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Aristotelia Alkaloids: Synthetic and Biomimetic Studies

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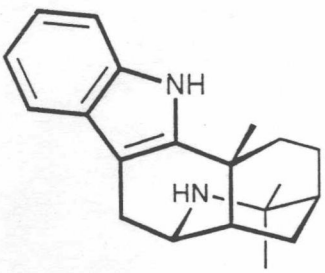
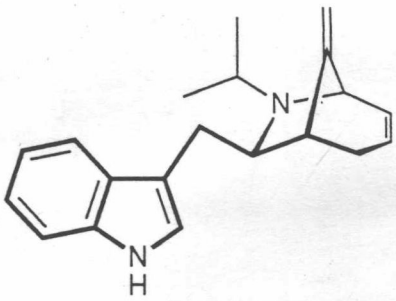
1.INTRODUCTION

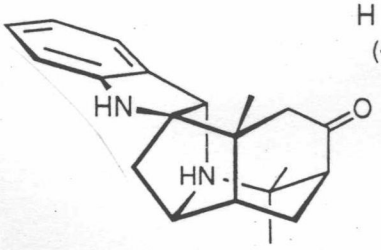
The *Aristotelia* alkaloid family comprises some forty representatives, all of which were isolated for the first time within the last 25 years from *Aristotelia* plants which abound in the southern hemisphere, especially in Australia and New Zealand. Despite the fact that extracts from these plants still find profitable use in folk medicine, very little is known about the pharmacology of these metabolites [1]. The main reason for this lies in their low concentration in natural sources: apart from aristoteline (**1**), peduncularine (**2**) and aristone (**3**), the remaining representatives occur in ppm-amounts only.



(+)-Aristoteline **1**



(-)-Peduncularine **2**



(-)-Aristone **3**

An excellent review article by *Bick* and *Hai* [1] covers all that was known about the *Aristotelia* alkaloids by 1985. However, as progress in this field has continued since that time, an update, mostly concerned with synthetic aspects, seemed warranted, especially because several alkaloid structures

had to be revised in the course of the investigations described in the present article.

From a structural point of view, the most conspicuous feature of almost all members of the *Aristotelia* alkaloid family consists in the presence of an intact, unrearranged monoterpene sub-unit, connected with tryptamine (**5**). Thus, unlike the vast majority of the more than 2000 known indole alkaloids [2], they are not derived from secologanin [1].

A hypothetical scheme for the biosynthesis of the *Aristotelia* alkaloids was put forward by *Bick* [7] and was later refined by *Hesse* [8]: it starts with a solvolysis of the leaving group of either linalyl- or neryl pyrophosphate (**4**), followed by a nucleophilic attack of the the ensueing allylic cation by the distal double bond. This ring closure produces the α-terpinyl carbenium ion which is intercepted by tryptamine (**5**) *(Scheme 1)* to yield *(S)*-α-terpinyl-tryptamine (**6**). While this first stable intermediate has not been isolated yet from natural sources[2], an oxidized version of this simple tricyclic skeleton is present in the metabolite (+)-fruticosonine (**7**), isolated from *A.fruticosa* by *Bick* and coworkers [9].

In order to undergo further ring closures, the secondary amine **6** has to be oxidized first to the corresponding *(E)*-aldimine **8.** The protonated form of this *Schiff* base adopts the chair-type conformation illustrated in *Scheme 1* and then undergoes an intramolecular iminium ion cyclization to give the pivotal carbenium ion **I.** This intermediate can be stabilized by simple proton elimination, a process that furnishes the tetracyclic alkaloid (+)-makomakine (**9**), isolated by *Bick* and *Hai* [12], as well as the corresponding regio isomer (-)-hobartine (**10**), a minor metabolite that was detected in *A.serrata* by *Bick* and *Hesse* and their coworkers [13].

Alternatively, the electron-deficient centre of **I** is attacked by the indole sub-unit. This process ultimately leads to (+)-aristoteline (**1**)[3], the key representative of the *Aristotelia* alkaloid family, whose structure was determined *via* two independent *X*-ray crystal analyses [14].

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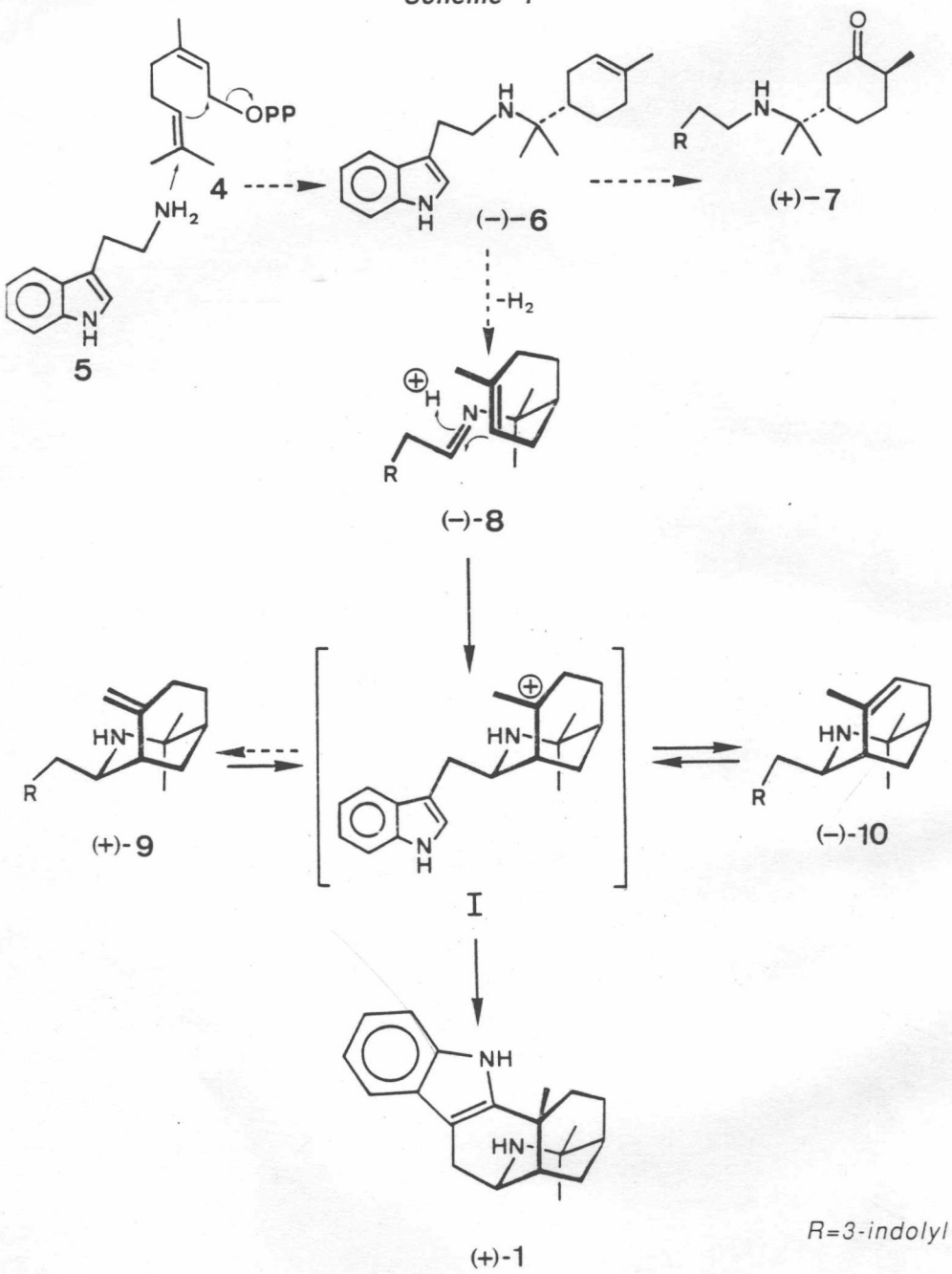
[1] Several other indole alkaloids containing an intact monoterpene unit have been isolated from different sources: borrecarpin from *Borreria capitata* [3], the hapalindoles from *Hapalosiphon fontinalis* [4], lyngbyatoxin from *Lyngbya majuscula* [5], and the telocidines from *Streptomyces mediocidicum* [6].

[2] This compound has been synthesized by us [10] and by *Gribble* and *Barden* [11] in optically pure form (see chapters 2 and 3).

[3] For a more detailed discussion concerning this transformation see chapter 4.

Scheme 1



Solid arrows: transformations mimicked in vitro (see Table 1).

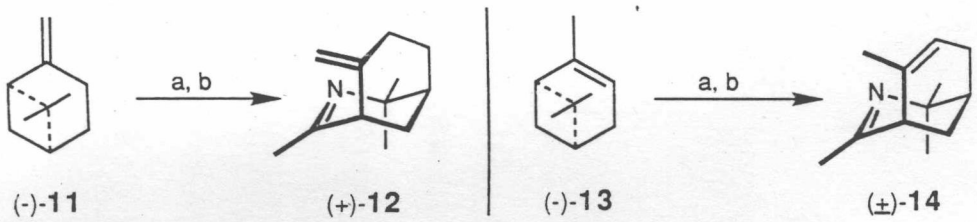
Dashed arrows: postulated biogenetic transformations.

2. SYNTHETIC WORK REPORTED BY OTHER GROUPS

The novel structures of the alkaloids mentioned in the previous section, such as makomakine (**9**), hobartine (**10**) and aristoteline (**1**), motivated several research groups to develop synthetic routes towards these metabolites.

The starting point for two approaches was the discovery of *Delpech* and *Khuong-Huu* [16] that (-)-β-pinene (**11**) *(Scheme 2)* is transformed into the bicyclic imine (+)-**12** upon exposure to mercuric nitrate in acetonitrile, and that an analogous treatment of (-)-α-pinene (**13**) furnishes the racemic isomer (±)-**14** [4]. Since these two 2-azabicyclo[3.3.1]nonane systems bear an obvious structural relation to makomakine and hobartine, respectively, they were taken advantage of in a straightforward manner by a French and an American team.

Scheme 2



(-)-**11** (+)-**12** (-)-**13** (±)-**14**

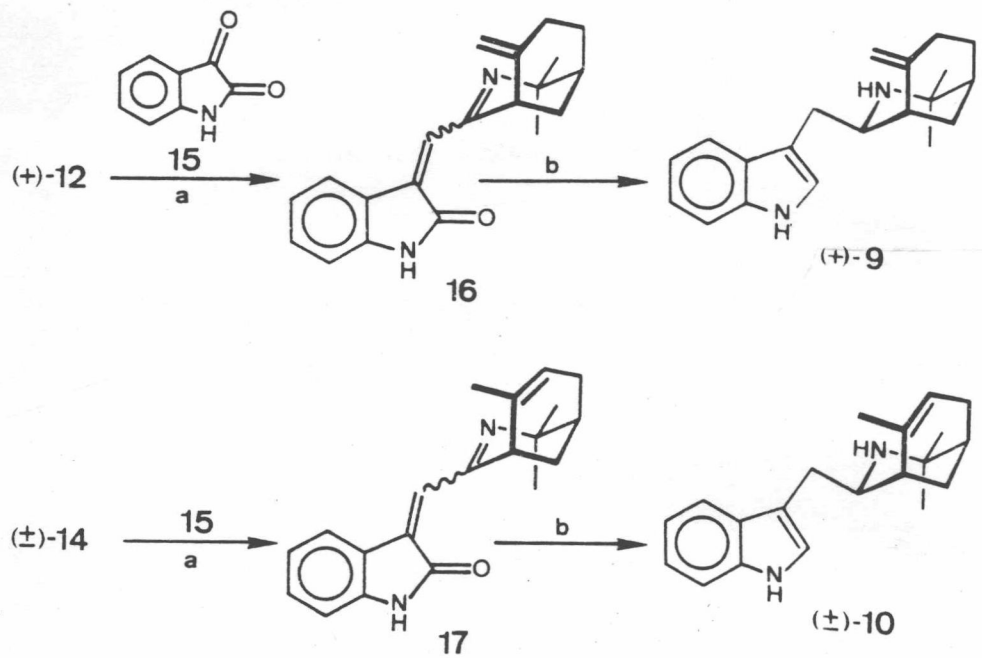
Reagents: a) $Hg(NO_3)_2/CH_3CN$; b) $NaBH_4$.

Lévy and coworkers [15] elaborated the bicyclic imine (+)-**12** into (+)-makomakine (**9**) in 22% overall yield as shown in *Scheme 3:* a base-catalyzed condensation of this material with isatin (**15**) led to the oxindole derivative **16** as an *(E/Z)*-mixture which was reduced stereoselectively in two steps to (+)-**9** (optical purity *ca.* 90%). In a completely analogous fashion, (±)-**14** was transformed into racemic hobartine ((±)-**10**) in 20% overall yield.

At the same time, the French group uncovered the best conditions reported till then for the transformation of both (+)-**9** and (±)-**10** into the pentacyclic alkaloid aristoteline (**1**) which was obtained optically pure in the former case and in racemic form in the latter case (for more details see section 4).

[4] For consonant rationalizations of the observed racemization see [16] and [17].

Scheme 3

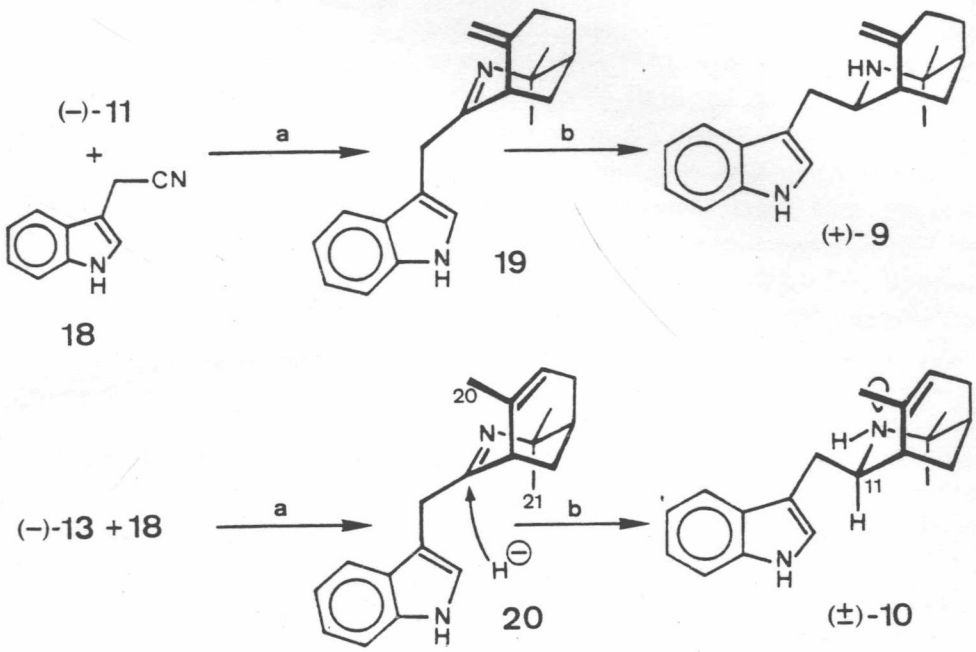


Reagents: a) Piperidine, EtOH, 30min reflux; b) 1. KBH_4, 2. $LiAlH_4$.

One year later, *Stevens* and *Kenney* [17] reported a similar approach which was more straightforward due to its perfectly convergent nature. They incorporated the nitrile function into the indole sub-unit and elaborated the tetracyclic alkaloid skeleton in a single step *via* *Khuong-Huu*'s Hg(II)-mediated *Ritter* type reaction between 3-indolyl-acetonitrile (**18**) and (-)-β-pinene (**11**). The resulting 11,12-dehydro-makomakine (**19**) was reduced *in situ* to (+)-makomakine (**9**) in 17% overall yield [5] *(Scheme 4)*. The same strategy, when applied to (-)-β-pinene (**13**), led to racemic hobartine (**10**) with comparable efficiency.

[5] This yield was subsequently improved to 28% by *Kenney* [17b] and finally to 42% [18] through modifications of the work-up and purification procedures.

Scheme 4

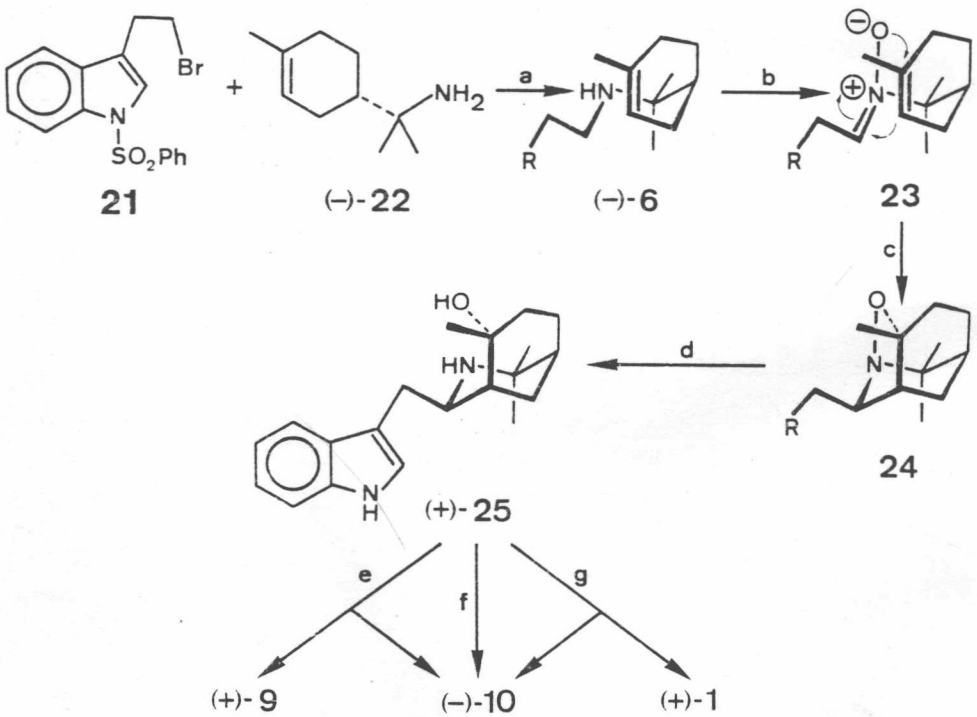


Reagents: a)$Hg(NO_3)_2$/CH_2Cl_2; b) $NaBH_4$.

As in the *Lévy* synthesis [15] and related cases [16a] (for an early example see [19]), the reduction of iminium salts, such as the ones generated by protonation of the imines **19** and **20**, proceeds under strict stereoelectronic control [20]: the approaching hydride ion invariably prefers a trajectory that is strictly *antiperiplanar* to the developing lone-pair at the emerging sp^3-hybridized nitrogen atom (the author does not agree with *Stevens'* prediction that - on purely steric grounds - an equatorial attack should be favored, because such a trajectory is probably as much hindered by the methyl group C(20), as the corresponding axial attack by the axial methyl group C(21)).

An altogether different approach to these alkaloids was conceived by *Gribble* and *Barden* [21]. The key step of their synthesis consists in an intramolecular nitrone-olefin 1,3-dipolar cycloaddition (for a recent review see [22]). The required substrate **23** *(Scheme 5)* was prepared by alkylation of *(S)*-α-terpinylamine (**22**) with indole-protected tryptophyl bromide (**21**) and a subsequent two-step oxidation procedure which furnished exclusively the expected *(Z)*-isomer **23**. The anticipated cycloaddition took place under mild conditions and produced the isoxazolidine derivative **24** as the single product. Successive removal of the protecting group and reductive cleavage of the N-O bond gave the pivotal tertiary alcohol (+)-**25**, from which the desired alkaloids (+)-**1**, (+)-**9** and (-)-**10** could be obtained under the appropriate dehydration conditions (**e-g**) (see also chapter 4, *Table 1)*.

Scheme 5



Reagents: a) $NaHCO_3$, MeCN, 15h r.t.; b) 1. m*-CPBA, CH_2Cl_2, 2. O_2, $Cu(OAc)_2$; c) toluene, 5h reflux; d) 1. Na/Hg, MeOH, 2. Zn, AcOH/H_2O; e) $POCl_3$, py; f) CF_3COOH, 12h reflux; g)* p*-TsOH, benzene, 30 min. reflux.*

Recently, *Klaver, Hiemstra* and *Speckamp* [23] disclosed an EPC-synthesis of the unique metabolite (-)-peduncularine (**2**), starting from *(S)*-malic acid, which was elaborated into **26** (mixture of diastereomers) in 6 high-yield steps (see *Scheme 6)*. Stereoselective alkylation of the corresponding dianion with 1-TMS-2-pentyne set the stage for the key step in this synthesis, an intramolecular N-acyliminium ion cyclization (for a review on this versatile method for the construction of N-heterocycles see [24]). The resulting allene **28**, which was obtained in 87% yield, was transformed in a straightforward manner into the (methylthio)iminium salt **33.** This material was treated with [3,3-(trimethylendioxy)propyl]magnesium bromide to give a 45:55-mixture of the addition products **34** and **35**. These two isomers were separated by chromatography and each of them was subjected to the *Fischer* indole synthesis, which finally led to (-)-peduncularine (**2**) and (+)-isopeduncularine (**36**) in 44% and 64% yield, respectively.

While synthetic (-)-**2** turned out to be identical with natural (-)-peduncularine [1,29], thus establishing the unknown absolute configuration of this metabolite, synthetic isopeduncularine (**36**) had spectroscopic properties that were decidedly different from the ones of an alkaloid, for which this very same structure had been proposed some time ago by *Bick et al.* [26]. *Speckamp*'s analysis of the ^{13}C-NMR data leaves no doubt as to whether his structural assignment to the synthetic samples are correct (shielding *syn*-γ-effect on C(10), C(15) and C(18)[6] observed for **36**).

Thus, the structure of natural 'iso-peduncularine' must be wrong. Actually, as correctly pointed out by the Dutch group [23], the data of the natural products peduncularine and 'isopeduncularine' is so similar, that one has to conclude that both specimen have in fact the **same** structure (-)-**2** [7].The minor deviations in the reported NMR spectra probably have their origin in slightly different recording conditions; according to our own experience, the chemical shifts depend critically on the purity of the solvent (most often $CDCl_3$), when less than *ca.* 2 mg of a given compound are submitted to an NMR experiment. In such cases it is advisable to employ $CDCl_3$ which has been passed through basic alumina, activity 1, immediately before use).

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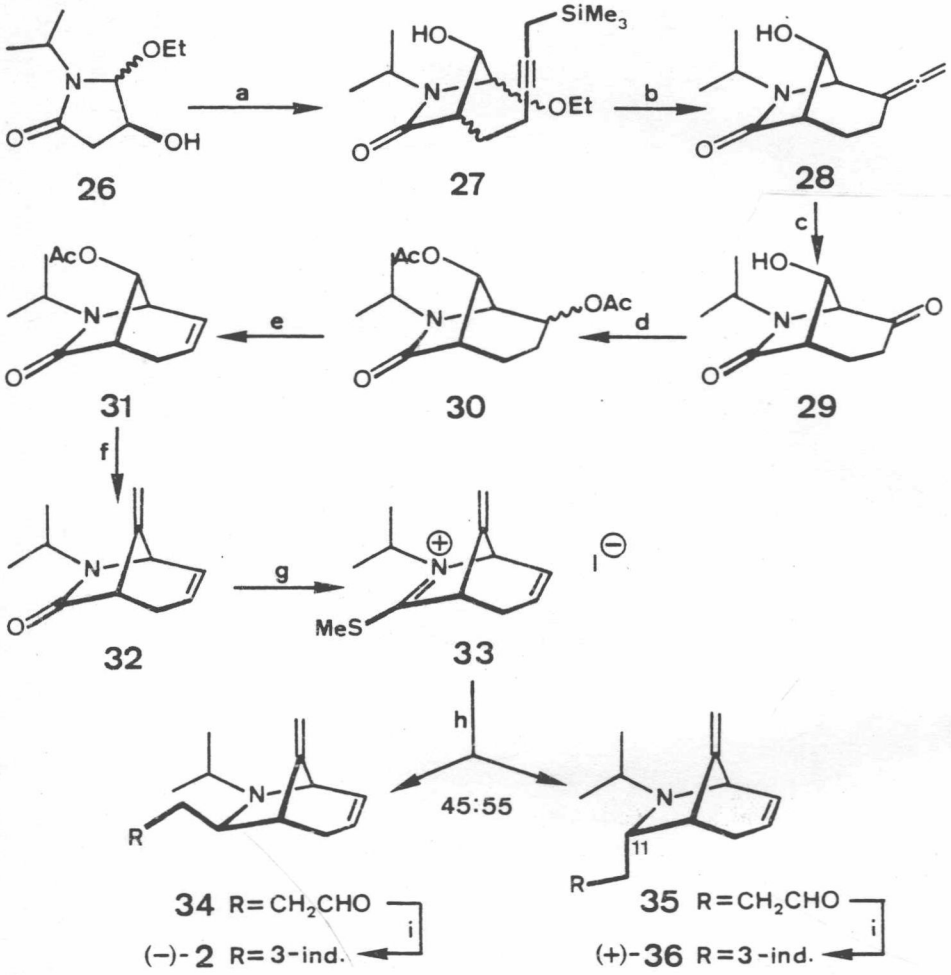
[6] For the sake of clarity and internal consistency, the author strictly adheres to the biogenetic numbering system proposed by *Bick* and *Hesse* [8] (see *Appendix)*. Unfortunately, other workers have employed different nomenclatures.

[7] We are convinced that the same holds true for the pair sorelline/ 'isosorelline' (see chapter 6) and, possibly, for hobartine/'isohobartine' as well.

Scheme 6



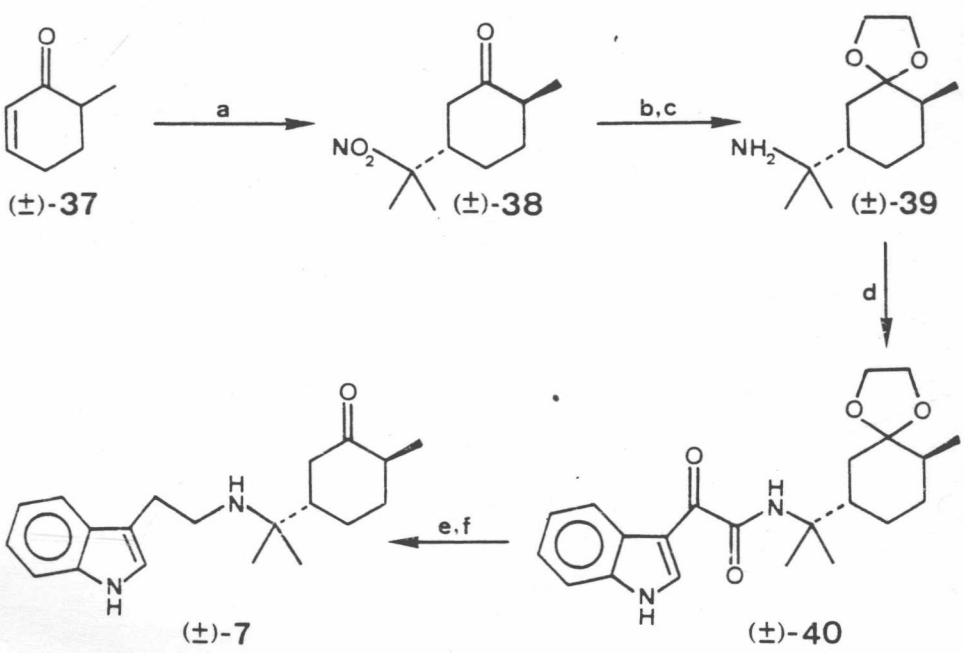
26 27 28 29 30 31 32 33

Reagents: a) 1. LDA, THF; 2. $TMSCH_2$-CC-CH_2CH_2I; b) 1. HCOOH; 2. NH_3/MeOH; c) 1.O_3, 2. Me_2S; d) Ac_2O, py; e) 600°; f) 1. NaOEt, 2. $(ClCO)_2$, DMSO, 3. $Ph_3P=CH_2$; g) Lawesson's *reagent, 2. MeI; h) 1. [3,3'-(trimethylenedioxy)propyl]MgBr, 2. $NaBH_3CN$, AcOH, i)* Fischer *indole synthesis.*

Fruticosonine (**7**), the only tricyclic representative that has been isolated from natural sources, was synthesized by *Bick*'s group [9] in racemic form. This first successful synthesis within the field of the *Aristotelia* alkaloids is outlined in *Scheme 7:*

The starting material **37** was prepared by *Birch* reduction of *o*-toluidine, followed by hydrolysis of the intermediate enamine, and was allowed to react with 2-nitropropane and NaOEt. This highly diastereoselective *Michael* addition produced **38** in excellent yield. Two straightforward steps led to the aminoketal **39** which was condensed with 3-indolyloxalyl chloride to furnish the α-ketoamide **40.** Reduction and deprotection completed the only reported synthesis of racemic fruticosonine (**7**).

Scheme 7



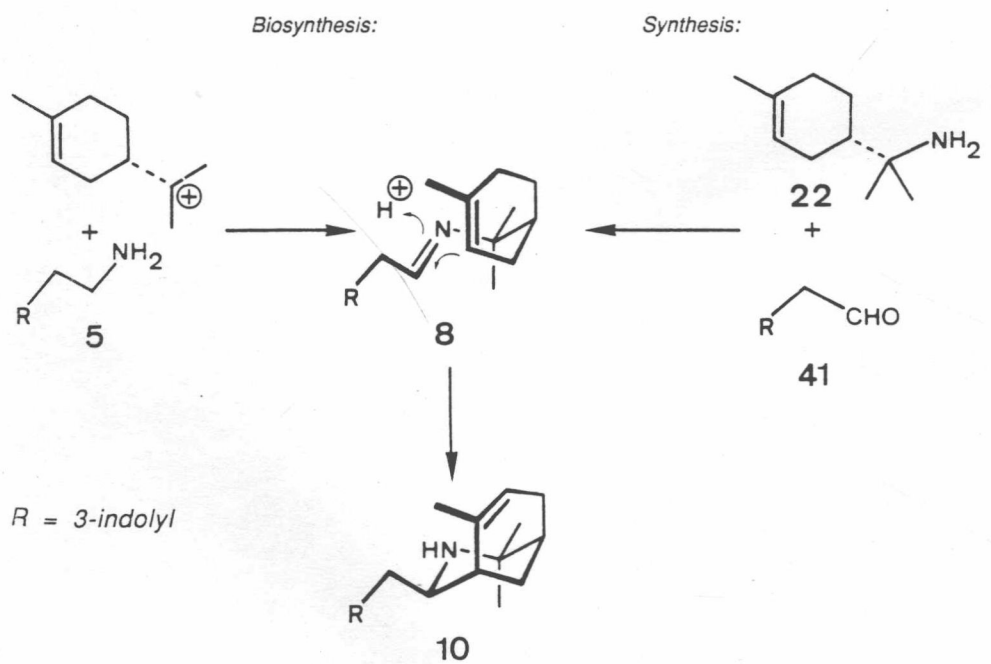
Reagents: a) 2-nitropropane, NaOEt; b) ethane-1,2-diol, p-TsOH; c) $LiAlH_4$; d) 3-indolyl-oxalyl chloride; e) $LiAlH_4$; f) H_3O^+.

3. BIOMIMETIC SYNTHESIS OF (-)-HOBARTINE

We launched our *Aristotelia*-program roughly ten years ago for two main reasons: In many cases the low concentration of these alkaloids in natural sources prevented a thorough characterization and an assessment of their pharmacological properties. When studying the pertinent literature, we noticed several inconsistencies which called for a more thorough investigation with the aid of synthetically prepared material. As will be shown in the following sections, our suspicions turned out to be justified in all the cases we scrutinized so far.

An inspection of the syntheses presented in the previous section reveals that part of their comparatively low over-all efficiency is caused by the fact that the primary targets are situated on too high an oxidation level as compared to the final goal. As a consequence, subsequent reduction steps are required which proceed with rather low yields. To avoid this problem, we envisaged a biomimetic route to (-)-hobartine (**10**). As was mentioned in the introduction, this alkaloid is believed to be derived biosynthetically from the imine **8** *(Scheme 8) via* an enzymatically controlled cyclization.

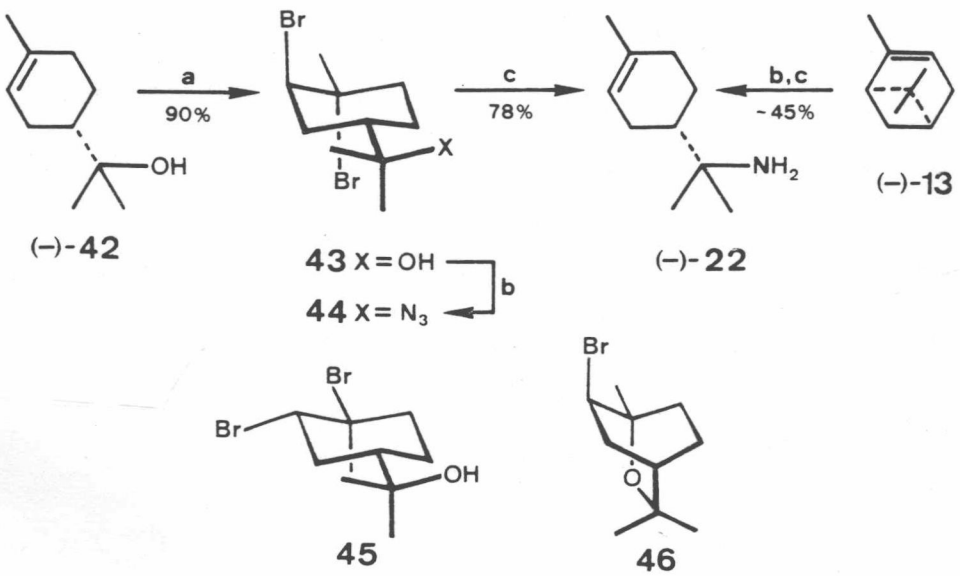
Scheme 8



From a retrosynthetic point of view, intermediate **8** is obviously most conveniently assembled through condensation of the two building blocks *(S)*-terpinylamine (**22**) and 3-indolylacetaldehyde (**41**) *(Scheme 8)*.

Both starting materials were known compounds at the time we started our investigations, but the reported procedures for their preparation turned out to be unsuitable for our purposes. *(S)*-α-Terpinylamine (**22**) was first prepared in unspecified yield and purity by *Khuong-Huu* and coworkers [30] by treatment of (-)-α-pinene (**13**) with HN_3/BF_3, followed by reduction of the formed 8-azido-1-*p*-menthene with $LiAlH_4$. In our hands, this method gave a 62% yield of (-)-**22** which was contaminated with *ca.* 25% of isomeric amines. Purification with the aid of a spinning-band column distillation furnished the chemically pure compound which had an optical purity of 70% [8]. For this reason an alternative route to (-)-**22** was developed.

Scheme 9



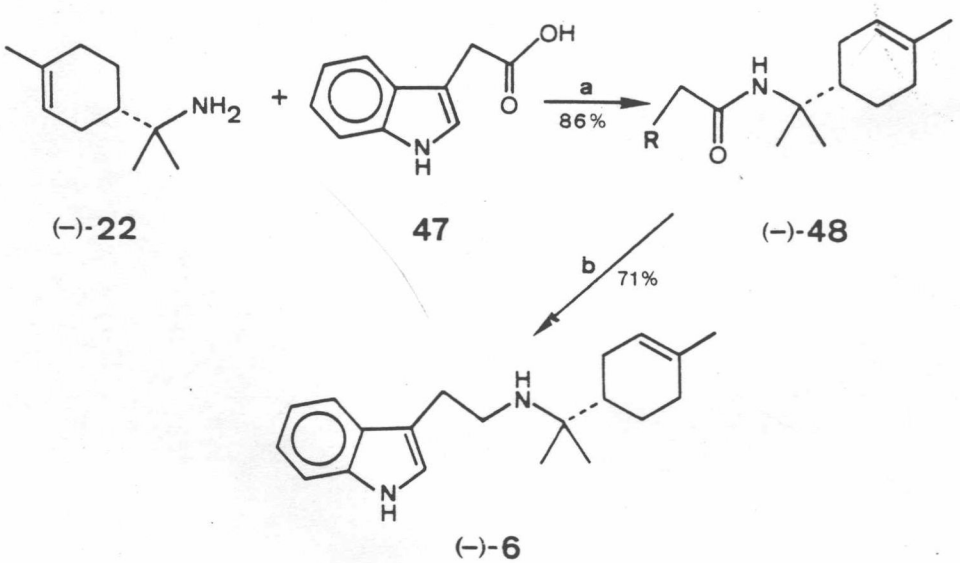
Reagents: a) Br_2, CCl_4; b) HN_3/BF_3, benzene; c) $LiAlH_4$, Et_2O.

[8] Similar observations were made by *Perni* [27], *Gribble* and *Barden* [11], as well as by *Kyburz* [29] who had to purify the crude amine by HPLC.

Commercially available, partly racemic *(S)*-α-terpineol (**42**) was transformed into optically pure material by recrystallization from low-boiling petroleum ether [31]. To prevent extensive racemization during the following step, the double bond of **42** was protected by bromination which led to a mixture consisting of 90% **43**, 5% **45** and 4% **46** [18]*(see Scheme 9)*. Treatment of the crude material with HN_3/BF_3 in benzene gave the dibromoazide **44**, which was reduced immediately with $LiAlH_4$ to (-)-**22** in 71% overall yield. Samples prepared in this way are free of other isomers and have optical purities in the range of 85-90% [10]. Optically pure (-)-**22** can be obtained *via* recrystallization of its *(R,R)*-tartaric-acid salt.

As shown in *Scheme 10*, this compound served as a convenient starting material for an expeditious synthesis of the first stable intermediate in the proposed biogenesis of the *Aristotelia* alkaloids, namely of N-*(S)*-α-terpinyltryptamine (**6**) [32]. The best method for preparing amide **48** turned out to be *Mukaiyama*'s protocol [33] which furnished the desired intermediate in 86% yield. This material was reduced with LAH to give the anticipated (-)-**6**, a colorless crystalline compound which has not been isolated yet from natural sources.

Scheme 10

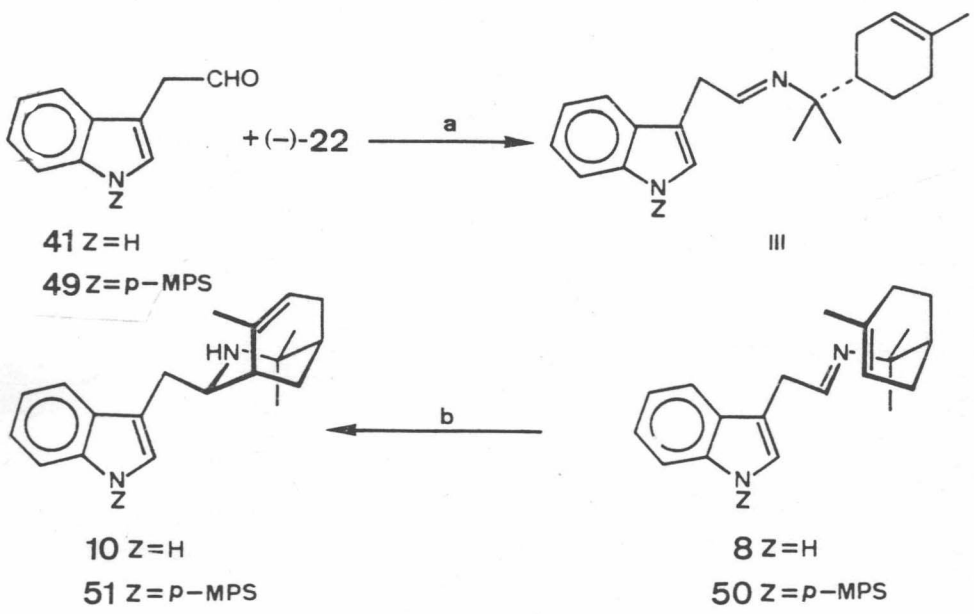


Reagents: a) 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2; b) $LiAlH_4$, Et_2O, 16h reflux.

Next, the amine (-)-**22** was condensed with 3-indolylacetaldehyde (**41**) to give the crystalline imine (-)-**8** *(Scheme 11)* in 62% yield [10]. While this compound is perfectly stable in the crystalline state, it decomposes rapidly in solution. Therefore, it came as no surprise that we experienced enormous difficulties when attempting to mimic the crucial cyclization to hobartine ((-)-**10**)) *in vitro*. Eventually, it was found that treatment of (-)-**8** with strictly anhydrous formic acid, the reagent promoted by *Speckamp* for his N-acyl iminium-ion cyclizations [24], does the job; after 16 hours at room temperature (-)-**10** is formed in 60-70% yield. The stereoselectivity of this reaction is quite remarkable: the result that the indolyl side-chain ends up exclusively in the more stable equatorial *endo*-position was not surprising in the light of earlier model studies (for leading references see [10]), but the fact that not even traces of the isomer makomakine (**9**) could be detected in the crude reaction mixture is without precedent, since in all other cases mixtures of double bond isomers had been obtained.

This straightforward synthesis of (-)-hobartine (**10**) established the then unknown absolute configuration of this metabolite as represented in the *Scheme* below.

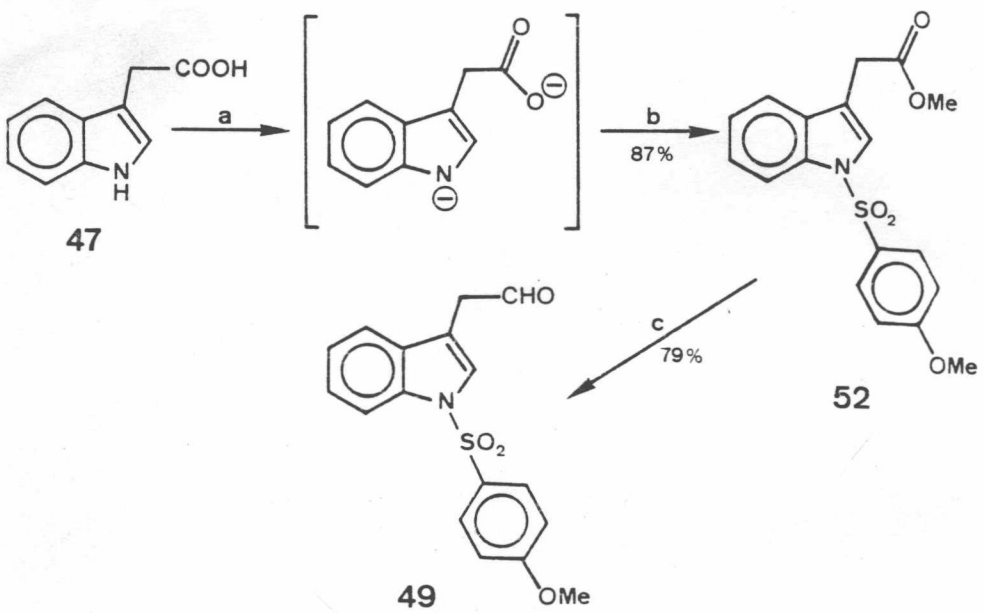
Scheme 11



Reagents: a) benzene, 60 min at 4°, b) HCOOH, 16 h at r.t.

Later on, it turned out that the free aldehyde **41** is too unstable to be of much use for more elaborate syntheses (see chapters 5-7). Therefore, we took recourse to the indole-protected derivative **49**[9] which is readily prepared *via* N-sulfonation of twice deprotonated 3-indolylacetic acid (**47**), esterification with CH_2N_2 and subsequent reduction with DIBAH [32], as shown in *Scheme 12*. Repetition of our hobartine synthesis, this time starting with **49** instead of **41**, furnished the indole-protected alkaloid **51** in 60% overall yield [32a] (see *Scheme 11*).

Scheme 12



Reagents: a) 2eq. n-BuLi,THF, 1h at -70°; b) 1. p-MPS-Cl, 16 h r.t.; 2. CH_2N_2, CH_2Cl_2/Et_2O; c) DIBAH, CH_2Cl_2, -78° 15 min.

[9] The use of the (*p*-methoxyphenyl)sulfonyl- (=*p*-MPS) protecting group was recommended to the author by Professor *Philip Magnus*, Indiana University.

4. THE HOBARTINE-ARISTOTELINE TRANSFORMATION

The first successful realization of a biomimetic transformation of tetracyclic *Aristotelia* alkaloids into the pentacyclic representative aristoteline (**1**) *(Scheme 13)* was reported in 1981 by *Bick*'s group [12]. They treated natural (+)-makomakine (**9**) with aq. HBr and obtained (+)-**1** in 10% yield, which was later improved to 33% by *Hai* [35] (see *Table 1)*. The so far best conditions were developed by *Lévy* and coworkers [15], who used boiling conc. HCl and thus obtained (+)-**1** in 50% yield. We employed essentially the same procedure for the analogous conversion of synthetic (-)-hobartine (**10**) into (+)-aristoteline (**1**) [10].

Table 1. *Acid-catalyzed conversion of various precursors into aristoteline.*

Entry	Substrate	Conditions	Yield of (+)-1	Ref.
1	(+)-**9**	48% HBr, r.t.	10%	[12]
2	(+)-**9**	48% HBr, 18h r.t.	33%	[35]
3	(+)-**9**	conc.HCl, 3h reflux	50%	[15]
4	(+)-**9**	conc.HCl, 4h reflux	28%	[17]
5	(+)-**9**	20% HCl, 4h reflux	56% [a]	[18]
6	rac.-**10**	conc.HCl, 8h reflux	62% [b]	[15]
7	(-)-**10**	20% HCl, 8h reflux	70% [a]	[10]
8	(+)-**53**	5% H_2SO_4, 18h r.t.	47%	[36]
9	(+)-**25**	TsOH, bz, 30min reflux	28% [c]	[11]

[a] In addition, 11% of (+)-neohobartine (**55**) were isolated (see below).

[b] Aristoteline was obtained in racemic form.

[c] Under these conditions (-)-**10** was formed in 50% as well.

TLC- and NMR-evidence disclosed that (-)-hobartine (**10**) is formed as the first detectable product, when (+)-**9** is treated with mineral acid [18]. As has been pointed out by *Bick* and *Hesse* [8], in the next step the electron-deficient centre of intermediate **I** is probably attacked preferentially by C(3), definitely the most nucleophilic site of the indole sub-unit, to furnish the two epimeric spiro-indolenine derivatives **53** and **54,** respectively. These alleged intermediates obviously do not survive the rather harsh reaction conditions, but rearrange rapidly to the stable end product (+)-aristoteline (**1**).