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Toward the Synthesis of Phormidolides

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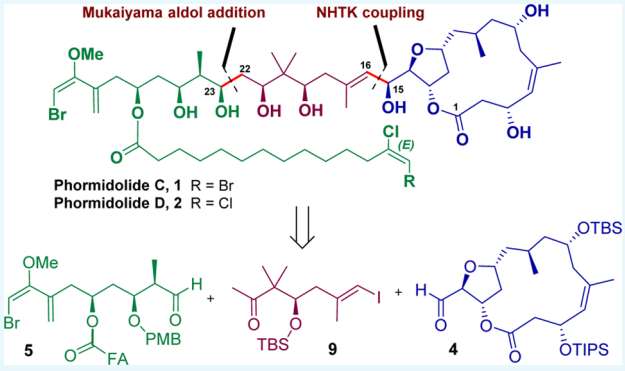
Supporting Information

ABSTRACT: A convergent and stereoselective approach for the synthesis of marine natural product (MNP) phormidolide D (PM D) is proposed. Two main disconnections divided PM D in three molecular fragments: the macrocyclic core **4**, the stapling iodoalkene **9** corresponding to the central part of PMs, and the east fragment **5** that includes the unusual bromo-methoxy-diene moiety and a tetradecanoic acid ended with a (*E*)-dichloro-ene functionality. Procedures for the preparation of compounds **5**, **9**, and the never-reported fatty acids **7** and **8**, present in PMs C and D, respectively, have been afforded with good yields and high degree of stereoselectivity. The absolute configuration of all of the generated stereocenters has been established. The reaction to link iodoalkene **9** and formylmacrolactone **4**, using the Nozaki−Hiyama−Takai−Kishi coupling, gave an advanced synthetic intermediate with total stereocontrol. Finally, a deeper study of protecting groups and reaction conditions for the last step of the synthesis is needed. All the information gathered in this publication will be of great value to continue performing synthetic studies for the preparation of these NPs. The versatility and the presence of a common polyol chain in oscillariolide and PMs A−C would allow applying the same retrosynthesis for the synthesis of the mentioned MNP.



INTRODUCTION

Polyketides, and more specifically macrolides, represent a family of marine natural products (MNPs) of great interest from a biological-therapeutical point of view,[1] but at the same time, they show high complex molecular architectures that make their syntheses a real challenge. Phormidolides C and D (Scheme 1, PMs C and D, **1**−**2**) are marine polyketides isolated by the biotech company *PharmaMar* that showed cytotoxic activity in three tumor cell lines with an unknown mechanism of action.[2] From a structural point of view, PMs C and D present 13 stereocenters and 5 di- and trisubstituted double bonds distributed in the following moieties: a tetrahydrofuran (THF)-containing macrolide (C1−C14), a polyhydroxylated chain (C15−C31) terminated with a unusual bromo-metoxy-diene moiety, and two different tetradecanoic fatty acids (C39−C52) containing a terminal (*E*)-dichloro-ene or (*E*)-bomo-chloro-ene functionalities linked to the C27 hydroxylic position.[a] So far, and to the best of our knowledge, no total synthesis of PMs C and D or the related PM A[3] and oscillariolide[4] has been described.

The structural and stereochemical elucidation of PMs C and D were carried out through mono- and bidimensional advanced NMR techniques (^{1}H, ^{13}C, 1D-TOCSY, gCOSY, gHSQC, and gHMBC) and high-resolution mass spectroscopy (HRMS).[b] The relative configuration of stereocenters present in the macrocyclic core was determined using rotational nuclear Overhauser effect spectroscopy combined with the J-based configuration analysis and nuclear Overhauser effect experiments. The two only stereocenters, with unclear configuration after the NMR analysis, were C3 and C14 positions. To solve this issue, our group reported the chemical syntheses of three different diastereomeric protected macrocyclic cores (C1−C15 fragment). NMR comparison of the synthetic and natural products suggested to us that the 3R,14R configuration was the most plausible one.[2] A second-generation synthesis of the C1−C15 moiety with the mentioned stereochemistry, after the removal of the protecting groups, enabled a second NMR comparison with the NP which showed high similarity, hence confirming our 3R and 14R stereochemical hypothesis.[5]

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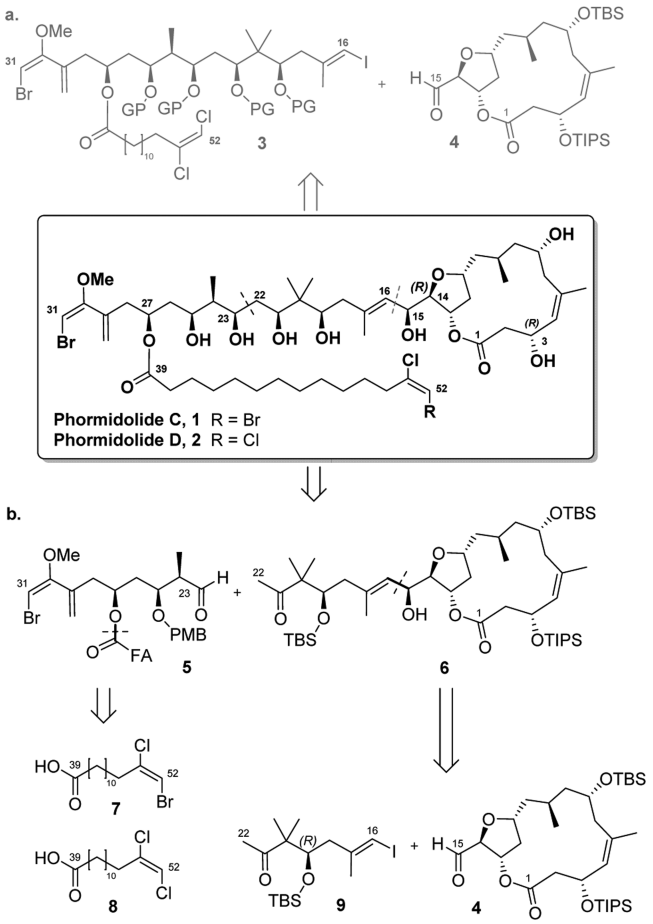
Scheme 1. (a) First Retrosynthetic Analysis for the Preparation of PMs C and D and (b) Second-Generation Retrosynthesis Described in This Publication



Stereochemistry of the C15−C31 fragment, common to oscillariolide[4] and PM A,[3] was determined by the chemical shift and the coupling constant in comparison with PM A, whose absolute configuration was previously determined by Gerwick and co-workers. Recently, our group described the synthesis of the C19−C31 polyhydroxylated chain,[6] including the tricky bromo-methoxy-diene motif.[7] This allowed a new NMR chemical shift comparison between the synthetic and NPs showing high degree of similarity, thereby confirming the absolute configuration of the polyol chain by chemical synthesis.

Our initial proposed retrosynthesis (Scheme 1, a) explained during the enantioselective synthesis of the polyhydroxylated chain was based on a single disconnection through the C15−C16 bond.[6] Both fragments **3** and **4** would be linked in the last step of the synthesis through a Nozaki−Hiyama−Takai−Kishi[8] (NHTK) coupling reaction. However, this approach posed some clear disadvantages. First, a high number of linear synthetic steps for the preparation of **3** would be required, and the introduction of the C16 iodoalkene functionality would not be trivial. Second, a possible lack of chemoselectivity in the formation of C15−C16 bond using NHTK conditions could have occurred because of the presence of other reactive positions in **3** such as C31 or C52. For these reasons, a new retrosynthetic analysis that overcame all the above-mentioned problems was necessary.

The new synthetic approach (Scheme 1, b) envisions a disconnection through the C22−C23 bond to create it at the end of the route through a previously optimized[6] Mukaiyama aldol addition from aldehyde **5** (C23−C31) and methyl ketone **6** (C1−C22). Fatty acids **7** and **8** present in different PMs would be synthesized separately and esterified at the C27 position during the synthetic route toward **5**. Then, fragment **6** would be planned to be prepared by means of the NHTK[8] coupling of enantiopure iodoalkene **9** (C16−C22) and the previously reported C1−C15 fragment aldehyde **4**.[5] A reliable preparation of central fragment **9** is crucial because of its useful bivalent nature (methyl ketone and iodoalkene) that allows its use as a "stapling" compound between macrocycle **4** and aldehyde **5**.

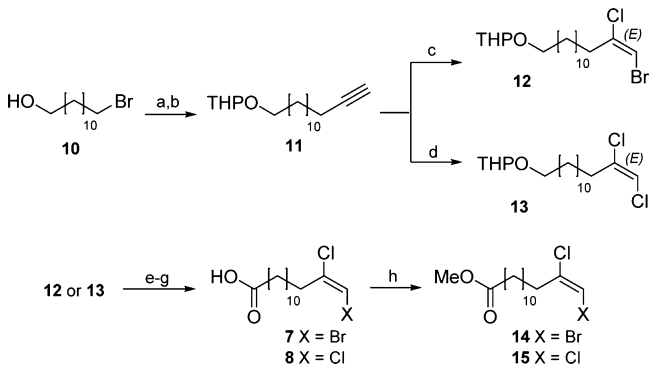
Herein, we report the preparation of fatty acids **7** and **8**, present on both PMs C and D, and the synthesis of aldehyde **5** and iodoalkene **9**. Furthermore, with fragments **5**, **9**, and **4** in hand, the first synthetic approach for the synthesis of MNP PM D (PM D) is discussed.

RESULTS AND DISCUSSION

Fatty Acids Preparation. Tetradecanoic acids containing (E)-dihalogenated terminal double bonds were prepared by direct dihalogenation of the corresponding terminal alkyne using the methodology developed by Negoro and Ikeda.[9] The use of these halogenation conditions had important advantages such as good yields, easy experimental setup, mild conditions, stereospecificity toward the (E) double bond, and regioselectivity for the desired isomer in the case of bromochlorination.

The synthetic route was initially started using commercially available 11-bromo-1-dodecanol **10** through the protection of the hydroxyl prior to the alkyne introduction and through triple bond halogenation. The tetrahydropyranyl (THP) protecting group was chosen as the most convenient protecting group for the whole synthetic route.[c] After the THP protection of **10** and acetylide introduction, alkyne **11** was obtained in high yield. This compound is common to both synthetic routes for the preparation of fatty acids **7** and **8** (Scheme 2). The key reaction of **11** with tetrabutylammonium dichlorobromide (TBADCB)

Scheme 2. Preparation of the Fatty Acids Present in PMs C and D[a]



[a]Reagents and conditions: (a) PPTS, CH_2Cl_2, 3,4-dihydro-2*H*-pyran, rt, 95%; (b) lithium acetylide−diethylamine complex, DMSO, rt, 99%; (c) TBADCB, CH_2Cl_2, rt; (d) tetrabutylammonium trichloride, CH_2Cl_2, rt; (e) *p*-TsOH, MeOH, rt; (f) DMP, CH_2Cl_2, rt; (g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $^tBuOH/H_2O$, rt; and (h) $TMSCHN_2$, CH_2Cl_2, MeOH. Yields: **14** = 20% from **11**; **15** = 12% from **11**.

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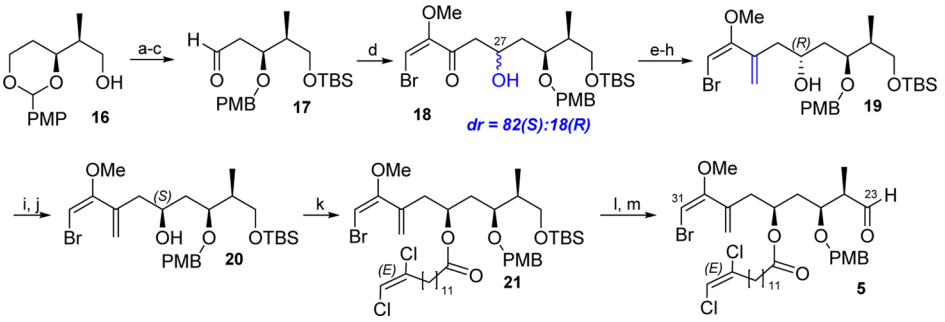
Scheme 3. Preparation of Compound 5, Fragment C23−C31[a]



[a]Reagents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, 86%; (b) DIBAL, CH_2Cl_2, −20 to 0 °C, 90%; (c) DMSO, $(COCl)_2$, Et_3N, DCM, −78 °C, 80%; (d) **(*E*)-((4-bromo-3-methoxybuta-1,3-dien-2-yl)oxy)trimethylsilane**, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 47%; (e) TESCl, imidazole, CH_2Cl_2, 86%; (f) Tebbe reagent, pyridine, THF, 50 °C, 81%; (g) PPTS, MeOH, 88%; (h) diastereomer column chromatography separation; (i) PPh_3, *p*-nitrobenzoic acid, DIAD, THF; (j) K_2CO_3, MeOH, 59% for two steps; (k) **8**, EDC·HCl, Et_3N, DMAP, 61%; (l) TBAF, THF, 77%; and (m) DMP, $NaHCO_3$, CH_2Cl_2, 93%.

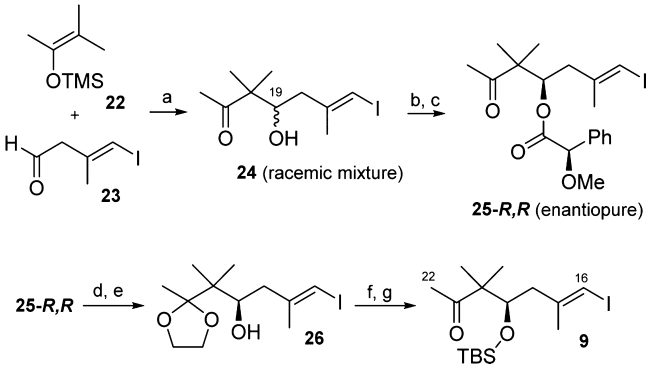
in CH_2Cl_2 at room temperature (rt) produced terminal alkene **12** as a single (E) double-bond isomer. (E) Stereochemistry was obtained due to the reaction mechanism.[9] However, compound **12** was obtained as an 89:11 mixture of inseparable regioisomers.[d] The THP removal followed by a double Dess−Martin and Pinnick oxidation rendered fatty acid **7** found in PM C. Finally, **7** was protected as a methyl ester and purified to obtain **14** in good yield with a single final purification from **11**. It is important to mention that this final protection was performed to facilitate the purification process and to enhance the stability of the compound for long-term storage.

A similar synthetic route was followed for the preparation of **8**, using tetrabutylammonium trichloride for the halogenation of **11**. This salt was prepared by the reaction of tetrabutylammonium chloride with in situ generated chlorine.[10] Protected alkene **13** was obtained as a single stereoisomer and then, a deprotection−oxidation sequence similar to that used for **7** delivered fatty acid **8**. Finally, methyl ester protection and purification produced ester **15**. These two simple synthetic routes allowed an easy, efficient, and scalable preparation of the fatty acids present in PMs C and D.

Preparation of Fragment C23−C31 (5). With both fatty acids in hand, the challenging preparation of aldehyde **5**, the east end of the molecule, was investigated. The route was started from the previously reported alcohol **16** (Scheme 3).[6] t-Butyldimethylsilyl (TBS)-hydroxyl protection, DIBAL-H regioselective ketal reduction,[11] and Swern oxidation afforded aldehyde **17** with good synthetic yields at the gram scale. Then, the Mukaiyama aldol addition of **(*E*)-((4-bromo-3-methoxybuta-1,3-dien-2-yl)oxy)trimethylsilane**[6] produced ketol **18** as an inseparable mixture of diastereomers (82:18) enriched in the undesired C27-(S) isomer.[e] Then, as it happened in our previous work,[6] a three-step procedure was necessary to introduce the methylidene moiety including triethylsilane (TES) protection of **18**, olefination using the Tebbe reagent and TES pyridinium *p*-toluenesulfonate (PPTS)-mediated removal to afford homoallylic alcohol **19** in good yield. At this point, C27-diastereomers were separated by column chromatography and the absolute configuration of the major isomer was confirmed using Mosher's derivatization.[12f] Mitsunobu hydroxyl inversion[13] of **19**, followed by basic hydrolysis of the generated nitrobenzoate, cleanly delivered the C27-(S) isomer compound **20**. Then, alcohol **20** was esterified with (*E*)-13,14-dichlorotetradec-13-enoic acid (**8**) to obtain the protected C23−C31 fragment of PM D, ester **21**. *tert*-Butyldimethylsilyl (TBS) removal at position C23 and Dess−Martin oxidation gave us access to aldehyde **5** in 12 steps with useful yields from alcohol **16**.

Preparation of Fragment C16−C22 (9). The synthesis of the central bifunctionalized C16−C22 fragment **9** (Scheme 4)

Scheme 4. Preparation of Compound 9, Fragment C16−C22[a]



[a]Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 63%; (b) (*R*)-MPA, EDC·HCl, DMAP, THF; (c) column chromatography to isolate C19 diastereomers **25-R,R**, 41% and **25-S,R**, 42%; (d) TMSOTf, 1,2-bis(trimethylsiloxy)ethane, −78 °C to rt, 97%, (e) LiOH·H_2O, MeOH, 65 °C, 92%; (f) TBSOTf, Et_3N, CH_2Cl_2, 74%; and (g) PPTS, MeOH, quant.

began with the aldol addition of silylenolether **22**[14] to aldehyde **23**[15] to obtain ketol **24** as a C19 epimeric mixture. Several reported enantioselective strategies using *N*-Ts-L-valine or a tryptophan-derived oxazaborolidine as chiral inductors for this addition were tested unsuccessfully.[16,17] The racemic mixture **24** was reacted with the chiral (*R*)-methoxyphenylacetic acid (MPA) to obtain the corresponding diastereomeric esters that were easily separated via column chromatography to isolate the desired C19-R epimer **25-R,R** and its diastereomer **25-S,R**. Taking advantage of the fact that **25-S,R** is the enantiomer of **25-R,S**, and therefore spectroscopically identical; it was possible to identify **25-R,R** without additional derivatizations using Mosher's model.[18f]

Ester basic hydrolysis at this point was nonviable probably because of methyl ketone known basic media instability;

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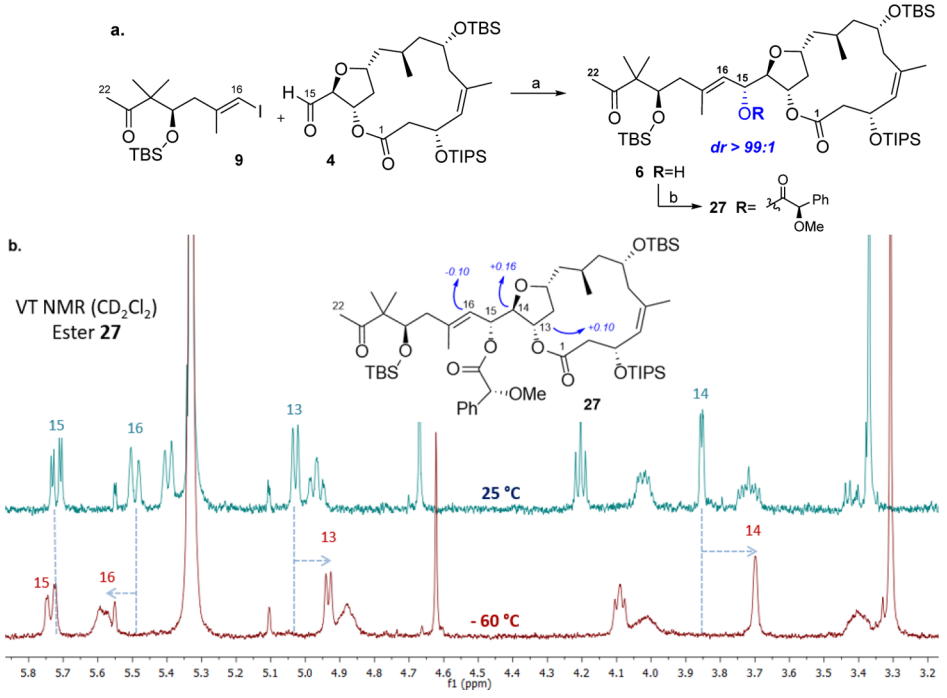
Scheme 5. (a) NHTK Coupling To Obtain Alcohol 6, the C1−C21 Fragment and (b) Determination of C15 Absolute configuration Using VT Mosher Methodology[19a]



[a]Reagents and conditions: (a) $CrCl_2$, $NiCl_2$, DMF, 48 h, 18% and (b) (*R*)-MPA, EDC·HCl, DMAP, THF, 48 h.

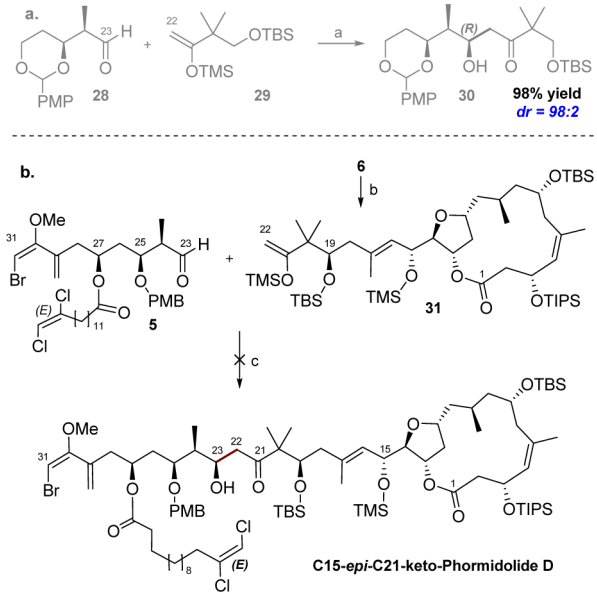
therefore, C21 position had to be protected. Mild protecting conditions[20] to install the ketone 1,3-dioxolane protecting group were used and subsequent LiOH-mediated ester saponification rendered alcohol **26** in high yield for this two-step transformation. Finally, alcohol protection using TBSOTf and ketal removal to recover the methyl ketone delivered the desired iodoalkene **9** as a single (R) enantiomer, as needed.

Endgame of the Synthesis. Having synthesized fragments **5**, **9**, and **4**,[5] the pieces of the synthetic puzzle should be put together. First of all, the union of aldehyde **4** and iodoalkene **9** using the $CrCl_2$−$NiCl_2$-mediated NHTK coupling (Scheme 5, a) was attempted.[8,21] This methodology allowed the selective formation of the C15−C16 bond in the presence of methyl ketone because of the well-known chemoselectivity of NHTK coupling toward aldehydes, thereby demonstrating the useful orthogonal reactivity of compound **9**. Unfortunately, the reaction between **9** and **4** gave stereoselectively compound **6** possessing the configuration R-C15 with only 18% yield.[8]

Because of the low amount of compound **6** available, it was decided to use the variable temperature (VT) Mosher determination that allows assigning the absolute configuration of a secondary alcohol performing a single derivatization.[19] First, alcohol **6** was converted into its corresponding (*R*)-methoxyphenylacetic ester **27**. Then, ^{1}H NMR of compound **27** in CD_2Cl_2 was recorded at 25 and −60 °C, and the C15-(R) configuration was confirmed by calculating the increment in chemical shift (Scheme 5, below).[g]

When the synthetic route was planned, the formation of the C22−C23 bond was envisioned as its last step based on our previous outstanding results on the formation of this bond while working in the synthesis of the polyhydroxylated chain. As depicted in Scheme 6a, the Mukaiyama addition of silylenolether **29**[22] to aldehyde **28** gave not only almost quantitative yield but also total stereoselectivity toward the desired C23-(R) diastereomer **30**.[6] Bearing this precedent in mind, methyl ketone and the hydroxyl present in compound **6** were simultaneously transformed into the corresponding silylenolether and protected hydroxyl in quantitative yield to render the nucleophile for the final Mukaiyama addition, compound **31** (Scheme 6, b). However, when the Mukaiyama

Scheme 6. (a) Precedent Work in the Formation of the C22−C23 Bond and (b) Endgame of the Total Synthesis[a]



[a]Regents and conditions: (a) BF_3·Et_2O, −78 °C, CH_2Cl_2 (5% Et_2O), 2 h, 98%, *dr* = 98:2; (b) TMSOTf, Et_3N, DMAP, CH_2Cl_2, rt, 4 h, quant.; and (c) BF_3·Et_2O, −78 °C, CH_2Cl_2 (5% Et_2O), 2 h, no reaction.

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addition of silylenolether **31** to aldehyde **5** (using the same conditions applied for the preparation of **30**) was performed,[6] no conversion toward the product took place, recovering both starting materials after column purification. Modification of the reaction conditions by increasing the equivalents of $BF_3{\cdot}Et_2O$ and the temperature to 0 °C resulted in no reaction either. After these negative results, it was concluded that the formation of the C22−C23 bond using the Mukaiyama methodology with the coupling partners **5** and **31** was not possible in this case.

The reason for this lack of reactivity is unknown, but by comparison with our reported precedents, it can be hypothesized that steric congestion around carbons C22 and C23 hinders reagents approximation. The presence of a tetradecanoic ester (C27) and *p*-methoxybenzyl (PMB) (C25) in aldehyde **5** reduces somehow the necessary carbonyl activation by $BF_3{\cdot}Et_2O$. In addition, a secondary TBSO-protected hydroxyl (C19) in the large functionalized compound **31** could suppress its reactivity as a nucleophile.

CONCLUSIONS

Highly convergent strategies are the process of choice for the total synthesis of large NPs such as PM D. The synthetic approach reported herein is composed of a total of 73 reactions, but the longest synthetic sequence to achieve PM D is only 20 steps long (the preparation of **5** from the commercially available starting material plus Mukaiyama addition and C21 reduction). The use of highly convergent strategies normally relies on final complex reactions because large molecular entities have to be efficient and stereoselectively linked.

In summary, this publication reports a highly convergent approach toward the NP PM D. A robust and scalable synthesis of fatty acids **7** and **8**, present in PMs C and D, using a stereoselective and regioselective halogenation of acetylene to obtain (E)-dihalogenated terminal double bonds with high yield under mild conditions is described. Stereoselective efficient strategies for the preparation of **5** (C23−C31 fragment) and **9** (C16−C22 fragment) are fully described setting up the conditions to achieve total synthesis. A notable NHTK coupling of macrocyclic fragment **4** and iodoalkene **9** was performed in useful yield and with total substrate-controlled diastereoselectivity.

Finally, the last C22−C23 bond formation using the Mukaiyama methodology to link aldehyde **5** and silylenolether **31** did not work despite our previous encouraging results with smaller molecules. These adverse results do not invalidate the proposed retrosynthetic strategy that probably could give good results using less hindered protecting groups. Therefore, a revision of the protecting groups in positions C19 and C25 should be carried out before embarking on the synthesis of these complex NPs. Consequently, all the information reported in this publication will be of great value in the development of the total synthesis of MNPs PMs B−D.

EXPERIMENTAL SECTION

General Procedures. THF and *N*,*N*-dimethylformamide (DMF) were dried using a PureSolv solvent purification system. All other solvents and reagents were used as purchased without further purification, unless otherwise indicated. Flash column chromatography was performed on silica gel (60A 35−70 μm) as a stationary phase. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates (0.2 mm thick, 20 × 20 cm) and visualized under UV light (254 and 360 nm), with anisaldehyde in concd H_2SO_4 or with phosphomolybdic acid in ethanol. Chemical shifts are reported in parts per million (ppm) referenced to the appropriate residual solvent peaks ($CDCl_3$), and coupling constants are reported in hertz. Multiplicity of the carbons was assigned with gHSQC experiments. Standard abbreviations for off-resonance decoupling were employed: s = singlet, d = doublet, t = triplet, q = quadruplet, bs = broad singlet, bd = broad doublet, and m = multiplet. The same abbreviations were also used for the multiplicity of signals in ^{1}H NMR. HRMS was performed in an Agilent LC/MSD-TOF 2006 system using the electrospray ionization mass spectrometry (ESI-MS) technique.

2-((12-Bromododecyl)oxy)tetrahydro-2H-pyran. PPTS (282 mg, 1.3 mmol) was added to a stirred solution of commercial 12-bromododecan-1-ol (**10**) (2.00 g, 7.5 mmol) in CH_2Cl_2 (50 mL), the reaction mixture was stirred for 5 min, and 3,4-dihydro-2*H*-pyran (0.95 g, 11.3 mmol) was added. The reaction mixture was allowed to stir at rt overnight under N_2. Then, it was quenched with a saturated solution of $NaHCO_3$, and the organic layer was extracted three times with Et_2O. The organic extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure. The crude obtained (2.75 g) was purified by silica gel column chromatography with hexane/EtOAc (95:5 to 90:10) to obtain the title compound (2.51 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24−1.34 (m, 14H), 1.39−1.44 (m, 2H), 1.51−1.61 (m, 6H), 1.66−1.76 (m, 1H), 1.78−1.90 (m, 3H), 3.32−3.42 (m, 3H), 3.46−3.53 (m, 1H), 3.73 (dt, J = 9.6, 6.9 Hz, 1H), 3.82−3.90 (m, 1H), 4.55−4.60 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.7 (t), 25.5 (t), 26.2 (t), 28.2 (t), 28.7 (t), 29.4 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.5 (t), 29.7 (t), 30.8 (t), 32.8 (t), 34.0 (t), 62.3 (t), 67.7 (t), 98.8 (d).

2-(Tetradec-13-yn-1-yloxy)tetrahydro-2H-pyran (11). The lithium acetylide−ethylenediamine complex (1.37 g, 13.35 mmol) was stirred in dimethyl sulfoxide (DMSO, 10 mL) at 15−20 °C for 1 h. Then, a solution of the above-mentioned bromide (2.51 g, 6.36 mmol) in DMSO (10 mL) was added at rt for 2 h and under N_2. The resulting mixture was stirred for 12 h. Then, it was quenched with water (10 mL), and the organic layer was extracted three times with hexane. The organic extract was washed several times with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure. The crude obtained (2.10 g) was purified by silica gel column chromatography with hexane/EtOAc (99:1 to 97:3) to obtain **11** (1.47 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22−1.39 (m, 15H), 1.47−1.61 (m, 9H), 1.64−1.74 (m, 1H), 1.76−1.86 (m, 1H), 1.92 (t, J = 2.7 Hz, 1H), 2.17 (td, J = 7.1, 2.7 Hz, 2H), 3.37 (dt, J = 9.5, 6.9 Hz, 1H), 3.45−3.52 (m, 1H), 3.72 (dt, J = 9.5, 6.9 Hz, 1H), 3.86 (ddd, J = 11.1, 6.9, 3.4 Hz, 1H), 4.53−4.58 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.4 (t), 19.7 (t), 25.5 (t), 26.2 (t), 28.5 (t), 28.7 (t), 29.1 (t), 29.5 (t), 29.5 (t), 29.7 (t), 30.8 (t), 62.3 (t), 67.7 (t), 68.0 (d), 84.8 (s), 98.8 (d).

(E)-2-((14-Bromo-13-chlorotridec-13-en-1-yl)oxy)-tetrahydro-2H-pyran (12). TBADCB (4.16 g, 10.6 mmol) was added to a solution of alkyne **11** (880 mg, 2.98 mmol) in anhydrous CH_2Cl_2 (20 mL) at rt and under N_2. The reaction mixture was stirred for 2.5 h. Then, it was quenched with water (10 mL), and the organic layer was extracted three times with CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure to obtain 3.62 g of crude **12** as an 89:11 mixture of regioisomers which was used in the next step without further

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purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23−1.30 (m, 12H), 1.44−1.55 (m, 8H), 1.61−1.71 (m, 6H), 2.14 (td, J = 7.1, 2.7 Hz, 1H), 2.44−2.52 (m, 1H), 3.43−3.49 (m, 1H), 3.61 (t, J = 6.7 Hz, 1H), 3.66−3.71 (m, 1H), 3.79−3.87 (m, 1H), 4.52−4.56 (m, 1H), 6.18 (s, 1H).

*(E)-14-Bromo-13-chlorotetradec-13-en-1-ol (**S1**).* *p*-TsOH (103 mg, 0.60 mmol) was added to a solution of alkene **12** (1.21 g, 2.97 mmol) in MeOH (20 mL), and the mixture was stirred for 3 h at rt. Then, it was quenched with a saturated solution of $NaHCO_3$ (10 mL), and the organic layer was extracted three times with Et_2O. The organic layer was washed with a saturated solution of $NaHCO_3$ several times, dried over $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure. The crude of **S1** (1.22 g) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (m, 14H), 1.56 (d, J = 7.4 Hz, 6H), 2.36−2.44 (m, 1H), 2.48−2.55 (m, 1H), 3.64 (t, J = 6.6 Hz, 2H), 6.22 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 25.7 (t), 26.3 (t), 28.5 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.6 (t), 29.6 (t), 32.8 (t), 35.1 (t), 63.1 (t), 101.0 (d), 136.9 (s).

*(E)-14-Bromo-13-chlorotetradec-13-enal (**S2**).* DMP (1.18 g, 2.70 mmol) was added to a solution of **S1** (703 mg, 2.15 mmol) in dry CH_2Cl_2 (20 mL) at rt and under N_2. The reaction mixture was stirred for 3 h. Then, it was quenched with a saturated solution of $NaHCO_3$, and the saturated solution of NaS_2O_3 and the mixture were left stirring for 20 min. The aqueous layer was extracted three times with EtOAc, dried over $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure. The crude of **S2** (751 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (m, 14H), 1.57−1.66 (m, 4H), 2.40−2.45 (m, 2H), 2.53 (t, J = 7.4 Hz, 2H), 6.22 (s, 1H), 9.77 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 22.1 (t), 26.3 (t), 28.5 (t), 29.2 (t), 29.3 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 35.1 (t), 43.9 (t), 101.1 (d), 136.9 (s), 202.9 (s).

*(E)-14-Bromo-13-chlorotetradec-13-enoic Acid (**7**).* $NaClO_2$ (832 mg, 9.2 mmol) was added to a solution of aldehyde **S2** (750 mg, 2.3 mmol) in ^{t}BuOH/H_2O (10 mL/2 mL), in the presence of NaH_2PO_4 (1.4 g, 11.5 mmol) and 2-methyl-butene (806 mg, 11.5 mmol), at rt. The reaction mixture was stirred for 2 h and 30 min. Then, it was quenched with water and $Na_2S_2O_3$. The organic phase was extracted three times with EtOAc and washed with brine. The organic extract was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude **7** (794 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29−1.36 (m, 14H), 1.53−1.68 (m, 4H), 2.35 (t, J = 7.5 Hz, 2H), 2.50−2.55 (t, J = 7.4 Hz, 2H), 6.22 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.7 (t), 26.4 (t), 28.5 (t), 29.0 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 33.9 (t), 35.1 (t), 101.1 (d), 136.9 (s), 179.0 (s).

*Methyl (E)-14-Bromo-13-chlorotetradec-13-enoate (**14**).* Trimethylsilyldiazomethane ($TMSCHN_2$; 778 mg, 6.81 mmol) was added to a solution of **7** (774 mg, 2.27 mmol) in CH_2Cl_2/MeOH (9:1) at 0 °C and under N_2. The reaction mixture was stirred for 3 h at 0−5 °C. The solvent was evaporated under reduced pressure, and the residue was purified in preparative RP-HPLC to obtain **14** (209 mg). Global yield from **11** to **14** 20%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22−1.33 (m, 14H), 1.51−1.65 (m, 4H), 2.29 (t, J = 7.5 Hz, 2H), 2.46−2.55 (m, 2H), 3.66 (s, 3H), 6.21 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.9 (t), 26.3 (t), 28.5 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 34.1 (t), 35.1 (t), 51.4 (q), 101.0 (d), 136.9 (s), 174.3 (s). HRMS (ESI+) m/z: calcd for $C_{15}H_{27}BrClO_2$ (M + H), 353.0883; found, 353.0857.

*(E)-2-((13,14-Dichlorotetradec-13-en-1-yl)oxy)tetrahydro-2H-pyran (**13**).* TBATC (3.96 g, 10.6 mmol) was added to a solution of alkyne **11** (880 mg, 2.98 mmol) in dry CH_2Cl_2 (20 mL) at rt and under N_2. The reaction mixture was stirred for 2.5 h and quenched with water (10 mL). The organic layer was extracted three times with CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure. Crude **13** obtained (957 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24−1.35 (m, 14H), 1.47−1.63 (m, 12H), 2.50 (t, J = 7.4 Hz, 2H), 3.38 (dt, J = 9.6, 6.7 Hz, 2H), 3.49 (m, 1H), 3.72 (dt, J = 9.6, 6.7 Hz, 1H), 3.87 (m, 1H), 4.57 (m, 1H), 6.13 (s, 1H).

*(E)-13,14-Dichlorotetradec-13-en-1-ol (**S3**).* *p*-TsOH (262 mg, 1.52 mmol) was added to a solution of alkene **13** (926 mg, 2.54 mmol) in MeOH (20 mL) at rt. The reaction mixture was stirred for 1.5 h, then quenched with a saturated solution of $NaHCO_3$ (10 mL), and extracted three times with Et_2O. The organic layer was washed with a saturated solution of $NaHCO_3$ several times, dried over $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure. The crude of **S3** (819 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24−1.34 (m, 14H), 1.41−1.51 (m, 4H), 1.52−1.62 (m, 2H), 2.50 (t, J = 7.4 Hz, 2H), 3.64 (t, J = 6.6 Hz, 2H), 6.13 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 25.7 (t), 26.3 (t), 28.5 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.6 (t), 29.6 (t), 32.8 (t), 33.1 (t), 63.1 (t), 113.5 (d).

*(E)-13,14-Dichlorotetradec-13-enal (**S4**).* DMP (1.55 g, 3.5 mmol) was added to a solution of **S3** (779 mg, 2.7 mmol) in dry CH_2Cl_2 (20 mL) at rt and under N_2. The reaction was quenched with a saturated solution of $NaHCO_3$, and the saturated solution of NaS_2O_3 and the mixture were left stirring for 20 min. The aqueous layer was extracted three times with EtOAc, dried over $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure. The crude of **S4** (605 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (m, 14H), 1.44−1.66 (m, 4H), 2.35 (t, J = 7.5 Hz, 2H), 2.50 (t, J = 7.4 Hz, 2H), 6.13 (s, 1H), 9.76 (t, J = 2.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 22.1 (t), 26.3 (t), 28.5 (t), 29.1 (t), 29.3 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 33.1 (t), 43.9 (t), 113.5 (d), 136.6 (s), 203.0 (s).

*(E)-13,14-Dichlorotetradec-13-enoic Acid (**8**).* $NaClO_2$ (734 mg, 8.12 mmol) was added to a solution of aldehyde **S4** (565 mg, 2.03 mmol) in ^{t}BuOH/H_2O (14 mL/6 mL), containing NaH_2PO_4 (1.21 g, 10.15 mmol) and 2-methyl-butene (0.711 g, 10.15 mmol), at rt. The reaction mixture was stirred for 2 h and 30 min. The reaction was quenched with water and $Na_2S_2O_3$. The organic phase was extracted three times with EtOAc and washed with brine. The organic extract was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Crude **8** (602 mg) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (m, 14H), 1.45−1.62 (m, 4H), 2.35 (t, J = 7.5 Hz, 2H), 2.49 (d, J = 7.4 Hz, 2H), 6.13 (s, 1H). ^{13}C NMR (101 MHz, chloroform-*d*): δ 24.7 (t), 26.3 (t), 28.5 (t), 29.0 (t), 29.2 (t), 29.4 (2C, t), 29.4 (t), 29.5 (t), 33.1 (t), 34.0 (t), 113.5 (d), 136.6 (s), 179.7 (s).

*Methyl (E)-13,14-Dichlorotetradec-13-enoate (**15**).* $TMSCHN_2$ (0.651 g, 5.7 mmol) was added to a solution of acid **8** (0.562 g, 1.9 mmol) in dichloromethane (DCM)/MeOH (9:1) at 0 °C and under N_2. The reaction mixture was

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stirred for 3 h at 0−5 °C. The solvent was evaporated under reduced pressure, and the residue was purified in preparative RP-HPLC to obtain **15** (0.110 g, 0.35 mmol). Global yield from **11** to **15**: 12%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (m, 14H), 1.59−1.65 (m, 4H), 2.30 (t, J = 7.5 Hz, 4H), 2.50 (t, J = 7.4 Hz, 3H), 3.66 (s, 3H), 6.13 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 25.0 (t), 26.3 (t), 28.5 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.4 (t), 29.5 (t), 33.1 (t), 34.1 (t), 51.4 (q), 113.5 (d), 136.4 (s), 174.3 (s). HRMS (ESI+) m/z: calcd for $C_{15}H_{27}Cl_2O_2$ (M + H), 309.1388; found, 309.1383.

*tert-Butyl((2S)-2-((4S)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)propoxy)dimethylsilane (**S5**).* *tert*-Butyldimethylsilyl chloride (TBSCl; 1.25 g, 8.3 mmol) was added to a solution of alcohol **16**[6] (1.70 g, 6.7 mmol) and imidazole (684 mg, 10.1 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred for 90 min. After this time, the mixture was washed with water, dried over $MgSO_4$, and filtered and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (95:5) yielded **S5** (2.0 g, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.05 (s, 3H), 0.91 (s, 9H), 1.00 (d, J = 6.9 Hz, 3H), 1.45 (dtd, J = 13.2, 2.4, 1.4 Hz, 1H), 1.78 (pt, J = 6.9, 5.1 Hz, 1H), 1.95 (tdd, J = 13.2, 12.3, 11.3, 5.1 Hz, 1H), 3.55 (dd, J = 9.9, 5.1 Hz, 1H), 3.64 (dd, J = 9.9, 6.9 Hz, 1H), 3.80 (s, 3H), 3.83−4.01 (m, 2H), 4.27 (ddd, J = 11.3, 5.1, 1.4 Hz, 1H), 5.46 (s, 1H), 6.84−6.95 (m, 2H), 7.37−7.46 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ −5.4 (q), −5.4 (q), 11.9 (q), 18.3 (s), 25.9 (q), 28.7 (t), 40.6 (d), 55.2 (q), 64.5 (t), 67.2 (d), 77.4 (d), 101.0, 113.4 (d), 127.2 (d), 131.7 (s), 159.7 (s). HRMS (ESI+) m/z: calcd for $C_{20}H_{34}NaO_4Si$ [M + Na]$^+$, 389.2119; found, 389.2111.

*(3S,4S)-5-((tert-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-4-methylpentan-1-ol (**S6**).* A solution of diisobutylaluminium hydride 1 M in heptane (1.3 mL, 1.3 mmol) was added to a solution of **S5** (355 mg, 0.97 mmol) in CH_2Cl_2 (15 mL) at −20 °C. The reaction mixture was stirred at 0 °C for 2 h. Then, a saturated solution of Rochelle's salt (15 mL) was added, and the mixture was stirred for 1 h until the formation of two layers. The organic solution was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (8:2) yielded **S6** (285 mg, 90% br s m) as a colorless oil and 43 mg of recovered starting material. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.90 (s, 9H), 0.95 (d, J = 6.9 Hz, 3H), 1.67−1.83 (m, 2H), 1.85−2.00 (m, 1H), 2.17 (m, 1H), 3.50 (dd, J = 9.9, 6.9 Hz, 1H), 3.62−3.78 (m, 4H), 3.80 (s, 3H), 4.46 (d, J = 11.0 Hz, 1H), 4.55 (d, J = 11.0 Hz, 1H), 6.83−6.92 (m, 2H), 7.22−7.31 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ −5.4 (q), −5.4 (q), 12.6 (q), 18.3 (s), 25.9 (q), 33.6 (t), 39.0 (d), 55.3 (q), 61.2 (t), 64.7 (t), 71.9 (t), 79.2 (d), 113.8 (d), 129.5 (d), 130.7 (s), 159.2 (s). HRMS (ESI+) m/z: calcd for $C_{20}H_{37}O_4Si$ [M + H]$^+$, 369.2456; found, 369.2446.

*(3S,4S)-5-((tert-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-4-methylpentanal (**17**).* DMSO (0.031 mL, 0.44 mmol) was added to a solution of oxalyl chloride (0.019 mL, 0.22 mmol) in CH_2Cl_2 (2 mL) at −78 °C, and the reaction mixture was stirred for 30 min. A solution of alcohol **S6** (40 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added, and the mixture was stirred for 45 min at the same temperature. Et_3N (0.123 mL, 0.88 mmol) was added, and the reaction mixture was stirred for 30 min at 0 °C. Then, it was quenched with NH_4Cl saturated solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. Purification by silica gel chromatography with hexane/EtOAc (9:1) yielded aldehyde **17** (32 mg, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (2s, 6H), 0.90 (s, 9H), 0.93 (d, J = 7.0 Hz, 3H), 1.81−1.92 (m, 1H), 2.56 (ddd, J = 16.4, 4.6, 2.0 Hz, 1H), 2.71 (ddd, J = 16.4, 7.8, 2.0 Hz, 1H), 3.53 (dd, J = 10.0, 5.7 Hz, 1H), 3.61 (dd, J = 10.0, 6.5 Hz, 1H), 3.80 (s, 3H), 4.03−4.10 (m, 1H), 4.49 (s, 2H), 6.83−6.88 (m, 2H), 7.20−7.25 (m, 2H), 9.76 (t, J = 2.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ −5.5 (q), −5.4 (q), 12.1 (q), 18.2 (s), 25.9 (q), 39.7 (d), 46.6 (t), 55.3 (q), 64.5 (t), 72.0 (t), 74.8 (d), 113.8 (d), 129.3 (d), 130.5 (s), 159.2 (s), 201.9 (s). HRMS (ESI+) m/z: calcd for $C_{20}H_{34}NaO_4Si$ [M + Na]$^+$, 389.2119; found, 389.2130.

*(5S,7S,8S,E)-1-Bromo-9-((tert-butyldimethylsilyl)oxy)-5-hydroxy-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methylnon-1-en-3-one (**18**).* A solution of silylenolether (***E***)-((**4-bromo-3-methoxybuta-1,3-dien-2-yl)oxy)trimethylsilane**[6] (527 mg, 2.1 mmol) in CH_2Cl_2 (10 mL) was added to a cooled (−78 °C) solution of aldehyde **17** (503 mg, 1.37 mmol) in CH_2Cl_2 (30 mL), and then $BF_3{\cdot}OEt_2$ (155 μL, 1.26 mmol) was added dropwise. The reaction was stirred at −78 °C for 60 min, quenched with the saturated solution of $NaHCO_3$ (30 mL), and extracted three times with CH_2Cl_2. The organic solution was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (8:2) afforded **18** (312 mg, 47%) as an 82:17 mixture of diastereomers. Mayor diastereomer data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 0.94 (d, J = 6.9 Hz, 3H), 1.60−1.64 (m, 2H), 1.87−1.93 (m, 1H), 2.76−2.85 (m, 2H), 3.44−3.52 (m, 1H), 3.63 (s, 3H), 3.66 (dd, J = 9.9, 5.8 Hz, 1H), 3.80 (s, 3H), 3.80−3.81 (m, 1H), 4.23−4.35 (m, 1H), 4.46−4.57 (m, 2H), 5.66 (s, 1H), 6.82−6.89 (m, 2H), 7.24−7.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ −5.4 (q), −5.3 (q), 12.5 (q), 18.3 (s), 25.9 (q), 38.3 (t), 39.4 (d), 47.1 (t), 55.3 (q), 56.0 (q), 64.7 (d), 64.8 (t), 72.4 (t), 76.8 (d), 84.4 (d), 113.8 (d), 129.5 (d), 130.9 (s), 152.9 (s), 159.2 (s), 197.7 (s). HRMS (ESI+) m/z: calcd for $C_{25}H_{41}BrNaO_6Si$ [M + Na]$^+$, 567.1748; found, 567.1744.

*(5S,7S,8S,E)-1-Bromo-9-((tert-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-5-((triethylsilyl)oxy)non-1-en-3-one (**S7**).* Imidazole (140 mg, 2 mmol), TESCl (0.14 mL, 0.85 mmol), and DMAP (6 mg, 0.05 mmol) were added sequentially to a solution of **18** (290 mg, 0.53 mmol) in CH_2Cl_2 (10 mL). The cloudy solution was stirred 45 min until the TLC analysis showed complete conversion of the starting material. The reaction was quenched with the saturated solution of NH_4Cl (10 mL) and extracted three times with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. Purification with deactivated (1% Et_3N) silica gel column chromatography with hexane/EtOAc (95:5) afforded **S7** (300 mg, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.56−0.63 (m, 6H), 0.89 (s, 9H), 0.89−0.96 (m, 12H), 1.68 (dt, J = 6.6, 5.4 Hz, 2H), 1.89 (qd, J = 6.9, 3.2 Hz, 1H), 2.78 (dd, J = 16.3, 5.4 Hz, 1H), 2.95 (dd, J = 16.3, 6.6 Hz, 1H), 3.41 (dd, J = 9.8, 7.0 Hz, 1H), 3.59 (s, 3H), 3.61−3.67 (m, 2H), 3.80 (s, 3H), 4.31−4.38 (m, 1H), 4.39−4.51 (m, 2H), 5.58 (s, 1H), 6.83−6.88 (m, 2H), 7.22−7.26 (m, 2H). HRMS (ESI+) m/z: calcd for $C_{31}H_{56}BrO_6Si_2$ [M + H]$^+$, 659.2793; found, 659.2762.

(5R,7S,8S,E)-1-Bromo-9-((tert-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylene-

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*5-((triethylsilyl)oxy)non-1-ene (**S8**)*. A solution of the Tebbe reagent in toluene (0.5 M, 3.62 mL, 1.81 mmol) was added to a solution of **S7** (290 mg, 0.45 mmol) and pyridine (0.150 mL, 1.81 mmol) in THF (12 mL) at 0 °C. The reaction mixture was warmed to rt and then heated up at 50 °C for 90 min. Then, it was quenched at rt with the saturated solution of Rochelle's salt (3 mL) and extracted three times with Et_2O. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (95:5) yielded alkene **S8** (235 mg, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.54−0.64 (m, 6H), 0.87−0.90 (m, 12H), 0.92−0.97 (m, 9H), 1.43−1.50 (m, 1H), 1.76−1.85 (m, 1H), 1.92 (qd, J = 6.8, 3.2 Hz, 1H), 2.29 (dd, J = 13.8, 9.0 Hz, 1H), 2.61 (dd, J = 13.8, 4.2 Hz, 1H), 3.41 (dd, J = 9.8, 7.2 Hz, 1H), 3.49 (s, 3H), 3.62−3.72 (m, 2H), 3.80 (s, 3H), 3.88−3.96 (m, 1H), 4.42 (d, J = 11.1 Hz, 1H), 4.50 (d, J = 11.1 Hz, 1H), 5.26 (s, 1H), 5.33 (s, 1H), 5.38 (s, 1H), 6.79−6.88 (m, 2H), 7.23−7.26 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 5.3 (t), 7.2 (q), 12.1 (q), 26.1 (q), 38.9 (t), 39.4 (d), 43.4 (t), 55.3 (q), 55.4 (q), 65.1 (t), 68.5 (d), 71.0 (t), 77.0 (d), 78.4 (d), 113.5 (d), 121.3 (t), 128.6 (d). HRMS (ESI+) m/z: calcd for $C_{32}H_{58}BrO_5Si_2$ $[M + H]^+$, 657.3001; found, 657.2991.

*(5R,7S,8S,E)-1-Bromo-9-((tert-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenon-1-en-5-ol (**19**)*. PPTS (17 mg, 0.07 mmol) was added to a solution of **S8** (235 mg, 0.357 mmol) in MeOH (13 mL) at 0 °C, and the reaction mixture was stirred for 45 min at rt. After this time, the reaction mixture was quenched with the saturated solution of $NaHCO_3$ (5 mL) and extracted three times with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (85:15) yielded alcohol **19** (170 mg, 88%) as a colorless oil (mixture of isomers). Separation of diastereomers was performed at this point via silica column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.90 (s, 9H), 0.94 (d, J = 6.9 Hz, 3H), 1.52−1.65 (m, 2H), 1.84−1.93 (m, 1H), 2.28 (dd, J = 13.8, 9.0 Hz, 1H), 2.44 (dd, J = 13.8, 4.0 Hz, 1H), 3.46 (dd, J = 9.9, 6.9 Hz, 1H), 3.56 (s, 3H), 3.67 (dd, J = 9.9, 5.8 Hz, 1H), 3.80 (s, 3H), 3.83 (s, 1H), 3.86 (s, 1H), 4.48 (d, J = 10.9 Hz, 1H), 4.54 (d, J = 10.9 Hz, 1H), 5.32 (s, 1H), 5.38 (s, 2H), 6.84−6.89 (m, 2H), 7.25−7.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ −5.4 (q), −5.3 (q), 12.5 (q), 18.3 (s), 25.9 (q), 38.4 (t), 39.5 (d), 43.1 (t), 55.3 (q), 55.6 (q), 64.9 (t), 66.5 (d), 72.5 (t), 77.1 (d), 78.6 (d), 113.8 (d), 122.1 (t), 129.5 (d), 131.1 (s), 139.7 (s), 159.1 (s), 159.1 (s). HRMS (ESI+) m/z: calcd for $C_{26}H_{43}BrNaO_5Si$ $[M + Na]^+$, 565.1955; found, 565.1943.

General Procedure for Derivatization with MPA. α-MPA (5 equiv) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC)·HCl (5 equiv) were added to a solution of alcohol **10(*5R*)** (1 equiv) in THF, then DMAP (0.1 equiv) was added, and the solution was stirred for 2 h at 40 °C. The solution was filtered through Celite 545, poured into Et_2O, and washed with NH_4Cl saturated solution. The organic residue was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (90:10) yielded the corresponding esters as colorless oils.

*(5R,7S,8S,E)-1-Bromo-9-((tert-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenon-1-en-5-yl-(R)-2-methoxy-2-phenylacetate (**S9**)*. Alcohol **19** (4 mg, 0.007 mmol) and (*R*)-MPA (5 equiv) afforded (*R*)-MPA ester **S9** (4 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.67 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 1.55−1.58 (m, 2H), 1.64−1.69 (m, 1H), 2.49 (dd, J = 14.5, 6.4 Hz, 1H), 2.58 (dd, J = 14.5, 5.8 Hz, 1H), 2.79 (dt, J = 8.5, 3.9 Hz, 1H), 3.21−3.32 (m, 1H), 3.41 (s, 3H), 3.49−3.52 (m, 1H), 3.53 (s, 3H), 3.79 (s, 3H), 3.85 (d, J = 10.3 Hz, 1H), 4.07 (d, J = 10.3 Hz, 1H), 4.72 (s, 1H), 5.18−5.26 (m, 1H), 5.30 (s, 1H), 5.33 (d, J = 1.4 Hz, 1H), 5.42 (d, J = 1.4 Hz, 1H), 6.81−6.85 (m, 2H), 7.15−7.20 (m, 2H), 7.30−7.37 (m, 3H), 7.43−7.47 (m, 2H). HRMS (ESI+) m/z: calcd for $C_{35}H_{55}BrNO_7Si$ $[M + NH_4]^+$, 708.2926; found, 708.2876.

*(5R,7S,8S,E)-1-Bromo-9-((tert-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenon-1-en-5-yl-(S)-2-methoxy-2-phenylacetate (**S10**)*. Alcohol **19** (4 mg, 0.007 mmol) and (*S*)-MPA (5 equiv) afforded (*S*)-MPA ester **S10** (5 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.86 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 1.68−1.74 (m, 2H), 1.76−1.83 (m, 1H), 2.35 (dd, J = 14.5, 5.7 Hz, 1H), 2.47 (dd, J = 14.5, 6.7 Hz, 1H), 3.32−3.36 (m, 1H), 3.38−3.41 (m, 1H), 3.41 (s, 3H), 3.45 (s, 3H), 3.61 (dd, J = 9.8, 6.0 Hz, 1H), 3.79 (s, 3H), 4.20 (d, J = 10.5 Hz, 1H), 4.32 (d, J = 10.5 Hz, 1H), 4.72 (s, 1H), 5.03 (d, J = 1.4 Hz, 1H), 5.21 (s, 3H), 6.82−6.86 (m, 2H), 7.22−7.26 (m, 2H), 7.30−7.35 (m, 3H), 7.42−7.47 (m, 2H). HRMS (ESI+) m/z: calcd for $C_{35}H_{55}BrNO_7Si$ $[M + NH_4]^+$, 708.2926; found, 708.2921.

*(5S,7S,8S,E)-1-Bromo-9-((tert-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenon-1-en-5-ol (**20**)*. Diisopropyl azodicarboxylate (DIAD; 0.22 mL, 1.06 mmol) was slowly added to a solution of **19** (105 mg, 0.19 mmol), *p*-nitrobenzoic acid (170 mg, 1 mmol), and PPh_3 (294 mg, 1 mmol) in benzene (8 mL), and the yellowish solution was stirred for 4 h at 40 °C. The reaction mixture was quenched with the saturated solution of $NaHCO_3$ (10 mL) and extracted three times with Et_2O. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude was filtered through a plug of silica using hexane/EtOAc 9:1 to eliminate the *p*-nitrobenzoic acid and PPh_3O (R_f = 0.1). After evaporation, the resulting crude was dissolved in MeOH (10 mL), K_2CO_3 (180 mg, 1.30 mmol) was added, and the mixture was stirred for 2 h until TLC indicated total hydrolysis. The reaction mixture was quenched with the saturated solution of NH_4Cl (10 mL) and extracted three times with AcOEt. The organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure, and purified by silica gel column chromatography with hexane/EtOAc 9:1 to obtain **20** as a colorless oil (60 mg, 59% for two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.90 (s, 9H), 0.92 (d, J = 7.0 Hz, 3H), 1.59−1.72 (m, 2H), 1.91−2.00 (m, 1H), 2.35 (dd, J = 13.8, 6.4 Hz, 1H), 2.45 (dd, J = 13.8, 6.8 Hz, 1H), 3.46−3.51 (m, 1H), 3.57 (s, 3H), 3.67 (dd, J = 9.9, 5.9 Hz, 1H), 3.71−3.77 (m, 2H), 3.79 (s, 3H), 4.43 (d, J = 10.9 Hz, 1H), 4.55 (d, J = 10.9 Hz, 1H), 5.31 (s, 1H), 5.36 (s, 2H), 6.84−6.89 (m, 2H), 7.22−7.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ −5.4 (q), −5.3 (q), 12.3 (q), 18.3 (s), 25.9 (q), 37.3 (t), 38.7 (d), 42.6 (t), 55.3 (q), 55.6 (q), 64.5 (t), 69.3 (d), 71.5 (t), 78.6 (d), 80.2 (d), 113.8 (d), 121.8 (t), 129.4 (d), 130.5 (s), 139.5 (s), 159.0 (s), 159.2 (s). HRMS (ESI+) m/z: calcd for $C_{26}H_{43}BrNaO_5Si$ $[M + Na]^+$, 565.1955; found, 565.1959.

*(5S,7S,8S,E)-1-Bromo-9-((tert-butyldimethylsilyl)oxy)-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenon-1-en-5-yl-(E)-13,14-dichlorotetradec-13-enoate (**21**)*. (*E*)-13,14-Dichlorotetradec-13-enoic acid (**8**) (82 mg, 0.28

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mmol) was added to a solution of EDC·HCl (268 mg, 1.4 mmol), Et_3N (0.195 mL, 1.4 mmol), and DMAP (171 mg, 1.4 mmol) in CH_2Cl_2 (3 mL), and the solution was stirred for 20 min. Alcohol **20** (50 mg, 0.092 mmol) dissolved in CH_2Cl_2 (2.5 mL) was added, and the solution was stirred for 16 h. The reaction mixture was quenched with the saturated solution of NH_4Cl (8 mL) and extracted three times with AcOEt. The organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure, and purified by silica gel column chromatography with hexane/EtOAc 95:5 to obtain ester **21** as a colorless oil (35 mg, 56% br s m) and recovered **20** (8 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.86 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 1.25−1.31 (m, 14H), 1.55 (s, 4H), 1.76−1.91 (m, 3H), 2.23 (td, J = 7.6, 3.8 Hz, 2H), 2.47−2.59 (m, 4H), 3.44 (dd, J = 9.8, 6.5 Hz, 1H), 3.54 (s, 3H), 3.56−3.62 (m, 2H), 3.80 (s, 3H), 4.41 (d, J = 11.1 Hz, 1H), 4.48 (d, J = 11.1 Hz, 1H), 5.00 (p, J = 6.5 Hz, 1H), 5.31 (s, 1H), 5.34 (d, J = 1.3 Hz, 1H), 5.41 (d, J = 1.3 Hz, 1H), 6.13 (s, 1H), 6.84−6.88 (m, 2H), 7.25−7.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ −5.4 (q), −5.4 (q), 11.0 (q), 18.2 (s), 24.9 (t), 25.9 (q), 26.3 (t), 28.5 (t), 29.2 (t), 29.3 (t), 29.3 (t), 29.5 (t, 2C), 29.5 (t), 33.1 (t), 34.5 (t), 35.3 (t), 38.8 (t + d, 2C), 55.3 (q), 55.6 (q), 64.9 (t), 70.0 (d), 71.2 (t), 75.7 (d), 78.7 (d), 113.5 (d), 113.6 (d), 122.0 (t), 129.1 (d), 131.2 (s), 136.6 (s), 138.4 (s), 141.7 (s), 158.5 (s), 173.0 (s). HRMS (ESI+) m/z: calcd for $C_{40}H_{69}BrCl_2NO_6Si$ $[M + NH_4]^+$, 836.3449; found, 836.3439.

*(5S,7S,8S,E)-1-Bromo-9-hydroxy-2-methoxy-7-((4-methoxybenzyl)oxy)-8-methyl-3-methylenenon-1-en-5-yl-(E)-13,14-dichlorotetradec-13-enoate (**S11**).* A 1 M TBAF solution (0.071 mL, 0.071 mmol) was added to a solution of **21** (29 mg, 0.035 mmol) in THF (0.7 mL), and the solution was stirred at rt for 6 h. The reaction mixture was quenched with the saturated solution of NH_4Cl (1 mL) and extracted three times with Et_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated under reduced pressure, and purified by silica gel column chromatography with hexane/EtOAc 7:3 to obtain alcohol **S11** as a colorless oil (19 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (d, J = 7.1 Hz, 3H), 1.25−1.31 (m, 14H), 1.55−1.59 (m, 4H), 1.78−1.86 (m, 1H), 1.87−1.95 (m, 1H), 2.04−2.08 (m, 1H), 2.19−2.28 (m, 2H), 2.46−2.56 (m, 4H), 3.56 (s, 3H), 3.50−3.64 (m, 3H), 3.80 (s, 3H), 4.40−4.52 (m, 2H), 5.02 (p, J = 6.5 Hz, 1H), 5.32 (s, 1H), 5.35 (d, J = 1.4 Hz, 1H), 5.43 (d, J = 1.4 Hz, 1H), 6.13 (s, 1H), 6.85−6.89 (m, 2H), 7.24−7.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 11.2 (q), 24.9 (t), 26.3 (t), 28.5 (d), 29.2 (t), 29.3 (t), 29.3 (t), 29.5 (t), 29.5 (t), 33.1 (t), 34.3 (t), 34.6 (t), 36.9 (d), 39.2 (t), 55.3 (q), 55.6 (q), 66.0 (t), 69.8 (d), 70.9 (t), 77.8 (d), 78.8 (d), 113.5 (d), 113.8 (d), 122.2 (t), 129.4 (d), 130.3 (s), 134.4 (s), 138.2 (s), 158.3 (s), 159.2 (s), 173.3 (s). HRMS (ESI+) m/z: calcd for $C_{34}H_{55}BrCl_2NO_6$ $[M + NH_4]^+$, 722.2584; found, 722.2588.

*(5S,7S,8R,E)-1-Bromo-2-methoxy-7-((4-methoxybenzyl)-oxy)-8-methyl-3-methylene-9-oxonon-1-en-5-yl-(E)-13,14-dichlorotetradec-13-enoate (**5**).* $NaHCO_3$ (4 mg, 0.047 mmol) and DMP (5 mg, 0.118 mmol) were added to a solution of **S11** (2.5 mg, 0.0035 mmol) in CH_2Cl_2 (0.8 mL), and the solution was stirred for 30 min. The reaction mixture was diluted with Et_2O (10 mL) and quenched with saturated solutions of $NaHCO_3$ and $Na_2S_2O_3$ (2 + 2 mL). The crude was extracted twice with Et_2O, and the organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (8:2) yielded aldehyde **5** (2.3 mg, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, J = 7.0 Hz, 3H), 1.27 (s, 14H), 1.56 (s, 4H), 1.85 (ddd, J = 14.5, 7.5, 4.2 Hz, 1H), 1.98 (ddd, J = 14.5, 8.5, 5.8 Hz, 1H), 2.19−2.27 (m, 2H), 2.46−2.61 (m, 5H), 3.56 (s, 3H), 3.79 (s, 3H), 3.91 (ddd, J = 7.5, 5.8, 3.0 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 4.44 (d, J = 11.2 Hz, 1H), 4.94−5.05 (m, 1H), 5.33 (s, 1H), 5.36 (s, 1H), 5.44 (s, 1H), 6.13 (s, 1H), 6.83−6.88 (m, 2H), 7.18−7.23 (m, 2H), 9.64 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 7.5 (q), 24.9 (t), 26.3 (t), 28.5 (t), 29.2 (t), 29.3 (d), 29.5 (t), 29.5 (t), 33.1 (t), 34.5 (t), 35.3 (t), 39.2 (t), 49.2 (d), 55.3 (q), 55.6 (q), 69.3 (d), 70.8 (t), 74.3 (d), 78.9 (d), 113.5 (d), 113.8 (d), 122.4 (t), 129.3 (d), 130.1 (s), 136.6 (s), 138.0 (s), 158.2 (s), 159.2 (s), 173.6 (s), 204.1 (s). HRMS (ESI+) m/z: calcd for $C_{34}H_{53}BrCl_2NO_6$ $[M + NH_4]^+$, 720.2428; found, 720.2447.

*(E)-4-Hydroxy-7-iodo-3,3,6-trimethylhept-6-en-2-one (**24**).* A solution of silylenolether **22**[14] (1.15 g, 7.3 mmol) in CH_2Cl_2 (10 mL) was added to a cooled solution (−78 °C) of aldehyde **23**[23] (1.26 g, 6 mmol) in CH_2Cl_2 (65 mL). BF_3·OEt_2 (0.58 mL, 4.71 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 2 h and quenched with the saturated solution of $NaHCO_3$ (75 mL). The residue was extracted three times with CH_2Cl_2, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (8:2) afforded 1.13 g of **24** (63%) as a racemic mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 3H), 1.17 (s, 3H), 1.89 (d, J = 0.9 Hz, 3H), 2.18 (s, 3H), 2.22−2.32 (m, 2H), 3.80−3.90 (m, 1H), 6.03 (q, J = 0.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 19.6 (q), 21.6 (q), 23.9 (q), 26.4 (q), 41.9 (t), 51.5 (s), 73.4 (d), 77.2 (d), 145.0 (s), 214.5 (s). HRMS (ESI+) m/z: calcd for $C_{10}H_{18}IO_2$ $[M + H]^+$, 297.0346; found, 297.0340.

*(R,E)-1-Iodo-2,5,5-trimethyl-6-oxohept-1-en-4-yl-(R)-2-methoxy-2-phenylacetate (**25**).* (*R*)-(−)-α-MPA (565 mg, 3.4 mmol) and EDC·HCl (862 mg, 4.5 mmol) were added to a solution of alcohol **24** (596 mg, 2 mmol) in THF (15 mL), then DMAP (60 mg, 0.5 mmol) was added, and the solution was stirred at 45 °C for 16 h. The solution was poured into Et_2O (15 mL) and washed with NH_4Cl saturated solution (2 × 15 mL). The organic residue was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (90:10) yielded the corresponding esters **25-R,R** (366 mg, 41%) and **25-R,S** (375 mg, 42%) as colorless oils.

***25-R,R** Characterization.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (s, 3H), 0.94 (s, 3H), 1.89 (d, J = 0.8 Hz, 3H), 1.90 (s, 3H), 2.20−2.35 (m, 2H), 3.43 (s, 3H), 4.65 (s, 1H), 5.36 (dd, J = 10.3, 2.5 Hz, 1H), 5.88 (br s, 1H), 7.31−7.42 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 19.6 (q), 21.4 (q), 23.5 (q), 26.0 (q), 40.7 (t), 51.1 (s), 58.0 (q), 74.5 (d), 77.7 (d), 82.6 (d), 127.3 (d), 128.7 (d), 128.9 (d), 136.3 (s), 143.9 (s), 169.7 (s), 210.7 (s). HRMS (ESI+) m/z: calcd for $C_{19}H_{25}INaO_4$ $[M + Na]^+$, 467.0690; found, 467.0692.

***25-R,S** Characterization.* ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 3H), 1.12 (s, 3H), 1.76 (d, J = 1.1 Hz, 3H), 2.12 (s, 3H), 2.13−2.15 (m, 2H), 3.40 (s, 3H), 4.69 (s, 1H), 5.33 (d, J = 1.1 Hz, 1H), 5.40 (t, J = 6.0 Hz, 1H), 7.32−7.40 (m, 5H).

*(R,E)-6-Iodo-2,5-dimethyl-2-(2-methyl-1,3-dioxolan-2-yl)-hex-5-en-3-yl-(R)-2-methoxy-2-phenylacetate (**S12**).* Trimethylsilyl trifluoromethanesulfonate (TMSOTf; 15 μL, 0.08 mmol) was added over a solution of ketone **25-R,R** (360 mg, 0.81 mmol) and 1,2-bis(trimethylsiloxy)ethane (500 mg, 2.43 mmol) in CH_2Cl_2 at −78 °C, and the mixture was left to evolve to rt and stirred at rt for additional 48 h. The reaction mixture

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was quenched with 0.1 mL of pyridine, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (90:10) yielded ketal **S12** (335 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.62 (s, 3H), 0.73 (s, 3H), 1.12 (s, 3H), 1.87 (s, 3H), 2.43 (dd, J = 14.3, 11.3 Hz, 1H), 2.68 (dd, J = 14.3, 1.9 Hz, 1H), 3.43 (s, 3H), 3.69−3.88 (m, 4H), 4.63 (s, 1H), 5.19 (dd, J = 11.3, 1.9 Hz, 1H), 5.88 (s, 1H), 7.28−7.43 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 17.7 (q), 20.0 (q), 20.5 (q), 23.6 (q), 41.4 (t), 45.8 (s), 58.2 (q), 64.4 (t), 64.7 (t), 75.0 (d), 76.9 (d), 82.7 (d), 112.4 (s), 127.4 (d), 128.4 (d), 128.6 (s), 136.5 (s), 145.1 (s), 169.7 (s). HRMS (ESI+) m/z: calcd for $C_{21}H_{29}INaO_5$ $[M + Na]^+$, 511.0952; found, 511.0962.

*(R,E)-6-Iodo-2,5-dimethyl-2-(2-methyl-1,3-dioxolan-2-yl)-hex-5-en-3-ol (**26**).* LiOH·H_2O (315 mg, 8.3 mmol) was added to a solution of **S12** (320 mg, 0.65 mmol) in MeOH (8 mL), and the solution was stirred at 65 °C for 16 h. The reaction mixture was added to a separatory funnel containing Et_2O (10 mL) and H_2O (10 mL), and it was extracted two times with Et_2O (10 mL). The organic layer was washed with $NaHCO_3$ saturated solution (15 mL) and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure yielding alcohol **26** (205 mg, 0.60 mmol) that was used in the next step without further purification.

*(R,E)-tert-Butyl((6-iodo-2,5-dimethyl-2-(2-methyl-1,3-dioxolan-2-yl)hex-5-en-3-yl)oxy)dimethylsilane (**S13**).* Triethylamine (0.33 mL, 2.4 mmol) and TBSOTf (0.23 mL, 1 mmol) were sequentially added to a solution of crude alcohol **26** (205 mg, 0.60 mmol) in CH_2Cl_2 (8 mL) at −20 °C, and the mixture was stirred for 15 min at −20 °C and then 60 min at rt. The reaction mixture was quenched with NH_4Cl saturated solution (10 mL), extracted with CH_2Cl_2 (2 × 10 mL), and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (95:5) yielded **S13** (200 mg, 68% for two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.05 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 0.94 (s, 3H), 0.97 (s, 3H), 1.29 (s, 3H), 1.82 (s, 3H), 2.32 (dd, J = 14.5, 9.0 Hz, 1H), 2.88 (dd, J = 14.5, 2.1 Hz, 1H), 3.70 (dd, J = 9.0, 2.1 Hz, 1H), 3.81−3.96 (m, 4H), 5.91 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ −3.5 (q), −3.2 (q), 18.4 (q), 20.8 (q), 23.0 (q), 23.9 (q), 26.2 (q), 30.3 (s), 45.0 (t), 47.4 (s), 64.3 (t), 64.7 (t), 75.2 (d), 77.9 (d), 113.2 (s), 145.8 (s). HRMS (ESI+) m/z: calcd for $C_{18}H_{35}INaO_3Si$ $[M + Na]^+$, 477.1298; found, 477.1299.

*(R,E)-4-((tert-Butyldimethylsilyl)oxy)-7-iodo-3,3,6-trimethylhept-6-en-2-one (**9**).* PTSA·H_2O (3.8 mg, 0.02 mmol) was added to a solution of **S13** (66 mg, 0.15 mmol) in acetone (5 mL), and the reaction mixture was stirred at rt for 30 min. Then, it was quenched with two drops of triethylamine, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (95:5) yielded enantiopure ketone **9** (59 mg, quant.) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.01 (s, 3H), 0.02 (s, 3H), 0.87 (s, 9H), 1.10 (s, 6H), 1.82 (s, 3H), 2.14 (s, 3H), 2.21−2.24 (m, 2H), 4.05−4.09 (m, 1H), 5.94 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ −4.0 (q), −3.7 (q), 18.2 (s), 19.6 (q), 22.9 (q), 23.8 (q), 26.0 (q), 27.1 (q), 44.8 (t), 53.0 (s), 74.0 (d), 78.8 (d), 144.5 (s), 213.4 (s). HRMS (ESI+) m/z: calcd for $C_{16}H_{31}INaO_2Si$ $[M + Na]^+$, 433.1036; found, 433.1039.

*(1S,5R,9S,11S,13R,15R,Z)-9-((tert-Butyldimethylsilyl)oxy)-15-((1R,5R,E)-5-((tert-butyldimethylsilyl)oxy)-1-hydroxy-3,6,6-trimethyl-7-oxooct-2-en-1-yl)-7,11-dimethyl-5-((triisopropylsilyl)oxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-en-3-one (**6**).* DMF was degassed using a freeze-thaw-pump technique. $CrCl_2$ and $NiCl_2$ were weighted in a glovebox. A mixture of iodoalkene **9** (52 mg, 0.13 mmol) and aldehyde **4**[5] (50 mg, 0.083 mmol) in DMF (0.5 + 0.2 mL rinse) was cannulated to a solution of $CrCl_2$ (202 mg, 1.64 mmol) and $NiCl_2$ (2 mg, 1 m/m % $CrCl_2$) in DMF (1 mL), and the solution was stirred at rt for 48 h. The reaction mixture was filtered through Celite and washed with Et_2O. The organic ethereal phase was washed with H_2O (2 × 10 mL) and brine (10 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (8:2) yielded alcohol **6** (13.5 mg, 19%) as a single diastereomer as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 0.91 (d, J = 6.1 Hz, 3H), 1.03 (br s, 21H), 1.09 (s, 3H), 1.12 (s, 3H), 1.27 (m, 1H), 1.42 (m, 1H), 1.60 (m, 1H), 1.70 (m, 1H), 1.71 (s, 3H), 1.72 (s, 3H), 1.91 (m, 1H), 2.03−2.11 (m, 2H), 2.11 (m, 1H), 2.14 (s, 3H), 2.24 (m, 1H), 2.39 (m, 1H), 2.50 (m, 1H), 2.70 (m, 1H), 2.73 (m, 1H), 3.89 (dd, J = 4.6, 1.3 Hz, 1H), 4.06 (m, 1H), 4.19 (t, J = 6.1 Hz, 1H), 4.33 (m, 1H), 4.43 (m, 1H), 5.05 (m, 1H), 5.15 (d, J = 5.6 Hz, 1H), 5.42 (m, 1H), 5.44 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ −4.4 (q), −4.1 (q), −3.9 (q), 12.3 (d), 17.4 (q), 17.7 (s), 17.9 (q), 18.1 (s), 19.3 (q), 20.7 (q), 23.0 (q), 23.1 (q), 25.9 (q), 26.0 (q), 26.7 (d), 27.1 (q), 33.9 (t), 38.3 (t), 40.9 (t), 45.0 (t), 46.0 (t), 46.9 (t), 53.1 (s), 68.4 (d), 69.0 (d), 70.3 (d), 74.1 (d), 76.1 (d), 78.5 (d), 87.3 (d), 125.7 (d), 132.7 (d), 138.9 (s), 143.4 (s), 171.1 (s), 213.9 (s). HRMS (ESI+) m/z: calcd for $C_{48}H_{92}NaO_8Si_3$ $[M + Na]^+$, 903.5992; found, 903.5993.

*(1R,5R,E)-5-((tert-Butyldimethylsilyl)oxy)-1-((1S,5R,9S,11S,13R,15S,Z)-9-((tert-butyldimethylsilyl)oxy)-7,11-dimethyl-3-oxo-5-((triisopropylsilyl)oxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-en-15-yl)-3,6,6-trimethyl-7-oxooct-2-en-1-yl-(R)-2-methoxy-2-phenylacetate (**27**).* (*R*)-(−)-α-MPA (7 mg, 0.04 mmol) and EDC·HCl (10 mg, 0.05 mmol) were added to a solution of alcohol **6** (4.3 mg, 0.005 mmol) in THF (0.25 mL), then DMAP (catalytic) was added, and the solution was stirred at 35 °C for 2 h. The solution was poured into Et_2O (5 mL) and washed with NH_4Cl saturated solution (2 × 3 mL). The organic residue was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Purification by silica gel column chromatography with hexane/EtOAc (90:10) yielded the corresponding ester **27** (2.2 mg, 48% br s m) and **6** (0.5 mg). ^{1}H NMR (500 MHz, $CDCl_2$-d_2): δ 0.04 (s, 6H), 0.08 (s, 6H), 0.82 (d, J = 6.1 Hz, 3H), 0.86 (s, 9H), 0.90 (s, 9H), 1.07 (s, 21H), 1.09 (s, 3H), 1.11 (s, 3H), 1.13−1.16 (m, 1H), 1.23−1.27 (m, 1H), 1.36−1.42 (m, 1H), 1.51−1.54 (m, 1H), 1.55−1.57 (m, 1H), 1.65 (d, J = 13.9 Hz, 1H), 1.73 (d, J = 1.4 Hz, 3H), 1.79 (d, J = 1.3 Hz, 3H), 1.86−1.91 (m, 1H), 2.08−2.11 (m, 1H), 2.14 (s, 3H), 2.21−2.29 (m, 2H), 2.44 (dd, J = 13.8, 7.4 Hz, 1H), 2.62−2.69 (m, 2H), 3.40 (s, 3H), 3.75 (ddd, J = 12.0, 7.9, 4.5 Hz, 1H), 3.88 (dd, J = 3.0, 1.2 Hz, 1H), 4.05 (dd, J = 9.9, 3.8 Hz, 1H), 4.23 (t, J = 5.8 Hz, 1H), 4.70 (s, 1H), 4.97−5.03 (m, 1H), 5.06 (dd, J = 6.0, 1.2 Hz, 1H), 5.40−5.45 (m, 1H), 5.49−5.54 (m, 1H), 5.75 (dd, J = 9.3, 3.0 Hz, 1H), 7.32−7.49 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_2$-d_2): δ −4.3 (q), −3.9 (q), −3.5 (q), 12.8 (d), 17.9 (q), 18.1 (q), 18.2 (q), 18.4 (s), 18.5 (s), 20.1 (q), 20.8 (q), 22.1 (q), 23.3 (q), 26.1 (q), 26.2 (q), 27.0 (d), 27.0 (q), 33.9 (t), 38.7 (t), 41.6 (t), 45.0 (t), 46.2 (t), 47.1 (t), 57.7 (q), 68.8 (d), 70.8 (d), 71.9 (d), 74.5 (d), 75.7 (d), 78.9 (d), 83.1 (d), 86.0 (d), 121.5 (d), 128.2 (d), 129.0 (d),

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129.2 (d), 132.9 (d), 133.5 (s), 137.1 (s), 142.1 (s), 169.9 (s), 170.8 (s), 213.0 (s). HRMS (ESI+) m/z: calcd for $C_{57}H_{104}NO_{10}Si_3$ $[M + NH_4]^+$, 1046.6963; found, 1046.6961.

*(1S,5R,9S,11S,13R,15S,Z)-9-((tert-Butyldimethylsilyl)oxy)-15-((4R,8R,E)-8-((tert-butyldimethylsilyl)oxy)-2,2,6,9,9,12,12-heptamethyl-10-methylene-3,11-dioxa-2,12-disilatridec-5-en-4-yl)-7,11-dimethyl-5-((triisopropylsilyl)oxy)-2,14-dioxabicyclo[11.2.1]hexadec-6-en-3-one (**31**).* Et_3N (14 μL, 0.1 mmol) and TMSOTf (11 μL, 0.06 mmol) were sequentially added to a solution of ketone **6** (8 mg, 0.01 mmol) in CH_2Cl_2 (0.7 mL) at 0 °C. The reaction mixture was stirred for 3 h at rt, diluted with CH_2Cl_2 (2 mL), and quenched with diluted NH_4Cl (1 mL). The organic layer was washed three times with diluted NH_4Cl, dried over $MgSO_4$, and concentrated under reduced pressure to obtain silylenolether **31** as a brownish oil (10 mg, quant). The crude was pure enough to continue the synthesis. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.00 (s, 3H), 0.03 (s, 3H), 0.06 (s, 6H), 0.07 (s, 9H), 0.21 (s, 9H), 0.85 (s, 9H), 0.86 (s, 9H), 0.88 (d, J = 2.9 Hz, 3H), 0.93 (s, 3H), 1.02 (s, 3H), 1.05 (s, 21H), 1.28−1.29 (m, 1H), 1.66 (s, 3H), 1.72 (s, 3H), 1.73−1.76 (m, 1H), 1.93−2.04 (m, 3H), 2.07−2.17 (m, 3H), 2.20−2.30 (m, 2H), 2.47−2.58 (m, 2H), 2.68 (dd, J = 14.6, 3.7 Hz, 1H), 3.94−3.96 (m, 2H), 3.96−4.00 (m, 2H), 4.10 (d, J = 1.6 Hz, 1H), 4.29−4.38 (m, 1H), 4.44 (dd, J = 9.1, 2.7 Hz, 1H), 4.89−4.95 (m, 1H), 5.21 (d, J = 5.7 Hz, 1H), 5.24−5.27 (m, 1H), 5.40−5.43 (m, 1H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b00125.

Absolute configuration determinations and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ ADDITIONAL NOTES

[a]From now onward in this publication, carbon numeration used in the structure determination of PMs B−D will be used for every molecular structure.

[b]The structural and stereochemical characterization was performed in the R + D department of PharmaMar.

[c]Other protecting groups such as TBS or PMB were tested with worst synthetic results.

[d]Two singlets at 6.18 and 6.25 ppm with 89:11 relative area were observed in the ^{1}H NMR.

[e]The proportion of diastereomers was determined by the NMR analysis of the purified ketol.

[f]See Supporting Information.

[g]The C15-(R) configuration is the opposite to the one present in the NPs PMs C and D. See Supporting Information.

■ REFERENCES

(1) Lorente, A.; Makowski, K.; Albericio, F. Bioactive Marine Polyketides as Potential and Promising Drugs. *Ann. Med. Chem. Res.* **2014**, *1*, 1003−1013.

(2) Lorente, A.; Gil, A.; Fernández, R.; Cuevas, C.; Albericio, F.; Álvarez, M. Phormidolides B and C, Cytotoxic Agents from the Sea: Enantioselective Synthesis of the Macrocyclic Core. *Chem.—Eur. J.* **2015**, *21*, 150−156.

(3) Williamson, R. T.; Boulanger, A.; Vulpanovici, A.; Roberts, M.; Gerwick, W. H. Structure and Absolute Stereochemistry of Phormidolide, a New Toxic Metabolite from the Marine Cyanobacterium Phormidium Sp. *J. Org. Chem.* **2002**, *67*, 7927−7936.

(4) Murakami, M.; Matsuda, H.; Makabe, K.; Yamaguchi, K. Oscillariolide, a Novel Macrolide from a Blue-Green Alga Oscillatoria Sp. *Tetrahedron Lett.* **1991**, *32*, 2391−2394.

(5) Gil, A.; Lorente, A.; Albericio, F.; Álvarez, M. Stereoselective Allylstannane Addition for a Convergent Synthesis of a Complex Molecule. *Org. Lett.* **2015**, *17*, 6246−6249.

(6) Gil, A.; Lamariano-Merketegi, J.; Lorente, A.; Albericio, F.; Álvarez, M. Enantioselective Synthesis of the Polyhydroxylated Chain of Oscillariolide and Phormidolides A−C. *Org. Lett.* **2016**, *18*, 4485−4487.

(7) Gil, A.; Lamariano-Merketegi, J.; Lorente, A.; Albericio, F.; Álvarez, M. Synthesis of (E)-4-Bromo-3-Methoxybut-3-En-2-One, the Key Fragment in the Polyhydroxylated Chain Common to Oscillariolide and Phormidolides A-C. *Chem.—Eur. J.* **2016**, *22*, 7033−7035.

(8) Gil, A.; Albericio, F.; Álvarez, M. Role of the Nozaki−Hiyama−Takai−Kishi Reaction in the Synthesis of Natural Products. *Chem. Rev.* **2017**, *117*, 8420−8446.

(9) Negoro, T.; Ikeda, Y. Regio- and Stereochemistry of Bromochlorinations of Alkynes with Molecular Bromine Chloride and Dichlorobromate(1−) Ion. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3515−3518.

(10) De Meyer, M.; Levert, J. M.; Vanclef, A. Étude Vibrationnelle Des Trichlorures Organiques: (N-C4H9)4NCl3, ϕ4AsCl3, C5H6NCl3, ϕ4PCl3. *Bull. Soc. Chim. Belg.* **2010**, *92*, 699−710.

(11) Oikaw, Y.; Yoshioka, T.; Yonemitsu, O. Protection of Hydroxy Groups by Intramolecular Oxidative Formation of Methoxybenzylidene Acetals with DDQ. *Tetrahedron Lett.* **1982**, *23*, 889−892.

(12) Hoye, T. R.; Jeffrey, C. S.; Shao, F. Mosher Ester Analysis for the Determination of Absolute Configuration of Stereogenic (Chiral) Carbinol Carbons. *Nat. Protoc.* **2007**, *2*, 2451−2458.

(13) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. Mitsunobu and Related Reactions: Advances and Applications. *Chem. Rev.* **2009**, *109*, 2551−2651.

(14) Blanco, L.; Amice, P.; Conia, J.-M. Reaction of Chloromethylcarbene with Trimethylsilyl Enol Ethers; Preparation of α-Methylene Ketones and α-Methyl-A,β-Unsaturated Ketones and Aldehydes. *Synthesis* **1981**, 291−293.

(15) Amans, D.; Bareille, L.; Bellosta, V.; Cossy, J. Synthesis of the Monomeric Counterpart of Marinomycin A. *J. Org. Chem.* **2009**, *74*, 7665−7674.

(16) Bülow, L.; Naini, A.; Fohrer, J.; Kalesse, M. A Kiyooka Aldol Approach for the Synthesis of the C(14)−C(23) Segment of the Diastereomeric Analog of Tedanolide C. *Org. Lett.* **2011**, *13*, 6038−6041.

DOI: 10.1021/acsomega.8b00125
ACS Omega 2018, 3, 2351−2362

(17) Corey, E. J.; Cywin, C. L.; Roper, T. D. Enantioselective Mukaiyama-Aldol and Aldol-Dihydropyrone Annulation Reactions Catalyzed by a Tryptophan-Derived Oxazaborolidine. *Tetrahedron Lett.* **1992**, *33*, 6907−6910.
(18) Seco, J. M.; Quiñoá, E.; Riguera, R. The Assignment of Absolute Configuration by NMR. *Chem. Rev.* **2004**, *104*, 17−118.
(19) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. Are Both the (R)- and the (S)-MPA Esters Really Needed for the Assignment of the Absolute Configuration of Secondary Alcohols by NMR? The Use of a Single Derivative. *J. Am. Chem. Soc.* **1998**, *120*, 877−882.
(20) Yen, C.-F.; Liao, C.-C. Concise and Efficient Total Synthesis of Lycopodium Alkaloid Magellanine. *Angew. Chem.* **2002**, *114*, 4264−4267.
(21) Lamariano-Merketegi, J.; Lorente, A.; Gil, A.; Albericio, F.; Álvarez, M. Addition of Vinylmetallic Reagents to Chiral 2-Formyltetrahydrofuran. *Eur. J. Org. Chem.* **2015**, 235−241.
(22) Pulukuri, K. K.; Chakraborty, T. K. Formal Synthesis of Actin Binding Macrolide Rhizopodin. *Org. Lett.* **2014**, *16*, 2284−2287.

DOI: 10.1021/acsomega.8b00125
ACS Omega 2018, 3, 2351−2362