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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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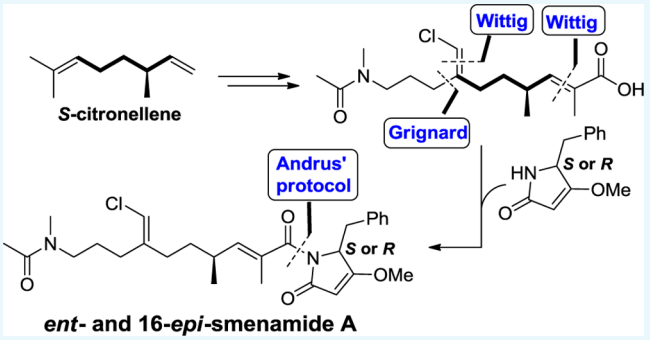
Supporting Information

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[1] 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

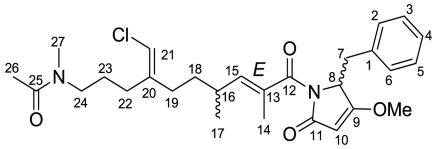


Figure 1. Structures of smenamide A (**1**) and B (**2**) as determined in a previous study.[5]

chlorinated hybrid peptide/polyketide metabolites isolated in microgram amounts from the Caribbean sponges *Smenospongia aurea*[5] 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 jamaicamides[7] and malingamides[8] and the recently isolated smenothiazoles[9] and conulothiazoles.[6] The dolapyrrolidinone terminus is a structural feature found, among others, in dolastatin-15,[10] mycapolyols A−F,[11] and belamide A.[12] Smenamides are bioactive substances and promising anticancer lead compounds. In particular, smenamide A is strongly cytotoxic on lung cancer Calu-1 cells at nanomolar concentrations[5] 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

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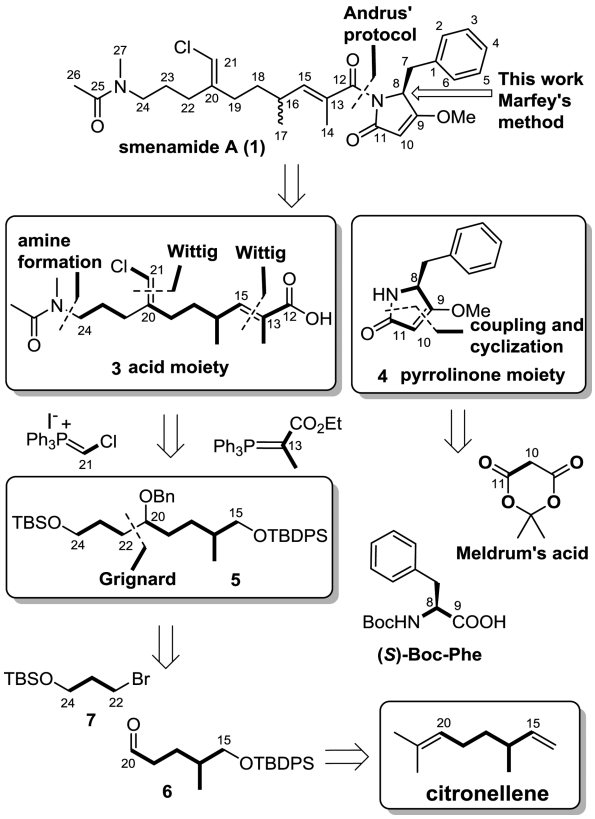
construction of the *Z*-chlorovinyl function. Various approaches have been used to build this function in related substances,[14] but relatively a few methods have been reported for the stereoselective preparation of chloroolefins. Paige et al.[15] used the palladium-mediated regio- and stereospecific silylstannylation of a terminal alkyne[16] 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,[17a,b] 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.[14a−d,f] Although this approach suffers from the lack of stereoselectivity, sound precedents exist for the photochemical isomerization of strictly related chloroolefins,[14d] 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

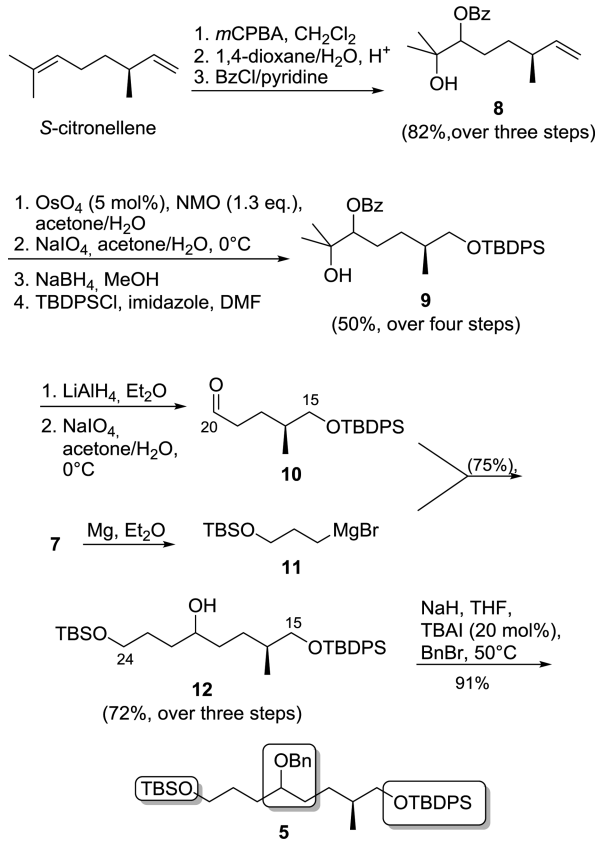
Scheme 1. Retrosynthetic Analysis of Smenamide A



gave carboxylic acid **3** (C12−C27 fragment) and pyrrolinone **4** (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 **5** 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*-butyldimethylsilyl (TBS), Bn, and *tert*-butyldiphenylsilyl (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 α,β-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.[18] Therefore, a racemization-free synthetic route has been used[18,19] to obtain fragment **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

Scheme 2. Synthesis of the Fully Protected C15−C24 Triol Fragment 5



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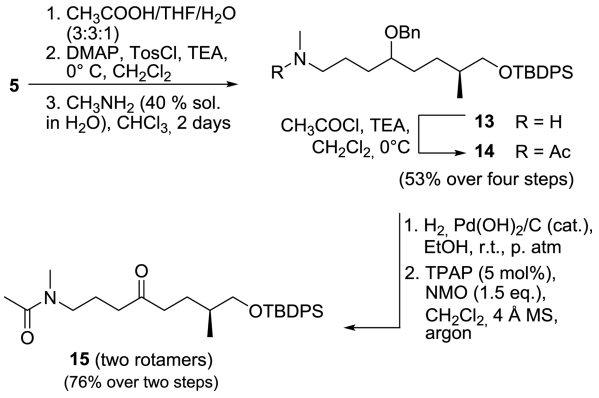
steps). The terminal olefin was dihydroxylated under Sharpless conditions with OsO_4 (catalyst)/*N*-methylmorpholine *N*-oxide (NMO), and the obtained diol was cleaved with sodium periodate to afford the C-15 aldehyde. Reduction of the latter with sodium borohydride and protection of the primary alcohol 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

Scheme 3. Installation of the *N*-Methylacetamide Function

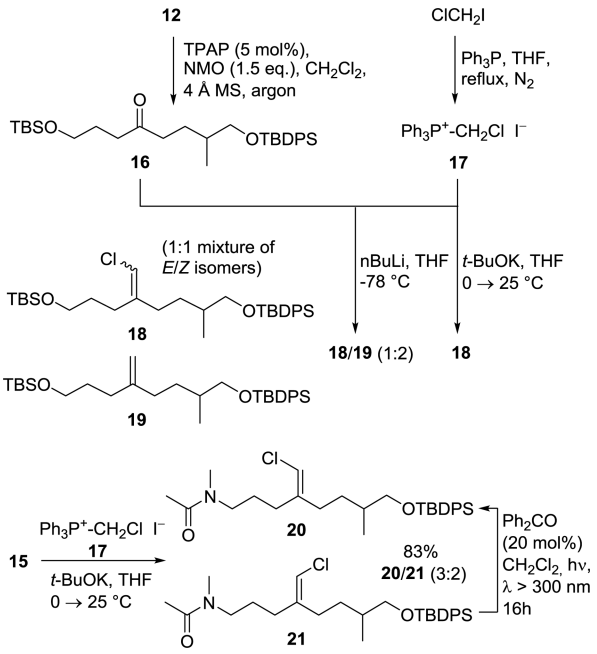


of the TBS group with AcOH/tetrahydrofuran(THF)/H_2O (3:1:1) followed by tosylation and treatment of tosylate with excess NH_2CH_3 (40% soln in water)[20] afforded the secondary amine **13**. Acetylation of the latter with AcCl/triethylamine (TEA) gave the desired *N*-methylacetamide **14** in a 65% 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[21] (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%).[21] The required phosphonium salt, (chloromethyl)triphenylphosphonium iodide **17** (Scheme 4), was prepared by the reaction of iodochloromethane with triphenylphosphine.[14a] According to the literature, the Wittig reaction was conducted in the presence of *n*BuLi in THF at −78 °C.[14c,d] 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[14a] as the base smoothly led to the

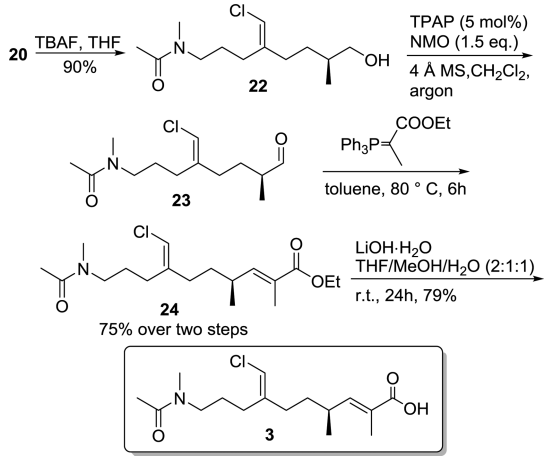
Scheme 4. Chloromethylenation of Model Compound 16 and Synthetic Intermediate 15



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,[14d] irradiation of **21** with $\lambda > 300$ 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

Scheme 5. Synthesis of Acid Moiety 3



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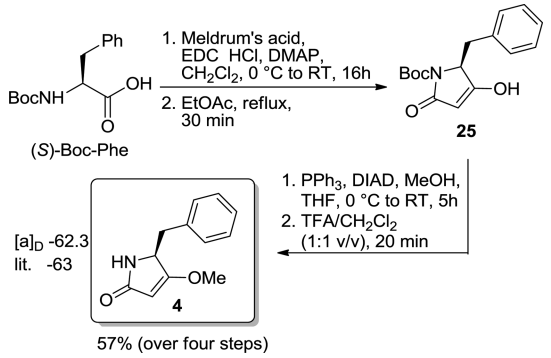
group in **20** with tetrabutylammonium fluoride (TBAF)/THF followed by oxidation of the alcohol **22** with the TPAP (5 mol %)/NMO system gave aldehyde **23**, which was subjected to the subsequent *E*-selective Wittig olefination without further purification. Thus, the reaction of **23** with $Ph_3P{=}CH(Me)$-CO_2Et afforded α,β-unsaturated ester **24**, which was hydrolyzed to acid **3** on treatment with lithium hydroxide hydrate. Overall, compound **3** was obtained with a 53% yield over four steps.

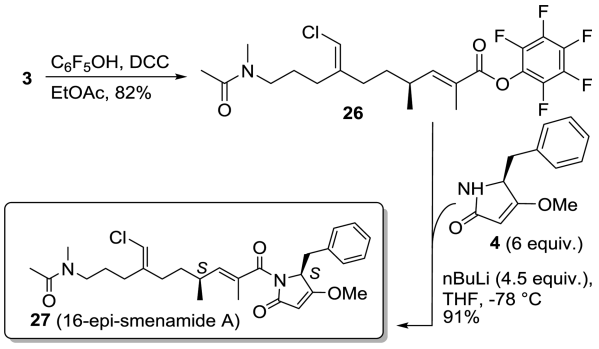
Pyrrolinone moiety **4** was synthesized in a 57% overall yield according to the previously developed racemization-free route shown in Scheme 6.[19] Briefly, the reaction of (*S*)-Boc-phenylalanine with Meldrum's acid, followed by the reflux of the crude in AcOEt for 30 min gave the Boc-protected tetramic 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; lit. −63),[22] indicating its high enantiopurity.

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



Finally, the two building blocks **3** and **4** were coupled by using the Andrus protocol[23] (Scheme 7). Thus, the acid moiety **3** was activated as the pentafluorophenyl ester **26** by reaction with C_6F_5OH/*N*, *N*′-dicyclohexylcarbodiimide (DCC) (82%). Coupling of **26** with an excess of lithium imidate derived 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.

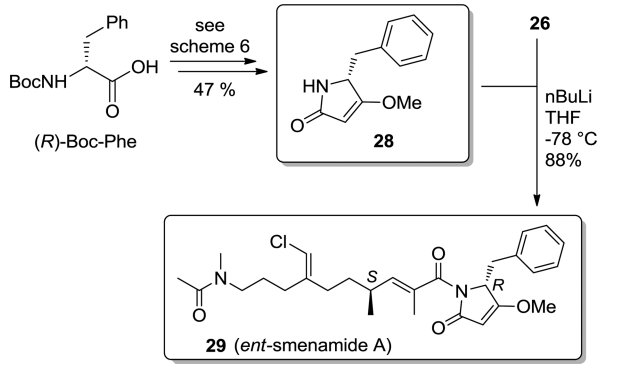
Scheme 7. Coupling of 3 and 4[a]



[a]Synthesis of 16-*epi*-smenamide A.

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-*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 *ent*-smenamide A was carried out by coupling (*R*)-pyrrolinone **28**[24] with pentafluorophenyl ester **26** (Scheme 8). Starting from (*R*)-Boc-phenylalanine, compound **28** was obtained in a straightforward manner in a 47% overall yield. Finally, the coupling of compounds **26** and **28** using the Andrus method proceeded smoothly in this case too to give *ent*-smenamide A **29** in an 88% yield. The proton spectrum of this material perfectly matched that of natural smenamide A, confirming that the configuration at C-16 in smenamide A was indeed *R*. In addition, as expected, natural smenamide A and *ent*-smenamide A had mirror-image CD spectra. Compound **29** was obtained in a 2.6% overall yield (LLS = 23 steps).

Scheme 8. Synthesis of the (*R*)-Pyrrolinone Moiety and *ent*-Smenamide A



CONCLUSIONS

In conclusion, the syntheses of *ent*-smenamide A and 16-*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. β-citronellene was purchased from Sigma Aldrich (ee ≥ 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. $MgSO_4$ 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 $CDCl_3$. Proton chemical shifts were referenced to the residual $CHCl_3$ 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

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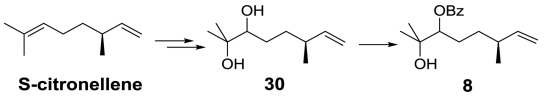
on a PerkinElmer spectrum 100R spectrophotometer and are reported in cm^{-1}. Optical rotations were measured using a JASCO P-2000 polarimeter at the sodium D line. ECD spectra were recorded using a JASCO J-710 spectropolarimeter. HRMS spectra were recorded by infusion on a Thermo LTQ Orbitrap XL mass spectrometer equipped with an electrospray source in the positive mode using MeOH as the solvent.

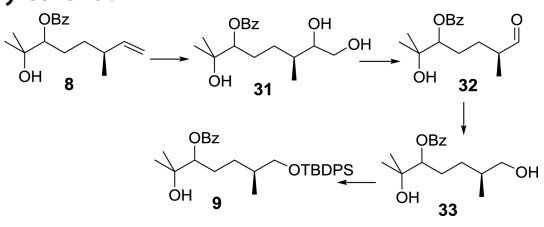
Benzoate 8.



According to a literature procedure,[25] β-citronellene (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 flask containing the crude epoxide in 1,4-dioxane/H_2O (34 mL, 2:1), concentrated H_2SO_4 (3 drops) was added. After 1 h, solid $NaHCO_3$ 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%) as 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}: 3410, 2957, 2927, 2858, 1699, 1640, 1454, 1378, 1271, 1167, 1069, 995, 911, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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, all s, 2 × $C(CH_3)_2$), 1.02, 1.01 (3H each, both d, J = 6.7, 2 × H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{10}H_{20}NaO_2$ $[M + Na]^+$ 195.1361; found 195.1348.

To a stirred solution of diol **30** (7.34 g, 42.6 mmol) in pyridine (20 mL), benzoyl 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 $CHCl_3$ (50 mL) and washed with a saturated aqueous $NaHCO_3$ solution and water. The organic phase was dried, filtered, and evaporated in vacuo. Purification over silica gel (hexane/EtOAc, 9:1) gave benzoate **8** (11.0 g, 94%), as a colorless oil, a mixture of two diastereomers. IR (neat) ν_{max}: 3482, 2974, 2929, 1718, 1704, 1452, 1275, 1177, 1113, 1070, 1027, 711 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$): δ 8.07 (4H, d, J = 7.1, ArH), 7.57 (2H, t, J = 7.5, ArH), 7.46 (4H, t, J = 7.6, ArH), 5.71−5.55 (2H, m, 2 × H-15), 5.12−5.02 (2H, m), 5.01−4.87 (4H, m), 2.22−2.04 (2H, m), 1.94 (2H, bs, 2 × OH), 1.85−1.58 (4H, m), 1.43−1.29 (4H, m), 1.26 (12H, s, 2 × $C(CH_3)_2$), 0.96 (6H, d, J = 6.9, H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798; found 277.1788.

Silylether 9.



To a stirred solution of benzoate **8** (7.93 g, 28.7 mmol) in acetone/water (120 mL, 5:1), OsO_4 (369 mg, 14.5 mmol, 5 mol %) was added. After 2 h, the reaction was quenched by the addition of solid $Na_2S_2O_5$ (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 ($CHCl_3$/CH_3OH, 9:1) for characterization. Mixture of four diastereomers, IR (neat) ν_{max}: 3400, 2971, 2932, 1716, 1701, 1452, 1278, 1177, 1115, 1071, 1017, 712 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$): 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), 1.26, 1.25 (6H each, both s, 2 × $C(CH_3)_2$), 0.89, 0.88, 0.863, 0.858 (3H each, d's, J = 6.7, 4 × H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 166.9, 166.76, 166.73, 133.2, 133.1, 130.02, 129.99, 129.94, 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, 65.0, 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, 26.7, 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 calcd for $C_{17}H_{26}NaO_5$ $[M + Na]^+$ 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, $NaBH_4$ (376 mg, 9.9 mmol) was added in portions. After 1 h, the reaction was quenched by dropwise addition of CH_3COOH (3.5 mL). Then, the reaction mixture was concentrated in vacuo, treated with a saturated aqueous solution of $NaHCO_3$ (30 mL), and extracted using EtOAc (3 × 30 mL). The organic phase was dried and evaporated under reduced pressure to give crude **33** (5.29 g). An analytically pure sample of this compound was obtained using chromatography over silica gel ($CHCl_3$/CH_3OH, 9:1) for characterization. Mixture of two diastereomers, IR (neat) ν_{max}: 3400, 2972, 2930, 1716, 1699, 1451, 1277, 1177, 1113, 1070, 1027, 711 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$): δ 8.07 (4H, d, J = 7.1, ArH), 7.57 (2H, t, J = 7.5, ArH), 7.46 (4H, t, J = 7.6, ArH), 5.11−5.04 (2H, m, 2 × H-20), 3.53−3.36 (4H, m, 2 × H_2-15), 1.91−1.11 (10H, m), 1.28 (12H, s, 2 × $C(CH_3)_2$), 0.92, 0.90 (3H each, both d, J = 6.9, 2 × H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 166.7, 133.06, 133.08, 130.0, 129.6, 128.4, 80.7, 80.4, 72.64, 72.57, 67.9, 67.6, 35.43, 35.39, 29.7, 29.4, 26.9, 26.1, 25.43, 25.39, 16.7, 16.3; HRMS (ESI) m/z calcd for $C_{16}H_{24}NaO_4$ $[M + Na]^+$ 303.1572; found 303.1561.

To a stirred solution of alcohol **33** (5.29 g, 19.0 mmol) in dimethlformamide (DMF, 19 mL), imidazole (1.56 g, 23 mmol) and *tert*-butyldiphenylsilyl chloride (6.32 g, 5.88 mL, 23 mmol) were sequentially added at room temperature (RT). After 40 min, DMF was evaporated in vacuo, and the residue was taken up in $CHCl_3$ and washed with brine. The organic phase was dried, concentrated in vacuo, and purified using

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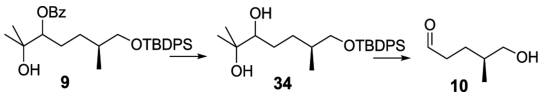
chromatography over silica gel (hexane/EtOAc, 95:5) to give TBDPS ether **9** (7.54 g, 50% over four steps), as a colorless oil. Mixture of two diastereomers, IR (neat) ν_{max}: 3485, 2960, 2931, 2858, 1715, 1602, 1588, 1472, 1452, 1428, 1275, 1112, 1071, 824, 806, 741, 703 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$): δ 8.07 (4H, d, J = 7.1, ArH), 7.67−7.29 (26H, overlapped m's, ArH), 5.07 (2H, d, J = 8.7, 2 × H-20), 3.44 (4H, m, 2 × H_2-15), 2.00−1.46 (10H, m), 1.27, 1.26 (6H each, both s, 2 × $C(CH_3)_2$), 1.00, 0.97 (9H each, both s, 2 × $C(CH_3)_3$), 0.91 (6H, d, J = 6.5, 2 × H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 135.6, 133.9, 133.0, 130.1, 129.7, 129.5, 128.4, 127.5, 80.8, 80.6, 72.7, 68.7, 68.4, 35.7, 35.5, 29.8, 29.6, 27.3, 27.0, 26.8, 26.7, 26.6, 26.5, 25.16, 25.11, 19.23, 19.18, 17.0, 16.6; HRMS (ESI) m/z calcd for $C_{32}H_{42}NaO_4Si$ $[M + Na]^+$ 541.2750; found 541.2733.

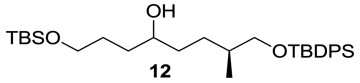
Aldehyde 10.



To a stirred solution of silyl ether **9** (7.54 g, 14.5 mmol) in dry Et_2O (50 mL) at 0 °C, $LiAlH_4$ (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) ν_{max}: 3412, 2958, 2931, 2858, 1472, 1461, 1428, 1388, 1112, 1075, 702 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$): 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 × $C(CH_3)_2$), 0.95, 0.92 (3H each, both d, J = 6.7, 2 × H_3-17), ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{25}H_{38}NaO_3Si$ $[M + Na]^+$ 437.2488; found 437.2473.

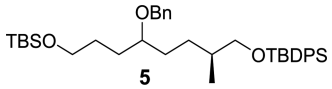
To a stirred solution of diol **34** (4.83 g, 11.6 mmol) in acetone/water 5:1 (57 mL) at 0 °C, sodium periodate (4.98 g, 23.2 mmol) was added. After a few minutes, a large amount of white solid precipitated. After 4 h, the reaction mixture was filtered under vacuum, and the precipitate was carefully 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, $CDCl_3$): δ 9.74 (1H, s, CHO), 7.66 4H, d, J = 7.1, ArH), 7.46−7.34 (6H, m, ArH), 3.50 (2H, m, H_2-15), 2.47−2.31 (2H, m, H_2-19), 1.87−1.75 (1H, m), 1.75−1.61 (1H, m), 1.55−1.43 (1H, m), 1.06 (9H, s, $C(CH_3)_3$), 0.92 (3H, d, J = 6.7, H_3-17).

Alcohol 12.



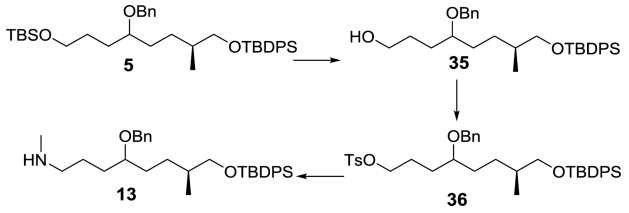
To a suspension of magnesium turnings (583 mg, 24.0 mmol) in anhydrous THF (30 mL), a catalytic amount of iodine was added. After 10 min, (3-bromopropoxy)-*tert*-butyldimethylsilane (4.56 g, 4.17 mL, 18.0 mmol) in THF (20 mL) was slowly added at RT under argon. During the addition, the temperature was 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 NH_4Cl 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) ν_{max}: 3420, 2954, 2930, 2858, 1472, 1464, 1428, 1389, 1256, 1111, 1007, 835, 777, 740, 702 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$): δ 7.70 (8H, d, J = 7.0, ArH), 7.47−7.35 (12H, m, ArH), 3.69 (4H, bt, J = 5.2), 3.63−3.53 (4H, m), 3.53−3.45 (2H, m, H-20), 2.45 (2H, bs, 2 × OH), 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 × $C(CH_3)_3$), 0.970 (3H, d, J = 6.6, H_3-17), 0.965 (3H, d, J = 6.6, H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{31}H_{53}O_3Si_2$ $[M + H]^+$ 529.3528; found 529.3506.

Fully Protected Triol 5.



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 $NaHCO_3$ 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) ν_{max}: 2955, 2929, 2858, 1472, 1473, 1463, 1428, 1388, 1255, 1112, 1095, 835, 776, 738, 701 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$): δ 7.67 (8H, d, J = 7.3, ArH), 7.45−7.28 (22H, m, ArH), 4.48 (4H, d, J = 3.3, OCH_2Ph), 3.60 (4H, bt, J = 6.0, 2 × H_2-24), 3.52 (2H, m, 2 × H_a-15), 3.45 (2H, m, 2 × H_b-15), 3.36 (2H, m, 2 × H-20), 1.71−1.10 (18H, overlapped m's), 1.05 (18H, s, 2 × $C(CH_3)_3$), 0.93 (6H, bd, J = 6.6, 2 × H_3-17), 0.05 (12H, s, 2 × $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 135.6, 134.0, 129.5, 128.3, 127.7, 127.5, 127.3, 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, 18.3, 16.9, −5.3; HRMS (ESI) m/z calcd for $C_{38}H_{58}NaO_3Si_2$ $[M + Na]^+$ 641.3822; found 641.3804.

Amine 13.



DOI: 10.1021/acsomega.7b00095
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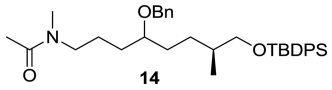
To a flask containing compound **5** (2.05 g, 3.32 mmol) at RT, a premixed solution of AcOH/THF/H_2O (3:1:1, 34 mL) was added. After 4 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (20 mL) and extracted using EtOAc. The organic phase was washed with water, dried, filtered, 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) ν_{max}: 3400, 2930, 2857, 1455, 1428, 1389, 1112, 1066, 824, 739, 701 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$), 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, OCH_2Ph), 4.47 (2H, m, OCH_2Ph), 3.62 (4H, t, J = 5.2, OCH_2), 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's, 8 × CH_2), 1.28−1.09 (2H, m), 1.06, (18H each, s, 2 × $C(CH_3)_3$), 0.93 (6H, bd, J = 6.6, 2 × H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 135.6, 134.0, 129.5, 128.3, 127.8, 127.6, 79.11, 79.06, 70.86, 70.82, 68.78, 68.74, 63.1, 35.9, 35.8, 30.9, 30.7, 30.25, 30.16, 28.7, 28.5, 26.9, 19.3, 16.88, 16.83; HRMS (ESI) m/z calcd for $C_{32}H_{44}NaO_3Si$ $[M + Na]^+$ 527.2957; found 527.2953.

To a stirred solution of alcohol **35** (763 mg, 1.51 mmol) in dry CH_2Cl_2 (12 mL) at 0 °C, 4-dimethylaminopyridine (DMAP) (111 mg, 0.906 mmol), *p*-toluenesulfonyl chloride (345 mg, 1.81 mmol), and triethylamine (230.8 mg, 0. 318 mL, 1.51 mmol) were added in sequence. After 4.5 h, the suspension was diluted with Et_2O (30 mL) and stirred for 30 min. Then, the precipitate was removed by filtration. The organic phase was washed with a 10% $CuSO_4$ solution (2 × 100 mL), a 10% $NaHCO_3$ 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, 7:3) for characterization. Mixture of two diastereomers, IR (neat) ν_{max}: 2960, 2929, 2857, 1455, 1428, 1361, 1261, 1176, 1111, 1028, 814, 740, 702, 664 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$): δ 7.83 (4H, d, J = 7.9, ArH), 7.74 (8H, d, J = 7.9, ArH), 7.50−7.39, 7.39−7.27 (overall 26H, m's, ArH), 4.52 (2H, A part of an apparent AB system further coupled, dd, J = 11.5, 3.7, OCH_2Ph), 4.43 (2H, B part of an apparent AB system further coupled, bd, J = 11.5), 4.08 (4H, bd, J = 5.9), 3.56 (4H, m), 3.37 (2H, bs, 2 × H-20), 2.45 (6H, s, 2 × CH_3PhSO_3−), 1.90−1.10 (18H, overlapped m's), 1.13 (18H, s, 2 × $C(CH_3)_3$), 0.99 (6H, d, J = 6.7, 2 × H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 138.8, 135.7, 134.0, 133.3, 129.9, 129.6, 128.4, 127.9, 127.76, 127.70, 78.3, 77.5, 70.92, 70.90, 70.86, 70.82, 68.8, 36.00, 35.9, 31.1, 31.0, 29.7, 29.6, 28.7, 28.6, 27.0, 24.92, 24.88, 21.6, 19.4, 17.0; HRMS (ESI) m/z calcd for $C_{39}H_{50}NaO_5SSi$ $[M + Na]^+$ 681.3046; found 681.3037.

To a solution of tosylate **36** (946 mg, 1.43 mmol) in $CHCl_3$ (22.8 mL), methylamine (40% solution in water, 22.8 mL) was added. The mixture was vigorously stirred for 2 days at RT and then poured into a separatory funnel. The organic phase was separated, and the water phase was extracted using $CHCl_3$ (2 × 50 mL). The combined organic phases were dried and concentrated in vacuo. Purification using silica gel chromatography ($CHCl_3$/CH_3OH, 8:2) gave amine **13** (562 mg, 72% over two steps) as a colorless oil. Mixture of two diastereomers, IR (neat) ν_{max}: 2959, 2928, 2855, 1456, 1428, 1261, 1112, 800, 740, 702, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (8H, d, J = 7.8, ArH), 7.45−7.35 (12H, m, ArH), 7.33 (10H, m, ArH), 4.51 (2H, apparent dd, J = 11.5, 4.7, OCH_2Ph), 4.49 (2H, apparent dd, J = 11.5, 1.9, OCH_2Ph), 3.56−3.43 (4H, m, OCH_2TBDPS), 3.37 (2H, bs, 2 × H-20), 2.58 (4H, bs, 2 × H_2-24), 2.43 (6H, s, 2 × H_3-27), 1.71−1.08 (18H, overlapped m's), 1.07 (18H, s, 2 × $C(CH_3)_3$), 0.94 (6H, d, J = 6.5, 2 × H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 135.5, 134.0, 129.4, 128.2, 127.7, 127.5, 127.3, 79.0, 70.8, 70.7, 68.8, 52.1, 36.3, 35.9, 35.8, 31.45, 31.36, 31.1, 31.0, 28.7, 28.6, 26.8, 25.6, 25.5, 19.2, 16.8; HRMS (ESI) m/z calcd for $C_{33}H_{48}NO_2Si$ $[M + H]^+$ 518.3449; found 518.3434.

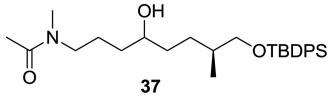
Amide 14.



14

To a stirred solution of amine **13** (526 mg, 1.02 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C, excess Et_3N (0.720 mL, 5.15 mmol) was added, followed by dropwise addition of acetyl chloride (160 mg, 0.15 mL, 2.04 mmol). After 30 min, the reaction mixture was diluted with CH_2Cl_2, and a few drops of water were added. The reaction mixture was washed with a saturated aqueous $NaHCO_3$ solution and brine. 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 ($CHCl_3$/CH_3OH, 95:5) for characterization. Mixture of two diastereomers, IR (neat) ν_{max}: 2955, 2925, 2858, 1632, 1465, 1455, 1261, 1112, 803, 739, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 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, OCH_2Ph), 3.57−3.43 (m), 3.42−3.32 (m), 3.23 (2H, t, J = 7.1, H_2-24), 2.93 (1.5 H, s, H_3-27), 2.89 (1.5 H, s, H_3-27), 2.06 (1.5 H, s, H_3-26), 2.05 (1.5 H, s, H_3-26), 1.74−0.98 (18H, overlapped multiplets), 1.07 (18H, s, 2 × $C(CH_3)_3$), 0.94 (6H, bd, J = 6.4, 2 × H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): 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, 31.0, 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 $C_{35}H_{49}NNaO_3Si$ $[M + Na]^+$ 582.3379; found 582.3369.

Alcohol 37.



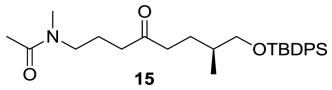
37

Amide **14** (511 mg, 0.91 mmol) and $Pd(OH)_2/C$ (274 mg 20% w/w) were suspended in EtOH (14 mL). The mixture was hydrogenated under atmospheric pressure for 2 days. Then, the reaction mixture was filtered over celite, and the filtrate was dried under reduced pressure to give alcohol **37** (371 mg, 87%) as a colorless oil. An analytically pure sample of this compound was obtained using chromatography over silica gel ($CHCl_3$/CH_3OH, 98:2) for characterization. Mixture of two diastereomers, IR (neat) ν_{max}: 3416, 2931, 2858, 1631, 1472, 1456, 1428, 1261, 1112, 824, 741, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 7.66 (8H, d, J = 6.9, ArH), 7.46−7.31 (12H, m, ArH), 3.59−3.39 (6H, m, 2 × H-20 and 2 × H_2-15), 3.25 (4H, bt, J = 7.6, 2 × H_2-24), 2.95 (1.5H, s, H_3-27), 2.89 (1.5H, s, H_3-27), 2.07 (1.5H, s, H_3-26), 2.04 (1.5H, s, H_3-26), 1.80−1.08 (18H, overlapped multiplets, 8 × CH_2 and 2 × CH), 1.05 (18H, s, 2 × $C(CH_3)_3$), 0.92 (3H, d, J = 6.4, H_3-16), 0.91 (3H, d, J = 6.4, H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.4, 135.5, 133.95, 133.90, 129.5, 129.4,

DOI: 10.1021/acsomega.7b00095
ACS Omega 2017, 2, 1477−1488

127.5, 71.7, 71.6, 71.5, 68.8, 68.7, 68.6, 50.8, 47.4, 36.0, 35.73, 35.68, 35.6, 35.0, 34.1, 33.9, 33.8, 33.1, 29.07, 29.02, 26.8, 24.55, 24.50, 23.46, 23.43, 21.8, 21.2, 19.2, 16.85, 16.79, 16.76; HRMS (ESI) m/z calcd for $C_{28}H_{44}NO_3Si$ $[M + H]^+$ 470.3085; found 470.3067.

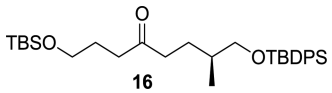
Ketone 15.



15

To a stirred solution of alcohol **37** (368 mg, 0.79 mmol) in CH_2Cl_2 (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 ($CHCl_3$/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. $[\alpha]_D^{20}$ = +2.7 (c = 1.0, $CHCl_3$); IR (neat) ν_{max}: 2958, 2924, 2854, 1715, 1651, 1462, 1367, 1261, 1111, 800, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 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, 2 × H_2-15), 3.34 (0.6 H, t, J = 7.1, H_2-24), 3.24 (0.4 H, t, J = 7.4, H_2-24), 2.96 (1.8 H, s, H_3-27), 2.90 (1.2 H, s, H_3-27), 2.48−2.28 (8H, m, H_2-22 and H_2-19), 2.08 (1.2 H, s, H_3-26), 2.05 (1.8 H, s, H_3-26), 1.86−1.20 (18H, overlapped multiplets, 8 × CH_2 and 2 × CH), 1.05 (18H, s, 2 × $C(CH_3)_3$), 0.90 (6H, bd, J = 6.5, 2 × H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.5, 209.7, 170.6, 170.4, 135.5, 133.8, 129.51, 129.48, 127.5, 68.43, 68.39, 49.8, 46.6, 40.5, 40.4, 39.5, 38.6, 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 $C_{28}H_{42}NO_3Si$ $[M + H]^+$ 468.2928; found 468.2913.

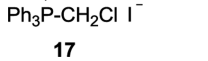
Ketone 16.



16

To a stirred solution of alcohol **12** (102.3 mg, 0.194 mmol) in CH_2Cl_2 (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 of stirring, 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 eluting with CH_2Cl_2/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. $[\alpha]_D^{20}$ = −1.8 (c = 1.0, $CHCl_3$); IR (neat) ν_{max}: 2957, 2930, 2858, 1717, 1472, 1464, 1428, 1389, 1257, 1112, 836, 777, 740, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (8H, d, J = 6.6, ArH), 7.47−7.36 (12H, m, ArH), 3.63 (4H, bt, J = 6.3), 3.51 (4H, m), 2.47 (2H, t, J = 7.3), 2.41 (2H, m), 1.08 (9H, s, $C(CH_3)_3$), 0.94 (3H, d, J = 6.7, H_3-17), 0.91 (9H, s, $C(CH_3)_3$), 0.06 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.0, 135.6, 133.8, 129.5, 127.6, 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 $C_{31}H_{51}O_3Si_2$ $[M + H]^+$ 527.3371; found 527.3379.

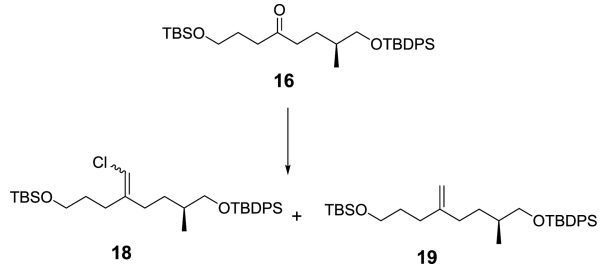
Phosphonium Salt 17.



17

(Chloromethyl)triphenylphosphonium iodide **17** was prepared through a modification of the reported procedure,[14a] starting from triphenylphosphine (31.44 g, 120 mmol) and chloroiodomethane (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.)[14a]]; ^1H NMR: (400 MHz, DMSO-d_6) δ 8.01−7.75 (15H, m, ArH), 6.08 (2H, d, J = 6.8); ^{13}C NMR (100 MHz, DMSO-d_6): 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).

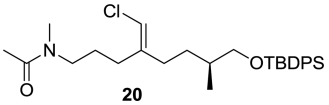
Wittig Reaction on Model Ketone 16 Using *n*BuLi as the Base.



To a stirred suspension of (chloromethyl)-triphenylphosphonium iodide **17** (338 mg, 0.772 mmol) in THF (10 mL), *n*BuLi (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 NH_4Cl 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)-triphenylphosphonium 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.[14a] 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 NH_4Cl solution (10 mL) and extracted using Et_2O (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, $CDCl_3$): 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 × OCH_2), 2.29−2.04 (m, H_2-19 and H_2-22), 1.71−1.51 (m), 1.06, 0.89 (both s, 2 × $C(CH_3)_3$), 0.041 (m, $(CH_3)_2Si$); HRMS (ESI) m/z calcd for 559.3189 $[M + H]^+$; found 559.3178.

Chlorovinyl Derivative 20.



20

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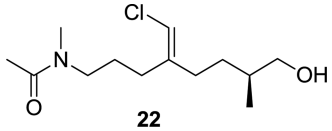
To a stirred suspension of (chloromethyl)-triphenylphosphonium iodide **17** (128 mg, 0.292 mmol) in THF (5 mL), *tert*-BuOK (0.281 mL, 0.7281 mmol, 1.0 M sol. in THF) was added dropwise at 0 °C under argon.[14a] The solution immediately became yellow. After 30 min at 0 °C, a solution of ketone **15** (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 NH_4Cl solution (10 mL) and extracted using Et_2O (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**. $[\alpha]_D^{20} = -1.6$ (c = 0.23, $CHCl_3$); IR (neat) ν_{max}: 2955, 2930, 2858, 1652, 1428, 1112, 824, 798, 741, 703 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$, 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, H_2-15), 3.37, 3.25 (1H each, both t, J = 7.6, H_2-24), 2.97 (1.5H, s, H_3-27), 2.90 (1.5H, s, H_3-27), 2.24−2.13 (2H, m), 2.13−1.95 (5H, overlapped signals including a singlet at 2.07 for H_3-26), 1.77−1.53 (4H, m), 1.34−1.13 (1H, m), 1.06 (9H, s, $C(CH_3)_3$), 0.91 (3H, d, J = 6.6, H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): 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, 33.1, 32.25, 32.22, 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 $C_{29}H_{42}ClNNaO_2Si$ $[M + Na]^+$ 522.2566; found 522.2541. Compound **21**. $[\alpha]_D^{20} = -1.4$ (c = 0.6, $CHCl_3$); IR (neat) ν_{max}: 2958, 2931, 2858, 1627, 1428, 1112, 823, 802, 742, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): mixture of rotamers, δ 7.66 (4H, d, J = 7.5, ArH), 7.45−7.34 (6H, m, ArH), 5.80 (1H, s, vinyl proton), 3.50 (2H, m, H_2-15), 3.32 (0.6 H, t, J = 7.7, H_2-24), 3.21 (0.4 H, t, J = 7.7, H_2-24), 2.94 (1.8 H, s, H_3-27), 2.89 (1.2 H, s, H_3-27), 2.21 (2H, m), 2.10−2.02 (5H, overlapped signals including a singlet at 2.06 for H_3-26), 1.77−1.56 (4H, m), 1.31−1.15 (1H, m), 1.05 (9H, s, $C(CH_3)_3$), 0.95 (3H, d, J = 6.6, H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 170.3, 142.05, 141.5, 135.6, 134.0, 133.9, 129.5, 127.6, 112.9, 112.3, 68.6, 68.5, 50.2, 47.2, 36.1, 35.7, 33.1, 32.0, 31.7, 30.3, 27.7, 27.5, 26.9, 26.2, 25.2, 21.9, 21.2, 19.3, 16.6; HRMS (ESI) m/z calcd for $C_{29}H_{42}ClNNaO_2Si$ $[M + Na]^+$ 522.2566; found 522.2562.

Photochemical Isomerization of 21 in 20. To a solution of **21** (10.5 mg, 0.021 mmol) in CH_2Cl_2 (7 mL), benzophenone (1.3 mg, 0.007 mmol) was added. The reaction mixture was irradiated with ultraviolet light ($\lambda \geq 300$ nm). After 16 h, the solvent was evaporated under reduced pressure. Separation using preparative TLC (hexane/EtOAc, 8:2) gave unreacted **21** (7.9 mg) and *Z*-isomer **20** (2.1 mg, 20%).

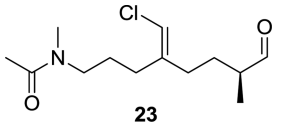
Alcohol 22.



22

To a solution of **20** (47.2 mg, 0.094 mmol) in THF (6.7 mL), TBAF (0.142 mL, 0.142 mmol, 1.0 M solution in THF) was added dropwise at 0 °C. The reaction mixture was allowed to reach RT and stirred for 1 h. Then, the reaction was quenched with a saturated aqueous solution of NH_4Cl (2 mL). The phases were separated, and the aqueous layer was extracted using EtOAc (3 × 20 mL). The combined organic phases were dried and evaporated in vacuo. Purification using column chromatography over silica gel ($CHCl_3/CH_3OH$, 99:1) gave alcohol **22** (21.4 mg, 87%) as a colorless oil. $[\alpha]_D^{20} = -63.4$ (c = 1.5, $CHCl_3$); IR (neat) ν_{max}: 3410, 2953, 2927, 2858, 1634, 1489, 1456, 1404, 1046, 795 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$, mixture of rotamers): δ 5.86 (0.4H, s, vinyl proton), 5.82 (0.6H, s, vinyl proton), 3.46 (2H, t, J = 5.3), 3.42−3.24 (2H, m's), 2.99 (1.8 H, s, H_3-27), 2.89 (1.2 H, s, H_3-27), 2.27−2.02 (7H, overlapped signals including two singlets at 2.09 and 2.07 for H_3-26), 1.78−1.52 (4H, m), 1.30−1.15 (1H, m), 0.93, 0.91 (overall 3H, overlapped doublets, both J = 6.0, H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.4, 142.0, 141.3, 113.2, 112.6, 67.8, 67.7, 50.5, 47.3, 36.1, 35.2, 33.2, 32.3, 32.2, 31.1, 31.0, 27.4, 27.3, 25.8, 24.6, 21.9, 21.2, 16.44, 16.38; HRMS (ESI) m/z calcd for $C_{13}H_{25}ClNO_2$ $[M + H]^+$ 262.1568; found 262.1564.

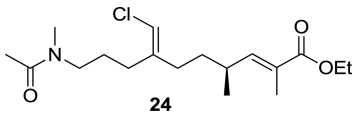
Aldehyde 23.



23

To a stirred solution of alcohol **22** (16.2 mg, 0.062 mmol) in CH_2Cl_2 (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 $CHCl_3$/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.

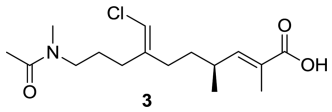


24

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 all 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 ($CHCl_3/CH_3OH$, 95:5) afforded ethyl ester **24** (16.3 mg, 76% over two steps) as a colorless oil. $[\alpha]_D^{20} = +127.4$ (c = 0.5, $CHCl_3$); IR (neat) ν_{max}: 2957, 2927, 2858, 1707, 1651, 1596, 1459, 1424, 1373, 1262, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 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, J = 7.0, O $\underline{CH_2}CH_3$), 3.37, 3.27 (1H each, both t, J = 7.6, H_2-24), 2.99 (1.5H, s, H_3-27), 2.91 (1.5H, s, H_3-27), 2.46 (1H, m, H-16), 2.18 (2H, m), 2.09 (1.5H, s, H_3-26), 2.08 (1.5H, s, H_3-26), 2.01 (2H, t, J = 8.6), 1.83 (1.5H, d, J = 1.2, H_3-14), 1.82 (1.5H, d, J = 1.2, H_3-14), 1.30 (3H, t, J = 7.0, $OCH_2\underline{CH_3}$), 1.02 (1.5H, d, J = 6.6, H_3-17), 1.00 (1.5H, d, J = 6.6, H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.3, 168.3, 168.2, 146.9, 146.6, 141.6, 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 $C_{18}H_{30}ClNNaO_3$ $[M + Na]^+$ 366.1812; found 366.1802.

DOI: 10.1021/acsomega.7b00095
ACS Omega 2017, 2, 1477−1488

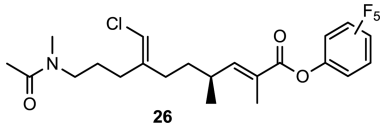
Carboxylic Acid 3.



3

To a stirred solution of ester **24** (6.3 mg, 0.018 mmol) in THF (0.075 mL) and CH_3OH (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. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ 6.63 (1H, d, J = 8.8, H-15), 6.60 (1H, d, J = 8.9, H-15), 5.83 (0.5H, s, vinyl proton), 5.78 (0.5H, s, vinyl proton), 3.37, 3.28 (1H each, both t, J = 7.4, H_2-24), 3.00 (1.5H, s, H_3-27), 2.92 (1.5H, s, H_3-27), 2.49 (1H, m, H-16), 2.19 (2H, m), 2.10 (1.5H, s, H_3-26), 2.09 (1.5H, s, H_3-26), 2.02 (2H, m), 1.84 (3H, s, H_3-14), 1.03 (1.5H, d, J = 6.7, H_3-17), 1.01 (1.5H, d, J = 6.7, H_3-17); HRMS (ESI) m/z calcd for $C_{16}H_{26}ClNNaO_3$ $[M + Na]^+$ 338.1499; found 338.1510.

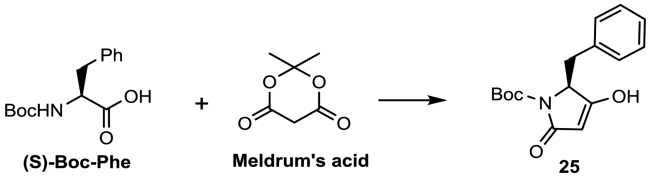
Pentafluorophenyl Ester 26.



26

To 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 ($CHCl_3$/CH_3OH, 95:5) gave pentafluorophenyl ester **26** (5.5 mg, 82%) as a colorless oil. IR (neat) ν_{max}: 2962, 2917, 2949, 1683, 1626, 1521, 1261, 1096, 1022, 801, 760 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$, mixture of rotamers): δ 6.85 (1H, d, J = 10.1, H-15), 5.86 (0.5H, s, vinyl proton), 5.80 (0.5H, s, vinyl proton), 3.39, 3.29 (1H each, both t, J = 7.7, H_2-24), 3.00 (1.5H, s, H_3-27), 2.92 (1.5H, s, H_3-27), 2.58 (1H, m, H-16), 2.20 (2H, m), 2.09 (1.5H, s, H_3-26), 2.08 (1.5H, s, H_3-26), 2.07 (2H, t, J = 8.5), 1.97 (1.5H, d, J = 1.2, H_3-14), 1.96 (1.5H, d, J = 1.2, H_3-14), 1.10 (1.5H, d, J = 6.8, H_3-17), 1.08 (1.5H, d, J = 6.8, H_3-17); ^{13}C NMR (100 MHz, $CDCl_3$): 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 calcd for $C_{22}H_{26}ClF_5NO_3$ $[M + H]^+$ 482.1516; found 482.1499.

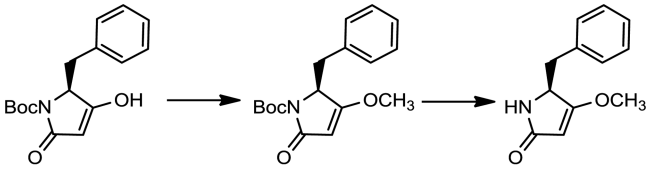
Pyrrolinone 25.



(S)-Boc-Phe Meldrum's acid 25

To a stirred solution of Meldrum's acid (1.60 g, 11.1 mmol) and DMAP (1.57 g, 12.9 mmol) in CH_2Cl_2 (60 mL), Boc-(L)-Phe-OH (2.44 g, 9.21 mmol) was added followed by EDC·HCl (1.76 g, 11.1 mmol) at 0 °C. The yellow mixture was stirred overnight at RT, then poured into EtOAc (200 mL), and sequentially washed with brine (2 × 100 mL), 5% citric acid solution (3 × 300 mL), and again brine (1 × 300 mL). The organic phase was refluxed for 1 h and evaporated under reduced pressure to give compound **25** (2.69 g) that was applied to the next step without further purification.

Pyrrolinone 4.

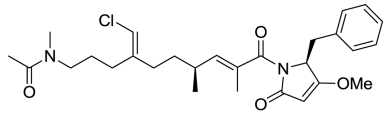


25 38 4

To a stirred solution of pyrrolinone **25** (1.0 g, 3.46 mmol) and triphenylphospine (1.36 g, 5.19 mmol) in CH_2Cl_2 (20 mL), CH_3OH (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 pyrrolinone **38** (621 mg, 57% over three steps) as a colorless oil. $[\alpha]_D^{20}$ = +203.3 (c = 1.0, CH_3OH); IR (neat) ν_{max}: 2980, 2940, 1779, 1733, 1705, 1634, 1456, 1319, 1246, 1152, 1094, 1073, 981, 848, 808, 757, 701, 667 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$): 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, OCH_3), 3.31 (1H, dd, J = 13.8, 5.1, H_a-7), 2.98 (1H, dd, J = 13.8, 3.0, H_b-7), 1.48 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{17}H_{22}NO_4$ $[M + H]^+$ 304.1543; found 304.1532.

To a stirred solution of **38** (212 mg, 0.66 mmol) in CH_2Cl_2 (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 pyrrolinone **4** (144 mg, quant.) as a white waxy solid. mp 84−85 (EtOAc/hexane) [lit. 103−104[22]]; $[\alpha]_D^{20}$ = −62.3 (c = 1.0, $CHCl_3$) [lit. −63.0 (c = 1.0, $CHCl_3$)[22]]; IR (neat) ν_{max}: 3238, 3030, 2939, 2848, 1683, 1623, 1497, 1455, 1365, 1344, 1232, 989, 806, 700 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$): 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, OCH_3), 3.17 (1H, dd, J = 13.7, 3.4, H_a-7), 2.78 (1H, dd, J = 13.7, 7.6, H_b-7); ^{13}C NMR (100 MHz, $CDCl_3$) 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 calcd for $C_{12}H_{14}NO_2$ $[M + H]^+$ 204.1019; found 204.1011.

16-*epi*-Smenamide 27.



16-*epi*-smenamide A **27**

To a stirred solution of pyrrolinone **4** (9.9 mg, 0.049 mmol) in THF (0.1 mL), *n*BuLi (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 NH_4Cl 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: H_2O; eluent B: CH_3CN; gradient:

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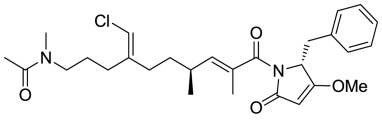
50 → 100% B, over 35 min, flow rate 1 mL min^{-1}] to give 16-*epi*-smenamide A (t_R = 17.5 min, 1.3 mg, 84%) as a colorless oil. $[\alpha]_D^{20}$ = 86.9 (*c* = 0.1, $CHCl_3$); IR (neat) ν_{max}: 2958, 2928, 2857, 1731, 1631, 1455, 1308, 1245, 1197, 1024, 965, 807, 753, 708 cm^{-1}; 1H NMR: (400 MHz, CD_3OD, mixture of rotamers): δ 7.26−7.20 (3H, m, H-3, H-4, H-5), 6.99 (2H, m, H-2, H-6), 6.00 (0.5H, s, H-21), 5.97 (0.5H, s, H-21), 5.41 (1H, bdd, *J* = 10.0, 1.5, H-15), 5.40 (1H, bdd, *J* = 10.0, 1.5, H-15), 5.03 (0.5H, s, H-10), 5.02 (0.5H, s, H-10), 5.00 (1H, m, H-8), 3.96 (3H, s, OCH_3), 3.46−3.33 (3H, overlapped multiplets), 3.19 (1H, dd, *J* = 14.0, 2.4), 3.03 (1.5H, s, H_3-27), 2.89 (1.5H, s, H_3-27), 2.44 (1H, m), 2.32−2.13 (3H, overlapped multiplets), 2.13−2.02 (4H, overlapped signals including a singlet at 2.07 for H_3-26), 1.81−1.60 (5H, overlapped signals including two doublets for H_3-14 at 1.714 and 1.708, both *J* = 1.3), 1.60−1.50 (1H, m), 1.39−1.27 (1H, m), 0.99 (1.5H, d, *J* = 7.1, H_3-17), 0.98 (1.5H, d, *J* = 7.1, H_3-17); ^{13}C NMR (126 MHz, CD_3OD) δ 180.0, 143.2, 143.0, 142.6, 142.2, 135.6, 133.2, 130.9, 129.2, 128.2, 114.2, 114.0, 95.4, 60.6, 59.5, 51.5, 36.6, 36.2, 36.1, 34.7, 33.6, 33.4, 33.22, 33.17, 28.2, 28.0, 26.6, 25.7, 21.7, 21.1, 20.3, 20.2, 14.3, 14.2; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{38}ClN_2O_4$ $[M + H]^+$ 501.2515; found 501.2493.

***ent*-Smenamide 29.**



ent-smenamide A **29**

To a stirred solution of pyrrolinone **28** (9.9 mg, 0.049 mmol) in THF (0.1 mL), *n*BuLi (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 NH_4Cl 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: H_2O; eluent B: CH_3CN; gradient: 50 → 100% B, over 35 min, flow rate 1 mL min^{-1}] to give *ent*-smenamide A **29** (t_R = 18.5 min, 1.4 mg, 88%) as a colorless oil. $[\alpha]_D^{20}$ = −9.8 (*c* = 0.1, $CHCl_3$); IR (neat) ν_{max}: 2958, 2923, 2853, 1729, 1631, 1455, 1306, 1205, 1132, 1026, 802 cm^{-1}; 1H- and ^{13}C NMR (see Table S1). HRMS (ESI) *m*/*z* calcd for $C_{28}H_{38}ClN_2O_4$ $[M + H]^+$ 501.2515; found 501.2495.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00095.

Experimental details, characterization data, experimental details of Marfey's method, NMR data and CD spectra of *ent*-smenamide A and natural smenamide A, and copies of NMR data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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