23. Synthesis of *Aristotelia*-Type Alkaloids

Part XV[1])

Total Synthesis of (+)-Hobartinol

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Synthetic (+)-makomakine (**6**) was transformed in six steps into (+)-(17*R*,18*R*)-17,18-dihydrohobartine-17,18-diol ((+)-**5**) with an overall yield of 38% (*Scheme 2*). This compound was shown to be identical with natural hobartinol, a monoterpene indole alkaloid from *Aristotelia australasica*, originally believed to be the (17*S*)-epimer **1**. At the same time, the synthesis of (+)-**5** delineates the hitherto unknown absolute configuration of this metabolite.

1. Introduction. – In 1986, *Quirion* reported the isolation of several novel monoterpene indole alkaloids from the aerial parts of the shrub *Aristotelia australasica* [4][3]) (for a review, see [5]). Among them was a compound named hobartinol having the elementary composition $C_{20}H_{28}N_2O_2$. The constitutional formula of this metabolite and the relative configuration at C(11), C(16), and C(18) were readily deduced on the basis of spectroscopic arguments. On the other hand, the configuration at the quaternary centre C(17) could only tentatively be assigned as shown in formula **1** (*Scheme 1*), the putative argument being the fact that, on treatment with Ac_2O in hot pyridine, hobartinol was transformed into a diacetyl derivative. This compound was believed to be *O,O*-diacetate **2**, and the ready acetylation of the tertiary OH group was explained by invoking a neighbouring-group effect of the piperidine N-atom[4]); thus, it was assumed that the OH group at C(17) occupies the *endo*-position in the parent alkaloid [4].

A critical re-evaluation of the reported ^{1}H-NMR data of the above diacetate, however, rather points to an $N(12),O^{18}$-diacyl derivative, since both Me groups attached to C(13) are deshielded by more than 0.4 ppm as compared to hobartinol (see below,

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

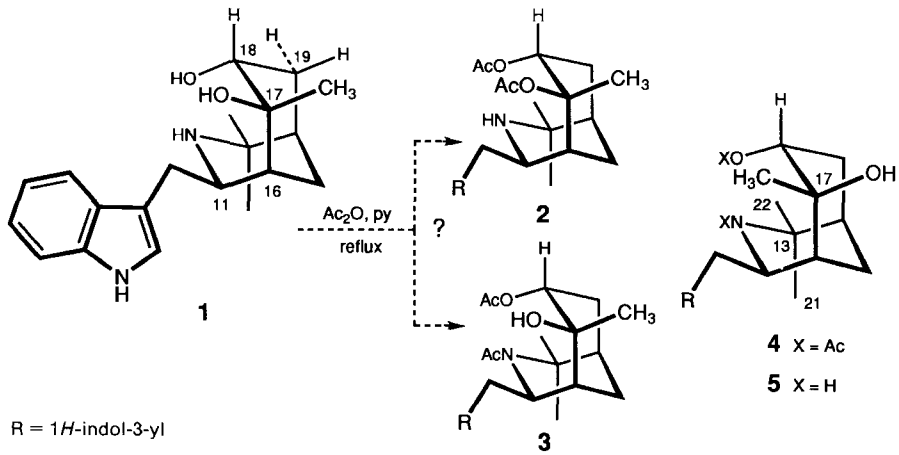
[2]) Taken in part from the diploma theses of *J. C. A.* [2], participant of the Imperial College (London)/ETH exchange scheme, and *M. J.* [3].

[3]) The authors would like to thank Prof. *H.-P. Husson* for providing them with a copy of this thesis.

[4]) During the presumed transformation of **1** into **2**, the intermediacy of **3** was invoked [4]. However, at least in the most stable conformation of **3**, the two centers of interest (*O*–C(17) and O=*C*–N(12)) seem too far apart for a significant interaction. Furthermore, amide **3** conceivably is thermodynamically more stable than ester **2**, so there is no obvious reason why the *N*-acetyl derivative **3** should rearrange to the latter.

Table 1) [6][5]). Provided that this new interpretation is correct, the argument originally put forward to delineate the relative configuration at C(17) of hobartinol is no longer valid, and either of the structure proposals **1** or **5** is compatible with the data gathered so far from this alkaloid [5]. With the aim to clarify this situation, the following investigation was undertaken.

Scheme 1



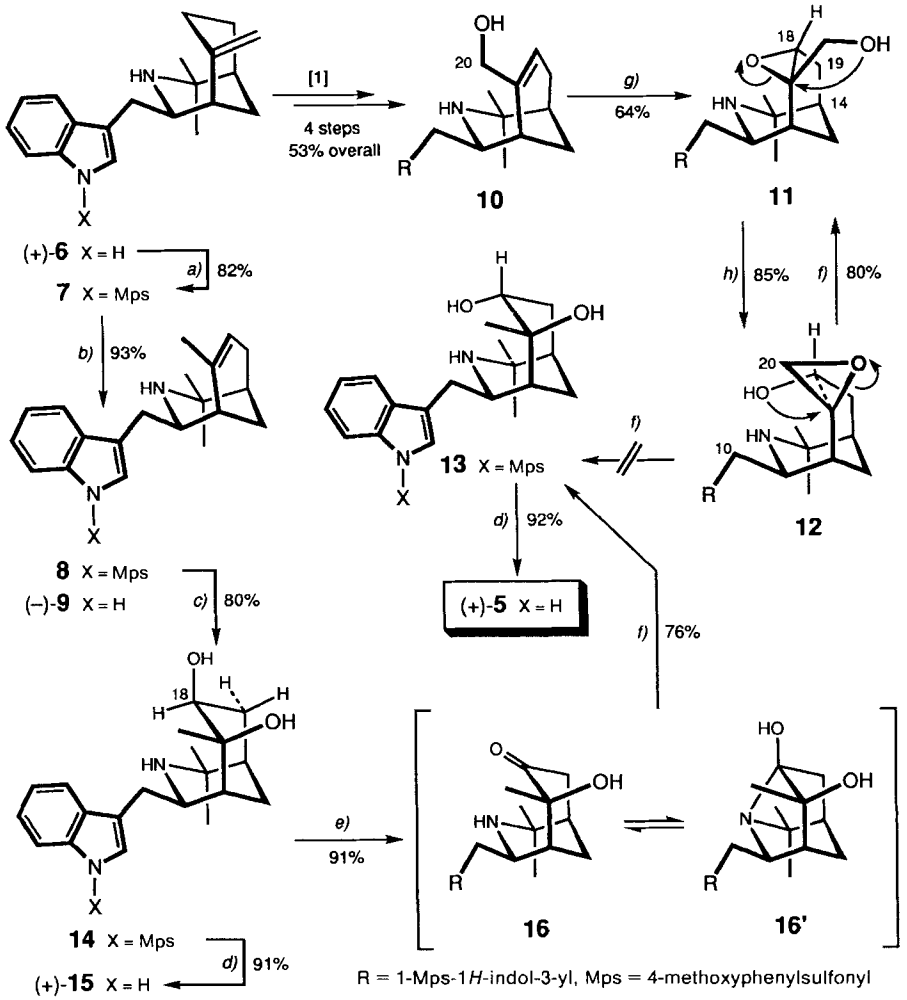
2. Results and Discussion. – Synthetic (+)-makomakine (**6**) [8] (*Scheme 2*) served as a convenient starting material for the envisaged transformations. The required amounts of optically pure (+)-**6** were prepared in two steps from (−)-β-pinene and (1*H*-indol-3-yl)-acetonitrile by employing a modified version [1] [9] of the original protocol developed by *Stevens* and *Kenney* [10]. After protection of the indole moiety with the 4-methoxyphenylsulfonyl group (Mps), the resulting **7** [1] was isomerized to the indole-protected derivative **8** of hobartine ((−)-**9**) in almost quantitative yield by simple treatment with hot mineral acid.

Our first attempt to synthesize (+)-**5** was governed by the finding that **8** furnished exclusively the corresponding (17*S*,18*R*)-epoxide when exposed to an organic peracid [2]. A similar treatment of indole-protected hobartin-20-ol **10**, which has become readily available in 100-mg quantities [1] [11], furnished the analogous epoxide **11** as the single product. The configuration at the new asymmetric centres followed from the observation that in the ^{1}H-NMR spectrum of **11**, one of the two H–C(19) shows only a geminal coupling (J = 16.7 Hz), the vicinal couplings with H–C(14) and H–C(18) amounting to less than 0.5 Hz. An inspection of *Dreiding* models showed that the required dihedral angles in the vicinity of 90° can only be assumed if the oxirane ring is placed on the concave face of the molecule (see *Fig. 1*)[6]).

[5]) Similarly, both Me groups show up at 1.64 ppm in the ^{1}H-NMR spectrum of the *N*(12)-acetyl derivative of hobartine (**9**), and at 1.74 and 1.43 ppm in the *N*-acetyl derivative of makomakine (**6**) [7].

[6]) The powerful *cis*-directing effect of the protonated piperidine N-atom on epoxidation reactions in this series was observed and discussed before [9] [12].

Scheme 2



a) 1. NaH, THF; 2. Mps-Cl. *b*) HCl, AcOH, 30 min reflux. *c*) 1. 1 equiv. of OsO_4, THF, 15 h at 25°; 2. Na_2SO_3, H_2O. *d*) 6% Na/Hg, NaH_2PO_4, MeOH. *e*) DMSO, $(CF_3CO)_2O$, CH_2Cl_2. *f*) $LiBHEt_3$, THF. *g*) 3-$ClC_6H_4CO_3H$, CF_3COOH, CH_2Cl_2, 72 h at 25°. *h*) $NaBH_4$, NaOH, *t*-BuOH, 25°.

Surprisingly, during an attempted reduction with $NaBH_4$, epoxide **11** was transformed into an isomeric compound which, according to its spectral data, must have structure **12** (see *Tables 1* and *2*). This outcome of a *Payne* rearrangement [13] was not unwelcome, since we hoped that **12** could be reduced to diol **13**, the immediate precursor of (+)-**5**. However, all attempts to bring about this reduction failed. Treatment with *Super Hydride*®, *e.g.*, just gave back the original epoxide **11**! Therefore, the following alternative route was developed.

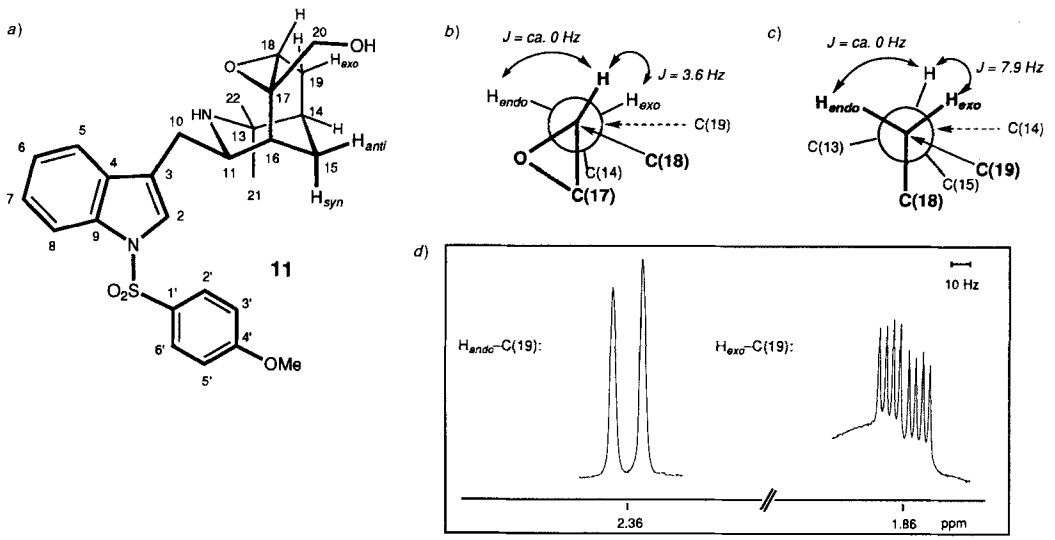


Fig. 1. a) *Biogenetic numbering of the hobartine skeleton.* b) Newman *projection along the C(18)–C(19) bond.* c) Newman *projection along the C(19)–C(14) bond.* d) ^{1}*H-NMR section of the* CH_2*(19) group*

cis-Hydroxylation of **8** with OsO_4 (stoichiometric amount or catalytic version [14]) furnished *exo*-diol **14** as the single isolable product in excellent yield. The configuration at C(18) followed from the evidently axial nature of H–C(18) which shows up in the ^{1}H-NMR spectrum as *dd* (J = 11.3 and 5.9 Hz) at 4.53 ppm[7]). Deprotection of **14** with sodium amalgam in MeOH [16] led to diol (+)-**15**, a diastereoisomer of hobartinol that has not been detected yet in natural sources. The corresponding (17*R*,18*R*)-diol **13** was prepared from **14** through a two-step oxidation/reduction procedure: the intermediate hydroxy-ketone **16** was obtained in high yield by applying *Banwell*'s method [17] and was found to exist as a 1:1 mixture of the keto and hemiaminal form **16'** which could not be separated. Reduction of the crude material with *Super Hydride*® produced the desired epimeric diol **13** as the single product. Standard deprotection furnished diol (+)-**5** which we believe to have the same structure as natural hobartinol.

This identification was not as straightforward and unambiguous as one might wish: synthetic (+)-**5** has m.p. 95–96°, *e.g.*, whereas the natural product was reported to melt at 270° after crystallization from $CHCl_3$ [4]. Since this value seemed suspiciously high for a tetracyclic *Aristotelia* alkaloid, we suspected that in the original work, the hydrochloride of hobartinol had actually been analyzed[8]). The same seems to hold for the determination

[7]) As in the analogous OsO_4 oxidation of 7 [1], the aliphatic amino group apparently exerts no *cis*-directing effect, which was shown recently to operate in the case of a vaguely similar substrate [15]. The reason might be that in our case, the N–Os bond of a complex between reagent and substrate (if formed at all) is exclusively equatorially aligned for steric reasons. Such an 'unproductive' complex seemingly cannot compete with the uncomplexed reagent attacking from the less hindered convex face of the olefinic double bond.

[8]) Conceivably, hydrochloric acid which is invariably present in commercial $CHCl_3$ caused formation of the hydrochloride. The same problem was encountered before in the *Aristotelia* alkaloid family, such as in the case of peduncularine [18] and of aristofruticosine [19].

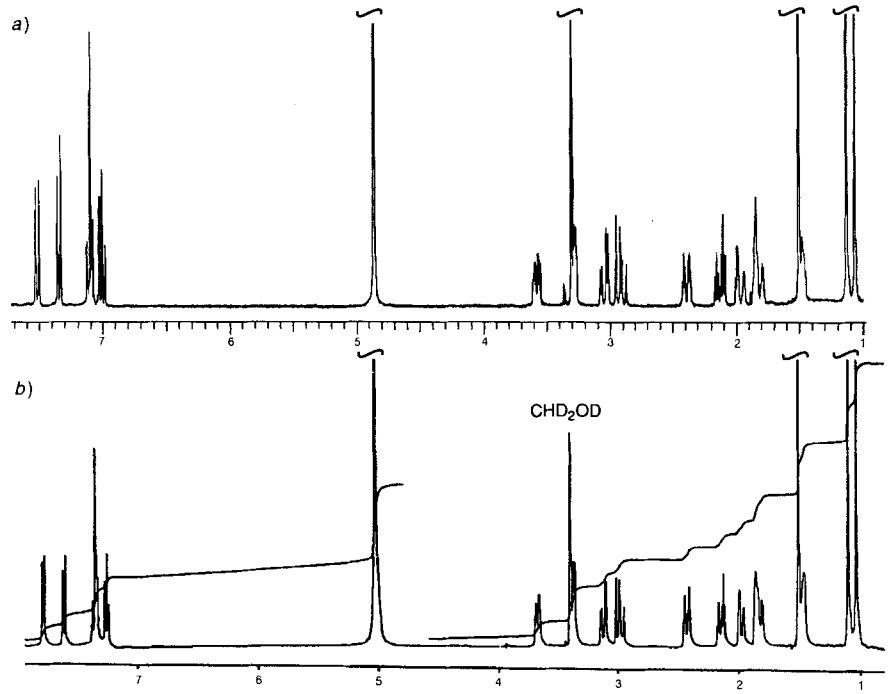


Fig. 2. *^{1}H-NMR Spectrum* (400 MHz, CD_3OD) a) *of synthetic (+)-***5** *and* b) *of natural (+)-hobartinol*

of the optical rotation $[\alpha]_D$ which was reported to amount to +120 [4], whereas our sample, derived from optically pure (+)-**6**, showed a value of only + 71.4. Therefore, the hydrochloride of synthetic (+)-**5** was prepared and analyzed, and indeed, the agreement between the two samples (m.p. 254° *vs.* 270° and $[\alpha]_D = +115$ *vs.* +120) was now significantly better. In addition, the ^{1}H-NMR spectra of the two specimen are virtually superimposable (see *Fig. 2*), and the readily prepared diacetate **4** displays ^{1}H- and ^{13}C-NMR data that coincide within experimental error with the one reported for the diacetate derived from natural hobartinol [4] (see *Tables 1* and *2*). Therefore, we believe that hobartinol has

Table 1. *^{1}H-NMR Chemical-Shift Values* δ [ppm]. In $CDCl_3$, unless stated otherwise.

	4	**4**[a])	**5**[b])	**5**[a])[b])	**9**	**15**	**8**	**14**	**13**	**11**	**12**
H–C(2)	7.03	7.00	7.10	7.35	7.09	7.01	7.44	7.34	7.36	7.44	7.38
H–C(5)	7.55	7.55	7.51	7.80	7.64	7.60	7.48	7.47	7.48	7.49	7.49
H–C(6)	7.11	7.11	7.01	7.27	7.11	7.11	7.22	7.24	7.25	7.22	7.25
H–C(7)	7.20	7.21	7.10	7.35	7.18	7.20	7.30	7.33	7.34	7.30	7.35
H–C(8)	7.37	7.37	7.34	7.62	7.35	7.36	7.99	8.01	8.02	7.98	8.02
H–C(10)	3.57	3.56	3.05	3.11	2.82	3.01	2.67	2.89	2.95	2.96	2.97
H′–C(10)	3.48	3.49	2.92	2.97	2.69	2.86	2.54	2.76	2.89	2.87	2.87
H–C(11)	4.14	4.15	3.59	3.67	3.49	3.52	3.38	3.41	3.45	3.29	3.41
H–C(14)	1.48	1.48	1.48	1.48	1.46	1.49	1.47	1.47	1.48	1.58	1.46
H_α–C(15)	1.80	1.74	1.80	1.83	2.08	1.74	2.08	1.70	1.78	1.98	2.09
H_β–C(15)	2.09	?	2.39	2.43	1.62	2.21	1.61	2.21	2.36	1.41	1.97

Table 1 (cont.)

	4	**4**[a])	**5**[b])	**5**[a])[b])	**9**	**15**	**8**	**14**	**13**	**11**	**12**
H–C(16)	1.86	1.86	1.85	1.87	2.17	1.91	2.09	1.86	1.79	1.65	1.64
H_α–C(18)	–	–	–	–	5.63	4.59	5.63	4.53	–	–	–
H_β–C(18)	4.86	4.88	3.30	3.27	–	–	–	–	3.31	3.14	3.08
H_α–C(19)	2.03	?	1.96	1.98	2.28	2.07	2.26	2.04	2.09	2.36	2.16
H_β–C(19)	2.03	?	2.13	2.15	2.08	1.55	2.07	1.56	2.02	1.86	1.96
Me(20)	1.48	1.49	1.51	1.52	1.81	1.53	1.72	1.46	1.53	3.55/3.45	2.96/2.71
Me(21)	1.60[c])	1.60[c])	1.07	1.02[c])	1.16	0.99	1.15	0.92	1.03[c])	1.21	1.12
Me(22)	1.58[c])	1.57[c])	1.13	1.10[c])	1.09	1.05	1.09	1.02	1.15[c])	1.08	1.17
H–C(2′), H–C(6′)	–	–	–	–	–	–	7.78	7.77	7.79	7.79	7.79
H–C(3′), H–C(5′)	–	–	–	–	–	–	6.85	6.85	6.87	6.85	6.87
MeOAr	–	–	–	–	–	–	3.78	3.77	3.78	3.78	3.79
Me–CCO	2.11	2.13	–	–	–	–	–	–	–	–	–
Me–CCO	2.09	2.07	–	–	–	–	–	–	–	–	–

[a]) Values taken from [4]. The systematic deviations in the low-field area of natural **5** are probably due to a scaling error in the previous work (see also *Fig. 2*).

[b]) CD_3OD as solvent.

[c]) Tentative assignments.

Table 2. *^{13}C-NMR Chemical-Shift Values* δ [ppm]. In $CDCl_3$, unless stated otherwise.

	7	**8**[a])	**14**	**13**	**11**	**12**	**4**	**4**[b])	**5**[a])[c])	**6**[a])	**9**[a])	**15**
C(2)	123.8	123.5	123.2[d])	123.4[d])	123.6	123.9	122.5	122.7	122.6	122.3	122.3	121.7
C(3)	120.6	119.8	121.4	120.3	120.8	119.1	114.4	114.6	113.2	113.9	113.5	114.4
C(4)	131.4	131.0	130.9	130.6	131.3	130.6	127.1	127.4	128.6	128.0	127.6	127.5
C(5)	119.7	119.6	119.5	119.4	119.6	119.4	119.5	119.6	119.2	119.3	118.9	119.3
C(6)	122.9	123.1	123.1[d])	123.3[d])	123.1	123.4	118.5	118.6	119.8	119.1	118.9	118.9
C(7)	124.6	125.9	124.9	125.1	124.7	125.1	122.1	122.3	123.8	121.8	121.6	122.1
C(8)	113.8	113.7	113.9	114.0	113.8	114.0	111.3	111.5	112.5	110.0	111.0	111.1
C(9)	135.5	135.2	135.6	135.6	135.3	135.5	136.5	136.8	138.4	136.5	136.3	136.5
C(10)	31.8	29.7	32.1	31.4	30.2	30.2	31.0[e])	31.2	32.7	31.5	31.7	32.4
C(11)	53.3	54.1	55.0	54.7	54.2	52.9	59.6	59.9	57.0	54.2	54.6	55.8
C(13)	53.1	55.5	53.0	52.6	50.9	52.4	58.9	59.1	53.5	53.1	54.2	53.0
C(14)	36.5	34.8	38.4	37.1	28.7	36.8	41.8	42.0	38.7	35.9	35.1	38.6
C(15)	33.0	28.7	28.8	28.2	28.0[d])	29.2	29.8[e])	30.0	29.1	33.3	29.3	28.9
C(16)	43.2	36.7	46.5	45.1	34.6	41.6	43.4	43.9	45.8	43.5	38.3	46.5
C(17)	150.0	132.2	74.4	75.2	64.3	59.7	74.3	74.6	75.7	150.6	133.5	74.6
C(18)	31.1	124.7	71.0	72.3	52.1	70.7	74.3	74.5	73.1	32.0	124.7	71.0
C(19)	29.2	27.6	33.9	30.9	26.1[d])	33.6	30.8[e])	30.9	31.8	29.4	27.9	34.0
C(20)	109.0	25.1	28.0	28.7[e])	63.7	54.0	29.5	29.6	28.6	108.6	25.7	28.0
C(21)	27.2	25.6	26.3	25.9	26.1	26.0	26.6	26.6	25.8	27.2	25.9	26.3
C(22)	29.8	28.9	29.5	28.8[e])	29.7	29.7	30.4	30.5	28.8	29.8	30.0	29.5
C(1′)	129.8	129.7	129.7	129.6	129.8	129.6	–	–	–	–	–	–
C(2′), C(6′)	128.9	129.0	128.9	128.9	129.0	129.0	–	–	–	–	–	–
C(3′), C(5′)	114.3	114.4	114.4	114.5	114.3	114.5	–	–	–	–	–	–
C(4′)	163.6	163.7	163.7	163.8	163.6	163.8	–	–	–	–	–	–
MeO	55.6	55.6	55.6	55.6	55.6	55.7	–	–	–	–	–	–

[a]) Assignments corroborated through HETCOR experiments.

[b]) Taken from [4]. The signals in the aliphatic section were not assigned and their multiplicities not specified [4].

[c]) In CD_3OD.

[d])[e]) Assignments may be interchanged.

the relative and absolute configuration shown in formula **5**. For comparison purposes and for a final settlement of the argument, it would have been ideal to have access to compound **1** as well, but unfortunately, all attempts to prepare **1** have failed up to now.

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Experimental Part

General. Reagents and solvents: 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], $\log\varepsilon$ [dm^3/mol·cm]): *Kontron Uvikon 869*. IR Spectra ($\tilde{\nu}_{max}$ [cm^{-1}]): *Perkin-Elmer-PE-781* spectrometer. ^{1}H-NMR Spectra: δ in ppm. rel. to internal $SiMe_4$ (= 0 ppm), J in Hz; 400 MHz, *Bruker AMX 400;* 500 MHz, *Bruker AMX 500*. ^{13}C-NMR Spectra: 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, $\delta(^{13}C)/\delta(^1H)$('s). 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.

Standard Deprotection Procedure [16]. To a soln. of the specified amount of the indole-protected component in MeOH (90 ml per mmol of substrate) were added 2 equiv. of NaH_2PO_4 and 8 equiv. of 6% sodium amalgam. After stirring at 25° for 4–12 h (TLC control), the solvent was decanted from the inorg. material and evaporated. The residue was purified as indicated.

1-[(4-Methoxyphenyl)sulfonyl]hobartine (= *(1S,4R,5S)-4-{{1-[(4-Methoxyphenyl)sulfonyl]-1H-indol-3-yl}methyl}-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-6-ene*; **8**). To a soln. of 1 g (2.16 mmol) of **7** [1] in 80 ml of AcOH were added 200 ml of conc. aq. HCl soln. and 200 ml of H_2O at r.t. under Ar. The mixture was refluxed for 30 min, cooled to 0°, and then poured onto ice-cold 30% aq. NaOH soln. Workup with CH_2Cl_2 furnished 934 mg (93%) of **8**. White foam. IR ($CHCl_3$): 2915, 1593, 1578, 1495, 1444, 1367, 1260, 1182, 1162, 1126, 1117, 1097, 1018, 971, 828. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.99 (*dm*, J = 8.2, 1 H); 7.78 (*dm*, J = 9.1, 2 H); 7.48 (*dm*, J = 7.7, 1 H); 7.44 (*s*, 1 H); 7.30 (*ddd*, J = 8.4, 7.3, 1.2, 1 H); 7.22 (*ddd*, J = 8.2, 7.4, 1.1, 1 H); 6.85 (*dm*, J = 9.1, 2 H); 5.63 (*m*, 1 H); 3.78 (*s*, 3 H); 3.38 (*dt*, 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 (75 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), 165 (16), 164 (100), 130 (11).

17,18-Dihydro-1-[(4-methoxyphenyl)sulfonyl]hobartine-17β,18β-diol (= *(1R,4R,5R,6R,7S)-4-{{1-[(4-Methoxyphenyl)sulfonyl]-1H-indol-3-yl}methyl}-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonane-6,7-diol;* **14**). To a soln. of 100 mg (0.216 mmol) of **8** in 25 ml of THF were added 56.2 mg (0.216 mmol) of OsO_4 (*Fluka, puriss.*) at 0°. After stirring for 3 h at 25°, the yellow mixture was refluxed for 12 h. After cooling to 25°, a soln. of 200 mg of Na_2SO_3 in 10 ml of H_2O was added. Workup with $CHCl_3$ and aq. NH_3 soln. furnished a crude product that was chromatographed (silica gel, AcOEt/hexane 2:1); 86.2 mg (80%) of **14**. Colorless crystals. M.p. 79–81° (AcOEt). IR ($CHCl_3$): 3540, 3500, 2940, 1592, 1575, 1491, 1367, 1306, 1268, 1161, 1094, 1016, 972. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.01 (*dt*, J = 8.2, 0.8, 1 H); 7.77 (*dm*, J = 9.1, 2 H); 7.47 (*dtm*, J = 7.6, 0.9, 1 H); 7.34 (*s*, 1 H); 7.33 (*ddd*, J = 8.2, 7.3, 1.2, 1 H); 7.24 (*ddd*, J = 8.2, 7.3, 1.0, 1 H); 6.85 (*dm*, J = 9.1, 2 H); 4.53 (*dd*, J = 11.3, 5.9, 1 H); 3.77 (*s*, 3 H); 3.41 (*dt*, J = 11.3, 2.6, 1 H); 2.89 (*ddd*, J = 14.6, 2.9, 1.1, 1 H); 2.76 (*dd*, J = 14.5, 10.6, 1 H); 2.21 (*dt*, J = 13.1, 3.2, 1 H); 2.12 (br. *s*, 2 H); 2.04 (*ddt*, J = 13.0, 5.9, 2.3, 1 H); 1.86 (*q*, J = 2.5, 1 H); 1.70 (*dq*, J = 13.1, 2.8, 1 H); 1.56 (*ddd*, J = 13.0, 11.3, 4.2, 1 H); 1.47 (*m*, 1 H); 1.46 (*s*, 3 H); 1.02 (*s*, 3 H); 0.92 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.7 (*s*); 135.6 (*s*), 130.9 (*s*); 129.7 (*s*); 128.9 (2*d*); 124.9 (*d*); 123.2 (*d*); 123.1 (*d*); 121.4 (*s*); 119.5 (*d*); 114.4 (2*d*); 113.9 (*d*); 74.4 (*s*); 71.0 (*d*); 55.6 (*q*); 55.0 (*d*); 53.0 (*s*); 46.5 (*d*); 38.4 (*d*); 33.9 (*t*); 32.1 (*t*); 29.5 (*q*); 28.8 (*t*); 28.0 (*q*); 26.3 (*q*). EI-MS: 498 (< 1, M^+), 483 (3), 309 (7), 198 (100), 171 (11), 130 (28), 107 (14), 77 (12), 56 (13), 43 (12).

(+)-17,18-Dihydrohobartine-17β,18β-diol (= *(1R,4R,5R,6R,7S)-4-[(1H-Indol-3-yl)methyl]-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonane-6,7-diol;* (+)-**15**). The general deprotection method, applied to 50 mg (0.1 mmol) of

14, furnished a crude product that was chromatographed (silica gel, AcOEt/MeOH 5:1): 29.8 mg (91%) of (+)-**15**. Colorless crystals. M.p. 80–81° (AcOEt). $[\alpha]_D = +51.1$ ($c = 1.17$, $CHCl_3$). UV (EtOH): 290 (3.49), 282 (3.56), 222 (4.32). IR ($CHCl_3$): 3540, 3460, 3300, 2940, 1592, 1449, 1373, 1082, 1011, 903. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.08 (br. *s*, 1 H); 7.60 (*dm*, $J = 8.0$, 1 H); 7.36 (*dt*, $J = 8.1, 0.9$, 1 H); 7.20 (*ddd*, $J = 8.3, 7.1, 1.1$, 1 H); 7.11 (*ddd*, $J = 8.0, 7.1, 1.1$, 1 H); 7.01 (*d*, $J = 2.3$, 1 H); 4.59 (*dd*, $J = 11.2, 6.0$, 1 H); 3.52 (*ddd*, $J = 10.5, 2.9, 2.5$, 1 H); 3.01 (*ddd*, $J = 14.3, 3.2, 1.0$, 1 H); 2.86 (*dd*, $J = 14.3, 10.5$, 1 H); 2.21 (*dt*, $J = 13.1, 3.2$, 1 H); 2.07 (*ddt*, $J = 13.0, 6.0, 2.7$, 1 H); 1.91 (*m*, 1 H); 1.74 (*dq*, $J = 13.1, 2.9$, 1 H); 1.55 (*ddd*, $J = 13.0, 11.2, 4.2$, 1 H); 1.53 (*s*, 3 H); 1.49 (*m*, 1 H); 1.05 (*s*, 3 H); 0.99 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 136.5 (*s*); 127.5 (*s*); 122.1 (*d*); 121.7 (*d*); 119.3 (*d*); 118.9 (*d*); 114.4 (*s*); 111.1 (*d*); 74.6 (*s*); 71.0 (*d*); 55.8 (*d*); 53.0 (*s*); 46.5 (*d*); 38.6 (*d*); 34.0 (*t*); 32.4 (*t*); 29.5 (*q*); 28.9 (*t*); 28.0 (*q*); 26.3 (*q*). EI-MS: 328 (2, M^+), 313 (12), 311 (10), 199 (13), 198 (100), 180 (17), 130 (28).

*(+)-Hobartinol (=(1*R*,4*R*,5*R*,6*R*,7*R*)-4-[(1H-Indol-3-yl)-methyl]-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonane-6,7-diol; (+)-***5***).* To a soln. of 0.60 ml (7.5 mmol) of DMSO in 15 ml of CH_2Cl_2 under Ar were added 1.1 ml (7 mmol) of trifluoroacetic anhydride (*Fluka, puriss.*) at −78°. The slightly turbid mixture was stirred at −78° for 1 h, then there was added slowly a soln. of 200 mg (0.40 mmol) of **14** in 5 ml of CH_2Cl_2. After stirring for 90 min at −78°, 3 ml of Et_3N were added, and stirring was continued for 1 h. Workup with $CHCl_3$ furnished a yellow oil that was filtered through a small column (2 g of silica gel, AcOEt/hexane 1:1) to give 181 mg (91%) of **16**/**16′** as a slightly yellow unstable oil that was not further purified nor characterized. To a soln. of 115 mg (0.232 mmol) of this intermediate in 20 ml of THF were added 0.5 ml of 1M $LiBHEt_3$ in THF (*Aldrich*) at 0° under Ar. After stirring for 30 min at 0°, the cooling bath was removed and stirring continued for an additional 30 min. Workup with aq. NH_3 soln. and $CHCl_3$ furnished a crude product that was chromatographed (silica gel, AcOEt/MeOH 5:1) to give 88 mg (76%) of **13** as a colorless crystalline compound (m.p. 109–110° (Et_2O)). Standard deprotection of 45 mg (0.90 mmol) of **13** furnished a crude product that was chromatographed (silica gel, AcOEt/MeOH 5:1): 27.3 mg (92%) of (+)-**5**. Colorless crystals. M.p. 95–96° (Et_2O; [4]: 270° ($CHCl_3$)). $[\alpha]_D = +75.8$ ($c = 0.5$, $CHCl_3$). $[\alpha]_D = +71.4$ ($c = 0.8$, MeOH; [4]: +120 ($c = 0.8$, MeOH)). UV (EtOH): 290 (3.59), 282 (3.65), 250 (3.41), 222 (4.43). IR ($CHCl_3$): 3470, 3290, 2955, 2900, 1450, 1423, 1381, 1113, 1070, 1028, 970, 878. ^{1}H-NMR (400 MHz, CD_3OD): 7.51 (*dt*, $J = 7.8, 1.1$, 1 H); 7.34 (*dt*, $J = 8.1, 0.9$, 1 H); 7.10 (*s*, 1 H); 7.10 (*ddd*, $J = 8.1, 7.0, 1.2$, 1 H); 7.01 (*ddd*, $J = 7.8, 7.0, 1.1$, 1 H); 3.59 (*ddd*, $J = 10.2, 4.0, 2.6$, 1 H); 3.30 (*m*, 1 H); 3.05 (*ddd*, $J = 14.3, 3.1, 0.9$, 1 H); 2.92 (*dd*, $J = 14.3, 10.3$, 1 H); 2.39 (*dt*, $J = 13.1, 3.1$, 1 H); 2.13 (*dt*, $J = 14.9, 4.7$, 1 H); 1.96 (*dq*, $J = 14.7, 2.1$, 1 H); 1.85 (*m*, 1 H); 1.80 (*dq*, $J = 13.0, 3.0$, 1 H); 1.51 (*s*, 3 H); 1.48 (*m*, 1 H); 1.13 (*s*, 3 H); 1.07 (*s*, 3 H); max. deviation from natural (+)-**5** [4]: ± 0.05 ppm in the aliphatic region. ^{13}C-NMR (100 MHz, CD_3OD): 138.4 (*s*); 128.6 (*s*); 123.8 (*d*); 122.6 (*d*); 119.8 (*d*); 119.2 (*d*); 113.2 (*s*); 112.5 (*d*); 75.7 (*s*); 73.1 (*d*); 57.0 (*d*); 53.5 (*s*); 45.8 (*d*); 38.7 (*d*); 32.7 (*t*); 31.8 (*t*); 29.1 (*t*); 28.8 (*q*); 28.6 (*q*); 25.8 (*q*). HETCOR: 123.8/7.10; 122.6/7.10; 119.8/7.01; 119.2/7.51; 112.5/7.34; 73.1/3.30; 57.0/3.59; 45.8/1.85; 38.7/1.48; 32.7/3.05, 2.92; 31.8/2.13, 1.96; 29.1/2.39, 1.80; 28.8/1.13; 28.6/1.51; 25.8/1.07. EI-MS: 328 (5, M^+), 313 (7), 198 (100), 180 (12), 159 (34), 154 (14), 131 (31), 130 (77), 117 (24), 58 (48), 43 (33).

*17α,18α-Epoxy-17,18-dihydro-1-[(4-methoxyphenyl)sulfonyl]hobartin-20-ol (=(1*R*,4*R*,5*R*,6*R*,7*R*)-6,7-Epoxy-4-{{1-[(4-methoxyphenyl)sulfonyl]-1*H*-indol-3-yl}methyl}-2,2-dimethyl-3-azabicyclo[3.3.1]nonane-6-methanol;* **11**).* *Method A:* To a soln. of 50 mg (0.10 mmol) of **10** [1] [11] in 10 ml of CH_2Cl_2 were added 10 µl (0.12 mmol) of CF_3COOH (*Fluka, purum*) at 0° and a soln. of 18.2 mg of 3-chloroperbenzoic acid (*Fluka, pract.*; purified according to [20]) in 1 ml of CH_2Cl_2. After stirring for 72 h at 25°, 0.5 ml of Me_2S (*Fluka, puriss.*) were added, and the mixture was worked up with $CHCl_3$ and aq. NH_3 soln. Chromatography (silica gel, AcOEt/MeOH 1:1) furnished 33 mg (64%) of **11**. Colorless crystals. M.p. 85–86° (Et_2O). IR ($CHCl_3$): 3550, 2960, 2900, 1596, 1577, 1496, 1448, 1369, 1261, 1164, 1097, 908, 831. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.98 (*dt*, $J = 8.2, 0.9$, 1 H); 7.79 (*dm*, $J = 9.1$, 2 H); 7.49 (*ddd*, $J = 7.8, 1.1, 0.8$, 1 H); 7.44 (*s*, 1 H); 7.30 (*ddd*, $J = 8.3, 7.3, 1.1$, 1 H); 7.22 (*ddd*, $J = 7.9, 7.3, 1.0$, 1 H); 6.85 (*dm*, $J = 9.1$, 2 H); 3.78 (*s*, 3 H); 3.55 (*d*, $J = 12.4$, 1 H); 3.45 (*d*, $J = 12.4$, 1 H); 3.29 (*ddd*, $J = 9.0, 5.3, 2.8$, 1 H); 3.14 (*d*, $J = 3.6$, 1 H); 2.96 (*ddd*, $J = 15.3, 9.0, 0.7$, 1 H); 2.87 (*ddd*, $J = 15.3, 5.3, 1.5$, 1 H); 2.36 (*d*, $J = 16.7$, 1 H); 1.98 (*dm*, $J = 13.1$, 1 H); 1.86 (*ddd*, $J = 16.7, 7.9, 3.6$, 1 H); 1.65 (*q*, $J = 3.0$, 1 H); 1.58 (*dt*, $J = 7.9, 3.5$, 1 H); 1.41 (*dt*, $J = 13.1, 3.4$, 1 H); 1.21 (*s*, 3 H); 1.08 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 163.6 (*s*); 135.3 (*s*); 131.1 (*s*); 129.8 (*s*); 129.0 (2*d*); 124.7 (*d*); 123.6 (*d*); 123.1 (*d*); 120.8 (*s*); 119.6 (*d*); 114.3 (2*d*); 113.8 (*d*); 64.3 (*s*); 63.7 (*t*); 55.6 (*q*); 54.2 (*d*); 52.1 (*d*); 50.9 (*s*); 34.6 (*d*); 30.2 (*t*); 29.7 (*q*); 28.7 (*d*); 28.0 (*t*); 26.12 (*t*); 26.07 (*q*). FAB-MS: 497 (100, $[M + 1]^+$), 196 (28), 123 (52), 107 (96), 91 (23), 81 (64), 78 (52), 77 (80), 69 (92), 55 (98).

Method B: A soln. of 10 mg (0.02 mmol) of **12** (see below) in 5 ml of THF was cooled to − 20° under Ar. With rapid stirring, 0.1 ml of 1M $LiBHEt_3$ in THF (*Aldrich*) was added *via* syringe. Then the cooling bath was removed and stirring continued for 16 h at 25°. Quenching with 2 ml of sat. aq. NHCl soln., followed by workup with $CHCl_3$ and aq. NH_3 soln., and chromatography (silica gel, AcOEt) furnished 8 mg (80%) of crystalline **11** which was indistinguishable from a sample prepared by *Method A*.

17β,20-Epoxy-17,18-dihydro-1-[(4-methoxyphenyl)sulfonyl]hobartin-18α-ol (= *(1*R,*4*R,*5*R,*6*S,*7*R*)-4-{[1-[(4-Methoxyphenyl)sulfonyl]-1*H*-indol-3-yl}methyl}-2,2-dimethylspiro[3-azabicyclo[3.3.1]nonane-6,2'-oxiran]-7-ol;* **12**). To a soln. of 27 mg (0.055 mmol) of **11** in 8 ml of *t*-BuOH were added 2 ml of aq. 0.25N NaOH and 5 mg of $NaBH_4$ (*Fluka, purum*) at 25°. After stirring for 12 h, the mixture was worked up with $CHCl_3$ and aq. NH_3 soln. Chromatography (silica gel, AcOEt/MeOH 1:0 → 1:2) furnished 23 mg (85%) of **12**. Colorless plates. M.p. 84–85° (Et_2O). IR ($CHCl_3$): 3550, 2960, 2920, 1593, 1578, 1496, 1460, 1446, 1370, 1260, 1162, 1100, 1083, 908, 831. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.02 (*dt*, *J* = 8.3, 0.8, 1 H); 7.79 (*dm*, *J* = 9.1, 2 H); 7.49 (*dm*, *J* = 7.9, 1 H); 7.38 (*s*, 1 H); 7.35 (*ddd*, *J* = 8.3, 7.3, 1.1, 1 H); 7.25 (*ddd*, *J* = 8.1, 7.3, 1.0, 1 H); 6.87 (*dm*, *J* = 9.1, 2 H); 3.79 (*s*, 3 H); 3.41 (*dt*, *J* = 10.1, 3.1, 1 H); 3.08 (*dm*, *J* = 3.6, 1 H); 2.97 (*dd*, *J* = 14.6, 10.4, 1 H); 2.96 (*d*, *J* = 4.5, 1 H); 2.87 (*ddd*, *J* = 14.6, 3.8, 0.8, 1 H); 2.71 (*d*, *J* = 4.5, 1 H); 2.16 (*dq*, *J* = 15.0, 1.5, 1 H); 2.09 (*dq*, *J* = 13.3, 3.2, 1 H); 1.97 (*dt*, *J* = 13.3, 3.0, 1 H); 1.96 (*dt*, *J* = 15.0, 5.1, 1 H); 1.64 (*m*, 1 H); 1.46 (*m*, 1 H); 1.17 (*s*, 3 H); 1.12 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 163.8 (*s*); 135.5 (*s*); 130.6 (*s*); 129.6 (*s*); 129.0 (2*d*); 125.1 (*d*); 123.9 (*d*); 123.4 (*d*); 119.4 (*d*); 119.1 (*s*); 114.5 (2*d*); 114.0 (*d*); 70.7 (*d*); 59.7 (*s*); 55.7 (*q*); 54.0 (*t*); 52.9 (*d*); 52.4 (*s*); 41.6 (*d*); 36.8 (*d*); 33.6 (*t*); 30.2 (*t*); 29.7 (*q*); 29.2 (*t*); 26.0 (*q*). EI-MS: 496 (1, M^+), 481 (3), 325 (12), 196 (100), 178 (62), 171 (31), 130 (65), 123 (21), 117 (12), 107 (59), 93 (17), 92 (35), 91 (22), 81 (18), 78 (13), 77 (73), 69 (34), 58 (54), 55 (40).

(+)-12,O^{18}-Diacetylhobartinol (=*18-Acetoxy-12-acetyl-17,18-dihydrohobartin-17-ol* = *(1*R,*4*R,*5*R,*6*R,*7*R*)-7-Acetoxy-3-acetyl-4-[(1*H*-indol-3-yl)methyl]-2,2,6-trimethyl-3-azabicyclo[3.3.1]nonan-6-ol;* (+)-**4**). To a soln. of 6 mg (0.018 mmol) of synthetic (+)-**5** in 4 ml of CH_2Cl_2/pyridine 1:1 was added 1 ml of Ac_2O at 25°. After stirring for 72 h, the mixture was diluted with 20 ml of CH_2Cl_2 and washed with 20 ml of sat. aq. $NaHCO_3$ soln. and with 20 ml of sat. aq. $CuSO_4$ soln. After drying (K_2CO_3) and evaporation of the org. phase, the crude product was chromatographed (silica gel, AcOEt): 5.2 mg (69%) of (−)-**4**. Oil. $[\alpha]_D = -107$ (*c* = 0.28, $CHCl_3$). IR ($CHCl_3$): 3611, 2970, 1720, 1621, 1442, 1388, 1242, 1041, 875, 649. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.02 (br. *s*, 1 H); 7.55 (*dm*, *J* = 7.9, 1 H); 7.37 (*dt*, *J* = 8.1, 0.9, 1 H); 7.20 (*ddd*, *J* = 8.1, 7.1, 1.1, 1 H); 7.11 (*ddd*, *J* = 7.9, 7.1, 1.0, 1 H); 7.03 (*d*, *J* = 2.3, 1 H); 4.86 (*m*, 1 H); 4.14 (*ddd*, *J* = 8.7, 6.9, 1.0, 1 H); 3.67 (*s*, 1 H); 3.57 (*ddd*, *J* = 14.9, 6.9, 0.9, 1 H); 3.48 (*dd*, *J* = 14.9, 8.7, 1 H); 2.11 (*s*, 3 H); 2.09 (*s*, 3 H); 2.09 (*dt*, *J* = 12.9, 3.0, 1 H); 2.05–2.00 (*m*, 2 H); 1.86 (*m*, 1 H); 1.80 (*dm*, *J* = 12.9, 1 H); 1.60 (*s*, 3 H); 1.58 (*s*, 3 H); 1.48 (*s*, 3 H); 1.48 (*m*, 1 H); max. deviation from **4**, derived from natural (+)-**5** [4]: ± 0.06 ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): 172.4 (*s*); 171.0 (*s*); 136.5 (*s*); 127.1 (*s*); 122.5 (*d*); 122.1 (*d*); 119.5 (*d*); 118.5 (*d*); 114.4 (*s*); 111.3 (*d*); 74.3 (*d* + *s*); 59.6 (*d*); 58.9 (*s*); 43.4 (*d*); 41.8 (*d*); 31.0 (*t*); 30.8 (*t*); 30.4 (*q*); 29.8 (*t*); 29.5 (*q*); 26.6 (*q*); 23.7 (*q*); 21.1 (*q*); max. deviation from **4**, derived from natural (+)-**5** [4]: ± 0.5 ppm. EI-MS: 240 (36, [M −172]$^+$), 180 (15), 169 (30), 168 (22), 156 (11), 130 (100), 117 (14), 100 (17), 98 (26), 58 (16), 43 (93).

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