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Synthesis and absolute configuration of (*S*)-(+)-chichimol ketone: the defensive secretion of walking stick *Agathemera elegans*

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ABSTRACT

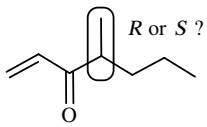
The first enantioselective synthesis of chichimol ketone (4-methyl-1-hepten-3-one) is described and the absolute configuration of the main semiochemical compound is determined as having an (*S*)-configuration. The synthesis features the use of a ruthenium catalytic asymmetric hydrogenation reaction to introduce chirality into acid **2**. The synthetic chichimol ketone (*S*)-**1** displayed a specific rotation that was in accordance with that of the natural product, thereby supporting the (*S*) configuration for natural chichimol ketone. To assure the correct stereochemical assignment, (*S*)-**1** was converted in the known ketone (*S*)-**5**: the main alarm pheromone of the ant *Atta texana* that is 400 times more active than its (*R*)-enantiomers.

1. Introduction

Organic synthesis has remained an important branch of chemistry, while chemical ecology is a new and interdisciplinary branch of science developed since the 1970s. Chemical ecology deals with the chemistry and biology of inter- and intraspecific interactions among organisms, by means of semiochemicals (signal substance). Semiochemicals are biomolecules that spread information between individuals. The word is synonymous with 'signal substances' and is derived from 'semio' (Greek = sign). Many insects rely on the use of chemical compounds for communication, chemical signaling, and defense. In the Phasmatodea order, around 2500 species of walking stick insects are known to produce noxious defensive secretions. However, the defensive chemistry of only a few species to date has been elucidated.[1] Insects of the genus Agathemera (Phasmatidae) live in the Chilean Andes over 3500 m above sea level. Under stress, the insects release a spray that can cause temporary blindness in humans.[2] The composition of chemicals used for defense by South American phasmids was studied by Schmeda-Hirschmann, who reported that both the female and male defensive secretion of *Agathemera elegans* are made up of 4-methyl-1-hepten-3-one (Fig. 1).[3] This compound was reported for the first time as a natural product; however, its absolute configuration was not determined.

Herein, we report a short approach to the synthesis of chichimol ketone **1** (Fig. 1). The synthetic route envisioned for chichimol ketone features the preparation of (*S*)-methylalkyl acids, the key intermediate in our approach, through the asymmetric hydrogenation of α,β-unsaturated acids employing Ru catalysts, followed by the addition of a vinyl Grignard to a Weinreb amide to give **1** (Scheme 1).

As part of our current interest in the use of asymmetric hydrogenation catalysis,[4] we figured out the synthesis of (*S*)-**1** by hydrogenation of *E*-2-methyl-2-pentenoic acid **2** employing (*S*)-H8-BINAP-Ru(OAc)$_2$ catalyst.[5] Transition-metal-catalyzed asymmetric hydrogenation of prochiral double bonds represents one of the most efficient and atom economic methods for preparing chiral compounds, and has attracted increasing attention in both industrial production and academic research. Catalytic enantioselective hydrogenation of α,β-unsaturated carboxylic acids is a straightforward method for the synthesis of chiral carboxylic acids, which are important intermediates for the construction of biologically active compounds.[6] Thus, (*S*)-**3** was obtained by employing the asymmetric Ru-hydrogenation of acid **2** in 85% yield, Scheme 2.[7] The enantiomeric excess of **3** was determined after derivatization with aniline to give the phenylamide. The phenylamide derivative of **3** was subjected to HPLC analysis by employing a chiral Welch-01 column; the enantiomeric excess for the hydrogenation



1
chichimol ketone

Figure 1. *Agathemera elegans* found in cordillera Chilean valleys and chichimol ketone isolated as the main semiochemical.[3]

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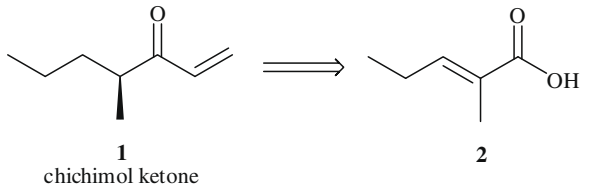
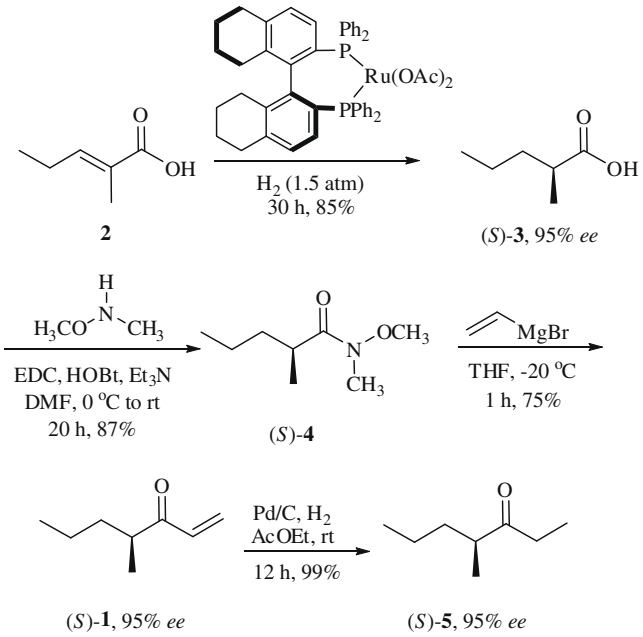


Scheme 1. Retrosynthetic analysis of chichimol ketone **1**.



Scheme 2.

of **2** was determined as >95%, as depicted in Figure 2. (*S*)-BINAP was also tested as a ligand in the hydrogenation of **2**, but the catalytic selectivities were not satisfactory. It was seen that (*S*)-H8-BINAP is better than (*S*)-BINAP for the hydrogenation of prochiral acrylic acid **2**. Using (*S*)-BINAP as a diphosphine ligand resulted in lower enantioselectivities by 10% (86% ee) when compared with (*S*)-H8-BINAP. To prevent any racemization during the following reactions, all glassware apparatus were treated with 1.0 mL of chlorotrimethylsilane (freshly distilled from calcium hydride), which was removed under reduced pressure.

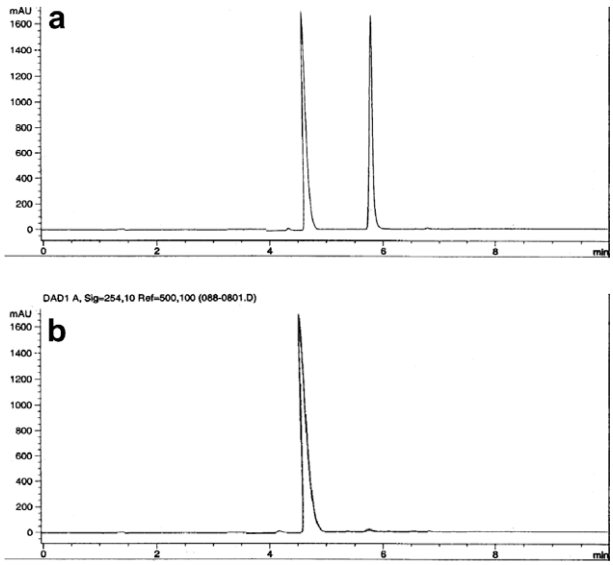


Figure 2. HPLC analysis of phenylamide derivative of **3**: (a) racemic mixture, (b) synthesized compound. Condition: *n*-hexane/isopropanol = 9:1, 1.0 mL/min, 254 nm UV detector, t_R = 4.65 min for (*S*)-enantiomer and t_R = 5.88 min for (*R*)-enantiomer.

Next carboxylic acid (*S*)-**3** was converted into the corresponding Weinreb amide **4** using *N*,*O*-dimethylhydroxyamine, EDC, and HOBt in DMF,[8] as depicted in Scheme 2. The higher reactivity of the amide allowed us to introduce the vinyl group with a Grignard reagent at −20 °C (Scheme 2). The reaction of the Weinreb amide (*S*)-**4** with vinyl magnesium bromide provided enone derivative (*S*)-**1** in 75% yield. GC analysis using chiral Heptakis column was performed to assure the ee of **1**. The racemic standard (±)-**1** was obtained from (±)-**3** to assure the reliability of the ee analysis. No epimerization was observed in the further steps of the synthesis, which was prevented by using TMSCl in all the glassware employed.

Herein, the correct stereochemical assignment of (*S*)-**1** was probed by its hydrogenation to the known ketone (*S*)-**5**. Ketone (*S*)-**5** is interesting due to the fact that it is 400 times more active than its (*R*)-enantiomers,[9] and it is the main alarm pheromone of the ant *Atta texana*. Herein, (*S*)-**5** was identified in several exocrine glands of ants exhibiting particularly widespread taxonomic distribution. Furthermore, it was identified as an alarm pheromone in ants of the Myrmicinae subfamily,[10] as a component of the defensive secretion of the *Leiobunum vittatum* (Opiliones),[11] and is also produced by the elm bark beetles *Scolytus multistriatus* and *Scolytus scolytus*.[12] Ketone (*S*)-**5** is a common secondary metabolite in insects and other arthropods, which has communicatory and ecological functions.[13] Ketone **5** is also an interesting compound that was described as an alarm pheromone and used to coordinate recruitment to food sources,[14] Opilionids (Arachnida) employ (*S*)-**5** as a defensive allomone against ants.[15] Furthermore, in the interaction between the ant *Paraponera clavata* and its parasite *Apocephalus paraponerae* (Diptera), it was discovered that (*S*)-**5** is useful as a kairomone, a semiochemical that disfavors the emitter and benefits another organism.[16]

2. Conclusion

In conclusion, the first asymmetric synthesis of chichimol ketone [4-(*S*)-methyl-1-hepten-3-one] is described and the absolute configuration of the main semiochemical compound isolated from *A. elegans* is determined to be the (*S*)-configuration. Our approach to probe the absolute configuration of **1** is also useful for the synthesis of (*S*)-4-methyl-3-heptanone **5**, which was obtained by catalytic hydrogenation of (*S*)-**1** employing Pd/C in AcOEt as solvent in 99% yield. The spectroscopic data for synthetic (*S*)-**5** are in accordance with described previously by other groups.[17]

3. Experimental

^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Bruker instrument using $CDCl_3$ as solvent and tetramethylsilane as the internal standard. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hertz. Infrared spectra were recorded as film on KBr cells on a Nicolet Nexus FT-IR instrument and the wavenumbers are expressed in cm^{-1}. GC analyses were recorded on Hewlett–Packard 5890 instrument, and GC–MS analyses were recorded on Perkin Elmer Turbo Mass using a fused silica capillary column, MDN-5 (Supelco), 30 m × 0.25 μm. HRMS analyses were recorded on a Micromass Q-Tof 1 instrument.

3.1. (*S*)-2-Methylpentanoic acid 3

TLC (hexane/EtOAc, 1:1) R_f 0.45. $[\alpha]_D$ = +15.8 (*c* 1.0, $CHCl_3$), HPLC condition for corresponding phenylamide derivative: chiral Welch-01 column, *n*-hexane/isopropanol = 9:1, 1.0 mL/min, 254 nm UV detector, t_R = 4.65 min for (*S*)-enantiomer and t_R = 5.88 min for (*R*)-enantiomer. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.90 (3H, t, *J* = 7.1 Hz, CH_3), 1.15 (3H, d, *J* = 6.5 Hz, CH_3), 1.44–1.33 (3H, m, CH_2), 1.72–1.64 (1H, m, CH_2), 2.50–2.41 (1H, m, CH), 11.45 (1H, br s, COOH). HRMS [ESI(+)-MS]: $[C_6H_{12}O_2+H]^+$ *m/z* calcd 117.0916, found 117.0910.

3.2. (2*S*)-*N*-Methoxy-*N*,2-dimethylpentanamide 4

$[\alpha]_D$ = +18.3 (*c* 1.0, $CHCl_3$); FT-IR (KBr film) 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.85 (3 H, t, *J* = 7.3 Hz), 1.08 (3H, d, *J* = 6.8 Hz), 1.25–1.35 (3H, m), 1.54–1.68 (1H, m), 2.83–2.86 (1H, m), 3.15 (3H s), 3.67 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.0, 17.4, 20.7, 32.3, 34.8, 36.0, 61.4, 178.2. HRMS [ESI(+)-MS]: $[C_8H_{18}NO_2+H]^+$ *m/z* calcd 160.1338, found 160.1343.

3.3. Chichimol ketone 1

$[\alpha]_D$ = +2.0 (*c* 1.0, $CHCl_3$), lit.[3] $[\alpha]_D$ = +2.1 (*c* 6.4, $CHCl_3$); FT-IR (KBr film) 1696. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 0.94 (3H, t, *J* = 7.2 Hz), 1.12 (3H, d, *J* = 7.0 Hz), 1.31–1.42 (2H, m), 1.33–1.39 (1H, m), 1.68–1.71 (1H, m), 2.83–2.86 (1H, m), 5.81 (1H, dd, *J* = 1.5 and 10.5 Hz), 6.29 (1H, dd, *J* = 1.5 and 17.5 Hz), 6.46 (1H, dd, *J* = 17.5 and 10.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.1, 16.3, 20.5, 35.4, 43.3, 125.8, 135.3, 204.2. HRMS [ESI(+)-MS]: $[C_8H_{14}O+H]^+$ *m/z* calcd 127.1123, found 127.1115.

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