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Enantioselective synthesis and absolute configuration of the sex pheromone of *Hedypathes betulinus* (Coleoptera: Cerambycidae)

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ABSTRACT

The male-produced sex pheromone of *Hedypathes betulinus* was identified as a mixture of (*E*)-6,10-dimethyl-5,9-undecadien-2-one (geranylacetone) (**1**) and its respective alcohol (**2**) and acetate (**3**). Kinetic resolution of alcohol (**2**) promoted by CAL-B in organic media provided both, (*R*)-(−)-(*E*)-6,10-dimethyl-5,9-undecadien-2-yl acetate (**3**) and (*S*)-(+)-(*E*)-6,10-dimethyl-5,9-undecadien-2-ol (**2**) in high enantiomeric purity. Comparative GC analysis using a chiral column revealed the natural constituents as being (*R*)-(**3**) and a mixture of (*R*)- and (*S*)-(**2**) in a ratio of 82.3% and 17.6%, respectively.

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Hedypathes betulinus (Coleoptera: Cerambycidae: Lamiinae) (Klug, 1825) is the most serious pest of green mate (*Ilex paraguariensis*) in the southern region of Brazil.[1] Three male-specific components were detected by gas chromatography, and the presence of a pheromone regulating the mating behavior of this insect was determined.[1] The chemical structure of these compounds were recently identified as (*E*)-6,10-dimethyl-5,9-undecadien-2-one (gera-nylacetone) (**1**), (*E*)-6,10-dimethyl-5,9-undecadien-2-ol (**2**), and (*E*)-6,10-dimethyl-5,9-undecadien-2-yl acetate (**3**) (major component) (Fig. 1).[2]

The compound (*E*)-6,10-dimethyl-5,9-undecadien-2-ol (**2**) was identified as the main component of the sex pheromone of *Tetropium fuscum* and *Tetropium acinnamopterum* and was named fuscumol[3], whereas (*E*)-6,10-dimethyl-5,9-undecadien-2-yl acetate (**3**) is unprecedented in pheromone chemistry.

Behavioral tests using the synthetic racemic compounds showed that these compounds are attractive for female *H. betulinus*.[2] However, the presence or absence of the unnatural isomer may have an influence on the behavior of the insects, supporting the importance of knowing the stereochemistry of naturally produced compounds.[4] *H. betulinus* aeration extracts provided a few microgram of each compound, making it impractical to use conventional methods of absolute configuration assignment.[2]

Therefore, the best way to establish the absolute configuration of the pheromone is by enantioselective gas chromatography and comparison of retention times of synthetic enantiomers with corresponding data of the natural compounds.[4] Biocatalysis is a powerful tool to obtain enantiopure molecules in organic synthesis.[5] Several secondary alcohols have been resolved with high enantiomeric excess employing CAL-B (Novozymes 435®—immobilized *Candida antarctica* lipase B) over the past few years.[5]

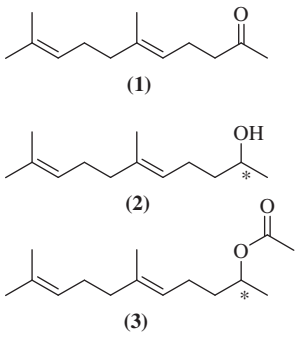

Figure 1. Male-produced sex pheromone of *H. betulinus*.

This paper describes the enantioselective synthesis and determination of the absolute configuration of the sex pheromone components from *H. betulinus* employing a kinetic resolution promoted by CAL-B.

Racemic alcohol (**2**) and acetate (**3**) were synthesized by the reduction of geranylacetone (**1**) with LAH[6], followed by acetylation of the hydroxyl group using Ac_2O and pyridine[7] to afford alcohol (**2**) and acetate (**3**) in 90% and 85% yield, respectively (Fig. 2).

The studies started with the investigation of the reaction time and the solvent type in the kinetic resolution of (**2**), (Fig. 2). The kinetic resolution of the racemic secondary alcohol was evaluated

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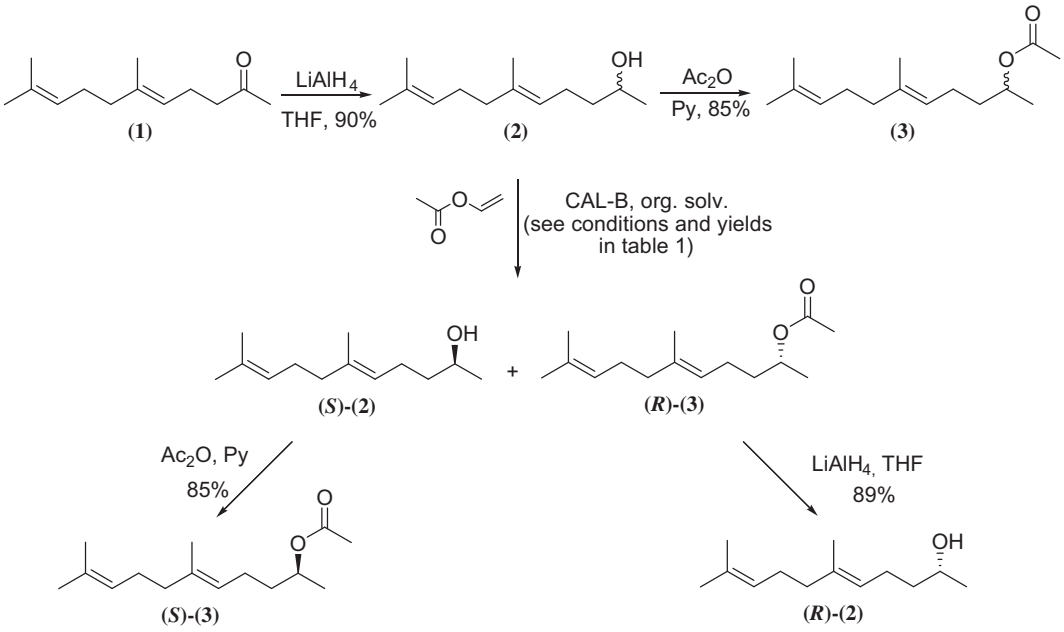

Figure 2. Synthesis of enantiopure (*S*)-(**2**), (*S*)-(**3**), (*R*)-(**2**), and (*R*)-(**3**).

in organic media with vinyl acetate as acetate donor.[8] Three organic solvents, TBME, hexane, and THF, and five different reaction times were employed in the assays (Table 1).

The assays were performed by addition of CAL-B to a solution of alcohol (**2**) and vinyl acetate in the appropriate solvent at 32 °C. The conversions were determined by analyzing the formed products by enantioselective GC. In all reactions, the formation of the enantiopure acetate (*R*)-(**3**) and the reminiscence of the alcohol (*S*)-(**2**) was observed (Fig. 2), which agrees with Kazlauska's rule for CAL-B.[5,9]

Assays in THF showed a lower level of conversion of the substrate in all reaction times investigated (maximum of 34.4%). Tests in hexane and TBME showed a better level of conversion (almost 50%), and the best enantioselectivity was achieved with TBME that yielded (*S*)-(**2**) and (*R*)-(**3**) in an enantiomeric excess of 93.7% and >99%, respectively, within 120 min (Table 1). Madyastha and Gururaja (1994) found an $[\alpha]_D = +3.4$ (*c* 5.0, $CHCl_3$) for the alcohol (*S*)-(**2**).[10] In our experiments, we found an $[\alpha]_D = +3.2$ (*c* 5.0, $CHCl_3$) for the alcohol (*S*)-(**2**).

The best condition was obtained on a preparative scale to synthesize the alcohol (*R*)-(**2**) ($[\alpha]_D = -3.6$) by LAH reduction of the acetate (*R*)-(**3**) ($[\alpha]_D = -2.8$) and the acetate (*S*)-(**3**) ($[\alpha]_D = +2.9$), by acetylation of the alcohol (*S*)-(**2**), using Ac_2O and pyridine (Fig. 2).

The absolute configuration of the alcohol and the acetate present in the natural extract were assigned according to results from enantioselective GC employing a β-CD column (HP-Chiral 20B (20% permethylated β-CD, 30 m × 0.25 mm × 0.25 μm), maintaining the oven in an isothermal of 100 °C during 170 min) to compare the retention times of the compounds of the extracts with the standards obtained from CAL-B resolution. Alcohol (**2**) (the minor component of the pheromone) is present in the extract in both enantiomeric forms in a ratio of 82.3% (*R*)-(**2**) and 17.6% (*S*)-(**2**), as shown in Figure 3A. The major component released by *Hedypathes betulinus* was determined to be the enantiopure (*R*)-(−)-(*E*)-6,10-dimethyl-5,9-undecadien-2-yl acetate, (*R*)-(**3**), which is unprecedented in pheromone chemistry (Fig. 3B).

Table 1
Kinetic resolution of the alcohol (±)-(**2**) employing CAL-B and different organic media[a] with five different reaction times

Enzyme	Solvent	Time	Conversion (c)[b] (%)	ee (*S*)-(**2**)[c] (%)	ee (*R*)-(**3**)[d] (%)	*E*[e]	Abs. config. (acetate)
CAL-B (Novozymes 435)®	TBME	15 min	20.5	25.6	99	>200	*R*
		30 min	33.8	50.5	99	>200	*R*
		60 min	47.9	90.9	99	>200	*R*
		120 min	48.6	93.7	>99	>200	*R*
		24 h	38.6	60.9	97	123	*R*
	Hexane	15 min	12.1	13.6	99	>200	*R*
		30 min	32.7	48.2	99	>200	*R*
		60 min	45.4	82.4	99	>200	*R*
		120 min	42.3	72.6	99	>200	*R*
		24 h	40.1	65.1	97	129	*R*
	THF	15 min	5.8	6.2	99	>200	*R*
		30 min	9.1	9.9	99	>200	*R*
		60 min	23.2	29.9	99	>200	*R*
		120 min	34.4	52.0	99	>200	*R*
		24 h	32.0	46.5	99	>200	*R*

[a] TBME, Hexane, or THF.
[b] Conversion (%)—calculated from the ee's of the substrate (ee_s) and the product (ee_p): $ee_s/(ee_s + ee_p)$.
[c] Enantiomeric excess of (*S*)-(**2**) after resolution.
[d] Enantiomeric excess of (*R*)-(**3**) after resolution.
[e] Enantiomercic ratio (describes the enantioselectivity of the enzyme): $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 + ee_p)]$.

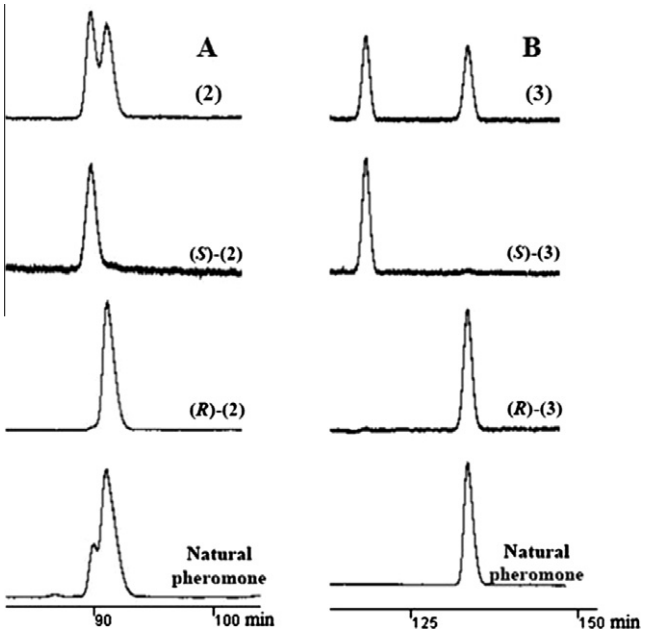

Figure 3. Determination of the absolute configuration of the alcohol (A) and the acetate (B) released by *H. betulinus*.

Experiments to evaluate the behavior of *H. betulinus* in the presence of enantiomerically pure compounds are underway.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data, chiral chromatograms, and copies of ^{1}H, ^{13}C NMR for (**2**) and (**3**) are available) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.024.

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