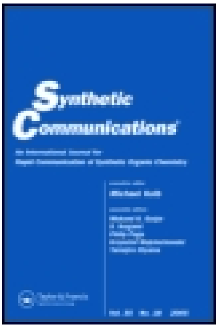

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Synthesis of 2-Hydroxy-3-methyl-2-cyclo-pentenone, Corylone, from 2-Ketoglutaric Acid

Maria Lucília dos Santos [a] & Gouvan C. de Magalhães [a]

[a] Department de Química, Universidade de Brasília, 70.910, Brasília, DF, Brasil

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SYNTHETIC COMMUNICATIONS, 21(17), 1783-1788 (1991)

SYNTHESÍS OF 2-HYDROXY-3-METHYL-2-CYCLO-PENTENONE, CORYLONE, FROM 2-KETOGLUTARIC ACID

Maria Lucília dos Santos and Gouvan C. de Magalhães *

Departamento de Química - Universidade de Brasília
70.910 - Brasília, DF - Brasil

ABSTRACT: Treatment of 2-ketoglutaric acid with diazomethane gave 2-(metoxycarbonyl)-oxiranepropanoic acid methyl ester (**2**) wich lead to 2-hydroxy-2-methyl-glutaric acid dimethyl ester (**3**) by catalytic hydrogenation, wich was further processed to the title compound.

2-Hydroxy-3-methyl-2-cyclopentenone(**1**), corylone, is a commercially important perfumery and flavouring material. In 1963, this compound was identified, along with some other cyclic 1,2-diketones, as a component of the roasted coffee aroma complex[1]. In large part because of the importance conferred on it by its organoleptic properties, (**1**) has been the target of much synthetic activity[2]. We now wish to describe a simple synthesis of (**1**) starting from 2-ketoglutaric acid.

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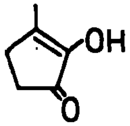
* To whom correspondence should be addressed.

Treatment of 2-ketoglutaric acid with diazomethane at 0 - 10°C gave 2-(methoxycarbonyl)-oxiranepropanoic acid methyl ester (2) in 93% yield[3]. This adduct underwent a catalytic hydrogenation at 90 psi to give glutaric acid 2-hydroxy-2-methyl dimethyl ester (3) in 99% yield[4].



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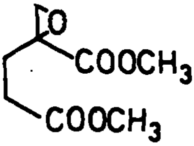

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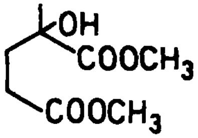

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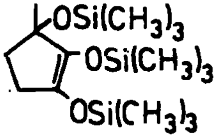

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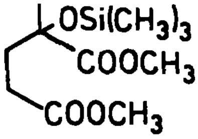

(5)

Our initial intent was cyclise the diester (3) by acyloin reaction[5] to give the tri-(trimethylsilyl)ether. Therefore, it was found necessary to protect the hydroxyl before acyloin condensation, with trimethylsilyl chloride[6], the protected intermediate, (5), was formed in almost quantitative yield.

To our surprise, in the next step, the diester (5) was directly cyclised to 2-hydroxy-3-methyl-2-cyclopentanone(1) pure in 73% yield.

This method constitutes a highly efficient synthesis of corylone in 59% yield from 2-ketoglutaric acid a very inexpensive starting material.

EXPERIMENTAL SECTION

2-(Methoxycarbonyl)-oxiranepropanoic acid methyl ester (2).

2-Ketaglutaric acid (3,0 g, 0,02 mol) was dissolved in 5 mL of methanol and 25 mL of ether and cooled in ice-bath. A solution of diazomethane (0,07 mol) in ether (prepareted immediatly prior to use from Diazald)[7], was added dropwise over 1 h. After stirring overnight, the solvent was evaporated and the residue distilled to give (2) (3,5 g, 93% yield; b.p. 115-120°C /2,7 mm Hg).

I.R. 3005, 2940, 1745, 1440, 1370, 1200, 1020 cm^{-1}.

^1H NMR ($CDCl_3$) δ 3,76 (3H, s), 3,67 (3H, s), 3,06 (1H, d), 2,82 (1H, d), 2,00-2,55 (4H, m).

2-Hydroxy-2-methyl-glutaric acid dimethyl ester (3).

2-(Methoxy carbonyl)-oxirane propanoic acid methyl ester (2) (3,0 g, 0,16 mol) was dissolved in 150 mL of ethanol in a 500 mL hydrogenation flask, and palladium-charcoal activated catalyst (Pd. 10%, 0,45 g) was added[4]. The reaction mixture was maintained at 90 psi for about 15 hrs. After the removal of the catalyst, the solvent was evaporated and the residue distilled to obtain (**3**) as a clear liquid (2,9 g, 95% yield; bp 85-90°C/1,5 mm Hg).

I.R. (film) 3510, 2970, 1750, 1449, 1270, 1210, 1120 cm^{-1}.

^1H NMR (CCl_4) δ 3,78 (3H, s), 3,63 (3H, s), 2,6-1,7 (4H, m), 1,37 (3H, s).

2-Methyl-2-(trimethylsilyl-oxy)-glutaric acid dimethyl ester (**5**).

2-Hydroxy-2-methyl-glutaric acid dimethyl ester (**3**) (2,0 g, 0,01 mol) in pyridine (2mL) was treated with hexamethyldisilazane (1,6 g, 0,01 mol), followed by chlorotrimethylsilane (0,54 g, 0,005 mol). After 24 hrs at 20°C, 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; b.p. 82-5°C, 3 mm Hg).

I.R. 2960, 1750, 1435, 1250, 1040, 840 cm^{-1}.

^1H NMR ($CDCl_3$) δ 3,75 (3H, s), 3,57 (3H, s), 2,6-1,9 (4H, m), 1,45 (3H,s) 0,12 (9H, s).

2-Hydroxy-3-methyl-2-cyclopentenone (**1**).

To a 250 mL, three-necked flask containing a egg-shape stirring bar, equipped with a reflux condenser and a dropping funnel (maintained under oxygen-free nitrogen), was added toluene (100 mL) and sodium (0,35 g, 15 mmol). The toluene was brought to reflux on a oil-bath (120°C) and the mixture stirred until a fine dispersion of sodium had been produced. 2-Methyl ester (**5**) (1 g, 3,8 mmol) and chlorotrimethylsilane (0,4 g, 3,8 mmol) (distilled from calcium hydride, under nitrogen, immediately prior to use) in dry toluene (20 mL) was added dropwise over 40 minutes. A dark purple precipitate appeared within a few 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 2-hydroxy-3-methyl-2-cyclopentenone (**1**), (312 mg, 73% yield; Mp 103-104°C).

I.R. 3300, 1705, 1650 cm^{-1}.

^{1}H RMN ($CDCl_3$) δ 2,03 (3H, s), 2,45 (4H, s), 5,) (1H, br.s).

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