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SYNTHESIS OF THE INSECT PHEROMONE (+)-ELDANOLIDE BY ENANTIOSELECTIVE HOMOALDOL REACTION

Holger Paulsen and Dieter Hoppe*

Institut für Organische Chemie der Universität Kiel
Olshausenstr. 40-60, W-2300 Kiel 1, Germany

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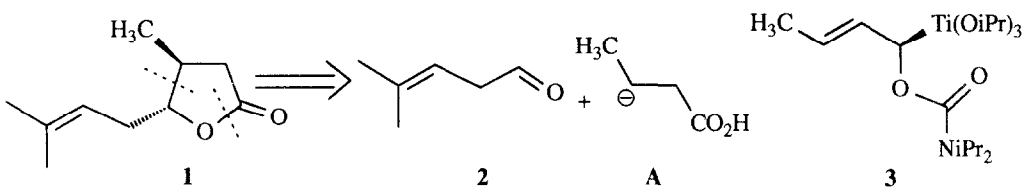
Summary: (+)-Eldanolide [(3*S*,4*R*)-3,7-dimethyl-6-octen-4-olide] was synthesized with 92 % *ee* from (*E*)-2-butenyl *N*,*N*-diisopropylcarbamate via homoaldol reaction. The chirality-inducing step consists in the (-)-sparteine-assisted enantioselective deprotonation. A new protocol for the oxidative deprotection of vinyl carbamates was developed.

(+)-Eldanolide[1] (**1**), one of the pheromones of the male African sugar-cane borer, *Eldana saccharina* (Wlk.), has been synthesized by various methods[1]. Several multistep syntheses start from optical active natural products like L-glutamic acid[1a], D-ribose[1b], (-)-β-pinene[1c], (+)-pulegone[1d] or (*S*)-lactic acid[1e]. In most of these synthetic sequences, intermediates endangered by racemization occur. The most straightforward homoaldol approach which consists in the assembly of the β-enolate of butyric acid **A** and 4-methyl-3-pentenal (**2**) (Scheme 1) has been realized only for the racemate[2].

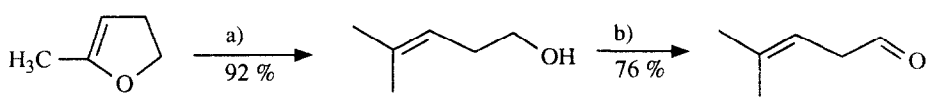
Scheme 1



1 **2** **A** **3**

We recently reported a general synthesis of non-racemic β-methyl-γ-lactones which is based on the enantiomerically enriched (1-titanio-2-butenyl) *N*,*N*-diisopropylcarbamate **3** as a chiral homoenolate reagent[3]. First, a reliable method was developed for the preparation of the volatile, sensitive aldehyde **2**[4]. Vinylic methylation of 4,5-dihydro-2-methylfuran (**4**) according to Kocieński[5] afforded the homoallylic alcohol **5**, which was converted to 4-methyl-3-pentenal (**2**) by Dess-Martin oxidation[6].

Scheme 2

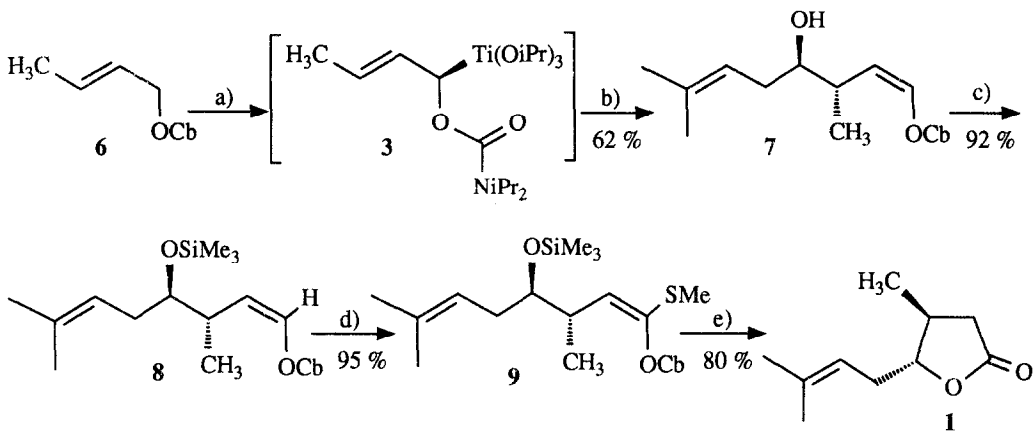


4 **5** **2**

a) [dppe]$NiCl_2$, MeMgBr, benzene, reflux, 30 min[5] b) Dess-Martin periodinane, CH_2Cl_2, r.t.[6]

The (-)-sparteine-induced lithiation[3] of the (*E*)-crotyl carbamate **6**, followed by treatment with excess titanium tetraisopropoxide[7] (TIPT) and addition of **2** yielded the homoaldol product **7** with > 98 % *ds* and 92 % *ee* (Scheme 3). The usual method for oxidative lactonization[3b,8] is not applicable to vinyl carbamate **7** due to the additional trisubstituted double bond. Therefore we developed an indirect oxidation method by vinylic deprotonation[9] and methylsulfenylation of the silyl ether **8** to yield the ketene monothioacetal **9**. On treatment with methanesulfonic acid and methanol, **9** is readily desilylated, solvolyzed and lactonized to afford (+)-eldanolide **1**. The conversion of **7** to **1** can also be performed in a one-flask procedure without isolation of the intermediates in 75 % overall yield. The enantiomeric purity of (+)-**1** was found to be 92 % *ee* by GC analysis on a chiral column.

Scheme 3



a) i. *n*-BuLi/(-)-sparteine/cyclohexane, crystallization; ii. $Ti(OiPr)_4$; b) aldehyde **2**; aq. HCl;
c) Me_3SiCl/NEt_3 in CH_2Cl_2; d) i. *n*-BuLi/TMEDA ii. MeSSMe e) $MeSO_3H$ in MeOH

Altogether, the method, demonstrated for (+)-eldanolide, offers a general and efficient protocol for the enantioselective synthesis of β-methyl-γ-lactones bearing unsaturated substituents.

Experimental. All organometallic reactions were performed under Ar at -78°C with exclusion of air and moisture. Pentane and tetrahydrofuran (THF) were distilled over $LiAlH_4$, dichloromethane and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) were dried over CaH_2. Tetra(isopropoxy)titanium (TIPT) was distilled at 0.3 mbar with exclusion of moisture. LC separations were carried out at 1-2 bar on silica gel 32-63 (ICN, Biomedicals GmbH, Eschwege), or without pressure on silica gel (0.06 - 0.2 mm), respectively. Enantiomeric excesses of the homoaldol product **7** were determined by 90-MHz-^{1}H-NMR-spectroscopy with tris[(heptafluoropropylhydroxymethylen)-d-camphorato]europium(III), [Eu(hfc)$_3$, that of (+)-eldanolide by GC analysis on CP-cyclodextrin-2,3,6-M-19 (Chrompack 50•0.25 fused silica). All new compounds gave satisfactory elemental analysis (C,H ± 0.3 %).

4-Methyl-3-penten-1-ol (**5**) was prepared from 4,5-dihydro-2-methylfuran according to Kocieński[5], but isolated as the free alcohol by chromatography of the benzene solution on silica gel with ether/pentane (1:2), yield 92 % (contaminated by 2 % of the 4-alkenol).

4-Methyl-3-pentenal (**2**) was prepared from **5** by oxidation with 1.3 equiv. of Dess-Martin periodinane[6] at room temperature for 30 min in dichloromethane. The reaction was quenched by addition of 5 equiv. $Na_2S_2O_3$, dissolved in aq. sat. $NaHCO_3$, and stirring it for 15 min. The aq. phase was extracted with dichloromethane and the combined org. solns. washed with aq. sat. $NaHCO_3$ and this aq. phase again

extracted with dichloromethane. The combined org. solns. were dried over $MgSO_4$. After careful evaporation of the major part of the solvent in vacuum the yield was determined ^{1}H-NMR-spectroscopically to give 76 % of **2** as a 33 % soln. in dichloromethane.

(1*Z*,3*S*,4*R*)-(+)-3,7-*Dimethyl*-4-*hydroxy*-1,6-*octadienyl N,N-diisopropylcarbamate* (**7**): The (-)-sparteine-assisted deprotonation of (*E*)-2-butenyl *N,N*-diisopropyl carbamate (**6**) was performed on a 2 mmol scale according to ref. 3. Aldehyde **2** (2.1 mmol) was added to titanium reagent **3** as a 33 % solution in dichloromethane. Aqueous workup and purification by flash chromatography afforded 371 mg (62 %) of **7**: $[\alpha]_D^{22}$= +44.6 (for 92 % *ee*, *c* = 1.1, MeOH); R_F = 0.33 (E/P 1:1); IR(film): 3460 (OH), 1700, 1690 (C=O); 200-MHz-^{1}H-NMR ($CDCl_3$): δ = 1.06 (d, $J_{3\text{-}CH3,3}$= 6.9 Hz; 3-CH_3); 1.2-1.39 {br., N[CH(CH_3)$_2$]$_2$}; 1.63 (br., 8-H); 1.65 (br., OH); 1.72 (dt, $J_{7\text{-}CH3,5}$= 1.3 Hz, $J_{7\text{-}CH3,6}$= 1.3 Hz, 7-CH_3); 2.19 (m, 5-H); 2.80 (dddq, $J_{3,2}$= 9.9 Hz, $J_{3,4}$= 5.3 Hz, $J_{3,1}$= 0.9 Hz, $J_{3,3CH3}$= 6.9 Hz, 3-H); 3.48 [q (br.), $J_{4,3}$= $J_{4,5}$= 5.9 Hz, 4-H]; 3.80, 4.11 {br., N[C*H*(CH_3)$_2$]$_2$}; 4.73 (dd, $J_{2,1}$= 6.5 Hz, $J_{2,3}$= 9.9 Hz, 2-H); 5.20 (tqq, $J_{6,5}$= 7.3 Hz, $J_{6,7\text{-}CH3}$= $J_{6,8}$= 1.5 Hz, 6-H); 7.12 (dd, $J_{1,2}$= 6.5 Hz, $J_{1,3}$= 1.0 Hz, 1-H); 50-MHz-^{13}C-NMR ($CDCl_3$): δ = 17.49 (3-CH_3); 17.98 (7-CH_3), 20.60, 21.39 {N[CH(*C*H$_3$)$_2$]$_2$}; 25.91 (C-8); 33.50 (C-5); 35.66 (C-3); 46.19 {N[*C*H(CH$_3$)$_2$]$_2$}; 74.98 (C-4); 112.20 (C-2); 120.37 (C-6); 134.59 (C-7), 136.02 (C-1); 152.96 [OC(O)N].

(1*E*,3*S*,4*R*)-(+)-3,7-*Dimethyl*-1-*methylthio*-4-*trimethylsilyloxy*-1,6-*octadienyl N,N-diisopropylcarbamate* (**9**): **7** (288 mg, 0.97 mmol), trimethylsilyl chloride (158 mg, 1.46 mmol), and triethylamine (177 mg, 1.75 mmol) in dry dichloromethane (3 mL) were stirred at 0°C for 2 h. Aqueous workup with ether (20 mL), aq. sat. NH_4Cl (5 mL), aq. sat. $NaHCO_3$ (5 mL), drying with $MgSO_4$, dilution with toluene (20 mL) and evaporation of the solvent in vacuum afforded the crude silylether **8** (330 mg, 0.89 mmol).
To the solution of crude **8** (0.89 mmol) and TMEDA (137 mg, 1.18 mmol) in dry THF (4 mL), 1.6N *n*-BuLi in hexane (0.87 mL, 1.39 mmol) were slowly introduced below -70°C, followed by dimethyl disulfide (140 mg, 1.49 mmol) after 3 h stirring. Aqueous workup was performed after stirring for 3 h at -78°C and 30 min at 20°C. LC on silica gel with ether/pentane (1:10) afforded 352 mg (95 %) of **9**: $[\alpha]_D^{22}$= +9.2 (for 92 % *ee*, *c* = 1.0, CH_2Cl_2); R_F = 0.66 (E/P = 1:1); IR (film): 1710, 1720 (C=O); 200-MHz-^{1}H-NMR ($CDCl_3$): δ = 0.08 [s, OSi(CH_3)$_3$]; 0.97 (d, $J_{3\text{-}CH3,3}$= 6.9 Hz, 3-CH_3); 1.24, 1.28 {br., N[CH(C*H*$_3$)$_2$]$_2$}; 1.59 (br. 8-H); 1.67 (dt, $J_{7\text{-}CH3,6}$= 1.2 Hz, $J_{7\text{-}CH3,5}$= 1.2 Hz, 7-CH_3); 2.09 (m, 5-H); 2.28 (s, 1-SCH_3); 2.49 (ddq, $J_{3,2}$= 10.0 Hz, $J_{3,4}$= 3.4 Hz, $J_{3,3\text{-}CH3}$= 6.9 Hz, 3-H); 3.51 (dt, $J_{4,5}$= 6.5 Hz, $J_{4,3}$= 3.4 Hz, 4-H); 3.94 {br., N[C*H*(CH_3)$_2$]$_2$}; 5.09 (tqq, $J_{6,5}$= 7.4 Hz, $J_{6,7\text{-}CH3}$= $J_{6,8}$= 1.4 Hz, 6-H); 5.51 (d, $J_{2,3}$= 9.9 Hz, 2-H); 50-MHz-^{13}C-NMR ($CDCl_3$): δ = 0.00 [OSi(CH_3)$_3$]; 16.44 (1-SCH_3, 3-CH_3); 17.44 (7-CH_3); 20.11, 20.94 {N[CH(*C*H$_3$)$_2$]$_2$}; 25.35 (C-8); 33.79 (C-5); 36.65 (C-3); 46.00 {N[*C*H(CH$_3$)$_2$]$_2$}; 75.50 (C-4); 120.91 (C-6); 124.86 (C-2); 132.34 (C-7); 142.68 (C-1); 151.91 [OC(O)N].

(3*S*,4*R*)-(+)-3,7-*Dimethyl*-6-*octen*-4-*olide*; (+)-*Eldanolide* (**1**): (+)-**9** (257 mg, 0.62 mmol) and methanesulfonic acid (86 mg, 0.89 mmol) in methanol/water (2 mL + 11 mg) were stirred at 40°C for 21 h. The mixture was diluted with ether (5 mL), poured on 5 mL 2N aq. HCl, and the aqueous soln. three times extracted with ether (5-10 mL each). The combined etheral solns. were washed with aq. sat. $NaHCO_3$ (5 mL) dried with $MgSO_4$ and the solvent evaporated in vacuum. Purification by flash chromatography on silica gel yielded 83 mg (80 %) of **1**: R_F = 0.38 (E/P 1:1); $[\alpha]_D^{22}$= +50.9 (for 92 % *ee*, *c* = 1.1; MeOH); 300-MHz-^{1}H-NMR ($CDCl_3$): δ = 1.14 (d, $J_{3\text{-}CH3,3}$= 6.6 Hz, 3-CH_3); 1.64 (dt, $J_{8,6}$= 1.4 Hz, $J_{8,5}$= 1.2 Hz, 8-H); 1.73 (dt, $J_{7\text{-}CH3,6}$= 1.4 Hz, $J_{7\text{-}CH3,5}$= 1.2 Hz, 7-CH_3); 2.18 (dd, $J_{2A,2B}$= 16.5 Hz, $J_{2A,3}$= 9.1 Hz, 2-H_A); 2.28 (dddq, $J_{3,2A}$= 9.1 Hz, $J_{3,2B}$= 7.3 Hz, $J_{3,3\text{-}CH3}$= 6.6 Hz, 3-H); 2.36 (dddqq, $J_{5A,5B}$= 14.9 Hz, $J_{5,6}$= 7.3 Hz, $J_{5,4}$= 7.3 Hz, ($J_{5,8}$, $J_{5,7\text{-}CH3}$) = (1.0 Hz, 1.1 Hz), 5-H_A); 2.42 (dddqq, $J_{5A,5B}$= 14.9 Hz, $J_{5,6}$= 7.3 Hz, $J_{5,4}$= 5.4 Hz, ($J_{5,8}$, $J_{5,7\text{-}CH3}$) = (1.0 Hz, 1.1 Hz), 5-H_B); 2.67 (dd, $J_{2B,2A}$= 16.4 Hz, $J_{2B,3}$= 7.4 Hz, 2-H_B); 4.06 (ddd, $J_{4,5}$= 7.3 Hz, $J_{4,5}$= 5.3 Hz, $J_{4,3}$= 6.3 Hz, 4-H); 5.17 (tqq, $J_{6,5}$= 7.3 Hz, $J_{6,7\text{-}CH3}$= $J_{6,8}$= 1.4 Hz, 6-H); 75-MHz-^{13}C-NMR ($CDCl_3$): δ = 17.75 (3-CH_3); 17.93 (7-CH_3); 25.76 (C-8); 32.25 (C-2); 35.12 (C-3); 37.07 (C-5); 87.04 (C-4); 117.97 (C-6); 135.31 (C-7); 176.24 (C-1).

In a synthesis starting with 694 mg (2.3 mmol) of **7**, performed without purification of the intermediates, 294 mg (75 %) of **1** were obtained.

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