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Direct, biomimetic synthesis of (+)-artemone via a stereoselective, organocatalytic cyclization

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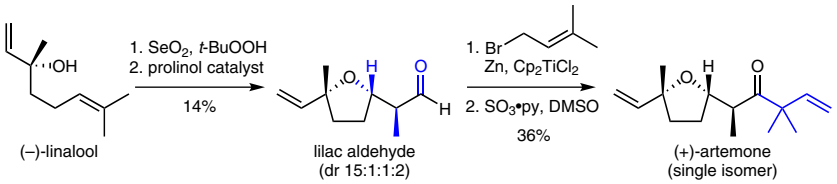

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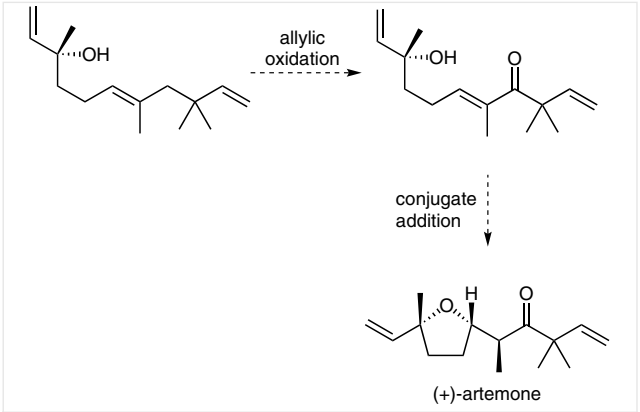
Abstract We present a four-step synthesis of (+)-artemone from (–)-linalool, featuring iminium organocatalysis of a doubly diastereoselective conjugate addition reaction. The strategy follows a proposed biosynthetic pathway, rapidly generates stereochemical complexity, uses no protecting groups, and minimizes redox manipulations.

Key words natural products, cyclization, terpenoids, total synthesis, stereoselective synthesis, green chemistry, organocatalysis, biomimetic synthesis

Artemone is a sesquiterpene natural product from the Indian sage *Artemisia pallens*.[1] Some of the other metabolites from this plant have been shown to possess useful medicinal properties,[2] though none have yet been disclosed for artemone. Many related compounds have desirable olfactory properties.[3]

The only reported stereoselective syntheses of artemone are a 20-step route by Honda and co-workers,[4] which results in a 1:2 mixture of artemone and davanone, and our recent six-step synthesis via a diastereoselective allylic O-alkylation.[5] We sought a shorter route to artemone and looked for inspiration to the plausible biosynthetic pathway in Scheme 1,[6] an alternative biomimetic approach to our previous studies on davanone.[7] We propose that the final steps in the biosynthesis of artemone are an allylic oxidation and an intramolecular conjugate addition reaction. The latter step generates the ring and introduces two new stereocenters in a single operation.

Our strategy is similar to that of Naegeli and co-workers, though their early work lacked stereocontrol, resulting in an equal mixture of all eight possible stereoisomers.[1a,8] Thus, a key element to our synthesis is the identification of

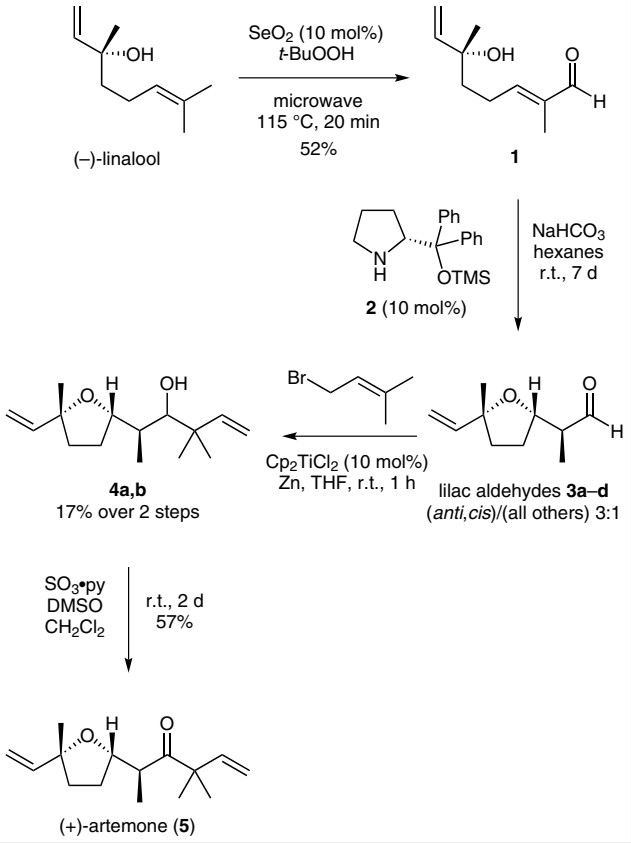


Scheme 1 Proposed biosynthesis of artemone

a stereoselective conjugate addition reaction. We were also guided by Gaich and Baran's description of an ideal synthesis[9] and aimed to avoid protecting groups and unnecessary functional group transformations, even being willing to sacrifice chemical yield for a maximally direct route.

We selected (–)-linalool, an inexpensive monoterpene, as our starting material (Scheme 2). The selenium dioxide mediated oxidation of linalool to enal **1** is a known reaction.[10] While we never obtained the impressively high yield (79%) that Sharma and Chand reported for this transformation, we could reliably access **1** at room temperature or with microwave heating. Column chromatography readily separated the enal from residual linalool and the intermediate diol.

The conjugate addition step is pivotal, as it establishes the remaining two stereocenters not already present in linalool. This is a challenging reaction, however, as the tertiary alcohol is a poor nucleophile and the α-methyl group disfavors enal activation with bulky amines or metal–ligand complexes. Also, the vast majority of published stereoselec-



Scheme 2 Four-step synthesis of (+)-artemone

tive conjugate addition reactions merely offer stereoselectivity at the β-position and not at both the β- and α-carbons.[11] Our transformation requires stereoselectivity in the nucleophilic attack as well as the subsequent α-protonation step.

After screening a number of organic and inorganic catalysts known to activate enals, we established that Jørgensen–Hayashi catalyst **2**[12] (Scheme 2) conferred the greatest selectivity in this reaction. Other optimal parameters included a nonpolar solvent such as hexanes or cyclohexane, performing the reaction at room temperature, and the addition of sodium bicarbonate. Our most selective conditions provided diastereomeric ratios of up to 5:1 for the desired *anti*,*cis*-lilac aldehyde (**3**) versus the sum of the other three (*anti*,*trans*, *syn*,*trans*, and *syn*,*cis*) lilac aldehydes that are also products of this reaction; however, this level of selectivity was only observed early in the reaction. To obtain useful amounts of product, prolonged exposure to the catalyst was necessary and resulted in degraded stereoselectivity. We found the most practical balance of selectivity and yield required one week at room temperature. These conditions were 65–75% stereoselective for the desired *anti*,*cis*-lilac aldehyde (**3a**). Column chromatography removed unconverted enal **1** and residual catalyst **2**, but lilac aldehydes **3a**–**d** were inseparable from each other; further purification was achieved after the subsequent prenylation step.

Addition of the γ-prenyl group was most convenient using Fleury and Ashfeld's titanium-catalyzed organozinc addition protocol.[13] Despite the fact that this reaction introduced an additional stereocenter, the desired epimeric secondary alcohols **4a**,**b** could be isolated more readily by column chromatography than their lilac aldehyde precursor (**3a**). The sterically congested alcohols **4a** and **4b** were oxidized slowly but cleanly to (+)-artemone (**5**), completing the synthesis. Our synthetic artemone matched the data of Honda and co-workers[4] and material obtained from our previous route.[5]

In conclusion, we have described a very short, biomimetic synthesis of (+)-artemone from (–)-linalool using an organocatalytic cyclization. This route avoids protecting groups and is redox economic.[14] The two-step preparation of lilac aldehyde (**3**) is much more direct and atom economic than Sabitha and co-workers' eight-step synthesis,[15] though our yields and selectivities are more modest.

All reactions, unless otherwise noted, were carried out under an atmosphere of argon using oven-dried glassware and magnetic stirring. Anhydrous hexanes, THF, and CH_2Cl_2 were obtained from a SolvPure solvent system using activated alumina. Microwave reactions were performed with a Biotage Initiator 2.5 system. Reactions were monitored by TLC on glass plates coated with 400-mesh silica gel and visualized using UV radiation and either anisaldehyde or ceric sulfate stain. Column chromatography was performed using 60-mesh silica gel. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer using an iD5 diamond ATR accessory. GC-MS was performed with an Agilent 5975C system using electron-impact ionization. ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance 400 spectrometer at ambient temperature. Chemical shifts are expressed in ppm (δ) using TMS as the internal standard. For ^{13}C spectra, chemical shifts are referenced to $CDCl_3$ at 77.0 ppm. Optical rotation measurements were made using a Jasco P-1010 polarimeter. High-resolution mass spectrometry (HRMS) was performed using a chemical ionization (CI) source on an Agilent 6210 time-of-flight mass spectrometer.

(3*R*,6*E*)-8-Oxolinalool (1)

Depending on the time available and scale required, hydroxyenal **1** was prepared by either a conventional or a microwave procedure.

Conventional Procedure: (–)-Linalool (7.13 g, 46 mmol) was dissolved in CH_2Cl_2 (10 mL). Separately, SeO_2 (554.8 mg, 5.00 mmol) and 70% aq *t*-BuOOH (41.0 mL, 38.6 g, 300 mmol) were added to CH_2Cl_2 (85 mL) in a round-bottom flask. To the resulting cloudy mixture, the (–)-linalool solution was added. The reaction mixture was stirred at r.t. for 7 d, and then diluted with additional CH_2Cl_2 (105 mL). The organic layer was washed successively with 2.0 M KOH (105 mL), water (105 mL), and brine (105 mL), then dried ($MgSO_4$), filtered, and concentrated. The crude product was purified using flash chromatography (hexanes–EtOAc, 5:1) to afford hydroxyenal **1** as a slightly yellow oil; yield: 1.22 g (16%).

Microwave Procedure: To a microwave vial were added SeO_2 (53.3 mg, 0.48 mmol) and 70% aq *t*-BuOOH (3.96 mL, 3.7 g, 28.8 mmol), followed by a solution of (–)-linalool (0.73 g, 4.8 mmol) in anhydrous CH_2Cl_2 (9 mL). The vial was sealed and the reaction mixture was stirred under microwave irradiation (250 W) at 115 °C for 20 min. The two-layer reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 2.0 M KOH (20 mL), deionized water (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified using flash chromatography (hexanes–EtOAc, 5:1) to afford hydroxyenal **1** as a slightly yellow oil; yield: 0.42 g (52%).

$[\alpha]_D^{23}$ –12.0 (*c* 1.0, $CHCl_3$); R_f = 0.56 (hexanes–EtOAc, 4:1).

IR: 3458, 1739, 1685, 1640 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.39 (s, 1 H), 6.50 (dt, *J* = 1.3, 7.4 Hz, 1 H), 5.93 (dd, *J* = 11, 17 Hz, 1 H), 5.26 (dd, *J* = 1.0, 17 Hz, 1 H), 5.13 (dd, *J* = 1.0, 11 Hz, 1 H), 2.37–2.44 (m, 2 H), 1.66–1.76 (m, 2 H), 1.74 (s, 3 H), 1.60 (br s, 1 H), 1.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.3, 155.1, 144.2, 138.9, 112.2, 72.6, 40.1, 27.9, 23.7, 8.9.

HRMS: *m*/*z* [M + H^+] calcd for $C_{10}H_{17}O_2$: 169.1223; found: 169.1225.

2-(5-Methyl-5-vinyltetrahydrofuran-2-yl)propionaldehyde (Lilac Aldehydes, 3a–d)

To hydroxyenal **1** (201.5 mg, 1.20 mmol) were added hexanes (10 mL), organocatalyst **2** (5.5 mg/mL in hexanes, 7.04 mL, 0.12 mmol), and $NaHCO_3$ (303.5 mg, 3.61 mmol). The reaction mixture was stirred at r.t. for 7 d, then was diluted with hexanes (20 mL). The solution was washed with 1 M HCl (2 × 20 mL), sat. aq $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified using flash chromatography (hexanes–EtOAc, 20:1) to provide an *anti*,*cis*-enriched mixture of lilac aldehydes (**3a**–**d**); yield: 54.3 mg (27%). Although chromatography did not separate **3a** from its diastereomers, it did remove residual traces of organocatalyst **2** which otherwise promoted undesired diastereomeric equilibration to give equal amounts of **3a**–**d**. The diastereomeric mixture (typically containing 65–75% **3a**) was carried on through the next step.

R_f = 0.49 (hexanes–EtOAc, 5:1).

IR: 1727 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (characteristic peaks) = 9.81 (d, *J* = 2.5 Hz, 1 H, **3a** –*CH*O), 9.80 (d, *J* = 1.3 Hz, 1 H, **3b** –*CH*O), 9.79 (d, *J* = 2.3 Hz, 1 H, **3c** –*CH*O), 9.77 (d, *J* = 1.5 Hz, 1 H, **3d** –*CH*O), 1.16 (d, *J* = 7.0 Hz, 3 H, **3d** CHCH_3), 1.12 (d, *J* = 7.0 Hz, 3 H, **3b** CHCH_3), 1.08 (d, *J* = 7.0 Hz, 3 H, **3c** CHCH_3), 1.05 (d, *J* = 7.0 Hz, 3 H, **3a** CHCH_3).

HRMS: *m*/*z* [M + H^+] calcd for $C_{10}H_{17}O_2$: 169.1223; found: 169.1229.

4,4-Dimethyl-2-(5-methyl-5-vinyltetrahydrofuran-2-yl)hex-5-en-3-ol (Artemols, 4a,b)

Zinc dust (56.3 mg, 0.861 mmol) and Cp_2TiCl_2 (8.2 mg, 0.033 mmol) were added to THF (5 mL). The flask was sealed under nitrogen. Upon stirring for 10 min, the reaction color progressed from blood red to green. In a separate vial, the above mixture of **3a**–**d** (54.0 mg, 0.321 mmol) and 3,3-dimethylallyl bromide (0.11 mL, 143.5 mg, 0.963 mmol) were dissolved in THF (1 mL). This solution was then added to the reaction mixture. After 1 h, sat. aq NH_4Cl (10 mL) and Et_2O (10 mL) were added. The reaction mixture was extracted with Et_2O (3 × 10 mL). The organic layers were combined, washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was then purified using flash chromatography (hexanes–EtOAc, 50:1 → 25:1) to afford 28.1 mg of artemol **4a** and 20.9 mg of artemol **4b** (17% combined two-step yield from **1**) as clear, colorless oils.

Alcohol 4a

$[\alpha]_D^{23}$ +9.2 (*c* 1.7, $CHCl_3$); R_f = 0.41 (hexanes–EtOAc, 5:1).

IR: 3466 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.98 (m, 1 H), 5.91 (dd, *J* = 11, 17 Hz, 1 H), 5.18 (dd, *J* = 1.6, 17 Hz, 1 H), 5.04 (app s, 1 H), 5.00 (dd, *J* = 1.5, 6.4 Hz, 1 H), 4.97 (dd, *J* = 1.6, 11 Hz, 1 H), 3.93 (m, 1 H), 3.73 (d, *J* = 3.9 Hz, 1 H), 1.57–1.98 (m, 5 H), 1.29 (s, 3 H), 1.08 (s, 3 H), 1.06 (s, 3 H), 0.88 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.0, 144.5, 112.1, 111.5, 82.8, 82.5, 76.7, 41.9, 38.9, 38.0, 29.7, 26.4, 24.8, 23.9, 11.3.

HRMS: *m*/*z* [M + H^+] calcd for $C_{15}H_{27}O_2$: 239.2006; found: 239.2001.

Alcohol 4b

R_f = 0.63 (hexanes–EtOAc, 5:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.94 (dd, *J* = 11, 17 Hz, 1 H), 5.87 (dd, *J* = 11, 17 Hz, 1 H), 5.20 (dd, *J* = 1.6, 17 Hz, 1 H), 5.01 (dd, *J* = 1.6, 11 Hz, 1 H), 4.95–4.98 (m, 2 H), 4.34 (d, *J* = 6.8 Hz, 1 H), 3.97 (ddd, *J* = 5.1, 9.7, 9.7 Hz, 1 H), 3.22 (app t, *J* = 6.8 Hz, 1 H), 1.99 (m, 1 H), 1.89 (m, 1 H), 1.67–1.76 (m, 2 H), 1.48–1.57 (m, 1 H), 1.30 (s, 3 H), 1.06 (s, 3 H), 1.05 (s, 3 H), 0.86 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.6, 144.2, 111.5, 111.2, 83.5, 83.1, 77.2, 42.7, 41.0, 37.3, 31.3, 27.0, 25.2, 21.5, 17.6.

(2*S*)-4,4-Dimethyl-2-[(2*S*,5*R*)-5-methyl-5-vinyltetrahydrofuran-2-yl]hex-5-en-3-one (*anti*,*cis*-Artemone, 5)

A solution of artemol (**4a**; 26.9 mg, 0.113 mmol) in CH_2Cl_2–DMSO (4:1, 1 mL) was stirred for 2 min at r.t., followed by 7 min at 0 °C. Et_3N (0.14 mL, 1.03 mmol) and sulfur trioxide–pyridine complex (119 mg, 0.749 mmol) were added and the reaction mixture was allowed to warm to r.t. The solution changed from pale yellow to deep red. After 2 d, the reaction was quenched with sat. aq $NaHCO_3$ (1 mL) and the mixture was extracted with hexanes–Et_2O (2:1, 3 × 1 mL). The organic layers were combined, washed with brine (3 × 1 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (hexanes–EtOAc, 40:1 → 10:1) afforded (+)-artemone (**5**) as a clear, pale yellow oil; yield: 15.3 mg (57%).

$[\alpha]_D^{23}$ +49.4 (*c* 0.7, $CHCl_3$); R_f = 0.82 (hexanes–EtOAc, 4:1).

IR: 1709, 1634 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.99 (dd, *J* = 11, 17 Hz, 1 H), 5.90 (dd, *J* = 11, 17 Hz, 1 H), 5.20 (dd, *J* = 0.9 Hz, 17 Hz, 1 H), 5.17 (dd, *J* = 1.0, 11 Hz, 1 H), 5.15 (dd, *J* = 1.6, 17 Hz, 1 H), 4.94 (dd, *J* = 1.6, 11 Hz, 1 H), 4.13 (dt, *J* = 5.9, 8.7 Hz, 1 H), 3.05 (dq, *J* = 8.5, 6.9 Hz, 1 H), 1.97 (m, 1 H), 1.88 (m, 1 H), 1.73 (m, 1 H), 1.61 (m, 1 H), 1.26 (s, 3 H), 1.24 (s, 3 H), 1.23 (s, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.6, 144.8, 142.3, 114.2, 111.0, 82.6, 80.8, 51.4, 46.0, 37.5, 29.3, 26.4, 23.2, 23.1, 15.2.

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Supporting Information

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