11. Synthesis of *Aristotelia*-Type Alkaloids

Part VI[1])

Biomimetic Synthesis of (+)-Aristofruticosine

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(*S*)-Perilla alcohol (**5**) was transformed into (*S*)-7-(phenylthio)-*p*-menth-1-en-8-amine (**11**) in five steps. Condensation of this building block with 1-(4-methoxyphenylsulfonyl)-1*H*-indole-3-acetaldehyde (**12**) led to the expected imine **15** which cyclized in 54% yield to protected 20-(phenylthio)hobartine **16** upon exposure to anh. HCOOH. Treatment of this intermediate with an alkylating reagent led to (+)-aristofruticosine protected in the indole moiety *via* an intramolecular, allylic nucleophilic displacement reaction. Subsequent reductive removal of the protecting group completed the first synthesis of the *Aristotelia* alkaloid (+)-aristofruticosine ((+)-**4**). This straightforward synthesis confirmed the tentative structure (+)-**4**, proposed by *Bick* and *Hai*, and established the hitherto unknown absolute configuration of this metabolite.

1. Introduction. – The indole alkaloid (+)-aristofruticosine ((+)-**4**) was isolated by *Bick* and *Hai* [2] [3] as a constituent of the New Zealand plant *Aristotelia fruticosa* HOOK F. Spectroscopic evidence led the same authors to propose the tentative structure (+)-**4** for this metabolite (*Scheme 1*). Furthermore, they speculated that (+)-**4** is formed biogenetically *via* protonation of (+)-sorelline (**2**) [4] at C(19)[3]), followed by intramolecular quenching of the incipient allyl cation by nucleophilic attack of N(12) at C(18) [3]. Although an enzymatically controlled version of such a process seems entirely feasible, there is little chance to mimic this reaction *in vitro*[4]), because the aliphatic amino group is far more basic than the diene unit. The following, alternative synthetic route to (+)-**4** circumvents this problem and thus seemed more attractive: given access to a hobartine derivative bearing a leaving group X at C(20)[5]), the critical N(12)–C(18) bond could be formed under *basic* conditions *via* an intramolecular S_Ni' process (*Scheme 1*).

Since earlier attempts to functionalize C(20) of synthetic (–)-hobartine (**1**) [9] had been unsuccessful [10], the necessary functional group had to be incorporated into the monoterpene building block required according to our general strategy towards the synthesis of *Aristotelia* alkaloids [9] [11].

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[1]) Part V: [1].

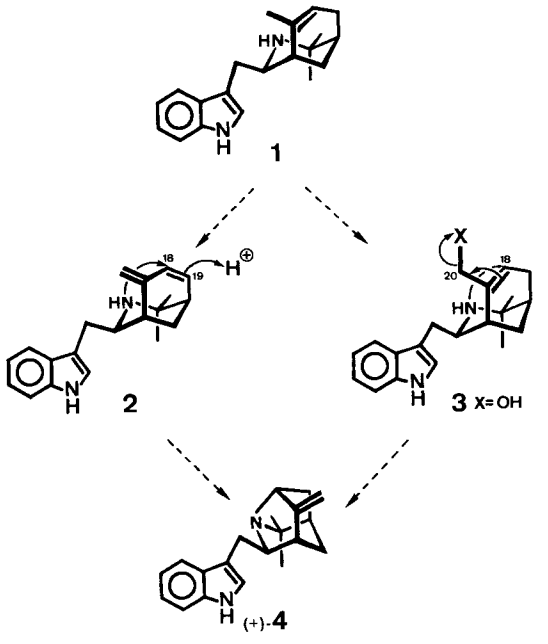
[2]) Taken in part from the diploma thesis of *R. B.*, ETH Zürich, 1988.

[3]) Biogenetic numbering [5].

[4]) Racemic and optically pure samples of sorelline (**2**) have been synthesized recently in our laboratory [6][7].

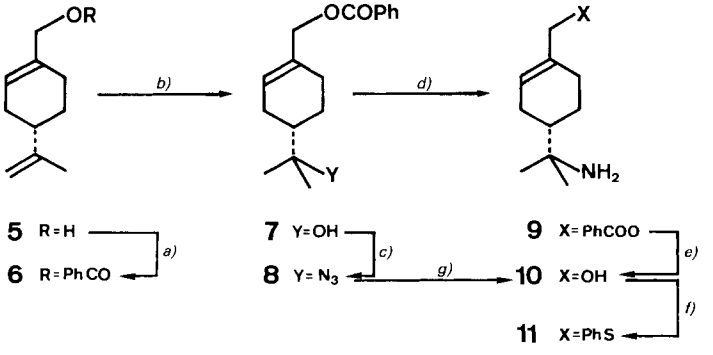
[5]) Hobartin-20-ol (**3**) has been isolated from *Aristotelia australasica* [8] and may well represent the biological precursor of **2** and **4**.

Scheme 1



2. Results and Discussion. – Commercially available (*S*)-perilla alcohol (**5**) served as convenient starting material and was transformed into amino alcohol **10** *via* the route shown in *Scheme 2*. Regioselective oxymercuration [12] of benzoate **6** furnished alcohol **7** which was then transformed into the corresponding azide **8** upon treatment with HN_3/BF_3 [9] [13]. Subsequent reduction with NaHTe [14] led to the amino benzoate **9** which was saponified to furnish the target molecule **10**. This compound could also be obtained directly through reduction of the intermediate azido benzoate **8** with $LiAlH_4$.

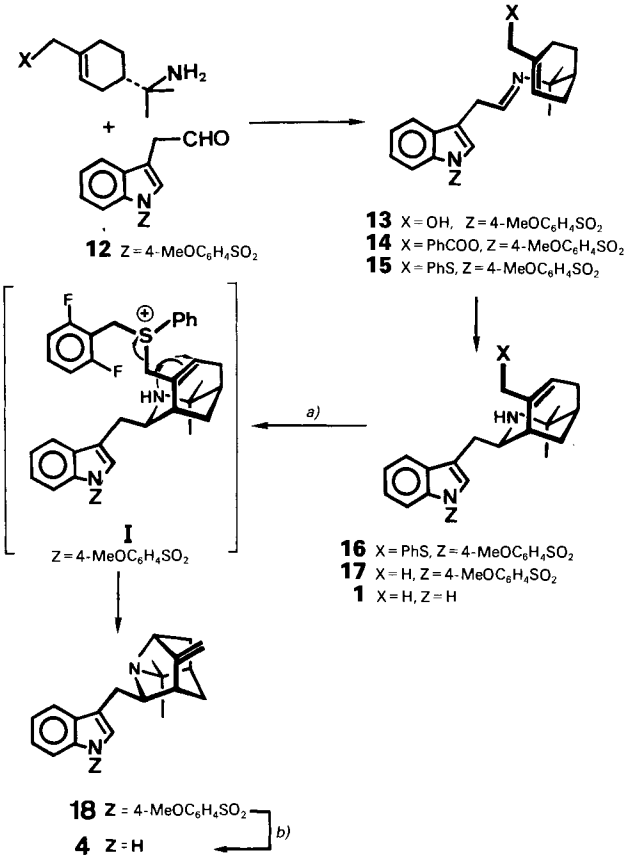
Scheme 2



a) PhCOCl, py. *b*) 1) $Hg(OAc)_2$; 2) $NaBH_4$. *c*) HN_3, BF_3. *d*) NaHTe. *e*) NaOMe. *f*) PhSSPh, Bu_3P, py. *g*) $LiAlH_4$.

Whereas condensation of **9** and **10** with indole-protected indole-3-acetaldehyde **12** [11] readily led to the expected imines **13** and **14** (*Scheme 3*), these intermediates did not react further to the desired hobartine derivatives under our established cyclization conditions [9] [11]. Since this lack of reactivity can hardly be explained by steric hindrance arguments, we suspect that the strongly electronegative allylic O-substituents reduce the nucleophilicity of the olefinic double bond to such an extent that the desired cyclization

Scheme 3



a) 2,6-Difluorobenzyl bromide, $AgBF_4$, 1,2,2,6,6-pentamethylpiperidine. *b*) 6% Na/Hg, MeOH.

process can not compete with other, imine-decomposition reactions[6]). Therefore, the O-substituent was replaced by the less electronegative phenylthio group, introduced according to the method of *Nakagawa* and *Hata* [15]. Application of their procedure to **10** furnished (phenylthio)amine **11** in 90% yield (*Scheme 2*).

[6]) The same tendency, though less pronounced, was observed in the case of the imine formed by condensation of **12** with *trans*-3-[(2,6-difluorobenzyl)oxy]-1-*p*-menthen-8-amine [1]. For an early strategic exploitation of such an effect, see [16].

A routine check of the optical purity of **11** revealed that it amounted to only 70%. Presumably, some racemization took place during the transformation **6** → **7** or **7** → **8**. Optically pure **11** was obtained *via* recrystallization of its (+)-L-mandelic acid salt from $MeOH/H_2O$.

Gratifyingly, the condensation/cyclization sequence worked well in the case of **11**, furnishing *ca.* 50% of the desired hobartine derivative **16** (*Scheme 3*). The phenylthio group of **16** was transformed into a better leaving group *via* *S*-alkylation with 2,6-difluorobenzyl bromide in the presence of $AgBF_4$ [17] and pentamethylpiperidine. Under these conditions, the intermediate sulfonium salt **I** cyclized smoothly to the expected indole-protected (+)-aristofruticosine **18** (55% yield). Reductive removal of the protecting group [18] furnished crystalline (+)-aristofruticosine ((+)-**4**) in quantitative yield. The product obtained was identified through its IR, ^{1}H-NMR, and ^{13}C-NMR spectra[7]).

There is a significant discrepancy between the optical-rotation values of our synthetic material ($[\alpha]_D^{20} = +15.5$ ($c = 0.8$, $CHCl_3$)) and the reported data of natural (+)-**4** ($[\alpha]_D^{15} = +50.5$ ($c = 0.53$, $CHCl_3$)). Since partial racemization during the step **15** → **16** could not be ruled out *a priori*, the optical purity of **16** was checked *via* a chemical correlation with (−)-hobartine (**1**) and found to amount to more than 90% (see *Exper. Part*). The higher reported $[\alpha]_D$ value of natural (+)-**4** probably originated either from the presence of a strongly dextrorotatory impurity or from the presence of HCl in the $CHCl_3$ utilized by the Australian workers[8]).

3. Conclusion. – The unique indole alkaloid (+)-aristofruticosine ((+)-**4**) has been synthesized in optically pure form in a seven-step sequence which proceeds with an overall yield of *ca.* 15%. The straightforward transformations outlined in *Schemes 2* and *3* unambiguously established the tentative structure proposed by *Bick et al.* [3], as well as the hitherto unknown absolute configuration of (+)-**4**. The synthetic potential of the versatile intermediate **16** is presently being investigated in this laboratory.

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Experimental Part

General. All solvents employed as reaction media were reagent grade (*Fluka, puriss.*) and were further purified and dried as follows: CH_2Cl_2, dist. from P_2O_5; $CHCl_3$, filtered through Al_2O_3 (*Woelm*, basic act. I); Et_2O, dist. from $LiAlH_4$; THF, dist. from K under N_2; pyridine and Et_3N, dist. from CaH_2; benzene and toluene, dist. from $LiAlH_4$; HCOOH, dist. from. anh. $CuSO_4$ at 200 Torr. M.p. (not corrected): *Tottoli* apparatus, sealed evacuated capillaries. Optical rotations ($[\alpha]_\lambda^T$): *Perkin-Elmer 241*. UV/VIS spectra (λ_{max} [nm] (ε [dm^3/mol·cm])): *Uvikon 860*. CD spectra ($\lambda(\Delta\varepsilon)$ [nm]): *Jobin-Yvon Mark III*. IR spectra ($\tilde{\nu}$ [cm^{-1}]): *Perkin-Elmer 781* ($CHCl_3$ and CCl_4) or *Perkin-Elmer 983* (KBr). ^{1}H-NMR spectra (δ [ppm] from TMS, appearant coupling constants J[Hz]): *Bruker WM 300* (300 MHz) or *Bruker AMX 400* (400 MHz). ^{13}C-NMR spectra (δ [ppm] from TMS, multiplicities as determined from DEPT spectra): *Varian XL-300* (75 MHz) or *Bruker AMX 400* (100 MHz). Mass spectra (m/z [amu] (% base peak)): *Hitachi-Perkin-Elmer RMU-6D* (EI, 70 eV) or *VG TRIBID* (EI, 70 eV).

(S)-p-Mentha-1,8-dien-7-yl Benzoate (**6**). To a soln. of 15 g (100 mmol) of *perylla alcohol* (**5**; *Aldrich*, technical grade, 92%) in 150 ml of benzene were added 148 mg (1 mmol) of 4-pyrrolidinopyridine (*Fluka, purum*),

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[7]) The authors thank Prof. *I. R. C. Bick*, University of Tasmania, for providing us with copies of the spectra of natural (+)-**4**.

[8]) Natural (+)-**4** was described as being an amorphous solid (no m.p. given) [2][3], whereas our synthetic sample is a colorless crystalline material (m.p. 146°). When the $CHCl_3$ solution having been used for the determination of the optical rotation of synthetic (+)-**4** was acidified by adding 20 µl of CF_3COOH, the value of $[\alpha]_D^{20}$ rose from +15.5 to +57.3.

8 g of pyridine and 14.5 g (100 mmol) of benzoyl chloride (*Fluka, puriss.*). The mixture was stirred at 0° for 2 h and then kept at r.t. for 14 h. Workup with Et_2O/0.5M aq. H_3PO_4 furnished 26 g of a slightly yellow oil which was purified by chromatography (hexane/Et_2O 9:1): 23.04 g. An anal. sample was prepared by distillation (110°/0.01 Torr). $[\alpha]_D^{25} = -58.5$ ($c = 0.95$, $CHCl_3$). IR (CCl_4): 1727, 1452, 1317, 1270, 1178, 1110, 1099, 891, 710. ^{1}H-NMR (300 MHz): 8.07 (*m*, 2 H); 7.54 (*m*, 1 H); 7.44 (*m*, 2 H); 5.85 (*m*, 1 H); 4.73 (br. *s*, 4 H); 2.2 (*m*, 4 H); 2.0 (*m*, 1 H); 1.88 (*m*, 1 H); 1.75 (*s*, 3 H); 1.52 (*m*, 1 H). ^{13}C-NMR (75 MHz): 166.5 (*s*); 149.6 (*s*); 132.9 (*d*); 132.7 (*s*); 130.4 (*s*); 129.6 (2*d*); 128.4 (2*d*); 125.7 (*d*); 108.8 (*t*); 68.9 (*t*); 40.9 (*d*); 30.5 (*t*); 27.4 (*t*); 26.5 (*t*); 20.8 (*t*). MS: 256 (4, M^+), 134 (37), 119 (26), 106 (17), 105 (100), 93 (18), 92 (21), 91 (25), 79 (14), 77 (35), 68 (18), 41. (13). Anal. calc. for $C_{17}H_{20}O_2$ (256.34): C 79.65, H 7.86; found: C 79.50, H 7.88.

*(S)-8-Hydroxy-*p*-menth-1-en-7-yl Benzoate* (**7**). To a rapidly stirred soln. of 10.1 g (39.4 mmol) of **6** in 200 ml of THF/H_2O 4:1 were added 31.4 g (98.5 mmol) of $Hg(OAc)_2$ (*Merck, p.a.*) at 0°. The deep orange soln. was stirred at r.t. for 5 h. Then the turbid yellow suspension was neutralized with 2.5N aq. NaOH and cooled to 0°. In small portions, 3.1 g (80 mmol) of $NaBH_4$ (*Fluka, purum*) were added, and stirring was continued for 30 min at 0°. The colorless mixture was decanted from the Hg formed and extracted with Et_2O (3 × 300 ml). The combined org. extracts were washed once with aq. phosphate buffer soln. (pH 6.5), dried ($MgSO_4$), and evaporated. Chromatography (benzene/AcOEt 3:1) furnished 1.08 g (10.7%) of starting **6** and 7.65 g (71%) of **7**. An anal. sample was prepared by distillation (150°/0.004 Torr). Colorless viscous oil. $[\alpha]_D^{25} = -45.2$ ($c = 0.85$, $CHCl_3$). IR (CCl_4): 3620, 1725, 1452, 1317, 1270, 1250, 1110, 1099, 711. ^{1}H-NMR (300 MHz): 8.07 (*m*, 2 H); 7.57 (*m*, 1 H); 7.45 (*m*, 2 H); 5.85 (*m*, 1 H); 4.74 (*s*, 2 H); 2.2 (*m*, 3 H); 2.00 (*m*, 1 H); 1.92 (*m*, 1 H); 1.59 (*dddd*, $J = 12.5, 11.5, 4.6, 2.2$, 1 H); 1.33 (*dddd*, $J = 12.5, 12.2, 11.0, 5.8$, 1 H); 1.22 (*s*, 3 H); 1.20 (*s*, 3 H); 1.7–1.2 (br., 1 H). ^{13}C-NMR (75 MHz): 166.5 (*s*); 132.9 (*d*); 130.4 (*s*), 129.6 (2*d*); 128.4 (2*d*); 125.7 (*d*); 72.6 (*s*); 68.8 (*t*); 44.9 (*d*); 27.4 (*q*); 26.9 (*t*); 26.7 (*t*); 26.4 (*q*); 23.5 (*t*); the missing *s* is probably hidden beneath one of the *d*'s between 130 and 125 ppm. MS: 256 (2, $[M - 18]^+$), 128 (18), 134 (23), 123 (16), 122 (27), 119 (17), 105 (100), 94 (33), 93 (23), 92 (38), 91 (39), 79 (34), 77 /75), 59 (47), 51 (26), 43 (33), 41 (15), 39 (12). Anal. calc. for $C_{17}H_{22}O_3$ (274.36): C 74.42, H 8.08; found: C 74.41, H 7.96.

*(S)-8-Amino-*p*-menth-1-en-7-yl Benzoate* (**9**). To a cold soln. of 1.85 g (6.74 mmol) of **7** in 40 ml of a HN_3 soln. in benzene (prepared from 2.2 g (33.7 mmol) of NaN_3 [19]) were added 1.3 ml (10.1 mmol) of $BF_3 \cdot Et_2O$ (*Fluka, pract.*; freshly distilled). The mixture was stirred at r.t. for 3 h. Workup with Et_2O and aq. 1M Na_2CO_3 gave 1.46 g (72%) of crude azido benzoate **8**. A soln. of 1.23 g (4.1 mmol) of crude **8** in Et_2O was added at r.t. under Ar to a soln. of 10 mmol of NaHTe in 20 ml of EtOH [14]. After stirring for 15 min, air was bubbled through the mixture for 10 min. Filtration trough *Celite®* and evaporation gave 908 mg of an orange oil which was chromatographed ($CHCl_3$/MeOH/conc. aq. NH_3 soln. 98:2:5) to yield 115 mg (9%) of **8** and 590 mg (53%) of oily, rather unstable **9** which was characterized as *N,O*-dibenzoyl derivative prepared by treating a sample of **9** with PhCOCl in pyridine (16 h, r.t.). Oil. $[\alpha]_D^{25} = -9.7$ ($c = 1.8$, $CHCl_3$). IR (CCl_4): 1725, 1694, 1670, 1271, 710. ^{1}H-NMR (300 MHz): 8.05 (*m*, 2 H); 7.71 (*m*, 2 H); 7.55 (*m*, 1 H); 7.46–7.38 (*m*, 5 H); 5.89 (br., 1 H); 5.83 (*m*, 1 H); 4.73 (*d*, $J = 12.5$, 1 H); 4.68 (*d*, $J = 12.5$, 1 H); 2.45 (*dddd*, $J = 12.8, 12, 5, 2.5$, 1 H); 2.25–2.11 (*m*, 3 H); 2.02–1.87 (*m*, 2 H); 1.46 (*s*, 3 H); 1.42 (*s*, 3 H); 1.36 (*m*, 1 H). ^{13}C-NMR (75 MHz): 166.9 (*s*); 166.5 (*s*); 136.0 (*s*); 133.1 (*s*); 132.8 (*d*); 131.1 (*d*); 130.5 (*s*); 129.6 (2*d*); 128.5 (2*d*); 128.3 (2*d*); 126.7 (2*d*); 125.6 (*d*); 68.7 (*t*); 56.7 (*s*); 41.0 (*d*); 27.2 (*t*); 26.6 (*t*); 24.3 (2*q*); 23.9 (*t*). MS: 257 (2, $[M - 120]^+$), 162 (26), 122 (26), 105 (100), 77 (69), 51 (32), 50 (18).

*(S)-8-Amino-*p*-menth-1-en-7-ol* (**10**). *Method A:* To a soln. of 3.56 g (66 mmol) of NaOMe in 90 ml of MeOH were added 3.00 g (11 mmol) of **9**. After stirring under Ar for 3 h at r.t., the solvent was evaporated and the residue taken up in 50 ml of 1N aq. H_2SO_4 and 50 ml of Et_2O. The aq. phase was adjusted to pH 11 (2.5N NaOH) and extracted with 6 × 100 ml of Et_2O. The combined extracts were dried (K_2CO_3) and evaporated: 1.55 g (83%) of crystalline **10**. M.p. 78° (benzene/hexane). $[\alpha]_D^{25} = -69.2$ ($c = 1.3$, $CHCl_3$; optical purity 70%). IR ($CHCl_3$): 3615, 3200 (br.), 1586, 1386, 1369, 971. ^{1}H-NMR (300 MHz): 5.70 (*m*, 1 H); 4.00 (*s*, 2 H); 2.2–2.0 (*m*, 3 H); 1.95–1.8 (*m*, 2 H); 1.41 (*dddd*, $J = 12.5, 11.5, 5, 2.2$, 1 H); 1.22 (*dddd*, $J = 12.5, 12, 11.5, 5.5$, 1 H); 1.6–1.45 (br., 3 H); 1.08 (*s*, 3 H); 1.07 (*s*, 3 H). ^{13}C-NMR (75 MHz): 137.7 (*s*); 122.2 (*d*); 66.7 (*t*); 51.2 (*s*); 45.3 (*d*); 28.4 (*q*); 27.7 (*q*); 26.9 (*t*); 26.5 (*t*); 23.7 (*t*). MS: 154 (1, $[M - 15]^+$), 152 (4), 121 (3), 109 (4), 79 (6), 70 (10), 58 (100), 41 (10). Anal. calc. for $C_{10}H_{19}NO$ (169.27): C 70.96, H 11.31; found: C 70.73, H 10.99.

Method B: To a soln. of HN_3 (prepared from 19.7 g NaN_3) in 120 ml of benzene were added 7.65 g (27.9 mmol) of **7** and 5.7 ml (44 mmol) of $BF_3 \cdot Et_2O$ (*Fluka, pract.*; freshly dist.). The resulting soln. was stirred at 0° for 30 min and then distributed between Et_2O and aq. 1N $NaHCO_3$. The org. phase was dried (Na_2SO_4) and concentrated to *ca.* 20 ml. This residue was added slowly to a refluxing suspension of 3.08 g (88 mmol) of $LiAlH_4$ in 200 ml of Et_2O. After 16 h at reflux, the mixture was decomposed by adding the required amount of H_2O at 0°. After filtration, the filtrate was extracted with 3 × 50 ml of 1N aq. H_2SO_4. The combined extracts were basified (pH 12) by adding 20% aq. NaOH soln. Extraction with 8 × 100 ml of Et_2O, drying (K_2CO_3), and evaporation gave 3.95 g of crude, semi-crystalline **10**. Recrystallization (benzene/hexane) furnished 1.70 g of pure **10** (m.p. 77°). The mother liquor

was chromatographed ($CHCl_3$/MeOH/conc. NH_3 soln. 200:2:5) to yield 1.89 g of **10** (m.p. 78°). Combined yield: 3.59 (76%). $[\alpha]_D^{25} = -73$ ($c = 1.1$, $CHCl_3$; optical purity 73%).

(S)-7-(Phenylthio)-p-menth-1-en-8-amine (**11**). To a soln. of 1.69 g (10 mmol) of **10** and 6.55 g (30 mmol) of Ph_2S_2 (*Fluka, pract.*) in 20 ml of pyridine at 0° were added 6.07 g (30 mmol) of Bu_3P (*Fluka, pract.*) within 20 min. After stirring for 30 min at 0° and 2 h at r.t., the mixture was worked up with Et_2O and 1N aq. NaOH. The combined org. phases were dried (K_2CO_3) and evaporated. The residue was chromatographed (500 ml of $CHCl_3$, then $CHCl_3$/MeOH/conc. NH_3 soln. 200:2:5): 2.48 g (95%) of pure **11**. Oil. $[\alpha]_D^{25} = -44$ ($c = 1.1$, $CHCl_3$; optical purity 73%). IR (CCl_4): 1586, 1480, 1440, 1384, 1367, 690. ^{1}H-NMR (300 MHz): 7.2–7.05 (*m*, 5 H); 5.56 (*m*, 1 H); 3.45 (*s*, 2 H); 2.3–2.0 (*m*, 3 H); 1.91 (*m*, 1 H); 1.78 (*m*, 1 H); 1.35 (*dddd*, $J = 12.5, 11, 5, 2$, 1 H); 1.22 (*qd*, $J = 12, 5.6$, 1 H); 1.06 (*s*, 3 H); 1.04 (*s*, 3 H); 1.4–1.0 (br., 2 H). ^{13}C-NMR (75 MHz): 136.9 (*s*); 133.0 (*s*); 130.1 (2*d*); 128.6 (2*d*); 126.1 (*d*); 125.3 (*d*); 51.0 (*s*); 45.1 (*d*); 41.7 (*t*); 28.5 (*q*); 28.5 (*t*); 27.7 (*q*); 26.9 (*t*); 23.9 (*t*). MS: 152 (68) ([$M - 109$]$^+$), 136 (4), 135 (22), 109 (11), 93 (18), 79 (14), 77 (12), 70 (12), 58 (100). Anal. calc. for $C_{16}H_{23}NS$ (261.43): C 73.51, H 8.87, N 5.36; found: C 73.32, H 8.92, N 5.27.

Mosher *Derivative of* **11**. To a soln. of 26 mg (0.1 mmol) of **11** (prepared as described above) in 0.5 ml of pyridine were added 2 equiv. of a 1M stock soln. of (*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl chloride [20] in benzene. After standing at r.t. for 16 h, the mixture was worked up (Et_2O/1M aq. H_3PO_4) to give 37 mg of crude material which was chromatographed (hexane/$CHCl_2$/$CHCl_3$ 4:1:1): 25 mg of a diastereoisomeric mixture of amides. ^{1}H-NMR (300 MHz, C_6D_6; signals used for assay): 6.24 (br. *s*, 0.83 H); 6.17 (br. *s*, 0.17 H); 3.16 (*q*, $J = 1.6$, 0.45 H); 3.14 (*q*, $J = 1.6$, 2.55 H); 1.12 (*s*, 0.52 H); 1.10 (*s*, 2.48 H); 1.08 (*s*, 2.48 H); 0.99 (*s*, 0.52 H); amount of (*S,R*)-amide, 86%; (*R,R*)-amide, 14% (after correction for the optical purity of the reagent). Optical purity of **11**: 72%.

Upgrading of the Opitcal Purity of **11**. To a soln. of 1.7 g (10 mmol) of **11** in 5 ml of MeOH was added an equimolar amount of (+)-L-mandelic acid (*Fluka, puriss.*) dissolved in 5 ml of MeOH. After addition of 3 ml of H_2O, the mixture was allowed to stand at r.t. for 48 h. The long colorless needles (m.p. 151–152°) were collected (1.92 g) and dried (16 h, r.t./high vacuum). A suspension of this material in 20 ml of 2.5N aq. NaOH was extracted with CH_2Cl_2 (3 × 20 ml). The combined org. extracts were dried (K_2CO_3) and evaporated: 1.02 g (6 mmol) of optically pure **11** as colorless oil which solidified when stored at −20°. M.p. *ca.* 27°. $[\alpha]_D^{25} = -60.2$ ($c = 1.1$, $CHCl_3$).

(+)-1-[(4-Methoxyphenyl)sulfonyl]-20-(phenylthio)hobartine (= *(1R,4R,5S)-4-{{1-[(4-Methoxyphenyl)sulfonyl]-1H-indol-3-yl}methyl}-2,2-dimethyl-6-[(phenylthio)methyl]-3-azabicyclo[3.3.1]non-6-ene*; **16**). To a soln. of 775 mg (1.84 mmol) of **12** [11] and 400 mg (1.53 mmol) of optically pure **11** in 10 ml of $CHCl_3$ were added 4 g of molecular sieves (*Fluka; Union Carbide*, type *3A, 1/16", pellets*; activated overnight at 320°/0.01 Torr). After stirring for 2 h at r.t. under Ar, 20 ml of dry, cool HCOOH were added. The resulting orange soln. was kept at r.t. for 47 h and then added slowly to 150 ml of cold 2.5N aq. NaOH and 100 ml of cold sat. aq. Na_2CO_3 soln. The combined $CHCl_3$ extracts (3 × 300 ml) were dried (Na_2SO_4) and evaporated to give 2.77 g of a brown oil. Chromatography ($CHCl_3$/EtOH 10:1) yielded 352 mg (0.615 mmol, 40%) of pure **16**. Further elution with $CHCl_3$/EtOH/Et_2NH 20:2:1 furnished 103 mg of **11**. Yield of **16** based on consumed **11**, 54%. M.p. 48–51°. $[\alpha]_D^{25} = +1.5$ ($c = 1.2$, $CHCl_3$). IR (CCl_4): 1599, 1581, 1497, 1380, 1261, 1170, 1099, 673. ^{1}H-NMR (300 MHz): 7.99 (*dt*, $J = 8.3, 1.1$, 1 H); 7.78 (*m*, 2 H); 7.46 (*m*, 2 H); 7.32 (*ddd*, $J = 8.3, 7.3, 1.2$, 1 H); 7.21 (*ddd*, $J = 7.7, 7.3, 1.0$, 1 H); 7.2–7.05 (*m*, 5 H); 6.79 (*m*, 2 H); 5.71 (br. *t*, $J = 6.5$, 1 H); 3.71 (*s*, 3 H); 3.58 (*d*, $J = 12.6$, 1 H); 3.44 (*td*, $J = 7.2, 2.5$, 1 H); 3.24 (br. *d*, $J = 12.6$, 1 H); 2.66 (*dd*, $J = 15.0, 7.0$, 1 H); 2.60 (*m*, 1 H); 2.54 (br. *dd*, $J = 15,7$, 1 H); 2.28 (*dm*, $J = 19$, 1 H); 2.14 (*dm*, $J = 12.6$, 1 H); 2.01 (*dm*, $J = 19$, 1 H); 1.52 (*dt*, $J = 12.6, 3.5$, 1 H); 1.45 (*m*, 2 H); 1.16 (*s*, 3 H); 1.08 (*s*, 3 H). ^{13}C-NMR (75 MHz): 163.6 (*s*); 136.1 (*s*); 135.3 (*s*); 131.9 (*s*); 131.1 (*s*); 130.8 (2*d*); 129.7 (*d*); 128.9 (2*d*); 128.6 (2*d*); 126.3 (*d*); 124.7 (*d*); 123.6 (*d*); 120.0 (*s*); 119.4 (*d*); 114.4 (2*d*); 113.9 (*d*); 55.5 (*q*); 53.6 (*s*); 53.5 (*d*); 43.0 (*t*); 34.9 (*d*); 34.5 (*d*); 30.9 (*t*); 29.9 (*q*); 29.0 (*t*); 27.9 (*t*); 25.8 (*q*). MS: 463 (5, [$M - 109$]$^+$), 293 (11), 272 (89), 171 (41), 162 (27), 159 (22), 155 (25), 130 (94), 123 (47), 110 (29), 109 (49), 108 (25), 107 (57), 77 (100), 58 (37).

(−)-Hobartine (= *(1R,4R,5S)-4-[(1H-Indol-3-yl)methyl]-2,2,6-trimethyl-3-azabicyclo[3.3.1]non-6-ene*; **1**). To a soln. of 97 mg (0.17 mmol) of **16** and 194 mg (0.82 mmol) of $NiCl_2 \cdot 6\,H_2O$ in 6 ml of MeOH/CH_2Cl_2 5:1 were added 51.4 mg (1.36 mmol) of $NaBH_4$ in small portions. After stirring at r.t. for 15 min, the black suspension was filtered through sintered glass. The filtrate was diluted with 10 ml of sat. aq. Na_2CO_3 soln. and extracted with CH_2Cl_2 (3 × 40 ml). The combined extracts were dried (Na_2SO_4) and evaporated: 78 mg of yellow foam. Chromatography (hexane/benzene/Et_2O/Et_2NH 13:8:4:1) furnished 52 mg of pure **17**. $[\alpha]_D^{25} = -35.6$ ($c = 0.5$, $CHCl_3$). To a soln. of this material in 5 ml of MeOH were added 50 mg of NaH_2PO_4 and 15 equiv. of 6% Na amalgam. After stirring for 2 h at r.t., the supernatant was decanted and evaporated; the residue was partitioned between 10% aq. NH_3 soln. and $CHCl_3$. The org. phase was dried (K_2CO_3), evaporated, and filtered through 1 g of silica gel (benzene/Et_2O/Et_2NH 8:4:1) to yield 20 mg of pure **1** which was identified by ^{1}H-NMR. $[\alpha]_D^{25} = -24.3$ ($c = 0.4$,

$CHCl_3$; [9]: $[\alpha]_D = -28$ ($c = 1.2$, $CHCl_3$); [4]: $[\alpha]_D = -20 \pm 3$ ($c = 1.66$, $CHCl_3$); [21]: $[\alpha]_D = -27 \pm 3$ ($c = 1.69$, $CHCl_3$)).

(+)-Aristofruticosine (= *(1R,4R,5S,7R)-4-[(1H-Indol-3-yl)methyl]-2,2-dimethyl-6-methylidene-3-azatricyclo[3.3.1.0^{3,7}]nonane*; (+)-**4**). To a soln. of 114 mg (0.2 mmol) of **16** and 166 mg (0.8 mmol) of 2,6-difluorobenzyl bromide in 10 ml of dry MeCN were added 124 mg (0.8 mmol) of 1,2,2,6,6-pentamethylpiperidine (*Fluka, purum*) and 156 mg (0.8 mmol) of $AgBF_4$ (*Fluka, purum*). The resulting mixture was stirred at r.t. in the dark for 7 days. The solvent was removed under reduced pressure and the black residue partitioned between 5% aq. NH_3 soln. and $CHCl_3$. The combined org. extracts were dried (K_2CO_3), evaporated, and filtered through 30 g of silica gel ($CHCl_3$/MeOH/conc. aq. NH_3 soln. 500:2:5): 128 mg of yellow oil. To a soln. of this material in 20 ml of MeOH were added 100 mg of KH_2PO_4 and 1.2 g of 6% Na amalgam (15 equiv.). After stirring at r.t. for 90 min, the solvent was decanted from the Hg and evaporated. The residue was purified by chromatography ($CHCl_2$/MeOH/conc. aq. NH_3 soln. 98:2:5): 32 mg (55%) of crystalline **4**. M.p. 146° (benzene). $[\alpha]_D^{25} = +15.5$ ($c = 0.8$, $CHCl_3$)[8]). IR (KBr): 1678, 1620, 1456, 1231, 1188, 879, 775, 740. ^{1}H-NMR (400 MHz): 7.61 (*dm, J* = 7.9, 1 H); 7.34 (*dt, J* = 8.0, 0.9, 1 H); 7.17 (*ddd, J* = 8.0, 7.1, 1.2, 1 H); 7.10 (*ddd, J* = 7.9, 7.1, 1.1, 1 H); 6.94 (br. *d, J* = 2.1, 1 H); 4.82 (*s*, 1 H); 4.72 (*s*, 1 H); 3.91 (br. *d, J* = 7.0, 1 H); 3.75 (*dd, J* = 10.8, 4.7, 1 H); 2.81 (*ddd, J* = 14.2, 4.7, 0.5, 1 H); 2.66 (*dd, J* = 14.2, 10.8, 1 H); 2.52 (*ddt, J* = 11.7, 7.0, 2.7, 1 H); 2.25 (*t, J* = 2.6, 1 H); 1.96 (*dq, J* = 13.2, 2.6, 1 H); 1.85 (*q, J* = 2.7, 1 H); 1.71 (*d, J* = 11.7, 1 H); 1.47 (*dt, J* = 13.2, 2.9, 1 H); 1.43 (*s*, 3 H); 1.14 (*s*, 3 H); agreement with the reported data of natural (+)-**4** [2a], ±0.06 ppm. ^{13}C-NMR (100 MHz): 158.7 (*s*); 136.2 (*s*); 127.8 (*s*); 122.0 (*d*); 121.8 (*d*); 119.2 (*d*); 119.1 (*d*); 113.5 (*s*); 111.0 (*d*); 99.0 (*t*); 65.9 (*s*); 64.8 (*d*); 62.3 (*d*); 44.8 (*d*); 43.0 (*t*); 42.9 (*d*); 33.8 (*t*); 30.8 (*q*); 30.8 (*t*); 24.0 (*q*). MS: 292 (28, M^+), 277 (14), 163 (13), 162 (100), 157 (10), 140 (13), 130 (53), 121 (11), 120 (12), 91 (10).

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