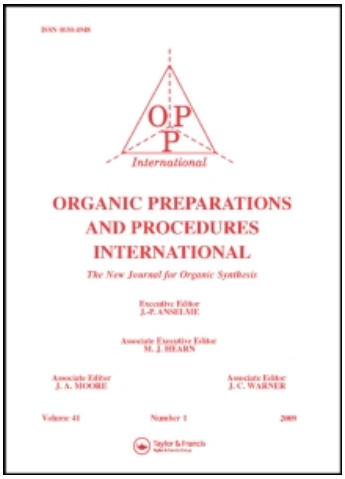

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SYNTHESIS OF 2-HYDROXY-3-METHYLCYCLOPENT-2-EN-1-ONE FROM LINALYL ACETATE

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SYNTHESIS OF 2-HYDROXY-3-METHYLCYCLOPENT-2-EN-1-ONE FROM LINALYL ACETATE

Submitted by (11/09/92) Maria Lucilia dos Santos and Gouvan C. de Magalhães*

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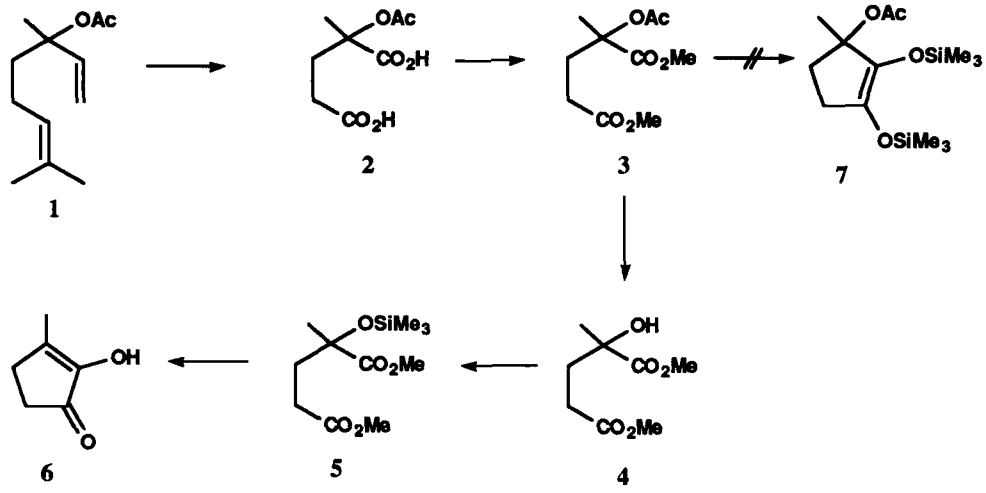
2-Hydroxy-3-methylcyclopent-2-en-1-one (**6**, corylone) is a commercially important perfumery and flavouring material. In 1963, it was identified, along with some other cyclic 1,2-diketones, as a component of the roasted coffee aroma complex.[1] Mainly because of its organoleptic properties **6** has been the target of a great deal of synthetic activity. Indeed, its value does not reside solely on its aroma and flavor: the compound has also been found useful as a synthetic precursor of cyclopentenoid natural products, including dihydrojasmone,[2] methylenomycin B[3] and oxaprostaglandins analogs.[4] A preceding paper, described a synthesis of 2-hydroxy-3-methylcyclopent-2-en-1-one (**6**). The key to this synthesis was the preparation of 2-hydroxy-2-methylglutaric acid dimethyl ester (**4**) from 2-ketoglutaric acid.[5] The present work, describes a alternative synthesis of compound **4** starting from linalyl acetate (**1**).

Treatment of linalyl acetate by von Rudloff permanganate-periodate method[6] gave 2-acetoxy-2-methylglutaric acid (**2**). Methylation of this crude product with diazomethane[7] gave 2-acetoxy-2-methylglutaric acid dimethyl ester (**3**). Our initial intent was cyclize diester **3** by the acyloin condensation to give the bis(trimethylsilyl) ether (**7**).[8] Simple hydrolysis and dehydration of this ether would give **6**. To our surprise, however, the reaction of **3**, under the usual conditions[9] used for the acyloin condensation failed. We suspected the source of our problem to be the presence of the group acetoxy. In order to overcome this problem, compoud **3** was treated with K_2CO_3/MeOH to give **4**. It was necessary to protect the hydroxyl group before acyloin condensation. The trimethylsilyl ether (**5**),

formed in almost quantitative yield from **4** with chlorotrimethylsilane and hexamethyldisilazane,[10] was smoothly reduced by sodium in boiling toluene to give **6** in 73% yield. The proposed method not only constitutes a highly efficient synthesis of corylone (**6**) in 46% yield from linalyl acetate, but also has the additional advantage that the desired product was generated directly in the reaction medium.



EXPERIMENTAL SECTION

The essential oil was obtained from Aldrich. Organic solvents, reagents and adsorbents were used as received from commercial supplier (Aldrich, Merck and Grupo Química). All reactions were monitored by thin layer chromatography (TLC) in the usual manner. IR spectra were recorded on a Perkin-Elmer 283B or Nicolet 5ZDX FT-IR Spectrometer. ^{1}H NMR spectra were obtained on a Varian EM 390 Spectrometer.

2-Acetoxy-2-methylglutaric Acid (2)[6].- Linalyl acetate (432 mg, 2.2 mmols) was mixed in glass-stoppered flask (1000 mL) with a solution of water - *tert*-butanol 10% (500 mL), potassium carbonate (670 mg), and stock oxidant solution (200 mL), which consisted of an aqueous solution of sodium metaperiodate (97.5 mmols/L) and potassium permanganate (2.5 mmols/L). The mixture was shaken for 24 hrs. The oxidant solution in excess was reduced with a minimum quantity of potassium bisulfite and evaporated in vacuum (rotatory-evaporator) to a small volume. The residue from the evaporation was completely reduced with bisulfite, acidified, and extracted with ether. The ethereal solution was dried and evaporated to give the crude acidic oxidation product (400 mg). IR: (film)ν: 3600-2800(br), 1739, 1735, 1723, 1719, 1380, 1250, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.24 (br), 2.9-2.4 (m), 2.35-2.1 (m), 2.05 (s), 1.6 (s).

2-Acetoxy-2-methylglutaric Acid Dimethyl Ester (3).- 2-Acetoxy-2-methylglutaric acid (**2**) the crude sample (400 mg) was dissolved in 10 mL of ether and cooled in ice-bath. A solution of diazomethane (0.01 mol) in ether (prepared immediately prior to use from Diazald),[7] was added dropwise over 20 min. After stirring for 1 hr, excess diazomethane was destroyed with acetic acid; the residue was chromatographed on silica gel and elution with hexane-ethyl acetate (4:1) gave **3** (380

mg, 74% yield from linalyl acetate). IR: (film): 1770, 1775, 1740, 1377, 1257cm^{-1}. ^{1}H NMR (CCl_4): δ 3.68 (3H, s), 3.61 (3H, s), 2.5-2.05 (4H, m), 2.0 (3H,s), 1.5 (3H,s).

2-Hydroxy-2-methylglutaric Acid Dimethyl Ester (4).- 2-Acetoxy-2-methylglutaric acid dimethyl ester (**3**) (170 mg, 0,73 mmol) was dissolved in cold 0.5 M methanolic K_2CO_3 solution (6 mL) and stirred at 0°. After 1 hr, the reaction mixture was filtered, and the filtrate was neutralized with aqueous HCl. The methanol was removed in vacuum and aqueous phase extracted with dichloromethane. The combined organic phase were dried, concentrated, and the residue was chromatographed over silica gel with hexane-ethyl acetate (4:1) to give **4** (131 mg, 94% yield). IR: (film) ν : 3500, 1733, 1259, 1201, 1177, 1121 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.75 (3H, s), 3.61 (3H, s), 3.45 (1H, br), 2.7-2.15 (2H, m), 2.15-1.8 (2H, m), 1.35 (3H, s).

2-Methyl-2-(trimethylsilyloxy)glutaric Acid Dimethyl Ester (5).- 2- Hydroxy-2-methyl-glutaric acid dimethyl ester (**4**) (2.0 g, 0.01 mol) in pyridine (2 mL) was treated with hexamethyldisilazane (1.6 g, 0.01 mol), followed by chlorotrymethylsilane (0.54 g, 0.005 mol). After 24 hrs at 20°, the mixture was filtered throught celite, and the filtrate was washed with aqueous $NaHCO_3$, extracted with ether, dried with $MgSO_4$ and evaporated. The residue was distilled under vacuum to give **5** (2.5 g, 90.7 % yield; bp. 82-85° at 3 mm Hg). IR: (film) : 2960, 1750, 1435, 1250, 1040, 840 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.75 (3H, s), 3.57 (3H, s), 2.6-1.90 (4H, m), 1.45 (3H, s), 0.12 (9H,s).

2-Hydroxy-3-methylcyclopent-2-en-1-one (6). - To a 250 mL, three-necked flask containing a egg-shape stirring bar, equipped with a reflux condenser and a dropping funnel (mantained under oxygen-free nitrogen), was added sodium (345 mg, 15 mmol) and toluene (50 mL). The mixture was brought to reflux on a oil bath (120°) and stirred until a fine dispersion of sodium had been produced. Methyl ester (**5**) (1 g, 3.8 mmol) and chlorotrimethylsilane (1.6 g, 15 mmol) [distilled from calcium hydrite, under nitrogen, immediately prior to use] in dry toluene (20 mL) was added dropwise over 40 minutes after the ester being added. After heating and stirring for further 2 hrs, the contents of the flask were cooled and filtered, under nitrogen, throught a sintered funnel. The precipitated was washed with dry toluene, then it was dissolved in ethanol. Ethyl acetate was added and the mixture was washed with water. The organic phase was evaporated under reduced pressure to give 340 mg of a solid. The solid was recrystallized in water to give **6** (312 mg, 73 % yield; mp. 103-104°; lit.:[1] 102-104°). IR: (KBr) : 3300, 1705, 1650 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.03 (3H, s), 2.45 (4H, s), 5.0 (1H; br).

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A SIMPLE SYNTHESIS OF BRASSILEXIN, A *CRUCIFERAE* PHYTOALEXIN

Submitted by (12/08/92)

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Brassilexin (**2**) was previously isolated from plants of the *Cruciferae* family[1,2] together with other sulfur-containing indole-derived phytoalexins.[3] Brassilexin is a powerful anti-fungal compound and is endowed with general cytotoxic properties in human cell cultures.[4] A synthesis of brassilexin (three steps, 11% yield) has been reported previously.[5] It was subsequently demonstrated that the periodate induced oxidation of cyclobrassinin, another Cruciferae phytoalexin, gave brassilexin through a ring contraction of the thiazine moiety.[6a] According to this synthetic scheme, cyclobrassinin monosulfoxide[6b,7] led to a better yield of **2**. Recently, the synthesis of isothiazines through a Lewis acid-promoted attack of the 2-disulfide of a 1-methylketone by ammonia has been reported.[8] According to this report, the resulting sulfenamide easily cyclized to the isothiazole.[9] Thus, the commercially available indole-3-carboxaldehyde **1** was choosen as starting material and converted to the disulfide. The use of BF_3 in methanol in the presence of ammonia triggered the rupture of the disulfide bridge to afford a 30% yield of brassilexin (**2**) in addition to other products. A control experiment, showed that BF_3 was not necessary to the reaction. The prolonged action of ammonia on the disulfide in methanol gave the same yield of **2**. Typically, indole-3-carboxaldehyde (**1**) was heated for a few minutes in a