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STEREOSELECTIVE SYNTHESIS OF (±)-INTEGERRINECIC ACID

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A synthesis of (±)-integerrinecic acid, an acid part of 12-membered bislactonic pyrrolizidine alkaloid, has been achieved stereoselectively starting from 2-methyl-2-cyclopentenone .

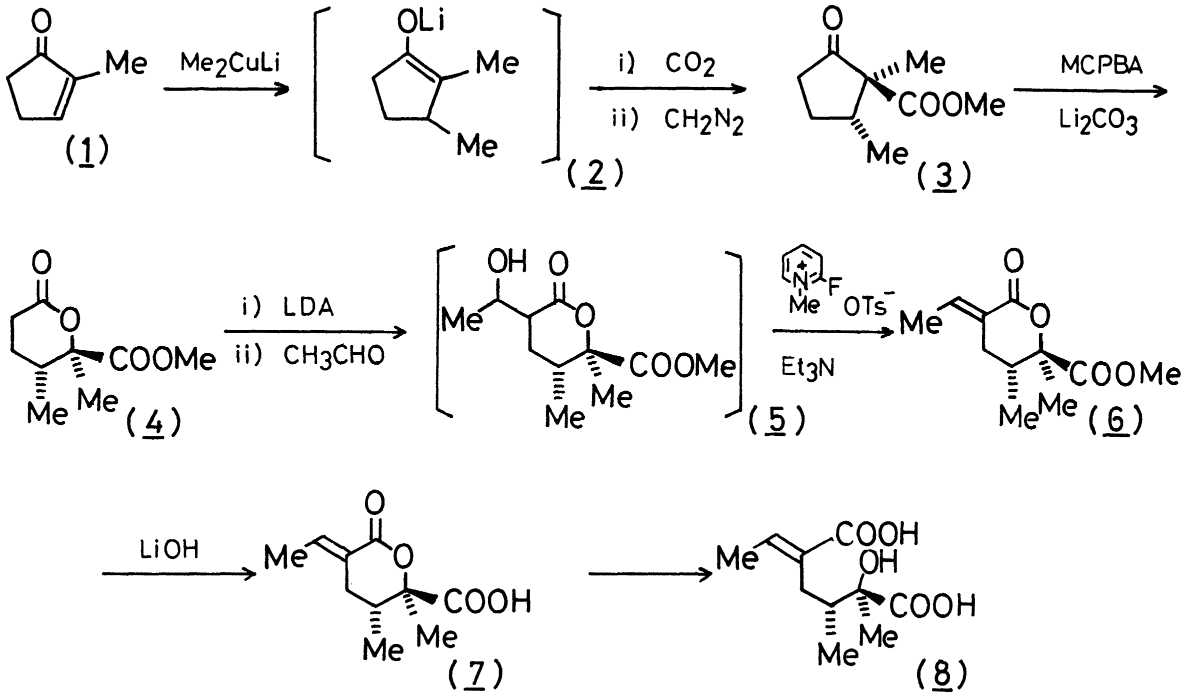
Recently, the synthesis of pyrrolizidine alkaloids, especially large-ring bislactone compounds, has attracted the attention of synthetic chemists.1) Much efforts have been directed to the synthesis of necine bases, but there are few reports on the synthesis of acid parts of large-ring pyrrolizidine alkaloids.1d,2) In this communication, we wish to report the stereoselective and convenient synthesis of (±)-integerrinecic acid (8), the acid part of integerrimine (9).3)

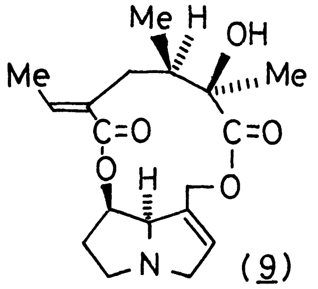
The synthesis is started from 2-methyl-2-cyclopentenone, and the stereochemistry of C-2 and C-3 is controlled by carboxylation reaction of the lithium enolate of cyclopentanone system. 2-Methyl-2-cyclopentenone (1) was allowed to react with dimethylcopper lithium at 0°C in ether, and then the resulting enolate (2) was carboxylated with dry ice at -78°C. The reaction mixture was quenched with water and acidified with hydrochloric acid to pH 3. The extraction with ether and the treatment of the extract with diazomethane gave desired 2,3-cis-dimethyl-2-methoxycarbonylcyclopentanone (3)4) in 80% yield.

Then this β-ketoester (3) was submitted for the Baeyer-Villiger reaction to prepare the lactone (4). When a methylene chloride solution of ketoester (3) and a slightly excess amount of m-chloroperbenzoic acid was refluxed for 48 hr in the presence of 5 mole % of lithium carbonate, the reaction proceeded smoothly and desired 5-methoxycarbonyl-4,5-cis-dimethyl-5-pentanolide (4) was obtained in 76% yield along with the small amount (13%) of the regio isomer (10).

The aldol reaction of lithiated lactone (4) (LDA in THF at -78°C) with acetaldehyde afforded the adduct (5), which was used for next reaction without isolation. No satisfying results were obtained in the dehydration of the adduct (5) by conventional methods, such as p-toluenesulfonic acid catalyst or methanesulfonyl chloride-triethylamine. However, when the crude 5 was treated with 2-fluoro-1-methylpyridinium p-toluenesulfonate (1.5 mole eq. to 4)5) and triethylamine (3 mole eq.) in methylene chloride at r.t., (2E)-ethylidene pentanolide (6) and the (2Z)-isomer were produced in 60% and 9% yields respectively. Hydrolysis of the methyl ester of 6 with 1.1 eq. of lithium hydroxide at 0°C in THF-H_2O afforded integerrinecic acid lactone (7)6) quantitatively. The transformation of 7 to integerrinecic acid (8) by alkaline hydrolysis had been known,2c) so the synthesis of integerrinecic acid was accomplished according to this procedure.

It is noted that the stereoselective and practical synthesis of integerrinecic acid is now achieved by the present route.





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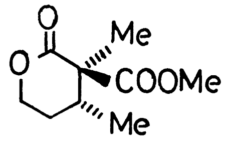

(10)

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4. By glpc analysis, 3 was contaminated with less than 6% of the stereoisomer.
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6. The mp of 7 was identical with that of literature; mp 141-143°C (lit. 142-143°C)$^{2c)}$; NMR ($CDCl_3$) δ 1.00 (d, J=5 Hz, 3H), 1.47 (s, 3H), 1.73 (d, J=7 Hz, 3H), 2.00-3.10 (m, 3H), 7.10 (q, J=7 Hz, 1H).

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