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Synthesis of *Aristotelia*-Type Alkaloids. Part X[1]. Biomimetic Transformation of Synthetic (+)-Aristoteline into (-)-Alloaristoteline.

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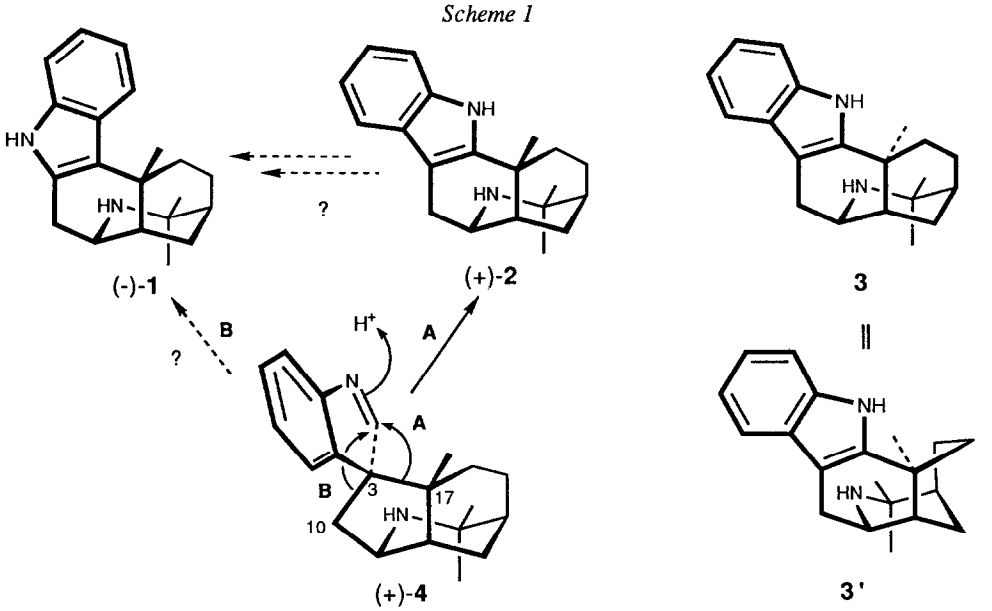
Abstract: Synthetic (+)-aristoteline (**2**) was transformed into (-)-alloaristoteline (**1**) in 4 steps with an overall yield of 86 %. This successful biomimetic interconversion established the previously unknown absolute configuration of this unusual natural product which contains an inverted indole moiety. The first intermediate along this route turned out to be identical with natural (-)-serratoline (**5**), and a rearrangement product thereof corresponded to (+)-aristotelone (**6**), an alkaloid that has been isolated by others from *Aristotelia chilensis* in 1976. Our investigations unambiguously confirmed the tentative structure of this metabolite, which is endowed with a spiro[4.4]nonane-3-oxindole sub-unit.

In 1988 an isomer of aristoteline (**2**) [2] was isolated from *A. australasica* and assigned structure **3** [3] *(Scheme 1)* and named 'epi-11-aristoteline'. As was correctly pointed out by *Saxton* [4], this skeleton would be extremely strained and we subsequently postulated that this metabolite in fact possesses structure **1** and should be renamed 'alloaristoteline' [5]. This hypothesis was corroborated recently through a total synthesis of racemic **1** [1].

Scheme 1

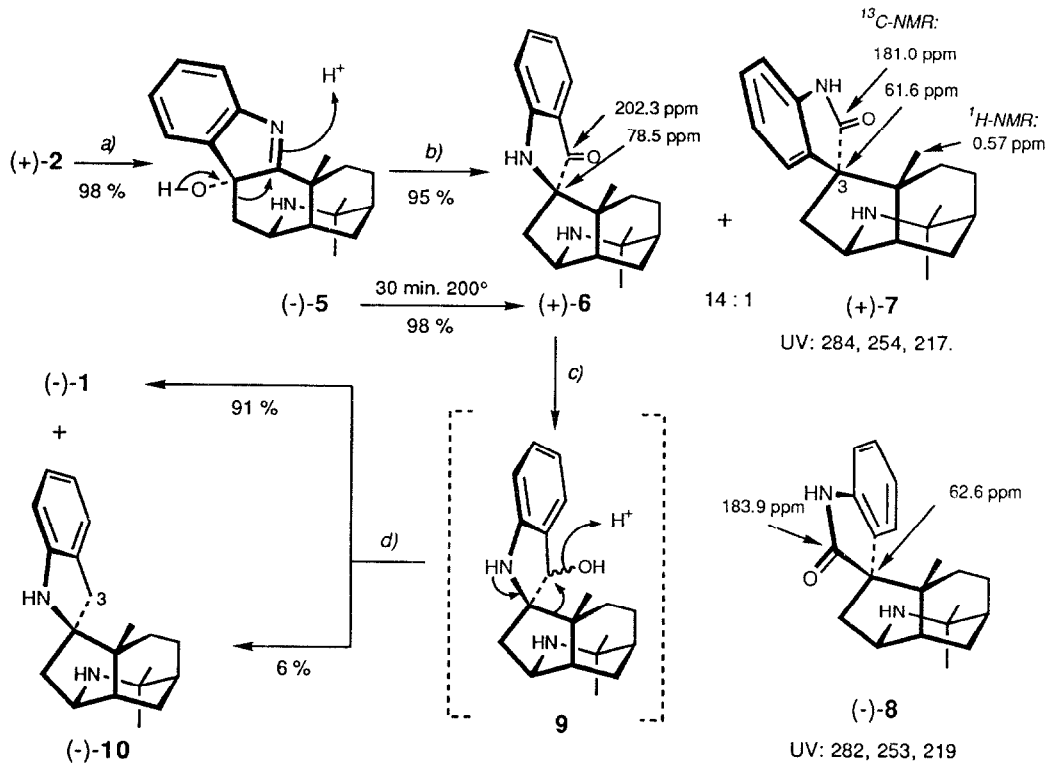


What the biogenetic origin of alloaristoteline (**1**) is concerned, at least two alternatives for the formation of the unprecedented, inverted indole sub-unit, formally derived from **2**-indolyl-2-ethylamine, can be taken into consideration: one possibility would invoke a 1,2-migration of the C(3)-C(10) bond (*Scheme 1*, path **B**) following protonation of (+)-aristoserratenine (**4**), an alkaloid that has been isolated from *A.serrata* [6], and which is believed to be a key intermediate in the biogenetic transformation of tetracyclic precursors into the pentacyclic metabolite aristoteline (**2**) [7]. However, the alternative process **A** should be preferred for electronic reasons [8] and it is not surprising that up to now all *in vitro*-cyclizations of **4**, as well as of the corresponding tetracyclic precursors thereof, invariably furnished only aristoteline (**2**), but no alloaristoteline (**1**) [9]. Whether *Aristotelia* plants contain an enzyme that catalyzes pathway **B** is not known, and at present this question can not easily be addressed experimentally.

As an alternative, the route depicted in *Scheme 2* can be envisaged for a possible biotransformation of (+)-**2** into alloaristoteline (**1**) [10]. Significantly, the first two intermediates in this reaction sequence, namely (-)-serratoline (**5**) [11] and (+)-aristotelone (**6**) [12], have been isolated from *A. serrata* and *A. chilensis*, respectively. To check the feasibility of this scheme and to determine the previously unknown absolute configuration of alloaristoteline (**1**), it was decided to mimic this transformation *in vitro*.

Oxidation of synthetically prepared (+)-aristoteline (**2**) [13] with *m*-chloroperbenzoic acid [14] under acidic conditions [15] proceeded with remarkably high diastereoselectivity and furnished (-)-serratoline (**5**) [16] in nearly quantitative yield.

Scheme 2



Reagents: a) 1. m-chloroperbenzoic acid, CF_3COOH, CH_2Cl_2, 1h at - 40° C; 2. Me_2S.
b) $(H_3PO_4)_n$, EtOH, 24 h reflux. c) $NaBH_4$, dioxane/H_2O. d) HCl, 30 min. 50° C.

Next, the transformation of synthetic (-)-serratoline (**5**) into (+)-aristotelone (**6**) was investigated. This rearrangement step has been effected by *Stoermer* and *Heathcock* [14] under basic conditions in 90% yield. We had decided before to employ the acidic treatment (5% H_2SO_4) described by *Bick* and coworker [11b] who claimed to have obtained a compound in 60% yield, which they tentatively identified as (+)-aristotelone (**6**) [17]. The most salient spectroscopic feature of their preparation was the appearance of signal at 0.57 ppm (*s*, 3H) in the ^{1}H-NMR spectrum, which they assigned to the methyl group C(20). When repeating this experiment we found that under the reported conditions two isomeric compounds are formed, the minor component (5-10% yield) being undoubtedly identical with the product obtained by the Australian group. However, the spectroscopic data of this compound is clearly not consistent with structure **6**, but rather is very reminiscent of the properties reported for (-)-tasmanine (**8**) [7]. Therefore, we assume that the structure of our minor product is represented by formula **7** (3-epi-tasmanine).

On the other hand, the spectral data of the major component, obtained in 89% yield upon treatment of **5** with polyphosphoric acid in EtOH, is identical with the values obtained by *Stoermer* and *Heathcock* [14] and is fully consistent with structure **6**. The critical relative configuration at the spiro center was determined unambiguously through nuclear *Overhauser* experiments (see *Figure*). Since an authentic specimen is lacking, a thorough comparison of our material with natural aristotelone is presently not possible. However, the difference in the melting points of (+)-**6** and (-)-**11** (see below) amounts to *ca.* 50°. The (fortunate!) fact that the reported melting point for natural aristotelone [17] coincides within experimental error with the one of the *higher*-melting isomer (+)-**6** allows the conclusion that the structure of the natural product is indeed represented by this formula.

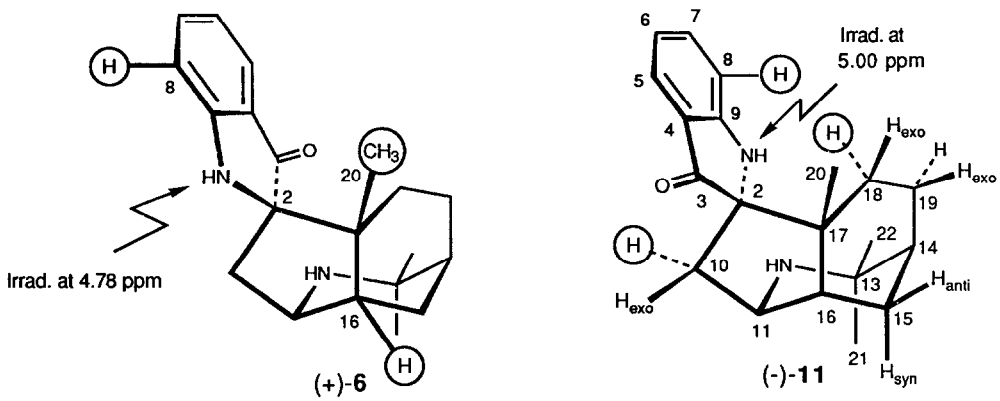
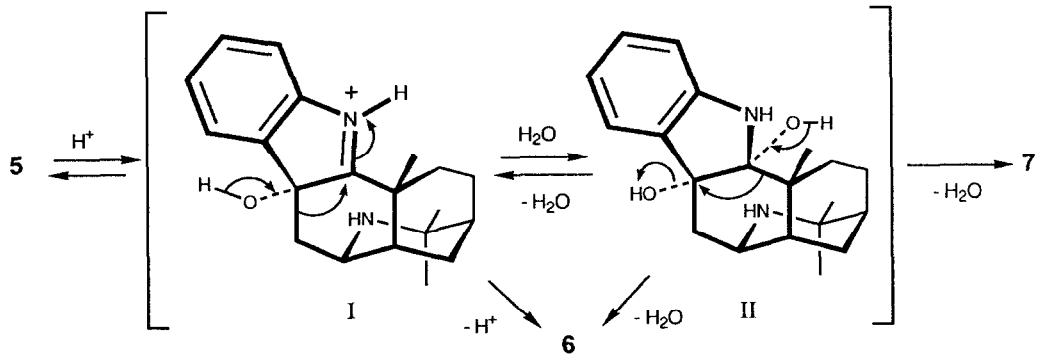


Figure. Nuclear Overhauser *experiments with (+)-aristotelone (6) and (-)-2-epi-aristotelone (11). (The circled hydrogen atoms were detected in difference nOe experiments, when the respective aniline NH was irradiated).*

The formation of 3-epi-tasmanine (**7**) under acidic conditions can be explained as shown in *Scheme 3:* protonated serratoline (**I**) is probably in equilibrium with the hydrated form **II**. The resulting *cis*-diol can then undergo a pinacol type rearrangement to give **7** [18]. The first step in this sequence is rather unfavored, because structural constraints force the cyclohexane ring that undergoes contraction to assume a twist-boat conformation.

The method of choice for preparing (+)-**6** was detected through an investigation of the behaviour of (-)-**5** at it's melting point: it was found that it decomposes quantitatively into aristotelone under normal pressure (Ar) above 190° (TLC- and ^{1}H-NMR evidence). Thus, thermal treatment (30 min. at 200°) of neat (-)-**5**, followed by sublimation under high vacuum, furnished analytically pure (+)-**6** in virtually quantitative yield.

Scheme 3



The remaining steps were straightforward: reduction of aristotelone (**6**) with $NaBH_4$ in aqueous dioxane led to carbinol **9** (mixture of diastereoisomers) which was treated *in situ* with HCl (30 min. at 50° C) to furnish (-)-alloaristoteline (**1**) in 91 % yield. In addition, deoxoaristotelone ((-)-**10**), a side product resulting from hydrogenolysis of intermediate **9**, was isolated in 6 % yield. The spectral data of (-)-**1** was identical in all respects with the one described for the natural product [3], as well as for synthetic (±)-**1** [1]. The only significant difference between synthetic (-)-**1** and natural alloaristoteline concerns the optical rotation of this compound: *Quirion* [19] reported a value of *ca.* 0 (c = 0.4, chlf.), whereas our preparation showed $[\alpha]_D$ = - 35 (c =1, chlf.). The origin of this deviation not clear; possibly the sample isolated from natural sources was contaminated with some strongly dextrorotatory impurity. Interestingly, natural aristolasicone (= 19-oxo-alloaristoteline) [3], the only other *Aristotelia* alkaloid endowed with an inverted indole nucleus [5, 20], also shows a negative optical rotation ($[\alpha]_D$ = - 161 (c = 0.8, chlf.) [19].

Contrary to aristoteline (**2**), alloaristoteline (**1**) is a quite labile compound which decomposes rapidly in chloroform solution. This behaviour came to light when 2D NMR experiments were recorded: after 72 hours measurement time cross peaks corresponding to signals that were not present in the original sample could be detected. TLC- and NMR controls showed that a single new product had been formed which was isolated by chromatography. Since the spectral data of this compound is very similar to the one of (+)-aristotelone (**6**) (see *Table 1 and 2)* and since it is strongly laevorotatory, we believe it to be (-)-2-epi-aristotelone (**11**) *(Scheme 4)*. This structure proposal was corroborated through nOe experiments (see *Figure)*. Presumably, alloaristoteline (**1**) is oxidized by $^3O_2$ to 3-epi-allosarratoline (**12**), which rearranges *in situ* to (-)-**11**.

Scheme 4

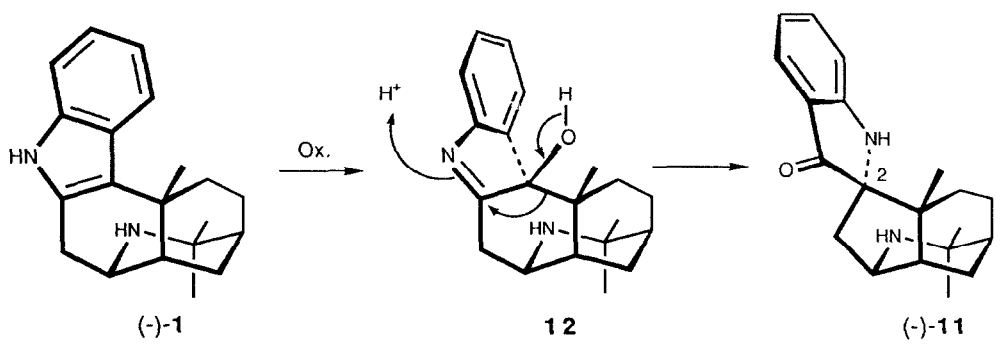


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Table 1. ^{13}*C-NMR values (100 MHz, $CDCl_3$, ppm from TMS, assignments corroborated through* ^{1}*H /*^{13}*C-COSY spectroscopy).*

Nr. \ Cpd.	1	5	6	7	8 a)	10	11
2	129.5	190.2	78.5	181.0	183.9	77.5	78.7
3	119.7	83.9	202.3	61.6	62.6	37.0	206.5
4	126.1	141.1	121.8	136.3	131.6	128.0	120.5
5	120.1	122.2	124.3	124.1	126.4	124.4	124.5
6	118.8	125.9	118.3	121.8	121.5	117.8	117.9
7	120.6	129.5	136.9	127.4	127.5	127.2	136.7
8	110.6	120.5	111.3	108.9	108.8	108.3	111.2
9	136.6	152.6	159.8	140.1	141.1	150.1	160.8
10	30.9	42.9	46.0	43.8	44.4	54.2	45.5
11	50.7	52.5	52.8	54.0	53.4	51.6	52.7
13	53.5	54.2	53.1	53.3	53.6	52.9	53.6
14	35.5	35.6	35.6	35.3	36.0	35.9	35.8
15	28.2	26.3	23.7	24.0	23.8	23.4	23.2
16	40.1	44.0	45.5	44.0	41.4	43.7	41.2
17	33.7	41.5	49.0	49.1	48.0	45.1	46.4
18	36.2	28.1	28.5	30.2	32.2	30.5	31.8
19	25.6	24.3	25.0	25.6	25.9	25.0	25.4
20	26.1	23.6	19.3	20.7	19.7	19.9	19.7
21	27.7	27.5	27.2	27.2	27.6	27.3	27.3
22	29.0	29.2	30.0	29.9	30.5	30.3	30.3

a) Values taken from a synthetic sample of (-)-8 [23], deviation from the reported data of natural (-)-8 at most 0.4 ppm. Some of the original assignments [7] have been revised.

Table 2. ^{1}*H-NMR chemical shift values (400 MHz, $CDCl_3$, ppm from TMS).*

Nr. \ Cpd.	1	5	6	7	8	10	11
5	7.67	7.38	7.55	7.12	7.39	7.04	7.51
6	7.03	7.19	6.76	6.79	6.99	6.63	6.71
7	7.08	7.32	7.40	7.16	7.17	6.97	7.37
8	7.28	7.54	6.77	6.80	6.81	6.49	6.77
10_{exo}	3.19	1.52	2.29	2.41	2.55	2.38	2.47
10_{endo}	2.52	2.57	2.11	2.12	1.76	1.87	1.62
11	3.55	3.60	3.69	3.80	3.76	3.58	3.68
14	1.40	1.55	1.32	1.31	1.31	1.32	1.32
15_{anti}	2.03	2.03	1.66	1.63	1.56	1.66	1.54
15_{syn}	2.07	1.99	2.15	2.18	2.10	2.10	2.03
16	1.62	1.55	1.58	1.99	2.53	1.56	2.36
18_{endo}	2.05	3.02	2.83	2.99	3.03	2.16	2.69
18_{exo}	2.05	1.39	0.91	0.95	0.75	1.21	1.20
19_{endo}	1.88	2.05	1.99	2.07	1.94	1.93	1.95
19_{exo}	1.72	1.79	1.56	1.59	1.53	1.62	1.60
20	1.65	1.57	0.91	0.57	0.88	0.99	0.83
21	1.29	1.35	1.17	1.20	1.20	1.15	1.19
22	1.07	1.29	1.15	1.17	1.14	1.08	1.11

Experimental Section

General. All solvents employed as reaction media were reagent grade *(Fluka, puriss.)* and were further purified and dried as follows: CH_2Cl_2 and $CHCl_3$, filtered through Al_2O_3 *(Woelm*, basic act. I). M.p. (not corrected): *Tottoli* apparatus, scaled evacuated capillaries, unless mentioned otherwise. Optical rotations: *Perkin-Elmer 241*. UV spectra: *Uvikon 860*. IR spectra: *Perkin-Elmer 781*. ^{1}H-NMR spectra (δ [ppm] from TMS, appearant coupling constants *J* [Hz]): *Bruker AMX 400* (400 MHz). ^{13}C NMR spectra (δ [ppm] from TMS, multiplicities as determined from DEPT spectra): *Bruker AMX 400* (100 MHz). ^{1}H / ^{13}C-COSY spectra were recorded on a *Varian Gemini* (200/50 MHz). Mass spectra (m/z [amu] (% base peak)): *VG TRIBID* (EI, 70 eV).

(-)-Serratoline ((-)-5). To a cold (- 40° C) solution of 1.517 g (5.15 mmol) of synthetic (+)-aristoteline (**2**) in 200 ml of CH_2Cl_2 were added 6.5 ml CF_3COOH *(Fluka, purum)*. After stirring for 5 min. at - 40°C under Ar, a solution of 1.160 g (*ca.* 6 mmol) of purified [21] *m*-chloroperbenzoic acid in 20 ml of CH_2Cl_2 was added *via* a syringe. After stiring for 1 h at this temperature, 0.2 ml of dimethylsulfide *(Fluka, purum)* were added and the cold mixture was poured onto 30 ml of conc. aq. NH_3 and 130 ml of H_2O.Two extractions with CH_2Cl_2 furnished 1.61 g of an amorphous white solid, which consisted of virtually pure (-)-**5** (TLC-, ^{1}H- and ^{13}C-NMR evidence). Recrystallization of this material from THF / cyclohexane / Et_3N furnished 1.535 g (4.94 mmol, 96 %) of analytically pure, colorless (-)-**5** that was identical with natural (-)-serratoline [16].

M.p.: 178° (decomposes at the m.p. to (+)-**6**) [Lit.: 157-160° (MeOH) [16]].

$[\alpha]_D$: - 64 (c = 0.91, chlf.) [Lit.: - 68.3 (chlf.) [16]].

UV(EtOH): 261 (3.02), 223 (3.58), 219 (3.69) [Lit.: 263 (3.48), 227 (3.79), (MeOH) [16]].

IR($CHCl_3$): 3480, 3190(br.), 2980. 2960, 2940, 1616, 1605, 1572, 1386, 1261, 1107.

^{1}H-NMR: 7.54(*d, J*=7.6, 1H); 7.38(*d, J*=7.3, 1H); 7.32(*td, J*=7.6, 1.3, 1H); 7.19(*td, J*=7.4, 0.9, 1H); 3.60(*q, J*=2.9, 1H); 3.02(*td, J*=14.3, 6.0 ,1H); 2.57(*dd, J*=14.3, 2.8, 1H); 2.05(*tm, J*=14.1, 1H); 2.03(*dt, J*=13.4, 3, 1 H); 1.99(*dt, J*=13.4, 3, 1H); 1.79(*tdd, J* =14.1, 6.0, 3.9, 1H); 1.57(*s*, 3H); 1.56(*m*, 1H); 1.52(*dd, J*=14.7, 3.0, 1H); 1.39(*dd, J*=14.1, 5.5, 1H); 1.35(*s*, 3H); 1.29(*s*, 3H).

^{13}C-NMR: 190.2*(s)*, 152.6*(s)*, 141.1*(s)*, 129.2*(s)*, 125.9*(d)*, 122.2*(d)*, 120.5*(d)*, 83.9*(s)*, 54.2*(s)*, 52.5*(d)*, 44.0*(d)*, 42.9*(t)*, 41.5*(s)*, 35.6*(d)*, 29.2*(q)*, 28.1*(t)*, 27.5*(q)*, 26.3*(t)*, 24.3*(t)*, 23.6*(q)*.

MS: 310 (25, M^+), 296 (21), 295 (100), 277 (25), 227 (48), 164 (22), 159 (16), 84 (45).

Thermal Treatment of (-)-Serratoline ((-)-5). 101 mg (0.325 mmol) of pure (-)-**5** were heated under Ar in a glass tube for 30 min. (oil bath at 200° C). Then the bath temperature was lowered to 185° and the yellow residue was sublimed under high vacuum to give 99.3 mg (98 %) of analytically pure (+)-aristotelone ((+)-**6**. For data see below.

Acid Treatment of (-)-Serratoline ((-)-5). The above material was dissolved in 30 ml of EtOH and added to a boiling solution of 10.2 g of polyphosphoric acid *(Fluka, purum)* in 300 ml of EtOH. The resulting yellow homogeneous solution was refluxed for 24 h under Ar. Most of the solvent was distilled off under reduced pressure and the residue was diluted with 160 g of crushed ice, rendered basic (pH *ca.*11) through addition of 150 ml of conc. aq. NH_3 and extracted 3 times with 400 ml of CH_2Cl_2. The combined organic layers were dried (K_2CO_3) and evaporated to give 1.61 g of a yellow-green solid, which according to ^{1}H-NMR spectroscopy consisted of a 14:1-mixture of (+)-**6** and (+)-**7**. Column chromatography (cyclohexane / THF / Et_3N 100:18:5) furnished 1.411 g (4.54 mmol, 88%) of (+)-aristotelone ((+)-**6**) and 98 mg (0.29 mmol, 5.6 %) of (+)-3-epi-tasmanine ((+)-7).

Data of (+)-Aristotelone ((+)-6): long yellow needles from THF / cyclohexane / Et_3N.

M.p.: 224.5-225° (normal pressure; subl. under high vacuum) [Lit.: 218-222° (MeOH) [12]].

$[\alpha]_D$: + 264 (c = 1.12, $CHCl_3$).

UV (EtOH): 406 (2.74), 234 (3.55), 225 (3.54).

IR ($CHCl_3$): 3420, 3360 (br.), 1691, 1619, 1483, 1469,1320, 1302, 1100, 1070, 897.

^{1}H-NMR: 7.55(*dddd, J*=7.7, 1.3, 0.7, 0.6, 1H); 7.40(*ddd, J*=8.2, 7.0, 1.3, 1H); 6.77(*dt, J*=8.2, 0.8, 1H); 6.76(*ddd, J*=7.8, 7.1, 0.8, 1H); 4.77(br.*s*, 1H); 3.69(*ddd, J*=7.1, 5.4, 1.5, 1H); 2.83(*ddd, J*=14.7, 14.5, 6.1, 1H); 2.29(*dd, J*=15.3, 7.2, 1H); 2.15(*dq, J*=13.6, 3.2, 1H); 2.11(*dd, J*=15.3, 1.6, 1H); 1.99(*dm, J*=14.5, 1H); 1.66(*dt, J*=13.5, 3.0, 1H); 1.57(*m*, 1H); 1.56(*tdd, J*=14.5, 6.0, 4.0, 1H); 1.32(*dq, J*=4.0, 3.3, 1 H); 1.17(*s*, 3H); 1.15(*s*, 3H); 0.89(*d, J*=0.8, 3H); 0.91(*ddm, J*=14.6, 6.0, 1H).

^{13}C-NMR: 202.3*(s)*, 159.8*(s)*, 136.9*(d)*, 124.3*(d)*, 121.8*(s)*, 118.3*(d)*, 111.3*(d)*, 78.5*(s)*, 53.1*(s)*, 52.8*(d)*, 49.0*(s)*, 46.0*(t)*, 45.5*(d)*, 35.6*(d)*, 30.0*(q)*, 28.5*(t)*, 27.2*(q)*, 25.0*(t)*, 23.7*(t)*, 19.3*(q)*.

MS: 310 (38, M^+), 295 (12), 174 (20), 173 (18), 165 (14), 164 (100), 147 (11), 146 (13), 84 (13).

Identical NMR data has been obtained by *Stoermer* and *Heathcock* for a product which they isolated in 90 % yield upon treatment of synthetic (-)-**5** with hot aq. NaOH, and to which they have independently assigned structure **6** [14].

Data of (+)-3-epi-Tasmanine ((+)-7):

M.p.: 242.5-243° (normal pressure; subl. at *ca.* 150° under high vacuum) [Lit.: 217-218° (MeOH) [11b]].

$[\alpha]_D$: + 105° (c = 1.19, $CHCl_3$) [Lit.: + 41°($CHCl_3$) [11b]; + 63° (c = 0.04, MeOH) [22]].

UV(EtOH): 282 (3.19), 255 (3.77), 208(sh) (4.50).

IR ($CHCl_3$): 3440, 1720(sh), 1716, 1702(sh), 1620, 1485, 1471, 1388, 1324, 1102, 1012.

^{1}H-NMR: 7.18(br.*s*, 1H); 7.16(*ddd*, *J*=7.9, 7.3, 1.2, 1H); 7.12(*dm*, *J*=7.3, 1.2, 0.6, 1H); 6.97(*ddd*, *J*=7.9, 7.6, 1.0, 1H); 6.80(*dm*, *J*=7.8, 1H); 3.80(*m*, 1H); 2.99(*tdm*, *J*=14.4, 5.9, 1H); 2.41(*dd*, *J*=14.9, 7.1, 1H); 2.18(*dq*, *J*=13.5, 3.5, 1H); 2.12(br.*d*, *J*=14.9, 1H), 2.07(*dm*, *J*=14.4, 1H): 1.99(*m*, 1H); 1.63(*dt*, *J*=13.5, 3.5, 1H); 1.59(*tdd*, *J*=14.4, 5.8, 4.5, 1H); 1.31(*m*, 1H); 1.20(*s*, 3H); 1.17(*s*, 3H); 0.95(br.*dd*, *J*=14.4, 5.8, 1H); 0.57(*s*, 3H).

[Lit. (270 MHz): 7.3-6.8(*m*, 4H); 3.8(*m*, 1H); 2.97(*m*, 1H); 2.5-2.25(*m*, 1H); 2.2-1.5(*m* 6H); 1.4-1.2(*m*, 1H); 1.18(*s*, 3H); 1.15(*s*, 3H); 0.57(*s*, 3H) [22]].

^{13}C-NMR: 181.0(*s*), 140.1(*s*), 136.3(*s*), 127.4(*d*), 124.1(*d*), 121.8(*d*), 108.9(*d*), 61.6(*s*), 54.0(*d*), 53.3(*s*), 49.1(*s*), 44.0(*d*), 43.8(*t*), 35.3(*d*), 30.2(*t*), 29.9(*q*), 27.2(*q*), 25.6(*t*), 24.0(*t*), 20.7(*q*).

MS: [Lit.: 310 (50, M^+), 295 (22), 174 (55), 173 (24), 164 (100), 146 (16), 111 (16), 97 (27) [22]].

(-)-Alloaristoteline ((-)-1): To a solution of 220 mg (0.709 mmol) of (+)-aristotelone (6) in 8 ml of dioxane was added a suspension of 114 mg $NaBH_4$ *(Fluka, purum)* in 5 ml dioxane / H_2O 4:1. After stirring at r.t. for 3 h, the same amount of reducing agent was added and stirring was continued for further 4 h. Then an additional amount of 145 mg $NaBH_4$, dissolved in 1 ml of H_2O was added. After a total reaction time of 21 h, 5 ml of conc. HCl were added slowly and the warm mixture was stirred for 5 min. at *ca.* 50°. Standard work-up with CH_2Cl_2 / conc. aq. NH_3 furnished 209 mg of a slightly yellow foam. This crude material was chromatographed (benzene / Et_2O / Et_2NH 80:40:6) to furnish 189.4 mg (0.643 mmol, 91%) of (-)-alloaristoteline ((-)-1) and 12 mg (6%) of (-)-3-desoxoaristotelone ((-)-**10**).

Data of (-)-1:

M.p.: 219.5° (normal pressure; subl. under high vacuum) (after recrystallization from THF / cyclohexane / Et_3N).

$[\alpha]_D$: - 35° (c =1, $CHCl_3$) [Lit.: *ca.* 0° [19]].

The UV-, IR-, ^{1}H-NMR- and ^{13}C-NMR data of this material agrees within experimental error with the one obtained before for racemic (±)-1 [1].

Data of (-)-10:

M.p.: 152-153° (normal pressure; subl. at *ca.* 140° under high vacuum).

$[\alpha]_D$: - 37.5° (c =1, $CHCl_3$).

UV(EtOH): 302 (3.25), 249 (3.85), 205(sh) (4.38).

IR($CHCl_3$): 3455, 1702(sh), 1699(sh), 1693, 1685(sh), 1487, 1470, 1322, 1262, 1149, 1099.

^{1}H-NMR: 7.04(*dm*, *J*=7.2, 1H); 6.97(*tm*, *J*=7.6, 1H); 6.63(*td*, *J*=7.4, 1.0, 1H); 6.49(br.*d*, *J*=7.6, 1H); 3.58 (*ddd*, *J*=6.8, 5.7, 1.1, 1H); 3.11(*d*, *J*=15.9, 1H); 2.82(*d*, *J*=15.8, 1H); 2.38(*dd*, *J*=15.2, 7.2, 1H); 2.16(*td*, *J*=13.7, 5.9, 1H); 2.10(*dq*, *J*=13.4, 3.3, 1H); 1.93(*dm*, *J*=14.2, 1H); 1.87(*dd*, *J*=15.2, 1.0, 1H); 1.66(*dt*, *J*=13.4, 3.0, 1H); 1.62(*m*, 1H); 1.56 (*m*, 1H); 1.32(*quint.*, *J*=3.2, 1H);1.21(*ddt*, *J*=13.3, 6.0, 1.4, 1H); 1.15(*s*, 3H); 1.08(*s*, 3H); 0.99(*d*, *J*=0.7,3H).

^{13}C-NMR: 150.1(*s*), 128.0(*s*), 127.2(*d*), 124.4(*d*), 117.8(*d*), 108.3(*d*), 77.5(*s*), 54.2(*t*), 52.9(*s*), 51.6(*d*), 45.1(*s*), 43.7(*d*), 37.0(*t*), 35.9(*d*), 30.5(*t*), 30.3(*q*), 27.3(*q*), 25.0(*t*), 23.4(*t*), 19.9(*q*).

MS: 296 (21, M^+), 281 (7), 167 (20), 166 (100), 158 (10), 130 (14), 84 (14), 58 (29).

(-)-2-epi-Aristotelone ((-)-11): A solution of 5.3 mg of (-)-1 was kept in 0.6 ml of $CDCl_3$ for 72 h at 25°. After that time, a 2D NMR spectrum showed cross-peaks originating from signals that were not present in the original sample. Chromatography (benzene/ Et_2O/ Et_3N 80:40:10) furnished 2.9 mg (55 %) of starting material ((-)-1) and 1.1 mg (20 %) of (-)-**11**:

M.p.: 177.5-178° (normal pressure; subl. at 140° under high vacuum); yellow crystals.

$[\alpha]_D$: - 183.5° (c = 0.14, $CHCl_3$).

UV(EtOH): 404 (3.09), 333 (2.82), 280 (2.92), 234 (4.00), 225 (4.00).

IR($CHCl_3$): 3455, 1699(sh), 1693, 1620, 1487, 1470, 1322, 1262, 1149, 1099, 1011.

^{1}H-NMR: 7.51(*dddd*, *J*=7.7, 1.4, 0.7, 0.6, 1H); 7.37(*ddd*, *J*=8.2, 7.1, 1.4, 1H); 6.77(*ddd*, *J*=8.2, 0.8, 0.7, 1H); 6.71(*ddd*, *J*=7.7, 7.1, 0.8, 1H); 5.00(br.*s*, 1H); 3.68(*t*, *J*=5.6, 1H); 2.69(*td*, *J*=12.9, 5.5, 1H); 2.47(*dd*, *J*=14.3, 6.2, 1H); 2.36(*m*, 1H); 2.03(*dq*, *J*=13.6, 3.3, 1H); 1.95(*ddq*, *J*=14.1, 6, 2.8, 1H); 1.60(*tdd*, *J*=13.7, 5.7, 4.0, 1H); 1.62(br.*dd*, *J*=13.7, 1.7, 1H); 1.54(*dt*, *J*=13.7, 3.0, 1H); 1.32(*m*, 1H); 1.20(*m*, 1H); 1.19(*s*, 3H); 1.11(*s*, 3H); 0.83(*d*, *J*=0.6, 3H).

^{13}C-NMR: 206.5(*s*), 160.8(*s*), 136.7(*d*), 124.5(*d*), 120.5(*s*), 117.9(*d*), 111.2(*d*), 78.7(*s*), 53.6(*s*), 52.7(*d*), 46.4(*s*), 45.5(*t*), 41.2(*d*), 35.8(*d*), 31.8(*t*), 30.3(*q*), 27.3(*q*), 25.4(*t*), 23.2(*t*), 19.7(*q*).

MS: 310 (80, M^+), 308 (10), 296 (27), 295 (100), 237 (11), 174 (40), 173 (30), 165 (16), 146 (20), 91 (12), 84 (11), 81 (14), 77 (14), 58 (16).

References and Notes

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15. In the absence of trifluoroacetic acid, complex mixtures resulted in which products derived from 3-epi-serratoline dominated [23]. Seemingly, the protonated piperidine nitrogen exerts a strong *syn*-directing force upon the attacking peracid. Such effects were noted first in the case of allylic alcohols:
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16. The authors would like to thank Professor *I.R.C. Bick*, University of Tasmania, Hobart, Australia, for a generous gift of natural (-)-serratoline (**5**).
17. Natural aristotelone, a poorly characterized alkaloid, has been isolated by *Silva* and coworker [12] from *A. chilensis*. IR- and UV-evidence, as well as biogenetic considerations, led them to propose structure **6** for this metabolite.
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