# Construction of the Tricyclic A-B-C Core of the *Veratrum* Alkaloids

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S *Supporting Information*

ABSTRACT: Organocatalyzed enantioselective allylation of 2-iodocyclohexenone followed by methylation and oxy-Cope rearrangement delivered enantiomerically enriched 2-methyl 3-allyl cyclohexanone, which engaged in acid-catalyzed Robinson annulation to give the bicyclic enone. Subsequent elaboration of the pendant allyl group into an α-diazo β-keto ester set the stage for Rh-mediated cyclization to deliver the tricyclic A-B-C core of the *Veratrum* alkaloids.
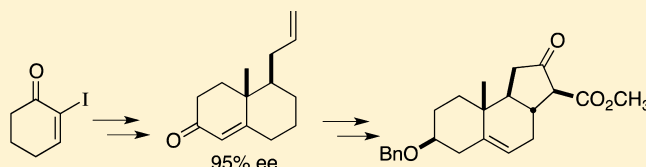
■ INTRODUCTION

The *Veratrum* alkaloids (Figure 1) contain a 6−6−5−6 carbocyclic scaffold connected to either a piperidine system
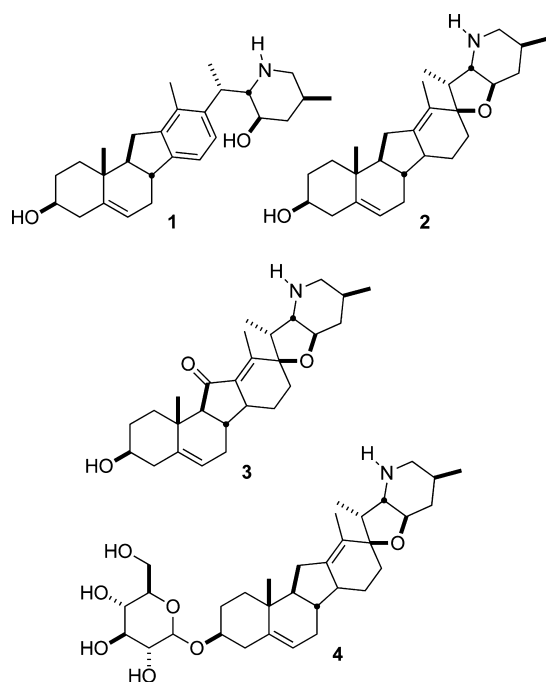

Figure 1. Members of the *Veratrum* family of alkaloids.

or a 5−6 tetrahydrofuran/piperidine system.[1] Members of this family of natural products include veratramine **1**, cyclopamine **2**, jervine **3**, and cycloposine **4**. In particular, cyclopamine has been investigated for its activity against certain cancers, especially basal cell carcinoma, pancreatic cancer, medulloblastoma, and small cell lung cancer.[2] These cancers propagate via the Hedgehog pathway, of which cyclopamine **2** is a known inhibitor.

To date, no direct synthetic route to the 6−6−5 tricyclic core system of the *Veratrum* alkaloids has been described. We envisioned (eq 1) an approach to the β-keto ester **5** by way of the key enone **6**.
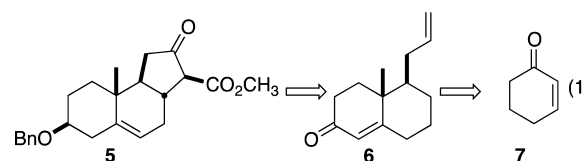
■ RESULTS AND DISCUSSION

The Wieland−Miescher ketone **8** (Figure 2), both in racemic[3] and enantiomerically pure[4] form, has been a workhorse for
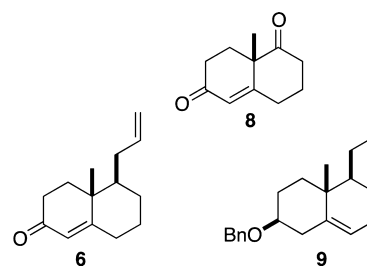

Figure 2. Chirons for polyalicyclic synthesis.

polyalicyclic synthesis. We hypothesized that the enantiomerically pure enone **6** and the deconjugated ether **9** could be similarly versatile chirons.

Preparation of the Enone 6. The preparation (Scheme 1) of the enone **6** began with the crystalline α-iodo enone **10**.[5] As we have reported,[6] asymmetric allylation proceeded smoothly using the Schaus[7] protocol, allyl borane **11** in the presence of catalytic *R*-Br₂BINOL, to deliver the alcohol **12** in high yield

Scheme 1

Scheme 2

Scheme 3
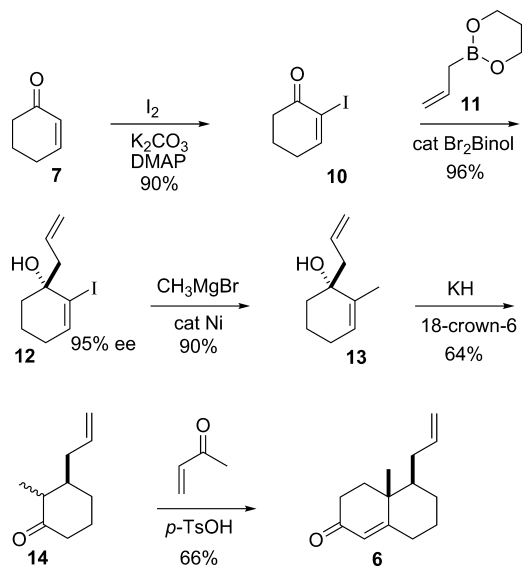
and 95% ee. For this conversion to be practical, the catalyst ($200/g) needed to be recycled. We were pleased to find that an aqueous extraction using 5% NaOH enabled 90−95% catalyst separation and recovery.

A Kumada coupling[8] was employed to convert **12** to **13**. The oxy-Cope rearrangement of **13** in toluene using KH in paraffin[9] initially presented some difficulty, due to the low molecular weight of **14**. Extractive workup with low boiling diethyl ether reduced the amount of volatile product lost during the purification. Direct filtration of the concentrated toluene extract through silica gel then delivered the pure ketone **14**.

Rounding out the synthesis was a Robinson annulation with methyl vinyl ketone to give the enantiomerically pure enone **6**. The acid-mediated Robinson annulation proceeded to ∼35% conversion before decomposition set in. Attempts to increase conversion through additional equivalents of methyl vinyl ketone were not successful. However, the unreacted ketone **14** was readily recovered in the course of the purification of **6**.

Preparation of the Ether 9. Many polyalicyclic natural products, including **1−4**, have an equatorial hydroxyl group in the A ring with the alkene beginning at C-5. We therefore applied (Scheme 2) the classic deconjugating protocol[10] to the enone **6**. The crude enol acetate **15** was reduced[11] with NaBH$_4$ to give the alcohol **16** as a 4:1 mixture of diastereomers. A survey of protecting groups led to the crystalline 3-bromobenzoate **17**, the structure, including absolute configuration, of which was confirmed by X-ray crystallography (Supporting Information).

Exposure of the recrystallized **17** to CH$_3$OH/K$_2$CO$_3$ liberated the pure equatorial alcohol **18**, which was carried on to the benzyl ether **9**. The protection of **18** with BnBr and NaH gave incomplete conversion, even at elevated temperatures. Alternatively, with KH in paraffin,[12] the alcohol was converted to the benzyl ether **9** smoothly at room temperature.

Preparation of a Tricyclic β-Keto Ester. The alkaloids **1−4** each have a *trans*-fused five-membered C-ring. Given the literature precedent,[13] it seemed likely that the α-diazo β-keto ester **20** (Scheme 3) would, under Rh catalysis, cyclize to **5**.

In a preliminary investigation, the terminal alkene of racemic **9** was selectively converted to the methyl ketone **19** using the modified Wacker oxidation developed by Sigman,[14] *tert*-butyl
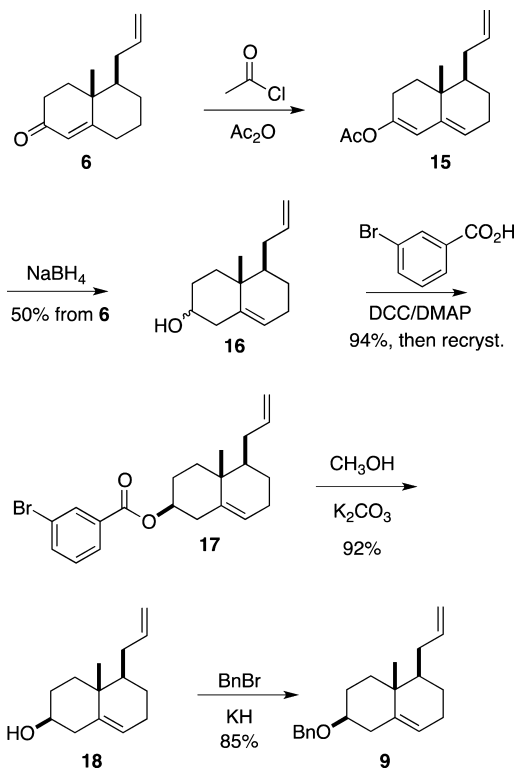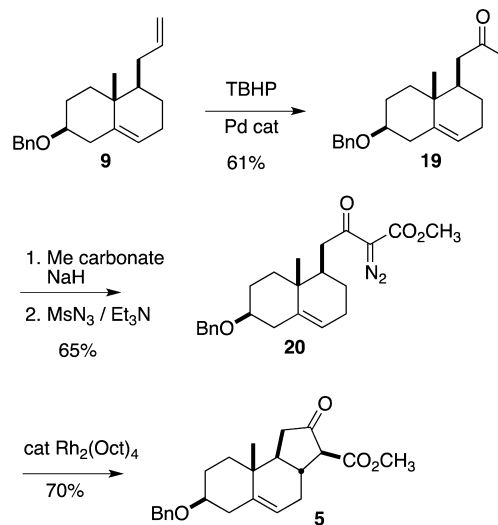
hydroperoxide in the presence of a Pd(quinox)Cl$_2$ complex. Diazo transfer[15] on the derived β-keto ester delivered the desired α-diazo β-keto ester **20**.

In the event, cyclization proceeded smoothly, to give the crystalline tricyclic ketone **5** as a single diastereomer. The assignment of the relative configuration of **5** was supported by the ring methines at δ 62.3, 48.5, and 37.7 in the ^{13}C NMR, as well as by the 12.0 Hz coupling constant of the β-keto ester methine in the ^{1}H NMR.

■ **CONCLUSION**

We have developed a scalable, enantioselective route to the bicyclic chirons **6** and **9** and to the tricyclic β-keto ester **5**. We

believe that these now readily available chirons will have wide applicability in target-directed synthesis.[16]

■ EXPERIMENTAL SECTION

General Procedures. ^{1}H NMR and ^{13}C NMR were measured at 400 MHz for ^{1}H and 90 and 100 MHz for ^{13}C in $CDCl_3$. [13]C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d", from methylene and quaternary carbon as "u". The infrared (IR) spectra were determined as neat oil. High resolution mass spectra (HRMS) were obtained by electron impact (EI) or chemical ionization (CI). R_f values indicated refer to thin layer chromatography (TLC) on 2.5 cm × 10 cm, 250 μm analytical plates coated with silica gel GF, developed in the solvent system indicated. Flash chromatography was performed using silica gel 60 (40−60 μm). Solvents are referred as vol/vol mixtures. All air- and moisture-sensitive reactions were performed in oven-dried glassware under a positive pressure of nitrogen. All solvents were purified immediately prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium metal/benzophenone under nitrogen. Dichloromethane, toluene, and acetonitrile (MeCN) were distilled from CaH_2 under nitrogen. All reaction mixtures were stirred magnetically under nitrogen atmosphere. MTBE is *tert*-butyl methyl ether, PE is 30−60 petroleum ether, DME is dimethoxyethane, and MeOH is methanol. HRMS were recorded in EI mode on a double-focusing instrument.

2-Iodocyclohex-2-enone 10. Following the reported procedure,[5] 2-cyclohexenone (35.0 g, 0.365 mol) was dissolved in a 1:1 mixture of THF/H_2O and stirred at 0 °C for 5 min. Next, K_2CO_3 (60.375 g, 0.438 mol) was added, followed by DMAP (8.893 g, 7.29 mmol). The reaction mixture turned a series of colors before finally turning brown. The solution was stirred for 10 min. I_2 (111.1 g, 0.437 mol) was then added slowly to avoid forming a solid mass at the bottom of the flask. The reaction turned black and was stirred overnight open to the atmosphere at room temperature. The mixture was then partitioned between EtOAc and, sequentially, 0.1 M aqueous HCl, saturated aqueous $Na_2S_2O_3$, and brine. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was filtered through a silica plug to give enone **10** (72.89 g, 90% yield) as a yellow crystalline solid. The spectral data matched that of the previously synthesized material.[5b] TLC R_f (MTBE/PE, 1:4) 0.40; ^{1}H NMR ($CDCl_3$) δ 7.77 (t, J = 4.4 Hz, 1H), 2.67 (t, J = 6.8 Hz, 2H), 2.44 (m, 2H), 2.09 (m, 2H); ^{13}C NMR δ (u) 192.2, 103.9, 37.3, 30.0, 22.9; (d) 159.5.

B-Allyl-1,3,2-dioxaborinane 11. Following the reported procedure,[17] a solution of trimethyl borate (22.76 mL, 200 mmol) was dissolved in 200 mL of Et_2O at −78 °C, and allylmagnesium bromide (1.0 M in Et_2O, 200 mL, 200 mmol) was added. The resulting white suspension was stirred at this temperature for 2 h before the dry ice bath was removed and the solution allowed to warm to −20 °C. Aqueous HCl (3 M, 200 mL) was added, and the mixture turned clear as the solids dissolved. The solution was stirred for 20 min at room temperature. The layers were separated, and the aqueous layer was extracted × 3 with Et_2O. The organic layers were dried and concentrated to about 200 mL on a rotovap with the bath set no higher than 30 °C. Then 100 mL of dry Et_2O was added along with 1,3-propanediol (15.2 g, 200 mmol) and activated 4 Å molecular sieves (36 g). The reaction mixture was stirred at room temperature for 20 h. The reaction mixture was filtered through glass wool, and the molecular sieves were washed × 2 with Et_2O. The reaction mixture was concentrated without having the water bath exceed 30 °C. The resulting clear solution was dissolved in 200 mL of pentane, and the excess 1,3-propanediol (bottom layer) was removed via pipet. The solution was filtered through Celite and concentrated under reduced pressure to give compound **11** (17.1 g, 68% yield) as a clear oil. The spectra matched that of the previously synthesized compound.[7] ^{1}H NMR ($CDCl_3$) δ 5.86 (m, 1H), 4.92 (m, 2H), 3.99 (t, J = 5.6 Hz, 4H), 1.95 (m, 2H), 1.64 (d, J = 7.2 Hz, 2H); ^{13}C NMR δ (u) 113.9, 61.8, 27.3; (d) 135.5.

(R)-1-Allyl-2-iodocyclohex-2-enol 12. Following the reported procedure,[7] to a round-bottom flask were added (R)-BINOL-Br$_2$ (0.750 g, 1.689 mmol), *t*-BuOH (4.65 g, 62.83 mmol), and the allylborane **11** (6.861 g, 54.46 mmol). This mixture was stirred for 10 min at room temperature, then 2-iodocyclohex-2-enone **10** (9.3 g, 41.89 mmol) was added all at once, and the mixture was stirred for 24 h at room temperature. The mixture was then diluted with PE and extracted with 5% aqueous NaOH solution × 3. The aqueous phase was then back extracted once with diethyl ether, and the combined organics were dried (Na_2SO_4) and concentrated. The residue was passed through a small plug of silica gel to give alcohol **12**[18] (10.6 g, 96% yield) as a light yellow oil. $[\alpha]^{20}_D$ = −34.6 (*c* 1.00, CH_2Cl_2), 95% ee; TLC R_f (MTBE/PE, 1:4) 0.54; ^{1}H NMR ($CDCl_3$) δ 6.57 (m, 1H), 5.78 (m, 1H), 5.19 (d, J = 6.0 Hz, 1H), 5.15 (s, 1H), 2.44 (d, J = 7.2 Hz, 2H), 2.04 (m, 4H), 1.89 (m, 1H), 1.72 (m, 2H); ^{13}C NMR δ (u) 119.0, 111.8, 73.0, 47.2, 34.2, 29.7, 18.9; (d) 141.9, 132.9; IR 3435, 1638, 1436, 1329, 1171, 1081, 981, 918, 764 cm^{-1}; HRMS calcd for $C_9H_{12}I$ (M − OH) 246.9984, obsd 246.9992. **Recovery of catalyst.** The basic aqueous phase was acidified with conc aqueous HCl until the pH was ∼1. The aqueous layer was extracted × 3 with Et_2O, and the combined organics were dried (Na_2SO_4), rotovaped to silica gel, and purified through a silica plug to give recovered (R)-BINOL-Br$_2$ (0.690 g, 92% recovered).

Determination of Enantiomeric Excess. An HPLC was used, along with a UV−vis detector and a Chiracel OD column (150 mm × 20 mm). A 20-μL portion of a 1 mg/mL sample of alcohol **12** in PE was injected, and a linear run (1 mL/min) was employed ranging from 0.2% isopropanol in hexane at 0 min to 0.3% isopropanol in hexane at 70 min. The detector was set at a wavelength of 254 nm. The retention time of the major enantiomer was 19.012 min, and that of the minor enantiomer was 21.062 min.

(R)-1-Allyl-2-methylcyclohex-2-enol 13.[6] To a slurry of NiCl$_2$·dppp (23 mg, 0.5 mol %) in dry Et_2O (40 mL) was added MeMgBr (3.0 M in Et_2O, 6.7 mL, 20.04 mmol) via syringe, and the mixture was stirred at room temperature for 10 min under N_2. Iodide **12** (2.30 g, 8.71 mmol) was slowly added in 10 mL of Et_2O. The reaction was stirred overnight at room temperature. Once the reaction was complete by TLC, Na_2SO_3 (5 g) was added, and the mixture stirred vigorously for 5 min. The atmosphere was purged completely with N_2, and the solution was sparged with N_2. The solution was then *rapidly quenched with saturated aqueous $Na_2S_2O_3$ under N_2 atmosphere*. PE was then immediately added to dilute the solution. The layers were separated and the aqueous layer was extracted × 3 with Et_2O. The solution was then dried (Na_2SO_4 and Na_2SO_3) and concentrated. The solution was filtered through a small plug of silica gel to give alcohol **13** (1.196 g, 90% yield) as a light yellow oil. $[\alpha]^{20}_D$ = −34.9 (*c* 1.00, CH_2Cl_2); TLC R_f (MTBE/PE, 1:4) 0.46; ^{1}H NMR δ 5.78 (m, 1H), 5.64 (m, J = 1.6 Hz, 1H), 5.15 (m, 1H), 5.11 (t, J = 1.2 Hz, 1H), 2.40 (dt, J = 7.2, 1.2 Hz, 2H), 1.98 (m, 2H), 1.78 (m, 4H), 1.64 (m, 4H); ^{13}C NMR δ (u) 137.0, 118.2, 71.6, 43.6, 35.7, 25.6, 19.1; (d) 134.1, 126.6, 17.8; IR 1639, 1440, 1174, 973, 912 cm^{-1}; HRMS calcd for $C_{10}H_{15}$ (M − OH) 135.1174, obsd 135.1173.

(R)-3-Allyl-2-methylcyclohexanone 14. Following the literature procedure,[6,19] 18-crown-6 (4.113 g, 15.58 mmol) was dissolved in dry toluene (80 mL), *t*-BuOK (3.489 g, 31.16 mmol) was added, and the mixture was stirred under N_2 for 5 min at room temperature. Alcohol **13** (3.383 g, 22.26 mmol) in 15 mL of dry toluene was added dropwise over 5 min. The mixture was then heated to 85 °C (bath temperature) for 1 h, cooled to room temperature, and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted × 3 with PE, and the combined organic layers were dried (Na_2SO_4). The toluene/PE solution was then diluted with more PE and placed directly on a column for purification by silica gel chromatography to afford ketone **14** (2.162 g, 64% yield, mixture of *trans/cis* diastereomers) as a light yellow oil. $[\alpha]^{20}_D$ = +10.0 (*c* 1.00, CH_2Cl_2, 2:1 mixture of *trans/cis* diastereomers); TLC R_f (MTBE/PE, 1:4) 0.67; ^{1}H NMR δ 5.85−5.73 (m, 1H, *trans* diastereomer), 5.75−5.63 (m, 1H, *cis* diastereomer), 5.11−5.03 (m, 2H, *trans* diastereomer), 5.03−4.98 (m, 2H, *cis* diastereomer), 2.66−2.00 (m, 6H), 1.93−1.41 (m, 4H), 1.05 (d, J = 12.8 Hz, 3H, *trans* diastereomer), 1.02 (d, J = 12.8 Hz, 3H, *cis* diastereomer); ^{13}C NMR (*trans* diastereomer) δ (u) 213.4, 117.1, 41.5, 38.2, 30.3, 25.7; (d) 135.5, 49.4, 45.2, 11.9; (*cis* diastereomer) δ

(u) 214.5, 116.3, 39.8, 33.7, 26.7, 23.7; (d) 136.5, 48.7, 41.9, 11.5; IR 1711, 1640, 1447, 1221, 999, 914 cm^{-1}; HRMS calcd for $C_{10}H_{17}O$ (M + H) 153.1279, obsd 153.1283.

(4aR,5R)-5-Allyl-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one 6. To a solution of ketone **14** (1.360 g, 8.95 mmol) in dry toluene (30 mL) were added p-toluenesulfonic acid monohydrate (0.170 g, 0.89 mmol) and a small amount of methylene blue dye as a free radical inhibitor. The mixture was stirred for 5 min at room temperature, then methyl vinyl ketone (1.565 g, 22.37 mmol) was added, and the mixture was heated to reflux overnight. The reaction was then cooled to room temperature and quenched with saturated aqueous NaHCO$_3$. The layers were separated, and the aqueous layer was extracted × 3 with Et$_2$O. The combined organic layers were then dried (Na$_2$SO$_4$), and the ether was removed (setting the rotovap bath no higher than 30 °C). The toluene solution was diluted with PE and placed directly on a column for purification by silica gel chromatography to afford enone **6** (417 mg, 66% brsm, 23% overall) as an orange oil along with 887 mg of ketone **14**. $[\alpha]^{20}_D$ = +69.8 (c 1.00, CH$_2$Cl$_2$); TLC R_f (MTBE/PE, 1:4) 0.35; ^{1}H NMR δ 5.86−5.66 (m, 2H), 5.08−4.98 (m, 2H), 2.50−2.08 (m, 6H), 1.92−1.71 (m, 4H), 1.43−1.25 (m, 3H), 1.13 (s, 3H); ^{13}C NMR δ (u) 199.5, 171.8, 116.2, 39.2, 35.4, 34.1, 33.9, 33.5, 26.8, 26.3; (d) 137.7, 124.2, 48.4, 16.8; IR 1673, 1615, 1441, 995, 912 cm^{-1}; HRMS calcd for $C_{14}H_{21}O$ (M + H) 205.1592, obsd 205.1588.

(4aR,5R)-5-Allyl-4a-methyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol 16. The enone **6** (0.400 g, 1.96 mmol) was dissolved in acetic anhydride (5 mL), and acetyl chloride (0.769 g, 9.80 mmol) was then added. The mixture was heated to 65 °C for 4 h. The acetic anhydride and acetyl chloride were removed via bulb to bulb distillation under vacuum (heating no higher than 40 °C). The residue was then dissolved in CH$_2$Cl$_2$, rotovaped to silica gel, and purified by column chromatography to afford (4aR,5R)-5-allyl-4a-methyl-3,4,4a,5,6,7-hexahydronaphthalen-2-yl acetate **15** along with unidentified contaminants (0.320 g total weight). This crude mixture (which included acetate **15**) was dissolved in 13 mL of a 1:1 mixture of THF/t-BuOH. The solution was cooled to 0 °C and stirred for 5 min. NaBH$_4$ (0.395 g, 10.41 mmol) in a 1:1 mixture of H$_2$O/THF (3 mL) was then added dropwise at 0 °C. The reaction mixture was placed in the freezer (−20 °C) for 48 h and then stirred at room temperature for 48 h. The solvent was removed under reduced pressure, and 0.5 M aqueous HCl was added to the residue. The aqueous layer was extracted × 3 with Et$_2$O. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated. The residue was purified via column chromatography to afford alcohol **16** (206 mg, 50% yield from **6**) as a 4:1 mixture of diastereomers (clear oils). $[\alpha]^{20}_D$ = −71.0 (c 1.00, CH$_2$Cl$_2$, 4:1 mixture of diastereomers); TLC R_f (MTBE/PE, 1:4) 0.28; ^{1}H NMR (CDCl$_3$) δ 5.77 (m, 1H), 5.40 (m, 1H), 5.01 (m, 2H), 3.54 (m, 1H), 2.35−1.07 (m, 14H), 0.95 (s, 3H); ^{13}C NMR δ (u) 140.7, 115.5, 42.2, 36.9, 34.6, 31.6, 25.9, 23.0; (d) 138.7, 122.8, 71.9, 46.1, 18.2; IR 1641, 1439, 1357, 1049, 906 cm^{-1}; HRMS calcd for $C_{14}H_{21}$ (M − OH) 189.1643, obsd 189.1640.

(4aR,5R)-5-Allyl-4a-methyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl 3-Bromobenzoate 17. Alcohol **16** (0.227 g, 1.10 mmol), m-Br benzoic acid (0.244 g, 1.21 mmol), and DMAP (34 mg, 0.275 mmol) were combined in a round-bottom flask along with 5 mL of CH$_2$Cl$_2$. The solution was cooled to 0 °C and stirred for 5 min. DCC in 2 mL of CH$_2$Cl$_2$ was added slowly. The ice bath was removed, and the reaction was stirred overnight at room temperature. The solids were filtered out and washed with CH$_2$Cl$_2$. The filtrate was concentrated, and the residue was rotovaped to silica gel and chromatographed to give ester **17** (353 mg, 94% yield) as a clear oil (4:1 mixture of diastereomers). $[\alpha]^{20}_D$ = −39.2 (c 1.00, CH$_2$Cl$_2$, after crystallization, 14:1 mixture of diastereomers); TLC R_f (MTBE/PE, 5:95) 0.69; ^{1}H NMR (CDCl$_3$) δ 8.19 (t, J = 1.6 Hz, 1H), 8.00 (dt, J = 7.6, 1.2 Hz, 1H), 7.70 (dt, J = 8.0, 1.2 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 5.80 (m, 1H), 5.50 (s, 1H), 5.05 (m, 2H), 4.88 (m, 1H), 2.47 (m, 2H), 2.34 (dd, J = 12.4, 1.2 Hz, 1H), 2.02 (m, 4H), 1.76 (m, 3H), 1.26 (m, 3H), 1.03 (s, 3H); ^{13}C NMR δ (u) 164.7, 139.4, 132.7, 122.4, 115.6, 38.0, 37.0, 36.6, 34.5, 27.8, 26.0, 23.0; (d) 138.6, 135.7, 132.6,

129.9, 128.2, 124.1, 75.1, 46.0, 18.2; IR 1719, 1285, 1255, 1123, 987, 747 cm^{-1}.

Enantioenriched Alcohol 18. Ester **17** was recrystallized by dissolving in a minimal amount of boiling MeOH and allowing the solution to stand and cool until crystals formed. The diastereomeric ratio of the isolated crystals ranged from 9:1 to 20:1. $[\alpha]^{20}_D$ = −39.2 (14:1 ratio), mp = 77−79 °C. After recrystallization, ester **17** (103 mg, 0.264 mmol) was stirred in 4 mL of MeOH. Then K$_2$CO$_3$ (146 mg, 1.059 mmol) was added, and the suspension was stirred at room temperature for 2.5 h. The MeOH was removed under reduced pressure, and the residue was rotovaped to silica gel and chromatographed to give enantioenriched alcohol **18** (50 mg, 92% yield) $[\alpha]^{20}_D$ = −92.8 (c 1.00, CH$_2$Cl$_2$, 20:1 diastereomeric ratio) as a clear oil. The spectra matched those of alcohol **16**.

(1R,6S,8aR)-1-Allyl-6-(benzyloxy)-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene 9. The alcohol **18** (90 mg, 0.44 mmol) was dissolved in 5 mL of THF and KH(P) (70 mg at 50% w/w in paraffin, 0.874 mmol) was added. The mixture was stirred at room temperature for 30 min, and then tetrabutylammonium iodide (16 mg, 0.044 mmol) was added, followed by BnBr (75 mg, 0.437 mmol). The reaction mixture was stirred for 1 h at room temperature and then rotovaped to silica gel and chromatographed to give benzyl ether **9** (110 mg, 85% yield) as a clear oil. TLC R_f (MTBE/PE, 1:4) 0.82; ^{1}H NMR δ 7.39−7.22 (m, 5H), 5.76 (m, 1H), 5.38 (m, 1H), 5.00 (m, 2H), 4.56 (s, 2H), 3.29 (m, 1H), 2.44 (m, 1H), 2.35−1.00 (m, 12H), 0.95 (s, 3H); ^{13}C NMR δ (u) 140.9, 139.0, 115.6, 70.0, 39.1, 37.3, 36.8, 34.6, 28.4, 26.0, 23.0; (d) 138.8, 128.4, 127.6, 127.5, 122.7, 78.6, 46.1, 18.2; IR 1451, 1357, 1094, 909, 735 cm^{-1}; HRMS calcd for $C_{14}H_{21}$ (M − OBn) 189.1643, obsd 189.1647.

1-((1R,6S,8aR)-6-(Benzyloxy)-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-1-yl)propan-2-one 19. Pd(quinox)Cl$_2$[14] (14 mg, 8.5 mol %) and AgSbF$_6$ (40 mg, 24 mol %) were stirred with 3 mL of CH$_2$Cl$_2$ for 10 min at room temperature in the dark. $tert$-Butyl hydroperoxide (70% in H$_2$O, 677 mg, 5.27 mmol) was added at room temperature, and the mixture was stirred for 10 min. The solution was then cooled to 0 °C and stirred for 5 min. Benzyl ether **9** (130 mg, 0.439 mmol) in 1 mL of CH$_2$Cl$_2$ was then added slowly over 5 min. The reaction mixture was stirred until the starting material was consumed, as monitored by TLC. The excess TBHP was reduced by adding saturated aqueous Na$_2$S$_2$O$_3$ and stirring for 30 min. The aqueous layer was extracted × 3 with CH$_2$Cl$_2$. The combined organics were washed with brine, dried (Na$_2$SO$_4$), and concentrated. The residue was chromatographed to afford ketone **19** (130 mg, 61% yield) as a clear oil. TLC R_f (MTBE/PE, 1:4) 0.42; ^{1}H NMR δ 7.39−7.25 (m, 5H), 5.42 (s, 1H), 4.59 (s, 2H), 3.36−3.25 (m, 1H), 2.59−2.40 (m, 2H), 2.30−2.20 (m, 2H), 2.17 (s, 3H), 2.10−1.09 (m, 9H), 0.98 (s, 3H); ^{13}C NMR δ (u) 208.2, 139.2, 137.9, 69.0, 43.7, 38.0, 35.7, 35.6, 27.2, 24.6, 23.5; (d) 127.4, 126.6, 126.4, 121.7, 77.4, 40.6, 29.6, 17.5; IR 1714, 1453, 1359, 1274, 1094, 738 cm^{-1}; HRMS calcd for $C_{21}H_{29}O_2$ (M + H) 313.2168, obsd 313.2176.

Methyl 2-Diazo-4-((1R,6S,8aR)-6-(benzyloxy)-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-1-yl)-3-oxobutanoate 20. NaH (60% in mineral oil, 50 mg, 1.25 mmol) and dimethyl carbonate (187 mg, 2.08 mmol) were stirred in 3 mL of dry DME. The solution was heated to reflux (bath temperature = 95 °C, condenser attached), and 2 drops of MeOH were added. Ketone **19** (65 mg, 0.208 mmol) in 2.5 mL of DME was added, and the mixture was heated to reflux for 12 h. The solution was cooled, and 10% aqueous HCl was added. The aqueous layer was extracted × 3 with Et$_2$O. The combined organics were dried (Na$_2$SO$_4$) and concentrated. The residue was chromatographed to give methyl 4-((1R,6S,8aR)-6-(benzyloxy)-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-1-yl)-3-oxobutanoate (59 mg) as a clear oil. TLC R_f (MTBE/PE, 1:4) 0.39; ^{1}H NMR δ 7.31 (m, 5H), 5.40 (m, 1H), 4.56 (s, 2H), 3.74 (s, 3H), 3.46 (s, 2H), 3.30 (m, 1H), 2.65 (dd, J = 16.8, 2.4 Hz, 1H), 2.45 (m, 1H), 2.33 (dd, J = 16.8, 10.4 Hz, 1H), 2.24 (m, 1H), 2.10−1.06 (m, 9H), 0.96 (s, 3H); ^{13}C NMR δ (u) 202.7, 167.6, 140.1, 138.9, 70.1, 49.5, 44.2, 39.0, 36.8, 36.6, 28.3, 25.6, 24.5; (d) 128.4, 127.6, 127.5, 122.7, 78.4, 52.4, 41.4, 18.5; IR 1742, 1712, 1442, 1314, 1241, 1079

cm^{-1}; HRMS calcd for C$_{23}$H$_{30}$O$_4$Na: 393.2042 (M + Na), obsd 393.2037.

The β-keto ester (55 mg, 0.149 mmol) was dissolved in 3 mL of dry MeCN, and MsN$_3$[15] (36 mg, 0.297 mmol) was added. The solution was stirred for 5 min at 0 °C, and NEt$_3$ (45 mg, 0.445 mmol) was added in 1 mL of MeCN. The solution was stirred overnight at room temperature. The solution was evaporated directly onto silica gel and chromatographed to give diazo ester **20** (50 mg, 65% yield from **19**) as a light yellow oil. TLC R_f (MTBE/PE, 1:4) 0.44; ^{1}H NMR δ 7.34 (m, 5H), 5.42 (m, 1H), 4.59 (s, 2H), 3.86 (s, 3H), 3.38−3.26 (m, 1H), 2.97 (dd, J = 16.0, 2.4 Hz, 1H), 2.75 (dd, J = 16.0, 10.8 Hz, 1H), 2.51−1.12 (m, 11H), 1.04 (s, 3H); ^{13}C NMR δ (u) 193.0, 161.8, 140.4, 139.0, 74.2, 70.0, 41.0, 39.0, 37.0, 36.7, 28.3, 25.7, 24.3; (d) 128.4, 127.6, 127.5, 122.6, 78.5, 52.2, 42.2, 18.6; IR 2061, 1748, 1718, 1447, 1319, 1247, 1088 cm^{-1}; HRMS calcd for C$_{23}$H$_{28}$O$_4$N$_2$Na (M + Na) 419.1947, obsd 419.1942.

(3aR,7S,9aR,9bS)-Ethyl 7-(Benzyloxy)-9a-methyl-2-oxo-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1H-cyclopenta[a]-naphthalene-3-carboxylate 5. Rhodium(II) octanoate (2 mg) was stirred in 2.5 mL of CH$_2$Cl$_2$ that had been filtered through anhydrous K$_2$CO$_3$. Diazo ester **20** (50 mg, 0.126 mmol) was dissolved in 3 mL of CH$_2$Cl$_2$ (filtered through anhydrous K$_2$CO$_3$) and added dropwise under N$_2$. The solution was stirred for 1 h at room temperature. The reaction mixture was evaporated onto silica gel and chromatographed to afford tricyclic ketone **5** (32 mg, 70% yield) as an off white solid. TLC R_f (MTBE/PE, 1:4) 0.20; mp = 107−110 °C (recrystallized from MeOH); ^{1}H NMR δ 7.37−7.29 (m, 5H), 5.43 (m, 1H), 4.59 (s, 2H), 3.77 (s, 3H), 3.33 (m, 1H), 2.91 (d, J = 12.0 Hz, 1H), 2.58−2.18 (m, 6H), 2.05−1.17 (m, 6H), 1.10 (s, 3H); ^{13}C NMR δ (u) 210.1, 169.3, 141.2, 138.7, 70.1, 38.9, 38.7, 38.2, 36.5, 31.4, 27.9; (d) 128.4, 127.6, 127.6, 120.8, 78.1, 62.3, 52.5, 48.5, 37.7, 18.4; IR 1756, 1728, 1438, 1264, 1128, 1094, 736 cm^{-1}; HRMS calcd for C$_{23}$H$_{29}$O$_4$ (M + H) 369.2066, obsd 369.2060.

ASSOCIATED CONTENT

⊙ Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all new compounds as well as 50% probability figures and CIR files for **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

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NOTE ADDED AFTER ASAP PUBLICATION

Scheme 1 contained an error in the version published ASAP August 6, 2013; the correct version reposted August 23, 2013.