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A TOTAL SYNTHESIS OF CHELIDONINE

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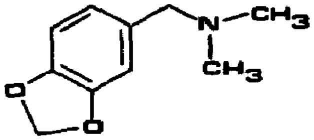
Abstract. Condensation of homophthalic anhydride 3 with the Schiff base 4 is exploited as the key step in a total synthesis of the benzophenanthridine alkaloid (±)-chelidonine (8).

(+)-Chelidonine (8), a major secondary metabolite of Chelidonium majus[1], is the first benzophenanthridine alkaloid to have had its structure elucidated. Extensive degradative studies led to a correct structure in 1930,[2] and a B/C cis ring fusion together with an axial hydroxyl group were later proposed to account for the presence of an intramolecular hydrogen bond detected by ir spectroscopy.[3,4] Contrary to earlier studies,[5] (+)-chelidonine was recently reassigned the absolute configuration depicted in structure 8 by x-ray analysis of the p-bromobenzoate.[6] The racemic mixture (diphylline),[7] as well as either enantiomer,[8] can be isolated from various plants of the Papaveraceae. A total synthesis of (±)-chelidonine has already been executed.[9,10] We wish to report a second total synthesis of (±)-chelidonine which is noteworthy because of its brevity and simplicity.

Metalation of the amine 1 with 1.2 equiv of n-BuLi in THF (-78°C, 2 h), followed by addition of excess ethyl chloroformate to the ortho-lithiated intermediate, gave the carbethoxylated benzyl chloride 2 in 45% yield.[11] Compound 2 was transformed into the known homophthalic anhydride 3[12] in 64% yield after displacement of the chloride with cyanide (KCN, DMSO, reflux, 3 h), basic hydrolysis (aq. KOH, reflux, 3 h), and cyclodehydration (AcCl, reflux, 6 h). Condensation of the anhydride 3 with the Schiff base 4 (CH_3CN, reflux, 1 h) afforded a diastereomeric mixture of isoquinolones (67% cis, 33% trans) from which the desired cis isomer 5 (J_{AB} = 6 Hz), mp 219-221°C (dec), could be isolated in 62% yield.[13] A variety of reaction conditions (Table I) did not further improve the ratio of isomers. The desired cis diastereomer 5 is unfortunately the thermodynamically less stable, since on heating in refluxing acetic acid (13 h) it was transformed completely into the unwanted trans isomer (J_{AB} = 0 Hz).[13] Addition of thionyl chloride to a solution of the triethylamine salt of 5 in benzene/CH_2Cl_2 (0°C, 2 h) gave a crude acid chloride which without purification was treated immediately with excess diazomethane in Et_2O (-10°C, 20 min), affording a 50% yield of the diazoketone 6.[14] Compound 6 on treatment with CF_3COOH (0°C, 1



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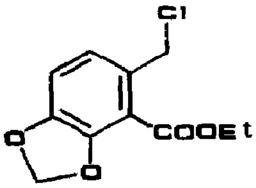

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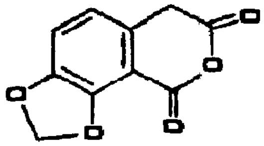

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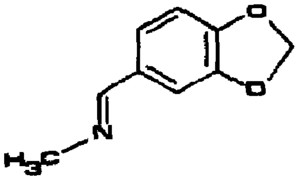

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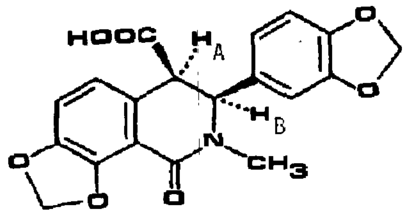

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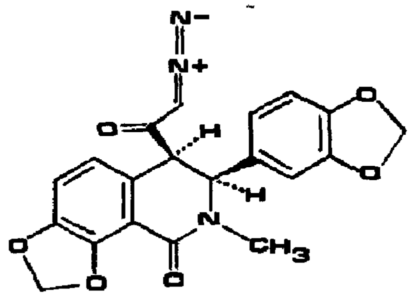

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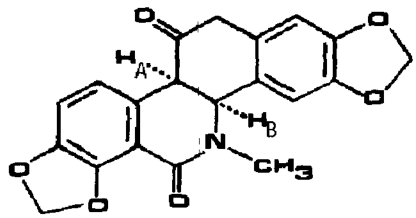

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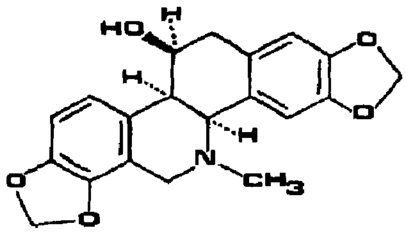

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min) gave a mixture of products from which the cyclized ketone 7 (J_{AB} = 4 Hz), mp 253°C (dec), could be isolated by fractional crystallization in 19% yield.[15] Lithium aluminum hydride reduction of 7 (THF, reflux, 17 h) provided (±)-chelidonine, mp 217-218°C, in 93% yield. The 360 MHz nmr spectra and ir spectra (KBr) of the synthetic compound and authentic (+)-chelidonine[16] are identical.

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Table I. The Effect of Reaction Conditions on the Stereochemical Outcome of the Condensation of 3,4-Methylenedioxyhomophthalic Anhydride (3) and Piperonylidenemethylamine (4).[a]

Solvent	Temp (time)[b]	% cis[c]	% trans
CH_3CN	82°C (1 h)	67	33
$CH_3CN + Et_3N$ (9:1)	23°C (40 min)	58	42
CH_3NO_2	23°C (30 min)	38	62
t-BuOH	23°C (27 min)	23	77
THF	23°C (65 min)	20	80
Neat[d]	23°C (1 min)	20	80
CH_3CN	-22°C (57 min)	20	80
CH_2Cl_2	23°C (15 min)	17	83
CH_2Cl_2	-78°C (72 min)	11	89
$ClCH_2CH_2Cl$	83°C (103 min)	11	89
$\emptyset CH_2CN$	183°C (59 min)	8	92

[a] The combined yields of the diastereomers are essentially quantitative. [b] Reaction times include slow additions of the reagents. [c] Estimated by nmr integrations. [d] The neat reaction was performed by shaking the two solids in a wiggle-bug ball mill.

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