Synthesis of *Aristotelia*-Type Alkaloids

Part XVI[1])

Syntheses of the Natural Products (−)-Serratenone and (+)-11,12-Didehydromakonin-10-one

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Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

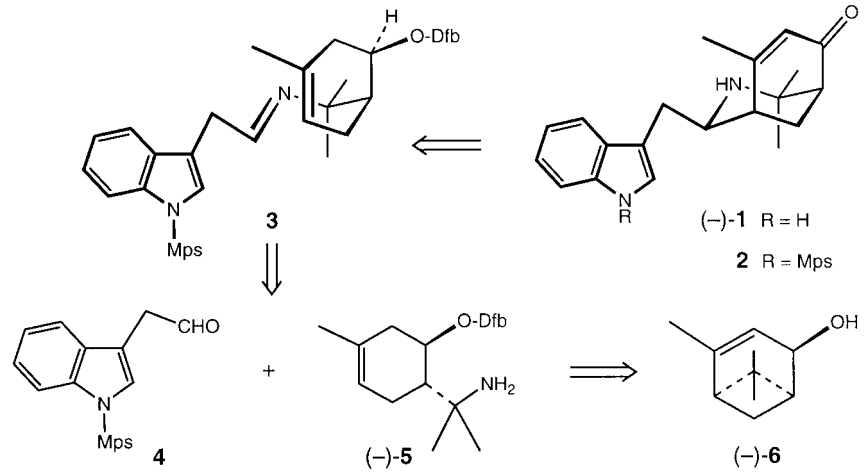
Two independent total syntheses of the *Aristotelia* alkaloid (−)-serratenone ((−)-**1**) are disclosed, one starting with (−)-α-pinene, the other one with (*S*)-α-terpineol. These correlations led to a revision of the originally proposed absolute configuration of the natural product. In the course of systematic investigations of the behavior of the indole alkaloids (+)-makomakine ((+)-**18**) and (−)-hobartine ((−)-**22**) towards oxidizing reagents, it was found that treatment with I_2 leads to no less than five different products. Depending on the exact reaction conditions, each of them can be obtained as the major component in yields between 40 and 60%. One of these compounds was shown to be identical with the natural product (+)-11,12-didehydromakonin-10-one ((+)-**28**).

1. Introduction. – The *Aristotelia* alkaloid (−)-serratenone ((−)-**1**) (*Scheme 1*) was isolated by *Bick* and co-workers as an amorphous powder from *Aristotelia serrata* W. R. B. OLIVER where it occurs in concentrations ranging from 7 to 30 ppm [6][7]. The proposed constitutional formula and relative configuration of this regular monoterpene indole alkaloid was corroborated a few years later through a total synthesis of its racemic form [8]. A peculiar feature of natural (−)-serratenone is that – according to circular dichroism (CD) evidence [9] – its absolute configuration is opposite to the one found for all other *Aristotelia* alkaloids (for reviews, see [10]). To clarify this point, a stereoselective synthesis of (−)-**1** was undertaken. Our retrosynthetic plan detailed in *Scheme 1* takes recourse to an acid-catalyzed cyclization of the intermediate imine **3**, which can be disconnected into protected (1*H*-indol-3-yl)acetaldehyde **4** and the *p*-menth-1-en-8-ylamine derivative (−)-**5**. The latter can be traced back to (−)-*trans*-verbenol ((−)-**6**), a building block of established absolute configuration derived from the chiral pool [11].

2. Results and Discussion. – *Synthesis of (−)-Serratenone, First Approach.* Following a procedure published by *Goré* and co-workers [12], we transformed (−)-

[1]) Part XV: see [1].
[2]) Taken from the Ph.D. Theses of *R. G.* [2], *M. D.* [3], and *R. G.* [4].
[3]) Taken from the Diploma Thesis of *R. S.* [5].

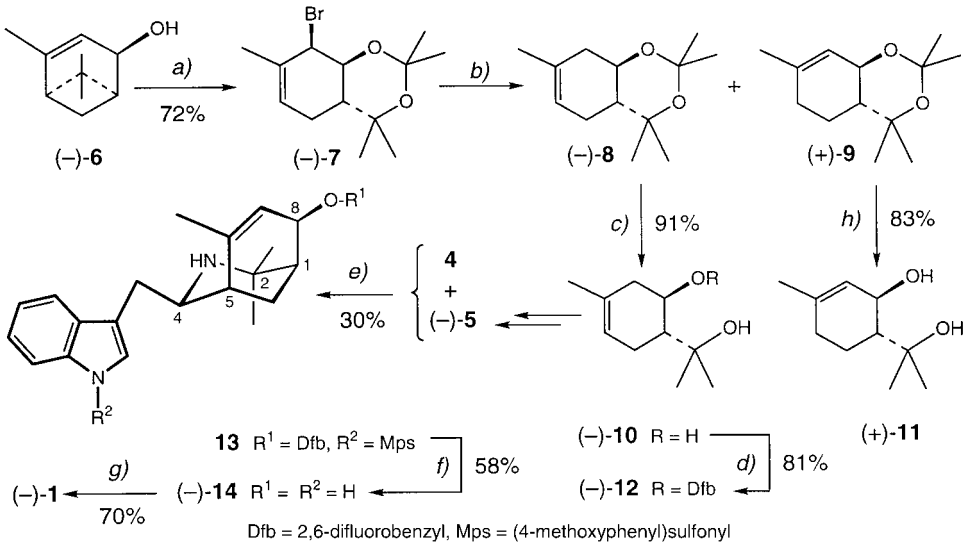
Scheme 1



Mps = (4-methoxyphenyl)sulfonyl, Dfb = 2,6-difluorobenzyl

trans-verbenol ((–)-**6**) into bromoacetal (–)-**7** (*Scheme 2*). In our hands, reduction of this intermediate with $LiAlH_4$ according to the original procedure invariably gave a 1:2 mixture of (–)-**8** and (+)-**9**, the undesired major product evidently arising *via* an S_N2' process. This is in contrast with the claim that, under these conditions, only (–)-**8** is

Scheme 2



Dfb = 2,6-difluorobenzyl, Mps = (4-methoxyphenyl)sulfonyl

a) *N*-Bromosuccinimide (NBS), acetone. *b*) See text. *c*) Py·TsOH, EtOH. *d*) NaH, 2,6-difluorobenzyl bromide, [15]crown-5, THF. *e*) HCOOH, 16 h at 23°. *f*) Li, 4,4′-di(*tert*-butyl)biphenyl, THF, 2 h at –70°. *g*) Pyridinium chlorochromate (PCC) on Al_2O_3, CH_2Cl_2. *h*) $CHCl_3/H_2O$, 6 d at 23°.

formed in 90% yield [12]. A comparison of the NMR data of our two products with the one originally described for (−)-**8** [12] showed that the earlier workers must actually have isolated and characterized (+)-**9** instead. This conclusion was corroborated by a long-range $^1H/^{13}C$-HETCOR experiment performed on (+)-**9**, which displayed all of the expected relevant connectivities. In addition, the spectra of the two diols (−)-**10** and (+)-**11**, resulting from hydrolysis of the acetonide groups of (−)-**8** and (+)-**9**, respectively, were identical with the ones of racemic reference compounds, prepared before *via* altogether different routes [8][13]. Fortunately, it turned out that a change of the reducing agent from $LiAlH_4$ to $LiBHEt_3$ (*Super Hydride*™) leads to the desired compound (−)-**8** as the single reaction product in over 90% yield.

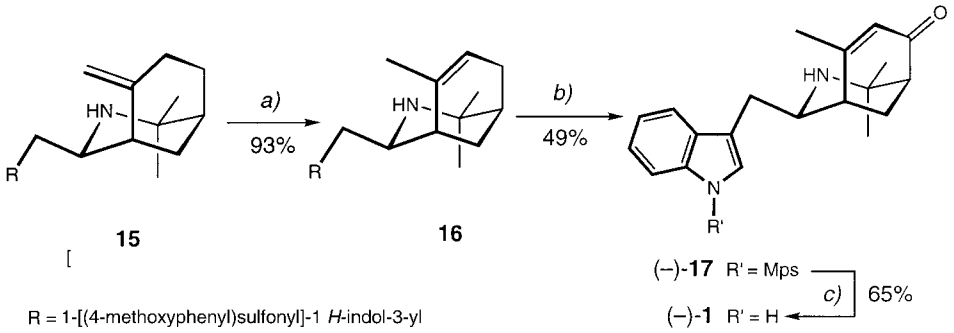
The secondary OH group of diol (−)-**10** was selectively protected as 2,6-difluorobenzyl ether to furnish (−)-**12**. Recrystallization of this material served to increase its optical purity from 78% to 93%. The transformation of (−)-**12** into the final target (−)-serratenone ((−)-**1**) closely followed the pathway developed for the racemic series and proceeded with similar yields [8]. Whereas a comparison of the spectroscopic data (see *Table* and *Exper. Part*) of synthetic (−)-**1** with the published values of natural serratenone showed no significant discrepancies, there is a noticeable deviation between the values of the optical rotation ($[\alpha]_D = -89.5$ ($c = 0.29$, $CHCl_3$) for synthetic *vs.* $[\alpha]_D = -45.3$ ($c = 1$, $CHCl_3$) for natural (−)-**1**). Most likely, the lower value for natural (−)-**1** is caused by the presence of impurities that, at the same time, prevented crystallization of the amorphous natural product, whereas we obtained the synthetic sample in the form of colorless prisms, melting sharply at 184–185°. If correct, this interpretation is tantamount to the conclusion that natural (−)-serratenone has the same absolute configuration as all other *Aristotelia* alkaloids.

Table. *Assignments of ^{1}H-NMR Chemical Shift Values* δ [ppm] *in* $CDCl_3$

	(−)-**1**	(+)-**18**	(+)-**19**	(−)-**20**	(−)-**21**	(−)-**22**	**23**	(−)-**24**	**25**	**26**	(+)-**27**	(+)-**28**
H–C(2)	7.12	7.00	5.30	–	–	7.09	5.24	–	–	4.12	7.02	8.32
H–C(5)	7.63	7.63	7.17	7.37	7.61	7.64	7.18	7.37	7.63	7.39	7.67	8.48
H–C(6)	7.14	7.10	6.73	6.85	6.92	7.11	6.74	6.83	6.91	6.71	7.10	7.25
H–C(7)	7.22	7.18	7.10	7.21	7.28	7.18	7.11	7.20	7.28	7.03	7.17	7.28
H–C(8)	7.39	7.34	6.55	7.17	7.16	7.35	6.54	7.15	7.15	6.60	7.34	7.37
H–C(10)	2.89	2.76	2.05	6.30	–	2.82	2.13	6.44	–	2.39	3.68	-
H′–C(10)	2.67	2.62	2.05	–	–	2.69	1.91	–	–	1.94	3.52	-
H–C(11)	3.71	3.49	3.23	–	–	3.49	3.06	–	–	3.69	–	-
H–C(14)	2.01	1.40	1.36	1.58	1.61	1.46	1.42	1.65	1.66	1.28	1.70	1.85
H_{anti}–C(15)	2.26	1.59	1.57	1.60	1.64	1.62	1.51	1.69	1.72	1.70	1.46	1.75
H_{syn}–C(15)	2.26	2.12	2.05	2.77	2.78	2.08	1.96	2.75	2.76	2.34	1.87	2.08
H–C(16)	2.47	2.27	2.24	2.92	2.93	2.17	1.93	2.63	2.66	1.56	2.93	3.94
H_{endo}–C(18)	6.07	3.08	2.94	2.01	2.09	5.63	5.49	5.28	5.31	–	2.15	2.10
H_{exo}–C(18)	–	2.18	2.05	1.96	1.94	–	–	–	–	1.56	2.15	2.10
H_{endo}–C(19)	–	2.07	2.05	2.11	2.09	2.28	2.30	2.41	2.43	2.34	2.02	2.12
H_{exo}–C(19)	–	1.49	1.44	1.44	1.42	2.08	1.99	2.06	2.07	1.70	1.50	1.62
H–C(20)	2.08	4.77	4.72	4.75	4.94	1.81	1.72	1.62	1.72	1.34	4.70	4.86
H′–C(20)	–	4.58	4.53	4.67	4.75	–	–	–	–	–	4.68	4.69
Me(21)	1.05	1.10	1.36	1.51	1.51	1.16	1.31	1.53	1.54	1.29	1.39	1.32
Me(22)	1.18	1.14	1.27	1.92	1.93	1.09	1.26	1.92	1.92	1.25	1.27	1.52

Synthesis of (−)-Serratenone, Second Approach. In the course of systematic investigations on the possibilities of oxidizing free or indole-protected *Aristotelia* alkaloids [2], a much simpler route to (−)-serratenone (**1**) was uncovered (*Scheme 3*). An acid-catalyzed C=C isomerization of the readily obtainable indole-protected makomakine **15** [14] led to the thermodynamically more stable hobartine derivative **16** in high yield [1]. Oxidation of the allylic CH_2 group with CrO_3/3,5-dimethyl-1*H*-pyrazole [15] gave a 49% yield of indole-protected serratenone (−)-**17**, from which the alkaloid (−)-**1** could readily be obtained by reductive removal of the protective group. Clearly, this second approach is superior to the method described above what length, efficiency, and overall yields are concerned.

Scheme 3



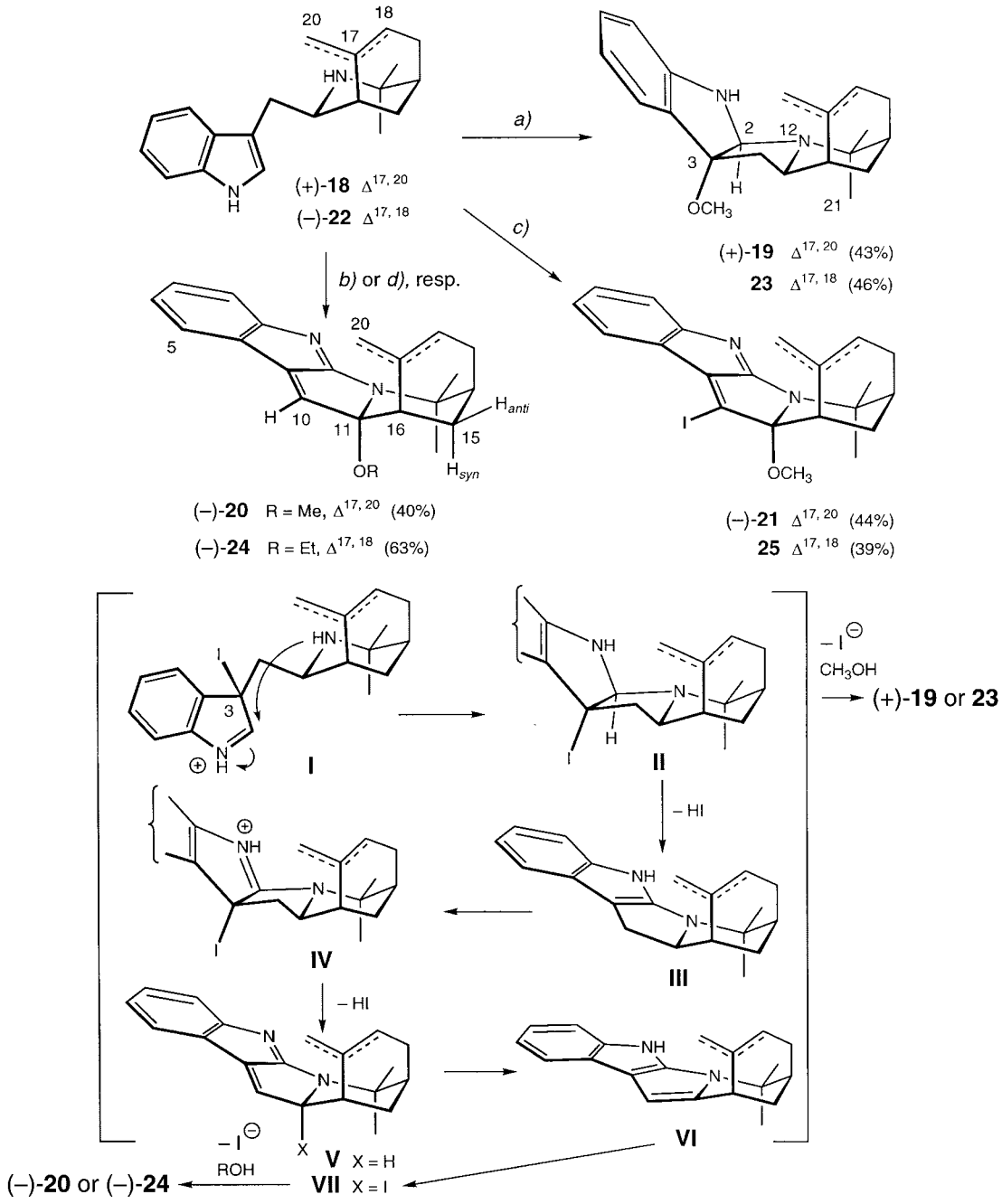
a) HCl, H_2O/AcOH, 40 min at 110°. *b*) CrO_3, CH_2Cl_2, 3,5-dimethyl-1*H*-pyrazole. *c*) Na, naphthalene, THF.

Oxidation of (+)-Makomakine ((+)-**18**) *and (−)-Hobartine* ((−)-**22**) *with Iodine.* Recently, we showed that I_2 serves as a selective and effective oxidant for the transformation of the pentacyclic *Aristotelia* alkaloid aristoteline into a variety of natural products characterized by higher oxidation levels [16]. The same reagent was also tested within the tetracyclic series [2], namely with the targets (+)-makomakine ((+)-**18**) and (−)-hobartine ((−)-**22**). In these cases, the results, displayed in *Scheme 4*, tend to be less reproducible, and they depend critically on the exact reaction conditions. Careful oxidation with 1 equiv. of I_2 in MeOH led to the dehydrogenation products (+)-**19** and **23**, respectively. The ^{1}H- and ^{13}C-NMR spectra (see *Table*) point to unaltered aliphatic subunits, but, in both cases, serious changes in the aromatic sections were noticed. Obviously, the former indole chromophores had been replaced by *o*-substituted aniline units. In addition, 1 equiv. of the solvent was incorporated into the isolated products.

The fact that C(3) of (+)-**19** now appears as a *s* at 92.4 ppm indicates that the MeO group did enter in this position. In the HETCOR spectrum of (+)-**19**, a *s* at 5.30 ppm correlates with a *d* at 79.5 ppm, which is consistent with C(2) now being substituted by two N-atoms. The relative configuration at the two new chiral centers were established by NOE experiments: irradiation at 5.30 ppm led to enhanced ^{1}H-NMR signals for H−N(1), MeO−C(3), and Me(21).

The spectral data are fully compatible with the proposed structure (+)-**19**. Seemingly, the starting materials are attacked by I_2 at their most nucleophilic position,

Scheme 4



a) 1 Equiv. of I_2, AcONa, MeOH. *b*) 5 Equiv. of I_2, K_2CO_3, MeOH, CH_2Cl_2. *c*) 5.4 Equiv. of I_2, AcONa, MeOH. *d*) 3 Equiv. of I_2, K_2CO_3, $CHCl_3$/EtOH.

i.e., C(3) [17], to give the 3-iodoindolenium species **I**, which then cyclizes to **II**[4]). Afterwards, solvolysis under retention of configuration transforms the I-substituent into a MeO group *via* an S_N1 process to furnish (+)-**19** or **23**, depending on the starting material.

When (+)-makomakine ((+)-**18**) was treated with an excess of I_2 and K_2CO_3 in MeOH, the orange product (−)-**20** was isolated in *ca.* 40% yield. The observed color is caused by a long-wave UV maximum at 422 nm (log ε 3.02). This points to a severe alteration of the former indole chromophore, a fact borne out by the ^{13}C-NMR spectrum, in which an additional C-atom shows up in the aromatic region. The spectral data confirmed the proposed structure of (−)-**20**.

The additional *d* for *C*H(10) of (−)-**20** in the aromatic region appears at the expense of the formerly aliphatic *C*H_2(10) group. The original *d* of C(11) is replaced by a *s* at 105.2 ppm, and as the product is endowed again with an additional MeO unit, this functional group must be located at C(11). In addition, the presence of an axial MeO group at C(11) is evident due to the marked deshielding of the protons H_{anti}−C(15) (+0.65 ppm as compared to (+)-**18**) and Me(21) (+0.4 ppm) (see *Table*). The assumed configuration at C(11) was further corroborated by a NOE experiment: irradiation of H−C(10), which appears as a *s* at 6.30 ppm, led to enhanced signals of H−C(5) and of both H-atoms of the H−C(20) group.

A compound with closely related spectroscopic properties, (−)-**24**, was isolated when (−)-hobartine ((−)-**22**) was oxidized with excess I_2 in $CHCl_3$. However, in this case, the substituent at C(11) was an EtO group which must have been introduced due to the presence of *ca.* 1% of EtOH, which is commonly added to commercial $CHCl_3$ as a phosgene quencher.

Under similar conditions, but with sodium acetate as the base, both alkaloids were transformed into the iodinated analogues (−)-**21** and **25**, respectively. Their spectroscopic properties (see *Table* and *Exper. Part*) closely resemble the ones of compounds (−)-**20** and (−)-**24**, apart from the now missing *s* of H−C(10) and the additional *s* accounting for this C-atom in the ^{13}C-NMR spectra at the expense of the former *d*.

Possible mechanistic pathways to these compounds are sketched in *Scheme 4* (→ **III**–**VII**). An attempt was made to prepare the putative intermediate **III** by an acid-catalyzed elimination of MeOH from compound (+)-**19**. However, the only product we were able to isolate had an entirely different and unexpected structure (*Scheme 5*). Its UV spectrum was almost identical with the one of *o*-toluidine and showed the characteristic hypsochromic shift upon addition of acid. Extensive 2D-NMR experiments (ROESY, NOSY, HETCOR, and HMBC)[5]) unambiguously led to structure **26** for this compound, which bears a strong resemblance to neohobartine, a by-product in the acid-catalyzed cyclization of hobartine (**22**) to the pentacyclic alkaloid aristoteline [19]. One of several possible pathways from (+)-**19** to **26** is displayed in *Scheme 5* and starts with an acid-mediated hydrolysis of the aminal grouping (**VIII** → **IX**). The following intramolecular iminium-ion condensation involving intermediate **IX** seems unlikely for stereoelectronic reasons. However, this problem can be circumvented by

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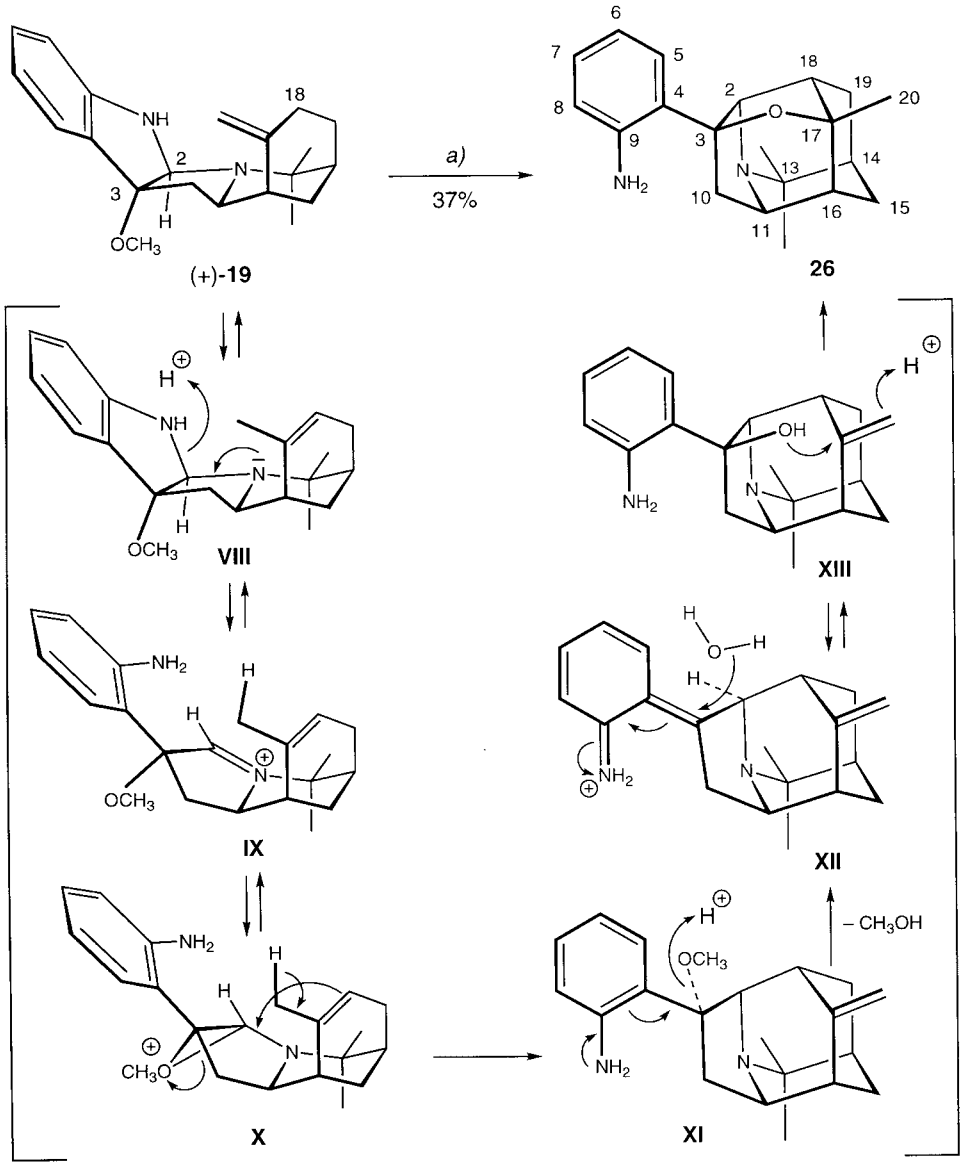
4) A compound with this partial structure was isolated in 81% yield by *Pellegrini* upon treating the diketopiperazide prepared from 1-[(*tert*-butoxy)carbonyl]tryptophan and 2-(3,3-dimethylallyl)piperidine-2-carboxylic acid with I_2 and K_2CO_3 in THF [18].

5) The authors would like to thank Prof. *B. Jaun* (Laboratory for Organic Chemistry of the ETHZ) for recording these spectra and for his help with their interpretation.

Scheme 5



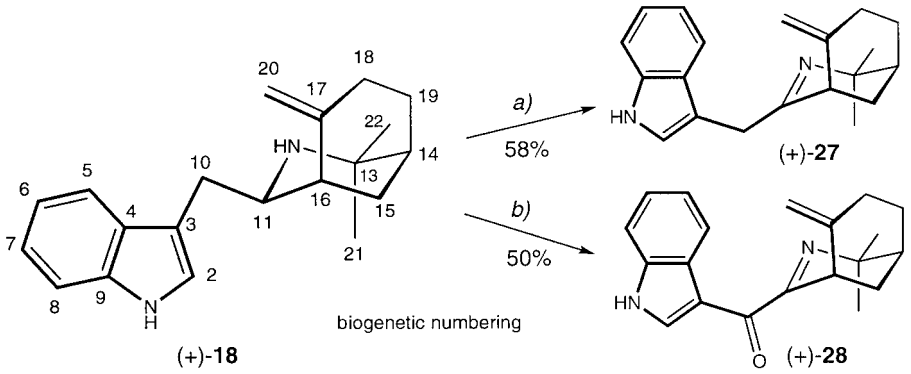
a) HBF_4, AcOH, 1 h at 100°.

invoking intermediate **X** derived from **IX** by neighboring group participation. Hydrolysis of the resulting vinylogous hemiaminal **XI** leads to **XIII**, which undergoes an acid-catalyzed intramolecular etherification to yield the final product **26**.

In an attempt to employ the reaction conditions that had been very successful in the pentacyclic series [16], (+)-makomakine ((+)-**18**) was treated with I_2 in $CHCl_3$, which

resulted in the formation of the known imine (+)-**27** [20] (*Scheme 6*). On the other hand, oxidation of (+)-**18** with an excess of I_2 in a two-phase system furnished the natural product (+)-11,12-didehydromakonin-10-one ((+)-**28**) in 50% yield. This compound was isolated from *A. chilensis* by *Silva* and co-workers in 1989 [21] and was synthesized before *via* a different route [14]. To our disappointment, (−)-hobartine ((−)-**22**) failed to give any well-defined oxidation products upon similar treatment [5].

Scheme 6



a) 1. 1.3 Equiv. of I_2, $CHCl_3$; 2. Et_3N. *b*) 1.3 Equiv. of I_2, aq. $NaHCO_3$ soln., $CHCl_3$; 2. Et_3N.

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Experimental Part

General. Reagents and solvents were purchased from *Fluka AG* in the highest obtainable purity, unless stated otherwise. $CHCl_3$ and $CDCl_3$ were passed through basic alumina (*Woelm*, act. I) immediately before use. M. p. (not corrected): *Tottoli* apparatus, sealed evacuated capillaries. Optical rotations: *Perkin-Elmer 241* at 25° and 589 nm (Na_D). UV/VIS Spectra (λ_{max} [nm], log ε [dm^3/mol·cm]): *Kontron Uvikon 869*. IR: *Perkin-Elmer PE-781* spectrometer; ν_{max} in cm^{-1}. ^{1}H-NMR: δ in ppm rel. to $SiMe_4$ (=0 ppm), J in Hz; 400 MHz: *Bruker AMX-400*; 500 MHz: *Bruker AMX-500.* ^{13}C-NMR: multiplicities from DEPT experiments; 100 MHz: *Bruker AMX-400*; 125 MHz: *Bruker AMX-500.* NOE: *Bruker WM-300* (300 MHz, $CDCl_3$); irradiated proton → affected signal(s). HETCOR: *Varian Gemini-300* (300 MHz, $CDCl_3$): cross peaks: δ(C)/δ(H). Mass spectra (*m*/*z* [amu] (% base peak)): *Hitachi-Perkin-Elmer, VG Tribrid*; EI at 70 eV, unless stated otherwise; FAB in 3-nitrobenzyl alcohol as matrix.

*(−)-(1*R*,6*R*)-3,3,5,5,9-Pentamethyl-2,4-dioxabicyclo[4.4.0]dec-8-ene* ((−)-**8**). *Method A:* To a soln. of 7.90 g (26.5 mmol) of (−)-**7**[6]) in 200 ml of Et_2O were added 1.5 equiv. of 1M $LiBHEt_3$ (=super-Hydride™; *Fluka*, *pract.*) in THF at 0° over 30 min. After stirring for 15 h at 23°, the mixture was cooled to 0° and treated with 27 ml of 2N aq. NaOH. After stirring for 4 h, the mixture was diluted with 200 ml of Et_2O and extracted 3 times with sat. aq. Na_2CO_3 soln. The org. phase was dried (K_2CO_3) and evaporated: 5.50 g (98.7%) of >95% pure (−)-**8** (by ^{1}H-NMR). Clear, slightly yellow oil. $[\alpha]_D = -22.6$ ($c = 0.73$, $CHCl_3$). IR ($CHCl_3$): 2995, 2910, 2850, 1450, 1438, 1378, 1364, 1303, 1261, 1195, 1190, 1122, 1052, 1000, 971, 947, 908, 824. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.34 (*m*, 1 H); 3.95 (*ddd*, *J* = 11.0, 9.3, 6.2, 1 H); 2.33 (*ddm*, *J* = 16.6, 5.5, 1 H); 2.06–1.98 (*m*, 2 H); 1.76 (*m*, 1 H); 1.66 (br. *s*, 3 H); 1.61 (*td*, *J* = 11.4, 5.2, 1 H); 1.49 (*d*, *J* = 0.4, 3 H); 1.39 (*d*, *J* = 0.5, 3 H); 1.28 (*s*, 3 H); 1.21 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 131.5 (*s*); 119.7 (*d*); 97.7 (*s*); 73.5 (*s*); 65.4 (*d*); 44.5 (*d*); 37.2 (*t*); 32.3 (*q*);

[6]) Prepared from (−)-α-pinene (*Aldrich*, *puriss.*; 78% ee) according to [12].

31.3 (*q*); 25.6 (*t*); 24.8 (*q*); 24.3 (*q*); 23.2 (*q*). EI-MS: 195 (7, $[M-15]^+$), 153 (2), 136 (12), 135 (100), 119 (10), 107 (36), 94 (22), 93 (90), 91 (21), 85 (12), 79 (43), 77 (16), 59 (16), 43 (77).

Method B: To a suspension of $LiAlH_4$ (9 mmol) in 20 ml of Et_2O at 0° was added a soln. of 1.30 g (4.36 mmol) of (−)-**7** [12] in 10 ml of Et_2O within 10 min. After stirring at 23° for 3 h, excess reagent was destroyed by dropwise addition of H_2O. Flash chromatography of the crude material (silica gel, petroleum ether/Et_2O 40:1) furnished 198.3 mg (21.6%) of the minor product, identical with (−)-**8** (see above), and 568.7 mg (62%) of the main product (+)-**9**. Data of *(+)-(1*R*,6*R*)-3,3,5,5,9-pentamethyl-2,4-dioxabicyclo[4.4.0]dec-9-ene* ((+)-**9**): Oil. $[\alpha]_D = +41.2$ ($c = 0.41$, $CHCl_3$). IR ($CHCl_3$): 2990, 2935, 2830, 1454, 1441, 1378, 1260, 1242, 1190, 1121, 1059, 1042, 1012, 969, 930, 904, 886, 810. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.35 (*m*, 1 H); 4.30 (*dm*, $J = 9.8$, 1 H); 2.09 (*m*, 1 H); 2.06–2.0 (*m*, 2 H); 1.97 (br. *dd*, $J = 17.1$, 5.4, 1 H); 1.68 (br. *s*, 3 H); 1.64 (br. *ddt*, $J = 13.0$, 5.9, 1.9, 1 H); 1.52 (*ddd*, $J = 12.9$, 9.7, 2.4, 1 H); 1.50 (*d*, $J = 0.5$, 3 H); 1.40 (*d*, $J = 0.6$, 3 H); 1.27 (*ddd*, $J = 12.9$, 11.6, 5.9, 1 H); 1.25 (*s*, 3 H); 1.22 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 137.0 (*s*); 123.1 (*d*); 98.7 (*s*); 74.7 (*s*); 66.3 (*d*); 46.5 (*d*); 32.1 (*q*); 30.9 (*t*); 30.3 (*q*); 24.8 (*q*); 23.1 (*q*); 23.0 (*q*); 21.9 (*t*). EI-MS: 210 (0.5, M^+), 195 (27), 152 (23), 136 (10), 135 (100), 134 (25), 132 (16), 119 (49), 117 (17), 109 (21), 107 (13), 94 (34), 93 (36), 91 (35), 81 (27), 79 (35), 77 (16), 69 (22), 59 (12), 43 (40). According to its NMR data, this product is identical with compound **4a** in [12], which was erroneously assigned structure **8**.

*(−)-(4*R*,5*R*)-*p*-Menth-1-ene-5,8-diol* ((−)-**10**). To a soln. of 6.40 g (30.4 mmol) of (−)-**8** in 150 ml of EtOH were added 1.2 g of pyridinium tosylate, and the mixture was kept at 23° for 14 h. After evaporation of most of the solvent, the residue was distributed between CH_2Cl_2 and sat. aq. Na_2CO_3 soln. The org. phase was dried (K_2CO_3) and evaporated: 5.18 g (100%) of (−)-**10**. Oil. $[\alpha]_D = -59.6$ ($c = 1.01$, $CHCl_3$). IR ($CHCl_3$): 3600, 3420, 2990, 2900, 2850, 1445, 1380, 1155, 1031, 912, 870, 828. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.26 (*m*, 1 H); 3.98 (*tm*, $J =$ 9.9, 5.7, 1 H); 3.85 (br. *s*, 1 H); 3.60 (br. *s*, 1 H); 2.25 (br. *dd*, $J = 16.6$, 5.7, 1 H); 2.16–2.06 (*m*, 2 H); 1.75–1.67 (*m*, 2 H); 1.65 (br. *s*, 3 H); 1.64 (*td*, $J = 11.4$, 5.2, 1 H); 1.28 (*s*, 3 H); 1.20 (*s*, 3 H); max. deviation from the data of (±)-**10** [8]: ±0.01 ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): 131.7 (*s*); 119.7 (*d*); 74.7 (*s*); 70.8 (*d*); 49.3 (*d*); 40.7 (*t*); 29.5 (*q*); 28.4 (*t*); 23.0 (*q*); 22.8 (*q*); max. deviation from the data of (±)-**10** [8]: ±0.1 ppm. HETCOR (300/75 MHz, $CDCl_3$): 119.7/5.26; 70.8/3.98; 49.3/1.7; 40.7/2.25 and 2.1; 29.5/1.20; 28.4/2.1 and 1.7; 23.0/1.28; 22.8/1.65. EI-MS: 152 (10, $[M-18]^+$), 137 (19), 119 (30), 109 (100), 94 (75), 79 (91), 68 (21), 59 (77), 43 (41).

*(+)-(3*R*,4*R*)-*p*-Menth-1-ene-3,8-diol* ((+)-**11**). To a soln. of 1.20 g (5.7 mmol) of (+)-**9** in 45 ml of $CHCl_3$ were added 5 ml of H_2O, and the mixture was stirred at 23° for 6 days. The mixture was washed with 20 ml of sat. aq. $NaHCO_3$ soln., dried (K_2CO_3), and evaporated to yield 0.893 g of a slightly yellow oil. Chromatography (silica gel, Et_2O/petroleum ether 1:1) furnished 0.81 g of a colorless oil, which crystallized after trituration with cold Et_2O. M.p. 77–78° (hexane) ([13]: m.p. 76° for (±)-**11**). $[\alpha]_D = +57.2$ ($c = 0.78$, $CHCl_3$) for material of 78% ee. IR, ^{1}H- and ^{13}C-NMR, and mass spectra: in agreement with those obtained earlier for (±)-**11** [13].

*(−)-(4*R*,5*R*)-5-[(2,6-Difluorobenzyl)oxy]-*p*-menth-1-en-8-ol* ((−)-**12**). Prepared as described for racemic material [8]. M.p. 77–78° (Et_2O) ([8]: m.p. 92° for (±)-**12**). $[\alpha]_D = -110.8$ ($c = 0.97$, $CHCl_3$) for material of 78% ee.

*Upgrading of the Optical Purity of (−)-***12**. To a warm soln. of 11.0 g of (−)-**12** (optical purity: 78%) in 10 ml of Et_2O were added 30 ml of petroleum ether (40–60°). The clear soln. was inoculated with a single crystal of (−)-**12**, and the mixture was kept at 23° for 84 h. The resulting cubic crystals were collected and dried at 0.002 Torr for 16 h to yield 7.4 g (67%) of a material with $[\alpha]_D = -132.4$ ($c = 1.33$, $CHCl_3$) pointing to an optical purity of 93%, which was confirmed by ^{1}H-NMR (300 MHz, 1% in $CDCl_3$ in the presence of tris{3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato}europium(III) shift reagent (*Aldrich*, gold label)).

*(−)-(4*S*,5*R*)-5-[(2,6-Difluorobenzyl)oxy]-*p*-menth-1-en-8-amine* ((−)-**5**). Prepared as described for racemic material [8]. Oil. $[\alpha]_D = -68.2$ ($c = 1.03$, $CHCl_3$) for material of 93% optical purity.

19-exo-*[(2,6-Difluorobenzyl)oxy]-1-[(4-methoxyphenyl)sulfonyl]hobartine* (=*(1*S*,4*R*,8*R*)-8-[(2,6-Difluorobenzyl)oxy]-4-{[1-[(4-methoxyphenyl)sulfonyl]-1*H*-indol-3-yl]methyl}-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-6-ene*; **13**). Prepared as described for racemic material [8]. Yield 30%, besides 42% of starting (−)-**5**. Pale-yellow needles. M.p. 69–70° (CH_2Cl_2).

(−)-19-exo-*Hobartin-19-ol* (=*(1*S*,4*R*,8*R*)-4-(1*H*-Indol-3-ylmethyl)-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-6-en-8-ol*; (−)-**14**). Prepared according to *Method B* in [8]. Yield 58%. Pale-rose needles. M.p. 98–100° (Et_2O). $[\alpha]_D = -59.7$ ($c = 1.33$, $CHCl_3$). UV (EtOH): 290 (3.58), 282 (3.67), 275 (sh, 3.63), 222 (4.41). IR, ^{1}H- and ^{13}C-NMR data: identical with those of (±)-**13** [8]. FAB-MS: 311 (100, $[M+1]^+$), 293 (42), 289 (18), 199 (14), 181 (16), 180 (67), 159 (37), 130 (28), 107 (31), 89 (25), 77 (26), 57 (22).

(−)-Serratenone (=*(1*S*,4*R*)-4-(1*H*-Indol-3-ylmethyl)-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-6-en-8-one*; (−)-**1**). *Method A:* To a soln. of 11.5 mg of (−)-**14** in 10 ml of CH_2Cl_2 were added 165 mg of PCC on Al_2O_3, freshly prepared according to [22] (content: *ca.* 6% of active Cr^{VI}). After stirring for 20 min, the mixture was

filtered through *Celite* and the filtrate worked up with CH_2Cl_2 and sat. aq. Na_2CO_3 soln. to furnish 21.3 mg of crude material. Chromatography (silica gel, $CHCl_3$/MeOH/conc. aq. NH_3 soln. 198:2:5) gave 8.1 mg (70% yield) of (−)-**1**. Colorless prisms. M.p. 184–185° (Et_2O) ([6]: amorphous). $[\alpha]_D = -89.5$ ($c = 0.29$, $CHCl_3$) ([6]: $[\alpha]_D = -45.3$ ($c = 1$, $CHCl_3$) for natural (−)-**1**). UV (EtOH): 290 (3.51), 282 (3.53), 222 (4.35). IR ($CHCl_3$): 3480, 3310 (br.), 3060, 3040, 3005, 2930, 2800, 2855, 1659, 1651, 1620, 1456, 1388, 1431, 1419, 1375, 1338, 1310, 1301, 1179, 1091, 1030, 1011, 880. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.04 (br. *s*, 1 H); 7.63 (*dm*, *J* = 7.8, 1 H); 7.39 (*dt*, *J* = 8.1, 0.9, 1 H); 7.22 (*ddd*, *J* = 8.1, 7.2, 1.2, 1 H); 7.14 (*ddd*, *J* = 7.8, 7.1, 1.1, 1 H); 7.12 (*d*, *J* = 2.5, 1 H); 6.07 (*t*, *J* = 1.1, 1 H); 3.71 (*ddd*, *J* = 8.6, 5.6, 2.6, 1 H); 2.89 (*ddd*, *J* = 14.4, 5.6, 0.8, 1 H); 2.67 (*ddd*, *J* = 14.4, 8.6, 0.8, 1 H); 2.47 (*q*, *J* = 3.1, 1 H); 2.26 (*t*, *J* = 3.1, 2 H); 2.08 (*d*, *J* = 1.3, 3 H); 2.01 (*t*, *J* = 3.0, 1 H); 1.18 (*s*, 3 H); 1.05 (*s*, 3 H); deviations from natural (−)-**1** [6]: at most ± 0.03 ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): 202.0 (*s*); 161.5 (*s*); 136.4 (*s*); 129.8 (*d*); 127.4 (*s*); 122.3 (2*d*); 119.5 (*d*), 118.8 (*d*); 112.9 (*s*); 111.3 (*d*); 52.8 (*d*); 50.91 (*s*); 50.88 (*d*); 40.9 (*d*); 32.8 (*t*); 31.6 (*t*); 29.8 (*q*); 26.0 (*q*); 24.9 (*q*). EI-MS: 308 (40, M^+), 293 (11), 200 (12), 199 (38), 183 (11), 179 (27), 178 (100), 159 (32), 158 (21), 144 (21), 143 (27), 131 (36), 130 (58), 117 (35), 110 (28), 88 (15), 81 (19), 80 (22), 78 (22), 58 (14), 43 (13).

Method B: To a cold (−40°) soln. of 834 mg (1.74 mmol) of (−)-**17** (see below) in 25 ml of THF (dist. from K/benzophenone) was slowly added a deep-green soln. of Na/naphthalene, prepared by dissolving 1.13 g (49.2 mmol) of Na and 6.4 g (49.9 mmol) of naphthalene in 95 ml of THF followed by stirring for 6 h at 23°. After addition of 18.2 ml of this reagent, the mixture stayed green, and the addition was stopped at once. The mixture was quenched by adding 10 ml of sat. aq. NH_4Cl soln. Workup with Et_2O and sat. aq. Na_2CO_3 soln., followed by chromatography (silica gel, CH_2Cl_2/MeOH 24:1) furnished 327 mg (61%) of (−)-**1**, indistinguishable from the sample prepared according to *Method A*.

1-[(4-Methoxyphenyl)sulfonyl]hobartine (=*(1S,4R)-4-{[1-[(4-Methoxyphenyl)sulfonyl]-1*H*-indol-3-yl]-methyl}-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-6-ene*; **16**). A soln. of 1.0 g (2.16 mmol) of **15** [14] in 80 ml of AcOH, 200 ml of H_2O and 200 ml of 37% aq. HCl soln. was refluxed for 40 min, cooled to 0° and then poured into 30% aq. NaOH soln. The mixture having now pH 10 was extracted with CH_2Cl_2 (3×). The combined org. extracts were dried (K_2CO_3) and evaporated: 930 mg (93%) of **16**. Colorless foam. IR ($CHCl_3$): 3030, 3005, 2910, 2840, 1593, 1578, 1494, 1460, 1444, 1364, 1300, 1260, 1182, 1162, 1128, 1119, 1097, 1018, 971, 828. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.99 (*dm*, *J* = 8.2, 1 H); 7.78 (*m*, 2 H); 7.48 (*dm*, *J* = 7.7, 1 H); 7.44 (*s*, 1 H); 7.30 (*ddd*, *J* = 8.3, 7.3, 1.2, 1 H); 7.22 (*ddd*, *J* = 8.2, 7.4, 1.1, 1 H); 6.85 (*m*, 2 H); 5.63 (*m*, 1 H); 3.78 (*s*, 3 H); 3.38 (*td*, *J* = 7.3, 2.3, 1 H); 2.67 (*ddd*, *J* = 15.1, 6.7, 0.9, 1 H); 2.54 (*ddd*, *J* = 15.1, 7.6, 1.1, 1 H); 2.26 (br. *d*, *J* = 18.5, 1 H); 2.11–2.05 (*m*, 3 H); 1.72 (*q*, *J* = 1.9, 3 H); 1.61 (*dt*, *J* = 12.5, 3.1, 1 H); 1.47 (*m*, 1 H); 1.15 (*s*, 3 H); 1.09 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.7 (*s*); 135.2 (*s*); 132.2 (*s*); 131.0 (*s*); 129.7 (*s*); 129.0 (2 *d*); 125.9 (*d*); 124.7 (*d*), 123.5 (*d*); 123.1 (*d*); 119.8 (*s*); 119.6 (*d*); 114.4 (2*d*); 113.7 (*d*); 55.6 (*q*); 55.5 (*s*); 54.1 (*d*); 36.7 (*d*); 34.8 (*d*); 29.7 (*t*); 28.9 (*q*); 28.7 (*t*); 27.6 (*t*); 25.6 (*q*); 25.1 (*q*). EI-MS: 464 (0.5, M^+), 449 (2), 293 (5), 171 (9), 165 (16), 164 (100), 130 (11), 93 (9).

1-[(4-Methoxyphenyl)sulfonyl]serratenone (=*(1S,4R)-4-{[1-[(4-Methoxyphenyl)sulfonyl]-1*H*-indol-3-yl]-methyl}-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-6-en-8-one*; (−)-**17**). To a suspension of 2.79 g (27.9 mmol) of CrO_3 (*Fluka*, *puriss.*) in 45 ml of CH_2Cl_2 were added 2.80 g (29.1 mmol) of 3,5-dimethyl-1*H*-pyrazole (*Fluka*, *puriss.*) at −20°. To the resulting brown-orange mixture was added within 5 min a soln. of 1.30 g (2.8 mmol) of **16** in 5 ml of CH_2Cl_2 at −20°. After stirring at −20° for 7 h, there were added 50 ml of 5N aq. NaOH, and stirring was continued for 16 h. The mixture was worked up with CH_2Cl_2 and chromatographed (silica gel, CH_2Cl_2/AcOEt 1:1): 651 mg (49%) of (−)-**17**. White foam. $[\alpha]_D = -114$ ($c = 0.51$, $CHCl_3$). IR ($CHCl_3$): 3010, 2980, 2940, 1659, 1598, 1498, 1447, 1373, 1264, 1167, 1130, 1099, 1032, 977, 834. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.01 (*dm*, *J* = 8.3, 1 H); 7.78 (*m*, 2 H); 7.48 (*dm*, *J* = 7.8, 1 H); 7.45 (*s*, 1 H); 7.33 (*ddd*, *J* = 8.3, 7.2, 1.1, 1 H); 7.25 (*ddd*, *J* = 7.8, 7.1, 1.1, 1 H); 7.12 (*d*, *J* = 2.5, 1 H); 6.07 (*t*, *J* = 1.1, 1 H); 3.71 (*td*, *J* = 7.5, 1.0, 1 H); 6.86 (*m*, 2 H); 6.05 (*t*, *J* = 1.1, 1 H); 3.78 (*s*, 3 H); 3.61 (*ddd*, *J* = 8.6, 5.6, 2.7, 1 H); 2.74 (*ddd*, *J* = 14.9, 5.6, 0.9, 1 H); 2.53 (*ddd*, *J* = 14.9, 8.6, 1.0, 1 H); 2.40 (*q*, *J* = 2.7, 2 H); 2.30–2.21 (*m*, 2 H); 2.00 (*m*, 1 H); 2.00 (*d*, *J* = 1.4, 3 H); 1.35 (br. *s*, 1 H); 1.16 (*s*, 3 H); 1.03 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 201.7 (*s*); 163.7 (*s*); 160.8 (*s*); 135.4 (*s*); 130.8 (*s*); 129.7 (*s*); 128.9 (2 *d*); 124.9 (*d*); 123.8 (*d*), 123.2 (*d*); 119.6 (*s*); 114.4 (2*d*); 114.0 (*d*); 55.6 (*q*); 52.1 (*d*); 50.7 (*s*); 50.5 (*d*); 40.7 (*d*); 32.6 (*t*); 31.0 (*t*); 29.7 (*q*); 25.8 (*q*); 24.9 (*q*). EI-MS: 479 (38), 478 (3, M^+), 369 (14), 309 (23), 252 (10), 199 (38), 198 (11), 179 (10), 178 (79), 162 (14), 140 (100), 131 (21), 130 (46), 108 (25), 58 (23).

(+)-2,3-Dihydro-3-methoxy-2,12-cyclomakomakine (=*(1S,4S,8R,10R)-8-Methoxy-2,2-dimethyl-12-methyl-enebenzo[6,7]-3,5-diazatetracyclo[9.3.1.0^{3,10}0^{4,8}]pentadecane*; (+)-**19**). To a cold (−15°) soln. of 74.7 mg (0.25 mmol) of synthetic (+)-makomakine ((+)-**18**) [14] and 433 mg (5.27 mmol) of NaOAc in 10 ml of MeOH was added a soln. of 59 mg (0.23 mmol) of I_2 in 14 ml of MeOH over 2 h. The stirred mixture was allowed to reach 23° within 2 h and was then quenched by adding 2 ml of sat. aq. $Na_2S_2O_3$ soln. Workup with

CH_2Cl_2 and 1M aq. $NaHCO_3$ soln., followed by chromatography (silica gel, hexane/AcOEt 10:1 → 2:1) furnished 35 mg (43%) of colorless crystals. M.p. 140–141°. $[\alpha]_D = +286$ ($c = 0.1$, EtOH). UV (EtOH): 308 (3.45), 246 (3.98). UV (EtOH, 1 drop of conc. H_2SO_4): 298 (3.21), 239 (3.76). IR ($CHCl_3$): 3400 (br.), 3060, 3000, 2930, 2860, 2820, 1641, 1609, 1483, 1467, 1455, 1380, 1361, 1312, 1298, 1239, 1161, 1112, 1093, 1081, 1058, 1017, 999, 978, 888. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.17 (*ddd*, $J = 7.4, 1.3, 0.6$, 1 H); 7.10 (*ddd*, $J = 7.8, 7.4, 1.3$, 1 H); 6.73 (*td*, $J = 7.4, 1.0$, 1 H); 6.55 (*ddd*, $J = 7.8, 1.0, 0.6$, 1 H); 5.30 (*s*, 1 H); 4.72 (*t*, $J = 2.4$, 1 H); 4.53 (*t*, $J = 2.4$, 1 H); 3.85 (br. *s*, 1 H); 3.23 (*ddd*, $J = 10.0, 5.9, 3.4$, 1 H); 3.09 (*s*, 3 H); 2.94 (*tdt*, $J = 13.7, 6.0, 2.7$, 1 H); 2.24 (br. *q*, $J = 2.9$, 1 H); 2.11–1.95 (*m*, 5 H); 1.57 (*dt*, $J = 12.8, 3.2$, 1 H); 1.44 (*tdd*, $J = 13.7, 6.0, 4.2$, 1 H); 1.36 (*s*, 3 H); 1.36 (*m*, 1 H); 1.27 (*s*, 3 H). NOE (300 MHz, $CDCl_3$): 5.30 (H–C(2)) → 3.85 (H–N), 3.09 (MeO), 1.36 (Me(21)), and, at the limit of significance, 3.23 (H–C(11)) and 2.94 (H_{endo}–C(18)); 3.09 (MeO) → 7.17 (H–C(5)) and 5.30 (H–C(2)). ^{13}C-NMR (100 MHz, $CDCl_3$): 151.2 (*s*); 150.8 (*s*); 129.4 (*d*); 128.2 (*s*); 124.6 (*d*); 118.3 (*d*), 109.2 (*d*); 108.6 (*t*); 92.4 (*s*); 79.5 (*d*); 56.1 (*d*); 55.0 (*s*); 52.5 (*q*); 43.0 (*t*); 42.2 (*d*); 40.6 (*d*); 32.0 (*t*); 31.3 (*t*); 29.0 (*t*); 27.1 (*q*); 25.2 (*q*). HETCOR (300/75 MHz, $CDCl_3$): 129.4/7.10; 128.2/7.17; 124.6/6.73; 118.3/6.55; 108.6/4.72 and 4.53; 79.5/5.30; 56.1/3.23; 52.5/3.09; 43.0/2.02 (2×); 42.2/2.24; 40.6/1.36; 32.0/2.02 and 1.57; 31.3/2.94 and 2.01; 29.0/2.01 and 1.44; 27.1/1.36; 25.2/1.27. EI-MS: 324 (14, M^+), 310 (22), 309 (100), 293 (11), 290 (28).

(−)-1,10-Didehydro-11-methoxy-2,12-cyclomakomakine (= *(1S,10S)-10-Methoxy-2,2-dimethyl-12-methylenebenzo[6,7]-3,5-diazatetracyclo[9.3.1.0^{3,10}0^{4,8}]pentadeca-4,8-diene*; (−)-**20**). To a soln. of 113 mg (0.38 mmol) of (+)-makomakine (**18**) [14] in 20 ml of CH_2Cl_2 were added 380 mg (2.75 mmol) of K_2CO_3 and 0.5 ml of MeOH and then 484 mg (1.91 mmol) of I_2. After stirring for 1 h at 23°, the mixture was poured on 20 ml of 1M aq. $Na_2S_2O_3$ and extracted with 30 ml of CH_2Cl_2 (3×). The combined org. extract was dried (K_2CO_3) and evaporated and the crude product chromatographed (silica gel, hexane/AcOEt 10:1): 49 mg (40%) of **20**. Orange foam. $[\alpha]_D = -70$ ($c = 0.05$, EtOH). UV (EtOH): 422 (3.02), 303 (3.31), 260 (4.69), 254 (4.67). UV (EtOH, 1 drop of conc. H_2SO_4): 376 (3.09), 308 (3.62), 246 (4.02). IR ($CHCl_3$): 3070, 3050, 3000, 2960, 2930, 1581, 1562, 1442, 1426, 1388, 1297, 1185, 1169, 1143, 1116, 1080, 1067, 1043. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37 (*dm*, $J = 7.3$, 1 H); 7.21 (*ddd*, $J = 7.9, 7.2, 1.3$, 1 H); 7.17 (*ddd*, $J = 7.9, 1.4, 0.7$, 1 H); 6.85 (*td*, $J = 7.2, 1.4$, 1 H); 6.30 (*s*, 1 H); 4.75 (*t*, $J = 2.1$, 1 H); 4.67 (*t*, $J = 2.1$, 1 H); 3.10 (*s*, 3 H); 2.92 (*m*, 1 H); 2.77 (*dm*, $J = 12.9$, 1 H); 2.14–1.93 (*m*, 3 H); 1.92 (*s*, 3 H); 1.61–1.55 (*m*, 2 H); 1.51 (*s*, 3 H); 1.44 (*tdd*, $J = 13.5, 6.4, 2.9$, 1 H). NOE (300 MHz, $CDCl_3$): 6.30 (H–C(10)) → 7.37 (H–C(5)), 4.75 (H–C(20)), 4.67 (H′–C(20)), 3.10 (MeO), and 2.92 (H–C(16)); 3.10 (MeO) → 6.30 (H–C(10)) and 1.51 (Me(21)). ^{13}C-NMR (100 MHz, $CDCl_3$): 173.0 (*s*); 166.6 (*s*); 146.0 (*s*); 140.6 (*s*); 131.1 (2*d*); 123.3 (*d*); 122.2 (*s*); 120.9 (*d*), 117.7 (*d*); 111.5 (*t*); 105.2 (*s*); 58.7 (*s*); 49.8 (*q*); 46.7 (*d*); 38.9 (*d*); 28.6 (*t*); 28.2 (*t*); 27.7 (*t*); 27.6 (*q*); 27.4 (*q*). EI-MS: 320 (44, M^+), 305 (58), 291 (22), 290 (100), 289 (70), 288(22), 273 (16), 247 (18), 245 (20), 220 (30), 219 (48), 207 (24), 185 (69), 171 (61), 156 (27), 155 (26).

(−)-1,10-Didehydro-10-iodo-11-methoxy-2,12-cyclomakomakine (= *(1S,10R)-9-Iodo-10-methoxy-2,2-dimethyl-12-methylenebenzo[6,7]-3,5-diazatetracyclo[9.3.1.0^{3,10}.0^{4,8}]pentadeca-4,8-diene*; (−)-**21**). To a soln. of 22 mg (0.075 mmol) of (+)-makomakine (**18**) [14] in 3 ml of MeOH were added 100 mg (1.22 mmol) of NaOAc and 102 mg (0.40 mmol) of I_2. After stirring for 1 h at 23°, the mixture was poured on 20 ml of 1M aq. $Na_2S_2O_3$ soln. and extracted with 30 ml of CH_2Cl_2 (3×). The combined org. extract was dried (K_2CO_3) and evaporated and the crude product chromatographed (silica gel, hexane/AcOEt 85:15): 15 mg (44%) of **21**. Orange foam. $[\alpha]_D = -128$ ($c = 0.06$, EtOH). UV (EtOH): 431 (3.04), 328 (3.84), 260 (4.69), 316 (9.92), 260 (4.50). UV (EtOH, 1 drop of conc. H_2SO_4): 386 (3.33), 328 (3.99). IR ($CHCl_3$): 3070, 3040, 3000, 2960, 2930, 1581, 1561, 1441, 1428, 1381, 1285, 1187, 1161, 1145, 1114, 1080, 1069, 1011. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.61 (*ddd*, $J = 7.3, 1.3, 0.6$, 1 H); 7.28 (*td*, $J = 7.7, 1.4$, 1 H); 7.16 (*dt*, $J = 7.9, 0.8$, 1 H); 6.92 (*td*, $J = 7.4, 1.0$, 1 H); 4.94 (*t*, $J = 2.0$, 1 H); 4.75 (*t*, $J = 2.0$, 1 H); 3.05 (*s*, 3 H); 2.93 (*m*, 1 H); 2.78 (*dq*, $J = 12.7, 2.9$, 1 H); 2.15–2.02 (*m*, 2 H); 1.96–1.92 (*m*, 4 H, incl. 1.93 (*s*, 3 H)); 1.65–1.55 (*m*, 2 H); 1.51 (*s*, 3 H); 1.42 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.9 (*s*); 165.8 (*s*); 147.1 (*s*); 144.3 (*s*); 131.9 (*d*); 122.7 (*d*); 122.5 (*s*); 120.9 (*d*), 117.9 (*d*); 113.4 (*t*); 104.6 (*s*); 101.5 (*s*); 59.8 (*s*); 49.6 (*q*); 46.1 (*d*); 39.3 (*d*); 28.8 (*t*); 28.1 (*t*); 27.73 (*q*); 27.70 (*t*); 27.4 (*q*). EI-MS: 446 (40, M^+), 431 (35), 417 (22), 416 (100), 415 (43), 319 (29), 311 (31), 297 (19), 289 (14), 287 (11), 245 (16), 219 (18), 183 (12).

2,3-Dihydro-3-methoxy-2,12-cyclohobartine (= *(1S,4S,8R,10R)-8-Methoxy-2,2,12-trimethyl-benzo[6,7]-3,5-diazatetracyclo[9.3.1.0^{3,10}.0^{4,8}]pentadec-12-ene*; **23**). To a cold (−40°) soln. of 22.5 mg (0.076 mmol) of synthetic (−)-hobartine (**22**) [23] and 74.6 mg (0.91 mmol) of NaOAc in 5 ml of MeOH was added a soln. of 15.4 mg (0.061 mmol) of I_2 in 5 ml of MeOH over 40 min. The stirred mixture was allowed to reach 23° within 2 h and was then quenched by adding 3 ml of 1M aq. $Na_2S_2O_3$. Workup with CH_2Cl_2 and 1M aq. $NaHCO_3$, followed by chromatography (silica gel, hexane/AcOEt 10:1 → 1:1) furnished 11.3 mg (46%) of **23**. White foam. IR

($CHCl_3$): 3420 (br.), 3050, 3000, 2930, 2825, 1610, 1483, 1468, 1380, 1361, 1312, 1298, 1251, 1239, 1169, 1110, 1083, 1010, 960. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.18 (*ddd*, *J* = 7.4, 1.3, 0.6, 1 H); 7.11 (*ddd*, *J* = 7.8, 7.4, 1.3, 1 H); 6.74 (*td*, *J* = 7.4, 0.9, 1 H); 6.54 (*dm*, *J* = 7.8, 1 H); 5.49 (*m*, 1 H); 5.24 (*s*, 1 H); 3.90 (br. *s*, 1 H); 3.06 (*dt*, *J* = 11.2, 3.9, 1 H); 3.04 (*s*, 3 H); 2.30 (*dm*, *J* = 18.9, 1 H); 2.13 (*dd*, *J* = 11.0, 4.4, 1 H); 2.01 – 1.90 (*m*, 4 H); 1.72 (*q*, *J* = 2.0, 3 H); 1.51 (*dt*, *J* = 12.1, 3.0, 1 H); 1.42 (*m*, 1 H); 1.31 (*s*, 3 H); 1.26 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 151.6 (*s*); 133.4 (*s*); 129.6 (*d*); 127.7 (*s*); 124.7 (*d*); 124.0 (*d*); 118.2 (*d*), 108.9 (*d*); 92.3 (*s*); 79.6 (*d*); 56.2 (*d*); 55.1 (*s*); 52.4 (*q*); 43.5 (*t*); 39.8 (*d*); 37.1 (*d*); 27.5 (2*t*); 27.4 (*q*); 25.5 (*q*); 24.6 (*q*).

(−)-1,10-Didehydro-11-ethoxy-2,12-cyclohobartine (= *(1*S*,10*S*)-10-Ethoxy-2,2,12-trimethyl-benzo[6,7]-3,5-diazatetracyclo[9.3.1.0^{3,10}.0^{4,8}]pentadeca-4,8,12-triene*; (−)-**24**). To a soln. of 108 mg (0.37 mmol) of (−)-hobartine (**22**) [23] in 6 ml of $CHCl_3$ containing 1% of EtOH as stabilizer were added 104 mg (0.75 mmol) of K_2CO_3 and 268 mg (1.05 mmol) of I_2. After stirring for 6 h at 23°, an additional 97 mg (0.7 mmol) of K_2CO_3 were added, and stirring was continued for 2 h. Then the mixture was poured on 20 ml of 1M aq. $Na_2S_2O_3$ and extracted with 30 ml of CH_2Cl_2 (3×). The combined org. extract was dried (K_2CO_3) and evaporated and the crude product chromatographed (silica gel, hexane/AcOEt 2 : 1): 48 mg (39%) of **24**. Orange foam. $[\alpha]_D = -380$ (*c* = 0.07, EtOH). UV (EtOH): 418 (3.00), 255 (4.59). UV (EtOH, 1 drop of conc. H_2SO_4): 372 (3.08). IR ($CHCl_3$): 3050, 3000, 2970, 2930, 1613, 1581, 1558, 1440, 1428, 1386, 1318, 1293, 1189, 1171, 1160, 1148, 1114, 1095, 1056. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37 (*dm*, *J* = 7.2, 1 H); 7.20 (*td*, *J* = 7.6, 1.3, 1 H); 7.15 (*dm*, *J* = 7.9, 1 H); 6.83 (*td*, *J* = 7.3, 1.3, 1 H); 6.44 (*s*, 1 H); 5.28 (*m*, 1 H); 3.37 (*m*, 2 H); 2.75 (*dm*, *J* = 12.6, 1 H); 2.63 (*m*, 1 H); 2.41 (*dm*, *J* = 19.4, 1 H); 2.06 (*dm*, *J* = 19.4, 1 H); 1.92 (*s*, 3 H); 1.69 (*dt*, *J* = 12.6, 3.1, 1 H); 1.65 (*m*, 1 H); 1.62 (*m*, 3 H); 1.53 (*s*, 3 H); 1.19 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 173.1 (*s*); 167.0 (*s*); 140.1 (*s*); 131.1 (*s*); 131.0 (*d*); 130.9 (*d*); 124.8 (*d*), 123.0 (*d*); 122.2 (*s*); 120.4 (*d*); 117.5 (*d*); 106.4 (*s*); 59.1 (*s*); 58.7 (*t*); 43.4 (*d*); 37.5 (*d*); 28.3 (*q*); 27.7 (*q*); 27.3 (*t*); 25.3 (*q*); 23.7 (*t*); 15.1 (*q*). HETCOR (200/50 MHz, $CDCl_3$): 131.0/6.44; 130.9/7.20; 124.8/5.28; 123.0/7.37; 120.4/6.83; 117.5/7.15; 58.7/3.37; 43.4/2.63; 37.5/1.63; 28.3/1.92; 27.7/1.53; 27.3/2.41 and 2.06; 25.3/1.62; 23.7/2.75 and 1.69; 15.1/1.19. EI-MS: 334 (34, M^+), 306 (22), 305 (100), 290 (28), 219 (7), 211 (7), 172 (11), 171 (87).

1,10-Didehydro-10-iodo-11-methoxy-2,12-cyclohobartine (= *(1*S*,10*R*)-9-Iodo-10-methoxy-2,2,12-trimethyl-benzo[6,7]-3,5-diazatetracyclo[9.3.1.0^{3,10}.0^{4,8}]pentadeca-4,8,12-triene*; **25**). To a soln. of 22 mg (0.074 mmol) of (−)-hobartine (**22**) [23] in 3 ml of MeOH were added 113 mg (1.37 mmol) of NaOAc and 102 mg (0.40 mmol) of I_2. After stirring for 6 h at 23°, the mixture was quenched by adding 3 ml of 1M aq. $Na_2S_2O_3$ and 20 ml of 1M aq. $NaHCO_3$ and was then extracted with 30 ml of CH_2Cl_2 (3×). The combined org. extract was dried (K_2CO_3) and evaporated and the crude product chromatographed (silica gel, hexane/AcOEt 85 : 15): 21 mg (63%) of **25**. Orange foam. IR ($CHCl_3$): 3000, 2960, 2835, 1614, 1580, 1561, 1442, 1428, 1379, 1320, 1284, 1253, 1094, 1066, 1049, 1011. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.63 (*ddd*, *J* = 7.3, 1.3, 0.6, 1 H); 7.28 (*td*, *J* = 7.7, 1.3, 1 H); 7.15 (*dt*, *J* = 7.8, 0.8, 1 H); 6.91 (*td*, *J* = 7.4, 1.0, 1 H); 5.31 (*m*, 1 H); 3.08 (*s*, 3 H); 2.76 (*dm*, *J* = 13.0, 1 H); 2.66 (*t*, *J* = 2.9, 1 H); 2.43 (*dm*, *J* = 19.4, 1 H); 2.07 (*dm*, *J* = 19.4, 1 H); 1.92 (*s*, 3 H); 1.72 (*m*, 3 H); 1.72 (*dt*, *J* = 12.5, 3.0, 1 H); 1.66 (*m*, 1 H); 1.54 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.1 (*s*); 166.2 (*s*); 147.3 (*s*); 131.9 (*d*); 130.7 (*s*); 125.8 (*d*); 122.6 (*d*), 122.4 (*s*); 120.6 (*d*); 117.8 (*d*); 107.4 (*s*); 101.0 (*s*); 60.3 (*s*); 50.1 (*q*); 42.6 (*d*); 37.9 (*d*); 28.2 (*q*); 27.8 (*q*); 27.7 (*t*); 26.3 (*q*); 23.9 (*t*).

17,20-Dihydro-3,17-epoxyneohobartine (= *2-[(1*S*)-4,4,8-Trimethyl-3-aza-12-oxapentacyclo[6.3.1^{5,9}.0^{2,7}.0^{3,10}]-tridec-1-yl]benzenamine*; **26**). To a soln. of 77.5 mg (0.24 mmol) of (+)-**19** in 1 ml of AcOH were added 10 ml of 48% aq. HBF_4 soln. The mixture was heated to 100° for 1 h and then poured on ice. The mixture was rendered basic by adding conc. aq. NH_3 soln. and extracted with 30 ml of CH_2Cl_2 (3×). The combined org. extract was dried (K_2CO_3) and evaporated and the crude product chromatographed (silica gel, AcOEt/MeOH 5 : 1): 27.7 mg (37%) of **26**. White powder. IR ($CHCl_3$): 3480, 3360, 3230, 2990, 2960, 2920, 2900, 1633, 1610, 1578, 1491, 1452, 1381, 1374, 1303, 1295, 1262, 1130, 1121, 1099, 1060, 1034, 1012. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.39 (*dd*, *J* = 7.7, 1.6, 1 H); 7.03 (*ddd*, *J* = 7.6, 7.3, 1.6, 1 H); 6.71 (*td*, *J* = 7.5, 1.2, 1 H); 6.60 (*dd*, *J* = 7.9, 1.2, 1 H); 4.27 (br. *s*, 2 H); 4.12 (*dm*, *J* = 4.2, 1 H); 3.69 (*dm*, *J* = 3.7, 1 H); 2.39 (*dd*, *J* = 11.4, 4.5, 1 H); 2.34 (*ddt*, *J* = 13.7, 3.9, 3.1, 1 H); 2.16 (*dq*, *J* = 13.7, 3.1, 1 H); 1.94 (*d*, *J* = 11.4, 1 H); 1.74 – 1.68 (*m*, 2 H); 1.57 – 1.56 (*m*, 2 H); 1.34 (*s*, 3 H); 1.29 (*s*, 3 H); 1.28 (*m*, 1 H); 1.25 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 143.9 (*s*); 127.6 (*d*); 126.0 (*s*); 125.7 (*d*); 117.4 (*d*); 115.9 (*d*); 88.3 (*s*), 83.4 (*s*); 66.8 (*d*); 59.6 (*d*); 53.7 (*s*); 43.4 (*t*); 42.4 (*d*); 37.8 (*d*); 31.0 (*d*); 29.0 (*t*); 27.6 (*q*); 26.5 (*t*); 26.4 (*q*); 20.8 (*q*). HETCOR (300/75 MHz, $CDCl_3$): 127.6/7.03; 125.7/7.39; 117.4/6.71; 115.9/6.60; 66.8/4.12; 59.6/3.69: 43.4/2.39 and 1.94; 42.4/1.56; 37.8/1.56; 31.0/1.28; 29.0/2.16 and 1.7; 27.6/1.29; 26.5/2.16 and 1.7; 26.4/1.25; 20.8/1.34. HMBC (300 MHz, $CDCl_3$): 143.9/7.39 and 7.03; 127.6/7.39; 126.0/6.71 and 6.60; 125.7/7.03; 117.4/6.60; 115.9/6.71; 88.3/7.39, 3.69 and 1.94; 83.4/4.12, 3.69, 2.39, 2.16 and 1.34; 66.8/3.69, 1.94 and 1.7; 59.6/4.12, 2.39 and 1.7; 53.7/1.7, 1.29 and 1.25; 43.4/4.12; 42.4/1.34; 37.8/2.39 and 1.34; 31.0/1.29 and 1.25. EI-MS: 310 (68, M^+), 295

(30), 199 (14), 190 (45), 176 (17), 158 (11), 146 (21), 130 (52), 120 (100), 93 (34), 92 (48), 77 (33), 65 (37), 58 (65), 43 (40), 42 (25), 41 (49).

(+)-11,12-Didehydromakomakine (=*(5*S*)-2-(1*H*-Indol-3-ylmethyl)-4,4-dimethyl-8-methylene-3-azabicyclo[3.3.1]non-2-ene*; (+)-**27**). To a soln. of 201.5 mg (0.68 mmol) of synthetic (+)-makomakine ((+)-**18**) in 7 ml of $CHCl_3$ were added 261.3 mg (1.03 mmol) of I_2. After stirring at 23° for 75 h, Et_3N (0.08 ml) was added. The mixture was poured onto 60 ml of H_2O and 6 ml of conc. aq. NH_3 soln. and extracted with 100 ml of $CHCl_3$ (3×). The combined org. extract was dried (K_2CO_3) and evaporated and the crude product chromatographed (silica gel, $CHCl_3$/Et_2O/Et_2NH 80:20:1): 114 mg (57%) of (+)-**27**. White powder. M.p. 100–108°. $[\alpha]_D = +188$ ($c = 1.3$, $CHCl_3$). UV (EtOH): 314 (3.42), 291 (3.54), 266 (3.70). IR ($CHCl_3$): 3480, 3070, 3000, 2935, 1629, 1518, 1456, 1421, 905. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.22 (br. *s*, 1 H); 7.67 (*dm*, *J* = 8.1, 1 H); 7.34 (*dt*, *J* = 8.1, 0.9, 1 H); 7.17 (*dddd*, *J* = 8.1, 7.2, 1.2, 0.3, 1 H); 7.10 (*ddd*, *J* = 7.9, 7.1, 1.0, 1 H); 7.02 (*m*, 1 H); 4.70 (*t*, *J* = 2.0, 1 H); 4.68 (*t*, *J* = 2.0, 1 H); 3.68 (*d*, *J* = 14.4, 1 H); 3.52 (*dd*, *J* = 14.4, 1.2, 1 H); 2.93 (*m*, 1 H); 2.18–1.99 (*m*, 2 H); 2.02 (*dm*, *J* = 13.5, 1 H); 1.87 (*dq*, *J* = 12.4, 3.1, 1 H); 1.70 (*m*, 1 H); 1.50 (*tdd*, *J* = 13.5, 5.8, 3.9, 1 H), 1.46 (*ddd*, *J* = 12.4, 3.4, 2.2, 1 H); 1.39 (*s*, 3 H); 1.27 (*s*, 3 H); deviations from reported chemical shifts [20b] at most ± 0.04 ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): 167.9 (*s*); 148.5 (*s*); 136.4 (*s*); 127.9 (*s*); 122.7 (*d*); 121.9 (*d*); 119.5 (*d*), 119.3 (*d*); 112.2 (*s*); 111.0 (*d*); 108.6 (*t*); 58.0 (*s*); 42.4 (*d*); 35.5 (*t*); 35.4 (*d*); 31.5 (*q*); 30.0 (*t*); 29.8 (*t*); 29.2 (*t*); 27.2 (*q*); deviations from reported chemical shifts [20b] at most ±0.2 ppm. EI-MS: 292 (90, M^+), 277 (10), 220 (15), 205 (30), 156 (100), 130 (17), 93 (17).

(+)-11,12-Didehydromakomakin-10-one (=*(5*S*)-4,4-Dimethyl-8-methylene-3-azabicyclo[3.3.1]non-2-en-2-yl 1*H*-indol-3-yl ketone* = 8-Oxo-9-dehydromakomakine [21b]; (+)-**28**). To a soln. of 149 mg (0.51 mmol) of synthetic (+)-makomakine ((+)-**18**) in 7 ml of $CHCl_3$ were added 5 ml of 1M aq. $NaHCO_3$ and 165.5 mg (0.65 mmol) of I_2. After stirring at 23° for 3 h, Et_3N (0.045 ml) was added. The mixture was stirred for an additional 30 min at 23° and then poured onto 45 ml of aq. 1M $Na_2S_2O_3$ and 6 ml of conc. aq. NH_3 soln. Extraction with 90 ml of $CHCl_3$ (3×), followed by drying the combined org. extracts (K_2CO_3) and evaporation led to a orange crude product, which was purified by chromatography (silica gel, $CHCl_3$/THF/Et_3N 100:20:5): 75 mg (50%) of (+)-**28**. Slightly yellow powder, which was crystallized from Et_2O. This product was identical in every respect with a compound synthesized earlier *via* a different route [14].

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