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8-*O*-Methyldioncophyllinol B and revised structures of other 7,6′-coupled naphthylisoquinoline alkaloids from *Triphyophyllum peltatum* (Dioncophyllaceae)☆

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Abstract

The isolation and structural elucidation of a new naphthylisoquinoline alkaloid, 8-*O*-methyldioncophyllinol B, from *Triphyophyllum peltatum* (Hutch. et Dalz.) Airy Shaw (Dioncophyllaceae) is described, together with the revised structures of other 'B-type' compounds previously misidentified as dioncophylline D, dioncophyllinol D, and 8-*O*-methyldioncophylline D. All of the presently described structures are 7,6′-coupled and thus have to be addressed as 'B-type' naphthylisoquinoline alkaloids. This is in contrast to the initially defined 'D-type' structures, which are 7,8′-coupled as confirmed by a total synthesis of dioncophylline D. Some of these natural and synthetic naphthylisoquinolines were found to display good in vitro antiplasmodial activities.

Keywords: *Triphyophyllum peltatum*; Dioncophyllaceae; Structural elucidation; Naphthylisoquinoline alkaloids; 8-*O*-Methyldioncophyllinol B; Dioncophyllinol B; 1-*epi*-Dioncophylline B; 8-*O*-Methyl-1-*epi*-dioncophylline B; Dioncophyllinol D; Dioncophylline D; 8-*O*-Methyldioncophylline D; Antimalarial activity

1. Introduction

The West African liana *Triphyophyllum peltatum* (Dioncophyllaceae) is a versatile producer of structurally, pharmacologically, and biosynthetically interesting naphthylisoquinoline alkaloids (Bringmann and Pokorny, 1995; Bringmann et al., 1998b). The manifold structural features of these natural products, especially the different positions of the biaryl axis between the two molecular 'halves', the oxygen substitution pattern, and the stereocenters in the tetrahydroisoquinoline part, lead to a great variability, as illustrated by dioncophyllines A (**1**, 7,1′-coupled), B (**2**, 7,6′-coupled) (Bringmann et al., 1991a), and C (**3**, 5,1′-coupled) (Fig. 1). In most of these secondary metabolites, e.g. in **1** and **3**, the biaryl axis is configurationally stable due to the high rotational barrier and is thus an additional stereoelement, whereas e.g. in **2** the axial configuration is unstable because of the presence of only two *ortho*-substituents. Dioncophyllacine B (**4**), the only other known 7,6′-coupled naphthylisoquinoline alkaloid till date, is characterized by a dehydrogenated heterocyclic part and thus by the lack of any stereogenic centers and is, therefore, even achiral at room temperature (Bringmann et al., 1992).

In this paper, we report on the isolation and structural elucidation of a new, minor alkaloid **5**, with a

☆ Part 136 in the series 'Acetogenic isoquinoline alkaloids'. For part 135, see Bringmann et al. (2000a).

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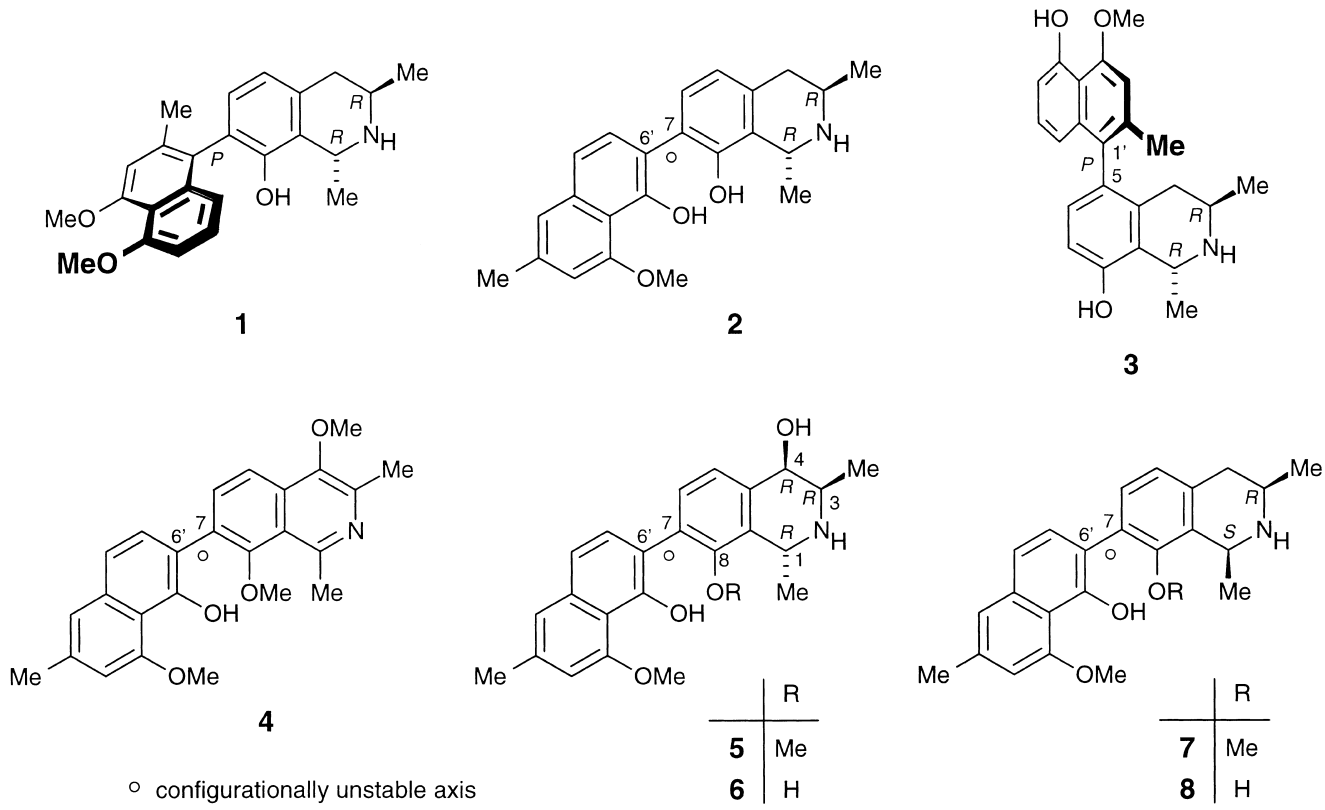


Fig. 1. Naphthylisoquinoline alkaloids from *T. peltatum*.

hydroxy function at C-4. Its spectral similarity to compounds previously isolated from this plant that had been assigned structures corresponding to the 7,8′-coupled compounds dioncophyllinol D, dioncophylline D and 8-*O*-methyldioncophylline D (Bringmann et al., 1998c, 1998d), necessitated the re-isolation and renewed structural investigation of these three further alkaloids from *T. peltatum*. Accordingly, these three naturally occurring alkaloids have been reassigned the revised structures **6**, **8**, and **7**, i.e. all with 7,6′ coupling sites ('B-type'), not 7,8′ ('D-type') as initially supposed and have thus been renamed as dioncophyllinol B, 1-*epi*-dioncophylline B, and 8-*O*-methyl-1-*epi*-dioncophylline B, respectively. The new compound 8-*O*-methyldioncophyllinol B (**5**), the alkaloids **6**, **7**, and **8**, as well as authentic dioncophylline D, which has been synthesized for the first time, were found to exhibit good antiplasmodial activities.

2. Results and discussion

The MeOH/HCl extract of the leaves of *T. peltatum* was perforated with chloroform. The organic layer was then resolved by CC, yielding the alkaloid previously identified as 'dioncophyllinol D' and a slightly less polar minor compound, the mass peak of which, together with HREIMS, hinted at the molecular formula $C_{24}H_{27}NO_4$. The ^{1}H NMR spectrum exhibited the typical signals of a naphthyl-4-hydroxy-1,3-dimethyltetrahydroisoquinoline alkaloid. The singlets at 3.36 and 4.03 ppm (see Fig. 2), each corresponding to three protons, indicated the presence of two methoxy groups. One of them (3.36 ppm) is connected to C-8 of the isoquinoline part as deduced from Heteronuclear Multiple Bond Correlation (HMBC) and Rotating Frame Overhauser Enhancement Spectroscopy (ROESY) measurements (see Fig. 2). The high-field shifted position of this methoxy group must result from the anisotropic effect caused by the naphthalene substituent, thus providing evidence for a coupling position *ortho* to this methoxy group and hence at C-7. This assumption is supported by HMBC interactions from H-5 and H-7′ to the quaternary C-7 (see Fig. 2).

In the naphthalene part, the biaryl axis cannot be positioned in the methyl-substituted ring, as can clearly be deduced from the 'normal', i.e. not high-field shifted 2′-methyl group signal (2.46 ppm) and must thus be located at C-6′ as in **5A** — or at C-8′ as in the likewise imaginable structure **5B**. The differentiation between these two possibilities — and therefore the decision whether the signal at 7.24 ppm has to be attributed to H-8′ (for **5A**) or H-6′ (for **5B**) — turned out to be quite difficult since neither the chemical shifts nor H,H-COSY measurements are indicative of the coup-

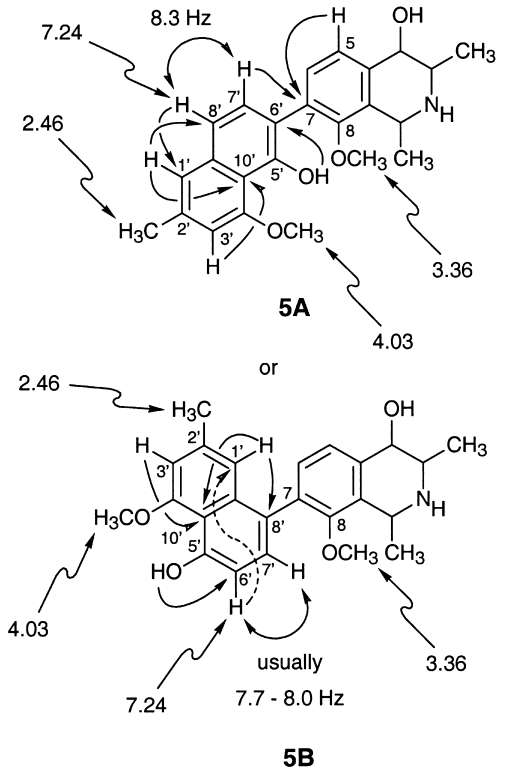
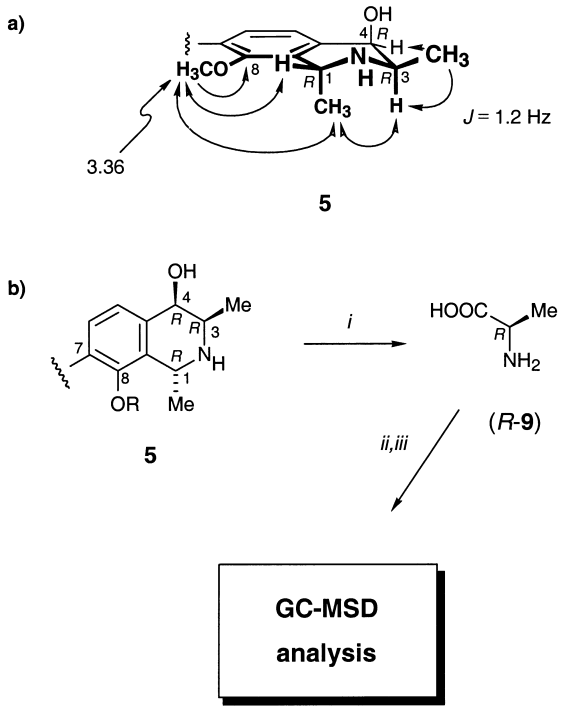


Fig. 2. The two initially possible constitutions **5A** and **5B** of the new alkaloid together with selected chemical shifts and the HMBC interactions as well as the coupling constants indicative of the coupling type; the interaction from H-8′ to C-1′ in **5A**, which would, for **5B**, correspond to an (impossible) interaction between H-6′ and C-1′ (dotted line), proves **5A** to be the correct constitution.

ling site. In the present molecule, only HMBC correlations of H-1′ and H-8′ (for **5A**) or H-6′ (for **5B**) allow for an unambiguous attribution of the coupling type (see Fig. 2): in 5′-hydroxy-4′-methoxy-2′-methylnaphthalenes with an isoquinoline residue at C-6′ as given for **5A**, HMBC interactions between H-1′ and C-8′ (which has to be tertiary) and from H-8′ to C-1′ are to be expected, the latter of which should not be observable in 8′-coupled ones. In the present alkaloid, both correlations are observed, unambiguously proving C-6′ to be the coupling position in the naphthalene part, as in **5A**. This is supported by an HMBC interaction between the hydrogen-bridged 5′-hydroxy proton and C-6′, which is quaternary (not tertiary as would have been in **5B**) and must, therefore, bear the biaryl axis. A confusion of C-6′ with the likewise quaternary C-10′ is excluded by HMBC interactions from H-1′ and H-3′ to that same carbon. Further evidence of the presence of structure **5A** is given by the fact that the carbon atom identified by the described HMBC interaction of H-1′ (i.e. C-8′), is observed to be tertiary, while it would be quarternary in **5B**. Like dioncophylline B (**2**), hence, the new alkaloid is 7,6′, not 7,8′-coupled, and thus must have the constitution **5A**.

This assumption is further confirmed by examination of the coupling constants of the aromatic protons in the non-methyl substituted ring, i.e. of H-7′ with H-8′ (in 7,6′-coupled naphthylisoquinolines) or H-7′ with H-6′ (in 7,8′-coupled ones), thus indicating whether the coupling partner of H-7′ is H-6′ or H-8′. The lower double bond character of the C-6′–C-7′ bond as compared to the C-7′–C-8′ bond (Hesse et al., 1991) leads to coupling constants of ca. 7.7–8.0 Hz for H-7′ in 7,8′-coupled alkaloids (see, e.g., Bringmann et al., 1996b), whilst in 7,6′-coupled ones such as **2** the coupling constant of H-7′ is significantly higher (8.4–8.6 Hz) (Bringmann et al., 1991a). The present alkaloid shows a J value of ca. 8.3 Hz for these protons, typical of a 7,6′ coupling, thus again supporting the structure **5A**.

The relative configuration of these three stereocenters of the isoquinoline was found to be as depicted in Scheme 1(a) by virtue of ROESY measurements and by analysis of the coupling constants. The absolute configuration was elucidated by oxidative degradation (Bringmann et al., 1996a), now leading to D-alanine (D-**9**), exclusively. With the relative configuration established above, a 1*R*,3*R*,4*R*-array of the substitu-



Scheme 1. Relative configuration (and further proof of constitution) of the new alkaloid: (a) by selected ROESY correlations (double-headed arrows) and an HMBC interaction; absolute configuration of the compound (b) by oxidative degradation and analysis by Gas Chromatography with Mass Sensitive Detection (GC-MSD). (i) $RuCl_3$, $NaIO_4$; (ii) esterification with MeOH; (iii) '*R*-MTPA-Cl' ('Mosher's chloride') (b).

ents at the isoquinoline moiety becomes evident (Scheme 1(b)).

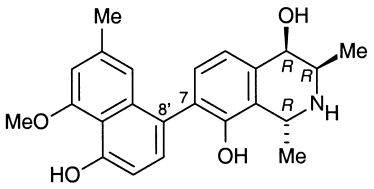
The new alkaloid from *T. peltatum* consequently must have structure **5** (see Fig. 1), it is thus the first 7,6′-coupled naphthylisoquinoline alkaloid containing three stereocenters in the tetrahydroisoquinoline part and hence resembles likewise the 7,6′-coupled and 4-oxygenated, but dehydrogenated alkaloid dioncophyllacine B (**4**), of which it might be the biogenetic precursor.

The unexpected similarity of the spectra of **5** to those of the previously isolated compound identified initially as 'dioncophyllinol D', the only other known 4-hydroxylated naphthylisoquinoline alkaloid, necessitated a structural analysis of that alkaloid, in order to check whether that compound is really 7,8′-coupled as assumed before (Bringmann et al., 1998d) — or possibly likewise 7,6′. The isolation of larger amounts of the compound from *T. peltatum* and its structural reelucidation indeed led to the finding that its coupling type is 7,6′ instead of 7,8′, as now proven by the presence of all those diagnostically significant HMBC interactions described above for **5A** (see Fig. 2) and by the NMR coupling constant of H-7′ with its vicinal aromatic proton (J = 8.6 Hz). Therefore, the compound previously misidentified as the 7,8′-coupled dioncophyllinol D (**10**, Fig. 3) actually has the 7,6′-coupled structure **6** (see Fig. 1), characteristic of a 'B-type' rather than a 'D-type' coupling. The initial erroneous attribution of the 7,8′ coupling type to **6** might have been possibly due to a misinterpretation of the 2D NMR spectra and a partial decomposition of the alkaloid samples during the HMQC and the HMBC measurements. The new alkaloid, **5**, is thus the 8-*O*-methylated analog of **6**, hence to be named 8-*O*-methyldioncophylline B.

This, in turn, gave rise to the revision of the previously assigned 7,8′-coupled structures **11** and **12** of the two other alkaloids from *T. peltatum*, now correctly represented by **8** and **7** (see Fig. 1), i.e. likewise with a 7,6′ coupling.

The above-described revised structure assignments raised the question whether 7,8′-coupled alkaloids are present in this plant at all. To help address this question, as well as to further probe structural requirements for antiparasitic activity, authentic dioncophylline D was first prepared by an unambiguous total synthesis of this structure. Availability of this material by synthesis also seemed especially desirable in light of the antimalarial activity of other 7,8′-coupled alkaloids such as ancistroheynine A from *Ancistrocladus heyneanus* (Ancistrocladaceae) (Bringmann et al., 1996b) and yaoundamine A from *A. korupensis* (Hallock et al., 1997), and, in particular, of some closely related but 7,6′- and 5,1′-coupled alkaloids such as **2** and **3**. Starting from the precursors **13** and **14**, both of which had already been used for other naphthylisoquinoline alkaloid syntheses (Bringmann et al., 1996c; Bringmann and Günther, 1999), a Stille reaction yielded the desired product **15** in a good coupling yield of 63%. Final deprotection of **15** gave **11** as the first synthetic 7,8′-coupled naphthylisoquinoline. The compound was found to be a mixture of two rapidly interconverting atropisomers, which, already by TLC, proved not to be identical with the compound previously isolated from *T. peltatum* now identified as 1-*epi*-dioncophylline B. While the latter natural compound thus clearly does not have the initially assumed structure **11**, but rather is **8**, compound **11** still is a potential — but not yet identified — natural product: *T. peltatum* does produce alkaloids with the two molecular moieties of **11** (e.g. **2** and **3**), and naphthylisoquinoline alkaloids, with an accurately established 7,8′ coupling type, do indeed occur in related plants, e.g. ancistroheynine A and yaoundamine A (Scheme 2).

The last problem to be solved was the configuration in the isoquinoline parts of **7** and **8**. The oxidative degradation had resulted in an unambiguous attribution of a 3*R*-configuration (Bringmann et al., 1998c). From NOE interactions between H-1 and H-3, a *cis*-



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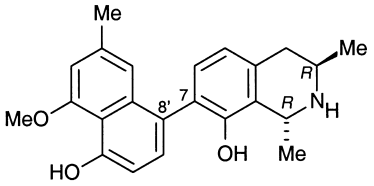

11

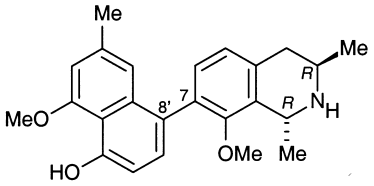

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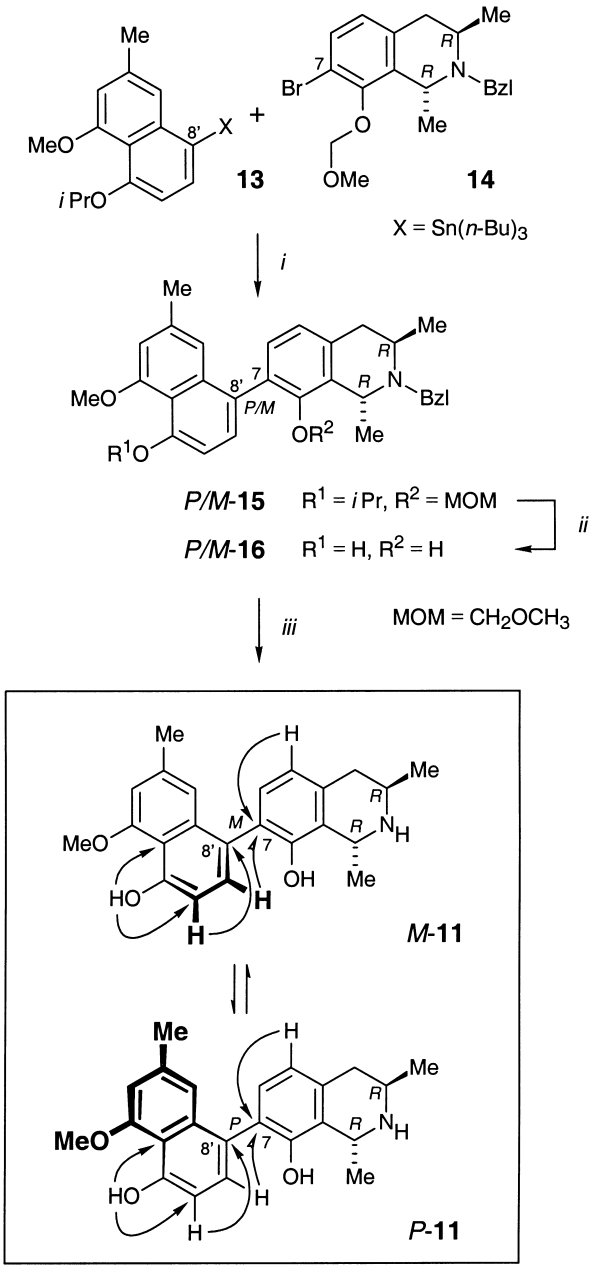
Fig. 3. Structures **10**, **11**, and **12** previously attributed to the natural products **6**, **8**, and **7**, respectively. For the correct structures see Fig. 1.



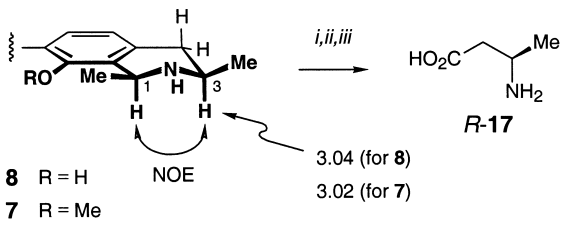
Scheme 2. Synthesis of dioncophylline D (**11**): (i) $Pd(PPh_3)_2Cl_2$, PPh_3, CuBr, LiCl, DMF, 135°C, 63%; (ii) BCl_3, CH_2Cl_2, 94%; (iii) Pd black, HCOOH, MeOH, 65%.

arrangement of the two methyl groups was now deduced for both **7** and **8** (Scheme 3).

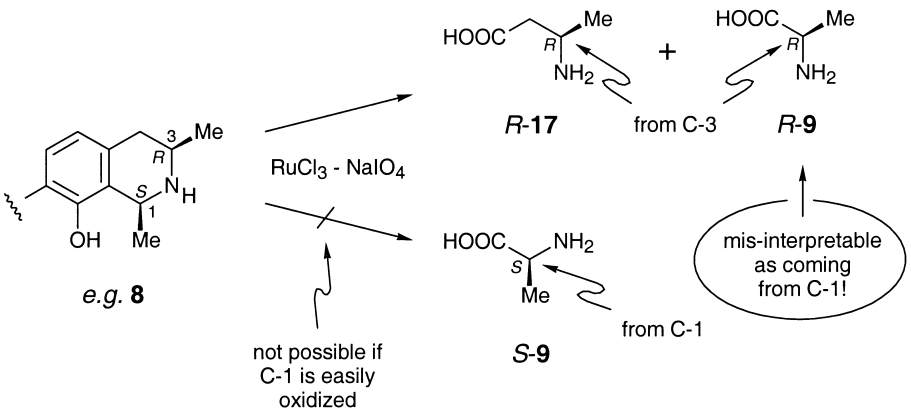
This *cis*-array is in agreement with the chemical shift of H-3 around 3.0 ppm (Scheme 3), which lies in the typical range for *cis*-substituted 1,3-dimethyl-tetrahydroisoquinolines (Bringmann et al., 1990, 1998a), while the *trans*-epimers usually give δ values around 3.2–3.4. From this relative *cis*-configuration and an absolute *R*-configuration at C-3 as deduced from our oxidative degradation procedure, C-1 can be established to be *S*-configured, which leads to the full absolute stereostructures **8** and **7** for the two 4-hydroxylated alkaloids of *T. peltatum*, hence to be named 1-*epi*-dioncophylline B and 8-*O*-methyl-1-*epi*-dioncophylline B, respectively. That **8** is the *cis*-configured 1-epimer of dioncophylline B (**2**), is further corroborated by the chromatographic behaviour of **8** as compared with that of **2** (slightly more rapid elution on silica gel for *cis*- as compared to *trans*-isomers within the series) (Govindachari et al., 1974).

The initially wrong attribution of a *trans*-configuration in **7** and **8** had resulted from the unfortunate fact that the alanine formed in the degradation reaction was likewise D-configured. This amino acid had erroneously been attributed as originating from C-1, but can indeed also — but here for the first time exclusively! — be generated from C-3, due to the ease of oxidation at C-1 in 1,3-*cis* epimers (Bringmann et al., 1991b) and thus quantitative destruction of that stereocenter and hence of the entire source of L-alanine (Scheme 4). Thus, this example shows that for *cis*-configured naphthylisoquinoline alkaloids reliable results can be obtained only for the C-3 configuration, whereas the configuration at C-1 (relative to the hence secure absolute configuration at C-3) must be deduced from ROESY and NOE measurements.

In conclusion, besides isolating and structurally elucidating the new alkaloid 8-*O*-methyldioncophyllinol B (**5**), we have now achieved an unambiguous structural revision of compounds **6**, **8**, and **7** from *T. peltatum* previously misidentified as of the old (erroneous) structures of 'dioncophyllinol D' (**10**), 'dioncophylline D' (**11**), and '8-*O*-methyldioncophylline D' (**12**), respectively. With now six representatives, the 7,6′ coupling type, once seemingly very rare, has been shown to occur more frequently than hitherto assumed, and the same applies for the 1,3-*cis* configuration in this class of alkaloids. Of biogenetic interest, dioncophyllacine B (**4**), with its additional, apparently not acetate-derived oxygen at C-4, might ultimately arise from **8**, possible intermediates being the 4-oxygenated alkaloids **6** and



Scheme 3. Relative *cis*-configuration of **7** and **8**, as deduced from NOE interactions between H-1 and H-3, and confirmed by the chemical shifts (δ in ppm) for 3-H; absolute configurations as elucidated by oxidative degradation; for the reaction conditions see Scheme 1.



Scheme 4. Oxidative degradation of *cis*-configured tetrahydroisoquinolines.

5 — or from dioncophylline B (**2**) via **7** and related (not yet detected) *cis*-configured 4-oxygenated alkaloids.

The now achieved synthetic availability of **11**, i.e. authentic dioncophylline D, made it rewarding to test this and all the other compounds described or structurally revised in this paper, for their antimalarial activities and to compare them with structurally closely related, in part very active naphthylisoquinolines of related structures such as dioncophyllines B (**2**) and C (**3**), in contrast to dioncophylline A (**1**), which is only moderately active. IC_{50} values of the naphthylisoquinolines **5**, **6**, **7**, and **8** against *Plasmodium falciparum* are given in Table 1. The most active of these compounds, besides the known highly active dioncophylline C (**3**), are dioncophyllinol B (**6**) and the authentic dioncophylline D (**11**). These values underline the high pharmacological potential of 7,6′ and 7,8′-coupled naphthylisoquinolines and can be seen as useful data points for ongoing quantitative structure–activity relationship investigations (Bringmann and Feineis, 2000b).

Table 1
Activities of the naphthylisoquinolines discussed in this paper on chloroquine resistant (K1-strain) and susceptible (NF54-strain) strains of *Plasmodium falciparum* and of chloroquine for comparison

Compound	K1 strain IC_{50} (ng ml^{-1})	NF54 strain IC_{50} (ng ml^{-1})	MIC (μg ml^{-1})
1	144 (44[a])	237 (3.1[a])	37
2	84[b] (44[a])	119b (3.1[a])	67
5	654 (60[a])	245 (3.3[a])	90
6	34 (44[a])	43 (3.1[a])	> 200
7	402 (69[a])	1007 (4.2[a])	33
8	155 (44[a])	273 (3.1[a])	> 200
11	58 (95[a])	70 (4.3[a])	67

[a] Respective value for chloroquine in the same test series.
[b] For the isolation of **2**, see Bringmann et al. (1991a). For previous results on **2** with a similar test system, see François et al. (1994).

3. Experimental

3.1. General

Optical rotations: 10 cm cell, $CHCl_3$. IR: KBr. ^1H NMR (600 MHz, Bruker) and ^{13}C NMR (150 MHz, Bruker) were recorded in $CDCl_3$ (solvent as internal standard, δ 7.26 and δ 77.01, resp.). Proton-detected, heteronuclear correlations were measured using HMQC (optimized for $^1J_{HC}$ = 145 Hz) and HMBC (optimized for $^nJ_{HC}$ = 7 Hz). EIMS: 70 eV. CC: silica gel (60–200 mesh, Merck). TLC: precoated silica gel 60 F_{254} plates (Merck). Spots were detected under UV light. HPLC: symmetry RP-18 (7.8 × 300 mm, Waters), flow 3 ml min^{-1}; UV detection 200–400 nm (photodiode array detector). HSCCC: $CHCl_3$–EtOAc–MeOH–0.1 N HCl (28:17:28:17), mobile phase: lower phase, (H) → T, Tripple® coil, 1.7 × 106, 500 mm (large coil) and 1.7 × 37, 000 mm (middle coil), elution mode: forward, TLC detection (see above); flow 4 ml min^{-1}, 850 min^{-1}.

3.2. Plant material

Leaves of *T. peltatum* were 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, Herbarium Bringmann (no. 2).

3.3. 8-O-Methyldioncophyllinol B (5)

Dried leaves of *T. peltatum* (400 g) were powdered and macerated for 7 days with 4 l MeOH–1 N HCl

(1:1) at room temp. with ultrasonic assistance. After removal of MeOH, the aqueous solution was re-extracted with $CHCl_3$ (1.5 l) to yield 2 g of a brownish crude extract, which was chromatographed over silica gel (200 g, deactivated with 7.5% NH_3) using CH_2Cl_2–MeOH (93:7) as the eluent. Further purification on CC (CH_2Cl_2–MeOH, 95:5) gave 5 (1.2 mg) as a yellow solid. $[\alpha]_D^{25}$ −12.8° ($CHCl_3$ *c* 0.7). CD: $\Delta\varepsilon_{200}$ − 2.67, $\Delta\varepsilon_{220}$ 1.74, $\Delta\varepsilon_{241}$ − 0.08, $\Delta\varepsilon_{285}$ 1.49, $\Delta\varepsilon_{328}$ 0.34 (EtOH, *c* 0.02). IR ν_{max} cm^{-1}: 2920, 2840, 1660, 1570, 1440, 1250, 1085, 790. ^1H NMR (600 MHz, $CDCl_3$): δ 1.38 (3H, *d*, *J* = 6.0 Hz, CH_3-3), 1.55 (3H, *d*, *J* = 6.7 Hz, CH_3-1), 2.46 (3H, *s*, CH_3-2′), 3.36 (3H, *s*, OCH_3-8), 3.47 (1H, m_c, H-3), 4.03 (3H, *s*, OCH_3-4′), 4.33 (1H, *d*, *J* = 1.2 Hz, H-4), 4.51 (1H, *m*, H-1), 6.64 (1H, *d*, *J* = 1.1 Hz, H-3′), 7.17 (1H, *d*, *J* = 7.9 Hz, H-5), 7.21 (1H, *s*, H-1′), 7.24 (1H, *d*, *J* = 8.4 Hz, H-8′), 7.32 (1H, *d*, *J* = 7.77 Hz, H-6), 7.33 (1H, *d*, *J* = 8.3 Hz, H-7′), 9.59 (1H, *s*, OH-5′).^{13}C NMR (150 MHz, $CDCl_3$): δ 17.32 (CH_3-3), 20.45 (CH_3-1), 21.91 (CH_3-2′), 46.96 (C-3), 48.37 (C-1), 56.11 (OCH_3-4′), 60.41 (OCH_3-8), 68.64 (C-4), 106.68 (C-3′), 113.31 (C-10′), 118.05 (C-8′), 119.30 (C-6′), 120.91 (C-1′), 125.03 (C-5), 130.24 (C-7′), 131.06 (C-7), 131.42 (C-6), 131.74 (C-9), 136.0 (C-10, C-9′, and C-2′), 150.93 (C-5′), 154.9 (C-8), 156.2 (C-4′). The ^{13}C attributions were achieved by HMQC and HMBC experiments. EIMS *m/z* (rel. int.): 393 $[M]^+$ (19), 378 $[M - CH_3]^+$ (78), 373 (86), 358 (41), 350 $[M - C_2H_5N]^+$ (100), 189 $[M - CH_3]^{2+}$ (15). HREIMS *m/z* 393.1934 $[M]^+$ ($C_{24}H_{27}NO_4$ requires 393.1940).

3.4. Dioncophyllinol B (*6*)

^1H NMR (600 MHz, $CDCl_3$): δ 1.29 (3H, *d*, *J* = 6.5 Hz, CH_3-3), 1.51 (3H, *d*, *J* = 6.7 Hz, CH_3-1), 2.48 (3H, *s*, CH_3-2′), 3.41 (1H, *dq*, *J* = 6.5, 2.0 Hz, 3-H), 4.08 (3H, *s*, OCH_3-4′), 4.28 (1H, *d*, *J* = 2.1 Hz, H-4), 4.48 (1H, *q*, *J* = 6.6 Hz, H-1), 6.71 (1H, *s*, H-3′), 7.04 (1H, *d*, *J* = 7.9 Hz, H-5), 7.24 (1H, *d*, *J* = 7.6 Hz, H-6), 7.25 (1H, *s*, H-1′), 7.33 (1H, *d*, *J* = 9.5 Hz, H-8′), 7.37 (1H, *d*, *J* = 8.4 Hz, H-7′). ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.97 (CH_3-3), 19.90 (CH_3-1), 21.93 (CH_3-2′), 46.46 (C-3), 48.15 (C-1), 56.37 (OCH_3-4′), 69.07 (C-4), 107.34 (C-3′), 112.92 (C-10′), 118.89 (C-6′), 119.80 (C-8′), 121.00 (C-1′), 122.28 (C-5), 126.05 (C-7), 128.30 (C-9), 129.62 (C-6), 130.94 (C-7′), 136.41 (C-2′ and C-9′), 137.88 (C-10), 149.26 (C-5′), 150.27 (C-8), 155.76 (C-4′).

3.5. 1-epi-Dioncophylline B (*8*)

^1H NMR (600 MHz, $CDCl_3$): δ 1.37 (3H, *d*, *J* = 6.3 Hz, CH_3-3), 1.68 (3H, *d*, *J* = 6.5 Hz, CH_3-1), 2.49 (3H, *s*, CH_3-2′), 2.69 (1H, *m*, H_{ax}-4), 2.75 (1H, *dd*, *J* = 15.6, 2.9 Hz, H_{eq}-4), 3.04 (1H, *m*, H-3), 4.08 (3H, *s*, OCH_3-4′), 4.55 (1H, *q*, *J* = 6.4 Hz, H-1), 6.71 (1H, *d*, *J* = 1.0 Hz, H-3′), 6.78 (1H, *d*, *J* = 7.8 Hz, H-5), 7.14 (1H, *d*, *J* = 7.8 Hz, H-6), 7.24 (1H, *s*, H-1′), 7.33 (1H, *d*, *J* = 8.6 Hz, H-8′), 7.37 (1H, *d*, *J* = 8.4 Hz, H-7′). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.71 (CH_3-3), 21.93 (CH_3-2′), 22.10 (CH_3-1), 38.49 (C-4), 48.85 (C-3), 50.47 (C-1), 56.37 (OCH_3-4′), 107.29 (C-3′), 112.93 (C-10′), 118.99 (C-6′), 119.75 (C-8′), 120.97 (C-1′), 121.37 (C-5), 124.56 (C-7), 124.80 (C-9), 128.98 (C-6), 131.03 (C-7′), 136.29, 136.36, 136.41 (C-2′, C-9′, C-10), 149.22 (C-5′), 151.23 (C-8), 155.74 (C-4′).

3.6. 8-O-Methyl-1-epi-dioncophylline B (*7*)

The CH_2Cl_2 extract of the leaves of *T. peltatum* was resolved by HSCCC under the conditions described above. One of these frs. was purified by HPLC using MeOH–H_2O 52.5:47.5 as eluent. Free base: ^1H NMR (600 MHz, $CDCl_3$): δ 1.31 (3H, *d*, *J* ≈ 6.4 Hz, CH_3-3), 1.63 (3H, *d*, *J* = 6.3 Hz, CH_3-1), 2.47 (3H, *s*, CH_3-2′), 2.64 (1H, *m*, H_{ax}-4), 2.76 (1H, *dd*, *J* = 15.8, 2.8 Hz, H_{eq}-4), 3.02 (1H, *m*, H-3), 3.35 (3H, *s*, OCH_3-8), 4.03 (3H, *s*, OCH_3-4′), 4.46 (1H, *m*, H-1), 6.64 (1H, *s*, H-3′), 6.90 (1H, *d*, *J* = 7.8 Hz, H-5), 7.21 (1H, *d*, *J* not measurable due to signal overlap, H-6), 7.23 (1H, *s*, H-1′), 7.25 (1H, *d*, *J* not measurable due to signal overlap, H-8′), 7.36 (1H, d, *J* = 8.3 Hz, H-7′), 9.60 (1H, *s*, OH-5′). **7** · CF_3COOH: ^1H NMR (600 MHz, $CDCl_3$): δ 1.57 (3H, *d*, *J* = 6.4 Hz, CH_3-3), 1.82 (3H, *d*, *J* = 6.6 Hz, CH_3-1), 2.48 (3H, *s*, CH_3-2′), 2.86 (1H, *dd*, *J* = 17.0, 2.7 Hz, H_{eq}-4), 3.20 (1H, *dd*, *J* = 12.0, 16.4 Hz, H_{ax}-4), 3.35 (3H, *s*, OCH_3-8), 3.39 (1H, *m*, H-3), 4.05 (3H, *s*, OCH_3-4′), 4.83 (1H, *m*, H-1), 6.66 (1H, *s*, H-3′), 6.95 (1H, *d*, *J* = 7.8 Hz, H-5), 7.24 (1H, *s*, H-1′), 7.27 (1H, *d*, *J* ≈ 8.5 Hz, H-8′), 7.32 (2H, *d*, *J* = 8.2 Hz, H-6 and H-7′), 9.65 (1H, *s*, OH-5′). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.37 (CH_3-3), 20.29 (CH_3-1), 21.91 (CH_3-2′), 34.55 (C-4), 50.24 (C-3), 51.23 (C-1), 56.13 (OCH_3-4′), 60.22 (OCH_3-8), 106.70 (C-3′), 113.29 (C-10′), 118.17 (C-8′), 118.40 (C-6′), 120.88 (C-1′), 123.42 (C-5), 126.25 (C-9), 130.02 (C-7 and C-7′), 132.15 (C-6), 132.95 (C-10), 136.11 (C-2′), 136.58 (C-9′), 150.93 (C-5′), 155.80 (C-8), 156.20 (C-4′). The ^{13}C attributions were achieved by HMQC and HMBC experiments using the trifluoroacetate of **7**.

3.7. (1R,3R)-N-Benzyl-7-(5′-isopropoxy-4′-methoxy-2′-methyl-8′-naphthyl)-8-methoxymethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (*15*)

A mixture of **14** (45.5 mg, 117 μmol), $Pd(PPh_3)_2Cl_2$ (16.2 mg, 23.0 μmol), PPh_3 (18.3 mg, 69.7 μmol), LiCl (40.7 mg, 960 μmol), and CuBr (1.5 mg, 10.4 μmol) was dried in vacuo, dissolved in freshly distilled abs. DMF (5 ml), and heated to 135°C. After 5 min, a solution of **13** (197 mg, 379 μmol) in 2 ml of dry DMF

was added in two portions over 1 h. Upon completion of the reaction (2 h), the solvent was removed by distillation. CC on deactivated (7.5% NH_3) silica gel using CH_2Cl_2 as the eluent yielded **15** (39.6 mg, 73.3 μmol, 63%). $[\alpha]_D^{25}$ −55.6° ($CHCl_3$, *c* 0.25). IR ν_{max} cm^{-1}: 2930 (C–H), 1560, 1350, 1255, 1135, 1095. Isomer 1: ^1H NMR (600 MHz, $CDCl_3$): δ 1.35 (3H, *d*, *J* = 6.5 Hz, CH_3-3)[1], 1.40–1.44 [6H, *m*, $(CH_3)_2CH$][1], 1.48 (3H, *d*, *J* = 6.9 Hz, CH_3-1), 2.32 (3H, *s*, CH_3-2′), 2.55 (3H, *s*, CH_2OCH_3), 2.70–2.80 (2H, *m*, CH_2-4)[1], 3.45 (1H, *d*, *J* = 14.3 Hz, NC*H*HPh), 3.61 (1H, m_c, H-3)[1], 3.91 (1H, *d*, *J* = 14.5 Hz, NCH*H*Ph)[1], 3.93 (3H, *s*, OCH_3-4′), 4.04 (1H, *d*, *J* = 5.8 Hz, OC*H*HO), 4.07 (1H, *q*, *J* = 6.8 Hz, H-1), 4.35 (1H, *d*, *J* = 5.8 Hz, OCH*H*O), 4.56 [1H, sept, *J* = 6.1 Hz, $CH(CH_3)_2$][1,2], 6.65 (1H, *s*, H-3′), 6.84 (1H, *s*, H-1′), 6.90 (1H, *d*, *J* = 7.9 Hz, H-6′), 6.98 (1H, *d*, *J* = 7.7 Hz, H-5), 7.09 (1H, *d*, *J* = 7.8 Hz, H-6)[1, 2], 7.24–7.32 (4H, *m*, Ph and H-7′)[2], 7.36–7.45 (2H, *m*, Ph)[1,2]. ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.82 (CH_3-3), 19.90 (CH_3-1), 22.06, 22.10, 22.13 [$CH(CH_3)_2$ and CH_3-2][1], 32.21 (C-4), 45.71 (C-3), 49.87 (CH_2Ph), 51.91 (C-1), 56.22 (CH_2OCH_3), 56.37 (OCH_3-4′)[2], 72.96 [$CH(CH_3)_2$], 98.38 (OCH_2O), 108.82 (C-3′), 111.77 (C-6′), 117.49 (C-10′), 118.95 (C-1′), 124.66 (C-5), 126.44 (Ph)[2], 128.08 (Ph)[2], 128.35 (Ph)[2], 128.47 (Ph)[2], 129.00 (C-7′)[2], 129.53 (C-6), 130.38 (C-8′), 131.88 (C-7), 132.94 (C-9), 135.31 (C-10)[1], 135.71 (C-2′), 136.11 (C-9′)[1], 153.49 (C-8), 154.53 (C-5′), 156.73 (C-4′).

Isomer 2: ^1H NMR (600 MHz, $CDCl_3$): δ 1.36 (3H, *d*, *J* = 6.4 Hz, CH_3-3)[1], 1.40–1.44 [6H, *m*, $(CH_3)_2CH$][1], 1.46 (3H, *d*, *J* = 6.9 Hz, CH_3-1), 2.40 (3H, *s*, CH_3-2′), 2.66 (3H, *s*, CH_2OCH_3), 2.70 – 2.80 (2H, *m*, CH_2-4)[1], 3.52 (1H, *d*, *J* = 14.1 Hz, NC*H*HPh), 3.61 (1H, m_c, H-3)[1], 3.92 (1H, *d*, *J* = 14.5 Hz, NCH*H*Ph)[1], 3.95 (3H, *s*, OCH_3-4′), 4.12 (1H, *q*, *J* = 6.6 Hz, H-1), 4.14 (1H, *d*, *J* = 5.9 Hz, OC*H*HO), 4.17 (1H, *d*, *J* = 5.7 Hz, OCH*H*O), 4.56 [1H, sept, *J* = 6.1 Hz, $CH(CH_3)_2$][1,2], 6.67 (1H, *s*, H-3′), 6.88 (1H, *d*, *J* = 8.0 Hz, H-6′), 6.95 (1H, *d*, *J* = 7.8 Hz, H-5), 7.09 (1H, d, *J* = 7.8 Hz, H-6)[1,2], 7.16 (1H, *s*, H-1′), 7.24–7.32 (4H, *m*, Ph and H-7′)[2], 7.36–7.45 (2H, *m*, Ph)[1,2]. ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.70 (CH_3-1), 20.02 (CH_3-3), 22.14, 22.14, 22.18 [$CH(CH_3)_2$ and CH_3-2′][1], 32.53 (C-4), 45.68 (C-3), 49.98 (CH_2Ph), 51.82 (C-1), 56.37 (OCH_3-4′)[2], 56.40 (CH_2OCH_3), 72.84 [$CH(CH_3)_2$], 98.74 (OCH_2O), 108.65 (C-3′), 111.63 (C-6′), 117.97 (C-10′), 118.03 (C-1′), 123.90 (C-5), 126.44 (Ph)[2], 128.08 (Ph)[2], 128.35 (Ph)[2], 128.47 (Ph)[2], 128.61 (C-8′), 129.00 (C-7′)[2], 130.25 (C-6), 131.29 (C-7), 133.49 (C-9), 135.25 (C-9′)[1], 135.59 (C-10)[1], 135.98 (C-2′), 153.82 (C-8), 154.34 (C-5′), 157.04 (C-4′).

The ^{13}C attributions were achieved by HMQC and HMBC experiments. EIMS *m*/*z* (rel. int.): 539 $[M]^+$ (0.4), 524 $[M\text{-}CH_3]^+$ (6), 360 (16), 296 (11), 91 $[CH_2Ph]^+$ (100). HREIMS *m*/*z* 524.2806 $[M\text{-}CH_3]^+$ ($C_{34}H_{38}NO_4$ requires 524.2801).

3.8. (1R,3R)-N-Benzyl-7-(5′-hydroxy-4′-methoxy-2′-methyl-8′-naphthyl)-8-hydroxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (*16*)

To a cooled (−10 °C) solution of **15** (39.6 mg, 73.3 μmol) in dry CH_2Cl_2 (3 ml) a 1 M solution of BCl_3 in *n*-hexane (147 μl, 147 μmol) was added dropwise over 10 min. After further 15 min, the reaction was quenched with dry MeOH (2 ml). CC on deactivated silica gel with CH_2Cl_2–MeOH (99:1) as the eluent yielded **16** (31.4 mg, 69.2 μmol, 94%). $[\alpha]_D^{20}$ 71.9° ($CHCl_3$, c 0.29). IR ν_{max} cm^{-1}: 2360 (C-H), 1614, 1584, 1431, 1262. ^1H NMR (200 MHz, $CDCl_3$): δ 1.32/1.33 (3H, *d*, *J* = 6.9/6.7 Hz, CH_3-3), 1.38/1.42 (3H, *d*, *J* = 6.7/6.6 Hz, CH_3−1), 2.35/2.40 (3H, *d*, *J* = 0.7/0.7 Hz, CH_3-2′), 2.73 (2H, *m*, CH_2-4), 3.40/3.44 (1H, *d*, *J* = 14.4/14.0 Hz, NCH*H*Ph), 3.58 (1H, m_c, H-3), 3.89/3.91 (1H, *d*, *J* = 14.1/14.0 Hz, NC*H* HPh), 4.07/4.08 (3H, *s*, OCH_3-4′), 4.75/4.76 (1H, *s*, 1-H), 6.66 (1H, *br. s*, H-3′), 6.78 (1H, *d*, *J* = 7.9 Hz, H-5), 6.88 (1H, *d*, *J* = 7.9 Hz, H-6′), 6.95/6.98 (1H, *br. s*, H-1′), 7.01 (1H, *d*, *J* = 8.1 Hz, H-6), 7.20–7.40 (6H, *m*, Ph and H-7′), 9.50 (1H, *s*, OH-5′). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.25/19.42 (CH_3-1), 19.54 (CH_3-3), 22.19 (CH_3-2′), 32.30 (C-4), 45.84 (C-3), 50.05 (CH_2Ph), 51.69/51.90 (C-1), 56.25 (OCH_3-4′), 106.79 (C-3′), 109.76 (C-6′), 113.73 (C-10′), 118.63 (C-1′), 120.48 (C-5), 123.63 (Ph), 123.93 (Ph), 126.40 (Ph and C-9), 128.12 (Ph), 128.44 (Ph and C-8′), 130. 81 (C-6 and C-7), 136.65 (C-2′, C-9′, and C-10), 150.77 (C-8), 155.08 (C-5′), 156.40 (C-4′). Probably due to more rapid rotation around the axis, the two isomers are not separately observable in the NMR spectra. The ^{13}C attributions were achieved from analogy to the data of compound **15**. The signal of C-7′ is overlayed. EIMS *m*/*z* (rel. int.): 453 $[M]^+$ (1), 438 $[M - CH_3]^+$(100), 423 $[M - 2CH_3]^+$ (7), 347 $[M - CH_3\text{-}CH_2Ph]^+$ (14), 219 $[M]^{2+}$ (5), 188 $[C_{12}H_{12}O_2]^+$ (9), 91 $[CH_2Ph]^+$ (76). HREIMS *m*/*z* 438.2070 $[M-CH_3]^+$ ($C_{29}H_{28}NO_3$ requires 438.2069).

3.9. Dioncophylline D (*11*)

To a solution of **16** (31.4 mg, 69.2 μmol) in dry MeOH (1 ml) Pd black (3.5 mg, 32.8 μmol) and HCO_2H (100 μl, 2.65 mmol) were added. The suspension was stirred for 1 h and then partitioned between H_2O and CH_2Cl_2. The combined organic layers were

[1] Attributions interchangeable in pairs for two isomers.
[2] Superposition of the signals of the two isomers.

evaporated and subjected to CC on deactivated silica gel (7.5% NH_3) with CH_2Cl_2–MeOH (95:5) as the eluent gave **11** (16.4 mg, 45.1 μmol, 65%). $[\alpha]_D^{20}$ -54.3° ($CHCl_3$, *c* 0.14). IR ν_{max} cm^{-1}: 3380 (O–H), 2890 (C-H), 1595, 1415, 1245, 1115. Isomer 1: ^1H NMR (600 MHz, $CDCl_3$): δ 1.25 (3H, *d*, *J* = 5.6 Hz, CH_3-3), 1.47 (3H, *d*, *J* = 6.7 Hz, CH_3-1), 2.35 (3H, *s*, CH_3-2′), 2.55 (1H, *dd*, *J* = 16.6, 10.9 Hz, H_{ax}-4), 2.84 (1H, *dd*, *J* = 16.6, 4.0 Hz, H_{eq}-4)[2], 3.37 (1H, m_c, H-3)[2], 4.08 (3H, *s*, OCH_3-4′), 4.45 (1H, q, *J* = 7.0 Hz, H-1), 6.66 (1H, *br. s*, H-3′), 6.74 (1H, *d*, *J* = 7.7 Hz, H-5), 6.88 (1H, *d*, *J* = 7.9 Hz, H-6′)[2], 6.92 (1H, *br. s*, H-1′), 6.99 (1H, *d*, *J* = 7.7 Hz, H-6)[1,2], 7.31 (1H, *d*, *J* = 7.9 Hz, H-7′), 9.49 (1H, *s*, OH-5′)[1].

Isomer 2: ^1H NMR (600 MHz, $CDCl_3$): δ 1.24 3H, *d*, *J* = 5.6 Hz, CH_3-3), 1.49 (3H, *d*, *J* = 6.7 Hz, CH_3-1), 2.37 (3H, *s*, CH_3-2′), 2.50 (1H, *dd*, *J* = 16.6, 11.0 Hz, H_{ax}-4), 2.84 (1H, *dd*, *J* = 16.6, 4.0 Hz, H_{eq}-4)[2], 3.37 (1H, m_c, H-3)[2], 4.09 (3H, *s*, OCH_3-4′), 4.39 (1H, *q*, *J* = 6.7 Hz, H-1), 6.68 (1H, *br. s*, H-3′), 6.75 (1H, *d*, *J* = 7.7 Hz, H-5) 6.68 (1H, *d*, *j* = 7.9 Hz, H-6′)[2], 6.97 (1H, *br. s*, H-1′), 6.98 (1H, *d*, *J* = 7.7 Hz, H-6)[1,2], 7.28 (1H, *d*, *J* = 7.8 Hz, H-7′), 9.49 (1H, *s*, 5′-OH)[1]. ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.04 (CH_3-1), 22.16 (CH_3-2′), 22.83/22.91 (CH_3-3), 37.58 (C-4), 41.81/42.01 (C-3), 47.71/47.80 (C-1), 56.23 (OCH_3-4′), 106.78/106.82 (C-3′), 109.68/109.77 (C-6′), 113.65 (C-10′), 118.61 (C-1′), 120.66 (C-5), 123.64/123.83 (C-7), 126.83/127.19 (C-9), 128.63/128.73 (C-6), 130.76/130.83 (C-7′), 135.12/153.33 (C-8′), 135.58 (C-10), 136.66/136.77 (C-9′), 149.62/149.71 (C-8), 155.07 (C-5′), 156.33 (C-4′). Due to low resolution of the two isomers in the HMBC spectrum, these data are not given separately for the two compounds. EIMS *m/z* (rel. int.): 363 $[M]^+$ (12), 348 $[M-CH_3]^+$ (100), 333 $[M-2CH_3]^+$ (22), 174 $[M-CH_3]^{2+}$ (14). HREIMS *m/z* 363.1825 $[M-CH_3]^+$ ($C_{22}H_{22}NO_3$ requires 363.1834).

3.10. Biological experiments

The activity against *P. falciparum* was tested by the semiautomated microdilution assay against intraerythrocytic forms derived from asynchronous stock cultures as previously described (Desjardins et al., 1979) with minor modifications (Ridley et al., 1996). Antimalarial activities were determined using two parasite strains: K1 (Thailand; resistant to chloroquine and pyrimethamine) and NF54 (an airport strain of unknown origin; susceptible to standard antimalarials). The activities are given as IC_{50} values (ng ml^{-1}). Chloroquine was used as the standard All data are the mean values from three measurements. Cytotoxicity was tested against rat skeletal muscle myoblast (L-6) cells using Alamar Blue to assess cell viability (Pagé et al., 1993). The assay procedure was similar to the one developed for trypanosomes (Raez et al., 1997) using fluorometric reading to quantify the change in color.

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