# Total Synthesis of (±)-Antroquinonol D

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S Supporting Information

ABSTRACT: Total synthesis of (±)-antroquinonol D, which is isolated from very expensive and rarely found *Antrodia camphorata* and which has potential anticancer properties, was achieved from 4-methoxyphenol. In addition, a Michael addition to dimethoxy cyclohexadienones was studied. The main step involved chelation and substrate-controlled diastereoselective reduction of cyclohexenone and lactonization. Lactone synthesis facilitated the diastereoselective reduction of ketone, which help control the desired stereochemistry at the crucial stereogenic center in the natural product. Other key reactions in the synthesis involved a Michael addition of dimethyl malonate on cyclohexadienone, dihydroxylation, and Wittig olefination. A sesquiterpene side chain was synthesized through coupling with geranyl phenyl sulfide and Bouveault−Blanc reduction.
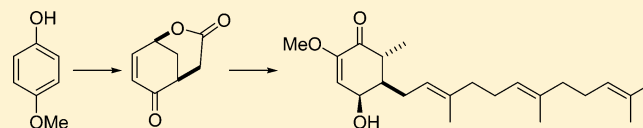
INTRODUCTION

Antrodia camphorata has long been used by aboriginal people to treat hepatitis, cirrhosis, and liver cancer, and it has been used in Taiwan to cure diarrhea, abdominal pain, hypertension, and skin itching.[1] A number of structurally diverse molecules, including terpenoids, benzenoids, lignans, benzoquinone derivatives, succinic derivatives, maleic derivatives, and polysaccharides, have been isolated from this medicinal fungus.[2] Ubiquinone derivatives, antroquinonol (**1**), antroquinonol B (**2**), antroquinonol C (**3**), antroquinonol D (**4**), and compounds **5** and **6** (Figure 1), have also been isolated from expensive and rarely found mycelia and the fruiting bodies of *A. camphorata*.[3] All these quinonol molecules possess a sesquiterpene side chain attached to a quinonol framework, and they feature the same relative stereochemistry in the cyclohexenone ring. Most of the quinonol compounds exhibit potential anticancer activities against highly variable cancer cells.[4] The effectiveness of antroquinonol (**1**) for the treatment of multiple forms of cancer has been proven in vivo.[5] Antroquinonol D has recently been isolated and identified as a new DNMT1 (DNA (cytosine-5)-methyltransferase 1) inhibitor that induces DNA demethylation and reverses the silencing of multiple tumor suppressor genes; it also induces cancer cell death and inhibits cell migration.[6] Moreover, it inhibits the growth of MCF7, T47D, and MDA-MB-231 breast cancer cells with GI_{50} = 8.01, 3.57, and 25.08 μM, respectively.

However, despite these intriguing biological properties, detailed pharmacological and pharmacokinetic studies of these compounds have been hindered by the limited supplies and extremely slow growth rate of *A. camphorata*. The mycelium of *A. camphorata* has recently been developed by industrial companies as a health food and has been reported to have anticancer effects.[3] Accordingly, developing methods for the synthesis of these bioactive compounds would not only serve to maintain an ample supply of this class of natural products but also facilitate further biological evaluation. Herein we report the first total synthesis of (±)-antroquinonol D,

which involves a Michael addition, lactonization, diastereose-lective reduction of ketone, Appel halogenations, Wittig olefination, and Bouveault−Blanc reduction.

RESULTS AND DISCUSSION

Antroquinonol and antroquinonol D share a common sesquiterpene side chain and differ only with regard to substitution at C_3 of the cyclohexenone core structure. A retrosynthetic approach for the synthesis of antroquinonol (**1**) and antroquinonol D (**4**) is shown in Scheme 1. Both these molecules can be synthesized from common intermediate cyclohexanone **7** by elimination of the β-methoxy group or by generating α,β-unsaturated cyclohexenone. It was envisaged that cyclohexanone **7** could be synthesized from cyclohexanone **8** by first attaching a sesquiterpene chain and then performing diastereoselective methylation. It was anticipated that the diastereoselective reduction of cyclohexenone **9** could provide the cis geometry between C_4−OH and C_5−C_7. We envisaged that oxa-bicyclo[3.3.1]nonene compound **9** could be prepared through a Michael addition of dimethyl malonate on *p*-benzoquinone dimethyl ketal **10**, the diastereoselective reduction of intermediate cyclohexanone, and lactonization.

The cyclohexenone core of antroquinonol molecules can be accessed by Michael addition of a suitable precursor for the sesquiterpene side chain on 4,4-disubstituted cyclohexadie-nones followed by stereoselective reduction of the keto group. Organocuprate compounds are among the most widely used reagents for C−C bond formation because they can facilitate conjugate addition to prochiral enones, and considerable progress has been made in the field of enantioselective copper-catalyzed 1,4-addition reactions.[7] Accordingly, 4,4-disubstituted cyclohexadienones **12** and **13** were synthesized by oxidizing 2,3,4-trimethoxy-6-methylphenol (**11**)[8] with hypervalent iodine reagents (PIDA or PIFA). An organozinc
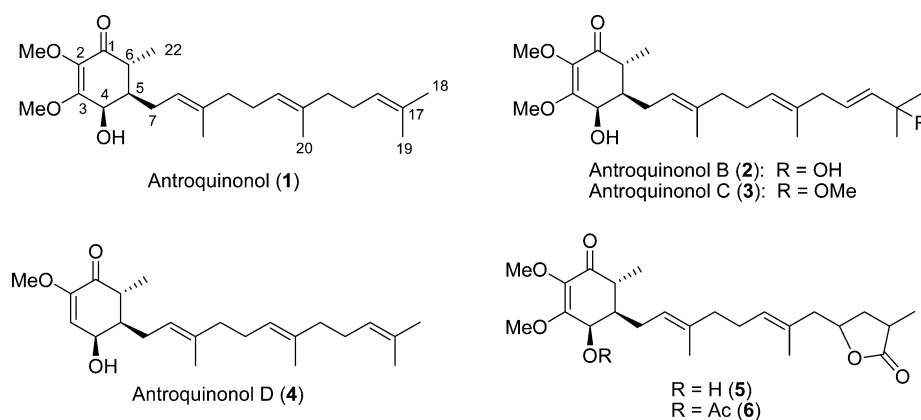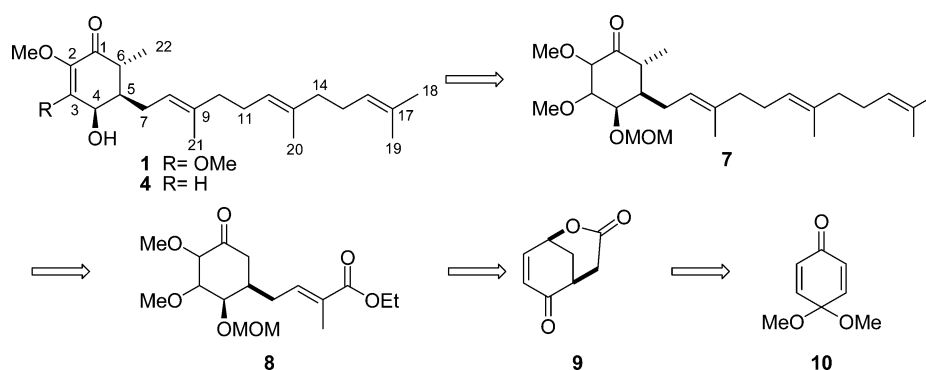
Figure 1. Quinonolic derivatives isolated from *A. camphorata*.

Scheme 1. Retrosynthetic Analysis

reagent in the presence of Cu(OTf)$_2$ or an organocuprate reagent prepared from ethyl bromoacetate could not provide the conjugate addition product with cyclohexadienones **12** and **13** (Scheme 2). Moreover, the enolate generated from dimethyl malonate was unreactive toward cyclohexadienone **12** and **13**. A plausible reason for these observations is that the steric resistance and low electrophilicity of the carbonyl group resulting from the resonance of dimethoxy substituents prevented conjugate addition. After several abortive attempts at conjugate addition, it was thought that intramolecular radical cyclization could provide the requisite product, and when the PIDA-mediated oxidation of 2,3,4-trimethoxy-6-methylphenol (**11**) was carried out in the presence of 2-bromoethanol, it provided the cyclohexadienone **14** in 91% yield. Intramolecular cyclization of the free radical produced from the bromo **14** by using AIBN as the initiator in toluene at 80 °C proceeded smoothly to afford the cyclized product **15** in 75% yield. At this stage, reduction of cyclohexenone could provide allylic alcohol, which could be converted to the required lactone. The reduction of cyclohexanone **15** under Luche conditions or with DIBAL-H at −78 °C could not deliver the allylic alcohol **16**; rather, elimination of the allylic methoxy group and aromatization readily occurred to afford dihydrobenzofuran **17** and hexenol **18**, respectively, as the major products (Scheme 2). We postulate that the resonance associated with an electron pair of the methoxy group facilitated the elimination of the allylic methoxy group during the reduction reaction.

After several unsuccessful attempts at reduction because of concomitant demethoxylation, we performed the Michael addition of dimethyl malonate on unsubstituted cyclohexadienones **19a** and **19b** prepared from 4-methoxyphenol.[9] As the

elimination of the methoxy group was the main concern, cyclic acetal was used, and the Michael addition of dimethyl malonate with **19a** provided conjugate adduct **20a** (R = −CH$_2$CH$_2$−) in 53% yield (Scheme 3). Chemoselective reduction of cyclohexenone **20a** under Luche conditions followed by lactonization afforded the required lactone **21a** in 47% yield.[10] Much to our delight, the reduction and lactonization of dimethoxy ketal adduct **20b** under the same conditions provided lactone **21b** in 99% yield. The diastereoselective reduction of ketone may have resulted from chelation control (CeCl$_3$) or substrate control as the attack of the hydride donor mainly occurs on the side opposite to the bulky malonate group because of less steric hindrance (kinetic control). Furthermore, the *cis* product is also more stable than the *trans* product, as both substituents on the ring can be in an equatorial position. Decarboxylation of malonate **21** was achieved by using a mild nucleophile such as DABCO in toluene and water (Scheme 3).[11] The deprotection of the ketal group with 1 N HCl afforded the known 2-oxabicyclo[3.3.1]non-7-ene-3,6-dione **9** in 64% yield. As expected, the reduction of 2-oxabicyclo[3.3.1]non-7-ene-3,6-dione **9** with NaBH$_4$ diastereoselectively provided the *endo* alcohol **23** in 94% yield.[12]
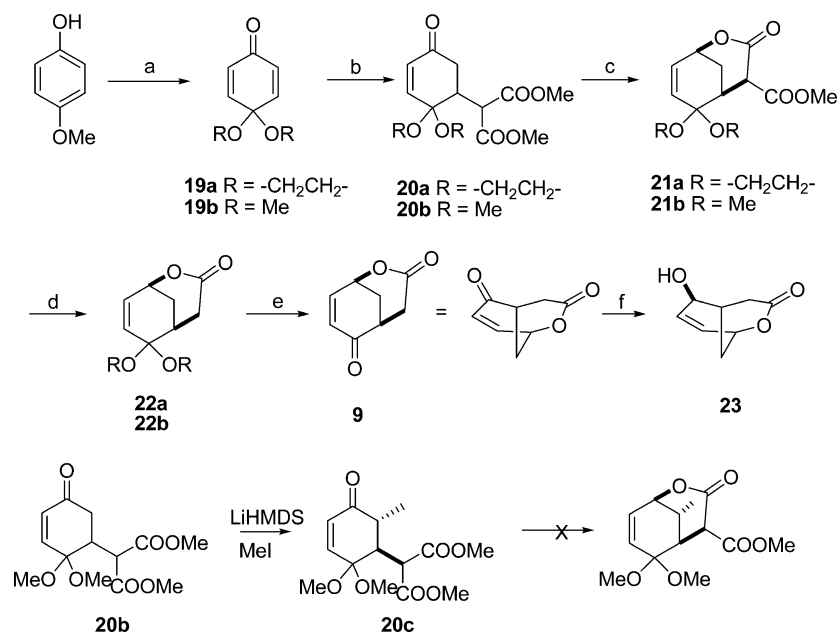
The diastereoselective methylation of the dianion derived from Michael adducts **20b** at −78 °C with LiHMDS provided the required *trans* product **20c** (Scheme 3). However, the diastereoselective reduction of cyclohexenone **20c** under Luche conditions was not possible owing to the *trans* orientation of the methyl and malonate groups, and several attempts to synthesize the lactone from the corresponding alcohol were unsuccessful.

**Scheme 2. Attempted Michael Addition Reaction on Dimethoxycyclohexadienone[a]**
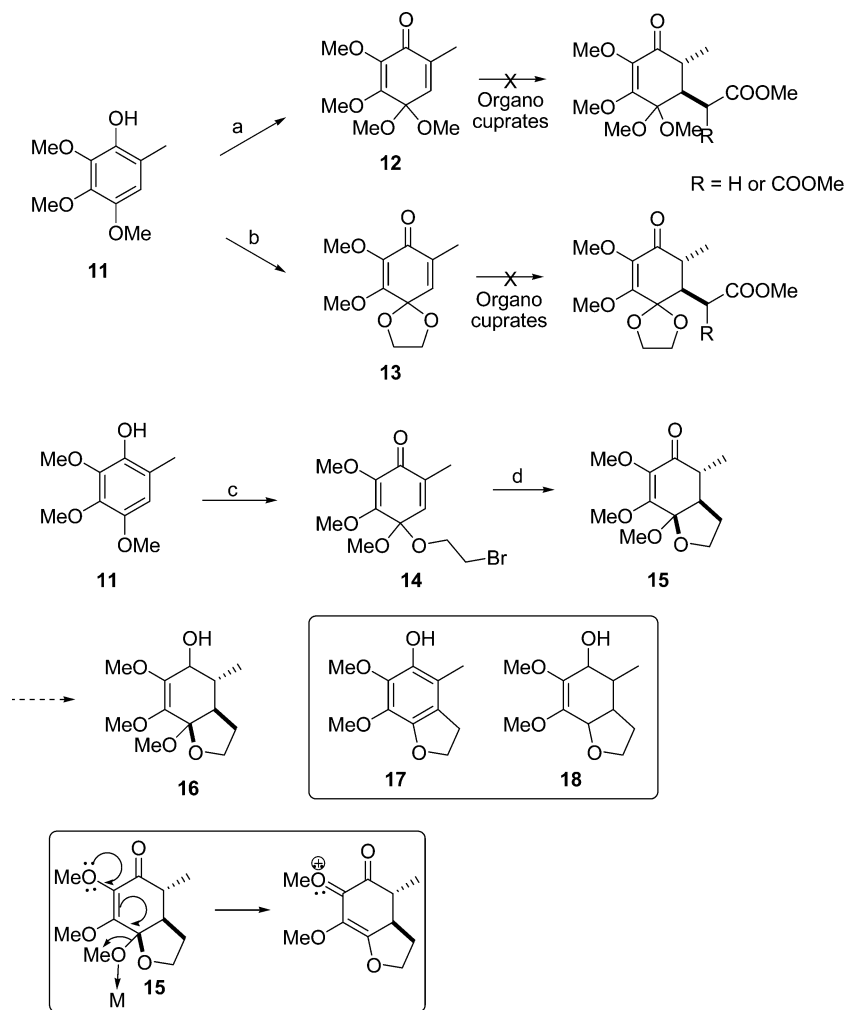
[a]Reagents and conditions: (a) PIDA, MeOH, rt, 80%; (b) PIFA, ethylene glycol, CH$_2$Cl$_2$, rt, 92%; (c) PIDA, 2-bromoethanol, CH$_2$Cl$_2$, rt, 91%; (d) AIBN, Bu$_3$SnH, toluene, 80 °C, 75%.

After synthesis of the required *endo* alcohol, it was protected as MOM ether **24**, and dihydroxylation was investigated next. Cyclohexene **24** was oxidized with a catalytic amount of OsO$_4$ and NMO in acetone−H$_2$O to afford the *cis*-diol **25**. The steric factor of the *endo* OMOM substituent assured *exo* dihydroxylation (dr = 15:1). Methylation was carried out with methyl iodide and silver oxide at 80 °C in a sealed tube to obtain lactone **25** in 78% yield. After the synthesis of most of the core part, the next step was the synthesis of the sesquiterpene side chain. For that, latone **25** was reduced to lactol with DIBAL-H at −78 °C, and the lactol was then condensed with ylide Ph$_3$PC(Me)CO$_2$Et in benzene to yield the desired *trans*-olefin. The subsequent protection of the secondary alcohol as TBS ether afforded **26** in 84% yield (over three steps). Next, the conjugated ethyl ester was reduced to allylic alcohol, and this was followed by bromination under Appel reaction conditions (CBr$_4$/PPh$_3$, DCM, 0 °C) to provide the allylic bromide **27** in 86% yield. The coupling of the allylic bromide **27** with lithioanion derived from geranyl phenyl sulfide[13] **28** provided a coupling product that was subjected to desulfurization using lithium in liq NH$_3$ to afford the required sesquiterpene side chain of the antroquinonol.[14]

After the synthesis of the sesquiterpene side chain, the construction of the enone moiety was the next objective. Deprotection of TBS ether **29** with TBAF in THF followed by the oxidation of the intermediate alcohol with Dess−Martin periodinane in CH$_2$Cl$_2$ afforded cyclohexanone **30** in 87% yield. After the synthesis of the cyclohexanone core, methylation was next investigated. When the carbanion produced from cyclohexanone **30** by LDA or LiHMDS at −78 °C in THF was treated with iodomethane, methylation could not proceed. However, when the temperature was increased the elimination of the β-methoxy group was observed to give cyclohexenone **31** as the major product. Disappointingly, none of the conditions examined for the methylation resulted in any conversion to cyclohexanone **7**. Therefore, we decided to generate the enone system by eliminating the β-methoxy group and then performing methylation. This was achieved by first reacting cyclohexanone **30** with 2 equiv of base at −40 °C and then adding iodomethane to afford the methylated product **32** in 77% yield. Finally, deprotection of MOM was achieved with TFA in DCM to afford (±)-antroquinonol D. Spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS analyses) for the synthetic antroquinonol D (**4**) were in full agreement with those reported for the natural product.

Scheme 3. Synthesis of Lactone[a]

19a R = -CH₂CH₂-
19b R = Me

20a R = -CH₂CH₂-
20b R = Me

21a R = -CH₂CH₂-
21b R = Me

22a
22b

9

23

LiHMDS
MeI

20b

20c

[a]Reagents and conditions: (a) PIDA, MeOH or ethylene glycol, rt; (b) dimethyl malonate, DBU, THF; (c) (i) CeCl₃·7H₂O, NaBH₄, MeOH, 0 °C; (ii) NaH, DMF, rt; (d) DABCO, toluene, H₂O, reflux, 24 h; (e) 1 N HCl, rt, 64% (over two steps); (f) CeCl₃·7H₂O, NaBH₄, MeOH, −20 °C, 94%.

Scheme 4. Synthesis of Antroquinonol D[a]

23

24

25

26

27

29

30

31, R = H
32, R = CH₃

28

4
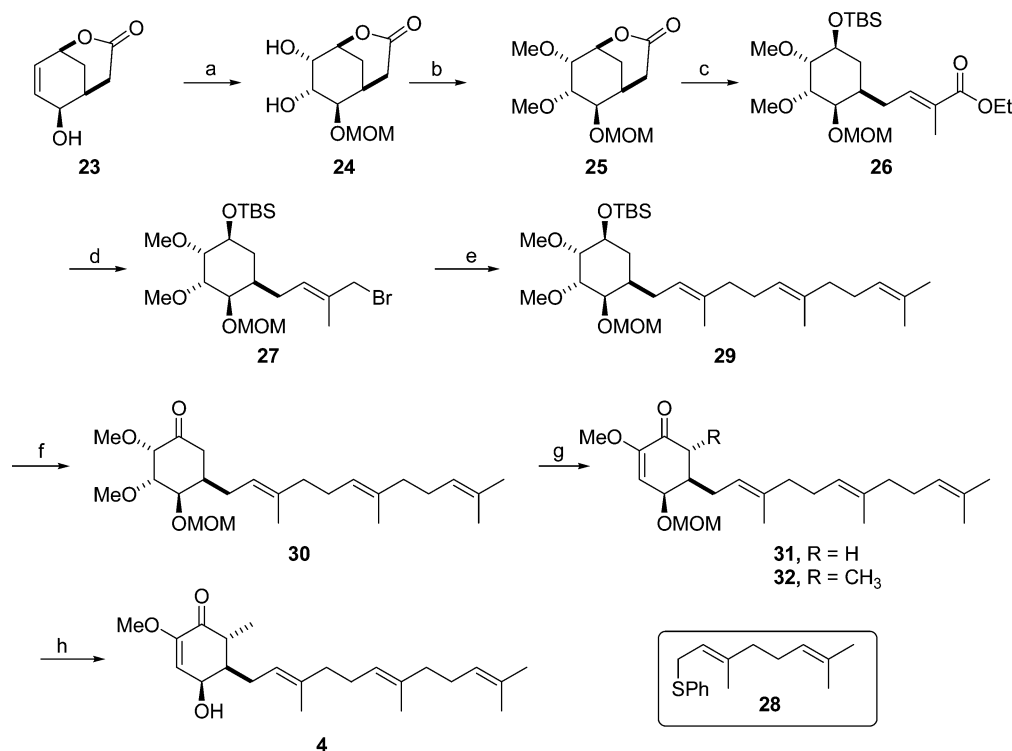
[a]Reagents and conditions: (a) (i) MOM bromide, DIPEA, EDC, 70 °C, 2 h, 87%; (ii) cat. OsO₄, NMO, acetone/water, rt, 24 h, 95%; (b) MeI, Ag₂O, 70 °C, 48 h, 78%; (c) (i) DIBAL-H, CH₂Cl₂, −78 °C, 1 h; (ii) Ph₃PCH(CH₃)COOEt, benzene, reflux, 6 h, (iii) TBSCl, imidazole, DMF, rt, 24 h, 84% (over three steps); (d) (i) DIBAL-H, CH₂Cl₂, −78 °C, 1 h; (ii) CBr₄, Ph₃P, CH₂Cl₂, 0 °C, 10 min, 86% (two steps); (e) (i) **28**, n-BuLi, THF, −78 °C; (ii) Li, liq NH₃, −60 °C, 30 min, 84% (two steps); (f) (i) TBAF, THF, reflux, 24 h, (ii) DMP, CH₂Cl₂, rt, 2 h, 87%; (g) LiHMDS, MeI, THF, −40 °C, 77%; (h) TFA, DCM, rt, 2 h, 64%.

In summary, the first total synthesis of (±)-antroquinonol D was achieved from commercially available 4-methoxyphenol. Synthesis of lactone **9** was the crucial part, which helps realize

the desired stereochemistry at the key stereogenic centers. Other key reactions in the synthesis involved a Michael addition, the diastereoselective reduction of cyclohexenone,

coupling of geranyl phenyl sulfide, and the Bouveault–Blanc reduction for the synthesis of the sesquiterpene side chain. Unfortunately, initial synthetic attempts using the conjugate addition of organocuprate or organozinc reagents to dimethoxycyclohexadienones were unfruitful, and further studies are required to achieve this pivotal addition. The overall approach should be scalable, and the strategy presented here is expected to be useful for the synthesis of structurally similar natural products. Studies on the asymmetric addition of dimethyl malonate or organocopper reagents prepared from ethyl bromoacetate with cyclohexadienone are currently underway and will be reported in due course.

■ EXPERIMENTAL SECTION

General Techniques. All moisture- and air-sensitive reactions were performed in oven- or flame-dried glassware under argon atmosphere with dry, freshly distilled solvents under anhydrous conditions using standard syringe septum techniques. Tetrahydrofuran (THF) was freshly distilled before use from sodium using benzophenone as an indicator. Dichloromethane (CH_2Cl_2) was freshly distilled before use from calcium hydride (CaH_2). All other anhydrous solvents were dried over 3 or 4 Å molecular sieves. NMR spectra were recorded on a 400 MHz spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) as values relative to the internal chloroform 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. The standard abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Coupling constants (J) have been reported in hertz. Infrared (IR) spectra were recorded as neat samples (liquid films on KBr plates). HRMS spectra were recorded with a TOF detector. Hexane refers to the petroleum ether fraction boiling between 60 and 80 °C. Reactions were monitored by thin-layer chromatography (TLC) that was analyzed by fluorescence upon 254 nm irradiation or by staining with p-anisaldeyde/AcOH/H_2SO_4/EtOH, $12MoO_3 \cdot H_3PO_4$/EtOH, or $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$/$H_2SO_4$ and heating the plate at ca. 120 °C. The products were purified by either open chromatography over silica gel (spherical, neutral, 70–230 mesh) or flash chromatography over silica gel (spherical, neutral, 230–400 mesh). All compounds were named according to IUPAC rules. For simplicity, the numbering of the carbon atoms of a given structure does not follow IUPAC rules.

2,3,4-Trimethoxy-6-methylphenol (11). To a stirred solution of 2,3,4-trimethoxy-6-methylbenzaldehyde (4.16 g, 19.77 mmol) in MeOH (150.00 mL) were added $KHSO_4$ (5.40 g, 39.67 mmol) and H_2O_2 (4.00 mL), and stirring was continued for 1 h at rt. After the starting material was consumed, MeOH was removed under reduced pressure and the residue obtained was diluted with water and extracted with EtOAc (2 × 30 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated, and the residue obtained was purified by column chromatography over silica gel (hexanes/EtOAc, 9:1) to give 2,3,4-trimethoxy-6-methylphenol (11) (3.48 g, 17.46 mmol): yield 89%; ^1H NMR (400 MHz, $CDCl_3$) δ 6.43 (s, 1H), 5.44 (s, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 146.0, 141.1, 140.0, 140.0, 117.9, 109.5, 61.2, 61.0, 56.6, 15.5; HRMS-EI (m/z) calcd for $C_{10}H_{14}O_4$ [M]$^+$ 198.0892, found 198.0892.

2,3,4,4-Tetramethoxy-6-methylcyclohexa-2,5-dienone (12). Diacetoxyiodobenzene (0.20 g, 0.65 mmol) was dissolved in dry MeOH (4.00 mL) and cooled to 0 °C. 2,3,4-Trimethoxy-6-methylphenol (0.12 g, 0.59 mmol) was added, and the reaction mixture was slowly warmed to room temperature over 1 h. It was quenched with saturated $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phase was dried over anhydrous sodium sulfate and concentrated to give a residue that was purified by column chromatography over silica gel (hexanes/EtOAc, 4:1) to give 2,3,4,4-tetramethoxy-6-methylcyclohexa-2,5-dienone product 12 (0.11 g, 0.47 mmol): yield 80%; ^1H NMR (400 MHz,

$CDCl_3$) δ 6.27 (s, 1H), 4.17 (s, 3H), 3.75 (s, 3H), 3.30 (s, 6H), 1.94 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 183.8, 155.0, 138.6, 137.2, 135.4, 96.8, 61.2, 60.4, 51.4, 15.4; HRMS-EI (m/z) calcd for $C_{11}H_{16}O_5$ [M]$^+$ 228.0998, found 228.0996.

Cyclohexadienone (13). 2,3,4-Trimethoxy-6-methylphenol (11) (0.37 g, 1.86 mmol) and ethylene glycol (0.15 mL, 2.68 mmol) were dissolved in CH_2Cl_2 (10.00 mL), and the mixture was cooled to 0 °C. PIFA (1.00 g, 2.33 mmol) was added at 0 °C, and the mixture was allowed to reach room temperature and stirred for 2 h. After completion of the reaction, it was quenched with saturated $NaHCO_3$ solution (5 mL) and then extracted with CH_2Cl_2 (10 mL), the organic phase was dried over anhydrous magnesium sulfate and concentrated, and the residue was then purified by column chromatography over silica gel (hexane/EtOAc, 4:1) to give the product 13 (0.39 g, 1.71 mmol): yield 92%; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15–6.15 (d, J = 1.5 Hz, 1H), 4.28–4.24 (m, 2H), 4.14–4.11 (m, 2H), 4.09 (s, 3H), 3.72 (s, 3H), 1.86–1.86 (d, J = 1.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 184.3, 156.9, 136.5, 136.0, 134.2, 101.1, 66.9, 61.0, 60.7, 15.2; HRMS-EI (m/z) calcd for $C_{11}H_{14}O_5$ [M]$^+$ 226.0841, found 226.0845.

4-(2-Bromoethoxy)-2,3,4-trimethoxy-6-methylcyclohexa-2,5-dienone (14). K_2CO_3 (1.30 g, 9.40 mmol) was added into the solution of PIDA (1.84 g, 5.71 mmol) in CH_2Cl_2 (10 mL). 2,3,4-Trimethoxy-6-methylphenol (11) (0.95 g, 4.79 mmol) and 2-bromoethanol (1.33 mL, 18.84 mmol) were dissolved in CH_2Cl_2 (10.00 mL) and then added slowly to the solution at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min. It was quenched with saturated $NaHCO_3$ (5 mL) solution and extracted with ether (2 × 15 mL), the organic phase was dried over anhydrous magnesium sulfate and concentrated, and the residue obtained was purified by column chromatography over silica gel column (hexanes/EtOAc, 4:1) to afford 14 (1.37 g, 4.26 mmol): yield was 91%; IR (KBr) 2950, 2834, 1745, 1657, 1620, 1451, 1368, 1302, 1210, 1167, 1077, 922, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.31–6.30 (d, J = 1.4 Hz, 1H), 4.17 (s, 3H), 3.81–3.78 (t, J = 6.4 Hz, 2H), 3.76 (s, 3H), 3.48–3.44 (td, J_1 = 6.2 Hz, J_2 = 1.0 Hz, 2H), 3.33 (s, 3H), 1.95–1.94 (d, J = 1.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 183.6, 154.8, 138.4, 137.2, 135.2, 96.4, 63.9, 61.2, 60.6, 51.5, 30.0, 15.4; HRMS-EI (m/z) calcd for $C_{12}H_{17}BrO_5$ [M]$^+$ 320.0259, found 320.0263.

6,7,7a-Trimethoxy-4-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one (15).[15] The bromo compound 14 (1.33 g, 4.14 mmol) was dissolved in toluene (90 mL), and the solution was degassed with argon. AIBN (0.41 g, 2.47 mmol) and n-Bu$_3$SnH (1.67 mL, 6.20 mmol) were dissolved in toluene (30.00 mL) and added after 4 h into the reaction mixture at 80 °C. Stirring was continued for 8 h followed by distillation under reduced pressure to remove toluene, the mixture was diluted with water and extracted with EtOAc, and the organic phase was dried over anhydrous magnesium sulfate and concentrated. The residue obtained was then purified by column chromatography over silica gel (hexane/EtOAc, 9:1) to give the product 15 (0.75 g, 3.10 mmol): yield 75%; IR (KBr) 2940, 2835, 1740, 1674, 1615, 1451, 1377, 1319, 1284, 1210, 1135, 1103, 1078, 1040, 992, 955, 939, 901, 852, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 3H), 4.03–3.99 (m, 2H), 3.67 (s, 3H), 3.43 (s, 3H), 2.83–2.74 (m, 2H), 2.11–2.05 (m, 1H), 1.96–1.61 (m, 1H), 1.19–1.17 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 194.9, 157.1, 137.1, 106.5, 67.5, 60.3, 60.2, 50.0, 44.2, 39.3, 28.1, 12.9; HRMS-EI (m/z) calcd for $C_{12}H_{18}O_5$ [M]$^+$ 242.1154, found 242.1155.

6,7-Dimethoxy-4-methyl-2,3-dihydrobenzofuran-5-ol (17). The hexenone 15 (0.04 g, 0.16 mmol) was dissolved in MeOH (5.00 mL) and cooled to −78 °C. $CeCl_3 \cdot 7H_2O$ (0.06 g, 0.16 mmol) and $NaBH_4$ (0.01 g, 0.26 mmol) were added, and the mixture was stirred for 1h. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The mixture was allowed to come to room temperature and extracted with CH_2Cl_2, and the organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue obtained was purified by column chromatography over silica gel (hexane/EtOAc, 4:1) to give the aromatized product 17 (15 mg, 0.07 mmol): yield of 46%; ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 (s,

1H), 4.57−4.53 (t, J = 8.6 Hz, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.10−3.06 (t, J = 8.6 Hz, 2H), 2.12 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 143.7, 140.9, 137.9, 134.9, 122.2, 114.2, 71.4, 61.4, 60.4, 29.3, 12.4; HRMS-EI (m/z) calcd for C$_{11}$H$_{14}$O$_4$ [M]$^+$ 210.0892, found 210.0897.

6,7-Dimethoxy-4-methyl-2,3,3a,4,5,7a-hexahydrobenzofuran-5-ol (18). To a stirred solution of hexenone **15** (0.10 g, 0.41 mmol) in DCM (4 mL) at −78 °C was added DIBAL-H (0.6 mL, 1 M). Stirring was continued for 1 h, the reaction was quenched with MeOH, and the mixture was allowed to come to room temperature. Sodium potassium tartrate solution (5 mL, 1 M) was added and the mixture stirred for 2 h. It was extracted with CH$_2$Cl$_2$ (3 × 5 mL), and the combined organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography over silica gel (hexane/EtOAc, 4:1) to give **18** (0.053 g, 0.25 mmol): yield of 60%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.64−4.62 (d, J = 7.9 Hz, 1H), 4.21−4.20 (d, J = 4.2 Hz, 1H), 3.97−3.92 (m, 1H), 3.76 (s, 3H), 3.74 (s, 1H), 2.49−2.41 (m, 1H), 2.33−2.24 (m, 1H), 2.07−1.99 (m, 1H), 1.96−1.88 (m, 1H), 1.86 (br, 1H), 1.25 (s, 1H), 1.17−1.15 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 141.2, 138.8, 76.0, 70.1, 67.3, 58.9, 57.9, 41.8, 32.7, 27.8, 15.1; HRMS-EI (m/z) calcd for C$_{11}$H$_{18}$O$_4$ [M]$^+$ 214.1205, found 214.1211.

2-(8-Oxo-1,4-dioxaspiro[4.5]dec-9-en-6-yl)malonic Acid Dimethyl Ester (20a). KO^{t}Bu (0.11 g, 1.00 mmol) was added into the solution of DMM (0.11 mL, 1.00 mmol) in THF (10.00 mL). 1,4-Dioxaspiro[4.5]deca-6,9-dien-8-one **19a** (0.12 g, 0.84 mmol) was added and the mixture stirred for 10 min. The reaction mixture was diluted with NH$_4$Cl solution and extracted with ethyl acetate. The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. the residue obtained was purified by column chromatography over silica gel (hexane/EtOAc, 5:1) give the product **20a** (0.12 g, 0.44 mmol): yield 52%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.64−6.62 (d, J = 10.2 Hz, 1H), 6.03−6.00 (d, J = 10.2 Hz, 1H), 4.13−4.08 (m, 2H), 4.04−3.98 (m, 2H), 3.74 (s, 3H), 3.72−3.70 (d, J = 5.4 Hz, 1H), 3.30−3.24 (q, J = 7.4 Hz, 1H), 2.77−2.75 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 197.1, 168.4, 168.2, 145.4, 129.9, 104.9, 65.3, 65.2, 52.8, 52.5, 50.7, 42.4, 38.3; HRMS-EI (m/z) calcd for C$_{13}$H$_{16}$O$_7$ [M]$^+$ 284.0896, found 284.0898.

Dimethyl 2-(2,2-Dimethoxy-5-oxocyclohex-3-enyl)malonate (20b). The diacetoxyiodobenzene (25.95 g, 80.55 mmol) was dissolved in CH$_2$Cl$_2$ (150 mL) and cooled to 0 °C. 4-Methoxyphenol (10.00 g, 80.55 mmol) in MeOH (80 mL) was added slowly, and the mixture was allowed to reach room temperature and then stirred for 2 h. After completion of the reaction, saturated aqueous sodium bicarbonate solution (50 mL) solution was added, and the mixture was extracted with CH$_2$Cl$_2$. The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure and then distilled under high vacuum to remove iodobenzene. The resulting crude product **19b** was dissolved in THF (80 mL), DBU (12.02 mL, 80.55 mmol) and dimethyl malonate (9.25 mL, 80.55 mmol) were added, and the mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated, and the residue obtained was purified with column chromatography over silica gel (hexane/EtOAc, 9:1) to give **20b** (18.90 g, 66.52 mmol): two-step yield 83%; IR (KBr): 3630, 2955, 2839, 1737, 1691, 1629, 1506, 1437, 1380, 1290, 1260, 1228, 1197, 1156, 1110, 1076, 1052, 965, 924, 794 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.75−6.72 (d, J = 10.4 Hz, 1H), 6.02−5.99 (d, J = 10.3 Hz, 1H), 3.64 (s, 3H), 3.61−3.59 (m, 1H), 3.57 (s, 3H), 3.25−3.24 (m, 1H), 3.20 (s, 3H), 3.19 (s, 3H), 2.68−2.63 (dd, J$_1$ = 17.6 Hz, J$_2$ = 4.7 Hz, 1H), 2.57−2.51 (dd, J$_1$ = 17.5 Hz, J$_2$ = 6.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 196.6, 168.6, 168.5, 145.6, 131.8, 98.0, 52.7, 52.3, 50.5, 50.3, 49.5, 40.2, 37.5; HRMS-EI (m/z) calcd for C$_{13}$H$_{18}$O$_7$ [M]$^+$ 286.1053, found 286.1058.

Compound 21a. To a solution of **20a** (0.12 g, 0.44 mmol) and CeCl$_3$·7H$_2$O (0.16 g, 0.44 mmol) in MeOH (5.00 mL) was added NaBH$_4$ (0.02 g, 0.53 mmol) at 0 °C and the mixture stirred for 2 h. After the completion of the reaction it was quenched with a saturated aqueous NaHCO$_3$ solution and extracted with ether. The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated to give the crude residue. The resulting crude

product was dissolved in DMF (2.50 mL), and NaH (0.50 g) was added and heated to 70 °C for 4 h. After completion of the reaction, it was cooled to 0 °C and carefully quenched with a saturated aqueous NH$_4$Cl solution. It was extracted with CH$_2$Cl$_2$ (10 mL), the combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product obtained was purified by column chromatography over silica gel (hexane/EtOAc, 3:2) to give the product **21a** (0.05 g, 0.21 mmol): two-step yield 47%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.21−6.18 (q, J = 4.9 Hz, 1H), 5.75−5.72 (q, J = 1.3 Hz, 1H), 4.82−4.81 (d, J = 2.5 Hz, 1H), 4.07−4.01 (m, 3H), 3.95−3.90 (m, 2H), 3.78 (s, 3H), 2.52−2.52 (d, J = 0.9 Hz, 1H), 2.41−2.29 (m, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 169.9, 166.6, 131.1, 129.8, 105.1, 69.9, 65.3, 65.1, 53.1, 48.8, 38.8, 26.2; HRMS-EI (m/z) calcd for C$_{12}$H$_{14}$O$_6$ [M]$^+$ 254.0790, found 254.0786.

Methyl 6,6-Dimethoxy-3-oxo-2-oxabicyclo[3.3.1]non-7-ene-4-carboxylate (21b). To a stirred solution of **20b** (0.67 g, 2.35 mmol) and CeCl$_3$·7H$_2$O (0.88 g, 2.35 mmol) in MeOH (20 mL) was added NaBH$_4$ (0.09 g, 2.38 mmol) at 0 °C, and stirring was continued. After completion of reaction saturated aqueous NaHCO$_3$ solution (5 mL) was added. Methanol was removed, and the residue obtained was diluted with water and extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting crude product was dissolved in DMF (5 mL), and NaH (0.40 g, 8.3 mmol) was added and stirred for 1 h at 70 °C. After completion of the reaction, the mixture was cooled, quenched with a saturated NH$_4$Cl solution, and extracted with CH$_2$Cl$_2$ (2 × 10 mL), and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a crude product. The residue obtained was purified by column chromatography over silica gel (hexane/EtOAc, 7:3) to afford **21b** (0.60 g, 2.34 mmol): two-step yield of 99%; IR (KBr) 2964, 2836, 2361, 1749, 1730, 1437, 1398, 1345, 1302, 1268, 1240, 1210, 1154, 1114, 1060, 1030, 983, 952 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.11−6.08 (m, 1H), 5.87−5.85 (d, J = 10.1 Hz, 1H), 4.74−4.73 (t, J = 1.0 Hz, 1H), 3.72−3.71 (t, J = 1.0 Hz, 3H), 3.66−3.65 (d, J = 2.2 Hz, 1H), 3.17−3.15 (m, 6H), 2.66 (s, 1H), 2.25−2.24 (d, J = 2.4 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 170.0, 166.9, 130.7, 129.4, 98.0, 70.2, 53.0, 49.5, 48.2, 47.5, 36.6, 25.5; HRMS-EI (m/z) calcd for C$_{12}$H$_{16}$O$_6$ [M]$^+$ 256.0947, found 256.0940.

Compound 22a. To a stirred solution of **21a** (0.05 g, 0.21 mmol) in toluene (2 mL) was added DABCO (0.09 g, 0.83 mmol), and the mixture was heated at reflux for 24 h. The reaction mixture was cooled and washed with 1 N HCl followed by saturated aqueous NaHCO$_3$. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue obtained was purified with column chromatography over silica gel (hexane/EtOAc, 1:1) (50:50) to give the product (0.03 g, 0.16 mmol): yield 79%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.17−6.13 (m, 1H), 5.74−5.72 (m, 1H), 4.75−4.75 (d, J = 1.3 Hz, 1H), 4.03−4.01 (m, 3H), 3.92−3.86 (m, 1H), 2.95−2.90 (m, 1H), 2.78−2.70 (m, 1H), 2.31−2.29 (d, J = 10.7 Hz, 1H), 2.13−2.09 (m, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 170.6, 130.8, 129.4, 106.2, 69.1, 65.2, 64.9, 34.3, 31.3, 27.7; HRMS-EI (m/z) calcd for C$_{10}$H$_{12}$O$_4$ [M]$^+$ 196.0736, found 196.0740.

2-Oxabicyclo[3.3.1]non-7-ene-3,6-dione (9). To a solution of **21b** (1.76 g, 6.90 mmol) in toluene (50 mL) were added DABCO (3.10 g, 27.60 mmol) and H$_2$O (0.10 mL), and then the mixture was heated at reflux for 24 h. The reaction mixture was cooled, acidified with 1 N HCl, and stirred for 30 min. The reaction mixture was diluted with water, the organic layer was separated, the aqueous layer was extracted with EtOAc, and the combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue obtained was purified by column chromatography over silica gel (hexane/EtOAc, 4:1) to give the product **9** (0.68 g, 4.44 mmol): yield 64%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.21−7.17 (q, J = 6.0 Hz, 1H), 6.16−6.14 (d, J = 9.8 Hz, 1H), 5.06−5.05 (t, J = 1.6 Hz, 1H), 3.02−2.96 (m, 2H), 2.73−2.69 (m, 1H), 2.41 (s, 2H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 199.1, 168.0, 144.9, 130.2, 69.1, 40.2, 34.2, 29.7; HRMS-EI (m/z) calcd for C$_8$H$_8$O$_3$ [M]$^+$ 152.0473, found 152.0468.

Dimethyl 2-(2,2-Dimethoxy-6-methyl-5-oxocyclohex-3-enyl)malonate (20c). To a solution of **20b** (0.18 g, 0.62 mmol) in

THF (5 mL) at −78 °C was added LiHMDS (1.70 mL, 1.87 mmol) and the mixture stirred for 1 h. MeI (0.04 mL, 0.68 mmol) was added at −78 °C, and the mixture was allowed to reach room temperature and stirred for 5 h. The reaction was quenched with a saturated NH$_4$Cl solution and extracted with CH$_2$Cl$_2$, and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. Crude product was purified by column chromatography over silica gel to give the product **20c** (0.10 g, 0.33 mmol): yield 52%; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.76−6.73 (d, J = 10.4 Hz, 1H), 6.09−6.07 (d, J = 10.4 Hz, 1H), 3.79−3.78 (d, J = 3.2 Hz, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 3.25 (s, 3H), 3.23 (s, 3H), 3.08−3.07 (d, J = 3.1 Hz, 1H), 3.01−2.97 (t, J = 7.0 Hz, 1H), 1.25−1.23 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 200.2, 169.8, 168.7, 144.4, 131.9, 98.2, 52.8, 52.0, 50.1, 49.6, 49.5, 46.1, 42.1, 15.7; HRMS-EI (m/z) calcd for C$_{14}$H$_{20}$O$_7$ [M]$^+$ 300.1209, found 300.1204.

6-Hydroxy-2-oxabicyclo[3.3.1]non-7-en-3-one (23). To a stirred solution of **9** (0.023 g, 0.15 mmol) and CeCl$_3$·7H$_2$O (0.06 g, 0.15 mmol) in MeOH (5 mL) at −20 °C was added NaBH$_4$ (5.80 mg, 0.15 mmol) and the mixture stirred for 10 min. The reaction mixture was quenched with a saturated aqueous NH$_4$Cl solution and extracted with EtOAc (2 × 5 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated, and the crude product was purified by column chromatography over silica gel (hexane/EtOAc, 4:1) to afford endo alcohol **23** (0.022 g, 0.14 mmol): yield 94%; IR (KBr) 3398, 3038, 2930, 2867, 2361, 1716, 1449, 1374, 1319, 1257, 1208, 1172, 1107, 1066, 1036, 997, 978, 959, 918, 847, 783, 741, 667, 634, 612, 519 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.95−5.92 (m, 1H), 5.83−5.80 (d, J = 9.9 Hz, 1H), 4.68−4.68 (d, J = 2.4 Hz, 1H), 4.42 (s, 1H), 3.64−6.62 (d, J = 10.2 Hz, 1H), 2.94−2.89 (d, J = 19.5 Hz, 1H), 2.56−2.49 (dd, J_1 = 19.5 Hz, J_2 = 8.4 Hz, 1H), 2.45 (br, 1H), 2.16−2.13 (d, J = 14.2 Hz, 1H), 1.92−1.88 (dd, J_1 = 14.0 Hz, J_2 = 0.9 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 173.0, 134.7, 126.5, 69.7, 69.4, 31.1, 28.6, 28.2; HRMS-EI (m/z) calcd for C$_8$H$_{10}$O$_3$ [M]$^+$ 154.0630, found 154.0625.

6-(Methoxymethoxy)-2-oxabicyclo[3.3.1]non-7-en-3-one. To a stirred solution of alcohol **23** (0.884 g, 5.74 mmol) in EDC (10.00 mL) were added DIPEA (2 mL, 11.48 mmol) and MOMBr (1.07 g, 8.61 mmol), and the mixture was heated to 70 °C for 2 h. The reaction mixture was cooled, diluted with CH$_2$Cl$_2$ (10 mL), and washed with 1 N HCl followed by a saturated aqueous NaHCO$_3$ solution. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue obtained was purified with column chromatography over silica gel (hexane/EtOAc, 7:3) to afford 6-(methoxymethoxy)-2-oxabicyclo[3.3.1]non-7-en-3-one (0.99 g, 5.00 mmol): yield 87%; IR (KBr) 2946, 2893, 2826, 2361, 2340, 1731, 1650, 1541, 1472, 1447, 1399, 1369, 1318, 1257, 1214, 1169, 1149, 1104, 1068, 1036, 1016, 996, 963, 917, 856, 776, 743, 668, 650 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.00−5.97 (m, 1H), 5.85−5.82 (d, J = 10.0 Hz, 1H), 4.68 (s, 3H), 4.28 (s, 1H), 3.35 (s, 3H), 2.94−2.87 (m, 1H), 2.62−2.54 (m, 2H), 2.19−2.15 (d, J = 14.0 Hz, 1H), 1.93−1.89 (d, J = 14.0 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 171.6, 132.8, 127.2, 95.7, 75.4, 69.3, 55.7, 29.3, 29.0, 28.3; HRMS-EI (m/z) calcd for C$_{10}$H$_{14}$O$_4$ [M]$^+$ 198.0892, found 198.0899.

7,8-Dihydroxy-6-(methoxymethoxy)-2-oxabicyclo[3.3.1]-nonan-3-one (24). To a solution of 6-(methoxymethoxy)-2-oxabicyclo[3.3.1]non-7-en-3-one (0.99 g, 4.98 mmol) in acetone/H$_2$O (33 mL, 10:1) were added OsO$_4$ (0.12 g, 0.49 mmol) and NMO (0.58 g, 5.00 mmol) at room temperature, and stirring was continued for 24 h. The reaction mixture was quenched with 10% Na$_2$S$_2$O$_3$· 5H$_2$O, stirred for 30 min, and then extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. Crude product was then purified by column chromatography over silica gel (MeOH/EtOAc, 1:9) to give the diol product **24** (1.09 g, 4.72 mmol, dr> 15:1): yield 95%; IR (KBr) 3901, 3747, 3675, 3615, 3421, 2940, 2904, 2829, 1724, 1649, 1541, 1517, 1455, 1419, 1378, 1339, 1251, 1212, 1095, 1035, 919, 618 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.71−4.67 (q, J = 7.0 Hz, 2H), 4.61 (s, 1H), 4.18−4.16 (d, J = 9.9 Hz, 1H), 3.68−3.64 (dd, J_1 = 5.6 Hz, J_2 = 4.2 Hz, 1H), 3.57−3.55 (m, 2H), 3.37 (s, 3H), 2.92−2.87 (d, J = 18.9 Hz, 1H), 2.52−2.45 (dd, J_1 = 19.1 Hz, J_2 = 7.4 Hz, 1H), 2.40 (s,

1H), 2.18−2.15 (d, J = 14.2 Hz, 1H), 1.90−1.86 (d, J = 14.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 170.4, 97.2, 80.6, 76.8, 70.1, 68.3, 55.9, 30.9, 30.7, 23.5; HRMS-EI (m/z) calcd for C$_{10}$H$_{16}$O$_6$ [M]$^+$ 232.0947, found 232.0940.

7,8-Dimethoxy-6-(methoxymethoxy)-2-oxabicyclo[3.3.1]-nonan-3-one (25). To the solution of diol **24** (0.5 g, 2.15 mmol) in MeI (5.00 mL) was added Ag$_2$O (1.5 g, 6.45 mmol) in a sealed tube. The reaction mixture was stirred for 48 h at 70 °C, and then it was cooled and filtered through Celite, washed with EtOAc, and concentrated under reduced pressure. The crude product was then purified with column chromatography over silica gel (hexane/EtOAc, 7:3) to give product **25** (437 mg, 1.68 mmol): yield 78%; IR (KBr) 2935, 2828, 1738, 1650, 1541, 1452, 1378, 1291, 1248, 1206, 1125, 1106, 1078, 1039, 916, 765, 692, 646, 608, cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.78−4.76 (d, J = 6.8 Hz, 1H), 4.68−4.65 (d, J = 6.7 Hz, 2H), 3.87−3.82 (m, 2H), 3.47 (s, 3H), 3.45 (s, 3H), 3.35 (s, 3H), 3.23−3.20 (dd, J_1 = 10.1 Hz, J_2 = 3.6 Hz, 1H), 3.02−2.97 (dd, J_1 = 18.9 Hz, J_2 = 1.8 Hz, 1H), 2.54−2.47 (dd, J_1 = 19.0 Hz, J_2 = 7.3 Hz, 1H), 2.41 (s, 1H), 2.12−2.09 (d, J = 14.3 Hz, 1H), 1.89−1.85 (d, J = 14.4 Hz, 1H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 170.0, 96.9, 78.2, 77.2, 76.9, 74.8, 59.5, 58.5, 55.6, 30.9, 30.8, 23.7. HRMS-EI (m/z) calcd for C$_{12}$H$_{20}$O$_6$ [M]$^+$ 260.1260, found 260.1263.

(E)-Ethyl 4-(5-(tert-Butyldimethylsilyloxy)-3,4-dimethoxy-2-(methoxymethoxy)cyclohexyl)-2-methylbut-2-enoate (26). Lactone **25** (0.35 g, 1.35 mmol) was dissolved in CH$_2$Cl$_2$ (5 mL) and cooled to −78 °C under argon atmosphere. DIBAL-H (1.1 M solution in cyclohexane) (1.35 mL, 1.48 mmol) was added and the mixture stirred for 1 h at −78 °C. The reaction was quenched with MeOH and warmed to room temperature. Sodium potassium tartrate solution (5 mL, 1 M) was added and the mixture stirred for 2 h. The mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL), and the combined organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The resulting crude product was then dissolved in benzene (10 mL), ylide Ph$_3$PCH(CH$_3$)COOEt was added at 80 °C, and then the mixture was stirred at reflux for 6 h. After the reaction mixture was cooled, the solvent was concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel (hexane/EtOAc, 4:1) to give the (E)-ethyl 4-(5-hydroxy-3,4-dimethoxy-2-(methoxymethoxy)cyclohexyl)-2-methylbut-2-enoate (400 mg, 1.16 mmol), yield 86%. To the solution of (E)-ethyl 4-(5-(tert-butyldimethylsilyloxy)-3,4-dimethoxy-2-(methoxymethoxy)-cyclohexyl)-2-methylbut-2-enoate (0.40 g, 1.16 mmol) in DMF (5 mL) were added TBSCl (0.23 g, 1.50 mmol), imidazole (0.16 g, 2.31 mmol), and DMAP (1.7 mg, 0.01 mmol). The reaction mixture was stirred for 24 h at room temperature, quenched with saturated aqueous NaHCO$_3$, and extracted with ether (3 × 10 mL), and the combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with column chromatography over silica gel (hexane/EtOAc, 9:1) to furnish **26** (0.51 g, 1.11 mmol): yield of 96%; IR (KBr) 2932, 2897, 2824, 2362, 1713, 1650, 1462, 1198, 1175, 1128, 1039, 1007, 991, 935, 919, 836, 777, 747, 670 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.77−6.74 (t, J = 7.0 Hz, 1H), 4.69−4.67 (d, J = 6.9 Hz, 1H), 4.62−4.60 (d, J = 6.9 Hz, 1H), 4.21−4.16 (q, J = 7.1 Hz, 2H), 3.87−3.81 (m, 1H), 3.76−3.75 (t, J = 3.4 Hz, 1H), 3.68 (s, 1H), 3.46 (s, 3H), 3.43 (s, 3H), 3.41 (s, 3H), 3.24−3.21 (dd, J_1 = 9.1 Hz, J_2 = 2.8 Hz, 1H), 2.28−2.23 (m, 1H), 2.19−2.11 (m, 1H), 2.01−1.95 (m, 1H), 1.83 (s, 3H), 1.65−1.58 (m, 1H), 1.48−1.39 (m, 1H), 1.30−1.27 (t, J = 7.1 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 168.1, 140.3, 128.8, 97.7, 83.7, 78.6, 77.2, 70.1, 60.5, 58.9, 58.7, 55.9, 35.2, 32.2, 30.6, 25.9, 18.1, 14.3, 12.6, −4.5, −4.7; HRMS-EI (m/z) calcd for C$_{23}$H$_{44}$O$_7$Si [M]$^+$ 460.2856, found 460.2859.

(E)-(5-(4-Bromo-3-methylbut-2-enyl)-2,3-dimethoxy-4-(methoxymethoxy)cyclohexyloxy)(tert-butyl)dimethylsilane (27). To a stirred solution of ester compound **26** (436 mg, 0.95 mmol) in CH$_2$Cl$_2$ (10 mL) was added DIBAL-H (2.15 mL, 2.37 mmol) at −78 °C. After completion of the reaction, MeOH was added to terminate the reaction, 1.2 M sodium potassium tartrate (5 mL) was added, and the solution was allowed to reach room temperature. It was extracted with CH$_2$Cl$_2$ (2 × 10 mL), the combined organic phase was

dried over anhydrous sodium sulfate and concentrated, then it was purified by column chromatography over silica gel (hexane/EtOAc, 4:1) to give the alcohol compound (346 mg, 0.83 mmol): yield 87%; IR (KBr) 3447, 2931, 2824, 1472, 1462, 1389, 1374, 1253, 1192, 1151, 1099, 1039, 934, 919, 876, 777, cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.42−5.39 (t, J = 7.0 Hz, 1H), 4.68−4.66 (d, J = 6.9 Hz, 1H), 4.62−4.60 (d, J = 6.9 Hz, 1H), 4.01 (s, 2H), 3.85−3.79 (m, 1H), 3.74−3.73 (t, J = 3.4 Hz, 1H), 3.70 (s, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 3.41 (s, 3H), 3.24−3.21 (dd, J_1 = 9.2 Hz, J_2 = 2.9 Hz, 1H), 2.16−2.08 (m, 1H), 2.04−1.97 (m, 1H), 1.86−1.82 (m, 1H), 1.66 (s, 3H), 1.64−1.35 (m, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s,3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 136.0, 124.4, 97.7, 83.83, 78.7, 77.2, 70.3, 69.0, 58.8, 58.8, 55.9, 35.2, 34.6, 39.4, 25.9, 18.1, 13.9, −4.5, −4.7; HRMS-EI (m/z) calcd for C$_{21}$H$_{42}$O$_6$Si [M]$^+$ 418.2751, found 418.2759.

To the solution of above alcohol (346 mg, 0.83 mmol) in CH$_2$Cl$_2$ (8 mL) were added PPh$_3$ (0.24 g, 0.90 mmol) and CBr$_4$ (0.30 g, 0.90 mmol) successively at 0 °C, and stirring was continued for 10 min. It was quenched with saturated aqueous NaHCO$_3$ solution, and the organic layer was separated. The solvent was concentrated under reduced pressure and then purified by column chromatography over silica gel (hexane/EtOAc, 9:1) to give bromo compound 27 (381 mg, 0.80 mmol): yield 96%; IR (KBr) 2931, 2823, 1700, 1650, 1541, 1521, 1393, 1253, 1208, 1152, 1129, 1100, 1039, 1007, 919, 879, 777 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.62−5.58 (t, J = 6.8 Hz, 1H), 4.69−4.67 (d, J = 6.9 Hz, 1H), 4.63−4.61 (d, J = 7.0 Hz, 1H), 3.97 (s, 2H), 3.85−3.79 (m, 1H), 3.75 (s, 1H), 3.67 (s, 1H), 3.46 (s, 3H), 3.42, (s, 3H), 3.41 (s, 3H), 3.23−3.20 (dd, J_1 = 9.1 Hz, J_2 = 2.7 Hz, 1H), 2.12−1.97 (m, 2H), 1.87−1.85 (m, 1H), 1.76 (s, 3H), 1.62−1.56 (m, 1H), 1.43−1.34 (m, 1H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 133.4, 129.8, 97.8, 83.9, 78.8, 77.2, 70.4, 59.0, 58.9, 56.0, 41.6, 35.2, 34.6, 30.2, 26.0, 18.3, 15.0, −4.4, −4.6.

tert-Butyl(2,3-dimethoxy-4-(methoxymethoxy)-5-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)cyclohexyloxy)dimethylsilane (29). To a stirred solution of sulfide 28 (28.0 mg, 0.12 mmol) in THF (5.00 mL) at −78 °C was added n-BuLi (0.06 mL, 0.13 mmol), and the mixture was stirred for 1 h at the same temperature. Then the solution of allyl bromide 27 (41.8 mg, 0.09 mmol) in THF (1 mL) was added, and stirring was continued for 1 h. It was quenched with a saturated aqueous NH$_4$Cl solution and allowed to reach room temperature. It was extracted with ether (2 × 10 mL), the organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated, and the residue obtained was used as is for the next step.

Li (0.7 mg, 1 mmol) was added to the liq NH$_3$ at −78 °C, which gave dark blue color to the solution. Then the above coupled product in ether (2 mL) was added and the mixture stirred for 30 min at −60 °C. It was quenched with MeOH and slowly warmed to room temperature during which time ammonia evaporated. It was diluted with a saturated NH$_4$Cl solution and extracted with ether (2 × 10 mL), the organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated, and then the obtained residue was purified by chromatography over silica gel (hexane/EtOAc, 15:1) to give the product 29 (41.2 mg, 0.08 mmol): yield 84%; IR (KBr) 2930, 1650, 1540, 1524, 1390, 1254, 1140, 1103, 1008 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.29−5.28 (d, J = 3.3 Hz, 1H), 5.11−5.09 (d, J = 6.5 Hz, 3H), 4.67−4.60 (dd, J_1 = 21.8 Hz, J_2 = 6.8 Hz, 2H), 3.83−3.79 (m, 1H), 3.73−3.71 (d, J = 9.7 Hz, 2H), 3.47 (s, 3H), 3.41 (s, 3H), 3.40 (s, 3H), 3.24−3.22 (d, J = 7.4 Hz, 1H), 2.06−1.97 (m, 12H), 1.68 (s, 6H), 1.43−1.36 (m, 4H), 1.25 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 136.4, 135.1, 131.3, 124.4, 124.2, 122.7, 97.7, 83.9, 78.9, 70.45, 58.8, 58.6, 55.8, 40.0, 39.9, 39.7, 35.2, 34.8, 29.7, 26.9, 26.8, 25.9, 25.7, 18.1, 17.7, 16.2, 16.0, −4.5, −4.7; HRMS-EI (m/z) calcd for C$_{31}$H$_{58}$O$_5$Si [M]$^+$ 538.4054, found 538.4058.

2,3-Dimethoxy-4-(methoxymethoxy)-5-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)cyclohexanone (30). TBAF (0.15 mL, 0.15 mmol) was added to the solution of 21 (41.2 mg, 0.077 mmol) in THF (3 mL), and the mixture was stirred for 24 h at reflux. After the reaction mixture was cooled to room temperature, the solvent was concentrated under reduced pressure and then purified by

column chromatography over silica gel (hexane/EtOAc, 3:2) to give the alcohol compound. To a solution of this alcohol in CH$_2$Cl$_2$ (5 mL) was added Dess−Martin periodinane (0.045 g, 0.10 mmol), and stirring was continued at rt for 2 h. The reaction mixture was then diluted with CH$_2$Cl$_2$, quenched with a saturated aqueous solution of sodium bicarbonate, and washed with brine. Usual workup and flash column chromatography (hexane/EtOAc, 9:1) afforded keto compound 30 (28 mg, 0.066 mmol) in 87% over two steps: IR (KBr) 2924, 2854, 1716, 1456, 1383, 1254, 1145, 1008 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.11−5.07 (m, 3H), 4.79−4.77 (d, J = 6.8 Hz, 1H), 4.73−4.71 (d, J = 6.8 Hz, 1H), 4.22−4.21 (d, J = 3.0 Hz, 1H), 4.06−4.05 (d, J = 3.6 Hz, 1H), 3.88 (m, 1H), 3.49 (s, 3H), 3.45 (s, 3H), 3.44 (s, 3H), 2.64 (m, 1H), 2.33−1.95 (m, 12H), 1.67 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 206.8, 137.3, 135.2, 131.2, 124.3, 124.0, 121.5, 97.9, 84.0, 82.9, 76.8, 59.2, 58.6, 56.1, 41.9, 39.7, 39.7, 38.3, 26.7, 26.6, 25.9, 25.7, 22.7, 17.6, 16.0; HRMS-EI (m/z) calcd for C$_{25}$H$_{42}$O$_5$ [M]$^+$ 422.3032, found 422.3034.

2-Methoxy-4-(methoxymethoxy)-5-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)cyclohex-2-enone (31). To a solution of cyclohexanone 30 (30 mg, 0.071 mmol) in THF (1 mL) at −78 °C was added LiHMDS (1 M solution in THF) (75 μL, 0.075 mmol) and the stirred for 30 min at −78 °C. Methyl iodide (11 μL, 0.075 mmol) was added, the mixture was stirred for 1 h at the same temperature, and then the temperature was increased to 0 °C. The reaction was quenched with NH$_4$Cl solution and extracted with ether (2 × 5 mL), the organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated, and then the crude product was purified by column chromatography over silica gel (hexane/EtOAc, 9:1) to give the product 31 (22 mg, 0.057 mmol): yield 82%; R_f (hexane/EtOAc, 4:1) 0.53; IR (film) 2927, 1680, 1460, 1360, 1245, 1148, 981 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.92 (d, J = 5.7 Hz, 1H), 5.10 (m, 3H), 4.74 (d, J = 6.8 Hz, 1H), 4.68 (d, J = 6.8 Hz, 1H), 4.28 (m, 1H), 3.63 (s, 3H), 3.37 (s, 3H), 2.69 (m, 2H), 2.30−1.92 (m, 9H), 1.65 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 196.3, 151.5, 137.3, 135.3, 131.2, 124.3, 124.0, 121.5, 113.3, 96.5, 70.5, 55.5, 54.8, 44.6, 41.1, 39.7, 39.7, 27.0, 26.7, 26.5, 25.7, 17.7, 16.9, 16.8; HRMS-EI (m/z) calcd for C$_{24}$H$_{38}$O$_4$ [M]$^+$ 390.2770, found 390.2764.

2-Methoxy-4-(methoxymethoxy)-6-methyl-5-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)cyclohex-2-enone (32). To a solution of cyclohexanone 30 (25 mg, 0.059 mmol) in THF (1 mL) at −40 °C was added LiHMDS (1 M solution in THF) (0.148 mL, 0.15 mmol) and the mixture stirred for 30 min at −40 °C. The reaction mixture was cooled to −78 °C, methyl iodide (9 μL, 0.065 mmol) was added, and then the temperature was increased to 0 °C and the mixture stirred for 1 h. The reaction was quenched with NH$_4$Cl solution and extracted with ether (2 × 5 mL), the organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated, and then the crude product was purified by column chromatography over silica gel (hexane/EtOAc, 9:1) to give the product 32 (18.4 mg, 0.045 mmol): yield 77%; R_f (hexane/EtOAc, 4:1) 0.53; IR (film) 2921, 2851, 1682, 1640, 1456, 1365, 1148, 976 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.87 (d, J = 5.5 Hz, 1H), 5.10 (m, 3H), 4.72 (d, J = 6.8 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.33 (m, 1H), 3.62 (s, 3H), 3.36 (s, 3H), 2.75 (m, 1H), 2.30−1.92 (m, 9H), 1.67 (s, 3H), 1.56 (s, 6H), 1.52 (s, 3H), 1.16 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 196.5, 151.4, 137.4, 135.2, 131.3, 124.3, 124.0, 121.7, 113.4, 96.4, 71.0, 55.5, 54.9, 45.7, 42.8, 39.8, 39.7, 27.1, 26.8, 26.5, 25.7, 17.7, 16.2, 16.0, 12.9; HRMS-EI (m/z) calcd for C$_{25}$H$_{40}$O$_4$ [M]$^+$ 404.2927, found 404.2924.

4-Hydroxy-2-methoxy-6-methyl-5-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)cyclohex-2-enone (4). To MOM compound 32 (10 mg, 0.024 mmol) was added 40% trifluoroacetic acid in CH$_2$Cl$_2$ (1 mL) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was concentrated and the residue obtained was purified by column chromatography over silica gel (hexane/EtOAc, 4:1) to give the product 4 (5.7 mg, 0.016 mmol): yield 64%; R_f (hexane/EtOAc, 7:3) 0.4; IR (film) 2920, 2851, 1685, 1637, 1442, 1376, 1247, 1148, 1080 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 5.92 (d, J = 5.6 Hz, 1H), 5.22 (t, J = 7.3 Hz, 1H), 5.10 (m, 2H), 4.49 (dd, J_1

= 5.2 Hz, J_2 = 3.8 Hz, 1H), 3.61 (s, 3H), 2.68 (m, 1H), 2.27−1.97 (m, 10H), 1.80 (m, 1H), 1.67 (s, 3H), 1.63 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.16 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, CD$_3$OD) δ 198.8, 152.1, 138.1, 136.0, 132.1, 125.4, 125.36, 123.30, 116.7, 65.1, 55.3, 47.5, 43.4, 40.94, 40.87, 28.1, 27.8, 27.4, 25.9, 17.8, 16.2, 16.1, 13.1; HRMS-EI (m/z) calcd for C$_{23}$H$_{36}$O$_3$ [M]$^+$ 360.2664, found 360.2668.

■ ASSOCIATED CONTENT

ⓈSupporting Information

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

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Notes

The authors declare no competing financial interest.

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