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Enantioselective Synthesis of (3*S*,5*R*,6*E*,8*E*)-Deca-6,8-dien-1,3,5-triol, a New Metabolite from *Streptomyces Fimbriatus* via Asymmetric Reaction of Diketene with 2,4-Hexadienal Promoted by Chiral Schiff Base–Titanium Alkoxide Complexes

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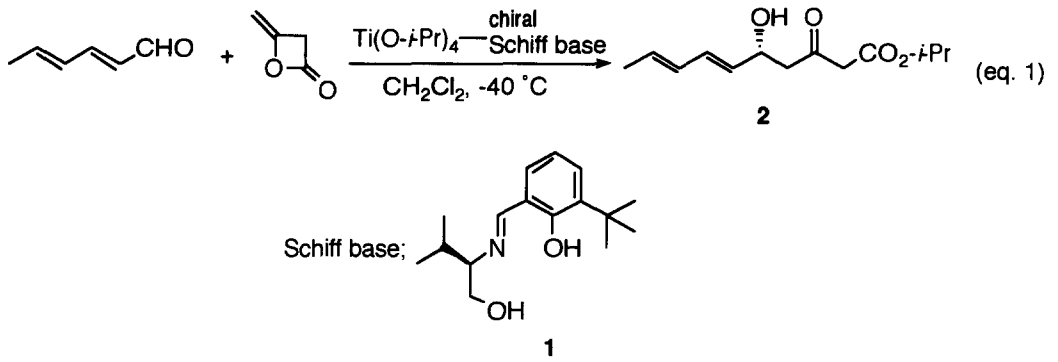
Abstracts: (3*S*,5*R*,6*E*,8*E*)-Deca-6,8-dien-1,3,5-triol, **6** which was isolated from the culture filtrate of *Streptomyces fimbriatus* has been synthesized efficiently via the enantioselective reaction of diketene with 2,4-hexadienal promoted by a novel chiral Schiff base–titanium alkoxide complex.

There are many optically active secondary alcohols possessing biological and physiological activities. Enantioselective addition of carbon nucleophiles to aldehydes provides one of the most efficient methods for the synthesis of optically active secondary alcohols. Among those, optically active 5-hydroxy-3-oxoesters can be converted into 6-substituted 4-hydroxy lactones which are common structural components of compactin and mevinolin known inhibitors of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) reductase.[1] To date several methods have been reported for the synthesis of optically active 6-substituted-4-hydroxy lactones *via* 5-hydroxy-3-oxoesters or *syn*-3,5-dihydroxy esters.[2] Most of them, however, required several steps to prepare these compounds. For example, Johnson *et al.*, reported the diastereoselective addition of 1,3-bis-(trimethylsiloxy)-1-methoxybuta-1,3-diene to a chiral acetal to give 5-alkoxy-3-oxoesters.[2d] Saburi and co-workers reported the asymmetric hydrogenation of 3,5-dioxoesters catalyzed by a Ru-BINAP complex, giving the 6-substituted-5,6-dihydro-2-pyrones.[2g,h] Furthermore, Hiyama *et al.* recently reported the diastereoselective reduction of chiral 3,5-diketo esters to give *syn*-3,5-dihydroxy esters.[3]

On the other hand, Mukaiyama reported the synthesis of racemic 5-hydroxy-3-oxoesters by the reaction of aldehydes with diketene promoted by $TiCl_4$ in 1975.[4] However, an asymmetric version of this reaction leading to optically active 5-hydroxy-3-oxoesters had not been reported before our first report in 1994, which included the enantioselective reaction of diketene with aldehydes promoted by chiral Schiff base–titanium alkoxide complexes.[5,6]

In this paper, we describe the first and highly efficient asymmetric synthesis of (3*S*,5*R*,6*E*,8*E*)-deca-6,8-diene-1,3,5-triol **6** based on the enantioselective reaction of diketene with 2,4-hexadienal promoted by chiral Schiff base–titanium alkoxide complexes. The title compound **6** is a new metabolite which was recently isolated from the culture filtrate of *Streptomyces fimbriatus*.[7]

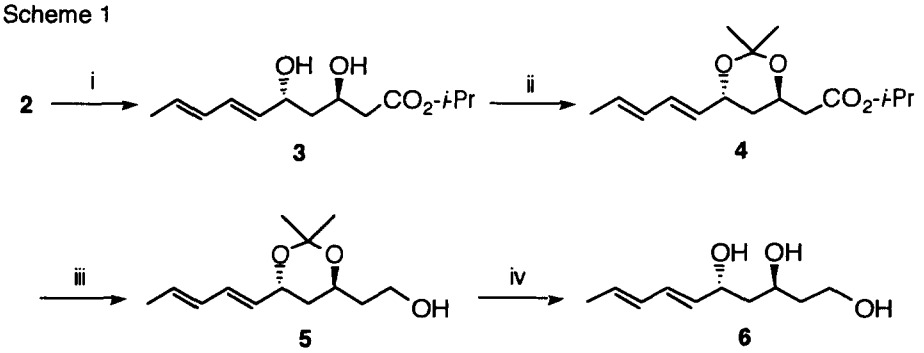
Dedicated to the memory of Professor Hidemasa Takaya, deceased on 5 October 1995



(eq. 1)

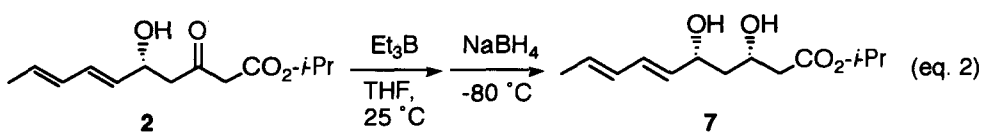
The reaction of 2,4-hexadienal with diketene proceeded in the presence of Schiff base **1**—titanium isopropoxide complex at -40 °C to give isopropyl (*5R*,*6E*,*8E*)-5-hydroxy-3-oxodeca-6,8-dienoate **2** in 90% e.e. and in 56% chemical yield (eq. 1).

Scheme 1



i, $(CH_3)_4NHB(OAc)_3$, CH_3CN, AcOH, -40 °C, 18 h, 92%. ii, $(CH_3)_2C(OCH_3)_2$, PTS, 0 °C, 10 min, 64%. iii, $LiAlH_4$, THF, 45 °C, 2 h, 91%. iv, 80% CH_3COOH, 20 °C, 30 min, 41%

Scheme 1 shows the procedure for conversion of compound **2** to **6**. The stereoselective reduction of **2** with $(CH_3)_4NHB(OAc)_3$ in acetonitrile according to Evans' procedure[8] afforded *anti*-diol esters **3**. The formation of *syn*-diol ester **7** was not observed, which was confirmed by ^1H and ^{13}C NMR spectra (see experimental section). The authentic *syn*-diol ester could be prepared by Narasaka's method using Et_3B—$NaBH_4$ system reduction of **2** (eq. 2).[9] The diol ester **3** was then converted into acetonide **4**, followed by reduction of **4** with



(eq. 2)

$LiAlH_4$ gave **5**. Deacetalization of **5** by treatment with 80% acetic acid gave the triol **6** whose spectral data were consistent with those of natural product.[7]

Thus, the natural product **6** was easily prepared in 90% e.e. by our new asymmetric catalysed reaction by

the titanium complex.

Experimental Section

General. All melting points were measured by using a Yanaco MP-500D apparatus and were uncorrected. ^{1}H NMR spectra were measured on a JEOL GSX-400 (400 MHz) or a Hitachi R-250 (250 MHz) Fourier Transfer NMR spectrometer using chloroform-d as a solvent and recorded in ppm relative to internal tetramethylsilane standard. ^{13}C NMR (62.9 MHz) spectra were measured on Hitachi R-250 Fourier Transfer NMR spectrometer *J*. Values are given in Hz. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. High resolution mass spectra (HRMS) were measured on a JEOL JMS-SX102 (EI). IR spectra were obtained with a Hitachi 270-50. Optical rotations were measured on a JASCO DIP-4 digital polarimeter. HPLC analyses were carried out on a JASCO PU-980 liquid chromatography with a JASCO UV-970 detector. The column used for HPLC analyses was Daicel CHIRALPAK AD. All experiments were carried out under an argon atomosphere.

Materials. 3-*tert*-Butylsalicylaldehyde was prepared by the modification of Casnati's method[10]: A 1-L three-necked round-bottomed flask equipped with a ball condenser is charged with 2-*tert*-butylphenol (30.0 g, 200 mmol), paraformaldehyde (18.0 g, 600 mmol), anhydrous tin(II) chloride (3.78 g, 20 mmol), 4-picolin (7.79 mL, 80 mmol), and toluene (400 mL). This mixture was stirred at 95 °C for 6 h. After cooling to room temperature, the mixture was filtered, and the filtrate was evaporated. The residue obtained was extracted with diethyl ether (50 mL x 2), and the combined organic layer was washed with brine (50 mL), and dried over anhydrous Na_2SO_4. After evaporation, the residue was distilled under reduced pressure to give 3-*tert*-butylsalicylaldehyde (18.7 g, 53%). b.p. 120—122 °C/17 mmHg.

(*R*)-2-(*N*-3-*tert*-Butylsalicylidene)amino-3-methyl-1-butanol 1. A mixture of 3-*tert*-butylsalicylaldehyde (10.3 g, 49.9 mmol), (*R*)-valinol (5.15 g, 49.9 mmol), and methanol (280 mL) were refluxed for 9 h in the presence of anhydrous Na_2SO_4 (40 g). The mixture was filtered through a pad of Celite, and the filtrate was evaporated up, then the obtained residue was purfied by recrystallization from petroleum ether to give **1** (12.3 g, 94%) as a yellow needle. m.p. 57.2 °C. $[\alpha]_D^{24}$ +39.5 (*c* 1.0, $CHCl_3$). IR ν_{max}: 3250, 2960, 1630, 1270 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.95 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 1.4 (s, 9H), 1.6 (br s, 1H), 2.0 (m, 1H), 3.0 (m, 1H), 3.8 (m, 2H), 6.8—7.5 (m, 3H), 8.37 (s, 1H), 13.5 (br s, 1H). Anal. Calcd for $C_{16}H_{25}NO_2$; C, 72.97; H, 9.57; N, 5.32: Found; C, 73.33; H, 9.83; N, 5.32.

Isopropyl (5*R*,6*E*,8*E*)-5-hydroxy-3-oxodeca-6,8-dienoate 2. In a Schlenk tube were placed Schiff base **1** {(*R*)-2-(*N*-3-*tert*-butylsalicylidene)amino-3-methyl-1-butanol} (8.50 g, 32.3 mmol) and CH_2Cl_2 (45 mL). To this solution was added Ti(O-*i*-Pr)4 (8.8 mL, 29.5 mmol) at room temperature, and the resulting solution was stirred for 1 h, and the mixture was then cooled to -40 °C. 2,4-Hexadienal (3.24 mL, 29.5 mmol) and diketene (4.55 mL, 59.0 mmol) were added to the solution, and the whole was stirred for 96 h at this temperature. The mixture was poured into a mixture of 1N HCl (50 mL) and diethyl ether (50 mL) and stirred vigorously for 24 h at room temperature. The mixture was then extracted with ethyl acetate (50 mL x 3), and the combined extracts were washed with saturated $NaHCO_3$ solution (50 mL x 2), brine (50 mL x 2), and dried over Na_2SO_4. After evaporation of the volatiles, the residue was chromatographed on silica-gel [eluent, hexane—ethyl acetate (3:1)] to give **2** (4.0 g, 56.4%) as a colorless oil. *Rf* 0.36 (33% ethyl acetate in hexane). $[\alpha]_D^{24}$ +9.1 (*c* 1.0, $CHCl_3$). The e.e. was determined as 90% by HPLC analysis [column, CHIRALPAK AD; eluent, hexane—ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min]. t_R of *S* isomer: 19 min; t_R of *R* isomer: 24 min. IR ν_{max}: 3437, 2981, 1735, 1711, 1645, 1105, 990 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.26 (d, *J*

= 6.7 Hz, 6H), 1.75 (dd, *J* = 6.7 Hz, 2.0 Hz, 3H), 2.7 (br s, 1H), 2.77 (d, *J* = 6.4 Hz, 2H), 3.44 (s, 2H), 4.63 (dt, *J* = 6.8 Hz, 6.4 Hz, 1H), 5.06 (sept, *J* = 6.7 Hz, 1H), 5.54 (dd, *J* = 15.4 Hz, 6.4 Hz, 1H), 5.72 (dq, *J* = 16.8 Hz, 6.4 Hz, 1H), 6.02 (ddq, *J* = 10.4 Hz, 16.8 Hz, 2.0 Hz, 1H), 6.23 (dd, *J* = 15.4 Hz, 10.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 17.5, 21.1, 49.4, 49.8, 67.6, 68.5, 129.6, 130.2, 130.4, 130.7, 166.1, 201.9. HRMS (EI) *m/z* Calcd for $C_{13}H_{20}O_4$ (M^+): 240.1362. Found: 240.1367.

Isopropyl (3*S*,5*R*,6*E*,8*E*)-3,5-dihydroxydeca-6,8-dienoate 3. To a solution of tetramethylammonium triacetoxyborohydride (26.3 g, 100 mmol) in 55 mL of anhydrous acetonitrile was added 55 mL of anhydrous acetic acid at 0 °C, and the mixture was stirred for 30 min. at room temperature. The mixture was cooled to -40 °C, and a solution of **2** (3.0 g, 12.5 mmol) in 17 mL of acetonitrile was added. The mixture was stirred at this temperature for 18 h. The reaction was quenched with 125 mL of 0.5N sodium potassium tartrate and the nixture was allowed to warm slowly to room temperature. The mixture was extracted with ethyl acetate (50 mL x 3), and the combined extracts were washed with saturated $NaHCO_3$ solution (50 mL x 2), brine (50 mL x 2), and dried over Na_2SO_4. After evaporation of the volatiles, the residue was chromatographed on silica-gel [eluent, hexane—ethyl acetate (2:1)] to give **3** (2.8 g, 92.1%) as a colorless oil. *Rf* 0.19 (33% ethyl acetate in hexane). $[\alpha]_D^{24}$ -11.7 (*c* 1.0, $CHCl_3$). IR ν_{max}: 3412, 2984, 2936, 2920, 1726, 1406, 1378, 1294, 1258, 1176, 1108, 1066, 990 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.25 (d, *J* = 6.4 Hz, 6H), 1.6—1.7 (m, 2H), 1.76 (dd, *J* = 6.8 Hz, 2.0 Hz, 3H), 2.4—2.5 (m, 2H), 2.6 (br s, 1H), 3.5 (br s, 1H), 4.33 (m, 1H), 4.47 (m, 1H), 5.05 (sept, *J* = 6.4 Hz, 1H), 5.61 (dd, *J* = 15.1 Hz, 6.4 Hz, 1H), 5.71 (dq, *J* = 15.2 Hz, 6.8 Hz, 1H), 6.05 (ddq, *J* = 10.8 Hz, 15.2 Hz, 2.0 Hz, 1H), 6.24 (dd, *J* = 15.1 Hz, 10.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 18.0, 21.8, 41.7, 42.3, 65.7, 68.3, 69.6, 129.8, 130.5, 130.8, 132.6, 172.2. HRMS (EI) *m/z* Calcd for $C_{13}H_{22}O_4$ (M^+): 242.1518. Found: 242.1503.

Isopropyl (3*S*,5*R*,6*E*,8*E*)-3,5-isopropylidendioxydeca-6,8-dienoate 4. To a mixture of **3** (2.4 g, 9.92 mmol) and 2,2-dimethoxypropane (25 mL) was added small amount of camphorsulfonic acid. The mixture was stirred at 0 °C for 10 min. The reaction was quenched with 20 mL of saturated $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (50 mL x 3), and the combined extracts were washed with brine (50 mL x 2) and dried over Na_2SO_4. After evaporation of the volatiles, the residue was chromatographed on silica-gel [eluent, hexane—ethyl acetate (2:1)] to give **4** (1.8 g, 63.6%) as a colorless oil. *Rf* 0.69 (33% ethyl acetate in hexane). $[\alpha]_D^{24}$ +32.5 (*c* 0.7, $CHCl_3$). IR ν_{max}: 2988, 2936, 1734, 1382, 1204, 1176, 1110, 990 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.23 (d, *J* = 6.4 Hz, 6H), 1.37 (s, 3H), 1.39 (s, 3H), 1.70 (ddd, *J* = 12.9 Hz, 6.4 Hz, 2.9 Hz, 1H), 1.74 (dd, *J* = 6.8 Hz, 2.0 Hz, 3H), 1.84 (ddd, *J* = 12.9 Hz, 8.9 Hz, 3.9 Hz, 1H), 2.41 (dd, *J* = 15.4 Hz, 5.4 Hz, 1H), 2.51 (dd, J = 15.4 Hz, 8.3 Hz, 1H), 4.3—4.4 (m, 2H), 5.03 (sept, *J* = 6.4 Hz, 1H), 5.57 (dd, *J* = 15.1 Hz, 6.8 Hz, 1H), 5.71 (dq, *J* = 15.2 Hz, 6.8 Hz, 1H), 6.03 (ddq, *J* = 10.7 Hz, 15.2 Hz, 2.0 Hz, 1H), 6.17 (dd, *J* = 15.1 Hz, 10.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 18.5, 22.3, 25.3, 25.9, 37.9, 41.9, 63.9, 67.8, 68.2, 101.0, 130.5, 130.9, 131.4, 131.7, 170.7. HRMS (EI) *m/z* Calcd for $C_{16}H_{26}O_4$ (M^+): 282.1831. Found: 282.1846.

(3*S*,5*R*,6*E*,8*E*)-3,5-*O*-isopropylidenedeca-6,8-dien-1,3,5-triol 5. To a mixture of $LiAlH_4$ (0.21 g, 5.6 mmol) and THF (30 mL) was added THF (15 mL) solution of **4** (1.6 g, 5.6 mmol) dropwisely at 0 °C. The mixture was stirred at 45 °C for 2 h. The reaction was quenched with 0.8 mL of H_2O and 0.2 mL of 15% aqueous NaOH solution. The mixture was extracted with ethyl acetate (50 mL x 3), and the combined extracts were washed with brine (50 mL x 2) and dried over Na_2SO_4. After evaporation of the volatiles, the residue was chromatographed on silica-gel [eluent, hexane—ethyl acetate (2:1)] to give **5** (1.14 g, 91.2%) as a colorless oil. *Rf* 0.26 (33% ethyl acetate in hexane). $[\alpha]_D^{24}$ +33.6 (*c* 1.0, $CHCl_3$). IR ν_{max}: 3428, 2992,

2940, 1382, 1224, 1168, 1054, 988 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.41 (s, 3H), 1.76 (dd, *J* = 6.8 Hz, 1.2 Hz, 3H), 1.7—1.8 (m, 4H), 2.5 (br s, 1H), 3.7—3.8 (m, 2H), 4.0—4.1 (m, 2H), 4.3—4.4 (m, 2H), 5.56 (dd, *J* = 15.1 Hz, 6.3 Hz, 1H), 5.71 (dq, *J* = 14.5 Hz, 6.8 Hz, 1H), 6.00 (ddq, *J* = 10.3 Hz, 14.5 Hz, 1.2 Hz, 1H), 6.17 (dd, *J* = 15.1 Hz, 10.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 17.4, 24.3, 24.9, 37.1, 37.3, 65.4, 66.9, 67.0, 99.8, 129.3, 129.8, 130.2, 130.5. HRMS (EI) *m/z* Calcd for $C_{13}H_{22}O_3$ (M^+): 226.1569. Found: 226.1597.

(3*S*,5*R*,6*E*,8*E*)-Deca-6,8-dien-1,3,5-triol 6. A mixture of **5** (0.7 g, 3.13 mmol) and 80% acetic acid (60 mL) was stirred at 25 °C for 30 min. The reaction was quenched with 20 mL of saturated $NaHCO_3$ solution. The mixture was extracted with chloroform (50 mL x 5), and the combined extracts were washed with brine (50 mL x 2) and dried over Na_2SO_4. After evaporation of the volatiles, the residue was chromatographed on silica-gel [eluent, ethyl acetate—methanol (95:5)] to give **6** (0.24 g, 41.4%) as a colorless oil. *Rf* 0.32 (5% ethyl acetate in hexane). $[\alpha]_D^{24}$ +6.7 (*c* 0.3, $CHCl_3$) (lit.[7] $[\alpha]_D^{23}$ +8.2 (*c* 0.98, $CHCl_3$) IR ν_{max}: 3416, 3376, 3336, 2940, 1060, 990 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.6—1.9 (m, 4H), 1.76 (dd, *J* = 6.7 Hz, 1.5 Hz, 3H), 2.9 (br s, 2H), 3.7 (br s, 1H), 3.8—3.9 (m, 2H), 4.1—4.2 (m, 1H), 4.5—4.6 (m, 1H), 5.62 (dd, *J* = 15.2 Hz, 6.4 Hz, 1H), 5.71 (dq, *J* = 15.0 Hz, 6.7 Hz, 1H), 6.03 (ddd, *J* = 15.0 Hz, 10.4 Hz, 1.5 Hz, 1H), 6.17 (dd, *J* = 15.2 Hz, 10.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 18.5, 39.0, 43.5, 62.2, 70.0, 70.1, 130.7, 131.2, 131.4, 133.0. HRMS (EI) *m/z* Calcd for $C_{10}H_{16}O_2$ (M^+-18): 168.1150. Found: 168.1112.

Isopropyl (3*R*,5*R*,6*E*,8*E*)-3,5-dihydroxydeca-6,8-dienoate 7. To a THF—MeOH (4:1, 100 mL) solution of tetraethylborane (1M in hexane, 13.7 mL, 13.7 mmol) and **2** (3.0 g, 12.5 mmol) was introduced small amount of air, and the solution was stirred for 2 h at room temperature under an argon atomosphere. Then, the solution was cooled to -80 °C, and solid $NaBH_4$ (1.53 g, 13.7 mmol) was added. The mixture was stirred for 1 h at this temperature. After this, 31% H_2O_2 (63 mL) was added to the mixture at this temperature, then the whole was added to a mixture of phosphate buffer (pH 6.88, 126 mL) and MeOH (190 mL) at 0 °C. The organic solvent was removed under reduced pressure, and the residual aqueous solution was extracted with CH_2Cl_2 (50 mL x 3). The extract was dried over Na_2SO_4 and concentrated. Then, the oily residue was chromatographed on silica-gel (hexane—ethyl acetate 2:1) to afford **7** (1.7 g, 56%) as a colorless oil. *Rf* 0.19 (33% ethyl acetate in hexane). $[\alpha]_D^{24}$ +4.4 (*c* 1.0, $CHCl_3$). IR ν_{max}: 3432, 3412, 2984, 2936, 1728, 1414, 1404, 1378, 1328, 1322, 1292, 1266, 1178, 1108, 990 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.24 (d, *J* = 6.3 Hz, 6H), 1.6—1.7 (m, 2H), 1.75 (dd, *J* = 6.4 Hz, 1.5 Hz, 3H), 2.4—2.5 (m, 2H), 3.3 (br s, 1H), 3.8 (br s, 1H), 4.26 (m, 1H), 4.41 (m, 1H), 5.03 (sept, *J* = 6.3 Hz, 1H), 5.54 (dd, *J* = 15.2 Hz, 6.4 Hz, 1H), 5.70 (dq, *J* = 15.1 Hz, 6.4 Hz, 1H), 6.03 (ddq, *J* = 10.5 Hz, 15.1 Hz, 1.5 Hz, 1H), 6.20 (dd, *J* = 15.2 Hz, 10.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 17.9, 21.7, 42.0, 42.9, 68.1, 69.0, 72.1, 129.8, 130.5, 130.8, 132.5, 171.8. HRMS (EI) *m/z* Calcd for $C_{13}H_{22}O_4$ (M^+): 242.1518. Found: 242.1536.

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