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The Alkaloids of *Triphyophyllum peltatum* (Dioncophyllaceae) [1]

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Dedicated to Professor *Meinhart H. Zenk*, University of Munich, on the occasion of his 65th birthday.

Abstract. A great diversity of naphthylisoquinolines, presumably acetogenic biaryl alkaloids, has been obtained from the West-African liana *Triphyophyllum peltatum*. By the example of dioncophylline A, the main alkaloid from *T. peltatum*, we illustrate the various methods of structural elucidation established in our laboratory. The structural peculiarities of some of the minor alkaloids from the same species are discussed. A perspective on the interesting biological activities of various alkaloids from *T. peltatum* and related plants is given. The most promising lead is dioncophylline C, marked by pronounced antiplasmodial activity. Chemical syntheses, especially dimerization of naphthylisoquinolines, and QSAR-guided modifications of the most active structures are featured as rewarding strategies in the search for improved drugs. A chemotaxonomic summary is presented.

1. Introduction

Dimeric naphthylisoquinoline alkaloids, *e.g.* michellamine B (**1**, *Fig. 1*), are most promising novel antiviral compounds from African plants [2–4]. They occur in one single species, *Ancistrocladus korupensis*, which is endemic to a small region at the Cameroonian/Nigerian border and has been discovered within an anti-HIV screening program initiated by the US National Cancer Institute [5][6]. In collaboration with Dr. *Boyd* and his NCI group, we have elucidated the stereostructure of michellamine B and related compounds [2][6–8] and have achieved first total syntheses of these challenging and attractive target molecules [9–12]. One of the latest achievements of our group is the detection and characterization of dimerization enzymes which transform the monomeric precursors, named korupensamines, into michellamines [13].

This paper will deal mainly with such monomers, especially those from *Triphyophyllum peltatum*, since they likewise display intriguing structural, biosynthetic, and pharmacological (in particular antimalarial) properties. *T. peltatum* is the most widespread species of the Dioncophyllaceae, a small plant family consisting of only three species of lianas climbing up high trees, by means of hooked leaves (*cf. Fig. 19*) [14]. Unique are the large thin seeds with large membranous wings (*Fig. 2*), which during maturation exceed the size of the fruits they are borne from [15]. From these seeds, we have succeeded in cultivating juvenile plants of *T. peltatum* (*Fig. 3*). At the end of the juvenile growth period, just before it starts climbing, *T. peltatum* forms leaves with stalked glands and reduced lamina that capture and digest invertebrates [16]; it is a 'part-time' carnivorous plant [17]. Phytochemically, *T. peltatum* proved to be a rich source of novel alkaloids.

2. Dioncophylline A as a Probe Alkaloid for the Analytical Methodology

For the rapid and unambiguous attribution of the full stereostructures of such compounds, we have established and further developed a broad series of analytical methods. The first alkaloid to be investigated was dioncophylline A [18][19], the main secondary metabolite of *T. peltatum*. It is easily accessible by standard isolation procedures, and was found to have a naphthylisoquinoline basic structure mainly by NMR investigations (*Fig. 4*). It has three stereogenic units: two stereocenters (C(1), C(3)) and a stereogenic axis (C(7)→C(1')). Its structural elucidation thus requires at least three pieces of stereochemical information.

2.1. *The Relative Configuration at the Stereocenters: through NMR*

From an NOE interaction of the axial proton at C(3) (*Fig. 5*) with the likewise axial Me group at C(1), a relative *cis*-array of these two spin systems and thus *trans*-orientation of the two Me groups was deduced, establishing an (*R,R*)- (or an (*S,S*)-!) configuration [18] – the first required stereochemical information.

2.2. *The Absolute Configuration at C(3) (and thus C(1)): through Total Synthesis*

The absolute configuration at C(3) was established by a stereochemically unambiguous total synthesis of the alkaloid from alanine (*Scheme 1*) [19][20]. For the regio- and stereoselective construction of the biaryl axis, the 'lactone method' was applied, an efficient synthetic procedure developed in our group [21][22]: Prefixation of the two molecular moieties *via* an ester bridge (*cf.* **2**) and subsequent intramolecular C,C-bond formation gave the lactone-bridged biaryl **3**, which is configuratively unstable – it rapidly isomerizes at the axis. But out of this equilibrium of helimeric forms **3a** and **3b**, it can be cleaved such that optionally either of the atropiso-

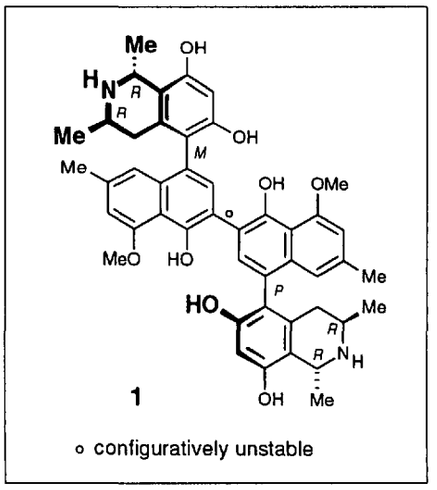

Fig. 1. *Michellamine B, a dimeric naphthylisoquinoline with high anti-HIV activity*

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Fig. 2. *Seeds of* Triphyophyllum peltatum *(Dioncophyllaceae), showing the large circular wing*

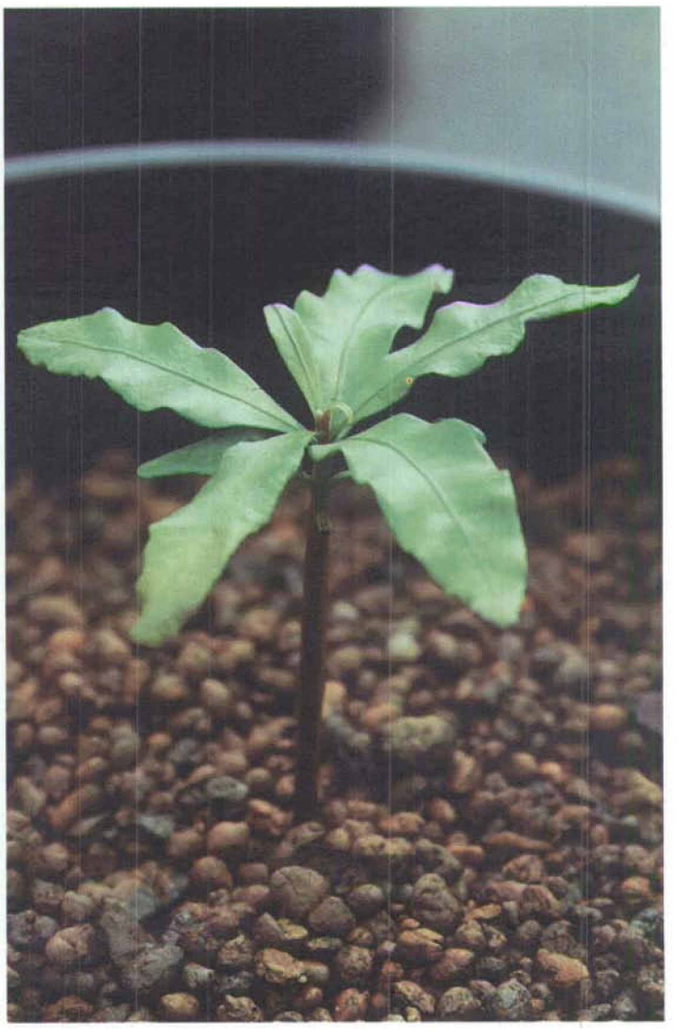

Fig. 3. *A juvenile plant of* T. peltatum, *several weeks after germination*

meric products is obtained in high selectivity [20] – a stereochemically efficient and mechanistically remarkable reaction. One of the products ultimately obtained is fully identical with natural dioncophylline A, whereas the other one is diastereomeric – when starting from D-alanine, while L-alanine leads to the wrong enantiomeric series [19]. This shows dioncophylline A to have (*R*)-configuration at C(3) (and thus also at C(1)) – the second stereoinformation achieved.

2.3. *The Absolute Axial Configuration: by Experimental CD Spectroscopy*

While we had selectively produced dioncophylline A and its stereoisomers, its axial configuration was still unclear at this point. This missing third stereoinformation was acquired by CD spectroscopy, for which the molecule first had to be modified by dehydrogenation to give **5** so that, by enlargement of the isoquinoline chromophor, the *Exciton Chirality* method [23] became applicable (*Scheme 2*). This had to be done under the mildest possible conditions to avoid isomerization at the axis. From the positive first *Cotton* effect in the experimental CD spectrum of **5**, a likewise 'positive chirality' was deduced, thus establishing *P*-configuration at the biaryl axis.

2.4. *Further Support for the Axial Configuration: Quantum Chemical CD Calculations*

By these three pieces of stereoinformation, the full absolute stereostructure **4** of dioncophylline A as shown in *Scheme 2* had become evident. Possibly the same compound, but named 'triphyophylline', had previously been isolated by a French group [24][25], who had correctly assigned the constitution and the relative configuration at C(1) and C(3), but had erroneously assumed the absolute configuration at the stereocenters to be (*S,S*), while the chirality of the biaryl axis had been disregarded. Additional severe inconsistencies in the literature [24–26] necessitated a new naming for **4**, subsequently termed dioncophylline A [18].

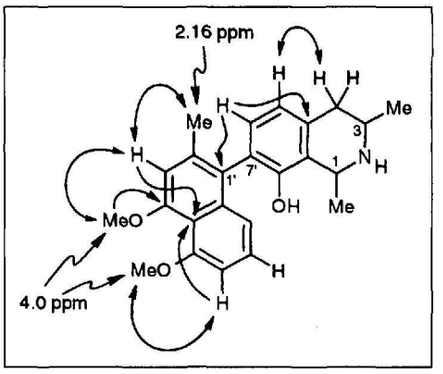

Fig. 4. *Constitution of dioncophylline A by selected HMBC and NOE interactions and chemical shifts*

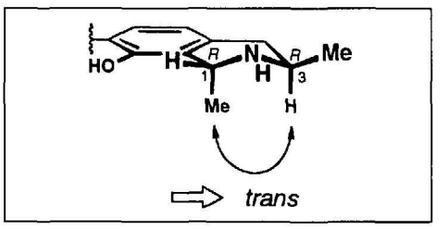

Fig. 5. *Relative configuration at C(1)* vs. *C(2) of dioncophylline A by NOE*

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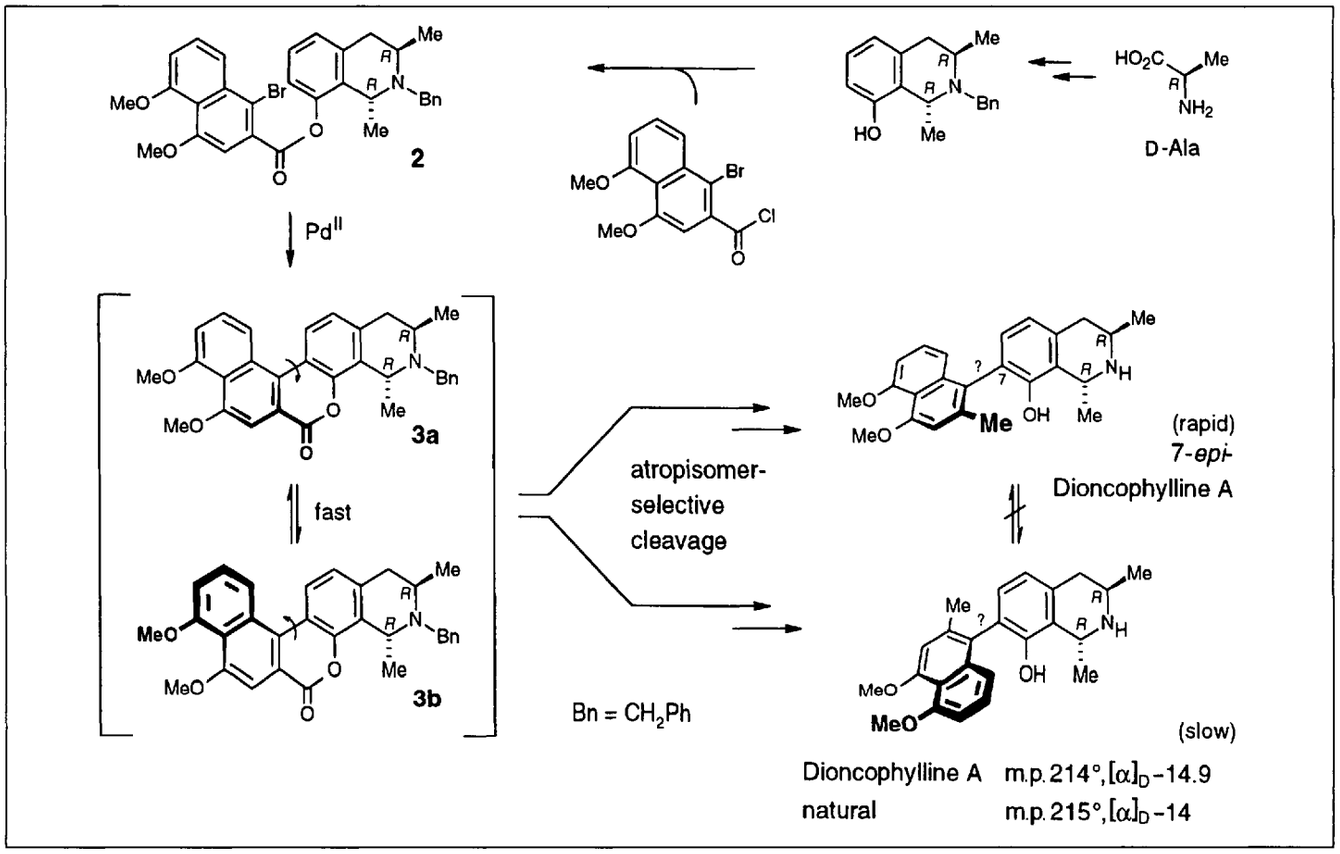
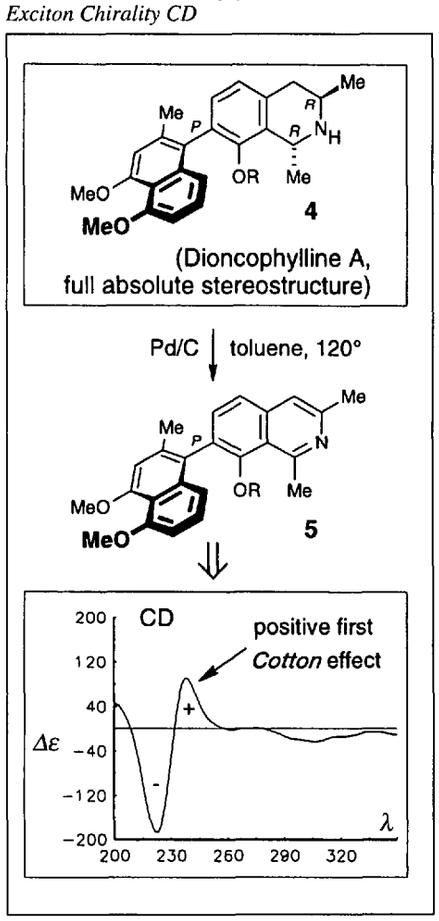
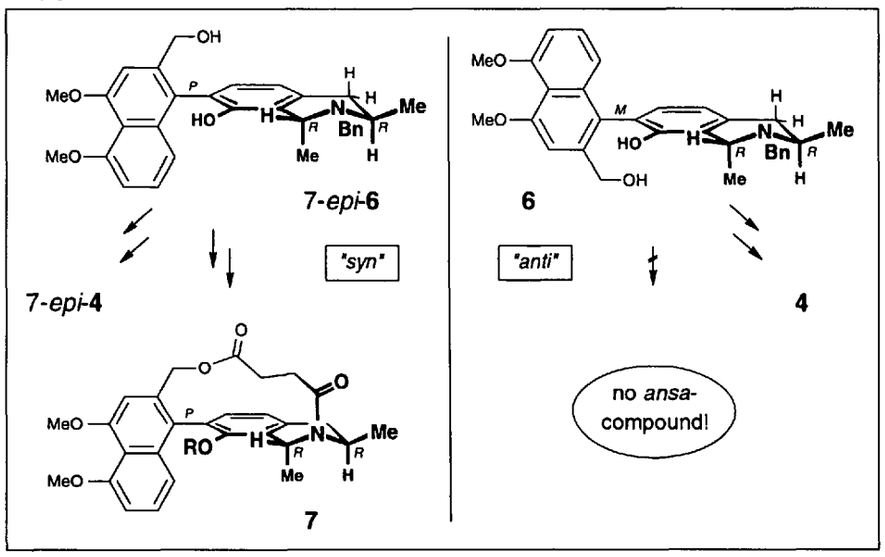
Scheme 1. *Total Synthesis Establishing the Absolute Configuration at C(3) (and C(1))*



Scheme 2. *Absolute Configuration at the Axis by Exciton Chirality CD*



Scheme 3. *An Atropisomer-Differentiating Reaction for the Chemical Analysis of the Relative Configuration at the Axis*



For this reason, we kept looking for further confirmation of our revised structure **4**. Therefore, any new method that we introduced into naphthylisoquinoline chemistry was first tested on this important alkaloid, exemplarily.

For a first additional support of the absolute stereostructure, we have applied the quantum chemical calculation and thus prediction of CD spectra, established and further developed in our group [27–29]. As shown in *Fig. 6*, the theoretical CD spectrum (dotted) for the dehydrogenation product of dioncophylline A matches very well with the experimental one (full line), in particular in the region of the crucial couplet. This unambiguously confirms the absolute axial *P*-configuration of dioncophylline A [30] – stereochemical information no. 4.

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2.5. *Relative Axial* vs. *Centrochirality: a Chemical Method*

Furthermore, we have developed a chemical method for the analysis of the relative configuration at the biaryl axis as compared to the stereocenters [31]. Of the two atropo-diastereomeric synthetic precursors **6** and 7-*epi*-**6** to dioncophylline A (**4**) and its atropisomer (7-*epi*-**4**) (*Scheme 3*), specifically only the *syn*-compound 7-*epi*-**6** can be bridged by a succinate unit to give **7**, whereas the *anti*-diastereomer **6** does not give a similar *ansa*-compound. This strictly atropisomer-differentiating reaction (here stereochemical information no. 5) again confirms the relative axial configuration attributed above.

2.6. *Relative Axial* vs. *Central Chirality: by Long-Range NOE Interaction*

Even without any chemical modification, such a *syn*/*anti*-relationship can be analyzed by NMR: Despite the long distances between the diagnostically decisive nuclei, the crucial long-range NOE interactions that specifically confirm the configuration at the axis relative to the centers can be observed (*Fig. 7*) – the sixth independent stereochemical information [32].

2.7. *Absolute Configuration at Both Stereocenters: by Chemical Degradation*

For an additional proof of the absolute configuration at the stereocenters, we have developed a ruthenium-mediated oxidative degradation reaction, which neatly cuts out the centers by transforming them into 3-aminobutyric acid (ABA) and alanine (Ala) [33] (*Scheme 4*). From the (*R*)-configuration of the two amino acids, dioncophylline A is clearly confirmed to be (*R*)-configurated at both stereocenters providing stereochemical informations no. 7 and 8. This useful reaction can be performed down to submilligram quantities. It is also applicable to *N*-methylated and *N*,*N*-dimethylated cationic analogs, and even to β-carboline alkaloids [34][35]. We perform it routinely for several other research groups [36–38].

2.8. *Constitution and All Relative Configurations: by a 'Normal' Crystal-Structure Analysis*

It was only after all the aforementioned stereochemical investigations that we happened to obtain crystals suited for an X-ray structure analysis [39] – but only from CH_2Cl_2, which turned out to be an integral part of the crystal (*Fig. 8*). This crystal-structure analysis fully confirms the constitution and all of the relative configurations of dioncophylline A and thus provides two further pieces of stereochemical information.

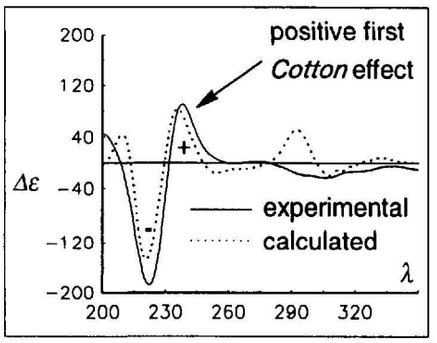


Fig. 6. *Absolute axial configuration through quantum-chemical CD calculation*

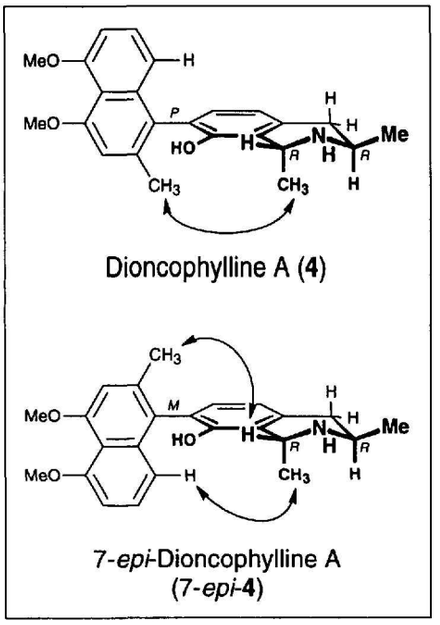


Fig. 7. *Long-range NOE: relative axial* vs. *central chirality*

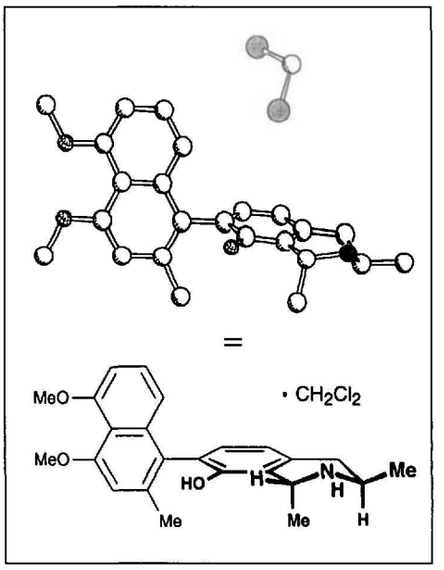


Fig. 8. *X-ray structure analysis: constitution and full relative configuration*

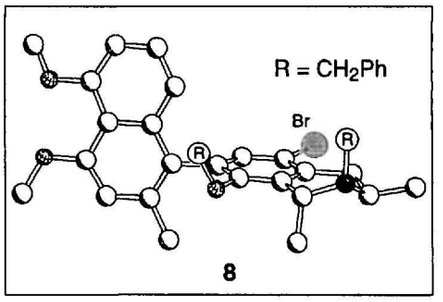
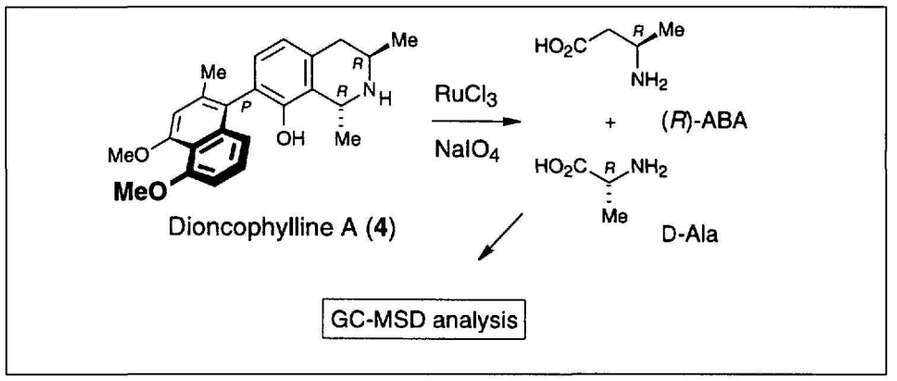


Fig. 9. *Full absolute stereostructure through anomalous X-ray diffraction of a bromo derivative*

Scheme 4. *Oxidative Degradation: Absolute Configurations at C(1) and C(3)*



2.9. *The Full Absolute Stereostructure: by Anomalous X-Ray Diffraction*

More recently, another crystal-structure analysis (*Fig. 9*) on 5-bromo-*O*,*N*-dibenzyldioncophylline A (**8**) allowed a confirmation of the full *absolute* stereostructure of dioncophylline A (here with benzyl abbreviated as R) through anomalous X-ray diffraction [40]. This corresponds to three pieces of stereochemical information in one experiment.

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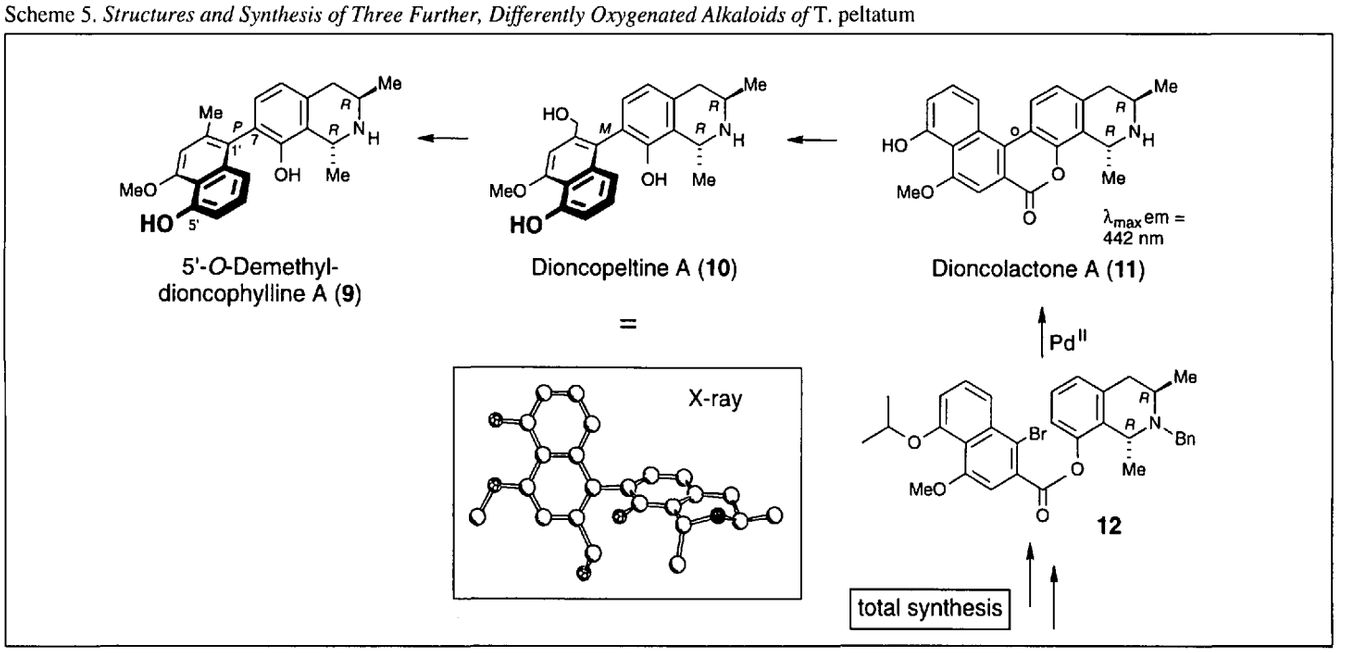
Scheme 5. *Structures and Synthesis of Three Further, Differently Oxygenated Alkaloids of* T. peltatum



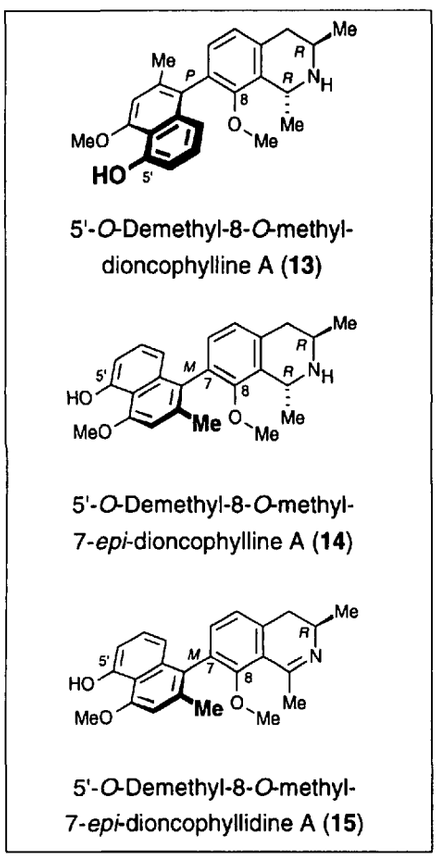


Fig. 10. *Further minor 'A-type' alkaloids, from both atropisomeric series*

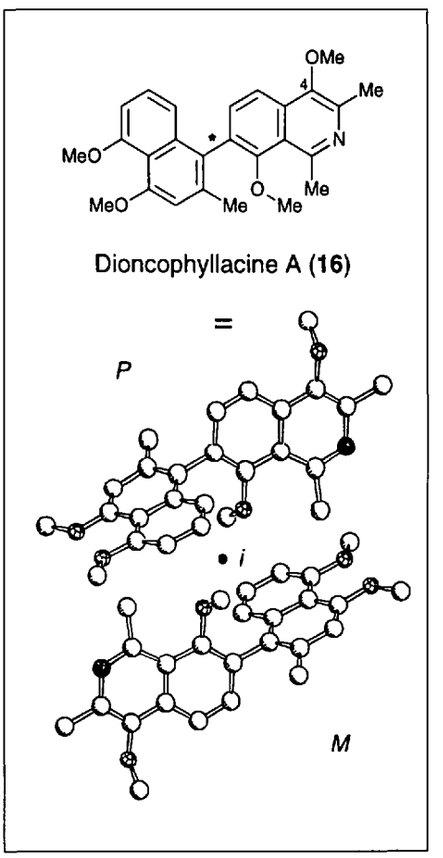


Fig. 11. *Dioncophyllacine A: fully dehydrogenated and axially chiral – but racemic*

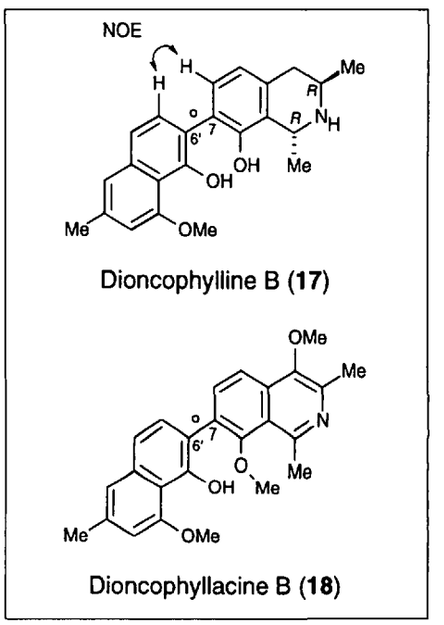


Fig. 12. *7,6'-coupled alkaloids, only known from* T. peltatum

2.10. *Conclusive Remark*

All of the methods described above fully confirmed the assignment of the complete absolute stereostructure of dioncophylline A as **4**. This broad analytical arsenal was now available to be applied to the numerous other alkaloids likewise produced by *T. peltatum*.

3. Further Related 'A-Type' (*i.e.*, 7,1'-Coupled) Alkaloids of *T. peltatum*

Three such new alkaloids **9**–**11** with a 7,1'-linkage of the aryl moieties ('A-type') like dioncophylline A (**4**), but with a free, not *O*-methylated OH function at C(5') [41][42] are seen in *Scheme 5*. Dioncopeltine A (**10**) is the as yet only known naphthylisoquinoline with an additional oxygen function at the methyl group of the naphthalene moiety; its structure was confirmed by X-ray diffraction analysis. Still further oxidized is the strongly fluorescent alkaloid dioncolactone A (**11**), which is closely related to the synthetic lactone-bridged biaryl precursor **3** to dioncophylline A (*cf. Scheme 1*). It was thus an easy and rewarding task to synthesize all of these three compounds at a blow – despite their additional free C(5')–OH group – by intramolecular biaryl coupling of the ester-type prefixed precursor **12** and subse-

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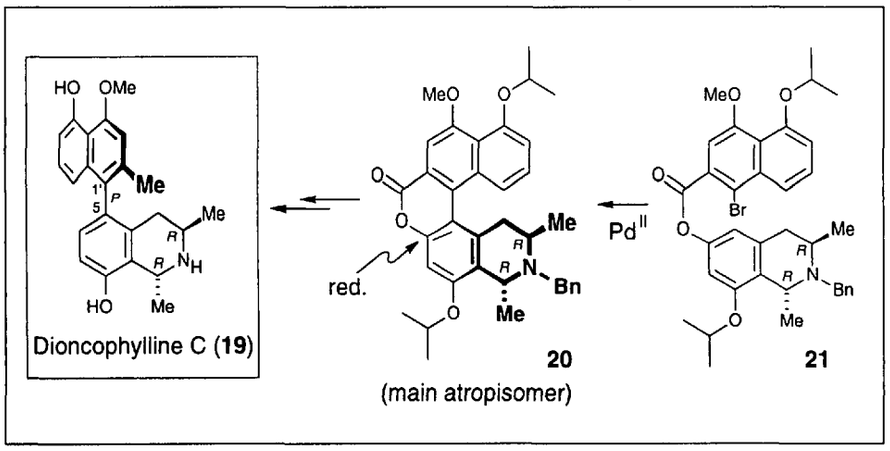
Scheme 6. *Dioncophylline C, the Only 5,1'-Coupled Alkaloid from* T. peltatum



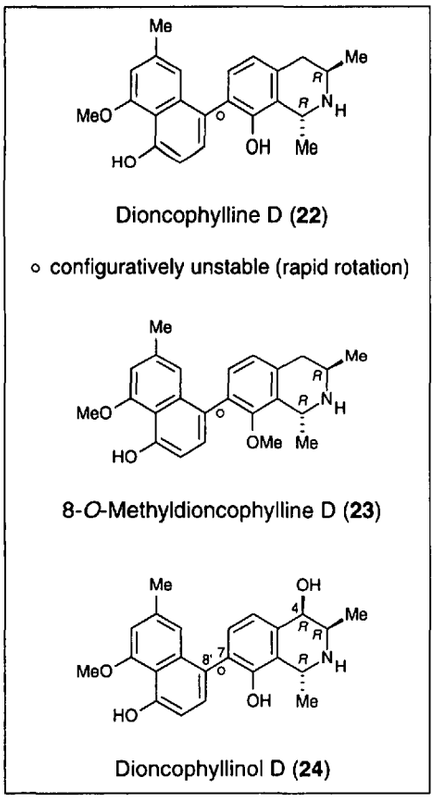


Fig. 13. *Dioncophyllinol D (24) and two further 7,8'-coupled alkaloids* 22 *and* 23

quent stereoselective ring opening and deoxygenation [42].

Fig. 10 shows three further related 'A-type' alkaloids, **13–15**, again all of them with an 'OH-OMe'-substitution pattern on the naphthalene, including, for the first time, representatives **14** and **15** of the other atropo-diastereomeric series, and the first dihydroisoquinoline **15** within this class of compounds [2][43].

Even further dehydrogenated and with an unprecedented additional OMe function at C(4) is dioncophyllacine A (**16**, *Fig. 11*). It has no stereocenters, but of course disposes of axial chirality [44]. Still, it is not optically active, since it is the first naphthylisoquinoline alkaloid that is racemic! As seen by an X-ray structure analysis, both atropo-enantiomers are present also in the crystal.

4. Alkaloids with Other Coupling Positions

4.1. *'B-Type' (i.e.,* 7,6'-Coupled) *Alkaloids*

A representative of the less frequently occurring 7,6'-coupling type, as found in dioncophylline B (**17**) [45], is seen in *Fig. 12*. Here the coupling position allows a free rotation around the axis, so that there is no stable axial configuration, only the stereocenters C(1) and C(3). Similar to **16**, dioncophyllacine B (**18**) has an additional OMe group at C(4) and a fully dehydrogenated isoquinoline moiety and thus has no stereocenters [2][46]. Since it does not have a configuratively stable biaryl axis either, it is the only fully achiral naphthylisoquinoline alkaloid.

4.2. *A 'C-Type' (i.e.,* 5,1'-Coupled) *Alkaloid*

There is only one 5,1'-coupled naphthylisoquinoline from *T. peltatum*: Dioncophylline C (**19**) [47] (*Scheme 6*). It is also the only one without an oxygen function next to the biaryl axis. Nonetheless, we have synthesized the molecule *via* our 'lactone procedure', by intramolecular coupling of the ester **21** to a helimeric bridged biaryl **20** [2][48], ring opening, and eventual reductive elimination of the useful intermediate 'bridgehead' oxygen function.

4.3. *The 'D-Type' (i.e.,* 7,8'-Coupled) *Alkaloids*

We have recently detected a fourth coupling type, which is based on a 7,8'-linkage, as found in the three new alkaloids **22–24** (*Fig. 13*) [2][49]. One of them, dioncophyllinol D (**24**), is the first alkaloid of this type to have a free OH group at C(4) – and is thus the first monomeric naphthylisoquinoline to have a maximum number of stereocenters. By D-NMR, **24** was shown to be a mixture of two rapidly interconverting atropo-diastereomers. This isomerization can be 'frozen' at *ca.* 190 K to give two sets of signals for the two atropo-diastereomeric species.

4.4. *Triphyophyllum Alkaloids – a Broad Series of Biaryl Alkaloid Structures*

Thus, *T. peltatum* from Ivory Coast is a rich source of a plethora of meanwhile nearly 20 different naphthylisoquinoline

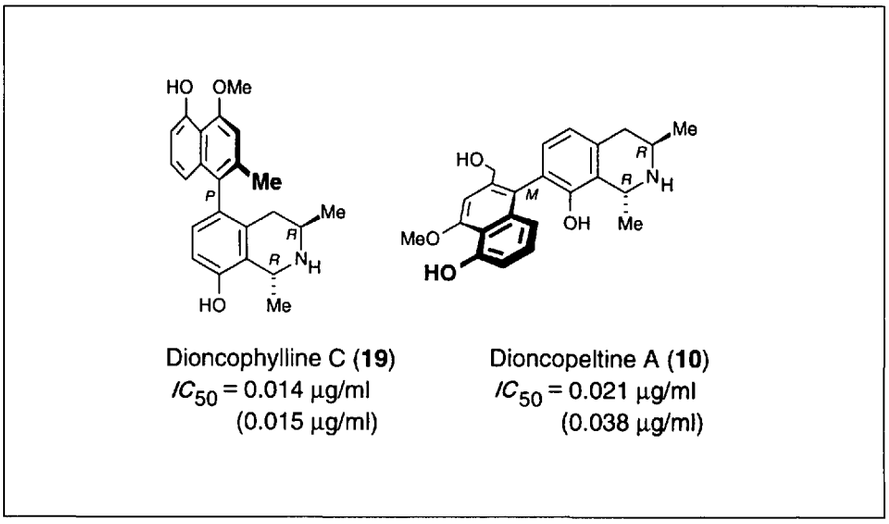


Fig. 14. *Antimalarial activities of naphthylisoquinolines against* P. falciparum *(and* P. berghei*) in vitro: the 'top two'*

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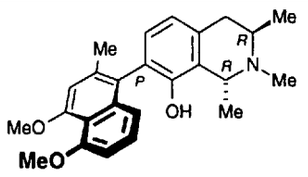
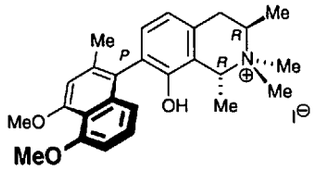
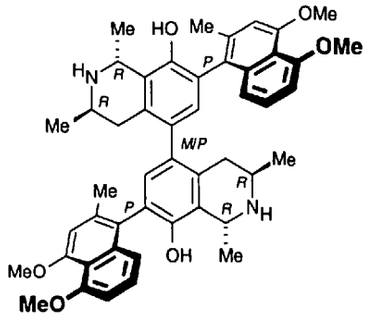


N-Methyl-
dioncophylline A (**25**)
(IC_{50} = 13.6 µg/ml)



N,N-Dimethyl-
dioncophyllinium A Iodide (**26**)
(IC_{50} = 0.63 µg/ml)



(*M/P*)-Jozimine A (**27**)
(IC_{50} = 0.075 µg/ml !)

Fig. 15. In vitro *activities of dioncophylline A analogs against* P. falciparum

alkaloids. Most of them have the normal 7,1'-coupling type as realized in dioncophylline A, but there are also the less frequent types B, C, and D. All of these structures are unique and intriguing, nice textbook examples of compounds with both stereocenters and -axes, with atropisomerization barriers ranging from unmeasurably low for bridged or low-substituted species, *via* rotations that can be frozen at low temperatures, up to atropisomers that are stable to above 150°.

5. Naphthylisoquinolines as Promising Leads in Pharmacology and Plant Protection

The high diversity in the chemical structure of naphthylisoquinolines is paralleled by their various biological activities, among them activity against plant-pathogenic fungi [2][50] and antifeedant and growth-retarding activity against herbivorous insects like *Spodoptera littoralis* [51][52]. Even more importantly, some of our alkaloids are strong agents in connection with the widespread tropical diseases schistosomiasis and, in particular, malaria.

5.1. *Molluscicidal Activity of Dioncophylline A*

In cooperation with Prof. *Hostettmann*, good molluscicidal activities against *Biomphalaria glabrata*, the intermediate host of bilharzia, were found in the first line for dioncophylline A (**4**). It kills all of the snails within 24 h at a concentration of 20 ppm [53]. By derivatization of the natural product, the activity was increased significantly [54]. We expect further improvement along these lines in the future.

5.2. *Antimalarial Activity of Dioncophylline C and other Naphthylisoquinolines*

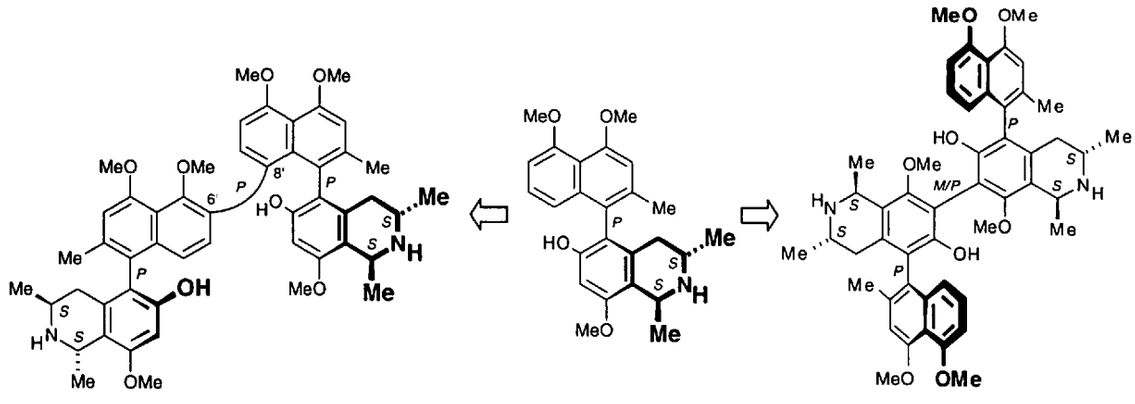
Of the greatest pharmacological significance is the distinct antiplasmodial activity against *Plasmodium falciparum*, the pathogenic agent of the pernicious *malaria tropica* [55][56]. Already the extracts of *T. peltatum* exhibit very good activities, also against chloroquine-resistant strains. Among the pure isolated compounds tested, in particular dioncophylline C (**19**) and dioncopeltine A (**10**, *Fig. 14*) show excellent IC_{50} values [57]. Likewise good *in vitro* activity was found against the related parasite, *Plasmodium berghei*.

First *in vivo* experiments on the curative potential of naphthylisoquinoline alkaloids in this rodent system showed *P. berghei*-infected OF1 mice to be healed by treatment with dioncophylline C, their parasitaemia was reduced to zero from day four on. Without any noticeable side effects, the animals survived for months, whereas all of the control animals, which had been infected but not treated with the alkaloid, had died soon after infection [58].

A most promising further perspective for this new antimalarial lead structure is given by the fact that naphthylisoquinolines do not only act efficiently against the more susceptible blood forms of *Plasmodium* spp., but also against the more persistent liver forms [59].

5.3 *Dimerization may Improve Antimalarial Activity of Naphthylisoquinolines*

In a first attempt to further improve the antimalarial activity of naphthylisoquinolines, we have prepared a broad series of structural analogs, *e.g.*, of dioncophylline A (**4**), one of the moderately active mono-



Jozimine B (**28**)
(IC_{50} = 0.90 µg/ml)

Ancistrocladine (**29**)
(IC_{50} = 18.4 µg/ml)

Isojozimine B (**30**)
(IC_{50} = 0.54 µg/ml)

Fig. 16. *Increase of antimalarial activity of ancistrocladine by dimerization*

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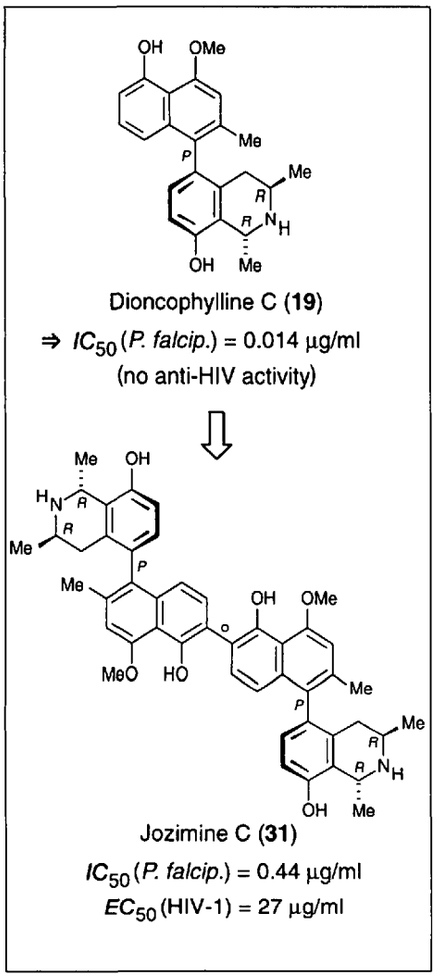

Fig. 17. *Antimalarial and anti-HIV activities of mono- and dimeric dioncophylline C*

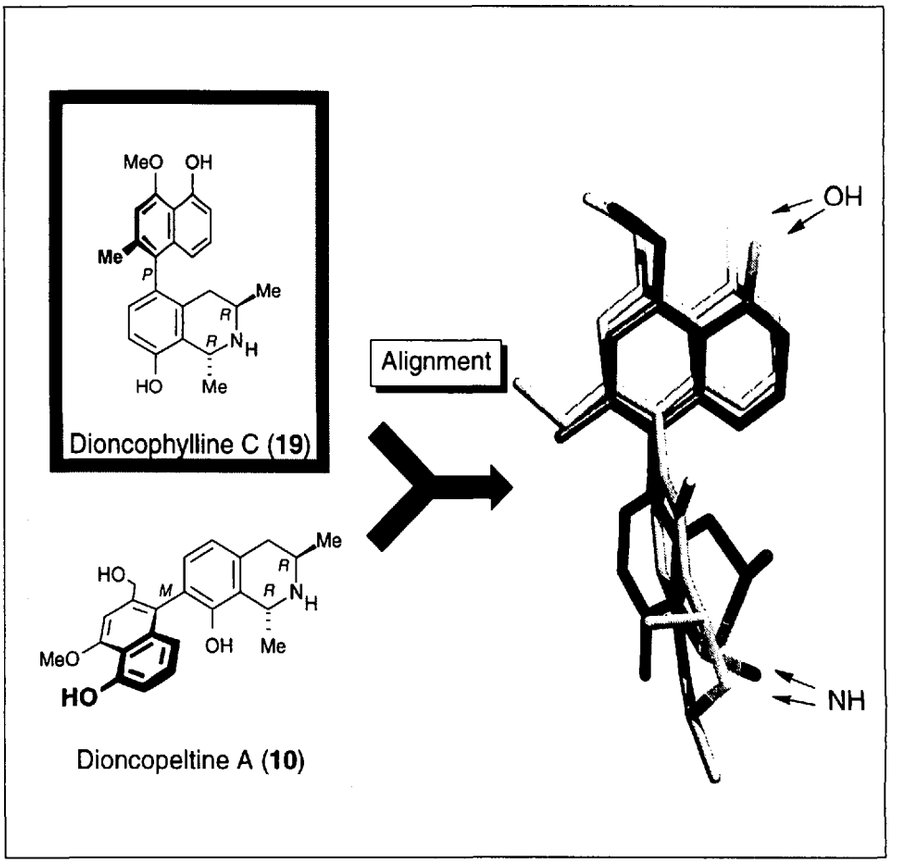

Fig. 18. *Optimum alignment for the two most active antimalarial naphthylisoquinolines*

mers, which, however, is available in larger quantities. *Fig. 15* shows three examples, **25–27**, that reveal, for instance, *N*-methylation to decrease activity, while a second *N*-methylation, which establishes a positive charge on the nitrogen, increases the antiplasmodial activity *vs.* the natural product [35].

An unexpectedly positive result was obtained through chemical coupling of dioncophylline A (**4**) to give its unnatural dimer **27**, named jozimine A [60], which is *ca.* 20 times more active than the monomeric parent compound **4**. It is now one of the three most active naphthylisoquinolines at all, after dioncophylline C (**19**) and dioncopeltine A (**10**)!

Also for ancistrocladine (**29**) (*Fig. 16*), an alkaloid of the related (*v.i.*) Ancistrocladaceae family, an increase of antimalarial activity by dimerization was accomplished [3]: Jozimine B (**28**), a constitutionally unsymmetric dimer of **29**, has a 20-fold increased activity, and iso-jozimine B (**30**), an isoquinoline-isoquinoline-coupled dimer, is even more active by a factor of 34 [61].

Unfortunately, this effect was not observed for dioncophylline C (**19**), still the best monomer. Its dimer, named jozimine C (**31**) (*Fig. 17*) [3][48][62], has a lower activity than **19**. This was not entirely unexpected, because the structurally closely related dimers of antimalarial korupensamines, the michellamines, *e.g.*, **1**, are virtually inactive towards *P. falciparum* [63]. On the other hand, this structural relationship to michellamines may account for the appreciable anti-HIV activity displayed by **31** – it is, actually, the most active unnatural dimer of a natural monomeric naphthylisoquinoline ever prepared.

5.4. *Quantitative Structure-Activity Relationship (QSAR) Investigations*

A most promising further strategy of improving antimalarial activity is to try to *predict* structures with higher activities from structure-activity correlations, even though neither the molecular target nor the mode of action are known yet. It is, therefore, rewarding to find out what the structural requirements for high activities are. The most active naphthylisoquinolines so far, dioncophylline C (**19**) and dioncopeltine A (**10**), however, look quite different at first sight (*cf. Fig. 14*). From an alignment of these and the other molecules, better analogs might be predicted (and then prepared). For this purpose, we have started to perform quantitative structure-activity relationship (QSAR) investigations, using the CoMFA technique [64].

For a comparison of the joint structural properties of naphthylisoquinolines, the existence of different coupling types and atropo-diastereomers has to be taken into consideration. A most efficient alignment is attained by a combined match for the isoquinoline and the naphthalene part, such that the assumedly pharmacophoric functions, in particular the free phenolic OH groups of the naphthalene parts, respectively the basic N-atoms are close to each other. As shown in *Fig. 18*, we have thus achieved a compact stereochemical match, *e.g.*, of the two as yet best candidates, dioncophylline C (**19**) and dioncopeltine A (**10**), which have so similar biological activities and indeed look quite similar when aligned in this way [65].

With this alignment and a training set of 34 compounds, we have found a very good correlation ($q^2 = 0.76$) between calculated and experimental values, which now allows us to predict IC_{50} values for unknown or not yet measured structural analogs. Based on these first QSAR investigations, we have started to predict and synthesize new and hopefully still more active compounds.

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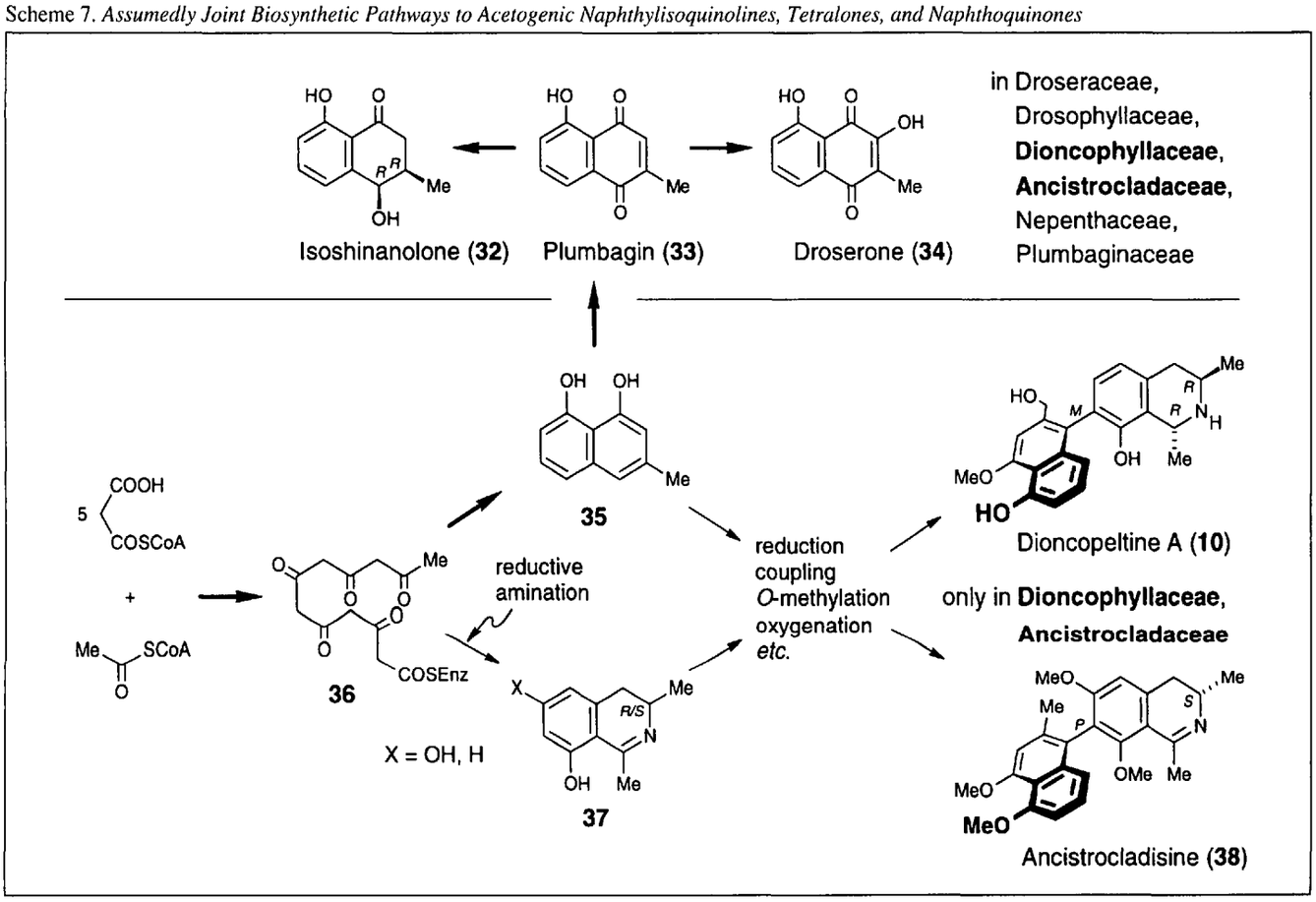
Scheme 7. *Assumedly Joint Biosynthetic Pathways to Acetogenic Naphthylisoquinolines, Tetralones, and Naphthoquinones*



6. The Chemotaxonomic 'Neighborhood' of *T. peltatum*

Another approach to look for new structural analogs, is to investigate related plants. As mentioned earlier, the family Dioncophyllaceae is extremely small: Besides *Triphyophyllum peltatum* there are only the very rare further species *Habropetalum dawei* from Sierra Leone and Liberia, and *Dioncophyllum thollonii* from Gabon and Congo [15]. At first sight, these two closest relatives of *T. peltatum*, which have recently become available to us, seem entirely different: just abundant amounts of the isocyclic natural products isoshinanolone (**32**), plumbagin (**33**), and droserone (**34**), which are apparently derived from the naphthalene part **35** of naphthylisoquinoline alkaloids, were found (*Scheme 7*). Only by applying HPLC-MS trace analytical techniques, we detected low quantities of dioncophylline A (**4**) and related compounds in these species.

Besides the Dioncophyllaceae, the only other plant family known to produce naphthylisoquinolines, are the closely related Ancistrocladaceae. This small palaeotropical family consists of a single genus (*Ancistrocladus*) with *ca.* 22 species. The further related families Drosophyllaceae, Droseraceae, Nepenthaceae (all carnivorous), and Plumbaginaceae (subfamily Plumbaginoideae) likewise do produce naphthalene-related metabolites [66], but apparently no naphthylisoquinolines.

7. The Bottleneck Reaction in Naphthylisoquinoline Biosynthesis: The Reductive Introduction of Nitrogen

All these metabolites are likely derived from a common polyketide precursor **36**, the ability to produce naphthylisoquinolines obviously depending on a unique reductive amination step to give the dihydroisoquinoline **37** (*Scheme 7*). For Dioncophyllaceae, this step yields exclusively (3*R*)-configurated alkaloids that lack an oxygen function at C(6) (*e.g.*, dioncopeltine A (**10**) *Scheme 7*) – the so-called Dioncophyllaceae-type [2], whereas for Ancistrocladaceae, the situation is more complex: while Asian Ancistrocladaceae contain only 'Ancistrocladaceae-type' alkaloids [2] like ancistrocladisine (**38**) (*Scheme 7*), which are characterized by their (*S*)-configuration at C(3) and an oxygen function at C(6), West-African Ancistrocladaceae like *A. abbreviatus* and *A. korupensis* produce typical Ancistrocladaceae-type alkaloids, pure Dioncophyllaceae-type alkaloids, and, in addition, mixed, hybrid-type alkaloids with a great structural diversity, including dimers (like michellamines, *cf. Fig. 1*), naphthalene-free quaternary isoquinolinium salts

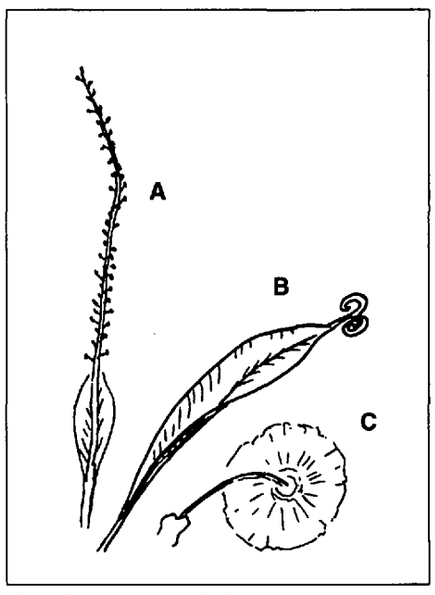


Fig. 19. *Unique morphological characteristics of* T. peltatum

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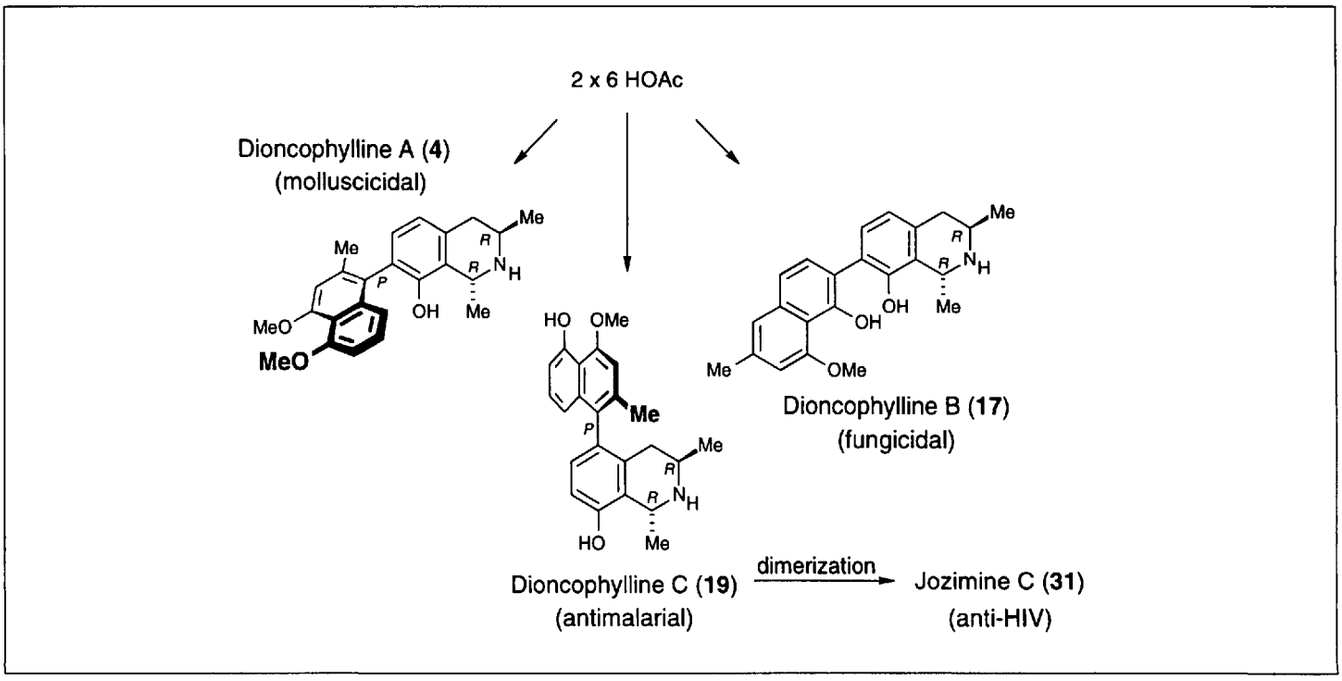
Scheme 8. *Biologically Active and Biogenetically Unprecedented Alkaloids of* T. peltatum



[67], and naphthylisoquinoline glycosides [37].

8. Conclusion

Triphyophyllum peltatum does not produce dimers, glycosides, isoquinolinium salts, (*S*)-configurated or 6-oxygenated alkaloids as Ancistrocladaceae do, still it occupies an outstanding position and is a particularly rewarding plant species, and thus the main topic of this paper:

1) It has characteristic morphological features (*Fig. 19*): the carnivorous organs, the clawed leaves, and the bizarre seeds, for which the species bears the name '*peltatum*' (= shielded).

2) It contains most peculiar chemical constituents, *i.a.* dioncophyllines A (**4**), B (**17**), and C (**19**) of likewise unprecedented biosynthetic origin from acetate units (*Scheme 8*).

3) It has promising biological properties, *e.g.*, molluscicidal activity for dioncophylline A (**4**), fungicidal activity for dioncophylline B (**17**), and, in particular, excellent antimalarial activity for dioncophylline C (**19**). Moreover, jozimine C (**31**), the apparently unnatural dimer of **19**, shows a very high anti-HIV activity, an additional novel dimension of these *Triphyophyllum* alkaloids.

Thus, we have true hits in four important fields of indications. All this, along with a lot of scientific satisfaction, we owe to this most peculiar and productive African plant, which will certainly yield most interesting further results in the near future.

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