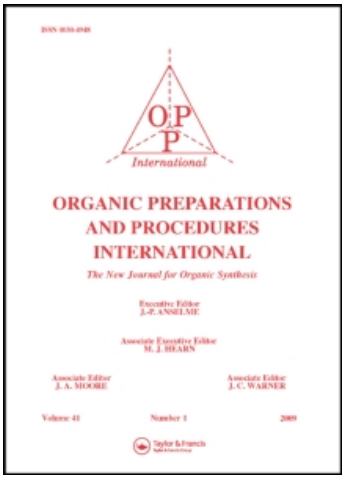

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AN EFFICIENT SYNTHESIS OF (*S*)-(+)-2-TRIDECANOL ACETATE, AN AGGREGATION PHEROMONE OF *DROSOPHILA MULLERI*

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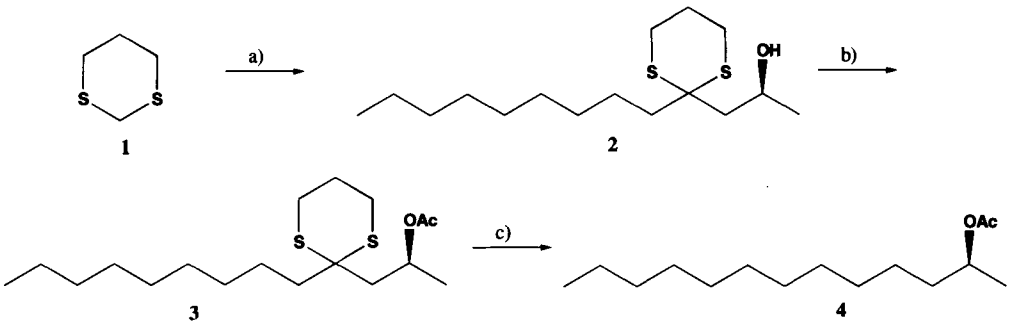
(*S*)-(+)-2-Tridecanol acetate (**4**), an aggregation pheromone of *Drosophila mulleri*,[1] has been the subject of several synthetic investigations in the past few years. Besides four multistep-approaches,[1-4] an enzymatic resolution[5] of *rac*-**4** giving the pheromone in poor enantiomeric purity has been described. This report describes a novel efficient preparation of **4** starting from readily available compounds.

1,3-Dithiane (**1**) was deprotonated with *n*-butyllithium and then treated with (*S*)-propylene oxide.[6] The resulting alkoxide was further deprotonated at C-2 of the dithiane ring with *n*-butyllithium to give a dianion[7] which yielded **2** on subsequent C-alkylation with nonyl iodide and aqueous workup. The overall yield of this one-pot reaction was 80%. The alcohol **2** then was converted to the acetate **3** with acetic anhydride. Reductive desulfurization of **3** to give the title pheromone **4** was most conveniently performed with tributyltin hydride/AIBN.[8] This reagent was superior to the commonly used *Raney* nickel. The enantiomeric excess (ee) of **4** was determined by GLC after ester hydrolysis (2 M KOH) and derivatization of the resulting (*S*)-2-tridecanol with (*R*)-phenylethyl isocyanate and found to be >98%. This novel synthesis of pheromone **4** in three steps (overall yield of 64%) should be generally applicable to the synthesis of (*S*)- as well as (*R*)-2-alkanols starting from enantiomeric pure propylene oxides.

Work is in progress to apply this methodology to the synthesis of other chiral natural products containing a methylcarbinol moiety.



a) *i*) *n*-BuLi, THF, *ii*) (*S*)-propylene oxide, *iii*) *n*-BuLi, *iv*) nonyl iodide;
b) Ac_2O, DMAP (cat.), Et_3N, CH_2Cl_2; c) Bu_3SnH, AIBN (cat.), toulene

EXPERIMENTAL SECTION

Elemental analyses were performed on a Carlo Erba CHNO Elemental Analyzer 1106. Optical rotations were determined on a Perkin Elmer 241. GLC was performed on a Shimadzu GC-14A with an FID detector; column: AT-50 (Alltech). IR spectra were obtained on a Philips PU 9800 FTIR-Spectrometer. NMR spectra were obtained on a Bruker AM 400 and a Jeol JNM-GX-400, TMS as internal standard. Mass spectra were obtained on a Finnigan MAT 8430 and a Vacuum Generators 7070 H. Kieselgel 60 (230-400 mesh) was used for Flash Column Chromatography (FCC).

(*S*)-2-(2-Hydroxypropyl)-2-nonyl-1,3-dithiane (2).- A solution of 1,3-dithiane (**1**) (4.0 g, 33.3 mmol) in anhydrous THF (50 mL) was cooled to -40° under a nitrogen atmosphere. Then *n*-butyllithium solution (1.6 M in hexane; 25.0 mL, 40.0 mmol) was added slowly with stirring. The reaction mixture was was warmed up to -20° within 2 hrs and then cooled to -40° again and treated dropwise with (*S*)-propylene oxide (2.1 g, 36.2 mmol). The mixture was stirred at -40° for 1 hr and at 0° for 12 hrs and then cooled to -40° again. Then *n*-butyllithium solution (1.6 M in hexane; 25.0 mL, 40.0 mmol) was added dropwise and the mixture was warmed up to 0° within 2 hrs. After cooling to -40° again, *n*-nonyl iodide (10.16 g, 40.3 mmol) was added and the mixture was stirred at -40° for 1 hr and at 0° for 12 hrs. Then water (100 mL) was added, the solution was adjusted to pH 5 with 2 M HCl and extracted with ethyl acetate (100 mL). The organic layer was dried (Na_2SO_4), evaporated and the residue was purified by FCC (hexane/ ethyl acetate, 4:1) to give **2** (7.9 g, 80%) as a yellow oil; $[\alpha]_D^{20}$ = +18.43° (c 1.98, $CHCl_3$); MS (EI, 70 eV): *m/z* (%): 304 (M^+, 56), 245 (66), 197 (70), 177 (100), 133 (59); IR (film, NaCl): 3448, 2914, 2848, 1461, 1419, 1371, 1272, 1239, 1131, 1059, 927, 909, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88 (t, J = 6.3 Hz, 3 H, CH_3), 1.19 (d, J = 6.0 Hz, 3 H, CH_3), 1.27-1.45 (m, 13 H), 1.54 (m, 1 H), 1.84-2.07 (m, 5 H), 2.34 (dd, J = 9.2 Hz, J = 15.2 Hz, 1 H), 2.73-2.81 (m, 2 H, S-CH_2), 2.91-3.06 (m, 2 H, S-CH_2), 3.64 (s, 1 H, OH), 4.12 (m, 1 H, C*H*-CH_3); ^{13}C NMR ($CDCl_3$): δ 14.0, 22.5, 23.7 (2 C), 24.9, 25.9, 26.3, 29.1, 29.3, 29.4, 29.7, 31.7, 39.9, 45.7, 51.9, 54.6.

Anal. Calcd. for $C_{16}H_{32}OS_2$: C, 63.10; H, 10.59. Found: C, 62.80; H, 10.11

(*S*)-1-(2-Nonyl-1,3-dithian-2-yl)-2-propyl acetate (3).- A solution of **2** (4.0 g, 13.1 mmol), triethylamine (2.7 g, 26.7 mmol), and 4-dimethylaminopyridine (90 mg, 0.74 mmol) in anhydrous

dichloromethane (50 mL) was cooled to 0° under a nitrogen atmosphere and treated dropwise with acetic anhydride (2.05 g, 20.3 mmol). Then the ice-bath was removed and the mixture was stirred at room temperature. After 12 hrs 2 M HCl (80 mL) was added followed by extraction with diethyl ether (150 mL). The organic layer was dried (Na_2SO_4), evaporated and the residue purified by FCC (hexane/ ethyl acetate, 9:1) to give **3** (4.4 g, 97%) as a yellow oil; $[\alpha]_D^{20} = +7.55°$ (c 1.79, $CHCl_3$); MS (EI, 70 eV): *m/z* (%): 346 (M^+, 1), 182 (38), 87 (60), 43 (100); IR (film, NaCl): 2928, 2855, 1740, 1371, 1240, 1130, 1066, 1047, 1016, 953, 908 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3 H, CH_3), 1.26 (d, J = 6.2 Hz, 3 H, CH_3), 1.20-1.50 (m, 14 H, -$(CH_2)_7$-), 1.83-1.98 (m, 4 H), 2.00 (s, 3 H, CH_3CO), 2.02 (dd, J = 2.5 Hz, J = 15.5 Hz, 1 H), 2.36 (dd, J = 8.1 Hz, J = 15.5 Hz, 1 H), 2.73-2.89 (m, 4 H, 2 S-CH_2), 5.19 (m, 1 H, C*H*-CH_3); ^{13}C NMR ($CDCl_3$): δ 14.1, 21.5, 21.8, 22.7, 24.1, 25.2, 26.1 (2 C), 29.3, 29.5, 29.6, 29.9, 31.9, 39.0, 43.5, 51.9, 68.1, 170.2.

Anal. Calcd. for $C_{18}H_{34}O_2S_2$: C, 62.39; H, 9.89. Found: C, 62.34; H, 9.84

(*S*)-2-Tridecanol acetate (4).- A solution of **3** (3.50 g, 10.1 mmol), AIBN (100 mg, 0.61 mmol), and tributyltin hydride (17.7 g, 60.8 mmol) in anhydrous toluene was refluxed under a nitrogen atmosphere for 12 hrs. Then the solvent was removed by distillation and the residue was purified by FCC (hexane/ ethyl acetate, 9:1) to give **4** (2.01 g, 82%) as a pale yellow oil; $[\alpha]_D^{20} = +4.42°$ (c 1.34, hexane), lit.[3]: $[\alpha]_D^{23} = +4.31°$; ee >98%. The ^1H NMR and ^{13}C NMR spectra were identical to those reported.[3]

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