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A SHORT ACCESS TO IRIDOID PRECURSORS

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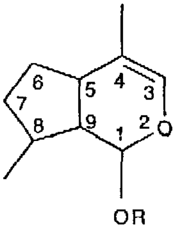
Abstract: A general approach to C-5 oxygenated iridoids is obtained by photoreductive cyclization of δ,ε-acetylenic cyclopentanones.

The iridoids represent a class of highly oxygenated monoterpenes characterized by a cis-fused cyclopentapyran ring system 1[1]. The location and the stereochemistry of the oxygen functionality in iridoids are very diversified. We were particularly interested in iridoids containing a C-5 hydroxy group such as lamiol 2, lamioside 3[2] and theviridoside 4[3].



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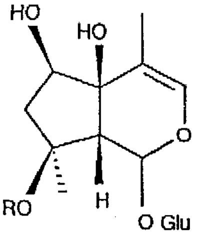
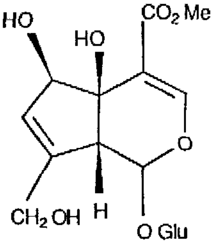


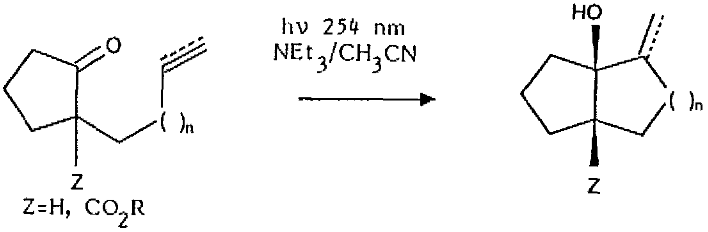
2 R=H Lamiol
3 R=OMe Lamioside



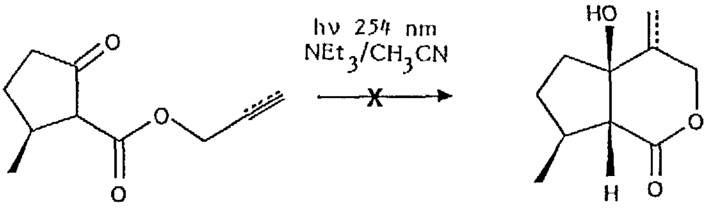
4 Theviridoside

Numerous strategies leading to iridoids have been developed[4], but none has allowed the introduction of a hydroxy group on C-5.

Recently, we discovered that the photoreductive cyclization reaction of δ,ε-unsaturated ketones permits the formation of substituted cyclopentanols[5] as follows :



Unfortunately, the application of this reaction to unsaturated ketoesters 5 does not lead to the expected bicyclic compounds 6 due to the ester conformation[6].

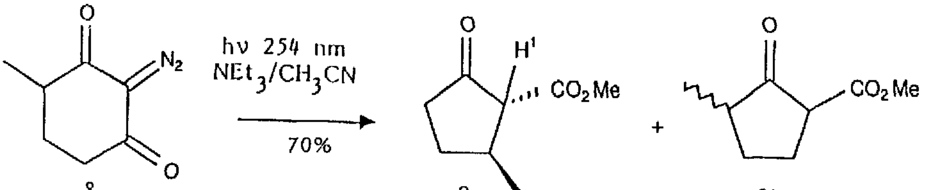


5

6

In order to avoid the conformational effect of the ester, the annulation of the unsaturated β-ketoacetal 14 was investigated as a model for the synthesis of C-5 oxygenated iridoids.

Compound 15, which can be a precursor for C-5 oxygenated iridoids, was synthesized from 4-methylcyclohexane-1,3-dione 7[7] (Scheme I). Treatment of 4-methylcyclohexane-1,3-dione with tosyl azide in the presence of triethylamine led to the corresponding diazo compound 8[8]. The irradiation of the diazo compound 8 in acetonitrile at 254 nm with 4 equivalents of methanol led to the formation of the products 9 and 9' by Wolff rearrangement. 9 can be obtained in multigram quantities by flash chromatography. The ratio of 9/9' is 1.8/1. Compound 9 was found to be the isomer where the methyl is trans to the ester group ; the structural assignment being *readily made by coupling constant analysis*[9]. In contrast, 9' consisted of a mixture of stereoisomers that we were unable to separate.

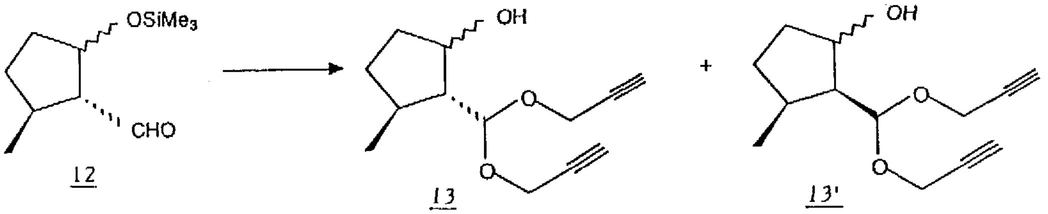


8

9

9'

After reduction of the β-ketoester 9 by LAH, 10 was obtained in 80% yield. Two steps are necessary to oxidize diol 10 chemoselectively into an aldehydo-alcohol: silylation of the diol, followed by oxidation. The bis-silylation of 10, carried out with a mixture of hexamethyldisilazane and trimethylsilyl chloride[10], gave the expected silyloxy compound 11 in 90% yield. Exposure of 11 to chromic acid oxidation produced the silyloxy-aldehyde 12 in 55% yield[11]. Acetalisation of 12 by propargylic alcohol in the presence of p-toluenesulfonic acid led to an inseparable mixture of *two isomers 13 and 13'*[12]*. After several unsuccessful attempts to synthesize 13, it was found that* when 12 is treated with trimethylsilyl chloride and propargylic alcohol in methylene chloride[13] the desired isomer 13 (yield 45%) is obtained exclusively.



	13	13'
TsOH	25%	25%
TMSCl	45%	-

13 was then oxidized with PCC to the corresponding ketone 14 (yield 80%). Finally, irradiation of 14 at 254 nm in acetonitrile with 10 equivalents of triethylamine led to the formation of 15.

This work should provide a general entry into a class of iridoids possessing a hydroxy group on C-5.

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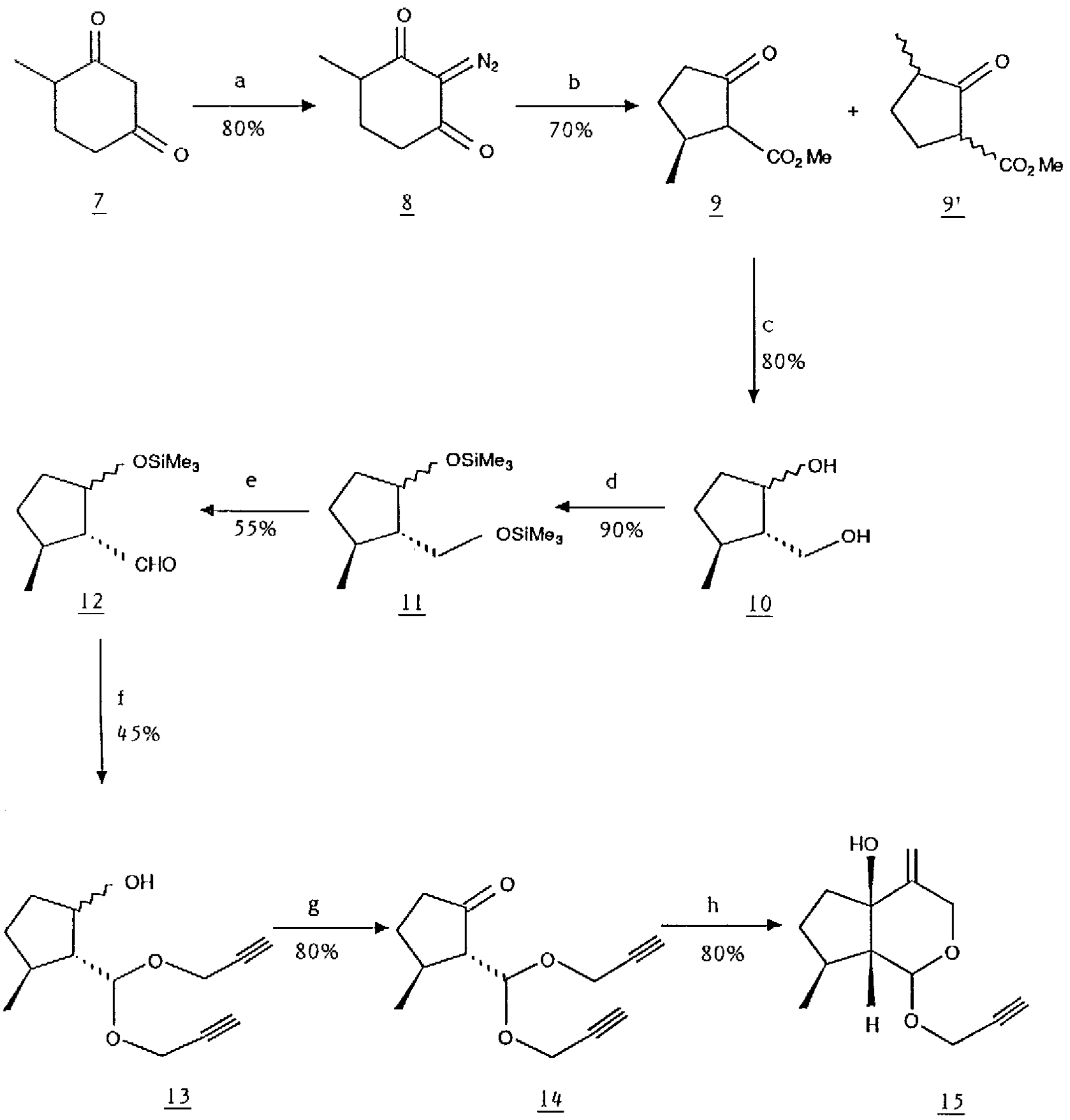
Scheme I



a) NEt_3 (1 eq); TSN_3 (1 eq)/CH_2Cl_2 (0°, 2h).

b) 8 (5×10^{-2}M); CH_3OH (4 eq)/CH_3CN; hν 254 nm (3h). Separation by flash chromatography. Eluent: AcOEt/Hexane = 10/90.

c) $LiAlH_4$/ether (0°C).

d) HMDS (2.5 eq); TMSCl (2.5 eq)/CH_2Cl_2 (0°C, 1h).

e) CrO_3-pyridine/CH_2Cl_2 (room temp. 1h).

f) TMSCl (4 eq); propargylic alcohol (4 eq)/CH_2Cl_2 (reflux 12h).

g) PCC, molecular sieves 4 A/CH_2Cl_2 (3h).

h) NEt_3 (10 eq)/CH_3CN ; hν 254 nm (2h).

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