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REINVESTIGATION OF THE CLASSICAL TOTAL SYNTHESIS OF MAKOMAKINE

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#Dedicated to Professor Albert Padwa on the occasion of his 75th birthday

Abstract – Reinvestigation of the original Stevens synthesis of makomakine showed that the yield of the Ritter reaction of 3-indoylacetonitrile with (–)-β-pinene could be increased by employing Hg(OTf)₂.

Makomakine (**1**)¹ was isolated from *Aristotelia serrata* in 1981, and it was found that **1** is a biogenetic precursor of aristoteline (**2**), isolated from *A. serrata* in 1975 (Figure 1).²

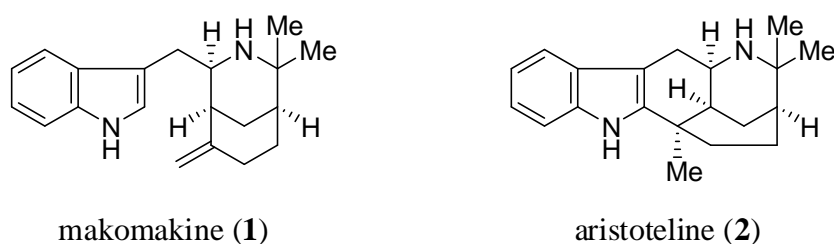
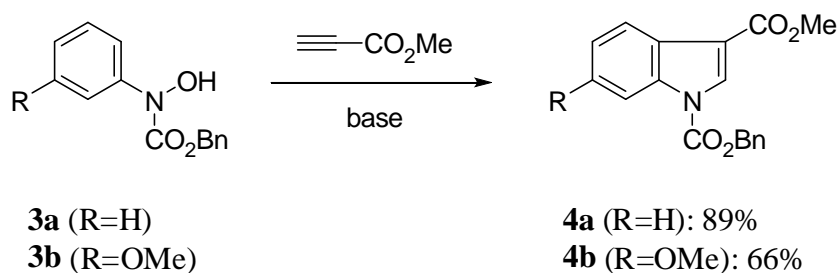


Figure 1. Structures of makomakine (**1**) and aristoteline (**2**)

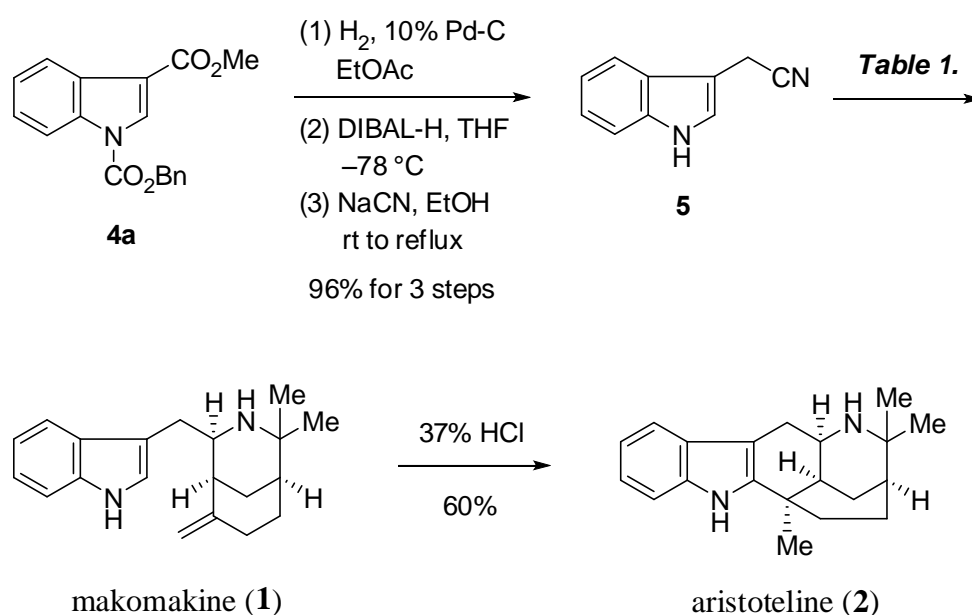
In 1983, Stevens demonstrated an elegant total synthesis of makomakine (**1**) and aristoteline (**2**) using the Ritter reaction as a key step of the synthesis.³ The yield of the Ritter reaction in this synthesis was improved from 17% to 39% by Heathcock,⁴ however, there is room for further yield improvement. Because we had developed a novel methodology for constructing 3-carbomethoxyindole derivatives (Scheme 1),⁵ we became interested in the syntheses of makomakine (**1**) and aristoteline (**2**) and in improving their yields. Herein, we present experimental results related to the Ritter reaction.

Although 3-indoylacetonitrile (**5**) is commercially available, **4a** was converted to **5** in a 96% overall yield⁵ to enable the analogue syntheses of makomakine (**1**) and aristoteline (**2**) using **4b**.



Scheme 1. Tandem Michael addition–[3,3]sigmatropic rearrangement

We initially examined the Ritter reaction of **5** with (–)- β -pinene using 1.1 equivalents of anhydrous mercuric nitrate according to the literature.⁴ After the reaction had gone to completion, the resulting crude product was subjected to NaBH_4 reduction to provide makomakine (**1**) in a 41% yield (entry 1). Performance of the Ritter reaction and the subsequent hydride reduction in the presence of catalytic amounts of anhydrous mercuric nitrate provided a trace amount of **1**, as detected by ^1H NMR spectroscopy (entry 2). To improve the environmental impact of the synthesis, the Ritter reaction was performed in the presence of a variety of harmless metals. Disappointingly, CuOTf , AuCl , $\text{Pd}(\text{OAc})_2$, PdCl_2 , and $\text{Pd}(\text{OCOCF}_3)_2$ did not yield the desired products (entries 3–7). Fortunately, the yield of the Ritter reaction was increased by employing $\text{Hg}(\text{OTf})_2$, and makomakine (**1**) was obtained in a 72% overall yield in two steps (entry 8).⁶ It should be noted that the Ritter reaction using catalytic amounts of $\text{Hg}(\text{OTf})_2$ met with failure. Finally, makomakine (**1**) was transformed into aristoteline (**2**) in 60% yield by applying Stevens' protocol.³



Scheme 2. Total syntheses of makomakine (**1**) and aristoteline (**2**)

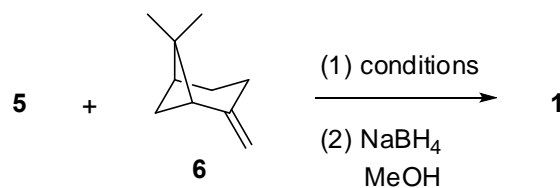


Table 1. The Ritter reaction of 3-indoylacetonitrile (**5**) with (–)-β-pinene (**6**)

entry	reagent ^a	solvent	yield (%) ^b
1	Hg(NO ₃) ₂	CH ₂ Cl ₂	41
2	Hg(NO ₃) ₂ (10 mol %)	CH ₂ Cl ₂	trace
3	CuOTf	CH ₂ Cl ₂	0
4	AuCl (20 mol %)	CH ₂ Cl ₂	0
5	Pd(OAc) ₂	CH ₂ Cl ₂	0
6	PdCl ₂	CH ₂ Cl ₂	0
7	Pd(OCOCF ₃) ₂	CH ₂ Cl ₂	0
8	Hg(OTf) ₂	CH ₂ Cl ₂	72
9	Hg(OTf) ₂ (10 mol %)	CH ₂ Cl ₂	0

a) All reactions were run in the presence of 1.1 eq. (based on **6**) of reagent.

b) Yields refer to the overall conversion of (–)-β-pinene (**6**) to makomakine (**1**)

In conclusion, Hg(OTf)₂ proved to be an efficient reagent for the Ritter reaction of 3-indoylacetonitrile with (–)-β-pinene in the makomakine synthesis. The methodology developed here should also provide access to synthetic analogues of makomakine (**1**) and aristoteline (**2**).

EXPERIMENTAL

IR spectra were measured on a SHIMADZU FT-IR 8300 spectrophotometer. ¹H NMR spectra were recorded on Varian 400 MR (400 MHz) spectrometers with CHCl₃ (δ 7.26) as an internal standard. ¹³C NMR spectra were recorded on JEOL JX-500 (125 MHz) spectrometer with CHCl₃ (δ 77.16) as an internal standard. All compounds purified by chromatography were sufficiently pure (> 95% by ¹H NMR analysis) for use in subsequent reactions.

(+)-Makomakine (1). To a stirred solution of 3-indoylacetonitrile (**5**) (1.87 g, 12.0 mmol) and Hg(OTf)₂ (997.46 mg, 2.0 mmol) in dry CH₂Cl₂ (10 mL) was added dropwise (–)-β-pinene (0.28 mL, 1.8 mmol) at –40 °C, and then the resulting mixture was allowed to warm to room temperature over 3 h. After cooling

to 0 °C, 3 M NaOH in MeOH (7.2 mL) was added. Slow addition of an excess amount of NaBH₄ and stirring at 0 °C gave the mixture which was filtered through Celite. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried, and evaporated to afford the crude product which was purified by flash column chromatography. Elution with hexane-acetone (12:1) and 3% triethylamine afforded makomakine (**1**) (380.8 mg, 72% for 2 steps) as a solid. $[\alpha]_{\text{D}}^{25} +112.2$ (c 0.80, CHCl₃) (lit.¹ $[\alpha]_{\text{D}}^{19} +131.2$ (c 0.5, CHCl₃), Mp 95-97 °C (lit.¹ 99-100 °C). ¹H NMR (CDCl₃, 400 MHz): δ 1.10 (s, 3H), 1.14 (s, 3H), 1.38-1.42 (m, 1H), 1.49 (dddd, 1H, $J = 4.0, 6.0, 13.6$ and 13.6 Hz), 1.58 (ddd, 1H, $J = 3.6, 3.6$ and 12.8 Hz), 2.04-2.11 (m, 1H), 2.12-2.15 (m, 1H), 2.14-2.22 (m, 1H), 2.25-2.29 (m, 1H), 2.62 (dd, 1H, $J = 8.0$ and 14.4 Hz), 2.76 (dd, 1H, $J = 6.0$ and 14.4 Hz), 3.02-3.12 (m, 1H), 3.49 (ddd, 1H, $J = 2.8, 6.0$ and 8.0 Hz), 4.58 (dd, 1H, $J = 2.4$ and 2.4 Hz), 4.77 (dd, 1H, $J = 2.4$ and 2.4 Hz), 7.02 (d, 1H, $J = 2.0$ Hz), 7.10 (ddd, 1H, $J = 0.8, 7.2$ and 7.2 Hz), 7.10 (ddd, 1H, $J = 0.8, 7.2$ and 7.2 Hz), 7.19 (ddd, 1H, $J = 0.8, 7.2$ and 7.2 Hz), 7.36 (ddd, 1H, $J = 0.8, 0.8$ and 8.4 Hz), 7.64 (dd, 1H, $J = 0.8$ and 8.4 Hz), and 7.95 (br s, 1H). ¹³C NMR (CDCl₃, 125 MHz): δ 150.6, 136.5, 128.0, 122.5, 121.9, 119.3, 119.1, 113.8, 111.1, 108.9, 54.2, 53.2, 43.4, 36.8, 33.3, 32.1, 31.5, 29.9, 29.4, and 27.2. IR (CHCl₃, cm⁻¹) 3416, 3061, 2923, 1637, 1455, 886, and 740. LRMS m/z 294 (M⁺). HRMS calcd for C₂₀H₂₆N₂ 294.2096, found: 294.2099.

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