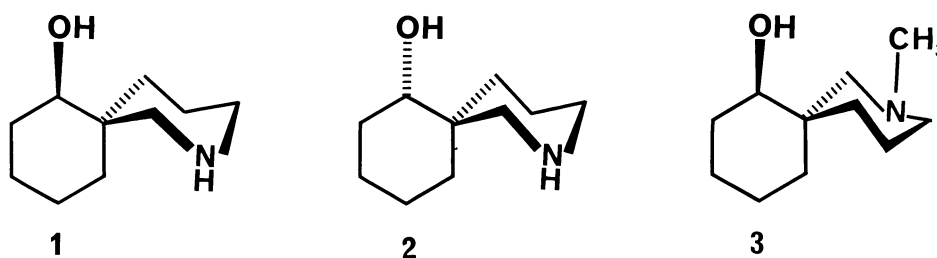


Stereoselective Synthesis of (±)-Isonitramine and (±)-Sibirine

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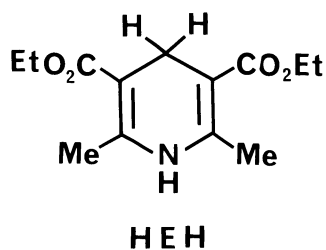
Spirocyclic alkaloids, (±)-isonitramine and (±)-sibirine were synthesized in high overall yields *via* a chemoselective reduction by Hantzsch ester (HEH), a coenzyme NADH model compound.

Nitramine (1), isonitramine (2) and sibirine (3) are the piperidine alkaloids isolated from plants of the genus *Nitraria*.¹⁾ Because the *Nitraria* alkaloids possess an unusual 2-azaspiro-[5,5]-undecane skeleton which resembles that of the neurotoxic alkaloid histrionicotoxin,²⁾ they have attracted widespread pharmacological and synthetic interest.³⁾ Naturally occurring isonitramine (2) has been shown to be the diastereomer of nitramine (1) and sibirine (3) to be the enantiomer of N-methylisonitramine.⁴⁾

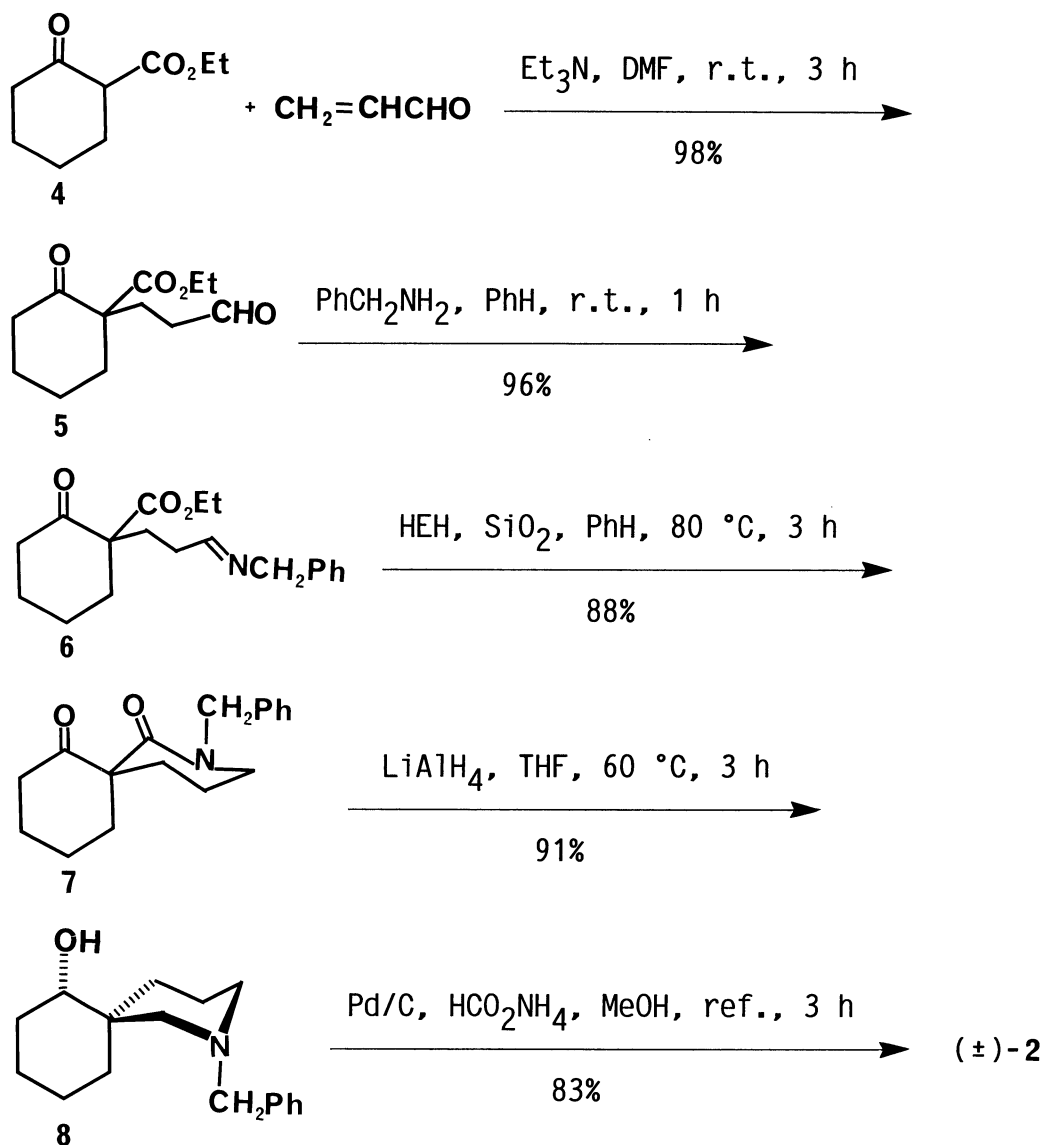


Recently, the authors have reported that Diethyl 2,6-dimethyl-1,4-dihydro-3,5-pyridinedicarboxylate (Hantzsch ester, HEH), a coenzyme NAD(P)H model, is a mild and selective reagent for reductions of activated olefins and imines by the aid of silica gel catalyst.⁵⁾

We now describe a convenient route to the stereocontrolled synthesis of (±)-isonitramine (2) and (±)-sibirine (3) *via* the chemoselective reduction by HEH-SiO₂ system.



Isonitramine (2) was synthesized as shown in Scheme 1.

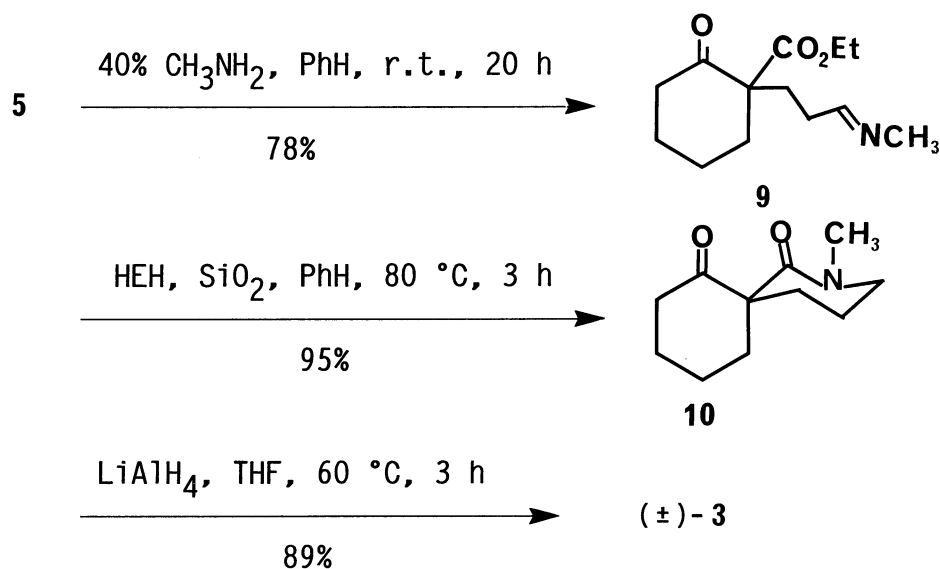


Scheme 1.

The reaction of commercially available ethyl 2-cyclohexanonecarboxylate (4) with acrolein was carried out in the presence of 10 %mol of

triethylamine in DMF at room temperature to give keto aldehyde 5 in 98% yield. The keto imine 6 was obtained in 96% yield only by stirring 5 and benzylamine in benzene at room temperature. Reduction of imine 6 by HEH in the presence of SiO_2 in benzene at 80°C gave spirocyclic keto amide 7 in 88% yield which could be formed by cyclization of reduction product from 6 under acid catalysis of silica gel.⁶⁾ Reduction of 7 with LiAlH_4 (4 equiv.) in THF at $0-60^\circ\text{C}$ gave N-benzylisonitramine (8) as a sole product in 91% yield. Treatment of 8 and ammonium formate with palladium-charcoal in refluxing methanol under a nitrogen atmosphere for 3 hours yielded the target molecule 2 in 83%. All the products obtained above were fully characterized by IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, and GC-mass. The assignment of stereochemistry of 8 and 2 was performed by comparison of the $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra with those reported in the literatures.³⁾

Sibirine (3) was synthesized along a similar pathway to that for isonitramine as shown in Scheme 2.



Scheme 2.

Imine derivative 9 obtained by the condensation of keto aldehyde 5 with methylamine was reduced by HEH- SiO_2 ⁶⁾ to give spirocyclic keto lactam 10 in 95% yield. Reduction of 10 with LiAlH_4 in THF gave (±)-3 in 65% overall yield based on 4. The spectra of 3 showed good agreement with published data.³⁾

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- 6) Experimental procedure is as follows; a solution of **6** (10 mmol), HEH (11 mmol) and 10 g of silica gel (NAKARAI Silica Gel 60, 35-70 mesh) in benzene 30 ml was stirred under a nitrogen atmosphere at 80 °C for 3 h. Silica gel was filtered off and the filtrate was subjected to a column chromatography on silica gel using CH₂Cl₂/CH₃CO₂Et (90/10) as an eluent to give **7** in 88% yield as a colorless oil. 90 MHz ¹H NMR (CDCl₃) δ = 1.3-2.4 (m, 12H), 3.1-3.4 (m, 2H), 3.6 (s, 2H), and 7.1-7.5 (m, 5H). IR (neat) 1730 (s), and 1640 cm⁻¹ (s). GC-mass m/z 271 (M⁺).

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