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A Piperidine Chiron for the *Veratrum* Alkaloids

Douglass F. Taber* and Peter W. DeMatteo

Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716

Abstract

A *Veratrum* piperidine chiron was prepared over 11 steps (7.9% yield) from (–)-citronellal. Three methods for the installation of the propargylic sidechain onto a cyclic enamide are presented.

Introduction

Veratramine (**1**) is an alkaloid isolated from plants of the genus *Veratrum*.¹ This class of alkaloids also includes (Fig. 1) cyclopamine (**2**) and germine (**3**). The hedgehog pathway, which is blocked by cyclopamine, has come to prominence as a potential chemotherapeutic target over the course of the last decade for the treatment of inoperable cancers such as basal cell carcinoma, medulloblastoma, and rhabdomyosarcoma.²

A semi-synthetic derivative of cyclopamine **2**, IPI-926 **4** (Eq 1) is currently³ in Phase 2 clinical trials for pancreatic cancer. As natural supplies of *Veratrum* alkaloids are limited, modern synthetic approaches towards them are being pursued.^{4,5} As part of our research towards a convergent total synthesis of (–)-veratramine **1**, we have prepared the *Veratrum* piperidine chiron **7** (Scheme 1) from commercial (–)-citronellal **5**.

(1)

* taberdf@udel.edu.

Supporting Information Available: ¹H NMR and ¹³C NMR spectra for all new compounds as well as 50% probability figures and .cif files for compounds **13**, **14**, **17**, **18**, **19** and **25** are available free of charge via the internet at <http://pubs.acs.org>.

Results and Discussion

The starting point for the synthesis was the protected (–)-norcitronellamine **9** (Scheme 2). While this could be synthesized by our previously-reported method,⁶ the one-carbon degradation of (–)-citronellic acid was more readily scalable.

The first step was the oxidation of commercial (–)-citronellal to (–)-citronellic acid. The gram-scale Tollens oxidation introduced by Paquette⁷ proved particularly efficient. It was convenient to recycle the stoichiometric silver residues produced in the oxidation by digestion with concentrated nitric acid.

Carbamate inversion of the acid was accomplished *via* a mixed anhydride approach.⁸ Ozonolysis of (–)-*N*-tosyl norcitronellamine **9** proceeded, after filtration through silica gel, directly to the enesulfonamide **6**.

Exposure of **6** (Scheme 3) to *N*-bromosuccinimide at low temperatures delivered the crystalline bromohydrin **10** as a single dominant diastereomer. Potassium hydride in paraffin [KH(P)]⁹ was used to generate the epoxide *in situ*. Addition of commercial 2-butenylmagnesium chloride then delivered a separable 1:1 mixture of the two crystalline diastereomers **13** and **14**, the relative configurations of which were established by X-ray crystallography. Sequential benzylation¹⁰ and conversion to the alkyne¹¹ completed the preparation of the *Veratrum* chiron **7** (11 steps, 7.9% overall yield from commercial (–)-citronellal).

In order to access a complementary 2,5-*cis* piperidine scaffold, Lewis acid-mediated homologation was attempted on the bromohydrin **10** (Scheme 4). Such additions are known for cyclic hemiacetals¹² and hemiaminals,¹³ but none had been reported utilizing the Marshall reagent, (*M/P*)-1-tributylstannyl-1,2-butadiene **16**,¹⁴ a propargylic methyl chiron that heretofore has only been applied to polyketide synthesis.¹⁵ Reaction of bromohydrin **10** with the *P*-allene gave adduct **17** as the only diastereomer detected, while reaction with the *M*-allene gave adduct **18**. The structures were unambiguously established by X-ray crystallography. The facial selectivity of the addition was controlled by the adjacent bromine, while the absolute configuration at the propargylic position was defined by the enantiomer of allene used. These readily-prepared piperidines might well be useful for the preparation of other alkaloids, such as (–)-deoxynupharidine.¹⁶

In an attempt to prepare **7** via the Lewis-acid/allene approach, the bromohydrin **10** (Scheme 5) and the *M*-allene were combined and exposed sequentially to KH(P), to convert **10** into the corresponding epoxide, and then to BF₃·OEt₂. The result was a complicated mixture that contained no detectable traces of debenzylated **7** by ¹H NMR. The prolinol **19**, also characterized by X-ray crystallography, was the only product identified from the reaction. Apparently, exposure of the intermediate epoxide to Lewis acid effected rearrangement to the aldehyde, to which the allene then added. While there were superficial differences between isomers **13** and **19** by ¹H NMR, the ¹³C NMR spectra showed the aminated methylene resonance at δ > 50 for piperidine **13** and at δ < 50 for pyrrolidine **19**.

Recently, Giannis described the preparation of the lactone **24**^{5b} (Scheme 6). We used the approach outlined above to prepare **24**, then investigated its methylation. While we did not optimize this conversion, we did observe that **25**, the only diastereomer detected, had the same relative and absolute configuration (X-ray) as **7**.

Conclusion

Two approaches toward the preparation of the *Veratrum* chiron **7** have been established. The flexibility of bromohydrins **10** and **22** and their *in situ* derived epoxides under cationic and anionic conditions have been demonstrated. We have also shown that addition of (*M/P*)-1-tributylstannyl-1,2-butadiene to the bromohydrin **10** delivered predictable and complementary diastereomers. Further application of **7** in the total synthesis of (–)-veratramine will be reported in due course.

Experimental Section

General Procedures

¹H NMR and ¹³C NMR spectra were recorded, as solutions in deuteriochloroform (CDCl₃) unless otherwise indicated, at 400 and 100 MHz, respectively. ¹³C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as “down” from methylene and quaternary carbons as “up”. *R_f* values indicated refer to thin-layer chromatography (TLC) on 2.5 × 10 cm, 250 μm analytical plates coated with silica gel GF, and developed in the solvent system indicated. All glassware was rinsed with dry solvent before use. THF and diethyl ether were distilled from sodium metal/benzophenone ketyl under dry nitrogen. Toluene and dichloromethane were distilled from calcium hydride under dry nitrogen. MTBE is methyl-tert-butyl ether, and PE is petroleum ether. All reactions were conducted under N₂ and stirred magnetically unless otherwise noted.

Revised Tollens Procedure / Procedure for Recycling Ag⁰/Ag₂O Solids / Preparation of (–)-Citronellic acid (**7**)

The combined solids from a previous Tollens oxidation (105 g) were washed with 3 × 100 mL hot water and 1 × 100 mL acetone. The solids were then vacuum filtered to dryness. The solids were transferred to a 3-neck 2 L flask fitted with a mechanical stirrer and air inlet. The filter funnel was then rinsed with cHNO₃ into the 3-neck flask. Minimum water was added to slurry the black solids and cHNO₃ was added dropwise with evolution of reddish-brown gas. Acid addition was continued with stirring until no more black precipitate remained and gas evolution ceased, as evidenced by no color in the reaction headspace (c.a. 85 mL cHNO₃, 1.35 mol). The solution was then filtered to remove solids, giving a pale yellow HNO₃/AgNO₃ solution, suitable for incorporation into the next Tollens oxidation. The solution was diluted to 250 mL and returned to the 3-neck flask. At this point one can follow the procedure put forth by Paquette et al., which is included here for convenience.⁸ Aqueous NaOH solution (250 mL, 5M) was added dropwise to the AgNO₃ solution with vigorous stirring. The pH = 14 at about 75% addition of the NaOH solution. The remainder of the NaOH solution was added and the slurry was let age approximately 30 minutes. (–)-Citronellal (21.73 g, 140 mmol) was added in one portion and rinsed down with petroleum ether (~25 mL). The suspension

was let stir overnight under air. In the morning a silver mirror was observed on the glassware and GC analysis of an acidified aliquot indicated complete conversion of the aldehyde. The foamy black suspension was then vacuum filtered with 3×100 mL rinses of hot water to give ~ 1 L aqueous carboxylate solution that was then acidified with 25 mL CHCl_3 . The system was then extracted with 3×250 mL of EtOAc and the combined organic extracts were dried (Na_2SO_4) and concentrated to leave citronellic acid (23.73 g, 139 mmol, 99%). The 3*S*-citronellic acid so prepared could be used without further purification.

(S)-N-(2,6-Dimethylhept-5-enyl)-4-toluenesulfonamide (9)—To (–)-citronellic acid **8** (8.00 g, 47 mmol) in 240 mL anhydrous acetone was added triethylamine (8.0 mL, 57.5 mmol). The solution was cooled to 0°C . Ethyl chloroformate (8.00 g, 73.7 mmol) was then added with vigorous stirring causing a white precipitate to form instantaneously. After 60 minutes, sodium azide (8.0 g, 123 mmol dissolved in 60 mL H_2O) was added and the biphasic mixture was stirred for another hour. H_2O (200 mL) was then added and the organic phase partitioned. The aqueous phase was extracted with another 3×125 mL EtOAc. The combined organic extracts were then partitioned against 100 mL of brine and dried with Na_2SO_4 . After decantation, benzyl alcohol (16 mL, 154 mmol), 4Å molecular sieve (10.00 g), and toluene (50 mL) were added and the solution was subjected to atmospheric pressure short-path distillation which was halted when the head temperature reached 110°C . The bottoms were then taken up with 3×50 mL EtOAc. The solution was filtered, and the filtrate was concentrated. The residue was subjected to bulb-to-bulb distillation (pot = 100°C , 2 mm Hg) to ensure complete removal of the toluene and residual benzyl alcohol.

Diethyl ether (300 mL) was then used to dissolve the pot residue (under N_2), and 300 mL of anhydrous NH_3 was condensed into the system. Li metal (high Na, 3.0 g) was then added until a deep blue color persisted for 5 min, indicating complete reduction of the benzylic position. The solution was then allowed to come to RT, and 300 mL of H_2O was added to dissolve the remaining solids. The biphasic solution was acidified to pH=5 with concentrated HCl and then rendered alkaline to pH=11 with solid sodium bicarbonate (foams!). *p*-Toluenesulfonyl chloride (9.5 g, 50 mmol) was then added with an equimolar amount of NaHCO_3 (3.7 g, 50 mmol) and 100 mL of ethyl acetate, and the solution was allowed to stir overnight. The mixture was extracted with ethyl acetate (3×100 mL). The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed to yield **9** as an oil that solidified on standing (11.12 g, 37.6 mmol, 80% yield from **5**).

TLC R_f = 0.20 (10% EtOAc/PE); $[\alpha]_D^{20}$ = 5.48 (c = 0.157 CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ ppm 0.86 (d, J = 6.7 Hz, 3 H), 1.04 – 1.16 (m, 1 H), 1.27 – 1.39 (m, 1 H), 1.49 – 1.70 (m, 7 H), 1.90 (td, J = 15.8, 7.3 Hz, 2 H), 2.42 (s, 3 H), 2.66 – 2.93 (m, 2 H), 4.94 – 5.08 (m, 2 H), 7.27 – 7.32 (d, J = 7.2 Hz, 2 H), 7.74 – 7.79 (d, J = 7.2 Hz, 2 H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm (up) 143.2, 136.8, 131.7, 48.9, 33.9, 25.0 (down) 129.6, 127.0, 123.9, 32.5, 25.6, 21.5, 17.5, 17.2; IR (film) 3283, 2963.3, 2924, 1452, 1325, 1150 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{25}\text{NO}_2\text{NaS}$ 318.1504, obsd 318.1510.

(S)-3-Methyl-1-tosyl-1,2,3,4-tetrahydropyridine (6)—The sulfonamide **9** (3.0 g, 10 mmol) was taken up in 100 mL of CH₂Cl₂. Sudan III (10 mg) was added as an indicator. The solution was cooled to –78°C and ozone was bubbled through until the red color faded. Methyl sulfide (1.0 mL, 13.5 mmol) was then added to reduce the ozonide. The solution was evaporated to silica gel and directly chromatographed to give **6** as an off-white solid (1.6 g, 6.5 mmol, 65% yield from **9**); mp = 83–85°C; TLC *R_f* = 0.36 (10% EtOAc/PE);

$[\alpha]_D^{18} = -3.6$ (c = 0.02 CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.91 (d, *J* = 6.7 Hz, 3 H), 1.54 (dd, *J* = 17.4, 9.3 Hz, 1 H), 1.71 – 1.82 (m, 1 H), 1.94 – 2.04 (m, 1 H), 2.42 (s, 3 H), 2.64 (t, *J* = 10.8 Hz, 1 H), 3.59 (d, *J* = 11.7 Hz, 1 H), 4.89 – 4.96 (m, 1 H), 6.63 (d, *J* = 8.1 Hz, 1 H), 7.31 (d, *J* = 7.9 Hz, 2 H), 7.66 (d, *J* = 7.9 Hz, 2 H); ¹³C NMR (101 MHz, CDCl₃) δ ppm (up) 143.5, 135.1, 49.8, 29.3; (down) 129.7, 127.0, 124.5, 107.3, 26.4, 21.5, 18.6. IR (film) 3062, 2950.0, 2922, 1649, 1598, 1458, 1347, 1257 cm^{–1}; HRMS calcd for C₁₃H₁₇NO₂NaS 274.0878, obsd 274.0886.

(2R, 3S, 5S)-3-Bromo-5-methyl-1-tosylpiperidin-2-ol (10)—The ene sulfonamide **6** (1.30 g, 5.3 mmol) was dissolved in 100 mL of 95% acetone/water at rt. Ammonium acetate (100 mg, 1.3 mmol) was added as a catalyst. The solution was cooled to –78°C and N-bromosuccinimide (1.15 g, 6.4 mmol) was added in one portion. The yellow mixture was allowed to warm to rt over 3 h. Sodium bisulfite (1.0 g, 10 mmol) was then added and the acetone was removed via rotary evaporation. Water (20 mL) was added to dissolve solids and the resulting biphasic solution was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extract was dried (Na₂SO₄) and evaporated directly to silica gel for chromatography to give the bromohydrin **10** (1.206 g, 3.6 mmol, 70% yield from **6**). mp = 100–102°C,

crystals from EtOAc/heptanes; TLC *R_f* = 0.64 (25% EtOAc/PE); $[\alpha]_D^{20} = 7.14$ (c = 0.11 CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.93 (d, *J* = 6.8 Hz, 3 H), 1.84 – 2.02 (m, 2 H), 2.17 (dt, *J* = 6.8, 4.5 Hz, 1 H), 2.44 (s, 3 H), 2.80 – 2.92 (m, 2 H), 3.46 (dd, *J* = 11.6, 4.3 Hz, 1 H), 4.29 (q, *J* = 2.8 Hz, 1 H), 5.56 (t, *J* = 2.8 Hz, 1 H), 7.29 – 7.36 (m, 2 H), 7.78 – 7.85 (m, 2 H); ¹³C NMR (101 MHz, CDCl₃) δ ppm (up) 143.9, 136.1, 45.7, 34.0; (down) 129.6, 127.6, 78.9, 48.9, 25.2, 21.5, 18.1; IR (film) 3473, 2958, 2876, 1598, 1458, 1334, 1162 cm^{–1}; HRMS calcd for C₁₃H₁₈NO₃NaSBr 370.0088, obsd 370.0078.

(2S, 3R, 5S)-2-((R/S)-But-3-en-2-yl)-5-methyl-1-tosylpiperidin-3-ol (13/14)—KH(P) (480 mg, 6.0 mmol) was suspended in 10 mL toluene and brought to 60°C with stirring. Stirring was stopped and the KH precipitated. Approximately 9 mL of toluene was then removed from the reactor as it cooled to RT. CH₂Cl₂ (3.0 mL) was added and stirring was resumed. The bromohydrin **9** (694 mg, 2 mmol) was added dropwise as a solution in 5.0 mL CH₂Cl₂ over 5 min. The opaque yellow solution was stirred for an additional 30 min. Commercial 2-butenylmagnesium chloride (6.0 mL, 0.5 M in THF) was diluted with an equal portion of THF and cooled to –78°C. The cyclized bromohydrin mixture was added dropwise to the Grignard solution with stirring. Upon completion of addition, the cooling bath was removed and the reaction was allowed to come to rt over 45 min. The reaction was quenched with 10 mL of saturated aqueous NH₄Cl. The aqueous layer was separated and extracted with 3 × 10 mL methylene chloride. The combined organic extracts were dried

(Na₂SO₄) and chromatographed to give 210 mg of diastereomer **13** and 210 mg of diastereomer **14** in 65% total yield from the starting bromohydrin.

Front diastereomer - (2*S*,3*R*,5*S*)-2-((*R*)-but-3-en-2-yl)-5-methyl-1-tosylpiperidin-3-ol

(**13**): TLC R_f = 0.40 (30% EtOAc/PE); $[\alpha]_D^{19} = -19.6$ (c=0.01 CHCl₃); mp = 103–104°C; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.81 (d, J =6.8 Hz, 3 H) 0.93 (d, J =7.1 Hz, 3 H) 1.31 – 1.43 (m, 1 H) 1.75 – 1.91 (m, 2 H) 1.99 (d, J =6.1 Hz, 1 H) 2.31 – 2.46 (m, 4 H) 3.21 (dd, J =13.6, 4.3 Hz, 1 H) 3.40 – 3.52 (m, 1 H) 3.66 (d, J =10.9 Hz, 1 H) 3.92 (m, 1 H) 4.95 – 5.08 (m, 2 H) 5.64 (ddd, J =17.0, 10.0, 9.1 Hz, 1 H) 7.26 – 7.30 (d, J =8.3 Hz, 2 H) 7.76 (d, J =8.3 Hz, 2 H); ¹³C NMR (101 MHz, CDCl₃) δ ppm (up) 143.1, 137.9, 115.8, 45.5, 32.0; (down) 140.9, 129.4, 127.5, 66.7, 63.5, 39.1, 26.0, 21.5, 20.7, 18.1; IR (film) 3524, 2928, 1598, 1456, 1324, 1152 cm⁻¹; HRMS calcd for C₁₇H₂₅NO₃NaS 346.1447, obsd 346.1448.

Back diastereomer - (2*S*,3*R*,5*S*)-2-((*S*)-but-3-en-2-yl)-5-methyl-1-tosylpiperidin-3-ol (14**):**

TLC R_f = 0.27 (30% EtOAc/PE); $[\alpha]_D^{19} = 34.6$ (c=0.01 CHCl₃); mp = 107–108°C; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.04 (m, 7 H) 1.41 – 1.51 (m, 1 H) 1.78 – 1.95 (m, 2 H) 2.25 (d, J =6.6 Hz, 1 H) 2.35 – 2.47 (m, 4 H) 3.23 (m, 1 H) 3.51 (m, 1 H) 3.64 (d, J =10.4 Hz, 1 H) 3.92 (m, 1 H) 4.71 (dd, J =10.1, 1.5 Hz, 1 H) 4.92 (dd, J =17.2, 1.5 Hz, 1 H) 5.23 (m, 1 H) 7.26 – 7.33 (d, J =8.3 Hz, 2 H) 7.73 (d, J =8.3 Hz, 2 H); ¹³C NMR (101 MHz, CDCl₃) δ ppm (up) 143.0, 138.0, 114.5, 45.9, 32.7; (down) 140.5, 129.3, 127.6, 66.5, 64.1, 39.1, 26.0, 21.5, 20.8, 18.6; IR (film) 3520, 2929, 1598, 1458, 1325, 1150 cm⁻¹; HRMS calcd for C₁₇H₂₅NO₃NaS 346.1447, obsd 346.1445.

(2*S*,3*R*,5*S*)-3-Benzoyloxy-2-((*S*)-but-3-en-2-yl)-5-methyl-1-tosylpiperidine (15**)—**

KH(P) (160 mg, 2 mmol) was suspended in 10 mL toluene and brought to 60°C with stirring. Stirring was ceased and the KH precipitated. Approximately 9 mL of toluene was then removed from the reactor as it cooled to rt. Benzyl bromide (1 mL) was then added and the suspension was then re-heated to 60°C. The alcohol **13** (210 mg, 0.65 mmol) in 5.0 mL THF was added dropwise to the KH suspension over 5 min. After 3h, the mixture was quenched with 10 mL of H₂O, then extracted with 3 × 10 mL CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄) and chromatographed to give **15** (256 mg, 0.60 mmol, 95%) as a colorless oil; TLC R_f = 0.52; (15% EtOAc/PE); $[\alpha]_D^{19} = 73.8$ (c=0.01 CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.67 (d, J =7.0 Hz, 3 H) 1.08 (d, J =6.6 Hz, 3 H) 1.34 – 1.45 (m, 1 H) 1.69 – 1.86 (m, 2 H) 2.31 (s, 3 H) 2.36 – 2.49 (m, 1 H) 3.08 – 3.28 (m, 2 H) 3.53 – 3.62 (m, 1 H) 4.08 (d, J =10.1 Hz, 1 H) 4.36 – 4.54 (m, 2 H) 4.98 – 5.07 (m, 2 H) 5.93 (m, 1 H) 6.97 (d, J =8.2 Hz, 2 H) 7.22 – 7.42 (m, 5 H) 7.66 (d, J =8.2 Hz, 2 H); ¹³C NMR (101 MHz, CDCl₃) δ ppm (up) 142.2, 138.3, 138.2, 114.7, 70.1, 46.1, 29.6; (down) 141.0, 128.8, 128.2, 127.7, 127.5, 127.4, 73.6, 61.3, 39.6, 26.0, 21.4, 20.0, 18.8; IR (film) 2927, 1716, 1599, 1456, 1330, 1152 cm⁻¹; HRMS calcd for C₂₄H₃₁NO₃NaS 436.1966, obsd 436.1961.

(2*S*,3*R*,5*S*)-3-Benzoyloxy-2-((*S*)-but-3-yn-2-yl)-5-methyl-1-tosylpiperidine (7**)—**

Olefin **15** (256 mg, 0.60 mmol) and methanesulfonamide (95 mg, 1 mmol) were combined with 5 mL of *t*-BuOH and 5 mL of H₂O with good stirring. After dissolution, the solution was cooled to 0°C and 1.4 g AD-mix α was added. After a week of stirring at room temperature, TLC indicated complete consumption of the olefin. NaHSO₃ (0.5 g, 5 mmol)

was added along with 10 mL of CH₂Cl₂ and the suspension was stirred for 1 h. The suspension was then extracted with 3 × 20 mL CH₂Cl₂ and the combined organic phases were concentrated.

The residue was taken up in 10 mL of Et₂O, 10 mL of H₂O, and 3 mL of saturated aqueous NaHCO₃. The biphasic mixture was cooled to 0°C and NaIO₄ (426 mg, 2.0 mmol) was added in one portion. After 6 h, the reaction was extracted with 3 × 20 mL Et₂O. The combined organic extracts were dried (Na₂SO₄) and chromatographed to give the intermediate aldehyde which was not characterized, as well as 116 mg of recovered diols, that was recycled into recycled into subsequent cleavage reactions. For the **15-diols** mixture: ¹H NMR (400 MHz, CDCl₃) δ 0.66 – 0.75 (m, 3 H), 0.95 (d, *J*=7.1 Hz, 3 H), 1.74 – 1.88 (m, 2 H), 2.08 – 2.17 (m, 1 H), 2.27 – 2.38 (m, 3 H), 3.08 – 3.18 (m, 1 H), 3.47 (dd, *J*=13.5, 4.9 Hz, 1 H), 3.56 (dd, *J*=12.0, 8.5 Hz, 1 H), 3.63 – 3.70 (m, 1 H), 3.90 – 3.98 (m, 1 H), 4.07 – 4.13 (m, 1 H), 4.41 (d, *J*=1.5 Hz, 2 H), 6.93 – 7.05 (d, *J*=8.1 Hz, 2 H), 7.19 – 7.28 (m, 2 H), 7.31 – 7.42 (m, 3 H), 7.65 – 7.74 (m, 2 H).

The crude aldehyde was dissolved in 5 mL THF and added immediately to an aged solution (15 min) of TMS diazomethane (1.0 mL of 2.0 M) and *n*BuLi (0.75 mL of 2.5 M) in 3 mL THF at –78°C. The cooling bath was removed. After 30 min, the mixture was quenched with 10 mL of saturated aqueous NH₄Cl. The mixture was extracted with 3 × 20 mL CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄) and chromatographed to give the alkyne (100 mg, 0.24 mmol, 40% yield from **15** (70% based on recovered diols)); TLC *R_f* = 0.50 (15% EtOAc/PE); [α]_D¹⁹ = 53.5 (c=0.01 CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.72 (d, *J*=6.9 Hz, 3 H), 1.22 – 1.29 (m, 1 H), 1.32 (d, *J*=7.0 Hz, 3 H), 1.77 – 1.90 (m, 2 H), 2.12 (d, *J*=2.6 Hz, 1 H), 2.34 (s, 3 H), 2.84 (m, 1 H), 3.15 (dd, *J*=13.4, 5.2 Hz, 1 H), 3.54 (dd, *J*=13.4, 5.2 Hz, 1 H), 3.61 (td, *J*=4.7, 2.3 Hz, 1 H), 4.17 (dd, *J*=7.5, 2.3 Hz, 1 H), 4.39 – 4.52 (m, 2 H), 7.24 – 7.38 (m, 5 H), 7.65 – 7.77 (m, 2 H); ¹³C NMR (101 MHz, CDCl₃) δ ppm (up) 142.6, 138.2, 137.7, 85.4, 71.5, 70.2, 46.7, 30.4; (down) 129.0, 128.3, 127.8, 127.5, 127.5, 74.6, 60.7, 29.0, 26.0, 21.5, 20.2, 18.8; IR (film) 3302, 3032, 2931, 2254, 1810, 1731, 1599, 1496, 1456, 1331 cm⁻¹; HRMS calcd for C₂₄H₂₉NO₃NaS 434.1760, obsd 434.1759.

(2R, 3S, 5S)-3-Bromo-2-((R)-but-3-yn-2-yl)-5-methyl-1-tosylpiperidine (17)—

Bromohydrin **10** (0.549 g, 1.64 mmol) and *P*-Marshall reagent **16** (600 mg, 1.74 mmol) were dissolved in 16 mL of CH₂Cl₂ at RT. The solution was cooled to –78°C and BF₃·OEt₂ (250 μL, 1.92 mmol) was added in one portion. TLC indicated reaction completion in 30 minutes. Saturated aqueous NaHCO₃ (1 mL) along with 1 mL of saturated aqueous KF were added and the reaction was allowed to come to rt. Precipitates were filtered and the resulting biphasic solution was extracted with methylene chloride (3 × 25 mL). The combined organic fractions were dried (Na₂SO₄) and evaporated to silica gel for chromatography to give **17** as a white crystalline solid (338 mg, 0.88 mmol, 54%); TLC *R_f* = 0.34 (15% EtOAc/PE);

[α]_D¹⁸ = – 13.6 (c=0.07 CHCl₃); mp = 153–155°C; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.84 (d, *J*=6.1 Hz, 3 H), 1.37 (d, *J*=6.9 Hz, 3 H), 1.82 – 2.03 (m, 3 H), 2.12 (d, *J*=2.5 Hz, 1 H), 2.42 (s, 3 H), 2.82 – 3.02 (m, 2 H), 3.59 (dd, *J*=14.3, 4.1 Hz, 1 H), 4.37 (d, *J*=7.8 Hz, 1 H), 4.49 (d, *J*=1.8 Hz, 1 H), 7.20 – 7.39 (m, 3 H), 7.87 (d, *J*=8.3 Hz, 2 H); ¹³C NMR (101 MHz,

CDCl₃) δ ppm (up) 142.9, 137.9, 84.97, 72.6, 47.6, 36.8; (down) 129.1, 128.0, 62.9, 48.9, 39.2, 24.4, 21.5, 19.6, 18.1; IR (film) 2954, 2871, 1737, 1453, 1336, 1169 cm⁻¹; HRMS calcd for C₁₇H₂₃NO₂SBr 384.0633, obsd 384.0630.

(2R,3S,5S)-3-bromo-2-((S)-but-3-yn-2-yl)-5-methyl-1-tosylpiperidine (18)—

Bromohydrin **10** (0.247 g, 0.74 mmol) and *M*-Marshall reagent **16** (330 mg, 1.0 mmol) were dissolved in 10 mL of CH₂Cl₂ at RT. The solution was cooled to -78°C and BF₃·OEt₂ (125 μ L, 1.0 mmol) was added in one portion. TLC indicated that the reaction was complete in 30 min. Saturated aqueous NaHCO₃ (1 mL) along with 1 mL of saturated aqueous KF were added and the reaction was allowed to come to rt. Precipitates were filtered and the resulting biphasic solution was extracted with methylene chloride (3 $\times$ 25 mL). The combined organic fractions were dried (Na₂SO₄) and evaporated to silica gel for chromatography to give **18** as a white crystalline solid (159 mg, 0.42 mmol, 76%). Crystals precipitated spontaneously during column chromatography. X-ray quality crystals could be grown in a diffusion chamber from hexanes and CHCl₃. mp = 104–106°C; TLC *R*_f = 0.36 (15% EtOAc/PE);

[α]_D¹⁸ = +8.7 (c=0.03 CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.82 (d, *J*=6.5 Hz, 3 H), 1.34 (d, *J*=6.9 Hz, 3 H), 1.69 – 1.78 (m, 1 H), 1.79 – 1.89 (m, 1 H), 1.90 – 1.98 (m, 1 H), 2.22 (d, *J*=2.4 Hz, 1 H), 2.42 (s, 3 H), 2.53 (dd, *J*=14.0, 11.4 Hz, 1 H), 2.73 – 2.87 (m, 1 H), 3.55 (dd, *J*=14.0, 4.00 Hz, 1 H), 4.33 (d, *J*=10.4 Hz, 1 H), 4.93 – 5.01 (m, 1 H), 7.23 – 7.34 (m, 2 H), 7.79 – 7.90 (m, 2 H). ¹³C NMR (101 MHz, CDCl₃) δ ppm (up) 143.14, 137.53, 84.87, 71.74, 46.77, 36.18; (down) 129.05, 127.87, 63.33, 49.12, 26.80, 24.31, 21.50, 18.42, 18.06; IR (film) 2954, 2871, 1737, 1453, 1336, 1169 cm⁻¹; HRMS calcd for C₁₇H₂₃NO₂SBr 384.0633, obsd 384.0631.

(1R,2R)-2-Methyl-1-((2R,4S)-4-methyl-1-tosylpyrrolidin-2-yl)but-3-yn-1-ol (19)—

KH(P) (240 mg, 3.0 mmol) was suspended in 10 mL toluene and brought to 60°C with stirring. Stirring was ceased and the KH precipitated. Approximately 9 mL of toluene was then removed from the reactor as it cooled to rt. Then 3.0 mL of CH₂Cl₂ was added and stirring was resumed. To this was added dropwise a solution comprised of bromohydrin **10** (296 mg, 1.0 mmol) and *M*-Marshall reagent **16** (332 mg, 1.0 mmol) dissolved in 5 mL of CH₂Cl₂. After 30 min of stirring at rt, the solution was cooled to -78°C and BF₃·OEt₂ (125 μ L, 1.0 mmol) was added in one portion. After 1 h, 1 mL of saturated aqueous NaHCO₃ was added along with 1 mL of saturated aqueous KF. The reaction was allowed to come to rt. Precipitates were filtered and the resulting biphasic solution was extracted with CH₂Cl₂ (4 $\times$ 10 mL). The combined organic fractions were dried (Na₂SO₄) and evaporated directly to silica gel for chromatography to give **19** initially as an oil (97 mg, 0.30 mmol, 30% yield from **10**). X-ray quality crystals were grown in a diffusion chamber from hexanes and CHCl₃. TLC *R*_f = 0.32 (15% EtOAc/PE); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.70 (d, *J*=6.7 Hz, 3 H), 1.20 (dt, *J*=12.6, 8.8 Hz, 1 H), 1.35 (d, *J*=6.8 Hz, 3 H), 2.04 – 2.11 (m, 1 H), 2.13 (d, *J*=2.4 Hz, 1 H), 2.25 – 2.43 (m, 3 H), 2.45 (s, 3 H), 2.59 – 2.70 (m, 1 H), 3.62 (dd, *J*=9.6, 6.5 Hz, 1 H), 3.92 (ddd, *J*=8.9, 4.2, 2.5 Hz, 1 H), 4.12 (dt, *J*=9.6, 2.8 Hz, 1 H), 7.34 (d, *J*=8.1 Hz, 2 H), 7.74 (d, *J*=8.1 Hz, 2 H); ¹³C NMR (101 MHz, CDCl₃, rotamers) δ ppm (up) 143.8, 132.8, 85.4, 70.1, 57.0, 33.3; (down) 129.6, 128.0, 75.7, 62.6, 31.9, 29.3, 21.6, 18.1, 17.6.

(S)-Benzyl 3-Methyl-3,4-dihydropyridine-1(2H)-carboxylate (18)—(2S)-N-Cbz norcitronellamine **20** (1.36 g, 4.6 mmol) prepared as for **9** was taken up in 100 mL of CH₂Cl₂. Sudan III (10 mg) was then added as an indicator. The solution was cooled to –78°C and ozone was bubbled through until the red color faded. Methyl sulfide (1 mL) was then added to reduce the ozonides and the mixture was concentrated to an oil. Toluene (100 mL) and 10 mg of pyridinium *p*-toluenesulfonate were added, and the mixture was subjected to Dean-Stark distillation until 20 mL of distillate was collected. The solution was then cooled and evaporated directly to silica gel for chromatography to give **21** as an oil (465 mg, 2.0 mmol, 44%); TLC *R_f* = 0.70 (15% EtOAc/PE); $[\alpha]_D^{18} = +41.7$ (c = 0.09 CHCl₃); ¹H NMR (400 MHz, CDCl₃, rotamers) δ ppm 0.94 – 1.02 (m, 3 H), 1.61 – 1.72 (m, 1 H), 1.90 (d, *J* = 3.2 Hz, 1 H), 2.09 (dt, *J* = 17.2, 5.0 Hz, 1 H), 2.84 – 3.02 (m, 1 H), 3.77 – 3.99 (m, 1 H), 4.75 – 5.01 (m, 1 H), 5.17 (s, 2 H), 6.73 – 6.93 (m, 6 H), 7.26 – 7.48 (m, 5 H); ¹³C NMR (101 MHz, CDCl₃, rotamers) δ ppm (up) 153.4, 153.0, 136.2, 67.3, 67.2, 48.4, 48.0, 29.7, 29.5; (down) 128.3, 128.0, 127.8, 124.8, 124.3, 26.8, 26.7, 18.6; IR (film): 2956, 1711, 1655, 1411, 1344 cm^{–1}; HRMS calcd for C₁₄H₁₈NO₂ 232.1338, obsd 232.1344.

(2S,3R,5S)-Benzyl 2-Allyl-3-hydroxy-5-methylpiperidine-1-carboxylate (23)—Enecarbamate **21** (911 mg, 3.9 mmol) was dissolved in 100 mL of 95% acetone/H₂O at RT. Ammonium acetate (20 mg) was added as a catalyst. The solution was cooled to –78°C and N-bromosuccinimide (842 mg, 4.7 mmol) was added in one portion. The yellow solution was allowed to warm to rt over 3h. Sodium bisulfite (1 g) was then added and the acetone was removed via rotary evaporation. Water (20 mL) was added to dissolve solids and the resulting biphasic solution was extracted with CH₂Cl₂ (3 × 50 mL). The organic extract was dried (Na₂SO₄) and evaporated directly to silica gel for chromatography to give **22** as an oil (846 mg, 2.4 mmol, 62%); TLC *R_f* = 0.38 (25% EtOAc/PE); $[\alpha]_D^{18} = +26.0$ (c = 0.075 CHCl₃); ¹H NMR (400 MHz, CDCl₃, rotamers) δ ppm 0.93 (d, *J* = 6.47 Hz, 3 H), 1.87 – 2.05 (m, 2 H), 2.19 (td, *J* = 11.32, 6.63 Hz, 1 H), 4.36 (br s, 1 H), 5.14 (s, 2 H), 5.90 (br s, 1 H), 7.28 – 7.41 (m, 5 H); ¹³C NMR (101 MHz, CDCl₃) δ ppm (up) 136.2, 67.6, 34.6; (down) 128.6, 128.2, 128.0, 49.9, 25.0, 18.3; IR (film): 3394, 2956, 1681, 1431, 1343, 1253 cm^{–1}.

KH(P) (1.0 g, 13.6 mmol) was suspended in 20 mL toluene and brought to 60°C with stirring. Stirring was ceased and the KH precipitated. Approximately 19 mL of toluene was removed from the reactor as it cooled to rt. Methylene chloride (10 mL) was added and stirring was resumed. Bromohydrin **22** (1.11 g, 3.4 mmol) was added dropwise as a solution in 10 mL of CH₂Cl₂. The opaque yellow solution was allowed stirred for an additional 30 min. The solution was then cooled to –78°C. Stirring was increased, and allylmagnesium chloride (4.0 mL, 1.7 M in THF) was added dropwise over 5 min. Upon completion of addition, the cooling bath was removed. The reaction was allowed to come to rt over 45 min, then quenched with 25 mL of saturated aqueous NH₄Cl. The aqueous layer was separated and extracted with 3 × 10 mL CH₂Cl₂. The combined organic extracts were dried (Na₂SO₄) and chromatographed to give **23** (840 mg, 53% yield from **21**); TLC *R_f* = 0.2 (30% EtOAc/PE); $[\alpha]_D^{19} = +37.17$ (c = 0.035 CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ ppm 0.90 (t, *J* = 6.95 Hz, 1 H), 1.17 (d, *J* = 6.82 Hz, 2 H), 1.21 – 1.39 (m, 1 H), 1.52 (d, *J* = 13.89 Hz, 1 H), 1.73 (d, *J* = 18.95 Hz, 2 H), 1.86 – 2.03 (m, 2 H), 2.22 – 2.47 (m, 2 H), 3.15 (dd, *J* = 13.52, 3.92 Hz, 1

H), 3.77 (d, $J=13.39$ Hz, 1 H), 3.85 (br s, 1 H), 4.27 (t, $J=6.57$ Hz, 1 H), 4.99 – 5.26 (m, 4 H), 5.69 – 5.85 (m, 1 H), 7.30 – 7.44 (m, 5 H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm (up) 156.9, 136.9, 117.5, 67.1, 44.3, 34.7, 33.1 (down) 134.4, 128.4, 127.9, 127.8, 68.7, 57.9, 27.0, 20.4; IR (film): 3426, 2928, 1677, 1430, 1320, 1250 cm^{-1} ; HRMS calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_3$ 290.1756, obsd 290.1742.

(3 α ,6S,7 α ,R)-benzyl 6-Methyl-2-oxo-hexahydrofuro[3,2- β]pyridine-4(2H)-carboxylate (24**)**—The alcohol **23** (720 mg, 2.5 mmol) was dissolved in 50 mL 95% acetone/ H_2O solution.¹⁷ The solution was cooled to -78°C and ozone was bubbled through until the solution turned blue. The solution was sparged with air until colorless and then 1 mL of methyl sulfide was added. The bulk of the acetone was removed by rotary evaporation, and the residue was partitioned between 20 mL of brine and 100 mL CH_2Cl_2 . The combined organic extracts were dried (Na_2SO_4) and concentrated to an oil, which was then dissolved in 5 mL of *t*-BuOH. K_2CO_3 (552 mg, 4.0 mmol) and I_2 (756 mg, 3.0 mmol) were added sequentially and the solution was heated at 60°C overnight under N_2 . Water (10 mL) was then added along with 0.50 g of sodium bisulfite and the solution was stirred until the iodine color faded. The mixture was extracted with CH_2Cl_2 (3 $\times$ 25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated directly to silica gel for to give the bicyclic lactone **24** as an oil (380 mg, 1.31 mmol, 53% yield from **23**). The spectroscopic data (^1H , ^{13}C NMR) matched that which was previously published.^{5b}

(3R,3 α ,S,6S,7 α ,R)-Benzyl 3,6-Dimethyl-2-oxo-hexahydrofuro[3,2- β]pyridine-4(2H)-carboxylate (25**)**—Bicyclic lactone **24** (80 mg, 0.28 mmol) was dissolved in 3.0 mL THF at rt. Triphenylmethane (10 mg) was added as an indicator. In a separate vessel at 0°C , 9.0 mL THF, diisopropyl amine (303 mg, 3.0 mmol) and *n*-BuLi (1.0 mL, 2.49 M) were combined. The LDA solution was aged 15 min. Meanwhile, the lactone solution was cooled to -78°C , at which point the LDA solution was added dropwise until an olive green color persisted (~ 1 mL). After 30 min, iodomethane (200 μL , 3.2 mmol) was added in one portion and the solution turned yellow. The solution was diluted with water and extracted with CH_2Cl_2 (3 $\times$ 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated directly to silica gel for chromatography gave **25** as an oil (30 mg, 0.10 mmol, 30% yield from **24**). Crystallization was effected in a CH_2Cl_2 /PE diffusion chamber; mp = $105\text{--}106^\circ\text{C}$; TLC R_f = 0.57 (30% EtOAc/PE); ^1H NMR (400 MHz, CDCl_3) δ ppm 1.06 (d, $J=6.7$ Hz, 3 H), 1.22 – 1.31 (m, 4 H), 1.81 – 1.96 (m, 1 H), 2.33 (dt, $J=11.1$, 3.9 Hz, 1 H), 2.58 (dd, $J=13.0$, 11.1 Hz, 1 H), 3.19 (dd, $J=10.1$, 6.7 Hz, 1 H), 3.30 (quin, $J=7.2$ Hz, 1 H), 4.02 (dd, $J=13.0$, 4.0 Hz, 1 H), 4.14 (ddd, $J=11.9$, 10.0, 4.0 Hz, 1 H), 5.15 (s, 2 H), 7.31 – 7.47 (m, 5 H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm (up) 177.8, 157.0, 135.7, 67.8, 53.1, 35.6; (down) 128.7, 128.6, 128.5, 128.4, 77.2, 62.1, 41.4, 28.7, 19.1, 9.5.

Supplementary Material

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Figure 1.
Three representative *Veratrum* alkaloids.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.