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SYNTHETIC STUDIES ON JASMONOIDS (II)[1]: A NEW SYNTHESIS OF METHYL *dl*-JASMONATE

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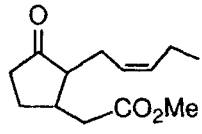
SUMMARY: Successive dialkylation of methyl acetoacetate with allylic functions **2** and **5**, followed by oxidation, gave an α,β-unsaturated aldehyde **7**. Intramolecular Michael addition of **7** to give a cyclopentanone **8**, conversion to diester **9**, and Krapcho decarbomethoxylation furnished methyl *dl*-jasmonate.

Methyl jasmonate[2], one of the essential constituents of jasmine oil, has been known recently as the senescence-promoting agent of wormwood,[3] an insect sex-attractant pheromone, and a new member of plant hormones. Because of the importance in perfumery industry, it has long been a target of synthetic chemistry. Although the synthesis of the racemic form *via* diverse routes has been reported,[4] most of the starting materials or synthetic intermediates were expensive or not readily available. We report here a new synthesis of methyl *dl*-jasmonate **1**, which is reasonably short and inexpensive. In the present work, we did not utilized troublesome reagents, such as 2-cyclopentenone or its derivatives, as starting materials or synthetic intermediates. Moreover, we prepared a 2,3-disubstituted cyclopentanone, as a precursor of **1**, directly by the intramolecular Michael reaction of a readily accessible acyclic compound.



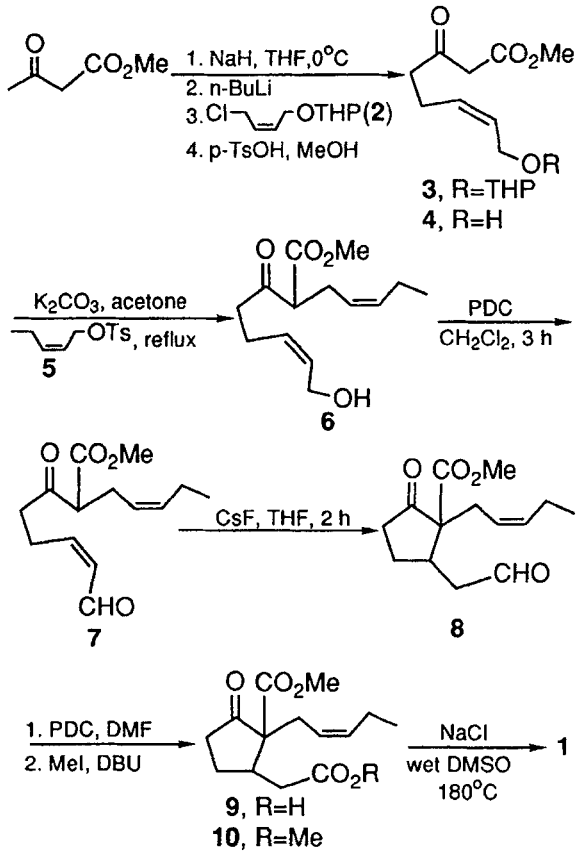
1

Our route leading to **1** is outlined in Scheme, which begins with successive dialkylation of methyl acetoacetate. In general, dialkylation of acetoacetate *via* dianion is inefficient because of the difficulty of the second alkylation. Fortunately, however, alkylating groups in our synthesis are allylic functions that easily undergo substitution reaction.

The first allylation was carried out by treating a solution of methyl acetoacetate in tetrahydrofuran (THF) with sodium hydride (NaH) and *n*-butyllithium (*n*-BuLi), successively, to give an orange solution of dianion,[5] followed by adding 4-chloro-*cis*-2-butenyl THP ether (**2**),[6] to provide a mono-allylated product **3**. The THP group in **3** was removed by stirring with *p*-toluenesulfonic acid in MeOH, to give the corresponding ketonic alcohol **4** as an oil in 73% overall yield. The second allylation was carried out by refluxing for 12 h a solution of **4** and *cis*-2-penten-1-yl tosylate (**5**) in acetone in the presence of potassium carbonate (K_2CO_3), to give a diallylated product **6**. Subsequent oxidation of **6** with pyridinium dichromate (PDC)[7] yielded the corresponding α,β-unsaturated aldehyde **7**.

Intramolecular Michael addition[8] was effected by treating of **7** with cesium fluoride (CsF) to afford a 5-membered ring compound **8** in 89% isolated yield. In this cyclization reaction, stronger bases such as sodium methoxide or sodium hydride are less efficient than CsF, though they have been utilized in the Michael reaction. Oxidation of the aldehyde **8** with PDC in DMF gave the corresponding acid **9** in 77% isolated yield. Esterification of **9** with methyl iodide in the

Scheme



presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[9] afforded a diester **10** in 84% yield. Krapcho decarbomethoxylation[10] of the β-ketoester **10** was accomplished by heating a mixture of **10**, wet DMSO, and sodium chloride at 180 °C for 4 h in a sealed tube, to give 78% of methyl *dl*-jasmonate **1** as an oil.

In summary, we have shown a synthesis of **1** proceeding with an economy of steps which involve, (1) successive allylation of acetoacetate to give efficiently a

diallylated intermediate, and (2) direct formation of 2,3-dialkylcyclopentanone as a precursor of **1**, without *via* 2-cyclopentenone derivatives that are not readily available.

Experimental Section

General. Reactions requiring anhydrous conditions were performed with the precaution for rigorous exclusion of air and moisture. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from EM reagents and visualized with 254-nm UV light or ceric sulfate-ammonium molybdate-sulfuric acid spray. The ^1H NMR and ^{13}C NMR spectra were recorded at 80 and 200 MHz on Brucker AC-80 and Varian VXR-200s spectrometer, respectively. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane. IR spectra were obtained on Perkin-Elmer Model 782 spectrometer. Mass spectra were recorded on a VG-7025 normal geometry or Shimazu-LKB 9000 GC/MS system. Chemicals were purified, when necessary, according to the reported procedure.[11]

Methyl (*Z*)-8-Hydroxy-3-oxo-6-octenoate (4). Sodium hydride (3.2 g, 100 mmol; 75% in mineral oil) was washed twice with tetrahydrofuran (THF), and added under nitrogen to THF (100 mL). To this suspension was added dropwise with stirring a solution of methyl acetoacetate (11.6 g, 100 mmol) in THF (20 mL) at ice-salt temperature. The mixture was stirred for more than 10 min until all of the sodium hydride was consumed. To this clear solution was added slowly *n*-butyllithium (*n*-BuLi, 2.0 M, 50 mL) through a syringe, and the yellow-orange solution formed was stirred at 0 °C for 10 min. A solution of 4-chloro-2-butenyl THP ether **2** (20.9 g, 110 mmol) in THF (10 mL) was added dropwise, the reaction mixture was stirred for 2 h, and allowed to warm to room temperature.

The reaction mixture was neutralized with dilute HCl (2.0 N, 100 mL). The solvent was removed *in vacuo*, and the residue was extracted with dichloromethane, and dried ($MgSO_4$). Evaporation of the solvent gave **3**, which was deprotected without further purification: *p*-Toluenesulfonic acid (1 g) was added to a solution of the crude **3** in methanol (200 mL), and the mixture was stirred for 1 h. Water (250 mL) was added, and the solvent was removed under reduced pressure. The residue was extracted with dichloromethane, dried ($MgSO_4$), and the solvent was evaporated. The chromatography on silica gel eluting with dichloromethane gave **4** (13.58 g, 73%) as an oil: IR (neat, NaCl disc) 3400 (broad, OH), 2950, 1735, 1710, 1435, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92-2.04 (broad, 1H, OH), 2.32-2.45 (m, 2H, CH_2CH=CH), 2.66 (t, J = 6.6 Hz, 2H, O=CCH_2CH_2), 3.45 (s, 2H, CH_2CO_2Me), 3.74 (s, 3H, CO_2CH_3), 4.20 (d, J = 6.8 Hz, 2H, CH_2OH), 5.36-5.55 (m, 1H, vinyl), 5.60-5.76 (m, 1H, vinyl); ^{13}C NMR ($CDCl_3$) δ 21.1, 42.1, 49.8, 52.1, 57.8, 129.7, 129.9, 167.4, 202.1; HRMS calculated for $C_9H_{12}O_3$ ($M^+ - H_2O$) 168.0786, found 168.0789 ($M^+ - H_2O$).

Methyl (*Z*)-8-Hydroxy-3-oxo-2-[(*Z*)-2-pentenyl]-6-octenoate (6). To a solution of **4** (7.45 g, 40 mmol) and (Z)-2-penten-1-yl tosylate **5** (10.57 g, 44 mmol) in acetone (300 mL) was added K_2CO_3 (22.1 g, 160 mmol), and the suspension was stirred at room temperature for 1 h and then refluxed for additional 12 h. Insoluble precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO_2 / CH_2Cl_2) to give **6** (7.32 g, 72%) as a colorless oil: IR (neat, NaCl disc) 3400 (broad, OH), 2950, 1740, 1710, 1445, 1170, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.81-2.72 (m, 9H, 4 CH_2 and OH), 3.43 (t, J = 7.2 Hz, 1H, O=CC$H$$CO_2Me$), 3.70 (s, 3H, CO_2CH_3), 4.15 (d, J = 6.4 Hz, 2H, CH_2OH), 4.94-5.78 (m, 4H, vinyl); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.2, 21.0, 25.7, 41.5, 52.0, 57.7,

58.4, 123.7, 129.7, 129.8, 134.4, 169.5, 204.2; HRMS calculated for $C_{14}H_{20}O_3$ ($M^+ - H_2O$) 236.1412, found 236.1407 ($M^+ - H_2O$).

Methyl (Z)-7-Formyl-3-oxo-2-[(Z)-2-pentenyl]-6-octenoate (7). A solution of the alcohol **6** (6.4 g, 25 mmol) and pyridinium dichromate (PDC, 19.0 g, 50 mmol) in dichloromethane (100 mL) was stirred for 3 h at room temperature. The crude reaction mixture was filtered through a short silica gel column, eluting several times with ether. After evaporating the solvent, the crude product was purified by chromatography (SiO_2/ CH_2Cl_2) to afford **7** (4.8 g, 76%) as a pale yellow oil: IR (neat, NaCl disc) 2960, 1740, 1720, 1690, 1635, 1125, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.81-2.81 (m, 8H, 4 CH_2), 3.52 (t, J = 7.2 Hz, 1H, O=CC*H*CO_2Me), 3.73 (s, 3H, CO_2CH_3), 5.08-5.52 (m, 2H, vinyl), 6.09 (dd, J = 16, 8 Hz, 1H, =C*H*CHO), 6.64-7.02 (m, 1H, C*H*=CHCHO), 9.49 (d, J = 8 Hz, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 13.6, 20.2, 20.3, 25.9, 39.9, 52.2, 58.3, 123.7, 133.2, 134.8, 155.8, 169.4, 193.3, 202.8; MS *m/z* (relative intensity) 252 (M^+, 6), 141 (100), 109 (59), 83 (63).

3-[(Formyl)methyl]-2-methoxycarbonyl-2-[(Z)-2-pentenyl]cyclopentanone (8). A solution of the aldehyde **7** (3.7 g, 14.7 mmol) and a catalytic amount of CsF (0.5 g) in THF (50 mL) was stirred for 2 h. The reaction mixture was poured into cold, dilute aq. ammonium chloride, the solvent was removed under reduced pressure, and extracted with dichloromethane. Evaporation of the solvent and subsequent chromatography on silica gel eluting with *n*-hexane/ether (3:1, v/v) furnished **8** (3.29 g, 89%) as an oil: IR (neat, NaCl disc) 2960, 1750, 1735, 1725, 1145, 915, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.70-2.91 (m, 11H, 5 CH_2 and CH), 3.67 (s, 3H, CO_2CH_3), 4.92-5.70 (m, 2H, vinyl), 9.76 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 13.6, 20.5, 26.4, 28.9, 37.3, 38.4, 45.4, 52.1, 62.0, 122.0, 136.4, 170.7, 198.7, 214.0; HRMS calculated for $C_{14}H_{20}O_4$ 252.1361, found 252.1366.

3-[(Carboxy)methyl]-2-methoxycarbonyl-2-[(Z)-2-pentenyl]cyclopentanone (9). A solution of aldehyde **8** (1.7 g, 6.7 mmol) in DMF (10 mL) containing PDC (5.0 g, 13.4 mmol) was stirred for 4 h at room temperature. The reaction mixture was poured into cold water (100 mL), extracted several times with ether, and dried ($MgSO_4$). Removal of the solvent *in vacuo*, and chromatography on silica gel eluting with *n*-hexane/ether (3:1, v/v) afforded **9** (1.39 g, 77% yield) as a colorless oil: IR (neat, NaCl disc) 3300-2700 (broad, CO_2H), 2960, 1735, 1720, 1710, 1080, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.65-2.81 (m, 11H, 5 CH_2 and CH), 3.70 (s, 3H, CO_2CH_3), 4.94-5.64 (m, 2H, vinyl), 6.40-7.38 (broad, 1H, CO_2H); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.6, 26.3, 29.0, 35.6, 38.5, 39.5, 52.2, 62.2, 121.9, 136.6, 170.6, 177.4, 214.3; MS *m/z* (relative intensity) 268 (M^+, 8), 236 (8), 179 (100), 141 (21), 109 (21).

2-Methoxycarbonyl-3-[(methoxycarbonyl)methyl]-2-[(Z)-2-pentenyl]cyclopentanone (10). To a solution of acid **9** (0.8 g, 3 mmol) and DBU (0.53 g, 3.5 mmol) in benzene (15 mL) was added methyl iodide (0.28 mL, 4.5 mmol) in benzene (5 mL) at ice-bath temperature. The reaction mixture was stirred for 2 h at room temperature, poured into cold water (20 mL), and extracted with ether. The organic solution was dried ($MgSO_4$), and evaporated. The crude product was chromatographed on a silica gel column eluting with *n*-hexane/ether (5:1, v/v), to give **10** (0.71 g, 84%) as an oil. IR, ^1H NMR, ^{13}C NMR and MS data were well agreed with those on literature[3]: IR (neat, NaCl disc) 2950, 1750, 1730, 1720, 1130, 1080, 980, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.60-2.90 (m, 11H, 5 CH_2 and CH), 3.69 (s, 6H, 2 CO_2CH_3), 5.05-5.20 (m, 1H, vinyl), 5.44-5.61 (m, 1H, vinyl); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.4, 26.1, 28.7, 35.4, 38.3, 39.5, 51.4, 51.6, 62.0, 121.9, 136.2, 170.4, 171.6, 214.0; MS *m/z* (relative intensity) 282 (M^+, 3), 193 (100), 141 (22), 109 (16).

Methyl *dl*-jasmonate (1); *3-[(Methoxycarbonyl)methyl]-2-[(Z)-2-pentenyl]cyclopentanone.* A mixture of **10** (100 mg, 0.35 mmol), H_2O (80 mg), NaCl (40 mg) and DMSO (6 mL) was heated with stirring for 4 h at 180 °C in a sealed tube. The reaction mixture was poured into ice-cold brine, extracted with *n*-hexane, the organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was chromatographed on silica gel eluting with *n*-hexane / ether (7:1, v/v), to give methyl *dl*-jasmonate **1** (62 mg, 78%) as an oil: IR, ^{1}H NMR, ^{13}C NMR and MS data were consistent with those reported in the literature[3]: IR (neat, NaCl disc) 2950, 1735, 1725, 1690, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.40-2.90 (m, 12H, 5 CH_2 and 2 CH), 3.69 (s, 3H, CO_2CH_3), 5.19-5.28 (m, 1H, vinyl), 5.40-5.48 (m, 1H, vinyl); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.6, 25.6, 27.2, 37.7, 38.0, 38.8, 51.6, 54.0, 124.9, 134.1, 172.5, 218.8; MS *m/z* (relative intensity) 224 (M^+, 51), 193 (16), 151 (58), 109 (23), 83 (100).

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