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Synthetic Studies on Jasmonoids (I): Jasmone, Dihydrojasmone, and Tetrahydrojasmone

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Facile and efficient syntheses of terpenic perfumeries *cis*-jasmone, dihydrojasmone, and tetrahydrojasmone have been investigated. *Cis*-jasmone was synthesized by successive metallation followed by alkylation of acetone N,N-dimethylhydrazone with (Z)-2-penten-1-yl tosylate (or 2-pentyn-1-yl tosylate) and propylene oxide in one flask to give a ketonic alcohol, which was oxidized to the corresponding diketone, followed by base-catalyzed intramolecular aldol condensation to give a regioselective cyclization product.

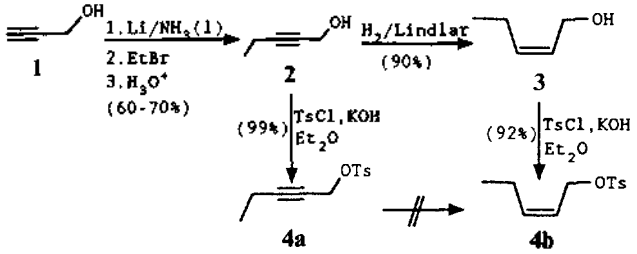
Dihydrojasmone and tetrahydrojasmone could be conveniently obtained from 2-octanone. The dimethylhydrazone of the ketone was lithiated with butyllithium and reacted with propylene oxide to give a ketonic alcohol, which was oxidized to a diketone, followed by base-catalyzed intramolecular cyclization to afford dihydrojasmone. Tetrahydrojasmone was prepared by converting the ketonic alcohol into corresponding iodoketone, followed by base-catalyzed intramolecular cycloalkylation to furnish an odoriferous product.

Introduction

Jasmine and rose oils have long been the core of the finest perfumes, and constant efforts have been made to better understand the composition of these oils. Chemical research on jasmine oil, obtained from the flowers of *Jasminium grandiflorum L.*, was started in 1899 by Verley,[1] followed by Hesse and Müller[2,3] who identified half a dozen compounds. *Cis*-jasmone(**9b**), a naturally occurring derivative of cyclopentenone, is one of the essential components of jasmine oil. Because of the difficulty of its manufacture, the price is still relatively high, and studies have been continuing to find more economical procedures for the synthesis of jasmone and structurally related compounds such as dihydro- and tetrahydro- analogs that are useful in perfumery. We now wish to describe a new and efficient synthesis of *cis*-jasmone (**9b**), dihydrojasmone(**14**), and tetrahydrojasmone(**16**) using chemicals of reasonable price.

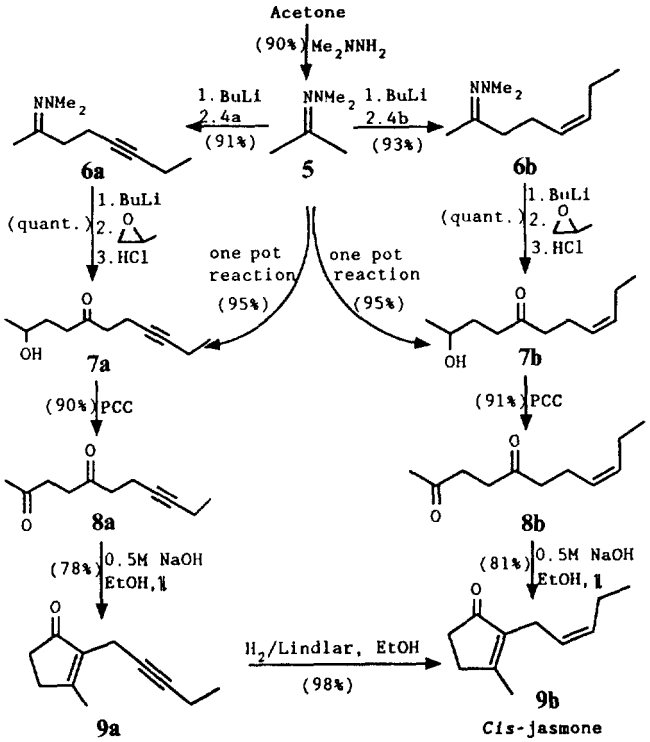
Results and Discussion

Several syntheses of *cis*-jasmone(**9b**)[4-9] have been published. In this investigation, we developed a new synthesis of **9b** by means of successive dialkylation technic of acetone N,N-dimethylhydrazone. The starting materials **4a** and **4b** were prepared from propargyl alcohol(**1**) by the procedure as shown in Scheme 1. The propynol 1 was ethylated without protection of hydroxy group, but by treating it with lithium amide followed by reacting the resulted dianion[10] with ethyl bromide to give 2-pentyn-1-ol(**2**). The propargylic alcohol 2 was hydrogenated in the presence of Lindlar catalyst to (Z)-2-penten-1-ol(**3**), which was then tosylated to **4b**. The tosylate **4a** was obtained by treating 2 with tosyl chloride, but it could not be converted efficiently to **4b** by hydrogenation even in the presence of Lindlar catalyst, probably because the hydrogenation was accompanied by reductive cleavage of the tosyl ester moiety.

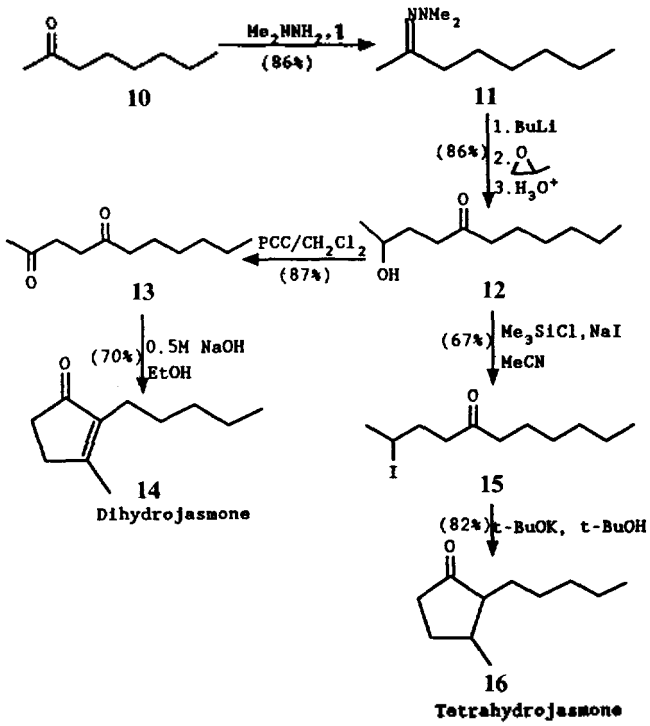


Scheme 1.

An effective synthesis of *cis*-jasmone(**9b**) was carried out by the procedure as shown in Scheme 2. Acetone N,N-dime-



Scheme 2.



Scheme 3.

thylhydrazone(**5**)[11] was monoalkylated[12,13] by α-lithiating it with n-butyllithium, followed by reacting with tosylate **4** to give monoalkylation products **6** in good yields. In this reaction, though relatively unstable, **4b** was more easily alkylated than **4a** that was stable and could be easily stocked. The monoalkylated dimethylhydrazones **6** were again alkylated with propylene oxide in the same way to obtain ketonic alcohols **7**.

Acetone dimethylhydrazone(**5**) was completely metallated by n-butyllithium at −78℃ within 1-2 h. In the first alkylation step, polyalkylation products were not be detected by NMR and TLC analysis, which has the advantage of monoalkylation as compared to di- and polyalkylation of the corresponding enolates. In the metallation of **6** with n-butyllithium at −78℃, **6a** was easier (40 min) than **6b** (150 min) under the same condition. The completion of metallation could be detected by the formation of yellowish, milky suspension. Metallation of **6** gave kinetically controlled anion very selectively at the less alkylated carbon,[14] and no position isomeric and polyalkylation products could be detected. This is why dimethylhydrazones are amenable to a broad range of valuable synthetic operation.[15,16]

However, the preparation of **7** by dialkylation[12,13] of **5** could also be directly carried out by successive alkylation[12] of **5** in one flask: After the addition of n-BuLi to a solution of **5** at −78℃, 1 equiv of **4** was added and the mixture was stirred for 6 h at room temperature. After cooling the mixture to −78℃ again, n-BuLi was added, followed by addition of excess propylene oxide to give a dialkylation product **7**.

The ketonic alcohols **7** were oxidized with PCC to give diketones **8** in good yields. The *cis*-jasmone(**9b**) could be obtained by the base-catalyzed intramolecular aldol condensation[4,7,12] of **8b**. It can also be obtained by base-catalyzed condensation of **8a** to **9a** followed by Lindlar catalyzed hydrogenation.

Dihydrojasmone(**14**) and tetrahydrojasmone(**16**) are closely related to jasmone both in structure and in odor. Several syntheses of **14**[9,17-21] and **16**[21] have been reported by some workers. Herein, we wish to report new and facile syntheses of **14** and **16** by taking advantage of a cheap starting material, 2-octanone(**10**), as is shown in Scheme 3. Heating at reflux a neat mixture of **10** and dimethylhydrazine gave the corresponding dimethylhydrazone **11** in good yield. Kinetically controlled α-metallation of **11** by BuLi, followed by the reaction of the resulted anion with propylene oxide afforded 2-hydroxyundecan-5-one(**12**) in reasonable yield. Oxidation of the ketonic alcohol **12** with PCC to 2,5-undecanedione(**13**), and base catalyzed intramolecular aldol condensation of **13** resulted in the formation of an odoriferous cyclic ketone, dihydrojasmone(**14**). Treatment of a solution of **12** and NaI in acetonitrile with trimethylsilyl chloride(TMSCl)[22] provided the corresponding iodide **15**, which was then converted by base catalyzed intramolecular alkylation into an odoriferous cyclic compound, tetrahydrojasmone(**16**). For the conversion of **12** into **16**, we were planning at first the conversion of **12** into the corresponding tosylate, followed by base catalyzed cyclization of the tosylate to give **16**. However, it was unable to prepare the tosylate by treating **12** with tosyl chloride in pyridine, or with tosyl chloride and potassium hydroxide in ether.

In summary, the results described in the present paper indicate that the perfumery compounds *cis*-jasmone and the analogs could be easily synthesized by one-pot successive lithiation followed by alkylation of acetone N,N-dimethylhydrazone with an alkyl tosylate and then with propylene oxide to give a dialkylated product, 4-hydroxyketone, which was then oxidized to a 1,4-diketone, followed by base-catalyzed

intramolecular aldol condensation to give a 2-cyclopentenone. We, however, note that dihydrojasmone was synthesized conveniently by the regioselective alkylation of kinetically controlled anion of 2-octanone N,N-dimethylhydrazone to give a 4-hydroxyketone, which then converted *via* two steps into a 2-cyclopentenone by the same procedure as that of *cis*-jasmone. It was also noticed that tetrahydrojasmone could be synthesized by base-catalyzed intramolecular cycloalkylation of an 4-iodoketone to afford a cyclopentanone.

Experimental Section

General. All non-aqueous reactions were conducted with the unusual precautions for rigorous exclusion of air and moisture. Diethyl ether and tetrahydrofuran were purified by refluxing for hours with sodium ketyl under nitrogen, followed by distilling prior to use. Dichloromethane was dried by distilling over calcium hydride. Flash chromatography was carried out using silica gel 60(E.M. Merck, 230-400 mesh ASTM). Proton NMR spectra were recorded on a Bruker AC-80 FT NMR spectrometer to an internal standard of tetramethylsilane. Infrared spectra were obtained on a Perkin-Elmer Model 782 spectrometer. Chemicals were purified, when necessary, according to the reported procedure.[23]

2-Pentyn-1-ol(2). By use of the literature procedure,[10] 1 mole of lithium amide was prepared by dissolving metallic lithium(7.0 g, 1.0 mol), in the presence of catalytic amount (0.1 g) of ferric nitrate, in 700 m*l* of liquid ammonia cooled in a bath of dry-ice/acetone. To the vigorously stirred suspension of lithium amide(1.0 mol) in liquid ammonia, was added with stirring freshly distilled **1**(28 g, 500 mmol) over a period of 20 min. To this mixture, was added ethyl bromide (55 g, 500 mmol) dropwise with stirring, during 30 min under nitrogen. Stirring was continued for 3 h, and the ammonia was allowed to evaporate. To the yellowish residue was added ice-water(200 m*l*), extracted several times with ether, dried the combined organic layer over anhyd. $MgSO_4$ and evaporated the solvent. The crude product was purified by distillation to afford a pentynol **2**, bp. 73-75℃/35 torr(lit.[24] 62℃/29 torr), in 65-70% yield. ^{1}H-NMR($CDCl_3$) δ 4.24(t, J=2 Hz, 2H, CH_2O), 2.40-2.06(q, 2H, CH_2CH_3), 2.15(s, 1H, OH), 1.14(t, J=7 Hz, 3H, CH_3). IR(neat, NaCl disc) 3330(OH), 2975, 2940, 2920, 2875, 2290(w) and 2225(s) (C≡C), 1450, 1430, 1375, 1140, 1010 cm^{-1}.

(Z)-2-Penten-1-ol(3). A solution of **2**(17 g, 200 mmol) in hexane(200 m*l*) was hydrogenated for 7 h at room temperature in the presence of Lindlar catalyst(800 mg). The mixture was filtered, evaporated the solvent, and the residue was distilled to give a pentenol **3**, bp. 61℃/35 torr(lit.[24] 50℃/15 torr) in the yield of 90%. ^{1}H-NMR($CDCl_3$) δ 5.75-5.42(m, 2H, CH=CH), 4.11(d, 2H, CH_2O), 2.10(m, 2H, CH_2CH_3), 1.67 (s, 1H, OH), 1.00(t, 3H, CH_3). IR(neat, NaCl disc) 3330(OH), 3020(CH=CH), 2970, 2935, 2875, 1655(C=C), 1460, 1040, 1000 cm^{-1}.

2-Pentyn-1-yl p-Toluenesulfonate(4a). A mixture of **2**(8.4 g, 100 mmol), p-TsCl(19.1 g, 100 mmol) and diethyl ether(200 m*l*) was stirred at room temperature until the p-TsCl had passed into solution. To the stirred solution, was added powdered KOH(22 g) in small portions and stirred for 30 min. The reaction mixture was poured with stirring into ice-water(300 m*l*), separated the organic layer, and the aqueous layer was extracted three times with ether. The combined etherial solution was dried over anhyd. $MgSO_4$, evaporated the solvent at a reduced pressure, and chromatographed on a silica gel column using methylene chloride to provide a yellowish oil of **4a** in almost quantitative yield. But, it could not be purified by distillation because of decomposition during the heating. ^{1}H-NMR($CDCl_3$) δ 7.85-7.27(m, 4H, ArH), 4.67(t, J=2 Hz, 2H, CH_2O), 2.44(s, 3H, $ArCH_3$), 2.04(q, 2H, CH_2CH_3), 1.01(t, J=7 Hz, 3H, CH_3). IR(neat, NaCl disc) 3050, 2975, 2935, 2875, 2315(w) and 2240(s)(C≡C), 1600, 1450, 1360, and 1180(S=O), 1090, 835, 815 cm^{-1}.

(Z)-2-Penten-1-yl p-Toluenesulfonate(4b). The tosylate **4b** also was prepared by the same procedure as in the preparation of **4a** in 92% yield. ^{1}H-NMR($CDCl_3$) δ 7.85-7.27 'm, 4H, ArH), 5.80-5.20(m, 2H, CH=CH), 4.60(dd, 2H, CH_2 O), 2.44(s, 3H, $ArCH_3$), 2.00(dq, 2H, CH_2CH_3), 0.93(t, J=7 Hz, 3H, CH_3). IR(neat, NaCl disc) 3060, 2975, 2935, 2875, 1660, 1495, 1460, 1360, 1275, 1190, 1100, 720 cm^{-1}.

Acetone Dimethylhydrazone(5). This hydrazone was prepared by an adaptation of literature procedure[25] which involves reaction at reflux temperature of acetone and N,N-dimethylhydrazine for 24 h, followed by work-up and distillation at 93-95℃(lit.[12] 95℃), to give **5** in 90-95% yield.

5-Octyn-2-one Dimethylhydrazone(6a). To a solution of **5**(1.0 g, 10 mmol) in THF(30 m*l*), cooled to −78℃, was added with stirring n-BuLi(10 mmol; 1.0 m*l*, 10 M in hexane) using a syringe under nitrogen. After stirring for 30 min was added dropwise **4a**(2.4 g, 10 mmol), and stirring was continued for 6 h at room temperature. To this mixture was added water(10 m*l*), removed the solvent *in vacuo*, extracted three times with methylene chloride. The combined organic layer was dried over anhyd. $MgSO_4$, and evaporated the solvent. The crude product was purified by chromatography (basic alumina/n-hexane) to give a yellowish liquid product in 91% yield. ^{1}H-NMR($CDCl_3$) δ 2.47-1.96(m, 6H, $3CH_2$), 2.43(s, 6H, NMe_2), 1.96(s, 3H, CH_3-C), 1.09(t, J=7 Hz, 3H, $CHCH_3$), IR(neat, NaCl disc) 2980, 2950, 2860, 2820, 2775 (NMe_2), 1640(C=N), 1470-1440, 1360, 1320, 1155, 1050, 1020, 990, 960 cm^{-1}.

(Z)-5-Octen-2-one Dimethylhydrazone(6b). This compound could also be prepared by the same procedure as that of **6a**. Metallation of **6**(1.0 g, 10 mmol) with n-BuLi(10 mmol), followed by alkylation with the tosylate **4b**(2.42 g, 10 mmol) afforded 93% yield of yellowish oil **6b**. ^{1}H-NMR ($CDCl_3$) δ 5.60-5.10(m, 2H, CH=CH), 2.42(s, 6H, NMe_2), 2.42-1.87(m, 6H, $3CH_2$), 1.93(s, 3H, CH_3-C), 0.97(t, J=7 Hz, 3H, CH_2CH_3). IR(neat, NaCl disc) 3020, 2960, 2855, 2820, 2775 (NMe_2), 1640(C=N), 1465, 1450, 1360, 1020, 965, 720(*cis*-olefin) cm^{-1}.

2-Hydroxy-8-undecyn-5-one(7a).[26] To a solution of **6a**(1.66 g, 10 mmol) in THF(30 m*l*), cooled to −78℃, was added carefully n-BuLi(10 mmol) through a syringe under nitrogen. After stirring for 40 min, propylene oxide(1.2 g, 20 mmol) was added and stirred for 8 h, allowing the mixture to warm to room temperature. To this reaction mixture, HCl(2 N, 30 m*l*) was added, removed the solvent, extracted with methylene chloride, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude product, which was chromatographed on a silica gel column using methylene chloride to give a yellowish oil of **7a** in almost quantitative yield. ^{1}H-NMR($CDCl_3$) δ 3.89-3.66(m, 1H, OCH-

CH_3), 2.62-1.75(m, 11H, $5CH_2$ and OH), 1.19(d, J=6 Hz, 3H, $OCHCH_3$), 1.08(t, J=7 Hz, 3H, $CHCH_3$), ^{1}H-NMR($CDCl_3+D_2O$) δ 3.74(sext, 2H, CH-O), 2.66-1.66(m, 10H, $5CH_2$), 1.19(d, J=6 Hz, 3H, $OCHCH_3$), 1.08(t, J=7 Hz, 3H, CH_2CH_3). IR(neat, NaCl disc) 3400, 2990, 2940, 2890, 1720, 1460, 1380, 1325, 1080, 935 cm^{-1}. MS(*m/z*) 182(M^+), 164(M^+-H_2O).

One-Pot Conversion of **5** *into* **7a**. The hydroxyketone **7a** could also be prepared directly by successive dialkylation of **5** in one flask: To a THF solution of **5**(1.0 g 10 mmol) was added n-BuLi(10 mmol) at −78℃ under nitrogen, stirred for 30 min, added **4a**(2.40 g, 10 mmol), and stirred for 6 h at room temperature. The mixture was cooled to −78℃, added n-BuLi(10 mmol), stirred for 40 min, added propylene oxide (1.2 g, 20 mmol), and stirred for 6 h at room temperature under nitrogen. The dialkylated dimethylhydrazone formed was hydrolyzed, without separation, with HCl(2 N, 30 m*l*), removed the solvent, extracted with dichloromethane, dried over anhyd. $MgSO_4$. After evaporated the solvent, the crude product was purified chromatography(SiO_2/CH_2Cl_2) to provide a yellowish oil of **7a** in 90-95% yield.

(Z)-2-Hydroxy-8-undecen-5-one(7b).[27] To a solution of **6b**(1.68 g, 10 mmol) was added n-BuLi(10 mmol) at −78℃ under nitrogen, stirred for 150 min, added propylene oxide (1.2 g, 20 mmol), and stirred for 6 h, allowing the mixture to warm to room temperature. The monoalkylated dimethylhydrazone was hydrolyzed, without separation, with HCl(2 N, 30 m*l*), extracted with dichloromethane, dried over anhyd. $MgSO_4$, and removed the solvent. The crude product was purified by chromatography(silica gel/dichloromethane) to give a yellowish oil of **7b** almost quantitatively. ^{1}H-NMR($CDCl_3$) δ 5.60-5.10(m, 2H, CH=CH), 3.76(sext, 1H, CH-O), 2.71-1.60 (m, 11H, $5CH_2$ and OH), 1.18(d, J=6 Hz, 3H, $CHCH_3$), 0.95(t, J=7 Hz, 3H, CH_2CH_3). ^{1}H-NMR($CDCl_3+D_2O$) δ 5.57-5.08(m, 2H, CH=CH), 3.75(sext, 1H, CH-O), 2.63-1.62(m, 10H, $5CH_2$), 1.19(d, J=6 Hz, 3H, $CHCH_3$), 0.95(t, J=7 Hz, 3H, CH_2CH_3). IR(neat, NaCl disc) 3450, 3020, 2975, 2940, 2880, 1715, 1460, 1410, 1380, 1130, 1075 cm^{-1}. MS(*m/z*) 184(M^+), 166(M^+-H_2O).

One-Pot Conversion of **5** *into* **7b**. The hydroxyketone **7b** could also be synthesized by successive dialkylation of **5** in one flask: To a solution of **5**(1.0 g, 10 mmol) was added n-BuLi(10 mmol) at −78℃ under nitrogen, stirred for 30 min, added **4b**(2.42 g, 10 mmol), and stirred for 6 h at room temperature. The mixture was cooled again to −78℃, added n-BuLi(10 mmol), stirred for 150 min, added propylene oxide (1.2 g, 20 mmol), and stirred for 6 h, allowing the mixture to warm to room temperature. The reaction mixture was treated with HCl(2 N, 30 m*l*), removed the solvent, extracted with dichloromethane, dried(anhyd. $MgSO_4$), and removed the solvent *in vacuo*. The crude product was purified by chromatography(SiO_2/CH_2Cl_2) to furnish a yellowish oil of **7b** in 90-96% yield.

8-Undecyne-2,5-dione(8a). A mixture of pyridinium chlorochromate(PCC; 3.2 g, 15 mmol), dichloromethane(20 m*l*), and **7a**(1.82 g, 10 mmol) was stirred for 3 h. To this reaction mixture was added dry ether(30 m*l*), stirred and decanted the supernatant from the black gum. The insoluble black residue was washed thoroughly with anhydrous ether. The combined organic solution was passed through a short silica gel column using ether as an eluent, and evaporated the solvent. The crude product was purified by chromatography(SiO_2/CH_2Cl_2) to afford a yellowish oil **8a** in 90% yield. The spectral data were almost consistent with those reported in the literature.[26] ^{1}H-NMR($CDCl_3$) δ 2.70(s, 4H, $O=CCH_2CH_2C=O$), 2.73-2.00(m, 6H, $3CH_2$), 2.18(s, 3H, $CH_3C=O$), 1.09(t, J=7 Hz, 3H, CH_2CH_3). IR(neat, NaCl disc) 2975, 2930, 2915, 2875, 1715(C=O), 1405, 1365, 1175, 1095 cm^{-1}. MS(*m/z*) 180 (M^+).

(Z)-8-Undecene-2,5-dione(8b). The hydroxyketone **7b** (1.84 g, 10 mmol) was oxidized with PCC(3.2 g, 15 mmol) in dichloromethane(20 m*l*) by the same procedure as that of **8a**, to give yellowish oil of **8b** in 91% yield. The NMR, IR, and MS spectral data were well agreed with those on the literature.[27-29]

3-Methyl-2-(2-pentynyl)-2-cyclopentenone(9a). To a mixture of EtOH(25 m*l*) and aq. NaOH(0.5 N, 25 m*l*) was added the diketone **8a**(1.8 g, 10 mmol), followed by refluxing for 7 h. The reaction mixture was extracted with diethyl ether, washed with brine, dried over anhyd. $MgSO_4$, and removed the solvent at reduced pressure. The crude product was chromatographed(silica gel/methylene chloride) to provide a cyclopentenone **9a** in the yield of 78%. The spectral data were almost consistent with those reported in the literature.[7,26,30]

***Cis*-Jasmone(9b).** To a mixture of EtOH(25 m*l*) and aq. NaOH(25 m*l*) was added the diketone **8b**(1.82 g, 10 mmol), refluxed for 7 h, and cooled to room temperature. After removed the ethanol, the reaction mixture was extracted with ether, washed with brine, dried(anhyd. $MgSO_4$), and evaporated the solvent *in vacuo*. The crude product was purified by chromatography(SiO_2/CH_2Cl_2) to furnish *cis*-jasmone as a yellowish oil in 81% yield. The NMR, IR, and MS spectral data were consistent with those reported in the literature.[28,31,32]

Cis-Jasmone(**9b**) could also be obtained by the reduction of **9a**: A solution of **9a**(1.62 g, 10 mmol) in ethanol was hydrogenated in the presence of Lindlar catalyst(40 mg) for 1 h at room temperature. The mixture was filtered, evaported the solvent, followed by distillation to give **9b** in 98% yield.

2-Octanone Dimethylhydrazone(11). A mixture of 2-octanone(5.9 g, 46 mmol) and N,N-dimethylhydrazine(3.6 g, 60 mmol) was heated at reflux with stirring for 24 h. The reaction mixture was cooled to room temperature, water was added, extracted several times with ether, and the combined organic layer was dried over anhyd. Na_2SO_4, followed by evaporation of the solvent carefully at a reduced pressure. The crude product was purified by fractional distillation using a 20 cm Vigreux column to give 6.8 g(86%) of 2-octanone dimethylhydrazone(80℃/70 torr). ^{1}H-NMR($CDCl_3$) δ 2.40(s, 6H, NMe_2), 2.17(t, J=7 Hz, 2H, $N=C-CH_2$), 1.90(s, 3H, $CH_3C=N$), 1.58-1.10(m, 8H, $4CH_2$), 0.90(s, J=6 Hz, 3H, CH_2CH_3). IR(neat, NaCl disc) 2775(NMe_2), 1640(C=N), 1150, 1020, 970 cm^{-1}.

2-Hydroxyundecan-5-one(12). In a 50-m*l* three-necked round-bottomed flask was dissolved **11**(1.7 g, 10 mmol) in THF(30 m*l*). To this mixture, cooled to −78℃, was added with stirring BuLi(10 mmol; 4 m*l*, 2.5 M in hexane) using a syringe under nitrogen. To this mixture stirred for 3 h at −78℃, propylene oxide(1.2 g, 20 mmol) was added using a syringe, and the mixture was allowed to warm to room temperature with stirring for 12 h under nitrogen. The alkylated dimethylhydrazone produced was hydrolyzed *in situ* with HCl(2 N, 30 m*l*), removed the solvent at a reduced

pressure, extracted with dichloromethane, dried(anhyd. Na_2SO_4), and evaporated the solvent. The crude product was purified by chromatography(SiO_2/CH_2Cl_2) to furnish a yellowish oil of **12** in 86.0% yield. ^{1}H-NMR($CDCl_3$) δ 3.82-3.66(m, 1H, O-CH), 2.64-2.33(m, 2H, O=CCH$_2$), 1.98-1.24(m, 11H, 5 CH$_2$ and OH), 1.19(d, J=6 Hz, 3H, O-CHCH$_3$), 0.88(t, J=6 Hz, 3H, CH$_2$CH$_3$). IR(neat, NaCl disc) 3400, 2950, 2920, 2850, 1700(C=O), 1450, 1400, 1370, 1130, 930 cm^{-1}. MS(*m/z*) 186 (M^+), 168($M^+ - H_2O$), 111, 98, 83, 55.

2,5-Undecanedione(13). To a solution of the ketonic alcohol **12**(1.58 g, 8.5 mmol) in anhydrous methylene chloride (30 m*l*) was added PCC(3.2 g, 15 mmol) and stirred for 3 h. To this reaction mixture was added dry ether(2×30 m*l*), stirred, and decanted the supernatant from the black gum. The insoluble black residue was washed thoroughly with ether and the combined organic layer was passed through a short silica gel column using ether as an eluent. After evaporated the solvent, the crude product was purified by chromatography(SiO_2/CH_2Cl_2) to afford a yellowish liquid of a diketone **13** in 82% yield. ^{1}H-NMR($CDCl_3$) δ 2.66(s, 4H, O=CCH$_2$CH$_2$C=O), 2.44(t, J=7 Hz, 2H, O=CCH$_2$), 2.17 (s, 3H, CH$_3$C=O), 1.40-1.22(m, 8H, 4CH$_2$), 0.87(t, J=6 Hz, 3H, CH$_2$CH$_3$). IR(neat, NaCl disc) 2945, 2920, 2850, 1700(C=O), 1410, 1365, 1175, 1090 cm^{-1}. MS(*m/z*) 184(M^+).

Dihydrojasmone(14). To a mixture of EtOH(25 m*l*) and aq. NaOH(0.5 N, 25 m*l*) was added the diketone **13**(1.30 g, 7.0 mmol), and the mixture was refluxed for 7 h. The reaction mixture was cooled to room temperature, removed EtOH by evaporation, extracted with ether, washed with brine, dried(anhyd. Na_2SO_4), and evaporated the solvent at a reduced pressure. The crude product was purified by chromatography(SiO_2/CH_2Cl_2) to provide an odoriferous dihydrojasmone(**14**) as a yellowish oil in the yield of 55-60%. The NMR, IR and mass spectral data were consistent with those on the literature.[33-35]

2-Iodoundecan-5-one(15). In a 25-m*l* three-necked round-bottomed flask, were placed **12**(1.3 g, 7.0 mmol), NaI (1.05 g, 7.0 mmol), and acetonitrile(15 m*l*) under nitrogen. To this mixture was added slowly chlorotrimethylsilane(TMSCl; 0.76 g, 7.0 mmol) with good stirring. After stirring for 1 h at room temperature, the reaction mixture was taken with ether, washed with water, aq. sodium thiosulfate(10%, 10 m*l*) and brine successively. Evaporation of the solvent afforded a crude product which was chromatographed(SiO_2 /CH_2Cl_2) to give iodoketone **15** as a yellowish oil in 67% yield. ^{1}H-NMR($CDCl_3$) δ 4.19(q, J=7 Hz, 1H, ICH), 2.51(quint, J=7 Hz, 4H, two O=CCH$_2$), 1.93(d, J=7 Hz, 3H, ICHCH$_3$), 1.57-1.16(m, 10H, 5CH$_2$), 0.88(t, J=6 Hz, 3H, CH$_2$CH$_3$). IR (neat, NaCl disc) 2940, 2920, 2870, 1710(C=O), 1450, 1440, 1400, 1375, 1060, 720 cm^{-1}. MS(*m/z*) 296(M^+), 168($M^+ - HI$), 111, 98, 83, 55.

Tetrahydrojasmone(16). In a 100-m*l* round-bottomed flask were placed the iodoketone **15**(13.0 g, 43 mmol), t-BuOK(11.2 g, 100 mmol), t-butyl alcohol(80 m*l*), and the mixture was stirred for 12 h at room temperature. The reaction mixture was poured into cold water, extracted with ether, washed with aq. ammonium chloride solution and brine successively, and dried over anhydrous $MgSO_4$. After the solvent was removed, the crude product was chromatographed(SiO_2 /CH_2Cl_2) to furnish 6.0 g(82%) of odoriferous product, tetrahydrojasmone(**16**).[36] ^{1}H-NMR($CDCl_3$) δ 2.50(t, J=7 Hz, 2H, O=CCH$_2$), 1.70-1.55(m, 3H, CH$_2$ and O=CCHCH$_2$ in ring), 1.43-1.21(m, 9H, 4CH$_2$ in chain and CHCH$_3$ in ring), 1.10(d, J=5 Hz, 3H, CHCH$_3$), 0.88(t, J=6 Hz, 3H, CH$_2$CH$_3$). IR(neat, NaCl disc) 2950, 2920, 2880, 1695(C=O), 1400, 1380, 1085, 860 cm^{-1}. EIMS(*m/z*) 168(M^+), 126, 111, 98, 83, 55. HRMS calcd for $C_{11}H_{20}O$ 168.1514, found 168.1513.

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Novel Syntheses of Isomers of Damascenone from Ethyl 2,6,6-Trimethyl-4-oxo-2-cyclohexene-1-carboxylate

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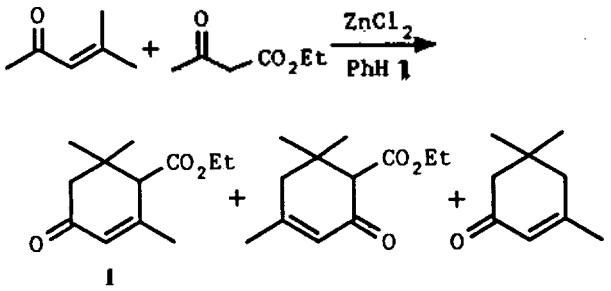
Three isomers of damascenone, odorous terpenic ketones, have been synthesized conveniently from a same starting material, ethyl 2,6,6-trimethyl-4-oxo-2-cyclohexene-1-carboxylate(**1**), which was easily available by the acid-catalyzed condensation of mesityl oxide or acetone with ethyl acetoacetate. α-Damascenone(**7**) was prepared by converting the enone ester **1** into the corresponding tosylhydrazone(**4**), followed by treating with 4 molar equiv of allyllithium. β-Damascenone(**12**) was synthesized by chemoselective reduction of **1** with sodium borohydride/cerium chloride to give corresponding allylic alcohol **8**, conversion of **8** into acetate **9**, and thermal decomposition of **9** with DBU to afford ethyl β-safranate(**10**), followed by reaction with an excess amount of allyllithium. γ-Damascenone(**15**) was obtained by dehydration of **8** with boric acid to furnish γ-safranate(**13**), followed by treatment with 2 molar equiv of allyllithium.

Introduction

β-Damascenone(**12**), a terpenic ketone first isolated from Bulgarian rose oil[1] (*Rosa damascena* Mill) and later found in the essential oils of other natural materials,[2,3] is a highly odoriferous compound important in the creation of modern fragrances. Because of its industrial importance, much effort has been devoted[1,4-16] to the synthesis of this enone as well as its structurally related isomers, α-damascenone(**7**) and γ-damascenone(**15**), which are of equal industrial interest. Existing syntheses proceed from β-cyclocitral,[1,7] ethyl β-safranate,[5] 5-acetyl-4,4-dimethylcyclohexene,[11] dimedone,[14] or from 2,2,6-trimethylcyclohexanone derivatives. However, these methods not only require starting materials which are not readily available, but also result in poor product selectivity and low total yield. In this paper we describe a full account of new and efficient syntheses of α-, β-, and γ-damascenones from a common starting material, ethyl 2,6,6-trimethyl-4-oxo-2-cyclohexene-1-carboxylate(**1**).

Results and Discussion

The enone ester **1** has been prepared by zinc chloride[17] or boron trifluoride[18] catalyzed condensation of mesityl oxide with ethyl acetoacetate or by boron trifluoride catalyzed condensation of ethyl acetoacetate with acetone.[18,19] In the preparation of **1** by the literature procedure of Surmatis *et al.*[17] (Scheme 1), we examined various catalysts such as chlorides



Scheme 1.

of antimony, cadmium, mercury, silver, tin and titanium, and formic acid and titanium dichlorodiisopropoxide, though the zinc chloride was found to be the best one.

This reaction must proceed *via* acid-catalyzed Michael addition of ethyl acetoacetate to mesityl oxide, followed by intramolecular aldol condensation of the addition product, to give a mixture product containing an enone ester **1** and the isomer. Because of lower yield and some troubles in separation of **1** from the other side products of this reaction, we tried a preparation of pure enone diester **3** by the analogous reaction using an enone ester **2**, for it could be expected to convert **3** into pure **1** by regioselective decarboethoxylation. In spite of structural advantage, the enone ester **2** did not react with ethyl acetoacetate even under various catalysts to give the anticipated enone diester **3**. Better preparation of the enone ester **1** has not been developed so far.