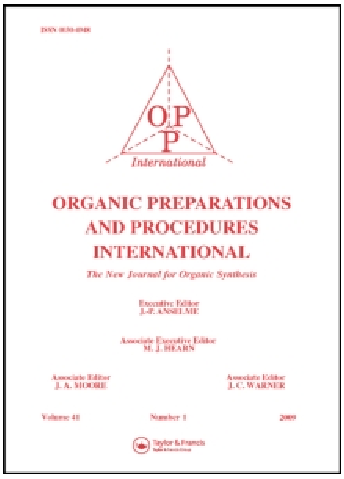

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

NEW AND SIMPLE SYNTHESIS OF THE PHEROMONE COMPONENT OF MALE MELON FLY

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To cite this Article Yen, Yao-Pin and Chen, Jay-Hung(2006) 'NEW AND SIMPLE SYNTHESIS OF THE PHEROMONE COMPONENT OF MALE MELON FLY', Organic Preparations and Procedures International, 38: 5, 500 — 504
To link to this Article: DOI: 10.1080/00304940609356445
URL: http://dx.doi.org/10.1080/00304940609356445

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NEW AND SIMPLE SYNTHESIS OF THE PHEROMONE COMPONENT OF MALE MELON FLY

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(07/07/06)

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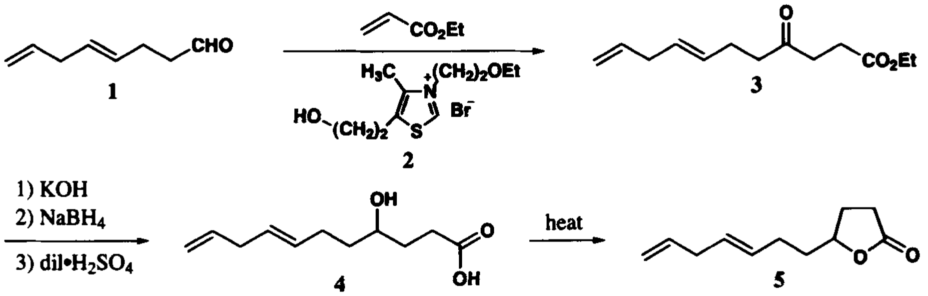
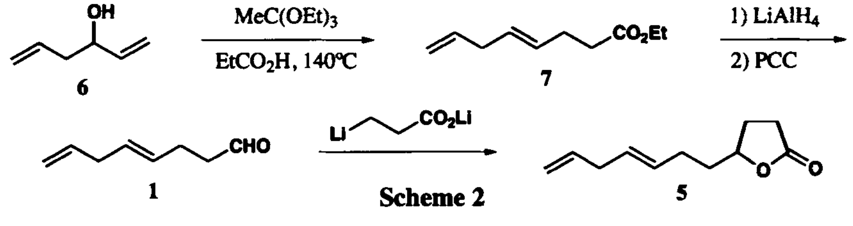
Our laboratory has been involved in the synthesis of sex pheromones and attractants.[1] We are currently investigating the pheromone component of the male melon fly (*Dacus cucurbitae Coquillett*) which is one of the most active and destructive fruit fly pests which infests more than 80 plant species.[2] Ohinata *et al.*[3] isolated and identified 5-(3*E*,6-heptadienyl)dihydro-2(3H)-furanone (**5**) as an active component of the pheromone, visible as smoke emitted at dusk during the mating period of male melon flies. Some methods for its preparation are however, cumbersome and give low overall yields. Voaden reported[4a] the synthesis of **5** from 3-(2-

ethoxyethyl)-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium bromide (**2**) catalyzed reaction of (*E*)-4,7-octadienal (**1**) with ethyl acrylate to the corresponding γ-keto ester (**3**). Alkaline hydrolysis of **3**, followed by reduction with $NaBH_4$ and acidification, afforded (*E*)-4-hydroxy-7,10-undecadienoic acid (**4**), which on heating was dehydrated and cyclized to **5** with an overall yield of less than 5%. This method required the preparation of the catalyst, 3-(2-ethoxyethyl)-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium bromide (*Scheme 1*).



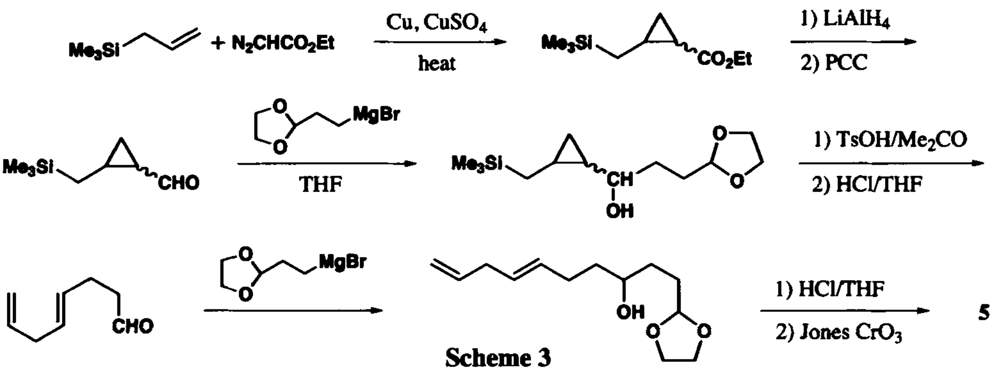
Scheme 1

An alternative way[4b] for the synthesis of **5** involves the Claisen orthoester rearrangement of 1,5-hexadien-3-ol (**6**) to yield ethyl (E)-4,7-octadienoate (**7**), which upon reduction with $LiAlH_4$ and then oxidation with PCC afforded the corresponding dienal (**1**). The dienal was subsequently treated with lithium 3-lithiopropionate to give the desired product with an overall yield of less than 18% yield from **6** (*Scheme 2*).



Scheme 2

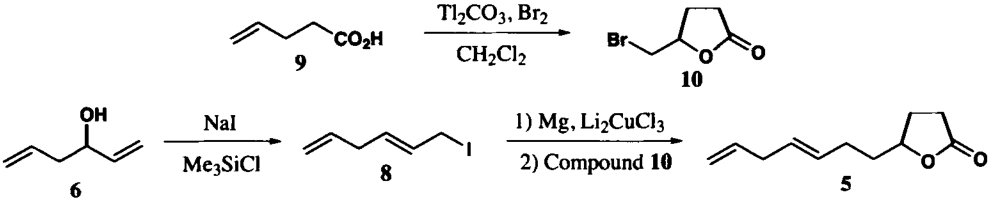
Although Wilson and coworkers[4c] reported a good yield (70%) in the final step of their synthesis, it involved several steps and proceeded in less than 10% overall yield (*Scheme 3*).



Scheme 3

All the synthetic approaches mentioned above are lengthy and time-consuming. We previously reported a facile generation of C-C bonds by a "cuprate-catalyzed" Grignard coupling method[5] and our goal was to overcome these difficulties and improve the overall yield of **5**. We now describe a simple and convenient method for its synthesis *via* a similar coupling reaction in better yields.

Commercially available 1,5-hexadiene-3-ol (**6**) was efficiently converted into (*E*)-1-iodo-2,5-hexadiene (**8**) at 86% yield by treatment with hydrogen iodide, generated *in situ* from chlorotrimethylsilane/sodium iodide and water[6] and 4-pentenoic acid (**9**) was converted to 5-(bromomethyl)dihydrofuran-2(3H)-one (**10**) in 82% yield by treatment with thallium(I) carbonate and bromine in dichloromethane.[7] Coupling of the γ-bromolactone (**10**) with (*E*)-hexa-2,5-dienylmagnesium iodide, generated *in situ* from **8** and magnesium powder in THF, in the presence of dilithium trichlorocuprate afforded the desired product,[5] purified using column chromatography to afford pure 5-(3*E*,6-heptadienyl)-dihydro-2(3H)-furanone (**5**) with an overall yield of 46% from **6** (*Scheme 4*).



Scheme 4

In conclusion, we have developed a new synthetic approach which is simple, convenient, and with a much higher overall yield than those of the previous reports.

EXPERIMENTAL SECTION

The IR spectra were recorded on a Perkin-Elmer 2000 FT-IR. The ^1H NMR spectra were obtained on a Brucker AC-250 Spectrometer, and the mass spectra were recorded using an HP 5890 and HP 5971 MSD. Reagents (obtained from Aldrich) and solvents were purified using standard techniques. Solvents were dried over an appropriate drying agent before use: CH_3CN and CH_2Cl_2 over CaH_2, THF over Na with benzophenone as an indicator. The preparation of Li_2CuCl_3 was followed the previous procedures.[5]

(E)-1-Iodo-2,5-hexadiene (8).- To an efficiently stirred solution of NaI (1.50 g, 10 mmol) in CH_3CN (15 mL), Me_3SiCl (1.25 mL, 10 mmol), and water (0.09 mL, 5 mmol), were slowly added followed by 1,5-hexadien-3-ol (1.13 mL, 10 mmol). The mixture was allowed to react at room temperature for 1 h. After quenching with water (10 mL), the product was extracted with ether (3 x 15 mL). The ethereal layer was washed with 10% $Na_2S_2O_3$ solution (15 mL) and dried ($MgSO_4$). Evaporation of the solvent gave the crude product as a yellow liquid which was purified by column chromatography on silica gel with *n*-hexane as the eluent to afford (E)-1-iodo-

2,5-hexadiene[6] (1.78 g, 86%) as a yellow liquid, bp 52-53°C/30 mm Hg. IR (neat): 3412, 3077, 3004, 2978, 2900, 1639, 1428, 1151, 992, 965, 918, 542 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.78-2.80 (m, 2H), 3.88-3.92 (m, 2H), 5.03-5.07 (m, 2H), 5.73-5.83 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 135.6, 132.3, 128.9, 115.9, 35.9, 6.1 (*lit.*[6] ^{13}C NMR ($CDCl_3$): δ 135.4, 132.1, 128.8, 115.7, 35.8, 5.9); MS m/z (%): 208 (M$^+$, 0.1), 127 (16), 81 (100), 79 (28), 53 (23), 41 (24).

Anal. Calcd for C_6H_9I: C, 34.64; H, 4.36. Found: C, 34.69; H, 4.43

5-(Bromomethyl)dihydrofuran-2(3H)-one (10).- Thallium(I) carbonate (1.78 g, 3.8 mmol) was added to a stirred solution of 4-pentenoic acid (0.48 mL, 4.7 mmol) in CH_2Cl_2 (50 mL) and after 2 h Br_2 (0.36 mL, 7.1 mmol) in CH_2Cl_2 (50 mL) was added, and the mixture was stirred for a further 24 h. The mixture was centrifuged to give a solution, which was washed with sat. aq. $NaHSO_3$ solution (100 mL), sat. aq. $NaHCO_3$ solution (100 mL), and water (100 mL). Solvent was removed from the dried ($MgSO_4$) solution under reduced pressure, and the bromolactone was then purified by column chromatography on silica gel with ether as the eluent to give product **10**[7] (0.71 g, 82% yield) as a colorless liquid, bp 86-87°C/2 mm Hg, *lit*,[7] bp 79-80°C/0.1 mm Hg. IR (neat): 3531, 2961, 1770, 1421, 1339, 1162, 1023, 989, 917, 650 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.99-2.20 (m, 1H), 2.41-2.71 (m, 3H), 3.47-3.60 (m, 2H), 4.72-4.78 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 176.1, 77.8, 34.0, 28.3, 26.2; MS m/z (%): 180 (M$^+$+2, 0.1), 178 (M$^+$, 0.1), 99 (M$^+$-Br, 0.2), 85 (100), 55 (11).

5-(3E,6-Heptadienyl)dihydro-2(3H)furanone (5).- (E)-Hexa-2,5-dienylmagnesium iodide was prepared by the slow dropwise addition of a solution of (E)-1-iodo-2,5-hexadiene (0.20 g, 0.96 mmol) in THF (3 mL) to magnesium powder (35.60 mg, 1.5 mmol) in THF (5 mL). Freshly prepared[5] Li_2CuCl_3 (0.1 M, 0.48 mL, 0.48 mmol) was added to 5-(bromomethyl)-dihydrofuran-2(3H)- one (86.40 mg, 0.48 mmol) in THF (2 mL) at room temperature. The solution of the Grignard reagent (0.96 mmol) was then added dropwise. The reaction mixture was stirred and heated to reflux for 12 h. After cooling to room temperature, the solution was quenched with sat. aq. NH_4Cl solution (5 mL). The organic layer was separated and the aqueous layer extracted with ether (3 x 5mL). The combined organic solution was washed with brine, dried, and concentrated in vacuum. The residue was purified by chromatography on silica gel eluting with ethyl acetate/n-hexane (1:2) to produce pure **5**[4] (45.8 mg, 53% yield) as a colorless liquid, bp 115-116°C/1 mm Hg, *lit*,[4c] bp 172°C/18 mm Hg. IR (neat): 3077, 2938, 1770, 1638, 1424, 1355, 1179, 994, 914, 808 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.66-1.71 (m, 1H), 1.78-1.91 (m, 2H), 2.13-2.21 (m, 2H), 2.30-2.37 (m, 1H), 2.51-2.56 (m, 2H), 2.74-2.77 (m, 2H), 4.48-4.52 (m, 1H), 4.97-5.05 (m, 2H), 5.42-5.52 (m, 2H), 5.76-5.85 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 177.2, 137.0, 129.6, 129.1, 115.0, 80.3, 36.6, 35.3, 28.8, 28.3, 27.9; MS m/z (%): 180 (M$^+$, 0.2), 111 (7), 93 (9), 91 (9), 85 (23), 81 (14), 80 (100), 79 (53), 77 (8).

Acknowledgement.- Financial support of this work by the council of Agriculture of the Republic of China is gratefully acknowledged.

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