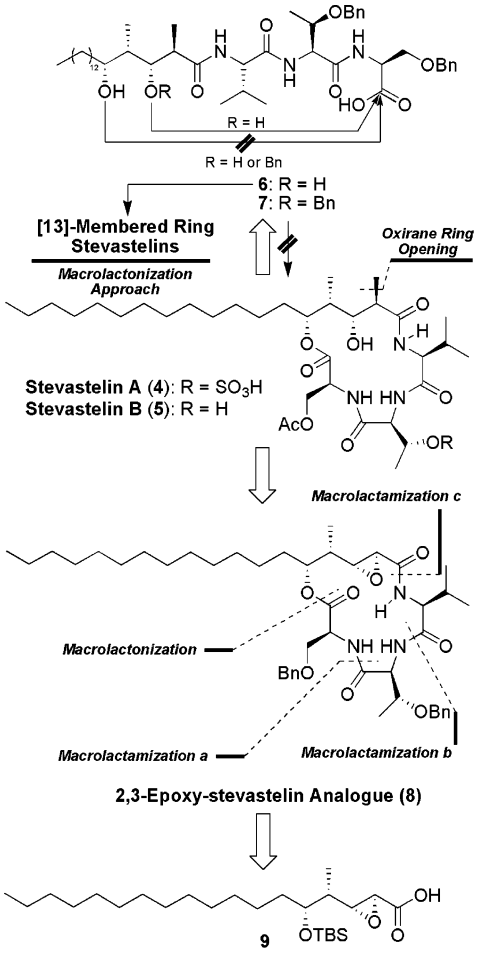


FIGURE 1. Structures of stevastelins A3 (**1**), B3 (**2**), C3 (**3**), A (**4**), and B (**5**).

relationship studies. A number of recent publications have reported upon the total syntheses of stevastelin B (**5**),[9,10] stevastelin B3 (**2**),[11] and the recently structurally revised stevastelin C3 (**3**),[11a] together with different synthetic approaches[12] and various analogue syntheses,[5] indicating the great interest for this class of products in the scientific community.

Structurally, the stevastelins contain two main frameworks: (a) a stearic acid unit with a typical tetrade fragment derived from the polypropionate biosynthetic pathway and (b) a peptidic chain comprised of L-serine, L-threonine, and L-valine amino acids residues, connected by an ester and amide linkages to constitute two families of [13]- and [15]-membered ring components (Figure 1). Our preliminary synthetic studies utilizing a macrolactonization-based strategy[13] led to the synthesis of the [13]-membered ring containing stevastelin C3 (**3**) from the acyclic precursor **6**; unfortunately, preparation of the [15]-membered ring compound was found to be impossible using this strategy. Similarly, the 3-*O*-benzyl protected acyclic derivative **7** proved to be an unsuitable precursor for the synthesis of the coveted [15]-membered cyclic depsipetides.[12] As an alternative that would permit access to the targeted [15]-membered ring stevastelins, we devised the epoxy-peptide **8** as a suitable precursor for the macrocyclic depsipeptides, by which an oxirane ring opening reaction would provide the corresponding natural stevastelin. In addition, the precursor offers the opportunity of incorporating structural modifications for the preparation of 2-C-alkyl stevastelin analogues by opening of the oxirane with different nucleophiles. Toward this aim, the synthesis of epoxy peptide **8** could be efficiently achieved through a macrocyclization process,

SCHEME 1. Synthetic Approaches to [13]- and [15]-Membered Ring Stevastelins and Retrosynthetic Analysis of Stevastelin B (5)



via macrolactamizations *a*, *b*, or *c* or by a macrolactonization reaction. This extensive macrocyclizations study should require the preparation of the corresponding acyclic epoxy amino acids,[14] representing epoxy acid **9** as a common intermediate for the delivery of all of these acyclic precursors (Scheme 1).

Results and Discussion

Toward the Synthesis of Stevastelin B (5) through the 2,3-Epoxy Analogue 8. The synthesis of 2,3-epoxy-stevastelin **8** commenced with the preparation of the subtarget compound **9** as described in Scheme 2. Accordingly, reaction of tetradecanal **11** with the boron enolate of oxazolidinone **10**[15] furnished compound **12** in an 85% yield. The conversion of this compound to the diol **13** was achieved by treatment with lithium borohydride[16] and, after a sequence of selective protection and deprotection

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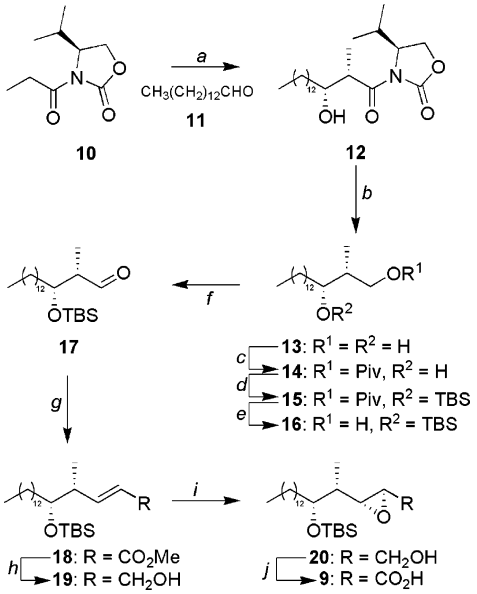
(16) Smith, A. B., III; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249−1252.

SCHEME 2. Synthesis of the Stearic Acid Derivative (9)[a]



[a] Reagents and Conditions: (a) 1.1 equiv of *n*-Bu_2BOTf, 1.1 equiv of Et_3N, CH_2Cl_2, 0 °C, 0.5 h, then 1.1 equiv of **12**, −78 °C, 12 h, 85%. (b) 8.8 equiv of $LiBH_4$, THF, −20 → 0 °C, 2 h, 92%. (c) 1.3 equiv of PivCl, CH_2Cl_2, pyridine, −20 °C, 0.5 h, 94%. (d) 1.5 equiv of TBSCl, 2.0 equiv of imidazole, DMF, 25 °C, 12 h, 96%. (e) 2.2 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 0.5 h, 98%. (f) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 6.0 equiv of Et_3N, CH_2Cl_2, −78 °C, 0.5 h, 94%. (g) 2.0 equiv of Ph_3PCHCO_2Me, C_6H_6, 80 °C, 12 h, 92%. (h) 2.2 equiv of DIBAL-H, CH_2Cl_2, −78 °C, 0.5 h, 98%. (i) 0.4 equiv of D-(−)-DET, 0.4 equiv of $Ti(Oi\text{-}Pr)_4$, 3.6 equiv of TBHP, CH_2Cl_2, −20 °C, 24 h, 91% (de 84%). (j) 0.01 equiv of $RuCl_3$, 4.2 equiv of $NaIO_4$, $CH_3CN/CCl_4/H_2O$ (1:1:1), 0 °C, 0.5 h, 64%.

steps, was transformed into the alcohol **16**. Alcohol **16** was then subjected to a Swern oxidation,[17] and the resulting aldehyde **17** was reacted with methyl (triphenylphosphoranylidene)acetate to give the *E* alkene **18** in a 92% yield. The DIBAL-H reduction of **18** afforded allylic alcohol **19**, which was subjected to a Sharpless asymmetric epoxidation,[18] using (−)-DET, to obtain the epoxy alcohol **20** in very good yield (91%), although in a modest 85% diastereomeric excess.[19] The exposure of epoxy alcohol **20** to the action of catalytic amounts of ruthenium trichloride and sodium periodate as cooxidant[20] furnished epoxy acid **9** in a 64% yield.

The macrocyclization studies directed toward the synthesis of the key cyclic precursor of stevastelins, the epoxy analogue **8**, required the coupling of epoxy acid **9** with different amino acids (**21**−**23**) and peptide derivatives (**24**−**26**), depicted in Figure 2, which were either commercially available[21] or prepared by conventional peptide

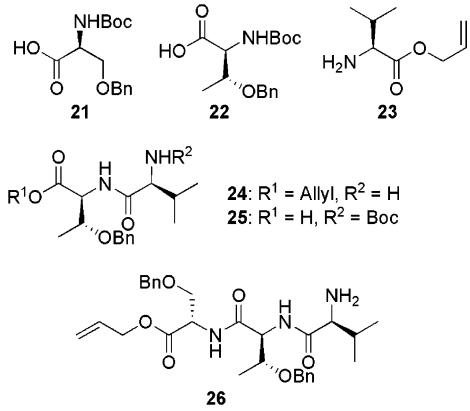


FIGURE 2. Structures of amino acids and peptidic derivatives.

chemistry.[22] Thus, the precursor for the macrolactonization reaction, epoxy peptide **29**, was efficiently prepared by coupling of acid **9** with tripeptide **26** by the action of EDCI, to obtain epoxy peptide **27** in a 74% yield. The transformation of the silyl ether **27** to the alcohol **28**, by the action of HF·pyridine, was followed by the allyl ester cleavage under the influence of $Pd[PPh_3]_4$ and morpholine[23] to obtain the acyclic precursor **29**. In a similar way, the coupling of **9** with dipeptide **24** was undertaken under identical conditions as for **27**, to furnish epoxy peptide **30** in a 70% yield, which was subjected to the action of HF·pyridine to yield alcohol **31**. The coupling of **31** with the L-serine derivative **21** was accomplished, according to the Yamaguchi protocol,[24] to afford acyclic depsipeptide **32** in an 86% yield and with no detection of appreciable epimerization as determined by NMR analysis. The elaboration of this compound to the second acyclic precursor **34** was carried out in two steps, involving allyl ester and Boc cleavages by the action of $Pd[PPh_3]_4$ and TFA, respectively, (Scheme 3).

The preparation of the acyclic precursor **41** was performed according to a synthetic course similar to that for the preparation of **34**, with the introduction of the L-valine derivative **23**, with the formation of epoxy amide **35** in a 66% yield, followed by the linkage of the L-serine residue via esterification of **36** with **21** by the Yamaguchi methodology, to obtain ester **37** (90%), and subsequent coupling of the resulting amine **38**, obtained by Boc cleavage of **37**, with the L-threonine derivative **22** to obtain epoxy peptide **39** in a poor 41% yield, which, finally was prepared for the macrocyclization reaction via a similar sequence of cleavage reactions as described before for **34**, to obtain epoxy peptide **41**. The synthesis of the fourth precursor, epoxy peptide **48**, proceeded in a slightly different synthetic sequence, requiring the previous formation of the allyl ester **42**, from epoxy acid **9**, and subsequent TBAF treatment to obtain alcohol **43**.

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(19) The low degree of diastereoselectivity found on this asymmetric epoxidation was attributed to the fact that the pairing of substrate **19** with (−)-DET constitutes a mismatched case due to the opposite stereofacial preference that both components display. See : Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−30.

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(21) Amino acid derivatives **21** and **22** were purchased from Nova-Biochem.

(22) Amino acid derivative **23** and peptides **24**−**26** were prepared according to conventional chemistry of peptides, following general procedures as described by: Jones, J. In *Amino Acid and Peptide Synthesis*; Oxford Chemistry Primers Series 7; Oxford University Press: New York, 1992.

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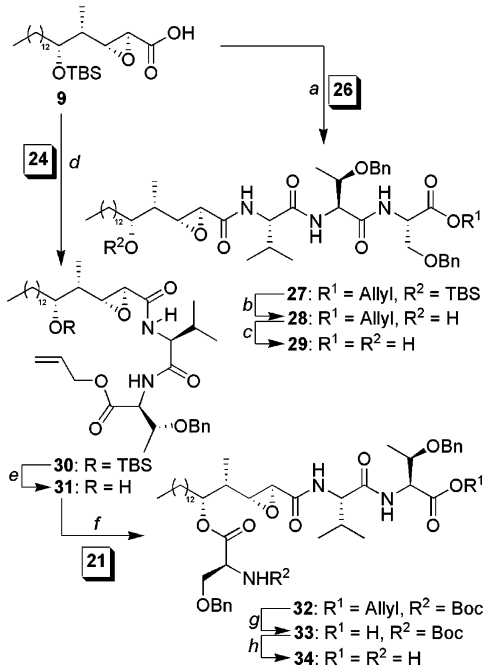
(24) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

SCHEME 3. Synthesis of Acyclic Precursors of Epoxy-Stevastelins 29 and 34[a]

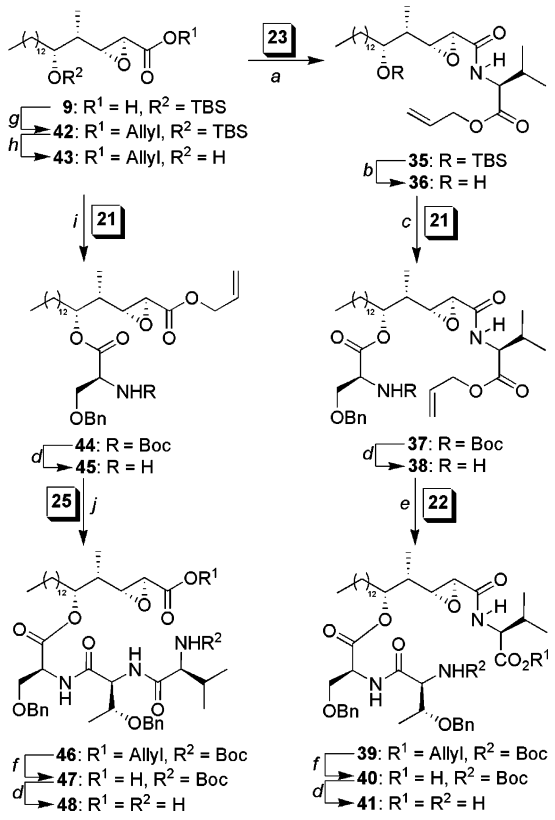


[a] Reagents and Conditions: (a) 1.0 equiv of **9**, 1.0 equiv of HOBt, 1.4 equiv of EDCI, 1.6 equiv of **26**, DCM, 25 °C, 0.5 h, 74%. (b) HF·pyridine (70% w/v), THF, 25 °C, 12 h, 96%. (c) 0.15 equiv of $Pd[PPh_3]_4$, 10.0 equiv of morpholine, THF, 25 °C, 1 h, 89%. (d) 1.0 equiv of **9**, 1.1 equiv of HOBt, 1.4 equiv of EDCI, 1.2 equiv of **24**, DCM, 25 °C, 1 h, 70%. (e) HF·pyridine (70% w/v), THF, 25 °C, 8 h, 95%. (f) 1.5 equiv of **21**, 3.0 equiv of TEA, 2.3 equiv of 2,4,6-$Cl_3C_6H_2COCl$, THF, 0 °C, 2 h, then added over 1.0 equiv of **31**, 1.3 equiv of 4-DMAP, toluene, 25 °C, 15 min, 86%. (g) 0.1 equiv of $Pd[PPh_3]_4$, 5.0 equiv of morpholine, THF, 25 °C, 0.5 h, 94%. (h) TFA (excess), DCM, 25 °C, 0.5 h, 100%.

The coupling with the L-serine derivative **21** was accomplished in a similar manner as for **32** to furnish epoxy peptide **44** in an 85% yield, which was reacted with TFA to yield amine **45**, prior to the coupling with dipeptide **25** that afforded epoxy peptide **46** in a moderate 60% yield. The two final deprotection steps were conducted under similar conditions as those described in previous schemes for the other acyclic precursors, to obtain precursor **48** (Scheme 4).

With the delivery of acyclic epoxy amino acids **29**, **34**, **41**, and **48** from the previous synthetic schemes, we initiated the macrocyclization studies to determine which of these compounds represented the most appropriate precursor for the coveted epoxy cyclodepsipeptide **8**. With the exception of epoxy peptide **29**, which was subjected to macrolactonization reaction conditions, following Yamaguchi methodology,[25] the other precursors (**34**, **41**, and **48**) were exposed, under high dilution conditions, to a variety of coupling reagents,[26] including diethyl cyanophosphonate (DEPC), diphenyl phosphoryl azide (DPPA),

SCHEME 4. Synthesis of Acyclic Precursors of Epoxy-Stevastelins 41 and 48[a]



[a] Reagents and Conditions: (a) 1.0 equiv of **9**, 1.1 equiv of HOBt, 1.4 equiv of EDCI, 1.1 equiv of **23**, DCM, 25 °C, 1.0 h, 66%. (b) HF·pyridine (70% w/v), THF, 25 °C, 7 h, 99%. (c) 1.4 equiv of **21**, 2.7 equiv of TEA, 2.2 equiv of 2,4,6-$Cl_3C_6H_2COCl$, THF, 0 °C, 2 h, then added over 1.0 equiv of **36**, 0.4 equiv of 4-DMAP, toluene, 25 °C, 0.5 h, 90%. (d) TFA (excess), DCM, 25 °C, 0.5 h, 100% for **38**, **41**, **45**, and **48**. (e) 1.0 equiv of **38**, 1.2 equiv of **22**, 1.3 equiv of HOBt, 1.7 equiv of EDCI, DCM, 25 °C, 0.5 h, 41%. (f) 0.1 equiv of $Pd[PPh_3]_4$, 5.0 equiv of morpholine, THF, 25 °C, 0.5 h, 95% for **40** and **47**. (g) 4.0 equiv of allylic alcohol, 1.5 equiv of EDCI, 0.1 equiv of 4-DMAP, DCM, 25 °C, 3 h, 75%. (h) HF·pyridine (70% w/v), THF, 25 °C, 12 h, 95%. (i) 1.5 equiv of **21**, 2.0 equiv of EDCI, 0.1 equiv of 4-DMAP, DCM, 25 °C, 40 min, 85%. (j) 1.6 equiv of **25**, 1.6 equiv of HOBt, 2.6 equiv of EDCI, DCM, 25 °C, 1 h, 60%.

O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate/1-hydroxybenzotriazole (HATU/HOBt), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate/HOBt (HBTU/HOBt), EDCI/HOBt, and pentafluorophenol/EDCI (PFP/EDCI), in different solvents (DCM, THF, DMF, MeCN). The results from these studies revealed that, whereas the macrolactonization did not work at all for compound **29**, resulting in a complex mixture of decomposition products, the macrolactamizations provided more positive results, especially with the epoxy peptide **34**, which afforded the best yields for the desired macrocycle **8** when it was treated with DPPA[27] or DEPC[28] as coupling reagents and DMF as solvent. The epoxy peptide that was obtained

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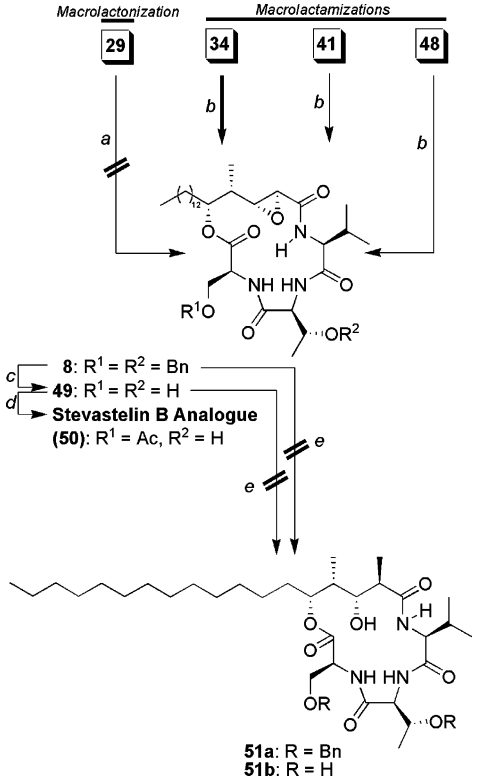
SCHEME 5. Synthesis of Epoxy-Stevastelin B Analogue 50[a]



[a] Reagents and Conditions: (a) 2.7 equiv of TEA, 2.2 equiv of 2,4,6-$Cl_3C_6H_2COCl$, THF, 0 °C, 2 h, then 2.2 equiv of 4-DMAP, toluene, 70 °C, 0.5 h, decomposition. (b) See Table 1. (c) Pd−C (10%), MeOH/EtOAc, 45 min, 92%. (d) 6.0 equiv of Ac_2O, pyridine, 0 °C, 3 h, 70%. (e) 10.0 equiv of Me_2CuLi, THF, 0 → 25 °C, 12 h, or 20.0 equiv of Me_4AlLi, THF, 0 °C, 1 h, no reaction in both cases.

represents an interesting compound for the preparation of the 2,3-epoxy analogue of stevastelin B, as well as representing the direct precursor for the natural compound. Thus, compound **8** was subjected to catalytic hydrogenation to provide diol **49**, which was treated with acetic anhydride to obtain stevastelin analogue **50** in a 64% overall yield from **8**. The final key opening reaction was then attempted. Unfortunately, the desired oxirane ring opening did not take place under the influence of various nucleophiles, including organocopper reagents, in order to introduce the methyl group contained in natural stevastelins (Scheme 5).

In light of this rather unexpected outcome, presumably due to a conformational disposition of the oxirane ring that prevented the attack of the nucleophile, as was revealed later from the minimized structures of epoxy stevastelins **8** and **49**,[29] we altered our synthetic strategy to overcome the synthetic difficulties arising from the epoxide opening step, opting to undertake the opening of the oxirane ring with an earlier intermediate, epoxide **20**, as we describe in the following section.

Total Synthesis of Stevastelin B (5). This new route for the synthesis of the stevastelins would lead us to the same synthetic intermediate, represented by compound **52**, of Chida's synthesis, proceeding in a similar synthetic sequence as they described.[9] To support our ongoing research involving the search for new stevastelin-type immunosuppressive agents with the objective of gaining insight into the structural elements that play an essential role in their biological properties, we decided to undertake the preparation of the natural substance. Thus, epoxy alcohol **20** was treated with lithium dimethyl cuprate,[30] to yield the oxirane ring opening product **52** in an 88% yield. Protection of the 1,3-diol as the acetal, followed by TBS deprotection, provided the corresponding alcohol **54** in good yield (69%). The coupling of **54** with the serine derivative **55** was accomplished by use of the Yamaguchi protocol, to furnish the ester **56** in an 84% average yield, but with 5−8% epimerization at C-2 of the serine residue, which was anticipated based on observations by Chida's group.[9] Other reagents, including EDCI/4-DMAP,[31] which worked well for the epoxy analogue in the synthesis of epoxy peptide **8** and with a lower degree of epimerization, failed on this occasion. After incorporation of the serine amino acid residue, the introduction of the rest of the peptidic chain was undertaken without further problems, through free amino derivative **57**, followed by coupling with the dipeptide Boc-Val-Thr-OH.[32] The preparation of the resulting coupling product for the key macrocyclization reaction was followed according to the synthesis described by Chida, initiated with the acetal cleavage by the action of acetic acid, selective oxidation of the primary hydroxyl group by the sequential action of TEMPO/NaClO[33] and $NaClO_2$[34] to the corresponding acid, macrocyclization reaction by treatment of the resulting seco amino acid with diethyl cyanophosphonate (DECP), debenzylation,[35] and final selective monoacetylation to yield stevastelin B (**5**) (Scheme 6).[36]

Total Synthesis of Stevastelin B3 (2). We surmised that a translactonization reaction[37] would be possible from the corresponding [15]-membered ring derivatives to access the [13]-membered ring components of stevastelins. In this sense, [15]-cyclodepsipeptide **58** was pre-

(29) Theoretical calculations were performed with HyperChem 5.0, using OPLS as the force field with a gradient limit of 0.001 kcal/(Å mol). See Supporting Information for more details.

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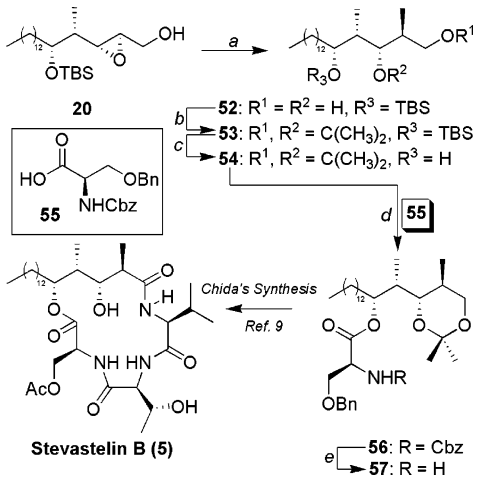
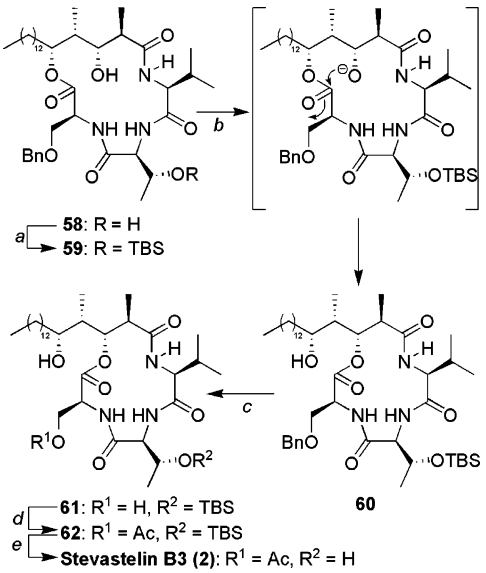
(37) Representative examples of natural products synthesis based on a translactonization reaction: (a) Corey, E. J.; Brunelle, D. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1977**, *99*, 7359−7360. (b) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S., Jr.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620−4622. (c) Nagel, A. A.; Celmer, W. D.; Jefferson, M. T.; Vincent L. A.; Whipple, E. B.; Schulte, G. *J. Org. Chem.* **1986**, *51*, 5397−5400. (d) Kirst, H. A.; Wind, J. A.; Paschal, J. W. *J. Org. Chem.* **1987**, *52*, 4359−4362. (e) Kibwage, I. O.; Busson, R.; Janssen, G.; Hoogmartens, J.; Vanderhaeghe, H.; Bracke, J. *J. Org. Chem.* **1987**, *52*, 990−996. (f) Adachi, T. *J. Org. Chem.* **1989**, *54*, 3507−3510. (g) Kretzschmar, G.; Krause, M.; Radics, L. *Tetrahedron* **1997**, *53*, 971−986. (h) Ohara, T.; Kume, M.; Narukawa, Y.; Motokawa, K.; Uotani, K.; Nakai, H. *J. Org. Chem.* **2002**, *67*, 9146−9152. (i) Trost, B. M.; Papillon, J. P. N. *J. Am. Chem. Soc.* **2004**, *126*, 13618−13619.

SCHEME 6. Total Synthesis of Stevastelin B (5)[a]



[a] Reagents and Conditions: (a) 10.0 equiv of CuI, 20.0 equiv of 1.6 M MeLi, THF, 0 °C, 4.0 h, 88%. (b) 3.0 equiv of $Me_2C(OMe)_2$, 0.05 equiv of CSA, DMF, 0 °C, 2 h, 95%. (c) 3.0 equiv of TBAF, THF, 25 °C, 4 days, 69%. (d) 6.4 equiv of **55**, 9.0 equiv of 2,4,6-$Cl_3C_6H_2COCl$, 9.0 equiv of Et_3N, THF/toluene, 0 °C, 1.5 h, then 0.5 equiv of 4-DMAP, 0 °C, 2.5 h, 84% (6:1 epimeric mixture). (e) 0.1 equiv of 10% Pd/C−ethylenediamine complex, H_2, MeOH, 25 °C, 0.5 h.

SCHEME 7. Total Synthesis of Stevastelin B3 (2)[a]



[a] Reagents and Conditions: (a) 2.0 equiv of 2,6-lutidine, 1.5 equiv of TBSOTf, DCM, 0 °C, 15 min, 86%. (b) 2.0 equiv of NaHMDS, THF, 0 °C, 15 min, 50%. (c) Pd−C (10%), MeOH, 25 °C, 15 min. (d) 10.0 equiv of Ac_2O, 0.01 equiv of 4-DMAP, pyridine, 0 °C, 5 h. (e) HF·pyridine (70% w/v), THF, 25 °C, 3 h, 55% from **60**.

pared for this reaction by the protection of the secondary hydroxyl group, located at the L-threonine residue, as the silyl ether **59**. The treatment of **59** with sodium hexamethyldisilylamide (NaHMDS) at 0 °C revealed the formation of a new product, which, after purification by flash column chromatography, was identified as the [13]-membered ring derivative **60**, obtained in 50% yield with recovered starting compound **59** in a 48% yield. Attempts to improve the degree of conversion by employing different bases or reaction conditions were unsuccessful. On the other hand, we tried to promote the translactonization reaction by use of acidic conditions ($Ti(O\textit{i}\text{-}Pr)_4$[38] or Otera's catalyst[39]), but again, the results were unsuccessful with the recovery of starting [15]-membered lactone. Finally, as shown in Scheme 7, compound **60** was converted to stevastelin B3 (**2**) through the sequential steps involving debenzylation of **60**, acetylation of the resulting alcohol **61**, and final desilylation of **62** to provide stevastelin B3 (**2**), whose physical and spectroscopic properties were identical to those reported in the literature.[40]

Conclusions

In conclusion, we have described the synthesis of the natural products stevastelin B (**5**) and stevastelin B3 (**2**). In the first case, we have demonstrated that the route designed by the Chida group proved to be the most adequate to reach the [15]-membered ring stevastelins, after failure with our attempt to reach this kind of cyclic depsipeptides through the 2,3-epoxy analogue **8**. In the case of stevastelin B3 (**2**), a new synthesis was established via a translactonization process from the corresponding [15]-membered stevastelins. This new convergent approach to the [13]-membered ring components represents a highly convergent route for this family of stevastelins from their corresponding [15]-membered ring counterparts and provides a new direction in the design of new potentially bioactive analogues,[41] especially taking into account that the [13]-membered stevastelins possess greater potency than the [15]-membered congeners.

Experimental Section

Compound 12. To a solution of oxazolidinone **10** (2.74 g, 14.8 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (55 mL) was added a freshly distilled solution of di-*n*-butylboron triflate (0.93 M in CH_2Cl_2, 17.5 mL, 16.3 mmol, 1.1 equiv) and anhydrous TEA (2.3 mL, 16.3 mmol, 1.1 equiv) at 0 °C. After 30 min at this temperature, the solution was cooled to −78 °C, and then, a solution of tetradecanal **11**[42] (3.5 g, 16.3 mmol, 1.1 equiv) in anhydrous CH_2Cl_2 (55 mL) was added dropwise. After 12 h at −78 °C, methanol (30 mL) and 30% H_2O_2 (20 mL) were sequentially added, and the resulting mixture was allowed to warm to ambient temperature. The solvents were removed by concentration under vacuum, and the crude mixture was diluted with diethyl ether, methanol, and a small amount of water to obtain a homogeneous solution which was left at ambient temperature for 2 h. The resulting mixture was diluted with CH_2Cl_2 and washed with water, and after separation of the phases, the aqueous phase was extracted with CH_2-

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(40) Synthetic stevastelins B3 (**2**) and B (**5**) exhibited identical properties (TLC, $[\alpha]_D$, ^1H and ^{13}C NMR, and HRMS) with those reported for the natural compounds, matching ^1H and ^{13}C NMR spectra by direct comparison with spectra of natural substances: Morino, T.; Nishimoto, M.; Nishide, M. U.; Masuda, A.; Yamada, M.; Kawano, E.; Nishikiori, T.; Saito, S. EP0525361, **1993**.

(41) See the following paper in this series: Sarabia, F.; Chammaa, S.; García-Castro, M. *J. Org. Chem.* **2005**, *70*, 7858−7865.

(42) Tetradecanal **11** was prepared from commercially available 1-tetradecanol by oxidation according to the SO_3·pyr method: Parikh, J. R.; Von Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes) to obtain **12** (5.0 g, 85%) as a pale yellow liquid: $R_f = 0.62$ (silica gel, 30% EtOAc in hexanes). $[\alpha]^{25}_D = +51.1°$ ($c = 1.4$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 7.0$ Hz, 3 H, CH_3CH_2), 0.86 (d, $J = 7.0$ Hz, 3 H, $CH(CH_3)_2$), 0.90 (d, $J = 7.0$ Hz, 3 H, $CH(CH_3)_2$), 1.32−1.21 (m, 27 H, 12 × CH_2, $CH(CH_3)$), 2.33 (dsept, $J = 7.0$, 4.1 Hz, 1 H, $CH(CH_3)_2$), 2.98 (d, $J = 2.3$ Hz, 1 H, OH), 3.74 (dq, $J = 7.0$, 2.3 Hz, 1 H, $CH(CH_3)$), 3.94−3.88 (m, 1 H, CH(OH)), 4.20 (dd, $J = 9.4$, 3.5 Hz, 1 H, $CH_2OC(=O)$), 4.27 (dd, $J = 9.4$, 8.2 Hz, 1 H, $CH_2OC(=O)$), 4.45 (ddd, $J = 8.2$, 7.0, 3.5 Hz, 1 H, CHN). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.6$, 14.0, 14.6, 17.8, 22.6, 25.9, 28.2, 29.2, 29.47, 29.49, 29.50, 29.55, 29.58, 31.8, 33.7, 41.9, 58.1, 63.2, 71.1, 153.4, 177.8. FAB HRMS (NBA): *m/e* 398.3272, M + H^+; calcd for $C_{23}H_{43}NO_4$ 398.3270.

Diol 13. To a solution of the aldol product **12** (3.64 g, 9.17 mmol, 1.0 equiv) in THF (42 mL) at −20 °C was added $LiBH_4$ (2 M in THF, 10.1 mL, 20.17 mmol, 8.8 equiv). The reaction mixture was allowed to warm to 0 °C and, after 2 h, was carefully treated with water and saturated aqueous NH_4Cl solution. The organic phase was separated, the aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 35% EtOAc in hexanes) to obtain **13** (2.29 g, 92%) as a white solid: $R_f = 0.27$ (silica gel, 30% EtOAc in hexanes). $[\alpha]^{25}_D = +14.3°$ ($c = 0.8$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 7.0$ Hz, 3 H, CH_3CH_2), 0.90 (d, $J = 7.0$ Hz, 3 H, $CH(CH_3)$), 1.22−1.32 (m, 22 H, 11 × CH_2), 1.37−1.51 (m, 2 H, $CH_2CH(OH)$), 1.70−1.85 (m, 1 H, $CH(CH_3)$), 3.70 (d, $J = 4.7$ Hz, 2 H, CH_2OH), 3.78−3.83 (m, 1 H, CH(OH)). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.0$, 14.1, 22.7, 26.2, 29.3, 29.59, 29.61, 29.65, 31.9, 34.1, 39.0, 67.2, 74.6. FAB HRMS (NBA): *m/e* 295.2612, M + Na^+; calcd for $C_{17}H_{36}O_2$ 295.2613.

Pivaloyl Ester 14. To a solution of the diol **13** (1.55 g, 5.69 mmol, 1.0 equiv) in pyridine (8.0 mL) and CH_2Cl_2 (4.0 mL) at −20 °C was added pivaloyl chloride (0.9 mL, 7.30 mmol, 1.3 equiv). After 30 min at this temperature, 0.2 mL more of pivaloyl chloride was added to complete the reaction. After additional 10 min, the reaction mixture was diluted with CH_2Cl_2 and treated with saturated aqueous $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with brine, separated, dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to obtain monopivaloyl ester **14** (1.91 g, 94%) as a colorless oil: $R_f = 0.35$ (silica gel, 10% EtOAc in hexanes). $[\alpha]^{25}_D = +7.5°$ ($c = 1.3$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 7.0$ Hz, 3 H, CH_3CH_2), 0.89 (d, $J = 7.0$ Hz, 3 H, $CH(CH_3)$), 1.19 (s, 9 H, $C(CH_3)_3$), 1.32−1.21 (m, 22 H, 11 × CH_2), 1.35−1.46 (m, 1 H, $CH_2CH(OH)$), 1.53−1.36 (m, 2 H, $CH_2CH(OH)$), 1.89−1.80 (m, 1 H, $CH(CH_3)$), 3.55−3.61 (m, 1 H, CH(OH)), 3.91 (dd, $J = 11.2$, 5.9 Hz, 1 H, $CH_2OCOC(CH_3)_3$), 4.18 (dd, $J = 11.2$, 7.6 Hz, 1 H, $CH_2OCOC(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.0$, 14.1, 22.6, 26.2, 27.2, 29.3, 29.57, 29.62, 31.9, 34.3, 37.7, 38.8, 66.8, 71.4, 178.9. FAB HRMS (NBA): *m/e* 357.3372, M + H^+; calcd for $C_{22}H_{44}O_3$ 357.3369.

Silyl Ether 15. A solution of the pivaloyl ester **14** (866 mg, 2.29 mmol, 1.0 equiv) in DMF (5 mL) was treated with imidazole (313 mg, 4.6 mmol, 2.0 equiv) and *tert*-butyldimethylsilyl chloride (544 mg, 3.5 mmol, 1.5 equiv) at 0 °C. After 24 h, the reaction mixture was treated with methanol (1.0 mL), diluted with diethyl ether, and washed with saturated aqueous NH_4Cl solution. After decantation, the aqueous phase was extracted with diethyl ether, and the combined organic solution was washed with water and brine, dried ($MgSO_4$), and concentrated. The resulting crude was purified by flash column chromatography (silica gel, 3% EtOAc in hexanes) to afford silyl ether **15** (1.08 g, 96%) as a colorless oil: $R_f = 0.40$ (silica gel, 3% EtOAc in hexanes). $[\alpha]^{25}_D = -12.7°$ ($c = 0.64$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.01$ (s, 3 H, CH_3Si), 0.02 (s, 3 H, CH_3Si), 0.84 (d, $J = 7.0$ Hz, 3 H, $CH(CH_3)$), 0.84−0.88 (m, 12 H, $SiC(CH_3)_3$, CH_3CH_2), 1.18 (s, 9 H, $C(CH_3)_3$), 1.20−1.30 (m, 22 H, 11 × CH_2), 1.34−1.53 (m, 2 H, $CH_2CH(OTBS)$), 1.87 (dddq, $J = 7.0$, 2.9 Hz, 1 H, $CH(CH_3)$), 3.69 (ddd, $J = 7.0$, 5.9, 2.9 Hz, 1 H, CH(OTBS)), 3.92 (dd, $J = 10.6$, 7.6 Hz, 1 H, $CH_2OCOC(CH_3)_3$), 3.96 (dd, $J = 10.6$, 6.5 Hz, 1 H, $CH_2OCOC(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.7$, −4.1, 10.3, 14.1, 18.1, 22.7, 25.7, 25.9, 27.2, 29.4, 29.59, 29.63, 29.66, 29.71, 31.9, 34.3, 36.7, 38.8, 66.6, 71.9, 178.5.

Alcohol 16. A solution of the pivaloyl ester **15** (1.03 g, 2.19 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was cooled to −78 °C and subjected to the action of DIBAL-H (1 M in CH_2Cl_2, 4.8 mL, 4.8 mmol, 2.2 equiv). After stirring for 30 min at −78 °C, the resulting mixture was diluted with ethyl acetate at the same temperature and allowed to warm to 25 °C. Then, a saturated aqueous Na/K tartrate solution was added, and the mixture was vigorously stirred for 30 min. After this time, the phases were separated, the aqueous phase was extracted with ethyl acetate, and the final organic layer was sequentially washed with saturated aqueous Na/K tartrate solution, water, and brine. After treatment with $MgSO_4$, the organic solution was filtered and concentrated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, 5% EtOAc in hexanes) to obtain alcohol **16** (762 mg, 98%) as a colorless oil: $R_f = 0.44$ (silica gel, 10% EtOAc in hexanes). $[\alpha]^{25}_D = +1.2°$ ($c = 0.6$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.05$ (s, 3 H, CH_3Si), 0.07 (s, 3 H, CH_3Si), 0.78 (d, $J = 7.0$ Hz, 3 H, $CH(CH_3)$), 0.86 (t, $J = 7.0$ Hz, 3 H, CH_3CH_2), 0.87 (s, 9 H, $(CH_3)_3CSi$), 1.21−1.31 (m, 22 H, 11 × CH_2), 1.38−1.48 (m, 2 H, $CH_2CH(OTBS)$), 1.89−1.99 (m, 1 H, $CH(CH_3)$), 2.66 (dd, $J = 6.5$, 3.5 Hz, 1 H, CH_2OH), 3.50 (ddd, $J = 11.2$, 6.5, 5.9 Hz, 1 H, CH_2OH), 3.64−3.75 (m, 2 H, CH_2OH, CH(OTBS)). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.5$, −4.4, 12.0, 14.1, 22.7, 25.8, 26.3, 29.4, 29.59, 29.63, 29.67, 29.8, 31.9, 32.2, 39.5, 66.1, 76.0. FAB HRMS (NBA): *m/e* 387.3655, M + H^+; calcd for $C_{23}H_{50}O_2Si$ 387.3658.

Aldehyde 17. To a solution of oxalyl chloride (0.46 mL, 5.18 mmol, 2.0 equiv) in CH_2Cl_2 (15 mL) was added dropwise DMSO (0.75 mL, 10.36 mmol, 4.0 equiv) at −78 °C. After the mixture was stirred for 15 min, a solution of alcohol **16** (1.0 g, 2.59 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added dropwise at −78 °C over a 10 min period. The solution was stirred for a further 30 min at −78 °C, and TEA (2.5 mL, 15.54 mmol, 6.0 equiv) was added at the same temperature. The reaction mixture was allowed to warm to 0 °C over 30 min, and then diethyl ether was added, followed by saturated aqueous NH_4Cl solution. The organic phase was separated, and the aqueous phase was extracted with diethyl ether. The combined organic solution was sequentially washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 2% EtOAc in hexanes) provided aldehyde **17** (952 mg, 94%) as a colorless oil: $R_f = 0.69$ (silica gel, 40% CH_2Cl_2 in hexanes). $[\alpha]^{25}_D = +40.4°$ ($c = 1.2$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.01$ (s, 3 H, CH_3Si), 0.04 (s, 3 H, CH_3Si), 0.84 (s, 9 H, $(CH_3)_3CSi$), 0.86 (t, $J = 7.0$ Hz, 3 H, CH_3CH_2), 1.03 (d, $J = 7.0$ Hz, 3 H, $CH(CH_3)$), 1.20−1.31 (m, 22 H, 11 × CH_2), 1.38−1.52 (m, 2 H, $CH_2CH(OTBS)$), 2.42 (ddq, $J = 7.0$, 3.5, 1.2 Hz, 1 H, $CH(CH_3)CHO$), 4.07 (dt, $J = 6.5$, 3.5 Hz, 1 H, CH(OTBS)), 9.75 (d, $J = 1.2$ Hz, 1 H, CHO). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.7$, −4.2, 7.6, 14.1, 18.0, 22.7, 25.72, 29.3, 29.54, 29.59, 29.61, 29.63, 29.66, 31.9, 34.5, 51.2, 72.1, 205.6.

α,β-Unsaturated Ester 18. Aldehyde **17** (713 mg, 1.86 mmol, 1.0 equiv) was dissolved in benzene (12 mL), and (carbomethoxymetilen)triphenylphosphorane (1.24 g, 3.72 mmol, 2.0 equiv) was added at room temperature. The reaction mixture was heated at reflux until the reaction was complete as judged by TLC (ca. 12 h). The solvents were removed by

concentration under reduced pressure, and the resulting crude product was purified by flash column chromatography (silica gel, 30% CH_2Cl_2 in hexanes) to obtain the α,β-unsaturated ester **18** (740 mg, 92%) as a colorless oil: $R_f = 0.58$ (silica gel, 10% EtOAc in hexanes). $[\alpha]^{25}_D = +31.0°$ ($c = 1.02$, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.01$ (s, 3 H, CH_3Si), 0.02 (s, 3 H, CH_3Si), 0.86 (t, $J = 7.0$ Hz, 3 H, CH_3CH$_2$), 0.87 (s, 9 H, (CH_3)$_3$CSi), 0.99 (d, $J = 7.0$ Hz, 3 H, CH(CH_3)), 1.19−1.41 (m, 24 H, 12 × CH_2), 2.38−2.48 (m, 1 H, CH(CH$_3$)), 3.55−3.61 (m, 1 H, CH(OTBS)), 3.71 (s, 3 H, CH_3O), 5.78 (dd, $J = 15.8$, 1.2 Hz, 1 H, CH=CHCO$_2$CH$_3$), 7.00 (dd, $J = 15.8$, 7.0 Hz, 1 H, CH=CHCO$_2$CH$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.5$, −4.4, 14.0, 14.1, 18.1, 22.7, 25.3, 25.9, 29.4, 29.58, 29.62, 29.64, 29.67, 29.74, 31.9, 34.0, 41.7, 51.4, 75.2, 120.2, 152.5, 167.2.

Allylic Alcohol 19. To a solution of ester **18** (1.07 g, 2.44 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added DIBAL-H (1 M in CH_2Cl_2, 5.4 mL, 5.4 mmol, 2.2 equiv) at −78 °C. After 30 min at this temperature, EtOAc was added, and the reaction mixture was allowed to warm to ambient temperature. Then, saturated aqueous Na/K tartrate solution was added, and the resulting mixture was vigorously stirred for 30 min at ambient temperature. The organic phase was separated, the aqueous layer was extracted with ethyl acetate, and the combined organic solution was washed with water and brine. After drying with $MgSO_4$, the solvents were evaporated, and the crude product was purified by flash column chromatography (silica gel, 8% EtOAc in hexanes) to obtain the allylic alcohol **19** (923 mg, 98%) as a colorless oil: $R_f = 0.27$ (silica gel, 10% EtOAc in hexanes). $[\alpha]^{25}_D = +22.7°$ ($c = 0.5$, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.00$ (s, 3 H, CH_3Si), 0.01 (s, 3 H, CH_3-Si), 0.86 (t, $J = 7.0$ Hz, 3 H, CH_3CH$_2$), 0.87 (s, 9 H, (CH_3)$_3$-CSi), 0.94 (d, $J = 6.5$ Hz, 3 H, CH(CH_3)), 1.17−1.42 (m, 24 H, 12 × CH_2), 2.24−2.34 (m, 1 H, CH(CH$_3$)), 3.47−3.52 (m, 1 H, CH(OTBS)), 4.09 (dd, $J = 5.9$, 5.3 Hz, 2 H, CH_2OH), 5.59 (ddt, $J = 15.8$, 5.9, 1.2 Hz, 1 H, CH=CHCH$_2$OH), 5.70 (ddt, $J = 15.8$, 7.0, 1.2 Hz, 1 H, CH=CHCH$_2$OH). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.4$, −4.3, 14.1, 15.0, 18.2, 22.7, 25.3, 25.9, 29.4, 29.61, 29.64, 29.68, 29.8, 31.9, 33.7, 41.3, 64.1, 75.9, 128.3, 136.1. FAB HRMS (NBA): *m/e* 435.3627, M + Na^+; calcd for $C_{25}H_{52}O_3Si$ 435.3634.

Epoxy Alcohol 20. To a cooled suspension of 4 Å molecular sieves (1.4 g) in CH_2Cl_2 (48 mL) was sequentially added at −20 °C, titanium tetraisopropoxide (0.73 mL, 2.41 mmol, 0.4 equiv), d-(−)-DET (0.42 mL, 2.41 mmol, 0.4 equiv), and a solution of the allylic alcohol **19** (2.48 g, 6.03 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL). After 30 min at this temperature, TBHP (5.5 M in decane, 3.0 mL, 21.5 mmol, 3.6 equiv) was added. The reaction mixture was stirred at −20 °C, and after 24 h, the reaction was quenched by addition of dimethyl sulfide (2.1 mL) at 0 °C. After 30 min, the crude mixture was filtered, the solvents were evaporated, and the resulting crude product was purified by flash column chromatography (silica gel, 15% EtOAc in hexanes) to afford epoxy alcohol **20** together with its β-epoxide epimer (2.41 g, 91% total yield) as an inseparable mixture in an approximately 92:8 proportion by ^{1}H NMR (de 85%): $R_f = 0.47$ (silica gel, 20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.00$ (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3-Si), 0.86 (t, $J = 7.0$ Hz, 3 H, CH_3CH$_2$), 0.87 (s, 9 H, (CH_3)$_3$-CSi), 0.97 (d, $J = 7.0$ Hz, 3 H, CH(CH_3)), 1.15−1.31 (m, 23 H, 11 × CH_2, CH_2CH(OTBS)), 1.37−1.53 (m, 2 H, CH(CH$_3$), CH_2-CH(OTBS)), 2.92 (dd, $J = 7.6$, 2.3 Hz, 1 H, CH(O)CHCH$_2$OH), 2.98 (ddt, $J = 4.7$, 2.3 Hz, 1 H, CH(O)CHCH$_2$OH), 3.57 (dd, $J = 12.6$, 4.7 Hz, 1 H, CH_2OH), 3.59−3.64 (m, 1 H, CH(OTBS)), 3.91 (dd, $J = 12.3$, 2.3 Hz, 1 H, CH_2OH). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.6$, −4.3, 11.7, 14.1, 18.0, 22.6, 25.7, 25.8, 29.3, 29.55, 29.56, 29.60, 29.64, 29.7, 31.9, 33.9, 40.7, 58.2, 58.5, 61.8, 74.4. FAB HRMS (NBA): *m/e* 451.3599, M + Na^+; calcd for $C_{25}H_{52}O_3Si$ 451.3583.

Epoxy Acid 9. A solution of epoxy alcohol **20** (1.08 g, 2.45 mmol, 1.0 equiv) in a system formed by CCl_4 (12 mL), CH_3CN (12 mL), and H_2O (12 mL) was treated with $NaIO_4$ (2.22 g, 10.36 mmol, 4.2 equiv) and $RuCl_3$ (5 mg, 0.0245 mmol, 0.01 equiv) at 0 °C. After vigorous stirring for 30 min, a saturated aqueous $NaHSO_3$ solution was added, and after decantation, the aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The obtained crude product was purified by flash column chromatography (silica gel, 25% EtOAc and 5% MeOH in hexanes) to obtain epoxy acid **9** (692 mg, 64%) as colorless liquid: $R_f = 0.27$ (silica gel, 20% EtOAc and 10% methanol in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = -0.02$ (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.81−0.88 (m, 12 H, (CH_3)$_3$CSi, CH_3CH$_2$), 0.97 (d, $J = 7.0$ Hz, 3 H, CH(CH_3)), 1.12−1.31 (m, 22 H, 11 × CH_2), 1.37−1.58 (m, 2 H, CH_2CH-(OTBS)), 2.33−2.45 (m, 1H, CH(CH$_3$)), 3.20 (dd, $J = 7.0$, 1.8 Hz, 1 H, CH(O)CH), 3.31 (d, $J = 1.8$ Hz, 1 H, CH(O)CO$_2$H), 3.66 (dt, $J = 6.5$, 3.5 Hz, 1 H, CH(OTBS)). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.7$, −4.3, 11.0, 14.1, 25.8, 29.3, 29.55, 29.63, 29.65, 29.69, 40.6, 52.1, 61.5, 74.0, 174.6. FAB HRMS (NBA): *m/e* 443.3536, M+H^+; calcd for $C_{25}H_{50}O_4Si$ 443.3557.

Epoxy Peptide 30. A solution of epoxy acid **9** (676 mg, 1.53 mmol, 1.0 equiv) in CH_2Cl_2 (9.0 mL) was treated with HOBt (240 mg, 1.68 mmol, 1.1 equiv) and EDCI (419 mg, 2.14 mmol, 1.4 equiv) at 25 °C. After stirring for 10 min, a solution of dipeptide **24** (642 mg, 1.84 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added. After 1 h at room temperature, the depletion of starting epoxyacid was detected by TLC, and a 30% aqueous NH_3 solution was added, before addition of a saturated aqueous NH_4Cl solution. After decantation of both phases, the aqueous layer was extracted with CH_2Cl_2, and the resulting organic solution was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The obtained crude product was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to afford epoxy peptide **30** (817 mg, 70%) as a white solid: $R_f = 0.45$ (silica gel, 20% EtOAc in hexanes). $[\alpha]^{25}_D = +10.4°$ ($c = 0.23$, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: −0.02 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.83−0.96 (m, 21 H, (CH_3)$_3$CSi, CH_3CH$_2$, CH(CH_3), CH(CH_3)$_2$), 1.20 (d, $J = 6.4$ Hz, 3 H, (CH_3)CH(OBn)), 1.20−1.29 (m, 22 H, 11 × CH_2), 1.39−1.47 (m, 2 H, CH_2CH-(OTBS)), 1.51−1.59 (m, 1 H, CH(CH$_3$)), 2.03−2.13 (m, 1 H, CH(CH$_3$)$_2$), 3.03 (dd, $J = 5.9$, 2.1 Hz, 1 H, CH(O)CH), 3.24 (d, $J = 2.1$ Hz, 1 H, CH(O)CON), 3.72 (dt, $J = 6.4$, 3.2 Hz, 1 H, CH(OTBS)), 4.17 (dq, $J = 6.4$, 2.1 Hz, 1 H, (CH$_3$)CH(OBn)), 4.25 (dd, $J = 9.1$, 6.4 Hz, 1 H, CHNH−Val), 4.35 (d, $J = 11.8$ Hz, 1 H, CH_2Ph), 4.47−4.60 (m, 3 H, CH_2Ph, CO$_2$CH_2CH=CH$_2$), 4.62 (dd, $J = 9.1$, 2.1 Hz, 1 H, CHNH−Thr), 5.17−5.29 (m, 2 H, CO$_2$CH$_2$CH=CH_2), 5.74−5.85 (m, 1 H, CO$_2$CH$_2$CH=CH$_2$), 6.34 (d, $J = 8.6$ Hz, 1 H, NH), 6.70 (d, $J = 8.6$ Hz, 1 H, NH), 7.20−7.34 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −4.7, −4.2, 9.9, 14.1, 16.2, 18.0, 19.1, 22.7, 25.8, 29.3, 29.56, 29.59, 29.63, 29.66, 29.7, 31.3, 31.9, 34.0, 40.2, 54.3, 56.8, 57.6, 62.1, 66.1, 70.8, 73.84, 73.85, 119.1, 127.8, 128.4, 131.5, 137.7, 168.7, 169.9, 170.9. FAB HRMS (NBA): *m/e* 795.5341, M+Na^+; calcd for $C_{44}H_{76}N_2O_7Si$ 795.5320.

Epoxy Peptide 31. To a solution of silyl ether **30** (817 mg, 1.06 mmol, 1.0 equiv) in THF (15.0 mL) was added HF·pyridine (4 mL, 70% w/v) at 25 °C. After stirring for 12 h at 25 °C, a saturated aqueous $NaHCO_3$ solution was added until release of CO_2 ceased. The resulting crude mixture was extracted with CH_2Cl_2, and the organic phase was washed with water and brine. After separation of both phases, the organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The obtained crude product corresponded to epoxy peptide **31** (660 mg, 95%), which was used in the next step without further purification: $R_f = 0.53$ (silica gel, 50% EtOAc in hexanes). $[\alpha]^{25}_D = +3.8°$ ($c = 0.95$, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85 (t, $J = 7.0$ Hz, 3 H, CH_3CH$_2$), 0.90 (d, $J = 6.4$ Hz, 3 H, CH(CH_3)$_2$), 0.94 (d, $J = 6.4$ Hz, 3 H, CH-(CH_3)$_2$), 0.98 (d, $J = 7.0$ Hz, 3 H, CH(CH_3)), 1.19 (d, $J = 6.4$ Hz, 3 H, (CH_3)CH(OBn)), 1.20−1.30 (m, 22 H, 11 × CH_2), 1.40−1.48 (m, 2 H, CH_2CH(OH)), 1.51−1.60 (m, 1 H, CH(CH$_3$)), 1.84 (bs, 1 H, CH(OH)), 2.05−2.15 (m, 1 H, CH(CH$_3$)$_2$), 3.00 (dd, $J = 6.4$, 2.1 Hz, 1 H, CH(O)CH), 3.31 (d, $J = 2.1$ Hz, 1 H,

C*H*(O)CON), 3.68−3.74 (m, 1 H, C*H*(OH)), 4.16 (dq, J = 6.4, 2.1 Hz, 1 H, (CH$_3$)C*H*(OBn)), 4.25 (dd, J = 9.1, 6.4 Hz, 1 H, C*H*NH−Val), 4.34 (d, J = 11.8 Hz, 1 H, C*H*$_2$Ph), 4.46−4.60 (m, 3 H, C*H*$_2$Ph, CO$_2$C*H*$_2$CH=CH$_2$), 4.62 (dd, J = 9.1, 2.1 Hz, 1 H, C*H*NH−Thr), 5.17−5.29 (m, 2 H, CO$_2$CH$_2$CH=C*H*$_2$), 5.74−5.84 (m, 1 H, CO$_2$CH$_2$C*H*=CH$_2$), 6.46 (d, J = 9.1 Hz, 1 H, N*H*(Thr)), 6.73 (d, J = 8.6 Hz, 1 H, N*H*(Val)), 7.20−7.33 (m, 5 H, Ph). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 9.9, 14.1, 16.2, 18.0, 19.1, 22.7, 26.0, 29.3, 29.52, 29.56, 29.58, 29.62, 29.64, 31.3, 31.9, 34.6, 40.5, 54.5, 56.8, 57.8, 62.2, 66.1, 70.8, 73.0, 73.8, 119.1, 127.8, 128.4, 131.4, 137.6, 168.7, 169.9, 170.9. FAB HRMS (NBA): *m/e* 659.4621, M+H$^+$; calcd for C$_{38}$H$_{62}$N$_2$O$_7$ 659.4635.

Epoxy Peptide 32. A solution of Boc-Ser(Bn)-H (436 mg, 1.48 mmol, 1.5 equiv) in THF (13 mL) was treated with anhydrous TEA (0.41 mL, 2.96 mmol, 3.0 equiv) and 2,4,6-trichlorobenzoyl chloride (0.35 mL, 2.22 mmol, 2.3 equiv) at 0 °C. After stirring for 2 h at this temperature, the resulting crude mixture was added dropwise over a solution of epoxy peptide **31** (648 mg, 0.98 mmol, 1.0 equiv) and 4-DMAP (157 mg, 1.27 mmol, 1.3 equiv) in toluene (20 mL) via cannula. The reaction mixture was allowed to warm to ambient temperature and stirred for 15 min, prior to the addition of a saturated aqueous NH$_4$Cl solution and CH$_2$Cl$_2$. After separation of both phases, the aqueous layer was extracted with CH$_2$Cl$_2$, and the combined organic solution was washed with water and brine and then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 25% EtOAc in hexanes) of the resulting crude product provided ester **32** (785 mg, 86%) as a colorless oil: R_f = 0.42 (silica gel, 30% EtOAc in hexanes). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 0.86 (t, J = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 0.92 (d, J = 6.5 Hz, 3 H, CH(C*H*$_3$)), 0.95 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$), 1.15−1.27 (m, 28 H, 11 × CH$_2$, CH(C*H*$_3$)$_2$, (C*H*$_3$)CH(OBn)), 1.42 (s, 9 H, C(C*H*$_3$)$_3$), 1.52−1.69 (m, 3 H, C*H*$_2$CHOC(=O), C*H*(CH$_3$)), 2.03−2.13 (m, 1 H, C*H*(CH$_3$)$_2$), 2.87 (dd, J = 7.6, 1.8 Hz, 1 H, C*H*(O)CH), 3.28 (d, J = 1.8 Hz, 1 H, C*H*(O)CON), 3.67 (dd, J = 9.4, 3.5 Hz, 1 H, C*H*$_2$OBn), 3.87 (dd, J = 9.4, 2.9 Hz, 1 H, C*H*$_2$OBn), 4.16 (dq, J = 6.5, 2.5 Hz, 1 H, (CH$_3$)C*H*(OBn)), 4.27 (dd, J = 8.8, 7.0 Hz, 1 H, C*H*NH−Val), 4.34 (d, J = 11.7 Hz, 1 H, C*H*$_2$Ph), 4.45−4.6 (m, 6 H), 4.62 (dd, J = 9.4, 2.4 Hz, 1 H, C*H*NH−Thr), 4.84−4.91 (m, 1 H, C*H*OC(=O)), 5.17−5.29 (m, 2 H, CO$_2$CH$_2$CH=C*H*$_2$), 5.69 (d, J = 9.4 Hz, 1 H, N*H*Boc), 5.74−5.85 (m, 1 H, CO$_2$CH$_2$C*H*=CH$_2$), 6.41 (d, J = 8.8 Hz, 1 H, N*H*), 7.20−7.34 (m, 11 H, 2 × Ph, N*H*). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 12.5, 14.1, 16.1, 18.1, 19.2, 21.0, 22.7, 25.7, 28.3, 29.29, 29.33, 29.5, 29.62, 29.63, 29.66, 31.1, 31.9, 38.8, 54.2, 54.8, 56.7, 58.1, 59.7, 60.4, 66.1, 70.1, 70.7, 73.4, 73.8, 80.0, 119.0, 127.6, 127.8, 128.36, 128.37, 131.4, 137.3, 137.6, 156.1, 168.2, 169.9, 170.5, 171.1. FAB HRMS (NBA): *m/e* 958.5753, M+Na$^+$; calcd for C$_{53}$H$_{81}$N$_3$O$_{11}$ 958.5769.

Epoxy Peptide 33. To a solution of allyl ester **32** (785 mg, 0.839 mmol, 1.0 equiv) in THF (10.0 mL) was added morpholine (0.37 mL, 4.28 mmol, 5.0 equiv) and Pd[PPh$_3$]$_4$ (100 mg, 0.084 mmol, 0.10 equiv) at 25 °C. After 30 min, the reaction mixture was diluted with diethyl ether and treated with a 0.5 M aqueous solution of citric acid. Separation of both phases was followed by extraction of the aqueous layer with diethyl ether, and the combined organic extracts were washed with water and brine, dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (silica gel, 38% EtOAc and 2% AcOH in hexanes) to obtain epoxy acid **33** (705 mg, 94%) as a colorless oil: R_f = 0.62 (silica gel, 36% EtOAc and 4% AcOH in hexanes). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 0.87−1.07 (m, 12 H, C*H*$_3$CH$_2$, CH(C*H*$_3$), CH(C*H*$_3$)$_2$), 1.15−1.34 (m, 25 H, 11 × CH2, (C*H*$_3$)CH(OBn)), 1.46 (s, 9 H, C(C*H*$_3$)$_3$), 1.56−1.78 (m, 3 H, C*H*$_2$CHOC(=O), C*H*(CH$_3$)), 2.05−2.16 (m, 1 H, C*H*(CH$_3$)$_2$), 2.95−3.01 (m, 1 H, C*H*(O)CH), 3.38−3.41 (bs, 1 H, CH(O)C*H*), 3.67−3.75 (m, 1 H), 3.82−3.89 (m, 1 H), 4.18−4.25 (m, 1 H), 4.35−4.64 (m, 8 H), 7.23−7.36 (m, 10 H, 2 × Ph), 8.03 (bd, 1 H, N*H*), 8.24 (bd, 1 H, N*H*). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 12.8, 14.5, 16.8, 18.8, 19.8, 23.8, 27.0, 28.8, 30.4, 30.5, 30.7, 30.77, 30.81, 30.85, 31.1, 32.2, 33.1, 40.5, 55.5, 55.8, 58.1, 59.6, 60.7, 71.0, 72.3, 74.4, 76.0, 78.2, 80.9, 128.7, 128.9, 129.0, 129.3, 129.5, 139.1, 139.7, 158.2, 170.6, 172.4, 173.3, 173.7. FAB HRMS (NBA): *m/e* 918.5470, M + Na$^+$; calcd for C$_{50}$H$_{77}$N$_3$O$_{11}$ 918.5456.

Epoxy Peptide 34. To a solution of epoxy peptide **33** (705 mg, 0.787 mmol) in anhydrous CH$_2$Cl$_2$ (20.0 mL) was added TFA (14 mL) at 0 °C. The reaction mixture was stirred for 1 h at that temperature, and after that time, the solvents were evaporated under reduced pressure and the crude product diluted with toluene (20.0 mL) and concentrated again, repeating this operation twice. The resulting ammonium trifluoroacetate salt of **34** (727 mg, 100%) was used for the macrocyclization step without any purification.

Epoxy Cyclodepsipeptide 8. Macrolactamizations of Acyclic Epoxy amino Acids 34, 41, and 48. A solution of the trifluoroacetate salt of amines **34**, **41**, or **48** (872 mg, 0.958 mmol, 1.0 equiv) in DMF (400 mL, 2.4 mM) was treated with DEPC (0.32 mL, 1.92 mmol, 2.0 equiv) at 25 °C, and, after 30 min, with DIPEA (0.34 mL, 1.92 mmol, 2.0 equiv). The reaction mixture was allowed to react at this temperature for 16 h, after which DMF was removed by distillation under vacuum (0.5 mm of Hg) at 50 °C. The resulting crude product was purified by flash column chromatography (silica gel, 3% MeOH and 27% EtOAc in hexanes) to obtain the macrocyclic epoxy peptide **8** (332 mg, 45%) as a white solid: R_f = 0.54 (silica gel, 30% EtOAc and 10% MeOH in hexanes). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 0.86 (t, J = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 0.95 (d, J = 6.5 Hz, 3 H, CH(C*H*$_3$)$_2$), 0.97 (d, J = 6.5 Hz, 3 H, CH(C*H*$_3$)$_2$), 1.10 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)), 1.14−1.30 (m, 25 H, 11 × CH$_2$, (C*H*$_3$)CH(OBn)), 1.40−1.67 (m, 3 H, C*H*$_2$CHOC(=O), C*H*(CH$_3$)), 2.64−2.76 (m, 1 H, C*H*(CH$_3$)$_2$), 2.97 (dd, J = 8.2, 2.4 Hz, 1 H, C*H*(O)CH), 3.14 (d, J = 2.4 Hz, 1 H, C*H*(O)CON), 3.30 (dd, J = 11.2, 7.6 Hz, 1 H, C*H*NH−Val), 3.54 (dd, J = 9.4, 6.5 Hz, 1 H, C*H*$_2$OBn), 3.69 (dd, J = 9.4, 5.3 Hz, 1 H, C*H*$_2$OBn), 4.11 (dq, J = 6.5, 3.5 Hz, 1 H, (CH$_3$)C*H*(OBn)), 4.40 (s, 2 H, C*H*$_2$-Ph), 4.45 (d, J = 11.7 Hz, 1 H, C*H*$_2$Ph), 4.46−4.60 (m, 2 H), 4.60 (d, J = 11.7 Hz, 1 H, C*H*$_2$Ph), 5.22−5.29 (m, 1 H, C*H*OC-(=O)), 6.57 (d, J = 7.0 Hz, 1 H, CHN*H*(Val)), 7.20−7.32 (m, 11 H, 2 × Ph, CHN*H*), 7.43 (d, J = 9.4 Hz, 1 H, CHN*H*(Ser)). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 11.7, 14.1, 16.2, 19.6, 19.7, 22.7, 25.4, 27.4, 29.3, 29.34, 29.4, 29.56, 29.61, 29.63, 29.65, 29.68, 30.4, 31.9, 39.3, 53.5, 54.8, 57.7, 61.7, 66.5, 69.1, 71.0, 73.3, 73.9, 75.7, 127.6, 127.7, 127.8, 128.4, 128.5, 137.5, 137.6, 170.2, 170.25, 170.3, 172.0. FAB HRMS (NBA): *m/e* 800.4832, M+Na$^+$; calcd for C$_{45}$H$_{67}$N$_3$O$_8$ 800.4826.

Epoxy Peptide 49. To a solution of cyclic depsipeptide **8** (333 mg, 0.427 mmol, 1.0 equiv) in EtOAc/MeOH (20 mL, 1:1) was added 10% Pd/C (50 mg). The reaction was allowed to proceed under an atmosphere of H$_2$ at ambient temperature. After 45 min, the suspension was filtered through a silica gel pad, and the solid washed with MeOH and CH$_2$Cl$_2$. The combined clear organic solution was concentrated under reduced pressure to obtain crude product **49** (234 mg, 92%) which was used in the next step without purification. **[49]**: Colorless oil. R_f = 0.39 (silica gel, 10% MeOH and 40% EtOAc in hexanes). $[\alpha]^{25}_D$ = −64.5° (c = 0.4, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (t, J = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 0.91 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)), 0.94 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$), 0.97 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)$_2$), 1.00 (d, J = 6.5 Hz, 3 H, (C*H*$_3$)CH(OH)), 1.15−1.29 (m, 22 H, 11 × CH$_2$), 1.31−1.42 (m, 1 H, C*H*$_2$CHOC(=O)), 1.48−1.62 (m, 1 H, C*H*$_2$CHOC(=O)), 1.74−1.83 (m, 1 H, C*H*(CH$_3$)), 2.00−2.12 (m, 1 H, C*H*(CH$_3$)$_2$), 2.82 (dd, J = 5.9, 2.2 Hz, 1 H, C*H*(O)CH), 3.32 (d, J = 2.2 Hz, 1 H, C*H*(O)CON), 3.61−3.76 (m, 2 H, C*H*$_2$OH), 3.87 (dd, J = 9.7 Hz, 1 H, C*H*NH(Val)), 3.96−4.04 (m, 1 H, C*H*(OH)), 4.18 (dd, J = 9.1, 2.7 Hz, 1 H, C*H*NH(Thr)), 4.25−4.32 (m, 1 H, C*H*NH(Ser)), 4.89 (dt, J = 10.2, 2.7 Hz, 1 H, C*H*OC(=O)), 4.97 (t, J = 5.9 Hz, 1 H, CH$_2$O*H*), 5.02 (d, J = 4.8 Hz, 1 H, CH-(O*H*)), 7.52 (d, J = 9.1 Hz, 1 H, N*H*(Thr)), 8.12 (d, J = 7.5 Hz, 1 H, N*H*(Ser)), 8.74 (d, J = 9.1 Hz, 1 H, N*H*(Val)). ^{13}C NMR

(100 MHz, DMSO-d_6) δ: 12.3, 13.9, 19.2, 20.0, 22.0, 25.3, 27.8, 28.6, 28.7, 28.8, 28.87, 28.95, 28.98, 29.0, 29.02, 31.2, 37.4, 52.8, 54.8, 57.6, 58.2, 61.1, 62.5, 66.4, 76.3, 167.9, 169.7, 170.1, 170.9. FAB HRMS (NBA): *m/e* 620.3885, M + Na^+; calcd for $C_{31}H_{55}N_3O_8$ 620.3887.

Epoxy Stevastelin B (50). To a solution of epoxy cyclodepsipeptide **49** (60 mg, 0.1 mmol, 1.0 equiv) in pyridine (8.0 mL) was added Ac_2O (60 μL, 0.6 mmol, 6.0 equiv) at 0 °C. After 3 h at this temperature, MeOH was added, and the resulting solution was concentrated under reduced pressure. The obtained crude product was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to afford epoxystevastelin B analogue **50** (45 mg, 70%) as a white solid: R_f = 0.59 (silica gel, 10% MeOH and 60% EtOAc in hexanes). $[\alpha]^{25}_D$ = −27° (c = 0.2, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.76 (d, J = 7.0 Hz, 3 H, CH(CH_3)), 0.85 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 0.92 (d, J = 7.0 Hz, 3 H, CH(CH_3)$_2$), 0.94 (d, J = 6.5 Hz, 3 H, CH(CH_3)$_2$), 0.97 (d, J = 6.5 Hz, 3 H, (CH_3)CH(OH)), 1.19−1.31 (m, 23 H, 11 × CH_2, CH_2CHOC(=O)), 1.40−1.60 (m, 2 H, CH_2CHOC(=O), CH(CH$_3$)), 1.99 (s, 3 H, CH_3C(=O)O−), 1.96−2.02 (m, 1 H, CH(CH$_3$)$_2$), 2.15−2.23 (m, 1 H, CH(CH$_3$)), 2.67 (bs, 1 H, CH(O)CH), 3.40 (d, J = 1.6 Hz, 1 H, CH(O)-CON), 3.73 (t, J = 8.6 Hz, 1 H, CHNH(Val)), 3.86−3.94 (m, 1 H, CH(OH)), 4.13 (dd, J = 8.1, 3.8 Hz, CHNH(Thr)), 4.17−4.29 (m, 2 H, CH_2OAc), 4.30−4.38 (m, 1 H, CHNH(Ser)), 4.85−4.91 (m, 1 H, CHOC(=O)), 4.96 (d, J = 4.8 Hz, 1 H, CH$_2$OH), 7.13 (d, J = 7.5 Hz, 1 H, NH(Ser)), 8.50 (d, J = 7.0 Hz, 1 H, NH(Thr)), 8.54 (d, J = 8.1 Hz, 1 H, NH(Val)). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 10.1, 13.9, 19.2, 19.4, 20.5, 22.0, 25.3, 27.5, 28.62, 28.67, 28.78, 28.87, 28.93, 28.96, 31.2, 35.4, 50.6, 51.0, 56.8, 57.6, 62.2, 62.7, 66.5, 77.1, 168.6, 169.0, 169.6, 170.1, 170.9. FAB HRMS (NBA): *m/e* 662.3941, M + Na^+; calcd for $C_{33}H_{57}N_3O_9$ 662.3993.

Diol 52. To a suspension of CuI (6.811 g, 35.05 mmol, 10.0 equiv) in THF (23 mL) was added dropwise MeLi (1.6 M, 43.8 mL, 70 mmol, 20.0 equiv) at 0 °C. The resulting colorless solution of Me_2CuLi was added to a solution of epoxy alcohol **20** (1.5 g, 3.51 mmol, 1.0 equiv) in THF (23 mL) at 0 °C. The reaction mixture was stirred for 4 h at this temperature and quenched by careful addition of a minimal amount of aqueous saturated NH_4Cl solution. The resulting suspension was then filtered, and the solids washed with diethyl ether several times. The organic extracts were sequentially washed with aqueous saturated NH_4Cl solution, water, and brine. After treatment with $MgSO_4$, the solvents were removed by reduced pressure to obtain a crude product, which was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to afford diol **52** (1.34 g, 88%) as a colorless oil: R_f = 0.33 (silica gel, 20% EtOAc in hexanes). $[\alpha]^{25}_D$ = −2.2° (c = 0.33, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si), 0.73 (d, J = 6.5 Hz, 3 H, CH(CH_3)), 0.84−0.88 (m, 15 H, (CH_3)$_3$CSi, CH_3CH$_2$, CH(CH_3)), 1.20−1.30 (m, 22 H, 11 × CH_2), 1.39−1.49 (m, 1 H, CH_2CH(OTBS)), 1.50−1.60 (m, 1 H, CH_2CH(OTBS)), 1.64−1.72 (m, 1 H, CH(CH$_3$)), 1.81−1.90 (m, 1 H, CH(CH$_3$)), 3.57−3.69 (m, 3 H, CH_2OH, CH(OH)), 3.83−3.88 (m, 1 H, CH(OTBS)). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.6, −3.5, 4.8, 13.7, 14.1, 18.0, 22.7, 25.5, 25.8, 29.3, 29.5, 29.59, 29.63, 29.65, 29.69, 31.9, 34.9, 36.3, 37.5, 68.9, 79.0, 82.6. FAB HRMS (NBA): *m/e* 467.3901, M + Na^+; calcd for $C_{26}H_{56}O_3Si$ 467.3896.

Acetal 53. A solution of diol **52** (1.37 g, 3.07 mmol, 1.0 equiv) in DMF (30 mL) was cooled to 0 °C. 2,2-Dimethoxypropane (1.14 mL, 9.21 mmol, 3.0 equiv) and CSA (35 mg, 0.15 mmol, 0.05 equiv) were sequentially added, and the reaction mixture was stirred at 0 °C for 2 h. Then, TEA was added, followed by diethyl ether, and the resulting mixture was washed with a saturated aqueous solution of NH_4Cl. After separation of both layers, the aqueous phase was extracted with diethyl ether, and the organic extracts were combined, washed with water and brine, dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure to afford acetal **53** (1.43 g, 95%), which was used in the next step without purification: R_f = 0.52 (silica gel, 5% AcOEt in hexanes). $[\alpha]^{25}_D$ = +20.8° (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H, CH_3Si), 0.02 (s, 3 H, CH_3Si), 0.66 (d, J = 6.5 Hz, 3 H, CH(CH_3)), 0.83−0.89 (m, 15 H, (CH$_3$)$_3$CSi, CH_3CH$_2$, CH(CH_3)), 1.21−1.28 (m, 22 H, 11 × CH_2), 1.31 (s, 3 H, C(CH_3)$_2$), 1.39 (s, 3 H, C(CH_3)$_2$), 1.38−1.47 (m, 2 H, CH_2CH(OTBS)), 1.71 (dq, J = 7.0, 1.6 Hz, 1 H, CH(CH$_3$)), 1.75−1.86 (m, 1 H, CH(CH$_3$)), 3.48 (dd, J = 11.3 Hz, 1 H, CH_2O−), 3.53−3.58 (m, 1 H, CH(OTBS)), 3.63−3.69 (m, 2 H, CH_2O, CH(O)). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.3, 10.0, 12.6, 14.1, 18.1, 18.9, 22.7, 24.5, 26.0, 29.3, 29.58, 29.6, 29.65, 29.67, 29.69, 29.72, 30.0, 30.8, 31.9, 33.2, 38.4, 66.6, 73.4, 74.6, 97.7. FAB HRMS (NBA): *m/e* 507.4213, M + Na^+; calcd for $C_{29}H_{60}O_3Si$ 507.4209.

Alcohol 54. A solution of acetal **53** (1.43 g, 2.96 mmol 1.0 equiv) in THF (35 mL) was treated with TBAF (1 M in THF, 8.9 mL, 8.9 mmol, 3.0 equiv) at 25 °C. After being stirred for 4 days, the reaction mixture was diluted with diethyl ether and washed with water. The aqueous solution was extracted with diethyl ether, and the combined organic phase was sequentially washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (silica gel, 10% of EtOAc in hexanes) to provide alcohol **54** (900 mg, 69% overall yield for three steps from epoxyalcohol **9**), as a colorless oil: R_f = 0.34 (silica gel, 10% EtOAc in hexanes). $[\alpha]^{25}_D$ = +19.8° (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69 (d, J = 7.0 Hz, 3 H, CH(CH_3)), 0.85 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 0.91 (d, J = 7.5 Hz, 1 H, CH(CH_3)), 1.21−1.30 (m, 22 H, 11 × CH_2), 1.35 (s, 3 H, C(CH_3)$_2$), 1.35−1.45 (m, 1 H, CH_2CH(OH)), 1.45 (s, 3 H, (CH_3)$_2$C), 1.49−1.58 (m, 1 H, CH_2CH(OH)), 1.61−1.70 (m, 1 H, CH(CH$_3$)), 1.84−1.96 (m, 1 H, CH(CH$_3$)), 3.51 (dd, J = 11.3 Hz, 1 H, CH_2O), 3.67 (dd, J = 11.3, 4.8 Hz, 1 H, CH_2O), 3.71 (dd, J = 10.2, 2.2 Hz, 1 H, CH(O)), 3.72−3.76 (m, 1 H, CH(OH)). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.8, 12.0, 14.1, 19.2, 22.7, 25.6, 26.2, 29.3, 29.59, 29.63, 29.66, 29.7, 30.0, 30.5, 31.9, 35.0, 36.8, 66.1, 76.7, 81.4, 98.2. FAB HRMS (NBA): *m/e* 393.3345, M + Na^+; calcd for $C_{23}H_{46}O_3$ 393.3345.

Ester 56. A solution of the protected amino acid **55** (2.39 g, 7.27 mmol, 6.4 equiv) in THF (20 mL) was treated at 0 °C with Et_3N (1.53 mL, 10.9 mmol, 9.0 equiv) and 2,4,6-trichlorobenzoyl chloride (1.76 mL, 10.9 mmol, 9.0 equiv). The reaction mixture was stirred at 0 °C for 1.5 h and then was diluted with toluene (17 mL). The resulting suspension was filtered through a silica gel pad, under Ar atmosphere, followed by washing with toluene (10 mL) and THF (10 mL). The resulting clear solution was then added to a solution of alcohol **54** (448 mg, 1.21 mmol, 1.0 equiv) in toluene (20 mL) at 0 °C, and after 2.5 h, a solution of DMAP (0.06 M, 10.1 mL, 0.61 mmol, 0.5 equiv) in toluene was added at this temperature. The reaction mixture was allowed to warm to room temperature and stirred for one additional hour. After this time, diethyl ether was added, and the resulting mixture was sequentially washed with water and brine, and the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 13% EtOAc in hexanes) furnished ester **56** (518 mg, 84% based on a 75% conversion), as a 6:1 mixture of epimers at C-α of the serine residue, recovering starting alcohol **54** (113 mg, 25%). **56** (colorless oil): R_f = 0.35 (silica gel, 15% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) (major epimer): δ = 0.66 (d, J = 6.5 Hz, 3 H, CH(CH_3)), 0.86 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 0.88 (d, J = 6.5 Hz, 3 H, CH(CH_3)), 1.14−1.30 (m, 22 H, 11 × CH_2), 1.29 (s, 3 H, C(CH_3)$_2$), 1.34 (s, 3 H, C(CH_3)$_2$), 1.48−1.58 (m, 2 H, CH_2CHOC(=O)), 1.77−1.86 (m, 2 H, 2 × CH(CH$_3$)), 3.46 (dd, J = 11.3 Hz, 1 H, CH_2O−), 3.56 (d, J = 10.2 Hz, 1 H, CH(O−)), 3.65 (dd, J = 11.3, 4.8 Hz, 1 H, CH_2O−), 3.71 (dd, J = 9.1, 2.7 Hz, 1 H, CH_2OBn), 3.90 (dd, J = 9.1, 2.7 Hz, 1 H, CH_2OBn), 4.43−4.52 (m, 3 H, CH_2-Ph, CHNH), 4.98−5.05 (m, 1 H, CHOC(=O)), 5.10 (s, 2 H, CH_2-Ph(Cbz)), 5.66 (d, J = 8.6 Hz, 1 H, NHCbz), 7.21−7.36 (m, 10 H, 2 × Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.5, 12.2, 14.1, 18.6, 22.7, 24.9, 29.3, 29.45, 29.52, 29.53, 29.62, 29.65, 29.67,

30.5, 31.5, 31.9, 36.8, 54.6, 66.1, 66.9, 70.1, 73.4, 75.3, 78.4, 97.9, 127.5, 127.7, 128.0, 128.1, 128.3, 128.5, 137.4, 155.8, 169.9. FAB HRMS (NBA): *m/e* 682.4656, M + H^+; calcd for $C_{41}H_{63}NO_7$ 682.4683.

Amine 57. To a solution of *N*-Cbz amino ester **56** (70 mg, 1.0 equiv) in MeOH (0.01 M) was added 10% Pd/C−ethylendiamine complex[43] (0.1 equiv). The reaction was allowed to proceed under an atmosphere of H_2 at 25 °C. After 30 min, the suspension was filtered through Celite, and the solid was washed with MeOH and CH_2Cl_2. The clear solution was concentrated under reduced pressure, and the resulting crude product was used in the next step without further purification. **[57]**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.64 (d, J = 7.0 Hz, 3 H, CH(CH_3)), 0.83−0.88 (m, 6 H, CH_3CH$_2$, CH(CH_3)), 1.15−1.32 (m, 22 H, 11 × CH_2), 1.30 (s, 3 H, C(CH_3)$_2$), 1.36 (s, 3 H, C(CH_3)$_2$), 1.45−1.63 (m, 2 H, CH_2CHOC(=O)), 1.75−1.88 (m, 2 H, 2 × CH(CH_3)), 3.00 (bs, 2 H, NH_2), 3.45 (dd, J = 11.3 Hz, 1 H, CH_2O−), 3.54 (d, J = 10.2 Hz, 1 H, CHO−), 3.56−3.63 (m, 1 H, CH(NH$_2$)), 3.65 (dd, J = 11.3, 4.8 Hz, 1 H, CH_2O−), 3.83 (bs, 2 H, CH_2OBn), 4.50 (s, 2 H, CH_2Ph), 4.95−5.03 (m, 1 H, CHOC(=O)), 7.22−7.32 (m, 5 H, Ph). FAB HRMS (NBA): *m/e* 548.4285, M + H^+; calcd for $C_{33}H_{57}NO_5$ 548.4315.

Cyclic Depsipeptide 59. To a solution of diol **58** (50 mg, 0.0696 mmol, 1.0 equiv) in CH_2Cl_2 (4.0 mL) was added at 0 °C, 2,6-lutidine (16 μL, 0.139 mmol, 2.0 equiv) and TBSOTf (24 μL, 0.104 mmol, 1.5 equiv). After stirring for 15 min, the reaction crude was treated with MeOH and diluted with diethyl ether. Then, the organic phase was sequentially washed with saturated aqueous NH_4Cl solution, water, and brine. The combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure, to obtain a crude product that was purified by flash column chromatography (silica gel, 35% EtOAc and 5% methanol in hexanes) to afford silyl ether **59** (50 mg, 86%) as a colorless oil: R_f = 0.38 (silica gel, 50% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.06 (s, 3 H, CH_3Si), 0.08 (s, 3 H, CH_3Si), 0.85 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 0.86 (s, 9 H, (CH_3)$_3$CSi), 0.89 (d, J = 7.5 Hz, 3 H, CH(CH_3)), 0.95 (d, J = 7.5 Hz, 3 H, CH(CH_3)), 1.00 (d, J = 6.4 Hz, 3 H, CH(CH_3)), 1.05 (d, J = 6.4 Hz, 3 H, CH(CH_3)), 1.11 (d, J = 6.4 Hz, 3 H, CH(CH_3)), 1.16−1.30 (m, 22 H, 11 × CH_2), 1.41−1.50 (m, 1 H, CH_2CHOC(=O)), 1.64−1.75 (m, 2 H, CH_2CHOC(=O), CH(CH$_3$)), 1.78−1.89 (m, 1 H, CH(CH$_3$)$_2$), 2.25−2.34 (m, 1 H, CH(CH$_3$)CONH), 3.43 (bs, 1 H, CH(OH)), 3.84 (bs, 1 H, CH_2OBn), 4.09 (dd, J = 9.1, 3.2 Hz, 1 H, CH_2OBn), 4.23 (dd, J = 9.1 Hz, 1 H, CHNH(Val)), 4.46 (s, 2 H, CH_2Ph), 4.51 (dd, J = 9.1, 1.1 Hz, 1 H, CHNH-(Thr)), 4.65−4.75 (m, 2 H, CHNH(Ser), (CH$_3$)CH(OTBS), 4.81−4.86 (m, 1 H, CHOC(=O)), 6.20 (d, J = 9.1 Hz, 1 H, NH(Thr)), 7.26−7.37 (m, 6 H, Ph, NH(Val)), 7.58 (d, J = 8.1 Hz, 1 H, NH(Ser)). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −4.9, −4.7, 14.1, 17.1, 17.8, 19.0, 19.3, 20.9, 22.7, 25.6, 25.7, 26.0, 29.3, 29.47, 29.53, 29.63, 29.66, 31.4, 31.5, 31.9, 40.4, 45.5, 53.6, 57.5,61.5, 67.9, 71.1, 74.0, 77.2, 80.3, 128.2, 128.4, 128.7, 137.5, 169.5, 169.8, 171.6, 176.4. FAB HRMS (NBA): *m/e* 840.5531, M + Na^+; calcd for $C_{45}H_{79}N_3O_8Si$ 840.5534.

[13]-Cyclic Depsipeptide 60. To a solution of the cyclic depsipeptide **59** (18 mg, 0.022 mmol, 1.0 equiv) in THF (2.0 mL) was added at 0 °C NaHDMS (0.25 mL, 0.1M, 0.025 mmol, 1.14 equiv). After 10 min at this temperature, the reaction crude was diluted with diethyl ether and washed with a 0.5 M aqueous citric acid solution, followed by washings with water and brine. After separation of both phases, the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure, to obtain a crude product which was subjected to purification by flash column chromatography (silica gel, 45% EtOAc in hexanes) to afford the [13]-membered stevastelin derivative **60** (7 mg, 39%) together with starting material **59** (7 mg, 39%). **[60]**: R_f = 0.63 (silica gel, 50% EtOAc in hexanes). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.07 (s, 6 H, 2 × CH_3Si), 0.53 (d, J = 6.4 Hz, 3 H, CH(CH_3)), 0.85 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 0.85−0.89 (m, 12 H, CH(CH_3), (CH_3)$_3$CSi), 0.91 (d, J = 6.4 Hz, 3 H, CH(CH_3)), 1.06 (d, J = 5.9 Hz, 3 H, CH(CH_3)), 1.10 (d, J = 7.0 Hz, 3 H, CH(CH_3)), 1.19−1.40 (m, 24 H, 12 × CH_2), 1.61−1.71 (m, 1 H, CH(CH$_3$)), 1.97−2.09 (m, 1 H, CH(CH$_3$)$_2$), 2.87 (dq, J = 7.0, 1.6 Hz, 1 H, CH(CH$_3$)-CONH), 3.58 (dd, J = 9.7, 3.2 Hz, 1 H, CH_2OBn), 3.82 (bs, 1 H, CH(OH)), 3.91 (dd, J = 9.7, 4.3 Hz, 1 H, CH_2OBn), 4.00 (bs, 1 H, CHNH(Val)), 4.15 (dq, J = 5.9, 5.4 Hz, 1 H, (CH$_3$)-CH(OTBS)), 4.23 (dd, J = 10.2, 5.4 Hz, 1 H, CHNH(Thr)), 4.47 (d, J = 12.4 Hz, 1 H, CH_2Ph), 4.57 (d, J = 12.4 Hz, 1 H, CH_2-Ph), 4.79 (bs, 1 H, CHNH(Ser)), 4.96 (dd, J = 10.2, 1.6 Hz, 1 H, CHOC(=O)), 7.24−7.37 (m, 6 H, Ph, NH(Val)), 7.70 (d, J = 9.7 Hz, 1 H, NH(Thr)), 7.93 (d, J = 8.6 Hz, 1 H, NH(Ser)).

Dihydroxy Cyclodepsipeptide 61. To a solution of macrocycle **60** (6 mg, 0.0073 mmol) in MeOH (2.0 mL) was added 10% Pd−C (6 mg). The reaction was allowed to proceed under an atmosphere of H_2 at ambient temperature. After 15 min, the suspension was filtered and the solid washed with methanol. The organic solution was concentrated under reduced pressure to afford diol **61** (5 mg) which was used in the next step without any purification: R_f = 0.58 (silica gel, 55% EtOAc and 5% MeOH in hexanes). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.07 (s, 3 H, CH_3Si), 0.07 (s, 3 H, CH_3Si), 0.52 (d, J = 6.4 Hz, 3 H, CH(CH_3)), 0.82−0.88 (m, 15 H, CH_3CH$_2$, CH(CH_3), SiC(CH_3)$_3$), 0.90 (d, J = 6.4 Hz, 3 H, CH(CH_3)), 1.08 (d, J = 5.9 Hz, 3 H, CH(CH_3)), 1.13 (d, J = 7.5 Hz, 3 H, CH(CH_3)), 1.20−1.38 (m, 24 H, 12 × CH_2), 1.53−1.66 (m, 1 H, CH(CH$_3$)), 2.08−2.21 (m, 1 H, CH(CH$_3$)$_2$), 2.84 (dq, J = 7.0, 2.1 Hz, 1 H, CH(CH$_3$)CONH), 3.52−3.59 (m, 1 H, CH_2OH), 3.83 (bs, 1 H, CH(OH)), 3.87−3.94 (m, 1 H, CH_2OH), 3.97−4.07 (m, 1 H, CHNH(Val)), 4.10−4.22 (m, 2 H, (CH$_3$)CH(OTBS), CHNH-(Thr)), 4.33 (d, J = 5.9 Hz, 1 H, CH(OH)), 4.56−4.62 (m, 1 H, CHNH(Ser)), 4.91 (dd, J = 9.7, 2.1 Hz, 1 H, CHOC(=O)), 5.07−5.12 (m, 1 H, CH$_2$OH), 7.48 (bs, 1 H, CHNH), 8.03 (bs, 1 H, CHNH), 8.24 (bs, 1 H, CHNH).

Stevastelin B3 (2). To a solution of diol **61** (5 mg, 0.0068 mmol, 1.0 equiv) in pyridine (1.5 mL) was added Ac_2O (7 μL, 0.068 mmol, 10.0 equiv) and 4-DMAP (7 μL, 0.01M, 0.01 equiv) at 0 °C. After 5 h at this temperature, the reaction mixture was treated with MeOH, and the resulting solution was concentrated under reduced pressure. The resulting acetyl **62** was dissolved in THF (3.0 mL) at 25 °C and treated with HF·pyridine (70% w/v, 0.4 mL) at this temperature. After 3 h, a saturated aqueous $NaHCO_3$ solution was added until the release of CO_2 ceased. Then, the crude mixture was extracted with CH_2Cl_2, and the organic phase was washed with water and brine, dried ($MgSO_4$), and filtered. After concentration under reduced pressure, the resulting crude product was purified by flash column chromatography (silica gel, 2% methanol in $CHCl_3$) to afford stevastelin B3 (**2**) (2.6 mg, 55% over three steps from **60**) as a colorless oil: R_f = 0.17 (silica gel, 3% MeOH in $CHCl_3$). $[\alpha]^{25}_D$ = −54.0° (c = 0.05, $CHCl_3$) (natural stevastelin B3: $[\alpha]^{25}_D$ = −53.0° (c = 0.1, $CHCl_3$)). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.54 (d, J = 7.0 Hz, 3 H, CH-(CH_3)), 0.85 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 0.89 (d, J = 6.4 Hz, 3 H, CH(CH_3)), 0.93 (d, J = 6.4 Hz, 3 H, CH(CH_3)), 1.07 (d, J = 6.4 Hz, 3 H, CH(CH_3)), 1.11 (d, J = 7.0 Hz, 3 H, CH(CH_3)), 1.17−1.37 (m, 24 H, 12 × CH_2), 1.67−1.77 (m, 1 H, CH(CH$_3$)), 1.96−2.08 (m, 1 H, CH(CH$_3$)$_2$), 2.01 (s, 3 H, CH_3C(=O)O−), 2.90 (dq, J = 7.0, 1.6 Hz, 1 H, CH(CH$_3$)CONH), 3.84 (m, 1 H, CH(OH)), 3.98−4.06 (m, 2 H, (CH$_3$)CH(OH), CHNH(Val)), 4.12 (dd, J = 10.2, 2.7 Hz, 1 H, CHNH(Thr)), 4.18 (dd, J = 11.3, 5.4 Hz, 1 H, CH_2OAc), 4.35 (d, J = 5.9 Hz, 1 H, CH(OH)), 4.38 (dd, J = 11.3, 5.4 Hz, 1 H, CH_2OAc), 4.89−4.95 (m, 1 H, CHNH(Ser)), 4.91 (dd, J = 9.7, 1.6 Hz, 1 H, CHOC(=O)), 5.24 (d, J = 4.3 Hz, 1 H, (CH$_3$)CH(OH)), 7.49 (bs, 1 H, NH(Val)), 7.67 (d, J = 10.2 Hz, 1 H, NH(Thr)), 7.72 (d, J = 9.1 Hz, 1 H, NH(Ser)). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 9.2, 13.8, 14.0, 19.0, 19.2, 20.7, 20.9, 22.1, 25.7, 28.7, 29.0, 31.3, 34.9, 41.1, 50.2, 59.4, 61.6, 63.3, 65.2, 69.0, 80.3, 168.8, 170.1, 170.5, 170.7, 170.8.

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Supporting Information Available: Table of macrolactamization results of epoxypeptides **34**, **41**, and **48**, figures of minimized structures of compounds **8** and **49**, experimental procedures and spectroscopic data for all other compounds, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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