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Formal Total Synthesis of Amphidinolide Q

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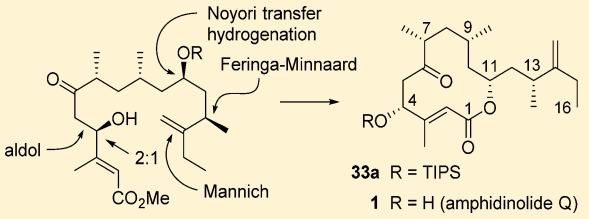
Supporting Information

ABSTRACT: With the preparation of macrolactone **33a** we describe a formal total synthesis of amphidinolide Q. The corresponding seco acid **32** originated from an aldol reaction between methyl ketone **6** and methyl (*E*)-3-methyl-4-oxobut-2-enoate (**5**). The synthesis of ketone **6** (C5−C16 fragment) started with desymmetrized *meso*-diol **9**. Chain extension reactions involving cyanide, lithium trimethylsilylacetylide, and a Wittig reaction led to aldehyde **22**. The two additional stereocenters at C11 and C13 were set by a Noyori transfer hydrogenation on alkynone **14** and a Feringa−Minnaard methyl cuprate addition on enoate **21**. The but-1-ene-2-yl subunit on the side chain terminus was created from an unsaturated aldehyde by a substitution reaction on a derived allylic tosylate.



INTRODUCTION

Amphidinolides are a family of bioactive macrolides that have been isolated from marine dinoflagellates.[1] The structures of these macrolides vary from relatively simple to rather complex molecules. Thus, amphidinolides with ring sizes from 12 to 29 are known in the literature. Amphidinolide Q (**1**) and W (**2**) both feature a 12-membered lactone ring, whereas amphidinolide H (**3**) with a ring size of 29 is the biggest of these natural products (Figure 1). Some of the amphidinolides display very

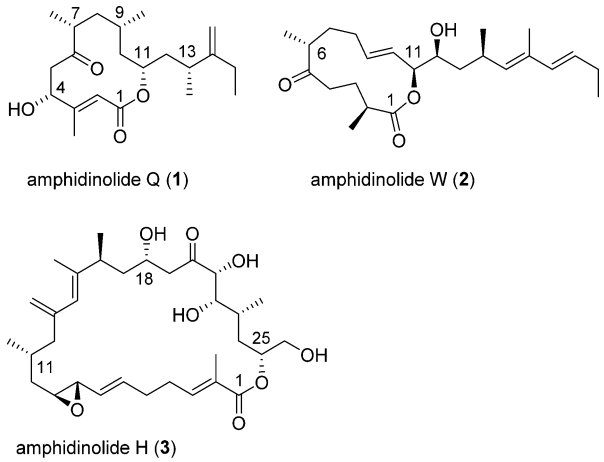


Figure 1. Structures of the 12-membered amphidinolides Q (**1**), W (**2**), and the 26-membered amphidinolide H (**3**).

potent cytotoxicity against tumor cell lines. These more active representatives contain a vinyl epoxide in the macrocyclic ring. The cytotoxicity for **1** and **2** lies in the lower micromolar range (L210 marine lymphoma cells).[1]

Even though the amphidinolides are polyketides, their biosynthesis in part is rather unusual. Thus, labeling studies showed that the side chain methyl and methylene carbons are not from propionate building blocks, but rather originate from C2 of acetates. As the isolated amounts of the amphidinolides are rather small, total synthesis is the only alternative to secure material for further biological studies.[2] Therefore, we became interested in the synthesis of amphidinolide Q (**1**). It was isolated by the Kobayashi group from the cultured marine dinoflagellate *Amphidinium* sp., and its structure could be elucidated by NMR spectroscopy.[3,4] Even though it is of moderate complexity only one total synthesis is known so far.[5] Some synthetic studies have also been described.[6]

RESULTS AND DISCUSSION

As an initial toehold in the retrosynthetic analysis we recognized the presence of the *syn*-1,3-dimethyl groups at C7 and C9. Accordingly, our aim was to trace back the carbon skeleton of **1** to *meso*-diol **8** (Scheme 1). Thus, seco acid **4** was disconnected to known aldehyde[7] **5** and methyl ketone **6**. The butenyl fragment attached to C13 was thought to come from a Mannich reaction and a substitution reaction on an allylic alcohol derivative. This led to thioester **7** as advanced precursor. The stereocenter at C11 would be generated by a Noyori transfer hydrogenation on an alkynone whereas C13 would be obtained via an asymmetric methylcuprate addition to an unsaturated thioester.

Accordingly, *meso*-diol **8** was converted to alcohol **9** via enzyme-mediated desymmetrization as a key step.[8] Chain extension on the derived tosylate[8f] **10** led to nitrile **11**.[9] Its reduction to aldehyde **12**, followed by reaction with lithium trimethylsilylacetylide, led to propargylic alcohol **13** as a mixture of C11 diastereomers (Scheme 2). After oxidation of **13** to alkynone **14** with Dess-Martin periodinane a Noyori transfer hydrogenation[10] using (*R*,*R*)-Ru catalyst **15** gave alkynol (3*R*)-**13** as essentially one diastereomer. Further steps that included silylation of the hydroxyl group to silyl ether **16**, base-induced cleavage of the trimethylsilyl group, and Lindlar

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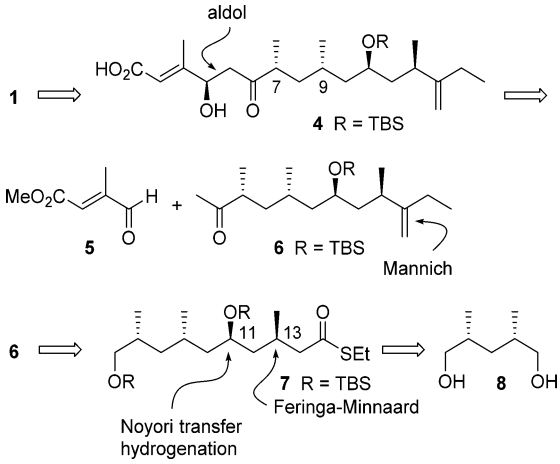
Scheme 1. Retrosynthetic Plan for the Synthesis of Amphidinolide Q Featuring an Aldol Reaction To Create the C4−C5 Bond, a Noyori Transfer Hydrogenation To Establish the C11 Stereocenter, and a Feringa−Minnaard Asymmetric Cuprate Addition To Create Stereocenter C13 Leading to *meso*-Diol 8 as Starting Material

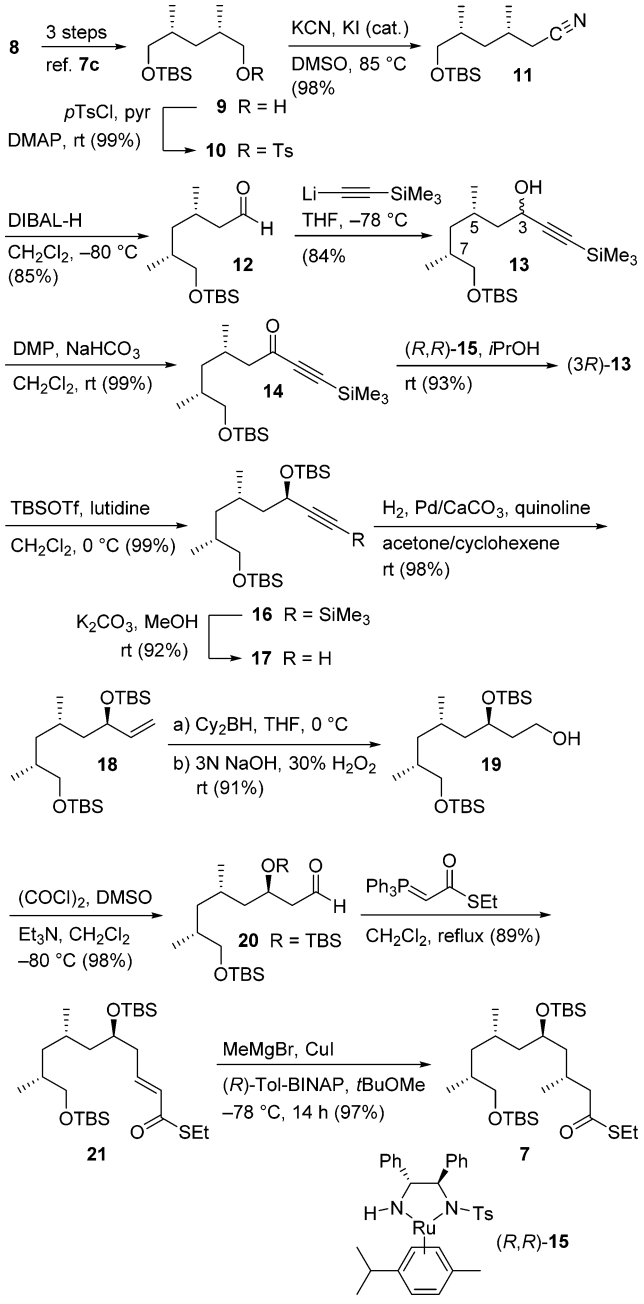


hydrogenation secured terminal alkene **18**. Hydroboration of the double bond using dicyclohexylborane followed by oxidative workup led to primary alcohol **19** in good overall yield. We also tried to perform a Brown allylation[11] on aldehyde **12** using the allylation reagent obtained from (−)-Ipc$_2$BOMe. However, this reaction gave only around 15% of the desired homoallylic alcohol together with recovered starting material. Continuing with the synthesis, the alcohol function of **19** was oxidized to aldehyde **20** which was subjected to chain extension with *S*-ethyl 2-(triphenyl-λ^5-phosphanylidene)ethanethioate[12] giving rise to unsaturated thioester **21**. The asymmetric methylcuprate addition[13,14] in the presence of (*R*)-Tol-BINAP provided thioester **7** (C6−C15 fragment) on gram scale.

We next required chain extension on both sides of this fragment. First, ester **7** was reduced to aldehyde **22**, before a Mannich reaction[15] was performed to give enal **23** (Scheme 3). After reduction of the aldehyde to allylic alcohol **24**, and reaction of this alcohol with toluenesulfonic anhydride in the presence of Et$_3$N, tosylate **25** was obtained.[16] Treatment of **25** with dimethylcuprate at low temperature completed this region of the molecule. Conversion of **26** to methyl ketone **6** involved selective cleavage of the primary silyl ether, oxidation of alcohol **27** to aldehyde **28**, reaction of **28** with methyllithium, and Swern oxidation of the intermediate secondary alcohol to ketone **6**.

With building block **6** in hand, we now could focus on the crucial aldol reaction with aldehyde **5** (Table 1). Using LDA as base in THF at −78 °C a low yield of the hydroxyketones **29** was obtained (Scheme 4). The observed diastereoselectivity of 1:1 indicated that there was no substrate control operative. An even lower yield (14%) resulted when trichloro isopropoxy titanium was used for the enolization. Higher chemical yields were realized if boron enolates of methyl ketone **6** were employed. Thus, with dicyclohexylboron triflate (Cy$_2$BOTf)/Et$_3$N in CH$_2$Cl$_2$ the derived enolate reacted with aldehyde **5** in 71% yield (dr = 1:1). Even higher yields were observed when (−)-diisopinocamphenyl boron triflate/Hünig's base was used for enolate formation. In this case, the desired C4 diastereomer was formed as the major one. Unfortunately, the two

Scheme 2. Conversion of *meso*-Diol 8 to Thioester 7



diastereomers could not be separated. Moreover, there were no peaks in the ^{1}H NMR that could have been used for determination of the ratio by integration. We hoped that it would be possible to separate the isomers on the macrolactone stage.

Continuing toward the macrolactone, the 4-OH group was protected as triisopropylsilyl ether before the TBS ether at C11 was cleaved by acid induced transetherification. Gratifyingly, at the stage of hydroxyl ester **31**, separation of the C4 isomers was possible, which allowed determination of the ratio by weight. While classical base mediated saponification of ester **31** turned out to be difficult, hydrolysis of **31** with trimethyltin hydroxide[17] was possible (79% yield). Subjecting the seco acid **32** to the conditions of a Yamaguchi macrolactonization led to two macrolactones **33a** and **33b** that indeed could be separated by chromatography even more easily than hydroxy

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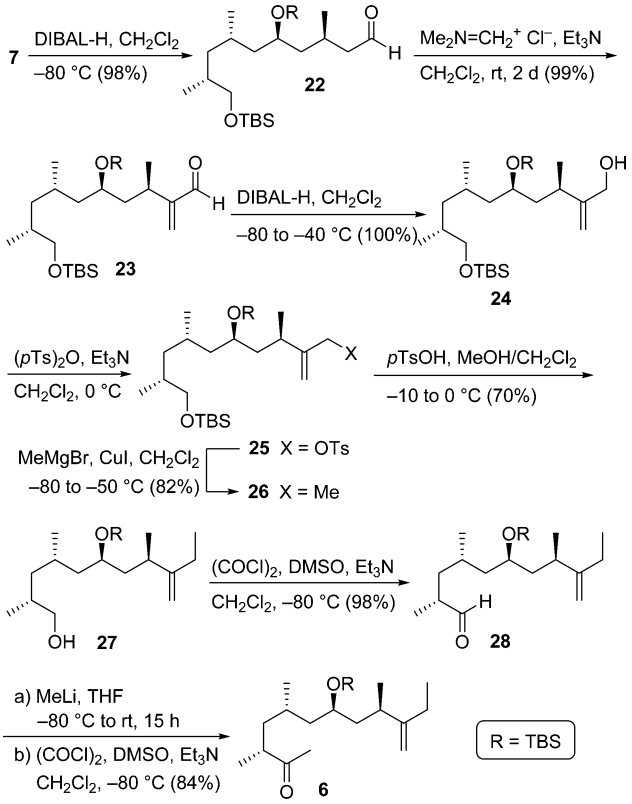
Scheme 3. Conversion of Thioester 7 to Methyl Ketone 6[a]



[a]Installation of the butenyl group via Mannich reaction on aldehyde **22** and reaction of derived tosylate **25** with dimethylcuprate.

Table 1. Summary of the Results for the Aldol Reactions

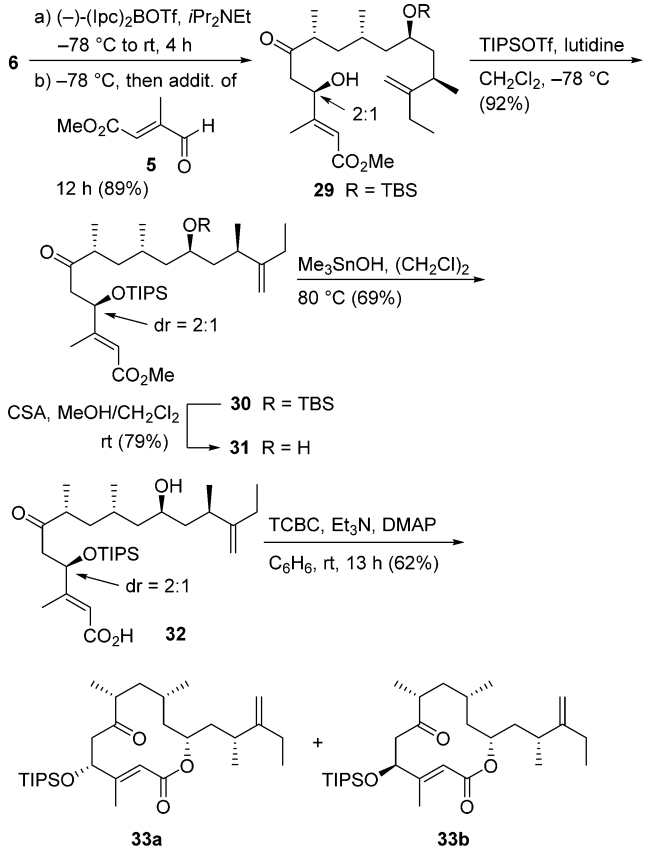
entry	reagent	enolization temp	yield (%)	dr
1	$TiCl_3(OiPr)$	−78 °C	14	1:1
2	LDA	−78 °C	24	1:1
3	$cHex_2BOTf$	−78 °C	71	1:1
4	$(-)\text{-}(Ipc)_2BOTf$	−78 °C to rt	89	2:1
5	$(-)\text{-}(Ipc)_2BOTf$	−78 °C to −50 °C	80	2:1

ester **31**. Therefore, in practice, the mixture of diastereomers from the aldol reaction was carried on to the macrolactone stage. The NMR data of the major isomer **33a** perfectly matched with the published data.[5]

CONCLUSION

In conclusion, we developed a novel route to the macrolactone amphidinolide Q. Even though seco acid **4** was further disconnected into fragments of unequal sizes, the C5−C16 fragment **6** could be efficiently prepared from known alcohol **9**, which itself is easily available from *meso*-diol **8**, in a sequence of 22 steps. Key steps include a Noyori transfer hydrogenation on alkynone **14**, a Feringa−Minnaard asymmetric cuprate addition on unsaturated thioester **21**, and a Mannich reaction on aldehyde **22**. The resulting enal **23** served as an entry point to create the butenyl terminus of this natural product. Thus, the derived allylic alcohol **24** was converted to the corresponding tosylate which upon reaction with dimethylcuprate gave the required functionality. The key fragments, aldehyde **5** and methyl ketone **6**, were combined in a boron aldol reaction. After Yamaguchi macrolactonization, the C4 diastereomers (2:1 ratio) could be separated by chromatography.

Scheme 4. Aldol Reaction of Methyl Ketone 6 with Aldehyde 5 and Completion of the Formal Synthesis of Amphidinolide Q (1)



TCBC = 2,4,6-trichlorobenzoyl chloride.

EXPERIMENTAL SECTION

General. Reactions were generally run under a nitrogen atmosphere in oven-dried glassware. Progress of the reactions was followed using TLC plates "POLYGRAM SIL G/UV254", petroleum ether, ethyl acetate (EtOAc), cyclohexane (*c*Hex), dichloromethane, methanol, and mixtures of them as an eluent. Dry diethyl ether (Et_2O) and tetrahydrofuran were distilled from sodium and benzophenone, whereas dry CH_2Cl_2, methanol, and ethyl acetate were distilled from CaH_2. Distilled petroleum ether with a boiling range of 40−60 °C was used. ^1H NMR (400.160 MHz) and ^{13}C NMR (100.620 MHz) spectra were measured using $CDCl_3$ as solvent at room temperature. Peak assignments were done by NMR spectroscopy (^1H, ^{13}C, DEPT-135, H,H−COSY, HSQC, and HMBC). High-resolution mass spectra (HRMS) were recorded on an instrument with electron spray ionization (ESI) and a TOF mass detector (mass range: 50−20 000 *m*/*z*, mass accuracy: 600 ppb RMS error). Optical rotations: Here, the sodium D line (589 nm) was used, *c* = g per 100 mL. Not all the compound names may correspond to IUPAC nomenclature.

(2S,4R)-5-{(tert-Butyldimethylsilyl)oxy}-2,4-dimethylpentyl-4-methylbenzenesulfonate[8f] ***(10).*** To a solution of alcohol[8e] **9** (1.00 g, 4.06 mmol) in pyridine (2 mL) were added *para*-toluenesulfonyl chloride (0.97 g, 5.07 mmol, 1.25 equiv) and DMAP (0.008 g, 0.08 mmol, 0.02 equiv) at 0 °C. The reaction mixture was allowed to warm and stirred for 3 h at room temperature, before it was quenched with HCl (1.0 N, 7 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with saturated Na_2CO_3 solution (2 × 7 mL) and saturated NaCl solution (1 × 7 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give 1.60 g (99%) of tosylate **10** as a yellow oil. The crude product was used in next step without further purification. R_f = 0.3 (petroleum ether/ethyl acetate, 9:1); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s,

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6H, $(CH_3)_2Si$), 0.82 (d, J = 6.8 Hz, 3H, 4-CH_3), 0.86 (s, 9H, $(CH_3)_3Si$), 0.90 (d, J = 6.8 Hz, 3H, 2-CH_3), 0.88−0.93 (m, 1H, 3-H), 1.29−1.40 (m, 1H, 3-H), 1.50−1.64 (m, 1H, 4-H), 1.82−1.95 (m, 1H, 2-H), 2.44 (s, 3H, p-CH_3), 3.29 (dd, J = 6.1, 9.8.Hz, 1H, 1-H), 3.36 (dd, J = 5.6, 9.8 Hz, 1H, 1-H), 3.73 (dd, J = 7.1, 9.3 Hz, 1H, 5-H), 3.89 (dd, J = 5.0, 9.3 Hz, 1H, 5-H), 7.33 (d, J = 8.6 Hz, 2H, m-H), 7.77 (d, J = 8.3 Hz, 2H, o-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.5 ($(CH_3)_2Si$), 17.36, 17.40 (4-CH_3, 2-CH_3), 18.2 ($(CH_3)_3CSi$), 21.6 (p-CH_3), 25.8 ($(CH_3)_3CSi$), 30.4 (C-2), 32.8 (C-3), 36.8 (C-4), 67.8 (C-5), 75.1 (C-1), 127.0 (Ar), 127.9 (Ar), 129.8 (Ar), 130.2 (Ar), 133.1 (Ar).

*(3S,5R)-6-{(tert-Butyldimethylsilyl)oxy}-3,5-dimethylhexanenitrile[9] (**11**).* To a solution of tosylate **10** (1.54 g, 3.84 mmol) in dry DMSO (12 mL) were added KCN (0.626 g, 9.61 mmol, 2.5 equiv) and a small amount of potassium iodide (catalytic amount, about 10 mg) at room temperature. The reaction mixture was then stirred for 2 h at 85 °C, before it was cooled to 0 °C, diluted with water (10 mL), and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (2 × 10 mL) and saturated NaCl solution (10 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to afford pure nitrile **11** (0.90 g, 98%) as a colorless oil. R_f = 0.2 (petroleum ether/ethyl acetate, 9:1); $[\alpha]^{22}_D$ = +10.8 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_2Si$) (d, J = 6.7 Hz, 3H, 5-CH_3), 1.07 (d, J = 6.7 Hz, 3H, 3-CH_3), 1.01−1.13 (m, 1H, 4-H), 1.41−1.49 (m, 1H, 4-H), 1.56−1.69 (m, 1H, 3-H), 1.89−2.03 (m, 1H, 5-H), 2.16 (dd, J = 7.1, 16.7 Hz, 1H, 2-H), 2.31 (dd, J = 5.0, 16.7 Hz, 1H, 2-H), 3.34−3.43 (m, 2H, 6-H): ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.5 ($(CH_3)_2Si$), 17.1 (5-CH_3), 18.2 ($(CH_3)_3CSi$), 20.1 (3-CH_3), 24.3 (C-3), 25.8 ($(CH_3)_3CSi$), 28.0 (C-2), 33.1 (C-5), 40.0 (C-4), 67.9 (C-6), 118.7 (CN); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{29}NOSiNa$ 278.1911; found 278.1913.

*(3S,5R)-6-{(tert-Butyldimethylsilyl)oxy}-3,5-dimethylhexanal (**12**).* To a solution of nitrile **11** (0.825 g, 3.23 mmol) in CH_2Cl_2 (35 mL) at −80 °C was added DIBAL-H in hexane (1 M, 6.5 mL, 6.46 mmol, 2.0 equiv) in a dropwise fashion. After stirring the mixture at −80 °C for 3.5 h, excess DIBAL-H was quenched with ethyl acetate (2 mL) before saturated NH_4Cl solution (30 mL) was added. The mixture was transferred to a separation funnel, and both layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude aldehyde was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give pure aldehyde **12** (0.705 g, 85%) as a colorless oil. R_f = 0.4 (petroleum ether/ethyl acetate, 20:1); $[\alpha]^{22}_D$ = +0.5 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3Si$) (d, J = 6.7 Hz, 3H, 5-CH_3), 0.95 (d, J = 6.7 Hz, 3H, 3-CH_3), 0.97−1.04 (m, 1H, 4-H), 1.31−1.41 (m, 1H, 4-H), 1.57−1.68 (m, 1H, 5-H), 2.10−2.19 (m, 2H, 3-H, 2-H), 2.32−2.42 (m, 1H, 2-H), 3.35 (dd, J = 6.1, 9.6 Hz, 1H, 6-H), 3.41 (dd, J = 5.6, 9.6 Hz, 1H, 6-H), 9.73 (t, J = 2.0 Hz, 1H, 1-CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.4 ($(CH_3)_2Si$), 17.3 (5-CH_3), 18.3 ($(CH_3)_3CSi$), 20.7 (3-CH_3), 25.7 (C-3), 25.9 ($(CH_3)_3CSi$), 33.1 (C-5), 40.9 (C-4), 50.8 (C-2), 67.98 (C-6) 203.0 (CHO); HRMS (ESI-TOF) m/z: [M + Na + CH_3OH (hemiacetal)]$^+$ calcd for $C_{15}H_{34}O_3SiNa$ 313.2169; found 313.2172.

*(5S,7R)-8-{(tert-Butyldimethylsilyl)oxy}-5,7-dimethyloct-1-yn-3-ol (**13**).* A solution of trimethylsilylacetylene (0.463 mL, 3.25 mmol, 1.2 equiv) in dry THF (9 mL), cooled to −78 °C, was treated dropwise with nBuLi (2.5 M in hexane, 1.3 mL, 3.25 mmol, 1.2 equiv). The reaction mixture was stirred for 30 min at −78 °C, before a solution of aldehyde **12** (0.70 g, 2.71 mmol) in THF (15 mL) was added dropwise via cannula. After 3 h of stirring at −78 °C, the reaction mixture was quenched with saturated NH_4Cl (10 mL) and the cooling system was removed. The mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl solution (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to afford pure alkynol **13** (0.810 g, 84%) as a colorless oil (mixture of diastereomers at C3, (3R)-**13**/(3S)-**13** approximately 40:60).

*(5S,7R)-8-{(tert-Butyldimethylsilyl)oxy}-5,7-dimethyl-1-(trimethylsilyl)oct-1-yn-3-one (**14**).* To a solution of alkynol **13** (0.810 g, 2.27 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added DMP (0.963 g, 2.27 mmol, 1.0 equiv) and $NaHCO_3$ (0.191 g, 2.27 mmol, 1.0 equiv). After addition, the cooling bath was removed and the mixture was stirred for 4 h at room temperature. Most of the solvent was removed in vacuo and the crude ketone was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give pure alkynone **14** (0.80 g, 99%) as a colorless oil. $[\alpha]^{22}_D$ = −8.4 (c = 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6H, $(CH_3)_2Si$), 0.21 (s, 9H, TMS), 0.87 (s, 9H, $(CH_3)_3CSi$), (d, J = 6.7 Hz, 3H, 7-CH_3), 0.92 (d, J = 6.3 Hz, 3H, 5-CH_3), 0.98 (td, J = 6.3, 12.9 Hz, 1H, 6-H), 1.31 (td, J = 6.3, 13.6 Hz, 1H, 6-H), 1.57−1.69 (m, 1H, 7-H), 2.11−2.21 (m, 1H, 5-H), 2.25 (dd, J = 9.0, 15.0 Hz, 1H, 4-H), 2.54 (dd, J = 4.0, 15.0 Hz, 1H, 4-H), 3.32 (dd, J = 6.6, 9.8 Hz, 1H, 8-H), 3.42 (dd, J = 5.3, 9.8 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.4 ($(CH_3)_2Si$), 0.80 (TMS), 17.2 (7-CH_3), 18.3 ($(CH_3)_3CSi$), 20.6 (5-CH_3), 25.9 ($(CH_3)_3CSi$), 27.2 (C-5), 33.2 (C-7), 40.7 (C-6), 52.5 (C-4), 68.1 (C-8), 97.3 (C-1), 102.3 (C-2), 187.7 (C═O).

*(3R,5S,7R)-8-{(tert-Butyldimethylsilyl)oxy}-5,7-dimethyl-1-(trimethylsilyl)oct-1-yn-3-ol [((3R)-**13**].* To a solution of alkynone **14** (0.266 g, 0.75 mmol) in isopropanol (25 mL) was added dropwise RuCl[R,R]-NTsCH(Ph)CH(Ph)NH$_2$(η^6-cymene)[10] (R,R)-**15** (0.016 g, 10 mol %) in CH_2Cl_2 (0.5 mL) at room temperature. After stirring of the mixture for 50 min at this temperature, most of the isopropanol was removed in vacuo. The crude propargylic alcohol was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to afford pure alkynol (3R)-**13** (0.250 g, 93%) as a colorless oil. $[\alpha]^{22}_D$ = +10.9 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.21 (s, 9H, TMS), 0.88 (s, 9H, $(CH_3)_3CSi$), (d, J = 7.6 Hz, 3H, 7-CH_3), 0.92 (d, J = 6.6 Hz, 3H, 5-CH_3), 0.92−0.95 (m, 1H, 6-CH), 1.27−1.44 (m, 2H, 6-H, 7-H), 1.68−1.88 (m, 4H, 5-H, 4-H), 3.30 (dd, J = 6.8, 9.6 Hz, 1H, 8-H), 3.45 (dd, J = 5.0, 9.6 Hz, 1H, 8-H), 4.40 (dd, J = 5.0, 8.0 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.4 ($(CH_3)_2Si$), −0.14 (TMS), 17.5 (7-CH_3), 18.3 ($(CH_3)_3CSi$), 20.3 (5-CH_3), 25.9 ($(CH_3)_3CSi$), 26.6 (C-5), 33.1 (C-7), 41.2 (C-6), 45.0 (C-4), 60.9 (C-3), 68.2 (C-8), 88.9 (C-1), 107.4 (C-2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{19}H_{40}O_2Si_2Na$ 379.2459; found 379.2460.

*NMR Data for (3S)-**13**.* ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H, $(CH_3)_2Si$), 0.15 (s, 9H, TMS), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.85−0.95 (m, 7H, 5-CH_3, 7-CH_3, 6-CH), 1.31−1.50 (m, 2H, 6-H, 7-H), 1.63−1.80 (m, 4H, 5-H, 4-H), 3.35 (dd, J = 6.6, 9.5 Hz, 1H, 8-H), 3.44 (dd, J = 5.3, 9.6 Hz, 1H, 8-H), 4.41 (dd, J = 6.3, 8.1 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.4 ($(CH_3)_2Si$), −0.14 (TMS), 17.2 (7-CH_3), 18.4 ($(CH_3)_2CSi$), 20.8 (5-CH_3), 26.0 ($(CH_3)_3CSi$), 27.1 (C-5), 33.0 (C-7), 41.0 (C-6), 44.7 (C-4), 61.7 (C-3), 68.3 (C-8), 89.5 (C-1), 106.9 (C-2).

*(3R,5S,7R)-3,8-Di{(tert-butyldimethylsilyl)oxy}-5,7-dimethyl-1-(trimethylsilyl)-1-octyne (**16**).* To a solution of alcohol (3R)-**13** (0.840 g, 2.35 mmol) in CH_2Cl_2 (20 mL) was added at 0 °C 2,6-lutidine (0.615 mL, 5.17 mmol, 2.2 equiv), followed by TBSOTf (0.69 mL, 2.60 mmol, 1.1 equiv). After stirring of the mixture for 2.5 h at 0 °C, saturated $NaHCO_3$ solution (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed successively with saturated $NaHSO_4$ solution (2 × 10 mL), saturated $NaHCO_3$ solution (20 mL), and saturated NaCl solution (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude silyl ether was purified by flash chromatography (Et_2O/petroleum ether, 50:1) to give product **16** (1.100 g, 99%) as a colorless oil. R_f = 0.7 (petroleum ether/diethyl ether, 49:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, $(CH_3)_2Si$), 0.10 (s, 6H, $(CH_3)_2Si$), 0.13 (s, 6H, $(CH_3)_2Si$), 0.14 (s, 9H, TMS), 0.86 (d, J = 5.8 Hz, 6H, 5-CH_3, 7-CH_3), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.89 (s, 9H, $(CH_3)_3CSi$), 0.84−0.91 (m, 1H, 6-H), 1.22−1.32 (m, 2H, 6-H, 5-H), 1.62−1.86 (m, 3H, 4-H, 7-H), 3.29 (dd, J = 7.1, 9.6 Hz, 1H, 8-H), 3.45 (dd, J = 5.3, 9.6 Hz, 1H, 8-H), 4.39 (dd, J =

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4.0, 9.1 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.5 (CH_3)$_2$Si), −5.0 (CH_3)$_2$Si), −4.3 (CH_3)$_2$Si), −0.16 (TMS), 17.2 (7-CH_3), 18.2 ((CH_3)$_3$CSi), 18.4 ((CH_3)$_2$CSi), 20.0 (5-CH_3), 25.7, 25.8 ((CH_3)$_3$CSi), 26.0 ((CH_3)$_3$CSi) 26.2 (C-5), 33.1 (C-7), 41.2 (C-6), 45.5 (C-4), 61.2 (C-3), 68.4 (C-8), 88.1 (C-1), 108.4 (C-2); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{25}H_{54}O_2Si_3Na$ 493.3324; found 493.3326.

*(3R,5S,7R)-3,8-Di{(tert-butyldimethylsilyl)oxy}-5,7-dimethyl-1-octyne (**17**).* A solution of alkyne **16** (3.150 g, 6.69 mmol) in methanol (13 mL) was treated with dry K_2CO_3 (1.109 g, 8.03 mmol, 1.2 equiv), and the mixture was stirred at room temperature for 3 h. Most of the methanol was removed in vacuo before the residue was redissolved in Et_2O (30 mL), and the solution was washed with water (30 mL). The aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude alkyne was purified by flash chromatography (Et_2O/petroleum ether, 50:1) to give product **17** (2.445 g, 92%) as a colorless oil. R_f = 0.5 (petroleum ether/diethyl ether, 49:1); $[\alpha]^{22}_D$ = +110.1 (*c* = 1.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, (CH_3)$_2$Si), 0.10 (s, 3H, (CH_3)$_2$Si), 0.14 (s, 3H, (CH_3)$_2$Si), 0.88 (s, 9H, (CH_3)$_3$CSi), 0.89 (s, 9H, (CH_3)$_3$CSi), 0.84−0.96 (m, 7H, 7-CH_3, 5-CH_3, 6-CH), 1.22−1.36 (m, 2H, 6-H, 5-H), 1.63−1.72 (m, 1H, 7-H), 1.73−1.83 (m, 2H, 4-H), 2.35 (d, *J* = 2.3 Hz, 1H, 1-H), 3.31 (dd, *J* = 6.8, 9.8 Hz, 1H, 8-H), 3.44 (dd, *J* = 5.3, 9.8 Hz, 1H, 8-H), 4.39 (ddd, *J* = 2.0, 4.3, 8.8 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.4 (CH_3)$_2$Si), −5.2 (CH_3)$_2$Si), −4.4 ((CH_3)$_2$Si), 17.3 (7-CH_3), 18.1 ((CH_3)$_3$CSi), 18.4 ((CH_3)$_3$CSi), 20.1 (5-CH_3), 25.7 ((CH_3)$_3$CSi), 26.0 ((CH_3)$_3$CSi), 26.2 (C-5), 33.1 (C-7), 41.2 (C-6), 45.0 (C-4), 60.6 (C-3), 68.2 (C-8), 71.8 (C-1), 86.2 (C-2); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{22}H_{46}O_2Si_2Na$ 421.2929; found 421.2931.

*(3R,5S,7R)-3,8-Di{(tert-butyldimethylsilyl)oxy}-5,7-dimethyl-1-octene (**18**).* To a solution of alkyne **17** (2.445 g, 6.13 mmol) in a mixture of acetone/cyclohexene (65 mL, 50:15) was added quinoline (7.2 mL, 61.3 mmol, 10 equiv). This solution was flushed with N_2 and treated with (5% Pd) palladium/calcium carbonate (0.526 g, 0.24 mmol, 4 mol %) before hydrogen gas was bubbled through the solution via a hydrogen balloon through an inlet needle and keeping the thin outlet needle free. The reaction progress was monitored by TLC (petroleum ether/diethyl ether, 49:1). After completion of the reaction (after about 30 min), the catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was redissolved in Et_2O (20 mL), and this solution washed successively with saturated $NaHSO_4$ solution (2 × 10 mL), saturated $NaHCO_3$ solution (10 mL), and saturated NaCl solution (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude alkene was purified by flash chromatography (Et_2O/petroleum ether, 50:1) to give alkene **18** (2.40 g, 98%) as a colorless oil. R_f = 0.5 (petroleum ether/diethyl ether, 49:1); $[\alpha]^{22}_D$ = +2.8 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3H, (CH_3)$_2$Si), 0.02 (s, 6H, (CH_3)$_2$Si), 0.40 (s, 3H, (CH_3)$_2$Si), 0.88 (s, 18H, (CH_3)$_3$CSi), 0.85−0.90 (m, 6H, 7-CH_3, 5-CH_3), 0.90−0.95 (m, 1H, 6-H), 1.00−1.09 (m, 1H, 6-H), 1.21−1.29 (m, 1H, 7-H), 1.49−1.58 (m, 1H, 5-H), 1.63−1.75 (m, 2H, 4-H), 3.28 (dd, *J* = 6.8, 9.6 Hz, 1H, 8-H), 3.45 (dd, *J* = 5.3, 9.6 Hz, 1H, 8-H), 4.11−4.18 (m, 1H, 3-H), 4.98 (ddd, *J* = 1.0, 1.8, 10.4 Hz, 1H, 1-H), 5.11 (ddd, *J* = 1.0, 1.5, 16.9 Hz, 1H, 1-H), 5.70−5.83 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.3 (CH_3)$_2$Si), −4.9 ((CH_3)$_2$Si), −4.1 ((CH_3)$_2$Si), 17.4 (7-CH_3), 18.2 ((CH_3)$_3$CSi), 18.4 ((CH_3)$_3$CSi), 20.4 (5-CH_3), 25.9 ((CH_3)$_3$CSi), 26.0 ((CH_3)$_3$CSi), 26.1 (C-5), 33.1 (C-7), 41.2 (C-6), 45.0 (C-4), 68.4 (C-8), 71.9 (C-3), 113.2 (C-1), 142.6 (C-2); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{22}H_{48}O_2Si_2Na$ 423.3085; found 423.3088.

*(3R,5S,7R)-3,8-Bis{(tert-butyldimethylsilyl)oxy}-5,7-dimethyl-octan-1-ol (**19**).* To a solution of BH_3·SMe_2 complex (2 M in THF, 9 mL, 18.00 mmol, 3 equiv) in THF (50 mL) was added cyclohexene (3.65 mL, 36.00 mmol, 6 equiv) dropwise at 0 °C followed by stirring of the mixture for 30 min. Then the ice bath was removed, and the mixture was allowed to stir at room temperature for 1 h. It was recooled to 0 °C before alkene **18** (2.31 g, 5.76 mmol, 1 equiv) in THF (30 mL) was added dropwise. After 3 h of stirring at 0 °C, NaOH (3 N, 60 mL) and H_2O_2 solution (30%, 60 mL) were added and the mixture was stirred for 3 h. Thereafter, the mixture was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to give alcohol **19** (2.20 g, 91%) as a colorless oil. R_f = 0.3 (petroleum ether/ethyl acetate, 9:1); $[\alpha]^{22}_D$ = −2.0 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, (CH_3)$_2$Si), 0.07 (s, 6H, (CH_3)$_2$Si), 0.09 (s, 3H, (CH_3)$_2$Si), 0.88 (s, 18H, (CH_3)$_3$CSi), 0.85−0.91 (m, 6H, 7-CH_3, 5-CH_3, 6-H), 1.14−1.22 (m, 2H, 6-H), 1.26−1.36 (m, 1H, 5-H), 1.49−1.72 (m, 4H, 2-H, 7-H, 4-H), 1.89−1.91 (m, 1H, 2-H), 3.22 (dd, *J* = 6.5, 9.8 Hz, 1H, 8-H), 3.43 (dd, *J* = 5.3, 9.8 Hz, 1H, 8-H), 3.65−3.72 (m, 1H, 3-H), 3.81−3.89 (m, 1H, 1-H), 3.96−4.04 (m, 1H, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.4 (CH_3)$_2$Si), −4.5 ((CH_3)$_2$Si), −4.4 ((CH_3)$_2$Si), 17.7 (7-CH_3), 17.9 ((CH_3)$_3$CSi), 18.3 ((CH_3)$_3$CSi), 20.7 (5-CH_3), 25.8 ((CH_3)$_3$CSi), 25.9 ((CH_3)$_3$CSi), 26.6 (C-5), 33.0 (C-7), 38.5 (C-6), 44.2 (C-4), 44.2 (C-2), 60.1 (C-1), 67.9 (C-8), 69.8 (C-3); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{22}H_{50}O_3Si_2Na$ 441.3191; found 441.3194.

*(3R,5S,7R)-3,8-Bis{(tert-butyldimethylsilyl)oxy}-5,7-dimethyl-octan-1-al (**20**).* To a solution of oxalyl chloride (0.67 mL, 7.83 mmol, 1.6 equiv) in CH_2Cl_2 (30 mL) at −80 °C was added DMSO (1.11 mL, 15.65 mmol, 3.2 equiv) dropwise. The resulting mixture was stirred 15 min before alcohol **19** (2.050 g, 4.89 mmol) in CH_2Cl_2 (8 mL) was added dropwise within 15 min. After stirring the mixture for 1 h at −80 °C, Et_3N (4.23 mL, 29.34 mmol, 6 equiv) was added slowly. Then the reaction mixture was allowed to warm to room temperature. For workup water (20 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give aldehyde **20** (1.98 g, 98%) as a colorless oil. R_f = 0.6 (petroleum ether/ethyl acetate, 9:1); $[\alpha]^{22}_D$ = +15.9 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6H, (CH_3)$_2$Si), 0.05 (s, 3H, (CH_3)$_2$Si), 0.60 (s, 3H, (CH_3)$_2$Si), 0.86 (s, 9H, (CH_3)$_3$CSi), 0.87 (s, 9H, (CH_3)$_3$CSi), 0.86 (d, *J* = 6.6 Hz, 3H, 7-CH_3), 0.88 (d, *J* = 6.6 Hz, 3H, 5-CH_3), 1.08−1.17 (m, 1H, 6-H), 1.19−1.32 (m, 2H, 6-H, 5-H), 1.54−1.71 (m, 3H, 4-H, 7-H), 2.47 (ddd, *J* = 3.0, 5.3, 15.7 Hz, 1H, 2-H), 2.54 (ddd, *J* = 3.0, 5.6, 15.7 Hz, 1H, 2-H), 3.31 (dd, *J* = 6.6, 9.6 Hz, 1H, 8-H), 3.42 (dd, *J* = 5.3, 9.6 Hz, 1H, 8-H), 4.20−4.27 (m, 1H, 3-H), 9.80 (t, *J* = 3.0 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.4 (CH_3)$_2$Si), −5.4 ((CH_3)$_2$Si), −4.5 ((CH_3)$_2$Si), −4.4 ((CH_3)$_2$Si), 17.5 (7-CH_3), 17.9 ((CH_3)$_3$CSi), 18.3 ((CH_3)$_3$CSi), 20.3 (5-CH_3), 25.8 ((CH_3)$_3$CSi), 25.9 ((CH_3)$_3$CSi), 26.4 (C-5), 33.0 (C-7), 41.3 (C-6), 45.3 (C-4), 51.8 (C-2), 66.1 (C-3), 68.0 (C-8), 200.2 (CHO); HRMS (ESI-TOF) *m*/*z*: [M + Na + CH_3OH (hemiacetal)]$^+$ calcd for $C_{23}H_{52}O_4Si_2Na$ 471.3296; found 471.3300.

*S-Ethyl (3R,5S,7R)-3,10-bis{(tert-butyldimethylsilyl)oxy}-7,9-dimethyldec-2-enethioate (**21**).* To a solution of aldehyde **20** (1.94 g, 4.65 mmol) in CH_2Cl_2 (50 mL) was added *S*-ethyl 2-(triphenyl-λ^5-phosphanylidene)ethanethioate[12] (2.04 g, 5.58 mmol, 1.2 equiv). The resulting solution was refluxed for 2 d and then cooled to room temperature before it was concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/petroleum ether, 1:50) to give enoate **21** (2.08 g, 89%) as a yellow oil. R_f = 0.5 (petroleum ether/diethyl ether, 40:1); $[\alpha]^{22}_D$ = +22.5 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, (CH_3)$_2$Si), 0.04 (s, 3H, (CH_3)$_2$Si), 0.40 (s, 3H, (CH_3)$_2$Si), 0.85 (d, *J* = 6.8 Hz, 6H, 9-CH_3, 7-CH_3), 0.87 (s, 9H, (CH_3)$_3$CSi), 0.88 (s, 9H, (CH_3)$_3$CSi), 0.88−0.93 (m, 1H, 8-H), 0.98−1.07 (m, 1H, 8-H), 1.27 (t, *J* = 7.5 Hz, 3H, CH_3CH_2S), 1.20−1.32 (m, 1H, 6-H), 1.42−1.52 (m, 1H, 6-H), 1.58−1.72 (m, 2H, 7-H, 9-H), 2.25−2.38 (m, 2H, 4-H), 2.93 (q, *J* = 7.5 Hz, 2H, CH_3CH_2S), 3.29 (dd, *J* = 6.8, 9.8 Hz, 1H, 10-H), 3.43 (dd, *J* = 5.0, 9.8 Hz, 1H, 10-H), 3.81−3.90 (m, 1H, 5-H), 6.09 (dt, *J* = 1.3, 15.7 Hz, 1H, 2-H), 6.81−6.92 (m, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.4 (CH_3)$_2$Si), −5.3 ((CH_3)$_2$Si), −4.6 ((CH_3)$_2$Si), −4.2 ((CH_3)$_2$Si), 14.6 (CH_3CH_2S), 17.4 (9-CH_3), 18.0 ((CH_3)$_3$CSi), 18.4 ((CH_3)$_3$CSi), 20.4 (7-CH_3), 23.0 (CH_3CH_2S), 25.8 ((CH_3)$_3$CSi),

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26.0 ((*C*H$_3$)$_3$CSi), 26.2 (C-7), 33.0 (C-9), 41.1 (C-8), 41.5 (C-4), 44.7 (C-6), 68.2 (C-10), 69.0 (C-5), 130.6 (C-2), 141.7 (C-3), 189.9 (C-1); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{26}H_{54}O_3SSi_2Na$ 525.3224; found 525.3230.

*S-Ethyl (3R,5R,7S,9R)-5,10-Bis{(tert-butyldimethylsilyl)oxy}-3,7,9-trimethyldecanethioate (**7**).* To a solution of (*R*)-Tol-BINAP (0.045 g, 0.065 mmol, 0.016 equiv) in dry *tert*-butyl methyl ether (15 mL) was added copper iodide (0.008 g, 0.043 mmol, 0.010 equiv). This suspension was stirred for 1 h at room temperature turning into a dark yellow solution. The solution was cooled to −78 °C and treated dropwise with a solution of MeMgBr in Et$_2$O (3 M 7.4 mL, 26.22 mmol, 6.6 equiv). The resulting mixture was stirred for 30 min before a solution of enoate **21** (2.000 g, 3.98 mmol) in *tert*-butyl methyl ether (7 mL) was added dropwise using a syringe pump within 2 h. The mixture was stirred overnight during at −78 °C. The reaction was quenched with MeOH (1 mL) and saturated NH_4Cl solution (10 mL), the cooling system was removed, and the layers were separated. The aqueous layer was extracted with Et$_2$O (2 × 20 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (Et$_2$O/petroleum ether, 1:50) afforded pure ester **7** (2.00 g, 97%) as colorless oil. R$_f$ = 0.6 (petroleum ether/diethyl ether, 40:1); $[\alpha]^{22}_D$ = +23.1 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 12H, (CH$_3$)$_2$Si), 0.03 (s, 3H, (CH$_3$)$_2$Si), 0.05 (s, 3H, (CH$_3$)$_2$Si), 0.87 (s, 9H, (CH$_3$)$_3$CSi), 0.88 (s, 9H, (CH$_3$)$_3$CSi), 0.83−0.90 (m, 7H, 7-CH$_3$, 9-CH$_3$, 8-H), 0.92 (d, *J* = 6.6 Hz, 3H, 3-CH$_3$), 1.03−1.12 (m, 1H, 8-H), 1.23 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$S), 1.18−1.26 (m, 1H, 6-H), 1.29−1.46 (m, 3H, 6-H, 4-H), 1.62−1.73 (m, 2H, 9-H, 7-H), 2.01−2.16 (m, 1H, 3-H), 2.33 (dd, *J* = 8.3, 14.6 Hz, 1H, 2-H), 2.55 (dd, *J* = 5.6, 14.6 Hz, 1H, 2-H), 2.86 (q, *J* = 7.3 Hz, 2H, CH$_3$C*H*$_2$S), 3.28 (dd, *J* = 7.0, 9.6 Hz, 1H, 10-H), 9.60 (dd, *J* = 5.1, 9.6 Hz, 1H, 10-H), 3.71−3.80 (m, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.3 ((CH$_3$)$_2$Si), −4.4 ((CH$_3$)$_2$Si), −4.0 ((CH$_3$)$_2$Si), 14.6 (*C*H$_3$CH$_2$S), 17.4 (9-CH$_3$), 18.0 ((CH$_3$)$_3$CSi), 18.4 ((CH$_3$)$_3$CSi), 19.6 (7-CH$_3$), 20.4 (3-CH$_3$), 23.3 (CH$_3$*C*H$_2$S), 25.9 ((*C*H$_3$)$_3$CSi), 26.0 ((*C*H$_3$)$_3$CSi), 26.1 (C-7), 27.8 (C-3), 33.0 (C-9), 41.8 (C-8), 44.1 (C-4), 44.3 (C-6), 51.8 (C-2), 68.1 (C-10), 68.4 (C-5), 198.9 (C-1); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{27}H_{58}O_3SSi_2Na$ 541.3537; found 541.3541.

*(3R,5R,7S,9R)-5,10-Bis{(tert-butyldimethylsilyl)oxy}-3,7,9-trimethyldecanal (**22**).* To a solution of thioester **7** (2.00 g, 3.85 mmol) in CH_2Cl_2 (70 mL) at −80 °C was added DIBAL-H in hexane (1 M, 4.04 mL, 4.04 mmol, 1.05 equiv) dropwise. After 30 min of stirring at −80 °C the excess DIBAL-H was quenched with ethyl acetate (1 mL) and saturated NH_4Cl solution (5 mL). After having reached room temperature, the layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extract were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give pure aldehyde **22** (1.73 g, 98%) as a colorless oil. *R*$_f$ = 0.4 (petroleum ether/diethyl ether, 40:1); $[\alpha]^{22}_D$ = +36.4 (*c* = 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6H, (CH$_3$)$_2$Si), 0.03 (s, 6H, (CH$_3$)$_2$Si), 0.86 (s, 9H, (CH$_3$)$_3$CSi), 0.88 (s, 9H, (CH$_3$)$_3$CSi), 0.84−0.89 (m, 6H, 7-CH$_3$, 9-CH$_3$), 0.89−0.92 (m, 1H, 8-H), 1.40 (d, *J* = 6.6 Hz, 3H, 3-CH$_3$), 1.05−1.16 (m, 1H, 8-H), 1.18−1.28 (m, 1H, 6-H), 1.36−1.46 (m, 3H, 6-H, 4-H), 1.62−1.74 (m, 2H, 9-H, 7-H), 2.07−2.17 (m, 1H, 3-H), 2.21 (ddd, *J* = 2.8, 8.3, 16.2 Hz, 1H, 2-H), 2.24 (ddd, *J* = 1.7, 4.8, 16.2 Hz, 1H, 2-H), 3.28 (dd, *J* = 6.8, 9.6 Hz, 1H, 10-H), 3.44 (dd, *J* = 5.3, 9.6 Hz, 1H, 10-H), 3.74−3.84 (m, 1H, 3-H), 9.73 (t, *J* = 2.0 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.3 ((CH$_3$)$_2$Si), −4.4 ((CH$_3$)$_2$Si), −4.0 ((CH$_3$)$_2$Si), 17.4 (9-CH$_3$), 18.0 ((CH$_3$)$_3$CSi), 18.4 ((CH$_3$)$_3$CSi), 20.2 (3-CH$_3$), 20.4 (7-CH$_3$), 24.8 (C-3), 25.9 ((CH$_3$)$_3$CSi), 26.0 ((CH$_3$)$_3$CSi), 26.2 (C-7), 33.0 (C-9), 41.8 (C-8), 44.2 (C-4), 45.4 (C-6), 51.5 (C-2), 68.1 (C-5), 68.4 (C-10), 200.3 (CHO).

*(3R,5R,7S,9R)-5,10-Bis{(tert-butyldimethylsilyl)oxy}-3,7,9-trimethyl-2-methylenedecanal (**23**).* To a solution of aldehyde **22** (1.60 g, 2.53 mmol) in CH_2Cl_2 (30 mL) was added Et$_3$N (1.1 mL, 7.59 mmol, 3 equiv) and Eschenmoser's salt ($Me_2N{=}CH_2^+$ Cl^-) (0.59 g, 6.32 mmol, 2.5 equiv).[15] The reaction mixture was stirred at room temperature for 2 d and then concentrated in vacuo. Purification of the residue by flash chromatography (ethyl acetate/petroleum ether, 1:20) gave pure enal **23** (1.18 g, 99%) as a colorless oil. *R*$_f$ = 0.5 (petroleum ether/ethyl acetate, 33:1). $[\alpha]^{22}_D$ = +34.0 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3H, (CH$_3$)$_2$Si), 0.02 (s, 9H, (CH$_3$)$_2$Si), 0.86 (s, 9H, (CH$_3$)$_3$CSi), 0.88 (s, 9H, (CH$_3$)$_3$CSi), 0.83−0.96 (m, 7H, 7-CH$_3$, 9-CH$_3$, 8-H), 1.05 (d, *J* = 6.8 Hz, 3H, 3-CH$_3$), 1.09−1.26 (m, 2H, 8-H, 6-H), 1.35−1.52 (m, 2H, 6-H, 4-H), 1.57−1.74 (m, 3H, 9-H, 7-H, 4-H), 2.67−2.78 (m, 1H, 3-H), 3.27 (dd, *J* = 7.1, 9.6 Hz, 1H, 10-H), 3.46 (dd, *J* = 5.3, 9.8 Hz, 1H, 10-H), 3.68−3.78 (m, 1H, 5-H), 5.96 (s, 1H, *H*$_2$C═CCHO), 6.20 (s, 1H, *H*$_2$C═CCHO), 9.51 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.3 ((CH$_3$)$_2$Si), −4.4 ((CH$_3$)$_2$Si), −4.1 ((CH$_3$)$_2$Si), 17.4 (9-CH$_3$), 18.0 ((CH$_3$)$_3$CSi), 18.4 ((CH$_3$)$_3$CSi), 19.8 (3-CH$_3$), 20.4 (7-CH$_3$), 25.9 ((CH$_3$)$_3$CSi), 26.0 ((CH$_3$)$_3$CSi), 26.2 (C-7), 28.3 (C-3), 33.1 (C-9), 41.8 (C-8), 43.9 (C-4), 44.3 (C-6), 68.4 (C-5), 68.5 (C-10), 132.8 (*C*H$_2$═CCHO), 155.7 (CH$_2$═*C*CHO), 194.4 (CHO); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{26}H_{54}O_3Si_2Na$ 493.3504; found 493.3507.

*(3R,5R,7S,9R)-5,10-Bis{(tert-butyldimethylsilyl)oxy}-3,7,9-trimethyl-2-methylenedecan-1-ol (**24**).* To a solution of enal **23** (1.180 g, 2.50 mmol) in CH_2Cl_2 (25 mL) at −80 °C was added DIBAL-H in hexane (1 M, 2.62 mL, 2.62 mmol, 1.05 equiv) dropwise. After complete addition, the reaction mixture was allowed to warm to −40 °C within 1 h. Excess DIBAL-H was quenched with ethyl acetate (1 mL) and saturated NH_4Cl solution (3 mL), and after having reached room temperature, the layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to give pure allyl alcohol **24** (1.18 g, 100%) as a colorless oil. *R*$_f$ = 0.2 (petroleum ether/ethyl acetate, 20:1); $[\alpha]^{22}_D$ = +9.6 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H, (CH$_3$)$_2$Si), 0.04 (s, 6H, (CH$_3$)$_2$Si), 0.87 (s, 9H, (CH$_3$)$_3$CSi), 0.88 (s, 9H, (CH$_3$)$_3$CSi), 0.83−0.95 (m, 7H, 7-CH$_3$, 9-CH$_3$, 8-H), 1.04 (d, *J* = 6.8 Hz, 3H, 3-CH$_3$), 1.07−1.16 (m, 1H, 8-H), 1.18−1.28 (m, 1H, 6-H), 1.36−1.50 (m, 2H, 6-H, 7-H), 1.52−1.74 (m, 4H, 9-H, 4-H), 2.18−2.28 (m, 1H, 3-H), 3.27 (dd, *J* = 7.1, 9.8 Hz, 1H, 10-H), 3.45 (dd, *J* = 5.3, 9.8 Hz, 1H, 10-H), 3.72−3.80 (m, 1H, 5-H), 4.10 (s, 2H, 1-H), 4.88 (m, 1H, C*H*$_2$═CCH$_2$OH), 5.03 (m, 1H, C*H*$_2$═CCH$_2$OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.3 (CH$_3$)$_2$Si), −4.3 ((CH$_3$)$_2$Si), −4.0 ((CH$_3$)$_2$Si), 17.4 (9-CH$_3$), 18.1 ((CH$_3$)$_3$CSi), 18.4 ((CH$_3$)$_3$CSi), 20.3 (3-CH$_3$), 20.6 (7-CH$_3$), 25.9 ((CH$_3$)$_3$CSi), 26.0 ((CH$_3$)$_3$CSi), 26.3 (C-7), 33.1 (C-3), 33.1 (C-9), 41.8 (C-8), 44.3 (C-4), 44.5 (C-6), 64.9 (C-1), 66.5 (C-10), 68.9 (C-5), 108.0 (*C*H$_2$═CCH$_2$OH), 154.4 (CH$_2$═*C*CH$_2$OH); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{26}H_{56}O_3Si_2Na$ 495.3660; found 495.3660.

*(3R,5R,7S,9R)-5,10-Bis{(tert-butyldimethylsilyl)oxy}-2-ethyl-3,7,9-trimethyl-1-decene (**26**). (a) Tosylate **25**.* To a cooled (0 °C) solution of alcohol **24** (0.250 g, 0.53 mmol) and Et$_3$N (0.076 mL, 0.53 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added *para*-toluenesulfonic anhydride (0.175 g, 0.53 mmol, 1.0 equiv). After being stirred for 30 min at 0 °C, water (2 mL) was added to the reaction mixture, the layers were separated, and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give crude tosylate **25** (0.320 g, 96%) which was used for the next step without further purification.

(b) Substitution of Tosylate. The crude tosylate **25** was dissolved in CH_2Cl_2 (5 mL), and CuI (0.010 g, 0.051 mmol, 10 mol %) was added. This mixture was cooled to −80 °C and treated with a solution of MeMgBr in diethyl ether (3 M, 0.7 mL, 2.1 mmol, 4 equiv) in a dropwise fashion. The reaction mixture was allowed to warm to −50 °C within 1.5 h before it was quenched with MeOH (0.2 mL) and saturated NH_4Cl solution (1 mL). The cooling system was removed, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with saturated NaCl solution (5 mL), dried over anhydrous Na_2SO_4,

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filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (Et_2O/petroleum ether, 1/50) to afford pure alkene **26** (0.205 g, 82%) as a colorless oil. R_f = 0.6 (petroleum ether/diethyl ether, 49:1); $[\alpha]^{20}_D$ = +21.8 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H, $(CH_3)_2Si$), 0.04 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.89 (s, 9H, $(CH_3)_3CSi$), 0.83−0.96 (m, 7H, 7-CH_3, 9-CH_3, 8-H), 0.98−1.13 (m, 7H, 8-H, 3-CH_3, CH_3CH_2), 1.17−1.29 (m, 1H, 6-H), 1.35−1.46 (m, 2H, 6-H, 7-H), 1.52−1.62 (m, 1H, 4-H), 1.63−1.77 (m, 2H, 4-H, 9-H), 1.94−2.06 (m, 2H, CH_2CH_3), 2.09−2.21 (m, 1H, 3-H), 3.27 (dd, J = 7.1, 9.8 Hz, 1H, 10-H), 3.46 (dd, J = 5.3, 9.8 Hz, 1H, 10-H), 3.68−3.78 (m, 1H, 5-H), 4.66−4.77 (m, 2H, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.3 ($(CH_3)_2Si$), −4.3 ($(CH_3)_2Si$), −4.0 ($(CH_3)_2Si$), 12.4 (CH_3CH_2) 17.4 (9-CH_3), 18.1 ($(CH_3)_2CSi$), 18.4 ($(CH_3)_2CSi$), 20.0 (3-CH_3), 20.5 (7-CH_3), 25.9 ($(CH_3)_3CSi$), 26.0 ($(CH_3)_3CSi$), 26.3 (C-7), 26.4 (CH_2CH_3), 33.1 (C-3), 36.8 (C-9), 42.0 (C-8), 44.5 (C-4), 44.6 (C-6), 68.5 (C-10), 68.9 (C-5), 106.3 (C-1), 156.4 (C-2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{27}H_{58}O_2Si_2Na$ 493.3868; found 493.3869.

*(2R,4S,6R,8R)-6-{(tert-Butyldimethylsilyl)oxy}-2,4,8-trimethyl-9-methyleneundecan-1-ol (**27**).* To a stirred solution of disilyl ether **26** (0.190 g, 0.403 mmol) in MeOH/CH_2Cl_2 (5:1, 6 mL) at −10 °C was added pTsOH·H_2O (0.010 g, 0.05 mmol, 0.13 equiv). The temperature was maintained between −10 and 0 °C throughout the reaction which was stirred for 4 h. Solid $NaHCO_3$ (10 mg) was added, and most of the solvent was removed in vacuo. This solid was redissolved in ethyl acetate (5 mL), and the solution was washed with water (2 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to afford pure alcohol **27** (0.100 g, 70%) as a colorless oil. R_f = 0.2 (petroleum ether/ethyl acetate, 9:1); $[\alpha]^{21}_D$ = +33.7 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.88−0.92 (m, 6H, 2-CH_3, 11-CH_3), 0.93−0.98 (m, 1H, 3-H), 0.98−1.05 (m, 6H, 4-CH_3, 8-CH_3), 1.06−1.15 (m, 1H, 3-H), 1.98−1.30 (m, 2H, 5-H), 1.34−1.45 (m, 1H, 7-H), 1.51−1.60 (m, 1H, 4-H), 1.65−1.78 (m, 2H, 2-H), 1.95−2.02 (m, 2H, 10-H), 2.09−2.19 (m, 1H, 8-H), 3.36 (dd, J = 6.8, 10.6 Hz, 1H, 1-H), 3.49 (dd, J = 5.3, 10.6 Hz, 1H, 1-H), 3.67−3.77 (m, 1H, 6-H), 4.66−4.77 (m, 2H, C=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.3 ($(CH_3)_2Si$), −4.0 ($(CH_3)_2Si$), 12.4 (C-11), 17.4 (2-CH_3), 18.1 ($(CH_3)_3CSi$), 20.0 (8-CH_3), 20.4 (4-CH_3), 25.9 ($(CH_3)_3CSi$), 26.2 (C-4), 26.4 (C-10), 33.0 (C-8), 36.8 (C-2), 41.8 (C-3), 44.3 (C-7), 44.6 (C-5), 68.5 (C-1), 68.9 (C-6), 106.3 (9-CCH_2), 156.4 (C-9); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{44}O_2SiNa$ 379.3003; found 379.3005.

*(2R,4S,6R,8R)-6-{(tert-Butyldimethylsilyl)oxy}-2,4,8-trimethyl-9-methyleneundecanal (**28**).* To a solution of oxalyl chloride (0.036 mL, 0.42 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL) at −80 °C was added DMSO (0.060 mL, 0.84 mmol, 3.0 equiv) in a dropwise fashion. The resulting mixture was stirred for 15 min at this temperature. Then alcohol **27** (0.100 g, 0.28 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise within 15 min. After the mixture was stirred for 1 h, Et_3N (0.242 mL, 1.68 mmol, 6 equiv) was added slowly before the reaction mixture was allowed to warm to room temperature. Subsequently, water (1 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give aldehyde **28** (0.098 g, 98%) as colorless oil. R_f = 0.6 (petroleum ether/ethyl acetate, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.86−0.94 (m, 3H, 11-CH_3), 0.97−1.09 (m, 9H, 2-CH_3, 4-CH_3, 8-CH_3), 1.12−1.22 (m, 2H, 5-H), 1.32−1.45 (m, 2H, 4-H, 5-H), 1.51−1.77 (m, 4H, 3-H, 7-H), 1.91−2.06 (m, 2H, 10-H), 2.08−2.20 (m, 1H, 8-H), 2.26−2.49 (m, 1H, 2-H), 3.36−3.82 (m, 1H, 6-H), 4.68−4.75 (m, 2H, C=CH_2), 9.57 (d, J = 2.3 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.3 ($(CH_3)_2Si$), −4.0 ($(CH_3)_2Si$), 12.4 (C-11), 13.8 (2-CH_3), 18.0 ($(CH_3)_3CSi$), 20.0 (8-CH_3), 20.1 (4-CH_3), 25.9 ($(CH_3)_3CSi$), 26.2 (C-10), 26.5 (C-4), 36.8 (C-8), 38.7 (C-3), 44.0 (C-7), 44.2 (C-2), 44.5 (C-5), 68.7 (C-6), 106.0 (C=CH_2), 156.4 (C-9), 205.3 (CHO).

*(3R,5S,7R,9R)-7-((tert-Butyldimethylsilyl)oxy)-3,5,9-trimethyl-10-methylenedodecan-2-one (**6**). (a) Addition of MeLi to Aldehyde **28**.* To a solution of aldehyde **28** (0.382 g, 1.08 mmol) in THF (8 mL) at −80 °C was added a solution of MeLi·LiBr in diethyl ether (2.2 M, 2.45 mL, 5.40 mmol, 5 equiv). The reaction mixture was allowed to warm to room temperature within 15 h. Before quenching with saturated NH_4Cl (2 mL) the reaction mixture was recooled to −80 °C, and then the mixture was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl solution (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to the give crude secondary alcohol **S1** (0.411 g) as a colorless oil. This material was subjected to the subsequent oxidation without further purification. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{46}O_2SiNa$ 393.31565; found 393.31607.

*(b) Oxidation to Ketone **6**.* To a solution of oxalyl chloride (0.260 mL, 3.0 mmol, 2.78 equiv) in CH_2Cl_2 (10 mL) at −80 °C was added DMSO (0.430 mL, 6.0 mmol, 5.5 equiv) dropwise. The resulting mixture was stirred for 15 min at this temperature before the foregoing alcohol (0.411 g) in CH_2Cl_2 (2.5 mL) was added dropwise within 15 min. After the mixture was stirred for 1 h at −80 °C, Et_3N (1.73 mL, 12.0 mmol) was added slowly. Thereafter, the reaction mixture was allowed to warm to room temperature, water (5 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:20) to give methyl ketone **6** (0.336 g, 84%, 2 steps) as a colorless oil. R_f = 0.6 (petroleum ether/ethyl acetate, 9:1); $[\alpha]^{21}_D$ = +30.6 (c = 1.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.87−0.94 (m, 3H, 5-CH_3), 0.97−1.08 (m, 9H, 3-CH_3, 12-H, 9-CH_3), 1.10−1.19 (m, 2H, 4-H, 6-H), 1.31−1.45 (m, 2H, 6-H, 8-H), 1.51−1.71 (m, 3H, 8-H, 5-H, 4-H), 1.94−2.04 (m, 2H, 11-H), 2.11 (s, 3H, 1-H), 2.12−2.18 (m, 1H, 9-H), 2.54−2.66 (m, 1H, 3-H), 3.66−3.77 (m, 1H, 7-H), 4.67−4.75 (m, 2H, 10-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.3 ($(CH_3)_2Si$), −4.0 ($(CH_3)_2Si$), 12.4 (C-5), 16.7 (3-CH_3), 18.0 ($(CH_3)_3CSi$), 19.9 (9-CH_3), 20.0 (C-12), 25.9 ($(CH_3)_3CSi$), 26.3 (C-11), 26.8 (C-5), 27.7 (C-9), 36.8 (C-1), 41.1 (C-4), 44.4 (C-8), 44.5 (C-6), 44.8 (C-3), 68.7 (C-7), 106.0 (10-CH_2), 156.4 (C-10), 212.9 (C-2); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{44}O_2SiNa$ 391.3003; found 391.3002.

*(7R,9S,11R,13R,E)-Methyl 11-((tert-butyldimethylsilyl)oxy)-4-hydroxy-3,7,9,13-tetramethyl-14-methylene-6-oxohexadec-2-enoate (**29**).* The aldol reaction between methyl ketone **6** and aldehyde **5** was carried out using different reaction conditions:

Enolate Generation with Trichloroisopropoxytitanium(IV) [$TiCl_3$(O*i*Pr)]. To solution of $TiCl_4$ (0.006 mL, 0.06 mmol, 0.82 equiv) in CH_2Cl_2 (0.02 mL) was added Ti(O*i*Pr)$_4$ (0.006 mL, 0.02 mmol, 0.27 equiv) at 0 °C. The solution turned to white and was stirred at 0 °C for 15 min and at room temperature for 10 min to complete the metathesis. Then it was diluted with CH_2Cl_2 (0.02 mL), resulting in a colorless solution. This colorless solution was added dropwise to a cooled solution of methyl ketone **6** (0.030 g, 0.07 mmol) and *i*Pr_2NEt (0.015 mL, 0.08 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) at −78 °C. The resulting dark red solution was stirred for 30 min at −78 °C. Then neat aldehyde[7] **5** (0.022 g, 0.18 mmol, 2.6 equiv) was added dropwise, and stirring was continued for 30 min at this temperature. The reaction was quenched with saturated NH_4Cl solution (1 mL), allowed to warm to room temperature, and diluted with Et_2O (10 mL) before the layers were separated. The organic layer was washed with saturated $NaHCO_3$ solution (3 mL), saturated NaCl solution (3 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to give the hydroxy ketone **29** (5 mg, 14%, dr 1:1) as a colorless oil.

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Enolate Generation with Lithium Diisopropylamide (LDA). To a solution of diisopropylamine (0.014 mL, 0.10 mmol, 2.5 equiv) in THF (0.5 mL) was added *n*-BuLi (1.6 M in hexanes, 0.05 mL, 0.08 mmol, 2 equiv) at −78 °C. The solution was stirred for 15 min at 0 °C and then cooled again to −78 °C. Next, a solution of methyl ketone **6** (0.015 g, 0.04 mmol) in THF (0.5 mL) was added to the LDA solution and the mixture stirred for 3 h at −78 °C before neat aldehyde[7] **5** (0.010 g, 0.08 mmol, 2.0 equiv) was added to the enolate solution. The reaction was left to stir overnight at −78 °C. The temperature was allowed to rise to 0 °C, and then the reaction was quenched with saturated aquous NH_4Cl solution (1 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to give hydroxyl ketone **29** (5 mg, 24%, dr 1:1) as a colorless oil.

Enolate Generation with Dicyclohexylboron Trifluoromethanesulfonate (*c*Hex$_2$BOTf). To a cooled solution of methyl ketone **6** (0.020 g, 0.054 mmol) and Et_3N (0.034 mL, 0.235 mmol, 4.3 equiv) at −78 °C was added a precooled (−78 °C) solution of *c*Hex$_2$BOTf[18] {0.062 g, 0.19 mmol, 3.5 equiv, dissolved in hexane (0.020 mL) and diluted with CH_2Cl_2 (0.040 mL)} dropwise. After 3 h of stirring at −78 °C, neat aldehyde **5** (0.025 g, 0.19 mmol, 2 equiv) was added and the reaction mixture was stirred overnight, while it was allowed to warm to 0 °C. For workup, phosphate buffer (pH 7, 1 mL) and 30% H_2O_2 (1 mL) were added and stirring was continued for the next 2 h. The reaction mixture was diluted with water (1 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (3 mL) and saturated NaCl solution (3 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to give unreacted ketone **6** (0.010 g, 0.027 mmol) and the product **29** (0.010 g, 71%, dr 1:1) as colorless oils.

Enolate Generation with Diisopinocampheylboron Triflate (−)-(Ipc)$_2$BOTf. To a suspension of (−)-(Ipc)$_2$BH[19] (0.500 g, 1.75 mmol) in hexane (0.5 mL) at 0 °C was added trifluoromethanesulfonic acid (0.154 mL, 1.75 mmol) dropwise. The resulting two-phase mixture was stirred at room temperature until completion of the reaction (about 1 h). The upper colorless hexane solution was used for the aldol reaction assuming 60% conversion (0.6 mL of 1.7 M solution of the triflate). To a cooled solution of methyl ketone **6** (0.030 g, 0.07 mmol) and *i*Pr$_2$NEt (0.04 mL, 0.21 mmol, 2.4 equiv) in CH_2Cl_2 (0.5 mL) at −78 °C was added a precooled (−78 °C) solution of the above (−)-(Ipc)$_2$BOTf (1.7 M in hexane, 0.1 mL, 0.17 mmol) dropwise. After stirring of the mixture at −78 °C to −50 °C for 4 h, neat aldehyde[7] **5** (0.022 g, 0.18 mmol, 2.6 equiv) was added at −78 °C and the reaction mixture was stirred overnight, allowing it to warm to 0 °C. Thereafter, phosphate buffer (pH 7, 1 mL) and 30% H_2O_2 (1 mL) were added, and stirring was continued for the next 2 h. The reaction mixture was diluted with water (1 mL), and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (3 mL) and saturated NaCl solution (3 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to give unreacted ketone **6** (0.010 g, 0.027 mmol) and the aldol product **21** (0.025 g, 89%, dr 2:1) as a colorless oil. R_f = 0.5 (petroleum ether/ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.81−0.90 (m, 3H, 9-CH_3), 0.97−1.16 (m, 10H, 7-CH_3, 13-CH_3, 16-H, 8-H), 1.28−1.47 (m, 2H, 8-H, 10-H), 1.49−1.68 (m, 4H, 9-H, 10-H, 12-H), 1.91−2.04 (m, 2H, 15-H), 2.11 (s, 3H, 3-CH_3), 2.11−2.19 (m, 2H, 13-H), 2.52−2.68 (m, 2H, 5-H), 2.68−2.78 (m, 1H, 7-H), 3.70−3.76 (m, 1H, 11-H), 3.69 (s, 3H, OMe), 4.46−4.56 (m, 1H, 4-H), 4.68−4.76 (m, 2H, 14-CH_2), 6.02 (s, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.3 ($(CH_3)_2Si$), −4.0 ($(CH_3)_2Si$), 12.4 (C-16), 15.4 (3-CH_3), 16.5, 18.0 ($(CH_3)_3CSi$), 20.0, 25.9 ($(CH_3)_3CSi$), 26.3, 26.7, 36.8, 40.8, 44.2, 44.5, 44.6, 44.7, 45.59, 45.3 (C-5, C-7), 51.0 (OMe), 68.4 (C-11), 71.7 (C-4), 106.4 (14-CH_2), 115.0 (C-2), 156.3 (C-14), 157.9 (C-3), 167.2 (CO_2Me), 215.0 (C-6); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{31}H_{58}O_5SiNa$ 561.3946; found 561.3946.

*(7R,9S,11R,13R,E)-Methyl 11-((tert-butyldimethylsilyl)oxy)-3,7,9,13-tetramethyl-14-methylene-6-oxo-4-((triisopropylsilyl)oxy)-hexadec-2-enoate (**30**).* To a solution of TIPSOTf (0.065 mL, 0.24 mmol, 4 equiv) in CH_2Cl_2 (0.5 mL) at −78 °C was added 2,6-lutidine (0.035 mL, 0.30 mmol, 5 equiv) dropwise followed by the addition of hydroxy ketone **29** (0.030 g, 0.06 mmol) in CH_2Cl_2 (0.025 mL). The mixture was stirred for 3 h at −78 °C, then warmed to −40 °C, and stirred at this temperature for 45 h. Thereafter, water (1 mL) was added, and the mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with saturated NH_4Cl solution (3 mL), saturated $NaHCO_3$ solution (3 mL), and saturated NaCl solution (3 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O/petroleum ether, 1:50) to give unreacted alcohol **29** (5 mg) and silyl ether **30** (30 mg, 92%) as colorless oils. R_f = 0.5 (petroleum ether/ethyl acetate, 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3H, $(CH_3)_2Si$), 0.04 (s, 3H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.81−0.90 (m, 3H, 9-CH_3), 0.96−1.05 (m, 29H, $((CH_3)_2CH)_3Si$, 7-CH_3, 13-CH_3, 16-H, 8-H), 1.06−1.14 (m, 3H, $((CH_3)_2CH)_3Si$), 1.30−1.45 (m, 2H, 9-H, 10-H), 1.46−1.59 (m, 2H, 10-H, 12-H), 1.60−1.70 (m, 1H, 12-H), 2.00 (q, *J* = 7.5 Hz, 2H, 15-H), 2.10 (d, *J* = 1.1 Hz, 3H, 3-CH_3), 2.10−2.17 (m, 1H, 13-H), 2.45−2.66 (m, 2H, 5-H, 7-H), 2.68−2.78 (m, 1H, 5-H), 3.67 (s, 3H, OMe), 3.68−3.76 (m, 1H, 11-H), 4.68−4.76 (m, 2H, 14-CH_2), 4.77 (t, *J* = 5.9 Hz, 1H, 4-H), 5.90−5.96 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.3 ($(CH_3)_2Si$), −4.0 ($(CH_3)_2Si$), 12.4, 14.5, 15.8, 18.0 ($(CH_3)_3CSi$), 20.0, 20.3, 25.9 ($(CH_3)_3CSi$), 26.3, 26.7, 36.8, 40.4, 43.9, 44.5, 44.6, 48.1, 48.7 (C-5), 51.0 (OMe), 68.7 (C-11), 73.3 (C-4), 106.4 (14-CH_2), 115.4 (C-2), 156.3 (C-14), 160.1 (C-3), 167.2 (C-1), 211.0 (C-6); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{37}H_{72}O_5Si_2Na$ 675.4811; found 675.4816.

*(7R,9S,11R,13R,E)-Methyl 11-Hydroxy-3,7,9,13-tetramethyl-14-methylene-6-oxo-4-((triisopropylsilyl)oxy)hexadec-2-enoate (**31**).* To a solution of silyl ether **30** (0.023 g, 0.035 mmol) in CH_3OH/CH_2Cl_2 (0.3 mL, 2:1) was added camphorsulfonic acid (2 mg, 0.007 mmol, 0.2 equiv). After 50 min of stirring at room temperature, Et_3N (0.020 mL) was added to the mixture, and then the volatiles solvent was removed in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9, 1:5) to give hydroxy ester **31** (15 mg, 79%, 10 mg major isomer, 5 mg minor isomer) as a colorless oil. R_f = 0.5 (petroleum ether/ethyl acetate, 5:1). The chromatographic separation on this stage is possible, but it is more convenient to perform the separation on the stage of the macrolactones **33a** and **33b** due to the larger difference in their retention factors.

Major Isomer. R_f = 0.5 (petroleum ether/ethyl acetate, 5:1); $[\alpha]^{20}_D$ = +1.8 (*c* = 0.83, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.4 Hz, 3H, 9-CH_3), 0.96−1.10 (m, 31H, 3 x $SiCH(CH_3)_2$, 8-H, 10-H, 16-H, 7-CH_3, 13-CH_3), 1.34−1.45 (m, 2H, 12-H, 10-H), 1.46−1.54 (m, 1H, 12-H), 1.60−1.67 (m, 2H, 8-H, 9-H), 1.92−2.06 (m, 2H, 15-H), 2.10 (d, *J* = 1.1 Hz, 3H, 3-CH_3), 2.36−2.47 (m, 1H, 13-H), 2.50−2.59 (m, 1H, 7-H), 2.68 (dd, *J* = 1.8, 5.8 Hz, 2H, 5-H), 3.59−3.74 (m, 1H, 11-H), 3.67 (s, 3H, OMe), 4.73−4.82 (m, 3H, 14-CH_2, 4-H), 5.90−5.96 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3 (C-16), 14.4 (3-CH_3), 16.4 (7-CH_3), 18.0 ($SiCH(CH_3)_2$), 20.0 (13-CH_3), 20.8 (9-CH_3), 25.5 (C-15), 27.3 (C-9), 37.3 (C-13), 40.4 (C-10), 43.8 (C-12), 44.8 (C-7), 48.1 (C-5), 51.0 (OMe), 67.6 (C-11), 73.1 (C-4), 107.3 (14-CH_2), 115.4 (C-2), 155.8 (C-14), 160.1 (C-3), 167.2 (C-1), 211.3 (C-6); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{31}H_{58}O_5SiNa$ 561.3946; found 561.3945.

Minor Isomer. R_f = 0.6 (petroleum ether/ethyl acetate, 5:1); $[\alpha]^{22}_D$ = −13.8 (*c* = 0.38, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.4 Hz, 3H, 9-CH_3), 0.97−1.07 (m, 31H, 3 × $SiCH(CH_3)_2$, 8-H, 10-H, 16-H, 7-CH_3, 13-CH_3), 1.33−1.46 (m, 2H, 12-H, 10-H), 1.47−1.54 (m, 1H, 12-H), 1.56−1.68 (m, 2H, 8-H, 9-H), 1.93−2.06 (m, 2H, 15-H), 2.11 (d, *J* = 1.1 Hz, 3H, 3-CH_3), 2.36−2.48 (m, 1H, 13-H), 2.50−2.78 (m, 3H, 7-H, 5-H), 3.59−3.71 (m, 1H, 11-H), 3.68 (s, 3H, OMe), 4.73−4.82 (m, 3H, 14-CH_2, 4-H), 5.89−5.94

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(m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3 (C-16), 14.4 (3-CH_3), 16.5 (7-CH_3), 17.7, 18.0 ($SiCH(CH_3)_2$), 20.0 (13-CH_3), 20.8 (9-CH_3), 25.5 (C-15), 27.3 (C-9), 37.2 (C-13), 40.5 (C-10), 43.7 (C-12), 44.8 (C-8), 44.9 (C-7), 48.7 (C-5), 51.0 (OMe), 67.5 (C-11), 73.2 (C-4), 107.3 (14-CH_2), 115.4 (C-2), 155.8 (C-14), 160.1 (C-3), 167.2 (C-1), 211.3 (C-6); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{31}H_{58}O_5SiNa$ 561.3946; found 561.3946.

*(7R,9S,11R,13R,E)-11-Hydroxy-3,7,9,13-tetramethyl-14-methylene-6-oxo-4-((triisopropylsilyl)oxy)hexadec-2-enoic Acid (**32**).* To a solution of ester **31** (0.012 g, 0.022 mmol) in 1,2-dichloroethane (0.4 mL) was added Me_3SnOH (0.017 g, 0.11 mmol, 5 equiv). After stirring for 2 d at 80 °C, the reaction mixture was diluted with $KHSO_4$ solution (1 mL, 5% in water) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 3 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:3) to give seco acid **32** (8 mg, 69%) as a colorless oil. R_f = 0.4 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, J = 4.0 Hz, 3H, 9-CH_3), 0.99−1.08 (m, 30H, 3 × $SiCH(CH_3)_2$, 16-H, 7-CH_3, 13-CH_3), 1.25−1.33 (m, 2H, 8-H, 12-H), 1.35−1.46 (m, 2H, 12-H, 10-H), 1.47−1.54 (m, 1H, 10-H), 1.56−1.69 (m, 2H, 8-H, 9-H), 1.93−2.07 (m, 2H, 15-H), 2.11 (s, 3H, 3-CH_3), 2.36−2.47 (m, 1H, 13-H), 2.50−2.60 (m, 1H, 7-H), 2.62−2.76 (m, 2H, 5-H), 3.59−3.71 (m, 1H, 11-H), 4.73−4.84 (m, 3H, 14-CH_2, 4-H), 5.90−5.96 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3 (C-16), 14.8 (3-CH_3), 16.5 (7-CH_3), 17.8, 18.0 ($SiCH(CH_3)_2$), 20.0 (13-CH_3), 20.8 (9-CH_3), 25.4 (C-15), 27.3 (C-9), 37.3 (C-13), 40.4 (C-10), 43.7 (C-12), 44.8 (C-7), 48.1 (C-5), 67.6 (C-11), 73.1 (C-4), 107.4 (14-CH_2), 115.4 (C-2), 155.7 (C-14), 162.8 (C-3), 170.8 (C-1), 211.1 (C-6); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{30}H_{56}O_5SiNa$ 547.3789; found 547.3787.

4-*O*-Triisopropylsilyl-amphidinolide Q (33a and 33b). To a solution of hydroxy acid **32** (5 mg, 0.009 mmol) in benzene (25 mL) were added Et_3N (0.021 mL, 148 mmol, 16 equiv) and 2,4,6-trichlorobenzoyl chloride (TCBC) (0.011 mL, 0.072 μmol, 8 equiv). The reaction mixture was stirred at room temperature for 1.5 h before DMAP (0.017 g, 0.142 mmol) was added and the reaction mixture was stirred overnight. It was diluted with Et_2O (70 mL) and washed with saturated NH_4Cl solution (30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude lactone mixture was purified (Et_2O/petroleum ether, 2:50) to give macrolactones **33a** and **33b** (2 mg, 1 mg, 62%) as colorless oils. The NMR spectra of **33a** matched with the published one.[5]

*4-(R)-O-Triisopropylsilyl-amphidinolide Q (**33a**).* R_f = 0.2 (petroleum ether/ethyl acetate, 33:1); $[\alpha]^{21}_D$ = +32.3 (c = 0.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.6 Hz, 3H, 19-H), 1.00−1.09 (m, 32H, 3 × $SiCH(CH_3)_2$, 16-H, 18-H, 20-H), 1.27−1.30 (m, 1H, 10-H), 1.43 (ddd, J = 7.5, 10.9, 14.1 Hz, 1H, 10-H), 1.50−1.62 (m, 2H, 12-H), 1.90 (dd, J = 2.9, 14.4, 1H, 8-H), 1.94−2.05 (m, 2H, 15-H), 2.06−2.12 (m, 1H, 7-H), 2.14 (d, J = 1.0 Hz, 3H, 17-H), 2.26 (dd, J = 7.1, 14.3 Hz, 1H, 13-H), 2.60 (dd, J = 6.2, 12.6 Hz, 1H, 5-H), 2.79 (dd, J = 3.2, 12.6 Hz, 1H, 5-H), 4.58 (dd, J = 3.1, 6.1 Hz, 1H, 4-H), 4.75−4.79 (m, 2H, 21-H), 4.88−5.00 (m, 1H, 11-H), 6.05 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2 (C-16), 16.7 (C-17), 18.0 ($SiCH(CH_3)_2$), 18.2 (C-18), 21.1 (C-20), 23.6 (C-19), 26.2 (C-15), 29.7 (C-9), 31.9 ($SiCH(CH_3)_2$), 37.0 (C-13), 39.9 (C-8), 41.3 (C-12), 44.9 (C-10), 46.3 (C-5), 49.6 (C-7), 73.9 (C-4), 75.1 (C-11), 107.1 (C-21), 117.6 (C-2), 155.3 (C-14), 155.9 (C-3), 168.1 (C-1), 211.5 (C-6); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{30}H_{54}O_4SiNa$ 529.3684; found 529.3684.

*4-(S)-O-Triisopropylsilyl-amphidinolide Q (**33b**).* R_f = 0.3 (petroleum ether/ethyl acetate, 33:1); $[\alpha]^{22}_D$ = +78.7 (c = 0.17, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, J = 6.6 Hz, 3H, 19-H), 0.98−1.07 (m, 30H, 3 × $SiCH(CH_3)_2$, 8-H, 16-H, 18-H, 20-H), 1.35−1.49 (m, 1H, 10-H), 1.52−1.58 (m, 2H, 10-H, 12-H), 1.90−2.11 (m, 4H, 15-H, 9-H, 7-H), 2.18 (d, J = 1.1 Hz, 3H, 17-H), 2.15−2.27 (m, 1H, 13-H), 2.51 (dd, J = 5.0, 11.0 Hz, 1H, 5-H), 2.94 (t, J = 11.0 Hz, 1H, 5-H), 4.50 (dd, J = 4.9, 10.6 Hz, 1H, 4-H), 4.73−4.79 (m, 2H, 21-H), 4.98−5.07 (m, 1H, 11-H), 5.59 (m, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3 (C-16), 17.7 (C-17), 17.9 ($SiCH(CH_3)_2$), 18.0 (C-18), 21.1 (C-20), 23.7 (C-19), 26.1 (C-15), 29.7 (C-9), 33.0 (C-13), 37.0 (C-7), 39.9 (C-12), 41.3 (C-10), 44.5 (C-5), 49.5 (C-8), 74.3 (C-4), 76.8 (C-11), 107.1 (C-21), 116.8 (C-2), 155.1 (C-14), 155.8 (C-3), 166.8 (C-1), 213.6 (C-6); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{30}H_{54}O_4SiNa$ 529.3684; found 529.3686.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01806.

A Table listing the carbon shifts of **33a** in comparison with literature values, and copies of NMR spectra (PDF)

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Notes

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