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Green and Catalytic Synthesis of Dominicalure I, Major Component of the Aggregation Pheromone of Rhyzpertha dominica (Fabricius) (Coleoptera: Bostrichidae

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Green and catalytic synthesis of Dominicalure I, major component of the aggregation pheromone of *Rhyzpertha dominica* (Fabricius) (Coleoptera: Bostrichidae

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Abstract

A new concise and efficient catalytic synthesis of Dominicalure I, the male-produced aggregation pheromone of the grain borer *Rhyzopertha dominica* is here reported. The synthetic route was designed starting from easily available propanal through an organocatalytic key step, and completed with biocatalytic procedures.





1. INTRODUCTION

The lesser grain borer *Rhyzopertha dominica* (Fabricius) (Coleoptera: Bostrichidae) is a worldwide distributed pest of stored grains. Together with *Sitophilus* spp., they constitute the major stored grain pests, and *R. dominica* must be regarded as a primary pest due to its ability to disperse by flight, and high resistance to pesticides.^[1] Both, larvae and adults cause significant damage in whole grains. The use of insect pheromones for pest monitoring constitutes a valuable tool for the development of integrated pest management programs, with the aim of reducing the use of pesticides.^[2]

The male-produced aggregation pheromone of this beetle was isolated and identified as a mixture of (S)-(+)-1-methylbutyl (*E*)-2-methyl-2-pentenoate and (S)-(+)-1-methylbutyl (*E*)-2,4-dimethyl-2-pentenoate, Dominicalure I and II respectively (Figure 1),^[3] attracting both, males and females.^[1]

Both components of the pheromone were synthesized through different synthetic approaches, but up to date, all of them involve either long synthetic sequences or expensive reagents, making them inadequate for monitoring or control purposes. The first synthesis of this pheromone was described by Williams *et al.* using (*S*)-2-pentanol, obtained from D-glutamic acid, as source of chirality.^[3] Almost a decade later, Liu and Lin reported the synthesis of Dominicalure I and II with 30% overall yield and 90% enantiomeric excess, employing a modification of Sharpless asymmetric epoxidation as the key step to introduce the adequate chirality.^[4] A stereoselective synthesis of Dominicalure II was also described by using 1-silyl-1-stannylethenes as key intermediates.^[5] Razkin *et al.* reported the stereoselective synthesis of both components

of the pheromone, through an asymmetric reduction of 3-penten-2-one to the corresponding (*S*)-3-penten-2-ol with (*S*)-BINAL-H as chiral auxiliary, and further diimide-mediated reduction of the double bond.^[6] Das and co-workers later reported an efficient synthetic route exploiting the potential of Baylis-Hillman adducts for furnishing trisubstituted C=C bonds with (*E*)-configuration, as key intermediates.^[7,8] Enzyme-mediated introduction of the proper chirality in Dominicalure I and II was only described by Morgan *et al.*, with the Porcine Pancreatic Lipase (PPL)-mediated kinetic resolution of racemic (*E*)-3-penten-2-ol using trifluoromethyl laurate as acyl donor.^[9] After 45 hours, the reaction achieved 39% conversion, and an enantiomeric ratio of 45. The unreacted material was then subjected to a second resolution followed by further hydrogenation of the remaining alcohol, yielding (*S*)-2-pentanol with high enantiomeric purity.

It is worth to notice, there are no recent reports regarding the preparation of either components of the aggregation pheromone of *R. dominica*. This fact, gives this contribution an additional impact, since it not only gives a concise, efficient and environmentally responsible synthetic approach, but also is an up to date in the field of pheromone chemistry.

Although pheromone chemistry has been widely developed during the last decades, stereoselective syntheses are still challenging tasks for classical organic chemistry.^[10] As part of our ongoing program devoted to the synthesis of insect pheromones for developing monitoring programs for agricultural pests,^[11-13] we attempt to introduce catalytic methodologies (both bio- and organocatalytic ones) in our designed synthetic

routes, as a strategy to achieve efficient, economical and environmentally benign procedures. The use of small organic molecules as catalysts for the preparation of chiral synthons was described for the first time by Eder and Hajos.^[14,15] Nevertheless, it was not until the decade of 2000, with the outstanding contribution of List, Lerner and Barbas III,^[16] that the high potential of this methodology was rediscovered and originated an intense study of its synthetic possibilities.

Here we report a strategy that combines both, bio- and organocatalytic approaches for the synthesis of Dominicalure I, component of the aggregation pheromone of *R. dominica* as a single isomer. A similar procedure is currently being developed for the preparation of Dominicalure II.

2. RESULTS AND DISCUSSION

A retrosynthetic analysis of Dominicalure I shows that it can be obtained through an esterification reaction of the corresponding α , β -unsaturated carboxylic acid with (*S*)-2-pentanol or transesterification of its derivative. The carboxylic moiety can be prepared by performing Pyrrolidine-catalyzed self-aldol condensation of propanal and further oxidation, whereas (*S*)-2-pentanol comes from the enzyme-catalyzed kinetic resolution of the corresponding racemic mixture (Scheme 1).

The first step in the synthetic sequence was the pyrrolidine-catalyzed self-aldol condensation of propanal. The reaction was conducted in hexane at room temperature and it was completed after 48 hours. After addition of a solution of 10% HCl the organic

solvent was distilled under atmospheric pressure, as well as the resulting α , β -unsaturated aldehyde $2^{[17]}$ (Scheme 2). The reaction was highly stereoselective, giving *trans*-2 as a single stereoisomer. It is worth to notice that herein we improved the efficiency of the reaction also contributing to a greener synthetic approach, compared to previously reported by Ishikawa and Saito,^[18] since we conducted it at room temperature, and with less than 10% of the catalyst, obtaining aldehyde 2 with a better yield.

The next step is the oxidative esterification of **2**. The oxidation of the unsaturated aldehyde is not an easy task, given its instability. Looking for mild conditions, an easy protocol developed by Corey was found, which, besides being adequate for the oxidation of labile α , β -unsaturated aldehydes, leads directly to an ester group.^[19] This method is suitable to conjugated aldehydes, and effectively suppresses the isomerization of the double bond.^[20] The reaction involves the attack of a cyanide ion to the carbonyl group generating a cyanohydrin. The subsequent oxidation of this intermediate to an acylnitrile using MnO₂ as oxidizing agent, and a final nucleophilic attack of methanol (also used as solvent) to provide the corresponding methyl ester (Scheme 3). Secondary alcohols are not adequate nucleophiles for this reaction,^[21] so the ester of (S)-2-pentanol could not be obtained directly.

The corresponding methyl ester $\mathbf{3}^{[17]}$ was successfully obtained in 80% isolated yield. A final treatment with (*S*)-2-pentanol is needed in order to obtain the pheromone component.

Enantiomerically pure (*S*)-2-pentanol was obtained through the enzyme-catalyzed kinetic resolution of racemic 2-pentanol using lipase B from *Candida antarctica* (CaL B, Novozym 435) and vinyl butyrate as acylating agent. The reaction was performed in absence of solvent, with orbital shaking (150 rpm) and at 37 °C (Scheme 3). After 15 minutes, the reaction yielded the unreacted (*S*)-2-pentanol (49%, > 99% *ee*, $[\alpha]_D^{25}$ = +13.5 (*c* = 0.5 g/100 ml, CHCl₃)) and the corresponding (*R*)-butylester (48%, 98% *ee*) – in agreement to Kaszlauskas's rule–,^[22] which were successfully separated by column chromatography. The same reaction was also carried out under microwave heating at 50 °C using a previously described protocol,^[23] and (*S*)-2-pentanol and the corresponding (*R*)-butylester were obtained in 5 minutes with the same yields, and enantiomeric purities (Scheme 4). The reactions were monitored by chiral gas chromatography. Both procedures also fit well with green chemistry principles,^[24] being more environmentally responsible than when using organic solvents^[25] or ionic liquids.^[26]

The last step in the synthetic route to Dominicalure I was the transesterification of **3** with (*S*)-2-pentanol. Although it is well known that (*S*)-secondary alcohols are not the preferred substrates for lipases, the reaction was performed anyway due to the mildness of this procedure. As expected, using CaL B as catalyst, the reaction rate was considerably slow, but Dominicalure I^[4] ($[\alpha]_D^{25} = +13.4$ (c = 0.180 g/100 ml, ether) was obtained with 90% yield and > 99% *ee* after 96 hours (Scheme 5). The same yield was obtained under microwave irradiation and in solvent free conditions,^[23] but considerably less time was needed, obtaining Dominicalure I in 4 hours.

In summary, the synthesis of Dominicalure I was achieved through a concise three steps sequence, with an overall yield of 68% and > 99% *ee* starting from inexpensive materials.

3. EXPERIMENTAL

3.1. Materials And Methods

Solvents were purified and dried by conventional methods. Commercial reagents were purchased from Sigma-Aldrich Inc. Lipase Novozym 435 (Lipase B from C. antarctica, CaL B) was obtained from Novozymes. The purity of the reactants, as well as the development of the reactions, were controlled using analytical TLC on silica gel (Kieselgel HF 254 from Macherey-Nagel) and visualized with UV light (254 nm) and/or *p*-anisaldehyde in acidic ethanolic solution. Flash chromatography was performed using silica gel (Kieselgel 60, EM reagent, 230-400 mesh). Further analyses were performed by gas chromatography (GC) in a Shimadzu 2010 equipment, with a FID detector. Chiral gas chromatography was conducted using a Megadex DET-TBS ($25 \text{ m} \times 0.25 \text{ mm} \times 0.25$ μm) column. Temperature program: 38 °C (10 min) / 1 °C/min / 60 °C / 10 °C/min / 200 °C (5 min). T_{SPLIT}: 150 °C, T_{FID}: 200 °C. GC-MS analysis were performed using a Hewlett Packard 5890 GC-MS equipment coupled to a Hewlett Packard 5971 mass spectrometer at an ionizing potential of 70 eV., with a DB5 column (Alltech, $30 \text{ m} \times 0.25$ mm \times 0.25 µm) operated under constant carrier flow of 1 ml/min (He). Temperature program: 70 °C / 10 °C/min / 320 °C. T_{SPLIT}: 220 °C, interphase temperature: 250 °C. Injection $(1 \ \mu L)$ was in the split mode, and Total Ion Current detection was used. NMR spectra (¹H and ¹³C) were carried out in a Bruker Avance DPX 400 MHz equipment. All experiments were performed at 30 °C and CDCl3 was used as solvent. Proton chemical

reference, and carbon chemical shifts are reported in ppm relative to the center line of the CDCl₃ triplet (77.0 ppm). Optical rotations were measured at 25 °C on a Zuzi 412 polarimeter using a 0.5 dm cell. $[\alpha]_D$ values are given in units of deg.cm².g⁻¹ and concentration values are expressed in g/100ml. Biotransformations were conducted in an orbital shaker Thermoforma model 420. All spectral data and optical rotations of known intermediates and final products compares well with literature ones. **3.2. Description Of The Experiments**

(E)-(S)-(+)-1-methylbutyl 2-methyl-2-pentenoate (Dominicalure I).^[4]

shifts (δ) are reported in parts per million (ppm) downfield from TMS as an internal

(S)-2-Pentanol (0.2 g, 2.4 mmol) and lipase B from C. antarctica (Novozym 435, 30 mg) were added to a solution of 3 (200 mg, 1.6 mmol) in 3 ml of hexane. The reaction mixture was stirred in an orbital shaker (150 rpm) at 37 °C for 96 hours. The enzyme was filtered and the crude mixture was purified by column chromatography (Hexane:AcOEt 95:5). Yield: 90%. $[\alpha]_D^{25} = +13.4$ (Et₂O, c = 0.184 g/100 ml).¹H NMR: δ (ppm) = 6.72 $(tq; J_1 = 7.3 \text{ Hz}, J_2 = 1.4 \text{ Hz}, 1\text{H}), 4.95-5.02 \text{ (m; 1H)}, 2.18 \text{ (br q; } J = 7.5 \text{ Hz}, 2\text{H}), 1.82 \text{ (br q)}$ d; J = 1.3 Hz, 3H), 1.61-1.66 (m; 1H), 1.47-1.55 (m; 1H), 1.30-1.42 (m; 3H), 1.26 (d, J = 6.3, 3H), 1.05 (t; J = 7.6 Hz, 3H), 0.92 (t; J = 7.3 Hz, 3H). ¹³C NMR: δ (ppm) = 168.0, 143.3, 127.6, 70.7, 38.2, 22.0, 20.0, 18.7, 14.0, 13.1, 12.2. GC: R_t = 11.67 min (DB5 column). MS (IE; 70 eV: $m/z = 184 (M^+, 1\%), 155 (5\%), 141 (1\%), 116 (5\%), 115 (88\%),$ 114 (10%), 99 (4%), 98 (8%), 97 (100%), 96 (3%), 87 (6%), 85 (2%), 71 (11%), 70 (43%), 69 (50%), 68 (4%), 67 (9%), 55 (18%), 54 (4%), 53 (9%), 45 (8%), 43 (51%), 42 (13%), 41 (63%), 40 (7%), 39 (18%), 32 (31%), 29 (14%).

SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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Scheme 1. Retrosynthetic analysis of Dominicalure I

Scheme 2. Pyrrolidine-catalyzed self-aldol condensation of propanal



Scheme 3. Oxidative esterification of 2 under Corey's conditions







Scheme 5. CaL B-catalyzed transesterification of 3 with (S)-2-pentanol, affording

Dominicalure I



Figure 1. Dominicalure I and II, components of the aggregation pheromone of

Rhyzopertha dominica (F.)

0 Ö 0 **Dominicalure I Dominicalure II**