Enantioselective Synthesis of (-)-Methyl Jasmonate and (+)-Methyl Epijasmonate

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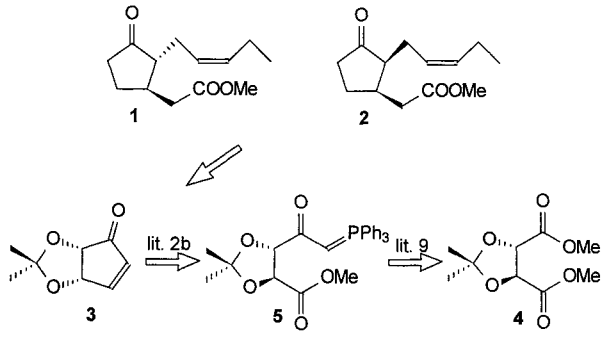
Abstract: An efficient and flexible enantioselective synthesis of (-)-methyl jasmonate and (+)-methyl epijasmonate, two important phytohormones, is described. The procedure makes use of a chiral cyclopentanoid building block that can easily be prepared from tartaric acid by phosphorus ylide chemistry.

In 1986 we reported the synthesis of optically active cyclopentanes from tartaric acid employing phosphorus ylide chemistry.[1] Many cyclopentanoid natural products can be obtained using these compounds as chiral building blocks.[2,3] Herein, we present the total syntheses of (-)-methyl jasmonate **1** and (+)-methyl epijasmonate **2**, the fragrance constituents of jasmine oil.[4] The need for a highly flexible synthetic access to these compounds stems from the fact that they display several interesting biological activities including plant growth regulation,[5] mediation in the defense mechanism of plants[6] and signal transmission in interplant communication.[7] As compound **2** is prone to *in vivo* and *in vitro* epimerisation, **1** and **2** occur in a ratio of 9:1 in nature.[8] However, only (+)-methyl epijasmonate **2** seems to have physiological activity.

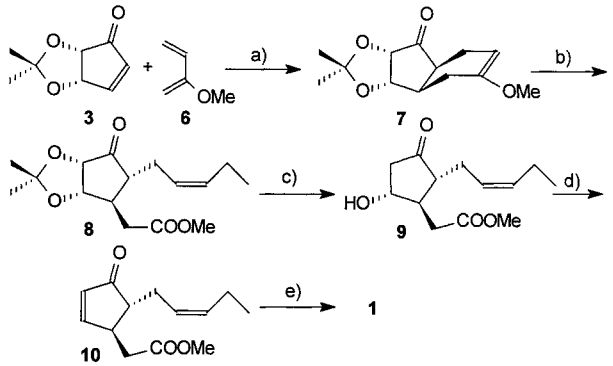


Scheme 1

Our retrosynthetic analysis shows the optically active cyclopentenone[2,3] **3** as an ideal precursor for the construction of both diastereomers (Scheme 1). In analogy to previously reported experimental procedures[2b] **3** is accessible from (+)-dimethyl-2,3-*O*-isopropylidene-*D*-tartrate **4** in five steps. Furthermore, the synthesis of acylphosphorane **5**, a key compound on the way to **3**, has been improved in our laboratories. Therefore, the chiral building block **3** and its enantiomer are now available in three steps and an overall yield of 48 %.[9]

The key-step in constructing the side chains of **2** in the required *cis* stereochemistry makes use of the Diels-Alder reaction of **3** with 2-methoxybutadiene[10] **6**. While no addition occurred performing the reaction at high temperatures and pressure, **7** can easily be obtained when using a 5 M solution of $LiClO_4$ in diethylether as solvent.[11] Unfortunately, the once established *cis* stereochemistry could not be preserved in our first synthetic approach to **2**. Nevertheless, our early efforts resulted in a short five-step sequence for the construction of (-)-methyl jasmonate **1** (Scheme 2).

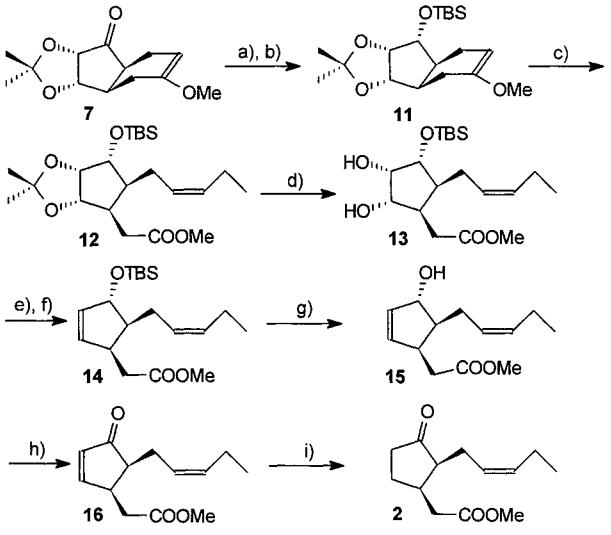
Ozonolysis of **7** followed by immediate Wittig reaction of the resulting aldehyde with *n*-propylidenetriphenylphosphorane (after exchange of solvent) gave compound **8** with *trans* stereochemistry of the side chains.[12] The 1,3-dioxolan moiety could be removed by reduction with freshly prepared aluminum amalgam.[3a] Dehydration of the resulting



Scheme 2

a) Et_2O (5 M $LiClO_4$), rt, 1 d; 84 %. b) O_3, CH_2Cl_2, -78 °C, 10 min; then PPh_3 (2 equiv), -78 °C to rt, 3 h; *n*-propylidenetriphenylphosphorane (1 equiv), THF, -78 °C to rt, 3 h; 19 %. c) Al/Hg (excess), THF/H_2O (8:1), rt, 4 d; 77 %. d) MsCl (1.5 equiv), NEt_3 (3 equiv), CH_2Cl_2, rt, 10 h; 58 %. e) $[(Ph_3P)CuH]_6$ (0.35 equiv), H_2O (3 equiv, degassed), C_6H_6, rt, 2 h; 79 %.

β-hydroxy-ketone **9** under standard conditions furnished (-)-4,5-didehydro methyl jasmonate **10**. After selective reduction of the conjugated double bond with triphenylphosphane copper(I) hydride hexamer (Stryker reagent)[13] **1** could be isolated in a total yield of 6 % from **3**.[14]



Scheme 3

a) $NaBH_4$ (1.5 equiv), EtOH, -10 °C, 45 min; 88 %. b) TBSOTf (1.5 equiv), 2,6-lutidine (2 equiv), CH_2Cl_2, rt, 15 min; 91 %. c) O_3, CH_2Cl_2, -78 °C, 10 min; then PPh_3 (2 equiv), -78 °C to rt, 3 h; *n*-propylidene-triphenylphosphorane (1 equiv), THF, -78 °C to rt, 3 h; 67 %.
d) $FeCl_3 \cdot 6H_2O$ (cat.), SiO_2, $CHCl_3$, rt, 10 h; 87 %.
e) Pentafluorophenylchlorothionoformiate (2 equiv), py (7.5 equiv), DMAP (cat.), C_6H_6, rt, 10 h; 81 %. f) 1,3-Dimethyl-2-phenyl-1,3-diazaphospholidine (3 equiv), THF, 60 °C, 4 d; 89 %. g) TBAF•$3H_2O$ (2 equiv), THF, rt, 1 h; 75 %. h) Dess-Martin periodinane[19], CH_2Cl_2, rt, 5 h; 73 %. i) $[(Ph_3P)CuH]_6$ (0.35 equiv), H_2O (3 equiv, degassed), C_6H_6, rt, 2 h; 91 %.

(+)-Methyl epijasmonate **2** became available through a modification of the original procedure (Scheme 3). Epimerisation was avoided by transforming the carbonyl group of compound **7** into the TBS-ether **11** by diastereoselective reduction and protection of the resulting alcohol.

As a result ozonolysis and Wittig reaction now furnished **12** with *cis* stereochemistry regarding the jasmonate side chains.[15] The removal of the 1,3-dioxolan moiety was initiated by ketal cleavage with $FeCl_3 \cdot 6H_2O$ on silica gel.[16] Deoxygenation of the resulting 1,2-diol **13** was best performed by Corey-Winter reaction of the cyclic thiocarbonate of **13** with 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine.[17] Removal of the silyl protecting group from **14** furnished (+)-4,5-didehydro methyl cucurbate **15**.[18] A lot of reagents were tested for the crucial oxidation to (+)-4,5-didehydro methyl epijasmonate **16**. The method of choice turned out to be the Dess-Martin protocol[19] which occurred without any detectable isomerisation of **16**.[20] Selective reduction of the conjugated double bond with the Stryker reagent[13] produced **2** with 80 % *cis* selectivity. The observed epimerisation is clearly a result of chromatography, not of the reaction procedure.

The depicted reaction sequence results in a global transfer of chirality from one half of the five-membered ring to the other. (+)-Methyl epijasmonate **2** was produced by this method in an overall yield of 14 % from **3**.[21]

This approach not only gives rise to the natural compounds **1** and **2**, it also produces some unnatural jasmonate and cucurbate derivatives that could be interesting candidates for structure-activity relationships. The Wittig step and the α,β-unsaturated ketones **8** and **16** offer synthetic flexibility and should allow the synthesis of a variety of jasmonate related substances by modification of reagents. Furthermore, the enantiomers of the natural jasmonates **1** and **2** (and of all other intermediates) should be available by simply using *ent*-**3** as starting material.

In summary, we have developed an efficient and flexible access to jasmonoids making use of the chiral building block **3** that can be prepared easily from tartaric acid by phosphorus ylide chemistry.

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18. Analytical data for **15**: $[\alpha]_D$ = +123 (c = 0.94, $CHCl_3$). IR (film): 3400 (br), 3050 (w), 3000 (m), 2960 (s), 1740 (s), 1430 (m), 1260 (s). ^1H NMR (C_6D_6, 400 MHz): δ = 5.88 (m, 1H), 5.66 (m, 1H), 5.38-5.32 (m, 2H), 4.30 (m, 1H), 3.31 (s, 3H), 3.17 (m, 1H), 2.32 (dd, $^3J_{1H,H}$ = 15 Hz, $^3J_{2H,H}$ = 6 Hz, 1H), 2.13 (m, 1H), 1.99-1.86 (m, 5H), 1.34 (s, 1H), 0.88 (t, $^3J_{H,H}$ = 7 Hz, 3H). ^{13}C NMR (C_6D_6, 100 MHz): δ = 172.67, 136.61, 134.98, 132.92, 128.59, 81.61, 51.05, 50.99, 42.86, 35.28, 26.38, 20.99, 14.27. MS (EI): 224 (M^+, 8), 206 (M^+-H_2O, 25), 167 (15), 154 (30), 117 (30), 95 (100), 79 (35). $C_{13}H_{20}O_3$ (224.30); calcd.: C 69.61, H 8.99; found: C 69.20, H 8.73.

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20. Analytical data for **16**: $[\alpha]_D$ = +91 (c = 0.85, $CHCl_3$). IR (film): 3000 (m), 2960 (s), 1740 (s), 1710 (s), 1590 (w), 1430 (m). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.68 (dd, $^3J_{1H,H}$ = 6 Hz, $^3J_{2H,H}$ = 2 Hz, 1H), 6.19 (dd, $^3J_{1H,H}$ = 6 Hz, $^3J_{2H,H}$ = 1 Hz, 1H), 5.41 (m, 1H), 5.30 (m, 1H), 3.68 (s, 3H), 3.45 (m, 1H), 2.73 (dd, $^3J_{1H,H}$ = 16 Hz, $^3J_{2H,H}$ = 6 Hz, 1H), 2.56-2.46 (m, 2H), 2.21-1.99 (m, 4H), 0.94 (t, $^3J_{H,H}$ = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 210.02, 172.33, 165.87, 133.66, 133.18, 126.16, 51.86, 48.34, 40.42, 34.43, 24.40, 20.78, 13.84. MS (EI): 222 (M^+, 80), 193 (25), 191 (18), 154 (100), 133 (25), 95 (75). $C_{13}H_{18}O_3$ (222.28); calcd.: C 70.24, H 8.16; found: C 69.85, H 8.23.

21. Optical rotation, ^{13}C NMR and ^1H NMR data of compound **2** were identical with those reported in lit. 4i.