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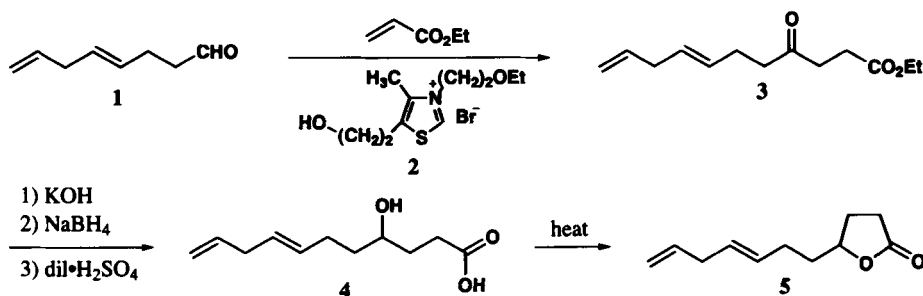
NEW AND SIMPLE SYNTHESIS OF THE PHEROMONE COMPONENT OF MALE MELON FLY

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(07/07/06)

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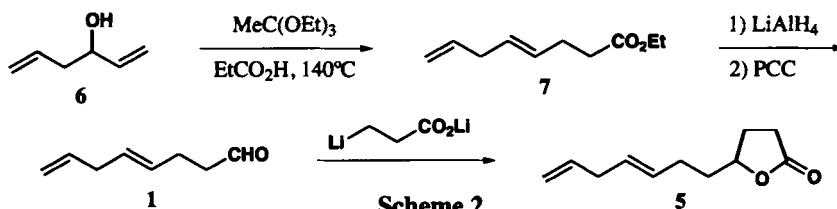
Our laboratory has been involved in the synthesis of sex pheromones and attractants.¹ We are currently investigating the pheromone component of the male melon fly (*Dacus cucurbitae* Coquillett) which is one of the most active and destructive fruit fly pests which infests more than 80 plant species.² Ohinata *et al.*³ isolated and identified 5-(3*E*,6-heptadienyl)dihydro-2(3*H*)-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*).



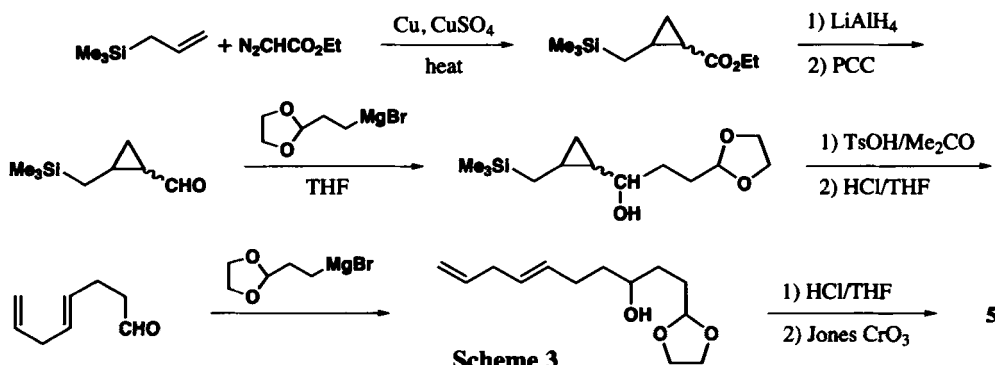
Scheme 1

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

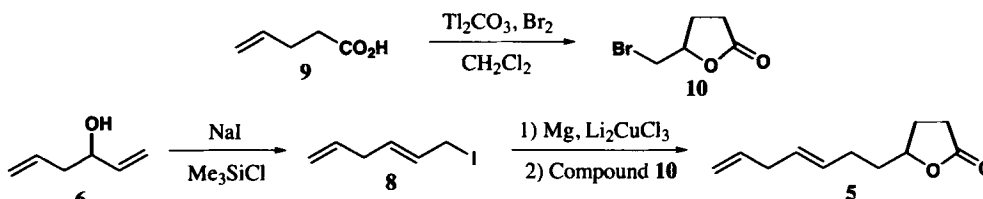
Although Wilson and coworkers^{4c} reported a good yield (70%) in the final step of their synthesis, it involved several steps and proceeded in less than 10% overall yield (*Scheme 3*).



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 method⁵ 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 water⁶ 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 Bruker 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: CH₃CN and CH₂Cl₂ over CaH₂, THF over Na with benzophenone as an indicator. The preparation of Li₂CuCl₃ 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 CH₃CN (15 mL), Me₃SiCl (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% Na₂S₂O₃ solution (15 mL) and dried (MgSO₄). 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-hexadiene⁶ (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; ¹H NMR (CDCl₃): 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); ¹³C NMR (CDCl₃): δ 135.6, 132.3, 128.9, 115.9, 35.9, 6.1 (*lit.*⁶ ¹³C NMR (CDCl₃): 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 C₆H₈I: 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 CH₂Cl₂ (50 mL) and after 2 h Br₂ (0.36 mL, 7.1 mmol) in CH₂Cl₂ (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. NaHSO₃ solution (100 mL), sat. aq. NaHCO₃ solution (100 mL), and water (100 mL). Solvent was removed from the dried (MgSO₄) 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; ¹H NMR (CDCl₃): 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); ¹³C NMR (CDCl₃): 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 prepared⁵ Li₂CuCl₃ (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. NH₄Cl solution (5 mL). The organic layer was separated and the aqueous layer extracted with ether (3 x 5 mL). 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; ¹H NMR (CDCl₃): 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); ¹³C NMR (CDCl₃): 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).

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