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Enantioselective synthesis of preclavulone A and its methyl ester

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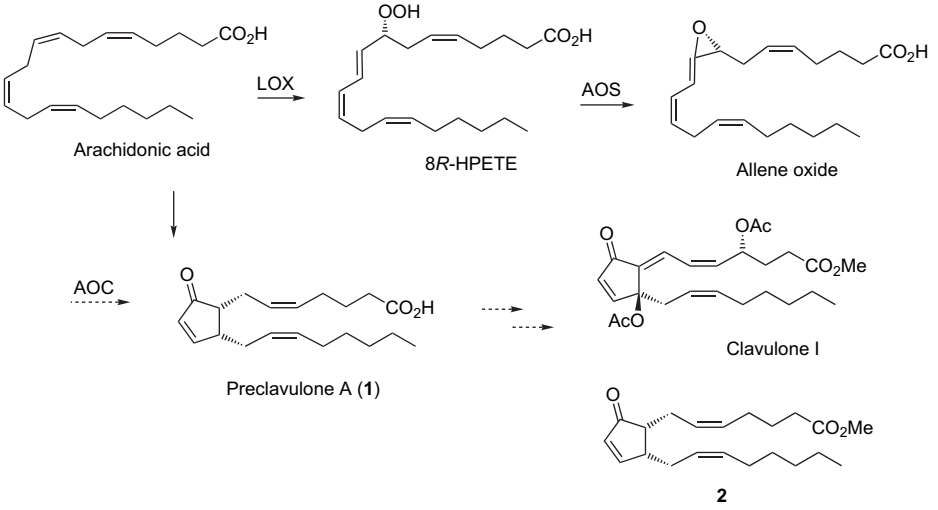
Abstract—A highly enantioselective synthesis of the (8*S*,12*S*)-enantiomer of preclavulone A and its methyl ester is described featuring the Julia protocol for installing the (*Z*)-double bond in the lower chain. This procedure is suitable for the preparation of labeled preclavulone analogues for biosynthetic studies on marine clavulones.

1. Introduction

Marine prostaglandins and related eicosanoids such as clavulones and halogenated clavulones have been found in different species of marine invertebrates and red algae.[1] They have attracted much attention because of their unique structural features, potent biological activities, including strong antitumor and antiviral properties, and intriguing biosynthesis.[1,2] In fact, although it has been proved that arachidonic acid (AA) is converted to marine prostaglandins via the conventional cyclooxygenase route,[3] the biogenetic pathway from AA to clavulones is still under debate.[4] In Corey's proposed pathway to clavulone I, preclavulone A (**1**) is a key intermediate, arising from lipoxygenase mediated oxidation of AA to a dienyl hydroperoxide, followed by enzymatic cyclization of a derived allene oxide (Scheme 1).[5]

In experiments done with a cell-free extract of the Okinawan octocoral *Clavularia viridis*, preclavulone A was, indeed, obtained from labeled AA as well as from labeled (8*R*)-HPETE, however, its enantiomeric purity and absolute configuration could not be determined due to the poor amounts isolated.[6] These stereochemical data are of paramount importance to support the hypothesis of an enzymatically stereocontrolled biogenesis of **1**. In fact, there is increasing evidence that various prostanoid-like compounds are formed also in a non-stereocontrolled fashion by non-enzymatic free radical oxidation of unsaturated fatty acids in membrane



Scheme 1. Corey's suggested biosynthesis of clavulones (LOX, lipoxygenase; AOX, allene oxide synthase; AOC, allene oxide cyclase).

Keywords: Preclavulone A; Marine clavulones; Enantioselective synthesis; Julia olefination.
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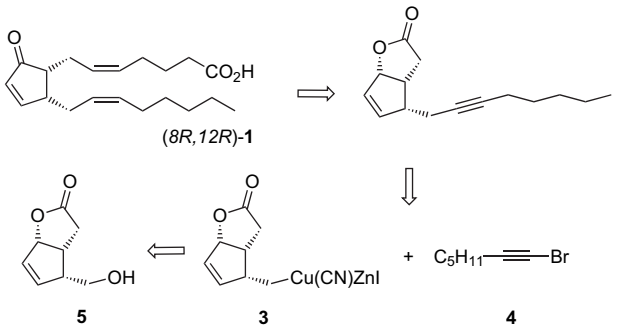
lipids, apparently in all mammalian cell types and tissues in vivo.[7] In this regard, the recent isolation by Iguchi of nearly racemic (8%, ee) methyl ester of preclavulone A (**2**) along with its 8-epimer from a methanol extract of *C. viridis*,[8] reinforces uncertainties on the stereospecific biogenesis of compound **1**.

The major enantiomer (8*R*,12*R*)-**2** of the natural mixture isolated by Iguchi was first synthesized by Corey and Xiang,[9a] and very recently by the Iguchi's group along with its (8*S*,12*R*)-diastereomer.[9b] A synthesis of racemic **2** was reported by Traverso et al. years ago,[9c] and later by Iguchi.[9d]

We have recently published the first truly enantioselective route to (8*R*,12*R*)-preclavulone A (**1**) reporting, for the first time, its fully spectroscopic characterization, including the optical rotation.[10,11] In this approach, the upper chain was positioned following the usual Wittig strategy used in many prostaglandin syntheses, while installation of the lower side chain was achieved via Knochel coupling of 1-bromoheptyne **4** with the copper/zinc reagent **3** derived from enantiomerically enriched alcohol **5** (Scheme 2).



Scheme 2. Retrosynthesis of preclavulone A (**1**) based on Knochel's organozinc chemistry.[10]

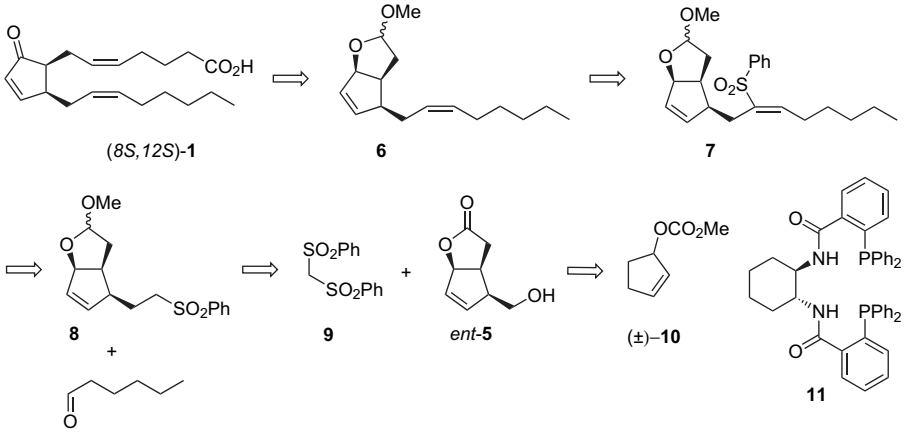
In continuing our efforts in this field, we anticipated possible difficulties in extending this methodology to the synthesis of oxidized derivatives of **1**, e.g., clavulone I. In addition, in order to facilitate biosynthetic studies of preclavulones, we were interested in finding a synthetic route easily extendable to the preparation of labeled derivatives.

In this paper, we describe the first synthesis of the (8*S*,12*S*)-enantiomer of preclavulone A (**1**) and the corresponding methyl ester (8*S*,12*S*)-**2**,[12] whose (*Z*)-olefin in the lower chain was installed via the corresponding vinylsulfone (Scheme 3) using the Julia protocol.[13] This concise procedure appears, indeed, to be well suitable for the preparation of more oxidized derivatives and also of labeled preclavulone analogues since the sulfonyl group can easily be replaced with deuterium in regio- and stereospecific fashions.[14]

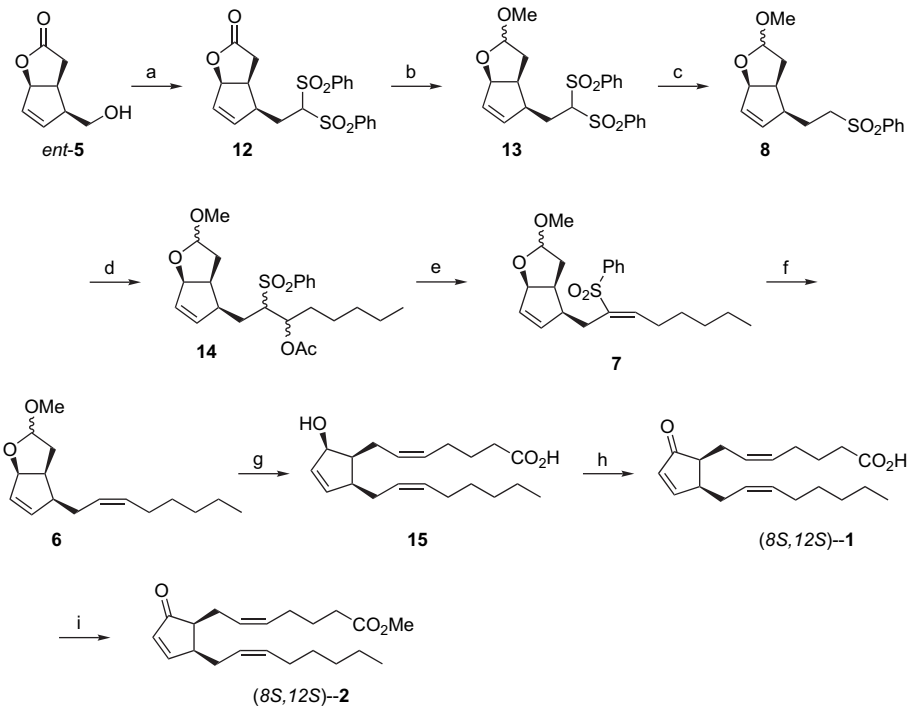
2. Results and discussion

Our vinylsulfone based retrosynthetic analysis of preclavulone A **1** is depicted in Scheme 3. The alkylsulfone **8**, required for coupling with hexanal, was envisaged to arise from monodesulfonylation of the bis-sulfone produced from the Mitsunobu condensation of hydroxy-lactone *ent*-**5** with bis(phenylsulfonyl)methane **9**.[15] The starting compound *ent*-**5**, $[\alpha]_D^{20}$ −4.61 (*c* 0.8, CH_2Cl_2), 98% ee (chiral GC),[16] was obtained in 11 steps from racemic cyclopentenyl carbonate **10** following the same route previously described for **5**,[10] enantiodivergence being achieved by using the (*R*,*R*)-antipode of the Trost ligand **11** in the asymmetric step.[17]

Alkylation of *ent*-**5** with bis-sulfone **9** in the presence of DEAD and Ph_3P[18] afforded geminal bis-sulfonyl-lactone **12** in 87% isolated yield (Scheme 4). DIBAL-H reduction and in situ protection of the obtained lactol readily gave the corresponding methyl acetal **13** (MeOH, HCl, −35 °C) in 93% isolated yield. Subsequent selective monodesulfonylation of compound **13** proceeded very rapidly at room temperature with SmI_2 (4 equiv) in THF,[15] delivering sulfone **8** in 87% yield. A highly stereoselective fourstep procedure developed by Julia and collaborators[13,14] allowed coupling of **8** with hexanal and subsequent stereoconvergent conversion of intermediate stereoisomers **14** to the required *Z*-olefin **6**. Thus, the lithio derivative of phenyl sulfone **8** gave an adduct with hexanal, which was acetylated in situ to afford a mixture of diastereomeric β-acetoxysulfones **14** in a gratifying 90% isolated yield. Compounds **14** underwent β-elimination readily on exposure to powdered NaOH in dioxane at rt delivering vinylsulfone **7** as a single stereoisomer (^{1}H NMR analysis). In the last step of the Julia sequence, the



Scheme 3. Retrosynthetic analysis of preclavulone A based on Julia vinylsulfone chemistry.



Scheme 4. Reagents and conditions: (a) $(PhSO_2)_2CH_2$, Ph_3P, DEAD, PhH, rt, 1.5 h, 87%; (b) (i) DIBAL-H, THF, −78 °C, 1.5 h; (ii) MeOH, HCl (37% solution, 0.05 equiv), −35 °C, 15 h, 93%; (c) SmI_2 (1 M THF solution), THF, rt, 15 min, 87%; (d) (i) *n*-BuLi, THF, −78 to −40 °C, 1 h, followed by addition of hexanal (THF solution), −40 °C, 30 min; (ii) Ac_2O, rt, 30 min, 90%; (e) NaOH, 1,4-dioxane, rt, 1 h, 90%; (f) $Na_2S_2O_4$ (15 equiv), $NaHCO_3$ (30 equiv), H_2O/EtOH (1:1), reflux, 2 h, 76%; (g) (i) 0.25 M HCl, THF/H_2O (1:1), rt, 5 h, 96%; (ii) $BrPh_3P(CH_2)_4CO_2H$, *t*-BuOK, THF, rt, 30 min, 96%; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h, 96%; (i) CH_2N_2, Et_2O, 0 °C, 97%.

stereospecific desulfonylation of compound **7** smoothly proceeded on exposure to $Na_2S_2O_4$ and $NaHCO_3$ in a mixture of H_2O/EtOH (1:1), affording olefin *Z*-**6** in 76% isolated yield.[19]

With the stereodefined olefin **6** in hand, the upper side chain of preclavulone A was then installed via standard Wittig methodology. Thus, olefination of the carbonyl function released from acetal **6** with the non-stabilized phosphorane derived from $BrPh_3P(CH_2)_4CO_2H$, smoothly gave the corresponding *Z*-olefin **15** in 96% isolated yield.[19] With the two side chains positioned with the required cis-stereochemistry, completion of the synthesis of preclavulone A **1** required the mild oxidation of the sensitive cyclopentenol **15** to the corresponding stereochemically labile cyclopentenone. In the event, oxidation of **15** with the Dess–Martin periodinane reagent in dichloromethane[20] produced the (8*S*,12*S*)-enantiomer of preclavulone A (**1**) in 96% isolated yield as a colorless oil, $[\alpha]_D^{20}$ +126 (*c* 0.2, CH_2Cl_2) [lit.[10] −125.6 (*c* 0.18, CH_2Cl_2) for (8*R*,12*R*)-**1**]. The corresponding methyl ester (8*S*,12*S*)-**2** was readily obtained in quantitative yield by exposing (8*S*,12*S*)-**1** to diazomethane in Et_2O. The spectroscopic data of the ester nicely corresponded with those reported by Ito and Iguchi for (8*R*,12*R*)-**2**,[9b] except the opposite sign was observed for the optical rotation, $[\alpha]_D^{20}$ +136.4 (*c* 0.17, THF) compared to $[\alpha]_D^{20}$ −135.3 (*c* 0.13, THF), respectively.[9b]

3. Conclusion

In conclusion, the first asymmetric synthesis of the (8*S*,12*S*)-enantiomer of preclavulone A (**1**) and its methyl ester (8*R*,12*R*)-**2** has been achieved. It features a convergent sequence of highly stereoselective transformations from the key chiral building block *ent*-**5**, which is available in multigram amount using an enantioselective organometallic approach.[10] The same strategy opens the way to the preparation of more oxidized preclavulone derivatives containing the two *Z*-olefin structural moieties.[1] In addition, labeled preclavulone analogues for the elucidation of the biosynthetic pathway of clavulones might be obtained according to a known procedure, labeling being introduced during the construction of the lower-chain olefin with the Julia protocol.[14]

4. Experimental

4.1. General

Tetrahydrofuran was distilled over sodium/benzophenone and methylene chloride was distilled over calcium hydride. Commercially available reagents were used as supplied without further purification. All reactions were performed under a slight positive static pressure of argon in glassware that had been dried in an oven at 140 °C for at least 3 h prior to use and allowed to cool in a desiccator over self-indicating silica gel pellets. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P_2O_5 before use. Routine monitoring of reactions was performed using GF-254 Merck (0.25 mm), aluminum-supported SiO_2 TLC plates. Compounds were visualized by UV irradiation at a wavelength of 254 nm or stained by exposure to a 0.5% solution of vanillin in H_2SO_4/EtOH followed by charring. Flash column chromatography was

performed using Kieselgel 60 Merck (40–63 μm). Yields are reported for chromatographically and spectroscopically pure isolated compounds. Melting points were determined on a Fisher-Johns hot plate and are uncorrected. $[\alpha]_D$ values are given in (deg mL)/(g dm); *c* is in g/100 mL and the path length *l* is in decimeters. NMR chemical shifts are reported in δ units relative to residual $CHCl_3$ [δ_H 7.26, δ_C (central line of t) 77.0]; the abbreviations s=singlet, d=doublet, t=triplet, q=quartet, qu=quintuplet, m=multiplet, and br=broad are used throughout. Coupling constants (*J*) are given in Hz. The multiplicity of each carbon atom was determined by DEPT experiments. Infrared absorption spectra were recorded in the range of 4000–600 cm^{-1}.

4.1.1. (3a*S*,4*S*,6a*R*)-4-(2,2-Bis(phenylsulfonyl)ethyl)-3a,4-dihydro-3*H*-cyclopenta[*b*]furan-2(6aH)-one (12). Triphenylphosphine (511 mg, 1.95 mmol, 1.5 equiv), bis-(phenylsulfonyl)methane (385 mg, 1.3 mmol, 1 equiv), and alcohol *ent*-**5** (200 mg, 1.3 mmol), obtained from racemic **10** following the same route previously described for **5**,[10] were dissolved in dry benzene (15 mL) under an argon atmosphere. DEAD (0.307 mL, 1.95 mmol, 3 equiv) was added and the resulting mixture was stirred for 1.5 h, and concentrated in vacuo to give a residue, which was purified by flash chromatography on silica gel. Elution with CH_2Cl_2/EtOAc (95:5) gave compound **12** (507 mg, 87%) as a white solid. Mp 176–178 °C; R_f=0.28 (CH_2Cl_2/EtOAc, 95:5); $[\alpha]_D^{20}$ −26.8 (*c* 0.5, CH_2Cl_2). IR (Nujol) ν cm^{-1}: 2881, 1775, 1449, 1172, 1327, 1151, 1137, 1076. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.5–8.0 (10H, m, Ph), 5.78 (1H, dt, *J*=6.0, 1.0 Hz), 5.72 (1H, br d, *J*=6.0 Hz), 5.38 (1H, br d, *J*=7.0 Hz), 4.32 (1H, t, *J*=6.0 Hz), 3.32–3.40 (1H, m), 3.16–3.27 (1H, ddd, *J*=14.2, 9.3, 6.7 Hz), 2.31 (1H, dd, *J*=17.5, 9.7 Hz), 2.17–2.22 (2H, m), 2.10–2.22 (1H, dd, *J*=7.0, 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.8 s, 137.3 s, 137.1 s, 136.8 d, 134.9 d, 129.8 d, 129. 5 d, 129.2 d, 128.2 d, 88.1 d, 82.0 d, 44.1 d, 39.8 d, 28.8 t, 26.9 t. CIMS: *m*/*z* (%): 450 $(M+NH_4)^+$, 310 (10), 293 (20), 278 (10), 180 (20), 117 (10). Anal. Calcd for $C_{21}H_{20}O_6S_2$: C, 58.32; H, 4.66. Found: C, 58.22; H, 4.72.

4.1.2. (3a*S*,4*S*,6a*R*)-4-(2,2-Bis(phenylsulfonyl)ethyl)-3,3a,4,6a-tetrahydro-2-methoxy-2*H*-cyclopenta[*b*]furan (13). DIBAL-H (0.324 mL, 1 M in hexane, 2 equiv) was added to a solution of lactone **12** (70 mg, 0.16 mmol) in dry THF (5 mL) cooled to −78 °C under an argon atmosphere. After 1.5 h MeOH (1 mL) was added and the resulting mixture was concentrated under reduced pressure. The residue was then dissolved in MeOH (10 mL) and 37% HCl was added to obtain a clear solution. The resulting mixture was stirred at −35 °C for 15 h. An excess of $NaHCO_3$ was added to quench the residual acid, and the resulting mixture was filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and H_2O (30 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with CH_2Cl_2/Et_2O (95:5) gave the desired acetal **13** (65 mg, 93%) as a white solid. Mp 54–55 °C; R_f=0.22 (CH_2Cl_2/Et_2O, 95:5). IR (Nujol) ν cm^{-1}: 3063, 2907, 2830, 1584, 1152, 1078, 1035. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.54–8.00 (10H, m, Ph), 5.75 (1H, br d, *J*=6.0 Hz), 5.49 (1H, d, *J*=6.0 Hz), 5.10 (1H, d, *J*=8.0 Hz), 4.93 (1H, d, *J*=4.3 Hz), 4.43 (1H, t, *J*=6.0 Hz), 3.32 (s, 3H), 3.23–3.29 (m, 1H), 3.11 (1H, ddd, *J*=15.0, 12.0, 8.0 Hz), 2.25 (2H, t, *J*=6.0 Hz), 1.76 (1H, dd, *J*=13.0, 8.0 Hz), 1.51–1.56 (1H, dt, *J*=13.0, 4.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.6 s, 137.3 s, 134.6 d, 134.5 d, 133.6 d, 133.2 d, 133.0 d, 131.8 d, 129.7 d, 129.6 d, 129.4 d, 129.0 d, 128.9 d, 105.3 d, 88.1 d, 82.3 d, 54.3 q, 43.1 d, 41.2 d, 33.3 t, 26.3 t. HREIMS calcd for $C_{22}H_{24}O_6S_2$: 448.1014 $(M)^+$, found: 448.1018. Anal. Calcd for $C_{22}H_{24}O_6S_2$: C, 58.91; H, 5.39. Found: C, 59.06; H, 5.26.

4.1.3. (3a*S*,4*S*,6a*R*)-3,3a,4,6a-Tetrahydro-2-methoxy-4-(2-(phenylsulfonyl)ethyl)-2*H*-cyclopenta[*b*]furan (8). A solution of compound **13** (70 mg, 0.156 mmol) in dry THF (3 mL) was added to a 1 M solution of SmI_2 in THF (6.24 mL, 0.62 mmol, 4.0 equiv). The instantaneous reaction was followed by the addition of EtOAc (10 mL) and a saturated solution of $Na_2S_2O_3$ (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with CH_2Cl_2/Et_2O (98:2) gave the desired sulfone **8** (42 mg, 87%) as a colorless oil. R_f=0.31 (CH_2Cl_2/Et_2O, 98:2). IR (liquid film) ν cm^{-1}: 3090, 2984, 2948, 2906, 1446, 1152. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.50–7.95 (5H, m, Ph), 5.74 (1H, br d, *J*=6.0 Hz), 5.53 (1H, d, *J*=6.0 Hz), 5.06 (1H, d, *J*=7.0 Hz), 4.90 (1H, d, *J*=5.0 Hz), 327 (3H, s), 2.95–3.20 (3H, m), 2.74 (1H, br q, *J*=7.0 Hz), 1.88 (1H, m), 1.72 (1H, dd, *J*=12.0, 8.0 Hz), 1.52 (1H, dt, *J*=12.0, 5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.9 s, 133.9 d, 133.7 d, 133.5 d, 133.2 d, 133.1 d, 129.6 d, 129.1 d, 105.3 d, 87.9 d, 55.1 d, 54.2 q, 44.1 d, 41.2 d, 33.1 t, 23.3 t. HREIMS calcd for $C_{16}H_{20}O_4S$: 308.1082 $(M)^+$, found: 308.1094. Anal. Calcd for $C_{16}H_{20}O_4S$: C, 62.31; H, 6.54. Found: C, 62.46; H, 6.46.

4.1.4. 1-((3a*S*,4*S*,6a*R*)-3,3a,4,6a-Tetrahydro-2-methoxy-2*H*-cyclopenta[*b*]furan-4-yl)-2-(phenylsulfonyl)octan-3-yl acetate (14). *n*-BuLi (2.3 M in hexane, 0.271 mL, 1.2 equiv) was added to a solution of compound **8** (160 mg, 0.52 mmol) in dry THF (4 mL) at −78 °C. After stirring at −78 °C for 30 min, the reaction mixture was allowed to warm to −40 °C, while a yellow color developed. Hexanal (0.075 mL, 0.62 mmol, 1.2 equiv) in dry THF (2 mL) was added via cannula, followed, after 30 min, by excess Ac_2O (0.088 mL, 0.93 mmol, 1.8 equiv) and a catalytic amount of DMAP (4 mg). The resulting mixture was warmed to rt and stirred for 30 min, followed by the addition of a saturated solution of NH_4Cl (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (8:2) gave the desired diastereomeric mixture **14** (218 mg, 90%) as a colorless oil, which was immediately submitted to the elimination step. R_f=0.22 (hexane/AcOEt, 9:1). IR (liquid film) ν cm^{-1}: 2954, 2926, 1741, 1231, 1148, 1036. CIMS: *m*/*z* (%): 468 $(M+NH_4)^+$.

4.1.5. (3a*S*,4*S*,6a*R*)-3,3a,4,6a-Tetrahydro-2-methoxy-4-((*E*)-2-(phenylsulfonyl)oct-2-enyl)-2*H*-cyclopenta[*b*]-furan (7). NaOH (35 mg, 0.88 mmol, 2 equiv) was added to a solution of compound **14** (200 mg, 0.44 mmol) in 1,4-dioxane (2 mL). The resulting mixture was stirred for 1 h followed by addition of Et_2O (20 mL) and H_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (8:2) gave the desired vinylsulfone **7** (155 mg, 90%) as a pale yellow oil. R_f=0.34 (hexane/EtOAc 8:2). IR (liquid film) ν cm^{-1}: 3060, 2954, 2927, 1638, 1446, 1303, 1149, 1036. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.82 (5H, m, Ph), 6.93 (1H, t, J=7.3 Hz), 5.64 (1H, d, J=6.0 Hz), 5.47 (1H, d, J=6.0 Hz), 5.00 (1H, br d, J=6.0 Hz), 4.87 (1H, d, J=4.0 Hz), 3.24 (3H, s), 2.92–3.05 (2H, m), 2.05–2.30 (4H, m), 1.71–1.87 (1H, m), 1.50–1.60 (1H, m), 1.19–1.25 (6H, m), 0.82 (3H, t, J=6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.3 s, 143.7 s, 139.6 s, 134.3 d, 133.1 d, 132.9 d, 131.5 d, 130.9 d, 129.0 d, 127.9 d, 105.4 d, 88.0 d, 54.2 q, 44.1 d, 42.2 d, 33.9 t, 28.6 t, 28.5 t, 27.9 t, 22.2 t, 13.8 q. CIMS: m/z (%): 408 $(M+NH_4)^+$, 333 (30), 313 (50), 296 (100), 268 (30), 240 (15), 153 (10). Anal. Calcd for $C_{22}H_{30}O_4S$: C, 67.66; H, 7.74. Found: C, 67.51; H, 7.85.

4.1.6. (3a*S*,4*S*,6a*R*)-3,3a,4,6a-Tetrahydro-2-methoxy-4-((*Z*)-oct-2-enyl)-2*H*-cyclopenta[*b*]furan (6). $Na_2S_2O_4$ (534 mg, 3.07 mmol) and $NaHCO_3$ (517 mg, 6.15 mmol) were added to a solution of sulfone **7** (80 mg, 0.20 mmol) in H_2O/EtOH 1:1 (5 mL) and the resulting mixture was heated under reflux for 2 h. EtOH was removed under reduced pressure and the aqueous residue was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (9:1) gave the desired olefin **6** (38 mg, 76%) as a colorless oil. R_f=0.31 (hexane/EtOAc, 9:1). IR (liquid film) ν cm^{-1}: 2954, 2925, 2855, 1446, 1199, 1038. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.75 (1H, ddd, J=5.5, 2.5, 2.0 Hz), 5.67 (1H, dt, J=5.5, 1.5 Hz), 5.35–5.47 (2H, m), 5.11 (1H, dq, J=7.0, 1.5 Hz), 4.97 (1H, d, J=4.5 Hz), 3.32 (3H, s), 3.10 (1H, ddd, J=15.2, 10.4, 7.3 Hz), 2.72–2.83 (1H, m), 1.86 (1H, dd, J=12.0, 8.0 Hz), 1.70 (4H, m), 1.70 (1H, ddd, J=12.2, 10.4, 4.5 Hz), 1.20–1.42 (6H, m), 0.88 (3H, t, J=6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.9 d, 131.0 d, 130.9 d, 127.4 d, 105.5 d, 88.3 d, 54.2 q, 45.8 d, 41.6 d, 33.6 t, 31.3 t, 29.5 t, 29.1 t, 28.2 t, 22.4 t, 13.9 q. CIMS: m/z (%): 268 $(M+NH_4)^+$, 253 (60), 236 (100), 219 (40). Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.88; H, 10.53.

4.1.7. (5*Z*)-7-((1*S*,2*R*,5*S*)-2-Hydroxy-5-((*Z*)-oct-2-enyl)-cyclopent-3-enyl)hept-5-enoic acid (15). Acetal **6** (30 mg, 0.12 mmol) was dissolved in THF/H_2O 1:1 (5 mL) and 0.25 N HCl (50 μL) was added. The resulting mixture was stirred for 5 h followed by addition of excess $NaHCO_3$ to quench the residual acidity. THF was removed under reduced pressure and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield the corresponding lactol intermediate (28 mg, 96%) as a colorless oil. R_f=0.23 (hexane/EtOAc, 8:2). IR (liquid film) ν cm^{-1}: 3405, 2995, 2924, 2855, 1459, 1031. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.70–5.80 (1H, m), 5.68 (1H, d, J=6.0 Hz), 5.51 (1H, d, J=3.0 Hz), 5.35–5.45 (2H, m), 5.24 (1H, d, J=7.3 Hz), 3.15–3.30 (1H, m), 2.75–2.90 (2H, m), 1.62–2.21 (5H, m), 1.20–1.44 (6H, m), 0.89 (3H, t, J=6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.9 d, 131.1 d, 130.9 d, 127.5 d, 99.0 d, 88.6 d, 45.0 d, 41.3 d, 34.3 t, 30.2 t, 29.1 t, 28.2 t, 27.3 t, 22.4 t, 13.9 q. *t*-BuOK (284.8 mg, 2.38 mmol, 8 equiv) was added to a stirred suspension of the phosphonium salt $BrPh_3P(CH_2)_4CO_2H$ (531 mg, 1.20 mmol, 4 equiv) in dry THF (3.5 mL) at rt. The mixture was allowed to react for 30 min; afterward, to the red suspension of the resulting ylide, the previously prepared lactol (70.5 mg, 0.3 mmol) in THF (2.5 mL) was added via cannula. The resulting mixture was stirred for 2 h and then quenched by the successive addition of a saturated solution of NH_4Cl (20 mL) and AcOH (0.14 mL, 8.4 equiv). The suspension was diluted with Et_2O (15 mL) and the two layers were separated; the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (4:1) delivered compound **15** (92.1 mg, 96%) as a colorless oil, $[\alpha]_D^{20}$ +33 (c 0.3, CH_2Cl_2); R_f=0.22 (hexane/EtOAc, 4:1). IR (liquid film) ν cm^{-1}: 3416, 2926, 1708, 1406, 1240, 1049. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.14 (1H, dd, J=5.7, 2.6 Hz), 5.97 (1H, m), 5.25–5.6 (4H, m), 4.5 (1H, dd, J=5.8, 2.6 Hz), 2.6 (1H, m), 2.0–2.5 (11H, m), 1.75 (2H, quintet, J=7.5 Hz), 1.3 (8H, m), 0.9 (3H, t, J=7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.9 s, 140.9 d, 131.9 d, 131.3 d, 129.6 d, 129.0 d, 127.4 d, 76.2 d, 46.2 d, 45.5 d, 33.2 t, 31.3 t, 30.0 t, 28.2 t, 27.2 t, 26.5 t, 24.3 t, 23.0 t, 22.3 t, 13.8 q; ESIMS (APCI): m/z 303 $[M+1-H_2O]^+$. HREIMS calcd for $C_{20}H_{32}O_3$: 320.2351 $(M)^+$, found: 320.2355.

4.1.8. (8*S*,12*S*)-Preclavulone A (1). Dess–Martin periodinane (75.6 mg, 0.177 mmol, 1.4 equiv) was added to a stirred solution of alcohol **15** (40.8 mg, 0.127 mmol) in dry CH_2Cl_2 (3.5 mL) under an argon atmosphere. After 3 h, Et_2O (15 mL) was added and the resulting mixture was filtered through a pad of Celite. The solution was then concentrated under reduced pressure at rt. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (4:1) delivered compound **1** (38.8 mg, 96%) as a pale yellow oil, $[\alpha]_D^{20}$ +126 (c 0.2, CH_2Cl_2) [lit.[10] −125.6 (c 0.18, CH_2Cl_2) for (8*R*,12*R*)-**1**]; R_f=0.23 (hexane/EtOAc, 4:1). IR (liquid film) ν cm^{-1}: 3600–3100, 2930, 1708, 1585, 1198, 737. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.7 (1H, dd, J=5.7, 2.7 Hz), 6.2 (1H, dd, J=5.7, 1.8 Hz), 5.5 (4H, m), 3.1 (1H, m), 2.45–2.55 (3H, m), 2.38 (2H, t, J=7.5 Hz), 1.9–2.3 (4H, m), 1.75 (2H, quintet, J=7.5 Hz), 1.3 (8H, m), 0.9 (3H, t, J=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208 s, 178.6 s, 165.1 d, 132.0 d, 131.6 d, 129.3 d, 128.7 d, 126.0 d, 48.6 d, 43.6 d, 32.7 t, 31.1 t, 28.8 t, 28.1 t, 27.0 t, 26.2 t, 23.9 t, 23.6 t, 22.2 t, 13.6 q; ESIMS (APCI): m/z 319 $(M+H)^+$, 301 $(M+H-H_2O)^+$. HREIMS calcd for $C_{20}H_{30}O_3$: 318.2195 $(M)^+$, found: 318.2201.

4.1.9. (8*S*,12*S*)-Preclavulone A methyl ester (2). An ethereal solution of freshly prepared diazomethane was added

dropwise to an ethereal solution of (8*S*,12*S*)-preclavulone A (**1**) (5 mg) at 0 °C, until a yellow color persistence, and the mixture was left at 0 °C for an additional 5 min. Excess CH_2N_2 was destroyed with AcOH and volatiles were removed in vacuo. (8*S*,12*S*)-Chromatographically pure preclavulone A methyl ester (**2**) was obtained as a colorless oil in quantitative yields, $[\alpha]_D^{20}$ +136.4 (*c* 0.17, THF) [lit.[9b] $[\alpha]_D^{20}$ −135.3 (*c* 0.13, THF) for (8*R*,12*R*)-**2**]; R_f=0.51 (hexane/EtOAc, 4:1). The NMR data of compound **2** were in perfect agreement with those reported in the literature.[8,9a]

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References and notes

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12. Since preclavulone A is widespread among coral species,[6b] and its biosynthesis seems to be non-stereospecific,[8] it is highly possible that (8*S*,12*S*)-**1** is the most abundant stereoisomer in some of them.
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