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SYNTHESIS OF OXYGEN-BRIDGED DECAHYDROAZULENE DERIVATIVES: SIMPLIFIED ANALOGUES OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS

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Dedicated to Professor Victor Snieckus on the occasion of his 77th birthday

Abstract – Decahydroazulene derivatives having an ether bridge were synthesized. They are structurally simplified analogues of the biologically active guaiane sesquiterpenes englerin A and orientalol F.

Englerin A (**1**),[1,2] isolated from the root and bark of *Phyllanthus engleri* in 2009, and orientalol F (**2**),[3] isolated from the rhizome of *Alisma orientalis* in 2003, are biologically active guaiane sesquiterpenes sharing a common oxygen-bridged decahydroazulene skeleton as depicted in Figure 1. Englerin A (**1**) possesses selective inhibitory activity toward the growth of renal cancer cell lines at nanomolar levels. The structural complexities and biological activities of these compounds have fascinated synthetic researchers, resulting in many synthetic and biological studies of these sesquiterpenes to date.[4–12] Although numerous analogues with various ester side chains of englerin A have been synthesized and tested for their biological activities,[13–15] the pharmacophore of englerin A is not yet known. Therefore, synthesis of structurally simplified analogues **3** and **4** as target molecules is proposed in order to explore their structure–activity relationships. In this paper, we describe the synthesis of oxygen-bridged decahydroazulene derivatives via epoxide ring-opening and aldol condensation to construct the perhydroazulene skeleton.

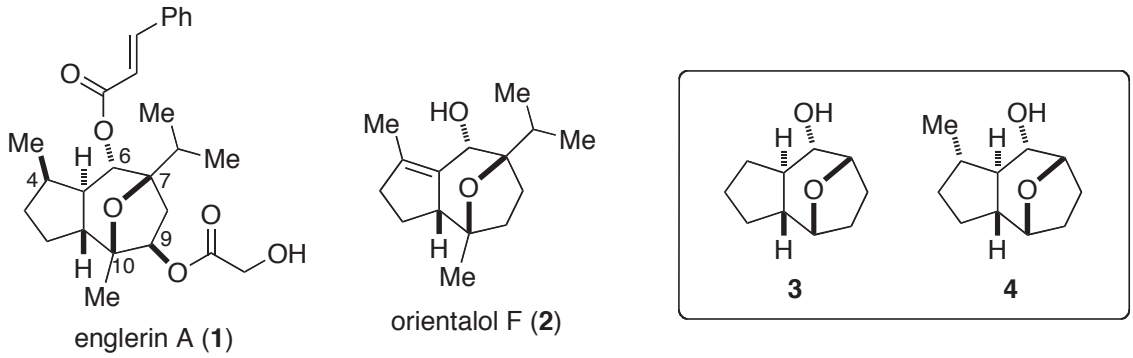
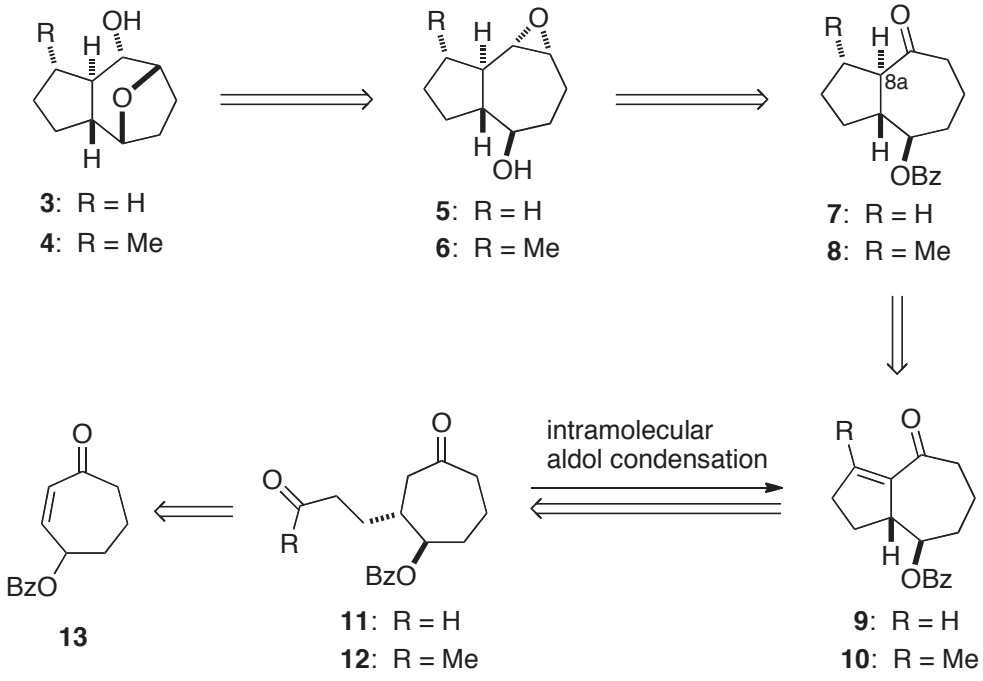


Figure 1. Structures of natural products englerin A (**1**), orientalol F (**2**), and target molecules **3** and **4**.

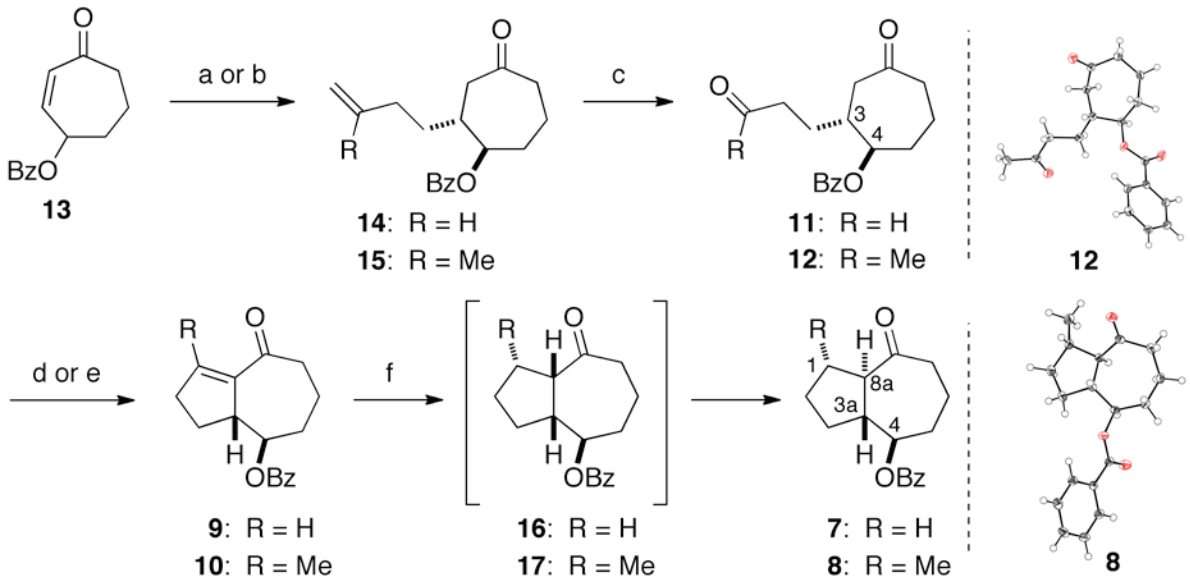
Our synthetic plan for target molecules **3** and **4** is outlined in Scheme 1. Synthesis of these structurally simplified analogues would be accomplished by epoxide ring-opening and ether-cyclization of epoxyalcohols **5** and **6**, which would be derived from decahydroazulenone derivatives **7** and **8**. Bicyclic compounds **7** and **8** would be obtained through two-step operations involving aldol condensation of diketones **11** and **12**, followed by hydrogenation of enones **9** and **10**, accompanied by epimerization at H8a to form the *trans*-fused bicyclic system. Diketone derivatives **11** and **12** would be synthesized by 1,4-addition of cycloheptenone derivative **13**[16,17] to appropriate side chain units.



Scheme 1. Synthetic plan for oxygen-bridged decahydroazulene derivatives **3** and **4**.

The investigation began with the preparation of decahydroazulenones **7** and **8** from γ-benzoyloxycycloheptenone **13**[16,17] as shown in Scheme 2. The 1,4-addition reaction of **13** with

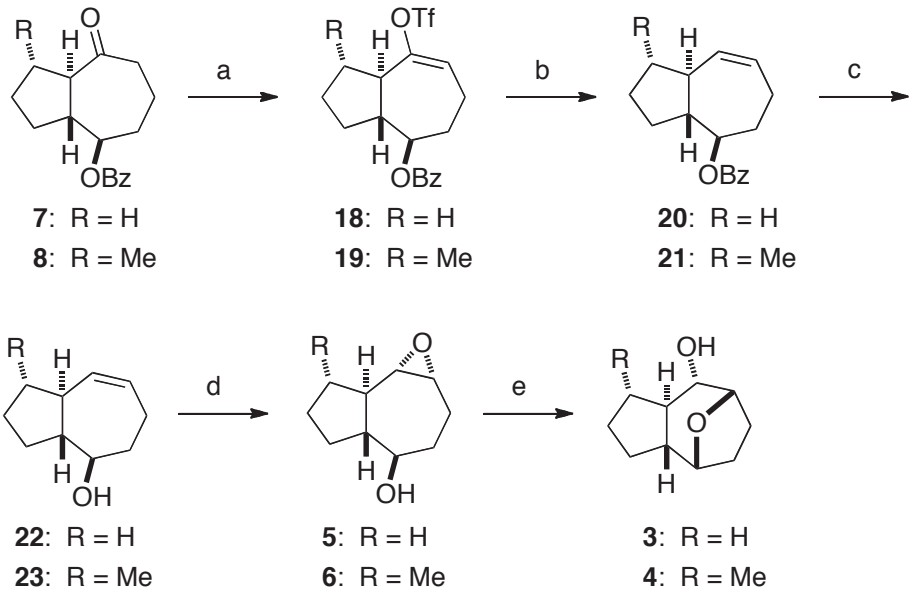
Grignard reagents, prepared from magnesium and 3-butenyl bromide or 3-methyl-3-butenyl bromide, gave the 3,4-*trans* adducts **14** or **15**, respectively. The relative configurations at C3 and C4 of the adducts were confirmed by X-ray crystallographic analysis[18] of the resulting diketone **12**, which was obtained by ozonolysis of **15** as depicted in Scheme 2. Construction of the perhydroazulenone skeletons was achieved by intramolecular aldol condensation. After numerous attempts, the intramolecular aldol condensation of **11**, obtained by ozonolysis of **14**, was accomplished under acidic conditions [TsOH/THF, reflux] to give **9** in 69% yield. For the aldol condensation of **12**, the azulenone derivative **10** was produced under basic conditions [*t*-BuOK/*t*-BuOH, rt] in 66% yield. Hydrogenation of **9** and **10** with palladium on carbon in EtOH gave **7** and **8** in 90% and 78% yields, respectively. The stereochemistry of the resulting **8** was determined by X-ray crystallographic analysis as 1*R**,3a*S**,4*S**,8a*S**.[19] This result reveals that hydrogenation of the double bond of enone **10** occurred from the same face as the hydrogen atom at C3a. Subsequent epimerization at C8a of the resulting **16** was carried out to give *trans*-fused decahydroazulene derivative **8**. When the reaction time was shortened, an inseparable mixture of *cis*-fused **16** and *trans*-fused **7** or *cis*-**17** and *trans*-**8** were obtained, respectively.



Scheme 2. Synthesis of decahydroazulenone derivatives **7** and **8**. *Reagents and Conditions:* a) 3-butenylmagnesium bromide, CuCN, THF, –78 °C, 74% for **14**. b) 3-methyl-3-butenylmagnesium bromide, CuCN, THF, –78 °C, 80% for **15**. c) O_3, CH_2Cl_2, –78 °C, then Ph_3P, rt, 4 h, 97% for **11**, 76% for **12**. d) TsOH, THF, reflux, 3 h, 69% for **9**. e) *t*-BuOK, *t*-BuOH, rt, 0.5 h, 66% for **10**. f) H_2, Pd–C, EtOH, 24 h, 90% for **7**, 78% for **8**.

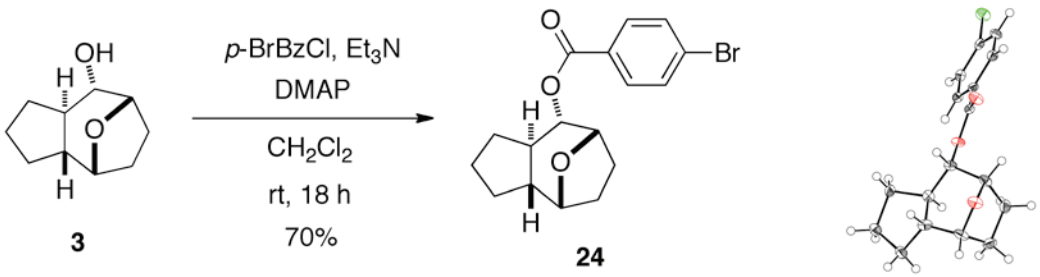
With the *trans*-fused decahydroazulenone derivatives in hand, we turned our attention to the construction of the oxygen-bridged moiety to complete the target molecules. Alkenes **20** and **21** were obtained in two-step procedures from **7** and **8**, respectively, as shown in Scheme 3. Treatment of **7** or **8** with KHMDS and $PhNTf_2$, followed by palladium-catalyzed reduction [$Pd(OAc)_2$, dppp, Et_3SiH] of the

resulting enol triflates **18** or **19**, afforded the alkenes **20** and **21** in good yields. After deprotection of **20** and **21**, epoxidation of the resulting **22** and **23** with mCPBA afforded the precursors **5** and **6** in 51% or 54% yields, respectively. Finally, ether cyclization involving epoxide ring-opening to construct the oxygen-bridged decahydroazulene skeleton was achieved with TsOH in refluxing THF to produce the target molecules **3** and **4** in 64% and 59% yields.



Scheme 3. Synthesis of target molecules **3** and **4**. *Reagents and Conditions:* a) KHMDS, $PhNTf_2$, THF, –50 °C, 1 h, 89% for **18**, 99% for **19**. b) $Pd(OAc)_2$, dppp, Et_3SiH, DMF, 0.5 h, 85% for **20**, 98% for **21**. c) K_2CO_3, MeOH, 70 °C, 3 h, 95% for **22**, 52% for **23**. d) *m*CPBA, Na_2HPO_4, CH_2Cl_2, rt, 3 h, 51% for **5**, 54% for **6**. e) TsOH, THF, reflux, 3 h, 64% for **3**, 59% for **4**.

To confirm the stereochemistry of the obtained target molecules, X-ray crystallographic analysis was carried out as shown in Scheme 4. After protection of the hydroxyl group of **3**, recrystallization of the resulting *p*-bromobenzoate **24** gave a single crystal. The stereochemistry of **24** was determined as 3a*R**,4*R**,7*S**,8*S**,8a*R**.[20]



Scheme 4. Synthesis and X-ray structure of *p*-bromobenzoate **24**.

In conclusion, we synthesized the very simplified analogues of biologically active guaiane sesquiterpenes, englerin A and orientalol F. Biological studies of these structurally simple analogues are now in progress.

EXPERIMENTAL

(1*R**,2*R**)-2-(But-3-en-1-yl)-4-oxocycloheptyl benzoate (**14**)

To a suspension of CuCN (156 mg, 1.74 mmol) in THF (17 mL) was added 3-butenylmagnesium bromide (0.5 M in THF, 3.48 mL) at –78 °C under Ar. After the resulting suspension was stirred for 15 min, a solution of enone **13** (200 mg, 0.869 mmol) in THF (2 mL) was added to this suspension. After stirred for 2 h at –78 °C, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution. The mixture was extracted with Et_2O (3 x 50 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane/AcOEt, 20:1) to give **14** (183 mg, 74%) as colorless oil. IR (neat): 2932, 1712, 1638, 1601, 1451, 1314, 1272, 1175, 1111, 1070, 1026, 772, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.31–1.58 (2H, m), 1.69–1.80 (1H, m), 1.88–2.28 (6H, m), 2.33–2.61 (3H, m), 2.96 (1H, dd, *J* = 13.4, 2.4 Hz), 4.95 (1H, d, *J* = 10.5 Hz), 5.02 (1H, dd, *J* = 17.1, 1.6 Hz), 5.22 (1H, ddd, *J* = 6.0, 6.0, 3.0 Hz), 5.74 (1H, dddd, *J* = 17.1, 10.5, 6.7, 6.7 Hz), 7.41–7.49 (2H, m), 7.53–7.60 (1H, m), 8.01–8.08 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8, 30.4, 30.7, 31.2, 38.5, 42.6, 43.5, 75.8, 115.4, 128.4 (2C), 129.5 (2C), 130.3, 133.0, 137.5, 165.5, 213.0; HRESIMS calcd for $C_{18}H_{22}O_3Na$ $[M+Na]^+$ 309.1467, found 309.1457.

(1*R**,2*R**)-2-[(2-Methyl)but-3-en-1-yl]-4-oxocycloheptyl benzoate (**15**)

To a suspension of CuCN (240 mg, 2.70 mmol) in THF (27 mL) was added 3-methyl-3-butenylmagnesium bromide (0.5 M in THF, 5.4 mL) at –78 °C under Ar. After the resulting suspension was stirred for 15 min, a solution of enone **13** (412 mg, 1.79 mmol) in THF (4 mL) was added to this suspension. After stirred for 2 h at –78 °C, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution. The mixture was extracted with Et_2O (3 x 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane/AcOEt, 20:1) to give **15** (431 mg, 80%) as colorless oil. IR (neat): 2939, 2868, 1722, 1715, 1698, 1651, 1602, 1453, 1275, 1176, 1112, 1071, 1026, 890, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34–1.49 (1H, m), 1.53–1.84 (5H, m, including 3H, s, at δ 1.68), 1.93–2.23 (6H, m), 2.35–2.63 (3H, m), 2.97 (1H, dd, *J* = 13.4, 2.4 Hz), 4.69 (1H, s), 4.71 (1H, s), 5.23 (1H, ddd, *J* = 6.0, 6.0, 3.2 Hz), 7.42–7.49 (2H, m), 7.54–7.62 (1H, m), 8.01–8.09 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 22.2, 29.4, 31.3, 34.3, 38.7, 42.7, 43.5, 75.9, 110.7, 128.5 (2C), 129.5

(2C), 130.4, 133.1, 144.7, 165.6, 213.2; HRESIMS calcd for $C_{19}H_{24}O_3Na$ $[M+Na]^+$ 323.1623, found 323.1623.

(1*R**,2*R**)-4-Oxo-2-(3-oxopropyl)cycloheptyl benzoate (**11**)

Ozone gas was bubbled through a solution of **14** (164 mg, 0.572 mmol) in CH_2Cl_2 (12 mL) until a pale blue color persisted at –78 °C. Triphenylphosphine (299 mg, 1.14 mmol) was added to this mixture, and the mixture was stirred for 4 h at room temperature. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane/AcOEt, 3:1) to give **11** (160 mg, 90%) as colorless oil. IR (neat): 2929, 1714, 1601, 1451, 1315, 1273, 1176, 1112, 1070, 1026, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.47–1.64 (2H, m), 1.73–1.91 (2H, m), 1.96–2.19 (4H, m), 2.35–2.78 (4H, m), 2.98 (1H, dd, *J* = 13.2, 2.2 Hz), 5.15–5.23 (1H, m), 7.39–7.50 (2H, m), 7.51–7.64 (1H, m), 8.01–8.08 (2H, m), 9.78 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8, 23.8, 31.3, 38.8, 40.7, 42.4, 43.5, 75.8, 128.5 (2C), 129.6 (2C), 130.4, 133.2, 165.5, 200.9, 213.0; HRESIMS calcd for $C_{17}H_{20}O_4Na$ $[M+Na]^+$ 311.1259, found 311.1270.

(1*R**,2*R**)-4-Oxo-2-(3-oxobutyl)cycloheptyl benzoate (**12**)

This compound was obtained as colorless needles (Mp 94–95 °C) in 76% yield from **15** (1.53 g, 5.01 mmol) in CH_2Cl_2 (50 mL), as descrived above for the preparation of **11**. IR (KBr): 2944, 1716, 1654, 1560, 1451, 1364, 1315, 1274, 1175, 1113, 1071, 1026, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.39–1.55 (1H, m), 1.69–1.85 (2H, m), 1.92–2.17 (7H, m, including 3H, s, at δ 2.11), 2.32–2.54 (4H, m), 2.55–2.71 (1H, m), 2.92 (1H, dd, *J* = 13.3, 2.2 Hz), 5.14–5.20 (1H, m), 7.41–7.49 (2H, m), 7.54–7.60 (1H, m), 8.02–8.08 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.7, 25.1, 29.9, 31.0, 38.7, 40.2, 42.4, 43.4, 75.7, 128.4 (2C), 129.5 (2C), 130.2, 133.1, 165.5, 207.6, 212.8; HRESIMS calcd for $C_{18}H_{22}O_4Na$ $[M+Na]^+$ 325.1416, found 325.1407.

(3a*R**,4*R**)-8-Oxo-2,3,3a,4,5,6,7,8-octahydroazulen-4-yl benzoate (**9**)

A mixture of **11** (2.93 g, 10.2 mmol) and *p*-toluenesulfonic acid monohydrate (965 mg, 5.10 mmol) in THF (100 mL) was refluxed for 3 h. After the reaction was quenched with H_2O, the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine, and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane/AcOEt, 6:1) to give **9** (1.89 g, 69%) as colorless oil. IR (neat): 2927, 1716, 1677, 1603, 1560, 1315, 1270, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42–1.59 (1H, m), 1.63–1.98 (3H, m), 2.11–2.59 (6H, m), 3.15–3.27 (1H, m), 4.81 (1H, ddd, *J* = 10.7, 10.7, 3.6 Hz), 6.91 (1H, s), 7.34–7.43 (2H, m), 7.45–7.54 (1H, m), 7.96–8.03 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 28.6, 30.4, 36.0, 43.7, 49.4, 77.7, 128.1 (2C), 129.3 (2C), 130.1, 132.7, 142.5, 145.8, 165.5, 198.9; HRESIMS calcd

for $C_{17}H_{18}O_3Na$ $[M+Na]^+$ 293.1154, found 293.1167.

(3a*R**,4*R**)-1-Methyl-8-oxo-2,3,3a,4,5,6,7,8-octahydroazulen-4-yl benzoate (**10**)

To a solution of **12** (2.89 g, 9.56 mmol) in *tert*-BuOH (96 mL) was added potassium *tert*-butoxide (2.14 g, 19.1 mmol) at room temperature. After stirred for 0.5 h, the mixture was quenched with saturated NH_4Cl aqueous solution at 0 °C. The mixture was extracted with Et_2O (3 x 200 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane/AcOEt, 3:1) to give **10** (1.79 g, 66%) as colorless needles. Mp 102–103 °C; IR (KBr): 2936, 2864, 1715, 1672, 1602, 1451, 1315, 1272, 1178, 1112, 1070, 1026, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.51–1.80 (3H, m), 1.89–2.16 (5H, m, including 3H, s, at δ 2.11), 2.25–2.40 (2H, m), 2.42–2.58 (3H, m), 3.20–3.37 (1H, m), 4.89 (1H, ddd, *J* = 10.5, 10.5, 3.8 Hz), 7.41–7.49 (2H, m), 7.52–7.61 (1H, m), 8.01–8.09 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.1, 20.7, 26.7, 36.3, 38.1, 44.8, 51.4, 77.5, 128.4 (2C), 129.6 (2C), 130.5, 132.9, 134.1, 159.9, 165.9, 201.7; HRESIMS calcd for $C_{18}H_{20}O_3Na$ $[M+Na]^+$ 307.1310, found 307.1322.

(3a*R**,4*R**,8a*R**)-8-Oxodecahydroazulen-4-yl benzoate (**7**)

To a solution of **9** (1.89 g, 6.98 mmol) in EtOH (70 mL) was added 10% palladium on carbon (377 mg), and the mixture was stirred for 24 h under H_2 (1 atm) at room temperature. The catalyst was filtered off, and the solvent was removed in vasuo. The resulted residue was purified by column chromatography (hexane/AcOEt, 6:1) to give **7** (1.71 g, 90%) as colorless oil. IR (neat): 2943, 2873, 1710, 1694, 1450, 1314, 1272, 1116, 1070, 1024, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.37–1.79 (5H, m), 1.84–2.12 (4H, m), 2.21–2.67 (4H, m), 2.84–2.97 (1H, m), 5.08 (1H, ddd, *J* = 10.3, 10.3, 4.1 Hz), 7.41–7.48 (2H, m), 7.52–7.60 (1H, m), 8.00–8.06 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 23.7, 26.0, 32.6, 34.7, 43.0, 48.9, 51.8, 79.8, 128.4 (2C), 129.6 (2C), 130.5, 133.0, 165.9, 212.0; HRESIMS calcd for $C_{17}H_{20}O_3Na$ $[M+Na]^+$ 295.1310, found 295.1319.

(1*R**,3a*S**,4*S**,8a*S**)-1-Methyl-8-oxodecahydroazulen-4-yl benzoate (**8**)

This compound was obtained as colorless needles (Mp 117–118 °C) in 78% yield from **10** (288 mg, 1.01 mmol) in EtOH (10 mL), as descrived above for the preparation of **7**. IR (KBr): 2942, 2869, 1711, 1690, 1453, 1383, 1322, 1274, 1118, 1071, 1027, 960, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, d, *J* = 6.5 Hz), 1.20–1.35 (1H, m), 1.40–1.62 (3H, m), 1.74–2.18 (5H, m), 2.30–2.62 (4H, m), 5.05 (1H, ddd, *J* = 10.6, 10.6, 4.2 Hz), 7.41–7.48 (2H, m), 7.54–7.60 (1H, m), 7.99–8.05 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3, 19.9, 29.7, 32.0, 34.3, 35.0, 43.4, 48.8, 59.7, 79.9, 128.4 (2C), 129.6 (2C), 130.4, 133.0, 165.9, 212.2; HRESIMS calcd for $C_{18}H_{22}O_3Na$ $[M+Na]^+$ 309.1467, found 309.1469.

(3a*R**,4*R**,8a*S**)-1,2,3,3a,4,5,6,8a-Octahydroazulen-4-yl benzoate (**20**)

To a solution of potassium hexamethyldisilazide (0.5 M in toluene, 3.64 mL, 1.82 mmol) in THF (12 mL) was added a solution of **7** (329 mg, 1.21 mmol) in THF (1.2 mL) at –78 °C under Ar. After stirred for 1 h at –78 °C, a solution of *N*-phenylbis(trifluoromethanesulfonamide) (648 mg, 1.82 mmol) in THF (2 mL) was added to the reaction mixture for 1 h at –78 °C. The reaction was quenched with saturated $NaHCO_3$ aqueous solution, extracted with Et_2O (3 x 50 mL), and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane/AcOEt, 20:1) to give **18** (438 mg, 89%) as white crystals. This compound was dissolved in DMF (11 mL), and palladium acetate (4.7 mg, 0.0209 mmol) and 1,3-bis(diphenylphosphino)propane (8.6 mg, 0.0209 mmol) were added to this solution at room temperature. After the reaction mixture was warmed to 60 °C, triethylsilane (0.418 mL, 304 mg, 2.62 mmol) was added dropwise to this mixture. After stirred for 0.5 h at 60 °C, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution, extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane/AcOEt, 50:1) to give **20** (241 mg, 85%) as colorless oil. IR (neat): 2944, 2871, 1715, 1602, 1585, 1451, 1314, 1270, 1176, 1113, 1070, 1026, 960, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.17–1.71 (5H, m), 1.78–2.43 (7H, m), 5.04 (1H, ddd, *J* = 9.9, 9.9, 3.9 Hz), 5.69–5.85 (2H, m), 7.38–7.48 (2H, m), 7.51–7.58 (1H, m), 8.02–8.08 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.9, 23.4, 31.3, 32.3, 33.7, 41.5, 49.6, 81.6, 128.3 (2C), 129.5 (2C), 130.7, 130.9, 132.7, 135.9, 165.9; HRESIMS calcd for $C_{17}H_{20}O_2Na$ $[M+Na]^+$ 279.1361, found 279.1365.

(1*R**,3a*S**,4*S**,8a*R**)-1-Methyl-1,2,3,3a,4,5,6,8a-octahydroazulen-4-yl benzoate (**21**)

This compound was obtained as colorless oil in 97% yield for two-step operations from **8** (100 mg, 0.349 mmol), as descrived above for the preparation of **20**. IR (neat): 2951, 2869, 1715, 1602, 1444, 1314, 1270, 1112, 1070, 1026, 955, 884, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97–1.09 (4H, m, including 3H, d, *J* = 5.5 Hz, at δ 1.04), 1.16–1.30 (1H, m), 1.39–1.61 (2H, m), 1.74–2.18 (6H, m), 2.23–2.33 (1H, m), 5.04 (1H, ddd, *J* = 9.2, 9.0, 3.8 Hz), 5.71–5.76 (1H, m), 5.82–5.90 (1H, m), 7.40–7.46 (2H, m), 7.49–7.59 (1H, m), 8.02–8.05 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 23.4, 29.0, 31.9, 32.2, 41.2, 48.8, 49.5, 81.8, 128.3 (2C), 129.5 (2C), 131.0, 131.3, 132.7, 134.5, 165.9; HRESIMS calcd for $C_{18}H_{22}O_2Na$ $[M+Na]^+$ 293.1517, found 293.1527.

(3a*R**,4*R**,8a*S**)-1,2,3,3a,4,5,6,8a-Octahydroazulen-4-ol (**22**)

A mixture of **20** (159 mg, 0.622 mmol) and potassium carbonate (258 mg, 1.87 mmol) in MeOH (6 mL) was stirred for 3 h at 70 °C. After added H_2O to this mixture, and this mixture was extracted with Et_2O

(3 x 50 mL). The combined organic layers were washed with brine, and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane/AcOEt, 7:1) to give **22** (90.3 mg, 95%) as white crystals. Mp 47 °C; IR (KBr): 3249, 3012, 2926, 2874, 1654, 1472, 1440, 1354, 1234, 1140, 1121, 1081, 1019, 966, 715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.30–1.68 (6H, m), 1.86–2.24 (7H, m), 3.41–3.52 (1H, m), 5.61–5.77 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.9, 23.4, 31.3, 33.5, 35.2, 41.2, 52.1, 79.3, 130.6, 135.9; HRESIMS calcd for $C_{10}H_{16}ONa$ $[M+Na]^+$ 175.1099, found 175.1108.

(1*R**,3a*S**,4*S**,8a*R**)-1-Methyl-1,2,3,3a,4,5,6,8a-octahydroazulen-4-ol (**23**)

This compound was obtained as colorless oil in 52% yield from **21** (91.0 mg, 0.337 mmol) in MeOH (4 mL), as descrived above for the preparation of **22**. IR (neat): 3351, 3017, 2950, 2916, 2869, 1715, 1652, 1445, 1376, 1353, 1016, 972, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (3H, d, *J* = 5.6 Hz), 1.15–2.16 (11H, m), 2.14–2.24 (1H, m), 3.49 (1H, ddd, *J* = 8.8, 8.8, 3.9 Hz), 5.63–5.69 (1H, m), 5.76–5.84 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0, 23.4, 29.0, 32.0, 35.2, 41.0, 48.7, 52.0, 79.6, 131.3, 134.6; HRESIMS calcd for $C_{11}H_{18}ONa$ $[M+Na]^+$ 189.1255, found 189.1261.

(1a*R**,4*R**,4a*R**,7a*R**,7b*S**)-Decahydroazuleno[4,5-*b*]oxiren-4-ol (**5**)

To a solution of **22** (14.9 mg, 0.0979 mmol) in CH_2Cl_2 (1 mL) was added *m*-chloroperbenzoic acid (29.0 mg, 0.118 mmol) at 0 °C under Ar. After stirred for 3 h at room temperature, the reaction was quenched with saturated $NaHCO_3$ aqueous solution at 0 °C. The mixture was extracted with Et_2O (3 x 10 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane/AcOEt, 5:1) to give **5** (8.4 mg, 51%) as colorless oil. IR (neat): 3401, 2944, 2869, 1453, 1092, 1040, 925, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18–1.76 (8H, m), 1.85–2.29 (5H, m), 2.80 (1H, dd, *J* = 6.0, 4.9 Hz), 2.96–3.05 (1H, m), 3.34 (1H, ddd, *J* = 9.7, 9.7, 3.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2, 24.8, 30.9, 31.9, 32.3, 42.1, 51.4, 53.8, 59.0, 78.6; HRESIMS calcd for $C_{10}H_{16}O_2Na$ $[M+Na]^+$ 191.1048, found 191.1054.

(1a*R**,4*R**,4a*R**,7*S**,7a*R**,7b*S**)-7-Methyldecahydroazuleno[4,5-*b*]oxiren-4-ol (**6**)

This compound was obtained as colorless oil in 54% yield from **23** (31.6 mg, 0.190 mmol) in CH_2Cl_2 (2 mL), as descrived above for the preparation of **5**. IR (neat): 3395, 2950, 2869, 1722, 1455, 1378, 1351, 1268, 1169, 1095, 1056, 1023, 957, 898, 835, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.95–1.31 (7H, m, including 3H, d, *J* = 6.0 Hz, at δ 1.12), 1.37–1.58 (2H, m), 1.72–2.06 (5H, m), 2.15–2.27 (1H, m), 2.79 (1H, dd, *J* = 6.3, 4.9 Hz), 2.95–3.01 (1H, m), 3.33 (1H, ddd, *J* = 9.7, 9.7, 3.9 Hz); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 18.9, 24.7, 28.8, 32.1, 32.8, 41.5, 50.1, 50.7, 52.9, 57.9, 78.7; HRESIMS calcd for $C_{11}H_{18}O_2Na$ $[M+Na]^+$ 205.1204, found 205.1204.

(3a*R**,4*R**,7*S**,8*S**,8a*R**)-Decahydro-4,7-epoxyazulen-8-ol (**3**)

A mixture of **5** (14.1 mg, 0.0839 mmol) and *p*-toluenesulfonic acid monohydrate (7.9 mg, 0.0415 mmol) in THF (1 mL) was refluxed for 3 h. After the reaction was quenched with H_2O, the mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane/AcOEt, 5:1) to give **3** (9.1 mg, 64%) as colorless needles. Mp 82–84 °C; IR (KBr): 3402, 2953, 1719, 1458, 1072, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.95–1.30 (4H, m), 1.52–2.05 (9H, m), 3.54–3.60 (1H, m), 4.15–4.21 (1H, m), 4.31–4.37 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 24.3, 25.0, 25.4, 27.2, 44.0, 48.8, 74.4, 77.3 (2C); HRESIMS calcd for $C_{10}H_{16}O_2Na$ $[M+Na]^+$ 191.1048, found 191.1042.

(1*R**,3a*S**,4*S**,7*R**,8*R**,8a*S**)-1-Methyldecahydro-4,7-epoxyazulen-8-ol (**4**)

This compound was obtained as colorless oil in 59% yield from **6** (18.6 mg, 0.102 mmol) in THF (10 mL), as descrived above for the preparation of **3**. IR (neat): 3436, 2950, 2870, 1720, 1654, 1468, 1377, 1232, 1133, 1079, 1025, 980, 908, 804, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.75–0.86 (1H, m), 1.10–1.25 (5H, m, including 3H, d, J = 6.4 Hz, at δ 1.14), 1.53–1.94 (9H, m), 3.64 (1H, dd, J = 9.7, 3.6 Hz), 4.10–4.16 (1H, m), 4.25–4.30 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 24.2, 24.6, 25.0, 31.7, 37.8, 48.9, 50.0, 74.7, 77.4, 77.6; HRESIMS calcd for $C_{11}H_{18}O_2Na$ $[M+Na]^+$ 205.1204, found 205.1197.

(3a*R**,4*R**,7*S**,8*S**,8a*R**)-Decahydro-4,7-epoxyazulen-8-yl 4-bromobenzoate (**24**)

To a solution of **3** (18.6 mg, 0.111 mmol), triethylamine (46.2 μL, 33.6 mg, 0.332 mmol) and 4-dimethylaminopyridine (2.7 mg, 0.0221 mmol) in CH_2Cl_2 (1 mL) was added *p*-bromobenzoyl chloride (36.4 mg, 0.166 mmol) at room temperature. After stirred for 18 h, the reaction was quenched with H_2O, and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were washed with brine, and dried over $MgSO_4$. After the solvent was removed in vacuo, the resulted residue was purified by column chromatography (hexane/AcOEt, 20:1) to give **24** (27.1 mg, 70%) as colorless needles. Mp 106–108 °C; IR (KBr): 2954, 2871, 1721, 1589, 1484, 1466, 1397, 1269, 1113, 1102, 1012, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.00–1.14 (1H, m), 1.22–1.35 (1H, m), 1.78–2.00 (10H, m), 4.40–4.45 (2H, m), 4.93 (1H, dd, J = 10.1, 3.7 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.88 (2H, d, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 24.2, 25.4, 26.0, 27.6, 41.4, 49.0, 74.5, 76.4, 77.5, 128.0, 129.2, 131.1 (2C), 131.7 (2C), 165.1; HRESIMS calcd for $C_{17}H_{19}BrO_3Na$ $[M+Na]^+$ 373.0415, found 373.0416.

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19. CCDC 934492 contains the supplementary crystallographic data of **8** for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

20. CCDC 934500 contains the supplementary crystallographic data of **24** for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.