Studies on the Stereochemistry of Nucleophilic Additions to Tetrahydropyridinium Salts. Expeditious Stereospecific Total Syntheses of (+)-Makomakine, (+)-Aristoteline, and (±)-Hobartine

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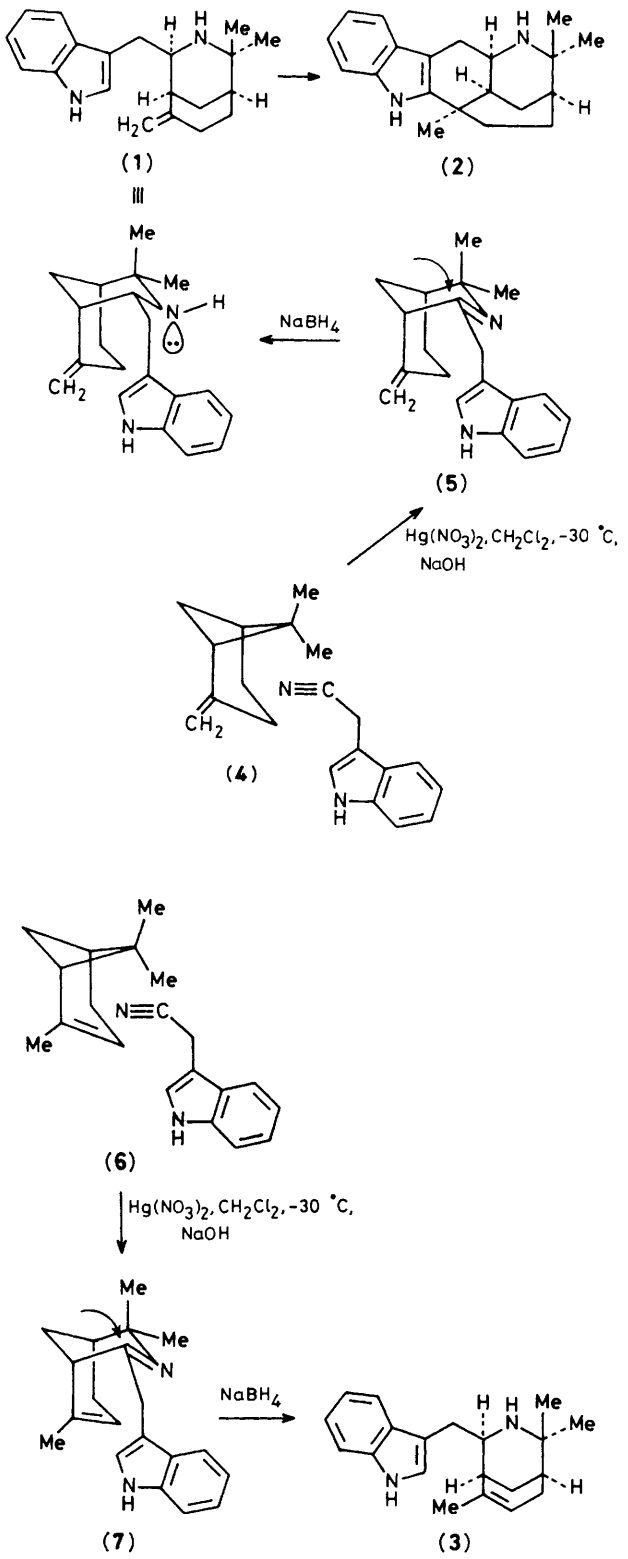
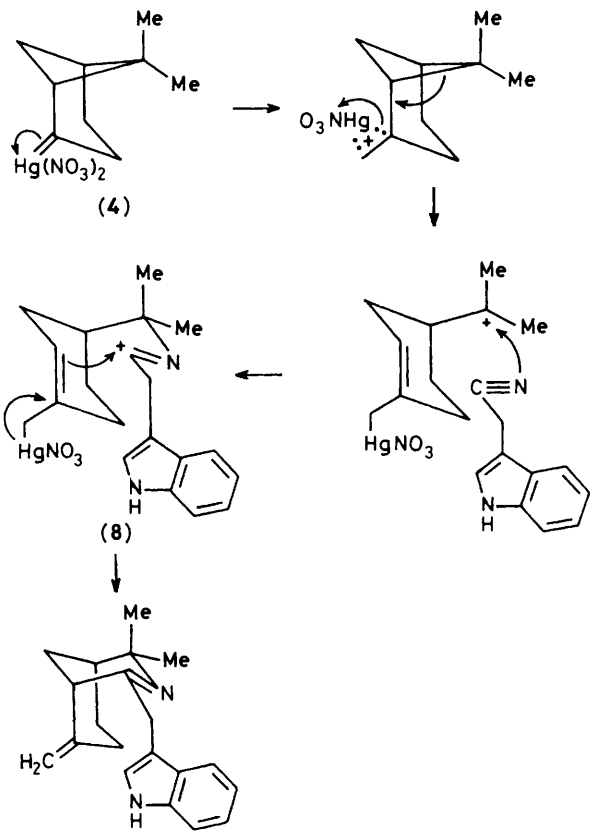
The *Aristotelia* alkaloids (+)-makomakine, (+)-aristoteline, and (±)-hobartine have been synthesised stereospecifically *via* reduction of the corresponding tetrahydropyridines formed in the mercury(II) nitrate-mediated Ritter coupling of indol-3-ylacetonitrile with (−)-β-pinene and (+)-α-pinene, respectively.

Recent studies from our laboratory have focused on the stereochemistry of nucleophilic additions to tetrahydropyridinium salts as a powerful heuristic principle for the stereospecific synthesis of alkaloids.[1,2] The *Aristotelia*

alkaloids, makomakine (**1**),[3] aristoteline (**2**),[4,5] and hobartine (**3**)[6] are new indole alkaloids derived *in vivo* from tryptamine and an unrearranged monoterpene moiety[7] and provide an interesting test of the stereoelectronic principles advanced previously.[1,2] Thus, hydride reduction of the imine (**5**) is predicted[1,2] stereoelectronically to afford makomakine (**1**). However, such a reduction clearly suffers from a 1,3-diaxial interaction with one of the flanking methyl groups. Inspection of models reveals that attack from the opposite face does not suffer from any serious steric interactions (note that the carbon which is three atoms removed is sp^2-hybridized). Similarly, reduction of the imine (**7**) is predicted stereoelectronically to provide hobartine (**3**) but suffers the same steric problems. A recent report[8] on the synthesis of these alkaloids prompts us to communicate our syntheses of these alkaloids by a similar though more expeditious route and which employs the recently described mercury(II) nitrate-initiated Ritter reaction of nitriles with α- and β-pinene.[9]

In the case of (+)-makomakine (**1**), (−)-β-pinene (**4**) was added to a dichloromethane solution of indol-3-ylacetonitrile (6 equiv.) and mercury(II) nitrate (1.1 equiv.) at −30 °C. Upon warming to 0 °C the resultant imine (**5**) was reduced with sodium borohydride in 3 M sodium hydroxide–methanol. After purification and crystallization pure (+)-makomakine (**1**)† was isolated in 17% yield (not yet optimized). No other stereoisomers were detected in the reaction mixture. In order to confirm the stereospecific nature of the reduction we have also isolated the imine (**5**) and subjected it to the reduction conditions. No significant amounts of other products could be detected. Thus it would appear that the stereochemical course of the reduction is dictated by stereoelectronic considerations and that these over-ride the simple steric effect exerted by the neighbouring axial methyl group. Treatment of (**1**) with concentrated hydrochloric acid[3,8] afforded (+)-

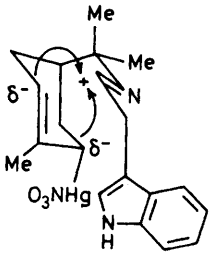




† (+)-Makomakine (**1**): m.p. 106—106.5 °C (lit.,[3] m.p. 99—100 °C); $[\alpha]_D^{25}$ + 142.5 ° (*c* 2.69, $CHCl_3$) {lit.,[3] $[\alpha]_D^{25}$ +131.2 °}; the i.r. and ^1H n.m.r. spectra are in agreement with those reported; ^{13}C n.m.r. spectrum (23 MHz, $CDCl_3$) δ 150.5, 136.4, 127.9, 122.3, 121.8, 119.2, 119.0, 113.7, 111.0, 108.7, 54.1, 43.3, 36.7, 33.2, 32.0, 31.4, 29.7, 29.3, and 27.1 p.p.m.

aristoteline (**2**).‡ Similarly racemic hobartine (**3**)§ was prepared from (+)-α-pinene in 11% yield.

The enantiospecificity observed in the cyclisation of (−)-β-pinene to (+)-makomakine is not observed in the (+)-α-pinene case which gives racemic hobartine. In the former case, the intermediate allylic mercurial [(**8**), or its equivalent] can only cyclise in the fashion shown, thus retaining the chirality of its precursor. By contrast, the equivalent intermediate (**9**)



(**9**)

derived from α-pinene can cyclize at either of the two enantiomeric sites shown leading to a racemic product.

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‡ (+)-Aristoteline (**2**): m.p. 158—159 °C (lit.,[5] 160—162.5 °C); the ^{1}H n.m.r., i.r., rotation, and mass spectral data are in agreement with the literature data.

§ (±)-Hobartine (**3**): m.p. 165—166 °C (lit.,[8] m.p. 166—167 °C); the i.r., ^{1}H and ^{13}C n.m.r., and mass spectral data are in agreement with the literature data.