125. Synthesis of *Aristotelia*-Type Alkaloids

Part XII[1])

Total Synthesis of (−)-Tasmanine. Stereoelectronic Factors that Control the Rearrangement of 3*H*-Indol-3-ol Derivatives to Oxindoles (= 1,3-Dihydro-2*H*-indol-2-ones) or to Pseudoindoxyls (= 1,2-Dihydro-3*H*-indol-3-ones)

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The oxidative transformation of (+)-aristoteline ((+)-**5**) into its metabolites, the recently synthesized indole alkaloids (−)-serratoline ((−)-**6**), (+)-aristotelone ((+)-**2**), and (−)-alloaristoteline ((−)-**22**), was investigated in more detail. It was demonstrated that the diastereoface selectivity of the reaction of (+)-**5** with 3-chloroperbenzoic acid can be altered by variation of the solvent as well as by addition of CF_3COOH. The chemoselectivity of the 1,2-rearrangement of the intermediate 3*H*-indol-3-ol derivatives could be controlled as follows: treatment of 3*H*-indol-3-ols with aqueous polyphosphoric acid led to the pseudoindoxyl (= 1,2-dihydro-3*H*-indol-3-one) derivatives, whereas an analogous treatment of the corresponding *O*-benzoates furnished exclusively the corresponding, constitutionally isomeric 2-oxindole (= 1,3-dihydro-2*H*-indol-2-one) products. Exploitation of these and related findings led to efficient total syntheses of the *Aristotelia* alkaloid (−)-tasmanine ((−)-**1**) and of the corresponding unnatural epimer (+)-**12**, as well as of the two pseudoindoxyls (+)-aristotelone ((+)-**2**) and (−)-2-epiaristotelone ((−)-**11**). All these transformations were carried out with synthetic (+)-aristoteline ((+)-**5**) as the single indole alkaloid precursor.

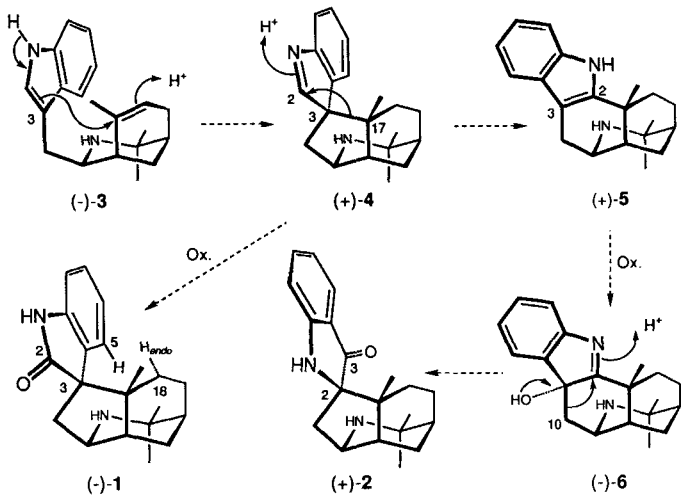
1. Introduction. – The oxindole (= 1,3-dihydro-2*H*-indol-2-one) alkaloid (−)-tasmanine ((−)-**1**) was first isolated in 1981 by *Bick*, *Hesse*, and coworkers from the Tasmanian species *Aristotelia peduncularis* (content: 0.5 ppm of the dried plant material) [2]. They derived structure **1** (*Scheme 1*) by spectroscopic means and deduced the relative configuration at C(3) on the basis of ^{1}H-NMR anisotropy effects (biogenetic numbering). Three years later, this assignment was confirmed by means of a NOE experiment, which was carried out with material isolated from *A. serrata* (positive NOE between *H*−C(5) and H_{endo}−C(18)) [3]. The absolute configuration of (−)-**1** was established by way of a chemical correlation with (+)-aristoteline ((+)-5) [3]. (−)-Tasmanine ((−)-**1**) is believed to arise biogenetically through oxidation of (+)-3-epiaristoserratenine ((+)-**4**)[2]), which was isolated from *A. australasica* [4][3]). At the same time, this spiro-3*H*-indole alkaloid (+)-**4**

[1]) Part XI: see [1].

[2]) In [2] (there Scheme 2, Formula **7**), this compound, which had not been characterized yet at that time, was mistakenly named 'serratoline'. This was probably caused by the originally proposed incorrect serratoline structure [5], which was subsequently revised to **6** (*Scheme 1* in the present paper) [6].

[3]) Our *in vitro* experiments (see below) suggest that alternative biogenetic pathways, such as **5** → **7** → **1** (*Scheme 2*), should be considered as worthy alternatives to the above proposal.

Scheme 1[a])



[a]) Biogenetic numbering.

(and/or the corresponding epimer, (+)-aristoserratenine [7]) represents the alleged intermediate in the (−)-hobartine ((−)-**3**)→(+)-aristoteline ((+)-**5**) transformation [2].

Aristotelone (**2**), a constitutional isomer of tasmanine (**1**), was isolated from *Aristotelia chilensis* by *Silva* and coworkers [8], who postulated the pseudoindoxyl (= 1,2-dihydro-3*H*-indol-3-one) structure **2** on the basis of IR, UV, and MS evidence, combined with biogenetic considerations. We recently confirmed this proposal through an unambiguous biomimetic total synthesis of (+)-**2**, which started with synthetic (+)-aristoteline ((+)-**5**) and proceeded *via* (−)-serratoline ((−)-**6**) to (+)-**2** in 90% overall yield [9][4]).

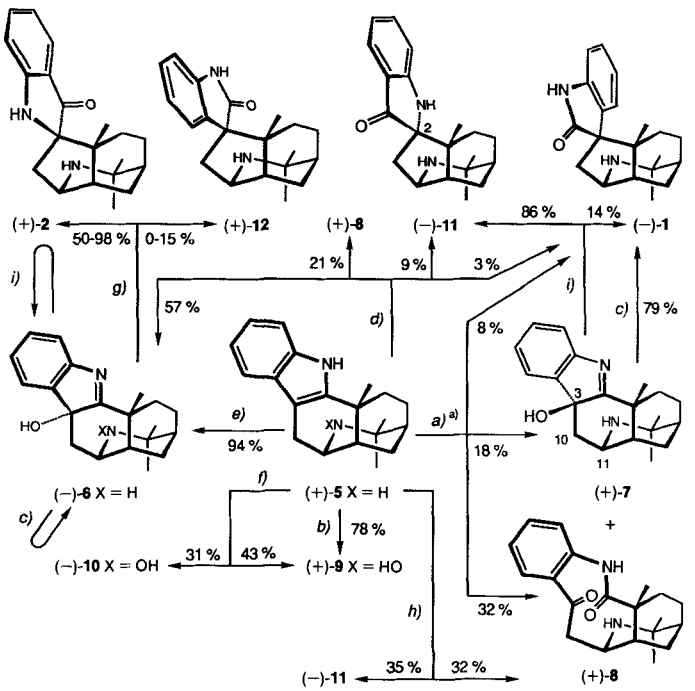
Since intermediate (+)-**4** was detected in none of the many reported [11] [3] *in vitro* cyclizations of tetracyclic precursors (such as (−)-**3**) into the pentacyclic alkaloid (+)-aristoteline ((+)-**5**), spiro compound (+)-**4** has remained synthetically inaccessible so far. Therefore, as long as no alternative strategy leading to (+)-**4** has been worked out, a total synthesis of (−)-tasmanine ((−)-**1**) *via* the route (+)-**4** →(−)-**1** does not seem feasible. In connection with not directly related research [9], we have now come across a route that circumvents this problem.

2. Results and Discussion. – When (+)-aristoteline ((+)-**5**) was oxidized with 3-chloroperbenzoic acid (3-$ClC_6H_4CO_3H$) [12] in petroleum ether, the major product was the hydroxylamine derivative (+)-**9** (*Scheme 2*). The same product was formed in 43% yield when the solvent was changed to CH_2Cl_2. Under these conditions, 30% of (−)-serratolin-12-ol ((−)-**10**) could be isolated as well (for similar oxidations, see [13] and ref. cit. therein). With the aim to avoid formation of these undesired hydroxylamine derivatives, we repeated the reaction in the presence of excess CF_3COOH and in CH_2Cl_2 as solvent at 25°. Indeed, no hydroxylamine derivatives could be detected under these conditions, and the major product (57% yield) was the desired target (−)-serratoline ((−)-**6**). However,

[4]) For a very similar approach, see [10]. We would like to thank these authors for a preprint of their paper.

considerable amounts of the over-oxidized lactam **8**[5]) and of the rearrangement products of (+)-**7**, namely (−)-**1** and (−)-**11**, were also present in the mixture. Consequently, the reaction was repeated at −40°, and under these conditions, (+)-aristoteline ((+)-**5**) could be oxidized in very high yield and with virtually complete diastereoselectivity to (−)-serratoline ((−)-**6**) [9].

Scheme 2[a])



a) 1. 3-$ClC_6H_4CO_3H$, CF_3COOH, THF; 2. chromatography[a]). *b*) 3-$ClC_6H_4CO_3H$ petroleum ether, 10 min reflux. *c*) $CDCl_3$, 6 d at 25°. *d*) 3-$ClC_6H_4CO_3H$, CF_3COOH, CH_2Cl_2, 1 h, 25°. *e*) 3-$ClC_6H_4CO_3H$, CF_3COOH, CH_2Cl_2, 1 h, −40°. *f*) 3-$ClC_6H_4CO_3H$, CH_2Cl_2, 10 min reflux. *g*) See [9]. *h*) 3-$ClC_6H_4CO_3H$, CF_3COOH, THF, 100 h, 25°. *i*) NaOEt, EtOH, 22 h, 25°.

[a]) The crude mixture consisted of (+)-**5**/(+)-**7**/(+)-**8** in a ratio of 1:1:1 (no (−)-**1** present; see *Exper. Part*).

The excellent diastereoface selectivity of the attacking peracid in the presence of CF_3COOH in favor of the less accessible concave side of the starting material is quite remarkable (→(−)-**6**) and must result from a strong *cis*-directing effect of the protonated piperidine N-atom (see *Chapt. 3*). For reasons detailed below, we were also interested in gaining access to the unnatural epimer 3-episerratoline ((+)-**7**). Hoping that a solvent with good cation-stabilizing and H-bond acceptor properties might overpower the *cis*-directing effect of the piperidinium moiety, we repeated the above reaction, using THF as

[5]) This compound was isolated as an inseparable 2:1 mixture, conceivably of lactam (*E*)/(*Z*)-isomers that are in thermodynamic equilibrium. This type of oxidation product was observed before, when indole derivatives were treated with various oxidizing reagents. For a review, see [14].

solvent. Under these conditions, the oxidation process was indeed much slower than in CH_2Cl_2 (no reaction after 30 min at −18°), and the anticipated epimer (+)-**7** was formed as the major product at 25° in the presence of CF_3COOH. The relative configuration at C(3) of the 3*H*-indol-3-ol derivatives (−)-**6** and (+)-**7** was deduced by analysis of the ^{1}H-NMR coupling constants between *H*−C(11) and the methylene protons at C(10) (see *Fig.* and *Table 1*)[6]. These assignments were corroborated by NOE experiments with the corresponding epimeric *O*-benzoates (see below, (−)-**15** and (+)-**17**, respectively, and *Exper. Part*).

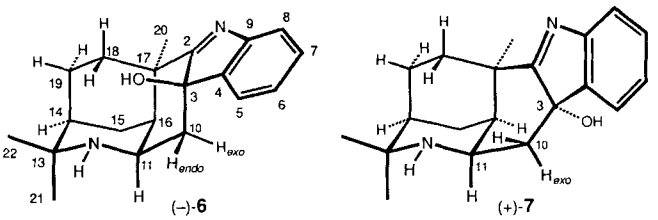


Figure. *Dihedral angles* (Φ) *and coupling constants* (*J*) *between H−C(11) and CH_2(10) in (−)-serratoline* ((−)-**6**) *and (+)-3-episerratoline* ((+)-**7**). Biogenetic numbering [2].

Table 1. *Selected NMR Parameters of 3,3-Disubstituted 3*H*-Indole Derivatives*

	Ring C	*J* [Hz]		δ(^{1}H) [ppm]			δ(^{13}C) [ppm][a]					
		J(10*exo*, 11)	*J*(10*endo*, 11)	H_{exo}−C(10)	H_{endo}−C(10)	H−C(11)	C(2)	C(3)	C(10)	C(11)	C(16)	C(17)
(−)-**6**	chair	3.0	2.8	1.52	2.57	3.60	190.2	83.9	42.9	52.5	44.0	41.5
(−)-**15**	chair	4.5	2.1	1.61	3.04	3.40	186.3	86.8	43.0	50.8	45.6	42.9
(−)-**10**	chair	2.9	2.8	1.26	3.17	3.37	189.6	84.3	39.2	61.6	46.7	41.7
(+)-**7**	boat	8.4	1.9	2.93	1.16	3.59	195.6	83.0	41.4	48.3	36.5	38.2
(+)-**17**	boat	8.6	2.4	3.38	1.18	3.70	190.8	86.9	40.4	48.0	37.1	38.5

[a]) The ^{13}C-assignments were corroborated through ^{1}H,^{13}C-COSY experiments.

In marked contrast to (−)-**6**, the unnatural epimer (+)-**7** is a very labile compound and was transformed into (−)-tasmanine ((−)-**1**)[7]) when kept in $CDCl_3$ containing a trace of Et_2NH at 25° overnight (under the same conditions, (−)-**6** remained unchanged[8]) for at least 3 months). To account for this striking difference in reactivity between (−)-**6** and

[6]) The same argument was utilized before by *Bick* and coworkers to delineate the relative configuration at C(3) of natural (−)-serratoline ((−)-**6**) [6].

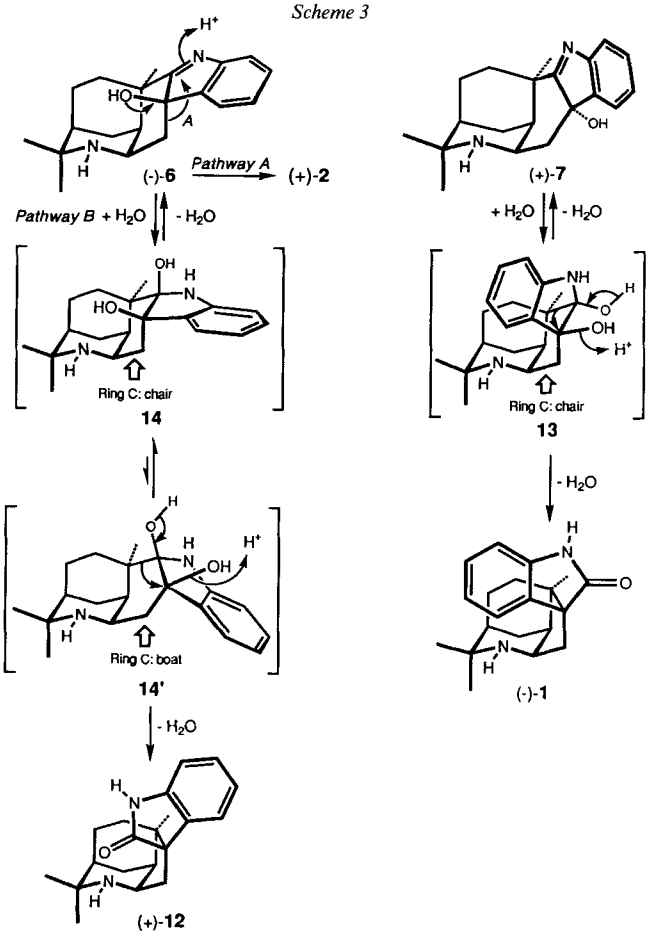
[7]) The interesting question, whether (−)-tasmanine ((−)-**1**) is a true natural product or an artifact, cannot be answered definitely at this point. What can be stated with confidence, however, is that if 3-episerratoline ((+)-7) were a plant metabolite, it would not have survived the isolation and purification procedures employed by *Bick* and *Hesse* [2] or by *Husson* [4]. Instead, it would have been transformed into an equivalent amount of (−)-tasmanine ((−)-**1**) under those circumstances.

[8]) Under more drastic conditions, such as heating for 30 min at 200°, (−)-**6** rearranged to (+)-aristotelone ((+)-**2**) in quantitative yield. Under acidic conditions, up to 15% of (+)-3-epitasmanine ((+)-**12**) were formed besides (+)-**2** [9]. When (−)-**6** was treated with NaOEt in EtOH at 25°, it was transformed very slowly into (+)-**2** (16% yield after 13 days, 35% after 45 days).

(+)-**7**, we put forward the following working hypothesis: in the case of the unnatural epimer (+)-**7**, a (reversible) addition of H_2O to the protonated imine moiety from the more accessible '*exo*'-face furnishes the intermediate *cis*-diol **13** (*Scheme 3*)[9]). This hydration should be favored, because, in the course of the reaction, the strain caused by the geometrically imposed boat conformation of ring C in (+)-**7** is relieved (in **13**, this ring can readily adopt a chair conformation). The subsequent rearrangement to (−)-tasmanine ((−)-**1**) should be an equally favored process, because, in intermediate **13**, the bonds that are stereoelectronically relevant for an ensueing ring contraction are aligned in perfectly antiperiplanar fashion[10]).

On the other hand, an analogous hydration of the comparatively less strained (−)-**6** would have to occur from the '*endo*'-face of this molecule[11]) to give *cis*-diol **14** (*Pathway B*

Scheme 3



[9]) Recently, *Sakai* and coworkers invoked an analogous *cis*-diol as the reactive intermediate in the oxidative rearrangement of an indole precursor into a 2-oxindole derivative on treatment with OsO_4 [15].

[10]) For exhaustive discussions of this topic, see [16].

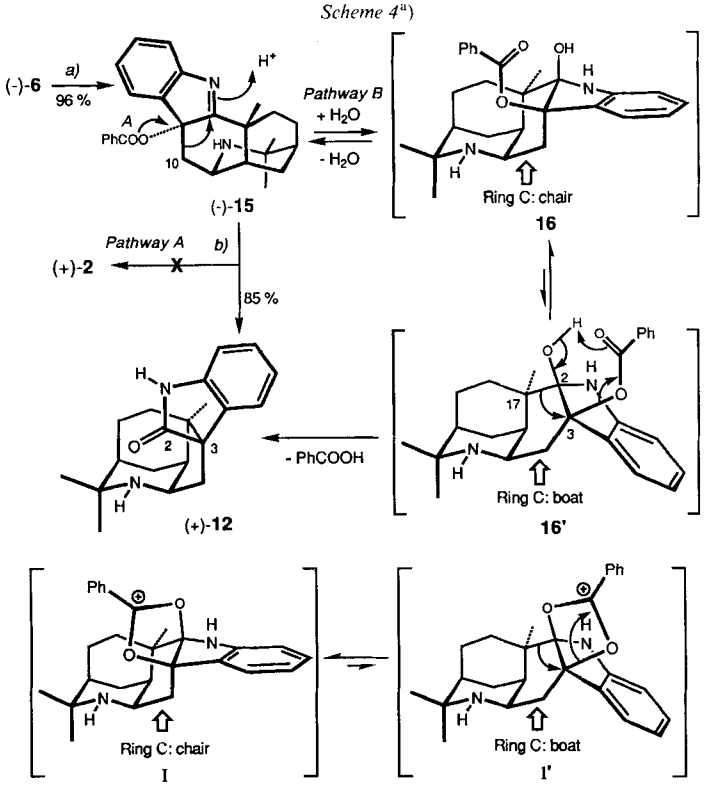
[11]) The *trans*-diol resulting from an attack from the '*exo*'-face would be severely strained.

in *Scheme 3*). As long as ring C of this intermediate remains in the chair conformation, a ring contraction to give (+)-**12** is not feasible because the pertinent bonds are arranged in a synclinal manner relative to each other. The stereoelectronic requirements for a rearrangement to (+)-**12** are met only in the thermodynamically unfavorable boat-like conformation **14'**. As a consequence, the natural epimer (−)-**6** seemingly prefers the alternative, direct ring contraction (*Pathway A*) to the pseudoindoxyl derivative (+)-**2**.

The higher reactivity of (+)-**7** as compared to (−)-**6** was also noted, when the two epimers were treated with NaOEt in EtOH: after 22 h at 25°, the former was transformed quantitatively into a 86:14 mixture of (−)-**11** and (−)-**1** (*Scheme 2*), whereas the latter reacted only very slowly under the same conditions[8]).

Next, we wanted to find out what would happen when the OH substituent at C(3) was replaced by a less potent π-donor group[12]), such as a benzoyloxy unit [18]. The epimer (−)-**15** (natural configuration at C(3)) was prepared in 96% yield from synthetic (−)-serratoline ((−)-**6**) by benzoylation (PhCOCl, pyridine) in the presence of 4-(dimethylamino)pyridine [19] (*Scheme 4*). Treatment of (−)-**15** with aqueous polyphosphoric acid

Scheme 4[a])



a) PhCOCl, py, 4-(dimethylamino)pyridine. *b*) $(H_3PO_4)_n$, EtOH/H_2O, 1 h reflux.

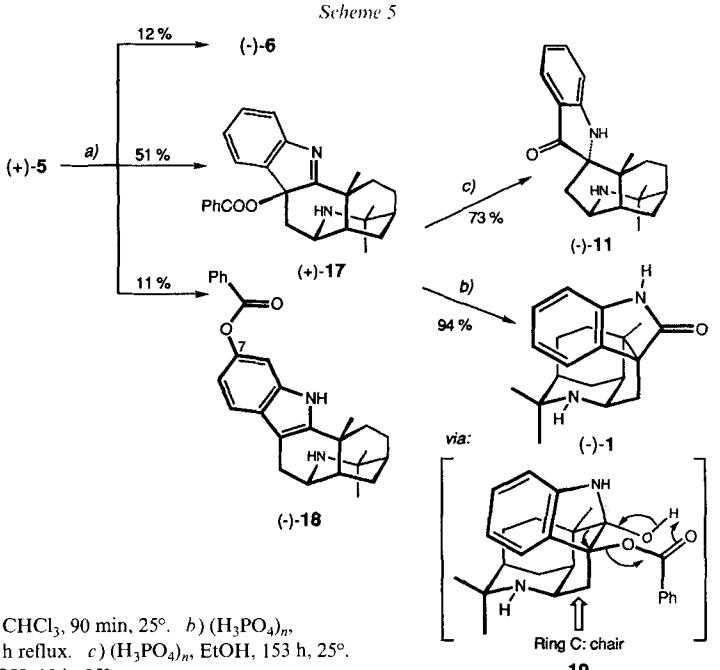
[a]) Biogenetic numbering.

[12]) The markedly different electron-releasing capability of *O*-alkyl *vs.* *O*-acyl substituents is of fundamental importance for the 'armed/disarmed' glycosidation protocol. See, *e.g.*, [17] and ref. cit. therein.

furnished the 2-oxindole derivative (+)-3-epitasmanine ((+)-**12**) in 85% yield. This result remarkably contrasts the previous observation that (−)-**6** furnishes almost exclusively the pseudoindoxyl (+)-aristotelone ((+)-**2**) under the same conditions [9] (see *Scheme 2*). It seems that the electron-donating properties of the *O*-benzoyl group of (−)-**15** are insufficient to induce a direct 1,2-rearrangement to (+)-**2** (*Pathway A*) and that the starting material, therefore, prefers *Pathway B via* **16** and the corresponding boat conformer **16′** to give (+)-3-epitasmanine ((+)-**12**). As an alternative, the 1,3-dioxolane cations **I** and **I′**, formed through neighboring-group participation, or the corresponding ortho esters, can also be considered as reactive intermediates in this rearrangement.

The epimeric *O*-benzoyl-3-episerratoline ((+)-**17**, *Scheme 5*) was obtained as the major product in *ca.* 50% yield, when (+)-aristoteline ((+)-**5**) was treated with 1 equiv. of dibenzoyl peroxide in $CHCl_3$[13]). Under aqueous acidic conditions, (+)-**17** behaved as one would expect according to the above hypothesis: it rearranged cleanly and efficiently to (−)-tasmanine ((−)-**1**), conceivably *via* the hydrated intermediate **19**. This diol can undergo a stereoelectronically favorable ring contraction (ring C in a chair conformation, leaving group antiperiplanar to the migrating bond). On the other hand, treatment of the same starting material with NaOEt in EtOH furnished exclusively the expected pseudoindoxyl compound (−)-2-epiaristotelone ((−)-**11**), obviously *via* the intermediate 3-episerratoline ((+)-**7**). Thus, the sequences (+)-**5** → (+)-**17** → (−)-**1** and (+)-**5** → (+)-**17** → (−)-**11** represent valuable alternatives to the routes displayed in *Scheme 2*.

Scheme 5

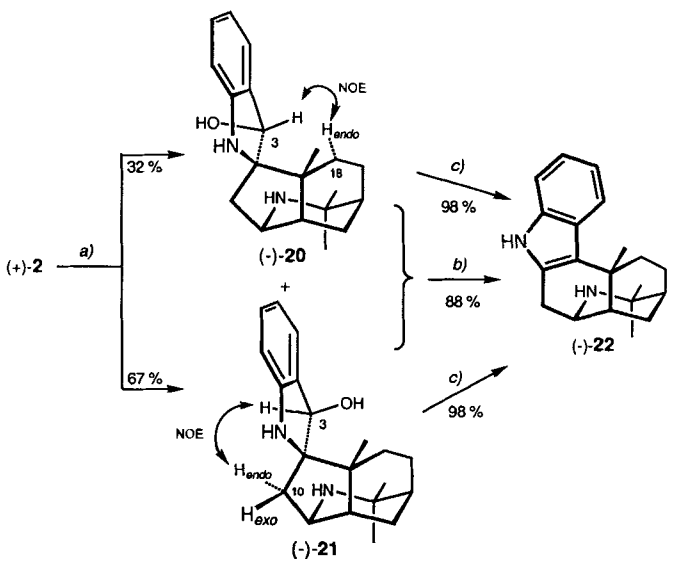


a) $(PhCOO)_2$, $CHCl_3$, 90 min, 25°. *b*) $(H_3PO_4)_n$, $EtOH/H_2O$, 1 h reflux. *c*) $(H_3PO_4)_n$, EtOH, 153 h, 25°. *d*) NaOEt, EtOH, 10 h, 25°.

[13]) Besides small amounts of (−)-**6**, several products resulting from oxidation of the benzene ring were also isolated, the most prominent being (−)-7-*O*-benzoylaristoteline ((−)-**18**).

Finally, the behavior of the inverted indole alkaloid (−)-alloaristoteline [20] ((−)-**22**) under oxidizing conditions was examined briefly. This compound was obtained in a one-pot procedure from synthetic (+)-**2** (reduction with $NaBH_4$, followed by acid treatment of the resulting 1:2 mixture (−)-**20**/(−)-**21**[14]) [9]). In a different experiment, this mixture was separated by chromatography and the relative configuration of the two epimers determined unambiguously by means of NOE difference experiments (see *Scheme 6* and *Exper. Part*). We found that both epimers were transformed quantitatively into (−)-**22** when heated to 190° under Ar for a few min.

Scheme 6[a])



a) $NaBH_4$, dioxane/H_2O. *b*) See [9]. *c*) 7 min, 195°.

[a]) Biogenetic numbering.

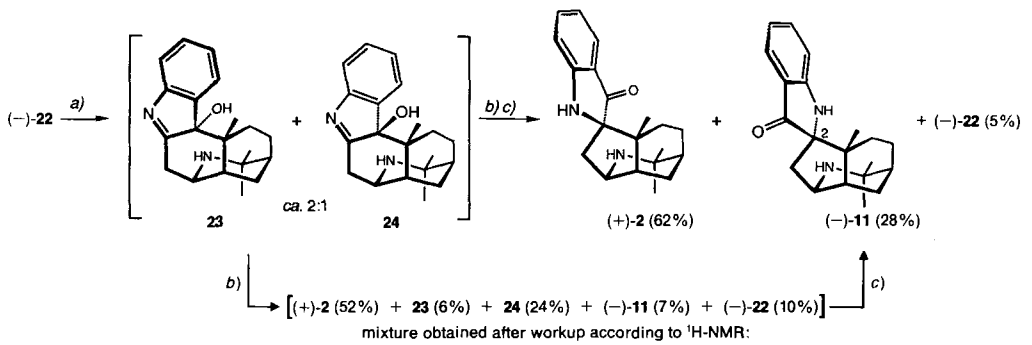
Treatment of (−)-alloaristoteline ((−)-**22**) with 3-$ClC_6H_4CO_3H$ in the presence of CF_3COOH gave an intermediate product that, according to an analysis of the products derived thereof, must have consisted of a 2:1 mixture[15]) of alloserratoline (**23**) and 3-epialloserratoline (**24**) (*Scheme 7*). The standard workup procedure led to a rather complex mixture that contained significant amounts of the rearranged pseudoindoxyl derivatives **2** and **11**, besides **23**, **24**, and some starting material. Evidently, the intermedi-

[14]) A 1:1 mixture of these compounds (relative configuration at C(3) not determined) was obtained by *Stoermer* and *Heathcock* [10] upon treatment of (+)-**2** with $LiAlH_4$. Whereas their NMR spectral parameters coincide within experimental limits with our data, there are significant deviations between the melting points. The observed differences probably have to be ascribed to a partial transformation of these compounds into (−)-**22** in the relevant temperature range. More difficult to reconcile, however, is the difference between the observed values for the optical rotation of (−)-**21** ($[\alpha]_D = -146.8$ *vs.* +140 [10], see *Exper. Part*).

[15]) An examination of *Dreiding* models of (+)-**5** and (−)-**22** showed that in the latter case the concave '*endo*'-face is sterically less accessible than in the regular series. But even in this very unfavorable situation, the *cis*-directing effect of the protonated piperidine N-atom is so strong that '*endo*'-isomer **23** still represents the major product (*ca.* 60% yield, *vs.* 30% of **24**).

ates **23** and **24** are rather labile substrates and, not surprisingly, the base-catalyzed 1,2-transpositions **23** → (+)-**2** and **24** → (−)-**11**[16]) went to completion during an attempted chromatographic separation of the five-component mixture.

Scheme 7



a) 3-$ClC_6H_4CO_3H$, CF_3COOH, CH_2Cl_2. *b*) Workup with aq. NH_3 soln. *c*) Chromatography.

3. Conclusion. – The stereoselective oxidative transformation of 1*H*-indole derivatives into the corresponding 2-oxindoles (= 1,3-dihydro-2*H*-indol-2-ones) or pseudoindoxyls (= 1,2-dihydro-3*H*-indol-3-ones), respectively, represents a challenge that can be met successfully only if the following two conditions are fulfilled: the first one concerns the diastereoface selectivity of the oxidation to 3-hydroxy-, 3-acyloxy-, or 3-chloro-3*H*-indoles, which ultimately determines the configuration at the asymmetric spiro center that is created in the subsequent rearrangement step [12][17]). Traditionally, this requirement presented a major obstacle and, as a rule, yield and/or face selectivity were rather low (for pertinent examples, see [23] [10]). The discovery that the protonated piperidine N-atom exerts a strong *cis*-directing effect on the attacking peracid[18]) now provides a diastereoselective entry to 3*H*-indol-3-ol alkaloids. In those cases where the aliphatic N-atom is located in the sterically less accessible hemisphere, the resulting configuration at C(3) is opposite, and thus complementary, to the outcome of alternative procedures, such as oxidation with *tert*-butyl hypochlorite, $Pb(OAc)_4$, and $(PhCOO)_2$ [23] [10]; $^3O_2$ [21], $^1O_2$ [30], or OsO_4 [15].

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[16]) This compound was shown before to represent the major autooxidation product of (−)-alloaristoteline ((−)-**22**) [9]. In this context, it is of interest to note that some time ago, *Cava* and coworkers transformed iboga alkaloids like voacristine and iboxygaine into the corresponding 3*H*-indol-3-ols by aerating $CHCl_3$ solutions of such compounds for several days [21].

[17]) For altogether different approaches to 2-oxindole substrates, see [22].

[18]) It was demonstrated some time ago that secondary benzamide [24] or acetamide functional groups [25] exhibit *cis*-directing effects which supersede the influence of allylic or homoallylic OH substituents [26]; for a review, see [27]. For an interesting study on the interaction of H_2O_2 with tertiary amines, see [28]. The *cis*-directing power of a protonated piperidine ring, displayed by (+)-**5** and (−)-**22**, now provides an explanation for an earlier observation, namely that (−)-hobartine ((−)-**3**) had furnished exclusively the corresponding '*endo*'-epoxide upon exposure to CF_3CO_3H/CF_3COOH in CH_2Cl_2 [29]. The fact that treatment of (+)-**5** with 3-$ClC_6H_4CO_3H$ in the absence of CF_3COOH furnished predominantly (+)-**9** and (−)-**10** seems to indicate that the hydroxylamino group also exerts a *cis*-directing effect on peracids (see *Scheme 2*).

The second challenge is represented by the chemoselectivity of the rearrangement step which determines whether the final product is a pseudoindoxyl or a 2-oxindole derivative. Up to now, the latter type of product was generally synthesized by treatment of 3-chloro-3*H*-indoles with aqueous AcOH, whereas pseudoindoxyls were usually prepared by treatment of 3*H*-indol-3-ols with a strong base [23] [10]. We have now demonstrated that starting with a single 3*H*-indol-3-ol substrate either of the two alternative pathways can be enforced: treatment with aqueous acid furnishes the pseudoindoxyl derivative, whereas the route *via* the corresponding *O*-benzoyl derivative leads to the related γ-lactam under the same conditions.

Various combinations of the principles discussed above have led to efficient syntheses of all four possible spiro 2- and 3-oxindoles starting from synthetic (+)-aristoteline ((+)-**5**) as the single common precursor (see *Scheme 8* and *Table 2*). We are presently trying to take advantage of these findings for the synthesis of oxindole and pseudoindoxyl alkaloids that do not belong to the *Aristotelia* family [31].

The authors would like to express their gratitude to the *Swiss National Science Foundation* (project No. 20-28267.90) for financial support.

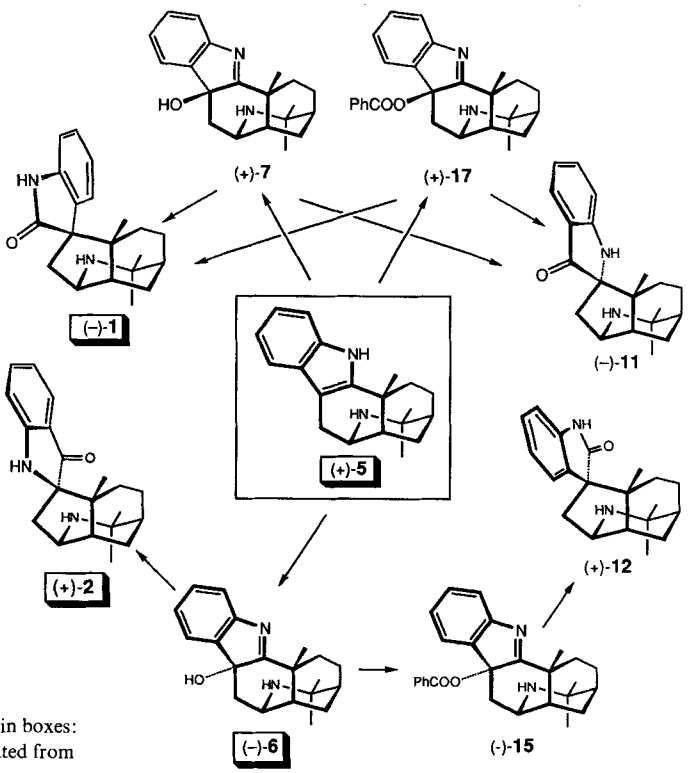
Experimental Part

General. See [32]. Moreover: Dibenzoyl peroxide (*Fluka*, purum) was recrystallized from $CHCl_3$/MeOH and dried 24 h at 25°/0.001 Torr, and 3-chloroperbenzoic acid (3-$ClC_6H_4CO_3H$; *Fluka*, pract.) purified according to [33]. NOE (biogenetic numbering): irradiated proton→affected signal(s).

(−)-O-Benzoylserratoline (= *(3S,4aS,5R,10bR,11aR)-2,3,4-4a,5,10b,11,11a-Octahydro-2,2,5-trimethyl-3,5-ethano-1H-pyrido[3,2-b]carbazol-10b-yl Benzoate*; (−)-**15**). A mixture of synthetic (−)-**6** [9] (205 mg, 0.66 mmol) and 4-(dimethylamino)pyridine (168 mg; *Fluka, purum*) was dried (1 h, 25°/0.001 Torr) and dissolved afterwards in dry benzene (20 ml). To the resulting soln. was slowly added benzoyl chloride (0.13 ml, 157 mg, 1.11 mmol; *Fluka, puriss.*). After stirring for 21 h at 25° under Ar, the mixture was poured onto crushed ice (50 g) and extracted twice with CH_2Cl_2 (100 ml). To the aq. phase was added conc. aq. NH_3 soln. (3 ml) and the extraction repeated. The combined org. extracts were dried (K_2CO_3) and evaporated: 316 mg of white foam. Crystallization from MeOH furnished pure (−)-**15** (158 mg, 58%). The mother liquor was chromatographed (silica gel, cyclohexane/THF/Et_3N 100:14:5) to give additional crystalline (−)-**15** (109 mg, 40%). An anal. sample was prepared by sublimation (200°/0.001 Torr). M.p. 211° (normal pressure; subl. at *ca.* 200°/high vacuum). $[\alpha]_D = -85.4$ ($c = 1.1$, $CHCl_3$). UV (EtOH): 264 (3.73), 226 (4.39, sh), 222 (4.40). IR ($CHCl_3$): 1732, 1616, 1602, 1567, 1470, 1460, 1452, 1382, 1270, 1092, 1070, 1025. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.03 (*ddm*, $J = 8.4, 1.3$, 2 H); 7.64 (*dt*, $J = 7.7, 0.8$, 1 H); 7.57 (*tt*, $J = 7.4, 1.3$, 1 H); 7.43 (*ddt*, $J = 8.1, 7.4, 1.6$, 2 H); 7.36 (*td*, $J = 7.6, 1.3$, 1 H); 7.27 (*ddd*, $J = 7.2, 1.2, 0.6$, 1 H); 7.15 (*td*, $J = 7.4, 1.0$, 1 H); 3.40 (br. *m*, 1 H); 3.04 (*dd*, $J = 15.3, 2.1$, 1 H); 2.73 (*td*, $J = 13.6, 5.9$, 1 H); 2.04 (*dm*, $J = 14$, 1 H); 2.01 (*dt*, $J = 14, 3.1$, 1 H); 1.82 (*dm*, $J = 13.7$, 1 H); 1.73 (*tdd*, $J = 13.9, 5.5, 4.0$, 1 H); 1.62 (*s*, 3 H); 1.61 (*dd*, $J = 15.3, 4.5$, 1 H); 1.39 (*m*, 2 H); 1.28 (*ddm*, $J = 13.6, 5.3$, 1 H); 1.23 (*s*, 3 H); 1.08 (*s*, 3 H). NOE: 2.73 (H_{endo}–C(18))→8.03 (2 H_o of Ph), 1.82 (H_{endo}–C(19)), 1.10 (3 H–C(22)); 8.03 (H_o of Ph)→7.43 (H_m of Ph); 1.10 (3 H–C(22)). ^{13}C-NMR (100 MHz, $CDCl_3$): 186.3 (*s*); 163.9 (*s*); 152.8 (*s*); 139.6 (*s*); 133.3 (*d*); 129.9 (2*d*); 129.7 (*s*); 129.5 (*d*); 128.5 (2*d*); 126.0 (*d*); 121.0 (*d*); 120.8 (*d*); 86.8 (*s*); 52.6 (*s*); 50.8 (*d*); 45.6 (*d*); 43.0 (*t*); 42.9 (*s*); 35.2 (*d*); 29.4 (*q*); 27.0 (*q*); 26.9 (*t*); 26.5 (*t*); 24.1 (*t*); 22.8 (*q*). MS: 414 (3, M^+), 400 (25), 399 (84), 309 (11), 292 (26), 277 (100), 235 (20), 220 (12), 194 (14), 180 (15), 105 (28), 84 (15), 77 (14).

(+)-3-Epitasmanine (= *(3S,4aS,5R,6S,7aR)-1,2,3,4,4a,6,7,7a-Octahydro-2,2,5-trimethylspiro[3,5-ethano-6H-cyclopenta[b]pyridine-6,3′-[3H]indol]-2′(1′H)-one*; (+)-**12**). To a soln. of (−)-**15** (258 mg, 0.622 mmol) in EtOH (10.8 ml; *Fluka, puriss.*) was added a soln. of polyphosphoric acid (3.4 g; *Fluka, purum*; 85% P_2O_5) in EtOH (31 ml) and then H_2O (28 ml) with rapid stirring at r.t. The resulting suspension was warmed gently to obtain a homogeneous mixture which was then heated under reflux for 1 h. The resulting pale yellow soln. was concentrated to ½ of the original volume at *ca.* 100 Torr and then poured onto crushed ice (50 g). The mixture was rendered basic by adding conc. aq. NH_3 soln. (15 ml) and worked up with CH_2Cl_2 (3 × 100 ml) to give crude amorphous

Scheme 8



a) Key numbers in boxes: compounds isolated from *Aristotelia* species.

Table 2. *Best Routes for the Preparation of the Four Possible Spiro-Oxindole Derivatives* (−)-**1**, (+)-**2**, (−)-**11**, *and* (+)-**12**, *Starting from Synthetic Aristoteline* ((+)-**5**)

Target	Route	Steps	Overall yield [%]	*Scheme* (*s*)
Tasmanine ((−)-**1**)	(+)-**5**→(+)**7**→(−)-**1**	2	44	*2*
	(+)-**5**→(+)-**17**→(−)-**1**	2	35	*5*
3-Epitasmanine ((+)-**12**)	(+)-**5**→(−)-**6**→(−)-**15**→(+)-**12**[a])	3	80	*4*
Aristotelone ((+)-**2**)	(+)-**5**→(−)-**6**→(+)-**2**	2	92	*2*
2-Epiaristotelone ((−)-**11**)	(+)-**5**→(+)-**7**→(−)-**11**	2	25	*2*
	(+)-**5**→(+)-**17**→(−)-**11**	2	37	*5*
	(+)-**5**→(−)-**6**→(+)-**2**→(−)-**22**→(−)-**11**	4	23	*6* and *7*

[a]) A simpler and even more efficient route to (+)-**12** consists in treatment of (−)-**6** with BF_3 in hot CH_2Cl_2 [31].

material (195 mg). Crystalization from THF/cyclohexane furnished pure colorless (+)-**12** [9] (140 mg). Chromatography of the mother liquor (silica gel, cyclohexane/THF/Et_3N 20:5:1) gave additional (+)-**12** (24 mg, combined yield, 85%), *(−)-serratoline* [9] ((−)-**6**; 10 mg, 5%) *(+)-aristotelone* [9] ((+)-**2**; 6 mg, 3%), and *(−)-tasmanine* ((−)-**1**; 2 mg, 1%; for data, see below).

(+)-O-Benzoyl-3-episerratoline (= *(3S,4aS,5R,10bS,11aR)-2,3,4,4a,5,10b,11,11a-Octahydro-2,2,5-trimethyl-3,5-ethano-1H-pyrido[3,2-b]carbazol-10b-yl Benzoate*; (+)-**17**). To a soln. of synthetic (+)-aristoteline ((+)-**5**; 97 mg, 0.33 mmol) in $CHCl_3$ (6 ml) was added dibenzoyl peroxide (160 mg) at 25° under Ar with rapid stirring. After 90 min at r.t., there was slowly added a mixture of Et_3N (0.2 ml) and Et_2NH (0.3 ml), and stirring was

continued for 1 h. Workup with H_2O and $CHCl_3$ (2 × 30 ml) furnished a brownish foam (176 mg) which was chromatographed (silica gel, $CHCl_3$/EtOH 25:1): (+)-**17** (69.5 mg, 51%), (−)-**6** [9] (12.4 mg, 12%), and (−)-**18** (15 mg, 11%).

Data of (+)-**17**: M.p. 90–93° (sintering at 89°). $[\alpha]_D = +131.3$ ($c = 1.19$, $CHCl_3$). UV (EtOH): 268 (3.71), 228 (4.35), 224 (4.35). IR ($CHCl_3$): 1729, 1601, 1457, 1451, 1381, 1314, 1270, 1260, 1103, 1093, 1023, 1009. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.98 (*dd*, $J = 8.5, 1.3$, 2 H); 7.57 (*m*, 2 H); 7.44 (*m*, 2 H); 7.33 (*m*, 2 H); 7.12 (*td*, $J = 7.4, 1.0$, 1 H); 3.70 (*dt*, $J = 8.7, 2.7$, 1 H); 3.38 (*dd*, $J = 15.8, 8.6$, 1 H); 2.59 (*td*, $J = 14.2, 5.6$, 1 H); 2.31 (*m*, 1 H); 2.03 (br. *dd*, $J = 14.2, 5.6$, 1 H); 1.96 (*m*, 2 H); 1.85 (*dt*, $J = 13.5, 3.2$, 1 H); 1.84 (br. *s*, 1 H); 1.70 (*tdd*, $J = 14.2, 5.6, 3.8$, 1 H); 1.41 (*s*, 3 H); 1.22 (*s*, 3 H); 1.18 (*dd*, $J = 15.8, 2.4$, 1 H); 1.09 (*s*, 3 H). NOE: 1.41 (3 H–C(20))→7.98 (2 H_o of Ph), 2.31 (H–C(16)), 2.03 (H_{exo}–C(18)), 1.85 (H_{anti}–C(15)), 1.70 (H_{exo}–C(19)). ^{13}C-NMR (100 MHz, $CDCl_3$): 190.8 (*s*); 164.1 (*s*); 154.4 (*s*); 137.7 (*s*); 133.3 (*d*); 129.7 (2 *d*); 129.5 (*d*); 128.5 (2 *d*); 125.8 (*d*); 121.4 (*d*); 120.7 (*d*); 86.9 (*s*); 53.4 (*s*); 48.0 (*d*); 40.4 (*t*); 38.5 (*s*); 37.1 (*d*); 35.2 (*d*); 34.4 (*t*); 29.1 (*q*); 27.1 (*q*); 26.3 (*t*); 26.1 (*q*); 25.1 (*t*); the missing *s* is probably hidden beneath the signal at 129.7. MS: 414 (21, M^+), 399 (77), 309 (50), 294 (41), 293 (63), 292 (53), 291 (40), 279 (35), 277 (54), 237 (41), 236 (29), 235 (41), 211 (25), 182 (39), 181 (38), 180 (39), 122 (57), 105 (100), 77 (54).

Data of (−)-7-(Benzoyloxy)aristoteline (= *2,3,4,4a,5,6,11,11a-Octahydro-2,2,5-trimethyl-3,5-ethano-1*H*-pyrido[3,2-*b*]carbazol-8-yl Benzoate*; (−)-**18**): M.p. 130–132°. $[\alpha]_D = -6.5$ ($c = 0.93$, $CHCl_3$). UV (EtOH): 282 (4.02), 231 (4.81). IR ($CHCl_3$): 3475, 3325 (br.), 1729, 1468, 1451, 1265, 1138, 1078, 1063, 1023. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.24 (*dd*, $J = 8.5, 1.3$, 2 H); 7.81 (br. *s*, 1 H); 7.63 (*tt*, $J = 6.8, 1.3$, 1 H); 7.51 (*tm*, $J = 7.6$, 2 H); 7.44 (*d*, $J = 8.5$, 1 H); 7.16 (*d*, $J = 2.1$, 1 H); 6.90 (*dd*, $J = 8.4, 2.1$, 1 H); 3.63 (*dm*, $J = 5.7$, 1 H); 3.07 (*dd*, $J = 16.4, 5.7$, 1 H); 2.60 (*d*, $J = 16.4$, 1 H); 2.30 (*m*, 1 H); 2.06 (*dddd*, $J = 13.4, 3.2, 3.1, 2.8$, 1 H); 1.97 (*dt*, $J = 13.4, 3.2$, 1 H); 1.92 (*dm*, $J = 14.2$, 1 H); 1.70 (*m*, 1 H); 1.66 (*tdd*, $J = 13.5, 5.8, 3.6$, 1 H); 1.45 (*s*, 3 H); 1.41 (*m*, 1 H); 1.30 (*s*, 3 H); 1.09 (*s*, 3 H). NOE: 2.60 (H_{endo}–C(10))→7.44 (H–C(5)), 3.63 (H–C(11)), 3.07 (H_{exo}–C(10)); 3.07 (H_{exo}–C(10))→7.44 (H–C(5)), 3.63 (H–C(11)), 2.60 (H_{endo}–C(10)), 1.70 (H–C(16)). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.9 (*s*); 146.1 (*s*); 143.4 (*s*); 136.0 (*s*); 133.3 (*d*); 130.2 (2 *d*); 130.1 (*s*); 128.5 (2 *d*); 126.4 (*s*); 118.5 (*d*); 113.3 (*d*); 104.6 (*s*); 103.8 (*d*); 53.3 (*s*); 50.4 (*d*); 39.4 (*d*); 35.9 (*t*); 35.7 (*d*); 33.3 (*s*); 29.2 (*q*); 28.6 (*t*); 27.9 (*t*); 27.6 (*q*); 25.5 (*t*); 25.2 (*q*). MS: 414 (72, M^+), 399 (61), 358 (10), 357 (30), 331 (47), 263 (14), 105 (100), 77 (21).

(−)-2-Epiaristotelone (= *(3*S*,4a*S*,5*R*,6*S*,7a*R*)-1,2,3,4,4a,5,7,7a-Octahydro-2,2,5-trimethylspiro[3,5-ethano-6*H*-cyclopenta[*b*]pyridine-6,2′-[2*H*]indol]-3′(1′*H*)-one*; (−)-**11**). *Method A:* To a soln. of (+)-**17** (24 mg, 0.058 mmol) in EtOH (0.6 ml; *Fluka, puriss.*) was added a soln. of Na (72 mg) in EtOH (0.6 ml). After stirring at 25° under Ar for 10 h, the homogeneous mixture was quenched with crushed ice (5 g) and extracted with $CHCl_3$ (3 × 10 ml). The residue was chromatographed (silica gel, benzene/Et_2O/Et_2NH 8:4:1): (−)-**11** [9] (13.2 mg, 73%).

Method B: A soln. of (+)-**7** (2.1 mg), containing 12% of an unknown impurity, in 4M NaOEt/EtOH (0.5 ml) was kept under Ar for 22 h at 25°. Standard workup. ^{1}H-NMR: 76% of (−)-**11**, 12% of (−)-**1**, and 12% of the unknown impurity that was already present in the starting material.

Base Treatment of (+)-**17**/(−)-**15** 8:5. To 24.6 mg of a mixture containing 61.5% of (+)-**17** and 38.5% of (−)-**15** in EtOH (2 ml; *Fluka, puriss.*) was added NaOEt (56 mg; *Fluka, pract.*) at 25°. After stirring for 6 h at 25° under Ar, the mixture was diluted with H_2O (3 ml) and extracted with $CHCl_3$ (3 × 10 ml). The combined extracts were dried (K_2CO_3) and evaporated: 17.9 mg of (−)-**11**/(−)-**1**/(−)-**6** 50:12:38 (by ^{1}H-NMR (200 MHz, $CDCl_3$)).

(−)-Tasmanine (= *(3*S*,4a*S*,5*R*,6*R*,7a*R*)-1,2,3,4,4a,5,7,7a-Octahydro-2,2,5-trimethylspiro[3,5-ethano-6*H*-cyclopenta[*b*]pyridine-6,3′-[3*H*]indol]-2′(1′*H*)-one*; (−)-**1**). *Method A:* A soln. of (+)-**17** (200 mg, 0.483 mmol) in EtOH (1.7 ml; *Fluka, puriss.*) was added under Ar to a boiling soln. of polyphosphoric acid (3.48 g; *Fluka, purum*; 85% P_2O_5) in H_2O (32.9 ml). After 20 h at reflux, the mixture was cooled to 0° by adding crushed ice (20 g), rendered basic by dropwise addition of conc. aq. NH_3 soln., and worked up with $CHCl_3$: brownish foam (153 mg). Chromatography (silica gel; cyclohexane/THF/Et_3N 100:22:6) furnished 141 mg (94%) of colorless microcrystalline (−)-**1**. Colorless needles after recrystallization from MeOH. M.p. 241–242° for sublimed material ([2]: 250°). $[\alpha]_D = -147$ ($c = 0.46$, $CHCl_3$; [2]: $[\alpha]_D = -132$ ($c = 0.4$, $CHCl_3$); [11b]: $[\alpha]_D = -150$ ($c = 1$, MeOH)). UV (EtOH): 282 (3.31; flat maximum, extending from 280–290), 253 (3.81). IR ($CHCl_3$): 3440, 1703, 1620, 1483, 1470, 1381, 1329, 1264, 1170, 1099 ([2]: IR (nujol); 3441, 1706). ^{1}H-NMR (400 MHz, $CDCl_3$): 8.21 (br. *s*, 1 H); 7.39 (*dm*, $J = 7.5$, 1 H); 7.17 (*ddd*, $J = 7.7, 7.5, 1.2$, 1 H); 6.99 (*ddd*, $J = 7.7, 7.5, 1.1$, 1 H); 6.81 (*ddm*, $J = 7.6, 0.5$, 1 H); 3.76 (*'t'*, $J = 5.7$, 1 H); 3.03 (*ddd*, $J = 13.8, 13.0, 5.7$, 1 H); 2.55 (*m*, 1 H); 2.54 (*dd*, $J = 14.3, 6.5$, 1 H); 2.10 (*dddd*, $J = 13.7, 3.2$, *ca.* 2.5, *ca.* 1.5, 1 H); 1.94 (*m*, 1 H); 1.76 (*dd*, $J = 14.3$, < 1, 1 H); 1.56 (*ddd*, $J = 13.7, 2.5, 2.5$, 1 H); 1.53 (*dddd*, $J = 14, 13.8, 4.9, 4.5$, 1 H); 1.31 (*m*, 1 H); 1.20 (*s*, 3 H); 1.14 (*s*, 3 H); 0.88 (*d*, $J = 0.6$, 3 H); 0.75 (*ddt*, $J = 13.0, 5.4, 1.4$, 1 H); deviation from reported data of natural (−)-**1** [2]: ±0.02 ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): 183.9 (*s*); 141.2 (*s*); 131.6 (*s*); 127.5 (*d*); 126.4 (*d*); 121.5 (*d*); 108.8 (*d*); 62.6 (*s*); 53.6 (*s*); 53.4 (*d*); 48.0 (*s*); 44.4 (*t*); 41.4 (*d*); 36.0 (*d*); 32.2 (*t*); 30.5 (*q*); 27.6 (*q*); 25.9 (*t*); 23.8 (*t*); 19.7 (*q*); deviation from reported data of

natural (−)-**1** [2]: ±1.3 ppm; aliphatic region: ±0.1 ppm. MS: 310 (31, M^+), 295 (100), 178 (11), 174 (35), 173 (19), 164 (17), 146 (18), 84 (38). HR-MS: 310.2077 (M^+, calc. 310.2045).

Method B: see below (*Oxidation of (+)-Aristoteline: Method D*).

Reduction of (+)-Aristotelone ((+)-**2**). To a soln. of pure synthetic (−)-**2** [9] (400 mg, 1.29 mmol) in dioxane (14.8 ml; *Fluka, puriss.*) was added a soln. of $NaBH_4$ (185 mg) in dioxane/H_2O 4:1 (10 ml) under Ar at r.t. After stirring for 29 h, there was added crushed ice (10 g) and the pH of the mixture ajdusted to 3 by adding cold 1N aq. HCl. Then the medium was rendered basic by addition of conc. aq. NH_3 soln. Extraction with $CHCl_3$ (3 × 100 ml) furnished (−)-**20**/(−)-**21** 1:2 (410 mg) which was separated by FC (cyclohexane/THF/Et_3N 20:5:1): 270 mg (67%) of the less polar (−)-**21** and 130 mg (32%) of (−)-**20**.

Data of (3S,3'R,4aS,5R,6R,7aR)-1,1',2,3,3'4,4a,5,7,7a-Decahydro-2,2,5-trimethylspiro[3,5-ethano-6H-cyclopenta[b]pyridine-6,2'-[2H]indol]-3'-ol ((−)-**21**): M.p. 166–167° (normal pressure; subl. under high vacuum; [10]: 160.5–161.5°). $[\alpha]_D = -146.8$ ($c = 1.04$, $CHCl_3$); [10]: $[\alpha]_D = +140$ ($c = 0.41$, $CHCl_3$)). IR ($CHCl_3$): 3585, 3395 (br.), 1610, 1480, 1464, 1385, 1379, 1320, 1260, 1250, 1152, 1099, 1071, 1015, 961, 882. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.28 (*ddd*, $J = 7.3, 0.7, 0.6$, 1 H); 7.12 (*td*, $J = 7.6, 1.3$, 1 H); 6.75 (*td*, $J = 7.4, 1.0$, 1 H); 6.67 (*dm*, $J = 7.8$, 1 H); 4.89 (*s*, 1 H); 3.76 (br. *s*, 1 H); 3.56 (*ddd*, $J = 6.9, 5.8, 1.5$, 1 H); 2.52 (*td*, $J = 13.7, 6.0$, 1 H); 2.07 (*dddd*, $J = 13.5, 3.7, 3.2, 3.1$, 1 H); 1.95 (*dm*, $J = 14.4$, 1 H); 1.87 (*dd*, $J = 15.1, 6.7$, 1 H); 1.86 (*m*, 1 H); 1.80 (*dd*, $J = 15.1, 1.6$, 1 H); 1.73 (*dt*, $J = 13.6, 3.0$, 1 H); 1.67 (*tdd*, $J = 14.0, 6.1, 4.0$, 1 H); 1.60 (*m*, 1 H); 1.40 (br. *s*, 1 H); 1.33 (*quint.*, $J = 3.2$, 1 H); 1.30 (*d*, $J = 0.6$, 3 H); 1.15 (*s*, 3 H); 1.11 (*s*, 3 H). NOE 4.89 (H–C(3))→7.28 (H–C(5)), 2.52 (H_{endo}–C(18), 1.80 (H_{endo}–C(10)); 3.56 (H–C(11))→1.87 (H_{exo}–C(10)), 1.80 (H_{endo}–C(10)), 1.60 (H–C(16)), 1.15 (3 H–C(21)); 2.52 (H_{endo}–C(18))→4.89 (H–C(3)), 1.95 (H_{endo}–C(19)), 1.80 (H_{endo}–C(10)), 1.11 (3 H–C(22)). ^{13}C-NMR (100 MHz, $CDCl_3$): 150.1 (*s*); 130.7 (*s*); 129.9 (*d*); 125.3 (*d*); 119.0 (*d*); 110.9 (*d*); 80.2 (*d*); 79.9 (*s*); 53.0 (*s*); 52.2 (*t*); 52.1 (*d*); 45.3 (*d*); 44.7 (*s*); 36.1 (*d*); 30.3 (*q*); 30.2 (*t*); 27.3 (*q*); 24.9 (*t*); 23.1 (*t*); 21.8 (*q*). MS: 312 (4, M^+), 294 (37), 280 (15), 279 (56), 237 (18), 222 (22), 220 (28), 205 (100), 182 (22), 84 (42).

Data of (3S,3'S,4aS,5R,6R,7aR)-1,1',2,3,3',4,4a,5,7,7a-Decahydro-2,2,5-trimethylspiro[3,5-ethano-6H-cyclopenta[b]pyridine-6,2'-[2H]indol]-3'-ol ((−)-**20**): M.p. 184–187° (normal pressure; subl. under high vacuum; [10]: 160.5–162°). $[\alpha]_D = -0.7$ ($c = 0.49$, $CHCl_3$) ([10]: $[\alpha]_D = -2.9$ ($c = 0.68$, $CHCl_3$)). IR ($CHCl_3$): 3580, 1611, 1483, 1467, 1384, 1366, 1318, 1259, 1150, 1102, 1050, 1013, 1001. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.24 (*dt*, $J = 7.4, 1.4$, 1 H); 7.06 (*tdd*, $J = 7.6, 1.3, 0.6$, 1 H); 6.72 (*td*, $J = 7.4, 0.9$, 1 H); 6.53 (*dm*, $J = 7.8$, 1 H); 5.09 (*s*, 1 H); 3.65 (br. *s*, 1 H); 3.53 (*ddd*, $J = 6.1, 4.8, 1.0$, 1 H); 2.59 (*dd*, $J = 15.0, 1.0$, 1 H); 2.37 (*td*, $J = 13.5, 6.2$, 1 H); 2.07 (*dq*, $J = 12.0, 3.0$, 1 H); 1.96 (*ddt*, $J = 14.1, 9.0, 3.0$, 1 H); 1.74 (*dd*, $J = 15.0, 6.1$, 1 H); 1.66 (*dm*, $J = 12.5$, 1 H); 1.64 (*m*, 1 H); 1.61 (*tdd*, $J = 14.1, 6.2, 4.2$, 1 H); 1.35 (*m*, 1 H); 1.62 (br. *s*, 1 H); 1.27 (*ddd*, $J = 13.5, 6.1, 2.0$, 1 H); 1.18 (*s*, 3 H); 1.11 (*s*, 3 H); 0.99 (*d*, $J = 0.6$, 3 H): NOE: 3.53 (H–C(11))→2.59 (H_{endo}–C(10)), 2.07 (H_{syn}–C(15)), 1.74 (H_{exo}–C(10)), 1.64 (H–C(16)), 1.18 (3 H–C(21)); 5.09 (H–C(3))→7.24 (H–C(5)), 2.37 (H_{endo}–C(18)), 1.35 (H_{exo}–C(18)), 0.99 (3 H–C(20)); 2.37 (H_{endo}–C(18))→5.09 (H–C(3)), 2.59 (H_{endo}–C(10)), 1.35 (H_{exo}–C(18)), 1.11 (3 H–C(22)). ^{13}C-NMR (100 MHz, $CDCl_3$): 148.8 (*s*); 130.0 (*s*); 129.0 (*d*); 124.4 (*d*); 118.3 (*d*), 108.7 (*d*); 81.9 (*s*); 74.1 (*d*); 53.1 (*s*); 51.8 (*d*); 44.8 (*d*); 44.5 (*s*); 43.9 (*t*); 35.6 (*d*); 30.1 (*t*); 29.8 (*q*); 27.5 (*q*); 25.2 (*t*); 23.9 (*t*); 22.1 (*q*). MS: 312 (0.6, M^+), 295 (18), 294 (76), 280 (22), 279 (100), 237 (38), 222 (39), 194 (19), 183 (16), 182 (28), 181 (12), 180 (16), 167 (14).

(−)-Alloaristoteline (= *(3S,4aS,5R,11aR)-2,3,4,4a,5,10,11,11a-Octahydro-2,2,5-trimethyl-2,5-ethano-1H-pyrido[2,3-b]carbazole;* (−)-**22**). *Method A:* see [9].

Method B: In a microsublimation apparatus ('cold finger') was placed (−)-**21** (43 mg, 0.138 mmol). Air was removed thoroughly and replaced by Ar. After heating to 195° (oil bath) for 7 min, the apparatus was cooled to 50° and evacuated (0.002 Torr). The product was sublimed (195°/0.002 Torr) in the same apparatus: pure (−)-**22** (40 mg, 98%). Data: see [9].

Method C: as *Method B*, but with (−)-**20** as starting material. Yield: 98% of (−)-**22**.

Oxidation of (−)-Alloaristoteline ((−)-**22**). To a cold (−40°) soln. of synthetic (−)-**22** (20 mg) in CH_2Cl_2 (4 ml) was added CF_3COOH (0.1 ml; *Fluka, puriss.*). After stirring for 5 min at −40°, a soln. of purified 3-$ClC_6H_4CO_3H$ (16 mg) in CH_2Cl_2 (0.3 ml) was added. After stirring for 30 min at −40° Me_2S (60 µl; *Fluka, puriss.*) was added and the mixture worked up with cold conc. aq. NH_3 soln. and CH_2Cl_2. ^{1}H-NMR: (+)-**2** (52%), **23** (6%), **24** (24%), (−)-**11** (7%), and (−)-**22** (10%). The yellow foam (26 mg) was submitted to prep. TLC (benzene/Et_2O/Et_2NH 8:4:1): 13 mg (62%) of *(+)-aristotelone* [9] ((+)-**2**), 6 mg (28%) of *(−)-2-epiaristotelone* [9] ((−)-**11**), and 1 mg (5%) of starting (−)-**22**.

Oxidation of Synthetic (+)-Aristoteline ((+)-**5**). *Method A:* To a boiling soln. of synthetic (+)-**5** [11e] (55 mg, 0.187 mmol) in petroleum ether (50 ml; boiling range 50–70°, dist. from NaH) was added dibenzoyl peroxide (2 mg) and purified 3-$ClC_6H_4CO_3H$ (33 mg). The mixture was refluxed for 10 min and then cooled to 0°. After addition of sat. aq. K_2CO_3 soln. (12 ml) and 2N aq. NaOH (4 ml), the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The

combined extracts were dried (K_2CO_3) and evaporated. The crude mixture was chromatographed (silica gel; $CHCl_3$/EtOH 100:0.8): 45.5 mg (78%) of *(+)-aristoteline-N^{12}-ol* (= *(3S,4aS,5R,11aR)-2,3,4,4a,5,6,11,11a-octahydro-2,2,5-trimethyl-3,5-ethano-1H-pyrido[3,2-b]carbazol-1-ol*; (+)-**9**). M.p. 135.5° (sintering at 125°). $[\alpha]_D = +10.4$ ($c = 0.6$, $CHCl_3$). IR ($CHCl_3$): 3685, 3480, 1469, 1383, 1298, 1281, 1262, 1149, 1130, 1091, 1016, 1009. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.77 (br. *s*, 1 H); 7.48 (*dm*, $J = 7.5$, 1 H); 7.29 (*dm*, $J = 8.0$, 1 H); 7.10 (*m*, 1 H); 7.06 (*m*, 1 H); 4.55 (br. *s*, 1 H); 3.48 (*m*, 1 H); 3.37 (*dd*, $J = 16.8$, 0.5, 1 H); 2.74 (*dd*, $J = 16.8$, 5.0, 1 H); 2.34 (*m*, 1 H); 2.04 (*dq*, $J = 13.2$, 3.2, 1 H); 1.98 (*m*, 1 H); 1.92 (*dm*, $J = 13.4$, 1 H); 1.81 (*dt*, $J = 13.2$, 2.8, 1 H); 1.65 (*m*, 1 H); 1.56 (*tdd*, $J = 13.5$, 5.5, 3.6, 1 H); 1.53 (*dm*, $J = 13.5$, 1 H); 1.43 (*s*, 3 H); 1.25 (*s*, 3 H); 1.18 (*s*, 3 H). NOE: 4.55 (OH–N(12))→3.48 (H–C(11)), 3.37 (H_{endo}–C(10)), 1.25 (CH_3(22)), 1.18 (CH_3(21)); 3.37 (H_{endo}–C(10))→7.48 (H–C(5)), 4.55 (OH–N(12)), 2.74 (H_{exo}–C(10)); 2.74 (H_{exo}–C(10))→3.48 (H–C(11)), 3.37 (H_{endo}–C(10)), 1.98 (H–C(16)). ^{13}C-NMR (100 MHz, $CDCl_3$): 143.0 (*s*); 136.1 (*s*); 128.1 (*s*); 121.0 (*d*); 119.1 (*d*); 118.1 (*d*); 110.5 (*d*); 104.8 (*s*); 62.6 (*s*); 59.7 (*d*); 42.5 (*d*), 41.4 (*d*); (*d*); 35.9 (*t*); 33.8 (*s*); 26.9 (*t*); 26.5 (*q*); 25.3 (*t*); 24.8 (*q*); 24.2 (*t*); 17.9 (*q*). MS: 310 (100, M^+), 296 (20), 295 (93), 294 (16), 293 (52), 237 (10), 222 (17), 194 (31), 182 (38), 181 (29), 180 (39), 167 (28), 130 (15).

Method B: To a boiling soln. of (+)-**5** (49 mg, 0.166 mmol) in CH_2Cl_2 (5 ml) was added a soln. of 3-$ClC_6H_4CO_3H$ (41 mg) in CH_2Cl_2 (1 ml). The mixture was refluxed for 10 min and then cooled to 25°; then there were added Me_2S (0.2 ml), CH_2Cl_2 (10 ml), and H_2O (10 ml). The org. phase was dried (K_2CO_3) and evaporated: 59 mg of a yellow foam. Chromatography (silica gel; gradient $CHCl_3$/EtOH 100:1→10:1) furnished 22 mg (43%) of (+)-**9**, 15.9 mg (31%) of (−)-**10**, and 9.3 mg (19%) of starting material.

Data of Serratolin-N^{12}-ol (= *(3S,4aS,5R,10bR,11aR)-2,3,4,4a,5,10b,11,11a-Octahydro-2,2,5-trimethyl-3,5-ethano-1H-pyrido[3,2-b]carbazole-1,10b-diol*; (−)-**10**): M.p. 174–175° (dec.). $[\alpha]_D = -45.4$ ($c = 0.88$, $CHCl_3$). IR ($CHCl_3$): 3562, 3425, 1571, 1456, 1383, 1369, 1262, 1150, 1130, 1108, 1092, 1071, 1018. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.53 (*ddd*, $J = 7.7$, 0.9, 0.6, 1 H); 7.42 (*ddd*, $J = 7.3$, 1.2, 0.6, 1 H); 7.32 (*td*, $J = 7.6$, 1.3, 1 H); 7.20 (*td*, $J = 7.4$, 1.0, 1 H); 7.04 (br. *s*, 1 H); 5.69 (br. *s*, 1 H); 3.37 (*q*, $J = 2.9$, 1 H); 3.17 (*dd*, $J = 14.7$, 2.8, 1 H); 2.77 (*td*, $J = 14.2$, 6.3, 1 H); 2.06 (*m*, 2 H); 1.82 (*dt*, $J = 13.5$, 2.9, 1 H); 1.75–1.67 (*m*, 3 H); 1.56 (*d*, $J = 0.4$, 3 H); 1.40 (*ddm*, $J = 14.4$, 5.8, 1 H); 1.24 (*dd*, $J = 14.7$, 2.8, 1 H); 1.22 (*s*, 3 H); 1.21 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 189.6 (*s*); 152.7 (*s*); 140.7 (*s*); 129.3 (*d*); 125.9 (*d*); 122.3 (*d*); 120.6 (*d*); 84.3 (*s*); 62.9 (*s*); 61.6 (*d*); 46.7 (*d*); 41.7 (*s*); 41.0 (*d*); 39.2 (*t*); 28.9 (*t*); 26.5 (*q*); 25.6 (*t*); 24.0 (*t*); 23.4 (*q*); 18.8 (*q*). MS: 326 (2, M^+), 309 (7), 308 (29), 307 (17), 295 (10), 294 (23), 293 (100), 235 (16), 234 (16), 220 (14), 194 (22), 193 (21), 181 (21), 180 (15), 146 (12), 130 (12), 91 (16), 84 (13), 77 (21), 41 (39).

Method C: To a soln. of (+)-**5** (90 mg, 0.3 mmol) in CH_2Cl_2 (20 ml) was added CF_3COOH (0.45 ml) at 25°. After stirring for 4 min, 3-$ClC_6H_4CO_3H$ (87 mg; *Fluka, pract.*; not purified) was added and stirring at 25° continued for 1 h. Following addition of Me_2S (0.1 ml; *Fluka, puriss.*), the mixture was worked up with conc. aq. NH_3 soln. and CH_2Cl_2. Chromatography (silica gel, $CHCl_3$/EtOH/Et_2NH 100:10:0.7) of the crude material furnished 54 mg (57%) of *(−)-serratoline* [9] ((−)-**6**), 21 mg (21%) of (+)-**8** (2:1 mixture of 2 isomers), 9 mg (9%) of (−)-**11** [9], and 3 mg (3%) of (−)-**1**.

Data of 2,3,4,4a,13,13a-Hexahydro-2,2,5-trimethyl-3,5-ethano-1H-pyrido[3,2-d][1]benzoazonine-6,12-(5H,7H)-dione (**8**; 2:1 mixture of isomers): $[\alpha]_D = +32$ ($c = 1.04$, $CHCl_3$). UV (EtOH): 223 (4.32, sh), 319 (3.01). IR ($CHCl_3$): 1684 (sh), 1675, 1609, 1581, 1539, 1488, 1478, 1452, 1387, 1303, 1299, 1091, 1012. ^{1}H-NMR (400 MHz, $CDCl_3$): major component: 10.18 (br. *s*, 1 H); 7.54 (*td*, $J = 7.7$, 1.6, 1 H); 7.45 (*dd*, $J = 7.7$, 1.4, 1 H); 7.40 (*dm*, $J = 7.6$, 1 H); 7.31 (*td*, $J = 7.9$, 1.1, 1 H); 3.90 (*ddd*, $J = 12.0$, 4.3, 1.2, 1 H); 3.05 (*dd*, $J = 12.9$, 4.3, 1 H); 2.80 (*dd*, $J = 12.9$, 11.8, 1 H); 2.59 (*m*, 1 H); 2.04–1.94 (*m*, 2 H); 1.68 (*ddd*, $J = 13.7$, 5.9, 3.7, 1 H); 1.65 (*m*, 2 H); 1.55 (*m*, 1 H); 1.48 (*quint.*, $J = 3.1$, 1 H); 1.40 (*s*, 3 H); 1.33 (*s*, 3 H); 1.18 (*s*, 3 H), minor component: 7.54 (*tm*, $J = 7.5$, 1 H); 7.36 (*dm*, $J = 7.5$, 1 H); 7.33 (*tm*, $J = 7.6$, 1 H); 7.21 (*dm*, $J = 7.9$, 1 H); 6.90 (br. *s*, 1 H); 3.84 (*ddd*, $J = 12.0$, 4.9, 2.3, 1 H); 3.21 (*dd*, $J = 14.9$, 12.0, 1 H); 2.79 (*dd*, $J = 14.5$, 5.7, 1 H); 2.60 (*m*, 1 H); 2.22 (*dd*, $J = 15.1$, 5.0, 1 H); 2.04–1.90 (*m*, 3 H); 1.81 (*m*, 1 H); 1.61 (*m*, 1 H); 1.41 (*s*, 3 H); 1.38 (*m*, 1 H); 1.21 (*s*, 3 H); 1.12 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): major component: 205.1 (*s*); 177.3 (*s*); 137.9 (*s*); 136.2 (*s*); 132.7 (*d*); 128.2 (*d*); 126.6 (*d*); 126.1 (*d*); 54.9 (*s*); 53.4 (*d*); 45.7 (*t*); 44.5 (*s*); 42.6 (*d*); 35.8 (*d*); 32.4 (*t*); 31.0 (*t*); 28.6 (*q*); 28.3 (*q*); 25.7 (*t*); 23.7 (*q*); minor component: 206.8 (*s*); 180.9 (*s*); 141.9 (*s*); 134.8 (*s*); 131.2 (*d*); 130.4 (*d*); 128.1 (*d*); 125.3 (*d*); 54.0 (*d*); 53.1 (*s*); 47.4 (*t*); 43.6 (*s*); 416 (*d*); 35.7 (*d*); 29.1 (*q*); 28.1 (*t*); 27.5 (*q*); 27.1 (*t*); 24.6 (*q*); 23.6 (*t*). MS: 326 (40, M^+), 311 (100), 293 (19), 164 (8), 146 (33).

Method D: To a soln. of (+)-**5** (50 mg, 0.17 mmol) in dry THF (5 ml) was added CF_3COOH (30 µl). After stirring for 5 min at 25°, a soln. of 3-$ClC_6H_4CO_3H$ (38 mg) in THF (1.3 ml) was added. Stirring was continued for 40 min, then ½ of the mixture was worked up with aq. NH_3 soln. and $CHCl_3$. ^{1}H-NMR (200 MHz, $CDCl_3$): (+)-**5**/(+)-**7**/(+)-**8** 37:47:16 (less than 2% of tasmanine (−)-**1** present). Separation by chromatography (silica gel,

$CHCl_3$/EtOH 100:7) furnished 10.5 mg (18%) of the very labile *3-episerratoline* ((+)-**7**), 4.9 mg (8%) of (−)-**1**, 20 mg (32%) of (+)-**8**, 2.5 mg (4%) of (−)-**6**, and 16.8 mg (37%) of starting material.

Data of (3S,4aS,5R,10bS,11aR)-2,3,4,4a,5,10b,11,11a-Octahydro-2,2,5-trimethyl-3,5-ethano-1H-pyrido[3,2-b]carbazol-10b-ol ((+)-**7**): Amorphous foam. $[\alpha]_D = +133$ ($c = 0.22$, $CHCl_3$). IR ($CHCl_3$): 3474, 3300 (br.), 2955, 2925, 1578, 1463, 1456, 1380, 1261. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.48 (*ddd*, $J = 7.6, 0.9, 0.7$, 1 H); 7.32 (*dddd*, $J = 7.6, 7.2, 1.3, 0.7$, 1 H); 7.30 (*dd*, $J = 7.6, 1.3$, 1 H); 7.15 (*ddd*, $J = 7.6, 7.2, 0.9$, 1 H); 3.59 (*ddd*, $J = 8.4, 2.7, 2.1$, 1 H); 2.93 (*dd*, $J = 15.3, 8.4$, 1 H); 2.61 (*q*, $J = 3.1$, 1 H); 2.53 (*td*, $J = 14.1, 5.9$, 1 H); 2.0–1.8 (*m*, 3 H); 1.89 (*dt*, $J = 13.5, 3.2$, 1 H); 1.68 (*tdd*, $J = 14.0, 5.8, 3.8$, 1 H); 1.50 (*d*, $J = 0.5$, 3 H); 1.32 (*m*, 1 H); 1.19 (*s*, 3 H); 1.16 (*dd*, $J = 15.3, 1.9$, 1 H); 1.05 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 195.6 (*s*); 153.8 (*s*); 141.0 (*s*); 129.5 (*d*); 125.8 (*d*); 121.7 (*d*); 120.5 (*d*); 83.0 (*s*); 53.3 (*s*); 48.3 (*d*); 41.4 (*t*); 38.2 (*s*); 36.5 (*d*); 35.2 (*d*); 33.9 (*t*); 29.2 (*q*), 27.3 (*q*); 26.8 (*q*); 26.6 (*t*); 25.4 (*q*). After the NMR soln. (5.3 mg of (+)-**7** in 0.5 ml of $CDCl_3$) had been kept at 25° for a week, it consisted of (+)-**7**/(−)-**1**, 1:5. Prep. TLC (benzene/Et_2O/Et_2NH 8:4:1) furnished 4.2 mg (79%) of pure (−)-**1**.

In a similar experiment, an analogous mixture was allowed to stand at 25° for 92 h. Workup as above. ^{1}H-NMR: (+)-**5**/(+)-**7**/(+)-**8**/(−)-**1**/(−)-**11** 27:18:21:10:24.

Method E: To a soln. of (+)-**5** (70 mg, 0.238 mmol) in THF (4.5 ml) were added CF_3COOH (90 µl) and a soln. of 3-$ClC_6H_4CO_3H$ (70 mg) in THF (1.3 ml) at 25°. The mixture was stirred under Ar for 4 days and then worked up as above. Chromatography of the crude mixture (silica gel, cyclohexane/THF/Et_2O 100:18:5) furnished 26 mg (35%) of *2-epiaristotelone* ((−)-**11**; for data, see [9]), 25 mg (32%) of (+)-**8**, and 18 mg (26%) of starting material.

Method F: To a soln. of (+)-**5** (50 mg, 0.17 mmol) in THF (10.5 ml) were added CF_3COOH (100 µl) and a soln. of 3-$ClC_6H_4CO_3H$ (46 mg) in THF (3.1 ml) at 25°. The mixture was stirred under Ar for 12 min and then worked up as above. The crude material (61 mg of a slightly yellow foam) was dissolved in $CHCl_3$ (1.3 ml) and allowed to stand at 25° in the dark for 12 days. Prep. TLC (benzene/Et_2O/Et_2NH 80:40:10) of the crude product furnished 14.7 mg (29%) of (+)-**5**, 19.1 mg (34%) of (+)-**8**, and 16.3 mg (31%); 44% based on recovered (+)-**5**) of (−)-**1**.

Method G: [9]. To a cold (−40°) soln. of synthetic (+)-**5** (1.517 g, 5.15 mmol) in CH_2Cl_2 (200 ml) was added CF_3COOH (6.5 ml; *Fluka, purum*). After stirring for 5 min at −40° under Ar, a soln. of 3-$ClC_6H_4CO_3H$ (1.160 g, *ca.* 6 mmol) in CH_2Cl_2 (20 ml) was added *via* a syringe. After stirring for 1 h at −40°, Me_2S (0.2 ml; *Fluka, purum*) was added and the cold mixture poured onto conc. aq. NH_3 soln. (30 ml) and H_2O (130 ml). Two extractions with CH_2Cl_2 furnished an amorphous white solid (1.61 g) which consisted of virtually pure (−)-**6** (TLC, ^{1}H- and ^{13}C-NMR evidence [9]). Recrystallization of this material from THF/cyclohexane/Et_3N furnished 1.535 g (96%) of anal. pure, colorless (−)-**6**, identical with natural (−)-serratoline [6] [9].

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