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Efficient Total Synthesis of Sapinofuranone B

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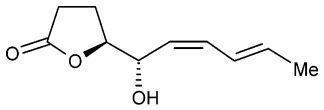

sapinofuranone B 1

An efficient enantioselective synthesis of sapinofuranone B (**1**) using Sharpless asymmetric dihydroxylation, Sonogashira coupling, and Wittig olefination as the key steps is described.

During a screening program for inhibition of benzodiazepine binding to the $GABA_A$ receptor, xenovulene A was isolated from submerged cultures of the fungus *Acremonium strictum*.[1] While optimizing the production of xenovulene A in the preliminary fermentation work, Simpson and co-workers isolated a novel metabolite from fermentation extracts and named it (4*S*,5*S*,6*Z*,8*E*)-5-hydroxydeca-6,8-dien-4-olide [(*S*,*S*)-sapinofuranone B] **1**.[2] At almost the same time, two closely related lactones, sapinofuranones A (**2**) and B (***ent*-1**), were isolated from liquid cultures of *Saphaeropsis sapinae*, a phytopathogenic fungus causing a wide range of disease symptoms on conifers.[3] Both the structures and stereochemistry of sapinofuranones were determined by spectroscopic methods. The optical rotations of sapinofuranones A (**2**) and B (***ent*-1**) were reported to be +65.9 and −18.9 and stereochemistries at C-5 were designated as *S* and *R*, respectively. Comparison of these data with those for the *A. strictum* metabolite **1** indicated that sapinofuranones A and B isolated from *S. sapinae* must be the (4*R*,5*S*)-diastereomer (**2**) and (4*R*,5*R*)-enantiomer (***ent*-1**), respectively. The *A. strictum* lactone **1** was therefore described as (4*R*,5*S*)-(+)-sapinofuranone B (Figure 1). The structure of **1** was further established by spectroscopic studies and chemical correlation with the known L-factor **3**, which is a reduced form of **1**, isolated from *Streptomyces griseus*.[2] Definitive proof for the structures and stereochemistry of **1** has been provided by a stereoselective total synthesis from tartaric acid as a chiral pool material. The absolute configuration at C-4 and C-5 in **1**, isolated from

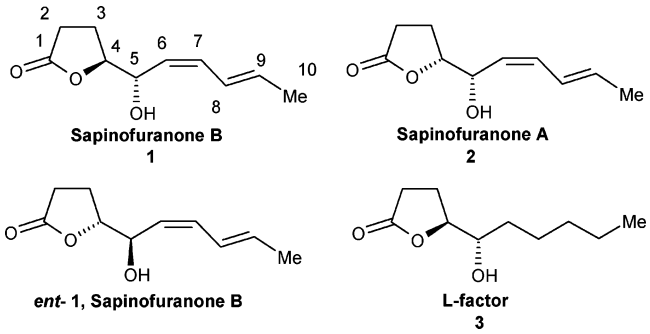

FIGURE 1. Structures of sapinofuranones and L-factor.

A. strictum, was further confirmed by the catalytic hydrogenation of the diene and by comparing the optical rotations of the saturated product with that of L-factor **3**.[2] From a synthetic point of view, there has been only one literature report on the total synthesis of **1** in which asymmetric centers at C-4 and C-5 were elaborated from dimethyl L-tartrate and the 6,8-diene moiety was introduced via Stille coupling of (*E*)-prop-1-enyltributyltin with a (*Z*)-vinylic iodide.[2] As a part of our research program aimed at developing enantioselective synthesis of naturally occurring lactones[4] and amino alcohols,[5] we have accomplished the stereoselective synthesis of sapinofuranone B employing Sharpless asymmetric dihydroxylation as the source of chirality from the commercially available starting material 1,4-butanediol.

Results and Discussion

Our retrosynthetic strategy for the synthesis of sapinofuranone B is outlined in Scheme 1. We envisioned that the 1,3-diene system could be prepared by Wittig olefination of an aldehyde or partial hydrogenation of 1,3-enyne **13**, which in turn would be obtained from acetylene **12** by Sonogashira coupling. The acetylene **12** could be obtained from the alcohol **9** through a Corey−Fuchs protocol. In this strategy, both the stereogenic centers could be obtained through Sharpless asymmetric dihydroxylation of an olefin **6**.

The synthesis of sapinofuranone B **1** started from commercially available 1,4-butanediol as illustrated in Scheme 2. Selective monohydroxyl protection of **4** with *p*-methoxybenzyl bromide in the presence of NaH gave **5** in 90% yield. Compound **5** was oxidized to the corresponding aldehyde under standard Swern conditions[6] and

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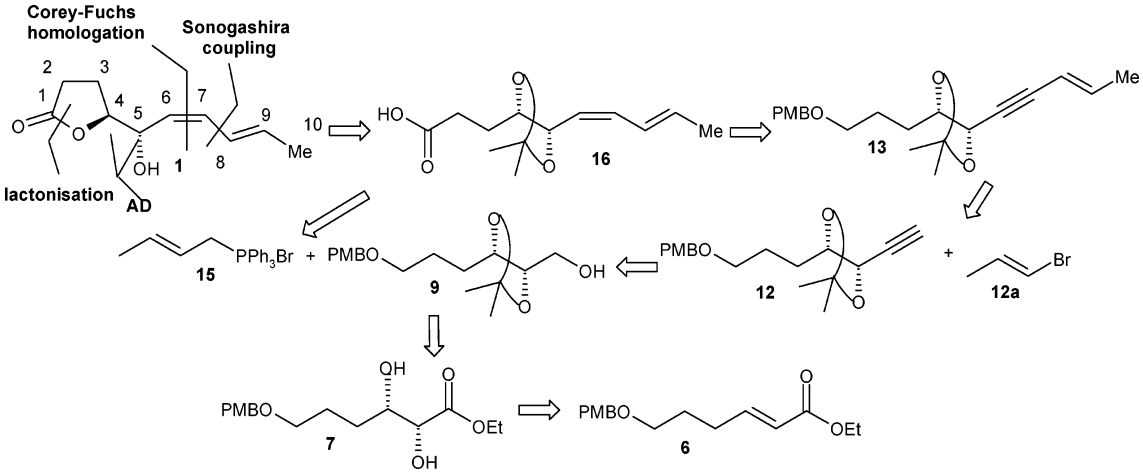
SCHEME 1. Retrosynthetic Analysis for Sapinofuranone B (1)



subsequently treated with (ethoxycarbonylmethylene)-triphenylphosphorane in benzene under reflux conditions to furnish the trans olefinic product **6**[7] in 89% yield. The olefin **6** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2PHAL$ ligand under AD conditions[8] to give the diol **7** in 96% yield with 97% ee.[9] Treatment of diol **7** with 2,2-dimethoxypropane in the presence of *p*-TSA gave compound **8**, which on reduction with DIBAL-H furnished the alcohol **9** in excellent yield. Subsequent homologation to acetylene **12** was carried out using the Corey−Fuchs protocol[10] in a three-step sequence involving Swern oxidation, dibromomethylenation, of the aldehyde and dehalogenation. Thus, compound **9** was oxidized to the aldehyde **10** using standard Swern conditions followed by dibromomethylenation with CBr_4 and PPh_3 to furnish the dibromo olefin **11** in essentially quantitative yield. Treatment of **11** with an excess of *n*-BuLi in THF at −78 °C provided the acetylene **12** in 92% yield. The Sonogashira coupling[11] of **12** with commercially available *trans*-1-bromopropene **12a** was successfully carried out with $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine to furnish the 1,3-enyne product **13** in excellent yield. The partial hydrogenation of the triple bond in **13** proved to be challenging. Irrespective of whether catalytic quantities or several molar equivalents of quinoline were present, a mixture of **14** and over-hydrogenated product was formed. The use of 1-octene[12] as a cosolvent along with EtOAc in the presence of pyridine (EtOAc/pyridine/1-octene = 10:1:1) furnished the diene **14** as a single product (Scheme 3). Thus, the use of the Corey−Fuchs protocol and Sonogashira coupling followed by hydrogenation for the synthesis of the 1,3-diene system is an improvement over the first reported synthesis.[2] Alternatively, the diene **14** was also obtained by the Wittig olefination (Scheme 4). Thus, the aldehyde **10** was treated with the Wittig salt **15** in THF at −80 °C in the presence of LiHMDS to furnish a mixture of cis and trans Wittig products (*Z*:*E* = 80:20). The desired (*Z*)-isomer **14** was easily separated by silica gel column chromatography. The subsequent deprotection of the *p*-methoxybenzyl group with DDQ furnished the alcohol **16** in 94% yield. Oxidation of the resulting alcohol to the corresponding aldehyde using Swern conditions and further oxidation using sodium chlorite in DMSO under buffer conditions afforded the acid **17**. Finally, the deprotection of acetonide as well as cyclization was achieved in one-pot by using catalytic concentrated HCl in methanol to furnish the target molecule **1** in 67% overall yield from alcohol **16**, $[\alpha]_D^{25}$ +19.6 (*c* 1.0, $CHCl_3$), [lit.[2] $[\alpha]_D^{20}$ +19.0 (*c* 0.77, $CHCl_3$)]. The physical and spectroscopic data of **1** were in accord with those reported for the same compound obtained from a natural source.[2]

In conclusion, a practical and enantioselective total synthesis of sapinofuranone B has been achieved using Sharpless asymmetric dihydroxylation, Sonogashira coupling, and Wittig olefination as the key steps. The obvious advantages of our synthesis in terms of high overall yields, ready access to the 1,3-diene system and stereogenic centers, high enantioselectivity, and various possibilities available for structural modifications are noteworthy.

Experimental Section

2,3-Dihydroxy-6-(4-methoxybenzyloxy)-hexanoic Acid Ethyl Ester (7). To a mixture of $K_3Fe(CN)_6$ (18.45 g, 56.0 mmol), K_2CO_3 (7.74 g, 56.0 mmol), and $(DHQ)_2PHAL$ (145 mg, 1 mol

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(9) For the measurement of enantiomeric excess, the diol **7** was converted into its dibenzoate. The enantiomeric purity of the dibenzoate was estimated to be 97% by chiral HPLC analysis using Lichocart 250-4 (4 mm i.d. x 25 cm) HPLC-Cartridge (R.R.-Whelk-01), 1% *i*PrOH in hexane, 1 mL/min.

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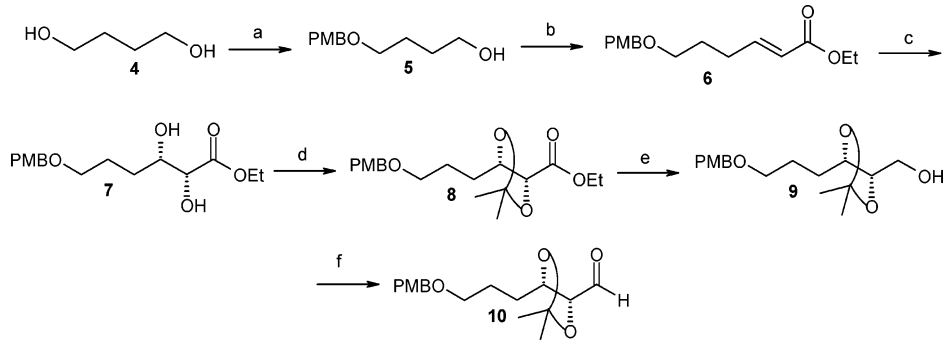
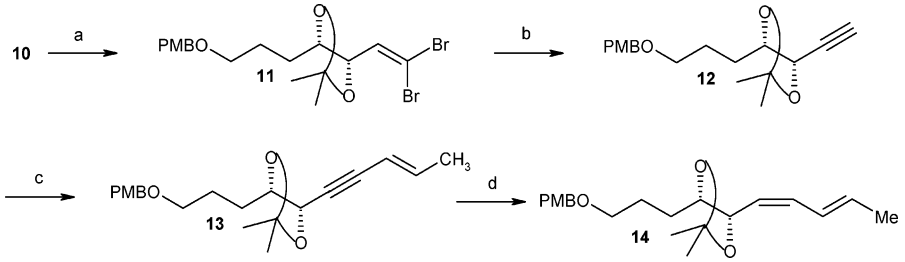
SCHEME 2[a]



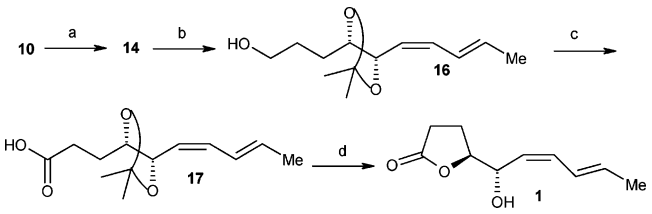
[a] Reagents and conditions: (a) *p*-$OCH_3C_6H_5CH_2Br$, NaH, dry DMF, cat. TBAI, 0 °C to room temperature, 1 h, 90%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −60 °C, 95%; (ii) $Ph_3P{=}CHCO_2Et$, C_6H_6, reflux, 6 h, 89%; (c) $(DHQ)_2PHAL$ (1 mol %), 0.1 M OsO_4 (0.4 mol %), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O 1:1, 0 °C, 24 h, 96%; (d) *p*-TSA, 2,2-DMP, CH_2Cl_2, rt, overnight, 95%; (e) DIBAL-H, CH_2Cl_2, 0 °C to room temperature, 2 h, 96%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −60 °C, 94%.

SCHEME 3[a]



[a] Reagents and conditions: (a) CBr_4, PPh_3, CH_2Cl_2, −78 °C, 2 h, 98%; (b) *n*-BuLi, THF, −78 °C, 1 h, 92%; (c) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, **12a**, 6 h, 85%; (d) H_2, Lindlar's catalyst, EtOAc/pyridine/1-octene (10:1:1), 6 h, 95%.

SCHEME 4[a]



[a] Reagents and conditions: (a) $CH_3CH{=}CHCH_2Ph_3P^+Br^-$ (**15**), LiHMDS, THF, −80 °C, 2 h, 76%; (b) DDQ, CH_2Cl_2/H_2O (18:1), rt, 1 h, 94%; (c) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −60 °C; (ii) $NaClO_2$, DMSO, NaH_2PO_4, rt, overnight; (d) HCl (*cat.*), MeOH, rt, overnight, 67% from **16**.

%), in *t*-BuOH−H_2O (1:1, 100 mL) cooled at 0 °C, was added OsO_4 (0.79 mL, 0.1 M solution in toluene, 0.4 mol %) followed by methanesulfonamide (1.78 g, 18.71 mmol). After stirring for 5 min at 0 °C, the olefin **6** (5.20 g, 18.68 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (25 g). The stirring was continued for 45 min, and the solution was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed (10% KOH, then brine), dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as an eluent gave the diol **7** (5.63 g, 96%) as a colorless, syrupy liquid: $[\alpha]^{25}_D$ −7.0 (*c* 1.6, $CHCl_3$); IR (neat) ν_{max} 3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, 2H, J = 10.1 Hz), 6.87 (d, 2H, J = 10.1 Hz), 4.44 (s, 2H), 4.26 (q, 2H, J = 5.0 Hz), 4.06 (m, 1H), 3.91(d, 1H, J = 5.3 Hz), 3.80 (s, 3H), 3.49 (t, 2H, J = 6.1 Hz), 2.82 (brs, 2H), 1.73 (m, 4H), 0.88 (t, 3H, J = 6.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 158.8, 130.1, 128.9, 113.4, 73.4, 72.1, 69.5, 61.2, 54.8, 42.5, 30.0, 25.6, 13.7. Anal. Calcd for $C_{16}H_{24}O_6$ (312.36): C, 61.52; H, 7.74. Found: C, 61.66; H, 7.70.

5-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolane-4-carboxylic Acid Ethyl Ester (8). To a solution of the diol **7** (4.50 g, 14.41 mmol) and *p*-TSA (100 mg) in CH_2Cl_2 (100 mL) was added 2,2-dimethoxypropane (2.25 g, 21.60 mmol) and reaction mixture stirred overnight at room temperature. Solid $NaHCO_3$ (1 g) was added and mixture again stirred for 30 min. The reaction mixture was filtered through a pad of neutral alumina, and the filtrate was concentrated. Silica gel column chromatography using petroleum ether/EtOAc (9:1) as an eluent gave **8** (4.82 g, 95%) as a colorless liquid: $[\alpha]^{25}_D$ −26.2 (*c* 2.1, $CHCl_3$); IR (neat) ν_{max} 2864, 1736, 1612, 1513, 1248, 1130, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, 2H, J = 10.0 Hz), 6.91 (d, 2H, J = 10.0 Hz), 4.52 (s, 2H), 4.22 (q, 2H, J = 7.3 Hz), 4.10−4.14 (m, 1H), 3.80 (s, 3H), 3.53 (t, 3H, J = 5.8 Hz), 1.72−1.93 (m, 4H), 1.47 (s, 3H), 1.44 (s, 3H), 1.29 (t, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 158.9, 130.4, 128.8, 113.5, 110.4, 78.89, 78.71, 72.2, 69.2, 60.9, 54.9, 29.8, 26.9, 25.5, 25.4, 13.8. Anal. Calcd for $C_{19}H_{28}O_6$ (352.42): C, 64.75; H, 8.01. Found: C, 64.69; H, 8.24.

{5-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]-dioxolan-4-yl}-methanol (9). To a solution of **8** (4.0 g, 11.35 mmol) in dry CH_2Cl_2 (80 mL) at 0 °C was added dropwise DIBAL-H (22.70 mL, 22.70 mmol, 1 M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 2 h and then recooled to 0 °C and treated with saturated solution of sodium/potassium tartrate. The solid material was filtered through a pad of Celite and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as an eluent gave **9** (3.38 g, 96%) as a colorless oil: $[\alpha]^{25}_D$ −11.7 (*c* 1.8, $CHCl_3$); IR (neat) ν_{max} 3440, 2938, 2860, 1361, 1204, 1126, 1038 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, 2H, J = 8.7 Hz), 6.89 (d, 2H, J = 8.7 Hz), 4.44 (s, 2H), 3.90 (dt, J = 7.6, 4.0 Hz, 1H), 3.81 (s, 3H), 3.76 (m, 2H), 3.60 (dd, 1H, J = 7.5, 4.4 Hz), 3.46−3.53 (m, 2H), 2.18 (s, 1H), 1.62−1.84 (m, 4H), 1.41 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 130.5, 129.1, 113.7, 108.5, 81.5, 76.7, 72.4, 69.6,

62.1, 55.1, 29.7, 27.2, 26.9, 26.0. Anal. Calcd for $C_{17}H_{26}O_5$ (310.39): C, 65.78; H, 8.44. Found: C, 65.71; H, 8.51.

4-Ethynyl-5-[3-(4-methoxybenzyloxy)-propyl]-2,2-dimethyl-[1,3]dioxolane (12). To a cooled (−78 °C) and stirred solution of **11** (5.8 g, 12.49 mmol) in THF (50 mL) was added *n*-BuLi (1.6 M solution in hexane, 39.06 mL, 62.47 mmol) dropwise under argon. After 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as an eluent gave **12** (3.49 g, 92%) as a yellowish oil: $[\alpha]^{25}_D$ −12.4 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2943, 2859, 1615, 1518, 1244, 1132, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, 2H, J = 8.0 Hz), 6.90 (d, 2H, J = 7.6 Hz), 4.46 (s, 2H), 4.23 (d, 1H, J = 7.9 Hz), 4.06 (dt, J = 7.9, 3.6 Hz, 1H), 3.82 (s, 3H), 3.48−3.54 (m, 2H), 2.53 (s, 1H), 1.71−1.82 (m, 4H), 1.47 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 130.5, 129.0, 113.6, 109.8, 81.2, 80.7, 74.5, 72.4, 70.1, 69.4, 55.1, 28.9, 26.9, 26.0, 25.7. Anal. Calcd for $C_{18}H_{24}O_4$ (304.38): C, 71.03; H, 7.95. Found: C, 71.21; H, 8.01.

4-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-5-pent-3-en-1-ynyl-[1,3]dioxolane (13) (Sonogashira Coupling). To a stirred mixture of $Pd(PPh_3)_2Cl_2$ (738 mg, 1.05 mmol) and CuI (621 mg, 3.26 mmol) in Et_3N (2 mL) were added solutions of *trans*-1-bromopropene **12a** (2.54 g, 21.0 mmol) in Et_3N (2 mL) and acetylene **12** (3.2 g, 10.51 mmol) in Et_3N (2 mL) under argon. After 6 h, the reaction mixture was filtered through Celite and filtrate was concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as an eluent gave **13** (3.08 g, 85%) as a pale yellow oil: $[\alpha]^{25}_D$ −11.4 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2952, 2854, 1615, 1514, 1232, 1132, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 7.9 Hz, 2H), 6.89 (d, J = 7.6 Hz, 2H), 6.21 (d, J = 15.7 Hz, 1H), 5.69 (dq, J = 14.9, 7.0 Hz, 1H), 4.45 (s, 2H), 4.2 (d, J = 8.0 Hz, 1H), 4.01−4.08 (m, 1H), 3.82 (s, 3H), 3.50 (t, J = 5.4 Hz, 2H), 1.84 (d, J = 7.8 Hz, 3H), 1.54−1.79 (m, 4H), 1.46 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 133.8, 132.5, 130.5, 129.0, 113.6, 109.8, 81.2, 82.1, 74.5, 72.4, 70.1, 69.4, 55.1, 28.9, 26.9, 26.0, 25.7. Anal. Calcd for $C_{21}H_{28}O_4$ (344.45): C, 73.23; H, 8.19. Found: C, 73.42; H, 8.02.

4-[3-(4-Methoxybenzyloxy)-propyl]-2,2-dimethyl-5-penta-1,3-dienyl-[1,3]dioxolane (14). To a solution of **13** (3.08 g, 8.94 mmol) in 5 mL of ethyl acetate/pyridine/1-octene (10:1:1) was added Lindlar's catalyst (6 mg). The reaction mixture was stirred for 6 h under a balloon of H_2 at room temperature and filtered through a Celite pad. The filtrate was concentrated, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as an eluent to give **14** (2.94 g, 95%) as a pale yellow oil: $[\alpha]^{25}_D$ −16.7 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2952, 2854, 1613, 1300, 1204, 1100, 1038 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.23 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 10.0 Hz, 2H), 6.38 (m, 2H), 5.82 (dq, J = 14.8, 7.1 Hz, 1H), 4.50−4.57 (m, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.62−3.72 (m, 1H), 3.47 (t, J = 6.1 Hz, 3H), 1.81 (ddd, J = 6.8, 1.5, 1 Hz, 3H), 1.61−1.68 (m, 4H), 1.43 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 133.9, 132.9, 130.5, 129.1, 126.2, 124.3, 113.6, 108.3, 80.7, 76.8, 72.3, 69.6, 55.2, 28.2, 27.2, 27.0, 26.1, 18.3. Anal. Calcd for $C_{21}H_{30}O_4$ (346.46): C, 72.80; H, 8.73. Found: C, 72.61; H, 8.82.

3-(2,2-Dimethyl-5-penta-1,3-dienyl-[1,3]dioxolan-4-yl)-propan-1-ol (16). To a solution of compound **14** (230 mg, 0.66 mmol) in CH_2Cl_2 (18 mL) and H_2O (1 mL) at 0 °C was added DDQ (180 mg, 0.79 mmol) in portions. The resultant mixture was stirred at room temperature for 1 h, and then saturated aqueous $NaHCO_3$ (10 mL) was added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (6:4) as an eluent afforded alcohol **16** (141 mg, 94%) as a pale yellow oil: $[\alpha]^{25}_D$ +17.7 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3460, 2941, 2858, 1612, 1300, 1204; ^1H NMR (200 MHz, $CDCl_3$) δ 6.36 (m, 2H), 5.81 (dq, J = 15.2, 7 Hz, 1H), 5.26 (dd, J = 10.9, 2 Hz, 1H), 4.43−4.60 (m, 1H), 3.80−3.86 (m, 1H), 3.67 (t, J = 8.0 Hz, 2H), 2.64 (brs, 1H), 1.81 (ddd, J = 6.9, 2.0, 1.0 Hz, 3H), 1.60−1.74 (m, 4H), 1.42 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8, 132.9, 126.3, 124.3, 108.3, 80.7, 72.3, 67.9, 28.8, 27.2, 27.0, 26.1, 18.3. Anal. Calcd for $C_{13}H_{22}O_3$ (226.31): C, 68.99; H, 9.80. Found: C, 68.42; H, 9.89.

To a solution of oxalyl chloride (0.118 g, 0.081 mL, 0.93 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C was added dropwise dry DMSO (0.146 g, 0.132 mL, 1.87 mmol) in CH_2Cl_2 (5 mL). After 30 min, alcohol **16** (141 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at −78 °C, the reaction mixture was brought to −60 °C, and Et_3N (0.252 g, 0.347 mL, 2.49 mmol) was added slowly and stirred for 30 min, allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into water (50 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic layers were washed with water (3 × 30 mL) and brine (30 mL), dried (Na_2SO_4), and passed through a short pad of silica gel. The filtrate was concentrated to give the aldehyde (140 mg) as a pale yellow syrup, which was used as such for the next step without purification.

A solution of 79% $NaClO_2$ (91 mg, 1.00 mmol) in 1.0 mL of water was added dropwise to a stirred solution of the above crude aldehyde (140 mg, 0.62 mmol) in 0.5 mL of DMSO and NaH_2PO_4 (60 mg, 0.50 mmol) in 1.0 mL of water over 5 min at room temperature. The mixture was left overnight at room temperature, and then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted three times with CH_2Cl_2 and washed with brine, dried (Na_2SO_4), and concentrated to give the acid **17**, which was used as such for the next step without purification.

The above crude acid was dissolved in methanol (5 mL), and a catalytic amount of concentrated HCl was added. The reaction mixture was stirred at room temperature overnight and then quenched with solid $NaHCO_3$ and filtered, and the filtrate was concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (6:4) as an eluent gave **1** (73 mg, 67% from **16**) as an oil: $[\alpha]_D^{25}$ +19.6 (*c* 1.0, $CHCl_3$) [lit.[2] $[\alpha]_D^{20}$ +19.0 (*c* 0.77, $CHCl_3$)]; IR ($CHCl_3$) ν_{max} 3450, 2811, 1772, 1641, 1513, 1239, 1130, 1032; ^1H NMR (200 MHz, $CDCl_3$) δ 6.12−6.37 (m, 2H), 5.82 (dq, 1H, J = 14.8, 7.0), 5.26 (dd, 1H, J = 10.8, 2.0 Hz), 4.65 (ddd, 1H, J = 8.9, 5.0, 1.5 Hz), 4.52 (ddd, 1H, J = 7.6, 6.9, 5.5 Hz), 2.48−2.72 (m, 3H), 2.10−2.35 (m, 2H), 1.82 (ddd, 3H, J = 7.1, 1.7, 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1, 134.1, 133.1, 126.4, 125.8, 85.1, 69.8, 29.1, 24.6, 18.4.

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Supporting Information Available: Spectroscopic data and full experimental procedure for compounds **5**, **6**, **11**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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