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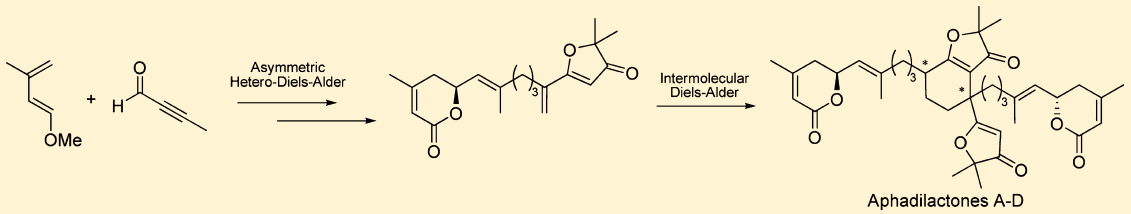
Total Synthesis of Aphadilactones A−D

Jian-Peng Yin,[†] Min Gu,[‡] Ying Li,*[,†] and Fa-Jun Nan*[,‡]

[†]State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, PR China

[‡]The National Center for Drug Screening, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, PR China

Supporting Information



ABSTRACT: The first total synthesis of aphadilactones A−D, diastereomeric natural products recently isolated from the Meliaceae plant *Aphanamixis grandifolia* by Yue and co-workers, which possess an unprecedented carbon skeleton, has been achieved. The synthesis features a catalytic asymmetric hetero-Diels−Alder reaction to form the dihydropyran ring, concurrent installation of the lactone and furan moieties via a tandem acid-catalyzed acetal cleavage, oxidation, and cyclization process, and an intermolecular Diels−Alder reaction to forge the target products.

INTRODUCTION

Aphadilactones A−D (**1**−**4**), a novel class of diterpenoid dimers, were first isolated from the leaves of *Aphanamixis grandifolia*, an arbor tree that grows mainly in the tropical and subtropical areas of Asia, by Yue and co-workers.[1] Yue et al. have proposed that the aphadilactones are formed via a biosynthetic [4 + 2] dimerization of monomer. Aphanamenes A and B (**5**, **6**), which may originate from dimerization of a similar monomer, have been isolated from the same plant by Kong and co-workers.[2] Monomer derivatives nemoralisins (**7**−**10**) have also been reported by Yue[3] and Kong[4] (Figure 1). Aphadilactone C has exhibited significant inhibitory activity against diacylglycerol *O*-acyltransferase 1 (DGAT-1) with an IC_{50} of 0.46 ± 0.09 μM and high selectivity for DGAT-2 (selectivity index >217).[1] DGAT-1 and DGAT-2 have been reported to play important roles in triglyceride synthesis and metabolism; the accumulation of triglycerides in adipocytes is associated with a number of human diseases such as obesity, diabetes, and steatohepatitis.[5−8] In this paper, we report a full account of the first total synthesis of aphadilactones A−D.

RESULTS AND DISCUSSION

The isolation team proposed a reasonable biosynthetic pathway for the assembly of aphadilactones A−D, with a [4 + 2] dimerization of monomer **12** at its heart (Scheme 1).[1] A concerted Diels−Alder cycloaddition of the starting diene **12** would be expected to afford the key intermediate **11**. Although a stepwise Diels−Alder reaction cannot be excluded, we believe that a concerted Diels−Alder reaction might followed by a fast, thermodynamically favorable 1,3-hydrogen migration, leading to the formation of the aphadilactones (Scheme 1).

The diastereomeric aphadilactones A−D were obtained in similar amount from their natural source, which strongly suggests that the final dimeric reaction is a nonenzymatically catalyzed process. Following these considerations, our synthetic design (Scheme 1) hinged upon the use of this bioinspired [4 + 2] dimerization of *S*-dienelactone **12**, and as such, it follows in the footsteps of other successful biomimetic syntheses. Further disconnection of monomer **12** was envisioned via Suzuki and aldol couplings to introduce the two termini, and a tandem acid-catalyzed acetal cleavage, oxidation, and cyclization reaction. An asymmetric catalytic hetero-Diels−Alder reaction would provide a highly efficient route to the required chiral lactone.

With this in mind, our investigation began with synthesis of oxidation/cyclization precursor **13**, as shown in Scheme 2. In seeking an efficient, enantioselective method for the preparation of alkynyl acetal **15**, we were particularly intrigued by the possibility of applying the recently developed Cr-catalyzed hetero-Diels−Alder (HDA) reaction to this task. In earlier studies, cycloadditions between 1-methoxybutadiene and simple aldehydes catalyzed by complex **S3** or its enantiomer (developed by Jacobsen and co-workers[9−12]) proceeded with high enantioselectivity; this approach has also successfully been applied in other natural product total syntheses.[13,14] Upon investigation of the reaction of alkoxybutadiene derivatives with 2-butynal **17**, we were pleased to find that **17** was indeed an effective partner in the asymmetric HDA reaction, affording cycloadducts in good yield (84%) and enantioselectivity (98%

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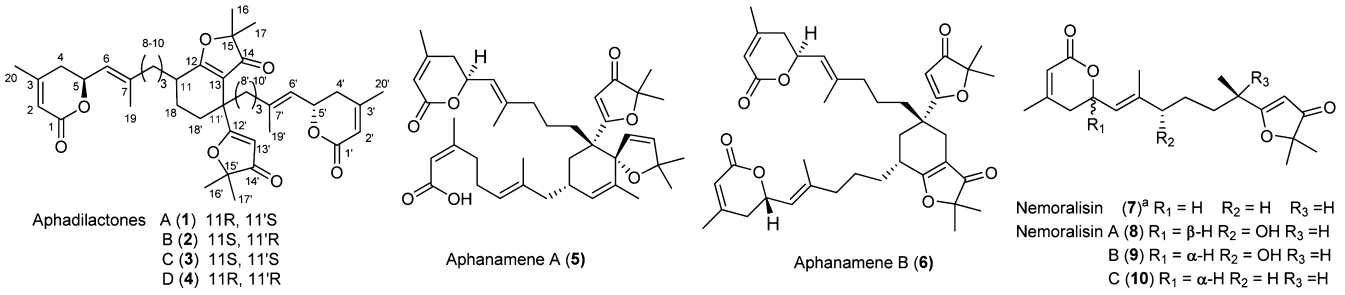
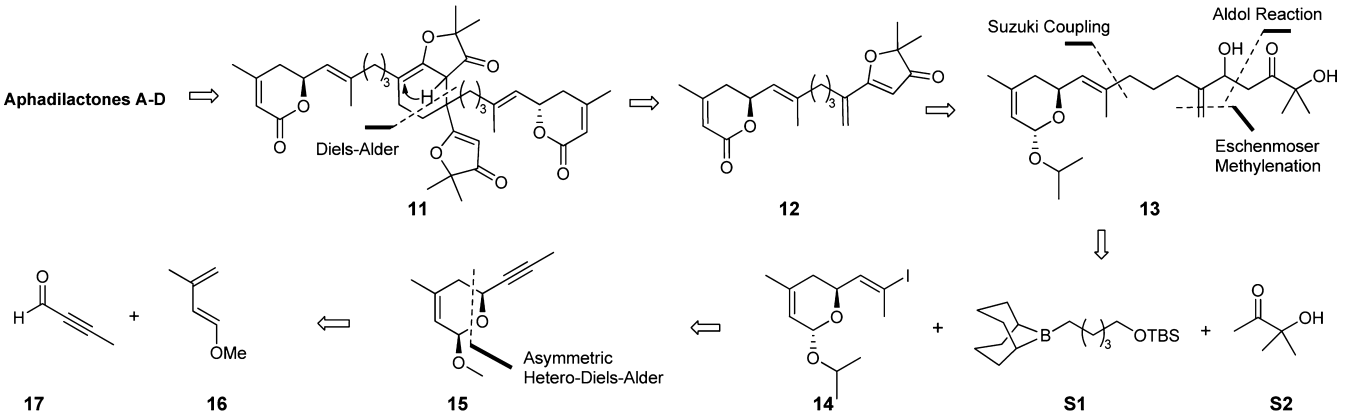
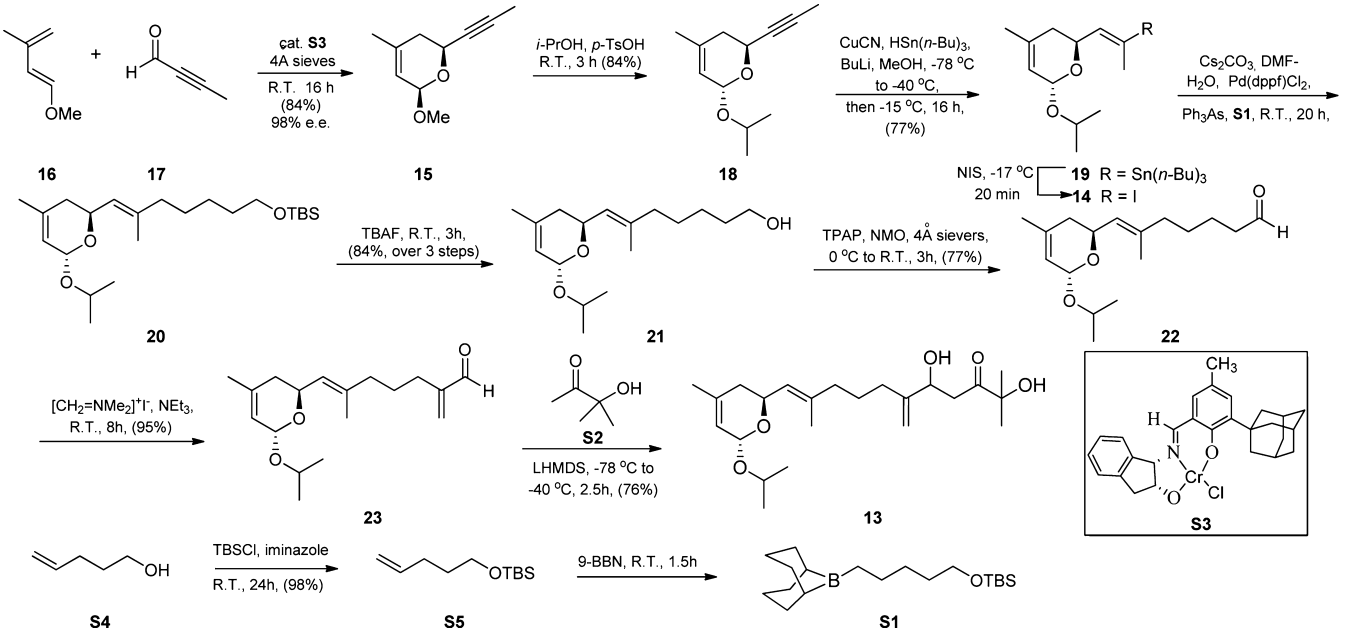


Figure 1. Diterpenoids and diterpenoids dimers from *Aphanamixis grandifolia*. [a]The absolute configuration of **7** is not known.

Scheme 1. Retrosynthetic Analysis of Aphadilactones A–D



Scheme 2. Synthesis of the Oxidation/Cyclization Precursor Diene 13



ee). Acetal **15** was transformed to the thermodynamically more stable **18** in the presence of acid in *i*-PrOH, and was isolated as a single diastereomer.[13,14] Conversion of **18** to the desired *E*-vinyl iodide **14** was achieved by stannylation with in situ generated $Bu_3Sn(Bu)CuCNLi_2$ followed by Sn–I exchange with NIS.[15] Alternative methods for the formation of the metalated vinyl intermediate required for this transformation, such as Pd mediated hydrostannylation or the use of Schwartz reagent, afforded the desired product in low yields and as mixtures of regioisomers (*E*/*Z* ratios between 5:1 and 1:1). Subsequent Suzuki cross-coupling with readily available organoborane reagent **S1** gave the trisubstituted *E*-**20**.[16] Deprotection and oxidation with TPAP/NMO gave aldehyde **22**;[17] other oxidation methods, including Swern oxidation, PCC, and Dess–Martin, failed to afford the target product. Methylenation with Eschenmoser's salt using Et_3N as the base installed the methylene functionality in **23** in a single step.[18] **23** could then be used for an aldol reaction with 3-hydroxy-3-methyl-2-butanone (**S2**). Intermediate **13** was synthesized in gram quantities.

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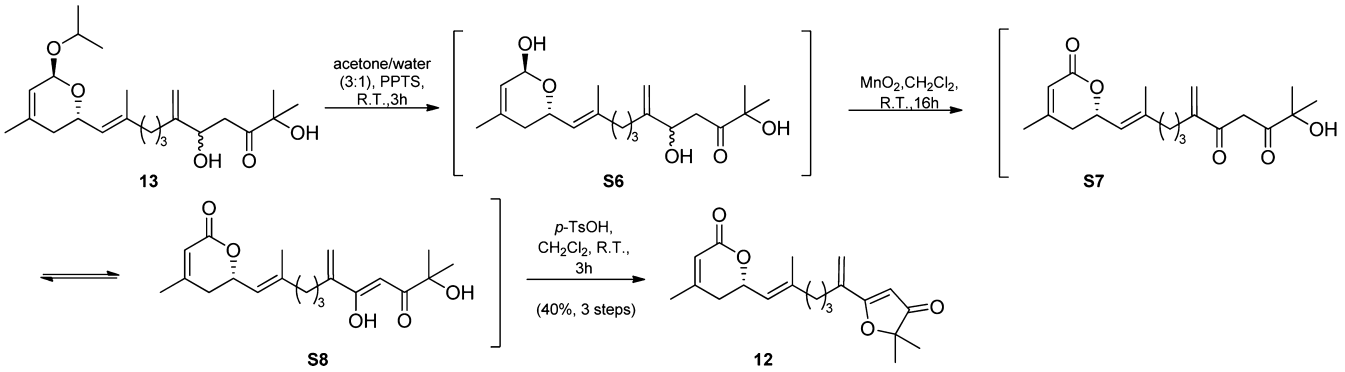
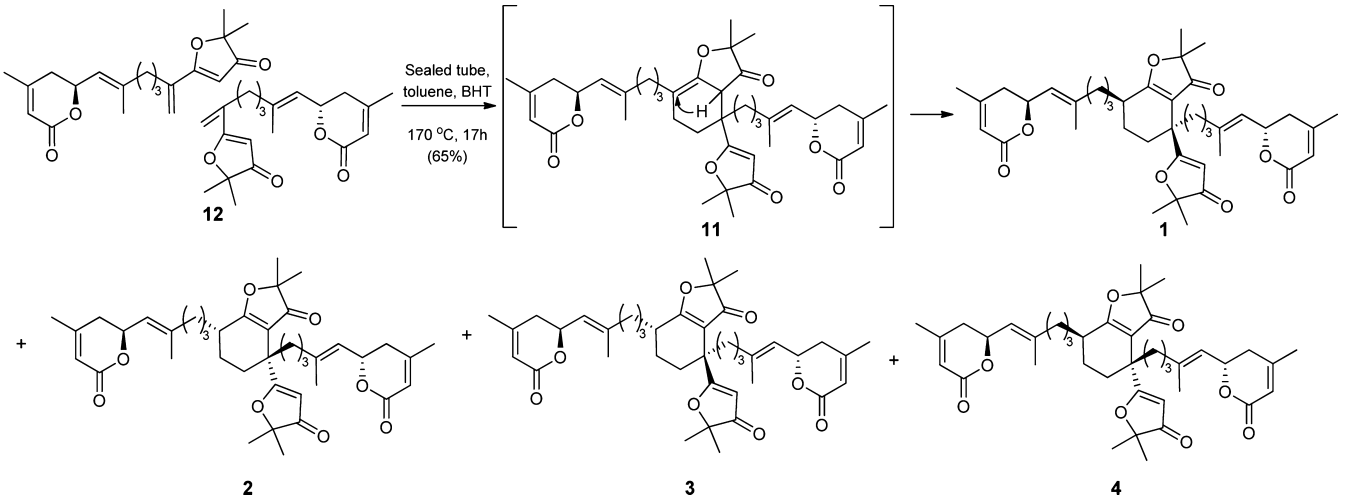
Scheme 3. Synthesis of the Monomer 12



Scheme 4. Bioinspired [4 + 2] Dimerization of Diene Latone 12 to Aphadilactones A–D



With key precursor **13** in hand, the synthesis of **12** was then accomplished in a three-step tandem sequence. Acid-catalyzed cleavage of the acetal was followed by oxidation of MnO_2. The filtrate of the reaction mixture was then treated with *p*-TsOH. Thus, through a short and high yielding synthetic sequence, diene lactone **12** was synthesized in 40% yield (3 steps, Scheme 3).

Having accessed monomer **12**, the stage was now set to explore the bioinspired [4 + 2] dimerization/1,3 σ-hydrogen migration sequence to reach our target. Reaction conditions were optimized for solvent, Lewis acid, temperature, and reaction time. To our great satisfaction, when the reaction was performed in toluene with BHT at 170 °C for 17 h, aphadilactones A–D were formed in an approximate 1:1:1:1 mixture in 65% yield (Scheme 4). The single isomers were obtained by semipreparative HPLC separation (C18 silica gel column and then chiral AD-H column as reported[1]). Our synthetic samples matched the ^{1}H and ^{13}C NMR spectra of natural aphadilactones A–D (see Tables 1–3). The assignments of the synthetic samples were further secured by analyses of specific optical rotations, as measured in MeOH solution according to the reference (A, $[\alpha]_D^{22}$ −8.3 *c* 0.145 MeOH; B, $[\alpha]_D^{22}$ −40.7 *c* 0.150 MeOH; C, $[\alpha]_D^{20}$ +4.0 *c* 0.125 MeOH; D, $[\alpha]_D^{20}$ −15.1 *c* 0.185 MeOH). The synthetic samples were found to exhibit an optical rotation of A, $[\alpha]_D^{22}$ −0.6 c 0.137 MeOH; B, $[\alpha]_D^{22}$ −28 *c* 0.150 MeOH; C, $[\alpha]_D^{22}$ −1.0 *c* 0.088 MeOH; D, $[\alpha]_D^{22}$ −23 *c* 0.088 MeOH, respectively. The observed difference in absolute values between the optical rotation of synthetic aphadilactones A–D and that reported in the literature may be due to differences in purity of the samples (comparing the purity of natural compounds and synthetic samples by ^{1}H NMR), which would cause significant underestimation of its own chiral properties.

In summary, we have accomplished the first total synthesis of aphadilactones A–D, diterpenoid dimers discovered by Yue and co-workers,[1] in 11 steps from known compounds **16** and **17** in 6.6% overall yield. Key features of the synthesis include (i) a catalytic asymmetric hetero-Diels–Alder reaction to form the dihydropyran ring; (ii) a tandem reaction of acid-catalyzed cleavage of the acetal, oxidation, and cyclization to install the lactone and furan rings simultaneously; and (iii) an intermolecular Diels–Alder reaction to forge the target products aphadilactones A–D.

EXPERIMENTAL SECTION

General Methods. All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry and freshly distilled solvents under anhydrous conditions, unless otherwise noted. Anhydrous THF, toluene and Et_2O were distilled over sodium benzophenone ketyl under Ar. Anhydrous CH_2Cl_2 was distilled over calcium hydride under Ar. All other solvents and reagents were used as obtained from commercial sources without further purification. Optical rotations were measured on a polarimeter using a 10 cm cell at approximately 25 °C. NMR spectra were recorded at 300 and 75 MHz for ^{1}H and ^{13}C nuclei, or at 600 and 150 MHz for for ^{1}H and ^{13}C nuclei, respectively. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in

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Table 1. ^{1}H NMR Data Comparison of 1 and 2 [δ_H (mult, J in Hz)] in CD_3OD

proton	1[a]	1[b]	2[a]	2[b]
2	5.79 (m)	5.79 (br s)	5.79 (br s)	5.79 (br s)
4a	2.35 (dd, 18.0, 4.3)	2.35 (dd, 18.6, 4.2)	2.38 (m)	2.38 (m)
4b	2.43 (dd, 18.0, 10.9)	2.43 (dd, 18.0, 10.2)	2.45 (dd, 18.1, 10.2)	2.45 (dd, 18.0, 10.8)
5	5.21 (m)	5.21 (m)	5.22 (m)	5.21 (m)
6	5.35(br d, 8.5)	5.35(br d, 9.6)	5.36 (br d, 8.1)	5.36 (br d, 10.8)
8	2.09 (m, 2H)	2.09 (m, 2H)	2.10 (m, 2H)	2.10 (m, 2H)
9	1.53 (m, 2H)	1.53 (m, 2H)	1.53 (m, 2H)	1.53 (m, 2H)
10a	1.54 (m)	1.54 (m)	1.53 (m)	1.53 (m)
10b	1.76 (m)	1.76 (m)	1.79 (m)	1.79 (m)
11	2.74 (m)	2.74 (m)	2.75 (m)	2.74 (m)
16	1.38 (s, 3H)	1.38 (s, 3H)	1.38 (s, 3H)	1.38 (s, 3H)
17	1.39 (s, 3H)	1.39 (s, 3H)	1.39 (s, 3H)	1.39 (s, 3H)
18α	2.03 (m)	2.03 (m)	1.48 (m)	1.48 (m)
18β	1.48 (m)	1.48 (m)	2.05 (m)	2.05 (m)
19	1.73 (d, 0.8, 3H)	1.73 (d, 0.6, 3H)	1.73 (br s, 3H)	1.73 (d, 1.2, 3H)
20	2.02 (br s, 3H)	2.02 (br s, 3H)	2.02 (br s, 3H)	2.02 (br s, 3H)
2′	5.79 (br s)	5.79 (br s)	5.79 (br s)	5.79 (br s)
4′a	2.34 (dd, 18.0, 4.2)	2.34 (dd, 18.6, 4.2)	2.34 (dd, 18.1, 4.4)	2.34 (dd, 18.0, 4.2)
4′b	2.43 (dd, 18.0, 10.9)	2.43 (dd, 18.0, 10.8)	2.45 (dd, 18.1, 10.2)	2.45 (dd, 18.0, 10.8)
5′	5.21 (m)	5.21 (m)	5.20 (m)	5.21 (m)
6′	5.33 (br d, 8.5)	5.33 (br d, 8.4)	5.34 (br d, 8.2)	5.34 (br d, 8.4)
8′	2.06 (m, 2H)	2.06 (m, 2H)	2.06 (m, 2H)	2.06 (m, 2H)
9′a	1.29 (m)	1.29 (m)	1.24 (m)	1.24 (m)
9′b	1.50 (m)	1.50 (m)	1.50 (m)	1.50 (m)
10′a	1.89 (ddd, 13.0, 13.0, 4.4)	1.89 (ddd, 13.2, 13.2, 4.8)	1.82 (m)	1.82 (m)
10′b	2.09 (m)	2.09 (m)	2.16 (m)	2.16 (m)
13′	5.29 (s)	5.29 (s)	5.27 (s)	5.28 (s)
16′	1.33 (s, 3H)	1.33 (s, 3H)	1.33 (s, 3H)	1.33 (s, 3H)
17′	1.36 (s, 3H)	1.36 (s, 3H)	1.36 (s, 3H)	1.36 (s, 3H)
18′α	1.82 (ddd, 13.4, 13.4, 2.7)	1.82 (ddd, 13.2, 13.2, 3.0)	2.07 (m)	2.07 (m)
18′β	2.11 (m)	2.11 (m)	1.86 (m)	1.86 (m)
19′	1.71 (d, 0.7, 3H)	1.71 (d, 1.2, 3H)	1.69 (br s, 3H)	1.69 (d, 1.2, 3H)
20′	2.02 (br s, 3H)	2.02 (br s, 3H)	2.01 (br s, 3H)	2.01 (br s, 3H)

[a]Natural product. [b]Synthesized compound.

$CDCl_3$/ TMS solvent, or the residual chloroform (δ 7.26 ppm) or methanol (δ 3.31 ppm) peaks. The ^{13}C NMR values were referenced to the residual chloroform (δ 77.0 ppm), or methanol (δ 49.0 ppm) peaks. ^{13}C NMR values are reported as chemical shift δ, multiplicity and assignment. ^{1}H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (J in Hz) and assignment. Analytical gas chromatography (GC) was performed on Dex 120 capillary column, column temperature = 105 °C (isothermal), inject temperature = 220 °C, detector temperature = 220 °C. Flow = 1.2 mL/min. High resolution mass spectroscopy (HRMS) was performed on a TOF instrument with ESI in positive ionization mode. Semipreparative reversed-phase high-performance liquid chromatography: the flow rate was 1 mL/min mobile phase, acetonitrile/water = 50/50, UV detection at 266 nm. Semipreparative normal-phase high-performance liquid chromatography: the flow rate was 1 mL/min mobile phase, hexane/ethanol = 90/10, UV detection at 266 nm.

Synthetic Procedures and Characterization Data. *Aphadilactones A–D (**1**–**4**).* To a solution of monomer **12** (65 mg, 0.20 mmol) in toluene (2.0 mL) was added BHT (5 mg) under argon, and the mixture was heated in a sealed tube (ø = 1.0 cm, length = 9.0 cm, the section below the level of solution was immersed in the oil bath) at 170 °C for 17 h. The reaction was left to cool to room temperature. The mixture was purified by column chromatography on silica gel (hexane:EtOAc:CH_2Cl_2 = 1:1.5:1) to afford 42 mg dimer products (65%). (6.0 mg, 9% of **12** recovered). The dimer products were further separated by semipreparative reversed-phase high-performance liquid chromatography and semipreparative normal-phase high-performance liquid chromatography in sequence. Compounds **1**, **2**, **3** and **4** can be gained separately.

Optical rotations. **1**: $[\alpha]_D^{22}$ −0.6 *c* 0.137 MeOH. **2**: $[\alpha]_D^{22}$ −28.0 *c* 0.150 MeOH. **3**: $[\alpha]_D^{22}$ −1.0 *c* 0.088 MeOH. **4**: $[\alpha]_D^{22}$ −23.0 *c* 0.088 MeOH.

HRMS (TOF ESI). **1**: calcd for $C_{40}H_{52}NaO_8$ 683.3560 $[M + Na]^+$, found 683.3566. **2**: calcd for $C_{40}H_{52}NaO_8$ 683.3560 $[M + Na]^+$, found 683.3572. **3**: calcd for $C_{40}H_{52}NaO_8$ 683.3560 $[M + Na]^+$, found 683.3555. **4**: calcd for $C_{40}H_{52}NaO_8$ 683.3560 $[M + Na]^+$, found 683.3557.

*tert-Butyldimethyl(pent-4-en-1-yloxy)silane (**S5**).* To a suspension of 4-penten-1-ol **S4** (4.30 g, 50.0 mmol, 1.00 equiv) in CH_2Cl_2 (90 mL) at room temperature was added imidazole (4.42 g, 65.0 mmol, 1.30 equiv). Then TBSCl (9.80 g, 65.0 mmol, 1.30 equiv) was added. The mixture was stirred at room temperature for 12 h, then diluted with CH_2Cl_2 (100 mL), washed with H_2O, and brine, then dried ($MgSO_4$) and filtered. The residue was purified by flash chromatography on silica gel (hexane:Et_2O = 20:1) to give **S5** (9.51 g, 47.6 mmol, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.86–5.78 (m, 1H), 5.02 (d, J = 9.0 Hz, 1H), 4.95 (d, J = 6.0 Hz, 1H), 3.62 (t, J = 6.0 Hz, 2H), 2.13–2.08 (m, 2H), 1.64–1.58 (m, 1H), 0.90 (s, 9H), −0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6, 114.5, 62.5, 32.0, 30.0, 26.0 (3C), 18.34, −5.30 (2C).

*(S,E)-6-(6-(5,5-Dimethyl-4-oxo-4,5-dihydrofuran-3-yl)-2-methylhepta-1,6-dien-1-yl)-4-methyl-5,6-dihydro-2H-pyran-2-one (**12**).* To a solution of **13** (194.0 mg, 0.492 mmol, 1.00 equiv) in a mixture of acetone/water (3/1) (40 mL), PPTS (123.5 mg, 0.492 mmol, 1.00 equiv) was added, and the resulting solution stirred at room

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Table 2. ^{1}H NMR Data Comparison of 3 and 4 [δ_H (mult, J in Hz)] in CD_3OD

proton	3[a]	3[b]	4[a]	4[b]
2	5.78 (br s)	5.78 (br s)	5.78 (br s)	5.78 (br s)
4a	2.35 (dd, 18.2, 4.7)	2.35 (dd, 18.0, 4.2)	2.37 (m)	2.37 (m)
4b	2.44 (m)	2.44 (m)	2.44 (m)	2.44 (m)
5	5.23 (m)	5.23 (m)	5.23 (m)	5.22 (m)
6	5.39 (br d, 8.6)	5.39 (br d, 8.4)	5.39 (br d, 8.6)	5.39 (br d, 9.0)
8	2.14 (br t, 7.1, 2H)	2.14 (br t, 7.8, 2H)	2.14 (m, 2H)	2.14 (m, 2H)
9	1.63 (m, 2H)	1.63 (m, 2H)	1.63 (m, 2H)	1.63 (m, 2H)
10a	1.56 (m)	1.56 (m)	1.60 (m)	1.60 (m)
10b	1.78 (m)	1.78 (m)	1.76 (m)	1.76 (m)
11	2.64 (m)	2.64 (m)	2.65 (m)	2.65 (m)
16	1.37 (s, 3H)	1.37 (s, 3H)	1.37 (s, 3H)	1.37 (s, 3H)
17	1.37 (s, 3H)	1.37 (s, 3H)	1.38 (s, 3H)	1.37 (s, 3H)
18α	1.92 (m)	1.92 (m)	1.82 (m)	1.82 (m)
18β	1.82 (m)	1.82 (m)	1.92 (m)	1.92 (m)
19	1.76 (d, 1.3, 3H)	1.76 (d, 1.2, 3H)	1.76 (d, 1.2, 3H)	1.76 (br s, 3H)
20	2.02 (br s, 3H)	2.02 (br s, 3H)	2.02 (br s, 3H)	2.02 (br s, 3H)
2′	5.78 (br s)	5.78 (br s)	5.78 (br s)	5.78 (br s)
4′a	2.34 (dd, 18.2, 4.7)	2.34 (dd, 18.0, 4.2)	2.34 (dd, 18.1, 4.5)	2.34 (dd, 18.6, 4.2)
4′b	2.42 (m)	2.42 (m)	2.44 (m)	2.44 (m)
5′	5.21 (m)	5.21 (m)	5.21 (m)	5.21 (m)
6′	5.32 (br d, 8.6)	5.33 (br d, 9.0)	5.35 (br d, 8.6)	5.35 (br d, 8.4)
8′	2.07 (br t, 7.4, 2H)	2.07 (br t, 7.2, 2H)	2.09 (m, 2H)	2.09 (m, 2H)
9′a	1.35 (m)	1.35 (m)	1.33 (m)	1.33 (m)
9′b	1.47 (m)	1.47 (m)	1.46 (m)	1.46 (m)
10′a	1.87 (m)	1.87 (m)	1.84 (m)	1.84 (m)
10′b	2.03 (m)	2.03 (m)	2.05 (m)	2.05 (m)
13′	5.34 (s)	5.34 (s)	5.33 (s)	5.33 (s)
16′	1.31 (s, 3H)	1.31 (s, 3H)	1.31 (s, 3H)	1.31 (s, 3H)
17′	1.35 (s, 3H)	1.35 (s, 3H)	1.35 (s, 3H)	1.35 (s, 3H)
18′α	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)
18′β	1.92 (m)	1.92 (m)	1.92 (m)	1.92 (m)
19′	1.71 (d, 1.2, 3H)	1.71 (d, 1.2, 3H)	1.68 (d, 1.2, 3H)	1.68 (br s, 3H)
20′	2.02 (br s, 3H)	2.02 (br s, 3H)	2.02 (br s, 3H)	2.02 (br s, 3H)

[a]Natural product. [b]Synthesized compound.

temperature for 4 h. The reaction was diluted with water, extracted with EtOAc (3 × 50 mL), and the combined organic layer dried (Na_2SO_4) and concentrated. The crude semiacetal was dissolved in dried DCM (30 mL), and then neutral activated MnO_2 (856 mg, 9.84 mmol, 20.0 equiv) was added. The mixture was stirred in room temperature for 16 h and was filtered over Celite, washed with CH_2Cl_2. PTSA (1.00 equiv) was added to the filtrate, and the mixture was stirred in room temperature for 3 h. Then the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution (3 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 2:1) providing **12** (65.0 mg, 0.197 mmol, 40%, over 3 steps): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.01 (s, 1H), 5.82 (s, 1H), 5.55 (s, 1H), 5.43 (s, 1H), 5.35 (d, J = 9.0 Hz, 1H), 5.15−5.07 (m, 1H), 2.41 (dd, J = 12.0, 18.0 Hz, 1H), 2.30 (t, J = 9.0 Hz, 2H), 2.21 (dd, J = 3.0, 18.0 Hz, 1H), 2.09 (t, J = 6.0 Hz, 2H), 1.99 (s, 3H), 1.71 (s, 1H), 1.68−1.64 (m, 2H), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.6, 183.3, 165.2, 156.9, 141.8, 138.2, 122.5, 121.0, 116.7, 99.9, 88.4, 74.1, 38.8, 35.1, 31.9, 26.2, 23.1 (2 C), 23.00, 16.72; $[\alpha]^{22}_D$ −19.5 (c 0.625, MeOH); HRMS (TOF ESI) calcd for $C_{20}H_{26}NaO_4$ 353.1723 $[M + Na]^+$, found 353.1749.

*(E)-2,5-Dihydroxy-11-((2S,6S)-6-isopropoxy-4-methyl-3,6-dihydro-2H-pyran-2-yl)-2,10-dimethyl-6-methyleneundec-10-en-3-one (**13**).* To a solution of $LiN(SiMe_3)_2$ in THF at −40 °C, 3-hydroxy-3-methyl-2-butone **S2** (777 mg, 7.62 mmol, 3.00 equiv) in THF (3 mL) was added dropwise. After the addition, the stirring was continued for 3 h at −40 °C. The mixture was then cooled to −78 °C, and a solution of **23** (741 mg, 2.54 mmol, 1.00 equiv) in THF was added dropwise over 20 min. After another 20 min, the flask was moved to −40 °C for 1.5 h. The reaction was quenched by the addition of saturated NH_4Cl aqueous (20 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layer was separated, and the aqueous layer was extracted with ether. The combined organic solution was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 5:1 → 2:1) providing **13** (760 mg, 1.93 mmol, 76%) as a clear, colorless oil that was a 1:1 mixture of diastereomers at the position of hydroxyl (inseparable by flash column chromatography): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.42 (s, 1H), 5.21 (d, J = 9.0 Hz, 1H), 5.11 (s, 1H), 5.06 (s, 1H), 4.90 (s, 1H), 4.71−4.63 (m, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.02−3.94 (m, 1H), 3.73 (d, J = 6.0 Hz, 1H), 2.94−2.84 (m, 1H), 2.67 (dd, J = 3.0, 18.0 Hz, 1H), 2.08−1.96 (m, 5H), 1.77 (dd, J = 3.0, 18.0 Hz, 1H), 1.71 (br s, 3H), 1.69 (br s, 3H), 1.66−1.56 (m, 2H), 1.36 (br s, 6H), 1.21 (d, J = 6.0 Hz, 3H), 1.15 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.8, 214.8, 150.0(2C), 139.6, 139.5, 137.2, 125.1, 125.1, 120.0, 110.1, 110.0, 98.6, 93.2, 70.8, 68.9, 68.9, 63.4, 41.9, 41.8, 39.1, 39.0, 35.7, 31.4, 31.2, 26.3, 25.6, 25.5, 23.8, 22.8, 21.9, 16.5, 16.5; $[\alpha]^{20}_D$ −4.0 (c 0.10, $CHCl_3$); HRMS (TOF ESI) calcd for $C_{23}H_{38}NaO_5$ 417.2611 $[M + Na]^+$, found 417.2612.

*(2S,6S)-2-((E)-2-Iodoprop-1-en-1-yl)-6-isopropoxy-4-methyl-3,6-dihydro-2H-pyran (**14**).* A solution of the above vinylstannane **19** (2.32 g, 4.78 mmol) in THF (50 mL) was cooled to −17 °C (NaCl/ice) followed by addition of NIS (1.61 g, 7.17 mmol, 1.50 equiv) in

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Table 3. ^{13}C NMR Data Comparison of 1, 2, 3 and 4 in CD_3OD

carbon	1[a]	1[b]	2[a]	2[b]	3[a]	3[b]	4[a]	4[b]
1	168.1	168.1	168.0	168.0	167.9	168.0	167.9	168.0
2	116.4	116.5	116.4	116.5	116.5	116.5	116.4	116.5
3	161.2	161.2	161.2	161.2	161.1	161.1	161.1	161.1
4	35.8	35.8	35.7	35.7	35.8	35.8	35.8	35.8
5	76.0	76.0	75.9	75.9	76.0	76.1	76.0	76.0
6	123.6	123.7	123.7	123.7	123.9	123.9	123.8	123.8
7	143.6	143.6	143.5	143.6	143.4	143.4	143.5	143.6
8	40.2	40.2	40.2	40.2	40.0	40.0	40.1	40.1
9	25.0	25.1	24.9	24.9	25.9	25.9	25.9	25.9
10	31.2	31.2	31.1	31.1	32.1	32.2	32.1	32.1
11	37.7	37.7	37.6	37.6	36.5	36.6	36.6	36.6
12	193.1	193.1	193.2	193.2	193.1	193.1	193.1	193.2
13	112.4	112.4	112.3	112.3	112.1	112.1	112.0	112.0
14	206.9	206.9	206.8	206.8	206.6	206.7	206.6	206.7
15	89.4	89.4	89.4	89.4	89.2	89.2	89.2	89.2
16	23.1	23.1	23.1	23.1	23.1	23.1	23.1	23.1
17	23.4	23.4	23.4	23.4	23.5	23.4	23.4	23.4
18	25.9	25.9	25.9	25.9	24.9	25.0	24.8	24.8
19	16.7	16.7	16.6	16.6	16.6	16.6	16.6	16.6
20	23.0	23.0	23.0	23.0	23.0	23.0	23.0	23.0
1′	168.1	168.0	168.0	168.0	167.9	168.0	167.9	168.0
2′	116.4	116.5	116.4	116.5	116.5	116.5	116.5	116.5
3′	161.2	161.1	161.2	161.1	161.1	161.1	161.2	161.2
4′	35.8	35.8	35.8	35.8	35.8	35.9	35.8	35.8
5′	76.0	76.0	76.0	76.0	76.0	76.0	76.0	76.0
6′	123.6	123.6	123.9	123.9	123.6	123.6	124.0	124.0
7′	143.5	153.5	143.4	143.4	143.4	143.4	143.3	143.3
8′	40.4	40.4	40.5	40.5	40.4	40.4	40.5	40.5
9′	23.4	23.4	23.2	23.2	23.7	23.7	23.6	23.6
10′	35.6	35.6	35.2	35.3	35.8	35.8	35.6	35.6
11′	43.5	43.5	43.4	43.5	43.1	43.1	43.1	43.1
12′	197.9	197.9	198.0	198.0	197.5	197.6	197.6	197.7
13′	102.2	102.2	102.2	102.2	101.9	101.9	101.9	101.9
14′	209.8	209.7	209.7	209.7	209.8	210.0	209.9	210.0
15′	90.6	90.5	90.5	90.5	90.3	90.3	90.5	90.4
16′	23.0	23.0	23.0	23.0	23.0	23.0	23.0	23.0
17′	23.0	23.0	23.0	23.0	23.0	23.0	23.0	23.0
18′	31.6	31.6	31.5	31.5	30.4	30.5	30.5	30.5
19′	16.6	16.6	16.5	16.5	16.8	16.8	16.5	16.5
20′	23.0	23.0	23.0	23.0	23.0	23.0	23.0	23.0

[a]Natural product. [b]Synthesized compound).

THF (5 mL), to give an almost clear yellow solution. After 20 min, a mixture of saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) was added followed by Et_2O (50 mL). Stirring was continued for 2 min until two clear, colorless phases were formed. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by flash chromatography on deactivated silica gel (hexane:EtOAc = 50:1) to afford the desired product **14** (ca. 1.46g) as a yellow oil. The crude vinyl iodide can also be used directly in the next step without purification: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.23 (dd, J = 3.0, 9.0 Hz, 1H), 5.42 (br s, 1H), 5.06 (br s, 1H), 4.67−4.59 (m, 1H), 4.03−3.95 (m, 1H), 2.48 (d, J = 3.0 Hz, 3H), 2.05 (dd, J = 9.0, 18.0 Hz, 1H), 1.81 (dd, J = 3.0 Hz, 18.0 Hz), 1.73 (s, 3H), 1.21 (d, J = 6.0 Hz, 3H), 1.16 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.9, 120.1, 98.8, 93.3, 89.5, 69.3, 64.3, 34.8, 28.3, 23.8, 22.7, 21.9; $[\alpha]^{24}_D$ −26.8 (c 0.45, $CHCl_3$); HRMS (TOF ESI) calcd for $C_{12}H_{19}INaO_2$ 345.0322 $[M + Na]^+$, found 345.0329.

(2S,6R)-6-Methoxy-4-methyl-2-(prop-1-yn-1-yl)-3,6-dihydro-2H-pyran (15). In a 100 mL flask under argon was added 4 Å molecular sieves (4.0 g), catalyst **S3**[20] (730 mg, 1.50 mmol, 3.00 mol %), 2-butynal **17** (3.5 g, 50.0 mmol, 1.00 equiv). The mixture was stirred for 1.5 h at room temperature. Then 1-methoxy-3-methyl-1, 3-butadiene **16** (4.9 g, 50.0 mmol, 1.00 equiv) was added, and the mixture was stirred at room temperature for 18 h. The reaction was diluted with Et_2O, filtered through Celite and concentrated under atmospheric pressure at 43 °C. The residue was purified by flash chromatography on silica gel (pentane:Et_2O = 15:1) to give **15** (7.0 g, 42.2 mmol, 84%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.40−5.39 (m, 1H), 5.01−5.00 (m, 1H), 4.50−4.45 (m, 1H), 3.48 (s, 3H), 2.30 (dd, J = 9.0, 18.0 Hz, 1H), 2.10 (dd, J = 3.0, 18.0 Hz, 1H), 1.84 (d, J = 3.0 Hz, 3H), 1.73 (d, J = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.8, 120.9, 98.2, 80.7, 78.3, 61.9, 55.4, 36.4, 22.9, 3.9; $[\alpha]^{25}_D$ −44.8 (c 0.86, $CHCl_3$); HRMS (TOF ESI) calcd for $C_{10}H_{14}NaO_2$ 189.0886 $[M + Na]^+$, found 189.0863.

GC (β-dex chiral column) (T = 105 °C): t_{R1}(minor) = 28.05 min, t_{R2} (major) = 28.71 min, and ee = 98.0.

1-Methoxy-3-methylbuta-1,3-diene (16). To a suspension of t-BuOK (9.12 g, 80.0 mmol) in anhydrous Et_2O (100 mL) under argon at 0 °C was added (methoxymethyl)triphenylphosphonium chloride

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(28.8 g, 60.0 mmol) over 5 min. The resultant reddish suspension was stirred for 1 h at 0 °C, and a solution of **S9** (5.0 mL, 60.0 mmol) in Et_2O (5 mL) was then added. Stirring was continued for 10 min, and then warmed to room temperature for 0.5 h, The resultant solution was poured into brine (50 mL) and pentane (100 mL). Triphenylphosphine oxide was filtered off through a pad of Celite. The filtrate was extracted twice with a pentane/ether (1:1) mixture (totally 100 mL). The combined organic layer was washed with brine (50 mL) and dried over $MgSO_4$. After careful distillation under atmospheric pressure, the residue was distilled under reduced pressure to give 1-methoxy-l, 3-pentadiene **16** in 62% yield (~3.64 g, *E*:*Z* = 5:4). ***E***: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81 (m, 3H), 3.59 (s, 3H), 4.69 (m, 1H), 4.77 (m, 1H), 5.64 (d, *J* = 12.9 Hz, 1H), 6.58 (d, *J* = 12.9 Hz, 1H). ***Z***: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (m, 3H), 3.64 (s, 3H), 4.77 (m, 1H), 4.81 (d, *J* = 6.9 Hz, 1H), 4.99 (m, 1H),5.87(d, *J* = 6.9 Hz, 1H).[19]

*But-2-ynal (**17**).* To a solution of compound **S10** (3.50 g, 50.0 mmol, 1.00eq) in CH_2Cl_2 (150 mL) was added PCC (19.44 g, 90.0 mmol, 1.80 equiv) at 0 °C, and then warmed to room temperature slowly. The mixture was stirred for 2 h at room temperature and filtered through a short silica gel column. It was washed with 150 mL of CH_2Cl_2. Filtrate was condensed under reduced pressure at 0 °C until 15 mL of solution was left. The crude aldehyde **17** can be used directly in the next step without CH_2Cl_2 completely removed: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.15 (s, 1H), 2.07 (s, 3H).

*(2S,6S)-6-Isopropoxy-4-methyl-2-(prop-1-yn-1-yl)-3,6-dihydro-2H-pyran (**18**).* To a solution of compound **15** (7.0 g, 42.2 mmol, 1.00eq) in *i*-PrOH (100 mL) was added *p*-TsOH (76.0 mg, 0.40 mmol, 1.00 equiv), and the solution was stirred at room temperature for 3 h. The reaction was quenched with dilute $NaHCO_3$ and extracted with Et_2O (2 × 100 mL). The organic layer was washed with water (3 × 100 mL); water layer was extracted with Et_2O (2 × 100 mL); organic layer was washed with water again (3 × 100 mL); all organic layers were dried ($MgSO_4$), filtered and concentrated under atmospheric pressure at 43 °C. The residue was purified by flash chromatography on silica gel (pentane:Et_2O = 20:1) to give **18** (6.86 g, 35.4 mmol, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.43 (br s, 1H), 5.11 (br s, 1H), 4.65 (br d, *J* = 6.0 Hz, 1H), 4.07−4.03 (m, 1H), 2.33 (dd, *J* = 9.0, 12.0 Hz, 1H), 2.02 (dd, *J* = 3.0, 12.0 Hz, 1H), 1.88 (d, *J* = 3.0 Hz, 3H), 1.73 (d, *J* = 1.2 Hz, 3H), 1.27 (d, *J* = 3.0 Hz, 3H), 1.18 (d, *J* = 3.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.5, 119.9, 93.3, 80.8, 78.2, 69.4, 57.5, 36.4, 23.8, 22.6, 21.9, 3.6; $[\alpha]^{25}_D$ −34.3 (*c* 0.36, $CHCl_3$); HRMS (EI) calcd for $C_{12}H_{18}O_2$ 194.1307, found *m*/*z* 194.1312.

*Tributyl((E)-1-((2S,6S)-6-isopropoxy-4-methyl-3,6-dihydro-2H-pyran-2-yl)prop-1-en-2-yl)stannane (**19**).* To a suspension of CuCN (2.78 g, 30.93 mmol, 5.00 equiv) in THF (90 mL) at −78 °C was added a solution of *n*-BuLi (1.6 M in hexane, 38.6 mL, 61.80 mmol, 10.00 equiv). After 5 min the flask was immersed in a cooling bath at −40 °C, resulting in the formation of a pale-yellow, almost clear solution. The mixture was cooled back to −78 °C after 10 min, which made it become slightly heterogeneous. Neat Bu_3SnH (16.6 mL, 61.80 mmol, 10.00 equiv) was then added dropwise, immediately leading to a turbid yellow solution with liberation of gas. After 20 min at −78 °C the mixture was stirred for 5 min at −40 °C, giving an almost clear golden-yellow solution. After 10 min at −40 °C the solution was cooled back to −78 °C followed by addition of MeOH (27.5 mL, 680.0 mmol, 110.00 equiv) under vigorous stirring. After 10 min at −78 °C the flask was immersed in a cooling bath at −40 °C; the reaction mixture now was a clear red solution. After 40 min at −40 °C this solution was cooled back to −78 °C, and a solution of **18** (1.20 g, 6.18 mmol, 1.00 equiv) in THF (5 mL) was added. The mixture was stirred for 15 h, during which period the temperature was allowed to rise to −15 °C. Saturated aqueous NH_4Cl (30 mL) and 25% aqueous NH_4OH (6 mL) were then added together with Et_2O (50 mL). Stirring was continued for 30 min, the two almost clear phases were separated, and the aqueous phase was extracted with Et_2O (2 × 150 mL). The combined organic extracts were dried over $MgSO_4$, and the solution was concentrated under reduced pressure. Purification of the residue by flash chromatography on deactivated silica gel (hexane 2% NEt_3 (v/v)) gave the vinylstannane **19** (2.32 g, 4.78 mmol, 77%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.57 (d, *J* = 6.0 Hz, 1H), 5.44 (br s, 1H), 5.09 (br s, 1H), 4.89−4.82 (m, 1H), 4.05−3.96 (m, 1H), 1.98 (dd, *J* = 6.0, 12.0 Hz, 1H), 1.91 (s, 3H), 1.80 (dd, *J* = 3.0, 18.0 Hz, 1H), 1.73 (s, 3H), 1.54−1.44 (m, 6H), 1.35−1.25 (m, 6H), 1.22 (d, J = 6.0 Hz, 3H), 1.16 (d, *J* = 6.0 Hz, 3H), 0.92−0.86 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.4, 140.2, 137.3, 120.1, 93.5, 69.1, 62.5, 35.4, 29.1 (3C), 27.3 (3C), 23.8, 22.9, 22.1, 19.7, 13.7 (3C), 9.1 (3C); $[\alpha]^{24}_D$ −20.2 (*c* 0.50, $CHCl_3$); HRMS (TOF ESI) calcd for $C_{24}H_{46}NaO_2Sn$ 509.2412 $[M + Na]^+$, found 509.2422.

*tert-Butyl(((E)-7-((2S,6S)-6-isopropoxy-4-methyl-3,6-dihydro-2H-pyran-2-yl)-6-methylhept-6-en-1-yl)oxy)dimethylsilane (**20**).* In a flame-dried 10 mL conical flask equipped with a magnetic stir bar, septum, and argon inlet needle, olefin **S5** (1.36 g, 6.80 mmol, 1.50 equiv) was dissolved in anhydrous THF (2 mL). A freshly prepared solution of 9-BBN (0.5 M in THF, 27.2 mL, 13.6 mmol, 3.00 equiv) was added dropwise at room temperature. Then it was stirred at room temperature for 1.5 h. In a separate 100 mL conical flask, Cs_2CO_3 (4.43 g, 13.59 mmol, 3.0 equiv) and $AsPh_3$ (278 mg, 0.91 mmol, 0.20 equiv) was dissolved in DMF (25 mL) and water (10 mL) followed by the addition of hydroboration reaction mixture. Then the crude vinyl iodide **14** (1.46 g, 4.53 mmol, 1.00 equiv) was added and argon inlet needle. Pd(dppf)Cl_2 (665 mg, 0.91 mmol, 0.20 equiv) was added at last. The reaction was stirred for 15 h at room temperature, and then diluted with Et_2O (100 mL), washed with H_2O, and brine, then dried ($MgSO_4$) and filtered. Evaporation of solvent, and the residue was filtered through short flash chromatography deactivated silica gel (hexane:EtOAc = 30:1) to give **20** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.42 (br s, 1H), 5.19 (d, *J* = 9.0 Hz, 1H), 5.07 (br s, 1H), 4.70−4.62 (m, 1H), 4.04−3.95 (m, 1H), 3.58 (t, *J* = 6.0 Hz, 2H), 2.03−1.98 (m, 3H), 1.83 (dd, *J* = 3.0, 18.0 Hz, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.55−1.40 (m, 4H), 1.35−1.25 (m, 2H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H), 0.87 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.0, 137.3, 124.6, 120.0, 98.7, 93.2, 68.8, 63.4, 63.2, 39.5, 35.7, 32.7, 27.4, 25.9 (3 C), 25.4, 23.8, 22.8, 21.8, 16.5, −5.3 (2 C); $[\alpha]^{25}_D$ −7.8 (*c* 0.96, $CHCl_3$); MS (EI) *m*/*z* 396 (M^+); HRMS (EI) calcd for $C_{23}H_{44}SiO_3$ 396.3060, found *m*/*z* 396.3068.

*(E)-7-((2S,6S)-6-Isopropoxy-4-methyl-3,6-dihydro-2H-pyran-2-yl)-6-methylhept-6-en-1-ol (**21**).* The TBS ether **20** (ca. 1.6 g, 4.04 mmol, 1.00 equiv) was placed in a flame-dried two-neck round-bottom flask, under argon atmosphere. To this was added anhydrous THF (50 mL), and then TBAF (1.0 M in THF, 4.85 mL, 4.85 mmol, 1.20 equiv) was added slowly at room temperature. The mixture was allowed to stir at room temperature for 6 h. After complete conversion, the mixture was diluted with Et_2O (100 mL), washed with H_2O, and brine, and then dried (Na_2SO_4) and filtered. Solvent was evaporated, and the residue was purified by flash chromatography deactivated silica (hexane:EtOAc = 10:1 → 5:1 → 3:1) to give **21** (7.0 g, 42.2 mmol, 84%, over 3 steps) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.40 (br s, 1H), 5.18 (dd, *J* = 3.0, 9.0 Hz, 1H), 5.06 (br s, 1H), 4.69−4.61 (m, 1H), 4.02−3.94 (m, 1H), 3.60 (t, *J* = 6.0 Hz, 2H), 2.05−1.98 (m, 3H), 1.75 (dd, *J* = 3.0, 18.0 Hz, 1H), 1.70 (s, 3H), 1.67 (d, *J* = 1.2 Hz, 3H), 1.60−1.50 (m, 2H), 1.48−1.40 (m, 2H), 1.38−1.30 (m, 2H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.9, 137.3, 124.6, 120.0, 93.2, 68.9, 63.4, 62.8, 39.4, 35.7, 32.6, 27.3, 25.3, 23.8, 22.8, 21.8, 16.5; $[\alpha]^{24}_D$ −14.6 (*c* 0.35, $CHCl_3$); HRMS (TOF ESI) calcd for $C_{17}H_{30}NaO_3$ 305.2087 $[M + Na]^+$, found 305.2106.

*(E)-7-((2S,6S)-6-Isopropoxy-4-methyl-3,6-dihydro-2H-pyran-2-yl)-6-methylhept-6-enal (**22**).* Anhydrous powdered 4 Å molecular sieves (1.8 g, ~0.5 g/mmol) were placed in flame-dried round-bottom flask under argon atmosphere, and then it was cooled to 0 °C, and anhydrous CH_2Cl_2 (40 mL) was added. Alcohol **21** (980 mg, 3.47 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (10 mL) was added and stirred for 10 min. Then 4-methylmorpholine-*N*-oxide (610 mg, 5.21 mmol, 1.50 equiv) was added, followed by tetrapropylammoniumperruthenate (74 mg, 0.21 mmol, 6.0 mol %) at 0 °C, and the mixture was allowed to stir at room temperature for 2 h. After the completion of the reaction, the reaction mixture was filtered through Celite and concentrated. The residue was purified by flash chromatography on

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silica gel (hexane:EtOAc = 5:1) to give **22** (750 mg, 2.68 mmol, 77%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.75 (t, J = 1.2 Hz, 1H), 5.42 (br s, 1H), 5.20 (dd, J = 0.9, 9.0 Hz, 1H), 5.06 (br s, 1H), 4.68−4.63 (m, 1H), 4.03−3.95 (m, 1H), 2.43 (dt, J = 0.9, 6.0 Hz, 2H), 2.07−1.97 (m, 3H), 1.78 (dd, J = 3.0, 18.0 Hz, 1H), 1.71 (s, 3H), 1.68 (s, 3H), 1.66−1.58 (m, 2H), 1.52−1.44 (m, 2H), 1.21 (d, J = 6.0 Hz, 3H), 1.14 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.6, 139.2, 137.2, 125.1, 120.1, 93.3, 68.9, 63.4, 43.7, 39.1, 35.7, 27.0, 23.8, 22.8, 21.9, 21.6, 16.5; $[\alpha]^{20}_D$ −15.9 (c 0.50, $CHCl_3$); HRMS (TOF ESI) calcd for $C_{17}H_{28}NaO_3$ 303.1931 $[M + Na]^+$, found 303.1933.

*(E)-7-((2S,6S)-6-Isopropoxy-4-methyl-3,6-dihydro-2H-pyran-2-yl)-6-methyl-2-methylenehept-6-enal (**23**).* To a solution of **22** (750 mg, 2.68 mmol, 1.00 equiv) in dried CH_2Cl_2 (40 mL) and Et_3N (1.9 mL, 13.4 mmol, 5.00 equiv) was added Eschenmoser's salt (2.48 g, 13.4 mmol, 5.00 equiv). After stirring for 10 h, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution (20 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 5:1) providing **23** (741 mg, 2.54 mmol, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.53 (s, 1H), 6.25 (s, 1H), 5.99 (s, 1H), 5.42 (s, 1H), 5.21 (d, J = 9.0 Hz, 1H), 5.07 (s, 1H), 4.70−4.63 (m, 1H), 4.03−3.95 (m, 1H), 2.22 (t, J = 6.0 Hz, 2H), 2.06−1.96 (m, 2H), 1.78 (dd, J = 3.0, 18.0 Hz, 1H), 1.72 (s, 3H), 1.69 (s, 3H), 1.58 (t, J = 6.0 Hz, 2H), 1.21 (d, J = 6.0 Hz, 3H), 1.15 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.6, 150.1, 139.2, 137.3, 134.1, 125.3, 120.1, 93.3, 68.9, 63.4, 39.0, 35.7, 27.4, 25.7, 23.8, 22.8, 21.9, 16.5; $[\alpha]^{20}_D$ −8.1 (c 0.20, $CHCl_3$); HRMS (TOF ESI) calcd for $C_{18}H_{28}NaO_3$ 315.1931 $[M + Na]^+$, found 315.1956.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of the novel precursors. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: liying@lzu.edu.cn

*E-mail: fjnan@simm.ac.cn

Notes

The authors declare no competing financial interest.

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