A Simple Synthesis of 6,8-Dihydroxy-3-(3',5'-dihydroxyphenyl)methylisocoumarin, Related to Deacetylferalolide

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Introduction

In 1993, G. Speranza *et al.* [1] isolated a new dihydroisocoumarin from commercial sample of Cape aloe, which they named as *feralolide* (1, R=Ac). Commercial Cape aloe is the dried exudate of *Aloe ferox* Miller, family Liliaceae. Aloe (or bitter aloes) is a natural drug well known for its cathartic properties and also as a bittering agent in alcoholic beverages.

The structure of feralolide was established by FT IR, various techniques of PMR (COLOC, NOE experiments etc.), CMR ^{13}C-^{1}H COSY FAB and HR EI mass spectra as (3*R*)-3,4-dihydro-6,8-dihydroxy-3-(2'-acetyl-3',5'-dihydroxyphenyl) methylisocoumarin). The absolute configuration of the asymmetric C-3 was inferred by a comparison of CD spectrum of deacetylferalolide (1, R=H) with that of agrimonolide and the X-ray analysis.

Synthesis

A simple synthesis of title isocoumarin related to deacetylferalolide, was carried out. The isocoumarin (5) can then be converted into dihydro derivative by the standard procedure.

The two step simple and efficient synthesis involved the direct condensation [2-4] of 3,5-dimethoxyhomophthalic acid (2) [5] with 3,5-dimethoxyphenylacetyl chloride (3) [6] at 200° to afford 6,8-dimethoxy-3-(3',5'-dimethoxyphenyl) methylisocoumarin (4) as an oil. IR showed strong absorption at 1651 and 1630 cm^{-1} for lactonic carbonyl. PMR showed two proton singlet at δ 3.30 for the CH_2 bridging the aromatic moiety at C-3, two three proton singlets at δ 3.67, 3.69 for C-6, and C-8 aromatic methoxy groups, a six proton singlet at 3.75 for C-3', and C-5' and the characteristic singlet for H-4 at δ 5.16 ppm.

Complete demethylation of (4) using boron tribromide in refluxing dichloromethane afforded the 6,8-dihydroxy-3-(3',5'-dihydroxyphenyl) methylisocoumarin. (5) as colourless needles m.p. 84-45°. IR showed hydroxylic absorption at 3406, 3244 cm^{-1}, and at 1626 cm^{-1} for lactonic carbonyl. PMR showed the signals at 3.30 (2H, s, CH_2), 6.20 (1H, s, H-7), 6.21 (1H, s, H-5), 5.21 (1H, s, H-4), 6.32 (1H, d, *J*=16.5 Hz, H-7'), 6.33 (1H, d, *J*=7.5Hz, H-5')

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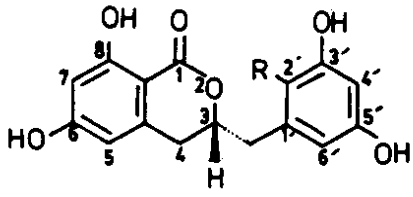

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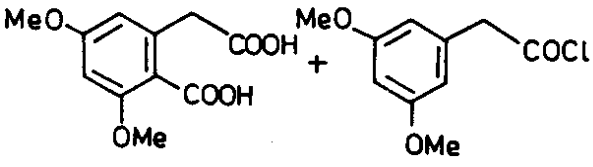

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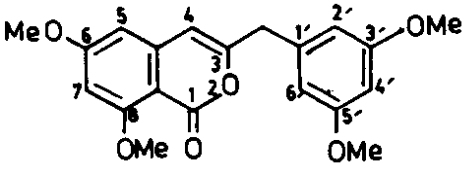

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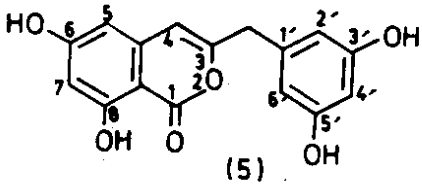

(5)

Synthetic Scheme

Experimental

The IR spectra were recorded on a Hitachi spectrophotometer Model-270 as KBr discs or as neat liquids. PMR (360 MHz) recorded on a Bruker AM-300 as CD_3OD solutions, using TMS as internal standard and the EIMS on a MAT-112-S machine.

6,8-Dimethoxy-3-(3',5'-dimethoxyphenyl) methylisocoumarin (4)

A mixture of 3,5-dimethoxyhomophthalic acid (2) (0.25 g, 0.001 mol) and 3,5-dimethoxyphenylacetyl chloride (3), (0.86 g, 0.004 mol) was heated at 200° in an oil bath for 5 hour and then refluxed for 1 hour with methanol (50 ml) to convert excess of acid chloride into corresponding ester. The residue was purified by thick layer chromatography and recrystallized to afford 6,8-dimethoxy-3-(3',5'-dimethoxyphenyl) methylisocoumarin (4) as an oil (0.25 g, 0.00071 mol, 71%).

IR (KBr): 1651, 1630, 1602, 1595 cm^{-1}. δ (CD_3OD): 3.30 (2H, s, CH_2), 3.67 (3H, s, OMe), 3.89 (3H, s, OMe), 3.75 (6H, s, OMex2), 3.89 (3H, s, OMe), 5.16 (1H, s, H-4), 6.21 (1H, d, *J*=2.2 Hz, H-5), 6.23 (1H, d, *J*=2.2 Hz, H-7), 6.29 (1H,d, *J*=16.5 Hz, H-7'), 6.31 (1H, d *J*=7.5 Hz, H-5') ppm. MS m/z : 356 (M^+), 205, 177.

6,8-Dihydroxy-3-(3',5'-dihydroxyphenyl) methylisocoumarin (5)

Two ml of 1.0 M solution of boron tribromide in dichloromethane was added dropwise to a stirred solution of 6,8-dimethoxy-3-(3',5'-dimethoxyphenyl)methylisocoumarin (4) (0.25g, 0.00071 mol) in dry dichloromethane (5 ml) at 0° under nitrogen. The mixture was refluxed for 2 hr. After cooling, the reaction mixture was poured into ice-water, and extracted with dichloromethane (3x 30 ml). The concentrated residue was crystallized from methanol to afford 6,8-dihydroxy-3-(3',5'-dihydroxyphenyl)methylisocoumarin (5) (0.13g, 0.00041 mol, 59%) as colourless neeldes m.p. 81-82°. IR 3406, 3244, 1626, 1605 cm^{-1}. δ (CD_3OD): 3.30 (2H, s, CH_2), 3.67 (3H, s, OMe) 3.69 (3H, s, OMe), 3.75 (6H, s, OMe x 2), 3.89 (3H, s, OMe), 5.16 (1H, s, H-4), 6.21 (1H, d, *J*=2.2 Hz, H-5), 6.23 (1H, d, *J*=2.2 Hz, H-7), 6.29 (1H, d, *J*=16.5 Hz, H-7'), 6.31 (1H, d, *J*=7.5 Hz, H-5') ppm. MS m/z : 300 (M^+), 177,149.

References

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