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Enantioselective synthesis of (*R*)- and (*S*)-2-methyl-4-octanol, the male-produced aggregation pheromone of Curculionidae species

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Abstract—This work describes an enantioselective synthesis of (*R*)- and (*S*)-2-methyl-4-octanol, a compound that has been identified as the aggregation pheromone of some sugarcane weevils. (*S*)-2-Methyl-4-octanol was efficiently prepared in five steps and 20% overall yield, and its (*R*)-enantiomer, in six steps and 14% overall yield, both from commercial isovaleryl chloride. The key step of our synthetic route is the asymmetric reduction of ethyl 5-methyl-3-oxohexanoate with *Saccharomyces cerevisiae* to its corresponding (*S*)-alcohol in good yield and high enantiomeric excess.

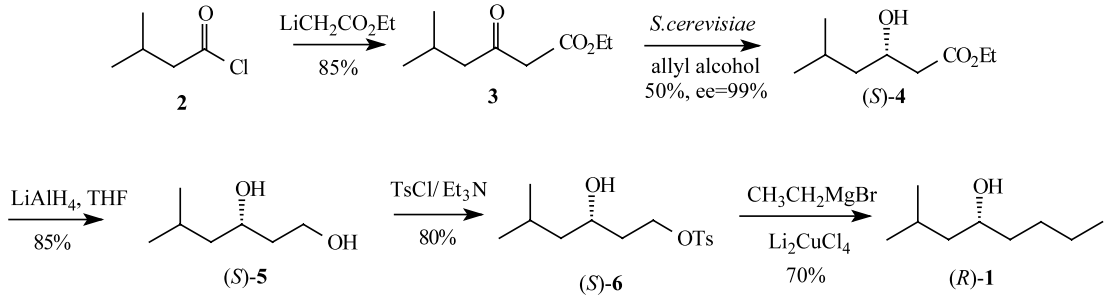
1. Introduction

The use of pheromones in integrated pest management has been increasing due to environmental concerns. This development is accompanied by the search for simple, efficient and less aggressive synthetic methodologies for the preparation of pheromones. One of these methodologies includes microbiological reactions, more specifically, the asymmetric reduction of β-ketoesters with baker's yeast (BY, *Saccharomyces cerevisiae*).

Methyl-4-octanol **1** has been described as a male-produced aggregation pheromone component of sugarcane weevils from Curculionidae species, *Metamasius hemipterus*,[1] *Sphenophorus levis*[2] and *Rhabdoscelus obscurus*.[3] The synthesis of both enantiomers of **1** is necessary to establish the absolute configuration of the naturally occurring product and also to clarify the relationship between stereochemistry and pheromone activity. Only one synthesis of (*S*)- and (*R*)-**1** has been found in literature, which was published by Mori et al., starting from (*R*)- and (*S*)-leucine in five steps and 11% overall yield, respectively.[4] Herein, we present a short and efficient enantioselective synthesis of (*R*)- and (*S*)-2-methyl-4-octanol from commercially available isovaleryl chloride.

2. Results and discussion

The synthetic route for the synthesis of (*R*)-**1** is described in Scheme 1. The β-ketoester **3** was prepared



Scheme 1.

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by the reaction of isovaleryl chloride with the corresponding enolate of ethyl acetate in 85% yield. The microbiological reduction of **3** with BY has not been found in the literature, thus it was necessary to perform a systematic study to optimize the reaction conditions. Different strains of yeast and inhibitors were tested at room temperature (Table 1) and enantiomeric excesses determined by gas chromatography on a chiral stationary phase via the area percent ratio.

Surprisingly, in all experiments (*S*)-**4** was obtained as the major enantiomer. This is probably due to the presence of the isopropyl moiety in **3**, which would direct the interaction with the active site of the enzyme or its 3D structure. The best result was obtained as described in entry 11, which afforded (*S*)-**4** in 50% isolated yield and enantiomeric excess of 99% (Fig. 1, a and b).

The hydroxy ester (*S*)-**4** was then reduced to the diol (*S*)-**5** with LAH and THF in 85% yield. Monotosylation afforded (*S*)-**6** in >95:5>95:580% yield, which was then converted to (*R*)-2-methyl-4-octanol **1**, in 70% yield, using ethylmagnesium bromide and a catalytic amount of Li_2CuCl_4.[5]

Since it was not possible to obtain (*R*)-**4** in the asymmetric reduction with BY, it was prepared from (*S*)-**4**,

Table 1. Different reaction conditions tested for the asymmetric reduction of **3**

Entry	BY (g)[a]	**3** (g/mL)	Time (h)[b]			*c* (g/L)[c]	Inhib.[d]/others[e]	Quant.[f]	E.e. (%)[g]	Yield (%)[h]
			F	P	R					
1	10 (*S*)	2.0	–	–	96	312.5	–	–	75	40
2	10 (*S*)	2.0	–	–	126	312.5	–	–	80	55
3	10 (*E*)	2.0	–	–	100	312.5	–	–	80	30
4	16 (*S*)	0.072	6	–	72	100	Ethanol	8 mL	57	55
5	16 (*S*)	0.072	6	–	72	100	Na_2HPO_4	10%	57	40
6	48 (S)	0.22	6	–	56	100[i]	Na_2HPO_4	10%	65	30
7	48 (*S*)	0.22	6	1	54	100	AA[k]	10%	67	50
8	48 (*S*)	0.22	5	1	60	100[i]	AA[k]	10%	72	40
9	48 (*S*)	0.22	5	1	60	100[i]	AA[k]	15%	72	40
10	48 (*S*)	0.22	5	1	60	100[i]	HOAc[k]	10%	72	40
11	48 (*M*)	0.12	24	–	56	125[j]	AA	100%	99	50
12	48 (*M*)	0.062	24	–	56	0.312[j]	BP	0.33 mM	60	40
13	48 (*M*)	0.062	24	–	56	0.312[j]	BP	0.54 mM	70	50
14	48 (*M*)	0.062	24	–	56	0.312[j]	EP	0.33 mM	70	40

[a] Sources of BY = SUPREMA (*S*), EMULZINT (*E*), MAURI (*M*).
[b] Time: F - fermentation; P - preincubation; R - reaction.
[c] Concentration of glucose solution in water.
[d] Inhibitors: AA - allyl alcohol; HOAc - acetic acid; EB - ethyl bromoacetate; BP - bromoacetophenone.
[e] Others: co-solvent (EtOH) and buffer Na_2HPO_4.
[f] Quantity of inhibitors in relation to the substrate **3** in % or m*M*.
[g] Determined by GC using a chiral column; absolute configuration: *S*.
[h] Isolated yield after purification by column chromatography in silica gel.
[i] Added in portion (4×12 g in 12 h).
[j] Only H_2O (L).
[k] AA and 10% of buffer Na_2HPO_4.

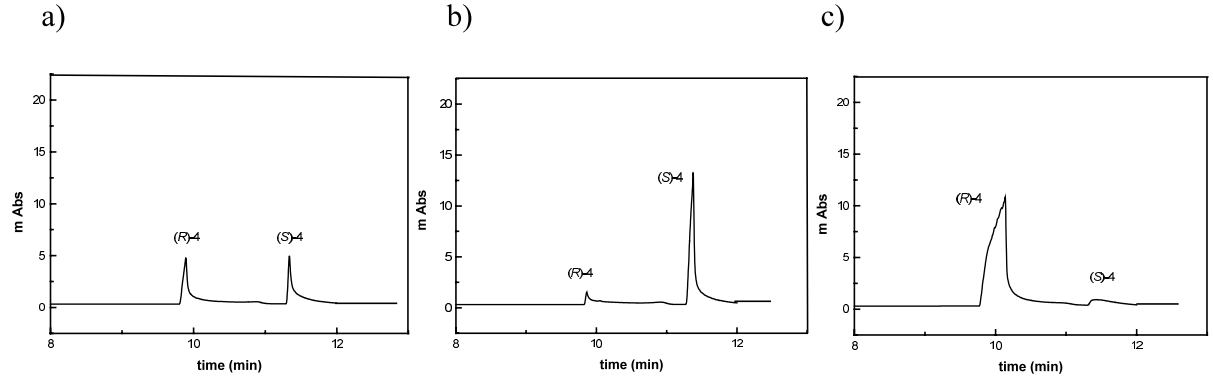
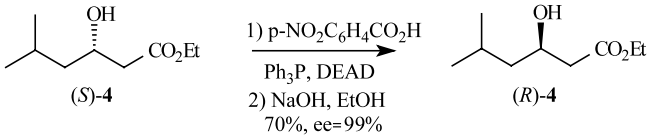


Figure 1. Chiral GC analysis. (a) racemic ethyl 5-methyl-3-hydroxyheptanoate **4**. (b) (*S*)-**4** from microbiological reduction of **3**. (c) (*R*)-**4** from the Mitsunobu reaction.

employing the Mitsunobu reaction (Scheme 2, Fig. 1c). Then, (*R*)-**1** was also prepared using the same synthetic route described in Scheme 1.



Scheme 2.

In conclusion, (*S*)-2-methyl-4-octanol was efficiently prepared in five steps and 20% overall yield, and its enantiomer, (*R*)-**1**, in six steps and 14% overall yield, both from commercially available isovaleryl chloride and with an enantiomeric excess of 99%.

3. Experimental

Unless otherwise noted, all commercially available reagents were purchased from Aldrich Chemical Co. Reagents and solvents were purified when necessary according to the usual procedures described in the literature. The IR spectra refer to films and were measured on a Bomem M102 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-200 (200 and 50 MHz, respectively) and ARX-400 (400 and 100 MHz, respectively). Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Mass spectra were recorded on a Shimadzu GCMS-QP5000. Analytical thin-layer chromatography was performed on a 0.25 μm film of silica gel containing fluorescent indicator UV_{254} supported on an aluminum sheet (Sigma-Aldrich). Flash column chromatography was performed using silica gel (Kieselgel 60, 230–400 mesh, E. Merck). Gas chromatography was performed in a Shimadzu GC-17A with H_2 as carrier and using a DB-5 column. Chiral GC was performed in a HP 5890 with H_2 as carrier (14 psi) using a heptakis (2,6-di-*O*-methyl-3-*O*-phenyl)-β-cyclodextrin column (20% in OV 1701, w/w, 25 m, 0.25 mm i.d.) column, condition: isothermal at 70°C. Elemental analyses were performed on a Fisons EA1108 CHNS-O.

3.1. Ethyl 5-methyl-3-oxohexanoate 3

To a round-bottom flask was added, under nitrogen, diisopropylamine (19.3 mL, 13.7 mmol) in dry THF (117 mL). The resulting solution was cooled at 0°C, and then a solution of *n*-BuLi in hexane (2.5 M, 50 mL, 13.7 mmol) was added dropwise and the mixture stirred for 10 min. This mixture was cooled at −70°C and dry ethyl acetate (6.7 mL, 6.84 mmol) was added and stirred for 30 min. 3-Methylbutanoyl chloride (8.36 mL, 6.84 mmol) was added dropwise in dry THF (6.8 mL). The mixture was stirred for 40 min, then an aqueous solution of ammonium chloride (5 mL) was added at −70°C, and the reaction was extracted with ether (3×5 mL). The organic layer was dried with $MgSO_4$. After evaporation of the solvent, the residue was purified on a silica gel column, using hexane:ethyl acetate 70:30 as eluent to afford the desired β-ketoester **3** (9.9 g, 85%) yield. IR (ν_{max}, film, cm^{-1}): 2979, 2936, 2907, 1735, 1719, 1375, 1300, 1183. ^{1}H NMR (200 MHz-$CDCl_3$) δ: 0.93 (d, J=6.7 Hz, 6H), 1.28 (t, J=7.1 Hz, 3H), 2.19 (non, J=6.7 Hz, 1H), 2.41 (d, J=6.7 Hz, 2H), 3.4 (s, 2H), 4.23 (q, J=7.1 Hz, 2H). ^{13}C NMR (50 MHz-$CDCl_3$) δ: 14.0, 22.3, 24.2, 26.1, 49.6, 51.8, 61.1, 167.0, 202.3.

3.2. Ethyl (*S*)-3-hydroxy-5-methyl-hexanoate 4

To a flask containing deionized water (125 mL) dry baker's yeast Mauri (25.0 g) and allyl alcohol (0.3 mL, 4.4 mmol) were added and the mixture was stirred for 24 h at room temperature. The β-ketoester **3** (121 mg, 0.74 mmol) was added and the resulting mixture was stirred for 24 h, then filtered through Celite. The aqueous layer was extracted with ethyl acetate (3×200 mL), dried over sodium sulfate and then evaporated under reduced pressure. The residue was purified on a silica gel column, using hexane:ethyl acetate 70:30 as eluent to afford the desired (*S*)-hydroxy ester **4** (54 mg, 50%). IR ($\nu_{max,}$ film, cm^{-1}): 3357, 2959, 2919, 1717, 1470, 1365, 1040, and 1004. ^{1}H NMR (200 MHz-$CDCl_3$) δ: 0.92 (d, J=6.6 Hz, 6H); 1.18 (ddd, J=4.5; 8.6; 13.8 Hz, 1H); 1.27 (t, J=7 Hz, 3H); 1.49 (ddd, J=5.5; 8.8; 13.8 Hz, 1H); 1.63–1.90 (m, 1H), 2.37 (dd, J=8.4; 16.5 Hz, 1H); 2.50 (dd, J=3.6; 16.5 Hz, 1H), 2.9 (brs, 1H), 4.17 (q, J=7 Hz, 2H); 4.06 (quint., J=4.2 Hz, 1H). ^{13}C NMR (50 MHz-$CDCl_3$) δ: 14.1, 22.0, 23.2, 24.4, 41.8, 45.6, 60.6, 66.1, 173.0. Anal. calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.04; H, 10.41%. $[\alpha]_D^{25}=-9.95$ (c 12.72, $CHCl_3$), ee=99% by gas chromatography using the area percent ratio in a chiral stationary phase.

3.3. Ethyl (*R*)-3-hydroxy-5-methyl-hexanoate 4

To a flask was added a solution of (*S*)-**4** (100 mg, 0.57 mmol) in dry THF (2 mL) followed by PPh_3 (178 mg, 0.68 mmol). In another flask at 0°C was added diethyl azodicarboxylate (120 mg, 0.68 mmol) to a solution of benzoic acid (84 mg, 0.68 mmol) in dry THF (2 mL). The two mixtures were stirred for 15 min then the second solution was added to the first one, and the resulting mixture was stirred for 24 h. Then the solvent was evaporated in reduced pressure, and a solution of hexane:ethyl acetate 2:1 (5 mL) was added. After filtration and evaporation, the residue was purified by column chromatography, using hexane:ethyl acetate 8:2 as eluent. Then a 5% solution of NaOH in MeOH (5 mL) was added to the product and the mixture stirred for 3 h. The solution was concentrated, water (5 ml) was added, followed by extraction with ethyl acetate (3×2 mL). The organic layer was dried over Na_2SO_4 concentrated under reduced pressure and the residue was purified by column chromatography using hexane:ethyl acetate 90:10 as eluent to afford the desired alcohol (*R*)-**4** (50 mg, 70%). $[\alpha]_D=+10.3$ (c 8.0, $CHCl_3$).

3.4. (*S*)- and (*R*)-5-Methylhexane-1,3-diol 5

To a stirred solution of $LiAlH_4$ (165 mg, 0.95 mmol) in diethyl ether (5 mL) was added a solution of ester **4**

(216 mg, 1.24 mmol) in diethyl ether (2 mL) at 0–5°C. After stirring for 12 h at rt, the mixture was cooled and water (0.33 mL) was added followed by 10% aqueous NaOH (0.24 mL). The resulting mixture was filtered through Celite using diethyl ether (10 mL) as eluent. The organic layer was dried over $MgSO_4$ and concentrated in vacuum. The residue was purified on a silica gel column, using hexane:ethyl acetate 60:40 as eluent. Diol **5** was obtained in 85% yield (106 mg). IR (ν_{max}, film, cm^{-1}): 3407; 2943; 2871; 1727; 1635; 1475. ^1H NMR (200 MHz-$CDCl_3$) δ: 0.93 (d, $J=6.6$ Hz, 6H), 1.4–1.7 (m, 5 H), 3.8–4.0 (m, 3H). ^{13}C NMR (50 MHz-$CDCl_3$) δ: 14.2, 19.3, 22.1, 23.30, 24.35, 38.6, 46.9, 61.8, 70.3. MS (% rel. intensity) m/z: 114 (1.2), 85 (26), 75 (100), 57 (94). Anal. calcd for $C_7H_{16}O_2$: C, 63.59; H, 12.19. Found: C, 63.74; H, 12.34. (*S*)-**5**: $[\alpha]_D^{25}=+16.3$ (*c* 1.9, $CHCl_3$). (*R*)-**5**: $[\alpha]_D^{25}=-15.4$ (*c* 1.5, $CHCl_3$).

3.5. (*S*)- and (*R*)-3-Hydroxy-5-methylhexyl-p-toluenosulfonate 6

A solution of **5** (250 mg, 1.9 mmol) in anhydrous triethylamine (0.4 mL, 2.85 mmol) and dry dichloromethane (10 mL) was cooled at 0–5°C and then was added in portions *p*-toluenesulfonyl chloride (4×100 mg, 2.28 mmol) during 6 h. The mixture was maintained at this temperature for 24 h. The reaction was quenched with ice–water (3 mL) and the aqueous layer was extracted with ether (3×2 mL). The combined ether extracts were washed with saturated $NaHCO_3$ (3 mL) and brine (3 mL), then dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified on a silica gel column, using hexane:ethyl acetate 70:30 as eluent to afford tosylate **6** (430 mg, 80%). IR (ν_{max}, film, cm^{-1}): 3531, 2956, 2933, 1598, 1357, 1189, 966, 917, 765. ^1H NMR (200 MHz-$CDCl_3$) δ: 0.88 (d, $J=6.6$ Hz, 3H), 0.90 (d, $J=6.6$ Hz, 3H), 1.17 (ddd, $J=4.4$; 8.1; 13.1 Hz, 1H), 1.39 (ddd, $J=5.3$; 8.7, 13.1 Hz, 1H), 1.57–1.91 (m, 3H), 2.4 (s, 3H), 3.74–3.81 (m, 1H), 4.13 (ddd, $J=4.8$; 5.9; 10.0 Hz, 1H), 4.28 (ddd, $J=5.1$; 8.7; 10.0 Hz, 1H), 7.3 (d, $J=8$ Hz, 2H), 7.8 (d, $J=6.5$ Hz, 2H). ^{13}C NMR (50 MHz-$CDCl_3$) δ: 21.6, 22.0, 23.3, 24.6, 36.9, 46.7, 66.6, 67.9, 127.9, 129.9, 133.2, 144.8. Anal. calcd for $C_{14}H_{22}O_4S$: C, 58.71; H, 7.74; S, 11.19. Found: C, 58.58; H, 7.77; S, 11.38%. (*S*)-**7**: $[\alpha]_D^{25}=-5.2$ (*c* 0.4, $CHCl_3$). (*R*)-**7**: $[\alpha]_D^{25}=+5.0$ (*c* 0.5, $CHCl_3$).

3.6. (*S*)- and (*R*)-2-Methyl-4-octanol 1

To a mixture of magnesium turnings (21 mg, 0.875 mmol) in anhydrous diethyl ether (6 mL) was added ethyl bromide (65.3 μL, 0.875 mmol). After disappearance of the metal, this solution was transferred via a cannula to a solution containing tosylate **6** (50 mg, 0.18 mmol) in dry diethyl ether (2 mL) at –100°C under nitrogen. Then a 0.10 M solution of lithium tetrachlorocuprate in THF (13 μL, 0.013 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 12 h. Then, the mixture was washed with saturated aqueous solution of NH_4Cl (2 mL). The aqueous layer was extracted with diethyl ether (3×2 mL), then the combined organic layers were washed with H_2O (1 mL), dried over $MgSO_4$ and concentrated in vacuum. The residue was purified by column chromatography using hexane:ethyl acetate 8:2 as eluent, affording the desired alcohol **1** (17 mg, 70%). IR (ν_{max}, film, cm^{-1}): 3350, 2964, 2928, 1468, 1367, 1026. ^1H NMR (200 MHz-$CDCl_3$) δ: 0.90 (d, $J=6.6$ Hz, 3H), 0.92 (d, $J=6.6$ Hz, 3H), 1.27–1.41 (m, 11H), 1.74–1.71 (m, 1H), 3.6–3.7 (m, 1H). ^{13}C NMR (50 MHz-$CDCl_3$) δ: 14.0, 22.0, 22.7, 23.4, 24.6, 27.8, 37.8, 46.8, 69.9. Anal calcd. for $C_9H_{20}O$: C, 74.94; H, 13.97. Found: C, 74.74; H, 13.84. (*R*)-**1**: $[\alpha]_D^{25}=-10.4$ (*c* 0.5, $CHCl_3$), lit.[4] $[\alpha]_D^{23}=-10.5$ (*c* 1.17 $CHCl_3$). (*S*)-**1**: $[\alpha]_D^{25}=+11.5$ (1.04, MeOH), lit.[4] $[\alpha]_D^{22}=+11.6$ (*c* 1.04, MeOH).

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