Supporting Information

Formal Total Synthesis of (±)-Hirsutic Acid C Using Tandem Rh(I)-Catalyzed [(5+2)+1] Cycloaddition/Aldol Reaction

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1. General

Air and moisture sensitive reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of dry argon. Similarly sensitive liquids and solutions were transferred via syringe. Reactions were stirred using Teflon-coated magnetic stir bars. Elevated temperatures were maintained using Thermostat-controlled silicone oil baths. Organic solutions were concentrated using a Büchi rotary evaporator with a desktop vacuum pump. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium and benzophenone prior to use. Dichloromethane was distilled from CaH2 prior to use. Dichloroethane was distilled from P2O5 prior to use. Synthetic reagents were purchased from Acros, Aldrich, and Alfa Aesar and used without further purification, unless otherwise indicated. Analytical TLC was performed with 0.25 mm silica gel G plates with a 254 nm fluorescent indicator. The TLC plates were visualized by ultraviolet light and treatment with phosphomolybdic acid stain followed by gentle heating. Purification of products was accomplished by flash chromatography on silica gel and the purified compounds showed a single spot by analytical TLC.

NMR spectra were measured on Varian Mercury Plus 300 (1H at 300 MHz, 13C at 75.5 MHz), Bruker ARX 400 (1H at 400 MHz, 13C at 100 MHz), and Bruker AVANCE 600 (1H at 600 MHz, 13C at 150 MHz) nuclear magnetic resonance spectrometers. Data for 1H-NMR spectra are reported as follows: chemical shift (ppm, referenced to TMS; s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dm = doublet of multiplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet), coupling constant (Hz), and integration. Data for 13C-NMR are reported in terms of chemical shift (ppm) relative to residual solvent peak (CDCl3: 77.0 ppm). 1D nOe experiments were conducted on a Bruker AVANCE 600 nuclear magnetic resonance spectrometer. Infrared spectra were recorded on Mettler-Toledo ReactIR iC10 system with a SiComp probe and are reported in wavenumbers (cm⁻¹). High-resolution mass spectra (HRMS) were recorded on a Bruker Apex IV FTMS mass spectrometer (ESI).

Abbreviations:

DIBAL-H = diisobutylaluminum hydride
EA = ethyl acetate
PE = petroleum ether
TBS = tert-butyldimethylsilyl
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TLC = thin layer chromatography
2. Experimental Procedures and Characterization Data

Experimental procedures for the formal total synthesis of (±)-hirsutic acid C

Methyl 2-formyl-2-methylpent-4-enoate (8)

A solution of diester 7 (12.55 g, 67.4 mmol) in anhydrous CH₂Cl₂ (140 mL) was cooled to −78 ºC under argon. To the stirred solution DIBAL-H (140 mL, 1 M in hexane, 140 mmol) was slowly added, maintaining the inner temperature below −70 ºC. Then the reaction mixture was stirred for 30 min. Acetone (10 mL) was added dropwise to quench the reaction, keeping the inner temperature below −60 ºC. Then aqueous HCl (120 mL, 2 M) was added and the reaction mixture was allowed to warm to room temperature. Concentrated aqueous HCl was added until a clear solution formed. The organic phase was separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic phase was washed with saturated aqueous potassium sodium tartrate, dried over MgSO₄, and concentrated. The crude product was distilled under reduced pressure to afford aldehyde 8 (b.p. 76-84 ºC/10 mmHg, 9.28 g, 88%).

Compound 8: Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.31 (s, 3H), 2.50 (dd, J = 7.4 and 13.8 Hz, 1H), 2.63 (dd, J = 7.4 and 13.8 Hz, 1H), 3.76 (s, 3H), 5.11-5.15 (m, 2H), 5.63-5.73 (m, 1H), 9.70 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 16.7, 38.5, 52.4, 57.5, 119.5, 131.7, 172.1, 199.0. IR (neat): ν 2961, 1751, 1728, 1441, 1300, 1240 cm⁻¹. HRMS (ESI) calcd for C₁₈H₁₂NaO₃ (M+Na): 179.0679. Found: 179.0674.

Methyl 2-methyl-2-(2-oxoethyl)pent-4-enoate (9)

To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (18.57 g, 54.2 mmol) in 80 mL of anhydrous THF was slowly added a solution of KOBu⁺ (5.83 g, 52.0 mmol) in THF (50 mL) at −40 ºC. The resulting cherry-red solution was stirred at −40 ºC for 20 min. A solution of aldehyde 8 (3.73 g, 23.9 mmol) in THF (20 mL) was added dropwise, and the resulting mixture was allowed to warm to room temperature during 1 h. The reaction was quenched by addition of saturated aqueous NH₄Cl (1 mL) and the reaction mixture was stirred for 5 min. The reaction mixture was filtrated, and the filtrate was evaporated under reduced pressure. Pentane was added, the resulting mixture was stirred for 1 h, and then filtrated. The filtrate was concentrated and the crude product was dissolved in CHCl₃ (50 mL). A solution of TFA-H₂O (20 mL, 1:1) was added dropwise and the resulting reaction mixture was stirred for 40 min. The aqueous phase was separated, and the organic phase was washed successively with water and saturated aqueous NaHCO₃, dried over MgSO₄, and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 30:1 to 10:1) to afford aldehyde 9 (2.03 g, 50%).

Compound 9: Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.29 (s, 3H), 2.32-2.43 (m, 2H), 2.52 (dd, J = 1.9
and 17.4 Hz, 1H), 2.81 (d, J = 17.4 Hz, 1H), 3.70 (s, 3H), 5.06-5.13 (m, 2H), 5.70 (ddt, J = 10.4, 17.2, and 7.4 Hz, 1H), 9.74 (t, J = 1.6 Hz, 1H). 13C NMR (75.5 MHz, CDCl3): δ 22.5, 43.3, 43.5, 50.7, 52.1, 119.2, 132.6, 176.1, 200.4. IR (neat): ν 2987, 1747, 1728, 1468, 1222 cm⁻¹. HRMS (ESI) calcd for C₉H₁₄NaO₃ (M+Na): 193.0835. Found: 193.0830.

**Methyl (Z)-2-allyl-2,5-dimethyl-6-oxohept-4-enoate (10)**

To a solution of bis(2,2,2-trifluoroethyl) 3-oxobutan-2-ylphosphonate (2.46 g, 77% purity, 5.99 mmol) and 18-crown-6 (1.66 g, 6.28 mmol) in anhydrous THF (50 mL) at −78 °C was added a solution of KOBu’ (679 mg, 6.05 mmol) in THF (20 mL) dropwise under argon. After stirring for 20 min at −78 °C, a solution of aldehyde 9 (852 mg, 5.01 mmol) in THF (20 mL) was added dropwise at −78 °C and the resulting mixture was stirred for another 2 h at −78 °C. The reaction was gradually warmed to room temperature. Saturated NH₄Cl was added and the reaction mixture was extracted with ether twice. The combined organic extract was washed with brine, dried over Na₂SO₄, and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 30:1 to 10:1) to afford (Z)-enone 10 (751 mg, 71%) and a mixture of (Z)- and (E)-enone 10 (165 mg, 16%, Z:E = 1:1.4, determined by 1H NMR integration of the enone olefinic proton). The overall yield of (Z) - and (E)-enone 10 was 87%, Z:E = 8.6:1.

**Compound 10:** Colorless oil. 1H NMR (400 MHz, C₆D₆): δ 1.15 (s, 3H), 1.55-1.56 (m, 3H), 1.83 (s, 3H), 2.13 (dd, J = 7.6 and 13.6 Hz, 1H), 2.39 (dd, J = 7.0 and 13.6 Hz, 1H), 2.67 (ddm, J = 7.7 and 15.4 Hz, 1H), 2.79 (dd, J = 7.0 and 15.4 Hz, 1H), 3.32 (s, 3H), 4.94-4.98 (m, 2H), 5.54 (tm, J = 7.5 Hz, 1H), 5.66-5.77 (m, 1H). 13C NMR (75.5 MHz, C₆D₆): δ 21.0, 21.6, 29.5, 38.4, 43.6, 46.4, 51.3, 118.2, 133.0, 134.2, 137.9, 176.1, 201.0. IR (neat): ν 2987, 1732, 1695, 1464, 1382 cm⁻¹. HRMS (ESI) calcd for C₁₃H₂₀NaO₃ (M+Na): 247.1305. Found: 247.1299.

**Methyl (Z)-2-allyl-6-(tert-butyldimethylsiloxy)-2,5-dimethylhepta-4,6-dienoate (11)**

Triethyl amine (1.29 g, 12.8 mmol) and TBSOTf (2.26 g, 8.55 mmol) was sequentially added to a solution of (Z)-enone 10 (721 mg, 3.43 mmol) in anhydrous ether (30 mL) at 0 °C. After stirred for 1 h at 0 °C, brine was added and the resulting mixture was extracted by ether. The combined extract was dried over Na₂SO₄ and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 50:1 to 20:1, containing 1% Et₃N) to afford silyl enol ether 11 (1.005 g, 86%).

**Compound 11:** Colorless oil. 1H NMR (400 MHz, C₆D₆): δ 0.14 (s, 6H), 0.94 (s, 9H), 1.19 (s, 3H), 1.82-1.83 (m, 3H), 2.17 (dd, J = 8.0 and 13.7 Hz, 1H), 2.45 (dd, J = 6.9 and 13.7 Hz, 1H), 2.61 (ddm, J = 7.8 and 15.0 Hz, 1H), 2.71 (ddm, J = 6.5 and 15.0 Hz, 1H), 3.36 (s, 3H), 4.25 (s, 1H), 4.39 (s, 1H), 4.97-5.02 (m, 2H), 5.33 (tm, J =
7.3 Hz, 1H), 5.71-5.81 (m, 1H). 13C NMR (100 MHz, C6D6): δ −4.5, 18.3, 21.7, 22.8, 25.9, 38.7, 43.6, 46.4, 51.2, 94.1, 118.0, 124.8, 134.6, 136.4, 156.8, 176.3. IR (neat): ν 2961, 2868, 1736, 1624, 1464, 1333, 1214 cm⁻¹. HRMS (ESI) calcd for C19H34NaO3Si (M+Na): 361.2169. Found: 361.2168.

**Methyl (Z)-2-allyl-5-(1-(tert-butyldimethylsilyloxy)cyclopropyl)-2-methylhex-4-enoate (12)**

![Chemical structure](image)

Diethyl zinc solution (2.9 mL, 1 M in hexane, 2.90 mmol) and CH3I2 (845 mg, 3.16 mmol) were sequentially added to a solution of silyl enol ether 11 (880 mg, 2.60 mmol) in anhydrous CH2Cl2 (26 mL) at 25 °C. The reaction mixture was stirred for 1.5 h and was quenched with saturated aqueous NH4Cl. The resulting mixture was extracted with CH2Cl2 and the combined organic extract was treated with acetic acid (25 mL) under room temperature for 20 min to hydrolyze the unreacted silyl enol ether. The solution was successively washed with water and saturated aqueous NaHCO3, dried over Na2SO4, and concentrated. The residue was purified by flash column chromatography on silica gel (eluted with PE/EA 100:1 to 30:1) to afford β-ene-VCP 12 (688 mg, contains ca. 28% biscyclopropane, 54%).

**Compound 12:** Colorless oil. 1H NMR (400 MHz, CDCl3): δ 0.05 (s, 6H), 0.56-0.65 (m, 2H), 0.82 (s, 9H), 0.83-0.89 (m, 2H), 1.13 (s, 3H), 1.74-1.75 (m, 3H), 2.19 (dd, J = 7.8 and 13.6 Hz, 1H), 2.44 (dd, J = 7.2 and 13.6 Hz, 1H), 2.56-2.59 (m, 2H), 3.66 (s, 3H), 5.03-5.06 (m, 2H), 5.14 (tm, J = 7.1 Hz, 1H), 5.66-5.79 (m, 1H). 13C NMR (100 MHz, CDCl3): δ −3.8, 14.2, 14.3, 17.7, 21.3, 22.4, 25.6, 37.7, 43.6, 46.2, 51.5, 55.8, 117.9, 125.5, 134.2, 137.8, 177.2. IR (neat): ν 2961, 2861, 1739, 1464, 1233 cm⁻¹. HRMS (ESI) calcd for C20H36NaO3Si (M+Na): 375.2326. Found: 375.2323.

**1,4-Dimethyl-8-hydroxy-4-methoxycarbonyl[tricyclo[6.3.0.0²,6]undecan-11-one (13a and 13b)]**

![Chemical structure](image)

A solution of β-ene-VCP 12 (534 mg, 72% purity, 1.08 mmol) and [Rh(CO)2Cl]2 (41.5 mg, 107 μmol) in anhydrous dioxane (55 mL) was degassed by bubbling CO/N2 (1:4 V/V) for 5 min. The solution was heated to 80 °C in an oil bath with stirring under a positive pressure of the mixture gas for 22 h. The solution was cooled to room temperature, and was treated with HCl (5 mL, 1 M in MeOH-H2O 5:1) under room temperature for 8 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (eluted...
with PE/EA 10:1 to 2:1) to afford tricyclic hydroxyl ketones 13a and 13b (150 mg, 52%, 13a:13b = 1:1.5).\(^1\)

Compounds 13a+13b: Pale yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.97 (s, 3H, 13a), 0.99 (s, 3H, 13b), 1.20 (s, 3H, 13b), 1.31 (s, 3H, 13a), 1.52-1.76 (m, 3H, 13a and 13b), 1.87-1.96 (m, 3H, 13a and 13b), 2.09-2.33 (m, 3H, 13a and 13b), 2.45-2.59 (m, 3H, 13a and 13b), 2.68-2.75 (m, 1H, 13a), 2.80-2.88 (m, 1H, 13b), 3.66 (s, 3H, 13a), 3.68 (s, 3H, 13b). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 12.4, 12.7, 22.5, 24.3, 32.1, 32.1, 35.06, 35.11, 38.0, 39.2, 39.6, 40.3, 44.3, 44.4, 44.5, 45.8, 48.1, 48.5, 50.8, 51.8, 51.8, 52.2, 60.0, 60.3, 88.7, 89.1, 178.0, 178.2, 221.1, 221.4. IR (neat): \(v\) 3475, 2957, 1732, 1464, 1255, 1211 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{15}\)H\(_{22}\)NaO\(_4\) (M+Na): 289.1410. Found: 289.1411.

1,4-Dimethyl-8-hydroxy-4-methoxycarbonyl-11-methylenetricyclo[6.3.0.0\(2,6\)]undecane (16a and 16b) and 5,8-dimethyl-4-methylene-13-oxa-12-oxotetracyclo[6.3.2.0\(1,5.0^6,10\)]tridecane (17)

To a solution of KOBu\(_t\) (222 mg, 1.98 mmol) in \(\text{tBuOH} (3 \text{ mL})\) and benzene (12 mL) was added at room temperature under argon methyltriphenylphosphonium bromide (709 mg, 1.98 mmol) in one portion, and the resulting yellow solution was stirred at room temperature for 30 min. A solution of tricyclic hydroxyketone 13 (13a+13b mixture, 13a:13b = 1:1.5, 176 mg, 0.66 mmol) in dry benzene (3 mL) was added and the reaction mixture was brought to reflux for 1 h in a 100 °C oil bath. The resulting mixture was cooled, concentrated, and filtered through a thin pad of silica gel (eluted with PE/EA 5:1). The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel (eluted with PE/EA 30:1 to 5:1) to afford tetracyclic compound 17 (14.0 mg, 9%, 15% based on 13b), tricyclic enol 16a (52.5 mg, 30%, 75% based on 13a), and then tricyclic enol 16b (13.1 mg, 7%, 12% based on 13b).

Compound 16a: Colorless oil. \(R_f = 0.40\) (PE/EA = 5:1). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 0.98 (s, 3H), 1.32 (s, 3H), 1.29-1.32 (m, 1H), 1.40 (s, 1H), 1.54 (dd, \(J = 4.9\) and 14.0 Hz, 1H), 1.61-1.66 (m, 2H), 1.88 (ddd, \(J = 4.3, 8.8,\) and 12.7 Hz, 1H), 1.97 (dd, \(J = 9.2\) and 14.0 Hz, 1H), 2.42-2.56 (m, 4H), 3.66 (s, 3H), 4.81-4.82 (m, 2H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 17.9, 25.0, 28.7, 35.9, 40.0, 40.1, 45.0, 45.5, 51.8, 52.3, 53.4, 55.7, 92.0, 105.8, 160.0, 178.6. IR (neat): \(v\) 3527, 2957, 1721, 1468, 1315, 1199 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{16}\)H\(_{25}\)O\(_3\) (M+H): 265.1798. Found: 265.1799.

Compound 16b: Colorless oil. \(R_f = 0.27\) (PE/EA = 5:1). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 1.00 (s, 3H), 1.21 (s, 3H), 1.29-1.32 (m, 1H), 1.40 (s, 1H), 1.54 (dd, \(J = 4.9\) and 14.0 Hz, 1H), 1.61-1.66 (m, 2H), 1.88 (ddd, \(J = 4.3, 8.8,\) and 12.7 Hz, 1H), 1.97 (dd, \(J = 9.2\) and 14.0 Hz, 1H), 2.42-2.56 (m, 4H), 3.66 (s, 3H), 4.81-4.82 (m, 2H).

(1) The assignment of the relative configuration of cycloadducts 13a and 13b was achieved by oxidation of the stereochemically well-defined compound 16a and comparison of the product’s \(^1\)H NMR spectrum with that of 13a and 13b mixture. Oxidation of compound 16a by K\(_2\)OsO\(_4\)-NaIO\(_4\) gave 13a, indicating that it has identical relative configuration to the natural product.

Procedure for K\(_2\)OsO\(_4\)-NaIO\(_4\) oxidation: To a stirred solution of compound 16a (4.6 mg, 0.017 mmol) in THF-H\(_2\)O (1 mL, 4:1) was added K\(_2\)OsO\(_4\)-2H\(_2\)O (1.0 mg, 0.0027 mmol) and NaIO\(_4\) (10.1 mg, 0.047 mmol). The resulting mixture was stirred at room temperature for 9 h. Water was added to quench the reaction, and the reaction mixture was extracted with ether. The combined organic phase was dried over Na\(_2\)SO\(_4\) and concentrated. The residue was purified by column chromatography to give crude ketone 13a (4.5 mg), which gave identical \(^1\)H NMR spectra to the minor diastereomer of the 13a and 13b mixture.
3H), 1.49 (s, 1H), 1.60-1.70 (m, 3H), 1.83-1.93 (m, 3H), 2.02 (dd, J = 9.2 and 14.3 Hz, 1H), 2.19 (t, J = 12.1 Hz, 1H), 2.31-2.37 (m, 1H), 2.47-2.54 (m, 2H), 2.63 (dt, J = 11.6 and 8.8 Hz, 1H), 3.68 (s, 3H), 4.82-4.84 (m, 2H).

$^{13}$C NMR (150 MHz, CDCl$_3$): \(\delta\) 18.2, 23.3, 29.0, 36.2, 38.7, 39.5, 44.5, 45.1, 50.8, 51.8, 53.1, 55.8, 91.8, 105.8, 160.7, 178.6. IR (neat): \(\nu\) 3509, 2957, 1724, 1460, 1255 cm$^{-1}$. HRMS (ESI) calcd for C$_{16}$H$_{24}$NaO$_3$ (M+Na): 287.1618. Found: 287.1619.

Compound 17: Colorless crystals, m.p. 125-127 °C. \(R_f\) = 0.68 (PE/EA = 5:1). $^1$H NMR (600 MHz, CDCl$_3$): \(\delta\) 0.93 (s, 3H), 1.35 (s, 3H), 1.53-1.63 (m, 2H), 1.72-1.77 (m, 2H), 1.95-2.00 (m, 2H), 2.04 (dd, J = 9.3 and 14.8 Hz, 1H), 2.14 (d, J = 13.7 Hz, 1H), 2.32-2.38 (m, 1H), 2.61-2.67 (m, 1H), 2.75-2.79 (m, 1H), 2.86 (t, J = 7.7 Hz, 1H), 4.77-4.78 (m, 1H), 4.82-4.83 (m, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$): \(\delta\) 18.2, 25.0, 27.1, 28.9, 39.9, 40.4, 44.7, 47.2, 48.7, 51.6, 56.9, 95.0, 105.2, 156.4, 178.3. IR (neat): \(\nu\) 2972, 1721, 1464, 1117 cm$^{-1}$. HRMS (ESI) calcd for C$_{15}$H$_{20}$NaO$_2$ (M+Na): 255.1356. Found: 255.1352.

The structure of tetracyclic lactone 17 was determined by X-ray single crystal analysis (Figure S1). CCDC 779815 contains 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/data_request/cif.

![Figure S1. ORTEP figure of compound 17. Ellipsoids are drawn at 50% probability.](image)

1,4-Dimethyl-8-hydroxy-4-methoxycarbonyl-11-methylenetricyclo[6.3.0.0$^{2,6}$]undecan-10-one (18)

To a stirred solution of tricyclic enol 16a (20.6 mg, 0.078 mmol) in CH$_2$Cl$_2$ (1.5 mL) was sequentially added SeO$_2$ (5.6 mg, 0.050 mmol) and $^1$BuOOH (65% aqueous solution, 42 mg, 0.30 mmol). The resulting solution was stirred at room temperature for 2 h. The reaction mixture was poured into water, extracted with CH$_2$Cl$_2$, dried over MgSO$_4$, and concentrated. The residue was filtered through a thin pad of silica gel (eluted with PE/EA 2:1 to 1:1) and the filtrate was concentrated. Anhydrous CH$_2$Cl$_2$ (1 mL) was added, and then to the resulting solution
was added powdered NaHCO₃ (23.0 mg, 0.27 mmol) and Dess-Martin periodinane (57.0 mg, 0.13 mmol). The reaction mixture was stirred under room temperature for 30 min and then directly subjected to flash column chromatography on silica gel (eluted with PE/AE 5:1 to 3:1) to afford the tricyclic hydroxyl enone 18 (17.3 mg, 80% over 2 steps).

**Compound 18**: Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.15 (s, 3H), 1.34 (s, 3H), 1.32–1.36 (m, 1H), 1.67–1.73 (m, 2H), 1.77 (s, 1H), 1.92 (dd, J = 8.4 and 14.1 Hz, 1H), 2.28 (ddd, J = 1.7, 8.0, and 12.7 Hz, 1H), 2.45 (d, J = 18.8 Hz, 1H), 2.48-2.54 (m, 2H), 2.60 (d, J = 18.8 Hz, 1H), 2.59-2.65 (m, 1H), 3.67 (s, 3H), 5.24 (s, 1H), 6.03 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 17.7, 24.5, 40.1, 40.2, 45.6, 49.4, 51.9, 52.7, 55.0, 86.8, 117.4, 155.0, 178.1, 203.8. IR (neat): v 3464, 2961, 1732, 1724, 1635, 1464, 1207 cm⁻¹. HRMS (ESI) calcd for C₁₆H₂₃O₄ (M+H): 279.1591. Found: 279.1589.

1,4-Dimethyl-4-methoxycarbonyl-11-methylenetricyclo[6.3.0.0²,6]undec-8-en-10-one (19)

To a solution of tricyclic hydroxy enone 18 (16.6 mg, 0.060 mmol) in benzene (3 mL) was added p-TsOH·H₂O (1.0 mg, 0.0053 mmol). The resulting solution was heated to reflux in a 100 °C oil bath under stirring for 1 h and then allowed to cool to room temperature. The reaction mixture was evaporated and the crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 10:1 to 5:1) afforded tricyclic dienone 19 (14.5 mg, 93%).

**Compound 19**: Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.18 (s, 3H), 1.30 (t, J = 12.1 Hz, 1H), 1.38 (s, 3H), 1.57-1.64 (m, 1H), 2.30 (ddd, J = 1.8, 7.3, and 15.2 Hz, 1H), 2.38-2.46 (m, 2H), 2.56 (ddd, J = 0.9, 7.3, and 12.6 Hz, 1H), 2.65-2.76 (m, 1H), 2.80 (dd, J = 8.6 and 14.8 Hz, 1H), 3.66 (s, 3H), 5.17 (s, 1H), 5.89-5.90 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 23.4, 24.4, 32.3, 37.0, 44.9, 46.4, 48.2, 51.7, 52.0, 54.9, 113.3, 123.5, 153.7, 177.8, 189.2, 197.5. IR (neat): v 2972, 1736, 1706, 1624, 1468, 1199 cm⁻¹. HRMS (ESI) calcd for C₁₆H₂₀NaO₃ (M+Na): 283.1305. Found: 283.1302. The spectroscopic data is identical to that previously reported.²

**Experimental procedures for the synthesis of 1-ene-VCP 12’ and its tandem [(5+2)+1]/aldol reaction**

**Isopropyl 2-allyl-2-methylpent-4-enoate (S2)**

A solution of n-BuLi (1.6 M in hexane, 53 mL, 85 mmol) in anhydrous THF (50 mL) was cooled to −10 °C under argon. To the stirred solution HMDS (14.92 g, 92.4 mmol) was added dropwise, and the resulting mixture was stirred for 10 min. The solution was cooled to −78 °C, and a solution of ester S1 (3.65 g, 31.4 mmol) in anhydrous THF (50 mL) was slowly added. After stirred for 30 min, a solution of allyl bromide (12.03 g, 99.4 mmol) in anhydrous THF (50 mL) was added. The reaction mixture was stirred and allowed to warm to room temperature.

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(2) Banwell, M. G.; Ausin, K. A. B.; Willis, A. C. *Tetrahedron* 2007, 63, 6388.
temperature over 16 h. Saturated aqueous NH₄Cl was added to quench the reaction, and the resulting mixture was extracted with CH₂Cl₂. The organic phase was washed sequentially with aqueous 1 M H₂SO₄, saturated NaHCO₃, and brine. The organic solution was dried over Na₂SO₄ and concentrated. The crude product was distilled under reduced pressure to afford ester S₂ (b.p. 84-88 ºC/10 mmHg, 3.16 g, 51%).

Compound S₂: Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.12 (s, 3H), 1.22 (d, J = 6.4 Hz, 6H), 2.19 (dd, J = 7.6 and 13.3 Hz, 2H), 2.38 (dd, J = 7.1 and 13.3 Hz, 2H), 5.00 (heptet, J = 6.2 Hz, 1H), 5.03-5.08 (m, 4H), 5.67-5.78 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 21.3, 21.8, 42.9, 45.5, 67.5, 118.0, 133.9, 175.7. IR (neat): ν 2983, 1724, 1646, 1471, 1378, 1218, 1110 cm⁻¹. HRMS (ESI) calcd for C₁₂H₂₀NaO₂ (M+Na): 219.1356. Found: 219.1351.

Isopropyl 2-methyl-2-(2-oxoethyl)pent-4-enoate (S₃)

To a solution of diene S₂ (1.42 g, 7.23 mmol) in CH₂Cl₂ (15 mL) was added a solution of mCPBA (70%, 1.23 g, 4.99 mmol) in CH₂Cl₂ (35 mL). The reaction mixture was stirred for 19.5 h under room temperature. Another batch of mCPBA (70%, 0.36 g, 0.15 mmol) was added, and the reaction mixture was further stirred for 45 min. Saturated aqueous NaHCO₃ was added to quench the reaction, and the resulting mixture was extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄ and concentrated, and the crude product was directly used in the next step. To a stirred solution of the above crude product in THF (30 mL) was successively added a solution of H₅IO₆ (1.65 g, 7.24 mmol) in water (10 mL) and a solution of NaIO₄ (1.55 g, 7.25 mmol) in water (10 mL). The resulting mixture was stirred under room temperature for 1 h. Saturated aqueous NaHCO₃ was added to quench the reaction, and the resulting mixture was extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄ and concentrated, and the crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 50:1 to 3:1) to afforded the unreacted diene S₂ (400 mg, 28%) and aldehyde S₃ (579 mg, 40%).

Compound S₃: Colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 1.23 (d, J = 6.3 Hz, 3H), 1.24 (d, J = 6.4 Hz, 3H), 1.29 (s, 3H), 2.34 (dd, J = 7.5 and 13.7 Hz, 1H), 2.40 (dd, J = 7.5 and 13.7 Hz, 1H), 2.48 (dd, J = 2.0 and 17.0 Hz, 1H), 2.78 (d, J = 17.0 Hz, 1H), 5.03 (heptet, J = 6.4 Hz, 1H), 5.06-5.13 (m, 2H), 5.71 (ddt, J = 10.0, 17.1, and 7.5 Hz, 1H), 9.78 (t, J = 1.7 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 21.6, 22.6, 43.3, 43.5, 50.6, 68.2, 119.0, 132.7, 175.0, 200.5. IR (neat): ν 2987, 1721, 1460, 1378, 1218, 1110 cm⁻¹. HRMS (ESI) calcd for C₁₁H₁₈NaO₃ (M+Na): 221.1148. Found: 221.1143.

Isopropyl (Z)-2-allyl-2,5-dimethyl-6-oxohept-4-enoate (S₄)

S8
To a solution of bis(2,2,2-trifluoroethyl) 3-oxobutan-2-ylphosphonate (1.24 g, 80% purity, 3.14 mmol) and 18-crown-6 (890 mg, 3.37 mmol) in anhydrous THF (30 mL) at −78 °C was added a solution of KOBu’ (360 mg, 3.21 mmol) in THF (10 mL) dropwise under argon. After stirring for 20 min at −78 °C, a solution of aldehyde S3 (550 mg, 2.81 mmol) in THF (10 mL) was added dropwise at −78 °C and the resulting mixture was stirred for another 2 h at −78 °C. The reaction was gradually warmed to room temperature. Saturated NH4Cl was added and the reaction mixture was extracted with ether twice. The combined organic extract was washed with brine, dried over Na2SO4, and concentrated. The crude product was purified by flash column chromatography on silica gel (eluted with PE/EA 30:1 to 10:1) to afford (Z)-enone S4 (600 mg, 85%) and its (E)-isomer (98 mg, 14%). The overall yield of (Z)- and (E)-enone S4 was 99%, Z:E = 6.1:1.

**Compound S4**: Colorless oil. 1H NMR (400 MHz, C6D6): δ 0.99 (d, J = 6.3 Hz, 6H), 1.18 (s, 3H), 1.56-1.57 (m, 3H), 1.84 (s, 3H), 2.16 (dd, J = 7.8 and 13.6 Hz, 1H), 2.43 (dd, J = 7.3 and 13.7 Hz, 1H), 2.70 (ddm, J = 7.7 and 15.6 Hz, 1H), 2.83 (ddm, J = 6.8 and 15.6 Hz, 1H), 4.95-5.04 (m, 3H), 5.62 (tm, J = 7.5 Hz, 1H), 5.71-5.85 (m, 1H). 13C NMR (100 MHz, C 6D6): δ 21.1, 21.65, 21.69, 29.5, 38.5, 43.6, 46.0, 67.5, 118.1, 133.4, 134.3, 137.7, 175.2, 200.9. IR (neat): ν 2983, 1724, 1698, 1460, 1378, 1199, 1106 cm⁻¹. HRMS (ESI) calcd for C15H24NaO3 (M+Na): 275.1618. Found: 275.1615.

Isopropyl (Z)-2-allyl-5-(1-(tert-butyldimethylsilyloxy)cyclopropyl)-2-methylhex-4-enoate (12′)

Triethyl amine (1.0 mL, 7.2 mmol) and TBSOTf (1.07 g, 4.05 mmol) was sequentially added to a solution of (Z)-enone S4 (500 mg, 1.98 mmol) in anhydrous ether (20 mL) at 0 °C. After stirred for 2.5 h at 0 °C, brine was added and the resulting mixture was extracted by ether. The combined extract was dried over Na2SO4 and concentrated. The crude product was filtered through a pad of silica gel (eluted with PE/EA 50:1 to 20:1, containing 1% Et3N) to afford the crude silyl enol ether. Diethyl zinc solution (5.1 mL, 0.57 M in hexane, 2.90 mmol) and CH2I2 (648 mg, 2.42 mmol) were sequentially added to a solution of the crude silyl enol ether in anhydrous CH2Cl2 (20 mL) at 25 °C. The reaction mixture was stirred for 2 h and was quenched with saturated aqueous NH4Cl. The resulting mixture was extracted with CH2Cl2 and the organic phase was dried over Na2SO4 and concentrated. The residue was purified by flash column chromatography on silica gel (eluted with PE/EA 100:1 to 50:1) to afford β-ene-VCP 12′ (565 mg, contains ca. 35% biscyclopropane, 49%).

**Compound 12′**: Colorless oil. Due to the inseparable impurities, NMR data is not reported. See page S26 for its 1H and 13C NMR spectra (300 MHz, C6D6). IR (neat): ν 2939, 2864, 1732, 1643, 1464, 1378, 1233, 1110 cm⁻¹. HRMS (ESI) calcd for C22H41O3Si (M+Na): 381.2820. Found: 381.2822.
1,4-Dimethyl-8-hydroxy-4-isopropylxycarbonyltricyclo[6.3.0.0²,6]undecan-11-one (13a’ and 13b’)

A solution of β-ene-VCP 12’ (135 mg, 65% purity, 0.231 mmol) and [Rh(CO)₂Cl]₂ (6.0 mg, 15 μmol) in anhydrous dioxane (8 mL) was degassed by bubbling CO/N₂ (1:4 V/V) for 5 min. The solution was heated to 80 °C in an oil bath with stirring under a positive pressure of the mixture gas for 48 h. The solution was cooled to room temperature, and was treated with HCl (5 drops, 1 M in EtOH-H₂O 5:1) under room temperature for 2 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (eluted with PE/EA 3:1 to 1:1) to afford tricyclic hydroxyl ketones 13a’ and 13b’ (25.6 mg, 38%, 13a’:13b’ = 1:1.3).

Compounds 13a’+13b’: Pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 0.97 (s, 3H, 13a’), 1.00 (s, 3H, 13b’), 1.19 (s, 3H, 13b’), 1.21 (d, J = 5.9 Hz, 3H, 13a’), 1.22 (d, J = 5.9 Hz, 3H, 13a’), 1.23 (d, J = 6.4 Hz, 6H, 13b’), 1.29 (s, 3H, 13a’), 1.52 (dd, J = 11.5 and 12.8 Hz, 1H, 13a’), 1.61-1.67 (m, 1H, 13a’ and 13b’), 1.74 (dd, J = 5.1 and 14.9 Hz, 1H, 13b’), 1.85-1.99 (m, 3H, 13a’ and 13b’), 2.08-2.34 (m, 3H, 13a’ and 13b’), 2.43-2.57 (m, 2H, 13a’ and 13b’), 2.67-2.74 (m, 1H, 13a’), 2.78-2.83 (m, 1H, 13b’), 4.92-5.01 (m, 1H, 13a’ and 13b’). ¹³C NMR (75.5 MHz, CDCl₃): δ 12.4, 12.8, 21.62, 21.64, 21.7, 22.7, 24.3, 32.1, 32.2, 35.1, 35.2, 37.9, 39.1, 39.7, 40.4, 44.2, 44.4, 44.7, 45.5, 48.3, 48.4, 50.9, 52.5, 60.1, 60.3, 67.46, 67.54, 88.9, 89.3, 176.9, 177.3, 220.9, 221.6. IR (neat): ν 3485, 2938, 1721, 1409, 1106 cm⁻¹. HRMS (EI, 70 eV) calcd for C₁₇H₂₆O₄ (M⁺): 294.1831. Found: 294.1828.
3. $^1$H and $^{13}$C-NMR Spectra for New Compounds
12 (contains unseparable bincyclopropane)
mixture, 13a:13b = 1:1.5
13a + 13b, assignment for the relative configuration

Crude product 13a from K$_2$OsO$_4$-NaIO$_4$ oxidation of compound 16a:

Mixture of 13a and 13b:

Comparison of the $^1$H NMR spectrum indicates that the minor isomer 13a has the correct relative configuration.
12' (contains inseparable impurities)
mixture, $13a':13b' = 1:1.3$