SYNTHESIS OF METHYL (R,S)-LICHENSTERINATE[1]

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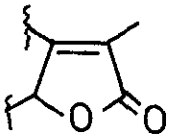
The methyl ester of (R,S)-lichensterinic acid was synthesized from methyl α-ketopalmitate and 1-diethylaminopropyne in three steps in 58% overall yield.

Recently a new synthesis of the 3-methyl-2(5H)-furanoid structural unit (1) from α-epoxyketones and 1-diethylaminopropyne was reported from this laboratory.[2] A modification of this method in the synthesis of a natural product is now reported.

(R,S)-Lichensterinic acid[1] (2, R = H) has been isolated from some lichen species such as Icelandic moss (Cetraria islandica)[3,4,5] and its synthesis has been reported involving the isomerization[3,5,6] of protolichensterinic acid (3), another lichen constituent. Both 2 and 3 show antibacterial activity toward Gram positive organisms.[5]



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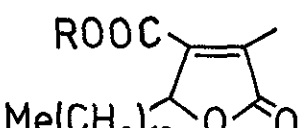

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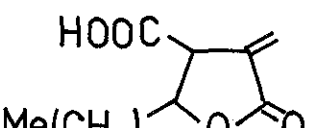

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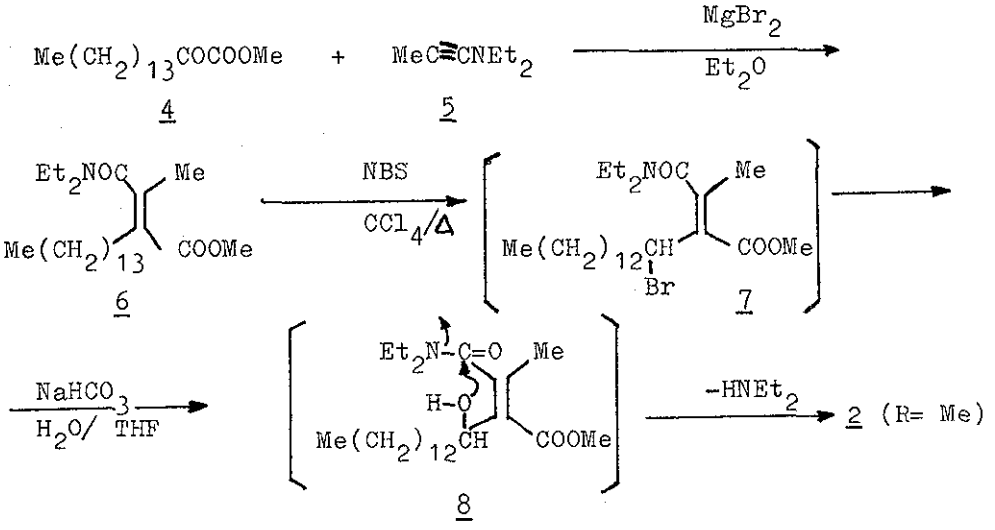
Insofar β-epoxy-α-ketoesters are not very readily available, it was reasoned that the furanoid ether oxygen of 1 could perhaps be indroduced at a later stage of synthesis, allowing α-ketoester to be used as the starting material. Thus, using methyl α-ketopalmitate[7] (4) only three synthetic steps were required to convert

it to 2 (R = Me), the two last steps being carried out in one pot (Scheme 1).



Scheme 1.

The ynamine 5 reacted smoothly with the keto group of 4 giving via the oxetene rearrangement the expected product 6 in 86% yield. The allylic Wohl-Ziegler bromination[8] (methylene attack preferred to methyl) of 6 led to the intermediate 7 which was not isolated, but the reaction mixture was treated directly with aqueous sodium bicarbonate. Hydrolysis of the reactive allylic bromide[9] occurred, followed by spontaneous lactonization and expulsion of diethylamine. After purification a pale yellow, viscous oil was obtained. According to the spectral data the oil was identified as the expected (R,S)-mixture of 2 (R = Me). Asano and Kanematsu[4] give the melting point of pure R-form of 2 (R = Me) as 53-4°C. The yield was 67% and thus the overall yield was 58%.

Experimental

Compound 6:[2]

To a mixture of 200 mg (0.7 mmol) of methyl ∝-ketopalmitate[7] and 0.10 ml (0.7 mmol) of 1-diethylaminopropyne[10] in 10 ml of dry ether 200 mg (1.1 mmol) of dry magnesium bromide was added and the reactants were stirred under argon for 30 mins. During this time a very viscous syrup developed on the walls of the reaction flask. Water was added and the ether solution was dried with Na_2SO_4 followed by the evaporation of ether. The product 6 was isolated from the residue by preparative TLC (silica gel ; elution with EtOAc /$CHCl_3$, 1:9). The yield was 238 mg (86%) of a pale yellow, viscous oil.

δ: 3.63 (3H, s), 3.24 (4H, q, 7 Hz), 2.30 (2H, t, 7 Hz), 1.90 (3H, s), 1.32 (22H, broad s), 1.10 (6H, t, 7 Hz), 1.00 (3H, t, 7 Hz).

m/e: 395 (M^+).

Compound 2 (R = Me):

100 mg (0.25 mmol) of the adduct 6 and 50 mg (0.28 mmol) of NBS in 5 ml of CCl_4 were refluxed for 3 hrs.[8] The mixture was cooled and CCl_4 was evaporated under reduced pressure. The residue was dissolved into 10 ml of H_2O / THF (1:2) and 200 mg of $NaHCO_3$ was added and the mixture was refluxed for 5 hrs.[9] After evaporation of the solvents the product 2 was isolated by preparative TLC (silica gel; elution with EtOAc / $CHCl_3$, 1:9). The yield was 57 mg (67%) of a pale yellow, viscous oil.

δ : 3.70 (3H, s), 3.68 (1H, t, 7 Hz), 1.90 (3H, broad s), 1.30 (24 H, broad s), 1.00 (3H, t 7 Hz).

m/e: 338, 323 (M^+-15; base peak).

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References and footnotes

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