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A TOTAL SYNTHESIS OF (±)-INTEGERRIMINE

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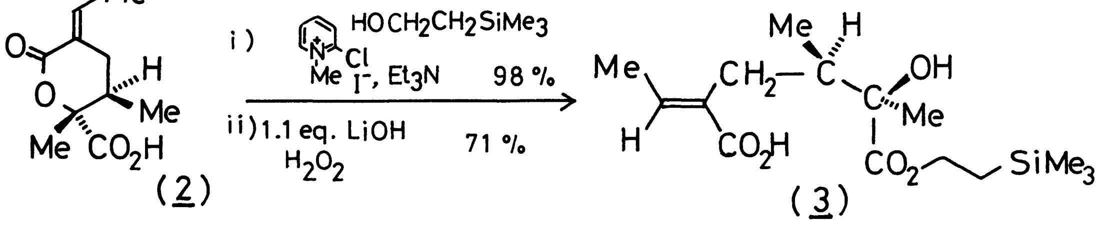
A total synthesis of a 12-membered bislactonic pyrrolizidine alkaloid, integerrimine, has been achieved.

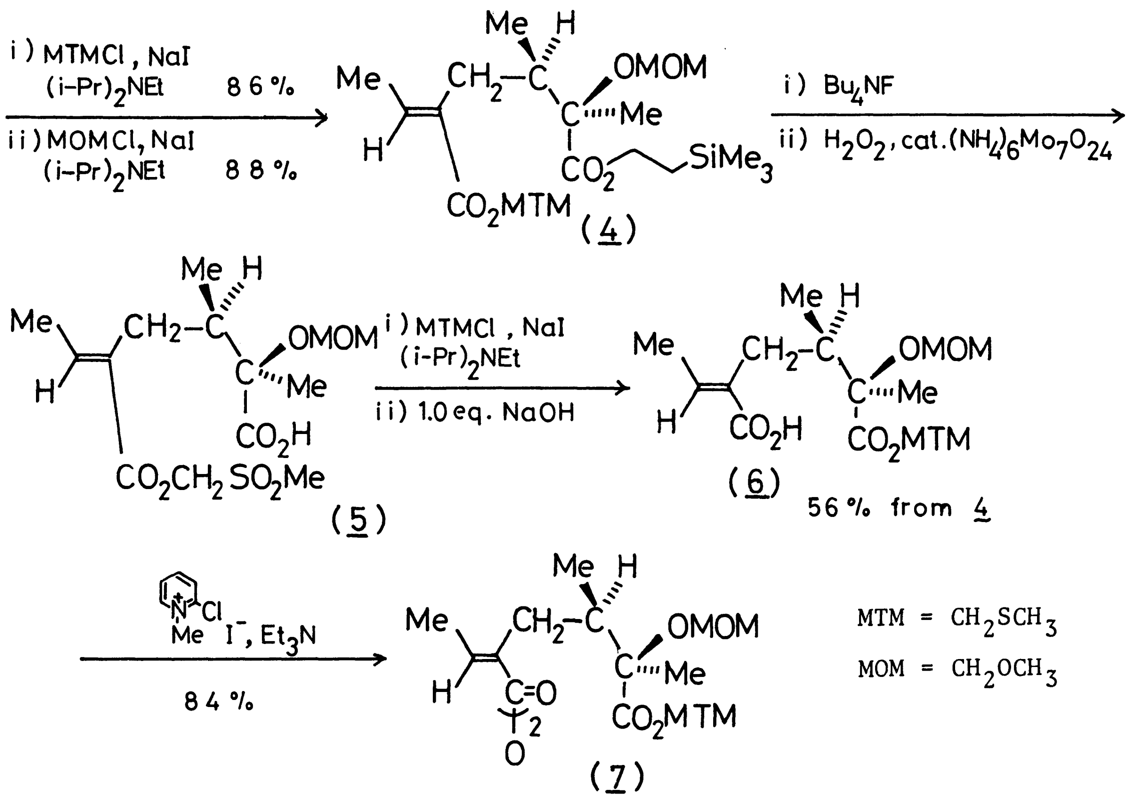
Large-ring bislactonic pyrrolizidine alkaloids have been one of the attractive synthetic targets because of the wide range of biological activities as well as their characteristic structures.1,2) We now wish to describe the first total synthesis of a naturally occurring bislactonic pyrrolizidine alkaloid, integerrimine (1).3) First object of our synthetic strategy is the stereoselective preparations of suitably protected retronecine (11) and integerrinecic acid (6), two components obtained by hydrolysis of integerrimine. The synthesis of integerrimine (1) is completed by coupling of these two components to form an α,β-unsaturated ester (12), followed by lactonization.

We have already reported the stereoselctive synthesis of (±)-integerrinecic acid lactone (2).4) Starting from 2, the introduction of protecting groups to tertiary alcohol and tertiary carboxylic acid is performed by the following procedure; the acid lactone (2) is converted to the trimethylsilylethyl ester by treatment with trimethylsilylethanol, 2-chloro-1-methylpyridinium iodide5) and triethylamine, and the selective hydrolysis of the δ-lactone is carried out with 1.1 eq. of LiOH in the presence of excess H_2O_2 to give an α,β-unsaturated acid (3). The hydroxy acid (3) is successively protected as MTM ester6) and as MOM ether (4). The trimethylsilylethyl group is removed, and the MTM ester is oxidized7) to yield sulfone (5). Finally, the tertiary carboxylic acid is protected as the MTM ester and the methanesulfonylmethyl moiety is selectively hydrolyzed with 1.0 eq. of NaOH. Then the resulting acid (6) obtained as a viscous oil is converted to the acid anhydride (7) for the effective coupling with retronecine.



(2)

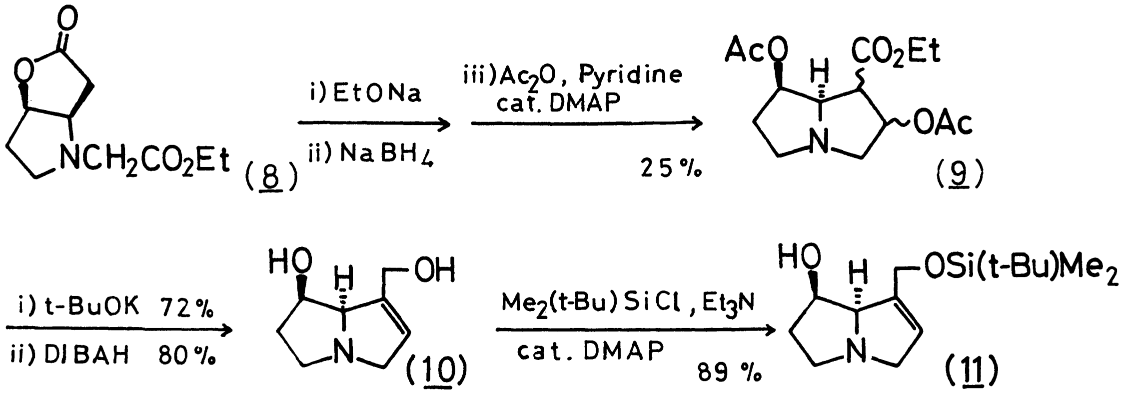
(3)



MTM = CH_2SCH_3

MOM = CH_2OCH_3

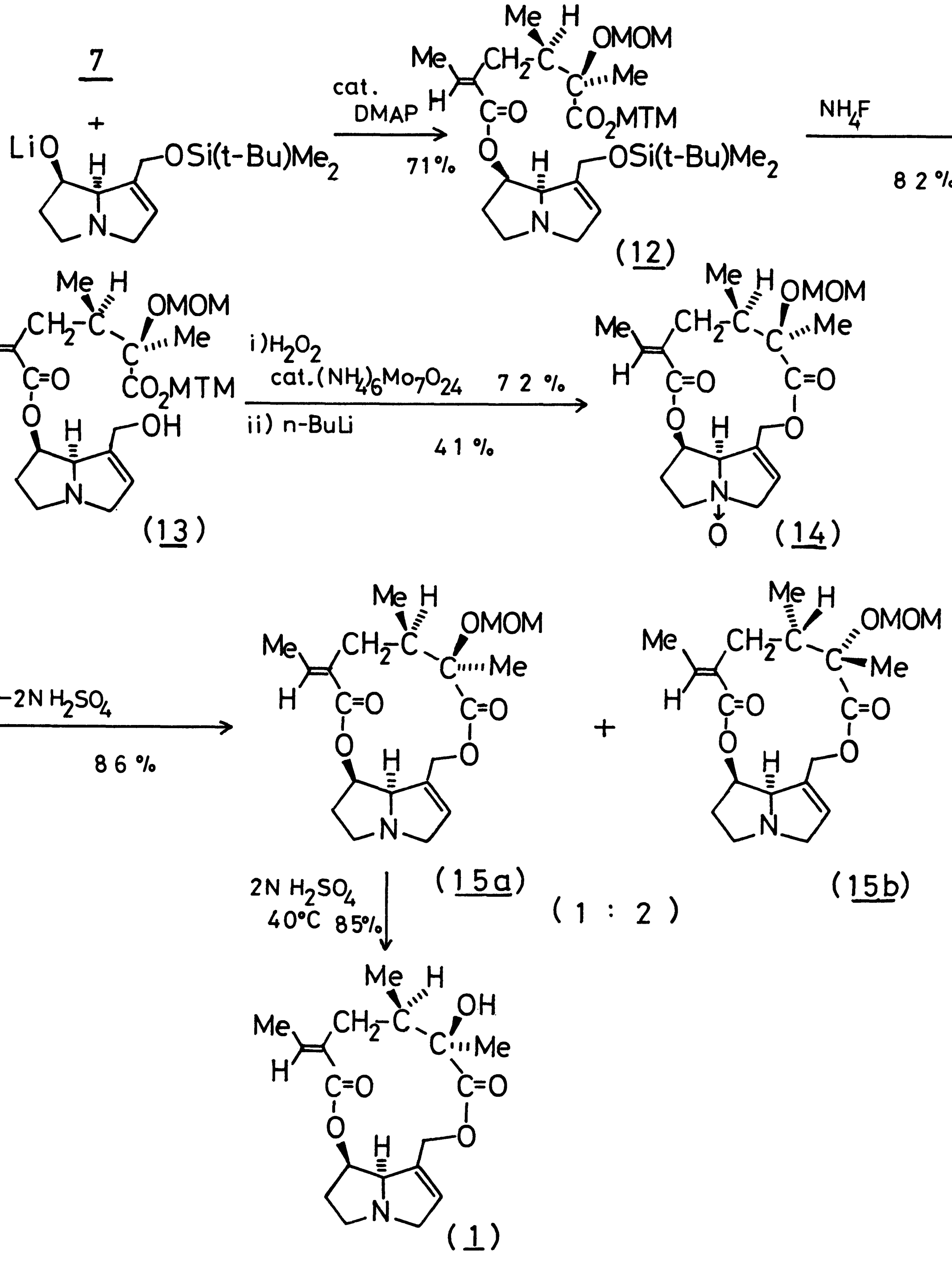
The necine part, retronecine (10), is synthesized by a modification of Geissman's route.8) A bicyclic lactone (8) prepared according to Geissman's report is submitted to the Dieckmann condensation, and after neutralization, treatment of the reaction mixture with $NaBH_4$, followed by acetylation affords β-acetoxy ester (9). The ester (9) is transformed to an unsaturated ester on treatment with t-BuOK, and the successive reduction with excess DIBAH yields (±)-retronecine (10).9) The allylic hydroxyl group of 10 is selectively protected as t-butyldimethylsilyl ether (11).10)



DMAP = 4-Dimethylaminopyridine, DIBAH = $(i\text{-}Bu)_2AlH$

Many trials for the coupling of the two components, (6) and (11), were attempted, and only when the acid anhydride (7) is employed is a successful result obtained.

Treatment of acid anhydride (7) with the lithium salt of the t-buthyldimethylsilyl ether of retronecine (11) in THF in the presence of catalytic amount of DMAP gives an acid sensitive ester (12).[11] After the removal of the silyl group using ammonium fluoride, the cyclization is performed by a novel lactonization procedure.[12] Conversion of the MTM moiety to methanesulfonylmethyl group and treatment of the methanesulfonylmethyl derivative with an equimolar amount of butyllithium in THF from -78°C to -25°C affords oily cyclization product (14). After the reduction



of the N-oxide in 14 by Zn-2N H_2SO_4,13) integerrimine MOM ether (15a) and the diastereomer (15b) are separated by tlc on aluminium oxide.14) The regeneration of the tertiary hydroxy group under acidic conditions gives (±)-integerrimine (1).15)

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9) Mp. 129-130.5°C (lit., 130-131°C)8); Mass, M^+ 155; The Rf value of 10 on neutral alumina is completely identical with that of authentic (+)-retronecine, and the nmr spectrum in D_2O agrees well with the literature data.16)
10) S. K. Chaudhary and O. Hernandez, Tetrahedron Lett., 1979, 99.
11) At this stage, two the two diastereomers of 12 are not separated by tlc.
12) The detail of this unique method for lactonization will be published later.
13) C. C. J. Culvenor and L. W. Smith, Aust. J. Chem., 19, 2127 (1966).
14) The desired isomer (15a) is less polar on aluminium oxide tlc, and the ratio of 15a:15b is about 1:2.
15) Mp. 162°C. Mass and NMR spectra of the synthetic (±)-integerrimine (1) completely agree with those of an authentic sample. Identification of the synthetic (1) with the natural specimen was also made based on comparison by tlc on aluminium oxide.
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