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ORIGINAL ARTICLE

Formal synthesis of englerin A utilizing regio- and diastereoselective [4+3] cycloaddition

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Englerin A, a guaiane sesquiterpene isolated from *Phyllanthus engleri*, showed highly potent and selective growth inhibitory activities against renal cancer cell lines. We synthesized the key tricyclic intermediate from commercially available 2,2-dimethyl-1,3-dioxan-5-one via regio- and diastereoselective [4+3] cycloaddition between the formyl enol silyl ether and the disubstituted furan, in 4.8% total yield over 10 steps.
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INTRODUCTION

In 2009, Beutler and co-workers isolated englerin A (**1**, Figure 1) from the bark of *Phyllanthus engleri*, a plant of the Euphorbiacea family found in East Africa, particularly Tanzania and Zimbabwe, and **1** showed highly potent and selective growth inhibitory activities against renal cancer cell lines (GI_{50} 1–87 nM).[1] The guaiane sesquiterpene **1** has the unique tricyclic structure including 8-oxabicyclo[3.2.1]octane core. The characteristic structure and interesting biological properties of **1** attracted the attention of the synthetic chemistry community. Christmann and co-workers reported the first synthesis of **1** and determined its absolute configuration.[2] Two research groups of Ma[3] and Echavarren[4] individually constructed the tricyclic skeleton of **1** from linear precursor via Au-catalyzed cycloisomerization. Nicolaou, Chen, and co-workers elegantly synthesized **1** utilizing [5+2] cycloaddition of oxopyrilium species and acrylate in the formation of 8-oxabicyclo[3.2.1]octane framework.[5] On the other hand, the 8-oxabicyclo[3.2.1]octane skeleton was also prepared via [4+3] cycloaddition between furans and enol silyl ethers.[6,7] Moreover, several other research groups achieved total or formal synthesis of **1**.[8–15] Although many synthetic approaches have been reported, more efficient strategies are demanded. Herein, we report a formal synthesis of (±)-englerin A (**1**) via regio- and diastereoselective [4+3] cycloaddition between the 2,5-disubstituted furan and formyl enol silyl ethers, which possesses all skeletal carbon atoms enabling the short-step preparation of **1**.

Our retrosynthesis of (±)-englerin A (**1**) is illustrated in Scheme 1. We envisaged that (±)- **1** should be prepared from the tricyclic diol **2** according to Sun's synthesis.[7] The methylcyclopentane moiety in **2** would be constructed via Wacker oxidation of the terminal alkene in ketoalkene **3** followed by intramolecular McMurry coupling and hydrogenation. A few research groups have utilized [4+3] cycloaddition for the formation of the 8-oxabicyclo[3.2.1]octane skeleton in the synthesis of **1**, they required oxidation and carbon–carbon bond-formation steps after the cycloaddition. For this reason, we employed the formyl enol silyl ether **4**, which had oxygen function at 6-position and full skeletal carbons for the methylcyclopentane ring, and 2-isopropyl-5-methylfuran (**5**)[16] as the substrates for the [4+3] cycloaddition. The biggest problem that should be overcome in the cycloaddition was regio- and diastereoselectivities in the reaction because eight isomers could possibly be produced.

RESULTS AND DISCUSSION

The preparation of formyl enol silyl ether **4a** was commenced from commercially available 2,2-dimethyl-1,3-dioxan-5-one (**6**) as shown in Scheme 2. In order to avoid the self-dimerization under the basic conditions applied for the side-chain elongation, ketone **6** was converted to less electrophilic cyclohexylimine. Monoalkylation of the resulting imine with homoallylic iodide under the basic conditions followed by acidic treatment provided monoalkylketone **7**. Formation of enol silyl ether using sodium bis(trimethylsilyl)amide and *tert*-butyldimethylsilyl (TBS) chloride and the subsequent thermal treatment successfully afforded the formyl enol silyl ether **4a**.[17]

As the desired formyl enol silyl ether **4a** was in hand, the regio- and diastereoselective [4+3] cycloaddition between **4a** and **5** was investigated. Lewis acid-mediated [4+3] cycloadditions using Me_2AlCl,[17] $Sc(OTf)_3$,[18] and $TiCl_4$ in dichloromethane resulted in complex mixture, probably due to the coordination of the furan to the Lewis acids to deactivate them. On the other hand, Brønsted acid such as trifluoromethanesulfonic acid successfully promoted the [4+3] cycloaddition to afford the desired 8-oxabicyclo[3.2.1]octane framework whereas the regioselectivity was low (**3a**+**3e**:**8a**+**8e** = 1:1). Interestingly, two out of the eight isomers were selectively obtained probably due to the formation of *cis*-oxyallyl cation intermediate with

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Dedicated to Professor K.C. Nicolaou and his Outstanding Contributions to Complex Natural Product Total Synthesis and Chemical Biology.
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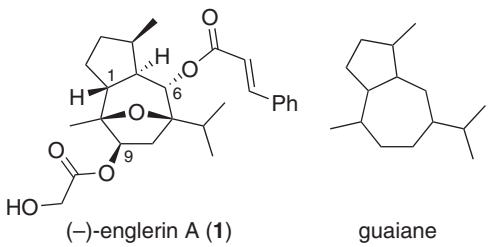
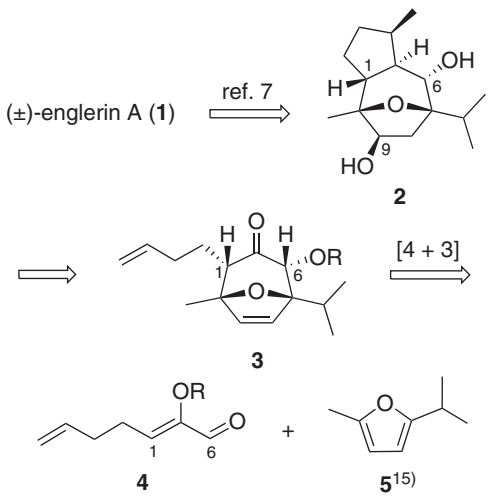
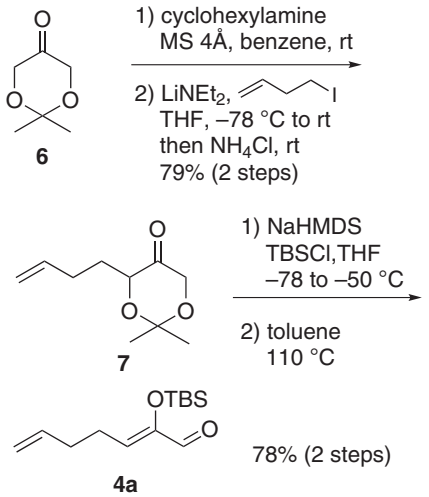


Figure 1 Structures of (–)-englerin A (**1**) and guaiane.



Scheme 1 Retrosynthesis of (±)-englerin A (**1**) via [4+3] cycloaddition.



Scheme 2 Preparation of formyl enol silyl ether **4a**.

less steric repulsion, followed by *endo* selective [4+3] cycloaddition with some removal of the *tert*-butyldimethylsily group under acidic conditions (Table 1, entry 1). When toluene was used as the solvent, the regioselectivity between **3** and **8** considerably improved (**3a**+**3e**:**8a**+**8e** = 8.3:1) to afford the desired bicycloketone **3a** and **3e** in 50% yield (entry 2). From these results, protonation on the silyl enol ether and the subsequent silyl group migration onto the terminal oxygen atom in dichloromethane might proceed faster than that in toluene, which might cause the steric repulsion between the silyl and isopropyl groups. On the other hand, protonation on the formyl group followed by the formation of the oxyallyl cation and the [4+3] cycloaddition avoiding the steric repulsion between the alkenyl chain and the isopropyl group to form the bicycle compound **3** might be predominant in toluene. To prevent the cleavage of the silyl ether in the reaction mixture, bulkier triisopropylsilyl (TIPS) group was employed. As a result, the yield of **3b** increased but the regioselectivity deteriorated instead (entry 3). In the case of triethylsilyl (TES) group, the regioselectivity was almost the same with *tert*-butyldimethylsily group (entry 4). Finally, the formyl enol silyl ether **4d** possessing diethylisopropylsilyl group furnished the desired bicycloketone **3d** and **3e** in high yield with excellent regioselectivity (**3d**+**3e**:**8d**+**8e** = 11:1, entry 5). The stereochemistry of the two bicycloketones **3e** and **8e** was determined by nuclear overhauser effect (NOE) experiment as shown in Figure 2.

As the bicycloketone framework was successfully constructed, the formation of the methylcyclopentane moiety was investigated next. Though Wacker oxidation on the terminal alkenes of **3c** and **3e** smoothly proceeded, the following intramolecular McMurry coupling under acidic conditions resulted in low yield. In these reactions, the major side reactions were cleavage of the silyl ether bond for **3c** and reduction of the hydroxy group into hydrogen atom for hydroxyketone **3e**, respectively. Therefore, the hydroxy group on **3e** was protected as acid-stable benzyl ether. Benzylation using benzyltrichloroimidate, TriBOT[19] and Dudly reagent[20] resulted in low yield or complex mixture. On the other hand, treatment of alcohol **3e** with excess amounts of benzyl bromide in the presence of silver (I) oxide and tetrabutylammonium iodide afforded the benzyl ether in 90% yield (Scheme 3). The subsequent Wacker oxidation of the resulting alkene followed by intramolecular McMurry coupling successfully provided the cyclopentene **9** in good yield. Hydroboration of the disubstituted alkene **9** using 9-borabicyclo[3.3.1]nonane required harsh conditions, whereas the desired alcohol **10** was exclusively produced in moderate yield after oxidative treatment of the corresponding alkyl borane as reported.[6,7] Finally, reductive removal of the benzyl ether concomitant with hydrogenation of the tetrasubstituted alkene on tricyclic compound **10** furnished tricyclic diol **2**, which was the key synthetic intermediate for the total synthesis of englerin A (**1**). The ^{1}H NMR spectral data of **2** were in good accordance with those reported by Sun and co-workers.[7]

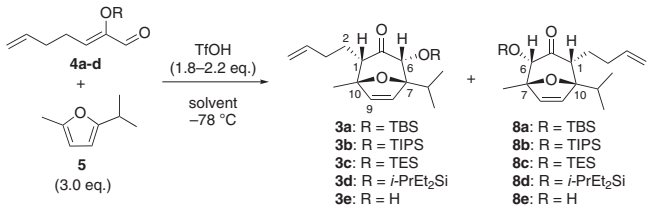
In conclusion, we accomplished the formal synthesis of englerin A (**1**) from commercially available 2,2-dimethyl-1,3-dioxan-5-one (**6**) into the key intermediate **2** in 4.8% total yield over 10 steps. The key step was the regio- and diastereoselective [4+3] cycloaddition between the 2,5-disubstituted furan and the formyl enol silyl ether, and the product possessed all skeletal carbon atoms of the key intermediate for the synthesis of **1**.

EXPERIMENTAL PROCEDURES

General

Merck silica gel 60 F_{254} thin-layer plates (1.05715.0001) was used for analytical TLC. Merck silica gel 60 F_{254} thin-layer plates (1.057440001, 0.5 mm thickness) and silica gel 60 (spherical and neutral; 63–210 μm, 37565-84) from Kanto Chemical Co. (Tokyo, Japan) were used for preparative TLC and column chromatography, respectively. IR spectra were measured as ATR on a JEOL FT-IR SPX60 spectrometer or IRTracer-100. ^{1}H NMR spectra were measured at 400 or 500 MHz on VARIAN 400-MR or 500-MR spectrometers and ^{13}C NMR spectra were measured at 100 or 125 MHz on VARIAN 400-MR or 500-MR

Table 1 [4+3] cycloadditions between 4a-d and 5



			Yield[a]		*Ratio*
Entry	*R*	*Solvent*	***3***	***8***	***3:8***
1	TBS (**4a**)	CH_2Cl_2	32% (**3a**: 23%; **3e**: 9%)	33% (**8a**: 25%; **8e**: 8%)	1:1
2	TBS (**4a**)	Toluene	50% (**3a**: 20%; **3e**: 30%)	6% (**8a**: 2%; **8e**: 4%)	8.3:1
3	TIPS (**4b**)	Toluene	64% (**3b** only)	17% (**8b** only)	3.8:1
4	TES (**4c**)	Toluene	58% (**3c**: 37%; **3e**: 21%)	7% (**8c** only)	8.3:1
5	*i*-$PrEt_2Si$ (**4d**)	Toluene	76% (**3d**: 11%; **3e**: 65%)	7% (**8d**: 5%; **8e**: 2%)	11:1

[a]Calculated by ^1H NMR.

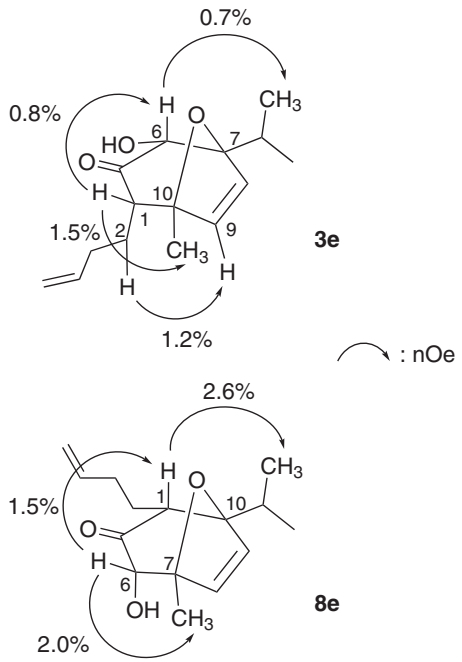
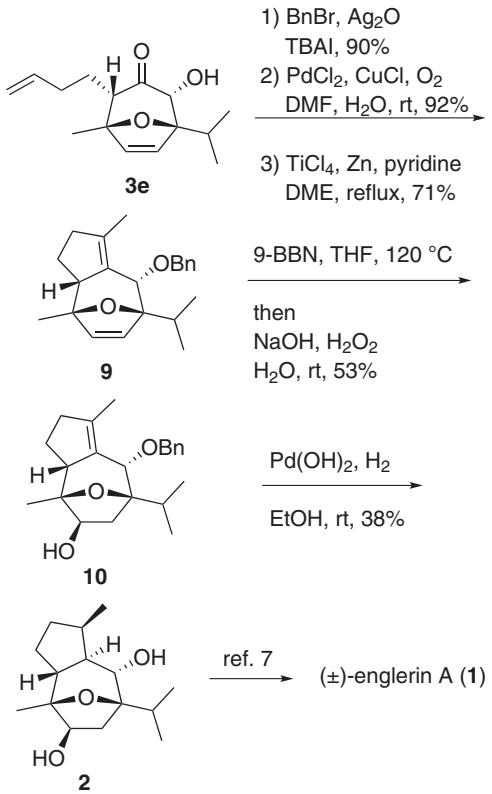


Figure 2 nOe correlations of bicycloketones **3e** and **8e**.



Scheme 3 Formal synthesis of (±)-englerin A (**1**).

spectrometers, respectively. High-resolution mass spectra were recorded on a JEOL JMS-700 MStation spectrometer or a JEOL JMS-T100LP Accu TOF spectrometer.

4-(3-Butenyl)-2,2-dimethyl-1,3-dioxan-5-one (7)

To a solution of 2,2-dimethyl-1,3-dioxan-5-one (**6**, 200 mg, 1.54 mmol) in dry benzene (5.0 ml) was added cyclohexylamine (352 µl, 3.1 mmol) and molecular sieves (4 Å, 400 mg). The mixture was stirred for 15 h at room temperature and filtered. The filtrate was concentrated *in vacuo* to give the crude imine. To a solution of lithium diethylamide, which was prepared by the addition of *n*-butyllithium (1.56 M in hexane, 1.0 ml, 1.54 mmol) to a solution of diethylamine (0.158 ml, 1.54 mmol) in dry tetrahydrofuran (THF) (1.6 ml) at −35 °C under argon atmosphere, was added a solution of the above imine in dry THF (1.6 ml) at −78 °C over 10 min. The mixture was warmed to −35 °C over 2 h and re-cooled to −78 °C. To the solution was added 4-iodobutene (279 mg, 1.54 mmol) and warmed to room temperature over 2 h. To the reaction mixture was added saturated NH_4Cl aq. solution and the resultant mixture was stirred for 12 h at that temperature. The mixture was diluted with Et_2O and the organic layer was washed with brine. The solution was dried over

anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with hexane-EtOAc (20:1) to afford ketone **7** (225 mg, 79%) as a colorless oil. The NMR spectrum was identical with that reported previously.[21]

(*Z*)-2-(*tert*-Butyldimethylsiloxy)hepta-2,6-dienal (4a)

To a solution of NaHMDS (1.9 M in THF, 0.42 ml, 0.81 mmol) in dry THF (2.8 ml) was added a solution of ketone **7** (100 mg, 0.54 mmol) in THF (5.0 ml) over 10 min at −78 °C under argon atmosphere. To the solution was added TBSCl (105 mg, 0.70 mmol) and the solution was warmed to −50 °C over 2 h. The reaction was quenched with saturated $NaHCO_3$ aq. solution and the mixture was diluted with hexane. The organic layer was washed with brine and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with hexane-EtOAc (20:1) to afford the dioxin (148 mg, 92%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.14 (s, 3H), 0.92 (s, 9H), 1.43 (s, 3H), 1.45 (s, 3H), 1.63–1.69 (m, 1H), 1.81–1.88 (m, 1H), 2.09–2.23 (m, 2H), 4.13 (ddd, *J*=1.3, 3.0, 6.9 Hz, 1H), 4.94 (dd, *J*=2.0, 10.0 Hz, 1H), 5.02 (dd, *J*=16.9, 2.0 Hz, 1H), 5.84 (tdd, *J*=5.8, 10.0, 16.9 Hz, 1H), 6.12 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, −4.4, 17.9, 20.9, 25.6, 27.8, 28.5, 30.3, 69.2, 93.3, 114.4, 126.4, 134.4, 138.7; FT-IR (neat) ν 3081, 2954, 2914, 2877, 2858, 1641, 1460, 1369, 1265, 1203, 1174, 1140, 1003, 910, 860, 727 cm^{-1}; HRMS (FAB) calculated for $C_{16}H_{29}O_3Si$: 297.1886, Found: 297.1887.

A solution of the above dioxin (50 mg, 0.16 mmol) in dry toluene (1.7 ml) was stirred for 2 h at 110 °C under argon atmosphere and cooled to room temperature. The solution was concentrated *in vacuo* and the residue (**4a**, 36 mg, 78% over two steps) was used for the next reaction without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17 (s, 6H), 0.95 (s, 9H), 2.23 (q, *J*=7.3 Hz, 2H), 2.44 (q, *J*=7.3 Hz, 2H), 5.01 (dd, *J*=1.4, 10.0 Hz, 1H), 5.06 (dd, *J*=1.4, 17.1 Hz, 1H), 5.71 (t, *J*=7.3 Hz, 1H), 5.82 (tdd, *J*=6.6, 10.2, 17.1 Hz, 1H), 9.16 (s, 1H). The enhancement of signal (2.3%) for H-3 was observed by a NOE, when H-1 was irradiated.; ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.1, 18.6, 25.3, 25.8, 32.4, 115.5, 135.1, 137.2, 151.5, 188.9; FT-IR (neat) ν 3081, 2954, 2925, 2898, 2366, 2341, 1641, 1471, 1369, 1251, 1205, 1172, 1139, 877, 838, 777, 688 cm^{-1}; HRMS (DART) $[M+H]^+$ calculated for $C_{13}H_{25}O_2Si$: 241.1624, found: 241.1640.

(*Z*)-2-(Triisopropylsiloxy)hepta-2,6-dienal (4b)

The reaction was carried out in a similar manner for preparation of **4a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, *J*=7.5 Hz, 18H), 1.27 (sept, *J*=7.5 Hz, 3H), 2.23 (q, *J*=7.3 Hz, 2H), 2.48 (q, *J*=7.3 Hz, 2H), 5.01 (dd, *J*=1.4, 10.3 Hz, 1H), 5.06 (tdd, *J*=1.4, 1.7, 17.1 Hz, 1H), 5.67 (t, *J*=7.3 Hz, 1H), 5.83 (tdd, *J*=6.6, 10.3, 17.1 Hz, 1H), 9.14 (s, 1H). The enhancement of signal (2.8%) for H-3 was observed by a NOE, when H-1 was irradiated.; ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 18.1, 25.3, 32.4, 115.4, 134.4, 137.4, 152.1, 188.9; FT-IR (neat) ν 3080, 2945, 2866, 1693, 1630, 1464, 1398, 1371, 1321, 1248, 1182, 1122, 1016, 993, 914, 881, 816, 737, 679, 645 cm^{-1}. HRMS (DART) $[M+H]^+$ calculated for $C_{16}H_{31}O_2Si$: 283.2093, found: 283.2111.

(*Z*)-2-(Triethylsiloxy)hepta-2,6-dienal (4c)

The reaction was carried out in a similar manner for preparation of **4a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.72 (q, *J*=8.1 Hz, 6H), 0.96 (t, *J*=8.1 Hz, 9H), 2.22 (q, *J*=7.1 Hz, 2H), 2.44 (q, *J*=7.3 Hz, 2H), 5.02 (tdd, *J*=1.7, 1.7, 10.7 Hz, 1H), 5.06 (tdd, *J*=1.7, 1.7, 17.1 Hz, 1H), 5.71 (t, *J*=7.3 Hz, 1H), 5.82 (tdd, *J*=6.6, 10.2, 16.8 Hz, 1H), 9.15 (s, 1H). The enhancement of signal (2.8%) for H-3 was observed by a NOE, when H-1 was irradiated.; ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.7, 6.8, 25.2, 32.4, 115.5, 134.9, 137.4, 151.7, 189.1; FT-IR (neat) ν 3084, 2956, 2912, 1691, 1633, 1458, 1398, 1369, 1321, 1240, 1182, 1117, 1001, 912, 733 cm^{-1}. HRMS (DART) $[M+H]^+$ calculated for $C_{13}H_{25}O_2Si$: 241.1624, found: 241.1607.

(*Z*)-2-(Diethylisopropylsiloxy)hepta-2,6-dienal (4d)

The reaction was carried out in a similar manner for preparation of **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (q, *J*=8.2 Hz, 4H), 0.96 (d, *J*=7.7 Hz, 3H), 0.99 (t, *J*=8.2 Hz, 6H), 1.01 (d, *J*=6.6 Hz, 3H), 1.06–1.19 (m, 1H), 2.18 (q, *J*=6.7 Hz, 2H), 2.45 (q, *J*=7.4 Hz, 2H), 5.01 (tdd, *J*=1.4, 1.8, 10.1 Hz, 1H), 5.06 (tdd, *J*=1.6, 1.7, 17.0 Hz, 1H), 5.70 (t, *J*=7.2 Hz, 1H), 5.82 (tdd, *J*=6.6, 10.2, 17.0 Hz, 1H), 9.14 (s, 1H). The enhancement of signal (1.0%) for H-3 was observed by a NOE, when H-1 was irradiated.; ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.7, 7.0, 13.8, 17.2, 25.2, 32.4, 115.4, 134.7, 137.4, 151.8, 189.0; FT-IR (neat) ν 3077, 2952, 2875, 1693, 1633, 1462, 1398, 1371, 1319, 1242, 1182, 1119, 1012, 991, 912, 881, 721 cm^{-1}. HRMS (DART) $[M+H]^+$ calculated for $C_{14}H_{27}O_2Si$: 255.1780, found: 255.1791.

(1*R**,2*S**,4*R**,5*S**)-2-(3-Butenyl)-4-hydroxy-5-isopropyl-1-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (3e)

To a solution of enal **4d** (168 mg, 0.66 mmol) and furan **5** (236 mg, 1.9 mmol) in toluene (0.5 ml) was added TfOH (112 μl, 1.3 mmol) in toluene (5.5 ml) over 1.5 h at −78 °C by syringe pump under argon atmosphere. The reaction was quenched with pyridine. To the mixture was added MeOH (3.3 ml) and the solution was warmed to room temperature and stirred for 12 h at that temperature. The reaction mixture was concentrated and diluted with CH_2Cl_2. The solution was washed with saturated $NaHCO_3$ aq. solution and the organic materials were extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with hexane-EtOAc (100:1) to afford **3e** (108 mg, 65%), a mixture of **3d** and **8d** (40 mg, total 16%), and **8e** (3.0 mg, 2%) as colorless oil. Other [4+3] cycloadditions in Table 1 were carried out in similar manners as described above.

3e: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, *J*=6.9 Hz, 3H), 1.09 (d, *J*=6.9 Hz, 3H), 1.33 (dddd, *J*=2.7, 6.8, 9.8, 16.1 Hz, 1H), 1.51 (s, 3H), 1.79 (dtd, *J*=5.6, 8.8, 14.4 Hz, 1H), 2.04–2.11 (m, 1H), 2.20–2.34 (m, 1H), 2.26 (sept, *J*=6.8 Hz, 1H), 2.59 (dd, *J*=2.9, 9.0 Hz, 1H), 3.61 (d, *J*=3.1 Hz, 1H), 4.22 (d, *J*=2.9 Hz, 1H), 5.00 (tdd, *J*=1.2, 2.2, 10.3 Hz, 1H), 5.02 (tdd, *J*=1.5, 1.7, 17.1 Hz, 1H), 5.78 (dddd, *J*=6.1, 7.1, 10.3, 17.1 Hz, 1H), 5.89 (d, *J*=5.8 Hz, 1H), 5.95 (d, *J*=5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4, 17.0, 21.7, 24.2, 29.3, 32.7, 58.7, 77.9, 88.6, 92.6, 115.4, 135.0, 135.5, 138.0, 209.9; FT-IR (neat) ν 3475, 2966, 2933, 2875, 2157, 1704, 1641, 1450, 1380, 1334, 1259, 1114, 1072, 991, 908, 836, 761, 688 cm^{-1}; HRMS (DART) $[M+H]^+$ calculated for $C_{15}H_{23}O_3$: 251.1647, found: 251.1656.

3d and **8d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.59–0.77 (m, 4H), 0.90–1.03 (m, 19H), 1.20–1.30 (m, 1H), 1.47 (s, 33/16H), 1.48 (s, 15/16H), 1.66 (dtd, *J*=5.3, 9.0, 14.1 Hz, 5/16H), 1.82 (dtd, *J*=5.3, 8.6, 13.9 Hz, 11/16H), 2.10–2.02 (m, 1.5H), 2.24–2.31 (m, 1.5H), 2.43 (dd, *J*=3.0, 8.3 Hz, 11/16H), 2.63 (dd, *J*=2.4, 9.2 Hz, 5/16H), 4.05 (s, 5/16H), 4.28 (s, 11/16H), 4.95–5.02 (m, 2H), 5.74–5.83 (m, 1H), 5.85 (d, *J*=5.8 Hz, 5/16H), 5.87 (d, *J*=6.1 Hz, 11/16H), 5.93 (d, *J*=5.9 Hz, 5/16H), 5.95 (d, *J*=5.8 Hz, 11/16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.7, 4.0, 4.1, 4.4, 7.1, 7.2, 7.3, 13.2, 13.4, 15.9, 16.1, 17.1, 17.3, 17.35, 17.41, 17.48, 20.6, 21.8, 23.5, 24.2, 28.1, 29.2, 32.9, 33.0, 55.8, 59.3, 79.6, 83.1, 87.6, 87.9, 92.8, 93.1, 115.1 (2C), 134.9, 135.6, 138.3, 138.4, 207.5, 207.8; FT-IR (neat) ν 3078, 2958, 2935, 2875, 2329, 2198, 1724, 1641, 1458, 1381, 1336, 1286, 1240, 1190, 1132, 1072, 1007, 910, 881, 818, 719 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{22}H_{38}NaO_3Si$: 401.2512, found: 401.2506.

8e: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, *J*=6.6 Hz, 3H), 1.02 (d, *J*=6.9 Hz, 3H), 1.35 (dddd, *J*=2.2, 7.3, 9.3, 16.1 Hz, 1H), 1.54 (s, 3H), 1.66 (dtd, *J*=5.3, 9.3, 13.9 Hz, 1H), 2.02–2.15 (m, 1H), 2.11 (sept, *J*=6.8 Hz, 1H), 2.23–2.35 (m, 1H), 2.78 (dd, *J*=2.2, 10.0 Hz, 1H), 3.64 (d, *J*=3.4 Hz, 1H), 3.99 (d, *J*=3.2 Hz, 1H), 4.99 (brd, *J*=10.8 Hz, 1H), 5.02 (brd, *J*=17.3 Hz, 1H), 5.79 (dddd, *J*=7.3, 7.3, 10.2, 17.1 Hz, 1H), 5.86 (d, *J*=5.8 Hz, 1H), 5.92 (d, *J*=5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 17.4, 20.2, 23.5, 29.2, 32.5, 55.2, 81.3, 87.4, 93.7, 115.5, 134.7, 136.0, 138.0, 210.0; FT-IR (neat) ν 3482, 2964, 2916, 2875, 2848, 1707, 1641, 1448, 1377, 1369, 1339, 1260, 1190, 1169, 1111, 1072, 1024, 978, 912, 799, 760 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{15}H_{22}NaO_3$: 273.1467, found: 273.1625.

(3a*R**,4*R**,7*S**,8*S**)-8-(Benzyloxy)-7-isopropyl-1,4-dimethyl-2,3,3a,4,7,8-hexahydro-4,7-epoxyazulene (9)

To a solution of alcohol **3e** (98 mg, 0.39 mmol) in BnBr (0.5 ml, 4.2 mmol) were added Ag_2O (362 mg, 1.6 mmol) and TBAI (15 mg, 0.039 mmol) and stirred for 22 h at room temperature. To the reaction mixture was added 2 M

NaOH aq. solution. The reaction mixture was filtered and washed with Et_2O and the organic layer was washed with brine. The solution was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with hexane-EtOAc (200:1) to afford the corresponding benzyl ether (136 mg, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, J=6.8 Hz, 3H), 0.88 (d, J=6.8 Hz, 3H), 1.24–1.30 (m, 1H), 1.48 (s, 3H), 1.83 (dtd, J=5.6, 8.5, 13.9 Hz, 1H), 2.05–2.13 (m, 1H), 2.26 (sept, J=6.8 Hz, 1H), 2.22–2.37 (m, 1H), 2.47 (dd, J=2.9, 8.3 Hz, 1H), 4.00 (s, 1H), 4.51 (d, J=11.2 Hz, 1H), 4.98–5.06 (m, 3H), 5.81 (tdd, J=7.0, 10.1, 16.7 Hz, 1H), 5.90 (d, J=5.9 Hz, 1H), 6.00 (d, J=6.1 Hz, 1H), 7.26–7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.1, 17.0, 21.8, 24.3, 28.4, 33.0, 59.7, 73.9, 84.1, 88.0, 92.1, 115.2, 127.8, 128.32, 128.33, 135.16, 135.22, 137.9, 138.3, 208.6; FT-IR (neat) ν 3342, 2970, 2929, 2837, 2339, 1718, 1653, 1454, 1381, 1334, 1119, 1070, 1024, 906 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{22}H_{28}NaO_3$: 363.1936, found: 363.1969.

To a solution of the above benzyl ether (224 mg, 0.66 mmol) in dimethylformamide (10 ml) and water (1 ml) were added $PdCl_2$ (6.0 mg, 0.033 mmol) and CuCl (13 mg, 0.13 mmol) at room temperature. The solution was stirred for 12 h at that temperature under O_2 atmosphere. The reaction mixture was filtered and washed with Et_2O and saturated $NaHCO_3$ aq. solution. The organic materials in the filtrate were extracted with Et_2O three times and the combined organic layers were washed with brine. The solution was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with hexane-EtOAc (10:1-3:1) to afford the corresponding diketone (230 mg, 92%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, J=6.8 Hz, 3H), 0.87 (d, J=7.1 Hz, 3H), 1.51 (s, 3H), 1.67 (dt, J=6.6, 7.3 Hz, 2H), 2.14 (s, 3H), 2.25 (sept, J=7.1 Hz, 1H), 2.48 (t, J=6.4 Hz, 1H), 2.49 (dt, J=7.5, 18.4 Hz, 1H), 2.84 (dt, J=7.1, 17.8 Hz, 1H), 4.00 (s, 1H), 4.49 (d, J=11.2 Hz, 1H), 5.01 (d, J=11.3 Hz, 1H), 5.91 (d, J=6.1 Hz, 1H), 6.00 (d, J=6.1 Hz, 1H), 7.27–7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.1, 17.0, 19.5, 21.6, 28.4, 29.9, 42.5, 59.8, 73.9, 84.3, 88.0, 92.1, 127.8, 128.25, 128.31, 135.1, 135.3, 137.8, 208.6, 209.0; FT-IR (neat) ν 2967, 2934, 2876, 1714, 1497, 1454, 1410, 1383, 1366, 1337, 1236, 1209, 1182, 1169, 1121, 1072, 1040, 1028, 989, 903, 766, 739, 700 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{22}H_{28}NaO_4$: 379.1885, found: 379.1899.

To a stirred suspension of activated zinc powder (72 mg, 1.1 mmol) in dry dimethoxyethane (2.3 ml) were added titanium (IV) chloride (60 µl, 0.56 mmol) and pyridine (45 µl, 0.56 mmol) at −78 °C under argon atmosphere. The suspension was warmed to room temperature and then refluxed for 2 h. Then the suspension was cooled to room temperature and to the suspension of titanium reagent were added the above diketone (20 mg, 0.056 mmol) in dimethoxyethane (0.56 ml). The mixture was refluxed for 20 h and cooled to room temperature. The reaction was quenched with 10% K_2CO_3 aq. solution at 0 °C and the mixture was filtered and washed with Et_2O. The organic materials in the filtrate were extracted with Et_2O. The precipitates on the celite were washed with 2 M HCl aq. solution and organic materials were extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with hexane-EtOAc (50:1-20:1) to afford cyclopentene **9** (13 mg, 71%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, J=6.9 Hz, 3H), 1.01 (d, J=6.9 Hz, 3H), 1.05–1.14 (m, 1H), 1.31 (s, 3H), 1.75 (s, 3H), 1.84 (tdd, J=1.3, 7.8, 12.3 Hz, 1H), 2.07 (dd, J=9.5, 15.6 Hz, 1H), 2.27 (sept, J=6.9 Hz, 1H), 2.23–2.35 (m, 1H), 2.66 (dt, J=1.4, 8.1 Hz, 1H), 4.24 (d, J=1.5 Hz, 1H), 4.67 (d, J=11.2 Hz, 1H), 4.77 (d, J=11.2 Hz, 1H), 5.84 (d, J=5.9 Hz, 1H), 6.01 (d, J=5.9 Hz, 1H), 7.26–7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 16.8, 17.8, 21.2, 25.1, 27.9, 38.9, 55.1, 73.6, 79.8, 87.5, 91.6, 127.36, 127.44, 128.3, 133.3, 133.6, 134.3, 134.5, 138.4; FT-IR (neat) ν 3329, 2943, 2835, 2337, 2044, 1653, 1448, 1404, 1111, 1020 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{22}H_{28}NaO_2$: 347.1987, found: 347.1973.

(3a*R**,4*S**,5*R**,7*R**,8*S**)-8-(Benzyloxy)-7-isopropyl-1,4-dimethyl-2,3,3a,4,5,6,7,8-octahydro-4,7-epoxyazulen-5-ol (10)

To a solution of alkene **9** (18 mg, 0.055 mmol) in a sealed tube was added a solution of 9-borabicyclo[3.3.1]nonane (1.16 ml, 0.5 M in THF). The solvent was vacuumed under reduced pressure to 80 µl to ensure the concentration based on benzyl ether **9** was 0.7 mol/l. The solution was heated for 22 h at 120 °C and cooled down to 0 °C. Then 3 M NaOH aq. solution (0.25 ml) and H_2O_2 (0.25 ml, 30% aq.) was added in sequentially and the resulting solution was stirred for 1 h at room temperature. The organic layer was washed with brine twice, and the organic materials were extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with hexane-EtOAc (50:1) to afford alcohol **10** (10 mg, 53%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, J=7.1 Hz, 3H), 1.03 (d, J=6.8 Hz, 3H), 1.20 (s, 3H), 1.35–1.43 (m, 1H), 1.79 (s, 3H), 1.91 (dtd, J=3.9, 10.0, 13.9 Hz, 1H), 2.06 (sept, J=6.9 Hz, 1H), 2.24–2.45 (m, 3H), 2.73 (br, 1H), 3.84 (dd, J=1.7, 7.6 Hz, 1H), 4.07 (br, 1H), 4.54 (d, J=11.2 Hz, 1H), 4.74 (d, J=11.5 Hz, 1H), 7.28–7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 17.5, 17.9, 18.4, 22.5, 31.3, 39.7, 42.0, 57.1, 72.9, 74.1, 82.1, 86.6, 87.6, 127.4, 127.5, 128.3, 130.8, 132.2, 138.2; FT-IR (neat) ν 3315, 2947, 2837, 2341, 1653, 1452, 1417, 1109, 1016 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{22}H_{30}NaO_3$: 365.2093, found: 365.2116.

(1*R**,3a*R**,4*S**,5*R**,7*R**,8*S**,8a*R**)-7-Isopropyl-1,4-dimethyldecahydro-4,7-epoxyazulene-5,8-diol (2)

To a solution of allylic alcohol **10** (1.4 mg, 4.0 µmol) in EtOH (1.0 ml) was added $Pd(OH)_2$ (20% on carbon, 5.0 mg, 7.0 µmol) and stirred for 15 h at room temperature under H_2 atmosphere. After filtration through a pad of celite, the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane-EtOAc (30:1–10:1) to afford diol **2** (0.4 mg, 38%) as a colorless oil. The ^{1}H NMR spectrum was identical with that reported previously.[7]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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