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Solid Phase Synthesis of Globomycin and SF-1902 A_5

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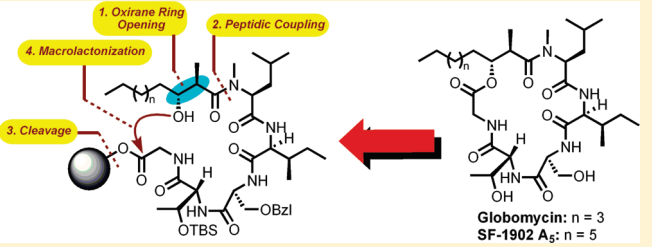
Supporting Information

ABSTRACT: The syntheses of the natural lipocyclodepsipeptide-type antibiotics globomycin and SF-1902 A_5 are reported, utilizing solid phase technology for the construction of the peptidic fragment and a new asymmetric methodology of epoxidation for the preparation of the lipidic chain. The linkage between both fragments was successfully achieved in solid phase to complete the syntheses via a macrolactonization reaction executed prior to the cleavage of the acyclic precursors from the solid support. These syntheses provide access to the rapid generation of a library of analogues via modification of the aminoacid residues as well as the lipidic chain, thus facilitating the identification of new antibiotics with interesting mechanisms of action based upon the inhibition of the enzyme signal peptidase II.



INTRODUCTION

The lipocyclodepsipeptides[1] represent a rich and intriguing class of natural products that possess a broad range of biological properties including antitumoral, antibiotic, antifungal, and anti-inflammatory activities.[2] Among them, globomycin (**1**)[3] and its congeners **2**−**6**[4] (Figure 1, part A), isolated from four different strains of actinomycetes in 1978, are representative and interesting examples, especially distinguished by their striking antibiotic activities against Gram-negative bacteria.[5] Recently proven as specific inhibitors of signal peptidase II,[6] an enzyme responsible for transforming acylated lipoproteins into apoliproteins,[7] these compounds trigger the accumulation of acylated forms of lipoproteins in the cytoplasmatic membrane, resulting in cell death. Therefore, this enzyme represents an attractive biological target for the development of new antibiotics[8] that has not been fully exploited. In fact, despite the discovery of this class of natural products being reported more than 30 years ago, globomycin (**1**), the major component of this family, has been commonly used as a biochemical tool for the identification of new lipoproteins amenable to acylation[9] and for biosynthetic studies of them.[10,11] Comparatively, globomycin and SF-1902 A_5 display greater antibiotic activities when compared to other antibiotics,[12] such as ampicillin or streptomycin, against *E. coli*, *Salmonella enteriditis*, and *Enterobacter cloacae*. On the other hand, SF-1902 A_5 is more active than globomycin (MIC against *E. coli* NIHJ JC-2: 6.25 μg/mL for **1**, 1.56 μg/mL for **2**), revealing that the lipidic chain plays an important role in the biological activity. More recently, it was discovered that globomycin exhibited antibacterial activity against *Mycobacterium tuberculosis*, showing that the biological action was not dependent on its inhibition of signal peptidase II, thus suggesting an alternative mechanism of action in this bacteria.[13] All of these biological properties render these cyclodepsipeptides as attractive synthetic endeavors in the search for new antibiotics. Chemically, the structure of globomycin, established by Haneishi et al. in 1980,[14] was recently confirmed with its first total synthesis in 2000 by the Kogen group.[15] This same group has investigated the initial chemistry in the area with the synthesis of SF-1902 A_5[16] and the preparation of a series of analogues with modifications of various constituents of the molecule including the amino acids, lipidic chain, stereochemistry, and heteroatoms.[12,17] This impressive chemical study led to the generation of a set of 15 analogues whose biological evaluation allowed the establishment of a preliminary structure−activity relationship describing the structural elements essentials for biological activity (Figure 1, part B).

On the basis of these chemical precedents and prompted by the potential that these compounds may represent in the field of antibiotics, as well as their unique mechanism of action, we decided to embark on a research program directed to the design of an efficient and readily accessible route toward this class of natural products and analogues. With this purpose in mind, we initially planned the synthesis of the more relevant natural members, globomycin (**1**) and SF-1902 A_5 (**2**), utilizing solid phase synthesis as a suitable technology to reach our goals. To this aim, resins **7** and **8** would contain the acyclic precursors of **1** and **2**, which would be prepared via a macrolactonization reaction after the cleavage of such precursors from the resin. Functionalized resins **7** and **8** would be prepared via coupling of the acids **9** or **10** with the peptidic chain linked in a solid support in the form of resin **11** (Scheme 1).

In the present article we describe the total synthesis of these natural products based on the delineated strategy to provide access to analogues with modification of the amino acids and the lipidic chain in an efficient and rapid way, taking advantage of solid phase methodology.

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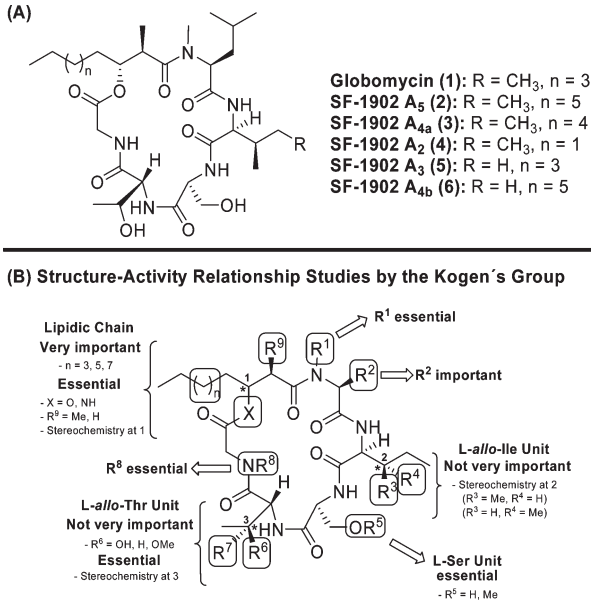
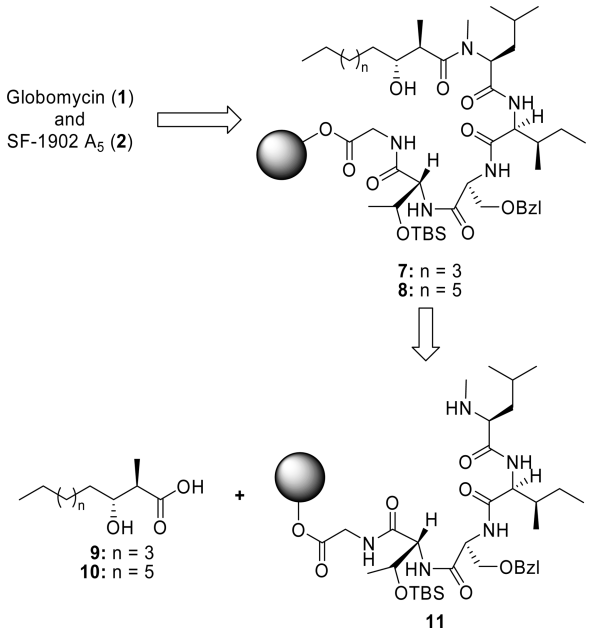


Figure 1. (A) Molecular structures of globomycin and its congeners. (B) SAR studies of analogues.

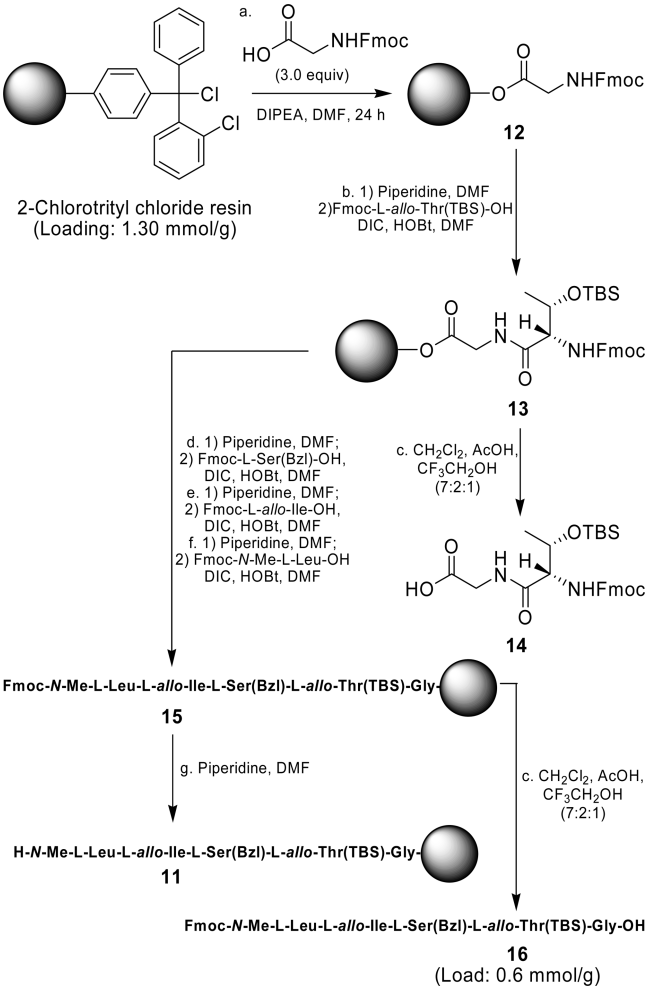
Scheme 1. Synthetic Plan for Globomycin and SF-1902 A_5



RESULTS AND DISCUSSION

We began the synthesis of globomycin and SF-1902 A_5 with the construction of the linear peptide on a 2-chlorotrityl chloride (CTC) resin[18] using the Fmoc strategy.[19] Thus, Fmoc-Gly was linked onto the CTC resin by esterification with *N*,*N*-diisopropylethylamine (DIPEA) to obtain resin **12**. After removing the Fmoc (9-fluorenylmethoxycarbonyl) group by treatment with 20% of piperidine in *N*,*N*-dimethylformamide (DMF), the following Fmoc aminoacid derivative, Fmoc-L-*allo*-Thr(TBS)-OH,[20] was loaded onto the resulting resin by the action of *N*,*N*′-diisopropylcarbodiimide (DIC) in the presence of 1-hydroxybenzotriazole (HOBt) in DMF. To check the loading of the

Scheme 2. Synthesis of the Peptidic Fragment in Solid Phase



amino acid and to ensure the effectiveness of the chosen coupling procedure, we decided to cleave the dipeptide by treatment of **13** with CH_2Cl_2/AcOH/CF_3CH_2OH (TFE) (7:2:1), which gave pure dipeptide **14**. The synthesis was continued from **13**, repeating the procedure of coupling and Fmoc deprotection steps for each amino acid being loaded in the following order: (1) Fmoc-L-Ser(Bzl)-OH, (2) Fmoc-L-*allo*-Ile-OH, and (3) Fmoc-*N*-Me-L-Leu-OH to obtain resin **15**. At this stage, we again checked the overall loading of the resin, and thus **15** was treated with CH_2Cl_2/AcOH/TFE (7:2:1) to provide pure Fmoc protected pentapeptide **16** in an amount that revealed a load of 0.6 mmol/g. Finally, resin **15** was treated with piperidine to remove the Fmoc group and prepare the polymer-bound pentapeptide **11** for the coupling with the fatty acid derivative **9** or **10** (Scheme 2).

For the synthesis of the lipidic fragments, we planned to apply the recent methodology of asymmetric epoxidation developed in our laboratories based on the use of cyclic sulfonium salts derived from α-amino acids[21] as a means of stereoselectively constructing an oxirane ring.[22] In fact, our experience in this field has allowed us to demonstrate the utility and efficiency of the resulting epoxy amides in reactions with nucleophiles with complete C-2 regioselectivity.[23] Thus, treatment of commercially available aldehydes **18** and **19** with the sulfur ylide, generated from its corresponding sulfonium salt **17**, provided epoxy amides

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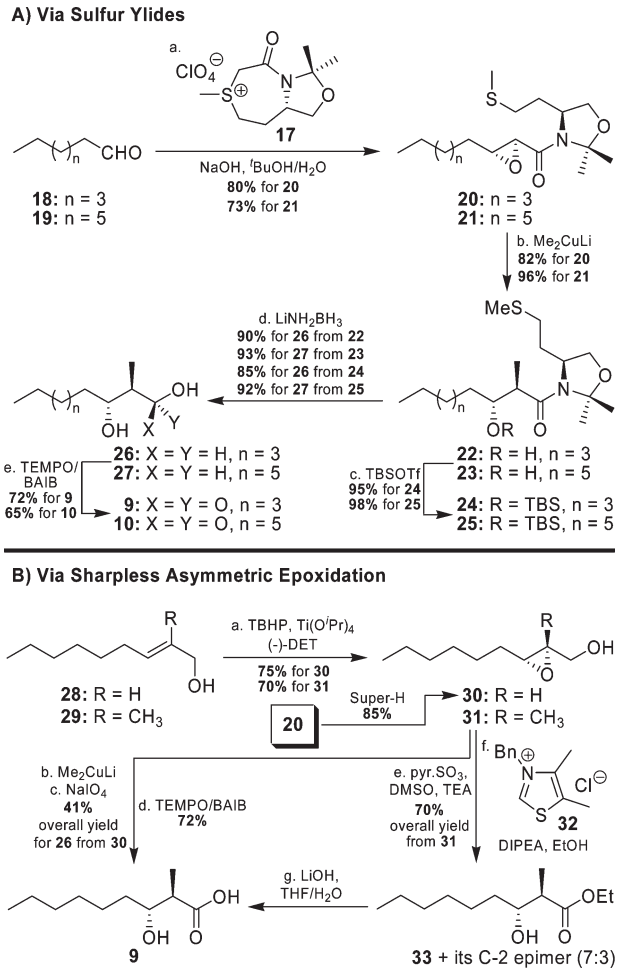
Scheme 3. Synthesis of the Lipidic Chains of Globomycin and SF-1902 A_5



20 and **21** in 80% and 73% yields, respectively, and excellent diastereoselectivities (>98% according to NMR and GC−MS analyses). This excellent diastereoselectivity was confirmed via reduction of epoxyamide **20** to epoxy alcohol **30** (see part B of Scheme 3) by the action of Super-H in 85% yield, displaying spectroscopic and physical properties, especially its optical rotation ($[\alpha]^{25}_D = +39.5$ (*c* 1.0, $CHCl_3$); lit.[24] $[\alpha]^{20}_D = +38.7$ (*c* 0.03, $CHCl_3$)), which matched with the described in the literature.[24]

Therefore, we proceeded with the introduction of the methyl groups at the C-2 position. To this end, epoxy amides **20** and **21** were exposed to the action of lithium dimethylcuprate[25] to obtain hydroxy amides **22** and **23** in excellent yields (82% and 96%, respectively). At this stage, protection of the hydroxyl groups of both hydroxy amides was required prior to the reduction of the amide functionality to the corresponding alcohol. Thus, **22** and **23** were transformed into their corresponding silyl ethers **24** and **25** and then subjected to the action of lithium triethylborohydride (Super-H).[26] Unexpectedly, these reactions did not proceed as desired, recovering starting material in both cases. The lack of reactivity of compounds **24** and **25** toward Super-H was ascribed to steric factors, thus prompting us to consider alternative methods to achieve the amide reduction. Among the various alternatives described in the literature,[27] we considered the use of $LiNH_2BH_3$, which has been proven to be an efficient reducing agent for the conversion of amides to alcohols.[28] Thus, when **24** and **25** were treated with this reagent at room temperature, a 1.5:1 mixture consisting of the desired alcohols[29] together with the desilylated derivatives, diols **26** and **27**, were obtained in 75% combined yields. In light of these promising results, we carried out this reaction under reflux in THF finding that, after 4 h, **24** and **25** were transformed into the corresponding diols **26** and **27** in 85% and 92% yields, respectively. Unable to preserve the silyl protecting group during the reduction process, we decided to attempt this transformation directly from the hydroxy amides **22** and **23** by use of a large excess of $LiNH_2BH_3$ in refluxing THF. To our delight, these reactions afforded very good results, providing the corresponding diols **26** and **27** in very high yields (90% and 93%, respectively). Finally, chemoselective oxidations of **26** and **27** to the targeted fatty hydroxy acids **9** and **10** were accomplished by the oxidative system 2,2,6,6-tetramethyl-1-piperidinyloxy free radical/bisacetoxyiodobenzene (TEMPO/BAIB) in the presence of water[30] (Scheme 3, part A). Comparatively, Sharpless asymmetric epoxidation[31] was similarly exploited for allylic alcohol **28** to obtain epoxy alcohol **30**[32] in 75% yield. However, the opening reaction of the oxirane ring with lithium dimethylcuprate furnished an inseparable mixture of 2-methyl and 3-methyl opened products[33] in a 3:1 ratio. The mixture was subjected to the action of sodium periodate, and the desired diol **26** was isolated in 41% yield from epoxy alcohol **30** after purification by flash column chromatography. Oxidation of **26** provided the desired hydroxy acid **9** as described above. In order to circumvent the lack of regioselectivity observed during the opening process, we prepared epoxy alcohol **31**,[34] via Sharpless asymmetric epoxidation of allylic alcohol **29** in 70% yield, which was then smoothly oxidized to the corresponding epoxy aldehyde with DMSO/pyr·SO_3.[35] With this epoxy aldehyde in hand, we planned to use Bode's carbene-catalyzed epoxide-opening reaction[36] utilizing the thiazolium salt **32**,[37] which has proven to be very efficient in stereoselective oxidative openings of epoxy aldehydes. In our case, this reaction afforded the corresponding 2-methyl-3-hydroxy ester **33** with an *anti* relative configuration accompanied with its *syn* isomer in a 7:3 ratio and in 70% overall yield from **31**. Finally, hydrolysis of **33** provided hydroxy acid **9** contaminated with its C-2 epimer, which was not separable by chromatographic methods (Scheme 3, part B). In summary, we concluded that our approach using sulfur ylides was more efficient than the Sharpless epoxidation approach in terms of chemical yields as well as in regio- and stereoselectivities.

Having extensively explored the synthesis of the lipidic chain via epoxide chemistry, with concomitant manipulation of the amide function by reduction to the alcohol and reoxidation to the carboxylic acid, we did not wish to discard the possibility of a direct hydrolysis of the amide group despite its recognized robustness. To this aim, we initially hydrolyzed the acetal function installed at the amino alcohol unit by treating hydroxy amide **22** with 1 N aqueous HCl in dioxane[38] to provide compound **34** in 98% yield. Attempts at direct amide hydrolysis of **22** or from **34** required harsh acidic conditions (H_2SO_4 in reflux)[39] and were unsuccessful as a result of decomposition of starting material for the first case and formation of hydroxy acid **9** for the second, albeit in poor yield (30%). Thus, we proceeded to investigate the hydrolysis of compound **34** under mild conditions. This task required activating the amide group for subsequent hydrolysis. For this objective, we considered different

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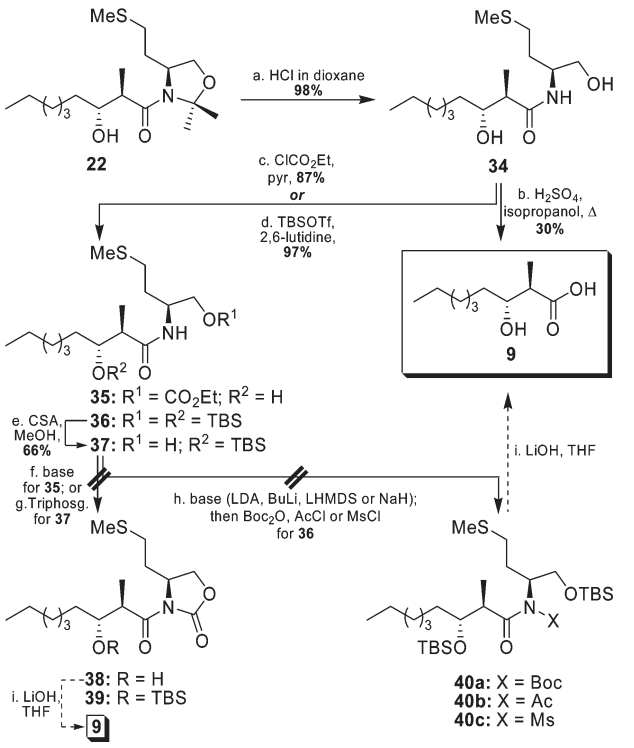
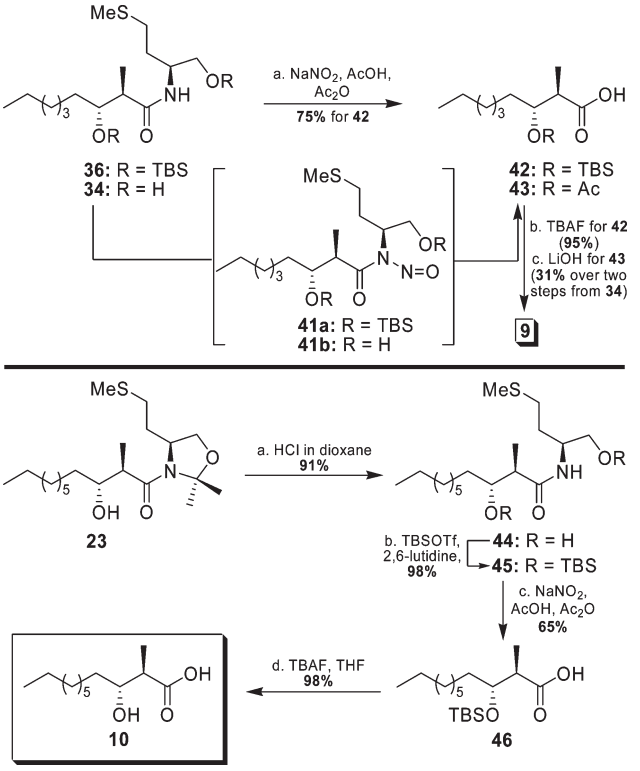
Scheme 4. Studies on Hydrolysis of Hydroxy Amide 22



Scheme 5. *N*-Nitrosations of Amides 36 and 45. Synthesis of Hydroxy Acids 9 and 10



possibilities. One of them was the formation of an oxazolidinone ring, amenable to hydrolysis under basic conditions.[40] For this purpose, dihydroxy amide **34** was transformed into its monocarbonate **35** by reaction with 1.0 equiv of ethyl chloroformate in good yield (87%), which was subjected to basic conditions provided by different bases such as LDA, LHMDS, or NaH. Unfortunately in all attempted cases, we were not able to construct the oxazolidinone ring, compound **38**, recovering starting material or obtaining **34** via hydrolysis of the carbonate group. Considering the possibility of an interference of the free hydroxyl group, we decided to prepare bis(silyl ether) **36** by treatment of **34** with excess of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), which was selectively desilylated by the action of (1*S*)-(+)-10-camphorsulfonic acid (CSA) to obtain hydroxy amide **37**. Reaction of **37** with ethyl chloroformate and subsequent basic treatment of the resulting carbonate or reaction of **37** with triphosgene[41] or *N*,*N*′-carbonyldiimidazole (CDI)[42] proved similarly unsuccessful in the formation of the coveted oxazolidinone **39**. In an alternative way, activation of the amide group by introduction of Boc,[43] Ac or Ms[44] groups via amide deprotonation of **36** by the action of base (LDA, BuLi, LHMDS or NaH), followed by the addition of the corresponding electrophilic agent, did not provide the expected products **40a**−**c**, recovering starting bis(silyl ether) **36** instead (Scheme 4).

In light of the lack of reactivity of **36** or related amides, as described before, we considered the introduction of a *N*-nitroso functional group as a way of activation of the amide group.[45] Interestingly, *N*-nitrosation of **36** under conventional conditions[45] afforded the silyloxy acid derivative **42** in 75% yield, probably formed through *N*-nitroso derivative **41a**, which surprisingly was not detected. Silyloxy acid **42** was subjected to treatment with tetrabutylammonium fluoride (TBAF) to provide the hydroxy acid **9** in 95% yield (Scheme 5). This interesting result encouraged us to try direct *N*-nitrosation of **34**, obtaining in this case acetate **43**, which under basic conditions afforded hydroxy acid **9** in a lower 31% overall yield. Then, we extended this synthetic path to amide **23** to get acid **46**, through compounds **44** and **45** obtained in very similar yields compared with the globomycin series, which was finally desilylated to acid **10** in 98% yield (Scheme 5).

With all this chemistry spread around hydroxy amides **34** and **44** and with both peptidic and lipidic key fragments prepared, we proceeded to completion of the synthesis of the natural cyclodepsipetides. For this purpose, we initially coupled hydroxy acids **9** and **10** with peptidic derivative **11** linked onto the resin by treatment with diethyl cyanophosphonate (DEPC).[46] This treatment was repeated once more in order to obtain a complete loading of acids **9** and **10** onto the solid support through an amide bond to give resins **7** and **8**. Once the acyclic precursors were prepared in solid phase, we then achieved the corresponding cleavages by the action of AcOH/CF_3CH_2OH in CH_2Cl_2 to obtain compounds **47** and **48** in high purity as determined by their NMR spectra and HPLC analyses, verifying the efficiency of the solid phase synthesis. The syntheses of globomycin (**1**) and SF-1902 A_5 (**2**) were then completed following the procedure described by Kogen et al. using a Yamaguchi macrolactonization[47] and final deprotection of the silyl and benzyl ether groups via compounds **49** and **51** for globomycin (**1**) and **50** and **52** for SF-1902 A_5 (**2**) (Scheme 6).

CONCLUSIONS

In conclusion, we have described new syntheses of the antibiotics globomycin (**1**) and SF-1902 A_5 (**2**) that incorporate

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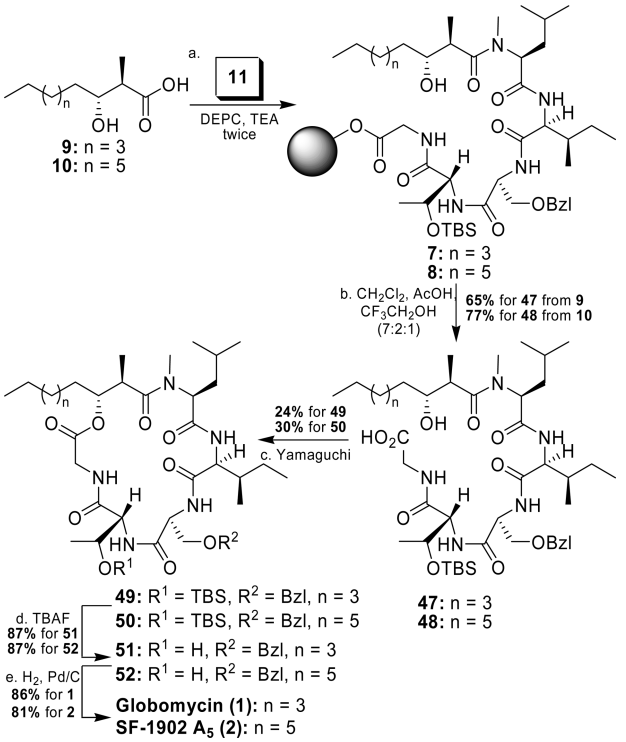
Scheme 6. Synthesis of Globomycin (1) and SF-1902 A_5 (2) via a Yamaguchi Macrolactonization



two important novel methodologies for the total syntheses of these cyclodepsipeptides: (1) the use of solid phase for the assembly of the peptidic and lipidic fragments that are found in these molecules, and (2) extension of our new asymmetric methodology of epoxidation for the stereoselective synthesis of the lipidic chains. The implementation of this new methodology of epoxidation offers the advantage of constructing the lipidic chain through an oxirane ring, a versatile functional group that allows the generation of 1,2-bifunctional groups. This in turn provides access to a broad variety of modified-lipidic chains that appear to play an essential role in the antibiotic properties of these compounds. This feature combined with the use of a solid phase-based synthesis allows rapid and easy access to a wide array of globomycin analogues in the quest for new antibiotics with novel mechanism of action. The generation of a broad library of globomycin analogues as well as their biological evaluations represent our priorities in current and future investigations.

EXPERIMENTAL SECTION[48]

Fmoc-Gly-OH Loaded 2-Chlorotrityl Resin 12. A 5 mL polypropylene syringe fitted with polyethylene porous disk charged with 2-chlorotrityl chloride resin (300 mg, L = 1.3 mmol/g, 0.39 mmol, 1.0 equiv), was loaded with a solution of Fmoc-Gly-OH (348 mg, 1.17 mmol, 3.0 equiv) and DIPEA (235 μL, 1.37 mmol, 3.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 30 h, the solution was unloaded, and the resin was washed by shaking with dry DMF (5 × 3 mL). The resulting swelled resin was used in the next step.

2-Chlorotrityl-Gly-L-*allo*-Thr(TBS)-Fmoc Resin 13. The polypropylene syringe loaded with the swelled resin **12** was treated with 20% piperidine in DMF (3 × 3 mL × 10 min). After the last run, the resin was washed with dry DMF (5 × 3 mL) and loaded with a solution of Fmoc-L-*allo*-Thr(TBS)-OH (355 mg, 0.78 mmol, 2.0 equiv), HOBt (107 mg, 0.78 mmol, 2.0 equiv) and DIC (155 μL, 1.0 mmol. 2.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 24 h, and then, the solution was unloaded and the resin washed with dry DMF (5 × 3 mL). The resulting swelled resin was used in the next step.

2-Chlorotrityl-Gly-L-*allo*-Thr(TBS)-L-Ser(Bzl)-L-*allo*-Ile-*N*-Me-L-Leu-Fmoc Resin 15. The polypropylene syringe loaded with the swelled resin **13** was treated with 20% piperidine in DMF (3 × 3 mL × 10 min). After the last run, the resin was washed with dry DMF (5 × 3 mL) and loaded with a solution of Fmoc-L-Ser(Bzl)-OH (559 mg, 1.18 mmol, 3.0 equiv), HOBt (161 mg, 1.17 mmol, 3.0 equiv) and DIC (216 μL, 1.37 mmol, 3.5 equiv) in dry DMF (3 mL). The resulting suspension was shaken at 280 rpm for 24 h, the solution was unloaded, and the resin was washed with dry DMF (5 × 3 mL). The resulting swelled resin was used in the next step. This sequence was repeated with Fmoc-L-*allo*-Ile-OH (276 mg, 0.78 mmol, 2.0 equiv), HOBt (107 mg, 0.78 mmol, 2.0 equiv) and DIC (155 μL, 1.0 mmol, 2.5 equiv), followed after treatment with 20% piperidine in DMF by loading of Fmoc-*N*-Me-L-Leu-OH (358 mg, 0.98 mmol, 2.5 equiv), HOBt (135 mg, 0.98 mmol, 2.5 equiv) and DIC (195 μL, 1.25 mmol, 3.2 equiv). Finally, the resin was washed with DMF (5 × 3 mL), DCM (3 × 3 mL), MeOH (3 × 3 mL) and Et_2O (3 × 3 mL). The resulting resin was dried under vacuum to recover 626 mg of polymer-bound *N*-Fmoc protected pentapeptide **15**.

Fmoc-*N*-Me-L-Leu-L-*allo*-Ile-L-Ser(Bzl)-L-*allo*-Thr(TBS)-Gly-OH (16). Release of a small amount of peptide from resin **15** (17.5 mg) by treatment with CH_2Cl_2/AcOH/TFE (1.0 mL, 7:2:1) gave the *N*-Fmoc protected pentapeptide **16** (9.6 mg), which revealed a load of 0.6 mmol/g for resin **15**. Data for **16**: ^{1}H NMR (400 MHz, DMSO-d_6, two rotamers in a 2.9:1 ratio) Major rotamer: δ 0.03 (s, 3 H), 0.01 (s, 3 H), 0.71−0.89 (m, 9 H), 0.80 (s, 9 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.95−1.07 (m, 1 H), 1.05 (d, J = 6.2 Hz, 3 H), 1.21−1.36 (m, 2 H), 1.47−1.61 (m, 2 H), 1.73−1.84 (m, 3/4 H), 2.68 (s, 9/4 H), 2.79 (s, 3/4 H), 3.52−3.59 (m, 3 H), 3.77 (dd, J = 17.5, 6.2 Hz, 1 H), 4.01 (q, J = 6.5 Hz, 1 H), 4.25−4.45 (m, 4 H), 4.38 (dd, J = 9.0, 7.2 Hz, 1 H), 4.48 (m, 2 H), 4.65−4.70 (m, 2 H), 7.24−7.33 (m, 7 H), 7.41 (t, J = 7.5 Hz, 2 H), 7.62−7.70 (m, 1 H), 7.63 (d, J = 7.1 Hz, 2 H), 7.89 (d, J = 7.5 Hz, 2 H), 7.99 (d, J = 9.0 Hz, 1 H), 8.05 (d, J = 7.6 Hz, 1 H), 8.16 (t, J = 5.0 Hz, 1 H); FAB HRMS (NBA) m/e 930.5043, M + H^+ calcd for $C_{50}H_{71}N_5O_{10}Si$ 930.5049.

Epoxy Amide 20. To a solution of sulfonium salt **17** (3.66 g, 11.59 mmol, 1.2 equiv) in ^{t}BuOH (20.0 mL) was added a solution of NaOH 3.0 M in H_2O (3.86 mL, 11.59 mmol, 1.2 equiv). After 1 h at 25 °C, a solution of heptanal **18** (1.34 mL, 9.66 mmol, 1.0 equiv) in ^{t}BuOH (5.0 mL) was added and the reaction mixture was vigorously stirred overnight at 25 °C. After this time, reaction mixture was diluted with Et_2O and H_2O, both phases were separated, and the aqueous layer extracted with Et_2O twice. Combined organic extracts were then washed with water and brine, filtered and concentrated. Purification by flash column chromatography (silica gel, 30% AcOEt in hexanes) provided epoxy amide **20** (2.55 g, 80%) as a colorless oil: R_f = 0.48 (silica gel, 50% AcOEt in hexanes); $[\alpha]^{25}_D$ = +11.9 (c 1.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3 H), 1.26−1.30 (m, 4 H), 1.32−1.36 (m, 2 H), 1.40−1.55 (m, 2 H), 1.51 (s, 3 H), 1.62 (s, 3 H), 1.67−1.74 (m, 2 H), 1.77−1.81 (m, 1 H), 2.01−2.07 (m, 1 H), 2.10 (s, 3 H), 2.45 (ddd, J = 13.1, 8.6, 7.0 Hz, 1 H), 2.58 (ddd, J = 12.7, 7.3, 5.2 Hz, 1 H), 3.15 (ddd, J = 6.0, 4.3, 1.9 Hz, 1 H), 3.32 (d, J = 1.9 Hz, 1 H), 3.88 (d, J = 9.2 Hz, 1 H), 3.99 (ddd, J = 9.2, 5.3, 1.3 Hz, 1 H), 4.28 (ddd, J = 10.3, 5.0, 3.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 16.0, 22.5, 22.9, 25.8, 26.3, 29.0, 30.9, 31.5, 31.7, 34.5, 53.9, 55.8, 58.5, 67.0, 95.8, 164.2; FAB HRMS (NBA) m/e 330.2093, M + H^+ calcd for $C_{17}H_{31}NO_3S$ 330.2103.

Epoxy Amide 21. To a solution of sulfonium salt **17** (2.51 g, 7.95 mmol, 1.2 equiv) in ^{t}BuOH (12.0 mL) was added a solution of NaOH 3.0 M in H_2O (2.65 mL, 7.95 mmol, 1.2 equiv). After 1 h at 25 °C, a solution of nonanal **19** (1.14 mL, 6.63 mmol) in ^{t}BuOH (5.0 mL) was

added and the reaction mixture was vigorously stirred overnight at 25 °C. After this time, reaction mixture was diluted with Et_2O and H_2O, both phases were separated, and the aqueous layer extracted with Et_2O twice. Combined organic extracts were then washed with water and brine, filtered and concentrated. Purification by flash column chromatography (silica gel, 30% AcOEt in hexanes) provided epoxy amide **21** (1.72 g, 73%) as a colorless oil: R_f = 0.51 (silica gel, 50% AcOEt in hexanes); $[\alpha]^{25}_D$ = +19.4 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3 H), 1.20−1.37 (m, 12 H), 1.43−1.49 (m, 1 H), 1.53 (s, 3 H), 1.64 (s, 3 H), 1.69−1.78 (m, 1 H), 1.79−1.84 (m, 1 H), 2.03−2.08 (m, 1 H), 2.12 (s, 3 H), 2.47 (ddd, *J* = 13.1, 8.7, 7.0 Hz, 1 H), 2.60 (ddd, *J* = 12.8, 7.4, 5.2 Hz, 1 H), 3.17 (ddd, *J* = 6.5, 4.6, 2.0 Hz, 1 H), 3.33 (d, *J* = 2.0 Hz, 1 H), 3.89 (d, *J* = 9.2 Hz, 1 H), 4.01 (ddd, *J* = 9.2, 5.3, 1.5 Hz, 1 H), 4.30 (ddd, *J* = 10.3, 4.9, 3.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 16.0, 22.6, 22.9, 25.9, 26.3, 29.2, 29.3, 29.4, 30.9, 31.5, 31.8, 34.6, 53.9, 55.8, 58.5, 67.0, 95.8, 164.2; FAB HRMS (NBA) *m/e* 358.2386, M + H^+ calcd for $C_{19}H_{35}NO_3S$ 358.2416.

Hydroxy Amide 22. To a suspension of CuI (925 mg, 4.84 mmol, 4.0 equiv) in THF (20 mL) was added dropwise MeLi (1.6 M in Et_2O, 6.10 mL, 9.68 mmol, 8.0 equiv) at 0 °C. Then, a solution of epoxy amide **20** (400 mg, 1.21 mmol, 1.0 equiv) in THF (5 mL) was added to the resulting colorless solution of Me_2CuLi at 0 °C. The reaction mixture was stirred for 8 h at this temperature and quenched by careful addition of aqueous saturated NH_4Cl solution, followed by dilution with Et_2O. After separation of both phases, the aqueous phase was extracted with Et_2O and the combined organic layers 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 crude 2-methyl-3-hydroxy amide, which was subjected to purification by flash column chromatography (silica gel, 50% AcOEt in hexanes) to obtain **22** (341 mg, 82%) as a colorless oil: R_f = 0.38 (silica gel, 33% AcOEt in hexanes); $[\alpha]^{25}_D$ = +19.7 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.26 (d, *J* = 7.0 Hz, 3 H), 1.27−1.32 (m, 8 H), 1.37−1.47 (m, 2 H), 1.55 (s, 3 H), 1.64 (s, 3 H), 1.72−1.78 (m, 1 H), 2.00−2.08 (m, 1 H), 2.12 (s, 3 H), 2.42 (ddd, *J* = 13.3, 9.4, 6.5 Hz, 1 H), 2.59 (ddd, *J* = 13.3, 6.7, 4.8 Hz, 1 H), 2.68 (dq, *J* = 7.0, 5.1 Hz, 1 H), 3.32 (d, *J* = 7.7 Hz, 1 H), 3.57−3.63 (m, 1 H), 3.84 (d, *J* = 9.2 Hz, 1 H), 3.98 (ddd, *J* = 9.1, 5.2, 1.5 Hz, 1 H), 4.14 (ddd, *J* = 10.6, 5.0, 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 15.8, 16.0, 22.6, 22.9, 25.8, 26.5, 29.3, 30.9, 31.8, 33.5, 43.1, 57.0, 66.5, 74.8, 95.3, 173.6; FAB HRMS (NBA) *m/e* 346.2428, M + H^+ calcd for $C_{18}H_{35}NO_3S$ 346.2416.

Hydroxy Amide 23. To a suspension of CuI (2.13 g, 11.20 mmol, 4.0 equiv) in THF (50 mL) was added dropwise MeLi (1.6 M in Et_2O, 14.0 mL, 22.40 mmol, 8.0 equiv) at 0 °C. Then, a solution of epoxy amide **21** (1.00 g, 2.80 mmol, 1.0 equiv) in THF (10 mL) was added to the resulting colorless solution of Me_2CuLi at 0 °C. The reaction mixture was stirred for 8 h at this temperature and quenched by careful addition of aqueous saturated NH_4Cl solution, followed by dilution with Et_2O. After separation of both phases, the aqueous phase was extracted with Et_2O and the combined organic layers 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 crude 2-methyl-3-hydroxy amide, which was subjected to purification by flash column chromatography (silica gel, 30% AcOEt in hexanes) to obtain **23** (1.0 g, 96%) as a colorless oil: R_f = 0.42 (silica gel, 33% AcOEt in hexanes); $[\alpha]^{25}_D$ = +19.3 (*c* 1.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3 H), 1.26 (d, *J* = 6.7 Hz, 3 H), 1.23−1.32 (m, 12 H), 1.41−1.48 (m, 1 H), 1.56 (s, 3 H), 1.64 (s, 3 H), 1.72−1.77 (m, 1 H), 1.79−1.88 (m, 1 H), 2.00−2.08 (m, 1 H), 2.13 (s, 3 H), 2.42 (ddd, *J* = 15.7, 9.4, 6.5 Hz, 1 H), 2.56−2.64 (m, 1 H), 2.68 (dq, *J* = 6.8, 5.1 Hz, 1 H), 3.58−3.62 (m, 1 H), 3.83 (d, *J* = 9.2 Hz, 1 H), 3.98 (ddd, *J* = 9.2, 5.2, 1.6 Hz, 1 H), 4.14 (ddd, *J* = 11.2, 5.1, 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 15.7, 15.9, 22.6, 22.8, 25.8, 26.5, 29.2, 29.5, 29.6, 30.9, 31.8, 33.5, 35.8, 43.1, 56.9, 66.5, 74.8, 95.3, 173.6; FAB HRMS (NBA) *m/e* 374.2735, M + H^+ calcd for $C_{20}H_{39}NO_3S$ 374.2729.

Silyl Ether 24. A solution of hydroxy amide **22** (2.92 g, 8.44 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was treated with *tert*-butyldimethylsilyl trifluoromethanesulphonate (TBSOTf) (3.9 mL, 16.88 mmol, 2.0 equiv) at 0 °C in the presence of 2,6-lutidine (2.5 mL, 21.10 mmol, 2.5 equiv). After 0.5 h at 0 °C, the reaction mixture was quenched by addition of MeOH (2.0 mL), followed by addition of aqueous saturated NH_4Cl solution and dilution with Et_2O (50 mL). After separation of both phases, the aqueous phase was extracted with Et_2O (2 × 30 mL), and the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, 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 silyl ether **24** (3.70 g, 95%) as a colorless oil: R_f = 0.40 (silica gel, 20% AcOEt in hexanes); $[\alpha]^{25}_D$ = −14.3 (*c* 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3 H), −0.02 (s, 3 H), 0.80 (s, 3 H), 0.83 (t, *J* = 7.1 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 1.18−1.23 (m, 12 H), 1.36−1.50 (m, 2 H), 1.51 (s, 3 H), 1.53 (s, 3 H), 1.62−1.72 (m, 1 H), 1.94−2.02 (m, 1 H), 2.07 (s, 3 H), 2.30−2.41 (m, 1 H), 2.48−2.57 (m, 1 H), 2.68 (dq, *J* = 13.7, 6.9 Hz, 1 H), 3.74 (d, *J* = 9.1 Hz, 1 H), 3.84 (ddd, *J* = 9.0, 4.8, 1.5 Hz, 1 H), 3.94 (dt, *J* = 9.0, 3.5 Hz, 1 H), 4.10 (ddd, *J* = 10.8, 4.8, 2.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = −4.9, −4.2, 13.9, 14.8, 17.8, 21.7, 22.5, 23.6, 25.8, 26.3, 29.6, 31.8, 32.9, 43.4, 56.4, 66.5, 73.7, 94.7, 172.6; FAB HRMS (NBA) *m/e* 460.3308, M + H^+ calcd for $C_{24}H_{49}NO_3SSi$ 460.3281.

Silyl Ether 25. A solution of hydroxy amide **23** (350 mg, 0.94 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was treated with *tert*-butyldimethylsilyl trifluoromethanesulphonate (TBSOTf) (0.43 mL, 1.88 mmol, 2.0 equiv) at 0 °C in the presence of 2,6-lutidine (0.27 mL, 2.35 mmol, 2.5 equiv). After 0.5 h at 0 °C, the reaction mixture was quenched by addition of MeOH (0.5 mL), followed by addition of aqueous saturated NH_4Cl solution and dilution with Et_2O (20 mL). After separation of both phases, the aqueous phase was extracted with Et_2O (2 × 10 mL), the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvents were removed by reduced pressure to obtain a crude product which was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford silyl ether **25** (450 mg, 98%) as a colorless oil: R_f = 0.28 (silica gel, 10% AcOEt in hexanes); $[\alpha]^{25}_D$ = −9.6 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.86 (s, 9 H), 0.87 (t, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 1.21−1.32 (m, 12 H), 1.42−1.53 (m, 2 H), 1.57 (s, 3 H), 1.58 (s, 3 H), 1.70−1.78 (m, 1 H), 1.99−2.08 (m, 1 H), 2.12 (s, 3 H), 2.43 (ddd, *J* = 13.3, 9.0, 6.9 Hz, 1 H), 2.58 (ddd, *J* = 12.3, 6.8, 5.0 Hz, 1 H), 2.74 (dq, *J* = 8.9, 6.8 Hz, 1 H), 3.80 (d, *J* = 9.0 Hz, 1 H), 3.89 (ddd, *J* = 9.0, 4.8, 1.3 Hz, 1 H), 3.99 (dt, *J* = 9.0, 3.3 Hz, 1 H), 4.16 (ddd, *J* = 10.7, 4.6, 2.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.1, 14.1, 14.9, 15.9, 17.9, 21.9, 22.7, 23.8, 25.9, 26.5, 29.3, 29.7, 30.1, 31.2, 31.9, 33.1, 33.3, 43.6, 56.6, 66.7, 73.9, 94.8, 172.8; FAB HRMS (NBA) *m/e* 488.3605, M + H^+ calcd for $C_{26}H_{53}NO_3SSi$ 488.3594.

Diol 26 from Hydroxy Amide 22. A freshly prepared solution of LDA [Diisopropylamine (0.41 mL, 2.90 mmol, 10.0 equiv) was added to a solution of *n*-BuLi (1.6 M solution in hexanes, 1.8 mL, 2.90 mmol, 10.0 equiv) in THF (5.0 mL) at 0 °C] was treated with borane-ammonia complex (90 mg, 2.90 mmol, 10.0 equiv) at 0 °C. After 15 min at this temperature, the resulting suspension was stirred at room temperature for additional 30 min before cooling again at 0 °C. Then, a solution of hydroxy amide **22** (100 mg, 0.29 mmol, 1.0 equiv) in THF (3.0 mL) was added. The reaction mixture was warmed to room temperature and then heated under reflux for 8 h. After this time, reaction mixture was allowed to warm to room temperature and hydride excess was quenched by careful addition of MeOH (2.0 mL). The crude mixture was then diluted with Et_2O and treated with a saturated aqueous NH_4Cl solution. The

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organic phase was separated, and the aqueous phase was extracted with Et_2O (twice). The combined organic solution was sequentially 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, 20% → 50% AcOEt in hexanes) to obtain to obtain diol **26** (45 mg, 90%) as a colorless oil: R_f = 0.45 (silica gel, 50% AcOEt in hexanes); $[\alpha]^{25}_D$ = +16.1 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 1.24−1.35 (m, 7 H), 1.39−1.58 (m, 3 H), 1.67(dsext, *J* = 7.2, 3.7 Hz, 1 H), 3.29 (s, 2 H), 3.53 (dt, *J* = 7.8, 3.2 Hz, 1 H), 3.59 (dd, *J* = 10.8, 7.3 Hz, 1 H), 3.75 (dd, *J* = 10.8, 3.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.1, 22.6, 25.1, 29.4, 31.8, 35.3, 39.7, 67.6, 77.3; FAB HRMS (NBA) *m*/*e* 175.1708, M + H^+ calcd for $C_{10}H_{22}O_2$ 175.1698.

Diol 26 from Silyl Ether 24. A freshly prepared solution of LDA [Diisopropylamine (0.44 mL, 3.2 mmol, 4.0 equiv) was added to a solution of *n*-BuLi (1.6 M solution in hexanes, 2.0 mL, 3.2 mmol, 4.0 equiv) in THF (5.0 mL) at 0 °C] was treated with borane-ammonia complex (100 mg, 3.2 mmol, 4.0 equiv) at 0 °C. After 15 min at this temperature, the resulting suspension was stirred at room temperature for additional 30 min before cooling again at 0 °C. Then, a solution of the silyl ether **24** (367 mg, 0.80 mmol, 1.0 equiv) in THF (5.0 mL) was added. The reaction mixture was warmed to room temperature and then heated under reflux for 4 h. After this time, reaction mixture was allowed to warm to room temperature and worked out as described in Procedure A to obtain a crude product that was purified by flash column chromatography (silica gel, 50% AcOEt in hexanes) to obtain diol **26** (119 mg, 85%) that exhibited identical physical and spectroscopic properties than the obtained from **22** as described above.

Diol 27 from Hydroxy Amide 23. A freshly prepared solution of LDA [Diisopropylamine (0.36 mL, 2.60 mmol, 10.0 equiv) was added to a solution of *n*-BuLi (1.6 M solution in hexanes, 1.6 mL, 2.60 mmol, 10.0 equiv) in THF (5.0 mL) at 0 °C] was treated with borane-ammonia complex (80 mg, 2.60 mmol, 10.0 equiv) at 0 °C. After 15 min at this temperature, the resulting suspension was stirred at room temperature for additional 30 min before cooling again at 0 °C. Then, a solution of hydroxy amide **23** (97 mg, 0.26 mmol, 1.0 equiv) in THF (3.0 mL) was added. The reaction mixture was warmed to room temperature and then heated under reflux for 8 h. After this time, reaction mixture was allowed to warm to room temperature and hydride excess was quenched by careful addition of MeOH (2.0 mL). The crude mixture was then diluted with Et_2O and treated with a saturated aqueous NH_4Cl solution. The organic phase was separated, and the aqueous phase was extracted with Et_2O (twice). The combined organic solution was sequentially 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, 20% → 50% AcOEt in hexanes) to obtain to obtain diol **27** (49 mg, 93%) as a colorless oil: R_f = 0.38 (silica gel, 50% AcOEt in hexanes); $[\alpha]^{25}_D$ = +22.7 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 1.22−1.39 (m, 12 H), 1.41−1.51 (m, 1 H), 1.53−1.58 (m, 1 H), 1.71 (dsext, *J* = 7.1, 3.8 Hz, 1 H), 2.59 (bs, 1 H), 2.83 (bs, 1 H), 3.55 (dt, *J* = 7.6, 3.2 Hz, 1 H), 3.62 (dd, *J* = 10.9, 7.1 Hz, 1 H), 3.76 (dd, *J* = 10.9, 3.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.1, 22.6, 25.2, 29.3, 29.6, 29.7, 31.9, 35.4, 39.9, 67.6, 77.4; FAB HRMS (NBA) *m*/*e* 203.2015, M + H^+ calcd for $C_{12}H_{26}O_2$ 203.2011.

Diol 27 from Silyl Ether 25. A freshly prepared solution of LDA [diisopropylamine (0.24 mL, 1.72 mmol, 4.0 equiv) was added to a solution of *n*-BuLi (1.6 M solution in hexanes, 1.1 mL, 1.72 mmol, 4.0 equiv) in THF (4.0 mL) at 0 °C] was treated with borane−ammonia complex (53 mg, 1.72 mmol, 4.0 equiv) at 0 °C. After 15 min at this temperature, the resulting suspension was stirred at room temperature for an additional 30 min before cooling again at 0 °C. Then, a solution of the silyl ether **25** (209 mg, 0.43 mmol, 1.0 equiv) in THF (4.0 mL) was added. The reaction mixture was warmed to room temperature and then heated under reflux for 4 h. After this time, reaction mixture was allowed to warm to room temperature and worked up as described in Procedure A to obtain a crude product that was purified by flash column chromatography (silica gel, 50% AcOEt in hexanes) to obtain diol **27** (80 mg, 92%) that exhibited identical physical and spectroscopic properties as that obtained from **23** as described above.

Hydroxy Acid 9. Diol **26** (100 mg, 0.57 mmol) was dissolved in a mixture of CH_3CN/H_2O (8.0 mL, 1:1) and the resulting solution was treated with BAIB (918 mg, 2.85 mmol, 5.0 equiv) followed by TEMPO (44 mg, 0.29 mmol, 0.5 equiv) at 25 °C. After 6 h, the crude mixture was diluted with AcOEt and quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution, and after separation of both layers, the aqueous phase was then extracted with AcOEt. The combined organic solution was washed with saturated aqueous $Na_2S_2O_3$ solution again and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. Purification of the crude acid by flash column chromatography (silica gel, 3% → 5% MeOH in CH_2Cl_2) provided hydroxy acid **9** (77 mg, 72%) as a colorless oil: R_f = 0.25 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = +5.0 (*c* 0.54, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.8 Hz, 3 H), 1.20−1.37 (m, 7 H), 1.23 (d, *J* = 7.2 Hz, 3 H), 1.40−1.57 (m, 3 H), 2.54 (quint, *J* = 6.9 Hz, 1 H), 3.64−3.70 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.2, 22.6, 25.4, 29.2, 31.8, 34.6, 45.2, 67.6, 77.3, 180.8; FAB HRMS (NBA) *m*/*e* 189.1504, M + H^+ calcd for $C_{10}H_{20}O_3$ 189.1491.

Hydroxy Acid 10. Diol **27** (70 mg, 0.37 mmol) was dissolved in a mixture of CH_3CN/H_2O (6.0 mL, 1:1) and the resulting solution was treated with BAIB (602 mg, 1.84 mmol, 5.0 equiv) followed by TEMPO (30 mg, 0.18 mmol, 0.5 equiv) at 25 °C. After 6 h, the crude mixture was diluted with AcOEt and quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution, and after separation of both layers, the aqueous phase was then extracted with AcOEt. The combined organic solution was washed with saturated aqueous $Na_2S_2O_3$ solution again and dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. Purification of the crude acid by flash column chromatography (silica gel, 3% → 5% MeOH in CH_2Cl_2) provided hydroxy acid **10** (49 mg, 65%) as a colorless oil: R_f = 0.29 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = +1.9 (*c* 2.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.9 Hz, 3 H), 1.24 (d, *J* = 7.2 Hz, 3 H), 1.25−1.39 (m, 11 H), 1.42−1.57 (m, 3 H), 2.56 (quint, *J* = 6.9 Hz, 1 H), 3.67−3.72 (m, 1 H), 6.22 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 22.6, 25.4, 29.2, 29.5, 31.8, 34.6, 45.2, 77.3, 180.9; FAB HRMS (NBA) *m*/*e* 217.1824, M + H^+ calcd for $C_{12}H_{24}O_3$ 217.1804.

Epoxy Alcohols 30 and 31. General Procedure. To a solution of titanium tetraisopropoxide (0.20 equiv) and 4 Å molecular sieves in CH_2Cl_2 (0.1 M) was added (−)-DET (0.25 equiv) at −23 °C. After 15 min at this temperature, a solution of allylic alcohols **28** or **29** (1.0 equiv) in CH_2Cl_2 (1.0 M) was added dropwise, followed by the addition, after additional 30 min, of TBHP (5.5 M solution in decane, 1.5 equiv) at −23 °C. After 8 h at this temperature, the reaction mixture was filtered and the filtrate was diluted with EtOAc and washed with a saturated aqueous solution of sodium sulfate. After decantation, the aqueous phase was extracted with EtOAc (3 times), and the combined organic layer was dried ($MgSO_4$), filtered and concentrated. The resulting crude products were purified by flash column chromatography (silica gel, 20% AcOEt in hexanes for both cases) to obtain epoxy alcohols **30** and **31** (75% and 70% yields, respectively). Data for **30**: described in the literature;[24] white solid; mp 45 °C; R_f = 0.39 (silica gel, 30% AcOEt in hexanes); $[\alpha]^{25}_D$ = +38.6 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3 H), 1.25−1.37 (m, 6 H), 1.41−1.46 (m, 2 H), 1.54−1.59 (m, 2 H), 1.89 (dd, *J* = 6.5, 6.1 Hz, 1 H), 2.92 (dt, *J* = 4.9, 2.5 Hz, 1 H), 2.95 (dt, *J* = 5.7, 2.5 Hz, 1 H), 3.61 (ddd, *J* = 11.5, 7.0, 4.4 Hz, 1 H), 3.90 (ddd, *J* = 12.6, 5.3, 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.4, 25.8, 28.9, 31.5, 31.6, 56.0, 58.7, 61.9. Data for **31**: colorless oil; R_f = 0.45 (silica gel, 20% AcOEt in hexanes); $[\alpha]^{25}_D$ = +16.2 (*c* 2.3, CH_2Cl_2); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 0.80 (t, J = 6.8 Hz, 3 H), 1.19−1.21 (m, 11 H), 1.41−1.51 (m, 2 H), 2.27 (bs, 1 H), 2.93 (t, J = 6.1 Hz, 1 H), 3.46 (dd, J = 12.1, 6.7 Hz, 1 H), 3.59 (d, J = 11.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 22.5, 26.3, 28.1, 29.0, 31.7, 60.3, 61.0, 65.4; FAB HRMS (NBA) m/e 173.1557, M + H^+ calcd for $C_{10}H_{20}O_2$ 173.1542.

Epoxy Alcohol 30 from Epoxyamide 20. To a solution of epoxyamide **20** (85 mg, 0.26 mmol, 1.0 equiv) in THF (4.0 mL) was added lithium triethylborohydride (Super-H) (1.0 M solution in THF, 0.78 mL, 0.78 mmol, 3.0 equiv) at 0 °C. After 15 min at this temperature, the excess of Super-H was carefully quenched by addition of MeOH (0.5 mL), and the resulting mixture diluted with Et_2O (5 mL) and washed with a saturated aqueous NH_4Cl solution (8 mL). After decantation, the aqueous phase was extracted with Et_2O (2 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and filtered. Concentration under reduced pressure provided a crude product that was purified by flash column chromatography (silica gel, 20% AcOEt in hexanes) to afford epoxy alcohol **30** (35 mg, 85% yield), whose physical and spectroscopic data were identical to those described in the literature and completely matched that obtained from Sharpless asymmetric epoxidation.

Diol 26 from Epoxy Alcohol 30. To a suspension of CuI (4.57 g, 24.0 mmol, 3.0 equiv) in THF (50 mL) was added dropwise MeLi (1.6 M in Et_2O, 30.0 mL, 48.0 mmol, 6.0 equiv) at 0 °C. Then, a solution of epoxy alcohol **30** (1.26 g, 8.0 mmol, 1.0 equiv) in THF (10 mL) was added to the resulting colorless solution of Me_2CuLi at 0 °C. The reaction mixture was stirred for 8 h at this temperature and quenched by careful addition of aqueous saturated NH_4Cl solution, followed by dilution with Et_2O. After separation of both phases, the aqueous phase was extracted with Et_2O and the combined organic layers 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 consisting of a mixture of 2- and 3-methyl opening products in a 3:1 proportion, which was subjected to the next step without purification. Thus, crude diol (1.39 g, 8.0 mmol, 1.0 equiv) in THF (30 mL) and water (30 mL) was treated with $NaIO_4$ (855 mg, 4.0 mmol, 0.5 equiv) at room temperature. After vigorous stirring for 18 h, the reaction mixture was diluted with Et_2O and water. After separation of both phases, the aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic layers were washed with brine. After treatment with $MgSO_4$, the solvents were removed by reduced pressure and the crude product purified by flash column chromatography (silica gel, 50% AcOEt in hexanes) to obtain the desired 1,3-diol **26** (571 mg, 41%) as a colorless oil and with physical and spectroscopic properties identical to those reported above.

Hydroxy Ester 33. To a solution of epoxy alcohol **31** (1.17 g, 6.80 mmol) in CH_2Cl_2 (20 mL) was sequentially added DMSO (8.0 mL), TEA (4.7 mL, 34.0 mmol, 5.0 equiv) and pyr·SO_3 complex (2.2 g, 13.60 mmol, 2.0 equiv) at 0 °C. After stirring for 2 h, the reaction mixture was diluted with Et_2O, and a saturated aqueous NH_4Cl solution added. The organic phase was separated, and the aqueous phase was extracted with Et_2O (twice). The combined organic solution was sequentially washed with water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting aldehyde was used in the next step without further purification. To a solution of catalyst **32** (163 mg, 0.68 mmol, 0.1 equiv) in CH_2Cl_2 (10 mL) was added crude aldehyde (~ 6.80 mmol), followed by EtOH (1.2 mL, 20.4 mmol, 3.0 equiv) and DIPEA (0.1 mL, 0.54 mmol, 0.08 equiv). The resulting yellow solution was stirred at 25 °C overnight, after which TLC analysis showed depletion of starting material. The reaction mixture was then treated with a saturated aqueous NH_4Cl solution and diluted with Et_2O. The organic phase was separated, and the aqueous phase was extracted with Et_2O (twice). The combined organic solution was sequentially 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, 20% AcOEt in hexanes) to obtain an inseparable mixture of hydroxy esters **33** and its C-2 epimer (1.0 g, 70% combined overall yield from epoxy alcohol **31**, dr 7:3 *anti:syn*) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.80 (t, J = 7.0 Hz, 3 H), 1.12 (d, J = 7.1 Hz, 3 H), 1.19 (t, J = 7.3 Hz, 3 H), 1.17−1.24 (m, 8 H), 1.32−1.42 (m, 2 H), 2.42 (quint, J = 7.1 Hz, 1 H), 3.57 (dt, J = 6.7, 3.3 Hz, 1 H), 4.08 (q, J = 7.3 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 14.0, 14.1, 14.3, 22.5, 25.4, 29.2, 31.7, 34.7, 45.1, 60.5, 73.3, 176.1; FAB HRMS (NBA) m/e 217.1815, M + H^+ calcd for $C_{12}H_{24}O_3$ 217.1804.

Acid 9 from Hydroxy Ester 33. A solution of hydroxy ester **33** (450 mg, 2.1 mmol) in THF (10 mL) was treated with a 1.0 M aqueous LiOH solution (4.2 mL, 4.2 mmol, 2.0 equiv) at 0 °C. After stirring for 8 h at 25 °C, the reaction mixture was treated with a 2.0 M aqueous HCl solution until pH 2. Then, the crude mixture was diluted with EtOAc and water, both phases were separated, and the aqueous phase extracted with AcOEt (3 × 15 mL). The combined organic extracts were sequentially washed with water and brine, dried over $MgSO_4$, filtered and concentrated by reduced pressure. The crude product was purified by flash column chromatography (silica gel, 3% → 5% MeOH in CH_2Cl_2) to provide hydroxy acid **9** contaminated with its 2-epimer (365 mg, 92% combined yield in a 7:3 proportion) as a colorless oil whose major isomer exhibited spectroscopic properties identical to those reported above.

Dihydroxy Amide 34. A solution of hydroxy amide **22** (1.86 g, 5.39 mmol) in dioxane (30 mL) was treated with a 2.7 M aqueous HCl solution (15 mL) at 25 °C. After stirring for 8 h at this temperature, a white solid was formed in the reaction mixture, which was filtered and washed with cold water (three times) and Et_2O (three times). After drying under high vacuum, a white solid was obtained that corresponded to the titled compound **34** (1.60 g, 98%) which did not require further purification: R_f = 0.35 (silica gel, 5% MeOH in CH_2Cl_2); mp 140−143 °C; $[\alpha]^{25}_D$ = −25.3 (c 0.9, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J = 6.8 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H), 1.21−1.27 (m, 8 H), 1.35−1.40 (m, 2 H), 1.53 (ddt, J = 14.6, 9.7, 5.0 Hz, 1 H), 1.76−1.84 (m, 1 H), 2.02 (s, 3 H), 2.25 (quint, J = 6.9 Hz, 1 H), 2.37 (ddd, J = 12.9, 9.7, 6.5 Hz, 1 H), 2.48 (ddd, J = 12.9, 10.0, 5.0 Hz, 1 H), 3.23 (dt, J = 10.7, 6.2 Hz, 1 H), 3.35 (dt, J = 10.5, 5.2 Hz, 1 H), 3.44 (bq, J = 6.7 Hz, 1 H), 3.74−3.83 (m, 1 H), 4.45 (d, J = 6.6 Hz, 1 H), 4.65 (t, J = 5.6 Hz, 1 H), 7.47 (d, J = 8.6 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 14.1, 14.6, 22.0, 25.0, 28.8, 29.9, 30.8, 31.3, 34.1, 45.5, 49.6, 63.2, 71.9, 174.7; FAB HRMS (NBA) m/e 306.2095, M + H^+ calcd for $C_{15}H_{31}NO_3S$ 306.2103.

Bis(silyl ether) 36. A solution of dihydroxy amide **34** (562 mg, 1.84 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (1.05 mL, 4.60 mmol, 2.5 equiv) at 0 °C in the presence of 2,6-lutidine (0.64 mL, 5.52 mmol, 3.0 equiv). After 1.0 h at 0 °C, the reaction mixture was quenched by addition of MeOH (1.0 mL), followed by addition of aqueous saturated NH_4Cl solution (15 mL) and dilution with Et_2O (20 mL). After separation of both phases, the aqueous phase was extracted with Et_2O (2 × 15 mL), and the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvents were removed under reduced pressure to obtain a crude product, which was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford bis(silyl ether) **36** (956 mg, 97%) as a colorless oil: R_f = 0.54 (silica gel, 10% AcOEt in hexanes); $[\alpha]^{25}_D$ = −29.7 (c 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.08 (s, 3 H), 0.09 (s, 3 H), 0.87 (t, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.92 (s, 9 H), 1.21 (d, J = 7.3 Hz, 3 H), 1.24−1.27 (m, 8 H), 1.48−1.62 (m, 2 H), 1.66−1.75 (m, 1 H), 1.83−1.92 (m, 1 H), 2.09 (s, 3 H), 2.45 (dq, J = 7.3, 3.4 Hz, 1 H), 2.47−2.51 (m, 2 H), 3.61 (d, J = 4.1 Hz, 2 H), 3.70 (ddd, J = 8.0, 5.4, 3.4 Hz, 1 H), 4.02−4.08 (m, 1 H), 6.75 (d, J = 8.9 Hz, 1 H); ^{13}C NMR (100

MHz, $CDCl_3$) δ −5.4, −4.8, −4.2, 14.0, 15.5, 16.5, 18.0, 18.3, 22.6, 25.7, 25.9, 26.0, 29.4, 30.9, 31.3, 31.7, 35.6, 45.9, 49.7, 64.9, 74.7, 174.7; FAB HRMS (NBA) *m/e* 534.3845, M + H^+ calcd for $C_{27}H_{59}NO_3SSi_2$ 534.3832.

Acid 42. To a stirred solution of bis(silyl ether) **36** (52 mg, 0.097 mmol, 1.0 equiv) in a mixture of Ac_2O (4 mL) and AcOH (2 mL) was portionwise added $NaNO_2$ (140 mg, 2.02 mmol, 20.0 equiv) at 0 °C. The reaction mixture was stirred for 4 h at this temperature, after which it was diluted with cold water (5 mL) and extracted with Et_2O (3 × 10 mL). Then, the combined organic solution was washed with a 5% aqueous $NaHCO_3$ solution several times until removal of acetic acid was complete (~10 × 10 mL). Finally, the ethereal solution was washed with brine (20 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, CH_2Cl_2 → 1% MeOH in CH_2Cl_2) furnished acid derivative **42** (22 mg, 75%) as a yellow oil: R_f = 0.43 (silica gel, 1% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = −2.7 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3 H), 0.11 (s, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.91 (s, 9 H), 1.21 (d, *J* = 7.2 Hz, 3 H), 1.24−1.33 (m, 8 H), 1.45−1.59 (m, 2 H), 2.67 (dq, *J* = 7.3, 4.3 Hz, 1 H), 3.85 (ddd, *J* = 5.4, 4.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.4, 14.1, 18.0, 22.6, 24.8, 25.7, 29.3, 31.7, 34.7, 44.7, 74.4, 177.7; FAB HRMS (NBA) *m/e* 303.2352, M + H^+ calcd for $C_{16}H_{34}O_3Si$ 303.2356.

Acid 9 from Silyloxy Acid 42. A solution of silyloxy acid **42** (13 mg, 0.043 mmol) in THF (3 mL) was treated with TBAF (1.0 M in THF, 65 μL, 0.065 mmol, 1.5 equiv) at 0 °C. After 2.0 h at 0 °C, the reaction mixture was diluted with EtOAc (5 mL) and washed with a saturated aqueous NH_4Cl solution (5 mL). After separation of both phases, the aqueous phase was extracted with AcOEt (3 × 5 mL), and the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvents were removed under reduced pressure to obtain a crude product which was purified by flash column chromatography (silica gel, 3% → 5% MeOH in CH_2Cl_2) to provide hydroxy acid **9** (7.8 mg, 95%), which exhibited spectroscopic properties identical to those reported above.

Dihydroxy Amide 44. A solution of hydroxy amide **23** (44 mg, 0.118 mmol) in dioxane (5 mL) was treated with a 2.7 M aqueous HCl solution (2.5 mL) at 25 °C. After stirring for 8 h at this temperature, a white solid was formed in the reaction mixture, which was filtered and washed with cold water (three times) and Et_2O (three times). After drying under high vacuum, a white solid was obtained that corresponded to the titled compound **44** (36 mg, 91%) and did not require further purification: R_f = 0.37 (silica gel, 5% MeOH in CH_2Cl_2); mp 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.7 Hz, 3 H), 1.25 (d, *J* = 7.1 Hz, 3 H), 1.26−1.32 (m, 12 H), 1.45−1.50 (m, 2 H), 1.81−1.96 (m, 4 H), 2.12 (s, 3 H), 2.29 (dq, *J* = 7.1, 5.4 Hz, 1 H), 2.48−2.59 (m, 2 H), 3.59−3.64 (m, 1 H), 3.65 (dd, *J* = 11.2, 5.2 Hz, 1 H), 3.71 (dd, *J* = 11.2, 3.6 Hz, 1 H), 4.02−4.09 (m, 1 H), 6.15 (d, *J* = 7.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 15.6, 15.7, 22.7, 25.8, 29.3, 29.5, 29.6, 30.4, 30.8, 31.9, 35.5, 46.5, 51.1, 65.1, 74.0, 176.6; FAB HRMS (NBA) *m/e* 334.2425, M + H^+ calcd for $C_{17}H_{35}NO_3S$ 334.2416.

Bis(silyl ether) 45. A solution of dihydroxy amide **44** (33 mg, 0.099 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (57 μL, 0.247 mmol, 2.5 equiv) at 0 °C in the presence of 2,6-lutidine (35 μL, 0.30 mmol, 3.0 equiv). After 1.0 h at 0 °C, the reaction mixture was quenched by addition of MeOH (0.2 mL), followed by addition of aqueous saturated NH_4Cl solution (10 mL) and dilution with Et_2O (10 mL). After separation of both phases, the aqueous phase was extracted with Et_2O (2 × 5 mL), and the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvents were removed under reduced pressure to obtain a crude product which was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford bis(silyl ether) **45** (55 mg, 98%) as a colorless oil: R_f = 0.59 (silica gel, 10% AcOEt in hexanes); $[\alpha]^{25}_D$ = −30.4 (*c* 2.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.036 (s, 3 H), 0.042 (s, 3 H), 0.085 (s, 3 H), 0.089 (s, 3 H), 0.85 (t, *J* = 7.0 Hz, 3 H), 0.87 (s, 9 H), 0.92 (s, 9 H), 1.21 (d, *J* = 7.2 Hz, 3 H), 1.22−1.27 (m, 12 H), 1.46−1.61 (m, 2 H), 1.66−1.75 (m, 1 H), 1.83−1.92 (m, 1 H), 2.08 (s, 3 H), 2.45 (dq, *J* = 7.3, 3.3 Hz, 1 H), 2.46−2.51 (m, 2 H), 3.60 (d, *J* = 4.1 Hz, 2 H), 3.69 (ddd, *J* = 8.3, 5.3, 3.3 Hz, 1 H), 4.02−4.08 (m, 1 H), 6.76 (d, *J* = 8.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −4.8, −4.2, 14.07, 14.09, 15.5, 16.5, 18.0, 18.3, 22.6, 25.7, 25.9, 26.0, 29.2, 29.5, 29.7, 30.9, 31.3, 31.6, 31.8, 35.6, 45.9, 49.7, 64.9, 74.7, 174.8; FAB HRMS (NBA) *m/e* 562.4149, M + H^+ calcd for $C_{29}H_{63}NO_3SSi_2$ 562.4145.

Acid 46. To a stirred solution of bis(silyl ether) **45** (51 mg, 0.091 mmol, 1.0 equiv) in a mixture of Ac_2O (4 mL) and AcOH (2 mL) was portionwise added $NaNO_2$ (125 mg, 1.81 mmol, 20.0 equiv) at 0 °C. The reaction mixture was stirred for 4 h at this temperature, after which it was diluted with cold water (5 mL) and extracted with Et_2O (3 × 10 mL). Then, the combined organic solution was washed with a 5% aqueous $NaHCO_3$ solution several times until removal of acetic acid was complete (~10 × 10 mL). Finally, the ethereal solution was washed with brine (20 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, CH_2Cl_2 → 1% MeOH in CH_2Cl_2) furnished acid derivative **46** (20 mg, 65%) as a yellow oil: R_f = 0.47 (silica gel, 1% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ = −3.5 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 3 H), 0.12 (s, 3 H), 0.88 (t, *J* = 7.2 Hz, 3 H), 0.91 (s, 9 H), 1.21 (d, *J* = 7.2 Hz, 3 H), 1.25−1.28 (m, 12 H), 1.47−1.59 (m, 2 H), 2.67 (dq, *J* = 7.1, 4.2 Hz, 1 H), 3.84 (ddd, *J* = 5.6, 4.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.4, 14.1, 18.0, 22.6, 24.8, 25.7, 29.2, 29.4, 29.6, 31.8, 34.8, 44.5, 74.4, 177.3; FAB HRMS (NBA) *m/e* 331.2674, M + H^+ calcd for $C_{18}H_{37}O_3Si$ 331.2668.

Acid 10 from Silyloxy Acid 46. A solution of silyloxy acid **46** (18 mg, 0.054 mmol) in THF (3 mL) was treated with TBAF (1.0 M in THF, 82 μL, 0.082 mmol, 1.5 equiv) at 0 °C. After 2.0 h at 0 °C, the reaction mixture was diluted with EtOAc (5 mL) and washed with a saturated aqueous NH_4Cl solution (5 mL). After separation of both phases, the aqueous phase was extracted with AcOEt (3 × 5 mL), and the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvents were removed under reduced pressure to obtain a crude product which was purified by flash column chromatography (silica gel, 3% → 5% MeOH in CH_2Cl_2) to provide hydroxy acid 10 (11.5 mg, 98%) which exhibited identical spectroscopic properties to those reported above.

Polystyrene-Bound Pentapeptide-NMe-nonanoyl Derivative 7. To a 10 mL polypropylene syringe fitted with a polyethylene porous disk and loaded with the polymer-bound Fmoc protected pentapeptide **15** (152 mg, L = 0.6 mmol/g, 0.091 mmol, 1.0 equiv) was added a solution of 20% piperidine in DMF (3 × 6 mL × 10 min), and the mixture was shaken at 280 rpm. After the last run, the resin was washed with dry DMF (5 × 6 mL) and treated with a solution of the hydroxyacid **9** (52 mg, 0.273 mmol, 3.0 equiv), TEA (39 μL, 0.273 mmol, 3.0 equiv) and DEPC (45 μL, 0.273 mmol, 3.0 equiv) in dry DMF (4 mL) for two times, 8 h each time. Once the solution was unloaded, the resin was washed with DMF (4 × 4 mL) and DCM (4 × 4 mL). The resulting swelled resin **7** was used in the next step.

Seco-acid 47. The resin **7** was treated with a solution of DCM/AcOH/TFE (7:2:1, 3 mL) for 30 min. After that, the solution was collected and the resin washed with DCM (2 × 3 mL). All the collected organic solvents were evaporated under reduced pressure and the resulting seco-acid **47**[16] (52 mg, 65%) was obtained as a white solid and not requiring further purification: $[\alpha]^{25}_D$ = −13.1 (*c* 0.16, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6, two rotamers in a 4:1 ratio) δ −0.03 (s, 3 H), 0.02 (s, 3 H), 0.69 (d, *J* = 6.8 Hz, 12/5 H), 0.74 (d, *J* = 6.9 Hz, 3/5 H), 0.79−0.91 (m, 12 H), 0.81 (s, 9 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 1.05 (d, *J* = 6.2 Hz, 3 H), 1.19−1.32 (m, 10 H), 1.33−1.55 (m, 4 H),

1.57−1.67 (m, 1 H), 1.74−1.82 (m, 1 H), 2.69 (s, 3/5 H), 2.78−2.89 (m, 1 H), 2.86 (s, 12/5 H), 3.49−3.61 (m, 4 H), 3.78 (dd, *J* = 17.5, 6.1 Hz, 1 H), 3.91 (dt, *J* = 15.0, 7.1 Hz, 1/5 H), 4.01 (q, *J* = 6.5 Hz, 4/5 H), 4.36−4.40 (m, 2 H), 4.48 (s, 2 H), 4.64−4.73 (m, 6/5 H), 5.11 (dd, *J* = 10.7, 4.8 Hz, 4/5 H), 7.25−7.34 (m, 6 H), 7.91 (d, *J* = 8.9 Hz, 1/5 H), 7.98 (d, *J* = 9.3 Hz, 1/5 H), 8.02 (d, *J* = 9.1 Hz, 3/5 H), 8.09 (d, *J* = 7.9 Hz, 1/5 H), 8.18 (d, *J* = 8.2 Hz, 4/5 H), 8.21 (t, *J* = 5.8 Hz, 4/5 H); ^{13}C NMR (100 MHz, DMSO-d_6, both rotamers) δ −5.1, −4.7, 11.6, 13.2, 14.0, 14.1, 17.7, 19.5, 21.5, 22.1, 23.3, 24.1, 25.1, 25.6, 25.8, 28.8, 30.5, 31.4, 33.4, 36.1, 37.2, 40.6, 41.4, 52.3, 53.2, 55.3, 58.2, 68.7, 69.9, 71.8, 72.1, 127.4, 127.5, 127.6, 128.2, 138.1, 169.2, 169.7, 170.3, 170.78, 170.83, 176.1.

Cyclodepsipeptide 49. To a suspension of the seco-acid **47** (50 mg, 0.057 mmol, 1.0 equiv) in dry THF (2 mL) were added dry TEA (25 μL, 0.171 mmol, 3.0 equiv) and 2,4,6-trichlorobenzoyl chloride (12 μL, 0.068 mmol, 1.2 equiv) at room temperature. After 24 h, the suspension was diluted with dry toluene (27 mL) and added over 5 h via a syringe pump into a refluxed solution of 4-DMAP (140 mg, 1.14 mmol, 20.0 equiv) in dry toluene (29 mL). The mixture was refluxed for an additional 2 h. Once cooled, the solvents were evaporated under reduced pressure, diluted with EtOAc and washed sequentially with 5% HCl, saturated $NaHCO_3$ and brine aqueous solutions. The organic layer was dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulted brown syrupe was purified by preparative HPLC (column: Phenomenex-luna C8(2), (10 mm × 250 mm), refraction index detector, flow rate: 4.7 mL/min with 90% MeOH) to give cyclic depsipeptide **49**[16] (12 mg, 24%) as a white solid: $[\alpha]^{25}_D$ = +16.0 (*c* 0.45, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers in a 7:3 proportion) δ 0.05 (s, 21/10 H), 0.06 (s, 9/10 H), 0.07 (s, 21/10 H), 0.08 (s, 9/10H), 0.84−0.99 (m, 15 H), 0.84 (s, 63/10 H), 0.85 (s, 27/10 H), 1.07−1.16 (m, 6 H), 1.20−1.40 (m, 11 H), 1.41−1.57 (m, 3 H), 1.63−1.75 (m, 27/10 H), 1.88−1.94 (m, 1 H), 1.98−2.03 (m, 3/10H), 2.09−2.14 (m, 3/10H), 2.16−2.24 (m, 7/10 H), 2.77 (s, 9/10 H), 3.01 (dq, *J* = 9.6, 7.0 Hz, 7/10 H), 3.11−3.16 (m, 3/10 H), 3.16 (s, 21/10 H), 3.54 (dd, *J* = 17.1, 3.6 Hz, 7/10 H), 3.71 (bs, 7/10 H), 3.77 (dd, *J* = 10.1, 6.3 Hz, 7/10 H), 3.85 (dd, *J* = 10.1, 4.8 Hz, 7/10 H), 3.89 (dd, *J* = 10.4, 5.5 Hz, 3/10 H), 3.93−4.01 (m, 1 H), 4.20−4.23 (m, 7/10 H), 4.30 (q, *J* = 4.6 Hz, 3/10 H), 4.38 (dd, *J* = 17.2, 8.8 Hz, 7/10 H), 4.42−4.49 (m, 18/10 H), 4.51 (d, *J* = 11.8 Hz, 7/10 H), 4.55 (dd, *J* = 7.9, 4.6 Hz, 3/10 H), 4.61 (d, *J* = 11.8 Hz, 7/10 H), 4.61−4.65 (m, 14/10 H), 4.76 (dd, *J* = 9.4, 3.9 Hz, 3/10 H), 4.83 (d, *J* = 10.7 Hz, 3/10 H), 5.28 (ddd, *J* = 9.9, 7.5, 2.9 Hz, 7/10 H), 6.39 (d, *J* = 7.5 Hz, 7/10 H), 6.42 (d, *J* = 2.5 Hz, 7/10 H), 6.69−6.71 (m, 6/10 H), 6.88 (d, *J* = 9.6 Hz, 3/10 H), 7.04 (t, *J* = 5.6 Hz, 3/10 H), 7.28−7.40 (m, 5 H), 7.71 (dd, *J* = 8.6, 3.6 Hz, 7/10 H), 8.21 (bs, 7/10 H); ^{13}C NMR (100 MHz, $CDCl_3$, both rotamers) δ −4.8, −4.7, −4.6, 11.9, 14.1, 14.2, 15.1, 15.2, 15.3, 18.1, 18.4, 19.0, 21.8, 22.6, 22.7, 23.2, 23.3, 24.1, 25.0, 25.3, 25.9, 26.5, 27.1, 27.2, 29.1, 29.2, 29.4, 29.5, 31.6, 31.8, 31.9, 37.5, 37.6, 38.2, 38.5, 39.6, 40.2, 40.6, 56.1, 56.2, 56.3, 56.7, 59.1, 59.3, 59.4, 66.8, 67.1, 68.03, 68.12, 73.6, 73.9, 76.4, 77.4, 78.4, 128.2, 128.3, 128.5, 128.6, 128.9, 136.8, 137.0, 168.9, 169.4, 169.5, 169.7, 169.9, 170.1, 171.8.

Cyclodepsipeptide 51. To a solution of cyclic compound **49** (8 mg, 9.3 μmol, 1.0 equiv) in dry THF (0.5 mL) were added at room temperature AcOH (40 μL, 0.698 mmol, 75.0 equiv) and TBAF (0.5 mL, 1 M solution in THF, 0.5 mmol, 54.0 equiv). After 26 h, the mixture was diluted with EtOAc and washed with a saturated aqueous $NaHCO_3$ solution and brine. Once dried over anhydrous $MgSO_4$ and the solvents evaporated under reduced pressure, the crude was purified by preparative HPLC (column: Phenomenex-luna 5 μm C8(2), (10 mm × 250 mm), refraction index detector, flow rate: 4.7 mL/min with 90% MeOH) to give cyclodepsipeptide **51**[16] (6 mg, 87%) as a white solid: $[\alpha]^{25}_D$ = +26.0 (*c* 0.25, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers in a 3.5/1 proportion) δ 0.85−0.98 (m, 15 H), 1.10 (d, *J* = 6.9 Hz, 12/5 H), 1.16 (d, *J* = 7.0 Hz, 3/5 H), 1.07−1.16 (m, 6 H), 1.20−1.40 (m, 11 H), 1.19−1.69 (m, 17 H), 1.74 (ddd, *J* = 14.0, 8.6, 5.6 Hz, 1 H), 1.99−2.06 (m, 1 H), 2.08−2.16 (m, 1 H), 2.78 (s, 3/5 H), 3.07−3.15 (m, 1 H), 3.18 (s, 12/5 H), 3.62 (dd, *J* = 17.2, 3.9 Hz, 4/5 H), 3.69 (bs, 4/5 H), 3.79 (dd, *J* = 18.5, 3.7 Hz, 1/5 H), 3.84 (dd, *J* = 10.0, 4.8 Hz, 1 H), 3.90 (dd, *J* = 10.0, 5.7 Hz, 1 H), 3.95 (dd, *J* = 10.1, 4.2 Hz, 1/5 H), 4.00 (dd, *J* = 11.3, 4.8 Hz, 1/5 H), 4.11−4.21 (m, 9/5 H), 4.29 (q, *J* = 5.0 Hz, 4/5 H), 4.34−4.47 (m, 2 H), 4.54 (d, *J* = 11.8 Hz, 1 H), 4.57 (d, *J* = 11.8 Hz, 1 H), 4.77 (dd, *J* = 9.4, 3.9 Hz, 1/5 H), 4.84 (d, *J* = 11.1 Hz, 1/5 H), 5.08−5.14 (m, 4/5 H), 6.71 (d, *J* = 4.1 Hz, 1/5 H), 6.80 (bs, 1 H), 6.89 (d, *J* = 7.7 Hz, 4/5 H), 7.19 (d, *J* = 9.2 Hz, 1/5 H), 7.29−7.39 (m, 5 H), 7.59 (dd, *J* = 8.6, 3.6 Hz, 4/5 H), 7.84 (d, *J* = 6.5 Hz, 4/5 H); ^{13}C NMR (100 MHz, $CDCl_3$, both rotamers) δ 11.69, 11.75, 11.8, 14.0, 14.7, 14.8, 15.1, 19.9, 20.0, 21.8, 22.5, 22.6, 23.06, 23.14, 24.2, 24.8, 25.2, 26.3, 26.9, 27.1, 28.8, 29.0, 29.2, 29.4, 29.7, 31.3, 31.6, 31.7, 36.8, 37.5, 38.1, 38.4, 39.5, 40.5, 40.8, 41.2, 55.4, 55.6, 56.3, 56.9, 57.2, 58.0, 59.3, 67.7, 67.8, 68.0, 73.5, 73.9, 77.7, 78.2, 127.9, 128.2, 128.5, 128.65, 128.72, 137.1, 169.1, 169.2, 170.9, 171.0, 171.6, 172.3, 172.8, 173.4, 174.2, 176.7.

Globomycin (1). Cyclodepsipeptide **51** (4.0 mg, 5.4 mmol) was dissolved in MeOH (1.5 mL) and to the mixture was added $Pd(OH)_2$ (2.5 mg, 20 wt %). Once the flask was purged of air, the reaction was carried out under H_2 atmosphere for 6 h. Then, once the flask was purged of H_2, the mixture was diluted with MeOH (3 mL), and the catalyst removed by filtration. The methanolic solution was then evaporated under reduced pressure, and the crude product purified by preparative HPLC (column: Phenomenex-luna 5 μm C8(2), (10 mm × 250 mm), refraction index detector, flow rate: 4.7 mL/min with 90% MeOH) to give globomycin (**1**) (3.0 mg, 86%): $[\alpha]^{25}_D$ = +21.9 (*c* 0.13, CH_3OH) (lit.[15] $[\alpha]^{25}_D$ = +23.8 (*c* 0.5, CH_3OH)); ^{1}H NMR (400 MHz, $CDCl_3$, 3.5 mM, two rotamers in a 5.9/1 proportion) δ 0.83−1.00 (m, 15 H), 1.09 (d, *J* = 6.9 Hz, 18/7 H), 1.17 (d, *J* = 6.9 Hz, 3/7 H), 1.19−1.44 (m, 13 H), 1.49−1.82 (m, 4 H), 1.98−2.06 (m, 2/7 H), 2.06−2.14 (m, 6/7 H), 2.19−2.28 (m, 6/7 H), 2.79 (s, 3/7 H), 2.95−3.01 (m, 1 H), 3.22 (s, 18/7 H), 3.60 (dd, *J* = 7.7, 5.6 Hz, 6/7 H), 3.81 (dd, *J* = 17.3, 4.6 Hz, 1 H), 3.91(t, *J* = 7.2 Hz, 6/7 H), 4.00 (d, *J* = 4.4 Hz, 6/7 H), 4.05−4.07 (m, 3/7 H), 4.08−4.16 (m, 6/7 H), 4.28 (dd, *J* = 17.4, 7.5 Hz, 1 H), 4.36 (q, *J* = 4.9 Hz, 1 H), 4.41−4.46 (m, 9/7 H), 4.48−4.58 (m, 5/7 H), 4.78 (dd, *J* = 9.9, 4.0 Hz, 1/7 H), 4.85 (d, *J* = 10.6 Hz, 1/7 H), 4.92 (dt, *J* = 9.2, 3.0 Hz, 6/7 H), 6.70 (bs, 1/7 H), 7.00 (bs, 6/7 H), 7.08 (bs, 1/7 H), 7.16 (d, *J* = 8.9 Hz, 1/7 H), 7.24 (bs, 3/7 H), 7.40−7.49 (m, 1 H), 7.55−7.61 (m, 1 H), 7.76−7.79 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, both rotamers) δ 11.7, 13.5, 14.1, 14.6, 15.0, 19.3, 20.2, 22.0, 22.6, 22.7, 23.1, 24.6, 25.1, 25.4, 27.1, 29.0, 29.7, 31.2, 31.7, 31.9, 35.9, 38.0, 40.1, 40.6, 41.0, 56.2, 56.9, 59.0, 61.6, 66.8, 169.1, 170.6, 171.1, 172.6, 174.1, 176.4.

Seco-Acid 48. Compound **48** was obtained following the same procedure described for the synthesis of compound **47**, using the polymer-bound Fmoc protected pentapeptide **15** (118 mg, L = 0.6 mmol/g, 0.071 mmol, 1.0 equiv), hydroxyacid **10** (44 mg, 0.213 mmol, 3.0 equiv), TEA (30 μL, 0.213 mmol, 3.0 equiv) and DEPC (35 μL, 0.213 mmol, 3.0 equiv) for two times, 18 h each time. After cleavage, compound **48**[16] was obtained (49 mg, 77%): ^{1}H NMR (400 MHz, DMSO-d_6, two rotamers in a 3.4:1 proportion) δ −0.03 (s, 3 H), 0.02 (s, 3 H), 0.70 (d, *J* = 6.9 Hz, 12/5 H), 0.74 (d, *J* = 6.9 Hz, 3/5 H), 0.79−0.91 (m, 12 H), 0.81 (s, 9 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 1.06 (d, *J* = 6.2 Hz, 3 H), 1.19−1.31 (m, 14 H), 1.32−1.54 (m, 4 H), 1.58−1.67 (m, 1 H), 1.74−1.82 (m, 1 H), 2.69 (s, 3/5 H), 2.78−2.84 (m, 1 H), 2.87 (s, 12/5 H), 3.48−3.55 (m, 8/5 H), 3.57−3.61 (m, 12/5 H), 3.78 (dd, *J* = 17.5, 6.2 Hz, 1 H), 4.02 (q, *J* = 6.6 Hz, 1 H), 4.36−4.41 (m, 2 H), 4.49 (s, 2 H), 4.64−4.72 (m, 2 H), 5.11 (dd, *J* = 10.6, 5.2 Hz, 1 H), 7.24−7.34 (m, 6 H), 7.90 (d, *J* = 9.5 Hz, 1/5 H), 7.94 (d, *J* = 8.8 Hz, 1/5 H), 7.98 (d, *J* = 9.1 Hz, 3/5 H,), 8.06 (d, *J* = 8.0 Hz, 1/5 H), 8.18−8.21 (m, 9/5 H); ^{13}C NMR (100 MHz, DMSO-d_6, both rotamers) δ −5.2, −4.8, 11.4, 13.1, 13.9, 14.1, 17.6, 19.5, 21.5, 22.1, 23.2, 24.1, 25.6, 28.6, 28.9, 29.1, 30.4,

31.2, 33.4, 36.0, 37.1, 40.6, 41.3, 52.2, 53.2, 55.3, 58.3, 68.6, 69.8, 71.8, 72.1, 127.4, 127.5, 128.2, 138.0, 169.2, 169.6, 170.2, 170.6, 170.8, 176.1.

Cyclodepsipeptide 50. Yamaguchi macrolactonization of compound **48** was carried out following the same procedure described for globomycin, using seco-acid **48** (46 mg, 50.8 μmol, 1.0 equiv), TEA (22 μL, 152.0 μmol, 3.0 equiv) and 2,4,6-trichlorobenzoyl chloride (12 μL, 66.0 μmol, 1.3 equiv). After purification by preparative HPLC (column: Phenomenex-luna C8(2), (10 mmx250 mm), refraction index detector, flow rate: 4.7 mL/min with 95% MeOH) the expected cyclic compound **50**[16] (13.4 mg, 30%) was obtained as a white solid: $[\alpha]^{25}_{D} = +10.0$ (c 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers in a 7:3 proportion) δ 0.056 (s, 21/10 H), 0.061 (s, 9/10 H), 0.067 (s, 21/10 H), 0.08 (s, 9/10H), 0.84−0.99 (m, 15 H), 0.84 (s, 63/10 H), 0.85 (s, 27/10 H), 1.06−1.19 (m, 6 H), 1.21−1.39 (m, 15 H), 1.41−1.56 (m, 3 H), 1.60−1.76 (m, 27/10 H), 1.88−1.95 (m, 1 H), 1.98−2.05 (m, 3/10H), 2.09−2.14 (m, 3/10H), 2.16−2.25 (m, 7/10 H), 2.77 (s, 9/10 H), 3.01 (dq, J = 9.6, 6.9 Hz, 7/10 H), 3.10−3.16 (m, 3/10 H), 3.16 (s, 21/10 H), 3.54 (dd, J = 17.1, 3.7 Hz, 7/10 H), 3.71 (bs, 7/10 H), 3.77 (dd, J = 10.2, 6.3 Hz, 7/10 H), 3.85 (dd, J = 10.1, 4.8 Hz, 7/10 H), 3.89 (dd, J = 10.2, 5.5 Hz, 3/10 H), 3.93−4.01 (m, 1 H), 4.20−4.23 (m, 7/10 H), 4.30 (q, J = 4.4 Hz, 3/10 H), 4.39 (dd, J = 17.3, 8.8 Hz, 7/10 H), 4.42−4.49 (m, 18/10 H), 4.51 (d, J = 11.8 Hz, 7/10 H), 4.54−4.57 (m, 3/10 H), 4.61 (d, J = 11.8 Hz, 7/10 H), 4.61−4.65 (m, 14/10 H), 4.77(dd, J = 9.4, 3.9 Hz, 3/10 H), 4.83 (d, J = 10.9 Hz, 3/10 H), 5.28 (ddd, J = 9.9, 7.4, 2.9 Hz, 7/10 H), 6.39 (d, J = 7.4 Hz, 7/10 H), 6.41 (d, J = 2.6 Hz, 7/10 H), 6.68−6.71 (m, 6/10 H), 6.88 (d, J = 9.2 Hz, 3/10 H), 7.04 (t, J = 5.5 Hz, 3/10 H), 7.28−7.40 (m, 5 H), 7.70 (dd, J = 8.8, 3.7 Hz, 7/10 H), 8.21 (bs, 7/10 H); ^{13}C NMR (100 MHz, $CDCl_3$, both rotamers) δ −4.9, −4.8, −4.7, 11.8, 14.1, 14.9, 15.1, 18.0, 18.2, 18.9, 21.6, 22.5, 22.6, 23.1, 23.3, 24.1, 24.9, 25.2, 25.7, 26.5, 27.0, 27.1, 29.0, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.5, 31.8, 31.9, 37.4, 37.5, 38.2, 38.5, 39.6, 40.1, 40.5, 56.1, 56.2, 56.3, 56.6, 59.1, 59.3, 59.4, 66.6, 66.9, 67.9, 68.0, 73.4, 73.9, 76.3, 77.2, 77.7, 78.2, 128.1, 128.4, 128.5, 128.7, 136.7 136.9, 168.8, 169.2, 169.3, 169.6, 169.7, 169.9, 171.7, 172.9, 173.1, 174.2, 174.5, 177.2.

Cyclodepsipeptide 52. The desilylation of **50** (6.0 mg, 6.8 mmol) was carried out using the same procedure described for globomycin, by treatment with AcOH (40 μL) and TBAF (0.5 mL, 1 M in THF). After purification by preparative HPLC (column: Phenomenex-luna C8(2), (10 mmx250 mm), refraction index detector, flow rate: 4.7 mL/min with 95% MeOH) cyclodepsipeptide **52**[16] (4.5 mg, 87%) was obtained as a white solid: $[\alpha]^{25}_{D} = +10.0$ (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, two rotamers in a 3.5/1 proportion) δ 0.85−1.03 (m, 15 H), 1.10 (d, J = 6.9 Hz, 12/5 H), 1.16 (d, J = 7.0 Hz, 3/5 H), 1.26−1.54 (m, 20 H), 1.55−1.67 (m, 1 H), 1.74 (ddd, J = 14.1, 8.6, 5.7 Hz, 1 H), 1.99−2.07 (m, 1 H), 2.08−2.17 (m, 1 H), 2.78 (s, 3/5 H), 3.07−3.15 (m, 1 H), 3.18 (s, 12/5 H), 3.62 (dd, J = 17.2, 3.9 Hz, 4/5 H), 3.68 (bs, 4/5 H), 3.80−3.94 (m, 3/5 H), 3.84 (dd, J = 10.0, 5.7 Hz, 4/5 H), 3.90 (dd, J = 10.0, 4.8 Hz, 4/5 H), 4.00−4.08 (m, 3/5 H), 4.13 (m, 4/5 H), 4.20 (dd, J = 8.2, 6.3 Hz, 4/5 H), 4.30 (q, J = 5.0 Hz, 4/5 H), 4.34−4.42 (m, 8/5 H), 4.46 (t, J = 7.1 Hz, 1/5 H), 4.52 (d, J = 11.8 Hz, 1/5 H), 4.53 (d, J = 11.8 Hz, 4/5 H), 4.57 (d, J = 11.8 Hz, 4/5 H), 4.60 (d, J = 11.8 Hz, 1/5 H), 4.77 (dd, J = 9.4, 3.6 Hz, 1/5 H), 4.82 (d, J = 10.9 Hz, 1/5 H), 5.11 (ddd, J = 9.3, 7.3, 4.3 Hz, 4/5 H), 6.78−6.84 (d, 7/5 H), 6.90 (d, J = 8.2 Hz, 4/5 H), 7.22 (bs, 1/5 H), 7.28−7.39 (m, 5 H), 7.59 (dd, J = 8.2, 3.3 Hz, 4/5 H), 7.84 (d, J = 6.6 Hz, 4/5 H); ^{13}C NMR (100 MHz, $CDCl_3$, both rotamers) δ 11.7, 11.8, 13.7, 14.1, 14.7, 14.8, 15.1, 19.8, 21.9, 22.5, 22.7, 23.0, 23.2, 24.2, 24.3, 24.7, 25.2, 26.3, 26.9, 27.0, 28.7, 29.2, 29.4, 29.6, 29.7, 31.3, 31.9, 36.8, 37.5, 38.1, 38.5, 39.5, 40.4, 40.7, 41.3, 55.4, 55.7, 56.2, 56.9, 57.5, 58.0, 59.1, 59.3, 67.6, 67.8, 68.0, 73.4, 73.9, 77.2, 77.7, 78.1, 127.9, 128.2, 128.3, 128.4, 128.6, 136.7, 137.1, 169.1, 169.2, 169.8, 170.1, 170.8, 171.0, 171.7 172.3, 172.8, 173.8, 174.2, 176.7.

SF 1902 A_5 (2). Natural compound SF 1902 A_5 (**2**) was obtained following the same procedure described for globomycin, by treatment of **52** (3.0 mg, 3.9 mmol) with $Pd(OH)_2$ (3 mg, 20 wt %) under H_2 atmosphere. After purification by preparative HPLC (column: Phenomenex-luna 5 μm C8(2), (10 mm × 250 mm), refraction index detector, flow rate: 4.7 mL/min with 90% MeOH) SF 1902 A_5 (**2**)[16] (2.2 mg, 81%) was obtained as a white solid: $[\alpha]^{25}_{D} = +25.8$ (c 0.12, CH_3OH) ($[\alpha]_D^{25} = +20.8$ (c 1.04, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$, 3.5 mM, two rotamers in a 5.7/1 proportion) δ 0.83−1.05 (m, 17 H), 1.09 (d, J = 6.9 Hz, 18/7 H), 1.16 (d, J = 6.9 Hz, 3/7 H), 1.19−1.42 (m, 15 H), 1.48−1.79 (m, 6 H), 2.05−2.15 (m, 1 H), 2.20−2.27 (m, 1 H), 2.79 (s, 3/7 H), 3.16−3.27 (m, 1 H), 3.22 (s, 18/7 H), 3.61 (dd, J = 8.7, 6.1 Hz, 6/7 H), 3.80 (dd, J = 17.3, 4.7 Hz, 6/7 H), 3.92 (t, J = 7.1 Hz, 6/7 H), 4.00 (d, J = 4.6 Hz, 12/7 H), 4.04−4.06 (m, 1/7 H), 4.09−4.11 (m, 1/7 H), 4.14−4.16 (m, 1/7 H), 4.28 (dd, J = 17.3, 7.9 Hz, 6/7 H), 4.35 (q, J = 5.1 Hz, 6/7 H), 4.39−4.46 (m, 16/7 H), 4.52 (t, J = 7.0 Hz, 1/7 H), 4.79 (dd, J = 9.4, 3.8 Hz, 1/7 H), 4.85 (d, J = 9.9 Hz, 1/7 H), 4.94 (td, J = 8.7, 2.9 Hz, 6/7 H), 6.81 (d, J = 8.9 Hz, 1/7 H), 6.99 (d, J = 9.5 Hz, 1/7 H), 7.05 (bs, 8/7 H), 7.15 (bs, 1/7 H), 7.43 (d, J = 8.2 Hz, 1/7 H), 7.49 (t, J = 5.9 Hz, 8/7 H), 7.56 (d, J = 6.1 Hz, 8/7 H); ^{13}C NMR (100 MHz, $CDCl_3$, 3.5 mM, both rotamers) δ 11.7, 14.1, 14.7, 14.9, 19.6, 22.0, 22.7, 23.2 24.8, 25.3, 27.1, 29.3, 29.4, 31.2, 31.9, 35.7, 37.9, 40.2, 41.1, 55.7, 57.0, 59.1, 61.7, 66.8, 77.7, 169.1, 170.4, 171.3, 172.3, 173.7, 176.1.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectroscopic data of all new compounds, as well as ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Sarabia, F.; Chammaa, S. *J. Org. Chem.* **2005**, *70*, 7846–7857. (b) Sarabia, F.; García-Castro, M.; Chammaa, S. *Tetrahedron Lett.* **2005**, *46*, 7695–7699. (c) Bisek, N.; Wetzel, S.; Arndt, H.-D.; Waldmann, H. *Chem.—Eur. J.* **2008**, *14*, 8847–8860 and references therein.

(2) Sarabia, F.; Chammaa, S.; Sánchez-Ruiz, A.; Martín-Ortiz, L.; López-Herrera, F. J. *Curr. Med. Chem.* **2004**, *11*, 1309–1332.

(3) (a) Inukai, M.; Enokita, R.; Torikata, A.; Ankara, M.; Iwado, S.; Arai, M. *J. Antibiot.* **1978**, *31*, 410–420. (b) Inukai, M.; Nakajima, M.; Osawa, M.; Haneishi, T.; Arai, M. *J. Antibiot.* **1978**, *31*, 421–425. (c) Nakajima, M.; Inukai, M.; Haneishi, T.; Terahara, A.; Enokita, R.; Arai, M.; Kinoshita, T.; Tamura, C. *J. Antibiot.* **1978**, *31*, 426–432.

(4) (a) Omoto, S.; Suzuki, H.; Inouye, S. *J. Antibiot.* **1979**, *32*, 83–86. (b) Omoto, S.; Ogino, H.; Inouye, S. *J. Antibiot.* **1981**, *34*, 1416–1423.

(5) (a) Fehri, L. F.; Wróblewski, H.; Blanchard, A. *Antimicrob. Agents Chemother.* **2007**, *51*, 468–474. (b) Malléa, M.; Chevalier, J.; Eyraud, A.; Pagès, J.-M. *Biochem. Biophys. Res. Commun.* **2002**, *293*, 1370–1373.

(c) Inukai, M.; Takeuchi, M.; Shimizu, K. *Agric. Biol. Chem.* **1984**, *48*, 513–518.

(6) (a) Inukai, M.; Takeuchi, M.; Shimizu, K.; Arai, M. *J. Antibiot.* **1978**, *31*, 1203–1205. (b) Hussain, M.; Ichihara, S.; Mizushima, S. *J. Biol. Chem.* **1980**, *255*, 3707–3712. (c) Dev, I. K.; Harvey, R. J.; Ray, P. H. *J. Biol. Chem.* **1985**, *260*, 5891–5894. (d) Geukens, N.; De Buck, E.; Meyen, E.; Maes, L; Vranckx, L.; Van Mellaert, L.; Anné, J.; Lammertyn, E. *Res. Microbiol.* **2006**, *157*, 836–841.

(7) (a) Sankaran, K. In *Handbook of Proteolytic Enzymes*; Barrett, A. J., Rawlings, N. D., Woessner, J. F., Eds.; Elsevier: Amsterdam, 2004; Vol. 1, 201−204. (b) Paetzel, M.; Karla, A.; Strynadka, N. C. J.; Dalbey, R. E. *Chem. Rev.* **2002**, *102*, 4549–4579. (c) Pugsley, A. P. *Microbiol. Rev.* **1993**, *57*, 50–108.

(8) (a) Walsh, C. In *Antibiotics: Actions, Origins, Resistance*, ASM Press: Washington, DC, 2003. (b) Chu, D. T. W.; Plattner, J. J.; Katz, L. *J. Med. Chem.* **1996**, *39*, 3853–3874. (c) Süssmuth, R. D. *ChemBioChem* **2002**, *3*, 295–298. (d) Gao, Y. *Nat. Prod. Rep.* **2002**, *19*, 100–107. (e) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096–2152.

(9) (a) Huang, H.; Lin, M.; Wang, X.; Kikuchi, T.; Mottaz, H.; Norbeck, A.; Rikihisa, Y. *Infect. Immun.* **2008**, *76*, 3405–3414. (b) Gibbons, H. S.; Wolschendorf, F.; Abshire, M.; Niederweis, M.; Braunstein, M. *J. Bacteriol.* **2007**, *189*, 5090–5100. (c) Lo, M.; Boyce, J. D.; Wilkie, I. W.; Adler, B. *Microb. Infect.* **2004**, *6*, 58–67. (d) Jackowski, S.; Rock, C. O. *J. Biol. Chem.* **1986**, *261*, 11328–11333. (e) Tokunaga, M.; Tokunaga, H.; Wu, H. C. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 2255–2259.

(10) Some relevant publications: (a) Ghrayeb, J.; Lunn, C. A.; Inouye, S.; Inouye, M. *J. Biol. Chem.* **1985**, *260*, 10961–10965. (b) Inukai, M.; Ghrayeb, J.; Nakamura, K.; Inouye, M. *J. Biol. Chem.* **1984**, *259*, 757–760. (c) Hussain, M.; Ichihara, S.; Mizushima, S. *J. Biol. Chem.* **1982**, *257*, 5177–5182. (d) Ichihara, S.; Hussain, M.; Mizushima, S. *J. Biol. Chem.* **1982**, *257*, 495–500. (e) Ichihara, S.; Hussain, M.; Mizushima, S. *J. Biol. Chem.* **1981**, *256*, 3125–3129. (f) Ichihara, S.; Hussain, M.; Mizushima, S. *J. Biol. Chem.* **1981**, *256*, 495–500. (g) Hussain, M.; Ichihara, S.; Mizushima, S. *J. Biol. Chem.* **1980**, *255*, 3707–3712.

(11) Recent publications in this area: (a) Banaei, N.; Kincaid, E. Z.; Lin, S.-Y. G.; Desmond, E.; Jacobs, W. R., Jr.; Ernst, J. D. *Antimicrob. Agents Chemother.* **2009**, *53*, 3799–3802. (b) Guglielmetti, S.; Tamagnini, I.; Mora, D.; Minuzzo, M.; Scarafoni, A.; Arioli, S.; Hellman, J.; Karp, M.; Parini, C. *Appl. Environ. Microbiol.* **2008**, *74*, 4695–4702. (c) Ashgar, S. S. A.; Oldfield, N. J.; Wooldridge, K. G.; Jones, M. A.; Irving, G. J.; Turner, D. P. J.; Ala'Aldeen, D. A. A. *J. Bacteriol.* **2007**, *189*, 1856–1865. (d) Valente, F. M. A.; Pereira, P. M.; Venceslau, S. S.; Regalla, M.; Coelho, A. V.; Pereira, I. A. C. *FEBS Lett.* **2007**, *581*, 3341–3344. (e) Neff, L.; Daher, S.; Muzzin, P.; Spenato, U.; Gülacar, F.; Gabay, C.; Bas, S. *J. Bacteriol.* **2007**, *189*, 4739–4748. (f) Gonnet, P.; Rudd, K. E.; Lisacek, F. *Proteomics* **2004**, *4*, 1597–1613. (g) Venema, R.; Tjalsma, H.; van Dijl, J. M.; de Jong, A.; Leenhouts, K.; Buist, G.; Venema, G. *J. Biol. Chem.* **2003**, *278*, 14739–14746. (h) Harrington, D. J.; Greated, J. S.; Chanter, N.; Sutcliffe, I. C. *Infect. Immun.* **2000**, *68*, 6048–6051.

(12) Kiho, T.; Nakayama, M.; Yasuda, K.; Miyakoshi, S.; Inukai, M.; Kogen, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2315–2318.

(13) Banaiee, N.; Jacobs, W. R.; Ernst, J. D. *J. Antimicrob. Chemother.* **2007**, *60*, 414–416.

(14) Haneishi, T.; Nakajima, M.; Inukai, M.; Terahara, A.; Arai, M.; Kinoshita, T.; Tamura, C. *Pept. Chem.* **1980**, *17*, 25–30.

(15) Kogen, H.; Kiho, T.; Nakayama, M.; Furukawa, Y.; Kinoshita, T.; Inukai, M. *J. Am. Chem. Soc.* **2000**, *122*, 10214–10215.

(16) Kiho, T.; Nakayama, M.; Kogen, H. *Tetrahedron* **2003**, *59*, 1685–1697.

(17) Kiho, T.; Nakayama, M.; Yasuda, K.; Miyakoshi, S.; Inukai, M.; Kogen, H. *Bioorg. Med. Chem.* **2004**, *12*, 337–361.

(18) Barlos, D.; Gatos, D.; Schäfer, W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 590–593.

(19) For recent examples of synthesis of peptidic chains in solid phase by a Fmoc strategy, see: (a) Izzo, I.; Acosta, G. A.; Tulla-Puche, J.; Cupido, T.; Martín-López, M. J.; Cuevas, C.; Albericio, F. *Eur. J. Org. Chem.* **2010**, 2536–2543. (b) Tannert, R.; Milroy, L.-G.; Ellinger, B.; Hu, T.-S.; Arndt, H.-D.; Waldmann, H. *J. Am. Chem. Soc.* **2010**, *132*, 3063–3077.

(20) The synthesis of this amino acid derivative is described in Supporting Information.

(21) (a) Sarabia, F.; Chammaa, S.; García-Castro, M.; Martín-Gálvez, F. *Chem. Commun.* **2009**, 5763–5765. (b) Sarabia, F.; Martín-Gálvez, F.; Chammaa, S.; Martín-Ortiz, L.; Sánchez-Ruiz, A. *J. Org. Chem.* **2010**, *75*, 5526–5532.

(22) Yudin, A. K., Ed. In *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

(23) (a) Sarabia, F.; Martín-Ortiz, L.; López-Herrera, F. J. *Org. Lett.* **2003**, *5*, 3927–3930. (b) Sarabia, F.; Sánchez-Ruiz, A.; Chammaa, S. *Bioorg. Med. Chem.* **2005**, *13*, 1691–1705. (c) Sarabia, F.; Martín-Ortiz, L. *Tetrahedron* **2005**, *61*, 11850–11865.

(24) Kitching, W.; Lewis, J. A.; Perkins, M. V.; Drew, R.; Moore, C. J.; Schurig, V.; König, W. A.; Francke, W. *J. Org. Chem.* **1989**, *54*, 3893–3902.

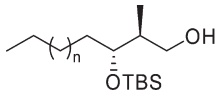
(25) (a) Sarabia, F.; Sánchez-Ruiz, A.; Martín-Ortiz, L.; García-Castro, M.; Chammaa, S. *Org. Lett.* **2007**, *9*, 5091–5094. (b) Sarabia, F.; Martín-Gálvez, F.; García-Castro, M.; Chammaa, S.; Sánchez-Ruiz, A.; Tejón-Blanco, J. F. *J. Org. Chem.* **2008**, *73*, 8979–8986.

(26) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1–12.

(27) (a) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408–3419. (b) Tessier, A.; Pytkowicz, J.; Brigaud, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3677–3681.

(28) (a) Myers, A. G.; Yang, B. H.; Chen, H.; Mckinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511. (b) Smith, A. B., III; Bosanac, T.; Basu, K. *J. Am. Chem. Soc.* **2009**, *131*, 2348–2358.

(29) See Supporting Information for the description of hydroxyl silylethers **SI-2** and **SI-3**.



SI-2: n = 3
SI-3: n = 5

(30) Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293–295.

(31) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.(b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, New York, 1993; pp 103−158.

(32) Preparation of epoxy alcohol **30** and its enantiomer by Sharpless asymmetric epoxidation were reported by Kitching;[24] however yields were not reported. Later, the enantiomer of **30** was described in 95% yield:Ortega, N.; Martín, T.; Martín, V. S. *Eur. J. Org. Chem.* **2009**, 554–563.

(33) Chong, J. M.; Cyr, D. R.; Mar, E. K. *Tetrahedron Lett.* **1987**, *28*, 5009–5012.

(34) As for **30**, the synthesis of the enantiomer of epoxy alcohol **31** via Sharpless asymmetric epoxidation in 52% yield has been reported: Tanaka, T.; Hiramatsu, K.; Kobayashi, Y.; Ohno, H. *Tetrahedron* **2005**, *61*, 6726–6742.

(35) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

(36) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127.

(37) Morrison, K. C.; Litz, J. P.; Scherpelz, K. P.; Dossa, P. D.; Vosburg, D. A. *Org. Lett.* **2009**, *11*, 2217–2218.

(38) Tiong, E. A.; Gleason, J. L. *Org. Lett.* **2009**, *11*, 1725–1728.

(39) Recent examples of amides hydrolysis under acidic conditions: (a) Arpin, A.; Manthorpe, J. M.; Gleason, J. L. *Org. Lett.* **2006**, *8*, 1359–1362. (b) Tannert, R.; Milroy, L.-G.; Ellinger, B.; Hu, T.-S.; Arndt, H.-D.; Waldmann, H. *J. Am. Chem. Soc.* **2010**, *132*, 3063–3077.

(40) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

(41) Sergeeva, N. N.; Golubev, A. S.; Hennig, L.; Burger, K. *Synthesis* **2002**, 2579–2584.
(42) Deutsch, H. M.; Glinski, J. A.; Hernandez, M.; Haugwitz, R. D.; Narayanan, V. L.; Suffness, M.; Zalkow, L. H. *J. Med. Chem.* **1989**, *32*, 788–792.
(43) For recent examples of *N*-Boc activation of amides, see: (a) Liu, W.-J.; Lv, B.-D.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 6503–6506. (b) Suarez del Villar, I.; Gradillas, A.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2010**, *51*, 3095–3098.
(44) For a recent example of *N*-sulfonyl activation of amides, see: Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 9594–9595.
(45) Sarabia, F.; Martín-Ortiz, L.; López-Herrera, F. J. *Org. Biomol. Chem.* **2003**, *1*, 3716–3725.
(46) Shioiri, T.; Yokoyama, Y.; Kasai, Y.; Yamada, S. *Tetrahedron* **1976**, *32*, 2211–2217.
(47) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
(48) See the Supporting Information for general techniques.