A Biomimetic Synthesis of (±)-Corydalic Acid Methyl Ester from Corysamine

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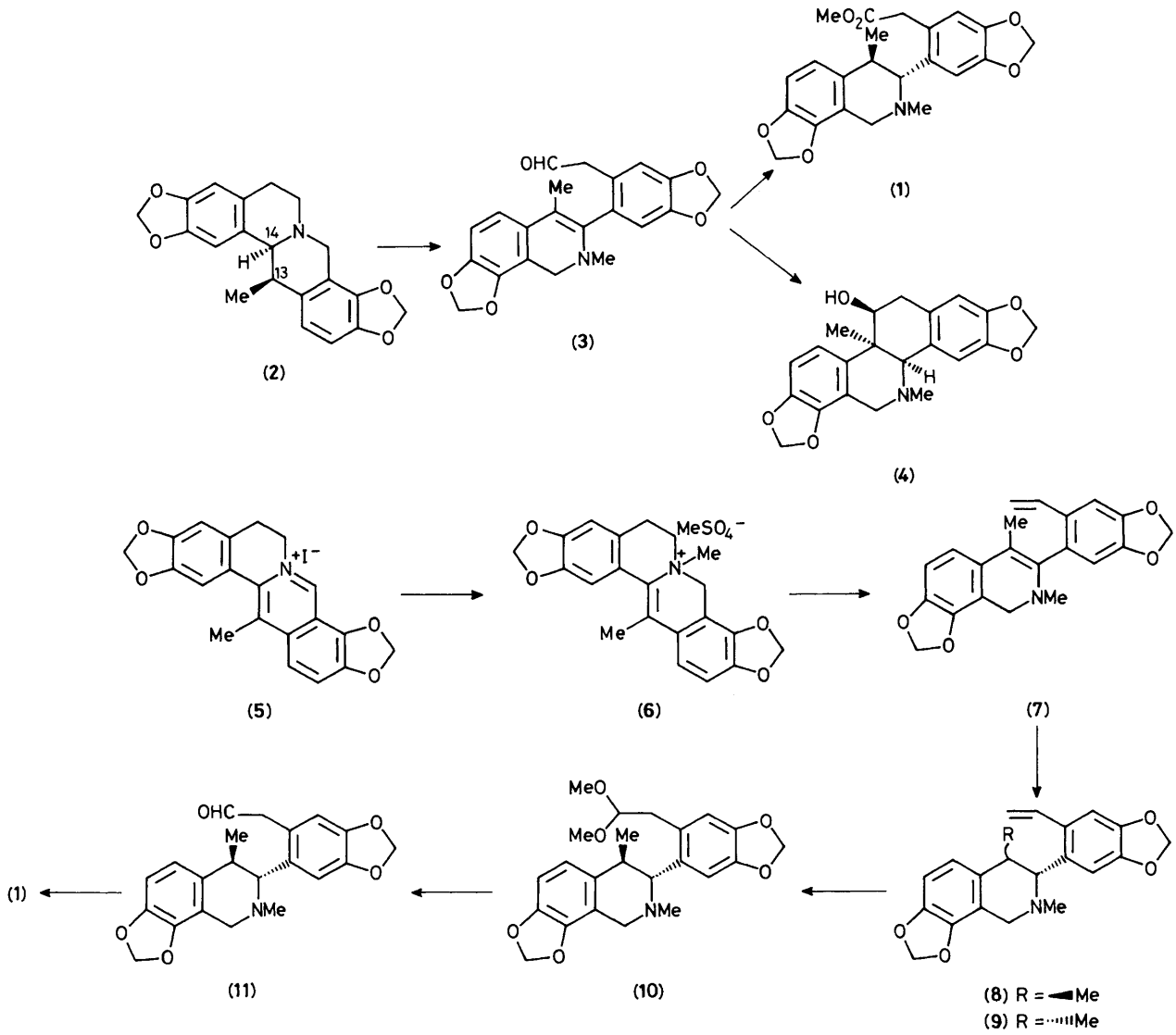
(±)-Corydalic acid methyl ester (**1**), a 3-arylisoquinoline alkaloid, was efficiently synthesised from the corresponding protoberberine alkaloid, corysamine (**5**) *via* a biogenetic route.

Corydalic acid methyl ester (**1**),[1,2] a representative 3-arylisoquinoline alkaloid, has been isolated along with some protoberberine and benzo[*c*]phenanthridine alkaloids from *Corydalis incisa* Pers. This alkaloid has been shown to be biosynthesised from the corresponding protoberberine alkaloid,[3] tetrahydrocorysamine (**2**) *via* the hypothetical aldehyde intermediate (**3**). The latter type of compound has also been suggested as a common intermediate for biosynthesis of benzo[*c*]phenanthridine alkaloids[3,4] such as corynoline (**4**) from protoberberine alkaloids. Recently the first total synthesis of (±)-corydalic acid methyl ester (**1**) was published.[5] We now report a novel and stereoselective synthesis of (**1**) from the corresponding protoberberine alkaloid, corysamine (**5**) according to the above biogenetic consideration.

Corysamine (**5**)[6] was reduced with $LiAlH_4$ in anhydrous tetrahydrofuran then treated with dimethyl sulphate in refluxing benzene to give the methosulphate (**6**) (85%; m.p. 247—248 °C). Upon treatment with 25% methanolic KOH, (**6**) underwent the Hofmann elimination to produce the enamine (**7**), which was subsequently reduced with $NaBH_3CN$† in refluxing Bu^{t}OH in the presence of 10% HCl to yield stereoselectively the desired *trans* derivative (**8**) [60%; *m/z* 351(M^+); ^{1}H n.m.r. δ 7.20 (1H, dd, *J* 17 and 11 Hz), 5.47 (1H, dd, *J* 17 and 1.5 Hz), 5.17 (1H, dd, *J* 11 and 1.5 Hz), 2.12 (3H, s), 1.04 (3H, d, *J* 6.5 Hz)] along with the *cis* derivative (**9**) [14%; m.p. 158.5—159.5 °C; *m/z* 351(M^+); ^{1}H n.m.r. δ 7.04 (1H, dd, *J* 17 and 11 Hz), 5.47 (1H, dd, *J* 17 and 1.5 Hz), 5.19 (1H, dd, *J* 11 and 1.5 Hz), 2.28 (3H, s), 1.04 (3H, d, *J* 7 Hz)]. On the other hand, this stereoselectivity disappeared‡ when the reduction of the enamine (**7**) was carried out with $NaBH_3CN$ in MeOH instead of Bu^{t}OH at room temperature.

† Reduction of the enamine (**7**) with $NaBH_4$ in refluxing EtOH for a long time was unsuccessful: (**7**) was recovered unchanged.

‡ The compounds (**8**) and (**9**) were obtained in 45 and 38% yields, respectively.



The spectral data of (**8**) are in good agreement with those reported for the *trans* derivative, which has previously been synthesised[2] from mesotetrahydrocorysamine,§ a diastereoisomer of tetrahydrocorysamine (**2**), through the Hofmann degradation.

Oxy-functionalisation of the terminal position of the styrene moiety in (**8**) was realised by treatment with thallium trinitrate[7] in MeOH at room temperature to afford the acetal (**10**) [76%; *m/z* 413(M^+); ^{1}H n.m.r. δ 4.52 (1H, t, *J* 5.5 Hz), 3.33 (6H, s)]. Hydrolysis of the acetal (**10**) with 5% HCl in acetone provided the expected aldehyde (**11**) [100%; *m/z* 367(M^+); i.r. ν_{max} 1720 cm^{-1}; ^{1}H n.m.r. δ 9.55 (1H, t, *J* 2.5 Hz)]. Jones oxidation of the aldehyde (**11**) followed by methylation with diazomethane gave (±)-corydalic acid methyl ester (**1**) [77%; m.p. 139—140 °C (lit.[5] m.p. 144—147 °C); *m/z* 397(M^+); i.r. ν_{max} 1730 cm^{-1}; ^{1}H.n.m.r. δ 3.66 (3H, s)]. The synthetic corydalic acid methyl ester was shown to be identical with natural corydalic acid methyl ester by spectral comparison and thin-layer chromatographic behaviour.

Thus, we have efficiently accomplished the first biomimetic transformation of a protoberberine alkaloid, corysamine (**5**) into a 3-arylisoquinoline alkaloid, corydalic acid methyl ester (**1**).

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§ Mesotetrahydrocorysamine was obtained as a minor product from corysamine by reduction with Zn–$MeCO_2H$.

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