A Concise Synthesis of (2*S*, 5*R*)-2-Methyl-5-hexanolide

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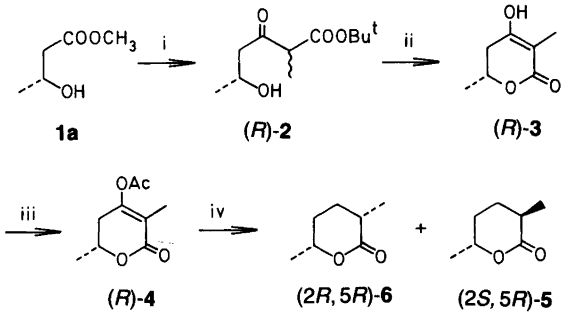
Enantiomerically pure (2*S*, 5*R*)-2-methyl-5-hexanolide, (2*S*, 5*R*)-**5**, ('carpenter bee pheromone' or its enantiomer) has been synthesized in four steps from methyl (*R*)-3-hydroxybutanoate. The *C*-acylation of a lithium ester enolate with a β-lactone (**7**) is part of a new route to β-keto-δ-lactones (e.g. **3**). These can be efficiently reduced in two steps to the saturated δ-lactones (e.g. **5**).

The major component of the sex pheromone which is excreted from the mandibular gland of the male carpenter bee (*Xylocopa hirutissima*) is *cis*-2-methyl-5-hexanolide; its absolute configuration is unknown.[1] This lactone has been synthesized in an optically active form [2–6] as well as in racemic form.[7–13] We present here a synthesis of (2*S*, 5*R*)-2-methyl-5-hexanolide, (2*S*, 5*R*)-**5** (Scheme 1) which starts from commercially available methyl (*R*)-3-hydroxybutanoate (**1a**). The choice of this starting material provides enantiomeric flexibility, since ethyl (*S*)-3-hydroxybutanoate (**1b**) is also available.[14] In the initial experiments of this work we used **1b** of 86 % e.e.

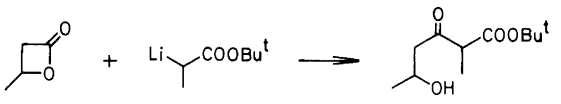
The first step, **1**→**2**, requires a directed Claisen condensation. This reaction was performed without resorting to protective group strategy. Ohta *et al.*[15] allowed (±)-**1a** to react at −78 °C (10 min) with two equiv. of the lithium ester enolate prepared from *tert*-butyl acetate, and obtained *tert*-butyl 5-hydroxy-3-oxohexanoate in 62 % yield. We found that the reaction of **1b** with *tert*-butyl propionate instead of *tert*-butyl acetate produced only a little (*S*)-**2**; 60–70 % of **1b** was recovered unchanged (^{13}C NMR). ^{13}C NMR spectroscopy was used in the analysis of all crude reaction products containing **2**. The yield of (*S*)-**2** did not increase when the reaction temperature was allowed to rise to −45 °C over 10 min. It seemed likely that the low yield was due to deprotonation of the hydroxy group forming *O*-lithiated **1b**, the ester group of which should be less electrophilic than that **1b**. A modified technique, designed to permit condensation with *O*-lithiated **1b**, was therefore introduced. The use of three equiv. of the ester enolate plus one equiv. of lithium diisopropylamide and a higher reaction temperature (−75 °C → +15 °C) proved satisfactory [70–75 % yield of (*S*)-**2**]. Substantial amounts of *tert*-butyl 2-methyl-3-oxopentanoate were obtained as a by-product. The crude (*S*)-**2** was hydrolysed with dilute alkali (cf. Ref. 16). Acidification, extraction, and crystallization gave (*S*)-**3** (55 % calc. on **1b**). The analogous reaction from **1a** gave a 45 % yield of (*R*)-**3**. Like its analogues,[17] **3** is in the enol form in the crystalline state (IR) and in D_2O (to ca. 80 %). A keto form, probably the *trans* isomer, predominates (90 %, NMR) in $CDCl_3$. The minor NMR signals observed probably originate from the *cis* keto form (ca. 5 %) and the enol form (ca. 5 %). Racemic **3** has been prepared by another route.[8]

Exhaustive reduction of the enol function in analogues of **3** has previously been carried out by means of various reduction–elimination–reduction sequences.[8,18,19] We recently used an efficient two-step technique for the reduction of a five-membered ring analogue[20] of **3**, and this technique proved fruitful also for (*R*)-**3**. Thus, acetylation with acetyl chloride and *N*-ethyldiisopropylamine gave crystalline (*R*)-**4** in 92 % yield. *O*-Acylation is the predominant reaction in these systems.[21] Hydrogenation of (*R*)-**4** using platinum(IV) oxide gave mixtures of the *cis* and *trans* isomers **5** and **6** in which **5** predominated (ca. 85 %; GLC). The yield of the target compound (2*S*, 5*R*)-**5** was 73 % (GLC). A single purification by preparative GLC[4] gave (2*S*, 5*R*)-**5**, which showed $[\alpha]_D^{21}$ +96° and was contaminated with less than 0.05 % of **6** (GLC). Mori and Senda[2] prepared both enantiomers of the *cis*-lactone **5**, demonstrated (NMR) that both samples were enantiomerically pure, and obtained $[\alpha]_D^{20}$ −91° and $[\alpha]_D^{21}$ +93.5°. The specific rotation of our sample shows that this also is enantiomerically pure. On the other hand, the sample prepared from **1b** (86 % e.e.) showed $[\alpha]_D$ −66°, which corresponds to only 69 % e.e. of the 2*R*, 5*S* stereoisomer. Contrary to expectation,



Scheme 1. Reagents: i, LDA + $CH_3CHLiCOOBu^t$; ii, (1) OH^-, (2) H^+; iii, CH_3COCl + $EtNPr_2^i$; iv, H_2 + PtO_2.

the optical purity decreased during the synthesis. For instance, recrystallization of the enol acetate lowered its $[\alpha]_D^{22}$ from +105 to +93°, corresponding to 79 and 70% e.e., respectively. In order to prepare enantiomerically pure (2*R*, 5*S*)-**5**, one must either start with optically pure **1b** or find crystallization procedures which increase rather than decrease the optical purity. This synthesis of **5** or its enantiomer is the shortest published and requires no exclusive reagents. It is, however, only about 85% stereospecific. Another synthesis using ethyl (*S*)-3-hydroxybutanoate has been published.[3]



7 (±)-**2**

Scheme 2.

A brief investigation of the use of β-lactones in the *C*-acylation of lithium ester enolates was carried out (Scheme 2). The reactions with γ- or δ-lactones, but not β-lactones, have been studied previously and were found to stop at the initially formed tetrahedral intermediate if the reactions were run at −78 °C.[22] The tetrahedral intermediate obtained from a β-lactone should be more prone to undergo ring-opening thus creating a new electrophilic center, i.e. a keto carbonyl group, which could compete with the starting β-lactone in the reaction with the ester enolate. β-Lactone **7** has been prepared in optically active forms.[23] We used racemic **7**, allowed it to react with the previously used enolate, and obtained the highest yield of (±)-**2** (70–75%) when the solutions of the reactants (1.6 equiv. of the enolate) were cooled to ca. −100 °C (−78 °C was inferior). The solutions were then rapidly combined, and the exothermic reaction stopped with acetic acid at ca. −75 °C. Even lower starting temperatures would possibly be better but this was not tried.

Experimental

General. Tetrahydrofuran (THF) was distilled over $LiAlH_4$. A fused silica capillary column (SE-52, 25 m), mounted in a Hewlett-Packard 5830 A instrument, was used for analytical GLC. Preparative GLC was run at 115 °C using a glass column (1 m, inner diam. 4 mm) of 10% Carbowax 20M on Chromosorb W DMCS, 80–100 mesh, mounted in a Varian Aerograph 1400 chromatograph. The carrier gas throughout was N_2. Optical rotations were measured on a Perkin–Elmer 241 polarimeter and NMR spectra on a JEOL JNM-FX 100 or a JEOL GSX 270 spectrometer. Internal tetramethylsilane was used as the reference for samples in $CDCl_3$ and CD_3OD and internal sodium 2,2-dimethyl-2-silapentane-5-sulfonate for samples in D_2O. IR spectra were recorded on a Perkin–Elmer 257 instrument.

Commercial **1a** (Janssen) showed $[\alpha]_D^{22}$ −49.9° (*c* 1.4, $CHCl_3$) and was used without prior distillation; lit.,[24] rotation, $[\alpha]_D^{22}$ − 48.6° (*c* 1.6, $CHCl_3$).

Ethyl (*S*)-3-hydroxybutanoate (**1b**) of 86% e.e. was prepared by reduction of ethyl acetoacetate with baker's yeast;[14] $[\alpha]_D^{22}$ +37.4° (*c* 1.3, $CHCl_3$); lit.,[14] rotation, $[\alpha]_D$ +43.5° (*c* 1.0, $CHCl_3$).

(6R)-5,6-Dihydro-3,6-dimethyl-4-hydroxypyran-2-one [(*R*)-(**3**)]. *tert*-Butyl propionate (8.80 g, 67.7 mmol) was converted (−78 °C) into its lithium ester enolate using lithium diisopropylamide (91 mmol) in a mixture of THF (95 ml) and hexane (ca. 50 ml). A precooled (−76 °C) solution of **1a** (2.50 g, 21.2 mmol) in THF (25 ml) was added (5 min). The cooling bath was then removed. When the reaction mixture had reached +15 °C (45 min), it was poured onto stirred and ice-cooled hydrochloric acid (2.5 M, 80 ml) in brine. The organic phase was separated, the aqueous phase was extracted with diethyl ether (2×100 ml) and the organic phases were combined, washed with brine and concentrated. Dichloromethane was added and the solution was dried with Na_2SO_4. After the solution had been filtered and concentrated, most of the *tert*-butyl propionate was evaporated at ca. 100 Pa to leave a residue (8.10 g) which was dissolved in methanol (140 ml). This solution was added (15 min) to ice-cooled and stirred aq. NaOH (0.1 M, 1060 ml) and the mixture was left for 24 h at ca. +5 °C. The methanol was evaporated and the remaining aqueous solution was washed three times with diethyl ether and then cooled in an ice-bath. Hydrochloric acid (1 M) was added to ca. pH 2 and the acidic solution was then extracted four times with dichloromethane. After the combined organic phases had been dried (Na_2SO_4), the solvent was evaporated. The solid residue (2.43 g) was crystallized from acetonitrile (+45 °C → −18 °C); three crops yielded 1.34 g (45%), m.p. 149–151 °C. $[\alpha]_D^{22}$ −153° (*c* 1.5, EtOH. ^1H NMR ($CDCl_3$) of the major form, probably the *trans* keto form: δ 4.88 (m, 1 H), 3.57 (q, 1 H, *J* 6.6 Hz), 2.76 (δ_A) and 2.45 (δ_B) (2 H, AB part of ABX spectrum, J_{AB} 19.1, J_{AX} 2.9, J_{BX} 11.5 Hz), 1.52 (d, 3 H, *J* 6.0 Hz), 1.37 (d, 3 H, *J* 6.6 Hz). Evidence for the *cis* keto form (ca. 5%): δ 4.73 (m) or 4.51 (m), 3.33 (q, *J* ca. 7 Hz). Evidence for the enol form (ca. 5%): δ 4.73 (m) or 4.51 (m), 1.82 (dd, J_1+J_2 ca. 3 Hz). ^1H NMR (D_2O) (K = keto; E = enol): δ 5.06 (m, 0.2 H,K), 4.59 (m, 0.8 H,E), 3.0–2.4 (m, 2 H,K+E), 1.70 (s, 2.4 H,E), 1.46 (d, 0.6 H,K), 1.38 (d, 2.4 H,E), 1.24 (s, 0.6 H,K). ^{13}C NMR (CD_3OD): δ 172.5, 168.0, 98.9, 72.9, 35.7, 20.8, 8.6 (>95% enol form). IR (KBr): 3400–2100 (broad), 1725, 1600 cm^{-1} (broad). IR ($CHCl_3$): 1768, 1730 cm^{-1}.

(6R)-4-Acetoxy-5,6-dihydro-3,6-dimethylpyran-2-one [(*R*)-**4**]. Acetyl chloride (1.04 g, 13 mmol) was added to a solution of (*R*)-**3** (1.44 g, 10 mmol) and *N*-ethyldiisopropylamine (1.97 g, 15 mmol) in dichloromethane (50 ml). After 5 min, the solution was washed twice with dilute hydrochloric acid (pH 1–2), the aqueous phases were combined and extracted with dichloromethane, and all organic

phases were combined and dried (Na_2SO_4). Evaporation of the solvent gave a residue (1.96 g). Crystallization from diethyl ether yielded (*R*)-**4** (1.72 g, 92 %), m.p. 41–43 °C. $[\alpha]_D^{22}$ − 133° (*c* 1.2, chloroform); ^{1}H NMR ($CDCl_3$): δ 4.60 (m, 1 H), 2.66 (δ_A) and 2.46 (δ_B) (2 H, AB part of $ABXY_3$ spectrum, J_{AB} 17.4, J_{AX} 11.5, J_{BX} 4.0, J_{AY} 2.3, J_{BY} 1.2 Hz), 2.25 (s, 3 H), 1.80 (dd, 3 H, *J* 2.4, 1.1 Hz), 1.44 (d, 3 H, *J* 6.4 Hz). ^{13}C NMR ($CDCl_3$): δ 167.2, 166.7, 157.9, 115.6, 72.3, 34.2, 20.7, 20.4, 9.9.

(2S,5R)-2-Methyl-5-hexanolide [(2*S*, 5*R*)-**5**]. Enol acetate (*R*)-**4** (200 mg, 1.09 mmol) was hydrogenated (1 atm, 21 h) in diethyl ether (30 ml) using platinum(IV) oxide (30 mg). The catalyst was filtered off, the solution was rapidly washed with a small volume of saturated aq. $NaHCO_3$ and then brine, dried (Na_2SO_4) and finally analysed by GLC (SE-52, 150 °C); *trans* isomer (**6**), 6.76 min (ca. 15 %); *cis* isomer (**5**), 7.35 min (ca. 85 %). GLC–MS[1] clearly showed the two products to be stereoisomers. The yield of **5** + **6** as found by use of δ-valerolactone as an internal standard was 85 %. Preparative GLC: 8.2 mg of (2*S*, 5*R*)–**5** was collected (GLC purity, >99.95 %). $[\alpha]_D^{21}$ +96° (*c* 0.4, chloroform); lit.,[2] $[\alpha]_D$ +93.5° (*c* 0.8, chloroform) (−91° for the enantiomer). NMR spectra (^{1}H and ^{13}C) were indistinguishable from those of Mori and Senda.[2]

tert-*Butyl 2-methyl-3-oxopentanoate*[25] was needed as a reference in the interpretation of the ^{13}C NMR spectra of crude **2**; ^{13}C NMR ($CDCl_3$): δ 206.9, 169.9, 81.6, 53.6, 34.6, 27.9,12.8, 7.8.

4-Methyl-2-oxetanone (**7**) was prepared as described;[26] ^{13}C NMR ($CDCl_3$): δ 168.3, 68.1, 44.4, 20.6.

Synthesis of **2** *and* **3** *from* **7**. *tert*-Butyl propionate (6.05 g, 46.5 mmol) was transformed into the lithium ester enolate in THF (60 ml) using diisopropylamine (53 ml) and butyllithium (46.5 mmol) in hexane (ca. 25 ml). A solution of **7** (2.50 g, 29 mmol) in THF (11 ml) was placed in a dropping funnel. The temperatures of the enolate solution and the lactone solution were lowered to −105 and −95 °C, respectively, and the lactone solution was then rapidly added (<5 s) to the well stirred enolate solution under a pressure of nitrogen. Heat was evolved on mixing, and after 10 min of stirring the temperature was −76 °C. A solution of acetic acid (6 ml) in ethanol (30 ml) was then rapidly added and the cooling bath removed. When the mixture had attained 20 °C, it was poured into water (75 ml) and diethyl ether (150 ml). After being shaken together, the phases were separated. The aqueous phase was extracted with ether and the organic phases were combined, dried with NaCl (s), and concentrated. Addition of dichloromethane, drying (Na_2SO_4), evaporation of the solvent and concentration under low pressure (ca. 100 Pa) gave a liquid residue (5.95 g). Separation on a column (4 × 14 cm) of Kieselgel 60 (70–230 mesh) using chloroform as the eluant afforded **2** (4.78 g, 75 %). The purity, as estimated by ^{13}C NMR spectroscopy, was 90–95 %. ^{13}C NMR of **2** ($CDCl_3$): δ 207.1 (C-3), 169.5 (C-1), 82.0 [$C(CH_3)_3$], 63.9 and 63.8 (C-5), 54.3 (C-2), 49.7 and 49.5 (C-4), 27.9 [$C(CH_3)_3$], 22.5 and 22.4 (C-6), 12.5 and 12.4 [C(2)CH_3] (tentative assignments). The diastereomer ratio was ca. 48:52. Hydrolysis, work-up and crystallization as described above gave 0.63 g of (±)-**3** (44 % based on **7**).

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