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Synthesis of (4*R*,8*R*)- and (4*S*,8*R*)-4,8-dimethyldecanal: the common aggregation pheromone of flour beetles

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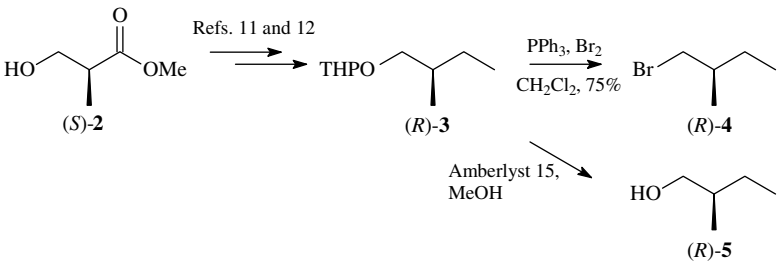
Abstract—The synthesis of (4*R*,8*R*)- and (4*S*,8*R*)-4,8-dimethyldecanal **1** and **1a** has been achieved connecting the chiral building block (*R*)-2-methyl-1-bromobutane **4** with (*R*)- and (*S*)-citronellol derivatives. The key intermediate **4** was obtained optically pure in five steps from methyl (*S*)-3-hydroxy-2-methylpropionate **2**.

The aggregation pheromone of the stored foodstuffs pests *Tribolium castaneum* and *Tribolium confusum* was isolated and identified by Suzuki as 4,8-dimethyldecanal **1**.[1] Mori and co-workers[2] developed the first total synthesis of all of the four possible isomers of **1**, stabilising the absolute configuration of the natural pheromone as (4*R*,8*R*)-**1**. Later, bioassays had shown that a mixture of the isomers (4*R*,8*R*) and (4*R*,8*S*), in a ratio of 8:2, was about 10 times more active than (4*R*,8*R*) itself.[3]

We have previously reported a versatile approach to the synthesis of the isomers (4*R*,8*S*)- and (4*S*,8*S*)-**1**,[4] and several other racemic and stereoselective synthesis have been published since the identification of this pheromone.[5–10]

Here we are describing the synthesis of two other isomers, (4*R*,8*R*)-**1** and (4*S*,8*R*)-**1a**. In this approach, the compound (*R*)-2-methyl-1-bromobutane **4** was employed as a chiral source to connect with the tosylates **8** and **8a**, derivate from (*R*)- and (*S*)-citronellol, respectively. This key intermediate **4** was synthesized optically pure from methyl (*S*)-3-hydroxy-2-methylpropionate **2** (see Schemes 1 and 2).

The (*R*)-2-methyl-1-(2-tetrahydropyranyloxy)butane **3** was readily obtained from **2** as previously described.[11,12] Compound **3** was converted into its corresponding bromine **4** using triphenylphosphine and bromine,[13] in 75% yield. In order to verify the enantiomeric excess of **4**, due to its high volatility, the measures were made preparing the Mosher ester of the corresponding synthetic alcohol (*R*)-2-methyl-1-butanol **5**, which was readily obtained from deprotection of **3** in methanol, using Amberlyst® 15 as catalyst[14] (Scheme 1).



Scheme 1. Synthesis of the key intermediate (*R*)-**4**.

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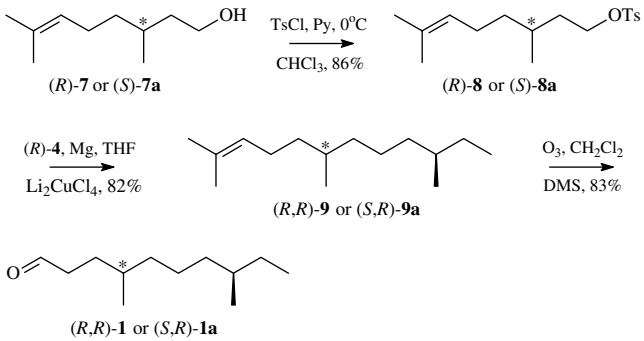

Scheme 2. Synthesis of the pheromone **1** and **1a**.

Mosher ester derivatives **6**, **6a** and **6b** were prepared by the reaction of (*S*)-(+)-α-methoxy-α-(trifluoromethyl) phenyl acetic acid (MTPA) chloride with the racemic-, (*S*)- and (*R*)-2-methyl-1-butanol **5**, respectively.[15,16] The resulting esters were analyzed by ^{1}H NMR spectroscopy, as shown in Figure 1.

The ester (2′*R*/*S*,2*R*)-**6** showed a multiplet (two double doublets and a doublet) between 4.04 and 4.30 ppm, corresponding to the carbinolic hydrogens. The ester (2′*S*,2*R*)-**6a** showed a single doublet at 4.16 ppm, while the ester (2′*R*,2*R*)-**6b** showed two double doublets, at 4.09 and 4.24 ppm, respectively (Fig. 1).

A comparative analysis of the signals at these spectrum region indicated that (*R*)-**3** was obtained in high enantiomeric excess (>99%). Considering that no racemization takes place during the conversion of **3** into its bromine **4**, the compound (*R*)-**4** should also appear with the same ee.

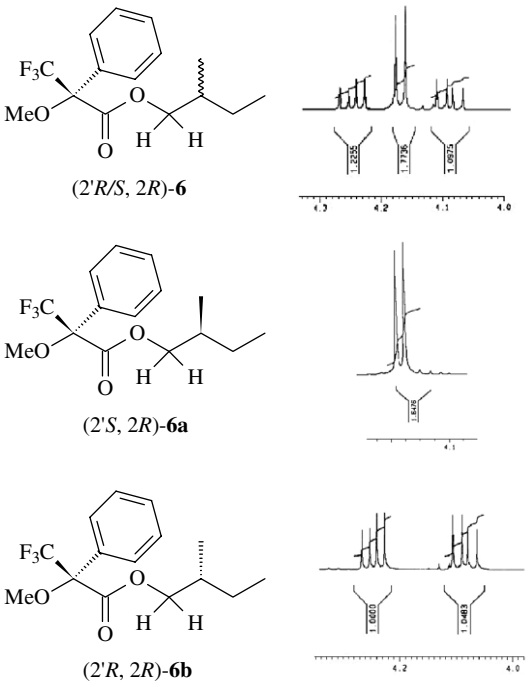

Figure 1.

The synthesis of (*R*,*R*)-**1** and (*S*,*R*)-**1a** could then be finished, as described in Scheme 2. (*R*)-Citronellol **7** (Aldrich, 97% ee) and (*S*)-**7a** (Aldrich, 67% ee) were transformed into the known tosylates **8** and **8a**[17] in 86% yield. Coupling of these compounds with a Grignard reagent prepared from (*R*)-2-methyl-1-bromobutane **4**, using Li_2CuCl_4 as catalyst,[18] yielded the hydrocarbons **9** and **9a** in 82%.[19] Compounds **9** and **9a** were submitted to ozonolysis in methanol–dichloromethane at −78 °C, followed by treatment with DMS,[20] affording the desired pheromones (4*R*,8*R*)-**1** and (4*S*,8*R*)-**1a**, respectively,[21] in 83% yield.

In summary, two isomers of 4,8-dimethyldecanal were readily synthesized in good yields and enantiomeric purity [(4*R*,8*R*)-**1**, $[\alpha]_D$ −7.12 (*c* 9.15, $CHCl_3$), lit.:[2,22] $[\alpha]_D$ −7.37 (*c* 2.04, $CHCl_3$); (4*S*,8*R*)-**1a**, $[\alpha]_D$ −7.85 (*c* 8.10, $CHCl_3$), lit.:[2,22] $[\alpha]_D$ −9.92 (*c* 2.51, $CHCl_3$)] and, in addition with our previous work,[4] we have synthesized all of the four possible stereoisomers of pheromone **1**. The difference observed on the value of the optical rotation among our synthetic (4*S*,8*R*)-**1a** and the one reported in the literature is due to the low enantiomeric enrichment of (*S*)-citronellol **6a**, used as starting material.

Acknowledgements

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13. Typical procedure: To a stirred suspension of $PH_3P{\cdot}Br_2$ (16.5 mmol) in dry CH_2Cl_2 (80 mL) was added a solution of the tetrahydropyranyl ether **3** (2.58 g, 15 mmol) in dry CH_2Cl_2(10 mL). After the yellow solution had been stirred at room temperature for 30 min, it was washed with water (2×40 mL) and the organic layer was separated and dried ($MgSO_4$). Removal of the solvent followed by flash chromatography of the residual oil in silica gel, provided 1.7 g (75% yield) of compound **4**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, $J = 7.4$ Hz, 3H); 1.01 (d, $J = 7.4$ Hz, 3H); 1.20–1.35 (m, 1H); 1.39–1.56 (m, 1H); 1.67–1.77 (m, 1H); 3.29–3.45 (m, 2H).
14. Typical procedure: Amberlyst® 15 (0.14 g) was added to a solution of **3** (0.8 g; 4.65 mmol) in methanol (9.3 mL). The mixture was stirred at 45 °C for 1 h, then the resin was filtered and the solution was concentrated by fractionated distillation at 1 atm, due to the volatility of product. GC analysis of the crude product showed 100% conversion to the desired alcohol **5**, which was employed directly in the next step without further purification.
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21. Anal. Calcd for $C_{12}H_{24}O$: C 78.20; H 13.12. Found: (4*R*,8*R*)-**1**: C, 78.29; H, 13.19; (4*S*,8*R*)-**1a**: C, 78.14; H, 13.07. (4*S*,8*R*)-**1a**: IR (ν_{max} film cm^{-1}): 2927, 2718, 1727, 1462, 1381, 1126; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84 (d, $J = 6.4$ Hz, 3H); 0.85 (t, $J = 6.8$ Hz, 3H); 0.88 (d, $J = 6.4$ Hz, 3H); 1.04–1.14 (m, 3H); 1.20–1.35 (m, 5H); 1.42–1.46 (m, 2H); 1.63–1.69 (m, 2H); 2.40–2.46 (m, 2H); 9.77 (t, $J = 1.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.4; 19.2; 19.4; 24.4; 28.9; 29.4; 32.4; 34.4; 36.8; 37.0; 41.2; 203.0; GC–MS (70 eV) *m*/*z* %: 140 ($M^+ - 44$, 4.05), 125 (3.28), 111 (10.09), 85 (28.74), 70 (57.00), 57 (81.00), 43 (100).
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