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Stereocontrolled Total Synthesis of (−)-Englerin A

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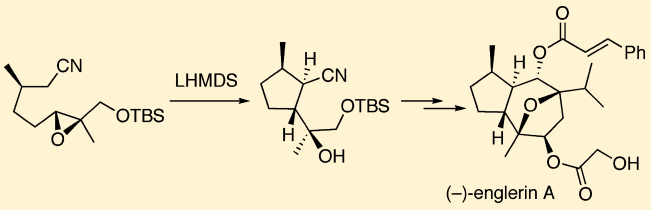
Supporting Information

ABSTRACT: The total synthesis of (−)-englerin A, a potent and selective inhibitor of renal cancer cell lines, is described. The key feature includes the stereocontrolled construction of the cyclopentane structure by taking advantage of a base-promoted epoxynitrile cyclization.

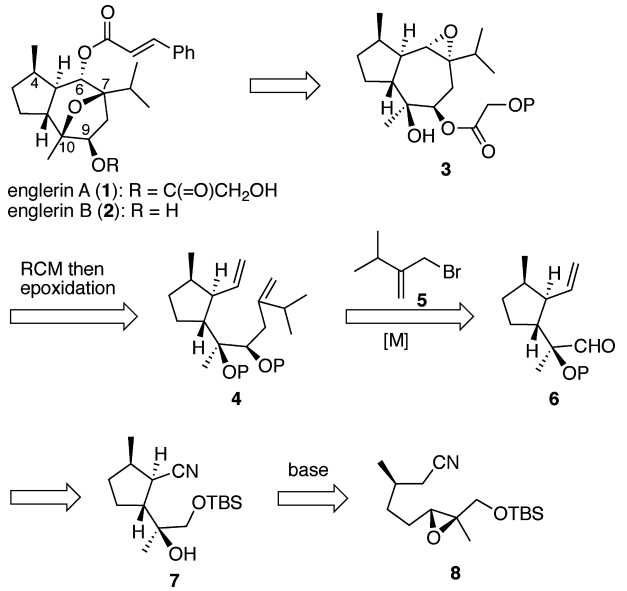


INTRODUCTION

Englerin A (**1**) is a guaiane sesquiterpene that was isolated by Beutler and co-workers from the stem bark of *Phyllanthus engleri*, a plant indigenous to the East African countries of Tanzania and Zimbabwe.[1] In a NCI 60-cell panel screening, this compound was found to be a potent and selective inhibitor of renal cancer cell lines at low nanomolar levels, while englerin B (**2**), lacking the C9 glycolate ester, was shown to be inactive.[1]

Englerin A (**1**) possesses a synthetically challenging oxatricyclic structure containing an ether bridge between the C7 and the C10 quaternary centers, and two different ester groups at C6 and C9. Because of the fascinating biological profile and the intriguing molecular architecture, englerin A (**1**) and its analogues have attracted much attention from the synthetic community,[2,3] resulting in six total syntheses[4,5] and four formal syntheses[6] based on elegant strategies for the past three years. In addition, the detailed SAR studies have been reported.[4e,7] Herein we report a novel total synthesis of (−)-englerin A (**1**), which features the highly stereoselective construction of the cyclopentane structure based on Stork's epoxynitrile cyclization.[8,9]

Scheme 1. Retrosynthetic Analysis of Englerin A



RESULTS AND DISCUSSION

From a retrosynthetic perspective, we focused on Christmann's approach[4a,e] to construct a 5,6,5-fused core structure, which involves ring closing metathesis[10] of **4** followed by stereoselective epoxidation of the resulting olefinic double bond and transannular epoxide-opening of **3** (Scheme 1). To stereoselectively access **4** we envisioned an approach from epoxynitrile **8** via base-promoted 5-exotet cyclization giving **7** and Barbier-type allylation of **6** using an allylmetal species derived from **5**.[4a,11]

Our synthesis commenced with an eight-step preparation of epoxynitrile **8** from commercially available ketone **9** (Scheme 2). Thus, Baeyer−Villiger oxidation of **9**,[12] DIBALH reduction of **10**, and Wittig reaction of the resulting lactol gave ester **11**. Upon successive tosylation, DIBALH reduction, and cyanation, **11** afforded allylic alcohol **12**. After Katsuki−Sharpless epoxidation of **12**,[13] silylation of **13** furnished epoxynitrile **8**.

The crucial base-promoted cyclization of **8** was then examined under various conditions according to Stork's protocol[8] (Table 1). When the reaction was conducted using 1.5 equiv of NHMDS or KHMDS in toluene at 0 °C, **7** was obtained in moderate yield (entries 1 and 3). In these cases, the use of 3 equiv of base at room temperature led to the production of γ-lactone **14** in very low yield without increase of the yield of **7**, suggesting the partial epimerization of **7** under the conditions (entries 2 and 4). The conditions using 1.2 or 2 equiv of LHMDS in THF at 0 °C turned out to cause a large extent of epimerization of **7**, although the cyclization occurred in acceptable yield (entries 5 and 6). On the other hand, when **8** was treated with 2 equiv of LHMDS in toluene−THF (2:1) at 0 °C, the cyclization took place stereoselectively to afford **7**

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Scheme 2. Preparation of Epoxynitrile 8

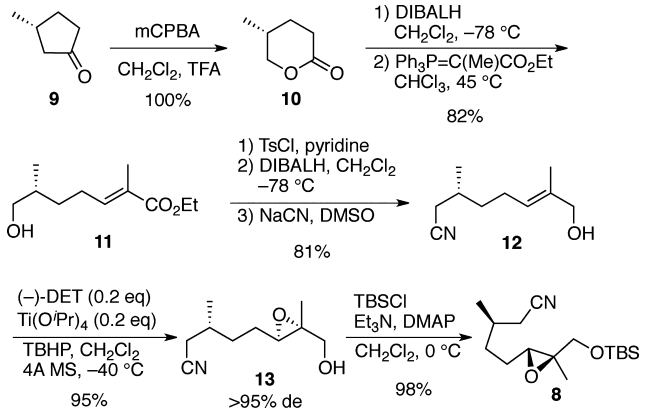
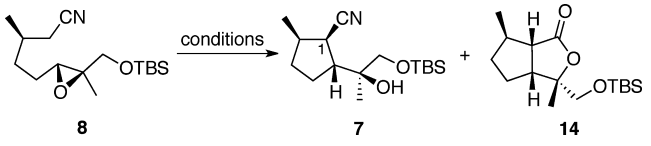


Table 1. Base-Promoted Cyclization of Epoxynitrile 8



entry	conditions	yield (%)[a] 7	14
1	NHMDS (1.5 equiv), toluene, 0 °C, 6 h	46	0
2	NHMDS (3.0 equiv), toluene, rt, 6 h	46	4
3	KHMDS (1.5 equiv), toluene, 0 °C, 6 h	62	0
4	KHMDS (3.0 equiv), toluene, rt, 1 h	53	3
5	LHMDS (1.2 equiv), THF, 0 °C, 2 h	84[b]	0
6	LHMDS (2.0 equiv), THF, 0 °C, 2 h	76[b]	0
7	LHMDS (2.0 equiv), toluene–THF (2:1), 0 °C, 3 h	87	0

[a]Isolated yield. [b]Obtained as a 1:1 mixture of **7** and its C1-epimer.

as the sole product in 87% yield (entry 7). In this particular case, the less polar toluene–THF solvent system effectively suppressed the epimerization, which was serious in the reactions using THF alone as solvent. The observed high stereoselectivity can be explained by assuming the preference of transition state **15a** over **15b** as depicted in Figure 1.

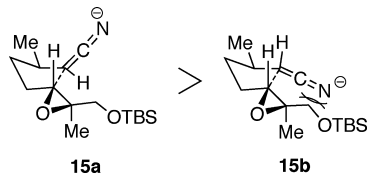


Figure 1. Stereoselectivity in the cyclization of epoxynitrile **8**.

After protection of the hydroxy group of **7** as its MOM ether (Scheme 3), **16** was converted to aldehyde **18** in good overall yield by a four-step sequence involving DIBALH reduction, Wittig methylenation, desilylation, and Swern oxidation. The stereostructure of **17** was confirmed by its NOESY spectrum.

Allylations of **18** with bromide **5** were examined under the conditions listed in Table 2. First, we investigated zinc-mediated coupling conditions following Christmann's procedure[4a] (entry 1); however, the reaction was rather sluggish and gave a 1.5:1 mixture of **19** and **20** in moderate yield. The increase of **5** and zinc did not much improve the diastereoisomeric ratio and the yield (entry 2). The conditions

Scheme 3. Preparation of Aldehyde 18

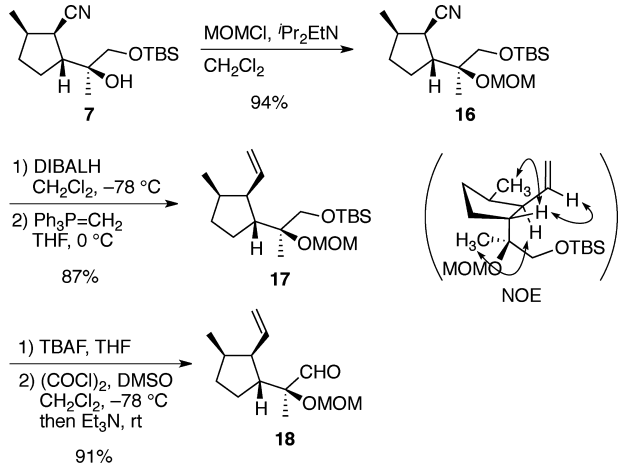
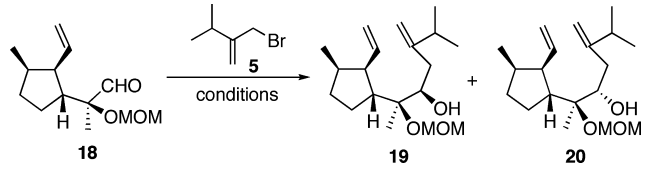


Table 2. Barbier-Type Allylations of 18 with 5



entry	conditions	yield (%)[a] 19 + 20	ratio 19:20[b]
1	**5** (2 equiv), Zn (3 equiv), aq NH_4Cl/THF, rt, 2 h; then sonication, rt, 1 h	47 (87)	1.5:1
2	**5** (4 equiv), Zn (6 equiv), aq NH_4Cl/THF, rt, 2 h; then sonication, rt, 1 h	62 (97)	1.7:1
3	**5** (4 equiv), Zn–Cu (6 equiv), aq NH_4Cl/THF, sonication, rt, 3 h	22 (44)	1:1
4	**5** (4 equiv), $CrCl_2$ (6 equiv), THF, rt, 3 h	82	1:1
5	**5** (6 equiv), In (4 equiv), THF, 0 °C, 4 h	95	8:1
6	**5** (4 equiv), In (4 equiv), $InBr_3$ (4 equiv), THF, 0 °C, 12 h	30	8:1

[a]The yields in parentheses are based on the recovered aldehyde **18**. [b]Determined by ^1H NMR analysis.

using zinc–copper couple in place of zinc did not promote the coupling effectively (entry 3). Nozaki–Hiyama allylation conditions[14] using $CrCl_2$ also did not show any diastereoselectivity, although the yield was satisfying (entry 4). On the other hand, the reaction using the allylindium species[15,16] generated by the action of **5** and indium powder afforded **19** in excellent yield and high diastereoselectivity (entry 5).[17] It turned out that the combination of $InBr_3$ and indium powder[18] promoted the reaction less effectively to afford a 8:1 mixture of **19** and **20** in 30% yield (entry 6). The high diastereoselectivity observed in the indium-mediated allylation is attributable to a predominant attack of an allylindium to a nonchelation Felkin–Ahn model.[16b]

With the key intermediate **19** in hand, we then addressed the construction of the 5,6,5-fused tricyclic core structure (Scheme 4). After removal of the MOM protecting group, the resulting diols became chromatographically separable to give **21** and its epimer in 84 and 11% yield, respectively. Diol **21** was converted to cyclic carbonate **22**, which was then subjected to ring closing metathesis using Grubbs II catalyst (10 mol %) to afford cyclized product **23** quantitatively.[19] The subsequent epoxidation of **23** using *m*CPBA afforded epoxide **24** in excellent diastereoselectivity (99% de), but the yield was moderate (50–

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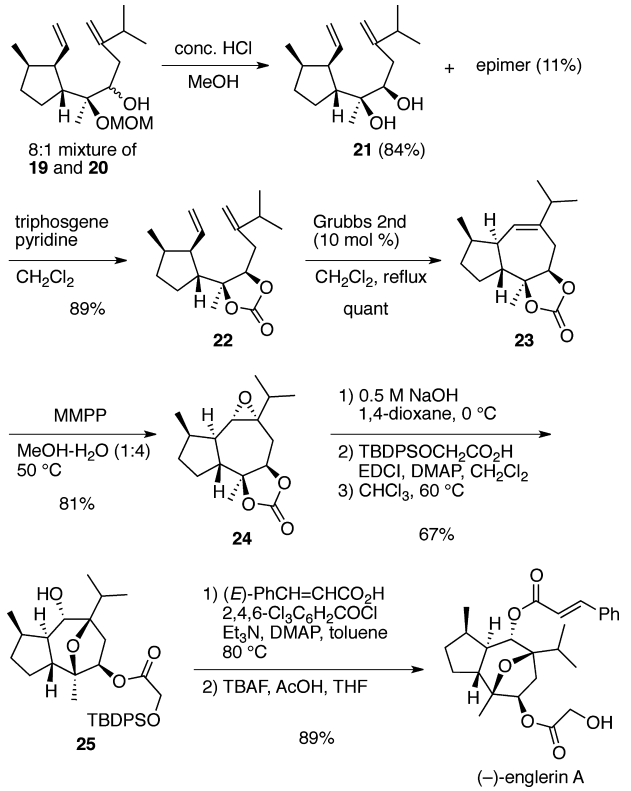
Scheme 4. Completion of the Synthesis of (−)-Englerin A



60%). After experimentation under various conditions, we eventually found satisfying epoxidation conditions. Thus, upon treatment of **23** with magnesium monoperoxyphthalate (MMPP)[20] in aqueous MeOH at 50 °C, epoxidation proceeded cleanly to give a separable 10:1 mixture of **24** and its diastereomer, from which **24** was isolated in 81% yield. The cyclic carbonate of **24** was removed by saponification without any trouble, while the difficulty of removing the corresponding acetonide group was reported by Christmann et al.[4e] The resulting diol was immediately subjected to esterification with (*tert*-butyldiphenylsilyloxy)acetic acid[21] followed by transannular cyclization[4a] under thermal conditions in $CHCl_3$ to give alcohol **25** in 67% yield. Finally, esterification of **25** with cinnamic acid under Yamaguchi's esterification conditions[22] and desilylation[4c] completed the total synthesis of (−)-englerin A (**1**). The spectroscopic data and the specific rotation of the synthetic substance were in accord with those reported[1] for natural englerin A.

■ CONCLUSION

We have accomplished the total synthesis of (−)-englerin A (**1**) from **9** in good overall yield (14%, 24 steps), which is highly stereoselective and applicable to the synthesis of various analogues with variations in not only ester groups but C4 and C7 substituents. In addition, the present work newly demonstrates the synthetic utility of Stork's epoxynitrile cyclization for the synthesis of highly substituted cyclopentanes.

■ EXPERIMENTAL SECTION

General Methods. Where appropriate, reactions were performed in flame-dried glassware under argon atmosphere. All extracts were dried over $MgSO_4$ or Na_2SO_4 and concentrated by rotary evaporation below 30 °C at 25 Torr unless otherwise noted. Commercial reagents and solvents were used as supplied with following exceptions. *N*,*N*-Dimethyformamide (DMF), dichloromethane (CH_2Cl_2), acetonitrile (MeCN), benzene, and pyridine were distilled from CaH_2. Thin-layer chromatography (TLC) was performed using glass-packed silica gel plates (0.2 or 0.5 mm thickness). Column chromatography was performed using silica gel (particle size 100−210 μm (regular), 40−50 μm (flush)). Optical rotations were recorded on a digital polarimeter at ambient temperature. Infrared spectra were measured on a Fourier transform infrared spectrometer. ^{1}H NMR (300, 400, and 500 MHz) and ^{13}C NMR (100 and 125 MHz) spectra were measured using $CDCl_3$ or CD_3OD as solvent, and chemical shifts are reported as δ values in ppm based on internal $(CH_3)_4Si$ (0.00 ppm, ^{1}H) or solvent peak. HRMS spectra were taken in EI (dual focusing sector field), ESI (TOF), or FAB (dual focusing sector field) mode.

***(R,E)*-Ethyl 6-(Hydroxymethyl)-2-methylhept-2-enoate (11).** To a stirred solution of lactone **10**[12] (4.21 g, 36.9 mmol) in CH_2Cl_2 (37.0 mL) was added DIBALH (1.02 M in hexane, 36.2 mL, 36.9 mmol) at −78 °C. After 4 h stirring at the same temperature, saturated Rochelle salt (20.0 mL) was added and further stirred for 6 h at room temperature. The mixture was extracted with CH_2Cl_2, dried, and evaporated to give the corresponding lactol as a yellow oil (13.8 g), which was used for the next reaction without purification. The crude product was dissolved into $CHCl_3$ (37.0 mL), and (1-ethoxycarbonylethylidene)triphenylphosphorane (20.1 g, 55.3 mmol) was added to the mixture at 0 °C. After being stirred at 45 °C for 16 h, the mixture was concentrated and chromatographed (SiO_2 300 g, hexane:AcOEt = 4:1) to give **11** (6.03 g, 82%) as a yellow oil: $[\alpha]_D^{23}$ +9.14 (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (t, *J* = 6.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.50 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.47 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.26−2.17 (m, 2H), 1.83 (s, 3H), 1.67−1.48 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.31−1.21 (m, 1H), 0.95 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 142.0, 127.8, 68.0, 60.4, 35.4, 31.9, 26.1, 16.4, 14.3, 12.3; FT-IR (neat) 3438, 2927, 1708, 1647, 1457, 1371, 1271, 1144, 1095, cm^{-1}; HRMS (EI) calcd for $C_{11}H_{20}O_3$ (M^+) 200.1412, found 200.1408.

***(R,E)*-Ethyl 2,6-Dimethyl-7-(tosyloxy)hept-2-enoate.** To a stirred solution of **11** (200 mg, 1.00 mmol) in pyridine (2.0 mL) was added TsCl (480 mg, 2.51 mmol) at 0 °C. After being stirred at room temperature for 3 h, the mixture was diluted with H_2O, extracted with Et_2O, washed with 1 M HCl, $NaHCO_3$, and brine, dried, concentrated, and chromatographed (SiO_2 10 g, hexane:AcOEt = 8:1) to give the tosylate (307 mg, 87%) as a colorless oil: $[\alpha]_D^{23}$ −4.97 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.64 (t, *J* = 7.6 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.86 (dd, *J* = 9.5, 2.2 Hz, 1H), 3.85 (dd, *J* = 9.5, 2.2 Hz, 1H), 2.45 (s, 3H), 2.15−2.07 (m, 2H), 1.84−1.78 (m, 1H), 1.78 (s, 3H), 1.55−1.46 (m, 1H), 1.31−1.24 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 144.7, 141.0, 132.9, 129.8, 128.2, 127.8, 74.4, 60.4, 32.4, 31.4, 25.6, 21.6, 16.2, 14.2, 12.3; FT-IR (neat) 2971, 1709, 1362, 1270, 1181, 1098 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{26}O_5S$ (M^+) 354.1501, found 354.1510.

***(R,E)*-7-Hydroxy-2,6-dimethylhept-5-enyl 4-Methylbenzenesulfonate.** To a solution of the tosylate (200 mg, 0.565 mmol) in CH_2Cl_2 (3.0 mL) was added DIBALH (1.02 M in hexane, 1.10 mL, 1.12 mmol) at −78 °C. After 2 h stirring at −78 °C, saturated Rochelle salt (3.0 mL) was added and further stirred for 6 h under room temperature. The mixture was extracted with AcOEt, dried and chromatographed (SiO_2 10 g, hexane:AcOEt = 4:1) to give the corresponding alcohol (168 mg, 96%) as a colorless oil: $[\alpha]_D^{23}$ −6.16 (*c* 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 5.32 (t, *J* = 7.1 Hz, 1H), 3.98 (s, 2H), 3.87 (dd, *J* = 9.3, 5.6 Hz, 1H), 3.84 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.45 (s, 3H), 2.03−1.95 (m, 2H), 1.83−1.78 (m, 1H), 1.48 (s, 3H), 1.48−1.38 (m, 1H), 1.25−1.17 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 135.2, 133.0, 129.8, 127.8, 125.3, 74.8, 68.7, 32.4, 32.3, 24.5, 21.6, 16.3, 13.6; FT-IR (neat) 3382, 2924, 1598, 1458, 1358, 1180 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{24}O_4S$ (M^+) 312.1395, found 312.1369.

***(R,E)*-8-Hydroxy-3,7-dimethyloct-6-enenitrile (12).** The alcohol (168 mg, 0.538 mmol) was dissolved in DMSO (2 mL). NaCN (58.0 mg, 1.18 mmol) was added at 0 °C, and the resulting mixture

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was stirred at room temperature for 12 h. The mixture was diluted with H_2O, extracted with Et_2O, washed with $NaHCO_3$ and brine, dried, concentrated, and chromatographed (SiO_2 10 g, hexane:AcOEt = 4:1) to give **12** (87 mg, 97%) as a colorless oil: $[\alpha]_D^{23}$ −8.01 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 (dd, *J* = 5.6, 6.8 Hz, 1H), 3.95 (s, 2H), 2.30 (dd, *J* = 16.7, 5.8 Hz, 1H), 2.22 (dd, *J* = 16.7, 5.8 Hz, 1H), 2.10−1.99 (m, 2H), 1.90−1.82 (m, 2H), 1.63 (s, 3H), 1.52−1.43 (m, 1H), 1.39−1.32 (m, 1H), 1.04 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 124.6, 118.7, 68.5, 35.4, 29.9, 24.7, 24.3, 19.2, 13.6; FT-IR (neat) 3510, 2938, 2247, 1671, 1462, 1019 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{17}NO$ (M^+) 167.1301, found 167.1300.

(*R*)-5-((2*R*,3*R*)-3-(Hydroxymethyl)-3-methyloxiran-2-yl)-3-methylpentanenitrile (13). To a suspension of powdered 4 A molecular sieves (100 mg) in CH_2Cl_2 (1.0 mL) were added (−)-DET (27 mg, 0.11 mmol) and $Ti(O^iPr)_4$ (30 μL, 0.10 mmol) at −40 °C, and the mixture was stirred at −40 °C for 50 min. TBHP (4.0 M in toluene, 0.40 mL, 1.6 mmol) was added, and then 30 min later, a solution of **12** (87 mg, 0.52 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring at −40 °C for 4 h, 20% aqueous acetone (20 mL) was added, and the mixture was stirred at room temperature for 30 min, filtrated through Celite, extracted with AcOEt, washed with brine, dried, and concentrated. The remaining TBHP was removed by azeotropic distillation with toluene. Purification of the residue by column chromatography (SiO_2 10 g, hexane:AcOEt = 4:1) gave **13** (90 mg, 95%) as a colorless oil: $[\alpha]_D^{24}$ +11.8 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (d, *J* = 12.2, 1H), 3.62−3.50 (m, 1H), 2.99 (m, 1H), 2.34 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.29 (dd, *J* = 16.8, 6.0 Hz, 1H), 2.15−2.05 (brs, 1H), 1.96−1.88 (m, 1H), 1.62−1.49 (m, 4H), 1.27 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.4, 65.2, 60.8, 59.5, 32.6, 30.1, 25.7, 24.2, 19.5, 14.2; FT-IR (neat) 3476, 2937, 2247, 1724, 1460, 1385, 1262, 1197, 1092 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{17}NO_2$ (M^+) 183.1246, found 183.1259.

(*R*)-5-((2*R*,3*R*)-3-((*tert*-Butyldimethylsilyloxy)methyl)-3-methyl-oxiran-2-yl)-3-methylpentanenitrile (8). To an ice-cooled stirred solution of **13** (363 mg, 1.98 mmol) in CH_2Cl_2 (4.0 mL) were added Et_3N (0.83 mL, 5.95 mmol), DMAP (24.2 mg, 0.198 mmol) and TBSCl (598 mg, 3.96 mmol). After being stirred at 0 °C for 24 h, the mixture was diluted with saturated NH_4Cl, extracted with AcOEt, dried, concentrated, and chromatographed (SiO_2 20 g, hexane:AcOEt = 10:1) to give **8** (575 mg, 98%) as a colorless oil: $[\alpha]_D^{24}$ +3.16 (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.56 (s, 2H), 2.81 (t, *J* = 4.8 Hz, 1H), 2.31 (dd, *J* = 5.9, 4.3 Hz, 1H), 2.27 (dd, *J* = 5.9, 4.3 Hz, 1H), 1.98−1.91 (m, 1H), 1.60−1.53 (m, 4H), 1.26 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.5, 67.6, 60.9, 60.4, 32.6, 30.1, 25.8, 25.7, 24.2, 19.5, 18.3, 14.3, −5.4; FT-IR (neat) 2930, 2859, 1464, 1384, 1253, 1097, 1006 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{31}NO_2Si$ (M^+) 297.2124, found 297.2102.

(1*R*,2*R*,5*R*)-2-((*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-hydroxypropan-2-yl)-5-methylcyclopentanecarbonitrile (7). To a stirred solution of **8** (196 mg, 0.659 mmol) in toluene (2.30 mL) was added LHMDS (1.0 M in THF, 1.34 mL, 1.34 mmol) at −78 °C. After being stirred at 0 °C for 3 h, the mixture was cooled to −78 °C and diluted with saturated NH_4Cl, extracted with AcOEt, dried, concentrated, and chromatographed (SiO_2 20 g, hexane:Et_2O = 5:1) to give **7** (171 mg, 87%) as a colorless oil: $[\alpha]_D^{24}$ −16.8 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.47 (d, *J* = 9.5 Hz, 1H), 3.37 (d, *J* = 9.5 Hz, 1H), 2.99 (dd, *J* = 7.2, 8.4 Hz, 1H), 2.41 (td, *J* = 8.5, 8.4 Hz, 1H), 2.34 (s, 1H), 2.22−2.15 (m, 1H), 1.87−1.73 (m, 2H), 1.65−1.55 (m, 1H), 1.41−1.33 (m, 1H), 1.24 (s, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.3, 72.8, 68.9, 51.8, 36.7, 34.6, 34.3, 26.3, 25.8, 23.6, 18.2, 16.9, −5.3; FT-IR (neat) 3482, 2956, 2930, 2857, 2360, 2236, 1460, 1383, 1254, 1094 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{31}NO_2Si$ $(M)^+$ 297.2124, found 297.2110.

(1*R*,2*R*,5*R*)-2-((*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)-propan-2-yl)-5-methylcyclopentanecarbonitrile (16). To an ice-cooled solution of **7** (2.2 g, 7.4 mmol) in CH_2Cl_2 (15 mL) were added DIPEA (5.2 mL, 30 mmol) and MOMCl (1.1 mL, 15 mmol). After stirring at room temperature for 12 h, MeOH (0.50 mL) was added at 0 °C. The mixture was diluted with Et_2O, washed with 1 M HCl, saturated $NaHCO_3$ and brine, dried, concentrated, and chromatographed (SiO_2 40 g, hexane:AcOEt = 12:1) to give **16** (2.4 g, 94%) as a colorless oil: $[\alpha]_D^{24}$ −12.4 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 2H), 3.57 (d, *J* = 9.7 Hz, 1H), 3.51 (d, *J* = 9.7 Hz, 1H), 3.34 (s, 3H), 3.04 (dd, *J* = 7.1, 8.4 Hz, 1H), 2.57 (td, *J* = 7.8, 8.4 Hz, 1H), 2.21−2.16 (m, 1H), 1.82−1.76 (m, 2H), 1.70−1.67 (m, 1H), 1.34 (s, 3H), 1.18 (d, *J* = 7.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.6, 91.5, 78.7, 67.7, 55.3, 52.2, 36.9, 34.4, 34.3, 26.0, 25.8, 20.0, 18.1, 16.9, −5.5,-5.7; FT-IR (neat) 2954, 2234, 1464, 1381, 1254, 1102, 1037 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{35}NO_3Si$ (M^+) 341.2386, found 341.2385.

(1*R*,2*R*,5*R*)-2-((*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)-propan-2-yl)-5-methylcyclopentanecarbaldehyde. To a solution of **16** (2.32 g, 6.80 mmol) in CH_2Cl_2 (23.0 mL) was added DIBALH (1.02 M in hexane, 13.3 mL, 13.6 mmol) at −78 °C. After stirring at −78 °C for 2 h, 10% H_2SO_4 (20 mL) was added, and the mixture was stirred at room temperature for 2 h. The mixture was extracted with AcOEt, washed with saturated $NaHCO_3$ and brine, dried, concentrated, and chromatographed (SiO_2 30 g, hexane:AcOEt = 15:1) to give the aldehyde (2.18 g, 93%) as a colorless oil: $[\alpha]_D^{23}$ +0.62 (*c* 0.91, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, *J* = 3.6 Hz, 1H), 4.75 (d, *J* = 7.1 Hz, 1H), 4.71 (d, *J* = 7.1 Hz, 1H), 3.54 (d, *J* = 10.2 Hz, 1H), 3.51 (d, *J* = 10.2 Hz, 1H), 3.33 (s, 3H), 2.84−2.27 (m, 2H), 2.41−2.32 (m, 1H), 1.85−1.68 (m, 3H), 1.35−1.23 (m, 1H), 1.13 (s, 3H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 91.4, 79.3, 67.8, 55.5, 55.2, 46.1, 38.8, 35.2, 26.4, 25.8, 19.5, 18.1, 15.9, −5.3; FT-IR (neat) 2962, 1725, 1463, 1380, 1298, 1257, 1213, 1046 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{36}O_4Si$ (M^+) 344.2383, found 344.2362.

(1*R*,2*R*,5*R*)-2-((*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)-propan-2-yl)-5-methyl-1-vinylcyclopentane (17). To a suspension of Ph_3PCH_3Br (6.56 g, 18.4 mmol), dried under reduced pressure at 100 °C for 3 h, in THF (20.0 mL) was added LHMDS (1.00 M in hexane, 15.3 mL, 15.3 mmol) at 0 °C. After stirring at 0 °C for 30 min, a solution of the aldehyde (2.11 g, 6.13 mmol) in THF (20.0 mL) was added, and the mixture was stirred at 0 °C for 12 h. The mixture was diluted with AcOEt, washed with saturated NH_4Cl and brine, dried, concentrated, and chromatographed (SiO_2 80 g, hexane:AcOEt = 20:1) to give **17** (1.98 g, 94%) as a yellow oil: $[\alpha]_D^{24}$ −20.0 (*c* 1.23, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.75- 5.66 (m, 1H), 4.94−4.90 (m, 2H), 4.83 (d, *J* = 7.1 Hz, 1H), 4.71 (d, *J* = 7.1 Hz, 1H), 3.51 (s, 2H), 3.36 (s, 3H), 2.41 (dd, *J* = 9.5, 6.1 Hz, 1H), 2.11 (td, *J* = 8.3, 6.1 Hz, 1H), 2.07−1.96 (m, 1H), 1.77−1.65 (m, 3H), 1.28−1.17 (m, 1H), 1.21 (s, 3H), 0.88 (s, 9H), 0.84 (d, *J* = 7.1 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 113.4, 91.6, 80.5, 68.6, 55.2, 50.4, 48.7, 39.3, 33.9, 26.1, 25.9, 18.5, 18.2, 16.1, −5.4, −5.6; FT-IR (neat) 2954, 2858, 1636, 1461, 1376, 1252, 1213, 1144, 1099 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{38}O_3Si$ (M^+) 342.2590, found 342.2599.

(*S*)-2-(Methoxymethoxy)-2-((1*R*,2*R*,3*R*)-3-methyl-2-vinylcyclopentyl)propan-1-ol. To an ice-cooled solution of **17** (788 mg, 2.30 mmol) in THF (12.0 mL) was added TBAF (1.00 M in THF, 3.50 mL, 3.50 mmol). After being stirred at room temperature for 6 h, the mixture was diluted with AcOEt, washed with saturated NH_4Cl and brine, dried, concentrated, and chromatographed (SiO_2 20 g, hexane:AcOEt = 5:1) to give the corresponding alcohol (499 mg, 2.19 mmol, 95%) as a colorless oil: $[\alpha]_D^{23}$ −4.17 (*c* 0.79, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 (ddd, *J* = 17.1, 11.6, 11.6 Hz, 1H), 4.94 (d, *J* = 11.6 Hz, 1H), 4.93 (d, *J* = 17.1 Hz, 1H), 4.83 (d, *J* = 7.1 Hz, 1H), 4.71 (d, *J* = 7.1 Hz, 1H), 3.53 (d, *J* = 9.1 Hz, 1H), 3.42 (s, 3H), 3.39 (d, *J* = 9.1 Hz, 1H), 2.42 (q, *J* = 6.1 Hz, 1H), 2.12 (td, *J* = 8.3, 6.1 Hz, 1H), 2.07−1.96 (m, 1H), 1.77−1.65 (m, 2H), 1.64−1.54 (m, 1H), 1.31−1.21 (m, 1H), 1.21 (s, 3H), 0.84 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 114.0, 90.7, 82.1, 67.6, 55.3, 49.8, 49.1, 39.2, 33.6, 26.1, 16.8, 15.8; FT-IR (neat) 3459, 3073, 2954, 1636, 1455, 1377, 1140, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{24}O_3Na$ $[(M + Na)^+]$ 251.1623, found 251.1637.

(*S*)-2-(Methoxymethoxy)-2-((1*R*,2*R*,3*R*)-3-methyl-2-vinylcyclopentyl)propanal (18). To a stirred solution of oxalyl

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chloride (0.780 mL, 9.21 mmol) in CH_2Cl_2 (6.0 mL) at −78 °C was added DMSO (1.30 mL, 18.3 mmol). After stirring at −78 °C for 1 h, a solution of the alcohol (700 mg, 3.07 mmol) in CH_2Cl_2 (4.0 mL) was added. After stirring at −78 °C for 1 h, Et_3N (3.60 mL, 25.7 mmol) was added, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated NH_4Cl, and the mixture was extracted with AcOEt, washed with brine, dried, concentrated and chromatographed (SiO_2 10 g, hexane:AcOEt = 15:1) to give aldehyde **18** (629 mg, 96%) as a colorless oil: $[\alpha]_D^{24}$ −68.7 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 5.66 (ddd, *J* = 16.9, 10.0, 10.0 Hz, 1H), 4.95 (d, *J* = 10.0 Hz, 1H), 4.93 (d, *J* = 16.9 Hz, 1H), 4.79 (d, *J* = 7.1 Hz, 1H), 4.62 (d, *J* = 7.1 Hz, 1H), 3.39 (s, 3H), 2.50 (dd, *J* = 9.5, 6.1 Hz, 1H), 2.12 (td, *J* = 8.3, 6.1 Hz, 1H), 2.06−1.96 (m, 1H), 1.82−1.61 (m, 3H), 1.28 (s, 3H), 1.27−1.23 (m, 1H), 0.85 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 140.7, 114.7, 92.2, 84.4, 55.7, 50.3, 48.1, 38.8, 33.8, 25.9, 15.7, 15.4; FT-IR (neat) 2942, 1715, 1465, 1383, 1295, 1243, 1213, 1046, cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{22}O_3Na$ [(M + Na)$^+$] 249.1467, found 249.1463.

Indium-Mediated Coupling of 18 and 5. To a degassed solution of **5**[11] (2.25 g, 13.9 mmol) in THF (10.0 mL) was added In-powder (956 mg, 8.39 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. A solution of **18** (629 mg, 2.78 mmol) in THF (4.0 mL) was then added at 0 °C, and the mixture was stirred at 0 °C for 4 h. The reaction was quenched with saturated NH_4Cl, and the mixture was filtrated through Celite. The filtrate was extracted with AcOEt, washed with H_2O, saturated $NaHCO_3$ and brine, dried, concentrated, and chromatographed (SiO_2 20 g, hexane:AcOEt = 15:1) to give a 8:1 mixture of **19** and **20** (820 mg, 95%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71−5.62 (m, 1H), 4.94−4.87 (m, 3H), 4.81−4.79 (m, 2H), 4.73 (d, *J* = 7.3 Hz, 1H), 3.63 (ddd, *J* = 11.0, 5.0, 2.2 Hz, 1H), 3.40 (s, 3H), 2.62 (d, *J* = 5.0 Hz, 1H), 2.52−2.37 (m, 2H), 2.28−2.21 (m, 1H), 2.18−2.05 (m, 1H), 2.03−1.93 (m, 1H), 1.87−1.80 (m, 1H), 1.73−1.67 (m, 2H), 1.26 (s, 3H), 1.26−1.17 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 141.8, 114.1, 108.8, 91.7, 83.5, 73.6, 55.7, 50.8, 49.2, 39.4, 36.5, 33.7, 33.1, 27.3, 22.1, 21.6, 16.1, 15.9; FT-IR (neat) 3469, 3075, 2957, 1638, 1458, 1378, 1143, 1032 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{34}O_3$ (M$^+$) 310.2508, found 310.2498.

Removal of the MOM Group from 19 and 20. The obtained mixture of **19** and **20** (820 mg, 2.64 mmol) was dissolved in MeOH (26.0 mL), and concentrated HCl (2.60 mL) was added. After being stirred at room temperature for 2 h, the mixture was neutralized with 1 M NaOH at 0 °C, extracted with AcOEt, washed with saturated $NaHCO_3$ and brine, dried, concentrated, and chromatographed (SiO_2 40 g, hexane:AcOEt = 10:1) to give **21** (593 mg, 84%) and 9-epimer of **21** (79 mg, 11%) each as a colorless oil.

Compound **21**: $[\alpha]_D^{24}$ −0.17 (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (ddd, *J* = 17.6, 9.7, 9.7 Hz, 1H), 4.96 (d, *J* = 17.6 Hz, 1H), 4.95 (d, *J* = 9.7 Hz, 1H), 4.94 (s, 1H), 4.82 (s, 1H), 3.58 (dd, *J* = 11.0, 2.2 Hz, 1H), 2.50−2.40 (m, 2H), 2.24−1.93 (m, 4H), 1.89−1.81 (m, 1H), 1.74−1.65 (m, 2H), 1.43−1.21 (m, 1H), 1.21 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 141.9, 114.2, 110.1, 76.2, 73.2, 49.8, 48.9, 39.4, 36.7, 33.7, 33.1, 26.7, 22.3, 21.5, 21.0, 16.0; FT-IR (neat) 3477, 3075, 2961, 1819, 1638, 1458, 1375, 1062 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{30}O_2$ (M)$^+$ 266.2246, found 266.2233.

9-Epimer of **21**: $[\alpha]_D^{24}$ −8.50 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 17.2, 10.0, 10.0 Hz, 1H), 4.99−4.95 (m, 2H), 4.93 (s, 1H), 4.83 (s, 1H), 3.67 (dd, *J* = 11.2, 2.4 Hz, 1H), 2.57−2.51 (m, 1H), 2.33 (d, *J* = 14.4 Hz, 1H), 2.26−2.20 (m, 1H), 2.10−1.99 (m, 3H), 1.78−1.59 (m, 3H), 1.31−1.25 (m, 3H), 1.11 (s, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 142.5, 113.8, 110.0, 76.4, 72.2, 50.8, 48.9, 39.2, 37.1, 34.0, 33.3, 26.2, 22.2, 21.6, 19.3, 15.9; FT-IR (neat) 3441, 3075, 2956, 2871, 1638, 1457, 1377, 1064 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{30}O_2$ (M)$^+$ 266.2246, found 266.2247.

(4*S*,5*R*)-4-Methyl-5-(3-methyl-2-methylenebutyl)-4-((1*R*,2*R*,3*R*)-3-methyl-2-vinylcyclopentyl)-1,3-dioxolan-2-one (22). To a stirred solution of diol **21** (300 mg, 1.13 mmol) in CH_2Cl_2 (2.0 mL) and pyridine (0.60 mL) at −70 °C was added triphosgene (167 mg, 0.562 mmol). After stirring at room temperature for 1.5 h, the reaction was quenched with H_2O. The mixture was extracted with Et_2O, washed with 1 M HCl, saturated $NaHCO_3$, and brine, dried, concentrated, and chromatographed (SiO_2 30 g, hexane:AcOEt = 20:1) to give **22** (293 mg, 89%) as a colorless oil: $[\alpha]_D^{24}$ +10.1 (*c* 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (ddd, *J* = 17.1, 10.0, 10.0 Hz, 1H), 5.05 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.00 (d, *J* = 17.1 Hz, 1H), 4.97 (s, 1H), 4.85 (s, 1H), 4.42 (dd, *J* = 10.0, 3.4 Hz, 1H), 2.52−2.36 (m, 3H), 2.29−2.19 (m, 2H), 2.11−2.04 (m, 1H), 2.02−1.93 (m, 1H),1.83−1.76 (m, 1H), 1.67−1.58 (m, 1H), 1.47 (s, 3H), 1.36−1.25 (m, 1H), 1.05 (d, *J* = 3.2 Hz, 3H), 1.03 (d, *J* = 3.2 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 150.2, 140.3, 115.5, 110.3, 88.7, 86.0, 49.8, 47.5, 38.8, 33.9, 33.7, 33.4, 27.2, 23.2, 21.6, 21.6, 15.7; FT-IR (neat) 2961, 1801, 1640, 1460, 1383, 1233, 1033 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{29}O_3$ [(M + H)$^+$] 293.2117, found 293.2110.

(*E*,3a*R*,6a*S*,7*R*,9a*R*,9b*S*)-3a,4,6a,7,8,9,9a,9b-Octahydro-5-isopropyl-7,9b-dimethylazuleno[5,4-*d*][1,3]dioxol-2-one (23). To a degassed solution of **22** (293 mg, 1.00 mmol) in CH_2Cl_2 (20.0 mL) was added Grubbs II catalyst (85.0 mg, 0.10 mmol). After being heated for 24 h under reflux, the mixture was concentrated and chromatographed (SiO_2 30 g, hexane:$CHCl_3$ = 1:5) to give **23** (264 mg, 100%) as a colorless oil: $[\alpha]_D^{24}$ −41.7 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (s, 1H), 4.25 (dd, *J* = 9.3, 2.4 Hz, 1H), 2.81−2.74 (m, 1H), 2.65−2.60 (m, 1H), 2.27−2.17 (m, 4H), 1.94−1.83 (m, 2H), 1.65−1.55 (m, 1H), 1.44 (s, 3H), 1.38−1.31 (m, 1H), 0.99 (d, *J* = 5.1 Hz, 3H), 0.98 (d, *J* = 5.1 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ154.2, 139.5, 124.1, 86.6, 84.2, 46.7, 42.1, 37.8, 36.9, 31.5,30.1, 24.6, 21.1, 19.7, 16.8; FT-IR (neat) 2959, 1810, 1460, 1383, 1296, 1231, 1144, 1037 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{24}O_3$ (M$^+$) 264.1725, found 264.1737.

(3*R*,3a*R*,3b*S*,4a*S*,5a*R*,8a*S*,8b*R*)-4a-Isopropyl-3,8a-dimethyldecahydro-oxireno[2′,3′:7,8]azuleno[4,5-*d*][1,3]dioxol-7-one (24). To an ice-cooled solution of **23** (42.0 mg, 0.159 mmol) in MeOH (3.0 mL) was added MMPP (65%, 965 mg, 1.62 mmol) in H_2O (3.0 mL). After being heated at 50 °C for 40 h, the mixture was cooled to room temperature, diluted with Et_2O, washed with H_2O, saturated $NaHCO_3$ and brine, dried and concentrated. Purification of the residue by preparative TLC (hexane:AcOEt = 4:1) gave **24** (36 mg, 81%) as a colorless oil: $[\alpha]_D^{24}$ −22.7 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (dd, *J* = 10.3, 5.2 Hz, 1H), 2.86 (s, 1H), 2.50−2.33 (m, 4H), 2.09 (dd, *J* = 12.4, 7.1 Hz, 1H), 1.97−1.86 (m, 2H), 1.57−1.51 (m, 2H), 1.44−1.35 (m, 1H), 1.41 (s, 3H), 1.01 (d, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 85.6, 81.8, 66.1, 60.5, 44.8, 41.6, 36.2, 35.8, 31.0, 28.3, 24.9, 19.8, 17.3, 17.2; FT-IR (neat) 2959, 2872, 1777, 1454, 1384, 1312, 1237, 1154, 1046 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{24}O_4$ (M$^+$) 280.1675, found 280.1684.

(1a*S*,3*R*,4*S*,4a*R*,7*R*,7a*R*,7b*S*)-4-Hydroxy-1a-isopropyl-4,7-dimethyldecahydroazuleno[4,5-*b*]oxiren-3-yl 2-((*tert*-Butyldiphenylsilyl)oxy)acetate. To an ice-cooled stirred solution of **24** (46 mg, 0.32 mmol) in 1,4-dioxane (0.8 mL) was added 0.5 M NaOH (0.98 mL, 0.49 mmol). After being stirred at 0 °C for 2 h, the mixture was extracted with AcOEt, washed with H_2O, and brine, dried, and concentrated to give the corresponding diol (43 mg), which was used for the next reaction without purification. To an ice-cooled solution of crude diol (43 mg) in CH_2Cl_2 (0.5 mL) were added DMAP (8.0 mg, 0.066 mmol), glycolic acid TBDPS ether[21,4c] ($TBDPSOCH_2CO_2H$, 0.10 g, 0.33 mmol) and EDCI (94 mg, 0.49 mmol). After stirring at room temperature for 2.5 h, H_2O was added, and the mixture was extracted with Et_2O, washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Purification of the residue by column chromatography (SiO_2 10 g, hexane:AcOEt = 7:1) gave a 16:1 mixture of the corresponding ester and **25** (100 mg) as a colorless oil. The pure ester shows the following spectra: $[\alpha]_D^{24}$ −14.1 (*c* 0.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67(m, 4H), 7.47−7.38(m, 6H), 4.86 (d, *J* = 8.8 Hz, 1H), 4.32 (d, *J* = 8.8 Hz, 1H), 4.27 (d, *J* = 16.4 Hz, 1H), 2.99 (d, *J* = 4.0 Hz, 1H), 2.45 (dd, *J* = 15.2, 10.0 Hz, 1H), 2.38−2.27

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(m, 1H), 2.20−2.13 (m, 1H), 1.83−1.57 (m, 5H), 1.55−1.48 (m, 1H), 1.41−1.34 (m, 1H) 1.09 (s, 9H), 1.00 (d, J = 8.0 Hz, 6H), 0.90 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 135.5, 132.5, 130.0, 127.9, 75.7, 75.6, 62.4, 61.1, 60.4, 46.8, 43.7, 36.6, 34.7, 34.5, 29.0, 26.6, 24.3, 21.0, 19.5, 19.2, 17.7, 17.5, 15.2, 14.2 ; FT-IR (neat) 3493, 2957, 1759, 1466, 1385, 1141, cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{46}O_5SiNa$ [(M + Na)$^+$] 573.3012, found 573.2993.

(1*R*,3a*R*,4*S*,5*R*,7*R*,8*S*,8a*R*)-8-Hydroxy-7-isopropyl-1,4-dimethyl-decahydro-4,7-epoxyazulen-5-yl 2-((*tert*-Butyldiphenylsilyl)-oxy)acetate (25). A solution of the ester (100 mg) in $CHCl_3$ (1.0 mL) was heated at 60 °C for 8 h. The mixture was concentrated and chromatographed (SiO_2 10 g, hexane:AcOEt = 7:1) to give **25** (61.0 mg, 0.11 mmol, 67% from **24**): $[\alpha]_D^{24}$ −34.5 (c 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.68(m, 4H), 7.43−7.39(m, 6H), 5.07 (dd, J = 8.0, 2.8 Hz, 1H), 4.25 (s, 2H), 3.65 (d, J = 10.0 Hz, 1H), 2.40 (dd, J = 14.4, 8.0 Hz, 1H), 2.38−2.28 (m, 1H), 2.06−1.91 (m, 2H), 1.72−1.53 (m, 3H), 1.35−1.18 (m, 3H), 1.09 (s, 9H), 1.08 (d, J = 5.6 Hz, 3H), 1.03 (d, J = 7.2 Hz, 3H), 1.02 (d, J = 7.2 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 135.6, 132.8, 129.9, 127.8, 84.4, 75.4, 70.6, 62.2, 47.9, 38.4, 32.0, 31.2, 30.5, 26.6, 25.5, 19.2, 18.9, 18.2, 17.3, 16.8; FT-IR (neat) 3515, 2955, 1752, 1464, 1142, 1010 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{46}O_5SiNa$ [(M + Na)$^+$] 573.3012, found 573.3035.

TBDPS-Protected Englerin A. To a stirred solution of cinnamic acid (19 mg, 0.12 mmol) in toluene (0.8 mL) were added Et_3N (35 μL, 0.24 mmol) and 2,4,6-trichlorobenzoyl chloride (22 μL, 0.14 mmol). After stirring at room temperature for 1 h, **25** (35 mg, 0.063 mmol, in 0.4 mL toluene) and DMAP (20 mg, 0.16 mmol) were added, and the mixture was stirred at 80 °C for 5 h. After addition of saturated $NaHCO_3$, the mixture was extracted with AcOEt, washed with brine, dried, concentrated, and chromatographed (SiO_2 10 g, hexane:AcOEt = 15:1) to give the TBDPS-protected Englerin A[4c] as a white solid (39 mg, 92%): $[\alpha]_D^{24}$ −22.8 (c 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.64 (m, 4H), 7.53 (m, 2H), 7.46−7.39 (m, 9H), 6.40 (d, J = 15.6 Hz, 1H), 5.15−5.10 (m, 2H), 4.28 (s, 2H), 2.62 (dd, J = 14.4, 8.0 Hz, 1H), 2.20−2.09 (m, 1H), 1.99−1.81 (m, 2H), 1.79−1.67 (m, 3H), 1.65−1.51 (m, 1H), 1.33−1.21 (m, 2H), 1.12 (s, 3H), 1.11 (s, 9H), 0.99 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 165.6, 145.1, 135.6, 134.3, 132.7, 130.4, 129.9, 128.9, 128.1, 127.8, 118.0, 85.4, 84.5, 75.3, 71.3, 62.2, 47.5, 46.9, 39.8, 32.8, 31.2, 30.9, 26.6, 24.6, 19.2, 18.9, 18.2, 17.4, 16.9; FT-IR (neat) 2954, 1715, 1636, 1459, 1273, 1145, 1011 cm^{-1}; HRMS (ESI) calcd for $C_{42}H_{52}O_6SiNa$ [(M + Na)$^+$] 703.3431, found 703.3441.

(−)-Englerin A.[1,4c] To an ice-cooled solution of TBDPS-protected englerin A (28 mg, 0.041 mmol) and AcOH (53 mg, 0.88 mmol) in THF (0.8 mL) was added TBAF (1 M in THF, 0.10 mL, 0.10 mmol). After stirring at room temperature for 7 h, saturated NH_4Cl was added at 0 °C. The mixture was extracted with AcOEt, washed with brine, dried, concentrated, and chromatographed (SiO_2 10 g, hexane:AcOEt = 4:1) to give englerin A (**1**) (18 mg, 97%); as a white solid: $[\alpha]_D^{23}$ −61.6 (c 0.85, MeOH) (lit.[1] $[\alpha]_D^{23}$ −63 (c 0.13, MeOH)); ^{1}H NMR (400 MHz, CD_3OD) δ 7.69 (d, J = 16.0 Hz, 1H), 7.62−7.60 (m, 2H), 7.42−7.40 (m, 3H), 6.51 (d, J = 16.0 Hz, 1H), 5.26 (dd, J = 8.0, 2.8 Hz, 1H), 5.12 (d, J = 9.8 Hz, 1H), 4.16 (s, 2H), 2.70 (dd, J = 14.5, 7.9 Hz, 1H), 2.18−2.09 (m, 1H), 2.04−1.96 (m, 1H), 1.90−1.83 (m, 2H), 1.79−1.64 (m, 3H), 1.36−1.24 (m, 2H), 1.19 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 7.2 Hz, 3H), 0.93 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.0, 167.3, 146.8, 135.7, 131.7, 130.1, 129.3, 118.8, 86.7, 86.1, 76.6, 72.5, 61.0, 48.9, 48.0, 40.7, 34.1, 32.5, 32.0, 25.5, 19.2, 18.6, 17.8, 17.2; FT-IR (neat) 3459, 2957, 1712, 1634, 1452, 1378, 1169, 1098, 1008 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{35}O_6$ [(M + H)$^+$] 443.2434, found 443.2447.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of synthetic intermediates and (−)-englerin A. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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