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Protecting-Group Directed Stereoselective Intramolecular Nozaki–Hiyama–Kishi Reaction: A Concise and Efficient Total Synthesis of Amphidinolactone A

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A convergent total synthesis of amphidinolactone A, a cytotoxic macrolide from the cultured dinoflagellate *Amphidinium* sp., is described in 13 linear steps. The key step in the synthetic sequence involves an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction for the construction of the 13-membered lactone ring by union of two fragments derived from a single chiral epoxide. The stereochemical outcome of the NHK reaction has been supported by computational studies.

Introduction

Amphidinolactone A (**1**) is a cytotoxic 13-membered macrolide isolated from a symbiotic dinoflagellate *Amphidinium* sp. (Y-25) obtained from an Okinawa marine acoel flatworm Amphiscolops sp.[1] The relative and absolute stereochemistries **1** were elucidated on the basis of extensive spectral analysis followed by a total synthesis outlined by Kobayashi et al.[2]

The interesting biological profile as well as the structural complexity of **1** (Figure 1) have attracted the attention of synthetic organic chemists worldwide. In this communication, we report a convergent approach to **1** using an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction for macrocyclization of **2** derived from the union of **6** and **8**, both prepared from epoxide **9**[3] (Scheme 1). Moreover, the synthetic protocol should sort out all the selectivity problems faced by Kobayashi et al. during the total synthesis.

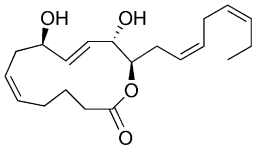
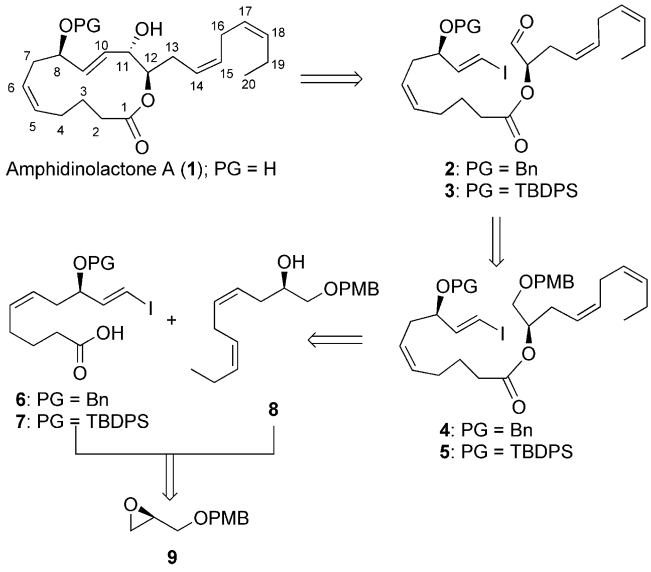


Figure 1. Structure of amphidinolactone A (**1**).



Scheme 1. Retrosynthetic analysis of amphidinolactone A (**1**).

Results and Discussion

Synthesis of fragment **6** started from known chiral epoxide **9**, which was prepared by using Jacobsen's hydrolytic kinetic resolution protocol.[4] Epoxide **9** underwent clean addition of the lithium acetylide prepared from the TBS-protected alkyne following treatment with *n*BuLi in THF at –78 °C in 89% yield.[5] The resulting secondary hydroxy group was protected as its benzyl ether by treatment with NaH and benzyl bromide at 0 °C to afford **11**. Removal of the silyl group with *p*-TsOH in MeOH at room temperature followed by partial hydrogenation[6] with Lindlar's catalyst afforded *Z*-olefin derivative **12** in 86% over two steps (Scheme 2). Oxidation of the resulting hydroxy group with

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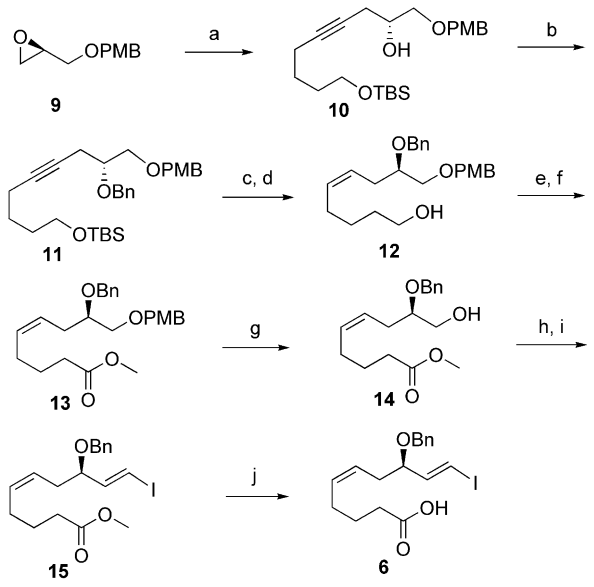
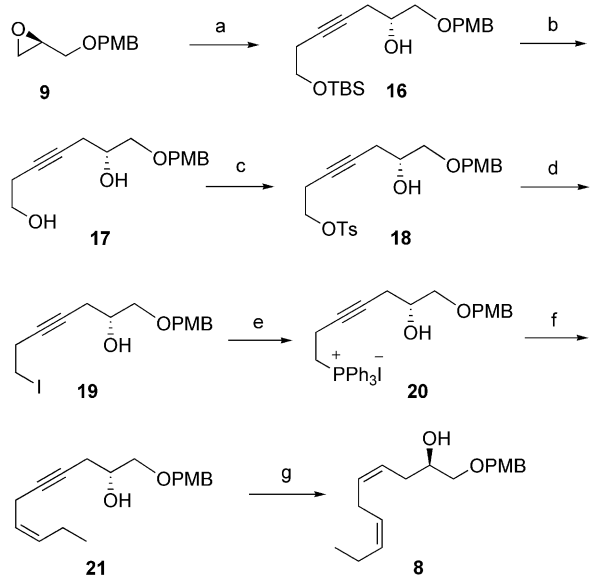
TEMPO[7] and BAIB followed by further Pinnick[8] oxidation with $NaClO_2$ in the presence of 2-methyl-2-butene afforded the acid, which upon treatment with CH_2N_2 in ether at 0 °C gave ester **13** in 81% yield over three steps. Removal of the PMB group with DDQ[9] in CH_2Cl_2/H_2O (19:1) at room temperature gave alcohol **14**, which upon Dess–Martin periodinane oxidation[10] followed by Takai olefination[11] afforded *trans*-vinyl iodide **15** as the only product. Saponification of the ester functionality with LiOH in THF/H_2O (3:2) afforded required acid fragment **6** in 91% yield.



Scheme 2. Reagents and conditions: (a) *n*BuLi, $BF_3{\cdot}OEt_2$, hexyne derivative, –78 °C, 1 h, 89%; (b) NaH, BnBr, 0 °C to r.t., 5 h, 90%; (c) *p*-TsOH, MeOH, 0 °C to r.t., 1 h, 91%; (d) H_2, Pd/C on $CaCO_3$, quinoline, r.t., 2 h, 95%; (e) TEMPO, BAIB, CH_2Cl_2, r.t.; (f) 1. $NaClO_2$, NaH_2PO_4, *t*BuOH, H_2O, 2-methyl-2-butene, r.t., 3 h, 85% over two steps; 2. CH_2N_2, ether, 0 °C to r.t., 10 min, 96%; (g) DDQ, CH_2Cl_2/H_2O (9:1), r.t., 2 h, 89%; (h) DMP, CH_2Cl_2, $NaHCO_3$, r.t., 3 h, 92%; (i) $CrCl_2$, CHI_3, THF, 16 h, 82%; (j) LiOH, THF/H_2O (3:1), r.t., 3 h, 91%.

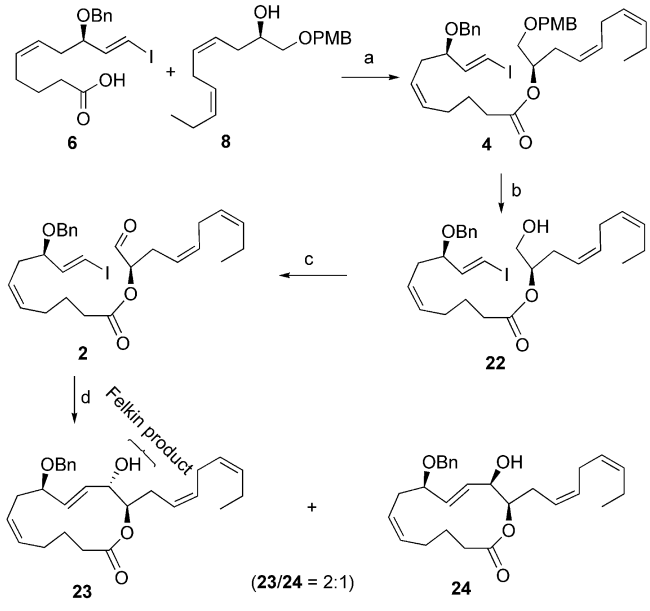
Treatment of chiral epoxide **9** with lithium acetylide followed by cleavage of the TBS ether linkage with *p*-TsOH in MeOH afforded **17** in 81% yield over two steps. The primary hydroxy group of **17** was first tosylated and then treated with NaI in acetone to afford iodide **19**. Wittig salt **20** was prepared in 94% yield by treating **19** with triphenylphosphane in acetonitrile at reflux (Scheme 3). The *cis* geometry at C17–C18 was then introduced by performing a Wittig reaction of **20** with *n*-propanal in the presence of *n*BuLi at –78 °C to obtain **21** in 83% yield as the only product. Partial hydrogenation using Lindlar's catalyst (Pd on $CaCO_3$) in the presence of quinoline (catalytic) afforded alcohol **8** in 91% yield.

Having acid **6** and alcohol **8** in hand, the stage was set for the combination of the two components and the formation of the macrocycle through an intramolecular NHK reaction. The coupling of C1–C10 fragment **6** and C11–C20 fragment **8** was initially performed by employing dicyclo-



Scheme 3. Reagents and conditions: (a) *n*BuLi, $BF_3{\cdot}OEt_2$, alkyne, –78 °C, 1 h, 86%; (b) *p*-TsOH, MeOH, 0 °C to r.t., 1 h, 94%; (c) TsCl, Et_3N, CH_2Cl_2, 0 °C, 6 h, 80%; (d) NaI, acetone, reflux, 3 h, 90%; (e) TPP, CH_3CN, 100 °C, 12 h, 94%; (f) *n*BuLi, propionaldehyde, –78 °C, 4 h, 83%; (g) H_2, Pd/C on $CaCO_3$, quinoline (catalytic), benzene, r.t., 3 h, 91%.

hexyl carbodiimide (DCC)[12] and a catalytic amount of DMAP in CH_2Cl_2 to afford ester **4** in 58% yield. Similarly, coupling in the presence of EDCI[13] and DMAP in CH_2Cl_2 furnished ester **4** in 70% yield. However, a better result was achieved under Yamaguchi conditions[14] to obtain ester **4** in 89% yield. It is important to note that compound **4** contains all 20 carbon atoms of the target molecule (Scheme 4).



Scheme 4. Reagents and conditions: (a) 1. DCC, DMAP, CH_2Cl_2, 0 °C to r.t. 12 h, 58%; 2. EDCI, DMAP, CH_2Cl_2, 0 °C to r.t., 12 h, 70%; 3. 2,4,6-trichlorobenzoyl chloride, DMAP, THF, toluene, r.t., 6 h, 89%; (b) DDQ, CH_2Cl_2/H_2O (9:1), r.t., 3 h, 91%; (c) DMP, CH_2Cl_2, r.t., 4 h; (d) $CrCl_2$, $NiCl_2$, DMSO/THF (3:1), r.t., 24 h, 81% over two steps.

Cleavage of the PMB ether in **4** upon treatment with DDQ afforded alcohol **22** in 90% yield. Dess–Martin periodinane oxidation of **22** gave required aldehyde **2** in 94% yield. The critical macrocyclization of **2** under NHK reaction conditions[15] follows Felkin–Anh[16] rules in that this key step allows macrolactonization and provides the required stereochemistry of the newly formed hydroxy group (for mechanism, see Figure 2). The yield and the rate of the NHK reaction are sensitive to the reaction medium and to the sequence of addition of the reagents. With a mixture of DMF and THF as solvent, the starting material was consumed fairly quickly (2–4 h) to give a low yield of the macrocycle. In DMSO/THF (3:1), the macrocycle was formed as a 2:1 mixture of inseparable diastereomeric allylic alcohols **23** and **24** in 81% yield. However, it took about 24 h for the starting material to be completely consumed. The diastereoselectivity of the cyclization appears to arise from the preference of the aldehyde at C11 to adopt a conformation in which the metal-complexed carbonyl oxygen atom is oriented away from the bulky benzyl group.

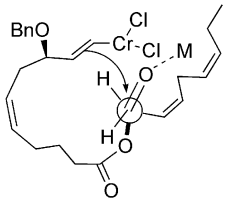
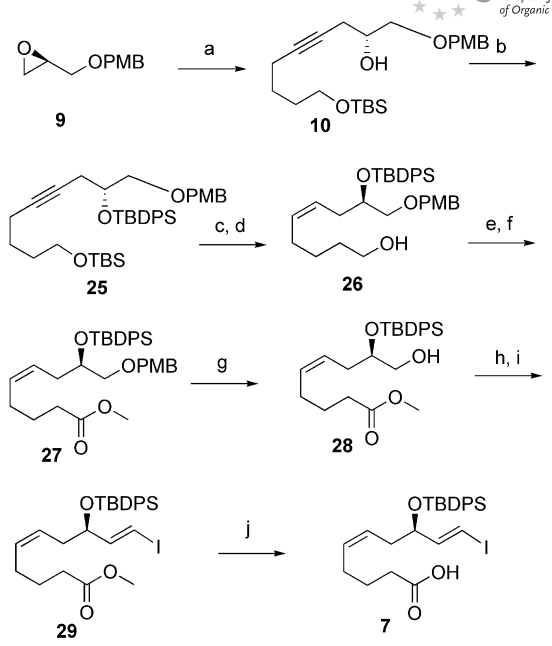


Figure 2. Diastereoselectivity in the formation of **23** as the major product.

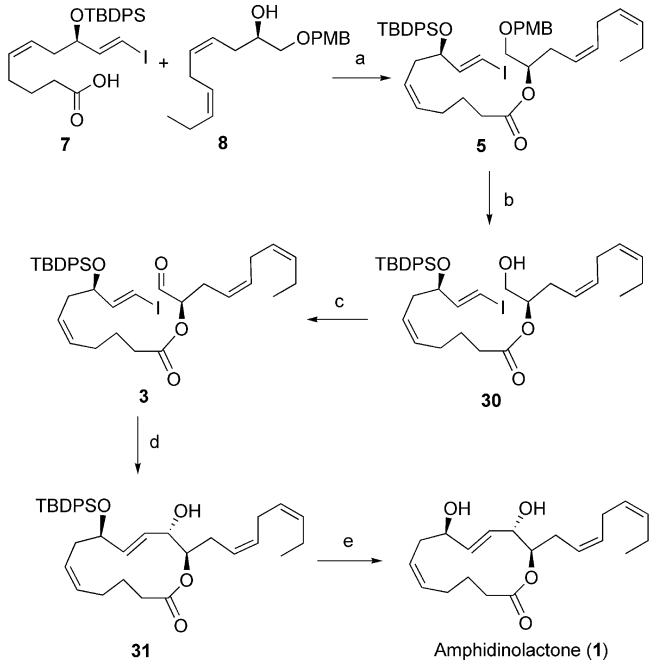
To desire to obtain a single isomer at this juncture forced us to make a judicious choice of protecting groups, which can determine and influence the facial selection of the carbonyl group. During our literature search, the success in the formation of the C6–C7 bond and the installation of the correct configuration at C7 in the total syntheses of decarestrictine D[17a] as well as the formation of the C7–C8 bond and the installation of the C8 stereocentre in the total synthesis of aspinolide B[17b] prompted us to attach a bulky protecting group at C8 to be employed in the intramolecular NHK coupling reaction and to verify the selectivity at C11 during the formation of the 13-membered lactone ring.

We first tried to replace the benzyl group in **15** with the bulky TDBPS group. Unfortunately, deprotection under several conditions (Li/liq. NH_3, Li/naphthalene, DDQ) gave an intractable mixture of products. The synthesis of **7** commenced with known chiral epoxide **9** and followed the same sequence of reactions except for the selective cleavage of the TBDMS ether linkage in the presence of the TBDPS ether by using *p*-TsOH in MeOH/CH_2Cl_2 (1:3) to obtain primary alcohol **26** (Scheme 5).

Compound **7** was coupled with alcohol fragment **8** following Yamaguchi esterification conditions to obtain acetate derivative **5** in 87% yield. Starting from **5**, the same sequence of reactions as those described in Scheme 4 afforded compound **31** as a single isomer. The formation of a single isomer appears to arise from the preference of the aldehyde at C11 to adopt a conformation in which the



Scheme 5. Reagents and conditions: (a) *n*BuLi, $BF_3{\cdot}OEt_2$, hexyne derivative, –78 °C, 1 h, 89%; (b) TBDPSCl, imidazole, DMF, 0 °C to r.t., 6 h, 97%; (c) *p*-TsOH, MeOH/CH_2Cl_2 (1:3), 0 °C to r.t., 1 h, 89%; (d) H_2, Pd/C on $CaCO_3$, quinoline, r.t., 2 h, 96%; (e) TEMPO, BAIB, CH_2Cl_2, r.t., 3 h, 91%; (f) 1. $NaClO_2$, NaH_2PO_4, *t*BuOH, H_2O, 2-methyl-2-butene, r.t., 3 h, 94%; 2. CH_2N_2, ether, 0 °C to r.t., 10 min, 95%; (g) DDQ, CH_2Cl_2/H_2O (9:1), r.t., 2 h, 88%; (h) DMP, CH_2Cl_2, r.t., 3 h, 96%; (i) $CrCl_2$, CHI_3, THF, 16 h, 84%; (j) LiOH, THF/H_2O (3:1), r.t., 3 h, 90%.



Scheme 6. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, DMAP, THF, toluene, r.t., 6 h, 87%; (b) DDQ, CH_2Cl_2/H_2O (9:1), r.t., 3 h, 92%; (c) DMP, CH_2Cl_2, r.t., 4 h; (d) $CrCl_2$, $NiCl_2$, DMSO, r.t., 24 h, 85% over two steps; (e) TBAF, AcOH, THF, 0 °C to r.t., 18 h, 87%.

metal-complexed carbonyl oxygen atom is oriented away from the highly bulky TBDPS group. Finally, cleavage of the TBDPS ether linkage with TBAF and acetic acid afforded amphidinolactone A (**1**) in 87% yield (Scheme 6).

To rationalize the observed experimental trends, quantum chemical calculations were carried out on the *anti* and *syn* isomers of the OBn- and OTBDPS-substituted systems. The proposed transition states (TS) corresponding to $CrCl_2$ migration, their corresponding intermediates (IN) and the final products (PR) were optimized at the PM3 level by using the SPARTAN program package. Because the TSs play a major role in the formation of the PRs, analysis was done on the basis of the relative energies of the *anti* and *syn* isomers of the TSs. As the variation in the experimental yields is mainly due to the OBn and OTBDPS groups, the side chain attached to the ether-linked carbon was substituted with a CH_3 group.

Figure 3 depicts the optimized structures along with the relative energies of the transition structures, intermediates and products, which help to rationalize the experimental observations. The relative energies of OBn-*anti*-TS and OBn-*syn*-TS versus those of OBn-*anti*-IN and OBn-*syn*-IN are 0.5 and 6.1 kcal/mol, respectively. The product stabilities of OBn-*syn*-Pr and OBn-*anti*-Pr are comparable, but there is a small preference for the former by a difference of 0.1 kcal/mol. Thus, considering the smaller difference in the energies between the TSs, one would expect the formation of both *anti* and *syn* isomers. However, the larger difference in the energies between the intermediates suggests the feasibility of PRs in unequal ratios. These results suggest that OBn substitution gives rise to the formation of the *anti* isomer in major quantities, which corroborates well with the observed experimental trends where *anti* and *syn* isomers are formed in a 2:1 ratio. Further, the differences in the

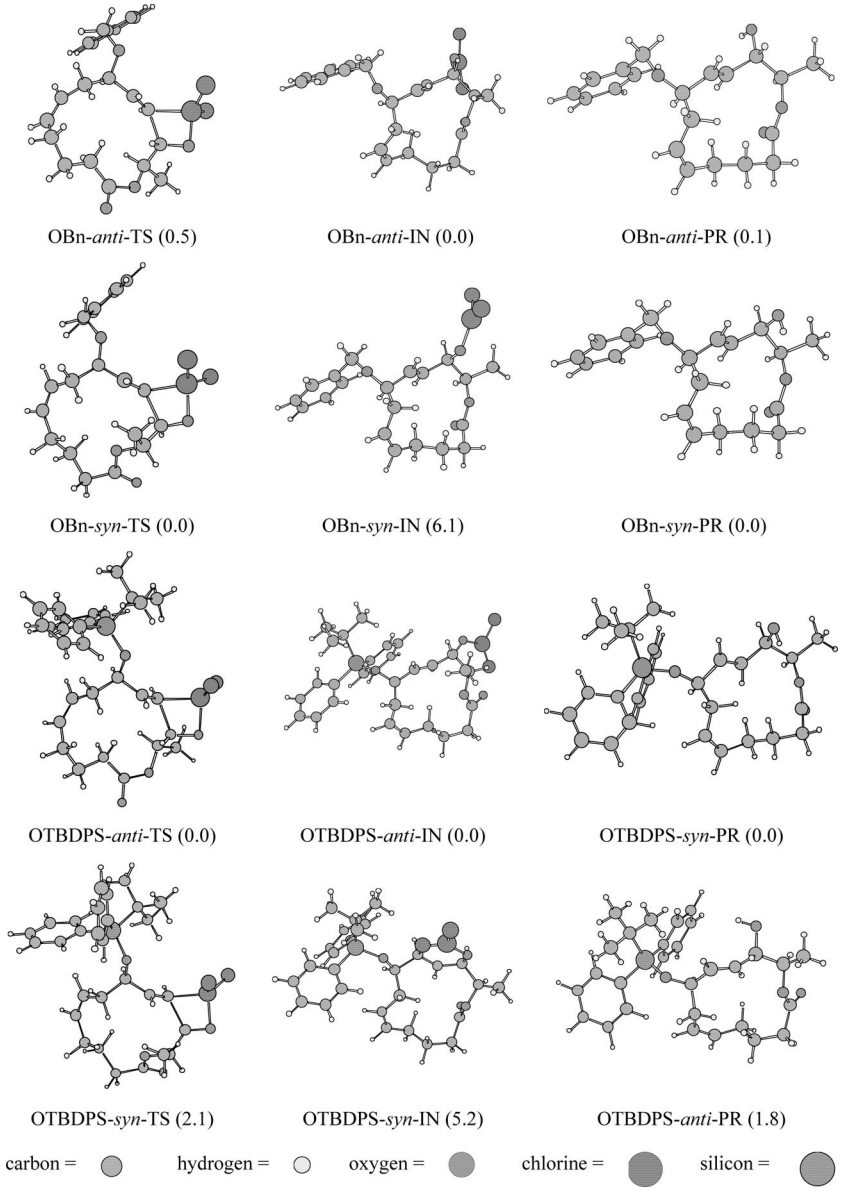


Figure 3. Optimized structures of the TSs, INs and PRs along with the relative energies in kcal/mol between the *syn* and *anti* isomers.

energies of OTBDPS-*anti*-TS and OTBDPS-*syn*-TS and those of OTBDPS-*anti*-IN and OTBDPS-*syn*-IN are 2.1 and 5.2 kcal/mol, respectively. The difference in the product energies between OTBDPS-*syn*-PR and OTBDPS-*anti*-PR is 1.8 kcal/mol. The larger difference in energies between the TSs as well as the INs suggests the exclusive formation of the *anti* isomer. From these results, it can be clearly understood that although the presence of a OBn group yields both *anti* and *syn* PRs in an unequal ratio, the presence of a OTBDPS group results in the exclusive formation of the *anti* isomer. Thus, the computational results corroborate well with the observed experimental trends.

Conclusions

In conclusion, we have accomplished the total synthesis of amphidinolactone A (**1**) starting from **9** in an overall yield of 22%.The longest linear synthetic sequence involved 13 steps. The important feature of our synthetic route is an intramolecular NHK reaction to construct the 13-membered lactone and to control the stereochemical outcome at C11 following esterification of two key intermediates prepared by using highly concise and efficient synthetic protocols.

Experimental Section

General Remarks: Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven- or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, benzene, toluene and diethyl ether from Na and benzophenone; CH_2Cl_2, quinoline and Et_3N from CaH_2; MeOH and EtOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out on silica gel (60–120 mesh). Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and are reported in wavenumber (cm^{-1}). ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane (TMS), and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad.

(2*R*)-9-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-[(4-methoxybenzyl)-oxy]-4-nonyn-2-ol (10): A flame-dried 500-mL round-bottomed flask was charged with TBS-protected 5-hexyne-1-ol (5.20 g, 24.74 mmol) in THF (250 mL) and cooled to –78 °C. To this solution was added *n*BuLi (2.5 M in hexanes, 9.92 mL, 24.74 mmol) dropwise by syringe. The resulting mixture was warmed slowly to 0 °C. During this time, the reaction mixture turned dark red in colour. After 30 min, (*S*)-PMB glycidyl (**9**; 4.0 g, 20.62 mmol) was slowly added, followed by $BF_3{\cdot}OEt_2$ (2.85 mL, 22.68 mmol) at –78 °C, and the mixture was stirred for an additional 30 min. The reaction was then quenched with saturated $NaHCO_3$, diluted with EtOAc and warmed to room temperature. The organic layer was extracted with EtOAc (3 × 100 mL), and the combined organic layer was washed with brine (100 mL), dried with Na_2SO_4 and concentrated. Purification by flash column chromatography (EtOAc/hexane, 1:3) provided **10** (8.90 g, 89%) as a colourless oil. $[\alpha]_D^{27}$ = –6.8 (*c* = 1.6, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3464, 2929, 2858, 2360, 1613, 1513, 1464, 1286, 1249 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 6.80 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 4.31 (q, *J* = 11.5 Hz, 2 H, OCH_2-Ar), 3.91 (m, 1 H, C*H*-OH), 3.79 (s, 3 H, O-CH_3), 3.60 (t, *J* = 6.2 Hz, 2 H, CH_2-OAr), 3.49–3.39 (m, 2 H, CH_2-OSi), 2.37–2.30 (m, 2 H, CH_2-C≡C), 2.18–2.08 (m, 2 H, C≡C-CH_2), 1.65–1.55 (m, 2 H, CH_2), 1.55–1.44 (m, 2 H, CH_2), 1.05 [s, 9 H, $SiC(CH_3)_3$], 0.06 [s, 6 H, $Si(CH_3)_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 130.3, 129.4, 113.4, 81.5, 76.7, 72.6, 62.01, 60.24, 55.02, 31.64, 26.7, 25.0, 24.4, 19.2, 18.4, –4.9 ppm. MS (ESI): *m*/*z* = 429 $[M + Na]^+$.

{(8*R*)-8-(Benzyloxy)-9-[(4-methoxybenzyl)oxy]-5-nonynyloxy}(*tert*-butyl)dimethylsilane (11): To a suspension of NaH (60% in mineral oil, 1.7 g, 42.36 mmol) in dry THF (60 mL) was added alcohol **10** (8.6 g, 21.18 mmol) in THF (40 mL) at 0 °C under a N_2 atmosphere. The suspension was stirred for 1 h at room temperature. Benzyl bromide (2.57 mL, 21.18 mmol) was added slowly to the above reaction mixture at the same temperature. The reaction mixture was stirred at room temperature for 4 h and then quenched with water at 0 °C. The reaction mixture was extracted with EtOAc (2 × 100 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated. Purification of the crude product by silica gel chromatography (EtOAc/hexane, 1:19) afforded **11** (9.4 g, 90%) as a light-yellow liquid. $[\alpha]_D^{27}$ = +3.2 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3462, 2930, 2858, 2363, 1615, 1513, 1465, 1283, 1249 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.33 (m, 5 H, C_6H_5), 7.29 (dd, *J* = 4.8, 7.1 Hz, 2 H, C_6H_4-OMe), 6.90 (dd, *J* = 5.6, 8.0 Hz, 2 H, C_6H_4-OMe), 4.70 (ABq, *J* = 12.7, 20.2 Hz, 2 H, OCH_2-C_6H_5), 4.53 (s, 2 H, OCH_2-C_6H_4-OMe), 3.85 (s, 3 H, OCH_3), 3.73 (m, 1 H, C*H*-OBn), 3.68–3.58 (m, 4 H, CH_2-OAr, CH_2-OSi), 2.52–2.47 (m, 2 H, CH_2-C≡C), 2.23–2.17 (m, 2 H, C≡C-CH_2), 1.66–1.52 (m, 4 H, CH_2-CH_2), 0.94 [s, 9 H, $SiC(CH_3)_3$], 0.09 [s, 6 H, $Si(CH_3)_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 138.5, 129.6, 129.1, 128.2, 127.7, 127.4, 113.6, 81.7, 76.9, 76.4, 73.0, 71.8, 71.3, 62.6, 55.2, 31.9, 25.9, 25.3, 21.8, 18.5, –5.3 ppm. MS (ESI): *m*/*z* = 497 $[M + H]^+$.

(*Z*,8*R*)-8-(Benzyloxy)-9-[(4-methoxybenzyl)oxy]-5-nonen-1-ol (12): To a stirred solution of TBS ether **11** (9.0 g, 18.14 mmol) in MeOH (70 mL) was added *p*-TsOH (catalytic) at 0 °C, and the resulting solution was stirred for 1 h at ambient temperature. The reaction mixture was quenched with aqueous $NaHCO_3$ (20 mL). MeOH was removed under reduced pressure, and the residue was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (50 mL), dried with Na_2SO_4 and concentrated. Purification of the crude product by silica gel column chromatography (EtOAc/hexane, 1:2) furnished the desired primary alcohol (6.3 g, 91%) as a viscous colourless liquid that was immediately used for next step. Lindlar's catalyst (Pd/C on $CaCO_3$) was added to a stirred solution of the alkyne (6.2 g, 16.23 mmol) in benzene (20 mL) followed by a catalytic amount of quinoline at room temperature under a hydrogen atmosphere. The mixture was vigorously stirred for 2 h at room temperature. After complete consumption of the starting material (checked by TLC), the black reaction mass was filtered through a pad of Celite, and the filtrate was concentrated. Purification of the crude mass by silica gel column chromatography (EtOAc/hexane, 1:4) afforded **12** (5.9 g, 95%). $[\alpha]_D^{27}$ = +2.8 (*c* = 1.9, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3474, 2928, 2857, 2360, 1620, 1464, 1427, 1245, 1112, 1074, 940 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (m, 5 H, C_6H_5), 7.24 (d, *J* = 8.3 Hz, 2 H, C_6H_4-OMe), 6.86 (d, *J* = 8.5 Hz, 2 H, C_6H_4-OMe), 5.49–5.40 (m, 2 H, C*H*=C*H*), 4.62 (ABq, *J* = 11.9, 20.0 Hz, 2 H, OCH_2-C_6H_5), 4.46 (s, 2 H, OCH_2-C_6H_4-OMe), 3.79 (s, 3 H, OCH_3), 3.64–3.53 (m, 3 H, CH_2-OAr, C*H*-OBn), 3.49 (d, *J* = 4.3 Hz, 2 H, CH_2-OH), 2.33 (t, *J* = 5.8 Hz, 2 H, CH_2-CH=CH), 2.09–1.98 (m, 2 H,

CH=CH-CH_2), 1.72 (br. s, 1 H, OH), 1.57–1.46 (m, 2 H, CH_2), 1.44–1.32 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 138.7, 132.8, 131.7, 130.3, 129.2, 128.2, 127.6, 126.0, 125.3, 113.7, 78.0, 72.9, 71.9, 71.7, 62.6, 55.2, 32.2, 29.6, 26.9, 25.6 ppm. HRMS (ESI): calcd. for $C_{24}H_{32}O_4$ [M + H]$^+$ 385.2373; found 385.2361.

Methyl (*Z*,8*R*)-8-(Benzyloxy)-9-[(4-methoxybenzyl)oxy]-5-nonenoate (13): To a stirred solution of primary alcohol **12** (5.7 g, 14.84 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added iodobenzenediacetate (5.26 g, 16.32 mmol) followed by TEMPO (0.46 g, 2.96 mmol), and the mixture was stirred at ambient temperature for 3 h. After complete consumption of the primary alcohol (monitored by TLC), the reaction was quenched with a saturated solution of sodium thiosulfate and extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated. Purification of the crude aldehyde by flash chromatography on silica gel (EtOAc/hexane, 1:9) afforded the corresponding aldehyde (5.2 g, 92%) as a thick viscous liquid that was used immediately in the next reaction. To a solution of the resulting aldehyde (5.0 g, 13.09 mmol) in *tert*-butyl alcohol (45 mL) was added 2-methyl-2-butene (2 M in THF, 7 mL, 13.09 mmol) at room temperature. Sodium dihydrogenphosphate (6.12 g, 39.26 mmol) and sodium chlorite (1.77 g, 19.63 mmol) were dissolved in water (20 mL) to make a clear solution, which was subsequently added to the above-mentioned reaction mixture at 0 °C. The mixture was stirred for another 3 h at room temperature. The reaction mixture was extracted with EtOAc (3 × 100 mL), and the combined organic layer was washed with brine, dried with anhydrous Na_2SO_4 and concentrated. Purification of the crude product by silica gel chromatography (EtOAc/hexane, 3:7) afforded the corresponding acid (5.4 g, 93%) as a colourless oil. $[\alpha]_D^{27}$ = +4.2 (*c* = 1.6, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3469, 2926, 2860, 1710, 1608, 1513, 1453, 1249, 1095, 1032, 824 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5 H, C$_6H_5$), 7.24 (d, *J* = 8.3 Hz, 2 H, C$_6H_4$-OMe), 6.86 (d, *J* = 9.2 Hz, 2 H, C$_6H_4$-OMe), 5.50–5.37 (m, 2 H, CH=CH), 4.61 (ABq, *J* = 12.0, 20.1 Hz, 2 H, OCH_2-C$_6H_5$), 4.46 (s, 2 H, OCH_2-Ar), 3.80 (s, 3 H, OCH_3), 3.60 (q, *J* = 5.3 Hz, 1 H, CH-OBn), 3.49 (d, *J* = 4.5 Hz, 2 H, CH_2-OAr), 2.32 (dd, *J* = 5.3, 12.0 Hz, 4 H, CH_2-CH=CH-CH_2), 2.07 (q, *J* = 7.6 Hz, 2 H, CH_2-COOH), 1.67 (pent., *J* = 7.6 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.3, 159.1, 138.6, 131.6, 130.5, 129.2, 128.2, 127.7, 127.4, 126.3, 113.7, 77.9, 72.9, 71.8, 71.7, 55.2, 33.3, 29.6, 26.5, 24.4 ppm. MS (ESI): *m*/*z* = 421 [M + Na]$^+$. To a stirred solution of the above acid (4.3 g, 10.80 mmol) in ether at 0 °C was added a freshly prepared solution of diazomethane in diethyl ether (50 mL). The reaction mixture was stirred for 10 min at the same temperature and then quenched with a saturated sodium thiosulfate solution at 0 °C. Two layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic fraction was dried with anhydrous Na_2SO_4, and the solvent was evaporated. Purification of the crude product by silica gel chromatography (EtOAc/hexane, 1:9) afforded **13** (4.3 g, 96%) as a light-yellow liquid. $[\alpha]_D^{27}$ = +5.4 (*c* = 1.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2945, 2860, 1736, 1612, 1513, 1454, 1248, 1095 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 4.3 Hz, 5 H, C$_6H_5$), 7.20 (d, *J* = 8.5 Hz, 2 H, C$_6H_4$-OMe), 6.82, (d, *J* = 8.5 Hz, 2 H, C$_6H_4$-OMe), 5.48–5.35 (m, 2 H, CH=CH), 4.59 (ABq, *J* = 11.9, 20.0 Hz, 2 H, OCH_2-C$_6H_5$), 4.43 (s, 2 H, OCH_2-Ar), 3.79 (s, 3 H, OCH_3), 3.63 (s, 3 H, COOCH_3), 3.55 (dd, *J* = 5.5, 10.6 Hz, 1 H, CH-OBn), 3.48–3.42 (m, 2 H, CH_2-OAr), 2.33–2.21 (m, 4 H, CH_2-CH=CH-CH_2), 2.05 (dd, *J* = 7.0, 13.6 Hz, 2 H, CH_2-COOMe), 1.65 (quint., *J* = 7.8 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 159.0, 138.7, 131.8, 130.7, 129.2, 128.2, 127.6, 127.4, 126.2, 113.7, 77.9, 72.9, 71.9, 71.7, 55.2, 51.4, 33.4, 31.9, 29.6, 26.6, 24.7 ppm. HRMS (ESI): calcd. for $C_{25}H_{32}O_5$ [M + Na]$^+$ 435.2142; found 435.2125.

Methyl (*Z*,8*R*)-8-(Benzyloxy)-9-hydroxy-5-nonenoate (14): To a solution of PMB ether **13** (4.2 g, 10.19 mmol) in CH_2Cl_2 (50 mL) and water (5 mL) at room temperature was added DDQ (3.47 g, 15.29 mmol), and the reaction mixture was stirred for 2 h at the same temperature. The reaction was quenched with saturated $NaHCO_3$ (15 mL), and the organic layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine (50 mL), dried with anhydrous Na_2SO_4 and evaporated to give a red-coloured product. Purification of the crude product by silica gel column chromatography (EtOAc/hexane, 1:4) afforded **14** (2.64 g, 89%) as a colourless liquid. $[\alpha]_D^{27}$ = +3.2 (*c* = 1.6, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3453, 2947, 2862, 1732, 1610, 1510, 1455, 1250, 1095 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 5 H, C$_6H_5$), 5.51–5.40 (m, 2 H, CH=CH), 4.66 (ABq, *J* = 11.7, 19.8 Hz, 2 H, OCH_2-C$_6H_5$), 3.70–3.63 (m, 4 H, COOCH_3, CH-OAr), 3.58–3.50 (m, 2 H, CH_2-OH), 2.40–2.25 (m, 4 H, CH_2-CH=CH-CH_2), 2.08 (dd, *J* = 6.9, 14.2 Hz, 2 H, CH_2-COOMe), 1.69 (quint., *J* = 7.5 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 138.2, 132.2, 131.1, 128.4, 127.7, 125.6, 79.4, 71.5, 63.9, 51.5, 33.3, 28.6, 26.6, 24.6 ppm. HRMS (ESI): calcd. for $C_{17}H_{24}O_4$ [M + Na]$^+$ 315.1567; found 315.1581.

Methyl (5*Z*,8*R*,9*E*)-8-(Benzyloxy)-10-iodo-5,9-decadienoate (15): To a stirred solution of primary alcohol **14** (2.5 g, 8.56 mmol) and solid anhydrous $NaHCO_3$ (2.0 g) in CH_2Cl_2 (30 mL) at 0 °C was added Dess–Martin periodinane (4.0 g, 9.41 mmol). The resulting reaction mixture was stirred at 0 °C for 3 h. After completion of the reaction (monitored by TLC), the mixture was filtered through filter paper. The filtrate was washed with saturated $NaHCO_3$ (2 × 20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layer was dried with anhydrous Na_2SO_4, and the solvent was removed. Purification of the crude mass by flash chromatography (EtOAc/hexane, 1:5) afforded the corresponding aldehyde (2.3 g, 92%) as a pale-yellow liquid. To a stirred suspension of $CrCl_2$ (5.56 g, 45.51 mmol) in THF (25 mL) at 0 °C under a nitrogen atmosphere was added the aldehyde (2.2 g, 7.58 mmol) and CHI_3 (8.85 g, 22.75 mmol) dissolved in THF (25 mL). The reaction mixture was protected from light and stirred at ambient temperature for 16 h. The green reaction mass was quenched with water. The organic layer was extracted with EtOAc (3 × 50 mL). The combined organic extract was washed with saturated aqueous $Na_2S_2O_3$ (2 × 25 mL) followed by brine (50 mL), dried with anhydrous Na_2SO_4 and concentrated. Purification by silica gel column chromatography (EtOAc/hexane, 1:19) afforded **15** (2.8 g, 82%) as a pale-yellow oil. $[\alpha]_D^{27}$ = +5.0 (*c* = 1.3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2946, 2861, 1733, 1510, 1465, 1427, 1363, 1278, 1112, 1075 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (m, 5 H, C$_6H_5$), 6.46 (dd, *J* = 7.4, 14.5 Hz, 1 H, CH=CHI), 6.28 (d, *J* = 14.7 Hz, 1 H, CH=CHI), 5.48–5.34 (m, 2 H, CH=CH), 4.58 (ABq, *J* = 12.0, 36.5 Hz, 2 H, OCH_2-C$_6H_5$), 3.72 (q, *J* = 6.8 Hz, 1 H, CH-OBn), 3.64 (s, 3 H, COOCH_3), 2.40–2.21 (m, 4 H, CH_2-CH=CH-CH_2), 2.05 (q, *J* = 6.7 Hz, 2 H, CH_2-COOMe), 1.66 (quint., *J* = 7.4 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 145.5, 138.1, 131.1, 128.4, 127.8, 125.2, 81.2, 78.6, 70.5, 51.4, 33.6, 33.1, 26.8, 24.7 ppm. MS (ESI): *m*/*z* = 415 [M + H]$^+$.

(5*Z*,8*R*,9*E*)-8-(Benzyloxy)-10-iodo-5,9-decadienoic Acid (6): To a stirred solution of ester **15** (2.1 g, 5.07 mmol) in THF (20 mL) and water (3 mL) was added LiOH (175 mg, 7.60 mmol), and the reaction mixture stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the mixture was extracted with diethyl ether, and the aqueous layer was acidified to pH 2 with

0.5 M HCl. The aqueous layer was extracted with EtOAc (4 × 25 mL), and the combined organic layer was washed with brine (20 mL), dried with anhydrous Na_2SO_4 and concentrated. Purification of the crude product by silica gel column chromatography (EtOAc/hexane, 1:2) afforded **6** (1.84 g, 91%) as a colourless oil.

(2*R*)-7-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-[(4-methoxybenzyl)-oxy]-4-heptyn-2-ol (16): A flame-dried 100-mL two-necked round-bottomed flask was charged with the alkyne (5.0 g, 27.2 mmol) in THF (60 mL) and cooled to –78 °C. To this solution was added *n*BuLi (2.5 M in hexane, 12 mL, 29.87 mmol) slowly under a nitrogen atmosphere at the same temperature. After 30 min when the solution turned light yellow, (*S*)-PMB-glycidol (**9**; 5.8 g, 29.87 mmol) in THF (30 mL) was slowly added at the same temperature followed by $BF_3{\cdot}OEt_2$ (4.2 g, 29.87 mmol). The reaction mixture was stirred for an additional 30 min and then the reaction was quenched with saturated $NaHCO_3$ (40 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (100 mL), dried with Na_2SO_4 and concentrated to afford a yellow oil. Purification of the crude product by silica gel column chromatography (EtOAc/hexane, 1:9) afforded **16** (8.5 g, 86%) as a colourless liquid. $[\alpha]_D^{27}$ = –11.0 (*c* = 1.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3466, 2927, 2855, 2362, 1610, 1515, 1466, 1280, 1245 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.20 (dd, *J* = 3.0, 11.5 Hz, 2 H, C_6H_4-OMe), 6.82 (d, *J* = 8.3 Hz, 2 H, C_6H_4-OMe), 4.46 (s, 2 H, OCH_2-Ar), 3.88–3.76 (m, 4 H, OCH_3, -C*H*-OH), 3.68–3.60 (m, 2 H, CH_2-OAr), 3.43–3.33 (m, 2 H, CH_2-OSi), 2.40–2.28 (m, 4 H, CH_2-C≡C-CH_2), 0.89 [s, 9 H, $SiC(CH_3)_3$], 0.05 [s, 6 H, $Si(CH_3)_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 130.0, 129.3, 113.8, 79.6, 76.8, 73.0, 72.7, 69.0, 62.1, 55.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{34}O_4Si$ $[M + NH_4]^+$ 396.2565; found 396.2561.

(6*R*)-7-[(4-Methoxybenzyl)oxy]-3-heptyne-1,6-diol (17): To a stirred solution of TBS ether **16** (8.5 g, 23.35 mmol) in MeOH (70 mL) was added camphorsulfonic acid (catalytic) at 0 °C, and the resulting solution was stirred for 1 h at ambient temperature. The reaction mixture was quenched with aqueous $NaHCO_3$ (25 mL), and MeOH was removed under reduced pressure. The residue was extracted with EtOAc (3 × 70 mL). The combined organic layer was dried with Na_2SO_4 and concentrated to obtain a yellow oil. Purification by silica gel column chromatography (EtOAc/hexane, 1:1) furnished **17** (5.5 g, 94%) as a colourless viscous liquid. $[\alpha]_D^{27}$ = –3.6 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3391, 2920, 2862, 2361, 1612, 1513, 1459, 1248, 1174, 1082, 1027 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 6.84 (d, *J* = 8.5 Hz, 2 H, C_6H_4-OMe), 4.47 (s, 2 H, OCH_2-Ar), 3.87 (m, 1 H, C*H*-OH), 3.80 (s, 3 H, OCH_3), 3.63 (t, *J* = 5.8 Hz, 2 H, CH_2-OH), 3.51 (dd, *J* = 4.2, 9.4 Hz, 1 H, C*H*-OAr), 3.41 (dd, *J* = 6.6, 9.4 Hz, 1 H, C*H*-OAr), 2.42–2.35 (m, 4 H, CH_2-C≡C-CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 131.7, 129.4, 113.8, 79.3, 77.8, 72.9, 72.7, 68.9, 61.0, 55.2, 23.7, 23.0 ppm. HRMS (ESI): calcd. for $C_{15}H_{20}O_4$ $[M + Na]^+$ 287.1254; found 287.1259.

(6*R*)-6-Hydroxy-7-[(4-methoxybenzyl)oxy]-3-heptynyl 4-Methyl-1-benzenesulfonate (18): To a solution of diol **17** (5.0 g, 20 mmol) dissolved in dry CH_2Cl_2 (50 mL) at 0 °C was added dry Et_3N (5.4 mL, 40 mmol) followed by TosCl (3.8 g, 20 mmol) and DMAP (catalytic). The reaction mixture was warmed to room temperature. After completion of the reaction (monitored by TLC), the reaction was quenched with water, and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine (50 mL) and concentrated to give a yellow oil. Purification by silica gel column chromatography (EtOAc/hexane, 1:4) afforded **18** (6.5 g, 80%) as a pale-yellow oil. $[\alpha]_D^{27}$ = –5.5 (*c* = 1.6, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3461, 2921, 2855, 1614, 1513, 1358, 1248, 1176, 1098, 974, 771 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.3 Hz, 2 H, SO_2-C_6H_4-CH_3), 7.33 (d, *J* = 8.1 Hz, 2 H, SO_2-C_6H_4-CH_3), 7.22 (d, *J* = 8.5 Hz, 2 H, C_6H_4-OMe), 6.84 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 4.47 (s, 2 H, OCH_2-Ar), 4.04 (t, *J* = 7.2 Hz, 2 H, CH_2-OTs), 3.84 (m, 1 H, C*H*-OH), 3.80 (s, 3 H, OCH_3), 3.50 (dd, *J* = 3.9, 9.4 Hz, 1 H, C*H*-OAr), 3.39 (dd, *J* = 6.6, 9.4 Hz, 1 H, C*H*-OAr), 2.51 (dt, *J* = 2.3, 6.9 Hz, 2 H, CH_2-C≡C), 2.45 (s, 3 H, C_6H_4-CH_3), 2.32 (dt, *J* = 2.5, 6.2 Hz, 2 H, C≡C-CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 144.8, 132.7, 129.8, 129.3, 127.7, 113.6, 78.4, 76.3, 72.9, 72.4, 68.7, 67.9, 55.1, 23.6, 21.5, 19.6 ppm. HRMS (ESI): calcd. for $C_{22}H_{26}O_6S$ $[M + Na]^+$ 441.1342; found 441.1339.

(2*R*)-7-Iodo-1-[(4-methoxybenzyl)oxy]-4-heptyn-2-ol (19): A 100-mL round-bottomed flask fitted with a reflux condenser was charged with a solution of **18** (6.0 g, 14.85 mmol) in dry acetone (40 mL). To this solution was added NaI (6.68 g, 44.55 mmol) at room temperature, and the resulting reaction mixture was then heated at reflux for 3 h. After complete consumption of the starting material (monitored by TLC), acetone was removed under reduced pressure to afford a solid mass that was dissolved in H_2O (50 mL). The aqueous layer was extracted and dried with Na_2SO_4. The organic layer was concentrated to give a yellow liquid, which after purification by silica gel column chromatography (EtOAc/hexane, 1:9), afforded **19** (4.8 g, 90%) as a pale-yellow oil. $[\alpha]_D^{27}$ = –30.8 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3442, 2919, 2859, 2357, 1612, 1513, 1461, 1302, 1247, 1172, 1101, 1034 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 6.88 (d, *J* = 8.5 Hz, 2 H, C_6H_4-OMe), 4.50 (s, 2 H, OCH_2-Ar), 3.92 (m, 1 H, C*H*-OH), 3.80 (s, 3 H, OCH_3), 3.58 (dd, *J* = 3.9, 9.6 Hz, 1 H, C*H*-OAr), 3.47 (dd, *J* = 6.6, 9.6 Hz, 1 H, C*H*-OAr), 3.17 (t, *J* = 7.2 Hz, 2 H, CH_2-I), 2.72 (dt, *J* = 2.3, 7.0 Hz, 2 H, CH_2-C≡C), 2.63 (br. s, 1 H, O*H*), 2.39 (dt, *J* = 2.3, 6.2 Hz, 2 H, C≡C-CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 129.8, 129.3, 113.7, 81.1, 78.0, 72.9, 72.5, 68.8, 55.2, 23.9, 23.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{19}IO_3$ $[M + Na]^+$ 397.0271; found 397.0264.

(6*R*)-6-Hydroxy-7-[(4-methoxybenzyl)oxy]-3-heptynyl(triphenyl)-phosphonium Iodide (20): A 50-mL round-bottomed flask fitted with a reflux condenser was charged with a solution of **19** (4.0 g, 11.11 mmol) in dry CH_3CN (20 mL). To this solution was added PPh_3 (3.2 g, 12.22 mmol), and the resulting mixture was heated at reflux for 12 h. After completion of the reaction, CH_3CN was removed under reduced pressure to give a white solid mass. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH: 32:1) to furnish **20** (6.5 g, 94%) as a white semi-solid. $[\alpha]_D^{27}$ = +5.2 (*c* = 1.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3356, 2920, 2862, 2358, 1611, 1512, 1438, 1294, 1246, 1177, 1112, 1029 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.86–7.77 (m, 8 H, Ar*H*), 7.74–7.67 (m, 4 H, Ar*H*), 7.35–7.31 (m, 3 H, Ar*H*), 7.24 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 6.87 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 4.45 (s, 2 H, OCH_2-Ar), 3.90–3.82 (m, 2 H, CH_2-PPh_3), 3.79 (s, 3 H, OCH_3), 3.72 (m, 1 H, C*H*-OH), 3.44–3.33 (m, 2 H, CH_2-OAr), 2.74 (dt, *J* = 6.6, 19.5 Hz, 2 H, CH_2-C≡C), 2.07–2.03 (m, 2 H, C≡C-CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 135.1, 133.9, 133.8, 133.5, 131.9, 130.4, 130.3, 130.0, 129.3, 128.7, 128.3, 118.3, 117.2, 113.7, 81.5, 78.2, 72.9, 72.6, 68.4, 55.3, 26.9, 23.8 ppm.

(2*R*,7*Z*)-1-[(4-Methoxybenzyl)oxy]-7-decen-4-yn-2-ol (21): Compound **20** (3.0 g, 4.82 mmol) in THF (30 mL) was stirred at room temperature under a nitrogen atmosphere until it was dissolved completely. To this solution was slowly added *n*BuLi (2.5 M in hexane, 4.24 mL, 10.60 mmol) at –78 °C, and the resulting solution was warmed to 0 °C. After 1 h, the reaction mixture was again

cooled to –78 °C and *n*-propanal (0.64 g, 10.6 mmol) was slowly added. The mixture was stirred at the same temperature for 4 h. After complete consumption of the starting material (monitored by TLC), the reaction was quenched with saturated NH_4Cl (30 mL) and warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (60 mL), dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (EtOAc/hexane, 1:12) afforded **21** (1.1 g, 83%) as a colourless liquid. $[\alpha]_D^{27}$ = –4.8 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3434, 2923, 2851, 1607, 1513, 1463, 1251 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.5 Hz, 2 H, C_6H_4-OMe), 6.82 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 5.44–5.27 (m, 2 H, C*H*=C*H*-), 4.47 (s, 2 H, OCH_2-Ar), 3.85 (m, 1 H, C*H*-OH), 3.79 (s, 3 H, OCH_3), 3.52 (dd, *J* = 3.8, 9.3 Hz, 1 H, C*H*-OAr), 3.40 (dd, *J* = 6.6, 9.4 Hz, 1 H, C*H*-OAr), 2.88–2.82 (m, 2 H, C≡C-CH_2-CH=CH), 2.42–2.32 (m, 2 H, CH_2-C≡C), 2.10–2.01 (m, 2 H, CH_2-CH_3), 0.99 (t, *J* = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 133.1, 129.9, 129.3, 123.9, 113.8, 81.0, 75.3, 73.0, 72.7, 69.1, 55.2, 23.8, 20.4, 17.0, 13.9 ppm. HRMS (ESI): calcd. for $C_{18}H_{24}O_3$ $[M + Na]^+$ 311.1618; found 311.1628.

(2*R*,4*Z*,7*Z*)-1-[(4-Methoxybenzyl)oxy]-4,7-decadien-2-ol (8): Lindlar's catalyst (Pd/C on $CaCO_3$) was added to a stirred solution of alkyne **21** (1.1 g, 4.01 mmol) in benzene (10 mL) followed by a catalytic amount of quinoline at room temperature under a hydrogen atmosphere. The mixture was vigorously stirred for 3 h at room temperature. After complete consumption of the starting material (monitored by TLC), the black reaction mass was filtered through a pad of Celite. The filtrate was concentrated, and purification of the crude product by silica gel column chromatography (EtOAc/hexane, 7:93) gave **8** (1.0 g, 91%). $[\alpha]_D^{27}$ = –3.6 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3430, 2927, 1717, 1612, 1513, 1460, 1248, 1089, 1033, 824 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 6.86 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 5.54–5.40 (m, 2 H, C*H*=C*H*), 5.40–5.22 (m, 2 H, C*H*=C*H*), 4.47 (s, 2 H, OCH_2-Ar), 3.80 (s, 4 H, C*H*-OH, OCH_3), 3.47 (dd, *J* = 3.4, 9.4 Hz, 1 H, C*H*-OAr), 3.32 (dd, *J* = 1.3, 7.4 Hz, 1 H, C*H*-OAr), 2.79 (m, 2 H, CH=CH-CH_2-CH=CH), 2.40–2.18 (m, 3 H, CH_2-CH=CH, CH-O*H*), 2.12–1.95 (m, 2 H, CH_2-CH=CH), 0.91 (t, *J* = 7.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 133.2, 130.0, 129.4, 123.9, 123.3, 113.8, 73.0, 72.7, 69.1, 55.3, 23.9, 20.4, 17.0, 14.0 ppm. MS (ESI): *m*/*z* = 308 $[M + NH_4]^+$.

(1*R*,3*Z*,6*Z*)-1-[(4-Methoxybenzyl)oxy]methyl-3,6-nonadienyl (5*Z*,8*R*,9*E*)-8-(Benzyloxy)-10-iodo-5,9-decadienoate (4)

Method A: To a stirred solution of acid **6** (1.0 g, 2.5 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added Et_3N (0.67 mL, 5 mmol) followed by DCC (0.77 g, 3.75 mmol) and DMAP (2.5 mmol, 0.32 g). The resulting mixture was stirred for 30 min. To this mixture was slowly added a solution of alcohol **8** (0.65 g, 2.25 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the mixture was then stirred for 12 h at room temperature. The white precipitate formed was filtered through a pad of Celite and washed with CH_2Cl_2 (20 mL). The filtrate was washed with H_2O (2 × 20 mL) and brine (2 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated to give a colourless oil. Purification by silica gel column chromatography (EtOAc/hexane, 3:97) furnished **4** (0.87 g, 58%, based on the starting alcohol) as a colourless liquid.

Method B: To a stirred solution of acid **6** (1.0 g, 2.5 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added Et_3N (0.67 mL, 5 mmol) followed by EDCI (0.720 g, 3.75 mmol) and DMAP (2.5 mmol, 0.32 g), and the resulting reaction mixture was stirred for 30 min. To this reaction mixture was slowly added a solution of alcohol **8** (0.65 g, 2.25 mmol) in CH_2Cl_2 (5 mL) at the same temperature, and the mixture was then stirred for 12 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and subsequently washed with H_2O (2 × 20 mL) and brine (2 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated to give a colourless oil. Purification by silica gel column chromatography (EtOAc/hexane, 3:97) furnished **4** (1.1 g, 70%, based on the starting alcohol) as a colourless liquid.

Method C: To a stirred solution of acid **6** (1.0 g, 2.5 mmol) in dry THF (15 mL) at 0 °C was added Et_3N (0.67 mL, 5 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.6 g, 2.5 mmol). The resulting mixture was stirred for 30 min at room temperature. THF and Et_3N were completely removed under reduced pressure to afford a semi-solid mass that was dissolved in dry benzene (10 mL). To this resulting solution was added alcohol **8** (0.65 g, 2.25 mmol) and DMAP (2.5 mmol, 0.32 g) separately dissolved in dry benzene (10 mL) at 0 °C, and the mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with EtOAc (20 mL) and subsequently washed with Na_2CO_3 (2 × 20 mL) and brine (2 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated to give a colourless oil. Purification by silica gel column chromatography (EtOAc/hexane, 3:97) furnished **4** (1.34 g, 89%, based on the starting alcohol) as a colourless liquid. $[\alpha]_D^{27}$ = +21.1 (*c* = 1.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2935, 2860, 2362, 1732, 1430, 1462, 1243, 1108, 1072, 942, 822, 772, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H, C_6H_5), 7.23 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 6.86 (d, *J* = 8.7 Hz, 2 H, C_6H_4-OMe), 6.48 (dd, *J* = 7.6, 14.5 Hz, 1 H, C*H*=CHI), 6.30 (d, *J* = 14.5 Hz, 1 H, CH=C*H*I), 5.50–5.22 (m, 6 H, C*H*=C*H*), 5.06 (quint., *J* = 6.4 Hz, 1 H, C*H*-OCO-), 4.58 (d, *J* = 11.9 Hz, 1 H, O-C*H*-C_6H_5), 4.45 (q, *J* = 11.7, 19.3 Hz, 2 H, O-CH_2-Ar), 4.37 (d, *J* = 11.9 Hz, 1 H, O-C*H*-C_6H_5), 3.79 (s, 3 H, OCH_3), 3.77–3.72 (m, 1 H, C*H*-OAr), 3.51–3.47 (m, 2 H, CH_2-OAr), 2.78 (t, *J* = 7 Hz, 2 H, CH=CH-CH_2-CH=CH-), 2.39 (t, *J* = 6.6 Hz, 2 H, CH_2-CH=CH), 2.35–2.25 (m, 4 H, CH_2-CH=CH), 2.10–2.00 (m, 4 H, CH_2-CH=CH, CH_2-COO), 1.67 (quint., *J* = 7.4 Hz, 2 H, CH_2), 0.96 (t, *J* = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 159.2, 146.4, 138.1, 132.1, 131.3, 130.1, 129.2, 128.3, 126.7, 125.0, 123.9, 113.7, 81.1, 78.3, 72.8, 72.1, 70.5, 70.3, 55.2, 33.9, 32.8, 28.9, 26.8, 25.6, 24.9, 20.5, 14.2 ppm. MS (ESI): *m*/*z* = 690 $[M + NH_4]^+$.

(9*R*,12*R*,13*R*)-9,12-Dihydroxy-13-[(2*Z*,5*Z*)-2,5-octadienyl]-1-oxa-6,10-cyclotridecadien-2-one (23) and (9*R*,12*S*,13*R*)-9,12-Dihydroxy-13-[(2*Z*,5*Z*)-2,5-octadienyl]-1-oxa-6,10-cyclotridecadien-2-one (24): To a solution of PMB ether **4** (0.6 g, 0.89 mmol) in CH_2Cl_2 (9 mL) and water (0.5 mL) at room temperature was added DDQ (0.41 g, 1.78 mmol), and the mixture was stirred for 2 h at the same temperature. The reaction was quenched with saturated $NaHCO_3$ (5 mL) solution. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed with brine (20 mL), dried with anhydrous Na_2SO_4 and concentrated to give the crude product. Purification by silica gel column chromatography (EtOAc/hexane, 1:6) afforded **22** (0.45 g, 91%) as a colourless liquid. To a stirred solution of **22** (0.3 g, 0.54 mmol) and solid anhydrous $NaHCO_3$ (0.2 g) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (0.47 g, 1.08 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. After complete consumption of the starting material (TLC monitored), the reaction mixture was filtered through filter paper. The filtrate was washed with saturated $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated. The crude mass was purified by flash chromatography (EtOAc/hexane, 1:9) to afford the aldehyde in quantitative yield, which was immedi-

ately used for the next reaction. A flame-dried 50-mL round-bottomed flask was charged with anhydrous $CrCl_2$ (1.4 g, 10.8 mmol), $NiCl_2$ (0.13 g, 1.08 mmol), DMSO (25 mL) and THF (8 mL), and the resulting mixture was vigorously stirred at room temperature for 30 min. To this reaction mixture was slowly added a solution of the aldehyde in dry DMSO (5 mL) at the same temperature. The reaction mixture was stirred for an additional 24 h at room temperature. The reaction was quenched with saturated NH_4Cl (15 mL) and extracted in diethyl ether (5 × 50 mL). The combined organic layer was washed with H_2O (2 × 50 mL) and brine (2 × 50 mL) and concentrated. Purification by silica gel column chromatography (EtOAc/hexane, 1:24) afforded a mixture of **23** and **24** (0.18 g, 81% over two steps) as a colourless oil. $[\alpha]_D^{27}$ = +5.5 (*c* = 1.8, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3430, 2938, 2862, 2360, 1730, 1428, 1455, 1240, 1112, 1070, 943, 821, 770, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 5 H, C_6H_5), 5.72–5.19 (m, 8 H, C*H*=C*H*), 4.80 (m, 1 H, C*H*-OCO), 4.50 (ABq, *J* = 11.9 Hz, 2 H, OCH_2-Ar), 4.08–3.87 (m, 2 H, C*H*-OH, C*H*-OAr), 2.88–2.75 (m, 2 H, CH=CH-CH_2-CH=CH), 2.60–2.44 (m, 1.5 H, CH_2-CH=CH), 2.45–2.37 (m, 1.5 H, CH_2-CH=CH), 2.37–2.20 (m, 3 H, CH_2-CH=CH), 2.14–1.97 (m, 2 H, CH_2-CO), 1.98–1.84 (m, 2 H, CH_2-CH=CH), 0.97 (t, *J* = 7.6 Hz, 2 H, CH_3), 0.88 (t, *J* = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 138.6, 135.1, 132.2, 131.9, 131.3, 130.9, 128.3, 127.6, 127.5, 126.8, 125.0, 124.0,79.1, 73.7, 73.5, 70.4, 70.2, 33.6, 32.3, 31.9, 29.7, 29.4, 29.0, 25.6, 22.7, 20.6,14.2, 14.1 ppm. MS (ESI): *m*/*z* = 447 $[M + Na]^+$.

***tert*-Butyl {(8*R*)-8-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-9-[(4-methoxybenzyl)oxy]-5-nonynyloxy}dimethylsilane (25):** To a stirred solution of alcohol **10** (8.6 g, 21.18 mmol) in dry DMF (30 mL) was added imidazole (3.16, 46.56 mmol) followed by TBDPSCl (5.8 g, 21.18 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 12 h at room temperature. The reaction was quenched with water (100 mL) after completion (monitored by TLC) and extracted with diethyl ether (3 × 100 mL). The combined organic layer was washed with brine (2 × 50 mL), dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (EtOAc/hexane, 1:99) furnished **25** (13.2 g, 97%) as a colourless liquid. $[\alpha]_D^{27}$ = –4.7 (*c* = 1.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3468, 2928, 2862, 2360, 1615, 1510, 1465, 1280, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.60 (m, 4 H, Ar*H*), 7.40–7.26 (m, 6 H, Ar*H*), 7.08 (d, *J* = 8.3 Hz, 2 H, C_6H_4-OMe), 6.76 (d, *J* = 8.5 Hz, 2 H, C_6H_4-OMe), 4.28 (s, 2 H, OCH_2-Ar), 3.92 (m, 1 H, C*H*-OSi), 3.76 (s, 3 H, OCH_3), 3.55 (t, *J* = 5.7 Hz, 1 H, C*H*-OAr), 3.48 (d, *J* = 4.5 Hz, 1 H, C*H*-OAr), 3.44–3.38 (m, 2 H, CH_2-OSi), 2.30 (m, 2 H, CH_2-C≡C), 2.07 (m, 2 H, C≡C-CH_2), 1.57–1.40 (m, 4 H, CH_2-CH_2), 1.02 [s, 9 H, SiC(CH_3)$_3$], 0.86 [s, 9 H, -SiC-(CH_3)$_3$], 0.02 [s, 6 H, -Si(CH_3)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 135.8, 134.0, 130.5, 129.5, 129.0, 127.6, 127.4, 113.5, 81.7, 76.6, 72.7, 71.0, 70.5, 62.6, 55.2, 31.9, 26.9, 25.9, 25.3, 24.5, 24.3, 19.2, 18.6, –5.30 ppm. MS (ESI): *m*/*z* = 667 $[M + Na]^+$.

(9*R*,12*S*,13*R*)-9-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-12-hydroxy-13-[(2*Z*,5*Z*)-2,5-octadienyl]-1-oxa-6,10-cyclotridecadien-2-one (31): To a stirred solution of primary alcohol **30** (0.45 g, 0.64 mmol) and solid anhydrous $NaHCO_3$ (0.2 g) in CH_2Cl_2 (15 mL) at 0 °C was added Dess–Martin periodinane (0.55 g, 1.28 mmol). The reaction mixture was stirred at 0 °C for 3 h. After completion of reaction (TLC monitored), the mixture was filtered through filter paper. The filtrate was washed with saturated $NaHCO_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic fraction was dried with anhydrous Na_2SO_4 and concentrated. Purification of the crude mass by flash chromatography (EtOAc/hexane, 1:9) afforded aldehyde **3** in quantitative yield, which was immediately used for the next reaction. To a flame-dried 50-mL round-bottomed flask was added anhydrous $CrCl_2$ (1.65 g, 12.8 mmol), $NiCl_2$ (0.15 g, 1.28 mmol) and dry DMSO (30 mL). The resulting mixture was vigorously stirred at room temperature for 30 min. To this reaction mixture was slowly added a solution of aldehyde **3** in DMSO (5 mL) at the same temperature, and the mixture was stirred for 24 h. The reaction was quenched with saturated NH_4Cl (20 mL) and extracted with diethyl ether (5 × 50 mL). The combined organic layer was washed with H_2O (2 × 50 mL) and brine (2 × 50 mL) and concentrated. Purification by silica gel column chromatography (EtOAc/hexane, 1:24) afforded **31** (0.31 g, 85% over two steps) as a colourless oil. $[\alpha]_D^{27}$ = –15.2 (*c* = 1.2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3429, 2940, 2858, 2359, 1732, 1427, 1454, 1238, 1107, 1071, 944, 821, 770, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.62 (m, 4 H, Ar*H*), 7.45–7.32 (m, 6 H, Ar*H*), 5.66 (q, *J* = 7.9 Hz, 1 H, C*H*=CH), 5.48 (dd, *J* = 7.4, 15.5 Hz, 2 H, C*H*=C*H*), 5.41–5.21 (m, 4 H, C*H*=C*H*), 4.88 (dd, *J* = 7.7, 15.7 Hz, 1 H, C*H*=CH), 4.66 (dt, *J* = 3.8, 9.1 Hz, 1 H, C*H*-OCO), 4.31 (m, 1 H, C*H*-OSi), 3.64 (dt, *J* = 2.6, 8.7 Hz, 1 H, C*H*-OH), 2.76 (t, *J* = 7.0 Hz, 2 H, CH=CH-CH_2-CH=CH), 2.47 (m, 1 H, CH_2-CH=CH), 2.39–2.17 (m, 7 H, CH_2-CH=CH), 2.05 (quint., *J* = 7.4 Hz, 2 H, CH_2-CO), 1.98–1.80 (m, 2 H, CH_2), 1.08 [s, 9 H, SiC(CH_3)$_3$], 0.96 (t, *J* = 7.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2, 137.1, 136.1, 135.8, 134.6, 134.0, 132.6, 131.1, 130.7, 129.6, 129.4, 128.9, 127.6, 127.4, 126.9, 125.0, 124.1, 73.6, 73.5, 73.2, 36.2, 32.0, 29.7, 26.9, 25.5, 25.2, 22.7, 20.5, 19.2, 14.2 ppm. HRMS (ESI): calcd. for $C_{36}H_{48}O_4Si$ $[M + H]^+$ 573.3400; found 667.3417.

(9*R*,12*S*,13*R*)-9,12-Dihydroxy-13-[(2*Z*,5*Z*)-2,5-octadienyl]-1-oxa-6,10-cyclotridecadien-2-one (1): To a stirred solution of macrolide **31** (0.14 g, 0.24 mmol) in dry THF (5.0 mL) was added acetic acid (0.2 mL) followed by TBAF (1 M in THF, 1.22 mL, 1.22 mmol) at 0 °C. The resulting mixture was stirred for an additional 18 h at room temperature. THF and acetic acid were removed under reduced pressure. The residue was diluted with diethyl ether (15 mL) and washed with Na_2CO_3 solution (2 × 10 mL) followed by brine (1 × 10 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated to afford a yellowish liquid. Purification by silica gel column chromatography (EtOAc/hexane, 2:3) furnished the final natural product amphidinolactone A (**1**) as a pale yellow viscous liquid (0.069 g, 87%). $[\alpha]_D^{27}$ = –58.2 (*c* = 0.4, C_6H_6). IR (KBr, neat): $\tilde{\nu}$ = 3392, 2360, 1720, 1427, 703 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 5.66 (m, 1 H, C*H*=CH), 5.59 (t, *J* = 6.3 Hz, 2 H, C*H*=C*H*), 5.54 (dd, *J* = 6.3, 15.8 Hz, 1 H, C*H*=CH), 5.49–5.34 (m, 2 H, C*H*=C*H*), 5.30 (m, 1 H, C*H*=CH), 5.24 (m, 1 H, C*H*=CH), 5.03 (m, 1 H, C*H*-OCO), 4.00 (m, 1 H, C*H*-OH), 3.83 (m, 1 H, C*H*-OH), 3.51 (br. s, 1 H, O*H*), 2.88 (m, 2 H, CH=CH-CH_2-CH=CH), 2.68 (m, 1 H, CH=CH-CH_2-CH=CH), 2.51 (m, 1 H, CH_2-CH=CH), 2.39–2.29 (m, 2 H, CH_2-CH=CH), 2.20 (m, 1 H, CH_2-CH=CH), 2.19 (m, 1 H, CH_2-COO), 2.11 (m, 1 H, CH_2-COO), 2.06 (m, 2 H, CH_2-CH$_3$), 1.87 (m, 2 H, CH_2-CH=CH), 1.26 (m, 2 H, CH_2, O*H*), 0.96 (t, *J* = 7.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 171.7, 136.3, 132.2, 131.2, 130.7, 127.6, 125.1, 124.9, 74.0, 73.8, 72.4, 35.9, 32.1, 29.5, 26.0, 25.6, 22.9, 20.9, 14.4 ppm. HRMS (ESI): calcd. for $C_{20}H_{30}O_4$ $[M + Na]^+$ 357.2041; found 357.2034.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic data and scanned copies of the ^1H and ^{13}C NMR spectra for new compounds.

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[1] Y. Takahashi, T. Kubota, J. Kobayashi, *Heterocycles* **2007**, *72*, 567–572.
[2] M. Hangyou, H. Ishiyama, Y. Takahashi, T. Kubota, J. Kobayashi, *Tetrahedron Lett.* **2009**, *50*, 1475–1477.
[3] a) A. B. Dounay, PhD Thesis, University of Minnesota, **2001**; b) K. C. Nicolaou, K. C. Fylaktakidou, H. Monenschein, Y. Li, B. Weyershausen, H. J. Mitchell, H. Wei, P. Guntupalli, D. Hepworth, K. Sugita, *J. Am. Chem. Soc.* **2003**, *125*, 15433–15442.
[4] a) M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936–938; b) M. E. Furrow, S. E. Schaus, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 6776–6777; c) P. Kumar, V. Naidu, P. Gupta, *Tetrahedron* **2007**, *63*, 2745–2785.
[5] a) T. M. Trygstad, Y. Pang, C. J. Forsyth, *J. Org. Chem.* **2009**, *74*, 910–913; b) P. Yu, C. Li, Z. Guozhu, Z. Liming, *J. Am. Chem. Soc.* **2009**, *131*, 5062–5063.
[6] H. Lindlar, R. Dubuis, *Org. Synth., Coll. Vol.* **1973**, *5*, 880–885.
[7] A. D. Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974–6977.
[8] B. S. Bal, W. E. Childers Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091–2096.
[9] a) K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, O. Yonemitsu, *Tetrahedron* **1986**, *42*, 3021–3028; b) C. C. Sanchez, G. E. Keck, *Org. Lett.* **2005**, *7*, 3053–3056.
[10] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7187.
[11] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
[12] a) B. Neises, W. Steglich, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522–524; b) A. Williams, I. T. Ibrahim, *Chem. Rev.* **1981**, *81*, 589–636; c) M. Mikolajczyk, P. Kielbasiński, *Tetrahedron* **1981**, *37*, 233–284.
[13] a) S. Nozaki, I. Muramatsu, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2165–2168; b) J. C. Sheehan, J. Preston, P. A. Cruickshank, *J. Am. Chem. Soc.* **1965**, *87*, 2492–2493.
[14] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
[15] a) H. Jin, J. Uenishi, W. J. Christ, Y. Kishi, *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646; b) K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto, H. Nozaki, *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050; for recent reviews, see: c) L. A. Wessjohann, G. Scheid, *Synthesis* **1999**, 1–36; d) M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Chem. Soc. Rev.* **1999**, *28*, 169–177; e) A. Fürstner, *Chem. Rev.* **1999**, *99*, 991–1046; f) G. C. Hargaden, P. Guiry, *Adv. Synth. Catal.* **2007**, *349*, 2407–2424; for other examples of intramolecular NHK reactions, see: g) R. A. Pilli, C. K. Z. de Andrade, C. R. O. Souto, A. de Meijere, *J. Org. Chem.* **1998**, *63*, 7811–7819; h) G. Oddon, D. Uguen, *Tetrahedron Lett.* **1998**, *39*, 1157–1160.
[16] a) A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191–1224; b) T. M. Baker, D. J. Edmonds, D. Hamilton, C. O'Brien, D. J. Procter, *Angew. Chem. Int. Ed.* **2008**, *47*, 5631–5633; c) J. Pospíšil, C. Müller, A. Fürstner, *Chem. Eur. J.* **2009**, *15*, 5956–5968.
[17] a) R. A. Pilli, M. M. Victor, *Tetrahedron Lett.* **2002**, *43*, 2815–2818; b) R. A. Pilli, M. M. Victor, A. de Meijere, *J. Org. Chem.* **2000**, *65*, 5910–5916.

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