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DIONCOPHYLLINE D AND 8-*O*-METHYLDIONCOPHYLLINE D, 7,8′-COUPLED NAPHTHYLISOQUINOLINE ALKALOIDS FROM *TRIPHYOPHYLLUM PELTATUM*†

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Key Word Index—*Triphyophyllum peltatum*; Dioncophyllaceae; dioncophylline D; 8-*O*-methyldioncophylline D; naphthylisoquinoline alkaloids; biaryls; atropisomerism; structural elucidation.

Abstract—The isolation and structural elucidation of two novel naphthylisoquinoline alkaloids, dioncophylline D and its 8-*O*-methyl analogue, from the West African liana *Triphyophyllum peltatum* are described. Their structures are based on the rare 7,8′-coupling between the two molecular moieties. The absolute configuration at the stereocentres of the isoquinoline half was established by oxidative degradation to give *R*-3-aminobutyric acid and D-alanine. Both alkaloids are characterized by a rapid rotation around the biaryl axis. The two new alkaloids are apparently found in young (carnivorous) plants, exclusively.

INTRODUCTION

Triphyophyllum peltatum Airy Shaw is a remarkable West African liana, endemic to the Ivory Coast, Sierra Leone, and Liberia [2]. Morphologically, it is characterized by the formation of three different types of leaves [2], from which the name of the genus, *Triphyophyllum*, is derived: 'Ordinary', lanceolate leaves as a juvenile plant; leaf-derived insect-trapping organs during an intervening carnivorous phase, and then leaves invested with apical hooks, from which the family name, Dioncophyllaceae (= doubly clawed leaves), is derived. Phytochemically, the species is characterized by a broad variety of apparently acetogenic naphthylisoquinoline alkaloids [3, 4]. For most of these alkaloids, the biaryl axis between the two molecular halves links C-7 of the isoquinoline and C-1′ of the naphthalene moiety—the 'A-type' coupling, as in dioncophylline A (**1**) [5]. In addition, there are also the less frequently occurring 7,6′- and 5,1′-coupling types ('types B and C') as in dioncophyllines B (**2**) [6] and C (**3**) [7]. More recently, we have detected a fourth structural type, as realized in dioncophyllinol D (**4**), in which the two molecular moieties are linked in a 7,8′-coupled way [8]. In this paper, we report on the isolation and structural elucidation of two further alkaloids with 7,8′-coupling type, i.e. dioncophylline D (**5**) and 8-*O*-methyl-dioncophylline D (**6**), from young carnivorous *T. peltatum* plants from the Ivory Coast. Part of this work has been reported in preliminary form [3].

RESULTS AND DISCUSSION

In the course of biosynthetic studies on the acetogenic origin of *Triphyophyllum* alkaloids, by feeding labelled precursors to the insect trapping organs [9, 10], young plants, just in the carnivorous phase, were collected in the Parc de Taï, Ivory Coast. Extraction of the leaves, stems and roots with 1 M HCl–MeOH (1:1), removal of the MeOH *in vacuo* and extraction of the aq. soln with $CHCl_3$ gave a mixture of alkaloids. From this, besides the known [5, 11] naphthylisoquinolines dioncophylline A (**1**) (in the case of stem and root materials) and dioncophyllacine A (from leaf material), two novel related alkaloids were obtained by CC and preparative TLC. Their final separation was effected by preparative HPLC on RP_{18} material to yield 5 mg of a more polar (**5**) and 4 mg of a less polar (**6**) alkaloid.

For the more polar alkaloid (**5**), the mass spectral data ($[M]^+ = m/z$ 363), as well as HRMS, revealed

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† Part 108 in the series 'Acetogenic Isoquinoline Alkaloids'. For part 107, see Ref. [1].

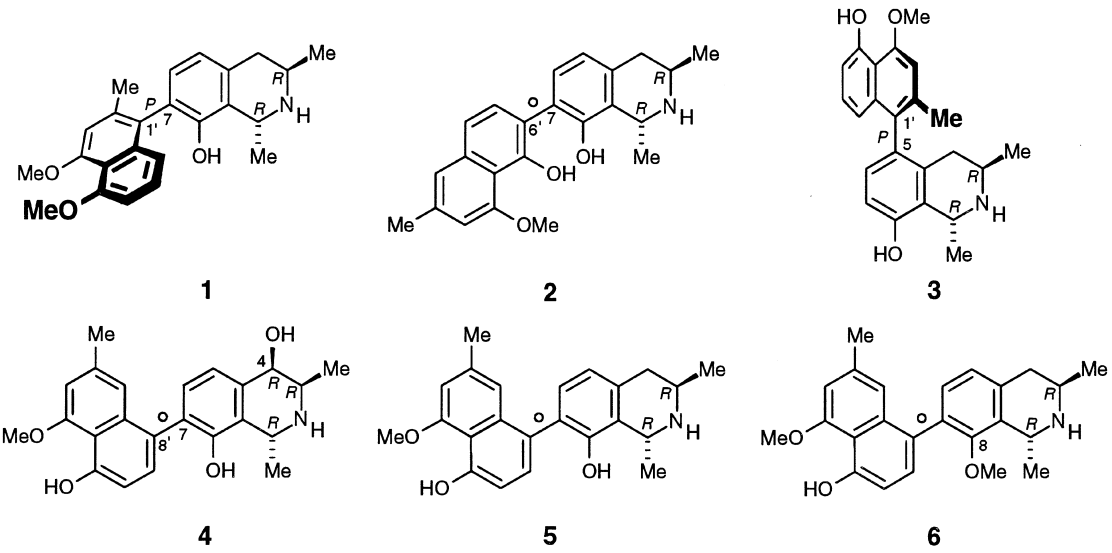


Fig. 1. Known (**1**–**4**) and new (**5**, **6**) alkaloids from *T. peltatum* (o: stereochemically unstable biaryl axis).

a molecular formula $C_{23}H_{25}O_3N$ that indicated the presence of a compound isomeric to dioncophyllines B (**2**) and C (**3**). NMR spectroscopic investigations (Fig. 2) confirmed the close structural relationship to these two alkaloids, a major difference being the presence of only two (instead of three) neighboring aromatic protons in the methyl-free ring of the naphthalene, which showed the biaryl axis to be located at C-6′ or C-8′. This was corroborated by the ordinary, i.e. not high-field shifted, Me-2′ signal at δ 2.43 (Fig. 2(a)), which excluded the isoquinoline substituent from being at C-1′ or C-3′. The fact that the signals of the protons at C-4 and C-3 and of the methyl group at C-3 were not high-field shifted either, indicated that the naphthalene substituent was not at C-5 of the isoquinoline moiety. The full constitution, including the rare 7,8′-coupling, the *O*-methyl group at O-4′ and two free phenolic OH functions located at C-8 and C-5′, was established through a series of NOE experiments (Fig. 2(a)) and HMBC interactions (see Fig. 2(b)) as that of a new alkaloid, subsequently named dioncophylline D. It is based on the rare 'D-coupling type' as previously found only in one other *Triphyophyllum* alkaloid, dioncophyllinol D (**4**) (cf Fig. 1) [8].

Stereochemically, the tetrahydroisoquinoline part with its two chiral centres, is fully identical with the isoquinoline parts of dioncophyllines A–C (**1**–**3**). The relative configuration was clearly established by the distinct NOE-effect from Me-1 to the likewise pseudo-

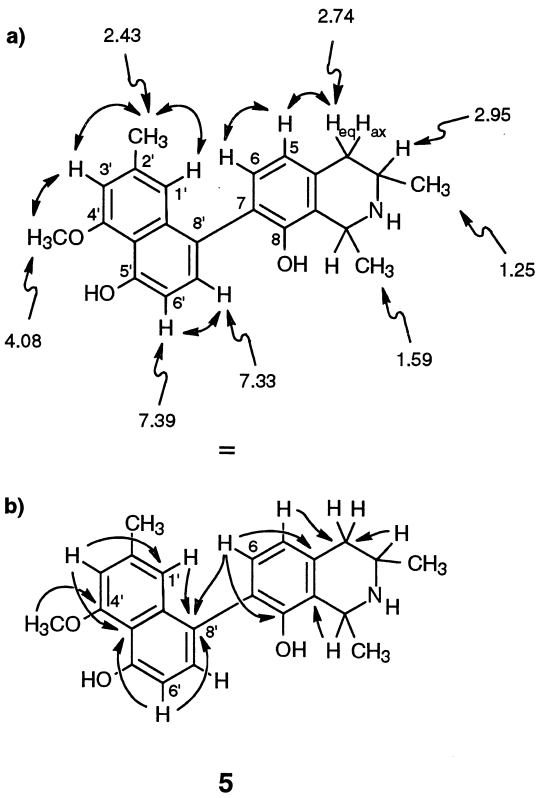


Fig. 2. Constitution of dioncophylline D as deduced from selected chemical shifts (δ-values in ppm) and NOE effects (a) and from HMBC interactions (b).

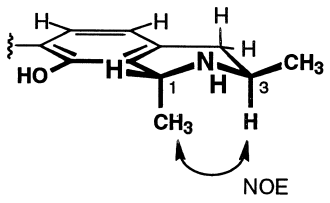


Fig. 3. Relative configuration of dioncophylline D through NOE; identical results were obtained for 8-*O*-methyldioncophylline D.

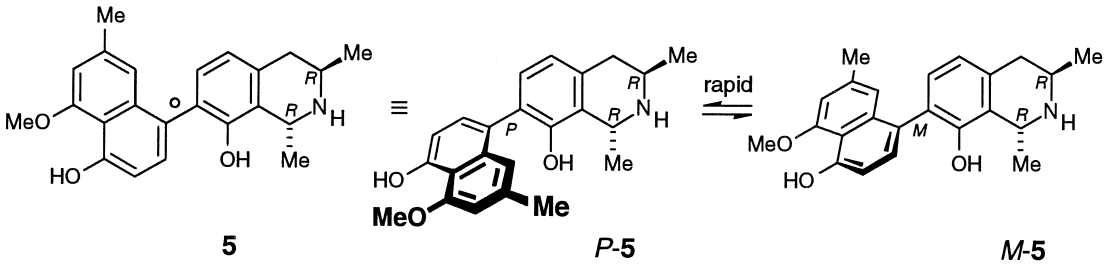
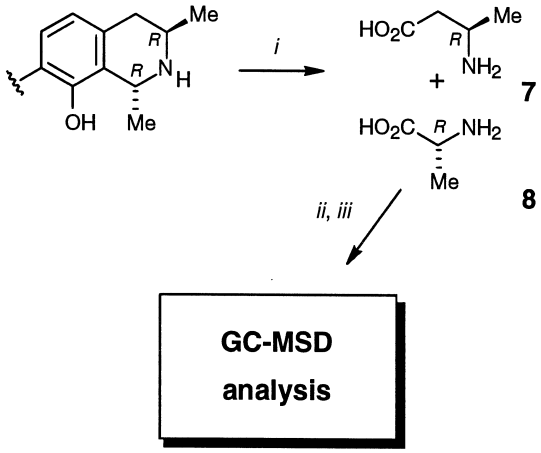


Fig. 4. Dioncophylline D (**5**) as a mixture of its two rapidly interconverting atropo-diastereomeric forms, *P*-**5** and *M*-**5**.

axial proton at C-3 (Fig. 3), indicating a *trans*-configuration at C-1 vs C-3.

Ruthenium-mediated oxidative degradation [12, 13] of the alkaloid gave (*R*)-3-aminobutyric acid (**7**) and (*R*)-alanine (**8**) (Scheme 1), thus unequivocally establishing the 1*R*,3*R*-configuration for dioncophylline D. Hence, the tetrahydroisoquinoline moiety of dioncophylline D is identical with that of **1**–**3**, in every detail for **1** and **2**, including the coupling site.



Scheme 1. Absolute configuration at C-1 and C-3 through oxidative degradation of **5** to *R*-aminobutyric acid (**7**) and D-alanine (**8**); identical results were obtained for the second new alkaloid (**6**) (i) $RuCl_3$, $NaIO_4$; (ii) esterification with MeOH; (iii) (*R*)-MTPA-Cl ('Mosher's chloride', see Ref. [14]).

From these results, dioncophylline D can unambiguously be attributed the stereostructure **5** (Fig. 4). As previously for dioncophyllinol D (**4**) [8], alkaloid **5** likewise has a low rotational barrier at the biaryl axis, which leads to a rapid interconversion of the two atropo-diastereomeric forms of dioncophylline D, P-**5** and M-**5**. The axis thus does not constitute an additional stable element of chirality in this case.*

The less polar alkaloid (**6**) ($C_{24}H_{27}O_3N$, based on HRMS analysis) showed an ^1H NMR spectrum very similar to that of **5**, the most obvious difference being an additional *O*-methyl signal at δ 3.36 (Fig. 5(a)). Its high-field shift compared to that of the other methoxy group (δ 3.95) pointed to its close proximity to the biaryl axis and thus indicated the additional *O*-methyl group was attached to O-8. This was confirmed by a NOE interaction of that OMe group with the (equatorial) proton at C-1 and an HMBC interaction with C-8 (Fig. 5(b)). A series of further NOE effects and HMBC interactions fully confirmed the second new alkaloid to have the same constitution as **5**, except for a methoxy group instead of an OH group at C-8.

As for **5** (cf Fig. 3), the relative *trans*-configuration at C-1 vs C-3 was established through a NOE interaction between Me-1 and H-3 and, likewise as for **5**

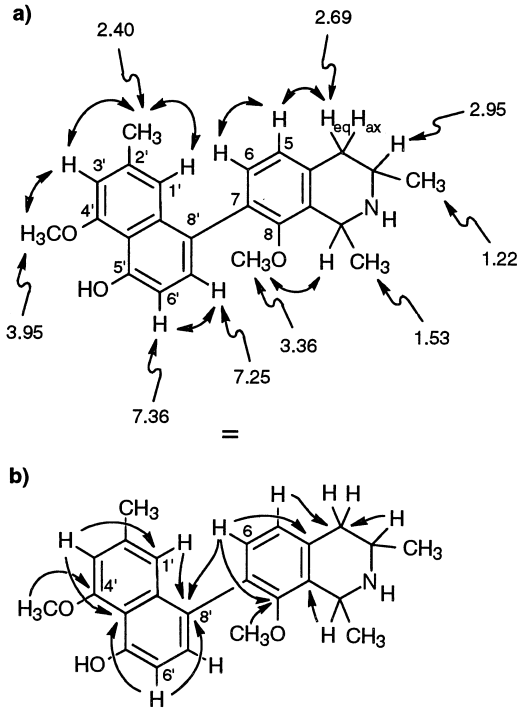


Fig. 5. Constitution of the second alkaloid through selected chemical shifts (δ-values) and NOE effects (a) and significant heteronuclear long-range couplings (b).

* The structure of dioncophylline D (**5**) has recently been mentioned in preliminary form, arbitrarily by drawing one of the two (configuratively unstable) atropodiastereomers [3].

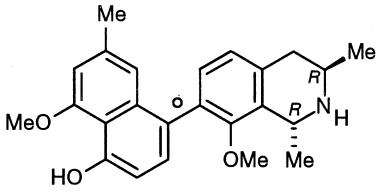


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Fig. 6. Full absolute stereostructure of the second new alkaloid, 8-*O*-methyldioncophylline D.

(cf Scheme 1), oxidative degradation again indicated both stereogenic centres to have *R* configuration. Consequently, the second alkaloid was identified as 8-*O*-methyldioncophylline D and is represented by the absolute stereostructure **6**, again with an unstable configuration at the biaryl axis.

The structures of the new alkaloids (**5** and **6**) described in this paper, further widen the variety of structures produced by the biosynthetically creative and productive tropical liana, *T. peltatum*. The fact that these alkaloids were not detected earlier, has to do with the fact that in adult plant material, as investigated in previous studies [3, 4], these metabolites apparently occur in traces only, whereas **4**, the corresponding 4-hydroxy analogue, is more abundant in the 'older' leaf material. The phytochemical investigation of young, still carnivorous plants, as first described in this paper, and the detection of the new alkaloids **5** and **6** therefrom, underlines how rewarding the search for still further, as yet unknown metabolites under particular conditions can be.

EXPERIMENTAL

General

Mps: uncorr; Optical rotations: 25°, 10 cm cell, $CHCl_3$; CD: 25°, EtOH; IR: KBr; ^1H NMR (600 MHz) and ^{13}C NMR (150.9 MHz): $CDCl_3$ with the solvent as int. standard ($CDCl_3$, δ 7.26 and δ 77.01, resp.). Proton detected, heteronuclear correlations were measured using HMQC (Heteronuclear Multiple Quantum Correlation, optimized for $^1J_{HC} = 150$ Hz) and HMBC (optimized for $^nJ_{HC} = 7$ Hz). EIMS: 70 eV; CC: 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 NH_3. Spots were visualized under UV light and by Dragendorff's reagent. Prep. TLC: plates with a layer thickness of 2 mm and a concentration zone (Merck) were used. 20–40 mg samples were applied and recovered with 25% MeOH in $CHCl_3$ after resolution. Prep. HPLC: Waters 600E pump, a Nova-Pak C_{18} (Waters, 200 × 25 mm, 6 μm, integrated guard pak) column, and a Waters 996 photodiode array detector.

Plant material

T. peltatum was collected and identified by L. Aké Assi and G. Bringmann in the Parc de Taï, West Ivory Coast, in March 1996. Herbarium specimens are deposited at the Centre National de Floristique, Abidjan, and at the Institut für Organische Chemie, Würzburg.

Extraction and isolation

Leaves (19.4 g) were dried, powd and extrd with 1M HCl–MeOH (1:1) at room temp. with ultrasonic assistance for 2 days. After evapn of the MeOH *in vacuo*, the aq. soln was extracted with $CHCl_3$. The solvent was evapd to yield a brownish crude extract (317 mg), which was subjected to CC over silica gel (40 g) using CH_2Cl_2–MeOH (19:1) as the eluent. Portions of 10 ml were collected and combined to give several frs, two of which contained the two new alkaloids.

Dioncophylline D (**5**). The more polar fraction (14 mg) was purified by prep. TLC using CH_2Cl_2–MeOH (19:1) as the eluent (R_f 0.58), and two-fold semiprep. HPLC on a Nova-Pak C_{18} (200 × 25 mm, 6 μm) column with MeOH–H_2O (3:1) as the eluent, to yield **5**, as a yellow amorphous solid (5 mg) (from MeOH). Mp 234–236°; $[\alpha]_D^{25} + 15.5°$ (EtOH; *c* 0.10); CD: $\Delta\varepsilon_{218}$ −8.0, $\Delta\varepsilon_{246}$ 5.2, $\Delta\varepsilon_{304}$ −7.4 (EtOH; *c* 0.10); IR ν_{max} cm^{-1}: 3450 (O-H), 2950 (N-H), 1660 (C═C), 1420, 1200, 1120, 1090 (C-O); ^1H NMR (600 MHz, $CDCl_3$): δ 1.25 (3H, *d*, $J = 6.4$ Hz, Me-3), 1.59 (3H, *d*, $J = 6.3$ Hz, Me-1), 2.43 (3H, *s*, Me-2′), 2.74 (1H, *dd*, $J_{gem} = 15.2$ Hz, $J_{ax} = 1.8$ Hz, H-4_{ax}), 2.95 (1H, *m*, H-3), 4.08 (3H, *s*, OMe-4′), 4.48 (1H, *q*, $J = 6.3$ Hz, H-1), 6.70 (1H, *d*, $J = 1.1$ Hz, H-3′), 6.78 (1H, *d*, $J = 7.7$ Hz, H-5), 7.12 (1H, *d*, $J = 7.8$ Hz, H-6), 7.25 (1H, *s*, H-1′), 7.33 (1H, *d*, $J = 8.6$ Hz, H-7′), 7.39 (1H, *d*, $J = 8.6$ Hz, H-6′); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 21.7 (Me-3), 21.9 (Me-2′), 22.1 (Me-1), 38.4 (C-4), 58.9 (C-3), 50.5 (C-1), 56.4 (OMe-4′), 107.3 (C-3′), 112.9 (C-4a′), 119.0 (C-8′), 121.6 (C-6), 120.8 (C-1′), 121.6 (C-5), 124.6 (C-7), 127.2 (C-8a), 129.0 (C-6′), 131.0 (C-7′), 136.3 (C-8a′), 136.4 (C-2′), 136.4 (C-4a), 149.2 (C-5′), 151.2 (C-8), 155.7 (C-4′). The ^{13}C assignments were achieved by HMQC and HMBC experiments. EIMS *m/z* (rel. int.): 363 $[M]^+$ (18), 362 $[M-H]^+$ (47), 348 $[M-Me]^+$ (100); HRMS *m/z* 348.160 $[M]^+$ ($C_{23}H_{25}O_3N$ requires: 348.160).

8-*O*-*Methyldioncophylline D* (**6**). Further purification of the less polar compound was done initially by prep. TLC using CH_2Cl_2–MeOH (19:1) as the eluent (R_f 0.63), and then by semiprep. HPLC using a Nova-Pak C_{18} (200 × 25 mm, 6 μm) column with MeOH–H_2O (3:1) as the eluent, to yield **6**, as a yellow amorphous solid (4 mg) (from MeOH). Mp 228–232°; $[\alpha]_D^{25} + 21°$ ($CHCl_3$: *c* 0.046); CD: $\Delta\varepsilon_{221}$ −7.6, $\Delta\varepsilon_{241}$ 5.4, $\Delta\varepsilon_{309}$ −7.2 (EtOH; *c* 0.1); IR ν_{max} cm^{-1}: 3400 (O-H), 2920 (N-H), 1650 (C═C), 1400, 1250, 1090 (C-O); ^1H NMR (600 MHz, $CDCl_3$): δ 1.22 (3H, *d*, $J = 6.1$ Hz, Me-3), 1.53 (3H, *d*, $J = 6.4$ Hz, Me-1), 2.40 (3H, *s*, Me-2′), 2.69 (1H, *dd*, $J_{gem} = 15.6$ Hz, $J_{ax} = 2.7$ Hz, H-4), 2.91 (1H, *m*, H-3), 3.36 (3H, *s*, OMe-8), 3.95 (3H, *s*, OMe-5′), 4.36 (1H, *q*, $J = 5.8$ Hz, H-1), 6.57 (1H,

d, $J = 1.2$ Hz, H-3′), 6.83 (1H, *d*, $J = 8.1$ Hz, H-5), 7.21 (1H, *d*, $J = 8.1$ Hz, H-6), 7.22 (1H, *d*, $J = 1.2$ Hz, H-1′), 7.25 (1H, *d*, $J = 8.5$ Hz, H-7′) 7.36 (1H, *d*, $J = 8.5$ Hz, H-6′); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 20.3 (Me-3), 21.9 (Me-1 and Me-2′), 37.0 (C-4), 49.5 (C-3), 50.9 (C-1), 56.1 (OMe-4′), 60.1 (OMe-8), 106.6 (C-3′), 113.3 (C-4a′), 118.0 (C-6 and C-8′), 120.8 (C-1′), 123.7 (C-5), 127.2 (C-8a), 129.7 (C-7), 130.3 (C-7′), 130.9 (C-6′), 136.3 (C-8a′), 135.9 (C-2′), 136.5 (C-4a), 150.9 (C-5′), 156.0 (C-8), 156.2 (C-4′). The ^{13}C assignments were achieved by HMQC and HMBC experiments. EIMS *m*/*z* (rel. int.): 378 $[M]^+$ (4), 377 $[M-H]^+$ (13), 362 $[M-Me]^+$ (100); HRMS *m*/*z* 362.175 $[M-Me]^+$ ($C_{23}H_{24}O_3N$ requires: 362.176).

Oxidative degradation of the alkaloids

The degradation, the derivatization of the resulting amino acids, and the subsequent GC-MSD analysis were carried out as described in Ref. [13].

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