Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Dianions of Unsaturated Carboxylic Acids in Synthesis. Synthesis of Juvocimene I

R. Mestres [a] & E. Muñoz [a]
[a] Departament de Química Orgànica , Universitat de València , Dr. Moliner 50, 46100, Burjassot, València, Spain
Published online: 15 Aug 2006.

To cite this article: R. Mestres & E. Muñoz (1996) Dianions of Unsaturated Carboxylic Acids in Synthesis. Synthesis of Juvocimene I, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:7, 1309-1319, DOI: 10.1080/00397919608003490

To link to this article: http://dx.doi.org/10.1080/00397919608003490

SYNTHETIC COMMUNICATIONS, 26(7), 1309-1319 (1996)

DIANIONS OF UNSATURATED CARBOXYLIC ACIDS IN SYNTHESIS. SYNTHESIS OF JUVOCIMENE I

R.Mestres* and E.Muñoz

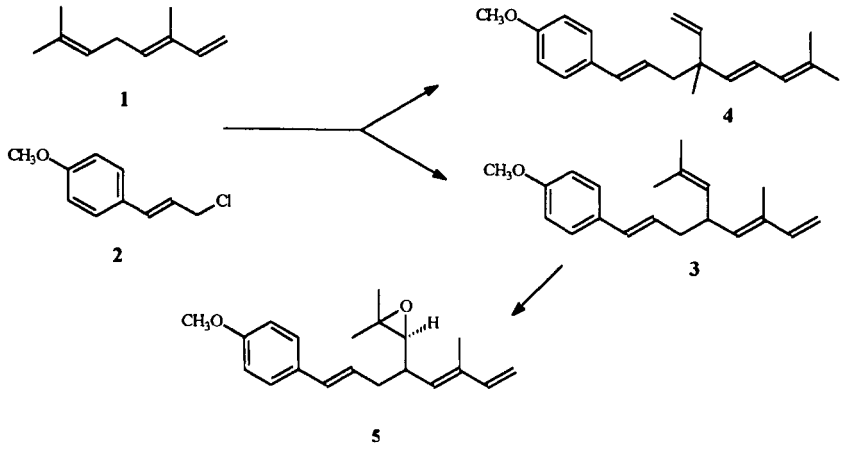
Departament de Química Orgànica, Universitat de València, Dr.Moliner 50, 46100, Burjassot, València, Spain.

ABSTRACT: Juvocimene I is prepared by a non ambiguous synthesis based on the regioselective alkylation of 4-methylhexa-2,4-dienoic acid, and Wittig olefination of the aldehyde corresponding to the alkylated acid.

Juvocimenes I and II **3** and **5** were isolated from Ocimum basilicum by Bowers, and both showed a very high juvenile hormone activity on Oncopeltus fasciatus.[1] Nishida and Bowers synthesized juvocimenes I by alkylation of *trans*-β-ocymene **1** with *p*-methoxycinnamyl chloride **2**, and juvocimene II **5** by epoxidation of the hydrocarbon **3** (Scheme 1). [2] Though apparently simple, the procedure requires a pure sample of β-ocymene, and this is obtained in low preparative yield by photolysis of β-pinene, [3] followed by silver nitrate/silicagel column

* To whom correspondence should be addressed

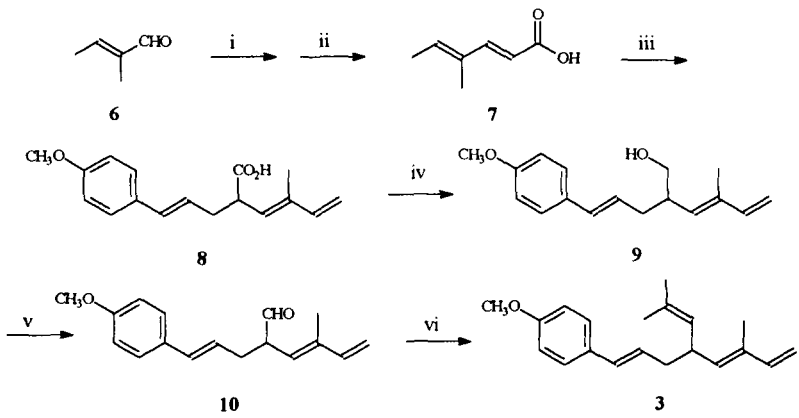
chromatography. Furthermore, the alkylation of β-ocymene is not regioselective, and resolution of the mixture of juvocimene I and the accompanying hydrocarbon **4** requires repetitive silver nitrate/silicagel column chromatography. [2]



Scheme 1

We wish to describe a new synthesis of juvocimene I, which is superior to that formerly described, in that alkylation is now entirely selective, the procedure is more easily scaled up, and higher partial and global yields are attainable without the need for refined chromatographic separations. The procedure is based on the selective α-alkylation of 4-methyl-2,4-hexadienoic acid **7** with p-methoxycinnamyl chloride **2**, reduction of the resulting acid to the corresponding alcohol, and then oxidation to the aldehyde, and Wittig olefination of the latter with isopropylphosphonium iodide, as shown in Scheme 2.

Methoxycinnamyl chloride **2** is common to this and to the former synthesis, and has been prepared now by addition of vinylmagnesium bromide to anisaldehyde, and treatment of the resulting alcohol with thionyl chloride, according to the procedure described by White and Fife.[4] On the other hand, the methylhexadienoic acid **7** had formerly been prepared by a Reformatsky reaction with tiglic aldehyde **4**, followed by dehydration and saponification of the hydroxy ester. Addition of the dilithium enediolate of acetic acid to the same aldehyde, and dehydration of the resulting hydroxy acid with cold conc sulfuric acid gave now the (E,E)-4-methylhexadienoic acid **7** in 67 % yield.



i.- a) CH_3CO_2H, 2 LDE; b) H_2O; ii.- H_2SO_4; iii.- a) 2 LDE; b) 2; c) H_2O; iv.- $LiAlH_4$; v.- DMSO/ClCOCOCl; vi.- $Ph_3P^+CH(CH_3)_2$, n-BuLi.

Scheme 2

Alkylation of the methylhexadienoic acid **7** with the methoxycinnamyl chloride **2** by deprotonation of the acid with two equivalents of lithium

diethylamide (LDE) gave the carboxylic acid **8** in 44 % yield after chromatographic purification. The yield for this alkylation is surprisingly low when compared to those found for other unsaturated carboxylic acids and alkylating reagents. Thus, in a parallel experiment, the same methylhexadienoic acid and cinnamyl bromide gave the corresponding alkylated acid in a 63 % yield.

The carboxylic acid **8** was reduced with excess $LiAlH_4$ in THF to the corresponding alcohol **9**, which was obtained in 82 % yield for purified material, and whose oxidation with DMSO and oxalyl chloride [6] led to the aldehyde **11** in 42 %. When this aldehyde **11** was allowed to react with the phosphonium ylide generated by deprotonation of isopropylphosphonium iodide with n-butyllithium in THF, juvocimene I **3** was obtained in 43 % for a purified material, whose ^1H and ^{13}C NMR spectra were in entire agreement with the structure, and with values described for the natural compound. [1,2]

The main difficulty found in the present synthesis derives from the instability of the synthetic intermediates, with the resulting reduction of yields on chromatographic purification of samples, whose ^1H NMR spectra showed to be only slightly impurified. However, when the sequence was carried out with the crude isolated intermediates **8**, **9**, and **10**, the purification of the resulting juvocimene I **3** required careful silver nitrate/silica gel chromatography, and the yield for the pure compound was lower. Work is being done in order to improve yields, and to introduce a protecting group for the dienic system.

EXPERIMENTAL

M.p.s were determined with a Reichert apparatus and are uncorrected. IR spectroscopic data were obtained for liquid film or KBr discs, with a FTS-7 Bio-Rad. spectrophotometer. Nmr spectra were recorded for $CDCl_3$ solutions, with a Bruker AC-200 (200 MHz), 300 Varian Unity (300 MHz) or Varian Unity 400 (400 MHz) spectrometers. Mass spectra were determined with a VG AutoSpec Spectrometer. Silica gel Merck 60 (0.06-0.20 mm) and 60 (230-400 mesh) was used for column and for flash column chromatography, respectively. Tetrahydrofuran (THF) was distilled from blue sodium diphenylketyl immediately before use. Diethylamine was dried over CaH_2 and distilled before use. Lithium diethylamide (LDE) has been generated from lithium, naphthalene, and diethylamine, as previously described. All reaction requiring inert conditions were carried out under argon atmosphere, using standard conditions for exclusion of moisture. The reaction temperature (-70°C) stands for cooling with a CO_2/acetone bath. Evaporation of solvents was carried out with a vacuum rotatory evaporator and a bath at 40°C.

(E,E)-4-Methyl-2,4-hexadienoic acid 7.- Acetic acid (6.5 ml; 0.11 mmol) in THF (80 ml) was added dropwise to a vigorously stirred solution of LDE [from lithium (1.64 g; 0.24 mmol), naphtalene (15., g; 0.12 mmol) and diethylamine (24.6 ml; 0.24 mmol)] in THF (80 ml). The solution was stirred for 20 min at 0° C and cooled again at -70° C Tiglic aldehyde (9.5 g; 0.11 mmol) in THF (80 ml) was

added dropwise, the solution was stirred for 15 min at the same temperature and for 1 h at ta, and poured into water (500 ml). The solvent was partly evaporated and the aqueous mixture was extracted with ethyl ether, and then carefully acidified with conc HCl under ice-water bath cooling. The mixture was saturated with NH_4Cl and extracted with ethyl acetate. The organic layer was washed with saturated NH_4Cl and dried ($MgSO_4$). Evaporation of the solvent gave crude 3-hydroxy-4-methyl-4-hexenoic acid (14.46 g; 79 %) as an orange oil; ν_{max} 3550-2500 (OH) and 1717 (C=O) cm^{-1}, δ_H 5.58 (1 H, q, J 1.5 Hz, C5-H), 4.46 (1 H, dd, J 9.3 and 3.9 Hz, C3-H), 2.64 (1 H, dd, J 16.2 and 9.3 Hz, C2-H), 2.54 (1 H, dd, J 16.2 and 3.9 Hz, C2-H), 1.63 (3 H, d, J 1.5, C6-H) and 1.60 (3 H, s, C4-CH_3) ppm.

Conc H_2SO_4 (1.3 ml; 25.1 mmol) cooled at 0° C was added to the above 3-hydroxy-4-methylhexenoic acid (3.6 g; 25.0 mmol) at 0° C. The mixture was stirred for 15 min at the same temperature, poured into ice-water (30 ml), and stirred for 20 min. Solid ammonium chloride was added, and the solution extracted with ethyl ether. The joint organic layers were washed with saturated NH_4Cl and dried ($MgSO_4$). Evaporation of the solvent gave the crude title acid (2.72 g; 86 %) as a yellow solid (lit[5] pf 94-95° C); ν_{max} 3300-2500 (OH) and 1704 (C=O) and 1616 (C=C) cm^{-1}, δ_H 7.40 (1 H, d J 15.8 Hz, C3-H), 6.07 (1 H, q, J 7.1 Hz, C5-H), 5.77 (1 H, d, J, 15.8 Hz, C2-H), 1.91 (3 H, d, J 7.1 Hz, C6-H) and 1.77 (3 H, s, C4-CH_3) ppm.

4-Carboxy-1-(4-methoxyphenyl)-6-methyl-1,5,7-octatriene 8.- (E,E)-4-methyl-1,5,7-octatriene (1.0 g; 7.93 mmol) in THF (10 ml) was added dropwise to

a vigorously stirred solution of LDE [from lithium metal (0.116 g; 15.7, naphtalene (1.07 g; 8.48 mmol), and diethylamine (1.7 ml; 16.6 mmol)] in THF (10 ml) at -70° C. The solution was stirred for 20 min at 0° C and cooled again to -70° C. p-Methoxycinnamyl chloride (1.45 g; 7.93 mmol) in THF was added dropwise, and the solution stirred for 25 min at the same temperature and for 2 h at ta, and poured into water (50 ml). The solvent was partly evaporated and the resulting aqueous mixture extracted with ether and then carefully acidified with conc HCl under cooling with an ice-water bath. The mixture was saturated with NaCl and extracted with ethyl acetate. The organic layer was washed with aqueous NH_4Cl and dried ($MgSO_4$). Evaporation of the solvent gave an orange oil which was purified by column chromatography (1:1 hexane/ether) to give **4-carboxy-1-(4-methoxyphenyl)-6-methyl-1,5,7-octatriene** (0.947 g; 44 %). Found: M^+ 272.140913. $C_{17}H_{20}O_3$ requires M^+ 272.141245. ν_{max} 3200-2700 (OH), 1707 (C=O), and 1608 (C=C) cm^{-1}; δ_H 7.23 (2 H, d, J 8. 6 Hz, Ph), 6.81 (2 H, d, J 8.6 Hz, Ph), 6.40 (1 H, t, J 10.8 Hz, C1-H ó C7-H), 6.35 (1 H, t, J 10.5 Hz, C7-H ó C1-H), 5.96 (1 H, m, C2-H), 5.49 (1 H, d, J 9.9 Hz, C5-H), 5.18 (1 H, d, J 17.1 Hz, C8-Ha), 5.03 (1 H, d J 10.8 Hz, C8-Hb), 3.77 (3 H, s, CH_3O), 3.50 (1 H, m, C4-H), 2.65 (1 H, m, C3-H), 2.45 (1 H, m, C3-H) and 1.79 (3 H, s, C6-CH_3) ppm; δ_{13C} 179.5 (CO), 159.0 (C), 140.6 (CH), 137.2 (C), 131.9 (CH), 130.1 (C), 128.3 (CH), 127.3 (CH), 123.9 (CH), 114.0 (CH), 112.9 (C8), 55.3 (CH_3O), 45.2 (C4), 36.1 (C3) and 12,3 (CH_3) ppm.

4-Hydroxymethyl-1-(4-methoxyphenyl)-6-methyl-1,5,7-octatriene 9.- 4-

Carboxy-1-(4-methoxyphenyl)-6-methyl-1,5,7-octatriene (0.752 g; 2.76 mmol) in THF (10 ml) was added dropwise to stirred $LiAlH_4$ (0.143 g; 3.77 mmol) in THF (5 ml) at 0° C. The mixture was stirred at 50° C for 2 h and 1 N HCl (20 ml) was carefully added. The mixture was saturated with NaCl, and extracted with ethyl ether. The organic layer was washed with 10 % NaOH and brine, and dried ($MgSO_4$). The solvent was evaporated, and a yellow oil was obtained, which was purified by column chromatography (7:3 hexane/ether) to give **4-hydroxymethyl-1-(4-methoxyphenyl)-6-methyl-1,5,7-octatriene** (0.582 g; 82 %) as a yellow oil. Found: M^+ 258.162584. $C_{17}H_{22}O_2$ requires 258.161980. ν_{max} 3400-3300 (OH), and 1608 (C=C) cm^{-1}; δ_H 7.25 (2 H, J 8.7 Hz, Ph), 6.83 (2 H, d J 8.7 Hz, Ph), 6.39 (2 H, m, C1-H y C7-H), 6.01 (1 H, m, C2-H), 5.33 (1 H, d, J 9.0 Hz, C5-H), 5.14 (1 H, d J 17.7 Hz, C8-Ha), 5.00 (1 H, d, J 10.5 Hz, C8-Hb), 3.79 (3 H, s, CH_3O), 3.65 (1 H, m, C4-CH_2), 3.50 (1 H, m, C4-CH_2), 2.80 (1 H, m, C4-H), 2.34 (1 H, m, C3-H), 2.22 (1 H, m, C3-H) and 1.80 (3 H, s, CH_3) ppm; δ_{13C} 158.8 (C), 141.2 (CH), 136.8 (C), 133.1 (CH), 130.9 (CH), 130.4 (C), 127.1 (CH), 125.6 (CH), 113.9 (CH), 118.8 (C8), 66.1 (CH_2OH), 55.3 (CH_3O), 41.5 (C4), 35.4 (C3) and 12.4 (CH_3) ppm.

4-Formyl-1-(4-methoxyphenyl)-6-methyl-1,5,7-octatriene 10.- DMSO (1.2 ml; 11.27 mmol) in dry dicholomethane (3 ml) was added to oxalyl chloride (0.46 ml; 5.28 mmol) in dichloromethane (10 ml) at -70° C. The solution was stirred for 2 min at the same temperature, and allowed to warm to -10° C. 4-Hydroxymethyl-1-(4-methoxyphenyl)-6-methyl-1,5,7-octatriene (0.58 g; 2.25

mmol) in dichloromethane (3 ml) was added dropwise. The mixture was stirred for 15 min at the same temperature and triethylamine (1.68 ml; 12.05 mmol) added. The mixture was stirred for 5 min at -10ª C, diluted with water (15 ml), and extracted with dichloromethane. The organic layer was washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave a yellow oil which was purified by column chromatography (9:1 hexane/ether) to give **4-formyl-1-(4methoxyphenyl)-6-methyl-1,5,7-octatriene** (0.242 g; 42 %) as a yellow oil. Found: M^+ 256.146.172. $C_{17}H_{20}O_2$ requires 256.14633. ν_{max} 1723 (C=O), and 1607 (C=C) cm^{-1}; δ_H 9.56 (1 H, s, CHO), 7.40 (2 H, d, J 8.7 Hz, Ph), 6.83 (2 H, d, J 8.7 Hz, Ph), 6.42 (2 H, m, C1-H y C7-H), 5.98 (1 H, dt, J 7.2 Hz, J 15.4 Hz, C2-H), 5.37 (1 H, d, J 9.3 Hz, C5-H), 5.22 (1 H, d, J 16.5 Hz, C8-Ha), 5.08 (1 H, d, J 10.8 Hz, C8-Hb), 3.79 (3 H, s, CH_3O), 3.48 (1 H, m, C4-H), 2.67 (1 H, m, C3-H), 2.46 (1 H, m, C3-H) and 1.83 (CH_3) ppm; δ_{13C} (APT) 200.0 (CO), 159.0 (C), 140.4 (CH), 139.0 (C), 131.8 (CH), 130.0 (C), 127.2 (CH), 125.7 (CH), 123.9 (CH), 113.9 (CH), 113.2 (C8), 55.3 (CH_3O), 52.5 (C4), 33.0 (C3) and 12.6 (CH_3) ppm.

1-(4-Methoxyphenyl)-6-methyl-4-(2-methyl-1-propenyl)-1,5,7-octatriene 3.- 1.6 M n-BuLi in hexane (0.56 ml; 0.889 mmol) was added to isopropylphosphonium iodide (0.388 g; 0.89 mmol) in THF (5 ml) at -70° C. The mixture was stirred for 40 min at -70° C, and for 10 min at 0° C. 4-Formyl-1-(4-methoxyphenyl)-6-methyl-1,5,7-octatriene (0.288 g; 0.89 mmol) in THF (5 ml) was added, and the solution stirred for 1 h at 0° C, and for 2 h at ta. Water (8 ml)

was added, and the mixture extracted with ethyl ether. The organic layer was washed twice with brine and dried ($MgSO_4$). Evaporation of the solvent gave a crude oil which was purified by column chromatography (0.9:0.5 hexane/ether) and 1-(4-methoxyphenyl)-6-methyl-4-(2-methyl-1-propenyl)-1,5,7-octatriene (0.85 g; 34 %) was obtained as a pale yellow oil. Found: M^+ 282.199320. $C_{20}H_{26}O$ requires M^+ 282.198366; ν_{max} 1607 (C=C) cm^{-1}; δ_H 7.25 (2 H, d, J 8.7 Hz, Ph), 6.83 (2 H, d, J 8.7 Hz, Ph), 6.34 (2 H, m, C1-H and C7-H), 5.99 (1 H, dt, J 7.2 Hz, J 15.8 Hz, C2-H), 5.36 (1 H, d, J 9.3 Hz, C5-H), 5.09 (1 H, d, J 17.7 Hz, C8-Ha), 5.03 (1 H, d, J 9.0 Hz, C1'-H), 4.94 (1 H, d, J 10.8 Hz, C8-Hb), 3.80 (3 H, s, CH_3O), 3.36 (1 H, m, C4-H), 2.23 (2 H, t, J 7.2 Hz, C3-H), 1.77 (3 H, s, C6-CH_3), 1.70 (3 H, s, CH_3) and 1.64 (3 H, s, CH_3) ppm; lit [2] δ_{13C} APT 158.6 (C), 141.7 (CH), 136.1 (CH), 132.6 (C), 131.3 (C), 130.7 (C), 130.3 (CH), 127.0 (CH), 126.4 (CH), 113.9 (CH), 110.8 (C8), 55.3 (CH_3O), 39.8 (C3), 38.3 (C4), 25.8 (CH_3), 18.2 (CH_3), and 12.1 (CH_3) ppm.

ACKNOWLEDGEMENTS: The present work has been financed by DGICYT (PB92-0871). One of us (EM) acknowledges a grant by Conselleria de Cultura de la Generalitat Valenciana.

REFERENCES

1.- Bowers, W.S.; Nishida, R; *Science*, **1980**, 209, 1030.

2.- Nishida, R.; Bowers, W.S.; Evans, P.H., *J.Chem.Ecology*, **1984**, 10, 1435.

3.- Kropp, P.J., *J.Am.Chem.Soc.*, **1969**, 91, 5783.

4.- White, W.N.; Fife, W.K., *J.Am.Chem.Soc.*, **1961**, 83, 3846. Wigfield, D.C.; Feiner, S.; Malbacho, G.; Taymaz, K., *Tetrahedron*, **1974**, 30, 2949.

5.- Owens, C.; Raphael, R.A., *J.Chem.Soc.Perkins Trans. I*, **1978**, 1508.

6.- Mancuso, A.J.; Swern, D., *Synthesis*, **1981**, 165.

7.- Aurell, M.J.; Gil, S.; Tortajada; A.; Mestres, R., *Synthesis*, **1990**, 317.

(Received in the UK 4th August 1995)