Two Atropisomeric *N*-Methyldioncophyllines A and *N*-Methylphylline, their Naphthalene-Free Heterocyclic Moiety, from *Ancistrocladus barteri*[*]

Gerhard Bringmann[a], Christoph Schneider[a], Ulrike Möhler[a], Robert-Michael Pfeifer[a], Roland Götz[a], Laurent Aké Assi[b], Eva-Maria Peters[c], and Karl Peters[c]

[a] Institute of Organic Chemistry, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany
[b] Centre National de Floristique (Conservatoire et Jardin Botaniques), Université d'Abidjan, 08 b.p. 172, Abidjan 08, Ivory Coast
[c] Max-Planck-Institut für Festkörperforschung, Heisenbergstraße 1, D-70506 Stuttgart, Germany

Reprint requests to Prof. Dr. G. Bringmann. Fax: +49 931 888 4755.
E-mail: bringman@chemie.uni-wuerzburg.de

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The West African plant *Ancistrocladus barteri* (Ancistrocladaceae) was investigated chemically for the first time. Besides the known naphthylisoquinoline alkaloids *N*-methyldioncophylline A and 7-*epi*-*N*-methyldioncophylline A (*i.e.* its atropo-diastereomer), a new naphthalene-free alkaloid, belonging to the 'Dioncophyllaceae type', was isolated. Its structure was elucidated by spectroscopic and degradative methods and confirmed by total synthesis. The new compound, named *N*-methylphylline, is exactly the isoquinoline "half" of both, *N*-methyldioncophylline A and its atropisomer. Furthermore, the related tetrahydroisoquinoline *O,N*-dimethylphylline, an intermediate in the chemical synthesis of *N*-methylphylline, was detected as a new natural product in crude extracts of *A. barteri*.

Key words: Structural Elucidation, Naphthylisoquinoline Alkaloids, Ancistrocladaceae, Crystal Structure

Introduction

The tropical plant family Ancistrocladaceae, consisting of the single genus *Ancistrocladus*, comprises about 20 species growing in the tropical rain forests of Africa and Asia [2]. These botanically exciting plants are known to produce a most intriguing class of natural products, the naphthylisoquinoline alkaloids [3], such as dioncophylline A (**1**) [4, 5] and ancistrocladine (**2**) [6] (Fig. 1), naturally occurring biaryl compounds otherwise found only in the Dioncophyllaceae family [7 – 9]. During the past years, the knowledge of the occurrence and structures of a rapidly growing number of such naphthylisoquinoline alkaloids has made considerable progress [1, 9 – 11]. Still, although first successful feeding experiments on the biosynthesis of the bicyclic precursors of these metabolites have been performed [12 – 14] and despite first enzymatic studies on oxidative coupling reactions to give dimeric naphthylisoquinoline alkaloids [15], not much is known about the biosynthetic formation of the biaryl axis between the naphthalene and isoquinoline parts of these secondary metabolites. In this respect, the occurrence of bicyclic metabolites such as plumbagin (**3**) [16, 17] and higher oxygenated naphthoquinones [18] and related tetralones [17], and especially naphthalene-free tetrahydroisoquinoline derivatives, as previously detected in Ancistrocladaceae [19 – 21] and Dioncophyllaceae, like *e. g.*, phylline (**4**), the molecular 'half' of dioncophylline A (**1**) [22], are of particular interest. In this paper, we describe the first phytochemical investigation of the hitherto unexplored West African species *Ancistrocladus barteri*, leading to the isolation of the known [23] compounds *N*-methyldioncophylline A (**5a**) and its atropo-diastereomer **5b**, and to the detection of the corresponding naphthalene-free heterocyclic moiety of these alkaloids, named *N*-methylphylline (**6**), which supports the hypothesis of a separate biosynthetic formation of the two molecular portions of naphthylisoquinoline alkaloids. Furthermore, the natural occurrence of the (as yet merely synthetic) related compound *O,N*-dimethylphylline (**7**) was evidenced, albeit in traces. Part of the work de-

[*] "Acetogenic Isoquinoline Alkaloids", Part 156. For Part 155, see: Lit. [1].

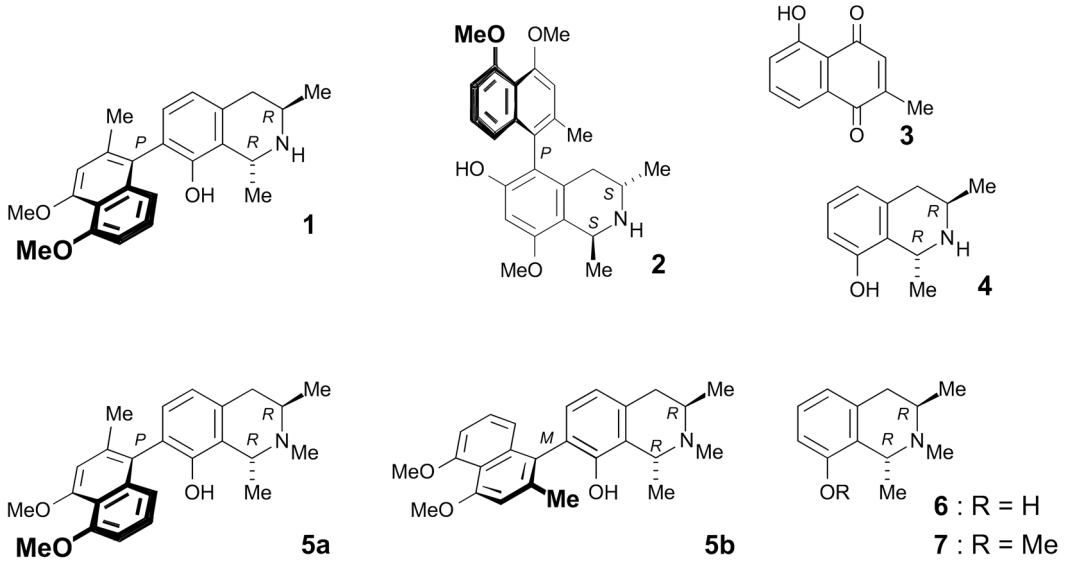
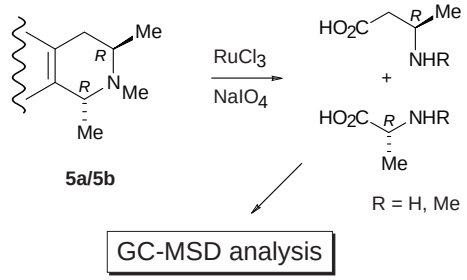


Fig. 1. Chemical structures of dioncophylline A (**1**), ancistrocladine (**2**), plumbagin (**3**), phylline (**4**), *N*-methyldioncophylline A (**5a**) and its atropo-diastereomer (**5b**), as well as *N*-methylphylline (**6**) and *O*,*N*-dimethylphylline (**7**).

scribed herein has previously been reported in preliminary form [24].

Results and Discussion

Freeze-dried and ground root bark material of *Ancistrocladus barteri* Scott Elliot [25] was extracted successively with petroleum ether and dichloromethane containing NH_3 (2.5 vol.%). TLC of the dichloromethane/NH_3 extract on silica gel revealed the presence of numerous Dragendorff-active compounds, one of which was chromatographically identical with the known [23] alkaloid *N*-methyldioncophylline A (**5a**). This compound was preparatively isolated by column chromatography on silica gel (see Experimental). NMR comparison of the TLC-pure substance with authentic material present from previous isolation work [23], however, showed the material to be a 1 : 1 mixture of *N*-methyldioncophylline A (**5a**) and its atropo-diastereomer, *N*-methyl-7-*epi*-dioncophylline A (**5b**). The likewise imaginable possibility that the two diastereomeric alkaloids isolated (both with a relative *trans*-configuration at C-1 *vs.* C-3 according to NMR) might also be realized by other diastereomeric combinations, such as **5a**/*ent*-**5b**, *ent*-**5a**/**5b**, or *ent*-**5a**/*ent*-**5b**, was clearly excluded by the stereoisomeric analysis developed by us earlier [23], by chromatography on a Chiralcel OD phase, an analytical device that permits unambiguous distinction between the four possible stereoisomeric forms of **5**. This was further substantiated by an oxidative degradation reaction introduced by our group [26], leading to *R*-configured aminoacids, exclusively (Scheme 1). Thus, as already known for the likewise West African plant species in *A. abbreviatus* [23], *A. barteri* produces approximately equal amounts of the naphthylisoquinoline alkaloids **5a** and **5b**, which both belong to the so-called Dioncophyllaceae type (*i. e.* no oxygen at C-6 and with 3*R*-configuration) [3].



Scheme 1. Oxidative degradation of **5a**/**5b**. (i) $RuCl_3$-$NaIO_4$; (ii) MeOH-HCl; (iii) 'MTPA-Cl' (Mosher's chloride).

According to TLC, also the other parts of the alkaloid pattern of *A. barteri* seemed to be quite similar to that of *A. abbreviatus*, a species broadly investigated earlier [3,23,27–31]. Yet, at least one of the most slowly eluting *N*-containing products seemed to be new. Due to the polar nature of this compound, we

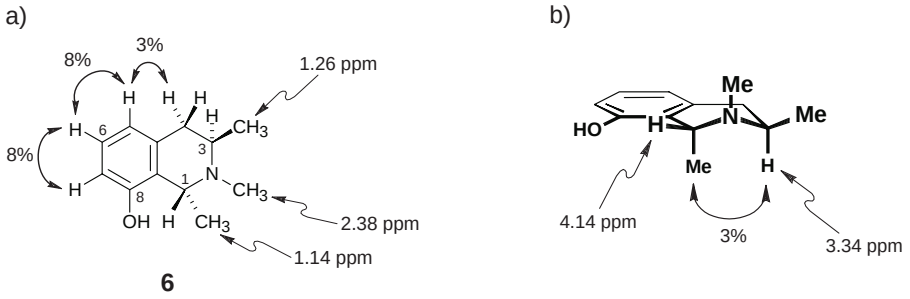
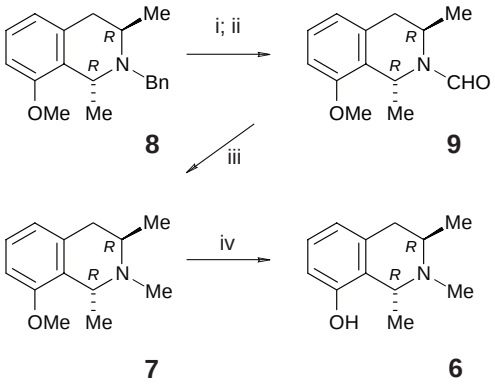


Fig. 2. Constitution of **6**, as deduced from selected NMR and NOE data (a), and its relative *trans*-configuration at C-1 *vs*. C- 3 (b) from characteristic chemical shifts and NOEs.

chose liquid-liquid chromatography techniques to isolate this new minor alkaloid. Thus, multilayer counter current chromatography (MLCCC) [26], with the solvent mixture $CHCl_3$-MeOH-H_2O (13 : 7 : 8), *i.e.* with MeOH-H_2O as the stationary phase and $CHCl_3$-MeOH as the mobile phase, gave 4.0 mg of an essentially pure oily compound, which was further purified by precipitation from a solution in MeOH, by using ether (b.p. 50 – 70 °C). On TLC already, this compound was different from "usual" naphthylisoquinoline alkaloids: in comparison to the intensity of its staining with iodine, it displayed a relatively weak UV absoption on TLC. This was underlined by the UV spectrum, which did not exhibit the typical long-wave absorptions as other naphthylisoquinolines (λ_{max} *e.g.* at 308, and 232 nm like for **5a**/**5b**, but rather showed the UV behavior of a simple substituted *benzene* derivative (λ_{max} *e.g.* at 277 and 220 nm).

But the most obvious hint at an unconventional alkaloid structure was found in the NMR spectrum, which, on the one hand, showed a close similarity to that of *N*-methyldioncophylline A (**5a**) and its atropodiastereomer **5b** with respect to the signals of the tetrahydroisoquinoline part; but on the other hand, it differed significantly by the complete absence of all the signals of the naphthalene moiety. This was confirmed by high resolution mass spectrometry ($m/z = 191.1222$), in agreement with the molecular formula $C_{12}H_{16}NO$ [M^+ - H]. More detailed information from ^{1}H NMR provided the constitution of a 1,2,3-trimethyl-8-hydroxy-1,2,3,4-tetrahydroisoquinoline **6** (see Fig. 2a), as deduced, *i. a.*, from the presence of three neighboring aromatic protons (*viz.* a "doublet-triplet-doublet" pattern), two *C*-bonded methyl groups, which appear as doublets, and an *N*-methyl group, and further confirmed by selected NOE correlations, clearly proving the oxygen function to be located at C-8, not, *e. g.*, at C-6.



Scheme 2. Total synthesis of the new natural products *O*,*N*-dimethylphylline (**7**) and *N*-methylphylline (**6**). (i) Pd/C, H_2; (ii) pivalic-formic anhydride; (iii) $LiAlH_4$; (iv) BBr_3.

Given the constitution of the new natural product as **5**, a first hint at the relative configuration of the two stereocenters, C-1 *vs*. C-3, was already obtained from the chemical shift of H-3 ($\delta = 3.34$ ppm), which is in the region characteristic for *trans*-1,3-dimethyl-tetrahydroisoquinolines (typically ranging from *ca.* $\delta =$ 3.05 – 3.5 ppm [29]), significantly different from the shifts of the corresponding *cis*-diastereomers (*ca.* $\delta =$ 2.6 – 2.9 ppm [29]). This was corroborated by a significant NOE interaction of H-3 with the likewise pseudoaxial methyl group at C-1 (Fig. 2).

Hence, from its constitution and its relative configuration, the new alkaloid is exactly the heterocyclic molecular "half" of both of the atropisomeric forms of *N*-methyldioncophylline A, **5a** and **5b**. To emphasize this structural relationship, the new alkaloid **6** was given a name that represents a fragment of their names: *N*-methylphylline.

Initially, not enough material **6** was available for an oxidative degradation, in contrast to the entire naphthylisoquinoline alkaloids **5a** and **5b**. Therefore, the

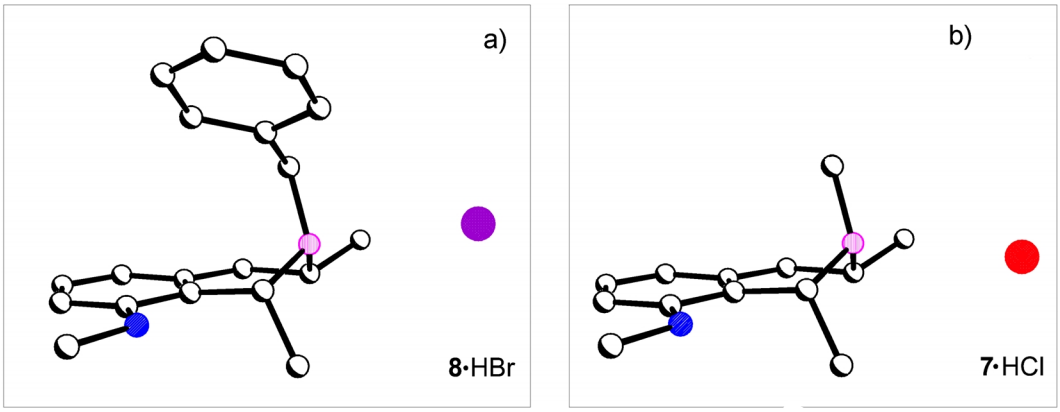
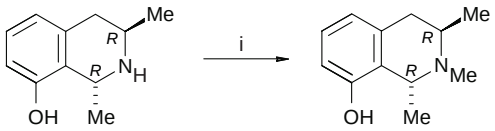


Fig. 3. Crystal structures of **8**·HBr (b), and **7**·HCl (a).

absolute configuration at the stereogenic centers of *N*-methylphylline (**6**) was elucidated by a first total synthesis. Given the close structural similarity of this naphthalene-devoid tetrahydroisoquinoline with the co-occurring naphthylisoquinolines **5a** and **5b**, which have both a 1*R*,3*R*-configuration, we assumed the same absolute stereochemical identity for *N*-methylphylline (**6**) and thus immediately synthesized the compound in this enantiomeric form (Scheme 2).

The synthesis started from the known [33] building block **8**, now prepared in sufficient quantities, thus also permitting to obtain, for the first times, crystals of its hydrobromide suited for an X-ray structure analysis. The crystal structure of **8**·HBr as shown in Fig. 3a fully confirms the anticipated structure with respect to the relative configuration at C-1 *vs*. C-3, and even the absolute configuration, given the presence of the bromide ion as a heavy atom. As in previous cases [34], the *N*-benzyl substituent adopts an axial position, with the 1-methyl group likewise axial and the one at C-3 equatorial, thus minimizing steric constrains in the highly substituted tetrahydropyrido ring.

N-Debenzylation by hydrogenation in the presence of Pd/C [33] and *N*-formylation using pivalic-formic anhydride yielded **9**, which was reduced with lithium alanate to give **7**. Again, as a result of the good crystallization properties of the hydrochloride salt of **7**, crystals suited for an X-ray diffraction analysis were obtained (see Fig. 3b), confirming again the full absolute stereostructure. Like for **8**·HBr, the *N*-substituent of **7**·HCl, this time the smaller *N*-methyl group, adopts an axial array, again with the 1-methyl group axial and the 3-methyl substituent equatorial. The synthesis of **6** was completed by *O*-demethylation of **7** with BBr_3.



10 **6**

Scheme 3. Preparation of **6** by *N*-methylation of synthetically available **10**. (i) CH_2O, $NaBH_4$.

Alternatively, due to the availability of the fully unprotected building block **10**, with its *O*- and *N*-functionalities unsubstituted, from former systematic investigations on the total synthesis of naphthylisoquinoline alkaloids [33], a second, even simpler synthesis was performed by reductive *N*-methylation of **10** with formaldehyde and sodium borohydride (Scheme 3).

The product of both synthetic pathways, **6**, turned out to be identical in all chromatographic and spectroscopic respects with natural *N*-methylphylline. Also with regard to the optical rotation, the 1*R*,3*R*-configured synthetic material corresponded to that of the natural product, considering especially the identical positive sign, thus supporting the proposed stereostructure of *N*-methylphylline as **6**. This was further confirmed by a comparison of the CD spectra (not shown) of the natural alkaloid and the synthetic products.

The synthetic intermediate **7** (see Scheme 1), differing from **6** by its *O*-methyl group, seemed to be another potential natural product. Indeed, both compounds, **6** and **7**, were detected in crude extracts from *A. barteri* by HPLC-MS/MS and coelution experiments.

The work described in this paper represents the isolation of new 'Dioncophyllaceae-type' naphthalene-free 8-hydroxy-1,3-trimethyl-1,2,3,4-tetrahydro-

isoquinolines, *i. e.* the heterocyclic molecular "halves" of naphthylisoquinoline alkaloids, from a natural source. The results are of biosynthetic relevance, since they indicate the probably independent formation of both aromatic portions (obviously *via* β-polycarbonyl chains [3, 12, 13]) and *subsequent* oxidative aryl aryl coupling of the pre-formed molecular moieties.

Experimental Section

General

Mps: uncorr. Optical rotations: 20 or 25°, 10 cm cell, $CHCl_3$ (filtered through basic Al_2O_3). CD: 20 °C, EtOH. UV: 20 °C, EtOH. IR: KBr. ^{1}H NMR (200 or 600 MHz) and ^{13}C NMR (62 or 100 MHz) spectra were recorded in $CDCl_3$ on Bruker AC 200 and DMX 600 spectrometers, respectively, with TMS as the internal standard. EIMS: 70 eV. Column chromatography: Silica gel (60-200 mesh, Merck) by addition of 7.5% aq. NH_3. TLC: precoated silica gel 60 F_{254} plates (Merck), deactivated with gas NH_3. Spots were visualized under UV light and by Dragendorff's reagent. LC-MS/MS: performed as described previously [35].

Plant material

Root bark of *A. barteri* Scott Elliot was collected in the West Ivory Coast in January 1988 and identified by one of us (L. Aké Assi). Voucher specimens are deposited at the Conservatoire et Jardin Botaniques de l'Université d'Abidjan, République de Côte d'Ivoire (UCJ) and at Herbarium Bringmann, Würzburg, Germany; Nos. 23 and 38.

Extraction and isolation

After pulverizing and freeze drying, the plant material (*ca.* 5.0 kg) was Soxhlet-extracted with petroleum ether (b.p. 40 – 60 °C) and then further extracted with CH_2Cl_2 (containing 2.5% aq. NH_3) to yield the crude alkaloid fraction. After evaporation under reduced pressure, the residue (*ca*. 25 g) was subjected to column chromatography on 800 g of silica gel eluted with mixture of CH_2Cl_2-MeOH of increasing polarity. Portions of 50 ml were collected, monitored by TLC, and combined, to give twelve fractions.

*Isolation of atropisomeric N-methyldioncophyllines A (***5a**/**5b***)*

The third fraction contained, as the main component, an alkaloid which was chromatographically (TLC) identical with authentic *N*-methyldioncophylline A (**5a**) or its atropo-diastereomer **5b**). The solution was evaporated under reduced pressure and subjected to column chromatography with a mixture of CH_2Cl_2-MeOH (98 : 2) as the eluent. TLC-uniform fractions were combined and evaporation of the solvent afforded 30 mg of the crude product. Crystallization from Me_2CO gave 24 mg of a microcrystalline white compound. 'Mixed' m. p. of **5a/5b** (*ca.* 1 : 1) 208 – 212 °C. – MS (EI, 70 eV): m/z (%) = 391 (2) [M^+], 376 (100) [M^+ - CH_3]. – $C_{22}H_{29}NO_3$ (391.5): calcd. C 76.78, H 7.47, N 3.58; found: C 76.10, H 7.54, N 3.76. For further spectroscopic data, see lit. [23].

*Oxidative degradation of the two atropisomeric N-methyldioncophyllines A (***5a**/**5b***)*

The degradation, derivatization of the amino acids, and the subsequent GC analysis were carried out as described in lit. [26].

Analytic separation of the two N-methyldioncophylline A stereoisomers **5a**/**5b** *on a chiral phase*

HPLC analysis was performed on a Chiracel OD column (10 μm, 250 mm × 4.6 mm, Daicel Chemical Industries Ltd.) at r. t.; eluent: *n*-hexane-*iso*-PrOH (9:1); flow rate 0.5 ml min^{-1}; detection at 230 nm. Synthetic *N*-methyldioncophylline A (**5a**); HPLC: R_t 19.3 min; ref. [23]: R_t 19.0 min; natural *N*-methyldioncophylline A (**5a**); HPLC: R_t 19.3 min; lit. [23]: R_t 19.0 min; natural *N*-methyl-7-*epi*-dioncophylline A (**5b**); HPLC: R_t 16.4 min; ref. [23]: R_t 16.1 min. Ratio of the two compounds *ca.* 1 : 1.

Multilayer-Countercurrent Chromatography (MLCCC)

$CHCl_3$–MeOH–H_2O (13 : 7 : 8), mobile phase: lower phase, TLC-detection, flow 1.0 ml min^{-1}, 600 min^{-1}.

*Isolation of N-methylphylline (***6***)*

250 mg of the CH_2Cl_2/NH_3 extract were dissolved in 5.0 ml $CHCl_3$-MeOH (65 : 35) and subjected to MLCCC. Portions of 10 ml were collected, monitored by TLC and combined, to give 10 fractions. Fractions 1 – 8 contained naphthylisoquinoline alkaloids like **5a/5b** (see above) and also **2**, which was chromatographically and spectroscopically identical to material isolated previously [m.p. 263 °C; $[\alpha]_D^{20}$ – 23° (MeOH); *c* 0.5; ref. [6] m.p. 265 – 267 °C; $[\alpha]_D^{20}$ – 25° ($CHCl_3$)]. Fractions 8 and 10 gave alkaloid **6** in a crude form (TLC). This procedure was carried out repeatedly, and TLC-uniform fractions were combined. Evaporation of the solution and treatment of the residue with a 1 : 1 mixture of MeOH-petroleum ether (b.p. 50 – 70 °C) gave **6** (4.0 mg, 2.1 μmol) as a yellow oil. $[\alpha]_D^{20}$ + 22° ($CHCl_3$; *c* 0.4). – CD: $\Delta\varepsilon_{225}$ + 65, $\Delta\varepsilon_{240}$ − 50, $\Delta\varepsilon_{275}$ + 25 (EtOH; *c* 0.01). – UV λ_{max} nm: 277, 220. – IR (KBr): ν 3400 (O-H), 2960, 2920, 2840 (C-H), 1580, 1470 (C=C), 1280, 1260 (C-O) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.26 (d, J = 6.6 Hz, 3 H, 3-Me), 1.41 (d, J = 6.7 Hz, 3 H, 1-Me), 2.38 (s, 3 H, N-Me), 2.65 (d, J = 8.0 Hz, 2 H, 4-H), 3.34 (m_c, 1 H, 3-H), 4.14 (q, J = 6.7 Hz, 1 H, 1-H), 6.52 (d, J = 8.4 Hz, 1 H, 7-H), 6.62 (d, J = 8.6 Hz, 1 H, 5-H), 6.98 (t,

$J = 8.6$ Hz, 1 H, 6-H), 8.05 (s, 1 H, O-H). – ^{13}C NMR ($CDCl_3$, 64 MHz): $\delta = 17.23$ (q, 3-Me), 18.71 (q, 1-Me), 32.46 (q, N-Me), 35.6 (t, C-4), 47.25 (d, C-3), 56.43 (d, C-1), 113.26 (d, C-6), 120.06 (d, C-8), 127.46 (d, C-7), 128.0 (s, C-10), 135.53 (s, C-9), 153.54 (s, C-8). – MS (EI, 70 eV): m/z (%) = 191 [M^+] (4), 176 [M^+ - CH_3] (100). – HRMS m/z 190.1222 [M^+ - H] ($C_{12}H_{16}NO$ requires: 190.1232).

Partial synthesis of **6** *starting with 1,2,3,4-tetra hydroisoquinoline* **8**

To a solution of **8** [33] (100 mg, 355 μmol) in MeOH (3 ml), a catalytic ammount of Pd/C was added and the reaction mixture was stirred for 3 h under hydrogen. After completion of the debenzylation reaction, the solvent was removed *in vacuo* and the residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH = 100 : 7). The obtained colorless oil was dissolved in CH_2Cl_2 (2 ml) and an excess of pivalic-formic anhydride [36] was added dropwise at r. t. until TLC showed quantitative conversion. After evaporation of the solution under reduced pressure and column chromatography on silica gel (CH_2Cl_2/MeOH = 100 : 1), evaporation of the solution under reduced pressure gave **9** (52 mg, 238 μmol) in 91% yield as an amorphous white solid. $[\alpha]_D^{25} + 34^\circ$ ($CHCl_3$; *c* 0.35); IR (KBr): ν 2950, 2910 (C-H), 1632 (C=O), 1572, 1462, 1385 (C=C), 1250 (C-O) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 200 MHz; **9** exists as a mixture of two formamide rotamers in a 7 : 3 ratio): Rotamer I: $\delta = 1.24$ (d, $J = 6.7$ Hz, 3 H, 1-Me), 1.36-1.44 (m, 3 H, 3-Me), 2.57-2.69 (m, 1 H, 4-H), 3.05-3.18 (m, 1 H, 4-H), 3.84 (s, 3 H, O-Me), 4.01- 4.11 (m, 1 H, 3-H), 5.61 (q, $J = 6.7$ Hz, 1 H, 1-H), 6.70-6.80 (m, 2 H, Aryl-H), 7.12-7.22 (m, 1 H, Aryl-H), 8.29 (s, 1 H, CHO). Rotamer II: $\delta = 0.96$ (d, $J = 6.1$ Hz, 3 H, 1-Me), 1.36-1.44 (m, 3 H, 3-Me), 2.57-2.69 (m, 1 H, 4-H), 3.05-3.18 (m, 1 H, 4-H), 3.78 (s, 3 H, OMe), 4.57- 4.62 (m, 1 H, 3-H), 5.15 (q, $J = 6.7$ Hz, 1 H, 1-H), 6.70-6.80 (m, 2 H, Aryl-H), 7.12-7.22 (m, 1 H, Aryl-H), 8.35 (s, 1 H, CHO). – ^{13}C NMR ^{1}H decoupled ($CDCl_3$, 63 MHz): Rotamer I: $\delta = 19.9$ (1-Me or 3-Me), 21.2 (1-Me or 3-Me), 36.3 (C-4), 43.94 (C-3), 47.5 (C-1), 55.2 (OMe), 108.5 (C-5 or C-7), 120.8 (C-5 or C-7), 126.3 (C-6), 127.4, 133.9, 155.5 (Ar-C), 160.9 (CHO). Rotamer II: $\delta = 19.0$ (Me-1 or Me-3), 25.0 (Me-1 or Me-3), 34.1 (C-4), 45.3 (C-3), 46.6 (C-1), 55.3 (OMe), 108.7 (C-5 or C-7), 121.3 (C-5 or C-7), 125.2 (C-6), 127.9, 134.9, 154.9 (Ar-C), 162.9 (CHO). – MS (EI, 70 eV): m/z (%) = 219 [M^+] (30), 204 [M^+ - Me] (100), 176 [204 - CHO] (73), 161 [176 - Me] (22), 146 [161 – Me] (30). – $C_{13}H_{17}NO_2$ (219.3): calcd. C 71.21, H 7.81, N 6.39; found: C 70.95, H 7.85, N 6.29.

Reduction of **9**

To **9** (43 mg, 196 μmol) in THF (2 ml), $LiAlH_4$ (16.8 mg, 443 μmol) was added in portions at 0 °C. The mixture was stirred at r. t. for 1.5 h, 2 ml of H_2O were added, and a pH of *ca*. 5 was adjusted with 2 N HCl. The mixture was extracted with CH_2Cl_2/EtOAc (90 : 10). The aqueous phase was then converted to pH 8 with 0.1 N NaOH and was extracted again as above. The organic phase was dried over $MgSO_4$, then the solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel (CH_2Cl_2/MeOH = 100 : 5), to give **7** (37.4 mg, 182 μmol) in 93% yield as a colorless oil, which was converted into the hydrochloride and recrystallized from Et_2O/CH_2Cl_2/petroleum ether (b.p. 40 – 60 °C). $[\alpha]_D^{25} + 39.1$ ($CHCl_3$; *c* 0.54). – IR (KBr): ν 2990, 2950, 2915 (C-H), 2415 (N-H), 1590, 1570, 1445, 1435 (C=C), 1255 (C-O). 1110, 1070, 1051 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 600 MHz; hydrochloride): $\delta = 1.61$ (d, $J = 6.5$ Hz, 3 H, 3-Me), 1.81 (d, $J = 6.0$ Hz, 3 H, 1-Me), 2.63 (s, 3 H, N-Me), 2.72 (dd, $J = 17.3$ Hz, $J = 12.9$ Hz, 1 H, 4-H_{ax}), 3.03 (dd, $J = 18.1$ Hz, $J = 4.3$ Hz, 1 H, 4-H_{eq}), 3.80 (s, 3 H, O-Me), 3.97 (m_c, 1 H, 3-H), 4.58 (q, $J = 6.0$ Hz, 1 H, 1-H), 6.73 (pseudo-t, $J = 8.3$, 8.4 Hz, 2 H, 2-H, 5-H, 7-H), 7.21 (t, $J = 8.0$, 7.8 Hz, 1 H, 6-H), 12.37 (s, 1 H, N-H). – ^{13}CNMR ($CDCl_3$, 100 MHz, hydrochloride): $\delta = 17.32$ (3-Me), 19.66 (1-Me), 32.88 (N-Me), 36.17 (C-4), 45.34 (C-3), 55.31 (C-1), 55.50 (O-Me), 107.45 (C-5 or C-7), 120.96 (C-5 or C-7), 126.38 (C-6), 128.32 (C-10), 135.25 (C-9), 156.53 (C-O). – MS (EI, 70 eV): m/z (%): 205 [M^+] (1), 190 [M^+ - CH_3] (100). – HRMS m/z 190.122 [M^+ - H] ($C_{12}H_{16}NO$ requires: 190.123).

O-Demethylation of **7**

To **7** (19.5 mg, 94.5 μmol) in CH_2Cl_2 (2 ml) boron tribromide (100 μl) was added at −78 °C and the solution was left to warm up to r.t. during 15 h. Methanol (0.5 ml) was added at 0 °C, the solution was evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel (CH_2Cl_2/MeOH = 100 : 7). After evaporation of the solvent under reduced pressure, **6** (15 mg, 78.4 μmol) was obtained in 83% yield as a viscous yellow oil. The material obtained was shown to be fully identical with natural **6** by IR, ^{1}H NMR, ^{13}C NMR, and MS (EI, 70 eV). $[\alpha]_D^{25} + 18^\circ$ ($CHCl_3$; *c* 0.54) CD: $\Delta\varepsilon_{225} + 190$, $\Delta\varepsilon_{240} - 10$, $\Delta\varepsilon_{275} + 70$ (EtOH; *c* 0.01).

Partial synthesis of **6** *starting with 1,2,3,4-tetrahydroisoquinoline* **10**

Synthetic **10** [33] (10 mg, 5.2 μmol) was dissolved in MeOH (10 ml) and treated with 40% aq. HCHO (0.43 ml) at r.t. for 7 h with stirring. After addition 1.5 eq. $NaBH_4$ (3 mg, 7.8 μmol) the mixture was stirred for 12 h and acidified with HOAc to pH 4 – 5. The pH value was then adjusted to 8 – 9 and the solution was extracted with CH_2Cl_2. After evaporation of the solvent of the organic layer, the residue was purified by column chromatography (CH_2Cl_2/MeOH = 100 : 7), to give **6** (7 mg, 36.6 μmol) in 93% yield. The ma-

Table 1. Crystal data and structure refinement of **7**·HCl and **8**·HBr.

Compound	**7**·HCl	**8**·HBr
Empirical formula	$C_{13}H_{20}NOCl$	$C_{19}H_{24}NOBr$
Molecular mass	241.71	362.31
Crystal system	monoclinic	orthorhombic
Space group	$P2_1$	$P2_12_12_1$
Unit cell dimensions	$a = 660.11$ (7) pm	$a = 794.2$ (1) pm
	$b = 1441.57$ (7) pm	$b = 1198.6$ (1) pm
	$c = 906.65$ (6) pm	$c = 1888.6$ (2) pm
	$\beta = 97.767(8)^\circ$	
Formula units per cell	2	4
Unit cell volume (V)	676.9 (1) pm^3	1797.7 (3) pm^3
Calculated density	1.186 Mg/m^3	1.338 Mg/m^3
Crystal size	$550 \times 750 \times 250$ μm^3	$150 \times 500 \times 750$ μm^3
Radiation, wavelength	Mo-K_α, 71.073 pm	Mo-K_α, 71.073 pm
Temperature of measurement	293 (1) K	293 (1) K
θ Range	$1.75^\circ - 27.5^\circ$	$1.75^\circ - 27.5^\circ$
Range in *hkl*	$-1 \le h \le +8$	$0 \le h \le +10$
	$-14 \le k \le +14$	$0 \le k \le +15$
	$-11 \le l \le +11$	$0 \le l \le +24$
Total no. reflections	3901	4444
Independent reflections	3104	3847
Reflections with $I > 3\sigma(I)$	2901	3401
Data / parameters	3104 / 148	3847 / 206
Goodness-of-fit on F^2	1.083	1.085
Final R indices[a] $[I > 2\sigma(I)]$	$R_1 = 0.0422$	$R_1 = 0.0422$
	$wR_2 = 0.1130$	$wR_2 = 0.1006$
R Indices (all data)	$R_1 = 0.0478$	$R_1 = 0.0520$
	$wR_2 = 0.1166$	$wR_2 = 0.1115$
Largest diff. peak and hole	$0.375/-0.228$	$0.404/-0.2703$

[a] $R_1 = \sum \|F_o\| - |F_c\| / \sum |F_o|$; $wR_2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}$, where $w = [\sigma^2(F_o^2) + (g_1P)^2 + g_2P]^{-1}$; $P = [\max(F_o^2, 0) + 2F_c^2]/3$.

terial obtained was identical [IR, ^{1}H NMR, ^{13}C NMR, MS (EI, 70 eV)] with the alkaloid **6**. $[\alpha]_D^{25} + 22^\circ$ ($CHCl_3$; *c* 0.54) CD: $\Delta\varepsilon_{225} + 190$, $\Delta\varepsilon_{240} - 10$, $\Delta\varepsilon_{275} + 70$ (EtOH; *c* = 0.01).

Crystal structure determination

The crystals of **7**·HCl and **8**·HBr were glued on the tip of a glass fibre and used for intensity data collection on a BRUKER AXS P4, employing Mo-K_α radiation in an Ω-scan mode. The structure was solved by direct methods (SHELXS) [37] and refined by full matrix least square calculations on F^2 (SHELXL) [37]. All non-hydrogen atoms in of **7**·HCl and **8**·HBr were located by difference Fourier syntheses and refined anisotropically. All hydrogen atoms were placed in idealized calculated positions and allowed to ride on their corresponding carbon atoms with fixed isotropic contributions. Further information on crystal data and data collection are summarized in Table 1. All other information on the crystal structure analysis has been deposited with the Cambridge Crystallographic Data Centre. The data are available free of charge as a CIF file upon request on quoting for compound **7**·HCl CCDC No. 199815, and for compound **8**·HBr 199814, the author names, the journal name and page numbers.

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