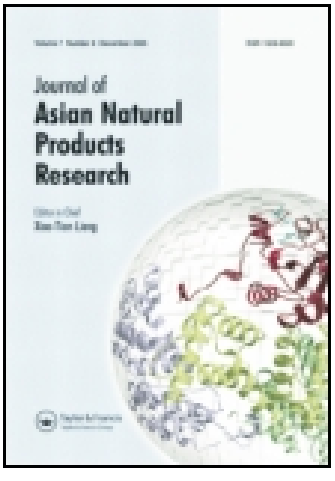

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Total synthesis of (+/ -)-4-demethylenglerin A

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Racemic 4-demethylenglerin A (**1′**), a simplified analog of the guaiane-type sesquiterpene englerin A (**1**), has been synthesized. The cyclic hydrocarbon core structure was built through modified Metz approach using epoxynitrile cyclization and direct Aldol reaction to prepare the precursor of RCM. The primary cytotoxicity test summarized that C4 methyl has marked impacts on the bioactivity.

Keywords: 4-demethylenglerin A; total synthesis; epoxynitrile cyclization

1. Introduction

(−)-Englerin A is a guaiane sesquiterpenoid which was extracted from *Phyllanthus engleri*, a plant surviving in the east African countries of Tanzania and Zimbabwe, by Beutler and his colleagues in 2008 [1] (Figure 1). It is shown to potently and selectively inhibit the proliferation of renal cancer cell lines [1,2]. By the way, renal cancer is a major cause of morbidity and mortality in adults [3], while due to the adverse effects of commercial drugs, their applications in treatment are restricted [4]. Furthermore, the molecular architecture of englerin A is fantastic, possessing a [5,6,5]-oxa-tricyclic ring system and seven chiral centers. With this background, englerin A has been of great concern and there are many studies on its total synthesis [5–11] and structure–activity relationships currently. It has been confirmed that two different ester groups at C6 and C9 were essential to keep its bioactivity [7] and that replacing the C7 isopropyl group with an ethyl group or a methyl group resulted in a significant decrease in activity [7]. However, the significance of 4-methyl has not been elucidated. With this in mind, our study on the total synthesis of 4-demethylenglerin A is carried out to identify the impact of 4-substituent.

2. Results and discussion

From our retrosynthetic analysis (Scheme 1), we turned to construct hydroazulene ring system by the modified procedure [11] of Metz which involves ring-closing metathesis of **5** followed by acylation and a transannular epoxide-opening from diol **3**, the acetyl unit could be used to set up the isopropyl group. We proposed that precursor **5** might be rapidly assembled by the direct Aldol reaction between the Weinreb amide **6** and compound **7** [12].

Our synthesis started with commercially available (z)-hex-4-en-1-ol (**8**) which could be converted into the key intermediate aldehyde **7** in good overall yield via eight-step preparation, involving in turn iodide of the enol, acetonitrile of **9**, epoxidation of **10** with 3-chloroperbenzoic acid

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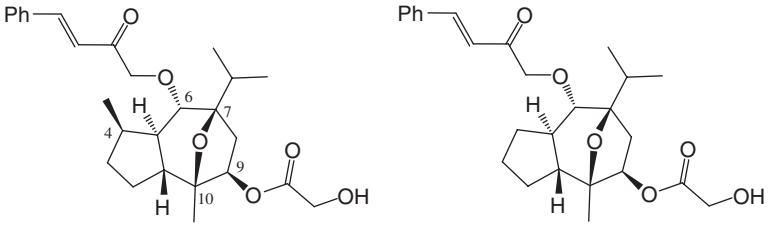


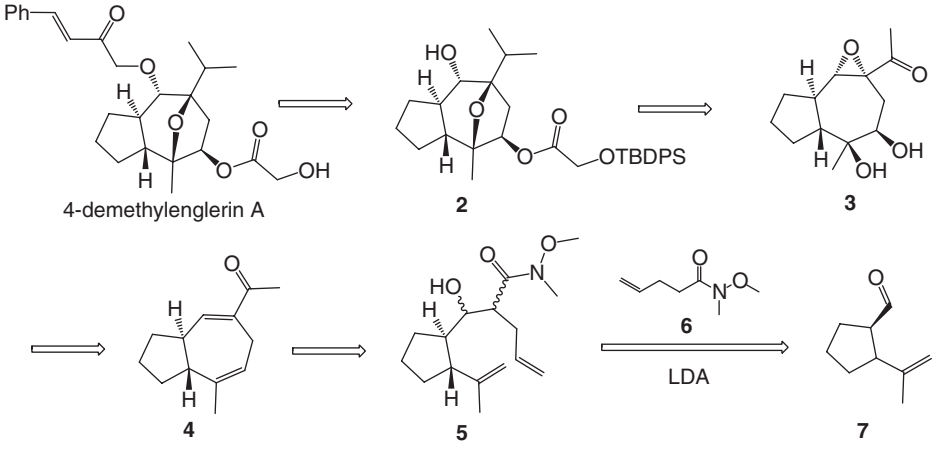
Figure 1. Structure of (+ / −)-4-demethy-lenglerin A (Compound **1′**).

(*m*-CPBA), and lithium hexamethyldisilazide (LHDMS)-promoted cyclization [10,13] of epoxynitrile **11** to afford cyclopentane **12**, whose relative configuration was inferred from the NOESY spectrum (Scheme 2). Followed by Swern oxidation of **12**, Wittig reaction of **13** and diisobutyl aluminum hydride (DIBALH) reduction furnished aldehyde **7** successfully (Scheme 2).

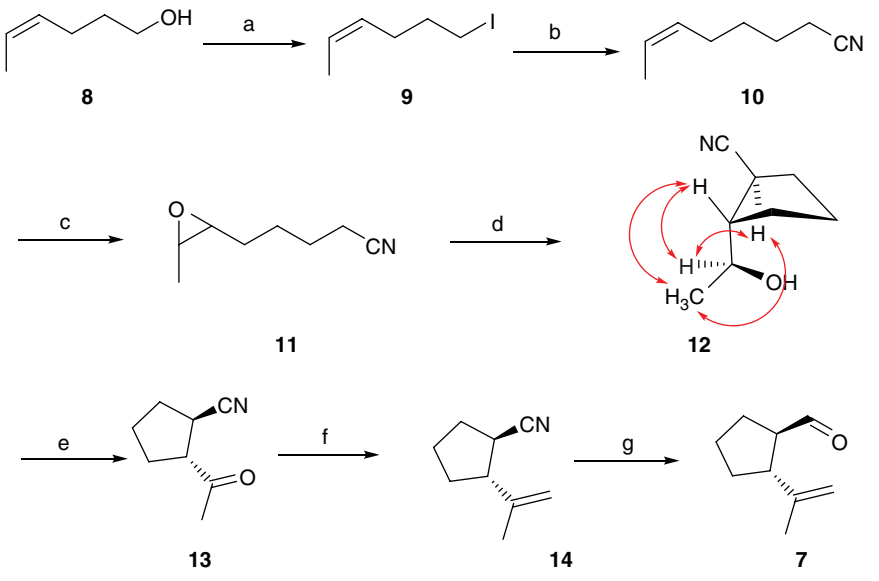
Afterwards, compound **5** could be prepared through the direct asymmetric Aldol reaction. In turn, compound **15** was obtained by the following ring-closing metathesis with the Grubbs II catalyst. After converting the Weinreb amide group to acetyl function [14], the elimination could go on smoothly by treating the acetyl derivate with methanesulfonyl chloride (MsCl) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a one-pot reaction [11]. The epoxidation would only happen to the double bonds which was conjugating with the carbonyl group in the Weitz–Scheffer conditions (NaOH, H_2O_2) (Scheme 3).

With compound **17** in hand, the cis-diol **3** could be obtained after treating with osmium tetroxide/*N*-methylmorpholine-N-oxide (NMO). Following Metz approach, when compound **3** was subjected to be esterified with (tert-butyldiphenylsilyloxy)acetyl chloride [15] in pyridine, compound **18** was received, but the isomer **18′** was found at the same time (Scheme 4)**.** The proportion of the two was 2.4:1. The structures of compounds **18** and **18′** were confirmed by their HSQC, HMBC, and COSY spectra correspondingly (Scheme 6). Their relative stereochemistry was determined by NOESY experiment (Scheme 6).

After methylenation of the acetyl unit, the desired oxygen-bridged moiety could be formed with high regioselectivity by simply treating with a catalytic amount of



Scheme 1. Retrosynthetic analysis of 4-demethylenglerin A.

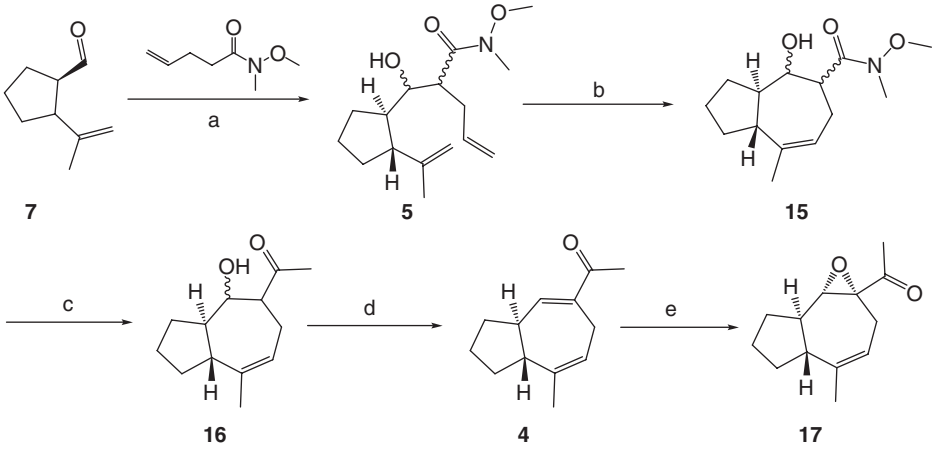


Scheme 2. Preparation of aldehyde **7**. Reagents and conditions: (a) I_2, Ph_3P, IMZ, 94%; (b) CH_3CN, *n*-BnLi; (c) *m*-CPBA; (d) LHDMS; (e) $(COCl)_2$, DMSO, Et_3N; (f) Ph_3PCH_2Br, *n*-BnLi; (g) DIBALH.

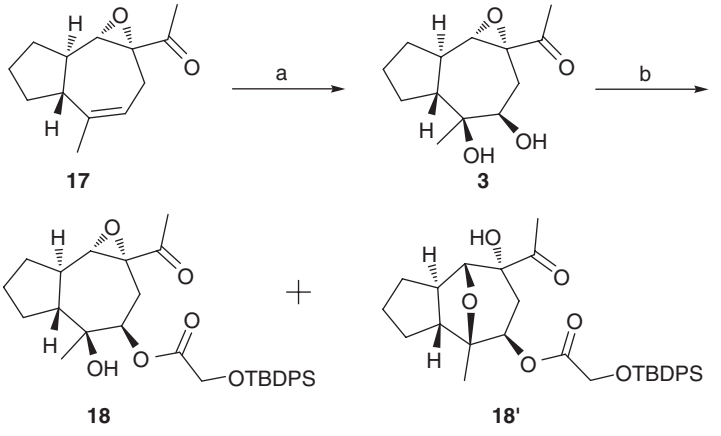
pyridinium *p*-toluenesulfonate (PPTS) at room temperature. After hydrogenation of **19** with Pd/C and Yamaguchi esterification [16] of **2**, we finally removed the TBDPS group at the glycolic acid moiety via tetrabutylammonium fluoride (TBAF) to achieve the target molecule **1′** (Scheme 5).

Unfortunately, in primary cytotoxicity test, compound **1′** showed no significant inhibitory effects against ACHN cell lines ($IC_{50} > 1$ μmol).

In summary, we have accomplished a racemic total synthesis of 4-demethylenglerin A through modified Metz approach



Scheme 3. Synthesis of compound **17**. Reagents and conditions: (a) LDA,THF, − 78°C; (b) Grubbs 2nd, DCM, reflux; (c) CH_3MgBr, 0°C r.t; (d) Et_3N, MsCl, DBU; (e) $NaOH,H_2O_2$.



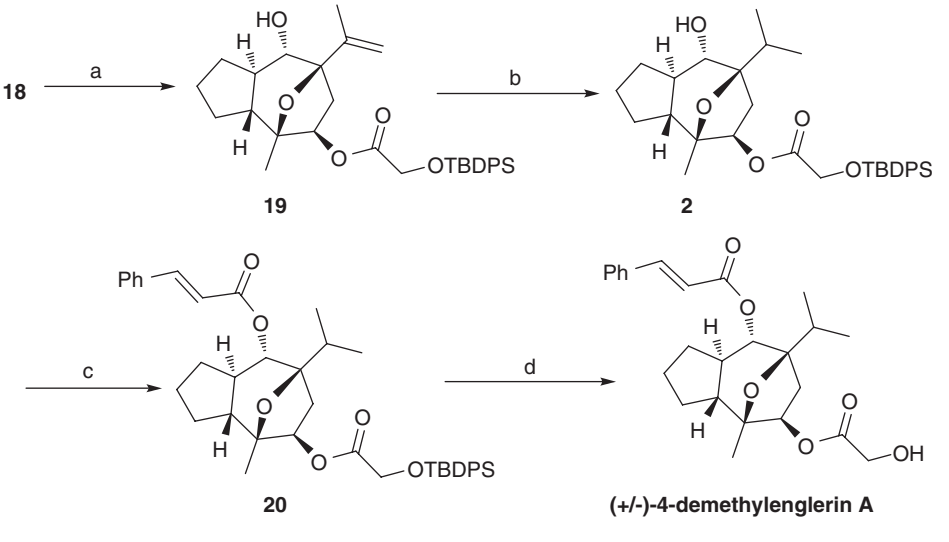
Scheme 4. Establishment of compound **18**. Reagents and conditions: (a) OsO_4, NMO; (b) $TBDPSOCH_2COCl$, Pyr.

using epoxynitrile cyclization and a ring-closing metathesis to give the hydroazulene ring systems as key operations. The strategy presented herein allows the preparation of compound **1′** in 18 steps with an overall yield of 8.0% commenced with commercial (z)-hex-4-en-1-ol (**8**). However, the cytotoxicity result summarized that C4 methyl may be crucial to maintain the biological activity.

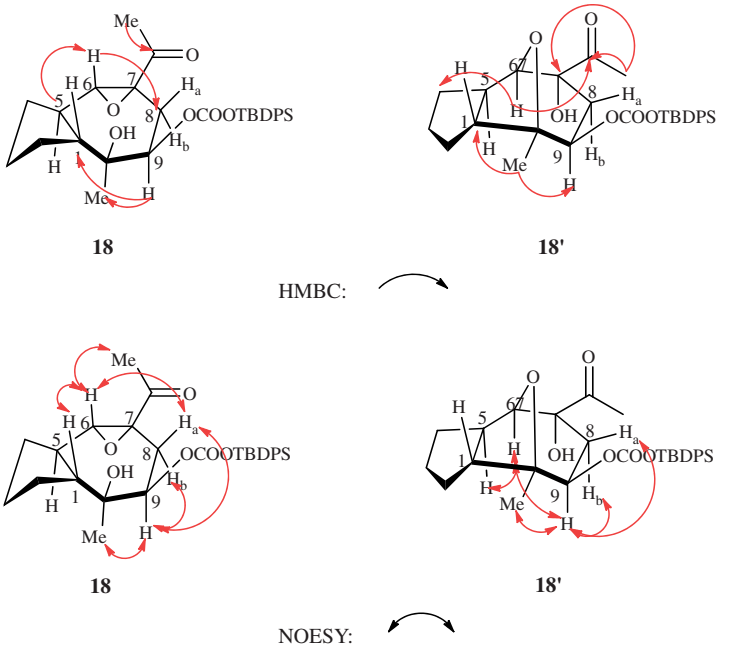
3. Experimental

3.1 General experimental procedures

NMR spectra were recorded on Mercury-plus 400 (Varian, Palo Alto, CA, USA) or else on a Varian Inova-600 NMR spectrometer (Varian, Palo Alto, CA, USA) with $CDCl_3$ (J&K, Beijing, China) as the solvent. HR-ESI-MS were determined on an Auto-Spec Ultima-TOF spectrometer (Agilent, Santa Clara, CA, USA). Column chroma-



Scheme 5. Completion of the synthesis of (+/−)-4-demethylenglerin A. Reagents and conditions: (a) Ph_3CH_2Br, *n*-BnLi, PPTS (b) H_2, Pd/C; (c) trans-cinnamoyl chloride, Et_3N, DMAP; (d) TBAF, HOAc.



Scheme 6. The key HMBC and NOESY correlations of compounds **18** and **18′**.

tography was carried out on silica gel (100–200 mesh; Qingdao Marine Chemical Inc., Qingdao, China). Reactions were monitored using thin-layer silica gel chromatography (TLC) using GF_{254} (Qingdao Marine Chemical Inc.). The spots were visualized under UV light or by spraying with 10% sulfuric acid in EtOH followed by heating. Cis-3-hexen-1-ol, *n*-BnLi, LHDMS, Ph_3PCH_3Br, DIBALH, and $MgCH_3Br$ were purchased from Acros Organics (Fair Lawn, NJ, USA) . DBU, NMO, and Grubbs II were purchased from Alfa Aesar (Tianjin, China). Other reagents and solvents were from Beijing Chemical Works (Beijing, China). Reactions were carried out under argon atmosphere.

3.2 (z)-6-Iodohex-2-ene (9)

To a solution of cis-3-hexen-1-ol **8** (10 g, 100 mmol) in CH_2Cl_2 (200 ml) at 0°C was added PPh_3 (39.3 g, 150 mmol), Imidazole (20.4 g, 300 mmol), and I_2 (38.1 g, 150 mmol). The reaction mixture was kept at 0°C for 4 h before being quenched with saturated aqueous Na_2SO_3. The aqueous layer was extracted with Et_2O (1 × 50 ml). The combined organic phases were washed with saturated aqueous NaCl (100 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo* carefully. The resulting oil was purified by flash column chromatography (Et_2O:petroleum ether (PE), 1:5) to afford the product **9** as a colorless oil (19.75 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.63–5.45 (m, 1H), 5.41–5.25 (m, 1H), 3.20 (t, J = 6.9 Hz, 2H), 2.16 (q, J = 7.2 Hz, 2H), 1.92–1.85 (m, 2H), 1.71–1.58 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 128.2, 125.5, 33.2, 27.6, 13.0, 6.6.

3.3 (z)-Oct-6-enenitrile (10)

To a solution of CH_3CN (14.2 ml, 270 mmol) in THF (150 ml) was added *n*-BnLi (2.4 M in THF, 93.8 ml, 225 mmol) at −78°C under argon atmosphere. After being stirred at −78°C for 1.5 h, **9** (18.8 g, 90 mmol) in THF (50 ml) was added, and the mixture was stirred at −78°C for 3 h.

The mixture was diluted with water and extracted with CH_2Cl_2, washed with brine, dried, concentrated, and purified by flash chromatography (Et_2O:PE, 1:5) to give the nitrile **10** (9.3 g, 84%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.54–5.45 (m, 1H), 5.39–5.31 (m, 1H), 2.35 (t, $J = 7.1$ Hz, 2H), 2.09 (q, $J = 7.2$ Hz, 2H), 1.72–1.64 (m, 2H), 1.61 (dd, $J = 6.7$, 0.8 Hz, 3H), 1.57–1.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 129.0, 124.5, 119.5, 28.2, 25.6, 24.6, 16.8, 12.5. HR-ESI-MS: *m/z* 124.0870 $[M + H]^+$ (calcd for $C_8H_{14}N$, 124.1120).

3.4 5-(3-Methyloxiran-2-yl) pentanenitrile (11)

To an ice-cooled solution of **10** (7 g, 56.8 mmol) in CH_2Cl_2 (90 ml) was added *m*-CPBA (8.7 g, 43 mmol) in portions. After being stirred at 0°C for 30 min, the mixture was moved to room temperature for further 1 h. The suspension was filtrated, extracted with CH_2Cl_2, washed with saturated $Na_2S_2O_3$ and $NaHCO_3$, dried, concentrated, and purified by column chromatography (Et_2O:PE, 1:7) to afford the epoxide **11** (6.9 g, 87%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.09–3.03 (m, 1H), 2.92–2.87 (m, 1H), 2.39 (t, $J = 6.9$ Hz, 2H), 1.80–1.72 (m, 2H), 1.71–1.48 (m, 4H), 1.27 (d, $J = 5.5$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 119.4, 56.4, 52.4, 26.7, 25.6, 25.03, 17.0, 13.1. HR-ESI-MS: *m/z* 140.1069 $[M + H]^+$ (calcd for $C_8H_{14}ON$, 140.1075).

3.5 (1R, 2R*)-2-(1-Hydroxyethyl) cyclopentanecarbonitrile (12)*

Compound **11** (6.9 g, 49.5 mmol) was dissolved in toluene (120 ml) under an argon atmosphere. Then LHMDS (1.0 M in THF, 99 ml, 99 mmol) was added at −78°C gradually. After being stirred at 0°C for 5.5 h, the mixture was cooled to −78°C and diluted with saturated NH_4Cl, extracted with AcOEt. The combined organic layers were dried over Na_2SO_4. The solvents were removed *in vacuo*, and the residue was purified by column chromatography (PE:AcOEt, 5:1) to give **12** (5.6 g, 82%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.68 (p, $J = 6.4$ Hz, 1H), 2.75 (dd, $J = 15.8$, 7.8 Hz, 1H), 2.25–2.16 (m, 1H), 2.10–1.99 (m, 1H), 1.97–1.82 (m, 2H), 1.80–1.65 (m, 2H), 1.45 (s, 1H), 1.41–1.30 (m, 1H), 1.26 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 124.0, 70.4, 52.7, 31.6, 29.7, 29.3, 25.3, 22.6. HR-ESI-MS: *m/z* 140.1067 $[M + H]^+$ (calcd for $C_8H_{14}ON$, 140.1075).

3.6 (1R, 2R*)-2-Acetylcyclopentanecarbonitrile (13)*

To a chilled (−78°C) solution of $(COCl)_2$ (6.9 ml, 80 mmol) in CH_2Cl_2 (100 ml) was added dropwise a solution of anhydrous DMSO (11.4 ml, 160.8 mmol) in CH_2Cl_2 (30 ml). After being stirred for 15 min at −78°C, a solution of **12** (5.6 g, 40 mmol) in CH_2Cl_2 (20 ml) was added gradually and the mixture was stirred for 30 min. Finally, Et_3N (43.1 ml, 200 mmol) was added dropwise at the same condition. After being stirred for another 30 min, the reaction mixture was allowed to warm up to room temperature and poured into water. The aqueous layer was extracted with Et_2O, dried, and chromatographed (Et_2O:PE, 1:5) to afford the corresponding ketone (**13**) (4.9 g, 89%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.31–3.20 (m, 2H), 2.24 (s, 3H), 2.24–2.06 (m, 2H), 2.02–1.91 (m, 1H), 1.91–1.79 (m, 1H), 1.75–1.66 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.0, 122.2, 56.3, 31.1, 29.4, 28.7, 28.4, 25.0.

3.7 (1R, 2R*)-2-(Prop-1-en-2-yl) cyclopentanecarbonitrile (14)*

Ph_3PCH_3Br (35.5 g, 99.7 mmol) was suspended in dry THF (100 ml), and a solution of *n*-BuLi (2.4 M in hexane, 41.5 ml, 99.7 mmol) was added at 0°C. After

stirring at 0°C for 1 h, a solution of the ketone **13** (4.5 g, 33.2 mmol) in THF (20 ml) was added, and the mixture was stirred at 0°C for 4.5 h. The mixture was diluted with water, washed with saturated NH_4Cl and brine, dried, concentrated, and chromatographed (Et_2O:PE, 1:20) to give **14** (4.1 g, 91%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.92–4.86 (m, 2H), 2.76 (dd, $J = 18.4$, 8.9 Hz, 1H), 2.64 (dd, $J = 18.1$, 9.0 Hz, 1H), 2.27–2.12 (m, 1H), 2.07–1.91 (m, 2H), 1.90–1.73 (m, 5H), 1.55 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.77, 122.52, 111.54, 52.35, 32.44, 30.76, 30.63, 24.01, 20.20. HR-ESI-MS: *m/z* 158.0941 $[M + Na]^+$ (calcd for $C_9H_{13}NNa$, 158.0940).

3.8 (1R*, 2R*)-2-(Prop-1-en-2-yl) cyclopentanecarbaldehyde (7)

To a solution of **14** (4.5 g, 33.3 mmol) in CH_2Cl_2 (70 ml) was added a solution of DIBALH (1.1 M in hexane, 60.5 ml, 66.6 mmol) dropwise at −78°C. The reaction mixture was maintained for 2 h and then quenched with MeOH (20 ml). Saturated aqueous potassium sodium tartrate (50 ml) was added and further stirred overnight at room temperature. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (Et_2O:PE, 1:50) afforded a pale yellow oil (3.2 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.59 (d, $J = 3.0$ Hz, 1H), 4.77 (d, $J = 6.8$ Hz, 2H), 2.75 (dd, $J = 16.8$, 8.4 Hz, 1H), 2.70–2.63 (m, 1H), 1.95–1.85 (m, 3H), 1.83–1.77 (m, 1H), 1.74 (s, 3H), 1.70–1.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.5, 145.8, 110.5, 55.5, 48.4, 31.8, 26.5, 24.8, 20.6.

3.9 2-(Hydroxyl((1R*,2R*)-2-(prop-1-en-2-yl)cyclopentyl)methyl)-N-methoxy-N-methylpent-4-enamide (5)

To a solution of Lithium diisopropylamide (35 mmol) which is prepared by addition of *n*-BuLi (2.4 M in hexane, 14.6 ml) to a solution of diisopropylamine (4.9 ml) in THF (20 ml) was added Weinreb amide **6** [17] (1.1 g, 7.73 mmol) in THF (5 ml) via cannula at −78°C. After the mixture was stirred for 15 min, a solution of **7** (480 mg, 3.48 mmol) in THF (5 ml) was added and stirred for 2 h. Then the mixture was quenched with saturated NH_4Cl, extracted with AcOEt, dried, concentrated, and chromatographed (PE:AcOEt, 3:1) to afford **5** (812 mg, 83% in total) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.81–5.69 (m, 1H), 5.08 (d, $J = 17.0$ Hz, 1H), 5.01 (d, $J = 10.0$ Hz, 1H), 4.73 (s, 2H), 3.75–3.71 (m, 1H), 3.70 (s, 3H), 3.18 (s, 3H), 3.03–2.98 (m, 1H), 2.50–2.35 (m, 3H), 1.93–1.84 (m, 1H), 1.81–1.73 (m, 1H), 1.67 (s, 3H), 1.64–1.58 (m, 4H), 1.51–1.41 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 176.4, 147.1, 135.4, 116.9, 110.8, 71.9, 61.4, 49.9, 46.6, 44.7, 34.5, 32.0, 31.7, 24.6, 24.4, 19.5. HR-ESI-MS: *m/z* 282.2064 $[M + H]^+$ (calcd for $C_{16}H_{28}O_3N$, 282.2063).

3.10 (3aR*,8aR*)-4-Hydroxy-N-methoxy-N,8-dimethyl-1,2,3,3a,4,5,6,8a-octahydroazulene-5-carboxamide (15)

To a degassed solution of **5** (500 mg, 2.7 mmol) in CH_2Cl_2 (30 ml) was added Grubbs II catalyst (100 mg, 0.12 mmol). After being heated to reflux for 24 h, the mixture was concentrated and chromatographed (PE:AcOEt, 2:1) to afford **15** (610 mg, 89%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.61–5.58 (m, 1H), 3.83 (t, $J = 9.8$ Hz, 1H), 3.71 (s, 3H), 3.21 (s, 3H), 2.62–2.59 (m, 1H), 2.49–2.32 (m, 2H), 2.26–2.19 (m, 1H), 2.09–1.97 (m, 2H), 1.89–1.84 (m, 1H), 1.74 (s, 3H), 1.71–1.65 (m, 2H), 1.65–1.49 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.2, 142.9, 123.4, 79.5, 61.4, 49.2, 46.6, 43.6, 32.0, 30.3, 30.2, 26.8, 23.7, 21.4. HR-ESI-MS: *m/z* 254.1743 $[M + H]^+$ (calcd for $C_{14}H_{24}O_3N$, 254.1750).

3.11 1-((3aR*,8aR*)-4-Hydroxy-8-methyl-1,2,3,3a,4,5,6,8a-octahydroazulen-5-yl)ethanone (16)

Compound **15** (70 mg, 0.276 mmol) was dissolved in anhydrous THF (5 ml) under an argon atmosphere, to which $MgCH_3Br$ (1.0 M in THF, 1.4 ml, 1.38 mmol) was added at 0°C gradually. After being stirred at room temperature for 5.5 h, the mixture was cooled to 0°C and diluted with saturated NH_4Cl, extracted with AcOEt, dried, concentrated, and chromatographed (PE:AcOEt, 5:1) to give **16** (50 mg, 87%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.59–5.54 (m, 1H), 3.77 (t, $J = 9.5$ Hz, 1H), 2.39–2.34 (m, 2H), 2.21 (s, 3H), 2.12–1.97 (m, 3H), 1.91–1.82 (m, 1H), 1.75–1.64 (m, 6H), 1.60–1.46 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 212.3, 143.2, 122.9, 79.7, 57.5, 49.2, 43.6, 30.2, 30.2, 29.8, 25.8, 23.7, 21.5. HR-ESI-MS: *m/z* 209.1533 $[M + H]^+$ (calcd for $C_{13}H_{21}O_2$, 209.1536).

3.12 1-((3aS*,8aR*)-8-Methyl-1,2,3,3a,6,8a-hexahydroazulen-5-yl) ethanone (4)

To an ice-cooled solution of **16** (440 mg, 2.13 mmol) in anhydrous CH_2Cl_2 (20 ml) were added Et_3N (1.8 ml, 12.8 mmol) and MsCl (1 ml, 12.8 mmol) in order. After being stirred at room temperature for 3 h, DBU (4.9 ml, 32.8 mmol) was added. The mixture was stirred overnight and quenched with saturated NH_4Cl, extracted with CH_2Cl_2 and dried. The solvents were removed under reduced pressure, and the residue was purified by chromatography (Et_2O:PE, 1:5) to afford the epoxide (390 mg, 97%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.92 (d, $J = 4.9$ Hz, 1H), 5.36 (d, $J = 5.9$ Hz, 1H), 3.29 (dd, $J = 17.7$, 7.9 Hz, 1H), 2.94 (d, $J = 17.8$ Hz, 1H), 2.85–2.70 (m, 1H), 2.31 (s, 3H), 2.22–2.18 (m, 1H), 2.16–2.01 (m, 2H), 1.76–1.66 (m, 2H), 1.65 (s, 3H), 1.63–1.53 (m, 1H), 1.52–1.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.1, 147.8, 141.8, 139.2, 119.9, 46.8, 43.7, 31.6, 31.0, 25.1, 23.8, 23.6, 21.7. HR-ESI-MS: *m/z* 191.1428 $[M + H]^+$ (calcd for $C_{13}H_{19}O$, 191.1430).

3.13 1-((1aR*,4aR*,7aR*,7bS*)-4-Methyl-1a,2,4a,5,6,7,7a,7b-octahydroazuleno[4,5-b]oxiren-1a-yl) ethanone (17)

α,β-Unsaturated ketone (20 mg, 106 μmol) was dissolved in methanol (2 ml). Afterwards, aqueous NaOH (2 N, 200 μl) and aqueous hydrogen peroxide solution (30%, 166 μl) were added in order. The mixture was stirred for 15 min and quenched with saturated aqueous $Na_2S_2O_3$ solution. The reaction mixture was extracted with CH_2Cl_2, dried, concentrated, and purified by flash chromatography (Et_2O:PE, 1:3) to give epoxide **17** as a white solid (20 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.39 (d, $J = 8.6$ Hz, 1H), 3.09 (d, $J = 7.5$ Hz, 1H), 2.87 (dd, $J = 15.9$, 8.7 Hz, 1H), 2.29–2.18 (m, 3H), 2.09–1.95 (m, 5H), 1.71–1.64 (m, 5H), 1.57–1.48 (m, 1H), 1.40–1.28 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 207.1, 139.1, 117.7, 64.9, 63.1, 47.9, 44.2, 30.9, 30.7, 27.6, 24.4, 23.2, 21.8. HR-ESI-MS: *m/z* 207.1375 $[M + H]^+$ (calcd for $C_{13}H_{19}O_2$, 207.1379).

3.14 1-((1aR*,3R*,4S*,4aR*,7aR*, 7bS*)-3,4-Dihydroxy-4-methy ldecahydroazuleno[4,5-b]oxiren-1a-yl) ethanone (3)

Compound **17** (20 mg, 97 μmol) and NMO (23 mg, 194 μmol) were dissolved in a 6:6:1 mixture of THF, acetone, and water (1.3 ml). Then the solution of potassium osmate dihydrate (1.7 mg, 0.68 μmol) in toluene was added. The reaction mixture was stirred at room temperature for 24 h, quenched with saturated aqueous $Na_2S_2O_3$ solution, extracted with AcOEt, and dried. The solvents were removed under reduced

pressure, and the residue was purified by flash chromatography (PE: AcOEt; 2:1) to give **3** (22 mg, 95%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.28 (s, 1H), 3.69 (d, $J = 7.0$ Hz, 1H), 3.08 (d, $J = 6.5$ Hz, 1H), 2.90 (s, 1H), 2.76 (dd, $J = 15.6$, 7.1 Hz, 1H), 2.30–2.14 (m, 2H), 2.08 (s, 3H), 1.86–1.76 (m, 1H), 1.72–1.55 (m, 4H), 1.52–1.43 (m, 1H), 1.04 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 212.8, 76.7, 73.4, 64.7, 62.0, 46.6, 43.0, 33.3, 30.6, 27.2, 25.9, 23.6, 17.7. HR-ESI-MS: *m/z* 263.1250 $[M + Na]^+$ (calcd for $C_{13}H_{20}O_4Na$, 263.1253).

3.15 (1aR,3R*,4S*,4aR*,7aR*,7bS*)-1a-Acetyl-4-hydroxy-4-methyldecahydroazuleno[4,5-b]oxiren-3-yl 2-((tert-butyldiphenylsilyl)oxy)acetate (18)*

Diol **3** (310 mg, 1.27 mmol) and the (*t*-butyldiphenylsilanyloxy) acetyl chloride [15] were dissolved in pyridine (20 ml). The solution was stirred at ambient temperature overnight. Then the solvent was removed *in vacuo*. The residue was purified chromatographically (Et_2O:PE, 1:5) to afford **18′** (170 mg) and **18** (410 mg, 60%) as a pale yellow oil.

1H NMR (400 MHz, CDCl3) δ: 7.70–7.63 (m, 4H), 7.45–7.36 (m, 6H), 4.91 (d, $J = 7.8$ Hz, 1H), 4.34–4.23 (m, 2H), 3.17–3.09 (m, 2H), 2.24–2.11 (m, 2H), 1.93 (s, 3H), 1.66–1.55 (m, 6H), 1.50 (d, $J = 15.5$ Hz, 1H), 1.09 (s, 3H), 1.08 (s, 9H). 13C NMR (150 MHz, CDCl3) δ: 205.8, 170.4, 135.5, 135.5, 135.5, 135.5, 132.8, 132.8, 130.0, 130.0, 127.9, 127.9, 127.8, 127.8, 75.8, 75.4, 64.2, 62.6, 62.6, 47.6, 42.7, 33.5, 26.9, 26.9, 26.7, 26.7, 26.7, 25.5, 22.8, 19.2, 18.4. HR-ESI-MS: *m/z* 559.2467 [M + Na] + (calcd for $C_{31}H_{40}O_6NaSi$, 559.2467).

(3a*R,4*S**,5*R**,7*R**,8*R**,8a*R**)-7-Acetyl-7-hydroxy-4-methyldecahydro-4,8-epoxyazulen-5-yl 2-((tert-butyldiphenylsilyl)oxy)acetate 18′**:^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, $J = 6.5$ Hz, 4H), 7.45–7.35 (m, 6H), 5.18–5.03 (m, 1H), 4.32 (q, $J = 16.5$ Hz, 2H), 3.03 (d, $J = 6.6$ Hz, 1H), 2.22 (d, $J = 13.6$ Hz, 1H), 2.18–2.12 (m, 2H), 2.02 (s, 3H), 1.77–1.54 (m, 7H), 1.09 (s, 9H), 1.03 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 206.7, 169.3, 135.6, 135.6, 135.5, 135.5, 132.7, 132.7, 123.0, 123.0, 127.9, 127.9, 127.8, 127.8, 76.1, 73.6, 64.8, 62.4, 61.8, 49.8, 39.6, 32.2, 30.6, 27.2, 26.7, 26.7, 26.7, 26.2, 24.9, 23.2, 19.2. HR-ESI-MS: *m/z* 559.2486 $[M + Na]^+$ (calcd for $C_{31}H_{40}O_6NaSi$, 559.2467).

3.16 (3aR,4S*,7R*,8aR*)-8-Hydroxy-4-methyl-7-(prop-1-en-2-yl)decahydro-4,7-epoxyazulen-5-yl 2-((tert-butyldiphenylsilyl)oxy)acetate (19)*

To a suspension of Ph_3PCH_3Br (798 mg, 2.24 mmol) in THF (12 ml) was added *n*-BnLi (2.4 M in hexanes, 870 μl, 2.08 mmol) at 0°C. After stirring at 0°C for 1 h, a solution of **18** (400 mg, 746 μmol) in THF (3 ml) was added, and the mixture was stirred at 0°C for 0.5 h. The mixture was diluted with saturated NH_4Cl, extracted with CH_2Cl_2, dried, and concentrated. Afterwards, the residue was dissolved in CH_2Cl_2 and PPTS (19 mg, 74.6 μmol) was added. After being stirred for two additional hours at ambient temperature, the resulting mixture was diluted with saturated $NaHCO_3$, extracted with CH_2Cl_2, dried, concentrated, and purified by chromatography (Et_2O:PE, 1:4) to give **19** (360 mg, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68–7.63 (m, 4H), 7.44–7.32 (m, 6H), 5.06 (d, $J = 4.8$ Hz, 1H), 5.03 (s, 1H), 4.76 (s, 1H), 4.22 (d, $J = 2.2$ Hz, 2H), 3.20 (d, $J = 9.0$ Hz, 1H), 2.70 (dd, $J = 14.0$, 8.0 Hz, 1H), 1.81 (s, 3H), 1.70–1.64 (m, 3H), 1.55–1.38 (m, 3H), 1.27–1.14 (m, 4H), 1.08 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8, 145.8, 135.6, 135.6, 135.6, 135.6, 132.7, 132.7, 129.9, 129.9, 127.8, 127.8, 127.8, 127.8, 113.8,

87.3, 84.2, 75.2, 73.0, 62.2, 52.0, 43.8, 40.1, 28.7, 26.7, 26.7, 26.7, 25.2, 21.4, 19.2, 19.0, 18.8. HR-ESI-MS: *m/z* 557.2685 $[M + Na]^+$ (calcd for $C_{32}H_{42}O_5NaSi$, 557.2693).

3.17 (3aR,4S*,5R*,7R*,8S*,8aR*)-8-Hydroxy-7-isopropyl-4-methyldecahydro-4,7-epoxyazulen-5-yl 2-((tert-butyldiphenylsilyl)oxy)acetate (2)*

To the solution of alkene **19** (200 mg, 374 μmol) in ethanol (10 ml), 10% Pd/C was added. The resulting mixture was stirred under hydrogen (1 atm) for 24 h. Then the solvent was removed. Flash chromatography of the residue gave **2** as a colorless oil (190 mg, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, $J = 7.2$ Hz, 4H), 7.46–7.35 (m, 6H), 5.06 (dd, $J = 7.9$, 2.7 Hz, 1H), 4.25 (s, 2H), 3.49 (d, $J = 8.8$ Hz, 1H), 2.41 (dd, $J = 14.5$, 7.9 Hz, 1H), 2.04–1.90 (m, 2H), 1.73–1.59 (m, 3H), 1.43 (d, $J = 3.5$ Hz, 1H), 1.37–1.15 (m, 4H), 1.09 (s, 9H), 1.07 (s, 3H), 1.01 (dd, $J = 10.3$, 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 135.6, 135.6, 135.6, 135.6, 132.8, 132.7, 129.9, 129.9, 127.8, 127.8, 127.8, 127.8, 85.9, 84.2, 75.5, 74.8, 62.2, 52.5, 45.6, 38.7, 31.6, 28.0, 26.6, 26.6, 26.6, 25.1, 21.5, 19.2, 18.7, 18.2, 17.2. HR-ESI-MS: *m/z* 559.2851 $[M + Na]^+$ (calcd for $C_{32}H_{44}O_5NaSi$, 559.2850).

3.18 (3aR,4S*,5R*,7R*,8S*,8aR*)-5-(2-((tert-Butyldiphenylsilyl)oxy)acetoxy)-7-isopropyl-4-methyldecahydro-4,7-epoxyazulen-8-yl cinnamate (20)*

To a solution of **2** (22 mg, 41 μmol) in CH_2Cl_2 (2.7 ml) and Et_3N (0.3 ml), trans-cinnamoyl chloride (20.5 mg, 123 μmol) and DMAP (15 mg, 123 μmol) were added. The resulting solution was heated to reflux and stirred for 4 h, concentrated, and purified by column chromatography (Et_2O:PE, 1:3) to give **20** (26 mg, 95%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, $J = 7.0$ Hz, 4H), 7.65 (d, $J = 16.0$ Hz, 1H), 7.56–7.50 (m, 2H), 7.48–7.36 (m, 9H), 6.39 (d, $J = 16.0$ Hz, 1H), 5.10 (dd, $J = 7.7$, 2.9 Hz, 1H), 4.95 (d, $J = 8.9$ Hz, 1H), 4.27 (s, 2H), 2.60 (dd, $J = 14.5$, 7.8 Hz, 1H), 1.87 (m, 1H), 1.74 (m, 4H), 1.49 (d, $J = 11.8$ Hz, 2H), 1.40 (d, $J = 14.8$ Hz, 2H), 1.30–1.20 (m, 2H), 1.11 (s, 3H), 1.10 (s, 8H), 0.95 (dd, $J = 13.6$, 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 165.9, 145.1, 135.6, 135.6, 135.6, 135.6, 134.3, 134.3, 132.8, 132.7, 130.4, 129.9, 129.9, 129.9, 129.9, 128.9, 128.9, 128.1, 128.1, 127.8, 118.0, 85.3, 84.5, 75.43, 75.0, 62.2, 52.3, 44.2, 40.3, 32.7, 28.5, 26.7, 26.7, 26.7, 25.0, 21.3, 19.2, 18.7, 18.2, 17.3. HR-ESI-MS: *m/z* 667.3417 $[M + H]^+$ (calcd for $C_{41}H_{51}O_6Si$, 667.3449).

3.19 4-Demethylenglerin A (1′)

To an ice-cooled solution of **20** (20 mg, 3 μmol) and AcOH (38 mg, 630 μmol) in THF (2 ml) was added TBAF (19 mg, 70 μmol). After being stirred at room temperature overnight, saturated NH_4Cl was added at 0°C. The mixture was extracted with AcOEt, dried, concentrated, and chromatographed (PE:AcOEt, 1:1) to give 4-demethylenglerin A (12 mg, 94%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, $J = 16.0$ Hz, 1H), 7.51 (m, 2H), 7.40–7.35 (m, 3H), 6.38 (d, $J = 16.0$ Hz, 1H), 5.17 (dd, $J = 7.8$, 2.8 Hz, 1H), 4.96 (d, $J = 9.0$ Hz, 1H), 4.18 (s, 2H), 2.66 (dd, $J = 14.5$, 7.8 Hz, 1H), 2.24 (s, 1H), 1.90 (dt, $J = 13.9$, 6.9 Hz, 1H), 1.81 (dd, $J = 14.7$, 2.6 Hz, 2H), 1.74–1.65 (m, 2H), 1.55–1.46 (m, 1H), 1.43–1.34 (m, 2H), 1.24 (s, 2H), 1.18 (s, 3H), 0.97 (dd, $J = 18.7$, 6.9 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 173.0, 165.9, 145.2, 134.3, 130.4, 128.9, 128.9, 128.1, 128.1, 117.9, 85.4, 84.5, 76.5, 74.8, 60.6, 52.3, 44.3, 40.4, 32.8, 28.5, 25.0, 21.2, 18.8, 18.2, 17.3. HR-ESI-MS: *m/z*

429.2272 $[M + H]^+$ (calcd for $C_{25}H_{33}O_6$, 429.2271).

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