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Stereoselective Convergent Synthesis of Carbon Skeleton of Cotylenin A Aglycone

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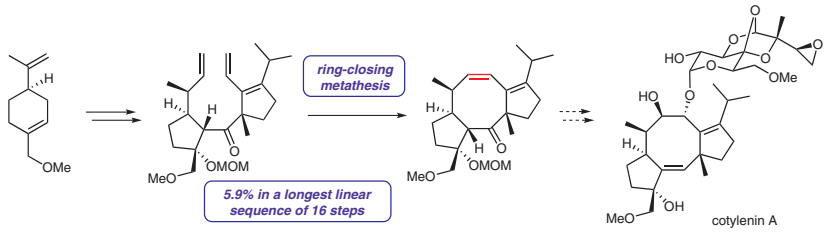

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Abstract In this paper, the synthesis of the carbon skeleton of cotylenin A aglycone is described. The key reactions, including an intramolecular aldol reaction, an aldol coupling reaction, and a ring-closing metathesis, allow for the effective and stereoselective access to the carbon skeleton of cotylenin A aglycone. The stereochemistry was confirmed by single-crystal X-ray crystallographic analyses of related compounds.

Key words cotylenin A, cotylenol, carbocycles, polycycles, natural products, ring-closing metathesis

Cotylenin A is a diterpene glycoside, isolated and structurally determined in 1975 from *Cladosporium* sp. 501-7W as a cytokinin-like bioactive compound (Figure 1).[1] It has been reported to modulate biological signals by stabilizing the protein–protein interaction (PPI) between a 14-3-3 protein and its target protein.[2]

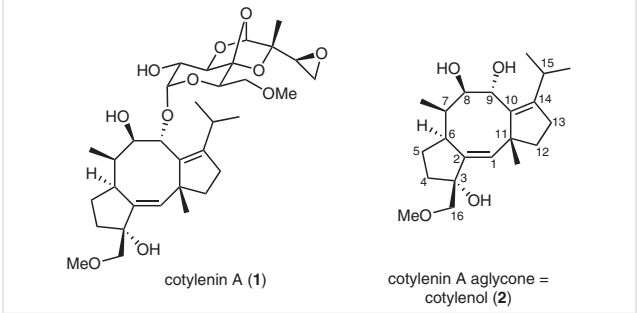


Figure 1 Structure of cotylenin A (**1**) and the numbering of cotylenin A aglycone

PPIs are very important in biological signaling because of the large number of proteins that participate in them. It has been suggested that there are approximately 130,000 different PPIs, but only 8% of them have known functions.[3] The relatively flat molecular surfaces involved in PPIs, with only shallow unevenness, provide few sites where small molecules can bind with high affinity. For these reasons, modulating PPIs with small molecules is considered to be challenging. However, because PPIs are observed in numerous signal transductions, PPI modulation offers an attractive opportunity for the development of drugs with novel mechanisms of action.

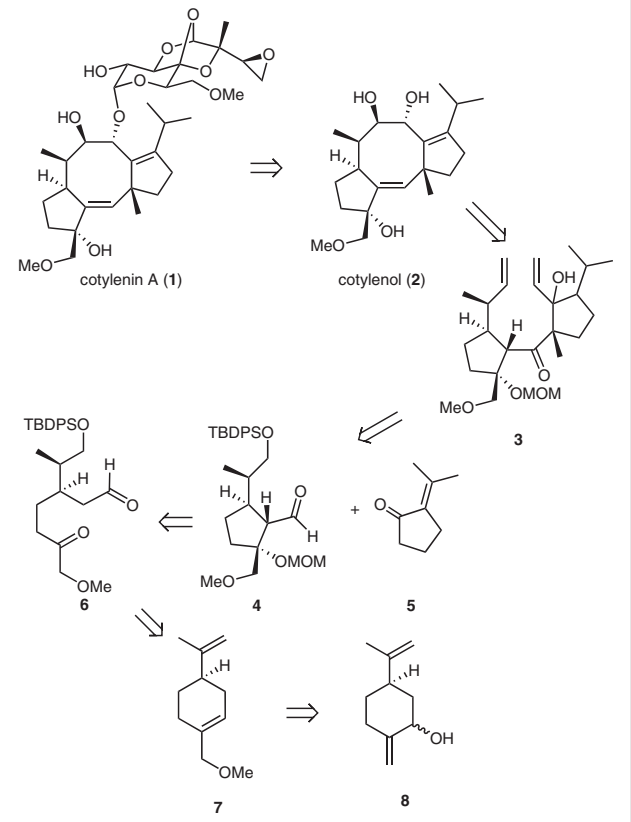
First isolated in 1967, the 14-3-3 proteins are adaptor proteins with a molecular weight of approximately 28,000. They consist of nine α-helices and exist in a dimeric form.[4] Seven isoforms have been identified, and interactions with hundreds of proteins have been found.[5] For example, 14-3-3 proteins have been reported to stabilize p53, a tumor suppressor, and to enhance its antitumor activity.[6]

Cotylenin A has been reported to induce differentiation of acute myeloid leukemia cells (HL-60).[7] However, at present, it is not possible to conduct research on the biological activity of cotylenin A because the fungal strain from which this compound was originally isolated has lost the ability to produce it. The total synthesis of cotylenin A has attracted the interest of synthetic organic chemists for providing an alternative supply, thus contributing to further research on its specific biological activity and PPI modulators in general.

To date, in addition to a synthetic study by Shoji, Sugai, and co-workers,[8] the synthesis of cotylenin A aglycone (i.e., cotylenol) by Kato and co-workers[9] and a total synthesis of cotylenin A by Nakada and co-workers[10] have been reported. Each of these approaches used a convergent synthetic strategy.

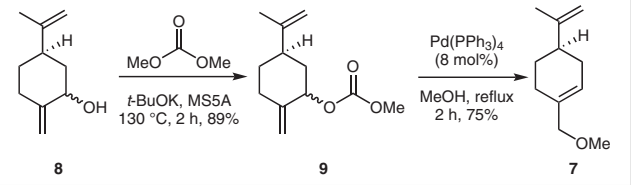
A retrosynthetic analysis of cotylenin A (**1**) is described in Scheme 1. We decided to first synthesize cotylenin A aglycone **2**. This compound can be accessed via eight-membered-ring construction by ring-closing metathesis of diene **3**, followed by functional group transformations. Diene **3**

was synthesized via the aldol coupling reaction of aldehyde **4** with cyclopentanone derivative **5**. Aldehyde **4** can be formed by the intramolecular aldol reaction of keto aldehyde **6**. Keto aldehyde **6** can be prepared via ozone oxidation of olefin **7**, in turn obtained from allyl alcohol **8**, which is easily formed in one step from commercially available (*R*)-limonene oxide.



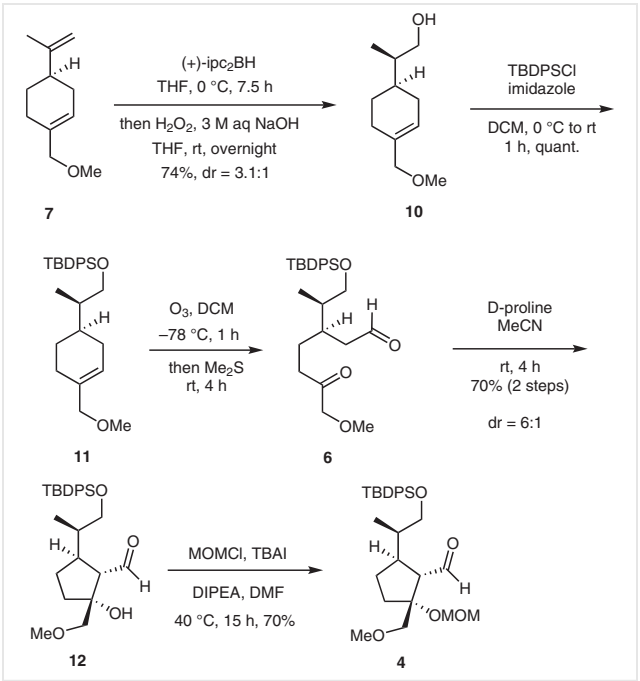
Scheme 1 Retrosynthetic analysis of cotylenin A (**1**)

Our synthesis began with the esterification of allyl alcohol **8** with dimethyl carbonate by using potassium *tert*-butoxide in the presence of molecular sieves (Scheme 2).[11] Next, the thus obtained carbonate **9** was treated with tetrakis(triphenylphosphine)palladium(0) in methanol to afford methyl ether **7** in 75% yield.



Scheme 2 Synthesis of methyl ether **7**

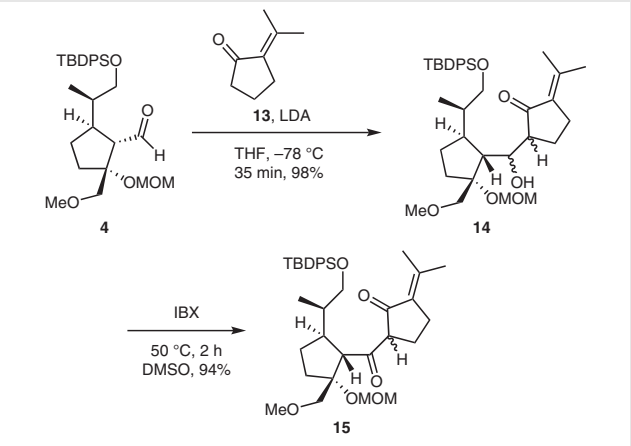
The hydroboration of methyl ether **7** with (+)-ipc$_2$BH was then performed to obtain alcohol **10** in 74% yield and in a 3.1:1 diastereomeric ratio (Scheme 3).[12] Alcohol **10** was quantitatively converted into silyl ether **11** by using TBDPSCl in the presence of imidazole. Then, the olefin group of **11** was oxidatively cleaved by ozone to form keto aldehyde **6**, which was treated with D-proline to produce β-hydroxy aldehyde **12** in 70% yield over two steps.[13] Subsequent MOM protection successfully afforded aldehyde **4** in 70% yield. This series of transformations from ozone oxidation to MOM protection had to be executed quickly to minimize the spontaneous cyclization of keto aldehyde **6** and the spontaneous ring-opening of β-hydroxy aldehyde **12**.



Scheme 3 Synthesis of aldehyde **4**

The aldol coupling reaction between aldehyde **4** and ketone **13** proceeded smoothly, yielding β-hydroxy ketone **14** in 98% yield (Scheme 4). Then, the resulting secondary alcohol was converted into the ketone by IBX oxidation to afford diketone **15**.

For the subsequent methylation step, both the solvent and base were examined to find the optimal conditions (Table 1). First, when acetone was used as the solvent and potassium carbonate as the base at room temperature, methylation proceeded in 98% yield, but the diastereomeric ratio was 1:1 (entry 1). When the solvent was changed to DMSO and the base to NaH, the result was a complex mixture of unknown compounds (entry 2). When cesium carbonate was used as the base in acetone, the methylation proceeded smoothly and a diastereomeric ratio favoring the desired product **16** was observed (entry 3). From then on, we fixed the base as cesium carbonate and examined the solvent effect. Since the diastereomeric ratio decreased to 1:1 in dichloromethane (entry 4), we attempted the reaction in THF, MeCN, MeOH, DMSO, and DMF with the expectation that

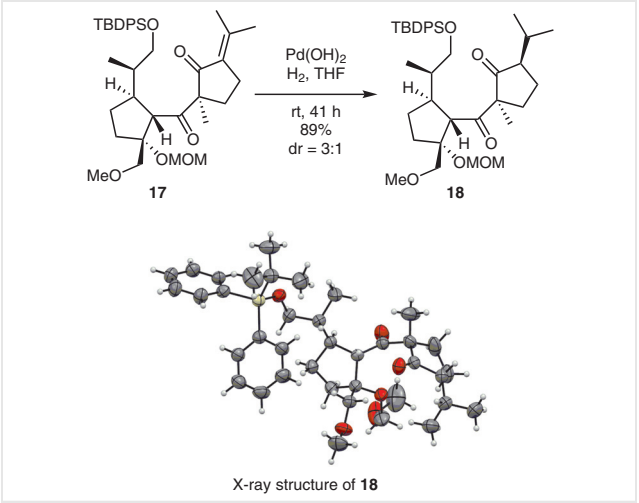


Scheme 4 Synthesis of diketone **15**

the diastereomeric ratio would be improved with the use of more polar solvents. In THF, the main product was the undesired diketone **17** (entry 5), but in other polar solvents, the diastereomeric ratio was improved, favoring **16** (entries 6–9).

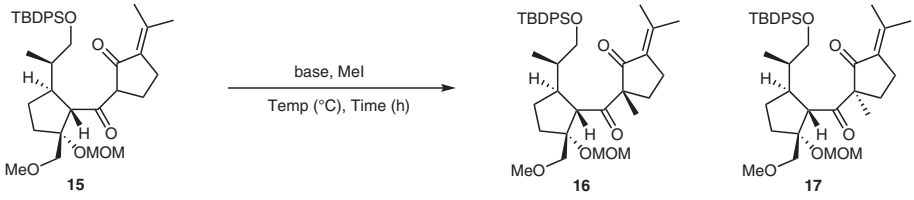
Next, to investigate the effect of the temperature, the reaction was carried out at –40 and –60 °C with cesium carbonate in DMF (Table 1, entries 10 and 11). It was found that the diastereomeric ratio improved with decreasing temperature, but the reaction rate decreased significantly at –60 °C (entry 11). Therefore, the conditions of entry 10 were deemed optimal.

At this stage, to confirm the stereochemistry, single-crystal X-ray crystallographic analysis was performed for diketone **18**, which was obtained via reduction of enone **17** with palladium hydroxide (Scheme 5).[14]



Scheme 5 Synthesis of diketone **18** and its absolute structure, obtained by X-ray crystallographic analysis

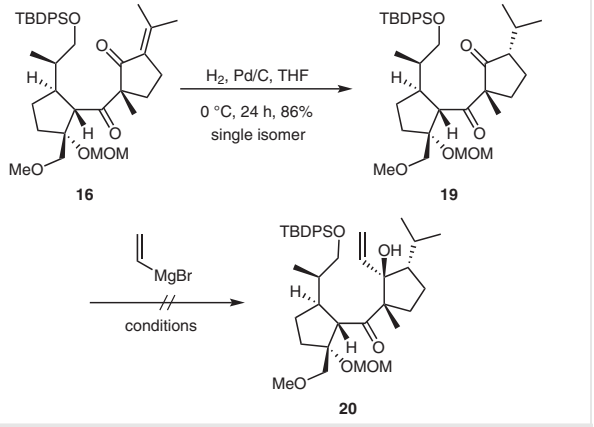
Table 1 Optimization of Methylation of Diketone **15**[a]



Entry	Solvent	Base	Temp (°C)	Time (h)	dr (**16**/**17**)[b]	Comment[c]
1	acetone	K_2CO_3	rt	14	1:1	98% yield
2	DMSO	NaH	rt	14	–	unknown compounds
3	acetone	Cs_2CO_3	rt	14	2:1	full conversion
4	DCM	Cs_2CO_3	rt	14	1:1	full conversion
5	THF	Cs_2CO_3	rt	14	1:1.7	full conversion
6	MeCN	Cs_2CO_3	rt	14	2:1	full conversion
7	MeOH	Cs_2CO_3	rt	14	2:1	full conversion
8	DMSO	Cs_2CO_3	rt	14	3:1	full conversion
9	DMF	Cs_2CO_3	rt	14	2.5:1	full conversion
10[e]	DMF	Cs_2CO_3	–40	24	3.5:1	90% yield
11	DMF	Cs_2CO_3	–60	24	4:1	SM **15** remained (ca. 80%)[d]

[a] Reaction conditions: **15** (8.05 μmol), MeI (50.0 equiv), base (15.0 equiv), solvent (0.400 mL).
[b] The dr was determined by ^{1}H NMR.
[c] Conversions and yields determined by ^{1}H NMR.
[d] SM = starting material.
[e] Reaction conditions: **15** (54.1 μmol), MeI (50.0 equiv), base (15.0 equiv), solvent (2.97 mL).

The desired product turned out to be diketone **17**. The reduction of enone **16** with palladium on carbon in THF was performed to obtain diketone **19** as a single diastereomer in 86% yield (Scheme 6). However, the Grignard reaction of **19** with vinylmagnesium bromide was not successful, although various conditions were investigated. Initially, the reaction was attempted in THF and toluene at –78 °C, which produced a complex mixture of products. Therefore, the amount of Grignard reagent was reduced from 10 to 5 equivalents, but no improvement was observed. Next, the Grignard reaction was attempted in the presence of cerium chloride and zinc chloride. Although the complication of the reaction was somewhat suppressed at –78 °C, the reaction became more complicated with an increase in temperature.



Scheme 6 Synthesis of diketone **19** and its attempted reaction with vinylmagnesium bromide to form **20**

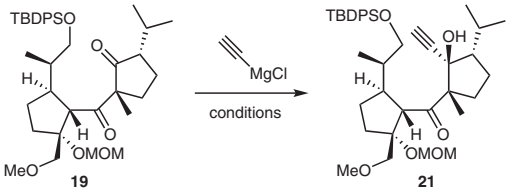
As a reagent with less steric demand, ethynylmagnesium chloride was selected instead as the Grignard reagent (Table 2). As a result, β-hydroxy ketone **21** was obtained in THF in only a trace amount (entry 1). However, when the solvent was changed to toluene, β-hydroxy ketone **21** was obtained quantitatively as a single diastereomer (entry 2).

Next, the partial reduction of alkyne **21** using a Lindlar catalyst afforded olefin **22** in quantitative yield (Scheme 7). The TBDPS group of **22** was successfully removed using TBAF in the presence of acetic acid to yield diol **23**. Oxidation of primary alcohol in **23** with DMP reagent, was followed by olefin formation using the Tebbe reagent to give diene **3** in 85% yield over two steps.

At this time, diol **25** was synthesized by reducing ketone **3**, and its absolute structure was determined by single-crystal X-ray crystallographic analysis (Scheme 8).[14]

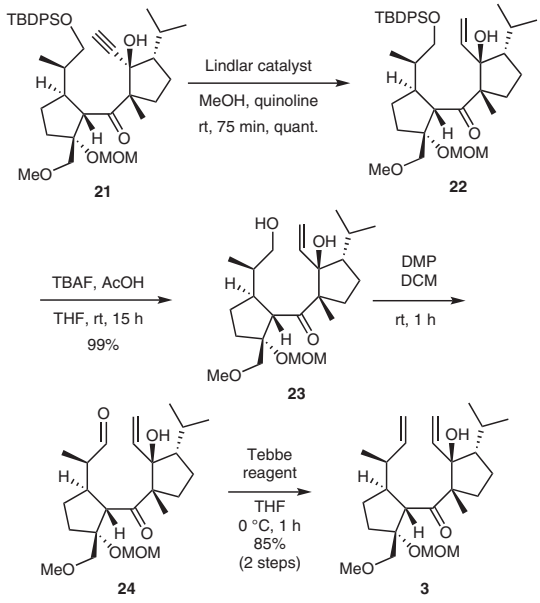
Then, the ring-closing-metathesis reaction on diene **3** to form the 8-membered ring of **26** was attempted with the Hoveyda–Grubbs second-generation catalyst (Scheme 9). First, the reaction was attempted at 110 °C in toluene,

Table 2 Optimization of Addition of Ethynylmagnesium Bromide to Diketone **19**



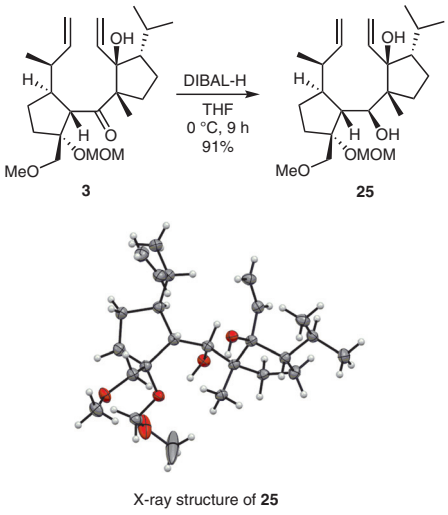
Entry	Solvent	Temp (°C)	Time (h)	Comments
1[a]	THF	–78 to 40	4.5	trace product[c]
2[b]	toluene	0	1.5	quant., single isomer

[a] Reaction conditions: **19** (4.7 μmol), ethynylmagnesium chloride (10.0 equiv), solvent (150 μL).
[b] Reaction conditions: **19** (1.06 mmol), ethynylmagnesium chloride (10.0 equiv), solvent (5.0 mL). Isolated yield.
[c] Product determined by ^{1}H NMR.

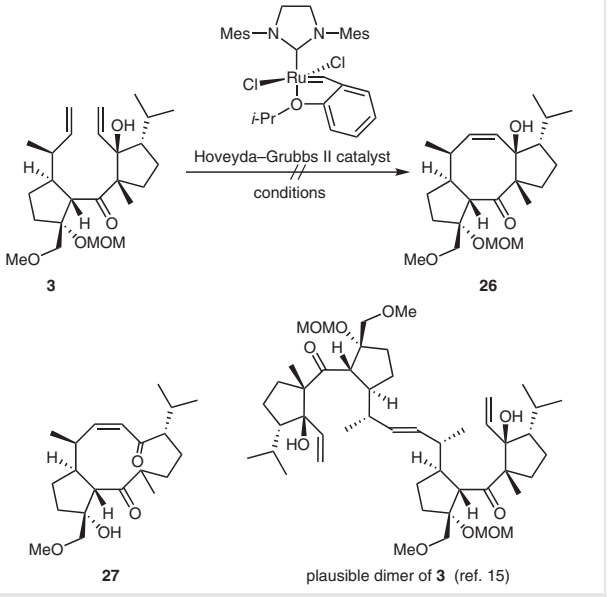


Scheme 7 Synthesis of diene **3**

which produced a complex mixture. Next, when the reaction was attempted after adding acetic acid, only the starting material was recovered. When the reaction was attempted in DMF, a compound that was presumed to be a dimer of diene **3**[15] was obtained, and even when the reaction was performed under highly diluted conditions, the desired tricyclic compound **26** was not obtained. When the reaction was carried out after adding acetic acid, the catalyst decomposed, and the addition of an excess amount was required. Diketone **27** with an 11-membered ring was obtained, which is thought to have been formed by ring-closing metathesis after a retro-aldol reaction.[16]

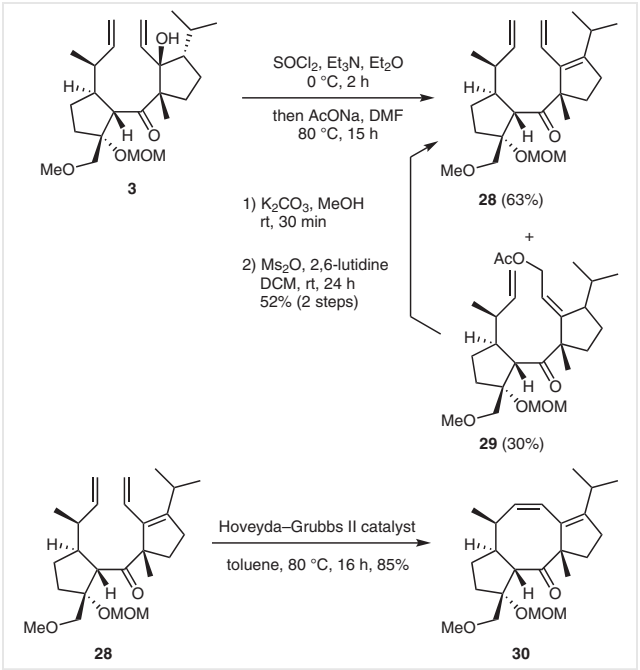


Scheme 8 Synthesis of diol **25** and its absolute structure, obtained by X-ray crystallographic analysis



Scheme 9 Attempted ring-closing metathesis of diene **3**

To promote the intended cyclization, it was decided to remove the hydroxy group in diene **3**, which was thought to be causing excessive steric hindrance. Therefore, diene **3** was treated with thionyl chloride for dehydration to give triene **28** in 63% yield; the formation of allyl chloride was also observed (Scheme 10). Then, by treating the crude products with sodium acetate in DMF, the allyl chloride was converted into the separable allyl acetate **29**. Ring-closing metathesis of triene **28** using the Hoveyda–Grubbs second-generation catalyst proceeded smoothly, and the tricyclic compound **30**, which possesses a 5-8-5 ring system, was synthesized in 85% yield. This product was obtained in an optically active form, and its stereochemistry was identical to that of the natural product.



Scheme 10 Synthesis of carbon skeleton of cotylenin A aglycone

In conclusion, we constructed the carbon skeleton of cotylenin A aglycone in 5.9% yield in a stereoselective synthesis, with the longest linear sequence of steps being 16. We started from reported compound **8**, which was easily accessible from commercially available (*R*)-limonene oxide in one step. The synthesis included as key steps an intramolecular aldol reaction, an aldol coupling reaction, and a ring-closing metathesis. X-ray crystallographic analyses of **18** and **25** confirmed the stereochemistry of the synthesized carbon skeleton of cotylenin A aglycone. We hope that this synthetic strategy will lead to an effective total synthesis of cotylenin A.

All reactions were carried out in a round-bottom flask or a test tube fitted with a three-way glass stopcock under argon atmosphere unless stated otherwise. Flash chromatography was performed using silica gel 60N (particle size: 40–50 μm) purchased from Kanto Chemical unless stated otherwise. All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Reagents were purchased from commercial suppliers and used as received unless stated otherwise. ^{1}H and ^{13}C NMR spectra were recorded on JEOL ECA-600 or Bruker AVIII 400 spectrometers, using $CDCl_3$ or acetone-d_6 as solvent. Chemical shift values are reported in δ (ppm) relative to residual solvent signals ($CDCl_3$: δ = 7.26, ^{1}H and 77.0, ^{13}C; acetone-d_6: δ = 2.04, ^{1}H and 29.8, ^{13}C). High-resolution mass spectra (ESI-TOF or EI) were measured on JEOL JMS-T100LP or JMS-700 spectrometers. Single-crystal X-ray analyses were performed on Rigaku

R-AXIS RAPID II-RF instruments. Optical rotation was measured on JASCO P-2200 instruments, and recorded as $[\alpha]_D$ values (concentration in g/100 mL). IR spectra were recorded on a JASCO FT/IR 4100 spectrophotometer.

Methyl [(5*R*)-2-Methylene-5-(prop-1-en-2-yl)cyclohexyl] Carbonate (9)

To a stirred solution of alcohol **8** (580 mg, 3.81 mmol) in dimethyl carbonate (5.05 mL) was added *t*-BuOK (430 mg, 3.83 mmol) at rt. After connection of a dropping funnel filled with 5A MS and a reflux condenser, the reaction mixture was refluxed for 2 h. The reaction mixture was cooled to rt and quenched with the addition of sat. aq NH_4Cl solution. The resulting mixture was diluted with DCM/H_2O and extracted three times with DCM. After the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated, the residue was purified by flash column chromatography (silica gel, hexane/DCM, 100:0 to 3:2) to give methyl carbonate **9**.

Yield: 710 mg (3.37 mmol, 89%); colorless oil; $[\alpha]_D^{25.0}$ –6.3 (*c* 1.00, $CHCl_3$).

IR (neat): 3083, 2939, 2858, 1750, 1655, 1645 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.25 (t, *J* = 2.8 Hz, 0.55 H), 5.12–5.05 (m, 0.45 H), 5.03 (t, *J* = 1.6 Hz, 0.55 H), 4.92 (t, *J* = 1.6 Hz, 0.55 H), 4.85 (dd, *J* = 2.8, 1.2 Hz, 0.45 H), 4.79 (dd, *J* = 2.8, 1.2 Hz, 0.45 H), 4.76–4.67 (m, 2 H), 3.81 (s, 1.35 H), 3.77 (s, 1.65 H), 2.52–2.33 (m, 1.55 H), 2.32–2.01 (m, 2.45 H), 1.93–1.80 (m, 1 H), 1.78–1.64 (m, 3 H), 1.62–1.17 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.1, 155.0, 148.7, 148.0, 145.6, 144.5, 113.3, 109.5, 109.2, 105.1, 78.4, 77.4, 54.8, 54.5, 43.7, 38.7, 38.4, 36.8, 33.8, 32.3, 32.2, 30.5, 20.8, 20.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{18}O_3Na^+$: 233.1148; found: 233.1156.

(*R*)-1-(Methoxymethyl)-4-(prop-1-en-2-yl)cyclohex-1-ene (7)

To a stirred solution of methyl carbonate **9** (109 mg, 0.518 mmol) in MeOH (9.5 mL) was added $Pd(PPh_3)_4$ (48.0 mg, 41.5 μmol) at rt. The solution was refluxed for 2 h. After the reaction mixture was cooled to rt, filtrated through Celite, and concentrated, the residue was purified by flash column chromatography (silica gel, hexane/DCM, 100:0 to 1:1) to give methyl ether **7** (75%). (Note: Methyl ether **3** still containing hexane/DCM was used in the next reaction and data measurements.)

Yield: 64.6 mg (0.389 mmol, 75%); colorless oil; $[\alpha]_D^{20.5}$ +14.8 (*c* 0.91, $CHCl_3$).

IR (neat): 2928, 2855, 2355, 2342, 1744 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.74–5.68 (m, 1 H), 4.75–4.71 (m, 2 H), 3.80 (s, 2 H), 3.45 (s, 3 H), 2.21–1.98 (m, 5 H), 1.90–1.82 (m, 1 H), 1.76 (s, 3 H), 1.57–1.43 (m, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 149.8, 134.6, 124.5, 108.6, 76.9, 57.6, 41.1, 30.5, 27.4, 26.3, 20.8.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{18}O_1$: 166.1358; found: 166.1359.

(*R*)-2-[(*R*)-4-(Methoxymethyl)cyclohex-3-en-1-yl]propan-1-ol (10)

Preparation of (+)-ipc$_2$BH: To a stirred solution of dimethyl sulfide borane (342 mg, 4.51 mmol) in THF (10 mL) was added (–)-α-pinene (1.25 g, 9.02 mmol) at –5 °C. After stirring for 36 h at the same temperature, (+)-ipc$_2$BH precipitated as a white solid.

*Synthesis of alcohol **10***: To a suspension of (+)-ipc$_2$BH in THF (prepared above) was added methyl ether **7** (500 mg, 3.01 mmol) at 0 °C. After the mixture had stirred for 7.5 h at the same temperature, 3 M aq NaOH (4.5 mL, 13.5 mmol) and 30% aq H_2O_2 solution (1.6 mL) were added. After stirring for 14 h at rt, the reaction mixture was quenched with the addition of sat. aq NH_4Cl solution. The resulting mixture was diluted with H_2O and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 1:4) to give alcohol **10**.

Yield: 411 mg (2.23 mmol, 74%); dr = 3.1:1 (note that the diastereomers could not be separated in this process); colorless oil; $[\alpha]_D^{26.5}$ +58.6 (*c* 1.00, $CHCl_3$).

IR (neat): 3565, 3398, 2959, 2918, 2884, 2837 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.69–5.65 (m, 1 H), 3.79–3.76 (s, 2 H), 3.70–3.61 (m, 1 H), 3.54–3.48 (m, 1 H), 3.30–3.28 (s, 3 H), 2.15–1.98 (m, 3 H), 1.92–1.74 (m, 2 H), 1.66–1.54 (m, 2 H), 1.40–1.20 (m, 2 H), 0.94 (d, *J* = 7.2 Hz, 0.73 H), 0.92 (d, *J* = 6.0 Hz, 2.27 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 134.4, 134.4, 124.7, 124.7, 76.7, 65.7, 65.6, 57.2, 39.8, 39.6, 35.1, 35.0, 29.4, 27.1, 26.6, 26.3, 26.1, 24.7, 13.3, 13.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{20}O_2Na$: 207.1356; found: 207.1357.

***tert*-Butyl{(*R*)-2-[(*R*)-4-(methoxymethyl)cyclohex-3-en-1-yl]propoxy}diphenylsilane (11)**

To a stirred solution of alcohol **10** (472 mg, 2.56 mmol) in DCM (5.4 mL) at 0 °C were added imidazole (357 mg, 5.24 mmol) and TBDPSCl (800 mL, 3.08 mmol). After stirring for 1 h at the same temperature, the reaction mixture was allowed to warm to rt, and quenched with the addition of sat. aq NH_4Cl solution. The resulting mixture was diluted with H_2O and extracted three times with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 4:1) to give silyl ether **11**.

Yield: 1.08 g (2.55 mmol, 100%); colorless oil; $[\alpha]_D^{26.9}$ +21.2 (*c* 1.00, $CHCl_3$).

IR (neat): 2958, 2930, 2890, 2857, 2361 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.60 (m, 4 H), 7.42–7.33 (m, 6 H), 5.61 (br, 1 H), 3.77 (m, 2 H), 3.64–3.58 (m, 1 H), 3.56–3.49 (m, 1 H), 3.28 (s, 3 H), 2.09–1.91 (m, 3 H), 1.84–1.59 (m, 4 H), 1.38–1.18 (m, 1 H), 1.05 (s, 9 H), 0.91–0.89 (m, 3 H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 136.3, 136.3, 135.8, 135.8, 134.6, 134.6, 130.6, 128.6, 124.7, 124.6, 77.2, 67.7, 67.6, 57.3, 40.9, 40.6, 36.1, 36.1, 30.3, 30.2, 28.4, 27.5, 27.2, 27.0, 26.9, 25.6, 20.1, 19.8, 14.0, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{38}O_2SiNa$: 445.2533; found: 445.2529.

(1*S*,2*R*,5*S*)-5-{(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]propan-2-yl}-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentane-1-carbaldehyde (4)

Ozone was bubbled through a solution of silyl ether **11** (103 mg, 0.244 mmol) in DCM (15.6 mL) at –78 °C until a pale blue color persisted (for 8 min). After argon gas was bubbled through the solution for 10 min, Me_2S (0.175 mL, 2.37 mmol) was added to the solution at –78 °C. The resultant solution was allowed to warm to rt, and then stirred for 4 h. The solution was concentrated and purified by short pad column

chromatography with EtOAc. The filtrate was concentrated to give crude keto aldehyde **6** (111 mg), which was used for the next reaction without further purification.

To a stirred solution of aldehyde **6** (111 mg, 0.244 mmol) in MeCN (1.2 mL) was added D-proline (56.3 mg, 0.489 mmol) at rt. The reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was quenched with the addition of sat. aq NH_4Cl solution. The resulting mixture was diluted with H_2O and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 1:1) to give aldehyde **12**; yield: 78.0 mg (0.172 mmol, 70%, dr = 6:1). Aldehyde **12** immediately turns to keto aldehyde **6**. Therefore, it needed to be used quickly for the next reaction.

To a stirred solution of aldehyde **12** (860 mg, 1.89 mmol) in DMF (5.4 mL) were added DIPEA (2.27 mL, 13.2 mmol), TBAI (699 mg, 1.89 mmol), and MOMCl (0.718 mL, 9.14 mmol) at rt. The reaction mixture was stirred for 15 h at 40 °C. The reaction mixture was cooled to rt, and quenched with the addition of sat. aq $NaHCO_3$ solution. The resulting mixture was diluted with H_2O and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 1:1) to give methoxymethyl ether **4**.

Yield: 656 mg (1.32 mmol, 70%; as diastereomeric mixture). Desired **4** was separated by using HPLC (CHIRALART Cellulose SC; hexane/iPrOH, 110:1; 30 mL/min; λ = 254 nm; R_t = 8 min); colorless oil; $[\alpha]_D^{27.3}$ –13.4 (*c* 1.00, $CHCl_3$).

IR (neat): 2957, 2931, 2897, 2857, 1718 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 9.75 (d, *J* = 3.0 Hz, 1 H), 7.65 (m, 4 H), 7.42–7.32 (m, 6 H), 4.70 (d, *J* = 7.2 Hz, 1 H), 4.67 (d, *J* = 7.2 Hz, 1 H), 3.61–3.55 (m, 2 H), 3.46 (dd, *J* = 10.2, 6.6 Hz, 1 H), 3.40 (d, *J* = 9.6 Hz, 1 H), 3.36 (s, 3 H), 3.34 (s, 3 H), 2.74–2.67 (m, 1 H), 2.65 (dd, *J* = 3.6, 9.6 Hz, 1 H), 1.98–1.89 (m, 2 H), 1.78–1.71 (m, 1 H), 1.68–1.60 (m, 1 H), 1.43–1.34 (m, 1 H), 1.06 (s, 9 H), 0.90 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 204.1, 135.6, 133.7, 129.6, 127.6, 91.7, 90.1, 76.0, 67.2, 61.4, 59.2, 55.6, 40.5, 39.9, 32.5, 27.5, 26.8, 19.2, 15.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{42}O_5SiNa$: 521.2674; found: 521.2694.

2-[((1*R*,2*R*,5*S*)-5-{(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]propan-2-yl}-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentyl)-(hydroxy)methyl]-5-(propan-2-ylidene)cyclopentan-1-one (14)

To a stirred solution of diisopropylamine (84.3 μL, 0.600 mmol) in THF (5.4 mL) was added *n*-BuLi (2.66 M, 0.226 mL, 0.600 mmol) at 0 °C. After the reaction mixture was stirred for 1 h at the same temperature, enone **13** (74.6 mg, 0.601 mmol) was added and the mixture was stirred for 1 h. Then the reaction mixture was cooled to –78 °C, and to this was added a solution of methoxymethyl ether **4** (94.1 mg, 0.189 mmol) in THF (1.0 mL). After stirring for 35 min at –78 °C, the reaction mixture was quenched with the addition of phosphate buffer solution (pH 7.0). The resulting mixture was diluted with H_2O/EtOAc and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 3:1) to give ketone **14**.

Yield: 116 mg (0.186 mmol, 98%); colorless oil; $[\alpha]_D^{26.4}$ –17.8 (*c* 1.00, $CHCl_3$).

IR (neat): 3734, 2962, 2956, 2890, 2360, 2342, 2330, 1732, 1716, 1698, 1684 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 4 H), 7.42–7.30 (m, 6 H), 4.77 (d, *J* = 7.8 Hz, 1 H), 4.73 (d, *J* = 7.8 Hz, 0.97 H), 4.69 (d, *J* = 7.2 Hz, 0.03 H), 4.36 (s, 0.97 H), 4.21 (d, *J* = 4.8 Hz, 0.03 H), 4.14–4.10 (m, 1 H), 3.77–3.67 (m, 1 H), 3.47–3.43 (m, 1 H), 3.37–3.33 (m, 4.1 H), 3.27 (s, 0.1 H), 3.27–3.19 (m, 2.9 H), 3.13 (d, *J* = 10.2 Hz, 0.9 H), 2.64–2.50 (m, 2 H), 2.46–2.31 (m, 2 H), 2.23–2.17 (m, 3 H), 1.97–1.82 (m, 6 H), 1.76–1.68 (m, 2 H), 1.58–1.54 (m, 1 H), 1.50–1.41 (m, 1 H), 1.34–1.25 (m, 1 H), 1.14–1.02 (m, 12 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 209.9, 135.7, 134.0, 131.2, 129.6, 127.70, 127.68, 92.3, 87.6, 76.9, 70.6, 66.2, 60.5, 59.1, 55.6, 53.0, 48.5, 39.7, 39.4, 32.0, 27.0, 25.4, 24.6, 23.7, 20.8, 17.5, 14.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{37}H_{54}O_6SiNa$: 645.3582; found: 645.3573.

2-((1*S*,2*R*,5*S*)-5-{(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]propan-2-yl}-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentane-1-carbonyl)-5-(propan-2-ylidene)cyclopentan-1-one (15)

To a stirred solution of alcohol **14** (1.85 g, 2.97 mmol) in DMSO (29.7 mL) was added IBX (1.10 g, 3.93 mmol) at rt. The reaction mixture was stirred for 2 h at 50 °C. Then the reaction mixture was cooled to rt, and quenched with the addition of sat. aq $NaHCO_3$ solution. The resulting mixture was diluted with H_2O and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 4:1) to give diketone **15**.

Yield: 1.73 g (2.79 mmol, 94%; note: some of it was observed as enol); colorless oil; $[\alpha]_D^{27.8}$ +5.0 (*c* 0.38, $CHCl_3$).

IR (neat): 2958, 2932, 2890, 2858, 2361, 2342, 2330, 1748, 1732, 1716, 1698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 14.8 (br, 0.7 H), 7.68–7.60 (m, 4 H), 7.42–7.30 (m, 6 H), 4.66 (s, 1.4 H), 4.63–4.57 (m, 0.6 H), 3.61–3.58 (m, 1 H), 3.54–3.30 (m, 5 H), 3.30–3.25 (m, 4 H), 2.75–2.30 (m, 5 H), 2.22 (br, 2 H), 2.19 (br, 1 H), 2.00–1.60 (m, 6 H), 1.58 (br, 0.3 H), 1.30–1.12 (m, 3 H), 1.03 (s, 9 H), 0.90–0.79 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 207.2, 187.6, 187.5, 171.2, 150.1, 142.1, 135.7, 135.6, 134.1, 133.9, 133.9, 132.3, 129.5, 129.4, 127.6, 115.5, 92.5, 92.2, 88.7, 88.3, 77.7, 76.6, 67.6, 67.5, 65.0, 60.4, 59.3, 59.2, 55.5, 55.3, 54.0, 43.2, 41.9, 41.1, 37.5, 35.1, 34.0, 33.1, 28.1, 27.5, 26.9, 26.7, 26.3, 24.8, 24.1, 22.6, 21.9, 21.1, 20.7, 20.3, 19.3, 16.1, 15.8, 14.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{37}H_{52}O_6SiNa$: 643.3425; found: 643.3411.

(*R*)-2-((1*S*,2*R*,5*S*)-5-{(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]propan-2-yl}-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentane-1-carbonyl)-2-methyl-5-(propan-2-ylidene)cyclopentan-1-one (16)

To a stirred solution of diketone **15** (34.1 mg, 54.1 μmol) in DMF (2.97 mL) were added Cs_2CO_3 (276 mg, 0.846 mmol) and MeI (176 μL, 2.83 mmol) at –40 °C. The reaction mixture was stirred for 24 h at the same temperature. Then the reaction mixture was quenched with the addition of sat. aq $NaHCO_3$ solution, and warmed to rt. The resulting mixture was diluted with H_2O and extracted three times with a hexane/EtOAc mixture (4:1). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/Et_2O, 100:0 to 7:3) to give diketone **16**.

Yield: 29.4 mg (46.3 μmol, 90%, dr = 3.5:1); colorless oil; $[\alpha]_D^{27.9}$ +56.6 (*c* 0.51, $CHCl_3$).

IR (neat): 2957, 2932, 2885, 2858, 2361, 2342, 2330, 1715, 1685, 1627 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 4 H), 7.47–7.44 (m, 6 H), 4.64 (d, *J* = 7.2 Hz, 1 H), 4.23 (d, *J* = 7.2 Hz, 1 H), 3.56 (dd, *J* = 9.6, 3.6 1 H), 3.43–3.40 (m, 2 H), 3.33–3.28 (m, 5 H), 3.25 (s, 3 H), 2.65–2.57 (m, 2 H), 2.48–2.34 (m, 2 H), 2.16 (s, 3 H), 1.92–1.78 (m, 5 H), 1.76–1.68 (m, 1 H), 1.55–1.49 (m, 1 H), 1.44 (s, 3 H), 1.41–1.35 (m, 1 H), 1.31–1.00 (m, 10 H), 0.87 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 210.2, 204.7, 149.4, 135.7, 135.6, 134.0, 133.9, 130.8, 129.5, 127.6, 127.5, 92.8, 88.6, 77.0, 66.9, 66.6, 59.1, 55.6, 55.2, 45.2, 40.5, 32.6, 31.7, 28.1, 26.9, 26.3, 24.6, 21.1, 20.7, 19.2, 16.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{38}H_{54}O_6SiNa$: 657.3582; found: 657.3568.

(*S*)-2-((1*S*,2*R*,5*S*)-5-{(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]propan-2-yl}-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentane-1-carbonyl)-2-methyl-5-(propan-2-ylidene)cyclopentan-1-one (17)

Colorless oil; $[\alpha]_D^{28.0}$ –67.7 (*c* 1.02, $CHCl_3$).

IR (neat): 2958, 2931, 2889, 2857, 2361, 2342, 2329, 1715, 1695, 1634 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.62 (m, 4 H), 7.44–7.32 (m, 6 H), 4.64 (d, *J* = 7.2 Hz, 1 H), 4.22 (d, *J* = 7.2 Hz, 1 H), 3.61 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.42–3.33 (m, 3 H), 3.30–3.25 (m, 4 H), 3.18 (s, 3 H), 2.83–2.76 (m, 1 H), 2.56–2.42 (m, 3 H), 2.25–2.24 (m, 3 H), 2.05–2.00 (m, 1 H), 1.82 (s, 3 H), 1.80–1.70 (m, 2 H), 1.55–1.45 (m, 2 H), 1.21 (s, 3 H), 1.10–1.04 (m, 10 H), 0.97 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.4, 205.1, 146.9, 135.6, 133.9, 133.8, 132.2, 129.5, 127.6, 92.8, 89.1, 76.9, 67.0, 65.2, 59.0, 55.4, 53.7, 43.9, 40.5, 32.0, 30.3, 28.0, 26.9, 25.7, 24.4, 23.0, 20.5, 19.3, 16.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{38}H_{54}O_6SiNa$: 657.3582; found: 657.3566.

(2*R*,5*R*)-2-((1*S*,2*R*,5*S*)-5-{(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]propan-2-yl}-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentane-1-carbonyl)-5-isopropyl-2-methylcyclopentan-1-one (18)

To a stirred solution of enone **17** (28.0 mg, 44.1 μmol) in THF (0.500 mL) was added $Pd(OH)_2$ on carbon (20 wt%, 16.6 mg) at 0 °C. The flask was evacuated under vacuum, backfilled with H_2 (3×), and stirred under H_2 atmosphere for 41 h. The reaction mixture was filtered through a pad of Celite, washed with EtOAc, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 4:1) to give diketone **18**.

Yield: 25.0 mg (39.2 μmol, 89%, dr = 3:1); colorless oil; major diastereomer isolated by recrystallization from hexane; white solid; mp 69.5–72.0 °C; $[\alpha]_D^{19.1}$ –49.3 (*c* 0.900, $CHCl_3$).

IR (neat): 3071, 2958, 2931, 2873, 2822, 2363, 1731, 1704 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 4 H), 7.44–7.34 (m, 6 H), 4.70–4.65 (m, 1 H), 4.51–4.46 (m, 1 H), 3.62–3.49 (m, 2 H), 3.40–3.21 (m, 9 H), 2.74–2.26(m, 2.5 H), 2.15–1.67 (m, 6 H), 1.56–1.44 (m, 2.5 H), 1.25 (s, 2 H), 1.13–0.95 (m, 17 H), 0.89–0.81 (m, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 218.3, 217.6, 209.9, 209.7, 135.6, 133.9, 133.8, 133.8, 129.5, 127.6, 93.5, 93.1, 89.3, 89.0, 77.2, 76.8, 67.1, 66.8, 63.9, 62.7, 59.0, 56.3, 55.7, 55.5, 55.5, 54.0, 53.4, 44.6, 42.8, 41.1, 40.1, 32.8, 31.9, 31.6, 31.5, 28.3, 27.7, 27.6, 26.9, 26.8, 23.8, 23.3, 22.2, 21.6, 21.1, 20.2, 19.8, 19.3, 18.4, 16.9, 16.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{38}H_{56}O_6SiNa$: 659.3738; found: 659.3737.

(2*S*,5*S*)-2-((1*S*,2*R*,5*S*)-5-{(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]propan-2-yl}-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentane-1-carbonyl)-5-isopropyl-2-methylcyclopentan-1-one (19)

To a stirred solution of enone **16** (534 mg, 0.842 mmol) in THF (8.4 mL) was added palladium on carbon (10 wt%, 218 mg) at 0 °C. The flask was evacuated under vacuum, backfilled with H_2 (3×), and stirred under H_2 atmosphere for 24 h. The reaction mixture was filtered through a pad of Celite, washed with EtOAc, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 4:1) to give diketone **19**.

Yield: 461 mg (0.724 mmol, 86%); colorless oil; $[\alpha]_D^{28.3}$ +29.7 (*c* 1.00, $CHCl_3$).

IR (neat): 2959, 2932, 2877, 2361, 2342, 2330, 1734, 1696 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.65 (m, 4 H), 7.43–7.32 (m, 6 H), 4.63 (d, *J* = 7.2 Hz, 1 H), 4.57 (d, *J* = 7.2 Hz, 1 H), 3.59 (dd, *J* = 10.2, 3.6 Hz, 1 H), 3.46 (d, *J* = 6.0 Hz, 1 H), 3.43 (d, *J* = 10.2 Hz, 1 H), 3.37 (dd, *J* = 10.2, 7.2 Hz, 1 H), 3.27 (s, 6 H), 3.23 (d, *J* = 10.2 Hz, 1 H), 2.64 (ddd, *J* = 13.2, 6.6, 3.0 Hz, 1 H), 2.42–2.33 (m, 1 H), 2.12–2.04 (m, 2 H), 1.99–1.86 (m, 2 H), 1.85–1.73 (m, 3 H), 1.50–1.39 (m, 5 H), 1.16–1.05 (m, 1 H), 1.03 (s, 9 H), 0.96 (m, 6 H), 0.79 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 218.7, 211.1, 135.8, 135.7, 134.0, 129.6, 127.7, 92.9, 88.7, 76.8, 66.8, 64.9, 60.5, 59.1, 55.8, 55.4, 45.1, 40.5, 34.6, 32.9, 27.9, 27.7, 27.0, 22.9, 22.0, 21.3, 19.4, 19.1, 17.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{38}H_{56}O_6SiNa$: 659.3738; found: 659.3706.

((1*S*,2*R*,5*S*)-5-{(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]propan-2-yl}-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentyl)[(1*S*,2*R*,3*S*)-2-ethynyl-2-hydroxy-3-isopropyl-1-methylcyclopentyl]methanone (21)

Under an argon atmosphere, ethynylmagnesium chloride (0.5 M, 21.2 mL, 10.6 mmol) was concentrated and the THF was removed; it was then dissolved in toluene (5.0 mL) and added to a solution of diketone **19** (671 mg, 1.06 mmol) in toluene (4.7 mL) at 0 °C. After stirring for 1.5 h, the reaction mixture was quenched with the addition of sat. aq NH_4Cl solution, and warmed to rt. The resulting mixture was diluted with H_2O and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 1:0 to 4:1) to give propargyl alcohol **21**.

Yield: 699 mg (1.05 mmol, 100%); colorless oil; $[\alpha]_D^{28.2}$ –35.7 (*c* 0.42, $CHCl_3$).

IR (neat): 2955, 2933, 2892, 2873, 2362, 2342, 2328, 1691 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.60 (m, 4 H), 7.47–7.34 (m, 6 H), 4.61–4.57 (m, 2 H), 3.63 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.53 (s, 1 H), 3.47 (s, 1 H), 3.45 (d, *J* = 4.0 Hz, 1 H), 3.40 (dd, *J* = 10.0, 7.6 Hz, 1 H), 3.28 (s, 3 H), 3.22 (s, 3 H), 3.15 (d, *J* = 10.0 Hz, 1 H), 2.57–2.47 (m, 1 H), 2.42–2.40 (m, 1 H), 2.39–2.31 (m, 1 H), 1.99–1.67 (m, 7 H), 1.55–1.46 (m, 1 H), 1.43 (s, 1 H), 1.14 (s, 3 H), 1.08 (d, *J* = 9.6 Hz, 3 H), 1.06–1.00 (m, 12 H), 0.92–0.86 (d, *J* = 8.4 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 216.7, 135.7, 133.9, 129.7, 127.7, 92.4, 89.3, 85.1, 79.1, 76.6, 74.6, 66.4, 63.1, 59.0, 55.7, 54.6, 51.8, 45.6, 38.8, 33.3, 31.9, 28.7, 27.0, 26.7, 24.2, 22.2, 21.5, 19.7, 19.4, 17.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{40}H_{58}O_6SiNa$: 685.3895; found: 685.3881.

((1*S*,2*R*,5*S*)-5-{(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]propan-2-yl}-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentyl)[(1*S*,2*S*,3*S*)-2-hydroxy-3-isopropyl-1-methyl-2-vinylcyclopentyl]methanone (22)

To a stirred solution of alkyne **21** (30.5 mg, 46.0 μmol) and quinoline (5.4 μL, 45 μmol) in MeOH (0.9 mL) was added Lindlar's catalyst (5%, 96.5 mg) at 0 °C. The flask was evacuated under vacuum, backfilled with H_2 (3×), and stirred under H_2 atmosphere for 75 min. The reaction mixture was filtered through a pad of Celite, washed with EtOAc, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 9:1) to give allyl alcohol **22**.

Yield: 30.5 mg (45.9 μmol, 100%); colorless oil; $[\alpha]_D^{28.4}$ –16.7 (*c* 1.43, $CHCl_3$).

IR (neat): 3524, 3071, 2956, 2932, 2890, 2874, 2361, 2842, 2830, 1688 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.65 (m, 4 H), 7.45–7.32 (m, 6 H), 5.81 (dd, *J* = 17.2, 11.2 Hz, 1 H), 5.33 (dd, *J* = 17.2, 1.2 Hz, 1 H), 5.05 (dd, *J* = 11.2, 1.2 Hz, 1 H), 4.60–4.59 (m, 2 H), 3.60 (dd, *J* = 10.2, 4.8 Hz, 1 H), 3.42 (d, *J* = 10.2 Hz, 1 H), 3.38 (d, *J* = 10.2, 7.8 Hz, 1 H), 3.33 (s, 3 H) 3.27 (d, *J* = 5.4 Hz, 1 H), 3.23 (s, 3 H), 3.12 (d, *J* = 10.2 Hz, 1 H), 2.98 (s, 1 H), 2.47 (m, 1 H), 2.41–2.31 (m, 1 H), 1.99–1.83 (m, 2 H), 1.83–1.70 (m, 3 H), 1.57–1.48 (m, 2 H), 1.41–1.22 (m, 2 H), 1.18 (s, 3 H), 1.16–1.07 (m, 1 H), 1.05–0.99 (m, 12 H), 0.95–0.86 (m, 3 H), 0.82 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 218.6, 139.5, 135.70, 135.69, 133.94, 133.87, 129.7, 127.7, 112.4, 92.6, 89.5, 85.0, 76.5, 66.6, 61.8, 59.0, 55.7, 54.7, 50.8, 45.0, 39.7, 32.9, 30.7, 28.3, 27.1, 27.0, 24.1, 22.4, 22.0, 20.7, 19.4, 17.4.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{40}H_{60}O_6SiNa$: 687.4051; found: 687.4051.

[(1*S*,2*S*,3*S*)-2-Hydroxy-3-isopropyl-1-methyl-2-vinylcyclopentyl]{(1*S*,2*R*,5*S*)-5-[(*R*)-1-hydroxypropan-2-yl]-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentyl}methanone (23)

To a stirred solution of alcohol **22** (249 mg, 0.374 mmol) in THF (3.7 mL) were added acetic acid (0.214 mL, 3.74 mmol) and TBAF in THF (1 M, 3.74 mL, 3.74 mmol) at rt. The reaction mixture was stirred for 15 h at the same temperature. Then the reaction mixture was quenched with the addition of sat. aq NH_4Cl solution. The resulting mixture was diluted with H_2O and extracted three times with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 19:1 to 3:2) to give diol **23**.

Yield: 158 mg (0.370 mmol, 99%); colorless oil; $[\alpha]_D^{21.5}$ –5.6 (*c* 0.39, $CHCl_3$).

IR (neat): 3503, 2955, 2889, 1687 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.84 (dd, *J* = 17.2, 10.8 Hz, 1 H), 5.34 (dd, *J* = 17.2, 1.6 Hz, 1 H), 5.09 (dd, *J* = 10.8, 1.6 Hz, 1 H), 4.64 (d, *J* = 7.6 Hz, 1 H), 4.58 (d, *J* = 7.6 Hz, 1 H), 3.62–3.54 (m, 2 H), 3.48 (d, *J* = 6.8 Hz, 1 H), 3.44–3.37 (m, 5 H), 3.32–3.30 (s, 3 H), 2.59–2.43 (m, 2 H), 2.02–1.90 (m, 3 H), 1.86–1.71 (m, 2 H), 1.69–1.61 (m, 2 H), 1.44–1.20 (m, 6 H), 0.91 (m, 6 H), 0.82 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 217.8, 139.4, 112.4, 92.7, 89.2, 85.2, 77.6, 65.9, 62.0, 59.3, 55.8, 54.9, 51.1, 45.2, 38.1, 33.7, 30.7, 28.6, 26.3, 24.2, 22.4, 21.7, 20.7, 16.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{42}O_6Na$: 449.2874; found: 449.2864.

{(1*S*,2*R*,5*S*)-5-[(*S*)-But-3-en-2-yl]-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentyl}[(1*S*,2*S*,3*S*)-2-hydroxy-3-isopropyl-1-methyl-2-vinylcyclopentyl]methanone (3)

To a stirred solution of diol **23** (136 mg, 0.320 mmol) in DCM (29.7 mL) was added DMP (349 mg, 0.823 mmol) at rt. After the reaction mixture was stirred for 1 h at the same temperature, the reaction mixture was filtered through a pad of Celite, and concentrated. The residue was passed through a pad of silica gel (hexane/EtOAc = 4:1), concentrated to give aldehyde **24**, and immediately used for the next reaction.

To a stirred solution of aldehyde **24** (136 mg, 0.320 mmol) in THF (12.8 mL) was added Tebbe reagent in toluene (0.5 M, 1.6 mL, 0.799 mmol) at –78 °C. After the reaction mixture was stirred for 1 h at 0 °C, the reaction mixture was quenched with the addition of sat. aq NH_4Cl solution. The resulting mixture was diluted with H_2O and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 4:1) to give diene **3**.

Yield: 115 mg (0.272 mmol, 85%, 2 steps); colorless oil; $[\alpha]_D^{21.8}$ +2.1 (*c* 0.200, $CHCl_3$).

IR (neat): 2959, 2888, 1698, 1664, 1540 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.82 (dd, *J* = 17.2, 10.8 Hz, 1 H), 5.66 (ddd, *J* = 17.4, 10.2, 9.0 Hz, 1 H), 5.35 (dd, *J* = 17.2, 1.2 Hz, 1 H), 5.12–4.97 (m, 3 H), 4.61 (m, 2 H), 3.43 (d, *J* = 10.2 Hz, 1 H), 3.33 (s, 3 H), 3.29 (s, 3 H), 3.23 (d, *J* = 10.2 Hz, 1 H), 3.17 (d, *J* = 6.6 Hz, 1 H), 2.95 (s, 1 H), 2.56–2.44 (m, 2 H), 2.17–2.07 (m, 1 H), 1.98–1.91 (m, 1 H), 1.91–1.86 (m, 2 H), 1.80–1.70 (m, 2 H), 1.60–1.55 (m, 1 H), 1.41–1.33 (m, 1 H), 1.33–1.23 (m, 2 H), 1.20 (s, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.0 Hz, 3 H), 0.81 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 217.9, 140.5, 139.5, 115.5, 112.6, 92.7, 89.4, 85.0, 76.4, 61.7, 59.1, 55.7, 55.2, 50.9, 47.2, 40.3, 33.0, 30.7, 28.3, 25.1, 24.1, 22.4, 21.5, 20.7, 19.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{42}O_5Na$: 445.2925; found: 445.2924.

(1*S*,2*R*,5*S*)-2-((*S*)-{(1*R*,2*R*,5*S*)-5-[(*S*)-But-3-en-2-yl]-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentyl}(hydroxy)methyl)-5-isopropyl-2-methyl-1-vinylcyclopentan-1-ol (25)

To a stirred solution of ketone **3** (4.5 mg, 10.6 μmol) in THF (1.0 mL) was added DIBAL-H in hexane (1 M, 0.200 mL, 0.200 mmol) at 0 °C. The reaction mixture was stirred for 9 h at the same temperature. Then the reaction mixture was quenched with the addition of sat. aq NH_4Cl solution. The resulting mixture was diluted with H_2O and extracted three times with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 1:0 to 4:1) to give diol **25**.

Yield: 4.1 mg (9.7 μmol, 91%); colorless oil; recrystallization from $CHCl_3$ gave single crystals; white solid; mp 155.0–155.5 °C; $[\alpha]_D^{17.3}$ –10.1 (*c* 0.055, $CHCl_3$).

IR (neat): 3070, 2959, 2929, 2858, 2356 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.99 (dd, *J* = 17.2, 10.8 Hz, 1 H), 5.80–5.71 (ddd, *J* = 17.2, 10.2, 5.4 Hz, 1 H), 5.35 (dd, *J* = 17.2, 1.8 Hz, 1 H), 5.11 (dd, *J* = 10.8, 1.8 Hz, 1 H), 5.07–5.02 (m, 1 H), 4.98 (m, 1 H), 4.76 (d, *J* = 7.8 Hz, 1 H), 4.70 (d, *J* = 7.8 Hz, 1 H), 3.90 (d, *J* = 10.2 Hz, 1 H), 3.61 (d, *J* = 10.2 Hz, 1 H), 3.48 (d, *J* = 10.8 Hz, 1 H), 3.38 (m, 6 H), 3.20 (d, *J* = 9.6 Hz, 1 H), 2.83 (s, 1 H), 2.43–2.27 (m, 2 H), 2.12 (d, *J* = 9.0 Hz,

1 H), 1.98–1.88 (m, 1 H), 1.86–1.73 (m, 4 H), 1.73–1.59 (m, 2 H), 1.43–1.32 (m, 1 H), 1.32–1.23 (m, 1 H), 1.16 (s, 3 H), 1.12–1.04 (m, 1 H), 1.02 (d, *J*= 6.6 Hz, 3 H), 0.89 (d, *J* = 6.0 Hz, 3 H), 0.82 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 140.2, 138.5, 114.3, 112.6, 92.3, 89.3, 85.7, 80.0, 76.4, 59.0, 56.4, 54.3, 54.0, 49.8, 46.8, 36.4, 35.5, 34.8, 30.7, 25.0, 23.6, 22.6, 20.6, 18.8, 18.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{44}O_5Na$: 447.3081; found: 447.3080.

Compounds 28 and 29

To a stirred solution of diene **3** (115 mg, 0.273 mmol) in Et_2O (12.8 mL) were added Et_3N (0.450 mL, 3.25 mmol) and $SOCl_2$ (0.118 mL, 1.63 mmol) at 0 °C. After the reaction mixture had stirred for 2 h at the same temperature, it was quenched by the addition of sat. aq $NaHCO_3$ solution. The resulting mixture was diluted with H_2O and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude mixture was dissolved in DMF (4.50 mL) and sodium acetate (227 mg, 2.77 mmol) was added. After the reaction mixture had stirred at 80 °C for 15 h, the oil bath was removed and the mixture was quenched by the addition of sat. aq NH_4Cl solution. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 4:1) to give triene **28** (63%) and allyl acetate **29** (30%).

{(1*S*,2*R*,5*S*)-5-[(*S*)-But-3-en-2-yl]-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentyl}[(*S*)-3-isopropyl-1-methyl-2-vinylcyclopent-2-en-1-yl]methanone (28)

Yield: 69.8 mg (0.173 mmol, 63%); colorless oil; $[\alpha]_D^{22.5}$ –17.8 (*c* 0.10, $CHCl_3$).

IR (neat): 2961, 2929, 2355, 2342, 1700 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.33 (dd, *J* = 18.0, 12.0 Hz, 1 H), 5.72 (m, 1 H), 5.07–4.93 (m, 4 H), 4.65 (d, *J* = 7.2 Hz, 1 H), 4.57 (d, *J* = 7.2 Hz, 1 H), 3.41 (d, *J* = 10.2 Hz, 1 H), 3.38 (d, *J* = 6.0 Hz, 1 H), 3.33 (s, 3 H), 3.26 (m, 4 H), 2.96–2.90 (m, 1 H), 2.60–2.55 (m, 1 H), 2.38–2.27 (m, 3 H), 2.20–2.16 (m, 1 H), 2.02–1.96 (m, 1 H), 1.94–1.87 (m, 1 H), 1.82–1.77 (m, 1 H), 1.51–1.62 (1 H covered with H_2O), 1.37 (s, 3 H), 1.23 (m, 1 H), 1.01 (m, 6 H), 0.97 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 215.5, 150.0, 140.6, 136.9, 130.7, 115.2, 114.9, 92.6, 88.7, 76.6, 64.1, 59.0, 55.5, 54.3, 47.7, 40.2, 36.2, 32.3, 29.3, 27.3, 25.2, 23.1, 21.5, 21.1, 19.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{40}O_4Na$: 427.2819; found: 427.2805.

2-((2*S*)-2-{(1*S*,2*R*,5*S*)-5-[(*S*)-But-3-en-2-yl]-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentane-1-carbonyl}-5-isopropyl-2-methylcyclopentylidene)ethyl Acetate (29)

Yield: 37.8 mg (81.3 μmol, 30%); colorless oil; $[\alpha]_D^{28.5}$ +64.0 (*c* 0.30, $CHCl_3$).

IR (neat): 2960, 2880, 2360, 2342, 2329, 1742, 1698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.78–5.71 (m, 1 H), 5.54–5.51 (m, 0.7 H), 5.46–5.44 (m, 0.3 H), 5.10–5.03 (m, 2 H), 4.71–4.51 (m, 4 H), 3.42–3.50 (m, 2 H), 3.36 (s, 3 H), 3.25–3.30 (m, 3.7 H), 3.18–3.23 (d, *J* = 18.6 Hz, 0.3 H), 2.61–2.16 (m, 4 H), 2.05–1.96 (m, 4 H), 1.90–1.77 (m, 3 H), 1.73–1.59 (m, 2 H), 1.49–1.41 (m, 3.3 H), 1.37–1.32 (m, 0.7 H), 1.32–1.22 (m, 1.3 H), 1.01 (d, *J* = 6.6 Hz, 0.7 H), 0.95–0.92 (m, 3 H), 0.84–0.79 (m, 5 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.7, 171.0, 156.9, 155.5, 153.9, 140.3, 140.0, 120.4, 118.8, 115.7, 115.3, 92.7, 92.5, 88.7, 88.5, 76.1, 76.0, 63.1, 63.0, 60.2, 60.1, 59.0, 55.5, 53.8, 53.7, 53.3, 50.0, 48.7, 47.5, 39.6, 39.6, 37.4, 35.1, 32.7, 32.3, 29.4, 28.7, 26.0, 26.0, 25.8, 24.9, 24.8, 24.7, 21.8, 21.5, 21.0, 19.7, 19.3, 19.2, 18.5, 18.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{44}O_6Na$: 487.3030; found: 487.3023.

{(1*S*,2*R*,5*S*)-5-[(*S*)-But-3-en-2-yl]-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentyl}[(*S*)-3-isopropyl-1-methyl-2-vinylcyclopent-2-en-1-yl]methanone (28)

To a stirred solution of allyl acetate **29** (37.5 mg, 80.7 μmol) in MeOH (12.8 mL) was added K_2CO_3 (55.7 mg, 0.403 mmol) at rt. After the reaction mixture had stirred for 30 min at the same temperature, it was quenched by the addition of water. The resulting mixture was extracted three times with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude mixture was dissolved in DCM (4.0 mL) and 2,6-lutidine (93.7 μL, 0.807 mmol) and Ms_2O (42.2 mg, 0.242 mmol) were added. After the reaction mixture had stirred at rt for 24 h, the reaction mixture was quenched by the addition of sat. aq $NaHCO_3$ solution. The resulting mixture was diluted with H_2O and extracted three times with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 4:1) to give triene **28**.

Yield: 17.1 mg (42.0 μmol, 52%, 2 steps).

(1*R*,3a*S*,4*S*,9a*S*,10a*S*,*Z*)-7-Isopropyl-1-(methoxymethoxy)-1-(methoxymethyl)-4,9a-dimethyl-2,3,3a,4,8,9,9a,10a-octahydrodicyclopenta[*a*,*d*][8]annulen-10(1*H*)-one (30)

To a stirred solution of triene **28** (10.9 mg, 26.9 μmol) in toluene (2.7 mL) was added the Hoveyda–Grubbs II catalyst (5.1 mg, 8.14 μmol). After the reaction mixture had stirred for 16 h at 80 °C, the reaction mixture was concentrated and purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 17:3) to give diene **30**.

Yield: 8.6 mg (22.8 μmol, 85%); colorless oil; $[\alpha]_D^{28.4}$ –22.8 (*c* 0.87, $CHCl_3$).

IR (neat): 2959, 2932, 2892, 2874, 2362, 2342, 2330, 1701 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.13 (d, *J* = 10.8 Hz, 1 H), 5.49 (dd, *J* = 10.8, 9.6 Hz, 1 H), 4.79 (d, *J* = 7.8 Hz, 1 H), 4.76 (d, *J* = 7.8 Hz, 1 H), 3.41 (m, 4 H), 3.31–3.26 (m, 4 H), 3.00 (d, *J* = 12.6 Hz, 1 H), 2.82–2.74 (m, 1 H), 2.51 (m, 1 H), 2.47–2.39 (m, 1 H), 2.39–2.28 (m, 2 H), 2.27–2.18 (m, 1 H), 2.10–2.01 (m, 1 H), 1.80–1.68 (m, 2 H), 1.44–1.30 (m, 4 H), 1.04 (s, 1 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 210.5, 147.1, 136.5, 132.6, 127.3, 92.1, 87.7, 76.3, 67.9, 58.8, 56.4, 55.4, 48.0, 31.98, 31.95, 31.8, 28.7, 28.1, 22.8, 22.7, 20.8, 20.7, 18.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{36}O_4Na$: 399.2506; found: 399.2506

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Supporting Information

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References

(1) (a) Sassa, T. *Agric. Biol. Chem.* **1970**, *34*, 1588. (b) Sassa, T.; Togashi, M.; Kitaguchi, T. *Agric. Biol. Chem.* **1975**, *39*, 1735. (c) Sassa, T.; Ooi, T.; Nukina, M.; Ikeda, M.; Kato, N. *Biosci., Biotechnol., Biochem.* **1998**, *62*, 1815.

(2) Ottmann, C.; Weyand, M.; Sassa, T.; Inoue, T.; Kato, T.; Wittinghofer, A.; Oecking, C. *J. Mol. Biol.* **2009**, *386*, 913.

(3) Venkatesan, K.; Rual, J.-F.; Vazquez, A.; Stelzl, U.; Lemmens, I.; Hirozane-Kishikawa, T.; Hao, T.; Zenkner, M.; Xin, X.; Goh, K.-I.; Yildirim, M. A.; Simonis, N.; Heinzmann, K.; Gebreab, F.; Sahalie, J. M.; Cevik, S.; Simon, C.; de Smet, A.-S.; Dann, E.; Smolyar, A.; Vinayagam, A.; Yu, H.; Szeto, D.; Borick, H.; Dricot, A.; Klitgord, N.; Murray, R. R.; Lin, C.; Lalowski, M.; Timm, J.; Rau, K.; Boone, C.; Braun, P.; Cusick, M. E.; Roth, F. P.; Hill, D. E.; Tavernier, J.; Wanker, E. E.; Barabási, A.-L.; Vidal, M. *Nat. Methods* **2009**, *6*, 83.

(4) Moore, B. W. In *Physiological and Biochemical Aspects of Nervous Integration*; Carlson, F. D., Ed.; Prentice Hall: Englewood Cliffs, **1967**, 343.

(5) Schumacher, B.; Mondry, J.; Thiel, P.; Weyand, M.; Ottmann, C. *FEBS Lett.* **2010**, *584*, 1443.

(6) Rose, R.; Erdmann, S.; Bovens, S.; Wolf, A.; Rose, M.; Hennig, S.; Waldmann, H.; Ottmann, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 4129.

(7) (a) Asahi, K.; Honma, Y.; Hazeki, K.; Sassa, T.; Kubohara, Y.; Sakurai, A.; Takahashi, N. *Biochem. Biophys. Res. Commun.* **1997**, *238*, 758. (b) Yamamoto, Y.; Yamada, K.; Ishii, Y.; Asahi, K.; Tomoyasu, S.; Honma, Y. *Brit. J. Haematol.* **2001**, *112*, 697.

(8) Kuwata, K.; Hanaya, K.; Higashibayashi, S.; Sugai, T.; Shoji, M. *Tetrahedron* **2017**, *73*, 6039.

(9) (a) Kato, N.; Nakanishi, K.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1109. (b) Okamoto, H.; Arita, H.; Kato, N.; Takeshita, H. *Chem. Lett.* **1994**, *23*, 2335. (c) Kato, N.; Okamoto, H.; Takeshita, H. *Tetrahedron* **1996**, *52*, 3921.

(10) Uwamori, M.; Osada, R.; Sugiyama, R.; Nagatani, K.; Nakada, M. *J. Am. Chem. Soc.* **2020**, *142*, 5556.

(11) Geoghegan, K.; Evans, P. *Tetrahedron Lett.* **2014**, *55*, 1431.

(12) Abbott, J. R.; Allais, C.; Roush, W. R. *Org. Synth.* **2015**, *92*, 26.

(13) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1915.

(14) CCDC 2048792 (**18**) and 2048793 (**25**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures. A summary of the crystallographic analysis and the crystal structure is provided in the Supporting Information.

(15) The structure of dimer of **3** was inferred from crude MS and NMR spectroscopy.

(16) (a) Damien, B.; Ange, P.; Steven, P. N.; Joelle, P. *J. Organomet. Chem.* **2002**, *643–644*, 247. (b) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706.