Synthetic Photochemistry. LXX. Efficient Formation of An Eudesmane Skeleton by the de Mayo Reaction between 1-Isopropyl-4-methylcyclohexa-1,3-diene and Methyl 2,4-Dioxopentanoate

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Synthetic Photochemistry. LXX.[1] Efficient Formation of An Eudesmane Skeleton by the de Mayo Reaction between 1-Isopropyl-4-methylcyclohexa-1,3-diene and Methyl 2,4-Dioxopentanoate

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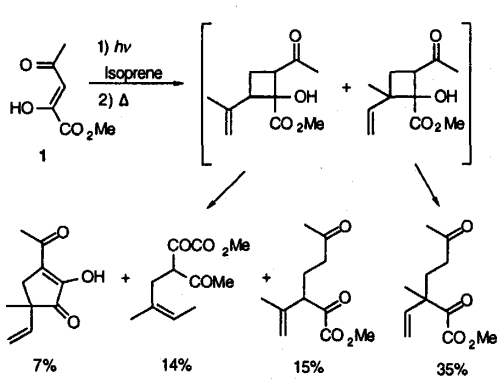
The de Mayo reaction of methyl 2,4-dioxopentanoate and 1-isopropyl-4-methylcyclohexa-1,3-diene afforded, together with an oxetane and a [4+2] adduct, a dihydropyran derivative, which gave an eudesmane derivative by acid treatment. The dihydropyran and the [4+2] adduct were formed from the common intermediate.

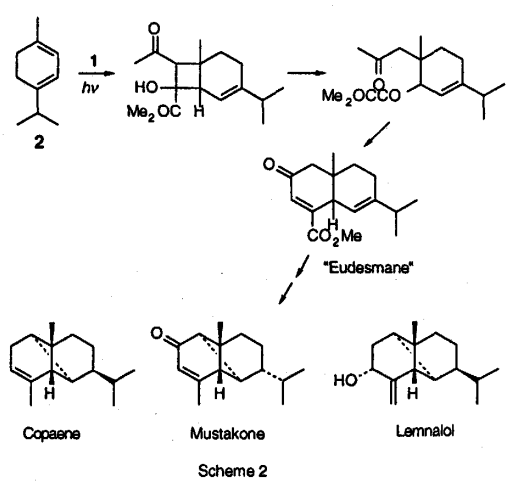
The de Mayo reaction, a photochemical [2+2] cycloaddition reaction between an enolizable β-diketone and an olefin, is one of the most widely-applied photochemical reactions in the syntheses of natural products as well as structurally complex polycyclic ring systems.[2] As an enolizable β-diketone, we have developed alkyl 2,4-dioxoalkanoates, which are existing in linearly conjugated structure in various media to cycloadd regiospecifically with various olefins upon UV irradiations. We have previously observed that methyl 2,4-dioxopentanoate (**1**) reacted with conjugated olefins such as cyclopentadiene,[3] indene,[4] and cycloheptatriene,[5] which usually work as a quencher of an excited state of an α,β-unsaturated ketone to intervene the formation of photoproducts.



Scheme 1

In the case of the photoaddition between **1** and isoprene, an unsymmetrical olefin, the main product was a 1,5-diketone derived from the primary photoadduct at the disubstituted double bond of isoprene.[6,7] Thus, **1** has an advantage to react site-selectively with conjugated dienes.

In this paper, we report the photocycloaddition reaction between **1** and 1-isopropyl-4-methylcyclohexa-1,3-diene, α-terpinene (**2**) to build up an eudesmane skeleton, from which it should be convertible to ylangene-type sesquiterpenoids such as mustakone,[8] copaene,[9] and lemnalol.[10]



Scheme 2

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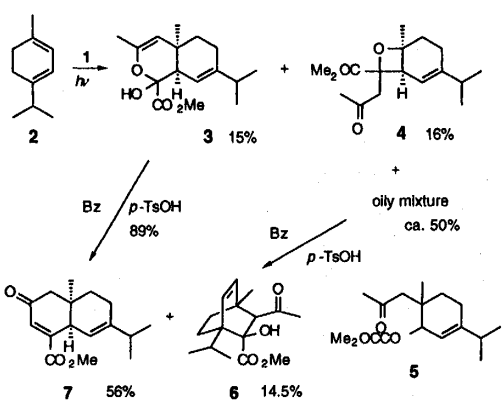
When an ethyl acetate solution of **1** and **2** was irradiated by means of a 400 W high-pressure mercury lamp, a crystalline product (**3**), an oily product (**4**), and an oily mixture were obtained in 15, 16, and ca. 50% yields, respectively, through silica-gel chromatography of a mixture of the photoproducts. The ^{1}H-NMR spectrum of **3** showed a singlet methyl signal at δ 0.95 and another methyl signal on the double bond at δ 1.76 instead of an acetyl methyl signal which was usually observed in photo-adducts between **1** and olefins. The methyl signal at δ 1.76 coupled with an olefinic proton at δ 4.51 with a range of the allylic coupling constant, 0.7 Hz. The ^{13}C-NMR spectrum showed an acetal carbon at δ 95.9 and four olefinic carbons at δ 108.9, 113.1, 144.3, and 147.5, two of which were assigned to the enolic carbons. Together with an appearance of an IR absorption band due to the hydroxyl group, these data deduced the structure of dihydropyran **3** as shown in Scheme 3.



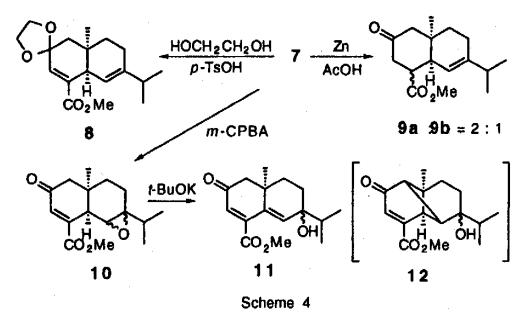
Scheme 3

Previously, dihydropyran derivatives have been already identified in the photoreaction of **1** and 2,5-dimethyl-2,4-hexadiene.[11] It has been observed that dihydropyran derivatives were not derived from the co-generated 1,5-diketone derivative and they were derived directly from a proto-photoadduct, cyclobutanol. The stereo-chemistry of **3**, therefore, was assigned to be *cis* on the basis of the result of **1** and 2,5-dimethyl-2,4-hexadiene.

The product **4** was also a 1:1 adduct. The ^{1}H-NMR spectrum of **4** showed a quaternary methyl signal at δ 1.53, an acetyl methyl signal at δ 2.10, and an *AB* pattern (*J*=17.2 Hz) at δ 2.83 and 2.95 due to the isolated methylene proton. The ^{13}C-NMR spectrum showed a carbonyl carbon at δ 205.5 and an ester carbonyl carbon at δ 174.0 as well as two carbons attached to an oxygen atom at δ 82.3 and 82.9. These spectral data supported that the structure of **4** was the oxetane reacted with the carbonyl group of the keto form of **1** and the less hindered double bond of **2**.[12]

The ^{1}H-NMR spectrum of the oily mixture indicated the presence of a 1,5-diketone (**5**), which should be the main product, and a [4+2] cycloadduct (**6**). The structure of **5** was determined from the ^{1}H-NMR data, which showed an acetyl signal at δ 2.09 and an *AB* quartet at δ 2.46 and 2.73 with a coupling constant of 16.5 Hz. The ^{13}C-NMR spectrum exhibited three carbonyl signals at δ 161.9, 193.6, and 209.7. The ^{1}H-NMR spectrum of **6** showed a presence of an etheno bridge observed as an *AB* quartet (*J*=8 Hz) at δ 5.92 and 6.04. This indicated that **6** was a [4+2] cycloadduct between **1** and **2**.[12] While the singlet methyl signal at δ 1.23 was irradiated, the singlet methine signal at δ 2.78 was enhanced. From the NOE result, the structure of **6** was determined as shown in Scheme 3.

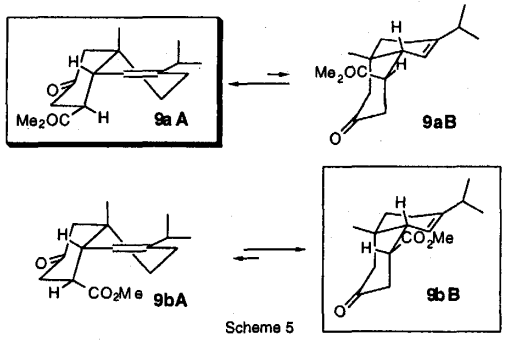
Dehydration of **3** with *p*-toluenesulfonic acid in benzene gave a colorless oil (**7**), whose ^{1}H-NMR spectrum showed that a methyl signal at δ 1.76 and an olefinic proton signal at δ 4.51 disappeared and that a newly-formed olefinic proton signal appeared at δ 6.67. Since the ^{13}C-NMR and UV spectra exhibited the presence of an α,β-unsaturated chromophore, the structure of **7** was determined to be an enone, which has an eudesmane skeleton. Compound **7** was also obtained in 56% yield as well as **6** in 14.5% yield by direct treatment with *p*-toluene-sulphonic acid of a mixture of the photoproducts.



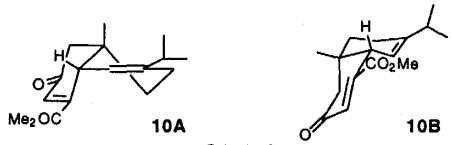
Scheme 4

Acetalization of **7** gave a single product **8**. When **7** was reduced by zinc in acetic acid, two isomers **9a** and **9b** were obtained in a 2:1 ratio. The olefinic proton of **9a** appeared at δ 5.10 as a broad singlet, while that of **9b** at δ 5.30 as a multiplet. If **7** were a trans isomer, a single product should be formed because one of the two

isomers has to have an axial ester group, which induced severe 1,3-diaxial interaction between the ester and the angular methyl groups. In the case of a *cis*-octalone system, it is possible to take two conformations as shown in Scheme 5. Conformers **9aA** and **9bB** with an equatorial methoxycarbonyl group are more stable than conformers **9aB** and **9bA**. When compared **9aA** with **9bB**, **9bB** is less stable than **9aA** due to the presence of an 1,3-diaxial interaction between the methyl group and the hydrogen atom on the carbon atom attached to the methoxycarbonyl group. From these evidences, the stereochemistry of the ring junction of **7** and **8** was assigned to be *cis*. MM2 calculations also supported that **7** is more stable than the corresponding trans isomer.[13]



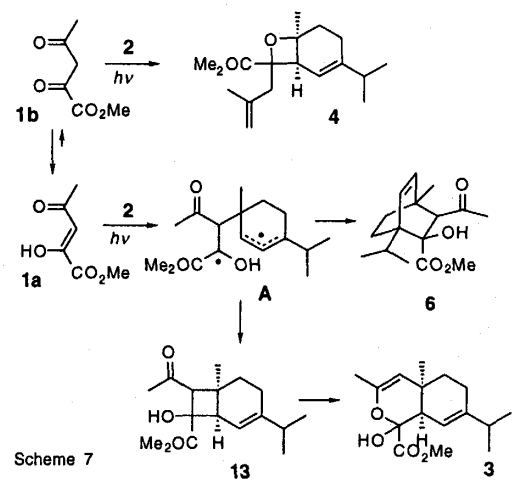
Scheme 5



Scheme 6

Next, *m*-chloroperbenzoic acid oxidation of **7** gave a 1:1 mixture of **10a** and **10b**. Epoxidation occurred in conformer **10B**, whose isolated double bond is less crowded than that of **10A** as shown in Scheme 6. When a mixture of **10a** and **10b** was treated with potassium *t*-butoxide, an alcohol **11** was obtained instead of the desired tricyclic compound **12**. The unsuccessful result must be due to the less mobile conformation of the cyclohexenone system and the formation of the unfavorable carbanion at the neopentyl position of **10**. The less crowded carbanion at the ring juncture made it possible to form **11**.

Finally, it is worth discussing the mechanism of the photoreaction of **1** and **2**. The oxetane must be produced *via* the Paterno-Büchi reaction of the keto form **1b** and **2** as observed previously.[11] Photochemical [4+2] cycloadditions of **1** have been reported in the reactions of **1** and cyclopentadiene,[3] cycloheptatriene,[5] and *p*-mentha-1,5-diene.[12] In the case of *p*-mentha-1,5-diene, however, we have observed that the transition states leading to [2+2] and [4+2] cycloadducts were mutually unrelated. In the present case, we speculated that the [2+2] and [4+2] cycloadditions proceeded *via* the common biradical intermediate **A**,[13] which was derived from the reaction of the enol form **1a** and **2**.



Scheme 7

Here, we could isolate the dihydropyran **3** instead of the 1,5-diketone **5**, which belongs to the ordinary products in the reaction of **1** and olefins. An eudesmane skeleton was constructed *via* only two steps through the de Mayo reaction and the following acid-catalyzed reaction from **1** and **2**.

Experimental

Elemental analyses were performed in this Institute, Kyushu University. The mps were measured with a Yanagimoto Micro mp apparatus and are not corrected. The NMR spectra were measured by JEOL FX 100 and GSX 270H spectrometers in $CDCl_3$, unless otherwise specified, and the chemical shifts expressed were in δ units. Mass spectra were measured with a JEOL 01SG-2 spectrometer. The IR spectra were taken as KBr disks for crystalline compounds or as liquid films inserted between NaCl plates for oily materials using a JASCO IR-A 102 spectrometer. The UV spectra were measured using Hitachi U-3200 and U-3410 spectrophotometers. The stationary phase for the column chromatography was Wakogel C-300 and the elution solvents were mixtures of hexane and ethyl acetate.

Photoreaction of 1 and α-Terpinene. An EtOAc solution of **1** (2.12 g) and α-

terpinene (21.4 g) was irradiated by means of a 400 W high-pressure Hg-lamp through a Pyrex glass filter for 3.5 h. After the volatile material was evaporated under reduced pressure, the residue was purified by a silica-gel column to give **3** (631 mg, 15%), **4** (672 mg, 16%), and the mixture (ca. 2.1g, 50%).

3: mp 94-94.5 °C. ^{1}H-NMR: δ=0.95 (3H, s), 0.99 (6H, d, *J*=7.0 Hz), 1.25 (1H, m), 1.76 (3H, d, *J*=0.7 Hz), 1.92-2.08 (3H, m), 2.22 (1H, sept, *J*=7.0 Hz), 2.50 (1H, d, *J*=4.7 Hz), 3.90 (3H, s), 3.94 (1H, d, *J*=1.5 Hz), 4.51 (1H, s), and 5.02 (1H, d, *J*=4.7 Hz). ^{13}C-NMR: δ=19.9, 21.1, 21.7, 22.3, 26.9, 29.4, 30.2, 35.4, 43.3, 53.5, 95.9, 108.9, 113.1, 144.3, 147.5, and 171.3. IR: ν 3500, 2950, 1750, 1700, 1440, 1380, 1270, 1205, 1150, and 1050. MS m/z (%): 280 (M^+, 40), 247 (11), 223 (28), 136 (52), 93 (63), 91 (37), 43 (100), and 41 (67). Found: C, 68.39; H, 8.70% m/z 280.1667. Calcd for $C_{16}H_{24}O_4$: C, 68.53; H, 8.63%, 280.1673.

4: oil. ^{1}H-NMR: δ=1.07 (6H, d, *J*=6.6 Hz), 1.20-1.35 (1H, m), 1.53 (3H, s), 1.75-1.90 (2H, m), 2.10 (3H, s), 2.83 (1H, d, *J*=17.2 Hz), 2.95 (1H, d, *J*=17.2 Hz), 3.37 (1H, d, *J*=6.2 Hz), 3.81 (3H, s), and 5.35 (1H, ddd, *J*=6.2, 2.5, 1.0 Hz). ^{13}C-NMR: δ=21.0, 21.3, 23.4, 27.9, 30.5, 33.5, 35.8, 44.1, 48.2, 52.6, 82.3, 82.9, 114.9, 151.2, 174.0, and 205.5. IR: ν 2950, 1723, 1430, 1360, 1280, 1195, and 1060 cm^{-1}. MS m/z (%): 280 (M^+, 2), 146 (14), 137 (11), 136 (100), and 135 (29). Found: m/z 280.1672. Calcd for $C_{16}H_{24}O_4$: 280.1673.

5: ^{1}H-NMR: δ=0.99 (6H, d, *J*=7.0 Hz), 1.0-1.35 (2H, m), 1.02 (3H, s), 1.9-2.1 (2H, m), 2.09 (3H, s), 2.22 (1H, sept, *J*=7.0 Hz), 2.46 (1H, d, *J*=16.5 Hz), 2.73 (1H, d, *J*=16.5 Hz), 3.90 (3H, s), 4.07 (1H, dd, *J*=5.0, 1.3 Hz), and 5.40 (1H, d, *J*=5.0 Hz). ^{13}C-NMR: δ=21.1, 21.5, 22.4, 24.0, 31.8, 32.5, 33.7, 35.2, 50.5, 50.7, 53.0, 113.0, 147.3, 161.9, 193.6, and 209.7.

Acid Treatment of 3. A benzene solution (10 cm^3) of **3** (250 mg) and a catalytic amount of *p*-TsOH was refluxed for 2 h. The mixture was washed with sat. $NaHCO_3$ and sat. NaCl solutions and dried on Na_2SO_4. The benzene layer was evaporated under reduced pressure to give the mixture, which was chromatographed on a silica-gel column to give **7** (208 mg, 89%).

7: oil. ^{1}H-NMR: δ=0.99 (3H, d, *J*=7.0 Hz), 1.00 (3H, d, *J*=7.0 Hz), 1.03 (3H, s), 1.59-1.64 (2H, m), 1.96 (1H, d, *J*=15.8 Hz), 2.01-2.06 (2H, m), 2.23 (1H, sept, *J*=7.0 Hz), 2.61 (1H, d, *J*=15.8 Hz), 3.19 (1H, m), 3.87 (3H, s), 5.21 (1H, br s), and 6.69 (1H, d, *J*=1.1 Hz). ^{13}C-NMR: δ=21.2, 21.5, 22.6, 26.6, 34.5, 35.0 (2C), 42.8, 44.1, 52.6, 116.8, 131.4, 143.6, 148.7, 167.0, and 200.8. IR: ν 2960, 2920, 1722, 1680, 1432, 1365, 1230, 1161, 1019, and 755 cm^{-1}. MS m/z (%): 262 (M^+, 100), 260 (13), 248 (12), 246 (24), 230 (13), 220 (43), and 206 (11). Found: C, 73.01; H, 8.48%. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%.

Acid Treatment of the Oily Mixture. The oily mixture was similarly heated with a catalytic amount of *p*-TsOH in refluxing benzene to give **7** (56%) and **6** (14.5%).

6: oil. ^{1}H-NMR: δ=0.91 (3H, d, *J*=7.0 Hz), 0.95 (3H, d, *J*=7.0 Hz), 1.2-2.0 (5H, m), 1.22 (3H, s), 1.92 (3H, s), 2.78 (1H, br s), 3.50 (1H, br s, D_2O exchangeable), 3.82 (3H, s), 5.92 (1H, d, *J*=8.0 Hz), and 6.04 (1H, d, *J*=8.0 Hz). ^{13}C-NMR: δ=18.8, 19.8, 22.5, 23.0, 26.0, 31.1, 32.7, 36.4, 49.2, 53.3, 64.5, 80.2, 135.5, 139.9, 177.6, and 205.8.

Acetalization of 7. An anhydrous benzene solution (50 cm^3) of **7** (84 mg), ethylene glycol (111 mg), and a catalytic amount of *p*-TsOH was refluxed for 3 h. The benzene layer was washed with aq. $NaHCO_3$ solution, water, and dried on Na_2SO_4. After removal of solvent, the residue was chromatographed on a silica-gel column to give **8** (93 mg, 95%).

8: oil. ^{1}H-NMR: δ=0.96 (3H, d, *J*=7.0 Hz), 0.97 (3H, d, *J*=7.0 Hz), 1.01-1.09 (1H, m), 1.03 (3H, s), 1.18 (1H, m), 1.36 (1H, d, *J*=13.6 Hz), 1.46-1.65 (2H, m), 2.07 (1H, d, *J*=13.6 Hz), 2.19 (1H, sept, *J*=7.0 Hz), 2.91 (1H, m), 3.79 (3H, s), 3.9-4.1 (4H, m), 5.16 (1H, br s), and 6.61 (1H, s). ^{13}C-NMR: δ=21.1, 21.5, 22.4, 27.2, 31.9, 34.9, 36.1, 38.2, 41.9, 51.9, 64.0, 65.0, 105.5, 118.6, 133.8, 134.8, 142.0, and 167.5. MS m/z (%): 306 (M^+, 100), 263 (24), 247 (14), and 220 (20). Found: m/z 306.1832. Calcd for $C_{18}H_{26}O_4$; 306.1832.

Reduction of 7 by Zinc in Acetic Acid. To a refluxing acetic acid solution (10 cm^3) of **7** (93 mg) was added powdered Zn (1.02 g) for 3 h. Zn was removed by filtration and the filtrate was diluted with ether. The ether layer was washed with water, dried on Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on a silica-gel column to give an oil **9** (**9a**:**9b**=2:1, 84 mg, 89%). Found: C, 72.55; H, 9.15%. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15%. IR: ν 2965, 2930, 2880, 1730 (br), 1465, 1440, 1277, 1265, 1200, and 1170 cm^{-1}.

9a: ^{1}H-NMR: δ=1.00 (6H, d, *J*=7.0 Hz),

1.04 (3H, s), 1.3-2.7 (10H, m), 3.12 (1H, ddd, J=12.5, 5.0, 4.5 Hz), 3.76 (3H, s), and 5.10 (1H, br s).

9b: ^{1}H-NMR: δ=0.98 (6H, d, J=7.0 Hz), 1.04 (3H, s), 1.3-2.7 (11H, m), 3.72 (3H, s), and 5.30 (1H, m).

Epoxidation of 7. To the methylene chloride solution (5 cm^3) of **7** (99.5 mg) was added *m*-chloroperbenzoic acid (110 mg) at -20 °C. The mixture was stirred for 2.5 h at room temperature. After aq. $Na_2S_2O_3$ and $NaHCO_3$ solutions were added to the mixture, the mixture was extracted with chloroform. The organic layer was washed with aq. NaCl solution, dried on Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on silica-gel column to give an oil **10** (a 1:1-mixture, 101 mg, 100%).

10: ^{1}H-NMR: δ=0.93 (3H, d, J=7.0 Hz), 0.94 (3H, s), 0.97 (3H, s, J=7.0 Hz), 0.98 (3H, s), 1.00 (3H, d, J=7.0 Hz), 1.02 (3H, s), 1.4-2.0 (10H, m), 1.91 (1H, d, J=16.1 Hz), 1.99 (1H, d, J=16.5 hz), 2.47 (1H, d, J=16.1 Hz), 2.70 (1H, s), 2.86 (1H, d, J=16.5 Hz), 2.88 (1H, s), 2.93 (1H, dd, J=3.3, 1.5 Hz), 3.27 (1H, d, J=3.3 Hz), 3.87 (3H, s), 3.90 (3H, s), 6.79 (1H, d, J=1.5 Hz), and 6.86 (1H, s). ^{13}C-NMR: δ=17.0, 17.5, 18.1, 18.5, 19.3, 19.9, 26.9, 27.9, 31.0, 32.7, 33.2, 33.8, 34.6, 35.5, 41.8, 42.7, 43.7, 46.7, 52.7, 52.9, 58.7, 60.2, 64.5, 66.0, 133.0, 133.3, 145.8, 146.5, 166.6, 167.0, 200.0, and 200.3.

Epoxy Ring Opening with t-BuOK. A THF solution (3 cm^3) of **10** (61 mg) and *t*-BuOK (16 mg) was stirred at room temperature for 10 min. After the reaction was quenched by water and neutralized by aq. HCl solution, the mixture was extracted with ether, dried on Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on a silica-gel column to give **11a** (7.7 mg, 15%) and **11b** (11 mg, 21%).

11a: oil. ^{1}H-NMR: δ=0.96 (3H, d, J=7.0 Hz), 1.00 (3H, d, J=7.0 Hz), 1.21 (3H, s), 1.55-1.75 (3H, m), 1.86 (1H, sept, J=7.0 Hz), 2.03 (1H, m), 2.34 (2H, br s), 2.39 (1H, br s), 3.86 (3H, s), 6.34 (1H, d, J=4.8 Hz), and 6.35 (1H, s).

11b: oil. ^{1}H-NMR: δ=0.93 (3H, d, J=7.0 Hz), 1.01 (3H, d, J=7.0 Hz), 1.09 (3H, s), 1.60-1.87 (5H, m), 2.43 (2H, m), 3.86 (3H, s), 6.25 (1H, s), and 6.37 (1H, s).

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