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A NOVEL AND BIOMIMETIC SYNTHESIS OF (±)-CHELAMINE, (±)-CHELIDONINE, SANGUINARINE, AND DIHYDROSANGUINARINE FROM COPTISINE VIA A COMMON INTERMEDIATE

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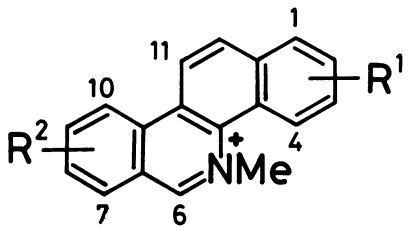
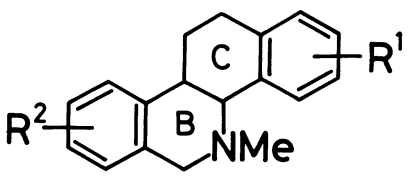
(±)-Chelamine and (±)-chelidonine, B/C *cis* hexahydrobenzo[*c*]-phenanthridine alkaloids were stereoselectively synthesized from coptisine *via* the key intermediate, which was also converted to fully aromatized benzo[*c*]phenanthridine alkaloids, sanguinarine and dihydrosanguinarine.

Benzo[*c*]phenanthridine alkaloids can be classified into two groups, fully aromatized benzo[*c*]phenanthridines and B/C hexahydro ones, and they have been shown to be biosynthesized from protoberberine alkaloids.[1] Many efforts[2] have been focused on development of efficient and convenient methods for a synthesis of fully aromatized benzo[*c*]phenanthridine alkaloids because of their potential pharmacological activities. Several syntheses of hexahydrobenzo[*c*]phenanthridine alkaloids[3,4,5] have also been reported. However, no report has so far been made on the synthesis of both types of alkaloids from a common intermediate. This communication deals with a novel and stereoselective synthesis of (±)-chelamine (7), (±)-chelidonine (8), sanguinarine (9), and dihydrosanguinarine (10) from coptisine (1), a protoberberine alkaloid, *via* the common and key intermediate (6) according to a biogenetic route, as a continuation of our synthetic studies on benzo[*c*]phenanthridine alkaloids.[6]



Fully Aromatized
Benzo[*c*]phenanthridine



B/C Hexahydro
Benzo[*c*]phenanthridine

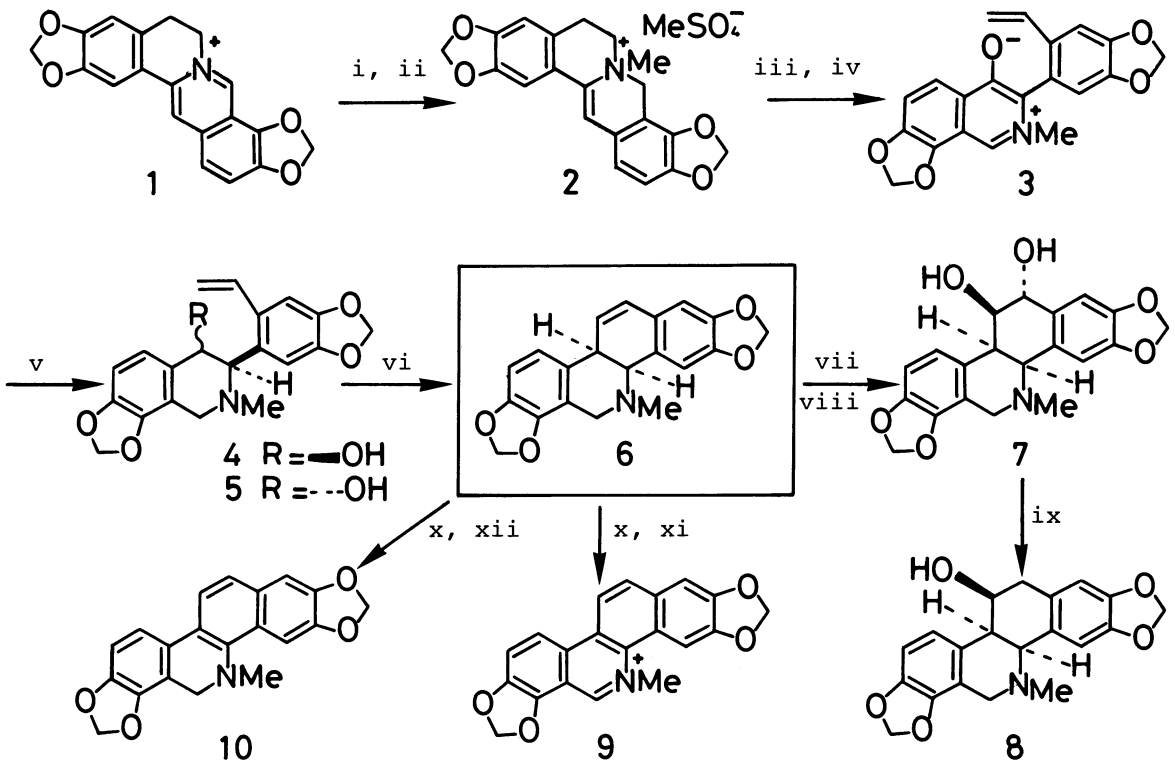
Reduction of coptisine (1) with lithium aluminium hydride in dry tetrahydrofuran, followed by methylation with dimethyl sulfate gave the methosulfate (2) [93%; mp 254-257 °C (dec.)]. The C_6-N bond fission and introduction of oxygen function at the C_{13} position of 2 were realized by the Hofmann elimination, followed by oxidation with *m*-chloroperoxybenzoic acid to afford the betaine (3) [96%; mp 227-229 °C; δ 8.16, 7.26 (2H, AB-q, *J*=9), 7.63 (1H, s), 6.32 (1H, dd, *J*=17.5 and 11), 5.55 (1H, dd, *J*=17.5 and 1.2), 5.08 (1H, dd, *J*=11 and 1.2)]. The betaine (3) was reduced with sodium borohydride in refluxing methanol to furnish predominantly the *cis* alcohol (4) [80%; mp 172-175 °C; δ 4.38 (1H, br-s), 3.88 (1H, d, *J*=2.2)] along with the *trans* alcohol (5) [15%; δ 4.78 (1H, d, *J*=8), 3.61 (1H, d, *J*=8)]. Treatment of the *cis* alcohol (4) with concentrated sulfuric acid in acetic acid at room temperature effected stereoselective cationic cyclization to provide the benzo[*c*]phenanthridine (6) [98%; mp 144-145 °C; δ 6.36 (1H, dd, *J*=9.5 and 3.1), 5.78 (1H, br-d, *J*=9.5), 3.71 (1H, m), 3.41 (1H, br-d, *J*=5.1)]. The *cis*-fused stereochemistry of 6 was unambiguously ascertained from the coupling constant between the H_{4b} and H_{10b} (*J*=5.1)[7] in its ^{1}H-NMR spectrum. In the same manner, the *trans* alcohol (5) also gave 6 exclusively in 94% yield.

Upon treatment with peroxyformic acid in formic acid,[8] the benzo[*c*]phenanthridine (6) underwent the *trans*-hydroxylation stereoselectively to yield (±)-chelamine (7) [91%; mp 246-247 °C; δ 4.82 (1H, d, *J*=2.2), 4.08 (1H, m), 3.55 (1H, m), 3.30 (1H, t, *J*=2.2)]. The stereochemistry of 7[9] was confirmed as depicted by spectral data and mechanistic consideration.[8a] The structure of chelamine, isolated from *Corydalis majus*,[10] was proposed to be 12-hydroxychelidonine[10,11] and its stereochemistry has recently been clarified from spectral data.[12] The above synthetic chelamine (7) was shown to be identical with natural chelamine by spectral comparison and thin-layer chromatographic behavior, therefore, the stereochemistry of chelamine is unambiguously established.

A hydroxy group at the C_{12} position in 7 was regioselectively removed with triethylsilane[13] in the presence of boron trifluoride etherate in chloroform to produce (±)-chelidonine (8) [82%; mp 214-215 °C (lit.[10] mp 215-216 °C)], which was identified with natural chelidonine by spectral comparison and thin-layer chromatographic behavior.

On the other hand, the benzo[*c*]phenanthridine (6) was dehydrogenated with 10% Pd-C in aqueous acetic acid in the presence of maleic acid to afford sanguinarine (9) [47%; mp 279-281 °C (lit.[14a] mp 286-288 °C)] after treatment with concentrated hydrochloric acid. Dehydrogenation of 6 followed by sodium borohydride reduction provided dihydrosanguinarine (10) [65%; mp 187-188 °C (lit.[14b] mp 188-189 °C)]. The synthetic sanguinarine and dihydrosanguinarine were proved to be identical with the corresponding alkaloids.

Thus, we have succeeded in not only a highly stereoselective synthesis of (±)-chelamine and (±)-chelidonine, but also an alternative synthesis of sanguinarine and dihydrosanguinarine from coptisine *via* a common intermediate (6) according to a biogenetic route. Therefore, this method provides a general method for a synthesis of B/C *cis* hexahydrobenzo[*c*]phenanthridine alkaloids as well as fully aromatized benzo[*c*]phenanthridine alkaloids.



i: $LiAlH_4$/THF; ii: Me_2SO_4/benzene; iii: 25%KOH/MeOH; iv: m-CPBA/CH_2Cl_2; v: $NaBH_4$/MeOH; vi: c.H_2SO_4/AcOH; vii: HCO_3H/HCO_2H; viii: 20%aq.KOH/EtOH; ix: Et_3SiH, $BF_3 \cdot OEt_2/CHCl_3$; x: 10% Pd-C/aq.AcOH, maleic acid; xi: c.HCl; xii: $NaBH_4$/MeOH

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