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A NOVEL AND HIGHLY STEREOSELECTIVE SYNTHESIS OF (±)-SIBIRICINE

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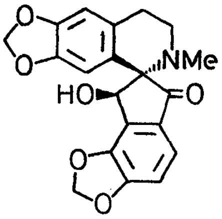
A novel and stereoselective synthesis of (±)-sibiricine (1), a spirobenzylisoquinoline alkaloid, from the corresponding protoberberine (3) was developed using photo-oxygenation and photo-isomerization.

KEYWORDS—— sibiricine; corydaine; sewercinine; ochrobirine; spirobenzylisoquinoline; protoberberine; stereoselective synthesis; photo-oxygenation; photo-isomerization

Sibiricine (1),[1)] isolated from *Corydalis sibirica*,[1)] *C. ledebouriana*,[2)] and *C. paniculigera*,[3)] is a representative spirobenzylisoquinoline alkaloid having a carbonyl group and a hydroxy group *trans* to the *N*-methyl group in the five-membered ring. (±)-Sibiricine has been synthesized[4,5)] together with its diastereomer, (±)-corydaine (2). Although 2 has been synthesized stereoselectively,[5,6)] stereoselective synthesis of 1 is difficult partially due to the isomerization of 1 to 2 through the retro-aldol reaction. This communication describes a simple and highly stereoselective synthesis of (±)-sibiricine (1) from the corresponding protoberberine (3)[7)] *via* four steps using photo-oxygenation and photo-isomerization as crucial steps.



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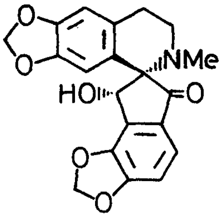

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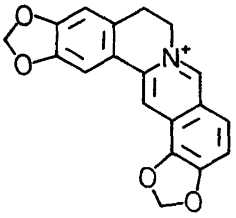
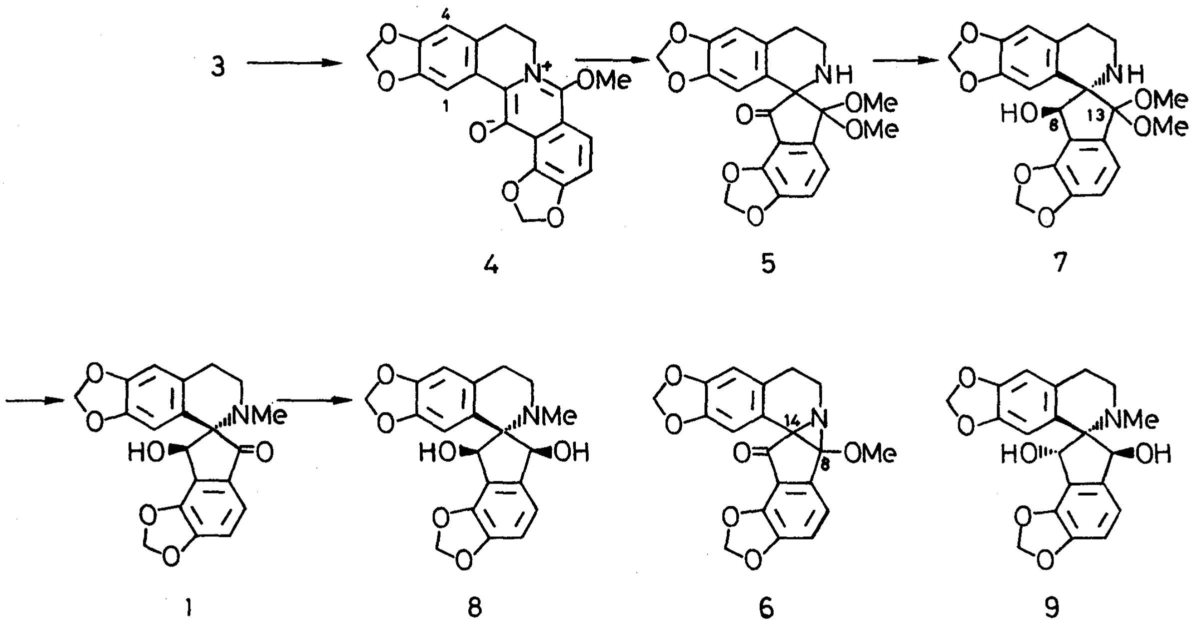


3

Irradiation[8,9)] of 3 with a halogen lamp in methanol containing sodium methoxide and rose bengal in a stream of oxygen at 0°C, followed by column chromatography on alumina, afforded the 8-methoxyphenolbetaine (4) [66%, *m/z* 365 (M^+), δ 9.06 (1H, s, C_1-H), 4.02 (3H, s, OCH_3)]. The betaine (4) was further irradiated[9,10)] with a mercury lamp through a Pyrex filter in methanol in a stream of nitrogen at 0°C to give the spirobenzylisoquinoline (5) [64%, mp 219-221°C, *m/z* 397 (M^+), ν 1715 (CO), δ 6.28 (1H, s, C_1-H), 3.19, 3.15 (each 3H, s, OCH_3 x 2)] as a protected form of a β-diketone. The formation of 5 can be well rationalized through the intermediacy of the 8,14-cycloberbine (6), which is formed by the photo-chemical valence isomerization of 4 and then converted to 5 by the subsequent attack of



methanol at C-8.[9,11]

Sodium borohydride reduction of 5 in methanol-chloroform (3:1) at 0°C gave stereoselectively the *trans*-alcohol (7) [100%, mp 194-196°C, *m/z* 384 (M^+-15), ν 3550 (OH), δ 5.10 (1H, br s, C_8-H)], the stereochemistry of which was supported by the appearance of the C_8-H at a lower field in its proton nuclear magnetic resonance spectrum.[12] Treatment of 7 with 37% formaldehyde and formic acid effected *N*-methylation and concomitant deacetalization to provide (±)-sibiricine (1) [91%, mp 220-222°C (lit.[4] mp 223-225°C), *m/z* 367 (M^+), ν 3550 (OH), 1710 (CO), δ 7.49, 7.01 (2H, AB-q, *J*=8 Hz, C_{11}- and C_{12}-H), 6.62 (1H, s, C_4-H), 6.21, 6.18 (2H, AB-q, *J*=1 Hz, OCH_2O), 6.03 (1H, s, C_1-H), 5.84 (2H, s, OCH_2O), 5.54 (1H, br s, C_8-H), 2.36 (3H, s, NCH_3)]. Synthetic 1 was identical with the authentic sample.

Reduction of 1 with sodium borohydride[13] in methanol yielded stereoselectively (±)-sewercinine (8) [91%, mp 118-120°C, *m/z* 369 (M^+), ν 3550 (OH), δ 6.86, 6.85 (2H, AB-q, *J*=8.5 Hz, C_{11}- and C_{12}-H), 6.67 (1H, s, C_4-H), 6.20 (1H, s, C_1-H), 6.07, 6.00 (2H, AB-q, *J*=1.5 Hz, OCH_2O), 5.85 (2H, s, OCH_2O), 5.42, 5.19 (each 1H, br s, C_8- and C_{13}-H), 2.59 (3H, s, NCH_3)]. Synthetic 8 was identical with natural sewercinine[13] by spectral comparison.

The present synthesis of (±)-sibiricine (1) also amounts to a formal synthesis of (±)-corydaine (2) and (±)-ochrobirine (9), since 1 has been converted to 2 by isomerization[4] and 2 has been reduced to 9.[4]

Thus, we have developed a novel and stereoselective synthesis of sibiricine and this method can be applied to a synthesis of any type of spirobenzylisoquinoline alkaloids.

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