In this paper, the synthesis of the carbon skeleton of cotylenin A aglycone has been suggested. There are approximately 130,000 different PPIs, but only 8% of them have known functions. 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.

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. 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. Seven isoforms have been identified, and interactions with hundreds of proteins have been found. For example, 14–3–3 proteins have been reported to stabilize p53, a tumor suppressor, and to enhance its antitumor activity. Cotylenin A has been reported to induce differentiation of acute myeloid leukemia cells (HL-60). 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, the synthesis of cotylenin A aglycone (i.e., cotylenol) by Kato and co-workers and a total synthesis of cotylenin A by Nakada and co-workers have been reported. Each of these approaches used a convergent synthetic strategy.
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).\textsuperscript{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\textsubscript{2}BH was then performed to obtain alcohol 10 in 74% yield and in a 3.1:1 diastereomeric ratio (Scheme 3).\textsuperscript{12} Alcohol 10 was quantitatively converted into silyl ether 11 by using TBDPSCI 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.\textsuperscript{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
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).

![Scheme 4](image)

**Scheme 4** Synthesis of diketone 15

![Scheme 5](image)

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

![Scheme 4](image)

**Table 1** Optimization of Methylation of Diketone 15

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>dr (16/17)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>acetone</td>
<td>K₂CO₃</td>
<td>rt</td>
<td>14</td>
<td>1:1</td>
<td>98% yield</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>NaH</td>
<td>rt</td>
<td>14</td>
<td>–</td>
<td>unknown compounds</td>
</tr>
<tr>
<td>3</td>
<td>acetone</td>
<td>Cs₂CO₃</td>
<td>rt</td>
<td>14</td>
<td>2:1</td>
<td>full conversion</td>
</tr>
<tr>
<td>4</td>
<td>DCM</td>
<td>Cs₂CO₃</td>
<td>rt</td>
<td>14</td>
<td>1:1</td>
<td>full conversion</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>Cs₂CO₃</td>
<td>rt</td>
<td>14</td>
<td>1:1:7</td>
<td>full conversion</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>Cs₂CO₃</td>
<td>rt</td>
<td>14</td>
<td>2:1</td>
<td>full conversion</td>
</tr>
<tr>
<td>7</td>
<td>MeOH</td>
<td>Cs₂CO₃</td>
<td>rt</td>
<td>14</td>
<td>2:1</td>
<td>full conversion</td>
</tr>
<tr>
<td>8</td>
<td>DMSO</td>
<td>Cs₂CO₃</td>
<td>rt</td>
<td>14</td>
<td>3:1</td>
<td>full conversion</td>
</tr>
<tr>
<td>9</td>
<td>DMF</td>
<td>Cs₂CO₃</td>
<td>rt</td>
<td>14</td>
<td>2.5:1</td>
<td>full conversion</td>
</tr>
<tr>
<td>10</td>
<td>DMF</td>
<td>Cs₂CO₃</td>
<td>–40</td>
<td>24</td>
<td>3.5:1</td>
<td>90% yield</td>
</tr>
<tr>
<td>11</td>
<td>DMF</td>
<td>Cs₂CO₃</td>
<td>–60</td>
<td>24</td>
<td>4:1</td>
<td>SM 15 remained (ca. 80%)</td>
</tr>
</tbody>
</table>

* Reaction conditions: 15 (8.05 μmol), MeI (50.0 equiv), base (15.0 equiv), solvent (0.400 mL).
* The dr was determined by ¹H NMR.
* Conversions and yields determined by ¹H NMR.
* SM = starting material.
* 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 complexity of the reaction was somewhat suppressed at −78 °C, the reaction became more complicated with an increase in temperature.

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, 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 23 was obtained, and even when the reaction was performed under highly diluted conditions, the desired tricycle 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
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. 1H and 13C NMR spectra were recorded on JEOL ECA-600 or Bruker AVIII 400 spectrometers, using CDCl3 or acetone-<sup>d6</sup> as solvent. Chemical shift values are reported in δ (ppm) relative to residual solvent signals (CDCl<sub>3</sub>): δ = 7.26, δH and 77.0, δC; acetone-d<sub>6</sub>: δ = 2.04, δH and 29.8, δC). 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.
Yield: 710 mg (3.37 mmol, 89%); colorless oil; the mixture was cooled to rt and quenched with the addition of sat. aq NaOH solution. The resulting mixture was diluted with DCM/H2O and extracted three times with DCM. After the combined organic layer was washed with brine, dried over Na2SO4, 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; [α]D20 +6.3 (c 1.00, CHCl3).

IR (neat): 3083, 2939, 2858, 1750, 1655, 1645 cm–1.


1H NMR (400 MHz, CDCl3): 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).

13C NMR (150 MHz, CDCl3): 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.


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

To a stirred solution of methyl carbonate 9 (580 mg, 3.81 mmol) in dimethyl carbonate (5.05 mL) was added r-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 NH4Cl solution. The resulting mixture was diluted with DCM/H2O and extracted three times with DCM. After the combined organic layer was washed with brine, dried over Na2SO4, 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; [α]D20 +6.3 (c 1.00, CHCl3).

IR (neat): 3083, 2939, 2858, 1750, 1655, 1645 cm–1.


1H NMR (400 MHz, CDCl3): 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).

13C NMR (150 MHz, CDCl3): δ = 155.1, 155.0, 148.7, 148.0, 145.6, 144.5, 113.3, 109.5, 109.2, 105.1, 78.4, 74.4, 54.8, 54.5, 43.7, 38.7, 38.4, 36.8, 33.8, 32.3, 32.2, 30.5, 20.8, 20.7.


tert-Butyl[(R)-2-[(R)-4-[(Methoxymethyl)cyclohex-3-en-1-yl]prop-2-yl]diphenylsiloxyl (11)

To a stirred solution of alcohol 10 (472 mg, 2.56 mmol) in DCM (5.4 mL) at 0 °C we 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 NH4Cl solution. The resulting mixture was diluted with H2O and extracted three times with DCM. The combined organic layer was washed with brine, dried over Na2SO4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/DCM, 100:0 to 4:1) to give silyl ether 11.

Yield: 1.08 g (2.55 mmol, 100%); colorless oil; [α]D20 +21.2 (c 1.00, CHCl3).

IR (neat): 2958, 2930, 2890, 2857, 2361 cm–1.

1H NMR (400 MHz, CDCl3): 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).

13C NMR (150 MHz, CDCl3): δ = 136.3, 136.3, 135.8, 135.8, 134.6, 134.6, 130.6, 128.6, 124.7, 124.7, 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, 26.3, 26.1, 24.7, 13.3, 13.0.


(15,2S,5S)-5-[(R)-1-[(tert-Butyldiphenylsiloxy)oxy]propan-2-yl]-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, Me2S (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 NH4Cl solution. The resulting mixture was diluted with H2O and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na2SO4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 100:0 to 1:1) to give diketone 12; yield: 268 mg (0.563 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 Cs2CO3 (276 mg, 0.846 mmol) and MeI (176 mL) at –40 °C. The reaction mixture was stirred for 2 h at 0 °C. Then the reaction mixture was cooled to rt. The resulting mixture was diluted with 1:1 hexane/EtOAc and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na2SO4, 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; Rf = 8 min); colorless oil; [α]D20 +13.4 (c 1.00, CHCl3).

IR (neat): 2957, 2931, 2897, 2857, 1718 cm–1.

1H NMR (400 MHz, CDCl3); δ = 6.78–7.62 (m, 4 H), 7.42–7.30 (m, 6 H), 4.77 (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).

13C NMR (150 MHz, CDCl3); δ = 204.1, 135.6, 133.7, 129.6, 127.6, 91.7, 79.6, 79.4, 79.2, 64.3, 64.1, 59.2, 55.6, 45.0, 39.9, 32.5, 27.5, 19.8, 15.7.


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

To a stirred solution of diisopropylamine (94.1 mg, 0.189 mmol) in THF (1.0 mL) was added 2-((1R,2R,5S)-5-[(R,5)-1-((tert-Butyldiphenylsilyl)oxy)propan-2-yl]-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentyl)-5-(propan-2-ylidene)cyclopentan-1-one (14).

Yield: 116 mg (0.186 mmol, 98%); colorless oil; [α]D20 +24.4 –17.8 (c 1.00, CHCl3).

IR (neat): 3734, 2962, 2956, 2890, 2360, 2342, 2330, 1732, 1716, 1698, 1684 cm–1.
IR (neat): 2957, 2932, 2885, 2858, 2361, 2342, 2330, 1715, 1685, 1627 cm⁻¹.

1H NMR (600 MHz, CDCl₃): 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 Hz, 1 H), 3.43–3.40 (m, 2 H), 3.32–3.28 (m, 3 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).

13C NMR (150 MHz, CDCl₃): δ = 210.2, 204.7, 149.4, 135.7, 135.6, 140.3, 139.9, 130.8, 129.5, 127.6, 127.9, 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.


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 H₂ (3×), and stirred under H₂ 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; [α]D²⁸ +29.7 (c 1.00, CHCl₃).

IR (neat): 2959, 2932, 2877, 2361, 2342, 2330, 1734, 1696 cm⁻¹.

1H NMR (600 MHz, CDCl₃): 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 (dd, J = 10.2, 7.2 Hz, 1 H), 3.27 (d, J = 10.2 Hz, 1 H), 3.48 (dd, 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), 0.93 (s, 9 H), 0.79 (d, J = 6.6 Hz, 3 H).

13C NMR (150 MHz, CDCl₃): δ = 218.1, 217.1, 135.8, 135.7, 134.0, 129.6, 127.9, 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, 19.3, 19.1, 17.2.


((15R,5S)-5-[(1R)-1-[[tet-Butylidiphenylsiloxy]propan-2-yl]-2-(methoxymethoxy)-2-(methoxymethyl)cyclopentyl]-15,2R,3S)-2-ethyln-2-hydroxy-3-isopropyl-1-methylcyclopentyl)methanol (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 NH₄Cl solution, and washed with EtOAc. The combined organic layer was washed with brine, dried over Na₂SO₄, 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; [α]D²⁸ –35.7 (c 0.42, CHCl₃).

IR (neat): 2955, 2933, 2892, 2873, 2362, 2342, 2328, 1691 cm⁻¹.

1H NMR (400 MHz, CDCl₃): 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 (dd, 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).

13C NMR (150 MHz, CDCl₃): δ = 216.7, 135.7, 133.9, 129.7, 127.7, 92.4, 89.3, 85.1, 79.1, 76.6, 74.4, 66.3, 63.1, 59.0, 55.7, 54.8, 51.8, 45.6, 38.8, 33.3, 31.9, 28.7, 27.0, 26.7, 24.2, 22.1, 21.5, 19.7, 19.4, 17.3.


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To a stirred solution of alcohol \( (136 \text{ mg, } 0.320 \text{ mmol}) \) in THF \((12.8 \text{ mL}) \) was added Tebbe reagent in toluene \((0.5 \text{ M, } 1.6 \text{ mL, } 0.799 \text{ mmol}) \) at \(–78 \degree \text{C} \). After the reaction mixture was stirred for 1 h at 0 \degree \text{C}, the reaction mixture was quenched with the addition of sat. aq \( \text{NH}_4\text{Cl} \) solution. The resulting mixture was diluted with \( \text{H}_2\text{O} \) and extracted three times with \( \text{EtOAc} \). The combined organic layer was washed with brine, dried over \( \text{Na}_2\text{SO}_4 \), filtered, and concentrated. The residue was purified by flash column chromatography \((\text{silica gel, hexane/\text{EtOAc}, 100:0 to 4:1}) \) to give diene \(3 \).

**Yield:** 115 mg \((0.272 \text{ mmol, 85%}) \) steps; colorless oil; \([\alpha]_D^{20} = 2.1 \text{ (c 0.200, CHCl}_3)\).

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

13C NMR (151 MHz, CDCl3): 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.


Compounds 28 and 29

To a stirred solution of diene 3 (115 mg, 0.273 mmol) in Et2O (12.8 mL) were added Et3N (0.450 mL, 3.25 mmol) and SOCl2 (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 NaHCO3 solution. The resulting mixture was diluted with H2O and extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na2SO4, filtered, and concentrated. The crude mixture was dissolved in DCM (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 NH4Cl solution. The combined organic layer was washed with brine, dried over Na2SO4, 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%).

Yield: 6.98 mg (0.173 mmol, 63%); colorless oil; [α]D<sub>28</sub> = 225° +17.8 (c 0.10, CHCl3).

IR (neat): 2961, 2929, 2855, 2342, 1700 cm⁻¹.

1H NMR (600 MHz, CDCl3): 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 H2O), 1.37 (s, 3 H), 1.23 (m, 1 H), 1.01 (m, 6 H), 0.97 (d, J = 6.6 Hz, 3 H).

13C NMR (150 MHz, CDCl3): δ = 215.5, 150.0, 140.6, 135.9, 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.


(1S,2S,5S)-5-(5S)-But-3-en-2-yl]-2-(methoxymethyl)-2-methoxymethylcyclopentyl]-(S)-3-isopropyl-1-methyl-2-vinylcyclopentane-2-en-1-yl]methanone (28)

To a stirred solution of allyl acetate 29 (37.5 mg, 0.87 µmol) in MeOH (12.8 mL) was added K2CO3 (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 Na2SO4, filtered, and concentrated. The crude mixture was dissolved in DCM (4.0 mL) and 2,6-lutidine (93.7 µL, 0.807 mmol) and MsCl (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 NaHCO3 solution. The resulting mixture was diluted with H2O and extracted three times with DCM. The combined organic layer was washed with brine, dried over Na2SO4, 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%).

Yield: 8.6 mg (22.8 µmol, 85%); colorless oil; [α]D<sub>28</sub> = 22.8° (c 0.87, CHCl3).

IR (neat): 2959, 2932, 2892, 2874, 2362, 2342, 2330, 1701 cm⁻¹.

1H NMR (600 MHz, CDCl3): δ = 6.63 (dd, J = 10.8, 9.6 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).

13C NMR (150 MHz, CDCl3): δ = 201.5, 147.1, 136.5, 132.6, 127.3, 92.1, 87.7, 76.3, 67.9, 58.8, 56.4, 55.4, 48.0, 31.8, 31.5, 28.1, 28.7, 28.1, 22.8, 22.7, 20.8, 20.7, 18.0.


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Supporting Information

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References


(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.