A Microbial Synthesis of R and S-9-Hydroxy-(E)-2-Decenoic Acid(9-HDA), A Queen Honeybee Pheromone

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Abstract: (R,E)-9-hydroxy-2-decenoic acid (9-HDA) and its (S,E)- isomer have been prepared by using an organic-microbial approach.

9-Hydroxy-(E)-2-decenoic acid (9-HDA), is a mandibular pheromone secreted by the queen honeybee.[1] Biological testing of both enantiomers showed that the (R)-isomer is 10 times more effective in swarm settling.[2] Although a number of syntheses of 1 involving the 9-keto intermediate 2 have been reported,[3,4] the lack of an effective chiral reduction reagent has resulted in, the final product so far being obtained only in racemic form.

(R)-1 (9 HDA)   2

To our knowledge only one enantiomeric synthesis of 9-HDA 1 has been reported where the desired stereogenic centre of unsaturated acid 1 was achieved by organocuprate-catalytic opening of homochiral methyl oxirane.[5] In this communication, we wish to report a new synthetic method for these two enantiomers utilizing a biotransformation with *Geotrichum sp.* G 38, a reducing fungus which we isolated from the soil samples and which shows high reduction activity and high enantioselectivity in the reduction of a variety of carbonyl compounds, as outlined in scheme 1.

2-Acetylcyclohexanone 3 was treated with 12N KOH solution first at 100°C and then at 125°C resulting in the cleavage of the cyclohexane ring. Acidification and esterification of the dried residue with diazomethane gave the corresponding 7-oxo ester 4 in 83% yield. Ketalization of 4 with ethylene glycol furnished methyl 7-ketal octanoate 5 in 96% yield, which on reduction with DIBAL at -78°C in dry toluene gave the aldehyde 6 in 81% yield. The 9-keto ester 7 was then obtained by treatment of 6 with trimethyl-phosphonoacetate in benzene followed by hydrolysis, in 78% yield. The trans/cis selectivity was more than 98% (as shown by ^{1}H NMR and by GC).

Having 7 in hand, we then turned our attention to its biotransformation. Many microorganisms from our type cultures were screened. The desired chiral hydroxy unsaturated ester was obtained with the resting cell of *Geotrichum sp.* G38 in 64% yield.[6] The same bioconversion failed with baker's yeast. The enantiomeric
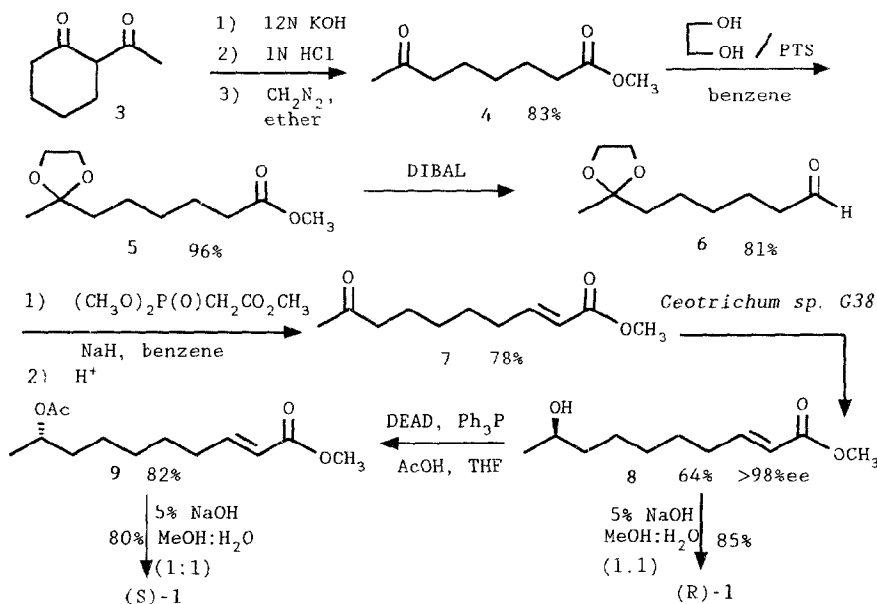
purity of (R)-8 was over 98%.[7] The (S)-isomer of 9 could be easily obtained in 82% yield from (R,E)-8 by essentially complete inversion of configuration according to Mitsunobu's method.[8] Thus, alkaline hydrolysis of (R)-8 and (S)-9 with 5% sodium hydroxide in methanol-water (1.1) afforded the (R)-1 and (S)-1, respectively.

Scheme 1

In conclusion, the (R,E)-9-hydroxy-2-decenoic acid (9-HDA),[9] the Italian queen honeybee pheromone, can be asymmetrically synthesized by using an organic-microbial approach with an overall yield of 32.9% over six steps as can its enantiomer, in 21.6% total yield over seven steps.

REFERENCES:

1. Callow, P.K.; Chapman, J.R.; Paton, P.N., J. Apic. Res., 1964, 3, 77.

2. Winston, M.L.; Slessor, K.N.; Smirle, L.G.; Kandil, A.A., J. Chem. Ecol. 1982, 8, 1283.

3. Bestmann, H.J.; Schmidt, M.; Schobert, R., Synthesis, 1988, 49.

4. Satoh, Y.; Tayano, T.; Hara, S.; Suzuki, A., Tetrahedron Lett., 1989, 30,5153.

5. Kandil, A.A.; Slessir, K.N., Can. J. Chem., 1983, 61, 1166.

6. For (R,E)-8: $[\alpha]_D$= -6.3(c 1.3, EtOH), 1H NMR (200MHz, CDCl$_3$) δ:1.2(d, J=6Hz,3H), 1.43(m, 8H), 2.19(q, J=6Hz, 2H), 2.7(s,1H), 3.73(s, 3H), 3.83(m, 1H), 5.85(d, J=16Hz, 1H), 6.92(dt, J=16.6Hz, 1H).

7. The enantiomeric excess was determined by 200MHz ^{1}H NMR spectra in the presence of Eu(hfc)$_3$ after conversion of (R)-8 to the corresponding acetate.

8. (S)-9: $[\alpha]_D$=2.15(c 1.3, EtOH). Mitsunobu, O., Synthesis, 1981,1.

9. For (R)-1: $[\alpha]_D$= -5.42(c 1.4, EtOH), ^{1}H NMR (200MHz, CDCl$_3$) δ:1.21(d, J=6Hz. 3H), 1.35(m, 8H), 2.33 (q, J=6Hz, 2H), 3.9(m, 1H), 5.82(d, J=16Hz, 1H), 6.95(dt, J=16.6Hz, 1H), 7.2(s, 2H).