CHAPTER 5

Palladium-Catalyzed Decarbonylative Dehydration for the Synthesis of α-Vinyl Carbonyl Compounds and Total Synthesis of (–)-Aspewentin B ÷

5.1 Introduction

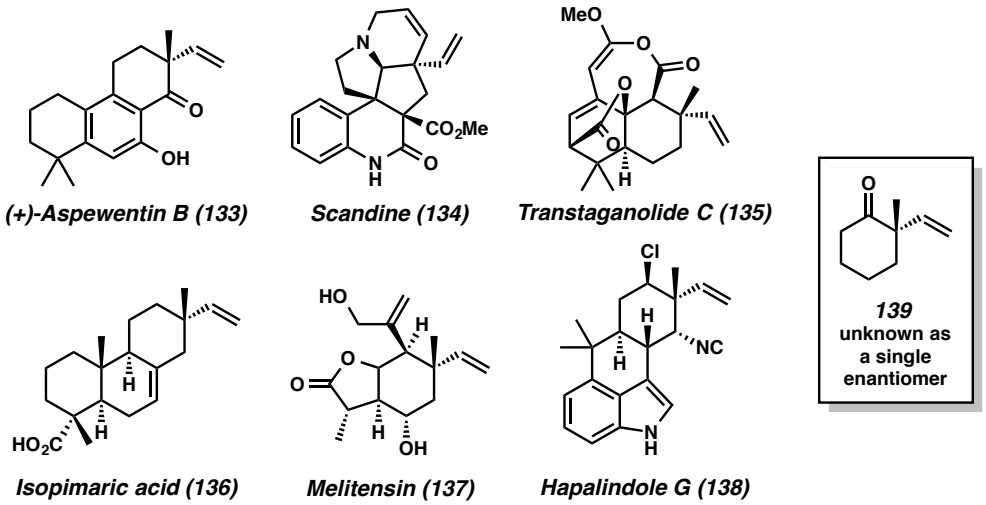
An all-carbon quaternary center bearing an ethylene substituent is a common structural motif in many natural products (Figure 5.1).[1] An important approach to the construction of this unit is the α-vinylation of carbonyl compounds. Two general methods have been developed. One is the direct coupling of an enolate nucleophile with a vinyl electrophile such as an alkenyl ether,[2] vinyl bromide,[3] or acetylene itself.[4,5] Although this approach can be extended to alkenylations as well, and asymmetric versions are known,[3a,3c,4c] the scope of the enolate nucleophile is generally limited to 1,3-dicarbonyl compounds[4] or those with only one enolizable position.[2,3,5b] A second tactic

---

÷ This work was partially adapted from a manuscript in preparation for submission to *Angew. Chem., Int. Ed.*

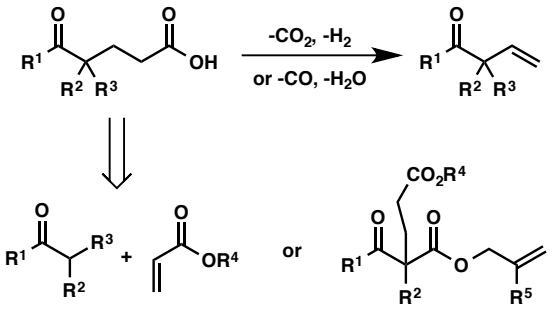
involves addition of the enolate nucleophile to a vinyl surrogate such as vinyl sulfoxide,[6] (phenylseleno)acetaldehyde,[7] or ethylene oxide,[8] followed by elimination. However, there are few reports of stereoselective additions that form the quaternary stereocenter,[9] and none are catalytic or enantioselective. Due to these constraints, even the simplest 2-methyl-2-vinylcyclohexanone (**139**) is not known as a single enantiomer in the literature.

Figure 5.1 Natural products with ethylene substituents



We envisioned an alternative approach to access α-vinyl carbonyl compounds, by employing a decarboxylative elimination of δ-oxocarboxylic acids (Scheme 5.1). These acids may be prepared by addition of an enolate nucleophile to an acrylate acceptor[10] or by palladium-catalyzed allylic alkylation.[11] Both methods allow for the enantioselective construction of the requisite quaternary stereocenter.

Scheme 5.1 Decarboxylative approach to vinylation

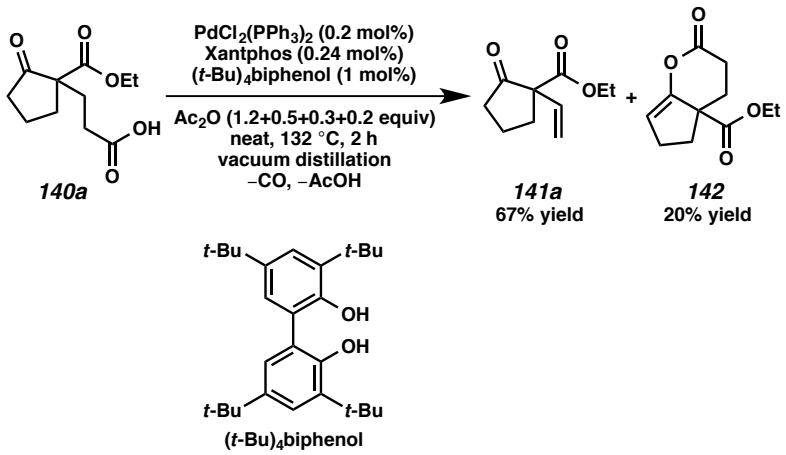


Recently, we reported on the palladium-catalyzed decarbonylative dehydration of fatty acids to form terminal olefins of one less carbon.[12] Due to the importance of α-vinyl carbonyl compounds and the challenges in their preparation, we became interested in applying our decarbonylative dehydration chemistry as an alternative strategy to α-vinylation. Since the carboxylic acid, which bears a quaternary center two atoms away from the reactive carboxyl group, is more hindered than a simple fatty acid, we expected that the reaction conditions would need to be tuned for this particular class of substrates. Additionally, from a practical standpoint, our previous studies were typically conducted on ~5 g fatty acid substrate without solvent, under vacuum distillation conditions. Thus, a smaller scale alternative for implementation on laboratory scale and in the context of multistep organic synthesis would need to be developed.

At the outset of our investigation, we prepared carboxylic acid **140a** and subjected it to palladium-catalyzed decarbonylative dehydration condition, with slightly higher loading of catalyst, ligand, and additive (Scheme 5.2). We were pleased to isolate vinyl cyclopentanone **141a** in 67% yield, along with cyclic lactone **142** in 20% yield as a byproduct. This result demonstrated that steric bulk at the quaternary center does not

significantly retard the reaction, but proximal functionality (e.g. the ketone) could alter the reaction pathway.

Scheme 5.2 Decarbonylative dehydration of δ-oxocarboxylic acid ***140a***

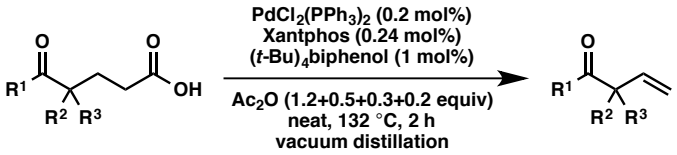


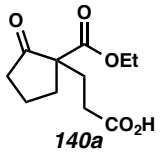
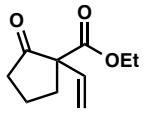
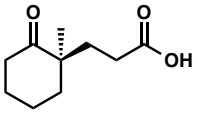
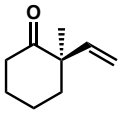
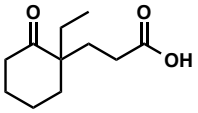
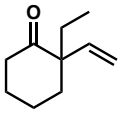
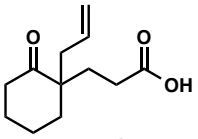
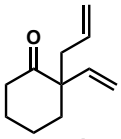
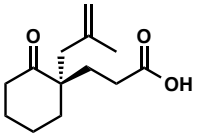
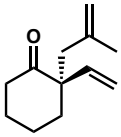
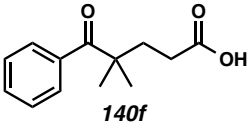
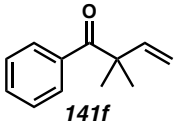
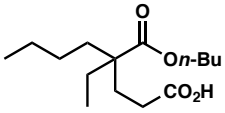
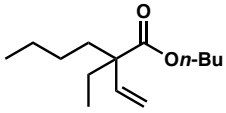
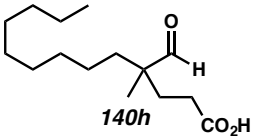
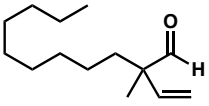
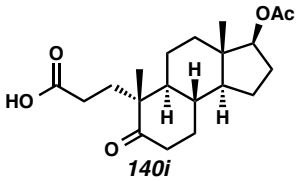
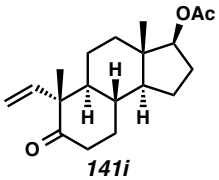
5.2 Study of Reaction Scope

With this exciting initial result in hand, we proceeded to investigate the scope of the reaction (Table 5.1). First, we synthesized (*R*)-3-(1-methyl-2-oxocyclohexyl)propanoic acid (**140b**) by enantioselective d'Angelo Michael addition,[10] and subjected it to decarbonylative dehydration (entry 2). We were delighted to obtain the desired product, (*R*)-2-methyl-2-vinylcyclohexanone (*ent*-**139**), in 60% yield and 92% ee. Likewise, 2-ethyl-2-vinylcyclohexanone (**141c**) was prepared in a similar fashion. Carboxylic acids bearing allyl or 2-methallyl substituents, which can be prepared via palladium-catalyzed allylic alkylation,[11] also underwent decarbonylative dehydration smoothly to provide the corresponding 2-allyl-2-vinyl-substituted cyclohexanones **141d** and **141e** (entries 4 and 5), the latter in 91% ee from enantioenriched acid **140e**. It is worth noting that double bond isomerization in the allyl moiety is negligible for **141d** and

does not occur at all for **141e**. Aside from cyclic substrates, we examined acyclic ones (entries 6–9), and found that α-vinyl ketone **141f**, ester **141g**, and aldehyde **141h** can all be prepared in good yields. More complex scaffolds such as acid **140i**, obtained by oxidative cleavage of testosterone,[13] also undergo the reaction to provide tricyclic vinyl compound **141i** (entry 10). While the reaction can be carried out in the absence of a solvent at a fairly large scale (5 mmol, entries 1–7), we found that for smaller scale synthesis it is more convenient to use NMP as solvent along with slightly modified conditions (entries 8–10).[14]

Table 5.1 Decarbonylative dehydration of δ-oxocarboxylic acids



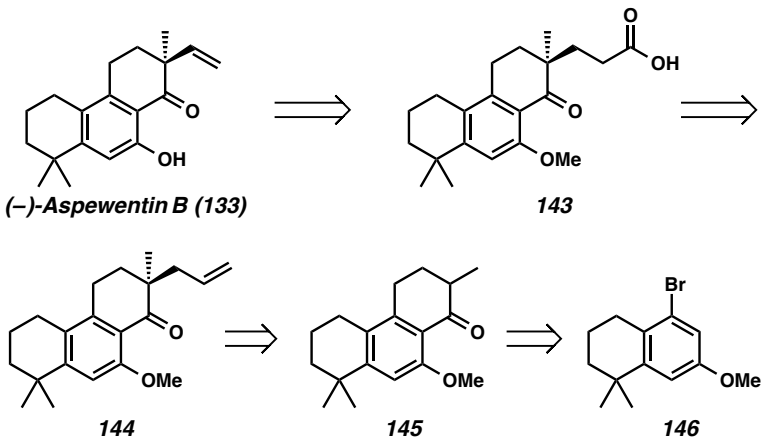
entry[a]	δ-oxocarboxylic acid	product	yield
1	 *140a*	 *141a*	67%
2	 *140b*	 *ent-139*	60% 92% ee
3	 *140c*	 *141c*	66%
4	 *140d*	 *141d*	54%[b]
5	 *140e*	 *141e*	69% 92% ee
6	 *140f*	 *141f*	75%
7	 *140g*	 *141g*	50%
8[c]			51%
9[c]	 *140h*	 *141h*	77%
10[c]	 *140i*	 *141i*	41%

[a] 5 mmol scale. [b] Isolated as a 95:5 mixture of desired product and internal olefin isomer. [c] Condition: 0.5 mmol substrate (1 equiv), benzoic anhydride (1.2 equiv), $PdCl_2$(nbd) (1 mol%), Xantphos (1.2 mol%), NMP (0.25 mL), 1 atm N_2, 132 °C, 3 h.

5.3 Total Synthesis of (–)-Aspewentin B

To further demonstrate the utility of our decarbonylative dehydration approach to vinylation, we embarked on a total synthesis of aspewentin B (**133**, Figure 5.1), a norditerpene natural product isolated from *Aspergillus wentii*.[15,16] This terpenoid contains an α-vinyl quaternary cyclohexanone scaffold, and is therefore ideally suited for our chemistry. Retrosynthetically (Scheme 5.3), we envisioned that the vinyl group could be formed by decarbonylative dehydration of δ-oxocarboxylic acid **143**, which might be obtained by elaboration of allyl ketone **144**.[17] The quaternary stereocenter would be set by palladium-catalyzed enantioselective allylic alkylation of tricyclic ketone **145**, which could be built from known aryl bromide **146**.[18]

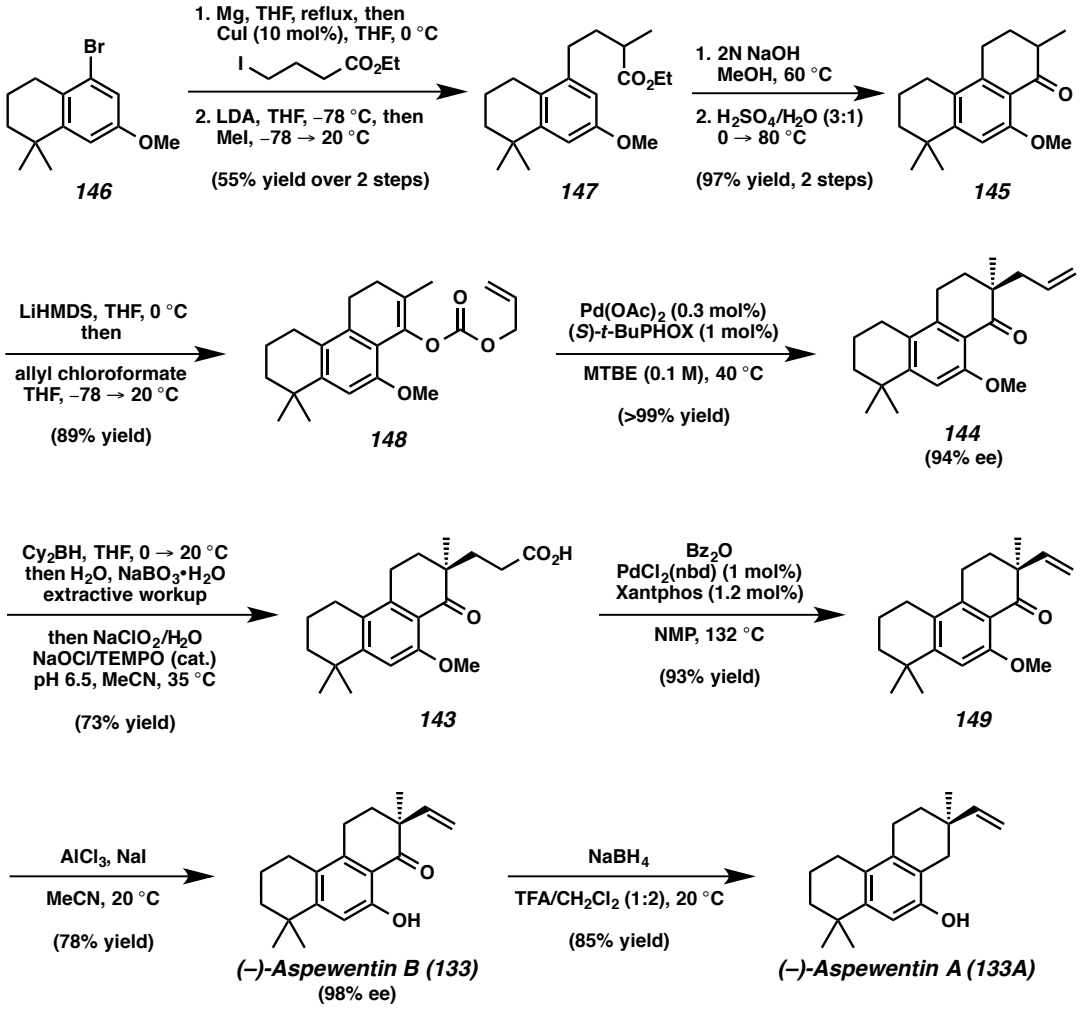
Scheme 5.3 Retrosynthetic analysis of (–)-aspewentin B



We commenced our total synthesis by copper-catalyzed coupling of a Grignard reagent derived from aryl bromide **146** with ethyl 4-iodobutyrate (Scheme 5.4). α-Methylation of the coupled product led to ester **147**, which was hydrolyzed to the corresponding carboxylic acid and then cyclized under acidic conditions to form tricyclic

ketone **145**. The ketone was converted to the corresponding allyl enol carbonate (**148**), and subjected to palladium-catalyzed enantioselective decarboxylative allylic alkylation to afford allyl ketone **144** in nearly quantitative yield and 94% ee. Interestingly, the allylic alkylation reaction proceeds efficiently with low palladium catalyst loading.[19] Hydroboration of the terminal olefin of **144** with dicyclohexylborane and oxidation with sodium perborate, followed by further oxidation with sodium chlorite catalyzed by TEMPO and bleach, delivered carboxylic acid **143** in 73% yield. Gratifyingly, palladium-catalyzed decarbonylative dehydration furnished α-vinyl ketone **149** in 93% yield.[20] Removal of the *O*-methyl group provided (–)-aspewentin B (**133**) in 78% yield.[21] Reduction of the ketone moiety of **133** using sodium borohydride and trifluoroacetic acid furnishes (–)-aspewentin A (**133A**) in 85% yield.[22]

Scheme 5.4 Total synthesis of (–)-aspewentin B



5.4 Concluding Remarks

In summary, we have developed a new approach to access α-vinyl quaternary carbonyl compounds via palladium-catalyzed decarbonylative dehydration of δ-oxocarboxylic acids. A variety of acids with different scaffolds and functional groups were transformed into the corresponding α-vinyl carbonyl compounds in moderate to good yields. We have also applied the method to the first enantioselective total synthesis

of (–)-aspewentin B. Further applications of this transformation in natural product synthesis are currently ongoing in our lab and will be reported in due course.

5.5 Experimental Section

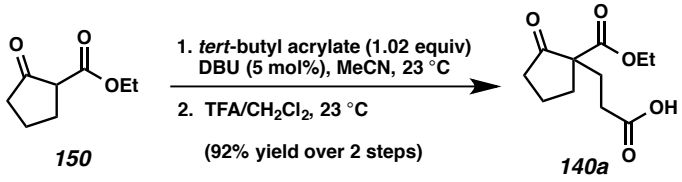
5.5.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents, or under vacuum without the use of solvents. Solvents were dried by passage through an activated alumina column under argon.[23] Reaction progress was monitored by thin-layer chromatography (TLC) or ^{1}H NMR analysis of the crude reaction mixture. TLC was performed using E. Merck silica gel 60 F254 pre-coated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, phosphomolybdic acid, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) or a Bruker CryoProbe Prodigy 400 spectrometer (400 MHz and 101 MHz, respectively) and are reported relative to residual $CHCl_3$ (δ 7.26 ppm and δ 77.16 ppm, respectively). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured

with a Jasco P-2000 polarimeter operating on the sodium D line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Analytical chiral GC was performed with an Agilent 6850 GC utilizing a G-TA (30 m x 0.25 mm) column (1.0 mL/min carrier gas flow). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak (AD-H or AS) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High-resolution mass spectra (HRMS) were provided by the California Institute of Technology Mass Spectrometry Facility using a JEOL JMS-600H High Resolution Mass Spectrometer (EI+ or FAB+), or obtained with an Agilent 6200 Series TOF using Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed ionization mode (MM: ESI-APCI).

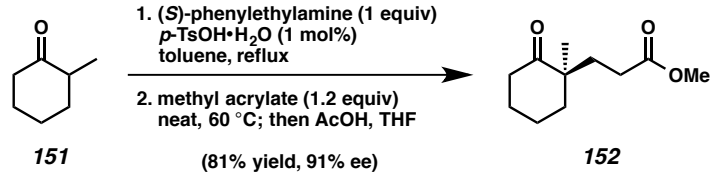
Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. *i*-Pr_2NH was distilled from calcium hydride prior to use. (*S*)-*t*-BuPHOX was prepared by a known method.[24]

5.5.2 Preparation of Carboxylic Acid Substrates



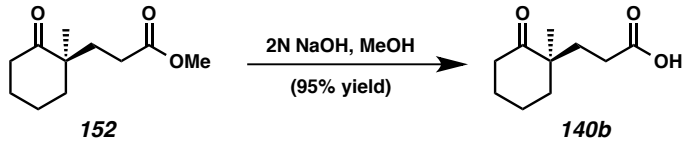
150 ***140a***

3-(1-(Ethoxycarbonyl)-2-oxocyclopentyl)propanoic acid (140a). A flame-dried 100 mL round-bottom flask was charged with a magnetic stir bar, anhydrous MeCN (30 mL), β-keto ester **150** (2.9 mL, 20 mmol, 1 equiv), *tert*-butyl acrylate (3.0 mL, 20.6 mmol, 1.02 equiv), and DBU (0.15 mL, 1 mmol, 0.05 equiv). The light yellow reaction mixture was stirred at 23 °C. After 12 h, TLC analysis indicated complete consumption of starting material. Solvents were evaporated, and the crude residue was purified by flash column chromatography on silica gel (10→16→25% EtOAc in hexanes) to afford a colorless oil (5.22 g). To a solution of this oil (1.42 g) in CH_2Cl_2 (4 mL) was added trifluoroacetic acid (4 mL). The reaction mixture was stirred at 23 °C for 30 min and concentrated under reduced pressure. Removal of remaining trifluoroacetic acid by azeotropic evaporation from toluene (5 mL x 5) afforded carboxylic acid **140a** (1.14 g, 92% yield over 2 steps) as a viscous colorless oil. R_f = 0.1 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.59 (ddd, *J* = 16.3, 10.2, 5.7 Hz, 1H), 2.53–2.36 (m, 3H), 2.30 (dt, *J* = 19.0, 8.0 Hz, 1H), 2.19 (ddd, *J* = 14.2, 10.2, 5.7 Hz, 1H), 2.09–1.92 (m, 3H), 1.89 (dt, *J* = 13.1, 7.4 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.7, 178.6, 171.1, 61.8, 59.2, 38.0, 34.0, 29.6, 28.2, 19.7, 14.2; IR (Neat Film, NaCl) 2979, 1713, 1408, 1158, 1028 cm^{-1}; HRMS (MM: ESI-APCI–) *m/z* calc'd for $C_{11}H_{15}O_5$ $[M–H]^-$: 227.0925, found 227.0925.



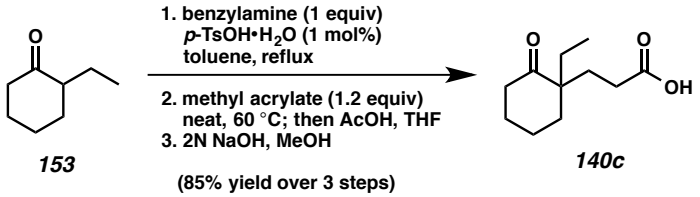
Methyl (*R*)-3-(1-methyl-2-oxocyclohexyl)propanoate (152). Synthesis of **152** was based on a literature procedure.[10] A 100 mL round-bottom flask was charged with a magnetic stir bar, 2-methylcyclohexanone (**151**, 3.7 mL, 30.6 mmol, 1 equiv), (*S*)-phenylethylamine (3.71 g, 30.6 mmol, 1 equiv), *p*-toluenesulfonic acid hydrate (58 mg, 0.306 mmol, 0.01 equiv), and toluene (30 mL). The flask was equipped with a Dean-Stark trap filled with toluene and a reflux condenser. The reaction mixture was heated at reflux for 3.5 h. The Dean-Stark trap was replaced with a distillation head, and the toluene was distilled off under reduced pressure. The residue was cooled to 60 °C under nitrogen and methyl acrylate (3.4 mL, 36.7 mmol, 1.2 equiv) was added. The reaction mixture was stirred at 60 °C for 12 h. After cooling to ambient temperature, the reaction mixture was quantitatively transferred to a 250 mL round-bottom flask by rinsing with THF (50 mL total). Aqueous 20% acetic acid (30 mL) was added and the solution was stirred at 23 °C for 5 h. THF was evaporated under reduced pressure and 1N HCl (11 mL) was added. The biphasic mixture was extracted with Et_2O (25 mL x 3). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5→6→10→12% EtOAc in hexanes) to afford δ-keto ester **152** (4.96 g, 81% yield over 2 steps) as a light brown oil. R_f = 0.4 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.46–2.26 (m, 3H), 2.22–2.10 (m, 1H), 2.11–1.98 (m, 1H), 1.93–1.67 (m, 6H), 1.67–1.54 (m, 1H), 1.07 (d, *J* = 2.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.4, 174.2, 51.8, 48.0, 39.4, 38.8, 32.6, 29.1, 27.6, 22.5, 21.1; IR (Neat Film, NaCl) 2936, 2865, 1740, 1705, 1437, 1378, 1304, 1197, 1172, 1123,

988 cm^{-1}; HRMS (ESI-APCI+) *m/z* calc'd for $C_{11}H_{19}O_3$ $[M+H]^+$: 199.1329, found 199.1325; $[\alpha]_D^{25}$ +31.5 (*c* 3.00, EtOH, 91% ee).

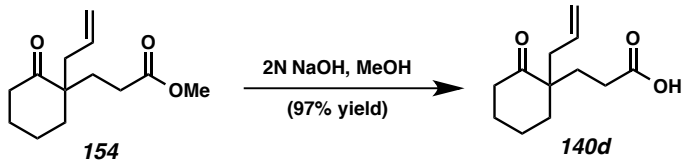


152 ***140b***

(*R*)-3-(1-Methyl-2-oxocyclohexyl)propanoic acid (140b). To a solution of **152** (2.37 g, 11.9 mmol, 1.0 equiv) in MeOH (11 mL) was added aqueous 2N NaOH (7.8 mL, 15.5 mmol, 1.3 equiv). The reaction mixture was stirred at 23 °C for 2 h, then MeOH was evaporated under reduced pressure. The aqueous layer was washed with Et_2O (10 mL x 1), acidified with 1N HCl (25 mL), and extracted with Et_2O (25 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to a wet residue. The residue was redissolved in CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford carboxylic acid **140b** (2.14 g, 95% yield) as a light yellow viscous oil. R_f = 0.1 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43–2.31 (m, 3H), 2.22 (ddd, *J* = 16.8, 13.2, 5.2 Hz, 1H), 2.06–1.96 (m, 1H), 1.89–1.68 (m, 6H), 1.66–1.56 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.5, 179.7, 48.0, 39.3, 38.8, 32.4, 29.1, 27.5, 22.6, 21.1; IR (Neat Film, NaCl) 2936, 1706, 1455, 1312, 1224, 1124, 1097, 902, 856 cm^{-1}; HRMS (ESI-APCI–) *m/z* calc'd for $C_{10}H_{15}O_3$ $[M-H]^-$: 183.1027, found 183.1034; $[\alpha]_D^{25}$ +36.0 (*c* 4.77, EtOH, 91% ee).

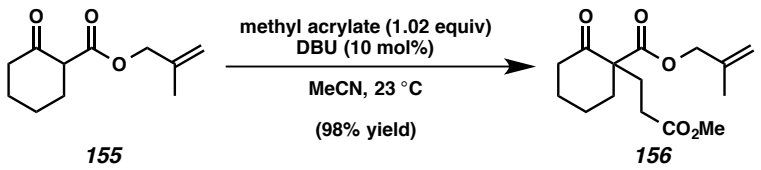


3-(1-Ethyl-2-oxocyclohexyl)propanoic acid (140c). Using 2-ethylcyclohexanone (**153**) as staring material, the procedure for the synthesis of **140b** was followed to provide carboxylic acid **140c** (3.85 g, 85% yield over 3 steps) as a white solid. R_f = 0.1 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45–2.26 (m, 3H), 2.23–2.12 (m, 1H), 1.93–1.58 (m, 9H), 1.54–1.43 (m, 1H), 0.77 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.1, 179.9, 51.1, 39.2, 35.8, 28.9, 28.8, 27.3, 27.2, 20.8, 7.8; IR (Neat Film, NaCl) 2939, 2868, 1704, 1455, 1423, 1312, 1229, 1127, 1091 cm^{-1}; HRMS (ESI-APCI–) *m/z* calc'd for $C_{11}H_{17}O_3$ [M–H]$^-$: 197.1183, found 197.1187.



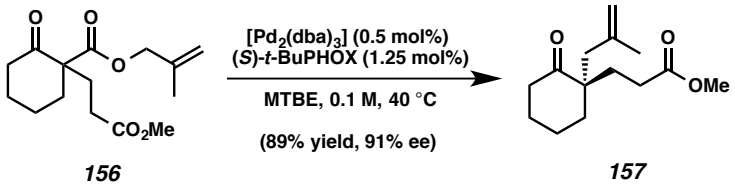
3-(1-Allyl-2-oxocyclohexyl)propanoic acid (140d). Basic hydrolysis of known δ-keto ester **154**[11] (2.24 g, 10.0 mmol, 1.0 equiv) afforded carboxylic acid **140d** (2.04 g, 97% yield) as a viscous colorless oil. R_f = 0.1 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.52 (br s, 1H), 5.64 (dq, *J* = 17.0, 7.7 Hz, 1H), 5.11–5.02 (m, 2H), 2.44–2.28 (m, 4H), 2.28–2.20 (m, 1H), 2.16 (ddd, *J* = 16.4, 11.2, 5.1 Hz, 1H), 1.96 (ddd, *J* = 15.8, 11.2, 5.0 Hz, 1H), 1.88–1.65 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.4, 179.7, 133.1, 118.7, 50.9, 39.2, 39.1, 36.2, 29.5, 28.7, 27.1, 20.8; IR (Neat Film, NaCl) 2937,

2866, 1704, 1419, 1312, 1221, 1126, 995, 917 cm^{-1}; HRMS (ESI-APCI–) *m/z* calc'd for $C_{12}H_{17}O_3$ $[M–H]^-$: 209.1183, found 209.1190.



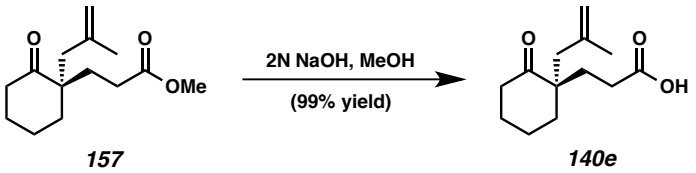
155 *156*

2-Methylallyl 1-(3-methoxy-3-oxopropyl)-2-oxocyclohexane-1-carboxylate (156). A flame-dried 100 mL round-bottom flask was charged with a magnetic stir bar, MeCN (30 mL), β-keto ester **155** (3.32 g, 16.9 mmol, 1.0 equiv), methyl acrylate (1.6 mL, 17.3 mmol, 1.02 equiv), and DBU (0.25 mL, 1.69 mmol, 0.1 equiv). The light yellow reaction mixture was stirred at 23 °C. After 14 h, TLC analysis indicated complete consumption of starting material. Solvents were evaporated, and the crude residue was purified by flash column chromatography on silica gel (8→16% EtOAc in hexanes) to afford ester **156** (4.69 g, 98% yield) as a colorless oil. R_f = 0.4 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (d, *J* = 16.1 Hz, 2H), 4.54 (s, 2H), 3.65 (s, 3H), 2.54–2.34 (m, 4H), 2.30–2.15 (m, 2H), 2.06–1.89 (m, 2H), 1.82–1.74 (m, 1H), 1.73 (s, 3H), 1.71–1.57 (m, 2H), 1.54–1.43 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.4, 173.6, 171.5, 139.2, 114.2, 68.8, 60.2, 51.8, 41.1, 36.4, 29.8, 29.5, 27.6, 22.6, 19.7; IR (Neat Film, NaCl) 2948, 2867, 1738, 1715, 1436, 1307, 1176, 1135, 990, 907 cm^{-1}; HRMS (ESI-APCI+) *m/z* calc'd for $C_{15}H_{23}O_5$ $[M+H]^+$: 283.1540, found 283.1533.



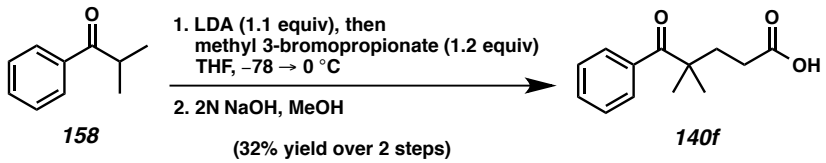
156 ***157***

Methyl (*R*)-3-(1-(2-methylallyl)-2-oxocyclohexyl)propanoate (157). In a nitrogen-filled glove box, a 250 mL Schlenk flask was charged with a magnetic stir bar, $Pd_2(dba)_3$ (32 mg, 0.035 mmol, 0.005 equiv), (*S*)-*t*-BuPHOX (34 mg, 0.0875 mmol, 0.0125 equiv), and MTBE (40 mL). The solution was stirred at ambient temperature for 30 min. Then additional MTBE (21 mL) and **156** (1.98 g, 7.0 mmol, 1.0 equiv) were added via syringe. The syringe was rinsed with MTBE (3 mL x 3) to ensure complete transfer of **156**. The Schlenk flask was sealed and taken out of the glove box. The reaction mixture was stirred at 40 °C for 28 h, then concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (6→10% EtOAc in hexanes) to afford δ-keto ester **157** (1.49 g, 89% yield) as a colorless oil. R_f = 0.5 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (s, 1H), 4.65 (s, 1H), 3.64 (s, 3H), 2.47 (dt, *J* = 14.0, 6.5 Hz, 1H), 2.42–2.27 (m, 4H), 2.15–2.06 (m, 1H), 2.02–1.92 (m, 1H), 1.91–1.65 (m, 7H), 1.64 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.4, 174.2, 141.9, 115.4, 51.8, 51.0, 42.9, 39.4, 36.7, 30.5, 28.9, 27.2, 24.5, 20.9; IR (Neat Film, NaCl) 2943, 2865, 1738, 1699, 1436, 1374, 1173, 1128, 1080, 895 cm^{-1}; HRMS (ESI-APCI+) *m/z* calc'd for $C_{14}H_{23}O_3$ $[M+H]^+$: 239.1642, found 239.1633; $[\alpha]_D^{25}$ +9.0 (*c* 1.00, $CHCl_3$, 91% ee).



157 ***140e***

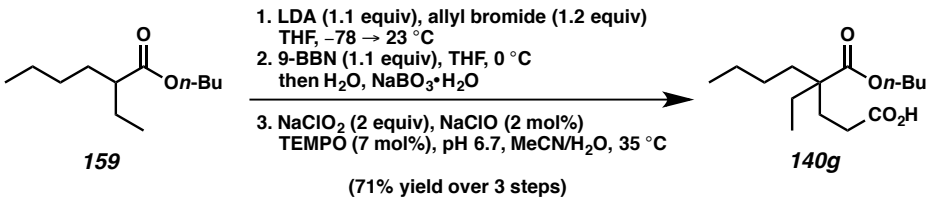
(*R*)-3-(1-(2-Methylallyl)-2-oxocyclohexyl)propanoic acid (140e). Basic hydrolysis of δ-keto ester **157** (1.49 g, 6.25 mmol, 1 equiv) afforded carboxylic acid **140e** (1.39 g, 99% yield) as a white solid. R_f = 0.1 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (s, 1H), 4.64 (s, 1H), 2.54–2.43 (m, 1H), 2.43–2.27 (m, 4H), 2.15 (ddd, *J* = 16.4, 10.8, 5.5 Hz, 1H), 1.96–1.69 (m, 7H), 1.69–1.63 (m, 1H), 1.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.7, 179.9, 141.7, 115.5, 51.0, 43.0, 39.3, 36.7, 30.1, 28.9, 27.1, 24.4, 20.9; IR (Neat Film, NaCl) 3074, 2940, 2866, 1704, 1455, 1312, 1219, 1128, 896 cm^{-1}; HRMS (ESI-APCI–) *m/z* calc'd for $C_{13}H_{19}O_3$ $[M–H]^-$: 223.1340, found 223.1345; $[\alpha]_D^{25}$ +5.4 (*c* 1.00, $CHCl_3$, 91% ee).



158 ***140f***

4,4-Dimethyl-5-oxo-5-phenylpentanoic acid (140f). A flame-dried 100 mL round-bottom flask was charged with a magnetic stir bar, THF (26 mL), and cooled to 0 °C. A solution of *n*-butyllithium in hexanes (2.5 M, 5.7 mL, 14.3 mmol, 1.1 equiv) was added, followed by dropwise addition of diisopropylamine (2.0 mL, 14.3 mmol, 1.1 equiv). The light yellow solution was stirred at 0 °C for 10 min, then cooled to –78 °C in a dry ice-acetone bath. Isobutyrophenone (**158**, 2.0 mL, 13 mmol, 1.0 equiv) was added dropwise. The orange-red solution was stirred at the same temperature for 30 min, and methyl 3-bromopropionate (1.7 mL, 15.6 mmol, 1.2 equiv) was added dropwise. The dry ice-

acetone bath was removed, and the yellow reaction mixture was warmed to 0 °C and stirred for an additional 2 h. The reaction was quenched with half saturated aqueous NH_4Cl solution (30 mL) and extracted with Et_2O (30 mL x 2). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (5% EtOAc in hexanes) to afford a colorless oil (1.20 g), which was subjected to basic hydrolysis to provide carboxylic acid **140f** (0.93 g, 32% yield over 2 steps) as a viscous colorless oil. R_f = 0.1 (25% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (m, 2H), 7.50–7.45 (m, 1H), 7.43–7.37 (m, 2H), 2.36–2.29 (m, 2H), 2.13–2.07 (m, 2H), 1.34 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2, 179.7, 138.6, 131.3, 128.4, 127.8, 47.2, 35.3, 29.9, 26.0; IR (Neat Film, NaCl) 2972, 1709, 1597, 1444, 1303, 1200, 962, 719, 700 cm^{-1}; HRMS (ESI-APCI–) *m/z* calc'd for $C_{13}H_{15}O_3$ $[M–H]^-$: 219.1027, found 219.1035.



4-(Butoxycarbonyl)-4-ethyloctanoic acid (140g). A flame-dried 50 mL round-bottom flask was charged with a magnetic stir bar, THF (10 mL), and cooled to 0 °C. A solution of *n*-butyllithium in hexanes (2.5 M, 2.4 mL, 6.09 mmol, 1.1 equiv) was added, followed by dropwise addition of diisopropylamine (0.93 mL, 6.65 mmol, 1.2 equiv). The light yellow solution was stirred at 0 °C for 10 min, then cooled to –78 °C in a dry ice-acetone bath. Butyl ester **159** (1.11 g, 5.54 mmol, 1.0 equiv) was added dropwise. The solution

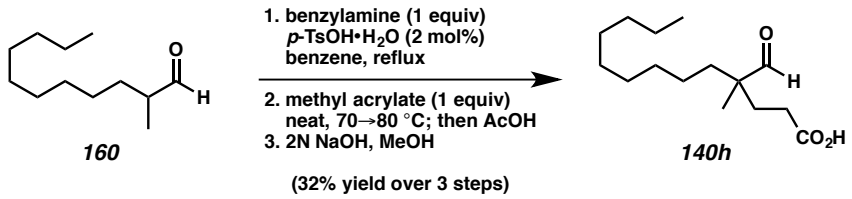
was stirred at the same temperature for 40 min, and allyl bromide (0.58 mL, 6.65 mmol, 1.2 equiv) was added dropwise. After stirring at –78 °C for 1 h, the dry ice-acetone bath was removed, and the yellow reaction mixture was warmed to 23 °C and stirred for an additional 1 h. The reaction was quenched with half saturated aqueous NH_4Cl solution (10 mL) and extracted with hexanes (30 mL x 2). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (3% Et_2O in hexanes) to afford the allylated ester as a colorless oil (1.24 g, R_f = 0.8 (10% Et_2O in hexanes)), which was used directly in the next reaction.

A solution of 9-BBN in THF (0.5 M, 10 mL, 5.0 mmol, 1.1 equiv) was added to a 50 mL round-bottom flask containing the allylated ester (1.24 g, 4.5 mmol, 1.0 equiv) at 0 °C. After 10 min, the ice bath was removed, and the reaction mixture was stirred for another 3 h. Water (10 mL) was added to the reaction mixture, followed by careful portionwise addition of sodium perborate hydrate (1.78 g, 17.8 mmol, 4.0 equiv) to oxidize the organoborane intermediate to the corresponding alcohol. The biphasic mixture was stirred for 40 min, and extracted with EtOAc (25 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (16→25% EtOAc in hexanes) to afford the desired primary alcohol as a colorless oil (1.14 g, R_f = 0.4 (25% EtOAc in hexanes)), which was used directly in the next reaction.

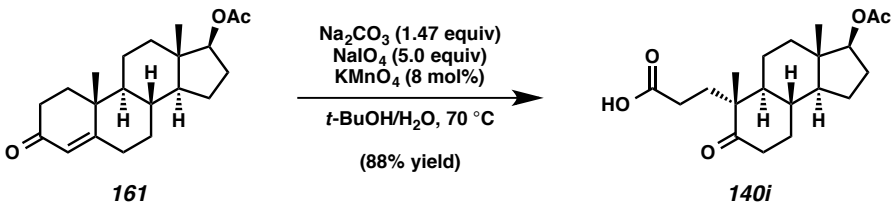
Oxidation of the primary alcohol to the corresponding carboxylic acid was carried out following a literature procedure.[25] A 100 mL round-bottom flask was charged with a magnetic stir bar, the primary alcohol (517 mg, 2.0 mmol, 1.0 equiv), TEMPO (22 mg,

0.14 mmol, 0.07 equiv), MeCN (10 mL), H_2O (2 mL), and aqueous phosphate buffer (0.33 M in NaH_2PO_4 and 0.33 M in Na_2HPO_4, 7.5 mL), and stirred at 20 °C for 5 min. Solid $NaClO_2$ (452 mg, 4.0 mmol, 2.0 equiv) was added to the flask and the reaction mixture was stirred for 2 min when the solid dissolved. A solution of NaClO (0.26 wt%, 1.1 mL, 0.04 mmol, 0.02 equiv) was added, and the reaction mixture immediately turned dark red. The flask was placed in a pre-heated 35 °C oil bath and stirred for 14 h. TLC analysis showed complete consumption of the alcohol. To the reaction mixture was added H_2O (15 mL) and 2N NaOH (4 mL) to bring the solution's pH to 10. The biphasic mixture was poured into an ice-cold solution of Na_2SO_3 (610 mg) in H_2O (10 mL), stirred for 30 min, and extracted with Et_2O (30 mL x 1). The ethereal layer was back-extracted with 0.7N NaOH (8 mL x 2). The alkaline aqueous layers were combined and acidified with 6N HCl (12 mL), and extracted with EtOAc (25 mL x 3). The combined EtOAc extracts were washed with H_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to a liquid/solid mixture. The mixture was dissolved in Et_2O and solid impurities were filtered off. The filtrate was concentrated and purified by flash column chromatography on silica gel (5% MeOH in CH_2Cl_2) to afford carboxylic acid **140g** (485 mg, 71% yield over 3 steps) as a viscous colorless oil. R_f = 0.3 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.27 (br s, 1H), 4.07 (t, *J* = 6.6 Hz, 2H), 2.29–2.19 (m, 2H), 1.95–1.85 (m, 2H), 1.64–1.55 (m, 4H), 1.55–1.49 (m, 2H), 1.43–1.33 (m, 2H), 1.33–1.23 (m, 2H), 1.20–1.05 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.79 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.9, 176.7, 64.4, 48.8, 34.0, 30.8, 29.3, 28.6, 27.2, 26.2, 23.3, 19.3, 14.1, 13.8, 8.4; IR (Neat Film, NaCl) 2961, 2875, 1716,

1458, 1207, 1133, 947 cm^{-1}; HRMS (ESI-APCI–) *m/z* calc'd for $C_{15}H_{27}O_4$ $[M–H]^-$: 271.1915, found 271.1923.



4-Formyl-4-methyltridecanoic acid (140h). Using 2-methylundecanal (**160**) as staring material, the procedure for the synthesis of **140b** was followed (Note: the conjugate addition reaction was allowed to proceed for 20 h at 70 °C and then 28 h at 80 °C) to provide carboxylic acid **140h** (481 mg, 32% yield over 3 steps) as a colorless oil. R_f = 0.2 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.35 (br s, 1H), 9.41 (s, 1H), 2.34–2.19 (m, 2H), 1.93–1.83 (m, 1H), 1.82–1.72 (m, 1H), 1.53–1.37 (m, 2H), 1.33–1.09 (m, 14H), 1.02 (s, 3H), 0.86 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.9, 179.7, 48.5, 35.6, 32.0, 30.3, 29.6, 29.5, 29.4, 29.4, 29.1, 23.9, 22.8, 18.2, 14.2; IR (Neat Film, NaCl) 2924, 2853, 1711, 1458, 1300, 1225, 913 cm^{-1}; HRMS (ESI-APCI–) *m/z* calc'd for $C_{15}H_{27}O_3$ $[M–H]^-$: 255.1966, found 255.1976.

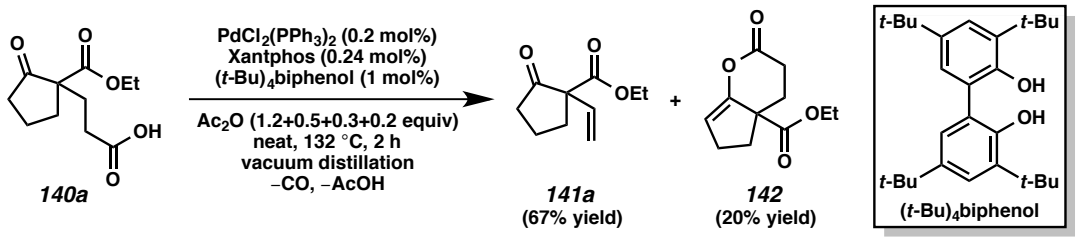


3-((3*S*,3a*S*,5a*S*,6*R*,9a*S*,9b*S*)-3-Acetoxy-3a,6-dimethyl-7-oxododecahydro-1*H*-cyclopenta[*a*]naphthalen-6-yl)propanoic acid (140i). Carboxylic acid **140i** was prepared based on a literature procedure.[26] A 250 mL round-bottom flask was charged

with a magnetic stir bar, testosterone acetate **161** (661 mg, 2.0 mmol, 1.0 equiv), Na_2CO_3 (312 mg, 2.94 mmol, 1.47 equiv), *t*-BuOH (21 mL) and H_2O (1 mL). The flask was placed in a pre-heated 70 °C oil bath, and a hot solution of $NaIO_4$ (2.14 g, 10.0 mmol, 5.0 equiv) and $KMnO_4$ (25 mg, 0.16 mmol, 0.08 equiv) in H_2O (21 mL) was added. The reaction mixture was stirred at 70 °C for 20 min when TLC analysis indicated complete consumption of starting material. The flask was cooled to ambient temperature, and 1N HCl (100 mL) was added. After stirring 2 min, the reaction mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (50% EtOAc in hexanes) to afford carboxylic acid **140i** (664 mg, 88% yield) as a solid/liquid mixture, which was recrystallized from hexanes:EtOAc 2:1 to give a white solid. R_f = 0.4 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (t, *J* = 8.5 Hz, 1H), 2.63–2.44 (m, 1H), 2.40–2.14 (m, 4H), 2.14–2.06 (m, 1H), 2.04 (s, 3H), 1.99–1.89 (m, 1H), 1.85–1.30 (m, 8H), 1.29–1.14 (m, 3H), 1.12 (s, 3H), 1.10–1.02 (m, 1H), 0.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.6, 179.6, 171.3, 82.5, 50.5, 50.2, 48.0, 42.7, 38.0, 36.4, 34.8, 30.9, 29.3, 29.2, 27.5, 23.7, 21.3, 21.1, 20.5, 12.2; IR (Neat Film, NaCl) 2941, 1732, 1705, 1448, 1375, 1248, 1043, 952, 735 cm^{-1}; HRMS (ESI-APCI–) *m/z* calc'd for $C_{20}H_{29}O_5$ $[M–H]^-$: 349.2020, found 349.2037.

5.5.3 Palladium-Catalyzed Decarbonylative Dehydration of Carboxylic Acids

General Procedure A: Large Scale Distillation Process



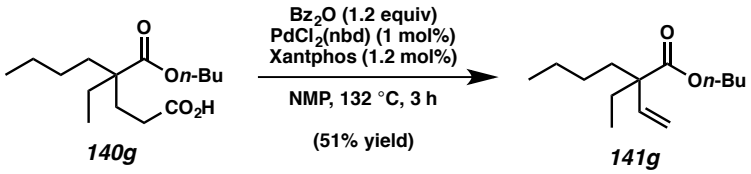
Ethyl 2-oxo-1-vinylcyclopentane-1-carboxylate (141a). A flame-dried 15 mL round-bottom flask was charged with a magnetic stir bar, $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol, 0.002 equiv), Xantphos (6.9 mg, 0.012 mmol, 0.0024 equiv), (*t*-Bu)$_4$biphenol[27] (20.5 mg, 0.05 mmol, 0.01 equiv), and carboxylic acid **140a** (1.14 g, 5.0 mmol, 1.0 equiv). The flask was equipped with a distillation head and a 25 mL round-bottom receiving flask. The closed system was connected to a vacuum manifold and equipped with a needle valve. The system was evacuated and backfilled with N_2 (x 3), and the first portion of acetic anhydride (6.0 mmol, 1.2 equiv) was added via syringe through the septum that seals the top of the distillation head. The flask was lowered into a pre-heated 60 °C oil bath and gradually heated to 132 °C in 18 min. When the oil bath temperature reached 122 °C, the needle valve was closed, switched to vacuum, and the needle valve carefully and slowly opened to allow distillation of acetic acid into a receiving flask, which was cooled to –78 °C. When the oil bath temperature reached 130 °C, time was recorded as t = 0. After distillation ceased (about t = 3 min), the needle valve was opened fully and a vacuum of 1–5 mmHg was drawn. At t = 30 min, the system was backfilled with N_2, and the second portion of acetic anhydride (2.5 mmol, 0.5 equiv) was added via syringe. The system was then gradually (t = 35 min) resubjected to a vacuum of 1–5 mmHg. Acetic anhydride was added as follows (0.3, 0.2 equiv) in the same manner every 30 min. The

reaction was stopped at t = 2 h and allowed to cool under N_2 to ambient temperature. The distillate was added to a saturated aqueous solution of $NaHCO_3$, stirred for 20 min, and the biphasic mixture was extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were dried over Na_2SO_4 and filtered into a 250 round-bottom flask. To this filtrate were added the residual dark red reaction mixture and the washings of the distillation head's inside (with ~5 mL CH_2Cl_2). The solvents were evaporated and the residue was purified by flash column chromatography on silica gel (5→8% EtOAc in hexanes for **141a** and then 16% EtOAc in hexanes for **142**) to afford vinyl ketone **141a** (613 mg, 67% yield) as a colorless, fragrant oil. R_f = 0.5 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 17.6, 10.7 Hz, 1H), 5.28 (d, *J* = 10.7 Hz, 1H), 5.19 (d, *J* = 17.6 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.63–2.55 (m, 1H), 2.45–2.27 (m, 2H), 2.23–2.15 (m, 1H), 2.07–1.87 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.5, 170.4, 134.5, 117.0, 63.5, 61.9, 37.7, 32.9, 19.6, 14.2; IR (Neat Film, NaCl) 2980, 1753, 1729, 1635, 1456, 1406, 1255, 1142, 1034, 927 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{14}O_3$ $[M]^+$: 182.0943, found 182.0939.

Ethyl 2-oxo-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-4a(2*H*)-carboxylate (142). The above reaction also furnished enol lactone **142** (206 mg, 20% yield) as a colorless oil. R_f = 0.2 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (app. s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.76–2.62 (m, 2H), 2.55–2.42 (m, 3H), 2.35–2.26 (m, 1H), 1.96–1.84 (m, 1H), 1.84–1.73 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 167.4, 151.6, 108.0, 61.8, 50.8, 35.9, 29.5, 28.1, 26.7, 14.2; IR (Neat Film, NaCl)

2940, 2862, 1768, 1726, 1668, 1456, 1248, 1159, 1124, 1020, 891, 805 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{14}O_4$ $[M]^+$: 210.0892, found 210.0910.

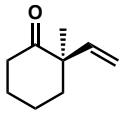
General Procedure B: Small Scale Nondistillation Process



Butyl 2-ethyl-2-vinylhexanoate (141g). A flame-dried 20 x 150 mm Kimax culture tube was charged with a magnetic stir bar, $PdCl_2$(nbd) (1.3 mg, 0.005 mmol, 0.01 equiv), Xantphos (3.5 mg, 0.006 mmol, 0.012 equiv), carboxylic acid **140g** (136 mg, 0.5 mmol, 1.0 equiv), and benzoic anhydride (136 mg, 0.6 mmol, 1.2 equiv). The tube was sealed with a rubber septum, and the system was evacuated and backfilled with N_2 (x 3). NMP (0.25 mL) was added via syringe. The reaction mixture was stirred at 20 °C for 2 min, then placed in a pre-heated 132 °C oil bath and stirred for 3 h. After cooling to ambient temperature, Et_3N (0.3 mL) was added, and the mixture was purified by flash column chromatography on silica gel (2% Et_2O in hexanes) to afford vinyl ester **141g** (58 mg, 51% yield) as a colorless oil. R_f = 0.5 (10% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (dd, *J* = 17.8, 10.9 Hz, 1H), 5.17 (d, *J* = 11.0 Hz, 1H), 5.07 (d, *J* = 17.8 Hz, 1H), 4.08 (t, *J* = 6.6 Hz, 2H), 1.77–1.69 (m, 2H), 1.69–1.63 (m, 2H), 1.63–1.55 (m, 2H), 1.45–1.23 (m, 4H), 1.23–1.08 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 140.3, 114.3, 64.5, 52.9, 35.7, 30.9, 29.0, 26.7, 23.4, 19.4, 14.1, 13.8, 8.9; IR (Neat Film, NaCl) 2960, 2874,

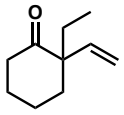
1731, 1459, 1380, 1240, 1206, 1136, 1001, 915 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{26}O_2$ $[M]^+$: 226.1933, found 226.1933.

5.5.4 Spectroscopic Data for Pd-Catalyzed Decarbonylative Dehydration Products



ent-139

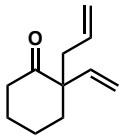
(*R*)-2-Methyl-2-vinylcyclohexan-1-one (*ent*-139). Ketone *ent*-**139** was prepared according to General Procedure A and isolated by silica gel chromatography (3% Et_2O in hexanes) as a colorless, fragrant oil. 60% yield. R_f = 0.6 (20% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (dd, *J* = 17.8, 10.8 Hz, 1H), 5.13 (d, *J* = 10.8 Hz, 1H), 4.98 (d, *J* = 17.7 Hz, 1H), 2.56–2.45 (m, 1H), 2.37–2.28 (m, 1H), 2.01–1.90 (m, 2H), 1.84–1.65 (m, 3H), 1.65–1.56 (m, 1H), 1.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.6, 142.7, 114.9, 52.2, 39.9, 39.3, 27.8, 24.0, 21.8; IR (Neat Film, NaCl) 2932, 2864, 1709, 1635, 1450, 1371, 1313, 1123, 1093, 986, 918 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_9H_{14}O$ $[M]^+$: 138.1045, found 138.1026; $[\alpha]_D^{25}$ +113.2 (*c* 1.03, $CHCl_3$, 92% ee).



141c

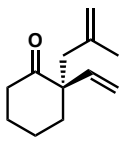
2-Ethyl-2-vinylcyclohexan-1-one (141c). Ketone **141c** was prepared according to General Procedure A and isolated by silica gel chromatography (2% Et_2O in hexanes) as a colorless, fragrant oil. 66% yield. R_f = 0.4 (10% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.90 (dd, *J* = 17.8, 10.9 Hz, 1H), 5.19 (d, *J* = 10.9 Hz, 1H), 4.96 (d, *J* =

17.7 Hz, 1H), 2.52–2.41 (m, 1H), 2.36–2.27 (m, 1H), 1.98–1.83 (m, 2H), 1.80–1.53 (m, 6H), 0.79 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.3, 141.5, 115.5, 55.5, 39.6, 35.6, 29.8, 27.4, 21.6, 8.2; IR (Neat Film, NaCl) 2938, 2863, 1707, 1448, 1313, 1230, 1124, 993, 918 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{10}H_{16}O$ $[M]^+$: 152.1201, found 152.1176.



141d

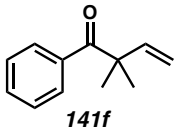
2-Allyl-2-vinylcyclohexan-1-one (141d). Ketone **141d** was prepared according to General Procedure A and isolated by silica gel chromatography (3% Et_2O in hexanes) as a colorless, fragrant oil. 54% yield. R_f = 0.4 (10% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dd, J = 17.7, 10.8 Hz, 1H), 5.68 (ddt, J = 18.0, 11.1, 7.3 Hz, 1H), 5.22 (d, J = 10.8 Hz, 1H), 5.05–4.95 (m, 3H), 2.54–2.45 (m, 1H), 2.42–2.27 (m, 3H), 1.99–1.88 (m, 2H), 1.81–1.60 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.7, 141.4, 134.3, 117.9, 116.2, 54.9, 42.0, 39.6, 36.0, 27.3, 21.6; IR (Neat Film, NaCl) 3077, 2936, 2864, 1708, 1636, 1448, 1314, 1222, 1124, 998, 916 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{16}O$ $[M]^+$: 164.1201, found 164.1173.



141e

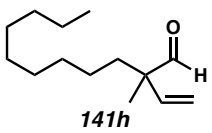
(*S*)-2-(2-Methylallyl)-2-vinylcyclohexan-1-one (141e). Ketone **141e** was prepared according to General Procedure A and isolated by silica gel chromatography (2→3%

Et_2O in hexanes) as a colorless, fragrant oil. 69% yield. R_f = 0.4 (10% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.94 (dd, *J* = 18.1, 11.1 Hz, 1H), 5.19 (d, *J* = 10.8 Hz, 1H), 4.98 (d, *J* = 17.8 Hz, 1H), 4.80 (s, 1H), 4.65 (s, 1H), 2.55–2.43 (m, 2H), 2.43–2.32 (m, 2H), 2.01–1.87 (m, 2H), 1.79–1.66 (m, 4H), 1.65 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.3, 142.5, 142.4, 115.8, 115.0, 54.8, 45.5, 39.5, 36.0, 27.1, 25.0, 21.7; IR (Neat Film, NaCl) 3075, 2938, 2863, 1707, 1641, 1448, 1125, 919, 892 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{18}O$ $[M]^+$: 178.1358, found 178.1350; $[\alpha]_D^{25}$ +129.5 (*c* 1.00, $CHCl_3$, 92% ee).



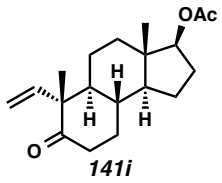
141f

2,2-Dimethyl-1-phenylbut-3-en-1-one (141f). Ketone **141f** was prepared according to General Procedure A and isolated by silica gel chromatography (2.5% Et_2O in hexanes) as a colorless oil. 75% yield. R_f = 0.4 (10% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.89–7.85 (m, 2H), 7.49–7.43 (m, 1H), 7.40–7.35 (m, 2H), 6.19 (dd, *J* = 17.6, 10.6 Hz, 1H), 5.26–5.18 (m, 2H), 1.40 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8, 144.0, 137.2, 131.8, 129.4, 128.1, 114.2, 50.3, 26.2; IR (Neat Film, NaCl) 3084, 2975, 2933, 1679, 1634, 1446, 1258, 971, 918, 719, 694 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{14}O$ $[M]^+$: 174.1045, found 174.1069.



141h

2-Methyl-2-vinylundecanal (141h). Aldehyde **141h** was prepared according to General Procedure B and isolated by silica gel chromatography (2% Et_2O in hexanes) as a colorless, fragrant oil. 77% yield. R_f = 0.5 (10% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 5.79 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.25 (d, *J* = 10.8 Hz, 1H), 5.11 (d, *J* = 17.5 Hz, 1H), 1.57 (td, *J* = 9.6, 5.9 Hz, 2H), 1.25 (br s, 14H), 1.15 (s, 3H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.2, 139.1, 116.6, 52.9, 35.7, 32.0, 30.3, 29.7, 29.6, 29.4, 24.0, 22.8, 17.8, 14.3; IR (Neat Film, NaCl) 2927, 2854, 1732, 1463, 998, 920 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{26}O$ $[M]^+$: 210.1984, found 210.2009.

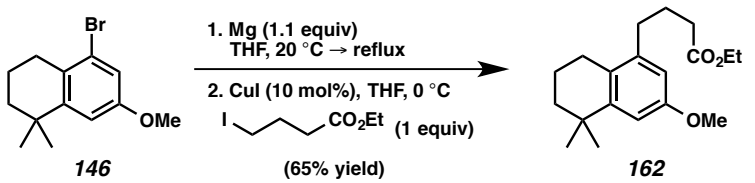


141i

(3*S*,3a*S*,5a*S*,6*R*,9a*S*,9b*S*)-3a,6-dimethyl-7-oxo-6-vinyldodecahydro-1*H*-cyclopenta[*a*]naphthalen-3-yl acetate (141i). Ketone **141i** was prepared according to General Procedure B and isolated by silica gel chromatography (10→14% EtOAc in hexanes) as a white solid. 41% yield. R_f = 0.3 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.24 (d, *J* = 10.9 Hz, 1H), 5.02 (d, *J* = 17.6 Hz, 1H), 4.59 (t, *J* = 8.5 Hz, 1H), 2.61 (td, *J* = 14.3, 6.3 Hz, 1H), 2.37–2.30 (m, 1H), 2.24–2.14 (m, 1H), 2.03 (s, 3H), 2.02–1.95 (m, 1H), 1.83–1.62 (m, 3H), 1.58–1.47 (m, 1H), 1.45–1.33 (m, 3H), 1.32–1.25 (m, 2H), 1.24 (s, 3H), 1.18–1.05 (m, 2H), 0.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.3, 171.2, 141.7, 114.7, 82.4, 54.6, 51.0, 50.4, 43.0, 38.0, 36.4, 34.8, 31.2, 27.6, 23.6, 21.9, 21.3, 15.2, 12.3; IR (Neat Film, NaCl) 2946,

2845, 1735, 1696, 1373, 1250, 1041, 922 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{28}O_3$ $[M]^+$: 304.2039, found 304.2044.

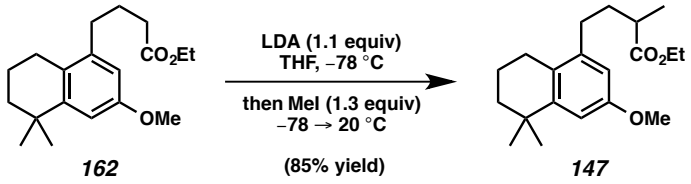
5.5.5 Total Synthesis of (–)-Aspewentin B and Related Compounds



146 (65% yield) ***162***

Ester 162. A 100 mL 2-necked round-bottom flask was charged with a magnetic stir bar and magnesium turnings (560 mg, 23.0 mmol, 1.1 equiv). The flask was equipped with a reflux condenser, flame-dried under vacuum, and allowed to cool to ambient temperature under N_2. THF (3 mL) was added, followed by a small portion (2 mL) of a solution of bromoarene **146**[18] (5.63 g, 20.9 mmol, 1.0 equiv) in THF (8.5 mL). DIBAL-H (0.4 mL, 1.0 M in hexanes, 0.4 mmol, 0.02 equiv) was added, and the reaction mixture was gently heated to reflux using a heat gun. Grignard reagent formation initiated as the reaction mixture turned dark with a strong exotherm. The remainder of the bromoarene solution in THF (ca. 6.5 mL) was added dropwise to maintain a gentle reflux. After addition was finished, the reaction mixture was further refluxed for 1 h, and allowed to cool to ambient temperature under N_2. The dark gray solution of Grignard reagent was taken up in a syringe and added dropwise to a separate 100 mL round-bottom flask containing a stirred suspension of CuI (400 mg, 2.09 mmol, 0.1 equiv) and ethyl 4-iodobutyrate (5.06 g, 20.9 mmol, 1.0 equiv) in THF (20 mL) at 0 °C. After 15 min, the reaction mixture was warmed to 20 °C and quenched with aqueous NH_4Cl and $NaHSO_4$ solution. The layers were separated, and the aqueous layer was extracted with EtOAc (30 mL x 3). The

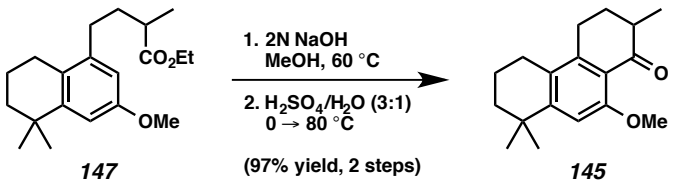
combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel (3→4→10% EtOAc in hexanes) furnished ester **162** (4.16 g, 65% yield) as a colorless oil. R_f = 0.5 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.56 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 2.62 (t, *J* = 6.4 Hz, 2H), 2.60–2.55 (m, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 1.95–1.85 (m, 2H), 1.84–1.76 (m, 2H), 1.66–1.60 (m, 2H), 1.30–1.25 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 157.3, 147.6, 140.7, 126.6, 112.1, 110.2, 60.4, 55.3, 39.0, 34.5, 34.3, 32.9, 32.2, 26.6, 25.3, 19.8, 14.4; IR (Neat Film, NaCl) 2930, 1734, 1603, 1465, 1304, 1254, 1188, 1116, 1065, 847 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{19}H_{29}O_3$ $[M+H]^+$: 305.2111, found 305.2105.



162 *147*

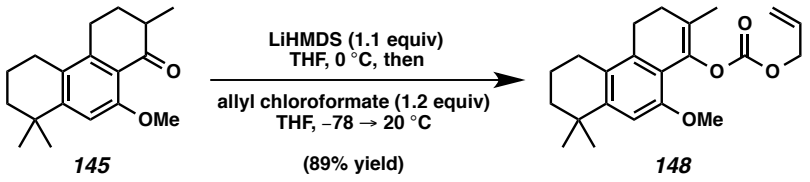
Ester 147. To a stirred solution of *n*-BuLi (3.2 mL, 2.5 M in hexanes, 8.10 mmol, 1.1 equiv) in THF (12 mL) was added *i*-Pr_2NH (1.2 mL, 8.83 mmol, 1.2 equiv) dropwise at 0 °C. The light yellow solution was stirred for 5 min, then cooled to –78 °C in a dry ice-acetone bath. A solution of ester **162** (2.24 g, 7.36 mmol, 1.0 equiv) in THF (6 mL) was added dropwise, followed by washings of the syringe (THF, 1 mL x 2). The reaction mixture was stirred at –78 °C for 15 min, and iodomethane (0.60 mL, 9.57 mmol, 1.3 equiv) was added dropwise. After stirring at –78 °C for another 45 min, the reaction mixture was allowed to warm to 20 °C, and quenched with aqueous 1N HCl (ca. 30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (30 mL x 3).

The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel (2.5→3% EtOAc in hexanes) furnished ester **147** (1.99 g, 85% yield) as a colorless oil. R_f = 0.6 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.56 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.61 (t, *J* = 6.5 Hz, 2H), 2.58–2.48 (m, 3H), 1.98–1.88 (m, 1H), 1.84–1.75 (m, 2H), 1.71–1.58 (m, 3H), 1.30–1.26 (m, 9H), 1.22 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7, 157.4, 147.6, 141.0, 126.5, 112.0, 110.2, 60.4, 55.3, 39.8, 39.0, 34.6, 34.3, 32.2, 32.2, 31.3, 26.6, 19.8, 17.4, 14.5; IR (Neat Film, NaCl) 2935, 1732, 1605, 1467, 1304, 1255, 1156, 1126, 1053, 864 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{20}H_{30}O_3$ $[M]^+$: 318.2195, found 318.2202.



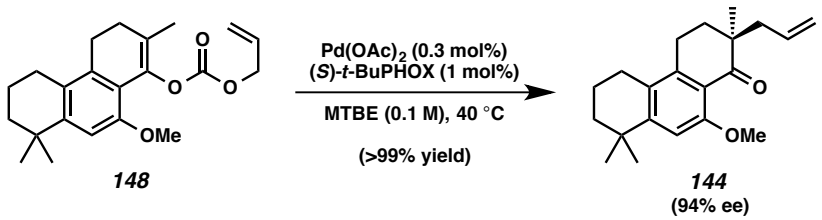
Ketone 145. To a 50 mL round-bottom flask containing ester **147** (1.96 g, 6.16 mmol, 1.0 equiv) was added a magnetic stir bar, MeOH (9 mL), and aqueous 2N NaOH (4.6 mL, 9.24 mmol, 1.5 equiv). The reaction mixture was stirred at 60 °C for 4 h and cooled to ambient temperature. Most of the MeOH was evaporated under reduced pressure, and the alkaline solution was acidified with 1N NCl (15 mL) and extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to the crude carboxylic acid as a colorless oil, which was used immediately for the next reaction.

The crude carboxylic acid was added dropwise to a mixture of conc. H_2SO_4 and H_2O (28 mL total, 3:1 v/v) at 0 °C via pipette. Washings of the pipette (Et_2O, 2 mL x 3) were also added. The cooling bath was removed, and the reaction mixture was stirred for 15 min, and then placed in a pre-heated 80 °C oil bath. After 20 min, the reaction mixture was allowed to cool to ambient temperature, diluted with ice water (ca. 90 mL), and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel (2.5→3% Et_2O in CH_2Cl_2) furnished ketone **145** (1.64 g, 97% yield over 2 steps) as a white solid. R_f = 0.7 (10% Et_2O in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H), 3.87 (s, 3H), 2.85 (dt, *J* = 17.6, 4.0 Hz, 1H), 2.72 (ddd, *J* = 17.0, 11.0, 5.2 Hz, 1H), 2.60–2.47 (m, 3H), 2.20–2.10 (m, 1H), 1.91–1.71 (m, 3H), 1.69–1.57 (m, 2H), 1.30 (s, 6H), 1.19 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.7, 158.0, 152.2, 144.3, 126.3, 120.9, 108.4, 56.1, 56.1, 43.1, 38.4, 31.7, 31.7, 30.7, 27.1, 26.8, 19.4, 15.5; IR (Neat Film, NaCl) 2928, 1685, 1591, 1559, 1457, 1317, 1246, 1102, 1012 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{18}H_{25}O_2$ $[M+H]^+$: 273.1849, found 273.1855.



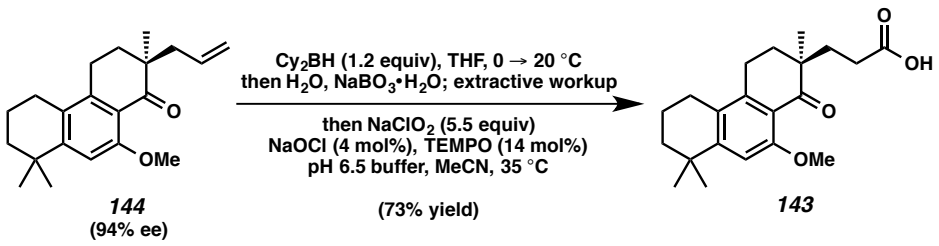
Allyl enol carbonate 148. To a stirred solution of LiHMDS (1.11 g, 6.61 mmol, 1.1 equiv) in THF (10 mL) at 0 °C was added a solution of ketone **145** (1.64 g, 6.01 mmol, 1.0 equiv) in THF (5 mL) via syringe. Washings of the syringe (THF, 1.5 mL x 2) were also added. The deep red solution was stirred at 0 °C for 1 h. In a separate, flame-dried

200 mL round-bottom flask, THF (34 mL) and allyl chloroformate (0.77 mL, 7.21 mmol, 1.2 equiv) were added, and the solution was cooled to –78 °C in a dry ice-acetone bath. To this cooled solution was added the deep red enolate solution dropwise via cannula (ca. 15 min addition time). The reaction mixture was stirred at –78 °C for another 15 min, and the cold bath was removed. After warming to room temperature, the reaction was quenched with half saturated NH_4Cl solution (ca. 50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel (3→5% EtOAc in hexanes) furnished allyl enol carbonate **148** (1.91 g, 89% yield) as a white solid. R_f = 0.6 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.06–5.96 (m, 1H), 5.41 (d, *J* = 17.1 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 4.70 (d, *J* = 5.8 Hz, 2H), 3.75 (s, 3H), 2.67 (t, *J* = 8.0 Hz, 2H), 2.56 (t, *J* = 6.5 Hz, 2H), 2.27 (t, *J* = 8.0 Hz, 2H), 1.85 (s, 3H), 1.83–1.76 (m, 2H), 1.64–1.58 (m, 2H), 1.27 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 152.8, 146.3, 140.3, 136.1, 132.0, 126.0, 123.5, 118.8, 117.2, 109.1, 68.7, 56.4, 38.7, 34.4, 31.9, 28.7, 27.5, 24.2, 19.7, 16.4; IR (Neat Film, NaCl) 2929, 1762, 1670, 1592, 1465, 1363, 1247, 1107, 1046 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{22}H_{28}O_4$ $[M]^+$: 356.1988, found 356.1979.



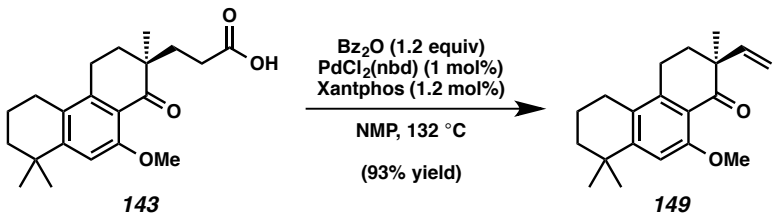
α-Allyl ketone 144. In a nitrogen-filled glove box, a 100 mL Schlenk flask was charged with $Pd(OAc)_2$ (2.7 mg, 0.012 mmol, 0.003 equiv), (*S*)-*t*-BuPHOX (15.5 mg, 0.0399

mmol, 0.01 equiv), and MTBE (15 mL). The solution was stirred at ambient temperature for 30 min. Another portion of MTBE (15 mL) was added, and then allyl enol carbonate **148** (1.42 g, 3.99 mmol, 1.0 equiv) was added as a solid to the reaction mixture. Washings of the vial containing **148** (MTBE, 2.5 mL x 4) were also added. The Schlenk flask was sealed with a Kontes valve, brought out of the glove box, and placed in a pre-heated 40 °C oil bath. The reaction mixture was stirred at this temperature for 17 h, at which time TLC analysis indicated complete conversion of starting material. Evaporation of solvent and flash column chromatography on silica gel (10% EtOAc in hexanes) afforded α-allyl ketone **144** (1.24 g, >99% yield) as a viscous colorless oil. R_f = 0.4 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H), 5.86–5.75 (m, 1H), 5.08–5.00 (m, 2H), 3.87 (s, 3H), 2.80–2.66 (m, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.37 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.28 (dd, *J* = 13.9, 7.3 Hz, 1H), 1.98 (dt, *J* = 13.2, 6.4 Hz, 1H), 1.88–1.78 (m, 3H), 1.69–1.60 (m, 2H), 1.30 (s, 3H), 1.29 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.1, 158.7, 152.2, 143.7, 134.7, 126.1, 119.8, 117.9, 108.6, 56.1, 45.1, 41.4, 38.4, 34.9, 32.9, 31.7, 31.7, 27.0, 23.6, 21.9, 19.5; IR (Neat Film, NaCl) 2928, 1684, 1591, 1559, 1457, 1318, 1245, 1104, 1016, 913 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{29}O_2$ $[M+H]^+$: 313.2162, found 313.2158; $[\alpha]_D^{25}$ –13.1 (*c* 1.00, $CHCl_3$, 94% ee).



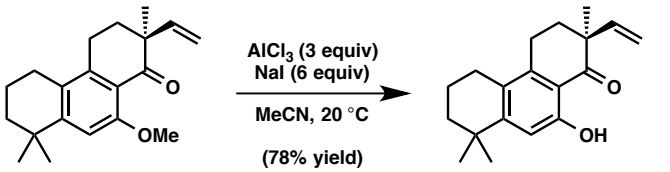
Carboxylic acid 143. A flame-dried 25 mL round-bottom flask was charged with a magnetic stir bar, $BH_3 \cdot SMe_2$ (0.6 mL, 2.0 M in THF, 1.2 mmol, 1.2 equiv), and THF (0.5 mL). The solution was cooled to 0 °C in an ice bath, and cyclohexene (0.23 mL, 2.3 mmol, 2.3 equiv) was added. After stirring at 0 °C for 1 h, a solution of α-allyl ketone **144** (312 mg, 1.0 mmol, 1.0 equiv) in THF (0.6 mL) was added. The vial containing **144** was washed with THF (0.6 mL x 2) and the washings were also added. The white slurry soon turned into a light yellow and clear solution (ca. 5 min). The ice bath was removed, and the solution was stirred at 20 °C for 12 h. TLC analysis then indicated almost complete consumption of starting material. To the solution was added H_2O (1 mL) and $NaBO_3 \cdot H_2O$ (350 mg). Additional H_2O (10 mL) was added to break up the white solid formed in the mixture. The aqueous phase was extracted with EtOAc (15 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and quantitatively transferred to a 50 mL round-bottom flask. To this flask was added a magnetic stir bar, TEMPO (22 mg, 0.14 mmol, 0.14 equiv), MeCN (5 mL), H_2O (2.6 mL), and aqueous phosphate buffer (0.33 M in NaH_2PO_4 and 0.33 M in Na_2HPO_4, 4 mL), and stirred at 20 °C for 5 min. Solid $NaClO_2$ (622 mg, 5.5 equiv) was added to the flask and the reaction mixture was stirred for 2 min when the solid dissolved. A solution of NaClO (0.26 wt%, 1.2 mL, 0.04 mmol, 0.04 equiv) was added, and the reaction mixture immediately turned dark red. The flask was placed in a pre-heated 35 °C oil bath and stirred for 53 h. TLC analysis showed complete consumption of the alcohol. After cooling to 23 °C, 2N NaOH (5 mL) was added, followed by a solution of Na_2SO_3 (0.88 g) in H_2O (6 mL). The mixture was stirred vigorously for 30 min, and extracted with Et_2O (30 mL x 1). The ethereal layer was discarded. The alkaline aqueous layer was acidified

with 8N HCl (ca. 3 mL), and extracted with EtOAc (30 mL x 1). The EtOAc layer was washed with 1N HCl (10 mL) and H_2O (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford carboxylic acid **143** (252 mg, 73% yield) as a viscous light brown oil. Recrystallization from hexanes/EtOAc gave pure **143** as white crystals. R_f = 0.4 (67% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1H), 3.85 (s, 3H), 2.82–2.68 (m, 2H), 2.51 (t, *J* = 6.5 Hz, 2H), 2.44 (dt, *J* = 16.5, 8.1 Hz, 1H), 2.34 (dt, *J* = 16.5, 8.2 Hz, 1H), 1.98 (dt, *J* = 13.1, 6.3 Hz, 1H), 1.94–1.79 (m, 5H), 1.66–1.60 (m, 2H), 1.30 (s, 3H), 1.29 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8, 179.5, 158.6, 152.5, 143.4, 126.2, 119.5, 108.6, 56.0, 44.5, 38.4, 34.9, 33.5, 31.7, 31.7, 31.6, 29.4, 27.0, 23.6, 21.9, 19.4; IR (Neat Film, NaCl) 2931, 1708, 1674, 1591, 1558, 1460, 1318, 1245, 1227, 1103, 913, 731 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{29}O_4$ $[M+H]^+$: 345.2060, found 345.2047; $[\alpha]_D^{25}$ –1.5 (*c* 1.00, $CHCl_3$).



α-Vinyl ketone 149. Following General Procedure B, palladium-catalyzed decarbonylative dehydration of carboxylic acid **143** (172 mg, 0.5 mmol, 1.0 equiv) and flash column chromatography on silica gel (7→10% EtOAc in hexanes) furnished α-vinyl ketone **149** (140 mg, 93% yield) as a colorless oil. R_f = 0.3 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.01 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.08–4.98 (m, 2H), 3.86 (s, 3H), 2.81–2.68 (m, 2H), 2.58–2.43 (m, 2H), 2.08 (dt, *J* =

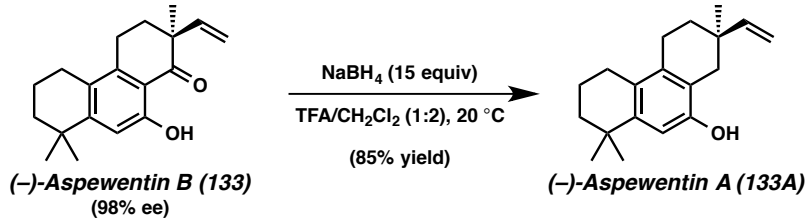
13.8, 5.1 Hz, 1H), 2.00–1.90 (m, 1H), 1.89–1.73 (m, 2H), 1.68–1.55 (m, 2H), 1.28 (s, 6H), 1.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.9, 158.5, 152.3, 143.7, 141.1, 126.0, 120.2, 114.4, 108.5, 56.1, 49.0, 38.4, 34.9, 34.5, 31.7, 31.6, 27.0, 24.0, 23.4, 19.4; IR (Neat Film, NaCl) 2928, 1684, 1591, 1559, 1458, 1318, 1245, 1105, 1020, 915 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{27}O_2$ $[M+H]^+$: 299.2006, found 299.1992; $[\alpha]_D^{25}$ –43.2 (*c* 1.00, $CHCl_3$).



149 ***(–)-Aspewentin B (133)*** **(98% ee)**

(–)-Aspewentin B (133). A 50 mL round-bottom flask was charged with a magnetic stir bar, NaI (329 mg, 2.20 mmol, 6.0 equiv), $AlCl_3$ (146 mg, 1.10 mmol, 3.0 equiv), and MeCN (4 mL) in air. To this slurry was added a solution of α-vinyl ketone **149** (109 mg, 0.37 mmol, 1.0 equiv) in MeCN (6 mL). The reaction mixture immediately turned yellow-orange. After stirring for 5 min, the reaction was quenched with 1N HCl (30 mL) and extracted with CH_2Cl_2 (10 mL x 4). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel (2.5% Et_2O in hexanes) furnished (–)-aspewentin B (**133**, 82 mg, 78% yield) as a light yellow oil. R_f = 0.7 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.40 (s, 1H), 6.84 (s, 1H), 5.98 (dd, *J* = 17.7, 10.8 Hz, 1H), 5.13 (d, *J* = 10.7 Hz, 1H), 5.03 (d, *J* = 17.6 Hz, 1H), 2.81–2.69 (m, 2H), 2.59–2.44 (m, 2H), 2.14–2.06 (m, 1H), 2.04–1.94 (m, 1H), 1.88–1.73 (m, 2H), 1.68–1.55 (m, 2H), 1.33 (s, 3H), 1.27 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.2, 160.9, 156.1, 142.3, 140.5, 124.7, 115.1, 114.6, 113.3,

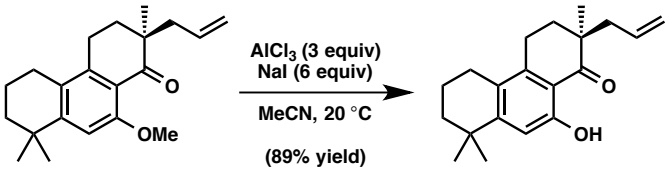
47.9, 38.3, 35.0, 34.4, 31.7, 31.6, 26.9, 23.4, 23.3, 19.4; IR (Neat Film, NaCl) 2929, 1635, 1464, 1358, 1222, 1083, 920, 809 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{25}O_2$ $[M+H]^+$: 285.1855, found 285.1842; $[\alpha]_D^{25}$ –90.5 (*c* 0.20, MeOH, 98% ee).



(–)-Aspewentin B (133) (98% ee) *(–)-Aspewentin A (133A)*

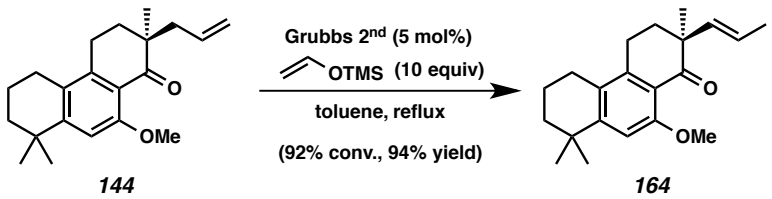
(–)-Aspewentin A (133A). A 20 mL scintillation vial was charged with a magnetic stir bar and $NaBH_4$ (38 mg, 1.0 mmol, 10 equiv). Trifluoroacetic acid (1 mL) was added carefully with stirring. Solids soon dissolved, with a slight exotherm. A solution of (–)-aspewentin B (**1**, 29 mg, 0.10 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added, and the reaction mixture immediately turned yellow. After stirring 1 h, additional $NaBH_4$ (7.5 mg, 0.20 mmol, 2.0 equiv) was added. After 45 min, a third portion of $NaBH_4$ (11 mg, 0.30 mmol, 3.0 equiv, 15 equiv total) was added. After stirring another 2 h, the reaction was quenched with saturated aq. $NaHCO_3$ solution (ca. 15 mL). Care should be taken during addition of $NaHCO_3$ due to rapid gas evolution. The biphasic mixture was extracted with EtOAc (15 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel (9% Et_2O in hexanes) furnished (–)-aspewentin A (**133A**, 23 mg, 85% yield) as a light orange oil. R_f = 0.4 (20% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.67 (s, 1H), 5.90 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.08–4.88 (m, 2H), 4.69 (br s, 1H), 2.66 (d, *J* = 16.3 Hz, 1H), 2.57 (t, *J* = 6.7 Hz, 2H), 2.50 (t, *J* = 6.5 Hz, 2H), 2.46 (d, *J* = 16.3 Hz, 1H), 1.86–1.79 (m, 2H), 1.76–1.70 (m, 1H), 1.69–1.60 (m, 3H),

1.27 (d, *J* = 1.6 Hz, 6H), 1.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3, 147.2, 143.9, 135.2, 126.5, 119.7, 111.2, 110.0, 38.8, 34.5, 34.5, 34.1, 33.9, 32.1, 32.0, 26.8, 26.0, 24.4, 19.7; IR (Neat Film, NaCl) 3307, 2923, 1606, 1456, 1418, 1324, 1252, 1019, 910, 858 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{26}O$ $[M]^+$: 270.1984, found 270.1972; $[\alpha]_D^{25}$ – 38.6 (*c* 0.20, MeOH).



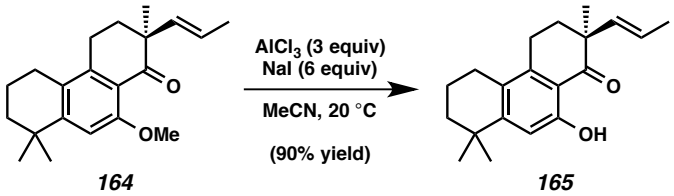
144 ***163***

Ketone 163. Using α-allyl ketone **144** as starting material (20 mg, 0.064 mmol, 1.0 equiv), and following the same procedure as that for (–)-aspewentin B (**1**), ketone **163** was obtained (17 mg, 89% yield) as a colorless oil. R_f = 0.7 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.47 (s, 1H), 6.84 (s, 1H), 5.83–5.72 (m, 1H), 5.13–5.05 (m, 2H), 2.82–2.66 (m, 2H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.46 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.26 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.08–1.98 (m, 1H), 1.90–1.77 (m, 3H), 1.65–1.59 (m, 2H), 1.28 (s, 6H), 1.19 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.1, 161.0, 156.0, 142.2, 133.8, 124.7, 118.6, 114.2, 113.4, 44.1, 41.2, 38.3, 35.0, 32.6, 31.6, 31.6, 26.9, 23.0, 22.2, 19.4; IR (Neat Film, NaCl) 2930, 1634, 1464, 1360, 1220, 1190, 919, 811 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{27}O_2$ $[M+H]^+$: 299.2006, found 299.1999; $[\alpha]_D^{25}$ – 23.5 (*c* 0.20, MeOH).

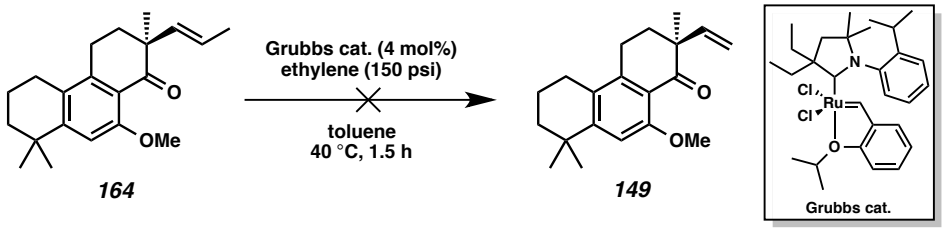


144 *164*

Ketone 164. To a solution of α-allyl ketone **144** (109 mg, 0.349 mmol, 1.0 equiv) and vinyloxytrimethylsilane (0.52 mL, 3.49 mmol, 10.0 equiv) in toluene (19 mL) was added Grubbs 2nd generation catalyst (14.8 mg, 0.01745 mmol, 0.05 equiv) at 20 °C. The purple reaction mixture was immersed in a pre-heated 128°C oil bath (color changed to yellow) and refluxed for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10% EtOAc in hexanes) to afford ketone **164** (103 mg, 92% conv., 94% yield) as a colorless oil. R_f = 0.4 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1H), 5.60 (d, *J* = 15.9 Hz, 1H), 5.48–5.38 (m, 1H), 3.86 (s, 3H), 2.79–2.66 (m, 2H), 2.58–2.45 (m, 2H), 2.08–1.99 (m, 1H), 1.96–1.88 (m, 1H), 1.87–1.74 (m, 2H), 1.68–1.56 (m, 5H), 1.30 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.4, 158.6, 152.1, 143.9, 133.6, 126.0, 125.0, 120.2, 108.5, 56.1, 48.2, 38.4, 35.1, 34.9, 31.8, 31.6, 27.0, 24.1, 24.0, 19.5, 18.5; IR (Neat Film, NaCl) 2928, 1683, 1591, 1558, 1456, 1318, 1245, 1106, 1020, 966 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{21}H_{29}O_2$ $[M+H]^+$: 313.2162, found 313.2154; $[\alpha]_D^{25}$ –49.0 (*c* 1.00, $CHCl_3$).



Ketone 165. Using ketone **164** as starting material (35 mg, 0.112 mmol, 1.0 equiv), and following the same procedure as that for (–)-aspewentin B (**133**), ketone **165** was obtained (30 mg, 90% yield) as a colorless oil. R_f = 0.7 (16% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.46 (s, 1H), 6.84 (s, 1H), 5.57 (d, *J* = 15.9 Hz, 1H), 5.49–5.39 (m, 1H), 2.79–2.67 (m, 2H), 2.59–2.44 (m, 2H), 2.09–2.00 (m, 1H), 2.00–1.91 (m, 1H), 1.89–1.74 (m, 2H), 1.66 (d, *J* = 5.9 Hz, 3H), 1.64–1.55 (m, 2H), 1.30 (s, 3H), 1.28 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.7, 160.9, 155.9, 142.5, 133.1, 125.9, 124.6, 114.6, 113.3, 47.1, 38.3, 35.1, 35.0, 31.7, 31.6, 26.9, 23.9, 23.5, 19.4, 18.4; IR (Neat Film, NaCl) 2929, 1634, 1464, 1359, 1267, 1221, 1191, 964 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{27}O_2$ $[M+H]^+$: 299.2006, found 299.2002; $[\alpha]_D^{25}$ –65.1 (*c* 0.20, MeOH).



Ethenolysis of 164. In a nitrogen-filled glove box, a Fisher-Porter bottle was charged with a magnetic stir bar, toluene (10 mL), and Grubbs catalyst (1.7 mg, 0.0028 mmol, 0.04 equiv). A solution of **164** (22 mg, 0.07 mmol, 1.0 equiv) in toluene (0.2 mL) was added. The head of the Fisher-Porter bottle was equipped with a pressure gauge, and a

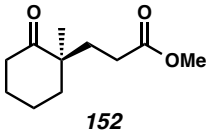
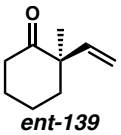
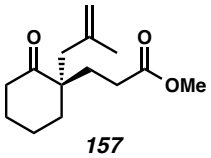
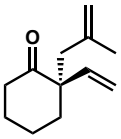
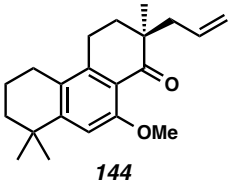
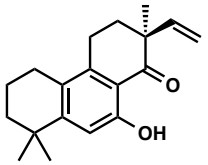
dip-tube was adapted on the bottle. The system was sealed and taken out of the glove box and connected to the ethylene line. The vessel was then purged with ethylene (polymer purity 99.9% from Matheson Tri Gas) for 5 min, pressurized to 150 psi, and placed in an oil bath at 40 °C. After stirring for 1.5 h, the solvent was evaporated, and the residue was diluted in EtOAc and passed through a short plug of silica gel to remove the ruthenium catalyst. The filtrate was concentrated under reduced pressure, and ^{1}H NMR analysis of the residue showed starting material **164** remaining, and no peaks corresponding to the desired product **149**.

Table 5.2 Comparison of Synthetic and Natural Aspewentin B

Synthetic (–)-Aspewentin B	**Natural (+)-Aspewentin B**[15]
^{1}H NMR (500 MHz, $CDCl_3$)	*^{1}H NMR (500 MHz, $CDCl_3$)*
12.40 (s, 1H)	12.40 (s, 1H)
6.84 (s, 1H)	6.84 (s, 1H)
5.98 (dd, *J* = 17.7, 10.8 Hz, 1H)	5.98 (dd, *J* = 17.6, 10.8 Hz, 1H)
5.13 (d, *J* = 10.7 Hz, 1H)	5.14 (d, *J* = 10.8 Hz, 1H)
5.03 (d, *J* = 17.6 Hz, 1H)	5.03 (d, *J* = 17.6 Hz, 1H)
2.81–2.69 (m, 2H)	2.75 (m, 2H)
2.59–2.44 (m, 2H)	2.51 (m, 2H)
2.14–2.06 (m, 1H)	2.10 (m, 1H)
2.04–1.94 (m, 1H)	2.00 (m, 1H)
1.88–1.73 (m, 2H)	1.81 (m, 2H)
1.68–1.55 (m, 2H)	1.61 (m, 2H)
1.33 (s, 3H)	1.33 (s, 3H)
1.27 (s, 6H)	1.28 (s, 3H), 1.27 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$)	*^{13}C NMR (125 MHz, $CDCl_3$)*
207.2	207.1
160.9	160.8
156.1	156.2
142.3	142.2
140.5	140.4
124.7	124.6
115.1	115.0
114.6	114.4
113.3	113.3
47.9	47.8
38.3	38.2
35.0	34.9
34.4	34.3
31.7	31.6
31.6	31.5
26.9	26.8
23.4	23.3
23.3	23.2
19.4	19.3
Optical Rotation	*Optical Rotation*
$[\alpha]_D^{25}$ –90.5 (*c* 0.20, MeOH, 98% ee)	$[\alpha]_D^{20}$ +23.3 (*c* 0.20, MeOH)

5.5.6 Methods for the Determination of Enantiomeric Excess

Table 5.3 Analytical HPLC and SFC assays and retention times

entry	compound	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 ***152***	HPLC Chiralcel OD-H 10% IPA in hexanes isocratic, 1.0 mL/min 220 nm	6.43	5.93	91
2	 ***ent-139***	GC G-TA 60 °C isotherm 5 min then ramp 2 °C/min	24.20	23.92	92
3	 ***157***	HPLC Chiralcel OD-H 5% IPA in hexanes isocratic, 1.0 mL/min 210 nm	8.08	9.99	91
4	 ***141e***	HPLC Chiralpak AS 0.2% IPA in hexanes isocratic, 1.0 mL/min 210 nm	9.50	7.89	92
5	 ***144***	SFC Chiralcel OB-H 3% MeOH in CO_2 isocratic, 3.0 mL/min 254 nm	8.82	6.41	94
6	 ***(–)-Aspewentin B (133)***	HPLC Chiralpak AD 0.5% IPA in hexanes isocratic, 1.0 mL/min 210 nm	7.22	6.56	98

5.6 Notes and References

(1) (a) Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. *Helv. Chim. Acta* **1969**, *52*, 1886–1905. (b) Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456–6457. (c) Masuda, T.; Masuda, K.; Shiragami, S.; Jitoe, A.; Nakatani, N. *Tetrahedron* **1992**, *48*, 6787–6792. (d) Rubal, J. J.; Moreno-Dorado, F. J.; Guerra, F. M.; Jorge, Z. D.; Saouf, A.; Akssira, M.; Mellouki, F.; Romero-Garrido, R.; Massanet, G. M. *Phytochemistry* **2007**, *68*, 2480–2486.

(2) Nishimoto, Y.; Ueda, H.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8073–8076.

(3) (a) Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897–1900. (b) Huang, J.; Bunel, E.; Faul, M. M. *Org. Lett.* **2007**, *9*, 4343–4346. (c) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900–9901.

(4) (a) Nakamura, M.; Endo, K.; Nakamura, E. *Org. Lett.* **2005**, *7*, 3279–3281. (b) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264–5271. (c) Fujimoto, T.; Endo, K.; Tsuji, H.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 4492–4496.

(5) (a) Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc.* **1999**, *121*, 4074–4075. (b) Arisawa, M.; Miyagawa, C.; Yoshimura, S.; Kido, Y.; Yamaguchi, M. *Chem. Lett.* **2001**, 1080–1081.

(6) Tanikaga, R.; Sugihara, H.; Tanaka, K.; Kaji, A. *Synthesis* **1977**, 299–301.

(7) (a) Kowalski, C. J.; Dung, J.-S. *J. Am. Chem. Soc.* **1980**, *102*, 7950–7951. (b) Clive, D. L. J.; Russell, C. G.; Suri, S. C. *J. Org. Chem.* **1982**, *41*, 1632–1641.

(8) Nozoye, T.; Shibanuma, Y.; Nakai, T.; Hatori, Y. *Chem. Pharm. Bull.* **1988**, *36*, 4980–4985.

(9) (a) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776–7778. (b) Kawashima, H.; Kaneko, Y.; Sakai, M.; Kobayashi, Y. *Chem. – Eur. J.* **2014**, *20*, 272–278.

(10) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273–274.

(11) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927.

(12) Liu, Y.; Kim, K. E.; Herbert, M. B.; Fedorov, A.; Grubbs, R. H.; Stoltz, B. M. *Adv. Synth. Catal.* **2014**, *356*, 130–136.

(13) de Avellar, I. G. J.; Vierhapper, F. W. *Tetrahedron* **2000**, *56*, 9957–9965.

(14) The small-scale reactions were performed under 1 atm N_2 (no distillation). Acetic anhydride was found to be unsuitable under such conditions, while benzoic anhydride proved to be optimal.

(15) Miao, F.-P.; Liang, X.-R.; Liu, X.-H.; Ji, N.-Y. *J. Nat. Prod.* **2014**, *77*, 429–432.

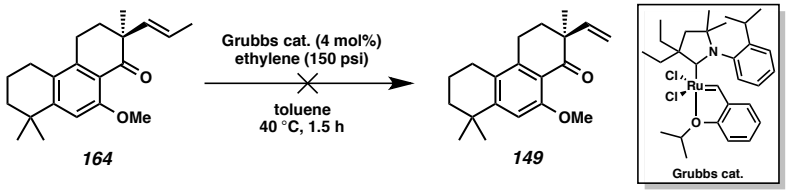
(16) The natural product has (+)-stereochemistry we synthesized the (–)-enantiomer due to the ready availability of the (*S*)-*t*-BuPHOX ligand.

(17) The enantioselective Michael addition does not work for 1-tetralone substrates. For details, see: d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron Asymmetry* **1992**, *3*, 459–505.

(18) Allergan, Inc. Patent WO2005/58301 A1, 2005.

(19) Stoltz, B. M. et al. Manuscript submitted to *Adv. Synth. Catal.*

(20) An alternative route from allyl ketone **144** to vinyl ketone **149** involves isomerization of the double bond to the internal position followed by ethenolysis. While the isomerization proceeded smoothly using the protocol developed by Nishida (Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732–4734) to afford internal olefin **164**, attempts at ethenolysis of the resulting internal olefin were unsuccessful, likely due to steric bulk at the adjacent quaternary center. See Experimental Section (5.5) for details.



(21) Spectroscopic data (^{1}H and ^{13}C NMR) and exact mass of the synthetic compound matches those of natural (+)-aspewentin B. Optical rotation, however, is significantly different (synthetic compound: $[\alpha]_D^{25}$ –90.5 (*c* 0.20, MeOH, 94% ee); natural product: $[\alpha]_D^{20}$ +23.3 (*c* 0.20, MeOH)). HPLC analysis showed the synthetic compound to be of 98% ee. Based on the stereoselectivity of the Pd-PHOX catalyst in previous examples, we reasoned that the absolute configuration of our synthetic compound is opposite to that of the natural product, and thus the sign of optical rotation is correct. The difference in magnitude may arise from the possibility that the natural product is a scalemic mixture (i.e. not enantiopure). For a review on non-enantiopure natural products, see: Finefield, J. M.; Sherman, D. H.; Kreitman, M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4802–4836. Another possibility is that the isolated natural product contained a small amount of impurity that had a large effect on optical rotation.

(22) G. Quandt, G. Höfner, K. T. Wanner, Bioorg. Med. Chem. 2013, 21, 3363–3378.

(23) Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

(24) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz‚J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547–7583.

(25) Zhao, M. M.; Li, J.; Mano, E.; Song, Z. J.; Tschaen, D. M. *Org. Syn.* **2005**, *81*, 195–203.

(26) Borthakur, M.; Boruah, R. C. *Steroids* **2008**, *73*, 637–641.

(27) Straub, B. F.; Wrede, M.; Schmid, K.; Rominger, F. *Eur. J. Inorg. Chem.* **2010**, 1907–1911.