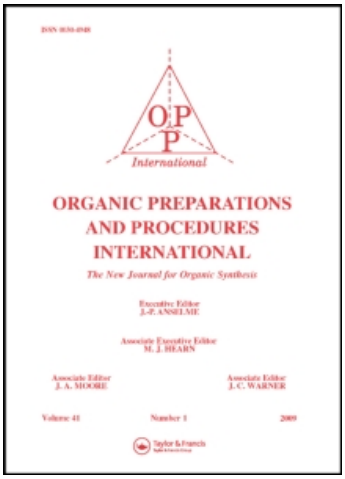


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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

Grzegorz Juszkiewicz[a]; Janusz Jurczak[ab]
[a] Department of Chemistry, Warsaw University, Warsaw, Poland [b] Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

To cite this Article Juszkiewicz, Grzegorz and Jurczak, Janusz(2002) 'A SHORT AND HIGHLY ENANTIOSELECTIVE SYNTHESIS OF (6*R*)-UNDECYLTETRAHYDROPYRAN-2-ONE, THE PHEROMONE OF *VESPA ORIENTALIS*', Organic Preparations and Procedures International, 34: 2, 187 — 190
To link to this Article: DOI: 10.1080/00304940209355756
URL: http://dx.doi.org/10.1080/00304940209355756

10. J. S. Ma, Q.-Q. Chen, C.-Q. Wang, Y.-Y. Liu, F. Yan, L.-J. Cheng, S. Jin and H. Falk, *Monatsh. Chem.* **126,** 201 (1995).

11. J. S. Ma, C. Q. Wang, F. Yan, Y. Y. Liu and J. H. Chen, *Chinese Chem. Lett.*, **1,** 39 (1990); *Chem. Abst.* **114**: 42351t (1991).

12. A. F. McDonagh, in *The Porphyrins*, D. Dolphin, Ed. Vol.VI. pp. 319-360, Academic Press, New York (1979).

13. F. R. Trull, W. Franklin and D. A. Lightner, *J. Heterocyclic Chem.*, **24**, 1573 (1987).

****

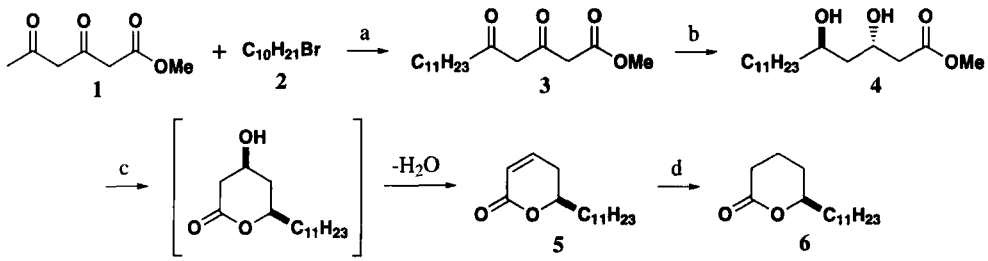
A SHORT AND HIGHLY ENANTIOSELECTIVE SYNTHESIS OF (6*R*)-UNDECYLTETRAHYDROPYRAN-2-ONE, THE PHEROMONE OF *VESPA ORIENTALIS*

Submitted by (03/08/01)

Grzegorz Juszkiewicz[†] and Janusz Jurczak*[†,††]

[†] *Department of Chemistry, Warsaw University*
Pasteura 1, 02-093 Warsaw, POLAND
[††] *Institute of Organic Chemistry, Polish Academy of Sciences*
Kasprzaka 44/52, 01-224 Warsaw, POLAND

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

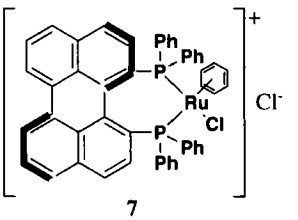


1 2 3 4 5 6

a) *i.* NaH, THF, 0°C, 0,5h; *ii. sec*-BuLi, reflux, 2h; b) **7** (cat), H_2, MeOH, 55°C, 150 atm, 48h; c) *p*-TsOH (cat), toluene, reflux, 3h; d) 10% Pd/C (cat), H_2, 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*,[4] 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,[5] was efficiently alkylated[6] 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.



7

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. ^{1}H and ^{13}C NMR spectra were recorded using a Varian Unity *plus* (200 MHz and 50 MHz respectively) spectrometer. Ee values were assigned from Eu(hfc)$_3$-shifted ^{1}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.[5]

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_2 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_f = 0.48 (hexane:ethyl acetate 4:1). ^{1}H NMR: δ 0.87 (t, 3H, CH_3, J=6.0 Hz); 1.25 (bs, 18H, $(CH_2)_9$); 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_2CH_3). ^{13}C NMR: δ 12.49 (CH_3); 21.06 (CH_2); 21.75 (CH_2); 24.09 (CH_2); 27.58 (CH_2); 27.70 (CH_2); 27.84 (CH_2); 27.98 (CH_2); 30.29 (CH_2); 36.21 (CH_2); 43.40 (CH_2); 50.81 (CH_2); 54.90 (CH_3-O); 98.15 (CH from enol form); 166.42 (C=O, CO_2CH_3); 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°.

$[\alpha]^{22}_D$= +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: δ 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: δ 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.*[7] mp. 34°.

$[\alpha]^{24}_D$= -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: δ 0.91 (t, 3H, CH_3 J = 6.0 Hz); 1.29-1.52 (m, 20H, $(CH2)_{10}$); 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: d 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.*[4] mp. 38°.

$[\alpha]^{24}_D$= + 35.3 (c = 0.4, THF), *lit.*[4] $[\alpha]^{24}_D$= + 39 (c = 1.76, THF). IR (KBr): 2920 (CH), 1696 cm^{-1} (C=O). ^1H NMR: δ 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: δ 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

Acknowledgment.- This work was supported by the State Committee for Scientific Research (Projects PBZ 6.05/T09/1999 and 3T09A 109 16).

REFERENCES

1. K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa and H. Takaya, *J. Org. Chem.*, **59**, 3064 (1994).

2. L. Shao, T. Seki, H. Kawano and M. Saburi, *Tetrahedron Lett.*, **32**, 7699 (1991).

3. L. Shao, H. Kawano, M. Saburi and Y. Uchida, *Tetrahedron*, **49**, 1997 (1993).

4. For previous enantioselective routes to (*R*)-undecylotetrahydropyran-2-one, see: J. L. Coke and A. B. Richon, *J. Org. Chem.*, **41,** 3516 (1976); S. Servi, *Tetrahedron Lett.*, **24**, 2023 (1983); K. Mori and T. Otsuka, *Tetrahedron*, **41**, 547 (1985); D. F. Taber, P. B. Deker, and M. D. Gaul, *J. Am. Chem. Soc.*, **109**, 7488 (1987); S. K. Kang, S. G. Kim, D. C. Park, J. S. Lee, W. J. Yoo, and C. S. Pak, *J. Chem. Soc. Perkin Trans. 1.*, 9 (**1993**); Ph. Coutrot, C. Grison, and C. Bomont, *Tetrahedron Lett.*, **35**, 8381 (1994); C. Paolucci, C. Mazzini, and A. Fava, *J. Org. Chem.*, **60**, 169 (1995).

5. J. G. Batelaan, *Synth. Commun.*, **6**, 81 (1976).

6. J. S. Hubbard and T. M. Harris, *J. Org. Chem.*, **46**, 2566 (1981).

7. S. Raina and V. K. Singh, *Tetrahedron Lett.* , **52**, 4479 (1996).

****

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

Submitted by Giorgio Ortar
(06/15/01)

Dipartimento di Studi Farmaceutici e Centro di Studio
per la Chimica del Farmaco del C.N.R.
Università 'La Sapienza', 00185 Roma, ITALY

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.[1] The synthesis of **3a** in five steps and ~10% overall yield has involved the non-