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THE TOTAL SYNTHESIS OF (±)-LATIFINE

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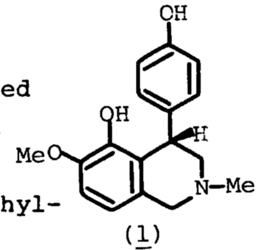
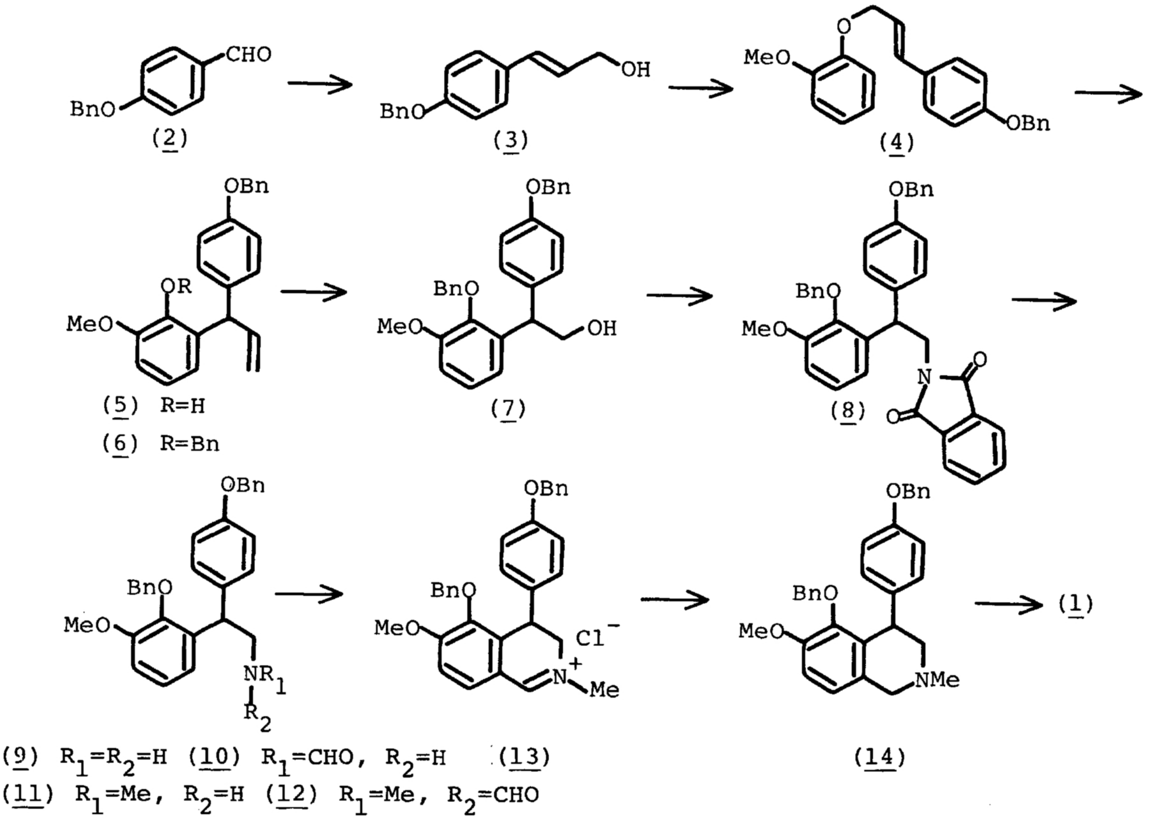
Latifine, a novel phenolic isoquinoline base from *Crinum latifolium* L. (Amaryllidaceae), has been synthesized.



(1)

Recently, the isolation of a unique phenolic isoquinoline base latifine (1) from *Crinum latifolium* L. (Amaryllidaceae) was reported by Kobayashi and co-workers.1) This compound is the first example of naturally occurring 4-aryl-5,6-dioxygenated isoquinoline base2) and claimed to be an anabolic or catabolic metabolite of O,N-dimethylnorbelladine. We report here the first synthesis of latifine (1) in racemic forms.

Treatment of 4-benzyloxycinnamyl alcohol (3),3) mp 113-114 °C, easily prepared from 4-benzyloxybenzaldehyde (2) in 81% yield (i: $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; ii: DIBAL, toluene, 0 °C), with guaiacol (1.05 equiv.) in the presence of diethyl azodicarboxylate (1.2 equiv.) and triphenylphosphine (1.2 equiv.)4,5) gave the allyl aryl ether (4), mp 91-93 °C, in 34% yield. Upon refluxing in N,N-dimethylaniline (50 min),6) 4 underwent smooth rearrangement to give the phenolic olefin (5), oil, in 75% yield. Benzylation of 5 (benzyl bromide, K_2CO_3, DMF, 80 °C, 9h) gave 83% of the ether (6), of which the newly introduced benzylic methylene group in ^1H-NMR spectrum appeared as an AB type quartet at δ 4.67 and 4.92 (J=11 Hz). The olefin (6), on ozonolysis followed by reduction with sodium borohydride in the same flask (ozonolysis: $MeOH-CH_2Cl_2$, -78 °C, 12 min; reduction: -78 °C - r.t.), afforded the primary alcohol (7), oil, in 87% yield. Treatment of 7 with phthalimide (1.5 equiv.) in the presence of diethyl azodicarboxylate (1.7 equiv.) and triphenylphosphine (1.3 equiv.)4) gave the imide (8), semi-solid, in 86% yield, which was treated with hydrazine hydrate (3.0 equiv., EtOH, reflux, 2.5 h) to give the primary amine (9), oil, in 96% yield. Neither the formamide (10), amorphous, obtained in 90% yield from 9 with acetic formic anhydride7) (0 °C - r.t., 45 min), under Bischler-Napieralski conditions (phosphorus oxychloride, benzene, reflux) nor the methylamine (11), oil, obtained in 89% yield from 10 with lithium aluminum hydride (THF, reflux, 3 h), under Pictet-Spengler conditions (37% formalin, hydrochloric acid, methanol, reflux) gave any isolable amount of the corresponding isoquinoline bases owing to concomitant decomposition. However, clean cyclization occurred with the tertiary amide (12), amorphous, obtained in 85% yield from 11 with acetic formic anhydride



(0 °C - r.t., 1 h),[7] which gave the desired isoquinoline (14) in 51% overall yield upon Bischler-Napieralski reaction (phosphorus oxychloride, 5 equiv., benzene, reflux, 45 min) followed by reduction of the crude imminium base (13) with sodium borohydride (MeOH, 0 °C, 1 h). The compound (14) exhibits characteristic two pairs of AX type signals of C-5 benzyloxymethylene protons (δ 3.91 and 4.80, J=10 Hz) and C-1 methylene protons (δ 3.30 and 3.85, J=14 Hz) in ^{1}H-NMR spectrum due to the anisotropic effect of the benzene ring at C-4 position. Catalytic debenzylation (H_2, 10% palladized carbon, 55 °C) of 14 afforded the diphenolic base (1), mp 212-215 °C (decomp)(natural,[1] mp 215-217 °C), in 84.5% yield, whose properties were identical in all respects (IR, TLC, NMR, MS) with optically active sample obtained by chiral synthesis[8] and those reported for natural product.[1]

References
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