

Synthesis of sterculic acid

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Dedicated to Professor Marcial Moreno-Manas on his 60th anniversary

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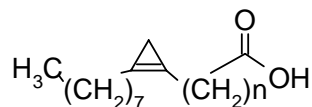
Abstract

Sterculic acid, a cyclopropene fatty acid, present in the seed oil of several species, has been synthesized on 10 g scale, based on the addition of ethyl diazoacetate on an alkyne derivative.

Keywords: Sterculic acid, methylstearolate

Introduction

Naturally occurring three-membered ring compounds are endowed with a large spectrum of biological properties, ranging from insecticidal, antifungal, antibiotic, antiviral, herbicidal, hormonal, carcinogenic or antitumoral activities, enzyme and gluconeogenesis inhibitions to neurochemical activity.^{1,2} Among them, two cyclopropene fatty acids, sterculic and malvalic acids (Fig. 1), which are present in seed oil of various species, including *Sterculia* or the common cotton plant, *Gossypium hirsutum*, are potent inhibitors of the Δ^9 -desaturation of stearic to oleic acid.^{3,4} Additionally, both acids inhibit the Δ^9 -desaturation of different C-12 to C-20 aliphatic acids.⁵



n = 6 Malvalic acid
n = 7 Sterculic acid 1

Figure 1

On the basis of degradation experiments Nunn⁶ proposed the structure 9,10-methano-9-octadecenoic acid for sterculic acid. Some reported syntheses of sterculic acid and the lower homologue, malvalic acid, are based on the addition of a methylene unit to an alkyne,⁷⁻⁹ the alkylation of a lithiocyclopropene¹⁰ or the deiodination of 1,2-diiodocyclopropanes.¹¹

Results and Discussion

As a part of a general project on lipid metabolism, a synthesis of sterculic acid has been developed, based on previous methods, at a 10 g scale, that includes reaction of methyl stearolate **3** and ethyldiazoacetate, to obtain the cyclopropene unit, with an overall yield in the last two steps (**6-7-1**, Scheme 1) of 45%, from commercial stearolic acid. A related route has been reported previously to provide methyl sterculate with a 20% yield in the same steps, at a scale of 0.5 g of the final product.¹²

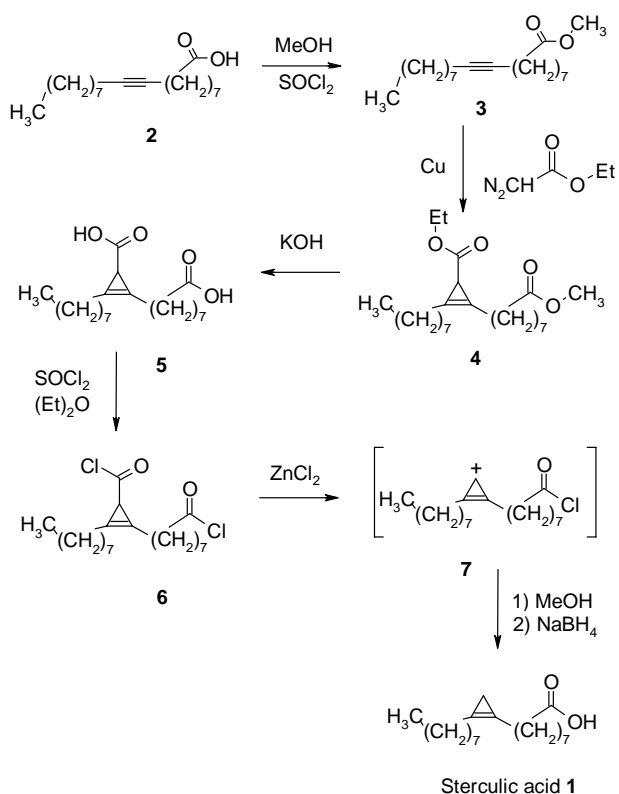
Methyl stearolate and ethyl diazoacetate reacted in the presence of copper bronze to form 2-(7-methoxycarbonylheptyl)-3-octylcycloprop-2-ene carboxylic acid ethyl ester **4**. Hydrolysis of **4**, followed by treatment with thionyl chloride gave the corresponding diacyl chloride **6**. This product, exposed to anhydrous zinc chloride, underwent decarbonylation, generating the cyclopropenium acid chloride intermediate **7**. After esterification with methanol, the resulting cyclopropenium ion was reduced with sodium borohydride to give sterculic acid (45% yield) and traces of methyl sterculate. An alternate method was tested,^{13,9} for direct decarbonylation of **4**, by employing chlorosulfonic acid. The obtained cyclopropenium derivative **7** yielded sterculic acid with an overall yield, in the steps **4-7-1**, of 20 % in 0.5 g scale, but this falls to 10 % at the 5 g scale.

In conclusion, a reliable method of synthesis of sterculic acid **1**, has been developed and scaled up to afford 10 g of the final product. The method can be used to produce sterculic acid derivatives, useful in fatty acid metabolism studies.

Experimental Section

General Procedures. Column chromatography was performed on silica gel Merck 60 (70-230 mesh) using the specified eluent. All solvents were used in p.a. quality and, when necessary, were dried by standard methods. ¹H NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz) in CDCl₃ with TMS as an internal standard. ¹³C NMR spectra were recorded on a Varian Gemini spectrometer (75 MHz) in CDCl₃ with TMS as an internal standard. IR spectra was recorded as KBr pellets using a Nicolet Impact-410 spectrophotometer. The elemental analysis was performed by the UCSA of the Universidad de Alcalá.

Hex-3-ynoic acid methyl ester (3). A 3 L reactor was charged with 150 g (0.535 mol) of stearolic (hex-3-ynoic) acid 2, dissolved in methanol (1.5 L). The mixture was stirred at room temperature, thionyl chloride (19 mL) was added, and stirring was maintained for 3 hours. Then, the mixture was concentrated under reduced pressure, yielding methyl stearolate as a brown oil (99%) which was used without further purification. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 3.65 (s, 3H), 2.31-2.10 (m, 6H), 1.63-1.26 (m, 22H), 0.87 (t, 3H, $J=6.85$ Hz).



Scheme 1

2-(Methoxycarbonyl-heptyl)-3-octylcycloprop-2-enecarboxylic acid ethyl ester (4). A 500 mL, three-necked flask was charged with 100 g (0.34 mol) of methyl stearolate 3 and 7.8 g of powdered cooper bronze. After replacing the air in the flask with nitrogen, the flask was placed in an oil bath preheated to 130-135 °C, and ethyl diazoacetate (71.4 mL, 0.679 mol) was added drop wise to the stirred mixture, care being taken to make the drops fall directly into the reaction mixture, avoiding preliminary contact with the side wall of the flask. After addition of all the diazoacetate (2.5 h) the reaction mixture was heated and stirred for another 3 hours. The crude product was filtered and the residue was chromatographed on silica gel (hexane:diethyl ether, 4:1). The resulting oil weighed 62.8 g (49%). $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 4.09 (q, 2H, $J=7.25$ Hz), 3.65 (s, 3H), 2.40-2.26 (m, 6H), 2.00 (s, 1H), 1.62-1.19 (m, 22 H), 0.87 (t, 3H, $J=7.25$ Hz).

2-(7-Carboxyheptyl)-3-octyl-cycloprop-2-enecarboxylic acid (5). A 500 mL flask was charged with 36 g (0.095 mol) of the diester 4, ethanol (200 mL) and 50 g (0.75 mol) of KOH. The mixture was stirred and refluxed for 1.5 hours. Then, it was treated with 35% HCl up to pH=1, diluted with water (200 mL) and extracted with diethyl ether (2x50 mL). The ether solution was dried with sodium sulfate, and the solvent removed leaving an orange oil (quantitative) which was used without further purification. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 12.00 (s, 2H), 2.42-2.30 (m, 6H), 2.02 (s, 1H), 1.64-1.18 (m, 22H), 0.87 (t, 3H, $J=6.85$ Hz).

2-(7-Chlorocarbonyl-heptyl)-3-octyl-cycloprop-2-ene carbonyl chloride (6). A 500 mL flask was charged with 32 g (0.094 mol) of diacid 5, dissolved in 300 mL of dry diethyl ether and, in the absence of light and at room temperature, 26.7 mL (0.369 mol) of thionyl chloride were added. The mixture was stirred for 4.5 hours, the solvent was distilled under reduced pressure, and the dichloride 6 appeared as a brown oil (33 g, 93%) which was used without further purification. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 2.87 (t, 2H, $J=7.22$ Hz), 2.47-2.33 (m, 6H), 2.00 (s, 1H), 1.69-1.25 (m, 22H), 0.86 (t, 3H, $J=6.83$ Hz).

8-(2-Octyl-cycloprop-1-enyl)-octanoic acid (1). Decarbonylation was obtained by stirring a mixture of the acid chloride 6 (10.8 g, 0.029 mol), anhydrous zinc chloride (3.9 g, 0.029 mol) and 100 mL of dichloromethane, in the absence of light and at room temperature. Dry nitrogen was bubbled through the reaction mixture during the process. After 4 hours, the dark purple mixture was cooled to 3 °C, and 1.2 mL (0.029 mol) of absolute methanol was added. The mixture was stirred at this temperature for 1 hour. To reduce the cyclopropene carbonium ion 7, the previous mixture was poured over a vigorously stirred solution of sodium borohydride (5.4 g, 0.143 mol) and sodium hydroxide (2.46 g) in 125 mL of anhydrous methanol, over a period of 55 minutes, at -33 °C. The purple colour disappeared very quickly, and the reaction mixture turned to yellow. After 15 additional minutes of stirring at -33 °C, and 30 minutes at room temperature, the reaction mixture was treated with 200 mL of water and then with ca. 99 mL of 10% HCl (to obtain pH=4). The mixture was extracted with dichloromethane and sequentially washed with: water, 10% NaHCO_3 , water and saturated NaCl solution. The organic layer was dried with sodium sulfate, and then evaporated under reduced pressure. The remaining oil was chromatographed over silica (hexane:diethyl ether, 3:1). The sterculic acid 1 was obtained as a colorless oil (3.80 g, 45 %). $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 2.39-2.32 (m, 6H), 1.65-1.51 (m, 6H), 1.32-1.27 (m, 16H), 0.87 (t, 3H, $J=6.5$ Hz), 0.76 (s, 2H). $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 179.0, 109.1, 108.9, 33.6, 31.5, 30.5, 29.0, 28.9, 28.8, 28.7, 27.0, 26.9, 25.7, 25.6, 24.3, 22.3, 13.7, 7.0. IR (\square max, cm^{-1}): 2927, 2856, 1735, 1715, 1458, 1428, 1361, 1284, 1219, and 1007. Anal. Calcd. for $\text{C}_{19}\text{H}_{34}\text{O}_2$: C, 77.49; H, 11.63. Found: C, 77.49; H, 11.78.

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