

33. Synthesis of *Aristotelia*-Type Alkaloids

Part V¹⁾

Biomimetic Synthesis of (±)-Aristomakine and (±)-Aristomakinine

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Biomimetic syntheses of racemic aristomakinine ((±)-**3**) and aristomakine ((±)-**4**), an unusual indole alkaloid bearing an *N*-isopropyl group, are described. The key step is a *Grob*-type fragmentation of *anti*-15-aristotelinyl methanesulfonate ((±)-**2**) to the intermediate iminium ion **1** which, upon subsequent hydrolysis, furnished aristomakinine ((±)-**3**). On the other hand, the same intermediate could be reduced *in situ* to aristomakine ((±)-**4**). The controversial relative configurations of the two alkaloids have been firmly established by means of NOE difference experiments.

1. Introduction. – (–)-Aristomakine ((–)-**4**; *Scheme 1*) has been isolated in small amounts from the New Zealand species *Aristotelia serrata* W. R. B. OLIVER by Bick and Hai [2]. They elucidated the unique structure of this plant metabolite by spectroscopic studies and by assuming a close biogenetic relationship between **4** and the other members of the *Aristotelia* alkaloid family [3]. Conceivably, *anti*-aristotelin-15-ol (**1**) undergoes a *Grob*-type fragmentation [4] after *O*-protonation or -phosphorylation to yield the iminium ion **1**. This intermediate is either reduced enzymatically to aristomakine (**4**) or is hydrolyzed to aristomakinine (**3**), another minor alkaloid found in *A. serrata* [3] [5].

A comparison of the CD spectra of (–)-aristomakine ((–)-**4**) with those of various yohimbane derivatives led Snatzke *et al.* [6] to revise the originally proposed structures **3** and **4** to **3A** and **4A**, respectively (*Scheme 2*). Surprisingly, these authors did not comment upon the fact that the configuration at C(17) of structures **3A** and **4A** is opposite to that of those *Aristotelia* alkaloids whose absolute configuration has been unambiguously established, such as (+)-makomakine [7], (–)-hobartine [8], (+)-aristotelin [9], (–)-tasmanine [10], (+)-aristoserratenine [10], (+)-aristotelinone [11], (–)-serrato-line [11], and (+)-makonine [12]²⁾.

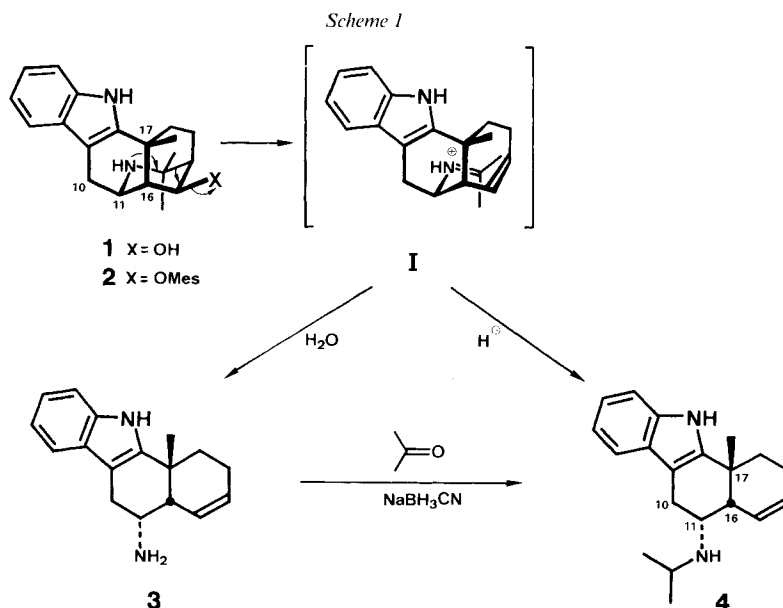
2. Results and Discussion. – Recently, we reported a synthesis of *anti*-aristotelin-15-ol ((±)-**1**) [1], the putative biological precursor of **3** and **4**. With the aim of demonstrating the feasibility of the biogenetic proposal shown in *Scheme 1*, we prepared the corresponding mesylate (±)-**2**. Solvolysis under mild conditions (THF/H₂O/Et₃N, 4 h, 0°) furnished the

¹⁾ Part IV: [1].

²⁾ Provided that the revised structure proposals **3A** and **4A** are indeed correct, biological pathways leading from **3** to **3A**, and from **4** to **4A**, must exist. A merely hypothetical isomerization route *via* the cyclodecadienes **5** and **6** is given in *Scheme 2*.

anticipated fragmentation product ($\pm$)-**3** as the only isolable material³). Since natural aristomakine ((-)-**3**) has not been sufficiently well characterized to permit a satisfactory comparison with our synthetic sample, ($\pm$)-**3** was transformed into racemic aristomakine (($\pm$)-**4**) by reductive amination⁴). The spectroscopic properties (IR, ¹H-NMR (see Fig. 1), ¹³C-NMR, MS) of ($\pm$)-**4** agreed well with the reported data⁵) of natural (-)-aristomakine ((-)-**4**) [2] [5]. Therefore, the two samples must have the same relative configuration⁶).

In a separate experiment, the intermediate obtained by mesylation of ($\pm$)-**1** was treated with an excess of NaBH₃CN [13] with the intention to mimic the corresponding biological reduction step **I** $\rightarrow$ **4** (Scheme 1). The only product which could be isolated³) proved to be indistinguishable from the sample of ($\pm$)-**4** obtained by reductive amination of ($\pm$)-**3**.



Concerning the controversy about the relative configuration of alkaloids **3** and **4**, the following arguments can be considered to favor the originally proposed *cis*-hexalin structures **3** and **4** [2] over their *trans*-counterparts **3A** and **4A** [6]: the rigid bridged skeleton of precursor **1** guarantees for the stereochemical integrity of the critical centres

³) Although all reactions described in this communication looked quite clean as judged by TLC and ¹H-NMR spectroscopy of the crude reaction mixtures, the yields of purified products were rather low (see *Exper. Part*). This is probably due to losses in the purification steps and to the instability of **3** and **4**.

⁴) Bick and Hai reported that natural (-)-**3** can be transformed into (-)-aristomakine ((-)-**4**) upon treatment with acetone/NaBH₄ (50% yield) [2] [5]. In our hands, ($\pm$)-**3** did not react under these conditions. However, clean reduction took place when NaBH₃CN [13] was employed as reagent.

⁵) We thank Prof. I. R. C. Bick, University of Tasmania, for providing us with copies of the IR- and ¹H-NMR spectra of natural (-)-**4**.

⁶) It can be safely predicted that diastereoisomers of **3** and **4**, such as **3A** and **4A**, should show significantly different ¹H- and ¹³C-NMR spectra (for a recent example in the *Aristolelia* alkaloid field, see [14]).

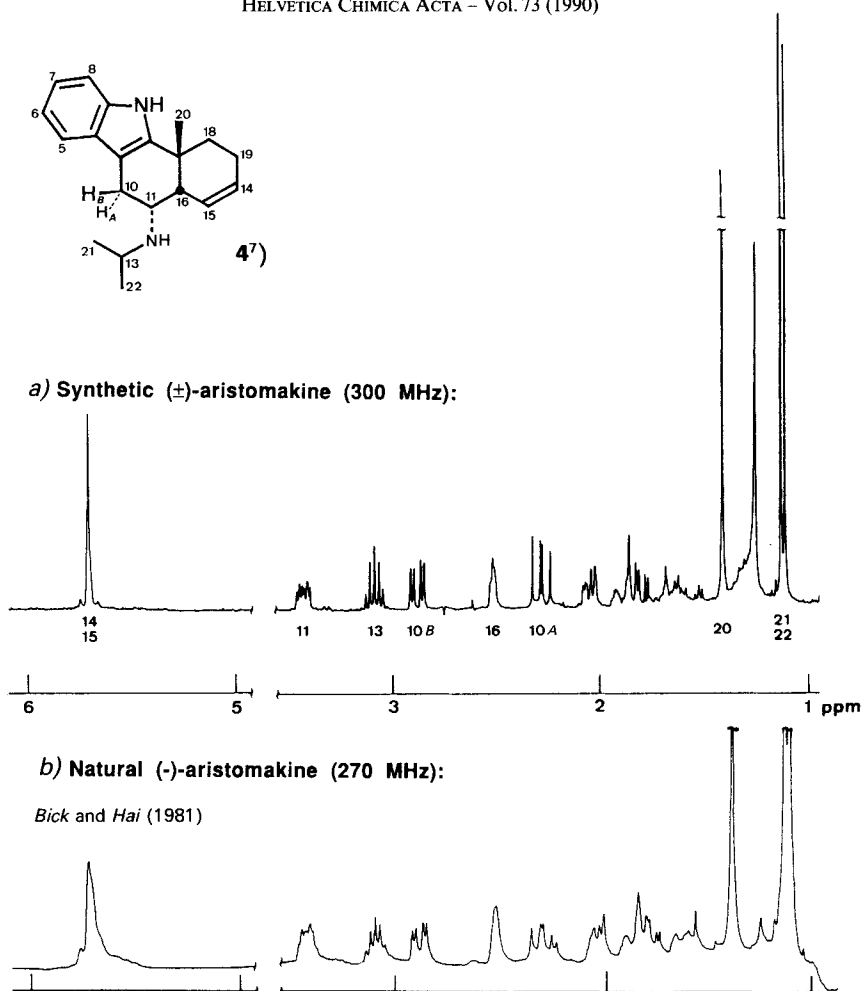


Fig. 1. High-field sections of the ¹H-NMR spectra (CDCl₃) of a) synthetic and b) natural aristomakine⁵⁾ (4)

C(11), C(16), and C(17)⁷⁾ during the fragmentation **2** → **1**. The hydrolysis or reduction that follows takes place under such mild conditions that a subsequent isomerization, *e.g.* of the type shown in Scheme 2, seems very unlikely. In addition, the unfavorable syn-periplanar 1,3-diaxial interaction between the quaternary Me group and *N*-C(11) present in the *trans*-isomers **3A** and **4A** probably render them thermodynamically less stable than the corresponding *cis*-derivatives **3** and **4**.

To obtain independent, spectroscopic evidence, recourse to NOE difference experiments was taken (for reviews see [16]). Irradiation at 1.42 ppm (CH₃-C(17)) led to significant NOE enhancements for the readily identified methine protons H-C(11) and H-C(16). This result and the fact that tickling of the olefinic protons (5.72 ppm) led to an NOE of H_A-C(10) can only be accounted for by assuming a *cis*-hexalin structure **4** for

⁷⁾ Biogenetic numbering [15].

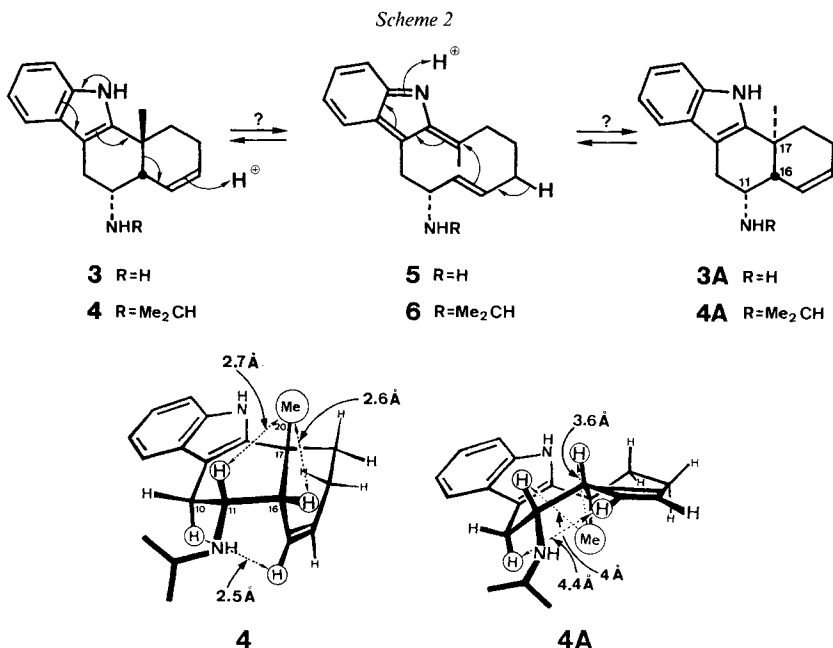


Fig. 2. Internuclear distances in **4** and **4A**, as measured from Dreiding models according to Bell and Saunders [19]

aristomakine since, in the case of the *trans*-arrangement **4A**, the internuclear distances in question are considerably longer than the critical value of *ca.* 3 Å [17] (see Fig. 2; for related cases, see [18]).

3. Conclusion. – The successful *in vitro* realisation of the fragmentation scheme presented in *Chapt. I* has led to the first syntheses of the rare alkaloids aristomakinine ((±)-**3**) and aristomakine ((±)-**4**) and lends experimental support to the biogenetic proposal made by Bick and Hai [3].

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Experimental Part

General. See [20].

(±)-Aristomakinine (= (4aRS,5SR,11bSR)-1,4a,5,6,11,11b-Hexahydro-11b-methyl-2H-benzof[a]carbazol-5-amine; (±)-**3**). To a soln. of 16 mg (0.052 mmol) of (±)-*anti*-aristolinel-15-ol [1] ((±)-**1**) in 2.5 ml of CH₂Cl₂ (Fluka, puriss.; dist. from P₂O₅) were added 0.2 ml of Et₃N (Fluka, puriss.; dist. from CaH₂) and 0.07 ml of methanesulfonyl chloride (MsCl; Fluka, puriss.) at 0°. After stirring for 150 min at 0°, 1.5 ml of THF/H₂O 4:1 were added. The mixture was stirred at 0° under Ar for 4 h and then for 1 h at r.t. Subsequent workup with 12% aq. NH₃ soln./CHCl₃ followed by drying (K₂CO₃) and evaporation led to 19 mg of a brown resin which was purified by chromatography (CHCl₃/MeOH/conc. aq. NH₃ soln. 150:2:5): 5 mg (38%) of (±)-**3** as a yellow unstable resin³. ¹H-NMR: 7.72 (br. s, 1 H); 7.44 (*dm*, *J* = 7.8, 1 H); 7.30 (*dm*, *J* = 7.4, 1 H); 7.12 (*ddd*, *J* = 7.8, 7, 1.3, 1 H); 7.06 (*ddd*, *J* = 7.4, 7, 1.2, 1 H); 5.78 (br. s, 2 H); 3.60 (*ddd*, *J* = 10.2, 5, 3.5, 1 H); 2.86 (*ddd*, *J* = 14.8, 5, 0.7, 1 H); 2.41 (*dd*, *J* = 14.8, 10.2, 1 H); 2.36 (*m*, 1 H); 2.03 (*m*, 1 H); 1.94 (*m*, 1 H); 1.82 (*m*, 1 H); 1.72 (*m*, 2 H); 1.68 (br. s, 2 H); 1.40 (s, 3 H). NOE difference experiment: irradiation at 1.40 → only 3 signals, at 7.72 (br. s, indole NH), 3.60 (H–C(11)), and 2.36 (H–C(16)).

($\pm$)-Aristomakine (= (4aRS,5SR,11bSR)-1,4a,5,6,11,11b-Hexahydro-N-isopropyl-11b-methyl-2H-benzo[*a*]carbazol-5-amine; ($\pm$)-4). *Method A*: To a soln. of 2 mg of ($\pm$)-3 (see above) and 5 mg of NaOAc in 0.4 ml of acetone (*Fluka, puriss.*), 0.4 ml of AcOH (*Fluka, puriss.*), and 0.6 ml of H₂O were added 80 mg of NaBH₃CN (*Fluka, prakt.*) in 8 equal portions at intervals of 10 min. After 2 h at 0°, the mixture was worked up with 12% aq. NH₃ soln. and CHCl₃. The combined org. extracts were dried and evaporated. The crude product was purified by prep. TLC (CHCl₃/MeOH/conc. aq. NH₃ soln. 98:2:3): 1.2 mg (ca. 50%) of ($\pm$)-4. ¹H-NMR: 7.61 (s, 1 H); 7.43 (dm, *J* = 7.8, 1 H); 7.28 (dm, *J* = 7.4, 1 H); 7.12 (ddd, *J* = 7.8, 7, 1.5, 1 H); 7.06 (ddd, *J* = 7.4, 7, 1.2, 1 H); 5.72 (br. s, 2 H); 3.43 (ddd, *J* = 10.8, 5, 3.2, 1 H); 3.09 (sept., *J* = 6.2, 1 H); 2.88 (ddd, *J* = 14.8, 5, 1.1, 1 H); 2.52 (m, 1 H); 2.29 (dd, *J* = 14.8, 10.8, 1 H); 2.06 (m, 1 H); 1.90 (m, 1 H); 1.80 (m, 1 H); 1.62 (m, 1 H); 1.42 (s, 3 H); 1.26 (br. s, 1 H); 1.13 (d, *J* = 6.2, 6 H). NOE difference experiments: irradiation at 1.42 → strong signals at 3.43 (H-C(11)) and 2.52 (H-C(16)) and weaker signal at 2.06 (H_{eq}-C(18)); irradiation at 5.72 → significant signals at 2.52 (H-C(16)) and 2.29 (H_{ax}-C(10)). ¹³C-NMR: 138.1 (s); 136.2 (s); 129.0 (d); 127.4 (s); 124.0 (d); 121.1 (d); 119.1 (d); 118.0 (d); 110.5 (d); 109.1 (s); 50.7 (d); 45.5 (d); 45.3 (d); 35.3 (s); 34.9 (t); 29.9 (q); 25.9 (t); 23.8 (q); 23.2 (q); 22.7 (t). MS: 279 (8, [*M* - 15]⁺), 251 (7), 236 (7), 184 (16), 183 (15), 180 (31), 170 (6), 130 (13), 124 (40), 98 (25), 85 (100).

Method B: To a soln. of 8 mg of ($\pm$)-1 in 1 ml of CH₂Cl₂ (*Fluka, puriss.*; dist. from P₂O₅) were added 0.075 ml of Et₃N (*Fluka, puriss.*) and 0.03 ml of MsCl (*Fluka, puriss.*). The mixture was allowed to stand at r.t. for 2 h and was then added to a soln. of 50 mg of NaBH₃CN (*Fluka, prakt.*) in 2 ml of THF/10% aq. NH₄Cl soln. 1:1 at r.t. At intervals of 15 min, 3 more portions of NaBH₃CN (20 mg) were added. The mixture was worked up with 12% aq. NH₃ soln./CHCl₃, dried (K₂CO₃), and evaporated: 7.8 mg of crude material which was purified by prep. TLC (*Empore*TM 3M silica sheets No. 412001, CHCl₃/MeOH/conc. aq. NH₃ soln. 98:2:5): 0.7 mg (ca. 10%) of ($\pm$)-4 which was identified by TLC and ¹H-NMR.

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