

A Second-Generation Synthesis of the Cyanthiwigin Natural Product Core

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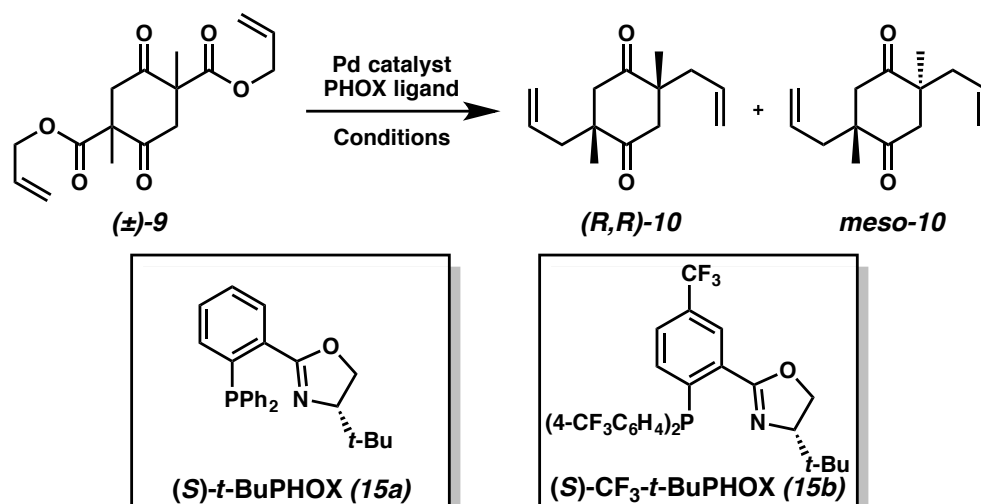
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Materials and Methods

Unless noted in the specific procedure, reactions were performed in flame-dried glassware under argon atmosphere. Dried and deoxygenated solvents (Fisher Scientific) were prepared by passage through columns of activated aluminum before use.¹ Anhydrous *tert*-butanol and nitromethane were purchased from Sigma Aldrich in sure-sealed bottles and used as received unless otherwise noted. Commercial reagents (Sigma Aldrich or Alfa Aesar) were used as received with the exception of palladium(II) acetate (Sigma Aldrich) which was stored in a nitrogen-filled glovebox. The modified Grubbs–Hoveyda II catalyst (**S3**)² was donated by Materia Inc. and used without further purification. The (*S*)-*t*-BuPHOX ligand **15a**,³ the (*S*)-CF₃-*t*-BuPHOX ligand **15b**,⁴ and bis(3,5-dimethoxydibenzylideneacetone)palladium⁵ were prepared according to known procedures. Alkyl iodide **S2**⁶ and vinyl boronate ester **12**⁷ were prepared according to known methods. Bis- β -ketoester **9**, bicyclic alkene **16**, and vinyl triflate **S1**, were prepared according to procedures previously reported by our group.⁸ Brine is defined as a saturated aqueous solution of sodium chloride. Reactions requiring external heat were modulated to the specified temperatures using an IKA Mag temperature controller. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ¹H and ¹³C NMR spectra were recorded on a Varian Inova 500 spectrometer (500 MHz and 126 MHz, respectively), a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively), or a Varian Mercury 300 spectrometer (300 MHz and 75 MHz, respectively) and are reported in terms of chemical shift relative to residual CHCl₃ (δ 7.26 and δ 77.16 ppm, respectively). Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Abbreviations are used as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = complex multiplet. Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer using thin film samples on KBr plates, and are reported in frequency of absorption (cm⁻¹). High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer with fast atom bombardment (FAB+) ionization mode or were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+) mode.

Optimization of the Double Catalytic Enantioselective Allylic Alkylation

Investigation of the Influence of Palladium Catalyst and PHOX Ligand:

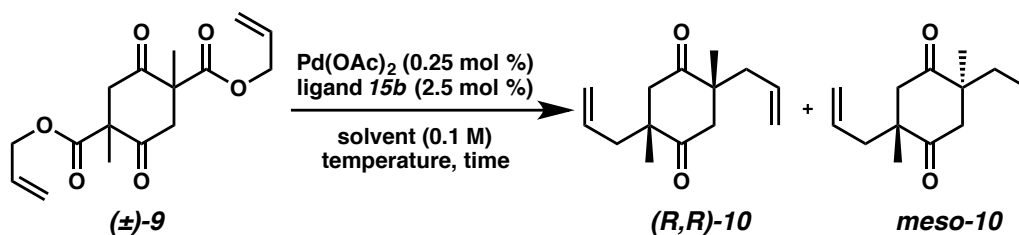


Entry	Pd cat. (mol %)	PHOX (mol %)	Solvent	Conc.	Temp.	Yield	d.r.	ee
1	Pd(dmdba) ₂ (5.0)	15a (5.5)	Et ₂ O	0.01 M	25 °C	78%	4.4 : 1.0	99% ^b
2	Pd(dmdba) ₂ (5.0)	15a (5.5)	2:1 PhMe:Hex	0.10 M	25 °C	75%	3.4 : 1.0	99%
3	Pd(dmdba) ₂ (5.0)	15b (5.5)	Et ₂ O	0.01 M	25 °C	92%	4.3 : 1.0	99% ^b
4	Pd(OAc) ₂ (0.25)	15a (2.5)	TBME	0.10 M	40 °C	83%	2.2 : 1.0	97%
5	Pd(OAc) ₂ (0.25)	15b (2.5)	TBME	0.10 M	40 °C	93%	3.5 : 1.0	99%

In a nitrogen-filled glovebox, a 20-mL scintillation vial equipped with a magnetic stir bar was charged with palladium catalyst and PHOX ligand. The solids were diluted with solvent (amount based on indicated concentration of substrate), the vial was sealed with a Teflon-lined cap, and the mixture was stirred at ambient temperature (25 °C) in the glovebox for 30 minutes. Neat bis-β-ketoester **9** was added to the mixture,⁹ and the vial was once again sealed and heated to the indicated temperature for the specified amount of time. Reaction progress was monitored by TLC. Upon full conversion of the substrate to the desired product, the reaction was allowed to cool to ambient temperature and removed from the glovebox. Concentration in vacuo followed by purification by silica gel column chromatography (3% ethyl acetate in hexanes) afforded diketone **10** as a colorless oil that matched previously reported characterization data:⁸ $R_f = 0.38$, 10% ethyl acetate in hexanes; ¹H NMR (CDCl₃, 300 MHz) δ 5.68 (dddd, $J = 18.3, 10.2, 6.9, 6.9$ Hz, 2H), 5.17–5.09 (comp. m, 3H), 5.07–5.04 (m, 1H), 2.82 (d, $J = 14.7$ Hz, 2H), 2.38 (d, $J = 15$ Hz, 2H), 2.34 (app ddt, $J = 13.2, 6.9, 1.0$ Hz, 2H), 2.09 (app ddt, $J = 13.5, 7.8, 0.9$ Hz, 2H), 1.10 (s, 6H); ¹³C NMR (CDCl₃, 126 MHz) δ 212.8, 132.4, 120.0, 49.4, 48.4, 43.8, 24.3; IR (Neat Film, NaCl) 3078, 2978, 1712, 1640, 1458, 1378, 1252, 1129, 1101, 998,

921 cm^{-1} ; HRMS (ESI+) m/z calc'd for $\text{C}_{14}\text{H}_{20}\text{O}_2$ $[\text{M}]^+$: 220.1463, found 220.1466; $[\alpha]_{\text{D}}^{25}$ -163.1 (c 0.52, CH_2Cl_2). Diastereomeric ratio and enantiomeric excess were determined by GC analysis. Chiral GC assay (GTA column): 100 °C isothermal method over 90 min. Retention times: 67.7 min (Major enantiomer, C_2 diastereomer), 74.1 min (Minor enantiomer, C_2 diastereomer), 77.4 min (*meso* diastereomer). Achiral GC assay (DB-Wax column): 100 °C isotherm over 2.0 min, ramp 5 °C/min to 190 °C, then 190 °C isotherm for 10.0 min. Retention times: 18.5 min (C_2 diastereomer), 18.7 min (*meso* diastereomer).

Investigation of the Influence of Solvent and Temperature:

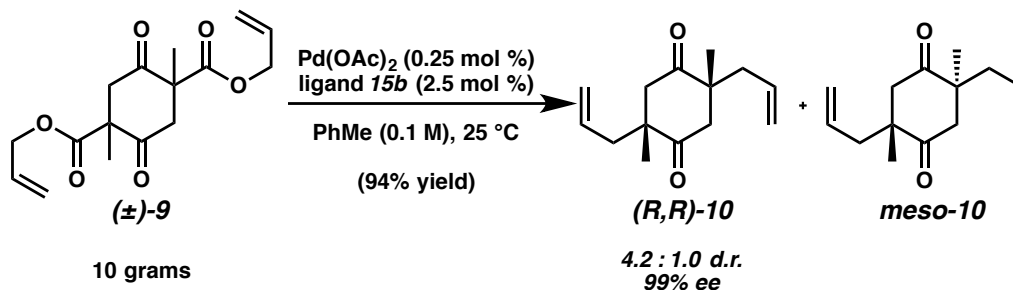


Entry	Solvent	Temperature	Time	Yield	d.r.	ee
1	TBME	40 °C	5 h	93%	3.5 : 1.0	99% ^b
2	TMBE	30 °C	5 h	97%	3.6 : 1.0	99%
3	Et ₂ O	30 °C	5 h	88%	3.7 : 1.0	99%
4	PhMe	30 °C	5 h	99%	4.3 : 1.0	99%
5	2:1 PhMe:Hex	30 °C	24 h	45%	2.8 : 1.0	97%
6	PhMe	25 °C	16 h	97%	4.9 : 1.0	99% ^c

In a nitrogen-filled glovebox, $\text{Pd}(\text{OAc})_2$ (1.4 mg, 6.3 μmol) was weighed into a 20-mL scintillation vial and dissolved in solvent (10 mL). In a separate 1-dram vial, (*S*)- CF_3 -*t*-Bu-PHOX (**15b**) (3.7 mg, 6.3 μmol) was dissolved in solvent (1 mL). To a 2-dram vial equipped with a magnetic stir bar, 1.0 mL of the $\text{Pd}(\text{OAc})_2$ solution was added (14 μg , 0.63 μmol , 0.25 mol %) followed by 1.0 mL of the (*S*)- CF_3 -*t*-BuPHOX solution (3.7 mg, 6.3 μmol , 2.5 mol %), washing with an additional 0.5 mL of solvent. The vial was sealed with a Teflon-lined cap, and the mixture was stirred at ambient temperature (25 °C) in the glovebox for 30 minutes. Neat bis- β -ketoester **9** (77 mg, 0.25 mmol, 1.0 equiv) was added to the mixture, and the vial was once again sealed and heated to the indicated temperature for the specified amount of time. Reaction progress was monitored by TLC. Upon full conversion of the substrate to the desired product ($R_f = 0.38$, 10% ethyl acetate in hexanes), the reaction was allowed to cool to ambient temperature and removed from the glovebox. Concentration in vacuo followed by purification by silica gel column

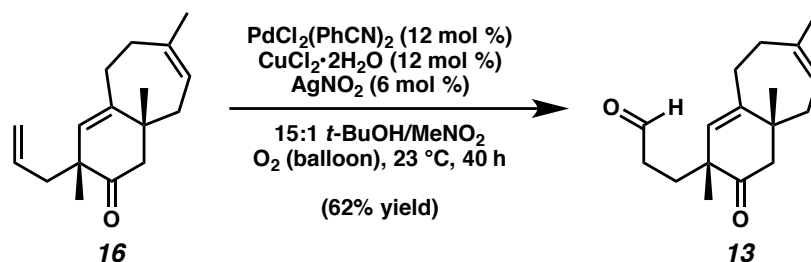
chromatography (3% ethyl acetate in hexanes) afforded diketone **10** as a colorless oil that matched previously reported characterization data (see above).⁸

Double Catalytic Enantioselective Allylic Alkylation Scale-up



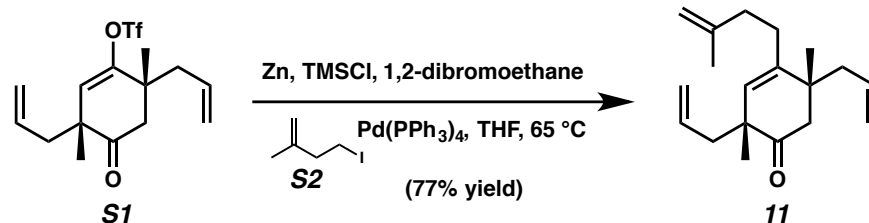
An oven-dried 500-mL round-bottom flask equipped with a magnetic stir bar was cooled to room temperature under vacuum in the antechamber of a nitrogen-filled glovebox. In the glovebox, the flask was charged with $\text{Pd}(\text{OAc})_2$ (18 mg, 0.081 mmol, 0.25 mol %), (*S*)- CF_3 -*t*-BuPHOX (480 mg, 0.81 mmol, 2.5 mol %), and toluene (300 mL). The flask was capped with a rubber septum, secured with electrical tape, and the contents were stirred at ambient temperature (25 °C) in the glovebox. After 1 hour, the septum was removed, and neat bis-β-ketoester **9** (10 g, 32 mmol, 1.0 equiv) was added to the bright yellow solution in one portion. The flask was re-sealed, and stirring continued at ambient temperature for 48 hours, at which time, the reaction was removed from the glovebox and concentrated in vacuo to a dark orange oil. Purification by silica gel column chromatography (3% ethyl acetate in hexanes) afforded pure diketone **10** as a colorless oil (6.7 g, 94% yield) that matched previously reported characterization data (see above).⁸

Procedure for the Aldehyde-Selective Tsuji–Wacker Oxidation

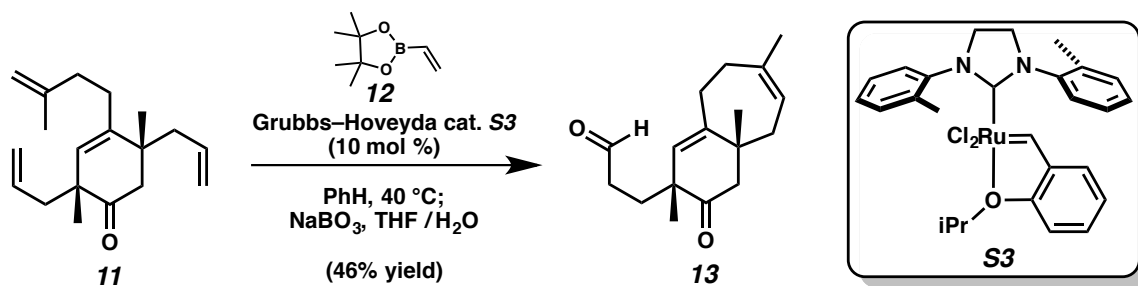


To a flame-dried 25-mL round-bottom flask with a magnetic stir bar were added bis(benzonitrile)palladium(II) chloride (5.7 mg, 0.015 mmol, 0.12 equiv), copper(II) chloride dihydrate (2.6 mg, 0.015 mmol, 0.12 equiv), and silver nitrite (1.2 mg, 0.0075 mmol, 0.06 equiv). The flask was capped with a rubber septum, and *tert*-butyl alcohol (2.3 mL) and nitromethane (0.20 mL) were added sequentially by syringe. The mixture was stirred at 23 °C and sparged with oxygen gas (balloon) for 3 minutes. Alkene **16** (30 mg, 0.12 mmol, 1.0 equiv) was added dropwise by syringe, and the reaction mixture was sparged with oxygen for another minute. The reaction was stirred under oxygen atmosphere at 23 °C for 20 hours, at which time another half portion of the catalyst system (2.9 mg Pd, 1.3 mg Cu, 0.6 mg Ag) was added to the reaction mixture. After 20 hours, the reaction mixture was diluted with water (4 mL) and extracted with dichloromethane (3 x 5 mL). The organic extracts were dried over sodium sulfate, then filtered and concentrated in vacuo. The crude residue was purified by silica gel column chromatography (3% ethyl acetate in hexanes), furnishing aldehyde **13** as a colorless oil (20 mg, 62% yield) that matched previously reported characterization data:⁸ $R_f = 0.20$ (10% ethyl acetate in hexanes); ¹H NMR (CDCl₃, 500 MHz) δ 9.71 (app t, $J = 1.3$, 1H), 5.38–5.31 (m, 1H), 5.15 (s, 1H), 2.70 (d, $J = 13.6$ Hz, 1H), 2.59–2.32 (comp. m, 5H), 2.12 (d, $J = 13.8$ Hz, 1H), 2.24–2.04 (comp. m, 2H), 1.89–1.64 (comp. m, 3H), 1.67 (s, 3H), 1.12 (s, 3H), 0.97 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz) δ 215.5, 201.6, 146.4, 138.7, 129.0, 120.1, 51.6, 47.7, 39.9, 37.6, 37.2, 33.1, 29.6, 27.8, 25.9, 23.9; IR (Neat Film, NaCl) 2960, 2927, 2360, 2341, 1711–1710 (overlapping peaks), 1452, 1374, 1296, 1163 cm⁻¹; HRMS (ESI+) m/z calc'd for C₁₇H₂₄O₂ [M]⁺: 260.1776, found 260.1784; $[\alpha]_D^{25} -83.5$ (c 1.09, CH₂Cl₂).

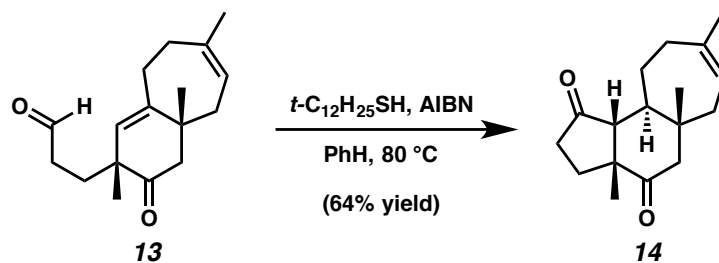
Modified Experimental Procedures



Tetraene 11. A flame-dried Schlenk flask equipped with a magnetic stir bar was charged with zinc dust (0.70 g, 11 mmol, 7.5 equiv) and evacuated and backfilled with argon (3x) before addition of THF (30 mL). Trimethylsilyl chloride (59 μL , 0.47 mmol, 0.33 equiv) and 1,2-dibromoethane (0.15 mL, 1.7 mmol, 1.2 equiv) were added sequentially to the suspension by syringe, and the flask was sealed and heated to 65 $^\circ\text{C}$. After 15 minutes, the mixture was cooled to 23 $^\circ\text{C}$, and neat alkyl iodide **S2** (0.27 mL, 2.1 mmol, 1.5 equiv) was added by syringe. The flask was re-sealed and heated to 65 $^\circ\text{C}$ for 2 hours. Meanwhile, in a nitrogen-filled glovebox, a separate flame-dried conical flask was charged with a solution of triflate **S1** (0.50 g, 1.4 mmol, 1.0 equiv) and tetrakis(triphenylphosphine)palladium(0) (82 mg, 0.071 mmol, 0.05 equiv) in THF (16 mL). This solution was added to the suspension in the Schlenk flask at 23 $^\circ\text{C}$, the flask was sealed, and the resulting olive green mixture was heated to 65 $^\circ\text{C}$. After 3 hours, the reaction was cooled to 23 $^\circ\text{C}$ and filtered over a pad of Celite, washing with excess diethyl ether (150 mL). The filtrate was diluted with brine and extracted with diethyl ether (4 x 50 mL), and the combined organics were washed sequentially with brine (50 mL) and saturated sodium thiosulfate (3 x 50 mL). The organic layer was dried over magnesium sulfate before filtration and concentration in vacuo. The crude residue was purified by silica gel column chromatography (1% \rightarrow 2% \rightarrow 3% Et_2O in hexanes) to afford pure tetraene **11** as a colorless oil (0.30 g, 77% yield) that matched previously reported characterization data: R_f = 0.50 (5% ethyl acetate in hexanes); ^1H NMR (CDCl_3 , 500 MHz) δ 5.77–5.61 (comp. m, 2H), 5.20 (s, 1H), 5.10–4.97 (comp. m, 4H), 4.74 (d, J = 8.8 Hz, 2H), 2.56 (d, J = 13.5 Hz, 1H), 2.40–2.13 (comp. m, 8H), 2.05–1.98 (m, 1H), 1.77 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz) δ 214.4, 145.5, 142.5, 134.1, 134.0, 128.6, 118.6, 117.9, 110.1, 49.5, 48.7, 44.4, 44.3, 43.2, 36.5, 28.6, 26.5, 24.7, 22.7; IR (Neat Film, NaCl) 3076, 2996, 2928, 2360, 1715, 1639, 1455, 1376, 1320, 1298, 1261, 1229, 1138, 1093, 996, 916, 887 cm^{-1} ; HRMS (ESI+) m/z calc'd for $\text{C}_{19}\text{H}_{28}\text{O}$ $[\text{M}]^+$: 272.2140, found 272.2138; $[\alpha]_D^{25}$ -72.4 (c 0.22, CH_2Cl_2).



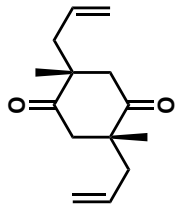
Aldehyde 13. A flame-dried round-bottom flask equipped with a magnetic stir bar was charged with tetraene **11** (0.25 g, 0.92 mmol, 1.0 equiv). Dry benzene (2 mL) was added, then evaporated under vacuum. This azeotropic drying procedure was repeated two additional times, and the resulting material was then dried under high vacuum and backfilled with argon, before dilution with benzene (10 mL). A solution of Grubbs-Hoveyda catalyst **S3** (26 mg, 0.046 mmol, 0.05 equiv) in THF (10 mL) was added slowly, and the resulting mixture was stirred at 25 °C. After 1 hour, boronate ester **12** (0.78 mL, 4.6 mmol, 5.0 equiv) was added dropwise, and another portion of catalyst **S3** (26 mg, 0.046 mmol, 0.05 equiv) in THF (10 mL) was added. The olive green mixture was heated to 40 °C. After 20 hours, the reaction was cooled to 0 °C, and ethyl vinyl ether (0.4 mL) was added to quench remaining catalyst. Volatiles were removed in vacuo, and the resulting residue was passed through a plug of silica, eluting with 20% ethyl acetate in hexanes (300 mL). Upon concentration, the resulting oil was diluted with THF (30 mL) and water (30 mL), treated with sodium perborate monohydrate (0.55 g, 5.5 mmol, 6.0 equiv), and stirred at 23 °C for 1.5 hours. The phases were separated, and the aqueous layer was extracted with ethyl acetate (4 x 50 mL). The combined organics were washed with brine and dried over magnesium sulfate. Upon filtration and concentration, the crude residue was purified by silica gel column chromatography (5% ethyl acetate in hexanes) to furnish pure aldehyde **13** as a colorless oil (0.11 g, 46% yield) that matched previously reported characterization data (see above).



Tricyclic Diketone 14. A flame-dried Schlenk flask equipped with a magnetic stir bar was charged with aldehyde **13** (20 mg, 0.076 mmol, 1.0 equiv), and dry benzene (2 mL) was added, then evaporated under vacuum. This azeotropic drying procedure was repeated two additional times, and the resulting material was then dried under high vacuum and backfilled with argon. *tert*-Dodecanethiol (54 μL , 0.23 mmol, 3.0 equiv) and azobisisobutyronitrile (19 mg, 0.12 mmol, 1.5 equiv) were added, and the resulting mixture was diluted with benzene (5 mL), then freeze-pump-thawed (3x) and backfilled with argon. The flask was sealed, and the contents were heated to 80 °C. After 48 hours, the reaction was cooled to 23 °C and concentrated in vacuo. The crude oil was purified by silica gel column chromatography (5.0% to 7.5% to 10.0% ethyl acetate in hexanes) to afford tricyclic diketone **14** as an amorphous solid (13 mg, 64% yield) that matched previously reported characterization data: $R_f = 0.40$ (10% ethyl acetate in hexanes); ^1H NMR (CDCl_3 , 500 MHz) δ 5.33 (ddq, $J = 5.13, 5.13, 1.71$ Hz, 1H), 2.65 (d, $J = 14.5$ Hz, 1H), 2.55–2.49 (m, 1H), 2.41–2.28 (m, 2H), 2.27–2.21 (m, 1H), 2.20–2.12 (m, 1H), 2.02 (d, $J = 14.5$ Hz, 1H), 2.01–1.93 (m, 2H), 1.89 (dd, $J = 12.2, 1.2$ Hz, 1H), 1.83–1.72 (m, 3H); 1.74 (s, 3H), 1.09 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (CDCl_3 , 126 MHz) δ 218.0, 212.8, 142.6, 121.0, 63.2, 52.6, 51.0, 47.8, 42.3, 40.1, 34.4, 32.4, 31.4, 25.4, 24.1, 21.7, 17.3; IR (Neat Film, NaCl) 2961, 2926, 2868, 1735, 1705, 1576, 1453, 1380, 1149 cm^{-1} ; HRMS (ESI+) m/z calc'd for $\text{C}_{17}\text{H}_{24}\text{O}_2$ $[\text{M}]^+$: 260.1777, found 260.1776; $[\alpha]_D^{25} -158.6$ (c 0.925, CH_2Cl_2).

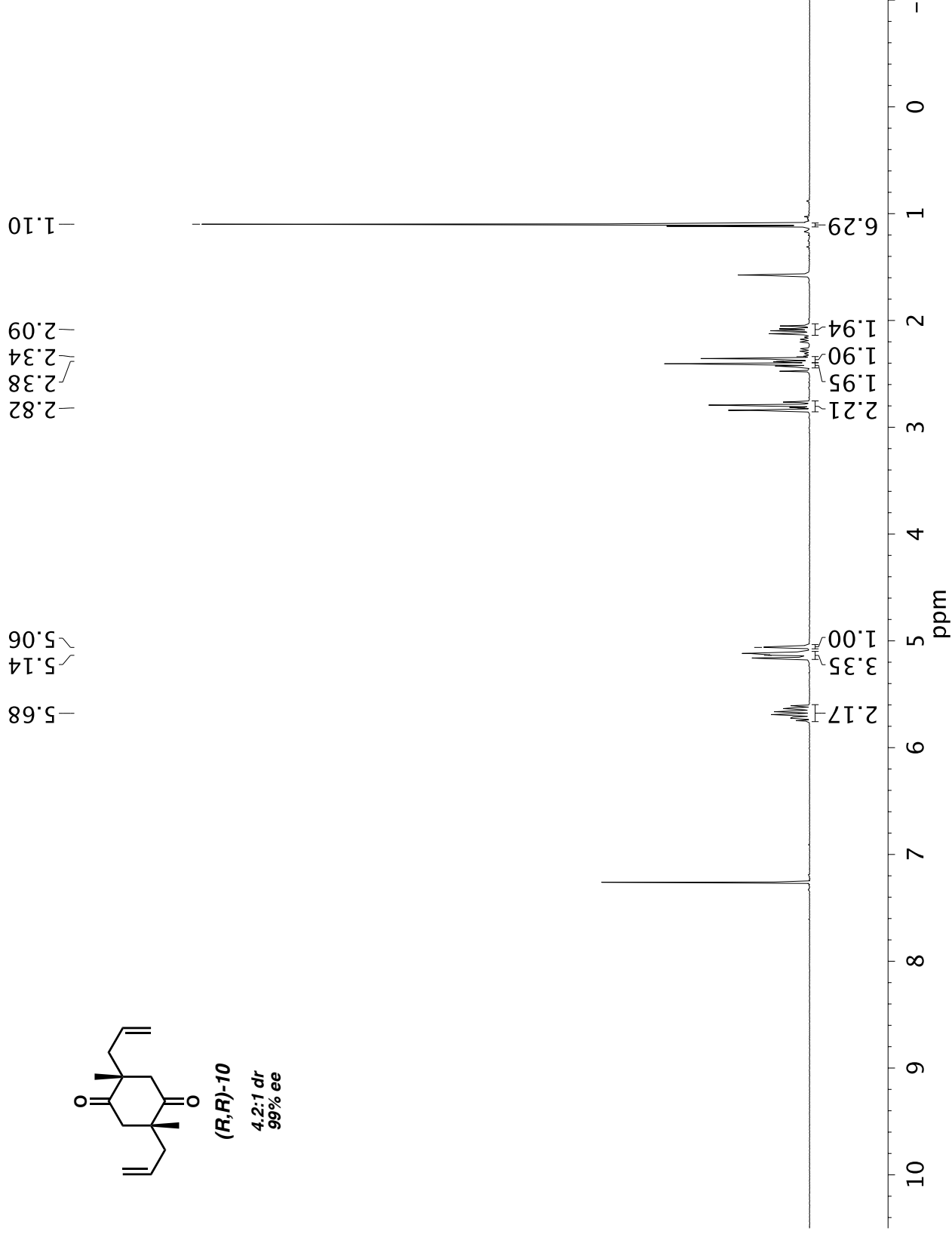
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9. Substrate **9** is prepared in two steps from diallyl succinate and is formed as a 1:1 mixture of the racemic and meso diastereomers, which are readily separable by silica gel column chromatography. The double catalytic enantioselective alkylation is effective on the diastereomeric mixture of **9**, but for ease of operation a single diastereomer was used for screening experiments.

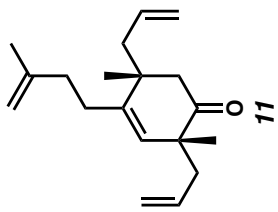
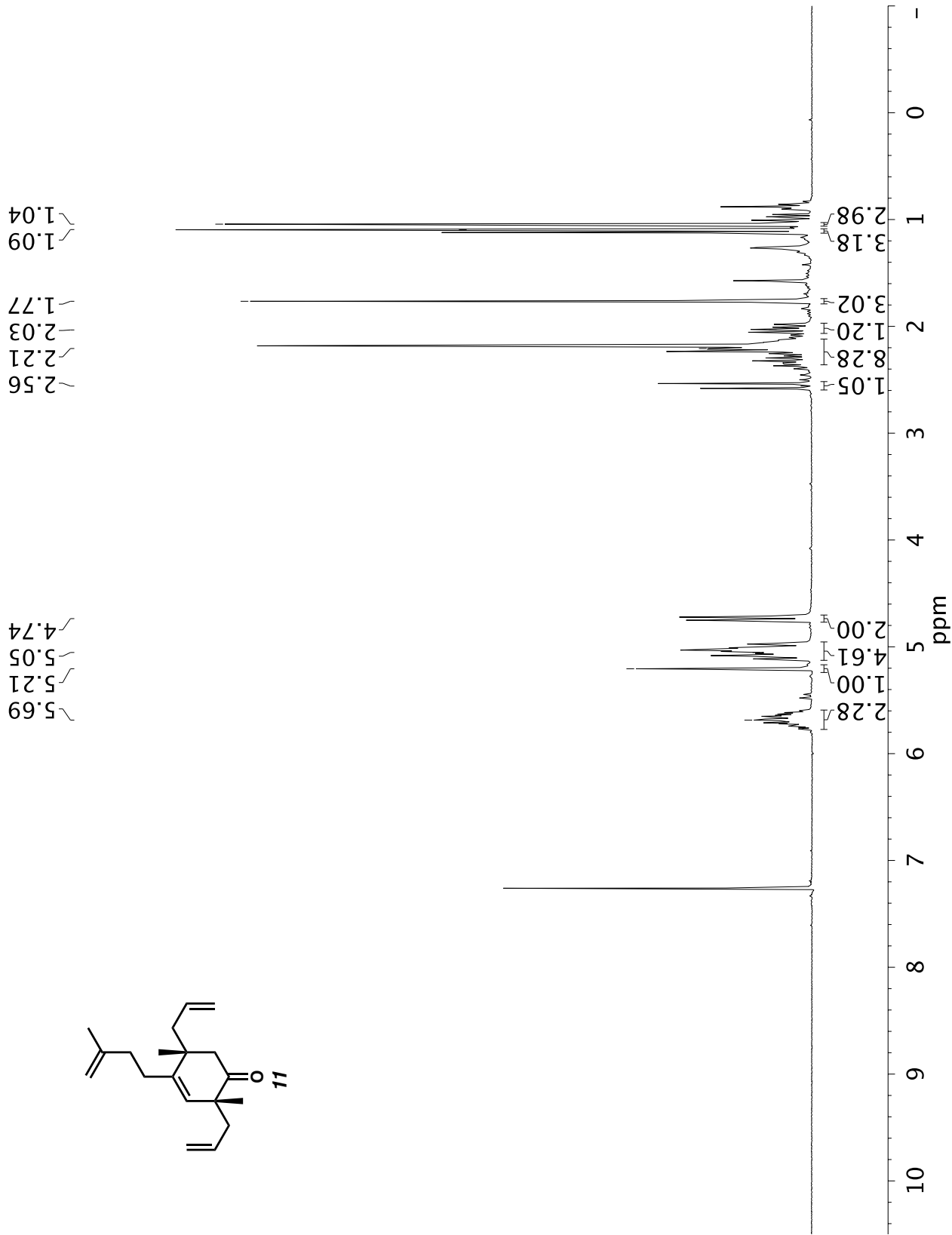


(R,R)-10

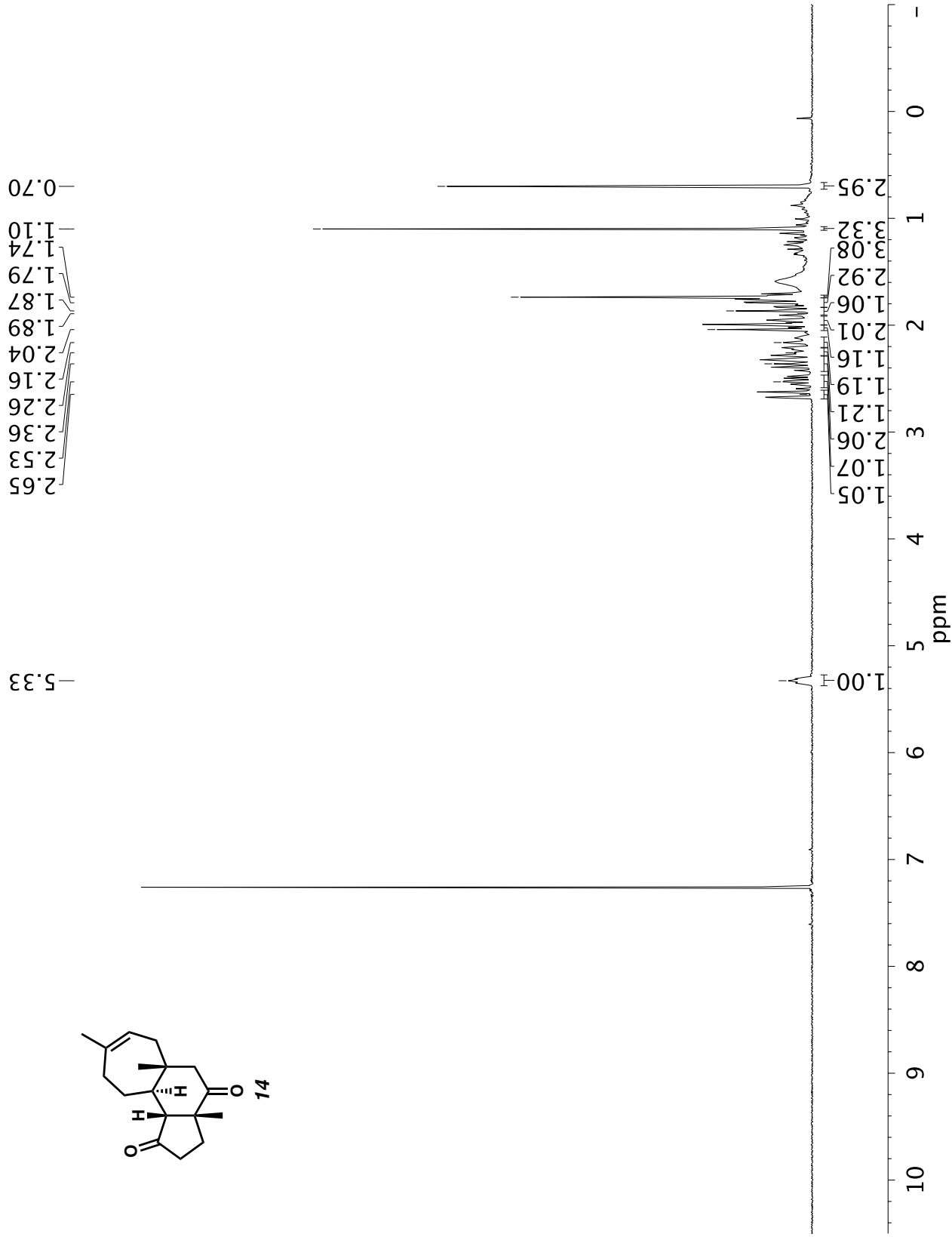
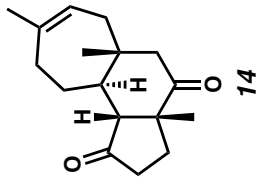
4.2:1 dr
99% ee



¹H NMR (300 MHz, CDCl₃) of compound **10**.



¹H NMR (300 MHz, CDCl₃) of compound 11.



¹H NMR (300 MHz, CDCl₃) of compound 14.