Studies toward the Synthesis of Smenamide A, an Antiproliferative Metabolite from Smenospongia aurea: Total Synthesis of ent-Smenamide A and 16-epi-Smenamide A

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ABSTRACT: A chiral pool protocol toward the synthesis of the smenamide family of natural products is described. Two stereoisomers of smenamide A, namely, ent-smenamide A and 16-epi-smenamide A were synthesized with a 2.6 and 2.5% overall yield, respectively. Their carboxylic acid moieties were assembled starting from S-citronellene via two Wittig reactions and a Grignard process. Its coupling with either (S)- or (R)-dolapyrrolidinone, synthesized from Boc-L-Phe and Boc-D-Phe, respectively, was accomplished by using the Andrus protocol. This work also established the previously unknown relative and absolute configurations of smenamide A.

INTRODUCTION

Marine sponges are considered to be one of the most productive sources of novel scaffolds for use as leads in antiinflammatory, immunomodulating, and anticancer drug research.2–4 Smenamides A (1) and B (2) (Figure 1) are chlorinated hybrid peptide/polyketide metabolites isolated in microgram amounts from the Caribbean sponges Smenospongia aurea5 and Smenospongia conulosa.6 The two smenamides differ only in the configuration of the C-13 double bond, which is E in smenamide A. Many of the structural motifs in smenamides are usually found in cyanobacterial metabolites, and it is likely that smenamides themselves are produced by a cyanobacterial symbiont in the sponge. In particular, the vinyl chloride function is shared with compounds such as jamaicamides7 and malingamides8 and the recently isolated smenothiazoles9 and conulothiazoles.6

Figure 1. Structures of smenamide A (1) and B (2) as determined in a previous study.5

Smenamide A is strongly cytotoxic on lung cancer Calu-1 cells at nanomolar concentrations through a clear proapoptotic mechanism. Further pharmacological studies of smenamides were hampered by the very limited amounts available, and total synthesis is a way to overcome this problem. Here, we report an efficient chiral pool convergent approach for the total synthesis of smenamides and its analogues, which resulted in the synthesis of ent-smenamide A and 16-epi-smenamide A.

RESULTS AND DISCUSSION

Smenamide A (1) contains two stereogenic centers, C-8 and C-16, whose configurations could not be assigned in the original study.5 Therefore, before designing the synthetic plan, the configuration at C-8 was determined using an improved Marfey’s method.6,13 In particular, the phenylalanine residue obtained from the degradation of smenamide A was found to have the L configuration based on the liquid chromatography–mass spectrometry (LC–MS) retention time of its 1-fluoro-2,4-dinitrophenyl-5-L-alaninamide (L-FDDA) derivative (see Figures S1 and S2). Determination of the configuration at C-16 is not trivial, and indeed, this was one of the objectives of the present synthesis work.

Smenamide A is a small but densely functionalized molecule comprising an N-methylacetamide, a chlorovinyl, and a tetramic acid unit in its enol ether form engaged into a mixed imide bond with an α,β-unsaturated carboxylic acid unit. A central point in a synthetic plan toward smenamide A is the
construction of the \( Z \)-chlorovinyl function. Various approaches have been used to build this function in related substances, but relatively a few methods have been reported for the stereoselective preparation of chloroolefins. Paige et al. used the palladium-mediated regio- and stereospecific silylstannylation of a terminal alkyne to set the basis for the stereoselectivity. However, the chlorodesilylation required to generate the chlorovinyl moiety from the intermediate alkenylsilane resulted in a moderate yield (42%), and similar results were obtained by others, with yields in the range 45–51%. We envisioned that this approach, although elegantly conducted to the required function in a stereoselective manner, would neither provide any advantage in terms of the overall efficiency of the synthesis nor decrease the need for chromatographic separations. The Wittig olefination, on the other hand, has been reported to be an easy, efficient, and direct process to build the chloroolefin function. Although this approach suffers from the lack of stereoselectivity, sound precedents exist for the photochemical isomerization of strictly related chloroolefins, opening the way to recycling the unwanted stereoisomer. Therefore, we decided to include this latter reaction in our plan.

Our retrosynthetic analysis is depicted in Scheme 1. Disconnection of smenamide A at the mixed imide function gave carboxylic acid (C12–C27 fragment) and pyrrolinone (C1–C11 fragment). Further simplification of fragment 3 could be achieved by the cleavage of the two carbon–carbon double bonds and the C24–N bond. This led to the fully protected C15–C24 triol as a versatile intermediate, where each alcohol function could be transformed into one of the functional groups belonging to fragment 3. The protecting groups in triol 5 were chosen in such a way that the tert-butylidemethylsilyl (TBS), Bn, and tert-butylidphenylsilyl (TBDPS) groups could be selectively removed according to the order of installation of the three functionalities, namely, first the \( N \)-methylacetamide, then the chlorovinyl function, and finally the \( \alpha,\beta \)-unsaturated acid unit. The presence of a methyl group at C-16 in 5 suggested a further C20–C22 disconnection, revealing the C15–C20 fragment 6 that was in turn traced back to citronellene. The protected bromoalcohol 7 was recognized as the functionalized form of the remaining C22–C24 structural fragment. All this implied that in the synthetic direction, two Wittig reactions, one of them \( E \)-selective (generating the \( E \) C13–C15 bond), and a Grignard reaction (generating the C20–C21 bond), could be used to build the whole carbon skeleton of the acid moiety, starting from a suitably functionalized C15–C20 fragment. It is important to say that the C-8 stereogenic center in the dolapyrrolidinone moiety of smenamide A is prone to racemization. Therefore, a racemization-free synthetic route has been used to obtain 4 starting from Meldrum’s acid and Boc-protected \( l \)-phenylalanine (Scheme 1).

As the configuration at C-16 in smenamide A is unknown, the citronellene enantiomer used as the starting material was arbitrarily chosen. Thus, starting from the cheaper, commercially available \( S \)-citronellene, the C15–C20 fragment 6 was synthesized as shown in Scheme 2. In particular, the chemoselective epoxidation of the trisubstituted double bond, followed by acid-catalyzed epoxide opening and benzoylation of the secondary alcohol function gave benzoate 8, as a 1:1 mixture of two diastereomers, in an 82% yield (over three steps).
steps). The terminal olefin was dihydroxylated under Sharpless conditions with OsO₄ (catalyst)/N-methylmorpholine N-oxide (NMO), and the obtained diol was cleaved with sodium periodate to afford the C-15 aldehyde. Reduction of the latter with sodium borohydride and protection of the primary alcohol with the TBDPS group gave compound 9 in a 50% yield (over four steps). Finally, the reductive removal of the benzoate with lithium aluminum hydride and the cleavage of the resultant diol afforded aldehyde 10, which was used in the next Grignard reaction without further purification. Reaction of aldehyde 10 with the Grignard reagent 11, prepared from the commercially available TBS-protected 3-bromo-propan-1-ol 7, afforded alcohol 12 as a 1:1 mixture of two diastereomers in a 72% yield (over three steps). Transformation of alcohol 11 into the corresponding benzyl ether under usual conditions [NaH, BnBr, and tetrabutylammonium iodide (TBAI) (catalytic amount), 91% yield] completed the preparation of the fully protected triol 5. Then, installation of the N-methylacetamide function was accomplished in three steps (Scheme 3). Removal of the TBS group with AcOH/tetrahydrofuran(THF)/H₂O (3:3:1) followed by tosylation and treatment of the tosylate with excess NH₂CH₃ (40% soln in water) afforded the secondary amine 13. Acetylation of the latter with AcCl/triethylamine (TEA) gave the desired N-methylacetamide 14 in a 65% overall yield (over four steps), as an approximately 1:1 mixture of rotamers.

Ketone 15 (Scheme 3) required for the Wittig olefination was obtained through the hydrogenolysis of the benzyl ether function of 14, followed by oxidation of the delivered alcohol with the catalytic system tetrapropylammonium perruthenate (TPAP) (5 mol %)/NMO, under Ley’s conditions (79% over two steps).

Initially, the Wittig process was tested using the model compound 16 (Scheme 4) obtained from alcohol 12 through TPAP/NMO catalytic oxidation (90%). The required phosphonium salt, (chloromethyl)triphenylphosphonium iodide 17 (Scheme 4), was prepared by the reaction of iodochloromethane with triphenylphosphine. According to the literature, the Wittig reaction was conducted in the presence of nBuLi in THF at −78 °C. However, although the mass recovery was satisfying, these conditions led to a large amount of the methylenation product 19 besides the expected chlorovinyl compound 18 (1:1 mixture of geometric isomers; 18/19 1:1, Scheme 4). A similar result was obtained when using the synthetic intermediate 15. Pleasingly, the use of potassium tert-butoxide as the base smoothly led to the desired product both with the model ketone 16 (18, 76%) and with compound 15. In the latter case, a 3:2 mixture of the two diastereomers 20 and 21, in favor of the desired Z isomer, was obtained with an 83% yield (Scheme 4). The two isomers could be easily separated using column chromatography, and Rotating-frame Overhauser Effect Spectroscopy (ROESY) data allowed us to assign the double bond configuration in each isomer.

As planned, to increase the yield of the synthetically useful isomer 20, photochemical isomerization of the E isomer 21 was addressed. According to the literature, irradiation of 21 with λ > 300 nm light (Scheme 4), in the presence of a catalytic amount of benzophenone, induced its conversion to the Z isomer 20 in a 20% yield. Although low-yielding, this process (unoptimized) was very clean, leading to only isomer 20 and unreacted 21, thus allowing recycling of this late synthetic material. Finally, the installation of the α,β-unsaturated acid moiety was addressed (Scheme 5). Removal of the TBDPS
phenylalanine with Meldrum’s acid, followed by the reflux of the crude in AcOEt for 30 min gave the Boc-protected tetrameric acid 25. Methylation of the latter under Mitsunobu conditions and the removal of the Boc protecting group gave the desired compound 4. The optical rotation measured for this material well matched the reported value \( ([\alpha]_D = -62.3; \text{lit.} \ -63) \), indicating its high enantiopurity.

Finally, the two building blocks 3 and 4 were coupled by using the Andrus protocol \(^{23} \) (Scheme 7). Thus, the acid moiety of smenamide A did not match that of the natural smenamide A, and, consequently, that the natural smenamide A possessed the \( R \) configuration at C16. At this point, to confirm the structure of smenamide A, the synthesis of \( \textit{ent}-\text{smenamide A} \) was carried out by coupling \( (R) \)-pyrrolinone 28 \(^{24} \) with pentafluorophenyl ester 26 (Scheme 8). Starting from \( (R) \)-Boc-

Scheme 6. Synthesis of \((S)\)-Pyrrolinone Moiety 4

3 was activated as the pentafluorophenyl ester 26 by reaction with \( \text{CF}_3\text{OH}/N, N’-\text{dicyclohexylcarbodiimide (DCC)} \) (82%). Coupling of 26 with an excess of lithium imide derivative from pyrrolinone 4 proceeded smoothly, giving the coupling product 27 in a 91% yield. Overall, compound 27 was obtained in a 2.5% yield with a longest linear sequence (LLS) of 23 steps.

Unfortunately, the proton spectrum of the synthetic smenamide A did not match that of the natural smenamide A (see Supporting Information). In particular, inter alia, the H-15 signals (for the two rotamers) adjacent to the C-16 stereogenic center had noticeably different shapes (see Supporting Information). This implied that compound 27 was \( 16\text{-epi-smenamide A} \) and, consequently, that the natural smenamide A possessed the \( R \) configuration at C16. At this point, to confirm the structure of smenamide A, the synthesis of \( \textit{ent}-\text{smenamide A} \) was carried out by coupling \( (R) \)-pyrrolinone 28 \(^{24} \) with pentafluorophenyl ester 26 (Scheme 8). Starting from \( (R) \)-Boc-

Scheme 8. Synthesis of the \((R)\)-Pyrrolinone Moiety and \( \textit{ent}-\text{Smenamide A} \)

**CONCLUSIONS**

In conclusion, the syntheses of \( \textit{ent}-\text{smenamide A} \) and \( 16\text{-epi-smenamide A} \) have been accomplished with a 2.6 and 2.5% overall yield, respectively, in 23 steps. The synthesis of natural smenamide A and its analogues, according to the developed synthetic protocol, and the evaluation of the antitumor activity of the synthesized substances are currently under way.

**EXPERIMENTAL SECTION**

General Experimental Methods. All reagents and anhydrous solvents were purchased (Aldrich and Fluka) at the highest commercial quality and used without further purification. \( \beta \)-citronellene was purchased from Sigma Aldrich (ee \( \geq 98.5\% \)). Where necessary, flame-dried and argon-charged glassware was used. The reactions were monitored using thin-layer chromatography (TLC) carried out on precoated silica gel plates (Merck 60, F254, 0.25 mm thick). Merck silica gel (Kieselgel 40, particle size 0.063–0.200 mm) was used for the column chromatography. MgSO4 was used as a drying agent for aqueous workup. Nuclear magnetic resonance (NMR) experiments were performed using Varian Unity Inova spectrometers at 400, 500, and 700 MHz in CDCl3. Proton chemical shifts were referenced to the residual CHCl3 signal (7.26 ppm). \(^{13} \)C NMR chemical shifts were referenced to the solvent (77.0 ppm). Abbreviations for signal coupling are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad. Infrared spectra were recorded under neat conditions.
on a PerkinElmer spectrum 100R spectrophotometer and are reported in cm⁻¹. Optical rotations were measured using a JASCO P-2000 polarimeter at the sodium D line. ECD spectra were recorded using a JASCO J-710 spectropolarimeter. HRMS spectra were recorded by infusion on a Thermo LTQ Orbitrap XL mass spectrometer equipped with an electrospray source in the positive mode using MeOH as the solvent.

**Benzaote 8.**

According to a literature procedure, β-citroneol (10 mL, 7.6 g, 54.9 mmol) was converted into the corresponding 6,7-epoxide (8.44 g, 100%), a smelling colorless oil. To a 5.01 g, 54.9 mmol) was converted into the corresponding 6,7-diastereomers, IR (neat) ν max: 3400, 2971, 2932, 1716, 1701, 1452, 1278, 1177, 1115, 1071, 1017, 712 cm⁻¹; 1H NMR: (400 MHz, CDCl3): δ 8.05 (4H, d, J = 7.5, ArH), 7.57 (2H, t, J = 7.8, ArH), 7.44 (4H, t, J = 7.6, ArH), 5.05 (2H, m, 2 × H-20), 3.77–3.37 (6H, overlapped m's), 2.55 (bs, OH's). 1.25–1.26 (6H each, both s, 2 × C(CH3)3), 0.89, 0.88, 0.863, 0.858 (3H each, d's, J = 6.7, 4 × H-17); 13C NMR (100 MHz, CDCl3): δ 167.0, 166.9, 166.7, 166.73, 133.2, 133.1, 130.2, 129.99, 129.91, 129.68, 129.67, 128.48, 128.47, 80.8, 80.5, 80.3, 80.2, 76.0, 75.6, 75.3, 74.9, 72.65, 72.62, 72.5, 65.6, 64.6, 64.50, 64.46, 35.7, 35.4, 35.3, 35.1, 29.7, 29.3, 29.2, 28.6, 27.0, 26.9, 26.8, 26.5, 26.0, 25.95, 25.88, 25.84, 25.73, 25.66, 25.62, 25.57, 15.5, 15.3, 14.6, 14.5; HRMS (ESI) m/z calc for C10H20NaO2 [M + Na]+ 333.1678; found 333.1663.

To a stirred solution of diol 31 (8.69 g, 29.0 mmol) in acetone/water (180 mL, 5:1) at 0 °C, sodium periodate (12.35 g, 58.0 mmol) was added. After a few minutes, a large amount of a white solid was precipitated. After 4 h, the reaction mixture was filtered under vacuum, and the precipitate was carefully washed with acetone. The solvent was evaporated in vacuo, and the aqueous suspension was extracted using EtOAc (3 × 30 mL). The organic layer was dried and concentrated in vacuo to give aldehyde 32 as a colorless oil (5.54 g), which was applied to the next step without further purification.

To a stirred solution of aldehyde 32 (5.52 g, 20.0 mmol) in methanol (70 mL) at 0 °C, NaBH4 (376 mg, 9.9 mmol) was added in portions. After 1 h, the reaction was quenched by dropwise addition of CH3COOH (3.5 mL). Then, the reaction mixture was concentrated in vacuo, treated with a saturated aqueous solution of NaHCO3 (30 mL), and extracted using EtOAc (3 × 30 mL). The organic phase was dried and evaporated under reduced pressure to give aldehyde 32 as a colorless oil (5.41 g), which was applied to the next step without further purification.

**Silylether 9.**

To a stirred solution of benzoate 8 (7.93 g, 28.7 mmol) in acetone/water (120 mL, 5:1), OsO4 (369 mg, 14.5 mmol, 5 mol %) was added. After 2 h, the reaction was quenched by the addition of solid Na2S2O5 (720 mg, 2.9 mmol), and the reaction mixture was stirred for further 30 min. Acetone was evaporated under reduced pressure, and the resultant aqueous suspension was extracted using EtOAc (3 × 50 mL). The organic phase was dried and evaporated in vacuo to give diol 31 (8.71 g) as a colorless oil. An analytically pure sample of this compound was obtained using chromatography over silica gel (CHCl3/CH3OH, 9:1) for characterization. Mixture of four diastereomers, IR (neat) ν max: 3482, 2974, 2929, 1718, 1704, 1452, 1275, 1177, 1113, 1070, 1027, 711 cm⁻¹; 1H NMR: (400 MHz, CDCl3): δ 5.76–5.61 (2H, m, 2 × H-15), 4.97 (2H, bd, J = 18.0, vinyl proton), 4.93, (2H, bd, J = 11.0, vinyl proton), 3.35 (2H, bt, J = 9.2, 2 × H-20), 2.14 (2H, m, 2 × H-16), 1.89 (bs, 2 × OH), 1.204, 1.203, 1.153, 1.147 (3H each, both s, 2 × C(CH3)3), 1.02, 1.01 (3H each, both d, J = 6.7, 2 × H-17); 13C NMR (100 MHz, CDCl3): δ 144.5, 144.3, 113.0, 112.8, 78.9, 78.5, 73.4, 73.3, 38.0, 37.8, 33.7, 33.4, 29.4, 29.2, 26.5, 23.1, 20.6, 20.2; HRMS (ESI) m/z calc for C10H20NaO2 [M + Na]+ 195.1361; found 195.1348.

To a stirred solution of diol 30 (7.34 g, 42.6 mmol) in pyridine (20 mL), benzyol chloride (0.052, 6 mL) was added. After 2.5 h, water (8 mL) was added, and the mixture was stirred for 15 min in a water bath and then dried. The residue was taken up in CHCl3 (50 mL) and washed with a saturated solution of NaHCO3 was added portion-wise until the effervescence ceased. The mixture was concentrated in vacuo and partitioned between water and EtOAc (3 × 20 mL). The organic phase was dried and evaporated in vacuo to give diol 30 (8.22 g, 87%), a colorless oil. An analytically pure sample of this compound was obtained using chromatography over silica gel (hexane/EtOAc, 7:3) for characterization. Mixture of two diastereomers, IR (neat) ν max: 3297, 711 cm⁻¹; 1H NMR: (400 MHz, CDCl3): δ 3.77 (4H, m, 2 × H-20), 3.36 (4H, m, 2 × H-15), 2.53 (bs, OH, 2H), 1.94 (2H, bs, 2 × OH), 1.85–1.58 (4H, m), 1.43–1.29 (4H, m), 1.26 (12H, s, 2 × C(CH3)3), 0.96 (6H, d, J = 6.9, H-17); 13C NMR (100 MHz, CDCl3): δ 166.63, 166.60, 144.2, 144.0, 133.0, 130.1, 129.6, 128.4, 113.2, 112.9, 80.7, 80.3, 72.7, 37.8, 37.6, 33.0, 32.7, 27.4, 27.2, 26.5, 25.1, 20.6, 20.0; HRMS (ESI) m/z calc for C17H26NaO5 [M + Na]+ 320.1270; found 320.1268.
Aldehyde 10.

To a stirred solution of silyl ether 9 (7.54 g, 14.5 mmol) in dry Et2O (50 mL) at 0 °C, LiAlH4 (762 mg, 20.1 mmol) was added in portions. The mixture was allowed to warm to RT for over 1 h, and then quenched by dropwise addition of wet ethyl ether and then water. After all inorganic materials were precipitated, the solid was filtered and washed with EtOAc (3 × 20 mL). The organic phase was dried, concentrated in vacuo, and purified using chromatography on silica gel (hexane/EtOAc, 85/15) to give diol 34 (5.71 g, 95%) as a colorless oil. Mixture of two diastereomers, IR (neat) vmax = 3412, 2958, 2931, 2858, 1472, 1461, 1428, 1388, 1112, 1075, 702 cm⁻¹; 1H NMR: (400 MHz, CDCl3): δ 7.66 (8H, d, J = 6.5, ArH), 7.45−7.33 (12H, m, ArH), 3.57 (4H, m), 3.42 (2H, m, 1.75−1.61 (4H, m), 1.19, 1.18, 1.14, 1.12 (3H each, all s, 2 × C(CH3)3), 0.95, 0.92 (3H each, both d, J = 6.7, 2 × H-17), 13C NMR (100 MHz, CDCl3): δ 135.6, 134.0, 129.5, 127.6, 79.1, 78.7, 73.1, 68.9, 68.5, 35.7, 35.6, 30.4, 30.3, 29.07, 29.02, 26.9, 26.49, 26.45, 23.17, 23.15, 19.3, 17.1, 16.8; HRMS (ESI) m/z calcld for C32H46NaO3Si [M + Na]⁺ 541.7250; found 541.7273.

To a stirred solution of diol 34 (4.83 g, 11.6 mmol) in acetone/water 5:1 (57 mL) at 0 °C, sodium periodate (4.98 g, 23.2 mmol) was added. After a few minutes, a large amount of white solid precipitated. After 4 h, the reaction mixture was filtered under vacuum, and the precipitate was carefully washed with acetone. The solvent was evaporated in vacuo, and the aqueous suspension was extracted using EtOAc (3 × 30 mL). The organic layer was dried and concentrated in vacuo to give aldehyde 10 as a colorless oil (4.34 g), which was applied to the next step without further purification. 1H NMR (400 MHz, CDCl3): δ 9.74 (1H, s, CHO), 7.66−7.34 (6H, m, ArH), 3.50 (2H, m, H2-15), 2.47−2.31 (2H, m, H2-19), 1.87−1.75 (1H, m), 1.75−1.61 (1H, m), 1.55−1.43 (1H, m), 1.06 (9H, s, C(CH3)3), 0.92 (3H, d, J = 6.7, H3-17).

Alcohol 12.

To a suspension of magnesium turnings (583 mg, 24.0 mmol) in anhydrous THF (30 mL), a catalytic amount of iodine was added. After 10 min, (3-bromopropoxy)-tert-butyldimethylsilane (4.56 g, 4.17 mL, 18.0 mmol) in THF (20 mL) was slowly added at RT under argon. During the addition, the temperature was maintained in the range of 30−35 °C. After the addition was completed, the reaction mixture was stirred at 40 °C for 1 h. To the above solution, crude aldehyde 10 (4.34 g, 12.2 mmol) in THF (10 mL) was added dropwise. After the addition was completed, the reaction mixture was stirred for 1 h at RT. Then, the reaction mixture was treated with a saturated aqueous NH4Cl solution (50 mL) and extracted using EtOAc. The organic phase was washed with brine, dried, concentrated in vacuo, and purified using chromatography on silica gel (hexane/EtOAc, 95:5) to give alcohol 12 (4.83 g, 75%) as a colorless oil. Mixture of two diastereomers, IR (neat) vmax = 3420, 2954, 2930, 2858, 1472, 1464, 1428, 1389, 1256, 1111, 1007, 835, 777, 740, 702 cm⁻¹; 1H NMR: (400 MHz, CDCl3): δ 7.70 (8H, d, J = 7.0, ArH), 7.47−7.35 (12H, m, ArH), 3.69 (4H, br, J = 5.2), 3.63−3.53 (4H, m), 3.53−3.45 (2H, m, H-20), 2.45 (2H, bs, 2 × OCH2Ph), 1.77−1.54 (8H, m), 1.54−1.34 (8H, m), 1.34−1.13 (2H, m), 1.09, 0.94 (18H each, both s, 2 × C(CH3)3), 0.970 (3H, d, J = 6.6, H3-17), 0.965 (3H, d, J = 6.6, H3-17), 13C NMR (100 MHz, CDCl3): δ 135.6, 134.0, 129.4, 127.5, 71.73, 71.66, 68.8, 68.7, 63.5, 35.8, 34.8, 34.7, 34.6, 34.4, 29.2, 29.15, 29.09, 29.07, 26.8, 25.9, 19.3, 18.2, 16.9, −5.4; HRMS (ESI) m/z calcld for C31H53O3Si2 [M + H]⁺ 529.3528; found 529.3506.

Amine 13.

To a stirred solution of alcohol 12 (1.93 g, 3.66 mmol) in anhydrous THF (40 mL), sodium hydride (60% dispersion in mineral oil, 292.8 mg, 7.32 mmol) was added under argon. After stirring at reflux for 5 min, benzyl bromide (0.790 mL, 6.59 mmol) was added, followed by TBAI (20 mol%, 271 mg, 0.732 mmol). The reaction was stirred at 50 °C for 24 h. After cooling to RT, the reaction mixture was diluted with EtOAc (50 mL) and quenched by careful addition of a saturated aqueous NaHCO3 solution (50 mL). The phases were separated, and the aqueous layer was extracted using EtOAc (2 × 50 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried, and concentrated in vacuo. Purification using column chromatography on silica gel (hexane/EtOAc, 95:5) gave fully protected triol 5 (2.05 g, 91%) as a colorless oil. Mixture of two diastereomers, IR (neat) vmax = 3295, 2929, 2858, 1472, 1473, 1463, 1428, 1388, 1255, 1112, 1095, 835, 776, 738, 701 cm⁻¹; 1H NMR: (400 MHz, CDCl3): δ 7.67 (8H, d, J = 7.3, ArH), 7.45−7.28 (22H, m, ArH), 4.48 (4H, d, J = 3.3, OCH2Ph), 3.60 (4H, br, J = 6.0, 2 × H-24), 3.52 (2H, m, 2 × H-15), 3.45 (2H, m, 2 × H-15), 3.36 (2H, m, 2 × H-20), 1.71−1.10 (18H, overlapped’s), 1.05 (18H, s, 2 × C(CH3)3), 0.93 (6H, bd, J = 6.6, 2 × H-17), 0.05 (12H, s, 2 × Si(CH3)3); 13C NMR (100 MHz, CDCl3): δ 139.0, 135.6, 134.0, 129.5, 128.3, 127.7, 127.5, 79.1, 70.73, 70.68, 68.8, 63.3, 35.95, 35.91, 31.3, 31.2, 30.0, 29.9, 28.82, 28.80, 28.61, 28.56, 26.9, 26.0, 19.3, 18.5, 16.9, −5.3; HRMS (ESI) m/z calcld for C36H58NaO3Si2 [M + Na]⁺ 641.8322; found 641.8304.
To a flask containing compound 5 (2.05 g, 3.32 mmol) at RT, a premixed solution of AcOH/THF/H2O (3:1:1, 34 mL) was added. After 4 h, the reaction mixture was quenched with a saturated aqueous NaHCO3 solution (20 mL) and extracted using EtOAc. The organic phase was washed with water, dried, filtered, and concentrated in vacuo. Purification using column chromatography over silica gel (hexane/EtOAc, 9:1) afforded alcohol 35 (1.52 g, 91%) as a colorless oil. Mixture of two diastereomers, IR (neat) νmax = 3400, 2930, 2857, 1455, 1248, 1389, 1112, 1066, 824, 739, 701 cm−1; 1H NMR (400 MHz, CDCl3), δ 7.67 (8H, d, J = 6.8, ArH), 7.44–7.30 (12H, m, ArH), 7.32 (10H, m, ArH), 4.51 (2H, m, OCH2Ph), 4.47 (2H, m, OCH2Ph), 3.62 (4H, t, J = 5.2, OCH2), 3.55–3.43 (4H, m), 3.43–3.36 (2H, m, 2 × H-20), 1.90 (2H, bs, 2 × OH), 1.70–1.40 (16H, overlapped m, 8 × CH2), 1.28–1.09 (2H, m), 1.06 (18H, each, s, 2 × C(CH3)3), 0.93 (6H, bd, J = 6.6, 2 × H-17); 13C NMR (100 MHz, CDCl3), δ 138.6, 135.6, 134.0, 129.5, 128.3, 127.8, 79.71, 79.06, 70.86, 70.82, 68.74, 63.1, 35.9, 35.8, 30.9, 30.7, 30.25, 16.28, 28.7, 28.5, 26.9, 19.3, 16.88, 16.83; HRMS (ESI) m/z calcd for C33H48NO12Si [M + Na]+ 573.3297; found 573.3295.

To a stirred solution of alcohol 35 (763 mg, 1.51 mmol) in dry DMAP (111 mg, 0.906 mmol), p-toluenesulfonyl chloride (345 mg, 1.81 mmol), and triethylamine (230.8 mg, 0.318 mmol, 1.51 mmol) were added in sequence. After 4.5 h, the suspension was diluted with Et2O (30 mL) and stirred for 30 min. Then, the precipitate was removed by filtration. The organic phase was washed with a 10% CuSO4 solution (2 × 100 mL), a 10% NaHCO3 solution (2 × 100 mL), and brine (100 mL). The combined organic phases were dried, filtered, and concentrated in vacuo to give tosylate 36 (946 mg) as a colorless oil. An analytically pure sample of this compound was obtained using chromatography over silica gel (hexane/EtOAc, 5:3) for characterization. Mixture of two diastereomers, IR (neat) νmax = 2955, 2925, 2858, 1632, 1465, 1455, 1261, 803, 739, 701 cm−1; 1H NMR (400 MHz, CDCl3, mixture of rotamers), δ 7.67 (8H, d, J = 7.1, ArH), 7.46–7.23 (12H, m, ArH), 4.58–4.39 (4H, m, OCH2Ph), 3.57–3.43 (3m), 3.42–3.32 (3m), 3.23 (2H, t, J = 7.1, H-24), 2.93 (1.5H, s, H-27), 2.89 (1.5H, s, H-27), 2.06 (1.5H, s, H-26), 2.05 (1.5H, s, H-26), 1.74–0.98 (18H, overlapped multiplets), 1.07 (18H, s, 2 × C(CH3)3), 0.94 (6H, bd, J = 6.4, 2 × H-17); 13C NMR (100 MHz, CDCl3), δ 170.3, 138.9, 138.6, 135.5, 133.93, 133.88, 129.45, 129.41, 128.3, 128.2, 127.6, 127.5, 127.3, 78.89, 78.87, 78.68, 78.62, 70.92, 70.86, 70.82, 68.73, 68.67, 68.65, 50.8, 47.3, 35.87, 35.85, 35.81, 35.77, 33.0, 31.2, 31.1, 30.9, 30.81, 30.78, 30.69, 28.70, 28.66, 28.58, 28.56, 26.8, 24.15, 24.11, 23.0, 22.9, 21.8, 21.2, 19.2, 16.8; HRMS (ESI) m/z calcd for C32H39NO12Si [M + Na]+ 582.3379; found 582.3369.

To a stirred solution of amine 13 (526 mg, 1.02 mmol) in CHCl3 (3.5 mL) at 0 °C, excess Et3N (0.720 mL, 5.15 mmol) was added, followed by dropwise addition of acetyl chloride (160 mg, 2.05 mL, 2.04 mmol). After 30 min, the reaction mixture was diluted with CH2Cl2 and a few drops of water were added. The reaction mixture was washed with a saturated aqueous NaHCO3 solution and then dried. The combined organic phases were dried and concentrated in vacuo to give amide 14 (512 mg, 90%) as a colorless oil. An analytically pure sample of this compound was obtained using chromatography over silica gel (CHCl3/CH2OH, 95:5) for characterization. Mixture of two diastereomers, IR (neat) νmax = 3416, 2931, 2858, 1631, 1472, 1456, 1428, 1261, 1112, 824, 741, 703 cm−1; 1H NMR (400 MHz, CDCl3, mixture of rotamers): δ 7.66 (8H, d, J = 6.9, ArH), 7.46–7.31 (12H, m, ArH), 3.59–3.39 (3H, m, 2 × H-20 and 2 × H-17), 2.35 (4H, bt, J = 7.6, 2 × H-24), 2.95 (1.5H, s, H-27), 2.89 (1.5H, s, H-27), 2.07 (1.5H, s, H-26), 2.04 (1.5H, s, H-26), 1.80–1.08 (18H, overlapped multiplets, 8 × CH2 and 2 × CH), 1.05 (18H, s, 2 × C(CH3)3), 0.92 (3H, d, J = 6.4, H-16), 0.91 (3H, d, J = 6.4, H-17); 13C NMR (100 MHz, CDCl3), δ 170.6, 170.4, 135.5, 133.95, 133.90, 129.5, 129.4.
To a stirred solution of alcohol 37 (368 mg, 0.79 mmol) in CH₂Cl₂ (55 mL), N-methylmorpholine-N-oxide (138 mg, 1.18 mmol) and powdered 4 Å molecular sieves (392 mg) were added under argon. After 10 min, TPAP (13.8 mg, 0.039 mmol, 5 mol %) was added. After 2.5 h, the reaction mixture was filtered through a short silica gel plug (CHCl₃/EtOAc, 8:2), and the filtrate was concentrated under reduced pressure. Purification using column chromatography over silica gel (hexane/EtOAc, 6:4) afforded ketone 15 (335 mg, 91%) as a colorless oil. [α]D²O = +2.7 (c = 1.0, CHCl₃); IR (neat) νmax: 2958, 2924, 2854, 1715, 1653, 1567, 1366, 1261, 1111, 800, 704 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): δ 7.65 (8H, d, J = 7.2, ArH), 7.46−7.33 (12H, m, ArH), 3.52−3.40 (4H, m, CH₂ and 2 × H₂-15), 3.34 (0.6 H, t, J = 7.1, H₂-24), 3.24 (0.4 H, t, J = 7.4, H₂-24), 2.96 (1.8 H, s, H₃-26), 2.90 (1.2 H, s, H₂-27), 2.48−2.28 (8H, m, H₂-22 and H₂-19), 2.08 (1.2 H, s, H₂-26), 2.05 (1.8 H, s, H₂-26), 1.86−1.20 (18H, overlapped multiplets, 8 × CH₃ and 2 × CH), 1.05 (18H, s, 2 × C(CH₃)₃), 0.90 (6H, bd, J = 6.5, 2 × H₂-17); ¹³C NMR (100 MHz, CDCl₃): δ 210.5, 209.7, 170.6, 170.4, 135.5, 133.8, 129.51, 129.48, 127.5, 68.43, 68.39, 49.48, 46.66, 40.5, 40.39, 39.36, 35.8, 35.2, 33.0, 27.1, 27.0, 26.8, 21.9, 21.7, 21.1, 19.2, 16.6; HRMS (ESI) m/z calcd for C₃₁H₅₁O₃Si [M + H]+ 468.2928; found 468.2928.

**Ketone 16.**

To a stirred solution of alcohol 12 (102.3 mg, 0.194 mmol) in CH₂Cl₂ (0.5 mL), N-methylmorpholine-N-oxide (34 mg, 0.291 mmol) and powdered 4 Å molecular sieves (94 mg) were added under argon. After 10 min, TPAP (3.4 mg, 0.0097 mmol, 5 mol %) was added. After 2.5 h, the reaction mixture was filtered through a short silica gel plug (CH₂Cl₂/EtOAc, 8:2) and concentrated in vacuo. Purification using preparative TLC (hexane/EtOAc, 8:2) and concentrated in vacuo. Purification using preparative TLC (hexane/EtOAc, 8:2) afforded ketone 16 (91.8 mg, 90%) as a colorless oil. [α]D = 1.8 (c = 1.0, CHCl₃); IR (neat) νmax: 3025, 2930, 2858, 1717, 1472, 1464, 1428, 1389, 1257, 1112, 836, 777, 740, 702 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): δ 7.67−7.36 (12H, m, ArH), 3.63 (4H, br, J = 6.3), 3.51 (4H, m), 2.47 (2H, t, J = 7.3), 2.41 (2H, m), 1.08 (9H, s, C(CH₃)₃), 0.94 (3H, d, J = 6.7, H₂-17), 0.91 (9H, s, C(CH₃)₃), 0.06 (6H, s, Si(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃): δ 211.0, 135.6, 133.8, 128.9, 125.7, 68.5, 62.2, 40.5, 38.9, 35.3, 27.2, 26.86, 26.82, 25.9, 19.3, 18.3, 16.7, −5.4; HRMS (ESI) m/z calcd for C₂₈H₄₂NO₃Si [M + H]+ 527.3371; found 527.3379.

**Phosphonium Salt 17.**

(Chloromethyl)triphenyolphosphonium iodide 17 was prepared through a modification of the reported procedure, starting from triphenyolphosphate (31.44 g, 120 mmol) and chloroiodo-methane (25 g, 10.3 mL, 142 mmol). In particular, the Widmer condenser was replaced by a double-jacketed condenser. After 4 h, the process was stopped by filtering the reaction mixture under argon to give compound 17 (14.23 g, 27%) as a light yellow powder. This compound could be stored in a desiccator without decomposition for several months. Crystallization from ethanol gave 12.55 g (24%) of 17 as white crystals. mp 186−187 (dec) [lit. 185−187 (dec)⁴]; ¹H NMR: (400 MHz, DMSO-d₆) δ 8.01−7.75 (15H, m, ArH), 6.08 (2H, d, J = 6.8); ¹³C NMR (100 MHz, DMSO-d₆): δ 135.6, 134.0 (d, J = 10.2), 130.3 (d, J = 12.6), 116.1 (d, J = 88.2), 32.0 (d, J = 55.4).

**Wittig Reaction on Model Ketone 16 Using nBuLi as the Base.**

To a stirred suspension of (chloromethyl)-triphenyolphosphonium iodide 17 (338 mg, 0.772 mmol) in THF (10 mL), nBuLi (0.362 mL, 0.579 mmol, 1.0 M soln in hexane) was added dropwise at −78 °C under argon. The white suspension became a red-orange solution. After 1 h at −78 °C, a solution of ketone 16 (101.4 mg, 0.193 mmol) in dry THF (1.3 mL) was added via a cannula, and the mixture was allowed to reach RT. After 2 h, the reaction was quenched with a saturated aqueous NH₄Cl solution (10 mL) and extracted using EtOAc (3 × 15 mL). The organic phase was washed with brine, dried, and evaporated under reduced pressure to give a mixture of compounds 18 and 19 (171.5 mg, 18.19, 1:1; ¹H NMR analysis) as a colorless oil.

**Wittig Reaction on Model Ketone 16 Using tert-BuOK as the Base.**

To a stirred suspension of (chloromethyl)-triphenyolphosphonium iodide 17 (137 mg, 0.31 mmol) in THF (3.5 mL), tert-BuOK (0.314 mL, 0.314 mmol, 1.0 M soln in THF) was added dropwise at 0 °C under argon.⁴ The solution immediately became yellow. After 30 min at 0 °C, a solution of ketone 16 (82.8 mg, 0.157 mmol) in dry THF (1.0 + 0.2 mL rinse) was added, and the mixture was allowed to reach RT. After 4 h, the reaction was quenched with a saturated aqueous NH₄Cl solution (10 mL) and extracted using EtOAc (3 × 15 mL). The organic phase was washed with brine, dried, and evaporated under reduced pressure. Purification using preparative TLC (hexane/EtOAc, 8:2) gave compound 18 (66.5 mg, 76%, 1:8:1 mixture of diastereomers, ¹H NMR analysis) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): mixture of two diastereomers, δ 7.72−7.27 (ArH), 5.78, 5.74 (both s, vinyl proton), 3.63−3.55, 3.52−3.45 (both m, 2 × OCH₂), 2.29−2.04 (m, H₂-19 and H₂-22), 1.71−1.51 (m), 1.06, 0.89 (both s, 2 × C(CH₃)₃), 0.041 (m, (CH₃)₂Si); HRMS (ESI) m/z calcd for 559.3189 [M + H]+; found 559.3178.
To a stirred suspension of (chloromethyl)-triphenylphosphonium iodide 17 (128 mg, 0.292 mmol) in THF (5 mL), tert-BuOK (0.281 mL, 0.7281 mmol, 1.0 M sol. in THF) was added dropwise at 0 °C under argon. The solution immediately became yellow. After 30 min at 0 °C, a solution of ketone 15 (45.5 mg, 0.097 mmol) in dry THF (1.0 + 1.0 mL rinse) was added, and the mixture was allowed to reach RT. After 4 h, the reaction was quenched with a saturated aqueous NH₄Cl solution (10 mL) and extracted using Et₂O (3 × 20 mL). The organic phase was washed with brine, dried, and evaporated under reduced pressure. Separation using column chromatography over silica gel (hexane/EtOAc, 8:2) gave compounds 20 (19.6 mg, 40.4%) and 21 (20.5 mg, 42.3%) as colorless oils. Compound 20. [α]D²⁰ = −1.6 (c = 0.23, CHCl₃). IR (neat) νmax: 2955, 2930, 2858, 1652, 1428, 1112, 824, 798, 741, 703 cm⁻¹; 1H NMR (400 MHz, CDCl₃, mixture of rotamers): δ 7.65 (4H, d, J = 6.9, ArH), 7.45–7.34 (6H, m, ArH), 5.81 (0.5H, s, vinyl proton). 5.75 (0.5H, s, vinyl proton), 3.48 (2H, bt, J = 5.6, H₂-15), 3.37, 3.25 (1H each, both J = 5.6, H₂-15), 2.97 (1.5H, s, H₂-17), 2.90 (1.5H, s, H₂-17), 2.24–2.13 (2H, m), 2.13–1.95 (5H, overlapped signals including a singlet at 2.07 for H₂-26), 1.77–1.53 (4H, m), 1.34–1.13 (1H, m), 1.06 (9H, s, C(CH₃)₃), 0.91 (3H, d, J = 6.6, H₂-17); 13C NMR (100 MHz, CDCl₃): δ 170.4, 170.3, 142.1, 141.4, 135.6, 133.89, 133.81, 129.59, 129.54, 127.6, 113.0, 112.3, 68.5, 68.4, 50.5, 47.1, 36.0, 35.2, 32.25, 32.20, 31.05, 30.99, 27.5, 27.3, 26.9, 25.8, 24.7, 21.9, 21.2, 19.3, 16.6; HRMS (ESI) m/z calcd for C₁₃H₂₅ClNO₂ [M + Na]⁺ 262.1568; found 262.1564.

Aldehyde 23.

To a stirred solution of alcohol 22 (16.2 mg, 0.062 mmol) in CH₂Cl₂ (0.3 mL), N-methylmorpholine-N-oxide (10.87 mg, 0.093 mmol) and powdered 4 Å molecular sieves (31 mg) were added under argon. After 10 min, TPAP (1.1 mg, 0.003 mmol, 5 mol %) was added. After 2 h, the reaction mixture was filtered through a short silica gel plug eluting with CHCl₃/EtOAc (8:2) and concentrated under reduced pressure to yield aldehyde 23 (13.7 mg) as a colorless oil, which was applied to the next step without further purification.

Ethyl Ester 24.

To a stirred solution of the aldehyde 23 (13.7 mg, 0.053 mmol) in anhydrous toluene (0.4 mL), (carboethoxyethylidene)-triphenylphosphorane (40.8 mg, 0.106 mmol) was added at once at 80 °C under argon. After 6 h, the reaction mixture was concentrated under reduced pressure. Purification using column chromatography over silica gel (CHCl₃/CH₂OH, 95:5) afforded ethyl ester 24 (16.3 mg 76% over two steps) as a colorless oil. [α]D²⁰ = +127.4 (c = 0.5, CHCl₃). IR (neat) νmax: 2957, 2927, 2858, 1707, 1651, 1596, 1459, 1424, 1373, 1262, 1122 cm⁻¹; 1H NMR (400 MHz, CDCl₃, mixture of rotamers): δ 6.49 (1H, d, J = 10.1, H-15), 5.82 (0.5H, s, vinyl proton), 5.76 (0.5H, s, vinyl proton), 4.18 (2H, q, q = 7.0, OCH₂CH₃), 3.37, 3.37 (1H each, both J = 7.6, H₂-24), 2.99 (1.5H, s, H₂-17), 2.91 (1.5H, s, H₂-17), 2.46 (1H, m, H-16), 2.18 (2H, m), 2.09 (1.5H, s, H₂-26), 2.08 (1.5H, s, H₂-26), 2.01 (2H, t, J = 8.6), 1.83 (1.5H, d, J = 1.2, H₂-14), 1.82 (1.5H, d, J = 1.2, H₂-14), 1.30 (3H, t, J = 7.0, OCH₂CH₃), 1.02 (1.5H, d, J = 6.6, H₂-17), 1.00 (1.5H, d, J = 6.6, H₂-17); 13C NMR (100 MHz, CDCl₃): δ 170.5, 170.3, 168.3, 168.2, 146.9, 146.6, 146.1, 140.8, 132.1, 132.0, 131.94, 131.91, 128.5, 128.4, 127.2, 127.0, 113.4, 112.7, 60.6, 60.5, 50.4, 47.1, 36.0, 34.7, 34.6, 33.1, 32.7, 27.4, 27.3, 25.7, 24.6, 21.9, 21.3, 20.01, 19.98, 14.3, 12.63, 12.61; HRMS (ESI) m/z calcd for C₁₉H₁₉ClN₂O₃ [M + Na⁺] 366.1812; found 366.1802.
Carboxylic Acid 3.

To a stirred solution of ester 24 (6.3 mg, 0.018 mmol) in THF (0.075 mL) and CH₂OH (0.038 mL), lithium hydroxide monohydrate (7.6 mg, 0.18 mmol) in water (0.038 mL) was added at RT. After 24 h, the pH was adjusted to 1.0 by the addition of HCl 2 N (0.1 mL), and the solution was extracted using ethyl acetate (3 × 5 mL). The organic phase was dried and evaporated in vacuo to give acid 3 (4.5 mg, 79%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): δ 6.63 (1H, d, J = 6.8, H₃-17), 1.08 (1.5H, d, J = 6.7, H₃-17), 1.01 (1.5H, d, J = 6.7, H₃-17); HRMS (ESI) m/z calced for C₁₆H₂₆ClNNaO₃ [M + Na⁺] = 338.1499; found 338.1510.

Pentafluorophenyl Ester 26.

To a solution of a solution of 3 (4.5 mg, 0.014 mmol) in EtOAc (0.130 mL), pentafluorophenol (4.0 mg, 0.022 mmol) and DCC (4.5 mg, 0.22 mmol) were added at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and 3 h at RT and evaporated under reduced pressure. Purification using preparative TLC (CDCl₃/CH₂OH, 95:5) gave pentafluorophenyl ester 26 (5.5 mg, 82%) as a colorless oil. IR (neat) ν max: 2980, 2940, 2848, 1683, 1626, 1521, 1261, 1096, 1022, 806, 760 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, mixture of rotamers): δ 6.85 (1H, d, J = 10.1, H₁₅), 5.86 (0.5H, s, vinyl proton), 5.80 (0.5H, s, vinyl proton), 3.39, 3.29 (1H each, both t, J = 7.1, ArH), 2.92 (1.5H, s, H₃-27), 2.58 (1H, m, H-16), 2.20 (2H, m), 2.09 (1.5H, s, H₃-26), 2.08 (1H, m, H-16), 1.97 (1H, d, J = 1.2, H₁₄-1), 1.96 (1H, d, J = 1.2, H₁₄-1), 1.10 (1.5H, d, J = 6.8, H₁₇-17), 1.08 (1.5H, d, J = 6.8, H₁₇-17); ¹³C NMR (100 MHz, CDCl₃): δ 152.4, 152.0, 141.3, 140.6, 124.4, 124.2, 113.7, 113.0, 50.4, 49.1, 47.1, 36.0, 34.5, 34.4, 33.9, 33.3, 33.1, 32.74, 32.68, 27.31, 27.29, 25.8, 25.6, 24.9, 24.6, 21.9, 21.3, 19.67, 19.64, 12.7; HRMS (ESI) m/z calced for C₁₂H₁₀ClF₅NO₃ [M + Na⁺] = 383.1499; found 383.1510.

Pyrrylone 4.

To a stirred solution of pyrrolinone 25 (1.0 g, 3.46 mmol) and triphenylphosphine (1.36 g, 5.19 mmol) in CH₂Cl₂ (20 mL), CH₂OH (0.21 mL, 5.19 mmol) and diisopropyl azodicarboxylate (DIAD) (1.0 mL, 5.19 mmol) were added at 0 °C under argon. The reaction mixture was allowed to warm to RT, and after 6 h, it was concentrated in vacuo. Purification using column chromatography over silica gel (hexane/EtOAc, 6:4) gave Boc-protected pyrrylone 38 (621 mg, 57% over three steps) as a colorless oil. [α]D20 = +203.3 (c = 1.0, CH₂OH); IR (neat) ν max: 2980, 2940, 1779, 1733, 1705, 1456, 1319, 1246, 1152, 1094, 871, 848, 808, 757, 701, 677 cm⁻¹; ¹H NMR: (400 MHz, CDCl₃): δ 7.11–7.00 (3H, m, ArH), 6.87 (2H, d, J = 7.1, ArH), 4.66 (1H, s, H-10), 4.52 (1H, bdd, J = 5.0, 3.0, H-8), 3.62 (3H, s, OCH₃), 3.31 (1H, dd, J = 13.8, 5.1, H₁₇-7), 2.98 (1H, dd, J = 13.8, 3.0, H-7), 1.48 (9H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 175.6, 168.0, 148.8, 133.5, 128.9, 127.6, 126.4, 94.5, 81.8, 59.5, 57.7, 34.7, 27.6; HRMS (ESI) m/z calced for C₁₇H₂₁NO₄ [M + H⁺] = 304.1543; found 304.1532.

To a stirred solution of 38 (212 mg, 0.66 mmol) in CH₂Cl₂ (2.5 mL), trifluoroacetic acid (TFA) (2.5 mL) was added. After 30 min, the reaction mixture was evaporated in vacuo. Residual TFA was removed by evaporation with toluene (3 × 1.5 mL) to give pyrrolone 4 (144 mg, quant.) as a white waxy solid. mp 84–85 (EtOAc/hexane) [lit. 103–104]; [α]D20 = −62.3 (c = 1.0, CH₂Cl₂) [lit. −63.0 (c = 1.0, CH₂Cl₂)]; IR (neat) ν max: 3238, 3030, 2939, 2848, 1683, 1623, 1497, 1455, 1365, 1344, 1323, 989, 806, 700 cm⁻¹; ¹H NMR: (400 MHz, CDCl₃): δ 7.32–7.20 (3H, m, ArH), 7.14 (2H, d, J = 7.1, ArH), 5.6 (br s, NH), 5.04 (1H, s, H-10), 4.33 (1H, m, H-8), 3.83 (3H, s, OCH₃), 3.17 (1H, dd, J = 13.7, 3.4, H-7), 2.78 (1H, dd, J = 13.7, 7.6, H-7); ¹³C NMR (100 MHz, CDCl₃) δ 177.2, 173.7, 136.3, 129.1, 128.4, 126.8, 94.0, 58.4, 58.1, 38.3; HRMS (ESI) m/z calced for C₁₂H₁₀NO₄ [M + H⁺] = 204.1019; found 204.1011.

16-epi-Smenamide 27.

To a stirred solution of pyrrolone 4 (9.9 mg, 0.049 mmol) in THF (0.1 mL), nBuLi (0.020 mL, 0.033 mmol, 1.6 M soln in hexane) was added dropwise at −78 °C. After 15 min, a solution of pentafluorophenyl ester 26 (1.5 mg, 0.0031 mmol) in THF (0.1 mL) was added via a syringe. After 2 h, the reaction was quenched with a saturated aqueous NH₄Cl solution (1 mL) and extracted using EtOAc (3 × 10 mL). The organic phase was washed with water (6 mL) and brine (6 mL), dried, and concentrated in vacuo. The crude was subjected to reversed-phase high-performance liquid chromatography (HPLC) separation [column Luna (Phenomenex) C18, 250 × 4.6 mm, 5 μm; eluent A: H₂O; eluent B: CH₃CN; gradient:
To a stirred solution of pyrrolinone 28 (9.9 mg, 0.049 mmol) in THF (0.1 mL), nBuLi (0.20 mL, 0.033 mmol, 1.6 M soln in hexane) was added dropwise at −78 °C. After 15 min, a solution of pentafluorophenyl ester 26 (1.5 mg, 0.0031 mmol) in THF (0.1 mL) was added via a syringe. After 2 h, the reaction was quenched with a saturated aqueous NH₄Cl solution (1 mL) and extracted using EtOAc (3 × 10 mL). The organic phase was washed with water (6 mL) and brine (6 mL), dried, and concentrated in vacuo. The crude was subjected to reversed-phase HPLC separation (column Luna (Phenomenex) C18, 250 × 4.6 mm, 5 μm; eluent A: H₂O; eluent B: CH₃CN; gradient: 50 → 100% B, over 35 min, flow rate 1 mL min⁻¹) to give 16-epi-smenamide A (m Letters declare no competing financial interest.

**ACKNOWLEDGMENTS**

This research program was funded by the European Union’s Seventh Framework Programme (FP7-KBBE) under the grant no. 311848 (BlueGenics) and by Università degli Studi di Napoli Federico II under the STAR project SeaLEADS.

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