JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

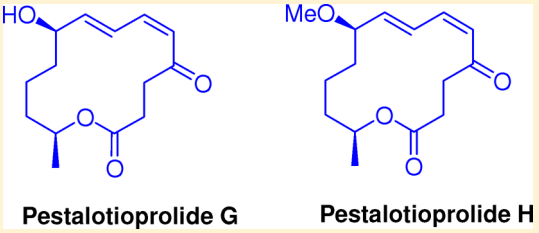
Total Synthesis of Pestalotioprolide G and Putative Structure of Pestalotioprolide H

Debobrata Paul, Sayantan Das, and Rajib Kumar Goswami*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata-700032, India

Supporting Information

ABSTRACT: A concise and convergent route for the stereoselective total synthesis of cytotoxic macrolides pestalotioprolides G and H has been developed for the first time. Intramolecular Heck coupling has been chosen to cyclize the 14-membered macrocycle. This synthetic study strongly suggests that the proposed structure of pestalotioprolide H may need to be corrected as the spectroscopic data on the synthesized molecule deviate from the values reported for the isolated natural product.



INTRODUCTION

Naturally occurring macrolides have attracted considerable interest to the scientific community due to their wide structural variations and broad range of biological activities.[1] During the search for new bioactive natural products from *Pestalotiopsis microspora*, an endophytic fungus collected from fresh fruits of the mangrove plant, *Drepanocarpus lunatus*, found in Cameroon, the research groups of Liu and Proksch, in 2016, isolated pestalotioprolides B–H (**1**–**7**; Figure 1), a series of 14-membered macrolides having diverse architectural features.[2] Many of these compounds exhibited good to moderate cytotoxic activities against mouse lymphoma (L5178Y) and human ovarian cancer (A2780) cell lines.[2] Attractive structural features, significant bioactivities, and their limited natural abundance made them promising targets for the synthesis. Shabita et al. recently developed an elegant route for the total synthesis of pestalotioprolide C, a member of this family of natural products, and its C7 epimer.[3] In continuation of our interest in the synthesis of bioactive natural products and their analogues,[4] we initially envisaged the total synthesis of pestalotioprolides G and H with the intension to obtain these materials in sufficient quantities to allow biological studies. The structures of these compounds were determined by spectroscopic analysis. Architecturally, pestalotioprolides G and H possess two stereogenic centers and a dienone with an *E*,*Z*-geometry.[2] The installation of the dienone moiety in a 14-membered macrocyclic ring is unprecedented and hence presents a formidable challenge. In this paper, we report for the first time a convergent and flexible common route for the target molecules which revealed that the proposed structure of pestalotioprolide H required structural revision.

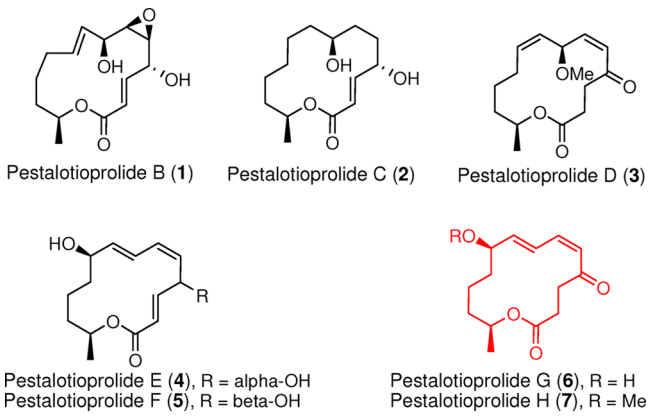
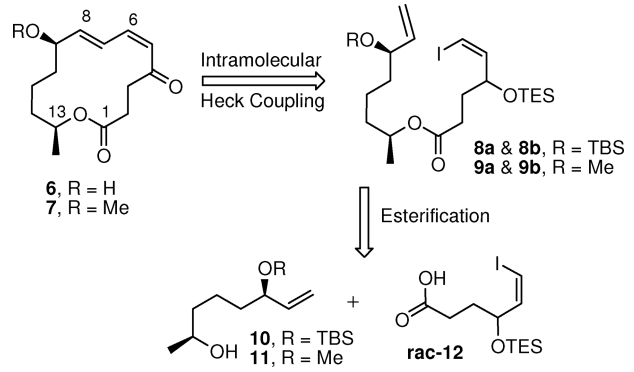


Figure 1. Structures of pestalotioprolides B–H (**1**–**7**).

RESULTS AND DISCUSSION

The retrosynthetic analysis of pestalotioprolides G (**6**) and H (**7**) is shown in Scheme 1. We planned for a metal-mediated intramolecular coupling to construct the macrocycle rather than the classical macrolactonization approach mainly for two reasons. First, the former strategy would make the synthetic

Scheme 1. Retrosynthetic Analysis of Pestalotioprolides G (6) and H (7)



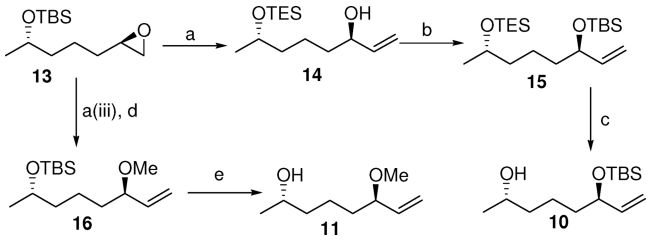
Received: May 8, 2017
Published: June 22, 2017

DOI: 10.1021/acs.joc.7b01115
J. Org. Chem. 2017, 82, 7437–7445

route more convergent compared to the latter, and second, the synthesis of the acid functionality at the C1 position (required for the latter approach) from its corresponding alcohol precursor in the presence of a sensitive diene moiety seemed to be difficult according to the literature precedent[5] and from our own experience. We became interested in exploiting the intramolecular Heck coupling for macrocylization[4c,6] rather than other metal-mediated couplings as the synthesis of the Heck coupling precursor in our case is much more convenient than that of the precursors essential for the other couplings. Furthermore, the fact that there are no reports of constructing such a 14-membered ring system using this strategy prodded us to explore this challenge. The Heck coupling would disconnect pestalotioprolides G (**6**) and H (**7**) eventually into two sets of precursors (**8a**, **8b** and **9a**, **9b**, respectively). However, this is not a severe predicament as the C4 hydroxy center would eventually be converted to a keto functionality. The esters **8a** and **8b** could be synthesized further from alcohol **10** and a mixture of acids *rac*-**12** by intermolecular esterification, whereas esters **9a** and **9b** could be constructed similarly from alcohol **11** and the same acids.

The synthesis C_7-C_{13} fragments (**10**, **11**) of pestalotioprolides G (**6**) and H (**7**) are depicted in Scheme 2. Our synthetic

Scheme 2. Synthesis of the C_7-C_{13} Fragments (10, 11) of Pestalotioprolides G and H[a]

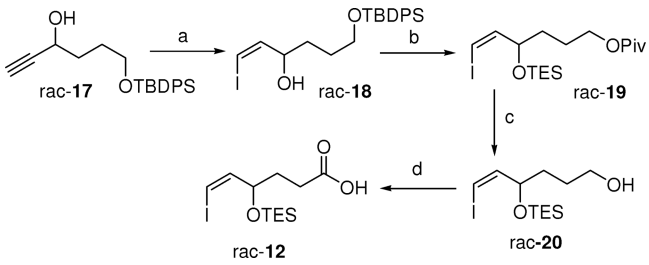


[a]Reagents and conditions: (a) (i) TBAF, THF, 0 °C to rt, 24 h; (ii) (TES)Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1 h, 92% over two step; (iii) Me_3SI, BuLi, THF, −20 °C, 1.5 h, 86%; (b) (TBS)OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 93%; (c) CSA, CH_2Cl_2/MeOH (8:1), 0 °C, 30 min, 86%; (d) MeI, NaH, THF, 0 °C, 1 h, 92%; (e) CSA, CH_2Cl_2/MeOH (4:1), 0 °C to rt, 1 h, 91%.

endeavor started from the known compound **13**, which was prepared from *S*-(−)-propylene epoxide following a literature procedure.[7] The TBS ether of compound **13** was deprotected by TBAF and subsequently protected as TES ether using (TES)Cl/Et_3N/DMAP to obtain the corresponding compound, which was then treated with Me_3SI/^{n}BuLi[4c,8] to obtain compound **14** in good overall yield (85%). The free hydroxy of compound **14** was protected as the TBS ether using (TBS)OTf/2,6-lutidine to give compound **15**, which was reacted further with CSA/CH_2Cl_2−MeOH to access the TES ether-deprotected intermediate **10** in 62% overall yield. Following the similar chemistry of compound **10**, the epoxide moiety of compound **13** was also opened, and the resultant allylic alcohol was treated with MeI/NaH to obtain compound **16**, which was finally treated with CSA/CH_2Cl_2−MeOH to provide intermediate **11** efficiently.

The synthesis of common acid intermediates (*rac*-**12**) of pestalotioprolides G (**6**) and H (**7**) is described in Scheme 3. We started our synthesis from the known mixture of intermediates *rac*-**17**,[9] which were subjected to hydroindation[10] in the presence of $InCl_3$/DIBAL-H/Et_3B followed by treatment

Scheme 3. Synthesis of Common C_1-C_6 Acid Segments (*rac*-12) for Pestalotioprolides G and H[a]



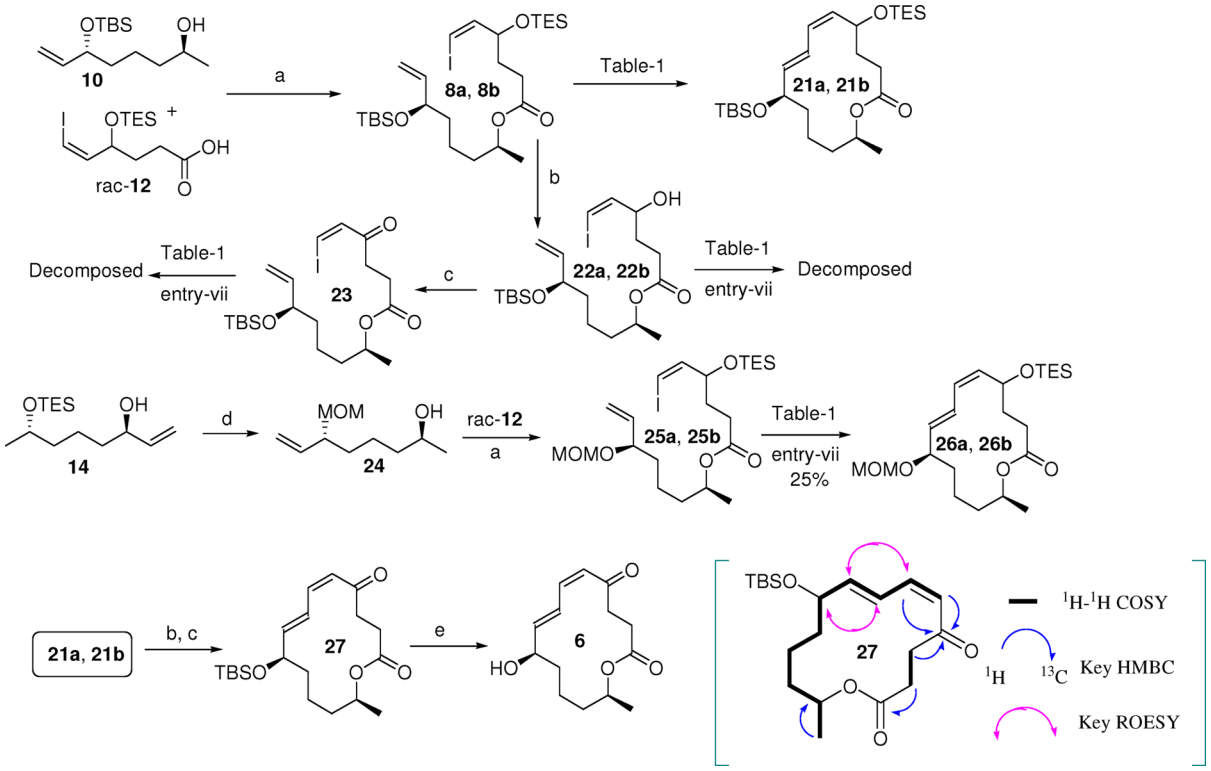
[a]Reagents and conditions: (a) $InCl_3$, DIBAL-H, Et_3B, I_2, THF, 6 h, 62%; (b) (i) TBAF, THF, 0 °C to rt, 2 h; (ii) PivCl, Et_3N, CH_2Cl_2, 0 °C to rt, 14 h; (iii) (TES)OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 72% over three steps; (c) DIBAL-H, CH_2Cl_2, −78 °C, 30 min, 90%; (d) (i) IBX, EtOAc, 80 0 °C, 3 h; (ii) $NaClO_2$, NaH_2PO_4, ^{t}BuOH/2-methyl-2-butene (2:1), 0 °C to rt, 1.5 h, quantitative over two steps.

with I_2 to result in *cis*-vinyl iodides *rac*-**18** in good yield. The TBDPS ethers of compounds *rac*-**18** were then deprotected by TBAF to obtain the corresponding alcohols, which were treated further with PivCl/Et_3N followed by (TES)OTf/2,6-lutidine to obtain compounds *rac*-**19** in 41% overall yield. The pivolyl ester units of compounds *rac*-**19** were then deprotected using DIBAL-H to yield compounds *rac*-**20**, which were subjected further to 2-iodoxybenzoic acid (IBX) oxidation[4b,11] followed by concomitant Pinnick oxidation[4c,12] to give the acids *rac*-**12** in an excellent overall yield.

The synthesis of pestalotioprolide G (**6**) is described in Scheme 4. Alcohol **10** and acids *rac*-**12** were subjected to an intermolecular esterification reaction following the Shiina protocol[13] to obtain an inseparable mixture of esters **8a** and **8b** with an overall 72% yield. The stage was set for the crucial macrocyclization using the intramolecular Heck protocol.[4c,6] A number of conditions (Table 1) have been screened to optimize the reaction conditions. In most of the cases, either the reaction did not proceed well or the starting material decomposed completely (entries i–vi). Fortunately, Pd(OAc)$_2$/Bu_4NCl/K_2CO_3 in DMF (entry vii) was the only condition which produced an inseparable mixture of compounds **21a** and **21b** with 23% overall yield. We rationalized that the steric effect experienced from the bulky allylic protecting groups might have some role in the observed yield. Thus, we evaluated if removal of any of the protection groups or functionalities or switching to other protection groups could increase the yield of the reaction. Therefore, the TES ethers of the mixture of compounds **8a** and **8b** were deprotected selectively using CSA/CH_2Cl_2−MeOH to obtain an inseparable mixture of compounds **22a** and **22b**, which were subjected further to the Heck coupling following the above condition (entry vii, Table-1). Unfortunately, the starting materials decomposed completely. This led us to plan for compound **23**, which was synthesized from the mixture of compounds **22a** and **22b** by DMP oxidation.[14] Compound **23** appeared to be a sterically less congested Heck precursor. This is because one of the allylic sp^3 centers present in both compounds **22a** and **22b** had been converted into an sp^2 center in compound **23**. Compound **23** was then subjected to Heck conditions (entry vii). However, it was quite embarrassing as compound **23** also decomposed completely, and no required product was obtained. These observations implied that the free allylic alcohol (**22a**, **22b**) or allylic keto (**23**) functionality in

DOI: 10.1021/acs.joc.7b01115
J. Org. Chem. 2017, 82, 7437−7445

Scheme 4. Synthesis of Pestalotioprolide G (6)[a]



[a]Reagents and conditions: (a) 2-methyl-6-nitrobenzoic anhydride, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 1 h, 71%; (b) CSA, CH_2Cl_2/MeOH (8:1), 0 °C, 1 h, 92%; (c) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 30 min, 66%; (d) (i) (MOM)Cl, DIPEA, CH_2Cl_2, 0 °C to rt, 3 h, 95%, (ii) CSA, CH_2Cl_2/MeOH (6:1), 0 °C to rt, 1 h, 90%; (e) CSA, CH_2Cl_2/MeOH (4:1), 0 °C to rt, 1 h, 72%.

Table 1. Optimization of Intramolecular Heck Coupling

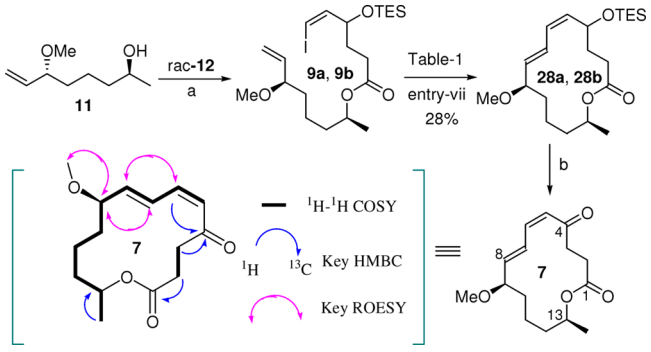
entry	reagents	temp	yield
i	$Pd(OAc)_2$, Et_3N, CH_3CN	60 °C	no reaction
ii	$PdCl_2(MeCN)_2$, Et_3N, CH_3CN	rt	decomposition
iii	$Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, CH_3CN	rt	no reaction
iv	$Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, CH_3CN	60 °C	decomposition
v	$Pd(OAc)_2$, Cs_2CO_3, Et_3N, DMF	rt	trace
vi	$Pd(OAc)_2$, Bu_4NCl, K_2CO_3, CH_3CN	60 °C	trace
vii	$Pd(OAc)_2$, Bu_4NCl, K_2CO_3, DMF	60 °C	23%

the Heck precursors might not be the right choice in these cases. Thus, we looked for other functional groups and planned to synthesize compounds **25a** and **25b** where one of the allylic silyl ethers was replaced with a relatively smaller MOM ether group. The free hydroxy group of compound **14** was protected as the MOM ether using (MOM)Cl/DIPEA, and subsequently, the TES ether was deprotected to obtain compound **24**. This was then subjected to esterification with acids *rac*-**12** to obtain an inseparable mixture of esters **25a** and **25b** in very good overall yield (70%). The mixture of esters **25a** and **25b** was finally subjected to the Heck coupling (entry vii) to yield an inseparable mixture of compounds **26a** and **26b** in 25% overall yield. At this point, the low yield in the Heck coupling step is attributed to the ring strain which is expected to develop during installation of the diene moiety in the 14-membered ring system. It was observed that the incorporation of the MOM ether group in Heck precursors **25a** and **25b** provided slightly better yields compared to those of the Heck precursors **8a** and **8b**, but we preferred to move forward with the mixture of Heck products **21a** and **21b** rather than compounds **26a** and **26b** for easier removal of the C9 protection group in the final stage of the synthesis. The mixture of compounds **21a** and **21b** was treated with CSA/MeOH to deprotect the TES ether selectively. The resultant alcohol moiety was oxidized using DMP to compound **27**, and its identity was ascertained by detailed NMR analysis (COSY, HSQC, HMBC, ROESY). Finally, compound **27** was reacted with CSA/CH_2Cl_2−MeOH to obtain compound **6** in 43% yield in three steps. The ^{1}H and ^{13}C NMR data[15] (please see the comparison Table S1 in the Supporting Information) and optical rotation [reported $[\alpha]_D^{20}$ = −177.0 (*c* 0.2, MeOH); observed $[\alpha]_D^{27}$ = −180.0 (*c* 0.05, MeOH)] of the synthesized compound **6** were in good agreement with the data reported for the isolated natural product, which unambiguously confirmed the first total synthesis of pestalotioprolide G (**6**).

The synthesis of the proposed structure of pestalotioprolide H (**7**) is illustrated in Scheme 5. Alcohol **11** was transmuted into an inseparable mixture of esters **9a** and **9b** by intermolecular esterification with acids *rac*-**12** following the similar chemistry described earlier. The mixture of esters **9a** and **9b** was then subjected to intramolecular Heck coupling following the above optimized condition (entry vii, Table 1) to yield an inseparable mixture of compounds **28a** and **28b** with an overall 28% yield. The above mixture of compounds was then treated with CSA/CH_2Cl_2−MeOH and subsequently by DMP to provide compound **7** in 58% overall yield. The ^{1}H and ^{13}C NMR spectra of compound **7** were recorded. Unfortunately, discrepancies between synthetic compound **7** and the isolated pestalotioprolide H were noted in the spectroscopic data (please see the comparison Table S2 in the Supporting Information) as well as in the optical rotation

DOI: 10.1021/acs.joc.7b01115
J. Org. Chem. 2017, 82, 7437−7445

Scheme 5. Completion of the Proposed Structure of Pestalotioprolide H (7)[a]



[a]Reagents and conditions: (a) *rac*-**12**, 2-methyl-6-nitrobenzoic anhydride, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 1 h, 71%; (b) (i) CSA, CH_2Cl_2/MeOH (8:1), 0 °C, 1 h, 90%, (ii) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 30 min, 68%.

[reported $[\alpha]_D^{20} = -38$ (*c* 0.2, MeOH); observed $[\alpha]_D^{20} = -75$ (*c* 0.08, MeOH)]. The major mismatches were observed for the protons resonating in the region of δ 2.81−2.53 ppm. We have recorded four methylene protons (C2- and C3-attached) from δ 2.81 ppm to δ 2.60 ppm, whereas three protons were reported for the isolated natural product having chemical shifts between δ 2.69 ppm and δ 2.53 ppm. These findings were in mutual disagreement. Our results were ascertained further from the reported data of pestalotioprolide G, which has a structure very similar to the proposed structure of pestalotioprolide H and possesses four methylene protons between δ 2.81 ppm and δ 2.53 ppm. Moreover, the signals of C10- and C12-attached methylene protons of the isolated natural product were well separated and had two distinct sets of chemical shifts at δ 1.73 and 1.36 ppm and δ 1.69 and 1.35 ppm, respectively, whereas all these protons in synthesized compound **7** resonated in a close proximity (δ 1.62−1.43 ppm). Apart from the minor variations, mismatches in the ^{13}C NMR spectra were also noted. The ^{13}C NMR signals of the C3, C10, C11, C12, and C14 carbons of the synthesized compound **7** were recorded at δ 39.6, 31.3, 21.3, 35.8, and 20.7 ppm, respectively, whereas these resonances were reported to be at δ 38.7, 33.2, 19.4, 34.4, and 18.9 ppm for the isolated compound. The identity of our synthesized compound **7** was confirmed further by detailed 2D NMR analysis (COSY, HSQC, HMBC, ROESY), which comprised the characteristic NMR correlations (Scheme 5).

To find the origin of the observed discrepancies, we revisited the NMR analysis of pestalotioprolide H reported by the isolation group. Careful analysis of the literature data[2] of isolated pestalotioprolide H revealed that the structure C5−C14 fragment of pestalotioprolide H was determined in correlation with the data of identical segments of pestalotioprolides E (**4**) and F (**5**), whereas the structure C1−C4 segment of this molecule was elucidated with comparison to the data of a similar moiety of pestalotioprolide D (**3**). We noticed that the correlations between the NMR data of the C1−C4 segments of pestalotioprolides H (**7**) and D (**3**) were not unambiguous. For example, the C1−C4 segment of pestalotioprolide D (**3**) had four protons resonating between δ 3.30 ppm and δ 2.39 ppm, whereas the same fragment of isolated pestalotioprolide H (**7**) showed three protons in that region. These results suggest that the proposed structure of isolated pestalotioprolide G (**7**) might not be completely accurate, and we believe, the description of the C1−C4 segment is likely to be erroneous.

CONCLUSION

In summary, we have achieved the first total synthesis of pestalotioprolide G and the reported structure of pestalotioprolide H in 10 and 7 linear steps, respectively, from the common intermediates **13** with overall yields of 4.4% and 7.6%, respectively. We have established the possibility of utilizing an intramolecular Heck coupling, for the first time, to construct a 14-membered macrocycle comprising a sensitive diene moiety with an *E*,*Z*-geometry. Our synthetic study revealed that the proposed structure of isolated pestalotioprolide H needs amendment. Efforts are currently in progress in our laboratory to synthesize the other structural isomers of the proposed structure of pestalotioprolide H to find the actual isolated structure, which will be disclosed in due course.

EXPERIMENTAL SECTION

General Experimental Procedure. All moisture-sensitive reactions were performed in oven- or flame-dried glassware with a Teflon-coated magnetic stirring bar under an argon atmosphere using dry, freshly distilled solvents, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via a gastight syringe and a stainless-steel needle. Reactions were monitored by thin-layer chromatography (TLC; silica gel 60 F254) plates with UV light, ethanolic anisaldehyde (with 1% AcOH and 3.3% concd H_2SO_4), heat, and aqueous $KMnO_4$ (with K_2CO_3 and 10% aqueous NaOH solution) as developing agents. All workup and purification procedures were carried out with reagent-grade solvents under the ambient atmosphere unless otherwise stated. Column chromatography was performed using 60−120, 100−200, and 230−400 mesh silica gel. Yields are for chromatographically and spectroscopically homogeneous materials unless otherwise stated. Optical rotations were measured only for pure compounds and not for mixtures using a sodium (589, D line) lamp and are reported as follows: $[\alpha]_D^{25}$ (*c* (mg/100 mL), solvent). IR spectra were recorded as thin films (for liquids). HRMS spectra were taken using a Quadruple-TOF (Q-TOF) micro-MS system using the electrospray ionization (ESI) technique. ^{1}H NMR spectra were recorded on 300, 400, and 500 MHz spectrometers in the appropriate solvents and calibrated using residual undeuterated solvent as an internal reference, and the chemical shifts are given on the parts per million scale. Multiplicities of the NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C and 2D NMR spectra were recorded on 75, 100, and 125 MHz spectrometers.

(3*R*,7*S*)-7-((Triethylsilyl)oxy)oct-1-en-3-ol (14). To an ice-cold solution of epoxide **13** (1.0 g, 4.1 mmol, 1 equiv) in anhydrous THF (15 mL) under argon was added TBAF (1 M solution in THF, 4.9 mL, 4.9 mmol, 1.2 equiv), and the reaction mixture was stirred further for 24 h at room temperature prior to being quenched with saturated NH_4Cl solution (5 mL). The resultant mixture was extracted with EtOAC (3 × 30 mL), washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the crude residue by column chromatography (SiO_2, 100−200 mesh, 30% EtOAc in hexane as eluent) afforded the corresponding alcohol (507 mg, 95%) as a colorless oil: R_f = 0.17 (30% EtOAc in hexane); $[\alpha]_D^{25} = -8.7$ (*c* 0.24 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.84−3.78 (m, 1H), 2.92−2.90 (m, 1H), 2.75 (t, *J* = 4.5 Hz, 1H), 2.49−2.46 (m, 1H), 1.61−1.51 (m, 6H), 1.20 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.1, 52.4, 47.2, 39.1, 32.5, 23.7, 22.47 ppm; IR (neat) ν_{max} 3336, 2924, 1428 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_7H_{14}O_2$ $[M]^+$ 130.0994, found 130.0997.

To an ice-cold solution of the above alcohol (442 mg, 3.4 mmol, 1 equiv) in anhydrous CH_2Cl_2 (10 mL) was added Et_3N (0.71 mL, 5.1 mmol, 1.5 equiv). The mixture was stirred for 5 min prior to addition of (TES)Cl (0.7 mL, 4.08 mmol, 1.2 equiv) and DMAP (21 mg, 0.17

DOI: 10.1021/acs.joc.7b01115
J. Org. Chem. 2017, 82, 7437−7445

mmol, 0.05 equiv). The reaction was continued at the same temperature for 1 h and subsequently quenched with a saturated solution of NH_4Cl (4 mL). The resultant mixture was extracted with CH_2Cl_2 (2 × 20 mL), washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude residue by flash column chromatography (SiO_2, 100−200 mesh, 1.0−1.5% EtOAc in hexane as eluent) provided the corresponding TES-protected epoxide (806 mg, 97%) as a colorless oil: R_f = 0.5 (5% EtOAc in hexane); $[\alpha]_D^{26}$ = +13.6 (*c* 0.29 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.83−3.77 (m, 1H), 2.92−2.89 (m, 1H), 2.76−2.73 (m, 1H), 2.47−2.45 (m, 1H), 1.54−1.45 (m, 6H), 1.14 (d, *J* = 6.3 Hz, 3H), 0.96 (t, *J* = 8.1 Hz, 9H), 0.58 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.5, 52.5, 47.3, 39.7, 32.7, 24.0, 22.4, 7.0, 5.2 ppm; IR (neat) ν_{max} 2924, 1459, 1377 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{28}O_2SiNa$ $[M + Na]^+$ 267.1756, found 267.1758.

To a solution of Me_3SI (1.84 g, 9.0 mmol, 3 equiv) in anhydrous THF (20 mL) at −20 °C was added dropwise ^{n}BuLi (1.6 M in hexane, 4.68 mL, 7.5 mmol, 2.5 equiv), and the resultant solution was stirred for 1 h at the same temperature. After the solution was stirred for 1 h, a solution of epoxide obtained from the above step (730 mg, 3.0 mmol, 1 equiv) in anhydrous THF (10 mL) was cannulated. The resultant cloudy suspension was stirred for another 1 h at the same temperature. After consumption of the starting material (monitored by TLC), the reaction mixture was quenched with water (8 mL). The resultant mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue by flash chromatography (8−10% EtOAc/hexanes) gave allylic alcohol **14** (659 mg, 85%) as a colorless liquid: R_f = 0.2 (5% EtOAc in hexane); $[\alpha]_D^{25}$ = +3.6 (*c* 0.37 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92−5.81 (m, 1H), 5.23 (d, *J* = 15.3 Hz, 1H), 5.10 (d, *J* = 10.5 Hz, 1H), 4.11 (m, 1H), 3.80−3.76 (m, 1H), 1.48−1.44 (m, 2H), 1.43−1.38 (m, 4H), 1.14 (d, *J* = 6.0 Hz, 3H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.59 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.4, 114.8, 73.4, 68.6, 39.8, 37.3, 23.9, 21.8, 7.0, 5.1 ppm; IR (neat) ν_{max} 3346, 2924, 1462, 1377 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{30}O_2SiNa$ $[M + Na]^+$ 281.1913, found 281.1914.

(5*R*,9*S*)-11,11-Diethyl-2,2,3,3,9-pentamethyl-5-vinyl-4,10-dioxa-3,11-disilatridecane (15). To an ice-cold solution of allylic alcohol **14** (323 mg, 1.25 mmol, 1 equiv) in anhydrous CH_2Cl_2 (6 mL) was added 2,6-lutidine (0.29 mL, 2.5 mmol, 2 equiv), and the mixture was stirred for 5 min prior to addition of (TBS)OTf (0.43 mL, 1.87 mmol, 1.5 equiv). The reaction was continued at the same temperature for 30 min and subsequently quenched with a saturated solution of $NaHCO_3$ (3 mL). The resultant mixture was extracted with CH_2Cl_2 (2 × 20 mL), washed with aqueous $CuSO_4$, water, and brine, dried with Na_2SO_4, and concentrated in vacuo. Purification of the crude residue by flash column chromatography (SiO_2, 100−200 mesh, 1.0−1.5% EtOAc in hexane as eluent) provided compound **15** (433 g, 93%) as a light yellow oil: R_f = 0.85 (5% EtOAc in hexane); $[\alpha]_D^{26}$ = −2.3 (*c* 0.82 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.84−5.73 (m, 1H), 5.12 (td, *J* = 1.5, 17.4 Hz, 1H), 5.01 (td, *J* = 1.2, 10.8 Hz, 1H), 4.07 (q, *J* = 6.3 Hz, 1H), 3.80−3.74 (m, 1H), 1.50−1.32 (m, 6H), 1.13 (d, *J* = 6.6 Hz, 3H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.89 (s, 9H), 0.59 (q, *J* = 7.8 Hz, 6H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.0, 113.6, 74.1, 68.7, 40.0, 38.4, 26.0, 24.0, 21.8, 18.4, 7.0, 5.1, −4.2, −4.7 ppm; IR (neat) ν_{max} 2927, 2857, 1461, 1005 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{44}O_2Si_2Na$ $[M + Na]^+$ 395.2778, found 395.2779.

(2*S*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)oct-7-en-2-ol (10). To an ice-cold solution of compound **15** (419 mg, 1.2 mmol, 1.0 equiv) in CH_2Cl_2−MeOH (8:1, 7 mL) was added CSA (catalytic). The reaction was continued for 1 h at the same temperature and subsequently quenched with Et_3N (0.1 mL). The resultant mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 100−200 mesh, 15−20% EtOAc in hexane as eluent) to obtain compound **10** (267 mg, 86%) as a colorless oil: R_f = 0.15 (10% EtOAc in hexane); $[\alpha]_D^{27}$ = +3.9 (*c* 0.94 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.85−5.73 (m, 1H), 5.13 (td, *J* = 1.5, 17.1 Hz, 1H), 5.02 (td, *J* = 1.5, 10.2 Hz, 1H), 4.09 (q, *J* = 5.7 Hz, 1H), 3.81−3.76 (m, 1H), 1.53−1.39 (m, 6H), 1.18 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.8, 113.8, 73.9, 68.2, 39.5, 38.1, 26.0, 23.6, 21.5, 18.4, −4.2, −4.7 ppm; IR (neat) ν_{max} 3344, 2928, 2857, 1252 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{30}O_2SiNa$ $[M + Na]^+$ 281.1913, found 281.1914.

***tert*-Butyl(((2*S*,6*R*)-6-methoxyoct-7-en-2-yl)oxy)-dimethylsilane (16).** Following the same experimental procedure as described for the preparation of compound **14**, compound **13** (270 mg, 1.1 mmol, 1.0 equiv) dissolved in anhydrous THF (15 mL) was treated with Me_3SI (729 mg, 3.3 mmol, 3 equiv) and ^{n}BuLi (1.6 M in hexane, 1.7 mL, 2.7 mmol, 2.5 equiv) to yield the corresponding allylic alcohol (247 mg, 87%, purification SiO_2, 100−200 mesh, 7% EtOAc in hexane as eluent) as a colorless liquid: R_f = 0.2 (5% EtOAc in hexane); $[\alpha]_D^{27}$ = +11.3 (*c* 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92−5.81 (m, 1H), 5.23 (td, *J* = 15.9, 1.5 Hz, 1H), 5.10 (d, *J* = 10.2 Hz, 1H), 4.10 (m, 1H), 3.79−3.75 (m, 1H), 1.47−1.38 (m, 6H), 1.12 (d, *J* = 6.3 Hz, 3H), 0.088 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.4, 114.8, 73.5, 68.7, 39.7, 37.2, 26.1, 23.9, 21.8, 18.3, −4.2, −4.5 ppm; IR (neat) ν_{max} 3345, 2924, 1462, 1376 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{30}O_2SiNa$ $[M + Na]^+$ 281.1913, found 281.1912.

To a stirred solution of the above allylic alcohol (142 mg, 0.55 mmol, 1.0 equiv) in anhydrous THF (5 mL) at 0 °C were added MeI (0.1 mL, 1.65 mmol, 3 equiv) and NaH (60% in mineral oil, 33 mg, 0.83 mmol, 1.5 equiv). The mixture was stirred at room temperature for 30 min, diluted with NH_4Cl (2 mL), and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried ($NaSO_4$), and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 100−200 mesh, 2% EtOAc in hexane eluent) to afford compound **16** (139 mg, 92%) as a colorless oil: R_f = 0.57 (20% EtOAc in hexane); $[\alpha]_D^{27}$ = +11.3 (*c* 0.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70−5.58 (m, 1H), 5.21−5.13 (m, 2H), 3.80−3.74 (m, 1H), 3.53−3.46 (m, 1H), 3.27 (s, 3H), 1.63−1.58 (m, 1H),1.53−1.35 (m, 5H), 1.11 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 117.1, 83.2, 68.8, 56.3, 39.8, 35.5, 26.1, 23.9, 21.7, 18.3, −4.25, −4.6 ppm; IR (neat) ν_{max} 2924, 1462, 1376 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{32}O_2SiNa$ $[M + Na]^+$ 295.2069, found. 295.2068.

(2*S*,6*R*)-6-Methoxyoct-7-en-2-ol (11). To an ice-cold solution of compound **16** (129 mg, 0.47 mmol, 1.0 equiv) in CH_2Cl_2−MeOH (4:1, 5 mL) under argon was added CSA (5 mg, 0.025 mmol, 0.05 equiv). The reaction was continued for 1 h at room temperature and subsequently quenched with Et_3N (0.1 mL). The resultant mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 100−200 mesh, 20−25% EtOAc in hexane as eluent) to obtain compound **11** (68 mg, 91%) as a colorless oil: R_f = 0.2 (15% EtOAc in hexane); $[\alpha]_D^{28}$ = −8.9 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70−5.59 (m, 1H), 5.21−5.15 (m, 2H), 3.84−3.74 (m, 1H), 3.54−3.48 (m, 1H), 3.27 (s, 3H), 1.62−1.58 (m, 1H), 1.56−1.42 (m, 5H), 1.18 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.9, 117.3, 83.1, 68.2, 56.3, 39.3, 35.4, 23.6, 21.6 ppm; IR (neat) ν_{max} 3370, 2928, 1093 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_9H_{18}O_2Na$ $[M + Na]^+$ 181.1204, found. 181.1203.

(*R*/*S*,*Z*)-6-((*tert*-Butyldiphenylsilyl)oxy)-1-iodohex-1-en-3-ol (*rac*-18). To a stirred suspension of anhydrous $InCl_3$ (566 mg, 2.56 mmol, 1.3 equiv) in anhydrous THF (20 mL) at −78 °C was added dropwise DIBAL-H (1.0 M hexane solution, 2.6 mL, 2.6 mmol, 1.3 equiv). After stirring was continued for 30 min at −78 °C, a solution of a mixture of alkynes *rac*-**17** (694 mg, 1.97 mmol, 1.0 equiv) in anhydrous THF (5 mL) and Et_3B (1 M hexane solution, 0.4 mL, 0.39 mmol, 0.2 equiv) were added to the reaction mixture. The suspension was stirred further for 2.5 h at the same temperature. I_2 (1.5 g, 5.9 mmol, 3 equiv) dissolved in anhydrous THF (6 mL) was then added to the reaction mixture, and the mixture was stirred further for 30 min at the same temperature. The reaction mixture was poured into a mixture of saturated $NaHCO_3$ and $Na_2S_2O_3$ solution (15 mL, 1:1). The resultant mixture was extracted with EtOAc (2 × 50 mL), and the combined extracts were washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, 100−200 mesh, 5−7% EtOAc in hexane as eluent) to give a mixture of vinyl iodides *rac*-**18** (587 mg,

DOI: 10.1021/acs.joc.7b01115
J. Org. Chem. 2017, 82, 7437−7445

62%) as a colorless oil: R_f = 0.5 (10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70−7.67 (m, 4H), 7.44−7.37 (m, 6H), 6.34−6.26 (m, 2H), 4.44−4.43 (m, 1H), 3.74−3.70 (m, 2H), 1.76−1.66 (m, 4H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.6, 135.7, 135.7, 133.7, 129.8, 127.8, 82.2, 74.5, 64.1, 33.2, 28.4, 27.0, 19.3 ppm; IR (neat) ν_{max} 3307, 2929, 2856, 1106 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{29}IO_2Si$ [M + Na]$^+$ 503.0879, found 503.0877.

(*R*/*S*,*Z*)-6-Iodo-4-((triethylsilyl)oxy)hex-5-en-1-yl Pivalate (*rac*-19). To an ice-cold solution of a mixture of compounds *rac*-**18** (3.92 g, 8.16 mmol, 1 equiv) in anhydrous THF (20 mL) under argon was added TBAF (17.93 mL, 17.93 mmol, 1 M solution in THF, 2.2 equiv). The reaction mixture was stirred for 4 h at room temperature prior to being quenched with a saturated NH_4Cl solution (5 mL). The mixture was extracted with EtOAc (3 × 50 mL), washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude residue by flash column chromatography (SiO_2, 60−120 mesh, 50% EtOAc in hexane as eluent) afforded the TBDPS-deprotected corresponding diol (1.74 g, 88%) as a colorless oil: R_f = 0.2 (40% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.34−6.26 (m, 2H), 4.42 (q, J = 6.3 Hz, 1H), 3.74−3.65 (m, 2H), 1.74−1.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.4, 82.3, 74.5, 62.9, 33.1, 28.6 ppm; IR (neat) ν_{max} 3306, 2960, 1471 cm^{-1}; HRMS (ESI) m/z calcd for $C_6H_{11}IO_2Na$ [M + Na]$^+$ 264.9701, found 264.9704.

To a stirred solution of the above diol (1.72 g, 7.11 mmol, 1 equiv) in anhydrous CH_2Cl_2 (21 mL) at 0 °C was added Et_3N (2.48 mL, 17.78 mmol, 2.5 equiv) followed by PivCl (0.92 mL, 7.47 mmol, 1.05 equiv). The mixture was stirred at room temperature for 12 h. After completion of the reaction, the mixture was quenched with a saturated aqueous solution of NH_4Cl (5 mL). The resultant mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give the crude material, which was purified by column chromatography (SiO_2, 100−200 mesh, 12% EtOAc in hexane as eluent) to provide the corresponding pivaloyl ester (2.1 g, 90%) as a colorless oil: R_f = 0.6 (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.36 (dd, J = 7.5, 0.6 Hz, 1H), 6.29−6.24 (t, J = 7.2 Hz, 1H), 4.47−4.39 (m, 1H), 4.13−4.06 (m, 2H), 1.83−1.73 (m, 2H), 1.71−1.60 (m, 2H), 1.20 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.7, 143.2, 82.8, 74.2, 64.2, 38.9, 32.3, 27.4, 24.6 ppm; IR (neat) ν_{max} 3439, 2969, 1726, 1286, 1161 cm-1; HRMS (ESI) m/z calcd for $C_{11}H_{19}IO_3Na$ [M + Na]$^+$ 349.0277, found 349.0279.

To an ice-cold solution of the above pivaloyl ester (1.72 g, 5.12 mmol, 1 equiv) in anhydrous CH_2Cl_2 (15 mL) under argon was added 2,6-lutidine (1.2 mL, 10.24 mmol, 2 equiv), and the reaction mixture was stirred for 5 min prior to addition of (TES)OTf (1.74 mL, 7.68 mmol, 1.5 equiv). The reaction was continued at the same temperature for 30 min and subsequently quenched with a saturated solution of $NaHCO_3$ (6 mL). The resultant mixture was extracted with CH_2Cl_2 (2 × 30 mL), washed with aqueous $CuSO_4$, water, and brine, dried with Na_2SO_4, and concentrated in vacuo. Purification of the crude residue by flash column chromatography (SiO_2, 100−200 mesh, 1.0−1.5% EtOAc in hexane as eluent) provided esters *rac*-**19** (2.05 g, 91%) as a colorless oil: R_f = 0.9 (20%EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22−6.21 (m, 2H), 4.40−4.34 (m, 1H), 4.10−4.06 (m, 2H), 1.79−1.70 (m, 2H), 1.68−1.60 (m, 2H), 1.20 (s, 9H), 0.95 (t, J = 7.8 Hz, 9H), 0.61 (q, J = 7.5 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.7, 144.3, 80.4, 74.9, 64.3, 38.9, 33.4, 27.4, 24.5, 6.9, 5.0 ppm; IR (neat) ν_{max} 2969, 1726, 1281 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{33}IO_3SiNa$ [M + Na]$^+$ 463.1141, found 463.1143.

(*R*/*S*,*Z*)-6-Iodo-4-((triethylsilyl)oxy)hex-5-en-1-ol (*rac*-20). To a cold solution (−78 °C) of the above esters *rac*-**19** (2.02 g, 4.58 mmol, 1 equiv) in anhydrous CH_2Cl_2 (20 mL) under argon was slowly added DIBAL-H (25% in toluene, 8.18 mL, 2.5 equiv), and the reaction was continued for 30 min at the same temperature before being quenched with MeOH (5 mL). A saturated solution of sodium potassium tartrate (15 mL) was added, and the mixture was warmed to room temperature. After 2 h of vigorous stirring, the resultant mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude residue by flash column chromatography (SiO_2, 100−200 mesh, 20% EtOAc in hexane as eluent) afforded alcohols *rac*-**20** (1.47 g, 90%) as a colorless liquid: R_f = 0.58 (20% EtOAc in hexane); ^{1}H NMR (CDCl3, 300 MHz) δ 6.28−6.21 (m, 2H), 4.46−4.39 (m, 1H), 3.68−3.64 (m, 2H), 1.97 (t, J = 5.4 Hz, 1H), 1.80−1.77 (m, 1H), 1.70−1.59 (m, 3H), 0.098 (t, J = 8.1 Hz, 9H), 0.62 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.7, 80.4, 75.3, 63.1, 33.6, 28.4, 6.9, 5.0, ppm; IR (neat) ν_{max} 3439, 2969, 1480, 1286 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{25}IO_2SiNa$ [M + Na]$^+$ 379.0566, found 379.0564.

(*R*/*S*,*Z*)-6-Iodo-4-((triethylsilyl)oxy)hex-5-enoic Acid (*rac*-12). To a stirred solution of alcohols *rac*-**20** (741 mg, 2.08 mmol, 1.0 equiv) dissolved in distilled EtOAc (12 mL) was added IBX (933 mg, 3.3 mmol, 1.6 equiv), and the reation mixture was refluxed (80 °C) for 3 h. The reaction mixture was then cooled to room temperature, filtered through a Celite pad, washed with EtOAc (3 × 10 mL), and concentrated in vacuo. The mixture of the corresponding crude aldehydes (R_f = 0.62, 10% EtOAc in hexane) was used for the next reaction without further purification and characterizations.

To a stirred solution of the above aldehydes in ^{t}BuOH−2-methyl-2-butene (2:1, 10 mL) at room temperature was added a freshly prepared mixture of an aqueous solution of $NaClO_2$ (564 mg, 6.24 mmol, 3.0 equiv) and $NaH_2PO_4{\cdot}2H_2O$ (974 mg, 6.24 mmol, 3.0 equiv). The reaction was continued for 3 h at room temperature prior to extraction with EtOAc (3 × 30 mL). The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude acids *rac*-**12** (R_f = 0.28, 10% EtOAc in hexane) were used for the next reaction without further characterizations.

(*R*/*S*,*Z*)-(2*S*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)oct-7-en-2-yl 6-Iodo-4-((triethylsilyl)oxy)hex-5-enoate (8a and 8b). To a stirred solution of the above acids *rac*-**12** (378 mg, 1.02 mmol, 1.1 equiv) and alcohol **10** (240 mg, 0.93 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under an argon atmosphere were sequentially added DMAP (5.7 mg, 0.05 mmol, 0.05 equiv), MNBA (351 mg, 1.02 mmol, 1.1 equiv), and Et_3N (0.8 mL, 5.6 mmol, 6 equiv). Stirring was continued at room temperature for 2 h. The reaction mixture was then diluted with water (3 mL) and extracted with EtOAc (2 × 30 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 100−200 mesh, 1.5% EtOAc in hexane as eluent) to obtain the mixture of esters **8a** and **8b** (409 mg, 72%) as a colorless oil: R_f = 0.77, 10% EtOAc in hexane; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.26−6.16 (m, 2H), 5.83−5.72 (m, 1H), 5.12 (d, J = 17.1 Hz, 1H), 5.01 (d, J = 10.2 Hz, 1H), 4.90 (q, J = 6.3 Hz, 1H), 4.40 (q, J = 6.4 Hz, 1H), 4.10−4.04 (m, 1H), 2.39−2.34 (m, 2H), 1.82 (q, J = 7.3 Hz, 2H), 1.61−1.55 (m, 2H), 1.49−1.44 (m, 2H), 1.38−1.34 (m, 2H), 1.20 (d, J = 6 Hz, 3H), 0.95 (t, J = 7.8 Hz, 9H), 0.89 (s, 9H), 0.66−0.57 (m, 6H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1, 143.9, 141.8, 113.8, 80.8, 74.4, 73.8, 71.1, 37.9, 36.0, 32.0, 30.2, 26.0, 21.1, 20.1, 18.4, 6.9, 5.0, −4.2, −4.7 ppm; IR (neat) ν_{max} 2953, 1730, 1078 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{52}IO_4Si_2$ [M + H]$^+$ 611.2449, found 611.2446.

(5*R*,6*Z*,8*E*,10*R*,14*S*)-10-((*tert*-Butyldimethylsilyl)oxy)-14-methyl-5-((triethylsilyl)oxy)oxacyclotetradeca-6,8-dien-2-one (21a and 21b). To a solution of compounds **8a** and **8b** (30 mg, 0.05 mmol, 1.0 equiv) in anhydrous and degassed DMF (15 mL, final concentration of substrate ~3.3 × 10^{-3} M) were added $Pd(OAc)_2$ (2 mg, 0.009 mmol, 0.15 equiv), Bu_4NCl (69 mg, 0.25 mmol, 5.0 equiv), and K_2CO_3 (130 mg, 0.5 mmol, 10.0 equiv) were added under an argon atmosphere. The reaction mixture was stirred for 1 h at 60 °C. The mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was concentrated under vacuum and purified by column chromatography (SiO_2, 230−400 mesh, 1% EtOAc in hexane as eluent) to give the mixture of compounds **21a** and **21b** (5.5 mg, 23%) as a colorless oil: R_f = 0.6, 10% EtOAc in hexane; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.47 (dd, J = 15.3, 9.6 Hz, 1H), 6.02 (t, J = 10.5 Hz, 1H), 5.55 (dd, J = 15.6, 4.2 Hz, 1H), 5.35 (t, J = 10.5 Hz, 1H), 4.85 (q, J = 6.9 Hz, 2H), 4.43−4.42 (m, 1H), 2.49−2.40 (m, 1H), 2.33−2.24 (m, 1H), 1.95−1.80 (m, 2H), 1.75−1.61 (m, 4H), 1.55−1.47 (m, 2H), 1.26−1.24 (m, 3H), 0.98−0.87 (m, 18H), 0.60 (q, J = 7.8 Hz, 6H), 0.06−0.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ

DOI: 10.1021/acs.joc.7b01115
J. Org. Chem. 2017, 82, 7437−7445

173.5, 135.9, 134.4, 127.9, 125.5, 71.6, 71.3, 68.6, 35.9, 34.7, 33.7, 31.6, 30.9, 30.4, 26.0, 20.6, 19.8, 18.4, 7.0, 5.0, −4.7, −4.8 ppm; IR (neat) ν_{max} 2924, 1732, 1462, 1376 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{50}O_4Si_2Na$ $[M + Na]^+$ 505.3145, found. 505.3144.

(*R*/*S*,*Z*)-(2*S*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)oct-7-en-2-yl 4-Hydroxy-6-iodohex-5-enoate (22a and 22b). To an ice-cold solution of the mixture of compounds **8a** and **8b** (43 mg, 0.07 mmol, 1.0 equiv) in CH_2Cl_2−MeOH (8:1, 3 mL) was added CSA (catalytic). The reaction was continued for 1 h at room temperature and subsequently quenched with Et_3N (0.1 mL). The resultant mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 100−200 mesh, 15−20% EtOAc in hexane as eluent) to obtain the mixture of compounds **22a** and **22b** (32 mg, 91%) as a colorless oil: R_f = 0.4 (20% EtOAc in hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.36 (d, *J* = 7.8 Hz, 1H), 6.27 (t, *J* = 7.5 Hz, 1H), 5.83−5.72 (m, 1H), 5.13 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.5 Hz, 1H), 4.92 (q, *J* = 6.2 Hz, 1H), 4.44 (m, 1H), 4.08 (q, *J* = 5.7 Hz, 1H), 2.45 (t, *J* = 7.4 Hz, 2H), 1.93−1.86 (m, 2H), 1.62−1.60 (m, 2H), 1.51−1.45 (m, 2H), 1.39−1.35 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5, 143.1, 141.8, 128.3, 127.8, 113.9, 82.7, 74.0, 73.8, 71.4, 37.9, 36.0, 30.9, 30.7, 26.0, 21.1, 20.0, 18.4, −4.2, −4.7 ppm; IR (neat) ν_{max} 3432, 2924,1730, 1094 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{37}IO4SiNa$ $[M + Na]^+$ 519.1403, found 519.1403.

(*Z*)-(2*S*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)oct-7-en-2-yl 6-Iodo-4-oxohex-5-enoate (23). To an ice-cold solution of the mixture of alcohols **22a** and **22b** (20 mg, 0.04 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (3 mL) under an argon atmosphere were added DMP (34 mg, 0.08 mmol, 2.0 equiv) and Na_2CO_3 (10 mg, 0.12 mmol, 3.0 equiv). The reaction was stirred for 45 min prior to being quenched with a mixture of saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 2 mL). The resultant mixture was stirred vigorously for 2 h and extracted with EtOAc (2 × 15 mL), washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude residue by flash column chromatography (SiO_2, 230−400 mesh, 10% EtOAc in hexane eluent) afforded compound **23** (13 mg, 67%) as a colorless liquid: R_f = 0.5, 20% EtOAc in hexane; $[\alpha]_D^{25}$ = −12 (*c* 0.5 $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.27 (m, 2H), 5.84−5.72 (m, 1H), 5.13 (td, *J* = 17.1, 1.5 Hz, 1H), 5.02 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.90 (q, *J* = 6.3 Hz, 1H), 4.08 (q, *J* = 6.3 Hz, 1H), 2.94−2.84 (m, 2H), 2.64 (t, *J* = 6.3 Hz, 2H), 1.64−1.59 (m, 1H), 1.55−1.45 (m, 3H), 1.38−1.25 (m, 2H), 1.20 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.0, 172.2, 141.8, 135.1, 113.8, 91.3, 73.7, 71.6, 39.0, 37.9, 36.0, 28.3, 26.0, 21.1, 20.0, 18.4, −4.2, −4.7 ppm; IR (neat) ν_{max} 2923, 1724, 1081 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{35}IO_4SiNa$ $[M + Na]^+$ 517.1247, found 517.1244.

(2*S*,6*R*)-6-(Methoxymethoxy)oct-7-en-2-ol (24). To a stirred solution of compound **14** (77 mg, 0.3 mmol, 1.0 equiv) and DIPEA (0.08 mL, 0.45 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (3 mL) under argon at 0 °C was added (MOM)Cl (0.03 mL, 0.36 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 5 h and then quenched with water (1 mL). The resultant mixture was extracted with EtOAc (15 mL). The extract was washed successively with saturated aqueous $NaHCO_3$, water, and brine, dried, and concentrated. Purification of the crude residue by flash column chromatography (SiO_2, 100−200 mesh, 1−2% EtOAc in hexane eluent) afforded the corresponding MOM ether (86 mg, 95%) as a colorless liquid (R_f = 0.6, 5% EtOAc in hexane); $[\alpha]_D^{24}$ = +56.1 (*c* 1.5 $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.72−5.60 (m, 1H), 5.21−5.16 (m, 2H), 4.70 (d, *J* = 6.6 Hz, 1H), 4.53 (d, *J* = 6.9 Hz, 1H), 4.00−3.93 (m, 1H), 3.81−3.75 (m, 1H), 3.37 (s, 3H), 1.50−1.37 (m, 6H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.58 (q, *J* = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6, 117.3, 93.8, 68.6, 55.5, 39.8, 35.7, 24.0, 22.0, 7.0, 5.1 ppm; IR (neat) ν_{max} 2929, 1415, 1098 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{34}O_3SiNa$ $[M + Na]^+$ 325.2175, found 325.2177.

To an ice-cold solution of the above MOM ether (75 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2−MeOH (8:1, 3 mL) was added CSA (catalytic). The reaction was continued for 1 h at room temperature and subsequently quenched with Et_3N (0.2 mL). The resultant mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 100−200 mesh, 15−20% EtOAc in hexane as eluent) to obtain compound **24** (42 mg, 90%) as a colorless oil: R_f = 0.15, 10% EtOAc in hexane; $[\alpha]_D^{23}$ = +81.3 (*c* 0.59 $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.72−5.60 (m, 1H), 5.22−5.16 (m, 2H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.53 (d, *J* = 6.3 Hz, 1H), 4.01−3.95 (m, 1H), 3.82−3.76 (m, 1H), 3.36 (s, 3H), 1.66−1.61 (m, 1H), 1.53−1.42 (m, 5H), 1.18 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 117.4, 93.9, 77.5, 68.1, 55.6, 39.3, 35.4, 23.6, 21.7, ppm; IR (neat) ν_{max} 3424, 2927, 1152, 1097 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{10}H_{20}O_3Na$ $[M + Na]^+$ 211.1310, found 211.1311.

(*R*/*S*,*Z*)-(2*S*,6*R*)-6-(Methoxymethoxy)oct-7-en-2-yl 6-Iodo-4-((triethylsilyl)oxy)hex-5-enoate (25a and 25b). Following the same experimental procedure as described for the preparation of compounds **8a** and **8b**, compound **24** (35 mg, 0.19 mmol, 1.0 equiv) dissolved in CH_2Cl_2 (5 mL) was treated with acids *rac*-**12** (78 mg, 0.21 mmol, 1.1 equiv), MNBA (72 mg, 0.21 mmol, 1.1 equiv), Et_3N (0.19 mL, 1.37 mmol, 6 equiv), and DMAP (1.2 mg, 0.009 mmol, 0.05 equiv) to yield the mixture of compounds **25a** and **25b** (72 mg, 70%, purification with SiO_2, 100−200 mesh, 2% EtOAc in hexane as an eluent) as a colorless liquid: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.26−6.16 (m, 2H), 5.71−5.60 (m, 1H), 5.22−5.16 (m, 2H), 4.91 (q, *J* = 5.8 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.52 (d, *J* = 6.8 Hz, 1H), 4.40 (q, *J* = 6.6 Hz, 1H), 4.00−3.94 (m, 1H), 3.37 (s, 3H), 2.39−2.34 (m, 2H), 1.85−1.78 (m, 2H), 1.66−1.60 (m, 2H), 1.52−1.37 (m, 4H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.61 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1, 143.9, 138.4, 117.4, 93.9, 80.8, 77.3, 74.5, 71.1, 55.6, 35.9, 35.3, 32.0, 30.2, 21.4, 20.1, 6.9, 5.0 ppm; IR (neat) ν_{max} 2952, 2877, 1731, 1092 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{41}IO_5SiNa$ $[M + Na]^+$ 563.1666, found. 563.1669.

(5*R*/*S*,6*Z*,8*E*,10*R*,14*S*)-10-(Methoxymethoxy)-14-methyl-5-((triethylsilyl)oxy)oxacyclotetradeca-6,8-dien-2-one (26a and 26b). Following the same experimental procedure as described for the preparation of compounds **21a** and **21b**, the mixture of compounds **25a** and **25b** (13 mg, 0.024 mmol, 1.0 equiv) dissolved in DMF (8 mL, final concentration of substrate ~3.0×10^{-3} M) was treated with $Pd(OAc)_2$ (1.0 mg, 3.6 μmol, 0.15 equiv), Bu_4NCl (34.2 mg, 0.12 mmol, 5 equiv), and K_2CO_3 (34.5 mg, 0.24 mmol, 10.0 equiv) under an argon atmosphere to yield the mixture of compounds **26a** and **26b** (2.5 mg, 25%, purification with SiO_2, 100−200 mesh, 2% EtOAc in hexane as eluent) as a colorless liquid: R_f = 0.72, 5% EtOAc in hexane; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.49 (dd, *J* = 15.9, 9.6 Hz, 1H), 6.03 (t, *J* = 10.5 Hz, 1H), 5.56 (dd, *J* = 15.9, 5.1 Hz, 1H), 5.39 (dd, *J* = 10.8, 8.7 Hz, 1H), 4.93−4.83 (m, 2H), 4.68−4.61 (m, 2H), 4.26−4.24 (m, 1H), 3.37 (s, 3H), 2.51−2.42 (m, 1H), 2.31−2.22 (m, 1H), 1.91−1.80 (m, 2H), 1.74−1.66 (m, 3H), 1.46−1.38 (m, 2H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.19−1.13 (m, 1H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.61 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6, 135.1, 132.5, 127.7, 127.4, 94.7, 75.2, 71.3, 68.7, 55.5, 35.7, 33.6, 32.4, 30.8, 20.5, 20.3, 7.0, 5.0 ppm; IR (neat) ν_{max} 2952, 1729, 1152, 1040 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{40}O_5SiNa$ $[M + Na]^+$ 435.2543, found. 435.2544.

(6*Z*,8*E*,10*R*,14*S*)-10-((*tert*-Butyldimethylsilyl)oxy)-14-methyloxacyclotetradeca-6,8-diene-2,5-dione (27). To an ice-cold solution of compounds **21a** and **21b** (8.3 mg, 17.2 μmol, 1.0 equiv) in CH_2Cl_2−MeOH (8:1, 2 mL) was added CSA (catalytic). The reaction was continued for 1 h at 0 °C and subsequently quenched with Et_3N (0.1 mL). The resultant mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 100−200 mesh, 10% EtOAc in hexane as eluent) to obtain the corresponding mixture of alcohols (5.8 mg, 92%) as a colorless oil: R_f = 0.1, 5% EtOAc in hexane; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.59 (dd, *J* = 15.6, 9.6 Hz, 1H), 6.12 (t, *J* = 10.4 Hz, 1H), 5.49 (dd, *J* = 15.9, 5.7 Hz, 1H), 5.26 (dd, *J* = 11.6, 7.2 Hz, 1H), 5.04−4.94 (m, 1H), 4.97−4.77 (m, 1H), 4.33−4.30 (m, 1H), 2.56 (ddd, *J* = 17.1, 11.1, 2.1 Hz, 1H), 2.38 (ddd, *J* = 17.1, 7.5, 2.1 Hz, 1H), 2.09−1.98 (m, 1H), 1.85−1.75 (m, 1H), 1.67−1.60 (m, 2H), 1.53−1.33 (m, 3H), 1.31−1.25 (m, 1H), 1.23 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.9, 137.5, 131.6, 130.3, 125.9, 72.2, 71.1, 70.0, 35.3, 34.5, 31.2, 30.3, 26.0, 19.9, 18.7, 18.4, −4.5, −4.7 ppm; IR (neat)

DOI: 10.1021/acs.joc.7b01115
J. Org. Chem. 2017, 82, 7437−7445

ν_{max} 2925, 1721, 1280 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{36}O_4Si$ $[M + Na]^+$ 391.2281, found 391.2283.

To an ice-cold solution of the above mixture of alcohols (4.8 mg, 13.6 μmol, 1.0 equiv) in anhydrous CH_2Cl_2 (2 mL) under an argon atmosphere were added DMP (11.0 mg, 26.0 μmol, 2.0 equiv) and $NaHCO_3$ (2.9 mg, 39.0 μmol, 3.0 equiv). The reaction mixture was stirred for 45 min prior to being quenched with a mixture of a saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 1 mL). The resultant mixture was stirred vigorously for 2 h, extracted with EtOAc (2 × 15 mL), washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude residue by flash column chromatography (SiO_2, 230−400 mesh, 10% EtOAc in hexane eluent) afforded pure compound **27** (3.1 mg, 65%) as a colorless liquid: R_f = 0.6, 20% EtOAc in hexane); $[\alpha]_D^{23}$ = −3.9 (c 0.19 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.63 (dd, J = 15.9, 10.5 Hz, 1H), 6.42 (t, J = 11.1 Hz, 1H), 6.04 (d, J = 11.4 Hz, 1H), 5.73 (dd, J = 15.9, 7.2 Hz, 1H), 5.05−5.95 (m, 1H), 4.24−4.17 (m, 1H), 2.80−2.73 (m, 3H), 2.59−2.47 (m, 1H), 1.70−1.62 (m, 2H), 1.43−1.35 (m, 4H), 1.15 (d, J = 6.3 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.9, 171.6, 143.4, 137.4, 128.0, 125.4, 73.2, 71.1, 38.4, 35.9, 34.4, 30.1, 26.0, 19.5, 19.0, 18.4, −4.4, −4.6 ppm; IR (neat) ν_{max} 2924, 1725, 1153 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{34}O_4SiK$ $[M+K]^+$ 405.1863, found 405.1865.

(6*Z*,8*E*,10*R*,14*S*)-10-Hydroxy-14-methyloxacyclotetradeca-6,8-diene-2,5-dione (6). To an ice-cold solution of compound **27** (2.8 mg, 7.6 μmol, 1.0 equiv) in CH_2Cl_2−MeOH (4:1, 1.5 mL) was added CSA (catalytic). The reaction was continued for 1 h at room temperature and subsequently quenched with Et_3N (0.1 mL). The resultant mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2, 100−200 mesh, 35% EtOAc in hexane as eluent) to obtain compound **6** (1.4 mg, 72%) as a colorless oil: R_f = 0.18, 30% EtOAc in hexane; $[\alpha]_D^{27}$ = −180 (c 0.05 $CHCl_3$); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.45 (t, J = 11.5 Hz, 1H), 6.36 (dd, J = 15.5, 10.5 Hz, 1H), 6.15 (d, J = 11.5 Hz, 1H), 5.73 (dd, J = 15.5, 7.5 Hz, 1H), 4.93 (d, J = 4 Hz, 1H) 4.89−4.87 (m, 1H), 4.04−4.00 (m, 1H), 2.72−2.68 (m, 1H), 2.65−2.60 (m, 2H), 2.46−2.40 (m, 1H), 1.60−1.54 (m, 2H), 1.33−1.26 (m, 3H), 1.08 (d, J = 6.6 Hz, 3H), 1.06−1.04 (m, 1H); ^{1}H NMR (CD_3OD, 300 MHz) δ 6.64−6.34 (m, 2H), 6.17 (d, J = 11.1 Hz, 1H), 5.74 (dd, J = 15.6, 7.5 Hz, 1H), 4.99 (dt, J = 6.3, 3.0 Hz, 1H), 4.18−4.11 (m, 1H) 2.81−2.71 (m, 2H), 2.70−2.65 (m, 1H), 2.58−2.50 (m, 1H), 1.74−1.59 (m, 3H), 1.38−1.36 (m, 3H), 1.15 (d, J = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 202.6, 171.0, 143.1, 135.9, 128.6, 125.0, 70.5, 70.0, 38.1, 34.8, 33.2, 29.5, 18.9, 18.2 ppm; IR (neat) ν_{max} 3433, 2924, 1720, 1259 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{20}O_4Na$ $[M + Na]^+$ 275.1259, found 275.1257.

(*R*/*S*,*Z*)-(2*S*,6*R*)-6-Methoxyoct-7-en-2-yl 6-Iodo-4-((triethylsilyl)oxy)hex-5-enoate (9a and 9b). Following the same experimental procedure as described for the preparation of compounds **8a** and **8b**, compound **11** (58 mg, 0.37 mmol, 1.0 equiv) dissolved in CH_2Cl_2 (5 mL) was treated with acids *rac*-**12** (151 mg, 0.41 mmol, 1.1 equiv), MNBA (191 mg, 0.56 mmol, 1.5 equiv), Et_3N (0.31 mL, 2.2 mmol, 6.0 equiv), and DMAP (2.6 mg, 0.02 mmol, 0.05 equiv) to yield the mixture of compounds **9a** and **9b** (134 mg, 71%, purification with SiO_2, 100−200 mesh, 1.5% EtOAc in hexane as an eluent) as a colorless liquid: R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.26−6.16 (m, 2H), 5.69−5.57 (m, 1H), 5.21−5.15 (m, 2H), 4.93−4.87 (m, 1H), 4.40 (q, J = 6.6 Hz, 1H), 3.49 (q, J = 6.4 Hz, 1H), 3.26 (s, 3H), 2.40−2.35 (m, 2H), 1.82 (q, J = 6.3 Hz, 2H), 1.62−1.59 (m, 1H), 1.51−1.41 (m, 3H), 1.39−1.21 (m, 2H), 1.21 (d, J = 6.6 Hz, 3H), 0.95 (t, J = 7.8 Hz, 9H), 0.61 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1, 144.0, 138.8, 117.4, 82.9, 80.8, 74.4, 71.0, 56.3, 36.0, 35.3, 32.0, 30.2, 21.3, 20.1, 7.0, 5.0 ppm; IR (neat) ν_{max} 2928, 1730, 1032 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{39}IO_4SiNa$ $[M + Na]^+$ 533.1560, found. 533.1562.

(5*R*/*S*,6*Z*,8*E*,10*R*,14*S*)-10-Methoxy-14-methyl-5-((triethylsilyl)oxy)oxacyclotetradeca-6,8-dien-2-one (28a and 28b). Following the same experimental procedure as described for the preparation of compounds **21a** and **21b**, a solution of compounds **9a** and **9b** (35 mg, 0.069 mmol, 1.0 equiv) in anhydrous DMF (15 mL, final concentration of substrate ~4.6 × 10^{-3} M) was treated with $Pd(OAc)_2$ (2.4 mg, 0.009 mmol, 0.15 equiv), Bu_4NCl (96 mg, 0.35 mmol, 5.0 equiv), and K_2CO_3 (95 mg, 0.69 mmol, 10.0 equiv) under an argon atmosphere to yield the mixture of compounds **28a** and **28b** (7.4 mg, 28%, purification SiO_2, 100−200 mesh, 2% EtOAc in hexane as an eluent) as a colorless liquid.: R_f = 0.53, 5% EtOAc in hexane; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.34 (dd, J = 15.6, 11.1 Hz, 1H), 6.10 (t, J = 10.8 Hz, 1H), 5.75 (dd, J = 15.3, 5.1 Hz, 1H), 5.32 (t, J = 9.9 Hz, 1H), 5.15−5.09 (m, 1H), 4.79 (dt, J = 9.3, 3.9 Hz, 1H), 3.85−3.80 (m, 1H), 3.27 (s, 3H), 2.38−2.28 (m, 1H), 2.18−2.11 (m, 1H), 1.80−1.71 (m, 2H), 1.54−1.46 (m, 4H), 1.41−1.34 (m, 2H), 1.18 (d, J = 6.3 Hz, 3H), 0.96 (t, J = 7.8 Hz, 9H), 0.63 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1, 134.8, 132.7, 128.5, 126.8, 78.6, 68.9, 67.0, 56.1, 34.7, 32.5, 31.2, 29.5, 20.0, 19.2, 6.9, 4.9 ppm; IR (neat) ν_{max} 2928, 1727, 1078 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{38}O_4SiNa$ $[M + Na]^+$ 405.2437, found. 405.2436

(6*Z*,8*E*,10*R*,14*S*)-10-Methoxy-14-methyloxacyclotetradeca-6,8-diene-2,5-dione (7). Following the same experimental procedure as described for the preparation of compound **27**, the mixture of compounds **28a** and **28b** (6.9 mg, 0.018 mmol, 1.0 equiv) dissolved in CH_2Cl_2−MeOH (8:1, 2 mL) was treated with CSA (catalytic) to yield the corresponding mixture of alcohols (4.3 mg, 90%, purification with SiO_2, 100−200 mesh, 2% EtOAc in hexane as an eluent) as a colorless liquid.: R_f = 0.12, (20% EtOAc in hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.38 (dd, J = 15.6, 10.8 Hz, 1H), 6.18 (t, J = 10.8 Hz, 1H), 5.78 (dd, J = 15.3, 5.1 Hz, 1H) 5.32 (t, J = 9.9 Hz, 1H) 5.13−5.08 (m, 1H), 4.90−4.84 (m, 1H), 3.84−3.79 (m, 1H), 3.27 (s, 3H), 2.43−2.35 (m, 1H), 2.23−2.17 (m, 1H), 1.81−1.67 (m, 2H), 1.54−1.42 (m, 4H), 1.38−1.29 (m, 2H), 1.18 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 133.6, 133.3, 130.2, 126.8, 78.6, 69.1, 66.7, 56.3, 34.8, 31.7, 31.2, 29.6, 20.1, 19.3 ppm; IR (neat) ν_{max} 3445, 2924, 1732, 1207, 1083 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{24}O_4Na$ $[M + Na]^+$ 291.1572, found. 291.1574.

Following the same experimental procedure as described for the preparation of compound **27**, the above alcohols (3.2 mg, 11.9 μmol, 1.0 equiv) dissolved in anhydrous CH_2Cl_2 (2 mL) were treated with DMP (10 mg, 23.8 μmol, 2.0 equiv) and Na_2CO_3 (2.6 mg, 35.7 μmol, 3.0 equiv) to yield compound **7** (2.2 mg, 68%), purification with SiO_2, 100−200 mesh, 35% EtOAc in hexane as an eluent) as a colorless liquid: R_f = 0.28 (20% EtOAc in hexane); $[\alpha]_D^{20}$ = −75.0 (c 0.08 MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 6.75 (dd, J = 16.0, 10.0 Hz, 1H), 6.49 (t, J = 11.0 Hz, 1H), 6.19 (d, J = 11.5 Hz, 1H), 5.72 (dd, J = 16.0, 7.5 Hz, 1H), 3.83 (m, 1H), 2.81−2.78 (m, 1H), 2.66−2.60 (m, 3H), 1.62−1.44 (m, 4H), 1.28−1.21 (m, 2H), 1.18 (d, J = 6.5 Hz, 3H); ^{13}C NMR (CD_3OD, 125 MHz) δ 204.7, 173.7, 140.7, 137.7, 129.9, 129.5, 82.0, 73.1, 56.8, 39.6, 35.8, 33.2, 31.3, 21.1, 20.7 ppm; IR (neat) ν_{max} 3429, 2925, 1722, 1276 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{22}O_4Na$ $[M + Na]^+$ 289.1416, found. 289.1417.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01115.

^{1}H and ^{13}C NMR comparison of natural pestalotioprolides G and H with synthetic pestalotioprolides G and H, NMR (^{1}H and ^{13}C) and HRMS spectra of representative compounds, and 2D NMR data of compounds **7** and **27** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ocrkg@iacs.res.in.

ORCID

Rajib Kumar Goswami: 0000-0001-7486-0618

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.joc.7b01115
J. Org. Chem. 2017, 82, 7437−7445

■ ACKNOWLEDGMENTS

D.P. and S.D. thank the Council of Scientific and Industrial Research, New Delhi, for a research fellowship. The financial support from the Science and Engineering Research Board (Project No. EMR/2016/000988), Department of Science & Technology (DST), India, to carry out this work is gratefully acknowledged.

■ REFERENCES

(1) (a) McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antibiot. Chemother.* **1952**, *2*, 281−283. (b) Zhanel, G. G.; Dueck, M.; Hoban, D. J.; Vercaigne, L. M.; Embil, J. M.; Gin, A. S.; Karlowsky, J. A. *Drugs* **2001**, *61*, 443−498. (c) Bryskier, A. *Expert Opin. Invest. Drugs* **1999**, *8*, 1171−1194. (d) Kirst, H. A. *Expert Opin. Ther. Pat.* **1998**, *8*, 111−120. (e) Labro, M. T. *J. Antimicrob. Chemother.* **1998**, *41*, 37−46. (f) Labro, M. T. *Expert Opin. Pharmacother.* **2004**, *5*, 541−550.

(2) Liu, S.; Dai, H.; Makhloufi, G.; Heering, C.; Janiak, C.; Hartmann, R.; Mándi, A.; Kurtán, T.; Müller, W. E. G; Kassack, M. U.; Lin, W.; Liu, Z.; Proksch, P. *J. Nat. Prod.* **2016**, *79*, 2332−2340.

(3) Reddy, K. S. N.; Sabitha, G. *Tetrahedron Lett.* **2017**, *58*, 1198−1201.

(4) (a) Guchhait, S.; Chatterjee, S.; Ampapathi, R. S.; Goswami, R. K. *J. Org. Chem.* **2017**, *82*, 2414−2435. (b) Das, S.; Kuilya, T. K.; Goswami, R. K. *J. Org. Chem.* **2015**, *80*, 6467−6489. (c) Das, S.; Paul, D.; Goswami, R. K. *Org. Lett.* **2016**, *18*, 1908−1911. (d) Das, S.; Goswami, R. K. *J. Org. Chem.* **2014**, *79*, 9778−9791. (e) Chatterjee, S.; Guchhait, S.; Goswami, R. K. *J. Org. Chem.* **2014**, *79*, 7689−7695.

(5) (a) Tanabe, Y.; Sato, E.; Nakajima, N.; Ohkubo, A.; Ohno, O.; Suenaga, K. *Org. Lett.* **2014**, *16*, 2858−2861. (b) Brun, E.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2016**, *81*, 8206−8221.

(6) For intramolecular Heck macrocyclization, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2963. (c) Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Am. Chem. Soc.* **2009**, *131*, 11678−11679. (d) Jägel, J.; Maier, M. E. *Synthesis* **2009**, *2009*, 2881−2892. (e) Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Org. Chem.* **2010**, *75*, 2429−2444. (f) Dieckmann, M.; Rudolph, S.; Dreisigacker, S.; Menche, D. *J. Org. Chem.* **2012**, *77*, 10782−10788. (g) Symkenberg, G.; Kalesse, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 1795−1798. (h) Reddy, K. M.; Yamini, V.; Singarapu, K. K.; Ghosh, S. *Org. Lett.* **2014**, *16*, 2658−2660. (i) Nguyen, M. H.; Imanishi, M.; Kurogi, T.; Smith, A. B. *J. Am. Chem. Soc.* **2016**, *138*, 3675−3678. (j) Yang, Z.; Xu, X.; Yang, C.-H.; Tian, Y.; Chen, X.; Lian, L.; Pan, W.; Su, X.; Zhang, W.; Chen, Y. *Org. Lett.* **2016**, *18*, 5768−5770.

(7) Murthy, I. S.; Sreenivasulu, R.; Alluraiah, G.; Raju, R. R. *Lett. Org. Chem.* **2014**, *11*, 327−332.

(8) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449−5452.

(9) Nonoyama, A.; Hamajima, A.; Isobe, M. *Tetrahedron* **2007**, *63*, 5886−5894.

(10) (a) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 6627−6631. (b) Yoshida, M.; Ohsawa, Y.; Ihara, M. *Tetrahedron* **2006**, *62*, 11218−11226.

(11) (a) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001−3003. (b) Ozanne, A.; Pouységu, L.; Depernet, D.; François, B.; Quideau, S. *Org. Lett.* **2003**, *5*, 2903−2906.

(12) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

(13) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, *31*, 286−287.

(14) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Thongsornkleeb, C.; Danheiser, R. L. *J. Org. Chem.* **2005**, *70*, 2364−2367.

(15) Note that there are some inconsistencies between the NMR data (^{1}H and ^{13}C) reported in Table 2 and the spectral data provided in the Supporting Information of ref 2. Accordingly, the ^{1}H and ^{13}C data obtained here are compared with the actual spectra provided in the Supporting Information of ref 2.

DOI: 10.1021/acs.joc.7b01115
J. Org. Chem. 2017, 82, 7437−7445