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Note

Enantioselective Synthesis of Both the Enantiomers of Jasmine Ketolactone and Its Epimer

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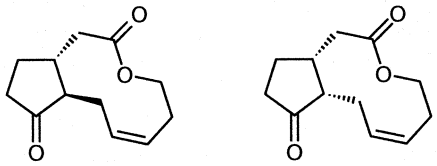
The enantioselective synthesis of jasmine ketolactone 1, which was isolated as a component of Italian jasmine oil, and its epimer 2 is described. Lactones 1 and 2 were synthesized in 5 and 4 steps, respectively, by Yamaguchi's macrolactonization method from alcohol 4.

Key words: jasmine ketolactone; *Jasminum grandiflorum* L.; macrolactonization; potato tuberization

Jasmine ketolactone **1** was isolated from *Jasminum grandiflorum* L. as a component of Italian jasmine oil by Naves in 1942,[1] and its structure was determined by Demole's group in 1964[2] as a cyclopentanone containing a ten-membered lactone ring with cis-olefin. Jasmonoids are well-known as valuable fragrance compounds, and recent reports[3] have shown their interesting activity for plant growth regulation (*e.g.* potato tuberization and eliciting phytoalexins). The progress of biological studies has made important the relationship between stereochemistry and bioactivity.[4] The need for the enantioselective synthesis of jasmonoids stemmed from these investigations.

The synthesis of **1** has been carried out by Gerlach,[5] our laboratory,[6] and Shimizu,[7] but all were for the racemate. Our laboratory has reported the synthesis of many optically active jasmonoids.[8–10] In the previous paper, we reported the enantioselective synthesis of methyl tuberonate and methyl β-D-glucopyranosyltuberonate by an efficient route from a common intermediate.[10] In this paper, we describe the synthesis of both the enantiomers of jasmine ketolactone **1** and its epimer **2** by the same strategy as that used in our previous synthesis.[10,11]

As a starting material, we chose alcohol (−)-**4**,[10] which was the intermediate for our jasmonoid syntheses, that was synthesized from commercially available enantiomerically pure dichlorolactone **3**,[8,9] the well-known intermediate for the syntheses of prostaglandins. Alkaline hydrolysis of the methyl ester of **4** (2N KOH aq.-MeOH) gave hydroxycarboxylic acid **5**, which was lactonized by Yamaguchi's method[12] (2,4,6-trichlorobenzoylchloride, Et_3N; DMAP, tol.) to give 10-membered lactone **6** as the sole product (2 steps, 72%). FABMS data [*m*/*z*: 325 $(M+H)^+$] confirmed that the 10-membered ring has been formed. The TBS ether was deprotected by 46% HF aq. in MeCN to give secondary alcohol **7** (90%), and then oxidation with the Dess-Martin reagent[13,14] in CH_2Cl_2 gave *epi*-jasmine ketolactone (+)-**2** without appreciable isomerization (88%). Finally, epimerization of **2** was carried by DBU in THF to give natural jasmine ketolactone (−)-**1** (90%, 51% from (−)-**4**), which was spectroscopically identical with that reported.[2] $[\alpha]_D^{18}$ −237 (*c* 0.80, MeOH); lit.[2] $[\alpha]_D^{20}$ −260 (*c* 3.05, MeOH). Similarly, antipodes (−)-**2** and (+)-**1** were synthesized from (+)-**4** (52% and 46% in 4 and 5 steps).



(−)-**1** (+)-**2**

Fig. 1. Jasmine Ketolactone **1** and Its Epimer **2**.

In conclusion, the first synthesis of jasmine ketolactone **1** and its epimer **2** in optically active form was achieved *via* Yamaguchi macrolactonization from common intermediate **4**. We are investigating the physiological activity of these products as a plant growth regulator, and the result will be published in due course.

Experimental

Melting point (mp) data were determined with YANACO micro-melting point apparatus. Infrared spectra were recorded with a JASCO FT/IR-230 spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ with a Bruker AC 300 NMR spectrometer, and mass spectra were recorded with a JEOL JMS-SX102/SX102 tandem mass spectrometer. Optical rotation values were recorded with a JASCO DIP-400 polarimeter, and column chromatography was performed on Merck Kieselgel 60, Art. No. 7734 or 7754.

(1R,7Z,10S,11R)-11-t-Butyldimethylsilyloxy-4-oxabicyclo[8.3.0]tridec-7-en-3-one (**6**). A solution of (−)-**4** (129 mg, 0.36 mmol) in 2N KOHaq.-MeOH (5 ml, 4:1) was stirred for 4 hr at 60°C. The reaction mixture was neutralized with 1N HCl aq. and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated un-

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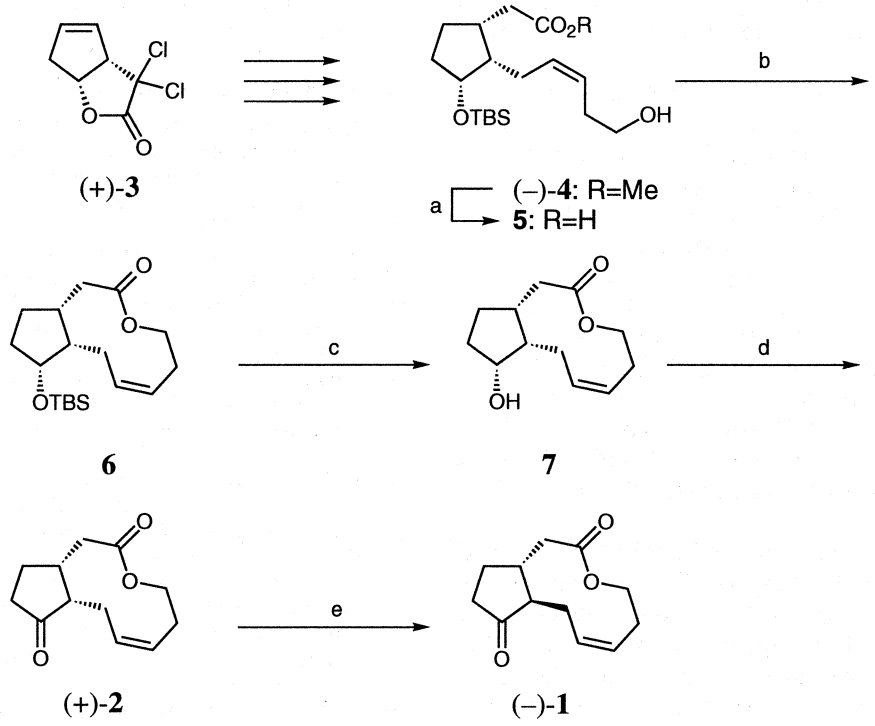

Fig. 2. Syntheses of **1** and **2**.
Reagents: (a) 2N KOH aq.-MeOH (4:1); (b) 2,4,6-trichlorobenzoylchloride, Et_3N, THF then DMAP, tol.; (c) HF aq.-MeCN; (d) Dess-Martin reag., CH_2Cl_2 (e) DBU, THF.

der vacuum to give crude carboxylic acid **5** (124 mg). To a stirred solution of crude carboxylic acid **5** (124 mg) in THF (5 ml) were added Et_3N (80 mg, 0.79 mmol) and 2,4,6-trichlorobenzoylchloride (176 mg, 0.72 mmol) in THF (0.5 ml) at room temp. under Ar. The mixture was stirred for 30 min., filtered through Celite and washed with toluene. The filtrate, containing the resulting mixed anhydride, was added to a solution of DMAP (264 mg, 2.16 mmol) in toluene (40 ml) over 5 hr at 100°C under Ar. The reaction mixture was stirred at room temp. for 30 min., diluted with Et_2O, successively washed with H_2O, 1N HCl aq., $NaHCO_3$ aq. and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was chromatographed over silica gel to give **6** (85 mg, 72%).

Similarly, *ent*-**4** (116 mg, 0.33 mmol) gave *ent*-**6** (86 mg, 82%).

6: Mp 81°C; $[\alpha]_D^{18}$ −24.6 (*c* 0.96, MeOH); IR ν_{max} (KBr disk): 3020(m), 1730(s), 1650(w), 1415(m), 1255(s), 1060(s); ^{1}H-NMR δ (300 MHz, $CDCl_3$): 0.035 (3H, s, SiCH_3), 0.039 (3H, s, SiCH_3), 0.97 (9H, s, SiC(CH_3)$_3$), 1.49–1.70 (2H, m), 1.75–2.01 (5H, m), 2.15 (1H, dd, J=2.7, 13.6 Hz, CHC=O), 2.52 (1H, m, CHCH_2C=O), 2.55–2.80 (2H, m, CHCH_2CH=CHCHHCH_2), 2.91 (1H, dd, J=12.7, 13.6 Hz, CHC=O), 4.09–4.30 (3H, m, CHOSi, OCH_2), 5.38–5.59 (2H, m, CH=CH). Anal. Calcd. for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94%. Found: C, 66.68; H, 9.91%. FABMS *m/z*: 325 $(M+H)^+$. *ent*-**6**: Mp 81°C; $[\alpha]_D^{18}$ +25.3 (*c* 1.05, MeOH). Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94%. Found: C, 66.23; H, 9.54%. IR and ^{1}H-NMR spectra were identical with those of **6**.

(1R,7Z,10S,11R)-11-Hydroxy-4-oxabicyclo[8.3.0]tridec-7-en-3-one (**7**). To a stirred solution of **6** (84 mg, 0.26 mmol) in MeCN (3 ml) was added 46% HF aq. (36 mg, 0.83 mmol) at 0°C. The mixture was stirred for 4 hr at 0°C, diluted with H_2O and extracted with EtOAc. The extract was successively washed with satd. $NaHCO_3$ aq. and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was chromatographed over silica gel to give **7** (49 mg, 90%).

Similarly, *ent*-**6** (130 mg, 0.40 mmol) gave *ent*-**7** (59 mg, 70%).

7: Mp 81°C; $[\alpha]_D^{18}$ −27.4 (*c* 0.99, MeOH); IR ν_{max} (KBr disk): 3480 (s), 3020 (m), 1710 (s), 1670 (w), 1155 (m), 1120 (m); ^{1}H-NMR δ (300 MHz, $CDCl_3$): 1.53–2.19 (7H, m), 2.23 (1H, dd, J=2.9, 13.6 Hz, CHC=O), 2.56 (1H, m, CHCH_2C=O), 2.60–2.85 (2H, m, CHCH_2CH=CHCHHCH_2), 2.82 (1H, t, J=13.6 Hz, CHC=O), 4.09–4.35 (3H, m, OCH_2, CHOH), 5.38–5.62 (2H, m, CH=CH). Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63%. Found: C, 68.21; H, 8.54%. *ent*-**7**: Mp 81°C; $[\alpha]_D^{20}$ +26.9 (*c* 0.99, MeOH). Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63%. Found: C, 68.94; H, 8.85%. IR and ^{1}H-NMR spectra were identical with those of **7**.

(1R,7Z,10S)-4-Oxabicyclo[8.3.0]tridec-7-ene-3,11-dione (**2**). To a solution of **7** (56 mg, 0.27 mmol) in CH_2Cl_2 (2 ml) was added Dess-Martin periodinane (170 mg, 0.40 mmol) at 0°C. The mixture was stirred for 50 min. at room temp., diluted with H_2O and extracted with Et_2O. The extract was successively washed with 15% $Na_2S_2O_3$ aq., satd. $NaHCO_3$ aq. and brine, dried

over $MgSO_4$ and concentrated under vacuum. The residue was chromatographed over silica gel to give **2** (49 mg, 88%).

Similarly, *ent*-**7** (57 mg, 0.27 mmol) gave *ent*-**2** (51 mg, 90%).

2: Mp 77°C; $[\alpha]_D^{20}$ +69.8 (*c* 0.36, MeOH); IR ν_{max} (KBr disk): 3040(m), 1735(s), 1725(s), 1650(m), 1415(m), 1115(s); ^{1}H-NMR δ (300 MHz, $CDCl_3$): 1.83 (1H, m), 1.96 (1H, m, =CHC*H*CH_2), 2.02–2.53 (8H, m), 2.70 (1H, m, =CHC*H*CH_2), 3.04 (1H, m, C*H*CH_2C(=O)O), 4.13 (1H, ddd, *J*=2.2, 10.5, 12.8 Hz, OC*H*), 4.32 (1H, ddd, *J*=2.0, 4.4, 10.5 Hz, OC*H*), 5.39–5.58 (2H, m, C*H*=C*H*). Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. Found: C, 69.16; H, 7.94%. *ent*-**2**: Mp 77°C; $[\alpha]_D^{24}$ −71.0 (*c* 0.43, MeOH). Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. Found: C, 69.22; H, 7.87%. IR and ^{1}H-NMR spectra were identical with those of **2**.

(1R,7Z,10R)-4-Oxabicyclo[8.3.0]tridec-7-ene-3,11-dione, (−)-Jasmine ketolactone (**1**). To a stirred solution of **2** (48 mg, 0.24 mmol) in THF (5 ml) was added a catalytic amount of DBU (5 mg, 0.03 mmol) at 0°C. The mixture was stirred overnight at room temp., then diluted with Et_2O, successively washed with 1N HCl aq., $NaHCO_3$ aq. and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was chromatographed over silica gel to give **1** (43 mg, 90%).

Similarly, *ent*-**2** (49 mg, 0.24 mmol) gave *ent*-**1** (44 mg, 90%).

1: Mp 101°C (lit.[2] 104°C); $[\alpha]_D^{18}$ −237 (*c* 0.80, MeOH); IR ν_{max} (KBr disk): 3030(m), 1735(s), 1725(s), 1650(w), 1420(m), 1120(s), 1025(s); ^{1}H-NMR δ (300 MHz, $CDCl_3$): 1.50 (1H, m), 1.90 (1H, m), 2.05–2.30 (4H, m), 2.35–2.60 (4H, m), 2.70 (1H, m), 2.76 (1H, dd, *J*=2.6, 14.0 Hz), 3.79 (1H, dt, *J*=3.6, 10.1 Hz, OC*H*), 4.64 (1H, dt, *J*=4.5, 10.1 Hz, OC*H*), 5.32–5.58 (2H, m, C*H*=C*H*). Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. Found: C, 68.93; H, 7.88%. *ent*-**1**: Mp. 101°C; $[\alpha]_D^{20}$ +240 (*c* 1.01, MeOH). Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. Found: C, 69.14; H, 7.84%. IR and ^{1}H-NMR spectra were identical with those of **1**.

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