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Synthesis of Aubergenone, a Sesquiterpenoid Phytoalexin from Diseased Eggplants[1]

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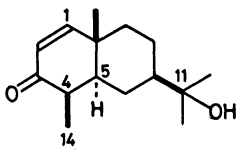
The synthesis of aubergenone, a stress metabolite isolated from diseased eggplants, from α-cyperone, which implies revision of the assigned structure to the metabolite, is described.

In 1975 Stoessl and coworkers[2] reported isolation of the title compound (**1**), aubergenone ("enone sesquiterpene"), as a stress metabolite from diseased eggplants (*Solanum melongena*, Solanaceae) and assigned 11-hydroxy-4β,5α-eudesm-1-en-3-one structure (**2**) on the basis of the extensive spectroscopic studies. However, in 1978 Canadian workers[3] and we[4] independently arrived at the same revised structure, 11-hydroxy-4α,5α-eudesm-1-en-3-one (**1**), by synthesis of 4-epiaubergenone (**2**) and anbergenone (**1**) itself, respectively. The sesquiterpene (**1**) is a sole stress compound with a 5α-eudesmane skeleton among the metabolites of the Family and hence stands unique on biogenetic grounds.[4-6] In the present paper we describe details of the synthesis of aubergenone (**1**) and its 4-epimer (**2**), which is divided into three sections as described in the following.



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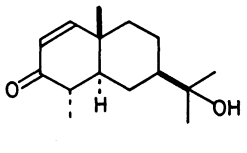

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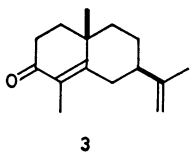
Results and Discussion

An Alternative Short-step Transformation of (−)-α-Santonin into (+)-α-Cyperone. A number of synthetic routes of (+)-α-cyperone (**3**) have been reported. Of these routes, most practical ones are those elaborated by Piers,[7] Caine,[8] and coworkers, which start with commercially available (−)-α-santonin (**4**) and (−)-carvone, respectively (overall yields, 20 and 25%). We also started with **4**, which was easily epimerized into epi-α-santonin[7,9] (**5**) in 73% yield. Treatment of **5** with lithium diisopropylamide (LDA, 1.5 equiv.) in tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPA) at −78 °C followed by addition of methyl iodide afforded 11-methyl-epi-α-santonin (**6**) as a single product, which on hydrogenation in the presence of tris(triphenylphosphine)chlororhodium in degassed dry benzene, formed the 1,2-dihydro derivative (**7**) in 71% yield from **5**. Irradiation of **7** with sunlight by the Ourisson method[10] effected photo-decarboxylation to give 10-epimaalienone,[10] an unstable cyclopropane derivative (**8**), in 68% yield. In accord with the assigned structure, compound **8** exhibited the following spectral data: MS, *m/e* 218 (M^+), 203, 190, and 175; IR, 1665, 1598, 1385, and 1360 cm^{-1}; NMR, δ 0.96, 1.09, 1.23, and 1.77 (each 3H, s). Further treatment of **8** with hydrogen chloride in ethanol gave rise to a known chloride[8] (**9**), mp 86—88 °C, $[\alpha]_D$ +159°, in 82% yield, which was completely identical with the reported data (mp, $[\alpha]_D$, MS, IR, and NMR). The compound (**9**) was converted readily into **3** by a known procedure.[11] This transformation of (−)-α-santonin (**4**) into (+)-α-cyperone (**3**) involved 6 steps and the overall yield amounted to 23.3%.



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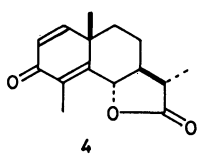

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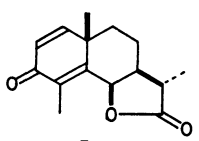

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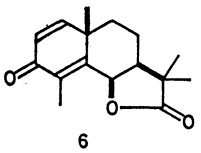

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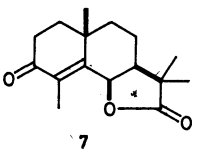

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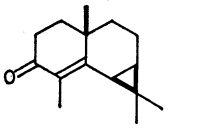

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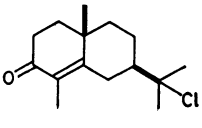

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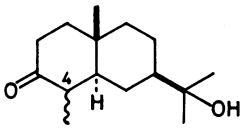
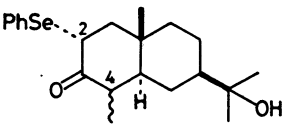
Transformation of (+)-α-Cyperone (3) into 4-Epiaubergenone (2). *trans*-Dihydrocarissone[12] (**10**) with the established configuration was first prepared from **3** in two steps (the Birch reduction[13] and oxymercuration-demercuration[14]) in 76% yield. Treatment of **10** with LDA (2.5 equiv.) in THF and then with benzeneselenenyl bromide (2.5 equiv.) in THF at −78 °C afforded its 2α-phenylseleno derivative (**11**) in 75% yield. Oxidation of **11** with sodium periodate (3 equiv.) in 85% aqueous methanol containing sodium hydrogencarbonate (1.5 equiv.) at room temperature[15] led to elimination of benzeneseleninic acid, giving 11-hydroxy-4β,5α-eudesm-1-en-3-one (**2**), mp 105—107 °C, $[\alpha]_D$ −53.5°, in 69% yield, which displayed the following spectra: MS, *m/e* 236 (M^+), 221, 218, 203, 178, and 59; UV_{max}, 228 nm (ε 5700); IR (Nujol), 3500, 1670, and 1655 (sh) cm^{-1}; NMR, δ 1.06 (3H, s, 15-H), 1.13 (3H, d, J=7 Hz, 14-H), 1.22 (6H, s, 12- and 13-H), 2.32 (1H, dq, J=11 and 7 Hz, 4-H), 5.84 and 6.71 (each 1H, ABq, J=10 Hz, 2- and 1-H). While these spectral data were consistent with the formula (**2**), those were different from the reported[2] for aubergenone. Significant difference in the coupling constant $J_{4,5}$ between the synthetic (11 Hz) and natural samples (6 Hz) suggested that the protons at C-4 and C-5 of the latter would probably be oriented *cis* (equatorial-axial).

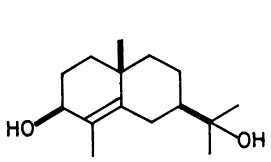


10, 4βH
14, 4αH



11, 4βH
15, 4αH

Synthesis of Aubergenone (1) from (+)-α-Cyperone (3). The synthesis required *cis*-addition of hydrogen atoms from the rear (α) side to the C-4–C-5 double bond of 4-eudesmene derivatives. Since hydrogenation of carissone, 11-hydroxyeudesm-4-en-3-one, over palladium in acetic acid or in alkaline ethanol gave *trans*-dihydrocarissone (**10**) as a major product, (+)-α-cyperone (**3**) was first transformed into eudesm-4-ene-3β,11-diol[16] (**12**) by a known two-step procedure.[16] Hydrogenation of **12** over platinum in a 40 : 1 mixture of ethyl acetate and acetic acid at room temperature[17] effected the relevant *cis*-hydrogenation to yield 4α,5α-eudesmane-3β,11-diol (**13**) [NMR, δ 3.75 (1H, dt, J=10 and 5.5 Hz, 3-H)], which in turn was oxidized with the Jones reagent, giving 11-hydroxy-4α,5α-eudesman-3-one (**14**) (ORD, a=+2[illegible].0) in 83% yield from **12**. The configurations of C-4 and C-5 of these compounds (**13**) and (**14**) were confirmed by quantitative conversion of **14** into **10** under basic conditions (5% KOH in MeOH, reflux, 6 h). The compound (**14**), when treated with LDA (2.5 equiv.) and then with benzeneselenenyl bromide (2.5 equiv.), afforded the corresponding 2α-phenylseleno derivative (**15**) [NMR, δ 2.61 (1H, qui, J=6 Hz, 4-H) and 4.49 (1H, dd, J=12 and 7 Hz, 2-H)] in 82% yield, which underwent oxidative elimination by treatment with sodium periodate (3 equiv.) in aqueous methanol at room temperature[15] to give α,β-unsaturated ketone, oil, $[\alpha]_D$ −4.0°, in 46% yield. The spectral data (see Experimental) of the ketone were completely identical with those (MS, UV, ORD, IR, ^{1}H and ^{13}C NMR) reported[2] for natural aubergenone. Naturally, aubergenone (**1**) was also converted quantitatively into its 4-epimer (**2**) under the basic conditions. The present result completes the synthesis of aubergenone (**1**) and also establishes the structure.



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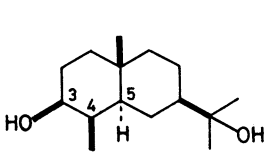

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Experimental

All the melting points were uncorrected. The homogeneity of each compound was always checked by TLC over silica gel (Wakogel B-5) under various solvent systems, the spots being developed with cerium(IV) sulfate in dilute sulfuric acid and/or iodine. The optical rotations, ORD curves, UV, IR, and NMR (100 MHz) spectra were measured in chloroform, in ethanol, in ethanol, in liquid state, and in chloroform-*d*, respectively, unless otherwise stated.

11-Methyl-epi-α-santonin (6). To a solution of diisopropylamine (0.92 ml, 6 mmol) in dry THF (20 ml) cooled at 0 °C was added dropwise a solution of butyllithium in hexane (3.4 ml, 6 mmol) under nitrogen, and the solution was stirred at 0 °C for 15 min. To the solution cooled at −78 °C was added a solution of epi-α-santonin (**5**) (1 g, 4 mmol) in THF (20 ml) and HMPA (2 ml). The mixture was stirred at −78 °C for 1 h, mixed with a solution of methyl iodide (1 ml, large excess) in THF (2 ml) and HMPA (2 ml), and stirred continuously for 1 h at the same temperature. The reaction mixture was then neutralized with 2 M† hydrochloric acid, concentrated *in vacuo*, diluted with water, and extracted with chloroform. The chloroform solution was washed with water and saturated brine, dried, and evaporated to leave pale yellow oil (4 g), which was purified by chromatography over silica gel. Fractions eluted with benzene–ether (2 : 1) gave **6** (0.83 g), mp 164—165 °C; MS, *m/e* 260 (M^+, base), 245, and 217; IR (Nujol), 1762, 1660, and 1625 cm^{-1}; NMR, δ 1.25 [6H, s, 11-$(CH_3)_2$], 1.36 (3H, s, 15-H), 2.04 (3H, s, 14-H), 5.50 (1H, d, J=5 Hz, 6-H), 6.20 and 6.72 (each 1H, d, J=9 Hz, 2- and 1-H). Found: C, 73.52; H, 8.01%. Calcd for $C_{16}H_{20}O_3$: C, 73.85, H, 7.69%.

11-Methyl-1,2-dihydro-epi-α-santonin (7). A solution of **6** (540 mg) in degassed dry benzene (5 ml) was hydrogenated in the presence of tris(triphenylphosphine)chlororhodium (150 mg) for 9 h at room temperature. After the catalyst was removed by filtration through alumina (10 g), the filtrate was evaporated to give crude product (600 mg), which was separated by preparative TLC over silica gel with benzene–ethyl acetate (4 : 1) to give **7** (480 mg), mp 124—125.5 °C (from ether–hexane), $[\alpha]_D$ −113.2°; MS, *m/e* 262 (M^+, base), 247, 219; IR (Nujol), 1790, 1695, 1640, and 1400 cm^{-1}; NMR, δ 1.25 [6H, s, 11-$(CH_3)_2$], 1.37 (3H, s, 15-H), 1.72 (3H, s, 14-H), and 5.43 (1H, d, J=5.5 Hz, 6-H). Found: C, 73.44; H, 8.37%. Calcd for $C_{16}H_{22}O_3$: C, 73.28; H, 8.40%.

10-Epimaalienone (8). Compound **7** (135 mg) was exposed under day light (February in Sapporo at about 0 °C) in a Pyrex vessel for 10 d. The reaction mixture was separated by preparative TLC over silica gel with benzene. Fractions (63 mg) with higher R_f value, showing a single spot on TLC, afforded **8**, oil, $[\alpha]_D$ −595°; MS, IR, and NMR, in the text. Found: C, 82.43; H, 10.40%. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16%. The spectral data of **8** were identical with the corresponding reported data.[10] Fractions (32 mg) with lower R_f value, afforded the unchanged starting material (**7**).

11-Chloroeudesm-4-en-3-one (9). A solution of **8** (100 mg) in ethanol saturated with hydrogen chloride (10 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ether, repeatedly. The ether solution was washed with saturated brine and water, dried, and evaporated to leave crude crystals (111 mg), which were recrystallized from hexane to give **9** (91 mg), mp 86—88 °C, $[\alpha]_D$ +159.4°; MS, *m/e* 254 (M^+) and 218; IR (Nujol), 1680, and 1625 cm^{-1}; NMR, δ 1.12 (3H, s, 15-H), 1.59 and 1.61 (each 3H, each s, 12- and 13-H), and 1.73 (3H, s, 14-H). The spectral data of **9** were identical with the corresponding reported data.[8]

trans-*Dihydrocarissone (10).* To liquid ammonia (150 ml) containing lithium (160 mg, 23 mmol) was added dropwise a solution of **3** (500 mg, 2.3 mmol) in ether (25 ml) for 5 min under cooling at −78 °C, and the mixture was stirred at the temperature for 1 h. After addition of ammonium chloride, the mixture was evaporated, mixed with water, and extracted with ether (3 × 50 ml). The ether solution was washed

† 1 M=1 mol dm^{-3}.

with 5% aqueous ammonium chloride and water, dried, and evaporated to leave oily residue (524 mg), which was separated by column chromatography over silica gel (15 g) with hexane. More mobile fractions, showing a single spot on TLC, gave 4β,5α-eudesm-11-en-3-one (340 mg), oil, $[\alpha]_D$ −20.9° (lit,[13] −15.1°); MS, *m/e* 220 (M^+), 205, 177, and 109 (base); IR, 3100, 1720, 1650, 1390, and 890 cm^{-1}; NMR, δ 0.99 (3H, d, J=7.5 Hz, 14-H), 1.10 and 1.74 (each 3H, s, 15- and 13-H), and 4.73 (2H, s, 12-H). Less mobile fractions afforded the unchanged material (**3**) (159 mg).

To a suspended mixture of mercury(II) acetate (611 mg) in THF (2 ml) and water (3 ml) was added the afore-mentioned eudesmene (210 mg, 0.95 mmol) in THF (1 ml), when the mixture became homogeneous and was stirred at 0 °C for 5 min. To the solution was added 3 M aqueous sodium hydroxide (1 ml) and then sodium borohydride (0.5 M) in 3 M aqueous sodium hydroxide (1.6 ml), when mercury precipitated out. After removal of the mercury by filtration over Celite, the filtrate was concentrated, mixed with water (20 ml), saturated with sodium chloride, and extracted with ethyl acetate (4×20 ml). The acetate solution was washed with water, dried, and evaporated to leave crude crystals (280 mg), which on recrystallization from ether–hexane gave **10** (147 mg). The mother liquors obtained on recrystallization was evaporated and purified by chromatography over silica gel (10 g) with benzene–ether (2 : 1) to yield an additional amount (29 mg) of **10**, mp 110—111 °C (from ether–hexane), $[\alpha]_D$ −7.5° (lit,[12] −11.7°), MS, *m/e* 238 (M^+), 223, 220, 205, 180, and 59 (base); ORD (dioxane), $[\phi]_{314}^{peak}$ +2430°, $[\phi]_{278}$ 0°, $[\phi]_{272}^{trough}$ −4180°, a=+66.1; IR ($CHCl_3$), 3480, 1710, and 1390 cm^{-1}; NMR, δ 0.99 (3H, d, J=7 Hz, 14-H), 1.06 (3H, s, 15-H), and 1.20 (6H, s, 12- and 13-H).

*2α-Phenylseleno-11-hydroxy-4β,5α-eudesm-3-one (**11**).* To a solution of LDA in THF, prepared by treatment of diisopropylamine (126 mg, 1.25 mmol) with butyllithium [0.78 M in hexane (0.70 ml)] in THF (5 ml), was added **10** (119 mg, 0.5 mmol) in THF (2 ml) and HMPA (179 mg, 1 mmol) at −78 °C under nitrogen, and the mixture was stirred at the temperature for 1 h. To the mixture was added dropwise benzeneselenenyl bromide (295 mg, 1.25 mmol) in THF (2 ml) at −78 °C, when the mixture became yellow, and was treated with dilute hydrochloric acid and extracted with ether (3× 20 ml). The ether solution was washed with saturated aqueous sodium hydrogencarbonate and saturated brine, dried and evaporated to leave oily residue (300 mg), which was purified by column chromatography over silica gel (10 g) with benzene–ether (1 : 1), giving **11** (141 mg) as needle crystals, mp 154—155 °C (from ethyl acetate–hexane), $[\alpha]_D$ −132.1°; MS, *m/e* 396, 394 (M^+), 392, 378, 376, 374, 218, and 59 (base); IR (Nujol), 3400, 1708, and 1380 cm^{-1}; NMR, δ 1.02 (3H, s, 15-H), 1.06 (3H, d, J=7 Hz, 14-H), 1.19 (6H, s, 12- and 13-H), 2.36 (1H, m, 4-H), and 4.36 (1H, dd, J=13 and 6 Hz, 2-H). Found: C, 63.81; H, 7.71%. Calcd for $C_{21}H_{30}O_2Se$: C, 64.10; H, 7.70%.

*4-Epiaubergenone (**2**)*: A solution of **11** (70 mg, 0.185 mmol) in methanol (5 ml) and water (1 ml) containing sodium hydrogencarbonate (40 mg) and sodium periodate (200 mg, 0.93 mmol) was stirred at room temperature for 3 h, when the solution gradually became heterogeneous. After addition of 10% aqueous sodium thiosulfate, the reaction mixture was concentrated and extracted with ethyl acetate (3×20 ml). The acetate solution was worked up as usual to leave oily residue (57 mg), which was purified by chromatography over silica gel (5 g) with benzene–ether (1 : 1) to yield crude crystals (37 mg). These were recrystallized from ether–hexane to give **2** (30 mg) in pure state, mp 105—107 °C, $[\alpha]_D$ −53.5°; MS, UV, IR, and NMR, in the text; ORD, $[\phi]$ 0°, −50°, −360°, −920°, 0°, +1280°, +510°, +2030°, +510°, and +2850° at 500, 450, 400, 365, 346, 328, 282, 255, 240, and 226 nm. Found: C, 76.43; H, 10.10%. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24%.

*4α,5α-Eudesmane-3β,11-diol (**13**).* Eudesm-4-ene-3β,11-diol[16] (**12**) (50 mg) in ethyl acetate (20 ml) and acetic acid (0.5 ml) was hydrogenated over pre-reduced platinum(IV) oxide (20 mg) at room temperature for 2 h, when 4.7 ml of hydrogen (0.9 mol equiv.) had been consumed. After removal of the catalyst, the filtrate was washed with saturated aqueous sodium hydrogencarbonate and saturated brine, dried, and evaporated to leave crystalline substance, which was recrystallized from ethyl acetate–hexane to give **13** (46 mg), mp 166—166.5 °C; $[\alpha]_D$ −2.7°; MS, *m/e* 228 (M^+ −18), 207, 204, 189, and 161 (base); IR ($CHCl_3$), 3360 and 3240 cm^{-1}; NMR, δ 0.86 (3H, d, J=7 Hz, 14-H), 0.89 (3H, s, 15-H), 1.20 (6H, s, 12- and 13-H), and 3.75 (1H, dt, J=10 and 5.5 Hz). Found: C, 74.83; H, 11.71%. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74%.

*11-Hydroxy-4α,5α-eudesm-3-one (**14**).* A solution of **13** (111 mg, 0.46 mmol) in acetone (15 ml) was treated with the Jones reagent (*ca.* 0.5 ml, excess) at room temperature for 30 min under stirring. After neutralization by addition of saturated aqueous sodium carbonate, the mixture was filtrated over Celite. The filtrate was concentrated and extracted with ethyl acetate (3×20 ml). The acetate solution was worked up as usual to leave oily residue (110 mg), which was purified by chromatography over silica gel (3 g) with benzene–ether (2 ; 1) to give **14** (100 mg), mp 41.5—43 °C (from ether–hexane), $[\alpha]_D$ +2.8°; MS, *m/e* 238 (M^+), 220, 205, 177, and 55 (base); ORD, $[\phi]_{314}^{peak}$ +1100°, $[\phi]_{300}$ 0°, $[\phi]_{285}^{trough}$ −1200°, a=+23; IR, 3500 and 1710 cm^{-1}; NMR, 1.10 (3H, s, 15-H), 1.10 (3H, d, J=7.5 Hz, 14-H), and 1.21 (6H, s, 12- and 13-H). Found: C, 75.27; H, 10.96%. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00%.

*2α-Phenylseleno-11-hydroxy-4α,5α-eudesm-3-one (**15**).* To a solution of LDA in THF, prepared by treatment of diisopropylamine (106 mg, 1.05 mmol) with butyllithium [1.7 M in hexane (0.6 ml)] in THF (5 ml), was added dropwise **14** (100 mg, 0.42 mmol) in THF (5 ml) at −78 °C with stirring under nitrogen, and the mixture was stirred at −78 °C for 1 h. To the mixture was added benzeneselenenyl bromide (295 mg, 1.05 mmol) in THF (3 ml) at the temperature, when the mixture became yellow, and was treated with dilute hydrochloric acid and extracted with ether (3×20 ml). The ether solution was worked up as uaual to leave oily residue, which was purified by chromatography over silica gel (10 g) with benzene–ether (2 : 1) to give **15** (130 mg), oil, showing a single spot on TLC, $[\alpha]_D$ −85.5°, MS, *m/e* 396, 394 (M^+), 392, 378, 376, 374, 218, 203, 178, and 59 (base); IR, 3500, 3030, and 1701 cm^{-1}; NMR, δ 1.02 (3H, s, 15-H), 1.14 (3H, d, J= 7.5 Hz, 14-H), 1.18 (6H, s, 12- and 13-H), 2.61 (1H, qui, J= 6 Hz, 4-H), and 4.49 (1H, dd, J=12 and 7 Hz, 2-H). Found: C, 63.83; H, 7.81%. Calcd for $C_{21}H_{30}O_2Se$: C, 64.10; H, 7.70%.

*Aubergenone (**1**).* A solution of **15** (54 mg, 0.14 mmol) in methanol (3 ml) and water (0.5 ml) containing sodium hydrogencarbonate (19 mg) and sodium periodate (94 mg, 0.44 mmol) was stirred at room temperature for 2.5 h, when the solution gradually became heterogeneous. The mixture was treated with 5% aqueous sodium thiosulfate, concentrated, and extracted with ethyl acetate (3×20 ml). The acetate solution was worked up as usual to leave oily residue (48 mg), which was separated by preparative TLC over silica gel with hexane–ethyl acetate (1 : 1). A fraction, showing a single spot, gave **1** (15 mg), oil, $[\alpha]_D$ −4.0°; MS, 236 (M^+), 218, 203, 175, and 59 (base); UV_{max}, 229 nm (ε 5800); ORD,

[ϕ] 0°, 0°, −130°, −520°, −1670°, 0°, +3830°, +4500°, +2800°, and +4500° at 589, 500, 450, 400, 368, 348, 310, 285, 280, and 275 nm; IR, 3400, 1670, 917, 824, and 752 cm^{-1}; ^1H NMR, δ 1.13 (3H, d, J=7.5 Hz, 14-H), 1.16 (3H, s, 15-H), 1.24 (6H, s, 12- and 13-H), 2.44 (1H, dq, J=6 and 8 Hz, 4-H), and 5.87 and 6.78 (each 1H, ABq, J=10 Hz, 2- and 1-H); ^{13}C NMR, δ 13.4, 20.7 (each q), 22.4, 26.0 (each t), 27.1, 27.5 (each q), 36.1 (s), 39.9 (t), 44.3, 45.2, 49.0 (each d), 72.5 (s), 125.8, 160.8 (each d), and 203.8 (s). Found: C, 76.03; H, 10.40%. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24%.

*Epimerization of **14** to **10** and **1** to **2**.* *a)*: A solution of **14** (20 mg) in methanol (10 ml) containing 5% potassium hydroxide was refluxed for 6 h under nitrogen. The solution was cooled, neutralized with 10% aqueous ammonium chloride, evaporated, and extracted with ethyl acetate (3× 20 ml). The acetate solution was washed with water, dried, and evaporated to leave oil (20 mg), showing a single spot on TLC, which was identified as **10** by comparison of the spectral data (IR and NMR).

b): Compound **1** (10 mg) was treated with 5% potassium hydroxide (10 ml) for 6 h under reflux under nitrogen. The reaction mixture was worked up as mentioned above to give oil (8 mg), showing a single spot on TLC, which was identified as **2** by comparison of the spectral data (IR and NMR).

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