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Synthesis of *Aristotelia*-Type Alkaloids. Part XIV[1]. Total Synthesis of (+)-Aristolone

Markus Dobler and Hans-Jürg Borschberg*

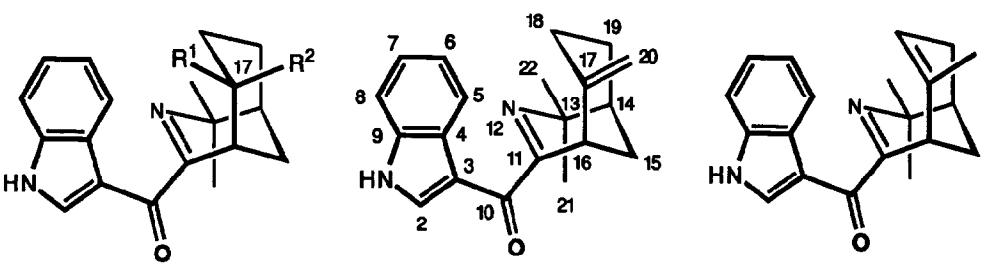
Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule,
ETH Zentrum, Universitätstrasse 16, CH - 8092 Zürich, Switzerland

Abstract: The first total synthesis of the highly functionalized monoterpenoid indole alkaloid (+)-aristolone ((+)-**2**) is described. This investigation uncovered the hitherto unknown relative and absolute configuration of this rare metabolite which had been isolated before by others in ppm-amounts from *Aristotelia australasica*. Dehydration of synthetic (+)-**2** led to a readily separable mixture of the two alkaloids 11,12-didehydro-10-oxomakomakine ((+)-**3**) and 11,12-didehydro-10-oxohobartine ((–)-**4**) which had been isolated in 1988 from *A. chilensis*.

INTRODUCTION

The *Aristotelia* alkaloid family comprises some forty, structurally closely interrelated members that arise biogenetically from tryptamine and an unrearranged monoterpene unit [2]. While several unfunctionalized representatives, such as makomakine ((+)-**5**) [3] and the related endocyclic double-bond isomer (–)-hobartine [4] have been synthesized before [5], we are not aware of any attempts aiming at a preparation of more highly oxidized metabolites like aristolone, for which formula **1** was derived originally [6], nor of the corresponding naturally occuring dehydration products **3** and **4** [7].

Scheme 1



1 $R^1 = CH_3$, $R^2 = OH$
(+)-**2** $R^1 = OH$, $R^2 = CH_3$

(+)-**3**

Biogenetic numbering [8]

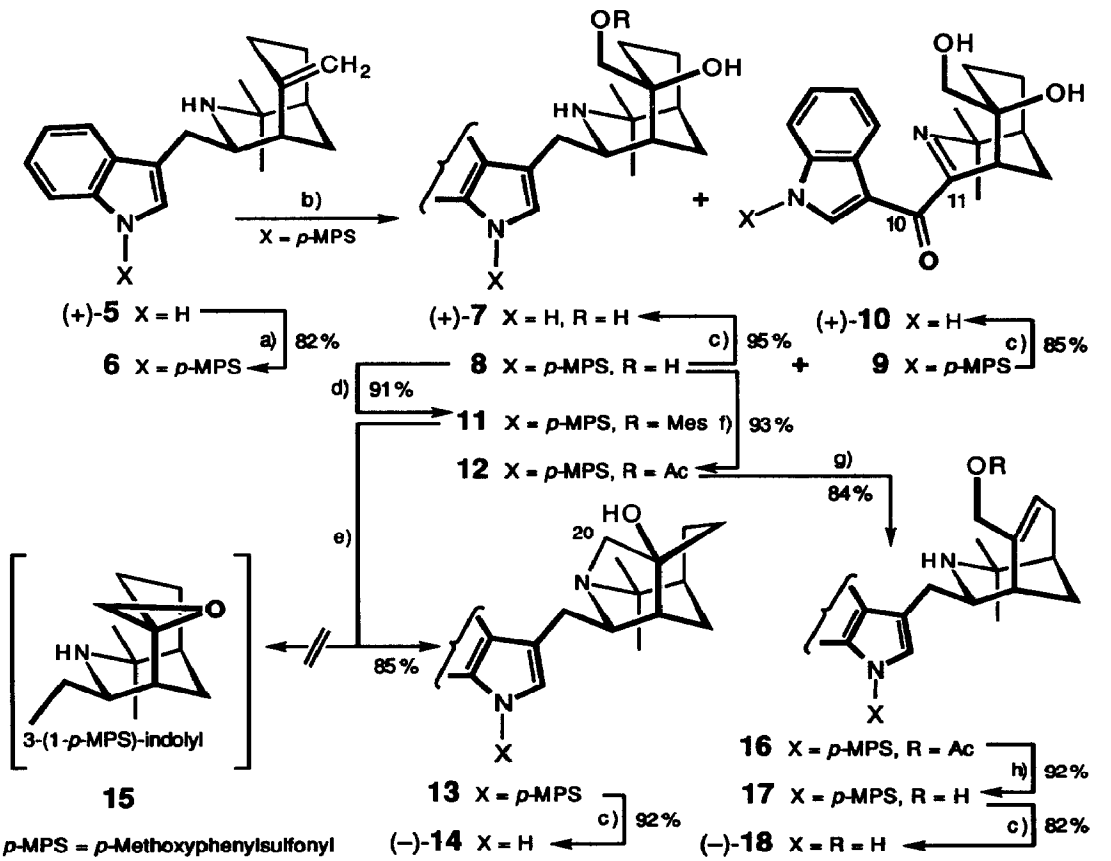
(–)-**4**

Aristolone was isolated in small amounts from *Aristotelia australasica* and characterized as a yellow oil that decomposed too rapidly to permit a determination of its optical rotation; its chiroptical properties were defined by means of a CD spectrum, however [6]. The constitutional formula of this metabolite was derived by means of an analysis of its spectral data, but no conclusive evidence concerning the relative configuration at C(17), assumed to be as shown in formula **1**, was put forward. The related compounds **3** and **4** were isolated from *Aristotelia chilensis* and their structures deduced by spectroscopic means [7]. In the case of **3** this proposal was corroborated through a single-crystal X-ray analysis [7b].

RESULTS AND DISCUSSION

Our initial plan to prepare compound **1** foresaw a reductive oxirane ring opening of an *exo*-17,20-epoxy-makomakine derivative, such as **15** *(Scheme 2)*, followed by oxidation at C(10) and C(11). The required starting alkaloid (+)-**5** was readily prepared in optically pure form starting from (–)-β-pinene by means of a modified version [9] of the original synthetic protocol of *Stevens* and *Kenney* [10]. After protection of the indole moiety the chemoselective oxidation of the exo-methylene double bond was investigated. Whereas several established methods failed to give useful amounts of defined products [11], the catalytic version of the OsO_4 oxidation furnished the expected 17_{exo},20-diol **8** in 73 % yield [12]. The unprotected alkaloid (+)-**7**, which has not yet been detected in natural sources, was prepared for the first time through reduction of **8** with sodium amalgam in methanol [13]. A byproduct formed in the OsO_4 oxidation had the same characteristic chromophore as aristolone and after deprotection this compound was identified as (+)-**10** by means of its highly characteristic spectroscopic data (see *Table* and *Exper. Part)*. When longer reaction times were chosen, **9** eventually became the major product and was formed in up to 50 % yield through an unprecedented pathway.

Scheme 2

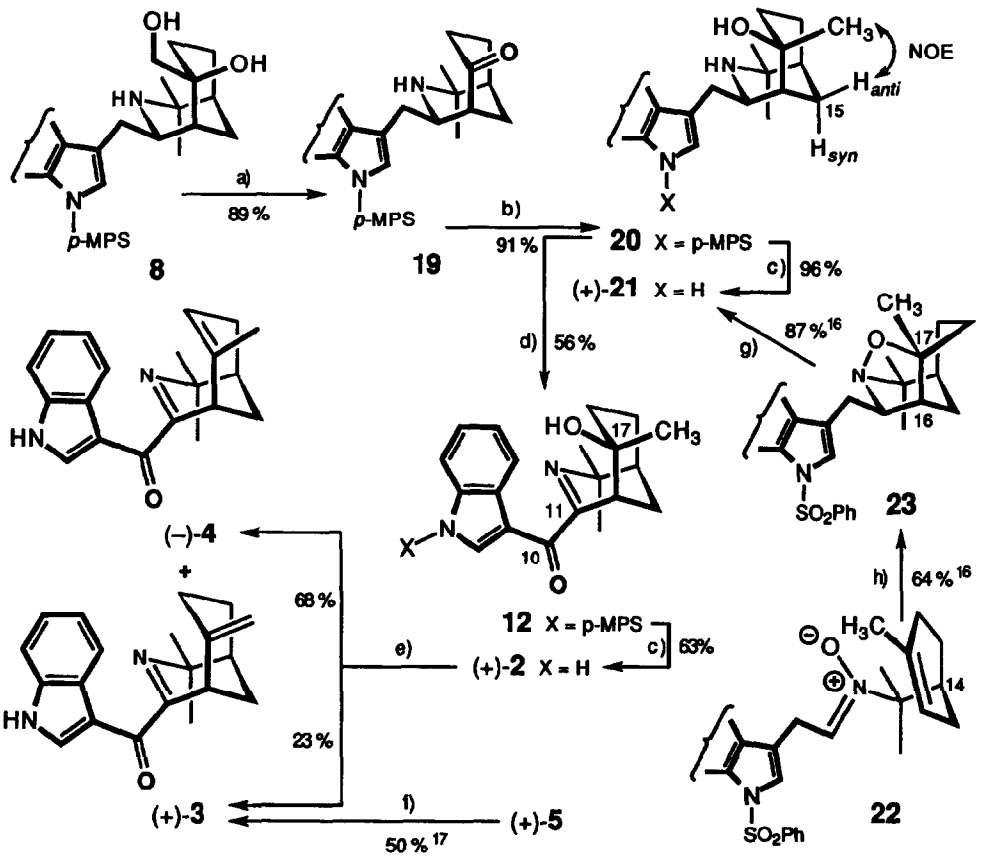


Reagents: a) 1. NaH, THF, 3 h at 0°, 2. *p*-methoxyphenylsulfonyl chloride, 16 h at 25°; b) *N*-methylmorpholine-*N*-oxide, OsO_4, dioxane / H_2O, A: 16 h at 25° → 73 % **8** + 15 % **9**; B: 48 h at 25° → 3 % **8** + 50 % **9**; c) Na / Hg, NaH_2PO_4, MeOH, 2 h 25°; d) mesyl chloride, pyridine, 2 h at 0°; e) pyridine / CH_2Cl_2, 2 h at 0°; f) acetic anhydride, pyridine, 4 h at 50°; g) thionyl chloride, pyridine, 30 min at 0°; h) KOH, EtOH, 24 h at 25°.

Unfortunately, all attempts to reduce the hydroxymethylene unit of **8** and **9** to a methyl group failed. Treatment of the derived mesylate **11** with base, for instance, did not lead to the epoxide **15**, but furnished the novel pentacyclic compound **13** in high yield. On the other hand, the corresponding acetate **12** could be dehydrated in good yield to protected 20-acetoxyhobartine (**16**) which had been prepared before via a different route [14].

As an alternative, we took recourse to the tactical manoeuvres shown in *Scheme 3*. Oxidative cleavage of glycol **8** with sodium periodate furnished the expected norketone **19** in good yield. Addition of methyl lithium proceeded with high diastereoslectivity from the more accessible convex face of the starting material, to produce *endo*-alcohol **20** as the single product [15]. Reductive removal of the protecting group furnished (+)-17,20-dihydro-17$_{endo}$-hydroxymakomakine (**21**) in virtually quantitative yield. The material obtained this way was identical with a compound that had been prepared before by *Gribble* and *Barden* through an intramolecular 1,3-dipolar cycloaddition of the nitrone-olefin **22**, followed by reductive N,O-cleavage of the resulting isoxazolidine ring system in **23** [16]. Obviously, the absolute configuration at C(14) of the precursor **22** dictates the stereochemistry of the newly created chiral centers C(16) and C(17) in **23** and **21** as shown in *Scheme 3*.

Scheme 3



Reagents: a) $NaIO_4$, THF, 1 h at 0°, 2 h at 25°; b) MeLi, Et_2O,10 h at –78°; c) Na/Hg, NaH_2PO_4, MeOH, 2 h at 0°; d) *N*-methylmorpholine-*N*-oxide, OsO_4, 1,4-dioxane/H_2O, 48 h at 25°; e) $SOCl_2$, pyridine/CH_2Cl_2, 2 h at 25°; f) 1. I_2, 1 M aq. $NaHCO_3$/$CHCl_3$, 2 h at 25°, 2. Et_3N, 30 min at 25°; g) 1. Na/Hg, Na_2HPO_4, 2. Zn, AcOH [16]; h) toluene, 5 h reflux [16].

Intermediate **20** could then be oxidized in decent yield to the C-acyl imine **12** with OsO_4/*N*-methylmorpholine-*N*-oxide by taking advantage of the serendipitous observation made while treating **6** with the same reagent *(Scheme 2)*. Reductive removal of the indole protecting group with sodium amalgam in methanol could be achieved chemoselectively, when the reaction was carried out at 0° and furnished (+)-**2** in 63% yield. Unfortunately, natural aristolone is no more available to permit a rigorous identification of our sample, but a comparison of the ^{13}C-NMR spectral data of the two specimen clearly points to their identity (see *Table*). Thus the originally proposed formula **1** *(Scheme 1)* has to be revised to **2**. Since the CD spectra of synthetic and natural (+)-**2** are very similar, the hitherto unknown absolute configuration of (+)-aristolone ((+)-**2**) must be as shown in *Scheme 3*. Treatment of synthetic (+)-**2** with thionyl chloride in pyridine furnished a 1:3-mixture of the two dehydration products (+)-**3** and (–)-**4**. While the minor product (+)-**3** could also be prepared directly from the parent alkaloid makomakine (**5**) through oxidation with iodine [9,17], a similar treatment of the corresponding double bond isomer hobartine failed to give (–)-**4**, but furnished products of a different nature [18].

Table. ^{13}C-NMR Chemical Shifts of Compounds 2-5,7,10, 14, and 21 (δ rel. to TMS in ppm,$CDCl_3$)

Cpd. / Carbon	2	2[a]	3	3[b]	4	10	5	7	14	21
2	136.5	136.9	135.6	135.6	135.8	137.2	122.4	121.8	121.8	122.3
3	114.6	114.7	115.5	115.5	115.4	114.6	113.8	114.2	114.4	114.6
4	127.0	127.2	126.8	126.8	126.7	126.8	127.9	127.4	127.8	127.7
5	122.7	122.8	122.8	122.9	122.8*	123.2	119.3	119.0	119.2	119.2
6	123.7	123.7	123.7	123.7	123.7	124.0	119.1	119.3	119.2	119.2
7	122.9	122.9	122.8	122.8	122.7*	122.8	121.9	122.1	122.5	121.9
8	111.2	111.5	111.1	111.1	111.1	111.3	111.1	111.2	111.1	111.1
9	135.9	136.2	135.8	135.9	135.9*	135.8	136.4	136.5	136.4	136.5
10	190.0	190.2	187.6	187.5	188.6	190.3	31.5	31.7	32.1	32.2
11	167.2	167.3	166.3	166.4	168.0	165.9	54.2	55.9	67.0	57.4
13	59.8	60.0	59.3	59.3	60.5	60.2	53.1	53.6	59.1	53.9
14	35.2	35.5	35.7	35.7[c]	34.3*	34.9	36.8	37.0	36.3	36.0
15	25.8	25.6	29.0	29.1	29.1	25.2*	33.2	29.4	29.0	30.6
16	41.9	42.2	39.6	39.6[c]	34.0*	37.5	43.4	40.8	45.8	42.9
17	72.5	72.7	146.2	146.1	135.5*	73.6	150.5	75.0	79.6	74.6
18	34.1	34.5	30.0	30.0	121.7	30.2	32.1	30.4	29.0	36.2
19	26.5	26.5	29.5	29.4	25.1	26.1*	29.3	24.4	21.4	24.8
20	26.8	26.9	110.0	110.1	23.1	66.6	108.8	70.6	59.7	31.1
21	26.4	26.7	27.0	27.0	27.7	26.3	27.2	26.9	26.8	26.5
22	31.3	31.5	31.2	31.2	31.4	31.6	29.9	29.4	28.0	29.1

* or °: Assignments may be interchanged.

[a] Values for natural (+)-**2** (50 MHz, $CDCl_3$), taken from ref. 6.

[b] Values for natural (+)-**3** (67.9 MHz, $CDCl_3$), taken from ref. 7b.

[c] The original assignments were interchanged in this table to obtain a better correlation with (+)-**2**, for which the critical assignments were corroborated by means of a HETCOR experiment.

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EXPERIMENTAL PART

General. All solvents employed as reaction media were reagent grade *(Fluka, puriss.)* and were stored over molecular sieves (4Å). M.p. (not corrected): *Tottoli* apparatus, sealed evacuated capillaries, unless mentioned otherwise. Optical rotations: *Perkin-Elmer 241* at 25° and 589 nm (Na_D). CD spectra ($\lambda_{max/min}$ [nm], log Δε in brackets): *JASCO J-600*. UV/VIS Spectra (λ_{max} [nm], log ε [dm^3/mol·cm]): *Kontron Uvikon 869*. IR spectra: *Perkin-Elmer 781*, ν_{max} in cm^{-1}. ^{1}H-NMR spectra (δ [ppm] from TMS, apparent coupling constants *J* [Hz]): 300 MHz: *Varian Gemini 300*; 400 MHz: *Bruker AMX 400*; 500 MHz: *Bruker AMX 500*. ^{13}C-NMR spectra (δ [ppm] from TMS, multiplicities as determined from DEPT spectra): 75 MHz: *Varian Gemini 300*; 100 MHz: *Bruker AMX 400*; 125 MHz: *Bruker AMX 500*. NOE: *Bruker WM 300* (300 MHz); irradiated proton → affected signal(s). HETCOR: *Varian Gemini 300*; indication of cross peaks as δ [^{13}C] / δ(s)[^{1}H]. Mass spectra (m/z [amu] (% base peak)): *Hitachi-Perkin-Elmer, VG TRIBRID* (EI at 70 eV, unless stated otherwise; for FAB: 3-nitrobenzyl alcohol as matrix). GC-MS: Gaschromatograph: *HP-5890 Series II*, He constant folw 0.3 m/s; MS: *HP-5971A*, 70 eV.

General procedures. A) Work-up: The mixture was poured onto sat. aq. Na_2CO_3 soln. and extracted with 3 portions of CH_2Cl_2. The combined extracts were dried (K_2CO_3), filtered and evaporated. B) Removal of the *p*-MPS protecting group: To a soln. of 0.08 mmol of the protected indole component in 7 ml of MeOH were added 0.16 mmol of NaH_2PO_4 and 0.64 mmol of 6% sodium amalgam. After stirring at 25° for 4-12 h the organic solvent was decanted from the inorganic material and evaporated. The residue was worked up as above.

(+)-Makomakine ((+)-5). Method: ref.10, modified acc. to ref. 9. To a suspension of 32.33 g (99.41 mmol) of dry $Hg(NO_3)_2$ in 50 ml of CH_2Cl_2 which was stirred at - 45° were added a soln. of 11.83 g (75.74 mmol) of 3-indolylacetonitrile (*Fluka, pract.*) in 5 ml of CH_2Cl_2 and then 12.6 g (92.5 mmol) of (–)-β-pinene (*Fluka, purum*). The resulting orange mixture was stirred at - 45° for 30 min and then for 5 h at 0°. The suspension was cooled to -20° and treated with a mixture of 63 ml 1 N aq. NaOH and 190 ml of MeOH. At the same temperature was carefully added a soln. of 7.5 g (197 mmol) of $NaBH_4$ in 63 ml of 1 N aq. NaOH and 190 ml of MeOH. After stirring for 30 min at 0°, 18 % aq. HCl was slowly added until the gas evolution had stopped. Work-up, followed by chromatography (silica gel; cyclohexane/THF/Et_3N 100:10:1) and recrystallization from MeOH furnished 7.6 g (34 %) of (+)-5 as colorless crystals.

M.p.: 104-105° (MeOH) Lit.: 106-106.5° [10] $C_{20}H_{26}N_2$ (294.44)

$[\alpha]_D$: + 145.4 (c = 0.92, $CHCl_3$). Lit.: + 142.5 (c = 2.7, $CHCl_3$)

IR (KBr): 3080, 1638, 1507, 1430, 1421, 884, 875, 755.

^{1}H-NMR: (400 MHz, $CDCl_3$) 7.95(br. *s*, 1H); 7.63(*dm*, *J*= 7.9, 1H); 7.34(*dt*, *J*= 8.1, 0.9, 1H); 7.18(*ddd*, *J*= 8.1, 7.0, 1.2, 1H); 7.10(*ddd*, *J*= 7.9, 7.0, 0.9, 1H); 7.00(*d*, *J*= 2.3, 1H); 4.77(*t*, *J*= 2.5, 1H); 4.58(*t*, *J*= 2.5, 1H); 3.49(*ddd*, *J*= 7.8, 5.9, 2.7, 1H); 3.08(*dddt*, *J*= 14.3, 13.4, 6.5, 2.5, 1H); 2.76(*ddd*, *J*= 14.2, 5.9, 0.8, 1H); 2.62(*ddd*, *J*= 14.2, 7.8, 0.7, 1H); 2.27(*m*, 1H); 2.18(br. *dd*, *J*= 14.3, 6.1, 1H); 2.12(*dt*, *J*= 12.7, 3.0, 1H); 2.07(*m*, 1H); 1.59(*dt*, *J* = 12.7, 3.1, 1H); 1.49(*tdd* , *J*= 13.4, 6.1, 4.1, 1H); 1.40(*m*, 1H); 1.14(*s*, 3H); 1.10(*s*, 3H).

^{13}C-NMR: (100 MHz, $CDCl_3$) 150.5 *(s)*, 136.4 *(s)*, 127.9 *(s)*, 122.4 *(d)*, 121.9 *(d)*, 119.3 *(d)*, 119.1 *(d)*, 113.8 *(s)*, 111.1 *(d)*, 108.8 *(t)*, 54.2 *(d)*, 53.1 *(s)*, 43.4 *(d)*, 36.8 *(d)*, 33.2 *(t)*, 32.1 *(t)*, 31.5 *(t)*, 29.9 *(q)*, 29.3 *(t)*, 27.2 *(q)*.

HETCOR: 122.4 / 7.00; 121.9 / 7.18; 119.3 / 7.63; 119.1/ 7.10; 111.1/ 7.34; 108.8 / 4.77 and 4.58; 54.2 /3.49; 43.4/ 2.27; 36.8/1.40; 33.2/2.12 and 1.59; 32.1/3.08 and 2.18; 31.5/2.76 and 2.62; 29.9/1.10; 29.3/2.07 and 1.49; 27.2/1.14.

MS (EI): 294 (7, M^+), 279 (4), 199 (2), 164 (100), 130 (30).

Oxidation of N(1)-p-MPS-makomakine (6). To a suspension of 10 g (250 mmol) NaH in 50 ml of THF was added a soln. of 6.48 g (22 mmol) of (+)-5 in 80 ml of THF at 0° under Ar. After stirring for 2 h a soln. of *p*-methoxybenzenesulfonyl chloride (*Fluka, pract.*, recr. from Et_2O) in 50 ml of THF was added and stirring continued at 25° for 16 h. To the resulting buff suspension were added 10 ml of H_2O and the mixture was worked up as usual after the hydrogen evolution had ceased. Chromatography (silica gel; $CHCl_3$/MeOH, gradient from 10:1 to 1:1) gave 8.37 g (82 %) of **6** as a buff foam. To a soln. of 1.76 g (13 mmol) of *N*-methylmorpholine-*N*-oxide monohydrate (*Fluka, purum*) and 50 mg of OsO_4 (0.2 mmol) *(Fluka, puriss.)* in 200 ml of 1,4-dioxane/H_2O 1:1 was added a soln. of 5.20 g (11.4 mmol) of **6** in 100 ml of 1,4-dioxane at 25°. After stirring for 12 h in the dark the black suspension was treated with a soln. of 4 g Na_2SO_3 in 150 ml of H_2O. After stirring for 30 min at 25° the mixture was filtered through Celite® and worked up as usual. Chromatography (silica gel; hexane/EtOAc 3:1) furnished 4.1 g (8.2 mmol, 72 %) of **8** and 0.23 g (4 %) of **9**. Standard deprotection of 40 mg (0.08 mmol) of **8** gave 25 mg (95 %) of (+)-7 as colorless crystals, first prepared in a slightly different fashion by *M. Juch* in our laboratory [19].

M.p.: 50-53° (CH_2Cl_2) $C_{20}H_{28}N_2O_2$ (328.46)

$[\alpha]_D$: + 54.7 (c = 1.1, MeOH).

UV (MeOH): 282 (3.85), 221 (4.69).

IR (KBr): 3412, 3053, 2952, 2921, 1614, 1453, 1430, 1378, 1355, 1317, 1255, 1233, 1183, 1156, 1090, 1025, 906, 737.

^{1}H-NMR: (400 MHz, $CDCl_3$) 8.06(br. *s*, 1H); 7.61(*dm*, *J*= 8.0, 1H); 7.35(*dt*, *J*= 8.1, 0.9, 1H); 7.19(*ddd*, *J*= 8.1, 7.1, 1.1, 1H); 7.11(*ddd*, *J*= 8.0, 7.1, 1.0, 1H); 7.04(*d*, *J*= 2.2, 1H); 3.77(*d*, *J*= 10.9, 1H); 3.66(*d*, *J*= 10.9, 1H); 3.58(*ddd*, *J*= 10.1, 3.6, 2.1, 1H); 3.07(*ddd*, *J*= 14.3, 3.6, 0.9, 1H); 2.81(*dd*, *J*= 14.3, 10.1, 1H); 2.44(*td*, *J*= 13.7, 5.2, 1H); 2.27(*m*, 1H); 2.20(*m*, 1H); 1.92-1.82(*m*, 3H); 1.73(*tdd*, *J*= 13.9, 5.3, 4.1, 1H); 1.47(*dd*, *J*= 13.5, 5.0, 1H); 1.37(*quint.*, *J*= 3.0, 1H); 1.06(*s*, 3H); 1.02(*s*, 3H).

^{13}C-NMR: (100 MHz, $CDCl_3$) 136.5 *(s)*, 127.4 *(s)*, 122.1 *(d)*, 121.8 *(d)*, 119.3 *(d)*, 119.0 *(d)*, 114.2 *(s)*, 111.2 *(d)*, 75.0 *(s)*, 70.6 *(t)*, 55.9 *(d)*, 53.6 *(s)*, 40.8 *(d)*, 37.0 *(d)*, 31.7 *(t)*, 30.4 *(t)*, 29.42 *(t)*, 29.38 *(q)*, 26.9 *(q)*, 24.4 *(t)*.

HETCOR: 122.1/ 7.19; 121.8 / 7.04; 119.3 / 7.11; 119.0 / 7.61; 111.2 / 7.35; 70.6 / 3.77 and 3.66; 55.9 / 3.58; 40.8 /1.85; 37.0 / 1.37; 31.7 / 3.07 and 2.81; 30.4 / 2.44 and 1.47; 29.42 / 2.27 and 1.88; 29.38 / 1.06; 26.9 / 1.02; 24.4 / 1.88 and 1.73.

MS (FAB): 329 (100, M^++1), 311 (50), 198 (91), 159 (31), 154 (27), 136 (20), 130 (41), 77 (13).

Standard deprotection of 100 mg (0.2 mmol) of **9** gave 56.7 mg (85 %) of (+)-**10** as colorless crystals.

M.p.: 97-98° (Et_2O) $C_{20}H_{24}N_2O_3$ (340.43)

$[\alpha]_D$: + 140.3 (c = 0.5, $CHCl_3$).

UV (EtOH): 313 (3.84), 266 (3.86), 255 (3.86), 209 (4.40)

IR ($CHCl_3$): 3450, 3250, 2921, 1601, 1579, 1513, 1419, 1100, 1043, 908, 887.

^{1}H-NMR: (400 MHz, $CDCl_3$) 8.83(br. *s*, 1H); 8.41(*dm*, *J*= 7.9, 1H); 7.39(*dm*, *J*= 7.6, 1H); 7.31(*ddd*, *J*= 7.6, 7.1, 1.4, 1H); 7.27(*ddd*, *J*= 7.9, 7.1, 1.5, 1H); 7.04(*d*, *J*= 2.2, 1H); 5.70(*s*, 1H); 3.80(br. *d*, *J*= 11.0, 1H); 3.66(br. *d*, *J*= 11.0, 1H); 3.15 (*m*, 1H); 2.55(*s*, 1H); 1.96-1.89(*m*, 2H); 1.79(*dq*, *J*= 10.5, 2.1, 1H); 1.78(*m*, 1H); 1.73(*dm*, *J*= 13.2, 1H); 1.52(*tt*, *J*= 14.5, 4.2, 1H); 1.45(*s*, 3H); 1.38(*s*, 3H); 1.35(*td*, *J*= 14.2, 4.8, 1H).

^{13}C-NMR: (100 MHz, $CDCl_3$) 190.3 *(s)*, 165.9 *(s)*, 137.2 *(d)*, 135.8 *(s)*, 126.8 *(s)*, 124.0 *(d)*, 123.2 *(d)*, 122.8 *(d)*, 114.6 *(s)*, 111.3 *(d)*, 73.6 *(s)*, 66.6 *(t)*, 60.2 *(s)*, 37.5 *(d)*, 34.9 *(d)*, 31.6 *(q)*, 30.2 *(t)*, 26.3 *(q)*, 26.1 *(t)*, 25.2 *(t)*.

MS (EI): 340 (6, M^+), 325 (5), 158 (11), 144 (100), 116 (41), 77 (11), 55 (28).

(–)-14.To a soln. of 100 mg (0.2 mmol) of **8** in 25 ml of CH_2Cl_2 were added 1 ml of pyridine and 23 µl (0.3 mmol) of mesyl chloride at 0°. After stirring for 5 h at 25° under Ar the mixture was worked up and chromatographed (silica gel; EtOAc) to furnish 105.3 mg (91 %) of **11** as yellowish crystals (m.p. 69-70°).

To a soln. of 50 mg (0.087 mmol) of **11** in 10 ml of CH_2Cl_2 were added 0.5 ml of Et_3N at 25°. Stirring for 12 h, followed by standard work-up resulted in 35.5 mg (85 %) of pure **13**. Standard deprotection furnished (–)-**14** in 92 % yield.

M.p.: 90-92° (CH_2Cl_2) $C_{20}H_{26}N_2O$ (310.43)

$[\alpha]_D$: – 43.5 (c = 2.2, MeOH).

UV (MeOH): 281 (3.50), 221 (4.36).

IR (KBr): 3410, 3240, 2922, 1615, 1470, 1452, 1385, 1340, 1309, 1285, 1253, 1231, 1207, 1091, 977, 907, 808, 738.

^{1}H-NMR: (400 MHz, $CDCl_3$) 8.30(br. *s*, 1H); 7.70(*dm*, *J*= 7.9, 1H); 7.33(*dm*, *J*= 8.0, 1H); 7.17(*ddd*, *J*= 8.1, 7.1, 1.2, 1H); 7.11(*ddd*, *J*= 8.0, 7.1, 1.1, 1H); 7.02(*d*, *J*= 2.0, 1H); 3.65(*ddd*, *J*= 10.7, 3.6, 2.3, 1H); 3.30(*dd*, *J*= 13.4, 1.5, 1H); 3.24(*dd*, *J*= 14.0, 10.7, 1H); 3.18(*dm*, *J*= 13.0, 1H); 2.90(*dd*, *J*= 14.0, 3.9, 1H); 1.96(*d*, *J*= 5.3, 1H); 1.83(*dd*, *J*= 6.5, 3.0, 1H); 1.81-1.68(m, 3H); 1.56(*dd*, *J*= 5.6, 1.8, 1H); 1.52(*dd*, *J*= 7.5, 3.3, 1H); 1.40(*ddd*, *J*= 8.3, 4.0, 1.7, 1H); 1.32(*s*, 3H); 1.18(*s*, 3H).

^{13}C-NMR: (100 MHz, $CDCl_3$) 136.4 *(s)*, 127.8 *(s)*, 122.5 *(d)*, 121.8 *(d)*, 119.20 *(d)*, 119.16 *(d)*, 114.4 *(s)*, 111.1 *(d)*, 79.6 *(s)*, 67.0 *(d)*, 59.7 *(t)*, 59.1 *(s)*, 45.8 *(d)*, 36.3 *(d)*, 32.1 *(t)*, 29.1 *(t)*, 29.0 *(t)*, 28.0 *(q)*, 26.8 *(q)*, 21.4 *(t)*.

MS (FAB): 311 (100, M^++1), 293 (6), 180 (8), 130 (13).

16.To a soln. of 150 mg (0.3 mmol) of **8** in 20 ml of pyridine were added 0.3 ml of acetic anhydride at 25°. After stirring for 8 h at 25° under Ar the mixture was worked up to yield 151 mg (93 %) of **12** as buff crystals (m.p. 50-53°).

To a soln. of 20 mg (0.037 mmol) of **12** in 2 ml of CH_2Cl_2 were added 15 µl of pyridine and 5.4 µl (0.3 mmol) of thionyl chloride at 0°. After stirring at 0° for 30 min, the deep yellow mixture was worked up and chromatographed (silica gel; EtOAc) to give 15.8 mg (82 %) of **16** as a white foam. This material was identical with compound **21** in ref. 14.

(+)-21.To a soln. of 200 mg (0.4 mmol) of **8** in 8 ml of THF was slowly added a soln. of 88 mg (0.41 mmol) $NaIO_4$ in 8 ml of H_2O. After stirring for 12 h at 25° the turbid mixture was filtered and the filtrate evaporated. Standard work-up, followed by chromatography (silica gel; hexane/EtOAc 2:1) furnished 166 mg (89 %) of **19** as colorless crystals (m.p. 98-99°).

A soln. of 460 mg (0.99 mmol) of **19** in 20 ml of Et_2O was cooled to -78° under Ar. At this temperature 0.94 ml of a 1.6 M MeLi soln. in Et_2O were added via a syringe. After stirring for 2 h at -78° the cooling bath was removed and the mixture allowed to reach

25°. Addition of 2 ml of satd. aq. NH_4Cl soln., followed by standard work-up and chromatography (silica gel; MeOH/EtOAc 1:1) furnished 435 mg (91 %) of **20** as colorless crystals (m.p. 67-68°).

Standard deprotection of 40 mg (0.083 mmol) of **20** gave 24.9 mg (96 %) of (+)-**21** as colorless crystals.

M.p.: 133-134° (Et_2O) $C_{20}H_{28}N_2O$ (312.46)

$[\alpha]_D$: + 65 (c = 0.85, $CHCl_3$).

IR ($CHCl_3$): 3600, 3480, 2981, 1455, 1418, 1382, 1339, 1261, 1103, 1080, 1012, 976, 908.

^{1}H-NMR: (400 MHz, $CDCl_3$) 8.07(br. *s*, 1H); 7.66(*dm*, *J*= 7.4, 1H); 7.38(*dt*, *J*= 8.1, 0.9, 1H); 7.20(*ddd*, *J*= 8.1, 7.1, 1.1, 1H); 7.12(*ddd*, *J*= 8.1, 7.1, 1.1, 1H); 7.09(*d*, *J*= 2.3, 1H); 3.58(*ddd*, *J*= 9.0, 5.5, 1.9, 1H); 3.29(*ddd*, *J*= 14.5, 5.5, 0.8, 1H); 3.21 (*ddd*, *J*= 14.5, 9.1, 0.5, 1H); 2.41(*td J*= 11.5, 3.6 1H); 2.01(*m*, 1H); 1.89(*dq*, *J*= 12.8, 2.5, 1H); 1.72(*m*, 1H); 1.69(*dt*, *J*= 12.9, 3.4, 1H); 1.58-1.48(*m*, 2H); 1.37 (*m*, 1H); 1.33(*s*, 3H); 1.11(*s*, 3H); 1.10(*s*, 3H).

^{13}C-NMR: (100 MHz, $CDCl_3$) 136.5 *(s)*, 127.7 *(s)*, 122.3 *(d)*, 121.9 *(d)*, 119.2 (2x*d*), 114.6 *(s)*, 111.1 *(d)*, 74.6 *(s)*, 57.4 *(d)*, 53.9 *(s)*, 42.9 *(d)*, 36.2 *(t)*, 36.0 *(d)*, 32.2 *(t)*, 31.1 *(q)*, 30.6 *(t)*, 29.1 *(q)*, 26.5 *(q)*, 24.8 *(t)*.

HETCOR: 122.3/7.09; 121.9/7.20; 119.2/7.66 and 7.12; 111.1/7.38; 57.4/3.58; 42.9/1.72; 36.2/2.41 and 1.51; 36.0/1.37; 32.2/3.29 and 3.21; 31.1/1.33; 30.6/1.89 and 1.69; 29.1/1.11; 26.5/1.10; 24.8/2.01 and 1.52.

MS (EI): 297 (3, M^+–15), 182 (100), 164 (21), 130 (36), 56 (35), 43 (12).

(+)-Aristolone ((+)-2). To a soln. of 62 mg (0.46 mmol) of *N*-methylmorpholine-*N*-oxide monohydrate (*Fluka, purum*) and 2 mg of OsO_4 (*Fluka, puriss.*) in 10 ml of 1,4-dioxane/H_2O 1:1 was added a soln. of 200 mg (0.41 mmol) of **6** in 3 ml of 1,4-dioxane at 25°. After stirring for 72 h in the dark the black suspension was treated with a soln. of 200 mg Na_2SO_3 in 5 ml of H_2O. After stirring for 30 min at 25° the mixture was filtered through Celite® and worked up as usual. Chromatography (silica gel; hexane/EtOAc 2:1) furnished 114.8 mg (56 %) of **12** as a buff foam. Standard deprotection at 0° of 100 mg (0.2 mmol) of **12** gave 41.3 mg (63 %) of (+)-**2** as a colorless oil that solidifies to a waxy compound in the refrigerator.

M.p.: Oil Lit: yellow oil [6]. $C_{20}H_{24}N_2O_2$ (324.44)

$[\alpha]_D$: + 36.9 (c = 0.44, $CHCl_3$).

CD (EtOH): 339 (–1.66), 319 (0), 304 (+1.37), 290 (0), 275 (–1.93), 254 (0), 247 (+1.54) [c = $2.6 \cdot 10^{-5}$ g/ml, d = 0.5 cm]. Lit.: 340 (–1.58), 276 (–2.97) [6].

UV (EtOH): 314 (3.85), 268 (3.87), 254 (3.87), 210 (4.30). Lit.: 313 (3.83), 267 (3.85), 254 (3.84), 210 (4.30) [6].

IR ($CHCl_3$): 3455, 1610, 1579, 1512, 1458, 1420, 1381, 1371, 1360, 1126, 1099, 1063, 1011, 980, 908, 889.

^{1}H-NMR: (500 MHz, $CDCl_3$) 8.82(br. *s*, 1H); 8.45(*dm*, *J*= 7.8, 1H); 7.36(*d*, *J*= 3.1, 1H); 7.35(*dm*, *J*= 8.0, 1H); 7.28(*ddd*, *J*= 7.8, 7.2, 1.2, 1H); 7.23(*ddd*, *J*= 8.0, 7.2, 1.3, 1H); 3.80(*s*, 1H); 3.09(*m*, 1H); 1.95(*m*, 2H); 1.81(*ddd*, *J*= 13.2, 3.5, 2.0, 1H); 1.75(*m*, 1H); 1.60-1.50(*m*, 3H); 1.47(*s*, 3H); 1.43(*d*, *J*= 0.5, 3H); 1.32(*s*, 3H).

Lit.: *inter alia:* 3.06(br. *s*, 1H); 1.48(*s*, 3H); 1.45(*s*, 3H); 1.33(*s*, 3H) [6].

^{13}C-NMR: (125 MHz, $CDCl_3$) 190.0 *(s)*, 167.2 *(s)*, 136.5 *(d)*, 135.9 *(s)*, 127.0 (s), 123.7 *(d)*, 122.9 *(d)*, 122.7 *(d)*, 114.6 *(s)*, 111.2 *(d)*, 72.5 *(s)*, 59.8 *(s)*, 41.9 *(d)*, 35.2 *(d)*, 34.1 *(t)*, 31.3 *(q)*, 26.8 *(q)*, 26.5 *(t)*, 26.4 *(q)*, 25.8 *(t)*.
Agreement with reported data for natural (+)-2: ± 0.4 ppm [6].

HETCOR: 136.5 / 7.36; 123.7 / 7.23; 122.9 / 7.28; 122.7 / 8.45; 111.2 / 7.35; 41.9 / 3.09; 35.2 / 1.75; 34.1/1.57 and 1.50; 31.3 / 1.32; 26.8 / 1.43; 26.5 / 1.95 and 1.59; 26.4 / 1.47; 25.8 / 1.95 and 1.81.

GC-MS: 324 (62, M^+), 309 (42), 158 (13), 144 (100), 117 (16), 116 (16), 89 (14), 43 (51).

Dehydration of (+)-Aristolone ((+)-2). A soln. of 30 mg (0.93 mmol) of (+)-**2** and 0.1 ml of pyridine in 5 ml of Et_2O was cooled to -20° and treated with 0.1 ml of thionyl chloride. After stirring for 30 min at -20° the mixture was allowed to reach room temperature. Standard work-up furnished a yellow oil that was chromatographed (silica gel; chloroform/THF/Et_3N 20:5:1) to give 19.2 mg (68 %) of (–)-**4** and 6.4 mg (23 %) of (+)-**3**.

Data of (–)-11,12-didehydro-10-oxohobartine ((–)-**4**): colorless plates.

M.p.: 224-225° (pet. ether/Et_2O 1:3) Lit.: 225° [7b] $C_{20}H_{22}N_2O$ (306.42)

$[\alpha]_D$: – 245 (c = 0.32, $CHCl_3$).

UV (EtOH): 315 (3.88), 265 (3.87), 255 (3.88), 208 (4.40).

IR ($CHCl_3$): 3455, 2935, 1620, 1579, 1510, 14180, 1257, 1098, 1008, 911, 890.

^{1}H-NMR: (400 MHz, $CDCl_3$) 8.59(br. *s*, 1H); 8.49(*dm*, *J*= 7.7, 1H); 8.19(*d*, *J*= 3.1, 1H); 7.39(*dm*, *J*= 7.2, 1H); 7.30(*td*, *J*= 7.2, 1.4, 1H); 7.27(*td*, *J*= 7.1, 1.5, 1H); 5.36(*m*, 1H); 3.62(br. *s*, 1H); 2.30(*m*, 2H); 2.00(*m*, 1H); 1.92(*dtd*, *J*= 12.2, 3.2, 0.8 1H); 1.76(*dt*, *J*= 12.2, 2.8, 1H); 1.60(*q*, *J*= 2.0, 3H); 1.36(*s*, 3H); 1.32(*s*, 3H).

Agreement with reported data for natural (–)-4 [7b]: ± 0.01 ppm.

^{13}C-NMR: (100 MHz, $CDCl_3$) 188.6 *(s)*, 168.0 *(s)*, 135.9 *(s)*, 135.8 *(d)*, 135.5 *(s)*, 126.7 *(s)*, 123.7 *(d)*, 122.8 *(d)*, 122.7 *(d)*, 121.7 *(d)*, 115.4 *(s)*, 111.1 *(d)*, 60.5 *(s)*, 34.3 *(d)*, 34.0 *(d)*, 31.4 *(q)*, 29.1 *(t)*, 27.7 *(q)*, 25.1 *(t)*, 23.1 *(q)*.

GC-MS: 306 (46, M^+), 291 (14), 144 (100), 116 (38), 93 (27), 89 (27), 77 (16).

Data of (+)-11,12-didehydro-10-oxomakomakine ((+)-**3**) :colorless plates.

M.p.: 240-241° (Et_2O) Lit.: 257° [7b] $C_{20}H_{22}N_2O$ (306.42)

$[\alpha]_D$: + 75 (c = 0.97, $CHCl_3$).

UV (EtOH): 316 (3.90), 265 (3.90), 257 (3.91), 209 (4.46), taken from refs. 9 and 17.

IR (KBr): 2972, 1622, 1610, 1575, 1517, 1452, 1431, 1128, 1107, 888, 751, taken from refs. 9 and 17.

^{1}H-NMR: (400 MHz, $CDCl_3$) 8.64(br. *s*, 1H); 8.48(*dm*, *J*= 7.7, 1H); 8.32(*d*, *J*= 3.1, 1H); 7.37(*dm*, *J*= 7.2, 1H); 7.28(*m*, 1H); 7.28(*m*, 1H); 7.25(*m*, 1H); 4.86(*m* 1H); 4.68(*m*, 1H);3.94(*m*, 1H); 2.16(*m*, 1H); 2.13(*m*, 1H); 2.10(*m*, 1H); 2.07(*m*, 1H); 1.85(*m*, 1H); 1.75(*ddd*, *J*= 12.5, 3.2, 2.2, 1H); 1.62(*tdd*, *J*= 15.3, 8.6, 3.8, 1H); 1.51(*s*, 3H); 1.32(*s*, 3H)., taken from refs. 9 and 17. Agreement with reported data for natural (+)-**3** [7b]: ± 0.01 ppm.

^{13}C-NMR: (100 MHz, $CDCl_3$) 187.6 *(s)*, 166.3 *(s)*, 146.2 *(s)*, 135.8 *(s)*, 135.6 *(d)*, 126.7 *(s)*, 123.7 *(d)*, 122.84 *(d)*, 122.77 *(d)*, 115.4 *(s)*, 111.1 *(d)*, 110.0 *(t)*, 59.3 *(s)*, 39.6 *(d)*, 35.7 *(d)*, 31.2 *(q)*, 30.0 *(t)*, 29.5 *(t)*, 29.0 *(t)*, 27.0*(q)*, taken from refs. 9 and 17. Agreement with reported data for natural (+)-**3** [7b]: ± 0.1 ppm.

GC-MS: 306 (31, M^+), 291 (10), 144 (100), 136 (6), 116 (37), 77 (12).

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