33. Synthesis of *Aristotelia*-Type Alkaloids

Part V[1])

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

by **Stefan Burkard** and **Hans-Jürg Borschberg***

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH–8092 Zürich

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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 **I** 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 **I**. 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], (+)-aristoteline [9], (–)-tasmanine [10], (+)-aristoserratenine [10], (+)-aristotelinone [11], (–)-serratoline [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 ($THF/H_2O/Et_3N$, 4 h, 0°) furnished the

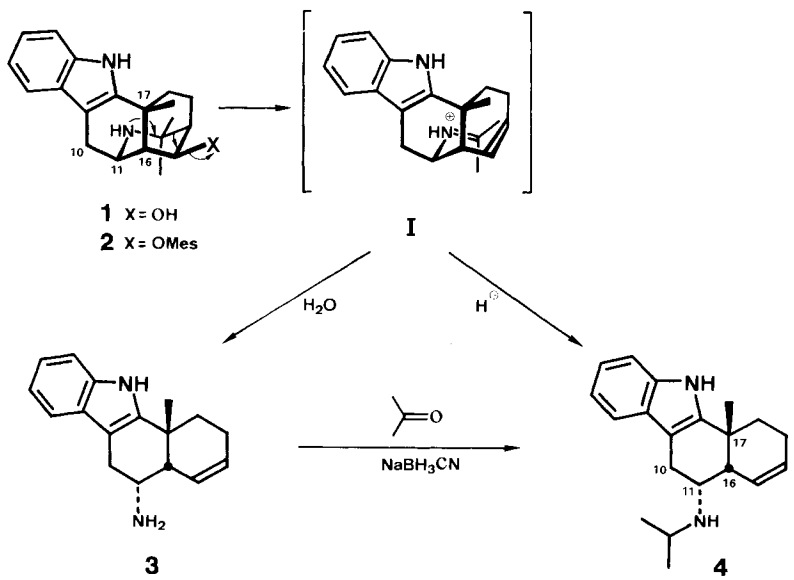
[1]) Part IV: [1].

[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 (±)-**3** as the only isolable material[3]). Since natural aristomakinine ((−)-**3**) has not been sufficiently well characterized to permit a satisfactory comparison with our synthetic sample, (±)-**3** was transformed into racemic aristomakine ((±)-**4**) by reductive amination[4]). The spectroscopic properties (IR, ^{1}H-NMR (see *Fig. 1*), ^{13}C-NMR, MS) of (±)-**4** agreed well with the reported data[5]) of natural (−)-aristomakine ((−)-**4**) [2] [5]. Therefore, the two samples must have the same relative configuration[6]).

In a separate experiment, the intermediate obtained by mesylation of (±)-**1** was treated with an excess of $NaBH_3CN$ [13] with the intention to mimic the corresponding biological reduction step **I** → **4** *(Scheme 1)*. The only product which could be isolated[3]) proved to be indistinguishable from the sample of (±)-**4** obtained by reductive amination of (±)-**3**.

Scheme 1



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

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[3]) Although all reactions described in this communication looked quite clean as judged by TLC and ^{1}H-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/$NaBH_4$ (50% yield) [2] [5]. In our hands, (±)-**3** did not react under these conditions. However, clean reduction took place when $NaBH_3CN$ [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 ^{1}H-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 ^{1}H- and ^{13}C-NMR spectra (for a recent example in the *Aristotelia* alkaloid field, see [14]).

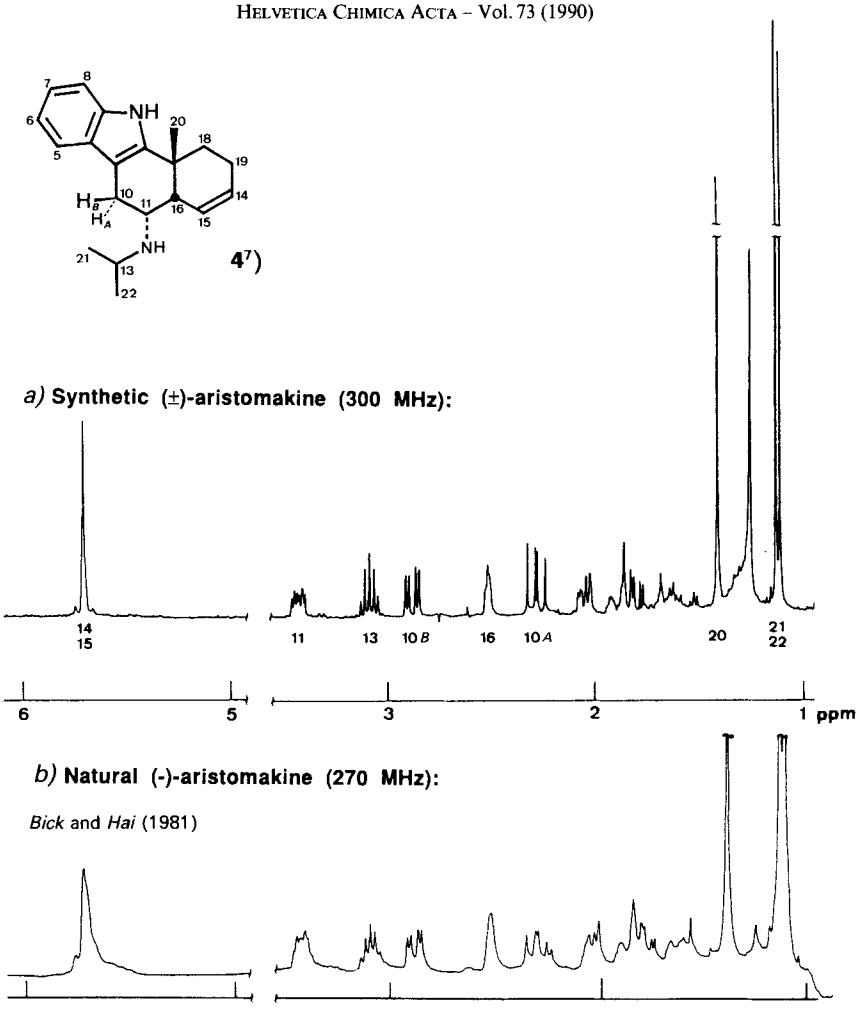


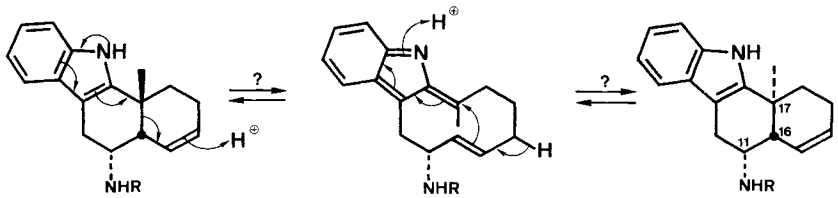
Fig. 1. *High-field sections of the* ^{1}*H-NMR spectra* ($CDCl_3$) *of* a) *synthetic and* b) *natural aristomakine*[5]) (**4**)

C(11), C(16), and C(17)[7]) during the fragmentation **2** → **I**. 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 (CH_3–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

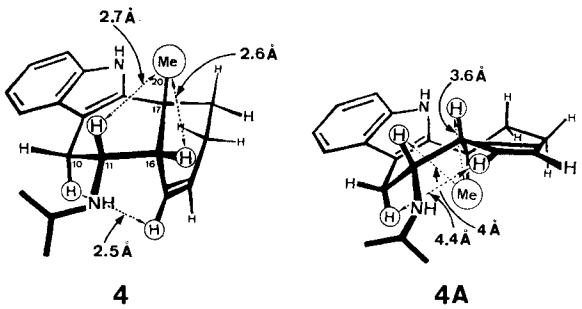
[7]) Biogenetic numbering [15].

Scheme 2



3 R=H **5** R=H **3A** R=H

4 R=Me_2CH **6** R=Me_2CH **4A** R=Me_2CH



4 **4A**

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. 1* 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-benzo[a]carbazol-5-amine; (±)-**3**). To a soln. of 16 mg (0.052 mmol) of (±)-*anti*-aristotelin-15-ol [1] ((±)-**1**) in 2.5 ml of CH_2Cl_2 (*Fluka, puriss.*; dist. from P_2O_5) were added 0.2 ml of Et_3N (*Fluka, puriss.*; dist. from CaH_2) and 0.07 ml of methanesulfonyl chloride (MsCl; *Fluka, puriss.*) at 0°. After stirring for 150 min at 0°, 1.5 ml of THF/H_2O 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. NH_3 soln./$CHCl_3$ followed by drying (K_2CO_3) and evaporation led to 19 mg of a brown resin which was purified by chromatography ($CHCl_3$/MeOH/conc. aq. NH_3 soln. 150:2:5): 5 mg (38%) of (±)-**3** as a yellow unstable resin[3]). ^{1}H-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)).

(±)-Aristomakine (= *(4aRS,5SR,11bSR)-1,4a,5,6,11,11b-Hexahydro-*N*-isopropyl-11b-methyl-2*H*-benzo-[a]carbazol-5-amine;* (±)-**4**). *Method A:* To a soln. of 2 mg of (±)-**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 H_2O were added 80 mg of $NaBH_3CN$ *(Fluka, prakt.)* in 8 equal portions at intervals of 10 min. After 2 h at 0°, the mixture was worked up with 12% aq. NH_3 soln. and $CHCl_3$. The combined org. extracts were dried and evaporated. The crude product was purified by prep. TLC ($CHCl_3$/MeOH/conc. aq. NH_3 soln. 98:2:3): 1.2 mg (*ca.* 50%) of (±)-**4**. ^{1}H-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)); irridation at 5.72 → significant signals at 2.52 (H–C(16)) and 2.29 (H_{ax}–C(10)). ^{13}C-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 (±)-**1** in 1 ml of CH_2Cl_2 *(Fluka, puriss.;* dist. from P_2O_5) were added 0.075 ml of Et_3N *(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 $NaBH_3CN$ *(Fluka, prakt.)* in 2 ml of THF/10% aq. NH_4Cl soln. 1:1 at r.t. At intervals of 15 min, 3 more portions of $NaBH_3CN$ (20 mg) were added. The mixture was worked up with 12% aq. NH_3 soln./$CHCl_3$, dried (K_2CO_3), and evaporated: 7.8 mg of crude material which was purified by prep. TLC (*Empore*^{TM} *3M* silica sheets No. 412001, $CHCl_3$/MeOH/conc. aq. NH_3 soln. 98:2:5): 0.7 mg (*ca.* 10%) of (±)-**4** which was identified by TLC and ^{1}H-NMR.

REFERENCES

[1] S. Burkard, H.-J. Borschberg, *Helv. Chim. Acta* **1989,** *72,* 254.

[2] I. R. C. Bick, M. A. Hai, *Tetrahedron Lett.* **1981,** 3275.

[3] I. R. C. Bick, M. A. Hai, in 'The Alkaloids', Ed. A. Brossi, Academic Press, New York, 1985, Vol. XXIV, Chapt. 3.

[4] a) C. A. Grob, *Angew. Chem.* **1969,** *81,* 543; b) T. Kiguchi, T. Naito, I. Ninomiya, *Heterocycles* **1987,** *26,* 1747.

[5] M. A. Hai, Ph. D. Thesis, University of Tasmania, Hobart, 1981.

[6] G. Snatzke, I. R. C. Bick, M. A. Hai, unpublished results, cited in [3], ref. 27.

[7] a) C. Mirand, G. Massiot, J. Lévy, *J. Org. Chem.* **1982,** *47,* 4169; b) R. V. Stevens, G. M. Kenney, *J. Chem. Soc., Chem. Commun.* **1983,** 384.

[8] a) T. Darbre, C. Nussbaumer, H.-J. Borschberg, *Helv. Chim. Acta* **1984,** *67,* 1040; b) G. W. Gribble, T. C. Barden, *J. Org. Chem.* **1985,** *50,* 5900.

[9] a) B. F. Anderson, G. B. Robertson, H. P. Avey, W. F. Donovan, I. R. C. Bick, J. B. Bremner, A. J. T. Finney, N. W. Preston, R. T. Gallagher, G. B. Russell, *J. Chem. Soc., Chem. Commun.* **1975,** 511; b) W. H. Watson, V. Zabel, M. Silva, M. Bittner, *Cryst. Struct. Commun.* **1982,** *11,* 141.

[10] M. A. Hai, N. W. Preston, H.-P. Husson, C. Kan-Fan, I. R. C. Bick, *Tetrahedron* **1984,** *40,* 4359.

[11] I. R. C. Bick, M. A. Hai, N. W. Preston, R. T. Gallagher, *Tetrahedron Lett.* **1980,** *545.*

[12] I. R. C. Bick, M. A. Hai, *Heterocycles* **1981,** *16,* 1301.

[13] C. F. Lane, *Synthesis* **1975,** 135.

[14] W. J. Klaver, H. Hiemstra, W. N. Speckamp, *J. Am. Chem. Soc.* **1989,** *111,* 2588.

[15] R. Kyburz, E. Schöpp, I. R. C. Bick, M. Hesse, *Helv. Chim. Acta* **1981,** *64,* 2555.

[16] a) G. E. Bachers, T. Schaefer, *Chem. Rev.* **1971,** 617; b) P. D. Kennewell, *J. Chem. Educ.* **1970,** 47, 278; c) J. K. M. Sanders, B. K. Hunter, 'Modern NMR Spectroscopy', Oxford University Press, Oxford, 1987, Chapt. 10.4; d) J. W. Emsley, J. Feeney, L. H. Sutcliffe, 'Progress in Nuclear Magnetic Resonance Spectroscopy', Pergamon Press, Oxford, 1983, Vol. 15, p. 353; e) S. A. Richards, 'Laboratory Guide to Proton NMR Spectroscopy', Blackwell Scientific Publications, Oxford, 1975, Chapt. 7.7.

[17] H. Friebolin, 'Ein- und zweidimensionale NMR-Spektroskopie', VCH, Weinheim, 1988, Chapt. 10.

[18] a) R. A. Bell, E. N. Osakwe, *J. Chem. Soc., Chem. Commun.* **1968,** 1093; b) N. Abe, R. Onoka, K. Ro, T. Kurihara, *Tetrahedron Lett.* **1968,** 1993; c) Y. Ishizaki, Y. Tanahashi, T. Takahashi, K. Tori, *J. Chem. Soc., Chem. Commun.* **1969,** 551; d) G. R. Newkome, N. S. Bhacca, *ibid.* **1969,** 385; e) L. D. Hall, J. K. M. Sanders, *J. Am. Chem. Soc.* **1980,** *102,* 5703.

[19] R. A. Bell, J. K. Saunders, *Can. J. Chem.* **1970,** *48,* 1114.

[20] R. K. Brunner, H.-J. Borschberg, *Helv. Chim. Acta* **1983,** *66,* 2608.