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Simple and efficient synthesis of highly functionalized cyclohexanes; formal total synthesis of ovalicin and fumagillin

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ABSTRACT

Two chiral cyclohexanes **4** and **6**, which are key intermediates for the total synthesis of ovalicin **1** and fumagillin **2**, respectively, were synthesized from (2*R*,3*S*) 1,2-epoxy-4-penten-3-ol. The key steps involve an efficient construction of divinylalcohol **7** using methallyl Grignard reagent **9c**, and an intramolecular olefin metathesis of **7**.

1. Introduction

Ovalicin **1** is a highly oxygenated sesquiterpenoid that was first isolated from cultures of *Pseudorotium ovalis* Stolk (Fig. 1), and exhibits antibiotic, antitumor and immunosuppressive activities.[1–3] Recent studies revealed **1** to be a nontoxic, noninflammatory and a more potent angiogenesis inhibitor[4] than the structurally related fumagillin **2**,[5–8] a well known anti-angiogenesis agent.[9] Angiogenesis, the growth and development of new capillary blood vessels, is an essential process of a variety of pathological states, such as diabetic retinopathy, psoriasis, rheumatoid arthritis, and tumor growth.[10] Thus, angiogenesis inhibitors are promising candidates for new types of drugs. The unique structural complexity of **1** and its biological activity have attracted much attention as an interesting synthetic target, and, since the first total synthesis of (±)-**1** reported by Corey et al.,[11] many approaches to this natural product have been devised.[4,12–18] Amongst them, the synthesis developed by Quiclet-Sire and Samadi et al. was based on a highly convergent strategy, which involved a coupling reaction of vinyllithium reagent **3** and a highly functionalized cyclohexanone **4** synthesized from L-quebrachitol, and required only three steps for preparation of **1** from the coupling product.[12,13] The alternative synthesis of **4** from (−)-quinic acid was also reported by Pollini et al.[14] In a previous paper,[15] we described a novel synthesis of **4** from D-mannose and an improved route from there to **1**. These synthetic examples, however, have mainly relied on the chemical manipulations of natural polyols, which required rather long synthetic routes, and were inconvenient for preparation of the antipode. More efficient syntheses of the key intermediate **4** are still required for further studies on the total synthesis of **1** and detailed examination of its biological activity with significant therapeutic potential.

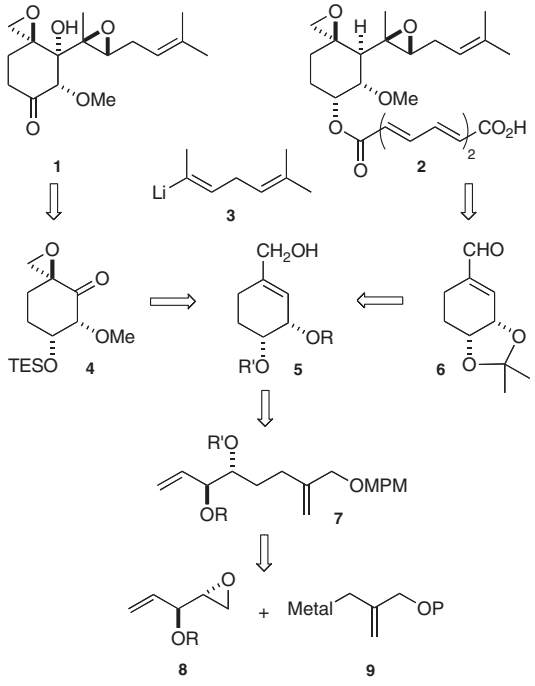

Figure 1. Structures of angiogenesis inhibitors and their synthetic plan.

Herein we report a short and efficient synthesis of **4** starting from **8**. In addition, the method developed here enabled us to achieve a high-yield synthesis of Sorensen's key intermediate **6**[19,20] for the total synthesis of **2**. This result is also discussed.

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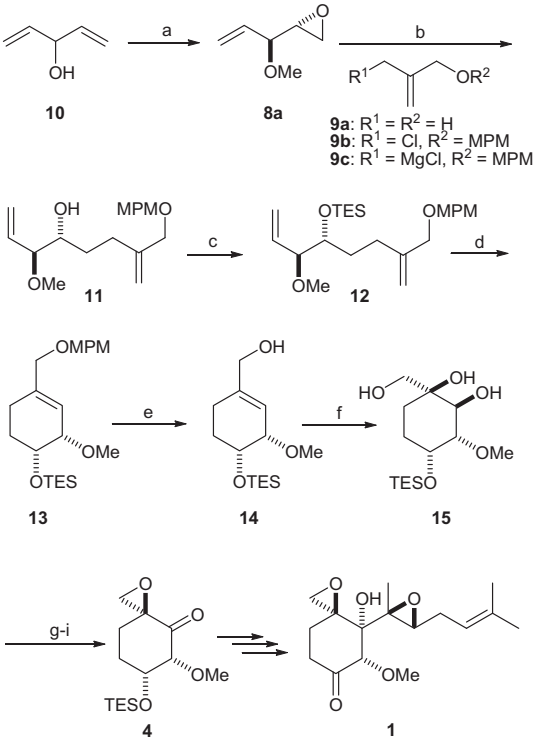
2. Results and discussion

2.1. Synthetic plan

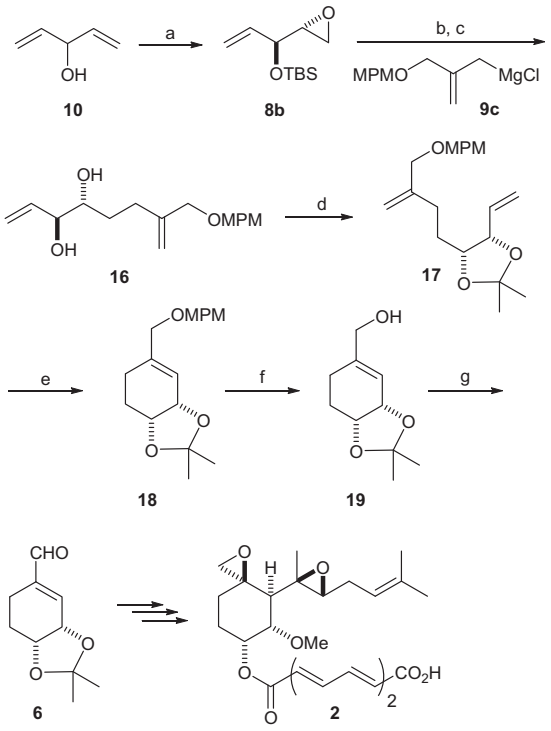
As shown in Figure 1, we envisioned cyclohexenol derivative **5** as a pivotal key intermediate for formal total synthesis of **1** and **2** because stereo- or chemoselective oxidation of **5** would be expected to produce the key intermediates **4** or **6**, respectively. Our synthetic strategy toward **5** included an efficient construction of divinylalcohol **7** using a coupling of chiral epoxide **8** with methallylic reagent **9**, and an intramolecular olefin metathesis[21] as key steps.

2.2. Formal total synthesis of ovalicin 1

The known epoxide **8a**[22] was prepared by Sharpless asymmetric epoxidation of commercially available **10** followed by O-methylation (Scheme 1). However, the introduction of a requisite C_4 unit into **8a** was not easy. The dianion[23] obtained by treatment of methallyl alcohol **9a** with *n*-BuLi-TMEDA or Grignard reagent[24] prepared via its transmetallation by $MgBr_2$ did not react cleanly with **8a**. The reaction of **8a** with Grignard reagent **9c**[25] derived from **9b** resulted in a low yield (~50%) of **11** because of the formation of ring-opened chlorohydrin, while the addition of CuI improved the reaction, giving the desired alcohol in high yield. This coupling reaction was quite sensitive toward oxygen, meaning that restricted oxygen-free conditions were required for obtaining **11** in high yield. This compound, however, was isolated as an inseparable mixture with degradation products of the Grignard reagent. Hence, the crude coupling product was, after chromatography through a short column of silica gel, submitted to silylation with chlorotriethylsilane–imidazole, giving TES derivative **12** in a pure form (92% yield from **8a**). Ring closing metathesis of **12** was effected by treatment of Grubbs catalyst 2nd generation in dichloromethane at 45 °C to afford a cyclohexene derivative **13** in 93% yield.[26] Upon treatment with DDQ in the presence of a phosphate buffer (pH 7.4), **13** gave **14** in 95% yield. The stereoselective oxidation of this with OsO_4-trimethylamine N-oxide proceeded nicely to afford **15** as a single isomer (90%). The spectroscopic and physical data were well matched with those of the known compound.[14,15] According to the previous method (1. *p*-TsCl, DMAP, Et_3N, CH_2Cl_2; 2. K_2CO_3, MeOH; 3. Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2),[14,15] **15** was transformed into **4** in 90% overall yield. Since the synthesis of **1** from **4** has already been established (39% overall yield[15] with four steps),[13] the present preparation of **4** constitutes a formal total synthesis of ovalicin **1**.



Scheme 1. (a) Ref. 22; (b) **9c**, CuI (0.14 equiv), THF, 0 °C–>rt; (c) chlorotriethylsilane (3.2 equiv), imidazole (6.4 equiv), DMF, rt, 92% from **8a** over two steps; (d) Grubbs cat. 2nd generation (0.05 equiv), CH_2Cl_2, 45 °C, 93%; (e) DDQ (3.0 equiv), phosphate buffer (pH 7.4), CH_2Cl_2, 0 °C, 95%; (f) OsO_4 (0.16 equiv), Me_3NO (1.5 equiv), *t*-BuOH, H_2O, rt, 90%; (g) *p*-TsCl (1.4 equiv), DMAP (0.1 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 0 °C; (h) K_2CO_3 (0.88 equiv), methanol, 0 °C, 93% over two steps; (i) Dess–Martin periodinane (1.8 equiv), $NaHCO_3$ (2.2 equiv), CH_2Cl_2, 0 °C, 97%.



Scheme 2. (a) Ref. 27; (b) **9c**, CuI (0.22 equiv), THF, 0 °C–>rt; (c) TBAF (1.1 equiv), THF, rt, 89% from **8b** over two steps; (d) 2,2-dimethoxypropane (1.5 equiv), CSA (0.2 equiv), CH_2Cl_2, rt, 95%; (e) Grubbs cat. 2nd generation (0.06 equiv), CH_2Cl_2, 45 °C, 91%; (f) DDQ (2.5 equiv), phosphate buffer (pH 7.4), CH_2Cl_2, 0 °C, 86%; (g) Dess–Martin periodinane (1.5 equiv), $NaHCO_3$ (1.5 equiv), CH_2Cl_2, 0 °C, 86%.

2.3. Formal total synthesis of fumagillin 2

A similar method via an oxirane-ring opening by Grignard reagent was applied to easily prepare compound **6** as follows (Scheme 2). The TBS analog **8b**[27] was prepared according to a known procedure. The coupling reaction of **8b** with Grignard reagent **9c** in THF proceeded nicely to give diol **16** in 89% yield after desilylation with TBAF. Isopropylidenation of **16** afforded **17** in 95% yield. Intramolecular olefin metathesis of this was performed by the action of Grubbs 2nd generation catalyst in dichloromethane at 45 °C to afford cyclohexene **18** in 91% yield.[26] After removing the MPM group, the resulting alcohol **19**[28] was oxidized with Dess–Martin periodinane in the presence of $NaHCO_3$, to give the key intermediate **6** in high yield, thus completing the formal total synthesis of fumagillin **2**.[19,20]

3. Conclusion

In summary, we have developed a short and efficient method for the synthesis of the key intermediates **4** and **6** for the total synthesis of angiogenesis inhibitors **1** and **2**. The synthesis of **4** required only eight steps and proceeded in 64% overall yield from chiral epoxide **8a** whereas **6** was obtained from **8b** within six steps in 57% overall yield. The strategy described herein would be useful for preparing analogues of **1** and **2** suitable for clinical usage.

4. Experimental

4.1. General procedures

All reactions were carried out under an argon atmosphere, unless otherwise noted. Optical rotations were measured with a JASCO DIP-370 polarimeter. IR spectra were recorded with a JASCO VALOR-III spectrophotometer by ATR method. ^{1}H NMR spectra were recorded at 500 MHz with Varian V-500 spectrometers. Chemical shifts were referenced to a residual signal of $CDCl_3$ (δ_H 7.26) or the solvent signal (δ_C 77.0). ESIMS were recorded on a Waters Micromass Quattro Premier XE mass spectrometer or JEOL JMS-T100LC mass spectrometer. Column chromatography was performed on Kanto silica gel 60 N (spherical, neutral; 40–100 μm). Merck precoated Silica Gel 60 F_{254} plates, 0.25 mm thickness, was used for analytical thin-layer chromatography. The solvent extracts were dried with magnesium sulfate, and the solutions were evaporated under diminished pressure at 40–42 °C.

4.2. (3*S*,4*R*)-3-Methoxy-7-((4-methoxybenzyloxy)methyl)-4-triethylsilyloxyocta-1,7-diene 12[29]

To a stirred suspension of magnesium turnings (340 mg, 13.9 mmol) in tetrahydrofuran (2.0 mL) was added dropwise 1,2-dibromoethane (20 μL) at 0 °C. When the reaction started, the mixture was diluted with tetrahydrofuran (1.0 mL). A solution of **9b** (453 mg, 1.99 mmol) in tetrahydrofuran (7.0 mL) was added dropwise during 1.5 h, and the resulting mixture was stirred for an additional 1 h. To the solution (3.0 mL) was added CuI (5.2 mg, 27.3 μmol) at 0 °C with stirring. After 10 min, a solution of **8a** (22 mg, 0.19 mmol) in tetrahydrofuran (0.3 mL) was added dropwise to the above solution at 0 °C and the resulting mixture was stirred for 1.5 h. After being quenched by the addition of saturated aqueous NH_4Cl, the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed successively with water, and brine. After removal of the solvent, the residue was passed through a short column of silica gel (*n*-hexane–ethyl acetate = 10:1–>4:1) to give 105 mg of a yellow syrup containing **11**, which was dissolved in *N*,*N*-dimethylformamide (2.0 mL). To this solution were added sequentially imidazole (82 mg, 1.2 mmol) and chlorotriethylsilane (0.1 mL, 0.6 mmol) at 0 °C with stirring, and the resulting mixture was stirred at the same temperature for 3 h. After the addition of ice-water, the resulting mixture was extracted with ether. The combined organic layers were washed successively with 5% HCl, water, saturated aqueous $NaHCO_3$, water, and brine. After removal of the solvent, the residue was chromatographed on silica gel (*n*-hexane–ether = 20:1→10:1→5:1) to give **12** (75 mg, 92% from **8a**) as a light-yellow liquid: $[\alpha]_D^{24} = +14.8$ (*c* 0.80, $CHCl_3$); IR (ZnSe) 3074, 2875, 1612, 1513, 1247, 1086, 889, 818, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (2H, d, *J* = 8.6 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 5.74 (1H, ddd, *J* = 17.3, 10.5, 7.9 Hz), 5.28 (1H, br d, *J* = 10.5 Hz), 5.22 (1H, br d, *J* = 17.3 Hz), 5.04 (1H, br s), 4.93 (1H, br s), 4.42 (2H, s), 3.93 (2H, s), 3.80 (3H, s), 3.72 (1H, dt, *J* = 7.8, 4.1 Hz), 3.45 (1H, dd, *J* = 7.9, 4.1 Hz), 3.27 (3H, s), 2.23 (1H, ddd, *J* = 14.9, 11.0, 4.1 Hz), 2.05 (1H, ddd, *J* = 14.9, 11.0, 5.9 Hz), 1.69–1.56 (2H, m), 0.96 (9H, t, *J* = 8.0 Hz), 0.60 (6H, q, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 146.2, 135.6, 130.5, 129.3, 118.9, 113.7, 111.3, 86.3, 74.5, 72.9, 71.5, 56.4, 55.2, 31.2, 29.1, 6.9, 5.1; HRMS (ESI$^+$) calcd for $C_{24}H_{40}O_4SiNa$ [M+Na]$^+$ 443.2594, found 443.2601.

4.3. (3*S*,4*R*)-3-Methoxy-1-((4-methoxybenzyloxy)methyl)-4-(triethylsilyloxy)cyclohex-1-ene 13

To a stirred solution of **12** (110 mg, 0.26 mmol) in dichloromethane (11.0 mL) was added Grubbs 2nd generation catalyst (14 mg, 16 μmol) and the resulting mixture was stirred at 45 °C for 2.5 h, and then cooled. After the addition of florisil, the resulting mixture was filtered through a pad of Celite, and then concentrated. The residue was chromatographed on silica gel (*n*-hexane–ether = 1:0→30:1→10:1) to give **13** (96 mg, 93%) as a colorless oil: $[\alpha]_D^{25} = +70.0$ (*c* 0.99, $CHCl_3$); IR (ZnSe) 2874, 1612, 1513, 1245, 1081, 819, 724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (2H, d, *J* = 8.6 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 5.80 (1H, m), 4.40 (2H, s), 3.89–3.84 (3H, m), 3.80 (3H, s), 3.63 (1H, m), 3.50 (3H, s), 2.18 (1H, m), 2.04 (1H, m), 1.98 (1H, m), 1.64 (1H, m), 0.98 (9H, t, *J* = 8.1 Hz), 0.62 (6H, q, *J* = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 138.9, 130.3, 129.2, 122.3, 113.7, 76.5, 73.3, 71.7, 70.3, 58.4, 55.2, 26.4, 25.4, 6.8, 4.8; HRMS (ESI$^+$) calcd for $C_{22}H_{36}O_4SiNa$ [M+Na]$^+$ 415.2281, found 415.2266.

4.4. (3*S*,4*R*)-1-Hydroxymethyl-3-methoxy-4-(triethylsilyloxy)-cyclohex-1-ene 14

To a stirred solution of **13** (26.0 mg, 66.2 μmol) in dichloromethane (5.0 mL) and phosphate buffer (pH 7.4; 0.5 mL) was added DDQ (45.0 mg, 0.20 mmol) at 0 °C and the resulting mixture was stirred for 2.5 h, and diluted with ether. The organic layer was separated and washed successively with saturated aqueous $NaHCO_3$: saturated aqueous $Na_2S_2O_3$ = 1:1, water, and brine. After removal of the solvent, the residue was chromatographed on silica gel (*n*-hexane–ethyl acetate = 1:0→10:1→4:1) to give **14** (17.2 mg, 95%) as a colorless oil: $[\alpha]_D^{24} = +112.5$ (*c* 0.23, $CHCl_3$); IR (ZnSe) 3380, 2859, 1450, 1230, 1098, 1078, 843, 719 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 (1H, m), 3.98 (2H, s), 3.87 (1H, dt, *J* = 10.5, 3.4 Hz), 3.62 (1H, t, *J* = 3.4 Hz), 3.49 (3H, s), 2.19–2.07 (2H, m), 2.02–1.90 (2H, m), 1.63 (1H, m), 0.96 (9H, t, *J* = 8.3 Hz), 0.61 (6H, q, *J* = 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 119.9, 76.4, 70.5, 66.0, 58.6, 26.3, 25.0, 6.8, 4.8; HRMS (ESI$^+$) calcd for $C_{14}H_{28}O_3SiNa$ [M+Na]$^+$ 295.1705, found 295.1715.

4.5. (1*S*,2*S*,3*R*,4*R*)-1-Hydroxymethyl-3-methoxy-4-(triethylsilyloxy)cyclohexane-1,2-diol 15

To a stirred solution of **14** (17.0 mg, 62 μmol) and trimethylamine N-oxide·2H_2O (10.0 mg, 94 μmol) in 2-methyl-2-propanol (0.60 mL) and water (0.4 mL) was added dropwise a 2.5 wt % solution of OsO_4 in 2-methyl-2-propoanol (0.1 mL) at rt and the resulting mixture was stirred at the same temperature for 8 h. After the addition of Na_2SO_3, the resulting mixture was stirred at rt for 30 min and then the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water, and brine. After removal of the solvent, the residue was chromatographed on silica gel (*n*-hexane–ethyl acetate = 10:1→4:1→1:1) to give **15** (17.1 mg, 90%) as a colorless oil: $[\alpha]_D^{24} = -66.2$ (*c* 0.31, $CHCl_3$) {lit. $[\alpha]_D^{25} = -63$ (*c* 2.39, $CHCl_3$),[14] $[\alpha]_D^{28} = -66.7$ (*c* 1.18, $CHCl_3$)[15]}; IR (ZnSe) 3384, 2875, 1119, 1072, 723 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (1H, m), 3.90 (1H, d, *J* = 11.2 Hz), 3.75 (1H, d, *J* = 11.2 Hz), 3.42

(1H, br d, J = 3.4 Hz), 3.39 (3H, s), 3.21 (1H, dd, J = 9.3, 2.5 Hz), 2.99 (1H, br s), 2.92–2.80 (2H, br s), 1.73 (1H, m), 1.67 (1H, m), 1.64 (1H, m), 1.45 (1H, m), 0.95 (9H, t, J = 8.0 Hz), 0.58 (6H, q, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 82.8, 73.4, 72.8, 70.7, 65.4, 57.1, 27.1, 26.0, 6.8, 4.9; HRMS (ESI$^+$) calcd $C_{14}H_{30}O_5SiNa$ $[M+Na]^+$ 329.1760, found 329.1753.

4.6. (3*S*,5*R*,6*R*)-5-Methoxy-6-triethylsilyloxy-1-oxaspiro[2.5]octan-4-one 4

To a stirred mixture of **15** (583 mg, 1.90 mmol), 4-dimethylaminopyridine (23.3 mg, 0.19 mmol), and triethylamine (1.32 ml, 9.51 mol) in dichloromethane (4.0 ml) was added *p*-toluenesulfonyl chloride (508 mg, 2.67 mol) at 0 °C, and the mixture was stirred at 0 °C for 21 h. After the addition of ice-water, the resulting mixture was stirred vigorously for 1.5 h, and then extracted with EtOAc. The combined organic layers were washed successively with 5% HCl, water, saturated aqueous $NaHCO_3$, water, and brine. After removal of the solvent, the residue was passed through a short column of silica gel (*n*-hexane–ethyl acetate = 7:2) to give a syrup, which was dissolved in methanol (4.0 ml). Potassium carbonate (231 mg, 1.61 mmol) was added to the solution at 0 °C; the mixture was stirred at 0 °C for 1.9 h, and then concentrated. Flash chromatography (*n*-hexane–ethyl acetate = 8:1) gave the corresponding epoxide (508 mg, 93%) as a colorless oil. To a stirred suspension of the epoxide (300 mg, 1.04 mmol) and $NaHCO_3$ (192 mg, 2.29 mmol) in dichloromethane (13.6 ml) was added Dess–Martin periodinane (794 mg, 1.87 mmol) at 0 °C. The mixture was stirred at 0 °C→rt for 3 h, and then poured into saturated aqueous $NaHCO_3$: saturated aqueous $Na_2S_2O_3$ = 1:1 with stirring. The resulting mixture was extracted with ether. The combined organic layers were washed successively with water, and brine. After removal of the solvent, the residue was chromatographed on silica gel (benzene–ether = 9:1) to give **4** (289 mg, 97%) as a light-yellow oil: $[\alpha]_D^{29} = -7.7$ (*c* 1.87, $CHCl_3$) {lit. $[\alpha]_D^{26} = -9.4$ (*c* 0.55, $CHCl_3$)[15], $[\alpha]_D^{20} = -87$ (*c* 1.15, $CHCl_3$)[13]}; IR (ZnSe) 2955, 1745, 1111, 1098, 1067, 1021, 749 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.38 (1H, m), 3.92 (1H, br d, J = 2.3 Hz), 3.40 (3H, s), 3.22 (1H, d, J = 4.9 Hz), 2.74 (1H, d, J = 4.9 Hz), 2.45 (1H, m), 2.06–1.98 (2H, m), 1.55 (1H, dt, J = 14.2, 4.6 Hz), 0.91 (9H, t, J = 7.7 Hz), 0.57 (6H, q, J = 7.7 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 202.1, 87.2, 71.8, 60.4, 58.2, 51.3, 28.7, 26.8, 6.8, 4.8; Anal. Calcd for $C_{14}H_{26}O_4Si$: C, 58.70; H, 9.15. Found: C, 58.59; H, 9.03

4.7. (3*S*,4*R*)-7-((4-Methoxybenzyloxy)methyl)octa-1,7-diene-3,4-diol 16[29]

To a stirred solution (8.0 mL) of Grignard reagent prepared from magnesium turnings (340 mg, 13.9 mmol), **9b** (453 mg, 2.00 mmol) and a trace amount of 1,2-dibromoethane in tetrahydrofuran (10.0 mL) as described for the preparation of **12** was added CuI (20.0 mg, 0.11 mmol) at 0 °C. After 15 min, a solution of **8b** (104 mg, 0.49 mmol) in tetrahydrofuran (0.7 mL) was added dropwise to the above solution at 0 °C and the resulting mixture was stirred for 1.5 h. After being quenched by the addition of saturated aqueous NH_4Cl, the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed successively with water, and brine. After removal of the solvent, the residue was passed through a short column of silica gel (*n*-hexane–ethyl acetate = 10:1–>4:1) to give a yellow syrup (271 mg), which was dissolved in tetrahydrofuran (2.0 mL). To this solution was added a 1.0 M solution of TBAF in tetrahydrofuran (0.5 mL, 0.5 mmol) at 0 °C with stirring. The resulting mixture was stirred at the same temperature for 2 h, and diluted with ethyl acetate. The organic layer was washed with brine. After removal of the solvent, the residue was chromatographed on silica gel (*n*-hexane–ethyl acetate = 10:1→6:1→4:1→1:1) to give **16** (126 mg, 89% from **8b**) as a light-yellow liquid: $[\alpha]_D^{24} = +2.5$ (*c* 0.33, $CHCl_3$); IR (ZnSe) 3305, 3220, 2840, 1655, 1612, 1517, 1250, 1030, 923, 818 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (2H, d, J = 8.8 Hz), 6.87 (2H, d, J = 8.8 Hz), 5.88 (1H, ddd, J = 17.2, 10.5, 6.6 Hz), 5.31 (1H, dt, J = 17.2, 1.5 Hz), 5.24 (1H, dt, J = 10.5, 1.5 Hz), 5.06 (1H, br s), 4.96 (1H, br s), 4.42 (2H, s), 4.08 (1H, br s), 3.94 (2H, s), 3.80 (3H, s), 3.68 (1H, m), 2.40 (1H, d, J = 4.7 Hz), 2.33 (1H, s), 2.30 (1H, ddd, J = 14.4, 9.3, 5.9 Hz), 2.15 (1H, dt, J = 14.4, 8.0 Hz), 1.65–1.52 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 145.5, 136.1, 130.2, 129.4, 117.5, 113.7, 112.5, 75.9, 73.5, 72.9, 71.7, 55.2, 29.9, 29.3; HRMS (ESI$^+$) calcd for $C_{17}H_{24}O_4Na$ $[M+Na]^+$ 315.1572, found 315.1568.

4.8. (3*S*,4*R*)-3,4-Isopropylidendioxy-7-((4-methoxybenzyloxy)-methyl)octa-1,7-diene 17

To a stirred solution of **16** (0.1 g, 0.34 mmol) and 2,2-dimethoxypropane (39 μL, 0.51 mmol) in dichloromethane (1.0 mL) was added CSA (16 mg, 69 μmol) at rt. The mixture was stirred at rt for 5 h, and diluted with ether. The organic layer was washed successively with saturated aqueous $NaHCO_3$, water, and brine. After removal of the solvent, the residue was chromatographed on silica gel (*n*-hexane–ethyl acetate = 10:1→4:1) to give **17** (108 mg, 95%) as a colorless oil: $[\alpha]_D^{25} = +2.2$ (*c* 0.74, $CHCl_3$); IR (ZnSe) 2910, 2845, 1610, 1510, 1243, 1065, 1035, 862, 818 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (2H, d, J = 8.5 Hz), 6.88 (2H, d, J = 8.5 Hz), 5.81 (1H, ddd, J = 17.1, 10.2, 7.8 Hz), 5.30 (1H, d, J = 17.1 Hz), 5.23 (1H, d, J = 10.2 Hz), 5.07 (1H, br s), 4.95 (1H, br s), 4.49 (1H, t, J = 7.8 Hz), 4.42 (2H, s), 4.15 (1H, dt, J = 7.8, 4.9 Hz), 3.94 (2H, s), 3.80 (3H, s), 2.26 (1H, ddd, J = 14.9, 10.5, 5.2 Hz), 2.12 (1H, ddd, J = 14.9, 10.3, 5.9 Hz), 1.66 (1H, m), 1.58 (1H, m), 1.49 (3H, s), 1.37 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 145.4, 134.3, 130.3, 129.2, 118.2, 113.6, 111.9, 108.0, 79.6, 77.6, 72.7, 71.5, 55.1, 29.5, 28.4, 28.2, 25.6; HRMS (ESI$^+$) calcd for $C_{20}H_{28}O_4Na$ $[M+Na]^+$ 355.1885, found 355.1882.

4.9. (3*S*,4*R*)-3,4-Isopropylidendioxy-1-((4-methoxybenzyl-oxy)methyl)cyclohex-1-ene 18

Following the same procedure as described for **13**, **17** (81.6 mg, 0.25 mmol) gave **18** (67.7 mg, 91%) as a colorless oil: $[\alpha]_D^{24} = -21.1$ (*c* 0.23, $CHCl_3$); IR (ZnSe) 2982, 2913, 1611, 1512, 1237, 1214, 1085, 1057, 1030, 880, 855, 817 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (2H, d, J = 8.6 Hz), 6.86 (2H, d, J = 8.6 Hz), 5.73 (1H, m), 4.50 (1H, t, J = 3.5 Hz), 4.40 (2H, s), 4.28 (1H, dt, J = 6.2, 3.5 Hz), 3.90 (2H, br s), 3.78 (3H, br s), 2.14 (1H, m), 1.94 (1H, m), 1.90 (1H, m), 1.79 (1H, m), 1.41 (3H, s), 1.37 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 139.6, 130.2, 129.2, 121.7, 113.6, 108.2, 73.1, 72.8, 71.7, 71.6, 55.1, 28.0, 26.2, 25.5, 21.5; HRMS (ESI$^+$) calcd for $C_{18}H_{24}O_4Na$ $[M+Na]^+$ 327.1572, found 327.1561.

4.10. (3*S*,4*R*)-1-Hydroxymethyl-3,4-isopropylidendioxycyclohex-1-ene 19

Following the same procedure as described for **14**, **18** (48.2 mg, 0.16 mmol) gave **19** (25.1 mg, 86%) as a colorless oil: $[\alpha]_D^{25} = -18.4$ (*c* 0.54, $CHCl_3$); IR (ZnSe) 3391, 2983, 2919, 1648, 1369, 1213, 1053, 1020, 851 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.66 (1H, m), 4.46 (1H, br s), 4.24 (1H, br dt, J = 3.9, 5.9 Hz), 3.98 (2H, s), 2.55 (1H, br s), 2.08 (1H, m), 1.88–1.80 (2H, m), 1.76 (1H, m), 1.35 (3H, s), 1.32 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.5, 119.0, 108.2, 72.9, 71.6, 65.8, 28.0, 26.1, 25.6, 21.3; HRMS (EI$^+$) calcd for $C_9H_{13}O_3$ $[M-Me]^+$ 169.0865, found 169.0871.

4.11. (3*S*,4*R*)-3,4-Isopropylidendioxycyclohex-1-enecarbaldehyde 6

Following the same procedure as described for **4**, **19** (21.7 mg, 0.12 mmol) gave **6** (18.4 mg, 86%) as a colorless oil: $[\alpha]_D^{24} = -48.3$ (*c* 0.44, $CHCl_3$) {lit.[20] $[\alpha]_D^{23} = -41.0$ (*c* 1.0, $CHCl_3$)}; IR (ZnSe) 2984, 2932, 2845, 1679, 1641, 1371, 1211, 1149, 1055, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.47 (1H, s), 6.55 (1H, m), 4.67 (1H, dt, J = 1.7, 3.4 Hz), 4.40 (1H, dt, J = 3.4, 5.4 Hz), 2.26–2.21 (2H, m), 2.06 (1H, ddd, J = 14.0, 9.3, 4.6 Hz), 1.75 (1H, m), 1.37 (3H, s), 1.32 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7, 144.9, 142.0, 109.2, 72.8, 71.5, 27.8, 26.1, 24.3, 16.0; HRMS (EI^+) calcd for $C_9H_{11}O_3$ $[M-Me]^+$ 167.0708, found 167.0714.

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