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### A SHORT AND HIGHLY ENANTIOSELECTIVE SYNTHESIS OF (6R)-UNDECYLTETRAHYDROPYRAN-2-ONE, THE PHEROMONE OF VESPA ORIENTALIS

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**A SHORT AND HIGHLY ENANTIOSELECTIVE SYNTHESIS  
OF (6*R*)-UNDECYLTETRAHYDROPYRAN-2-ONE,  
THE PHEROMONE OF *VESPA ORIENTALIS***

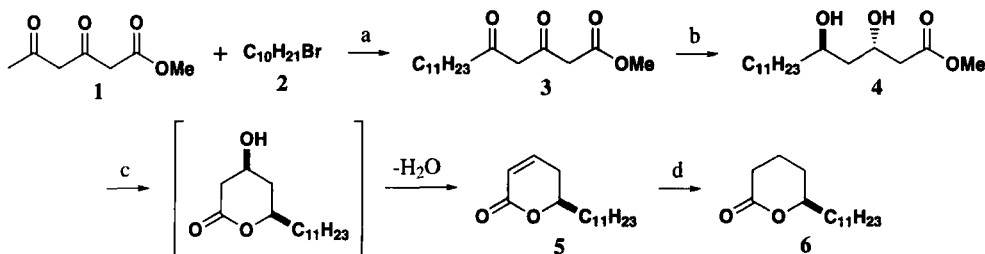
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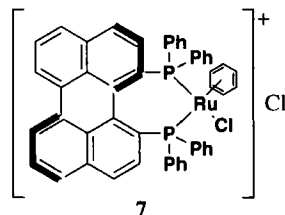
It has been recently shown that simple 3,5-dioxoalkanoates can be hydrogenated using various chiral phosphine-ruthenium complexes<sup>1</sup> as catalysts to afford *anti*-3,5-dihydroxyalkanoates in excellent yield and enantioselectivity.<sup>2</sup> Moreover, these compounds could be readily transformed into corresponding  $\delta$ -lactones.<sup>3</sup> This communication describes a general route to homochiral 6-substituted



a) *i.* NaH, THF, 0°C, 0.5h; *ii.* *sec*-BuLi, reflux, 2h; b) **7** (cat), H<sub>2</sub>, MeOH, 55°C, 150 atm, 48h;  
c) *p*-TsOH (cat), toluene, reflux, 3h; d) 10% Pd/C (cat), H<sub>2</sub>, AcOEt, rt, 1 atm, 3h.

derivatives of tetrahydropyran-2-one, based on above-mentioned findings, as exemplified by the synthesis of (6*R*)-undecyltetrahydropyran-2-one (6), the pheromone of *Vespa Orientalis*,<sup>4</sup> produced by the queen of the oriental hornet for the workers to stimulate the construction of queen cells.

Compound 1, readily available by a simple procedure,<sup>5</sup> was efficiently alkylated<sup>6</sup> with reagent 2 to afford the expected product 3 which, after chromatographic purification, was subjected to asymmetric hydrogenation in the presence of the catalyst 7 to give the *anti*-diol 4 (95% ee) in 73% yield. Heating 4 at reflux in toluene in the presence of catalytic amounts of *p*-toluenesulfonic acid, afforded unsaturated lactone 5 in 50% yield; finally catalytic hydrogenation in the presence of 10% palladium-on-charcoal furnished the pheromone (6*R*)-6 of very high enantiomeric purity (> 95% ee) in nearly quantitative yield.



We believe that the present approach to the preparation of 6-substitued derivatives of tetrahydropyran-2-one constitutes a general one and may be used in total syntheses of other natural products.

## EXPERIMENTAL SECTION

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Rotations were recorded using a Perkin-Elmer 241 polarimeter. IR spectra were obtained with a Magna 550 Nicolet spectrometer in KBr pellets. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded using a Varian Unity plus (200 MHz and 50 MHz respectively) spectrometer. Ee values were assigned from Eu(hfc)<sub>3</sub>-shifted <sup>1</sup>H NMR spectra. Mass spectra were recorded on an AMD-604 Intectra instrument using the electron impact (EI) technique. Silica gel (Merck Kieselgel 230-400 mesh) was used for column chromatography. THF and methanol for asymmetric hydrogenation were dried and stored under an argon atmosphere. Methyl 3,5-dioxohexanoate (1) was prepared by methanolysis of dehydroacetic acid as described by Batelaan.<sup>5</sup>

**Methyl 3,5-Dioxohexadecanoate (3).**— Methyl ester 1 (0.37 g, 2.34 mmol) was added slowly to a vigorously stirred a 50% suspension of NaH in oil (0.073 g, 3.04 mmol) in THF (3 mL) at 0°. After evolution of H<sub>2</sub> had ceased, 3.6 mL of *sec*-butyllithium solution in hexane (1.3 M, 4.68 mmol) were added at 0°. The red suspension was allowed to stand with stirring at 0° for 10 min. This solution was treated with bromide 2 (0.515 g, 2.34 mmol) dissolved in THF (10 mL) for 30 min at 25°, and the solution was heated at reflux for 2h. Workup included column chromatography on silica gel (hexane:ethyl acetate, 19:1) afforded 0.432g (62% yield) of the ester 3 as an oil. *R*<sub>f</sub> = 0.48 (hexane:ethyl acetate 4:1). <sup>1</sup>H NMR: δ 0.87 (t, 3H, CH<sub>3</sub>, *J*=6.0 Hz); 1.25 (bs, 18H, (CH<sub>2</sub>)<sub>9</sub>); 1.56-1.60 (m, 2H, 6-H); 2.16-2.33 (m, 2H); 3.35 (s, 2H); 3.47-3.58 (m, 2H); 3.73 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR: δ 12.49 (CH<sub>3</sub>); 21.06 (CH<sub>2</sub>); 21.75 (CH<sub>2</sub>); 24.09 (CH<sub>2</sub>); 27.58 (CH<sub>2</sub>); 27.70 (CH<sub>2</sub>); 27.84 (CH<sub>2</sub>); 27.98 (CH<sub>2</sub>); 30.29 (CH<sub>2</sub>); 36.21 (CH<sub>2</sub>); 43.40 (CH<sub>2</sub>); 50.81 (CH<sub>2</sub>); 54.90 (CH<sub>3</sub>-O); 98.15 (CH from enol form); 166.42 (C=O, CO<sub>2</sub>CH<sub>3</sub>); 185.57 (C=O); 191.77 (C=O). EI-MS: *m/z*, 298 (11%); 225 (25%); 183 (24%); 171(15%); 159 (12%); 158 (100%); 143 (40%); 139(18%); 126 (65%); 116 (35%); 101

(53%); 97 (14%); 84 (21%); 69 (25%); 57 (28%); 43 (34%).

*Anal.* Calcd for  $C_{17}H_{30}O_4$ : C, 68.42; H, 10.13. Found C, 68.38; H, 10.15

**General Procedure of the Asymmetric Hydrogenation of Methyl 3,5-Dioxohexadecanoate (3).**

To a glass vessel containing a solution of 3,5-dioxoester **3** (0.071 g, 0.24 mmol) in dried methanol (5 mL) was added the complex (*R*)-**7** (0.5 mol%). The vessel was placed in a 100-mL stainless steel autoclave. Hydrogen was introduced (150 atm) and the reaction mixture was stirred at 55° for 48h. After hydrogen pressure was released, the solvent was evaporated and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 14:1) to afford 3,5-dihydroxyester **4** (0.053 g, 73%) as a white solid, mp. 56-58°.

$[\alpha]_D^{22} = +5$  ( $c = 0.6$ ,  $CHCl_3$ ).  $R_f = 0.52$  (hexane:ethyl acetate 1:1). IR (KBr): 3530 (OH); 2950 (CH), 1740  $cm^{-1}$  (C=O).  $^1H$  NMR:  $\delta$  0.87 (t, 3H,  $CH_3$ ,  $J = 6.0$  Hz); 1.26-1.67 (m, 22H); 2.33-2.35 (d, 1H,  $J = 3.6$  Hz); 2.50-2.55 (m, 2H); 3.39 (d, 1H,  $J = 4.0$  Hz); 3.72 (s, 3H,  $CO_2CH_3$ ); 3.91 (m, 1H); 4.33-4.37 (m, 1H).  $^{13}C$  NMR:  $\delta$  14.73 ( $CH_3$ ); 23.30 ( $CH_2$ ); 26.32 ( $CH_2$ ); 29.81 ( $CH_2$ ); 29.94 ( $CH_2$ ); 30.07 ( $CH_2$ ); 30.21 ( $CH_2$ ); 32.52 ( $CH_2$ ); 38.44 ( $CH_2$ ); 40.78 ( $CH_2$ ); 45.64 ( $CH_3-O$ ); 53.07 (CHOH); 68.50 (CHOH); 100.40; 162.53 (C=O,  $CO_2CH_3$ ). LSIMS:  $m/z$ , (M+Na) 325 (33%); (M+H) 303 (90%); 285 (73%); 267 (25%); 235 (16%); 211 (40%); 193 (19%); 107 (37%); 95 (53%).

*Anal.* Calcd for  $C_{17}H_{30}O_4$ : C, 67.34; H, 11.24. Found: C, 67.42; H, 11.06

**(R)-Undecyl-5,6-dihydropyran-2-one (5).** 3,5-Dihydroxyester **4** (0.04 g, 0.128 mmol) was refluxed with a catalytic amount of *p*-TsOH in toluene (5 mL) for 3h. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (hexane:ethyl acetate, 19:1) to give (*R*)-**5** (0.016 g, 50%, 95% ee) as a white solid, mp. 36-38°C, *lit.*<sup>7</sup> mp. 34°.

$[\alpha]_D^{24} = -23$  ( $c = 0.8$ ,  $CHCl_3$ ).  $R_f = 0.54$  (hexane:ethyl acetate 2:1). IR (KBr): 2920 (CH); 1696  $cm^{-1}$  (C=O).  $^1H$  NMR:  $\delta$  0.91 (t, 3H,  $CH_3$ ,  $J = 6.0$  Hz); 1.29-1.52 (m, 20H,  $(CH_2)_{10}$ ); 2.33-2.39 (m, 2H); 4.38-4.52 (m, 1H); 6.02-6.08 (dt, 1H,  $J = 2.0$  Hz); 6.86-6.95 (m, 1H).  $^{13}C$  NMR:  $\delta$  14.14 ( $CH_3$ ); 22.71 ( $CH_2$ ); 24.83 ( $CH_2$ ); 29.35 ( $CH_2$ ); 29.39 ( $CH_2$ ); 29.48 ( $CH_2$ ); 29.55 ( $CH_2$ ); 29.63 ( $CH_2$ ); 31.92 ( $CH_2$ ); 34.89 ( $CH_2$ ); 78.01 (CH-O); 121.43 (CH=CH); 144.95 (C=O). EI-MS  $m/z$ , 252 (8%); 192 (13%); 97 (100%); 95 (12%); 81 (15%); 68 (53%); 55 (19%); 41 (31%).

*Anal.* Calcd for  $C_{16}H_{28}O_2$ : C, 76.21; H, 10.98. Found: C, 76.14; H, 11.00

**(R)-Undecyltetrahydropyran-2-one (6).** To a solution of (*R*)-**5** (0.021 g, 0.09 mmol) in dry ethyl acetate was added 10% Pd/C (0.002 g). The suspension was stirred at room temperature under hydrogen atmosphere for 3h, then the catalyst was filtered off and the solution was concentrated *in vacuo* to afford compound **6**. Recrystallization from methanol (0.4 mL MeOH, 0.022 g of **6**) gave white solid (0.020 g, 95%, 96% ee), mp. 36-37°, *lit.*<sup>4</sup> mp. 38°.

$[\alpha]_D^{24} = +35.3$  ( $c = 0.4$ , THF), *lit.*<sup>4</sup>  $[\alpha]_D^{24} = +39$  ( $c = 1.76$ , THF). IR (KBr): 2920 (CH), 1696  $cm^{-1}$  (C=O).  $^1H$  NMR:  $\delta$  0.87 (t, 3H,  $CH_3$ ,  $J = 6.2$  Hz); 1.25 (bs, 20H,  $(CH_2)_{10}$ ); 1.49-1.57 (m, 2H); 1.85-1.91 (m, 2H); 2.47-2.54 (m, 2H); 4.24-4.30 (m, 1H).  $^{13}C$  NMR:  $\delta$  14.15 ( $CH_3$ ); 18.54 ( $CH_2$ ); 22.71 ( $CH_2$ ); 24.95 ( $CH_2$ ); 27.82 ( $CH_2$ ); 29.35 ( $CH_2$ ); 29.44 ( $CH_2$ ); 29.50 ( $CH_2$ ); 29.57 ( $CH_2$ ); 29.65 ( $CH_2$ ); 31.93 ( $CH_2$ ); 35.86 ( $CH_2$ ); 80.61 (CH-O); 112.22. EI-MS  $m/z$ , 254 (4%); 236 (11%); 192 (11%); 114

(175); 111 (9%); 99 (100%); 83 (19%); 71 (27%); 55 (31%); 43 (35%).

HRMS: Calcd for  $C_{16}H_{30}O_2$ ,  $m/z$ , 254.22458. Found: 254.22857

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## AN IMPROVED PREPARATION OF 3-(5-BENZOFURANYL)-L-ALANINE

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3-(5-Benzofuranyl)-L-alanine (**3a**) has recently emerged as a highly promising non-canonical amino acid in the development of strategies for the site-specific *in vivo* incorporation of photoreactive amino acids.<sup>1</sup> The synthesis of **3a** in five steps and ~10% overall yield has involved the non-