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A Chemico-Enzymatic Synthesis of All Four Stereoisomers of 1,6-Dimethyloct-1-yl Formate, an Aggregation Pheromone Mimic for the Smaller Flour Beetle

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(2*R*,6*R*)-, (2*R*,6*S*)-, (2*S*,6*R*)- and (2*S*,6*S*)-2,6-dimethyloct-1-yl formates have been prepared from *S*-(+)- and *R*-(−)-enantiomers of 3,7-dimethylocta-1,6-diene *via* enantioselective hydrolysis of (2*R*/*S*,6*R*)- and (2*R*/*S*,6*S*)-2,6-dimethyloct-1-yl formates with porcine pancreatic lipase as the key step.

2,6-Dimethyloct-1-yl formate **1**, obtained as a racemic mixture of all four possible stereoisomers, was found to be a potent mimic of (*R*,*R*)-4,8-dimethyldecanal, the natural aggregation pheromone of *Tribolium confusum*.[1] Subsequent syntheses of this mimic[2] were also aimed at the racemic form of **1**. Here we report a short stereodivergent synthesis of all four stereoisomers of **1** from (*S*)-(+)- and (*R*)-(−)-enantiomers of 3,7-dimethylocta-1,6-diene **2**, commercially available from (+)- and (−)-α-pinene, respectively.†

The oxidation of (*S*)-**2** with SeO_2 and 90% *tert*-amylhydroperoxide, as described in ref. 3, afforded a 4:1 mixture of (*S*)-(+)-2,6-dimethylocta-2,7-dien-1-ol, (*S*)-**3**, with the respective α,β-enal. This mixture was reduced with $NaBH_4$ to give pure (*S*)-**3**, $[\alpha]_D^{22}$ +7.22° (*c* 1.55 in $CHCl_3$) in 72.3% overall yield.

Similarly, from (*R*)-**2** a sample of (*R*)-**3** with $[\alpha]_D^{22}$ −7.18° (*c* 1.32 in $CHCl_3$) was obtained. Exhaustive hydrogenation of (*S*)-**3** or (*R*)-**3** over 5% Pt(C) in MeOH afforded (2*R*/*S*,6*R*)-(−)-2,6-dimethyloctan-1-ol **4** or its (2*R*/*S*,6*S*)-(+)-counterpart **4′** in 85% yield each.‡ Alcohols **4** and **4′** on treatment with hot formic acid gave the corresponding formates, **5** and **5′**, in 90–95% yield.§

The key stage of our stereodivergent synthesis was the hydrolysis of formates **5** and **5′** in the presence of porcine pancreatic lipase (PPL).¶ The reaction was carried out in 0.1 M phosphate buffer at 37 °C; the pH was kept at 7.0 by continuous neutralization of the liberated acid with 1 M NaOH. At 50±2% conversion the hydrolysis was discontinued, the hydrolysates were saturated with NaCl and extracted with ether and the products were column chromatographed on SiO_2 (hexane–ether, 99:1→50:50, v/v). In this way formate **5** was partially hydrolysed to give the formate **6**, enriched with (*R*,*R*)-enantiomer, and the alcohol **7**, enriched with the (2*S*,6*R*)-enantiomer. Both products were levorotatory: $[\alpha]_D^{20}$ −9.21° (*c* 1.90 in hexane) for **6** and $[\alpha]_D^{20}$ −9.07° (*c* 1.10 in $CHCl_3$) for **7**. Alcohol **7**, on treatment with hot HCO_2H, afforded the respective formate **8** whereas alkaline hydrolysis of **6** gave alcohol **9**. Similarly, partial hydrolysis of formate **5′** resulted in the dextrorotatory formate enriched with the (2*R*,6*S*)-enantiomer, (*ent*-**8**), and the dextrorotatory alcohol, enriched with (2*S*,6*S*)-enantiomer, *ent*-**9**. Its formylation afforded the formate of the same configuration, *ent*-**6**.

The controlled PPL-catalysed hydrolysis of the quasi-racemic formate **5′** with various degrees of conversion showed the following trend.

Conversion (%)	*ent*-**9** ($[\alpha]_D^{20}$ in $CHCl_3$)	*ent*-**8** ($[\alpha]_D^{20}$ in hexane)
30	+4.62°	+4.54°
50	+4.05°	+5.45°
65	+3.98°	+5.51°

which implies that the kinetic resolution of *ent*-**8** and *ent*-**6** is nearly complete at 50% conversion. Alkaline hydrolysis of *ent*-**8**, recovered from the enzymatic hydrolysis of **5′** at 50% and 65% conversions, gave two specimens of the (2*R*,6*S*)-alcohol, *ent*-**7**, with $[\alpha]_D^{20}$ +6.08° and 6.02° (both in $CHCl_3$), respectively (Scheme 1).

The assignment of configurations to compounds **6**, **7**, *ent*-**8**, and *ent*-**9** is based on the well-known tendency of PPL to preferentially hydrolyse the *S*-configurated esters of the secondary and β-branched primary alcohols as well as the *pro-S* positioned ester group in the *meso*-diesters (see refs. 4 and 5 for a description and tentative explanation of this stereospecificity). This assignment is to some extent corroborated by the results of olfactometric studies of the stereoisomeric formates: compounds **6** and, particularly, *ent*-**8**, both of which are assumed to possess the (2*R*)-configuration, are more attractive for the mixed population of the adult *Tribolium confusum* beetles than the compounds **8** and *ent*-**6** which possess the (2*S*)-configuration.

This is reminiscent of earlier observations[6] concerning the reception of each of the four stereoisomers of 4,8-dimethyldecanal by *T. confusum* and *T. castaneum*: two aldehydes with (4*R*)-configuration were attractive, whereas their (4*S*)-antipodes were not. Since the former are isosteric with **6** and *ent*-**8**, this may imply the importance of chirality for pheromone reception of *T. confusum*.

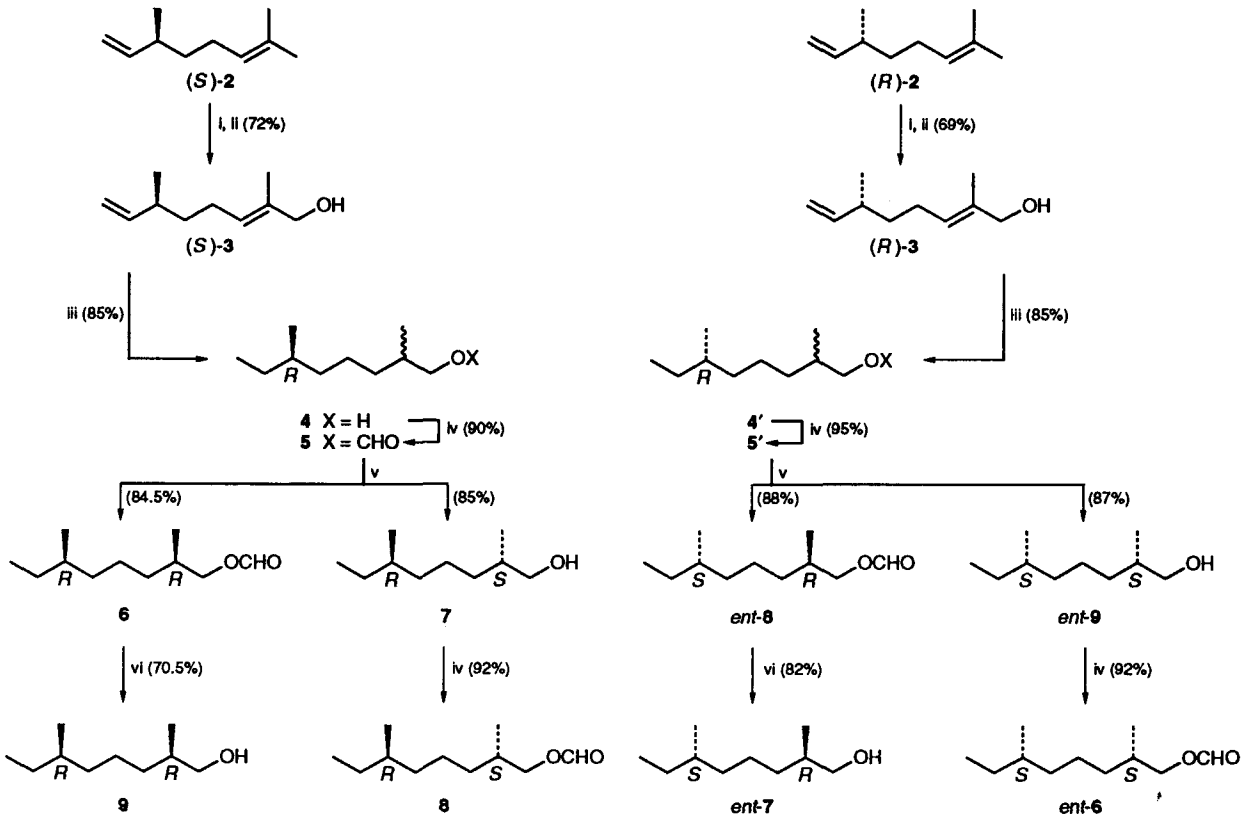
Note added in proof. Acetylation and subsequent PPL-

† Samples of (*S*)-**2** with $[\alpha]_D^{20}$ +9.7° and (*R*)-**2** with $[\alpha]_D^{20}$ −9.5° (Fluka AG) were used in this work.

‡ Somewhat unexpectedly, the amplitudes of specific rotation were markedly different for **4** ($[\alpha]_D^{20}$ −7.40° *c* 2.16 in $CHCl_3$) and for **4′** ($[\alpha]_D^{20}$ +5.32°, *c* 2.33, in $CHCl_3$); the possible nature of this discrepancy will be discussed elsewhere.

§ Again, the amplitudes of specific rotation for these quasi-racemic mixtures of epimeric formates were not equal: $[\alpha]_D^{20}$ −8.62° (*c* 1.02 in hexane) for **5** and $[\alpha]_D^{20}$ +4.82° (*c* 1.41 in hexane) for **5′**.

¶ Purchased from Olainpharm, Latvia; *ca.* 100 mg of PPL (47.8 U mg^{-1}) per 1 mmol of the formate was taken for each experiment.



Scheme 1 *Reagents and conditions*: i, SeO_2-*t*-AmO_2H/CH_2Cl_2, r. t., 7 h; ii, $NaBH_4$/EtOH, r. t. 16–18 h; iii, $2H_2$-Pt(C)/MeOH, r. t., 1 atm, 30–34 h; iv, HCO_2H, 65 °C, 30 min; v, PPL/H_2O (pH 7.0), 37 °C, conversion 50 ± 2%; vi, KOH–MeOH, r. t. 2.5 h.

catalysed hydrolysis of alcohol *ent*-**9** (conversion *ca.* 35%) affords a levorotatory specimen of *ent*-**9**, $[\alpha]_D^{20} - 6.9$ (in $CHCl_3$).

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References

1 K. Mori, S. Kuwahara and M. Fujivara, *Proc. Indian Acad. Sci.*, 1988, **100**, 113.
2 T. Chuman and O. Mikio, *Eur. Pat. Appl.* EP 395025 (1990); V. N. Odinokov, G.Yu. Ishmuratov, M. P. Yakovleva and G. A. Tolstikov, *Khim. Prir. Soedin.*, 1992, 571 [*Chem. Nat. Compd. (Engl. Transl.)*, 1992, 499]; G. D. Gamalevich and E. P. Serebryakov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 773 (in Russian).
3 B. B. Snider and J. V. Duncia, *J. Org. Chem.*, 1980, **45**, 3461.
4 J. Ehrler and D. Seebach, *Liebigs Ann. Chem.*, 1990, 379.
5 G. Guanti, L. Banfi and E. Narisano, *J. Org. Chem.*, 1992, **57**, 1540.
6 H. Z. Levinson and K. Mori, *Naturwissenschaften*, 1983, **70**, 190; T. Suzuki, J. Kozaki, R. Sugawara and K. Mori, *Appl. Entomol. Zool.*, 1984, **19**, 15.

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