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Synthesis of All Stereoisomers of the Norchrysanthemic Acid Methyl Ester

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ABSTRACT

Syntheses of eight stereoisomers of methyl norchrysanthemate, (*1R*)-*trans*-(*Z*)-isomer and (*1R*)-*trans*-(*E*)-isomer from (*1R*)-*trans*-chrysanthemic acid, and other six isomers from (+)-3-carene, are described.

Key Words: Norchrysanthemic acid; Pyrethroids; Metofluthrin; Norchrysanthemic acid.

Norchrysanthemic acid (**1**), or 2,2-dimethyl-3-(1-propenyl)cyclopropanecarboxylic acid, was first synthesized by Staudinger et al. in 1924 by the

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pyrolytic decarboxylation of chrysanthemum dicarboxylic acid (**2**). Some esters of norchrysanthemic acid were evaluated and revealed to be equipotent to the corresponding chrysanthemates.[2–8] However, no commercial use of norchrysanthemic acid was attained as an acid moiety of synthetic pyrethroids owing to the difficulty of the synthesis. Recently one of the present authors has invented metofluthrin[9] (**5**), or (2,3,5,6-tetrafluoro-4-methoxymethylphenyl)-methyl (*1R,3R*)-2,2-dimethyl-3-(1-propenyl)cyclopropanecarboxylate and profluthrin[9] (**6**), or (2,3,5,6-tetrafluoro-4-methylphenyl)methyl (*1R,3R*)-2,2-dimethyl-3-(1-propenyl)cyclopropanecarboxylate as novel pyrethroid insecticides for environmental health use. They have potent vapor action against household insect pests and both contain norchrysanthemic acid as an acid moiety. In order to clarify the relationship between stereochemistry and insecticidal activity of two new synthetic pyrethroids, it is required to establish the synthetic methods of all eight stereoisomers of norchrysanthemic acid. We now report the stereoselective syntheses of (*1R*)-*trans*-(*Z*)-norchrysanthemic methyl ester (**1a**) and (*1R*)-*trans*-(*E*)-norchrysanthemic acid methyl ester (**1b**) starting from (*1R*)-*trans*-chrysanthemic acid (**3**), and other six isomers, (*1R*)-*cis*-(*Z*)-norchrysanthemic acid methyl ester (**1c**), (*1R*)-*cis*-(*E*)-norchrysanthemic acid methyl ester (**1d**), (*1S*)-*trans*-(*Z*)-norchrysanthemic acid methyl ester (**1e**), (*1S*)-*trans*-(*E*)-norchrysanthemic acid methyl ester (**1f**),

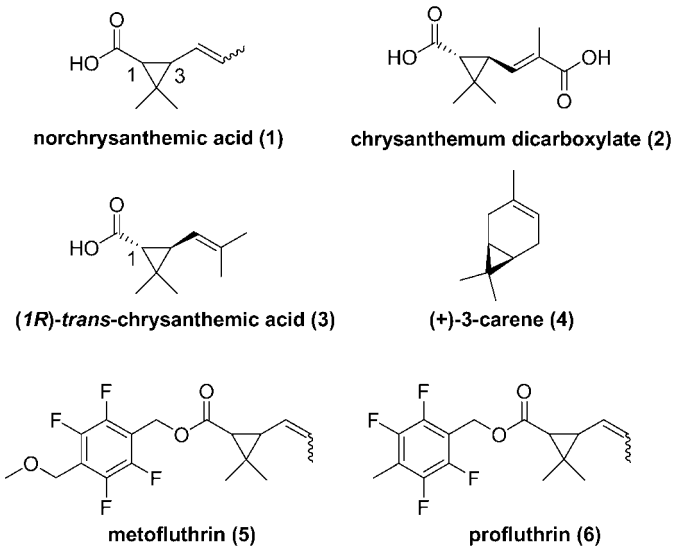

Figure 1.

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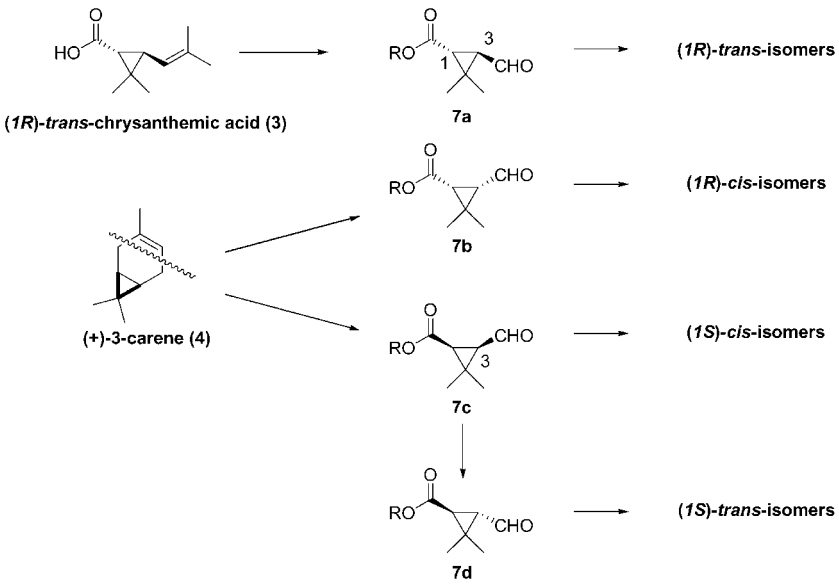

Figure 2.

(*1S*)-*cis*-(*Z*)-norchrysanthemic acid methyl ester (**1g**) and (*1S*)-*cis*-(*E*)-norchrysanthemic acid methyl ester (**1h**) from (+)-3-carene (**4**).

We planned to introduce a 1-propenyl side chain at the C-3 position by the Wittig-type reaction with caronaldehydic acids or the corresponding esters **7a**–**7d** on the last step. Thus (*1R*)-*trans*-caronaldehydic methyl ester (**7a**, R═Me) can be prepared by ozonolysis of (*1R*)-*trans*-chrysanthemic acid (**3**). For *cis*-isomers, (+)-3-carene (**4**) was transformed to (*1R*)-*cis*-caronaldehydic acid (**7b**, R═H) and (*1S*)-*cis*-caronaldehydic acid (**7c**, R═H) according to Dev's and Ho's procedures. (*1S*)-*trans*-isomer (**7d**, R═Me) could be prepared by epimerization at the C-3 carbon atom of **7c** (R═Me).

Synthesis of (*1R*)-*trans*-(*Z*)- and (*E*)-Isomers

Syntheses of these isomers were reported by Crombie[3] and Elliott[4] staring from (*1R*)-*trans*-chrysanthemic acid by means of the Wittig reaction. Their method were convenient to obtain (*Z*)-isomer (Sch. 1, step a) but not appropriate for the synthesis of (*E*)-isomer because of the (*Z*)-selective nature of the Wittig reaction. It was very difficult to obtain the pure (*E*)-isomer out of the (*E*)- and (*Z*)-mixture. This problem was overcome by use of the Takai's

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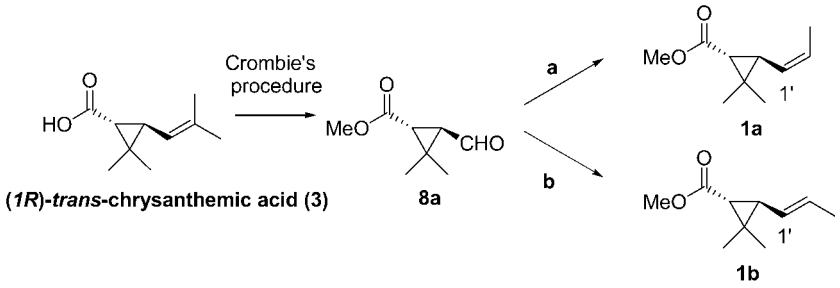
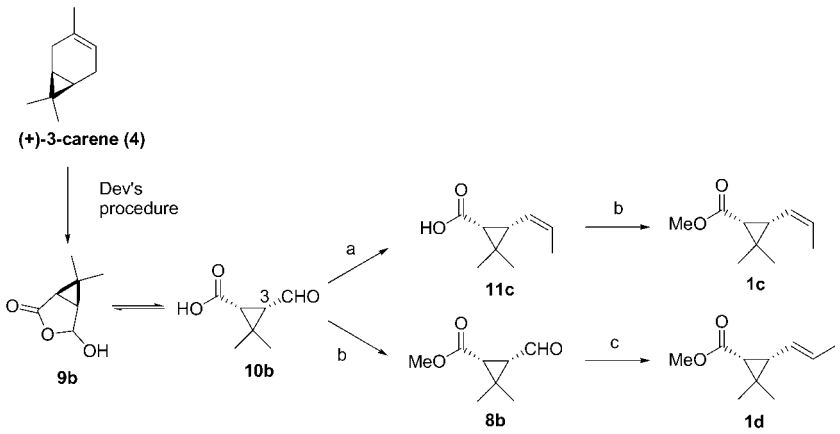


Scheme 1. (a) $CH_3CH{=}PPh_3$, THF; (b) CH_3CHI_2, $CrCl_2$, THF, rt.

method (Sch. 1, step b).[11] The (*E*)-selectivity of the double bond was fairly high ($E:Z = 89:11$).

Synthesis of (*1R*)-*cis*-(*Z*)- and (*E*)-Isomers

These isomers were synthesized as shown in Sch. 2. (*1R*)-*cis*-Caronaldehydic acid hemiacetal **9b**, which is the equivalent of (*1R*)-*cis*-caronaldehydic acid **10b**, could be prepared from (+)-3-carene (**4**) according to Dev's procedure.[12] The Wittig reaction of hemiacetal **9b** under ice-cooling gave not only desired (*1R*)-*cis*-(*Z*)-norchrysanthemic acid **11c** but also undesired

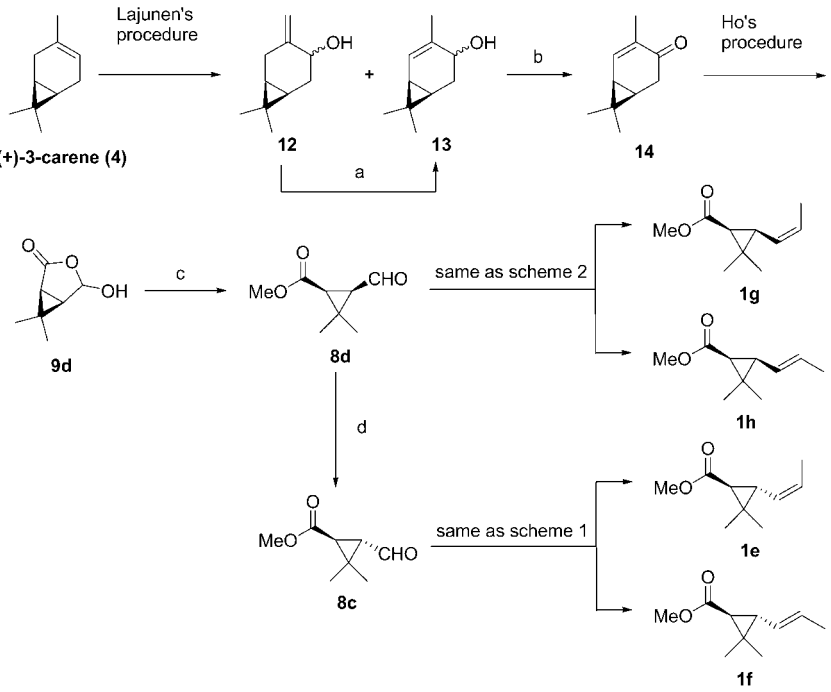


Scheme 2. (a) $CH_3CH_2PPh_3 \cdot Br$, *t*-BuOK, THF, $-40^\circ C$ to $0^\circ C$; (b) MeOH, *i*-PrOCO–N=N–CO_2*i*-Pr, Ph_3P, THF; (c) CH_3CHI_2, $CrCl_2$, THF, rt.

(*1R*)-*trans*-isomer (*cis* : *trans* = 80 : 20). Fortunately, this epimerization was prevented by performing the reaction at the lower temperature. Thus the Wittig reaction of hemiacetal **9b** with $CH_3CH{=}PPh_3$ at $-40^{\circ}C$ gave (*1R*)-*cis*-(*Z*)-norchrysanthemic acid **11c** free from the *trans*-isomer. The acid was converted to the corresponding methyl ester **1c** using the Mitsunobu reaction. (*1R*)-*cis*-(*E*)-isomer was prepared using the same procedure as the (*1R*)-*trans*-(*E*)-isomer *via* the Takai's method. However, the reaction resulted in the lower stereoselectivity (*E* : *Z* = 72 : 28) because of the more steric hindrance of the (*E*)-isomer with the ester group.

Synthesis of (*1S*)-*cis*-(*Z*)-, (*1S*)-*cis*-(*E*)-, (*1S*)-*trans*-(*Z*)-, and (*1S*)-*trans*-(*E*)-isomers

These isomers were synthesized as shown in Sch. 3. According to the Lajunen's procedure, (+)-3-carene was converted to a mixture of allyl



Scheme 3. (a) t-BuOK, DMSO, 100°C; (b) PCC, CH_2Cl_2; (c) MeOH, *i*-PrOCO-N=N-CO_2 *i*-Pr, Ph_3P, THF; (d) MeONa, MeOH.

alcohols **12** and **13** (9 : 1) in totally 60% yield.[14] The mixture was subjected to a basic condition to obtain the pure allyl alcohol **13** via the isomerization of the double bond. Subsequently the alcohol **13** was oxidized with PCC to give 2-caren-4-one **14**. The carenone was converted to (*1S*)-*cis*-caronaldehydic acid hemiacetal **9d**, which is an antipode of **9b**, according to Ho's procedure.[13] The (*1S*)-hemiacetal was transformed to the (*1S*)-*cis*-(*Z*)- and (*1S*)-*cis*-(*E*)-isomers according to the same procedures as (*1R*)-*cis*-isomers. For *trans*-isomers, the methyl ester **8d** was epimerized at the C-3 position to give the (*1S*)-*trans*-isomer by sodium methoxide. (*1S*)-*trans*-(*Z*)- and (*1S*)-*trans*-(*E*)-norchrysanthemic acid methyl esters were obtained as the same manner described in Sch. 1.

In conclusion, all of the eight isomers of norchrysanthemic acid methyl esters were synthesized in stereoselective manner from (*1R*)-*trans*-chrysanthemic acid or (+)-3-carene. All stereoisomers of metofluthrin and profluthrin were synthesized in our laboratory. Their relationship between stereochemistry and insecticidal activity will be published elsewhere.

EXPERIMENTAL

(*1R*)-*trans*-caronaldehydic acid methyl ester was prepared by the Crombie's method.[3] (*1R*)-*cis*-caronaldehydic acid hemiacetal was prepared by the Martel's method.[15] (*1S*)-*cis*-caronaldehydic acid hemiacetal was prepared by the Ho's method.[13] A mixture of (*1R*,*3RS*,*6S*)-7,7-dimethyl-4-methylenebicyclo[4.1.0]heptan-3-ol and (*1R*,*3R*,*6R*)-4,7,7-trimethylbicyclo[4.1.0]hept-4-en-3-ol was prepared by the Lajunen's method.[14] E/Z ratios were determined by GC-EIMS spectra. ^{1}H-NMR spectra were recorded in JEOL JNM-AL400 NMR spectrum meter with tetramethylsilane as an internal standard. IR spectra were recorded in Hitachi 270−30 infrared spectrometer. GC-EIMS spectra were recorded in Agilent 6890/5973 System (Agilent 19091S-433 HP-5MS 0.25 mm × 30 m × 0.25 μm; 300°C; flow rate 1.0 mL/min).

(*1R*,*3R*)-2,2-Dimethyl-3-((*1Z*)-propenyl)cyclopropanecarboxylic acid methyl ester (1a)

This compound was prepared in 92% from (*1R*)-*trans*-caronaldehydic acid methyl ester according to the known procedure[16] to give a 90 : 10 mixture of **1a** and **1b**. $[\alpha]_D^{24} + 6.5^\circ$ ($c = 2.4$, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.14 (s, 3H), 1.27 (s, 3H), 1.45 (d, 1H), 2.75 (dd, 1H), 3.68 (s, 3H), 5.05−5.18 (m, 1H), 5.52−5.68 (m, 1H). IR ν_{max} (neat): 2990, 1740, 1440, 1230, 1170 cm^{-1}. EIMS m/z: 168 (M^+, 13), 153 (8), 109 (100).

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(*1R*,*3R*)-2,2-Dimethyl-3-((*1E*)-propenyl)cyclopropanecarboxylic Acid Methyl Ester (1b)

To a stirring mixture of chromium(II) chloride (0.85 g, 6.9 mmol) in tetrahydrofuran (20 ml) was added a mixture of (*1R*)-*trans*-caronaldehydic acid methyl ester (0.16 g, 1.0 mmol) and 1,1-diiodomethane (0.60 g, 2.1 mmol) in tetrahydrofuran (5 mL). The mixture was stirred for 15 hr. It was filtered on a Celite pad, the filtrate was poured onto water and then extracted with *t*-butyl methyl ether, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel with *t*-butyl methyl ether + hexane (1 + 100 by volume) as eluant to give a 93 : 7 mixture of the methyl esters **1b** and **1a** (0.11 g, 63%) as a colorless oil. $[\alpha]_D^{24} + 31^\circ$ ($c = 2.4$, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.14 (3H, s), 1.24 (3H, s), 1.48 (1H, d, $J = 5.3$), 1.68 (3H, dd, $J = 6.5$, 1.6), 2.00 (1H, dd, $J = 5.3$, 8.2), 3.66 (3H, s), 5.24 (1H, ddq, $J = 15.2$, 8.2, 3.1), 5.61 (1H, dq, $J = 15.2$, 6.5). IR ν_{max} (neat): 2990, 1740, 1450, 1220, 1180 cm^{-1}. EIMS m/z: 168 (M^+, 14), 153 (10), 109 (100).

(*1R*,*3S*)-2,2-Dimethyl-3-((*1Z*)-propenyl)cyclopropanecarboxylic Acid Methyl Ester (1c)

A solution of potassium *tert*-butoxide (42 g, 380 mmol) in tetrahydrofuran (500 mL) was dropped to a stirring mixture of (ethyl)triphenylphosphonium bromide (150 g, 400 mmol) and tetrahydrofuran (500 mL) over 30 min under nitrogen atmosphere at $-40^\circ C$ for 15 min. (*1R*)-*cis*-Caronaldehydic acid hemiacetal (25.0 g, 176 mmol) was dropped to the mixture over 30 min at the same temperature and was left to stand at room temperature for 2 hr. The reaction mixture was poured onto 10% aqueous hydrochloric acid and then extracted with *t*-butyl methyl ether, washed with brine, dried over magnesium sulfate to give the crude acid. The acid was diluted with tetrahydrofuran (500 mL) and methanol (50 mL), and triphenylphosphine (46 g, 176 mmol) was added to the solution. To the mixture was added a solution of diisoporopyl azodicarboxylate (40% in toluene, 90 mL, 178 mmol) over 5 min and the resulting mixture was stirred for 1 hr at $0^\circ C$. It was then concentrated under reduced pressure, and the residue was chromatographed on silica gel with ethyl acetate + hexane (1 + 4 by volume) as eluant to give a 93 : 7 mixture of the methyl esters **1c** and **1d** (23.7 g, 80%) as a colorless oil. $[\alpha]_D^{24} + 97^\circ$ ($c = 2.5$, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.22 (3H, s), 1.26 (3H, s), 1.70 (3H, d, $J = 5.1$), 1.71 (1H, d, $J = 8.3$), 1.98 (1H, t, $J = 8.3$), 3.63 (3H, s), 5.6–5.7 (2H, m). IR ν_{max} (neat): 2990, 1740, 1450, 1180 cm^{-1}. EIMS m/z: 168 (M^+, 14), 153 (10), 109 (100).

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(*1R,3S*)-2,2-Dimethyl-3-((*1E*)-propenyl)cyclopropanecarboxylic Acid Methyl Ester (1d)

A solution of diisoporopyl azodicarboxylate (40% in toluene, 105 mL, 208 mmol) was dropped to a stirring mixture of (*1R*)-*cis*-caronaldehydic acid hemiacetal (28 g, 200 mmol), methanol (50 mL) and triphenylphosphine (55 g, 210 mmol) in tetrahydrofuran (500 mL) over 5 min at 0°C. After stirring for 2 hr, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate + hexane (1 + 4 by volume) as eluant to give methyl ester **8b** (17.8 g, 57%). The methyl ester was mixed with 1,1-diiodoethane (41 g, 145 mmol) and tetrahydrofuran (400 mL), then the resulting solution was added to a stirring mixture of chromium(II) chloride (48 g, 391 mmol) in tetrahydrofuran (500 mL) under nitrogen atmosphere. The stirring was continued for 12 hr. It was filtered on a celite pad, and then poured into water and extracted with *t*-butyl methyl ether. The extract was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate + hexane (1 + 20 by volume) as eluant to give a 72 : 28 mixture of the methyl esters **1d** and **1c** (10.4 g, 64%) as a colorless oil. $[\alpha]_D^{24} + 55^\circ$ ($c = 2.5$, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.14 (3H,s), 1.27 (3H, s), 1.63 (1H, d, $J = 8.8$), 1.80 (1H, t, $J = 9.0$), 3.63 (3H, s), 5.60–5.66 (1H, m), 5.75 (1H, ddd, $J = 13.8$, 8.6, 0.8). IR ν_{max} (neat): 3000, 1740, 1450, 1190, 1160 cm^{-1}. EIMS m/z: 168 (M^+, 14), 153 (10), 109 (100).

(*1E,6R*)-4,7,7-Trimethyl-bicyclo[4.1.0]hept-4-en-3-one (14)

Potassium *tert*-butoxide (0.25 g, 2.2 mmol) was added to a 9 : 1 mixture of (*1R,3RS,6S*)-7,7-dimethyl-4-methylenebicyclo[4.1.0]heptan-3-ol **6** and (*1R,3R,6R*)-4,7,7-trimethylbicyclo[4.1.0]hept-4-en-3-ol **7** (302 mg, 2.0 mmol) in dimethylsulfoxide (3 mL), and the mixture was heated to 120°C for 3 hr. It was poured onto water and then extracted with *t*-butyl methyl ether, washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give a crude (*1R,3RS,6R*)-4,7,7-trimethylbicyclo[4.1.0]hept-4-en-3-ol **13**, which was diluted with dichloromethane (20 mL) and then cooled to 0°C. Pyridinium chlorochromate (0.5 g, 2.5 mmol) was added to the mixture. The resulting mixture was stirred for 2 hr. It was passed through a Florisil pad, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate + hexane (1 + 20 by volume) as eluant to give enone **14** (142 mg, 47%). The enone was identified by ^{1}H-NMR spectrum.[17]

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(*1S,3R*)-3-Formyl-2,2-dimethylcyclopropanecarboxylic Acid Methyl Ester (8c)

A 28% solution of sodium methoxide in methanol (0.5 mL) was added to (*1S, 3S*)-3-formyl-2,2-dimethylcyclopropanecarboxylic acid methyl ester **8d** (156 mg, 1.0 mmol) at 0°C and stood for 5 min. It was poured onto saturated aqueous ammonium chloride and then extracted with *t*-butyl methyl ether, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate + hexane (1 + 4 by volume) as eluant to give the methyl ester **8c** (128 mg, 82%). $[\alpha]_D^{24}$ −11° ($c = 2.6$, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.31 (1H, s), 1.35 (1H, s), 2.45–2.50 (2H, m), 3.71 (1H, s), 9.59 (1H, d, $J = 2.0$).

The following compounds were prepared by the same procedures with their antipodes.

(*1S,3S*)-2,2-Dimethyl-3-((*1Z*)-propenyl)cyclopropanecarboxylic acid methyl ester (1e). $[\alpha]_D^{24}$ − 6.0° ($c = 2.4$, $CHCl_3$).

(*1S,3S*)-2,2-Dimethyl-3-((*1E*)-propenyl)cyclopropanecarboxylic acid methyl ester (1f). $[\alpha]_D^{24}$ − 31° ($c = 2.4$, $CHCl_3$).

(*1S,3R*)-2,2-Dimethyl-3-((*1Z*)-propenyl)cyclopropanecarboxylic acid methyl ester (1g). $[\alpha]_D^{24}$ − 94° ($c = 2.4$, $CHCl_3$).

(*1S,3R*)-2,2-Dimethyl-3-((*1E*)-propenyl)cyclopropanecarboxylic acid methyl ester (1h). $[\alpha]_D^{24}$ − 58° ($c = 2.5$, $CHCl_3$).

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