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SYNTHESIS OF BOTH THE ENANTIOMERS OF METHYL *CIS*-(*Z*)-DEHYDROJASMONATE, PRINCIPAL NOTE FOR THE SCENT OF *CYMBIDIUM GOERINGII*, TO DETERMINE THE ABSOLUTE CONFIGURATION†

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Abstract: Both the enantiomers of methyl *cis*-(*Z*)-dehydrojasmonate **1** were prepared from the common intermediate **4** of our jasmonoid synthesis. (2*S*,3*R*)-**1** was proved to be identical with the naturally occurring enantiomer by GC analysis using a chiral stationary phase.

INTRODUCTION

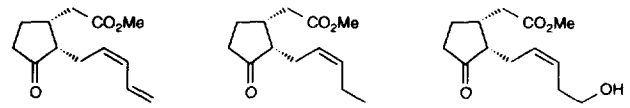
In the previous paper, we reported the synthesis of a key component in the scent of African orchid and the determination of its absolute configuration.[1] We describe herein another synthesis of unique fragrant substance of Asian orchid. *Cymbidiuim* species are very popular and common in eastern Asia, such as China, Formosa and Japan. Various types of those, so-called "Toyo Ran", usually emit extremely pleasant and fresh-floral note.

Kaiser analyzed the scent of *Cymbidium goeringii* (a kind of Shun-Ran) and identified more than 30 odor components.[2] Among them it was shown that methyl *cis*-(*Z*)-dehydrojasmonate **1** is principally responsible for the very pleasant odor and was contained in rather large quantities accompanied with methyl epijasmonate **2**. During the course of our continuing study on the synthesis of perfumery substances and related bioregulators, we investigated its synthesis to determine the absolute configuration. The result is described below.

† Synthesis of Perfumery Substances and Related Bioregulators, part 22. For part 21, see T. Nishi and T. Kitahara, *Proc. Japan Acad. Ser. B*, **1995**, *71*, 20.

SYNTHESIS

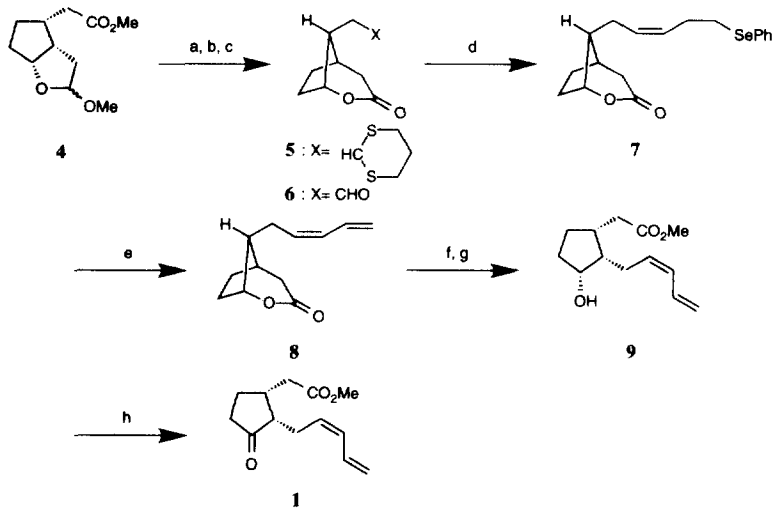
As the target molecule **1** is a congener of methyl epijasmonate **2** and methyl tuberonate **3**, it is apparently possible to use the similar strategy for our synthesis of **2**[3] and **3**.[4] The latter should be of choice, because stereoselectivity of the Wittig olefination was much higher than that of the former. Thus, the remaining problem is how to introduce additional terminal olefin and it was solved as the following way.



1 **2** **3**

Fig.

The acetal ester **4**[3] was converted to the known bridged lactone-thioacetal **5**[4,5] in two steps.[6] Hydrolysis of thioacetal with Hg^{2+} gave the aldehyde **6**, which was immediately treated with the phosphorane derived from 3-phenylselenopropyltriphenylphosphonium bromide[7] to give the olefin **7** (57% from **5**). Oxidative elimination of phenylselenide afforded the diene **8** (91%).



4 **5** **6** **7** **8** **9** **1**

Scheme

(a) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$ / $CHCl_3$; (b) *p*-TsOH / PhH, reflux; (c) HgO, $HgCl_2$ / 80% MeCNaq.; (d) $Ph_3P^+Br^-CH_2CH_2CH_2SePh$, *n*-BuLi / THF, HMPA; (e) H_2O_2, $NaHCO_3$ / THF; (f) 2N KOHaq.-MeOH (4:1); (g) CH_2N_2 / Et_2O; (h) Dess-Martin periodinane / CH_2Cl_2

Stereochemistry of disubstituted olefin in the side chain was determined at this stage and shown to be 95~98% pure (*Z*)-isomer by ^{1}H-NMR and GC analysis. Alkaline hydrolysis of bridged lactone moiety was followed by diazomethane treatment to give all *cis*-hydroxy ester **9** (97%). Finally oxidation of **9** with Dess-Martin reagent[8] afforded methyl *cis*-(*Z*)-dehydrojasmonate **1** without appreciable isomerization (98%).[9] The synthetic **1** was rather labile, but was indistinguishable with authentic sample of racemate (IR, NMR).[10]

As both the enantiomers of **4** were in our hands, both (2*S*,3*R*)-**1** and (2*R*,3*S*)-**1** were obtained in overall 34% and 19% yield respectively through 8 steps from **4**.

DETERMINATION OF ABSOLUTE CONFIGURATION

Only a mixture of natural scent was available in extremely minute amounts (less than ca. 5μg), so we again had to use capillary GC with a chiral stationary phase. Octakis (2,6-di-*O*-methyl-3-*O*-pentyl-γ-cyclodextrin)[11] was the best stationary phase of choice for the separation of the enantiomers of **1**. Table shows the result of GC analysis and by the comparison of t_R and Δt_R from the standard, it was determined that the natural methyl *cis*-(*Z*)-dehydrojasmonate **1** must have (2*S*,3*R*)- configuration.

Table Kovats index*1 of Methyl *cis*-(*Z*)-dehydrojasmonate

	Synthetic	Natural sample from *cymbidium goeringii*
(2*R*,3*R*)*2	1749	1750*3
(2*S*,3*S*)*2	1755	
(2*R*,3*S*)	1784	
(2*S*,3*R*)	1790	1791

*1 Which was calculated below.

Kovats index (KI)=100∗N+(t_{R2}-t_{R1})/(t_{R3}-t_{R1})∗100, N: standard paraffin carbon length, t_{R1}, t_{R3}: retention times of standard paraffins (carbon lengths were N and N+1 respectively), t_{R2}: retention time of the sample

*2 Which were prepared by the isomerization of synthetic (2*S*,3*R*)- and (2*R*,3*S*)- **1** with DBU.

*3 A little amount of methyl *trans*-(*Z*)-dehydrojasmonate was contaminated in natural scent mixture. The absolute configuration was determined as (2*R*,3*R*).

Operating conditions: Instrument, SHIMADZU GC-14A; Column, DMPGCD-TH; Carrier He, 1.0kg/cm^3; Temp., 70°C to 150°C (0.7°C/min)

In conclusion, both the enantiomers of methyl *cis*-(*Z*)-dehydrojasmonate **1** were synthesized from the common intermediate **4** and the absolute configuration of natural **1** was determined as (2*S*,3*R*) by the GC analysis using the synthetic samples. In this case too, combinations of enantioselective synthesis and GC technique was proved to be an efficient tool for the determination of stereochemistry.

As the titled compound **1** is a jasmonoid analog, we are investigating the physiological activity as a plant growth regulator, and the result will be published in due course.

EXPERIMENTAL

Melting points were determined on a YANACO micro melting point apparatus. Infrared spectra were measured with a JASCO IRA-102 or FT IR-230 spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a JEOL JNM EX-90 or a BRUKER AC-300 spectrometer with tetramethylsilane or chloroform as an internal standard. Optical rotations were measured with a JASCO DIP-140 polarimeter. Column chromatography was performed on MERCK Kieselgel 60, Art No. 7734.

(1*R*,5*R*,8*S*)-8-(1',3'-dithianyl-2')methyl-2-oxabicyclo[3,2,1]octan-3-one (5). To a stirred solution of boron trifluoride etherate (4.60g, 32.4mmol) in $CHCl_3$ (35ml) was added dropwise a solution of **4** (3.25g, 15.2mmol) and 1,3-propanedithiol (1.80g, 16.6mmol) in $CHCl_3$ (15ml) and cat. H_2O at 0°C. The reaction mixture was stirred for 12hr at room temp., then poured into ice-water and extracted with $CHCl_3$. The extract was washed with satd. $NaHCO_3$aq., water and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was chromatographed over silica gel to give the mixture of **5** and hydroxy ester. The mixture was dissolved in benzene (80ml) and to this was added a catalytic amount of *p*-TsOH•H_2O. The reaction mixture was refluxed by trapping MeOH with MS4A for 4hr, diluted with Et_2O, washed with satd. $NaHCO_3$aq. and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was chromatographed over silica gel and recrystallized from *i*-Pr_2O to give **5** (2.70g, 69%).

Similarly, *ent*-**4** (2.90g, 14.8mmol) gave *ent*-**5** (2.34g, 67%).

5: mp 101~102°C; $[\alpha]_D^{20}$ -82.9° (*c*=1.02, MeOH); IR ν_{max} (nujor) 2900 (m), 1722 (s); ^{1}H-NMR δ(90MHz, $CDCl_3$) 1.60~2.75 (m, 12H), 2.75~3.00 (m, 4H, CH_2S), 4.10(t, *J*=7.2Hz, 1H, SCHS), 4.65 (m, 1H, CHO); Anal. calcd for $C_{12}H_{18}O_2S_2$: C, 55.78; H, 7.02. Found: C, 55.61; H, 7.01. *ent*-**5**: mp 101~102°C; $[\alpha]_D^{21}$ +83.1° (*c*=1.03, MeOH); Anal calcd for $C_{12}H_{18}O_2S_2$: C, 55.78; H, 7.02. Found: C, 55.62; H, 7.03.; IR and ^{1}H-NMR spectra were identical with those of **5**.

(1*R*,5*R*,8*S*)-8-(5'-Phenylseleno-2'-*cis*-pentenyl)-2-oxabicyclo[3,2,1]octan-3-one (7). To a stirred suspension of HgO (1.49g, 6.88mmol) and $HgCl_2$ (3.75g, 13.8mmol) in 80% MeCNaq. (30ml) was added a solution of **5** (891mg, 3.45mmol) in 80% MeCNaq. (20ml) at 0°C. The reaction mixture was refluxed for 8hr under Ar and then filtrated through sufficient amount of celite. The filtrates were concentrated and the residue was chromatographed over silica gel to give crude aldehyde **6** (471mg). To a solution of **6** in THF (10ml) was added a salt-free THF solution (60ml) of 3-phenylselenoproplytriphenylphosphorane prepared from 3-phenylselenopropyltriphenylphosphonium bromide (16.8g, 31.1mmol), *n*-BuLi (16.2ml, 1.64mol/l in n-hexane), HMPA (5.3ml) and THF (80ml) at -78°C under Ar. The reaction mixture was stirred for 1hr at -78°C, then poured into ice-water and extracted with Et_2O. The extract was 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** (681mg, 57%).

Similarly, *ent*-**5** (151mg, 0.58mmol) gave *ent*-**7** (88mg, 43%).

7: $[\alpha]_D^{20}$ -35.6° (*c*=1.01, MeOH); IR ν_{max} (film) 2980 (m), 1730 (s), 740 (s); ^{1}H-NMR δ(90MHz, $CDCl_3$) 1.60~2.70 (m, 12H), 2.93 (t, *J*=6.6Hz, 2H, $SeCH_2$), 4.56 (m, 1H, CHO), 5.51 (m, 2H), 7.21~7.32 (m, 3H, Ar), 7.43~7.56 (m, 2H, Ar); Anal. calcd for $C_{18}H_{22}O_2Se$: C, 61.89; H, 6.35. Found: C, 61.92; H, 6.49. **ent-7**: $[\alpha]_D^{21}$ +34.7° (*c*=1.03, MeOH); Anal. calcd for $C_{18}H_{22}O_2Se$: C, 61.89; H, 6.35. Found: C, 62.12; H, 6.47.; IR and ^{1}H-NMR spectra were identical with those of **7**.

(1*R*,5*R*,8*S*)-8-(2',4'-*cis*-Pentadienyl)-2-oxabicyclo[3,2,1]octan-3-one (8). To a stirred a solution of **7** (144mg, 0.41mmol) in THF (6ml) was added $NaHCO_3$ (340mg, 4.0mmol) and H_2O_2 (1.7ml of a 34.5% solution) at 0 °C. The reaction mixture was stirred for 4hr at room temp., then diluted with H_2O and extracted with EtOAc. The extract was 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 the diene **8** (72mg, 91%).

Similarly, *ent*-**7** (91mg, 0.26mmol) gave *ent*-**8** (42mg, 84%).

8: $[\alpha]_D^{20}$ –69.0° (*c*=1.03, MeOH); IR ν_{max} (film) 2946 (m), 1731 (s), 1643 (s); ^{1}H-NMR δ(300MHz, $CDCl_3$) 1.60~2.12 (m, 5H), 2.32~2.58 (m, 4H), 2.70~2.85 (m, 1H), 4.61 (m, 1H, CHO), 5.16 (d, *J*=10.0Hz, 1H), 5.24 (d, *J*=16.6Hz, 1H), 5.48 (dt, *J*=10.5, 7.9Hz, 1H), 6.10 (t, *J*=11.0Hz, 1H), 6.62 (dt, *J*=16.6, 10.5Hz, 1H) , *E*/*Z*=4/96; Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.80; H, 8.53. *ent*-**8**: $[\alpha]_D^{20}$ +67.5° (*c*=1.07, MeOH); Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.73; H, 8.45.; IR and ^{1}H-NMR spectra were identical with those of **8**, *E*/*Z*=2/98.

(1*R*,2*S*,3*R*)-3-Methoxycarbonylmethyl-2-(2',4'-*cis*-pentadienyl)-1-cyclopentanol (9). A solution of **8** (73mg, 0.38mmol) in 2N KOHaq.-MeOH (2.5ml, 4:1) was stirred for 4hr at room temp. The solution was neutralized with 1N HClaq. (4ml). This was extracted with Et_2O, the residue was immediately treated with diazomethane in the usual manner and then chromatographed over silica gel to give the hydroxy ester **9** (83mg, 97%).

Similarly, *ent*-**8** (33mg, 0.17mmol) gave *ent*-**9** (35mg, 91%).

9: $[\alpha]_D^{20}$ -7.11° (*c*=1.03, MeOH); IR ν_{max} (film) 3508 (s), 2951 (m), 1732 (s), 1643 (s); ^{1}H-NMR δ(300MHz, $CDCl_3$) 1.55~2.00 (m, 6H), 2.18~2.30 (m, 1H), 2.35~2.60 (m, 4H), 3.66 (s, 3H, OMe), 4.20 (m, 1H), 5.13 (d, *J*=10.2Hz, 1H), 5.21 (d, *J*=16.9Hz, 1H), 5.50 (dt, *J*=10.7, 7.7Hz, 1H), 6.04 (t, *J*=11.1Hz, 1H), 6.69 (dt, *J*=17.0, 10.5Hz, 1H); Anal. calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.72; H, 9.08. *ent*-**9**: $[\alpha]_D^{19}$ +7.42° (*c*=0.97, MeOH); Anal. calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.27; H, 8.99.; IR and ^{1}H-NMR spectra were identical with those of **9**.

(2*S*,3*R*)-3-Methoxycarbonylmethyl-2-(2',4'-*cis*-pentadienyl)-1-cyclopentanone (natural Methyl *cis*-(*Z*)-dehydrojasmonate) (1). To a stirred solution of **9** (39mg, 0.17mmol) in CH_2Cl_2 (1ml) was added Dess-Martin periodinane (115mg, 0.27mmol) at 0 °C. The reaction mixture was stirred for 50min. at room temp., diluted with H_2O and extracted with Et_2O. The extract was 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 natural (+)-methyl *cis*-(*Z*)-dehydrojasmonate **1** (38mg, 98%).

Similarly, *ent*-**9** (32mg, 0.14mmol) gave unnatural (–)-methyl *cis*-(*Z*)-dehydrojasmonate *ent*-**1** (28mg, 88%).

1: $[\alpha]_D^{18}$ +40.5° (*c*=0.80, MeOH); IR ν_{max} (film) 2952 (m), 1736 (s), 1643 (s); ^{1}H-NMR δ(300MHz, $CDCl_3$) 1.77~1.92 (m, 1H), 1.99~2.65 (m, 8H), 2.80~2.95 (m, 1H), 3.69 (s, 3H, OMe), 5.15 (d, *J*=10.1Hz, 1H), 5.22 (d, *J*=16.7Hz, 1H), 5.43 (dt, *J*=10.9, 7.5Hz, 1H), 6.05 (t, *J*=11.0Hz, 1H), 6.59 (dt, *J*=16.8, 10.5Hz, 1H); Anal. calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.97; H, 8.17. *ent*-**1**: $[\alpha]_D^{18}$ –39.8° (*c*=0.83, MeOH); Anal. calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.42; H, 8.33.; IR and ^{1}H-NMR spectra were identical with those of **1**.

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