

Article

Stereospecific Synthesis of Two Isomers of (4,8) - Dimethyldecanal: The Aggregation Pheromone of *Tribolium spp*

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Uma síntese estereoespecífica para dois estereoisômeros, (4*R*, 8*S*) e (4*S*, 8*S*), do 4,8-dimetildecanal (**1**), entre os quatro possíveis, é descrita em apenas três etapas. A etapa chave emprega a reação de acoplamento dos tosilatos (**3**) e (**3a**), obtidos do (*R*)- e (*S*)-citronelol, com o reagente de Grignard preparado a partir do (*S*)-(+)-1-bromo-2-metilbutano (**4**) comercial.

A straightforward stereospecific synthesis of two stereoisomers, (4*R*, 8*S*) and (4*S*, 8*S*), of 4,8-dimethyldecanal (**1**), out of four possible isomers, is described. The key step employs the coupling reaction of tosylates (**3**) and (**3a**), which are obtained from (*R*)- and (*S*)- citronellol, with the chiral Grignard reagent prepared from comercial (*S*)-(+)-1-bromo-2-methylbutane (**4**).

Keywords: 4,8-dimethyldecanal, *Tribolium spp*, asymmetric synthesis, pheromone

Introduction

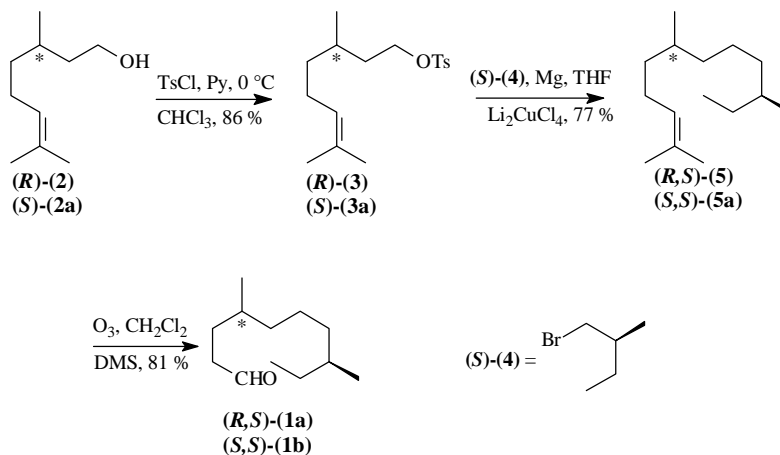
The red flour beetle *Tribolium castaneum* and the confused beetle *Tribolium confusum* are notorious pests of various stored foodstuffs which particularly consume the small fragments of cereal seeds and related products¹. In 1980 Suzuki identified and then synthesized the aggregation pheromone common to both species of *Tribolium*, the 4,8-dimethyldecanal (**1**)^{2,3}. In 1983 Mori and co-workers^{4,1} established the absolute configuration of this natural pheromone as (4*R*, 8*R*), when they carried out the synthesis of all of the four possible stereoisomers of (**1**). Bioassays with the synthetic samples has shown that (4*R*, 8*R*) and (4*R*, 8*S*) are active isomers. Suzuki *et al.*⁵ later found that a mixture of these isomers in a ratio of 8:2 was about 10 times more active than (4*R*, 8*R*) alone. Since identification of this structure, a number of racemic and stereoselective synthesis have been reported^{6,7}. Some of them involve many steps with complex experimental procedures^{8,9}. In this paper we

describe a very short synthesis of two of the isomers of 4,8-dimethyldecanal: (4*R*, 8*S*)-(**1a**) and (4*S*, 8*S*)-(**1b**) by connecting two chiral building blocks, in a synthetic route with only three steps and high overall yield (54 %) (Scheme 1).

Results and Discussion

Following the procedure of Varma¹⁰, the chiral citronellol (**2**) - (Aldrich, 97 % *e.e*) and (**2a**) - (Aldrich, 67 % *e.e*) were transformed into the known tosylates (**3**) and (**3a**)¹¹ in 86% yield. Coupling of these compounds with a Grignard reagent prepared from (*S*)-(+)-1-bromo-2-methylbutane¹² (**4**) under the condition of Schlosser¹³ yielded the hydrocarbons (**5**) and (**5a**) in 77%. Ozonolysis of (**5**) and (**5a**) in methanol-dichloromethane at -78 °C, followed by treatment with DMS¹⁴, afforded the desired pheromones (**1a**), ([α]_D + 7.80°, CHCl₃; lit⁴ [α]_D + 9.94°, CHCl₃) and (**1b**), ([α]_D + 7.00°, CHCl₃; lit⁴ [α]_D + 7.33°, CHCl₃) in 81% yield. The main advantage of the present approach is

† in memoriam



Scheme 1. Synthesis of (4*R*, 8*S*) - and (4*S*, 8*S*) - 4,8-dimethyldecanal (**1a**) and (**1b**).

that no labile stereocenters are present, thus preventing racemization. The difference observed on the value of the optical rotation between our product (4*R*, 8*S*)-(**1a**) and that reported in the literature is the result of the low enantiomeric enrichment of (*S*)-citronellol (**2a**) used as starting material.

Experimental

The IR spectra refer to films and were measured on a Bomem M-102 spectrometer. The ¹H-NMR spectra were recorded with TMS as an internal standard at 400 MHz on a Bruker ARX 400 spectrometer. The ¹³C-NMR spectra were recorded with TMS as an internal standard at 100 MHz on a Bruker ARX 400. Optical rotation was measured on a Perkin-Elmer 241 polarimeter. CHN data were obtained in an EA 1108 CHNS-O Fisons Instrument. GC-MS Analysis was carried out on a Shimadzu QP-5000 GC-MS spectrometer in a split injector mode. The DB-5 capillary column (30 m x 0.53 mm x 0.25) was operated at 70 °C for 1 min, increased to 270 °C at a rate of 7 °C/min and held at this temperature for 10 min. Column chromatography was carried out on columns packed with Merck Kieselgel 60, Art.-Nr. 7734.

(3*S*)-3,7-dimethyl-6-octenyl-4-methyl-1-benzenesulfonate (**3**)

(*R*)-Citronellol (**2**) (2.0 g, 12.8 mmol) was dissolved in chloroform (10 mL) and cooled in an ice bath (0 °C). Pyridine (2.0 mL, 25.6 mmol) was then added, followed by addition of *p*-toluenesulfonylchloride (3.65 g, 19.2 mmol) in small portions with constant stirring. The reaction was complete in 3.5 h. Ether (50 mL) and water (10 mL) were added and the organic layer was washed successively with HCl 10%, NaHCO₃ sat, and water and then dried (MgSO₄). The solvent was removed under reduced pressure and the crude tosylate was column chromatographed (hexane / ethyl acetate: 8 / 2) on a silica gel column yielding 3.0 g (86 %) of (*R*)-(**3**). IR (ν_{max} film cm⁻¹): = 3032, 2930, 1597,

1360, 1179, 948; ¹H-NMR (400 MHz, CDCl₃) δ: 0.81 (d, J = 6.4 Hz, 3H); 1.10-1.30 (m, 2H); 1.40-1.55 (m, 2H); 1.57 (s, 3H); 1.67 (d, J = 1.2 Hz, 3H); 1.82-1.96 (m, 2H); 2.45 (s, 3H); 4.01-4.10 (m, 2H); 5.02 (tq, J = 1.2, 7.2 Hz, 1H); 7.34 (d, J = 8 Hz, 2H); 7.79 (d, J = 8 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ: 17.5; 18.9; 21.5; 25.1; 25.6; 28.7; 35.5; 36.5; 68.9; 124.2; 127.7; 129.7; 131.3; 133.0; 144.6.

(3*S*)-3,7-dimethyl-6-octenyl-4-methyl-1-benzenesulfonate (**3a**)

In the same manner as described above, (*S*)-Citronellol (**2a**) was converted into tosylate (**3a**). The spectral data were identical with those of (*R*)-(**3**).

(6*R*, 10*S*)-(+)-2,6,10-trimethyl-2-dodecene (**5**)

The Grignard reagent was prepared from bromide (**4**) (4.40 g, 29.0 mmol) and magnesium (0.72 g) in dry THF (12 mL). This slurry was added dropwise to a solution of (**3a**) (2.0 g, 7.2 mmol) in dry THF (12 mL) with stirring and cooling below -60 °C. A solution of Li₂CuCl₄ in THF (0.1 M, 0.37 mL) was added to the mixture, and the temperature was gradually raised to room temp. After overnight stirring, the mixture was poured onto ice and ammonium chloride solution, and subsequently extracted with ether. The extract was washed with saturated NaHCO₃ solution and brine, dried with MgSO₄ and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane / ether : 9.5 / 0.5) to give the hydrocarbon (**5**) in 77 % yield (1.15 g). [α]_D²⁵ = + 7.96 (c = 7.30 in CHCl₃); IR (ν_{max} film cm⁻¹): = 2920, 1600, 1455, 1376, 1069; ¹H-NMR (400 MHz, CDCl₃) δ: 0.84 (d, J = 6.4 Hz, 3H); 0.85 (t, J = 6.4 Hz, 3H); 0.86 (d, J = 6.8 Hz, 3H); 1.00-1.15 (m, 4H); 1.26-1.29 (m, 8H); 1.60 (s, 3H); 1.68 (s, 3H); 1.90-2.00 (m, 2H); 5.11 (t, J = 6.4 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ: 11.5; 17.6; 19.2; 19.6; 24.5; 25.6; 25.8; 29.6; 32.4; 34.4; 36.9; 37.2; 37.3; 125.1; 130.9; GC-MS (70 eV) *m/z* %: 210 (M⁺, 16.17), 140 (5.68), 125 (16.63), 111 (25.59), 97 (16.46), 83

(35.42), 70 (100), 56 (92.00); (Anal. Calcd. for C₁₅H₃₀: C, 85.83%; H, 14.37%. Found: C, 85.35%; H, 14.44%).

(6*S*, 10*S*)-(+)-2,6,10-trimethyl-2-dodecene (5a)

As described above, compound (3) was converted into hydrocarbon (5a). The spectral data were identical with those of (*R*, *S*) - (5). $[\alpha]_D^{25} = + 6.47$ ($c = 17.0$ in CHCl₃) (Anal. Calcd. for C₁₅H₃₀: C, 85.83%; H, 14.37%. Found: C, 85.75%; H, 14.61%).

(4*R*, 8*S*)-(+)-4,8-dimethyldecanal (1a)

To a solution of (5) (1.0 g, 4.8 mmol) in methanol-dichloromethane (2:1, 200 mL) ozone was bubbled for 30 min at -78 °C. Dimethyl sulfite (10 mL) was added, and the reaction mixture stirred for another 10 h at room temperature. After concentration *in vacuo*, the residue obtained was chromatographed over silica gel (hexane / ethyl acetate : 7 / 3) affording 0.73 g of pheromone (1a) (81 %). $[\alpha]_D^{25} = + 7.80$ ($c = 7.12$ in CHCl₃); IR (ν_{\max} film cm⁻¹): 2927, 2718, 1727, 1462, 1381, 1126; ¹H-NMR (400 MHz, CDCl₃) 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); ¹³C-NMR (100 MHz, CDCl₃) 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); (Anal. Calcd. for C₁₂H₂₄O: C, 78.20%; H, 13.12%. Found: C, 78.14%; H, 13.07%).

(4*S*, 8*S*)-(+)-4,8-dimethyldecanal (1b)

As described above, compound (5a) was converted into pheromone (1b). The spectral data were identical with

those of (*R*, *S*) - (1a). $[\alpha]_D^{25} = + 7.00$ ($c = 9.15$ in CHCl₃) (Anal. Calcd. for C₁₂H₂₄O: C, 78.20%; H, 13.12%. Found: C, 78.29%; H, 13.19%).

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References

1. Levinson, H.Z.; Mori, K. *Naturwissenschaften* **1983**, *70*, 190-192.
2. Suzuki, T. *Agric. Biol. Chem.* **1981**, *45* (6) 1357-1363.
3. Suzuki, T. *Agric. Biol. Chem.* **1981**, *45* (11) 2641-2643.
4. Mori, K.; Kuwahara, S.; Ueda, H. *Tetrahedron* **1983**, *39* (14) 2439-2444.
5. Suzuki, T.; Kozaki, J.; Sugawara, R.; Mori, K. *Appl. Entomol. Zool.* **1984**, *19*, 15.
6. Breuer, E.; Deutsch, J.; Lazarovici, P. *Chem. and Ind.* **1982**, 907.
7. Fuganti, C.; Grasselli, P.; Servi, S.; Högberg, H.-E. *J. Chem. Soc., Perkin Trans. I* **1988**, 3061.
8. Schreiber, S.L.; Hullin, B. *Tetrahedron Lett.* **1986**, *27*, 4561.
9. Moinseenkov, A.M.; Ceskis, B.A. *Dokl. Akad. Nauk SSSR* **1986**, *290*, 1379.
10. Kabalka, G.W.; Varma, V.; Varma, R.S. *J. Org. Chem.* **1986**, *51*, 2386-2388.
11. Mori, K.; Wu, J. *Liebigs Ann. Chem.* **1991**, 783-788.
12. Mori, K. *Tetrahedron* **1974**, *30*, 3817.
13. Fouquet, C.; Schlosser, M. *Angew Chem. Int. Ed. Engl.* **1974**, *13*, 83.
14. Chan, T.; Xin, Y. *J. Org. Chem.* **1997**, *62*, 3500-3504.

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