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A concise synthesis of methyl dihydrojasmonate and methyl (5-methylidene-4-oxocyclopent-2-en-1-yl)acetate from D-glucose

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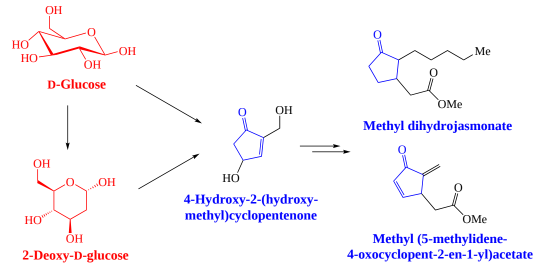
Methyl dihydrojasmonate and methyl (5-methylidene-4-oxocyclopent-2-en-1-yl)acetate were synthesized from 4-hydroxy-2-(hydroxymethyl)cyclopentenone, which, in turn, was obtained from D-glucose. The conditions for the key step, the Johnson–Claisen rearrangement, were optimized to get the maximum yield of the intermediate methyl 2-[2-methylene-3-oxo-5-(triisopropylsilyloxy)-cyclopentyl]acetate.



Keywords: fragrance, D-glucose, hedione, methyl dihydrojasmonate, cyclopentadienone, Johnson–Claisen rearrangement.

Methyl dihydrojasmonate **1**, also known as Hedione® or kharismal, has sweet-floral, jasmine-like and fruity odour being widely used in the fragrance industry.[1–3] Compound **1** has been also reported to present naturally in *Rosa damascene*, *Nyctanthes arbortristis*, *Jasminum grandiflorum* and tea.[4,5] Compound **1** has been reported to reduce subjective vicarious stress and can modulate human response to acute psychosocial stress by targeting the hypothalamus *via* binding to the VN1R1 receptor, which is expressed on the human nasal mucosa.[6,7] It was first synthesized by Demole followed by being used as an alternative to the natural product methyl jasmonate **2** in the perfumery industry (Figure 1).[8,9] It has been estimated that the worldwide consumption of **1** is more than 1000 metric tons every year.[10]

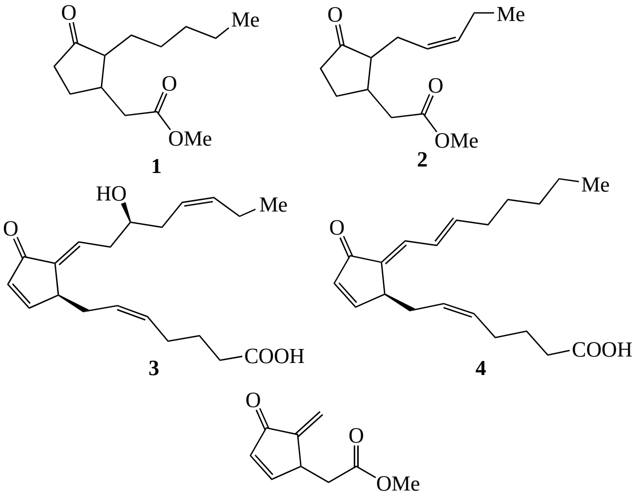


Figure 1 Structures of methyl dihydrojasmonate **1**, methyl jasmonate **2**, Δ^{12}-PGJ$_3$ **3**, 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ **4** and methyl (5-methylidene-4-oxo-cyclopent-2-en-1-yl)acetate **5**.

Cross-conjugated cyclopentadienones, for example Δ^{12}-PGJ$_3$ **3** and 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ **4** (see Figure 1), showed promising anticancer, antiviral and anti-inflammatory activity due to the presence of a special cyclic fragment containing double bond cross-coupled with a keto group.[11–13] Methyl (5-methylidene-4-oxocyclopent-2-en-1-yl)acetate **5** contains similar pharmacologically important cyclic fragment of such cross-conjugated cyclopentadienone. Compound **5** also showed anticancer activity against A549 and MCF7 cell lines.[14] Cyclopentadienone **5** may be used as a building block for the synthesis of wide range of pharmacologically important cyclopentenone prostaglandins and marine prostanoids.[15,16]

The synthesis of methyl dihydrojasmonate **1** has been reported from commercially available starting materials such as 2-cyclopenten-1-one, methyl acetoacetate, 2-pentyl-2-cyclopenten-1-one, sorbyl alcohol, *etc*.[17–25] Similarly, the synthesis of **5** from Corey lactone diol has been described.[26,27] These starting materials are mainly obtained from fossil fuels and petroleum-based resources.[28–30] The utilization of these resources leads to the release of greenhouse gases, resulting in significant environmental pollution. Therefore, it would be certainly useful to develop novel route for producing fragrances including **1**, **2** and other pharmacologically important molecules including **5**, that do not rely on fossil resources. The use of degraded biomass products is the safe and reliable alternative for over consumption of fossil resources. In our previous work, 4-hydroxy-2-(hydroxymethyl)cyclopentenone **9** was obtained from D-glucose **6** *via* the synthesis of D-glucal **7** or 2-deoxy-D-glucose **8** using catalyst-free hydrothermal reaction (Figure 2).[31,32] Compound **6** can be obtained in pilot scale by homogeneous, heterogeneous, and enzymatic hydrolysis of cellulose, which is present in very high quantity in the most abundant natural resource on Earth, *i.e.* cellulosic biomass.[33–35] In this work, compounds **1** and **5** were synthesized from precursor **9** which is one of the important small molecules obtained from cellulosic biomass.

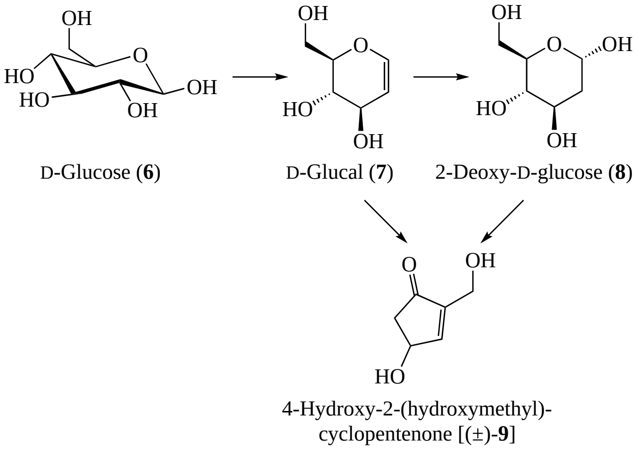
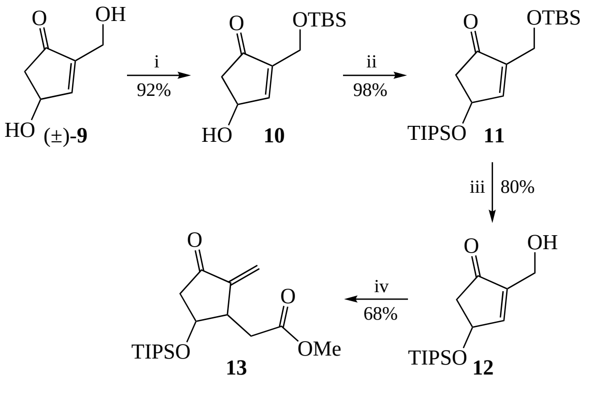


Figure 2 Conversion from D-glucose or 2-deoxy-D-glucose to 4-hydroxy-2-(hydroxymethyl)cyclopentenone.[31,32]

D-Glucose **6** was converted into tri-*O*-acetyl-D-glucal in one pot followed by removal of the acetyl group to obtain **7**. 4-Hydroxy-2-(hydroxymethyl)cyclopentenone **9** was then prepared by hydrothermal treatment of **7** at 120 °C for 24 h.[31] The primary hydroxy group of **9** was protected using *tert*-butyldimethylsilyl chloride (TBSCl) and triethylamine to provide **10** (Scheme 1). Consequently, the secondary hydroxy group was protected by treatment with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) and 2,6-lutidine to give **11**. Compound **12** was obtained by the regioselective desilylation of TBS in **11** under mild conditions using scandium(III) triflate as a catalyst (see Scheme 1).[36]

The Johnson–Claisen rearrangement reaction was employed to investigate the conversion of compound **12** to **13**.[37] The reaction conditions were optimized as shown in Table 1. In entry 1, the reaction was carried out at 150 °C in the presence of a minimum equivalence ratio of trimethyl orthoacetate and propionic acid. Under these conditions, a small amount of trimethyl orthoacetate was boiled and evaporated immediately, the reaction did not proceed at all, and reactant **12** only decomposed. In the next attempts, trimethyl orthoacetate was used in excess to act as the reactant and as the solvent. The isolated yield of methyl 2-[2-methylene-3-oxo-5-(triisopropylsilyloxy)cyclopentyl]acetate **13** was found 5 and 15% after 4 h and 15 min, respectively (entries 2 and 3). The results indicated that compound **13** may be degraded after being formed in reaction mixture at high temperature. For confirmation, the same reaction was carried out at lower temperatures (110 °C) for longer time and at 140 °C for shorter time. The starting material was unchanged in reaction mixture after 4 h at 110 °C and only 20% of desired compound **13** was obtained after 15 min at 140 °C (entries 4 and 5). Therefore, product **13** was obtained with optimized yield (55%) after reaction temperature was maintained at 140 °C for 15 min followed by its lowering to 110 °C and stirring for 45 min (entry 6). The same yield of compound **13** was achieved when isobutyric acid was used in place of propionic acid in the same quantity (entry 7). Moreover, compound **13** was successfully obtained with a yield of 68% by replacing propionic acid with slightly weaker pivalic acid (entry 8).[38] The yield of **13** was decreased with either decrease or increase in the propotion of propionic acid in the reaction mixture (entries 9 and 10). The ^{1}H and ^{13}C NMR spectra of synthesized compound indicated that it was a diastereomeric mixture. The diastereomeric ratio of **13** (*syn*/*anti* = 57 : 43) was determined by ^{1}H NMR.[37,39]



Scheme 1 *Reagents and conditions*: i, TBSCl (1.5 equiv.), Et_3N (2 equiv.), THF, room temperature, 20 h; ii, TIPSOTf (1.2 equiv.), 2,6-lutidine (1.5 equiv.), CH_2Cl_2, 1.5 h; iii, $Sc(OTf)_3$ (5 mol%), MeCN–H_2O (24 : 1), room temperature, 6.5 h; iv, $MeC(OMe)_3$ (10 equiv.), pivalic acid (1 equiv.), 140 °C (15 min) → 110 °C (45 min).

Table 1 Optimization of the reaction conditions for the conversion of **12** to **13**.

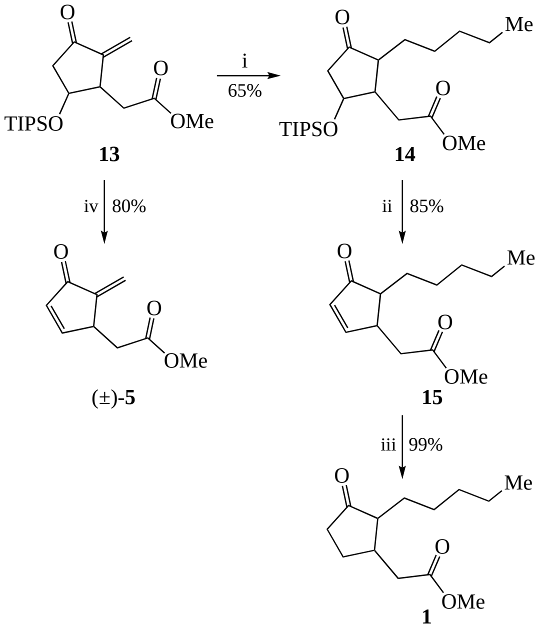
Entry	$MeC(OMe)_3$ (equiv.)	Promoter (equiv.)	Reaction conditions	Yield (%)[a]
1	1.2	$EtCO_2H$ (1)	150 °C, 4 h	decomp.
2	10	$EtCO_2H$ (1)	150 °C, 4 h	5
3	10	$EtCO_2H$ (1)	150 °C, 15 min	15
4	10	$EtCO_2H$ (1)	110 °C, 4 h	NR
5	10	$EtCO_2H$ (1)	140 °C, 15 min	20
6	10	$EtCO_2H$ (1)	140 °C (15 min) → → 110 °C (45 min)	55
7	10	Pr^iCO_2H (1)	140 °C (15 min) → → 110 °C (45 min)	55
8	10	Bu^tCO_2H (1)	140 °C (15 min) → → 110 °C (45 min)	68
9	10	$EtCO_2H$ (0.5)	140 °C (15 min) → → 110 °C (45 min)	5
10	10	$EtCO_2H$ (3)	140 °C (15 min) → → 110 °C (45 min)	10

[a] Isolated yield; decomp. means the starting material decomposed; NR is no reaction.

The diastereomeric mixture of **13** was used in the synthesis of **1** and **5**. For elimination of TIPSO group, compound **13** was treated with 1 M aqueous sulfuric acid in methanol at 90 °C for 1 h to get (±)-**5** (Scheme 2). The structure of synthesized (±)-**5** was confirmed by ^{1}H, ^{13}C NMR and HRMS spectra.[27] Methyl 2-[3-oxo-2-pentyl-5-(triisopropylsilyloxy)cyclopentyl]acetate **14** was synthesized by sonication of **13** with 1-iodobutane in ethanol/water (9 : 1) in the presence of Zn powder and cuprous iodide (see Scheme 2).[40] The introduction of the desired side chains at the C^2 and C^3 positions of **12** was accomplished in just two steps, which is a significant improvement compared to the time-consuming tedious process involved in the conventional synthesis of **1** from cyclopentanone and/or its derivatives.[17,19,21]

Compound **14** was treated with 1 M aqueous sulfuric acid in methanol at 90 °C to afford methyl 2-(4-oxo-5-pentylcyclopent-2-en-1-yl)acetate **15** (*syn*/*anti* = 66 : 34; determined by ^{1}H NMR). Compound **15** was converted to methyl dihydrojasmonate **1** upon the Pd/C-catalyzed hydrogenation of endocyclic double bond (see Scheme 2). ^{1}H and ^{13}C NMR spectra of synthesized product **1** were matched with the reported spectra and identified it as a diastereomeric mixture.[41,42] The diastereomeric ratio of synthesized compound **1** (*syn*/*anti* = 57 : 43) was determined by ^{1}H NMR.

In summary, the 4-hydroxy-2-(hydroxymethyl)cyclopentenone **9**, obtained from D-glucose, was converted to an important intermediate **13** in four steps using the Johnson–Claisen rearrangement as the key reaction. The reaction conditions for the synthesis of **13** from enone **12** were optimized



Scheme 2 *Reagents and conditions*: i, Zn powder (3 equiv. + 3 equiv.), CuI (1 equiv.), 1-iodobutane (2 equiv. + 2 equiv.), ethanol–H_2O (9 : 1), sonicate, 3 h; ii, MeOH, 1 M H_2SO_4, 90 °C, 45 min; iii, 10% Pd/C (10% w/w), H_2, MeOH, room temperature, 1 h; iv, MeOH, 1 M H_2SO_4, 90 °C, 1 h.

to get maximum yield (68%). The desired compounds Hedione® **1** and cyclopentadienone **5** were synthesized from common intermediate **13**. The overall yield of **1** and **5** from starting material **9** were found 27 and 40%, respectively.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.019.

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