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

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Abstract

Organocatalyzed enantioselective allylation of 2-iodocyclohexenone followed by methylation and oxy-Cope rearrangement delivered enantiomerically-enriched 2-methyl 3-allyl cyclohexanone, that 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 (Fig. 1) contain a 6-6-5-6 carbocyclic scaffold connected to either a piperidine system 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** (Fig. 2), both in racemic³ and enantiomerically-pure⁴ form, has been a workhorse for polycyclic 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 asymmetric allylation proceeded smoothly crystalline α -iodo enone **10**.⁵ As we have reported,⁶ using the Schaus⁷ protocol, allyl borane **11** in the presence of catalytic *R*-Br₂BINOL, to deliver the alcohol **12** in high yield and 95% ee. For this conversion to be practical, the catalyst (\$200/gram) 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 coupling⁸ was employed to convert **12** to **13**. The oxy-Cope rearrangement of **13** in toluene using KH in paraffin⁹ 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 polycyclic 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 protocol¹⁰ to the enone **6**. The crude enol acetate **15** was reduced¹¹ with NaBH₄ 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 CH₃OH/K₂CO₃ 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 *t*-butyl hydroperoxide in the presence of a Pd(quinox)Cl₂ complex. Diazo transfer¹⁵ 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 ¹³C NMR, as well as by the 12.0 Hz coupling constant of the β -keto ester methine in the ¹H 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

General Procedures

¹H-NMR and ¹³C-NMR measured at 400 MHz for ¹H, 90 MHz and 100 MHz for ¹³C in CDCl₃. ¹³C 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 × 10 cm, 250 micron analytical plates coated with silica gel GF, developed in the solvent system indicated. Flash chromatography was performed using silica gel 60 (40–60 μ m). Solvents are referred as volume/volume 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 (Et₂O) were distilled from sodium metal/benzophenone under nitrogen. Dichloromethane, toluene and acetonitrile (MeCN) were distilled from CaH₂ under nitrogen. All reaction mixtures were stirred magnetically under nitrogen atmosphere. MTBE is *t*-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:H₂O and stirred at 0 °C for 5 min. Next, K₂CO₃ (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. I₂ (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 Na₂S₂O₃, and brine. The combined organic layers were dried (Na₂SO₄) 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; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ 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 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 . 3 M aqueous HCl (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 x3 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 4Å 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 x2 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 pentane and the excess 1,3-propanediol (bottom layer) was removed via pipette. 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 $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ 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 was 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 x3. 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. $[\alpha]_D^{20} = -34.6^\circ$ (c = 1.00, CH_2Cl_2), 95% ee; TLC: R_f (MTBE/PE, 1:4) = 0.54; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ 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; HRMS calcd for $\text{C}_9\text{H}_{12}\text{I}$ ($M - \text{OH}$): 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 x3 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 × 20 mm). 20 μL 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 of the minor enantiomer was 21.062 min.

(R)-1-Allyl-2-methylcyclohex-2-enol **13**⁶

To a slurry of NiCl₂-dppp (23 mg, 0.5 mol%) in dry Et₂O (40 mL) was added MeMgBr (3.0 M in Et₂O, 6.7 mL, 20.04 mmol) via syringe and the mixture was then stirred at room temperature for 10 min under N₂. Iodide **12** (2.30 g, 8.71 mmol) was slowly added in 10 mL of Et₂O. The reaction was stirred overnight at room temperature. Once the reaction was complete by TLC, Na₂SO₃ (5 g) was added and the mixture stirred vigorously for 5 min. The atmosphere was purged completely with N₂ and the solution was sparged with N₂. The solution was then *rapidly quenched with saturated aqueous Na₂S₂O₃ under N₂ atmosphere*. PE was then immediately added to dilute the solution. The layers were separated and the aqueous layer was extracted x3 with Et₂O. The solution was then dried (Na₂SO₄ and Na₂SO₃) 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. [α]_D²⁰ = -34.9° (c = 1.00, CH₂Cl₂); TLC: R_f (MTBE/PE, 1:4) = 0.46; ¹H-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); ¹³C-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 C₁₀H₁₅(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) and *t*-BuOK (3.489 g, 31.16 mmol) was added and the mixture stirred under N₂ 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 NH₄Cl. The aqueous layer was extracted x3 with PE and the combined organic layers were dried (Na₂SO₄). 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. [α]_D²⁰ = +10.0° (c = 1.00, CH₂Cl₂, 2:1 mixture of trans:cis diastereomers); TLC: R_f (MTBE/PE, 1:4) = 0.67; ¹H-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); ¹³C-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 C₁₀H₁₇O (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) was 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 NaHCO₃. The layers were separated and the aqueous layer was extracted x3 with Et₂O. The combined organic layers were then dried (Na₂SO₄) 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**. $[\alpha]_D^{20} = +69.8^\circ$ (c = 1.00, CH₂Cl₂); TLC: *R_f* (MTBE/PE, 1:4) = 0.35; ¹H-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); ¹³C-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 C₁₄H₂₁O (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 CH₂Cl₂, 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. NaBH₄ (0.395 g, 10.41 mmol) in a 1:1 mixture of H₂O:THF (3 mL) was then added dropwise at 0 °C. The reaction mixture was placed in the freezer (-20 °C) for 48 h, 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 x3 with Et₂O. The combined organic layers were dried (Na₂SO₄) 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). $[\alpha]_D^{20} = -71.0^\circ$ (c = 1.00, CH₂Cl₂, 4:1 mixture of diastereomers); TLC: *R_f* (MTBE/PE, 1:4) = 0.28; ¹H-NMR (CDCl₃) 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); ¹³C-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 C₁₄H₂₁(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 CH₂Cl₂. The solution was cooled to 0 °C and stirred for 5 min. DCC in 2 mL CH₂Cl₂ 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 CH₂Cl₂. The filtrate was concentrated and the residue rotovaped to silica gel and chromatographed to give ester **17** (353 mg, 94% yield) as a clear oil (4:1 mixture of diastereomers). $[\alpha]_D^{20} = -39.2^\circ$ ($c = 1.00$, CH₂Cl₂, after crystallization, 14:1 mixture of diastereomers); TLC: R_f (MTBE/PE, 5:95) = 0.69; ¹H-NMR (CDCl₃) 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); ¹³C-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. $[\alpha]_D^{20} = -39.2^\circ$ (14:1 ratio), mp = 77–79 °C. After recrystallization, ester **17** (103 mg, 0.264 mmol) was stirred in 4 mL of MeOH. Then K₂CO₃ (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) $[\alpha]_D^{20} = -92.8^\circ$ ($c = 1.00$, CH₂Cl₂, 20:1 diastereomeric ratio) as a clear oil. The spectra matched those of alcohol **16**.

(1*R*,6*S*,8*aR*)-1-Allyl-6-(benzyloxy)-8*a*-methyl-1,2,3,5,6,7,8,8*a*-octahydronaphthalene **9**

The alcohol **18** (90 mg, 0.44 mmol) was dissolved in 5 mL THF and KH(P) (70 mg @ 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; ¹H-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); ¹³C-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 C₁₄H₂₁ (M – OBn): 189.1643, obsd: 189.1647.

1-((1*R*,6*S*,8*aR*)-6-(Benzyloxy)-8*a*-methyl-1,2,3,5,6,7,8,8*a*-octahydronaphthalen-1-yl)propan-2-one **19**

Pd(quinox)Cl₂¹⁴ (14 mg, 8.5 mol%) and AgSbF₆ (40 mg, 24 mol%) were stirred with 3 mL CH₂Cl₂ for 10 min at room temperature in the dark. *t*-Butyl hydroperoxide (70% in H₂O, 677 mg, 5.27 mmol) was added at room temperature and the mixture 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 CH₂Cl₂ 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 Na₂S₂O₃ and stirring for 30 min. The aqueous layer was extracted x3 with CH₂Cl₂. The combined organics were washed with brine, dried (Na₂SO₄)

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; $^1\text{H-NMR}$ 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); $^{13}\text{C-NMR}$ 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 $\text{C}_{21}\text{H}_{29}\text{O}_2$ (M+H): 313.2168, obsd: 313.2176.

Methyl 2-diazo-4-((1*R*,6*S*,8*aR*)-6-(benzyloxy)-8*a*-methyl-1,2,3,5,6,7,8,8*a*-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 MeOH were added. Ketone **19** (65 mg, 0.208 mmol) in 2.5 mL 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 x3 with Et_2O . The combined organics were dried (Na_2SO_4) and concentrated. The residue was chromatographed to give methyl 4-((1*R*,6*S*,8*aR*)-6-(benzyloxy)-8*a*-methyl-1,2,3,5,6,7,8,8*a*-octahydronaphthalen-1-yl)-3-oxobutanoate (59 mg) as a clear oil. TLC: R_f (MTBE/PE, 1:4) = 0.39; $^1\text{H-NMR}$ 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); $^{13}\text{C-NMR}$ 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 $\text{C}_{23}\text{H}_{30}\text{O}_4\text{Na}$: 393.2042 (M + Na), obsd: 393.2037.

The β -keto ester (55 mg, 0.149 mmol) was dissolved in 3 mL 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; $^1\text{H-NMR}$ 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); $^{13}\text{C-NMR}$ 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 $\text{C}_{23}\text{H}_{28}\text{O}_4\text{N}_2\text{Na}$ (M + Na): 419.1947, obsd: 419.1942.

(3*aR*,7*S*,9*aR*,9*bS*)-Ethyl 7-(benzyloxy)-9*a*-methyl-2-oxo-2,3,3*a*,4,6,7,8,9,9*a*,9*b*-decahydro-1*H*-cyclopenta[*a*]naphthalene-3-carboxylate **5**

Rhodium(II) octanoate (2 mg) was stirred in 2.5 mL CH_2Cl_2 that had been filtered through anhydrous K_2CO_3 . Diazo ester **20** (50 mg, 0.126 mmol) was dissolved in 3 mL CH_2Cl_2 (filtered through anhydrous K_2CO_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); $^1\text{H-NMR}$ 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 $\text{C}_{23}\text{H}_{29}\text{O}_4$ (M + H): 369.2066, obsd: 369.2060.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

Figure 2.
Chirons for polyalicyclic synthesis.

Scheme 1.

Scheme 2.

Scheme 3.