Total Synthesis of (+)-Antroquinonol D

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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 GI50 = 8.01, 3.57, and 25.08 μM, respectively.7

RESULTS AND DISCUSSION

Antroquinonol and antroquinonol D share a common sesquiterpene side chain and differ only with regard to substitution at C1 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 cyclohexanone 9 could provide the cis geometry between C4 and C5. 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 cyclohexadienones 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.8 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...
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 15 under Luche conditions could provide allylic alcohol, which could be converted to the required lactone. The reduction of cyclohexenone 15 under Luche conditions 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 = −CH₂CH₂−) 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 (CeCl₃) 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 NaBH₄ 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.
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, lactone \(25\) was reduced to lactol with DIBAL-H at −78°C, and the lactol was then condensed with ylide \(\text{Ph}_3\text{PC(Me)CO}_2\text{Et}\) 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.

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**Scheme 2. Attempted Michael Addition Reaction on Dimethoxycyclohexadienone**

- 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%.

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In summary, the first total synthesis of \((\pm)-\)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 dimethoxy-cyclohexadienones were unfurthilt, 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 organocuprate reagents prepared from ethyl bromoacetate with cyclohexadiene 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 (CH₂Cl₂) was freshly distilled, and the mixture was cooled to 0 °C. The products were purified by column chromatography over silica gel (hexanes/EtOAc, 9:1) to give 2,3,4-trimethoxy-6-methylphenol (0.12 g, 6.27 mmol) in 80% yield; 1H NMR (400 MHz, CDCl₃) δ 6.27 (s, 1H), 4.17 (s, 3H), 3.75 (s, 3H), 3.30 (s, 6H), 1.94 (s, 3H); 13C NMR (100.6 MHz, CDCl₃) δ 183.8, 155.0, 138.6, 137.2, 135.4, 96.8, 61.2, 60.4, 51.4, 15.4; HRMS-ESI (m/z) calcd for C₁₀H₁₄O₄ [M⁺] + 228.0998, found 228.0996.

### Cyclohexadiene (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 CH₂Cl₂ (10.00 mL), and the mixture was cooled to 0 °C. PIFA (1.0 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 NaHCO₃ solution (5 mL) and then extracted with CH₂Cl₂ (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, CDCl₃) 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); 13C NMR (100.6 MHz, CDCl₃) δ 184.3, 156.9, 136.0, 134.2, 101.1, 66.9, 61.0, 60.7, 15.2; HRMS-ESI (m/z) calcd for C₁₁H₁₄O₅ [M⁺] + 226.0841, found 226.0845.

### 4-(2-Bromoethoxy)-2,3,4-trimethoxy-6-methylcyclohexa-2,5-diene (14).
K₂CO₃ (1.30 g, 9.40 mmol) was added into the solution of PIDA (1.84 g, 5.71 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (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 NaHCO₃ (5 mL) and then 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, 2.42 mmol): yield was 91%; IR (KBr) 2940, 2835, 1740, 1674, 1615, 1451, 1377, 1319, 1284, 1210, 1135, 1103, 1078, 955, 939, 901, 852, 779 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.51 (d, J = 6.2 Hz, 1H), 4.12 (s, 3H), 3.70–3.65 (m, 2H), 3.55 (s, 3H); 13C NMR (100.6 MHz, CDCl₃) δ 136.3, 154.8, 138.4, 137.2, 135.2, 96.4, 63.9, 61.0, 60.6, 51.5, 30.0, 15.4; HRMS-ESI (m/z) calcd for C₁₂H₁₈O₅ [M⁺] + 242.1155, found 242.1154.

### 4,7-dimethoxy-6-methylcyclohexa-2,5-diene (15).
The bromo compound 14 (1.33 g, 4.14 mmol) was dissolved in toluene (90 mL), and the solution was degassed with argon. ABIN (0.41 g, 2.47 mmol) and n-BuSnH (1.67 mL, 6.27 mmol) were dissolved in toluene (30 mL) and then added over 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, 1:1) to give the product 15 (0.75 g, 3.10 mmol): yield 75%; IR (KBr) 2940, 2835, 1740, 1615, 1615, 1451, 1377, 1319, 1284, 1210, 1135, 1078, 1040, 992, 955, 939, 901, 852, 779 cm⁻¹; 1H NMR (400 MHz, CDCl₃) 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), 2.11–2.03 (m, 3H), 1.96–1.61 (m, 1H), 1.19–1.17 (d, J = 6.6 Hz, 3H); 13C NMR (100.6 MHz, CDCl₃) 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-ESI (m/z) calcd for C₁₀H₁₄O₅ [M⁺] + 214.1154, found 214.1155.

### 6,7-Dimethoxy-4-methyl-2,3,4-tetrahydrobenzofuran-5(7H)-one (16).
The hexone 15 (0.04 g, 0.16 mmol) was dissolved in MeOH (5.00 mL) and cooled to −78 °C. CeCl₃·7H₂O (0.06 g, 0.16 mmol) and NaBH₄ (0.01 g, 0.26 mmol) were added, and the mixture was stirred for 1 h. The reaction was quenched with a saturated aqueous NaOH solution. The mixture was allowed to come to room temperature and extracted with CH₂Cl₂ (10 mL), 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, 1:1) to give the chromatized product 17 (15 mg, 0.07 mmol): yield of 46%; 1H NMR (400 MHz, CDCl₃) δ 5.38, (s,
To a solution of 

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\text{DBU (0.05 g, 0.21 mmol): two-step yield 47%; \text{1H NMR (400 MHz, CDCl}_3) \delta 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, 1H), 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); \text{11C NMR (100.6 MHz, CDCl}_3) \delta 170.0, 166.9, 130.8, 129.4, 106.2, 69.1, 65.2, 64.9, 34.3, 31.7, 27.7; \text{HRMS-EI (m/z) calc for C}_{15}H_{19}O_{4} \text{N}^+ \text{calcd for } M^+ 256.0947, \text{found } 256.0940.\]

**2-Oxacyclo[3.3.1]non-3-ene-3-carboxylic acid (21b).** To a stirred solution of 20b (0.07 g, 0.35 mmol) and CeCl\textsubscript{3}·7H\textsubscript{2}O (0.08 g, 2.35 mmol) in MeOH (20 mL) was added NaBH\textsubscript{4} (0.09 g, 2.38 mmol) at 0 °C, and stirring was continued. After completion of reaction saturated aqueous NaHCO\textsubscript{3} solution (5 mL) was added. Methanol was removed, and the residue was diluted with water and extracted with CH\textsubscript{2}Cl\textsubscript{2} (2×10 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was obtained by column chromatography over silica gel (hexane/EtOAc, 7:3) to afford 21b (0.60 g, 2.34 mmol): two-step yield of 99%; \text{IR (KBr):} 2964, 2836, 1730, 1397, 1398, 1368, 1345, 1302, 1268, 1240, 1210, 1154, 1114, 1060, 1030, 983, 952 cm\textsuperscript{-1}; \text{1H NMR (400 MHz, CDCl}_3) \delta 6.11-6.08 (m, 1H), 5.87-5.85 (d, J = 10.1 Hz, 1H), 4.74-4.73 (t, J = 10.1 Hz, 1H), 3.72-3.71 (t, J = 10.0 Hz, 3H), 3.66-3.65 (d, J = 2.2 Hz, 1H), 3.17-3.15 (m, 4H), 2.66 (s, 1H), 2.25-2.24 (d, J = 2.4 Hz, 2H); \text{13C NMR (100.6 MHz, CDCl}_3) \delta 170.0, 166.9, 130.7, 129.4, 98.0, 70.2, 53.0, 49.5, 48.2, 47.5, 36.6, 25.5; \text{HRMS-EI (m/z) calc for C}_{15}H_{19}O_{4} \text{N}^+ \text{calcd for } M^+ 256.0947, \text{found } 256.0940.\]
6-Hydroxy-2-oxabicyclo[3.3.1]non-7-en-3-one (23). To a stirred solution of diol 24 (0.5 g, 2.15 mmol) in Me3SiO (10 mL) was added Ag2O (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 Et2O, and concentrated under reduced pressure. The crude product was then purified with column chromatography over silica gel (hexane/Et2O, 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, 1070, 1035, 976, 669, 646, 608, cm−1; 1H NMR (400 MHz, CDCl3) 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, J1 = 10.1 Hz, J2 = 3.6 Hz, 1H), 3.02–2.97 (dd, J1 = 18.9 Hz, J2 = 1.8 Hz, 1H), 2.54–2.47 (dd, J1 = 19.0 Hz, J2 = 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); 13C NMR (100.6 MHz, CDCl3) 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-ESI (m/z) calcd for C14H14O3M [M]+ 260.1260, found 260.1263.

(E)-4-(5-(tert-Butyldimethylsiloxy)-3,4-dimethoxy-2-(methoxymethoxy)cyclohexyl)-2-methylbut-2-enoate (26). Lactone 25 (0.35 g, 1.33 mmol) was dissolved in CH2Cl2 (5 mL) and cooled to −78 °C under an atmosphere of DIBA, 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 mixture was cooled 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 CH2Cl2 (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 benzeno (10 mL), ylide Ph2PC(CH2)3COEt was added at 80 °C, and then the mixture was stirred at reflux for 6 h. After the reaction mixture was cooled, the solution 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-butyldimethylsiloxy)-3,4-dimethoxy-2-(methoxymethoxy)cyclohexyl)-2-methylbut-2-enoate (0.40 g, 1.16 mmol) in DMF (5 mL) were added TBSCI (0.23 g, 1.50 mmol), imidazole (0.16 g, 2.51 mmol), and DMAP (1.7 mg, 0.01 mmol). The reaction mixture was stirred for 24 h at room temperature, quenched with saturated aqueous NaHCO3, and extracted with ether (3 × 10 mL), and the combined organic phase was dried over anhydrous sodium sulfate, and concentrated. The resulting crude product was then saturated with hexane/EtOAc, 9:1 to furnish 26 (0.51 g, 1.11 mmol; yield 96%); IR (KBr) 2932, 2979, 2824, 2362, 1713, 1650, 1462, 1198, 1175, 1128, 1039, 1007, 991, 935, 919, 836, 777, 747, 670 cm−1; 1H NMR (400 MHz, CDCl3) 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, J1 = 9.1 Hz, J2 = 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, 1H), 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); 13C NMR (100.6 MHz, CDCl3) 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-ESI (m/z) calcd for C22H30O5Si [M]+ 460.2856, found 460.2859.

(E)-4-(3-Bromo-3-methylbut-2-enyl)-2,3-dimethoxy-4-(methoxymethoxy)cyclohexyl)[(tert-butyldimethylsilyl)acetate (27). To a solution of ester compound 26 (1.46 mg, 0.95 mmol) in CH2Cl2 (10 mL) was added DIBA, 1.1 M solution in cyclohexane (1.35 mL, 1.48 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 CH2Cl2 (2 × 10 mL), the combined organic phase was
4.60 (d, 3H), 3.41 (s, 3H), 3.23 (m, 1H), 2.9-2.8 (m, 1H), 2.16-2.08 (m, 1H), 1.97-1.86 (m, 1H), 1.86-1.68 (m, 1H), 1.68-1.15 (m, 1H), 0.88 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H);13C NMR (100.6 MHz, CDCl3) δ 136.0, 124.4, 97.7, 83.8, 78.7, 77.2, 70.3, 69.0, 58.8, 58.8, 55.9, 53.2, 34.6, 39.4, 25.9, 18.1, 13.9, −4.5, −4.7; HRMS-EI (m/z) calc for C21H30O6Si [M]+ 418.2751, found 418.2759.

dimethylsilane (29). by chromatography over silica gel (hexane/EtOAc, 9:1) to give 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 29 (28 mg, 0.09 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 NH4Cl solution and extracted with ether (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 give the product 32 (18.4 mg, 0.045 mmol) yield 77%; Rf (hexane/EtOAc, 4:1) 0.53; IR (film) 2927, 1680, 1640, 1320, 1148, 981 cm−1; 1H NMR (400 MHz, CDCl3) 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, 2H), 2.69 (m, 2H), 2.30-1.92 (m, 9H), 1.65 (s, 3H), 1.56 (s, 9H); 13C NMR (100.6 MHz, CDCl3) δ 196.3, 151.5, 137.3, 135.3, 131.2, 124.3, 124.0, 121.5, 113.3, 96.6, 70.5, 55.5, 54.8, 44.6, 41.1, 39.7, 37.9, 27.0, 26.7, 26.5, 25.7, 17.7, 16.9, 16.8; HRMS-EI (m/z) calc for C20H26O2Si [M]+ 390.2770, found 390.2764.

2. Methoxymethyl-4-(methoxymethoxy)-5-(2E,6E)-3,7,11-trimethylododeca-2,6,10-trienyl)cyclohex-2-enone (32). To a solution of cyclohexanone (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 mixture stirred for 30 min at −78 °C. The reaction mixture was then cooled to −40 °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 NH4Cl solution and extracted with ether (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, 9:1) to give the product 31 (22 mg, 0.057 mmol) yield 82%; Rf (hexane/EtOAc, 4:1) 0.53; IR (film) 2927, 1680, 1640, 1320, 1148, 981 cm−1; 1H NMR (400 MHz, CDCl3) 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, 2H), 2.69 (m, 2H), 2.30-1.92 (m, 9H), 1.65 (s, 3H), 1.56 (s, 9H); 13C NMR (100.6 MHz, CDCl3) δ 196.3, 151.5, 137.3, 135.3, 131.2, 124.3, 124.0, 121.5, 113.3, 96.6, 70.5, 55.5, 54.8, 44.6, 41.1, 39.7, 37.9, 27.0, 26.7, 26.5, 25.7, 17.7, 16.9, 16.8; HRMS-EI (m/z) calc for C20H26O2Si [M]+ 390.2770, found 390.2764.
ASSOCIATED CONTENT

Supporting Information

*1H NMR and 13C 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

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