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Total Synthesis of Plakilactones C, B and *des*-Hydroxyplakilactone B by the Oxidative Cleavage of Gracilioether Furanylidenes

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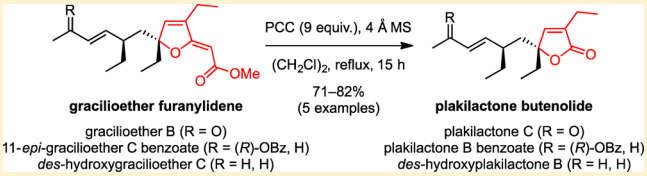
Supporting Information

ABSTRACT: A chemoselective oxidative cleavage of synthetic gracilioether B, 11-*epi*-gracilioether C benzoate, and *des*-hydroxygracilioether C with pyridinium chlorochromate, which proceeds with loss of the furanyl acetate, has enabled total synthesis and stereochemical elucidation of the marine sponge metabolites (4*R*,6*R*)-plakilactone C, (4*R*,6*R*,9*R*)-plakilactone B, and (4*R*,6*R*)-*des*-hydroxyplakilactone B. *des*-Hydroxygracilioether C, the putative biosynthetic precursor to hippolachnin A, was also found to undergo a facile ene cyclization on treatment with $SnCl_4$.



The polyketide secondary metabolites gracilioethers A–K and plakilactones A–I were recently isolated from marine sponges of the genera *Plakortis*, *Plakinastrella*, and *Agelas*.[1] Several of these compounds, and other related natural products,[2] are known to be agonists of peroxisome proliferator-activated receptor γ (PPARγ)[1b] and pregnane-X-receptor (PXR)[1d] and exhibit antimalarial,[1a,2a] antifungal,[2c] and anticancer properties.[2d] Metabolites in this family are notable for having unique polyoxygenated carbon scaffolds and can be classified as complex polycycles, such as gracilioether A (**1**)[1a] and hippolachnin A (**2**);[2c] butenolides, which include plakilactones C (**3**), B (**4**), and *des*-hydroxyplakilactone B (**5**);[1b] and furanylidenes, consisting of gracilioethers B (**6**), C (**7**),[1a,b] *des*-hydroxygracilioether C (**8**),[2a,d] and spongosoritin A (**9**)[2b,d] (Figure 1).[3] In recent years, several groups have targeted their synthesis,[4] but few have focused on the synthesis or structural elucidation of the plakilactone butenolides.[1e]

We have recently reported the first total synthesis of gracilioethers B (**6**) and C (**7**) using an approach modeled on a theory for the biogenesis of furanylidene metabolites.[5] With a short and high-yielding route to aldehyde dimethyl acetal **10**, we sought to extend the scope of this advanced intermediate to include synthesis of the related butenolides **3**–**5** (Scheme 1). Herein, we report the total synthesis and structural elucidation of plakilactones C (**3**), B (**4**) and *des*-hydroxyplakilactone B (**5**) from acetal **10** featuring a novel and chemoselective oxidation with pyridinium chlorochromate (PCC).

The polyketide natural products **1**–**9** each have a common furanyl heterocycle (Figure 1), which we have proposed to originate from the dehydrative ring contraction of related endoperoxide metabolites.[3,5] Since the carbon structures of many plakilactone butenolides and gracilioether furanylidenes appear to correlate, we suspect they may be linked biosynthetically by oxidative scission of the furanylidene enol ether.[3] This prompted us to examine the oxidation of furanylidenes **6**, **7**, and **8** to their corresponding butenolides, **3**, **4**, and **5**.

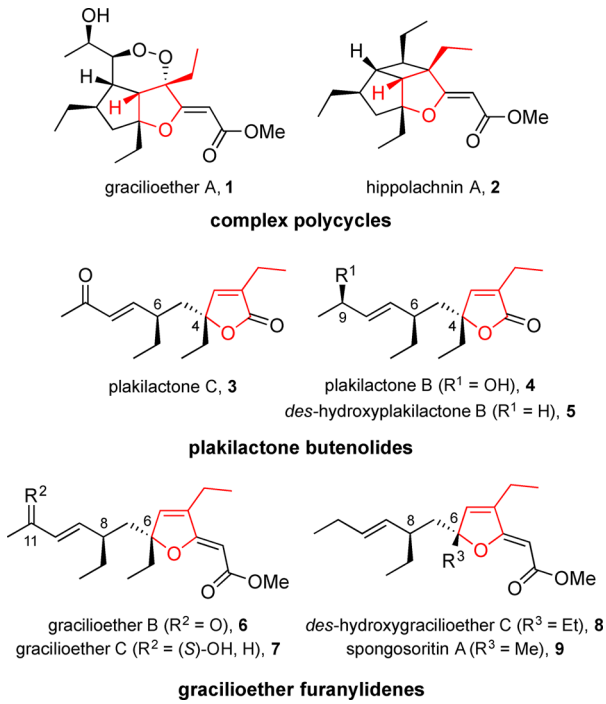


Figure 1. Complex polycycles, butenolides, and furanylidenes isolated from marine sponges. Common furanyl heterocycle highlighted in red.

While there are a number reagents capable of oxidative C–C bond cleavage,[6] many of these lack selectivity in the presence of multiple alkenes and other sensitive functional groups. We thus became interested in the use of chromate oxidants, especially PCC, which are known to be effective for the oxidation of

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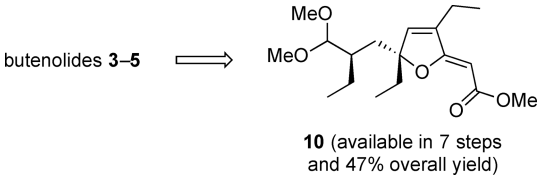
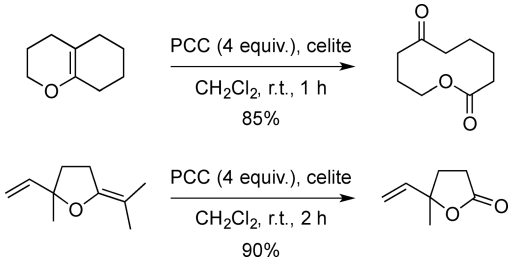
Scheme 1. Aldehyde Dimethyl Acetal 10 as an Advanced Intermediate for the Synthesis of Butenolides 3−5



electron-rich enol ethers,[7] with great potential for chemoselectivity (Scheme 2).[7b] However, application of this method-

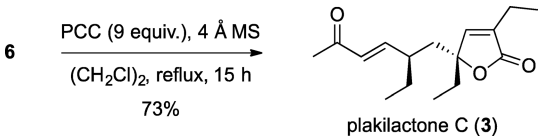
Scheme 2. Oxidation of Cyclic Enol Ethers with PCC



ology to a complex system, such as the gracilioether furanylidenes, had not been explored.

With synthetic gracilioether B (**6**) already in hand (prepared from acetal **10** in 86% yield over two steps),[5b] we attempted oxidation with PCC (1.5 equiv) and 4 Å MS in CH_2Cl_2 at ambient temperature, but only recovered starting material. After further experimentation, we were pleased to find that increasing the loading of PCC to a 9-fold excess, changing the solvent to $(CH_2Cl)_2$, and heating the mixture at reflux temperature for 15 h gave excellent conversion to butenolide **3** in 73% isolated yield (Scheme 3). Notably, oxidation was selective for the electron-rich

Scheme 3. Chemoselective PCC Oxidation of Gracilioether B (6) to Plakilactone C (3)

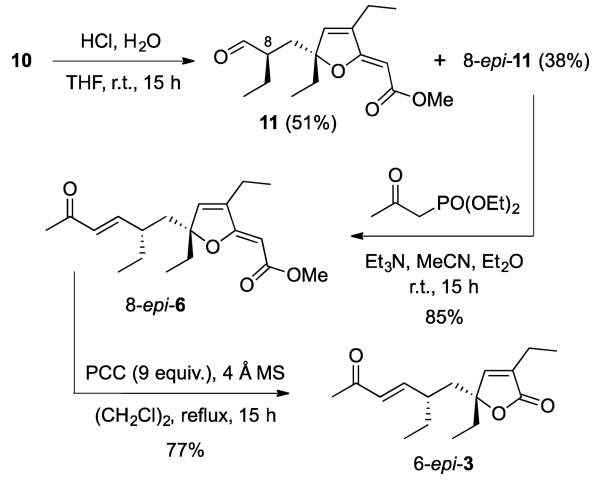


enol ether, as desired. While the ^{1}H NMR, ^{13}C NMR, and sign of specific rotation ($[\alpha]_D^{20}$ −165, *c* 0.65, $CHCl_3$; lit.[1b] $[\alpha]_D^{25}$ −64, *c* 0.11, $CHCl_3$) of synthetic **3** were consistent with those reported for plakilactone C,[1b,8] we wanted to support our configurational assignment through synthesis of the isomeric compound, 6-*epi*-**3** (Scheme 4).

Acetal **10** was hydrolyzed to give aldehyde **11** and useful quantities of the C8 epimer, 8-*epi*-**11**. Horner−Wadsworth−Emmons olefination[9] afforded ketone 8-*epi*-**6**, and oxidation with PCC under our optimized conditions gave butenolide 6-*epi*-**3** in 77% yield. The ^{1}H NMR and ^{13}C NMR of 6-*epi*-**3** did not match those of the natural product, thus supporting our initial structural and configurational assignment of plakilactone C as (4*R*,6*R*)-**3**.[8] Additionally, the ^{1}H NMR and ^{13}C NMR of ketone 8-*epi*-**6** did not match those of gracilioether B,[1a] which supports our original assignment of the natural product as (6*R*,8*R*)-**6**.[5b]

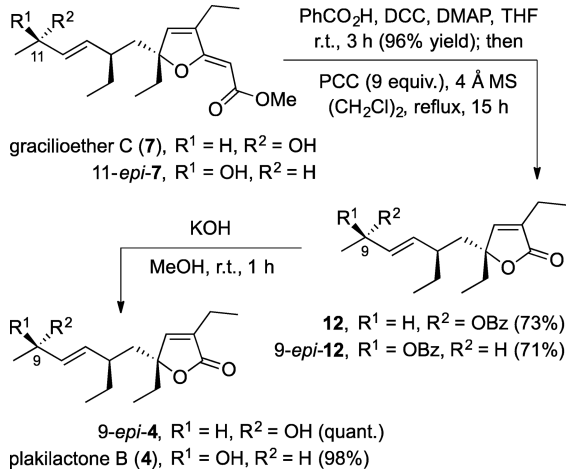
Further expanding the scope of our approach, Steglich esterification[10] of synthetic gracilioether C (**7**)[5b] with benzoic acid,

Scheme 4. Synthesis of Furanylidene 8-*epi*-6 and Butenolide 6-*epi*-3



followed by PCC oxidative cleavage, gave butenolide **12** in 70% yield over two steps, and without epimerization of the allylic alcohol stereocenter (Scheme 5). Hydrolysis of the resulting

Scheme 5. Synthesis of Butenolide 9-*epi*-4 and Plakilactone B (4)



benzoate ester with KOH and CH_3OH cleanly afforded alcohol 9-*epi*-**4**. However, the ^{1}H NMR and ^{13}C NMR of 9-*epi*-**4** showed subtle differences to those reported for plakilactone B.[1b,11] With the same strategy, 11-*epi*-gracilioether C (11-*epi*-**7**)[5b] was advanced to butenolide 9-*epi*-**12** in 68% yield over two steps and hydrolysis of the benzoate ester gave alcohol **4**.[12] The ^{1}H NMR and ^{13}C NMR of **4** matched those reported for plakilactone B[1b] and the sign of specific rotation ($[\alpha]_D^{20}$ −66, *c* 0.64, $CHCl_3$; lit.[1b] $[\alpha]_D^{25}$ −25, *c* 0.05, $CHCl_3$) was consistent, thereby elucidating the structure and absolute configuration of the natural product as (4*R*,6*R*,9*R*)-**4**.[11,13] It is interesting to note that the relative configuration of plakilactone B (**4**) does not match that of gracilioether C (**7**). We speculate that **4** might, therefore, be derived biosynthetically from oxidative cleavage of the C11 furanylidene epimer 11-*epi*-**7**.

Finally, Julia−Kocienski olefination[14] of aldehyde **11** with sulfone **13** afforded furanylidene **8** (Scheme 6) and the corresponding *Z* isomer in a 4:1 (*E*:*Z*) mixture (ratio determined by ^{1}H NMR). Although difficult to purify, it was possible to obtain

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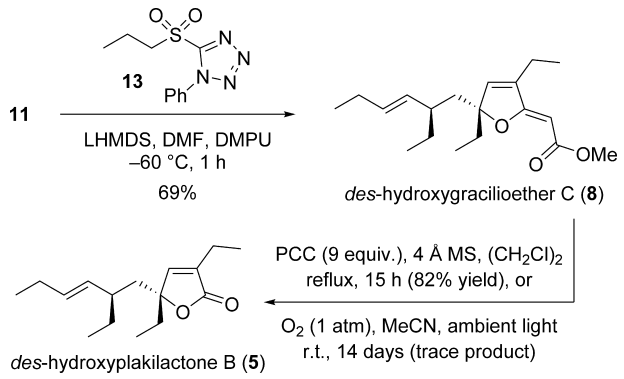
Scheme 6. Synthesis of *des*-Hydroxygracilioether C (8) and Oxidation to *des*-Hydroxyplakilactone B (5)

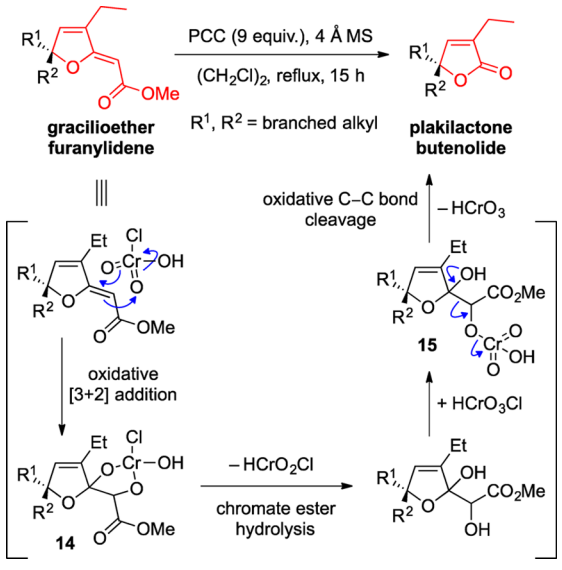


useable quantities of furanylidene **8** through silver-modified silica chromatography.[15] The ^{1}H NMR and ^{13}C NMR of **8** matched those reported for *des*-hydroxygracilioether C[1b,2a] and the sign of specific rotation ($[\alpha]_D^{20}$ −271, *c* 0.35, $CHCl_3$; lit.[1b] $[\alpha]_D^{25}$ −282, *c* 0.40, $CHCl_3$) was consistent, thus confirming the structure and absolute configuration of the natural product as (6*R*,8*R*).[16] Once again, PCC oxidation afforded the corresponding butenolide **5** in good yield. The ^{1}H NMR of **5** matched that reported for *des*-hydroxyplakilactone B,[1b,2a] and the sign of specific rotation ($[\alpha]_D^{20}$ −90, *c* 0.30, CH_3OH; lit.[1b] $[\alpha]_D^{25}$ −11, *c* 0.10, CH_3OH) was also consistent.[17]

We also found that simply exposing compound **8** to an atmosphere of oxygen in a sealed tube for 14 days and with ambient light gave trace quantities of butenolide **5** (Scheme 6), presumably through oxidation with singlet oxygen.[18] The apparent sensitivity of furanylidene substrates to selective oxidation of the enol ether, on exposure to oxygen (for compound **8**) and also PCC, would appear to demonstrate a clear biogenetic link between the gracilioether furanylidenes and plakilactone butenolides.[19]

As illustrated in Scheme 7, we presume that the reaction of PCC with furanylidene heterocycles begins with oxidative addition of chlorochromate to the electron-rich alkene.[7] Hydrolysis of the resulting chromium(IV) ester **14** and uptake of a second chlorochromate species may then give rise to a β-hydroxylated

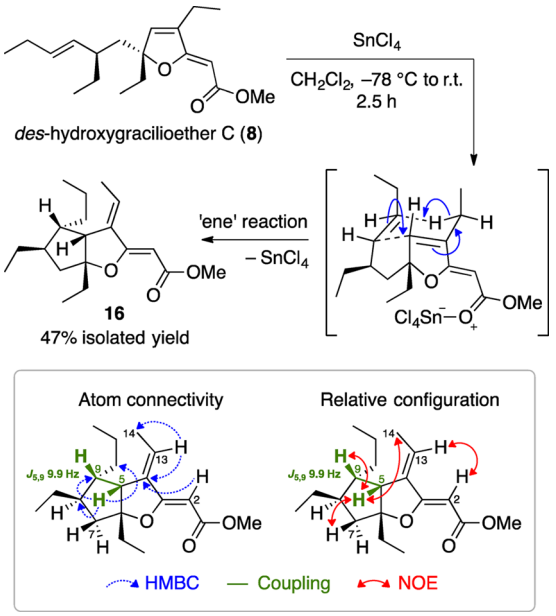
Scheme 7. Suggested Mechanism for PCC Oxidation of Furanylidene Substrates



chromium(VI) ester (such as **15**), which is activated toward oxidative C−C bond cleavage.[20]

Following our synthesis of *des*-hydroxygracilioether C (**8**), we also became interested in the possibility that furanylidene **8** may be a direct biogenetic precursor to hippolachnin A (**2**) through intramolecular [2 + 2] annulation, as postulated by Lin.[2c] Several attempts at photoinduced cyclization[4e] (250 W sunlamp, methylene blue/Me_2CO or 350 nm lamp) only caused epimerization of the conjugated enol ether or tethered olefin. Treatment with radical initiators, including AIBN/Se_2Ph_2 and Weitz' aminium salt (tris(4-bromophenyl)aminium hexachloroantimonate), or the photoredox catalyst $Ru(bipy)_3Cl_2$ also gave disappointing results. Heating in xylene (140 °C) failed to instigate a stepwise (ionic) cycloaddition;[21] and similar results were found when screening conditions with common Lewis acids, including $BF_3{\cdot}OEt_2$, $TiCl_4$, $Ti(O^iPr)_4$, $AlCl_3$, $FeCl_3$, and $In(OTf)_3$. However, on treatment with $SnCl_4$, we discovered that **8** undergoes a facile ene cyclization at low temperature, yielding the novel [3.3.0]-bicycle **16** (Scheme 8).[22] Key HMBCs, shown

Scheme 8. $SnCl_4$-Promoted Ene Reaction of *des*-Hydroxygracilioether C (8)



as dashed blue arrows in Scheme 8, clearly indicated shift of the furan olefin to the adjacent ethyl substituent and a new bond linking C5 and C9. NOEs, shown as red arrows in Scheme 8, were observed between the hydrogen atoms connected to C2 and C13, and between C5 and C14. Thus, the alkene geometries at C2 and C13 of compound **16** are *Z* and *E*, respectively. Further NOEs appeared between the hydrogen atoms connected to C5 and C9, and between C5 and C7, demonstrating that the C9 stereocenter is in the *S* configuration. The dihedral coupling constant ($J_{5,9}$ 9.9 Hz) observed for the hydrogen atoms connected to C5 and C9 was also consistent with that reported for the analogous bridgehead hydrogen atoms of gracilioether A (**1**, *J* 10.7 Hz),[1a] E (*J* 10.1 Hz), F (*J* 10.2 Hz), G (*J* 9.3 Hz), H (*J* 9.8 Hz), and I (*J* 10.3 Hz),[1b] which all contain a similar [3.3.0]-bicyclic arrangement. Despite many efforts, we have yet to achieve direct [2 + 2] annulation of furanylidene **8**.

In summary, a novel and chemoselective oxidation of synthetic gracilioether B (**6**), 11-*epi*-gracilioether C (11-*epi*-**7**) benzoate,

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and *des*-hydroxygracilioether C (**8**) with PCC has enabled total synthesis and stereochemical elucidation of the marine sponge metabolites plakilactones C (**3**), B (**4**) and *des*-hydroxyplakilactone B (**5**). The structures and absolute configuration of the natural products were determined as (4*R*,6*R*)-**3**, (4*R*,6*R*,9*R*)-**4**, and (4*R*,6*R*)-**5**, thus confirming the stereochemical assignments that were originally reported. Compound **8**, the putative biosynthetic precursor to hippolachnin A (**2**), was also found to undergo a facile $SnCl_4$-promoted ene cyclization, yielding a novel [3.3.0]-bicycle (**16**) with a similar carbon structure to several oxygenated gracilioether polycycles.

EXPERIMENTAL SECTION

All reactions without water as a solvent were carried out under an atmosphere of nitrogen in flame-dried glassware. CH_2Cl_2 and Et_3N were distilled over CaH_2; and THF and Et_2O were distilled over sodium and benzophenone. All other solvents were used as commercial reagent grade. Analytical thin layer chromatography was performed on $60F_{254}$ silica aluminum backed sheets, monitored by a UV lamp and developed in potassium permanganate. Column chromatography was performed on 230−400 mesh silica (particle size: 0.040−0.063 mm). Silver-modified silica, when required, was prepared according to a literature method.[15a] Electrospray ionization (ESI) mass spectra are reported as the observed molecular ion. Infrared spectra were recorded on an FTIR spectrometer with the absorptions reported in wavenumbers (cm^{-1}).

^1H NMR spectra were recorded at 600 MHz, and ^{13}C NMR spectra were recorded at 150 MHz. Where $CDCl_3$ is used as the solvent and internal lock, spectra are referenced to residual $CHCl_3$ (δ_H 7.26) for ^1H NMR and $CDCl_3$ (δ_C 77.0) for ^{13}C NMR. Where CD_3OD is used as the solvent and internal lock, spectra are referenced to residual CD_3OH (δ_H 3.30) for ^1H NMR and CD_3OD (δ_C 49.0) for ^{13}C NMR. For compounds **3**, 6-*epi*-**3**, **4**, and 9-*epi*-**4**, ^1H NMR spectra are referenced to residual CD_3OH (δ_H 3.31) for direct comparison to the data reported in ref 1b. Where C_6D_6 is used as the solvent and internal lock, spectra are referenced to residual C_6D_6 (δ_C 128.0) for ^{13}C NMR. Chemical shift values are reported in parts per million, and coupling constants are reported in hertz. ^1H multiplicity, as observed in 1D ^1H NMR spectra, is reported using the abbreviations s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet. Structural and stereochemical assignments, where required, were made using COSY, HSQC, HMBC, and NOESY 2D NMR experiments.

General Procedure for PCC Oxidation of Furanylidene Substrates. PCC (9.0 mmol) is added in a single portion to a stirred suspension of the furanylidene (1.0 mmol), 4 Å MS (1.94 g), and $(CH_2Cl)_2$ (19.4 mL) at room temperature. The mixture is heated at reflux temperature for 15 h. Once cooled, the crude residue is passed through a thick pad of silica (washing with excess 50% Et_2O/CH_2Cl_2) and concentrated *in vacuo* to afford the corresponding butenolide.

Plakilactone C (3). Prepared from furanylidene **6** (0.043 g, 0.13 mmol) according to the general procedure for PCC oxidation of furanylidene substrates. Flash chromatography (25% EtOAc/hexane) afforded **3** as a colorless oil (0.026 g, 73%): R_f (25% EtOAc/hexane) 0.25; $[\alpha]_D^{20}$ −165 (*c* 0.65, $CHCl_3$); ν_{max} (thin film) 2969, 2926, 2880, 1746, 1697, 1672, 1623, 1461, 1359, 1254, 1143, 1090, 1045, 954, 883, 803, 781 cm^{-1}; δ_H (600 MHz, CD_3OD) 7.07 (1H, s, C*H*=CCH$_2$CH$_3$), 6.62 (1H, dd, *J* 16.0, 9.4 Hz, C*H*=CHC(O)CH$_3$), 5.88 (1H, d, *J* 16.0 Hz, CH=C*H*C(O)CH$_3$), 2.25 (3H, s, C(O)C*H*$_3$), 2.24−2.19 (1H, m, CH=CC*H*$_A$H$_B$CH$_3$), 2.19−2.13 (1H, m, CH=CCH$_A$*H*$_B$CH$_3$), 2.10−2.08 (2H, overlapping peaks, C*H*CH$_2$CH$_3$, C*H*$_A$H$_B$CCH$_2$CH$_3$), 1.94 (1H, dd, *J* 15.0, 10.1 Hz, CH$_A$*H*$_B$CCH$_2$CH$_3$), 1.86−1.76 (2H, m, CH$_2$CC*H*$_2$CH$_3$), 1.53−1.47 (1H, m, CHC*H*$_A$H$_B$-CH$_3$), 1.39−1.33 (1H, m CHCH$_A$*H*$_B$CH$_3$), 1.10 (3H, t, *J* 7.5 Hz, CH=CCH$_2$C*H*$_3$), 0.85 (3H, t, *J* 7.4 Hz, CHCH$_2$C*H*$_3$), 0.79 (3H, t, *J* 7.5 Hz, CH$_2$CCH$_2$C*H*$_3$); δ_C (150 MHz, CD_3OD) 201.0, 175.6, 154.7, 153.1, 136.9, 132.3, 90.6, 42.4, 41.1, 32.0, 29.6, 26.9, 19.5, 11.9, 11.7, 7.9; HRMS (ESI): MNa^+, found 287.1624. $C_{16}H_{24}NaO_3^+$ requires 287.1623.

Methyl 2-[(2*Z*,5*R*)-3,5-Diethyl-5-[(2*R*)-2-ethyl-3-oxopropyl]-2(5*H*)-furanylidene]ethanoate (11) and Methyl 2-[(2*Z*,5*R*)-3,5-Diethyl-5-[(2*S*)-2-ethyl-3-oxopropyl]-2(5*H*)-furanylidene]-ethanoate (8-*epi*-11). HCl (1.0 mL, 10% aq) was added to a stirred solution of **10** (0.154 g, 0.47 mmol) in THF (10 mL) at room temperature. Stirring continued for 15 h before quenching with slow addition of $NaHCO_3$ (satd aq). The organic phase was separated and aqueous extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (20% EtOAc/hexane) afforded **11** (0.067 g, 51%) and 8-*epi*-**11** (0.050 g, 38%), each as a pale yellow oil. **11**: R_f (20% EtOAc/hexane) 0.31; $[\alpha]_D^{20}$ −98 (*c* 0.35, $CHCl_3$); ν_{max} (thin film) 2969, 2938, 2880, 1713, 1687, 1625, 1460, 1434, 1377, 1274, 1159, 1089, 1037, 975, 852, 806 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 9.53 (1H, d, *J* 1.8 Hz, C*H*O), 6.11 (1H, s, C*H*=CCH$_2$CH$_3$), 4.84 (1H, s, C*H*CO$_2$CH$_3$), 3.69 (3H, s, OC*H*$_3$), 2.26 (1H, dd, *J* 14.3, 9.0 Hz, C*H*$_A$H$_B$CCH$_2$CH$_3$), 2.19−2.15 (1H, m, C*H*CH$_2$CH$_3$), 2.16−2.12 (2H, m, CH=CC*H*$_2$CH$_3$), 1.93−1.87 (2H, overlapping peaks, CH$_A$*H*$_B$CCH$_2$CH$_3$, CH$_2$CC*H*$_A$H$_B$CH$_3$), 1.78 (1H, dq, *J* 14.4, 7.3 Hz, CH$_2$CCH$_A$*H*$_B$CH$_3$), 1.68−1.60 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.55−1.50 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.12 (3H, t, *J* 7.4 Hz, CH=CCH$_2$C*H*$_3$), 0.90 (3H, t, *J* 7.4 Hz, CHCH$_2$C*H*$_3$), 0.81 (3H, t, *J* 7.3 Hz, CH$_2$CCH$_2$C*H*$_3$); δ_C (150 MHz, $CDCl_3$) 204.3, 171.2, 166.7, 140.8, 139.1, 96.8, 84.5, 50.6, 48.1, 35.8, 31.7, 23.2, 18.5, 11.9, 11.0, 8.1; HRMS (ESI): MNa^+, found 303.1564. $C_{16}H_{24}NaO_4^+$ requires 303.1572. 8-*epi*-**11**: R_f (20% EtOAc/hexane) 0.17; $[\alpha]_D^{20}$ −83 (*c* 0.27, $CHCl_3$); ν_{max} (thin film) 2969, 2924, 2880, 2850, 1714, 1689, 1627, 1461, 1435, 1377, 1274, 1169, 1037, 975, 917, 875, 807 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 9.45 (1H, d, *J* 3.7 Hz, C*H*O), 6.13 (1H, s, C*H*=CCH$_2$CH$_3$), 4.85 (1H, s, C*H*CO$_2$CH$_3$), 3.67 (3H, s, OC*H*$_3$), 2.39 (1H, dd, *J* 14.8, 9.6 Hz, C*H*$_A$H$_B$CCH$_2$CH$_3$), 2.20−2.15 (2H, m, CH=CC*H*$_2$CH$_3$), 2.07−2.02 (1H, m, C*H*CH$_2$CH$_3$), 1.93−1.80 (1H, m, CH$_2$C-C*H*$_A$H$_B$CH$_3$), 1.80−1.72 (2H, overlapping peaks, C*H*$_A$H$_B$CCH$_2$CH$_3$, CH$_2$CCH$_A$*H*$_B$CH$_3$), 1.62−1.55 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.48−1.42 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.16 (3H, t, *J* 7.4 Hz, CH=CCH$_2$C*H*$_3$), 0.85 (3H, t, *J* 7.4 Hz, CHCH$_2$C*H*$_3$), 0.80 (3H, t, *J* 7.4 Hz, CH$_2$CCH$_2$C*H*$_3$); δ_C (150 MHz, $CDCl_3$) 203.5, 170.4, 166.5, 141.5, 137.9, 96.6, 85.2, 50.6, 48.8, 37.6, 31.7, 23.0, 18.5, 12.0, 11.1, 7.9; HRMS (ESI): MNa^+, found 303.1562. $C_{16}H_{24}NaO_4^+$ requires 303.1572.

8-*epi*-Gracilioether B (8-*epi*-6). Et_3N (0.16 mL, 1.15 mmol) was added to a solution of 8-*epi*-**11** (0.123 g, 0.44 mmol), diethyl 2-oxopropylphosphonate (0.16 mL, 0.83 mmol), and LiCl (0.048 g, 1.13 mmol) in MeCN (9.4 mL) at room temperature. Stirring continued for 15 h (progress monitored by TLC until completion) before partitioning between NH_4Cl (satd aq) and CH_2Cl_2. The organic phase was separated and aqueous extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (40% EtOAc/hexane) afforded 8-*epi*-**6** (0.120 g, 85%) as a colorless waxy solid: R_f (40% EtOAc/hexane) 0.41; $[\alpha]_D^{20}$ −269 (*c* 0.36, $CHCl_3$); ν_{max} (thin film) 2969, 2937, 2879, 1709, 1672, 1625, 1460, 1434, 1356, 1254, 1166, 1037, 974, 874, 805 cm^{-1}; δ_H (600 MHz, CD_3OD) 6.56 (1H, dd, *J* 16.0, 9.7 Hz, C*H*=CHC(O)CH$_3$), 6.46 (1H, s, C*H*=CCH$_2$CH$_3$), 5.60 (1H, d, *J* 16.0 Hz, CH=C*H*C(O)CH$_3$), 4.77 (1H, s, C*H*CO$_2$CH$_3$), 3.60 (3H, s, OC*H*$_3$), 2.18−2.13 (2H, m, CH=CC*H*$_2$CH$_3$), 2.13−2.11 (4H, overlapping peaks, C(O)C*H*$_3$, C*H*$_A$H$_B$CCH$_2$CH$_3$), 2.03 (1H, dd, *J* 14.7, 2.8 Hz, CH$_A$*H*$_B$CCH$_2$CH$_3$), 1.99−1.94 (1H, m, C*H*CH$_2$CH$_3$), 1.88−1.82 (1H, m, CH$_2$CC*H*$_A$H$_B$CH$_3$), 1.79−1.73 (1H, m, CH$_2$C-CH$_A$*H*$_B$CH$_3$), 1.51−1.44 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.36−1.29 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.18 (3H, t, *J* 7.4 Hz, CH=CCH$_2$C*H*$_3$), 0.81 (3H, t, *J* 7.4 Hz, CHCH$_2$C*H*$_3$), 0.75 (3H, t, *J* 7.4 Hz, CH$_2$CCH$_2$C*H*$_3$); δ_C (150 MHz, CD_3OD) 201.7, 173.9, 169.0, 155.2, 142.4, 141.1, 131.2, 99.5, 84.7, 51.1, 43.8, 43.1, 33.4, 29.3, 25.9, 19.4, 12.6, 11.8, 7.9; HRMS (ESI): MNa^+, found 343.1884. $C_{19}H_{28}NaO_4^+$ requires 343.1885.

6-*epi*-Plakilactone C (6-*epi*-3). Prepared from furanylidene 8-*epi*-**6** (0.044 g, 0.14 mmol) according to the general procedure for PCC oxidation of furanylidene substrates. Flash chromatography (25% EtOAc/hexane) afforded 6-*epi*-**3** as a colorless waxy solid (0.028 g, 77%): R_f (25% EtOAc/hexane) 0.21; $[\alpha]_D^{20}$ −6 (*c* 0.70, $CHCl_3$); ν_{max} (thin film) 2969, 2926, 2879, 1748, 1698, 1672, 1625, 1461, 1361,

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1254, 1138, 1044, 954, 877, 808, 780 cm^{-1}; δ_H (600 MHz, CD_3OD) 7.14 (1H, s, C*H*=CCH$_2$CH$_3$), 6.54 (1H, dd, *J* 16.0, 9.1 Hz, C*H*=CHC(O)CH$_3$), 5.71 (1H, d, *J* 16.0 Hz, CH=C*H*C(O)CH$_3$), 2.23 (3H, s, C(O)C*H*$_3$), 2.23−2.19 (2H, m, CH=CC*H*$_2$CH$_3$), 2.06−2.01 (3H, overlapping peaks, C*H*CH$_2$CH$_3$, C*H*$_2$CCH$_2$CH$_3$), 1.83 (1H, dq, *J* 14.5, 7.5 Hz, CH$_2$CC*H*$_A$H$_B$CH$_3$), 1.74 (1H, dq, *J* 14.5, 7.5 Hz, CH$_2$CCH$_A$*H*$_B$CH$_3$), 1.54−1.47 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.37−1.31 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.16 (3H, t, *J* 7.5 Hz, CH=CCH$_2$C*H*$_3$), 0.84 (3H, t, *J* 7.4 Hz, CHCH$_2$C*H*$_3$), 0.79 (3H, t, *J* 7.5 Hz, CH$_2$CCH$_2$C*H*$_3$); δ_C (150 MHz, CD_3OD) 201.3, 175.5, 154.3, 151.7, 138.0, 131.7, 91.1, 42.9, 42.0, 32.5, 29.3, 26.3, 19.4, 12.4, 11.7, 7.8; HRMS (ESI): MNa$^+$, found 287.1622. $C_{16}H_{24}NaO_3^+$ requires 287.1623.

Gracilioether C (7) Benzoate. DMAP (0.063 g, 0.52 mmol) was added in a single portion to a stirred solution of **7** (0.026 g, 0.08 mmol), $PhCO_2H$ (0.160 g, 1.31 mmol), and DCC (0.166 g, 0.81 mmol) in THF (4.0 mL) at room temperature. Stirring continued for 3 h before quenching with the addition of $NaHCO_3$ (50% satd aq). The mixture was filtered, organic phase separated, and aqueous extracted with Et_2O. The combined extracts were dried (Na_2SO_4), concentrated *in vacuo*, and triturated with 50% Et_2O/hexane. Flash chromatography (25% Et_2O/hexane) afforded **7** (0.033 g, 96%) as a pale yellow oil: R_f (25% Et_2O/hexane) 0.25; $[\alpha]_D^{20}$ −279 (*c* 0.19, $CHCl_3$); ν_{max} (thin film) 2925, 2857, 1715, 1627, 1453, 1377, 1269, 1162 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 8.04 (2H, apparent d, *J* 8.3 Hz, Ar*H*), 7.56 (1H, apparent t, *J* 7.6 Hz, Ar*H*), 7.44 (2H, apparent t, *J* 7.6 Hz, Ar*H*), 6.12 (1H, s, C*H*=CCH$_2$CH$_3$), 5.53 (1H, apparent p, *J* 6.6 Hz, C*H*(OBz)CH$_3$), 5.45 (1H, dd, *J* 15.4, 8.4 Hz, C*H*=CHCH(OBz)CH$_3$), 5.35 (1H, dd, *J* 15.4, 7.2 Hz, CH=C*H*CH(OBz)CH$_3$), 4.78 (1H, s, C*H*CO$_2$CH$_3$), 3.68 (3H, s, OC*H*$_3$), 2.03−1.97 (3H, overlapping peaks, CH=CC*H*$_2$CH$_3$, C*H*$_A$H$_B$CCH$_2$CH$_3$), 1.85−1.77 (3H, overlapping peaks, CH$_A$*H*$_B$C-CH$_2$CH$_3$, CH$_2$CC*H*$_A$H$_B$CH$_3$, C*H*CH$_2$CH$_3$), 1.69 (1H, dq, *J* 14.4, 7.3 Hz, CH$_2$CCH$_A$*H*$_B$CH$_3$), 1.45−1.38 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.40 (3H, d, *J* 6.4 Hz, CH(OBz)C*H*$_3$), 1.24−1.16 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 0.97 (3H, t, *J* 7.4 Hz, CH=CCH$_2$C*H*$_3$), 0.78 (3H, t, *J* 7.3 Hz, CHCH$_2$C*H*$_3$), 0.74 (3H, t, *J* 7.4 Hz, CH$_2$CCH$_2$C*H*$_3$); δ_C (150 MHz, $CDCl_3$) 171.9, 166.9, 165.8, 140.0, 139.5, 138.3, 132.8, 130.8, 129.9, 129.5 (2 peaks), 128.3 (2 peaks), 97.6, 83.5, 72.0, 50.5, 43.2, 39.3, 32.4, 29.1, 20.8, 18.5, 11.9, 11.3, 7.9; HRMS (ESI): MNa$^+$, found 449.2299. $C_{26}H_{34}NaO_5^+$ requires 449.2304.

9-*epi*-Plakilactone B Benzoate (12). Prepared from furanylidene **7** benzoate (0.030 g, 0.07 mmol) according to the general procedure for PCC oxidation of furanylidene substrates. Flash chromatography (20% Et_2O/hexane) afforded **12** as a pale yellow oil (0.019 g, 73%): R_f (20% Et_2O/hexane) 0.26; $[\alpha]_D^{20}$ −104 (*c* 0.37, $CHCl_3$); ν_{max} (thin film) 2925, 2856, 1755, 1716, 1603, 1452, 1315, 1269, 1110 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 8.04 (2H, d, *J* 7.2 Hz, Ar*H*), 7.57 (1H, apparent t, *J* 7.2 Hz, Ar*H*), 7.45 (2H, apparent t, *J* 7.8 Hz, Ar*H*), 6.71 (1H, t, *J* 1.6 Hz, C*H*=CCH$_2$CH$_3$), 5.52 (1H, apparent p, *J* 6.6 Hz, C*H*(OBz)CH$_3$), 5.44 (1H, dd, *J* 15.4, 8.4 Hz, C*H*=CHCH(OBz)CH$_3$), 5.32 (1H, dd, *J* 15.4, 7.3 Hz, CH=C*H*CH(OBz)CH$_3$), 2.14−2.05 (2H, m, CH=CC*H*$_2$CH$_3$), 1.95 (1H, apparent q, *J* 18.9, 6.8 Hz, C*H*$_A$H$_B$CCH$_2$CH$_3$), 1.81−1.73 (3H, overlapping peaks, CH$_A$*H*$_B$CCH$_2$CH$_3$, C*H*CH$_2$CH$_3$, CH$_2$C-C*H*$_A$H$_B$CH$_3$), 1.67 (1H, dq, *J* 14.4, 7.4 Hz, CH$_2$CCH$_A$*H*$_B$CH$_3$), 1.41 (3H, d, *J* 6.4 Hz, CH(OBz)C*H*$_3$), 1.40−1.34 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.25−1.18 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 0.92 (3H, t, *J* 7.4 Hz, CH=CCH$_2$C*H*$_3$), 0.79 (3H, t, *J* 7.3 Hz, CHCH$_2$C*H*$_3$), 0.77 (3H, t, *J* 7.3 Hz, CH$_2$CCH$_2$C*H*$_3$); δ_C (150 MHz, $CDCl_3$) 173.6, 165.9, 150.8, 138.2, 135.1, 132.9, 131.0, 130.7, 129.5 (2 peaks), 128.3 (2 peaks), 89.0, 72.0, 42.4, 38.9, 31.8, 29.3, 20.9, 18.5, 11.8, 11.4, 7.7; HRMS (ESI): MNa$^+$, found 393.2053. $C_{23}H_{30}NaO_4^+$ requires 393.2042.

9-*epi*-Plakilactone B (9-*epi*-4). KOH (0.107 g, 1.91 mmol) was added in a single portion to a stirred solution of **12** (0.014 g, 0.05 mmol) in MeOH (1.0 mL) at room temperature. Stirring continued for 1 h before quenching with the addition of NH_4Cl (satd aq) and Et_2O. The organic phase was separated and aqueous extracted with Et_2O. The combined extracts were washed with $NaHCO_3$ (50% satd aq) and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (25% EtOAc/hexane) afforded 9-*epi*-**4** (0.010 g, quant.) as a colorless oil: R_f (25% EtOAc/hexane) 0.25; $[\alpha]_D^{20}$ −46 (*c* 0.54, $CHCl_3$); ν_{max} (thin film) 3445, 3057, 2968, 2926, 2878, 1733, 1461, 1368, 1267, 1139, 1051 cm^{-1}; δ_H (600 MHz, CD_3OD) 7.10 (1H, t, *J* 1.5 Hz, C*H*=CCH$_2$CH$_3$), 5.33−5.26 (2H, overlapping peaks, C*H*=CHCH(OH)CH$_3$, CH=C*H*CH(OH)CH$_3$), 4.20−4.16 (1H, m, C*H*(OH)CH$_3$), 2.26 (2H, qd, *J* 7.5, 1.5 Hz, CH=CC*H*$_2$CH$_3$), 1.93 (1H, dd, *J* 14.7, 3.1 Hz, C*H*$_A$H$_B$CCH$_2$CH$_3$), 1.86−1.72 (4H, overlapping peaks, CH$_A$*H*$_B$CCH$_2$CH$_3$, C*H*CH$_2$CH$_3$, CH$_2$CC*H*$_2$CH$_3$), 1.42−1.34 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.27−1.20 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.21 (3H, d, *J* 6.4 Hz, CH(OH)C*H*$_3$), 1.16 (3H, t, *J* 7.5 Hz, CH=CCH$_2$C*H*$_3$), 0.82 (3H, t, *J* 7.4 Hz, CHCH$_2$C*H*$_3$), 0.79 (3H, t, *J* 7.4 Hz, CH$_2$CCH$_2$C*H*$_3$), missing O*H*; δ_C (150 MHz, CD_3OD) 176.0, 153.7, 136.5, 136.2, 135.3, 91.2, 69.1, 43.3, 40.5, 32.2, 30.4, 23.8, 19.4, 12.3, 11.8, 8.0; HRMS (ESI): MNa$^+$, found 289.1773. $C_{16}H_{26}NaO_3^+$ requires 289.1780.

11-*epi*-Gracilioether C (11-*epi*-7) Benzoate. DMAP (0.073 g, 0.60 mmol) was added in a single portion to a stirred solution of 11-*epi*-**7** (0.034 g, 0.11 mmol) and DCC (0.199 g, 0.96 mmol) in THF (5.0 mL) at room temperature. Stirring continued for 3 h before quenching with the addition of $NaHCO_3$ (50% satd aq). The organic phase was separated and aqueous extracted with Et_2O. The combined extracts were washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (25% Et_2O/hexane) afforded 11-*epi*-**7** (0.043 g, 96%) as a colorless oil: R_f (25% Et_2O/hexane) 0.25; $[\alpha]_D^{20}$ −167 (*c* 0.30, $CHCl_3$); ν_{max} (thin film) 3060, 2927, 2858, 1715, 1634, 1493, 1452, 1266, 1160, 1050 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 8.03 (2H, apparent d, *J* 7.2 Hz, Ar*H*), 7.55 (1H, apparent t, *J* 7.9 Hz, Ar*H*), 7.44 (2H, apparent t, *J* 7.7 Hz, Ar*H*), 6.17 (1H, s, C*H*=CCH$_2$CH$_3$), 5.53 (1H, apparent p, *J* 6.3 Hz, C*H*(OBz)CH$_3$), 5.45 (1H, dd, *J* 15.5, 8.7 Hz, C*H*=CHCH(OBz)CH$_3$), 5.39 (1H, dd, *J* 15.5, 6.0 Hz, CH=C*H*CH(OBz)CH$_3$), 4.81 (1H, s, C*H*CO$_2$CH$_3$), 3.69 (3H, s, OC*H*$_3$), 2.14 (2H, apparent q, *J* 7.7 Hz, CH=CC*H*$_2$CH$_3$), 1.97 (1H, dd, *J* 14.2, 3.2 Hz, C*H*$_A$H$_B$CCH$_2$CH$_3$), 1.87−1.75 (3H, overlapping peaks, CH$_A$*H*$_B$CCH$_2$CH$_3$, C*H*CH$_2$CH$_3$, CH$_2$CC*H*$_A$H$_B$CH$_3$), 1.70 (1H, dq, *J* 14.3, 7.3 Hz, CH$_2$CCH$_A$*H*$_B$CH$_3$), 1.43−1.37 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.41 (3H, d, *J* 6.4 Hz, CH(OBz)C*H*$_3$), 1.25−1.17 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.13 (3H, t, *J* 7.4 Hz, CH=CCH$_2$C*H*$_3$), 0.77 (3H, t, *J* 7.3 Hz, CHCH$_2$C*H*$_3$), 0.76 (3H, t, *J* 7.3 Hz, CH$_2$CCH$_2$C*H*$_3$); δ_C (150 MHz, $CDCl_3$) 171.8, 166.8, 165.8, 139.9, 139.7, 137.5, 132.8, 130.8, 129.6, 129.5 (2 peaks), 128.3 (2 peaks), 97.5, 83.6, 71.3, 50.5, 43.0, 39.2, 32.3, 29.0, 20.5, 18.6, 11.9, 11.3, 7.9; HRMS (ESI): MNa$^+$, found 449.2296. $C_{26}H_{34}NaO_5^+$ requires 449.2304.

Plakilactone B Benzoate (9-*epi*-12). Prepared from furanylidene 11-*epi*-**7** (0.034 g, 0.09 mmol) according to the general procedure for PCC oxidation of furanylidene substrates. Flash chromatography (20% Et_2O/hexane) afforded 9-*epi*-**12** as a pale yellow oil (0.021 g, 71%): R_f (20% Et_2O/hexane) 0.26; $[\alpha]_D^{20}$ −44 (*c* 0.25, $CHCl_3$); ν_{max} (thin film) 2968, 2927, 2859, 1751, 1716, 1603, 1494, 1452, 1270, 1111, 1050 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 8.04 (2H, apparent d, *J* 8.2 Hz, Ar*H*), 7.56 (1H, apparent t, *J* 7.5 Hz, Ar*H*), 7.45 (2H, apparent t, *J* 7.8 Hz, Ar*H*), 6.77 (1H, t, *J* 1.6 Hz, C*H*=CCH$_2$CH$_3$), 5.53 (1H, m, C*H*(OBz)CH$_3$), 5.44−5.37 (2H, overlapping peaks, C*H*=CHCH(OBz)CH$_3$, CH=C*H*CH-(OBz)CH$_3$), 2.33−2.21 (2H, m, CH=CC*H*$_2$CH$_3$), 1.94 (1H, dd, *J* 14.4, 2.7 Hz, C*H*$_A$H$_B$CCH$_2$CH$_3$), 1.83−1.65 (4H, overlapping peaks, CH$_A$*H*$_B$CCH$_2$CH$_3$, C*H*CH$_2$CH$_3$, CH$_2$CC*H*$_2$CH$_3$), 1.42 (3H, d, *J* 6.6 Hz, CH(OBz)C*H*$_3$), 1.40−1.33 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.27−1.20 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.14 (3H, t, *J* 7.4 Hz, CH=CCH$_2$C*H*$_3$), 0.79 (3H, t, *J* 7.4 Hz, CH$_2$CCH$_2$C*H*$_3$), 0.78 (3H, t, *J* 7.4 Hz, CHCH$_2$C*H*$_3$); δ_C (150 MHz, $CDCl_3$) 173.6, 165.8, 150.6, 137.0, 135.4, 132.9, 130.7, 130.6, 129.5 (2 peaks), 128.3 (2 peaks), 89.0, 71.2, 42.2, 38.9, 31.6, 29.3, 20.5, 18.6, 11.9, 11.3, 7.8; HRMS (ESI): MNa$^+$, found 393.2041. $C_{23}H_{30}NaO_4^+$ requires 393.2042.

Plakilactone B (4). KOH (0.095 g, 1.69 mmol) was added in a single portion to a stirred solution of 9-*epi*-**12** (0.017 g, 0.05 mmol) in MeOH (1.0 mL) at room temperature. Stirring continued for 1 h before quenching with the addition of NH_4Cl (satd aq) and Et_2O. The organic phase was separated and aqueous extracted with Et_2O. The combined extracts were washed with $NaHCO_3$ (50% satd aq) and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatog-

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raphy (25% EtOAc/hexane) afforded **4** (0.012 g, 98%) as a colorless oil: R_f (25% EtOAc/hexane) 0.25; $[\alpha]_D^{20}$ −66 (*c* 0.64, $CHCl_3$); ν_{max} (thin film) 3445, 2968, 2926, 2857, 1739, 1494, 1456, 1051 cm^{-1}; δ_H (600 MHz, CD_3OD) 7.07 (1H, t, *J* 1.6 Hz, C*H*=CCH$_2$CH$_3$), 5.34−5.28 (2H, overlapping peaks, C*H*=CHCH(OH)CH$_3$, CH=C*H*CH(OH)CH$_3$), 4.20−4.16 (1H, m, C*H*(OH)CH$_3$), 2.30−2.20 (2H, m, CH=CC*H*$_2$CH$_3$), 1.94 (1H, dd, *J* 14.1, 2.6 Hz, C*H*$_A$H$_B$CCH$_2$CH$_3$), 1.85−1.74 (4H, overlapping peaks, CH$_A$*H*$_B$CCH$_2$CH$_3$, C*H*CH$_2$CH$_3$, CH$_2$CC*H*$_2$CH$_3$), 1.42−1.34 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.28−1.23 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.21 (3H, d, *J* 6.4 Hz, CH(OH)C*H*$_3$), 1.16 (3H, t, *J* 7.4 Hz, CH=CCH$_2$C*H*$_3$), 0.84 (3H, t, *J* 7.4 Hz, CHCH$_2$C*H*$_3$), 0.78 (3H, t, *J* 7.4 Hz, CH$_2$CCH$_2$C*H*$_3$), missing O*H*; δ_C (150 MHz, CD_3OD) 176.0, 153.7, 136.4, 136.1, 135.3, 91.1, 69.1, 43.3, 40.4, 32.2, 30.4, 23.8, 19.5, 12.3, 11.8, 8.0; HRMS (ESI): MNa^+, found 289.1780. $C_{16}H_{26}NaO_3^+$ requires 289.1780.

***des*-Hydroxygracilioether C (8).** LHMDS (0.35 mL, 1.0 M in THF; 0.35 mmol) was added dropwise over 30 s to a stirred solution of sulfone **13** (0.100 g, 0.40 mmol) in DMF (3.0 mL) and DMPU (1.0 mL) at −60 °C. After 120 s, a solution of **11** (0.040 g, 0.14 mmol) in DMF (0.2 mL) was added dropwise. The mixture was stirred at −60 °C for 1 h before gradually warming to room temperature and quenching with the addition of NH_4Cl (satd aq) and Et_2O. The organic phase was separated and aqueous extracted with Et_2O. The combined extracts were washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Silver-modified silica chromatography (20% EtOAc/hexane) afforded **8** (0.030 g, 69%) as a pale yellow oil: R_f (10% EtOAc/hexane) 0.40 (nonmodified silica); $[\alpha]_D^{20}$ −271 (*c* 0.35, $CHCl_3$); ν_{max} (thin film) 2966, 2935, 2877, 1713, 1687, 1625, 1460, 1434, 1376, 1272, 1159, 1087, 1039, 973, 853, 804 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 6.17 (1H, s, C*H*=CCH$_2$CH$_3$), 5.22 (1H, dt, *J* 15.3, 6.4 Hz, CH=C*H*CH$_2$CH$_3$), 5.03 (1H, dd, *J* 15.3, 8.5 Hz, C*H*=CHCH$_2$CH$_3$), 4.80 (1H, s, C*H*CO$_2$CH$_3$), 3.68 (3H, s, OC*H*$_3$), 2.18−2.08 (2H, m, CH=CC*H*$_2$CH$_3$), 1.98−1.90 (3H, m, CH=CHC*H*$_2$CH$_3$, C*H*$_A$H$_B$CCH$_2$CH$_3$), 1.86−1.80 (1H, m, CH$_2$CC*H*$_A$H$_B$CH$_3$), 1.77−1.68 (3H, overlapping peaks, CH$_2$CCH$_A$*H*$_B$CH$_3$, C*H*CH$_2$CH$_3$, CH$_A$*H*$_B$CCH$_2$CH$_3$), 1.39−1.32 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.18−1.11 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.14 (3H, t, *J* 7.3 Hz, CH=CCH$_2$C*H*$_3$), 0.94 (3H, t, *J* 7.5 Hz, CH=CHCH$_2$C*H*$_3$), 0.78−0.75 (6H, overlapping peaks, CHCH$_2$C*H*$_3$, CH$_2$CCH$_2$C*H*$_3$); δ_C (150 MHz, C_6D_6) 171.5, 166.2, 139.7, 139.5, 134.5, 131.9, 97.2, 84.7, 50.3, 43.6, 39.9, 32.5, 29.7, 25.9, 18.6, 14.2, 11.8, 11.6, 7.9; HRMS (ESI): MNa^+, found 329.2092. $C_{19}H_{30}NaO_3^+$ requires 329.2093.

***des*-Hydroxyplakilactone B (5).** Prepared from furanylidene **8** (0.006 g, 0.02 mmol) according to the general procedure for PCC oxidation of furanylidene substrates. Flash chromatography (10% EtOAc/hexane) afforded **5** as a colorless oil (0.004 g, 82%): R_f (10% EtOAc/hexane) 0.44; $[\alpha]_D^{20}$ −90 (*c* 0.30, CH_3OH); ν_{max} (thin film) 3056, 2968, 2933, 2877, 1749, 1461, 1266, 1086, 1047, 970 cm^{-1}; δ_H (600 MHz, CD_3OD) 7.03 (1H, t, *J* 1.7 Hz, C*H*=CCH$_2$CH$_3$), 5.25 (1H, dt, *J* 15.2, 6.4 Hz, CH=C*H*CH$_2$CH$_3$), 5.06 (1H, ddt, *J* 15.2, 8.8, 1.5 Hz, C*H*=CHCH$_2$CH$_3$), 2.28−2.16 (2H, m, CH=CC*H*$_2$CH$_3$), 2.02−1.97 (2H, m, CH=CHC*H*$_2$CH$_3$), 1.89 (1H, dd, *J* 14.3, 2.9 Hz, C*H*$_A$H$_B$CCH$_2$CH$_3$), 1.84−1.69 (4H, overlapping peaks, CH$_A$*H*$_B$CCH$_2$CH$_3$, C*H*CH$_2$CH$_3$, CH$_2$CC*H*$_2$CH$_3$), 1.38−1.30 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.23−1.15 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.14 (3H, t, *J* 7.5 Hz, CH=CCH$_2$C*H*$_3$), 0.97 (3H, t, *J* 7.4 Hz, CH=CHCH$_2$C*H*$_3$), 0.80 (3H, t, *J* 7.5 Hz, CHCH$_2$C*H*$_3$), 0.77 (3H, t, *J* 7.4 Hz, CH$_2$CCH$_2$C*H*$_3$); δ_C (150 MHz, CD_3OD) 176.1, 153.8, 136.0, 135.0, 134.2, 91.2, 43.5, 40.9, 32.4, 30.7, 26.6, 19.5, 14.3, 12.1, 11.8, 7.9; HRMS (ESI): MNa^+, found 273.1834. $C_{16}H_{26}NaO_2^+$ requires 273.1831.

Methyl (*Z*)-2-[(3a*R*,4*S*,5*R*,6a*R*,*E*)-5,6a-Diethyl-3-ethylidene-4-propylhexahydro-2(2*H*)-cyclopenta[*b*]furanylidene]ethanoate (16). $SnCl_4$ (0.03 mL 0.26 mmol) was added dropwise to a stirred solution of **8** (0.015 g, 0.05 mmol) in CH_2Cl_2 (5 mL) at −78 °C. Stirring continued as the mixture warmed from −78 °C to room temperature over a period of 2.5 h, before quenching with the addition of $NaHCO_3$ (satd aq). The organic phase was separated and aqueous extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10% EtOAc/hexane) afforded **16** (0.007 g, 47%) as a colorless oil: R_f (10% EtOAc/hexane) 0.32; $[\alpha]_D^{20}$ +54 (*c* 0.39, $CHCl_3$); ν_{max} (thin film) 3055, 2962, 2927, 2874, 1705, 1627, 1436, 1371, 1263 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 6.27 (1H, apparent qd, *J* 7.1, 1.5 Hz, C=C*H*CH$_3$), 5.05 (1H, s, C*H*CO$_2$CH$_3$), 3.66 (3H, s, OC*H*$_3$), 3.08 (1H, d, *J* 9.9 Hz, C*H*C=CHCH$_3$), 2.37 (1H, dd, *J* 13.6, 5.5 Hz, C*H*$_A$H$_B$CCH$_2$CH$_3$), 1.81 (3H, d, *J* 7.1 Hz, C=CHC*H*$_3$), 1.75−1.60 (5H, overlapping peaks, CHC*H*$_A$H$_B$CH$_3$, CH$_2$CC*H*$_2$CH$_3$, C*H*CH$_2$CH$_3$, C*H*CH$_2$CH$_2$CH$_3$), 1.30−1.22 (4H, overlapping peaks, CHC*H*$_A$H$_B$CH$_2$CH$_3$, CHCH$_2$C*H*$_2$CH$_3$, CH$_A$*H*$_B$CCH$_2$CH$_3$), 1.21−1.14 (1H, m, CHCH$_A$*H*$_B$CH$_2$CH$_3$), 1.11−1.04 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 0.91 (3H, t, *J* 7.5 Hz, CH$_2$CCH$_2$C*H*$_3$), 0.88 (3H, t, *J* 7.3 Hz, CHCH$_2$C*H*$_3$), 0.83 (3H, t, *J* 7.2 Hz, CHCH$_2$CH$_2$C*H*$_3$); δ_C (150 MHz, $CDCl_3$) 169.4, 167.0, 139.0, 125.6, 101.3, 81.3, 50.4, 50.1, 48.4, 45.1, 41.9, 31.9, 31.5, 26.8, 22.1, 16.3, 14.5, 12.4, 8.8; HRMS (ESI): MNa^+, found 329.2090. $C_{19}H_{30}NaO_3^+$ requires 329.2093.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01196.

Tabulated spectral comparison of the synthetic and natural compounds and copies of ^1H and ^{13}C NMR spectra for compounds **3**−**5**, **8**, **11**, **12**, **16**, the epimers of **3**, **4**, **6**, **11**, **12**, the benzoate esters of **7** and **11**-*epi*-**7**, and the natural products plakilactone B and C (provided by C. Festa and A. Zampella) (PDF)

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Notes

The authors declare no competing financial interest.

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(8) In a personal communication with the authors of ref 1b (C. Festa and A. Zampella), slight anomalies were noted with the published data (ref 1b) for natural plakilactone C. Copies of the ^{1}H NMR and ^{13}C NMR spectra and tabulated data (^{1}H NMR and ^{13}C NMR) for natural plakilactone C were provided (see the Supporting Information). The data provided for natural plakilactone C follows: δ_H (400 MHz, CD_3OD) 7.07 (1H, broad t, C*H*=CCH_2CH_3), 6.62 (1H, dd, *J* 16.0, 9.4 Hz, C*H*=CHC(O)CH_3), 5.88 (1H, d, *J* 16.0 Hz, CH=C*H*C(O)CH_3), 2.25 (3H, s, C(O)C*H*$_3$), 2.22 (2H, m, CH=CCH_2CH_3), 2.09 (1H, overlapping, C*H*$_A$H$_B$$CCH_2CH_3$), 2.08 (1H, overlapping, C*H*CH_2CH_3), 1.94 (1H, dd, *J* 14.9, 9.9 Hz, CH$_A$*H*$_B$$CCH_2CH_3$), 1.83 (2H, m, $CH_2CCH_2CH_3$), 1.50 (1H, m, CHC*H*$_A$H$_B$$CH_3$), 1.37 (1H, m CHC*H*$_A$*H*$_B$$CH_3$), 1.10 (3H, t, *J* 7.4 Hz, CH=CCH_2CH_3), 0.85 (3H, t, *J* 7.4 Hz, $CHCH_2CH_3$), 0.79 (3H, t, *J* 7.5 Hz, $CH_2CCH_2CH_3$); δ_C (100 MHz, CD_3OD) 201.1, 175.6, 154.8, 153.1, 137.0, 132.3, 90.7, 42.4, 41.1, 32.0, 29.6, 26.9, 19.5, 11.9, 11.7, 7.9. Complete spectral comparison of synthetic **3** and 6-*epi*-**3** to natural plakilactone C is shown in the Supporting Information, and on close examination, it was verified that the ^{1}H NMR and ^{13}C NMR of synthetic compound **3** match those of natural plakilactone C and that synthetic compound 6-*epi*-**3** is different.
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(12) Itsuno−Corey reduction of **3** with the enantiomeric catalysts (*R*)- and (*S*)-2-methyl-CBS-oxazaborolidine also yielded 9-*epi*-**4** and **4** with good selectivity for the desired isomer. However, in each case, we were unable to separate the remaining minor isomer. This necessitated the protecting group strategy outlined in Scheme 5.
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(22) The Lewis acid catalyzed ene reaction of compound **8** in Scheme 8 is drawn to proceed through a concerted mechanism. However, it is possible that this reaction might proceed in a stepwise manner via discrete carbocation intermediates. Furthermore, we expect that the olefin at C13 is able to isomerize under the reaction conditions, and its geometry is thus under thermodynamic control.

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