

Short Enantioselective Formal Synthesis of (–)-Platencin

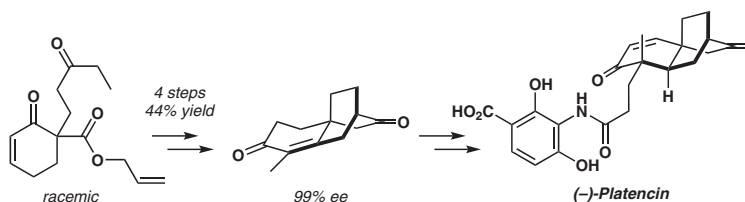
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Dedicated to Prof. Dr. Scott E. Denmark on the occasion of his 65th birthday.

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Abstract A short enantioselective formal synthesis of the antibiotic natural product platencin is reported. Key steps in the synthesis include enantioselective decarboxylative alkylation, aldehyde/olefin radical cyclization, and regioselective aldol cyclization.

Key words formal synthesis, palladium, enantioselective reactions, enantioconvergent synthesis, alkylation

The growing resistance of several pathogenic bacterial strains against commercially available antibiotics necessitates the rapid and efficient development of novel active ingredients. In this quest, natural products serve as valuable lead structures.³ Recently, platencin (**1**, Figure 1)⁴ and platensimycin (**2**)⁵ were isolated by Merck scientists and determined to be highly active in vitro and in vivo antibiotics possessing a novel mode of action. These natural products attracted tremendous interest from the synthetic community, and a number of different approaches to each natural product have been reported.^{6,7} Herein, we disclose a short and efficient enantioselective formal synthesis of platencin (**2**) making use of enantioconvergent alkylation methodology developed in our group.⁸

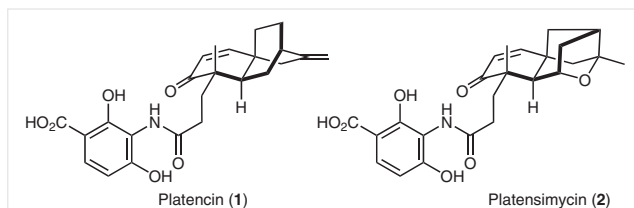
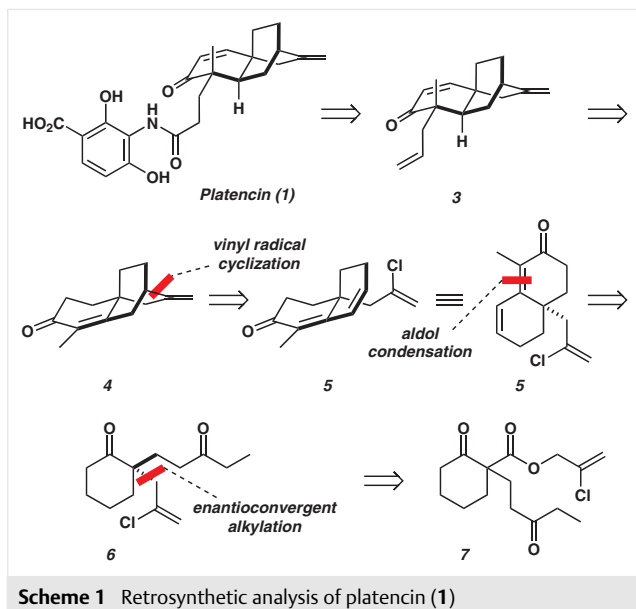


Figure 1 Structures of the antibiotics platencin (**1**) and platensimycin (**2**)

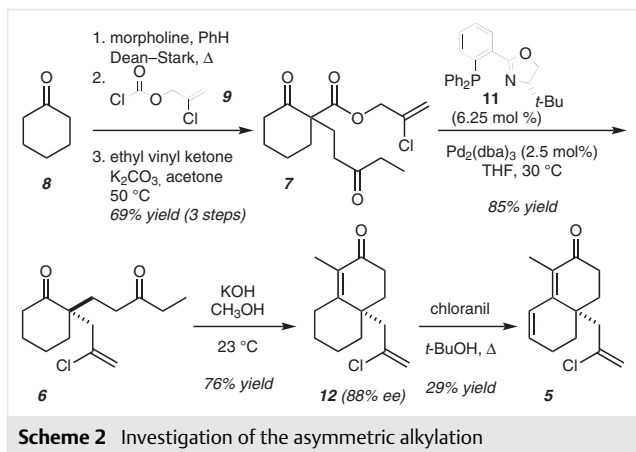
We have pursued a research strategy that consists of identifying particular structural challenges of natural products to guide the development of novel methods in enantioselective catalysis.⁹ In accord with this tactic, we have developed a series of Pd-catalyzed enolate alkylation reactions for the enantioselective synthesis of quaternary stereocenters and applied these transformations in synthetic studies toward several target molecules.^{10,11} The presence of two all-carbon quaternary stereocenters in both platencin (**1**) and platensimycin (**2**) entreated us to explore the synthesis of these molecules using our method. We first chose to explore the synthesis of platencin (**1**) because of the interesting carbon framework that could be accessible through several different approaches. Since Nicolaou^{6b} and Rawal^{6c} have reported procedures to introduce the aromatic portion of the natural product, we targeted tricyclic intermediate **3** (Scheme 1) for our synthetic studies.

Initially, our retrosynthetic plan included the assembly of the [2.2.2]bicyclic structure **4** by employing an intramolecular vinyl radical cyclization¹² of precursor **5** (Scheme 1). We envisioned constructing dienone **5** through an intramolecular aldol condensation with cyclohexanone **6**. The absolute stereochemistry of diketone **6** would be controlled via Pd-catalyzed enantioconvergent alkylation using racemic β -ketoester **7**.

The necessary precursor for the projected asymmetric alkylation was readily assembled through a three-step protocol (Scheme 2). Cyclohexanone (**8**) was converted into its corresponding morpholine enamine¹³ that then reacted with 2-chloroallyl chloroformate (**9**) to afford β -ketoester **10**. Subsequent alkylation with ethyl vinyl ketone yielded racemic alkylation precursor **7**. Subsequent enantioconvergent decarboxylative alkylation reaction of chloro-substituted β -ketoester **7** in the presence of the complex derived



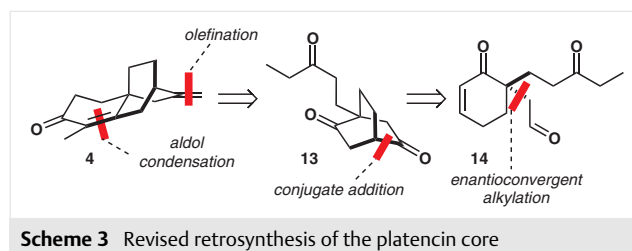
from $[\text{Pd}_2(\text{dba})_3]$ and phosphinooxazoline (PHOX) ligand **11**^{14,15} proceeded smoothly to provide cyclohexanone **6** in 85% yield. Interestingly, the related bromo-substituted β -ketoester remained unreactive under identical reaction conditions. We suspect that this is due to competitive oxidative insertion of Pd into the C–Br bond, which precludes the alkylation chemistry.



Further synthetic manipulations toward our target intermediate **4** involved annulation of alkylation product **6** by means of aldol cyclization (resulting in formation of bicyclic enone **12**, with a measured ee of 88%), followed by dehydrogenation¹⁶ to afford dienone **5** (Scheme 2). Several reaction conditions to effect the key cyclization to the bicyclo[2.2.2]octane **4** were examined, but none of these proved successful. Application of radical conditions (Bu_3SnH , AIBN, benzene, 80 °C)¹⁷ led only to recovery of starting material,

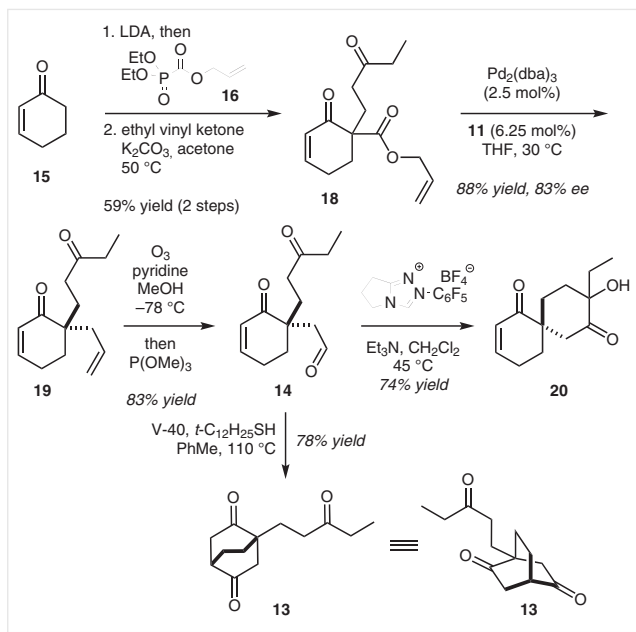
while anionic conditions ($t\text{-BuLi}$, CuCN , THF, -78°C)¹⁸ resulted in the formation of a complex mixture of unidentified products.

To tackle the challenging synthesis of the chiral bicyclo[2.2.2]octane scaffold, we reconsidered our retrosynthetic plan and decided to reverse the order of ring assembly (Scheme 3). Postponing the aldol condensation to a later stage in the synthesis, our focus shifted entirely towards construction of the chiral bicyclo[2.2.2]octadione **13**. We envisioned an umpolung strategy in which aldehyde **14** would undergo an intramolecular conjugate addition (Stetter cyclization).¹⁹ The aldehyde itself would again be the result of an enantioselective decarboxylative alkylation.

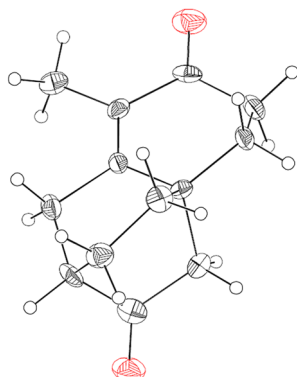


By following our revised strategy, the lithium enolate of cyclohex-2-en-1-one (**15**) was treated with allyl diethylphosphonoformate (**16**),²⁰ an inexpensive alternative to Mander's reagent²¹ (Scheme 4). The intermediate β -ketoester **17** was then alkylated with ethyl vinyl ketone to afford racemic substrate **18**. The subsequent enantioselective decarboxylative alkylation reaction proceeded smoothly to provide cyclohexenone **19** in good yield (88%) and 83% ee. Selective oxidative cleavage of the more electron-rich double bond in enone **19** was effected by ozone in the presence of pyridine.²² However, when aldehyde **14** was subjected to Stetter cyclization conditions promoted by thiazolium- or triazolium-based catalysts,²³ only the product of a benzoin-type cyclization (**20**) was isolated.²⁴ Given our recent success with an aldehyde/olefin radical cyclization in another synthetic effort,^{11c} we exposed tricarbonyl compound **14** to the radical initiator V-40 (1,1'-azobis(cyclohexanecarbonitrile)) and t -dodecanethiol in refluxing toluene. We were delighted to find that the radical cyclization conditions provided the desired chiral bicyclo[2.2.2]octadione **13** in 78% yield using this protocol.²⁵

The key bridged bicycle **13** was then subjected to basic conditions (KOH , MeOH , 23 °C, Scheme 5). These conditions promoted an intramolecular aldol cyclization that appeared to be completely regioselective for formation of the desired tricyclic compound **21**. Dione **21** was highly crystalline and a single recrystallization from hexanes allowed us to increase the enantiomeric excess to 99%. The structure of tricycle **21** was confirmed by single-crystal X-ray diffraction analysis (Figure 2).²⁶

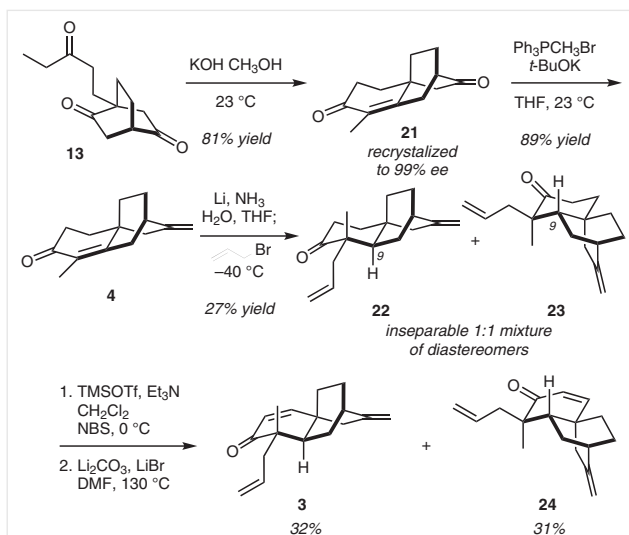


Scheme 4 Assembly of the bicyclo[2.2.2]octadione scaffold

Figure 2 ORTEP plot of dione **21** derived from X-ray crystallographic analysis (non-hydrogen atoms are shown with ellipsoids at 50% probability)

Chemoselective methylenation of the unconjugated ketone moiety of **21** was achieved in 89% yield by action of a Wittig reagent (Scheme 5). Exposure of the resulting alkene (**4**) to Li metal led to enone reduction with concomitant formation of a lithium enolate that was trapped with allyl bromide to provide ketones **22** and **23** as a 1:1 mixture of diastereomers. The configuration at C(9) is presumably set prior to alkylation, but with poor stereoinduction from the bicyclic system. This C(9) configuration then exerts strong control over the subsequent alkylation. This was confirmed by carrying out an analogous transformation quenching with MeI in place of allyl bromide, which also delivered a 1:1 mixture of C(9) epimers. This reductive alkylation has provided variable yields (up to ca. 85%), but reproducibly returns yields of ca. 25% in most cases. Extensive optimiza-

tion has not been pursued, however, although we observed no variability in the diastereoselectivity. The enone functionality present in the target structure (**3**) was introduced by means of a silyl enol ether. After this oxidation, it was possible to separate the diastereomers chromatographically to isolate both the desired compound **3** (32% yield) and the diastereomeric compound **24** (31% yield) in pure form. As compound **3** is an intermediate in Nicolaou's total synthesis of platencin (**1**),^{6a} this work constitutes a formal synthesis of the natural product.

Scheme 5 Formal synthesis of platencin (**1**)

In conclusion, we have developed a short enantioselective formal synthesis of the antibiotic platencin (**1**). Key features include the enantioconvergent catalytic alkylation to set the absolute configuration of the key all-carbon quaternary center, as well as a radical-mediated cyclization to assemble the core bicyclo[2.2.2]octane structure.

Unless otherwise stated, reactions were performed in oven-dried glassware using anhydrous, deoxygenated solvents under an atmosphere of dry nitrogen. Anhydrous dichloromethane (CH_2Cl_2), heptane, triethylamine (Et_3N), tetrahydrofuran (THF) (BHT-free) were purchased from Fisher or VWR, degassed with argon, and dried by passage through activated drying columns²⁷ on a Pure Process Technology system. Diisopropylamine was distilled from NaH immediately prior to use. Tris(dibenzylideneacetone)dipalladium(0) [$\text{Pd}_2(\text{dba})_3$]²⁸ and (*S*)-*t*-BuPHOX^{8a,15,29} were synthesized according to standard procedures and stored in a glovebox until immediately before use. All commercially obtained reagents were purchased from Sigma-Aldrich, Alfa Aesar, Oakwood Chemical, or Fisher Scientific and used as received. Reaction temperatures were controlled by an IKA Mag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) or Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or KMnO_4 staining. Flash chromatography³⁰ was performed using either

SilicycleSiliaFlash® P60 silica gel (40–63 μm particle size) or ICN Silica gel (particle size 0.032–0.063 mm). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralpak AD or Chiralcel OD-H columns (4.6 mm $\times$ 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. Deuterated chloroform (CDCl_3 , 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) or on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively) or Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si ($\delta = 0.0$ ppm). Data for ^1H NMR spectra 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, sept = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si ($\delta = 0.0$ ppm). IR spectra were recorded with either a Perkin Elmer Paragon 1000 or Nicolet iS5 FTIR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained either from the California Institute of Technology Mass Spectral Facility or the University of Illinois at Urbana–Champaign Mass Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.

2-Chloroallyl Chloroformate (9)

A 50 mL three-neck round-bottom flask equipped with a 25 mL addition funnel, a stir bar, and three septa was flame-dried under vacuum. After refilling with argon, anhydrous Et_2O (6 mL) was added via syringe, and the system was cooled to approximately -10°C . Diphosgene (1.0 mL, 8.46 mmol, 1.21 equiv) was added dropwise via syringe, and the solution was cooled to -20°C . A solution of 2-chloroallyl alcohol (0.56 mL, 7.0 mmol, 1.0 equiv) in anhydrous Et_2O (6 mL) was added dropwise via the addition funnel, and the solution was stirred at -20°C for an additional 15 min. The reaction was cooled to approximately -30°C , and triethylamine (1.17 mL, 8.37 mmol, 1.20 equiv) in anhydrous Et_2O (6 mL) was added dropwise via the addition funnel, generating a white precipitate. The reaction was then stirred for 3 h, at which time it was allowed to warm to 23°C . During this time, the reaction mixture became very thick, and anhydrous Et_2O (10 mL) was added to obtain a stirrable suspension. Argon was bubbled through the suspension for 2 h to remove excess phosgene. The reaction mixture was filtered via vacuum filtration through a fritted funnel, and the filtrate was concentrated by rotary evaporation under reduced pressure. The title compound **9** (553 mg, 3.57 mmol, 51%) was obtained as a colorless liquid. All spectroscopic data are in agreement with the literature data.^{11d}

2-Chloroallyl 2-Oxo-1-(3-oxopentyl)cyclohexanecarboxylate (7)

Cyclohexanone (3.8 mL, 40.8 mmol, 1.0 equiv) and morpholine (6.4 mL, 73.4 mmol, 1.8 equiv) were diluted in anhydrous benzene (12 mL) in a 50 mL round-bottom flask equipped with a Dean–Stark trap and a reflux condenser. The resulting reaction mixture was heated to reflux until no further separation of water was observed. The volatiles were removed by rotary evaporation under reduced pressure. The re-

sulting oily orange residue was distilled to remove excess morpholine and afford 5.0 g (29.9 mmol, 73%) of the morpholine enamine of cyclohexanone as a colorless liquid.

A portion of the morpholine enamine intermediate (971 mg, 5.8 mmol, 1.8 equiv) was diluted in benzene (5 mL). Under a nitrogen atmosphere, 2-chloroallyl chloroformate (500 mg, 3.23 mmol, 1.0 equiv) was slowly added via syringe while the enamine solution was stirred rapidly. After refluxing for about 10 h, the solution was cooled to 23°C and filtered. The solids were washed with anhydrous Et_2O . The combined filtrate and washings were returned to the reaction flask, and 10% aqueous HCl (7 mL) was added, and the mixture was stirred vigorously for 15–30 minutes. The layers were separated, the aqueous layer was extracted with diethyl ether (3×20 mL) and the combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo. Crude 2-chloroallyl 2-oxocyclohexanecarboxylate (**10**, 638 mg, 2.94 mmol, 91%) was used in the next step without additional purification.

The crude β -ketoester **10** (638 mg, 2.94 mmol, 1.0 equiv) was added to a suspension of potassium carbonate (814 mg, 5.89 mmol, 2.0 equiv) in acetone (4 mL). At 23°C , ethyl vinyl ketone (586 μL , 5.89 mmol, 2.0 equiv) was added slowly via syringe. The resulting heterogeneous mixture was stirred for 7 h at 50°C , and then cooled to 23°C , filtered, and the filtrate was concentrated by rotary evaporation under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , gradient from 15:1 to 3:1 hexanes/ EtOAc) to afford 2-chloroallyl 2-oxo-1-(3-oxopentyl)cyclohexanecarboxylate (**7**, 676 mg, 2.24 mmol, 76%) as a colorless liquid.

TLC (SiO_2): $R_f = 0.56$ (3:1 hexanes/ EtOAc ; *p*-anisaldehyde or KMnO_4 stains).

IR (neat): 2941, 2868, 1715, 1451, 1239, 1212, 1177, 1134, 1086, 906 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 5.50$ (s, 1 H), 5.44 (s, 1 H), 4.73 (d, $J = 13.3$ Hz, 1 H), 4.68 (d, $J = 13.3$ Hz, 1 H), 2.58–2.37 (m, 7 H), 2.16 (m, 2 H), 2.02–1.98 (m, 1 H), 1.91 (m, 2 H), 1.79–1.77 (m, 1 H), 1.67 (m, 2 H), 1.52 (m, 1 H), 1.03 (t, $J = 7.3$ Hz, 3 H).

^{13}C NMR (126 MHz, CDCl_3): $\delta = 210.4$, 207.5, 171.4, 135.3, 116.5, 66.8, 60.1, 40.9, 37.3, 36.5, 35.9, 28.3, 27.4, 22.4, 7.8.

HRMS (EI^+): m/z calcd for $\text{C}_{15}\text{H}_{22}\text{O}_4\text{Cl}$ [$M + \text{H}$] $^+$: 301.1201; found: 301.1205.

(R)-2-(2-Chloroallyl)-2-(3-oxopentyl)cyclohexanone (6)

A 25 mL Schlenk flask was equipped with a magnetic stir bar and flame-dried under vacuum. After cooling to 23°C under anhydrous argon, $\text{Pd}_2(\text{dba})_3$ (4.6 mg, 5 μmol , 5 mol%) and (*S*)-*t*-BuPHOX (4.8 mg, 12.5 μmol , 12.5 mol%) were added. The flask containing the solids was evacuated for 15 min and then refilled with dry argon. Anhydrous THF (3 mL) was then added and the resulting solution was stirred at 23°C for 30 min. At this point, 2-chloroallyl 2-oxo-1-(3-oxopentyl)cyclohexanecarboxylate (**7**, 30 mg, 0.1 mmol, 1.0 equiv) was added via syringe in one portion. The reaction was warmed to 30 – 35°C . When the reaction was complete as judged by TLC, the reaction mixture was evaporated under reduced pressure and the residue was purified by flash column chromatography (SiO_2 , 10:1 hexanes/ EtOAc) to afford (*R*)-2-(2-chloroallyl)-2-(3-oxopentyl)cyclohexanone **6** (21.7 mg, 85 μmol , 85%) as a colorless liquid. The enantiomeric composition was determined after the aldol cyclization on compound **12**.

$[\alpha]_D^{22.5} +20.4^\circ$ (c 1.04, CHCl_3); TLC (SiO_2): $R_f = 0.42$ (3:1 hexanes/ EtOAc ; *p*-anisaldehyde or KMnO_4 stains).

IR (neat): 2939, 2867, 1706, 1628, 1455, 1374, 1113, 889 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 5.28 (app. d, J = 1.2 Hz, 1 H), 5.13 (s, 1 H), 2.70 (d, J = 14.9 Hz, 1 H), 2.63 (d, J = 14.9 Hz, 1 H), 2.51–2.42 (m, 3 H), 2.40 (q, J = 7.3 Hz, 2 H), 2.18–2.09 (m, 2 H), 1.95–1.70 (m, 7 H), 1.03 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 213.7, 210.7, 138.5, 116.8, 50.7, 43.4, 39.1, 36.7, 36.1, 28.2, 26.9, 20.7, 7.8.

HRMS (EI^+): m/z calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2\text{Cl}$ [$\text{M} + \text{H}$] $^+$: 257.1303; found: 257.1317.

(*R*)-4a-(2-Chloroallyl)-1-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (12)

The 1,5-diketone **6** (210 mg, 0.82 mmol, 1.0 equiv) was added to a 1 M KOH soln (1.85 mL, 1.85 mmol, 3 equiv) in MeOH. The reaction mixture was stirred at 23 °C for 7 h during which time the color gradually changed from yellow to orange. After the reaction was complete as judged by TLC, ca. 4 mL Et_2O and ca. 4 mL H_2O were added. The organic phase was separated and the aq phase was acidified by addition of 10% aq HCl (ca. 2 mL). The aq phase was extracted with Et_2O (3×10 mL). The combined organic phases were washed with brine, dried (MgSO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2 , 10:1 hexanes/ EtOAc) to afford compound **12** (142 mg, 0.59 mmol, 73%) as a colorless liquid. The enantiomeric excess was determined to be 88% by HPLC using chiral stationary phase columns (Chiralcel OD-H, 1% isopropanol in hexanes, flow rate 1 mL/min, 254 nm, 10.9 min (major), 13.2 min (minor)).

$[\alpha]_{\text{D}}^{21.0}$ -70.7° (c 0.99, CHCl_3); TLC (SiO_2): R_f = 0.39 (3:1 hexanes/ EtOAc ; *p*-anisaldehyde or KMnO_4 stains).

IR (neat): 2932, 2862, 1665, 1627, 1608, 1456, 1362, 1304, 1163, 1076, 882 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 5.36 (d, J = 1.0 Hz, 1 H), 5.17 (s, 1 H), 2.78 (d, J = 14.6 Hz, 1 H), 2.77–2.73 (m, 1 H), 2.62 (d, J = 14.1 Hz, 1 H), 2.62–2.54 (m, 1 H), 2.40 (ddd, J = 3.9, 4.6, 17.3 Hz, 1 H), 2.18 (ddd, J = 3.9, 5.0, 13.9 Hz, 1 H), 2.15–2.07 (m, 1 H), 2.02 (ddd, J = 3.2, 5.4, 13.9 Hz, 1 H), 1.97–1.92 (m, 1 H), 1.78 (s, 3 H), 1.73–1.60 (m, 3 H), 1.44–1.34 (m, 1 H), 1.28 (ddd, J = 4.2, 13.5, 13.5 Hz, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 198.8, 161.2, 138.7, 129.9, 116.7, 42.1, 39.7, 38.1, 33.9, 33.1, 27.7, 26.7, 21.2, 11.1.

HRMS (EI^+): m/z calcd for $\text{C}_{14}\text{H}_{20}\text{ClO}$ [$\text{M} + \text{H}$] $^+$: 239.1197; found: 239.1209.

(*R*)-4a-(2-Chloroallyl)-1-methyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one (5)

A 20 mL glass scintillation vial was charged with a magnetic stir bar and a solution of compound **12** (66 mg, 0.28 mmol, 1 equiv) in *t*-BuOH (7.66 mL). Chloranil (205 mg, 0.84 mmol, 3 equiv) was added and then the vial was sealed with a cap and placed in an aluminum block preheated to 85 °C. The reaction was stirred for 2 h at which time TLC indicated consumption of starting material. The mixture was cooled to 22 °C and then filtered. The filtrate was concentrated in vacuo and purified by flash chromatography (SiO_2 , 20:1 hexanes/ EtOAc) to afford the desired compound dieneone **5** as a colorless oil (19 mg, 29%).

$[\alpha]_{\text{D}}^{23.4}$ -239.2° (c 0.026, CH_2Cl_2); TLC (SiO_2): R_f = 0.39 (3:1 hexanes/ EtOAc ; *p*-anisaldehyde or KMnO_4 stains).

IR (neat): 2923, 1652, 1614, 1579, 1449, 1426, 1405, 1375, 1355, 1322, 1305, 1271, 1217, 1163, 1133, 1079, 1047, 1008, 982, 900, 885, 833, 782, 754, 731, 702, 632, 611 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 6.50 (d, J = 9.4 Hz, 1 H), 6.25 (m, 1 H), 5.40 (s, 1 H), 5.21 (s, 1 H), 2.69 (ddd, J = 19.9, 15.0, 5.2 Hz, 1 H), 2.60 (d, J = 14.9 Hz, 1 H), 2.55–2.41 (m, 4 H), 2.33–2.16 (m, 2 H), 2.06 (dd, J = 13.8, 5.1 Hz, 1 H), 1.83 (s, 3 H), 1.71 (td, J = 14.2, 4.8 Hz, 1 H), 1.49 (td, J = 12.8, 5.6 Hz, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 198.9, 153.6, 138.6, 136.8, 128.7, 124.6, 116.8, 41.0, 36.9, 33.9, 32.4, 32.3, 23.3, 10.3.

HRMS (EI^+): m/z calcd for $\text{C}_{14}\text{H}_{18}\text{ClO}$ [$\text{M} + \text{H}$] $^+$: 237.1041; found: 237.1045.

Allyl 2-Oxocyclohex-3-enecarboxylate (17)

Allyl chloroformate (7.7 mL, 72 mmol, 1 equiv) was slowly added to triethyl phosphite (12.4 mL, 72 mmol, 1 equiv) in a 250 mL round-bottom flask. The reaction was very rapid at 23 °C, evolving heat and emitting bubbles of chloroethane. Stirring was continued for 1 h at 23 °C, during which time bubbling ceased. The mixture was diluted with THF (20 mL) and the crude allyl diethylphosphonoformate (**16**) solution used without further purification.

In a separate flask, lithium diisopropylamide was prepared by slow addition of *n*-butyllithium (2.5 M in hexanes, 26.4 mL, 66 mmol, 1.1 equiv) to a solution of diisopropylamine (10 mL, 72 mmol, 1.2 equiv) in THF (120 mL) at -78°C . The resulting colorless solution was stirred for 1 h at -78°C before a solution of freshly distilled cyclohex-2-enone (**15**, 5.8 mL, 60 mmol, 1.0 equiv) in THF (20 mL) was added slowly via cannula. The resulting yellow reaction mixture was stirred for 1 h at -78°C . A freshly prepared solution of allyl diethylphosphonoformate **16** (16 g, 72 mmol, 1.2 equiv) in THF (20 mL) was added to the reaction mixture via cannula at such a rate that the reaction temperature did not exceed -70°C . The resulting yellow reaction mixture was stirred for an additional 1 h at -78°C before it was allowed to warm to 23 °C over a period of 4 h. When the reaction was complete as judged by TLC, the reaction was quenched by the addition of saturated aq NH_4Cl (50 mL) at 23 °C. Most of the organic layer was evaporated by rotary evaporation under reduced pressure. The mixture was diluted with Et_2O (ca. 70 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine, dried (MgSO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2 , 3:1 hexanes/ EtOAc) to afford the title compound **17** (7.8 g, 43 mmol, 72%) as a colorless liquid.

TLC (SiO_2): R_f = 0.21 (3:1 hexanes/ EtOAc ; *p*-anisaldehyde or KMnO_4 stains).

IR (neat): 3624, 3084, 3034, 2941, 2878, 1740, 1681, 1650, 1455, 1426, 1373, 1388, 1307, 1232, 1166, 1124, 1078, 1040, 1023, 994, 937, 892 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.01 (ddd, J = 3.7, 3.7, 10.3 Hz, 1 H), 6.07 (ddd, J = 1.7, 1.7, 10.0 Hz, 1 H), 5.92 (dddd, J = 5.6, 5.6, 11.2, 16.1 Hz, 1 H), 5.34 (1.5, 1.5, 1.5, 17.3 Hz, 1 H), 5.24 (dd, J = 1.2, 10.5 Hz, 1 H), 4.70–4.62 (m, 2 H), 3.46–3.43 (m, 1 H), 2.54–2.36 (m, 3 H), 2.26–2.21 (m, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 193.7, 169.6, 150.6, 131.7, 129.1, 118.5, 65.7, 53.4, 25.6, 24.3.

HRMS (EI^+): m/z calcd for $\text{C}_{10}\text{H}_{12}\text{O}$ [M] $^+$: 180.0781; found: 180.0786.

Allyl 2-Oxo-1-(3-oxopentyl)cyclohex-3-enecarboxylate (18)

Allyl 2-oxocyclohex-3-enecarboxylate **17** (4.00 g, 22.2 mmol, 1.0 equiv) was added to a suspension of potassium carbonate (6.14 g, 44.4 mmol, 2.0 equiv) in acetone (30 mL) at 23 °C. Ethyl vinyl ketone (4.42 mL, 44.4 mmol, 2.0 equiv) was added slowly via syringe. The re-

sulting heterogeneous mixture was stirred for 2.5 h at 50 °C, then cooled to 23 °C, filtered, and the filtrate was concentrated by rotary evaporation under reduced pressure. The residue was purified by flash column chromatography (SiO₂, hexanes–EtOAc 5:1 to 3:1) to afford allyl 2-oxo-1-(3-oxopentyl)cyclohex-3-enecarboxylate **18** (4.77 g, 18.0 mmol, 82%) as a colorless liquid.

TLC (SiO₂): *R*_f = 0.19 (3:1 hexanes/EtOAc; *p*-anisaldehyde or KMnO₄ stains).

IR (neat): 3085, 3035, 2975, 2939, 1731, 1716, 1682, 1449, 1452, 1387, 1376, 1354, 1237, 1221, 1188, 1116, 1094, 993, 974, 943 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 6.92–6.88 (m, 1 H), 6.03 (ddd, *J* = 1.9, 1.9, 10.0 Hz, 1 H), 5.90–5.82 (m, 1 H), 5.31–5.27 (m, 1 H), 4.64–4.57 (m, 2 H), 2.61–2.50 (m, 1 H), 2.49–2.37 (m, 6 H), 2.20–2.14 (m, 1 H), 2.07–2.01 (m, 1 H), 1.97–1.92 (m, 1 H), 1.04 (t, *J* = 7.3 Hz, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 210.5, 196.1, 171.3, 149.2, 131.5, 129.1, 118.6, 65.8, 56.2, 37.6, 35.9, 31.0, 27.3, 23.5, 7.8.

HRMS (EI⁺): *m/z* calcd for C₁₅H₂₀O₄ [M]⁺: 264.1356; found: 264.1347.

(*R*)-6-Allyl-6-(3-oxopentyl)cyclohex-2-enone (**19**)

A 500 mL round-bottom flask was equipped with a magnetic stir bar and then flame-dried under vacuum. After cooling to 23 °C under dry argon, Pd₂(dba)₃ (260 mg, 0.28 mmol, 2.5 mol%) and (*S*)-*t*-BuPHOX (275 mg, 0.71 mmol, 6.25 mol%) were added. The flask containing the solids was evacuated for 15 min and then refilled with dry argon. Anhydrous THF (342 mL) was then added and the resulting solution stirred at 23 °C for 30 min. At this point, allyl 2-oxo-1-(3-oxopentyl)cyclohex-3-enecarboxylate **18** (3.00 g, 11.4 mmol, 1.0 equiv) was added via syringe in one portion. The reaction was warmed to 30 °C. When the reaction was complete as judged by TLC, the reaction mixture was evaporated under reduced pressure and the residue was purified by flash column chromatography (SiO₂, hexanes/EtOAc, 10:1) to afford (*R*)-6-allyl-6-(3-oxopentyl)cyclohex-2-enone **19** (2.19 g, 10.0 mmol, 88%) as a colorless liquid. The enantiomeric excess was determined to be 83% by SFC using chiral stationary phase columns (Chiralcel OD-H, 5% isopropanol in hexanes, flow rate 1 mL/min, 244 nm, 5.5 min (minor), 5.8 min (major)).

[α]_D^{20.9} +13.9° (c 1.09, CHCl₃, 83% ee); TLC (SiO₂): *R*_f = 0.25 (3:1 hexanes/EtOAc; *p*-anisaldehyde or KMnO₄ stains).

IR (neat): 3075, 3033, 2976, 2935, 1714, 1670, 1449, 1430, 1387, 1221, 1115, 997, 916 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 6.87 (ddd, *J* = 3.9, 3.9, 10.0 Hz, 1 H), 5.90 (ddd, *J* = 2.0, 2.0, 10.0 Hz, 1 H), 5.73–5.65 (m, 1 H), 5.09–5.05 (m, 2 H), 2.46–2.27 (m, 7 H), 2.20 (dd, *J* = 7.8, 13.9 Hz, 1 H), 1.93–1.75 (m, 4 H), 1.03 (t, *J* = 7.3 Hz, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 211.2, 202.6, 148.9, 133.5, 128.7, 118.4, 46.8, 38.8, 36.7, 36.0, 31.1, 27.6, 22.9, 7.8.

HRMS (EI⁺): *m/z* calcd for C₁₄H₂₀O₂ [M]⁺: 220.1458; found: 220.1487.

(*R*)-2-(2-Oxo-1-(3-oxopentyl)cyclohex-3-enyl)acetaldehyde (**14**)

A 500 mL round-bottom flask equipped with a stir bar was charged with enone **19** (2.19 g, 10.0 mmol, 1.0 equiv), pyridine (899 μL, 11.1 mmol, 1.12 equiv), and MeOH (331 mL). A small portion of Sudan Red 7B (5 mg) was added as an indicator to determine the end point of the ozonolysis (upon completion reaction with indicator turns from colorless to red/pink). A flow of ozone (125 mL/min oxygen flow, 302 mg/h) was passed through the solution until there was no starting material left by TLC analysis. The reaction flask was purged with nitrogen. Trimethyl phosphite (7.3 mL, 49.6 mmol, 5.0 equiv) was added via syringe, and the flask was allowed to slowly warm to 23 °C. Af-

ter stirring at 23 °C for 1 h, the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (SiO₂, 5:1 hexanes/EtOAc) to afford the title compound **14** (1.83 g, 8.25 mmol, 83%) as a colorless liquid.

[α]_D^{20.9} +36.6° (c 1.04, CHCl₃).

TLC (SiO₂): *R*_f = 0.18 (3:1 hexanes/EtOAc; *p*-anisaldehyde or KMnO₄ stains).

IR (neat): 2975, 2938, 2737, 1714, 1668, 1455, 1389, 1223, 1112, 940, 807 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 9.71 (m, 1 H), 6.94–6.91 (m, 1 H), 5.97 (ddd, *J* = 1.5, 2.4, 10.1 Hz, 1 H), 2.83 (dd, *J* = 1.5, 16.2 Hz, 1 H), 2.56–2.49 (m, 1 H), 2.45–2.31 (m, 6 H), 2.18 (dq, *J* = 5.4, 13.8 Hz, 1 H), 2.00 (dq, *J* = 5.4, 15.1 Hz, 1 H), 1.91–1.81 (m, 2 H), 1.03 (t, *J* = 7.3 Hz, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 210.2, 201.2, 200.9, 149.4, 128.1, 48.1, 46.1, 36.5, 36.1, 31.7, 27.5, 22.8, 7.8.

HRMS (EI⁺): *m/z* calcd for C₁₃H₁₈O₃ [M]⁺: 222.1250; found: 222.1233.

(6*R*)-9-Ethyl-9-hydroxyspiro[5.5]undec-2-ene-1,8-dione (**20**)

A 25 mL round-bottom flask was charged with a stir bar and CH₂Cl₂ (5 mL). The aldehyde **14** (100 mg, 0.45 mmol, 1.0 equiv), 2-(perfluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate **23** (124 mg, 0.45 mmol, 1.0 equiv), and triethylamine (63 μL, 0.45 mmol, 1.0 equiv) were added consecutively. The resulting yellow mixture was stirred at 45 °C for 2 h. After cooling to 23 °C, the reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (SiO₂, 2:1 hexanes/EtOAc) to afford the title compound **20** (74 mg, 0.33 mmol, 74%) as a colorless liquid comprising a 1:1 mixture of diastereomers.

TLC (SiO₂): *R*_f = 0.18 (3:1 hexanes/EtOAc; *p*-anisaldehyde or KMnO₄ stains).

IR (neat): 3477, 2956, 2938, 2922, 2877, 1710, 1672, 1463, 1386, 1259, 1218, 1155, 1132, 1023, 803 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 6.96–6.92 (m, 1 H), 6.01 (ddd, *J* = 2.0, 2.0, 10.3 Hz, 1 H), 3.89 (s, 1 H), 3.15 (d, *J* = 13.9, 1 H), 2.39–2.36 (m, 2 H), 2.23–2.16 (m, 2 H), 2.03–1.76 (m, 6 H), 1.71 (dddd, *J* = 7.3, 7.3, 7.3, 14.3 Hz, 1 H), 0.81 (t, *J* = 7.3 Hz, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 213.8, 199.7, 149.5, 128.1, 78.6, 50.0, 43.6, 35.6, 30.2, 29.3, 27.1, 22.6, 7.0.

HRMS (EI⁺): *m/z* calcd for C₁₃H₁₉O₃ [M + H]⁺: 223.1329; found: 223.1336.

(1*R*, 4*S*)-1-(3-Oxopentyl)bicyclo[2.2.2]octane-2,5-dione (**13**)

1,1'-Azobis(cyclohexanecarbonitrile) (V-40) (2.47 g, 10.1 mmol, 1.5 equiv) was added to a solution of the alkenal **14** (1.50 g, 6.75 mmol, 1.0 equiv) and *t*-dodecanethiol (4.76 mL, 20.2 mmol, 3.0 equiv) in anhydrous toluene (68 mL). The solution was degassed three times by the freeze-thaw procedure. The reaction mixture was then heated at reflux under argon atmosphere for 24 h. After cooling to 23 °C, the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, gradient from 3:1 to 1:1 hexanes/EtOAc) to afford bicyclo[2.2.2]octadione **13** (1.17 g, 5.26 mmol, 78%) as a white solid.

Mp 73 °C; [α]_D^{19.7} +29.3° (c 0.99, CHCl₃); TLC (SiO₂): *R*_f = 0.10 (3:1 hexanes/EtOAc; *p*-anisaldehyde or KMnO₄ stains).

IR (neat): 2940, 2879, 1720, 1450, 1399, 1115, 1086, 952 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 2.74 (quint, *J* = 2.9 Hz, 1 H), 2.53–2.33 (m, 8 H), 2.09–2.03 (m, 1 H), 1.98–1.91 (m, 1 H), 1.86–1.69 (m, 4 H), 1.05 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 211.7, 211.0, 210.6, 48.7, 44.8, 44.3, 40.7, 37.0, 35.9, 28.0, 26.8, 22.6, 7.8.

HRMS (EI^+): m/z calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3$ [M] $^+$: 222.1250; found: 222.1254.

(2*S*,4*aR*)-2,8-Dimethyl-1,2,5,6-tetrahydro-7*H*-2,4*a*-ethanonaphthalene-3,7(4*H*)-dione (21)

The 1,5-diketone **13** (1.75 g, 7.87 mmol, 1.0 equiv) was added to 1 M KOH (11.8 mL, 11.8 mmol, 1.5 equiv) in MeOH (33 mL). The reaction mixture was stirred at 23 °C for 7 h during which time the color gradually changed to orange. After the reaction was complete as judged by TLC, the reaction mixture was concentrated in vacuo. Subsequently, the residue was redissolved in Et_2O (30 mL) and H_2O (30 mL). The organic phase was separated and the aqueous phase was then acidified by addition of 10% aq HCl (ca. 12 mL) before it was extracted with Et_2O (3×30 mL). The combined organic phases were washed with brine, dried (MgSO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2 , 3:1 hexanes/ EtOAc). The colorless solid material was recrystallized from hexanes to afford **21** (1.31 g, 6.41 mmol, 81%) as colorless crystals suitable for X-ray analysis. The enantiomeric excess was determined to be 99% with HPLC using chiral stationary phase columns (Chiralpak AD, 10% isopropanol in hexanes, flow rate 1 mL/min, 254 nm, 13.3 min (major), 14.7 min (minor)).

Mp 110 °C; $[\alpha]_{\text{D}}^{20.0} +30.5^\circ$ (c 1.00, CHCl_3 , >99% ee); TLC (SiO_2): R_f = 0.13 (3:1 hexanes/ EtOAc ; p -anisaldehyde or KMnO_4 stains).

IR (neat): 2966, 2952, 2915, 1720, 1660, 1631, 1472, 1402, 1310, 1295, 1124, 889, 867, 709 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 2.65 (s, 2 H), 2.62 (t, J = 2.7 Hz, 1 H), 2.46–2.42 (m, 2 H), 2.37 (dd, J = 2.7, 18.7 Hz, 1 H), 2.23 (d, J = 18.5 Hz, 1 H), 2.01–1.96 (m, 2 H), 1.90–1.84 (m, 3 H), 1.72 (s, 3 H), 1.64–1.59 (m, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 213.5, 197.3, 157.2, 130.3, 48.4, 43.7, 38.2, 33.5, 32.4, 31.7, 29.9, 23.1, 10.6.

HRMS (EI^+): m/z calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$ [M] $^+$: 204.1145; found: 204.1114.

(2*S*,4*aR*)-2,8-Dimethyl-3-methylene-1,2,3,4,5,6-hexahydro-7*H*-2,4*a*-ethanonaphthalen-7-one (4)

A 25 mL round-bottom flask was charged with methyltriphenylphosphonium bromide (879 mg, 2.46 mmol, 1.5 equiv) and THF (8 mL). The solution was cooled to 0 °C and a solution of potassium *t*-butoxide (221 mg, 1.97 mmol, 1.2 equiv) in THF (2 mL) was slowly added via syringe. The solution was stirred at 0 °C for 15 min before a solution of dione **21** (335 mg, 1.64 mmol, 1.0 equiv) in THF (2 mL) was added via syringe. Upon addition the color of the reaction mixture changed from yellow to red/brown. Stirring was continued, first at 0 °C for 30 min, then at 23 °C for another 30 min. The reaction was quenched by addition of saturated aq NH_4Cl (7 mL) and Et_2O (7 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (5 mL), dried (MgSO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2 , 7:1 hexanes/ EtOAc) to afford enone **4** (295 mg, 1.45 mmol, 89%) as a colorless liquid.

$[\alpha]_{\text{D}}^{23.4} +21.9^\circ$ (c 2.4, CH_2Cl_2); TLC (SiO_2): R_f = 0.24 (3:1 hexanes/ EtOAc ; p -anisaldehyde or KMnO_4 stains).

IR (neat): 3069, 2928, 2870, 2823, 1666, 1630, 1449, 1308, 1198, 1082, 881, 754 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 4.83 (s, 1 H), 4.64 (s, 1 H), 2.52 (d, J = 2.4 Hz, 1 H), 2.45–2.30 (m, 5 H), 2.22 (d, J = 16.7 Hz, 1 H), 1.81–1.68 (m, 4 H), 1.65 (s, 3 H), 1.61 (m, 1 H), 1.47 (m, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 198.2, 182.2, 149.2, 129.0, 106.4, 40.2, 37.0, 36.4, 35.7, 33.8, 32.2, 30.7, 26.4, 10.3.

HRMS (EI^+): m/z calcd for $\text{C}_{14}\text{H}_{18}\text{O}$ [M] $^+$: 202.1352; found: 202.1351.

(2*S*,4*aR*,8*R*,8*aS*)-8-Allyl-8-methyl-3-methylenooctahydro-7*H*-2,4*a*-ethanonaphthalen-7-one (22) and (2*S*,4*aR*,8*R*,8*aS*)-8-Allyl-8-methyl-3-methylenooctahydro-7*H*-2,4*a*-ethanonaphthalen-7-one (23)

A 20 mL glass scintillation vial (equipped with a magnetic stir bar) pre-cooled to –78 °C in a dry-ice/acetone bath was charged with freshly condensed ammonia (6.64 mL) and metallic Li (11.5 mg, 1.66 mmol, 4 equiv). The resulting mixture turned dark blue within 1 min and was allowed to stir at –78 °C for 10 min. A solution of dienone **4** (84 mg, 0.415 mmol, 1 equiv) in THF (1.66 mL) and H_2O (7.5 μL , 0.415 mmol, 1 equiv) was then added to the dark-blue reaction mixture and the mixture was then allowed to warm to –40 °C by replacing the dry-ice/acetone bath with a dry-ice/acetonitrile bath. After stirring for 1 h at –40 °C, a portion of isoprene (116 μL , 1.66 mmol, 4 equiv) was added and reaction immediately turned clear and colorless. The reaction mixture was then cooled to –78 °C by replacing the dry-ice/acetonitrile bath with a dry-ice/acetone bath, and after 10 min at this temperature a portion of allyl bromide (144 μL , 1.66 mmol, 4 equiv) was added in one portion. After 1.5 h, TLC indicated complete consumption of the intermediates and the reaction was quenched with deionized H_2O (9 mL) and was allowed to warm to r.t. (23 °C). The crude mixture was then transferred to a 500 mL separatory funnel and diluted with 1 M aq HCl soln (ca. 30 mL, until pH 7–9), deionized H_2O (100 mL), aq NH_4Cl soln (100 mL), and EtOAc (60 mL). The aqueous phase was separated and then extracted with EtOAc (3×30 mL, monitored by TLC). The combined organic phases were dried over Na_2SO_4 , decanted, and concentrated in vacuo. Purification by flash chromatography (SiO_2 , 30:1 hexanes/ EtOAc) afforded the compounds **22** and **23** as 1:1 mixture of inseparable diastereomers that appear as a colorless oil (27 mg, 27%).

TLC (SiO_2): R_f = 0.32 (10:1 hexanes/ EtOAc ; p -anisaldehyde or KMnO_4 stains).

IR (neat): 3069, 2926, 2863, 1711, 1647, 1450, 1429, 1377, 1314, 1279, 1222, 1059, 1059, 1002, 973, 911, 874, 916, 728, 565 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 5.76–5.59 (m, 1 H), 4.98 (dd, J = 18.4, 9.2 Hz, 2 H), 4.80 (dd, J = 4.2, 2.0 Hz, 1 H), 4.62 (dd, J = 10.4, 1.8 Hz, 1 H), 2.77 (d, J = 17.3 Hz, 0.4 H), 2.57 (dddd, J = 13.8, 11.1, 5.2, 2.5 Hz, 1 H), 2.44 (dd, J = 13.8, 5.3 Hz, 1 H), 2.34 (s, 1 H), 2.28–2.18 (m, 1 H), 2.18–1.95 (m, 2.5 H), 1.86 (ddd, J = 31.3, 16.7, 9.7 Hz, 2.5 H), 1.76–1.58 (m, 5 H), 1.58–1.50 (m, 1.5 H), 1.46 (ddd, J = 12.7, 8.1, 1.9 Hz, 1 H), 1.43–1.33 (m, 1 H), 1.32–1.18 (m, 2.5 H), 1.14 (d, J = 11.8 Hz, 2 H), 1.06 (s, 1 H), 1.01–0.76 (m, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 216.1, 151.3, 150.9, 135.2, 135.1, 117.2, 117.1, 106.0, 105.1, 77.3, 77.0, 76.8, 50.8, 46.1, 42.3, 41.5, 41.4, 41.3, 37.5, 36.9, 36.3, 36.1, 35.6, 34.9, 32.6, 32.5, 28.1, 28.0, 27.9, 26.7, 25.8, 20.5.

HRMS (EI^+): m/z calcd for $\text{C}_{17}\text{H}_{24}\text{O}$ [$\text{M} + \text{H}$] $^+$: 245.1900; found: 245.1900.

(2*S*,4*aS*,8*S*,8*aR*)-8-Allyl-8-methyl-3-methylene-1,2,3,4,8,8*a*-hexahydro-7*H*-2,4*a*-ethanonaphthalen-7-one (3) and (2*S*,4*aS*,8*S*,8*aS*)-8-Allyl-8-methyl-3-methylene-1,2,3,4,8,8*a*-hexahydro-7*H*-2,4*a*-ethanonaphthalen-7-one (24)

A 4 mL glass scintillation vial (equipped with a magnetic stir bar) was charged with a solution of the diastereomeric mixture of compounds **22** and **23** (10 mg, 0.041 mmol, 1 equiv) in CH₂Cl₂ (0.1 mL) and placed in an ice bath. After stirring for 5 min, a portion of Et₃N (11.4 μ L, 0.082 mmol, 2 equiv) was added, followed by TMSOTf (9 μ L, 0.049 mmol, 1.2 equiv). The reaction mixture was allowed to stir at 0 °C for 30 min, and then a portion of NBS (8.7 mg, 0.049 mmol, 1.2 equiv) was added. After 50 min, TLC indicated complete consumption of starting material and the reaction was quenched with aq NH₄Cl soln (2 mL) and hexanes (2 mL). The aqueous phase was separated and then extracted with hexanes (1 $\times$ 2 mL). The combined organic phases were dried over Na₂SO₄, decanted, and concentrated in vacuo. Purification by flash chromatography (SiO₂, 20:1 hexanes/EtOAc) afforded a crude mixture of diastereomeric monobromides. This mixture was transferred to a 4 mL glass vial (equipped with a magnetic stir bar) and dissolved in DMF (0.2 mL), followed by addition of Li₂CO₃ (6 mg, 0.082 mmol, 2 equiv) and LiBr (3.6 mmol, 0.041 mmol, 1 equiv). The vial was then sealed with a cap and placed in an aluminum block preheated to 130 °C. The reaction was stirred for 1 h at which time TLC indicated consumption of starting material. The mixture was cooled to 22 °C, quenched with aq NH₄Cl soln (3 mL) and hexanes (2 mL). The aqueous phase was separated and then extracted with hexanes (3 $\times$ 2 mL, monitored by TLC). The combined organic phases were dried over Na₂SO₄, decanted, and concentrated in vacuo. Purification by flash chromatography (SiO₂, 30:1 hexanes/EtOAc) afforded the desired compound **3** (3.1 mg, 32%) along with its diastereomer **24** (3.0 mg, 31%), each as colorless oils.

Analytical Data for 3

[α]_D^{23.6} +58° (c 0.1, CH₂Cl₂); TLC (SiO₂): *R*_f = 0.27 (10:1 hexanes/EtOAc; *p*-anisaldehyde or KMnO₄ stains).

IR (neat): 3071, 2926, 2866, 1674, 1557, 1454, 1430, 1389, 1374, 1280, 1248, 1228, 1177, 1153, 1120, 1073, 1001, 911, 880, 826, 766, 723, 708, 647, 577 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 6.47 (d, *J* = 10.1 Hz, 1 H), 5.85 (d, *J* = 10.1 Hz, 1 H), 5.63 (dtd, *J* = 14.9, 9.8, 5.1 Hz, 1 H), 5.00 (dd, *J* = 28.2, 13.6 Hz, 2 H), 4.83 (s, 1 H), 4.66 (d, *J* = 1.6 Hz, 1 H), 2.65 (dd, *J* = 13.9, 5.0 Hz, 1 H), 2.40 (d, *J* = 2.7 Hz, 1 H), 2.28 (d, *J* = 16.1 Hz, 1 H), 2.07 (d, *J* = 17.0 Hz, 2 H), 1.92 (dd, *J* = 13.8, 9.6 Hz, 2 H), 1.77–1.62 (m, 3 H), 1.49 (dd, *J* = 14.3, 7.8 Hz, 3 H), 1.13 (s, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 204.3, 154.7, 149.1, 134.8, 126.3, 117.2, 106.9, 48.0, 44.3, 40.0, 39.6, 36.0, 29.7, 27.7, 26.7, 26.1, 20.7.

HRMS (EI⁺): *m/z* calcd for C₁₇H₂₂O [M + H]⁺: 243.1743; found: 243.1750.

Analytical Data for 24

[α]_D^{23.6} +114° (c 0.1, CH₂Cl₂); TLC (SiO₂): *R*_f = 0.31 (10:1 hexanes/EtOAc; *p*-anisaldehyde or KMnO₄ stains).

IR (neat): 3071, 2930, 2864, 1673, 1456, 1430, 1388, 1374, 1333, 1276, 1245, 1193, 1174, 1117, 1104, 1053, 1000, 976, 909, 872, 826, 770, 723, 710, 648, 567 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 6.46 (d, *J* = 10.1 Hz, 1 H), 5.85 (d, *J* = 10.1 Hz, 1 H), 5.67 (dddd, *J* = 19.9, 14.8, 9.9, 4.8 Hz, 1 H), 5.03 (dd, *J* = 29.0, 13.6 Hz, 2 H), 4.83 (d, *J* = 1.6 Hz, 1 H), 4.63 (d, *J* = 1.7 Hz, 1 H), 2.71–2.60 (m, 2 H), 2.39 (s, 1 H), 2.22–2.11 (m, 2 H), 1.90 (dd, *J* = 13.8, 9.8 Hz, 1 H), 1.81–1.73 (m, 1 H), 1.69 (dd, *J* = 8.4, 5.7 Hz, 2 H), 1.48 (dt, *J* = 13.0, 8.1 Hz, 2 H), 1.40 (ddd, *J* = 12.8, 8.5, 3.7 Hz, 1 H), 1.07 (s, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 204.3, 154.5, 149.4, 135.1, 126.2, 117.1, 105.6, 47.9, 39.9, 38.4, 36.0, 35.9, 35.6, 29.7, 26.8, 25.7, 20.9.

HRMS (EI⁺): *m/z* calcd for C₁₇H₂₂O [M + H]⁺: 243.1743; found: 243.1756.

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Supporting Information

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References

- (1) Currently at BASF Global Strategic Marketing Crop Protection, Limburgerhof, Rheinland-Pfalz, Germany.
- (2) Currently at Department of Chemistry, University of Illinois at Chicago, USA.
- (3) von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Häbich, D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5072.
- (4) (a) Jayasuriya, H.; Herath, K. B.; Zhang, C.; Zink, D. L.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Gonzalez, I.; Salazar, O.; Pelaez, F.; Cummings, R.; Ha, S.; Wang, J.; Sing, S. B. *Angew. Chem. Int. Ed.* **2007**, *46*, 4684. (b) Wang, J.; Kodali, S.; Lee, S. H.; Galgoci, A.; Painter, R.; Dorso, K.; Racine, F.; Motyl, M.; Hernandez, L.; Tinney, E.; Colletti, S. L.; Herath, K.; Cummings, R.; Salazar, O.; Gonzalez, I.; Basilio, A.; Vicente, F.; Genilloud, O.; Pelaez, F.; Jayasuriya, H.; Young, K.; Cully, D. F.; Singh, S. B. *Proc. Nat. Acad. Sci. USA* **2007**, *104*, 7612.
- (5) (a) Wang, J.; Soisson, S. M.; Young, K.; Shoop, W.; Kodali, S.; Galgoci, A.; Painter, R.; Parthasarathy, G.; Tang, Y. S.; Cummings, R.; Ha, S.; Dorso, K.; Motyl, M.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K. B.; Zhang, C. W.; Hernandez, L.; Allocco, J.; Basilio, A.; Tormo, J. R.; Genilloud, O.; Vicente, F.; Pelaez, F.; Colwell, L.; Lee, S. H.; Michael, B.; Felcetto, T.; Gill, C.; Silver, L. L.; Hermes, J. D.; Bartizal, K.; Barrett, J.; Schmatz, D.; Becker, J. W.; Cully, D.; Singh, S. B. *Nature* **2006**, *441*, 358. (b) Singh, S. B.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K. B.; Zhang, C. W.; Zink, D. L.; Tsou, N. N.; Ball, R. G.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Pelaez, F.; Young, K.; Wang, J. *J. Am. Chem. Soc.* **2006**, *128*, 11916. (c) Singh, S. B.; Herath, K. B.; Wang, J.; Tsou, N. N.; Ball, R. G. *Tetrahedron Lett.* **2007**, *48*, 5429. (d) Herath, K. B.; Attygalle, A. B.; Singh, S. B. *J. Am. Chem. Soc.* **2007**, *129*, 15422.
- (6) For syntheses of platencin, see: (a) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1780. (b) Hayashida, J.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2008**, *47*,

4373. (c) Tiefenbacher, K.; Mulzer, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 6199. (d) Jun, S. Y.; Zheng, J.-C.; Lee, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 6201. (e) Waalboer, D. C. J.; Schaapman, M. C.; van Delft, F. L.; Rutjes, F. P. J. T. *Angew. Chem. Int. Ed.* **2008**, *47*, 6576. (f) Nicolaou, K. C.; Toh, Q.-Y.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 11292. (g) Tiefenbacher, K.; Mulzer, J. *J. Org. Chem.* **2009**, *74*, 2937. (h) Varseev, G. N.; Maier, M. E. *Angew. Chem. Int. Ed.* **2009**, *48*, 3685. (i) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J.; Kar, M. J. *Am. Chem. Soc.* **2009**, *131*, 15909. (j) Ghosh, A. K.; Xi, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 5372. (k) Hirai, S.; Nakada, M. *Tetrahedron Lett.* **2010**, *51*, 5076. (l) Hirai, S.; Nakada, M. *Tetrahedron* **2011**, *67*, 518. (m) Li, P.; Yamamoto, H. *Chem. Commun.* **2010**, 6294. (n) Singh, V.; Sahu, B. C.; Bansal, V.; Mobin, S. M. *Org. Biomol. Chem.* **2010**, *8*, 4472. (o) Palanichamy, K.; Subrahmanyam, A. V.; Kaliappan, K. P. *Org. Biomol. Chem.* **2011**, *9*, 7877. (p) Leung, G. Y. C.; Li, H.; Toh, Q.-Y.; Ng, A. M.-Y.; Sum, R. J.; Bandow, J. E.; Chen, D. Y.-K. *Eur. J. Org. Chem.* **2011**, 183. (q) Yoshimitsu, T.; Nojima, S.; Hashimoto, M.; Tanaka, T. *Org. Lett.* **2011**, *13*, 3698. (r) Moustafa, G. A. I.; Saku, Y.; Aoyama, H.; Yoshimitsu, T. *Chem. Commun.* **2014**, 15706. (s) Yadav, J. S.; Goreti, R.; Pabbaraja, S.; Sridhar, B. *Org. Lett.* **2013**, *15*, 3782. (t) Zhu, L.; Zhou, C.; Yang, W.; He, S.; Cheng, G.-J.; Zhang, X.; Lee, C.-S. *J. Org. Chem.* **2013**, *78*, 7912. (u) Chang, E. L.; Schwartz, B. D.; Draffan, A. G.; Banwell, M. G.; Willis, A. C. *Chem. Asian J.* **2015**, *10*, 427.
- (7) For syntheses of platensimycin, see: (a) For a review on the various syntheses of platensimycin, see: Tiefenbacher, K.; Mulzer, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 2548. (b) Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S.; Ellery, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 16905. (c) Yun, S. Y.; Zheng, J.-C.; Lee, D. *J. Am. Chem. Soc.* **2009**, *131*, 8413. (d) Nicolaou, K. C.; Li, A.; Ellery, S. P.; Edmonds, D. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 6293. (e) McGrath, N. A.; Bartlett, E. S.; Sittihan, S. S.; Njardarson, J. T. *Angew. Chem. Int. Ed.* **2009**, *48*, 8543. (f) Palanichamy, K.; Kaliappan, K. P. *Chem. Asian J.* **2010**, *5*, 668. (g) Beaulieu, M.-A.; Sabot, C.; Achache, N.; Guérard, K. C.; Canesi, S. *Chem. Eur. J.* **2010**, *16*, 11224. (h) Tiefenbacher, K.; Tröndlin, L.; Mulzer, J.; Pfaltz, A. *Tetrahedron* **2010**, *66*, 6508. (i) Oblak, E. Z.; Wright, D. L. *Org. Lett.* **2011**, *13*, 2263. (j) Horii, S.; Torihata, M.; Nagasawa, T.; Kuwahara, S. *J. Org. Chem.* **2013**, *78*, 2798. (k) Zhu, Z.; Han, Y.; Du, G.; Lee, C.-S. *Org. Lett.* **2013**, *15*, 524. (l) Eey, S. T.-C.; Lear, M. *Chem. Eur. J.* **2014**, *20*, 11556. (m) Jiao, Z.-W.; Tu, Y.-Q.; Zhang, Q.; Liu, W.-X.; Wang, S.-H.; Wang, M. *Org. Chem. Front.* **2015**, *2*, 913.
- (8) (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924. (c) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, Jr. J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199. (d) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2012**, *4*, 130. (e) Bennett, N. B.; Duquette, D. C.; Kim, J.; Liu, W.-B.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2013**, *19*, 4414. (f) Reeves, C. M.; Eidamshaus, C.; Kim, J.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6718. (g) Craig, R. A. II.; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 5160. (h) Starkov, P.; Moore, J. T.; Duquette, D. C.; Stoltz, B. M.; Marek, I. *J. Am. Chem. Soc.* **2017**, *139*, 9615. (i) For a review of the development of the enantioselective Tsuji allylation in our labs and others, see: Mohr, J. T.; Stoltz, B. M. *Chem. Asian J.* **2008**, *2*, 1476.
- (9) Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323.
- (10) For recent reviews of allylic alkylation of ketone enolates, see: (a) Braun, M.; Meier, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6952. (b) You, S.-L.; Dai, L.-X. *Angew. Chem. Int. Ed.* **2006**, *45*, 5246. (c) Braun, M.; Meier, T. *Synlett* **2006**, 661. (d) Kazmaier, U. *Curr. Org. Chem.* **2003**, *7*, 317. (e) For a recent general review of enantioselective allylic alkylation, see: Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258.
- (11) For selected applications in total synthesis efforts in our group, see: (a) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738. (b) Enquist, J. A.; Stoltz, B. M. *Nature* **2008**, *453*, 1228. (c) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810. (d) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289. (e) Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293. (f) Numajiri, Y.; Pritchett, B. P.; Chiyoda, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2015**, *137*, 1040. (g) Loskot, S. A.; Romney, D. K.; Arnold, F. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2017**, *139*, 10196. (h) Pritchett, B. P.; Donckele, E. J.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 12624. (i) For a review, see: Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, *14*, 2745.
- (12) (a) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. (b) Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871.
- (13) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkowicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
- (14) For accounts of the development of PHOX ligands, see: (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (b) Williams, J. M. J. *Synlett* **1996**, 705.
- (15) We have developed an efficient multi-gram scale synthesis of PHOX ligands, see: (a) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529. (b) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181.
- (16) (a) Agnello, E. J.; Laubach, G. D. *J. Org. Chem.* **1960**, *25*, 4293. (b) Wijnberg, J. P. B. A.; Vader, J.; de Groot, A. J. *Org. Chem.* **1983**, *48*, 4380. (c) Guo, M.; Minuti, L.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1989**, *54*, 6138.
- (17) For relevant bond dissociation energies: C(sp²) C–X: C–Cl: 94 kcal/mol, C–Br: 79.6 kcal/mol, C–I: 61.9 kcal/mol. See: Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, **2007**.
- (18) (a) Piers, E.; Harrison, C. L.; Zetina-Rocha, C. *Org. Lett.* **2001**, *3*, 3245. (b) Pastor, I. M.; Yus, M. *Tetrahedron* **2001**, *57*, 2371.
- (19) Stetter, H.; Kuhlmann, H. *Chem. Ber.* **1976**, *109*, 2890.
- (20) (a) Hanessian, S.; Griffin, A. M.; Rozema, M. J. *Bioorg. Med. Chem. Lett.* **1997**, *14*, 1857. (b) Yamada, C. M.; Dellinger, D. J.; Carruthers, M. H. *J. Am. Chem. Soc.* **2006**, *128*, 5251.
- (21) (a) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425. (b) Donnelly, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1729.
- (22) (a) Slomp, G. Jr.; Johnson, J. L. *J. Org. Chem.* **1958**, *23*, 915. (b) Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 1964.
- (23) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725.
- (24) Other carbene catalysts provide either slower conversion into **20** or no detectable conversion.
- (25) (a) Yoshikai, K.; Hayama, T.; Nishimura, K.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2005**, *70*, 681. (b) For mechanistic investigations of this reaction, see: Yoshikai, K.; Hayama, T.; Nishimura, K.; Yamada, K.-i.; Tomioka, K. *Chem. Pharm. Bull.* **2005**, *53*, 586.

- (26) Crystallographic data: CCDC 686706 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- (27) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
- (28) Schlosser, M. *Organometallics in Synthesis*; Wiley-VCH: New York, **1996**.
- (29) 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.
- (30) Still, W. C.; Kahn, M.; Mitra, A. J. *Org. Chem.* **1978**, *43*, 2923.